Structure and Dynamics of Confined Polymers
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Preface

Polymers are essential to biology because they can have enough stable degrees of freedom to store the molecular code of heredity and to express the sequences needed to manufacture new molecules. Through these they perform or control virtually every function in life.

Although some biopolymers are created and spend their entire career in the relatively large free space inside cells or organelles, many biopolymers must migrate through a narrow passageway to get to their targeted destination. This suggests the questions: How does confining a polymer affect its behavior and function? What does that tell us about the interactions between the monomers that comprise the polymer and the molecules that confine it? Can we design and build devices that mimic the functions of these nanoscale systems?

The NATO Advanced Research Workshop brought together for four days in Bikal, Hungary over forty experts in experimental and theoretical biophysics, molecular biology, biophysical chemistry, and biochemistry interested in these questions. Their papers collected in this book provide insight on biological processes involving confinement and form a basis for new biotechnological applications using polymers.

In his paper Edmund DiMarzio asks: What is so special about polymers? Why are polymers so prevalent in living things? The chemist says the reason is that a protein made of $N$ amino acids can have any of 20 different kinds at each position along the chain, resulting in $20^N$ different polymers, and that the complexity of life lies in this variety. This argument is part of the answer, but the chemist is speaking only of the variety contained in a homogeneous, isotropic bag of stuff.

However, polymeric systems can also have many configuration degrees of freedom that undergo phase transitions, and these have profound consequences. There are 5 classes of phase transitions that occur only in polymeric systems. DiMarzio solves the problem of a polymer threading a membrane, shows that it has a phase transition, and uses it to explain why the other 4 classes also have phase transitions. With a suitable change of variables, each phase transition becomes a stable coordinate useful for storing data. A multimeric system has a very large number of these and thus can store huge amounts of data. DiMarzio argues that this provides a basis for biological self-assembly.

The processes of viral infection by phage, DNA transduction in bacteria, RNA translation, protein secretion, and muscle contraction all require biopolymers to migrate through, or function within, pores that are 1 to 10 nm in size. Lucienne Letellier discusses experimental studies on the transport of DNA across membranes by a phage, which tightly confines the molecule of
life in a capsid and delivers it into a target cell through a narrow portal. Sanford Simon, Stephan Nussberger and Walter Neupert, and Kathleen Kinnally extensively review the molecular mechanisms for targeting proteins to specific locations within cells and translocating them across membranes through nanoscale protein pores. The problem's significance is underscored by the fact that each of the $\sim 10^9$ proteins in each cell is replaced on a more or less regular basis. Without an efficient method to transport and target proteins to their proper locations, the cell's hierarchical organization would not exist.

Advances in experimental and theoretical methods have opened new opportunities to understand the physical properties of polymers confined in nanometer length-scale regions. Oleg Krasilnikov shows how the partitioning of linear, nonelectrolyte polymers can be used to deduce the diameter and other structural features of protein ion channels. Sergey Bezrukov and John Kasianowicz demonstrate that this simple method can also reveal information about the interactions between a nanopore and nonelectrolyte polymers that partition into it. Elie Raphaël and his colleagues discuss physical theories on how branched polymers partition into narrow pores. Nanopores might eventually be used to measure the physical properties of these complex polymers.

Bezrukov and Kasianowicz also observed that the mean occupancy time for nonelectrolyte polymers in a nanopore can be much greater than that predicted for a 1-dimensional diffusion process. These studies led to the direct measurement of individual polynucleotides through threading through a single ion channel (Kasianowicz, et. al., David Deamer, et al., Daniel Branton, et al., and Mark Akeson, et al.). Because of the great disparity in pore length scales and polymer persistence lengths, it is interesting to compare the processes of polynucleotide transport in a single nanopore with Björn Akerman's experimental results on the migration of single double-stranded DNA molecules through gels and other microscopic porous media (e.g. track-etched membranes and porous glasses). These molecules can evidently become trapped on features of widely disparate length scales. These features behave like snags and dominate the polymer diffusive motion through gels, whereas the rate of polynucleotide transport through a nanopore might be dominated by the polymer structure.

Murugappan Muthukumar, David Lubensky, and Wokyung Sung, and DiMarzio discuss several different theoretical approaches that describe the transport of polymers through gels and narrow pores. Their theories capture some of the essential features of polymer transport and provide a solid framework that will aid in the design of new experiments with these systems.

Imre Derenyi and Dean Astumian describe analytically the effects of different confinement geometries that create Brownian ratchet potentials. They illustrate models that use the random potentials to separate macromolecules and other models that use them to transport molecules across membranes,
even against a gradient in the chemical potential. Their models agree with experiment in every detail so far.

Many biopolymers, including those in muscle, function in tightly organized domains. Zoya Podlubnaya provides an overview of muscle structure and the mechanisms by which muscle contracts. Miklós Kellermayer shows how single molecule experiments can reveal detailed physical information about structural transitions in muscle proteins. In some cases, the results suggest that the behavior of single molecules accounts in part for some of the bulk tissue’s properties. Ultimately, one would like to use single molecule detection methods to probe these polymers in a state of confinement similar to that of their native environment. Zeno Farkas, Derenyi, and Tamas Vicsek explore the dynamics of actin filaments using elegant motility assays.

Alexei Khoklov and his colleagues are using Monte Carlo simulations to show that the properties of AB-copolymer globules depend strongly on whether the primary sequence of the A and B monomers is random, random-block, regular, or designed. A protein-like AB-copolymer is designed such that in the most dense globular conformation, all the hydrophobic B-units are in the core of the globule and the hydrophilic A-units form the envelope of the core. One of their interesting results shows that the A monomers in a protein-like 1-dimensional AB-copolymer are organized into blocks or domains of higher relative concentration with a long-range power-law correlation, which is fractal behavior, the signature of scale invariance.

New approaches are needed to understand the physics of polymers in extreme confinement. Advances here could have a major impact in biology, physics and chemistry and ultimately lead to the development of new methods in biotechnology. Peter Goodwin and colleagues illustrate a method for single molecule nucleic acid analysis by fluorescence flow cytometry. Jingyue Ju discusses the potential use of fluorescence energy transfer reagents for DNA sequencing. Deamer, et al., Branton and Meller, and Kasianowicz, et al. discuss the potential for using single nanopores to rapidly sequence DNA. Kasianowicz, et al. and Akeson et al. demonstrate how polymers and single nanopores might be used to detect and quantitate a wide variety of analytes in solution.

We are extremely grateful to the NATO Science Committee for its generous financial support that made the workshop and this book possible. Also appreciated is the additional financial support provided by Avanti Polar Lipids, the Hungarian Research and Development Committee, Incyte Pharmaceuticals, MATÁV Communications, and the Biotechnology Division at NIST. Finally, we thank the staff at the Puchner Castle for providing a lovely and comfortable meeting venue and Baldwin Robertson for assistance in editing this volume.
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