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Spare the (Elastic) Rod

Philip C. Nelson

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.

Emergence is often a function of increasing length scale. For example, the complex intermolecular dynamics of individual water molecules can be ignored in the design of plumbing; for this purpose, it suffices to know just two parameters for water: its mass density and its viscosity.

However, the very forgetfulness of nature that simplifies its long-scale character can also conceal the details that we need to know if we are to understand shorter-scale regimes.

The mechanical properties of DNA are a case in point. It is tempting to regard this famous molecule as just a database containing the algorithm for constructing an organism. But DNA is also a physical object that constantly bends, twists, and interacts with other bio-molecules. Particularly important, DNA is often observed to be tightly bent, in contexts such as gene regulation and packaging (see the figure).

Polymer physicists have long known that a stiff polymer like DNA will display emergence. 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 relation (Hooke’s Law). The mathematics of elastic rods was developed in the 19th century; all that is needed in the polymer context is to add the action of random thermal motion, which takes on crucial importance on the nanometer scale.

Some of the 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 the behavior of lambda phage DNA (2). This agreement became even more impressive with later experiments.

Could DNA be literally regarded as a linear elastic rod? The late Jonathan Widom (3) did not think so. He knew that the rod model required a prohibitive amount of elastic energy to be expended to form the structures shown in the figure; yet, these structures form readily.

To reduce uncertainties that arise from the complex cellular milieu, Cloutier and Widom undertook in vitro experiments with DNA fragments of length equal to the circumference of the nucleosome core particle. They assayed the ability of these fragments to form loops in the absence of the histone proteins that might be thought to facilitate loop formation. The results were astonishing. Not only did small loops form readily; for loops of biologically relevant sizes (see the figure), 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, and flipped-out base pairs. 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 structures like the nucleosome (7, 8). Accordingly, immediately after Cloutier and Widom’s work, theorists investigated simple models incorporating highly bendable behavior on short length scales (9, 10). Such models automatically

**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 base pairs of DNA into a small capsid. The results of Vafabakhsh and Ha bear on the question of how such structures can self-assemble despite the high elastic energy cost traditionally attributed to tightly bent DNA.
displayed emergent elastic-rod behavior on long length scales, thus reconciling the new experiments with the old ones. Later, a mesoscopic (intermediate-scale) model was found that incorporated still other experimental results, yet, like the original elastic rod, had only one free parameter (11).

Unfortunately, Cloutier and Widom’s experiments were fraught with uncertainties. Their assay relied on the large ligase enzyme, required an intricate protocol, and did not directly report looping rates. Later experiments have given similar results without use of ligase (11, 12), but in each case, some aspect of the assay did not resemble the situation in vivo.

Vafabakhsh and Ha now offer a clean, simple demonstration of non-rodlike behavior in DNA at biologically relevant scales. The new work is done in vitro, and hence is free from many unknowns in the cell, yet was not affected by some potential artifacts present in previous in vitro experiments, for example, the proximity of hard walls and large reporter beads. Not only do their results vindicate Widom’s intuition; they also show that this behavior occurs for generic sequences [it is even more pronounced for special ones (13)]. Finally, the experiment confirms the near independence of looping ability on DNA length in the relevant regime—a cardinal property in the theories of (9–11).

The new results will still need to be integrated with previous 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 the two-edged character of emergence: It can simplify behavior, but this is not always appropriate. To learn about a system on some length scale, we must devise experiments that specifically probe that particular scale.

References