

Polymer physics across scales: Modeling the multiscale behavior of functional soft materials and biological systems ^{EP}

Cite as: J. Chem. Phys. **151**, 230902 (2019); <https://doi.org/10.1063/1.5126852>

Submitted: 05 September 2019 . Accepted: 12 November 2019 . Published Online: 18 December 2019

Andrew J. Spakowitz 

COLLECTIONS

 This paper was selected as an Editor's Pick



View Online



Export Citation



CrossMark

ARTICLES YOU MAY BE INTERESTED IN

Thermodynamics of chemical waves

The Journal of Chemical Physics **151**, 234103 (2019); <https://doi.org/10.1063/1.5126528>

Supercooled water: A polymorphic liquid with a cornucopia of behaviors

The Journal of Chemical Physics **151**, 210401 (2019); <https://doi.org/10.1063/1.5135706>

How surface-specific is 2nd-order non-linear spectroscopy?

The Journal of Chemical Physics **151**, 230901 (2019); <https://doi.org/10.1063/1.5129108>

Lock-in Amplifiers
up to 600 MHz



Zurich
Instruments



Watch



Polymer physics across scales: Modeling the multiscale behavior of functional soft materials and biological systems

Cite as: J. Chem. Phys. 151, 230902 (2019); doi: 10.1063/1.5126852

Submitted: 5 September 2019 • Accepted: 12 November 2019 •

Published Online: 18 December 2019



Andrew J. Spakowitz^{1,2,3,4,a)} 

AFFILIATIONS

¹Department of Chemical Engineering, Stanford University, Stanford, California 94305, USA

²Department of Materials Science and Engineering, Stanford University, Stanford, California 94305, USA

³Department of Applied Physics, Stanford University, Stanford, California 94305, USA

⁴Biophysics Program, Stanford University, Stanford, California 94305, USA

^{a)}E-mail: ajspakow@stanford.edu

ABSTRACT

Polymeric materials are ubiquitous in our daily lives, and they play a significant role in many technological applications. The general predictive framework for the behavior of soft polymeric materials can be divided into two vastly different approaches. Highly coarse-grained models capture polymers as flexible random walks, resulting in general predictions of physical behavior but lack chemical specificity. Detailed atomistic models contain molecular detail but are frequently computationally intractable for exhaustive materials discovery. In this perspective, we discuss theoretical models that successfully bridge these disparate approaches. We identify intermediate-scale physical models that are amenable to theoretical analyses while containing sufficient granular detail to capture a range of molecular-level processes. We then provide several problems in materials engineering and biological physics where multiscale physics is essential in their behavior.

Published under license by AIP Publishing. <https://doi.org/10.1063/1.5126852>

INTRODUCTION

Soft polymeric-materials modeling is currently split into two different philosophical approaches. The *coarse-grained approach* aims to capture the collective behavior of polymeric materials based on simple random-walk chain descriptions and phenomenological interaction parameters, resulting in broadly generalizable predictions that can be applied to many polymer systems. The *microscopic approach* strives for molecular realism by including physical interactions at the highest level of detail (down to atomistic), providing a purely predictive framework that captures molecular detail and the corresponding physical effects. Direct communication between these approaches is not straightforward. Given the inherent advantages and shortcomings of both approaches, there is a significant need to bridge these scales with a continuum of approaches that effectively dial the level of detail to suit the problem.

A range of problems involve soft materials whose collective behavior is critically dependent on microscopic physical effects.

Thus, predictive modeling of such materials requires a framework that reliably captures molecular detail while maintaining computational tractability. Two areas where molecular detail is essential are in the physical modeling of biological phenomena and functional soft materials. In this perspective, we discuss intermediate-scale polymer models that are amenable to the study of such problems and identify physical phenomena in such problems that necessitate this level of microscopic detail in their study.

SEMIFLEXIBILITY IS A UNIVERSAL INTERMEDIATE-SCALE PHYSICAL BEHAVIOR

Many foundational studies in polymer science leverage theoretical descriptions of polymers as random walks.^{1–3} This successful approach relies heavily on the universal trend for any microscopic physical model to coarse grain to a Gaussian random walk at sufficiently large length scales—a consequence of the central limit

theorem. Although this approach is attractive in resolving the dominant physical behavior at large scales, it does not retain the underlying molecular detail that distinguishes one polymeric material from another. All molecular detail is subsumed into a couple of

phenomenological parameters. Since the Gaussian chain model is universal, this description can be viewed as a fundamentally distinct polymer model from all other approaches that aim to capture the microscale behavior of a specific polymer. Thus, microscale models,

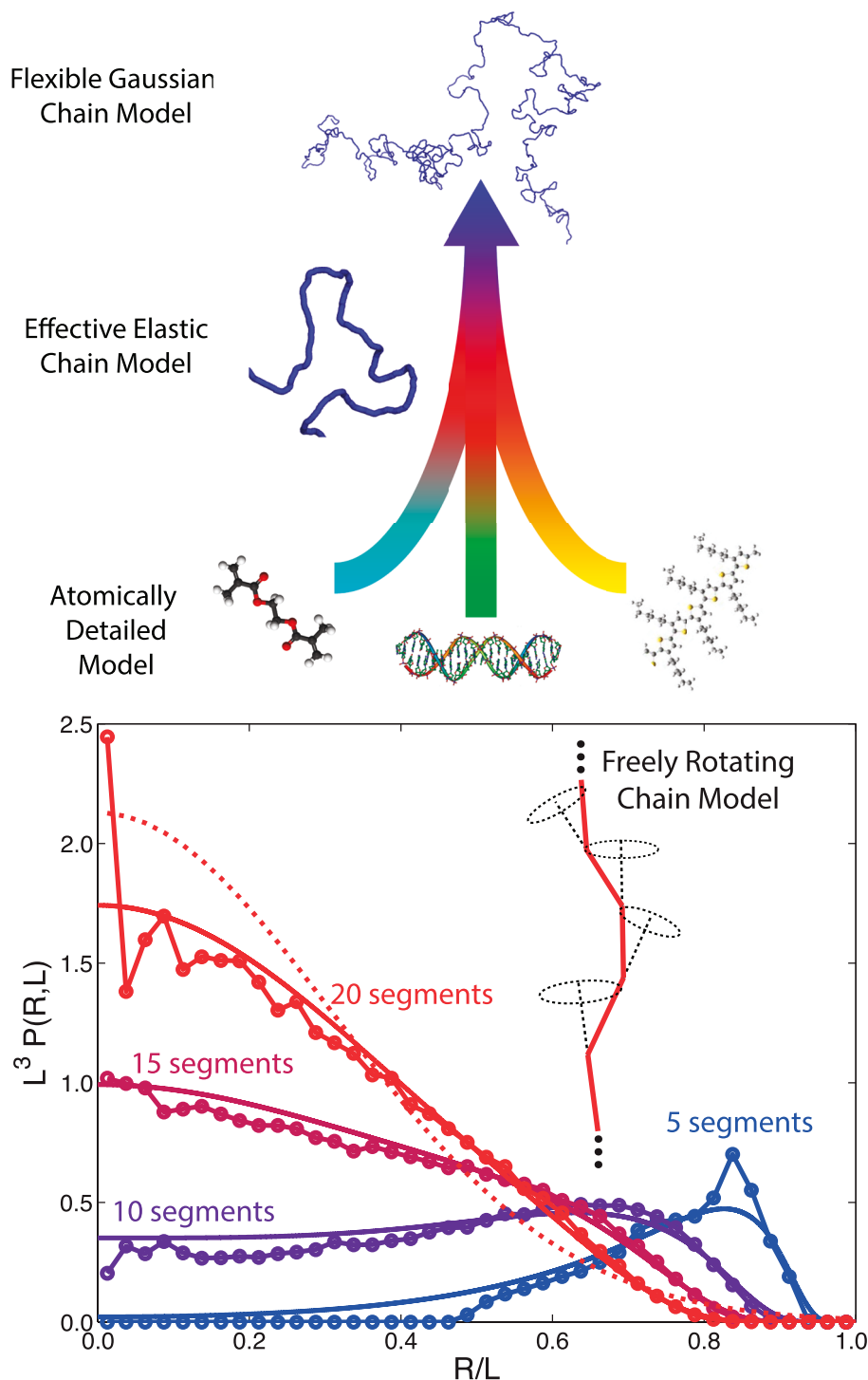


FIG. 1. Demonstration of a microscopic model (freely rotating chain model) behaving as an effective elastic chain at intermediate scales before approaching the Gaussian chain model. The dots represent results from Monte Carlo simulations of the freely rotating chain model for 5, 10, 15, and 20 segments (depicted in the inset), and we show the end distribution function for the worm-like chain model (solid curves)^{21,23–25} and the Gaussian chain model (dotted curve).

including fully atomistic descriptions, generally are viewed as complementary or competing descriptions of a specific system, and universal physical understanding cannot be easily extracted from such a study.

Recent work^{4–6} provides insight into exactly how microscale descriptions tend toward a Gaussian random walk. As the chain length increases, a polymer chain exhibits an intermediate-scale physical behavior where decaying structural correlations result in semiflexibility (see top image of Fig. 1). The prevailing model that captures semiflexibility is the wormlike chain model,^{7,8} which has its roots in elasticity theory.^{9,10} Superficially, this model describes an elastic thread that opposes bending deformation and is subjected to thermal fluctuations. However, an alternative view of an effective elastic chain (e.g., the wormlike chain model) is as a universal intermediate-scale model.

To demonstrate the utility of modeling polymers as effective elastic chains, Fig. 1 shows results for the statistical distribution for the freely rotating chain model (fixed intersegment angle of 45°). The dots are results from Monte Carlo simulations for 5, 10, 15, and 20 segments, which correspond to 0.87, 1.73, 2.60, and 3.47 Kuhn lengths, respectively. The statistical behavior of the wormlike chain model has been determined using approaches that leverage approximate representations,^{11–14} asymptotic solutions,^{15–18} and analytical techniques.^{19–25} The solid curves in Fig. 1 show our analytical solutions for the wormlike chain model,^{21,23–25} and the dashed curve for 3.47 Kuhn lengths is the distribution for the Gaussian chain model at this length. The freely rotating chain model plays the role of any detailed level of description, but an atomistic simulation would work as well. Note that these distributions converge at intermediate scales long before either distribution approaches the Gaussian chain model, as shown by the behavior at 20 segments. These results demonstrate that semiflexibility, as captured using an effective elastic chain model, serves as a bridge in the physical behavior between the large-length-scale Gaussian chain model and a detailed microscopic model (i.e., one with atomistic detail).

In a range of polymer applications, intermediate length-scale physical behavior leads to distinct phenomena that cannot be resolved without addressing this scale of physics. Therefore, it is essential to have a range of modeling approaches that are capable of incorporating molecular behavior at varying levels of detail, spanning the range of behavior over the spectrum shown in Fig. 1.

BIOLOGICAL SYSTEMS INVOLVE PHYSICAL PHENOMENA OVER A VAST RANGE OF SCALES

Every living organism is composed of soft polymeric materials, and every biological process involves the physical interaction and assembly of biopolymers. In this regard, virtually every biotechnology application and therapeutic intervention is fundamentally governed by the physical behavior of polymer molecules and assemblies. Admittedly, historical strides in our fundamental biological understanding and in human health have not typically relied on detailed physical characterization and models of the underlying molecular behavior. However, current progress in establishing a quantitative picture of the behavior in living systems necessitates the development of physically motivated models that capture the molecular behavior of biopolymer systems while maintaining computational tractability.

For example, the organization and dynamics of chromosomal DNA is essential to the biological function of the genome. DNA is not simply a repository of information through the base pair sequence. Rather, the multiscale organization of DNA and its associated proteins plays a key role in regulating protein expression, genetic recombination, and many other critical cellular processes. Our understanding of the physical behavior of DNA is dramatically influenced by coarse-grained models, particularly those rooted in the wormlike chain model.^{16,26–28} The consequence of the molecular mechanics of the DNA strand on various biological processes is a major focus of research in biophysics.

Figure 2 shows three biological processes where chromosomal DNA is manipulated and accessed at the nanometer length scale. At these scales, detailed molecular physics must be captured in theoretical treatments that capture the dominant behavior. The top image shows the local packaging of DNA into a nucleosome core particle,²⁹ where 147 base pairs are wrapped around a set of 8 histone proteins. Single-molecule experiments provide direct measurement of the physical forces that drive DNA packaging,^{30–32} and physical modeling of the unwrapping process provides a quantitative determination of the molecular-scale interactions between DNA and histone proteins.^{33–35}

The mechanical properties of DNA influence the positioning of nucleosomes,³⁶ which dramatically impacts the large-scale organization of chromatin.^{37,38} The physical packaging of DNA into a nucleosome influences the ability for proteins, such as RNA polymerase (middle image),⁶ to access the genomic information. The formation of regulatory complexes requires the spatial coordination of distal genomic sites, e.g., the binding of Lac repressor to its two operators^{39,40} serves as a prototypical regulatory complex. The physical looping of DNA into a regulatory complex involves the interplay between the mechanical response of the DNA and the entropic cost of loop formation.^{26,40–43} At slightly larger scales, proteins that seek to find specific target sites on DNA (bottom image) explore large regions of the chromosome while locally interrogating the DNA strand.^{44–46}

Historically, the central dogma of genetics asserted that DNA sequence holds all of the information that orchestrates cellular function. However, two cells with identical genetic information may have vastly different behavior due to chemical modifications in their genome packaging. This notion of *epigenetic regulation* represents a paradigm change in how we think about genetic traits. Epigenetic regulation is at the heart of numerous life-threatening diseases such as many cancers, developmental disorders, obesity, and diabetes.⁴⁷

Bridging the gap between the molecular-level packaging of DNA and genome-scale processes involving chromatin requires an in-depth quantitative prediction of chromosomal organization and its dependence upon protein manipulations and modifications. Chromosomal DNA within a nucleus segregates into condensed *heterochromatin* regions that are not expressed and uncondensed *euchromatin* regions that are available for protein expression (see left image of Fig. 3). The large-scale segregation of chromosomal DNA represents an example of a phase segregation within a living cell. Thus, chromosomal organization can be interpreted using the foundational principles established in condensed matter physics.^{48–53}

Genome-scale models predict chromosomal organization (right image of Fig. 3) while accounting for the local protein-DNA

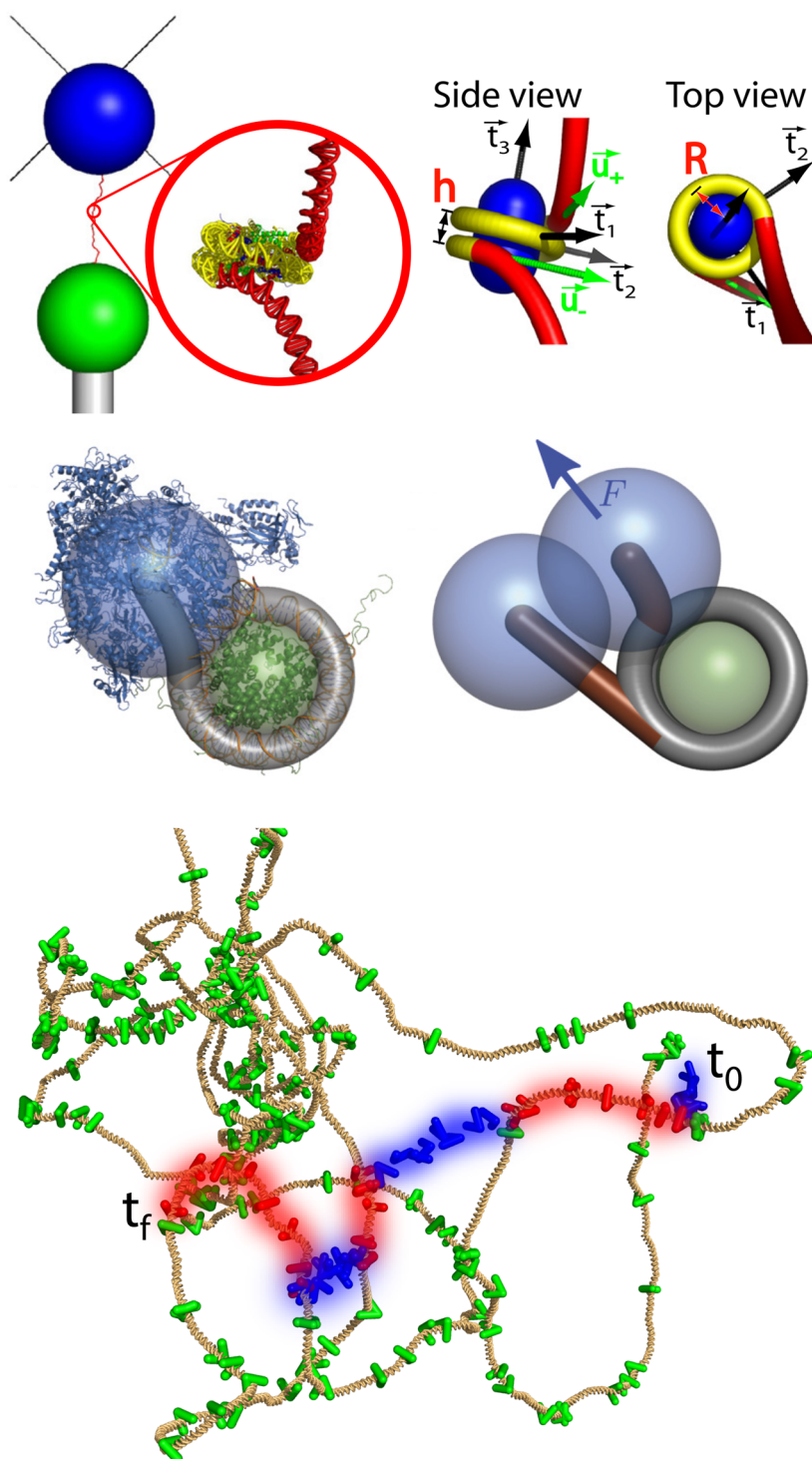


FIG. 2. Three biological processes that involve nanoscale physical manipulation of DNA. The top image shows the unraveling of a nucleosome core particle,^{33–35} as measured using single-molecule force spectroscopy.^{30–32} Reprinted with permission from B. Sudhanshu et al., PNAS, **108**(5), 1885 (2011). Copyright 2011 Author(s), licensed under a Creative Commons Attribution License.³³ The middle image shows RNA polymerase (blue) transcribing through a nucleosome (green).¹⁶⁸ Reprinted with permission from E. F. Koslover and A. J. Spakowitz, Phys. Rev. E **86**, 011906 (2012). Copyright 2012 American Physical Society.¹⁶⁸ The bottom image shows the search process of a protein seeking a specific target site on DNA.^{44–46} The protein cycles through being unbound from the DNA (blue) and nonspecifically bound (red) from the initial time t_0 to the final time t_f . Other bound proteins that impede the sliding motion of the protein are depicted in green.

interactions that drive condensation.^{49,53} Heterochromatin protein 1 (HP1) accumulates in the condensed heterochromatin regions,^{54,55} dynamically binding to nucleosomes that are methylated at lysine-9 of the histone protein H3 (H3K9).^{56,57} For a fixed methylation

profile, site-specific HP1 binding is a determinant of heterochromatin formation.⁵⁵ Theoretical modeling of epigenetic regulation acts as a foundation for addressing genome-scale segregation of chromosomal DNA based on physical interactions that occur on

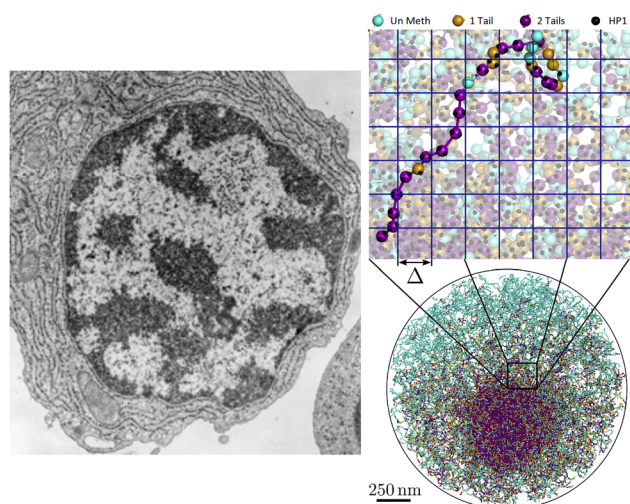


FIG. 3. Electron micrograph of nucleus (left image) shows heterochromatin (dark) and euchromatin (light) (Adapted from UCSF School of Medicine, *Prologue Histology Resource*). Coarse-grained theoretical modeling (right image) exhibits segregation between heterochromatin (blue) and euchromatin (red), bridging histone modifications to genome-scale organization.⁴⁹ Reprinted with permission from Q. MacPherson et al., PNAS, **115**(50), 12739 (2018). Copyright 2018 Author(s), licensed under a Creative Commons Attribution License.^{49,53}

the length scale of individual nucleosomes. Therefore, the collective condensation of genomic regions into chromosomal compartments is dictated by detailed sequence of chemical marks and interactions at the molecular level.

There are numerous advances made in experimental characterization of the 3D genome,^{58–61} resulting in a wealth of data to be explored. In particular, experimental measurements of genome contact (i.e., which chromosomal regions contact each other) provide a powerful approach to assessing theoretical models of chromosomal DNA.^{48–53} An enduring problem in this field is to establish a

connection between the genome organization and the expression of the genetic material. The physical segregation is shown to influence protein expression and serves as a physical basis for epigenetic regulation. An ongoing effort in this field is to connect the physical organization of chromosomal DNA with its function in a living cell.

FUNCTIONAL SOFT MATERIALS WHERE SEMIFLEXIBILITY IS PIVOTAL

Many materials applications involve physical processes that occur at length scales where the polymer chains exhibit conformation correlations associated with semiflexibility. Functional soft materials that exploit molecular-level physical phenomena offer new avenues for materials applications. However, establishing a predictive understanding of behavior in functional soft materials necessitates theoretical models that capture their multiscale and multiphysics behavior. Here, we discuss two soft materials—semiconducting polymers and polymer electrolytes—that exhibit complex mesoscale behavior.

Semiconducting polymers are a class of materials that are composed of polymers with π conjugation along the backbone to enable charge transport and sidechain modifications that control solubility. Both of these features confer elastic rigidity to the molecular chains. These materials play an important role in a wide range of optical and electronic material applications^{62–67} and organic solar-cell technologies.^{68–70} It is widely accepted that molecular ordering and mesoscale morphology impact charge transport in such devices. However, connecting molecular order to device performance is difficult due to a major need for characterization of conjugated-polymer materials across a range of length and time scales and a multiscale theory of charge transport in semiconducting polymers that captures essential transport processes at various scales.

Theoretical modeling of charge transport [see Fig. 4(a)]^{71–73} captures the complex trajectory of a charge undergoing intrachain and interchain hopping through an amorphous semiconducting-polymer environment. This theory elucidates the impact of polymer conformations on charge mobility and demonstrates that

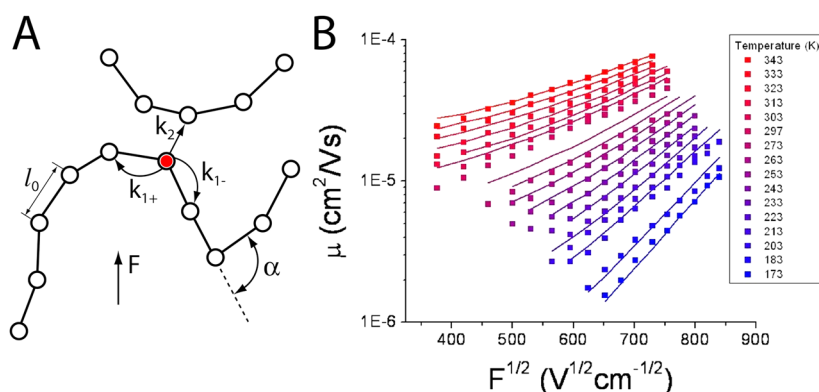


FIG. 4. Coarse-grained modeling of charge transport in conjugated polymer materials. A coarse-grained representation (a) of the essential intra- and interchain charge transport provides a predictive approach to modeling charge mobility (b). The chain configuration dictates field-dependent, intrachain hopping rates (k_{1-} and k_{1+}) to neighboring sites on the chain, and the interchain hopping rate defines the time scale of long-range charge mobility. The comparison between theoretical (solid curves) and experimentally observed (dots)¹⁶⁹ field-dependent mobility μ as a function of external field F (b) shows the Poole-Frenkel behavior at intermediate field values.

considerable improvements to device performance can be made by alignment of conjugated polymer chains. This puts an emphasis on engineering molecules and processing materials with control over molecular-level alignment. Current progress in improving the efficiency of conducting polymer devices has primarily come from synthesizing increasingly complex molecules with specific electronic properties. This proliferation of materials underscores the need for a predictive theory of semiflexible polymer thermodynamics in order to determine whether the microstructure that arises from a new molecule will be suitable for assembly and processing of new semiconducting materials with desirable physical properties.

A second example where mesoscale physics play a major role is in the thermodynamic behavior of polyelectrolyte solutions and materials.^{74–85} Polyelectrolyte solutions containing a mixture of model polyelectrolytes [positively charged poly(L-lysine) and negatively charged poly(L-glutamic acid)] in the absence of salt exhibit a liquid-liquid phase separation between a polymer-rich phase (associated with polyelectrolyte complexation) and a polymer-lean supernatant phase.⁸⁰ Small-angle X-ray scattering experiments of a semidilute solution of poly(L-lysine) at various polymer concentrations exhibit a peak at all concentrations that shift to higher q -values (decreasing length) with increasing polymer concentration. The associated correlation lengths from these measurements range from 0.5 nm to 3 nm over the range of polymer concentrations. The reported correlation lengths are comparable in scale to the reported Kuhn lengths that range from 1 nm to 7 nm.⁸⁰ At these length scales, charge correlations and solvent/ion structuring play a major role in the thermodynamic behavior and theoretical models that address charge correlations and dielectric inhomogeneity provide guidance on the impact of such granular effects.^{86–97} This example demonstrates that the essential physics for this problem occurs at length scales where the polymer rigidity is central to the behavior.

The thermodynamic behavior of polyelectrolytes has been analyzed based on flexible-chain theories,^{98–114} which provides fundamental insight into the behavior of polyelectrolyte solutions. Simulations provide a valuable approach to incorporating molecular detail into the study of polyelectrolyte solutions.^{115–121} However, there is a need for theoretical models that aim to capture semiflexibility in the study of polyelectrolytes. Previous theoretical efforts recognize this issue, and semiflexibility has been incorporated into field-theoretic treatments.^{87,89,122} Further development of a comprehensive treatment of semiflexible chain statistics that permits evaluation of chain correlations (up to quartic order in the density) is needed to address fluctuation effects in polyelectrolyte materials.

ESTABLISHING DESIGN PRINCIPLES FOR THE DISCOVERY OF SOFT MATERIALS

Phenomenological treatments play a crucial role in our understanding of soft polymer materials. Microphase segregation of block copolymers^{123–133} and random copolymers^{134–145} serves as an archetypical example of a research area in polymer science that is dramatically influenced by phenomenological theory. Block copolymers¹⁴⁶ are a class of soft polymeric materials that are able to self-assemble into a variety of mesostructured phases. This is achieved

when polymer blocks that would prefer to demix are covalently linked in a chain such that the blocks cannot escape each other. The resulting interfaces form mesoscale domains whose spatial dimensions and organization are dictated by the length of the blocks and the strength of demixing. Such microphases have a broad range of applications in energy technologies, including lithium ion batteries, fuel cell membranes, nanoparticle synthesis, nanolithography, and CO₂ separation.

The simplest example is the A - B diblock with lengths N_A and N_B of A and B blocks, defined by the fraction $f_A = N_A/(N_A + N_B)$. The self-assembly of this system into ordered microstructures has been extensively studied experimentally and theoretically.¹⁴⁶ The observed phase diagrams show that altering the A fraction f_A and increasing the strength of demixing (by experimentally lowering the temperature to raise the Flory-Huggins interaction parameter χ) results in a range of microphases, including planar lamellae (L), continuous gyroid (G), cylinders (C), and spheres (S). Theoretical phase diagrams found using self-consistent field theory (SCFT) exhibit remarkable agreement with the experimental phase diagrams for poly(isoprene-styrene) (determined using X-ray scattering). Each microphase is attractive for specific materials applications. For example, randomly oriented lamellae^{147,148} and continuous gyroid phases^{149,150} are particularly attractive for applications that require percolating structures, including pathways for ion transport in batteries and fuel cell membranes. Notably, the conditions where the gyroid phase prevails are extremely narrow. In fact, the gyroid phase was not found experimentally until the theoretical phase diagram revealed this specific microphase structure.¹⁴⁶

All theories mentioned above assume random-walk conformations of chains, which is only a valid assumption for materials composed of sufficiently long copolymer chains.¹²³ Ostensibly, the Kuhn length b identifies a length scale where the polymer transitions from a rigid chain to a flexible random walk, but the range and impact of the crossover between these two limiting behaviors are not immediately clear. To find the effect of chain semiflexibility on the phase behavior of diblock copolymers, past studies use SCFT of wormlike chains,^{151–157} neglecting concentration fluctuations. As the molecular weight of diblock copolymers is reduced, it is important to realize that not only the chain semiflexibility but also the accompanying concentration fluctuations need to be considered.

The top plot of Fig. 5 shows analytical results for the stability diagram (marking the order-disorder transition or ODT) of a semiflexible diblock copolymer based on a quartic-order expansion of the free energy, predicting the impact of concentration fluctuations based on a one-loop renormalization procedure.¹⁵⁸ The polymer structure factor for these predictions utilizes analytical results for the wormlike chain model,^{21,23–25} and the mean-field predictions (i.e., $\alpha \rightarrow \infty$) in Fig. 5 are consistent with previous treatments of semiflexible copolymers.^{152,153,159,160} We also show predictions for flexible polymer chains (dashed curves),¹²⁶ which show a monotonic elevation of the χ parameter at the ODT with decreasing chain length. Polymer semiflexibility and concentration fluctuations move the stability curve in opposite directions, and our current understanding of their combined influence cannot identify the direction of change (much less the magnitude). Thus, semiflexibility and concentration fluctuations need to be accurately captured to make an accurate prediction of the phase behavior in these systems.

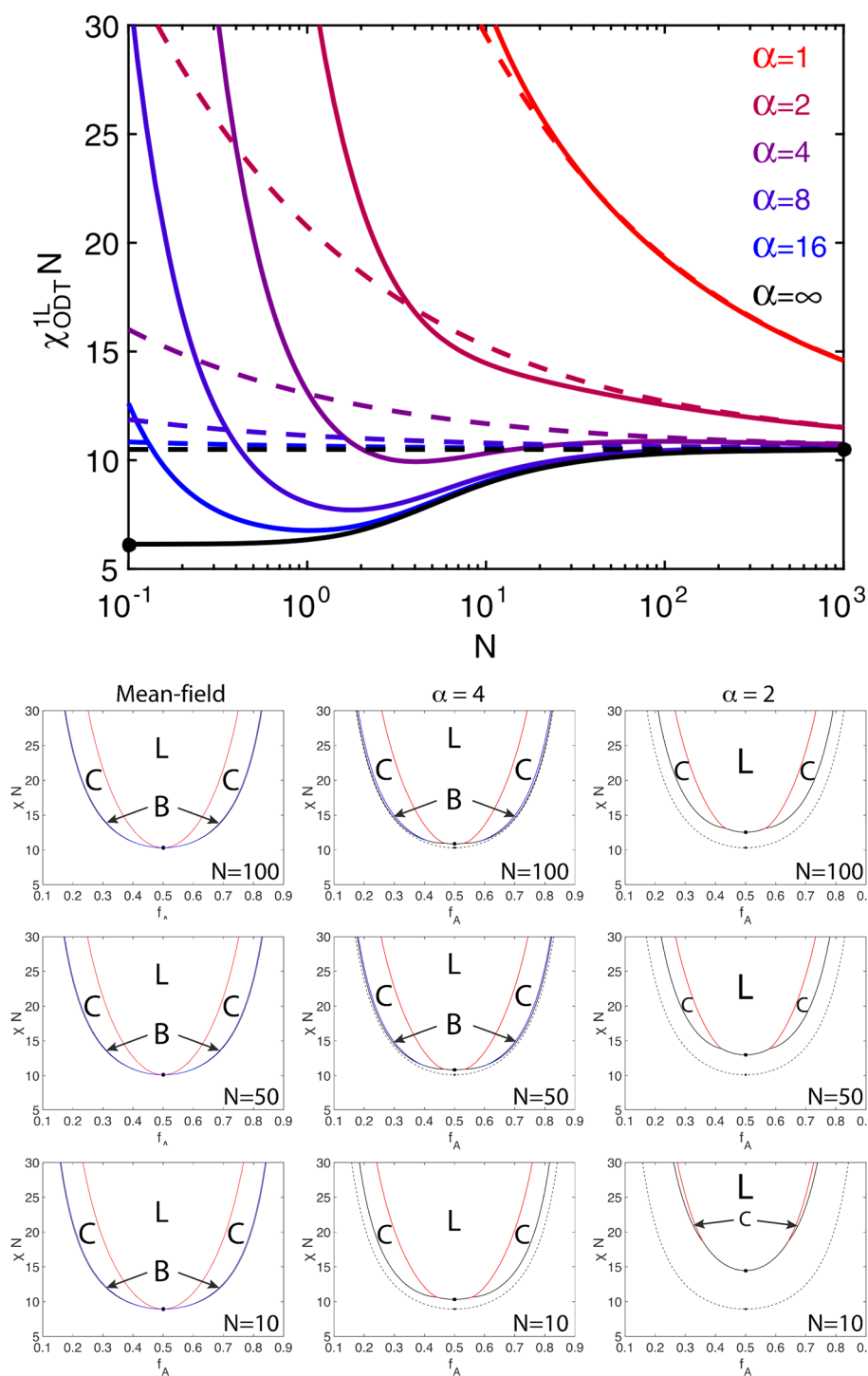


FIG. 5. Semiflexible diblock copolymer stability diagram based on a renormalization group treatment of semiflexible copolymer melts.¹⁵⁸ The top image shows theoretical predictions for thermodynamic stability of a semiflexible diblock copolymer (solid curves) for varying chain length $N = L/b$ (or number of Kuhn lengths). The bottom plots show phase diagrams of diblock copolymers with varying molecular weights N and monomer aspect ratio α . Letters indicate lamellar (L), body-centered cubic (B), and hexagonally packed cylinder (C) phases. Reprinted with permission from S. Mao, et al., *Phys. Rev. Lett.* **120**, 067802 (2018). Copyright 2018 American Physical Society.¹⁵⁸

The bottom plots of Fig. 5 show the phase diagrams for diblock copolymers with varying fraction of the A block f_A for chain lengths $N = 10, 50$, and 100 and $\alpha \rightarrow \infty$ (mean-field), $\alpha = 4$, and $\alpha = 2$. The phase diagram for $N \approx 100$ to $N \approx 10$ (note, $N = L/b$ is the number

of Kuhn lengths) exhibits considerable reduction in the ODT or the spinodal χ_s . To put this in perspective, even the seemingly modest change in χ_s from $N = 200$ to $N = 11$ in Fig. 5 corresponds to an approximate elevation of 50°C in the temperature at the ODT. The

treatment of fluctuations has been performed using the renormalization group^{144,158} and simulations,^{145,161} resulting in similar trends as shown in Fig. 5.

There is currently a need to determine the combined effect of both semiflexibility and concentration fluctuations on the self-assembly of copolymer and liquid crystalline materials. Furthermore, correlations within polyelectrolyte solutions play an important role in their thermodynamic behavior, and further work is needed to tackle such effects. The trend in many technological applications of copolymer materials is to achieve smaller feature sizes, and with decreasing size scale, the impact of semiflexibility and detailed molecular interactions is increasingly important to capture in theoretical models.

CONCLUSIONS

In this perspective, we discuss the development of intermediate-scale models for polymeric materials that systematically incorporate molecular detail while maintaining a computationally tractable approach. One advantage of coarse-grained descriptions is the ability to draw general conclusions that are transferrable to a wide range of problems. Thus, an intermediate-scale treatment should provide a level of treatment that captures essential microscopic physics at the simplest level of description that still captures collective behavior.

Figure 1 provides insight into the progression of polymer behavior across varying length scales. Atomically detailed models aim to capture specific chemical detail at the atomistic level—an approach that may be predictive for specific materials applications. Each material requires the development of a specific model, and general physical principles are difficult to extract from such treatments that can be applied across material classes. However, detailed models undergo a transition through behaving as coarse-grained, effective elastic chains at intermediate scales, suggesting that there is an intermediate scale of treatment that can retain some level of molecular detail. Since the Gaussian-chain limit no longer retains molecular detail, the goal of an intermediate-scale model is to incorporate the essential molecular granularity while capturing large-scale physical behavior. The general treatment of polymer molecules as an effective elastic chain serves as a generalizable framework for capturing this intermediate scale of physical behavior.

The implementation of semiflexible polymer models (such as the wormlike chain model) into simulation and theory is challenging due to the added complexity associated with capturing the local orientation degrees of freedom. Field theoretic methods such as SCFT of wormlike chains^{151–157} involve significant technical challenges relative to their Gaussian-chain analogs. The publicly available code for SCFT for flexible polymers (for example, code found at <http://pscf.cems.umn.edu/pscf> and described in Ref. 162) is a valuable resource for materials discovery. Although such a public resource would be valuable for the case of SCFT of wormlike chains, we argue in this perspective that concentration fluctuations play a significant role under conditions where semiflexibility is prevalent. Thus, simulations that incorporate concentration fluctuations based on a field-theoretic framework^{163–167} would be valuable for intermediate-scale physical phenomena discussed in this perspective. We have developed the code for particle-field Monte Carlo simulations that is available on our research group

website (<http://web.stanford.edu/~ajspakow/>), which has been used to address semiflexible copolymer assembly^{145,161} and chromosomal organization.⁵³ Further development of computational packages that facilitate the broad study of these problems is needed.

We proceed to discuss several problems in functional soft materials and biological physics that are modeled using coarse-grained descriptions using an intermediate scale of description. These problems involve very different classes of polymeric materials, and atomically detailed models to predict their behavior would necessitate the development of individually vetted approaches that are material specific. In this perspective, we discuss theoretical models that are rooted in an intermediate scale of description and are amenable to the study of these disparate problems, and general physical conclusions can be drawn. For example, the study of chromosomal organization (see Fig. 3) is informed by the study of copolymer materials (see Fig. 5), since the basic physical principles that drive segregation are common to both problems. Notably, molecular detail introduces effects that are not easily extrapolated from the flexible limit (as shown in Fig. 5), requiring fundamental studies of the impact of intermediate-scale physics on collective behavior.

The foundational principles of polymer physics can be broadly applied across a range of technological applications and scientific problems, and predictive understanding of the physical behavior of polymeric materials hinges on the application of coarse-grained descriptions. As such, it is desirable to establish a continuum of models that systematically incorporate molecular detail while retaining a connection to the foundational work based on flexible polymer-chain descriptions. With increased computational power, atomistic modeling is able to access larger systems, enabling the simulation of a broader range of materials. However, the extraction of general physical principles from simulations necessitates an intermediate-scale description. As such, many physical problems involving functional soft materials and living systems reside at the mesoscale. Further development of predictive models to tackle these problems requires a level of granular description that captures behavior at this scale.

There is a common thread among the range of problems discussed in this perspective. In each case, collective behavior is governed by physical processes at the nanoscale that cannot be captured by a flexible-chain description, where all microscale physics is encapsulated within a small set of phenomenological parameters. For example, protein action at the nanometer scale in living systems and intra- and interchain transport of charge in conjugated polymers both involve microscopic physical behavior that requires a detailed theoretical description to adequately capture large-scale behavior. The expansion of polymeric materials into new technological areas increasingly involves functional capabilities of molecular chains that involve novel physical effects at the nanoscale. Theoretical guidance in the development of functional soft materials is increasingly important due to the complexity in predicting behavior in these complex systems.

ACKNOWLEDGMENTS

We are grateful to Rob Riggelman for helpful discussions. This work was supported by the NSF program “Condensed Matter and Materials Theory” (Grant No. 1234298).

REFERENCES

- ¹P. J. Flory, *Principles of Polymer Chemistry* (Cornell University Press, 1953).
- ²P.-G. De Gennes, *Scaling Concepts in Polymer Physics* (Cornell University Press, 1979).
- ³M. Doi and S. F. Edwards, *The Theory of Polymer Dynamics* (Oxford University Press, 1988), Vol. 73.
- ⁴E. F. Koslover and A. J. Spakowitz, "Systematic coarse-graining of microscale polymer models as effective elastic chains," *Macromolecules* **46**, 2003–2014 (2013).
- ⁵E. F. Koslover and A. J. Spakowitz, "Discretizing elastic chains for coarse-grained polymer models," *Soft Matter* **9**, 7016–7027 (2013).
- ⁶E. F. Koslover and A. J. Spakowitz, "Multiscale dynamics of semiflexible polymers from a universal coarse-graining procedure," *Phys. Rev. E* **90**, 013304 (2014).
- ⁷N. Saitō, K. Takahashi, and Y. Yunoki, "The statistical mechanical theory of stiff chains," *J. Phys. Soc. Jpn.* **22**, 219–226 (1967).
- ⁸O. Kratky and G. Porod, "Röntgenuntersuchung gelöster fadenmoleküle," *Recueil Travaux Chimiques Pays-Bas* **68**(12), 1106–1122 (1949).
- ⁹L. D. Landau and E. Lifshitz, *Course of Theoretical Physics, Theory of Elasticity* Vol. 7, 3rd ed. (Elsevier Butterworth Heinemann, 1986).
- ¹⁰A. E. H. Love, *A Treatise on the Mathematical Theory of Elasticity* (Cambridge University Press, 2013).
- ¹¹J. B. Lagowski, J. Noolandi, and B. Nickel, "Stiff chain model—functional integral approach," *J. Chem. Phys.* **95**, 1266–1269 (1991).
- ¹²K. F. Freed, "Functional integrals and polymer statistics," *Adv. Chem. Phys.* **22**, 1–128 (1972).
- ¹³D. Thirumalai and B.-Y. Ha, "Semiflexible chains under tension," *J. Chem. Phys.* **106**, 4243 (1997).
- ¹⁴K. Ghosh, G. A. Carri, and M. Muthukumar, "Configurational properties of a single semiflexible polyelectrolyte," *J. Chem. Phys.* **115**, 4367–4375 (2001).
- ¹⁵H. E. Daniels, "XXI.—The statistical theory of stiff chains," *Proc. R. Soc. Edinburgh, Sect. A: Math. Phys. Sci.* **63**, 290–311 (1952).
- ¹⁶H. Yamakawa and T. Yoshizaki, *Helical Wormlike Chains in Polymer Solutions* (Springer, 1997), Vol. 1.
- ¹⁷H. Yamakawa and M. Fujii, "Statistical mechanics of helical wormlike chains. I. Differential equations and moments," *J. Chem. Phys.* **64**, 5222–5228 (1976).
- ¹⁸J. Wilhelm and E. Frey, "Radial distribution function of semiflexible polymers," *Phys. Rev. Lett.* **77**, 2581 (1996).
- ¹⁹S. Stepanow and G. M. Schütz, "The distribution function of a semiflexible polymer and random walks with constraints," *Europhys. Lett.* **60**, 546 (2002).
- ²⁰J. Samuel and S. Sinha, "Elasticity of semiflexible polymers," *Phys. Rev. E* **66**, 050801 (2002).
- ²¹A. J. Spakowitz and Z.-G. Wang, "Exact results for a semiflexible polymer chain in an aligning field," *Macromolecules* **37**, 5814–5823 (2004).
- ²²A. Prasad, Y. Hori, and J. Kondev, "Elasticity of semiflexible polymers in two dimensions," *Phys. Rev. E* **72**, 041918 (2005).
- ²³A. J. Spakowitz and Z.-G. Wang, "End-to-end distance vector distribution with fixed end orientations for the wormlike chain model," *Phys. Rev. E* **72**, 041802 (2005).
- ²⁴A. J. Spakowitz, "Wormlike chain statistics with twist and fixed ends," *Europhys. Lett.* **73**, 684 (2006).
- ²⁵S. Mehraeen, B. Sudhanshu, E. F. Koslover, and A. J. Spakowitz, "End-to-end distribution for a wormlike chain in arbitrary dimensions," *Phys. Rev. E* **77**, 061803 (2008).
- ²⁶J. Shimada and H. Yamakawa, "Ring-closure probabilities for twisted wormlike chains. Application to DNA," *Macromolecules* **17**, 689–698 (1984).
- ²⁷J. F. Marko and E. D. Siggia, "Statistical mechanics of supercoiled DNA," *Phys. Rev. E* **52**, 2912–2938 (1995).
- ²⁸J. D. Moroz and P. Nelson, "Torsional directed walks, entropic elasticity, and DNA twist stiffness," *Proc. Natl. Acad. Sci. U. S. A.* **94**, 14418–14422 (1997).
- ²⁹K. Luger, A. W. Mader, R. K. Richmond, D. F. Sargent, and T. J. Richmond, "Crystal structure of the nucleosome core particle at 2.8 Å resolution," *Nature* **389**, 251–260 (1997).
- ³⁰B. D. Brower-Toland, C. L. Smith, R. C. Yeh, J. T. Lis, C. L. Peterson, and M. D. Wang, "Mechanical disruption of individual nucleosomes reveals a reversible multistage release of DNA," *Proc. Natl. Acad. Sci. U. S. A.* **99**, 1960–1965 (2002).
- ³¹S. Mihadja, A. J. Spakowitz, Y. Zhang, and C. Bustamante, "Effect of force on mononucleosomal dynamics," *Proc. Natl. Acad. Sci. U. S. A.* **103**, 15871–15876 (2006).
- ³²S. Mochrie, A. Mack, D. Schlingman, R. Collins, M. Kamenetska, and L. Regan, "Unwinding and rewinding the nucleosome inner turn: Force dependence of the kinetic rate constants," *Phys. Rev. E* **87**, 012710 (2013).
- ³³B. Sudhanshu, S. Mihadja, E. Koslover, S. Mehraeen, C. Bustamante, and A. Spakowitz, "Tension-dependent structural deformation alters single-molecule transition kinetics," *Proc. Natl. Acad. Sci. U. S. A.* **108**, 1885–1890 (2011).
- ³⁴I. Kulić and H. Schiessel, "DNA spools under tension," *Phys. Rev. Lett.* **92**, 228101 (2004).
- ³⁵J. Lequeieu, A. Córdoba, D. C. Schwartz, and J. J. de Pablo, "Tension-dependent free energies of nucleosome unwrapping," *ACS Cent. Sci.* **2**, 660–666 (2016).
- ³⁶M. Zuddam, R. Everaers, and H. Schiessel, "Physics behind the mechanical nucleosome positioning code," *Phys. Rev. E* **96**, 052412 (2017).
- ³⁷J. Lequeieu, A. Córdoba, J. Moller, and J. J. de Pablo, "1CPN: A coarse-grained multi-scale model of chromatin," *J. Chem. Phys.* **150**, 215102 (2019).
- ³⁸J. Moller, J. Lequeieu, and J. J. de Pablo, "The free energy landscape of internucleosome interactions and its relation to chromatin fiber structure," *ACS Cent. Sci.* **5**, 341–348 (2019).
- ³⁹Y.-J. Chen, S. Johnson, P. Mulligan, A. J. Spakowitz, and R. Phillips, "Modulation of DNA loop lifetimes by the free energy of loop formation," *Proc. Natl. Acad. Sci. U. S. A.* **111**, 17396–17401 (2014).
- ⁴⁰P. J. Mulligan, Y.-J. Chen, R. Phillips, and A. J. Spakowitz, "Interplay of protein binding interactions, DNA mechanics, and entropy in DNA looping kinetics," *Biophys. J.* **109**, 618–629 (2015).
- ⁴¹T. Sutthibutpong, C. Matek, C. Benham, G. G. Slade, A. Noy, C. Laughton, J. P. K. Doye, A. A. Louis, and S. A. Harris, "Long-range correlations in the mechanics of small DNA circles under topological stress revealed by multi-scale simulation," *Nucleic Acids Res.* **44**, 9121–9130 (2016).
- ⁴²E. Pilyugina, B. Krajina, A. J. Spakowitz, and J. D. Schieber, "Buckling a semiflexible polymer chain under compression," *Polymers* **9**, 99 (2017).
- ⁴³R. M. Harrison, F. Romano, T. E. Ouldrige, A. A. Louis, and J. P. Doye, "Identifying physical causes of apparent enhanced cyclization of short DNA molecules with a coarse-grained model," *J. Chem. Theory Comput.* **15**, 4660–4672 (2019).
- ⁴⁴M. A. D. de la Rosa, E. F. Koslover, P. J. Mulligan, and A. J. Spakowitz, "Dynamic strategies for target-site search by DNA-binding proteins," *Biophys. J.* **98**, 2943–2953 (2010).
- ⁴⁵E. F. Koslover, M. A. D. de la Rosa, and A. J. Spakowitz, "Theoretical and computational modeling of target-site search kinetics *in vitro* and *in vivo*," *Biophys. J.* **101**, 856–865 (2011).
- ⁴⁶E. F. Koslover, M. D. de la Rosa, and A. J. Spakowitz, "Crowding and hopping in a protein's diffusive transport on DNA," *J. Phys. A: Math. Theor.* **50**, 074005 (2017).
- ⁴⁷T. J. Moss and L. L. Wallrath, "Connections between epigenetic gene silencing and human disease," *Mutat. Res.* **618**, 163–174 (2007).
- ⁴⁸D. Jost, P. Carrivain, G. Cavalli, and C. Vaillant, "Modeling epigenome folding: formation and dynamics of topologically associated chromatin domains," *Nucleic Acids Res.* **42**, 9553–9561 (2014).
- ⁴⁹P. J. Mulligan, E. F. Koslover, and A. J. Spakowitz, "Thermodynamic model of heterochromatin formation through epigenetic regulation," *J. Phys.: Condens. Matter* **27**, 064109 (2015).
- ⁵⁰M. Di Pierro, B. Zhang, E. L. Aiden, P. G. Wolynes, and J. N. Onuchic, "Transferable model for chromosome architecture," *Proc. Natl. Acad. Sci. U. S. A.* **113**, 12168–12173 (2016).
- ⁵¹M. Di Pierro, R. R. Cheng, E. L. Aiden, P. G. Wolynes, and J. N. Onuchic, "De novo prediction of human chromosome structures: Epigenetic marking patterns encode genome architecture," *Proc. Natl. Acad. Sci. U. S. A.* **114**, 12126–12131 (2017).
- ⁵²J. Nuebler, G. Fudenberg, M. Imakaev, N. Abdennur, and L. A. Mirny, "Chromatin organization by an interplay of loop extrusion and compartmental segregation," *Proc. Natl. Acad. Sci. U. S. A.* **115**, E6697–E6706 (2018).

- ⁵³Q. MacPherson, B. Beltran, and A. J. Spakowitz, "Bottom-up modeling of chromatin segregation due to epigenetic modifications," *Proc. Natl. Acad. Sci. U. S. A.* **115**, 12739–12744 (2018).
- ⁵⁴J. A. Powers and J. C. Eissenberg, "Overlapping domains of the heterochromatin-associated protein HP1 mediate nuclear localization and heterochromatin binding," *J. Cell Biol.* **120**, 291–299 (1993).
- ⁵⁵P. J. Verschure, I. Van Der Kraan, W. De Leeuw, J. Van Der Vlag, A. E. Carpenter, A. S. Belmont, and R. Van Driel, "In vivo HP1 targeting causes large-scale chromatin condensation and enhanced histone lysine methylation," *Mol. Cell Biol.* **25**, 4552–4564 (2005).
- ⁵⁶T. Cheutin, A. J. McNairn, T. Jenuwein, D. M. Gilbert, P. B. Singh, and T. Misteli, "Maintenance of stable heterochromatin domains by dynamic HP1 binding," *Science* **299**, 721–725 (2003).
- ⁵⁷R. Festenstein, S. N. Pagakis, K. Hiragami, D. Lyon, A. Verreault, B. Sekkali, and D. Kioussis, "Modulation of heterochromatin protein 1 dynamics in primary mammalian cells," *Science* **299**, 719–721 (2003).
- ⁵⁸E. Lieberman-Aiden *et al.*, "Comprehensive mapping of long-range interactions reveals folding principles of the human genome," *Science* **326**, 289–293 (2009).
- ⁵⁹T. B. Le, M. V. Imakaev, L. A. Mirny, and M. T. Laub, "High-resolution mapping of the spatial organization of a bacterial chromosome," *Science* **342**, 731–734 (2013).
- ⁶⁰J. H. Gibcus and J. Dekker, "The hierarchy of the 3D genome," *Mol. Cell* **49**, 773–782 (2013).
- ⁶¹S.-H. Hong, E. Toro, K. I. Mortensen, M. A. D. de la Rosa, S. Doniach, L. Shapiro, A. J. Spakowitz, and H. H. McAdams, "Caulobacter chromosome in vivo configuration matches model predictions for a supercoiled polymer in a cell-like confinement," *Proc. Natl. Acad. Sci. U. S. A.* **110**, 1674–1679 (2013).
- ⁶²J. H. Burroughes, D. D. C. Bradley, A. R. Brown, R. N. Marks, K. Mackay, R. H. Friend, P. L. Burns, and A. B. Holmes, "Light-emitting diodes based on conjugated polymers," *Nature* **347**, 539–541 (1990).
- ⁶³R. H. Friend, R. W. Gymer, A. B. Holmes, J. H. Burroughes, R. N. Marks, C. Taliani, D. D. C. Bradley, D. A. Dos Santos, J. L. Bredas, M. Logdlund, and W. R. Salaneck, "Electroluminescence in conjugated polymers," *Nature* **397**, 121–128 (1999).
- ⁶⁴G. Gustafsson, Y. Cao, G. M. Treacy, F. Klavetter, N. Colaneri, and A. J. Heeger, "Flexible light-emitting diodes made from soluble conducting polymers," *Nature* **357**, 477–479 (1992).
- ⁶⁵M. Granstrom, K. Petritsch, A. C. Arias, A. Lux, M. R. Andersson, and R. H. Friend, "Laminated fabrication of polymeric photovoltaic diodes," *Nature* **395**, 257–260 (1998).
- ⁶⁶F. Hide, M. A. Diaz-Garcia, B. J. Schwartz, M. R. Andersson, Q. B. Pei, and A. J. Heeger, "Semiconducting polymers: A new class of solid-state laser materials," *Science* **273**, 1833–1836 (1996).
- ⁶⁷N. Tessler, G. J. Denton, and R. H. Friend, "Lasing from conjugated-polymer microcavities," *Nature* **382**, 695–697 (1996).
- ⁶⁸B. de Boer, U. Stalmach, P. F. van Hutten, C. Melzer, V. V. Krasnikov, and G. Hadzioannou, "Supramolecular self-assembly and opto-electronic properties of semiconducting block copolymers," *Polymer* **42**, 9097–9109 (2001).
- ⁶⁹N. S. Sariciftci, L. Smilowitz, A. J. Heeger, and F. Wudl, "Photoinduced electron-transfer from a conducting polymer to buckminsterfullerene," *Science* **258**, 1474–1476 (1992).
- ⁷⁰N. Zhou, A. S. Dudnik, T. I. Li, E. F. Manley, T. J. Aldrich, P. Guo, H.-C. Liao, Z. Chen, L. X. Chen, R. P. Chang, A. Facchetti, M. Olvera de la Cruz, and T. J. Marks, "All-polymer solar cell performance optimized via systematic molecular weight tuning of both donor and acceptor polymers," *J. Am. Chem. Soc.* **138**, 1240–1251 (2016).
- ⁷¹R. Noriega, A. Salleo, and A. J. Spakowitz, "Chain conformations dictate multi-scale charge transport phenomena in disordered semiconducting polymers," *Proc. Natl. Acad. Sci. U. S. A.* **110**, 16315–16320 (2013).
- ⁷²S. A. Mollinger, B. A. Krajina, R. Noriega, A. Salleo, and A. J. Spakowitz, "Percolation, tie-molecules, and the microstructural determinants of charge transport in semicrystalline conjugated polymers," *ACS Macro Lett.* **4**, 708–712 (2015).
- ⁷³S. A. Mollinger, A. Salleo, and A. J. Spakowitz, "Anomalous charge transport in conjugated polymers reveals underlying mechanisms of trapping and percolation," *ACS Cent. Sci.* **2**, 910–915 (2016).
- ⁷⁴C. G. De Kruif, F. Weinbreck, and R. de Vries, "Complex coacervation of proteins and anionic polysaccharides," *Curr. Opin. Colloid Interface Sci.* **9**, 340–349 (2004).
- ⁷⁵F. Weinbreck, R. De Vries, P. Schrooyen, and C. De Kruif, "Complex coacervation of whey proteins and gum arabic," *Biomacromolecules* **4**, 293–303 (2003).
- ⁷⁶W. A. Petka, J. L. Harden, K. P. McGrath, D. Wirtz, and D. A. Tirrell, "Reversible hydrogels from self-assembling artificial proteins," *Science* **281**, 389–392 (1998).
- ⁷⁷D. Priftis and M. Tirrell, "Phase behaviour and complex coacervation of aqueous polypeptide solutions," *Soft Matter* **8**, 9396–9405 (2012).
- ⁷⁸J. Viereg, M. Lueckheide, L. Leon, A. Marciel, and M. Tirrell, "Nucleic acid-peptide complexes controlled by DNA hybridization," *Biophys. J.* **110**, 566a (2016).
- ⁷⁹J. Viereg, M. Lueckheide, L. Leon, A. Marciel, and M. Tirrell, "DNA-polycation complex phase controlled by hybridization," *Biophys. J.* **112**, 214a (2017).
- ⁸⁰A. B. Marciel, S. Srivastava, and M. V. Tirrell, "Structure and rheology of polyelectrolyte complex coacervates," *Soft Matter* **14**, 2454–2464 (2018).
- ⁸¹M. Piatkovsky, H. Acar, A. B. Marciel, M. Tirrell, and M. Herzberg, "A zwitterionic block-copolymer, based on glutamic acid and lysine, reduces the biofouling of UF and RO membranes," *J. Membr. Sci.* **549**, 507–514 (2018).
- ⁸²A. Jain and R. D. Vale, "RNA phase transitions in repeat expansion disorders," *Nature* **546**, 243 (2017).
- ⁸³P. Guenoun, H. T. Davis, M. Tirrell, and J. W. Mays, "Aqueous micellar solutions of hydrophobically modified polyelectrolytes," *Macromolecules* **29**, 3965–3969 (1996).
- ⁸⁴M. Maeda, A. Kumano, and D. A. Tirrell, "H⁺-induced release of contents of phosphatidylcholine vesicles bearing surface-bound polyelectrolyte chains," *J. Am. Chem. Soc.* **110**, 7455–7459 (1988).
- ⁸⁵F. Muller, M. Delsanti, L. Auvray, J. Yang, Y. Chen, J. Mays, B. Demé, M. Tirrell, and P. Guenoun, "Ordering of urchin-like charged copolymer micelles: Electrostatic, packing and polyelectrolyte correlations," *Eur. Phys. J. E* **3**, 45–53 (2000).
- ⁸⁶R. R. Netz and H. Orland, "Beyond Poisson-Boltzmann: Fluctuation effects and correlation functions," *Eur. Phys. J. E* **1**, 203–214 (2000).
- ⁸⁷I. Nakamura and Z.-G. Wang, "Salt-doped block copolymers: Ion distribution, domain spacing and effective χ parameter," *Soft Matter* **8**, 9356–9367 (2012).
- ⁸⁸Z.-G. Wang, "Effects of ion solvation on the miscibility of binary polymer blends," *J. Phys. Chem. B* **112**, 16205–16213 (2008).
- ⁸⁹I. Nakamura and Z.-G. Wang, "Effects of dielectric inhomogeneity in polyelectrolyte solutions," *Soft Matter* **9**, 5686–5690 (2013).
- ⁹⁰I. Nakamura, N. P. Balsara, and Z.-G. Wang, "Thermodynamics of ion-containing polymer blends and block copolymers," *Phys. Rev. Lett.* **107**, 198301 (2011).
- ⁹¹R. Wang and Z.-G. Wang, "Effects of ion solvation on phase equilibrium and interfacial tension of liquid mixtures," *J. Chem. Phys.* **135**, 014707 (2011).
- ⁹²R. Wang and Z.-G. Wang, "Effects of image charges on double layer structure and forces," *J. Chem. Phys.* **139**, 124702 (2013).
- ⁹³S. B. Hutchens and Z.-G. Wang, "Metastable cluster intermediates in the condensation of charged macromolecule solutions," *J. Chem. Phys.* **127**, 084912 (2007).
- ⁹⁴P. Zhang, N. M. Alsaifi, J. Wu, and Z.-G. Wang, "Salting-out and salting-in of polyelectrolyte solutions: A liquid-state theory study," *Macromolecules* **49**, 9720–9730 (2016).
- ⁹⁵R. Wang and Z.-G. Wang, "On the theoretical description of weakly charged surfaces," *J. Chem. Phys.* **142**, 104705 (2015).
- ⁹⁶C.-L. Ren, I. Nakamura, and Z.-G. Wang, "Effects of ion-induced cross-linking on the phase behavior in salt-doped polymer blends," *Macromolecules* **49**, 425–431 (2015).
- ⁹⁷K. Shen and Z.-G. Wang, "Electrostatic correlations and the polyelectrolyte self energy," *J. Chem. Phys.* **146**, 084901 (2017).
- ⁹⁸J. T. G. Overbeek and M. Voorn, "Phase separation in polyelectrolyte solutions. Theory of complex coacervation," *J. Cell. Comp. Physiol.* **49**, 7–26 (1957).

- ⁹⁹I. Michaeli, J. T. G. Overbeek, and M. Voorn, "Phase separation of polyelectrolyte solutions," *J. Polym. Sci.* **23**, 443–450 (1957).
- ¹⁰⁰A. Veis and C. Aranyi, "Phase separation in polyelectrolyte systems. I. Complex coacervates of gelatin," *J. Phys. Chem.* **64**, 1203–1210 (1960).
- ¹⁰¹J. M. Martin, W. Li, K. T. Delaney, and G. H. Fredrickson, "Statistical field theory description of inhomogeneous polarizable soft matter," *J. Chem. Phys.* **145**, 154104 (2016).
- ¹⁰²J. Joanny and L. Leibler, "Weakly charged polyelectrolytes in a poor solvent," *J. Phys.* **51**, 545–557 (1990).
- ¹⁰³J. Qin, D. Priftis, R. Farina, S. L. Perry, L. Leon, J. Whitmer, K. Hoffmann, M. Tirrell, and J. J. de Pablo, "Interfacial tension of polyelectrolyte complex coacervate phases," *ACS Macro Lett.* **3**, 565–568 (2014).
- ¹⁰⁴J. Qin and J. J. de Pablo, "Criticality and connectivity in macromolecular charge complexation," *Macromolecules* **49**, 8789–8800 (2016).
- ¹⁰⁵Q. Yan and J. J. de Pablo, "Phase equilibria of size-asymmetric primitive model electrolytes," *Phys. Rev. Lett.* **86**, 2054 (2001).
- ¹⁰⁶A. Veis, "Phase separation in polyelectrolyte solutions. II. Interaction effects," *J. Phys. Chem.* **65**, 1798–1803 (1961).
- ¹⁰⁷C. E. Sing, J. W. Zwanikken, and M. Olvera de la Cruz, "Effect of ion–ion correlations on polyelectrolyte gel collapse and reentrant swelling," *Macromolecules* **46**, 5053–5065 (2013).
- ¹⁰⁸C. E. Sing, J. W. Zwanikken, and M. Olvera de la Cruz, "Interfacial behavior in polyelectrolyte blends: Hybrid liquid-state integral equation and self-consistent field theory study," *Phys. Rev. Lett.* **111**, 168303 (2013).
- ¹⁰⁹C. E. Sing, J. W. Zwanikken, and M. Olvera de la Cruz, "Ion correlation-induced phase separation in polyelectrolyte blends," *ACS Macro Lett.* **2**, 1042–1046 (2013).
- ¹¹⁰C. E. Sing and M. Olvera de la Cruz, "Polyelectrolyte blends and nontrivial behavior in effective Flory–Huggins parameters," *ACS Macro Lett.* **3**, 698–702 (2014).
- ¹¹¹S. L. Perry and C. E. Sing, "PRISM-based theory of complex coacervation: Excluded volume versus chain correlation," *Macromolecules* **48**, 5040–5053 (2015).
- ¹¹²C. E. Sing, "Development of the modern theory of polymeric complex coacervation," *Adv. Colloid Interface Sci.* **239**, 2–16 (2017).
- ¹¹³M. Muthukumar, "Electrostatic correlations in polyelectrolyte solutions," *Polym. Sci. Ser. A* **58**, 852–863 (2016).
- ¹¹⁴G. S. Longo, M. Olvera de la Cruz, and I. Szleifer, "Molecular theory of weak polyelectrolyte gels: The role of pH and salt concentration," *Macromolecules* **44**, 147–158 (2010).
- ¹¹⁵Q. Yan and J. J. de Pablo, "Monte Carlo simulation of a coarse-grained model of polyelectrolyte networks," *Phys. Rev. Lett.* **91**, 018301 (2003).
- ¹¹⁶D.-W. Yin, Q. Yan, and J. J. de Pablo, "Molecular dynamics simulation of discontinuous volume phase transitions in highly-charged crosslinked polyelectrolyte networks with explicit counterions in good solvent," *J. Chem. Phys.* **123**, 174909 (2005).
- ¹¹⁷D.-W. Yin, M. Olvera de la Cruz, and J. J. de Pablo, "Swelling and collapse of polyelectrolyte gels in equilibrium with monovalent and divalent electrolyte solutions," *J. Chem. Phys.* **131**, 194907 (2009).
- ¹¹⁸D.-W. Yin, F. Horkay, J. F. Douglas, and J. J. de Pablo, "Molecular simulation of the swelling of polyelectrolyte gels by monovalent and divalent counterions," *J. Chem. Phys.* **129**, 154902 (2008).
- ¹¹⁹D. Priftis, X. Xia, K. O. Margossian, S. L. Perry, L. Leon, J. Qin, J. J. de Pablo, and M. Tirrell, "Ternary, tunable polyelectrolyte complex fluids driven by complex coacervation," *Macromolecules* **47**, 3076–3085 (2014).
- ¹²⁰Q. Yan and J. J. de Pablo, "Phase equilibria of charge-, size-, and shape-asymmetric model electrolytes," *Phys. Rev. Lett.* **88**, 095504 (2002).
- ¹²¹F. Léonforte and M. Müller, "Poly(*N*-isopropylacrylamide)-based mixed brushes: A computer simulation study," *ACS Appl. Mater. Interfaces* **7**, 12450–12462 (2015).
- ¹²²A. M. Rumyantsev and J. J. de Pablo, "Liquid crystalline and isotropic coacervates of semiflexible polyanions and flexible polycations," *Macromolecules* **52**, 5140–5156 (2019).
- ¹²³M. W. Matsen, "The standard Gaussian model for block copolymer melts," *J. Phys.: Condens. Matter* **14**, R21 (2002).
- ¹²⁴T. Ohta and K. Kawasaki, "Equilibrium morphology of block copolymer melts," *Macromolecules* **19**, 2621–2632 (1986).
- ¹²⁵L. Leibler, "Theory of microphase separation in block copolymers," *Macromolecules* **13**, 1602–1617 (1980).
- ¹²⁶G. H. Fredrickson and E. Helfand, "Fluctuation effects in the theory of microphase separation in block copolymers," *J. Chem. Phys.* **87**, 697–705 (1987).
- ¹²⁷J. Qin and D. C. Morse, "Fluctuations in symmetric diblock copolymers: Testing theories old and new," *Phys. Rev. Lett.* **108**, 238301 (2012).
- ¹²⁸R. K. Spencer, B. Vorselaars, and M. W. Matsen, "Continuous thermodynamic integration in field-theoretic simulations of structured polymers," *Macromol. Theory Simul.* **26**, 1700036 (2017).
- ¹²⁹J. Glaser, P. Medapuram, T. M. Beardsley, M. W. Matsen, and D. C. Morse, "Universality of block copolymer melts," *Phys. Rev. Lett.* **113**, 068302 (2014).
- ¹³⁰B. Vorselaars, P. Stasiak, and M. W. Matsen, "Field-theoretic simulation of block copolymers at experimentally relevant molecular weights," *Macromolecules* **48**, 9071 (2015).
- ¹³¹P. Stasiak and M. Matsen, "Monte Carlo field-theoretic simulations for melts of symmetric diblock copolymer," *Macromolecules* **46**, 8037–8045 (2013).
- ¹³²M. Olvera de la Cruz, S. Edwards, and I. Sanchez, "Concentration fluctuations in polymer blend thermodynamics," *J. Chem. Phys.* **89**, 1704–1708 (1988).
- ¹³³D. Frenkel and B. Smit, *Understanding Molecular Simulation: From Algorithms to Applications*, Computational Sciences Series Vol. 1 (Academic Press, 2002), pp. 1–638.
- ¹³⁴G. H. Fredrickson and S. T. Milner, "Thermodynamics of random copolymer melts," *Phys. Rev. Lett.* **67**, 835 (1991).
- ¹³⁵G. H. Fredrickson, S. T. Milner, and L. Leibler, "Multicritical phenomena and microphase ordering in random block copolymers melts," *Macromolecules* **25**, 6341–6354 (1992).
- ¹³⁶A. Nesarikar, M. Olvera de la Cruz, and B. Crist, "Phase transitions in random copolymers," *J. Chem. Phys.* **98**, 7385–7397 (1993).
- ¹³⁷J. Houdayer and M. Müller, "Deviations from the mean-field predictions for the phase behaviour of random copolymers melts," *Europhys. Lett.* **58**, 660 (2002).
- ¹³⁸J. Houdayer and M. Müller, "Phase diagram of random copolymer melts: A computer simulation study," *Macromolecules* **37**, 4283–4295 (2004).
- ¹³⁹B. Steinmüller, M. Müller, K. R. Hambrecht, and D. Bedrov, "Random block copolymers: Structure, dynamics, and mechanical properties in the bulk and at selective substrates," *Macromolecules* **45**, 9841–9853 (2012).
- ¹⁴⁰A. A. Gavrillov, Y. V. Kudryavtsev, P. G. Khalatur, and A. V. Chertovich, "Microphase separation in regular and random copolymer melts by DPD simulations," *Chem. Phys. Lett.* **503**, 277–282 (2011).
- ¹⁴¹G. Vanderwoude and A.-C. Shi, *Effects of Blockiness and Polydispersity on the Phase Behavior of Random Block Copolymers* (Macromolecular Theory and Simulations, 2016).
- ¹⁴²E. I. Shakhnovich, "Theoretical studies of protein-folding thermodynamics and kinetics," *Curr. Opin. Struct. Biol.* **7**, 29–40 (1997).
- ¹⁴³A. Gutin, C. Sfatos, and E. Shakhnovich, "Fluctuation effects on microphase separation in random copolymers," *J. Phys. A: Math. Gen.* **27**, 7957 (1994).
- ¹⁴⁴S. Mao, Q. J. MacPherson, S. S. He, E. Coletta, and A. J. Spakowitz, "Impact of conformational and chemical correlations on microphase segregation in random copolymers," *Macromolecules* **49**, 4358–4368 (2016).
- ¹⁴⁵S. Mao, Q. MacPherson, J. Qin, and A. J. Spakowitz, "Field-theoretic simulations of random copolymers with structural rigidity," *Soft Matter* **13**, 2760–2772 (2017).
- ¹⁴⁶F. S. Bates and G. H. Fredrickson, "Block copolymers—Designer soft materials," *Phys. Today* **52**(2), 32–38 (2008).
- ¹⁴⁷M. Singh, O. Odusanya, G. M. Wilmes, H. B. Eitouni, E. D. Gomez, A. J. Patel, V. L. Chen, M. J. Park, P. Fragouli, and H. Iatrou, "Effect of molecular weight on the mechanical and electrical properties of block copolymer electrolytes," *Macromolecules* **40**, 4578–4585 (2007).
- ¹⁴⁸M. Chintapalli, K. Higa, X. C. Chen, V. Srinivasan, and N. P. Balsara, "Simulation of local ion transport in lamellar block copolymer electrolytes based

on electron micrographs," *J. Polym. Sci., Part B: Polym. Phys.* **55**, 266–274 (2017).

- ¹⁴⁹W.-S. Young, W.-F. Kuan, and T. H. Epps III, "Block copolymer electrolytes for rechargeable lithium batteries," *J. Polym. Sci., Part B: Polym. Phys.* **52**, 1–16 (2014).
- ¹⁵⁰S. Choudhury, M. Agrawal, P. Formanek, D. Jehnichen, D. Fischer, B. Krause, V. Albrecht, M. Stamm, and L. Ionov, "Nanoporous cathodes for high-energy Li-S batteries from gyroid block copolymer templates," *ACS Nano* **9**, 6147–6157 (2015).
- ¹⁵¹S. Li, Y. Jiang, and J. Z. Chen, "Phase transitions in semiflexible-rod diblock copolymers: A self-consistent field theory," *Soft Matter* **10**, 8932–8944 (2014).
- ¹⁵²Y. Jiang and J. Z. Chen, "Self-consistent field theory and numerical scheme for calculating the phase diagram of wormlike diblock copolymers," *Phys. Rev. E* **88**, 042603 (2013).
- ¹⁵³Y. Jiang and J. Z. Chen, "Influence of chain rigidity on the phase behavior of wormlike diblock copolymers," *Phys. Rev. Lett.* **110**, 138305 (2013).
- ¹⁵⁴M. Matsen, "Melts of semiflexible diblock copolymer," *J. Chem. Phys.* **104**, 7758–7764 (1996).
- ¹⁵⁵W. Song, P. Tang, H. Zhang, Y. Yang, and A.-C. Shi, "New numerical implementation of self-consistent field theory for semiflexible polymers," *Macromolecules* **42**, 6300–6309 (2009).
- ¹⁵⁶W. Song, P. Tang, F. Qiu, Y. Yang, and A.-C. Shi, "Phase behavior of semiflexible-coil diblock copolymers: A hybrid numerical SCFT approach," *Soft Matter* **7**, 929–938 (2011).
- ¹⁵⁷D. Kipp and V. Ganesan, "Influence of block copolymer compatibilizers on the morphologies of semiflexible polymer/solvent blends," *J. Phys. Chem. B* **118**, 4425–4441 (2014).
- ¹⁵⁸S. Mao, Q. MacPherson, and A. J. Spakowitz, "Polymer semiflexibility induces nonuniversal phase transitions in diblock copolymers," *Phys. Rev. Lett.* **120**, 067802 (2018).
- ¹⁵⁹C. Singh, M. Goulian, A. J. Liu, and G. H. Fredrickson, "Phase behavior of semiflexible diblock copolymers," *Macromolecules* **27**, 2974–2986 (1994).
- ¹⁶⁰Y. Jiang, W.-Y. Zhang, and J. Z. Chen, "Dependence of the disorder-lamellar stability boundary of a melt of asymmetric wormlike AB diblock copolymers on the chain rigidity," *Phys. Rev. E* **84**, 041803 (2011).
- ¹⁶¹S. Mao, Q. MacPherson, and A. J. Spakowitz, "Fluctuation effects in semiflexible diblock copolymers," *ACS Macro Lett.* **7**, 59–64 (2017).
- ¹⁶²A. Arora, J. Qin, D. C. Morse, K. T. Delaney, G. H. Fredrickson, F. S. Bates, and K. D. Dorfman, "Broadly accessible self-consistent field theory for block polymer materials discovery," *Macromolecules* **49**, 4675–4690 (2016).
- ¹⁶³F. A. Detcheverry, D. Q. Pike, U. Nagpal, P. F. Nealey, and J. J. de Pablo, "Theoretically informed coarse grain simulations of block copolymer melts: Method and applications," *Soft Matter* **5**, 4858–4865 (2009).
- ¹⁶⁴D. Q. Pike, F. A. Detcheverry, M. Müller, and J. J. de Pablo, "Theoretically informed coarse grain simulations of polymeric systems," *J. Chem. Phys.* **131**, 084903 (2009).
- ¹⁶⁵F. A. Detcheverry, H. Kang, K. C. Daoulas, M. Müller, P. F. Nealey, and J. J. de Pablo, "Monte Carlo simulations of a coarse grain model for block copolymers and nanocomposites," *Macromolecules* **41**, 4989–5001 (2008).
- ¹⁶⁶K. T. Delaney and G. H. Fredrickson, "Recent developments in fully fluctuating field-theoretic simulations of polymer melts and solutions," *J. Phys. Chem. B* **120**, 7615–7634 (2016).
- ¹⁶⁷D. Düchs, K. T. Delaney, and G. H. Fredrickson, "A multi-species exchange model for fully fluctuating polymer field theory simulations," *J. Chem. Phys.* **141**, 174103 (2014).
- ¹⁶⁸E. F. Koslover and A. J. Spakowitz, "Force fluctuations impact kinetics of biomolecular systems," *Phys. Rev. E* **86**, 011906 (2012).
- ¹⁶⁹F. Laquai, G. Wegner, and H. Bässler, "What determines the mobility of charge carriers in conjugated polymers?" *Philos Trans A Math Phys Eng Sci* **365**, 1855, 1473–1487 (2007).