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Exploring Relationships Between Structure, Dynamics And The Effects Of Local Perturbations In Networks

Lia Papadopoulos
University of Pennsylvania

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Abstract
In recent years, an abundance of studies in complex systems research have focused on deciphering the properties and behaviors of networks. Within this arena, much effort has been devoted to characterizing the structural organization of networks with complicated topologies. However, network elements are often dynamical entities, and in this case, it becomes relevant to understand what collective dynamics arise from particular architectures, as those activity patterns may in turn shape system function. Moreover, a network's dynamical behaviors may be significantly affected if the underlying interactions can themselves evolve over time, or if external influences also act upon the system. In this thesis, we numerically study such scenarios using a generic model of interacting oscillators, and in the context of network models more closely inspired by neural population activity. Beginning with a system of canonical coupled phase-oscillators, we ask whether global synchronization can be enhanced in networks whose connectivity co-evolves with their dynamics. This work presents a simple adaptive strategy which, although it relies on only local information, can reorganize initially unstructured networks towards topologies that better support collective behavior. We next turn our attention to models inspired specifically by mesoscale and macroscale brain network dynamics. In particular, we start by studying small circuits of interacting oscillatory neuronal populations, wherein multistability can enable distinct network activity patterns to arise from a single anatomical backbone. For both deterministic and stochastic networks, we then show how different types of local perturbations can be harnessed to modulate these collective states in functionally meaningful ways, bypassing the need to rewire circuit structure. We then build a model of whole-brain network dynamics by coupling oscillatory neural masses according to empirically-derived anatomical connectivity, and we investigate the impacts of focal stimulation on the system's dynamics. Our results suggest that network responses can depend not only on the perturbed site within the structural scaffold, but also on the nature of the system's ongoing rhythmic activity at baseline. As a whole, this work aims to elucidate various interplays between structure, perturbations, and collective dynamics in model systems of interacting elements, including generic coupled oscillator networks and biologically-inspired brain networks.

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EXPLORING RELATIONSHIPS BETWEEN STRUCTURE, DYNAMICS AND THE EFFECTS OF LOCAL PERTURBATIONS IN NETWORKS

Evangelia Papadopoulos

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in

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For Mom and Dad, and for my sister, Anna.
I am filled with gratitude for so many people whose collective guidance, support, and encouragement have enabled me to pursue a graduate education.

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ABSTRACT

EXPLORING RELATIONSHIPS BETWEEN STRUCTURE, DYNAMICS AND THE EFFECTS OF LOCAL PERTURBATIONS IN NETWORKS

Evangelia Papadopoulos
Danielle S. Bassett

In recent years, an abundance of studies in complex systems research have focused on deciphering the properties and behaviors of networks. Within this arena, much effort has been devoted to characterizing the structural organization of networks with complicated topologies. However, network elements are often dynamical entities, and in this case, it becomes relevant to understand what collective dynamics arise from particular architectures, as those activity patterns may in turn shape system function. Moreover, a network’s dynamical behaviors may be significantly affected if the underlying interactions can themselves evolve over time, or if external influences also act upon the system. In this thesis, we numerically study such scenarios using a generic model of interacting oscillators, and in the context of network models more closely inspired by neural population activity. Beginning with a system of canonical coupled phase-oscillators, we ask whether global synchronization can be enhanced in networks whose connectivity co-evolves with their dynamics. This work presents a simple adaptive strategy which, although it relies on only local information, can reorganize initially unstructured networks towards topologies that better support collective behavior. We next turn our attention to models inspired specifically by mesoscale and macroscale brain network dynamics. In particular, we start by studying small circuits of interacting oscillatory neuronal populations, wherein multistability can enable distinct network activity patterns to arise from a single anatomical backbone. For both deterministic and stochastic networks, we then show how different types of local perturbations can be harnessed to modulate these collective states in functionally meaningful ways, bypassing the need to rewire circuit structure. We then build a model of whole-brain network dynamics by coupling oscillatory neural masses according to empirically-derived anatomical connectivity, and we investigate the impacts of focal stimulation on the system’s dynamics. Our results suggest that network responses can depend not only on the perturbed site within the structural scaffold, but also on
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Chapter 1

Introduction

Many different complex systems – spanning the physical, biological, social, and engineering sciences – can be naturally and conveniently represented as networks of interacting elements. Often, components in these networks are dynamical units with time-evolving states, and system function is determined by the collective behaviors of the network as a whole. In these cases, it becomes crucial to understand how interplays between units’ intrinsic properties and network coupling shape global activity patterns. Sometimes, the interactions themselves may vary over time in response to the system’s internal state, potentially enabling structural and dynamical organization to emerge on their own. Moreover, also important to the function of many networked systems is how their global behaviors are impacted by dynamical perturbations of certain units. Understanding these effects requires understanding not only the local response of an externally- or internally-triggered focal modulation, but also how the response propagates in the network to potentially induce distributed alterations to system behavior. One way to examine relationships between network coupling, external perturbations, and collective activity patterns is through the use of computational models, which is the approach taken in this thesis. In particular, we numerically explore some of the directions alluded to above in different networked systems exhibiting oscillatory dynamics. We first consider synchronization behavior in a model of generic coupled phase-oscillators whose interactions adaptively rewire over time. We then examine the effects of local perturbations on coordinated activity patterns arising in models inspired by mesoscale and macroscale brain network dynamics. Here in the introduction of this thesis, we review some
relevant background for the studies presented in subsequent chapters.

1.1 Networks

We begin in this section with a brief overview of the study of networks and their dynamics. In general, a network consists of a set of discrete units (nodes) that interact with one another through pairwise connections (edges) (Fig. 1.1A) [3, 4]. Importantly, diverse complex systems – varied in the nature of their components and the scales at which they manifest – can be naturally described or represented in this way [5]. The examples of networked systems abound, ranging from biological systems such as interconnected populations of cells in a brain [6], to physical systems like assemblies of contacting particles making up a granular material [7], to social systems comprised of whole communities of living organisms [8].

Networks can exist in many forms. For example, they can have regular structure or very heterogeneous topologies. Moreover, they may be composed of dynamically evolving subunits, or even have both nodes and edges that change in time. Because networks are by definition sets of interacting elements, they also often exhibit macroscopic phenomena that cannot be appreciated by examining the individual components in isolation. Rather, because these behaviors are inherently a result of the coupling between system components, they must be considered and studied in a network-based context.

Deciphering the complexities of networked systems begs for quantitative methods that can be used to characterize their organizational patterns and simplified models that can help us to understand the emergence of their collective properties and function. These are indeed the aims of network science, an emerging academic discipline – drawing on methods from physics, mathematics, computer science, and other fields – dedicated to studying the structure, dynamics, and function of networks. Recent years have seen a vast amount of research and progress in this area, which is evidenced, at least in part, by the many reviews and books that now exist on the subject [3, 4, 9–11].

1.1.1 Structural representation, characterization, and models

A common way to encode a network’s structure is with a mathematical object called a graph [4, 12, 3]. A graph $G$ consists of a set of nodes $V$ and a set of edges $E$, where edges link pairs of nodes. It is often helpful to compactly represent the information in a graph using an adjacency
matrix $A$, where the element $A_{ij}$ gives the strength (i.e., weight) of the connection from node $j$ to node $i$. A network is undirected if all edges are reciprocal with equal weights in both directions; in this case, the adjacency matrix will be symmetric such that $A_{ij} = A_{ji}$ for all $i$ and $j$. Moreover, a network is said to be unweighted if the elements of the adjacency matrix are all either 0 or 1, indicating only the presence or absence of a link.

In the context of network science, it is common to use the term “topology” as an umbrella term referring to the structural organization of a network. Due to its roots in graph theory [12, 4, 3], network science has traditionally focused on characterizing networks by developing metrics and tools to quantify and identify patterns in their topology. For example, assuming an unweighted and undirected network, one of the most commonly studied properties is node degree, which is often used as a proxy for a given unit’s importance in a network. The degree $k_i$ of node $i$ is simply the sum of the edge weights attached to it, given by the formula $k_i = \sum_{j=1}^{N} A_{ij}$, where $N$ is the number of nodes. The mean degree of a network can then be computed as $\langle k \rangle = 1/N \sum_{i=1}^{N} k_i$, which is related to the number of nodes $N$ and number of edges $M$ through $\langle k \rangle = 2M/N$. It is also sometimes useful to characterize a network using its degree distribution $P(k)$, which gives the probability that a node has degree $k$. Other common measures of network topology are quantities such as the clustering coefficient, which measures the density of triangles in a network, and the mean path length, which is the average of the shortest path of edges between each pair of nodes. Note that these descriptors, along with many others, can be generalized to weighted and directed networks as well. Though we only mention a few here, there are a great number of ways to characterize network structure (see, for example, Refs. [3] and [4]).

In addition to mapping out the topological properties of different empirical networks, much of network science is concerned with the construction and analysis of various graph models [3, 9]. One of the most famous is the canonical Erdős-Rényi model for generating random graphs [13, 14]. The small-world model of Watts and Strogatz is also well-known [15], and generates graphs that have both short average path lengths (like a random network) and also high clustering (like a lattice network). Another classic example is the Barabási-Albert model [16], which was designed to generate networks characterized by a heavy-tailed (specifically power-law) degree distribution. When trying to understand the organization of a real network, it is often helpful to compare it to a controlled graph model whose properties and construction are well understood.

As a final point, we also note that networked systems often exist in real, physical space [17]. For example, transportation networks [18, 19] and anatomical brain networks [20] both have this
feature. This fact means that, in addition to topology, spatial aspects of the network (such as the physical lengths of connections) may be important to consider as well. In the studies presented in Chapters 3 and 4, the spatial embedding of the networks leads us to incorporate time delays into the corresponding models used for their dynamics.

Figure 1.1: A network with dynamical elements and a schematic demonstrating the idea of adaptive networks. (A) In this thesis, we consider networks whose units (nodes) are dynamical elements with time-evolving states that are coupled via structural interactions (edges). (B) A schematic depicting the notion of an adaptive network. The topology of the network influences the dynamical states of each node, which in turn dictate how the connectivity is changed. This figure is taken directly from Gross and Blasius [21].

1.1.2 Dynamical networks

The principled study of network structure is critical for understanding networked systems. However, it is frequently the case that the functioning of a system depends not only on its static network connectivity, but also on the behavior of a dynamical process that is mediated through that structure [11, 22, 3, 23, 10]. For example, we might be interested in studying how diseases or opinions spread in a network of individuals. Or, we may wish to model the dynamics of electrical activity in a network of neurons. In these cases, a given node (an individual or a neuron) has an associated state that changes over time (Fig. 1.1A). The evolution of a node’s state will certainly be a function of its intrinsic dynamics and parameters, as well as inputs coming from outside the system. However, due to network interactions (e.g., social or synaptic contacts), the evolution of a node’s state will also depend, in part, on the states of the other units with which it interacts [22].
When considering a networked dynamical system, one is often interested in macroscopic behaviors that emerge due to the network coupling. For example, will all members in a social network converge to the same opinion? Or, will the neurons or brain areas in a network synchronize their activity? In order to understand these kinds of behaviors, researchers often turn to modeling. Importantly, even relatively simple dynamical models can give rise to fascinating network-level behaviors. Moreover, collective phenomena can be drastically altered by or dependent upon the organization of network connectivity, and there is now a vast literature investigating how topology affects different dynamical processes. We further discuss the example of synchronization of coupled oscillators in Sec. 1.2, in anticipation of the study presented in Chapter 2. Conversely, as we will see in Chapter 3, even seemingly simple network structures can give rise to complex collective activity patterns that have functional consequences for the system at hand.

Thus far we have acknowledged the crucial fact that the elements (nodes) in a network oftentimes have associated dynamics, rather than being structural entities alone. In fact, when we speak of the “function” of a networked system, we are typically referring to something about its dynamical state. However, it could just as well be the case that network connectivity itself is time-varying. Naturally, studies have traditionally considered how static connectivity affects network dynamics. But in adaptive systems (Fig. 1.1B), the reverse also occurs: the weights or placement of network interactions change over time in a manner that is dependent on the states of the nodes [21, 24, 25]. There are many examples of such coevolution in networks; for example, neuronal networks continuously reorganize via activity dependent plasticity and rewiring, and social networks restructure in response to epidemic spreading and opinion formation. There is now exciting literature exploring phenomena that can result from feedback between link topology and nodal dynamics, and our insights in the area of adaptive networks have again benefited from the use of idealized models [21, 24, 25].

Particularly interesting and relevant are scenarios where a network is reconfigured according to simple, \textit{local} rules that do not require a “top-down” or central control strategy. Focusing on such scenarios, a number of studies have shown how adaptive networks can give rise to different kinds of self-organization, meaning the formation of global patterns arising via only local interactions and changes to those interactions informed by only local information [21, 24, 25]. Importantly, the emergence of “order” in these systems can occur simultaneously in the structure of the network as well as in the nature of its dynamics. For example, different modeling studies have shown that complex topological properties such as modularity [26, 27] and power-law degree distributions [28] (both of which are widely observed in empirical systems [29–32])
can form through coevolutionary rules that couple network dynamics and structure. Hence, these investigations present various hypotheses for how such organization might arise in the first place. Moreover, other work has illustrated that adaptive processes can lead to critical dynamics in neural systems [33], change the nature of epidemic spreading on social networks [34], and more [21, 24, 25]. Still, the study of coevolutionary networks is an emerging area, and many directions remain to be explored.

1.2 Synchronization and the Kuramoto model

This thesis is mainly concerned with collective activity patterns arising in different networks composed of oscillatory subunits. A particularly fascinating collective phenomenon that can occur in these systems is synchronization or phase-locking, wherein some or even most of the system’s elements exhibit coherent activity patterns as a function of time. Synchronization is thus a type of ordered or cooperative state that can emerge due to interactions between dynamical units. Both rhythmic activity and synchronization are widespread behaviors that are critical to the function of many systems [35]. For example, the synchronization of pacemaker cells in the sinoatrial node of the heart is responsible for the heart’s rhythmic contractions [36] and the synchronization of neuronal networks generates coherent oscillations in the brain [37, 38]. Even consensus formation in social networks can be considered as a type of “synchrony” in a broader sense [39–41], and in Sec. 1.4, we will further discuss the role of interareal phase-locking as a mechanism for communication between distinct neural assemblies [42, 2].

The pervasiveness of synchronization phenomena in the world around us has motivated the development of many models to understand its emergence. Of the many that exist, perhaps the most canonical is Kuramoto’s model [43, 44], which built upon earlier intuitions from Arthur Winfree regarding collective synchrony in populations of heterogeneous, interacting oscillators. In this section, we present the original Kuramoto model and its extension for studying synchronization on complex networks. While we give only a very concise overview, it is worth noting that there are a number of reviews that cover the model in significant detail [45, 46, 23, 47]. The brief exposition presented here is in anticipation of our study in Chapter 2, which utilizes Kuramoto dynamics.

The Kuramoto model [43, 44] was formulated in the 1970s as a tractable model for studying synchronization in a collection of all-to-all coupled phase-oscillators with heterogeneously
The Kuramoto model is a canonical system for the study of synchronization. (A) Each oscillator is described by a phase variable $\theta_j$, which can be visualized as a point on the unit circle. The modulus $r$ of the complex order parameter $re^{i\psi}$ measures the level of phase coherence in the population, and the angle $\psi$ gives the average phase of the oscillators. This figure is taken directly from Strogatz [46]. (B) The long-time value of the order parameter $r_\infty$ as a function of the coupling strength $K_c$ for the original Kuramoto model. The critical coupling strength $K_c$ marks the onset of synchrony. This figure is taken directly from Strogatz [46].

distributed natural frequencies. The governing equations take the form

$$\dot{\theta}_i = \omega_i + \frac{K}{N} \sum_{j=1}^{N} \sin(\theta_j - \theta_i), \quad i \in \{1, ..., N\},$$

where $\theta_i$ and $\omega_i$ are the phase and natural frequency of the $i^{th}$ oscillator, respectively, $K$ is a global coupling strength, and each oscillator acts on every other according to a sinusoidal interaction. The natural frequencies are taken from a distribution $g(\omega)$, which, in the original formulation, is considered to be unimodal and symmetric about its mean $\langle \omega \rangle$.

To describe the macroscopic behavior of the system, Kuramoto introduced the complex order parameter

$$r(t)e^{i\psi(t)} = \frac{1}{N} \sum_{j=1}^{N} e^{i\theta_j(t)},$$

which can be thought of as the centroid of the $N$ phases on the unit circle, where the modulus $r(t)$ tracks the overall level of coherence in the population and the phase $\psi(t)$ tracks the average phase (Fig. 1.2A). In particular, the radius $r(t)$ is a number between zero and one; when the phases are synchronized in a tight cluster, $r(t) \approx 1$, whereas if they are spread relatively uniformly around the circle, the population coherence is low and $r(t) \approx 0$. 

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The Kuramoto model can be examined analytically for $N \to \infty$, but here we simply provide a few intuitions about its behavior and direct the reader to a number of references for further details [43, 44, 46, 45, 23, 47]. We first note that under the assumptions of the original model, the system undergoes a continuous transition from the incoherent state to a partially coherent state as the coupling $K$ is increased (Fig. 1.2B). Hence, beyond a certain point, the coupling is able to outweigh the differences in frequency between some of the oscillators, and a fraction of them (those with frequencies closer to the mean of the distribution) will lock. Assuming we have let $\theta_i \to \theta_i + \langle \omega \rangle t$ for all $i$ (which has the effect of translating the mean of the frequency distribution to zero while leaving all else about the governing equations unchanged), one can show that the critical coupling strength obeys $K_c = 2/\pi g(0)$. This fact indicates that the onset of synchrony will be reached sooner if the frequency distribution is more peaked (i.e., $g(0)$ is larger). As the coupling strength is increased further, the order parameter increases until full synchrony is reached.

Though originally analyzed in the context of an all-to-all coupled system of phase oscillators, the Kuramoto model can be extended to more general interaction topologies [23, 47, 22]. This extension is achieved simply by inserting an adjacency matrix $A_{ij}$ before the sinusoidal term in Eq. 1.1 to obtain

$$\dot{\theta}_i = \omega_i + K \sum_{j=1}^{N} A_{ij} \sin(\theta_j - \theta_i), \quad i \in \{1, \ldots, N\}. \quad (1.3)$$

Now, instead of the original mean-field coupling, oscillators interact with one another according to the specific network connectivity encoded in the adjacency matrix.

There has been a massive amount of research employing the Kuramoto model to examine how synchronization is affected when the interaction topology is made more complex [23, 47, 22]. It would be difficult to summarize the many findings here, so we simply note that a large body of work has shown that different network structures (e.g., random vs. modular vs. scale-free) can have large impacts on collective dynamics and can quite drastically change transitions to synchrony [23, 47, 22]. A number of studies have specifically examined how global synchronization can be optimized by varying network organization [48–50] and have uncovered the importance of considering how dynamical properties (e.g., the natural frequencies) are intertwined with a network’s structural properties. In fact, the presence of structural-dynamical correlations can bring about new phenomena such as “explosive” or first-order synchronization transitions.
Further extensions of the original Kuramoto model have also been considered, including those that evaluate the effects of time delays, different forms of the interaction term, and even synchronization on multilayer networks [23, 47].

1.3 Large-scale anatomical brain networks

In thinking about dynamical networks, perhaps some of the most complex and fascinating are those formed by biological neural systems. The latter two studies presented in this thesis (Chapters 3 and 4) examine relationships between anatomical connectivity and the effects of exogenous inputs on collective activity patterns generated by computational models inspired by brain network dynamics. In expectation of these studies, this section provides a brief introduction to the concept of structural brain networks.

The brain is a quintessential example of a complex system. It is composed of a massive number of dynamic, interacting elements that – despite being subject to physical constraints and laws – together give rise to a vast array of functions, including perception, attention, learning, memory, the generation of language, reasoning, and more. Underlying these functions is the structural substrate of the brain. On multiple spatial scales, this scaffold can be represented and understood as an intricate network composed of neural elements (nodes) linked to one another via anatomical connections (edges) [52].

As brought to light by the work of Ramón y Cajal [53], it is well-accepted that the fundamental computational units of the brain are neurons, and that these cells connect with one another via synapses to form dense and heterogeneous networks throughout the brain. On this microscopic level, the structural complexity of the brain as a networked system is often introduced by quoting the sheer number of components at play, which, for a human, involves on the order of $10^{11}$ neurons and on the order of $10^{14}$ synapses [52]. Though neurons and synapses represent the elementary units and connections making up neural systems, the brain can be described as a networked system on larger spatial scales as well. In fact, if we would like a picture of how multiple brain areas interact, or an image of brain connectivity as a whole, it is both helpful and technologically necessary to view the brain’s structure through a coarse-graining lens [52, 54, 55]. Though fine-scale details will undoubtedly be lost in this process, such an approach allows for an understanding of more macroscopic organizational patterns in large-scale neural systems, and in turn, the dynamical processes and computations that are supported by those distributed structures.
In this thesis, we will be concerned with spatial scales where network nodes correspond to large neuronal populations or brain areas, each composed of thousands to millions of individual cells. A network-based view of the brain at this level is supported by the fact that the brain’s gray matter is inherently composed of many functionally and structurally distinct neuronal assemblies that are connected to one another through long-range anatomical projections [52, 1, 54, 55]. For example, at scales of $\sim 0.3 - 0.6$ mm, cortex is organized into localized substructures called macro-columns [56, 57], and on larger scales (i.e., on the order of centimeters) brains can be parcellated into coarser regions based on differences in functional specialization, cytoarchitecture, or sulcal and gyral boundaries [52, 1, 54, 55, 58], for example. The study presented in Chapter 4 of this thesis utilizes a parcellation of the human brain wherein spatially contiguous regions (i.e., network nodes) are delineated based on local anatomic curvature information deduced from MRI scans [59].

Given a set of discrete brain areas, different experimental approaches allow for reconstructing interareal connectivity (network edges) between those neural elements. The main invasive technique is tract tracing [60, 61], which utilizes axon transport processes to enable a directed mapping of axonal projections between distributed neuronal populations. This method has been used to build structural brain networks for animals such as the macaque [62, 63], mouse [64], and cat [65].

For humans, however, non-invasive techniques must be employed. The most common method for unveiling long-range structural connectivity pathways in human brains (and the one

Figure 1.3 (following page): Construction of a large-scale human brain network as presented in Hagmann et al. [1]. (A) A T1-weighted MRI is taken, which is then segmented into gray and white matter. (B) A diffusion spectrum image (DSI) of the brain is also acquired, from which one can compute orientation distribution functions (ODFs) at different locations. These ODFs can be thought of as deformed spheres whose radius along a certain direction is a measure of diffusion strength along that direction [1, 66]. The surface colors (r,b,g) correspond to (x,y,z) directions. (C) Cortex is parcellated into different anatomical regions. (D) Tractography is performed on the diffusion-weighted data in order to map trajectories of white matter fibers across the brain. (E) A structural brain network is computed by using the tractography information to estimate connection strengths between each pair of regions from the anatomical partition. (F) One can also represent the structural brain network in the form of an adjacency matrix, where colors represent the edge weight between a given pair of nodes. Note that panels E and F are schematics, and were not determined from the data depicted in panels A–D. Panels A–D are taken directly from Hagmann et al. [1] with minor edits.
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A brain network

E adjacency matrix

D Tractography

B Diffusion Spectrum Imaging

C Partition into 66 anatomical subregions
utilized to construct the network used in Chapter 4) are based on diffusion magnetic resonance imaging (dMRI) [52, 1, 54, 55, 58]. Diffusion MRI can map the brain’s white-matter tracts, which are primarily composed of myelinated axon bundles that link distributed gray matter regions into large-scale anatomical networks. As its name suggests, dMRI maps certain details of tissue architecture by measuring the diffusion of water molecules in the tissue along different directions. In particular, the method relies on the fact that this diffusion will be more or less constrained in certain directions according to the tissue’s structural properties. In white matter, for example, rather than being isotropic, diffusion preferentially occurs along the lengths of the fibers, whereas it is slower in perpendicular directions.

Once the anisotropy of water diffusion in the brain is measured with dMRI, sophisticated tractography algorithms can be used to reconstruct white-matter trajectories [67]. The output of this tractography is then used to determine the presence or absence and strengths of structural connections between different anatomical areas. The end result of this process is a large-scale (potentially even whole-brain) network, where nodes correspond to gray matter regions determined from a given parcellation of the brain, and where edges correspond to white-matter streamlines that connect those areas. Fig. 1.3 depicts the typical steps involved in constructing a large-scale human brain network.

Many studies have examined the topological and spatial properties of large-scale brain networks, and have uncovered robust organizing principles. These include features such as modular structure, small-worldness, hubness, and tradeoffs between wiring costs and network efficiency [68, 69, 20, 70]. However, in concluding this section, we recall the key point that structure is only part of the story when it comes to understanding brain network function. In the remainder of this Introduction, we turn to the second part of the story: the dynamics of large-scale brain circuits.

1.4 Dynamics of multi-area brain circuits: Oscillations and interareal synchrony

In the previous section, we outlined the idea of structural brain networks, which describe the organization of anatomical connections linking different neural elements. But brains are not simply static, physical scaffolds. Rather, they are composed of units that are inherently dynamic in nature, characterized by state variables that evolve over time. Indeed, understanding the function
of a biological neural system requires not only a map of its structure, but also an understanding of its varied activity patterns: how they arise from the intrinsic biophysical properties of neural components, how they are constrained or supported by various features of underlying anatomical connectivity, how they are modulated by external inputs or internal regulatory processes, how they support computations, how they change across behavioral states, etc. These are not easy tasks, but much progress has been made with the advent of experimental techniques that can measure neural dynamics across a range of spatiotemporal scales.

1.4.1 Oscillatory activity

Importantly, because the brain exists as a networked system, neural activity can become coordinated at one (or more) scales to give rise to collective activity patterns that manifest at a coarser level. Hence, just as we can study network structure at different spatial scales, so too can we examine neural dynamics emergent at different anatomical resolutions. Chapters 3 and 4 of this thesis are concerned with the dynamics of large neuronal populations that are then coupled into small inter-areal circuits or whole-brain networks. At these scales, rhythmic activity has been commonly observed in empirical measurements and is thought to play important functional roles \[37, 38, 71–77, 42, 78, 79\]. In this section, we briefly review some important ideas and findings regarding collective oscillations in mesoscale and macroscale brain networks, which motivate the use of mean-field oscillatory network models like those we employ in the coming chapters.

To begin, we note that by “collective oscillation”, we mean a rhythmic electrical signal that emerges from the coordinated activity of a large population of interconnected neurons. To understand this phenomena further, we first recall that the fundamental dynamic units in a biological neural system are excitable cells called neurons. If a neuron is sufficiently excited by its inputs, it will generate a brief electrical pulse called an action potential or spike. The neuron can then transmit or “communicate” that signal to other neurons via synaptic connections. If many neurons are interacting in a network, it is possible for their spiking patterns to synchronize in a rhythmic manner, such that the aggregate activity of the network as a whole oscillates over time \[71, 74, 80\].

Hans Berger made the first discovery of oscillatory activity in the human brain in 1929 when he measured the alpha rhythm (\(\sim 8-12\) Hz) with EEG \[81\]. It is now known that collective rhythms are a ubiquitous feature of neural dynamics, and oscillations spanning frequencies of less than 0.1Hz to greater than 100Hz have been observed across different areas of the brain \[37, 38\]. From an experimental standpoint, brain rhythms have been measured in a number of
ways, including via electroencephalography (EEG), magnetoencephalography (MEG), electrocorticography (ECOG), and local field potentials (LFPs).

In general, there are many potential biophysical mechanisms that could underlie the generation of neural oscillations, especially since single neurons and synapses exhibit great biophysical diversity [71]. Moreover, mechanisms likely differ depending on the frequency band [71, 74]. For example, computational models have shown that gamma oscillations (∼30-80 Hz) can arise either through interactions between excitatory and inhibitory neurons or between inhibitory neurons alone in local populations [80, 82, 83]. Alternatively, alpha oscillations are thought to often involve interactions with the thalamus [84–86].

In general, it is still up for debate as to whether oscillations play a definitive causal role in brain function or whether they are an epiphenomenon [87–90]. However, there is a large body of work showing that rhythms associate with or are modulated by different cognitive processes and computations, lending support to the idea that oscillations are indeed functionally meaningful [37, 38, 71–77, 42]. For example, one well-studied potential role for oscillations is in regard to phase-coding. In phase-coding, a background population oscillation sets up a temporal reference frame, and information is then encoded in the timing of individual spikes relative to the phase of the ongoing rhythm [71]. This scheme is used, for example, by the hippocampus to represent spatial information [91, 92]. We discuss another possible consequential function for oscillations in the next subsection.

1.4.2 Long-range synchronization

Much can be learned by studying activity patterns in a single area, but the brain as a whole exists as a macroscopic web of many coupled regions (Sec. 1.3). Indeed, cognitive processes exist as a result of not only the activity in a given region by itself, but also of the dynamical coordination of that activity across large-scale networks [76, 77, 93, 94, 55, 95, 79]. However, it remains unclear exactly how the brain is able to combine activity from anatomically and functionally specialized areas into cooperative groups in a flexible manner.

Aside from their involvement in local information processing, one of the main reasons that collective oscillations are hypothesized to be important for brain function is precisely because of their potential to enable long-range coordination of brain dynamics [76, 77, 2, 42, 96, 79]. Specifically, this is thought to occur via the formation of specific temporal relationships between the rhythms of distributed areas. In the literature, the presence of such a statistical relation between a pair of regions is often thought to indicate a “functional interaction” or a “functional
connection”. Moreover, in direct analogy to the concept of a structural network, it is common to construct and study “functional networks”, where brain areas are again represented as nodes, but where edges correspond to the strength of a functional rather than structural link [52, 55, 54].

One of the most well-studied types of an oscillatory-based functional interaction is phase synchrony (sometimes also called phase locking or phase coherence) [76, 77, 2, 42, 79]. Given population rhythms from two different sources within a particular frequency band, the strength of their phase-synchrony is typically measured by assessing the consistency of their relative phase across a given time window [97]. Broadly, it is hypothesized that the establishment of significant inter-areal synchrony enables and reflects large-scale integration or communication in brain networks [76, 77, 2, 42, 96, 98, 79].

Significant empirical support exists for the idea that oscillatory coherence acts to coordinate distributed brain areas as required for a variety of computations. This evidence comes from experiments that have shown the emergence of synchrony between widespread, simultaneously recorded sites during processes that are known to require cross-regional interactions. One scenario in which inter-regional interactions are necessary, for example, is during multisensory processing, wherein the brain receives and needs to consolidate inputs from different sensory modalities (e.g., visual and auditory). Past work has suggested long-range coherence as a mechanism through which such multisensory integration can be achieved [99, 100]. In general, interareal synchrony has been implicated in a number of other brain functions, such as attention [101–104], perception [105, 106], and working memory [107].

Long-range synchrony between two areas or across a network is often broadly associated with the presence of meaningful functional interactions and has been shown to be correlated with or modulated by different neural processes. A theoretical hypothesis known as “communication-through-coherence” (CTC) formalizes an even more precise function for coordinated rhythmic activity [2, 42, 108, 73, 73]. The CTC framework – first popularized by Pascal Fries – posits that direct communication between anatomically coupled brain regions can be established when their oscillatory activities phase-lock with appropriate phase relations [42, 2]. In addition to the assumption that a neuronal population exhibits a collective oscillation, the key points behind this idea are (1) that a population rhythm sets up a scenario in which the excitability of the corresponding neuronal group varies rhythmically in time, and (2) that a population rhythm concentrates spike output to brief temporal windows. In this way, when multiple such areas are

\[\text{Many studies have also examined interactions between population activity using a quantity called coherence, which is a measure of the linear relationship between two signals in the frequency domain.}\]
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coupled, information will be most reliably transmitted from a sending area to a receiving area when the sender’s focused output repeatedly reaches the receiving population when the latter’s excitability is high (i.e., when the receiving area is most sensitive to input). Alternatively, incoherent oscillations will be less effective at establishing communication.

Figure 1.4: Schematic of the communication-through-coherence hypothesis from Pascal Fries [2]. In this example, three neuronal groups composed of excitatory and inhibitory neurons exhibit oscillatory activity. The top (purple) and bottom (green) neuronal groups both send anatomical projections to the middle area (gray). However, only excitation from the green area is repeatedly received by the gray area when the latter is in an excitable state (i.e., when inhibition in the gray area is low). This enables the top area to effectively transmit a message to the middle group. Conversely, excitation from the green area is received at the gray area when inhibition in the gray population is high, preventing communication. This figure has been copied from Fries [2] with some minor edits.

Beyond providing evidence for a general integrative role for oscillatory synchrony, there is now experimental and modeling work that has more directly tested certain consequences of the CTC hypothesis. For example, some studies have found that varying the interareal phase-relation can modulate the strength of effective interactions between neuronal groups [109–111] or shift the direction of information transfer between coupled areas [112, 113]. Other work has shown that selective coherence may enable selective routing of competing signals [112, 114, 115, 103, 116]. The modeling study we perform in Chapter 3 is highly-motivated by the CTC theory.

Many studies have considered synchronization between smaller sets of brain areas, but understanding functional interactions on a whole-brain scale is also of critical importance [54, 55]. From an empirical standpoint, this extension can be challenging due to the difficulty of obtaining measurements of neural activity at both high temporal and spatial resolutions across the brain. Nonetheless, there have been some studies utilizing EEG and MEG to characterize statistical dependencies between regional oscillations on a brain-wide level [117–122, 79]. For example, one early study found that these functional networks exhibit a “small-world” property in different frequency bands, which was hypothesized to be optimal for large-scale information processing.
More recent work provides evidence that whole-brain resting state MEG exhibits transient phase-locking states with different spatial and spectral patterns [121]. Other studies have also found that patterns of brain-wide synchrony are disrupted in pathological conditions [123–125] and modulated during cognitively-demanding tasks [106, 77]. As we discuss in the next section, there has also been much progress in our ability to build dynamical models capable of simulating oscillatory whole-brain activity patterns.

1.5 Reduced models for neural population activity and macroscale brain network dynamics

The brain is a highly complicated organ, both in terms of its anatomical organization and its dynamical capabilities. Moreover, it also seems that there is no single or “right” scale on which to study the brain [126]. Rather, grasping the principles behind its varied functions appears to require an understanding of its structure and dynamics at multiple levels, and, importantly, an understanding of how those scales relate to one another. In addition to experiment, a second way we can try to make sense of these complexities is to build and study models of brain structure and dynamics. Such an approach can be used to elucidate potential mechanisms underlying empirical observations, to explore directions or ideas that are not yet possible to test empirically, or to make new predictions that can guide experiment.

As alluded to in the previous paragraph, models of neural activity often depend upon the spatiotemporal scale that is under consideration. And, even at a given scale, a model can range in its level of complexity. For example, some models of neurons may attempt to detail the biophysics of spiking mechanisms with exceptional precision, whereas others may be constructed to be analytically tractable. In contrast to models of single neurons, neural mass models constitute an alternative model class focused on representing the aggregate behaviors of very large populations of cells [127, 128]. Because they provide coarse-grained descriptions of population dynamics, neural masses can also be coupled to one another in order to build biologically-motivated models of larger-scale dynamics arising from spatially-distributed networks of neuronal ensembles [129].

We use such an approach in the coming chapters. In particular, we numerically investigate the behaviors of neural-mass-based models in an attempt to understand links between structure, dynamics, and the effects of perturbations in mesoscale and macroscale brain networks. In anticipation of those studies, this section first provides a brief overview of the main idea of a neural
mass model, focusing in particular on the Wilson-Cowan model [130] that we use in later chapters. We then discuss how we can scale-up such a model in order to build large-scale models of whole-brain activity.

1.5.1 Neural mass models

In general, neural mass models (NMMs) constitute a tradeoff between biological realism and computational or analytic tractability. Rather than detailing the spiking dynamics of individual neurons, NMMs characterize the average activity (e.g., the mean firing rate or mean membrane potential) of a large neuronal ensemble [127–129] (Fig. 1.5A). The dynamics of these variables are typically described by a low-dimensional system of differential equations derived from phenomenological arguments and by making certain assumptions about the nature of the neuronal population.

Brief overview of single-neuron dynamics

To understand the utility and point of the neural mass approach, first recall that on the microscale, the brain is composed of neurons that are connected in massive networks via synapses. Neurons are composed of three main parts – a cell body, an axon, and dendrites – and generate electrical pulses called action potentials or spikes. These signals can be transmitted to other neurons via synaptic connections; a given neuron can make more than $10^4$ contacts with others [131]. At rest, the electric potential inside a neuron sits at $\sim-70$mV relative to the surrounding medium. Upon receiving inputs from other neurons, the membrane potential can fluctuate up (depolarization) or down (hyperpolarization) as a result of the flow of various ions across the membrane. A spike is generated when the potential exceeds a threshold value ($\sim-55$mV), and is characterized by a rapid rise and fall of the membrane potential that occurs over $\sim 1$-$2$ milliseconds. The dynamics of action potentials are a consequence of ion flow (such as sodium or potassium) regulated by voltage-dependent channels on the cell membrane. When a spike is generated, the signal propagates down the axon and can then be transmitted to another cell at a synapse that is typically located at the cell body or dendrites of the receiving neuron. Synapses can be either electrical or chemical. In the former case, neurons are linked by gap junctions that allow electrical current to flow from one neuron to another. In the latter case, the action potential induces the release of neurotransmitters at the axon terminal of the presynaptic neuron, which flow across the synaptic cleft and bind to chemically-gated channels on the postsynaptic
neuron. This binding can then cause ion flow across the postsynaptic cell membrane that either:
(1) depolarizes the postsynaptic neuron bringing it closer to its firing threshold (as happens at an excitatory synapse), or (2) hyperpolarizes the postsynaptic neuron pushing it further from its firing threshold (as happens at an inhibitory synapse). Whether or not an action potential occurs depends on the combination of all the excitatory and inhibitory influences on the neuron.

The well-known Hodgkin-Huxley (HH) model [132] is a biophysically-detailed model that can accurately describe the mechanics of action potential generation. The HH model consists of a system of four coupled, non-linear differential equations and various fixed parameters, and its development was an extremely important step for computational neuroscience. However, due to the relatively high-dimensionality and complexity of this type of biophysical model, it can be somewhat difficult to analyze. This challenge has led researchers to develop various 2-dimensional approximations, such as the Fitzhugh-Nagumo model [133], which can be easier to evaluate mathematically. A second approach is to consider simpler phenomenological models that ignore many biological details and that do not attempt to directly model action potential dynamics. A common model of this type is the integrate-and-fire (IF) point model of a neuron [131]. It uses a single differential equation to describe the subthreshold evolution of the membrane potential in the presence of a driving current; spikes are then said to occur whenever the potential crosses a fixed threshold, after which the potential is reset to a particular value below threshold.

**Motivation for neural mass approaches**

Often of interest is the collective dynamics of a large network of neurons, rather than the spiking behavior of a single neuron in isolation. Indeed, the brain tends to be organized into functionally and structurally segregated assemblies of interacting cells that may operate as coordinated units [57, 56]. Moreover, certain observed dynamical phenomena only manifest at a population scale. Collective oscillations, which we discussed in the previous section, are one example. Further, many experimental techniques (such as MEG and EEG) measure only ensemble-level signals rather than individual spikes.

One approach for examining the collective activity of neuronal populations is to directly simulate a network of coupled spiking neurons and synapses. This effort requires specifying how neurons connect to one another and the effects of synaptic coupling on their dynamics. The output of such a model would be a list of the spike times for every neuron in the network, from which one could then examine measures of ensemble activity (e.g., population firing rate).
Figure 1.5: Neural mass models, the Wilson-Cowan system, and large-scale brain network modeling. (A) A high-dimensional neuronal population vs. a lower dimensional neural mass model. The coupled-excitatory inhibitory circuit forms the basis of the Wilson-Cowan model [130]. (B) Schematic showing the concept of a brain network model. The system’s dynamics are modeled as a collection of neural masses coupled according to the pattern of empirically-derived structural connectivity. (C) All of these panels are taken directly from Wilson and Cowan [130]. Left: The sigmoidal activation function. Middle: A limit cycle in the phase-plane. Right: Oscillatory activity time-series of the excitatory population.

Researchers indeed utilize this approach, and can simulate networks of thousands of biophysical neurons.

Although large-scale simulations of spiking neurons are possible, they are not without their difficulties. Even considering a relatively simple neuron model, the large number of components within a neuronal pool means that we have to simulate an extremely high-dimensional system of equations. While this can work for populations up to a certain size, it is generally a computationally expensive approach. In turn, this means it can be burdensome to fully map the model’s behavior, and to find or explore relevant parameter regimes. Furthermore, if we wish to develop computational models for several interacting brain areas or the brain as a whole, simulating spik-
ing at the level of individual neurons quickly becomes intractable. Finally, even if such detailed whole-brain simulations were possible, the need for reduced, mathematically tractable models and theories to deepen our understanding and to explain results would still remain.

In order to meet these kinds of challenges, “mean-field” type frameworks have been developed, which largely draw on methods from statistical physics. Rather than focusing on the individual spikes of every neuron, these approaches attempt to describe the evolution of the average state (e.g., mean membrane potential or population firing rate) of large, homogeneous neuronal ensembles [129, 127, 128, 134]. These reduced descriptions and models of mesoscale neural activity can be used to understand collective phenomena such as neural rhythms, and data from measurements such as MEG and EEG. Moreover, as we discuss in the next section, low-dimensional models for single populations can be scaled up in order to build computational models of macroscale brain network dynamics.

One way to describe the collective activity of a neuronal pool is with a population or ensemble density approach [127, 135, 129]. In this method, one typically begins with a specified model of a neuronal network (e.g., the integrate-and-fire model). From those equations, one then attempts to derive a reduced description of the system in terms of the evolution of the distribution of neuron states. With the integrate-and-fire model, for example, the goal would be to describe the dynamics of the population density of membrane potentials. Many studies have employed this method to understand macroscopic dynamical behaviors in neuronal networks, such as the emergence of oscillatory synchrony [136, 137].

Another approach for describing the collective dynamics of large, spatially-homogeneous neuronal ensembles comes in the form of neural mass models (NMMs). Relative to population density approaches, NMMs make further simplifications, characterizing population dynamics with only a single (or a few) state variables [129, 127, 128, 134]. In particular, neuronal population activity in an NMM is typically described by ordinary differential equations that characterize the temporal evolution of mean firing rates or mean membrane potentials. These equations are derived by assuming that individual neuron-neuron interactions can be replaced by “effective” mean-field couplings, and often use phenomenological arguments for relating synaptic input to activity output for the population [134, 128]. By reducing the complexity of a very high-dimensional neuronal population to just a few state variables, NMMs are often amenable to mathematical analyses that allow for determining their key dynamical behaviors as a function of model parameters (e.g., average internal coupling strengths or external input strengths).

One of the earliest and most well-known NMMs is the Wilson-Cowan (WC) model [130].
It was developed in the early 1970s by Hugh R. Wilson and Jack D. Cowan, and is now considered a classic mean-field model that has inspired many others. Building on previous work that considered populations of purely excitatory neurons [138], the WC model describes the average firing rates of two spatially-homogeneous and interacting neuronal populations, one composed of excitatory (E) neurons and one composed of inhibitory (I) neurons (Fig. 1.5A,Bottom). In particular, the WC model is comprised of two ordinary differential equations of the form

\[ \tau_E \frac{dE(t)}{dt} = -E(t) + SE[c_{EE}E(t) - c_{IE}I(t) + P_E(t)] \] (1.4a)

\[ \tau_I \frac{dI(t)}{dt} = -I(t) + SI[c_{EI}E(t) - c_{II}I(t) + P_I(t)], \] (1.4b)

where \( E(t) \) and \( I(t) \) are the excitatory and inhibitory population activities (i.e., the proportion of E or I cells firing per unit time). The functions \( S_E(x) \) and \( S_I(x) \) are known as firing rate functions. In the WC model, these terms determine the fraction of neurons that are activated due to a given level of excitation and take a sigmoidal shape (Fig. 1.5C,Left) of the form

\[ S_{E/I}(x) = \frac{1}{1 + e^{-\alpha_{E/I}(x-\mu_{E/I})}}. \] (1.5)

Sigmoidal firing rate or activation functions are a common feature of NMMs more generally, and in the context of the WC system, this form comes from assuming a unimodal distribution of firing thresholds with mean \( \mu_{E/I} \) and where larger \( \alpha_{E/I} \) corresponds to a narrower spread. The average interaction strengths within each pool are given by \( c_{EE} \) and \( c_{II} \), the average coupling strengths between the two pools are given by \( c_{EI} \) and \( c_{IE} \), and \( P_{E/I} \) represent external inputs to the two populations. Finally, the overall time-scales of the dynamics are set by \( \tau_E \) and \( \tau_I \).

Wilson and Cowan performed a phase-plane analysis of this model to determine its dynamical behaviors. Perhaps one of the most important discoveries was that, with appropriate parameters, the model can exhibit oscillatory dynamics (Fig. 1.5C,Middle,Right). In particular, these rhythms arise due to feedback between the excitatory and inhibitory ensembles. The WC model hence presented a simple means by which oscillatory population activity can emerge due to interacting excitatory-inhibitory networks, which is a mechanism that has now been observed and studied in many other models as well [71]. The WC model is utilized for the studies performed in Chapters 3 and 4 of this thesis.
Biologically inspired neural mass descriptions are often employed to examine and explain rhythmic phenomena in the brain, and a number of different formulations exist. For instance, another well-known example is the model of Jansen and Rit [139], which built upon earlier work by Lopes da Silva and colleagues [140]. NMMs have also been used to study pathological brain states such as epileptic seizure dynamics [141, 144], and to model the effects of stimulation on population activity [142]. In addition, there are recent efforts to develop NMMs that incorporate more realistic aspects of brain organization like the layered organization of cortex, from which multiple oscillation frequencies may emerge [143, 144]. Finally, we note that neural population models can also come in the form of neural field models, which allow for describing dynamics over a spatially-extended piece of neural tissue [145, 146]. The next section outlines how NMMs can be coupled into larger networks to describe more macroscopic dynamics.

1.5.2 Large-scale models of brain network activity

Neural mass models balance biological plausibility with tractability. A key advantage of this tradeoff is that NMMs can be used to model neural dynamics that unfold across spatially distributed networks involving multiple brain areas [129]. This capability is made by possible by coupling multiple neural mass populations according to a specified network topology. In this way, a given NMM represents a local population or brain area, and interactions between them represent long-range anatomical connections or axonal projections. Once coupled, the collective activity patterns of the larger network can be studied. Building upon past work [113, 147–151], we use such a framework in Chapter 3 to study interareal phase-locking patterns in small model brain circuits.

Extending the coupled neural mass approach further, one exciting direction that has emerged within the past 15 years is whole-brain modeling [152, 129, 153]. In this type of framework, each region in a brain parcellation is treated as a distinct NMM, and individual units are then coupled according to empirically-measured large-scale structural connectivity (for example, from tract-tracing or diffusion MRI) (Fig. 1.5B). There are now many studies that have utilized this framework to gain insight into the structural and dynamical drivers of different whole-brain activity patterns in both healthy and pathological conditions (see Refs. [129, 154, 155] for recent reviews).

One particularly important and active area of research has been to use whole-brain neural mass modeling to posit mechanisms for “resting-state” brain activity [156–163]. Often, this is done by comparing the organization of functional connectivity generated by a specific model...
to the organization of empirical functional connectivity measured by techniques such as fMRI, EEG, and MEG. (Recall that functional connectivity is defined as a measure of statistical dependency between the activities of different brain areas). In this way, one can ask what features of a particular model allow it to best describe experimentally measured patterns of brain activity. Past modeling work has suggested that interareal coupling, time delays, and noise are all important in generating realistic resting-state dynamics from computational models. More recent investigations have also shown that model fits can be significantly improved by incorporating specific heterogeneities in the local circuit properties across brain areas [164] or by using models that allow for multiple oscillation frequencies in a single brain area [165]. Currently, there is now a large focus on utilizing computational models to understand the key principles underlying not only time-averaged measures of resting-state functional connectivity, but also time-varying patterns of interareal synchrony [166, 167].

More generally, there is a rich literature using computational neural mass modeling to understand relationships between brain network structure and brain network dynamics. For example, several studies have investigated the effects of time-delays [168] and the roles of specific topological features such as modular structure or hubs [169–171] in generating certain types of activity patterns in the brain. Neural mass models have also been used to investigate the dynamical effects of various structural perturbations (i.e., removing certain nodes or edges) [172] or structural plasticity [173, 174]. In addition, researchers have employed reduced neural mass models to study brain waves [175], the effects of neuromodulation on regulating dynamical integration and segregation [176, 177], the nature of multifrequency interactions in brain networks [143], and potential mechanisms that lead to brain dynamics being altered in certain diseases such as schizophrenia [178, 179] and epilepsy [180, 141, 181].

1.6 Overview of this thesis

Though much progress has been made, many open questions remain on the subject of relationships between network structure and collective dynamics, and in regard to the impacts of focal perturbations on global activity patterns in dynamical networks. In this dissertation, we aim to elucidate some of these interplays using a computational model of simple, interacting phase-oscillators, as well as in the context of biologically-inspired models of brain network activity. All of the studies we present have a common focus on oscillatory dynamics and coordinated behaviors such as synchronization and phase-locking, but each investigation is also inspired by some-
what distinct sets of questions relating to the general themes of structure, dynamics, and local perturbations. In what follows, we briefly outline each analysis.

Chapter 2 presents a numerical study on adaptively-rewiring networks of Kuramoto oscillators. Several analyses have investigated synchronization on static topologies, but much less is understood about the dynamics of networks whose interactions restructure as a function of node states. Moreover, while many studies have considered optimal topologies for synchrony via optimization methods that utilize complete information about the state of network structure, an important question is whether synchrony can be naturally enhanced in a system whose connectivity locally co-evolves with its dynamics. Through simulation, we show that a basic negative feedback process can reorganize initially unstructured networks towards topologies that better support cooperative group behavior. This work thus suggests a simple mechanism by which more ordered dynamics on a global level can emerge in a system that evolves according to a process that is governed by only local rules, in contrast to a top-down controller.

In Chapter 3, we turn to a study of collective phase-locking in small networks of coupled neural mass models. This project is motivated by the influential hypothesis that coherent rhythms may enable interareal communication in the brain, but also by the open question of how brain circuits can move between different global states without having to rewire long-range anatomical connections. In particular, we build upon past work that has proposed multistable phase-locking between the oscillations of different neural ensembles as a means of attaining such flexibility. Via simulation, we first show that the model supports this dynamical behavior, and then we show that the resulting activity patterns can be reconfigured via local external inputs. We characterize these effects both in a deterministic realization of the system, and in more realistic conditions where the neural populations are driven by a noisy environment. Our findings add to a body of work suggesting that multistability – in conjunction with modulatory control signals – could provide a means for diverse functional states to be realized in circuits of oscillatory neural populations whose structure cannot be readily adjusted on fast time scales.

Chapter 4 describes a computational modeling study investigating the impacts of localized dynamical modulations on whole-brain activity. Despite progress, our general understanding of how changes to oscillations in one brain area spread and affect distributed functional interactions remains incomplete. For example, relatively little work has considered how network structure in conjunction with the overall regime of network dynamics may collectively influence global responses to focal perturbations. To examine these questions, we implement a reduced model of brain network dynamics, wherein large-scale regions are modeled as neural masses and then cou-
pled via structural connectivity derived from diffusion MRI. We find that both the focal and system-wide impacts of regional excitation depend on the targeted site, but also on the nature of the network’s ongoing activity at baseline. Building upon past efforts, our results thus demonstrate that anatomical connectivity may not fully determine how locally-induced activity changes will manifest in the context of a large-scale brain network. Specifically, we find that the baseline dynamical state of the system could also play a role in our ability to predict these effects.

Finally, we conclude in Chapter 5 with a broad discussion and outlook for future work.
Chapter 2

Development of structural correlations and synchronization from adaptive rewiring in networks of Kuramoto oscillators

With the exception of minor edits, this chapter is reproduced from:


Abstract

Synchronization of non-identical oscillators coupled through complex networks is an important example of collective behavior, and it is interesting to ask how the structural organization of network interactions influences this process. Several studies have explored and uncovered optimal topologies for synchronization by making purposeful alterations to a network. On the other hand, the connectivity patterns of many natural systems are often not static, but are rather modulated over time according to their dynamics. However, this co-evolution - and the extent to which the dynamics of the individual units can shape the organization of the network itself - are less well understood. Here, we study initially randomly connected but locally adaptive networks of Kuramoto oscillators. In particular, the system employs a co-evolutionary rewiring strategy
that depends only on the instantaneous, pairwise phase differences of neighboring oscillators, and that conserves the total number of edges, allowing the effects of local reorganization to be isolated. We find that a simple rule - which preserves connections between more out-of-phase oscillators while rewiring connections between more in-phase oscillators - can cause initially disordered networks to organize into more structured topologies that support enhanced synchronization dynamics. We examine how this process unfolds over time, finding a dependence on the intrinsic frequencies of the oscillators, the global coupling, and the network density, in terms of how the adaptive mechanism reorganizes the network and influences the dynamics. Importantly, for large enough coupling and after sufficient adaptation, the resulting networks exhibit interesting characteristics, including degree-frequency and frequency-neighbor frequency correlations. These properties have previously been associated with optimal synchronization or explosive transitions in which the networks were constructed using global information. On the contrary, by considering a time-dependent interplay between structure and dynamics, this work offers a mechanism through which emergent phenomena and organization can arise in complex systems utilizing local rules.

2.1 Introduction

Exactly how dynamical processes unfold on networks with non-trivial coupling between individual units remains an important question in complex systems science [3, 11, 182, 183]. Examples of such dynamical systems on networks include the time-dependent patterns of electrical activity in populations of neurons [184, 136, 137, 185–188], the spread of information or disease across social networks [189–192], or regulatory mechanisms in biological networks [193–196]. In each case, the way the system evolves over time is dependent on the specific form of the dynamics, intrinsic properties of each element (either of nodes or edges), and the architecture of connectivity. Intriguing questions are if and how collective behavior can emerge in these systems. A significant and widespread manifestation of this is synchronization [197, 198, 35, 199, 23], in which a group of interacting elements converge to the same state or evolve in unison over time. Real-world illustrations of this phenomenon range from circadian clock cycles [200, 198], to the rhythmic patterns of functional activity in the human brain [42, 201, 202, 158, 203, 204, 119, 205, 96, 206, 38?], and synchronization in power-grid networks [207–210].

One of the most common and useful models for studying synchronization is the canonical Kuramoto model [43, 44], which originally described the evolution of a population of $N$ all-to-
all coupled phase oscillators that were in general non-identical (see [46, 45] for reviews). In recent years, this model has been extended to study systems with heterogeneous network topologies, in order to investigate how the architecture of complex connectivity affects the onset of synchronization in diverse oscillator populations [23, 47]. Such efforts have provided important insights into the nature of the synchronization transition in different graph models including those that display a scale-free degree distribution [211–214], those with small-world architecture [215], and those with community structure [216–221].

Within this body of work, particular attention has been paid to understanding what features of a network inhibit or enhance the ability to support collective dynamics. For the case of identical oscillators, this is often studied from the perspective of minimizing a ratio of eigenvalues that depend only on the structure of the network [222, 223]. However, the question of “optimal” networks for synchronization can be more interesting and complex when the oscillators’ natural frequencies are heterogeneous, a characteristic of many real-world systems. In particular, for non-identical oscillators, a crucial consideration becomes how the structure of the network is intertwined with dynamical properties. For example, in the Kuramoto model, synchronization can be enhanced when there are specific types of correlations between node degrees and oscillator frequencies or between the natural frequencies of adjacent oscillators [48, 49]. Gómez-Gardeñes et al. [51] demonstrated that in scale-free networks, positive frequency-degree correlations can lead to a first-order, or explosive, transition to synchronization. More recently, discontinuous transitions have been found by imposing constraints on the minimal difference between connected nodes’ natural frequencies [224, 225]. There has also been progress in analytical work on determining network topologies that enhance synchronization. For example, it has been shown that optimal networks for synchronizing collections of non-identical oscillators exhibit particular relationships between Laplacian eigenvectors and oscillator frequencies [50, 226, 227]. In addition, dimensionality reduction approaches [228] have recovered many previous numerical results, and have been used to derive analytical conditions for optimizing synchronization of Kuramoto oscillators in networks with attractive and repulsive interactions [229].

Notably, while the coupling structure between oscillators can drive their dynamics, network dynamics can also modulate structure. Specifically, in adaptive systems, the pattern of connectivity itself is continuously updated and modified in response to the dynamics that occur on top of it [24, 21, 25]. Systems that display these processes can be observed across biological, ecological, social, and distribution networks [21, 24], and collectively they can be characterized by topology and dynamical states that co-evolve with one another. Kuramoto-like models in partic-
ular provide a useful framework in which to explore the effects of co-evolution and adaptation [230, 231, 28, 232–239, 26, 240], and allow one to address questions such as (i) can and how might these systems organize themselves towards network configurations that enhance local or global synchronization?, and (ii) from an initially unstructured topology, can and how do different adaptive mechanisms lead to the emergence of certain architectural patterns or correlations between dynamical properties and network structure?

In addition to being adaptive, it is important to note that the evolution of many real-world networks is often governed by local rules, in which node dynamics update as a function of only neighboring node states, and in turn, the placement or weights of edges update primarily as a function of the states of the nodes they directly couple [24, 21, 25]. This type of behavior is especially pertinent in biological systems, which typically co-evolve in the absence of global or top-down controllers of node states and/or network structure. A particularly salient example of this occurs in biological neuronal networks, where, under Hebbian plasticity rules, increases in synaptic weights occur when connected neurons exhibit correlated dynamics [241–243], while under anti-Hebbian plasticity rules, the opposite occurs [244, 245]. Other systems that obey such local adaptation are prevalent, and studied examples include models of reconfiguration of social networks under disease propagation [34] and opinion formation [246], or reorganization under feedback mechanisms in Boolean models with applications to gene regulatory or neural networks [247, 248].

In this study, we use the Kuramoto model to investigate how a simple, adaptive rewiring scheme can evolve initially unstructured random graphs towards ordered topologies, and also simultaneously lead to enhanced synchronization in the system. Importantly, the rule is informed by only local information of neighboring nodes’ states at a given instant of time, and works by regularly breaking and randomly rewiring connections between more instantaneously phase-synchronized oscillators, while maintaining connections between more desynchronized pairs of oscillators. This process repeats continually over time, and can be thought of as a repulsive mechanism, or one that tends to represses assortativity (in terms of nodes connecting to other nodes with similar instantaneous states). We find that co-evolution of the network and dynamics can promote the degree of synchronization in the system, which occurs in tandem with the development of specific correlations between the topology and the natural frequencies of the oscillators. In previous work, these features have been imposed by purposeful selection, or have been shown to arise in work on optimizing synchronization. Here, however, the properties emerge from the interplay between network structure and dynamics. Focusing on the simplest
situation of binary, undirected networks, we isolate the effects of adaptive reconfiguration alone, and thereby uncover a process through which heightened collective dynamics and organized network structure can simultaneously arise in a local, unsupervised way.

The remainder of this study is organized as follows. Sec. 2.2 states the formulation of Kuramoto dynamics on complex networks. In Sec. 2.3 we first briefly outline past work to motivate the specific mechanism studied here, and then detail the proposed co-evolutionary strategy. Sec. 2.4 describes several interesting results of the adaptive process, and in Sec. 2.5 we discuss the implications of our findings and conclude.

2.2 The Kuramoto model on complex networks

Of the many models that exist for studying synchronization phenomena on complex networks, one of the most useful has been the paradigmatic Kuramoto model [43, 44]. It describes the dynamical evolution of a population of \( N \) phase oscillators coupled on a network according to the following equation:

\[
\dot{\theta}_i = \omega_i + \alpha \sum_{j=1}^{N} A_{ij} \sin(\theta_j - \theta_i) .
\]  

(2.1)

In this formulation, \( \theta_i \) is the instantaneous phase of the \( i^{th} \) oscillator, \( \omega_i \) is its natural frequency, \( \alpha \) is the overall coupling strength, and \( A \) is the \( N \times N \) adjacency matrix describing the connectivity of the network. In this report, we consider binary, undirected networks, such that

\[
A_{ij} = \begin{cases} 
1 & \text{if there is an edge between nodes } i \text{ and } j, \\
0 & \text{otherwise.} 
\end{cases}
\]  

(2.2)

The natural frequencies \( \{\omega_i\} \) are distributed according to a probability density \( g(\omega) \), which we will take to be symmetric and centered around a mean frequency of zero.

The overall amount of synchrony in the population at a given time \( t \) is typically quantified with the Kuramoto order parameter [43, 44]

\[
R(t)e^{i\psi(t)} = \frac{1}{N} \sum_{j=1}^{N} e^{i\theta_j(t)} ,
\]  

(2.3)

which can be thought of as the centroid of the \( N \) phases on a unit circle in the complex plane.
Here, $\psi$ is the average phase of the population, and the modulus $R$, given by,

$$R(t) = \frac{1}{N} \left| \sum_{j=1}^{N} e^{i\theta_j(t)} \right|,$$  \hspace{1cm} (2.4)

quantifies the amount of phase coherence. When the oscillators’ phases are uniformly spread, $R \approx 0$ and the system exhibits low synchrony. On the other hand, when the phases become tightly clustered, $R \approx 1$ and the system exhibits high levels of synchrony.

We can also use this order parameter, which ranges from $R = 0$ (complete incoherence) to $R = 1$ (complete phase synchronization), to monitor the global degree of synchrony in the system as a function of the coupling $\alpha$. In this case, one typically reports a time-averaged value

$$\langle R \rangle = \frac{1}{T_A} \int_{T_R}^{T_R+T_A} R(t) dt$$  \hspace{1cm} (2.5)

computed on an interval of length $T_A$ after several transient or relaxation time steps $T_R$ have been discarded.

### 2.3 Motivation and the co-evolutionary model

In this study, we consider a feedback process between dynamics and the restructuring of network topology that integrates different ideas and results from previous studies on adaptation or enhancing synchronization in networks of non-identical Kuramoto oscillators. To better frame and motivate our contributions, we briefly outline some past work on these topics below.

#### 2.3.1 Inspiration from prior investigations

In general, it is expected that different adaptive strategies will lead to the emergence of different patterns in both the network topology and the dynamics, and a number of studies have explored these ideas using, for example, chaotic dynamics \cite{249,28,250,232,231}, models of neuronal dynamics \cite{251,235,252}, and non-identical Kuramoto oscillators \cite{237,236,253,254,233,234,240,26,255,230,239,238,256–258}. Focusing on the latter of these classes, one early study found that dynamical rewiring to force links between nodes with more similar time-averaged frequencies creates strongly synchronized clusters of nodes, and the network reaches a small-world configuration \cite{236}. More recently local, competitive adaptation mechanisms,
which tend to strengthen (weaken) connections between more dynamically coherent (incoherent) oscillators have been shown to lead to the emergence of modular organization in Kuramoto networks [240, 26, 255, 230], and positive feedback can simultaneously enhance synchronization and percolation in initially fragmented networks [259]. In complementary efforts, Sendiña-Nadal et al. [239], Sendiña Nadal et al. [238] studied a growth process in which heterogeneous oscillators make connections to external pace-maker nodes so as to become locked with the pace-maker dynamics. When the attachment process is preferential and determined from differences in the dynamical states of the heterogeneous oscillators and pace-maker nodes, entrainment can occur simultaneously with the emergence of a power law degree distribution. In addition, adaptive processes that favor the strengthening of edges between more out of phase oscillators, can significantly improve global synchronization in non-identical Kuramoto networks [253, 254]. However, the resulting networks were not necessarily evolved under fixed total weight and the topology was not analyzed in depth for relationships between structure and dynamical properties as a function of the global coupling, both of which are aims of the present work.

Another line of inquiry revolves around the problem of optimizing synchronization of non-identical systems of Kuramoto oscillators in order to understand what structural properties of the network are important. For example, using an optimization procedure to maximize the order parameter \( R \), Brede [48, 49] uncovered key features that can enhance synchronization. These include the placement of more edges on oscillators with natural frequencies further from the mean (yielding positive correlations between degrees and frequency magnitudes), as well as the preferential attachment of oscillators with positive frequencies to other oscillators with negative frequencies (and vice-versa, yielding negative correlations between the intrinsic frequencies of adjacent oscillators. These findings have been corroborated in several other studies on optimizing networks of non-identical Kuramoto oscillators as well [260–263]. Furthermore, forcing positive versus negative correlations between adjacent frequencies appears to change the critical coupling and exponents for the synchronization transition [264]. Other work has considered the enhancement of both global and local phase synchronization [265, 266], finding that local synchronization leads to an onset of collective dynamics at lower couplings – facilitated by clustering and the grouping together of nodes with similar frequencies – but makes the state of full synchronization more difficult to achieve. More recently, spectral analyses have been employed to show that synchronization is optimized under specific couplings of the natural frequencies to eigenvectors of the Laplacian, i.e., when the frequencies are maximally aligned with the dominant eigenvector [50, 226, 227]. Importantly, the previously reviewed works indeed uncover
several crucial network features for optimizing collective dynamics. However, the question of if or via what type of mechanism such networks could be generated or evolved for using solely local adaptive strategies - and how such a process occurs over time and at different couplings - remains open.

In this study, we numerically investigate the interplay between network structure and oscillator dynamics. We report on a local, state-dependent rewiring mechanism that can (i) evolve initially random and uncorrelated networks towards structured configurations with specific relationships between dynamical and topological properties and (ii) through a reciprocal process, simultaneously improve synchronization. While the ideas of dynamical self-organization from local rules and network optimization strategies have been studied on separate fronts, here, we attempt to specifically consider them in tandem. In what follows, we first state the initial setup and parameters of the system (Sec. 2.3.2) and then describe the co-evolutionary process in detail (Sec. 2.3.3).

2.3.2 Initial network construction

All simulations were carried out with a 4th order Runge-Kutta method using a time step of $\Delta t = 0.02$. Initial phases $\{\theta_i(0)\}$ were distributed at random in the interval $[-\pi, \pi]$, and the natural frequencies $\{\omega_i\}$ were drawn at random from a uniform distribution in the range $[-2, 2]$, denoted as $\{\omega_U\}$. In Appendix A.2, we also show results for the case of a Gaussian distribution with zero mean and unit standard deviation, denoted as $\{\omega_G\}$.

The initial network configurations are binary and undirected Erdös-Renyi (ER) random graphs of type $G(N, M)$ (i.e., the network is drawn from the distribution of random graphs with $N$ nodes and $M$ edges), with corresponding average degree $\langle k \rangle = 2M/N$. Importantly, this initialization produces networks without special topological characteristics and without relationships between network properties and dynamical properties. We will denote the initial network configurations as $G_o$ and the networks at the end of the adaptive process as $G_\star$, and similarly we will use ‘o’ and ‘$\star$’ to denote quantities computed on each network. For the remainder of the main text, we fix $N = 100$ and examine two different values of $M$ chosen such that $\langle k \rangle = 12.5$ or $\langle k \rangle = 25$. (In the S.M. [? ], we also explore the robustness of several results with respect to variations in system size, the network density, the initial network topology, and the presence of asymmetry in the frequency distribution). Reported measures correspond to ensemble averages over independent simulations using different instantiations of the initial network, initial phases, and node frequencies.
2.3.3 Mechanism of adaptive rewiring

We turn now to an explanation of the co-evolutionary scheme, whereby the network is restructured according to the dynamics. Motivated by previous literature \[253, 254\], we take as our starting point a mechanism that aims to maintain connectivity between a given node and its neighbors with which it is more instantaneously out of phase, and rewire connections between a given node and its neighbor that it is most instantaneously synchronized with. After setting up the initial conditions and network \(G_0\) as described in Sec. 2.3.2, the dynamics are first run for a relaxation interval \(T_R\). Then at regular times \(t_m = T_R + mT\), where \(m\) is the number of attempted rewirings and \(T\) is an associated interval characterizing the adaptation process (which will be some multiple of the time step), rewiring is invoked as follows. A node \(i\) is chosen at random from the network and the quantity

\[f_{ij} = \frac{1}{2}[1 - \cos(\theta_i(t_m) - \theta_j(t_m))]
\]

is computed for all \(j \in \mathcal{N}_i\), where \(\mathcal{N}_i\) denotes the set of nodes directly connected to \(i\). Note that this function is local in the sense that it depends only on the instantaneous phases of node \(i\) and of the nodes \(j \in \mathcal{N}_i\) that are neighbors of \(i\) at the current time \(t_m\). It takes on a value of 1 when \(\theta_i - \theta_j = \pm \pi\) (maximal phase separation) and a value of 0 when \(\theta_i - \theta_j \mod 2\pi = 0\) (perfectly in-phase). The edge \((i, k)\), where \(k\) is the node in \(\mathcal{N}_i\) minimizing \(f_{ik}\), is then broken and a new link \((i, q)\) is formed between node \(i\) and a randomly selected node \(q\) that was not one of \(i\)'s
neighbors. This step corresponds to the breaking and rewiring of the link between node $i$ and the neighbor $k$ with which it is currently most in phase (Fig. 2.1). These dynamical update rules are repeated $m$ times, resulting in an evolved network $G_*$. We use $m = 2.5 \times 10^4$, which allows us to observe interesting dynamical and structural changes in the system, while being within enough computational reason to allow for the exploration of several different network and natural frequency parameter changes (however, we also point out places where the capability to run more adaptation steps may offer additional insight). Finally, once rewiring has ceased, the dynamics continue to run atop $G_*$ for another relaxation interval. For clarity, in the figures that follow, all quantities that change every time step will be plotted as a function of “time, $t$”, and all quantities that change only when the network is rewired will be plotted as a function of the “rewiring step, $m$”.

Before continuing, we wish to point out some features of this mechanism. First, it applies to the case of binary, undirected connectivity, and maintains the density of the network throughout co-evolution. Setting these constraints disambiguates the role of rearrangements in network topology in shaping results from other factors such as increases in the total number of edges, heterogeneous weighting, or directionality of edges. Furthermore, it allows for the cleanest comparison against much of the previous work on optimizing synchronization via rewiring. Second, we note that this adaptive process is a type of repulsive or suppressive strategy, but unlike [28, 253, 233, 232, 234, 231, 254], which consider weight plasticity, or [239, 238] which consider a growth mechanism, we consider connectivity reorganization where edges in an initially random configuration are periodically pruned and rewired between the most instantaneously and locally in-phase oscillators, but remain in place between the more locally dissonant oscillators. The random rewiring after edge deletion introduces realistic stochasticity and allows for a sampling of the network, without breaking the locality condition for determining which edge is rewired [21]. Though not a model of a specific system, this type of disassortative mechanism has real-world counterparts. For example, it is in the same vein as anti-Hebbian learning rules in neural systems, where synapses weaken between more dynamically correlated neurons and strengthen between more incoherent neurons [244, 245]. It may also mimic some strategies of opinion formation and influence on social networks, where people preferentially link with those of more different opinions from themselves [267].
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2.4 Results

2.4.1 Co-evolved networks exhibit enhanced global synchronization

Our first main result is that the adaptive rewiring mechanism is able to enhance global synchronization over a broad range of coupling values. This result holds for both frequency distributions (See Appendix A.2 for the analysis with the normally distributed frequencies) and values of average degree. In addition, the result is quite robust to an order of magnitude difference in the structural reconfiguration interval, $T$.

We first discuss the time evolution of the order parameter $R(t)$ for the co-evolving networks. Fig. 2.2 depicts examples of $R(t)$ vs. time $t$ for the case of uniformly distributed frequencies $\{\omega_U\}$ and $T = 0.2$ time units. The top row corresponds to networks with $\langle k \rangle = 25$, at representative couplings (a) $\alpha = 0.065$ and (b) $\alpha = 0.085$, and the bottom row corresponds to networks with $\langle k \rangle = 12.5$, at representative couplings (c) $\alpha = 0.135$ and (d) $\alpha = 0.22$. In each case, the dynamics are first run atop the initially static ER network for several time steps. Adaptation begins at the time denoted by the first red line, and ends after several time steps at the second red line. We observe that at lower coupling values - where the dynamics on the initial network exhibit little coherence across time - the adaptive strategy is able to significantly increase $R$ to an intermediate value during the rewiring stage, though the order parameter may still exhibit fluctuations. As $\alpha$ is increased, the order parameter in the non-adaptive regime sits at an intermediate average value, but once co-evolution begins, the self-organizing network rearranges such that $R$ again increases and reaches a value near 1. When rewiring ceases after several cycles, the resulting networks are able to maintain these states of heightened collective dynamics, and the global order parameter remains at an increased value from its initial location. However, though the time-averaged value $\langle R \rangle$ remains high for the networks with $\langle k \rangle = 12.5$, we find that in some cases the order parameter still exhibits fluctuations, even after the adaptation period has ceased. This intuitively suggests that the co-evolved networks with higher average degree are more robust to the stochasticity in the rewiring and the exact placement of edges in the network, in terms of their ability to support a smooth, frequency-synchronized steady-state. Appendix A.2 contains additional figures of $R(t)$ vs. time for the case of normally distributed frequencies. Also, in the S.M., we examine another measure of synchronization that quantifies how the number of locally-synchronized clusters [217] of oscillators changes as a function of time due to the network rearranging [? ].

In order to obtain a more complete picture of the effect of adaptive rewiring, we performed a sweep over a comprehensive coupling range. For $\langle k \rangle = 12.5$ we considered a range $\alpha \in [0, 0.4]$,
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Figure 2.2: Examples of the global order parameter \( R(t) \) vs. time \( t \) for various representative couplings \( \alpha \). In each case, the dynamics were first run atop an initially ER random graph with average degree \( \langle k \rangle \), after which co-evolution of the network and dynamics took place between the two red lines. The natural frequencies were drawn from the uniform distribution \( \{ \omega_U \} \), and the mean degree \( \langle k \rangle \) and coupling \( \alpha \) used for each panel were (a) \( \langle k \rangle = 25 \), \( \alpha = 0.065 \), (b) \( \langle k \rangle = 25 \), \( \alpha = 0.085 \), (c) \( \langle k \rangle = 12.5 \), \( \alpha = 0.135 \), (d) \( \langle k \rangle = 12.5 \), \( \alpha = 0.22 \). During the adaptation period, the network was continually rewired once every \( T = 0.2 \) time units. The co-evolving networks exhibit enhanced collective dynamics, as observed by increases in the global order parameter.

and for \( \langle k \rangle = 25 \), we considered \( \alpha \in [0, 0.2] \); in both cases, couplings were sampled at a resolution \( \Delta \alpha = 0.005 \). At each value of \( \alpha \), networks and initial conditions were initialized as described in Sec. 2.3.2. We then ran a set of simulations on the original, uncorrelated networks.
CHAPTER 2.

(a) (b)

Figure 2.3: The time-averaged order parameter $\langle R \rangle$ vs. coupling $\alpha$. In each panel, the gray data points correspond to static ER random graphs $G_o$, and the blue and yellow points correspond to the adapted networks $G_*$ evolved under rewiring time scales of $T = 0.2$ and $T = 2$, respectively. The frequencies were drawn from the uniform distribution $\{\omega_i\}$, and the mean degree of the networks are (a) $\langle k \rangle = 12.5$, and (b) $\langle k \rangle = 25$. All curves depict averages over 25 instantiations, and the lines between data points serve as guides for the eye.

We show the outcome of this analysis in Fig. 2.3, where each panel is a plot of $\langle R \rangle$ vs. $\alpha$. Panels (a) and (b) correspond to networks with $\langle k \rangle = 12.5$ and $\langle k \rangle = 25$, respectively. Furthermore, we plot curves for two different values of the waiting time between structural changes to the network: $T = 0.2$ and $T = 2$. As can be seen from each of the curves, there is a broad range of $\alpha$ over which the rewiring mechanism for network restructuring leads to improvements (higher values) of the time-averaged global order parameter compared to the random networks. This enhancement does not begin immediately at $\alpha = 0$, but once the coupling is high enough (still at a relatively low value), the order parameter for the adaptive networks $G_*$ begins to increase at a much steeper rate. Once this begins, we find that $\langle R \rangle$ remains noticeably higher for the adaptive networks compared to the static networks $G_o$, across all couplings beyond a certain point. These trends are robust for both rewiring intervals and average degree values, and as can been seen in Sec. A.2, the results hold for the case of normally distributed natural frequencies as

$G_o$, and obtained a time-averaged value of the global order parameter $\langle R \rangle$ (Eq. 2.5) over the last $1 \times 10^4$ time steps. A second set of simulations were then run with the same initial conditions, but under the co-evolutionary scheme (i.e. the network topology was allowed to co-evolve with the dynamics for $m$ rewiring steps, after which a time-averaged order parameter was computed on the final adapted network $G_*$). 

We show the outcome of this analysis in Fig. 2.3, where each panel is a plot of $\langle R \rangle$ vs. $\alpha$. Panels (a) and (b) correspond to networks with $\langle k \rangle = 12.5$ and $\langle k \rangle = 25$, respectively. Furthermore, we plot curves for two different values of the waiting time between structural changes to the network: $T = 0.2$ and $T = 2$. As can be seen from each of the curves, there is a broad range of $\alpha$ over which the rewiring mechanism for network restructuring leads to improvements (higher values) of the time-averaged global order parameter compared to the random networks. This enhancement does not begin immediately at $\alpha = 0$, but once the coupling is high enough (still at a relatively low value), the order parameter for the adaptive networks $G_*$ begins to increase at a much steeper rate. Once this begins, we find that $\langle R \rangle$ remains noticeably higher for the adaptive networks compared to the static networks $G_o$, across all couplings beyond a certain point. These trends are robust for both rewiring intervals and average degree values, and as can been seen in Sec. A.2, the results hold for the case of normally distributed natural frequencies as
well. (The S.M. [?] shows additional and qualitatively similar findings for simulations on slightly larger networks or those with lower mean degree, and for the case of a non-symmetric frequency distribution). It is also worth noting that – although the total number of times the network is allowed to rewire is limited by computational constraints – since there is no built-in condition for adaptation to cease and since there is a stochastic component to the network reconfiguration, the ability to run more adaptation steps may yield even further improved results.

2.4.2 Emerging structure and correlations between network topology and dynamical properties

Given that dynamical reconfiguration of the network - informed by local information on the states of connected oscillators - can improve the overall amount of synchronization in the system, a second line of inquiry is understanding what properties of the evolved networks lend themselves to this capability. In particular, does the self-enacted rewiring mechanism generate the interesting topological features and correlations that arise via optimization schemes, which in a cyclic process, then allow synchronization to occur?

We begin by investigating the networks $G_\ast$ for certain relationships between their topology and the natural frequencies of the oscillators. Two properties in particular – degree-frequency correlations and frequency-neighbor frequency correlations – have been associated with networks optimized for synchronization [48–50] (see Sec. 2.1 and Sec. 2.3).

Though the natural frequencies of each node remain fixed here, the way oscillators of different frequencies are coupled to one another changes over time from the initial, random configuration to the end of adaptation. In Fig. 2.4, we show examples of how two specific relationships manifest in an ER network $G_o$ and the corresponding adaptively rewired network $G_\ast$. The top and bottom two rows of Fig. 2.4 correspond to networks with $\langle k \rangle = 12.5$ and $\langle k \rangle = 25$, respectively, and in both cases, the first column corresponds to the ER network and the second column corresponds to the rewired network. For each node $i$, we first computed the offset $\bar{\omega}_i$ of $i$’s intrinsic frequency from the mean of the population, such that $\bar{\omega}_i = \omega_i - \langle \omega \rangle$ where $\langle \omega \rangle$ is the mean intrinsic frequency averaged over all oscillators. Panels $(a,b)$ and $(g,h)$ then show node degree $k_i$ vs. frequency offset $\bar{\omega}_i$, and panels $(d,e)$ and $(j,k)$ show the average frequency offset of oscillator $i$’s neighbors, $\langle \bar{\omega} \rangle_{N_i} = \sum_{j \in N_i} \bar{\omega}_j / k_i$, vs. frequency offset $\bar{\omega}_i$. Note that the coupling values $\alpha$ are such that the original networks exhibited intermediate levels of synchrony, and the reorganized networks were able to entrain the population to a higher level of synchrony.
Figure 2.4: Relationships between the network structure and the intrinsic frequencies of the oscillators. The top two rows show examples for a network with $\langle k \rangle = 12.5$, and the bottom two rows show examples for a network with $\langle k \rangle = 25$; in both cases, the frequencies were drawn from the uniform distribution $\{\omega_U\}$. For each network density, the first column corresponds to an ER random graph that exhibits only intermediate levels of synchrony at the displayed coupling $\alpha$ (as measured by $\langle R \rangle$), and the second column corresponds to the adapted network, which exhibits a higher level of synchrony. These plots highlight key relationships that emerge from the co-evolutionary network update rule. 

(a,b); (g,h) Node degree $k_i$ vs. frequency offset $\tilde{\omega}_i$. 

(d,e); (j,k) Average neighbor frequency offset $\langle \tilde{\omega} \rangle_{N_i}$ vs. frequency offset $\tilde{\omega}_i$. 

(c); (i) The correlation $C_{|\tilde{\omega}|,i}$ between node degree $k_i$ and the magnitude of the frequency offset $|\tilde{\omega}_i|$ vs. the number of rewiring steps $m$, and 

(f); (l) the mean fraction $f$ (i.e. averaged over all nodes in the network) of an oscillator’s neighbors that have frequency offsets of opposite sign compared to that of the central oscillator vs. the number of rewiring steps $m$. 

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As expected, initially there is little correlation present between the topology of the network and the dynamical property of oscillator frequency, as illustrated by the lack of organization in the plots in the first column of Fig. 2.4. However, from observation of the second column, it is evident that when the co-evolutionary mechanism can enhance synchronization, it simultaneously leads to the emergence of very specific correlations between the network connectivity and the intrinsic frequencies of the oscillators. We first note the appearance of the marked v-shaped curves characterizing the plots of $k_i$ vs. $\tilde{\omega}_i$ (panels (b) and (h)), which signify that the node degree becomes positively correlated with the absolute value of the oscillator frequency offset. In other words, nodes with natural frequencies further from the mean natural frequency of the population gather proportionately more edges.

A second finding is that when increased global synchrony arises from a restructuring of the network, the final arrangement exhibits distinct relationships between the frequency offsets of a given oscillator and the frequency offsets of that central oscillator’s direct neighbors on the network. The patterns in panel (e) and (k) showing $\langle \tilde{\omega} \rangle_{N_i}$ vs. $\tilde{\omega}_i$ point to the fact that oscillators with positive natural frequency offsets tend to become connected to other oscillators with, on average, negative natural frequency offsets. Since the mean frequency $\langle \omega \rangle \approx 0$ for the distributions we consider, this implies that oscillators with positive frequencies tend to become neighbored by oscillators with negative intrinsic frequencies, and vice-versa. In Sec. A.1 we also define an additional measure of frequency-neighbor frequency organization as the correlation $C_{\tilde{\omega}, \sum \tilde{\omega}}$ between natural frequency offsets and the sum of neighbor frequency offsets. Fig. A.1 shows examples of this quantity for the same networks as those in Fig. 2.4.

To quantify these relationships and study how they evolve with the number of rewiring steps, we considered two summary statistics, following [265, 48, 49, 264]. The first of these measures is a simple (Pearson) correlation coefficient, $C_{|\tilde{\omega}|, k}$, to quantify the strength of the relationship between node degree and the magnitude of the frequency offset. This measure increases steadily throughout co-evolution of the network and dynamics (Fig. 2.4c,i). In addition, for each node $i$, we calculated the fraction of its neighbors $f_i$ that had natural frequency offsets of the opposite sign as compared to the central oscillator $i$’s frequency offset, and then computed an average $f = \sum_i f_i / N$ over all nodes in the network. This metric also increases as the network is rewired, as observed in Fig. 2.4f,l. (See Fig. A.1 for an example of the evolution of the additional measure, $C_{\tilde{\omega}, \sum \tilde{\omega}}$).

We have thus far shown examples of emerging structural patterns that arise when a co-evolved network is clearly able to entrain the oscillators to a state of higher synchrony. However,
Figure 2.5: The correlation $C|\tilde{\omega}|,k$ between node degree $k_i$ and the magnitude of the frequency offset $|\tilde{\omega}_i|$, as a function of the coupling. In each panel, the gray data points correspond to the initial, uncorrelated ER random graphs $G_0$, and the blue and yellow points correspond to the adapted networks $G_\star$ evolved under rewiring time scales of $T = 0.2$ and $T = 2$, respectively. The frequencies were drawn from the uniform distribution $\{\omega_U\}$, and the mean degree of the networks are (a) $\langle k \rangle = 12.5$, and (b) $\langle k \rangle = 25$. The dip observed in (b) at $\alpha \approx 0.5$ is due to the localization of edges on a cluster of oscillators with natural frequencies near the mean; this is examined further in Sec. 2.4.3. All curves depict averages over 25 instantiations, and the lines between data points serve as guides for the eye.

the ability of this behavior to occur is also dependent on the coupling $\alpha$. In order to better understand the appearance of the topological and dynamical correlations and their dependence on the overall coupling, we computed the same measures ($C|\tilde{\omega}|,k$ and $f$) as a function of $\alpha$ (see Figs. 2.5, 2.6, respectively). In each case, the measures were computed on the final networks $G_\star$ that exist at the end of the adaptation period.

For each combination of natural frequency distribution, average degree, and rewiring interval, we observe robust trends. In particular, $C|\tilde{\omega}|,k$ remains near zero at low coupling values, and then proceeds to quickly increase as a function of $\alpha$ until it saturates to a relatively steady value close to 1. In other words, as the overall coupling increases, the correlation between the node degrees and the magnitude of the frequency offsets becomes more apparent. The frequency-neighbor frequency relationship follows a similar evolution. Specifically, the mean fraction $f$ (averaged over all nodes in the network) of an oscillator’s neighbors that have frequency offsets of opposite sign relative to that of the central oscillator also grows with $\alpha$, plateauing near a high value of $f \approx 0.9$. This points to a heightened mixing of oscillators with different intrinsic prop-
Figure 2.6: The mean fraction $f$ (averaged over all nodes in the network) of an oscillator’s neighbors that have frequency offsets of opposite sign compared to that of the central oscillator, as a function of the coupling. In each panel, the gray data points correspond to the initial, uncorrelated ER random graphs $G_o$, and the blue and yellow points correspond to the adapted networks $G_*$ evolved under rewiring time scales of $T = 0.2$ and $T = 2$, respectively. The frequencies were drawn from the uniform distribution $\{\omega_U\}$, and the mean degree of the networks are (a) $\langle k \rangle = 12.5$, and (b) $\langle k \rangle = 25$. All curves depict averages over 25 instantiations, and the lines between data points serve as guides for the eye.

There are three main features in these trends worth pointing out explicitly. First, for the rewiring intervals considered here, the general form of the curves appears to be relatively independent of the time $T$ between a structural perturbation to the network. Second, the two quantities considered, $C_{|\omega|, k}$ and $f$, both exhibit a clear change in behavior (signified by the onset of a rapid increase in value) at approximately the same coupling. Thus, in the proposed co-evolutionary scheme, the emergence of these relationships between the network topology and intrinsic properties of the dynamics seem to arise in tandem to one another, in that the appearance of one feature implies the development of the other. A final important observation is that the coupling at which these patterns begin to take shape is near the coupling at which the global order parameter begins to rise (compare to Fig. 2.3). (Fig. A.2 shows that consistent behavior is found for $C_{|\omega|, \sum \omega}$ as well). Thus, as found by Brede [265, 48, 49, 264] in his work on optimization of synchronization of
non-identical oscillators, enhanced collective behavior co-occurs with the materialization of specific relationships between network connectivity and the intrinsic frequencies. Here, we have shown that organized structure in the form of these correlations can emerge in networks from a simple, adaptive mechanism based on a combination of local state information and stochastic rewiring. We also again note that allowing the co-evolution to run longer may give heightened results, especially at low to intermediate couplings.

2.4.3 Analysis of the time-dependence of the adaptive mechanism

Our analysis thus far has considered the global order parameter and the correlations between the intrinsic frequencies and the network topology that arise in the adaptively rewired networks, and we have mainly focused on how these properties manifest after several rewirings of the network and how their strength depends on the overall coupling. While Figs. 2.2 and 2.4 do briefly examine the time-dependence of these properties as well, in order to gain a further understanding of the adaptation mechanism, we carry out a more in-depth exploration of how the co-evolutionary process unfolds over time at different couplings, and also how individual oscillators with different intrinsic dynamical properties (i.e. intrinsic frequencies) are affected by the rewiring mechanism.

Evolution of the instantaneous frequencies

To investigate the temporal evolution of the system - and how the adaptive scheme works from a more local standpoint - we first examine the instantaneous frequencies \( \dot{\theta}_i(t) \) as a function of time. Recall that the condition for a frequency-synchronized state corresponds to the instantaneous frequencies of all oscillators locking to the mean natural frequency of the population, \( \langle \omega \rangle \).

Thus, to better understand the mechanism of the co-evolution process, we specifically consider

Figure 2.7 (following page): Examples of the instantaneous frequencies \( \dot{\theta}_i(t) \) vs. time \( t \), for various representative couplings \( \alpha \). The mean degree of the networks are (a) \( \langle k \rangle = 12.5 \) and (b) \( \langle k \rangle = 25 \), and the natural frequencies \( \{\omega_U\} \) were drawn from the uniform distribution. In all panels, each row corresponds to one oscillator, and the rows from top to bottom are in displayed in ascending order of the quantity \( \tilde{\omega}_i = \omega_i - \langle \omega \rangle \) (i.e. the offset from the mean intrinsic frequency of the population). For each coupling, the dynamics were first run atop an initially ER random graph, after which co-evolution of the network and dynamics took place between the two black lines. During the adaptation period, the network was continually rewired once every \( T = 0.2 \) time units.
how oscillators of different intrinsic frequencies (in terms of how close or far $\omega_i$ is to the average natural frequency $\langle \omega \rangle$) evolve as a function of time, and how they may be differentially affected by the time-dependent rewiring of the network. Fig. 2.7 shows examples of $\dot{\theta}_i(t)$ vs. $t$ for several values of the coupling $\alpha$ around the point in which the dynamics transition to a synchronized state. The top set of panels (a) correspond to a network with $\langle k \rangle = 12.5$, and the bottom set of panels (b) correspond to a network with $\langle k \rangle = 25$; the frequencies are uniformly distributed and the same in both cases (Appendix A.2 contains additional figures for examples with normally distributed frequencies). Each row corresponds to one oscillator, and the rows from top to bottom are displayed in ascending order of the quantity $\tilde{\omega}_i = \omega_i - \langle \omega \rangle$ (i.e. the offset from the mean natural frequency of the population). Adaptation of the network sets in at the time denoted by the first black line and ends at the second black line.

At very low coupling, adaptively rewiring the network appears to have negligible effect on the instantaneous frequencies. But as the coupling increases to an intermediate value near the transition to synchronization (see Fig. 2.3), we observe a change in the dynamics: oscillators with intrinsic frequencies near the center of the distribution start evolving with a frequency near the mean earliest, and then later in time, more outlying oscillators become incorporated into the coherent group. For the denser networks in particular, there are a few sampled coupling values for which the co-evolution results in partial synchronization of those oscillators around the center of the natural frequency distribution, but that coherent core does not extend to the most disparate oscillators. Thus, there does seem to be a dependence on the natural frequencies in terms of how the co-evolution develops and affects different oscillators over time. However, at even larger coupling, the transition in the dynamics becomes much faster, and the dependence on the intrinsic frequencies is less noticeable. The findings are similar for the case of normally distributed frequencies (Appendix A.2, Fig. A.9)

Before continuing, we note that the figures shown here (and throughout the rest of Sec. 2.4.3) are for single realizations of the initial network topology and the intrinsic frequencies. For these particular instantiations, we have sampled coupling values that highlight different regimes – in regards to the behavior over time and the overall outcome – of the adaptive rewiring. However, it is important to state that over different realizations, we observe some variability in terms of how the co-evolution affects the dynamics and the network over time, and whether or not it is able to cause significant changes in the dynamics and the network structure at a given coupling. This is especially apparent for the sparser networks and low values of $\alpha$. Though it is beyond the scope of the current work, it may be interesting in future work to investigate the degree of this
variability and its dependence on the frequency distribution and properties of the network such as density.

**Evolution of the correlations between topology and natural frequencies**

We know from Sec. 2.4.2 that increases in the order parameter due to the adaptive mechanism are accompanied by the emergence of correlations between the network topology and the oscillator frequencies. Therefore, we now further examine how the network organization restructures over time as the system co-evolves. We focus in particular on the evolution of the degree of individual nodes across time, and also consider how the degree - natural frequency relationship proceeds as the network rearranges itself at different values of the global coupling.

For the same initial networks, natural frequencies, and coupling values, Fig. 2.8 shows the node degree $k_i$ vs. the rewiring step $m$ and Fig. 2.9 shows the correlation $C_{|\tilde{\omega}|,k}$ between the absolute value of the frequency offset $|\tilde{\omega}_i|$ and the node degree $k_i$ vs. the rewiring step $m$. In each case, panel (a) corresponds to a network with $\langle k \rangle = 12.5$ and panel (b) corresponds to a network with $\langle k \rangle = 25$. The natural frequencies were uniformly distributed in both cases.

Below, we discuss the observations for each of the densities in turn.

For $\langle k \rangle = 12.5$ and at low coupling (e.g. $\alpha = 0.04$), the rewiring does not noticeably affect how edges are distributed on particular oscillators, and $C_{|\tilde{\omega}|,k}$ fluctuates around zero. As the coupling increases, though, the co-evolution begins to cause significant changes in the network (see panels for $\alpha = 0.114$ and $\alpha = 0.0115$). In particular, there is a short period of time in which edges become concentrated on oscillators with natural frequencies near the mean, whereas oscillators with intrinsic frequencies on the ends of the distribution remain with relatively low degrees. This is followed by the gradual spreading out of edges onto the more outlying oscillators with subsequent rewiring. We can quantify this behavior by considering the value of the correlation $C_{|\tilde{\omega}|,k}$. For $\alpha = 0.114$ and $\alpha = 0.115$ in this example, we see that a slight negative degree-frequency correlation develops briefly in the initial stages of the rewiring, followed by an...
increase in this quantity to a high, positive value.

For the case of $\langle k \rangle = 25$, we again see that at very low coupling, the rewiring does not drive persistent changes in the system. Interestingly, though, for slightly larger coupling (e.g. $\alpha = 0.04$ and $\alpha = 0.05$ in this example) there is a regime during which edges consistently build up on oscillators with natural frequencies near the center of the distribution. This results in $C_{|\hat{\omega}|,k}$ becoming significantly negative due to the co-evolution of the network and dynamics, and unlike the situation in the sparser networks, this behavior can persist across the entire rewiring period (see, for example, $\alpha = 0.04$). The concentration of edges on oscillators near the center of the distribution explains the dips in Fig. 2.5b, which shows $C_{|\hat{\omega}|,k}$ vs. $\alpha$ for the case of $\langle k \rangle = 25$. We also note that near the value of the coupling where this dip occurs, the order parameter for the rewired networks begins to deviate in a positive direction from that of the ER networks (Fig. 2.3b), which is likely due to the formation of a locally synchronized cluster of oscillators with natural frequencies near the population average. We do not observe this type of organization for the sparser networks, suggesting an intricate dependence on the network density; this may be an interesting parameter to explore further in future work. As the coupling increases further to intermediate values (for example, $\alpha = 0.06$ and $\alpha = 0.065$), we find that there is first an increase in degree for oscillators with frequencies more closely surrounding the mean, which gives rise to a slightly negative degree-frequency correlation. But as the network continues to co-evolve, edges begin to localize on more outlying oscillators, and the degree-frequency correlation crosses zero and then starts to become positive. However, the most disparate oscillators may still not be able to gather enough edges, resulting in a positive correlation that is less than 1 (i.e., there is some scatter in the relationship).

As the coupling increases further, there is another shift in terms of how the adaptive mechanism affects the networks. For the example with $\langle k \rangle = 12.5$, we observe some fluctuation in $C_{|\hat{\omega}|,k}$ when the rewiring begins, but eventually the period of marked negative degree-frequency correlation disappears and the edges rapidly become redistributed onto oscillators with the most

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**Figure 2.9 (following page):** Examples of the evolution of the correlation $C_{|\hat{\omega}|,k}$ between oscillator frequency offset $\hat{\omega}_i$ and the node degree $k_i$, vs. the rewiring step $m$, for various representative couplings $\alpha$. The mean degree of the networks are (a) $\langle k \rangle = 12.5$ and (b) $\langle k \rangle = 25$, and the natural frequencies $\{\omega_U\}$ were drawn from the uniform distribution. In all panels, each row corresponds to one oscillator, and the rows are ordered by the quantity $\hat{\omega}_i = \omega_i - \langle \omega \rangle$ (i.e. the offset from the mean intrinsic frequency of the population). The network was continually rewired once every $T = 0.2$ time units.
disparate intrinsic frequencies. We also find that for the examples with $\langle k \rangle = 25$, $C_{|\tilde{\omega}|,k}$ almost immediately begins to rise – rather than decreasing first – at high coupling. In addition, the correlation in each case quickly saturates at a value close to 1, signifying a very strong degree-frequency relationship that extends to even the oscillators on the far edges of the natural frequency distribution. Thus, at large couplings the time evolution is similar for $\langle k \rangle = 12.5$ and $\langle k \rangle = 25$. If network co-evolution were allowed to increase for an even longer time, we may observe a plateau in $C_{|\tilde{\omega}|,k}$ for more intermediate values of $\alpha$, though not necessarily at a level corresponding to a near-perfect positive relationship. We repeat this analysis for the case of normally distributed frequencies $\{\omega_G\}$ in Sec. A.2 of the Appendix and find qualitatively similar results.

Although a rigorous mathematical treatment of the co-evolution is beyond the scope of this study, it is useful to postulate mechanisms that might be able to explain and complement at least some of the empirically-based descriptions discussed above. For example, one interesting observation is that, at low coupling and in the initial stages of rewiring, oscillators with more outlying natural frequencies tend to have lower degree than some oscillators with natural frequencies closer to the mean of the distribution. This seems to occur, at least to some extent, for both values of the network density and for both frequency distributions. In order to think about this phenomena, we first remark that changes in the structure of the network (and thus the dynamics) must be due to which edges are broken over time, since the location of a new edge is chosen at random. Second, oscillators with more disparate intrinsic frequencies will naturally want to rotate more rapidly than oscillators with more moderate intrinsic frequencies. Following this reasoning, we can then posit that the most outlying oscillators will have a greater chance of being most in phase with a focal node – which is selected at random – than oscillators with moderate intrinsic frequencies whose phases will tend to change less quickly and thus reduce the chance of being nearby the focal node. Therefore, this thought process suggests that when the selected focal node assesses its phase difference with its neighbors, the oscillators with natural frequencies most different from the mean will have a greater probability of becoming disconnected, and this would account for the observed lower degree of these nodes at low coupling and at the start of the adaptation period. Preliminary results show that making $T$ smaller can sometimes slightly enhance or extend the region of couplings over which $C_{|\tilde{\omega}|,k}$ goes negative, which is consistent with the proposed logic. Another observation, though, is that the degree-frequency correlation can change sign over time (go from slightly negative to positive), which does not seem directly obvious to explain from the previously outlined arguments. In order to make wholly concrete statements and to understand in more detail how the adaptation process gives rise to various re-
results – such as the intricacies of the time-evolution of the network and also the dependence of that time-evolution on parameters like the global coupling, network density, and frequency distribution – will require a much more in-depth investigation. While outside the main contributions of this study, it would be useful to formulate and carry out a more formal theoretical analysis in future work.

2.4.4 Spectral Analysis

As an additional connection to recent literature on optimizing synchronization in heterogeneous oscillator populations, we also carry out a spectral analysis, following the work of Skardal et al. [50]. In a series of papers [50, 226, 227], the authors derived conditions that describe the deviation from full phase locking, and also uncovered conditions for promoting synchronization. By considering a linearized form of the dynamics valid in the high-synchrony regime, one of the main analytical results is that the global order parameter, $R$ can in general be optimized by aligning the vector of intrinsic frequencies $\tilde{\omega}$ with the dominant eigenvector $v_N$ of the Laplacian matrix $L$ (where the elements of the Laplacian are defined as $L_{ij} = \delta_{ij}k_i - A_{ij}$). Given the enhanced synchronization found here, it is interesting to ask whether the local rewiring rule that we study generates networks with similar spectral properties.

To address this question, we examine the quantity $|\langle \tilde{\omega} \cdot \frac{v_N}{||v_N||} \rangle|$, where $\tilde{\omega}$ is the (normalized) vector of natural frequency offsets, and $\frac{v_N}{||v_N||}$ is the (normalized) dominant Laplacian eigenvector. In order to understand the dependence of this frequency-eigenvector alignment on the coupling strength, at each value of $\alpha$ we compute $|\langle \tilde{\omega} \cdot \frac{v_N}{||v_N||} \rangle|$ on the final, co-evolved networks $G_\star$, as well as on the original ER networks $G_o$, for comparison. Fig. 2.10 (a) and (b) depict the results of this analysis for the two different values of the mean degree (see Fig. A.12 for the corresponding analysis with normally distributed frequencies). At low coupling, $|\langle \tilde{\omega} \cdot \frac{v_N}{||v_N||} \rangle|$ for the rewired networks remains low, near its initial value. Note that in this regime the order parameter is low as well (Fig. 2.3). As $\alpha$ increases, however, the frequency-eigenvector overlap begins to grow, and rapidly increases until a leveling out with further increase in the coupling; the plateau occurs close to the maximal value of one for both values of the mean degree. As with the relationships between natural frequency and node degree, and between natural frequency and neighbor natural frequency considered in Sec. 2.4.2, the increasing projection of the intrinsic frequencies onto the dominant Laplacian eigenvector is accompanied by an increase in $R$. Thus, the adaptive reconfiguration can cause persistent changes to the organization of the network that are consistent with the conditions predicted by Skardal et al. [50] for optimizing synchronization,
and the result becomes more prominent at higher coupling. The investigation for the case of
normally-distributed frequencies yields similar conclusions (see Appendix A.2, Fig. A.12). This
analysis provides a more analytical understanding of how the adaptive process is able to enhance
the synchronization in the system.

2.5 Discussion and conclusions

In this study, we examined co-evolution of network topology and Kuramoto phase-oscillator
dynamics as a means to evolve initially unstructured networks towards organized architectures,
and to simultaneously enhance synchronization in the system. In terms of the interplay between
network topology and synchronization, it has been found that the presence of specific corre-
lations between the structural layout of the network and the oscillator frequencies (which is a
property of the dynamics) can greatly augment global synchronization. But these relationships
usually arise through optimization strategies that utilize global information about the network
or of node states [48, 49, 260–266, 50, 226, 227]. On the other hand, a different set of work

Figure 2.10: Evolution of the overlap $|\langle \tilde{\omega}, v_N \rangle| \, |\tilde{\omega}||v_N||$ between the intrinsic frequencies $\tilde{\omega}$
and dominant Laplacian eigenvector $v_N$ as a function of the coupling $\alpha$. In each panel, the
gray data points correspond to the original, uncorrelated ER random graphs $G_o$, and the blue
and yellow curves correspond to the adapted networks $G_\star$ evolved under rewiring time scales
of $T = 0.2$ and $T = 2$, respectively. The natural frequencies were drawn from the uniform
distribution $\{\omega_U\}$, and the mean degree $\langle k \rangle$ of the networks are (a) $\langle k \rangle = 12.5$ and (b) $\langle k \rangle = 25$.
All curves depict averages over 25 instantiations, and the lines between data points serve as guides
for the eye.
has shown that adaptive strategies that suppress phase differences between Kuramoto oscillators [253, 254] can lead to heightened synchronization. But in the latter case, the interactions between the topology of the adaptive networks and the node frequencies has not been explored or examined in depth. An interesting line of investigation is to therefore understand whether an adaptive rule for updating the structure of the network – based on local dynamical information – can shape the topological patterns and correlations with dynamical properties whose emergence simultaneously enhances synchronization. To this end, we studied a type of disassortative mechanism in which the edge between a randomly selected node and its most instantaneously synchronized neighbor is stochastically rewired, while all other edges are maintained. Co-evolution of the dynamics and network connectivity occurs through the repetition of this feedback process, whereby an initially random network continually reconfigures in response to the states of locally connected oscillators.

Through numerical simulation, we examined the time-evolution of this process and the dependence on the global coupling. We found that for a significant coupling range, the rewiring strategy was able to bring the system to a state of heightened collective behavior, as measured by the global order parameter. It is interesting to note that this eventual state of enhanced global coherency depended on the adaptive prevention of local synchronization, suggesting a trade-off between local and global dynamics. Other work on adaptive Kuramoto networks has shown that the opposite type of rule, i.e. a competitive strategy which strengthens connections between more in-phase oscillators at the expense of weakening connections elsewhere, can lead to modular organization and hence enhanced local rather than global synchrony [240, 26, 255]. Perhaps most importantly, the enhancement of synchronization indeed co-occurred with the emergence of correlations in the network that have been shown to arise through optimization of the global order parameter. In particular, when the oscillators exhibited more coherent dynamics, the evolved networks tended to exhibit (1) positive correlations between node degrees and the magnitude of oscillators’ difference in natural frequency from the mean of the population (i.e. magnitude of their frequency offset), and (2) the preference of connections between oscillators that have natural frequency offsets of opposite sign. We found that the emergence of these relationships and how the adaptive scheme reorganized the network topology over time depended on the global coupling parameter and the intrinsic frequencies, and - to some extent - the density of the network. We note that in addition to enhancing synchronization [265, 48, 49, 264], the purposeful placement of these types of correlations has also been associated with first order, or explosive, synchronization transitions [51, 224, 225]. Far fewer studies, however, have considered how these
structural patterns and relationships might arise in a network from local rearrangements or adaptation (though see [257] for one example).

It is important to state that the results found in this study are in line with previous work that has examined adaptive schemes in which weights grow or shrink as a function of phase differences, which also find that rules that actively suppress differences in state are able to improve synchronization. However, there are some important distinctions between the strategies studied in [253] and the one studied here. In regards to the former, the network starts as completely disconnected, with no edges between any oscillators. The edge weights between all pairs of nodes are then allowed to increase, up to some bound. In this way, the total density of the network is allowed to change, connections can theoretically occur between all pairs of oscillators at a given time, and the individual edge weights can fluctuate. Other work has considered a situation in which the topology of the network is pre-defined and constant, while the weights can change [254]. On the other hand, we wished to consider a situation in which the effect of topological organization alone could be isolated from other confounding features. We thus studied a case where the network begins connected, but in a random, disorganized arrangement, and then allowed the system to self-organize under the constraint of fixed total density and also binary and undirected connectivity. Together, these conditions mean that only a fraction of the nodes can be directly connected at a given time, and the goal is to understand if simple rearrangements in those connections, based on a local rule for determining the rewiring, can enhance synchronization. Thus, the path to a more coherent state is different here than in previous studies on co-evolutionary Kuramoto systems.

Of course, there are still some methodological considerations to make note of, as well as possibilities for future work. For example, we studied an adaptive mechanism that utilized only local information of a given node, and that preserved binary connectivity and the total number of edges, so as to isolate the effects of rearrangements in network topology from other factors. However, incorporating these constraints required that there be a random component to the rewiring process, and there was not a natural or self-employed stopping condition for network reconfiguration. One could thus further explore how results are affected by the length of time the system is allowed to co-evolve, and also how this relates to changes in other parameters, such as the size of the network, the mean degree, and the spread in the intrinsic frequencies. In addition, since some stochasticity or noise is likely a realistic feature of natural systems, it would be interesting to incorporate that into a related adaptation model that allows for weighted rather than just binary connectivity between network units. Another parameter that may be important to
examine more in depth is the time-scale of the adaptation in the network. It is also important to note that, while meaningful insights can be gained from the empirical and observational type of analysis carried out in this study, in forthcoming work it will be useful to try and understand the origins of various results from a more fundamental and theoretical standpoint. Finally, we point out that continued investigation into the role of network topology and adaptation in shaping dynamics and structure may lead to a better understanding of the development and function of real-world networks, such as neuronal assemblies or large-scale brain structure and activity patterns. Indeed, there are many computational models of these systems in which this can be studied [136, 137, 185, 186, 268? –270, 188, 235, 252]. In addition, for neural systems in particular, it is interesting to note that while synchronization is often a desired property, hyper-synchronization can also be detrimental, as is the case with epileptic seizures [271]. Therefore, further examination of the tradeoff and transition between local and global synchrony in biologically motivated models [272, 273] – and understanding how this might occur adaptively over time and influence the structure and function of a network – continues to be an exciting line of study.

In conclusion, understanding the concurrent influence of network architecture on the emergence of collective dynamics [197, 198, 11, 182, 183], and in turn, the effect of a dynamical process on reshaping or inducing network structure [24, 21, 25], is currently an active area of research across a broad set of disciplines, including the physical, social, and biological sciences. Along these lines, we have studied a dynamical rewiring scheme for networks of Kuramoto oscillators. The adaptive rule for the network was specifically inspired by previous work on optimizing networks for synchronization of heterogeneous oscillators [48, 49, 260–266, 50, 226, 227], from which we wished to uncover how similar dynamics and organization could occur through a co-evolution process. We found that a restructuring of the network, in which the effect of incoherence is suppressed by maintaining edges between disparate oscillators, while randomly rewiring edges between the most locally and instantaneously in-phase oscillators, led to the emergence of distinct topological patterns and correlations that concurrently enhance the system’s ability to synchronize. This study thus sheds light on a mechanism for how enhanced synchronization and network structure might arise in a system that evolves and reconfigures according to local information alone, without knowledge of global connectivity or node states.
A Additional analyses and robustness to alternative parameter choices

A.1 An additional measure to quantify relationships between network topology and oscillator frequencies

In Sec. 2.4.2, we used two measures to quantify emerging relationships between the intrinsic frequencies of the oscillators and the network topology: the correlation $C_{|\tilde{\omega}|,k}$ between the magnitude of the oscillator frequency offset $|\tilde{\omega}_i|$ and the node degree $k_i$, and the mean fraction $f$ of an oscillator’s neighbors that have natural frequency offsets of opposite sign compared to the frequency offset of the central oscillator (averaged across all nodes in the system) [48, 49].

Here we define a related measure to further understand the organization that arises in the adaptively rewired networks. In particular, for each oscillator $i$, we assess the association between the frequency offset $\tilde{\omega}_i$ and the sum of oscillator $i$’s neighbors’ frequency offsets $\sum_{j \in N_i} \tilde{\omega}_j$. We quantify this relationship in the system by considering the correlation $C_{\tilde{\omega},\sum \tilde{\omega}}$ between $\tilde{\omega}_i$ and $\sum_{j \in N_i} \tilde{\omega}_j$ across all nodes in the network.

Fig. A.1 gives examples of this relationship for the same networks as those in Fig. 2.4. The top and bottom rows correspond to networks with $\langle k \rangle = 12.5$ and $\langle k \rangle = 25$, respectively. Panels (a) and (d) show that in the ER networks, there is no clear relationship between frequency offset and the sum of neighbor frequency offsets, as expected. In the adaptively rewired networks – panels (b) and (e) – the order parameter has increased from its original value and there is a strong negative correlation between $\tilde{\omega}_i$ and $\sum_{j \in N_i} \tilde{\omega}_j$. Not only do connections tend to form between oscillators that have frequency offsets of opposite sign (as measured by $f$), but in addition, edges become distributed in the network such that the sum of each oscillator’s neighbor frequency offsets proportionately cancel out each oscillator’s own difference from the mean frequency of the population. Fig. A.1c,f shows how the strength of this relationship – quantified by the correlation $C_{\tilde{\omega},\sum \tilde{\omega}}$ – evolves as the network is rewired.

Fig. A.2 shows $C_{\tilde{\omega},\sum \tilde{\omega}}$ as a function of the coupling $\alpha$. As $\alpha$ increases, $C_{\tilde{\omega},\sum \tilde{\omega}}$ decreases to a strong negative value, and then remains approximately constant for larger values of the coupling. (Compare to Fig. 2.5 and Fig. 2.6, which show $C_{|\tilde{\omega}|,k}$ vs. $\alpha$ and $f$ vs. $\alpha$, respectively). Finally, note that the strong decreases in $C_{\tilde{\omega},\sum \tilde{\omega}}$ occur in conjunction with increases in the order parameter (Fig. 2.3).
The relationship between the oscillator frequency offset $\tilde{\omega}_i$ and the sum of neighbor frequency offsets $\sum_{j \in N_i} \tilde{\omega}_j$ can be used to further quantify the interplay between the network structure and the intrinsic frequencies of the oscillators that arises due to the co-evolutionary process. The top row shows an example of this relationship for a network with $\langle k \rangle = 12.5$, and the bottom row shows examples for a network with $\langle k \rangle = 25$; in both cases, the frequencies were drawn from the uniform distribution $\{\omega_U\}$. For each network density, the first column corresponds to an ER random graph that exhibits only intermediate levels of synchrony at the displayed coupling $\alpha$ (as measured by $\langle R \rangle$), and the second column corresponds to the adapted network, which exhibits a higher level of synchrony. (a,b); (d,e) The total neighbor frequency offset $\sum_{j \in N_i} \tilde{\omega}_j$ vs. frequency offset $\tilde{\omega}_i$. (c); (f) The correlation $C_{\tilde{\omega}, \sum \tilde{\omega}}$ between oscillator frequency offset $\tilde{\omega}_i$ and the sum of neighbor frequency offsets $\sum_{j \in N_i} \tilde{\omega}_j$ vs. the number of rewiring steps $m$.

A.2 Analysis with normally distributed frequencies

The analysis in the main text was carried out using natural frequencies $\{\omega_U\}$ drawn at random from the uniform distribution in the range $[-2, 2]$. To demonstrate that the main results are not specific to a single choice of the frequency distribution, in this Appendix, we also consider the case of frequencies $\{\omega_G\}$ drawn from a normal distribution with zero mean and unit standard deviation. The findings shown here are largely consistent with those reported in the main text.
Figure A.2: The correlation $C_{\tilde{\omega}, \sum \tilde{\omega}}$ between oscillator frequency offset $\tilde{\omega}_i$ and the sum of neighbor frequency offsets $\sum_{j \in N_i} \tilde{\omega}_j$ as a function of the coupling. In each panel, the gray data points correspond to the initial, uncorrelated ER random graphs $G_o$, and the blue and yellow points correspond to the adapted networks $G_*$ evolved under rewiring time scales of $T = 0.2$ and $T = 2$, respectively. The frequencies were drawn from the uniform distribution $\{\omega_U\}$, and the mean degree of the networks are (a) $\langle k \rangle = 12.5$, and (b) $\langle k \rangle = 25$. All curves depict averages over 25 instantiations, and the lines between data points serve as guides for the eye.

Dependence of the order parameter on time and global coupling

Fig. A.3 shows examples of the order parameter $R(t)$ vs. time $t$ at different values of the coupling and for the two different mean degrees $\langle k \rangle = 12.5$ and $\langle k \rangle = 25$. For these trials and values of the coupling, we observe that the order parameter increases due to the rewiring of the network, which takes place between the two red lines. (Fig. 2.2 shows examples for the case of uniformly distributed natural frequencies).

Fig. A.4 shows examples of the time-averaged order parameter $\langle R \rangle$ vs. the coupling $\alpha$. As with the case of uniformly distributed frequencies (Sec. 2.4.1, Fig. 2.3), we find that the adapted networks exhibit heightened synchronization over a large coupling range.

Correlations between network topology and the intrinsic frequencies

Fig. A.5 shows examples of node degree $k_i$ vs. intrinsic frequency offset $\tilde{\omega}_i$, average neighbor frequency offset $\langle \tilde{\omega} \rangle_{N_i}$ vs. node frequency offset $\tilde{\omega}_i$, and total neighbor frequency offset $\sum_{j \in N_i} \tilde{\omega}_j$ vs. frequency offset $\tilde{\omega}_i$ for ER networks and the corresponding co-evolved networks (see Sec. 2.4.2
Figure A.3: Examples of the global order parameter $R(t)$ vs. time $t$, for various representative couplings $\alpha$. In each case, the dynamics were first run atop an initially ER random graph with average degree $\langle k \rangle$, after which co-evolution of the network and dynamics took place between the two red lines. The natural frequencies were drawn from a normal distribution $\{\omega_G\}$, and the mean degree $\langle k \rangle$ and coupling $\alpha$ used for each panel were $(a) \langle k \rangle = 25, \alpha = 0.05$, $(b) \langle k \rangle = 25, \alpha = 0.075$, $(c) \langle k \rangle = 12.5, \alpha = 0.1$, $(d) \langle k \rangle = 12.5, \alpha = 0.2$. During the adaptation period, the network was continually rewired once every $T = 0.2$ time units. The co-evolving networks exhibit enhanced collective dynamics, as observed by increases in the global order parameter.
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Figure A.4: The time-averaged order parameter \( \langle R \rangle \) vs. coupling \( \alpha \). In each panel, the gray data points correspond to static ER random graphs \( G_o \), and the blue and yellow points correspond to the adapted networks \( G_a \) evolved under rewiring time scales of \( T = 0.2 \) and \( T = 2 \), respectively. The frequencies were drawn from the normal distribution \( \{\omega_G\} \), and the mean degree of the networks were (a) \( \langle k \rangle = 12.5 \), and (b) \( \langle k \rangle = 25 \). All curves depict averages over 25 instantiations, and the lines between data points serve as guides for the eye.

and Appendix A.1 for the definitions of these quantities). The top three and bottom three panels correspond to networks with \( \langle k \rangle = 12.5 \) and \( \langle k \rangle = 25 \), respectively, and the frequencies \( \{\omega_G\} \)

Figure A.5 (following page): Relationships between the network structure and the intrinsic frequencies of the oscillators. The top three rows show examples for a network with \( \langle k \rangle = 12.5 \), and the bottom three rows show examples for a network with \( \langle k \rangle = 25 \); in both cases, the frequencies were drawn from the normal distribution \( \{\omega_G\} \). For each network density, the first column corresponds to an ER random graph that exhibits only intermediate levels of synchrony at the displayed coupling \( \alpha \) (as measured by \( \langle R \rangle \)), and the second column corresponds to the adapted network, which exhibits a higher level of synchrony. These plots highlight key relationships that emerge from the co-evolutionary network update rule. (a,b); (j,k) Node degree \( k_i \) vs. frequency offset \( \tilde{\omega}_i \). (d,e); (m,n) Average neighbor frequency offset \( \langle \tilde{\omega} \rangle \) \( N_i \) vs. frequency offset \( \tilde{\omega}_i \). (g,h); (p,q) Total neighbor frequency offset \( \sum_{j \in N_i} \tilde{\omega}_j \) vs. frequency offset \( \tilde{\omega}_i \). (c); (l) The correlation \( C_{|\tilde{\omega}|,k} \) between node degree \( k_i \) and the magnitude of the frequency offset \( |\tilde{\omega}_i| \) vs. the number of rewiring steps \( m \). (f); (o) The mean fraction \( f \) (i.e. averaged over all nodes in the network) of an oscillator’s neighbors that have frequency offsets of opposite sign compared to that of the central oscillator vs. the number of rewiring steps \( m \). (i); (r) The correlation \( C_{\tilde{\omega},\sum \tilde{\omega}} \) between oscillator frequency offset \( \tilde{\omega}_i \) and the sum of neighbor frequency offsets \( \sum_{j \in N_i} \tilde{\omega}_j \) vs. the number of rewiring steps \( m \).
\( \langle k \rangle = 125, \alpha = 0.13 \)
were normally distributed. At the values of coupling used for these examples, we see that as the system reconfigures, the network begins to exhibit distinct patterns in terms of the organization of oscillators with different intrinsic frequencies. Each of the three metrics considered – \( C_{|\tilde{\omega}|, k}, f, \) and \( C_{\tilde{\omega}, \sum \tilde{\omega}} \) – exhibits a progression that allows for the eventual heightened degree of synchrony in the rewired network. These findings are similar to those discussed for the uniform frequency distribution (see Fig. 2.4 and Fig. A.1 and the corresponding text in Sec. 2.4.2).

**Figure A.6:** The correlation \( C_{|\tilde{\omega}|, k} \) between node degree \( k_i \) and the magnitude of the frequency offset \( |\tilde{\omega}_i| \), as a function of the coupling. In each panel, the gray data points correspond to the initial, uncorrelated ER random graphs \( G_0 \), and the blue and yellow points correspond to the adapted networks \( G_\star \) evolved under rewiring time scales of \( T = 0.2 \) and \( T = 2 \), respectively. The frequencies were drawn from the normal distribution \( \{ \omega_G \} \), and the mean degree of the networks are (a) \( \langle k \rangle = 12.5 \), and (b) \( \langle k \rangle = 25 \). The dip observed in (b) at \( \alpha \approx 0.4 \) is due to the localization of edges on a cluster of oscillators with natural frequencies near the mean of the distribution; this is examined further in Appendix A.2. All curves depict averages over 25 instantiations, and the lines between data points serve as guides for the eye.

We next show the evolution of the relationships between network topology and the intrinsic frequencies as a function of the coupling \( \alpha \). Figs. A.6, A.7, and A.8 show \( C_{|\tilde{\omega}|, k} vs. \alpha, f vs. \alpha, \) and \( C_{\tilde{\omega}, \sum \tilde{\omega}} vs. \alpha \), respectively. The conclusions drawn for the case of normally distributed frequencies shown here are the same as those for the uniformly distributed frequencies examined in the main text. (See Figs. 2.5, 2.6, and A.2 and the corresponding discussions in Sec. 2.4.2 and Appendix A.1). Briefly, each of the three measures exhibit transitions at similar values of the coupling, and the emergence of strong relationships between the network structure and oscillator frequencies arise near the coupling when the order parameter transitions from low to higher
Figure A.7: The mean fraction $f$ (i.e. averaged over all nodes in the network) of an oscillator’s neighbors that have natural frequency offsets of opposite sign compared to that of the central oscillator, as a function of the coupling. In each panel, the gray data points correspond to the initial, uncorrelated ER random graphs $G_0$, and the blue and yellow points correspond to the adapted networks $G_\star$ evolved under rewiring time scales of $T = 0.2$ and $T = 2$, respectively. The frequencies were drawn from the normal distribution $\{\omega_G\}$, and the mean degree of the networks are (a) $\langle k \rangle = 12.5$, and (b) $\langle k \rangle = 25$. All curves depict averages over 25 instantiations, and the lines between data points serve as guides for the eye.

deviation values.

Time-dependence of the instantaneous frequencies and network structure

Fig. A.9 shows examples of $\dot{\theta}_i(t)$ vs. $t$ for several values of the coupling $\alpha$ around the point in which the dynamics transition from an incoherent state to a synchronized state. The top set of panels (a) are for a network with $\langle k \rangle = 12.5$, and the bottom set of panels (b) are for a network with $\langle k \rangle = 25$; the frequencies $\{\omega_G\}$ were normally distributed and the same for both cases. Each row corresponds to one oscillator, and the rows from top to bottom are displayed in ascending order of the quantity $\bar{\omega}_i = \omega_i - \langle \omega \rangle$ (i.e. the offset from the mean intrinsic frequency of the population). Adaptation of the network takes place between the two black lines. The results are qualitatively consistent with those described in the main text for the uniformly distributed frequencies (see the discussion in Sec. 2.4.3 and Fig. 2.7 for comparison).

Fig. A.10 shows the node degree $k_i$ vs. the rewiring step $m$ and Fig. A.11 shows the correlation $C_{|\bar{\omega}|,k}$ between the absolute value of the frequency offset $|\bar{\omega}_i|$ and the node degree $k_i$ vs.
Figure A.8: The correlation $C_{\tilde{\omega}, \sum \tilde{\omega}}$ between oscillator frequency offset $\tilde{\omega}_i$ and the sum of neighbor frequency offsets $\sum_{j \in N(i)} \tilde{\omega}_j$, as a function of the coupling. In each panel, the gray data points correspond to the initial, uncorrelated ER random graphs $G_0$, and the orange and yellow points correspond to the adapted networks $G_\star$ evolved under rewiring time scales of $T = 0.2$ and $T = 2$, respectively. The frequencies were drawn from the normal distribution $\{\omega_G\}$, and the mean degree of the networks are (a) $\langle k \rangle = 12.5$, and (b) $\langle k \rangle = 25$. All curves depict averages over 25 instantiations, and the lines between data points serve as guides for the eye.

the rewiring step $m$ for the same set of networks, natural frequencies, and coupling values as in Fig. A.10. In both figures, panel (a) corresponds to a network with $\langle k \rangle = 12.5$, and panel (b) corresponds to a network with $\langle k \rangle = 25$; the natural frequencies $\{\omega_G\}$ are normally distributed and are the same in both cases. We observe similar types of behavior and regimes in terms of the evolution of these quantities as we did for the situation of uniformly distributed frequencies in Figure A.9 (following page): Examples of the instantaneous frequencies $\dot{\theta}_i(t)$ vs. time $t$, for various representative couplings $\alpha$. The mean degree of the networks are (a) $\langle k \rangle = 12.5$ and (b) $\langle k \rangle = 25$, and the natural frequencies $\{\omega_G\}$ were drawn from the normal distribution. In all panels, each row corresponds to one oscillator, and the rows from top to bottom are in displayed in ascending order of the quantity $\tilde{\omega}_i = \omega_i - \langle \omega \rangle$ (i.e. the offset from the mean intrinsic frequency of the population). For each coupling, the dynamics were first run atop an initially ER random graph, after which co-evolution of the network and dynamics took place between the two black lines. During the adaptation period, the network was continually rewired once every $T = 0.2$ time units.
\begin{align*}
\alpha &= 0.01 & \alpha &= 0.035 & \alpha &= 0.04 & \alpha &= 0.045 & \alpha &= 0.05 & \alpha &= 0.055 & \alpha &= 0.065 & \alpha &= 0.07 & \alpha &= 0.1 \\
\langle k \rangle &= 12.5 \quad \langle k \rangle &= 25 \quad \langle k \rangle &= 30 \quad \langle k \rangle &= 40 \quad \langle k \rangle &= 50 \quad \langle k \rangle &= 60
\end{align*}
the main text (see the discussion in Sec. 2.4.3 and Figs. 2.8 and 2.9 for comparison). Also, note that the concentration of edges on oscillators near the center of the distribution explains the dips in Fig. A.5. One interesting result to point out for the examples using normally distributed frequencies shown here, is that the correlation $C_{|\bar{\omega}|,k}$ plateaus at a value near 0.5 (for $\langle k \rangle = 12.5$) for several of the intermediate coupling values, before increasing further at higher coupling. As seen in Fig. A.10, this is due to the oscillators with the most outlying natural frequencies (which can sometimes be more extreme for the normal distribution than for the uniform distribution) remaining with low degree. Though the results are qualitatively similar between the two frequency distributions, further work is needed to quantify and understand what may be subtle and intricate differences.

Spectral Analysis

In Sec. 2.4.4 we carried out a spectral-based analysis of the co-evolved networks inspired by [50]. Fig. A.12 shows the results of this analysis for the case of normally distributed frequencies $\{\omega_G\}$, which are consistent with those previously discussed in Sec. 2.4.4 using uniformly distributed frequencies (compare to Fig. 2.10). In short, for both values of the mean degree ($\langle k \rangle = 12.5$ and $\langle k \rangle = 25$) the overlap $|\langle \frac{\bar{\omega}}{||\bar{\omega}||} : \frac{\bar{v}_N}{||\bar{v}_N||} \rangle|$ between the normalized natural frequency offsets and the normalized dominant Laplacian eigenvector of the rewired networks increases and then plateaus at a high value as the coupling increases (Fig. A.12a,b). We refer the reader to Sec. 2.4.4 for a more detailed discussion of these findings.

A.3 Time-evolution of synchronized clusters

The order parameter $R$ is a global measure of phase synchronization, and when the coupling is high enough, we found that network adaptation could increase this quantity from a regime of low synchrony to a regime of intermediate to high synchrony (Figs. 2.2, 2.3, A.3, A.4). As a

Figure A.10 (following page): Examples of the evolution of the node degree $k_i$ vs. the rewiring step $m$, for various representative couplings $\alpha$. The mean degree of the networks are (a) $\langle k \rangle = 12.5$ and (b) $\langle k \rangle = 25$, and the natural frequencies $\{\omega_G\}$ were drawn from the normal distribution. In all panels, each row corresponds to one oscillator, and the rows from top to bottom are in displayed in ascending order of the quantity $\tilde{\omega}_i = \omega_i - \langle \omega \rangle$ (i.e. the offset from the mean intrinsic frequency of the population). The network was continually rewired once every $T = 0.2$ time units.
supplement to this measure, we can also quantify changes in the system during the adaptation process on a more local level by considering the time-evolution of synchronized clusters of oscillators. For this analysis, we follow \cite{217}, who defined a local order parameter between pairs of oscillators as

\[ \rho_{ij}(t) = \cos[\theta_i(t) - \theta_j(t)], \tag{2.7} \]

and then constructed a binary phase-similarity matrix \( \tilde{\rho}(t) \) by setting entries less than or equal to some threshold \( \Delta \) to zero and by setting entries greater than \( \Delta \) to 1. Specifically,

\[ \tilde{\rho}_{ij}(t) = \begin{cases} 0 & \text{if } \rho_{ij}(t) \leq \Delta \\ 1 & \text{if } \rho_{ij}(t) > \Delta. \end{cases} \tag{2.8} \]

We use a value of \( \Delta = 0.999 \). The binary matrix \( \tilde{\rho}(t) \) contains information about which pairs of oscillators are strongly synchronized at a given time, and synchronized clusters or groups of oscillators can be extracted by finding the connected components of \( \tilde{\rho}(t) \). Finally, we can track the number of synchronized clusters \( n_{sc}(t) \) as a function of time \( t \), and observe how this quantity changes when the network begins to co-evolve with the dynamics. For low values of the coupling - where the adaptive strategy does not have a large influence on the dynamics - we expect \( n_{sc}(t) \) to remain high as a function of time. However when the coupling is increased and the rewiring causes consistent changes in the network and the dynamics, we expect a decrease in the number of synchronized clusters as the network evolves from a configuration that does not support collective dynamics to one that does.

Fig. A.13 shows examples of \( n_{sc}(t) \) vs. \( t \) for a single simulation of the dynamics, and for various values of the coupling \( \alpha \) (the mean degree is \( \langle k \rangle = 25 \) and the natural frequencies \( \{\omega_U\} \) are uniformly distributed). We see that the number of synchronized clusters is initially large, since the oscillators’ phases are distributed at random at \( t = 0 \). Before the red line, the system evolves on a static ER network, and depending on the coupling strength, the number of components either fluctuates around a high value or – after a short initial transient – rapidly decreases to a lower

\[ \text{Figure A.11 (following page): Examples of the evolution of the correlation } C_{|\tilde{\omega}_i|, k} \text{ between the magnitude of the oscillator frequency offset } |\tilde{\omega}_i| \text{ and the node degree } k_i \text{ vs. the rewiring step } m, \text{ for various representative couplings } \alpha. \] The mean degree of the networks are (\textit{a}) \( \langle k \rangle = 12.5 \) and (\textit{b}) \( \langle k \rangle = 25 \), and the natural frequencies \( \{\omega_G\} \) were drawn from the normal distribution. The network was continually rewired once every \( T = 0.2 \) time units.
value, denoting partial synchronization. Network adaptation begins at the time denoted by the red line, after which the behavior of \( n_{sc}(t) \) is again determined by the global coupling. For very low \( \alpha \), the co-evolution process does not significantly affect the number of synchronized clusters. However, as the coupling increases, the network rewiring begins to have an impact on the dynamical clustering. At intermediate values of \( \alpha \), the number of synchronized clusters slowly decreases as a function of time. For higher coupling values, this transition takes place more rapidly. However, it appears that no matter the coupling regime, the transition from high to lower \( n_{sc} \) does not occur abruptly at a single instance of time, but instead occurs over several time steps through the merging or growth of clusters. In addition to the curves depicting individual examples of the number of synchronized clusters vs. time, Fig. A.14 also shows averages of \( n_{sc}(t) \) vs. \( t \) over 10 simulations using different instantiations of the initial conditions.

Fig. A.15 and Fig. A.16 show \( n_{sc}(t) \) vs. time \( t \) and the ensemble averages \( \overline{n_{sc}(t)} \) vs. \( t \), respectively, for the case of mean degree \( \langle k \rangle = 12.5 \) and normally distributed natural frequencies \( \{\omega_G\} \). We find similar results to those for the denser networks. At low values of the coupling, network adaptation does not cause a consistent change in \( n_{sc} \). As the coupling increases, how-
Figure A.13: Examples of the number of synchronized clusters $n_{sc}(t)$ vs. time $t$, for various representative couplings $\alpha$. In each case, the dynamics were first run atop an ER random graph, after which co-evolution of the network and dynamics took place between the two red lines. The natural frequencies were drawn from the uniform distribution $\{\omega_U\}$ and the mean degree of the network was $\langle k \rangle = 25$. During the adaptation period, the network was continually rewired once every $T = 0.2$ time units. For high enough coupling, co-evolution results in a decrease in the number of synchronized clusters over time.
Figure A.14: Ensemble averages of the number of synchronized clusters $n_{sc}(t)$ vs. time $t$, for various representative couplings $\alpha$. In each case, the dynamics were first run atop an ER random graph, after which co-evolution of the network and dynamics took place between the two red lines. The natural frequencies were drawn from the uniform distribution $\{\omega_U\}$ and the mean degree of the network was $\langle k \rangle = 25$. During the adaptation period, the network was continually rewired once every $T = 0.2$ time units. The data in each panel corresponds to an average over 10 different simulations. For high enough coupling, co-evolution results in a decrease in the number of synchronized clusters over time.
\[ \langle k \rangle = 12.5, \{ \omega_G \} \]

Figure A.15: Examples of the number of synchronized clusters \( n_{sc}(t) \) vs. time \( t \), for various representative couplings \( \alpha \). In each case, the dynamics were first run atop an ER random graph, after which co-evolution of the network and dynamics took place between the two red lines. For these plots, the natural frequencies were drawn from the normal distribution \( \{ \omega_G \} \) and the mean degree of the network was \( \langle k \rangle = 12.5 \). During the adaptation period, the network was continually rewired once every \( T = 0.2 \) time units. For high enough coupling, co-evolution results in a decrease in the number of synchronized clusters over time.
Figure A.16: Ensemble averages of the number of synchronized clusters $n_{sc}(t)$ vs. time $t$, for various representative couplings $\alpha$. In each case, the dynamics were first run atop an ER random graph, after which co-evolution of the network and dynamics took place between the two red lines. The natural frequencies were drawn from the normal distribution $\{\omega_G\}$ and the mean degree of the network was $\langle k \rangle = 12.5$. During the adaptation period, the network was continually rewired once every $T = 0.2$ time units. The data in each panel corresponds to an average over 10 different simulations. For high enough coupling, co-evolution results in a decrease in the number of synchronized clusters over time.
ever, the number of components begins to decrease from its initial value, signifying the merging or growth of synchronized clusters due to rearrangements in the network. This decrease becomes more rapid at larger couplings, though does not occur discontinuously as a function of time.

### A.4 Variation of network size, initial network topology, and frequency distribution

Thus far we have considered a system size $N = 100$ and have initialized the coupling between oscillators to be ER random graphs with mean degree $\langle k \rangle = 25$ or $\langle k \rangle = 12.5$. Under those conditions, we then examined two symmetric distributions (uniform $\{\omega_U\}$ and normal $\{\omega_G\}$) for the intrinsic frequencies of the oscillators. In this section, we explore the robustness of some of the main results to simple variations in the network size, the initial network topology, and the frequency distribution.

#### Larger networks

We first investigate the effect of the co-evolutionary mechanism on the degree of synchronization in the system when the network is doubled in size to $N = 200$ (while also proportionately doubling the number of rewirings allowed for the adaptation process). Fig. A.17a shows the time-averaged order parameter $\langle R \rangle$ vs. coupling $\alpha$ for the case of uniformly distributed frequencies $\{\omega_U\}$, mean degree $\langle k \rangle = 25$, and a rewiring time scale of $T = 0.2$ time units. We find qualitatively similar results to that of $N = 100$ (Fig. 2.3b), in that the curve corresponding to the adapted networks (blue) is shifted to the left compared to the curve corresponding to a set of static, ER networks (gray). Thus, over a large range of global coupling, the co-evolved networks exhibit a heightened degree of collective dynamics.

In addition to the order parameter, we also assessed the co-evolved networks $G_*$ for the emergence of correlations between their topology and the intrinsic frequencies of the oscillators (as done in Secs. 2.4.2, A.1, and A.2). The results of this analysis are shown in Fig. A.17(b - d). We find that the same set of relationships appear when the system size is doubled as were found previously for the case of $N = 100$. Following the analysis described in the main text, for each node $i$, we computed its offset from the mean frequency $\bar{\omega}_i = \omega_i - \langle \omega \rangle$, where $\langle \omega \rangle$ is the mean natural frequency of the population. We then considered the correlations between $|\bar{\omega}_i|$ and node degree $k_i$, as a function of the coupling (Fig. A.17b), and between $\bar{\omega}_i$ and the total neighbor frequency offset $\sum_{j \in \mathcal{N}(i)} \bar{\omega}_j$ (forall $j \in \mathcal{N}(i)$) as a function of the coupling (Fig. A.17d). In addition,
for each oscillator $i$, we computed the fraction $f_i$ of $i$'s neighbors that had a value of $\tilde{\omega}$ of opposite sign compared to that of $\tilde{\omega}_i$, and then computed the average $f$ over all nodes in the network (Fig. A.17c). As the coupling increases, there is an increasingly positive correlation $C_{|\tilde{\omega}|,k}$ between node degree and the magnitude of the intrinsic frequency offset, and an increasingly negative correlation $C_{\tilde{\omega},\sum\tilde{\omega}}$ between the intrinsic frequency offset of each oscillator and the sum of its neighbors’ frequency offsets. Furthermore, oscillators tend to become connected to other oscillators that have intrinsic frequency offsets on the opposite side of the mean. Although an in-depth examination into the effect of system size is beyond the scope of this study, it is important that the results are consistent for at least somewhat larger networks. We refer the reader to [264] for a detailed finite-size study and analysis of the critical coupling and critical exponents in oscillator populations with purposefully constructed correlations.

**Smaller mean degree**

Here we briefly examine whether various results hold for networks with a lower mean degree of $\langle k \rangle = 6$. Fig. A.18a shows the time-averaged order parameter $\langle R \rangle$ vs. coupling $\alpha$ for the static ER networks (gray curve) and the adapted networks (blue curve). The network size was $N = 100$, the frequencies $\{\omega_U\}$ were uniformly distributed, and the rewiring time scale was $T = 0.2$ time units. As for the denser networks considered in the main text (Fig. 2.3), here we also observe a significant enhancement of the order parameter in the co-evolved systems.

We also examined the locally adapted systems for the previously described relationships between the natural frequencies and the topological organization of the network. Fig. A.18 panels (b-d) show $C_{|\tilde{\omega}|,k}$, $f$, and $C_{\tilde{\omega},\sum\tilde{\omega}}$, respectively, as a function of the coupling $\alpha$. Again we find that as the coupling increases, there is an increasingly positive correlation between degree and the magnitude of intrinsic frequency offset, and an increasingly negative correlation between the intrinsic frequency offset of an oscillator and the sum of its neighbors’ frequency offsets. Furthermore, oscillators tend to become connected to other oscillators with frequency offsets on the opposite side of the mean. Although the curves shown here for the case of $\langle k \rangle = 6$ exhibit somewhat more fluctuations compared to the case of $\langle k \rangle = 25$, the findings are in general robust and consistent with those found for networks with higher mean degree (compare to Figs. 2.5, 2.6, and A.2).
CHAPTER 2.

Initial network topology

The main interest and goal of this study has been to define and explore a simple, local mechanism that evolves some initial network of coupled oscillators to a structured configuration that in turn supports enhanced collective dynamics. Given this objective, ER random graphs – which are considered to be relatively “disordered” – are a natural family of networks on which to begin the co-evolution and also to compare the adapted systems against. However, it may still be useful to examine if the results hold for a different initial network topology. To test this, we constructed a set of modular-small world (MSW) networks, which consist of a specified number of fully connected communities that are then linked together by placing edges at random between the modules. In contrast to the ER random graph model, these networks contain a significant amount of planted structure. For this analysis, we used networks of size $N = 128$, with $N_c = 8$ communities, and a total number of edges such that the average degree was $\langle k \rangle = 20$. Fig. A.19 shows an example connection pattern.

Due to the nature of the adaptive mechanism, we expect that it will undo the community structure and evolve this class of networks towards topologies with the same set of features we have discussed previously. To test this expectation, we first simulated the Kuramoto dynamics on non-adaptive MSW networks, and then used the same set of MSW networks as the initial network configurations for the adaptive mechanism. Fig. A.20a shows the time-averaged order parameter $\langle R \rangle$ vs. coupling $\alpha$ for the case of uniformly distributed frequencies $\{\omega_U\}$, and a rewiring time scale of $T = 0.2$ time units. The adaptively rewired networks (blue curve) show heightened global synchronization across a large range of coupling values compared to the static MSW networks (gray curve). Turning next to the correlations between the natural frequencies and the network structure, we find results consistent with those described in the main text. In particular, strong degree-frequency correlations and frequency-neighbor frequency mixing emerge in the self-organized systems (see Fig. A.20b-d for plots of $C_{|\tilde{\omega}|,k}$, $f$, and $C_{\tilde{\omega},\sum \tilde{\omega}}$, respectively, vs. the coupling $\alpha$). This investigation provides some evidence that the adaptive mechanism is agnostic to the initial network configuration from which it begins.

Natural frequency distribution

One can also explore in more depth how the distribution of natural frequencies affects certain results. In this study, we considered two standard distributions – uniform and normal – that are often used in studies on the Kuramoto model. Here, we also show some brief results for the case
of natural frequencies \( \{\omega_P\} \) drawn from a power-law distribution in which \( P(\omega) \propto \omega^{-\gamma} \), with \( \gamma = 3 \). The dynamics and network co-evolution start from ER random graphs with \( N = 200 \) nodes and mean degree \( \langle k \rangle = 25 \). We find qualitatively similar results to those in the main text when using this skewed distribution for the intrinsic frequencies.

Fig. A.21 shows the time-averaged order parameter \( \langle R \rangle \) vs. coupling \( \alpha \) for the static ER networks (gray curve) and the adaptively rewired networks (blue curve). The rewiring time scale was \( T = 0.2 \) time units. As with the two symmetric frequency distributions, we observe an increase in the order parameter for the networks evolved according to the local mechanism. We also examined the co-evolved networks \( G_* \) for the correlations between the natural frequencies of the oscillators and the topological organization of the network. Fig. A.21b - d show plots of \( C_{|\tilde{\omega}|,k}, f, \) and \( C_{\tilde{\omega},\Sigma \tilde{\omega}} \), respectively, vs. the coupling \( \alpha \). Consistent with the findings in the main text, we observe the emergence of strong degree-frequency correlations and frequency-neighbor frequency mixing patterns.
Figure A.17: Analysis of the global synchronization and various correlations between the network topology and the intrinsic frequencies for networks of size $N = 200$. In each panel, the gray data points correspond to the initial ER random graphs $G_o$ with mean degree $\langle k \rangle = 25$, and the blue points correspond to the adapted networks $G_*$ evolved under a rewiring time scale of $T = 0.2$ time units. The natural frequencies were drawn from the uniform distribution $\{\omega_U\}$. 

(a) The time-averaged order parameter vs. coupling. 
(b) The correlation $C_{|\tilde{\omega}|,k}$ between node degree $k_i$ and the magnitude of the frequency offset $|\tilde{\omega}_i|$, as a function of the coupling. 
(c) The mean fraction $f$ of an oscillator's neighbors that have frequency offsets of opposite sign compared to that of the central oscillator, as a function of the coupling. 
(d) The correlation $C_{\tilde{\omega},\sum \tilde{\omega}}$ between oscillator frequency offset $\tilde{\omega}_i$ and the sum of neighbor frequency offsets $\sum_{j \in N(i)} \tilde{\omega}_j$, as a function of the coupling. All curves depict averages over 10 instantiations, and the lines between data points serve as guides for the eye.
Figure A.18: Analysis of the global synchronization and various correlations between the network topology and the intrinsic frequencies for networks with sparser connectivity. In each panel, the gray data points correspond to the initial ER networks $G_0$ with mean degree $\langle k \rangle = 6$, and the blue points correspond to the adapted networks $G_*$ evolved under a rewiring time scale of $T = 0.2$ time units. The natural frequencies were drawn from the uniform distribution $\{\omega_U\}$. (a) The time-averaged order parameter vs. coupling. (b) The correlation $C_{|\tilde{\omega}|,k}$ between node degree $k_i$ and the magnitude of the frequency offset $|\tilde{\omega}_i|$, as a function of the coupling. (c) The mean fraction $f$ of an oscillator’s neighbors that have frequency offsets of opposite sign compared to the central oscillator, as a function of the coupling. (d) The correlation $C_{\tilde{\omega},\sum_{j \in N(i)} \tilde{\omega}_j}$ between oscillator frequency offset $\tilde{\omega}_i$ and the sum of neighbor frequency offsets $\sum_{j \in N(i)} \tilde{\omega}_j$, as a function of the coupling. All curves depict averages over 10 instantiations, and the lines between data points serve as guides for the eye.
modular - small world network, \( \langle k \rangle = 20 \)

Figure A.19: An example connection pattern of a modular-small world network. The network size is \( N = 128 \), with 8 communities and a mean degree \( \langle k \rangle = 20 \).
Figure A.20: Analysis of global synchronization and various correlations between the network topology and the intrinsic frequencies when the initial network is modular-small world, rather than a random graph. In each panel, the gray data points correspond to the initial MSW networks $G_0$, and the blue points correspond to the adapted networks $G_*$ evolved under a rewiring time scale of $T = 0.2$ time units. The natural frequencies were drawn from the uniform distribution $\{\omega_U\}$. (a) The time-averaged order parameter vs. coupling. (b) The correlation $C_{|\tilde{\omega}|,k}$ between node degree $k_i$ and the magnitude of the frequency offset $|\tilde{\omega}_i|$, as a function of the coupling. (c) The mean fraction $f$ of an oscillator’s neighbors that have frequency offsets of opposite sign compared to the central oscillator, as a function of the coupling. (d) The correlation $C_{\tilde{\omega},\sum \tilde{\omega}}$ between oscillator frequency offset $\tilde{\omega}_i$ and the sum of neighbor frequency offsets $\sum_{j \in N(i)} \tilde{\omega}_j$, as a function of the coupling. All curves depict averages over 10 instantiations, and the lines between data points serve as guides for the eye.
Figure A.21: Analysis of the global synchronization and various correlations between the network topology and the intrinsic frequencies when the frequencies \( \{\omega_p\} \) are drawn from a power law distribution with exponent \( \gamma = 3 \). In each panel, the gray data points correspond to the initial ER networks \( G_o \), and the blue points correspond to the adapted networks \( G_e \) evolved under a rewiring time scale of \( T = 0.2 \) time units. The network size is \( N = 200 \) and the mean degree is \( \langle k \rangle = 25 \). (a) The time-averaged order parameter vs. coupling. (b) The correlation \( C_{|\tilde{\omega}|, k} \) between node degree \( k_i \) and the magnitude of the frequency offset \( |\tilde{\omega}_i| \). (c) The mean fraction \( f \) of an oscillator’s neighbors that have frequency offsets of opposite sign compared to the central oscillator, as a function of the coupling. (d) The correlation \( C_{\tilde{\omega}, \sum \tilde{\omega}} \) between oscillator frequency offset \( \tilde{\omega}_i \) and the sum of neighbor frequency offsets \( \sum_{j \in N(i)} \tilde{\omega}_j \), as a function of the coupling. All curves depict averages over 10 instantiations, and the lines between data points serve as guides for the eye.
Chapter 3

Modulating phase-locked dynamical states with local perturbations to multi-regional brain circuits

The work presented in this chapter was performed under the supervision of Danielle S. Bassett and Demian Battaglia.

Abstract

Oscillatory synchrony is hypothesized to support communication and the transfer of information between brain regions, with different phase-locked configurations enabling different functional interactions. Moreover, past work has proposed multistable phase-locking as a means for hardwired networks to flexibly support multiple functional states, without the need to reconfigure their anatomical connections. Given the potential link between interareal communication and phase-locked states, it is thus important to understand how these dynamical patterns could be controlled to achieve on-demand reconfiguration of functional connectivity patterns in interareal circuits. Here, we investigate functional state modulation in small model networks of coupled, oscillatory neural masses. In particular, beginning with deterministic networks that exhibit collective multistability, we study their global responses to external signals that target only a single area. We identify conditions under which these local inputs (i) ineffectively regulate net-
work states, (ii) are able to slightly adjust a particular phase-locked pattern (“state morphing”), or (iii) can trigger transitions to topologically different functional connectivity motifs that are simultaneously stable (“state switching”). We then show that these control strategies can also extend to a more realistic stochastic regime wherein oscillations become slightly irregular and where phase-locking in a particular configuration is only transient. In total, our results add to a growing literature highlighting that the modulation of collective dynamical multistability and phase-locking may provide a basis for flexible network operation.

3.1 Introduction

Brain function depends not only upon the behaviors and capabilities of single areas in isolation, but also on the ability of many distributed regions to coordinate and exchange information with one another. Nonetheless, understanding how interareal communication is established and reconfigured based on the dynamics and anatomical coupling of multiregion brain circuits remains an open question. One popular hypothesis for how information may be routed between different neuronal populations is that of communication-through-coherence (CTC) [42, 2, 274, 77, 108, 96, 79]. This mechanism suggests that communication between coupled neuronal areas can be established when the areas’ population activities oscillate and become phase-locked (coherent) with an “optimal” phase relation that allows input from one area to have an effect on a receiving site. Collective gamma rhythms, in particular (i.e. those with frequencies of $\approx 40-80$ Hz [71, 82]), are thought to play a major role in this process [2, 73, 78]. Moreover, the hypothesized link between coordinated oscillations and communication suggests that the pattern of phase relations emergent in an interareal network defines a “functional connectivity” state of the system. This collective state then determines which areas can effectively exchange information with which others [275, 276]. Indeed, by utilizing information-theoretic measures, prior studies have demonstrated direct ties between the sign and magnitude of the phase differences between collective neuronal rhythms and the directionality and strength of information flow among the areas in an anatomical circuit [113, 112, 277, 278].

In addition to establishing a means of communicating, it is also desirable that networks of anatomically linked brain regions are able to perform multiple functions. For example, how might these circuits be able to reconfigure how information is routed in different contexts? This question is especially interesting given that long-range structural couplings that determine direct routes for signal propagation cannot be drastically rewired on rapid time scales. This fact pre-
cludes structural changes from underlying the capability of a network to achieve many stable and rapidly adjustable functional states. In thinking about potential mechanisms by which an interareal network could generate a number of different dynamical configurations despite an inflexible anatomical scaffold, an exciting collection of past studies has suggested multistable phase-locking \[113, 112, 277, 279, 150, 278\]. There has also been some experimental work suggesting that multiple phase relations could exist within the same anatomical circuit, lending some initial support to this theoretical idea \[280\]. But, given that distinct phase-locked configurations in interareal brain networks may enable distinct computations or functional outcomes, a critical question arises. That is, how can specific collective states from a larger set be tuned or rapidly selected for – without rewiring anatomical connectivity – in order to achieve a desired pattern of functional interactions?

Building upon previous work \[113, 112, 277, 279, 278\], here we focus on this question of functional state control by building a reduced computational model of small but multiarea brain circuits. In particular, we examine how the collective network states that arise in this system can be modulated by different external signals that target only a single region. We begin our study by detailing the dynamical behaviors of the model brain networks at baseline, identifying parameter regimes that yield multistable phase-locking. In order to acquire a basic understanding of the circuits’ dynamics, we start with the simpler scenario in which network activity is deterministic. We then move on to analyze a more complicated but also more realistic situation in which the system operates in the presence of a stochastically fluctuating background environment. In this latter case, we explore functionally-relevant regimes where the multistable phase-locking becomes metastable, such that the network spontaneously switches between its assortment of collective states. After characterizing network behavior under baseline conditions, we proceed to model the effects of different types of local perturbations that could represent, for example, sensory inputs, artificial stimulation, or targeted signals coming from another brain area. In particular, we focus on how these locally-applied external inputs can be used to control the collective dynamical states of the network as a whole, without altering its structural connectivity.

For both the deterministic and the stochastic versions of the model networks, we study the consequences of two kinds of perturbations that target only a single area in the circuit. Starting with the deterministic scenario, we first analyze the effects of brief, excitatory pulses injected at one region. Given that the pulse is applied at a specific phase of the receiving area’s ongoing oscillation, these perturbations can induce a global reconfiguration of the activity pattern that manifests as a transition to a different dynamical attractor of the entire system. Moreover, we
find that even in the noisy scenario, this type of focal input can still be used to trigger very rapid state transitions with efficacies that exceed chance levels. We also describe, for the stochastic networks, a regime in which this control can break down and become ineffective. In addition to pulse inputs, we further consider the effects of sustained rhythmic stimulation applied to a single area. Depending upon its amplitude and frequency, we find that this type of external drive can lead to a shifting of the spatial configuration of the phase differences in the network. By inducing this morphing of the collective state, rhythmic input thus enables a different type of tuning of the temporal relations between regional activities. When background noise leads to spontaneous state-switching, steady sinusoidal input can still cause symmetry-breaking that shifts the phase relations of the collective states in which the network tends to dwell. Taken together, our results provide additional support to a collection of studies that have considered the control of dynamical multistability as a path towards flexible coordinated behavior in networks of neural populations that exhibit oscillatory activity.

3.2 Model and methods

3.2.1 Network architectures

To study phase-locking of neural oscillations and the response of mesoscale brain circuits to dynamical perturbations, we consider two simple network architectures: a 2-unit network with homogeneous, bidirectional connectivity and a 4-unit undirected network with homogeneous, all-to-all connectivity (Fig. 3.1A). Each of the \( N \) units or nodes in these circuits should be thought of as representing a localized brain region or large neuronal assembly that would be composed of tens of thousands of individual neurons. Moreover, edges in these networks correspond to direct anatomical couplings between the different neural areas.

3.2.2 Biophysical model of neural population activity

In this study, we numerically simulate neural population dynamics using a biophysically-motivated but coarse-grained model. In particular, each area in a model anatomical brain circuit is represented as a Wilson-Cowan (WC) neural mass [130] (Fig. 3.1B). As described previously in Sec. 1.5.1, the Wilson-Cowan model is a canonical mean-field formulation that describes the average activity of large, interacting excitatory and inhibitory neuronal subgroups. More specifically, the classic Wilson-Cowan model is comprised of two coupled differential equations, one each for
Figure 3.1: Schematics of the model setup. (A) The two different network architectures examined in this study: a bidirectional 2-area network (top) and an all-to-all 4-area network (bottom). Each node in each network represents a large neuronal population or brain area, and edges represent anatomical connections. (B) A schematic of the computational model of network dynamics for the 2-area system. Brain areas are modeled as Wilson-Cowan neural mass units, each of which are composed of coupled subpopulations of excitatory (E) and inhibitory (I) neural populations. Anatomical coupling between distinct regions is introduced by linking the excitatory pools of the corresponding areas. This interareal connectivity is characterized by a coupling strength $G_{EE}$ and a time-delay $T_D$. In addition to the generic background drive $P_E(t)$ that enters each region’s excitatory pool, the yellow population also receives an external perturbation signal $S(t)$ (indicated by the yellow lightning bolt). (C) Two different types of perturbations $S(t)$ are considered. In the top panel, the excitatory subgroup of the yellow brain area receives a brief square-wave pulse input. This perturbation is characterized by its duration $T_s$, its amplitude $A_s$, and the phase $\theta_{on}$ of the region’s ongoing oscillation (blue time-series) at which the pulse begins. In the bottom panel, the excitatory subgroup of the yellow brain area instead receives sustained rhythmic stimulation. This signal is characterized by its frequency $f_s$, its amplitude $A_s$, and the phase $\theta_{on}$ of the region’s ongoing oscillation (blue time-series) at which the stimulation is initiated.

the excitatory (E) and inhibitory (I) population activities. An important feature of the Wilson-Cowan system is that – under appropriate parameter choices – it generates average firing rates that oscillate in time. As we are interested in the control of interareal phase-locking between the
collective rhythms of coupled brain areas, we are interested in regimes where the neural masses exhibit oscillatory dynamics.

To study the collective activity of multiarea brain circuits, we couple individual Wilson-Cowan units according to the network architectures described in the previous section. In this way, the dynamics of the network as a whole are governed by both intrinsic properties of the individual regions as well as the circuit connectivity. This type of framework, in which the activity of a distributed brain network is modeled as a system of interacting neural masses, has been utilized in several previous investigations [129]. Importantly, there are different ways that one could incorporate long-range coupling between the neural populations. For simplicity (and in line with a number of past studies [281, 173, 157, 170, 161, 169, 175]), here we consider anatomical connections to link only the excitatory pools of distinct areas (Fig. 3.1B). One could also consider both long-range $E \rightarrow E$ and long-range $E \rightarrow I$ connections, but doing so would introduce an additional parameter. We also assume, in general, that distinct regions or populations are distributed in space, such that it may take some finite amount of time for activity to propagate from one area to another. Hence, a particular anatomical connection has both an associated coupling strength $G_{EE}$ and time-delay $T_D$.

A schematic of the model setup for the 2-region network is shown in Fig. 3.1B; the setup for the 4-area network is analogous, but involves four areas that are mutually connected through their excitatory pools rather than only two areas. Following the formulation of the WC model used in Ref. [282], the activity of the $j^{th}$ region evolves according to the following set of differential equations:

\begin{equation}
\tau_E \frac{dE_j(t)}{dt} = -E_j(t) + S_E[c_{EE}E_j(t) - c_{EI}I_j(t) - b_E + P_{E,j}(t)] + G_{EE} \sum_{i=1}^{N} A_{ij}E_i(t - T_D)]
\end{equation}

\begin{equation}
\tau_I \frac{dI_j(t)}{dt} = -I_j(t) + S_I[c_{EI}E_j(t) - c_{II}I_j(t) - b_I + P_{I,j}(t)]
\end{equation}

where

\begin{equation}
S_E(x) = \frac{1}{1 + e^{-x}}
\end{equation}
\[
S_I(x) = \frac{1}{1 + e^{-x}}.
\]  
(3.2b)

Here, \(E_j(t)\) and \(I_j(t)\) represent the mean firing rates of the excitatory and inhibitory subgroups. The internal parameters of a single WC unit are: the excitatory time constant \(\tau_E\), the inhibitory time constant \(\tau_I\), the local \(E \rightarrow E\) coupling \(c_{EE}\), the local \(E \rightarrow I\) coupling \(c_{EI}\), the local \(I \rightarrow E\) coupling \(c_{IE}\), a quantity that controls the firing threshold of the excitatory pool \(b_E\), and a quantity that controls the firing threshold of the inhibitory pool \(b_I\). In general, the \(E\) and \(I\) populations also receive generic background drives, represented by the variables \(P_{E,j}(t)\) and \(P_{I,j}(t)\). In addition, due to the long-range excitatory-to-excitatory coupling between different neural populations, the \(E\) pool of area \(j\) also receives input (which is potentially delayed) from other areas to which it is connected. This network-based influence is captured in the final term of Eq. 3.1a. Specifically, \(A_{ij}\) represents the strength of the anatomical connection from area \(i\) to area \(j\), \(G_{EE}\) is a global coupling that scales the weight of all network edges, and the term \(E_i(t - T_D)\) represents delayed excitatory input from area \(i\) to area \(j\), where the time-delay is given by \(T_D\). Note that we consider homogeneous time-delays between all region pairs.

Throughout this study, we consider two varieties of the network model presented above: one in which the neural population dynamics evolve deterministically and one in which the network activity is driven instead by stochastic background inputs. We describe each of these two cases in more detail in the following two sub-sections.

**Deterministic case**

In order to gain an intuition for the system’s behavior, we first study the deterministic version of the model. In this case, the background inputs to the \(E\) and \(I\) populations are deterministic and taken to be constant in time, such that \(P_{E,j}(t) := P_{E,j} \forall j \in \{1, ..., N\}\) and \(P_{I,j}(t) := P_I \forall j \in \{1, ..., N\}\). We explore the model’s behavior under these conditions in later sections.

**Including stochastic background drive**

Real brain activity is inherently noisy [283]. In order to incorporate this fact into the model and make our system slightly more realistic, we additionally study a scenario in which the background inputs to each unit, \(P_{E,j}(t)\) and \(P_{I,j}(t)\), are stochastic. In the presence of such noisy drive, the regional activities \(E_j(t)\) and \(I_j(t)\) will also exhibit stochastic fluctuations.
To operationalize this formulation, we consider a situation in which all background inputs to the $E$ and $I$ populations are modeled as independent Ornstein-Uhlenbeck (O.U.) processes. In particular, we have

$$\frac{dP_{E,j}(t)}{dt} = \alpha[P_{E,j} - P_{E,j}(t)] + \sigma \eta_j(t) \quad \forall j \in \{1, \ldots, N\} \tag{3.3a}$$

$$\frac{dP_{I,j}(t)}{dt} = \alpha[P_{I,j} - P_{I,j}(t)] + \sigma \xi_j(t) \quad \forall j \in \{1, \ldots, N\}, \tag{3.3b}$$

where $\eta_j(t)$ and $\xi_j(t)$ are Gaussian white noises that satisfy $\langle \eta_j(t) \rangle = 0$, $\langle \xi_j(t) \rangle = 0$, $\langle \eta_i(t) \eta_j(t') \rangle = \delta_{ij} \delta(t - t')$, $\langle \xi_i(t) \xi_j(t') \rangle = \delta_{ij} \delta(t - t')$, and $\langle \eta_i(t) \xi_j(t') \rangle = 0$. In other words, the noises are delta-correlated in time, and are spatially uncorrelated between different brain areas and also uncorrelated between the $E$ and $I$ populations of the same neural mass. In the above formulation, $P_{E,j}$ and $P_{I,j}$ correspond to the long-term means of the input to the $E$ and $I$ population, respectively, $\sigma$ sets the strength of the noise, and $\alpha$ is the speed of mean reversion (and also the inverse correlation time of the processes). In particular, in the limit $t \to \infty$, the mean, variance, and covariance of the O.U. process defined in Eq. 3.3a approach $\langle P_{E,j}(t) \rangle \to P_{E,j}$, $\text{var}[P_{E,j}(t)] \to \sigma^2/2\alpha$, and $\text{cov}[P_{E,j}(t), P_{E,j}(t')] \to \sigma^2/2\alpha(e^{-\alpha|t-t'|})$. Similar relations hold for the input to the $I$ population defined in Eq. 3.3b. We explore the model’s behavior under these conditions in later sections.

Default model parameters

The Wilson-Cowan model has a number of different parameters, but if chosen appropriately, the population activity can oscillate [130]. Because we are interested here in phase-locking between collective rhythms in mesoscale brain circuits, we wish to study parameter regimes in which individual units in the model can exhibit oscillatory dynamics. Using the system defined in Eqs. 3.1a and 3.1b (and with the deterministic setup), such a regime can be achieved, for example, by using the relevant default parameters from Ref. [282]. We present all model parameters and their default values (if applicable) in Table 3.1. Under the default conditions, a Hopf bifurcation occurs in an isolated unit as the strength of a constant input $P_E$ to its excitatory population is varied [282]. We study the dynamical behavior of an isolated unit in more detail in Secs. 3.3.1 and 3.3.1 of the Results.

We also note that, while rhythmic activity in the brain can occur across a wide range of fre-
quencies, we specify the time constants of the $E$ and $I$ populations of a single unit such that it oscillates in the gamma frequency range (~30-80 Hz). This choice is mainly motivated by the facts that gamma oscillations and gamma band coherence have been consistently observed in local excitatory-inhibitory circuits [71, 284, 285], are hypothesized to support communication and the flow of information between different brain areas [82, 2, 42], and have been empirically associated with a number of cognitive processes [78]. However, we note that our choice of oscillation frequency is somewhat arbitrary due to the highly-phenomenological nature of the model. We expect that similar results would hold for other frequencies that result from a scaling of the time constants, so long as quantities like the interareal time delay were also shifted accordingly.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau_E$</td>
<td>time constant of $E$ pool</td>
<td>2 ms</td>
</tr>
<tr>
<td>$\tau_I$</td>
<td>time constant of $I$ pool</td>
<td>4 ms</td>
</tr>
<tr>
<td>$c_{EE}$</td>
<td>local $E$-to-$E$ coupling</td>
<td>15</td>
</tr>
<tr>
<td>$c_{IE}$</td>
<td>local $I$-to-$E$ coupling</td>
<td>15</td>
</tr>
<tr>
<td>$c_{EI}$</td>
<td>local $E$-to-$I$ coupling</td>
<td>15</td>
</tr>
<tr>
<td>$c_{II}$</td>
<td>local $I$-to-$I$ coupling</td>
<td>7</td>
</tr>
<tr>
<td>$b_E$</td>
<td>firing threshold of $E$ pool</td>
<td>4</td>
</tr>
<tr>
<td>$b_I$</td>
<td>firing threshold of $I$ pool</td>
<td>4</td>
</tr>
<tr>
<td>$P_{E}$</td>
<td>mean input to $E$ pool</td>
<td>varied</td>
</tr>
<tr>
<td>$P_{I}$</td>
<td>mean input to $I$ pool</td>
<td>0</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>inverse correlation time of background drive</td>
<td>varied</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>noise strength of background drive</td>
<td>varied</td>
</tr>
<tr>
<td>$G_{EE}$</td>
<td>interareal $E$-to-$E$ coupling strength</td>
<td>varied</td>
</tr>
<tr>
<td>$T_d$</td>
<td>interareal time delay</td>
<td>varied</td>
</tr>
</tbody>
</table>

Table 3.1: Model parameters. Parameters with a corresponding numerical value are held constant for all simulations and analyses, while parameters labeled as “varied” indicate that we study model behavior as a function of or for different values of those parameters.

3.2.3 Incorporating the effects of local perturbations into the model

A main goal of this study is to understand how the collective dynamics of multiarea brain circuits respond to – and can potentially be controlled by – local perturbations. Here, a “local perturbation” refers to an additional external signal that is input to only a single area in the larger network. Because we consider fully symmetric networks, all units are topologically identical, but
for consistency and clarity, we always assign area 1 to be the perturbed site. For simplicity, we also examine the case that this external stimulation targets only the excitatory subpopulation of the perturbed brain region (though it may also be interesting to study the case that it targets only the inhibitory or both the excitatory and inhibitory subgroups together). With this setup, “baseline” conditions correspond to the scenario that the excitatory pool of all units $j \in \{1, \ldots, N\}$ receives only the background drive $P_{E,j}(t)$ (Eq. 3.1). A perturbation is then introduced by injecting the signal $S_1(t)$ — in addition to the background input $P_{E,1}(t)$ — into area 1 only. All other regions $j \neq 1$ receive the baseline background drive alone. This leads to the slightly modified system of equations for the network activity:

$$
\tau_E \frac{dE_j(t)}{dt} = -E_j(t) + S_E [c_{EE} E_j(t) - c_{IE} I_j(t) - b_E + P_{E,j}(t) + \delta_{j1} S_1(t)]
$$

$$
+ G_{EE} \sum_{i=1}^{N} A_{ij} E_i(t - T_D)]
$$

$$
\tau_I \frac{dI_j(t)}{dt} = -I_j(t) + S_I [c_{EI} E_j(t) - c_{II} I_j(t) - b_I + P_{I,j}(t)].
$$

In general, the signal $S_1(t)$ could take a range of forms. As described in more detail in the following two subsections, this study considers two different types of external inputs: transient pulse inputs and sustained rhythmic inputs.

**Transient pulse inputs**

One type of perturbation we study is a brief pulse input injected into the excitatory pool of a single network node. For these perturbations, the external signal $S_1(t)$ is a square wave pulse characterized by a duration $T_s > 0$ and an amplitude $A_s > 0$ (see Fig. 3.1C, Top). More specifically, we have that

$$
S_1(t) = \begin{cases} 
0 & \text{for } t < t_s \text{ and } t > t_s + T_s \\
A_s & \text{for } t_s \leq t \leq t_s + T_s,
\end{cases}
$$

where $t_s$ indicates the time at which the pulse is turned on. The pulses we consider are brief in the sense that their durations $T_s$ are always shorter than the average oscillation cycle.
For a dynamical unit that exhibits rhythmic activity, it is also critical to consider the timing of incoming stimuli relative to the phase of the unit’s ongoing oscillation. In particular, as detailed in the literature on phase-response curves and phase-resetting [286, 287], an external input pulse can have differing effects (e.g. induce a significant phase advance, induce a significant phase delay, or have little influence) depending on the oscillation phase at which it is received. We therefore also study network responses to pulse stimuli as a function of the onset phase $\theta_{on}$ (i.e., the phase of the directly perturbed area’s activity when the external input is first turned on).

Sustained rhythmic inputs

In addition to brief stimulation pulses, we also examine the effects of sustained rhythmic inputs that target the excitatory pool of a single region in the multiarea networks. In particular, we consider the external signal $S_1(t)$ to be a sine wave characterized by a fixed amplitude $A_s$ and a fixed frequency $f_s$ (Fig. 3.1C, Bottom). More specifically,

$$S_1(t) = \begin{cases} 
0 & \text{for } t < t_s, \\
A_s \sin[2\pi f_s(t - t_s)] & \text{for } t \geq t_s,
\end{cases} \quad (3.6)$$

where $t_s$ is again the time at which the external stimulation begins. As for the pulse inputs, it is also relevant to consider varying $t_s$ such that the rhythmic stimulation is initiated at different onset phases $\theta_{on}$ of the ongoing regional activity.

3.2.4 Numerical methods

All numerical simulations and subsequent analyses of the computational model were performed using MATLAB version 2020a. Simulations of the model without noise and without perturbations (e.g. baseline parameter sweeps) made use of built-in ordinary differential equation (ode45) and delay differential equation (dde23) solvers. For the stochastic version of the model and/or when perturbations were incorporated, we instead used custom scripts for numerical simulations. In particular, for the deterministic scenario with local external inputs, we used Euler’s method for the numerical integration with a time step $dt = 1 \times 10^{-5}$ s. For the scenario with noisy background drive, we used the Euler-Maruyama method for stochastic differential equations with a time step of $dt = 1 \times 10^{-5}$ s. In all cases, we assumed a constant history for the initial conditions, but chose a random value in the range [0,1] for the constant history of each unit and...
subpopulation. To obtain sufficient statistics, we often ran many realizations of the same system, each time picking the initial conditions anew (and always at random).

3.2.5 Defining phase variables from the population activity

In this study, we are specifically interested in rhythmic population dynamics and phase-locked states in networks of anatomically connected neural populations. In order to study phase-locking, we first need a means of defining instantaneous phases from the real-valued activity time-series generated from the WC-based network model. That is, given a real-valued oscillatory signal \( X(t) \), we need to extract a corresponding phase variable \( \theta(t) \). In order to do this, we carry out the following steps: (1) Find the set of times \( \{t_{n}^{\text{max}}\} \) for \( n \in \{1, \ldots, N_{\text{max}}\} \) that correspond to each of the \( N_{\text{max}} \) local maxima of the time-series \( X(t) \). Note that we only consider a peak in the activity time series to be a local maxima if the peak in question has the highest activity value within a time window centered on the peak location and spanning half of an average oscillation cycle in either direction \([112]\). The average oscillation period is approximated as the inverse of the frequency at maximum power computed across the length of the time-series in question using Welch’s method. (2) For each maxima \( n \in \{1, \ldots, N_{\text{maxima}} - 1\} \), let \( \theta(t_{n}^{\text{max}}) = 0 \) and let \( \theta(t_{n+1}^{\text{max}}) = 2\pi \). Then perform a linear interpolation (using the function ‘interp1’ in MATLAB) between the points \([t_{n}^{\text{max}}, \theta(t_{n}^{\text{max}})]\) and \([t_{n+1}^{\text{max}}, \theta(t_{n+1}^{\text{max}})]\). (3) From the linear interpolation, extract the value of the phase \( \theta(t) \) at each time point \( t \) in the range \([t_{n}^{\text{max}}, t_{n+1}^{\text{max}}]\) (in particular, we sample the phases at the same resolution of the original time-series). Throughout the study, we carry out the above procedure on the excitatory signal \( E_{i}(t) \) of each area \( i \in \{1, \ldots, N\} \) in order to extract the corresponding phase \( \theta_{i}(t) \) that tracks the oscillations.

3.2.6 Quantifying interareal phase-locking

Once instantaneous phases have been computed from each region’s activity in a network, the extent of phase-coherence between each pair of units can be computed using the phase-locking value \([97]\). In particular, the phase-locking value between units \( i \) and \( j \) – which we denote as \( \rho_{ij} \) – is defined as

\[
\rho_{ij} = \left| \frac{1}{t_{f} - t_{o}} \sum_{t = t_{o}}^{t_{f}} e^{i[\theta_{i}(t) - \theta_{j}(t)]} \right|,
\]

(3.7)
where $\theta_i(t)$ and $\theta_j(t)$ are the instantaneous phases of unit $i$ and unit $j$, and where $t_o$ and $t_f$ correspond to the times at the beginning and end of the time-window over which the phase-locking is evaluated. Intuitively, the phase-locking value measures the consistency of the phase difference $\Delta \theta_{ij} = \theta_i - \theta_j$ across a continuous segment of time. Moreover, $\rho_{ij} \in [0, 1]$, such that if the phase relation between the two units is fixed at a constant value across the window, then $\rho_{ij}$ will be equal to 1; if the phase difference is spread uniformly across the window, then $\rho_{ij}$ will be equal to zero; and if there is partial locking between the two units, then $\rho_{ij}$ will acquire a value between these two extremes.

3.3 Results

3.3.1 Characterizing the model’s baseline dynamical regimes

In order to understand how local perturbations affect collective activity patterns in the model brain circuits, it is necessary to first consider the system’s behavior in the absence of perturbations. In this section, we thus set out to characterize the baseline dynamical regimes of the model. We proceed from the simplest to the most complex instantiation of the system, studying first the behavior of a single WC neural mass, then the 2-area network, and finally the 4-area circuit. For each of these subcategories, we also separately consider the case for which the background drive is constant and deterministic versus the case for which the background drive is stochastic.

Behavior of an isolated Wilson-Cowan unit: Deterministic scenario

We begin here by examining the behavior of a single WC neural mass subject to a fixed and noiseless baseline input. The main control parameter we study for this scenario is the level of background drive $P_E$ received by the excitatory subpopulation. For the chosen model settings, it is known that $P_E$ is a bifurcation parameter that, when varied, changes the nature of the neural dynamics [130, 282]. In particular, for low values of $P_E$, the system has a stable fixed point that corresponds to a steady, low-activity state (Fig. 3.1A). In contrast, for high values of $P_E$, there is again a stable fixed point, but one that corresponds to a state of constant, high activity (Fig. 3.1C). Importantly, though, as $P_E$ is increased starting from the low activity regime, a Hopf bifurcation occurs at a critical value of the input. Here, the fixed point loses stability and a stable limit cycle appears. Thus, for intermediate values of $P_E$, the population activity oscillates in time.
Figure 3.1: Baseline dynamics of a single Wilson-Cowan unit with constant and deterministic background input. (A) Phase plane representations (top) and time series of the excitatory subpopulation (bottom) for $P_E = 1.0$. (B) Phase plane representations (top) and time series of the excitatory subpopulation (bottom) for $P_E = 1.5$. (C) Phase plane representations (top) and time series of the excitatory subpopulation (bottom) for $P_E = 7.0$. (D) The average activity level $\langle E(t) \rangle$ of the excitatory subpopulation as a function of the background input $P_E$. (E) The frequency of the excitatory subpopulation $f_E$ as a function of the background input $P_E$. The large jumps away from and towards a frequency of zero correspond to the onset and disappearance of oscillations.

(Fig. 3.1B). Because we are concerned with rhythmic dynamics and the emergence of interareal coherence of these rhythms in mesoscale neural mass networks, the regime of interest for this study is that in which the WC system oscillates.

In Figs. 3.1D-E, we more generally characterize the population activity as a function of $P_E$. For this analysis, we run one 4 second-long simulation at each working point, and examine sum-
mary statistics over the last 1 second of the excitatory time series. As determined previously, one
effect of increasing $P_E$ is to increase the mean (time-averaged) activity level of the neural mass
(Fig. 3.1D). For working points where the maximum minus the minimum value of the time-series
exceeds a small threshold of $1 \times 10^{-5}$, we also numerically estimate the frequency of the activity.
This estimation is performed by finding the local maxima of the time-series, finding the average
amount of time between the peaks, and computing the inverse of that time. Fig. 3.1E indicates
that the frequency of the activity first increases as the system enters the oscillatory regime and as
$P_E$ is increased in an intermediate range. With further addition of background drive, the oscil-
lation frequency starts to decrease until the rhythms disappear entirely and the high fixed-point
becomes stable. Note that this behavior has been previously reported in Ref. [282], which is the
study from which we adopted our parameters. As also noted in Ref. [282], the time constants $\tau_E$
and $\tau_I$ are such that the oscillation frequency of an isolated unit ranges between approximately
45 Hz and 65 Hz (i.e., the unit oscillates in the gamma frequency range).

**Behavior of an isolated Wilson-Cowan unit: Stochastic scenario**

In this section, we briefly consider the dynamics of a single WC neural mass when it is driven by
stochastically fluctuating background input (Eqs. 3.3a, 3.3b) in contrast to constant, determin-
istic input (Fig. 3.2). In particular, we assume that the inputs to the $E$ and $I$ populations evolve
according to independent Ornstein-Uhlenbeck processes (see Sec. 3.2.2). Moreover, we hold the
mean input level to the inhibitory population fixed at the default value $P_I = 0$, but consider
three different values of the mean excitatory input $P_E$.

We begin with a mean background input $P_E = 1.0$. In the case that this drive is noiseless
and constant across time, the system has a stable fixed point that corresponds to a low activity
steady state (Fig. 3.2A, Top). When the background drive instead fluctuates around this mean
value according to an OU process with $\alpha = 10$ and $\sigma = 0.25$, the population activity becomes
visibly noisy, but does not appear to acquire any additional structure (Fig. 3.2A, Bottom).

In Fig. 3.2B, we consider the case of a slightly higher mean input $P_E = 1.2$. For the noiseless
scenario (Fig. 3.2B, Top), the activity remains in a low activity equilibrium, but the slight increase
in background drive pushes the system slightly closer to the Hopf bifurcation at which oscilla-
tions emerge in the firing-rate activity. The consequence of this slight shift in working point is
evidenced in (Fig. 3.2B, Bottom), where the input has the same mean value, but instead evolves
stochastically via an OU process, again with $\alpha = 10$ and $\sigma = 0.25$. In particular, we observe
that, because the neural mass operates near the Hopf bifurcation, fluctuations of the noisy input
Figure 3.2: Baseline dynamics of a single Wilson-Cowan unit with stochastic background input. (A) For a mean excitatory input $P_E = 1.0$, the top panel shows the E-population activity (dark blue) for noiseless drive (light blue), and the bottom panel shows the E-population activity (dark blue) for stochastic drive (light blue) with $\alpha = 10$ and $\sigma = 0.25$. (B) For a mean excitatory input $P_E = 1.2$, the top panel shows the E-population activity (dark blue) for noiseless drive (light blue), and the bottom panel shows the E-population activity (dark blue) for stochastic drive (light blue) with $\alpha = 10$ and $\sigma = 0.25$. (C) For a mean excitatory input $P_E = 1.4$, the top panel shows the E-population activity (dark blue) for noiseless drive (light blue), and the bottom panel shows the E-population activity (dark blue) for stochastic drive (light blue) with $\alpha = 10$ and $\sigma = 0.25$.

are sometimes significant enough to induce brief episodes of irregular yet clearly oscillatory activity separated by periods of quiescence. Hence, due to the system’s proximity to the bifurcation, noise alone can be enough to cause transient explorations into the oscillatory regime. There have been a number of intriguing past works commenting on potential functional benefits to neural systems that are poised near such “critical” points that separate different dynamical operating modes [288].

We conclude this brief section by considering a working point with mean background input $P_E = 1.4$. Here, even when the input is constant and deterministic, it is high enough to place the
neural mass in the regime of sustained rhythmic activity (Fig. 3.2C, Top). In this case, making the environment noisy (i.e., generated from OU processes with $\alpha = 10$ and $\sigma = 0.25$) does not change the qualitative nature of population activity (Fig. 3.2C, Bottom). Still, stochastic fluctuations do induce visible amplitude fluctuations, and also cause some temporal irregularity in the system’s rhythms (which would evolve at a single, fixed frequency in the absence of noise).

**Behavior of 2-area circuits: Deterministic scenario**

In this section, we move on to explore the baseline dynamical behaviors of networks composed of 2 mutually-coupled brain areas. We begin again with the deterministic background drive scenario and assume that each unit has identical parameters fixed to those depicted in Table 3.1. Because this investigation is focused on oscillatory dynamics and phase-locking in multiarea neural circuits, we focus the subsequent analyses on these behaviors.

To start, we consider a situation where each area would exhibit rhythmic dynamics on its own, even if isolated from the other area. As an example, we set $P_{E,i} = 1.5$ for $i \in \{1, 2\}$ (observe the oscillatory dynamics of an uncoupled unit with this level of background drive in Fig. 3.3A). Recall next that, for a network of interacting areas, there are two key parameters that characterize the network’s organization. The first is the interareal coupling strength $G_{EE}$, and

**Figure 3.3 (following page): Baseline phase-locking behavior of a 2-area network with deterministic background input.** (A) We study a 2-area neural mass network, where each unit receives constant, deterministic background drive. The time-series in this first panel shows the oscillatory activity exhibited by an isolated WC unit with $P_{E} = 1.5$. (B) When the two areas are coupled with strength $G_{EE} = 0.2$ and time-delay $T_D = 1.5$ ms, different initial conditions give rise to two distinct states $S_1$ and $S_2$. These two asymmetric phase-locking states correspond to a different region taking on the role of the phase-leader. (C) The fraction of sampled, random initial conditions that result in a configuration where unit 1 leads unit 2 ($S_1$), and where unit 2 leads unit 1 ($S_2$). (D) Histogram of the time-averaged phase difference $\Delta \theta$ between the two model brain areas across many initial conditions. (E) The mean (over initial conditions) of the absolute time-averaged phase difference $\langle |\Delta \theta| \rangle$ as a function of the time delay $T_D$ and the coupling strength $G_{EE}$. (F) Top: Polar plots of the mean (over initial conditions) of the set of positive and negative time-averaged phase differences for four different values of the delay $T_D$, at a fixed $G_{EE} = 0.2$. Bottom: Time-series of the two units for the four different values of the delay. For the first three delays, the time-series depict the system in one of its two asymmetric states ($S_1$). For the last delay $T_D = 3$ ms, the system is in an anti-phase state where there is no global leader or lagger.
CHAPTER 3.

A

uncoupled coupled
state S1 state S2
A B
coupled
F
TD = 0.1 ms TD = 1 ms TD = 2 ms TD = 3 ms
E
C
D

B

state S1 state S2

1
0.5
0
activity
time (s)
2 2.05 2.1 2.15
2 2.05 2.1 2.15
time (s)

C

D

E

F

1
0.5
0
probability

0

-π/2 0 π/2 π
Δθ

0
0.2
0.4
0.6
fraction

Δθ > 0 (S1) Δθ < 0 (S2)
states

1
2
3
0
delay, T_D (ms)

1
0
0.5
1
2
3
0
coupling, G_{EE}

2
3
4
5
6
7
8
9
10
π/3 2π/3 π
Δθ

10
11
12
13
14
15
16
17
18
π/6 π/3 2π/3
Δθ

TD = 0.1 ms TD = 1 ms TD = 2 ms TD = 3 ms

103
the second is the signal propagation delay $T_D$ between the regions. What happens when two rhythmic neural masses are coupled with intermediate values of $G_{EE}$ and $T_D$? We show an example of the network’s dynamics for $G_{EE} = 0.2$ and $T_D = 1.5$ ms in Fig. 3.3B, where the two different panels correspond to two different initial conditions.

We find that upon coupling the two areas with the chosen parameters, the network locks into an out-of-phase configuration that, once reached, remains stable. Moreover, note that for such an asymmetric phase-locking state, it is possible to determine an area that leads in phase over the other. In Fig. 3.3B, Top, region 1 leads region 2. Crucially, this asymmetric configuration arises from an entirely symmetric network, and thus corresponds to a type of symmetry-breaking in the system’s collective dynamics. As reported and discussed in several previous studies that have examined phase-locking in model oscillatory networks [150, 113, 277, 289, 279, 290], an important consequence of an out-of-phase state that arises from purely symmetric coupling is that it can indicate the presence of collective multistability (or in the case of the two unit network here, bistability). In particular, when a different initial condition is used, the network settles into an equal-but-opposite dynamical state where the lead-lag relationship is switched but the absolute phase difference remains the same (Fig. 3.3B, Bottom). Hence, depending on the preparation of the system, two distinct dynamical configurations of the network are possible, and the system is bistable. Fig. 3.3C illustrates that across many random initial conditions, the fractions that result in state $S_1$ (area 1 leads area 2) and state $S_2$ (area 2 leads area 1) are approximately equal. Moreover, across the same large set of initial conditions, Fig. 3.3D indicates that the time-averaged phase difference $\Delta \theta$ between the two regions always concentrates at a specific out-of-phase value. In sum, similar to other models [150, 113, 112, 279, 289], we find here that in a 2-area WC network with delays, two distinct collective states are possible from a single structural network. As discussed further in the Introduction and Discussion, the emergence of such multistable phase-locking in mesoscale brain circuits may be very useful from a functional standpoint.

Thus far we have examined a single working point of the model. It is important, however, to understand how the aforementioned behaviors vary as a function of the key network parameters: the coupling strength $G_{EE}$ and the time delay $T_D$. To study this, we run 25 different 6-second simulations that use different random initial conditions, and compute (1) the phase-locking value between the two areas over the final 1 second of the simulations, and (2) the time-averaged phase difference $\overline{\Delta \theta}$ between the regions over the last 1 second of the simulations. Fig. 3.3E shows the absolute value of the phase difference $\langle |\Delta \theta| \rangle$ between the two units (averaged across initial conditions) as a function of the coupling $G_{EE}$ and delay $T_D$. Black areas indicate parameter com-
Combinations where the PLV – averaged across initial conditions – does not exceed a high threshold of 0.95. We observe from this analysis that for a fixed coupling strength, increasing the delay has the effect of increasing the absolute phase difference between the two areas’ activities until the anti-phase configuration $\Delta \theta = \pi$ is reached. This effect is not surprising; indeed, other studies have examined the effects of time delays in coupled oscillator systems and have reported similar findings [289]. Additionally, increasing the coupling can also change the phase difference and push the system into the antiphase state more rapidly as a function of the delay. In this way, there is an approximately wedge-shaped portion of parameter space where the phase difference is both fixed across time and also satisfies $0 < \Delta \theta < \pi$. For these working points, the system exists in a bistable out-of-phase regime. Fig. 3.3F shows more explicitly the evolution of the collective dynamics as a function of $T_D$ for a fixed $G_{EE} = 0.2$.

Figure 3.4 (following page): Baseline phase-locking behavior of a 2-area network with stochastic background input. (A) We study a 2-area neural mass network where each unit receives an independent stochastic background drive. Throughout, we hold $P_E = 1.35$, $P_I = 0$, $G_{EE} = 0.2$, $T_D = 1.5$ ms. (B) Left: Time-series of an uncoupled, deterministic WC unit. Right: Time-series of two coupled, deterministic WC units. (C) For $\alpha = 10$ and $\sigma = 0.1$, the distribution of phase differences between the two coupled areas across a long simulation (left) and a segment of their activity time-series (right). (D) For $\alpha = 10$ and $\sigma = 0.2$, the distribution of phase differences between the two coupled areas across a long simulation (left) and a segment of their activity time-series (right). Note the switch in the lead-lag relationship at $t \approx 14.75$s. (E) For $\alpha = 10$, the distribution of phase differences between the two coupled areas for varying $\sigma (\sigma = \{0.1, 0.15, 0.2, 0.25, 0.5\})$, increasing as the curves go from light to dark). (F) The mean state duration $\langle L_s \rangle$ as a function of the noise strength $\sigma$. (G) For $\alpha = 10$ and $\sigma = 0.15$, the distribution of phase differences between the two coupled areas across a long simulation (left) and a segment of their activity time-series (right). Note the switch in the lead-lag relationship at $t \approx 12.05$s. (H) For $\alpha = 25$ and $\sigma = 0.15$, the distribution of phase differences between the two coupled areas across a long simulation (left) and a segment of their activity time-series (right). (I) For $\sigma = 0.15$, the distribution of phase differences between the two coupled areas for varying $\alpha (\alpha = \{5, 10, 15, 20, 25\})$, increasing as the curves go from light to dark). (J) The mean state duration $\langle L_s \rangle$ as a function of the speed of reversion $\alpha$. Note: In all of the $\Delta \theta$ distributions, the gray vertical lines correspond to the stable phase differences that would exist in the absence of noise.
CHAPTER 3.

A noiseless coupled
noiseless uncoupled

B

\[ \sigma = 0.2 \]
\[ \sigma = 0.1 \]
\[ \sigma = 0.1 \]
\[ \sigma = 0.2 \]
\[ \alpha = 10 \]
\[ \alpha = 25 \]

C

\[ \sigma = 0.1 \]

D

\[ \sigma = 0.2 \]

E

\[ P(\Delta \theta) \]

F

\[ \text{state dur. } \langle L_s \rangle (s) \]

G

\[ \alpha = 10 \]

H

\[ \alpha = 25 \]

I

\[ P(\Delta \theta) \]

J

\[ \text{state dur. } \langle L_s \rangle (s) \]

reversion speed \( \alpha \)
Behavior of 2-area circuits: Stochastic scenario

Having characterized the baseline behavior of the 2-area network driven by constant, noiseless background inputs, we turn next to the case of a stochastic environment. In this latter scenario, each unit receives fluctuating background drives generated from independent OU processes with inverse correlation time $\alpha$ and noise strength $\sigma$ (see Eqs. 3.3a and 3.3b). Moreover recall that the inputs are also uncorrelated between the E and I populations within a single area. A schematic of the model setup for this scenario is shown in Fig. 3.4A. In order to obtain enough statistics to properly characterize system behavior, the results presented in the following exposition are based on very long simulations of 22 minutes in length.

How are collective phase-locking states in the neural mass circuits affected by temporally fluctuating, noisy inputs? To begin to understand these effects, we consider the simplest scenario of a 2-area motif with parameters such that an isolated area with deterministic dynamics would intrinsically oscillate (see Fig 3.4B, Left). In particular, we set the mean input levels of the excitatory and inhibitory populations to $\overline{P_{E,j}} = 1.35$ for $j \in \{1, 2\}$ and $\overline{P_{I,j}} = 0$ for $j \in \{1, 2\}$. For the network parameters, we then consider the example of an interareal coupling strength $G_{EE} = 0.2$ and time delay $T_D = 1.5$ ms. These choices give rise to out-of-phase locking under noiseless conditions (Fig. 3.4B, Right). We are now prepared to study how a stochastic background environment affects the system’s baseline dynamics in this regime. Recall that – in addition to the long-term mean values of the input $\overline{P_E}$ and $\overline{P_I}$ – the two other key parameters of the OU processes driving each area are the noise strength $\sigma$ and the speed of mean reversion $\alpha$. In the following exposition, we separately consider the effects of these two quantities on the network’s activity patterns.

To start, we fix $\alpha = 10$ and consider a non-zero but relatively low $\sigma = 0.1$. With these parameters, we observe that the noise induces fluctuations in the amplitude of the mean-field oscillations across time, and also causes some temporal irregularity of the oscillation period (Fig. 3.4C, Left). As is true for an uncoupled WC unit, these results are an effect of the noise causing transient increases and decreases in the level of input to each unit as a function of time. However, despite this temporal variation in each areas’ activity, we observe from the time-series that phase-locking can still be maintained in the network due to the interareal coupling, though it becomes imperfect. In this way, the noise causes excursions around the stable phase-locking attractors that exist in the deterministic system – which causes some shifting of the phase relation across time – but the noise does not completely destroy the presence of the underlying attractors all together.

Perhaps the most consequential effect of incorporating realistic stochasticity into the model
is that it induces spontaneous switching between the different phase-locking or functional connectivity patterns that are stable in the absence of noise. This fact is most easily appreciated by examining the distribution $P(\Delta \theta)$ of the instantaneous phase difference $\Delta \theta$ between the two units across a very long simulation (Fig. 3.4C, Right). This analysis reveals two clear out-of-phase peaks in the distribution of approximately equal height, which correspond to favored configurations of the emergent dynamics. These peaks are in fact signatures of the bistable collective states that exist in the noiseless system, and are indeed centered around the values of the two equal-but-opposite phase differences of the deterministic network (indicated by the vertical gray lines in the histogram). In the absence of noise, the $\Delta \theta$ distribution would be replaced by a delta function at either peak, the location of which would be determined by the initial conditions. But here, in a more realistic stochastic environment, the network exhibits synchronous episodes in which one of the two lead-lag relations is maintained for some finite duration, and these epochs are then separated by periods of asynchrony after which the system may re-enter the same configuration or spontaneously transition into the other state. Thus, in addition to causing temporal shifting of the precise phase relationship in a given lead-lag configuration (which is indicated by the spread in the distribution $P(\Delta \theta)$ around each peak), the addition of noise also allows the system to spontaneously sample and transition between entirely different functional states characterized by having a phase difference of the opposite sign. As noted in Palmigiano et al. [112], this natural switching between collective states may allow for flexible interareal communication in brain networks. Before continuing, it is also critical to point out that the types of behaviors found here have been reported in previous studies that used detailed, biophysical spiking neuron models [112, 279]. These past investigations significantly inspired and laid out key insights for the present work, in which we find that even a relatively simple mean-field model can exhibit rich dynamical behaviors that may underlie some aspects of brain function and computation.

Fig. 3.4D illustrates the results when the noise strength is increased to $\sigma = 0.2$. Importantly, we observe that the same qualitative effects are preserved: two well-defined peaks emerge in the phase difference distribution centered around the values that correspond to the noiseless attractors. The activity time-series in this case also highlights an example of the state-switching referred to previously. To the left of the gray bar, it is clear that the purple unit leads the yellow unit in phase. Then, around $t \approx 14.75$, the system transiently desynchronizes, and when it recovers, the other phase relation dominates (yellow leads purple). Fig. 3.4E more generally shows the distribution $P(\Delta \theta)$ for several different values of the noise strength $\sigma$ in the range $[0.1, 0.5]$. In alignment with intuition, increasing $\sigma$ has the effect of broadening and decreasing the peak
CHAPTER 3.

heights of $P(\Delta \theta)$. Though the presence of the two peaks remains intact over the considered values of $\sigma$, one would expect the distribution to become flat for large enough noise.

We also examine how incorporating noise into the model affects the length of time that the network dwells in one of its two states before undergoing a transition. Without noise or any external perturbations, this time would be infinite, but with the addition of stochasticity, the states become metastable and transient. To compute state durations, we first need to choose a working definition of “state”. For this analysis, we extract states in the simplest possible way: based on the sign of the phase difference $\Delta \theta$. Specifically, we define $\Delta \theta$ such that it is positive when unit 1 (yellow) leads unit 2 (purple). We then determine that the system is in state $S_1$ whenever $\Delta \theta > 0$ and in state $S_2$ whenever $\Delta \theta < 0$. In this way, a state “switch” corresponds to a change in the sign of the collective phase relationship, which could potentially reverse the direction of information routing in the network [112, 279, 113, 278]. Using these state definitions, we then calculate the set of state durations $\{L_s\}$ by computing the lengths of continuous time segments in which the system is in one state or the other. As a summary statistic, we consider the mean state duration $\langle L_s \rangle$ across the simulation. Fig. 3.4F shows $\langle L_s \rangle$ as a function of $\sigma$, from which a clear decreasing trend is apparent. Hence, increasing the level of noise reduces the average switching time, and by the point $\sigma = 0.5$, the mean state duration corresponds to only a few oscillation cycles.

For completeness, we show in Figs. 3.4G–J the effects of the inverse correlation time $\alpha$, the second parameter governing the OU processes that generate the background drive. In particular, we fix $\sigma = 0.15$ and vary $\alpha$ in the range [5, 25]. We find that the key behaviors of the model – transient phase-locking and noise-induced switching between the system’s underlying attractor states – are qualitatively preserved across this set of $\alpha$ values. However, increasing $\alpha$ does make the phase difference distribution $P(\Delta \theta)$ less broad and more sharply peaked (Fig. 3.4I). The intuition for this behavior is that, the shorter the correlation time, the less the system can deviate from its preferred configuration for extended periods of time. Note that these trends are in the opposite direction as for increasing $\sigma$, which agrees with the fact that the long-term variance of the OU process increases with increasing $\sigma$ but decreases with increasing $\alpha$ (see Sec. 3.2.2). Similarly, the mean state duration $\langle L_s \rangle$ is longer when the inputs revert to their mean more quickly, whereas when the stochastic drive takes a longer time to relax back to its mean, transient excursions that are significant enough to lead to state-switching become more probable and the average state duration decreases (Fig. 3.4J).

In summary, when the model brain areas exhibit robust intrinsic oscillations and multistable out-of-phase locking when coupled (as is the case for the parameters just considered), in-
Introducing stochastic background drive leads to a form of metastability: the system spontaneously samples its two underlying attractors and transitions naturally between the two different lead-lag configurations. Changing the parameters that govern the stochastic fluctuations of the environment can modulate the precise nature of these behaviors, but the overall effects remain.

We can additionally consider what occurs, however, for quantitatively different baseline dynamical regimes. For example, of interest is what happens for lower values of the drive \( P_E \) that would place the system at a working point just at the onset of oscillatory activity in an isolated, noiseless WC unit, or below the Hopf bifurcation altogether. We consider the former of these two possibilities first. In particular, we let \( P_{E,j} = 1.25 \) for \( j \in \{1, 2\} \) (and keep \( P_{I,j} = 0 \) for \( j \in \{1, 2\} \) as before). For this input level (in contrast to the previously examined working point), a deterministic, uncoupled node is very near to the Hopf bifurcation, and exhibits oscillations of almost vanishing amplitude (Fig. 3.5A, Left). When two noiseless areas are then coupled with \( G_{EE} = 0.3 \) and \( T_D = 1.5 \), the oscillation amplitude in each area increases significantly, but rather than out-of-phase locking, the two regions lock in-phase (Fig. 3.5A, Right). Consequently, there is no collective multistability in the network; only the single in-phase state occurs. Moreover, when stochastic background drive with relatively low \( \sigma = 0.15 \) and high \( \alpha = 15 \) is incorporated into the network, the distribution of phase differences exhibits a broad peak centered around \( \Delta \theta = 0 \) (Fig. 3.5B).

Interestingly, though, the general form of the phase difference distribution in this case depends on the noise parameters. For example, when \( \sigma \) is increased (Fig. 3.5C, Left) or when \( \alpha \) is decreased (Fig. 3.5D, Left) the symmetry around \( \Delta \theta = 0 \) is broken, and two clear peaks emerge in the distributions of \( \Delta \theta \) that correspond to the emergence of probable out-of-phase configurations. Examination of the time series for these alternate noise values (Figs. 3.5C and D, Right) indeed reveals the existence of transient synchrony and spontaneous switching between the different lead-lag relations. However, the metastable out-of-phase states at this working point arise for different reasons than their appearance at the \( P_E = 1.35 \) working point. At the higher drive working point, the network exhibited out-of-phase locking in the absence of noise, and the peaks in \( P_{\Delta \theta} \) were signatures of those underlying states. In contrast, the peaks for the lower-drive working point considered here are not truly blurred versions of states that exist in the deterministic scenario. Rather, the out-of-phase configurations are themselves induced by the stochastic fluctuations in the level of the input.

There are at least two ways the noise could cause the aforementioned behavior in the network’s dynamics. First, it could be that the input fluctuations transiently push the system into
a dynamical regime where – in a noiseless network subject to the same instantaneous levels of background drive – multistable out-of-phase locking would arise as it does for the higher drive working point. Alternatively, it could also be the case that stochastically fluctuating asymmetries in the level of background drive to each area in the network translate into dynamical asymmetries where one area briefly becomes the leader or lagger. Note that in both of these scenarios, the input needs to fluctuate significantly away from its mean value in order to induce the observed behavior, which provides some intuition for why $\sigma$ ($\alpha$) needs to be high (low) enough to induce the effects.

In our final analysis of this section, we consider a third working point where the background drive is even slightly smaller and set to $P_{E,j} = 1.20$ for $j \in \{1, 2\}$. In this regime, a deterministic and isolated WC unit is below the Hopf bifurcation and does not intrinsically oscillate (Fig. 3.5E, Left). Additionally, in contrast to the previous working point, coupling two areas with $G_{EE} = 0.3$ and $T_D = 1.5$ does not induce oscillatory activity either (Fig. 3.5E, Right). Thus, in this regime, the oscillations themselves are noise-driven. Starting again with relatively low $\sigma = 0.15$ and relatively high $\alpha = 15$ for the background noise, we observe that the phase difference distribution is very flat and unstructured (Fig. 3.5F). But, similar to before, increasing $\sigma$ (Fig. 3.5G) or decreasing $\alpha$ (Fig. 3.5H) brings about the two metastable peaks in $P(\Delta \theta)$. Because at this working point the system is even further from the regime in which multistable out-of-phase locking arises in the absence of noise, the preferred out-of-phase configurations observed in this case are likely induced by transient differences in the levels of instantaneous background drive to the two areas in the network.

Behavior of 4-area circuits: Deterministic scenario

In this section, we consider a slightly more complicated anatomical network composed of four identical, interacting neural populations coupled in an all-to-all topology (Fig. 3.6B). We also assume that the coupling strengths and the time-delays are identical for all pairs of regions. As for the 2-node system, we begin by quantifying the dynamical behaviors of the 4-area circuit in the deterministic scenario where each excitatory subpopulation receives a constant background drive of strength $P_E$. In particular, we consider the case $P_{E,i} = 1.325$ for all $i \in \{1, \ldots, 4\}$, for which an isolated WC unit with the default parameters exhibits rhythmic population activity (Fig. 3.6A). Because we are interested in the phenomena of interareal coherence, we first examine whether the network phase-locks as a function of the two main network properties: the coupling strength $G_{EE}$ and the time-delay $T_D$. 

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In order to determine the extent of phase-locking between regions’ oscillatory activity, we consider the phase-locking value $\rho_{ij}$ between a given pair of areas $i \neq j$ (see Sec. 3.2.5, 3.2.6). More specifically, for each parameter combination, we first run 100 separate 7-second simulations (where each simulation uses a different set of random initial conditions). For each simulation and each pair of regions, we then compute $\rho_{ij}$ using the last 2 seconds of the activity time-series. We then calculate an average phase-locking value $\langle \rho_{ij} \rangle$ by computing the mean of the $\rho_{ij}$’s across all region pairs and across the 100 simulations. We show $\langle \rho_{ij} \rangle$ as a function of $G_{EE}$ and $T_D$ in Fig. 3.6C, from which we observe that different portions of parameter space give rise to different behaviors in terms of the extent of phase-locking. In particular, we find that $\langle \rho_{ij} \rangle \approx 1$ for low delay and high coupling and also for intermediate-to-high delays at all couplings considered. Hence, the network indeed phase-locks for a large set of the depicted parameter combinations.

Interestingly, though, there is a regime in between where – for a range of low-to-intermediate delays – the average phase-locking clearly dips well below the maximum value of 1. This decrease in $\langle \rho_{ij} \rangle$ indicates that for the corresponding portion of parameter space, there is no fixed phase relation between the different areas’ activity and the network is not phase-locked.

Figure 3.5 (following page): Baseline phase-locking behavior of a 2-area network with stochastic background input in the low drive regime. (A) Here we study a 2-area neural mass network where each unit receives an independent stochastic background drive with $P_E = 1.25$ and $P_I = 0$, and where $G_{EE} = 0.3$ and $T_D = 1.5$ ms. For context, we first show the time-series of an uncoupled, deterministic WC unit (left) and the time-series of two coupled, deterministic WC units (right). (B) The distribution of phase differences between the two coupled areas across a long simulation for $\alpha = 15$ and $\sigma = 0.15$. (C) Left: Activity time-courses of the two areas. Right: The distribution of phase differences between the two coupled areas for $\alpha = 15$ and $\sigma = 0.25$. (D) Left: Activity time-courses of the two areas. Right: The distribution of phase differences between the two coupled areas for $\alpha = 5$ and $\sigma = 0.15$. (E) Here we study a 2-area neural mass network where each unit receives an independent stochastic background drive with $P_E = 1.20$ and $P_I = 0$, and where $G_{EE} = 0.3$ and $T_D = 1.5$ ms. For context, we first show the time-series of an uncoupled, deterministic WC unit (left) and the time-series of two coupled, deterministic WC units (right). (F) The distribution of phase differences between the two coupled areas across a long simulation for $\alpha = 15$ and $\sigma = 0.15$. (G) Left: Activity time-courses of the two areas. Right: The distribution of phase differences between the two coupled areas for $\alpha = 15$ and $\sigma = 0.25$. (H) Left: Activity time-courses of the two areas. Right: The distribution of phase differences between the two coupled areas for $\alpha = 5$ and $\sigma = 0.15$. Note: In all of the $\Delta \theta$ distributions, the gray vertical lines correspond to the stable phase differences for the selected parameters, but in the absence of noise.
CHAPTER 3.

noiseless coupled

\[ \alpha = 15, \sigma = 0.15 \]

noiseless uncoupled

\[ \alpha = 15, \sigma = 0.25 \]

\[ \alpha = 5, \sigma = 0.15 \]

\[ \alpha = 15, \sigma = 0.25 \]

\[ \alpha = 5, \sigma = 0.15 \]

noiseless coupled

\[ P_{E} = 1.25 \]

\[ P_{E} = 1.20 \]
To further unpack the nature of the system’s collective dynamics, we focus on a fixed coupling strength $G_{EE} = 0.2$ and study network activity for different values of the delay $T_D$ (Fig. 3.6D). As determined by the phase-locking value, when the delay is relatively low (e.g. 1 ms), the activity time-series reveal phase differences that shift across time (Fig. 3.6D, Left). In this regime, the dynamics are quasiperiodic in nature, and the relative lead-lag relationships change slowly as the dynamics evolve. Quasiperiodic dynamics have indeed been shown previously to arise in the WC model as well as other coupled neural mass models [151, 150, 291, 292]. Although interesting, we do not explore this regime further, as we focus in this study on phase-locked states.

If we instead consider the opposite end of the spectrum and examine a large delay (e.g. $T_D = 4$ ms), the collective dynamics of the network change (Fig. 3.6D, Right). Here, we observe the emergence of phase-locking between the regional oscillations in the form of a 2-cluster anti-phase state where a given pair of nodes is in-phase with one another and anti-phase with the other pair. This type of collective state has been observed in other types of coupled neural oscillator systems [293], and in the context we consider, could perhaps underlie a situation in

Figure 3.6 (following page): Baseline phase-locking behavior of a 4-area network with deterministic background input. (A) Oscillatory activity exhibited by an isolated WC unit subject to deterministic background input with $P_E = 1.325$. (B) We study a 4-area neural mass network composed of four units identical to that shown in panel (A) and coupled in an all-to-all fashion. For convenience, we label each of the four areas (depicted in the different colors) “1”, “2”, “3”, and “4”. (C) The average phase-locking value $\langle \rho_{ij} \rangle$ of the network as a function of the time-delay $T_D$ and the coupling strength $G_{EE}$. The average was taken across all pairs of units and across 100 simulations with different initial conditions. (D) We consider system behavior for a fixed coupling $G_{EE} = 0.2$ and for three different values of the delay $T_D$. Top: If the dynamics are phase-locked for the given delay, a polar plot is shown that depicts the unique phase differences observed between area 1 and area 2 from 100 simulations with different initial conditions. These phase differences were determined by computing the phase relation between areas 1 and 2 in each simulation, assigning each phase difference into 1 of 100 equally spaced bins that span the interval $[0, 2\pi]$, and then collecting the non-empty bins. Bottom: For each delay, a segment of the regions’ activity time-series from one instantiation of the dynamics. (E) For a delay $T_D = 2.5$ ms, there exist six different multistable collective states $\{S_1, \ldots, S_6\}$, each characterized by a distinct temporal ordering of the activity peaks (or phases) of different units. We write the phase-ordering and show time-series segments for each state. (F) The fraction of initial conditions that lead to each of the six configurations, computed across 2000 total simulations instantiated with different random initial conditions.
CHAPTER 3.

A uncoupled

B couple

C 

D 

E multistable collective states

F 


GEE = 0.2

not phase-locked

S1: 1 → 4 → 2 → 3 → 1

S2: 1 → 3 → 2 → 4 → 1

S3: 1 → 2 → 4 → 3 → 1

S4: 1 → 2 → 3 → 4 → 1

S5: 1 → 4 → 3 → 2 → 1

S6: 1 → 3 → 4 → 2 → 1

TD = 4 ms

TD = 2.5 ms

TD = 1 ms

GEE = 0.2

Figure showing the transition of states and activity over time with different delays.
which the in-phase pair of units can transfer information between themselves, but with minimal routing allowed between the well-separated out-of-phase pairs [113, 110, 294]. The bottom panel of Fig. 3.6D, Right shows an example where unit 1 and unit 3 are in-phase, and collectively out-of-phase with areas 2 and 4 (which are themselves in-phase). Importantly, though, this is a multistable dynamical regime in that a different set of initial conditions could lead to different pairs of units being in-phase with one another. Indeed, the top panel of Fig. 3.6D, Right is a polar plot showing the unique phase relations that arise between region 1 and region 2 across a set of 100 simulations each started with a different random initial condition. Note that both the anti-phase relationship and the in-phase relationship occur.

At an intermediate delay (e.g. $T_D = 2.5$ ms), yet a third dynamical regime is observed where the network is again phase-locked, but the pattern of phase relationships is different from that of the 2-cluster state (Fig. 3.6D, Middle). In particular, for these parameters the system settles into a state where the regional activities peak one after another sequentially in time, and such that the spacing is equal between consecutive pairs. In this way, in a reference frame that moves with the same constant frequency as each unit, the collective states would correspond to the phases of the four areas being fixed in an arrangement where they are spread uniformly around the unit circle. The bottom panel of Fig. 3.6D, Middle shows the activity time-courses for one such collective state characterized by the peak-ordering (or phase-ordering) $1 \rightarrow 4 \rightarrow 2 \rightarrow 3 \rightarrow 1$. For this configuration, $\Delta \theta_{1,2} = \pi$, $\Delta \theta_{1,3} = -\pi/2$ and $\Delta \theta_{1,4} = \pi/2$. Under the assumption that information flows preferentially from a phase-leading area to a phase-lagging area, this state could enable a scenario where region 1 sends information to unit 4, receives information from area 3, and does not communicate with region 2 (see Sec. 3.4 for a discussion on how one could more explicitly quantify information routing for a given set of phase relations by employing information-theoretic measures [113, 112, 277]). Crucially, though, the aforementioned pattern of phases again corresponds to one of only a larger set of collective states that are all multistable. For the example times-series shown, $\Delta \theta_{1,2} = \pi$, but the data in Fig. 3.6D, Middle & Top show that for different initial conditions, both $\Delta \theta_{1,2} = \pi/2$ and $\Delta \theta_{1,2} = -\pi/2$ also occur. Hence, we again have the situation where a single anatomical network is able to support several collective states.

Although the model brain circuit exhibits collective dynamical multistability for both the working points in Fig. 3.6D, Middle and in Fig. 3.6D, Right, we focus our subsequent analyses on the former scenario for which the out-of-phase relations may interestingly support directed functional interactions from a nonetheless undirected anatomical coupling structure. In this
regime, we can define six unique, stable states of the network \( \{S_1, ..., S_6\} \), where each state corresponds to a distinct temporal ordering of the regions’ phases (Fig. 3.6E). For example, in state \( S_1 \), the phases arrange in the repeating pattern \( 1 \rightarrow 4 \rightarrow 2 \rightarrow 3 \rightarrow 1 \), whereas in state \( S_2 \) the configuration is instead \( 1 \rightarrow 3 \rightarrow 2 \rightarrow 4 \rightarrow 1 \). Across many random initial conditions, each of these collective operating modes occurs with nearly equal likelihood (Fig. 3.6F), as expected. (Note that the small deviations from a perfectly equal fraction across all six states likely arise due to finite numerical sampling of the space of initial conditions). Working under the assumptions that the phase-locking of neural rhythms establishes a substrate for interareal communication, and that different lead-lag relationships enable different communication channels, each of the six emergent multistable states here could potentially allow for entirely different global information routing capabilities. It is this hypothesis that motivates our examination of how such multistability can be controlled via targeted dynamical perturbations to the network.

It is also important to note that for different values of the delay, the 4-area circuit exhibits dynamical regimes other than those illustrated in Fig. 3.6D. For example, at a delay of 3.5 ms, 500 numerical simulations that use different random initial conditions indicate that three families of multistable collective states are possible at a single model working point (see Fig. B.1 in Sec. B). The first group of phase-locked configurations corresponds to those depicted in Fig. 3.6D, Middle (Fig. B.1, Top), and the second group corresponds to those depicted in Fig. 3.6D, Right (Fig. B.1, Top). However, we also observe that some initial conditions give rise to an altogether distinct class of collective states wherein the activity of two regions locks in-phase, with the other two areas’ activity leading or lagging the in-phase cluster by \( 3\pi / 4 \) radians (Fig. B.1, Bottom). In this latter family of states, there are twelve multistable patterns. Hence, for this alternate value of the interareal delay, multistability arises both in terms of the family of states that exists, and also within each family itself. Further possibilities may arise at other delays between those shown in Fig. 3.6. Though we do not attempt it here, an analytical study of the system’s dynamics may enable a more complete mapping of the network’s collective states as a general function of the circuit parameters. As noted in the previous paragraph, the remainder of our analyses on the 4-area network will focus on the case illustrated in Fig. 3.6D, where there are six multistable states characterized by a uniform distribution of the units’ phases around the unit circle, but each with a unique relative ordering.
CHAPTER 3.

Behavior of 4-area circuits: Stochastic scenario

We conclude our analysis of the model’s baseline dynamical regimes by studying the effects of noise in the 4-area network (Fig. 3.7A). We incorporate stochasticity in the same way as for the 2-area circuit, which is by making the background inputs to the excitatory and inhibitory populations of each area evolve according to independent OU processes characterized by an inverse correlation time $\alpha$ and noise strength $\sigma$ (Eqs. 3.3a and 3.3b). Because a large amount of data is required to accurately map out the system’s dynamics in the noisy regime, the following analyses are based on a very long simulation of 22 minutes in length.

In order to understand how a stochastically fluctuating environment affects collective activity patterns, we examine the scenario in which an isolated deterministic WC unit intrinsically oscillates, and when the four regions are coupled, the network phase-locks into one of six unique multistable states (see Sec. 3.3.1). Throughout this section, we fix the input to the excitatory subpopulations at $P_{E,j} = 1.3^3$ for $j \in \{1, \ldots, 4\}$, the input to the inhibitory subpopulations at $P_{I,j} = 0$ for $j \in \{1, \ldots, 4\}$, the network coupling strength to $G_{EE} = 0.25$, and the interareal time delay to $T_D = 2.5$ ms. Fig. 3.7B, Left shows the intrinsic rhythm of a noiseless, uncoupled

![Figure 3.7](following page): Baseline phase-locking behavior of a 4-area network with stochastic background inputs. (A) We study a 4-area neural mass network, where the excitatory and inhibitory subpopulations within each area receive independent stochastic background drives generated from an OU process (blue and red inputs in the schematic). For this analysis, we set $P_E = 1.3, P_I = 0, G_{EE} = 0.25$, and $T_D = 2.5$ ms. When we make the background inputs stochastic, we use parameters $\alpha = 10$ and $\sigma = 0.2$. (B) Left: Time-series of an uncoupled, deterministic WC unit. Right: Example time-series of four all-to-all coupled deterministic WC units, where in this case, the system is in state $S_6$ characterized by the ordering $1 \rightarrow 3 \rightarrow 4 \rightarrow 2 \rightarrow 1$. (C) A snapshot of the network’s activity when the neural populations are driven by a noisy environment. Note the spontaneous switch from collective state $S_4$ to collective state $S_3$ at $t \approx 15.6$ seconds. (D) The distribution $P(\Delta \theta_{1,2})$ of the pairwise phase differences between area 1 and area 2 across a long simulation of the system. (E) The joint distribution $P(\Delta \theta_{1,2}, \Delta \theta_{1,3})$ of $\Delta \theta_{1,2}$ and $\Delta \theta_{1,3}$ across a long simulation. (F) In gray is the distribution $P(\Delta \theta_{1,2})$, and in purple is the conditional distribution $P(\Delta \theta_{1,2} | \Delta \theta_{1,3} \approx \Delta \theta_* \& \Delta \theta_{1,4} \approx -\Delta \theta_*)$ across a long simulation of the network. More specifically, we estimate the probability of observing a particular phase relation between areas 1 and 2, given that the conditions (1) $\pi/2 - \pi/6 < \Delta \theta_{1,3} < \pi/2 + \pi/6$ and (2) $-\pi/2 - \pi/6 < \Delta \theta_{1,3} < -\pi/2 + \pi/6$ are both satisfied. (G) A 10-second-long segment of the system that shows which of the six collective states is occupied (indicated by the thick gray bars) as a function of time.
CHAPTER 3.

A noiseless coupled

B noiseless uncoupled

C

D

E

F

G

119
WC unit with these parameters, and we show a recap of the deterministic activity time-series for the coupled 4-area circuit in Fig. 3.7B, Right. In this example, the system has settled into state $S_6$, in which the repeating ordering of the phases is $1 \rightarrow 3 \rightarrow 4 \rightarrow 2 \rightarrow 1$ and all phase differences $\Delta \theta_{i,j}$ take on values in the set $\{-\pi/2, \pi, \pi/2\}$.

To study the effects of noisy background drive, we now let the inputs to the E and I subpopulations of each region – $P_{E,j}(t)$ and $P_{I,j}(t)$ – evolve according to OU processes. In what follows, in addition to fixing the long-term means $\overline{P_{E,j}}$ and $\overline{P_{I,j}}$, we also fix the speed of mean reversion to $\alpha = 10$ and the noise strength to $\sigma = 0.2$. (We will briefly study the consequences of changing these two quantities at the end of this section). With the chosen parameters, we observe that regional activity becomes slightly more irregular over time, exhibiting both variation in oscillation amplitude and instantaneous frequency (Fig. 3.7C). In addition, while approximate phase-locking is still observed within certain time-segments, the relative phase relations become less rigid and fluctuate with some spread around the set of values $\Delta \theta \in \{-\pi/2, \pi, \pi/2\}$ observed in the noiseless case.

Nonetheless, it is still perfectly possible to define looser versions of six original collective states that emerge in the noiseless limit, and to track the temporal evolution of these patterns. For example, one could define states in the stochastic system by demanding that the set of instantaneous, pairwise phase differences $\{\Delta \theta_{i,j\neq i}(t)\}$ for $i, j \in \{1, ..., 4\}$ be close to the set of values observed in one of the noiseless collective states. This choice would require setting a threshold $\delta$ that defines an allowed spread around the noiseless phase relations $\Delta \theta \in \{-\pi/2, \pi, \pi/2\}$, and checking whether the instantaneous phase differences in the stochastic network meet the criteria. Either the criteria would be met and the particular set of phase differences would define the state label, or the criteria would not be met and one would conclude that at the given time, the network was not in any of the six pre-specified states. We elaborate on and use this state extraction method in later sections, but for the purposes of this exposition, we consider the simplest (and least strict) way of defining the network state at a given time, which is to just consider the instantaneous ordering of the phases (or activity peaks) of each unit.

Applying this simple state-extraction method to the activity time-series illustrated in Fig. 3.7C, we observe an example of spontaneous state-switching. At the beginning of the depicted time-window, the network is in a noisy version of state $S_4$ characterized by the phase ordering $1 \rightarrow 2 \rightarrow 3 \rightarrow 4 \rightarrow 1$. But at around $t \approx 15.6$ seconds, the green and the red area speed up/slow down relative to one another, which causes them to switch places. In turn, this switch induces a change in the collective activity pattern to a noisy version of state $S_3$ characterized by the
new ordering $1 \to 2 \to 4 \to 3 \to 1$. This behavior brings to light the important fact that the stochastically fluctuating environment that drives the network can induce random transitions in the system’s collective dynamics. In other words, the noise-driven variability in single areas’ activity can – at times – bring about an actual change in the network’s phase-locking pattern as a whole. Although a consequence of noise, such spontaneous state-switching may actually be beneficial to system function in some scenarios [112].

The fact that the network undergoes random transitions between noisy realizations of the collective states that exist in the absence of noise can perhaps be better recognized by examining distributions of the instantaneous phase relations across a very long simulation. We focus first on the distribution $P(\Delta \theta_{1,2})$ between a given pair of units 1 and 2 (note that any pair of units $i \neq j$ gives similar results). For the chosen parameters, this distribution exhibits three clear peaks located near the set of phase differences that arise in the deterministic limit (Fig. 3.7D). The presence of these modes indicates that even with some noise, there are still preferred dynamical configurations that the system moves between as it evolves. We can conclude from this analysis that in these preferred arrangements, the phase relation between a single pair of units fluctuates (approximately) around one of the three stable $\Delta \theta$’s from the deterministic scenario. Hence, though the network no longer exhibits perfect phase-locking, its dynamics are still structured and reminiscent of the noiseless case.

It is even more enlightening to estimate the joint distribution $P(\Delta \theta_{1,2}, \Delta \theta_{1,3})$ of $\Delta \theta_{1,2}$ and $\Delta \theta_{1,3}$. Doing so reveals six “hotspots” of particularly high likelihood (Fig. 3.7E). Furthermore, these frequently visited configurations correspond to both of the phase relations simultaneously occupying values close to what they would be if the system were in one of the six collective phase-locked patterns from the deterministic simulations. In particular, the high-density areas correspond to either $\Delta \theta_{1,2} \approx \pi/2$, $\Delta \theta_{1,3} \approx \pi$, $\Delta \theta_{1,2} \approx \pi/2$ and $\Delta \theta_{1,3} \approx -\pi/2$, $\Delta \theta_{1,2} \approx \pi$ and $\Delta \theta_{1,3} \approx \pi/2$, $\Delta \theta_{1,2} \approx \pi$ and $\Delta \theta_{1,3} \approx -\pi/2$, $\Delta \theta_{1,2} \approx -\pi/2$ and $\Delta \theta_{1,3} \approx \pi/2$, or $\Delta \theta_{1,2} \approx -\pi/2$ and $\Delta \theta_{1,3} \approx \pi$. The hotspots in the joint distribution are thus signatures of the six multistable attractors of the collective dynamics that we observed in the noiseless setting. In the presence of stochastic inputs, these states become blurred but still discernible versions of their noiseless selves. Moreover, adding stochastic fluctuations in the driving background environment allows the network to sample its state-space and spontaneously transition in and out of these different configurations. But, because these favored configurations correspond to stable valleys in the dynamical landscape, the network still tends to dwell near them.

To further analyze the collective dynamics of this system, we also estimate the conditional
distribution \( P(\Delta \theta_{1,2}|\Delta \theta_{1,3} \approx \Delta \theta_\ast \& \Delta \theta_{1,4} \approx -\Delta \theta_\ast) \) and compare it to the unconditioned distribution \( P(\Delta \theta_{1,2}) \) (Fig. 3.7F). More specifically, for the conditional distribution, we estimate the probability of observing a particular phase relation between areas 1 and 2, given that both (1) \( \pi/2 - \pi/6 < \Delta \theta_{1,3} < \pi/2 + \pi/6 \) and (2) \( -\pi/2 - \pi/6 < \Delta \theta_{1,3} < -\pi/2 + \pi/6 \) are satisfied. The purpose of this analysis is to further convince ourselves that if both \( \Delta \theta_{1,3} \) and \( \Delta \theta_{1,4} \) simultaneously take on values that would put the system near one of the six states from the noiseless case, then the third phase relation \( \Delta \theta_{1,2} \) fills the remaining condition for that state to be in existence. Indeed, the reduction of the peaks in the conditional distribution near \( \Delta \theta_{1,2} \approx \pm \pi/2 \) and the boosted peak near \( \Delta \theta_{1,2} \approx \pi \) support this conclusion.

Finally, we show in Fig. 3.7G the state occupation as a function of time across a relatively long 10-second window. For this analysis, we use the simple state-extraction method described above based on the ordering of the units’ phases. This figure illustrates the evolution of the network’s collective activity patterns and the spontaneous transitions between configurations. Note that for the chosen parameter set, the system often dwells in a particular state for on the order of \( \sim 1 \) second. Hence, although the network does switch between different states, this switching occurs on a relatively slow time-scale relative to the oscillation period.

We conclude this section by briefly studying the effects of the noise parameters \( \alpha \) and \( \sigma \). In general, we find results similar to those found for the 2-area network, and we refer the reader to Sec. 3.3.1 for a detailed discussion. First, we observe that increasing the noise strength \( \sigma \) (Fig. 3.8A) or decreasing the speed of mean reversion \( \alpha \) (Fig. 3.8D) both have the effect of reducing the height and broadening the width of the peaks in the phase difference distribution \( P(\Delta \theta_{1,2}) \) (note that the conclusions are similar for any pair of units \( i \neq j \)). Hence, these two parameters control the tightness of phase-locking in the network and the “blurriness” of the collective states relative to the deterministic limit. Importantly, if \( \sigma \) is too large (Fig. 3.8B) or if \( \alpha \) is too small (Fig. 3.8E), then the noise itself destroys the dynamical behavior of interest. In particular, if the network is overly noisy, then it is not possible to discern three clear peaks in the phase difference distributions \( P(\Delta \theta_{1,2}) \) (for both the cases of large \( \sigma \) and low \( \alpha \), the original mode at \( \Delta \theta_{1,2} \approx \pi \) is washed out). This, in turn, indicates the degradation of the phase-locking patterns that we wish to analyze. Going forward, we always work in a parameter regime where the stochastic network exhibits clear signatures of the collective states observed in the noiseless scenario.

We also examine the mean duration of collective states as a function of the noise parameters \( \alpha \) and \( \sigma \). In other words, how long – on average – does it take for the system to undergo a spon-
Figure 3.8: Effect of varying the noise parameters on the dynamics of a 4-area network with stochastic background inputs. For this analysis, we set $P_E = 1.3$, $P_I = 0$, $G_{EE} = 0.25$, and $T_D = 2.5$ ms. (A) For $\alpha = 10$, the distribution of phase differences $P(\Delta \theta_{1,2})$ between area 1 and area 2 for varying $\sigma$ ($\sigma = \{0.125, 0.15, 0.175, 0.2, 0.225, 0.25\}$, increasing as the curves go from light to dark). (B) Close-up of $P(\Delta \theta_{1,2})$ for $\alpha = 10$ and $\sigma = 0.25$. (C) The mean state duration $\langle L_s \rangle$ as a function of the noise strength $\sigma$. (D) For $\sigma = 0.2$, the distribution of phase differences $P(\Delta \theta_{1,2})$ between area 1 and area 2 for varying $\alpha$ ($\alpha = \{5, 10, 15, 20\}$, increasing as the curves go from light to dark). (E) Close-up of $P(\Delta \theta_{1,2})$ for $\sigma = 0.2$ and $\alpha = 5$. (F) The mean state duration $\langle L_s \rangle$ as a function of the reversion speed $\alpha$. 
taneous state transition? Accordingly, we extract the temporal evolution of the network’s state across a long simulation using the naive method that considers only the relative ordering of the units’ phases at a given moment. From this state “vector”, we calculate a set of state durations \( \{L_s\} \) by computing the lengths of time for which the network uninterruptedly remains in the same state before switching to a new configuration. The mean state duration \( \langle L_s \rangle \) is then calculated as the average of this set. Similar to the 2-area circuit, we find here that the mean duration \( \langle L_s \rangle \) decreases with increasing \( \sigma \) (Fig. 3.8C) or decreasing \( \alpha \) (Fig. 3.8F).

### 3.3.2 Investigating the effects of local perturbations on collective dynamical states

In the previous sections, we mapped out the dynamical behaviors of the 2-area and 4-area model brain circuits under baseline conditions. That is, we characterized each system in the absence of any perturbations. We also separately studied network activity patterns in the limit of deterministic background inputs and for stochastically fluctuating drives. Because our study is concerned with how functional connectivity may be flexibly modulated via external inputs, we focused the deterministic analyses on working points where multistable phase-locking emerged in the network dynamics, and we systematically quantified those states. For the stochastic scenario, we then identified parameter regimes where the collective dynamics manifested as noisy or blurred versions of the activity patterns that arose in the deterministic limit, such that the extraction of well-defined (but transient) collective states was still possible.

Having identified baseline parameter regimes of interest, we are now prepared to move on to the crux of our study: an investigation of how collective phase-locking patterns in multiarea brain circuits respond to different local dynamical perturbations. In particular, we are motivated by the question of how functional network states could be rapidly reconfigured via modulatory inputs, bypassing the need for difficult and costly structural modifications. To that end, the rest of the results section is organized as follows. In Sec. 3.3.3, we recap how a single Wilson-Cowan neural mass responds to brief input pulses and rhythmic stimulation. In Sec. 3.3.4, we study how the 2- and 4-area networks respond to brief input pulses applied to one area, and we consider both the deterministic and stochastic situations. In Sec. 3.3.5, we then examine how both circuits respond to rhythmic inputs applied to a single region, and we again separately study both the deterministic and stochastic settings. Finally, in Sec. B, we consider the robustness of various results to changes in the baseline model parameters.
3.3.3 Response of an isolated Wilson-Cowan unit to external inputs

In order to understand how a collective phase-locking state in a network of WC units responds to local perturbations, it is first helpful to consider how an isolated WC unit reacts. As described in Sec. 3.2.3, the two types of stimulation we study are (1) transient pulse inputs, and (2) sustained rhythmic inputs. Below, we examine how an uncoupled WC neural mass responds to each of these kinds of external signals in turn.

Pulse inputs

In this section, we present results regarding the response of a single WC unit to short input pulses. In what follows, we set the background input level to $P_E = 1.3$, such that the neural mass intrinsically oscillates at baseline (Fig. 3.9B). We then inject a square-wave input of some amplitude $A_s > 0$ and some duration $T_s > 0$ into the excitatory subpopulation of the WC oscillator (Fig. 3.9A offers a schematic of the model setup). As noted previously in Sec. 3.2.3 (which provides details on the protocol for the pulse stimulation), the effect of a brief perturbation on an oscillating system also depends on the phase of the ongoing oscillation at which the perturbation is applied, in addition to the strength and duration of the pulse. In particular, stimulation applied at different “onset phases” can transiently change the oscillation period by different amounts and

Figure 3.9 (following page): Response of an isolated Wilson-Cowan unit to pulse inputs. (A) Schematic of the model setup. We study the response of an isolated, oscillatory WC neural mass to an external input pulse of duration $T_s$, amplitude $A_s$, and onset phase $\theta_{on}$. The perturbation targets the excitatory subpopulation. (B) Activity time-series of the neural mass at baseline. The black dots show different stimulation times, which correspond to different phases $\theta_{on}$ of the ongoing oscillation. (C) Numerical phase-response curves for a fixed pulse amplitude $A_s = 1.5$ and varying $T_s$. Each curve shows the phase shift $\Delta \theta$ induced by a pulse input applied at different onset phases $\theta_{on}$. (D) Numerical phase-response curves for a fixed pulse duration $T_s = 1$ ms and varying $A_s$. Each curve shows the phase shift $\Delta \theta$ induced by a pulse input applied at different onset phases $\theta_{on}$. (E) Response of the oscillatory activity to a pulse of amplitude $A_s = 1.5$, duration $T_s = 1$ ms, and onset phase $\theta_{on} = 1.5$ rad (indicated by the vertical line). The gray time-series shows the unperturbed trajectory, and the yellow time-series shows the phase-delayed, perturbed trajectory. (F) Response of the oscillatory activity to a pulse of amplitude $A_s = 1.5$, duration $T_s = 1$ ms, and onset phase $\theta_{on} = 3.2$ rad (indicated by the vertical line). The gray time-series shows the unperturbed trajectory, and the yellow time-series shows the phase-advanced, perturbed trajectory.
CHAPTER 3.

A baseline activity

B baseline activity

C $A_s = 1.5$

D $T_s = 1.00 \text{ ms}$

E $\theta_{on} = 1.5 \text{ rad}$

F $\theta_{on} = 3.2 \text{ rad}$
even in different directions. These effects are often quantified with a phase-response curve (PRC) that measures the resulting shift in the oscillation phase induced by different perturbation onset phases [287, 286].

Here, we numerically compute PRCs for different pulse amplitudes and durations in order to quantify the response of a WC unit to brief pulse stimuli. In general, a perturbation can either cause a phase-advance or a phase-delay. A phase-advance occurs when the perturbation transiently shortens the oscillation period, causing the perturbed oscillation to begin a new cycle sooner than it would have without the perturbation. In contrast, a phase-delay occurs when the perturbation transiently lengthens the oscillation period, causing a delay in the next cycle relative to the unperturbed case. If we define the phase difference $\Delta \theta_s = \theta_p - \theta_o$ as the difference between the perturbed phase of the excitatory subpopulation $\theta_p$ and its original phase $\theta_o$, then $\Delta \theta > 0$ corresponds to a phase-advance and $\Delta \theta < 0$ corresponds to a phase-delay.

Concretely, we carry out the following steps to numerically compute PRCs. First, we run a 4-second simulation of the system with no perturbation applied. We then run a new simulation with the same initial conditions, allow the dynamics to settle for 1 second, and initiate the external pulse input the next time the ongoing oscillation phase is equal to a specific value $\theta_{on}$. We then assess the effect of the perturbation by computing the average phase difference between the unperturbed and perturbed phase time-series across a 1-second window that begins 1.5 seconds after the perturbation onset time. This process is repeated for 50 values of the onset phase $\theta_{on}$ spread uniformly in $[0, 2\pi]$, and the PRC is then computed as the curve of the induced phase shift $\Delta \theta$ as a function of $\theta_{on}$.

We plot numerical PRCs for a fixed pulse amplitude $A_s = 1.5$ and varying duration (Fig. 3.9C), and for a fixed pulse duration $T_s = 1.0$ ms and varying amplitude (Fig. 3.9D). In general, for fixed pulse parameters, the induced phase-shifts indeed depend heavily on the onset phase, peaking for specific values of $\theta_{on}$ and being near zero for others. (Recall that with our definition of the oscillation phase, $\theta_{on} = 0$ corresponds to the activity peaks). Furthermore, the maximum phase-shift across all onset phases increases with both the pulse duration and the pulse amplitude, as one would expect. For small pulse amplitudes or short pulse durations, perturbations induce mainly phase-advances (which correspond to positive phase-shifts in the PRCs). However, for strong enough or long enough stimulation, significant phase-delays (which correspond to negative phase-shifts in the PRCs) can also be induced. In fact, inputs of large enough strength or long enough duration can cause the PRC to become discontinuous [286], enabling both large phase-delays and phase-advances for certain onset phases. To see the effect of differently-timed
perturbations on the activity of the WC unit, we also show in Fig. 3.9E,F two examples of the activity time-series where the external input leads to either a phase-delay or a phase-advance. As we will see in coming sections, the analysis laid out here will provide a useful foundation and intuition for understanding the effects of pulse perturbations on phase-locking states in multiarea networks.

Sustained rhythmic inputs

![Figure 3.10: Response of an isolated Wilson-Cowan unit to rhythmic inputs. (A) Schematic of the model setup. We study the response of an isolated, oscillatory WC neural mass to a rhythmic external input signal with amplitude $A_s$ and frequency $f_s$. The perturbation targets the excitatory subpopulation. (B) The phase-locking value computed between the neural mass activity and the external stimulation.](image)

The second type of stimulation we consider is sustained rhythmic input. As described in Sec. 3.3.5, this is implemented by injecting a continuous sinusoidal drive of amplitude $A_s$ and frequency $f_s$ into the excitatory subpopulation of the WC unit (see Fig. 3.10A for a schematic). Here we are again interested in how the external input interacts with the ongoing oscillatory activity in the receiving neural mass. For this analysis, we thus set the baseline background drive to $P_E = 1.35$, which yields a rhythmic population firing rate in the isolated WC unit. The main effect we are interested in regarding the response to rhythmic stimulation is whether the neural population activity can phase-lock to the rhythm of the input, and how the phase-locking depends on the amplitude and the frequency of the external drive. This analysis is in anticipation of studying how collective phase-locking states in the multiregion networks respond when a single area is subject to a perturbation in the form of rhythmic drive.
To examine the response of an isolated WC unit to sinusoidal stimulation, we simulate system dynamics for 1 second without the external perturbation applied, and then turn on the stimulation for the remainder of a 6-second run. Phase-locking between the neural population activity and the external input is then quantified with the phase-locking value. In particular, we compute the PLV between the phase of the neural mass oscillation and the phase of the rhythmic input across a 1-second time window that begins 2 seconds after the initial onset of the stimulation. If the phase-locking value is equal to 1, this indicates that the oscillatory neural activity phase-locks to the external drive; otherwise, the two rhythms are incoherent.

We study the PLV as a function of the stimulation amplitude $A_s$ and the frequency offset $\Delta f_s = f_s - f_o$ between the stimulation frequency $f_s$ and the baseline oscillation frequency of the WC unit $f_o$ (Fig. 3.10B). This analysis reveals a classic triangular locking region, indicating that the population activity can more easily (i.e. with lower stimulation amplitude) lock to inputs that have frequencies more similar to its intrinsic oscillation speed. If the frequency offset is too large and the driving amplitude too low, phase-locking cannot be maintained. But, the locking region does expand (up to a certain point) along the frequency offset axis as the strength of the stimulation increases.

### 3.3.4 Pulse perturbations can induce state-switching in multiarea networks

Having gained intuition for how an isolated WC neural mass responds to different types of external input signals, we now seek to understand if and how localized perturbations can be used to control interareal phase-locking in multiarea brain circuits. We begin in this section by examining the response of network dynamics to brief stimulation pulses applied to only a single region in the larger system. Our analysis proceeds systematically along a direction of increasing complexity, beginning with 2-area and 4-area deterministic networks, and then moving on to 2-area and 4-area networks that operate in the presence of stochastic background inputs. In what follows, we establish circumstances where pulse perturbations are ineffective at modifying collective states, but also those where the perturbation can successfully induce switching between different functional connectivity patterns, hence enabling rapid state-selection in brain circuits that exhibit collective multistability.
2-area networks: Deterministic limit

In this section we consider 2-area networks that operate in the limit of deterministic background inputs, and with intrinsic and network parameters such that out-of-phase locking emerges in the collective dynamics. Sec. 3.3.1 provides an in-depth characterization of the baseline activity in this regime. Concretely, we consider parameters $P_{E,j} = 1.35$ for $j \in \{1, 2\}$, $G_{EE} = 0.2$, and $T_D = 1.5$ ms. Fig. 3.11B shows a segment of the activity time-series that illustrates one of the two possible multistable states. As described in Sec. 3.2.3, a local pulse perturbation is enacted by stimulating the excitatory subpopulation of one of the areas in the circuit with a square wave pulse of amplitude $A_s > 0$, duration $T_s > 0$, and at an onset phase $\theta_{on}$ of the ongoing oscillation (Fig. 3.11A).

In an isolated unit, we saw that precisely-timed external input pulses could cause the oscillatory activity to permanently advance or delay its phase relative to baseline. For the 2-area circuits, we are interested not only in the question of whether a pulse applied to one of the regions can cause phase-shifting locally, but also in the question of whether the perturbation can actually induce a switch in the network’s collective phase-locking state. That is, if the network is in state $S_2$ (unit 2 leads unit 1) at baseline, can an incoming pulse that targets either area 1 or area 2 bring about a state transition $S_2 \rightarrow S_1$, such that area 1 comes to lead area 2? Given the notion that

Figure 3.11 (following page): Response of a deterministic 2-area network to brief pulse perturbations. (A) Schematic of the model setup. We study the response of a deterministic 2-area brain circuit to a brief input pulse of amplitude $A_s$ and duration $T_s$. The perturbation targets only one of the two regions, which in this case is the area that leads in phase. Throughout, we set $P_E = 1.35, G_{EE} = 0.2$, and $T_D = 1.5$ ms. (B) Activity time-series of the two regions under baseline conditions. The network locks into collective state $S_2$, where area 2 leads area 1 in phase. (C) Surface plot that shows whether an external input pulse causes a switch in the phase-locking pattern (white area) as a function of the onset phase $\theta_{on}$ and the pulse duration $T_s$. (D) Surface plot that shows whether an external input pulse causes a switch in the phase-locking pattern (white area) as a function of the onset phase $\theta_{on}$ and the pulse amplitude $A_s$. (E) Activity time-series that shows the effects of a pulse perturbation applied to the purple area at the time denoted by the black line (pulse parameters are $A_s = 1, T_s = 5.5$ ms, $\theta_{on} = 1$ rad). The external input causes the purple area to undergo a phase-delay, which switches the phase-locking pattern. (F) Activity time-series that shows the effects of a pulse perturbation applied to the purple area at the time denoted by the black line (pulse parameters are $A_s = 1, T_s = 5.5$ ms, $\theta_{on} = \pi$ rad). The external input causes the purple area to undergo a slight phase-advance, and the phase-locking pattern is maintained.
CHAPTER 3.

A baseline

C

D

\( \theta_{on} = 1.0 \text{ rad} \)

\( \theta_{on} = 3.14 \text{ rad} \)

1

2

switch

no switch

E

F

\( \theta_{on} = 1.0 \text{ rad} \)

\( \theta_{on} = 3.14 \text{ rad} \)

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different lead-lag relationships may enable different pathways for information routing, the ability to control these configurations without rewiring structural connections could have important functional implications.

To answer this question, we first run a baseline simulation without a perturbation applied. In this case, the system quickly flows towards one of its stable phase-locking configurations. For the example shown in Fig. 3.11B, the network locks into collective state $S_2$, where region 2 leads region 1 in phase. We then run a second simulation using the same initial conditions, and again allow the system ample time (3 seconds) to fully settle into the same attractor. Then, unlike in the baseline simulation, we activate an external perturbation to the leading area (here area 2) at the next time its oscillation phase is equal to $\theta_{on}$. This process is repeated anew for 50 onset phases $\theta_{on}$ spaced evenly in the interval $[0, 2\pi]$ in order to examine the dependence on the timing of the stimulation relative to the perturbed area’s ongoing rhythm. Note that because the perturbation is transient in nature, the system will eventually reequilibrate into one of its two stable collective states. The key point of the analysis is to compare the collective state of the network prior to the perturbation to the collective state after the network has recovered from the stimulation pulse. We do this by determining whether the phase difference $\Delta \theta$ between the two areas in the simulation with the perturbation applied switches sign relative to the phase difference from the baseline simulation. Specifically, we compare $\Delta \theta$ across a 1-second window that begins 2.5 seconds after the onset of the stimulation. If, the sign of $\Delta \theta$ changes, then we conclude that the perturbation does indeed induce a state transition.

Our results indicate that for sufficiently strong and long enough pulse amplitudes and durations, appropriately-timed external stimulation pulses can cause a switching of the network’s phase-locking configuration (Figs. 3.11C,D). In particular, Fig. 3.11C shows a surface plot of the state-switching region as a function of the pulse duration $T_s$ and onset phase $\theta_{on}$ for fixed amplitude $A_s = 1.0$, and Fig. 3.11D shows the same information as a function of the pulse amplitude $A_s$ and onset phase $\theta_{on}$ for fixed duration $T_s = 5.5$ ms. From these analyses, we observe that there are specific ranges of onset phases for which a transition in the collective state occurs. Because we consider a perturbation of the phase-leader, the transition areas correspond to the stimulated region undergoing a phase-delay relative to the unperturbed region. Our analysis in Sec. 3.3.3 revealed that external input pulses could induce phase-delays in an uncoupled WC unit. Here, in the case of the 2-area circuit, we see that this effect can actually translate into a change in the network’s phase-locking configuration as a whole.

In our convention, $\theta = 0$ corresponds to the peaks of the oscillation cycles, and so we see
that for smaller amplitudes and durations, successful switching occurs on the falling side of the oscillation before the trough ($\theta = \pi$) is reached. For increasing pulse duration and amplitude, onset phases that lead to a state change tend to shift more towards $\theta = 0$, and perturbations that arrive just before or at the oscillation peak can also lead to state-switching. Fig. 3.11E and Fig. 3.11F show segments of the two units’ activity time-series just prior to and just after application of the stimulation pulse. Panel E is an example of a successful state-switch. Before the pulse, the purple unit leads the yellow unit in phase, and then at the time of the stimulation (indicated by the black bar), a new peak is initiated in the purple unit’s oscillation. That stimulation-induced effect subsequently induces a phase-delay of the purple area’s activity, which in turn allows the yellow area to become the phase-leader. Alternatively, panel F depicts an example of an unsuccessful state switch. While the amplitude and duration of the stimulation are kept the same, the onset phase here is such that the pulse begins near the trough of the purple area’s cycle. This scenario leads to a transient phase-advance for the purple unit, and it remains the phase-leader after the pulse is turned off.

In sum, we find that if the external pulse is activated within a “critical” portion of the receiving area’s oscillation, then the induced transient change in activity at the perturbed site can move the network from one of its stable phase-locked attractors to the other. Hence, it is possible to control the lead-lag relationships using localized stimulation. This result is consistent with the findings of other studies that have used models based on interneuron-mediated gamma rhythms [113, 112, 278, 279]. In Fig. B.2 we show that the main findings are robust to an alternative parameter choice, and in Fig. B.3 we show that perturbation of the phase-lagger can also bring about state-switching, albeit for a different range of onset phases.

4-area networks: Deterministic limit

Having studied the simplest possible network composed of 2 coupled regions, we now examine the response of the deterministic, 4-area network to local input pulses. For this analysis, we set the baseline network parameters to $P_{E,j} = 1.325$ for $j \in \{1, ..., 4\}$, $G_{EE} = 0.2$, and $T_D = 2.5$ ms. These choices yield oscillatory population activity at each model brain region, and the collective dynamics of the circuit as a whole exhibits multistable phase-locking, where a given initial condition leads to one of six possible collective states. We refer the reader to Sec. 3.3.1 and to Fig. 3.6 for a detailed description of the baseline dynamics and for a visual depiction of the six phase-locked configurations. We also show an example of a baseline network activity pattern here in Fig. 3.12B, where the network locks into state $S_1$ characterized by the phase-ordering...
As before, we introduce a local perturbation to the system by injecting a square wave pulse input of duration $T_s$, amplitude $A_s$, and onset phase $\theta_{on}$ into the excitatory subpopulation of one neural mass (Sec. 3.2.3), which here is area 1 (see Fig. 3.12A for a schematic of the model setup).

We again wish to understand whether a local perturbation can be used to shift the network’s phase-locking configuration from $S_1 \rightarrow S_j \neq 1$, bypassing the need to alter structural connections in order to alter the networks’ functional state. Accordingly, we begin in a similar manner to the 2-node case, and first allow the dynamics to evolve for a 7-second period in the absence of a perturbation. For the chosen initial conditions, the network settles into collective state $S_1$ (Fig. 3.12A).

We then run a new simulation wherein the dynamics are prepared in the same initial state, but after $t = 3$ seconds, a pulse perturbation of amplitude $A_s$ and duration $T_s$ is delivered to area 1, arriving at the next time area 1’s phase is equal to a particular onset phase $\theta_{on}$. This latter step is repeated for a range of pulse amplitudes and durations, and for 50 onset phases distributed uniformly across a full oscillation cycle of the receiving area. Recall that, because the network

Figure 3.12 (following page): Response of a deterministic 4-area network to brief pulse perturbations. (A) Schematic of the model setup. We study the response of a deterministic 4-area brain circuit to a brief input pulse of amplitude $A_s$ and duration $T_s$. The perturbation targets only one of the two regions, which in this case is area 1 (yellow). Throughout, we set the network parameters to $P_E = 1.325$, $G_{EE} = 0.2$, and $T_D = 2.5$ ms. (B) Activity time-series of the four areas under baseline conditions. The network locks into collective state $S_1$ (Fig. 3.12A). (C) Surface plot showing the phase-locking state that the network equilibrates to after a pulse input of varying duration and onset phase $\theta_{on}$ for fixed amplitude $A_s = 0.75$. (D) Surface plot showing the phase-locking state that the network equilibrates to after a pulse input of varying duration and onset phase $\theta_{on}$ for fixed amplitude $A_s = 1.5$. (E) Surface plot showing the phase-locking state that the network equilibrates to after a pulse input of varying amplitude and onset phase $\theta_{on}$ for fixed duration $T_s = 4.0$ ms. (F) Activity time-series showing the effects of a pulse perturbation applied to the yellow area at the time denoted by the black line (pulse parameters are $A_s = 1.25$, $T_s = 5$ ms, $\theta_{on} = 1.5$ rad). The external input causes the yellow area to phase-advance, such that the state switches from $S_1 \rightarrow S_6$. (G) Activity time-series showing the effects of a pulse perturbation applied to the yellow area at the time denoted by the black line (pulse parameters are $A_s = 1.25$, $T_s = 5$ ms, $\theta_{on} = 0.5$ rad). The external input causes the yellow area to phase-delay, such that the state switches from $S_1 \rightarrow S_4$. (H) Activity time-series showing the effects of a pulse perturbation applied to the yellow area at the time denoted by the black line (pulse parameters are $A_s = 1.25$, $T_s = 5$ ms, $\theta_{on} = 4.5$ rad). Though the external input induces a large transient effect at the stimulated site, it does not lead to a reconfiguration of the phase-locking pattern.
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A baseline

C $\theta = 4.5$ rad

D $\theta = 0.5$ rad

E $\theta = 1.5$ rad

F $\theta = 1.5$ rad

G $\theta = 0.5$ rad

H $\theta = 4.5$ rad

S(t) $\rightarrow$ S6

S(t) $\rightarrow$ S4

S(t) $\rightarrow$ S1

amplitude $A_s = 0.75$

amplitude $A_s = 1.50$

duration $T_s = 4.00$ ms

$S_1 \rightarrow S_6$

$S_1 \rightarrow S_4$

$S_1 \rightarrow S_1$

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is deterministic and the external stimulation is only applied briefly, the network will equilibrate back into one of its six multistable states. To determine if the phase-locking pattern can be re-configured by such external inputs, we thus compare the state of the network after the transient effects of the perturbation did away to the original state from the baseline condition. In particular we conclude that a state transition occurs if the collective state of the network (beginning 2.5 seconds after the perturbation) is distinct from that of the initial state $S_1$.

The complete results of our analysis are depicted in Fig. 3.12C–H. We first note that below a certain pulse amplitude and duration, the perturbation does not alter the functional state of the network, regardless of the onset phase. This fact is illustrated by the consistently gray region (indicating a trivial $S_1 \rightarrow S_1$ transition) as one scans the lower portions of Figs. 3.12C,E horizontally. But, if the strength and/or duration of the external input are strong enough and/or long enough, then the focal perturbation can indeed switch the collective state of the network into a new configuration (colored areas in Figs. 3.12C,D,E). Moreover, it is clear that if transitions in the phase-locking pattern do occur, then they only arise for specific onset phases. This effect is again consistent with the onset-phase-dependent perturbation-induced shifts in the oscillation cycle of a single WC unit detailed in Sec. 3.3.3 (i.e. the notion of a phase-response curve).

More specifically, Figs. 3.12C and D show surface plots of the state ID $S_i$ as a function of the onset phase $\theta_{on}$ and the pulse duration $T_s$ for fixed amplitude $A_s = 0.75$ and $A_s = 1.5$, respectively. Fig. 3.12E shows the state ID instead for fixed duration $T_s = 4$ ms and varying onset phase and amplitude. Examining these three figures, the first additional point we make is that for lower stimulation strengths (Fig. 3.12C), the observed non-trivial state transition corresponds to $S_1 \rightarrow S_6$ (light red region). Looking back at the set of collective states and their IDs (Fig. 3.6E), we see that $S_1$ transitions to $S_6$ via region 1 shifting one slot ahead of its position in $S_1$ (i.e. the yellow area 1 swaps places with the green area 3). We show an example of a pulse input to region 1 that induces the $S_1 \rightarrow S_6$ state switch in Fig. 3.12F. Note that the precisely timed perturbation causes area 1 (yellow) to undergo a phase-advance that then alters the phase-locking pattern in the long-term.

The second fact we wish to point out is that for larger pulse amplitudes and/or durations (Figs. 3.12D,E), two state transitions become unlocked for different sets of onset phases: $S_1 \rightarrow S_6$ (light red regimes) and $S_1 \rightarrow S_4$ (blue regimes). We already know that the former corresponds to the stimulated site phase-advancing by one position. Again referring to the dictionary of collective states laid out in Fig. 3.6E, we see that the latter transformation $S_1 \rightarrow S_4$ corresponds to the opposite scenario, where the perturbed area 1 falls back one space and comes to sit behind the red
area 4. This state-switch occurs for onset phases nearer to the peak of the ongoing rhythm. An example of a perturbation-induced switch from pattern $S_1$ to $S_4$ is depicted in Fig. 3.12G, where one can see that area 1 undergoes a phase-delay that leads to the change in the functional state. For completeness, we also show an example of an onset phase that does not lead to a change in the system’s state, despite the external stimulation causing a significant transient change in the perturbed regions’ activity (Fig. 3.12H).

We conclude this section by reiterating that collective multistability – in conjunction with precisely timed focal stimulation – provides a basis for switching between one of a larger number of functional states in an interareal network. While we considered the case of applying the perturbation to area 1, the symmetry of the system implies that results would be exactly the same for a different choice of the stimulated site, but some of the allowed transitions would be distinct.

2-area networks: Stochastic scenario

As we have noted previously, incorporating stochasticity into the dynamical model is an important step towards increasing the model’s applicability to real neural dynamics. In this section, we thus move on to analyze 2-area circuits subject to noisy background drive (Sec. 3.2.2), but that operate in regimes characterized by spontaneous switching between out-of-phase configurations (see Sec. 3.3.1 for analyses of the system’s baseline activity patterns in the presence of stochastic background drive). In such cases, it is still possible to extract noisy, transient versions of collective states, and the question we ask here is whether phase-locking can still be effectively controlled via brief, local input pulses in these more realistic regimes. In what follows, we analyze four different working points that are meant to demonstrate conditions under which rapid state-selection via local perturbations remains possible in the presence of noise, as well as when control capabilities begin to break down.

Before describing the effects of pulse inputs at different working points, we explain the general protocol we use to analyze the stochastic scenario. As before, we are concerned with whether or not the external input can switch the network’s lead-lag relation. But, because noise results in spontaneous state-switching and causes the phase-locking to become imperfect, assessing these effects becomes slightly more involved. For all parameter sets, we begin by running a long (150-second) simulation without perturbations applied; from the resulting time-series, we are able to reasonably resolve and characterize the network’s favored activity patterns. In order to extract preferred collective states, we compute the phase difference $\Delta \theta$ between the two units at each time point across the simulation, and bin the set of absolute values $\{|\Delta \theta|\}$ into 100 bins of equal
width; the preferred phase difference $\Delta \theta^*$ is defined as that corresponding to the peak of this histogram. The next step is to determine candidate windows for applying a perturbation. When it comes to this step, first note that we specifically consider the effect of applying a perturbation during windows in which the phase difference is near one of the preferred configurations $\pm \Delta \theta^*$ for at least one cycle. In other words, the question is: given that the system is close to one of its favored states prior to the perturbation, does a local pulse input change the sign of the phase difference and hence switch the lead-lag configuration. Note that requiring the two units to be locked around a certain $\Delta \theta$ for at least one cycle ensures that we can properly compare the effects of stimulating one of the two regions at different phases of its ongoing oscillation. Also note that we could consider a more constrained criteria in which the system must remain in a particular configuration for longer than one oscillation cycle, but in what follows, we consider the least stringent selection method. In particular, candidate perturbation windows are extracted by finding time segments during which the absolute phase difference $|\Delta \theta|$ satisfies $|\Delta \theta| \in [\Delta \theta^* - \delta, \Delta \theta^* + \delta]$ for at least one oscillation cycle, where $\delta$ is a threshold that determines how far $\Delta \theta$ can vary around the peak value $\Delta \theta^*$. The subsequent analyses all assume a default value of $\delta = \pi/6$, though we do also briefly examine the effect of varying this quantity (see Fig. B.4).

Of the full set of candidate windows, we select 100 of them at random in which to apply perturbations. Specifically, for each window, we run a new simulation that uses the exact same initial conditions and noise realization, but we perturb the phase-leading area with a square wave pulse of amplitude $A_s$, duration $T_s$, and onset phase $\theta_{on}$ (Sec. 3.2.3). For a given set of pulse parameters, onset phase, and time-window, the effect of the external input on the networks’ collective state is assessed by determining (1) if the sign of the phase difference switches within $n_s$ oscillation cycles after the perturbation onset, and (2) if the sign of the phase difference remains reversed for a subsequent $n_m$ cycles after the initial switch. If both of these criteria are met, then we conclude that the input pulse is able to successfully control the network activity pattern (for the given $n_s$ and $n_m$). To determine the overall efficacy of a perturbation with fixed parameters on inducing a lasting state-transition, we repeat the aforementioned process for each of the 100 randomly selected windows, and from these trials, we compute the fraction that lead to a successful alteration of the collective phase relation. In what follows, we will often refer to this fraction as the “switching probability” (or “transition probability”) $P_{\text{switch}}$, but note that because $P_{\text{switch}}$ is computed from a finite number of samples, it is only an estimate of the true value. Importantly, the collective state will switch on its own due to the stochastic environment. It is therefore helpful to compare the perturbation-induced switching probability to the chance of observing a spontaneous
neous change in the sign of the phase difference without applying the perturbation. To do this, we consider the same set of 100 time-windows, and compute the fraction of those windows for which both (1) the sign of the phase difference switches within $n_s$ oscillation cycles on its own, and (2) the new lead-lag relation is maintained for a subsequent $n_m$ cycles after the initial switch. This procedure allows us to ask whether the estimated likelihood of observing a state-transition due to the perturbation itself exceeds the estimated probability of the system transitioning on its own, due to noise. In the remainder of the text, we often refer to the estimated chance level of observing a state transition as the “spontaneous switching probability” or “spontaneous transition probability”.

Note that if given enough time, the lead-lag relation will change. Therefore, we are interested in the question of whether local perturbations can be harnessed to achieve “on-demand” or immediate state-selection. To this end, we consider a default value $n_s = 2$. Moreover, for coherent oscillatory activity to be functionally relevant, it is also necessary that a particular phase relationship be maintained for at least a few oscillation cycles; for this reason, we consider a default value $n_m = 5$. Unless stated otherwise, the reader can assume in the coming text that the above default values are used to compute the switching probabilities $P_{\text{switch}}$.

We now present our key results regarding the effects of local pulse perturbations on state-switching in stochastic 2-area networks. We refer the reader to Sec. 3.3.1 for a complete analysis of the baseline behaviors of 2-area networks with noisy background drive, as here we only provide a recap of the key points. To begin, we consider a baseline working point of $P_{E,j} = 1.35$ for $j \in \{1, 2\}$, $T_D = 1.5$ ms, $G_{EE} = 0.2$, $\alpha = 10$, and $\sigma = 0.2$ (Working Point 1; Fig. 3.13). For these parameters but in the absence of noise ($\sigma \to 0$), we saw that regional activity oscillated and the network exhibited out-of-phase locking (Fig. 3.11B), which could be controlled via appropriately-timed external input pulses (Fig. 3.11C–F). When the background drive is instead made stochastic, we observe that the baseline distribution of phase differences $P[\Delta \theta]$ develops two broad but still well-defined out-of-phase peaks that indicate preferred phase relations that the system spontaneously transitions between over time (Fig. 3.13A). In particular, a given lead-lag relationship (characterized by whether the sign of the phase difference between the two areas is positive or negative) lasts for on average $\langle L_s \rangle \approx 378$ ms before switching (Fig. 3.13B). Thus, for this operating point, it is possible to extract time-windows during which the system exists in blurred versions of the noiseless collective states. In particular, the vertical lines in the $P[\Delta \theta]$ histogram (Fig. 3.13A) show the thresholds used to select the candidate time-windows for applying pulse perturbations; note that this criteria extracts time-windows during which $\Delta \theta$ is near one
of its most probable out-of-phase configurations.

Although the system is now noisy, we find that for this working point, suitable external inputs that target the phase-leader can still very effectively control the phase-locking pattern. As an example, Fig. 3.13C shows the switching probability $P_{\text{switch}}$ as a function of the onset phase $\theta_{\text{on}}$ for pulses of fixed duration $T_s = 4.5$ ms and amplitude $A_s = 0.75$. Note that there are specific ranges of onset phases for which the perturbation-induced likelihood of triggering a state transition is well above the chance level. Indeed, the maximum switching probability reaches a value of near 0.8 if well-timed relative to the ongoing oscillation. To see more clearly how a local perturbation can induce a state-switch, we show an example of the activity time-series for a successful transition in Fig. 3.13G. Note that before the perturbation, the system resides in a noisy version of $S_1$, where area 1 (yellow) leads area 2 (purple). The input pulse then triggers a transient and immediate change in the oscillation of region 1 that quickly shifts the network into a noisy version of $S_2$, which is then maintained for several subsequent oscillation cycles. However, despite the high switching likelihood, the stochastic nature of the system still renders some perturbations ineffective, even if they arrive at an onset phase that would yield a switch in the deterministic limit. Fig. 3.13H depicts an example of an unsuccessful trial that uses the exact same pulse parameters as before. First note that, due to the imperfect phase-locking, the transient effect of the external input is noticeably different in comparing Figs. 3.13G and H. Moreover, while the perturbation can alter the sign of the phase difference for the couple of cycles right after its onset, this effect decays within a 5-cycle period for this time-window.

To better appreciate the influence of focal input pulses on collective phase-locking states, it is helpful to more carefully contrast the perturbation-induced effects to what would be expected spontaneously. Specifically, we compute the spontaneous switching probability for varying $n_s$ (holding $n_m = 5$) and compare the resulting curve to the maximum perturbation-induced transition probability across all onset phases for the smallest possible $n_s = 1$. This analysis reveals that the chance of observing a spontaneous state change within an allowed waiting time of up to 50 cycles is still well below the maximum switching probability triggered by a perturbation within only a single cycle (Fig. 3.13D). Hence, if the system is currently in a well-defined collective state near the peak of $P[\Delta \theta]$, then the efficacy of the perturbation-induced effects that occur immediately will not be matched in the spontaneous dynamics even if one waited tens of oscillation cycles. Crucially, this observation allows us to conclude that although state-control may be overall less efficient in the stochastic regime, perturbations are nonetheless able to elicit state switching on very fast time scales with efficacies that far exceed chance levels. In this way, the
functional benefits of multistable collective phase-locking and modulatory control inputs continue to hold under more realistic conditions.

The dependence of the transition probability $P_{\text{switch}}$ on the pulse parameters $A_s$ and $T_s$ and the onset phase $\theta_{\text{on}}$ is summarized in Figs. 3.13E,F. As expected, these plots resemble blurred versions of their counterparts from the noiseless system (Fig. 3.11C,D). For this reason, we do not unpack each feature again, and instead refer the reader to Sec. 3.3.4 for a detailed discussion. Here we just highlight that for strong enough and/or long enough external pulses, the switching probability peaks at values well above chance for specific ranges of the onset phase. These bands correspond to parameter combinations where focal perturbations successfully initiate rapid state transitions that would not occur on their own.

When the background inputs are made stochastic, there are even more knobs to tune, and it is impossible to completely explore the influence of the network’s baseline dynamics on the capacity for functional state control. Here we choose to examine one important aspect of the system, which is the signal-to-noise ratio. There are a number of ways this could be changed, but here we briefly consider the effect of keeping the network coupling, delay, and noise parameters the same, but lowering the mean background drive to $\overline{P_{E,j}} = 1.30$ for $j \in 1, 2$ (Working Point 2). As discussed in Sec. 3.1, this process has the effect of lowering the amplitude of regional oscillations at baseline, in turn making the network more susceptible to noise. Indeed, compared to the previous working point, lowering $\overline{P_{E}}$ leads to decreased peak heights in the phase difference distribution $P[\Delta \theta]$ (Fig. 3.14A) and decreased state durations (Fig. 3.14B). Nevertheless, it is still clear that the network has preferred dynamical configurations, allowing us to again assess the outcomes of external input pulses on collective states.

Proceeding with the same analyses as before, we first note that when the signal-to-noise ratio is decreased, the likelihood of inducing fast, lasting state-switches still remains well above chance levels if the input is received during certain phases of the ongoing oscillation (Figs. 3.14C,E,F). However, it is also apparent that the perturbation-induced switching probabilities undergo a global decrease compared to the previous working point (compare Figs. 3.14C,E,F to Figs. 3.13C,E,F). Thus, not surprisingly, the collective states are overall more difficult to control when the system is inherently more noisy. Additionally, because baseline state-switching is also faster, the likelihood of inducing an immediate state-switch with a perturbation will eventually be matched (and exceeded) in the spontaneous dynamics within a few tens of cycles (Fig. 3.14D). Even so, it remains a crucial point that despite the heightened noise, perturbations can still significantly accelerate transitions in the collective state. This fact allows for enhanced
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functional flexibility and significant probabilities of state reconfiguration within just one oscillation cycle (Figs. 3.14G,H). We also find that the perturbation-induced effects remain well above chance levels even when the window selection width $\delta$ is doubled (see Fig. B.4).

We next consider whether pulse inputs can still be used to modulate collective phase-locking for a quantitatively different dynamical regime where in the absence of noise, the system does not have attractors that correspond to out-of-phase states. In particular, we set the parameters to $P_{E,j} = 1.25$ for $j \in \{1, 2\}$, $T_D = 1.5$ ms, $G_{EE} = 0.3$, $\alpha = 10$, and $\sigma = 0.25$ (Working Point Figure 3.13 (following page): Response of a stochastic 2-area network to brief perturbation pulses applied to the phase-leader: Working Point 1. The key network parameters are: $P_E = 1.35$, $T_D = 1.5$ ms, $G_{EE} = 0.2$, $\alpha = 10$, $\sigma = 0.2$. (A) The baseline distribution of phase differences $\Delta \theta$ between the two coupled areas across a long simulation. The red lines around each peak indicate the range of $\Delta \theta$ values used to select candidate windows for perturbation; we consider a width $\pm \delta = \pi/6$ around each peak. (B) The distribution of state durations $L_s$ with the mean value $\langle L_s \rangle$ printed inside the panel. (C) The heights of the blue bars show the estimated switching probabilities $P_{\text{switch}}$ for pulse inputs applied at different onset phases $\theta_{\text{on}}$. A successful state transition is said to occur if the sign of the interareal phase relation switches within 2 cycles and the new configuration lasts for at least 5 more cycles following the initial switch. The pulse has amplitude $A_s = 0.75$ and duration $T_s = 4.5$ ms. The red horizontal line indicates the estimated likelihood of observing the same behavior spontaneously, i.e., in the absence of a perturbation. (D) Across all onset phases $\theta_{\text{on}}$, the blue line indicates the maximum switching probability $\max[P_{\text{switch}}]$. A successful state transition is said to occur if the sign of the interareal phase relation switches within 1 cycle and the new configuration lasts for at least 5 more cycles following the initial switch. The perturbation has amplitude $A_s = 0.75$ and duration $T_s = 4.5$ ms. The red curve shows the estimated likelihood of observing a spontaneous switch that lasts for at least 5 periods and that occurs within a varying number of oscillation cycles. (E) The estimated switching probability $P_{\text{switch}}$ as a function of the onset phase $\theta_{\text{on}}$ and the pulse duration $T_s$. The pulse amplitude is fixed at $A_s = 0.75$, and a successful state transition is said to occur if the sign of the interareal phase relation switches within 2 cycles and the new configuration lasts for at least 5 more cycles following the initial switch. (F) The switching probability $P_{\text{switch}}$ as a function of the onset phase $\theta_{\text{on}}$ and the pulse amplitude $A_s$. The pulse duration is fixed at $T_s = 4.5$ ms, and a successful state transition is said to occur if the sign of the interareal phase relation switches within 2 cycles and the new configuration lasts for at least 5 more cycles following the initial switch. (G) Activity time-series from a trial where a successful state-switch is induced by applying a pulse perturbation to the yellow area at the time denoted by the black bar (pulse parameters are $A_s = 0.75$, $T_s = 4.5$ ms, $\theta_{\text{on}} = 1.5$ rad). (H) Activity time-series from a different trial that shows an unsuccessful state-switch with the same pulse parameters.
$\theta_{on} = 1.5 \text{ rad}$

- Successful switch
- Unsuccessful switch

A. $P[\Delta \theta]$ vs $\Delta \theta$

B. $P[L_s]$ vs state dur. $L_s$ (ms)

$\langle L_s \rangle \approx 378 \text{ ms}$

C. $A_s = 0.75$, $T_s = 4.50 \text{ ms}$

D. $P_{\text{switch}}$ vs # cycles to switch

E. $\text{amplitude } A_s = 0.75$

F. $\text{duration } T_s = 4.50 \text{ ms}$

G. $\theta_{on} = 1.5 \text{ rad}$

- Successful switch

H. $\theta_{on} = 1.5 \text{ rad}$

- Unsuccessful switch
Note that here the background drive is such that an isolated WC unit would be operating just beyond the Hopf bifurcation (Sec. 3.3.1), and as discussed in Sec. 3.3.1, a deterministic network with these parameters actually locks into an in-phase configuration (Fig. 3.5A). However, as we saw previously in Sec. 3.3.1 and again here, the addition of appropriate background noise can lead to preferred out-of-phase configurations (Fig. 3.15A) and fast switching between lead-lag relations (Fig. 3.15B). Although out-of-phase locking arises here for a somewhat different reason than the previously examined operating points, the two clear peaks in the distribution $P(\Delta \theta)$.

Figure 3.14 (following page): Response of a stochastic 2-area network to brief perturbation pulses applied to the phase-leader: Working Point 2. The key network parameters are: $PE = 1.30, TD = 1.5$ ms, $G_{EE} = 0.2, \alpha = 10, \sigma = 0.2$. (A) The baseline distribution of phase differences $\Delta \theta$ between the two coupled areas across a long simulation. The red lines around each peak indicate the range of $\Delta \theta$ values used to select candidate windows for perturbation; we consider a width $\pm \delta = \pi/6$ around each peak. (B) The distribution of state durations $L_s$ with the mean value $\langle L_s \rangle$ printed inside the panel. (C) The heights of the blue bars show the estimated switching probabilities $P_{\text{switch}}$ for pulse inputs applied at different onset phases $\theta_{on}$. A successful state transition is said to occur if the sign of the interareal phase relation switches within 2 cycles and the new configuration lasts for at least 5 more cycles following the initial switch. The pulse has amplitude $A_s = 0.75$ and duration $T_s = 4.5$ ms. The red horizontal line indicates the estimated likelihood of observing the same behavior spontaneously, i.e., in the absence of a perturbation. (D) Across all onset phases $\theta_{on}$, the blue line indicates the maximum switching probability $\max[P_{\text{switch}}]$. A successful state transition is said to occur if the sign of the interareal phase relation switches within 1 cycle and the new configuration lasts for at least 5 more cycles following the initial switch. The perturbation has amplitude $A_s = 0.75$ and duration $T_s = 4.5$ ms. The red curve shows the estimated likelihood of observing a spontaneous switch that lasts for at least 5 periods and that occurs within a varying number of oscillation cycles. (E) The estimated switching probability $P_{\text{switch}}$ as a function of the onset phase $\theta_{on}$ and the pulse duration $T_s$. The pulse amplitude is fixed at $A_s = 0.75$, and a successful state transition is said to occur if the sign of the interareal phase relation switches within 2 cycles and the new configuration lasts for at least 5 more cycles following the initial switch. (F) The estimated switching probability $P_{\text{switch}}$ as a function of the onset phase $\theta_{on}$ and the pulse amplitude $A_s$. The pulse duration is fixed at $T_s = 4.5$ ms, and a successful state transition is said to occur if the sign of the interareal phase relation switches within 2 cycles and the new configuration lasts for at least 5 more cycles following the initial switch. (G) Activity time-series from a trial where a successful state-switch is induced by applying a pulse perturbation to the yellow area at the time denoted by the black bar (pulse parameters are $A_s = 0.75, T_s = 4.5$ ms, $\theta_{on} = 1.25$ rad). (H) Activity time-series from a different trial that shows an unsuccessful state-switch with the same pulse parameters.
\( \Theta_{on} = 1.25 \text{ rad} \)

- **successful switch**

- **unsuccessful switch**

**Figure C**: \( A_s = 0.75, T_s = 4.50 \text{ ms} \)

- \( P_{\text{switch}} \)

**Figure E**: amplitude \( A_s = 0.75 \)

- duration \( T_s = 4.50 \text{ ms} \)

**Figure G**: \( \Theta_{on} = 1.25 \text{ rad} \)

- successful switch

- unsuccessful switch

**Figure H**: 

- \( 1 \)

- \( 2 \)
allow us to extract windows that correspond to well-defined collective states in which we can test the effects of perturbations. Continuing as before, we find that there remains a band of onset phases (for strong and long enough pulses) in which the perturbation-induced switching probability exceeds the spontaneous level (Figs. 3.15C). Fig. 3.15G shows the activity time series just before and after a successful state change. But, notice that the peak transition probabilities across a range of pulse amplitudes and durations are quite drastically reduced, reaching levels of only about 0.25 (Figs. 3.15E,F). An example of an unsuccessful trial that uses the exact same pulse parameters is shown in Fig. 3.15H; here, the influence of the noise takes over after the perturbation is turned off, and prevents the triggered reverse in the lead-lag relationship from lasting more than just 2-3 oscillation cycles (thus resulting in failed state-control). Nonetheless, although overall performance is reduced in this regime, we still wish to underscore that brief external inputs are still more effective than chance at eliciting very rapid reconfigurations of functional connectivity. That is, approximately 25% of the time, carefully-timed pulses can lead to a sustained (lasting 5 cycles) change in the sign of the phase relation within one period, while one would need to wait about six cycles in the absence of a modulatory input (Fig. 3.15C).

Understanding when meaningful modulation of collective states breaks down is also important. While functional state control could become ineffective for multiple reasons, here we show that one scenario occurs when the background drive is decreased to a level that would place an isolated, deterministic WC unit below its Hopf bifurcation but close enough to still exhibit noise-induced oscillations. In particular, we consider the same parameters as used in Fig. 3.15, with the exception that we set $P_{E,j} = 1.20$ for $j \in \{1, 2\}$ (Working Point 4). The baseline dynamics for this situation were studied in detail in Sec. 3.3.1 and Fig. 3.5. The key point is that for this working point, even when the network is coupled, it is noise itself that induces robust regional oscillations and the subsequent out-of-phase locking. Nonetheless, we are able to select parameters such that when we only changed the mean background drive, the peak values of the phase difference distribution $P[\Delta \theta]$ were similar between the $P_E = 1.25$ and $P_E = 1.20$ working points (compare Figs. 3.15A and 3.16A). Hence, we control for significant variation in the noisiness of the collective states at different operating points (though do note that collective states are shorter lived when the background drive is lower; Fig. 3.16B). Interestingly, although sharp peaks still manifest in $P[\Delta \theta]$, the switching probabilities drop to $< 10\%$ and do not robustly exceed the spontaneous switching level (Fig. 3.16C). Fig. 3.16D shows an example of the activity time-series for an unsuccessful trial; due to the influence of noise over the system’s dynamics, precise and lasting state-switching is difficult to induce in this regime.
4-area networks: Stochastic scenario

In the preceding subsection, we identified conditions under which local perturbations could still modulate collective states in 2-area networks even when phase relations fluctuated spontaneously across time. Building upon those analyses, we now ask whether perturbation-induced switching between approximately phase-locked, multistable patterns can still be achieved in the slightly more complex case of a 4-area network, where the multiplicity of dynamical configurations is increased.

Figure 3.15 (following page): Response of a stochastic 2-area network to brief perturbation pulses applied to the phase-leader: Working Point 3. The key network parameters are: $P_E = 1.25$, $T_D = 1.5$ ms, $G_{EE} = 0.3$, $\alpha = 10$, $\sigma = 0.25$. (A) The baseline distribution of phase differences $\Delta \theta$ between the two coupled areas across a long simulation. The red lines around each peak indicate the range of $\Delta \theta$ values used to select candidate windows for perturbation; we consider a width $\pm \delta = \pi/6$ around each peak. (B) The distribution of state durations $L_s$ with the mean value $\langle L_s \rangle$ printed inside the panel. (C) The heights of the blue bars show the estimated switching probabilities $P_{\text{switch}}$ for pulse inputs applied at different onset phases $\theta_{\text{on}}$. A successful state transition is said to occur if the sign of the interareal phase relation switches within 2 cycles and the new configuration lasts for at least 5 more cycles following the initial switch. The pulse has amplitude $A_s = 0.75$ and duration $T_s = 4.5$ ms. The red horizontal line indicates the estimated likelihood of observing the same behavior spontaneously, i.e., in the absence of a perturbation. (D) Across all onset phases $\theta_{\text{on}}$, the blue line indicates the maximum switching probability $\max \{ P_{\text{switch}} \}$. A successful state transition is said to occur if the sign of the interareal phase relation switches within 1 cycle and the new configuration lasts for at least 5 more cycles following the initial switch. The perturbation has amplitude $A_s = 0.75$ and duration $T_s = 4.5$ ms. The red curve shows the estimated likelihood of observing a spontaneous switch that lasts for at least 5 periods and that occurs within a varying number of oscillation cycles. (E) The estimated switching probability $P_{\text{switch}}$ as a function of the onset phase $\theta_{\text{on}}$ and the pulse duration $T_s$. The pulse amplitude is fixed at $A_s = 0.75$, and a successful state transition is said to occur if the sign of the interareal phase relation switches within 2 cycles and the new configuration lasts for at least 5 more cycles following the initial switch. (F) The estimated switching probability $P_{\text{switch}}$ as a function of the onset phase $\theta_{\text{on}}$ and the pulse amplitude $A_s$. The pulse duration is fixed at $T_s = 4.5$ ms, and a successful state transition is said to occur if the sign of the interareal phase relation switches within 2 cycles and the new configuration lasts for at least 5 more cycles following the initial switch. (G) Activity time-series from a trial where a successful state-switch is induced by applying a pulse perturbation to the yellow area at the time denoted by the black bar (pulse parameters are $A_s = 0.75$, $T_s = 4.5$ ms, $\theta_{\text{on}} = 1.25$ rad). (H) Activity time-series from a different trial that shows an unsuccessful state-switch with the same pulse parameters.
A

\[ P(\Delta \theta) \]

\[ \Delta \theta \]

B

\[ P(L_s) \]

\[ (L_s) \approx 67 \text{ ms} \]

C

\[ A_s = 0.75, \ T_s = 4.50 \text{ ms} \]

\[ \theta_{on} = 1.25 \text{ rad} \]

successful switch

\[ \theta_{on} = 1.25 \text{ rad} \]

unsuccessful switch

D

\[ P_{\text{switch}} \]

\[ \# \text{ cycles to switch} \]

E

amplitude \[ A_s = 0.75 \]

\[ \text{duration} \ T_s = 4.50 \text{ ms} \]

\[ P_{\text{switch}} \]

F

G

\[ \theta_{on} = 1.25 \text{ rad} \]

successful switch

H

\[ \theta_{on} = 1.25 \text{ rad} \]

unsuccessful switch
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Figure 3.16: Response of a stochastic 2-area network to brief perturbation pulses applied to the phase-leader: Working Point 4. The key network parameters are: $P_E = 1.20$, $T_D = 1.5$ ms, $G_{EE} = 0.3$, $\alpha = 10$, $\sigma = 0.25$. (A) The baseline distribution of phase differences $\Delta \theta$ between the two coupled areas across a long simulation. The red lines around each peak indicate the range of $\Delta \theta$ values used to select candidate windows for perturbation; we consider a width $\pm \delta = \pi/6$ around each peak. (B) The distribution of state durations $L_s$ with the mean value $\langle L_s \rangle \approx 16$ ms printed inside the panel. (C) The heights of the blue bars show the estimated switching probabilities $P_{\text{switch}}$ for pulse inputs applied at different onset phases $\theta_{\text{on}}$. A successful state transition is said to occur if the sign of the interareal phase relation switches within 2 cycles and the new configuration lasts for at least 5 more cycles following the initial switch. The pulse has amplitude $A_s = 0.75$ and duration $T_s = 4.5$ ms. The red horizontal line indicates the estimated likelihood of observing the same behavior spontaneously, i.e., in the absence of a perturbation. (D) Across all onset phases $\theta_{\text{on}}$, the blue line indicates the maximum switching probability $\max[P_{\text{switch}}]$. A successful state transition is said to occur if the sign of the interareal phase relation switches within 1 cycle and the new configuration lasts for at least 5 more cycles following the initial switch. The perturbation has amplitude $A_s = 0.75$ and duration $T_s = 4.5$ ms. The red curve shows the estimated likelihood of observing a spontaneous switch that lasts for at least 5 periods and that occurs within a varying number of oscillation cycles. (E) Activity time-series showing a failed state-switch after applying a pulse perturbation to the yellow area at the time denoted by the black bar (pulse parameters are $A_s = 0.75$, $T_s = 4.5$ ms, $\theta_{\text{on}} = 1.25$ rad).
We characterized the baseline behavior of 4-region brain circuits in the presence of stochastic background drive in Sec. 3.3.1. There we saw that depending on the combination of the network and noise parameters, the system could naturally cycle through approximate forms of the multistable phase-locking patterns than manifest in the noiseless limit. Those are the regimes of interest for our current investigation, where we ask whether targeted external inputs can still control noisy collective states that spontaneously transition among one another at baseline. In order to investigate this question, the first step is to define a protocol that can be used to identify time windows during which the network resides in dynamical configurations reminiscent of the pristine phase-locked states seen without stochasticity (i.e., those in Fig. 3.6). One simple method is to define a state based on the relative ordering of the phases beginning from some reference node; we used this liberal technique briefly in Sec. 3.3.1 to demonstrate the spontaneous switching between different temporal arrangements of the population activity (Fig. 3.7G). For the purpose of the perturbation analysis we undertake here, though, we need to be a bit more precise with the state selection criteria.

To begin, we run a long, 150-second simulation of the dynamics without any perturbations. To extract time periods during which network activity is near one of the six multistable states $S_j$ that arise in the deterministic case, we make use of what the known phase relations are for each of those configurations. Specifically, in the absence of noise, each collective state corresponds to the four phases being distributed uniformly around the unit circle in a particular order (see Fig. 3.6). Thus, the phase difference between a given pair of regions will always take on one of three values, such that $\Delta \theta_{i,j} \in \{-\pi/2, \pi, \pi/2\}$ for $i \neq j$. For example, in state $S_1$, we have: $\Delta \theta_{1,2} = \pi$, $\Delta \theta_{1,3} = -\pi/2$, $\Delta \theta_{1,4} = \pi/2$, $\Delta \theta_{2,3} = \pi/2$, $\Delta \theta_{2,4} = -\pi/2$, and $\Delta \theta_{3,4} = \pi$. Similar phase relations can be defined for the five other unique states. To determine if the system exists in a blurred version of state $S_j$ when noise is present, we allow for some spread around the six noiseless phase differences. That is, if $\Delta \theta_{i,j}^*$ is the phase difference between unit 1 and 2 in the noiseless version of state $S_j$, then we would say that $\Delta \theta_{1,2}$ from the stochastic simulation should fall within $\Delta \theta_{1,2}^* - 2\delta < \Delta \theta_{1,2} < \Delta \theta_{1,2}^* + 2\delta$ (and analogously for the other five phase relations at the same time) in order for the system to be considered in a noisy version of $S_j$. In other words, if all six phase differences that correspond to a particular state are simultaneously within an allowed range $\pm \delta$ around their noiseless value, then we categorize the network as being in the corresponding state. In what follows, we use a generous default of $\delta = \pi/6$. Note that one could also use the three peaks of the $\Delta \theta$ histograms across a long simulation to determine the values to filter around, but we do not use that method here.
To assess whether pulse perturbations have a meaningful effect on the circuit’s dynamics, we next need to collect a set of candidate windows for applying the external input. The candidate set is determined by finding all windows during which the system remains in the same collective state for at least one cycle of the perturbed area’s baseline oscillation. We then select 100 of those candidate windows at random for further analysis. In this way, we ask: given that the network is near one of its preferred attractors when it receives a perturbation, can the external input induce a change in the collective state? To answer this question, for each selected window we run a new simulation where the noise realization and initial conditions are kept the same, but an input pulse of amplitude $A_s$ and duration $T_s$ is applied to region 1 at different phases $\theta_{on}$ of its ongoing oscillation. By continuing to let the dynamics evolve after receiving the perturbation, we analyze its effect on the network’s state by determining (1) if the perturbation caused the collective state to change to a new configuration within $n_s$ oscillation cycles after the perturbation onset, and if so, (2) whether the new state is maintained for a subsequent $n_m$ cycles after the initial switch.

Note that to determine a state transition, we only require that the relative ordering of the phases changes, but we do not put any further constraints on what the values of the phase differences must be afterwards. In what follows, we use default values $n_s = 2$ and $n_m = 5$; hence, we are interested in the ability to quickly shift the network activity pattern and have the alteration last for a functionally-relevant length of time.

To summarize the overall effect of an input pulse with certain parameters, we compute the fraction of the 100 selected windows for which the perturbation induces a phase-advancing (stimulated site moves ahead of the area initially preceding it) or phase-delaying (stimulated site moves behind the area initially lagging it) state transition. Note that these were the two types of state-transitions that we observed in studying the response of the noiseless 4-area circuit to brief input pulses (Sec. 3.3.4). In what follows, we denote these two fractions as $P_{\text{advance}}$ and $P_{\text{delay}}$, and often refer to them as the “phase-advancing transition probabilities” and the “phase-delaying transition probabilities”. (Note, though, that because $P_{\text{advance}}$ and $P_{\text{delay}}$ are determined from a finite number of samples, they are only estimates of the switching probabilities). The final step is to compare the perturbation-induced switching probabilities to the chance of observing the same effects in the spontaneous dynamics. To make this comparison, we consider the same time windows used for the perturbation analysis, and calculate the fraction for which the phase-ordering transitions to a configuration that corresponds to a phase-advance or phase-delay of area 1. As before, a successful trial is one in which the switch occurs within $n_s$ cycles from the time the perturbation would have been applied and where the new configuration lasts for at least $n_m$ cycles.
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afterward. In the coming expositions, we often refer to the estimated chance levels of observing phase-advancing or phase-delaying transitions as “spontaneous switching probabilities” or “spontaneous transition probabilities”.

We are now prepared to study the effects of brief input pulses on state-switching in 4-area networks driven by a noisy environment. We begin with a baseline operating point $P_{E,j} = 1.3$ for $j \in \{1, \ldots, 4\}$, $T_D = 2.5$ ms, $G_{EE} = 0.2$, $\alpha = 5$, and $\sigma = 0.1$ (Working Point 1). With these parameters, one can easily resolve three clear peaks in the distribution $P(\Delta \theta_{1,2})$ of the pairwise phase differences between area 1 and area 2 (Fig. 3.17), and these peaks are centered close to what the stable phase relations would be in the absence of noise. (Note that the results are similar for any pair of units $i \neq j$). As discussed thoroughly during our characterization of the baseline dynamics of stochastic 4-region circuits, the presence of these modes signifies that the system dwells in and spontaneously moves between variants of the multistable collective states that are attractors in the noiseless version of the network (please see Sec. 3.3.1 for complete details). Using the protocol outlined above, we can thus extract time windows during which the network resides in one of those configurations, and test whether an external stimulation signal can cause a reconfiguration of the activity pattern. For context, we note that for the chosen working point, it takes an average of $\langle L_s \rangle \approx 740$ ms for the relative ordering of the phases to change spontaneously. Hence, it is indeed pertinent to understand whether external inputs could bring about even more rapid state shifts.

When realistic stochasticity is incorporated into the model, controlled state-switching can no longer be evoked with 100% certainty. However, our analyses do indicate that aptly-timed perturbations can still bring about state transitions with efficacies well above chance levels (Fig. 3.17). To see this, first consider Fig. 3.17D, which shows the estimated phase-advancing transition probability $P_{\text{advance}}$ as a function of the onset phase $\theta_{\text{on}}$ (the pulse amplitude is $A_s = 1.5$ and the pulse duration is $T_s = 4$ ms). Of note is that for inputs received within a certain band of oscillation phases, $P_{\text{advance}}$ peaks at levels that reach $\approx 0.5$. In contrast, the likelihood that the same transitions would be observed spontaneously is zero; this is because when the network resides near one of its collective attractors, it takes much longer than just a couple of oscillation cycles for the background noise to elicit a state switch. Compounding on this, there would be no guarantee that the next state observed in the natural dynamics should be the one that corresponds to region 1 undergoing a 1-hop phase-advance. Thus, although the perturbation-induced phase-advancing transition probability is only about 50% at its maximum, this is still quite significant given the nature of the spontaneous dynamics. Fig. 3.17B offers an example of network activity just before
and after a perturbation to the yellow area that induces a successful phase-advance state transition. Before the external pulse arrives, the relative phase-order is $1 \rightarrow 3 \rightarrow 4 \rightarrow 2 \rightarrow 1$. When region 1 receives the stimulation, its oscillation undergoes a transient shifting that pushes it ahead of region 2. This in turn establishes the new phase-order $1 \rightarrow 2 \rightarrow 3 \rightarrow 4 \rightarrow 1$. Although the new state is transient and the corresponding phase relations imperfect, the effect of the perturbation may still be enough to briefly alter or disrupt the computation that was potentially enabled by the previous collective pattern.

In the deterministic limit, strong and long enough pulses could additionally trigger state transitions wherein the stimulated site underwent a phase-delay relative to its neighboring oscillation. Here we find that this effect can also be induced in the noisy system with likelihoods significantly above chance (Fig. 3.17G). As before, the stimulation must be carefully timed relative to the targeted area’s rhythm, but if this is the case, then the phase-delay transition probability $P_{\text{delay}}$ can also reach maximum values near 50% (at least for the chosen pulse parameters of $A_s = 1.5$ and $T_s = 4$ ms). An example of a successful trial in which this transition occurs is depicted in Fig. 3.17C; the external input causes a second peak in the yellow area’s oscillation that then leads to an overall 1-hop delay and change in the phase-order to the new state $1 \rightarrow 4 \rightarrow 2 \rightarrow 3 \rightarrow 1$.

We also study how the estimated state transition probabilities $P_{\text{advance}}$ and $P_{\text{delay}}$ vary as a function of the pulse amplitude and duration (Figs. 3.17E,F,H,I). It is no surprise that these heat maps look like probabilistic versions of Figs. 3.12D,E. Similar to the deterministic limit, the phase-delay transitions are more likely to occur for slightly earlier pulse onset phases than phase-advance transitions, and phase-delay transitions are only induced with reasonable likelihoods for slightly larger amplitudes than phase-advance switches. While we do see that there is some variation of the maximum values of the phase-advancing and phase-delaying transition probabilities as a function of the pulse amplitude and duration, the onset phase is undoubtedly the key to triggering reliable state switches. Importantly, we find that $P_{\text{advance}}$ and $P_{\text{delay}}$ can exceed 0.3 – which is well above the spontaneous switching probability – across a range of $A_s$-$T_s$ combinations so long as the timing of the pulse is within an optimal range.

Unfortunately, we do not have the computational resources to exhaustively explore how the baseline parameters of the circuit affect the ability of local stimulation to control network states. Here we thus choose to study one direction of interest, which is the effect of enhancing the noise strength. In particular, we increase $\sigma$ to 0.125 while keeping all other parameters identical (Working Point 2). Crucially, increasing the noise in this manner does not completely wipe-out the structure of the collective activity patterns that we wish to investigate in the first place, but
it does cause a smearing and reduction of the height of the peaks in the distribution $P(\Delta \theta_{1,2})$

Figure 3.17 (following page): Response of a stochastic 4-area network to brief perturbation pulses applied to area 1: Working Point 1. The key network parameters are: $P_E = 1.3$, $T_D = 2.5$ ms, $G_{EE} = 0.2$, $\alpha = 5$, $\sigma = 0.1$. (A) The baseline distribution $P(\Delta \theta_{1,2})$ of phase differences $\Delta \theta_{1,2}$ between areas 1 and 2 across a long simulation. The black lines indicate the values of the stable phase differences in the absence of noise. (B) Activity time-series from a trial where a successful phase-advance transition is induced by applying a pulse perturbation to the yellow area at the time denoted by the black bar (pulse parameters are $A_s = 1.5$, $T_s = 4.0$ ms, $\theta_{on} = 2.0$ rad). (C) Activity time-series from a trial where a successful phase-delay transition is induced by applying a pulse perturbation to the yellow area at the time denoted by the black bar (pulse parameters are $A_s = 1.5$, $T_s = 4.0$ ms, $\theta_{on} = 0.5$ rad). (D) The estimated phase-advancing transition probability $P_{\text{advance}}$ induced by pulse inputs applied at different onset phases $\theta_{on}$. A successful state transition occurs if the ordering of the phases switches to the correct configuration within 2 cycles and the new ordering lasts for at least 5 more cycles following the initial switch. The red horizontal line indicates the estimated likelihood of observing the same behavior spontaneously, i.e., in the absence of a perturbation. The pulse parameters are $A_s = 1.5$, $T_s = 4.0$ ms. (E) The estimated phase-advancing transition probability $P_{\text{advance}}$ as a function of the pulse onset phase $\theta_{on}$ and the pulse duration $T_s$, for fixed amplitude $A_s = 1.5$. A successful state transition occurs if the ordering of the phases switches to the correct configuration within 2 cycles and the new ordering lasts for at least 5 more cycles following the initial switch. (F) The estimated phase-advancing transition probability $P_{\text{advance}}$ as a function of the pulse onset phase $\theta_{on}$ and the pulse amplitude $A_s$, for fixed duration $T_s = 4.0$ ms. A successful state transition occurs if the ordering of the phases switches to the correct configuration within 2 cycles and the new ordering lasts for at least 5 more cycles following the initial switch. (G) The estimated phase-delaying transition probability $P_{\text{delay}}$ induced by pulse inputs applied at different onset phases $\theta_{on}$. A successful state transition occurs if the ordering of the phases switches to the correct configuration within 2 cycles and the new ordering lasts for at least 5 more cycles following the initial switch. The red horizontal line indicates the estimated likelihood of observing the same behavior spontaneously, i.e., in the absence of a perturbation. The pulse parameters are $A_s = 1.5$, $T_s = 4.0$ ms. (H) The estimated phase-delaying transition probability $P_{\text{delay}}$ as a function of the pulse onset phase $\theta_{on}$ and the pulse duration $T_s$, for fixed amplitude $A_s = 1.5$. A successful state transition occurs if the ordering of the phases switches to the correct configuration within 2 cycles and the new ordering lasts for at least 5 more cycles following the initial switch. (I) The estimated phase-delaying transition probability $P_{\text{delay}}$ as a function of the pulse onset phase $\theta_{on}$ and the pulse amplitude $A_s$, for fixed duration $T_s = 4.0$ ms. A successful state transition occurs if the ordering of the phases switches to the correct configuration within 2 cycles and the new ordering lasts for at least 5 more cycles following the initial switch.
CHAPTER 3.

A

1 2 3 4

phase-advance

phase-delay

D E F
C
G H I

150
(Fig. 3.18A; note that the conclusions are similar for any pair of units \(i \neq j\)). As determined in our analysis of baseline network dynamics (Sec. 3.3.1), increasing \(\sigma\) also reduces the time the system tends to spend in one phase ordering before switching. In particular, here \(\langle L_s \rangle\) decreases to \(\approx 428\) ms. Nonetheless, we can still use our methodology to select time-windows when the collective dynamics are in a well-defined state, and then test whether perturbations can robustly kick the circuit out of that configuration.

Carrying out the same set of analyses as for the previous working point, we find qualitatively similar results for the higher-noise setting (Fig. 3.18B–I). In particular, well-timed stimulation pulses can induce both rapid phase-advance and phase-delay state transitions with efficacies that exceed the spontaneous levels. Moreover, similar to the case with the 2-area network, we do also observe an overall reduction in \(P_{\text{advance}}\) and \(P_{\text{delay}}\) across the considered range of pulse parameters when compared to the less noisy regime. This finding is not unexpected; it simply quantifies the fact that state modulation becomes more difficult when the network operates in a more stochastic background environment. Nonetheless, we can still conclude that there is a range of noise levels for which perturbations can continue to have a meaningful influence over system dynamics. Though we do not follow-up on these points further, it may be possible to slowly increase the noise level until the perturbation-induced transition probabilities are reduced to near chance levels. Indeed, it may be interesting to see if this crossover regime occurs before a complete merging of the three peaks in the baseline phase difference distribution.

The final point we wish to make is that the efficacy of state-control also depends on the criteria used to select the perturbation windows. As the width parameter \(\delta\) is increased, the maximum state transition probabilities across all onset phases tend to decrease for a given fixed combination of the pulse amplitude and duration (see Fig. B.5). In other words, when network phase relations are more variable across the set of perturbation windows, it becomes more difficult to induce fast and sustained reconfigurations of the collective phase ordering. One reason this might occur is that if the set of phase relations is slightly different across the perturbation windows, then the optimal range of onset phases for inducing a state switch may also be slightly different from window to window. In turn, the state transition probabilities at a fixed \(\theta_{\text{on}}\) are likely to be smaller for larger \(\delta\). It is also generally reasonable to expect that perturbations applied during noisier time-windows will simply have less reliable effects than those applied in the middle of a time segment when the network is very close to one of the attractors from the noiseless system. Indeed, whether or not a perturbation yields a lasting change to the circuit’s activity pattern also depends on the evolution of the system after the perturbation is turned off. In this way, stimulation effects
will be cleaner if the stimulation is enacted in the midst of a time window when the stochastic system more closely resembles the deterministic one. Decreasing $\delta$ is more likely to select perturbation windows where that is the case. Importantly, windows where the phase configuration is tighter also constitute times when the network is very unlikely to change on its own, and are thus arguably when a perturbation may be most needed.

### 3.3.5 Rhythmic stimulation can induce state-morphing in multiarea networks

In the previous section we studied the effects of brief, targeted perturbation pulses on the collective dynamics of multiarea brain circuits. We found that under certain conditions, these external inputs could trigger a complete reorganization of the phase-locking state to a topologically distinct functional configuration. We turn next to an examination of how network activity is modulated by sustained rhythmic stimulation that again targets a single region. As before, we begin by understanding the simplest scenarios of 2-area and 4-area circuits in the deterministic limit, and then move to the more intricate case of stochastic background drive. In what follows, our analyses will reveal that, depending on the nature of the external input and/or the baseline dynamics, the focal stimulation will either lead to a breakdown of the collective phase-locking states or will enable more fine-tuned control of the interareal phase relationships.

#### 2-area networks: Deterministic limit

We start by investigating the ability of focused rhythmic stimulation to control the dynamical state of 2-region networks subject to deterministic background drive. As before, we set model parameters such that regional activity oscillates in time and the network phase-locks into a particular lead-lag configuration at baseline. For the following analysis, we use $P_{E,j} = 1.35$ for $j \in \{1, 2\}$, $G_{EE} = 0.2$, and $T_D = 1.5$ ms. Fig. 3.19B shows a brief segment of network activity at baseline for these parameters; for this example, the system falls into state $S_2$, for which area 2 leads area 1 in phase. The external stimulation is introduced by injecting a sinusoidal drive of amplitude $A_s$ and frequency $f_s$ into the excitatory pool of one region at an onset phase $\theta_{\text{on}}$ (see Sec. 3.2.3 for full details). Here we assume that the stimulation targets area 1 (Fig. 3.19A).

For a single WC unit, we saw that rhythmic external drive of different frequencies could speed up or slow down the regional activity. Here, we are interested in the question of how such targeted stimulation alters collective phase-locking across a multiarea network. To investigate
this question, we begin by simulating the network dynamics for 2 seconds with no stimulation.

**Figure 3.18 (following page):** Response of a stochastic 4-area network to brief perturbation pulses applied to area 1: Working Point 2. The key network parameters are: $P_E = 1.3$, $T_D = 2.5$ ms, $G_{EE} = 0.2$, $\alpha = 5$, $\sigma = 0.125$. (A) The baseline distribution $P(\Delta \theta_{1,2})$ of phase differences $\Delta \theta_{1,2}$ between areas 1 and 2 across a long simulation. The black lines indicate the values of the stable phase differences in the absence of noise. (B) Activity time-series from a trial where a successful phase-advance transition is induced by applying a pulse perturbation to the yellow area at the time denoted by the black bar (pulse parameters are $A_s = 1.5$, $T_s = 4.0$ ms, $\theta_{on} = 1.8$ rad). (C) Activity time-series from a trial where a successful phase-delay transition is induced by applying a pulse perturbation to the yellow area at the time denoted by the black bar (pulse parameters are $A_s = 1.5$, $T_s = 4.0$ ms, $\theta_{on} = 0.6$ rad). (D) The estimated phase-advancing transition probability $P_{\text{advance}}$ induced by pulse inputs applied at different onset phases $\theta_{on}$. A successful state transition occurs if the ordering of the phases switches to the correct configuration within 2 cycles and the new ordering lasts for at least 5 more cycles following the initial switch. The red horizontal line indicates the estimated likelihood of observing the same behavior spontaneously, i.e., in the absence of a perturbation. The pulse parameters are $A_s = 1.5$, $T_s = 4.0$ ms. (E) The estimated phase-advancing transition probability $P_{\text{advance}}$ as a function of the pulse onset phase $\theta_{on}$ and the pulse duration $T_s$, for fixed amplitude $A_s = 1.5$. A successful state transition occurs if the ordering of the phases switches to the correct configuration within 2 cycles and the new ordering lasts for at least 5 more cycles following the initial switch. (F) The estimated phase-advancing transition probability $P_{\text{advance}}$ as a function of the pulse onset phase $\theta_{on}$ and the pulse amplitude $A_s$, for fixed duration $T_s = 4.0$ ms. A successful state transition occurs if the ordering of the phases switches to the correct configuration within 2 cycles and the new ordering lasts for at least 5 more cycles following the initial switch. (G) The estimated phase-delaying transition probability $P_{\text{delay}}$ induced by pulse inputs applied at different onset phases $\theta_{on}$. A successful state transition occurs if the ordering of the phases switches to the correct configuration within 2 cycles and the new ordering lasts for at least 5 more cycles following the initial switch. The red horizontal line indicates the estimated likelihood of observing the same behavior spontaneously, i.e., in the absence of a perturbation. The pulse parameters are $A_s = 1.5$, $T_s = 4.0$ ms. (H) The estimated phase-delaying transition probability $P_{\text{delay}}$ as a function of the pulse onset phase $\theta_{on}$ and the pulse duration $T_s$, for fixed amplitude $A_s = 1.5$. A successful state transition occurs if the ordering of the phases switches to the correct configuration within 2 cycles and the new ordering lasts for at least 5 more cycles following the initial switch. (I) The estimated phase-delaying transition probability $P_{\text{delay}}$ as a function of the pulse onset phase $\theta_{on}$ and the pulse amplitude $A_s$, for fixed duration $T_s = 4.0$ ms. A successful state switch occurs if the ordering of the phases switches to the correct configuration within 2 cycles and the new ordering lasts for at least 5 more cycles following the initial switch.
CHAPTER 3.

A

1      2      3      4
phase

B

phase-advance

activity

time (s)

C

phase-delay

activity

time (s)

D

\[ A_s = 1.50, \ T_s = 4.00\text{ms} \]

\[ P(\Delta \theta_{1,2}) \]

\begin{align*}
&\Delta \theta_{1,2} \\
&\hspace{1cm} 0 \\
&\hspace{2cm} 0.01 \\
&\hspace{3cm} 0.02 \\
&\hspace{4cm} 0 \\
&\hspace{5cm} 2 \\
&\hspace{6cm} 4 \\
&\hspace{7cm} 6 \\
\end{align*}

E

amplitude \( A_s = 1.50 \)

duration \( T_s = 4.00 \text{ms} \)

F

amplitude \( A_s \)

duration \( T_s = 4.00 \text{ms} \)

G

amplitude \( A_s = 1.50 \)

duration \( T_s = 4.00 \text{ms} \)

H

amplitude \( A_s \)

duration \( T_s = 4.00 \text{ms} \)
Figure 3.19: Response of a deterministic 2-area network to rhythmic stimulation. (A) Schematic of the model setup. We study the response of a deterministic 2-area brain circuit to a sinusoidal input of amplitude $A_s$ and frequency $f_s$. The perturbation targets only one of the two regions. The network parameters are fixed to $P_E = 1.35$, $G_{EE} = 0.2$, and $T_D = 1.5$ ms. (B) Activity time-series of the two regions under baseline conditions. The network locks into collective state $S_2$, where area 2 leads area 1 in phase. (C) The phase-locking value $\rho_{1,2}$ between the two areas as a function of the stimulation frequency offset $\Delta f_s$ and the stimulation amplitude $A_s$. (D) The sign of the phase difference between the two regions’ activity as a function of the stimulation frequency offset $\Delta f_s$ and the stimulation amplitude $A_s$. (E) The value of the phase difference between the two regions’ activity as a function of the stimulation frequency offset $\Delta f_s$ and the stimulation amplitude $A_s$. The red bar on the color scale indicates the value of the phase difference at baseline. (F) Activity time-series showing the effects of stimulating the yellow area with $A_s = 0.2$ and $\Delta f_s = -2.50$ Hz. (G) Activity time-series showing the effects of stimulating the yellow area with $A_s = 0.2$ and $\Delta f_s = -1.00$ Hz. (H) Activity time-series showing the effects of stimulating the yellow area with $A_s = 0.2$ and $\Delta f_s = 2.00$ Hz.
applied. This allows the system to settle into a phase-locked attractor (here state $S_2$). After the system has relaxed to an equilibrium, the rhythmic stimulation is initiated the next time the phase of the receiving area’s intrinsic oscillation is equal to $\theta_{on}$, and it remains present for the rest of the simulation. To assess the dependence on the parameters of the external input, we repeat this protocol for 50 onset phases evenly spaced in the range $[0, 2\pi]$, and for a range of stimulation frequencies and amplitudes.

The effects of the external input on the network’s collective dynamical state are assessed in two ways. We first determine whether circuit activity remains phase-locked in the presence of the stimulation by computing the PLV between the two regions across a 2-second window that begins 2 seconds after the stimulation is first turned on. This is important to understand, as we are interested in coherent dynamics in the first place. If the network does remain in a locked configuration, we then measure the value and sign of the phase difference $\Delta \theta$ between the two areas over the same time segment. Both of these latter two quantities are then compared against their values in the baseline scenario. Note that in what follows, we quantify various results in terms of the frequency offset $\Delta f_s = f_s - f_o$ between the stimulation and intrinsic oscillation frequency.

Fig. 3.19C shows the phase-locking value $\rho_{1,2}$ between the two units in the network for different stimulation amplitudes and frequency offsets. Note first that the system remains phase-locked for a larger range of $\Delta f_s$ as the amplitude increases. Also observe that it is generally easier for the network to remain in a coherent state for positive values of $\Delta f_s$ than for negative ones. This fact implies that phase-locking is more easily maintained when the perturbed unit is driven at frequencies slightly greater than its baseline frequency compared to frequencies slightly less than its baseline frequency. Although we do not study a wider set of $\Delta f_s$ values here, we would expect the PLV to eventually drop off for large enough positive values as well. Importantly, outside of the locking region indicated by $\rho_{1,2} \approx 1$, the external stimulation actually destroys the functional connectivity states that we set out to examine in the first place. An example of such a breakdown is shown in Fig. 3.19F. While the ability to steer a multiarea circuit into an entirely new dynamical regime with focal inputs is important and interesting, we leave further investigation of this direction to future work.

We next consider the direction of the phase relation between the areas inside the phase-locked region. Recall that prior to the stimulation, the network exists in state $S_2$, where area 2 leads area 1 ($\Delta \theta < 0$). When area 1 receives the localized external input, however, we find that the lead-lag configuration is consistently altered such that region 1 leads region 2 ($\Delta \theta > 0$) and
that this result is independent of the onset phase (Fig. 3.19D). In other words, when the rhythmic stimulation is ongoing, its presence breaks the symmetry of the system and causes the perturbed area to become the phase-leader in parameter ranges where phase-locking is maintained. This is a form of persistent state control in which a rhythmic bias to one area selects that region as the phase-leader, and thus persistently shifts the phase relations. Perhaps of more interest is the fine-tuned modulation of the phase difference enabled by varying the frequency offset $\Delta f_s$. This effect is depicted in Fig. 3.19E, which shows the phase difference $\Delta \theta$ between the two areas (averaged over all onset phases) as a function of the stimulation amplitude and frequency offset. Here we observe that increasing $\Delta f_s$ widens the phase difference, whereas decreasing $\Delta f_s$ has the opposite effect. Hence, for a given amplitude, a large range of phase relations is possible via manipulation of the frequency offset. Examples of the activity time-series for negative and positive values of $\Delta f_s$ are shown in Figs. 3.19G and H, respectively.

To summarize, we find that for the 2-area circuit, locally-applied rhythmic stimulation first breaks the symmetry of the system and biases the dynamics into a specific phase ordering. Second, within that constraint, the spatial configuration of the areas’ oscillations can be varied by tuning the stimulation frequency. We refer to this latter type of regulation of the collective phase-locking state as “state-morphing”.

Figure 3.20 (following page): Response of a deterministic 4-area network to rhythmic stimulation. (A) Schematic of the model setup. We study the response of a deterministic 4-area brain circuit to a sinusoidal input of amplitude $A_s$ and frequency $f_s$. The perturbation targets only one of the four regions, which in this case is area 1 (yellow). The network parameters are: $P_E = 1.325$, $G_{EE} = 0.2$, and $T_D = 2.5$ ms. (B) Activity time-series of the four regions under baseline conditions. The network locks into collective state $S_1$. (C) The yellow area indicates where the network is collectively phase-locked as a function of the stimulation frequency offset $\Delta f_s$ and the stimulation amplitude $A_s$. (D) The state-morphing factor $M_f$ as a function of the stimulation frequency offset $\Delta f_s$ and the stimulation amplitude $A_s$. The white areas correspond to parameters where the circuit is not phase-locked. (E) The state-morphing factor $M_f$ as a function of the stimulation frequency offset $\Delta f_s$ for a fixed stimulation amplitude $A_s = 0.1$. In the gray area, network phase-locking breaks down due to the stimulation. (F) Relative phase configurations of the network for different frequency offsets $\Delta f_s$ for a fixed amplitude $A_s = 0.1$. (G) Snapshots of the activity time-series for different frequency offsets $\Delta f_s$ for a fixed amplitude $A_s = 0.1$. 

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CHAPTER 3.

A baseline

\[ \theta_{on} \]

S(t)

1 2 3 4

D E

S_1: 1 \rightarrow 4 \rightarrow 2 \rightarrow 3 \rightarrow 1

baseline

1/f_s

\[ \Delta f_s = 0.6 \text{ Hz} \]

\[ \Delta f_s = -0.6 \text{ Hz} \]

\[ \Delta f_s = -1.2 \text{ Hz} \]

\[ \Delta f_s = -2.2 \text{ Hz} \]

\[ \Delta f_s = -3.0 \text{ Hz} \]

locked

not locked

C

F

\[ \Delta f_s = -3.0 \text{ Hz} \]

\[ \Delta f_s = -2.2 \text{ Hz} \]

\[ \Delta f_s = -1.2 \text{ Hz} \]

\[ \Delta f_s = -0.6 \text{ Hz} \]

baseline

\[ \Delta f_s = 0.6 \text{ Hz} \]

E

amplitude \( A_s = 0.10 \)

G

activity

time (s)

activity

time (s)

activity

time (s)

activity

time (s)

activity

time (s)
4-area networks: Deterministic limit

In this section we examine the slightly more complex 4-area network in the deterministic limit, studying the response of its collective dynamics to focal but sustained rhythmic stimulation. For the baseline parameters of the circuit, we use the same ones as employed in Sec. 3.3.4 to investigate the effects of input pulses: $P_{E,j} = 1.325$ for $j \in \{1, \ldots, 4\}$, $G_{EE} = 0.2$, and $T_D = 2.5$ ms. For these values, population activity phase-locks across all areas, and depending on the initial conditions, the lead-lag relations correspond to one of six unique collective states (see Sec. 3.3.1, Fig. 3.6E for details). In what follows, the system is prepared in state $S_1$, and is then perturbed from that starting position. Fig. 3.20B shows a snapshot of the network’s activity pattern at baseline, from which one observes the phase-ordering $1 \rightarrow 4 \rightarrow 2 \rightarrow 3 \rightarrow 1$. Similar to the 2-area circuit, system dynamics are perturbed via a sinusoidal input to the excitatory subpopulation of area 1 (yellow unit). In terms of the stimulation, the parameters of interest are the frequency $f_s$ of the external input, its amplitude $A_s$, and the phase of the ongoing oscillation $\theta_{on}$ at which the stimulation is initiated (see Sec. 3.2.3 for complete details). Note also that we report results in terms of the frequency offset $\Delta f_s$ that measures the difference between the stimulation frequency and the baseline oscillation frequency of the areas in the circuit. A schematic of the system setup is depicted in Fig. 3.20A.

To understand how sustained rhythmic input may reshape or modulate the networks’ phase-locked activity patterns, we first need to map the conditions under which coherent dynamics are maintained in the presence of the stimulation. To determine these conditions, we scan over a range of stimulation frequencies and amplitudes, and from those simulations, compute the phase-locking value between all regions to determine if the network remains in a locked state for each parameter pair. More precisely, for a given stimulation frequency-amplitude combination, system dynamics are first allowed to settle into state $S_1$ across a 2-second window during which no external input is applied. After this relaxation time period, the stimulation is activated the next time the oscillation phase of the receiving area is $\approx \pi$, after which the stimulation remains on for the remainder of the simulation. We then compute the PLV between all region pairs across a 2-second window that begins 2 seconds after the stimulation onset, again in order to allow network dynamics to reequilibrate.

The “locking region” of the circuit (i.e., combinations of the frequency offset $\Delta f_s$ and amplitude $A_s$ for which the mean PLV over all region pairs exceeds a high threshold of 0.99) is presented in Fig. 3.20C. Interestingly, this analysis reveals that while the network can indeed remain in a phase-locked state for certain external inputs, the locking region is skewed towards
lower values of $\Delta f_s$. In other words, network-wide locking can be maintained at lower stimulation amplitudes when the stimulation frequency is slightly smaller than the baseline oscillation speed. Note that this does not mean the stimulated site itself cannot lock to higher frequency input, but that the network as a whole cannot remain in a coherent configuration if the external rhythm is too fast. Hence, the leftward skew in Fig. 3.20C is really a property of the entire coupled system, rather than of a single WC unit. Understanding this phenomenon on a deeper level would be an interesting direction for future work, though we do not explore it further here. A second albeit expected point to note based on Fig. 3.20C is that, as the stimulation amplitude is increased, the range of frequency offsets across which phase-locking is maintained expands. This is especially noticeable for $\Delta f_s > 0$. Finally, we note that the above results do not depend on the onset phase $\theta_{on}$.

Having delineated the locking-region for the network under focal rhythmic stimulation, we are now in a position to dig deeper into if and how the actual phase relations among the neural populations are modulated by the external drive. In general, we find that the rhythmic input can have two distinct effects on the collective state. First, if the stimulation is turned on at particular onset phases of the ongoing oscillation, then it can induce a change in the phase-ordering in a manner similar to the state-switching that occurs for the input pulses studied in Sec. 3.3.4 (not shown). Note that this effect occurs due to a transient shifting of the regional oscillations as they first react to the turning-on of the stimulation. Importantly, though, even if the onset phase is such that no switching is induced, the sustained rhythmic input still causes a separate modulation of the phase-locking pattern. Specifically, it induces a shifting – or “morphing” – of the spatial configuration of the phase relations relative to their geometric arrangement at baseline (Fig. 3.20F). That is, once a phase-ordering is established (whether or not it is different from that which existed prior to the stimulation onset), the external drive further regulates the actual phase differences between each pair of areas such that the $\Delta \theta_{ij}$’s between consecutive areas $i$ and $j \neq i$ are no longer necessarily equal to $\pm \pi/2$. We refer to this more fine-tuned realignment of the spatial layout of the oscillation phases within a particular phase-ordering as “state-morphing”.

In order to quantify the extent of state-morphing induced by a rhythmic external input to one region in the circuit, we define a quantity that we term the “state-morphing factor”, $M_f$. In order to do this, we first reiterate that “state-switching” refers to a change in the ordering of the phases relative to one another (i.e. it corresponds to a topological rearrangement of the functional state that depends on the area labels). In contrast, we would like our notion of state-morphing to be a measure of how much the geometrical organization of the phases differs between baseline
and the case of oscillatory external drive in a manner that is independent of the original node labeling/ordering. To define such a quantity, it is first helpful to introduce a bit more notation. Specifically, we let $S_j^s$ for $j \in \{1, \ldots, 6\}$ label the state of the system under focal stimulation (after transient effects have been discarded), where $j \in \{1, \ldots, 6\}$ indicates the ordering of the units’ activity peaks (or phases). $S_j^s$ has a corresponding baseline state $S_j$ with the same circular ordering of the phases. In addition to this topological information, we also tabulate the relative spatial positions of the phases in each state $S_j^s$ and $S_j$ relative to the same reference area (e.g., the stimulated region 1), which is assumed to always be located at zero. In other words, because the areas are phase-locked under both baseline and stimulation conditions, we can go into the reference frame that rotates with the same angular velocity as the system under study, and then recalibrate such that region 1 is at a phase of zero radians in that frame. Doing this for the stimulation condition, we can then define a set of phases $\{\theta_i^s\} \in [0, 2\pi]$ for $i \in \{1, \ldots, 4\}$ that indicate the angular positions of the four areas (note that $\theta_1^s = 0$). The same procedure can be carried out for the corresponding baseline state with the same phase-ordering, yielding another set of relative phases $\{\theta_i^b\} \in [0, 2\pi]$ for $i \in \{1, \ldots, 4\}$, where again $\theta_1^b = 0$. Once the relative phases are computed from the dynamics of the system under the influence of rhythmic simulation and of the corresponding baseline state, we calculate the state morphing factor as

$$M_f = \sum_{i=1}^{N} |\theta_i^s - \theta_i^b|.$$  

(3.8)

This quantity summarizes the extent of shifting of the phase configuration under focal stimulation relative to the arrangement at baseline with the same topological ordering.

In Fig. 3.20D, we show the state-morphing factor (within the phase-locked region) as a function of the stimulation amplitude $A_s$ and the frequency offset $\Delta f_s$. This analysis indicates that the extent of state-morphing is primarily modulated by the frequency offset, which is especially clear by examining values of $\Delta f_s < 0$ for fixed amplitude. In particular, we find that as $\Delta f_s$ decreases from zero, the amount of morphing of the collective state increases. This behavior indicates that the frequency of external input is a control parameter that tunes how much the geometric configuration of the phases changes relative to the baseline configuration. Also note, though, that near a frequency of $\Delta f_s = 0$, for example, that state-morphing can be induced simply by increasing the amplitude of the stimulation. Thus, both stimulation parameters can play a role in reorganizing the collective phase-locking state.
Going back to the dependence of $M_f$ on the frequency offset $\Delta f_s$, we observe that especially for smaller amplitudes, there are three main morphing regimes highlighted by the three main blocks of color in Fig. 3.20D. To see these regimes even more clearly, we consider a cross-section of the state morphing factor for fixed amplitude $A_s = 0.1$ but varying $\Delta f_s$ (Fig. 3.20E). Here one can see that for $\Delta f_s < 0$, there are three clusters that each contain points with relatively similar values of $M_f$, and the clusters themselves are separated by steeper vertical “jumps” as the frequency offset decreases. We also see that as $\Delta f_s$ increases in the positive direction, the state-morphing factor also increases, up until the point that phase-locking breaks down altogether.

In order to understand more fundamentally how the interareal phase relations are modulated at different levels of the state-morphing factor, we examine the relative phases of each area (Fig. 3.20F) and their activity time-series (Fig. 3.20G) for different values of the frequency offset $\Delta f_s$. We observe that for small negative frequency offsets all four regions remain separated by a non-zero phase difference, but the phase lag between the stimulated area 1 (yellow) and the area that leads it (region 3, green) increases slightly from baseline, and the stimulated region also slightly increases its phase-lead over region 4 (red). If the frequency offset is decreased slightly further, we enter the second $M_f$ cluster. In this regime, the area that initially lagged the stimulated region (area 4, red) and the area that was initially anti-phase with it (area 2, purple) merge with one another such that they become in-phase and collectively further behind the stimulated site. Simultaneously, the phase difference between area 3 (green) and the stimulated area increases. Decreasing $\Delta f_s$ slightly more within this same regime further modulates the spatial arrangement of the oscillatory activity peaks, such that area 1, which receives the external input, becomes a global phase-leader. When the frequency offset is made yet smaller, the circuit enters the third state-morphing cluster present in Fig. 3.20E. Here, all units except the stimulated region merge into a single in-phase cluster, which itself lags behind the stimulated site. We can also consider slightly positive frequency offsets at this same stimulation amplitude (before phase-locking breaks down). In this case, we see that the most dramatic effect is that the stimulated area moves closer to the region that leads it in phase; the other phase relations are also modulated slightly as well.

In sum, we see that focal, rhythmic stimulation morphs the collective phase-locking state, inducing shifts in the relative spatial arrangement of population oscillations. We discuss potential functional roles of this type of state control in the Discussion.
2-area networks: Stochastic scenario

In the previous two subsections, we examined the response of collective phase-locking states to rhythmic stimulation in the limit of deterministic dynamics. Here we continue this analysis for the more realistic scenario in which the model brain circuits are driven by a stochastically fluctuating background environment (Sec. 3.2.2). We begin with the 2-area system, and study the effects of sustained oscillatory input when the baseline parameters are $P_{E,j} = 1.35$ for $j \in \{1, 2\}$, $T_D = 1.5$ ms, $G_{EE} = 0.2$, $\alpha = 15$, and $\sigma = 0.15$. As detailed thoroughly in Sec. 3.3.1 and Fig. 3.4, introducing noise causes both lead-lag configurations to be sampled as the system evolves. A consequence of this behavior is the appearance of two metastable, out-of-phase peaks in the distribution of interareal phase differences $P[\Delta \theta]$ (see the gray curve in Fig. 3.21A, which was derived from a long baseline simulation of 22 minutes in length).

To assess the effects of focally-applied rhythmic input on the circuit’s collective dynamics, we examine how it alters the distribution $P(\Delta \theta)$ relative to the baseline shape. To do this, we stimulate area 1 in the same way as before, and again vary both the stimulation amplitude $A_s$ and
frequency offset $\Delta f_s$. Note that because the system is now stochastic, the oscillation frequency can vary from cycle to cycle, but the stimulation frequency can still be compared to the frequency that corresponds to the peak of the power spectra computed across the entirety of the baseline simulation. For each combination of $A_s$ and $\Delta f_s$, we run a simulation equal in length to the baseline version (i.e. 22 minutes in duration), and then recompute $P(\Delta \theta)$.

In Fig. 3.21A, we plot the distributions of phase differences $P(\Delta \theta)$ for different values of the frequency offset $\Delta f_s$ and for a fixed stimulation amplitude $A_s = 0.25$. As with the noiseless case (Fig. 3.19D,E) we find that the stimulation breaks the symmetry of $P(\Delta \theta)$ present at baseline and causes one of the two lead-lag directions to become preferred. Specifically, under the influence of rhythmic input, the two equally tall peaks disappear in favor of asymmetric distributions with boosted maxima at values $\Delta \theta > 0$. In this way, stimulating region 1 causes that area to preferentially become the phase-leader. Moreover, akin to the deterministic results, the frequency offset $\Delta f_s$ controls the location of the peak of $P(\Delta \theta)$. Hence, fine-tuning of the collective phase relation – albeit in a probabilistic manner – can be obtained by modulating a property of the external input.

For the stochastic scenario, we additionally observe that the peak height of $P(\Delta \theta)$ varies with $\Delta f_s$. In particular, stimulating with $\Delta f_s = 0$ Hz (such that the stimulation frequency is the same as the baseline frequency) yields the tallest and narrowest phase difference distributions. Shifting the frequency offset to the left or right of zero leads to broader and shorter distributions (less consistent phase-locking) with the effect being more drastic for negative frequency offsets $\Delta f_s < 0$. These results can be understood in the context of the noiseless case as well, where we saw that network phase-locking broke down more easily when $\Delta f_s$ was shifted away from zero in the negative direction than vice versa (Fig. 3.19C). Finally, we observe that for all frequency offsets, the peak of the phase difference distribution $P(\Delta \theta)$ increases with the stimulation amplitude $A_s$ (Fig. 3.21B). As we should expect, this behavior indicates that a stronger input leads to tighter phase relations.

**4-area networks: Stochastic scenario**

Continuing methodically, in this section we examine the response of stochastic 4-area networks to targeted rhythmic stimulation. To carefully compare with the deterministic case, we use the same baseline parameters as in Sec. 3.3.5 ($P_{E,j} = 1.325$ for $j \in \{1, ..., 4\}$, $T_D = 2.5$ ms, $G_{EE} = 0.2$). In terms of the noise, we set $\alpha = 15$ and $\sigma = 0.2$. A detailed characterization of the baseline dynamics of the circuit with stochastic inputs can be found in Sec. 3.3.1. Here we simply remind
Figure 3.22: Response of a stochastic 4-area network to rhythmic stimulation. The key network parameters are: $P_E = 1.325$, $T_D = 2.5$ ms, $G_{EE} = 0.2$, $\alpha = 15$, $\sigma = 0.2$. (A) The distribution $P(\Delta \theta_{1,2})$ of the phase difference between areas 1 and 2 (Left) and the joint distribution $P(\Delta \theta_{1,2}, \Delta \theta_{1,3})$ of $\Delta \theta_{1,2}$ and $\Delta \theta_{1,3}$ (Right) under baseline conditions. (B–E) The gray histograms in the left panels show the distribution $P(\Delta \theta_{1,2})$ of the phase difference between areas 1 and 2 for a stimulation amplitude $A_s = 0.1$ and for varying frequency offsets $\Delta f_s = \{0.5, -0.5, -1.5, -3.0\}$ Hz. For comparison, the green curves show the baseline distribution. The right panels show the joint distribution $P(\Delta \theta_{1,2}, \Delta \theta_{1,3})$ of $\Delta \theta_{1,2}$ and $\Delta \theta_{1,3}$ for a stimulation amplitude $A_s = 0.1$ and varying frequency offsets $\Delta f_s = \{0.5, -0.5, -1.5, -3.0\}$ Hz.
the reader that the noise causes the network to spontaneously sample collective activity patterns that resemble approximate forms of the six multistable states from the deterministic limit. This results in a trimodal distribution \( P(\Delta \theta_{1,2}) \) of the phase differences between a given pair of units 1 and 2 in the network (Fig. 3.22A, Left) and the emergence of six high density areas in the joint distribution \( P(\Delta \theta_{1,2}, \Delta \theta_{1,3}) \) of two unique pairs of phase relations (Fig. 3.22A, Right). Note that choosing other combinations of distinct units gives similar results.

We model rhythmic stimulation identically to the deterministic case, which is by injecting a sinusoidal input of amplitude \( A_s \) and frequency offset \( \Delta f_s \) into the excitatory subpopulation of area 1 (see Sec. 3.3.5 for details). In the absence of noise, a key finding of our analysis was that varying the frequency offset \( \Delta f_s \) resulted in a morphing of the collective state wherein a given phase-ordering was maintained but the precise values of the pairwise phase differences shifted relative to the baseline configuration (Sec. 3.3.5, Fig. 3.20). Here, we thus focus on how changing \( \Delta f_s \) modulates the univariate and bivariate distributions \( P(\Delta \theta_{1,2}) \) and \( P(\Delta \theta_{1,2}, \Delta \theta_{1,3}) \) relative to their baseline shapes (in what follows, note that the conclusions are the same for any \( P(\Delta \theta_{1,j\neq1}) \) and \( P(\Delta \theta_{1,j\neq1}, \Delta \theta_{1,k\neq j}) \)). To do this, we run long simulations (15 minutes in total length) for different values of the stimulation frequency offset, holding the stimulation amplitude fixed at a value \( A_s = 0.1 \). This procedure allows us to properly sample the phase-locking statistics of the network’s dynamics under different stimulation conditions. Note that the frequency offset is computed as the difference between the stimulation frequency and the peak frequency from the baseline power spectrum determined from the entire length of the simulation. The results of our analysis are presented in Fig. 3.22; the center panel corresponds to baseline conditions and the four panels around the edge correspond to stimulating area 1 with rhythmic input at four different values of \( \Delta f_s \). We unpack each case one-by-one.

To begin, we look more closely at \( \Delta f_s = 0.5 \) Hz, when the stimulation frequency is slightly higher than baseline (Fig. 3.22B). With this external input, the distribution \( P(\Delta \theta_{1,2}) \) exhibits three peaks of varying height, and the peak locations are also shifted relative to the peak locations at baseline. Six splotches can also still be resolved in the joint distribution \( P(\Delta \theta_{1,2}, \Delta \theta_{1,3}) \) (though some of them are more blurred along certain directions) indicating that there are still six different collective states. Based on the way the modes shift, we can begin to see that the peaks in the \( \Delta \theta_{1,2} \) histogram are signatures of the three distinct phase relations that exist between the stimulated node and the other areas in the network in the deterministic version of the system. In particular, the left peak shifts closer to \( \pi \), meaning that in a given collective state, the stimulated area will phase-lead one of the regions by a larger amount relative to baseline; this same effect can
be seen for one particular phase-ordering in column 6 of Fig. 3.20F, where the yellow and red areas move apart. With noise, the system will spontaneously visit different phase orderings, but in each case, there will always be one region that tends to lag further behind the stimulated area than it would in the corresponding baseline configuration with the same phase ordering. Similarly, we see that the middle and right peaks both shift towards $\Delta \theta_{1,2} = 2\pi$, indicating that the stimulated area narrows the gap but still lags behind the two other regions. This behavior is akin to the green and purple areas shifting towards the stimulated area in the deterministic example. In sum, we thus still observe the state morphing effects induced by rhythmic external input when the circuit is stochastic. One important point, though, is that while the noiseless results might lead us to conclude that all three peaks should be of approximately equal height in the noisy system, this is clearly not the case. Rather, we see that the peak heights decrease from left to right, suggesting that some of the phase relations are more stable and robust under noise than others. This manifests as a stretching of four of the six hotspots in the joint distribution as well. One reason peak asymmetry might occur is that for $\Delta f_s = 0.5$ Hz, the collective dynamics (in the deterministic system) are close to an instability in that increasing the frequency offset a bit further would lead to a breakdown of perfect phase-locking and the onset of quasiperiodic dynamics. In the latter case, the system will spend longer amounts of time near certain phase differences. It may be the case that – due to noise – the system exhibits signatures of this regime as well.

When the frequency offset is instead decreased to $\Delta f_s = -0.5$ Hz, we again see evidence of spontaneous switching between morphed versions of the six collective baseline states (Fig. 3.22C). In particular, $P(\Delta \theta_{1,2})$ remains trimodal, but the left and right peaks move towards $\pi$, indicating slightly increased absolute phase differences with the stimulated node relative to baseline. These modulations are relatively consistent with the picture in Fig. 3.20F, Column 4, where the green and red phases shift further away from the stimulated site, whereas the purple area remains near its location prior to stimulation. Note also that the precision of the two out-of-phase peaks becomes tighter under stimulation.

Continuing to decrease the frequency offset to $\Delta f_s = -1.5$ Hz results in even more drastic state morphing (Fig. 3.22C) that can yet again be understood or predicted from the corresponding deterministic scenario. For these conditions, the phase difference distribution $P(\Delta \theta_{1,2})$ exhibits only two peaks, each of which are also located at different positions than any of the three peaks in the baseline histogram. In addition, the left mode is significantly higher than the right mode. This situation corresponds loosely to the regime in the noiseless case where two of the non-stimulated areas merge to become in-phase with one another and collectively further lag the
stimulated region, while the third area increases its lead over the stimulated area (Fig. 3.20F, Column 3). There are thus two distinct phase relations regarding the stimulated site. In the stochastic circuit, this fact manifests as the distribution $P(\Delta \theta_{1,2})$ becoming bimodal: an area $j \neq 1$ (e.g., $j = 2$) will either lag the stimulated region in a given collective state (left peak) or lead the stimulated region (right peak). It is also more likely for a non-stimulated area to be part of the in-phase cluster than not, which explains the higher amplitude of the left mode relative to the right one. Also note that the joint distribution now exhibits three high-density areas, which are signatures of the now only three distinct collective states that the system spontaneously transitions among (either areas 2 and 3, 2 and 4, or 3 and 4 will comprise the in-phase group). Moreover, because it is more likely for one area to be leading the stimulated site and the other lagging it, the off-diagonal hotspots are more populated than the on-diagonal one.

If the stimulation frequency is reduced yet further relative to the peak baseline frequency (e.g. $\Delta f_s = -3.0$ Hz), the state morphing progresses further as well. Here we see that under stimulation, the phase difference distribution $P(\Delta \theta_{1,2})$ has only a single mode, with a position indicating that the stimulated area becomes a global phase-leader. Indeed, without noise, these stimulation parameters yield a state in which the three unperturbed nodes are drawn into a single in-phase cluster, which itself lags behind the activity of the stimulated site. As expected, in the stochastic network, the joint distribution $P(\Delta \theta_{1,2}, \Delta \theta_{1,3})$ now shows only a single well-populated region centered around the location where the two considered phase relations are approximately equal. This configuration corresponds to a smeared version of the single collective state that exists in the deterministic limit.

In total, the results of this section indicate that when the 4-area circuit is subject to stochastic background drive, targeted, rhythmic stimulation can still lead to approximate forms of collective state-morphing.

### 3.4 Discussion

Here we used computational modeling to investigate if and how coherence-based functional connectivity states in multiarea brain networks can be controlled via targeted stimulation. We specifically chose to work with a dynamical model, networks, and parameters that yielded multistable phase-locking patterns at baseline, allowing us to explore potential strategies for switching among a set of states that are all possible from a single underlying structure. Using simple 2-area and 4-area circuit motifs, we explored functional state modulation via locally-applied (i)
brief input pulses, and (ii) sustained rhythmic stimulation. When dynamics were deterministic, we found that short pulse stimuli injected into a single region could indeed induce transitions between different phase-locking patterns, so long as the input arrived within a specific range of the receiving unit’s oscillatory phase. Consistent with previous studies that have used models of interneuron-based gamma synchrony \([113, 279, 112, 278]\), in the 2-region network, this state-switching amounted to changing the sign of the collective phase relation. In the 4-region system, we further showed that two distinct state-transitions were possible, which involved either a phase-advance or a phase-delay of the perturbed site. In addition to reconfiguring the topological organization of collective states, we found that focal sinusoidal input could also modulate the geometry of the emergent phase relations, allowing for an additional type of state control. Finally, we studied the effects of incorporating realistic, stochastic background fluctuations into the model. At baseline, this caused the multistable activity patterns to become metastable. Nevertheless, the aforementioned control strategies could still be implemented successfully (albeit in a probabilistic manner) if noise levels were not too high. That said, we also showed that state-switching modulations became infeasible in a regime where regional oscillations were purely noise-driven, highlighting that the efficacy of state-control depends on how the states are generated.

3.4.1 Connections to past work and ideas

It is crucial to acknowledge the connections between our investigation and a number of inspiring studies that previously posited and explored the themes upon which our analysis rests. First, although functional interactions may take many forms, we focused here on those generated via the coherence of oscillatory activity from distributed neural populations. Hence, our study relied on the well-studied communication-through-coherence hypothesis postulating that effective communication between two neuronal groups arises when their intrinsic population rhythms lock with an appropriate phase relation \([2, 42, 108, 274, 77, 76]\). A number of experimental studies have lent support to this idea \([109, 295, 296, 106, 103, 101, 114]\), and it has also been explored in modeling efforts that use both reduced neural mass models \([113, 297]\) and more detailed spiking models \([279, 112, 278, 110, 111, 298]\).

Two other critical concepts at the heart of the present study are that of multistability and (when noise is present) metastability. These are dynamical mechanisms that have been thought to allow neural systems – across many spatial and temporal scales – to switch between a variety of different functions as the requirements of the system change \([299]\). This capability may be invaluable when the underlying structure or parameters of the system at hand cannot be changed
quickly enough to stabilize a necessary new state. Importantly, multistability could be an inherent property of a single dynamical element, or it could be an emergent, collective property of a multi-component system. The type of multistability in this work falls under the latter of those two forms. In particular, a “state” here was considered to be a particular pattern of network phase-locking, and that pattern as a whole was the multistable entity (rather than the nature of the activity in a single brain area). Other types of multistability may also manifest in brain dynamics and have been examined as well (see, e.g., Refs. [300–302]).

It is essential to emphasize that this study is not the first to propose multistable/metastable phase-locking and collective state control as mechanisms that could underlie flexible interareal communication in brain networks. On the contrary, our analysis builds directly upon the ideas presented in a collection of studies by Battaglia et al. [113], Witt et al. [279], and Palmigiano et al. [112]. Because the work presented here strongly draws from these past efforts, we feel it important to highlight their contributions and the relationships to the current study. We begin with Battaglia et al. [113], which, using both spiking simulations and a rate model, employed a causal analysis of information transfer for different multistable phase-locking states of 2-area and 3-area cortical circuits. This study showed that the different lead-lag relationships afforded by different multistable states differentially regulated the directionality of effective connectivity in the network. Hence, a direct connection between out-of-phase oscillatory coherence and flexible information flow was established. Moreover, the authors numerically and semi-analytically studied state-switching in the 2-area networks via pulse currents. The study in Witt et al. [279] also examined out-of-phase coherence in 2-area circuits by employing a spiking model, and focused specifically on formulating a detailed model of optogenetic stimulation. In particular, they developed a closed-loop stimulation protocol capable of carefully controlling the functional connectivity state of the network. We also bring specific attention to the work of Palmigiano et al. [112]. While the previously mentioned studies examined mainly a strongly synchronized regime, Palmigiano et al. [112] used a biophysically-detailed spiking model of coupled cortical areas to study out-of-phase locked states in a significantly more realistic transient synchrony regime. In particular, the authors used information-theoretic analyses to demonstrate that highly stochastic networks that exhibit only weak synchrony and short bursts of interareal coherence generated flexible information routing states dictated by collective phase relations during phase-locked windows.

Though our study was directly inspired by and bears many similarities with those noted in the previous paragraph, we point out here the main differences and extensions of the present
work. First, Refs. [113, 112, 279] used a model in which gamma oscillations and out-of-phase locking were generated by strong, delayed local inhibition. Here we instead used the classic Wilson-Cowan model, for which oscillations are generated through excitatory-inhibitory interactions, and where non-in-phase synchrony arises due to long-range delays. Importantly, we showed that many of the same conclusions could be drawn despite a different underlying model. A second difference is that – in addition to the 2-area networks – we added an analysis of collective phase-locking states and functional connectivity control in slightly larger 4-area circuits. Moreover, we also devoted significant effort to studying the effects of background noise on the baseline network dynamics and subsequently the efficacy of state modulation via local inputs. Finally, the crux of our analysis was a thorough investigation of how collective states respond to local stimulation, and we attempted to build upon and extend the previous analyses mainly on this front (for example, by studying both brief pulse perturbations and sustained rhythmic stimulation).

It is also important to note that, although we were interested here in multistable phase-locking in the context of interareal communication in large-scale brain circuits, an earlier-proposed functional role of multistable phase-locking relates to central pattern generators (CPGs) in the nervous system. CPGs are specialized neuronal circuits that can inherently produce rhythmic, phase-locked activity patterns thought to underlie repetitive motor functions such as breathing or walking [303, 304]. Past studies have shown that some biophysical models of these cellular networks are capable of producing multiple rhythmic states despite a single wiring structure [305–309], and have explored the ability of transient inputs to multistable CPGs to induce switching between patterns that generate different motor behaviors (e.g., those that correspond to different gaits of a quadruped [306] or those that correspond to cat locomotion vs. paw-shaking [310]). Despite the difference in the spatiotemporal scales and models relevant to studying CPGs vs. long-range communication in multiarea brain networks, it may be that similar dynamical mechanisms and control strategies apply in both cases.

### 3.4.2 Broader functional implications

In this section, we briefly expand on some potential broader implications of this work related to the operating principles of interareal brain networks. First, as initially suggested and discussed in previous studies [113, 112], the emergence of multistable phase-locking may be useful from a functional standpoint by enabling a single structural network to generate a multiplicity of effective connectivity states. In this way, the system would not necessarily need to rewire its structural
connections – which may be impossible on short time-scales or energetically expensive – to support different information routing pathways. However, if the system is deterministic (or even if the intrinsic dynamics strongly enough outweigh any background noise) having multistability alone is not enough for computational flexibility. In such a limit, once a particular phase-locking pattern stabilizes, it would never (or rarely) change. Even in regimes where stochastic background fluctuations induce spontaneous switching between the circuit’s collective attractors, proper network function may still require selecting certain states at specific times. In either of these scenarios, what is needed is a means of controlling the collective phase relations.

We thus set out to investigate the potential of targeted external inputs to reconfigure multistable phase-locking patterns in multiregional brain networks. Importantly, these modulatory signals could represent exogenously-generated sensory inputs or modulation from other brain areas. In any case, they should be thought of as dynamical instruments that the brain could learn to harness for self-regulation. Though one could study arbitrarily complex control signals, we considered two approachable types – single, brief pulse stimuli and sustained rhythmic stimulation – that may nonetheless be relevant for and utilized by neural systems. Moreover, we were interested here in what is attainable via inputs that target only one area. While “control” in the brain might often manifest as simultaneous manipulation of several areas, there is also appeal in considering strategies that do not require yet further calibration and coordination.

We began by considering functional connectivity modulation in noiseless interareal circuits. For the 2-area networks, we found that focal input pulses – if strong enough and long enough, and applied at an appropriate phase of the receiving oscillation – could cause the sign of the lead-lag relation to reverse. Importantly, this same effect has been reported previously in other studies that have used alternative neural population models [113, 279]. These works have also pointed out that, in the context of the CTC hypothesis, the ability to induce state-switching in this manner has quite significant functional implications. In particular, it would enable a complete reversal of the direction of information transfer.

Expanding upon past studies, we also considered slightly larger 4-unit motifs. This system was capable of six functional connectivity states that corresponded to different evenly-spaced phase-orderings of the four areas. Assuming these patterns correspond to distinct routing states with communication flowing from phase-leader to phase-lagger (and no transmission between far-separated anti-phase units), a configuration with the ordering $1 \rightarrow 2 \rightarrow 3 \rightarrow 4 \rightarrow 1$ would indicate that area 1 sends/receives information to/from areas 2 and 4, respectively, and does not communicate with area 3 (and similarly for the other units). In these networks, sin-
gle pulse inputs could also trigger topological reconfiguration of functional interactions, with the perturbed site either phase-advancing or phase-delaying relative to its neighbor depending on the onset phase. For the above illustration and assumptions, a phase-advance transition of area 1 would, for example, cause it to instead send information to area 4 and receive communication from region 3. These results again support the idea that a single, focal pulse can not only transiently affect the activity of the stimulated region, but can also induce a global alteration of interareal communication patterns, which may in turn allow the system to carry out a different task. Moreover, perturbation of a different area could lead to distinct transitions.

A key part of this study was the analysis of functional state modulation in the presence of realistic stochastic background drive. As in the more complex models presented in Refs. [279, 112], we found that incorporating noise causes the multistability to turn into metastability, such that the network resided near one collective state for some time before desynchronizing or transitioning into another of its favored configurations. Furthermore, we showed how changing the noise parameters or the working point of the model could shift the baseline volatility and fuzziness of the collective states at baseline. In the presence of noise, the notion of perturbation-induced state-switching thus becomes probabilistic and its effectiveness must be measured relative to the chance of observing the same result spontaneously. Indeed, if given long enough, the stochastic networks will sample each of their preferred arrangements on their own. However, critical to the functional capabilities of a circuit is also how quickly it is able to enter or leave a particular state. This fact implies the importance of investigating whether a local pulse input can induce an on-demand, lasting state switch at likelihoods that exceed chance levels. If this is the case, then the perturbation serves as a mechanism for de-selecting/selecting certain states at particular moments.

For both the 2-area and 4-area networks that operated in noisy versions of the multistable regime, we found that well-timed pulse inputs – if applied during coherent windows – could indeed significantly accelerate state switching. Hence, local control signals had consequential effects precisely when they were needed most; that is, when the collective state would take time to change on its own. Moreover, coherent windows in which the system naturally wants to reside near one of its attractors are also the times at which we would expect the effect of the perturbation to last for long enough to be functionally meaningful. It is also important to note, though, that the efficacies of perturbation-induced state switching decreased with decreasing signal-to-noise. This effect is certainly undesirable, but because the networks rarely exited a given phase-locked state within just a couple of cycles, perturbations continued to be useful for state regulation (al-
beit to a lesser extent) even when the baseline activity patterns were more volatile. One other point to comment on is that, even if the phase configuration after a perturbation cannot stabilize near one of the noiseless attractors, this does not automatically imply that the perturbation would have no functional consequence. Rather, it may be useful at times to simply prevent communication or information transfer in particular directions. This control could still be achieved through the topological reorganization induced by the perturbation, even if the new state is short-lived or if the resulting phase relations are not tightly aligned. In sum, our findings suggest that even in a stochastic setting, collective multistability – in conjunction with precisely timed perturbations – can be harnessed to rapidly reconfigure effective connectivity patterns in interareal networks. This rapid state-switching may enable the circuit to more quickly perform a different computation, or, at the very least, stop its current one immediately.

Also crucial to understand is how state-switching control can break down. In the context of our model, we showed that one scenario where this occurred is when regional oscillations and phase-locking were purely noise-driven. In particular, we studied a parameter set where the 2-area network was in a non-oscillatory state in the absence of noise, but with stochastic fluctuations, exhibited two out-of-phase peaks in its phase difference distribution. This was an important working point to consider, as it first showed how the presence of out-of-phase peaks do not in and of themselves indicate dynamical multistability in the deterministic limit. In the scenario discussed here, the asymmetrical states instead arose entirely due to transient differences in the level of background input to each unit. Nonetheless, it was still possible to extract phase-locked windows around the favored configurations and test the effects of pulse stimuli. In doing so, we found that state-switching could not be reliably induced at levels significantly above chance. Hence, while some statistics of the baseline dynamics appeared to have similar structure to other working points, the system was not controllable via brief inputs. This finding may seem surprising initially. But, further thought leads us to reason that if asymmetric phase-locking is a result only of noise rather than underlying multistability (or nearness to a multistable regime), then an only transient input should have a difficult time yielding a lasting effect (since the system does not truly have two attractors). In addition, the relatively low amplitude and very rapid dissolution of phase-locking likely also contribute to the inability to control collective states in such a regime. One other interesting implication of these findings is that it suggests focal perturbations may enable one to discern the dynamical nature/operating point of collective neural activity states in vivo, for example, via optogenetic stimulation [311].

We have thus far focused on the functional implications of being able to induce state-
CHAPTER 3.

switching – topological reorganizations of the collective state – via pulse inputs. In the second portion of our study, we also explored the influence of focal rhythmic stimulation, finding that a different type of state-modulation became possible in this case. For the 2-area networks with and without noise, the first consequence of oscillatory drive (with appropriate amplitude and frequency) was a symmetry-breaking effect: it caused the stimulated area to become the global phase-leader. A possible functional implication of this effect is that interareal communication would be prevented (or would be significantly more unlikely) in one direction and boosted in the other (given that the sign of the phase relation governs the direction of information flow). Additionally, we found that tuning the frequency of the input signal could enable a more fine-tuned shifting of the phase difference to larger or smaller values. This more tailored control may be important if the system requires a slight adjustment of a particular transmission line in order to more accurately perform a certain operation in a perturbed environment, for example.

The long-lasting effects of rhythmic stimulation on the collective states in 4-area circuits were slightly more complex, but they could still be characterized as a form of state-morphing: a modulation of the spatial arrangement of the phase relations relative to the corresponding uniform, baseline configuration. If the stimulation frequency was close to the baseline frequency, we found that the pairwise phase relations shifted relative to one another – with different pairs becoming closer together or farther apart – but all phase differences remained non-zero. We can again hypothesize about the importance of this fine-tuned adjusting within the CTC framework, where interareal phase relations define the efficiency of communication \[2, 42, 108, 274\]. In that setting, it could be beneficial for a network to have a means of slightly re-weighting (boosting or depressing) the strengths of its different routing channels in order to optimally process and transfer information depending on the broader context. In other words, a system might be roughly in the correct state, but with small corrections needed for optimal performance. Or, it may be that a system is in a pathological condition, and morphing control could enable a reduction or enhancement of effective interaction strengths that are abnormally high or low. We also found that morphing effects could be made more extreme by altering the stimulation frequency further. For example, two areas initially separated by a non-zero phase-lag could be pushed together, such that they merged into a single in-phase cluster. This type of modulation might allow for bidirectional information flow between the areas that coalesce into a single coherent group.
3.4.3 Limitations and future work

This investigation has limitations, and therefore leaves open a number of important directions to explore in forthcoming studies. First, in our use of the Wilson-Cowan model, we have studied a computationally tractable but highly idealized realization of neural population activity. On the one hand, the relative simplicity of the WC model permitted a thorough mapping of networks’ baseline dynamics in the presence of stochastic background inputs, as well as in-depth analyses of functional state manipulation at a variety of working points, for different networks, and for different perturbations. Moreover, it may even be possible to make some analytical progress in the context of this model in future work. On the other hand, though, only more biologically detailed models allow for (i) linking microscopic, spiking-level neuronal activity to population-level phase-locking [112] and collective state control [279], and (ii) an understanding of how macroscopic functional states relate to interareal communication and information flow at the level of individual spike patterns [113].

A second limitation of this study is the simplicity of the anatomical network connectivities. Specifically, we opted to examine canonical structural motifs that exhibited clean, multistable phase-locking in the deterministic limit and hence allowed us to focus on and parse the effects of dynamical perturbations (both with and without background noise). It is important to note that such small, strongly-coupled cliques do exist in the brain at different scales [312–317], and the results of our analysis are thus pertinent. One might even speculate that it could be functionally beneficial for these dense, highly-symmetric clusters to be widespread, since they can both engender a large multiplicity of states due to their symmetries [113, 150] and are also highly amenable to control. That said, in reality these motifs would be embedded into a broader network, and it may therefore be interesting to study such a scenario. It is also well-known that large-scale brain networks exhibit more complex and heterogeneous wiring. Another important direction would thus be to consider collective routing states and their control in larger brain networks with more varied connectivity. Actually, Kirst et al. [277] recently explored this avenue in a more general context (i.e., not just for neural dynamics) and found a number of compelling results, such as the possibility for remote control of distant functional interactions via local manipulations.

One could also study the control of collective states in interareal circuits that emerge from multifrequency oscillations [144]. While particular focus has been placed on the role of gamma oscillations for information routing between brain areas [318, 78], there is also evidence that other frequency bands may play a role in long-distance communication as well [76, 319, 77, 320]. For example, gamma band coherence is thought to regulate bottom-up information routing,
whereas alpha and beta band interactions are thought to regulate top-down communication [321, 322]. It would therefore be of interest to build computational network models capable of multifrequency interareal coherence [143, 144], and to again study the potential for flexible reconfiguration of these more complex communication pathways via targeted control signals.

Finally, we note that interareal coherence and the corresponding phase relations are really only proxies for the presence of interareal communication and causal functional interactions. Concretely proving that a particular phase-locking state truly engenders a particular pattern of information flow in a network with certain efficiencies of transmission requires more work. In particular, what is needed is a direct measure of the causal influence that each area has over every other. This kind of directed interaction can be quantified with information theoretic measures like transfer entropy [323, 324]. Applying such an information theoretic analysis to a system when it resides in different collective states or when it is subject to different external modulations could then show how altering the dynamical configuration of the system truly corresponds to altering the directions and levels of interareal information transmission [113].
B Supplementary figures and analyses

Here we briefly evaluate the effects of varying certain parameters of the model or of our subsequent analyses. Fig. B.1 shows the baseline phase-locking behaviors of a 4-area circuit with the same parameters as those in Fig. 3.6D, with the exception that the interareal delay is increased to $T_D = 3.5$ ms. In this case, three distinct families of multistable collective states manifest in the dynamics (see also Sec. 3.3.1 for more detail). Fig. B.2 shows the results of the same analysis carried out to generate Fig. 3.11, but for a different baseline working point. In particular, we consider the effects of pulse perturbations that target the phase-leader in a deterministic 2-area network, but with slightly lower background drive $P_{E,j} = 1.30$ for $j \in \{1, 2\}$. We find that the main conclusions are consistent across the two parameter choices. Fig. B.3 assesses the consequences of perturbing the phase-lagging (rather than the phase-leading) area in a deterministic 2-area network with the same baseline parameters as those in Fig. 3.11. In both scenarios, appropriately-timed pulse inputs can induce state-switching, though the ranges of relevant onset phases differ depending on whether the leading or the lagging region is stimulated. Fig. B.4 examines the consequences of increasing the allowed spread $\delta$ that determines how much the phase difference $\Delta \theta$ can vary around the preferred value $\Delta \theta^*$ within a candidate perturbation window for the stochastic 2-area networks (see Sec. 3.3.4). More specifically, we consider the effects of $\delta$ for the working point examined in Fig. 3.14, where the default value of $\delta = \pi/6$ was used. As expected, increasing $\delta$ results in a widening of the distributions of $\Delta \theta$ that manifest at the beginning of the time-windows selected for the application of perturbations (Fig. B.4A). Moreover, while the maximum switching probability $\max[P_{\text{switch}}]$ across onset phases tends to decrease with increasing $\delta$, the estimated probabilities remain well above the chance levels (which are less than 0.07 for all considered values of $\delta$). Finally, Fig. B.5 demonstrates the effect of varying the width parameter $\delta$ – used to select time windows for applying perturbations – on the efficacy of state-switching in a stochastic 4-area network. Recall that increasing $\delta$ allows the collective states to diverge further from their noiseless configurations and still be considered for perturbations. As anticipated, increasing $\delta$ decreases the maximum phase-advance and phase-delay transition probabilities for the chosen fixed pulse amplitude and fixed pulse duration (see Sec. 3.3.4 for further discussion on this point).
CHAPTER 3.

Figure B.1 (following page): Complex baseline phase-locking behavior of a deterministic 4-area network with an alternate value of the interareal delay. We study a 4-area neural mass network coupled in an all-to-all fashion with a background drive $P_E = 1.325$, an interareal coupling strength $G_{EE} = 0.2$, and an interareal time-delay $T_D = 3.5$ ms. The polar plots depict the relative phase configurations of the network for phase-locked states that appeared at least once across 500 different random initial conditions. Three distinct families of collective states are possible, which are labeled (i), (ii), and (iii) in the figure. Activity time-series for one state within each family are also shown. Note that although a state from each family was observed at least once across the set of initial conditions, the different families do not necessarily occur with equal likelihood.
\( G_{EE} = 0.2 \)

\( T_D = 3.5 \text{ ms} \)
Figure B.2 (following page): Robustness of state-switching effects in a deterministic 2-area network subject to brief input pulses: Alternative baseline working point. (A) Schematic of the model setup. We study the response of a deterministic 2-area brain circuit to a brief pulse input of amplitude $A_s$ and duration $T_s$. The perturbation targets only one of the two regions, which in this case is the area that leads in phase. Throughout, we fix $P_E = 1.30$, $G_{EE} = 0.2$, and $T_D = 1.5\text{ ms}$. (B) Activity time-series of the two regions under baseline conditions. The network locks into collective state $S_2$, where area 2 leads area 1 in phase. (C) Surface plot that shows whether an external input pulse causes a switch in the phase-locking pattern (white area) as a function of the onset phase $\theta_{on}$ and the pulse duration $T_s$. (D) Surface plot that shows whether an external input pulse causes a switch in the phase-locking pattern (white area) as a function of the onset phase $\theta_{on}$ and the pulse amplitude $A_s$. (E) Activity time-series showing the effects of a pulse perturbation applied to the purple area at the time denoted by the black line (pulse parameters are $A_s = 1$, $T_s = 5.5\text{ ms}$, $\theta_{on} = 0.8\text{ rad}$). The external input causes the purple area to undergo a phase-advance, which switches the phase-locking pattern. (F) Activity time-series showing the effects of a pulse perturbation applied to the purple area at the time denoted by the black line (pulse parameters are $A_s = 1$, $T_s = 5.5\text{ ms}$, $\theta_{on} = 4.0\text{ rad}$). The external input does not lead to a change in the sign of the phase difference..
CHAPTER 3.

A baseline

C

amplitude $A_s = 1.00$

D
duration $T_s = 5.50$ (ms)

E

$\theta_{on} = 0.8$ rad

F

$\theta_{on} = 3.14$ rad
Figure B.3 (following page): Robustness of state-switching effects in a deterministic 2-area network subject to brief input pulses: Perturbation of the phase-lagger. (A) Schematic of the model setup. We study the response of a deterministic 2-area brain circuit to a brief pulse input of amplitude $A_s$ and duration $T_s$. The perturbation targets only one of the two regions, which in this case is the area that lags in phase. Throughout, we fix $P_E = 1.35$, $G_{EE} = 0.2$, and $T_D = 1.5$ ms. (B) Activity time-series of the two regions under baseline conditions. The network locks into collective state $S_2$, where area 2 leads area 1 in phase. (C) Surface plot that shows whether an external input pulse causes a switch in the phase-locking pattern (white area) as a function of the onset phase $\theta_{on}$ and the pulse duration $T_s$. (D) Surface plot that shows whether an external input pulse causes a switch in the phase-locking pattern (white area) as a function of the onset phase $\theta_{on}$ and the pulse amplitude $A_s$. (E) Activity time-series showing the effects of a pulse perturbation applied to the yellow area at the time denoted by the black line (pulse parameters are $A_s = 1, T_s = 5.5$ ms, $\theta_{on} = 1.5$ rad). The external input causes the yellow area to undergo a phase-advance, which switches the phase-locking pattern. (F) Activity time-series showing the effects of a pulse perturbation applied to the yellow area at the time denoted by the black line (pulse parameters are $A_s = 1, T_s = 5.5$ ms, $\theta_{on} = 4.0$ rad). The external input does not lead to a change in the sign of the phase difference.
CHAPTER 3.

A baseline

\[ \theta_{on} = 1.5 \text{ rad} \]

\[ \theta_{on} = 4.0 \text{ rad} \]

B

baseline

activity

0.5

0

3

3.1

3.2

time (s)

C

amplitude \( A_s = 1.00 \)

D

duration \( T_s = 5.50 \text{ (ms)} \)

E

\( \theta_{on} = 1.5 \text{ rad} \)

F

\( \theta_{on} = 4.0 \text{ rad} \)
Figure B.4: Effect of varying the window selection width on the response of a stochastic 2-area network to brief pulse perturbations. The key network parameters are: $P_E = 1.30$, $T_D = 1.5$ ms, $G_{EE} = 0.2$, $\alpha = 10$, $\sigma = 0.2$. The perturbation is applied to the phase-leader. (A) Distributions of $\Delta \theta$ at the beginning of the oscillation cycles during which a pulse perturbation is applied. The three different panels correspond to three different thresholds $\delta$, which determine how much the phase difference between the two areas can vary around its peak baseline value across a candidate window for perturbation onset. (B) Across all onset phases $\theta_{on}$, the blue line shows the maximum switching probability $\max[P_{\text{switch}}]$ that a local pulse perturbation changes the phase-locking state as a function of the window width $\delta$. This analysis was carried out for input pulses with amplitude $A_s = 0.75$ and duration $T_s = 4.5$ ms. A state-switch was considered successful if the sign of the interareal phase relation switched within 2 cycles and if the new configuration lasted for at least 5 more cycles following the initial switch.
Figure B.5: Effect of varying the window selection width on the response of a stochastic 4-area network to brief pulse perturbations. The key network parameters are: $P_E = 1.3$, $T_D = 1.5$ ms, $G_{EE} = 0.2$, $\alpha = 5$, $\sigma = 0.1$. (A) The maximum phase-advance transition probability across all onset phases, $\max[P_{\text{advance}}]$, for three different values of the state-selection width $\delta$. A state transition was considered successful if the ordering of the phases switched to the correct configuration within 2 cycles and if the new ordering lasted for at least 5 more cycles following the initial switch. This analysis was carried out for input pulses with amplitude $A_s = 1.5$ and duration $T_s = 4.0$ ms. (B) The maximum phase-delay transition probability across all onset phases, $\max[P_{\text{delay}}]$, for three different values of the state-selection width $\delta$. A state transition was considered successful if the ordering of the phases switched to the correct configuration within 2 cycles and if the new ordering lasted for at least 5 more cycles following the initial switch. This analysis was carried out for input pulses with amplitude $A_s = 1.5$ and duration $T_s = 4.0$ ms.
Chapter 4

Relations between large-scale brain connectivity and effects of regional stimulation depend on collective dynamical state

With the exception of minor edits, this chapter is reproduced from:


Abstract

At the macroscale, the brain operates as a network of interconnected neuronal populations, which display coordinated rhythmic dynamics that support interareal communication. Understanding how stimulation of different brain areas impacts such activity is important for gaining basic insights into brain function and for further developing therapeutic neurmodulation. However, the complexity of brain structure and dynamics hinders predictions regarding the downstream effects of focal stimulation. More specifically, little is known about how the collective oscillatory regime of brain network activity – in concert with network structure – affects the outcomes of
perturbations. Here, we combine human connectome data and biophysical modeling to begin filling these gaps. By tuning parameters that control collective system dynamics, we identify distinct states of simulated brain activity and investigate how the distributed effects of stimulation manifest at different dynamical working points. When baseline oscillations are weak, the stimulated area exhibits enhanced power and frequency, and due to network interactions, activity in this excited frequency band propagates to nearby regions. Notably, beyond these linear effects, we further find that focal stimulation causes more distributed modifications to interareal coherence in a band containing regions’ baseline oscillation frequencies. Importantly, depending on the dynamical state of the system, these broadband effects can be better predicted by functional rather than structural connectivity, emphasizing a complex interplay between anatomical organization, dynamics, and response to perturbation. In contrast, when the network operates in a regime of strong regional oscillations, stimulation causes only slight shifts in power and frequency, and structural connectivity becomes most predictive of stimulation-induced changes in network activity patterns. In sum, this work builds upon and extends previous computational studies investigating the impacts of stimulation, and underscores the fact that both the stimulation site, and, crucially, the regime of brain network dynamics, can influence network-wide responses to local perturbations.

4.1 Introduction

The brain is a multiscale system composed of many dynamical units that interact to produce a vast array of functions. At a large scale, macroscopic regions – each containing tens of thousands of neurons – are linked by a physical web of white matter tracts that facilitate the propagation of activity between distributed network elements. At the level of large neuronal ensembles or brain areas, collective activity is often rhythmic in nature [37], and these rhythms can become temporally coordinated between distant regions, giving rise to so-called functional interactions [77]. Importantly, oscillations have been implicated in a number of cognitive processes [72, 71, 325, 78, 75, 326, 73], and coherent activity is hypothesized to play an important role in interareal communication and information transfer among distributed brain areas [78, 2, 325]. Nonetheless, despite progress in mapping and characterizing the brain’s anatomical pathways and measuring neural oscillations, a number of questions remain as to how individual components in a brain network shape and modulate system-wide dynamics.

Among these questions, understanding how large-scale, oscillatory brain dynamics respond
to localized perturbations is of critical importance [327–330, 75]. Because the brain is not a closed or static system, such activity changes could be induced by sensory inputs to primary sensory areas [331, 332], different tasks [333, 334], or other internal or regulatory processes [335–338]. In addition to naturally-induced changes, stimulation techniques such as transcranial magnetic stimulation [339], direct current stimulation [340], and alternating current stimulation [341] can also be employed to invoke modulations of dynamics in a specific brain area. By combining these techniques with imaging methods like EEG and MEG [342–347], it is possible to examine how the act of exciting a particular network component modifies rhythmic neural activity. Furthermore, in addition to its utility for basic science, neurostimulation has emerged as a promising approach for treating a number of neurological and psychiatric conditions [348–350].

Yet, while prior work has often focused on characterizing the proximal effects of local perturbations, a growing body of literature indicates that regional changes to neural activity can have more widespread consequences [330, 329, 327, 328]. The realization that stimulation can have network-wide effects necessitates further investigations into the operating principles underlying such phenomena [281, 351–353, 279, 277, 354, 355]. Furthermore, a crucial but seemingly understudied point is that the effects of perturbing a particular brain area can depend not only on the nature or location of the perturbation, but also on the intrinsic dynamical state of the system at baseline [356–358]. In particular, recent efforts have investigated the state-dependent effects of stimulation via precise experiments [359, 360] – focusing largely on alpha-band activity in single cortical areas – and via modeling [361–363]. These studies have uncovered robust relationships between the endogenous state of rhythmic activity and the capacity of external stimulation to modulate cortical oscillations in a given brain area. However, a pivotal next step is to extend the notion of state-dependence to the case of whole-brain networks, which acknowledge the fact that regions do not operate in isolation. Rather, in the case of large-scale brain networks, the macroscopic dynamical regime of the system arises from an interplay between units’ local activity and long-range anatomical coupling [129], leading to the emergence of collective oscillatory modes [364, 277]. Although it is reasonable to hypothesize that the global state of brain network activity should play a role in determining how a focal perturbation will manifest and influence distributed functional interactions, these ideas have yet to be systematically examined.

Thus, there is now a need to concurrently investigate and merge two outstanding questions: (1) how regional stimulation spreads to induce distributed effects on brain network dynamics, and (2) how the global dynamical regime of the system impacts these effects. Here, we investigate these questions by constructing a biophysically-motivated model of large-scale, oscillatory
brain activity, in which individual brain areas are modeled as Wilson-Cowan neural masses \([130]\) coupled according to empirically-derived anatomical connectivity \([129]\). We first demonstrate that, in the absence of stimulation, the interareal coupling strength and the baseline excitation of the network transition the system between qualitatively distinct collective dynamical states. By providing additional excitation to a single brain area, we then systematically examine the consequences of such local stimulation on network activity. The primary contribution of this study is an exploration of how the effects of focal perturbations can depend not only on which area is stimulated, but also on the baseline dynamical regime of the non-linear model. Hence, this work builds upon previous whole-brain modeling efforts that have examined the effects of regional perturbations \([351, 352, 281]\) with other work examining the state-dependent effects of stimulation in single cortical areas, but not large-scale networks \([361, 362]\).

We find that in states of low baseline excitation, stimulation can significantly increase the frequency and power of regional activity, whereas in states of high background drive, local dynamics are less sensitive to perturbations. Importantly, these results show qualitative similarities and agreement with past work examining the focal effects of stimulation \([361, 362]\). We further find that, due to network interactions, regional perturbations can propagate and interact with brain areas’ ongoing rhythms. In particular, depending on the system working point, downstream areas that are strongly anatomically linked to the stimulated site also develop spectral components at the excited frequency of the stimulated region. Crucially, though, modifications to interareal phase-locking can additionally be induced in a broader frequency band comprising brain areas’ spontaneous, baseline oscillations, which may be well-separated from the excited frequency. Moreover, changing the dynamical regime of the system modulates the strength of associations between network-wide responses to perturbations in the baseline frequency band and structural or functional network connectivity. Hence, changing the collective oscillatory state of the system – which need not be entirely determined by the anatomical network – qualitatively changes the distributed effects of focal perturbations, and alters the relations between those effects and measures of either structural or dynamical organization. In sum, we use a simplified, large-scale computational model to highlight that the effects of regional stimulation can depend both on the location of the perturbed site and on the global state of ongoing brain network dynamics. Though currently idealized, extending the reduced model to incorporate further biological realism and empirical constraints is an exciting direction for future work attempting to directly compare against experimental findings.
4.2 Materials and methods

4.2.1 Acquisition of empirical human structural brain data

Human anatomical brain networks were reconstructed by applying deterministic tractography algorithms to diffusion-weighted MRI. In this study, we used a group-representative composite network assembled from 30 subject-level networks [365–367]. The mean age of participants was 26.2 years, the standard deviation was 5.7 years, and 14 of the subjects were female. To map anatomical networks, diffusion spectrum and T1-weighted anatomical images were acquired for each individual. For the DSI scans, 257 directions were sampled using a Q5 half-shell acquisition scheme with a maximum $b$-value of 5000 s/mm$^2$ and an isotropic voxel size of 2.4 mm. We used an axial acquisition with repetition time TR = 5 seconds, echo time TE = 138 ms, 52 slices, and field of view of [231, 231, 125]mm. The T1 sequences used a voxel size of [0.9, 0.9, 1.0]mm, repetition time TR = 1.85 seconds, echo time TE = 4ms, and field of view of [240, 180, 160]mm. This data was initially collected for an earlier study [368], and was first published in [369]. The same data has also been used in several other prior investigations (e.g., [367, 370, 365]).

DSI Studio (www.dsi-studio.labsolver.org) was used to reconstruct DSI data using $q$-space diffeomorphic reconstruction (QSDR) [371], which reconstructs diffusion-weighted images in native space and computes the quantitative anisotropy (QA) of each voxel. Using the statistical parametric mapping nonlinear registration algorithm [372], the image is then warped to a template QA volume in Montreal Neurological Institute (MNI) space. Finally, spin-density functions were reconstructed with a mean diffusion distance of 1.25 mm with three fiber orientations per voxel. A modified FACT algorithm [373] was then used to perform deterministic fiber tracking with an angular cutoff of 55°, step size of 1.0 mm, minimum length of 10 mm, spin density function smoothing of 0.00, maximum length of 400 mm, and a QA threshold determined by DWI signal in the colony-stimulating factor [365–367, 370, 369, 374]. The algorithm terminated when 1,000,000 streamlines were reconstructed for each individual [365–367, 370, 369, 374] (Fig. 4.1A).

T1 anatomical scans were segmented using FreeSurfer [375] and parcellated using the Connectome Mapping Toolkit (http://www.connectomics.org) according to an $N = 82$ area atlas [58] of 68 cortical and 14 subcortical areas (Fig. 4.1B). The parcellation was registered to the $b_0$ volume of each subject’s DSI data, and region labels were mapped from native space to MNI coordinates using a $b_0$-to-MNI voxel mapping [365–367, 370, 369, 374]. While we use a relatively coarse-grained atlas, it aligns with atlas sizes used in other computational modeling studies.
(e.g., [281, 173, 156, 122, 163]), and was chosen to reduce the computational costs of numerical simulations. However, we do mention limitations involved with this choice in the Discussion.

**Ethics Statement**

All participants gave informed consent in writing and all protocols were authorized by the Institutional Review Board of the University of Pennsylvania.

### 4.2.2 Network representation of anatomical brain data

To incorporate the structure of interareal connections into the model of large-scale brain activity, we represented the anatomical brain data as a network. This was achieved by first mapping each of the \( N = 82 \) regions to a unique node in a structural brain network \( A \) (see [376] for the mapping

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**Figure 4.1 (following page):** Whole-brain imaging data, computational model of large-scale brain dynamics, and schematic of analysis. (A) An example of white matter streamlines reconstructed from diffusion imaging and tractography of a human brain. (B) Non-invasive magnetic resonance imaging scans of human brain anatomy are used to segment the cortex and subcortex into 82 regions. (C) Adjacency matrix for a group-averaged structural brain network. Individual brain areas are represented as network nodes, and normalized white matter streamline counts between region pairs are represented as weighted network edges. (D) Matrix of Euclidean distances between the centers of mass of all region pairs. (E) Left: Structural brain network representation; location of gray circles correspond to region centers of mass, and teal lines show the strongest 20% of interareal connections, with line thickness proportional to connection strength. The two encircled nodes correspond to an unperturbed region \( j \) and an excited region \( i \) in the large-scale brain network, with the perturbed region indicated by the yellow lightning bolt. Right: Schematic of the computational model of large-scale brain dynamics. The activity of a given brain region \( j \) is modeled as a Wilson-Cowan neural mass, composed of interacting populations of excitatory \( E \) and inhibitory \( I \) neurons. Neural masses are then coupled through their excitatory pools according to the structure of the anatomical brain network. A perturbation to region \( i \) (pictorially represented with the lightning bolt) is modeled as an increase in its excitatory input from \( P_E \rightarrow P_E + \Delta P_E \). (F) The computational model generates oscillatory time-series of neural population activity for each brain region. These time-series can then be analyzed in Fourier space to determine relevant frequency bands for further analysis. After filtering time-series within the same frequency band of interest, functional interactions between brain region pairs are determined by extracting phase variables from each region’s filtered activity via the Hilbert transform, and then computing the phase-locking value to assess the consistency of phase relations over time and trials.
between node numbering and brain region labels). The structural edge weight $A_{ij}$ between two brain areas (nodes) $i$ and $j$ was then defined as the total number of streamlines between the two areas divided by the geometric mean of their volumes [367, 365]. Note that due to limitations in the non-invasive techniques available for constructing human connectomes [377], the resulting structural network is weighted but undirected. Because the brain is a spatially-embedded system [378], each region $i$ also has a location $r_i = (x_i, y_i, z_i)$ in real space. In the network representation, we defined the location of each node to be the center of mass of the corresponding region, allowing us to calculate matrix elements $D_{ij}$ representing the Euclidean distance between nodes $i$ and $j$. Assuming a fixed conduction speed, these interareal distances are then used to approximate time delays for signal transmission in the computational model [152, 157, 281, 173, 156].

In this study, we report results using a group-representative structural brain network derived by combining individual brain networks across multiple subjects. We used a previously-established consensus method for constructing the group representative network that preserves both the average binary connection density of the individual brain networks, as well as the approximate edge-length distribution of intra- and inter-hemispheric connections [365]. More details on this pooling procedure can be found in [366]. A group-representative interareal distance matrix was constructed by averaging the pairwise Euclidean distance matrices across subjects. In what follows, we assume that $A$ (or $A_{ij}$) refers to the group-representative structural brain network, and that $D$ (or $D_{ij}$) refers to the group-averaged interareal distance matrix. We show the group-representative anatomical connectivity matrix in Fig. 4.1C, and we show the group-averaged distance matrix in Fig. 4.1D.

### 4.2.3 Biophysical model of large-scale brain dynamics

To model large-scale brain dynamics, we use a biophysically-motivated approach in which simulated activity is generated by a network of interacting neural masses [129]. In particular, the activity of each brain area is modeled as a Wilson-Cowan (WC) neural mass [130] and individual units are coupled according to the empirically-derived anatomical network. Importantly, these types of whole-brain computational models – which integrate non-linear, mean-field population dynamics with structural connectome architecture – have been utilized in a number of past efforts to gain insight into diverse neural phenomena [161, 281, 173, 157, 169, 175, 156, 170, 379, 380, 152, 153, 381, 163, 382, 155].

Here, we employ such an approach to conduct a basic examination of how localized (regional) changes in neural activity affect dynamics across the brain. We offer a schematic of the
model in Fig. 4.1E. On the left, we show the structural brain network in real space. We focus on the two interconnected regions \( i \) and \( j \) encircled in black, of which the lower one \( (i) \) receives additional excitation (as denoted by the yellow lightning bolt). On the right, we show the setup of the coupled WC system for these two units. In the WC model, the activity of a particular brain region is defined by a coupled system of excitatory \((E)\) and inhibitory \((I)\) neuronal populations, and the dynamical variables are the mean firing rates of the \( E \) and \( I \) pools. The time-evolution of the average firing rates are in general governed by both intrinsic properties of the populations in a single region, as well as delayed, long-range input from other areas as dictated by the pattern of anatomical connectivity. In line with several previous studies \([281, 173, 157, 161, 170, 175, 169, 381]\), we consider long-range connections to couple only the excitatory subpopulations of distinct brain areas.

The dynamics of the \( j^{th} \) brain area are governed by the following set of coupled differential equations:

\[
\begin{align*}
\tau_E \frac{dE_j(t)}{dt} &= - E_j(t) + [1 - E_j(t)]S_E[c_{EE}E_j(t) - c_{IE}I_j(t)] \\
&\quad + C \sum_i W_{ij}E_i(t - \tau_{ij}) + P_{E,j} + \sigma_E \xi(t),
\end{align*}
\]

and

\[
\begin{align*}
\tau_I \frac{dI_j(t)}{dt} &= - I_j(t) + [1 - I_j(t)]S_I[c_{EI}E_j(t) - c_{II}I_j(t)] \\
&\quad + P_{I,j} + \sigma_I \xi(t).
\end{align*}
\]

The variables \( E_j(t) \) and \( I_j(t) \) correspond to the firing rates of the excitatory and inhibitory populations of region \( j \), and \( \tau_E \) and \( \tau_I \) are the excitatory and inhibitory time constants, respectively. The non-linear activation functions \( S_E \) and \( S_I \) of the excitatory and inhibitory pools are given by the sigmoidals

\[
S_E(x) = \frac{1}{1 + e^{-a_E(x - \mu_E)}}
\]

and

\[
S_I(x) = \frac{1}{1 + e^{-a_I(x - \mu_I)}}.
\]

The quantities \( \mu_E \) and \( \mu_I \) give the mean firing thresholds for each subpopulation, and the gain parameters \( a_E \) and \( a_I \) set the spread of the firing thresholds for the two groups.

Dynamics of the excitatory ensemble are driven by \((I)\) the local interaction strength within
the excitatory population $c_{EE}$, (2) the interaction strength from the inhibitory population to the excitatory population $c_{IE}$, (3) constant, non-specific background drive $P_{E,j}$, and also (4) interactions $W_{ij}$ corresponding to long-range excitatory inputs from different populations $i$ that link to unit $j$ via anatomical connectivity. Following [170, 175, 164, 169], we let $W_{ij} = \frac{A_{ij}}{\sum_i A_{ij}}$, which is simply the connection weight from $i$ to $j$, normalized by the total input to region $j$. Furthermore, $C$ is a global coupling that tunes the overall interaction strength between different brain areas, and $\tau_{ij}$ is a time delay between regions $i$ and $j$ that arises due to the spatial embedding of the brain network and the fact that signal transmission speeds are finite [157, 281, 173, 156, 152, 163]. We set $\tau_{ij} = \frac{D_{ij}}{v}$, where $D_{ij}$ is the Euclidean distance between regions $i$ and $j$ and $v$ is a constant signal conduction speed. Activity in the inhibitory ensemble depends on (1) the interaction strength $c_{EI}$ from the excitatory population, (2) the local interaction strength within the inhibitory population $c_{II}$, and (3) other possible non-specific inputs $P_{I,j}$. Finally, to increase biological plausibility and incorporate the stochastic nature of neural dynamics, we add a term $\sigma_E \xi(t)$ to Eq. 4.1 and a term $\sigma_I \xi(t)$ to Eq. 4.2, which correspond to Gaussian white noise with zero mean and standard deviations $\sigma_E$ and $\sigma_I$, respectively [281, 157]. In what follows, we will take the excitatory population activities $E_j(t)$ of each brain area as the observables of interest [281, 173, 175, 155, 169].

Model parameters

Under appropriate parameter choices, the WC model can give rise to oscillatory dynamics [130]. Such rhythmic activity is ubiquitous in large-scale neural systems [37] and is the dynamical behavior of interest for this investigation. While oscillation frequencies observed in neural systems can span orders of magnitude [37], local neuronal populations often exhibit gamma band (30-90Hz) rhythms as a result of feedback between coupled excitatory and inhibitory neurons [71, 284, 285]. Furthermore, gamma oscillations and synchronization between distributed brain areas are associated with the flow of information between neuronal ensembles [2, 112, 113], are modulated by stimuli [332, 331], and are thought to underlie a number of cognitive processes [78]. Because gamma oscillations are robustly observed in excitatory-inhibitory circuits, we set parameters in the phenomenological WC model such that individual brain regions oscillate in the gamma band when coupled [157] (see Table 4.1). We also note that it may be interesting in future work to investigate other frequency bands or multiple frequency bands simultaneously [143].

As discussed further in Sec. C, the non-specific background input $P_E$ is the typical control parameter used to tune the behavior of an isolated WC unit. At low values of $P_E$, a single WC
Table 4.1: Parameter values for the large-scale Wilson-Cowan neural mass model and for the numerical simulations.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$v$</td>
<td>propagation speed</td>
<td>10m/s</td>
</tr>
<tr>
<td>$C$</td>
<td>global coupling strength</td>
<td>0–5</td>
</tr>
<tr>
<td>$\tau_E$</td>
<td>excitatory time constant</td>
<td>2.5ms</td>
</tr>
<tr>
<td>$\tau_I$</td>
<td>inhibitory time constant</td>
<td>3.75ms</td>
</tr>
<tr>
<td>$a_E$</td>
<td>excitatory gain</td>
<td>1.5</td>
</tr>
<tr>
<td>$a_I$</td>
<td>inhibitory gain</td>
<td>1.5</td>
</tr>
<tr>
<td>$\mu_E$</td>
<td>excitatory firing threshold</td>
<td>3.0</td>
</tr>
<tr>
<td>$\mu_I$</td>
<td>inhibitory firing threshold</td>
<td>3.0</td>
</tr>
<tr>
<td>$c_{EE}$</td>
<td>local $E$ to $E$ coupling</td>
<td>16</td>
</tr>
<tr>
<td>$c_{IE}$</td>
<td>local $I$ to $E$ coupling</td>
<td>12</td>
</tr>
<tr>
<td>$c_{EI}$</td>
<td>local $E$ to $I$ coupling</td>
<td>15</td>
</tr>
<tr>
<td>$c_{II}$</td>
<td>local $I$ to $I$ coupling</td>
<td>3</td>
</tr>
<tr>
<td>$P_{E,\text{base}}$</td>
<td>baseline excitatory background drive</td>
<td>0.5–0.85</td>
</tr>
<tr>
<td>$\Delta P_E$</td>
<td>perturbation strength</td>
<td>0.1</td>
</tr>
<tr>
<td>$P_I$</td>
<td>inhibitory background drive</td>
<td>0</td>
</tr>
<tr>
<td>$\sigma_E$</td>
<td>excitatory noise strength</td>
<td>$5 \times 10^{-5}$</td>
</tr>
<tr>
<td>$\sigma_I$</td>
<td>inhibitory noise strength</td>
<td>$5 \times 10^{-5}$</td>
</tr>
<tr>
<td>$dt$</td>
<td>integration time step</td>
<td>$5 \times 10^{-5}$s</td>
</tr>
<tr>
<td>$dt_{ds}$</td>
<td>downsampled time step</td>
<td>$1 \times 10^{-8}$s</td>
</tr>
</tbody>
</table>

unit flows towards a low-activity steady-state (Fig. C.1A), and at high values of $P_E$, the system reaches a stable high-activity steady-state (Fig. C.1C). At intermediate values of the excitatory drive, an isolated unit – with the parameters given in Table 4.1 – will undergo a bifurcation and exhibit rhythmic activity in the gamma frequency band (Fig. C.1B). Up to a point, increasing $P_E$ within this intermediate region leads to oscillations with increasing amplitude and frequency (Fig. C.1D–F).

The situation becomes more complex when multiple WC units are coupled via the structural connectome. In this scenario, an individual region’s dynamics are determined by a combination of the constant drive $P_E$ and the strength of delayed inputs from other parts of the network, which are modulated by the coupling $C$ and the structural connectivity $A$. To account for these two influences, we consider both $P_E$ and $C$ as tuning parameters, and examine working points at which the combination of $P_E$ and $C$ generate oscillatory activity in individual brain...
areas. Finally, we set the signal propagation speed to a fixed value of \( v = 10\, \text{m/s} \), which is in the range of empirical observations and previous large-scale modeling efforts [281].

**Incorporating local perturbations into the large-scale model**

The baseline condition of the network corresponds to the situation in which all brain areas receive the same level of background drive, such that \( P_{E,j} = P_{E}^{\text{base}} \) for all \( j \in \{1, \ldots, N\} \). To investigate how regional perturbations affect brain-wide dynamics, we examine the effects of increased excitation to a single brain area. This is modeled as a selective increase in drive to the excitatory population of the perturbed neural mass \( i \) such that \( P_{E,i} \rightarrow P_{E,i} + \Delta P_{E} \), where \( \Delta P_{E} > 0 \) denotes the strength of the perturbation [281] (see Fig. 4.1E for a schematic). The dynamics of the system in the baseline state can then be compared to the situation in which unit \( i \) receives additional input (i.e., where we have \( P_{E,i} = P_{E}^{\text{base}} + \Delta P_{E} \) and \( P_{E,j} = P_{E}^{\text{base}} \) for all \( j \neq i \)).

We note that, phenomenologically, excitation of a given brain area could occur through a number of mechanisms, including sensory input to primary sensory regions, brain stimulation, or, alternatively, via internal processes that regulate inputs to or excitability levels of specific neuronal populations. The goal of this work is to study the effects of localized excitations generally, rather than to design a detailed model of a specific type of perturbation. For this reason, we choose to study the simplest case of constant excitation.

**4.2.4 Numerical methods and simulations**

The equations governing the time evolution of the excitatory and inhibitory population activities form a system of coupled stochastic, delayed differential equations. We numerically integrate this system using the Euler-Maruyama method with a time step of \( \Delta t = 5 \times 10^{-5} \text{s} \). For the time delays, we round each \( \tau_{ij} \) to the nearest multiple of the integration time step \( \Delta t \), and for the initial conditions, we assume a constant history for each unit’s activity of length equal to the longest delay in the system. After running a simulation, we discard the first \( t_{\text{burn}} = 1 \text{ second} \) so that our analysis is not biased by transients or the specific choice of initial conditions. Each time-series is then downsampled to a resolution of \( \Delta t_{\text{ds}} = 1 \times 10^{-3} \text{s} \). The parameters for the numerical simulations are shown in Table 4.1.
### 4.2.5 Power spectra

Useful characteristics of the simulated activity are apparent in the frequency domain (see Fig. 4.1F). Here, we use Welch’s method (as implemented in MATLAB R2019a) to estimate the power spectral density (psd) of the excitatory population activities. We use window sizes of 1 second with 50% overlap, and subtract the mean of each time-series before computing the psd.

### 4.2.6 Quantifying interareal phase-locking

To quantify the extent of temporal coordination between different brain areas, we use the phase-locking value (PLV) [97]. This measure is commonly used to assess the level of coherence between phases in a given frequency band. Importantly, because the state variables in the WC model are real-valued signals with possibly multiple spectral components, we compute PLVs for a given frequency band by (1) filtering all raw excitatory time-series within the same specified frequency range, and (2) extracting instantaneous phases for the given frequency band using the Hilbert transform (see Fig. 4.1F). In the following two sections, we describe these steps in more detail.

**Instantaneous phases from the Hilbert transform**

Given a real-valued signal $X(t)$, it is possible to define instantaneous phase and amplitude variables that describe the signal using the Hilbert transform. Importantly, although the Hilbert transform can theoretically be computed for an arbitrary signal $X(t)$, the instantaneous amplitude $A(t)$ and phase $\theta(t)$ are only physically meaningful for relatively narrowband signals [35]. It is therefore necessary to filter a signal before taking the Hilbert transform. Here, raw time-series were bandpass filtered in a frequency range $f_0 \pm \Delta f$ Hz using a 6th-order Butterworth filter in the forward and backward directions. In the results section, we describe how $f_0$ and $\Delta f$ are determined during the presentation of various findings that depend on computing the Hilbert phase. Filtering was carried out in MATLAB using the ‘butter’ and ‘filtfilt’ functions. After filtering the simulated activity, the Hilbert transform was applied to extract instantaneous phases for the given frequency band. The Hilbert transform was implemented using the ‘hilbert’ function in MATLAB. More details on the Hilbert transform can be found in Sec. C.13.

**Functional connectivity from the phase-locking value**

The outputs of the filtering and Hilbert transform processes described in the previous section are instantaneous phases $\theta_i(f_0, t)$ derived from the excitatory activity $E_i(t)$ of each brain region
at a given central frequency $f_o$ and time $t$ (Fig. 4.1F). From these phases, we can quantify the extent of phase-coherence between brain areas’ signals in a given frequency band using the phase-locking value (PLV); see Fig. 4.1F. The PLV – here denoted symbolically as $\rho_{ij}$ – between two phase time-series $\theta_i(t)$ and $\theta_j(t)$ is given by

$$\rho_{ij} = \frac{1}{T_s} \sum_{t=1}^{T_s} e^{i[\theta_i(t) - \theta_j(t)]},$$

(4.5)

where $T_s$ is the number of sample time points over which the phase-locking is computed. If the phase difference $\Delta \theta_{ij}(t) = \theta_i(t) - \theta_j(t)$ is constant over a given time window, $\rho_{ij}$ will be equal to 1, whereas if the phase-differences are distributed uniformly, $\rho_{ij}$ will be approximately 0; in this way, $\rho_{ij} \in [0, 1]$.

We would also like to ensure that the PLV reflects the consistency of phase relations that arise from interactions (direct or indirect), and not locking arising from the fact that two regions happen to have the same frequency, but, possibly, a different phase relation in every trial. We therefore concatenate phase time-series from different trials before computing the PLV [383], where each trial is a simulation run with different random initial conditions and noise realizations. Accordingly, a high PLV indicates that across time and trials, the activity of the corresponding regions exhibits a consistent phase relationship within a particular frequency band.

As with structural connectivity, it is useful to think of a given $N \times N$ matrix of PLV values as a network where the element (edge) $\rho_{ij}$ is the phase-coherence between region (node) $i$ and region (node) $j$. In contrast to the structural network, this PLV-based network represents the presence of functional associations between brain regions’ activity. Following common terminology, we will thus often refer to phase-locking as “functional connectivity” and phase-locking matrices as “functional networks”.

### 4.2.7 Statistical analyses

All data and statistical analysis was performed in MATLAB release R2019a. Statistical dependencies between two variables were assessed via the Spearman rank correlation, using the built-in MATLAB function ‘corr’. Throughout the text, we denote the Spearman correlation coefficient as $r_s$. Rank correlations are considered statistically different from zero if the corresponding $p$-value is less than 0.05.
### 4.2.8 Summary of computed quantities

Throughout the text we compute a number of different measures to characterize the behavior of the system at baseline and under focal perturbation. To aid the readability of the text, we list these quantities in Table 4.2 with a brief summary. The measures are listed according to the section in which they first appear.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\langle E(t) \rangle$</td>
<td>time- and network-averaged firing rate</td>
</tr>
<tr>
<td>$\langle f_{\text{peak}} \rangle$</td>
<td>network-averaged peak frequency</td>
</tr>
<tr>
<td>$P^*_E(C)$</td>
<td>background drive at which oscillations emerge for a given coupling $C$</td>
</tr>
<tr>
<td>$\rho_{ij}$</td>
<td>PLV between units $i$ and $j$ at baseline</td>
</tr>
<tr>
<td>$\rho_{\text{global}}$</td>
<td>global phase-locking order parameter</td>
</tr>
<tr>
<td>$\rho_{\text{local}}$</td>
<td>local phase-locking order parameter</td>
</tr>
<tr>
<td>$f_{\text{peak}} i$</td>
<td>peak frequency of node $i$ at baseline</td>
</tr>
<tr>
<td>$f_{\text{peak}} i, \delta i$</td>
<td>peak frequency of node $i$ when stimulated</td>
</tr>
<tr>
<td>$\Delta f_{\text{peak}} i, \delta i$</td>
<td>change in peak frequency of node $i$ when stimulated</td>
</tr>
<tr>
<td>$\langle \text{psd} \rangle_{j \neq i}$</td>
<td>power spectra averaged over all units $j \neq i$</td>
</tr>
<tr>
<td>$\langle \Delta \text{psd} \rangle_{j \neq i}$</td>
<td>change in psd of node $j$ induced by excitation of node $i$, averaged over all nodes $j \neq i$</td>
</tr>
<tr>
<td>$s_{\text{struc}} i$</td>
<td>structural strength of node $i$</td>
</tr>
<tr>
<td>$s_{\text{func}} i$</td>
<td>functional strength of node $i$</td>
</tr>
<tr>
<td>$\langle</td>
<td>\Delta \rho_{\text{base}} i \delta i</td>
</tr>
<tr>
<td>$\langle</td>
<td>\Delta \rho_{\text{exc}} i \delta i</td>
</tr>
<tr>
<td>$\langle</td>
<td>\Delta \rho_{\text{base}}</td>
</tr>
<tr>
<td>$\langle</td>
<td>\Delta \rho_{\text{exc}}</td>
</tr>
<tr>
<td>$\text{CoV}[\langle</td>
<td>\Delta \rho_{\text{base}} i \delta i</td>
</tr>
<tr>
<td>$\text{std}[\langle</td>
<td>\Delta \rho_{\text{exc}} i \delta i</td>
</tr>
</tbody>
</table>

Table 4.2: List of computed measures.
4.3 Results

4.3.1 Baseline dynamical regimes of the brain network model

Depending on the values of various parameters, the brain network model exhibits different qualitative behaviors. Importantly, different baseline states may in turn result in distinct modulations of brain-wide activity patterns in response to local perturbations. We thus begin by characterizing the behavior of the system at baseline (i.e. in the absence of regional stimulation). This initial study will provide context for our subsequent investigations examining how the effects of focal excitations depend upon the system’s baseline state.

We focus on two parameters of interest: (1) the level of generic background input to the excitatory populations $P_{E}^{\text{base}}$ and (2) the global coupling strength $C$. Recall that for an isolated WC unit, $P_{E}^{\text{base}}$ is a bifurcation parameter that transitions population activity between a quiescent and an oscillatory state [130, 384]. However, when examining a network of coupled neural masses, the dynamics of each element are also dictated by inputs from other units in the system. The parameter $C$ is a second control parameter that globally scales the interaction strength between brain areas by tuning how much input a given region receives from its neighbors in the network. The nature of both local and network-wide dynamical behaviors will thus change depending on the combination of $P_{E}^{\text{base}}$ and $C$, allowing the system to exist in markedly different states. Though the tuning parameters in the network model are phenomenological, from a biological standpoint, global changes in these parameters could represent, for example, the effects of neuromodulation [385, 177, 386] – which exerts widespread influences across the brain [387] – or changes in brain state more generically.

To quantify how model behavior varies as a function of $P_{E}^{\text{base}}$ and $C$, we perform a sweep over a broad range of these parameters, considering values of $P_{E}^{\text{base}} \in [0.5, 0.85]$ in steps of $\Delta P_{E}^{\text{base}} = 0.05$, and values of $C \in [0, 5]$ in steps of $\Delta C = 0.1$. These ranges were chosen to allow for the exploration of multiple oscillatory regimes of the system. For each parameter combination, we run five, 2-second-long simulations. The values of all other parameters are defined in Table 4.1, with the exception that, for these sweeps, we run noiseless simulations in order to more precisely demarcate the boundaries between different dynamical modes of the model.
Long-range coupling strength and background drive tune baseline dynamical state

We begin by computing two measures that quantify regional dynamics: (1) the time-averaged firing rate $\overline{E(t)}$, and (2) the frequency at maximum power (peak frequency) $f_{\text{peak}}$ of a given region. To obtain summary measures characterizing the state of the system as a whole, we compute network-averages of these quantities, denoted by angled-brackets. In studying $\langle \overline{E(t)} \rangle$ as a function of $P_{\text{base}}^E$ and $C$, we observe three principal regimes (Fig. 4.1A). When both $P_{\text{base}}^E$ and $C$ are low, the system settles to a state of low average firing rate (white region); this state corresponds to a non-oscillatory, low-activity equilibrium. In contrast, when $P_{\text{base}}^E$ and $C$ are both high, the average firing rate saturates at a high level (dark green region); this state corresponds to a non-oscillatory, high-activity equilibrium. Finally, at intermediate values of these parameters, the mean firing rate varies between the low and high extremes, and the regional activity is oscillatory; because we wish to consider the rhythmic nature of brain activity, this is the relevant portion of parameter space.

Next we seek to understand how $\langle f_{\text{peak}} \rangle$ varies in the $P_{\text{base}}^E - C$ plane (Fig. 4.1B). A clear wedge-shaped area marks parameter combinations that give rise to network-averaged peak frequencies in the gamma range. As with the firing rate, the peak frequency tends to increase (decrease) with either increasing (decreasing) background excitation or coupling strength. By comparing Fig. 4.1B to Fig. 4.1A, we see that the white areas surrounding the purple wedge correspond to the regions of parameter space where the firing saturates at a fixed low or high value. In Sec. C.2, we describe a systematic method for determining boundaries in the 2D space spanned by $C$ and $P_{\text{base}}^E$ that indicate the onset or disappearance of oscillatory activity (see Fig. C.2). In what follows, we use $P_E^*(C)$ to denote the level of background drive at which oscillations begin to

Figure 4.1 (following page): Long-range coupling strength $C$ and background drive $P_{\text{base}}^E$ modulate firing rates and oscillation frequencies at baseline. (A) The time- and network-averaged population firing rate $\langle \overline{E(t)} \rangle$ as a function of $C$ and $P_{\text{base}}^E$ (units are arbitrary). (B) The network-averaged peak frequency of regional activity $\langle f_{\text{peak}} \rangle$ as a function of $C$ and $P_{\text{base}}^E$. (C) A segment of the activity of one brain area and (D) the corresponding power spectra of the same area at the working point denoted by the red dot in panels (A) and (B) ($P_{\text{base}}^E = 0.553, C = 2.5$). (E) A segment of the activity of one brain area and (F) the corresponding power spectra of the same area at the working point denoted by the orange dot in panels (A) and (B) ($P_{\text{base}}^E = 0.57, C = 2.5$). (G) A segment of the activity of one brain area and (H) the corresponding power spectra of the same area at the working point denoted by the yellow dot in panels (A) and (B) ($P_{\text{base}}^E = 0.7, C = 2.5$).
emerge for a fixed coupling strength $C$. We refer the reader to Sec. C.2 for a detailed description of how this value is determined from the simulations. Furthermore, we often plot quantities as functions of the relative drive $P_{\text{base}}^E - P^*_E(C)$, such that $P_{\text{base}}^E - P^*_E(C) = 0$ indicates the transition point from a low-activity state to an oscillatory state at a coupling $C$.

To provide further intuition for how dynamics vary within this parameter space, we study example time-series and power spectra for three different baseline states (colored dots in Figs. 4.1A,B). Note that these working points correspond to an intermediate coupling value of $C = 2.5$, but varying levels of the constant baseline input $P_{\text{base}}^E$. We begin with the working point $P_{\text{base}}^E = 0.553$, which sits just beyond the boundary indicating the transition to sustained rhythmic activity. From the time-series, we observe that the activity is oscillating (Fig. 4.1C), and the spectra indicates a peak frequency of $\approx 40$Hz on a broadband background (Fig. 4.1D). We next consider the working point $P_{\text{base}}^E = 0.57$. In this state, each unit receives slightly more drive, leading to higher-amplitude oscillations (Fig. 4.1E,F). However, although peak spectral power increases, amplitude modulations can still be seen in the corresponding time-series (Fig. 4.1E). Finally, we consider the working point $P_{\text{base}}^E = 0.7$. Here, the activity is characterized by regular, high-amplitude oscillations (Fig. 4.1G). Furthermore, inspection of the power spectra indicates a single, narrow peak at a slightly higher frequency than the previous working point (Fig. 4.1H).

**Global phase-coherence is non-monotonically modulated by coupling strength and background drive**

Both the firing rate and the power spectra are measures that quantify the nature of individual regions’ activity. For networks, it is also imperative to define measures that capture information about the extent of dynamical order in the system as a whole. Indeed, for networks of coupled units, the system’s “state” is defined not only by the behavior of individual units, but also by how their dynamics are interrelated. Here, we are interested in the degree to which regional dynamics are coherent, which we quantify via the PLV between regions’ activities. To compute PLVs for baseline conditions, we begin by filtering the activity of each unit in the same, common frequency band. This band is determined by first finding the peak frequency of each unit at the given working point. Hence, we obtain a set of $N$ values $\{f^\text{peak}_i\}$ corresponding to the peak frequencies of all units $i \in \{1, ..., N\}$ at baseline. We then filter the activity of every region in a frequency band spanning 10Hz above the maximum peak frequency in the network (max$\{f^\text{peak}_i\}$) and 10Hz below the minimum peak frequency in the network (min$\{f^\text{peak}_i\}$). After identically filtering each unit’s activity in this common band, we extract Hilbert phases from the filtered signals. Finally,
PLVs between all pairs of brain areas are computed according to Eq. 4.5, using 50 different simulations (trials) of 5 seconds each (with noise included).

To summarize how the overall level of coherence in the network varies as a function of the background drive and coupling strength, we defined a macroscopic order parameter as the average of the PLVs over all pairs of units in the network: $\rho_{\text{global}} = \langle \rho_{ij} \rangle$. This quantity ranges between 0 and 1, where larger values indicate a more dynamically ordered state of the network. In general, we find that the background input and the coupling strength interdependently tune the level of coherence in the system (Fig. 4.2A). At low coupling, brain areas cannot coordinate their dynamics and $\rho_{\text{global}}$ remains at a relatively low value for a range of drives. In contrast, as the coupling is increased, we begin to see a qualitative change in behavior. For higher values of $C$, we observe that $\rho_{\text{global}}$ varies non-monotonically (first increasing and then decreasing) as a function of the (relative) background drive. For a given coupling $C$, there appears to be a “critical” value at relatively small but non-zero $P_{E}^{\text{base}} - P_{E}^{*}(C)$ where the system develops a well-defined peak in global coherence. As the drive is increased further, $\rho_{\text{global}}$ begins to decrease and then eventually plateaus, albeit with some fluctuations. More specifically, at levels of background drive well beyond the state of peak coherence, $\rho_{\text{global}}$ relaxes to an intermediate value between its peak and its value at the lowest background input. In this regime, the system resides in a state of partial order. Increasing the coupling has the effect of amplifying the maximum value of $\rho_{\text{global}}$ (although $\rho_{\text{global}}$ remains well below 1 for all couplings considered), but does not appear to significantly affect the order parameter to the right side of the peak.

To provide further intuition for this behavior, we focus on an intermediate coupling of $C = 2.5$ and examine the pairwise coherence patterns $\rho_{ij}$ for several values of the background drive (Fig. 4.2C). At the lowest (relative) baseline input ($P_{E}^{\text{base}} - P_{E}^{*}(C) = 0$), some organization can be seen in the PLV matrix, but the system is weakly coherent overall. In this state, units exhibit relatively low amplitude oscillations, and are therefore more influenced by noise. It is thus reasonable to expect little phase-locking at low background drive. However, with only a small increase in the non-specific input (e.g., $P_{E}^{\text{base}} - P_{E}^{*}(C) = 0.003$), we observe distributed increases in coherence and a large spread of high, medium, and low coherence pairs dispersed throughout the network. Increasing the background drive slightly more (e.g., $P_{E}^{\text{base}} - P_{E}^{*}(C) = 0.02$) leads to the emergence of large, highly-coherent blocks that span the system. This working point sits near the peak of $\rho_{\text{global}}$ and represents a highly ordered state of the system. As the background drive is increased further, though, phase-locking begins to decrease widely throughout the network and the coherence pattern markedly changes into a more segregated architecture. In particular, for
high $P_E^{\text{base}} - P_E^*(C)$, we observe the emergence of smaller phase-locked clusters (Fig. 4.2C, Row 3). To understand this shift in behavior, it is important to note that increasing $P_E^{\text{base}}$ increases the extent to which regional activity is independently generated in each area vs. driven by long-range network interactions. The strengthening of regional oscillations and enhanced influence of local dynamics with increasing $P_E^{\text{base}}$ seems to eventually hinder the ability of units to adjust their rhythms and achieve widespread coherence. Note that phase-locking is also made especially difficult by the large variance in the distribution of interareal delays imposed by the connectome’s spatial embedding, and indeed, for high background drive conditions, more strongly connected and spatially nearby units are those able to maintain stronger coherence.

In general, our observations point to complex behavior in which the macroscopic order parameter varies non-monotonically as a function of the baseline input and network coupling strength (Fig. 4.2A,C). Therefore, a variety of qualitatively different regimes exist, beyond just a simple binary separation into a disordered and ordered state. To more quantitatively distinguish network states before and after the point of peak coherence, we also considered a local order parameter $\rho_{\text{local}} = \frac{\sum_{ij} A_{ij} \rho_{ij}}{\sum_{ij} A_{ij}}$, which is a weighted average of $\rho_{ij}$ with weights equal to the strength of structural network connections. In this way, $\rho_{\text{local}}$ will be larger when more strongly connected brain areas are more phase-locked. In Fig. 4.2B, we show $\rho_{\text{local}} - \rho_{\text{global}}$ vs. $P_E^{\text{base}} - P_E^*(C)$ for different values of the coupling $C$. Beyond a certain point, the curves for all

**Figure 4.2 (following page):** Long-range coupling strength $C$ and background drive $P_E^{\text{base}}$ modulate network phase-coherence and relationships between structural and functional connectivity at baseline. (A) The global order parameter $\rho_{\text{global}}$ vs. $P_E^{\text{base}} - P_E^*(C)$, for different fixed values of $C$. Error bars are estimated from 100 bootstrap samples of the simulations at each coupling and background drive, and correspond to ± one standard deviation of the bootstrap distribution of $\rho_{\text{global}}$. (B) The difference between the global and local order parameters, $\rho_{\text{global}} - \rho_{\text{local}}$, vs. $P_E^{\text{base}} - P_E^*(C)$, for different fixed values of $C$. Error bars are estimated from 100 bootstrap samples of the simulations at each coupling and background drive, and correspond to ± one standard deviation of the bootstrap distribution of $\rho_{\text{global}} - \rho_{\text{local}}$. (C) Region-by-region PLV matrices for various values of $P_E^{\text{base}} - P_E^*(C)$ at fixed $C = 2.5$. The boxed matrices correspond to the red, orange, and yellow working points in Fig. 4.1 and in panels A and B of this figure. (D) The Spearman correlation $r_s$ between structural node strength $s^{\text{struc}}$ and functional node strength $s^{\text{func}}$ vs. $P_E^{\text{base}} - P_E^*$ at fixed $C = 2.5$. Empty circles indicate that the correlation was not statistically significant at the $p = 0.05$ level. The arrows mark three different working points – WP1, WP2, and WP3 (which correspond to the red, orange, and yellow dots/boxes in this figure) – that will be studied in detail.
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A

\[ \rho_{\text{global}} \]

background drive, \( P_E^\text{base} - P_E^*(C) \)

B

\[ \rho_{\text{local}} - \rho_{\text{global}} \]

background drive, \( P_E^\text{base} - P_E^*(C) \)

C

\[ P_E^\text{base} - P_E^* = 0.000 \]

\[ P_E^\text{base} - P_E^* = 0.003 \]

\[ P_E^\text{base} - P_E^* = 0.006 \]

\[ P_E^\text{base} - P_E^* = 0.010 \]

\[ P_E^\text{base} - P_E^* = 0.020 \]

\[ P_E^\text{base} - P_E^* = 0.060 \]

\[ P_E^\text{base} - P_E^* = 0.080 \]

\[ P_E^\text{base} - P_E^* = 0.150 \]

D

\[ \text{correlation, } r_{s_{\text{struct}} vs. s_{\text{func}}} \]

background drive, \( P_E^\text{base} - P_E^* \)

A\_ij

structural strength, \( s_{\text{struct}} \)

\rho_{\text{ij}}

functional strength, \( s_{\text{func}} \)
couplings exhibit a clear upward trend where the extent of local coherence increases relative to
the extent of global coherence. This behavior indicates that the macroscopic state of the system
becomes increasingly constrained by structure as the background drive increases. Hence, even
though the level of global coherence can be similar to the left and right of peak $\rho^{\text{global}}$, the system
is in qualitatively different dynamical modes in the two regimes. Also note that for the higher
couplings, $\rho^{\text{local}} - \rho^{\text{global}}$ first decreases before consistently rising. This variation occurs because,
for large enough coupling strengths, the level of global coherence is able to compete with the level
of local coherence at background drives near peak $\rho^{\text{global}}$.

As a final demonstration of the complexity of the structure-function landscape across op-
erating points, we consider the relationship between brain areas’ structural and functional con-
nectivity strengths as a function of $P^\text{base} - P^\ast_E(C)$ for a fixed coupling $C = 2.5$ (Fig. 4.2D).
The structural strength of node $j$, $s_{\text{struc}}^j = \sum_{i=1}^{N} A_{ij}$, is a common measure of a brain area’s im-
portance in an anatomical network [27]. Similarly, the (baseline) functional strength of node $j$,$s_{\text{func}}^j = \sum_{i=1}^{N} \rho_{ij}$, quantifies how dynamically integrated that region is to the network as a whole.
From Fig. 4.2D, we observe that shifting the system’s working point can drastically alter how –
and the extent to which – structural strength and functional strength are related. Specifically,
while there tends to be a weak positive correlation between $s_{\text{struc}}$ and $s_{\text{func}}$ at high background
drives (e.g. at WP3), the correlation disappears (e.g. at WP2) and then reverses in sign (e.g. at
WP1) as the background drive is lowered. Critically, these transitions occur in the absence of
any change to the anatomical connectome, and are instead driven by a global change in the be-
havior of brain areas’ dynamics (induced by changing the level of background input). Also note
that when the correlations are significant, they are intermediately-valued. Together, these results
indicate that while a given structural network may only be able to support specific patterns of
coordinated activity, the relationships between the two are not trivial and are modulated by dy-
namic properties [388, 389]. In general, functional connectivity thus reflects a complex interplay
between both anatomical connectivity and the system’s dynamical state.

It is crucial to remark that the behaviors seen here are more diverse than what tends to oc-
cur in simpler phase-oscillator models, where coupling strength is the main control parameter
and typically induces a monotonic increase in synchrony. A critical difference between phase-
based models and the more realistic WC model considered here is that, for the latter case, unit
dynamics are described and coupled by real-valued signals that represent regional activity. Hence,
widespread changes in the amplitude or stability of areas’ dynamics (in addition to changes in
coupling strength) can affect the macroscopic state of the network. Indeed, the preceding analy-

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ses show that global modulations in the level of diffuse, constant input to the neural populations can push the system into very different oscillatory modes, beyond just a steady progression from an incoherent to a coherent state. In what follows, we will exploit this behavior to examine how the effects of focal perturbations depend not only on which region is targeted, but also on the baseline working point of brain network dynamics as a whole.

4.3.2 Effects of regional perturbations on brain network activity and dependence on dynamical state

To investigate how local perturbations modulate brain network dynamics, and specifically how the effects may depend on the system’s collective state, we begin with an in-depth examination of three distinct working points. In particular, we focus on a fixed intermediate coupling strength $C = 2.5$ for which the system exhibits a clear peak in $\rho_{\text{global}}$ (Fig. 4.2A). We then examine two values of the background drive $P_{E}^{\text{base}}$ that place the system either in a state preceding (WP1) or following (WP3) the global coherence peak. In Sec. C.3, we also present results for a state in which the system is approximately at peak global coherence (WP2). We then proceed to more generally characterize the global impacts of stimulation as the background drive is varied across a wide range. Throughout the text, stimulation of a single brain area $i$ is introduced by increasing its excitatory input by an amount $\Delta P_{E,i} = 0.1$, while keeping all other regions at their working-point-specific baseline drive. In the Supporting Information, we also verify that results hold for different values of $P_{E}^{\text{base}}$ in the vicinity of those studied in the main text (Sec. C.8), examine the effects of varying the perturbation strength (Sec. C.10), and consider an alternative value of the global coupling (Sec. C.11). Note that our goal is not to exhaustively analyze all possible parameter combinations, but rather to demonstrate that the network response to stimulation qualitatively varies for different dynamical regimes.

4.3.3 Working Point 1: Pre-global coherence peak

We begin with the working point WP1 located at $C = 2.5$ and $P_{E}^{\text{base}} - P_{E}^{*}(C) = 0.003$, below peak coherence (Fig. 4.2C, Row 1, Column 2). Here, the system is perched just past the boundary marking the transition between the quiescent state and the commencement of rhythmic dynamics. Hence, regional activity is oscillatory but of relatively low amplitude (see Fig. 4.1C), and the power spectra is broad (see Fig. 4.1D).
Local excitations induce distinct modifications to power spectra

We first examine the effects of a regional perturbation on areas’ time series and power spectra (Fig. 4.3A-C). In agreement with past experimental and modeling studies [390, 143, 332, 391], increased drive to the excitatory pool of region \( i \) increases the amplitude and frequency of its oscillations (Fig. 4.3C, Left). In particular, stimulation causes an increase in the power, narrowing of the spectra (associated with an increase in periodicity of regional activity), and a shift of the peak frequency from \( \approx 40 \text{Hz} \) at baseline to \( \approx 50 \text{Hz} \) when excited. We also note the appearance of modulation sidebands in the excited spectra to the left and right of the peak frequency, which arise due to the modulation of the excited region’s time-series by the lower-frequency input it receives from other areas in the network [383]. This modulation also results in a spectral peak at \( \approx 16 \text{Hz} \) – which is the difference between the new, excited frequency and the sideband peaks, and is a marker of quasiperiodic amplitude modulation in the time-series. To more carefully quantify the effects of an excitation to region \( i \), we consider the shift in the peak frequency of unit \( i \), \( \Delta f_{\text{peak}}^i = f_{\text{peak}}^{i,\text{exc}} - f_{\text{peak}}^i \), between its excited and baseline states (Fig. 4.3D). Calculating these differences for all choices of the stimulated brain area, we find that they range from about 6Hz to 16Hz, with an average value of \( \langle \Delta f_{\text{peak}}^i \rangle \approx 10.5 \text{Hz} \). These perturbation-induced shifts thus yield excited peak frequencies that are well-separated from the range of peak frequencies in the baseline state (Fig. 4.3E).

We next consider the power spectra of two other units \( j \) and \( k \) located at increasing topological distances from the excited region, where a shorter topological distance indicates that two areas are linked by a path of stronger structural connections [27]. (Fig. 4.3C, Middle, Right). We observe that unit \( j \) maintains its initial frequency content, but also develops new peaks centered at the frequency of the excited region and at the difference of the excited frequency and the baseline peak. In contrast, the spectra of unit \( k \) – which is more weakly structurally connected to the stimulated site – is relatively unchanged. Hence, depending on the network structure, stimulation of region \( i \) can also cause alterations to other regions’ spectra. In general, the power modulation of a downstream area’s spectra at the peak frequency of the stimulated site decays with increasing topological distance between the downstream area and the perturbed region (see Sec. C.5). To summarize how the spectra of other brain areas are altered by driving region \( i \) with additional input, we compare the average power spectral density \( \langle \text{psd} \rangle_{j\neq i} \) over all units \( j \neq i \) at baseline and when unit \( i \) is stimulated (Fig. 4.3F). At baseline, the network-averaged spectra is relatively broad and contains multiple peaks – a main one at 38Hz and a smaller peak around 34Hz. In addition, a local excitation produces complex and broadband alterations in power, as
expected in a scenario of quasiperiodic entrainment between nonlinear oscillators [392]. For this example, we observe the appearance of an entirely new peak at 50Hz, but also an enhancement of the lowest baseline peak and a depression of the highest baseline peak. These changes are perhaps more apparent in Fig. 4.3G, which shows the average difference \( \langle \Delta \text{psd}_{j,\delta_i} \rangle_{j \neq i} \) in the spectra of unit \( j \neq i \) between when unit \( i \) is excited and the baseline condition, where the average is over all units \( j \neq i \). In sum, we see that a regional enhancement of neural activity causes non-local modulations in power both at the frequency of the directly stimulated brain area, as well as at the system’s baseline oscillation frequencies. These analyses suggest that there are two relevant frequency bands to consider for subsequent analysis: (1) a relatively broad band containing the main frequencies of brain areas in the baseline state, and (2) a band centered around the peak frequency.

Figure 4.3 (following page): Regional excitation causes local and downstream changes to brain areas’ power spectra in different frequency bands at Working Point 1. (A) Schematic of a brain network depicting the stimulated site \( i \) in brightest red. The black arrows point to two other regions \( j \) and \( k \) that lie at progressively further topological distances from the perturbed area in the structural network. In this figure, regions \( i, j, \) and \( k \) correspond to brain areas 1 (R–Lateral Orbitofrontal), 4 (R–Medial Orbitofrontal), and 10 (R–Precentral), respectively. (B) Left: A segment of region \( i \)'s activity time-course in the baseline condition. Right: A segment of region \( i \)'s activity time-course when it is stimulated. (C) Power spectra of area \( i \) and two other downstream regions \( j \) and \( k \). In all three panels, the lighter curves correspond to the baseline condition, and the darker curves correspond to the state in which \( i \) is driven with additional input. The gray vertical lines indicate the peak frequency \( f_{\text{peak}}^{\text{exc}} \) of region \( i \) in the excited condition. (D) Histogram of the shift in peak frequency \( \Delta f_{\text{peak}}^{\text{exc}} \) induced by stimulating unit \( i \), plotted over all choices of the perturbed area. (E) Distribution of peak frequencies of all units in the baseline condition \( \{f_{\text{peak}}^{\text{exc}}\} \) (light gray) and distribution of the peak frequency units acquire when directly excited \( \{f_{\text{peak}}^{\text{exc}}\} \) (dark gray). (F) Average power spectra \( \langle \text{psd} \rangle_{j \neq i} \) over all units \( j \neq i \) at baseline (light gray) and when unit \( i \) is perturbed with additional input (dark gray). (G) Average difference \( \langle \Delta \text{psd}_{j,\delta_i} \rangle_{j \neq i} \) of the spectra of unit \( j \neq i \) when unit \( i \) is excited and in the baseline condition, where the average is over all units \( j \neq i \). For reference, the light gray vertical lines denote the minimum and maximum peak frequency across units in the baseline state, and the dark gray line indicates the peak frequency acquired by the stimulated region \( i \). Shaded boxes denote two frequency bands of interest: (1) the baseline band (purple) consisting of the main oscillation frequencies of brain areas under baseline conditions, and (2) the excited band (green) centered around the peak frequency that the stimulated region inherits. In subsequent analyses, we assess perturbation-induced changes in the PLV between brain areas in the baseline band, \( \Delta \rho_{\delta_i}^{\text{base}} \) (purple), and in the excited band \( \Delta \rho_{\delta_i}^{\text{exc}} \) (green).
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A baseline
B excited
C distance from excited region $i$
D baseline frequency band excited frequency band
E $\Delta f^{\text{peak}}_{i,k}$ (Hz)
F baseline $\Delta \rho^\text{base}_{\delta_k}$
G excited frequency band $\Delta \rho^\text{exc}_{\delta_k}$

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frequency of the excited unit. In what follows, we will denote these two bands as “baseline” and “excited”, and consider changes in phase-locking, $\Delta \rho_{\delta_i}^{\text{base}}$ and $\Delta \rho_{\delta_i}^{\text{exc}}$, in each band induced by local perturbations.

**Excitations of regional activity induce or alter interareal phase-locking in excited and baseline frequency bands**

We are now prepared to study how focal perturbations alter the coordination of network-wide dynamics. Specifically, we examine changes in interareal phase-locking. We separate our analysis into two frequency bands – baseline and excited – by filtering regional activity in each band, extracting Hilbert phases from the filtered signals, and then calculating the PLV for each pair of regions within each band (see Fig. 4.1E; 4.2). Since spectra are relatively broad at baseline, a single baseline frequency band for the network is determined by first finding the set of peak frequencies for each unit $i$ in the baseline state, $\{f_{\text{peak}}^i\}$. Next, the lower frequency for the common baseline band is set to $\min\{f_{\text{peak}}^i\} - 10$ Hz, and the upper frequency is set to $\max\{f_{\text{peak}}^i\} + 10$ Hz. A region-by-region PLV matrix corresponding to the single baseline band is then computed after identically filtering each unit’s activity in this frequency range. To examine phase-locking between units within the much narrower excited band corresponding to a given stimulated region $i$, we first extracted the peak frequency of region $i$ when it is stimulated, $f_{\delta_i}^{\text{peak}}$. A PLV matrix corresponding to unit $i$’s excited frequency is then computed after filtering each region’s activity in the same frequency band ranging from $f_{\delta_i}^{\text{peak}} - 1.5$ Hz to $f_{\delta_i}^{\text{peak}} + 1.5$ Hz. This range was chosen to contain the majority of the excited band peak, while including as little of the original baseline band as possible. If the peak frequency of the stimulated area was not more than 3.5 Hz above the largest baseline peak frequency, then we only examined PLV changes in the baseline frequency band. Our choices are motivated by the following observation: the notion of an excited frequency band is only meaningful when a perturbation introduces a new spectral peak into the system that is separated from the frequencies present in the baseline condition. Also note that, unlike in the baseline band, areas exhibit little power at the excited frequency prior to stimulation; hence, we use changes in excited-band PLV as a measure of how effectively induced activity at the excited frequency spreads in the network.

To provide intuition about how phase-locking is altered upon a local perturbation, we consider the effect of stimulating two different brain areas (left and right panels in Figs. 4.4A,C). These examples show that regional stimulation induces phase-locking at the excited frequency (Fig. 4.4C), but can also cause changes in coherence in the frequency band containing the orig-
inal oscillatory activity of the system (Fig. 4.4A). Note that the excited band effects are mostly positive (due to the fact that power in the excited band is boosted by stimulation), whereas the baseline band effects can be both positive and negative. Furthermore, the patterns induced in the excited band (Fig. 4.4C) are distinct from the modulations that occur in the baseline band (Fig. 4.4A), and the phase-locking changes are markedly different between perturbation of region \( i \) (left panels) and perturbation of region \( j \neq i \) (right panels). Thus, depending on the frequency band considered and the excited area’s location within the large-scale brain network, stimulation induces different responses across the system as a whole.

To summarize the global effect of regional excitation, we calculate the average absolute change in PLV induced by driving each brain area with additional input. We use the notation \( \langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle \) and \( \langle |\Delta \rho_{\delta_i}^{\text{exc}}| \rangle \) to denote the network-average of the absolute PLV changes in the baseline and excited frequency bands, respectively, induced by stimulating region \( i \). Note that since the PLV is always between 0 and 1, the maximum possible value of both quantities is 1. Furthermore, we use a phase-randomized null model (described in Sec. C.12) to assess whether pairwise PLV changes are significant. Prior to calculating the network-wide averages \( \langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle \) and \( \langle |\Delta \rho_{\delta_i}^{\text{exc}}| \rangle \), non-significant changes are set to zero. We observe that the global responses exhibit a large degree of variability across different choices of the stimulated area (Fig. 4.4B,D). That is, perturbation of some areas induces larger system-wide modulations of phase-locking than others. Furthermore, regions that induce the largest overall changes in PLV inside the excited frequency band are not necessarily those that cause the largest alterations of PLV in the baseline band. This

**Figure 4.4 (following page): Phase-locking changes at Working Point 1 are driven by local excitations of neural activity, differ between excited and baseline frequency bands, and are differentially related to structural and functional network properties.** (A) Pairwise changes in the PLV inside the baseline band \( \Delta \rho_{\delta_i}^{\text{base}} \) when region \( i \) (Left) or region \( j \neq i \) (Right) is perturbed. In this figure, regions \( i \) and \( j \) correspond to regions 4 (R–Medial Orbitofrontal) and 23 (R–Lateral Occipital), respectively. (B) Network-averaged absolute PLV changes in the baseline band \( \langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle \) caused by stimulation of different brain areas. (C) Pairwise changes in the PLV inside the excited band \( \Delta \rho_{\delta_i}^{\text{exc}} \) when region \( i \) (Left) or region \( j \neq i \) (Right) is perturbed. (D) Network-averaged absolute PLV changes in the excited band \( \langle |\Delta \rho_{\delta_i}^{\text{exc}}| \rangle \) induced by stimulation of different brain areas. (E) The quantity \( \langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle \) vs. structural node strength \( s_{i}^{\text{struc}} \) (Left), and the quantity \( \langle |\Delta \rho_{\delta_i}^{\text{exc}}| \rangle \) vs. structural node strength \( s_{i}^{\text{struc}} \) (Right). (F) The quantity \( \langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle \) vs. functional node strength \( s_{i}^{\text{func}} \) (Left), and the quantity \( \langle |\Delta \rho_{\delta_i}^{\text{exc}}| \rangle \) vs. functional node strength \( s_{i}^{\text{func}} \) (Right). In panels (E) and (F), insets indicate Spearman correlation coefficients between the plotted quantities and their associated \( p \)-values.

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A

perturb region $i$

perturb region $j$

baseline band

excited band

brain region

$\Delta \rho_{\text{base}}$

$\Delta \rho_{\text{exc}}$

$\rho_{\text{base}} > 0.22$

$\rho_{\text{base}} < -0.22$

$\rho_{\text{exc}} > 0.19$

$\rho_{\text{exc}} < -0.19$

B

avg. absolute response

perturb region

$\langle |\Delta \rho_{\text{base}}^i| \rangle$

perturb region

$\langle |\Delta \rho_{\text{exc}}^j| \rangle$

C

dependencies to network properties

E

avg. PLV responses vs. structural strength

avg. PLV responses vs. functional strength

D

$\rho_s = 0.96$

$p < 0.001$

$\rho_s = 0.08$

$p > 0.05$

$\rho_s = 0.71$

$p < 0.001$

$\rho_s = -0.34$

$p < 0.05$
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observation suggests that distinct aspects of the network may be indicative of the overall effects generated at the baseline and excited frequencies.

**Structural and functional connectivity are linked to different types of phase-locking modulations at Working Point 1**

What properties of the system drive or predict the diverse, distributed responses in the baseline and excited frequency bands brought about by focal stimulation? Because the network of anatomical connections couples different brain areas and allows them to directly interact, it is reasonable to hypothesize that the organization of this network should play a role in guiding the influence of a perturbation. To test this hypothesis, we study $\langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle$ and $\langle |\Delta \rho_{\delta_i}^{\text{exc}}| \rangle$ as functions of structural node strength $s_{\text{struc}}^i$ (Fig. 4.4E). Interestingly, the global PLV modulation induced in the network’s naturally-emergent frequency band is not well-predicted by the anatomical strength of the stimulated area (Fig. 4.4E, Left). In contrast, though, we do observe a strong association (Spearman correlation $r_s = 0.96, p < 0.001$) between structural strength and the PLV change elicited in the excited band (Fig. 4.4E, Right). This result indicates that more structurally connected units generate larger overall effects at the enhanced frequency of the directly stimulated area. Because the excited band response is strongly constrained by structure, we also examined whether the effects differed between two broad, anatomically-defined classes of nodes. In particular, we compared the average excited band response for stimulation of cortical vs. subcortical areas (both of which are included in the anatomical parcellation). Given this breakdown, we find that the overall effect is significantly higher upon perturbation of subcortical regions (see Fig. C.5). This result is consistent with the findings of [281, 380], and reflects the notion that subcortical nodes make strong, distributed structural connections that may support large-scale network communication [393].

Although the brain’s structural connectivity plays a crucial role, macroscale activity patterns generally reflect an interplay between connectome architecture and the network’s dynamic regime. Indeed, in Fig. 4.2D we observed that the correlation between structural and functional strength varies in intensity and sign with working point. Importantly, the presence of a functional connection between two brain areas implies an interdependence of their dynamics – enforced by the system’s oscillatory state – that can occur even in the absence of a direct structural connection. Intuitively, we may thus expect the organization of the system’s initial *functional* interactions (which could be non-trivially related to structure), to be indicative of how the coherence pattern is modulated under perturbation. Given this reasoning, we study $\langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle$ vs. 

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Relative to structural strength, we observe a strong positive relationship (Spearman correlation $r_s = 0.71$, $p < 0.001$) between the average absolute change in baseline band coherence and functional strength. Thus, areas that are initially more coherent with other regions in the network tend to yield larger global modulations to baseline band interactions when perturbed. This should be contrasted to the results from structural node strength, for which there was not a strong relationship with absolute coherence changes at the baseline oscillation frequencies. Finally, we consider $\langle |\Delta \rho_{\delta_i}^{\text{exc}}| \rangle$ vs. $s_i^{\text{func}}$ (Fig. 4.4F, Right). Though they are correlated, ($r_s = -0.34; p < 0.05$), the stimulation-induced responses in the excited band are much more strongly predicted by structural rather than functional strength.

The above results emphasize separate consideration of both anatomical network topology and the organization of emergent functional interactions, the latter of which is also driven by the dynamical regime of the system. In particular, for the working point considered here, structural and functional network properties relate to distinct types of perturbation-induced effects. First, phase-locking changes that arise in the excited band reflect the transmission and replication of oscillatory input from the directly excited area to and in downstream regions. If the structural connection between the stimulated site and a downstream area is strong enough, then the drive from the stimulated site will induce a new spectral component in the receiving area (see, e.g., Fig. 4.3C); consequently, the two regions will exhibit phase-locking at the excited frequency. In addition, even two areas that are not directly linked can display a high PLV in the excited band due to strong common input from the stimulated region, or due to the propagation of the stimulated site’s signal along alternative paths in the network. In sum, because spreading of the perturbed area’s activity is highly constrained by the presence of structural connections, regions with stronger anatomical connectivity to other areas more forcefully drive downstream regions and lead to larger excited band effects. Perhaps more interesting are the modulations in coherence that occur in the baseline frequency band. These changes arise not due to a direct transmission of input, but rather via adjustments to the ongoing, mutual entrainment between units’ spontaneous rhythms. For WP1, the resulting alterations to the strength of coherent interactions are more related to the stimulated region’s initial functional connectivity rather than its anatomical strength. Intuitively, this may in part be due to the fact that perturbing a particular area tends to decouple it from other areas at the original oscillation frequencies, such that stimulating regions that are strongly coherent to begin with effectively reconfigures existing functional interactions in the baseline frequency band. Notably, the observed correlation between functional strength and baseline band coherence modulations does not uncover the deeper, precise mechanisms be-
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hind the effects. However, because the brain’s collective dynamics can reflect a complex interplay between its oscillatory state and its structural connectivity, the result highlights the importance of considering both aspects when trying to understand network-wide responses to perturbations.

4.3.4 Working Point 3: Post-global coherence peak

Importantly, the collective state of the model can change even when anatomical connectivity is fixed (see Fig. 4.2). To explore how this affects the impacts of regional perturbations on brain network dynamics, we next examine another working point – WP3 – located at $C = 2.5$ and $P_{\text{base}} = 0.7$. (Note that a working point WP2 between WP1 and WP3 is analyzed carefully in Sec. C.3). In this high background drive state, regional activity is characterized by more regular and higher-amplitude oscillations (see Fig. 4.1G,H) relative to both WP1 and WP2. Furthermore, at WP3, the system resides well beyond the point of maximal coherence (Fig. 4.2A), and the baseline PLV matrix is more constrained by anatomical connectivity (Fig. 4.2C, Row 2, Column 4; Fig. 4.2D).

Spectral changes are more restrained at the high background drive working point

Inspection of a region’s activity time-series at baseline and when stimulated with additional input indicates noticeable differences in how perturbations alter local activity at WP3 versus at either WP1 or WP2. Specifically, when the system operates in the high-drive state, a perturbation of the same strength has a much less drastic effect on the stimulated region’s activity, inducing only relatively small changes to its amplitude and frequency (Fig. 4.5B).

Consequences of regions’ enhanced baseline activity for focal stimulation are perhaps more evident from examples of areas’ spectra at baseline and under stimulation (Fig. 4.5C). As for the lower-drive working points, the peak frequency and power of the stimulated region $i$ shift to higher values (Fig. 4.5C, Left). However, at WP3, the increase is modest relative to the shifts that occur at either WP1 or WP2, and no modulation sidebands arise in $i$’s spectra under excited conditions. As a result of the more unyielding nature of spontaneous dynamics, stimulation of unit $i$ also has relatively little impact on the spectra of downstream regions (Fig. 4.5C, Middle, Right), even if they are positioned topologically close to the perturbed site. To more generally quantify the effects of regional stimulation on areas’ power spectra, we examine the distribution of the shifts in peak frequency $\Delta f_{\text{peak}}^{i,\delta i}$ that occur due to perturbation of each unit. The largest of these shifts is only about 3Hz (Fig. 4.5D). Hence, relative to WP1 and WP2, the average shift...
in peak frequency $\langle \Delta f_{i,\delta}^{\text{peak}} \rangle$ is greatly reduced at the high-drive working point (see Fig. 4.5E). Furthermore, unlike the situation in the low-drive state, the distributions of peak frequencies at baseline and under focal stimulation begin to overlap at WP3 (Fig. 4.5F), precluding the notion of separate baseline and excited frequency bands. For this reason, in our subsequent analyses we only consider phase-locking changes inside a single frequency band (Fig. 4.5G). While we refer to this as the “baseline band”, we note that it still contains the peak frequency of the directly excited unit, since its frequency shift is so small.

The results presented in this section indicate that regional dynamics are more robust to perturbations at the high-drive working point. This can in part be understood by considering the effects of the background drive $P_{E}^{\text{base}}$, which is the parameter tuned to move from WP1 $\rightarrow$ WP2 $\rightarrow$ WP3. In particular, the increased baseline input level at WP3 means that each unit, if disconnected from the network, would operate closer to the bifurcation separating the quiescent and oscillatory state than would be the case at WP1 or WP2. As a result, stronger oscillations emerge at WP3 when the network coupling is introduced, reflecting the increased influence of

Figure 4.5 (following page): Effects of local excitations on power spectra are more restricted at the high background drive working point (Working Point 3). (A) Schematic of a brain network depicting the stimulated site $i$ in brightest red. The black arrows point to two other regions $j$ and $k$ that lie at progressively further topological distances from the perturbed area in the structural network. In this figure, regions $i$, $j$, and $k$ correspond to brain areas 1 (R–Lateral Orbitofrontal), 4 (R–Medial Orbitofrontal), and 10 (R–Precentral), respectively. (B) Left: A segment of region $i$’s activity time-course in the baseline condition. Right: A segment of region $i$’s activity time-course when it is stimulated. (C) Power spectra of area $i$ and two other downstream regions $j$ and $k$. In all three panels, the lighter curves correspond to the baseline condition, and the darker curves correspond to the state in which $i$ is driven with additional input. The gray vertical lines indicate the peak frequency $f_{i,\delta}^{\text{peak}}$ of region $i$ in the excited condition. (D) Histogram of the shift in peak frequency $\Delta f_{i,\delta}^{\text{peak}}$ induced by exciting unit $i$, plotted over all choices of the perturbed area. (E) The average shift in the peak frequency of the stimulated region $\langle \Delta f_{i,\delta}^{\text{peak}} \rangle$ for WP1, WP2, and WP3 (error bars indicate the standard deviation over all choices of the excited unit). (F) Distribution of peak frequencies of all units in the baseline condition $\{f_{i}^{\text{peak}}\}$ (light gray) and distribution of the peak frequency units acquire when directly excited $\{f_{i,\delta}^{\text{peak}}\}$ (dark gray). (G) Average power spectra $\langle \text{psd}_{j \neq i} \rangle$ over all units $j \neq i$ at baseline (light gray) and when unit $i$ is perturbed with additional input (dark gray). Because stimulation does not induce a well-separated excited frequency band, we only assess perturbation-induced changes in the PLV between brain areas for a single baseline frequency band (purple area).
CHAPTER 4.

![Image A](image.png)

**Baseline**

**Excited**

**Frequency Band**

**Distance from Excited Region**

**Histogram**

**Baseline Frequency Band**

**Excited Frequency Band**
recurrent dynamics. The high-amplitude rhythms that arise in the high-drive state are more difficult to disrupt, leading to minimal changes in the power spectra under local perturbations. For the same reasons, it is also more difficult for a local change in activity to propagate and influence the dynamics of remote areas. In contrast, when the system operates at either WP1 or WP2, the baseline oscillations at each brain area are weaker. This lower-amplitude activity is easier to override, yielding the system more plastic and susceptible to local perturbations. This flexibility at WP1 and WP2 is reflected by clear modifications to regional spectra upon local stimulation and the signatures of the stimulation effect in downstream regions (Fig. 4.3 and Fig. C.3).

Focal perturbations yield a distinct and more homogeneous set of phase-coherence modulations at the high-drive working point

While the rigidity of baseline rhythms at WP3 prevents the emergence of a well-defined excited frequency band, we can still assess the effects of selective perturbations on interareal phase-locking in the single, baseline frequency band. We carry out such an analysis in this section, focusing on contrasting the results obtained at WP3 to those obtained previously at WP1 (and WP2). To begin, we show examples of the pairwise changes in PLV induced by stimulation of two different brain areas $i$ and $j$ (Fig. 4.6A), and the average absolute changes $\langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle$ in phase-locking driven by perturbation of each brain area in the network (Fig. 4.6B). As with WP1, the statistical significance of PLV changes is first assessed with a phase-randomized null model (see Sec. C.12) before computing network averages. Despite differences in the induced average responses across regions, visual comparison of the distribution at WP3 (Fig. 4.6B) and at WP1 (Fig. 4.4B) suggests that there may be less variation across regions when the system operates in the high-drive state. Indeed, although the mean of the average absolute changes across all brain areas is approximately the same at WP1 and WP3, when we compare the coefficient of variation (CoV) of the two distributions of $\{ |\Delta \rho_{\delta_i}^{\text{base}}| \}$, we find that the CoV for WP3 is 0.25, while for WP1 it is 0.45. This indicates that global coherence modulations elicited by regional stimulation are more homogeneous across different choices of the stimulated brain area when the system operates in the high background drive regime. Because we are particularly interested in how perturbations may differentially affect network dynamics depending on baseline state, we also investigate if the average absolute PLV modulations are correlated between WP1 and WP3. This relationship is not significant (Fig. C.7), indicating that the rank-ordering of $\langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle$ is quite different between the low and high drive regimes.

We next considered the associations between structural or functional properties of network
Figure 4.6: Phase-locking modulations induced by regional stimulation at Working Point 3 and their associations with network properties. (A) Pairwise changes in the PLV inside the baseline band $\Delta \rho_{\text{base}}$ when region $i$ (Left) or region $j \neq i$ (Right) is perturbed. In this figure, regions $i$ and $j$ correspond to regions 10 (R–Precentral) and 15 (R–Isthmus), respectively. (B) Network-averaged absolute PLV changes in the baseline band $\langle |\Delta \rho_{\text{base}}| \rangle$ induced by stimulation of different brain areas. (C) The quantity $\langle |\Delta \rho_{\text{base}}| \rangle$ vs. structural node strength $s_i^{\text{struc}}$ (Left) and vs. functional node strength $s_i^{\text{func}}$ (Right). Insets indicate Spearman correlation coefficients between the plotted quantities and their associated $p$-values.

Nodes and the global phase-locking changes induced by regional stimulation (Fig. 4.6C). At WP3, we find a strong positive correlation between $\langle |\Delta \rho_{\text{base}}| \rangle$ and structural strength $s_i^{\text{struc}}$ ($r_s = 0.82$, $p < 0.001$; Fig. 4.6C, Left). Thus, larger coherence modulations at the high-drive working point are dependent on the presence of strong anatomical connections emanating from the stimulated region. Note that functional strength $s_i^{\text{func}}$ also exhibits a positive correlation with $\langle |\Delta \rho_{\text{base}}| \rangle$ ($r_s = 0.34$, $p < 0.05$; Fig. 4.6C, Right), which we might expect given the weak but positive correlation between $s_i^{\text{struc}}$ and $s_i^{\text{func}}$ at this working point (Fig. 4.2D). However, structural connectivity is undoubtedly a more robust predictor of these effects.

A supplementary analysis (see Fig. C.8) indicates that the association between $s_i^{\text{struc}}$ and
is (largely) explained by a relationship between structural strength and the bulk decreases in coherence induced by perturbations. Hence, units with stronger anatomical connectivity to the network as a whole generate larger global breakdowns in coherence when stimulated with constant, additional input. To gain intuition for this result, recall that in the high-drive regime, brain areas exhibit relatively strong and inflexible oscillations at baseline. Furthermore, though not enough to bring about an entirely new excited band, stimulation still slightly accelerates the frequency of the perturbed unit. As a consequence, we may expect stimulation of regions with stronger structural connections – which have more direct influence on other areas – to drive more disruptions in the network’s ongoing dynamics. That is, a given node will tend to be driven out of coherence with other units when stimulated (since it acquires a slightly increased frequency), and high-strength nodes in particular will also be able to decouple other areas from their baseline functional assemblies, in turn causing larger dissociations of functional connectivity.

To conclude this section, we highlight the observation that depending on the oscillatory regime, different aspects of the system best predict global responses to focal stimulation. In the low-drive state, emergent coordination between units activities at baseline is more strongly related to coherence modulations at regions’ spontaneous frequencies, whereas structure is more strongly associated with the effects in the high-drive regime.

4.3.5 System-wide effects of regional perturbations vary with dynamical state

We have examined distinct operating points characterized by varying regional oscillation strengths, and in turn, different large-scale coordination patterns and relationships to anatomical connectivity. We found that focal perturbations had markedly different effects on brain network dynamics and associations to network connectivity depending on the system’s oscillatory mode. In this section, we more generally examine the effects of perturbations as the nature of regional activity is smoothly varied – by tuning the level of background drive $P_{\text{base}}$ – while holding network structure constant. Throughout this exposition, we set the coupling $C = 2.5$, as before.

To summarize the response in the baseline band, we first stimulate each region $i$ to generate a set of $N$ average absolute coherence modulations $\{ |\Delta \rho_{\text{base}}^i| \}$. We then consider the mean of this set across regions, $\langle |\Delta \rho_{\text{base}}^i| \rangle$ (which we refer to as the “grand average”), and study its behavior as the background drive is varied (Fig. 4.7A, right axis). We find that the general shape
of $\langle|\Delta \rho_{\text{base}}^{|}\rangle$ as a function of the relative background drive $P_{E}^{\text{base}} - P_{E}^*$ tends to mimic that of the global baseline coherence $\rho_{\text{global}}$ (Fig. 4.7A,left axis), but with a slight shift towards lower $P_{E}^\text{base} - P_{E}^*$. Importantly, the peak in the PLV modulation curve at intermediate background drive signifies a distinct state at which regional perturbations generate the largest overall changes to coherence in the system’s baseline frequency band. Of note is that this working point occurs just prior to the global PLV peak. Intuitively, the system may exhibit the largest response at this working point because there is heightened potential to both enhance and depress functional interactions when the system is perched at the transition into the maximally ordered state. At lower values of $P_{E}^\text{base} - P_{E}^*$, stimulation of single brain areas has a smaller average effect, which likely occurs in part because there is less initial coherence for local excitations to disrupt. As $\rho_{\text{global}}$ begins to decline with increasing $P_{E}^\text{base} - P_{E}^*$, so too does the overall response to regional perturbation. The grand average of the baseline band PLV modulation approaches a local minimum at $P_{E}^\text{base} - P_{E}^* = 0.07$, after which it settles to intermediate values at high-drive working points well beyond peak $\rho_{\text{global}}$ (e.g., at WP3).

In addition to the grand average, we also examined the coefficient of variation (CoV) of the distribution of average absolute coherence changes, which we denote as $\text{CoV}[\langle|\Delta \rho_{\text{base}}^{|}\rangle]$. In general, $\text{CoV}[\langle|\Delta \rho_{\text{base}}^{|}\rangle]$ also exhibits a state dependence (Fig. 4.7B). Specifically, $\text{CoV}[\langle|\Delta \rho_{\text{base}}^{|}\rangle]$ begins at an intermediate value for the lowest background drive, increases to a global maximum, and then declines to below its initial value for high-drive states. This behavior indicates that global responses exhibit less variability across different choices of the stimulated site when the system operates in states of strong baseline rhythms. In contrast, the network-wide impacts of regional stimulation display more dispersion in the low-drive regime, with variability peaking near maximum $\rho_{\text{global}}$ (WP2). For these states, the overall response in the baseline band is thus more dependent on the precise location in the network that is perturbed.

We next assess how the dynamical state influences the global response induced in the excited frequency band. In this case, the grand average $\langle|\Delta \rho_{\text{exc}}^{|}\rangle$ of the absolute excited-band PLV changes steadily decays and eventually vanishes with increasing $P_{E}^\text{base} - P_{E}^*$ (Fig. 4.7C), as does the variability of the response distribution (Fig. 4.7D). This behavior is due to the amplification of baseline oscillations with increasing background drive: as regions’ spontaneous dynamics become more difficult for perturbations to override, the emergence of widespread phase-locking at regions’ excited frequencies declines. Eventually, stimulation no longer yields large enough frequency shifts to induce an excited band at all. This result thus indicates that activity from the stimulated area is most effectively propagated to downstream regions when the network operates
in a state of weak baseline activity.

For our final analysis, we examine more generally how the relationships between stimulation-induced PLV modulations and structural or functional network connectivity depend on the system’s operating point. In particular, we consider the correlations between the average absolute baseline band coherence changes $\langle |\Delta \rho_{\text{base}}^{\delta_i}| \rangle$ and the structural $s_i^{\text{struc}}$ or functional
Figure 4.8: Relationships between phase-locking modulations and the structural or functional connectivity of the stimulated site vary with working point. (A) Difference $\Delta r_s$ in the strength of the correlation between the average absolute baseline band PLV changes $\langle|\Delta \rho_{\delta_i}^{\text{base}}|\rangle$ and structural ($s_i^{\text{struc}}$) or functional ($s_i^{\text{func}}$) node strength, plotted as a function of the baseline drive $P_E^{\text{base}} - P_E^*$ for a coupling $C = 2.5$. The difference is defined such that when the curve is positive, overall coherence modulations exhibit a stronger correlation with functional rather than structural strength. The arrows mark the locations of the different working points studied in detail in the main or supporting text. (B) A schematic summarizing how structural $s_i^{\text{struc}}$ or functional $s_i^{\text{func}}$ strength are related to either baseline or excited band PLV changes for different dynamical regimes. As the background drive varies from low (WP1) to medium (WP2) to high (WP3), the oscillatory state of the system changes, and so does the association of different phase-locking modulations to structural or functional network properties.
strength of the perturbed unit. To highlight the differing levels of association between the global responses and either structural or functional connectivity, Fig. 4.8A shows how the difference $\Delta r_s$ in the strength of these correlations varies with background drive $P_E^{\text{base}} - P_E^{*}$ (individual correlations are shown in Fig. C.10). We observe that the relationships between phase-coherence modulations and structural or functional strength can depend strongly on the system’s baseline state. For the bulk of the “low”-drive regime (working points below peak global coherence), there is a stronger relationship between $\langle|\Delta \rho^{\text{base}}|\rangle$ and $s_{i}^{\text{func}}$ (rather than $s_{i}^{\text{struc}}$). This enhanced association between a region’s initial functional connectivity and the overall response it induces upon stimulation is largest at dynamical states near WP1, where there is an intermediate level of coherence in the network at baseline. In the “medium”-drive regime, stretching from just prior to peak global coherence up to the beginning of the plateau region in Fig. 4.2A, the correlation between $s_{i}^{\text{struc}}$ and $\langle|\Delta \rho^{\text{base}}|\rangle$ starts to increase, but functional strength continues to remain more strongly associated with the global modulations elicited in the baseline band. Finally, we observe a clear “switch” at $P_E^{\text{base}} - P_E^{*} \approx 0.07$, after which structural connectivity becomes relatively better at predicting the overall response to perturbation than functional connectivity (note that this transition occurs in tandem with baseline functional and structural strength becoming positively correlated; see Fig. 4.2D). This behavior marks the onset of the “high”-drive regime, and persists across the remainder of the background drives examined.

To conclude this section, we schematically summarize in Fig. 4.8B the most robust associations between either structural or functional connectivity and the PLV modulations induced by focal perturbations in either the baseline or excited frequency bands. Although we have not comprehensively detailed the effects of perturbations for all possible working points of the model, the results discussed throughout the text highlight the critical influence of a brain network’s collective dynamical state in dictating the outcomes of localized stimulation.

## 4.4 Discussion

In this study, we set out to explore relations between large-scale brain connectivity, dynamics, and the local and widespread impacts of regional perturbations to neural activity. Following the efforts of past work [281], we built a reduced computational model wherein brain areas were represented as Wilson-Cowan neural masses with long-range coupling between regions constrained by empirical diffusion tractography measurements. We then investigated how stimulation of a particular brain area affected network dynamics, and asked whether and how the collective dy-
namical state of the system plays a role in modulating such effects. Here, we chose to examine state-dependence by changing the combination of generic background drive and interareal coupling strength, which vary the extent to which local vs. network interactions drive regional dynamics, respectively. By tuning these parameters, we identified qualitatively distinct dynamical regimes of the model, and at these different working points, we assessed how local excitations of fixed strength induced or modulated interareal phase-locking. We found that, depending on the baseline regime of the system, the network exhibited different responses to regional perturbations. Furthermore, altering the working point of the model also qualitatively altered the relationships between stimulation-induced effects and properties of structural and functional network connectivity. To the best of our knowledge, these points have yet to be investigated at the whole-brain scale via computational modeling.

Before moving on to a further discussion of this study’s results and limitations, it is critical to state that it is not the first to examine the impacts of perturbations using computational models of brain dynamics. In fact, our work was motivated and inspired by a number of previous large-scale modeling studies that have uncovered key insights into either the network-wide [351, 281, 352, 353] or state-dependent [361–363] influences of stimulation. Because our study builds on its methodology, we specifically emphasize the investigation in [281], where (as here) the authors used interconnected Wilson-Cowan units to simulate brain activity, and then utilized recent advances in network control theory [394] to make predictions about the overall functional effects of regional stimulation. We also bring particular attention to the study conducted in [361], where the authors built a simplified model to examine the state-dependent effects of alternating current stimulation on local cortical oscillations. As part of their study, they found that the strength of endogenous oscillations altered the susceptibility of local dynamics to external stimulation. In the present investigation, we vary the background drive (the main tuning parameter in the WC model), which also modulates the amplitude of regional activity. Therefore, although our study is focused on the network-wide effects of focal perturbations, it is necessary to heed and connect our results to those previously reported in [361].

While our work builds upon these and other past efforts, it is important to highlight some key distinctions and extensions of our analysis. First, in contrast to [351], we opted to use the more complex – but in some ways more biophysically-motivated – Wilson-Cowan system as the fundamental dynamical unit in the model, rather than a pure phase oscillator. Studying models that incorporate both phase and amplitude dynamics will likely be critical for a more complete understanding of oscillatory neural activity, since variations in amplitude can affect functional
couplings in the brain, are modulated by behavioral conditions, and are also elicited by various forms of stimulation [122, 320, 391, 171, 395]. A second key difference between our study and those conducted in [281] and [352] is that the aforementioned studies analyzed a situation in which brain activity was assumed to be in a quiescent state prior to stimulation. Here, however, we were interested particularly in states corresponding to ongoing oscillatory activity, and the interaction between those baseline rhythms and increased excitation to a particular brain area.

Finally, in an extension of prior work that has begun to examine the state-dependent impacts of stimulation on single cortical areas [361], we wished to consider a large-scale network model that allowed for an analysis of how stimulation can disseminate to induce or modulate dynamical interactions between widespread brain areas. Hence, the key contribution of this study is its simultaneous investigation of (1) not only the focal, but also the distributed impacts of regional stimulation, and (2) how the collective regime of system activity (i.e., that arising from a combination of local dynamical properties and network coupling) influences such network-wide effects. To the best of our knowledge, it remains an open question how the collective state of brain activity alters the way focal stimulation impacts functional relations between distant brain areas.

In the rate model implemented here, the general focal effect of stimulation was to increase the amplitude and frequency of activity in the perturbed area. Such changes in neural activity are broadly consistent with the effects of natural stimulation of certain cortical areas, such as visual stimuli impinging on visual cortex [391, 332] and the effects of increased excitatory drive to neuronal populations generally [390]. However, we also observed that an excitation of fixed strength had significantly stronger effects on local activity (i.e., the induced shift in power and frequency was larger) for states of lower background drive (e.g., at WP1 and WP2). Thus, for these working points, perturbations led to the emergence of a new, “excited” frequency in the system that was well-separated from the main oscillation frequencies at baseline. In contrast, the enhanced regional activity present in the high-drive regime (WP3) was significantly less responsive to perturbations (in that stimulation did not generate a well-separated excited frequency). Though the analogy is not perfect, this behavior is undoubtedly akin to and consistent with the findings reported in [361], wherein alternating current stimulation induced the strongest effects at the stimulation frequency in the absence of strong endogenous oscillations.

Beyond local responses, it is also critical to acknowledge that a given neuronal population exists in the context of a larger network of areas, such that local changes in activity can induce distributed effects [330, 329, 327, 328]. Indeed, we found that in states of low background drive, areas topologically close to the stimulation site also developed spectral peaks at the frequency
of the stimulated region. These downstream signatures – caused by strong oscillatory drive from the directly excited area – are thus qualitatively similar to those induced by rhythmic stimulation, where activity in the targeted site shows enhanced power at the stimulation frequency [396, 361]. In general, the network’s global response in the excited frequency band was tightly constrained by anatomical connectivity, demonstrating that these effects arise due to a direct propagation of the stimulated area’s strong rhythmic activity along structural pathways. Interestingly, we found that focal perturbations could also modify downstream regions’ spectra at frequencies other than the peak frequency of the directly excited area. Such generic broad-band alterations of spectra can occur in coupled neuronal populations with long-range excitatory interactions [150]. Indeed, in one of only a few possible scenarios, interacting nonlinear oscillators engage first into quasiperiodic dynamics, and then develop chaos, which is associated with spectral changes over continuous ranges [392]. We additionally saw that local excitations could alter levels of temporal coordination between brain areas’ activity in a frequency band containing the system’s spontaneous, “baseline” oscillations. Furthermore, in the low-drive regime, we observed that global absolute modulations in baseline-band coherence were actually more strongly related to the stimulated region’s functional strength than structural strength. This is in contrast to the excited-band responses, which were clearly mediated by anatomical connectivity. Importantly, changes in the baseline band arise from modifications of the dynamic interactions between brain regions’ ongoing rhythms, which can depend on a more complex and intricate interplay between both network structure and the collective oscillatory state of the system. Finally, in the high-drive regime, system-wide changes in phase-locking became more homogeneous across different choices of the excited brain area, and were better predicted by the stimulated region’s structural strength. This reflects the idea that in a state of robust regional oscillations, focal stimulation will only yield a large global effect if the perturbed site has strong anatomical connectivity.

Although the field has not reached a clear consensus on the distributed effects of stimulation, the general finding in our study that increased drive to a single brain area can spread and reorganize functional interactions is consistent with previous modeling work [281, 352]. We also make some new, specific predictions about different types of changes that can occur and investigate potential mediators of these effects. Perhaps most interesting is the suggestion that both network structure and coordinated dynamical organization may play a role in guiding the non-local effects of perturbations. While network neuroscience has traditionally focused on how structure can predict function [161, 397–400], it is critical to acknowledge that the behavior of neural systems need not be completely constrained by structure alone [388, 277, 113, 401]. In
particular, by modulating intrinsic properties of neural units, a single structural connectome can generate different patterns of coordinated activity [389, 402, 403]. Indeed, we observed that although structural connectivity may partially constrain the organization of functional interactions, the way and the extent to which it does so is dependent on the nature of regional dynamics. Our findings indicate that, as a consequence, the collective oscillatory state of the system may also be important in determining how a perturbation can lead to distributed changes in functional interactions. Specifically, we found that in certain cases, functional connectivity was actually a better predictor of the overall response to perturbations than structural connectivity. Although the presence of an association with functional strength should not be misinterpreted as a mechanistic explanation for how stimulation alters dynamics, such an observation can provide insight, especially when contrasted with the role of structure alone. In total, our results indicate that depending on the collective state of network activity, the widespread impacts of focal perturbations can differ, and may be driven by distinct processes.

Though we examined a simplified model, our results may be relevant to other work and a growing literature on brain state-dependent stimulation [361–363, 356–360], which recognizes that the effects of exogenous perturbations can be conditional on the endogenous rhythmic or spontaneous activity of the system at the time of stimulation. For example, empirical studies have shown that outcomes of stimulation can differ as a function of cognitive state (i.e., task vs. rest) [357–360, 404]. Importantly, a few computational studies have investigated and provided explanations for such state-dependent responses to alternating current stimulation [361–363], though have only considered models of a single or a few coupled cortical and/or subcortical regions and have thus focused on stimulation’s local effects. Our goal here was to begin filling the need for larger-scale models that systematically consider the influence of whole-brain anatomical connectivity in conjunction with the collective dynamics of brain activity in shaping the widespread effects of stimulation. Importantly, stimulation also holds promise as a technique for moving the brain between specific, desired states [394, 354, 355]. The ability to control brain network dynamics has important applications in the treatment of neurological diseases such as Parkinson’s and epilepsy [349, 348, 350], in which neural activity goes awry. As they are refined, computational studies that put focus on how stimulation interacts with internal, ongoing dynamics in large-scale brain networks have the potential to inform future control and stimulation-based experiments and therapies [180, 405].

There are also a number of methodological considerations to comment on regarding this work. First, we used a relatively coarse-grained parcellation ($N = 82$ regions) to construct hu-
man structural brain networks. This resolution is roughly consistent with several other whole-brain modeling studies [281, 173, 156, 122, 163], and is tractable for computationally intensive simulations. However, the employed parcellation is a simplification of the underlying anatomy, since the regions represent large pieces of neural tissue and hence remain agnostic to potentially important structural heterogeneities at finer scales. Moreover, we used Euclidean distances between region centers to approximate structural connection lengths [163, 173], but one could derive perhaps more accurate estimates based on fiber trajectories [382]. It is also important to note that the limitations of human brain imaging and tractography preclude a perfect reconstruction of interareal connections [406]. One primary drawback is that these methods cannot resolve the directedness of interareal connections, which could impact subsequent results [377]. Finally, we used a group-representative connectome in this study. On the one hand, this allowed us to focus on general trends and behaviors, but on the other, it leaves no room for examining how individual differences may affect certain findings. In future work, it will be interesting to explore how various results generalize to both higher-resolution and higher-quality brain data, and to understand how variability in brain structure across different human subjects [379, 407, 408] or even across different species [409] may relate to differences in how perturbations of neural activity are expressed in system dynamics.

Another limitation of this study concerns the model used to simulate brain activity. We opted to use the canonical Wilson-Cowan model [130] – which embodies a tradeoff between biological realism and tractability – but future work could examine other choices for the node dynamics. Furthermore, while the WC model constitutes an arguably realistic improvement over simpler linear models, phase-oscillators, or generic Hopf bifurcation models, it is still phenomenological in nature and our implementation of the model is highly idealized. For example, the simulated oscillations in this work tend to be much more regular than physiological rhythms, which limits the model's biological plausibility. Similarly, the model yields unrealistically high levels of sustained, network-wide coherence. If observed in brain network dynamics, such states would be much more likely to occur in a transient manner as the brain transitions between segregated and integrated states dynamically [162, 410, 411, 386]. Though building whole-brain mean-field models that yield more realistic, transient and time-varying switches between synchronized or desynchronized states is difficult, this is an exciting direction for future study.

In general, there are several ways the model could be improved upon to increase its biological validity. For instance, for simplicity and in line with past work [281, 173, 169, 175, 161, 170, 381], we only considered long-range couplings between excitatory populations. However, inter-
areal connections likely target both excitatory and inhibitory neurons, and it would therefore be relevant to examine the effects of long-range excitatory-to-inhibitory coupling. We also used a fixed value for the signal propagation velocity. Although we attempted to choose an empirically constrained value, it is known that delays can have significant consequences on brain dynamics [157, 168], and this could be explored further. Moreover, in the WC model, oscillations are generated via the interaction of excitatory and inhibitory neuronal populations, which is considered a biophysically-plausible mechanism underlying rhythmicity in the gamma and beta bands [71, 412]. However, lower frequency oscillations (e.g. alpha band activity), may be generated – at least in part – by thalamocortical loops [86]. Importantly, past models of small thalamocortical circuits (i.e. with only a few coupled regions) have shown that these interactions are important for explaining empirical results regarding the state-dependent responses of cortical alpha oscillations to AC stimulation [361]. Along these lines, an interesting direction for future work would thus be to incorporate more realistic dynamics of subcortical regions and biologically-motivated thalamocortical couplings [300]. Another assumption of the model is that each unit has identical parameters. While this is a reasonable and useful setup to analyze first, there is an important body of literature detailing specific heterogeneities across brain areas. For example, different regions may operate at different intrinsic time-scales and have different intrapopulation architectures (e.g., excitatory or inhibitory coupling strengths) that lead to functional specialization [413]. Recent modeling efforts have begun to incorporate some of these additional complexities, finding that doing so can lead to more realistic baseline dynamics and can explain certain empirically-observed behaviors not accounted for by simpler models [164]. The model implemented here also assumes oscillations in a single gamma frequency range. However, brain areas can exhibit rhythmic activity in multiple frequency bands, which potentially arise from different cortical layers [414]. In future work, it will be important to ask how the impacts of perturbations depend on collective state when additional details about the heterogeneity of the underlying anatomy or dynamics of brain areas are included in the model [351, 143]. Indeed, these steps will allow one to make more concrete and biologically-meaningful statements about how different regions influence large-scale activity patterns. That said, we also stress that the model considered in the present work does not prevent the ensuing dynamics from being complex and rich, and actually allows us to appreciate how dynamical – in addition to structural – complexity can be a key driver of stimulation-induced effects.

With respect to our analysis, it is also important to state that we examined only a few representative working points of the model, out of the many that exist. Though our goal in this work
was to illustrate that the collective state of the system can influence the effects of local perturbations, we do not claim to have provided an exhaustive description of all possible behaviors. Furthermore, our analyses of the interareal coherence modulations induced by focal perturbations examined network-averaged responses and absolute changes. In other words, we focused on characterizing aggregate reorganizations in functional couplings. This focus leaves at least two clear and important directions for subsequent work. First, one could try to further disambiguate what leads to strengthening vs. weakening of interareal coherence upon focal perturbation. A deeper understanding of when each outcome occurs would likely require significantly more complex analyses of not only the structural and dynamical properties of the stimulated node, but also of other areas. Second, one could attempt to discern how focal perturbations alter dynamic interactions on finer scales, for example, between individual pairs of regions. Again, this would almost certainly require investigating which aspects of non-stimulated areas at baseline allow them to become engaged or disengaged when another region is perturbed. The complexity of both network structure and dynamics make these tasks challenging, but obtaining a more refined understanding of the underlying mechanisms is essential for making useful comparisons against empirical studies.

Perhaps the biggest limitation of the model presented here is that its baseline dynamics were not tuned according to empirical measurements of large-scale brain activity. To address this in future work, model parameters could be fit separately for different empirically-observed brain states [415], such that various aspects of simulated whole-brain activity match the experimental activity patterns in each case. Then, the effects of stimulation could be re-investigated in the context of the empirically-validated large-scale model to make more biologically-informed predictions. Because the current implementation lacks these constraints, it should be interpreted as a canonical, reduced example.

Another interesting direction for future work would be to systematically compare the impacts of perturbations when implemented on empirical brain network architecture versus other canonical network models. This may allow one to test which effects generalize across different network topologies and which are specific to brain network organization. For example, the recent study in [416] examines how human cortical networks may be structured to support ignition dynamics relative to other canonical network models, finding that the well-connected structural core present in actual brain networks plays a critical role. In extending this type of analysis, one could perhaps also consider whether the brain is especially well-organized for oscillatory control via localized perturbations, and how the brain’s controllability depends on its current state. In
other words, does the brain exhibit special topological or dynamical features that enhance the ability of focal stimulation to push it into particular collective, oscillatory modes? Importantly, the controllability of large-scale brain networks is often studied using tools from linear network control theory [394]; however, understanding the control of oscillatory activity in the brain will require extending this framework to incorporate non-linear behaviors [417].

In addition to investigating alternative and/or more detailed models, forthcoming studies could also consider different ways of operationalizing perturbations to neural activity. As a first step, here we implemented “stimulation” as a constant increase in excitatory drive [281]. Given the already complex nature of network dynamics in the absence of stimulation, starting with simple, constant perturbations is critical for building intuitions. However, it will be important for future whole-brain modeling studies to implement more realistic and experimentally viable forms of perturbations, which are often time-varying and transient in nature. One clear choice would be to model alternating current stimulation, for example. In this case, the stimulated area receives oscillatory input of a particular amplitude and frequency [418], both of which can be independently tuned. While this kind of stimulation has been examined in smaller thalamocortical circuits [361–363], it would be exciting to scale up to systems-level models. One could also investigate alternative ways of modulating brain state. In this study, we varied the baseline dynamical regime in perhaps the most straightforward way possible, by tuning the level of excitatory input globally for all network elements. This variation changed the local dynamics of each brain area, and in turn, the macroscopic state of the system as a whole. However, brain state could also be modulated by tuning a different physiologically-interpretable parameter, such as the gain in the sigmoidal activation functions. Indeed, recent modeling studies have shown that altering neural gain can lead to dynamical regimes in which functional integration and segregation are balanced [176]. It would also be interesting to understand how widespread changes of neural gain affect the way focal perturbations materialize.

In sum, we conducted an idealized investigation into the effects of focal stimulation on brain network dynamics, focusing on how the system’s collective state influences the distributed impacts of such perturbations. To the best of our knowledge, this latter point has only recently begun to be examined in the context of large-scale brain networks, and therefore warrants investigation via simplified models. However, the results of this study must be interpreted cautiously as they are yet to be validated by data. Comparing conjectures based on reduced models against empirical findings is necessary to substantiate whether or not the model provides biologically meaningful insight. One testable prediction from the model presented here is that focal stimulation
propagates to cause downstream modulations of power and phase-locking at both the dominant frequency acquired by the activated area, but also at regions’ baseline frequencies. Investigating this would require an experiment in which stimulation forces the perturbed area to oscillate at a well-defined frequency – which could perhaps be achieved by alternating current stimulation \cite{75} – and a simultaneous measurement of other brain areas’ dynamics. Moreover, testing variations in the global effects of perturbing different regions would require multiple brain areas to be stimulated and responses from distributed regions simultaneously recorded. Recent advances combining non-invasive brain stimulation with measurement modalities like EEG and MEG \cite{342–346} are making this increasingly possible. These types of experiments \cite{342–346} will be crucial in validating results from computational models that posit how stimulation alters functional couplings across different parts of the brain. Furthermore, one could test how widespread changes of power and phase-locking depend on baseline brain activity, for example, during resting vs. task conditions. Notably, some experimental studies have indeed begun to test how brain state affects the local outcomes of stimulation \cite{356–360}, which has also been examined in biophysical models \cite{361–363}. In order to use whole-brain simulation studies to better understand how the dynamic regime of the brain as a whole mediates the network-wide effects of stimulation, it will be necessary to inform these models with measurements of large-scale brain activity. Although here we implemented a more abstract model, working towards increasingly realistic and experimentally testable models is an exciting direction for forthcoming studies.

C Supporting Information

This supplementary text contains additional analyses and figures, and further descriptions of methods.

C.1 Dynamics of an isolated Wilson-Cowan unit

In this section we briefly describe the behavior of a single Wilson-Cowan (WC) unit, which forms the fundamental dynamical component of the whole-brain computational model. The excitatory and inhibitory pools of an isolated WC unit evolve according to Eqs. 4.1 and 4.2, with the coupling term set to $C = 0$. Here we take all other model parameters to be those displayed in Table 4.1, with the exception that we consider noiseless simulations for the purpose of demonstration.
A typical bifurcation parameter for the WC model is the drive $P_E$ to the excitatory population; when other parameters are appropriately tuned, varying $P_E$ can induce oscillatory activity. The top row of Fig. C.1 shows phase plane representations of a single WC unit for three different levels of the input $P_E$, and the bottom row of each panel shows the time-evolution of the excitatory activity $E(t)$ for the given parameter value. In the phase planes, the blue lines correspond to the excitatory variable nullcline ($dE/dt = 0$), the red lines correspond to the inhibitory variable nullcline ($dI/dt = 0$), and the purple lines show an example trajectory that begins at the point denoted by the star. For a low input level of $P_E = 0.6$ (panel A), the system has a single stable fixed-point corresponding to a low activity steady-state. For an intermediate drive of $P_E = 1.25$ (panel B), the system exhibits a stable limit cycle and the firing-rate activity oscillates in time. For a high input of $P_E = 3$ (panel C), the system again exhibits a single stable fixed-point, but corresponding to a high activity steady-state.

To summarize the effect of the drive $P_E$ on the behavior of an isolated WC unit, we first plot the time-average of the excitatory firing-rate $\overline{E(t)}$ as a function of the input $P_E$ (Fig. C.1, panel D). Note that $\overline{E(t)}$ increases with increasing drive. Second, we consider how the peak frequency $f_{\text{peak}}$ of the excitatory activity varies with the input level $P_E$ (Fig. C.1, panel E), where the peak frequency is that for which the Welch’s power spectral density of the excitatory time-series is maximum (see Sec. 4.2 for details). For low inputs, $f_{\text{peak}}$ is approximately zero; the system resides in the low activity steady-state and there are no intrinsic oscillations. As the input is increased, though, oscillations emerge with frequencies in the gamma range (30 - 70 Hz). Increasing the input $P_E$ in the oscillatory regime first raises the peak frequency from its initial value up to $\sim 65$ Hz. Such an increase in oscillatory frequency with increasing drive has also been found experimentally [332, 390, 295, 391]. However, beyond a certain point, further increasing the excitatory drive causes the peak frequency to decline back to zero as the system approaches the high activity fixed point where oscillations again cease completely. In Fig. C.1, panel F, we show excitatory activity time-series for three different values of the input $P_E$ that place the system in the oscillatory regime. It is clear by eye that for these parameters, increasing the excitatory drive increases the amplitude and frequency of the oscillations.
Figure C.1: Behavior of an isolated Wilson-Cowan unit. (A-C) Phase plane representations (top) and excitatory time series (bottom) for an isolated WC unit subject to varying levels of excitatory drive: $P_E = 0.6$ (A), $P_E = 1.25$ (B), and $P_E = 3.0$ (C). (D) The time-average of the excitatory firing-rate $E(t)$ as a function of the input $P_E$ for a single Wilson-Cowan unit. (E) The peak frequency $f^{\text{peak}}$ of the excitatory activity as a function of the input $P_E$ for a single Wilson-Cowan unit. (F) Examples of excitatory firing-rate activity for three different values of the input ($P_E = \{1.0, 1.2, 1.6\}$ from top to bottom) that place the system in the oscillatory regime.

C.2 Determining the onset of oscillatory activity in the whole-brain model

In order to systematically determine the boundary marking the onset of oscillatory activity as a function of the background drive $P_E^{\text{phase}}$ and the coupling $C$, we examine the network-average of the standard deviation of the excitatory activity across time, $\langle \text{std}[E_i(t)] \rangle$. This quantity measures the strength of fluctuations of the excitatory population activities around their mean values. Thus, by noting when $\langle \text{std}[E_i(t)] \rangle$ jumps from a value near zero to a higher, positive value, we
can qualitatively determine the transition from the state of low, non-oscillatory firing-rates to the onset of rhythmic dynamics in regional activity. Here, we are interested in finding the level of background excitation $P_E^*(C)$ that is needed to induce oscillations at each brain area for a given interareal coupling $C$. To determine these “boundary” points $P_E^*(C)$, we thus hold $C$ fixed, and consider the difference in $\langle \text{std}[E_i(t)] \rangle$ between consecutive values of $P_E^{\text{base}}$. We plot this difference $\Delta \langle \text{std}[E_i(t)] \rangle$ as a function of $P_E^{\text{base}}$ and $C$ in Fig. C.2, where we indeed observe a clear boundary separating the low-activity and oscillatory regimes. In particular, we define the border point for each coupling $C$ as the value $P_E^*(C)$ for which the difference $\Delta \langle \text{std}[E_i(t)] \rangle$ is maximized. We mark the boundary corresponding to the onset of oscillatory activity with red squares in Fig. C.2.

Figure C.2: The change in the network-average of the standard deviation of excitatory activity across time, $\Delta \langle \text{std}[E_i(t)] \rangle$, as a function of the global coupling $C$ and the non-specific background drive $P_E^{\text{base}}$. We compute the change in $\langle \text{std}[E_i(t)] \rangle$ as $P_E^{\text{base}}$ varies by taking the difference of this quantity between consecutive values of the input $P_E^{\text{base}}$, while holding the coupling $C$ fixed. The red squares denote the values $P_E^*(C)$ at which $\Delta \langle \text{std}[E_i(t)] \rangle$ is largest for each coupling $C$. These points delineate a transition in regional brain dynamics from a quiescent state to a state of oscillatory activity.

C.3 Working Point 2: Global coherence peak

In the main text, we examined in detail the effects of focal perturbations for two distinct working points – WP1 and WP3 – corresponding to low and high background drive states situated below and above peak global coherence, respectively. In this section, we also consider the effects of perturbations at WP2, for which $P_E^{\text{base}} = 0.57$ (the coupling is kept at $C = 2.5$). Here, the background input is intermediately valued, and the system resides at approximately the state of peak $\rho^{\text{global}}$ (see Fig. 4.2A). We thus observe blocks of relatively strong phase-locking in the base-
line PLV matrix (Fig. 4.2C, Row 2, Column 1) at this working point. However, note that the network-averaged PLV is only $\approx 0.57$, which is still significantly less than the maximum possible value of $\rho_{\text{global}} = 1$.

Spectral modifications in baseline and excited bands persist at state of peak coherence

Similar to WP1, stimulation of region $i$ causes an increase in the amplitude and frequency of its activity (Fig. C.3, panel B and Fig. C.3, panel C, Left). Depending on the stimulated site, the induced shift in peak frequency $\Delta f_{\text{peak},i,\delta_i}$ ranges between approximately 5 and 15 Hz (Fig. C.3, panel D). Consequently, there is a clear separation between the distribution of units’ peak frequencies in the baseline condition and when excited with additional input (Fig. C.3, panel E), indicating that there are again two frequency ranges of interest for further analysis. Due to interactions with the network, the excited area’s spectra also develops sidebands to the left and right of its main peak, and a second bump at a frequency equal to the difference in the sideband and peak frequencies. This latter feature reflects the enhanced amplitude modulations that emerge in the time-series of unit $i$ under stimulation (Fig. C.3, panel B, Right) and is indicative of quasiperiodic dynamics in the network. We also examine the power spectra of two downstream regions $j$ and $k$ located at increasing topological distances (hence receiving progressively weaker structural input) from the perturbed area $i$ (Fig. C.3, panel C, Middle, Right). As for WP1, downstream region $j$, which receives strong input from $i$, develops a new spectral component at the main frequency of the excited region, and also at a lower frequency approximately equal to the difference of its baseline peak and the excited peak. On the other hand, unit $k$, which is more weakly connected to $i$, does not exhibit these same modulations. In Sec. C.5, we show that the relationship between the strength of the power modulation at the peak frequency of the stimulated site $i$ and the topological distance from $i$ to the downstream unit holds across different choices of the excited area.

To see more generally how focal stimulation can modulate downstream spectra, we compute the average spectra $\langle \text{psd} \rangle_{j \neq i}$ over all units $j \neq i$ in the baseline state and in the state when unit $i$ is selectively excited (Fig. C.3, panel F) and the average difference $\langle \Delta \text{psd}_{j,\delta_i} \rangle_{j \neq i}$ of the spectra of unit $j \neq i$ between when unit $i$ is stimulated and in the baseline condition (Fig. C.3, panel G). We again observe power modulations in both the baseline frequency band and in an excited frequency band centered around the peak frequency of the directly stimulated region. However, for the perturbed area studied in the example shown at WP1 (Fig. 4.3F-G) and again here at WP2 (Fig. C.3, panels F-G), the maximum relative power modulations are weaker in the latter case.
In general, it is important to note that the strength of the observable changes to the power spectra induced by focal perturbations are dependent on the choice of the excited area and on the system’s working point. In the next section, we proceed to examine changes in the PLV in the baseline and excited bands – $\Delta \rho_{\delta_i}^{\text{base}}$ and $\Delta \rho_{\delta_i}^{\text{exc}}$ – induced by regional perturbations.

Structural and functional network connectivity continue to predict overall changes in excited and baseline band phase-locking at the peak-coherence working point

Akin to WP1, local stimulation at WP2 induces phase-locking changes that differ depending on which part of the network is perturbed and which frequency band is examined (Fig. C.4, panels A–D). To appreciate this fact, it is helpful to study examples that display the changes in the PLV

**Figure C.3 (following page):** Alterations to power spectra induced by focal stimulation at the state near peak baseline coherence (Working Point 2). (A) Schematic of a brain network depicting the stimulated site $i$ in brightest red. The black arrows point to two other regions $j$ and $k$ that lie at progressively further topological distances from the perturbed area in the structural network. In this figure, regions $i$, $j$, and $k$ correspond to brain areas 1 (R–Lateral Orbitofrontal), 4 (R–Medial Orbitofrontal), and 10 (R–Precentral), respectively. (B) Left: A segment of region $i$’s activity time-course in the baseline condition. Right: A segment of region $i$’s activity time-course when it is stimulated. (C) Power spectra of area $i$ and two other downstream regions $j$ and $k$. In all three panels, the lighter curves correspond to the baseline condition, and the darker curves correspond to the state in which $i$ is driven with additional input. The gray vertical lines indicate the peak frequency $f_{i,\delta_i}^{\text{peak}}$ of region $i$ in the excited condition. (D) Histogram of the shift in peak frequency $\Delta f_{i,\delta_i}^{\text{peak}}$ induced by stimulating unit $i$, plotted over all choices of the perturbed area. (E) Distribution of peak frequencies of all units in the baseline condition $\{f_{i,\delta_i}^{\text{peak}}\}$ (light gray) and distribution of the peak frequency units acquire when directly excited $\{f_{i,\delta_i}^{\text{peak}}\}$ (dark gray). (F) Average power spectra $\langle \text{psd}\rangle_j \neq i$ over all units $j \neq i$ at baseline (light gray) and when unit $i$ is perturbed with additional input (dark gray). (G) Average difference $\langle \Delta \text{psd}_{j,\delta_i} \rangle_j \neq i$ of the spectra of unit $j \neq i$ when unit $i$ is excited and in the baseline condition, where the average is over all units $j \neq i$. For reference, the light gray vertical lines denote the minimum and maximum peak frequency across units in the baseline state, and the dark gray line indicates the peak frequency acquired by the stimulated region $i$. Shaded boxes denote two frequency bands of interest: (1) the baseline band (purple) consisting of the main oscillation frequencies of brain areas under baseline conditions, and (2) the excited band (green) centered around the peak frequency that the stimulated region inherits. In subsequent analyses, we assess perturbation-induced changes in the PLV between brain areas in the baseline band, $\Delta \rho_{\delta_i}^{\text{base}}$ (purple), and in the excited band $\Delta \rho_{\delta_i}^{\text{exc}}$ (green).
CHAPTER 4.

A! B! baseline! excited! 
C! 
distance from excited region $i$! 
E! 
D! 
baseline 
frequency band! 
excited 
frequency band! 
F! G!
in both the baseline band and the excited band when either region \( i \) or region \( j \neq i \) is excited (Fig. C.4, panels A,C). To characterize the network-wide impact of stimulating each region, we set non-significant PLV changes to zero (determined by comparing the observed changes against phase-randomized surrogate data; see Sec. C.12) and then compute network-averages of the absolute PLV modulations. Upon examination of the global responses \( \langle |\Delta \rho_{\text{base}}^i| \rangle \) and \( \langle |\Delta \rho_{\text{exc}}^i| \rangle \) (Figs. C.4, panels B,D), we again find significant variability across the choice of the perturbed area. Actually, in comparing the overall baseline band changes at WP1 (Fig. 4.4B) to the changes at WP2 (Fig. C.4, panel B), we find that the dispersion (as quantified by the coefficient of variation of the set of changes \( \{ \langle |\Delta \rho_{\text{base}}^i| \rangle \} \) and the mean of the global responses are both larger at the second working point. We additionally note, however, that the mean response induced in the excited frequency band, \( \langle |\Delta \rho_{\text{exc}}^i| \rangle \), decreases from WP1 to WP2. Hence, when the system operates around the state of peak \( \rho_{\text{global}} \), the coherence modulations in the baseline frequency band are larger – on average – and also more heterogeneously distributed relative to the responses at the working point below the state of peak \( \rho_{\text{global}} \), while the average of the global responses in the excited band decreases. We consider these points further in Sec. 4.3.5, where we more generally examine the state-dependence of perturbation-induced changes in phase-locking.

To conclude this section, we consider the relationships between changes in phase-locking induced by stimulating a given region and the structural or functional node strength of the stimulated area. A number of the associations that exist at WP2 (Fig. C.4, panels E,F) were also observed at WP1 (see Fig. 4.4E,F). For example, the structural strength \( s_{i}^{\text{struc}} \) remains strongly

Figure C.4 (following page): Phase-locking changes at Working Point 2 are driven by local excitations of neural activity, differ between excited and baseline frequency bands, and are differentially related to structural and functional network properties. (A) Pairwise changes in the PLV inside the baseline band \( \Delta \rho_{\text{base}} \) when region \( i \) (Left) or region \( j \neq i \) (Right) is perturbed. In this figure, regions \( i \) and \( j \) correspond to regions 4 (R–Medial Orbitofrontal) and 23 (R–Lateral Occipital), respectively. (B) Network-averaged absolute PLV changes in the baseline band \( \langle |\Delta \rho_{\text{base}}^i| \rangle \) caused by stimulation of different brain areas. (C) Pairwise changes in the PLV inside the excited band \( \Delta \rho_{\text{exc}} \) when region \( i \) (Left) or region \( j \neq i \) (Right) is perturbed. (D) Network-averaged absolute PLV changes in the excited band \( \langle |\Delta \rho_{\text{exc}}^i| \rangle \) induced by stimulation of different brain areas. (E) The quantity \( \langle |\Delta \rho_{\text{base}}^i| \rangle \) vs. structural node strength \( s_{i}^{\text{struc}} \) (Left), and the quantity \( \langle |\Delta \rho_{\text{exc}}^i| \rangle \) vs. structural node strength \( s_{i}^{\text{struc}} \) (Right). (F) The quantity \( \langle |\Delta \rho_{\text{base}}^i| \rangle \) vs. functional node strength \( s_{i}^{\text{func}} \) (Left), and the quantity \( \langle |\Delta \rho_{\text{exc}}^i| \rangle \) vs. functional node strength \( s_{i}^{\text{func}} \) (Right). In panels (E) and (F), insets indicate Spearman correlation coefficients between the plotted quantities and their associated \( p \)-values.
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A

perturb region $i$

baseline band

brain region

$\Delta \rho_{\text{base}}$

perturb region $j$

excited band

brain region

$\Delta \rho_{\text{exc}}$

B

avg. absolute response

perturbed region

C

equil band

avg. PLV responses

structural strength

$\rho_s = 0.93$

$p < 0.001$

D

avg. absolute response

perturbed region

E

avg. PLV responses vs. structural strength

$\rho_s = 0.53$

$p < 0.001$

F

avg. PLV responses vs. functional strength

$\rho_s = 0.77$

$p < 0.001$
positively correlated with the mean absolute PLV change induced in the excited frequency band \( \langle |\Delta \rho_{\delta_i}^{exc}| \rangle \) (Fig. C.4, panel E, Right). Furthermore, functional strength \( s_{i,func}^{func} \) retains the strongest positive correlation with the absolute change in baseline band coherence \( \langle |\Delta \rho_{\delta_i}^{base}| \rangle \) (Fig. C.4, panel F, Left). Thus, global effects in the new, excited frequency band continue to be strongly predicted by anatomical connectivity, whereas fluctuations in the baseline frequency band continue to be best predicted by the strength of regions’ initial coherence with the system as a whole. The main difference between WP1 and WP2 is that for the second working point, a positive correlation also emerges between \( \langle |\Delta \rho_{\delta_i}^{base}| \rangle \) and \( s_{i,struct}^{struct} \) (Fig. C.4, panel E, Left), indicating that structural connectivity becomes partially indicative of stimulation-induced changes in baseline band phase-locking. In this way, the effects at WP2 have similarities to both WP1 and WP3.

C.4 Average excited-band responses differ between stimulation of cortical and subcortical areas

In this section we show that the overall responses induced in the excited frequency band (at WP1 and WP2) are – on average – larger for stimulation of subcortical vs. cortical brain areas. To do so, we first compute the average absolute change in excited-band phase-locking \( \langle |\Delta \rho_{\delta_i}^{exc}| \rangle \) for stimulation of each region \( i \in \{1, ..., N\} \). Note that for these computations, only statistically significant PLV changes are retained as non-zero (see Sec. C.12). We then collect the sets of responses \( \{\langle |\Delta \rho_{\delta_i}^{exc}| \rangle \}_c \) and \( \{\langle |\Delta \rho_{\delta_i}^{exc}| \rangle \}_s \) corresponding to perturbation of cortical and subcortical areas, respectively. Fig. C.5 shows the mean and spread of these two groups at WP1 (panel A) and at WP2 (panel B), from which we observe that the mean excited-band response is larger for stimulation of subcortical regions at both working points. To determine whether this effect is statistically significant, we perform a non-parametric permutation test of the null hypothesis that there is no difference in the mean excited-band response between cortical and subcortical areas. Using 1000 randomizations, we find that the mean excited-band responses are indeed significantly larger for stimulation of subcortical regions \( (p = 0.001) \) at both WP1 and WP2.

C.5 Topological distances in the structural network predict power modulations at frequency of stimulated unit

In the main and supplementary text, we show examples of how focal stimulation of one region in the network affects the spectra of downstream areas (see Figs. 4.3C, 4.5C, and C.3, panel C). At WP1 (Fig. 4.3C) and WP2 (C.3, panel C), we observed a propagation effect in which
a downstream area located at a short topological distance from the perturbed site developed an increase in power at the excited frequency of the directly stimulated area. In contrast, a unit located topologically further from the stimulated area exhibited much weaker power modulations. In this section, we show quantitatively that the topological distance from the perturbed site to downstream regions is a relatively good predictor of the downstream power modulation at the peak frequency of the stimulated unit. Hence, the effects observed in the examples shown in Figs. 4.3C and C.3, panel C, generalize to other choices of the stimulated unit.

To begin, we more formally define the measure of topological distance that we employ. In general, a topological distance between any two nodes $i$ and $j$ is the length of the shortest path between those nodes, where a path is a non-intersecting sequence of edges that share a common node. Hence, to compute a topological distance, we first need to assign lengths to each edge in the network. Here, we define the length of an edge to be the inverse of the corresponding structural connectivity edge weight \[27\]. (For this analysis, we use the edge weights from the normalized adjacency matrix $W_{ij}$; see Sec. 4.2). With this definition, the topological distance from node...
i to node j will thus be shorter when node i links to node j via a path of stronger structural connections.

Now, letting i denote the stimulated region and j ≠ i denote a downstream region, we define $D_{i,j}^t$ as the topological distance from node i to node j, and $\tilde{\Delta} P_j(f_{\text{peak}}^{i,\delta_i})$ as the relative change in power of unit j’s spectra at the excited peak frequency of the stimulated unit i. In particular, the relative change is computed between baseline and the condition in which i is driven with additional input.

With these quantities defined, we now study their relationship at WP1. Fig. C.6, panel A shows a plot of $\log|\tilde{\Delta} P_j(f_{\text{peak}}^{i,\delta_i})|$ vs. $D_{i,j}^t$ (i.e. we consider the case that the stimulated unit $i = 1$, which was the example in Fig. 4.3C.) This scatter plot exhibits a relatively clear negative trend, indicating that units located topologically nearer to the stimulated site (in the structural network) tend to exhibit stronger spectral modulations at the excited peak frequency of the stimulated region, whereas units that are further away (hence more weakly structurally connected) show little change. Furthermore, by examining the Spearman correlation between $\tilde{\Delta} P_j(f_{\text{peak}}^{i,\delta_i})$ and $D_{i,j}^t$ for all choices of the stimulated unit i, we see that this relationship holds more generally, regardless of which site is given the perturbation (Fig. C.6, panel B). Specifically, the correlation between the relative power modulation $\tilde{\Delta} P_j(f_{\text{peak}}^{i,\delta_i})$ and the topological distance $D_{i,j}^t$ is consistently negative and statistically significant across all choices of the stimulated area. Fig. C.6, panel C and Fig. C.6, panel D illustrate that the same conclusions generally hold for WP2 (although a few correlations lose statistical significance at this working point).

C.6 Average responses to perturbations in the baseline frequency band at Working Point 1 vs. Working Point 3

To investigate how the dynamical state of the brain network model influences the effects of focal stimulation, we consider the relationship between the global responses to stimulation at two different working points. In particular, we examine the average absolute change in phase-locking in the baseline frequency band, $\langle|\Delta \rho_{\delta_i}^{\text{base}}|\rangle$, at WP3 vs. at WP1 (Fig. C.7). Recall that WP1 corresponds to a low background drive working point preceding peak baseline coherence, whereas WP3 corresponds to a high background drive working point following peak baseline coherence. It is clear upon visual inspection of Fig. C.7 that there is no consistent relationship between these two quantities. Hence, regions that induce a large response at the system’s spontaneous frequencies at WP1 are not necessarily those that induce a large response at WP3.
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C.7 Negative phase locking value changes drive correlation with structural connectivity at Working Point 3

In the main text we observed a strong positive correlation between a node’s structural strength $s_i^\text{struc}$ and the absolute coherence modulation $\langle |\Delta \rho_i^\text{base}| \rangle$ it induces upon perturbation at WP3 (see Fig. 4.6). Here, Fig. C.8 demonstrates that this association is largely driven by a strong relationship between $s_i^\text{struc}$ and the network-averaged absolute decreases $\langle | \downarrow \Delta \rho_i^\text{base} | \rangle$ in baseline band coherence induced by the focal stimulation. In particular, $s_i^\text{struc}$ and $\langle | \downarrow \Delta \rho_i^\text{base} | \rangle$ have a Spearman correlation of $r_s = 0.72$, which is almost as strong as the correlation between structural strength $s_i^\text{struc}$ and the absolute change $\langle | \downarrow \Delta \rho_i^\text{base} | \rangle$ ($r_s = 0.82$).

C.8 Verification of relationships between phase-locking modulations and structural or functional connectivity at alternate working points in the low, medium, and high background drive regimes

At WP1, WP2, and WP3, we considered the associations between the average changes in phase-locking induced by regional perturbations (within both the baseline and excited frequency bands) and structural or functional network properties of the stimulated region. We found that, depending on the baseline state of the system, different relationships emerged between the perturbation-induced responses and structural or functional node strengths (see Figs. 4.4, C.4, and 4.6). In this section, we verify that qualitatively similar relationships hold for other working points in the immediate vicinity of those studied in the main text. Note that for each alternative working point, we consider the same excitation strength used originally (i.e., $\Delta P_{E,i} = 0.1$). Moreover, throughout this section, we set non-significant PLV changes to zero (determined by comparing the observed changes against phase-randomized surrogate data; see Sec. C.12) prior to computing network-averages of the absolute PLV modulations.

We begin by analyzing an alternative working point near WP1, which we term WP1$\_\text{alt}$. WP1 was located at $P_{E}^\text{base} = 0.553$ and $C = 2.5$; for WP1$\_\text{alt}$, we consider parameters $P_{E}^\text{base} = 0.555$ and $C = 2.5$. Note that because peak global baseline coherence $\rho_{\text{global}}$ is reached rapidly as a function of $P_{E}^\text{base}$ (see Fig. 4.2A), in order to consider a second working point located prior to $\rho_{\text{global}}$ but still near WP1, we can only shift $P_{E}^\text{base}$ slightly from its value at WP1. We find the same set of relationships between phase-locking modulations and structural or functional strength at WP1$\_\text{alt}$ as we did at WP1 (see Fig. C.9, panels A,D). Specifically: (1) the average absolute PLV change...
induced in the excited frequency band $\langle |\Delta \rho^\text{exc}_{\delta_i}| \rangle$ is most strongly associated with the structural strength of the perturbed region $s^\text{struc}_i$ (Fig. C.9, panel A,Bottom), and (2) the average absolute phase-locking modulation in the baseline frequency band $\langle |\Delta \rho^\text{base}_{\delta_i}| \rangle$ is most strongly associated with the functional strength of the perturbed region $s^\text{func}_i$ (Fig. C.9, panel D,Top). The relationships between $\langle |\Delta \rho^\text{base}_{\delta_i}| \rangle$ and $s^\text{struc}_i$, and between $\langle |\Delta \rho^\text{exc}_{\delta_i}| \rangle$ and $s^\text{func}_i$ are either not statistically significant or weaker, respectively (Fig. C.9, panel A,Top and Fig. C.9, panel D,Bottom).

We next analyze an alternative working point near WP2, WP2$_{alt}$. Recall that WP2 was located at $P^\text{base}_E = 0.57$ and $C = 2.5$; for WP2$_{alt}$, we consider $P^\text{base}_E = 0.572$ and $C = 2.5$. In order to examine a second working point in close vicinity of the peak in global baseline coherence – which was the condition used to determine parameters for WP2 – we again must consider only a small change in $P^\text{base}_E$ away from its value at WP2. As before, this is because the dynamical state of the system changes quickly as a function of $P^\text{base}_E$ in this regime (see Fig. 4.2A). Using the specified parameter choices, we find consistent relationships at WP2 and WP2$_{alt}$ in terms of how perturbation-induced phase-locking modulations are related to structural and functional node strength. First, the average absolute PLV changes that arise in the baseline frequency band $\langle |\Delta \rho^\text{base}_{\delta_i}| \rangle$ are significantly correlated with the structural strength of the perturbed region $s^\text{struc}_i$ (Fig. C.9, panel B,Top), but remain most strongly related to functional strength $s^\text{func}_i$ (Fig. C.9, panel E,Top). Second, the average absolute phase-locking modulations in the excited frequency band $\langle |\Delta \rho^\text{exc}_{\delta_i}| \rangle$ are strongly associated with the structural strength $s^\text{struc}_i$ of the perturbed region (Fig. C.9, panel B,Bottom), and are not significantly correlated with functional strength (Fig. C.9, panel E,Bottom).

Lastly, we analyze an alternative working point near WP3, WP3$_{alt}$. WP3 was located at $P^\text{base}_E = 0.7$ and $C = 2.5$; for WP3$_{alt}$, we consider $P^\text{base}_E = 0.68$ and $C = 2.5$. We once more find that the relationships between phase-locking modulations induced by regional stimulation and structural or functional node strength are consistent across WP3 and WP3$_{alt}$ (see Fig. C.9, panel C,F). In particular, there is a strong positive correlation between the average absolute phase-locking modulations induced in the baseline frequency band $\langle |\Delta \rho^\text{base}_{\delta_i}| \rangle$ and the structural strength of the perturbed region $s^\text{struc}_i$ (Fig. C.9, panel C,Top). The relationship between $\langle |\Delta \rho^\text{base}_{\delta_i}| \rangle$ and functional strength $s^\text{func}_i$ is weaker (Fig. C.9, panel F,Top). Finally, note that there is no excited frequency band at WP3 or WP3$_{alt}$.
CHAPTER 4.

C.9 General dependence of associations between phase-locking modulations and structural or functional connectivity as a function of background drive

In Fig. 4.8A of the main text, we showed the difference $\Delta r_s$ in the strength of the correlation between the average absolute baseline band PLV changes $\langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle$ and structural ($s_{i,\text{struc}}$) or functional ($s_{i,\text{func}}$) node strength, plotted as a function of the background drive $P_{E}^{\text{base}} - P_{E}^{*}$ for a coupling $C = 2.5$. Here, we additionally show plots of the individual Spearman correlations for $\langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle$ vs. $s_{i,\text{struc}}$ and for $\langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle$ vs. $s_{i,\text{func}}$ (Fig. C.10, panel A). Although the precise values of the correlations can vary in a somewhat complex manner as a function of the baseline input, we reiterate the key point that functional strength is more strongly related to baseline band coherence modulations in the low- and medium-drive regimes, whereas structural strength dominates in the high-drive regime.

We also examine the relationships between structural or functional node strength and the network-averaged absolute change $\langle |\Delta \rho_{\delta_i}^{\text{exc}}| \rangle$ in excited-band PLV induced by focal perturbations. Because stimulation fails to induce an excited band when the background drive is too high, we compute Spearman correlations between these quantities only for values of the drive where at least half of the regions yield an excited band upon perturbation. Furthermore, at each working point, correlations are computed only between regions that induce an excited band. We find that areas’ structural node strength robustly predicts the global response in the excited band (see Fig. C.10, panel B). In particular, the Spearman correlation coefficient $r_s$ between $s_{i,\text{struc}}$ and $\langle |\Delta \rho_{\delta_i}^{\text{exc}}| \rangle$ is greater than 0.89 across all baseline inputs for which at least half of the units in the network induce excited frequency bands. Furthermore, the strength of the correlation with structural connectivity is consistently much higher than the strength of the correlation using functional connectivity (compare yellow and blue curves in Fig. C.10, panel B). These results are consistent with the conclusions drawn in the main text positing that network structure mediates the excited-band effects.

C.10 Effects of perturbation strength

In the main text we studied a single perturbation strength of $\Delta P_{E,i} = 0.1$. In this section, we assess the dependence of various results on the level of additional excitatory input $\Delta P_{E,i}$ received by the stimulated unit (Fig. C.11). In particular, for both WP1 and WP3, we vary $\Delta P_{E,i}$ between 0.01 and 0.15 in steps of 0.02.
We first analyze how the perturbation strength affects the shift in the peak frequency of the stimulated area. As a summary measure, we consider the change in peak frequency averaged across all choices of the stimulated region, \( \langle \Delta f_{\text{peak}} \rangle \). As expected, this quantity increases with increasing perturbation strength for both WP1 (Fig. C.11, panel A) and WP3 (Fig. C.11, panel B). We next study the stimulation-induced changes in phase-locking in the baseline frequency band as a function of the stimulation strength. In particular, we examine the global response (grand average) \( \langle |\Delta \rho_{\text{base}}| \rangle \), where the mean change is computed first over all pairs of brain areas for a given stimulation site, and then across all choices of the perturbed region. For both working points, this measure also increases monotonically as a function of \( \Delta P_{E,i} \) (Fig. C.11, panels C,D). Hence, as the strength of the stimulation increases, so does the overall amount of functional reconfiguration at the system’s baseline frequencies. For WP1, we find that the grand average PLV change \( \langle |\Delta \rho_{\text{exc}}| \rangle \) in the excited band also grows as a function of the perturbation strength (Fig. C.11, panel E). Note, however, that at WP3 (Fig. C.11, panel F), no units generate an excited frequency band for \( \Delta P_{E,i} < 0.15 \), and for \( \Delta P_{E,i} = 0.15 \), only about 10% of units do so.

In the main text, we found that at WP1, the absolute change in baseline band phase-coherence induced by stimulating region \( i \), \( \langle |\Delta \rho_{\delta_{i}}^\text{base}| \rangle \), was strongly correlated with the functional strength of region \( i \), \( s_{i}^\text{func} \) (Fig. 4.4F, Left). In contrast, there was not a strong association between \( \langle |\Delta \rho_{\delta_{i}}^\text{base}| \rangle \) and the structural strength \( s_{i}^\text{struc} \) at WP1 (Fig. 4.4E, Left). Here, we observe that the nature of these two relationships remains qualitatively the same across the considered range of stimulation strengths \( \Delta P_{E,i} \) (Fig. C.11, panel G). A second result from the main text was a strong positive correlation between the PLV change induced in the excited frequency band \( \langle |\Delta \rho_{\delta_{i}}^\text{exc}| \rangle \), at WP1, and the structural strength \( s_{i}^\text{struc} \) of the stimulated unit (Fig. 4.4E, Right). The present analysis reveals that the relationship between \( \langle |\Delta \rho_{\delta_{i}}^\text{exc}| \rangle \) and \( s_{i}^\text{struc} \) holds across a range of perturbation strengths \( \Delta P_{E,i} > 0.05 \) (Fig. C.11, panel I), for which at least half of the units in the network yield an excited frequency band. Note that for \( \Delta P_{E,i} < 0.05 \), local excitations do not induce an excited frequency band at all (so the correlations are undefined) and for \( \Delta P_{E,i} = 0.05 \), fewer than half of the units generate excited frequency bands (so we do not consider correlations with structural or functional strength). Finally, for the case of \( \Delta P_{E,i} = 0.1 \) studied in the main text, there was a strong positive correlation between \( \langle |\Delta \rho_{\delta_{i}}^\text{base}| \rangle \) and \( s_{i}^\text{struc} \) at WP3 (Fig. 4.6C, Left) and a weaker positive correlation between \( \langle |\Delta \rho_{\delta_{i}}^\text{base}| \rangle \) and \( s_{i}^\text{func} \) (Fig. 4.6C, Left). These trends also hold across the range of stimulation strengths examined in this section (Fig. C.11, panel H). Note that we do not consider correlations between structural and functional node strength and excited band PLV changes, because at WP3, less than half of the network generates an excited
frequency band (even for the strongest stimulation strength).

In conclusion, we note that while an in-depth examination of the effects of the stimulation strength is beyond the scope of the present study, it is important that the main relationships between interareal phase-locking modulations and network properties hold over a range of values for this parameter.

### C.11 Results for an alternative value of the global coupling

In the main text, we examined the effects of focal excitatory stimulation for a global coupling of $C = 2.5$. Here, we analyze an alternative (but relatively nearby) coupling value of $C = 2.0$, and show that qualitatively similar results are found. As for $C = 2.5$, we consider three different working points by varying the level of background drive $P_{E}^{\text{base}}$, while holding the coupling fixed. Specifically, we consider $P_{E}^{\text{base}} = 0.60$ (WP1), $P_{E}^{\text{base}} = 0.615$ (WP2), and $P_{E}^{\text{base}} = 0.745$ (WP3), which place the system below, at, or above the state of peak global coherence (see Fig. 4.2A of the main text), respectively. As before, these working points represent three distinct dynamical states of the system.

We begin by considering the effects of regional stimulation on the power spectra of the perturbed area. To summarize this, we examine the average shift in the peak frequency of the stimulated region, $\langle \Delta f_{i,\delta i}^{\text{peak}} \rangle$, for each of the three working points (Fig. C.12). For all three states, additional excitation has the effect of increasing the peak frequency of the stimulated region. However, for WP1 and WP2, the peak frequency shifts by a noticeably larger amount ($\langle \Delta f_{i,\delta i}^{\text{peak}} \rangle = 9.5\text{Hz}$ for WP1 and $\langle \Delta f_{i,\delta i}^{\text{peak}} \rangle = 10.8\text{Hz}$ for WP2) relative to the more modest effect at WP3 ($\langle \Delta f_{i,\delta i}^{\text{peak}} \rangle = 2.2\text{Hz}$). These general trends are consistent with the results in the main text, and again demonstrate that individual areas are most responsive to additional excitation in states of lower background drive (WP1 and WP2). In contrast, given the same excitation strength, regional dynamics are relatively imperturbable when the system operates in the high background drive state (WP3).

We next examine how regional stimulation affects interareal phase-locking at each of the three working points. For WP1 and WP2 we analyze separate “baseline” and “excited” frequency bands, since the peak frequency of the stimulated area becomes separated from the peak frequencies of the system at baseline. For WP3, we consider a single “baseline” band, as the peak frequency of the excited area shifts only slightly and can overlap with the main frequencies at baseline. For the present analysis, we use the same protocol described in the main text to define baseline and excited frequency bands. In general, we refer the reader to Sec. 4.3 for further details.
and discussion regarding the results presented below.

We first show – for WP1 – examples of the phase-locking modulations within the baseline and excited frequency bands for two different choices of the stimulated area (Figs. C.13, panels A,B). As in the main text (see Figs. 4.4A,C), we see that the network response to a local perturbation differs between the two frequency bands, and for different choices of the stimulated region. We next study the associations between the network-wide average of the phase-locking modulations induced by regional stimulation and structural or functional strength (Figs. C.13, panels C,D). To characterize the network-wide impact of stimulating each region, we set non-significant PLV changes to zero (determined by comparing the observed changes against phase-randomized surrogate data; see Sec. C.12) and then compute network-averages of the absolute PLV modulations. In comparing the results presented here for a coupling of $C = 2$ to those in Fig. 4.4E,F of the primary text for $C = 2.5$, we find similar relations. Specifically, the average absolute change in the PLV for the baseline frequency band $\langle |\Delta \rho_{\delta_1}^{\text{base}}|\rangle$ is most strongly related to the baseline functional strength of the stimulated area $s_{\text{func}}^i$ (Fig. C.13, panel D, Left). In contrast, the network-average of the absolute changes in excited band PLV $\langle |\Delta \rho_{\delta_1}^{\text{exc}}|\rangle$ is most strongly related to the structural strength of the stimulated region $s_{\text{struc}}^i$ (Fig. C.13, panel C, Right). The other relationships are either weaker or not statistically significant.

We next conduct the same analyses regarding changes to interareal phase-locking, but for WP2. Here, Figs. C.14, panels A,B show examples of the phase-locking modulations within the baseline and excited frequency bands for two different choices of the stimulated area, and Figs. C.14, panels C,D depict relationships between the global PLV changes induced by regional stimulation and structural or functional node strength. We again find qualitatively similar behavior between the results shown here and those depicted in the main text. Note that for both values of the coupling ($C = 2$ here and $C = 2.5$), the main difference between WP1 and WP2 is that structural strength $s_{\text{struc}}^i$ also exhibits a positive correlation with the average absolute change in phase-coherence for the baseline frequency band $\langle |\Delta \rho_{\delta_1}^{\text{base}}|\rangle$ (Fig. C.14, panel C, Left). However, for both values of $C$, phase-locking modulations at the system’s spontaneous frequencies continue to be most strongly associated with the stimulated region’s baseline functional strength (Fig. C.14, panel D, Left).

For completeness, we lastly consider phase-locking changes induced by regional perturbations at WP3. Fig. C.15, panel A shows the change in PLV between each pair of regions (for the single, baseline frequency band) for two different choices of the stimulated area. As found in the main text (e.g., Fig. 4.6A), the response, in general, differs across the choice of the excited re-
The relationships between the phase-coherence modulations and structural or functional network strength found here for $C = 2$ (Fig. C.15, panel B) are also consistent with the analysis performed in the primary text for $C = 2.5$ (Fig. 4.6C). Namely, there is a strong, positive correlation between $\langle |\Delta \rho^\text{base}_{\delta_i} | \rangle$ and $s_i^{\text{struc}}$ and a weaker but still significant correlation between $\langle |\Delta \rho^\text{base}_{\delta_i} | \rangle$ and $s_i^{\text{func}}$.

C.12 Determining statistical significance of changes in phase locking value using phase randomized surrogates

Throughout the text, we compute changes in interareal phase-locking between baseline conditions and the case of focal stimulation. In particular, we subtract the PLV matrix computed from baseline simulations from the PLV matrix computed from simulations corresponding to regional stimulation. Of note is that this method does not account for the possibility that observed changes in phase-locking arise only from differences in the autocorrelation structures of units’ time-series in the baseline vs. stimulation conditions, which could affect results in the case of finite sample sizes. To determine when observed changes in phase-locking are different than the changes expected from a potential change in the autocorrelations of units’ dynamics alone, we can conduct statistical significance testing using autocorrelation-preserving surrogate data. We describe this methodology in what follows.

To begin, we will use the terminology $\Delta \rho^\text{base}_{jk,\delta_i}$ and $\Delta \rho^\text{exc}_{jk,\delta_i}$ to denote the change in baseline band and excited band PLV, respectively, between regions $j$ and $k$ induced by perturbation of unit $i$. Note that $i, j, k$ are all $\in \{1, \ldots, N\}$. To determine whether these changes are statistically significant, we need to build null distributions $\{\tilde{\Delta} \rho^\text{base}_{jk,\delta_i}\}$ and $\{\tilde{\Delta} \rho^\text{exc}_{jk,\delta_i}\}$ against which the observed changes are compared to. Furthermore, we want these null distributions to represent the expected changes in phase-locking for time-series that have the same autocorrelations as those from the baseline- and stimulation-condition simulations, but constructed such that the dependencies between surrogate time-series from different units are destroyed. One well-known autocorrelation-preserving surrogate method is that of phase-randomization [419]. This surrogate method maintains the power spectrum of an original signal $s(t)$, but randomizes its Fourier phases. In short, this is accomplished by computing the discrete Fourier transform of the original signal, adding phases drawn independently and at random from the interval $[0, 2\pi]$ to the phase for each frequency (while preserving the fact that the signal must be real), and then transforming back to the time-domain to obtain a “phase-randomized” surrogate $\tilde{s}(t)$ [420]. If a different
phase-randomization is applied to the surrogates corresponding to different units in the network, then each unit’s autocorrelation will be preserved, but interdependencies between different units will be destroyed. In this way, we can test the null hypothesis that the observed PLV changes $\Delta \rho^\text{base}_{jk,\delta_i}$ or $\Delta \rho^\text{exc}_{jk,\delta_i}$ are due only to finite sample size bias and the differing autocorrelation structures of units’ time-series between the baseline and stimulation simulations. If we can reject this null hypothesis, then we conclude that the observed modulations in phase-locking reflect actual changes in interareal coherence, beyond what is expected due to differing autocorrelations.

To generate the null distributions $\{\tilde{\Delta} \rho^\text{base}_{jk,\delta_i}\}$ and $\{\tilde{\Delta} \rho^\text{exc}_{jk,\delta_i}\}$, we follow the same steps used to generate the true changes $\Delta \rho^\text{base}_{jk,\delta_i}$ or $\Delta \rho^\text{exc}_{jk,\delta_i}$, with one exception: instead of using units’ actual excitatory time-series in the PLV calculations, we use corresponding phase-randomized surrogates. In particular, to generate one instance of $\{\tilde{\Delta} \rho^\text{base}_{jk,\delta_i}\}$ or $\{\tilde{\Delta} \rho^\text{exc}_{jk,\delta_i}\}$, we generate a phase-randomized surrogate from each unit’s activity in every trial, using different randomizations for all units and trials. Then, using the surrogate time-series, we compute one instance of $\tilde{\Delta} \rho^\text{base}_{jk,\delta_i}$ and $\tilde{\Delta} \rho^\text{exc}_{jk,\delta_i}$ following the same steps used to compute the original PLV changes in the baseline and excited frequency bands (see Sec. 4.2). This process is then repeated 50 times – each time using a different set of surrogate realizations – to generate null distributions $\{\tilde{\Delta} \rho^\text{base}_{jk,\delta_i}\}$ and $\{\tilde{\Delta} \rho^\text{exc}_{jk,\delta_i}\}$.

Once we have generated null distributions $\{\tilde{\Delta} \rho^\text{base}_{jk,\delta_i}\}$ and $\{\tilde{\Delta} \rho^\text{exc}_{jk,\delta_i}\}$ for a given choice of the excited unit $i$, the next step is to compare them to the observed differences $\Delta \rho^\text{base}_{jk,\delta_i}$ and $\Delta \rho^\text{exc}_{jk,\delta_i}$. To determine if an observed $\Delta \rho_{jk}$ is statistically different from a null distribution $\{\tilde{\Delta} \rho_{jk}\}$, we first check if $\Delta \rho_{jk}$ is positive or negative. If $\Delta \rho_{jk} > 0$, then we compute the fraction of surrogates $p_+$ for which $\tilde{\Delta} \rho_{jk} > \Delta \rho_{jk}$. If $p_+ < 0.05$, then we conclude that $\Delta \rho_{jk}$ is statistically greater than expected under the null distribution, and the increase in phase-locking is significant. If $\Delta \rho_{jk} < 0$, then we compute the fraction of surrogates $p_-$ for which $\tilde{\Delta} \rho_{jk} < \Delta \rho_{jk}$. If $p_- < 0.05$, then we conclude that $\Delta \rho_{jk}$ is statistically less than expected under the null distribution, and the decrease in phase-locking is significant. If the change in phase-locking $\Delta \rho_{jk}$ is not found to be statistically different from the null distribution, then we set its value to zero prior to computing network-averaged changes in the PLV. Using this procedure, we can check the statistical significance of all PLV changes in the baseline and excited frequency bands, and for each choice of the stimulated node.

The statistical significance testing described above is performed for WP1, WP2, and WP3 in the analyses where we consider network-averaged absolute modulations in phase-locking and their relationships to the structural or functional strength of the perturbed node (e.g., Fig. 4.6B,D–F, Fig. C.4, panels B–F, and Fig. 4.6B,C). In particular, at these working points,
PLV changes that are not significant (relative to the phase-randomized null model) are set to zero before computing the network-wide averages of PLV modulations in the baseline $\langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle$ and excited $\langle |\Delta \rho_{\delta_i}^{\text{exc}}| \rangle$ frequency bands. We do not repeat these comparisons against surrogate data for the parameter sweeps over the background drive and stimulation strength. However, findings from WP1, WP2, and WP3 (as well as WP1$^{\text{alt}}$, WP2$^{\text{alt}}$, and WP3$^{\text{alt}}$) indicate that results are largely unaffected by whether or not one sets non-significant PLV changes to zero prior to computing the global response. Throughout the text, we indicate when the statistical significance testing was performed on the PLV changes.

C.13 Details on the Hilbert Transform

A common way to extract an instantaneous phase variable from a real-valued, oscillatory signal is with the Hilbert transform. To begin, one writes the analytic (complex-valued) signal representation $X_A(t)$ of the real-valued time-series $X(t)$ as

$$X_A(t) = X(t) + iX_H(t) = A(t)e^{i\theta(t)},$$

where $X_H(t)$ is the Hilbert transform of $X(t)$, $A(t)$ is the instantaneous amplitude of $X(t)$, and $\theta(t)$ is the instantaneous phase of $X(t)$. Once one has computed $X_H(t)$ and thus $X_A(t)$, it is apparent from Eq. 4.6 that the phase $\theta(t)$ can be computed as

$$\theta(t) = \arg[X_A(t)].$$

The Hilbert transform of a signal $X(t)$ is defined as

$$X_H(t) = \frac{1}{\pi} \int_{-\infty}^{\infty} \frac{X(t')}{t-t'} dt',$$

where the integral is evaluated as a Cauchy principal value. From Eq. 4.8, one observes that the Hilbert transform is the convolution of $X(t)$ and $1/\pi t$: $X_H(t) = X(t) * 1/\pi t$, so the Fourier transform (FT) of $X_H(t)$, $\tilde{X}_H(f)$, is just the product of the FTs of $X(t)$ and $1/\pi t$. For frequencies $f > 0$, we thus have that $\tilde{X}_H(f) = -i\tilde{X}(f)$, from which it becomes clear that the Hilbert transform just induces a phase shift of $\pi/2$ to each frequency component in the signal.

In this study, we computed Hilbert transforms of the simulated neural activity using the ‘hilbert’ function in MATLAB. As described in Sec. 4.2, the Hilbert Transform was applied after first filtering the raw time-series in a specified frequency band, in order to ensure that the corre-
sponding phase variable is well-defined [35].

C.14 Brain region identification numbers and labels

A table with brain region ID numbers and their anatomical labels can be found in [376].
Figure C.6: Topological distances in the structural network predict power modulations at the excited frequency of the stimulated unit. (A) WP1: The logarithm of the absolute power modulation \( \log |\Delta P_j(f_{\text{peak}}^1)| \) of downstream regions \( j \neq 1 \) at the peak frequency of the stimulated area (unit 1) vs. the topological distance \( D_{1,j}^t \) of unit \( j \) from the stimulated site (in the structural network). (B) WP1: The Spearman correlation \( r_s \) between \( \Delta P_j(f_{\text{peak}}^i) \) and \( D_{i,j}^t \) (where \( j \neq i \)), shown for each choice of the stimulated area \( i \). The correlations are negative and statistically significant in all cases. (C) WP2: The logarithm of the absolute power modulation \( \log |\Delta P_j(f_{\text{peak}}^1)| \) of downstream regions \( j \neq 1 \) at the peak frequency of the stimulated area (unit 1) vs. the topological distance \( D_{1,j}^t \) of unit \( j \) from the stimulated site (in the structural network). (D) WP2: The Spearman correlation \( r_s \) between \( \Delta P_j(f_{\text{peak}}^i) \) and \( D_{i,j}^t \) (where \( j \neq i \)), shown for each choice of the stimulated area \( i \). The correlations are negative and statistically significant in almost all cases.
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Figure C.7: Network-averaged absolute change in baseline band phase-coherence $\langle |\Delta \rho_{\text{base}}^i| \rangle$ plotted at Working Point 3 vs. Working Point 1. Each point corresponds to a different choice of the stimulated region. Also note that PLV changes that were not statistically significant (see Sec. C.12) were set to zero before computing these network-wide averages.

\[ r_s = 0.72 \quad p < 0.001 \]

Figure C.8: The global decrease in baseline band phase-locking at the high-drive working point (Working Point 3) strongly correlates with the structural strength of the stimulated region. Scatter plot showing the structural strength $s_i^{\text{struc}}$ of the stimulated area vs. the absolute value of the network-averaged decrease in baseline band coherence $\langle | \downarrow \Delta \rho_{\text{base}}^i | \rangle$. The inset gives the corresponding Spearman correlation and p-value. Also note that only the statistically significant PLV changes (see Sec. C.12) are counted as non-zero when computing the network-wide average.
Figure C.9 (following page): Associations between stimulation-induced modulations in phase-locking and structural or functional connectivity hold for alternative working points near Working Point 1, Working Point 2, and Working Point 3. In all panels, $\langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle$ and $\langle |\Delta \rho_{\delta_i}^{\text{exc}}| \rangle$ correspond to the average absolute PLV changes that arise in the baseline or excited frequency bands, respectively, due to perturbation of unit $i$. Furthermore, $s_i^{\text{struc}}$ and $s_i^{\text{func}}$ are the structural and functional node strengths of region $i$. (A) At WP1$_{alt}$, the quantity $\langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle$ vs. $s_i^{\text{struc}}$ (Top) and the quantity $\langle |\Delta \rho_{\delta_i}^{\text{exc}}| \rangle$ vs. $s_i^{\text{struc}}$ (Bottom). (B) At WP2$_{alt}$, the quantity $\langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle$ vs. $s_i^{\text{struc}}$ (Top) and the quantity $\langle |\Delta \rho_{\delta_i}^{\text{exc}}| \rangle$ vs. $s_i^{\text{struc}}$ (Bottom). (C) At WP3$_{alt}$, the quantity $\langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle$ vs. $s_i^{\text{struc}}$ (Top). For this working point, there is no excited frequency band. (D) At WP1$_{alt}$, the quantity $\langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle$ vs. $s_i^{\text{func}}$ (Top) and the quantity $\langle |\Delta \rho_{\delta_i}^{\text{exc}}| \rangle$ vs. $s_i^{\text{func}}$ (Bottom). (E) At WP2$_{alt}$, the quantity $\langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle$ vs. $s_i^{\text{func}}$ (Top) and the quantity $\langle |\Delta \rho_{\delta_i}^{\text{exc}}| \rangle$ vs. $s_i^{\text{func}}$ (Bottom). (F) At WP3$_{alt}$, the quantity $\langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle$ vs. $s_j^{\text{func}}$ (Top). For this working point, there is no excited frequency band. In all panels, insets indicate Spearman correlation coefficients between the plotted quantities and their associated $p$-values.
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avg. PLV responses vs. functional strength

A

WP1

B

WP2

C

WP3

D

baseline band

E

excited band

baseline band

F

excited band

avg. PLV responses vs. structural strength

baseline band

excited band

avg. PLV responses vs. functional strength

\( r_s = 0.12 \)
\( p > 0.05 \)

\( r_s = 0.57 \)
\( p < 0.001 \)

\( r_s = 0.84 \)
\( p < 0.001 \)

\( r_s = 0.56 \)
\( p < 0.001 \)

\( r_s = 0.07 \)
\( p > 0.05 \)

\( r_s = -0.32 \)
\( p < 0.05 \)

\( r_s = 0.72 \)
\( p < 0.001 \)

\( r_s = 0.45 \)
\( p < 0.001 \)
Correlations between coherence modulations induced in the baseline band and structural or functional node strength depend on the system’s working point. (A) The y-axis shows the Spearman’s rank correlation coefficient $r_s$ between network measures of node strength and the average absolute change in baseline band phase-coherence $\langle |\Delta \rho_{\text{base}}^\delta_\delta | \rangle$ induced by stimulation of a single region. The x-axis is the level of background drive $P_E^{\text{base}} - P_E^*$ (for a coupling $C = 2.5$). The yellow curve shows the correlation between structural node strength $s_i^{\text{struc}}$ and $\langle |\Delta \rho_{\text{base}}^\delta_\delta | \rangle$, whereas the blue curve shows the correlation between functional node strength $s_i^{\text{func}}$ and $\langle |\Delta \rho_{\text{base}}^\delta_\delta | \rangle$. The arrows mark the locations of the working points studied in the main text and in the Supplement. Empty circles indicate that the correlation was not significant at the $p = 0.05$ level. (B) The y-axis shows the Spearman’s rank correlation coefficient $r_s$ between network measures of node strength and the absolute average change in excited band PLV $\langle |\Delta \rho_{\text{exc}}^\delta_\delta | \rangle$ induced by stimulation of a single region. The x-axis is the level of background drive $P_E^{\text{base}} - P_E^*$ (for a coupling $C = 2.5$). The yellow curve shows the correlation between structural node strength $s_i^{\text{struc}}$ and $\langle |\Delta \rho_{\text{exc}}^\delta_\delta | \rangle$, whereas the blue curve shows the correlation between functional node strength $s_i^{\text{func}}$ and $\langle |\Delta \rho_{\text{exc}}^\delta_\delta | \rangle$. Correlations are computed only between nodes that induce an excited band. The arrows mark the locations of working points studied in the main text and in the Supplement, and the grayed-out portion of the plot denotes baseline inputs at which at least half of the units fail to induce an excited band upon stimulation. Empty circles indicate that the correlation was not significant at the $p = 0.05$ level.
$r_s$ : baseline band PLV modulations $\langle |\Delta \rho_i^{\text{base}}| \rangle$ vs. structural ($s_i^{\text{struc}}$) or functional ($s_i^{\text{func}}$) strength

A

B

$\langle |\Delta \rho_i^{\text{exc}}| \rangle$ vs. structural ($s_i^{\text{struc}}$) or functional ($s_i^{\text{func}}$) strength

A

B

$\langle |\Delta \rho_i^{\text{exc}}| \rangle$ vs. structural ($s_i^{\text{struc}}$) or functional ($s_i^{\text{func}}$) strength
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Figure C.11 (following page): Effects of varying the perturbation strength $\Delta P_{E,i}$ at Working Point 1 and Working Point 3. (A) The average shift in peak frequency of the stimulated region $\langle \Delta f_{\text{peak},i}^{\text{peak}} \rangle$ vs. $\Delta P_{E,i}$ at WP1. (B) The average shift in peak frequency of the stimulated region $\langle \Delta f_{\text{peak},i}^{\text{peak}} \rangle$ vs. $\Delta P_{E,i}$ at WP3. (C) The grand average $\langle |\Delta \rho_{\text{base},i}^{\text{base}}| \rangle$ of the perturbation-induced absolute changes in baseline band PLVs vs. $\Delta P_{E,i}$ at WP1. (D) The grand average $\langle |\Delta \rho_{\text{base},i}^{\text{base}}| \rangle$ of the perturbation-induced absolute changes in baseline band PLVs vs. $\Delta P_{E,i}$ at WP3. (E) The grand average $\langle |\Delta \rho_{\text{exc},i}^{\text{exc}}| \rangle$ of the perturbation-induced absolute changes in excited band PLVs vs. $\Delta P_{E,i}$ at WP1. (F) The grand average $\langle |\Delta \rho_{\text{exc},i}^{\text{exc}}| \rangle$ of the perturbation-induced absolute changes in excited band PLVs vs. $\Delta P_{E,i}$ at WP3. (G) At WP1, the Spearman correlation $r_s$ between the network-averaged absolute PLV changes in the baseline band $\langle |\Delta \rho_{\text{base},i}^{\text{base}}| \rangle$ and (1) structural strength $s_{i}^{\text{struc}}$ (dark gray) or (2) functional strength $s_{i}^{\text{func}}$ (light gray), plotted as a function of $\Delta P_{E,i}$. (H) At WP3, the Spearman correlation $r_s$ between the network-averaged absolute PLV changes in the baseline band $\langle |\Delta \rho_{\text{base},i}^{\text{base}}| \rangle$ and (1) structural strength $s_{i}^{\text{struc}}$ (dark gray) or (2) functional strength $s_{i}^{\text{func}}$ (light gray), plotted as a function of $\Delta P_{E,i}$. (I) At WP1, the Spearman correlation $r_s$ between the network-averaged absolute PLV changes in the excited band $\langle |\Delta \rho_{\text{exc},i}^{\text{exc}}| \rangle$ and (1) structural strength $s_{i}^{\text{struc}}$ (dark gray) or (2) functional strength $s_{i}^{\text{func}}$ (light gray), plotted as a function of $\Delta P_{E,i}$. (J) Correlations with excited band changes are not considered at WP3 since no or fewer than half of units generate excited bands across all studied values of $\Delta P_{E,i}$. In panels G–I, filled-in circles indicate that the correlation is statistically significant at $p < 0.05$. 

270
mean shift in peak frequency of the stimulated region

mean of average absolute PLV changes across all choices of the stimulated region

correlations between average absolute PLV changes and structural or functional node strength

no excited band
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Figure C.12: Effect of background drive on stimulated regions’ power spectra at a coupling of $C = 2$. The average shift in the peak frequency of the perturbed region $\langle \Delta f_{i,\delta_i}^{\text{peak}} \rangle$ for WP1, WP2, and WP3 (error bars indicate ± one standard deviation over all choices of the excited unit).

Figure C.13 (following page): Phase-locking modulations induced by regional stimulation at Working Point 1 for a coupling of $C = 2$. (A) Pairwise changes in the PLV inside the baseline band $\Delta \rho_{\text{base}}$ when region $i$ (Left) or region $j \neq i$ (Right) is perturbed. In this figure, regions $i$ and $j$ correspond to regions 4 (R–Medial Orbitofrontal) and 23 (R–Lateral Occipital), respectively. (B) Pairwise changes in the PLV inside the excited band $\Delta \rho_{\text{exc}}$ when region $i$ (Left) or region $j \neq i$ (Right) is perturbed. (C) The quantity $\langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle$ vs. structural node strength $s_{i,\text{struc}}$ (Left), and the quantity $\langle |\Delta \rho_{\delta_i}^{\text{exc}}| \rangle$ vs. structural node strength $s_{i,\text{struc}}$ (Right). (D) The quantity $\langle |\Delta \rho_{\delta_i}^{\text{base}}| \rangle$ vs. functional node strength $s_{i,\text{func}}$ (Left), and the quantity $\langle |\Delta \rho_{\delta_i}^{\text{exc}}| \rangle$ vs. functional node strength $s_{i,\text{func}}$ (Right). In panels (C) and (D), insets indicate Spearman correlation coefficients between the plotted quantities and their associated $p$-values.
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**avg. PLV responses vs. functional strength**

**relationships to network properties**

- **Baseline band**
  - Perturb region $i$
  - Perturb region $j$

- **Excited band**
  - Perturb region $i$
  - Perturb region $j$

- **avg. PLV responses vs. structural strength**
  - $r_s = 0.20$, $p > 0.05$
  - $r_s = 0.97$, $p < 0.001$
  - $r_s = 0.68$, $p < 0.001$
  - $r_s = -0.30$, $p < 0.05$
Figure C.14 (following page): Phase-locking modulations induced by regional stimulation for Working Point 2 at a coupling of $C = 2$. (A) Pairwise changes in the PLV inside the baseline band $\Delta \rho_{\text{base}}$ when region $i$ (Left) or region $j \neq i$ (Right) is perturbed. In this figure, regions $i$ and $j$ correspond to regions 4 (R–Medial Orbitofrontal) and 23 (R–Lateral Occipital), respectively. (B) Pairwise changes in the PLV inside the excited band $\Delta \rho_{\text{exc}}$ when region $i$ (Left) or region $j \neq i$ (Right) is perturbed. (C) The quantity $\langle |\Delta \rho_{\text{base}}^i| \rangle$ vs. structural node strength $s_i^{\text{struc}}$ (Left), and the quantity $\langle |\Delta \rho_{\text{exc}}^i| \rangle$ vs. structural node strength $s_i^{\text{struc}}$ (Right). (D) The quantity $\langle |\Delta \rho_{\text{base}}^i| \rangle$ vs. functional node strength $s_i^{\text{func}}$ (Left), and the quantity $\langle |\Delta \rho_{\text{exc}}^i| \rangle$ vs. functional node strength $s_i^{\text{func}}$ (Right). In panels (C) and (D), insets indicate Spearman correlation coefficients between the plotted quantities and their associated $p$-values.
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Average PLV responses vs. functional strength

A. Perturb region $i$

B. Perturb region $j$

Baseline band

Excited band

Relationships to network properties

avg. PLV responses vs. structural strength

avg. PLV responses vs. functional strength

$r_s = 0.53$  $p < 0.001$

$r_s = 0.95$  $p < 0.001$

$r_s = 0.76$  $p < 0.001$

$r_s = 0.14$  $p > 0.05$
Figure C.15: Phase-locking modulations induced by regional stimulation for Working Point 3 at a coupling of $C = 2$. (A) Pairwise changes in the PLV inside the baseline band $\Delta p_{\text{base}}^i$ when region $i$ (Left) or region $j \neq i$ (Right) is perturbed. Note that in this figure, regions $i$ and $i$ correspond to regions 10 (R–Precentral) and 15 (R–Isthmus), respectively. (B) The quantity $\langle |\Delta p_{\text{base}}^i| \rangle$ vs. structural node strength $s_{i}^{\text{struc}}$ (Left), and the quantity $\langle |\Delta p_{\text{base}}^i| \rangle$ vs. functional node strength $s_{i}^{\text{func}}$ (Right). Insets indicate Spearman correlation coefficients between the plotted quantities and their associated $p$-values.
Chapter 5

Conclusion

In closing, it is helpful to briefly recall the broad motivations and questions that inspired the collection of studies we presented in this thesis. First, the uniting theme of our work has been its focus on networked systems, and in particular, those composed of coupled dynamical elements. Many complex systems can be described in this way, ranging from the macroscopic social networks in which we participate to the microscopic networks of cells that comprise neural systems. Importantly, the collective behaviors and function of such networks depend critically on interplays between the organization of structural couplings, the intrinsic properties of individual units, and network responses to targeted, dynamical modulations. However, understanding these relationships can be non-trivial for realistic systems whose network topology is elaborate or time-varying, and even simple network structures can yield complex collective behaviors due to a combination of interactions and non-linearities in the dynamics.

In this thesis, we approached these challenges by studying a set of dynamical models for different networked systems. Across all studies, we were interested in oscillatory behavior and in collective activity patterns such as synchronization or phase-locking. While these broad themes persisted across the work presented, each study was also motivated by a more specific system and set of questions. In particular, we used computational modeling to gain insights into synchronization on adaptive networks, the modulation of multistable phase-locking in small, interareal brain circuits, and the effects of regional excitation in large-scale brain networks. As a whole, this work attempts to shed light on various interplays between network structure, dynamics, and
responses to perturbations in an assortment of networked dynamical systems. In the following synopsis, we further summarize the motivations and key findings of our three investigations in turn. We then move to a general discussion and outlook regarding this work.

5.1 Synopsis

We began by examining how synchronization in a network of heterogeneous Kuramoto oscillators was altered under a specific type of co-evolution between dynamical states and network connectivity. The first motivation for this study was the fact that, in dynamical networks, a crucial question is how the structure of interactions influences or shapes a system’s macroscopic activity patterns. A key example of collective behavior is the emergence of synchronization among a network of coupled oscillators. Though synchronization dynamics are relevant to many individual systems, the Kuramoto model is widely used as an illustrative, canonical example for gaining insight into group phenomena in different scenarios. Moreover, while many studies have examined how static topologies shape synchronization, it can also be the case that network architecture is not fixed over time, but rather reconfigured in response to ongoing dynamics. In this way, new questions arise in regard to how collective behaviors are altered in adaptive systems that feature a feedback loop between network topology and the dynamical states of the nodes.

In contrast to global optimization strategies, we were particularly interested in the question of whether synchronization could naturally develop or become enhanced through a coevolution of network connectivity and dynamics that relied on only local information. To that end, we suggested a simple, adaptive rewiring scheme that preserved the total number of edges in the network and that only allowed a given oscillator to have knowledge about its neighbors’ phases. In particular, we proposed a type of negative feedback process wherein oscillators continuously re-route links away from other units with which they are most aligned and establish new connections at random. We found that this mechanism could evolve initially unstructured random graphs towards topologies with specific organizational principles that subsequently led to enhanced global synchronization. The structure that arose in the co-evolving systems manifested as specific relationships between the natural frequencies of the oscillators and the network topology. Importantly, these were properties that had previously been associated with optimal synchronization in which networks were purposefully designed using complete information about network and node properties. Alternatively, our study offered a means by which macroscopic coordination can emerge spontaneously through an interplay between node states and network topology that
utilizes only local rules.

In the next study, we shifted our attention to small circuits of oscillatory neuronal populations, where we specifically focused on collective phase-locking states and how they can be modulated via different perturbation signals. Phase-locking of rhythmic activity from spatially-distributed brain areas is thought to be one mechanism that could allow for information transfer among different neural populations, with communication dependent on relative phase relations. In addition to how brain areas functionally coordinate their activity, a second intriguing question is how networks of neural populations are able to carry out more than a single task, for example, have the capacity to reroute the flow of information depending on differing functional demands. Understanding how this capability might be realized is especially perplexing given that long-range connections – which constrain direct pathways for signal transmission – are relatively fixed on short time-scales. In particular, this fact would preclude structural reorganization as the driver of malleable network operation. To this end, past work examining motifs of coupled cortical areas has instead proposed multistable collective phase-locking as a possible way of achieving more than one functional state, despite a rigid anatomical backbone.

We considered and built upon the aforementioned idea in the context of small networks of coupled Wilson-Cowan neural mass units. Beginning with a deterministic version of the model, we first established conditions under which multistable phase-locking could arise, finding that the interareal time-delay is a critical factor. After characterizing those configurations, we proceeded to study the response of collective dynamical states in 2-area and 4-area networks to different types of local perturbations. These signals could represent external inputs from the environment or modulatory inputs from other brain areas. Our first key result was that properly timed, transient pulses applied to a single area could induce a lasting reconfiguration of the relative phase-ordering. In the 4-area network, we showed that from a given initial state, one of two transitions are possible corresponding to either a phase-delay or a phase-advance of the perturbed site. As an alternative to brief input pulses, we also considered the effects of sustained rhythmic stimulation of varying amplitude and frequency. Beyond state-switching, we found that steady sinusoidal input applied to a single population in the network can also induce a morphing of the phase-relations relative to baseline, which may allow for fine-tuning temporal relations between distinct brain areas. Importantly, we also extended our study to a more realistic setting in which the neural populations receive stochastic rather than deterministic background drive. We characterized this regime as a function of internal circuit parameters and those governing the stochastic environment, finding that noise can lead to spontaneous switching between the network’s at-
tractors, even in the absence of any additional driving. Nonetheless, we showed that for parts of
the stochastic regime, different types of local inputs could still be used to trigger state transitions
on fast time-scales or to cause longer-lasting symmetry-breaking that biases the probability of a
particular phase configuration. Importantly, we also illustrated a scenario where, although the
network occupied distinct phase-locking states at baseline, state-control broke down. In total,
our results contribute to the idea that the capacity to modulate multistable phase-locking states
could enable functional flexibility in multiarea brain circuits.

In our final study, we implemented a computational model to examine the effects of re-
gional perturbations on oscillatory activity patterns in a large-scale brain network, focusing in
particular on how network responses depend on the system’s baseline dynamical state. Differ-
ent from the elementary, “building-block” motifs we considered previously, at the whole-brain
level, anatomical connectivity is much more heterogeneous. The combination of the brain’s com-
plex architecture and dynamics at this scale in turn render it difficult to predict the outcomes
of targeted modulations. One challenge lies in understanding not only the focal, but also the
distributed consequences of a local perturbation. Moreover, while there has been much focus
on trying to predict function from structure, macroscale brain dynamics can exist in multiple
dynamical states, even though white matter connections remain relatively fixed. However, it is
unclear whether and how the widespread impacts of stimulation depend on the collective state
of network activity, in conjunction with anatomical wiring.

As a basic first step in addressing these questions, we constructed a model of large-scale brain
activity. In this setup, different anatomical regions in a human brain network were modeled as
Wilson-Cowan neural masses, and then coupled according to structural connectivity mapped via
diffusion imaging and tractography. In the context of this model, we varied the dynamical state of
the network by globally tuning a node-level bifurcation parameter, while leaving the anatomical
couplings entirely fixed. Importantly, we first observed that in addition to changing the nature
of regional activity, homogeneously shifting the working point of each region also altered coor-
dinated functional interactions across the network as a whole. This result indicated that struc-
tural connectivity is not the sole determinant of the system’s collective oscillatory mode. We then
selected qualitatively distinct working points, and in each case, tested the effects of focal excita-
tion by stimulating each region one-by-one. Our analysis revealed that global responses to these
modulations could indeed be contingent upon the dynamical state. In a regime of weak baseline
oscillations, we found that targeted input accelerated the activity of the directly affected site, and
also led to widespread effects at both the new, excited frequency, as well as in a much broader
frequency range including areas’ baseline frequencies. In this case, structural connectivity was a good predictor of responses in the “excited band”. Alternatively, depending on the working point, changes in “baseline band” coordination could be better predicted by the network’s initial functional connectivity, which depends both on network structure as well as the internal dynamical properties of the units. In a regime of strong baseline rhythms, external inputs induced much weaker changes to regional activity, and global alterations in functional interactions were most correlated with anatomical connection strength. By integrating and extending past efforts, our results thus indicated that the anatomical organization of a network, as well as its dynamical operating point, play a role in governing how focal stimulation modulates interactions between distributed network elements.

5.2 Final thoughts

In this dissertation, we used a suite of models to examine relationships between network structure and collective dynamics, and to elucidate how network activity patterns respond to targeted dynamical perturbations. Because our approach relies heavily on computational modeling, it is perhaps worth commenting on some of the strengths and weaknesses of this methodology, especially in the context of our work. In doing so, we can also point to some important directions for future study.

Rather than building precise models to explain specific empirical observations, we used more general implementations that enabled an exploration of various ideas regarding network-level phenomena. One strength of this kind of approach is that it allows one to develop new hypotheses and intuitions about dynamical network behaviors that may underlie or be relevant to the function of different systems. For example, in our first study, we wondered how global synchronization may be able to emerge in a network via local rules. While we do not claim that the Kuramoto model or the proposed adaptive mechanism are accurate descriptions of any real system, studying the model still provides insight about a possible path towards a fascinating macroscopic behavior. In the second study, we used a biophysically-motivated but reduced model to explore multistable phase-locking and its modulation under perturbations. Again, this was not to provide a mechanistic account of an experimental finding, but rather to offer potential mechanisms that might be realized in interareal brain circuits and that may lead to desirable functional capabilities. And finally, in our third study, we relied on modeling to test the general hypothesis that dynamical state influences the widespread impacts of focal stimulation in brain networks.
Though the model is highly simplified and is without comparison against data, we suggest that there is, nonetheless, utility in considering such idealized models. These rough realizations can serve as an initial test-bed for an idea, or as a way to illustrate a concept that can later be refined.

Aside from using them to explore a set of possible scenarios, or to shed light on potentially interesting directions for further study, computational models can also provide a means to bridge between different scales of a system. This may be especially important in our ability to understand neural systems, in particular, which appear to exhibit non-random organization on multiple spatiotemporal levels. For example, there exists a need to link the behaviors of single neurons to systems-level phenomena involving many spatially-distributed areas, but this is a daunting task due to the number and complexity of the components and their interactions. In conjunction with experiment, models are likely an important tool in this endeavor, as they can help us parse and understand why certain biophysical properties at one resolution will manifest in a certain way at the next scale up. Neural mass models, and the coupling of them into large-scale brain networks, are good examples of how we can begin to make progress in bridging multiple spatiotemporal scales. Moreover, while it may not always be possible to tune parameters or make perturbations experimentally, we can examine the consequences of such actions in a model. In turn, the results of manipulations carried out in the context of a model can subsequently be used to guide empirical investigation and to suggest causal tests of proposed mechanisms.

In concluding, we reiterate that it is also important to be wary of the overall limitations of the research presented in this thesis, and consequently, directions for future work. Though we refrain from repeating the extended discussions on these points contained within each chapter, we do wish to state again the necessity of validating models via comparison with experiment. As we have mentioned, a weakness of the modeling studies we conducted is that they were not directly tested against empirical findings. While a model may have utility without such comparisons, an end goal should be to provide mechanisms or explanations for observed phenomena. In this way, perhaps the most important next step in terms of the studies detailed here would be to combine and further inform them with data. For example, optogenetic stimulation techniques may allow for experimental testing of some of the ideas contained in Chapter 3 on the modulation of phase-locked states in small interareal circuits. And, in regard to the study presented in Chapter 4, it will be crucial to work towards constraining the baseline dynamics of the model with measurements of whole-brain activity. This, in combination with a more realistic implementation of external stimulation, may then enable more meaningful predictions in regard to the impacts of focal perturbations and contributions to stimulation-based therapies. We look forward to working on
these advancements in forthcoming investigations.
References


References


References


