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FIRST REACTIONS

Eliminating Fitting from the Modeling of Biological Processes

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The truth is like a lion; you don't have to defend it. Let it loose; it will defend itself.

—Saint Augustine of Hippo

The goal of establishing predictive theoretical models for the behavior of biopolymers, including DNA and proteins, is both fundamentally challenging and absolutely essential to fully establish our quantitative understanding of living systems. A fully predictive model must satisfy two main conditions. First, the model must be parameter free, meaning that it is exhaustively trained against experimental measurements and then used as an autonomous predictor of behavior. Second, the treatment must be capable of capturing behavior of experimentally relevant systems at experimentally relevant time scales. In the manuscript "Tension-Dependent Free Energies of Nucleosome Unwrapping",[1] Lequieu and co-workers present a novel treatment of the nucleosome that serves as a prototypical example of how to build a predictive model that satisfies these conditions.

The vetting of the author's DNA model is remarkably extensive, and this work demonstrates that the exhaustive vetting process has achieved a model that is capable of making predictions that do not have fitting parameters.

Theoretical and computational modeling is emerging as a valuable approach to understanding biological processes. However, various modeling techniques have limitations in satisfying the conditions for being predictive and autonomous. Atomistic simulations aim to be parameter free, but they are computationally intractable for more than a single protein at time scales beyond a microsecond. Highly coarse-grained models may be relevant to specific biological systems at experimentally relevant time scales. However, these models generally have free parameters that cannot be independently determined to establish a fully predictive treatment. Furthermore, highly coarse-grained approaches frequently require de novo development for each system of interest, requiring considerable effort before making a connection to experimental measurements.

Using a detailed model of the DNA–histone complex, Lequieu et al. explain the tension-dependent free energy of nucleosome unwrapping at a molecular level.

Lequieu and co-workers present a simulation study of the response of a single nucleosome subjected to tension on the DNA strands emanating from the nucleosome. The nucleosome, which is composed of approximately 150 basepairs of DNA wrapped around 8 histone proteins, is the fundamental unit of packaged chromosomal DNA. Thus, the structure and behavior of the nucleosome are of fundamental importance to our understanding of the in vivo behavior of genomic DNA. This study provides a predictive (i.e., zero free parameter) model that is used as a comparison to single-molecule experiments of a nucleosome under tension.[2] The model leverages the authors' expertise in the coarse-grained modeling of DNA and the histone octamer.

Single-molecule force spectroscopy and imaging provide exquisitely sensitive measurements of enzymatic function and protein/DNA interactions.[2−8] Refinement in measurement precision makes it possible to detect individual basepair steps of proteins along DNA,[6] and super-resolution imaging is capable of resolving structural details at nanometer length scales.[7,8] In many regards, theoretical and computational modeling efforts struggle to keep pace with such remarkable achievements, particularly if the goal is to establish quantitatively accurate models for experimental interpretation. This leaves an opportunity for the theoretical community to pioneer approaches that maintain or re-establish our standing as being predictive of experimental

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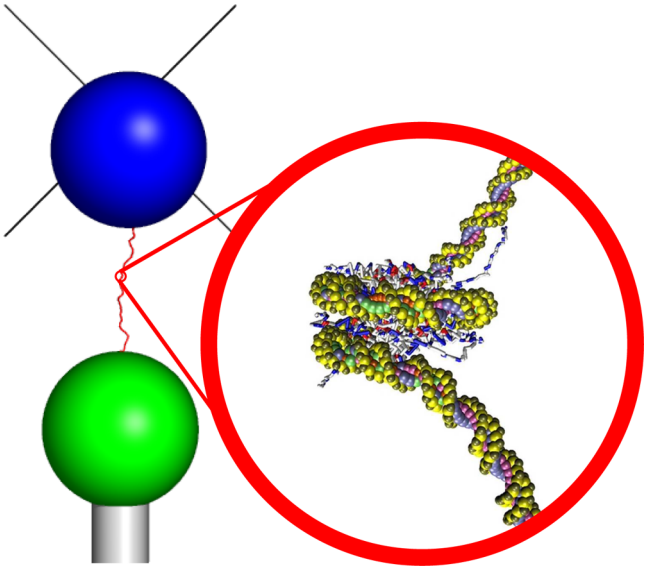

Figure 1. Theoretical modeling of biological systems is emerging as a critical tool in interpreting high resolution experimental measurements. In this work, Lequieu and co-workers have developed a predictive model for the response of nucleosomal DNA to tension, as applied in an optical tweezer measurement (shown schematically in this figure). This work builds a predictive framework that is capable of resolving detailed interactions between DNA and histone proteins, matching the level of refinement in the experimental counterpart.

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measurements, rather than being responsive as an interpretive tool.

The vetting of the author's DNA model is remarkably extensive, and this work demonstrates that the exhaustive vetting process has achieved a model that is capable of making predictions that do not have fitting parameters. The authors also perform a thermodynamic analysis rather than limiting their treatment to a dynamic simulation that is inconsistent with the time scales of the actual experiment. This is particularly important, since it provides an illustrative example of how a detailed model (whether coarse grained or atomistic) needs to be analyzed to effectively connect to the experiments.

Previous theoretical efforts[9,10] to interpret measurements of single nucleosome unwrapping are limited to simple models that lack descriptive specificity, so the simplicity of these models limits the ability to make detailed conclusions about these experimental measurements. The current work is capable of resolving the basic physical picture that the previous works had established, namely, the impact of force on the large-scale unwrapping processes within a nucleosome. However, the current theory now opens the door to addressing more granular features that single-molecule measurements[2,3] are capable of resolving. Given the precision of such experiments, this level of detail in a theoretical model is now essential to extend our understanding of the specific interactions within the nucleosome (and in other related biological systems).

The work of Lequieu and co-workers represents a step toward the establishment of a predictive model for DNA and associated proteins in a variety of biologically relevant processes. There remains a need to have theoretical approaches at varying levels of detail, ranging from atomistic to massively coarse grained, and the development of multiscale approaches that can bridge length and time scales is crucial for interpreting experimental measurements of biological processes. The present work serves as an example of how to build a predictive model that can successfully interface with such experiments.

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