Threading macromolecules through nanopores

Polymer Translocation by M. Muthukumar;

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Experiments by Krasilnikov, Parsegian and collaborators in the 80's and then Bezrukov, Kasianowicz, and their collaborators in the mid-1990s opened up a new door for probing single-molecule properties involving translocation of long macromolecules through nanopores. Detailed electrophysiological experiments were shown to be capable of tracing single macromolecules as they wiggle their way through nanopores, and allowed for a wealth of quantitative detail pertaining to this motion of single macromolecular chains to be properly analyzed. In this way, a new methodology became available for quantitative probing of biopolymer properties that was previously inaccessible. New experimental methods engender new questions, new conceptual frameworks, and new theoretical understanding. Single-molecule recordings of translocation processes in this way naturally lead to more detailed and sophisticated models of macromolecular statistics and/or dynamics. The book by Muthukumar stems from this general recent breakthrough in macromolecular science, providing a timely response to the need for a more detailed quantitative analysis of the new type of single-molecule data.

The book is, however, far from fulfilling only these very specific demands of translocation experiments. At the same time, it also presents a very concise, clearly written, lapidary, and delightfully argued introduction to polymer and polyelectrolyte physics by one of the prime movers in the field. As such, it will find its way to readers in the specialized polymer translocation and single-molecule physics research community as well as to the more general readership of graduate students in need of a good introduction to polymer physics in general.

Basic ideas that provide the framework of our present understanding of the translocation phenomena are contained in the first, *General Premise* chapter of the book. Translocation is of course of primary importance in the biological domain allowing the transport of materials to and from the “*Coulomb soup*”, an expression used by Muthukumar to describe the highly crowded environment of the cell. The nuclear pore complex, DNA threading out of bacteriophages, and gene swapping between conjugated bacteria all depend on the

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act of macromolecular translocation, while the need for fast and efficient gene sequencing enriches the translocation phenomenology by analyzing macromolecular motion through artificial nanopores and other simplified pore models. The basic physical idea behind the translocation is the *entropic barrier*. Macromolecular entropy stems from a large number of macromolecular configurations and is the core concept of polymer physics. Any constraints that modify the large macromolecular phase space will obviously affect its entropy, and threading through small pores is just such a process. In order to understand its details, one needs to consider drift-diffusion, capture, and translocation proper of the macromolecular chain. Muthukumar's book meticulously builds on well-presented fundamental polymer physics in order to be able to provide a firm theoretical basis for understanding the physics of translocation.

Key concepts of polymer physics are needed to explain either statistical underpinnings of the entropic barrier or the dynamics of drift-diffusion and capture. Muthukumar introduces these concepts in Chap. 2 (*Size, Shape and Structure of Macromolecules*), Chap. 5 (*Confinement, Entropic Barrier, and Free Energy Landscape*) and Chap. 6 (*Random Walks, Brownian Motion, and Drift*). In fact, these three chapters could be taken together as the basis for a separate graduate course on polymer physics not necessarily associated with the translocation phenomenology, while Chap. 2 on its own, being particularly well written and concise, could be in fact viewed as a quick course on polymer thermodynamics. These three chapters introduce the necessary conceptual apparatus of the polymer theory and could stand on their own. Conceptually, or even pedagogically, Muthukumar's book balances both traditional approaches to polymer physics: scaling analysis as well as mean-field arguments, being not exclusive in either. I believe this adds richness to the subject and encourages the motivated reader to become conversant in both languages. The derivations of fundamental results are sometimes given *in extenso*, where that makes sense and does not overload the reader with too much detail, and sometimes in the form of a formal torso, leaving out the more demanding but inessential computational pitfalls. I find this approach appropriate because it keeps the line of reasoning clear, providing as much detail as can be humanly handled by the interested reader. Chapter 5 proceeds to build up the formal and conceptual apparatus of the confinement and entropic barriers. The formal bases are the various guises of the Edwards equation for the polymer density field, solved in specialized geometries, providing a well-assembled compendium of the entropies for various confinement configurations. Following closely in its wake is Chap. 6, which covers polymer diffusion and macromolecular dynamics in general. The level here is set by the Langevin and the Fokker–Planck equations, whose solutions in the context of absorbing barriers are discussed in detail. One should note that most of the material contained in these chapters pertains to non-charged macromolecules and does not specifically refer to polyelectrolytes.

The physics of charged macromolecules is then the focus of Chap. 3 (*Electrolyte Solutions, Interfaces, and Geometric Objects*), Chap. 4 (*Flexible and Semiflexible Polyelectrolytes*) and Chap. 7 (*Polyelectrolyte Dynamics*). Electrolyte solutions are introduced on the mean-field, Poisson–Boltzmann level. Different charge configurations and geometries are described with special emphasis on cylindrical geometry, which is of course the most relevant in the context of flexible macromolecules. All fundamental results are derived explicitly, either exactly or in an illuminating approximate form. This conceptual framework is then applied to charged polymers in Chap 4, which deals specifically with the physics of polyelectrolytes. Electrostatic excluded volume and electrostatic persistence length are treated in detail and some pertaining results from experiments as well as

simulations are discussed, starting from simple mean-field-like arguments for long-range steric interactions and then proceeding all the way to very advanced concepts of charge self-regularization, which bring together various disjointed parts of polymer statistics, ion dissociation equilibria, and electrostatic interactions. The final chapter of polyelectrolyte physics is Chap. 7, which is entitled *Polyelectrolyte Dynamics*. Though it contains very advanced material, Muthukumar manages to present it in a form that would allow the interested reader to follow the conceptual buildup to the level needed for understanding charged macromolecular translocation. Again, the three electrostatic chapters together make for a nice and well-written introduction to the field of polyelectrolytes.

The rest of the book deals more specifically with the phenomenology of the translocation process proper. The methodology is introduced in Chap. 8 (*Ion Flow in Single Pores*). Poisson–Nernst–Planck formalism, combining the diffusion equation and the Poisson equation, is developed to formulate the problem of charge diffusion in solutions. From here, different steady-state solutions are first derived, finally paving the way towards charge flow in the context of ionic current through protein pores. Here, Muthukumar ties in the two most investigated experimental model systems: the gramicidin A and the alpha-hemolysin pores. Experimental phenomenology is described in detail with an illuminating treatment of the fluctuation phenomena in temporal current variations. Current fluctuations are experimentally of highest relevance because these fluctuations are an additional experimental output that needs to be understood and appropriately quantified. The following chapters, Chap. 9 (*Polymer Capture*) and Chap. 10 (*Translocation Kinetics: Nucleation and Threading*) are probably the core of the book, dealing specifically with the details of the translocation process. They are introduced through illuminating experimental phenomenology and then proceeding to conceptual and computational frameworks. Drift and convective capture are described and juxtaposed, leading to the effect of entropic barriers on the capture rate. This is the first stage of macromolecular translocation, corresponding to the polymer locating the pore. The follows the translocation proper where the macromolecular chain has to wiggle its way through the pore and emerge on the other side to conclude the process. The chapter describing this process starts with illuminating but not overwhelming experimental phenomenology, proceeding next to insightful simulation results, which I find to be a very appropriate way of introducing the complex features of the process, which can hardly be subsumed under simple conceptual umbrellas. Simulation results then pave the way to the theory of translocation kinetics, based on the Fokker–Planck equations, solved in the case of various entropic barrier configurations. This is probably the most technical part of the book and Muthukumar graciously provides us with limiting forms of the general results, which can be understood with more intuitive physical reasoning and scaling arguments. The chapter ends with the discussion of characteristic timescales of translocation, which are of course what one would like to understand and compare with experiments.

The last chapter (*Further Issues*) is a type of an afterthought, where Muthukumar discusses some of the open or forthcoming issues in the field, such as non-equilibrium conformation threading, amplification of chemical detail, and finally some cool biological examples, which he has been working on recently and which caught the general attention of the (bio)physics community. Most appropriately, the book ends with the problem of genome packing in bacteriophages that has as of late received the full attention of physicists, leading to a slew of important results culminating in the Gelbart–Ben-Shaul concept of osmotic release of bacteriophage DNA and the detailed analysis of the RNA polyelectrolyte packing in viruses with pronounced oppositely charged N-tails, a problem solved by Muthukumar himself.

Muthukumar's book, tying the macro with the nano world, serves a twofold purpose: on the one hand it is a well-written introduction to polymer physics written by one of the movers of the field, and on the other hand it is a detailed monograph describing the theoretical ramifications of the translocation process in the single-molecule physics domain. Because of its twofold nature, I can recommend the book first as essential reading for graduate students venturing into the field of polymer physics and soft material science, and then also as a technical introduction to the more advanced concepts of macromolecular translocation proper, suitable for postdocs and in general all researchers working in this fast-advancing field of single-molecule science. In conclusion, I can only say that this is a well-thought-out book, superbly written, and thus bound to remain a standard in the field.