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A Computational Model of the Nucleus Accumbens: Network Properties and their Functional Implications

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Abstract - **The Nucleus accumbens integrates convergent input from a number of limbic structures, and has been implicated in a variety of behavioral disorders including addiction and schizophrenia. The bistable membrane properties of the principal cell in the NAcb, the GABAergic medium spiny projection neuron (MSP), have been proposed to mediate afferent integration. To investigate how intrinsic properties may underlie this mechanism, we constructed a model of an MSP neuron in GENESIS, which preserves the main morphological features and relevant ionic/synaptic currents. The model captures the major properties of *in vivo* neurons, including a non-linear response to the number of afferent inputs. In order to examine network properties of the NAcb and its response to varying patterns of afferent input, a 100-cell network with modifiable levels of gap junctions and GABAergic synaptic connectivity was constructed. Afferent inputs were modeled as Poisson-distributed spike trains. Addition of lateral inhibition in the network led to a decrease in spike output for cells receiving less synchronized input, suggesting that this may be a mechanism for increasing the signal to noise ratio. Dopaminergic modulation of the whole network led to a slight increase in overall synchronization, but did not further segregate cells that were already receiving synchronous input.**

Keywords – **Computational Modeling, Network, Afferent Input, Striatum, Schizophrenia**

I. INTRODUCTION

The Nucleus accumbens, a ventral structure in the basal ganglia, receives afferent input from cognitive and "limbic" areas of the brain, including the prefrontal cortex, the amygdala, and the hippocampus. It also receives inputs from the thalamus, and a dense dopaminergic projection from the ventral tegmental area (VTA).[1] This pathway has been demonstrated to be involved in behaviors moderated by natural reinforcers and levels of expected reward.[2] The main outputs of this nuclei are to the ventral pallidum, with feedback to both the VTA and the PFC.[3] The primary output of the cells in the VP are to the thalamus, and thus the NAcb is thought to regulate feedback to PFC and other cortical areas.[4] Due to the large number of inputs that this area receives from limbic structures, as well as the large component of DA modulation it receives, it has also been implicated in many disorders, primarily addiction and schizophrenia.[5, 6]

The main cell in the NAcb is the medium spiny neuron (MSP), comprising 95% of the population of the nucleus. The other 5% is made up of inhibitory interneurons and cholinergic cells[1]. The cells in the NAcb exhibit an unusual "bistable" membrane potential whose origin and function have been debated in the literature.[7] The cells tend to alternate between a hyperpolarized "down" state (~-85mv), and a depolarized "up" state (~-60mv), firing only while in the up state. These properties are due to activation of an inward rectifying potassium channel in the down state (K_{IR}) and a number of A-type potassium channels in the up state. This behavior has been proposed to provide a "gating" mechanism regulating the sources of afferent input to the NAcb.[8] However, membrane potential shifts are recorded intracellularly in anesthetized animals, which leaves open the role of these states in the awake animal.

MSP cells are GABAergic and project out of the NAcb; in addition, a number of collaterals from these axons project locally.[9] This lateral inhibition provides one possible level of communication between cells in this nucleus. MSP cells are also coupled by dendro-dendritic gap connections. DA modulation has been demonstrated to affect the level of electrical coupling between cells.[10] An architecture composed of local GABAergic connections and gap junctions has been shown to be capable of rapid synchronization.[11, 12]

We have previously constructed a detailed biophysical level model of the NAcb MSP cell to examine the contribution of these currents to the bistable state.[13] In order to examine the network properties of the NAcb and the effects of afferent input on these properties we constructed a network of 100 MSP cells. Each cell is modeled with sufficient biophysical detail to capture the major behaviors of *in vivo* MSP cells. Our goal was to model the inputs to this network, to examine the effects of DA modulation, and to elucidate some of the properties of this network, specifically changes in synchronization.

II. METHODOLOGY

The main features of these cells were captured in a computational model written in GENESIS.[14] The model is a stylized representation of the MSP cell with approximate geometry and contains all of the known currents relevant to the cells behavior *in vivo*. The single cell was designed to match the passive properties determined experimentally for the NAcb cells *in vitro*.[15] Channel properties were collated from those described in the literature for both the ventral and dorsal striatum. MSP cells are hyperpolarized at rest (~-85mV) due to a large inward rectifying potassium conductance (K_{IR}).[7]

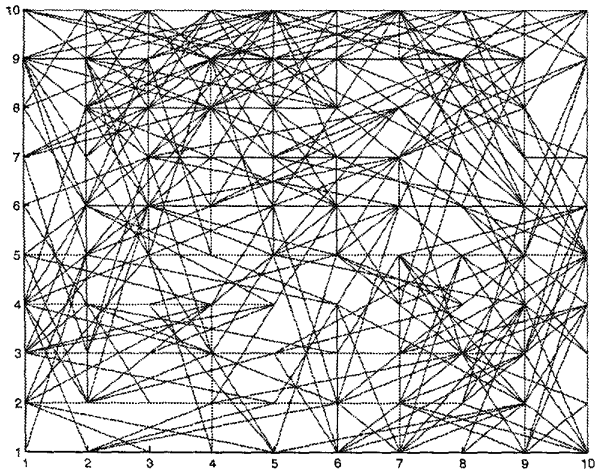

Fig.1 – A map of the gap connections between the 100 cells in an example network

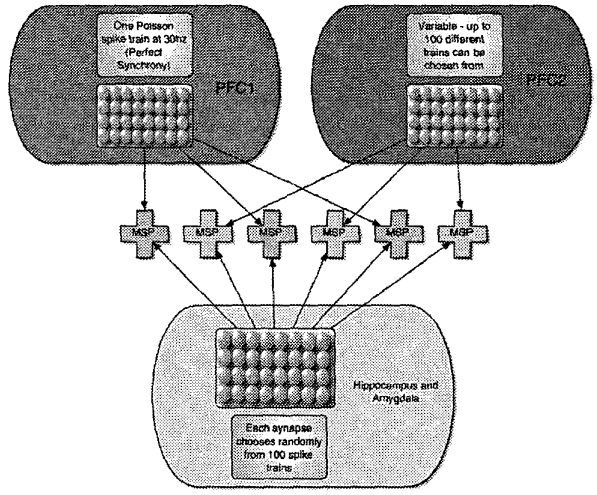

Fig.2 – Diagram of the connectivity and representative level of input to the MSP cells in the network model

Response to current injection is non-linear due to K_{IR} and a set of K^+ conductances that are activated at higher voltage ranges, collectively called K_A channels.[16] Implemented in the model were two Na+ currents (fast and persistent), a delayed rectifier potassium, three A-type potassium currents (K_{As}, K_{Af}, K_{rp}) and a high-voltage activated (HVA) calcium channel representing a collection of currents.[17] Synaptic currents (GABA, AMPA, and gap) were modeled as well. We chose to implement some currents that have been described only for the dorsal striatum, although some of these have yet to be confirmed in the ventral striatum. The conductances and kinetics of these channels were tuned to approximate as closely as possible the known electrophysiological behavior of the cells *in vitro* and *in vivo*.

The cells in the network were interconnected with dendro-dendritic gap connections. The gap connection strengths were randomized within a predefined range, and connectivity was limited to a predefined distance and number of connections. An example of a gap connection "map" is shown in Fig.1. Lateral GABAergic synapses were also implemented in order to study their effect on network activity. These GABAergic connections were also randomly generated and probability of interconnection decreased with distance between cells.

Afferent input was modeled with Poisson distributed spike trains. Mean firing rate of PFC efferents was 30Hz; afferents from cells representing a combined hippocampal and amygdalar input had mean firing rate of 10Hz.[18] The degree of "coherence" or synchronization of the incoming inputs was adjusted by selecting inputs from among large populations of modeled spike trains. All cells in a group of MSP neurons could receive the exact same set of afferent inputs, or each cell could receive a different mixture of spike trains with controlled degrees of commonality across the input streams. Each MSP cell received 12 synaptic inputs from PFC, but groups were differentiated based on the number of different PFC spike trains from which their inputs were randomly selected. NAcb cells were divided into three groups based on their afferent input. Each MSP cell which received inputs from "PFC1" received a set of 15 random spike trains, whereas MSP cells receiving inputs from "PFC2" received 15 identical spike trains. All remaining MSP cells received a randomly chosen set of trains from a pool of 100 trains. All cells received 32 hippocampal/amygdalar inputs chosen randomly from a separate pool of 100 spike trains.

DA modulation was implemented by increasing the number and conductance of gap connections, and by increasing the conductance of K_{IR} channels and HVA calcium channels.[19] We analyzed the degree of synchronization and temporal patterning in the network using a method of "gravitational analysis" developed by Gerstein.[20] Gravitational analysis utilizes an analogy to particles in a viscous medium in an n-dimensional space in order to evaluate the correlation in firing between many neurons. As a group of neurons fire in repeated temporal structures, the pair distance between the particles in the medium decreases, allowing for determination of which cells tend to fire together over time. Gravitational analysis is reported to be efficient at detecting ensembles of temporally coordinated cells, a more difficult task than detecting uniform synchronization.

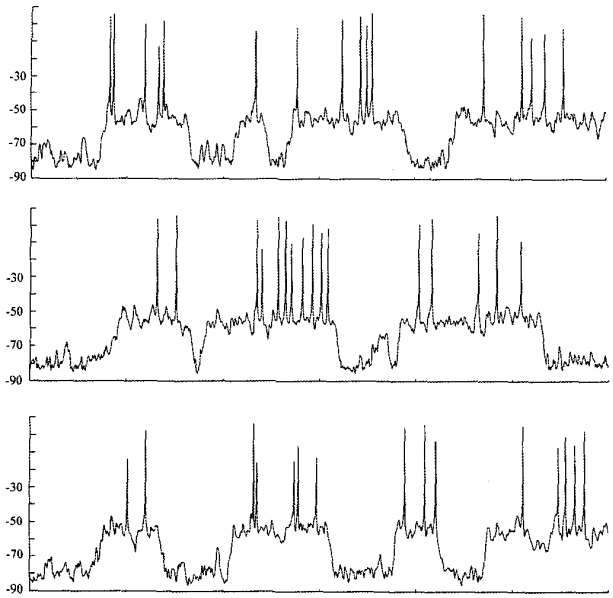

Fig.3 – Traces of the membrane potential of 3 example cells from the network simulation (Voltage in mV on the Y axis)

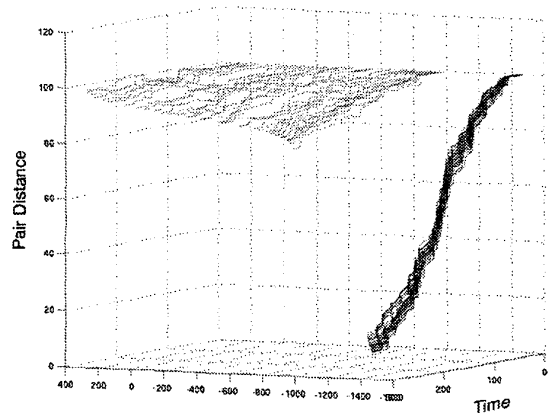

Fig.4 – Gravitational transformation of the output of a network simulation. The cells on the right have more synchronized input, leading to greater synchronization of the cells in the NAcb receiving the input. This is reflected in shorter pair distances between "particles" over time.

III. RESULTS

Single cell membrane potential records from the network model demonstrate behavior similar to that seen by cells *in vivo*. (Fig.3) Model cells make sharp transitions between "up" and "down" states depending on the level of input being received, and fire only in the up state.

Cells in the network fire at rates similar to those reported for *in vivo* activity (4-8hz) dependent upon afferent input. [1] Addition of gap connections to the network increased the synchronization of all the cells in the network to a slight degree. Turning on the lateral inhibition decreased the total number of spikes in the network. There was a reduction in total spikes of 7.8% for cells receiving synchronized input from PFC1, versus reductions of 14.8% in PFC2 cells (less synchronized) and 20% for the remaining cells (not synchronized). Thus, lateral inhibition reduced the total number of spikes more significantly for cells receiving unsynchronized input than for the cells receiving completely synchronized or slightly synchronized inputs.

DA modulation of the entire network had little effect on the level of synchronization of the cells receiving moderate levels of synchronized input, either via increasing the gap connections or by modulating K_{IR} and HVA Ca+ channels. Cell populations that were already segregated by synchronization of their inputs were not further segregated by global application of DA. However, preliminary results show that local applications of DA may lead to significant changes in temporal structures.

IV. CONCLUSIONS

We have developed a model of the MSP cell in the NAcb that mimics the passive properties and the dominant electrophysiological behavior of the cells *in vivo*. Once afferent input was introduced to the neurons, the bistable aspects of the membrane became apparent. Bistability could be eliminated by reducing or increasing the level of input stimulation, but the cells then either ceased firing, or fired at an unreasonably high rate. The model therefore predicts that the bistable behavior should be evident in the awake animal as well.

Incorporation of this model into a network with lateral inhibition, electrical coupling, and DA modulation has allowed us to examine the role each process plays in overall network function. The addition of lateral inhibition to the network suppresses firing of cells that receive less synchronized input. If we consider the synchronized input as the signal, e.g. from ensembles of PFC cells engaged in working memory tasks and the firing of MSP cells receiving non-synchronized input as the noise, then this behavior would lead to an increase in the signal to noise ratio in these areas of the larger network.[21] This would allow for preferential selection of outputs from cells whose inputs are from afferent groups of synchronized cells, such as a functional subassembly in the afferent networks.

Global application of DA antagonists is often used to evaluate the role of DA in reward and learning. Our results

suggest that modulation may be at a finer grain than the global level of the entire nucleus, as increasing the level of DA in the entire network leads to only small increases in synchronization of the network, and doesn't further separate the firing patterns from those not synchronized. DA terminals are juxtaposed to dendritic spines on MSP cells, which would allow for very specific local modulation from the VTA.[19] Although not addressed in these studies, DA modulation may act to form or strengthen assemblies of cells that make up functional units by selecting groups of cells for synchronization through electrical coupling. Cellular assemblies have been frequently discussed as possible functional units of information processing, and the output of the NAcb may emphasize certain sequences of motion or behavior.[22] Disruption or cooption of these processes may have implications for information processing in the NAcb, and therefore for disorders such as schizophrenia and addiction.

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