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Spare the (Elastic) Rod

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Abstract
Physicists love emergence. From a welter of complex details about a system's constituents, simple and universal rules sometimes emerge that adequately describe the collective behavior of the components. Even if these rules are not completely universal, they often have only a few relevant parameters, a vast simplification compared to the many that describe the constituents individually. But as Vafabakhsh and Ha remind us on page 1097 of this issue (*1*), emergent behavior can conceal important aspects of a system. Using a beautiful application of fluorescence microscopy, the authors provide the clearest evidence to date that the elastic-rod model for DNA mechanics, an emergent description that works well on long length scales, breaks down on shorter length scales relevant to cell biology.

Disciplines
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Physicists love emergence. Out of a welter of complex details about a system's constituents, sometimes simple and universal rules adequately describe their collective behavior. Or if the rules are not completely universal, often they have only a few relevant parameters, a vast simplification compared to the many that describe the constituents individually. But emergence can be a two-edged sword, as Vafabakhsh and Ha remind us this week [1].

Emergence is frequently observed as a function of increasing length scale. Thus the complex intermolecular dynamics of individual water molecules can all be forgotten when we design plumbing; for this purpose it suffices to know just two parameters (mass density and viscosity). However, the very forgetfulness of Nature that simplifies its long-scale character can also conceal from us the details that we need to know if we are to understand shorter-scale regimes. A case in point concerns the mechanical properties of DNA. It is tempting to regard this famous molecule as just a database containing the algorithm for constructing an organism—pure information. But DNA is also a *thing,* a physical object; its everyday transactions involve constantly bending, releasing, twisting, and so on. Particularly important, DNA is often observed to be tightly bent, in contexts such as gene regulation and packaging (Fig. 1).

Polymer physicists have long known that a stiff polymer like DNA will display emergence: For phenomena on long length scales, such a molecule may be adequately described as an elastic rod, that is, a rod that resists bending with a linear (Hooke-law) relation. The mathematics of elastic rods was well developed in the 19^{th} century; all that is needed in the polymer context is to

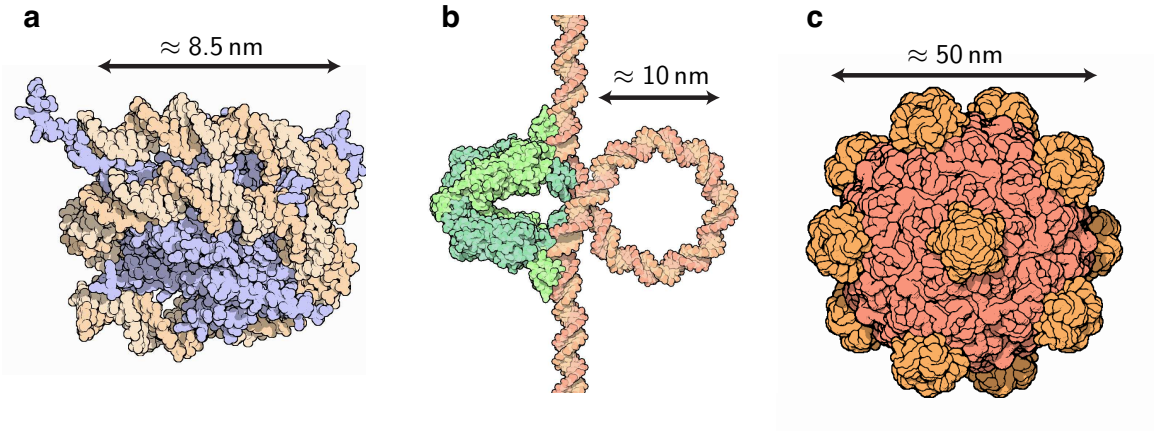

Figure 1: Biological examples of tightly bent DNA. (a) DNA winds around a protein core (lavender) to form the nucleosome; (b) A transcription factor (green) forces DNA into a tight loop; (c) A bacterial virus packs over 10 000 basepairs of DNA into a small capsid. (Illustration courtesy of David S. Goodsell and the RCSB Protein Data Bank.)

add the action of random thermal motion, which takes on crucial importance in the nanoworld. Gratifyingly, some of the very first single-molecule manipulation experiments on DNA found that the simple elastic rod model, despite having only a single free parameter, gave a quantitative account of experiments done on lambda phage DNA [2]. Some physicists took this agreement, which became even more impressive with later experiments, as a license to regard DNA as literally a linearly-elastic rod.

The late Jonathan Widom [3] was not satisfied with this state of affairs. He knew that, applied literally, the elastic rod model predicted that a prohibitive amount of elastic energy must be expended to form the structures in Fig. 1, and yet these structures do form readily. To reduce uncertainties from the complex cellular milieu, Widom undertook *in vitro* experiments with DNA fragments of length equal to the circumference of the nucleosome core particle, and assayed their ability to form loops. The assay was done in the absence of the histone proteins that one might have thought would facilitate loop formation, and the results were astonishing. Not only did small loops form readily; in fact, for loops of biologically-relevant sizes (Fig. 1) the ability to form spontaneously was found to be nearly *independent* of loop size (apart from a modulation with periodicity equal to the helical pitch) [4, 5].

Perhaps these results should not have come as a great surprise. It has long been known that DNA has discrete alternate conformations, attainable at a modest free energy cost, including some with sharply localized kinks [6], locally melted regions, flipped-out basepairs, and so on. Thus, just as bending a soda straw eventually gives a catastrophic breakdown of its rod elasticity, so too could severe nonlinearities enter DNA elasticity. Kinks were also known to form in tightly bent structure like the nucleosome [7, 8]. What remained unknown was the length scale at which such effects would be forgotten; would the simple emergent rod behavior be adequate for understanding the mesoscopic structures relevant to biology? Here, too, there were prescient early clues: DNA was known to display multibasepair-range correlations [9], which could in principle delay the onset of emergence and vitiate the elastic rod as a suitable description on mesoscopic scales. Indeed, immediately after Cloutier and Widom's work, theorists found simple models displaying highly bendable behavior on those scales, yet also consistent with the elastic-rod behavior familiar on long scales [10, 11].

Unfortunately, Cloutier and Widom's experiments were fraught with uncertainties. Their assay relied on the large ligase enzyme; it required an intricate protocol, including a special enzyme kinetics regime; it did not directly report looping rates. Although later experiments have given similar results without any use of ligase [12, 13], in each case some aspect of the assay did not resemble the situation *in vivo*. This week, however, Vafabakhsh and Ha offer a clean, simple demonstration of non-rodlike behavior in DNA at biologically relevant scales [1]. Not only does this experiment vindicate Widom's intuition; it also shows that this behavior occurs for generic sequences (it is even more pronounced for special ones). Finally, the experiment confirms the near-independence of looping ability on DNA length in the relevant regime—a cardinal property in both

the microscopic [10, 11] and mesoscopic [12] theories.

The new results will still need to be integrated with prior experiments, not all of which have seemed to fit the picture described above [14]. They will also provide guidance as theory seeks to go beyond generic models to ones predicting the details of sequence dependence. Already, however, they illustrate once again the power of fluorescence methods to probe not only static, but also dynamic details of the nanoworld.

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