

Modulating Electro-osmotic Flow with Polymer Coatings

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THESIS SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY IN PHYSICS

Ottawa Carleton Institute for Physics

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UNIVERSITY OF OTTAWA
January 2012

SUMMARY

Micro- and nano-fluidic devices represent an exciting field with a wide range of possible applications. These devices, typically made of either silica or glass, ionize when placed in contact with water. Upon the application of an electric field parallel to the wall, a flow is produced by the charged walls called the electro-osmotic flow (EOF). Since electric fields are so often used as the driving force in these devices, EOF is an extremely common phenomenon. For this reason it is highly desirable to be able to control EOF in order to optimize the functioning of these devices. One method which is quite common experimentally is the modification of the surface using polymer coatings. These coatings can be either adsorbed or grafted, and charged or neutral. The first part of this thesis looks at the role of neutral adsorbed polymer coatings for the modulation of EOF. Specifically our simulation results show that for adsorbed coatings made from a dilute polymer solution the strongest quenching of EOF is found for an adsorption strength at the phase transition for adsorption of the polymers. Further evidence is presented that shows that by using a high density of polymer solution and a polymer which has a strong attraction to the surface a very thick polymer layer can be created. Next the case of charged grafted polymer coatings is examined. The variation of the EOF with respect to several key parameters which characterize the polymer coating is investigated and compared to theory. The prediction that the electrophoretic velocity of the polymers is the same as the EOF generated by a coating made up of the same polymers is found to be false though the two values are quite close. The last section presents results which show how hydrodynamic interactions in charged polymer systems can be modeled mesoscopically without the use of explicit charges by forcing a slip between monomers and the surrounding fluid. This model is validated by simulating some surprising predictions made in the literature such as an object with no net charge having a non-zero force when subjected to an electric field, and how the velocity can even be perpendicular to the applied electric field. The thesis can be roughly divided into two topics: using polymer coatings to modulate EOF, and the free solution electrophoresis of polyelectrolytes. While EOF and free solution electrophoresis might seem unrelated it will be shown that the concepts are the same in both cases. In fact while not investigated in this thesis, the mesoscopic simulation methods for electrophoresis could be applied to the modulation of EOF with polymer coatings allowing for the simulation of longer length and time scales or more complex systems such as heterogeneously grafted colloids.

SOMMAIRE

Les appareils micro- et nano-fluidiques représentent un domaine de recherche excitant avec un large éventail d'applications possibles. Ces dispositifs, généralement faits de silice ou de verre, s'ionisent lorsqu'ils au contact de l'eau. Suite à l'application d'un champ électrique parallèle à la surface, un flux électro-osmotique (FEO) est produit par les murs chargés. Les champs électriques sont souvent utilisés comme force motrice dans ces dispositifs, ce qui fait du FEO un phénomène commun. Pour cette raison, il est très intéressant de pouvoir contrôler le FEO afin d'optimiser ces systèmes. Une méthode fréquemment utilisée expérimentalement est la modification des murs en utilisant des revêtements de polymères. Ces revêtements peuvent être soit adsorbés ou greffés, chargés ou neutres. La première partie de cette thèse se penche sur le rôle de revêtements de polymère neutres adsorbé pour la modulation du FEO. Nos résultats de simulation montrent que pour les revêtements adsorbés à partir d'une solution diluée de polymères, la plus forte réduction du FEO est trouvée pour une force d'adsorption à la transition de phase pour l'adsorption. Nous démontrons également qu'une couche très épaisse de polymères peut être créée en utilisant une solution concentrée et un polymère qui a une forte attraction sur la surface. Nous examinons ensuite le cas de revêtements de polymères chargés greffés. La variation du FEO en fonction de plusieurs paramètres clés est étudiée et comparée à la théorie. Nos résultats réfutent la prédiction voulant que la vitesse électrophorétique des polymères est la même que celle du FEO généré par un revêtement composé des mêmes polymères. Nos résultats montrent cependant que les deux valeurs sont comparables. La dernière section démontrent comment les interactions hydrodynamiques dans les systèmes de polymères chargés peuvent être modélisés de façon mésoscopique sans l'utilisation de charges explicites en forçant un glissement entre les monomères et le fluide environnant. Ce modèle est validé en simulant certaines prédictions surprenantes répertoriées dans la littérature comme celle voulant qu'un objet sans charge nette peut subir une force non nulle lorsqu'il est soumis à un champ électrique, et une autre prédisant comment la vitesse peut même être perpendiculaire au champ électrique appliqué. La présente thèse peut être divisée en deux thèmes, l'utilisation des revêtements de polymères pour moduler le FEO et l'électrophorèse de polyélectrolytes en solution libre. Le rapprochement entre les deux sujets sera démontré par la présentation de concepts communs aux deux cas. Les méthodes de simulation mésoscopique pourraient être appliquées à la modulation du FEO avec des revêtements de polymères permettant la simulation de plus grandes longueurs et échelles de temps, ainsi que l'étude de systèmes plus complexes tels que des colloïdes hétérogènes greffés.

STATEMENT OF ORIGINALITY

This work consists of research done during my doctoral studies at the University of Ottawa and represents original work in the field of biophysics. The ideas presented were developed, and the articles written, by me with the help of my collaborators.

ACKNOWLEDGEMENTS

It has been almost ten years since I first arrived at the University of Ottawa. I have spent a large portion of this time working with Dr. Gary W. Slater who has been a great source of ideas, support and good advice. I am also indebted to Dr. James L. Harden and Dr. Christian Holm who have also greatly expanded my understanding of physics while encouraging me to pursue my ideas. During my time I have also met many fellow students and postdocs who have helped me a great deal in my research. Over the years there have been so many colleagues who have not only helped me professionally but also been good friends. In particular I would like to thank Dr. Frédéric Tessier who supervised much of my early work with Dr. Slater and wrote many programs which I have used extensively in my research. I would also like to thank Tyler N. Shendruk with whom I have worked extensively in recent years. I would like to thank my friends and family who have offered their support throughout the years.

Table of contents

Summary	ii
Sommaire	iii
Statement of originality	iv
Acknowledgements	v
Table of contents	vi
1 Introduction	1
1.1 Overview	1
1.2 DNA electrophoresis	2
1.3 Theory of Electrohydrodynamics	3
1.4 Polymer Conformations	6
1.5 Electrohydrodynamics of Polyelectrolytes	9
1.6 Electric Field Driven Slip at Soft Interfaces	16
1.7 Molecular Dynamics	19
1.7.1 Polymer Model	19
1.7.2 Fluid Models	21
1.8 Simulations of Electrokinetics	24
1.9 Presentation of the Thesis	27
1.10 Other Contributions	29
1.11 References	32
2 Molecular Dynamics Simulations of Optimal Dynamic Uncharged Polymer Coatings for Quenching Electro-osmotic Flow	37

3	Time-dependent suppression of EOF by fresh polymer coatings: A computer simulation study	42
4	Influence of Charged Polymer Coatings on Electro-Osmotic Flow: Molecular Dynamics Simulations	53
5	Implicit Method for Simulating Electrohydrodynamics of Polyelectrolytes	63
6	Simulations of Free Solution Electrophoresis of Polyelectrolytes with Finite Debye Length Using the Debye-Hückel Approximation	68
7	Conclusion and Outlook	74
	7.1 References	79
8	Appendix A: Modeling the separation of macromolecules: A review of current computer simulation methods	81
9	Appendix B: Electrophoresis: When Hydrodynamics Matter	109
10	Appendix C: Effective molecular diffusion coefficient in a two-phase gel medium	119
11	Appendix D: The diffusion coefficient of a polymer in an array of obstacles is a non-monotonic function of the degree of disorder in the medium	124

Acronyms

BD	Brownian Dynamics
CPU	Central Processing Unit
DPD	Dissipative Particle Dynamics
DNA	Deoxyribonucleic Acid
EOF	Electro-osmotic Flow
ELFSE	End-Labeled Free Solution Electrophoresis
FENE	Finitely-extensible Non-linear Elastic
ICEO	Induced Charge Electro-Osmosis
LB	Lattice-Boltzmann
MD	Molecular Dynamics
MPCD	Multi-particle Collision Dynamics
P3M	Particle-particle Particle-mesh
WCA	Weeks-Chandler-Anderson

Symbols

ϕ	1) Electrostatic Potential; 2) Density
e	Fundamental Charge
ϵ	1) Dielectric Permittivity; 2) Molecular Dynamics Energy Scale
c	Concentration
z	Valency
k_B	Boltzmann's Constant
T	Temperature in Kelvin
κ	Inverse Debye Length
λ_D	Debye Length
v	Velocity
a	Acceleration
t	Time
E	Electric Field
ρ_e	Charge Density
η	Viscosity
ζ	1) Zeta Potential; 2) DPD Thermostat Coupling Parameter
μ	Electrophoretic Mobility
ξ	1) Hydrodynamic Friction Coefficient; 2) Blob Size
F	Force
R_H	Hydrodynamic Radius
R_G	Radius of Gyration
N	Degree of Polymerization
R	Position
γ	Grafting Density
H	Height
b	Kuhn Length
d	1) Number of Dimensions; 2) Distance Between Grafting Points
$v(T)$	First Virial Coefficient
Q	Charge
a	Sphere Radius

Ψ	Weighting Function
L	Typical Device Length
U	Potential Energy
S	Entropy
Ω	Number of States
σ	1) Molecular Dynamics Length Scale; 2) DPD Coupling Parameter
k	FENE Spring Parameter
R_0	Maximum Extension of FENE Bonds
m	Mass of Particle
w	Weighting Function

Introduction

1.1 Overview

Electrophoresis, the motion of a charged object in solution subject to an electric field, is typically carried out in a narrow channel the walls of which often become negatively charged when exposed to an aqueous solution. This creates a thin layer of positively charged fluid near the channel walls. When an electric field is applied parallel to the walls it creates a plug-like flow called electroosmotic flow (EOF). In order to minimize EOF neutral adsorbed polymer coatings are often used [1]. The initial motivation for this thesis was understanding how adsorbed polymer coatings with a varying adsorption strength to a surface modulate EOF and the results can be found in Chapters 2 and 3. In the course of this research I learned that by using charged polymer coatings EOF can actually be tuned to a specific magnitude which can, in certain cases, actually achieve better performance than a complete elimination of EOF [2]. This led to a detailed study on the role of charged polymer brushes for the control of EOF in Chapter 4.

These simulations used explicit ions and solvent particles in order to realistically model the flow through polymer coated channels and provided good results though the computational cost was quite large. In order to reduce the computation time for the simulations, I set about developing coarse grained techniques to simulate similar systems without the computationally expensive electrostatic calculations. During my doctorate I developed two new methods, one based on the Lattice-Boltzmann algorithm (Chapter 5) and another based on multi-particle collision dynamics (Chapter 6). These novel methods are significantly faster than existing ones and thus offer the possibility of exploring much larger time and length scales allowing for the possibility to study physical phenomena which were not feasible to simulate using existing algorithms. In order to understand both the modulation of EOF and the new mesoscopic techniques this introduction contains some basic background information.

The thesis starts with a brief introduction to DNA electrophoresis in Section 1.2. Next, Section 1.3 provides a brief introduction to electrohydrodynamics, the interplay of electrostatic and hydrodynamic interactions which is crucial to understanding both EOF and electrophoresis. Section 1.4 looks at the average static conformations of polymers in solution. These fundamental

concepts from polymer physics about chain conformations are necessary to understand the subsequent sections on the electrohydrodynamics of polyelectrolytes (Section 1.5) and the role of polymer coatings in the modulation of EOF and electrophoretic mobility of soft colloids (Section 1.6). Section 1.7 explains the basics of molecular dynamics simulations explaining both how polymers and the surrounding fluid are modeled. The last section of the introduction, Section 1.8, looks at a variety of recently published methods which aim to simulate electrohydrodynamics without explicitly including ions. This material should provide a decent background to understand the articles which follow. Even more basic background information about the simulation of polymers can be found in Appendix A.

1.2 DNA electrophoresis

Let us start by a very brief introduction to DNA electrophoresis and its important applications. The structure of DNA, while now well-known even outside of the scientific community, was only discovered by Watson and Crick in the early nineteen-fifties [3]. More recently, the Human Genome Project sequenced the three billion base pairs which make up the human genome. Understanding and improving the second step, the sequencing of DNA, is one of the potential applications of the work presented here. While new sequencing technologies are rapidly emerging, the sequencing of DNA is sometimes still based on separating DNA strands based on length. The technique consists of taking a DNA sample and replicating it many times via polymerase chain reaction (PCR). The replicated DNA is not the complete strand but stops at a random base and is fluorescently labeled with a color which indicates the identity of the last base. By separating these strands (which all start at the same location) based on length and detecting the fluorescence one can reconstruct the sequence of the original DNA fragment. Unfortunately, the process of separating DNA strands based on length turns out to be non-trivial. When DNA is placed in an aqueous solution and subject to an electric field, only very short strands migrate with different velocities while longer strands all move at the same velocity [4, 5]. For a long time this problem has been addressed by placing the DNA strands in a cross-linked polymer matrix which forces the strands to migrate in a snake-like motion called reptation. The physics needed to predict the length dependence of the velocity can become quite complicated [6] but the essence of why it works is the presence of not only an electric force, but also the mechanical resistance caused by the DNA fragments colliding with the polymer matrix.

Traditional gel electrophoresis has proved effective in sequencing DNA. However the demand for higher throughput and affordability has grown dramatically as our understanding of DNA and its meaning has increased and in turn the number of applications. To meet this need new techniques to sequence DNA have emerged based on different approaches. Techniques based on growing strands off a wall in what are called *colonies* make most of the headlines as they currently provide the highest throughput and lowest cost [7]. These techniques do however suffer from a notable drawback in that the sequence has a reduced accuracy compared to traditional methods which is an issue for certain uses such as forensic applications and genetic screening for diseases (both of which require a very high degree of accuracy). These techniques are also not currently capable of sequencing larger strands of DNA. While this is not an issue when trying to sequence an individual's genome, when one attempts to construct the genome of new species, short read lengths become a problem [7]. This has led to continued interest in DNA migration when subject to an electric field although now micro-machined devices are often being used in place of a polymer matrix [8]. In these systems hydrodynamic interactions, which were screened by the polymer matrix in older techniques [9], now become important. The charged chains exhibit complex behaviour when subject to an electric field since they attract counter-ions from the surrounding fluid which are also subject to the electric field. The use of DNA separation as a model system for theoreticians, simulators, and experimentalists arises from its importance in biology and the rapidly expanding applications of DNA sequencing. Understanding this simple system should also help to further our understanding of the separation of other biopolymers such as polysaccharides, cells coated with polymers, and proteins which also have important potential applications [6]. In the case of proteins and coated cells, unlike DNA, the charges are often inhomogeneously distributed leading to much more complex behavior as will be seen in Sections 1.5 and 1.6. To start, however, the electrokinetics of simple solid-liquid interfaces will be covered in the upcoming section.

1.3 Theory of Electrohydrodynamics

Proteins, polymers and surfaces frequently become charged when placed in an aqueous solution. In the case of surfaces both channels made of silica and glass acquire a negative charge when placed in contact with an aqueous solution. The same is true of many polymers, in particular DNA which also gain a large negative charge when dissolved in solution. The ionization of the object creates oppositely charged counter-ions in the fluid which aggregate near the surface of the object in addition to the salt ions present already in the solution. The first step in understanding the

physics behind electrohydrodynamics is calculating an approximate distribution for the counter-ions around a solid charged object. A fairly good start, for any geometry, is to assume that the ions in the surrounding fluid obey the Poisson-Boltzmann equation:

$$\nabla^2 \phi(\vec{r}) = -\frac{e}{\epsilon} \sum_{i=1}^n c_i z_i e^{-e z_i \phi(\vec{r})/k_B T} \quad (1.1)$$

where $\phi(\vec{r})$ is the electrostatic potential at position $\vec{r}$, e is the fundamental charge, ϵ is the permittivity, c_i and z_i are the concentration and valency of ionic species i , k_B is Boltzmann's constant, and T is the temperature. This is an approximation in that it is a continuum theory and does not account for the discrete nature of the charges (which results in correlations between them) and it also neglects steric interactions (which can become important for highly charged objects where the counter-ions start to show packing effects [10]). When the surface potential is small enough, the exponential can be Taylor-expanded further simplifying the equation, which is called the Debye-Hückel approximation. The equation thus becomes:

$$\nabla^2 \phi(\vec{r}) = \sum_{i=1}^n \frac{\epsilon c_i z_i^2 e^2}{k_B T} \phi(\vec{r}) = \kappa^2 \phi(\vec{r}) \quad (1.2)$$

where κ is defined as the inverse Debye length, λ_D^{-1} . Although the exact solution of this equation depends on the geometry of the object (e.g. spherical, cylindrical, planar, etc.), it is always an exponential decay in the fluid charge density as one moves away from the object with the characteristic length scale of the decay being λ_D .

When an electric field is applied to a charged object in solution, the net motion of the object is termed electrophoresis. The first layer of charged ions are generally considered to be condensed on the object and move with it in what is called the Stern layer. Beyond the Stern layer is the diffuse layer where the fluid and counter-ions are free to move independent of the object's velocity as seen in Fig. 1.1. In order to understand the slip between the edge of the Stern layer and the surrounding bulk fluid, one makes use of Stokes' equation:

$$\nabla^2 \vec{v}(\vec{r}) = -\frac{\vec{E} \rho_e}{\eta} \quad (1.3)$$

where $\vec{v}(\vec{r})$ is the fluid velocity at position $\vec{r}$, $\vec{E}$ is the electric field and η is the viscosity of the fluid. Next we substitute in Poisson's equation for the charge density ρ_e :

$$\nabla^2 \vec{v}(\vec{r}) = \frac{\epsilon \vec{E}}{\eta} \nabla^2 \phi(\vec{r}) \quad (1.4)$$

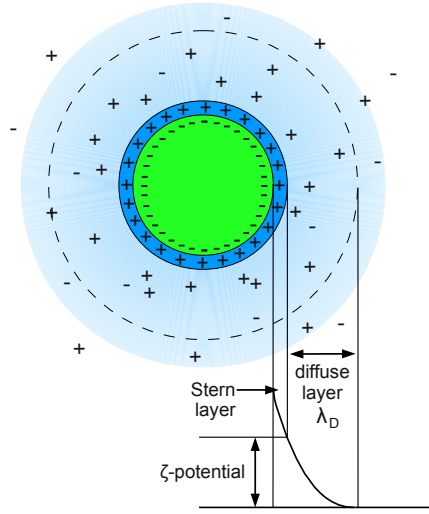


FIGURE 1.1 Schematic depiction of the electric double layer. The first layer of charged fluid is generally considered adsorbed and is called the Stern layer. Beyond the Stern layer is the diffuse layer where charges are free to migrate when an electric field is applied. This diffuse layer extends over a distance comparable to λ_D . The difference in the electrostatic potential between the interface of the two layers and the bulk is the ζ potential. Figure courtesy of Tyler Shendruk inspired by [11].

To solve this equation one must simply integrate twice yielding the Helmholtz-Smoluchowski equation:

$$v_0 = -\frac{\epsilon E \zeta}{\eta} \quad (1.5)$$

where ζ is the zeta potential (i.e. the difference between the electrostatic potential at the slip plane and far from the object's surface) and v_0 is the difference between the object's velocity and the bulk fluid velocity. The slip plane is the surface between the stationary Stern layer (usually considered to be the first layer of fluid atoms) and the mobile diffuse layer as shown in Fig. 1.1.

In practice it does not matter whether the object is stationary and the surrounding fluid is moving, a phenomena called electroosmosis, or if the object moves through a stagnant fluid, which is called electrophoresis, or some combination of the two. In the fields of electrophoresis and electroosmosis, it is common to divide the velocity by the electric field in order to define the electrophoretic mobility, μ_0 , since it is often field-independent:

$$\mu_0 = -\frac{\epsilon \zeta}{\eta} \quad (1.6)$$

This is widely accepted as a means of classifying a wide variety of different analytes for electrophoretic separations and has proven very effective for this purpose. It is known that for linear

polyelectrolytes whose contour length is much greater than the Debye length the mobility is independent of the length of the chain [4, 5]. The explanation of this is that the mobility can be thought of as the ratio of the effective charge (after charge condensation) to the effective friction coefficient (the dissipation caused by shearing the fluid within the Debye layer). For this reason it is often assumed, incorrectly, that hydrodynamic interactions are screened on the scale of the Debye layer. This turns out not to be true and the correct equation for classifying the motion of charged objects whose dimensions are greater than the Debye length was first proposed by Long *et al.* [12]:

$$\vec{F} - \xi(\vec{v} - \mu_0 \vec{E}) = 0 \quad (1.7)$$

where $\vec{F}$ is a non-electric force (e.g. gravity), $\vec{v}$ is the velocity of the object, and $\xi = 6\pi\eta R_H$ (where R_H is the hydrodynamic radius) is its hydrodynamic friction coefficient. At first glance this equation does not seem particularly surprising but it actually predicts some rather remarkable physics. In order to understand the surprising consequences of this as well as how polymer coatings effect electrokinetic responses we first need a basic understanding of static polymer conformations.

1.4 Polymer Conformations

Polymers have become ubiquitous in everyday life, mostly in the form of synthetic plastics. In biology, naturally occurring polymers are also abundant although they are often dissolved in solution and thus have different properties than the polymers which form the plastics used in modern manufacturing. One important property which will be used extensively in this thesis is the mean radius of gyration, R_G which characterises the size of a polymer coil as seen in Fig. 1.2 a). Mathematically it is simply the standard deviation of the monomer positions about the center of mass of the polymer. The following derivation is a somewhat shortened version of that which appears in Rubinstein and Colby [13]. The radius of gyration characterises the size of polymers and is formally defined as:

$$R_G^2 \equiv \frac{1}{N} \left\langle \sum_{i=1}^N (\vec{R}_i - \vec{R}_{CM})^2 \right\rangle = \frac{1}{N^2} \left\langle \sum_{i=1}^N \sum_{j=1}^N (\vec{R}_i - \vec{R}_j)^2 \right\rangle \quad (1.8)$$

where N is the number of monomers, $\vec{R}_i$ is the position of the i -th monomer, $\vec{R}_{CM}$ is the position of the center of mass of the polymer, and $\langle \rangle$ denotes the average over all accessible conformations. The last part, which does not include the position of the center of mass, is often more convenient

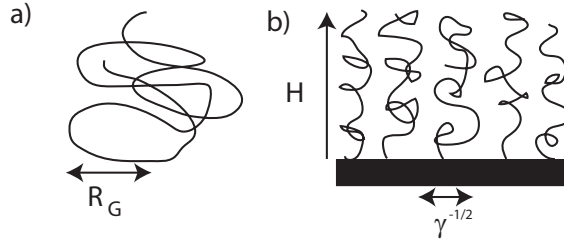


FIGURE 1.2 a) Illustration of the meaning of radius of gyration, R_G , for a linear polymer chain in free solution. b) Polymer brush with height H and separation between grafting points $\gamma^{-1/2}$.

both for deriving analytical solutions of R_G and computing it in a simulation. Let us consider the simplest case of a random walk polymer in which each bond is uncorrelated from all other bonds. In order to compute the radius of gyration let us use the average value of $(\vec{R}_i - \vec{R}_j)^2$ which consists of $j - i$ random steps $\vec{r}$ and is thus:

$$\langle (\vec{R}_i - \vec{R}_j)^2 \rangle = \sum_{k=0}^{j-i} \sum_{l=0}^{j-i} \langle \vec{r}_k \cdot \vec{r}_l \rangle. \quad (1.9)$$

If the steps are completely uncorrelated, $\langle \vec{r}_k \cdot \vec{r}_l \rangle$ is zero for $k \neq l$ and $\langle (\vec{R}_i - \vec{R}_j)^2 \rangle = (j - i)b^2$, where b is the length of the jump or Kuhn length. Then the summations are replaced with integrals to give the well known result:

$$R_G^2 = \frac{1}{N^2} \int_0^N \int_u^N (v - u)b^2 dv du = \frac{Nb^2}{6}. \quad (1.10)$$

While this is true for chains which do not have excluded volume interactions, in real systems two sections of the backbone of the polymer cannot overlap. In this case the radius of gyration can be estimated on the basis of a Flory free energy calculation. If one considers an ideal chain as a diffusive process one can assume it follows the equation $\frac{\partial P(\vec{R}, N)}{\partial N} = \frac{b^2}{6} \frac{\partial^2 P(\vec{R}, N)}{\partial^2 \vec{R}^2}$. The probability of a given end-to-end distance R is thus proportional to $\exp(-\frac{3R^2}{2Nb^2})$. Converting this into an entropy yields:

$$S = k_B \ln \Omega \sim -\frac{k_B R^2}{Nb^2}. \quad (1.11)$$

The other ingredient needed to find the radius of gyration is the energy of interaction between chain segments. To calculate this one considers the polymer as a gas of monomers with density $\phi = \frac{N}{R^d}$, where d is the number of dimensions. The energy is simply proportional to the odds of two monomers in the “gas” overlapping, ϕ multiplied by the number of monomers N , which

leads to the free energy

$$F = U - TS = k_B T \left[\frac{v(T)N^2}{R^d} + \frac{R^2}{Nb^2} \right], \quad (1.12)$$

where $v(T)$ is a constant related to the effective volume of the monomers which generally depends on temperature. Taking the derivative and setting it equal to zero gives the Flory radius of the polymer:

$$R_F = (b^2 v(T))^{1/(2d-1)} N^{3/(2d-1)}. \quad (1.13)$$

The Flory radius is not the same as the radius of gyration although the scaling exponent with respect to the properties of the polymer are the same making it a useful tool for characterizing polymer size. The scaling with respect to the degree of polymerization N is $\nu = 3/(2d - 1)$ where ν is called the Flory exponent. In three dimensions $\nu = 3/5$, which is fairly close to the exact result 0.588 that can be derived using renormalization group theory.

When polymers are densely grafted to a flat surface they form a polymer brush. In this case one first needs the height of the brush which is found by assuming that the polymers form an Alexander brush sketched schematically in Fig. 1.2 b). This approach assumes that the polymers form a layer of uniform density of height H [14, 15]. To get the height of the brush we assume that the polymers make blobs with a diameter proportional to the spacing between grafting points, $d \sim \gamma^{-1/2}$, where γ is the grafting density. Within the blob the polymer chain forms a self avoiding walk in good solvent such that $\xi \sim g^{3/5}b$, where ξ is the blob size and g is the number of monomers in the blob. The blob size must also be proportional to the spacing length d , i.e. $\xi \sim d \sim \gamma^{-1/2}$. This allows us to calculate the density in the brush $\phi \sim g/\xi^3 \sim b^{-5/3}\gamma^{2/3}$. To first order the density of the brush is uniform and the total number of monomers must scale like γN (the number of monomers per surface area). Thus $\gamma N \sim H\phi \sim Hb^{-5/3}\gamma^{2/3}$; rearranging gives the height of the brush $H \sim b^{5/3}\gamma^{1/3}N$. This is close to what has been found both in simulations, where $H \sim \gamma^{0.27}N^{0.86}$ [16], and experiments where $H \sim \gamma^{0.22}N^{0.86}$ [16, 17]. The structure of polymer brushes is crucial in the understanding of the electrohydrodynamics of soft interfaces (Section 1.6), while the radius of gyration is necessary to understand the surprising predicted effects for isolated polymers in the next section.

1.5 Electrohydrodynamics of Polyelectrolytes

A common misconception in the literature has been that hydrodynamic interactions are screened during the electrophoresis of polymers [6]. The reason for this is that long polymers have a mobility which is independent of the contour length. In order to explain this, the mobility is often seen as the ratio of the effective charge and the effective friction, both of which are seen as local properties of the chain's backbone and the surrounding fluid. Based on this understanding of the mobility of free-draining polyelectrolyte, it is tempting to believe that hydrodynamic interactions are screened on the length scale of the Debye length. It was pointed out by Long *et al.* [12] that this is in fact not the case and that this can lead to some surprising consequences.

One of the first experimental validations of the presence of long ranged hydrodynamic interactions were experiments carried out by Nkodo *et al.* [18] looking at the diffusion coefficient of electrophoresing polyelectrolytes. In the absence of an electric field it has long been known that the diffusion coefficient is inversely proportional to the hydrodynamic radius, $D \sim 1/R_G \sim 1/R_H$, of the polyelectrolyte. If hydrodynamic interactions were screened one would expect that the diffusion coefficient of a polyelectrolyte would be inversely proportional to the contour length and not the hydrodynamic radius. The experiments of Nkodo *et al.* [18] clearly showed that in fact even in the presence of an electric field the diffusion coefficient is inversely proportional to the hydrodynamic radius proving that hydrodynamic interactions are in fact not screened.

Previously we remarked that Eq. 1.7 has some surprising consequences for polyelectrolytes. Let us consider the equation now in the context of polymers:

$$\vec{F} - \xi_{\text{poly}}(\vec{v}_{\text{poly}} - \mu_0 \vec{E}) = 0, \quad (1.14)$$

where $\vec{v}_{\text{poly}}$ is the polymer's velocity. The equation represents the superposition of the flow field of the polymer slipping through the fluid with a velocity $\mu_0 \vec{E}$ as in electrophoresis and sedimenting with a velocity $\vec{F}/\xi_{\text{poly}}$. Since there is no long-range flow field generated by the electrophoresing polymer, the flow field is simply that of a polymer sedimenting with velocity $\vec{F}/\xi_{\text{poly}}$.

Now consider the simplest case of a polymer which is end-tethered such that $\vec{v}_{\text{poly}} = 0$; the force $\vec{F}$ necessary to hold the polymer in place is $\xi_{\text{poly}}\mu_0 \vec{E}$. This equation implies that the force to hold the polymer still is proportional to the polymer's hydrodynamic friction coefficient $\xi_{\text{poly}} \sim R_G \sim N^\nu$ (if the electric field does not stretch the chain) and not simply the total charge on the polymer which scales as N . In fact the force to hold the polymer in place is always less

than the total electric force applied to the polymer $Q_0 N \vec{E}$, where Q_0 is the charge of an individual monomer. This surprising result was first pointed out by Long *et al.* [12] and was later verified by Ferree and Blanch [19]. This was later confirmed by MD simulations using both explicit ions [20] and the implicit method presented in this thesis [21]. While this phenomenon may at first seem surprising, there is a simple intuitive explanation. Consider a small section of polymer backbone with its counter-ions. When an electric field is applied there is no net force to the system since the total charge of this entity is zero. When the polymer backbone is stationary, this essentially forces the surrounding fluid to move with a velocity $-\mu_0 E$, the Smoluchowski slip velocity. If one examines the flow field around a stalled polymer one sees that it indeed pumps the fluid and generates a Stokes like fluid velocity profile similar to a sedimenting polymer as shown in Fig. 1.3. It is this shearing of the fluid which is in fact the force to hold the polymer in place, which is less than the electric force applied to the polymer. The reason why it is tempting to believe that hydrodynamic interactions are simply screened is that when one looks at a free draining polymer there is no flow field around the polymer (also seen in Fig. 1.3) and thus no evidence of hydrodynamic interactions.

The physics for a charged sphere can also be approximated as the sum of the hydrodynamic interactions of a freely electrophoresing sphere and of a sphere undergoing sedimentation. There is an Oseen-like tensor to represent the fluid perturbation around a charged sphere [22]:

$$\begin{aligned} V_r(r, \theta) &= \mu_0 E (a^3/r^3) \cos \theta + (F/6\pi\eta a) \left[\frac{3a}{2r} - \frac{a^3}{r^3} \right] \cos \theta \\ V_\theta(r, \theta) &= \mu_0 E \frac{1}{2} (a^3/r^3) \sin \theta - (F/6\pi\eta a) \left[\frac{3a}{2r} - \frac{a^3}{r^3} \right] \sin \theta, \end{aligned} \quad (1.15)$$

where r and θ are the radial and angular coordinates of the fluid with respect to the sphere, and a is the radius of the sphere. The first term is simply the flow field around an electrophoresing sphere of radius a in free solution. The second term represents the additional flow field which is created when the sphere is subjected to an additional mechanical force F (the latter breaks the free-draining aspect of the problem). It should be noted that the second term simply subtracts off a part of the flow field of the electrophoresis portion while adding a Stokes' flow field generated by the mechanical force. When $F = 6\pi\eta a \mu_0 E$ causing the sphere to remain stationary, the resulting flow field is in fact identical to a sphere sedimenting with velocity $\mu_0 E$. Fourier transforming this result for a random coil and averaging over conformations leads to a surprising result. The mobility of a polyelectrolyte is found to depend on the charge distribution and not simply the net charge of

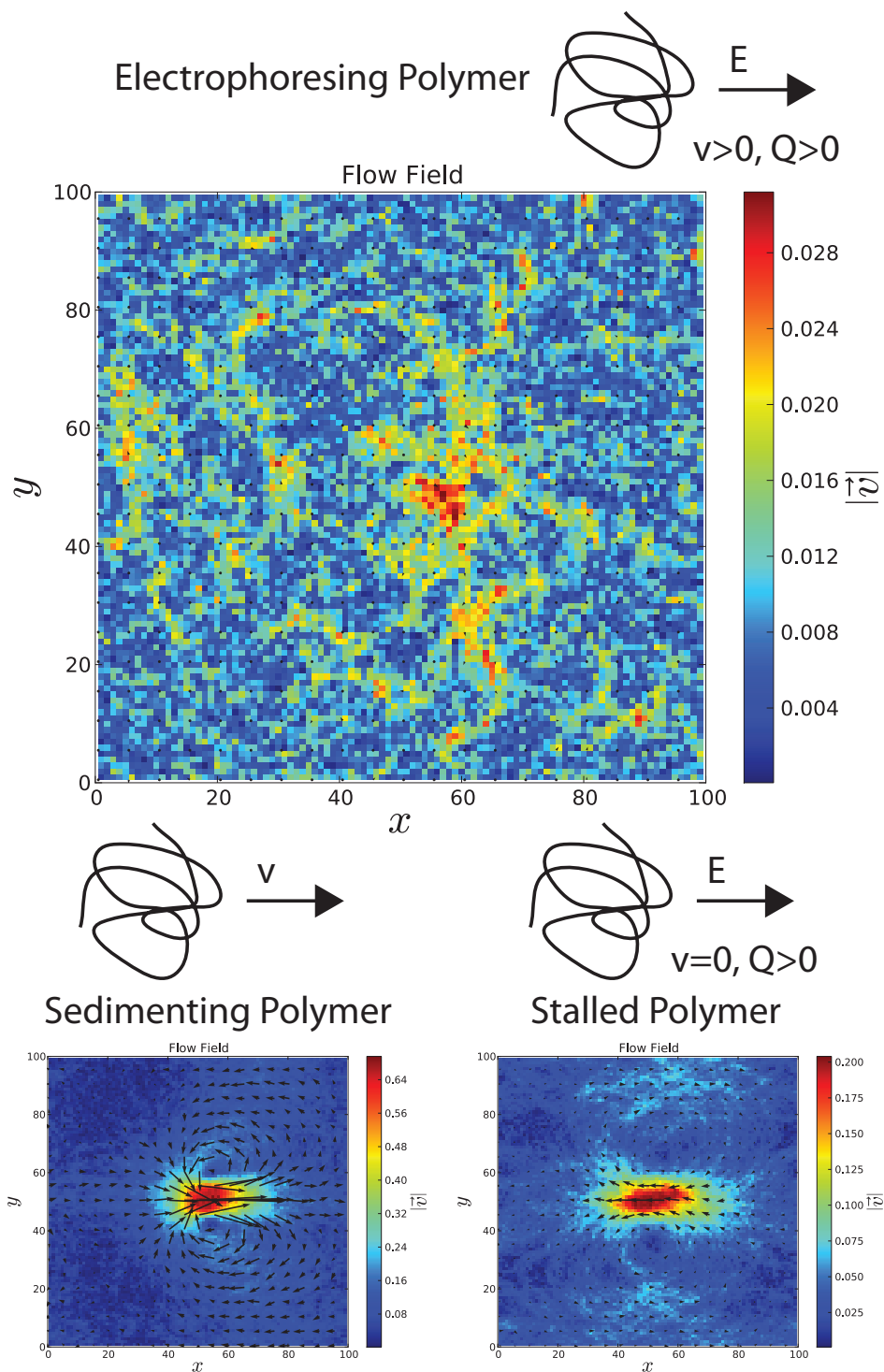


FIGURE 1.3 Results from our Multi-Particle Collision Dynamics simulations of the flow field around a polyelectrolyte which is undergoing free draining electrophoresis, sedimentation, or held in place (stalled) while subject to an electric field. The flow field around the sedimenting polymer is very similar to the stalled polymer while there is virtually no perturbation of the surround fluid for the freely draining polyelectrolyte electrophoresing through the fluid. The fact that there is no flow field in this case has led many scientists to incorrectly assume that hydrodynamic interactions are screened (and therefore irrelevant) during electrophoresis.

the chain. The resulting mobility as derived by Long *et al.* [23] can be written as:

$$\mu = \frac{1}{N} \int_0^N \mu_n \Psi\left(\frac{n}{N}\right) dn. \quad (1.16)$$

The form of the weight function $\Psi(n/N)$ can be approximated [23, 24] giving:

$$\Psi(n/N) = -0.65 + 0.62/(n/N)^{1/4} + 0.62/(1 - n/N)^{1/4}, \quad (1.17)$$

yielding the curve found in Fig 1.4. Essentially, the monomers on the ends of the polymer contribute more to the overall mobility than those in the middle of the chain. This has the implication that an overall neutral polymer can have a non-zero mobility when subject to an electric field as is presented in Chapter 5 of this thesis [21]. This result also has practical applications in End-Labeled Free Solution Electrophoresis (ELFSE) where DNA is separated by attaching a neutral drag tag. Since the ends of the polyampholyte matter more in determining the mobility, attaching two drag tags at both ends offers superior performance to attaching a drag tag with twice the hydrodynamic radius on one end [25].

There is a simple physical explanation for this end effect. In polymer physics it has long been known that a polymer in solution is not truly an ideal gas of monomers as is often assumed in Flory free energy calculations. In fact the end monomers tend to stay near the edge of the polymer coil in order to maximize the entropy of the chain. Since they tend to be on the outside they are more strongly coupled to the bulk and hence have a greater contribution to the mobility of the coil. There is an analogous system in induced-charged electro-osmosis (ICEO) which is intuitively easier to understand. In micro- and nano-fluidics it is often desirable to generate flow (in order to pump fluid) and a common technique is to place electrodes on the surface of the device. When an electric field is applied, charges are induced on the surfaces of the electrodes though the overall charge remains zero. By making asymmetric electrode arrays it has long been known that one can actually generate a net flow. Bazant and Ben realized that by elevating part of the electrode (as shown in 1.5 a)), one can form a conveyor-belt like effect and vastly increase the magnitude of the flow [26]. It is the same principle which causes the net-neutral polymer to tend to move in the direction which the ends are pulled.

Further interesting predictions have been made based on this simple approach to electrohydrodynamics of composite objects. One of the more interesting predictions was that a quadrupole subject to an electric field should in fact migrate perpendicular to the applied field [27]. This rather surprising phenomenon can be understood fairly easily by looking at the fluid flow around such

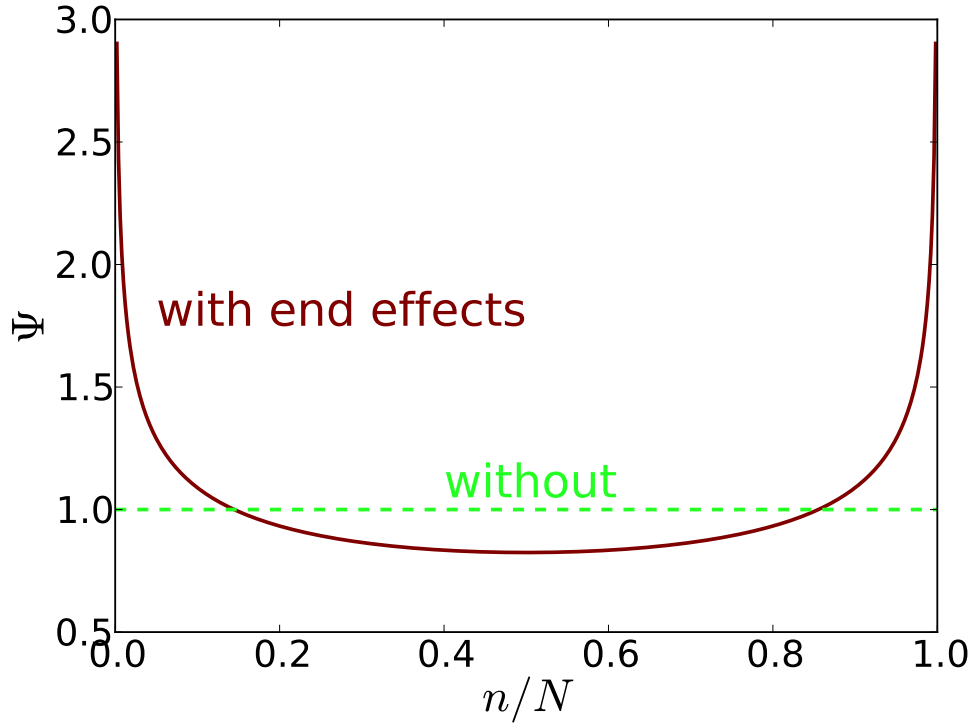


FIGURE 1.4 Weighting of the monomers' mobility as a function of relative monomer number, $\Psi(n/N)$, derived by Long *et al.* [23]. The mobility of the ends of the polymer play a larger role than those at the center. This can lead to a neutral polymer having a non-zero mobility which is about ten percent of the monomers' mobility as shown in chapter 5 [21]. Figure courtesy of Tyler Shendruk similar to figure found in [23].

an object as seen in Fig. 1.5 b). Keep in mind that the adjacent fluid carries a net charge opposite to the object; one can thus sketch fluid flow lines which qualitatively represent the real fluid flow. Given that the object pumps the fluid upwards when it is fixed in place it follows that when it is free to move it moves downwards. This phenomenon has actually been observed experimentally recently using Janus particles [28]. The particles which are composed half of metal and half of a dielectric material produce surface charges that produce a quadrupole when subject to an electric field. The velocity of the particles in the electric field was indeed found to be perpendicular to the applied field.

It should be noted that there are several interesting predictions in the literature which have yet to be verified either by experiment or computer simulations. Certain charge distributions, such as three quadrupoles linked together (see Fig. 1.5 c)), will rotate when subject to an electric field

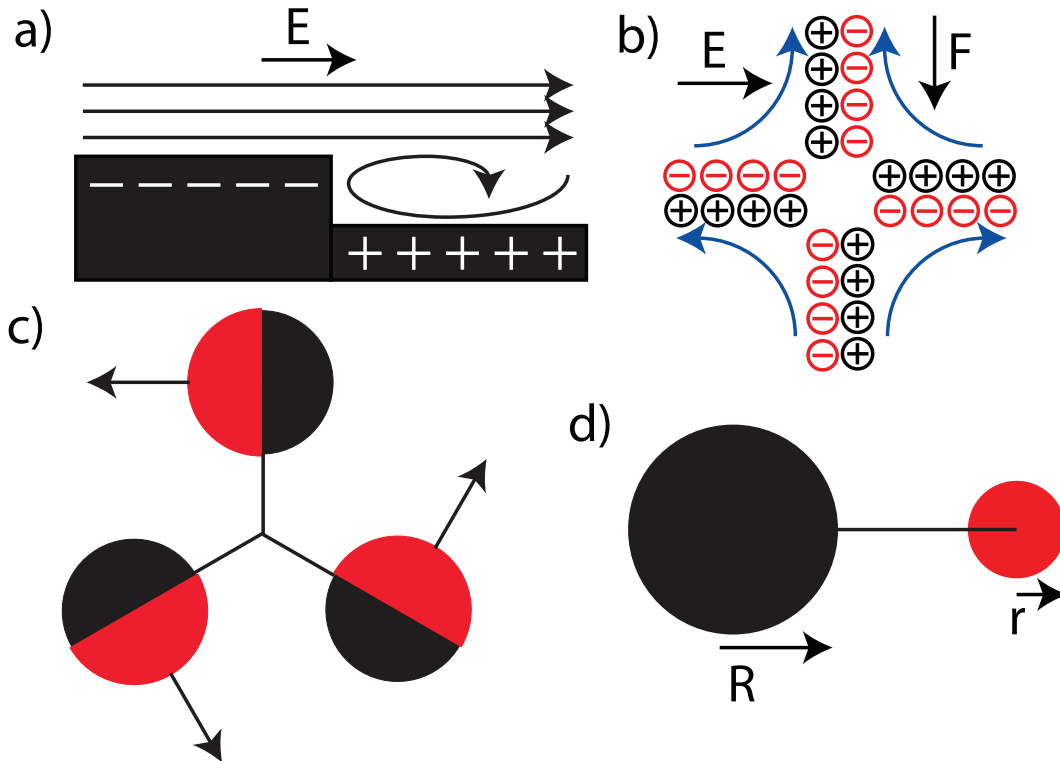


FIGURE 1.5 Examples of interesting phenomena arising from the interplay of electrostatic and hydrodynamic forces. Note that the fluid adjacent to a charge has an equal and opposite charge causing the fluid to move in the opposite direction as the electric field pulls the object itself. a) A 3d conveyor belt micropump based on induced-charge electrophoresis. The net charge on the electrodes is zero in total but it generates a net flow as the flow generated by the charges on the sunken portion merely generate an eddy current which acts to enhance the flow generated by the charges on the higher part of the electrode. b) An overall neutral object whose charges make a quadrupole causes the fluid to be pumped upwards. Since the object is pushing the fluid upwards the fluid pushes the object downwards, perpendicular to the applied field. c) Quadrupoles such as those sketched in b) when linked together in such a manner should rotate when subjected to an external field while having no net center-of-mass velocity. d) A simple system of two linked spheres with equal and opposite charge but different radii. This system has a non-zero mobility when subject to an electric field due to hydrodynamic interactions. Note that in a) and b) the electric field points to the right while for c) and d) the phenomena occurs regardless of the direction of the field.

without migrating in any direction [29]. There is also the simple system of two charged spheres with equal and opposite charge attached by a rod proposed by Long and Ajdari [30] (sketched in Fig. 1.5 d)). If we apply Eq. 1.7 we obtain (for each sphere): $\vec{F}_i = \xi_i(\vec{v}_i - \mu_{0i}\vec{E}) = 6\pi\eta R_i(\vec{v}_i - Q_i\lambda_D\vec{E}/R_i^2)$ where Q is the charge on the sphere. The non-electric force $\vec{F}_i$ in this case is simply the tension in the rod and thus must be equal and opposite for the two spheres. Since the two spheres are attached they must also have the same velocity $\vec{v}_i$ allowing us to calculate the mobility for the composite object [30]:

$$\mu = \lambda_D \frac{\frac{Q}{R} + \frac{q}{r}}{R + r} \quad (1.18)$$

where R and r are the sphere radii and Q and q are their respective charges. This equation states that the net velocity of the composite object depends on the sum $Q/R + q/r$ and not simply the sign of its net charge $Q + q$. This is perhaps the simplest example of interesting electrohydrodynamic phenomena which are not intuitively obvious when one is used to thinking about electrostatics in the more typical context of vacuum. The preceding section outlined interesting physical phenomena related to the electrohydrodynamics of isolated polymers, and while perhaps less intriguing, the electric response of polymer coated interfaces covered in the next section has important applications both for modifying EOF as well as understanding the electrophoresis of polymer coated cells and colloidal objects.

1.6 Electric Field Driven Slip at Soft Interfaces

Polymers can have a significant effect on the fluid velocity at a liquid-solid interface. When polymers are used to coat the surface it is referred to as a soft interface. One of the earliest studies of soft interfaces was carried out to understand the electrophoresis of human erythrocyte cells [31]. The naturally occurring polymer coating in these cells proved crucial in predicting the electrophoretic mobility of the cells. Researchers are still interested in exactly how polymers modify the mobility of cells and also artificial colloids coated with polymers [32].

The primary motivation for the research presented in this thesis is the closely related topic of using polymer coatings for the modulation of electro-osmotic flow (EOF) for the optimization of electrophoretic separations. As mentioned earlier, solid surfaces often become negatively charged when placed in contact with an aqueous solution creating a thin layer of oppositely charged fluid called the electric double layer. When an electric field is applied tangential to the surface, a plug-like flow develops called EOF. The finite nature of charged surface groups creates an inhomogeneous surface charge distribution, making the EOF non-uniform, and this tends to increase peak width during electrophoresis [33]. In order to control EOF, scientists have made use of a wide variety of polymer coatings which also help to prevent the analytes from adsorbing onto the surface which also increases dispersion [1]. Often a neutral polymer coating is used to simply eliminate the EOF although sometimes a non-zero EOF can lead to better separation results (this can be achieved using charged polymer coatings [2]). Since charged polymer coatings generate flow, they offer a promising possibility as pumps in microfluidics and even more so nanofluidics. In larger scale devices fluid is often pumped via a pressure gradient but the magnitude of the velocity generated in this manner decays as the typical device dimension L to the fourth power, $v \sim L^{-4}$. In contrast, EOF generated by a bare wall or a soft interface has a velocity independent of the device dimension, L , so long as L is larger than the Debye length, λ_D , and the height of the polymer coating, H . The velocity profile across the channel is also flat except in the interfacial region which may offer advantages over the parabolic velocity profile of pressure driven flow in certain situations (e.g. there is no Taylor dispersion with a plug-like flow [34]).

Perhaps one of the most exciting possibilities in the field of soft interfaces is using polymer coatings as “smart” nanovalves in micro- and nano-fluidics [35]. Consider the case of a nanotube with a polymer coating. If the fluid in the tube is a good solvent for the polymer it swells and essentially closes the valve while if it is a poor solvent the polymer collapses allowing fluid to

flow easily through the tube. There have been several simulation studies which suggest that this is indeed a viable technique for creating fluid gates in microfluidics [35–37]

As mentioned in Section 1.3, the use of a zeta potential, ζ , to characterize EOF is widespread experimentally. This is reasonable for the case of hard surfaces but not when the surface is coated with polymers [32]. The zeta potential is similarly a reasonable measure for the electrophoretic properties of a hard sphere colloid but not a colloid coated with polymers. Most of the theoretical and experimental work in this field have focused on the electrophoresis of colloids coated with polymers, called soft colloid electrophoresis [32]. Calculations are typically made using differential equations for solving both the distribution of ions and the fluid flow profile around the colloid [38]. The work presented in this thesis however focuses on the limit of infinitely thin Debye layers and polymer backbone, as studied by Harden *et al.* [39]. This greatly simplifies the analysis and is a reasonable approximation for polymers coating a surface for the purpose of modulating EOF. In the case of a sparsely grafted surface, a simple surface averaging approach gives rise to the equation:

$$\mu_{\text{EOF}} = \mu_w - (\mu_w + \mu_p)(\gamma R_G^2) \quad \text{for} \quad \gamma R_G^2 < 1, \quad (1.19)$$

where γ is the grafting density, μ_w is the electro-osmotic mobility of the bare wall and μ_p is the mobility of the polymers coating the walls. This is simply the sum of the surface area multiplied by the fluid velocity of the bare section of wall, $(1 - \gamma R_G^2)\mu_w E$, and the polymer covered surface $-\gamma R_G^2 \mu_p E$ as sketched in Fig. 1.6. This is only valid in the limit of small electric fields where there is no stretching of the polymers; when the electric fields starts to perturb the equilibrium structure of the grafted polymers, the expression can become much more complex [39].

In the work of Harden *et al.* [39], the shear of the fluid within the brush can be seen as the same as a porous medium with a typical pore size $d \approx \gamma^{-1/2}$, the distance between grafting points:

$$\nabla^2 v(z) \sim \frac{v(z) - \mu_p \vec{E}}{d} \quad z < H, \quad (1.20)$$

where H is the height of the polymer brush and z is the distance from the surface. This is only valid in the case of $H \gg \lambda_D$ since it assumes no net charge beyond $z = H$. The fluid flow profile within the brush is given by:

$$v(z) = (\mu_w E + \mu_p E) \frac{\cosh[\frac{H-z}{d}]}{\cosh[\frac{H}{d}]} - \mu_p E \quad z < H. \quad (1.21)$$

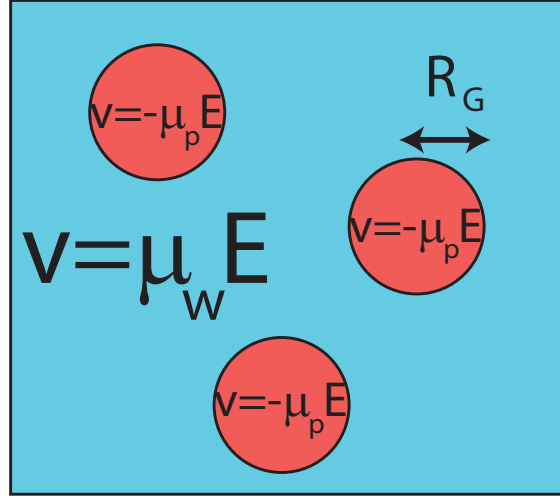


FIGURE 1.6 Schematic explanation of the derivation of Eq. 1.19. The net mobility of the interface is considered to simply be the average mobility of the surface. Within R_G of a grafting point it is assumed to be $-\mu_p$, while the mobility of the uncoated wall is μ_w everywhere else.

Beyond $z = H$ the fluid velocity profile is simply constant. It should be noted that there are different versions of Eq. 1.20 used in the literature. In fact, in the soft colloid electrophoresis community it is quite common to simply approximate the drag of the polymers as a random distribution of Stokesian spheres independent of the blob size [38]. That being said, the above equation was recently verified in simulations for frozen rigid rods protruding from a surface [40]. Substituting $z = H$ and replacing H/d yields the equation for the fluid flow beyond the polymer layer as a function of the free radius of gyration and the grafting density:

$$\mu_{\text{EOF}} = -\mu_p + (\mu_w + \mu_p) \frac{1}{\cosh[(\gamma R_G^2)^{(5/6)}]} \quad (1.22)$$

The equation's validity was confirmed for neutral polymer brushes by simulations of Tessier and Slater [41]. It should be noted that much like the equation for the mushroom regime (Eq. 1.19), there are corrections for large electric fields which deform the polymer that have been ignored here since the focus of the work presented in this thesis is the linear response regime.

Now that the basic physics behind the electrohydrodynamics of polymeric systems has been reviewed we shall now look at the simulation methods which can be used to model them.

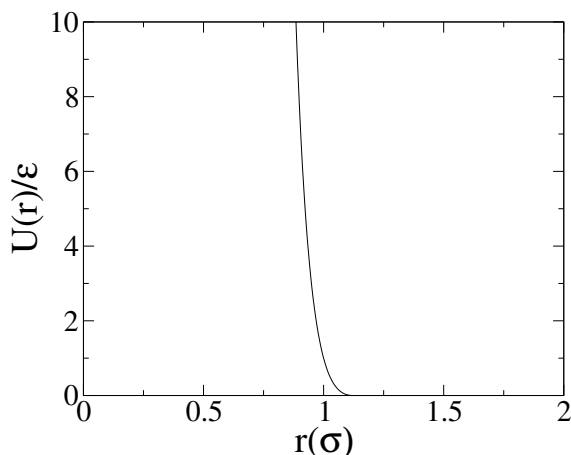


FIGURE 1.7 The WCA potential given in Eq. 1.23. By cutting off the Lennard-Jones potential at $r_0 = 2^{1/6}\sigma$ it becomes purely repulsive and both the potential and its derivative are continuous for all values of r .

1.7 Molecular Dynamics

1.7.1 Polymer Model

The results presented in this thesis were all performed using Molecular Dynamics (MD) simulations. The work presented in Chapters 2, 3, and 4 used a modified MD code developed by Dr. Frédéric Tessier. Chapter 6 utilized this code hybridized with a mesoscopic fluid code developed by Tyler N. Shendruk. The simulations in Chapter 5 were done with the simulation package ESPResSo [42]. The typical duration of the simulations is one week running on a single Central Processing Unit (CPU). The simulations all consist of two parts: a polymer model, and a fluid model. While different fluid models were used in the different publications in this thesis, the polymer model was the same in all publications.

The first step in setting up an MD simulation is the definition of potentials between nearby particles. Extensive work has been done creating realistic potentials for various atoms based on quantum Chemistry calculations. Determining the force between two isolated atoms is, relatively speaking, simple but unfortunately the presence of other atoms can affect the potential. Thankfully it has long been known that for simulating polymer systems, accuracy of inter-atom potentials is only necessary for predicting numerical values and not how physical quantities depend on the length of the polymers [43]. Grouping the atoms which make up monomers, and often several monomers, into a single bead also reduces the number of particles. This coarse grained approach of grouping atoms into beads is referred to as united atom molecular dynamics. In order to generate

self avoiding walk conformations one needs to have two basic ingredients: a repulsive potential at short distances and a bond between adjacent monomers. The repulsive force used in our work is a purely repulsive truncated Lennard-Jones potential, often referred to as the Weeks-Chandler-Anderson (WCA) potential [44]:

$$\frac{U_{\text{WCA}}(r)}{\epsilon} = \begin{cases} 4 \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right] + 1 & r \leq r_0 \\ 0 & r > r_0 \end{cases} \quad (1.23)$$

where σ and ϵ are the MD length and energy scales respectively and $r_0 = 2^{1/6}\sigma$. This has long been used in simulations and by cutting off the Lennard-Jones potential at the minimum it ensures that both the potential (energy) and its derivative (force) are continuous as seen in Fig. 1.7. Failing to meet these two conditions can lead to spurious results in certain instances. The cutoff also makes the beads similar to hard spheres due to the rapid rise as the distance between beads goes below σ , and thus for polymers makes the solvent essentially athermal, meaning that polymers will take on the same configuration regardless of the temperature [14]. While this cutoff was used in all of the simulations in this thesis, adding the attractive portion of the potential allows for the simulation of poor, theta, and good solvents depending on the temperature [14].

The other necessary potential is the bond potential between adjacent monomers. For this the finitely-extensible non-linear elastic (FENE) potential was used:

$$U_{\text{FENE}}(r) = -0.5kR_0^2 \ln \left[1 - (r/R_0)^2 \right]. \quad (1.24)$$

The parameters $k = 30\epsilon/\sigma^2$ and $R_0 = 1.5\sigma$ were first used by Grest and Kremer and are chosen to prevent unphysical bond crossing [45]. In order to simulate realistic statics and dynamics other potentials can again be used, such as a harmonic potential, as long as the potential is strong enough to prevent bond crossing or unrealistic stretching of the polymer along the backbone.

Once the potentials have been established, one must then simply apply Newton's equations of motion:

$$m \frac{\partial^2 \vec{r}}{\partial t^2} = -\nabla U(\vec{r}) + \vec{F}_{\text{therm}}, \quad (1.25)$$

where m is the mass of the particle, $U(\vec{r})$ is the sum of the various potentials and $\vec{F}_{\text{therm}}$ is an additional force which represents a thermostat. The $\vec{F}_{\text{therm}}$ term is not necessary for short simulations where there is no external driving force as in principle integrating Newton's equations of motion conserves energy. In practice, small numerical errors add up over time causing the

energy of the system to drift in an unphysical manner. The problem is far greater in the systems simulated in this thesis as there is usually a very large driving force pumping energy into the system. While there are a wide variety of methods for dissipating energy, there are two main criteria which should be satisfied. The first is that momentum be conserved locally as failure to do so can result in the screening of hydrodynamic interactions. The second is that the force be comprised of both a dissipative and a stochastic term which satisfy the fluctuation dissipation theorem in order to generate the right distribution of velocities. A common choice in modern MD simulations is the dissipative particle dynamics (DPD) thermostat [46]. This thermostat has the form:

$$\vec{F}_{\text{therm}} = -\zeta w^D(\vec{r}_{ij})(\vec{r}_{ij} \cdot \vec{v}_{ij})\vec{r}_{ij} + \sigma w^R(\vec{r}_{ij})\theta_{ij}\vec{r}_{ij} \quad (1.26)$$

where $\langle \theta_{ij}(t) \rangle = 0$ and $\langle \theta_{ij}(t)\theta_{ij}(t') \rangle = (\delta_{ik}\delta_{jl} + \delta_{il}\delta_{jk})\delta(t - t')$. This is simply white noise with unit variance. In order to satisfy the fluctuation-dissipation theorem one must have $\sigma^2 = 2k_B T \zeta$ and $[w^R(r)]^2 = w^D(r)$. These conditions ensure that the right distribution of relative velocities are sampled throughout the simulation. One must choose appropriate values for the dissipation constant, ζ , and the weighting function $w^D(r)$. While the specific choice of ζ and $w^D(r)$ are arbitrary, generally $\zeta \approx 1$ and $w^D(r)$ should extend only over about the length of a particle. In our simulations $\zeta = 1.5$ in order to maximize the dissipation and the weighting function $w^D(r)$ was set to 1 within the WCA cutoff and zero outside of it for computational efficiency.

In order to actually integrate Eq. 1.25 we make use of the velocity Verlet algorithm which consists of using an average acceleration:

$$\begin{aligned} \vec{r}(t + \Delta t) &= \vec{r}(t) + \vec{v}(t)\Delta t + \frac{1}{2}\vec{a}(t)\Delta t^2 \\ \vec{v}(t + \Delta t) &= \vec{v}(t) + \frac{\vec{a}(t) + \vec{a}(t + \Delta t)}{2}\Delta t \end{aligned} \quad (1.27)$$

where $\vec{v}$ is the velocity, $\vec{a}$ is the acceleration, t is the time, and Δt is the integration time step. This method is widely used as averaging the accelerations at t and $t + \Delta t$ increases the accuracy of the integration allowing for a longer time step.

1.7.2 Fluid Models

Electrostatic calculations are extremely difficult and slow in computer simulations. This is because the energy decays inversely with the distance r^{-1} meaning that to properly account for electrostatics one cannot simply look at nearby charges. In computer simulations with periodic boundaries

this means calculating the electrostatic potential not only of ions within the simulation box but also with the infinite number of image charges created by the periodic boundaries. In fluid dynamics, similar to electrostatics, the perturbation of the fluid about a sphere also decays as r^{-1} and so when one wants to account for hydrodynamic interactions between beads one cannot simply use an effective interaction amongst nearby beads. In this section we will consider the various fluid models used in MD simulations while adding electrostatic interactions shall be covered in the following section.

In this thesis simulations were carried out using three different models for the dynamics of the fluid. The simplest is the Lennard-Jones fluid which consists of inserting a large number of neutral Lennard-Jones beads which are unconnected to the other beads in the system and integrating as above. This explicit model of the fluid is simple and intuitive although the computation time is considerable [44]. In order to speed computation, mesoscopic fluid models have been developed in recent years, namely multi-particle collision dynamics (MPCD) and Lattice-Boltzmann (LB). In this section we will briefly review these two methods. It should be noted that both methods are quite similar and in fact there are only a few basic ingredients necessary to make a mesoscopic fluid which produces reasonable results, and this is no doubt why a large number of different models have emerged in recent years [44].

To start with let us consider our MPCD model used in the simulations of free solution electrophoresis. The model consists of a gas of MPCD particles which move ballistically for a time Δt . After this so called streaming step the particles are separated into boxes of size a . The position of the boxes are randomly shifted between 0 and a in order to achieve Gallilean invariance. This is common to all variants of MPCD and it is only the next part, the collision step, which is different between MPCD models. In the simulations presented in this thesis the collision is called an Andersen collision. The collision consists of taking all the particles in a given box and calculating the velocity of the center of mass of the box. All particles are then given this velocity along with some Gaussian random noise which ensures that the distribution of velocities fits the initial Maxwell-Boltzmann distribution. This method was chosen since it provides reasonable hydrodynamic interactions and also acts as a thermostat since it forces the velocities to satisfy the Maxwell-Boltzmann distribution. The fluid is coupled to the polymer beads simply by including them in the collision step. Typically the mass of the polymer beads is larger than that of the MPCD beads in order to have strong coupling between monomers and nearby MPCD fluid particles (this will ensure that the local fluid velocity is roughly equal to that of the monomer). While any choice

of parameters can be used in practice, one needs to be careful in order to get reasonable dynamics, particularly choosing a time step which is not too long and when driving the polymer using a force which is not too large. Failure to do so causes the polymer to move through the fluid faster than it couples to the local fluid velocity [47]. Recent simulations comparing an MPCD fluid to a Lennard-Jones fluid found that the MPCD fluid is computationally about fifty times faster [48].

The other mesoscopic model used in the simulations presented in this thesis is the Lattice-Boltzmann (LB) fluid. The model consists of a lattice with each lattice point containing populations of fluid particles (real numbers) going to adjacent lattice sites. The connectivity of lattice sites varies between different models in order to optimize accuracy and efficiency. In this work, the model used is D3Q19 as has been used previously [5]. The D3 is for 3 dimensions while the Q19 indicates that each node contains 18 population vectors connecting to adjacent nodes and one population which remains at the current lattice site. This particular choice has been shown to accurately represent the Maxwell-Boltzmann distribution allowing for accurate calculations with a longer time step. Much like in the MPCD algorithm there is a streaming step where populations migrate to the appropriate adjacent node. There is then a collision step for which, much like in MPCD, there are a wide variety of choices and the important thing is that momentum be conserved locally while relaxing the population vectors towards a Maxwell-Boltzmann distribution. In order to couple the fluid to the polymer beads, there is a Stokes-like drag applied to the polymer bead and an equal and opposite force applied to the local fluid nodes. The choice of the drag coefficient should be large enough that like in MPCD the local fluid velocity is always close to the monomer velocity but not too large to introduce numerical instabilities much like in MPCD [47]. The LB fluid is found to be about twenty times faster than the simple Lennard-Jones fluid model [49] and thus offers an increase in computational efficiency similar to the MPCD fluid discussed in the preceding paragraph.

In practice the Lennard-Jones fluid, MPCD, LB, and dissipative particle dynamics (DPD [50], which is not covered here) should all provide similar results. The exception to this is strong confinement where correlation effects with a stationary wall can affect fluid properties such as the viscosity. In this case the Lennard-Jones fluid should provide more realistic results though it is possible that an even more accurate representation of the fluid is required in this case. For polymers which are not strongly confined, the focus of this thesis, the mesoscopic fluid models have proved to be highly effective while reducing the computation time. The main reason for this is that the time step for the fluid can usually be about five times longer than that of the polymer while

maintaining accuracy. The different mesoscopic fluid models all have about the same computational speed and there is no clear reason to use one compared to another in general, although one algorithm may prove to be more effective for a specific problem. Recently, several groups (including ours) have suggested simple extensions of these methods to account for electrostatic effects without explicitly accounting for charges, something which is computationally expensive. Let us examine these ideas now.

1.8 Simulations of ElectrokINETICS

Simulations of systems with hydrodynamics (as described in the previous section) are still fairly computationally demanding. The problem is further exacerbated when electrostatics are added to the problem. There are a number of simulation methods which have been developed to study such problems [51]. Both hydrodynamic and electrostatic interactions decay like r^{-1} and thus are termed long-range. The slow decay in the interaction means that neither can be properly accounted for using a purely local method such as a short ranged cutoff. In this section we will briefly review methods of simulating the combined hydrodynamic and electrostatic problem with a focus on polyelectrolytes in the limit of thin Debye layers.

Perhaps the simplest way of simulating the electrokinetics of polyelectrolytes is by combining modern electrostatic simulation techniques with the new mesoscopic fluid models presented in the previous section. In order to do this one must first add explicit counter- and co-ions to the simulation along with the polyelectrolyte. These ions experience a WCA repulsion with each other and with the polyelectrolyte in addition to electrostatic forces calculated with the particle-particle particle-mesh (P3M) method [52]. The method consists of calculating Coulombic forces between nearby ions using Coulomb's law while long range electrostatic interactions are calculated using Fourier transforms on a mesh.

This method has been applied both to an LB fluid [5] as well as an MPCD fluid [47, 53]. Both of these simulation studies focused on the mobility of short polyelectrolytes as a function of the degree of polymerization N . The simulations managed to reproduce the experimentally observed maximum as N increases [4]. In fact, when renormalized to account for differing fluid viscosities, the data from the LB simulations matched almost exactly experimental results for sulfonated polystyrene over the range of polymer lengths studied [5]. The use of explicit ions allowed the simulations to show an initial rise in mobility due to cooperative shearing of the fluid within the

Debye layer and a subsequent drop in mobility due to increased counter ion condensation as the degree of polymerization is increased. This topic is covered in detail in Chapter 6.

While these simulations provide very realistic results, the use of P3M requires the use of significant computation time. For low salt concentrations the overhead is not very large since there are few charges in the system. As one increases the number of charges in the system (e.g. by increasing the salt concentration) the amount of time needed to calculate the electrostatic interactions scales as $N_{\text{Ion}} \log N_{\text{Ion}}$, where N_{Ion} is the total number of ions in the system. In recent years there have been a number of interesting simulation approaches aimed at realistic results for the case of thin Debye layers where the number of ions in the system is large.

The first such model based on the dissipative particle dynamics (DPD) fluid was developed by Duong-Hong *et al.* [54]. The simulations consist of a standard polymer model coupled to a DPD fluid with some slight modifications in order to produce realistic electrophoretic behavior. The first modification is that when a DPD solvent particle is within a Debye length of a monomer it acquires an effective charge. The monomer experiences a force in the direction of the external electric field while the solvent charged particle experiences an equal opposite force. In their simulations, these authors showed that this allowed the polymer to migrate through the fluid without producing a significant perturbation of the flow thus making them free draining as explained in Section 1.5 and seen in Fig. 1.3. Furthermore the simulations looked at both the mobility and diffusion coefficient and found that the former was independent of the polymer's length while the latter decayed like one over the hydrodynamic radius, in agreement with the experiments of Nkodo *et al.* [18]. The simulations were carried out for a microfluidic device and the EOF of the channel was added by using moving wall boundary conditions thus forcing a given velocity at the channel walls. In theory this technique should work for arbitrarily shaped boundary conditions.

Another interesting simulation approach is that which was proposed by Kekre *et al.* [55]. This method consists of essentially applying the flow field given in Eq. 1.15 within a Brownian dynamics (BD) simulation. The simulations were looking at the combined effect of electrophoresis and Poiseuille flow on a polyelectrolyte between parallel plates. To this end the reflection of the fluid flow profile by the walls was added by way of a Green's function. The motivation for the study was the fascinating experimental results of Zheng and Yeung [56]. In their experiments, they investigated the density distribution of polymers across a microchannel. When polymers are subject to either an electrophoretic drift or a Poiseuille flow the density distribution across the microchannel is essentially flat. If however both an electric field and a Poiseuille flow are

applied at the same time the chains either aggregate at the center of the channel (when both act in the same direction) or towards the channel walls (when they act in opposite directions). What is remarkable about the simulation study is that the computational results reproduce quantitatively the experimental results for both the case of a cylindrical channel and parallel plates. The speed of this method, while not mentioned in the article, is presumably much faster than those based on DPD, MPCD, or LB much like in the case of BD simulations for purely hydrodynamic problems [57]. The method does suffer from a limitation, namely it is only good for relatively simple boundary conditions. On the other hand the inclusion of the r^{-3} term from Eq. 1.15 could mean that the method provides reasonable results even in the case of thick Debye layers.

The last technique, which represents some of the original research to appear in this thesis, is based on transforming the monomer velocities prior to coupling them to a mesoscopic fluid [21]. In both LB and MPCD it is the bead's velocity which determines the coupling force between the bead and the fluid. If one simply subtracts off $\mu_0 E$ from the velocity prior to coupling the bead to the fluid one should in theory produce reasonable electrohydrodynamics. This was shown to produce realistic mobility and diffusion coefficients much like the DPD method of Duong-Hong *et al.* [54]. In addition to this, the method produced reasonable results for the stall force as well as the mobility of polyampholytes as seen in chapter 5. While this method provides electrohydrodynamics for the same cost as a purely hydrodynamic simulation it should be noted that it is only valid in the limit of thin Debye layers.

This section presented several modern techniques for simulating the electrohydrodynamics of polyelectrolytes. The techniques can be separated into two broad categories, those based on explicit ions and those which make use of an approximation for the local shear of the fluid around a charged bead. The methods which use an approximation should be significantly faster than those based on explicit ions. The lack of explicit ions however fails to capture effects such as overlapping Debye layers and ion condensation, crucial effects in the study of the electrophoretic mobility of short polymer segments [5, 53]. The different methods thus each have their own advantages and disadvantages and the best choice of simulation setup depends on the problem at hand. The newer methods focus on a mesoscopic approach which neglects some of the finer details but allow for the use of longer length and time scales. The next three chapters all use a more traditional microscopic approach using explicit ions to simulate electrohydrodynamics. The chapters cover the use of polymer coatings to modulate EOF. Despite being relatively small, uniform systems which are quick to reach equilibrium, they push the limits of what is doable using modern computers.

Chapters 5 and 6 present much faster algorithms which should allow for the simulation of larger, more complex systems.

1.9 Presentation of the Thesis

The bulk of this thesis consists of several journal articles some of which have already been published. Below is the list of the articles along with a brief summary of the contents. The first two look at the role of adsorbed polymer coatings in modulating EOF while the third examines charged, grafted polymer coatings. The last two articles present new simulation techniques for modeling the electrohydrodynamics of polyelectrolytes.

Chapter 2: OA Hickey, JL Harden, GW Slater. *Molecular Dynamics Simulations of Optimal Dynamic Uncharged Polymer Coatings for Quenching Electro-osmotic Flow* **Physical Review Letters** **102**, 108304 (2009).

Previous work in our research group confirmed scaling predictions for the screening of electro-osmotic flow (EOF) in the presence of neutral end-grafted polymer chains. This article investigated the more common experimental technique of adsorbed polymer coatings for the quenching of EOF. The main finding in the article was an explanation for why more weakly adsorbed coatings actually do a better job of quenching EOF. Experiments had shown only improved quenching with decreasing adsorption strength. The simulation results showed that the optimum adsorption strength is right at the phase transition for adsorption of the polymers — something which was not seen experimentally since only relatively strongly adsorbed coatings were studied. Surprisingly the simulations indicated that for the strongest adsorption strengths there could in fact be an enhancement of EOF. The simulations also confirmed that increasing the degree of polymerization of the coating polymers improved the quenching and seemed to indicate a power law dependence of the bulk flow on the length of the polymers.

Chapter 3: OA Hickey, JL Harden, GW Slater. *Time-dependent suppression of EOF by fresh polymer coatings: A computer simulation study* **Submitted**.

This article builds on the previous article and further examines the role of adsorbed polymer coatings for the modulation of EOF. The results indicate that at low polymer concentrations the EOF

is relatively stable while at high polymer concentrations long lived metastable states are possible. Over time at weak adsorption strengths some polymers desorb from the surface while others collapse onto the surface reducing the height of the polymer coating and thus increasing the EOF. For very strongly adsorbed coatings this metastable state appears to be long lived leading to a possible new set of parameters for strong quenching of EOF.

Chapter 4: OA Hickey, C Holm, JL Harden, GW Slater. *Influence of Charged Polymer Coatings on Electro-Osmotic Flow: Molecular Dynamics Simulations* **Macromolecules** **44**, 9455-9463 (2011)

This article presents detailed MD simulations on the effects of charged polymer coatings in the modulation of EOF. The results show that the EOF reverses direction before the net charge of the interface changes sign since charges on the polymers contribute more to the net EOF than those confined to the surface. The simulations also confirm scaling predictions for the EOF as a function of the grafting density and the degree of polymerization. The effect of both the electric field and the linear charge density along the polymer are also examined in detail. The EOF as a function of the linear charge density shows a strong similarity to recent experimental results.

Chapter 5: OA Hickey, C Holm, JL Harden, GW Slater. *Implicit Method for Simulating Electrohydrodynamics of Polyelectrolytes* **Physical Review Letters** **105**, 148301 (2010).

This article introduces a novel method of simulating polyelectrolytes in an electric field in the infinitely thin Debye layer limit. In this limit there is a difference between the local fluid velocity and the monomer velocity and it was shown that this can be achieved by changing the way monomers are coupled to a mesoscopic fluid, in this case a Lattice-Boltzmann fluid. In order to validate the model we first showed that it produces the correct velocity and diffusion coefficient during free solution electrophoresis. The model is then used to demonstrate a variety of the rather surprising phenomena predicted for the electrohydrodynamics of charged objects, namely that the interplay of electrostatics and hydrodynamics can produce objects with no net charge that still move when subject to an electric field. The article shows perhaps the rather astounding phenomena where that movement can even be perpendicular to the applied electric field.

Chapter 6: OA Hickey, TN Shendruk, JL Harden, GW Slater. *Simulations of Free Solution Electrophoresis of Polyelectrolytes with Finite Debye Length Using the Debye-Hückel Approximation*

Submitted

This work introduces an implicit method of simulating electrohydrodynamics of polyelectrolytes using multi-particle collision dynamics. The method uses the Debye Hückel approximation to assign appropriate forces to fluid particles surrounding charge monomers. The results provide reasonable behaviour of the mobility as a function of the degree of polymerization when compared to simulations based on explicit ions and experimental results. The model also gives good agreement for the effective charge and effective friction coefficient, giving it promise as a new mesoscopic technique for the simulation of polyelectrolytes subject to an electric field.

1.10 Other Contributions

During my doctorate I was also a contributing author on two review articles and published two articles that are not related to the main theme of my thesis which are listed below. I also had the opportunity to present my results at a variety of conferences also listed below.

Publications

- 1) GW Slater, C Holm, MV Chubynsky, HW de Haan, A Dubé, K Grass, OA Hickey, C Kingsbury, D Sean, TN Shendruk, L Zhan. *Modeling the separation of macromolecules: A review of current computer simulation methods. Electrophoresis* **30**, 792-818 (2009).
See **APPENDIX A**. This article reviews the main methods used for simulating the separation of polymers. The article then describes a set of systems on the frontier of simulations in this area. In this article I wrote the section on modulation of EOF by polymer coating as well as the explanation of the bond-fluctuation model.
- 2) TN Shendruk, OA Hickey, GW Slater, JL Harden. *Electrophoresis: When Hydrodynamics Matter. Current Opinion in Colloid and Interface Science Accepted*.
See **APPENDIX B**. This review examines the role of hydrodynamic interactions in a variety of systems related to polyelectrolyte electrophoresis. I wrote the section on soft interfaces while helping extensively with the editing of others.
- 3) OA Hickey, JF Mercier, MG Gauthier, F Tessier, S Bekhechi, GW Slater. *Effective molecular diffusion coefficient in a two-phase gel medium. The Journal of Chemical Physics* **124**, 204903 (2006).
See **APPENDIX C**. This work looked at the diffusion coefficient of a tracer particle using

exact solutions of Monte Carlo simulations. The system studied was a cross-linked polymer matrix with viscous spherical inclusions. I conducted the simulations along with Jean-Francois Mercier. I also came up with a formula to fit the data.

- 4) OA Hickey, GW Slater. *The diffusion coefficient of a polymer in an array of obstacles is a non-monotonic function of the degree of disorder in the medium. **Physics Letters A** 364, 448-552 (2007).*

See **APPENDIX D**. This article examined how the diffusion coefficients of polymers varied in arrays of obstacles as the obstacles went from periodic to random. The diffusion coefficient was found to initially rise with increasing randomness of the obstacles positions followed by a dramatic decrease. In this article I conducted the simulations and analyzed the results. I also wrote the article in collaboration with Dr. Slater.

Conference presentations

- 1) OA Hickey, GW Slater. *Molecular Dynamics Simulations of Quenching of Electro-osmotic Flow Using Dynamically Adsorbed Polymer Coatings. **Canada-America-Mexico Meeting**, Montreal, Canada (2007). Oral Presentation.*
<http://cam2007.triumf.ca>
- 2) OA Hickey, GW Slater. *Surprising non-monotonic dependence of a polymer's diffusion coefficient on the degree of disorder of the medium. **American Physical Society March Meeting**, Denver, United States (2007). Poster Presentation.*
<http://meetings.aps.org/Meeting/MAR07/Content/662>
- 3) OA Hickey, GW Slater. *Molecular Dynamics Simulations Of Dynamic Coatings For Quenching Electroosmotic Flow. **American Institute of Chemical Engineers Annual Meeting**, Salt Lake City, United States (2007). Oral Presentation.*
<http://apps.aiche.org/Proceedings/Conference.aspx?ConfID=Annual-2007>
- 4) GW Slater, OA Hickey, F Tessier. *Controlling EOF Using Polymer Coating: An Investigation Using Molecular Dynamics Simulations. **The 82nd American Chemical Society Colloid & Surface Science Symposium**, Raleigh, United States (2008).*
<http://acs.confex.com/acs/csss08/techprogram/MEETING.HTM>
- 5) GW Slater, OA Hickey. *Molecular Dynamics Simulation of the Effect of Polymer Brushes on EOF. **The 23rd International Symposium on MicroScale Bioseparations**, Boston, United States (2009). Poster Presentation.*

<http://www.casss.org/displayconvention.cfm?conventionnbr=5393>

- 6) OA Hickey, GW Slater. *Molecular Dynamics Simulations of Adsorbed Polymer Coatings for Modulating Electro-osmotic Flow*. **Gordon Conference: Microfluidics, Physics & Chemistry of**, Lucca, Italy (2009). Poster Presentation.
<http://www.grc.org/programs.aspx?year=2009&program=micrfluid>

- 7) OA Hickey, GW Slater. *Modulating Electro-osmotic Flow Using Charged Polymer Brushes*. **Frontiers in Polymer Science**, Mainz, Germany (2009). Poster Presentation.
<http://www.frontiersinpolymerscience.com/2009/index.htm>

- 8) OA Hickey, GW Slater, C Holm. *Electrophoretic mobility of short polymer chains*. **New Conceptual Approaches to Modeling and Simulation of Complex Systems**, Mainz, Germany (2009). Oral Presentation.
<http://www.mpip-mainz.mpg.de/theory/events/vw2009/program>

- 9) OA Hickey, JL Harden, C Holm, GW Slater. *MD simulations of the effect of grafted charged polymer coatings on electro-osmotic flow*. **American Physical Society March Meeting**, Portland, United States (2010). Poster Presentation.
<http://meetings.aps.org/Meeting/MAR10/Content/1812>

- 10) OA Hickey, JL Harden, C Holm, GW Slater. *A very mesoscopic approach to simulating the electrohydrodynamics of polyampholytes*. **Novel Simulation Approaches to Soft Matter**, Dresden, Germany (2010). Poster Presentation.
<http://www.mpipks-dresden.mpg.de/nsasm10/>

- 11) OA Hickey, JL Harden, C Holm, GW Slater. *Electrohydrodynamics of polyelectrolytes using Lattice-Boltzmann simulations without electrostatics*. **American Physical Society March Meeting**, Dallas, United States (2011). Oral Presentation.
<http://meetings.aps.org/Meeting/MAR11/Content/2061>

- 12) OA Hickey, TN Shendruk, JL Harden, C Holm, GW Slater. *Electrokinetics of Polyelectrolytes with an Effective Debye Length*. **CECAM workshop: New Challenges for the Simulation of Electrokinetic Phenomena**, Paris, France (2011). Oral Presentation.
<http://www.cecarn.org/workshop-0-574.html>

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Molecular Dynamics Simulations of Optimal Dynamic Uncharged Polymer Coatings for Quenching Electro-osmotic Flow

OA Hickey, JL Harden, GW Slater. *Physical Review Letters* **102**, 108304 (2009)

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Molecular Dynamics Simulations of Optimal Dynamic Uncharged Polymer Coatings for Quenching Electro-osmotic Flow

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(Received 21 July 2008; published 13 March 2009)

The suppression of electro-osmotic flow (EOF) through the use of a dynamically adsorbed polymer coating is a widely used technique in microfluidic devices. Recent experimental evidence has suggested that the most effective coatings are those which are only weakly adsorbed to the surface. We report molecular dynamics simulation results which show that the optimal adsorption strength for the suppression of EOF is around the transition for adsorption of the polymer. Our results should help to guide the design of novel polymer coatings for improved quenching of EOF.

DOI: 10.1103/PhysRevLett.102.108304

PACS numbers: 82.39.Wj, 47.11.Mn, 47.15.gm

Electro-osmotic flow (EOF) occurs in systems where a stationary interface becomes charged when placed in contact with a liquid. When an electric field is applied to such a system there is a net flow (the EOF) caused by counterions dragging the rest of the fluid. Commonly studied instances of EOF are flows of fluid through a cylindrical tube or between two parallel plates. Recently this topic has garnered significant interest as it is important in many novel microfluidic and nanofluidic devices [1–3]. These devices are often made of silica using lithographic techniques originally developed for the manufacturing of microelectronics. Silica surfaces become negatively ionized when exposed to aqueous buffers, leaving an excess of positive ions in the fluid. These counterions aggregate near the wall of the device forming a thin layer of charged fluid called the Debye layer. When an electric field is applied parallel to the surface of the device, the ions in the Debye layer generate a pluglike flow by viscous coupling of the fluid molecules in the bulk to the electrically driven flow in the Debye layer (since the Debye length is typically much less than the characteristic dimensions of the device, the resulting flow is essentially uniform except very near the surface).

Polymer coatings are often used in capillary or micro-channel electrophoresis in order to minimize wall-analyte interactions. These coatings have the additional benefit of being able to modify and control the EOF. Understanding how this occurs is key to designing coatings for optimal separations [4–7]. These coatings can be grouped into two major categories: those that are grafted to the surface and those that are adsorbed. The latter group is the focus of this Letter as adsorbed coatings are more common due to their ease in implementation.

More often than not polymer coatings have a tendency to reduce the EOF. The reduction of the flow is quite similar to the reduction caused by rough walls [8,9] and is a result of the momentum created in the Debye layer being transferred from the local fluid to the polymers (which then transfer it to the wall) instead of it being transferred to the bulk fluid by way of shear forces. There can also be

interesting effects caused by changes in the properties of the Debye layer [10–12].

Previously our group used coarse-grained molecular dynamics (MD) simulations in order to study the quenching of EOF using end-grafted polymer chains in good solvent conditions [13,14]. This work was able to confirm some of the scaling predictions made by Harden, Long, and Ajdari [15]. In this work we use MD simulations to look at *adsorbed neutral* polymer coatings, most notably trying to qualitatively reproduce and explain the remarkable experimental results of Doherty *et al.* [16]. In their experimental study, these authors found that strongly adsorbed coatings did a poorer job quenching the EOF than more weakly adsorbed ones. They hypothesized that this was due to the conformation of the polymers near the surface. The more weakly adsorbed chains have loops which stretch out through the Debye layer and impose additional dissipation in the bulk due to solvent drag on the polymer loops. Of course, polymer chains that have no attraction to the surface would fail to form a coating and simply flow through the center of the channel in the bulk. In this Letter we present simulation results that demonstrate the existence of an optimal adsorption strength for the quenching of EOF. We will also show results which indicate that the quenching is improved with increasing polymer length, a key finding of Doherty *et al.* [16].

In order to model adsorbed coatings and their quenching of EOF we make use of coarse-grained MD simulations (see Fig. 1 for a snapshot), similar to previous simulations on EOF done in our group [13,14]. As before, we employ a purely repulsive Lennard-Jones potential (characterized by a length σ and an energy ε) between all particles, the standard FENE bonds between monomers, wall beads coupled to an fcc lattice by way of a harmonic potential, and an electric force qE on all charged particles. The electrostatic interactions between charged particles were modeled using Coulomb's law with an appropriate cutoff as previously determined [14]. Note that the wall beads have a mass $m_w = 3m$ while all the other beads have a mass of $m_f = 1m$ where m is the characteristic mass of our

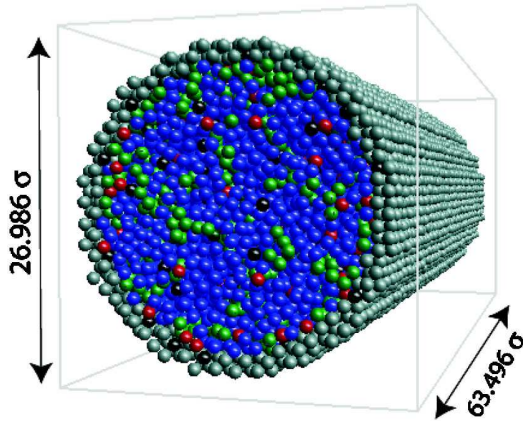


FIG. 1 (color online). A snapshot of our MD simulation system. Note that the length of this tube (63.496σ) is shorter than in the actual simulations (126.992σ). The system is held together by the light gray beads which make up the walls of the tube. The black beads on the wall represent negatively charged wall beads. Inside the channel there are blue (or dark gray) beads representing uncharged fluid, while black and red (or gray) beads represent negatively and positively charged fluid particles, respectively. Last, the green (or light gray) beads represent the monomers.

simulations. We set $k_B T = \epsilon = 1$, and use a dissipative particle dynamics thermostat to control the temperature [17]. An attractive potential, in addition to the diverging Lennard-Jones potential, is applied between the monomer and wall particles in order to model polymer adsorption. We opted to use a potential described in [18] since it extends over a finite distance and is easily differentiable making it computationally efficient:

$$\frac{U_{\text{ads}}(r)}{k_B T} = \begin{cases} -\phi & r \leq 2^{1/6}\sigma, \\ \frac{1}{2}\phi[\cos(\alpha r^2 + \beta) - 1] & 2^{1/6}\sigma \leq r \leq 1.5\sigma, \\ 0 & r \geq 1.5\sigma, \end{cases}$$

where $\alpha = \pi/(9/4 - 2^{1/3})\sigma^{-2}$ and $\beta = \pi(1 - 2^{1/3}/(9/4 - 2^{1/3}))$ in order to make U_{ads} and its derivative continuous everywhere. The parameter ϕ gives the strength of the potential between the wall and monomer beads and is nondimensionalized by $k_B T$. Note that [14] gives approximate SI values for the MD units given in this Letter. The electric field is significantly higher than is used in experiment in order to generate a higher signal-to-noise ratio.

All simulations were carried out using a tube of length $L = 126.992\sigma$ and outer diameter $d = 26.986\sigma$, and the particle density inside the channel was kept constant at $0.8\sigma^{-3}$. The polymer concentration used corresponds to one monomer per σ^2 of wall surface area; this is more than enough to coat the entire wall twice over. For $N = 100$ beads per polymer (the largest polymer length in our simulations), this concentration implies a population of $M = 83$ chains. The monomer concentration used in our study is thus $c = \frac{MN}{\pi R^2 L} \approx \frac{(83)(100)}{\pi(10.4\sigma)^2 127\sigma} \approx 0.192\sigma^{-3}$ (note that we use the inner radius of the tube for R). For $\phi =$

0 and $qE = 0$, the radius of gyration of our largest chain is $R_g(N = 100) \approx 5.2\sigma$; the overlap concentration is then $c^* \approx N/[\frac{4}{3}\pi(5.2\sigma)^3] \approx 0.141\sigma^{-3}$, which is slightly smaller than c . This is the farthest we probe into the semidilute regime in terms of bulk behavior as the overlap monomer concentration increases with decreasing N . Note that the monomer concentration in the region near the wall is often higher than c^* for finite values of ϕ . A rough estimation of the Reynolds number is $\text{Re} = \rho v_s D / \eta \approx (1)(0.1)(27)/(3) \approx 10$ (using viscosity calculations from [19]) which implies laminar flow well below the transition to turbulence.

First consider Fig. 2(a) which shows the radial monomer density profiles for various values of the adsorption strength ϕ . In these simulations we held the electric force $qE = 0$, the number of monomers $N = 100$, and the number of chains $M = 83$ constant. The $N = 100$ chains have an average radius of gyration R_g which varies between 5σ and 11σ depending on the strength of the electric field qE (which stretches the polymers), and the adsorption strength

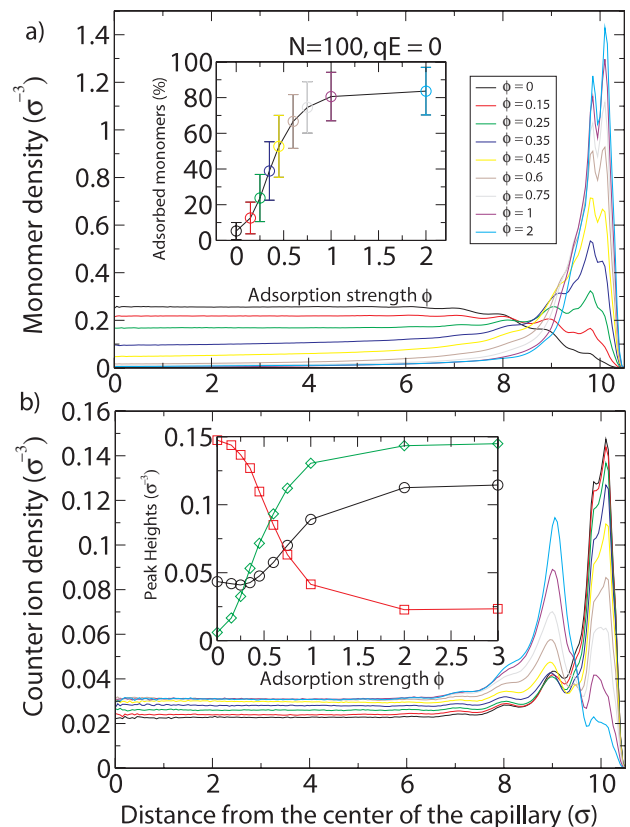


FIG. 2 (color online). (a),(b) Show the radial monomer and counterion densities, respectively, for various values of the adsorption strength ϕ . The error bars in the inset of (a) represent the standard deviation. The inset of (b) shows the position of the peaks in the counterion density closest (red squares) and second closest (black circles) to the wall, and the highest monomer density within 1σ of the wall (green diamonds), divided by ten for clarity.

ϕ (which confines the polymers to the surface causing two-dimensional behavior). In the nonadsorbing equilibrium case, $\phi = 0$ and $qE = 0$, we observe a reduction in the monomer density near the wall (extending over a distance comparable to R_g^0); this is due to the region near the wall being entropically unfavorable to the polymer chains. As ϕ increases we see a gradual increase in the monomer density near the wall, with an approximately flat profile for $\phi \approx 0.2$, and a saturation that starts near $\phi \approx 1$. The inset shows that the transition between bulk and adsorbed behavior occurs around $\phi \approx 0.35$ (the inflection point). When $\phi \geq 1$, the high density of monomers near the wall forces the counterions towards the center of the tube, effectively reducing its inner radius R [see Fig. 2(b)]. Note that both the large peaks for $\phi \geq 1$ and the oscillations in the density profiles near the wall are due to the short ranged pair correlations of the monomers with the highly ordered equilibrium positions of the wall beads.

Figure 3 shows the mean fluid velocity as a function of radial position for different values of ϕ with $qE = 3 \frac{k_B T}{\sigma}$. When $\phi = 0$, the EOF profile looks qualitatively similar to a polymer-free system: a sharp increase in the fluid velocity near the wall is followed by a plateau in the bulk. This similarity to the polymer-free system is only true of EOF profiles near $\phi = 0$. As ϕ is increased, the polymers start adsorbing, resulting in the coexistence of monomers and counterions in the region near the wall. Within the Debye layer we see a smaller rise in the fluid velocity as we move away from the wall that is followed by a decreased bulk EOF velocity as compared with the free polymer case ($\phi = 0$). Both of these effects are manifestations of the now anchored polymer layer creating drag on the fluid passing through it.

Figure 3 also shows *increased* bulk EOF when $\phi > 1$. As discussed in reference to Fig. 2, the counterions of the Debye layer in this regime are forced toward the center of the tube in order to accommodate the adsorption of the polymers. This reduces the effective inner radius of the

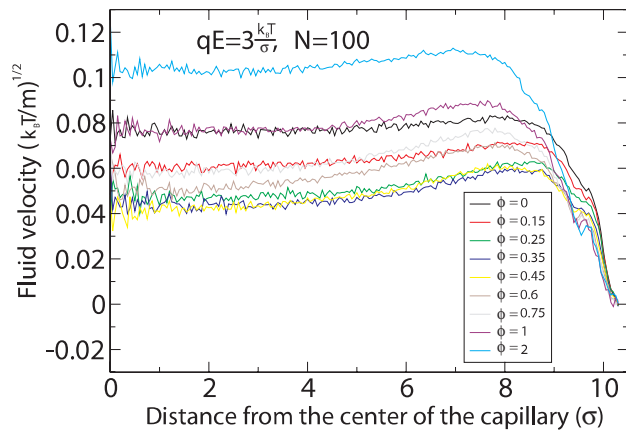


FIG. 3 (color online). The effect of varying the strength of adsorption, ϕ , on the EOF velocity.

channel by about 2σ . Since the surface area of the tube is effectively reduced while the number of counterions remains unchanged, we have an increased concentration of counterions in the Debye layer (see the drawings in Fig. 4 for a schematic representation of this effect). This increases both the zeta potential and the EOF, similar to results reported previously by Qiao [11]. It is important to note that there is an inherent roughening of the surface due to the adsorbed polymer coating which we might expect to decrease the EOF [9], but this appears to be a secondary effect in our system. Indeed, as the interfacial roughness in our system exhibits spatial and temporal fluctuations, the effects of roughness may be less than in other systems with static roughness.

As we see in Fig. 4, the bulk EOF velocity reaches a minimum at $\phi \approx 0.35$ for all three values of N . We note that $\phi \approx 0.35$ is also the location of the inflection point in the graph of percentage of adsorbed monomers versus adsorption strength shown in the inset to Fig. 2. In other words, the optimal regime for quenching the EOF is intermediate between the weak and strong adsorption regimes and corresponds to the transition between these two limiting cases. Finally, one can also see that the bulk fluid velocity for values of $\phi > 1$ is indeed significantly higher than the $\phi = 0$ case as discussed above. This is a result of decreasing the effective radius of the tube and the concomitant increase in the counterion density (see the inset of Fig. 2(b)). The effect of the polymer size N is also of importance here. The $N = 10$ curve is almost monotonically increasing with respect to the adsorption strength ϕ (the minimum is quite shallow) while the $N = 25$ and $N = 100$ curves display successively lower minima. We also simulated this system for various values of N between 10 and 100 at a fixed a value of $\phi = 0.35$ and found that the

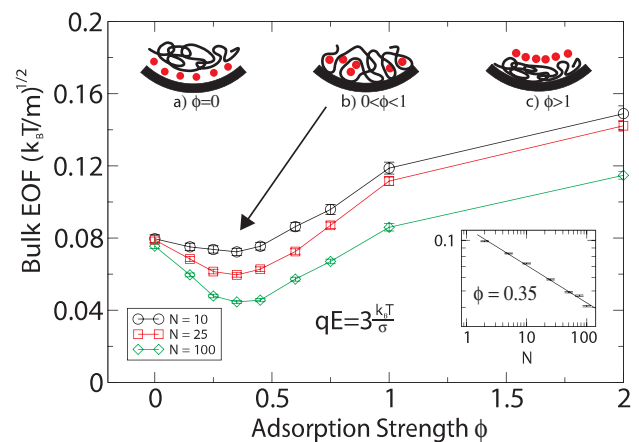


FIG. 4 (color online). The bulk fluid electro-osmotic velocity within 2σ of the center of our tube for different values of the adsorption strength ϕ and polymer lengths N . The inset shows bulk EOF values for $\phi = 0.35$ as a function of N , fitted with a power law. The figure also includes schematic representations of why the polymer coating becomes ineffective when $\phi > 1$ or as ϕ approaches 0.

minimum bulk fluid velocity decreases roughly like $N^{-0.22}$ (see the inset). While the reason for this power law behavior is unclear at this point it implies that quenching could be potentially increased dramatically by continuing to increase the polymer length, in agreement with experimental results [16].

In this Letter we examined how the strength of adsorption of an adsorbed polymer coating affects the quenching of the EOF in a tube geometry. Our simulations indicate that the optimal adsorption strength for the quenching of EOF is when it is near the characteristic value $\phi = 0.35$ separating the adsorbed and nonadsorbed polymer regimes [the inflection point in the inset of Fig. 2(a)]. When the polymers are not adsorbed to the surface there is little friction between the polymers and the walls of the tube [as a matter of fact, even the polymer length plays no role in this limit—see Fig. 4]. In order to quench the EOF, an adsorbed polymer must loop from the wall into the bulk of the fluid, imposing local friction between polymer and solvent beyond the Debye layer. In the limit of very strong adsorption ($\phi > 1$), the polymers simply collapse onto the wall leaving no loops which stretch into the bulk of the fluid. In addition, in this limit the counterions are pushed towards the center of the tube. The counterions are then distributed over a tube with an effective radius which is smaller than the original tube, thus increasing the surface charge density of counterions. This can cause an increase in the zeta potential which in turn increases the magnitude of the EOF in the bulk of the fluid, similarly to results obtained by Qiao [11].

Comparing to experiment, our findings are in good agreement with the results of Doherty *et al.* [16]. In their investigation, it was found that the more strongly a chain is adsorbed to the surface, the less it quenches the EOF. As shown in Fig. 4, this behavior is also observed in our simulations for $\phi > 0.4$. Furthermore, we were able to observe the rich behavior below $\phi \approx 0.35$ —a region which was not probed experimentally as the measurements were limited to relatively strongly adsorbed polymer layers. For $\phi < 0.35$ (corresponding to weak adsorption of polymers), we find a new result where the more weakly adsorbed chains actually prove to quench EOF less.

Our simulations also compare well qualitatively to experiment in terms of the dependence of the quenching on the degree of polymerization. In the experiments of Doherty *et al.* [16], the EOF decreases by orders of magnitude as the length of the polymers which make up the adsorbed coating is increased. This result is in agreement with our simulations where it was found that the short chains prove to make for ineffective coatings since they are not long enough to have both a well-anchored section and a loop that stretches out into the bulk of the fluid. Although the range of polymer lengths N in our study was relatively limited, the bulk EOF does appear to show a power law decay with respect to N (see the inset of Fig. 4). This implies that increasing N to much larger values could

provide a degree of quenching similar to what is found experimentally.

Considering their widespread application in DNA electrophoresis [4–7] research concerning adsorbed polymer coatings is an area of vital importance to electrophoretic separations. This Letter represents the first systematic computer simulations into dynamic coatings and their role in the modulation of EOF. These results are in good agreement with experimental observations as noted above and should provide a basis for future investigations into the role of adsorbed polymer coatings in the modulation of EOF.

The authors would like to thank Dr. Frédéric Tessier for helpful discussions about this work. This work was supported through NSERC discovery grants to G.W.S. and J.L.H., and an NIH grant to G.W.S. (Grant No. NHGRI R01 HG002918-01) through Northwestern University. The findings, opinions, and recommendations expressed in this Letter are those of the authors and not necessarily those of Northwestern University or the NIH. O. A. H. would also like to acknowledge funding from the University of Ottawa, OGS, and HPCVL. HPCVL also provided computational resources for this work.

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Time-dependent suppression of EOF by fresh polymer coatings: A computer simulation study

OA Hickey, JL Harden, GW Slater. Submitted

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Computer simulations of time-dependent suppression of EOF by polymer coatings

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Received: January 10, 2012/ Accepted: date

Abstract We use Molecular Dynamics simulations in order to investigate the time evolution of the effect of adsorbed polymer coatings on the electro-osmotic flow (EOF) in a capillary. Weakly adsorbed coatings show no time-dependent performance, but they do not strongly reduce the EOF. On the other hand, strongly adsorbed coatings made of longer polymer chains are often quenched in non-equilibrium conformations that can strongly reduce the EOF over extremely long periods of time. For intermediate adsorption strengths, we observe that the EOF increases as a function of time due to the relaxation of the coating layer. The concentration of polymers in solution and the length of the polymer chains also affect the time-dependence of the EOF. These results show that the quality of electrophoretic separations can depend on the waiting time between the formation of the coating and the beginning of the separation. We conclude by suggesting experimental tests of our predictions.

Keywords Electroosmotic flow, nanochannels, polymer coating, polymer adsorption, microfluidics

1 Introduction

In recent years there has been a move to shrink the size of fluidic devices for DNA and protein electrophoresis to the micro- and even the nano-scale. The devices are often made of either glass or silica. In both cases, the surface of the device becomes negatively charged when placed in contact with an aqueous solution. This results in a charged layer of fluid (the Debye layer) forming next to the surface. When an electric field is applied parallel to the surface, the ions which form the Debye layer move in the direction of the field, while those attached to the surface remain immobile. The mobile ions transfer a net amount of momentum to the uncharged fluid; the resulting flow is often called a plug flow since the ions only shear the fluid in the Debye layer (which is generally negligible in size compared to the diameter of the microchannel) adjacent to the wall while the fluid in the bulk moves at a constant velocity independent of the distance from the wall. This flow is termed electro-osmotic flow (EOF).

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In practice, EOF tends to have a deleterious effect on the resolution of a separation method. The main reason for this is that the EOF drags all solutes with the same velocity without improving their separation. This means that a device often needs to be longer in order to achieve the same peak separation. Another negative effect on the resolution is the increased dispersion caused by the inhomogeneity of the EOF due to the non-uniformity of the charge distribution on the wall.

In order to combat these negative effects, experimentalists have long made use of polymer coatings that can modulate or even eliminate the EOF (Chiari et al, 2000; Horvath and Dolník, 2001; Shendruk et al, 2011). Previously, our research group has investigated the case of grafted polymer coatings (Tessier and Slater, 2005, 2006) using Molecular Dynamics (MD) simulations. These simulations were able to confirm some of the scaling predictions (Harden et al, 2001) for grafted polymer coatings.

More recently, we have employed MD simulations to look at the case of a second class of polymer coatings: adsorbed polymers (Hickey et al, 2009). Adsorbed polymer coatings have not received as much computational or analytic attention, most likely due to the fact that the problem is much more difficult to treat. In contrast, adsorbed coatings are widespread in experiments due to their effectiveness (at controlling both EOF and analyte-wall interactions) and ease of use. Our simulations were able to reproduce the interesting results (Doherty et al, 2002) which found that more hydrophilic polymer coatings were better able to suppress EOF than those which were more hydrophobic. The key factor for controlling EOF was found to be the height of the polymer loops stretching out from the surface into the solution. Our simulations also showed that very strongly adsorbed polymer coatings can actually have the effect of increasing the EOF in a narrow-diameter device. Similar effects have been seen in recent simulations of grafted coatings (Qiao, 2006; Qiao and He, 2007; Cao et al, 2010, 2011). This raises interesting questions about the time-dependence of EOF modulated by adsorbed polymer coatings since these coatings evolve over long periods of time after adsorption starts.

In this article we report evidence for the existence of new dynamic regimes. Notably we observe a transient regime for high density coatings where the reduction in EOF is much larger than in the asymptotic (long-time) steady-state regime. At high adsorption strengths this strong quenching regime is long lived and is likely to be experimentally relevant. For moderate adsorption strengths we see a transition back to the asymptotic behaviour for low density coatings. At adsorption strengths below the phase transition for adsorption, the EOF is fairly constant throughout our simulations. We show evidence that the transition from strong to weak EOF quenching at moderate adsorption strengths is due to the rearrangement of the adsorbed polymers via competitive adsorption, something which is not seen at very strong and very weak adsorption strengths. These results should help our understanding of the mechanisms responsible for the instability of polymer coatings in modulating EOF as has been observed experimentally (Chiari et al, 2000; Horvath and Dolník, 2001).

2 Methods

The MD simulations utilized code that we have previously written and used for studying the effect of polymer coatings on EOF (Tessier and Slater, 2006; Hickey et al, 2009; Slater et al, 2009). Molecules are represented by beads of mass m interacting via a purely repulsive, shifted, truncated Lennard-Jones potential between all pairs of beads; this potential defines the characteristic length scale σ and energy scale ϵ . Note that we set $\epsilon = k_B T$ and control the temperature using a dissipative particle dynamics (DPD) thermostat (Soddemann et al, 2003), as before (Tessier and Slater, 2006; Hickey

et al, 2009). The Lennard-Jones fluid is simple and neglects important effects such as solvation and hydrogen bonding (Qiao, 2006). The choice of such a simplified model is due to the speed of computation while still accurately modeling long ranged hydrodynamic interactions (Slater et al, 2009). Monovalent charges e are added to some of the wall and fluid beads in the same manner as our previous simulations (Tessier and Slater, 2006; Hickey et al, 2009) and the electrostatic interactions are modeled using a Coulomb force with an appropriate cutoff and a Bjerrum length of $l_B = 2\sigma$. In addition, an electrophoretic force $F_E = eE = 3\epsilon/\sigma$ is added to each charged bead. This corresponds to an electric field of roughly 300 000 V/cm (Tessier and Slater, 2006). Such a large electric field is chosen in order to maximize the signal-to-noise ratio allowing the generation of results in a reasonable length of time. The polymers are modeled as a series of N uncharged beads linked together using a finitely extensible non-linear elastic (FENE) potential. This represents a coarse grained approach compared to more detailed simulation techniques (de Pablo, 2011). The advantage of this model is significant reduction in the time of computation and as such is a common tool in the simulation of polymeric systems where one is seeking to uncover generic trends in the system behaviour (Slater et al, 2009). The simulations are carried out using a tube of lengths $L = 127.0\sigma$ or $L = 63.5\sigma$ and inner diameter $d = 20.8\sigma$. The density of particles inside of the channel is kept at $0.8\sigma^{-3}$ and the system as a whole is electrically neutral.

We also apply an adsorption potential between monomer and wall particles. We opted to use the potential used by (Soddemanna et al, 2001) since it extends over a finite distance and is easily differentiable making it computationally efficient:

$$\frac{U_{\text{ads}}(r)}{k_B T} = \begin{cases} -\phi & \frac{r}{\sigma} \leq 2^{\frac{1}{6}} \\ \frac{\phi}{2} [\cos(\alpha r^2 + \beta) - 1] & 2^{\frac{1}{6}} \leq \frac{r}{\sigma} \leq \frac{3}{2} \\ 0 & \frac{r}{\sigma} \geq \frac{3}{2} \end{cases} \quad (1)$$

where $\alpha = \pi/(9/4 - 2^{1/3})\sigma^{-2}$ and $\beta = \pi(1 - 2^{1/3}/(9/4 - 2^{1/3}))$ in order to make U_{ads} and its derivative continuous everywhere. The parameter ϕ represents (in units of $k_B T$) the strength of the potential between the wall and monomer beads.

At the start of our simulations (time $t = 0\tau$, where $\tau = \sigma/(k_B T/m)^{1/2}$ is the characteristic MD time scale), the polymers are inserted at random coordinates in the tube and are built as self avoiding walks (SAWs). As we shall see, the distribution of polymers and the EOF start evolving immediately after the simulation starts, and they often do so over long periods of time. Our *standard* polymer concentration corresponds to a surface density, ρ_S of around one monomer per σ^2 of inner channel surface area. For $N = 100$ (the largest polymer contour length in our simulations), this requires a total of $M = 83$ chains in the tube. At $\phi = 0$ and $E = 0$, the radius of gyration of the $N = 100$ polymer chain is $R_g = 5.2\sigma$. This means that for $N = 100$, our standard polymer concentration $c \approx 0.19\sigma^{-3}$ would be close to the overlap monomer concentration of $c^* \approx N/\frac{4}{3}\pi(5.2\sigma)^3 \approx 0.17\sigma^{-3}$. Since the overlap monomer concentration $c^* \sim N/R_g^3$ increases with decreasing N , most of our simulations are actually in the dilute regime. However, the concentration of monomers in the region near the wall is much higher when $\phi > 0$ implying that the polymer layer can generally be seen as being in the semi-dilute regime. Note that data points are the result of a single simulation. In general the standard error is of the order of the symbol size. At large adsorption strengths their appears to be additional variation in the data due to the long lived polymer conformations.

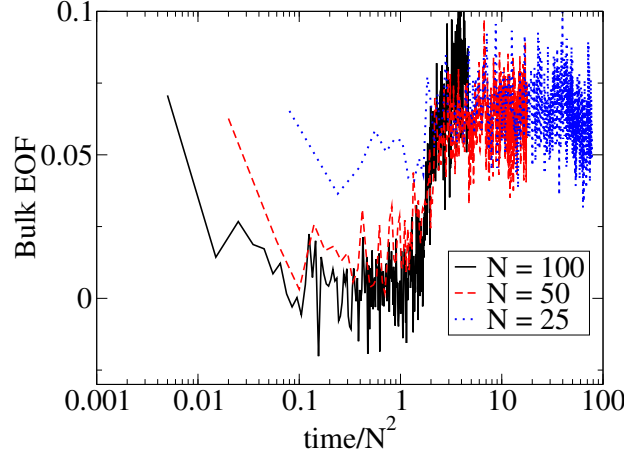


Fig. 1 The EOF velocity v_{EOF} within 2σ of the center of our tube as a function of time for an adsorption parameter $\phi = 1.1$ and three different polymer sizes N . The polymer concentration is $0.384\sigma^{-3}$

3 Results

3.1 EOF as a function of time

In this section we examine the time evolution of the EOF as a function of the adsorption strength ϕ for a fixed polymer concentration $c = 0.384\sigma^{-3}$ (which corresponds to a surface density $\rho_S \approx 2\sigma^{-2}$). Since the polymer-wall interaction is turned on at time $t = 0$, the coating starts forming immediately and then evolves towards an equilibrium state (note that the latter is not always achieved during the simulation). An example of the time evolution of the bulk EOF is shown in Fig. 1 (note that we rescaled the time axis by N^2). This is a case where the adsorption parameter has a moderate value $\phi = 1.1$ well above the threshold for polymer adsorption. In all cases, the initial value of the EOF velocity is $v_{EOF} = 0.067 \pm 0.05$ (note that all velocities will be in MD units of σ/τ in this article). This is followed by a very rapid decay to a minimum value of approximately 0.04 for the short $N = 25$ chains (which are not very good at controlling the EOF) and a minimum value of about ≈ 0.01 for the two longer polymers. This decay is due to the monomers that are initially close to the wall being adsorbed (this takes about $t \sim 300$). For $N = 25$, the EOF is then seen to quickly increase to a steady-state value of about $v_{EOF} = 0.07$, consistent with the fact that strongly adsorbed polymer coatings were previously found to be inefficient at reducing the EOF (Hickey et al, 2009; Doherty et al, 2002). The same behaviour is observed for the other two molecular sizes. In particular, our rescaling of the time axis shows that the N -dependence of the transition to the steady-state is very similar in all three cases. Most interestingly, we may conclude that the EOF is actually negligible for an extended period of (actual, non-scaled) time in the case of the long $N = 100$ polymer chains.

In order to study the long-time impact of the adsorption parameter ϕ and the molecular size N on the EOF, we will average the EOF over time windows of width 5000τ in the rest of this section. We will also follow the time evolution of the number of polymers and monomers in contact with the channel walls. Our results are shown in Fig. 2. The left column shows the mean EOF velocity v_{EOF} during various time intervals for a wide range of ϕ values and three molecular sizes N , while

the right column has adsorption data for the same molecular sizes. Looking at the EOF in the case of the shorter chain ($N = 25$), we observe a crossover point around $\phi \approx 1$. For weak adsorption strengths $\phi < 1$, the EOF decays with time as the polymers slowly adsorb on the wall. However, for stronger adsorption parameters $\phi > 1$, the situation is reversed: EOF increases with time because the polymers reach equilibrium conformations with very short loops that are inefficient at controlling EOF (this is consistent with previously reported results (Hickey et al, 2009; Doherty et al, 2002; Cao et al, 2011, 2010)). This remarkable result indicates that one can obtain very different performances if the duration of the experiment is comparable to the time required for the polymer coating to reach its final (equilibrium) state as compared with an experiment with a relatively shorter duration. As one can see in Fig. 2d, the reorganization of the polymer coating is relatively rapid for these short chains.

The situation is even more interesting for larger chains. When $N = 50$ and 100 , we observe three regimes instead of two. The first two regimes are similar to the ones mentioned above for $N = 25$: a small decrease of the EOF with time when ϕ is small, and a sharp increase with time for moderate values of ϕ . However, we now have a quenched regime for very large values of ϕ : the time required for the EOF to increase simply becomes larger than the simulation (or experimental) time. Although in principle these high- ϕ coatings should be inefficient at reducing the EOF, in practice they work well because they are quenched into their initial state with long loops extending through the Debye layer. As expected, the transition point for these regimes depends on the molecular weight of the polymers; in the case of the transition to the last regime, the critical value of ϕ also depends on the experimental time (this is obvious in Fig. 2b). Given enough time, we expect that Fig. 2b and c would look like Fig. 2 a; however, this asymptotic behaviour is not relevant since experimental studies are not using arbitrarily long preparation (or run) times.

To further study the causes for the time-evolution of the EOF with respect to time, we looked at some properties of the adsorbed polymers (the second column of graphs in Fig. 2). A monomer is considered to be adsorbed if it is within the cutoff range of the wall adsorption potential given in Eq. 1. We looked at the time evolution of both the fraction of adsorbed polymers (dashed lines) and the fraction of adsorbed monomers for polymers with at least one monomer adsorbed (solid lines). For very weak or negligible adsorption ($\phi = 0$) and very strong adsorption ($\phi = 5$), we see that both quantities remain relatively constant throughout the simulation (after some transient short-time changes) regardless of the value of N , much like the EOF itself. For $\phi = 1.1$, the dashed lines decrease for both $N = 50$ and $N = 100$ indicating that polymers are desorbing over the course of the simulation while the solid $\phi = 1.1$ lines increase meaning that more monomers per polymer are adsorbed. Some chains thus desorb in order to increase the entropy of the system while other chains become more completely adsorbed to the surface. This results in a polymer coating with a shorter height which is known to reduce the quenching of EOF (Wang and Dubin, 1999; Cao et al, 2010, 2011; Hickey et al, 2009; Doherty et al, 2002). These observations support the hypothesis that the change in EOF with time for moderate values of ϕ is indeed caused by the rearrangement of chains at the surface. The lack of time for this reorganization to take place explains why large values of ϕ can lead to efficient EOF control over extended periods of time. This clearly shows that both the channel preparation time and the experimental (run) time are key parameters to control in order to obtain efficient and reproducible EOF quenching.

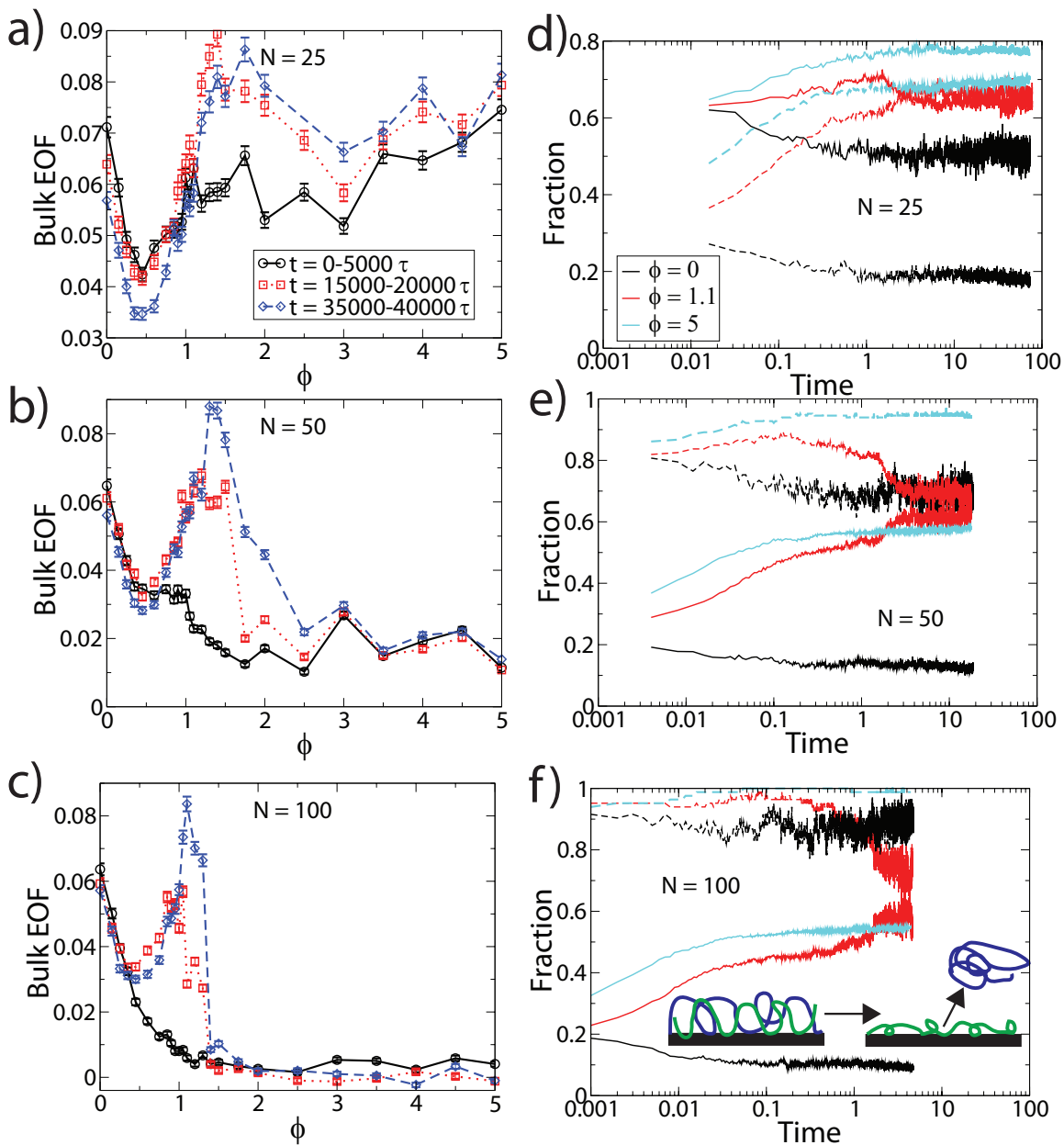


Fig. 2 The left column shows the EOF velocity v_{EOF} within 2σ of the center of the tube for $c = 0.384\sigma^{-3}$ and $N = 25, 50, 100$ and several values of the adsorption strength ϕ . The data points are averaged over 5000 MD time steps τ in order to get good statistics. The second column shows adsorption statistics as a function of time for the same systems for values of $\phi = 0$, $\phi = 1.1$, and $\phi = 5$; the time axis has been rescaled by a factor N^2 . The dashed lines represent the fraction of adsorbed polymers (defined as polymers with at least one adsorbed monomer), while the solid lines represent the average fraction of monomers adsorbed for adsorbed polymers

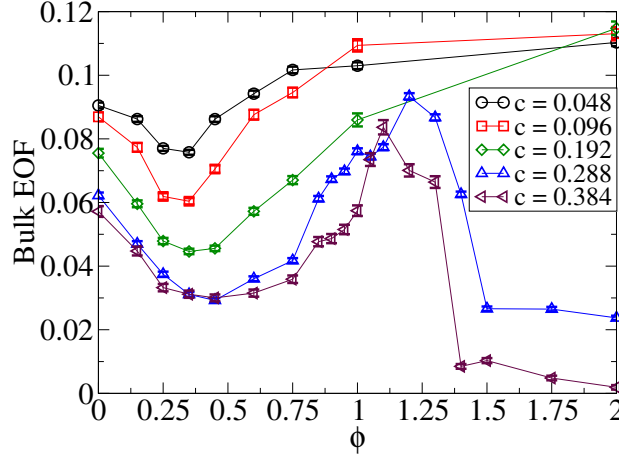


Fig. 3 The EOF velocity v_{EOF} within 2σ of the center of our tube as a function of the adsorption strength ϕ for the largest polymer size $N = 100$ and four different monomer concentrations c . For the three lower concentrations, the systems are in their steady-state, while for $c = 0.288\sigma^{-3}$ and $c = 0.384\sigma^{-3}$ the data points represent averages over the time period $t = 35000 - 40000\tau$, the longest times available

3.2 Effect of Polymer Density

We now examine how polymer density affects the quenching of EOF by adsorbed neutral polymers. In our previous work (Hickey et al, 2009), we looked at only one polymer concentration, $c = 0.19\sigma^{-3}$. In Fig. 3, we examine EOF velocities for various monomer concentrations c . At low monomer concentrations $c = 0.048, 0.096, 0.192\sigma^{-3}$, the trend is simple: more polymers lead to reduced EOF. We actually see the same behaviour as in our previous work (Hickey et al, 2009): there is an initial decrease in EOF as ϕ increases due to increased adsorption of polymers up until the phase transition for adsorption, which occurs around $\phi \approx 0.35$. The EOF then increases due to the polymers collapsing onto the wall and pushing the counter ions beyond the polymer layer. In all of these cases, the simulations were long enough for the polymers to reach steady-state conformations. The situation is not the same for the highest concentrations $c = 0.288\sigma^{-3}$ and $c = 0.384\sigma^{-3}$. Rather, we see that the EOF is reduced to negligible values for these two concentrations when $\phi > 1.3$ and $\phi > 1.5$, respectively, again because the polymer coating has not had time to relax after this period.

In order to better understand the role of polymer density, we chose to focus on the value $\phi = 2$ because it is in the strong quenching regime while being accessible in terms of computing times. To avoid observing the effect of the short-time reorganization of the polymer layer, we averaged the EOF velocity v_{EOF} at the center of the capillary over times $t = 5000 - 15000\tau$. Figure 4 shows this mean value of v_{EOF} as a function of monomer concentration c in the tube. All of the curves display an initial rise followed by a decay (except for $N = 1$ where there is no decay since a single monomer is incapable of forming loops extending beyond the Debye layer). While the initial rise is essentially independent of the polymer length N , the subsequent decrease depends on N . In equilibrium, these polymer coatings should not be able to properly control the EOF since $\phi = 2$ is well beyond the optimal value of $\phi = 0.35$; this is what we observe for low polymer concentrations. However, the polymer systems do not have time to relax at high concentrations, and as a result, they effectively

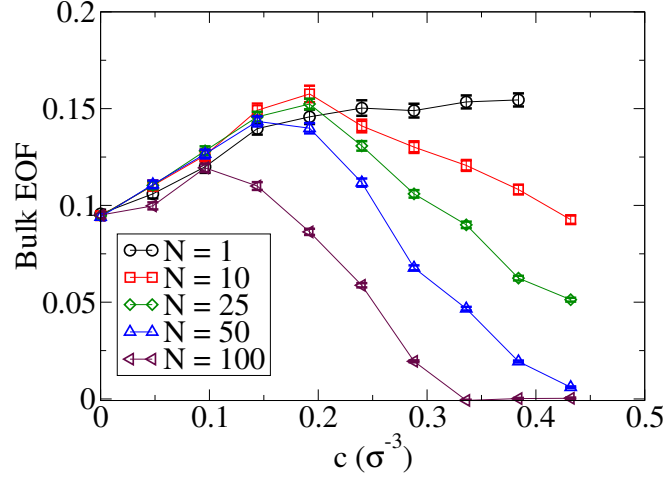


Fig. 4 The EOF velocity v_{EOF} within 2σ of the center of our tube as a function of the monomer volume concentration c for an adsorption parameter $\phi = 2$ and several polymer sizes N . The data was averaged over the simulation time period $t = 5000 - 15000\tau$

control the EOF because the chains in contact with the walls are quenched. The universal increase at low concentration is a nice demonstration that molecular weight is irrelevant in the steady-state if the chains are tightly adsorbed onto the walls, while the spread of the curves at high concentrations is due to the strong N -dependence of the relaxation/rearrangement time of the polymer coating.

More information can be gleaned by looking at snapshots of the simulation as seen in Fig. 5 which shows simulation snapshots for $N = 100$ at $\phi = 2$. In the two lower concentration cases in Fig. 5a and Fig. 5b it can be seen that the polymers are able to lie relatively flat on the wall leading to no reduction in the EOF. By contrast at the higher concentrations, shown in Fig. 5c and Fig. 5d, the polymers are no longer able to lie flat against the wall and extend into the center of the tube causing the dramatic reduction in EOF seen in Fig. 4 at higher concentrations.

4 Conclusion

In this article, we looked at the role of adsorbed polymer coatings in the controlled inhibition of EOF. As with our previous work (Hickey et al, 2009), an increase in the adsorption potential between monomers and the wall leads to an initial decrease in the EOF followed by a rise. However, we also find that for increased polymer concentrations a third regime appears at very high adsorption strengths where there is, for very long periods of time, dramatically lower EOF. Our data clearly demonstrate that this new regime is due to the quasi-irreversible adsorption of polymers to the surface. The polymers essentially adsorb into a metastable state which contains larger loops than in the equilibrium state. In our opinion, this helps to explain the experimentally observed changes in EOF with respect to time (Chiari et al, 2000; Horvath and Dolník, 2001). The time scale for the rearrangement of the chains in our simulations is about ten times the relaxation time of the end-to-end vector for the $N = 100$ chains as measured for $c = 0.048\sigma^{-3}$ and $\phi = 0$ (data not shown). Since the time for the relaxation of the coating appears to scale as N^2 this could mean that

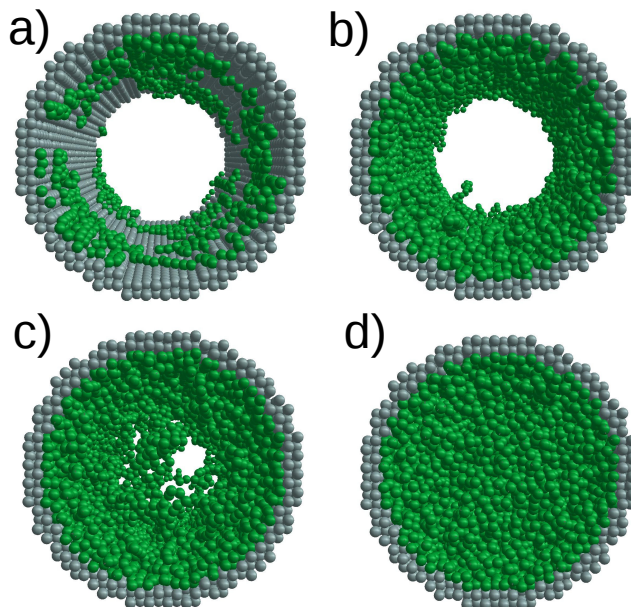


Fig. 5 *Simulation snapshots for $N = 100$, $\phi = 2$ at concentrations a): $c = 0.048\sigma^{-3}$, b): $c = 0.192\sigma^{-3}$, c): $c = 0.288\sigma^{-3}$, and d): $c = 0.432\sigma^{-3}$. The images include only the polymers and wall beads for clarity.*

a layer made up of very long polymers could remain in a metastable state for minutes or even hours (MacDonald et al, 2011). The simulations should also be applicable to soft colloid electrophoresis where adsorption of polymer chains to a colloid has shown to affect the electrophoretic mobility on the time scale of minutes (van Heiningen and Hill, 2011).

While reducing the adsorption strength (or hydrophobicity) improves quenching of the EOF, it also reduces the stability of the coating (Horvath and Dolnik, 2001). The strong quenching regime observed in our simulations at high adsorption strengths and large monomer concentrations could potentially guide the creation of coatings which strongly reduce EOF and yet remain stable for long periods of time. Our simulations indicate that the stability of coatings in this regime increase with both the degree of polymerization and the strength of the wall-monomer attraction. Hopefully our results will help in the future design of highly effective and highly stable polymer coatings.

5 Acknowledgments

We would like to thank Christian Holm for helpful discussion. This work was supported by the National Science and Engineering Research Council through Discovery Grants to GWS and JLH. OAH would also like to acknowledge funding from a University of Ottawa Entrance Scholarship and National Science and Engineering Research Council through the Canada Graduate Scholarship program. Sharcnet provided computational resources for this work.

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Influence of Charged Polymer Coatings on Electro-Osmotic Flow: Molecular Dynamics Simulations

OA Hickey, C Holm, JL Harden, GW Slater. *Macromolecules* **44**, 9455-9463 (2011)

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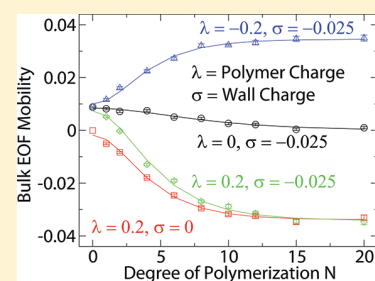
Influence of Charged Polymer Coatings on Electro-Osmotic Flow: Molecular Dynamics Simulations

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ABSTRACT: Electro-osmotic flow (EOF) plays a crucial role in the functioning of devices in micro- and nanofluidics. In order to optimize the operation of a device, polymer coatings are often used to control EOF. Our simulations examine the case of grafted, charged polymer coatings for this purpose and compare the electro-osmotic flow mobility produced by a given polymer coating to the free-flow electrophoretic mobility of the polymers making up that coating. The simulation results are compared to both experimental data and theoretical predictions. One particularly interesting result is that the direction of the EOF reverses well before the net charge of the interface changes sign.



I. INTRODUCTION

In micro- and nanofluidic devices surfaces frequently become charged when placed in contact with an aqueous buffer. This process creates a thin oppositely charged layer of mobile fluid next to the surface, called the Debye layer. When an electric field is applied parallel to the surface, this thin layer of fluid generates a pluglike flow outside the Debye layer called electro-osmotic flow (EOF). In the case of capillary electrophoresis, EOF increases dispersion in the system (thereby reducing resolution) due to the nonuniform character of the flow resulting from unavoidable heterogeneity in the surface charge of capillaries.¹ For this reason scientists have long sought to suppress EOF by making use of polymer coatings in capillary electrophoresis.^{2,3} In other situations, however, some EOF can actually be beneficial to the functioning of the system.⁴ For example, in many microfluidic devices, EOF is used as a pump to move chemicals and samples.⁵ In such cases it might be desirable to maximize EOF while keeping it as uniform as possible.⁶ Our interest here is the role of a charged polymer coating for the control of EOF in the context of capillary electrophoresis and other electro-osmotic microfluidic systems.

Recent computer simulations have probed the role of neutral grafted polymer coatings in modulating EOF.^{7–12} The simulations of Tessier and Slater^{7,8} provided the first computational evidence for the scaling predictions of Harden et al.¹³ for the effect of the length and grafting density of the polymers in the coating. Qiao has investigated the role of the electric field¹⁰ as well as the role of physicochemical interactions on scales smaller than the Debye length.⁹ Cao et al. studied how solvent quality changes the structure of polymer coatings and how this in turn affects EOF.^{11,12} Our group has also made use of coarse-grained molecular dynamics simulations in order to look at the role of dynamically adsorbed polymer coatings in the modulation of

EOF.¹⁴ These simulations were able to qualitatively reproduce the experimental results of Doherty et al.¹⁵

The relationship between polymer coatings and EOF in a tube is rather complex, as the structure of the layer and the flow through the layer are intimately related. This is particularly true in the nonlinear regime of flows that are sufficiently strong to deform the polymer conformations in the layer. In principle, the conformation of polymers and the EOF profile in the layer can be determined self-consistently for simplified models, but often important phenomena are ignored in such theoretical and computational studies. For instance, many studies neglect hydrodynamic interactions in the polymer layer. However, recent studies have shown that such a free-draining approximation is not generally valid, particularly when the Debye length is comparable to or smaller than the thickness of the layer.¹⁶ In fact, the force needed to hold a grafted polyelectrolyte still in an electric field is proportional to its hydrodynamic radius and not the total charge on the polymer in the limit of thin Debye layers,^{17,18} a direct reflection of the effective hydrodynamic drag on the polymer due to EOF. Another intriguing effect that has received some attention in recent years is the role of the relative distribution of charge between the bare surface and the polymer layer on the resulting EOF.^{9,11,14}

In this article, we present coarse-grained molecular dynamics (MD) simulation studies of the role of charged, grafted polymer coatings on EOF, highlighting several fascinating phenomena. First, results are presented showing that the EOF reverses direction before the net charge of the interface (the wall together with the grafted polymers) changes sign. Next, we compare simulation results to the predictions of Harden et al.¹³ and find

Received: August 31, 2011

Revised: October 24, 2011

Published: November 16, 2011

good agreement with their scaling predictions. We also test the hypothesis that for relatively thick polymer coatings the EOF is expected to be of equal magnitude but opposite sign to the electrophoretic mobility of the polymers which make up the coating. We find that while not precisely the same, the two values are indeed comparable. Finally, we look at the role of varying the linear charge density of the polymers and compare this to experiments carried out by Danger et al., which examined how varying the amount of charge in a polyelectrolyte affects not only its electrophoretic properties but also the EOF produced by the polymer when used as a coating.⁴

II. THEORETICAL BACKGROUND

The simplest EOF is for the case of a flat charged surface with a no-slip boundary condition and with free counterions that are able to move with the fluid in response to an electric field parallel to the surface. At low Reynolds number, the governing relation is the Stokes equation with a driving force proportional to the electric field:

$$\nabla^2 v(h) = -\frac{E\rho(h)}{\eta} \quad (1)$$

where $v(h)$ is the velocity of the fluid at a height h above the wall, E is the electric field, $\rho(h)$ is the charge density at h , and η is the viscosity of the fluid. In the continuum limit, we can simply replace the charge density $\rho(h)$ with the Poisson equation yielding

$$\nabla^2 v(h) = -\frac{\epsilon E}{\eta} \nabla^2 \phi(h) \quad (2)$$

where ϵ is the electric permittivity of the fluid and $\phi(h)$ is the potential at h . Integrating the above equation on both sides gives the well-known Helmholtz–Smoluchowski equation:

$$v_{\text{bulk}} = -\frac{\epsilon E \zeta}{\eta} \quad (3)$$

where v_{bulk} is the bulk solution velocity far from the wall and ζ is the zeta potential, the difference in the electrostatic potential of the bulk compared to where the liquid starts to shear near the surface. Often the bulk velocity is divided by the electric field in order to define the electro-osmotic mobility of the wall: $\mu_w \equiv v_{\text{bulk}}/E = \epsilon \zeta/\eta$. The zeta potential is often how surfaces are characterized in microfluidics although this concept is really only applicable to the case of uncoated capillaries.^{19,20}

When the capillaries are coated by polymers the situation is remarkably different. For the case of uncharged polymer layers, the EOF is diminished due to the enhanced hydrodynamic drag between the moving fluid and the immobilized polymers. When the polymers are charged, on the other hand, they also contribute to the generation of EOF within the polymer layer due to the counterions associated with the charged groups on the polymers. The case of end-grafted polymers, polymers attached irreversibly by one end to a surface, has been extensively studied both experimentally and theoretically.²⁰

For calculations of the EOF in the presence of surface grafted polymers, the scaling theory of Harden et al.,¹³ for instance, provides predictions for the EOF far from a grafted polymer layer as a function of the degree of polymerization N , the grafting density γ , the electric field E , the free electrophoretic mobility of the polymers μ_p , and the electro-osmotic mobility of the bare

wall μ_w . Thus, we discuss these predictions in some detail here in order to facilitate comparison with the simulation results of this paper.

The theoretical analysis of ref 13 considered the effects of grafted polymers on EOF in two regimes, namely the “mushroom” regime, where chains are sparsely grafted to the wall with little change in their equilibrium conformation, and the “brush” regime, where chains are grafted so densely that they tend to take on extended conformations due to the steric repulsion between adjacent chains. In the case of the mushroom regime in the low field limit, a simple scaling argument based on surface averaging of the EOF using the surface coverage of the polymer was predicted:

$$\mu_{\text{EOF}} = \mu_w - (\mu_w + \mu_p)(\gamma R_G^2) \quad \text{for } \gamma R_G^2 < 1 \quad (4)$$

where $R_G \sim N^{3/5}$ is the (equilibrium) lateral radius of gyration of the polymers. In the “brush” regime of densely grafted polymers, the surface averaging approach is replaced with one based on transport in a porous polymer layer, which results in

$$\mu_{\text{EOF}} = -\mu_p + (\mu_w + \mu_p) \frac{1}{\cosh[(\gamma R_G^2)^{5/6}]} \quad (5)$$

In both cases, nonlinear terms related to the effect of the electric field E have been neglected, which is appropriate for the limit where the electric field is low. In this article we will examine both the scaling of the EOF mobility μ_{EOF} with respect to N and γ as well as the prediction of eqs 4 and 5 that the EOF goes from μ_w to $-\mu_p$ as N and γ increase.

III. SIMULATION MODEL

The model we use is based previous work by our group on neutral grafted polymer coatings.^{7,8,21} We simulate EOF in a cylindrical tube with periodic boundary conditions along the axis of the tube. Simulations were conducted for both grafted and free polymers, the latter in order to measure their intrinsic electrophoretic mobility. The simulation’s elements included beads representing neutral fluid, salt ions, monomers, and wall particles. All beads experience a purely repulsive WCA potential between each other:

$$\frac{U_{\text{WCA}}(r)}{\epsilon} = \begin{cases} 4 \left[\left(\frac{\sigma_{\text{MD}}}{r} \right)^{12} - \left(\frac{\sigma_{\text{MD}}}{r} \right)^6 \right] + 1 & r \leq r_0 \\ 0 & r > r_0 \end{cases}$$

with $r_0 = 2^{1/6} \sigma_{\text{MD}}$. As is typical in MD simulations,²¹ we choose $\epsilon = k_B T$ as the fundamental MD energy scale and σ_{MD} as the fundamental MD length scale. The temperature is maintained via a dissipative particle dynamics thermostat (DPD).²² Monomers of the polymer chains are linked to each other via FENE bonds: $U_{\text{FENE}}(r) = -0.5kR_0^2 \ln[1 - (r/R_0)^2]$, where $R_0 = 1.5\sigma_{\text{MD}}$ is the maximum extension of the bond and $k = 30\epsilon/\sigma_{\text{MD}}^2$ is the effective spring constant for the interaction. This potential is also used to bind the end of the polymer to the wall. Monomers are charged randomly until the desired average charge per monomer λ is attained. This is done by picking monomers randomly from all of the polymers in the system and not on a chain by chain basis. Thus, although the average charge per polymer is well-defined, the net charge is different for each polymer. This charging scheme was chosen in an effort to represent the experiments of Danger et al.⁴ In their work they

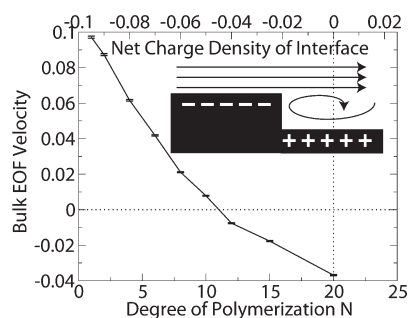


Figure 1. Average fluid velocity v_{EOF} within $2\sigma_{\text{MD}}$ of the center of the tube for the different values of N with $\gamma = 0.05$, $\lambda = 0.1$, $E = 3$, and $\sigma = -0.1$. The upper horizontal axis shows the effective interfacial charge density, $\sigma - \gamma\lambda N$, which is negative except for the last point where it is zero.

synthesized heteropolymers made up of both charged and neutral monomers. As this is a common method of varying the linear charge density of polymers, we opted to use a similar methodology in our simulations. We also reserve two percent of the volume for positively and negatively charged fluid beads to create a strong ionic solution (this yields a Debye length of about $1\sigma_{\text{MD}}$ ^{8,23}). In some simulations the wall beads are also charged randomly with σ charges per unit surface area. Additional fluid beads are charged in order to ensure that the whole system has a net charge of zero. Electrostatics are calculated using a Coulombic interaction with a cutoff of 1.5 times the diameter of the tube. The Bjerrum length was set to $2\sigma_{\text{MD}}$, an appropriate value for water.⁸ Wall beads experience a harmonic potential about a point on an FCC lattice. Note that the wall beads have a mass $m_w = 3m$ while all the other beads have a mass of m (m is thus the MD mass scale). All numerical values given in this article are in terms of the fundamental energy, ϵ , length σ_{MD} , and mass m units of our MD simulations. The important parameters whose role we investigate are the degree of polymerization of the polymers, N , the polymer grafting density, γ (number of chains per unit surface area), the linear charge density of the polymers, λ (in units of $e/\text{monomer}$), the electric force, qE (in units of $\epsilon/\sigma_{\text{MD}}$ applied in the direction of the tube), and the wall charge σ (charge per unit surface area e/σ_{MD} ²). For a more detailed account of the method the reader is directed to a previous article on the simulation of neutral grafted polymer coatings.⁸

IV. RESULTS

A. Flow Reversal. In this section we examine how grafting positively charged polymers (linear charge density $\lambda = 0.1$) to a negatively charge surface ($\sigma = -0.1$) affects the EOF (fluid velocity) far from the surface. Interestingly, we find that the direction of the EOF reverses well before the net charge of the polymer–wall interface changes sign. This can clearly be seen in Figure 1, which shows the bulk EOF velocity v_{EOF} generated by a layer of polyelectrolyte chains grafted at fixed density as a function of their degree of polymerization, N . The net charge of the wall plus polymer coating for the last point on the x axis ($N = 20$) is actually zero, while the simulations involving shorter polymers all have an interface with a net negative charge. Despite this, the EOF clearly drops below zero for chains longer than $N = 10$. The physical cause of this flow reversal is that the EOF generated by the charges closer to the wall is more screened by

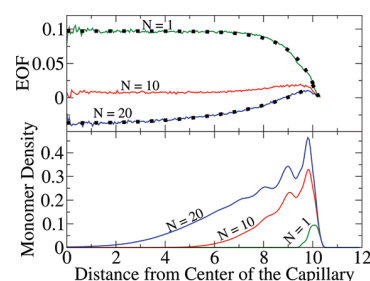


Figure 2. Fluid velocity and monomer density profiles as a function of r , the distance from the center of the capillary for $N = 1$ (green curves), $N = 10$ (red curves), and $N = 20$ (blue curves). The other simulation parameters are $\gamma = 0.05$, $\lambda = 0.1$, $E = 3$, and $\sigma = -0.1$ (the same as in Figure 1). The dotted lines (top panel) are fits, as described in the text.

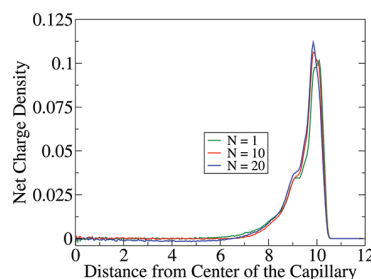


Figure 3. Net ion density (polymer and free ions) as a function of r , the distance from the center of the capillary for $N = 1$ (green curves), $N = 10$ (red curves), and $N = 20$ (blue curves). The other simulation parameters are $\gamma = 0.05$, $\lambda = 0.1$, $E = 3$, and $\sigma = -0.1$ (the same as in Figures 1 and 2).

the polymer layer than the EOF generated by those charges away from the wall. Thus, the EOF from charges localized on the wall is subject to the strongest quenching, while the EOF generated by charges along the grafted chains is progressively less screened as the free edge of the polymer layer is approached.

This surprising result has actually been seen in other electrokinetic systems. Polymers with both positive and negative monomers, but no net charge, in general have a nonzero mobility when subject to an electric field.^{18,24} The reason for this is that the ends contribute more to the mobility since they tend to exist on the outside of the coil. In the context of EOF it was pointed out that a surface which undulates and has an equal number of positive and negative charges will tend to generate EOF in the direction of the charges which protrude farthest into the bulk.²⁵ A nice example of this is the use of three-dimensional electrodes to increase the EOF generated in induced-charge electro-osmosis (ICEO) as shown schematically in Figure 1. Using this concept, one can create a conveyor belt effect that dramatically increases EOF.²⁶

Figure 2 shows the connection between the EOF and the density of polymers in the coating layer for chains of length $N = 1$, 10, and 20. The case of $N = 1$ corresponds to a nearly bare wall with a renormalized charge density. It is evident from the figure that there is a correlation between the radial variation of the EOF and the polymer density profiles due to a combination of polymer-induced EOF and hydrodynamic drag on the flow from the grafted polymer backbone. In particular, the magnitude of the fluid velocity changes where the monomer density is nonzero

while it is constant near the center of the capillary where the monomer density is negligible. The situation is qualitatively different for the $N = 1$ case, where the counterions which make up the Debye layer actually extend beyond the end of the polymer layer and hence the fluid velocity reaches its plateau at the end of the Debye layer (near $r \approx 8$, as shown in Figure 3).

Figure 2 also shows fits to some of the data (the dotted lines). The fit for the fluid velocity profile of the $N = 1$ data has the form of a constant plug flow superimposed with an exponentially decaying flow

$$v_{\text{EOF}}(r) = v_{\text{bulk}} \left(1 - \exp \left[\frac{-(R-r)}{\lambda_D} \right] \right) \quad (6)$$

where $\lambda_D = 1$ is the Debye length, v_{bulk} is the bulk EOF, and $R = 10.25$ is the radius of the capillary. This is the same profile as would be obtained for a simple Debye layer on a flat charged wall, which is a reasonable approximation given the large tube radius relative to the Debye length. The $N = 20$ data beyond the near wall region has been fit to the profile predicted by Harden et al.¹³ for EOF flow past a charged surface with a uniform grafted polymer layer

$$v_{\text{EOF}}(r) = (\mu_p + \mu_w) \cosh \left[\frac{H - (R-r)}{d} \right] - \mu_p \quad (7)$$

where H is the mean height of the brush and $d \approx \sigma^{-1/2}$ is the mean separation between grafted chains (both treated here as fitting parameters). The resulting values are $H = 9.78$, $d = 3.15$, $\mu_p = 0.042$, and $\mu_w = 0.022$, all of which are reasonable except for $\mu_w = 0.022$, which should be close to 0.1. The reason for this is that the parameter $\mu_p + \mu_w$ assumes that the velocity near the wall is still close to 0.1, the bare wall EOF velocity, though this is clearly not the case in Figure 2.

This form for the velocity profile within the brush has also been seen in MD simulations by Qiao and He for the case of neutral grafted chains.¹⁰ From the $N = 20$ monomer density profile it is clear that the brush is nonuniform (unlike in the work of Harden et al. and Qiao and He, where the polymers formed a layer of constant density from the grafting surface to the edge of the brush). Nevertheless, the agreement of the fluid velocity profile with the theoretical prediction of Harden et al. is still quite good.

In Figure 3 we plot the net charge within the tube including the monomers and we see that except in the Debye layer near the wall the fluid is neutral. This means that the monomers' counterions are always nearby, making the system locally electrically neutral. This is necessary in order for the thin Debye layer approximation to be valid and the fluid velocity profile to obey eq 7.

B. Polymer Mobility. The theoretical expression for the bulk EOF in the presence of charged polymer coatings, eq 5, predicts that the flow generated by the charged wall is strongly screened in the case of sufficiently long polymers and that the EOF is only dependent on the electrophoretic mobility of the polymers, $\mu_{\text{EOF}} = -\mu_p$, in this limit. In order to test this prediction, we ran comparative simulations to determine the electrophoretic mobility of free polymers in solution.

The free solution electrophoresis simulations were carried out using the same model in the absence of a tube using the simulation package ESPResSo,²⁷ in order to avoid effects of confinement within the tube and correctly model long-ranged electrostatics with P3M. The EOF simulations were carried out

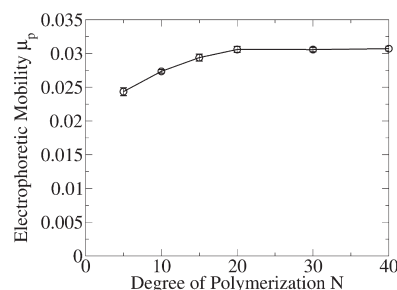


Figure 4. Electrophoretic polymer mobility μ_p as a function of chain length N of an isolated chain for $\lambda = 0.2$ and $E = 1$.

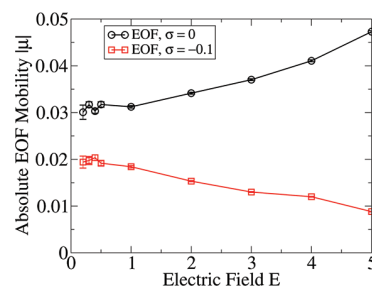


Figure 5. EOF mobility (both with and without wall charge) as a function of the electric field E for $N = 10$, $\gamma = 0.05$, and $\lambda = 0.2$.

in a confined geometry as described in a previous section. We first discuss the free-solution electrophoresis results. The data, shown in Figure 4, indicate an increase in the electrophoretic mobility of the polymers, μ_p , for short chains with a crossover to a constant mobility for sufficiently long chains, known as the free-draining limit. This is understood to be caused by the local balance of the electric driving force with the hydrodynamic friction caused by shearing of the fluid within the Debye layer.¹⁶ We note that our data do not show some of the complex behavior found for short, highly charged chains in other recent simulations,^{28,29} due to the low linear charge density λ which minimizes counterion condensation effects (note that the Bjerrum length was set at 2 while the charge density along the polymer was $\lambda = 0.2$).

Turning to the EOF simulations, we note that the relationship between bulk EOF in the presence of polymer coatings and the applied electric field is highly nonlinear at high electric fields. This has important implications for the effective mobility of the polymers in the grafted layer. In the case of neutral chains, the nonlinear response is caused by the stretching of the chains in the direction of the flow, which causes a reduction in the coating's height and thus increases the EOF.^{10–13,30} As we shall see, the physics is much more complicated in the case of charged chains where there is both a reduction in coating height and increased electrophoretic mobility of the polymers comprising the coating as they align with the electric field.

Figure 5 shows the effective EOF mobility in the presence of charged grafted polymers as a function of the electric field E (for $N = 10$, $\lambda = 0.2$, and $\gamma = 0.05$), both with and without wall charges. For low electric fields we see that the EOF mobility appears to be fairly constant both with and without wall charges. As the field increases, however, the EOF mobility in the absence of wall charge increases, due to the deformation and alignment of the chains with the electric field, which becomes large around

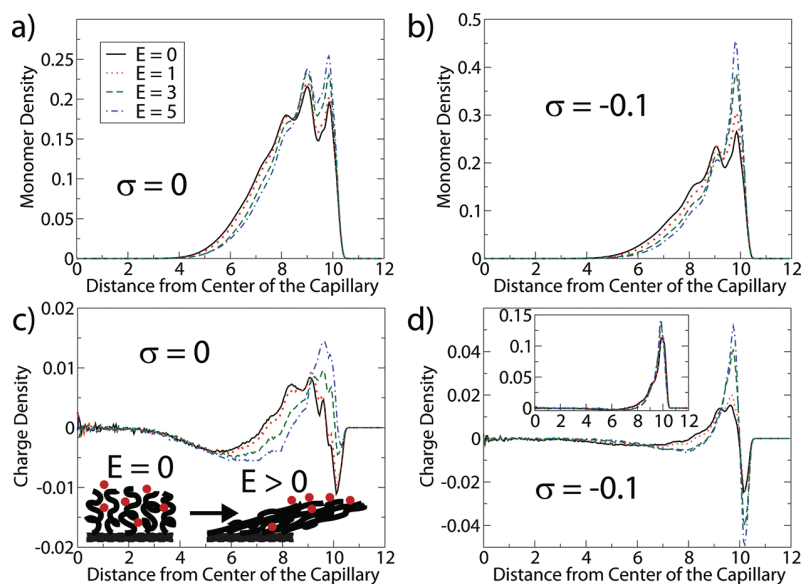


Figure 6. Radial monomer density profiles are shown for uncharged walls (a) and charged walls (b) at various values of the electric field E . Below the monomer density profiles are the radial charge density profiles again for uncharged walls (c) and charged walls (d). The inset in (d) is the charge density profile before subtracting off the charge density profile of a bare tube with the same wall charge. All simulations are done with $N = 10$, $\gamma = 0.05$, and $\lambda = 0.2$.

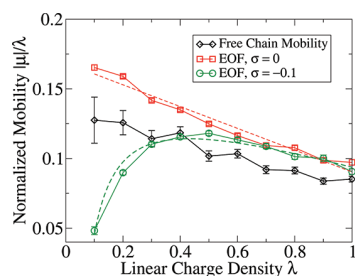


Figure 7. Effect of varying the linear charge density, λ , along the polymer backbone for $N = 10$, $\gamma = 0.05$ (for the two EOF cases), and $E = 1$. The results for EOF with and without a wall charge σ as well as the polymer's free-solution electrophoretic mobility are shown. All mobility values are renormalized by λ . The dashed lines are fits to the data, as described in the text. Note that the flow generated by the bare wall for the $\sigma = -0.1$ case would actually be in the opposite direction.

$E = 1$, and the concomitant change in the charge density profile away from the grafting wall, as seen in Figure 6a,c. Mobile negative charges are squeezed out of the collapsing polymer layer, leading to a contribution to the EOF that is not screened by the polymer layer. This effect is schematically illustrated in Figure 6c. Another possible mechanism for this increase in EOF is the increase in the mobility of the polyelectrolytes, μ_p , as the electric field causes the polymers to align with the electric field.^{31,32}

The nonlinear behavior is different for the case of charged walls ($\sigma = -0.1$) where the electro-osmotic mobility of the polymer–wall interface decreases with increasing electric field. In this case, the wall charge produces a flow in the direction of the field (which is the opposite direction of the net EOF caused by the polymers). This fluid flow causes hydrodynamic drag on the polymers along the capillary axis which helps to stretch the chains which are being pulled by both the electric field and the wall's EOF. This leads in turn to the coating being less effective in screening the flow caused by the wall charges, due to a reduction

in its height. The increased effect of the wall charge in this instance appears to dominate over the effects of the polymer layer conformation on the distribution of the mobile charges, as can be seen in Figure 6b,d. Since nonlinear effects due to the electric field become significant for $E > 1$, we use $E = 1$ in the rest of the article to study the simplest case.

C. Varying the Linear Charge Density. Next the effect on the mobility of varying the linear charge density, λ , on the backbone of the polymer was investigated for both free and grafted chains. Figure 7 shows the ratio $|\mu|/\lambda$ as a function of λ for $E = 1$, $N = 10$, and $\gamma = 0.05$ (for the grafted chains). Clearly, for all values of λ , the EOF mobility is slightly higher than the electrophoretic mobility in the case of an uncharged ($\sigma = 0$) wall although the two curves slowly converge. In the case of a charged wall ($\sigma = -0.1$), however, we see that at first the electrophoretic mobility is much higher than the EOF. This is because the parameters chosen for the grafted polymer coating are such that the flow caused by the wall charges is not entirely screened by the polymer coating. For sufficiently large λ , however, the influence of the polymer charges overwhelms that of the wall charges, and the normalized mobility values tend to converge for EOF in both cases. Figure 7 shows a crossover to polymer charge dominance at approximately $\lambda = 0.4$. In the large λ limit, the electrophoretic mobility is always smaller than the EOF mobility for both charged and uncharged walls.

These results are similar to the experimental results reported by Danger et al.,⁴ which compared the EOF and electrophoretic mobilities for heteropolymers with different net charges. For the experimental EOF measurements, the polymer coatings were composed of successively adsorbed polyelectrolyte layers, a situation that is qualitatively similar to having an underlying wall charge below a diffuse polymer layer. Contrary to the simulations, the electrophoretic mobility was found experimentally to be large compared to the effective EOF mobility for weakly charged chains. However, this difference became smaller with increasing charge on the polymer. These differences at small

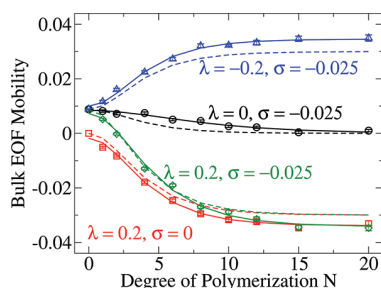


Figure 8. Bulk EOF mobility as a function of the polymer length N for $\gamma = 0.05$ and $E = 1$. The graph shows four different cases: neutral polymers, $\lambda = 0$, with wall charge $\sigma = -0.025$ (black circles); positively charged polymers, $\lambda = 0.2$, without wall charge (red squares) and with wall charge $\sigma = -0.025$ (green diamonds); and negatively charged polymers, $\lambda = -0.2$, with wall charge $\sigma = -0.025$ (blue triangles). The solid lines are best fits to the data using the functional form of eq 5 while the dashed lines use eq 5 with the theoretical parameters from Table 1.

λ between our simulations and the experiments could be due to differences in the stability between the physically adsorbed polymer layers of the experiments in comparison with the irreversibly grafted polymers considered by the simulations. In particular, Danger et al. hypothesized that the observed EOF was much lower than the electrophoretic mobility at low λ due to weak adsorption of charged polymers at low λ , leading to incomplete, patchy coverage of the surface. Although, as noted below, there are other equally plausible explanations.

For the $\sigma = 0$ simulation data, the scaled mobility appears to be a roughly linear function of λ , implying that $\mu_{\text{EOF}}/\lambda \approx C_0 - C_1\lambda$. The fit to this form (the dashed red line in the figure) for $\sigma = 0$ yields $C_0 = 0.17$ and $C_1 = -0.078$. More generally, in the presence of both polymer and wall charge, eqs 4 and 5 can be rewritten in a generic form: $\mu_{\text{EOF}} = A\mu_w + B\mu_p$ where A and B are constants that depend only on γR_G^2 (the height and density of the polymer layer). Substituting $\mu_p/\lambda \approx C_0 - C_1\lambda$ yields $\mu_{\text{EOF}} = A\mu_w + B\lambda(C_0 - C_1\lambda)$. This implies that the correct fit to the simulation data for the case where the wall charge is $\sigma = -0.1$ should have an additional term A/λ , $\mu_{\text{EOF}}/\lambda \approx A/\lambda + C_0 + C_1\lambda$, as long as the polymer brush conformation is unaffected by λ (a reasonable assumption for weak-to-moderate charging and small-to-moderate Debye lengths). For the particular case of $\sigma = -0.1$ shown in Figure 7, the best fit values are $C_0 = 0.17$, $C_1 = -0.063$, and $A = -0.116$ (the dashed green line in the figure). This result suggests an alternative to the explanation proposed by Danger et al. for the relatively small EOF mobility at small λ compared to the free solution electrophoretic mobility, namely the incomplete screening of the wall charge contribution to the EOF by the underlying polyelectrolyte layers. While this does not refute the hypothesis put forth by Danger et al. that there is incomplete surface coverage of the last layer, it suggests that the results might in fact simply be due to an incomplete screening of the EOF caused by the underlying polyelectrolyte layers.

We note that all three of the curves for μ/λ in Figure 7 have a downward slope at high λ . This reduced mobility, compared to what one might intuitively expect—a constant ratio of μ to λ reflecting a simple linear increase of μ with respect to λ —may be due to the condensation of counterions onto the backbone.³³ This phenomenon has been seen in other simulations of electrophoresis^{28,29} and also in the work of Danger et al.⁴

Table 1. Fitting Parameters for Figure 8 Using eq 5^a

set	fit parameters		
	μ_p	μ_w	H_0
$\lambda = 0, \sigma = -0.025$	-0.000 11	0.0087	5.1
$\lambda = 0, \sigma = -0.025$ theory	0	0.0088	8.7
$\lambda = 0.2, \sigma = 0$	0.034	-0.0018	9.9
$\lambda = 0.2, \sigma = 0$ theory	0.030	0	8.7
$\lambda = 0.2, \sigma = -0.0250$	0.034	0.0073	8.9
$\lambda = 0.2, \sigma = -0.0250$ theory	0.030	0.0088	8.7
$\lambda = -0.2, \sigma = -0.0250$	-0.035	0.010	10.1
$\lambda = -0.2, \sigma = -0.0250$ theory	-0.030	0.0088	8.7

^a Both theoretical values (for the dashed lines) and best fit values (for the solid lines) are given.

There may also be other sources of nonlinear response at large λ . This behavior could be induced by osmotic swelling of the polyelectrolyte layers, a well-known effect for grafted polyelectrolytes which we also see in our simulations for the highest values of λ (data not shown). Such nonlinear effects, while fascinating, are beyond the scope of this work. In the following, we chose to focus on the relatively small value of $\lambda = 0.2$, where such nonlinear behavior is not dominant.

D. Varying the Polymer Length. The results given in Figure 8 show in a systematic way how increasing the polymer length N affects the bulk EOF. The most basic case is that of a neutral polymer $\lambda = 0$ and a charged wall $\sigma = -0.025$ (black circles), a case previously studied using the same simulation method in our group.^{7,8} The results in this limit agree with the scaling arguments of Harden et al.^{8,13} Initially, the bulk EOF is determined by the electroosmotic mobility of the wall μ_w , but as the chain length increases, the EOF approaches zero asymptotically according to eq 5.

Slightly more complicated is the case of charged chains ($\lambda = 0.2$) grafted on an uncharged wall ($\sigma = 0$), represented by the red squares in Figure 8. In the limit $N \rightarrow 0$, the EOF largely determined by the electroosmotic mobility of the wall μ_w , which in this case is zero. With increasing N , the EOF approaches a value which is related to the electrophoretic mobility of a polymer chain, μ_p . In the limit of infinitely thin Debye layer and polymer backbone, the EOF mobility is predicted to be given by $\mu_{\text{EOF}} = -\mu_p = 0.03$ (from Figure 4) for sufficiently thick polymer layers.¹³

For the case of a charged polymer $\lambda = 0.2$ with an oppositely charged wall $\sigma = -0.025$ (the green diamonds in Figure 8), we see both effects. With increasing polymer length, the flow generated by the wall charges is not only quenched, but the flow generated by the counterions of the polymer coating becomes increasingly dominant. Consequently, for an increasingly thick polymer layer the bulk EOF is less and less dependent on the properties of the wall, μ_w , and more and more dependent on the properties of the polymer coating, μ_p , as previously predicted.¹³

The last curve shows the case of a negatively charged polymer $\lambda = -0.2$ on a negatively charged wall $\sigma = -0.025$ (blue triangles in Figure 8), where the EOF is much less dependent on the thickness of the polymer coating. This is because the EOF induced slip along the backbone of the polymer is similar to the electroosmotic mobility of the charged wall. Note that the value this curve approaches for large values of N is simply the

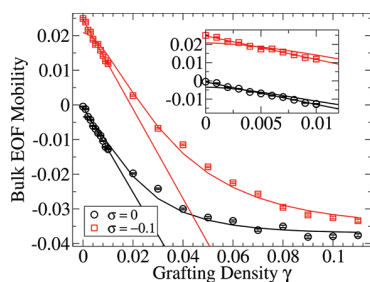


Figure 9. Effect of varying the grafting density, γ , of the polymer coating on the EOF for $N = 10$, $\lambda = 0.2$, and $E = 1$ in the case of a charged ($\sigma = -0.1$) and uncharged ($\sigma = 0$) wall. The inset shows a closeup of the region near $\gamma = 0$. The straight lines are the fits for the mushroom regime, eq 4, while the curved lines are fits for the brush regime, eq 8.

Table 2. Fitting Parameters for Figure 9 Using eq 8^a

set	fit parameters		
	μ_p	μ_w	H_0
$\sigma = 0$	-0.037	0.0034	8.58
$\sigma = 0$ theory	-0.030	0	8.05
$\sigma = -0.1$	-0.035	0.021	5.85
$\sigma = -0.1$ theory	-0.030	0.025	8.05

^a Both theoretical values and best fit values are given here while the graph shows only the curves for the best fit parameters.

opposite of the value of the two positively charged $\lambda = 0.2$ coatings, as expected.

For all of the curves we have successfully fit the data with eq 5, using μ_p , μ_w , and a numerical prefactor H_0 in the argument of the cosh as fitting parameters, given in Table 1. We also use the hydrodynamic radius R_H in place of the radius of gyration R_G as this has previously been shown to be the relevant quantity.⁸ With the addition of the of the numerical prefactor H_0 , eq 5 becomes

$$\mu_{\text{EOF}} = -\mu_p + (\mu_w + \mu_p) \frac{1}{\cosh[H_0(\gamma R_H^2)^{5/6}]} \quad (8)$$

The fitting values of these parameters can be compared with theoretical estimates. The theoretical value of $\mu_w = 0.0088$ given in the table is the bulk EOF generated in a simulation by a capillary with a wall charge of $\sigma = -0.025$ and no polymer coating, while the theoretical value of $\mu_p = 0.03$ is the asymptotic long chain mobility taken from Figure 4. We estimate the value for H_0 , the unspecified constant in the scaling expression for the height of the brush, eq 5, by imposing equality of the volume per grafted chain in the mushroom and brush regime at the crossover from mushroom to brush. In the mushroom regime, the volume is simply given by $V = MV_i = M(4/3\pi R_H^3)$ where M is the number of grafted polymers and V_i is the volume of each individual polymer. In the brush regime, the volume of the coating is $V = MV_i = MH/\gamma$, where the height of the brush is given by $H = H_0(\gamma R_H^2)^{5/6}$.¹³ Setting these two volumes equal yields $H_0 = (4/3\pi R_H^3)\gamma/(\gamma R_H^2)^{5/6}$, where R_H is chosen as the value which satisfies $\pi\gamma R_H^2 = 1$, a value we have previously identified as a reasonable condition for the crossover from mushroom to brush behavior.⁸

Overall, the tabulated results for the theoretical values and the best fits for these three parameters are in fairly good agreement,

as can be seen by comparing the two curves in Figure 8 generated by theoretical values (dashed lines) and the fit values (solid lines). The value of μ_w appears to be within about 20% of the expected value for all four curves. The value representing the free solution polymer mobility, μ_p , is very close for the three charged coatings. Interestingly, however, it is systematically higher than the theoretical value, which we ascribe to the finite extent of our Debye layer as described in more detail in the next section. The value of H_0 is also systematically higher than we expect, although it is within about 10% for the three cases where $\lambda \neq 0$. The fit for $\lambda = 0$, $\sigma = -0.025$ shows a value of H_0 which is about half as large as for the charged polymer coatings. We believe that this is because the charged brushes have an effective volume which incorporates not only the hydrodynamic radius, R_H , but also the Debye length, λ_D , giving them an effective hydrodynamic radius of $R_H + \lambda_D$. We will show further evidence for this in the next section which looks at the effect of the grafting density.

E. Varying the Grafting Density. In this section we investigate the validity of the scaling predictions for the EOF given in eqs 4 and 5 with respect to the grafting density γ . The results are summarized in Figure 9 and Table 2. For small values of γ (the sparsely grafted mushroom regime), we expect to see a roughly linear relationship between the EOF and γ , as predicted by eq 4. Such linear behavior does appear for $\gamma \leq 0.01$; however, the mushroom regime behavior clearly ends well before the expected crossover to brushlike behavior at $\gamma = 1/\pi R_H^2 \approx 0.059$. The best fit slopes to the MD data for $\gamma \leq 0.01$ are -1.29 and -1.23 for the cases of a charged wall ($\sigma = -0.1$) and an uncharged wall ($\sigma = 0$), respectively.

The values of the slopes in the low density regime are significantly different than those expected theoretically. According to Harden et al.¹³ and based on the results of Tessier and Slater,⁸ we would expect a slope of approximately $-\pi R_H^2(\mu_w + \mu_p)$. Using an estimate for the bare hydrodynamic radius based on simulation data, we obtain $R_H \sim 2.2R_G \approx 3.4$. In the case of the charged wall ($\sigma = -0.1$) this yields a slope of roughly -1 , while for the uncharged wall ($\sigma = 0$) we obtain a slope of roughly -0.58 . Thus, for both cases, there is a small deviation between the theoretically predicted and the observed slopes. One important difference between our simulation studies and the theoretical model is the finite value of the Debye length. Whereas the theoretical expressions are strictly only valid in the limit of an arbitrarily thin Debye layer around a structureless polymer backbone, our simulations consider a Debye length of $\lambda_D \approx 1$. This finite Debye length may contribute to a larger effective hydrodynamic radius. Interestingly, if we use a slightly modified expression for the slope that accounts for this increase in the effective hydrodynamic radius, $\pi(R_H + \lambda_D)^2(\mu_p) \approx 1.22$, we obtain a value which is quite close to the observed results for the case of the uncharged wall ($\mu_w = 0$). This value is also serendipitously close to the fitted value for the case of the charged surface as well, whereas one might expect that the value for the charged wall to be about twice as large, according to eq 4. The lack of difference between the charged and uncharged slope values may be due to a redistribution of the wall's counterions into the interstitial space between the sparsely grafted chains, thereby diminishing the μ_w dependence of the slope in the "mushroom" regime. We note, however, that this effect disappears in the more densely grafted limit.

For higher values of γ (the brush regime; $\gamma \gg 0.1$), the dependence of the EOF on γ takes the form of a hyperbolic cosine, eq 8, with a magnitude that asymptotically approaches μ_p ,

the electrophoretic mobility of the polymers which make up the coating. We fit the data (solid lines in Figure 9) using eq 8; the fit values are given in Table 2 along with theoretical predictions based on ref 13. The resulting values for μ_w and H_0 in Table 2 are in fair agreement with their theoretical counterparts, much like was seen in Table 1 and Figure 8. However, it is notable that the simulation values of the EOF at large values of γ significantly exceed the corresponding electrophoretic mobility of polymers with a linear charge density $\lambda = 0.2$, $\mu_p \approx 0.30$.

This is reminiscent of behavior seen in Figure 8 in the previous section and is suggestive of the influence of finite Debye length on the densely grafted polymers. In particular, the Debye length of our MD simulations, $\lambda_D = 1$, is comparable to the average distance between adjacent polymers at the higher grafting densities we have simulated, indicating significant overlap of Debye layers of adjacent grafted polyelectrolyte chains. In nanoscopic systems it is well-known that there must be corrections to classical theory due to overlapping Debye layers.^{23,34} In this case, the overlap of the Debye layers of adjacent polyelectrolytes leads to an increase of the electro-osmotic mobility of the coating beyond the electrophoretic mobility of the individual polymers due to the reduction in screening. This is the same effect that causes the initial increase in Figure 4 for the polymer mobility as a function of N .^{16,28,29} Similar results have also been observed in the electrophoresis of colloids in the low salt regime where the mobility was found to increase with increasing packing fraction in the very low concentration regime.

V. CONCLUSION

In this article we presented simulation results addressing the role of charged polymer coatings in the modulation of EOF. In particular, we focused on the case of grafted polymer coatings. We believe that the results found in our simulations are also relevant to the more common experimental practice of adsorbed, charged polymer coatings as we showed with our comparison to the experimental results of Harden et al.⁴ Our results show a strong similarity between successively adsorbed ionic coatings and our simulations of an ionic polymer coating grafted onto an oppositely charged wall. We attempted to compare our results to the theoretical predictions of Harden et al.,¹³ and we were able to establish evidence that there is a linear relationship between the EOF and the grafting density γ in the case of the mushroom regime. We also found good agreement with the scaling predictions both as a function of grafting density γ and degree of polymerization N for the brush regime.

One small difference between the results of our MD simulations and the theoretical predictions of Harden et al.¹³ is that we find EOF values which are somewhat larger than the electrophoretic mobility of the same polymers. The theoretical calculations of Harden et al.¹³ were based on the assumption that the Debye layer is infinitely thin and an infinitely thin polymer backbone, and we hypothesize that the fact that these assumptions are not true in the case of our simulations is the reason for $\mu_{EOF} > \mu_p$.

While our results focus on the role of polyelectrolytes grafted to a solid surface on EOF, they are also applicable to the electrophoresis of a colloid grafted with a polyelectrolyte.^{19,36–40} Essentially, the difference between the bulk fluid velocity and the stationary wall is governed by the same phenomena as the electrophoretic speed of these soft colloids. In fact, one of the first studies on the electrokinetic effects of polyelectrolytes grafted to a surface focuses on understanding the electrophoretic

behavior of human erythrocyte cells.⁴¹ The electrophoretic results indicated that the glycocalyx which coated the cell's surface acted essentially as a polyelectrolyte coating. The electrophoresis of cells is still often understood within this context.^{42,43}

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ACKNOWLEDGMENT

We thank Mark D. Whitmore for helpful discussions. This work was supported by NSERC Discovery grants to G.W.S. and J.L.H. C.H. thanks the Volkswagen foundation and the DFG through SimTech and the SFB 716 for financial support. O.A.H. also acknowledges funding from a University of Ottawa Entrance Scholarship and NSERC through the CGS and Michael Smith programs. Sharcnet provided computational resources for this work.

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Implicit Method for Simulating Electrohydrodynamics of Polyelectrolytes

OA Hickey, C Holm, JL Harden, GW Slater. *Physical Review Letters* **105**, 148301 (2010)

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Implicit Method for Simulating Electrohydrodynamics of Polyelectrolytes

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(Received 26 April 2010; published 29 September 2010)

We introduce a novel method to couple Lennard-Jones beads to a lattice-Boltzmann fluid by adding a term which represents the slip within the Debye layer with respect to the surrounding fluid. The method produces realistic electrophoretic dynamics of charged free chains, as well as the correct stall force in the limit of a thin Debye layer. Our simulations also demonstrate how a net-neutral polyampholyte can have a nonzero net force due to hydrodynamic interactions. This method represents an efficient way to simulate a wide variety of complex problems in electrohydrodynamics.

DOI: 10.1103/PhysRevLett.105.148301

PACS numbers: 82.35.Rs, 47.57.jd, 47.65.-d, 82.45.-h

Electrophoresis is of growing importance as a means to analyze charged particles and ions, colloids, and biomacromolecules such as DNA. In determining the velocity of the analyte the role of hydrodynamics is usually unimportant except at length scales of the order of the Debye length [1]. The long-ranged fluid velocity profile surrounding a sphere undergoing electrophoresis can be shown through a flow potential calculation to decay like $1/r^3$, where r is the distance to the center of the sphere [1,2]. The fast decrease in the hydrodynamic interactions with respect to r means that they can be neglected in certain cases and often are to save computation time [3–6]. In the case of electrophoresis of polyelectrolytes the conceptual framework of how hydrodynamics are screened on long length scales is called the local force or free-draining picture [7,8]. The mobility of a specific segment of a polyelectrolyte chain is seen as a balance between the electric force on the chain segment and the local hydrodynamic friction on the scale of the Debye length, λ_D .

Hydrodynamics do, however, play a crucial role in the electrophoresis of polyelectrolytes. For instance, Nkodo *et al.* [9] found that polyelectrolytes undergoing free-flow electrophoresis have diffusion coefficients which obey Zimm dynamics. Simulations have also shown the role of hydrodynamic interactions in determining the electrophoretic mobility of short polyelectrolytes [8,10–12].

Studies by Long, Viovy, and Ajdari [2,13–15] focused on the electrohydrodynamics of polyelectrolytes in the case where there is both a mechanical and an electrical force on the system. When the Debye length is much smaller than the other length scales in the system and at low Reynolds number (e.g., at moderate electric fields, $\zeta/\lambda_D \gg E$, where ζ is the zeta potential) they showed that one could simply superimpose the solutions for the flow field of the hydrodynamic problem (where a mechanical force, F_{ext} , is applied to a polyelectrolyte) to that of the electrophoretic problem (where an electric field E is applied to the charged object in solution). This yields the following general equation for the electrohydrodynamics of polyelectrolytes:

$$F_{\text{ext}} - \xi(v_{\text{polymer}} - \mu_0 E) = 0, \quad (1)$$

where $\xi = 6\pi\eta R_H$ is the drag coefficient, in which η is the viscosity and R_H is the hydrodynamic radius of the polymer conformation, v_{polymer} is the velocity of the polymer, and μ_0 is the electrophoretic mobility of the polymer. This equation yields some interesting results, most notably the force to hold a polyelectrolyte still in an electric field is not simply the external force applied to the polyelectrolyte QE (where Q is the charge on the polyelectrolyte) but rather $6\pi\eta R_H \mu_0 E$ [14]. There have been experimental studies on the stalling of a polyelectrolyte in an electric field [16–19] which support this conclusion, and it has been confirmed by computer simulations [20,21]. Recent experiments have also shown that Eq. (1) provides reasonable results for a colloid subjected to an electric field in an optical trap [22]. These results demonstrate that hydrodynamics can play an important role even on length scales much longer than the Debye length in contrast to prevailing views of how mobility is determined in free solution electrophoresis [7,8,10–12].

In this Letter we introduce a lattice-Boltzmann (LB) fluid model where the coupling to the classical molecular dynamics (MD) simulations is done via Eq. (1). The elimination of computationally demanding electrostatic calculations inherent in this method allows for the simulation of complex phenomena in mesoscopic systems in a wide range of applied field strengths, which would otherwise be impractical or take an extremely long time using explicit charges. First, we verify that the velocity of polymers in free solution electrophoresis is indeed $\mu_0 E$ and that their diffusion obeys Zimm dynamics for this model. We then show how long-ranged hydrodynamic interactions during free solution electrophoresis results in a polyampholyte with zero net charge having a nonzero mobility. Next we look at the stall force of a polyelectrolyte, and finally show how a special arrangement of charges can result in a net force perpendicular to the electric field.

Our computer simulations are carried out using the ESPRESSO simulation package [23]. The simulations consist of a coarse-grained bead spring model of the polyelectrolytes coupled to a mesoscopic fluid. The fluid is modeled as a lattice-Boltzmann fluid [8,10,24]. As in previous work we make use of the D3Q19 LB fluid model with a kinematic viscosity $\nu_{\text{kin}} = 3.0$, and a fluid density $\rho = 0.864$ yielding a dynamic viscosity of $\eta = 2.592$ [8,10]. The crucial difference in our model compared to other simulations is that we make use of Eq. (1) to couple the fluid to our polymer beads. Previous simulations have used a simple Stokes' drag term $F_D = \xi(v - v_f)$ [8,10,25], where v is the velocity of the Lennard-Jones bead and v_f is the local velocity of the fluid. In our simulations, a term representing the slip between the bead and the fluid, due to the electric field induced shearing in the Debye layer, is added to the total drag force:

$$F_D = \xi(v - v_f - \mu_0 E). \quad (2)$$

We show that this simple alteration of the coupling of an individual Lennard-Jones bead to the fluid provides realistic electrohydrodynamics for polyelectrolytes (in the limit of infinitely thin Debye layer) without needing to do any electrostatic calculations.

To test our approach we first model charged polymers undergoing free-flow electrophoresis. The nonbonded interactions between monomers are modeled by the Weeks-Chandler-Anderson (WCA) version of the Lennard-Jones potential with the standard energy (ϵ) and length (σ) parameters [3]. The bonded beads in the polyelectrolyte are linked via a finitely extensible nonlinear elastic (FENE) potential: $U_{\text{FENE}}(r) = -0.5kR_0^2 \ln[1 - (r/R_0)^2]$, where $R_0 = 1.5\sigma$ is the maximum extension of the bond and $k = 30\epsilon/\sigma^2$ is the energy scale for the interaction [3].

As a first test of the model, the velocity of polymers of lengths $N = 2$ –30 and with values of $\mu_0 E = 0.0001$ –1

was determined. The polymers were found to travel at $v = \mu_0 E$ regardless of the polymer length N (see inset of Fig. 1), as expected for free-draining polymers of size much larger than the Debye length [8,11,12]. Note that, had we simply applied a constant force to each bead, we would have found that $v \propto N^{1-\nu}$, where $\nu = 0.588$ is Flory's exponent. The main graph in Fig. 1 shows the diffusion coefficient D as a function of N , which fits a power law $D \propto N^{-0.54 \pm 0.02}$, consistent with Zimm dynamics, $D \propto N^{-\nu}$, rather than Rouse dynamics, $D \propto N^{-1}$. This result agrees with both MD simulations with explicit charges [8] as well as experimental results [9] and is, to the best of our knowledge, the first time both the correct mobility and diffusive behavior have been reproduced without the use of explicit charges.

As a second example we investigate the prediction made by Long *et al.* [15] that, depending on where it is cut, an overall neutral ring block copolymer can become a linear polymer with a nonzero mobility. The ring polymer consists of a positive and a negative block of equal length connected together to form a ring. If one cuts the ring polymer where the positive block connects to the negative block the resulting linear polymer has a net mobility of zero. If, however, one cuts the polymer in the middle of the positive block, the polymer will have a positive mobility. Monomers on the ends of the polymer matter more than those in the central portion for determining the overall mobility of the polymer. The results in Fig. 2 confirm the prediction that even an overall neutral polymer can have a nonzero mobility, and that the magnitude of the nonzero mobility depends on the charge layout along the backbone of the linearized polymer. The force is proportional to $\mu_0 E$, and by renormalizing the cut position by the total length N of our polymers (we used $N = 16, 32$), the results are largely insensitive to chain length. This is qualitatively consistent with the prediction of Long *et al.* [15], as

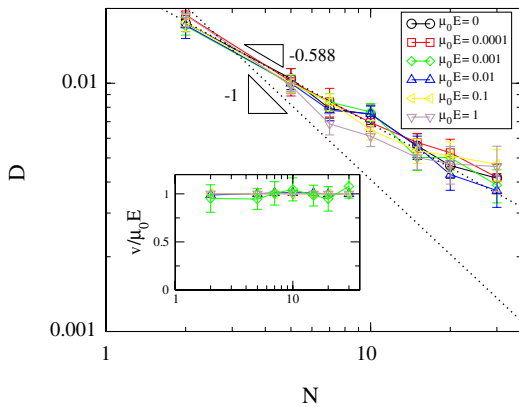


FIG. 1 (color online). The diffusion coefficient of polymers of various lengths N for several values of $\mu_0 E$. The dotted lines are slopes of -0.588 (the prediction for Zimm dynamics) and -1 (the prediction for Rouse dynamics). The inset shows the velocity renormalized by $\mu_0 E$.

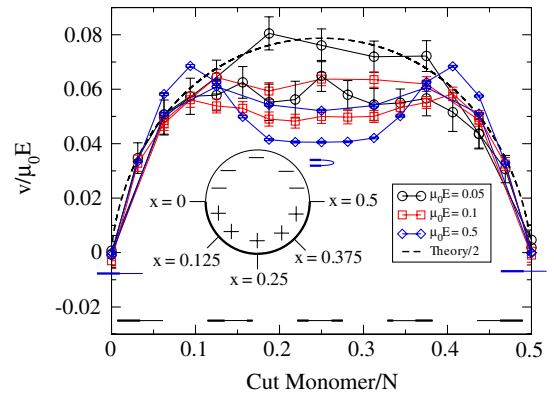


FIG. 2 (color online). The velocity of an overall neutral linear polymer renormalized by $\mu_0 E$ as a function of the charge distribution. The polymers are formed by taking the same ring copolymer and cutting it at different points along the positive block as depicted schematically. The dashed line represents the predictions of Long *et al.* [15] with a scaling factor.

shown rescaled by a factor of 2 in Fig. 2. For higher fields ($\mu_0 E = 0.5$), there is a dip in the middle of the curves. This is due to polymer chain extension causing the positive and negative sections of the polymer to hydrodynamically separate from each other, as has been discussed theoretically [26–28]. Essentially the two positive ends start to separate from the central negative segment due to stretching by the electric field as depicted schematically.

Next we reproduce, without the use of electrostatics, the MD results of Bertrand and Slater [20] that the stall force needed to hold a polyelectrolyte in place is $F = 6\pi\eta R_H \mu_0 E$ and not simply the electric force on the polyelectrolyte, $F_E = QE$. For these studies polymers are generated in both ideal random walk conformations (where $R_H \propto N^{0.5}$) and straight rod conformations (where $R_H \propto N/[\ln(2N/b) - 0.5]$). These polymer conformations are frozen and simulations are conducted in the absence of an LB thermostat similar to recent studies of electro-osmotic flow [29], to prevent stretching of the polymers by the electric field. This decoupling of electric field and polymer conformation allows us to focus on the electrokinetic phenomena associated with particular steady state chain conformations. Like Bertrand and Slater [20], we make a cylindrical channel of radius $R = 25\sigma$ of fixed Lennard-Jones beads in which we place the polymer. The wall beads are used to dissipate the linear momentum generated by the frozen monomers through the coupling of these beads to the LB fluid.

Figure 3 shows the stall force F divided by $\mu_0 E$ (which varies from 0.0001 to 1) as a function of the polymer length N , along with power law fits to the data. The data shows, that except for large values of N , the force on the polymer coil scales as $R_H \propto N^{0.5}$, and not as N , the total charge on the polymer. The discrepancy for larger values of N is due to R_H becoming on the order of the tube diameter, at which point the Stokes' velocity profile around the polymer is

affected by the tube walls. The results in Fig. 3 for a rodlike polymer conformation along the center of the tube also support the Stoke's drag picture for the stall force. Data for $\mu_0 E = 0.0001$ –1 are shown, and are identical for all values of $\mu_0 E$. The fits clearly show that the force to hold the polymer still in such a configuration is in agreement with the theoretical result for a rigid rod, $F/\mu_0 E \propto \xi_{\text{rod}} \propto N/[\ln(N/b) - 1]$.

Finally, we also applied our algorithm to the net-neutral, cross-charge configuration depicted in the bottom right of Fig. 4, and found that by choosing such a fixed configuration of charged beads, the net force in the direction of the field is exactly zero (due to symmetry) while there is a finite force perpendicular to it. This effect is caused by the electro-osmotic flow depicted by the curved arrows. Moreover, the magnitude of this transverse force was found to be a power law of the applied field, $F_{\perp} \propto (\mu_0 E)^3$, as shown in Fig. 4. This was a phenomenon proposed by Long and Ajdari [30], and has recently been observed experimentally [31]. Interestingly in the experimental work on asymmetric Janus particles [31] the velocity was also found to go like E^2 . To our knowledge these results are the first computational evidence for such an effect.

The coupling scheme we used for the case of an LB fluid might also be applicable for MD using multi-particle collision dynamics [11,12] or dissipative particle dynamics [32]. Applying the hydrodynamic tensor derived by Long *et al.* [13] could also be used in conjunction with Brownian dynamics simulations. One could also make the value of $\mu_0 E$ dependent on the local bond angle to incorporate the orientation dependent nature of μ_0 [18,33].

Certain aspects of electrohydrodynamics are neglected in this implicit method for thin Debye layers. Notably the lack of explicit charges in our approach makes it impossible to study the effect of charge condensation [34], an important phenomenon for both colloids and polyelectrolytes.

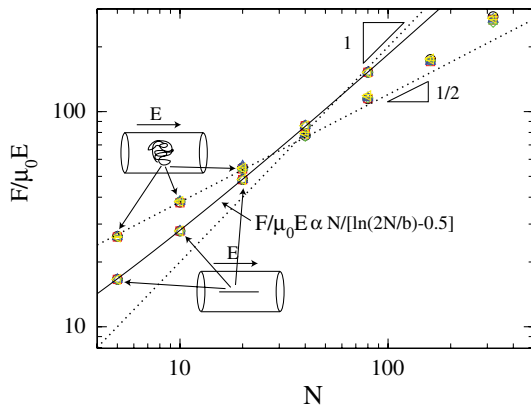


FIG. 3 (color online). Force needed to hold polymers of different lengths N stationary in a random walk or rod configuration for various values of the coupling constant $\mu_0 E$. Curves for $F \propto N^{0.5}$ and $F \propto N$ are shown as dashed lines, along with a solid line of the form $N/[\ln(2N/b) - 0.5]$ for the rod data.

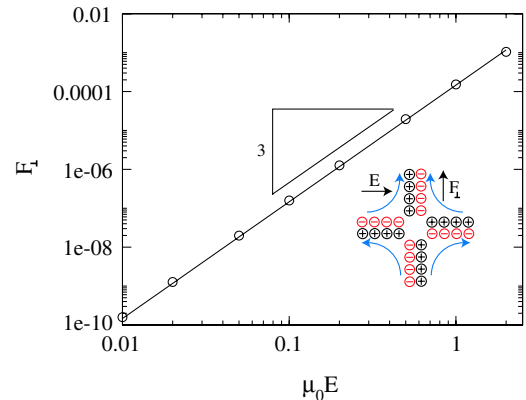


FIG. 4 (color online). The force perpendicular to the electric field on a cross of zero net charge as a function of the applied field $\mu_0 E$ showing $F_{\perp} \propto (\mu_0 E)^3$. The inset shows a schematic of the bead configuration along with the curved fluid flow lines which cause a force perpendicular to the electric field.

Swelling due to intramolecular electrostatic interactions in polyelectrolyte systems [35] would also not appear using our simulation technique. Our model would also miss important physics in polyelectrolyte solutions where intermolecular electrostatic interactions between chains are important. However, the focus of our method is on field-induced transport of individual polyelectrolytes or macroions in moderate-to-high ionic strength conditions. For such typical experimental conditions, the relevant physical parameters on the scale of the Debye layer (e.g., local charge densities and friction factors) are naturally combined into a single characteristic parameter, the mobility μ_0 , that controls the response of a polyelectrolyte to an applied field in free solution. As such, the particular conditions governing the static chain properties (such as chain conformation, solvation, and charge distribution) are inputs required for the method, which may be separately determined experimentally or by complementary computational methods.

The simulation of electrohydrodynamics through our implicit coupling scheme in lieu of explicit electrostatic calculations allows for the simulation of much longer length and time scales. Moreover our method does not suffer from the fluctuations inherent in the response of finite systems to weak applied fields, thereby allowing the study of experimentally important electrokinetic conditions. This model thus has the potential to be applied to a wide variety of problems in electrohydrodynamics, and electrophoresis, in particular. The technique could be applied to the simulation of the separation of DNA using ELFSE techniques [28,36], charged polymer coatings for the modulation of electro-osmotic flow [37], the electrophoresis of colloids and other mesoscale objects [22], induced charge electrophoresis and induced charge electro-osmotic flow [38], the dynamics of polyelectrolytes in complex microfluidic structures [6,39–41], and the stall force of a polyelectrolyte within a nanopore [19,21].

The authors would like to thank Stefan Kesselheim and Florian Rühle. This work was supported through NSERC Discovery Grants to G. W. S and J. L. H. C. H. acknowledges financial contributions from the VW Foundation and the DFG through SFB 716. O. A. H. would like to acknowledge financial support from the NSERC-CGS program. The authors are grateful to Sharcnet for providing computational resources for this work.

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Simulations of Free Solution Electrophoresis of Polyelectrolytes with Finite Debye Length Using the Debye-Hückel Approximation

OA Hickey, TN Shendruk, C Holm, JL Harden, GW Slater. Submitted

Simulations of Free Solution Electrophoresis of Polyelectrolytes with Finite Debye Length Using the Debye-Hückel Approximation

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(Dated: January 7, 2012)

We introduce a mesoscale simulation method based on multi-particle collision dynamics (MPCD) for the electrohydrodynamics of polyelectrolytes with short but non-zero Debye lengths. By applying the Debye-Hückel approximation to assign an effective charge to MPCD particles near charged monomers. Our simulations are able to reproduce the rapid rise in the electrophoretic mobility with respect to the degree of polymerization for the shortest polymer lengths followed by a small decrease for longer polymers due to charge condensation.

PACS numbers: 47.65.-d, 47.57.jd, 82.45.-h

The complex interplay between electrostatics and hydrodynamics can give rise to surprisingly counter-intuitive phenomena. Notably several papers by Long, Viovy, and Ajdari [1–4] predicted a variety of interesting physical behaviors for polyelectrolytes in which hydrodynamics play a crucial role. Despite this, early simulations of polyelectrolyte electrophoresis generally neglected long ranged hydrodynamic interactions. This is because they focused on understanding traditional gel electrophoresis through a cross-linked polymer matrix, where the matrix screens hydrodynamic interactions [3]. New methods have emerged over the past twenty years which use microfabricated devices instead of a polymer matrix to conduct polyelectrolyte electrophoresis [5]. In many of these systems hydrodynamic interactions are not totally screened, and thus in order to simulate them algorithms which take them into account are necessary.

There are a wide variety of methods which exist in the literature to simulate electrohydrodynamics [6]. For polyelectrolytes recent work has combined traditional Molecular Dynamics (MD) simulations for the electrostatic interactions with either a Lattice-Boltzmann (LB) fluid [7, 8] or one based on multi-particle collision dynamics (MPCD) [9, 10]. These methods reproduced reasonable electrophoretic behavior of short polyelectrolytes but the computational cost of calculating the hydrodynamic and electrostatic interactions explicitly is quite large. For this reason methods have been developed in order to model electrohydrodynamics while eliminating the costly electrostatic calculations.

Several methods use an infinitely thin Debye layer approximation where there is a Smoluchowski slip between the charged object and the surrounding fluid. Our previous work, which used a modified coupling of monomers to an LB fluid, was able to produce correct behavior for a variety of systems [11]. Simulations have also been done on electro-osmotic flow (EOF) in microfluidic devices in the thin Debye layer limit using both Navier-Stokes equations [12] and a dissipative particle dynamics

(DPD) fluid [13]. The DPD method has also been expanded to reproduce free draining behavior of long polyelectrolytes undergoing electrophoresis [14]. All of these methods focus on the thin Debye layer case since they do not reproduce the fluid velocity profile within the Debye layer and are thus only valid when the Debye length is significantly smaller than the other relevant length scales.

There have also been several interesting approaches based on Brownian Dynamics (BD) methods which use a tensor representing the long ranged interactions due to electrohydrodynamics [15, 16]. Work by Rex and Löwen [16] looked at the role of electrohydrodynamics in lane formation of colloidal suspensions with oppositely charged particles undergoing electrophoresis. The study of Kekre *et al.* [15] examined polyelectrolytes confined between parallel plates subject to both an electric field and a pressure driven flow. Their simulations were able to convincingly reproduce the intriguing results of Zheng and Yeung [17] with quantitative agreement. Neither of these approaches require thin Debye layers nor use costly electrostatic calculations. However, both do suffer the inherent difficulties of BD simulations, namely non-trivial boundary conditions [15], and poor scaling with system size [18].

It has long been known that the electrophoretic mobility of long polyelectrolytes is independent of the degree of polymerization N . For short polymers, it was shown by Hoagland *et al.* that there is an initial increase in mobility followed by a slight drop to the free-draining limit [19]. The cause of the rise for small values of N is that the counterion clouds of neighboring monomers overlap each other, something also seen for colloidal suspensions in low salt solutions [20]. In cases when the polymer's radius of gyration is smaller than the typical size of the counterion cloud, the overlapping Debye layers cause cooperative shearing of the surrounding fluid, which leads to an increased mobility. In general the polyelectrolyte's mobility $\mu(N)$ is seen as the ratio of an effective charge Q_{eff} to an effective friction coefficient Γ_{eff} :

$$\mu(N) = Q_{\text{eff}}/\Gamma_{\text{eff}}. \quad (1)$$

This cooperative shearing of the nearby fluid causes Q_{eff} to increase more rapidly than Γ_{eff} for small values of

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N [7–10, 21]. Since the mobility of a polyelectrolyte is the ratio of the two, the net result is an increase in the mobility with respect to N .

For highly charged chains at sufficiently large N , the electric forces pull counterions out of the solution and make them condense on the backbone of the chain. This phenomenon, known as Manning condensation [22], actually causes the mobility to be a nonmonotonic function of N . A slight maximum exists at intermediate lengths because the effective charge per monomer decreases for longer polymers lengths even after the effective friction per monomer becomes relatively constant. These results have been reproduced using LB-MD [7, 8] as well as MPCD-MD hybrid simulations [9, 10], both of which used explicit charges. As mentioned earlier, this suffers the drawback of requiring computationally expensive electrostatic calculations, thus limiting the length and time scales which can be explored. The cost of electrostatic calculations becomes extremely large for the case of short Debye lengths where a large amount of additional positive and negative salt ions are present.

In this letter, we develop a simulation technique using Multi-Particle Collision Dynamics (MPCD) that is valid in the limit of finite Debye lengths. By applying the Debye-Hückel approximation for the distribution of counterions surrounding a charge, we assign effective charges to MPCD fluid particles within a few Debye lengths of a charged monomer. This effectively approximates the counterion sheath without resorting to simulating the explicit long-time behavior of individual counterions. The computation time is significantly reduced and since the algorithm remains strictly local, simulation times scale linearly with system size. The use of MPCD also allows for the inclusion of complex boundary conditions with ease, a notable drawback of BD approaches. In order to validate our algorithm, we examine the electrophoretic mobility of linear polyelectrolytes as a function of the degree of polymerization and compare to experimental results as well as simulation results which use explicit charges, the only simulation approach that has successfully been employed to date [7–10].

We treat the polymers as being composed of monomers which have a purely repulsive form of the Lennard-Jones potential, termed the Weeks-Chandler-Andersen (WCA) potential [23], between all monomer pairs:

$$\frac{U_{\text{WCA}}(r)}{\epsilon} = \begin{cases} 4 \left[\left(\frac{\sigma_{\text{LJ}}}{r} \right)^{12} - \left(\frac{\sigma_{\text{LJ}}}{r} \right)^6 \right] + 1 & r \leq 2^{1/6} \sigma_{\text{LJ}} \\ 0 & 2^{1/6} \sigma_{\text{LJ}} < r \end{cases} \quad (2)$$

where σ_{LJ} is the length scale of the interaction and ϵ is the energy scale [23]. Our simulations set $\sigma_{\text{LJ}} = 0.5\sigma$ where σ is the MD length scale. The mass of the MD beads is set to $3m$ where m is the mass scale. The N monomers in the polymer are linked together by a finitely extensible non-linear elastic (FENE) bonds of the form

$$U_{\text{FENE}}(r) = -0.5kR_0^2 \ln \left[1 - (r/R_0)^2 \right] \quad (3)$$

where $R_0 = 0.75\sigma$ is the maximum extension of the bond

and $k = 120\epsilon/\sigma^2$ controls the strength of the bond. In addition, there is a Debye-Hückel potential between charged MD beads (but not MPCD beads):

$$\frac{U_C(r)}{k_B T} = \begin{cases} \frac{\lambda_B q_i q_j}{r} \exp(-r/\lambda_D) & r < r_{\text{cut}} \\ 0 & r > r_{\text{cut}} \end{cases} \quad (4)$$

where λ_B is the Bjerrum length, λ_D is the Debye length, and q_i is the valency of species i . In our simulations we set $\lambda_D = 1\sigma$; every monomer is given a valence of $q = 1$. The Bjerrum length is set to $\lambda_B = 1.5\sigma$, an appropriate value for reproducing experimental conditions [7], while $r_{\text{cut}} = 5\lambda_D = 5\sigma$. The integration time step was set to 0.01τ (where τ is the simulation time unit), a common value in MD simulations.

Our polymer is embedded in the coarse-grained MPCD fluid model, which was developed based on stochastic rotation dynamics originally proposed by Malevanets and Kapral [24]. In MPCD, detailed interactions between fluid molecules are omitted and replaced with a multi-particle collision that is not physical but rather is constructed to locally conserve mass, momentum, and energy. The collision step also ensures that a Maxwell-Boltzmann velocity distribution is reproduced and that the hydrodynamic equations of motion are obeyed on sufficiently long length and time scales [25].

MPCD simulations occur in two steps. During the first, or streaming-step, the particles move ballistically and without interaction such that their positions $\vec{r}(t)$ are updated in discrete time intervals δt as $\vec{r}(t + \delta t) = \vec{r}(t) + \vec{v}(t) \delta t$. The second, or collision-step, transfers momentum between particles by partitioning the simulation domain into cells. Each cell has a centre of mass velocity $\vec{v}_{\text{CM}}$, which corresponds to the local macroscopic fluid velocity. Collisions within each cell reassign random velocities to each cell's constituents while preserving $\vec{v}_{\text{CM}}$.

The implementation of MPCD used in this study integrates an Andersen thermostat directly into the collision operator $R = \vec{v}_{\text{ran}} - \langle \vec{v}_{\text{ran}} \rangle_{\text{cell}}$, where $\langle \cdot \rangle_{\text{cell}}$ is the average within a given cell and $\vec{v}_{\text{ran}}$ are randomly generated velocities for each of the MPCD particles in that cell [26, 27]. The distribution of $\vec{v}_{\text{ran}}$ is chosen such that the temperature $k_B T = \epsilon$. Polymers are coupled to the fluid by including monomers in the MPCD collision-step [28]. The density of the fluid is set to $5/a^2$ where a is the MPCD cell size. The MPCD streaming time is set to 0.05τ . Similar to previous MPCD-MD hybrid simulations we set $a = 2\sigma$ [9, 10]. The MPCD beads are given a mass m .

In order to add the effect of electrohydrodynamics, MPCD particles neighbouring monomers are given an effective charge. We assume that the counterion density, $\rho_e(r)$, is proportional to the electrostatic potential, $\phi(r)$, and that the latter obeys the Debye-Hückel approximation

$$\rho_e(r) \propto \phi(r) \propto \begin{cases} \exp(-r/\lambda_D)/r & r < r_{\text{cut}} \\ 0 & r > r_{\text{cut}} \end{cases} \quad (5)$$

where r_{cut} is a cutoff radius kept at $5\lambda_D$ (such that the results are independent of the cutoff). All MPCD particles

within r_{cut} of an MD bead receive a small partial charge proportional to Eq. 5 and normalized such that the sum of the partial charges is $1e$. When an MPCD bead is within r_{cut} of several MD particles the partial charges are summed. A force of magnitude $Q_i E$ (where Q_i is the charge on particle i) is then applied to both the charged MPCD particles and the MD beads. This method of assigning the counter force to the fluid ensures both local momentum conservation and a reasonable distribution of the force on the surrounding fluid. This mean field approach is similar in spirit to the algorithm employed by Duong-Hong *et al.* who artificially applied a force to DPD particles surrounding a polymer chain to represent the influence of counterions [14].

Additionally, the effect of charge condensation can be included in this model by considering an MPC counterion to be condensed if the charge on the particle exceeds some threshold value, Q_T . The threshold value is chosen in order to reproduce a reasonable effective charge for long polymers. This is estimated to be $Q_{\text{eff}} \approx b/\lambda_B \approx 0.3$ where b is the bond length [7]. By running a series of simulations, an appropriate value was chosen such that $Q_{\text{eff}} \approx 0.3$ for long chains. When a counterion is condensed, the charge on the MPCD particle is set to zero and the charge is subtracted from the corresponding MD beads from which it gained its charge via Eq. 5. After the charge of both the MD and MPCD particles is set, a force qE (with $E = 1$ in this work) is added to all charged particles to represent the external electric field. This simple method of including charge condensation provides quite reasonable results.

Consider a charged polymer subject to an electric field in free solution (free solution electrophoresis). When the degree of polymerization is increased from $N = 1$, there is an initial rise in the mobility, followed by a small maximum, before decreasing to the free-draining limit [19, 21] as discussed in the introduction. Figure 1 shows the mobility as a function of the degree of polymerization for a variety of simulation approaches (open symbols) as well as experimental results (filled symbols) [7]. Let us now compare the various simulation approaches to the experimental results in an effort to understand the rather complex behavior.

The open triangles show simulation results when monomers have their velocity reduced by $-\mu_0 E$ prior to the collision step. This is essentially the same technique that we used previously together with lattice-Boltzmann to simulate the infinitely thin Debye layer limit [11]. In those simulations the MD beads were coupled to the fluid, with a Stokes like drag force but with a reduced velocity $v - \mu_0 E$. In both cases, reducing the velocity by $\mu_0 E$ prior to coupling the beads to the fluid causes their velocities relax to be $\mu_0 E$ greater than the local fluid velocity instead of equal to it. In these techniques for thin Debye layers the mobility is independent of N . The net velocity of the beads with respect to the fluid is caused by the modified collision just described. Since each monomer collides independently with the fluid, both the effective

charge and the effective friction grow linearly with N resulting in a mobility independent of length. This is the drawback of simulation techniques based on the thin Debye layer assumption: while they may capture the correct behavior for large objects (such as polymers with a radius of gyration much greater than λ_D), when the length scale of the object is comparable to the Debye length complex behavior cannot be reproduced.

The open diamonds show the result for when the Debye-Hückel approximation is used to apply a counter force representing the electric field's effect on the surrounding counter-ion cloud without attempting to take into account charge condensation. In this case, there is a sharp rise of the mobility for small values of N followed by a plateau. While the initial rise is qualitatively correct, these simulations fail to reproduce the experimental data in two respects. First, the rise in mobility continues for larger values of N than in experiment. Second, these simulations can not reproduce the maximum and slight drop in mobility around $N = 10$ because the drop results from the condensed counterions lowering the effective charge of the polymer.

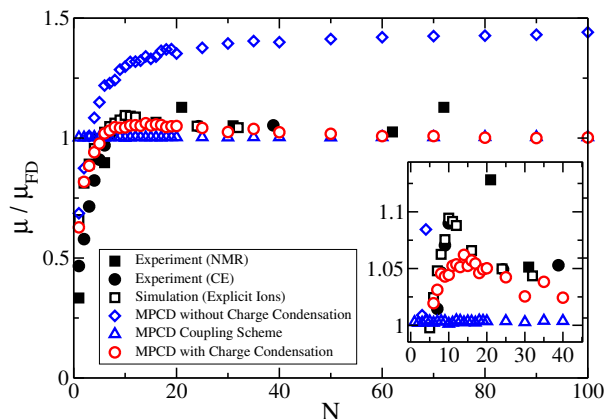


FIG. 1. (color online) The mobility of short polyelectrolytes as a function of the degree of polymerization N normalized by the free-draining value μ_{FD} . The results of our hybrid simulations with and without counterion condensation (open circles and open diamonds respectively), experimental results (filled symbols) and simulations using explicit ions (open squares). The open triangles are simulations using a thin Debye layer approximation. The experimental data and explicit ion simulation results are reproduced with permission from [7].

The open circles in Figure 1 show our simulation results when charge condensation is included. The results agree well with experiments (filled symbols) and explicit ion simulations (open squares) of Grass *et al.* [7]. The sharp initial rise at small N , the plateau to the free-draining mobility at large N and the slight maximum at intermediate N are all present. Figure 2 shows the effective friction Γ_{eff} and effective charge Q_{eff} values for both simulations using explicit ions [7], as well as the mean-field MPCD-MD Debye-Hückel approach proposed

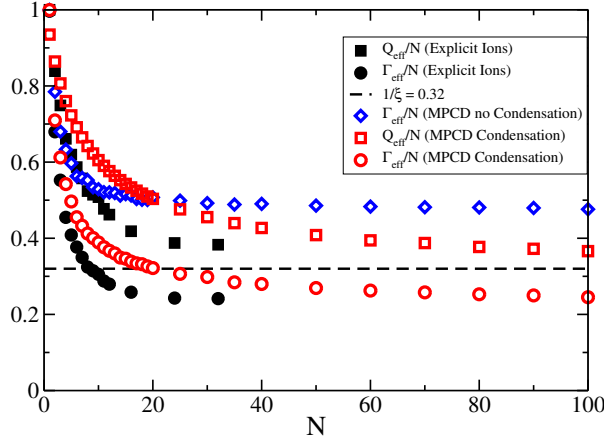


FIG. 2. (color online) The effective friction Γ_{eff} (circles) and effective charge Q_{eff} (squares) per monomer as a function of the degree of polymerization N . The filled symbols are our hybrid simulation results while the open symbols are simulations using explicit ions reproduced with permission from [7]. The diamonds show the effective friction when there is no charge condensation.

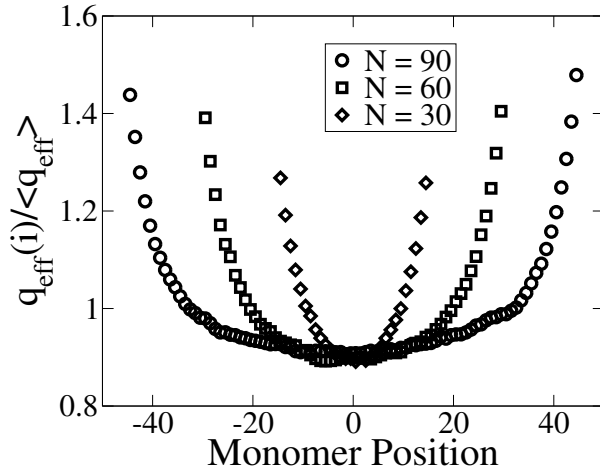


FIG. 3. The effective charge of a monomer as a function of monomer position normalized by the average effective charge on all monomers.

here. Since both the mobility and the effective charge are measured, the effective friction is also known. The filled squares show that the average effective charge Q_{eff} as a function of N for our approach agrees well with the simulations which used explicit ions. The effective friction Γ_{eff} also shows very similar behavior between our approach and explicit ion simulations. Notice that the effective friction coefficient for the MPCD algorithm with charge condensation is considerably lower than when there is no charge condensation. This is because the charges which adsorb to the polymer are those which are closest to the backbone and are thus the most strongly hydrodynamically

cally coupled to it. This is why the decrease in the mobility due to charge condensation in the large N limit is only about 40% despite the effective charge being reduced by about 66%.

Our method displays not only the right effective charge as a function of N but, despite using a simple approach based on the Debye-Hückel approximation, also a remarkably accurate distribution of effective charge as a function of monomer number as seen in Figure 3. The results are actually quite similar to those produced by Limbach and Holm [29] which looked at charge condensation with explicit ions in detail. The increased charge on the ends should produce slightly higher mobility [4, 11]. The fact that both the average effective charge as well as its distribution along the chain agree with results using explicit ions indicates that the simple approach taken to charge condensation is a reasonable approximation.

In this letter we reproduced the free solution electrophoretic behaviour of short polyelectrolytes as a function of the degree of polymerization, N , using a mean-field approach based on the Debye-Hückel approximation. The method consists of assigning an effective charge to MPCD particles near charged monomers using a weighting given by the Debye-Hückel approximation. If the charge on a given MPCD particle is over a certain threshold, it is then given no charge and the charge is subtracted from the monomers, thereby mimicking the effects of charge condensation.

In the absence of charge condensation the mobility displays a sharp rise for small values of N followed by a plateau. This is because of the cooperative shearing of the fluid due to overlapping Debye layers between neighboring monomers. When charge condensation is added, the simulations show a peak in mobility followed by a slight decay to the long chain limit at high N . Interestingly, the reduction in mobility due to charge condensation is significantly less than one might expect. The effective friction, charge, and charge distribution along the chain backbone show good agreement with more computationally expensive simulations which use explicit ions. The simulations also show that a simple transformation of the velocity prior to the collision step in the MPCD algorithm, similar to what has been done for LB-MD hybrid simulations [11], provides a mobility completely independent of N . The ability of the Debye-Hückel approximation to produce reasonable electrophoretic behavior for various polymer lengths means that it could be used to efficiently simulate electrohydrodynamics in more complex situations. While this approach is applied here to the free solution electrophoresis of polymers the idea of using the Debye-Hückel approximation to simulate realistic behaviour should also be applicable to other electrohydrodynamic problems. Notably the dynamics of polymers in confinement is still relatively ill-understood since the simulation of both electrostatics and hydrodynamics remains computationally prohibitive. The technique may also be useful for simulating electroosmotic flow in complex microstructures, polyelectrolyte medi-

ated electroosmotic flow, colloidal electrophoresis, and soft colloid electrophoresis.

ACKNOWLEDGEMENTS

We would like to thank Christian Holm and Mykyta Chubynsky for helpful discussions. This work was supported through NSERC Discovery Grants to G.W.S. and J.L.H. Financial support of O.A.H. and T.N.S. from the NSERC-CGS program is gratefully acknowledged. Computational resources were provided by Scinet.

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Conclusion and Outlook

The preceding work looked at two main topics: the coarse graining of models of polymer electrophoresis, and the modulation of fluid shear at a solid-liquid interface by the addition of polymers. While they are two distinct topics there is a clear relation between them in that the former can be applied to the latter. Both topics, together or separately, hold a wide variety of possibilities for further research in coming years. Let us briefly review the results presented in this thesis and look at potential future research which can be done on these topics.

This thesis presented two new coarse-grained models for the simulation of electrohydrodynamics of polyelectrolytes. The first (in Chapter 5), consisting of a lattice-Boltzmann fluid coupled to a molecular dynamics representation of the polymer, is based on an infinitely thin Debye layer approximation. The simulation results showed that the model reproduces both the right mobility and diffusion coefficient for polymers undergoing free solution electrophoresis. In agreement with previous molecular dynamics simulations using explicit ions [1], it was shown that the force necessary to hold a polyelectrolyte in place is proportional to the hydrodynamic radius of the chain and not the total charge on the polymer as one would intuitively expect. The simulations also showed how a net-neutral block copolymer consisting of both positive and negative charges can have a non-zero mobility due to hydrodynamic interactions, as had been predicted [2]. Even more surprising, the simulations confirmed the prediction that a specific arrangement of charges can actually generate an electrophoretic force perpendicular to the applied field [3]. The method is only valid when the Debye length (typically about 1 nm in experiments) is smaller than the typical device dimension, which is true in microfluidics.

The second coarse-grained method presented is based on a multi-particle collision dynamics fluid coupled to a molecular dynamics representation of the polymer and was presented in Chapter 6. Unlike the first method this algorithm was designed to take into account the effect of a finite Debye layer thickness by using the Debye-Hückel approximation to assign a force to the fluid. This method proved effective at modeling the electrophoresis of short polyelectrolytes, which is a highly non-trivial limit. Simulation results indicated that the behaviour of the mobility, the effective charge, and the effective friction coefficient as a function of the degree of polymerization

were in good agreement with the simulations done by Grass *et al.* [4] which use explicit ions. The simulations also showed that the distribution of the effective charge along the chain backbone was in agreement with the explicit ion simulations of Limbach and Holm [5].

The coarse-grained models of polymer electrophoresis should help to elucidate the role of hydrodynamic interactions when chains are electrophoresed in microfluidic devices. There have already been many simulations which have looked at electrophoresis in microfluidic devices; however, almost all have either ignored hydrodynamic interactions or modeled the electric part of the problem by simply adding a constant force to each monomer. Despite their simplicity, these studies have provided results which are in good agreement with experimental data. One issue is that the dimensions of the devices are typically smaller than the radius of gyration of the polymers in order to prevent free draining behaviour. The walls have a tendency to screen hydrodynamic interactions which may make the simpler simulation models of polymer electrophoresis sufficient in certain circumstances.

An interesting case study on the necessity of proper electrostatic and hydrodynamic interactions in the nanofluidic manipulation of polyelectrolytes is nanopore translocation. Simulations which look at the unbiased translocation of a polymer suggest that hydrodynamic interactions do not have a large impact on the dynamics [6]. This indicates that hydrodynamics are probably screened by the walls on the length scale of the polymer's radius of gyration. In contrast, when a polyelectrolyte undergoes driven translocation by the way of an electric field, theory [7], simulation [8], and experiment [9] indicate that electrohydrodynamics within the nanopore are what determine the magnitude of the electrophoretic driving force. The fact that nanopores are one of the most highly studied systems in the nanofluidic manipulation of polymers is probably why these rather subtle effects of electrohydrodynamics have been uncovered. There will no doubt be more interesting discoveries about electrohydrodynamics in the coming years as theory, experiments, and computer simulations continue to examine polymers subject to an electric field under strong confinement.

The systems which have attracted the most attention for the separation of DNA are collisions with posts and simple microfluidic devices (both reviewed in Appendix A). In both systems, despite a large amount of experimental and computational work, there is still very little work which looks at the role of hydrodynamic interactions. In the case of collisions with posts they should play a particularly strong role at low electric fields [10, 11]. For microfabricated devices long-range hydrodynamics are largely screened [12], but this has yet to be investigated in detail with either

experiment or simulation. Part of the reason for the lack of numerical work up to this point is the long run times required, something which the algorithms developed in this thesis should help to address.

Perhaps the most logical application of these methods however is End-Labeled Free Solution Electrophoresis (ELFSE). The system consists of a DNA molecule with a neutral polymeric label attached to it. The analytic equation to predict the mobility of the complex as a function of the length of the DNA strand shows very good agreement with experiments [13]. One thing which is still somewhat ill-understood however are the nonlinear effects with respect to the electric field, such as those seen in Chapter 5. Similar effects have been found in the case of ELFSE; however there exists a controversy in the literature between Nedelcu and Slater [14] (who calculated such effects to come into play around 700 V/cm) and McCormick and Slater [15] (who predicted such effects near 2 kV/cm) which has yet to be resolved. While accurate quantitative predictions are generally difficult in computer simulations, simple simulations should give an indication as to the correct value.

The first work, in Chapter 2, on the electrokinetics of soft interfaces, looked into the role of adsorbed polymer coatings for the modulation of electro-osmotic flow. The simulations showed that very strongly adsorbed polymer coatings did a poor job of reducing EOF since the polymers essentially collapsed onto the wall. In fact, at the highest adsorption strengths, the polymers actually increased the EOF as they effectively increased the surface charge density by reducing the radius of the capillary. Reducing the strength of adsorption improved the coating's ability to quench EOF as the thickness of the polymer coating increased. This trend ended at the phase transition for adsorption of the polymers. When the adsorption strength was below this threshold further reduction in the adsorption strength resulted in increased EOF since the polymers simply desorbed from the surface eliminating any friction with the walls, the mechanism by which the polymers dissipate the momentum produced by the mobile ions within the Debye layer. The simulations were in agreement with experimental results which showed that increased hydrophilicity of an adsorbed polymer coating caused increased quenching of EOF.

The article in Chapter 3 looked at how varying the monomer concentration affects the ability of dynamically adsorbed neutral polymer coatings to reduce EOF. The simulations found that at high polymer density and adsorption strength there is the possibility to create metastable polymer coatings which offer the potential to provide a significant reduction in the EOF. Experimentally, one important characteristic is the stability of the polymer coating as a very stable coating allows

many assays to be run with a high degree of reproducibility. The simulations indicated that while the coatings in this new regime were metastable, their stability increased with increasing adsorption strength and polymer length. The reason for the unstable nature of the coatings was shown to be closely related to the number of adsorbed polymers. When the EOF was strongly reduced, almost all of the chains had some monomers adsorbed to the capillary walls. Over time some polymers desorbed while others had a larger fraction of their monomers adsorbed to the surface as they collapsed onto the wall. Looking at the increase in EOF over time, it was clearly strongly correlated to this rearrangement of chains within the adsorbed coating. This prediction of improved EOF by using a strongly adsorbing coating is something which should be easily testable by simply increasing the concentration of polymer in the coating solution.

Chapter 4 looked at how charged grafted polymer coatings can be used to control EOF. The results were in fairly good agreement with the scaling predictions of Harden *et al.* [16] although the EOF was slightly higher than predicted. This was attributed to the finite Debye length compared to the predictions which were based on an infinitely thin Debye length. The article also looked at the complex non-linear dependence of the EOF on the applied electric field. Simulations examining the effect of the charge density along the polymer backbone were in good agreement with recent experimental results. It was also found that the direction of the EOF can change direction before the net charge of the interface (wall charges and those on the polymer) changes sign.

The study of the electrokinetics of soft interfaces has been examined theoretically for a long time but it is only recently that computer simulations have looked into the topic. The simulations almost all look at the case of neutral polymer chains and the case of thin Debye layers while the theoretical predictions and experimental results look at a much wider set of system parameters. The system is rather complex by nature given that both electrostatic and hydrodynamic interactions are involved and only now are the necessary computational algorithms beginning to emerge. Further simulations in this field should help to test the limits of the analytical expressions which exist in the literature and to better interpret experimental results.

In the soft colloid electrophoresis community, many scientists have done studies comparing analytic calculations and experiments for the mobility of a polymer coated colloid. Using fitting parameters, the theoretical equations can be used to effectively fit the experimental data [17]. The emergence of computer simulations offers the potential to be able to understand the microscopic origins of the parameters, such as the “softness parameter”, and to be able to predict them based on the system setup. One basic question which has yet to be answered is what is the proper

equation for predicting the fluid velocity profile within the polymer coatings [18]. Given that the microscopic details of the system are readily accessible in simulations, comparing the analytic theories to simulation should allow for a robust testing of analytical results.

This thesis probed the dynamics of polyelectrolytes in aqueous solution, a topic which has wide ranging applications biotechnology. Ever increasing computational power has allowed the exploration of longer and longer time and length scales. Despite these dramatic increases, simulations still aim to reach experimentally relevant scales in many systems. I believe the methods introduced in this thesis should help to achieve this important goal while the simulations of the electrohydrodynamics of soft interfaces lie on the edge of what can currently be achieved computationally.

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Appendix A: Modeling the separation of macromolecules: A review of current computer simulation methods

GW Slater, C Holm, MV Chubynsky, HW de Haan, A Dubé, K Grass, OA Hickey, C Kingsbury,
D Sean, TN Shendruk, L Zhan. *Electrophoresis* **30**, 792-818 (2009)
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Received October 15, 2008
 Revised December 15, 2008
 Accepted December 15, 2008

Review

Modeling the separation of macromolecules: A review of current computer simulation methods

Theory and numerical simulations play a major role in the development of improved and novel separation methods. In some cases, computer simulations predict counterintuitive effects that must be taken into account in order to properly optimize a device. In other cases, simulations allow the scientist to focus on a subset of important system parameters. Occasionally, simulations even generate entirely new separation ideas! In this article, we review the main simulation methods that are currently being used to model separation techniques of interest to the readers of *Electrophoresis*. In the first part of the article, we provide a brief description of the numerical models themselves, starting with molecular methods and then moving towards more efficient coarse-grained approaches. In the second part, we briefly examine nine separation problems and some of the methods used to model them. We conclude with a short discussion of some notoriously hard-to-model separation problems and a description of some of the available simulation software packages.

Keywords:

Computer simulations / Electrophoresis / Microfluidics / Modeling / Separation methods
 DOI 10.1002/elps.200800673

1 Introduction

Computers are getting cheaper and more powerful every year. At the same time, separation systems are getting smaller and faster. The convergence of these two trends has led to a situation where it is now possible to simulate the key parts of some separation systems at the molecular level. An example of this is the atomistic simulation of the translocation of an ssDNA molecule through a nanopore [1], a process that may lead to the \$1000 genome sought by the NIH in the USA.

Transport-based separation systems generally represent a compromise between the physical separation of several molecular species (*e.g.* due to their different velocities in the

device) and their spatial spreading due to various diffusion-related processes. Since most separation devices employ sieving, liquids and electric forces, modeling efforts must generally include long-range electrostatic forces, long-range hydrodynamic forces, frictional and diffusion contributions, conformational effects (for macromolecules), entropic factors, gradients of various types, and interactions with surfaces and obstacles. It is the role of the theoretician to reduce the number of factors to a bare minimum in order to design models that can be solved either analytically or numerically. For example, long-ranged hydrodynamic interactions (HI) are often neglected in the case of gel-based separations.

Simulating complex processes using numerical models that include various levels of detail is now widely seen as the third approach to scientific discovery, complementing the well-established experimental and theoretical methods. Computer simulations are more than mere attempts at reproducing experimental results. Because we have full control over the simulation parameters, and because we can measure every conceivable property (including correlations between properties) of a system during a numerical experiment, simulations allow detailed autopsies and diagnostics not normally achievable in a laboratory. They also allow us to explore numerous systems and geometries at relatively low cost.

Historically, several discoveries were first made on a computer, *i.e. in silico*. In the field of electrophoresis, one of us (G.W.S.) and his co-workers [2] first discovered the phenomenon of DNA band inversion using a computer simulation of the biased reptation model [3, 4]. Experiments

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Abbreviations: BD, Brownian dynamics; BFA, bond-fluctuation algorithm; DPD, dissipative particle dynamics; FENE, finitely extensible nonlinear elastic; HI, hydrodynamic interactions; LB, lattice Boltzmann; LD, Langevin dynamics; LJ, Lennard-Jones; LMC, lattice Monte Carlo; Mbp, megabase pairs; MC, Monte Carlo; MD, molecular dynamics; OMRC, Ogston–Morris–Rodbard–Chrambach; SRD, stochastic rotation dynamics; WCA, Weeks–Chandler–Andersen

later confirmed the existence of this counterintuitive phenomenon.

In view of the growing importance of computer simulations in the field of separation methods, we believe that this review is timely. Our hope is that it will be of equal interest to the experimentalist who wants to understand the relevant literature and use simulations to guide his/her laboratory work, to the theoretician who wants to explore novel systems using numerical methods, and finally to the computational scientist who wants to use new tools.

This review article has three main parts. In Section 2, we describe several approaches that are currently being used to model separation processes. We first examine methods that include molecular details, then describe algorithms that simplify the description of the liquid phase, and finish with several coarse-graining methods that generate even simpler numerical models. In Section 3, we review nine well-known problems and the simulation methods that are being used to study them. In Section 4, we look at the future and discuss a few problems that have proven hard to simulate and understand with the current methods. An Appendix then lists some of the most well-known software packages in the field; however, it is important to note that many (perhaps most) simulation studies have actually been based on simulation programs written by the researchers themselves. The choice of material is obviously that of the authors; we recognize that several important algorithms and problems are missing from this review. Among those, approaches based on the continuum description of the flow and the distribution of analytes [5, 6] and reptation models of gel electrophoresis [4, 7–12] are perhaps the most obvious.

2 Simulation methods

In this section we describe some of the most popular simulation techniques used in computational studies of electrophoretic separation methods. It is obviously impossible to review them all – as a matter of fact, new methods are proposed every year. In that light, we present some of the main methods in a way that we believe is both logical (from the more microscopic to the most simplified) and compact. For a more rigorous discussion on levels of coarse-graining see [13]. In our descriptions, we do not strive for the level of detail that would allow readers having no prior knowledge to do their own simulations. Rather, we present a bird's-eye view of the hierarchy of different computational methods. Correspondingly, the number of references is large as the interested reader will need to consult specialized texts in order to fully appreciate the intricacies of these simulation methods.

2.1 Molecular dynamics

The molecular dynamics (MD) technique is used to follow the evolution of a large number of interacting particles by

numerically integrating the classical equations of motion. Although MD is often used to simulate systems at the molecular level, it is also suitable for modeling larger-scale systems by implementing coarse-grained methodologies. Hence, it is a common approach to simulating polymer dynamics.

When performing MD simulations, the first step is to calculate the net force on each particle. Newton's second law $\mathbf{F} = m\mathbf{a} = m\ddot{\mathbf{r}}$ then provides the particle's acceleration. Numerically integrating by $\mathbf{v} = \mathbf{v}_0 + \mathbf{a}\Delta t$ yields the particle velocity at a short time Δt later; a second integration $\mathbf{x} = \mathbf{x}_0 + \mathbf{v}\Delta t$ gives its position (in practice, more accurate numerical integration techniques such as the velocity-Verlet algorithm [14, 15] are employed). After performing these calculations for each particle, the new configuration of the system at time $t + \Delta t$ is obtained. This process is repeated to generate trajectories for each particle that, together, comprise a series of snapshots describing the evolution of the system. For conceptual simplicity, we begin by describing a fully atomistic MD simulation (each atom is represented by one particle). However, as this is generally too computationally expensive, we subsequently introduce various techniques to “coarse-grain” the models and make MD a viable tool for studying separation methods. Although we will discuss only a few key topics, there are a great number of excellent books [14–17] and review articles [18–20] that can be used to explore the rich field of MD simulations in greater depth.

2.1.1 The force field

The interactions between the particles in the system obviously play a major role. The mathematical forms and parameters dictating these interactions are known as the “force field”; the key concepts used in this review are discussed below.

2.1.1.1 Lennard-Jones

The interaction between two free, uncharged atoms implies two primary effects. First, there is a short-ranged repulsion preventing overlap. Second, there is a long-range attraction arising from weak but favourable interactions due to induced dipole effects (dispersion forces). The Lennard-Jones (LJ) potential [21] is commonly used to model these effects:

$$U_{\text{LJ}}(r_{ij}) = 4\varepsilon_{ij} \left[\left(\frac{\sigma}{r_{ij}} \right)^{12} - \left(\frac{\sigma}{r_{ij}} \right)^6 \right] \quad (1)$$

where r_{ij} is the separation between the particles i and j , ε_{ij} is the depth of the potential well and σ is the effective size of the particle (see Fig. 1 for a plot of this potential). The numerical values used for ε and σ dictate the details of the interaction.

2.1.1.2 Coulombic forces

The other primary non-bonded interaction arises from the electrostatic interaction between pairs of particles given by

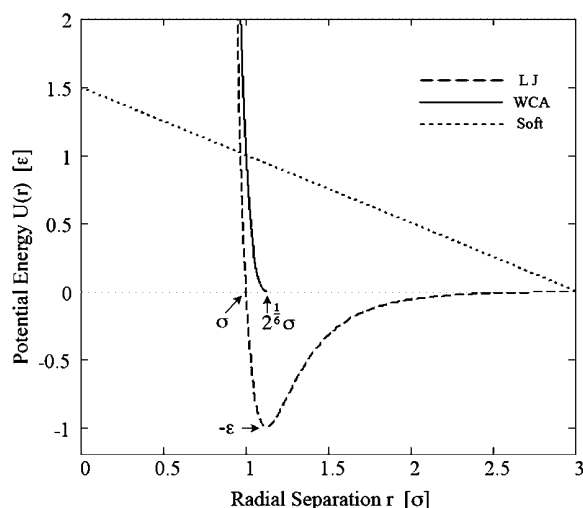


Figure 1. Plot of the full LJ potential, the purely repulsive WCA potential, and the soft potential common in DPD. The positive soft potential of DPD extends far further and avoids the singularity of the LJ and WCA potentials.

the Coulombic potential

$$U_{\text{Coul}}(r_{ij}) = \frac{1}{4\pi\epsilon_0} \frac{q_i q_j}{\epsilon r_{ij}}$$

Here, q_i and q_j are the effective charges on each particle, ϵ_0 is the permittivity of free space, and ϵ is the dielectric constant of the medium. In atomistic simulations with an explicit, polar solvent model, including ϵ is not necessary. However, for simulations with either implicit or non-polar solvent models (including the mesoscopic models common in coarse-grained simulations), ϵ is an effective dielectric constant that includes the screening effects due to the medium (e.g. $\epsilon = 80$ for water). Although the magnitude of the net charge is obvious for free ions, in molecules where charges are shared *via* bonds the value of the effective partial charges is a vital component of the force field. Unlike the LJ interaction that decays relatively quickly, the Coulombic interaction is long ranged. While a cut-off distance (beyond which contributions are not considered) is appropriate in one dimension, the long-ranged contributions are important in two or three dimensions. For this reason, inclusion of electrostatic effects can be computationally expensive and many sophisticated techniques have been developed to address this particular problem. For a review of many of these methods see [22, 23]; further methods are discussed in [24, 25].

2.1.1.3 Bonded interactions

In MD simulations, elements of chemical bonds are captured by implementing potentials to maintain bond lengths and bond angles. Although other forms are used, a common choice for both is a harmonic potential such that the bond stretching $U_{\text{BS}}(r_{ij})$ and bond bending $U_{\text{BB}}(\theta_{ijk})$

potentials are given by

$$U_{\text{BS}}(r_{ij}) = \frac{1}{2} k_{ij} (r_{ij} - r_0)^2 \quad (2)$$

$$U_{\text{BB}}(\theta_{ijk}) = \frac{1}{2} k_{ijk} (\theta_{ijk} - \theta_0)^2 \quad (3)$$

Here, k_{ij} and k_{ijk} are force constants, θ_{ijk} is the angle formed by the bonds joining atoms i , j , k , and r_0 and θ_0 are the equilibrium separation and bond angle respectively. Hence, in this model, atoms are bonded together *via* Hookean springs while the bond angles oscillate around the equilibrium value. In atomistic simulations, the various parameters are an essential part of the force field as they dictate the details of these interactions. Note that while we discuss only bond stretching and bending here, terms can be added to model effects such as restrictions to torsional angles and *cis versus trans* configurations [26].

2.1.2 Coarse graining

A fully atomistic MD simulation is quite detailed in the features it replicates and is appropriate to study dynamics on the nanosecond and nanometer scales. To probe larger systems on longer time scales, the use of coarse-graining techniques is essential.

2.1.2.1 United atoms

The first step in coarse-graining a system is to lump groups of atoms together and simulate them as a single “particle”. For example, in atomistic MD simulations of proteins, it is common to group the hydrogens of amino acid side chain carbons in with the carbon to form a united atom. Reducing the number of particles results in reduced computing time while preserving the dynamics of interest. One can extend this idea and model entire side chains (or even entire monomers) as single particles. From this, we can then simulate any polymer as a string of bonded generic beads – each of which represents a monomer. Of course, the interaction between adjacent beads is vital; such local effects can be incorporated by using, e.g. a potential between adjacent bonds in the chain to give a finite stiffness to the backbone (for example, the bond angle potential discussed above [27]).

We can extend the level of coarse-graining even further by lumping polymer beads together and simulating n monomers as a single particle that now represents a subchain of the polymer. If n is large enough such that the length of the subchain is equal to or exceeds the Kuhn length (a measure of the stiffness of the polymer chain), correlations between subchains are negligible and we can simulate the coarse-grained polymer as a freely jointed chain [28]. This is a standard model for studying a polymer *via* MD simulations as it allows for computational simplicity and efficiency while preserving the dynamics of interest. What is lost is the direct correspondence to the system in study and hence an extra layer of abstraction between simulation and reality is introduced.

2.1.2.2 The WCA potential

In coarse-grained simulations, it is common to use the purely repulsive Weeks–Chandler–Andersen (WCA) potential (also known as the truncated LJ potential) to model particle interactions [29]. This is an LJ potential that is shifted and truncated at its minimum value (see Fig. 1) so that it ends smoothly at a distance $r_c = 2^{1/6}\sigma$:

$$U_{\text{WCA}}(r_{ij}) = \begin{cases} 4\epsilon_{ij} \left[\left(\frac{\sigma}{r_{ij}} \right)^{12} - \left(\frac{\sigma}{r_{ij}} \right)^6 \right] + \epsilon_{ij} & \text{for } r_{ij} < r_c \\ 0 & \text{for } r_{ij} \geq r_c \end{cases} \quad (4)$$

However, the standard LJ interaction is often used to study systems with varying affinities between different types of particles (this is implemented by varying the ϵ_{ij} 's).

2.1.2.3 Finitely extensible bonds

In a coarse-grained model, the use of harmonic potentials to connect adjacent beads can lead to unphysical bond stretching effects. For this reason, a finitely extensible force is needed such that there is a hard limit on the bond length. The most common choice is the finitely extensible nonlinear elastic (FENE) potential:

$$U_{\text{FENE}} = -\frac{1}{2}kr_0^2 \ln \left(1 - \frac{r^2}{r_0^2} \right) \quad (5)$$

Here, k indicates the stiffness of the bond and r_0 gives the maximum bond length (the potential shoots to infinity as r approaches r_0). For appropriate values of k and r_0 , the occurrence of “bond crossing” is extremely rare and hence behaviour appropriate for a self-avoiding polymer is produced [30]. It is interesting to note that this form is an approximate solution to the inverse Langevin function; in some cases, it may thus account for the entropic restoring force, which arises from stretching a subchain [28].

2.1.3 Simulating a polymer

Putting the above together, the simplest model of a polymer in a coarse-grained simulation is a freely jointed chain of beads (which can either carry a net charge or be neutral) interacting by the WCA potential (or the LJ potential when short range attractions are desired) and with immediately neighbouring monomers bonded *via* the FENE potential. Extension to branched polymers is trivial. Although we have sacrificed many details, we have preserved effects such as excluded volume, the entropic elasticity, and the non-crossability of bonds. Although this model may seem very crude, it does allow for a realistic scaling behaviour of polymeric properties such as the radius of gyration and the diffusion coefficient with respect to the degree of polymerization. This approach also represents the most realistic model of polymers for which experimentally relevant simulations are feasible. Note that although this “bead-spring” model is a common approach, other models can be employed. For example, algorithms can be implemented to

maintain the bond distance at a fixed length [31, 32] resulting in a “bead-rod” model (or a “pearl-necklace” model for the case of the rod length being comparable to the diameter of the bead) [33].

Now that we have a model for the polymer, we can add other components. For example, a common scenario involves simulation of polyelectrolytes with free ions. To accomplish this, ions can be defined as WCA particles carrying a net charge. Additionally, one can include features such as obstacles or boundaries (e.g. walls) by building them out of particles or defining them using mathematical constraints. The final, and critical, component of the simulation system is the solvent. As the model used for the fluid impacts both the dynamics that are observed and the computational time, Sections 2.2–2.4 will focus on various ways of treating the fluid.

At this point, it is important to mention that choosing a method of controlling the temperature is often a crucial consideration in MD simulations; in fact, it is also one that is often intimately connected to the choice of solvent model. Implementing a thermostat is particularly critical when an external field is adding energy to the system – as in electrophoresis. Although there are schemes based on rescaling the velocities [34] or periodically assigning random velocities [35], such algorithms can lead to artefacts as local momentum is not conserved (a particular problem when hydrodynamics are of interest [36]). In coarse-grained simulations, the method chosen for treating the fluid often involves a particular temperature control scheme *via* the coupling of the analyte (e.g. the polyelectrolyte) to the fluid. An important case is the thermostat developed for dissipative particle dynamics (DPD) (Section 2.3.1), which can be used independently of the fluid model and, for several reasons, has been a significant advancement in the field [37]. Finally, in the case of performing Langevin dynamics (LD) or Brownian dynamics (BD), the temperature is explicitly in the equation of motion (Section 2.4). Although discussing the details of these algorithms (and others [38–41]) is beyond the scope of this review, the interested reader is encouraged to investigate these various schemes starting with the citations given and the discussion of solvent models in the following sections.

2.2. Explicit fluid

At the atomistic level, many models exist that explicitly describe a water molecule [42–45]. In fact, developing appropriate models for simulating water alone is the subject of active research. In coarse-grained simulations of solvents, we group atoms, and even molecules, together and simulate them as a single bead. The use of the WCA potential for this solution of beads is found to provide a good solvent, regardless of temperature [46]. The advantage of using an explicit fluid is that it is conceptually obvious and preserves the long-range HI that correlate the movement of objects in a fluid. However, in practice, this results in much of the simulation time being dedicated to calculating the details of

the fluid bead dynamics, which are often not of interest. For these reasons, several techniques for modeling the fluid to maintain the HI while neglecting the computationally costly details of the fluid motion have been developed. These models are discussed in the following section.

2.3 Mesoscopic fluid

It is possible to describe hydrodynamic effects without resorting to an explicit description of fluid molecules or the discretization of the continuous Navier–Stokes equations. In particular, a clever use of conservation laws allows mesoscopic methods to employ local algorithms that recover the solution to the hydrodynamics equations in the large-scale/long-time limit while at the same time bypassing the molecular details of the fluid and thus dramatically reducing the computational cost of the simulation. In the following sections we will review three mesoscopic approaches, namely DPD, stochastic rotation dynamics (SRD) and lattice Boltzmann (LB).

Following the description of these mesoscopic methods, Section 2.4 will introduce LD and BD. A comparison of the different methods discussed ensues in Section 2.5 where a schematic is presented to summarize each of the methods.

2.3.1 Dissipative particle dynamics

In DPD, the fluid is modelled by large particles interacting via a *soft* potential [47–49]. This allows for a reduction in computing time in two ways. First, as each DPD fluid bead represents a cluster of fluid molecules moving together in a coherent manner, the simulation tracks a much lower number of interacting objects. Second, since with a soft potential the forces cannot be arbitrarily large, we can reduce computing times by increasing the integration time step. All particles interact by three forces: a conservative force $\mathbf{F}^C$, a dissipative force $\mathbf{F}^D$, and a random force $\mathbf{F}^R$:

$$\mathbf{F}_i = \sum_{j \neq i} \left(\mathbf{F}_{ij}^C + \mathbf{F}_{ij}^D + \mathbf{F}_{ij}^R \right) \quad (6)$$

where it is assumed that the interactions are negligible beyond a cut-off radius r_c . Pairwise potentials ensure that momentum and angular momentum are conserved. The force $\mathbf{F}_{ij}^C$ represents and can include any conservative forces that act on the particle. A common choice is a soft repulsion (see Fig. 1) acting along the line of centres such as

$$\mathbf{F}_{ij}^C = \begin{cases} a_{ij}(r_c - r_{ij})\hat{\mathbf{r}}_{ij} & \text{for } r_{ij} < r_c \\ 0 & \text{for } r_{ij} \geq r_c \end{cases} \quad (7)$$

where a_{ij} parametrizes the maximum repulsion. The dissipative force is an inter-drag force between a pair of soft fluid particles moving through each other opposing their relative motion $\mathbf{u}_{ij}$ and dissipating heat:

$$\mathbf{F}_{ij}^D = -\omega^D(r_{ij})\zeta(\hat{\mathbf{r}}_{ij} \cdot \mathbf{u}_{ij})\hat{\mathbf{r}}_{ij} \quad (8)$$

where ζ is the friction constant between the two clusters. The random noise force is given by

$$\mathbf{F}_{ij}^R = \omega^R(r_{ij})\sqrt{2\zeta k_B T} \frac{\gamma_{ij}}{\sqrt{\Delta t}} \hat{\mathbf{r}}_{ij} \quad (9)$$

where γ_{ij} is a random number of zero mean and unit standard deviation. To satisfy the fluctuation–dissipation theorem, the dissipative and random forces are interrelated through the weight functions, as $\omega^D(r) = [\omega^R(r)]^2$.

The random and dissipative forces act as a source and a sink for heat, respectively. Therefore, DPD, unlike BD or LD is an implicit thermostat [37, 50] that conserves linear and angular momentum and thus recovers hydrodynamics in the macroscopic limit. It should be noted that DPD does not conserve total energy, but only mass and momentum. Solutes can be included as DPD beads and by the inclusion of a bead–spring type force in Eq. (6), DPD can simulate polymers as well [50, 51]. In fact, DPD can be used as an effective thermostat that conserves HI, independently of the fluid model [37].

2.3.2 Stochastic rotation dynamics

The DPD beads represent clusters of many particles but all bead–bead interactions must still be evaluated. In SRD [52–54], also called multiparticle collision dynamics [55, 56] or real-coded lattice gas [57, 58], collisions between fluid particles are replaced by multiparticle collision events that omit the molecular details and eliminate the need to calculate the forces between the fluid particles. These events are defined to conserve mass, momentum, and energy such that the hydrodynamic equations of motion are obeyed on sufficiently long length and time scales [59]. SRD simulations occur in two steps. During the first, or *streaming*, step, the particles move ballistically, and their positions $\mathbf{r}_i(t)$ are updated in discrete time intervals δt :

$$\mathbf{r}_i(t + \delta t) = \mathbf{r}_i(t) + \mathbf{v}_i(t)\delta t \quad (10)$$

The second, or collision, step transfers momentum between particles. The simulation domain is partitioned into cells. The number of particles in each cell may vary from one cell to another but the total number is conserved. Each cell has a centre of mass velocity $\mathbf{v}_{CM}$, which corresponds to the local macroscopic velocity. The collision step is a simple non-physical scheme that is constructed to conserve momentum. Multiparticle collisions within each cell are represented by the operation

$$\mathbf{v}_i(t + \delta t) = \mathbf{v}_{CM}(t) + \mathbf{R}(\mathbf{v}_i(t) - \mathbf{v}_{CM}(t)) \quad (11)$$

By making the collision operator, $\mathbf{R}$, a rotation through an angle α about a randomly chosen axis, conservation of energy, isotropy and a Maxwell–Boltzmann velocity distribution are met in the continuum limit. Other choices allow SRD to operate as a thermostat as well [60]. Unfortunately, Galilean invariance is broken by the discretization of space into cells. However, this can be completely remedied by performing the collision operation in a cell grid, which is shifted each time step by a random vector [61, 62].

When integrating SRD into a standard MD simulation the solute particles can be coupled to the momentum of the fluid by including them in the SRD collision step (Eq. 11) [55, 56, 63–65]. In typical simulations of a polymer, on the order of 10^2 MD time steps are performed between SRD collision events [54, 66–68]. This separation of time scales ensures that the momentum transferred to the polymer during the collision step is well distributed throughout the chain [69]. Another common scheme uses a hybrid SRD/MD approach in which not only the solute–solute but also the solute–solvent interactions are handled by an MD algorithm, while solvent–solvent interaction is simulated by SRD [53, 70, 71].

2.3.3 Lattice Boltzmann method

LB coarse-grained models [54, 72, 73] are based on a solution of the discretized Boltzmann transport equation. The main quantity in the LB approach is the velocity field, rather than fluid particles, and it is an inherently statistical approach, where discrete momentum distributions are represented on a spatial grid.

The discretization of positions and momenta using finite sets of directions greatly simplifies the problem. The most frequent mesh types for the LB simulations are the D2Q9, D3Q15, and D3Q19 lattices, where $DkQn$ refers to the number k of dimensions and to the discrete number n of velocity vectors, $\mathbf{e}_i$.

A set of distribution functions $\Gamma_i(\mathbf{r}, t)$ is defined on each lattice site $\mathbf{r}$. Each of these can be interpreted as the fraction of fluid that will move with the i th discretized velocity at time t . The discretized Boltzmann equation provides a generic description for the time evolution of the probability density, but there is freedom in the choice for the actual form of the collision integral. A common formulation is the Bhatnagar–Gross–Krook approximation, where

$$\Gamma_i(\mathbf{r} + \mathbf{e}_i \Delta t, t + \Delta t) = \Gamma_i(\mathbf{r}, t) - \frac{\Delta t}{\tau} (\Gamma_i(\mathbf{r}, t) - \Gamma_i^{\text{EQ}}(\mathbf{r}, t)) \quad (12)$$

where τ is the phenomenological relaxation time, which prescribes the timescale for the relaxation of the actual population Γ_i to the equilibrium particle distribution function Γ_i^{EQ} . In the low velocity approximation, Γ_i^{EQ} can be expressed as

$$\Gamma_i^{\text{EQ}} = w_i \rho \left[1 + \frac{\mathbf{e}_i \cdot \mathbf{u}}{c_s^2} + \frac{(\mathbf{e}_i \cdot \mathbf{u})^2}{2c_s^4} - \frac{u^2}{2c_s^2} \right] \quad (13)$$

where ρ is the hydrodynamic density and c_s is the speed of sound, which is determined by mesh properties. The weights, w_i , must be suitably chosen to recover the macroscopic Navier–Stokes equations and are dependent on the mesh configuration [54]. The viscosity of the LB fluid is determined by the choice of the relaxation rate.

LB can be coupled to small suspended spheres by treating them as point particles that interact with the fluid

through a friction force proportional to the relative velocity obtained via linear interpolation from the surrounding lattice sites [74, 75]. By adding fluctuation terms to both the fluid and the embedded particles, LB can operate as an adequate thermostat [74]. The correct treatment of a fluctuating LB algorithm has been recently addressed in several papers [76, 77].

2.4 Langevin and Brownian dynamics

Going beyond mesoscopic models, further coarse graining can be achieved by avoiding direct simulation of the fluid altogether. The timescale of individual collisions with solvent molecules (causing frictional drag and Brownian motion) is much smaller than the time scales relevant to electrophoresis. It is computationally advantageous to coarse grain out the fine details of the collisions and simply include their statistical effect on the solute. One may consider implicitly the two main effects of the fluid acting on the particle: (i) a frictional force opposing its motion and (ii) random kicks arising from collisions with the solvent. The frictional (or dissipative) force $\mathbf{F}^{\text{D}}(t)$ removes energy from the particle while the fluctuating Brownian force $\mathbf{F}^{\text{B}}(t)$ adds energy to the particle. Hence, at this coarse-grained level, the fluid is included solely in a statistical manner governed by the fluctuation-dissipation theorem. By replacing the explicit fluid with a drag and a Brownian force, we lose the long-range particle–particle interactions mediated by the fluid. This makes such an approach particularly tempting when the HI are negligible or not of primary concern. Nevertheless, we will see how they can still be included.

2.4.1 Pure Langevin and Brownian dynamics

In LDs, starting with Newton's second law as we did for pure MD, we now add a dissipative drag force $\mathbf{F}^{\text{D}}(t)$ and a Brownian force $\mathbf{F}^{\text{B}}(t)$ (in addition to the conservative forces we had before, $\mathbf{F}^{\text{C}}(t)$) to end up with Langevin's equation

$$m\mathbf{\ddot{r}}(t) = \mathbf{F}^{\text{C}}(t) + \mathbf{F}^{\text{D}}(t) + \mathbf{F}^{\text{B}}(t) \quad (14)$$

where m is the mass of the particle. For the dissipative term, one usually assumes Stokesian drag on a spherical particle, $\mathbf{F}^{\text{D}}(t) = -\zeta \mathbf{v}(t)$, ζ being the friction coefficient of the particle in the fluid. The velocity $\mathbf{v}(t)$ is then the velocity of the particle with respect to the local solvent velocity. This is an important detail if one wants to consider flow or long-range HI. Although $\mathbf{F}^{\text{B}}(t)$ is due to the solvent molecules colliding with the particle, it can only model the net effect of a large number of collisions. The Brownian force is taken as a centred Gaussian random variable [78] with zero mean and variance $2\zeta k_B T / \Delta t$, where Δt is the integration time step. The fact that the variance is related to the friction coefficient ζ is again a consequence of the fluctuation–dissipation theorem. On the time scale of

interest the values of the Brownian force are uncorrelated at different time steps.

It can be shown that the energy transferred to the particle from a single collision with a solvent molecule decays on the viscous time scale m/ζ [79]. If, as is typically the case, this is much smaller than the timescale over which $\mathbf{F}^C(t)$ changes (overdamped limit), we may set $m\mathbf{a}(t) = 0$ in the Langevin equation and obtain the following discretized equation of motion:

$$\mathbf{r}(t + \Delta t) = \mathbf{r}(t) + \frac{\Delta t}{\zeta} [\mathbf{F}^B(t) + \mathbf{F}^C(t)] \quad (15)$$

which defines BD. For a more rigorous derivation see [80].

2.4.2 Incorporating long-range hydrodynamic interactions

Traditionally, LD does not include HI between particles. This approximation is valid for certain systems (e.g. when HI are screened out), but in many cases HI have a significant impact on the dynamics [81].

To see how we can incorporate them, let us consider a particle i . As it is moving with a certain velocity, it slows down due to the drag force. Since the drag force exerted by the fluid on a particle must be equal and opposite in direction to the force exerted by the particle on the fluid, this causes the fluid to move. Hence, the effect particle i has on particle j is that the latter experiences a modified drag as it is no longer surrounded by a stationary fluid. The magnitude of this coupling depends on their relative separations. On the time scale of interest this perturbation can generally be considered to be felt instantaneously. In a many-particle system, a common approximation is to ignore screening issues and to consider a superposition of all pairwise HI [82].

Consideration of the fluctuation–dissipation theorem implies that any modulation of the drag term must be accompanied by correctly modifying the magnitude of the Brownian term. An interesting consequence is the correlation of the Brownian forces on different particles at the same time. In practice, the relationship between the drag and the Brownian term is determined *via* interaction tensors (mainly the Oseen or Rotne–Prager–Yamakawa tensor). Application details can be found in [79, 80, 82–87].

2.5 Comparison of fluid models

We have presented a hierarchy of fluid models from the most detailed explicit solvent models to the mesoscopic and, finally, implicit (LD and BD) approaches. Using explicit models (especially the atomistic variant) is essential when high accuracy and the chemical details (such as different hydrophobicities of different parts of the analyte) are required. In most other cases, simpler approaches should be used. All three mesoscopic methods (DPD, SRD, and LB) use a simple (but often sufficient)

model to describe fluid dynamics and can also act as thermostats that define the local temperature when coupled to MD particles.

Owing to their conceptual differences, these methods use different types of parameters to describe the fluid, which results in a different suitability for specific problems. For example, while the fluid viscosity is directly accessible in LB methods, it becomes a combination of different parameters and can be controlled only indirectly in DPD [88, 89]. Similarly, while DPD and LB can only approximate the continuous-time dynamics of the fluid when the discrete time step is small, SRD is proven to yield correct long-time hydrodynamics for any step size. However, SRD's transport properties depend explicitly on the chosen time step [59]. More differences between the methods arise if confined fluids or interactions with large obstacles or particles are studied. Here, the ability to treat different boundary conditions becomes important, which is covered in detail in the literature [53, 63, 90–94].

All three methods share a similar computational efficiency, and computation times depend mainly on the implementation, the computer system, and also the investigated system. However, the speedup over explicit fluid simulations can be a factor 20 or higher [74, 95].

These mesoscopic models describe compressible fluids in which hydrodynamic forces need time to propagate through the medium. For this reason, as well as considerations of computational speed, performing LD with proper inclusion of HI can be preferable in some cases [96]. Furthermore, if the full treatment of HI is not necessary, the use of pure LD or BD is advisable.

We summarize the different ways of treating the solvent in MD simulations with a schematic that depicts the most important features of different fluid models (Fig. 2).

2.6 Monte Carlo simulations

In addition to the coarse-graining introduced previously, it is reasonable to ask whether it is possible to also coarse-grain the dynamics itself in order to achieve further computational speedup. This is the motivation behind the development of the various Monte Carlo (MC) methods.

In the broadest sense of the term, any computational method involving randomness can be called an MC method (the name says it all!). This broad definition would, however, include, e.g. BD, already considered under the banner of MD. In the spirit of the preceding discussion, we would therefore call an MC method any approach that sacrifices at least some of the dynamical details of the MD methods. How much is sacrificed can vary. At one extreme are methods designed to study equilibrium properties by quickly exploring large parts of the phase space. In this case, unphysical moves, such as rotations of large parts of chains in the pivot algorithm [98], can be introduced on purpose to speed up the simulation. Since in simulations of electrophoresis and related separation methods we are primarily interested in the dynamics of the

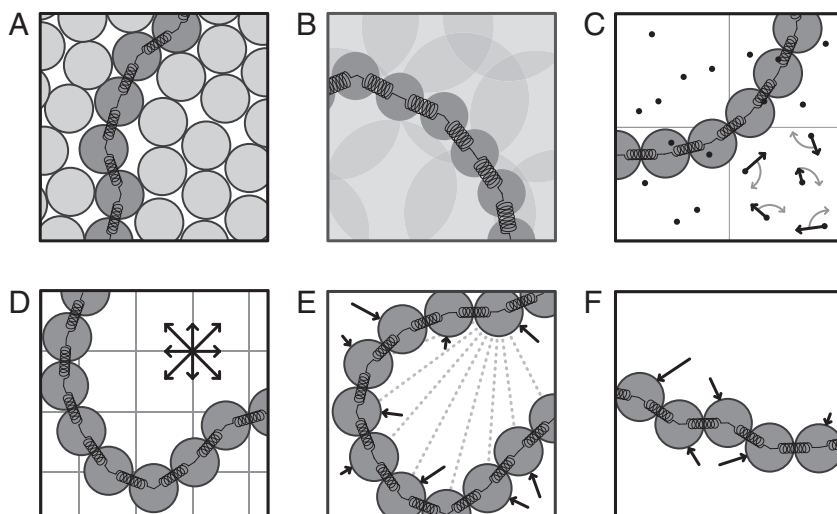


Figure 2. Schematic depicting different methods of modeling the solvent in MD simulations. In each case, a representative polymer is shown as a chain of beads connected by springs. (A) The explicit fluid approach models the solvent as beads interacting through a short-range potential and simulated to the same level of detail as the polymer. Fluid particles are often chosen to be the same size as the monomers. (B) The DPD method typically models the solvent as large, overlapping, softly repulsive spheres. (C) The SRD method replaces collisions between particles by a multiparticle collision operator, which models the local collisions as a rotation of particle velocity through an angle about a randomly chosen axis. (D) In LB the fluid is discretized to a grid. Arrows symbolize the discrete set of allowed velocities. The mesh shown is a D2Q9 (eight velocity vectors plus the zero velocity in two dimensions). (E) LD/BD represents the fluid implicitly by including a friction and a random term in the equation of motion of each monomer. HI can be included by introducing an additional long-range force between monomers (illustrated for one bead as a series of dashed lines). (F) Pure LD/BD neglects HI — friction and Brownian forces are the only effects of the solvent that are included. After Padding and Louis [97].

analytes, such MC approaches are less useful for our purposes, although they can be applied to some auxiliary problems, such as generating an equilibrated entangled sieving polymer solution in which the analytes would then migrate, studying the properties of capillary coatings, or finding the free energy of a DNA molecule as a function of its coordinate along a nanopore. We do not discuss these methods here; they are reviewed, *e.g.* in [99–101]. Instead, we concentrate on dynamical MC algorithms.

MC methods can be divided into two groups. In off-lattice MC methods, particles and monomers of polymer chains can occupy any positions in space. But one can also discretize the space allowing the particles to reside only at the nodes of a lattice. Such methods are known as Lattice MC (LMC). Since the sets of possible configurations and moves are then discrete, they can be described using integer arithmetic and often special computational techniques, such as multispin coding ([102], Section 15), which allow significant savings in computer time and memory compared with off-lattice MC. Of course, the cost of increased efficiency in LMC is even less realism!

Our ideal goal when simulating electrophoresis problems is to make quantitative predictions for the mobility and diffusivity of the analyte. Although this is possible in simple cases, MC simulations are generally used to predict trends (including scaling laws) and qualitative features, which in many cases is quite acceptable.

We start our discussion of MC methods with approaches to simulating hard particles. We then discuss some

chain simulation methods. As discussed in Section 1, we will not describe the MC methods used to simulate DNA reptation models [103].

2.6.1 Methods for particles

Consider a particle undergoing Brownian motion in the presence of an external force (*e.g.* an electric field) and some obstacles (*e.g.* gel fibres). In MC, this becomes a simple biased random walk. At each time step, a move is randomly selected from a predefined set, and a test is used to accept or reject it. A simulation is simply a series of such moves. Different MC algorithms are defined by: (i) the set of moves and the probability of selecting a particular move from that set; (ii) the acceptance test for the selected move; and (iii) the time step *per* move. Although the physics behind these three elements can be subtle (the main issue is generally the definition of the time scale), the simulation itself is often quite simple.

The most popular MC approach is Metropolis MC [104], a method designed to study equilibrium configurations. In the simplest lattice variant, at each step the particle simply tries to move to any of the neighbouring sites on the lattice, and all possible moves can be selected with equal probability. Moves can be accepted or rejected. If the change in energy from the initial to the final configuration is negative ($\Delta U < 0$), the move is accepted; otherwise, it is accepted with probability $\exp(-\Delta U/k_B T)$ (the Boltzmann factor). If the move is rejected, the particle remains in its previous

position, but the clock is still advanced by one unit of time. This is known as the Metropolis test. The latter guarantees that the correct equilibrium properties are obtained. However, reproducing the correct dynamics is problematic. First of all, how the MC unit of time (an attempted move) is related to actual time is usually left undefined, which makes quantitative predictions difficult. Moreover, in a high field the method is even qualitatively wrong: once $|\Delta U|/k_B T \gg 1$, all steps along the field are accepted and all those against the field are rejected; as a result, the velocity saturates and the diffusion coefficient vanishes. A different approach is then required.

In the 2-D lattice variant of such an approach [105], the system is modelled as a square lattice, where each node is either free or is an impenetrable obstacle. At each time step, the particle can move in one of four directions ($\pm\hat{x}, \pm\hat{y}$). Unlike in the Metropolis algorithm, the probabilities of selecting each of these moves are no longer equal; instead, if an external force $\vec{F} = F\hat{x}$ is applied to the particle, they are given by [105]

$$p_{\pm x}(\varepsilon) = \frac{1}{(1 + e^{\mp 2\varepsilon})(1 + \tanh(\varepsilon)/\varepsilon)} \quad (16)$$

$$p_{\perp}(\varepsilon) = \frac{1}{2(1 + \varepsilon \coth(\varepsilon))}$$

where the scaled force ε is given by

$$\varepsilon = \frac{Fa}{2k_B T} \quad (17)$$

with a the mesh size of the lattice. Note that the algorithm is rejection-free in the absence of obstacles; however, moves leading to an overlap between the particle and an obstacle are rejected. The time step is no longer arbitrary as it is given by the expression

$$\tau(\varepsilon) = \frac{\tau_B}{1 + \varepsilon \coth(\varepsilon)} \quad (18)$$

where $\tau_B \equiv \tau(\varepsilon = 0)$ is the mean duration of a (Brownian) jump in the absence of an external field. The latter is directly related to the free-space diffusion coefficient D_0 :

$$\tau_B = \frac{a^2}{2D_0} \quad (19)$$

It is this relation that connects the MC and experimental times. The above choice of transition probabilities and the time step can be shown [105] to give the correct average velocities for fields of arbitrary strength. However, the dispersion coefficient is correct only in the limit of a vanishingly small field [106]. In this limit, the dispersion coefficient D can actually be obtained more efficiently by using the Nernst–Einstein relation:

$$D = \lim_{F \rightarrow 0} k_B T \mu(F) \quad (20)$$

where $\mu(F) = v(F)/F$ is the mobility. In a non-vanishing field, the correct dispersion coefficient can be obtained by varying the time step (making it a random number) [106]. If a constant time step is desired (as is the case for the

numerically exact algorithm that we describe next), the MC moves themselves must be modified [106, 107].

2.6.1.1 Exact calculation method

Standard MC methods require a large amount of simulation data in order to have a low statistical error. In recent years, our group has developed a numerical method that allows one to compute the exact mean velocity and diffusion coefficient of a particle moving on a lattice with impenetrable obstacles. This method, which basically gives the exact solution to the MC simulation, is both faster and more precise. We now show the basics of this approach. For further details, the reader can refer to [108, 109].

The first step is to obtain the transition matrix T whose elements T_{ij} are probabilities that a particle on site j jumps to site i in a single time step. If at time t , the probability of presence of the particle on site i is $n_i(t)$, then after a single time step,

$$n_i(t + \tau) = \sum_j T_{ij} n_j(t) \quad (21)$$

Implicitly, this assumes that the time step is unique; since the latter depends on the field intensity, the method works only in a uniform field (unless the field is so weak that the field dependence of $\tau(\varepsilon)$ can be neglected). The steady state, defined by the equality $n_i(t + \tau) = n_i(t) \equiv n_i$, is thus the normalized eigenvector of T with the eigenvalue of unity (the normalization condition is $\sum_i n_i = 1$). This eigenvector, which can be obtained with an arbitrary precision by a simple numerical calculation, is the exact solution of the LMC algorithm.

Once the steady-state occupation probabilities $n_i(\varepsilon)$ are computed, the mean velocity of the particle, $v(\varepsilon)$, can be obtained by averaging over all sites, $v(\varepsilon) = \sum_i n_i(\varepsilon) v_i(\varepsilon)$, where the average local velocity on site i is

$$v_i(\varepsilon) = \frac{p_{+x}(\varepsilon)L_{+}(i) - p_{-x}(\varepsilon)L_{-}(i)}{\tau(\varepsilon)} \quad (22)$$

with the displacements $L_{\pm} = a$ if there is no obstacle in the given direction and zero otherwise.

The dispersion coefficient D in the zero-field limit can be calculated using Eq. (20). In a non-vanishing field, D can be obtained with a numerically exact method based on the generalized Taylor–Aris dispersion theory [110].

2.6.2 Methods for chains

Simulating polymer chains presents additional challenges since connectivity and (often) non-crossability of chains have to be maintained during the simulation. In MC simulations of polymer chain dynamics, only one monomer (or, at most, a small local group of monomers) is moved at each step. This choice is necessary in order to keep the frequency of moves leading to overlaps sufficiently low. However, a unit of time should now correspond to one attempted move per monomer.

2.6.2.1 Off-lattice methods

In the most straightforward and commonly used off-lattice MC method for bead–spring chains [111], a single step consists in displacing a monomer chosen at random along each axis, by an amount chosen from the uniform distribution on $[-\Delta/2, +\Delta/2]$, where Δ is a predefined constant. The event is accepted or rejected according to the Metropolis criterion, but all attempts make the clock advance. If the arbitrary parameter Δ is too small, the evolution of the system may be too slow; if Δ is too large, the rejection rate is too high. The optimal Δ normally corresponds to an acceptance rate of about 50%, although a lower Δ can make the dynamics more realistic. The same potentials as for MD (e.g. the FENE and WCA potentials) can be used. Besides this, one can use much simpler potentials, such as a square-well bond potential that is zero within a specified range and infinity outside, with the range chosen (just as in FENE) to avoid chain crossings. This improves the efficiency as the computation of complicated potential functions is avoided. However, in this case the chain will have no tension and so square-well potentials should be avoided in strong fields (see below).

In the bead–rod model [112], the bond lengths have to be preserved explicitly. The simplest moves are then rotations of a monomer around the axis connecting its two neighbours (for an end monomer, the rotation is on the sphere with the centre at its neighbour). Note, though, that in a strong electric field, when the chain is stretched, such moves are rather inefficient and this may lead to unphysical artefacts.

2.6.2.2 Bond-length-preserving lattice methods

In lattice models of polymers, monomers still hop between lattice sites, like in single-particle models. To avoid introducing a bond potential and still make sure that neighbouring monomers remain close in space, only those motions that keep all bond lengths within a certain range are allowed. The first models were particularly restrictive in this respect, keeping all bond lengths strictly fixed. Verdier and Stockmayer [113] have used a simple cubic lattice requiring the polymer bonds to coincide with the lattice bonds and thus making them all of unit length. In the first version of the model, only single-monomer motions were allowed. This was later found too restrictive and various two-monomer motions were added, the most popular of which is the so-called crankshaft motion [114]. Unfortunately, the dynamics in such models become very slow if we introduce excluded volume interactions by forbidding two monomers to reside on the same site. Moreover, Madras and Sokal [115] showed that for *any* model with *any* finite set of moves where neighbours along the chain remain neighbours on the lattice some configurations cannot be reached (i.e. the algorithm is non-ergodic). Nevertheless, in those cases where excluded volume interactions can be neglected, the Verdier–Stockmayer and other similar approaches can still be useful.

2.6.2.3 Bond-fluctuation algorithm

The deficiencies of the fixed bond length MC models led to the development of lattice methods with fluctuating bond lengths. The most popular one is the bond-fluctuation algorithm (BFA) first proposed by Carmesin and Kremer for 2-D problems [116] involving both linear and branched polymers. Although BFA is not strictly ergodic, its non-ergodicity problems can probably be neglected for all practical purposes. The algorithm was extended to 3-D by Deutsch and Binder [117].

In the BFA (Fig. 3), the monomer is represented by a 2×2 square (four lattice sites) in 2-D and a $2 \times 2 \times 2$ cube (eight lattice sites) in 3-D. A lattice site can be occupied by only one particle at a time. In 2-D, the bond lengths between connected monomers must be less than 4, while in 3-D bond lengths must be $\leq \sqrt{10}$, excluding $\sqrt{8}$. These simple conditions allow for a self-avoiding walk in which there is no crossing of bonds. Each attempted move consists of first picking a monomer at random and moving it by one lattice site along one of the lattice axes. As long as the new conformation does not create monomer overlaps or create a forbidden bond length the move is accepted. As before, a unit time corresponds to one attempted move *per* monomer.

For simulations of electrophoresis, obstacles can be placed at some lattice sites and the field is treated as in other models, by using the Metropolis test. In principle, other interactions, such as intra- and interchain interactions between monomers, can be included as well, but in most cases this is unnecessary (an exception is for the proper modeling of polymer stiffness, an important factor for DNA simulations).

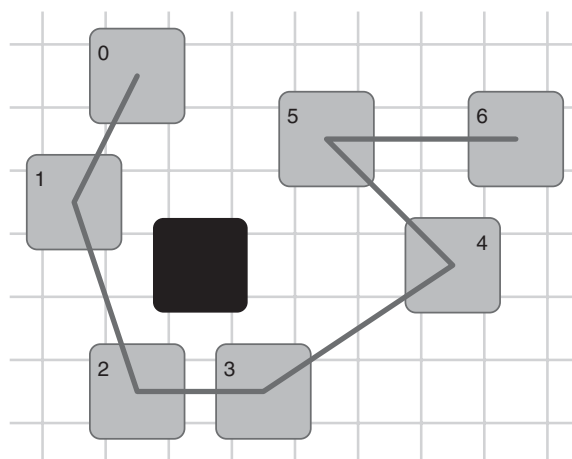


Figure 3. A polymer chain in the 2-D BFA. Each gray square represents a monomer occupying 2×2 sites. All allowed bond lengths from 2 (between monomers 2 and 3) to $\sqrt{13}$ (between monomers 3 and 4) are present in this figure. Allowing only these bond lengths and forbidding the monomers to overlap with the obstacle (black) is sufficient to ensure that the chain does not pass through the obstacle and does not cross itself. After Ref. [118]

2.6.2.4 Problems in strong fields

LMC models considered here have severe problems in strong electric fields. For instance, in gel electrophoresis simulations, the speed of the polymer decays exponentially as a function of the field, while experimentally, the electrophoretic mobility is essentially field-independent in the strong-field limit. To understand the reasons for this failure, consider a chain hooked upon a post with the two unequal arms pointing along the field and sliding off the post [119]. The sliding time is inversely proportional to the field intensity. But in LMC, since only local moves (*e.g.* single-monomer moves) are allowed, the only way for the chain to move is *via* chain slacks originating at the end of the short arm and propagating against the field. The probability for the slack to go all the way to the post decays exponentially with the potential energy difference between the tip of the arm and the post. If the short arm of the hooked conformation is of length L_s , the mean time between successful events will thus increase roughly like $\exp(+FL_s/kT)$, where F is the force on the monomer. This increase being an artefact of the model (the tension does not propagate along the backbone), the model can work only if the argument of this Boltzmann factor is much smaller than unity. Since L_s is proportional to the number of monomers in the chain, N , the maximum allowed external force scales like $F \propto N^{-1}$. This is too restrictive to be useful in practice. In order to solve this problem, one must modify the lattice models by adding *non-local moves*, an idea first implemented by Deutsch and Reger [119] and Duke and Viovy [11] for reptation models. Azuma and Takayama [120] added such moves to the BFA. Although their approach is not very carefully justified, it produces qualitatively reasonable results.

2.6.2.5 Numerically exact methods for chains

LMC algorithms for chains can sometimes be solved exactly, similar to how this is done for single particles. This was done by Boileau and Slater [121] for the BFA. The major complication is that each possible chain conformation and location should be considered a separate state and the number of such conformations grows exponentially with the chain length. For this reason, the approach is only practical for very short polymers (linear or branched). Of course, the solutions are only exact for the dynamics of specific algorithms, which are themselves approximate. We should also mention a numerically exact solution of the MC approach to studying polymer translocation through nanopores [122] that reduced this problem to a 1-D biased random walk by using a calculated dependence of the entropy of the chain on the number of monomers that have passed through the nanopore.

3 Simulation examples

In this section, we discuss nine current problems in the fields of separation science and electrophoresis. We examine

the systems by focusing on the type of simulation methods that are being used to study them. The choice of a numerical model is directly related to the question being asked. For example, coarse-grained methods are ideal for generic investigations of the basic mechanisms leading to separation while microscopic methods may be required when more specific problems are to be solved. To give the reader a broad view of the importance of simulations in our field, we have selected a wide range of problems.

3.1 EOF

EOF is ubiquitous in electrophoresis. EOF occurs when there is an electric field with a tangential component at a charged surface in contact with a liquid. The mobile counterions that make up the Debye layer next to the surface viscously drag the rest of the fluid. Although it is sometimes possible to solve for the fluid velocity profile analytically [123], computational modeling is often used to garner a better understanding of EOF. Let us examine the simple example shown in Fig. 4 where we can see the results of some MD simulations, which are described in detail by Tessier and Slater [124]. The solid line shows the net charge distribution, which has a maximum next to the wall followed by an

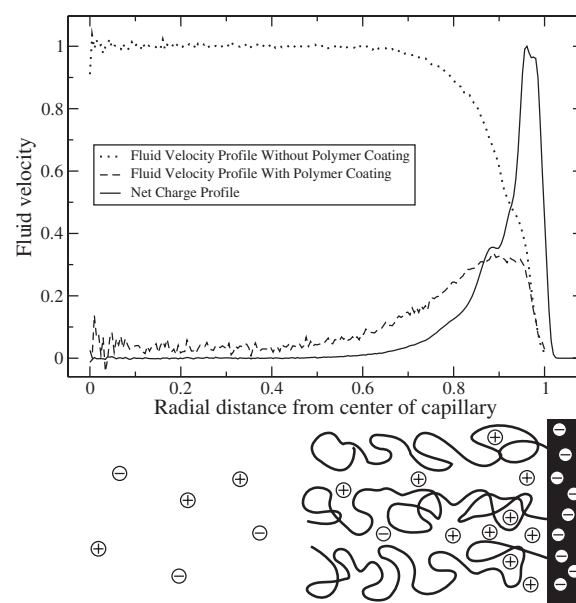


Figure 4. The radial profiles of the fluid velocity from MD simulations with and without a polymer coating, as well as the net charge density profile. The fluid velocities have been normalized by the bulk fluid speed in the coating-free case while the charge density has been normalized by its maximum value. The radial distance is in units of the inner radius of the tube. The fluid density is $0.8\sigma^{-3}$ while the bulk and surface charge densities are $0.02\sigma^{-3}$ and $0.1\sigma^{-2}$, respectively. The coating has a grafting density of $0.05\sigma^{-2}$ and degree of polymerization $N=20$. Further details can be found in [128, 124]. The schematic representation of the system is roughly aligned with the graph.

exponential decay as predicted by Debye–Hückel theory. The slight bump in this curve is the result of packing of the water beads near a fixed corrugated wall. This effect is even more evident if one looks at the individual ion density profiles. The fluid velocity (dotted curve) changes in the region where there is a net charge but takes on a bulk value outside of the thin charged region near the wall.

For microfluidic devices with complex geometries the EOF profile is often non-trivial to find. For the entropic trapping device developed by Han and Craighead [125], simulations were carried out using DPD with a slip boundary condition to reproduce a realistic EOF profile in order to include its effects in more complex simulations [126]. Similarly, it has been shown that the LB method can also be used to effectively model EOF [127]. The problem of EOF in complex geometries has also been investigated by solving the Navier–Stokes equation numerically [6]. In fact, the only fluid model presented in this review that has not been used for modeling EOF to our knowledge is the recently developed SRD algorithm.

In the context of electrophoretic separation, the presence of EOF often has a deleterious effect on the resolution. For example, the EOF increases dispersion in capillary electrophoresis because the EOF is non-uniform due to the non-uniform charge distribution on the wall [5, 124, 129]. For this reason, polymer coatings are often used to quench the EOF. They have the additional benefit of preventing wall–analyte interactions that cause additional dispersion in the system [130]. Simulations of polymer coatings tend to use a system size that is thicker than both the Debye layer and the polymer coating. Beyond the counterions and polymer coating the fluid velocity profile reaches a plateau. The fluid speed in this plateau region (referred to as the bulk speed) is the same regardless of the system size and thus these miniature (often nano-scale) simulation systems provide realistic models for much larger experimentally relevant systems.

Simulations of EOF in the presence of a polymer coating are fairly recent due to the high computational overhead involved in simulating them. Recent numerical investigations [124, 128] have been able to reproduce the scaling predictions of Harden *et al.* [131] for grafted polymer coatings using coarse-grained MD simulations. These studies looked in particular at the case when the polymer coating is thicker than the Debye length and looked at two regimes: the mushroom (isolated chains) and brush (high grafting density). In both regimes the MD simulations were able to confirm some of the predicted scaling behaviours of the bulk EOF with respect to the properties of the polymer layer such as the scaling with respect to the degree of polymerization N and grafting density. The dashed line in Fig. 4 shows a simulation where a polymer coating of length $N = 20$ beads and grafting density of $0.05\sigma^{-2}$ is used (here σ is the bead size in the WCA potential, Eq. (4)). Even these relatively short polymers clearly quench the majority of the EOF in the bulk of the fluid (note that in experiments the thin region near the wall where flow is generated makes up

only a very small fraction of the total system size). Simulations by Qiao and He [132] using the DPD algorithm investigated the same situation showing interesting nonlinearities in the EOF due to dynamic coupling between the polymer's conformation and the fluid velocity profile. The simulations also confirmed the fluid velocity profile as a function of the distance from the wall for a quenched polymer brush.

More detailed atomistic simulations by Qiao [133] have shown that for cases where the Debye layer is on the same scale as the polymer layer more complex behaviour can result. They found that at low grafting densities hydrophilic polymer coatings can actually increase the thickness of the Debye layer and thus the potential difference between the wall and the bulk fluid (termed the zeta potential) which increases the bulk EOF. This effect was attributed to a reduction in the amount of water in the region of the polymer layer, which caused the counterions to move further from the surface. At higher grafting densities, a larger suppression of EOF as the friction between the polymers and the fluid becomes larger was shown.

3.2 Free-flow electrophoresis

Free-flow electrophoresis is widely used to separate and characterize biomolecules. When a polyelectrolyte in gel-free solution is subject to a constant electric field, its average drift velocity depends not only on the applied field but also on interactions between the polyelectrolyte, the counterions and the solvent. Because the interrelation between the different forces is quite complex, free-solution electrophoresis is not easily accessible to complete analytical treatments. Results do exist for long-chain limits where certain simplifications are applicable [134–136] but experimental evidence indicates that these models are not sufficient to explain the behaviour of short chains [137–139].

In the schematic of the free-solution electrophoresis of flexible polyelectrolytes (Fig. 5), we see that the mobility is a function of length that approaches a constant with increased chain length so that separation of longer macromolecules by electrophoresis is not possible. This limit, called the free draining regime, is well described by analytical methods [134–136].

The behaviour of short chains, exhibiting not only length dependence but a non-monotonic behaviour in the transition from oligomers to long flexible chains, is not adequately described by current theoretical approaches. Here, modern simulation methods introduced in Section 2 provide much insight. The ability to coarse-grain certain interactions more than others facilitates probing different aspects of the behaviour one at a time.

In particular, fully atomistic MD (Section 2.1) can look at small oligomers, thereby focusing on chemical details, and has been employed to accurately describe the dynamic behaviour of short (3 and 6 units) fragments of ssRNA [140]. The diffusion coefficient (corrected for finite-size effects

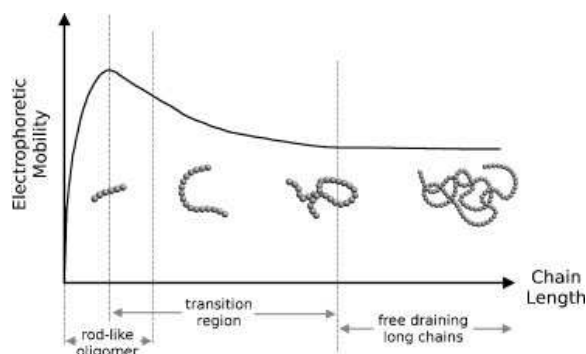


Figure 5. Schematic of the dependence of the electrophoretic mobility on the length of a flexible polyelectrolyte in free solution. Short rod-like oligomers show a sublinear increase in electrophoretic mobility with chain length. The mobility approaches a constant for long globular chains in the free draining regime. Between these two behaviours lies a transition region in which both counterion and hydrodynamic effects must be accounted for.

[141] and solvent viscosity) and the increase in electrophoretic mobility from 3 to 6 nucleotides are consistent with experimental results. The simulations show the importance of the counterions in reducing the effective charge by transiently binding to the polyelectrolyte resulting in the sublinear increase in the mobility with chain length that we see in Fig. 5. The fact that the mobility follows the increase in effective charge demonstrates how the hydrodynamic friction of short, rod-like polyelectrolytes depends only weakly on the length of the chain.

Longer-chain behaviour can be understood only by investigating the hydrodynamics of polyelectrolytes undergoing conformational changes from a rod-like to a globular state. As the number of counterions bound to the polyelectrolyte increases with length, in this midlength regime their contribution remains essential. Two recent studies using mesoscopic techniques (SRD (Section 2.3.2) and LB (Section 2.3.3)) have investigated the transition region between short fragments and long chains in detail [142, 143]. They show that without HI, mobility would actually decrease with length and approach a constant value for large molecular weights. However, by including HI, simulations accurately reproduce the experimentally observed non-monotonic behaviour of the mobility. By determining the effective charge, estimates of the effective friction were determined, and a transition from logarithmic to linear scaling with length was observed [144]. The microscopic interpretation of this phenomenon is still being discussed, but all of these studies [142–144] emphasized the importance of the interplay between HI and counterion condensation. This change is attributed to the correlated movement of the counterions in the vicinity of the polyelectrolyte, effectively cancelling long-range HI this signals the transition to a free draining regime.

When the chain length is increased further, screening eliminates the need to explicitly account for hydrodynamic

effects. In this case, implicit fluid techniques without hydrodynamics (Section 2.4) but with explicitly included counterions have been applied to study polyelectrolytes in electric fields, showing that below a critical field strength the static and dynamic properties of the polyelectrolyte remain unaffected and continue to agree with experimental data. However, when using high electric field strengths that exceed the fields in experiments by several orders of magnitude, alignment of the polyelectrolyte with the field and an increased electrophoretic mobility due to dissociation of counterions is observed [145, 146]. Whether these effects are of any practical relevance is not clear.

The above works emphasize the importance of correlations between counterions, the polyelectrolyte and the resulting screening of HI. Unlike the electrophoretic motion, the diffusive motion of the polyelectrolyte is not correlated with counterion motion and HI remain unscreened [143, 147]. It has been shown that the diffusion of long polyelectrolytes can be correctly modelled when the counterions are neglected as long as hydrodynamic effects are included [148]. In this simulation, the Rotne–Prager–Yamakawa formulation (Section 2.4.2) was used to quantitatively predict equilibrium and non-equilibrium diffusivity of DNA molecules up to 126 μm in length.

3.3 Polymer-obstacle collisions

In many electrophoretic methods, size selectivity is due to the interaction between the analyte and obstacles of some sort. To better understand this interaction, Deutsch and Madden [149, 150] have done pioneering 2-D BD simulations of a polymer migrating through an ordered matrix of obstacles. These authors found that in a very strong field, the polymer migrated through the gel in an unexpected fashion, very different from the conventional reptation picture [103]. The chain goes periodically through a sequence of states: a coil collides with a post, extends its arms around it, slides off the post leaving it in a fully extended state, and then collapses into a coil again. This process, termed geometration, was later observed in videomicroscopy experiments [151, 152]. Collision with a post is an important part of geometration; obviously, this process can be studied computationally in more detail if a system with just a single obstacle is considered.

Nixon and Slater [153] did the first such computational study using the BD approach in 2-D. They considered a chain of beads (without excluded volume) connected by FENE-like springs inside a narrow channel with an obstacle. The field was assumed to be uniform, *i.e.* the field lines penetrate the obstacle. The chain started in the random coil state. As the collision begins, the coil gets deformed and becomes pancake-shaped. The subsequent behaviour of the polymer is similar to that observed by Deutsch and Madden, but more clearly seen, as other neighbouring obstacles do not interfere. Based on these simulations, the authors developed an analytical theory predicting both the average

retardation of the polymer due to the collision and the variance of this retardation.

More detailed simulation studies of collisions using a very similar 2-D BD approach were carried out by Sevick and Williams [154] and Saville and Sevick [155]. The latter studied the properties of collisions as a function of the impact parameter, the initial distance in the direction perpendicular to the field between the centre of mass of the chain and the centre of the obstacle. Different obstacle sizes were also considered. These authors found that besides the “hooking” collisions studied by Nixon and Slater, another possibility is the “rolling off” collisions where the coil “rolls over” the surface of the obstacle and does not deform much during the collision (Fig. 6). For “rolling off” collisions that become dominant for large obstacles, the duration of the collision depends mostly on the obstacle size, rather than the chain length. Among “hooking” collisions, besides the conventional type (called U/J collisions, because the hooked chain conformation resembles these letters), collisions with multiple hooking (later termed W collisions [156], as the conformation can resemble a “double-U”) were also found.

More recently, Randall and Doyle [157] found in their fluorescence microscopy experiments that besides U/J and W collisions, yet another type of collision (called X for “extending”) is possible. These collisions resemble the U/J type, but the longer arm of the chain is not fully unwound at the beginning of the unhooking process, containing a coil at the end that unwinds gradually as the unhooking proceeds. To study this collision type in detail, Kim and Doyle [158] carried out 3-D BD simulations with excluded volume interactions. Unlike previous work, they did not make the assumption of a uniform electric field, instead calculating the field assuming that the obstacle (cylindrical in shape) is a perfect insulator. They indeed found X collisions, along

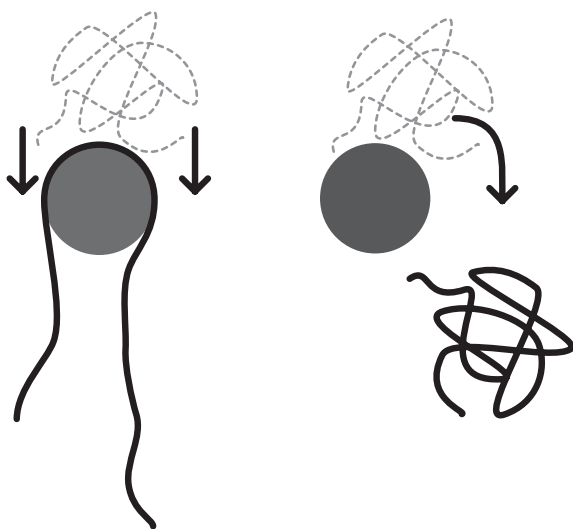


Figure 6. Different types of collisions of a chain with an obstacle: a collision involving hooking of the chain upon the obstacle (left) and a “rolling off” collision during which the chain remains a coil (right).

with previously known U/J and W types. It turned out that, surprisingly, the X type is the most dominant one in a broad range of chain lengths and field strengths. Given that this remains the case even in simpler models, perhaps previous authors simply did not distinguish between completely and incompletely unwound chains (for instance, [153] did not distinguish between these states).

The work discussed so far deals with the case of strong fields, when the thermal effects are negligible or at least secondary. A very recent paper by Holleran and Larson [159] also considers the case when, on the contrary, the field is weak and thermal diffusion dominates. In this case the arms are never extended and the polymer remains a coil that drifts slowly past the obstacle. In fact, in this regime the polymer, at least semi-quantitatively, can be considered as a rigid particle and be studied using, e.g. the exact MC methods described in Section 2.6.1. The paper is also interesting because of its use of a novel computational model of the chain (developed by the authors and described in a separate publication [160]), where the springs connecting the beads and not the beads themselves are repelled by the obstacles, which ensures that the chain cannot penetrate the obstacle even when the distance between the beads is much larger than the obstacle size. This allows the authors to treat very long chains (longer than 1000 Kuhn lengths).

All simulations discussed so far used BD neglecting Coulomb interactions between monomers and HI. Coulomb interactions are screened by counterions. The justification for neglecting HI offered by Kim and Doyle [158] is that both their simulation and the experiment it models [157] were carried out in a slit, in which case HI should be screened. However, even in the bulk the results are at least qualitatively correct, as the comparison with recent simulations by Kenward and Slater [161] using *explicit solvent* shows. Introducing a solvent can certainly produce some quantitative changes. Neglecting HI assumes that the polymer is free-draining, which is true in free solvent, but not when the chain is slowed down by an obstacle. The result is the modification of the friction force on the chain, which also becomes conformation-dependent. Kenward and Slater also studied collisions between two polymer chains, of which only one is driven by an external force, but both are mobile. Such collisions are important in the case of electrophoresis in polymer solutions [162, 163]. In this case, hydrodynamic effects influence the conformations of the chains. Similarly, studying situations where the colliding chain is driven by a flow, rather than an external field, is, of course, possible only when the solvent is included in some way; Kenward and Slater considered this case as well.

Finally, we mention other computational approaches applied to this problem. Starkweather *et al.* did off-lattice bead-rod MC simulations of a chain colliding with an immobile random coil [164] and a mobile chain [165]. As mentioned MC methods often have problems in strong fields, and their use is especially dangerous when applied to this problem, as it involves U-shaped chain configurations. The authors had to restrict themselves to moderate field

strengths, when the chain is far from being fully stretched. André *et al.* [156] used a special algorithm tracking the evolution of different loops and arms of the chain after the impact.

3.4 Ogston: Modeling sieving in hydrogels

A specific electrophoretic regime exists when the size of the analyte is smaller than or comparable to the mean pore size of the gel. This regime is often called the Ogston regime for electrophoretic sieving. Although the concept is technically restricted to rigid analytes, it is possible to extend its use to flexible polyelectrolytes such as DNA if one assumes that the chain takes on a spherical conformation with an effective radius R . By coarse-graining out the fine details of the individual monomers and considering the analyte as a solid sphere, we can discretize our system on a lattice (Fig. 7) and use simulations or exact calculation methods to study the electrophoretic mobility or diffusion coefficient of the analyte in this regime. A straightforward lattice approach to modeling the gel system would be to consider a gel fibre as an impenetrable obstacle. In Fig. 7, the analyte and the obstacles are of the same size (the lattice step size); although this is the case that we will consider below, it is equally easy to study larger obstacles and/or larger analytes that occupy more than one lattice unit (more on this later).

The first such numerical model was used by Slater and Guo [166] to test the key hypothesis of the Ogston–Morris–Rodbard–Chrambach (OMRC) model. According to the OMRC model, the mobility of the analyte in this regime is linearly proportional to the fractional gel volume that it can occupy, a purely geometric parameter that can be computed quite easily for the model shown in Fig. 7. All the other assumptions of the OMRC model (*e.g.* a low field intensity) being compatible with the numerical model, the results of the study represented a direct test of the fractional volume hypothesis. The Slater and Guo exact numerical calculations showed that the mobility of the analyte is higher in an ordered gel, compared with a random one, even if the fractional volume is the same. This was the first demonstration that the OMRC model is incomplete; in fact, these

authors also showed that the OMRC model corresponds to a mean-field model valid for an annealed gel (a gel with rapidly moving obstacles) [166].

As mentioned earlier, it is possible to extend the exact method to treat larger particles [167]. In this case, molecules are also viewed as rigid spherical particles, but can be larger than the obstacles. These results are valid in the zero-field limit since the interactions with the obstacles are assumed to be hard-core, *i.e.* the particles do not deform when colliding with an obstacle. It is also possible to extend this calculation method to treat attractive interactions between the analyte and the gel structure [168].

DNA molecules can also be modelled using the MC exact calculation method without making the hard sphere approximation [121]. Indeed, one can use multiple particles linked by bonds to represent a flexible chain. For example, such polymers can be described by self-avoiding walks and modelled by the BFA. This extension opens the door to a fundamental study of the electrophoretic sieving of oligomers, rod-like molecules, vesicles, star-shaped macromolecules, *etc.* One could argue that the MC exact calculation model is not a sufficiently good representation of a gel matrix since the field is assumed to be uniform throughout the gel. In reality, the field lines are affected by the gel structure (the obstacles). It has been shown [169] that the LMC exact method can also be extended to treat spatial variations of the electric field, and that this has little impact on the results at low field intensity.

It is possible to apply the exact method to treat high fields instead of vanishingly small external fields [105]. For non-deformable analytes, this can reproduce the trapping that sometimes occurs in real electrophoresis experiments. Multiple obstacle geometries have been studied and it is possible to properly model experimental observations of trapping and pulsed field de-trapping. A modified version of the initial algorithm [170] also allows the simultaneous calculation of the mobility and of the dispersion coefficient; this is obviously needed in order to predict the resolution of a specific device.

3.5 Microfluidic ratchets

The Brownian motion of particles is what gives rise to diffusion. It is possible to exploit these natural thermodynamic fluctuations for the separation of particles by adding an external force that biases the dynamics. Brownian ratchets are devices that use an asymmetry, either temporal or spatial, to drive the motion of a Brownian particle even when the net external force is zero. For example, a temporal asymmetry could be a zero-mean field alternating between a short high-intensity forward pulse and a longer low-intensity backward pulse. A spatial asymmetry could take the form of asymmetrically shaped obstacles or walls. Using any or all of these types of asymmetry, a non-zero net velocity can be observed in the presence of a field even if the net force is zero (hence the name *ratchet*). The random motion of the

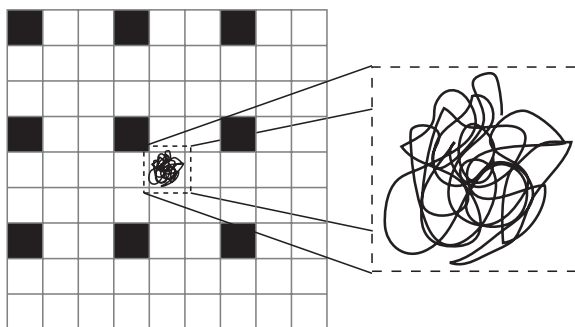


Figure 7. Modeling a polyelectrolyte in the Ogston regime with an LMC model.

particle then plays a major role (this is why it is called a *Brownian ratchet*).

As an example, consider the case of particles in a properly designed microfabricated array of obstacles (see Fig. 8). LMC methods can be used to simulate Brownian ratchets of this kind (see Section 2.6.1.1). First, the system is represented as an array of impenetrable obstacles. A starting point is chosen and the particle is moved randomly with the probabilities defined in Eq. (16). With this method, long computational times would be required in order to obtain statistically precise results. A faster and more precise computational method was described in Section 2.6.1.1. The increased accuracy is vital at very low fields, where the statistical uncertainty associated with the normal approach is often larger than the studied behaviour.

Gauthier and Slater [171] examined several ratchet systems using this simulation approach. The system shown on the right-hand side of Fig. 8 is interesting since it uses a symmetric array of obstacles together with an asymmetric pulsed field. These authors observed several current reversals (changes in direction) for different values of the field. For certain choices of parameters, particles of different sizes but having the same charge were predicted to move in opposite directions, a remarkable result (in some cases, a particle can even move against the direction of the net field, a phenomenon called absolute negative mobility). A Brownian ratchet of this type was later built experimentally by another group [172]. An aqueous solution of charged spheres of radius $2\text{ }\mu\text{m}$ was placed in a periodic array of misaligned posts with alternating small and large gaps. The applied asymmetric external field was a superposition of a constant (E_{DC}) and an alternating signal ($\pm E_{\text{AC}}$). The system behaved as expected and absolute negative mobility was observed – a nice example of the kind of new ideas that simulations can suggest.

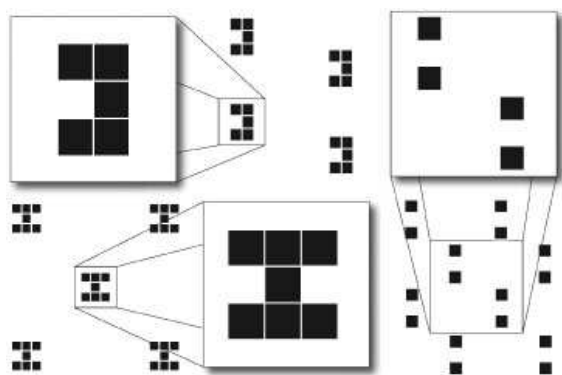


Figure 8. Three types of obstacles that can be used to design a Brownian ratchet separation system. Left, top: trap-shaped obstacles with a left-right spatial asymmetry. An unbiased AC electric field would lead to a net velocity pointing in the negative x direction. Left, bottom: symmetric obstacles with traps in both directions. Here, one would need an asymmetric pulsed field to drive the Brownian ratchet. Right: the distribution of obstacles proposed by Gauthier and Slater [171]: misaligned rows of obstacles. The lattices are not explicitly shown for clarity purpose.

Tessier *et al.* [173, 174] studied the system proposed by Han *et al.* [175] in the ratchet regime, both spatial and temporal. For the spatial asymmetry, the system was modified to introduce a geometrical asymmetry. The BFA (see Section 2.6) was used to model the polymer. Tessier *et al.* also simulated the system using a zero integrated pulsed field [176]. In both cases, separation was predicted. These predictions have yet to be tested.

3.6 Nanopore translocation

By threading ssDNA through a narrow pore (Fig. 9) and identifying the bases as they pass through, nanopores offer a promising avenue for the development of sequencing technologies [177]. In contrast to gel electrophoresis, nanopore sequencing could offer rapid (thousands of bases *per second*) sequencing of a single DNA molecule; a revolution which would have a great impact in fields associated with the life sciences. The same approach can also be used for other purposes, such as sizing molecular contour lengths. A significant advancement occurred in 1996 when Kasianowicz *et al.* demonstrated that RNA and DNA could be detected passing through a biological nanopore (α -haemolysin) by monitoring the disruption of ionic currents [178]. Subsequently, there have been a great number of theoretical [179–182] and experimental studies [183–188] focused on nanopore translocation (note that the number of nanopore related publications is staggering and in this very brief review, we are limited to providing only a few selected publications for each topic). Providing a bridge between theory and experiment, many computer simulations have also been performed and, in fact, most of the techniques discussed in Section 2 have been used to study the translocation process.

At the coarsest level, LMC simulations (see Section 2.6.2) are often performed in conjunction with theoretical studies to test the resulting predictions [181, 182, 189–193]. Other studies have used off-lattice MC to study translocation driven by an external or adsorption force [194–196]. Finally, one approach has mapped the translocation onto a 1-D diffusion process and then employed an exact numerical technique to obtain results [122, 197]. Although such studies are able to investigate very long polymers at low fields, the details of the dynamics are not produced and, additionally, the model is coarse to the extent that effects such as HI can be included only in an approximate manner. At the opposite end of the spectrum, fully atomistic MD simulations of DNA inside a channel have also been performed. These studies have revealed interesting details about the viability of distinguishing between bases of DNA translocating through a synthetic nanopore [1] and the dependence of various quantities on the DNA orientation inside the biological α -haemolysin channel [198]. They are, however, limited in terms of time scale and are unable to simulate the full translocation process. In between these extremes, many coarse-grained MD simulations using an implicit fluid [199–201], an explicit fluid

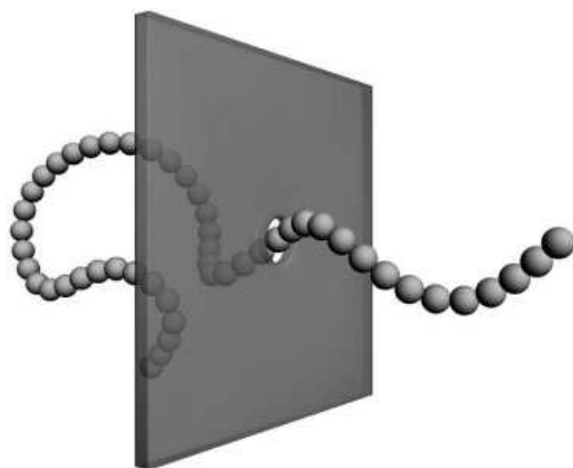


Figure 9. Schematic of a polymer translocating through a solid-state nanopore.

[202–204], or a mesoscopic fluid model [205–208] have been performed in an attempt to include the critical factors while requiring a reasonable level of computational power.

Using one or more these approaches, these studies have investigated the role of underlying physical mechanisms such as conformational entropy [197], HI [205], the solvent effect [209], counterions [204], pore-polymer interactions [210], and the pore geometry [211, 203]. Additionally, the dependence on the nature of the polymer has been studied by simulating charged polymers [212] and heteropolymers [213, 214]. Furthermore, considering application to sequencing, it is not surprising that a great number of studies have also examined driven translocation by implementing a pulling force [215], an adsorption force [196], or an external field (discussed below). As is obvious from this list, which is in itself incomplete, there is not enough space in this brief review to cover all of these results. Rather, as a single example, we will discuss some of the results for a key aspect of the general translocation problem: the scaling of the translocation time τ with the degree of polymerization N of the polymer for driven translocation.

In experiments on the biological α -haemolysin pore, both Kasianowicz *et al.* and Meller *et al.* found a linear dependence of the translocation time on the polymer length ($\tau \sim N$) for short ssDNA fragments [178, 188]. In contrast, the experiments of Storm *et al.* found a scaling of $\tau \sim N^{1.27}$ when driving long DNA strands (6500–97000 base pairs) through a solid-state nanopore [183]. This result is in agreement with their prediction that $\tau \sim N^{2\nu}$ for long polymers when HI are taken into account ($\nu \cong 3/5$ is the 3-D Flory exponent). From the analytical side, considering translocation driven by a chemical potential gradient, Muthukumar predicted linear scaling [189] while Kantor and Kardar predicted $\tau \sim N^{1+\nu}$ [191]. The latter group also performed bond-fluctuation MC simulations but were unable to verify the prediction due to limited polymer lengths. However, additional simulation studies for long

polymers have found a scaling of $\tau \sim N^{1+\nu}$ using 2-D fluctuating bond MC [216] and using the exact numerical method [197]. Finally, Dubbeldam *et al.* predicted a scaling of $\tau \sim N^{2/(2\nu+2-\gamma_1)}$ (where γ_1 is the surface exponent) [217] and found results consistent with this from off-lattice MC simulations. Moving towards a more detailed simulation of the dynamics, driven translocation has also been studied using LD and BD simulations. Performing 2-D LD simulations, one study found a scaling of $\tau \sim N^{1+\nu}$ [201] – a result consistent with the Kantor and Kardar prediction and the MC simulations cited above. Meanwhile, others have found a linear dependence [199, 200]. The discrepancies between these results may be attributed to differences in the particular system setups such as the pore length, polymer length, magnitude of the external field, and polymer model.

A limitation of all the simulation results cited thus far (MC and LD/BD) is that they neglect HI. As long ranged correlations through the fluid are conceivably important in the translocation process, much of the current work focuses on MD simulations using mesoscopic fluid models. Using the DPD approach, He *et al.* have found a linear dependence of τ on N [207]. Meanwhile, Izmitli *et al.* [205] and Fyta *et al.* [206], each using an LB fluid model but with different polymer models, have both found an exponent of 1.28, a result in good agreement with the experimental data of Storm *et al.* corresponding to $\tau \sim N^{2\nu}$. Both of these studies also directly tested the impact of HI by performing the same simulations without the LB solvent. Izmitli *et al.* found a negligible change as the exponent rose to 1.31 while Fyta *et al.* observed a slightly larger effect with the exponent rising to 1.36. The key parameter here appears to be the molecular size: is there a critical polymer size below which the HI are negligible because the translocation is then dominated by the polymer-pore interaction and not by the polymer-fluid interaction? In our opinion, a combination of careful simulations and experimental studies will be needed to answer this question.

As demonstrated by this one example, a wide range of simulation techniques have been employed to elucidate various details of the translocation process. In fact, given this wide array, one must keep in mind the scope of a particular simulation approach and the limitations of a chosen system setup when considering the results of each study. Ultimately, however, this diverse amount of information is an advantage in fully characterizing the system. While there are still many hurdles remaining before a nanopore sequencing device is realized (the development of a base identifying detector, slowing down the overall process, having the DNA find the pore), current simulations are giving insight on the fundamentals of polymer translocation.

3.7 Entropic trapping

In Ogston-type models of electrophoresis, it is assumed that analytes cannot pass through constrictions that are smaller

than their diameter. This is true for hard particles, but polymer coils can deform and still pass through holes that are much smaller than their radius of gyration R_g . However, as deformed coils are no longer completely random, this has an entropy cost and a polymer entering a narrow space has to overcome an *entropic barrier*. In a porous medium, such as a gel, such barriers are especially important when the average pore size is comparable to R_g so that there are pores both smaller and larger than R_g . In this situation, *entropic trapping* is possible, in which case the polymer can stay trapped for a long time in a large pore, since all ways out of it involve overcoming entropic barriers. The consequences of this were first studied in off-lattice MC simulations (Section 2.6.2) by Baumgärtner and Muthukumar [218–220]; one interesting result is a much stronger size dependence of the diffusion coefficient (and thus, *via* the Nernst–Einstein relation (Section 2.6.1), of the electrophoretic mobility) than predicted for larger polymers spanning many pores (the reptation regime). This was later confirmed experimentally [221].

Entropic trapping in gels, while an important issue, is still just one of the factors influencing the separation. On the other hand, Han *et al.* [124, 175, 222, 223] have fabricated and studied a device where, by design, entropic trapping is the dominant contribution to separation. The device is an array of cavities separated by long and narrow *slits*. The size of the cavities is much larger than R_g for the typical DNA sizes whose separation is desired, whereas the width of the slit is much smaller than R_g in one direction, but, importantly, is still $\gg R_g$ in the other direction. Han *et al.* found that the mobility *increases* as the size of the polymer increases. This is rather counterintuitive, given that larger polymers should deform more passing through the slit and this should be more entropically costly. Han *et al.* explained this by suggesting that rather than entering the slit as a whole, the polymer stays around the slit and loops (or *hernias*) get inserted in the slit (Fig. 10). Such insertion has an entropy cost proportional to the insertion length, but it also causes the decrease of the electrostatic energy proportional to the square of the length. As a result, the free energy increases until the top of the free energy barrier is reached, but then starts decreasing. The escape rate, as always in transition-state theory, depends exponentially on the barrier height, but also depends on the prefactor (the attempt frequency). It was argued that the barrier height is inversely

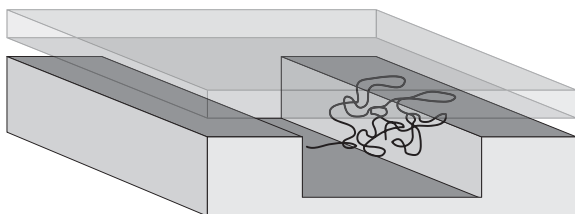


Figure 10. Schematic drawing of a part of the entropic trap device of Han *et al.* with a DNA chain near the entrance to a narrow slit. Several hernias are inserted in the slit.

proportional to the field strength, but is independent of the polymer size, and so the separation is entirely determined by the prefactor. This prefactor should be proportional to the size of the part of the polymer exposed to the slit, as this determines the number of hernias that can form simultaneously; this size is proportional to R_g which increases with the polymer size, and therefore the escape rate indeed increases with the size, as observed experimentally.

This simple theory, while appealing, was in need of verification by simulations, especially given that it relied on the independence of the free energy barrier height of the polymer size; since this barrier height enters in the exponent, even a slight dependence may completely overwhelm the dependence contained in the prefactor. With this in mind, several simulations have been carried out. Tessier *et al.* [173] used the MC BFA (Section 2.6.2.3). The field used in the simulation was computed by numerically solving the Laplace equation. The results for the mobility obtained in the simulations are in qualitative agreement with the experiments. Overall, the simulations confirmed the theory by Han *et al.*, but also further refined it. In particular, it was found that for weaker fields the mean trapping time indeed depends exponentially on the inverse field with the slope on the semi-logarithmic plot independent of the molecular size, confirming that the activation energy is indeed size-independent. On the other hand, for longer chains there was a deviation from the perfect exponential at higher fields attributed to the change in the shape of the coil near the entrance to the slit. At moderate fields the coil around the slit acquires a pancake shape and the radius of gyration behaves as that of a 2-D random walk; but as the field gets stronger, the escape into the slit is so fast that the coil has no time to deform. This has obvious consequences for the escape rate, as the prefactor depends on the extent of the coil along the slit entrance. The field dependence of the critical hernia length, as estimated by Tessier *et al.*, is also largely in agreement with the theory.

Chen and Escobedo [224] looked more directly at the free energy barrier associated with the entrance into the slit. Since free energy calculations are done in equilibrium, one of the equilibrium MC methods (in their case, configuration-bias MC [225]) was used (see Section 2.6). The advantage of this approach is that reliable results can be obtained even for very small fields, when the escape is so slow that good statistics cannot be obtained in dynamical simulations. The result of these free energy calculations is that over a large range of parameters, the barrier height is indeed polymer-size-independent, however, deviations are observed at very low fields for very short chains (the regime that Tessier *et al.* could not study very carefully). These deviations are not unexpected: at very low fields, the critical hernia length is very large, and if the chain is short, may actually become comparable to or even (in theory) exceed the chain length.

Streek *et al.* [226] used BD simulations (Section 2.4) to study essentially the same system. Based on their results, these authors suggest that in addition to entropic trapping, there exists another separation mechanism, due to size-dependent trapping of chains in the corners of the

cavity. The authors claim that it is this new mechanism, rather than entropic trapping, that is dominant. This may well be true at the rather high fields that they consider and especially in the case of constrictions that are wider than the radius of gyration of the chain (considered in a separate publication [227]), when the entropic barriers are essentially negligible. On the other hand, it is clear that at very low fields for narrow constrictions the entropic trapping mechanism should dominate, as no mechanism based on diffusion alone, without any activation barriers involved, would be able to compete. The intermediate case, when the entropic barrier height is $\sim k_B T$, is the most interesting practically and deserves further study; the answer may depend on many details, such as the size of the cavities.

We should also mention newer work likewise using BD. Panwar and Kumar [228] recognized that when the trapping barrier is not very high, two other time scales besides the trapping time contribute: the time it takes the DNA to approach the constriction and the crossing time. They studied the field and chain length dependencies of all three times. These authors used a bead-rod model of the DNA; Lee and Joo [229] did a similar study for a bead-spring chain.

All work described here uses methods that do not take hydrodynamic effects into account. For this reason, the DNA behaves as a free-draining chain when in reality a trapped chain is not free-draining. As Tessier *et al.* [173] point out, this implies that the field intensity needed to overcome the entropic barrier is underestimated by a factor of $\sim N^{2/5}$, where N is the chain length. As always at this level of modeling, quantitative comparisons with experiment are difficult, because the effective charge of the DNA is different from the bare charge due to counterion condensation. These effects need to be taken into account in future work.

3.8 Surface electrophoresis

A novel electrophoretic separation technique based on the DNA's interaction with a surface was first reported by Pernodet *et al.* [230] in 2000. By adsorbing DNA to a surface, length dependent separation on a flat surface without any restrictions or any sieving matrices was achieved (see Fig. 11A). It was found that the interactions between the molecule and the substrate essentially act as a length dependent source of friction, enabling electrophoretic separation. The initial experimental observations were accompanied by MD simulations [231, 232] and have been followed up by further studies [233, 234] under different conditions. The results showed that the DNA-surface interaction is a key parameter for the process: a strong attraction leaves the molecules fully adsorbed and no separation is possible, too weak an attraction lets molecules desorb and resume bulk behaviour, where likewise no separation is possible. Additionally, the interaction can be noticeably influenced by choosing a specially patterned surface [235, 236], an exciting and unique approach to designing optimized and custom-made separation systems.

Since the exact nature of the interaction and the resulting separation mechanism remain elusive at this point, there is a pressing need for more elaborate theoretical and computational studies that include electrostatic and hydrodynamic effects alike as they are crucial when the molecules approach the surface. This has been neglected so far.

3.9 Confinement-driven separation

Recent progress in design and fabrication of microfluidic devices on a sub-micrometer length-scale [237–239] demands a good understanding of the statics and dynamics of the polyelectrolytes under steric confinement. We can distinguish several regimes of confinement. In a device that is much larger than the size of the polyelectrolytes, given by their radius of gyration R_g , the conformations are unperturbed and isotropic (weak confinement). Reducing the dimensions of the devices to the order of R_g , the conformations of the polyelectrolytes start to become restricted by the walls and show deviations from the equilibrium (strong confinement, see Fig. 11B). With further reduction of the device size, the polyelectrolyte becomes extremely restricted and the static and dynamic properties undergo significant changes [240, 241] (Fig. 11C).

The decrease in size of microfluidic devices used in actual experiments and the growth in size of the systems that are addressable by means of computer simulations – due to advancement of simulation methods together with the increase of computer power – led to a cross-over creating systems that can be worked on from both sides. Recent experiments in slit-like nanochannels studied the static and dynamic properties of single molecules [242–248] and showed how confinement can be used as a tool to change polymer conformations as well as the dynamics through

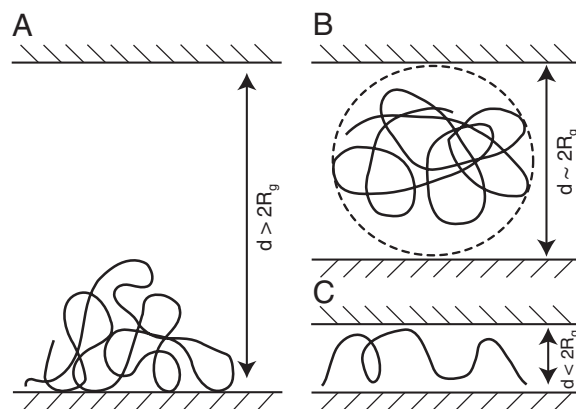


Figure 11. Different regimes of confinement used in some gel-free separation techniques: (A) weak confinement ($d > 2R_g$) in the presence of an attractive surface, (B) stronger confinement ($d \sim 2R_g$) that starts to influence the chain conformations, and (C) strong confinement ($d < 2R_g$) in which the chain conformations are determined by the walls of the channels.

modulation of the HI. Consequently, the role of hydrodynamics in confinement has been the focus of several recent computer studies [75, 96, 248–254]. The results indicate that, under weak confinement, the HI between polymer and wall drive the polymer to the centre of the channel if an external flow is applied. However, in high confinement, a migration towards the channel walls was observed. Since this interesting physical phenomenon depends on the ratio of the size of the polymer to the width of the channel as well as on the strength of the driving force, it seems to be an ideal candidate for free-solution separation of polyelectrolytes. Recently reported measurements on the diffusion and the electrophoretic mobility of DNA in strongly confined systems [255–257] indicate a possible electrophoretic separation mechanism based on the modified dynamics in strong confinement. A systematic simulation study of this subject has yet to be done in order to verify these results. In particular, electrostatic interactions and the influence of counterions on the HI have been neglected so far, but they should be assumed to be of great importance if the length scales of the system become comparable to the Debye length, below which electrostatic interactions are not fully shielded by the solvent [258, 254].

4 Outlook

This review has hopefully convinced the reader that the computational approach has been useful in understanding a large variety of electrophoretic separation systems and relevant electrokinetic phenomena. Compared with theory, many situations that cannot be studied theoretically without gross simplifications can be treated computationally; in fact, simulations provide valuable clues to theorists as to *exactly what* simplifications and assumptions they are allowed to make. Compared with experiments, simulations have an unmatched ability to look at the microscopic level; but perhaps the most important is the possibility to “switch on and off” different effects (such as HI) at will, something that is not available to experimentalists and yet is extremely helpful in developing a better understanding of the systems and phenomena of interest.

Considering the future of both the simulation methods and their applications to separation phenomena, the most straightforward approach is the “brute-force” one: harnessing the inevitable increases in computational power to conduct more detailed simulations of larger systems for longer times. However, in striving for more realistic simulations in this manner, it is important to recognize just how wide the gulf between experiments and detailed simulations is. To see this, consider atomistic MD simulations that are already being used to study DNA inside a nanopore (Section 3.6). While these simulations are yielding interesting results, significant increases in computational power would greatly enhance what they are able to study. For example, detailed atomistic simulations may be able to aid in the design of a probe to read the bases as they pass through the

channel. However, current atomistic MD simulations are typically limited to trajectories of hundreds of nanoseconds for limited system sizes. On the other hand, in the lab, the dynamics of interest can evolve on a time scale up to seconds or even longer. Consequently, while any increase in computational power is enthusiastically welcomed, the gap between detailed simulation and experiment remains large and the development of efficient techniques to appropriately coarse-grain the simulations is equally vital to broadening the scope and relevancy of computational studies.

Hence, as a final thought to this review, we examine a number of emerging or long-standing-but-difficult areas where new ideas and computer simulations will be needed over the next few years.

4.1 Multiscale simulations

In simulations, often different regions of the system require different levels of detail. For instance, a molecular-level fluid model may be required in the vicinity of the analyte, but at larger distances a faster mesoscopic approach may be sufficient. Likewise, the accuracy of a translocation simulation may be improved if the polymer is simulated atomistically in the vicinity of the nanopore. To avoid simulating the whole system with the highest level of detail needed only in a small region, multiscale simulations can be used. The biggest challenge is the seamless coupling between regions with different level of detail, which is especially difficult if the region boundaries are required to move. Several multiscale methods for fluids have appeared recently (see [259–264]). Such methods should see increased use in electrophoresis simulations. Besides, more “trivial” *serial* multiscale studies, where the outcome of a more detailed simulation is used to construct a coarse-grained model and *vice versa* [265], will be useful.

4.2 Mesoscopic solvents

SRD is a relatively new method of mesoscopically handling solvents and as such its full potential has yet to be captured. Despite being a model that is conceptually and relatively simple to implement, few of the electrophoretic simulation examples discussed above have taken advantage of SRD's ability to treat relatively large and multicomponent systems with complex and dynamic boundary conditions. Furthermore, careful choice of the multiparticle collision operator allows for hydrodynamics to be “turned off” and simply replaced with a Brownian heat bath in order to explore HI effects in the system.

4.3 Hydrodynamic effects in gel electrophoresis

The separation of small analytes by gel electrophoresis is often called “sieving”. “Small” typically means that the size

of the object is smaller than the mean pore size of the gel matrix. The word sieving suggests that separation is related to steric interactions restricting the motion of the analyte. Although detailed obstruction models have been proposed, their validity is not clear because they ignore HI and do not properly treat electrostatic interactions. Since we have three length scales here (the Debye length, the particle's radius and the mean pore size), many different regimes must exist. Understanding the simultaneous screening of the electrostatic and HI in a sieving matrix, especially if the latter is an entangled polymer solution, will require new ideas and probably extensive coarse-grained MD simulations.

4.4 Electrophoresis in polymer solutions

Electrophoresis in capillaries and microchips using polymer solutions as sieving matrices is increasingly important. Conventional wisdom is that well-entangled polymer solutions behave essentially like gels. However, the absence of crosslinking may be important, especially in strong fields typically used for capillary electrophoresis. Recent videomicroscopy experiments [266, 267] seem to suggest that the DNA is able to drag matrix polymers even well above the entanglement concentration. Simulations are needed to help understand this process. The consequences for the basic geometration mechanism of DNA motion can perhaps be understood even in rather simple models similar to that by Deutsch [149], but with “draggable” obstacles. Electrophoretic motion in more dilute solutions, around the critical entanglement concentration, is of interest as well.

4.5 Drag-tags for free-solution separation

Attaching suitable molecules to DNA fragments can restore size-dependent mobility regardless of the free-draining property [268–270]. The read length is optimized by choosing large but perfectly monodisperse drag-tags. As it is an experimental challenge to produce such polymer labels, two recently proposed alternatives seem promising: Haynes *et al.* [271] proposed to use branched polymers with well-defined architecture, whereas Grosser *et al.* [272, 273] introduced non-ionic surfactant micelles as drag-tags with very large hydrodynamic friction. Computer simulations can be used to characterize these new labels and provide ideas on how to extend these approaches.

4.6 EOF

As mentioned in Section 3.1, it has been shown that the mesoscopic fluid models such as LB and DPD provide realistic EOF profiles. It has also been shown that they provide realistic HI. One would suspect that given that they do these two things accurately, they will probably also be able to model EOF in the presence of polymer coatings.

If this is the case, mesoscopic models could allow for the simulation of more complex coatings and a wider range of parameters due to the increase in speed of computation.

4.7 DNA denaturation

As a means of sequence dependent separation, denaturing gradient gel electrophoresis exploits a rapid decrease in the mobility of a dsDNA fragment when sections of it denature. It is currently unclear whether the experimentally observed blocking is an actual trapping or a steep reduction in mobility. The bubble dynamics could play an important role in the blocking, thus a static helical-coil configuration may or may not be enough to give the correct picture. Unfortunately, simulating accurate bubble dynamics sets a coarse graining length scale to the length of a single base pair. A MD model that could incorporate the correct “breathing” dynamics of a dsDNA [274] in the presence of a gel while being able to treat dsDNA lengths of interest could be an important tool for investigating the blocking phenomenon.

4.8 Separation of large DNA

The idea of a Human Genome Project became realistic when PFGE made it possible to separate DNA molecules as large as a few megabase pairs (Mbp), a necessary step for chromosome mapping and sample preparation. After a few years of rapid progress, PFGE saturated at about 5 Mbp. Of course, the physics of PFGE is expected to be complicated for molecules that are millimeters in contour length! Agarose gels, with their sub- μm pores, are probably not the best material to extend the usefulness of PFGE. Recent ideas, based on new separation concepts, have yet to become commercial products. Computer simulations played a key role in the development of PFGE, and will again be needed in order to optimize the separation of such huge molecules and to design new and faster devices.

4.9 Protein separations

While the electrophoretic separation of nucleic acids, small ions and spherical particles has been modelled extensively, the same cannot be said of protein electrophoresis. Proteins are complex molecules, with non-trivial charge distributions on their surface. They can be separated in their native state or denatured, in free-flow electrophoresis or in gels, under uniform conditions or in the presence of gradients of various kinds. Although some models developed for particles or DNA can possibly be used for proteins as well, this has never been carefully tested. Computer simulations will be required to optimize the separation of proteins, which remains a difficult issue in the laboratory. However, generic simulation methods are not likely to work well since the precise shape and charge distribution that characterize a specific protein must be taken into account.

In conclusion, as computers become more powerful and new algorithms are developed, the future of computational studies of separation phenomena looks even brighter!

The authors are grateful to Dr. Marcello Sega for useful discussions during the process of writing this review. This research was supported by grants from AFMnet, NSERC, and the NIH (grant no. 2 R01 HG001970-07 through Stanford University). The findings, opinions, and recommendations expressed in this letter are those of the authors and not necessarily those of Stanford University or the NIH. Funds from the Volkswagen Foundation, the DAAD, and DFG under grant no. TR6 are also gratefully acknowledged. O.A.H. and T.N.S. would like to thank the NSERC-CGS program and the University of Ottawa for financial support.

The authors have declared no conflict of interest.

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fully atomistic force field it is easiest to start with a package that either comes with some force fields implemented (the first four packages in the list) or, at least, is designed to be compatible with the force fields from other packages (the next two entries). Similarly, all of the packages could be used for coarse-grained simulations. In fact, due to its efficiency in calculating non-bonded interactions, GROMACS, a biomolecule-oriented package, has been used for coarse-grained polymer simulation work. However, in choosing a more coarse-grained oriented package, one is more likely to find other useful elements such as the implementation of mesoscopic fluid models as found in the last two entries.

Finally, we include a “Free” column. A check mark here indicates that the program is free for academic use (at a minimum). This column is included to encourage the interested reader to download and begin experimenting without any monetary investment.

6 Appendix

MD simulation packages

While the theory behind an MD simulation is conceptually straightforward, in practice it can be a large undertaking to code from scratch. This is particularly true when one wishes to implement more involved algorithms in order to efficiently calculate long-ranged electrostatic interactions or incorporate mesoscopic fluid models. For this reason, there exists a multitude of simulation “packages” in which the routines necessary for performing the simulation have already been implemented. Hence, the user can simply supply input information pertaining to their system, select simulation features and parameters, and then use the packages to execute the simulation, produce trajectory files, and, frequently, perform analysis. Thus, to aid the interested reader, we present in this appendix a table of the more prominent MD simulation packages (note that the list given here is by no means exhaustive; see, for example, the Wikipedia article on MD at http://en.wikipedia.org/w/index.php?title=Molecular_Dynamics&oldid=231786544).

In addition to providing the simulation package name (and related references), we also include some details for each package. The information given here is meant to convey what the package is most often used for and also to indicate any special features unique to this package. These entries should not be interpreted as restrictive, but rather as highlighting interesting or distinct features among a group of software which all accomplish similar goals.

For example, consider delineating the packages between “atomistic” or “coarse-grained” simulations. In principle, all the cited packages are capable of performing fully atomistic simulations. But as such simulations require a

Name ^{a)}	Details	Free
GROMACS [275] www.gromacs.org	Includes force fields for fully atomistic Efficient calculation of non-bonded interaction	✓
CHARMM [276] www.charmm.org	Includes force fields for fully atomistic Pioneer for MD simulations	
NAMD [277] www.ks.uiuc.edu/Research/namd/	Includes force fields for fully atomistic Capable of steered and interactive MD	✓
AMBER [278] amber.scripps.edu	Includes force fields for fully atomistic AMBER force field is compatible with and used in many of these MD packages	
DL_Poly [279] www.ccp5.ac.uk/DL_POLY/	Compatible with GROMACS or AMBER force fields Includes potentials for non-biological materials	✓
LAMMPS [280] lammps.sandia.gov	Compatible with CHARMM, AMBER, and GROMACS force fields. Includes DPD	✓
ESPResSo [281] www.espresso.mpg.de	Designed for coarse-grained Includes many algorithms for electrostatics Includes LB, DPD	✓

a) Parallelized versions of all these packages exist to take advantage of high performance computing clusters.

Appendix B: Electrophoresis: When Hydrodynamics Matter

TN Shendruk, OA Hickey, GW Slater, JL Harden. *Current Opinion in Colloid and Interface Science* **Accepted**
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Electrophoresis: When hydrodynamics matter

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ARTICLE INFO

Article history:

Received 15 June 2011

Accepted 24 August 2011

Available online xxxx

Keywords:

Hydrodynamics

Electrophoresis

Debye length

DNA separation

Screening

Confinement

Electro-osmosis

ABSTRACT

The combination of hydrodynamic and electrostatic interactions leads to non-trivial effects that can be observed in various electrophoretic and electro-osmosis systems. In this article, we focus our attention on problems involving polyelectrolytes. First, we examine the free-draining behavior of polyelectrolytes such as DNA, a remarkable phenomenon that makes it impossible to use free-solution electrophoresis to fractionate nucleic acids. We show that the common assumption that hydrodynamic interactions are screened and therefore irrelevant in this system is wrong, and that one must be very careful when dealing with electro-hydrodynamics, especially when mechanical forces are also present. In the limit of small forces, one can superimpose the mechanical and hydrodynamic flow fields and make predictions that are often in excellent agreement with experiments. For DNA, the full electro- and hydrodynamics can then be reduced to the conformationally dependent superposition of a polymer sedimenting through a fluid and a polyelectrolyte being electrophoresed. This superposition or Electro-hydrodynamic Equivalence Principle has been used to explain a variety of problems and to propose methods that can allow the electrophoretic separation of DNA.

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1. Introduction

The electrophoresis of polyelectrolytes, particularly nucleic acids, has long been a topic of interest due to its practical importance. Essential to many electrophoretic assays of biomacromolecules is separation based on length, a key step in DNA sequencing. Unfortunately, due to the screening of hydrodynamic interactions, long polyelectrolytes cannot be separated in free solution and instead a polymer network is generally used as a sieving matrix [1]. Since hydrodynamic interactions are screened by the polymer network, traditional theoretical and computational studies have ignored them [2,3]. However, there are a wide variety of systems where polyelectrolytes are subject to an electric field in the absence of a polymer network, which have become of increasing interest in recent years. In these systems, hydrodynamic interactions are no longer screened and can in fact play a primary role in polyelectrolyte dynamics. This review introduces the basic theoretical framework used to understand electro-hydrodynamics of charged polymers and discusses several illustrative applications related to analytical biochemistry.

2. Electrophoresis of charged particles and polymers

The charged monomers of polyelectrolytes interact in non-trivial ways. We will first consider the electrophoretic motion of a single,

charged bead of radius R in an electrolyte solution of valency z , permittivity ϵ and viscosity η . Since this topic has been reviewed before [4], only material of direct interest to this article is presented.

2.1. Charged particles

A charged particle attracts counter-ions from the surrounding solvent and together with thermal fluctuations establishes a local concentration gradient called the *double layer*. The thin inner region around the particle, in which ions are effectively adsorbed to the surface, is called the *Stern layer*. The Stern layer creates an effective surface charge and establishes a potential (the ζ -potential) between its outer surface and the bulk solution. Beyond this layer is the *diffuse layer* in which ions are free to move. The potential ψ in the diffuse layer is related to the charge distribution through the Poisson–Boltzmann equation in situations where ion position correlations are not important. There is no known analytical solution for the Poisson–Boltzmann equation around a sphere. However, the *Debye–Hückel approximation* for small potentials ($ze\psi/k_B T < 1$) gives the approximate result $\frac{\psi(r)}{\zeta} \approx \frac{R}{r} \exp\left[-\frac{(r-R)}{\lambda_D}\right]$. In this linear limit, the counter-ion concentration decays exponentially over a characteristic length scale called the *Debye length*, λ_D , to the bulk solution's neutral background [4]. At length scales greater than λ_D , the counter-ions screen the particle's electric field.

The length scales R and λ_D determine the electrophoretic behavior. There are two revealing limits: the *Hückel* and *Smoluchowski* limits. In the Hückel limit $R/\lambda_D \ll 1$, a particle of charge Q may be

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treated as a point charge and balancing the driving and drag forces leads to a velocity

$$\vec{v} = \frac{Q\vec{E}}{6\pi\eta R} = \frac{2\zeta\epsilon}{3\eta}\vec{E}. \quad (1)$$

Note that the *electrophoretic mobility*, defined as the ratio $\mu \equiv v/E = 2\zeta\epsilon/3\eta$, is often used instead of the velocity. In the opposite (Smoluchowski) case of thin Debye layers, $R/\lambda_D \gg 1$, the interface appears planar to the counter-ions. The *electro-osmotic flow* (EOF) of the fluid approaches the *Smoluchowski slip velocity* in the rest frame of the surface

$$\vec{v}_s = \frac{\zeta\epsilon}{\eta}\vec{E}\left(1 + e^{-R/\lambda_D}\right) \approx \frac{\zeta\epsilon}{\eta}\vec{E}. \quad (2)$$

The particle is thus driven through a stagnant fluid at the Smoluchowski mobility $\mu = \zeta\epsilon/\eta$ and since λ_D is the only relevant length scale, the particle's size or shape does not enter the problem explicitly.

Notably, the mobilities in these two limits differ only by a numerical constant for a sphere. The mobility of spheres with finite Debye layers naturally fall somewhere between the Hückel and Smoluchowski limits, which suggests

$$\mu = \frac{\zeta\epsilon}{\eta} \times f_H(R/\lambda_D) \quad (3)$$

where Henry's function f_H is a coefficient of order 1 that satisfies both limits.

2.2. Oligomers

If we now consider a chain of charged beads (or monomers) of size b , we can see the transition from Hückel to Smoluchowski behavior as the number of monomers N increases. Since $\lambda_D > b$, a polyelectrolyte monomer ($N = 1$) is clearly in the Hückel limit. Thus, if a second monomer is bonded to it, their diffuse layers overlap. Because the shearing of the fluid happens over the length scale λ_D (the viscous drag depends on the size of the ion sheath), the drag of the dimer does not increase significantly. Since the charge increases and the drag does not, the mobility of the connected beads is much greater than that of the isolated monomer. As we continue to add monomers, the dimer becomes an *oligomer*. In a good solvent, sufficiently long oligomers adopt a self-avoiding coil configuration with a characteristic size $R_g(N)$, the *radius of gyration*. If $R_g \ll \lambda_D$ the entire oligomer is in the Hückel limit. However, as R_g becomes greater than λ_D , the viscous drag on the oligomer grows linearly with further increase of the contour length. With both the drag and the charge growing linearly with N , the mobility eventually saturates. This rise and saturation of μ is shown in the upper curve of Fig. 1.

Note that this is not what happens if hydrodynamic interactions (HI) are ignored. In the absence of HI, the drag on the monomers is generated locally and not over the extent of the ion sheath. In this case, overlapping diffuse layers are of no consequence, and the drag increases with N right from the start. Simulations that neglect HI completely fail to capture cooperative shearing and so the mobility decreases monotonically, as seen in the lower curve of Fig. 1 [5,6]. The reason for this somewhat surprising decrease in mobility is due to charge condensation effects. As the contour length $L = Nb$ increases the electrostatic potential energy within the Debye layer increases, causing counter-ions to condense out of the diffuse counter-ion cloud into the Stern layer. This so-called *Manning condensation* results in a reduced effective charge of each monomer, thereby reducing the electrophoretic mobility of the polyelectrolyte chain if HI are neglected. Recent

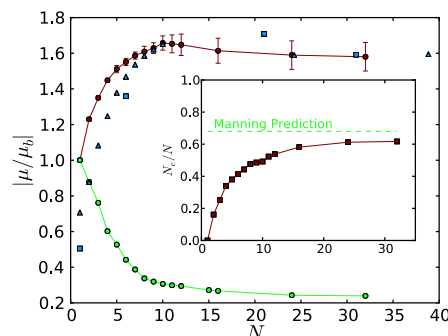


Fig. 1. Electrophoretic mobility of oligomers normalized by the mobility of a single monomer μ_b . Computer simulations that neglect HI are shown in green. Simulations that do include hydrodynamics (shown in red) agree well with experimental capillary electrophoresis (blue triangles) and electrophoretic NMR (blue squares) mobility. Inset: Fraction of monomers onto which a counter-ion has condensed, N_c/N , from simulations with hydrodynamic effects compared to the Manning prediction [5]. Produced from data provided by C. Holm.

simulations (reproduced in the inset of Fig. 1) confirm that counter-ion condensation increases with chain length [5,6].

Interestingly, the competition between the Manning condensation effect and the increase in mobility due to cooperative shearing effects in overlapping Debye layers is consistent with the observed non-monotonic dependence of μ on N shown in Fig. 1 [5,6]. The mobility reaches a maximum for intermediate sizes before decreasing towards the asymptotic mobility $\mu_0 \equiv \mu(N \rightarrow \infty)$. Presently, no theoretical argument correctly models the maximum in mobility of charged oligomers.

2.3. Free-draining behavior

Sufficiently long DNA molecules migrate with the same electrophoretic mobility μ_0 regardless of their contour length L . This plateau in mobility occurs because the effective charge and the effective friction both scale linearly with L [7,8]. This well-known effect precludes the use of free solution electrophoresis as a separation method for most polydisperse DNA samples. The key feature responsible for this effect is the screening of the HI between the DNA monomers. As a result, the DNA chain friction coefficient is simply N times a characteristic local monomer friction coefficient: $\xi = N\xi_b$. This so-called *free-draining* behavior is due to the complimentary response of charged monomers and their associated counter-ions to an electric field. When a moderate field is applied, the force on the monomer is equal and opposite to the force on its double layer. To first order, the momentum flux on the double layer is viscously transferred to the monomer and vice versa; the field pulls the monomer one way, and the counter-ions in the opposite way, and the viscous forces on the fluid from each cancel as schematically shown in Fig. 2.

For a thick Debye layer, the hydrodynamic flow field decays exponentially [9], whereas for thin Debye layers the residual hydrodynamic field goes as r^{-3} [3]. In either limit, the effective HI decay rapidly with distance. We contrast this with the fluid response to non-electric forces, such as applied mechanical forces acting on specific monomers or body forces such as gravity that act on all monomers, for which the HI set up by fluid flows decay as r^{-1} [10]. The resulting motion of all chain segments is coupled together, leading to collective and cooperative action, and the chain appears as a consolidated object opaque to fluid flow [11]. Thus, the friction on the polymer depends explicitly on its conformation and scales as its hydrodynamic radius $R_H \sim R_g$. Interestingly, Brownian thermal forces on the monomers also generate long-ranged hydrodynamic interactions between the monomers of a polyelectrolyte, even in the presence of an electric field. Thus, the motion of a polyelectrolyte during electrophoresis is a superposition of the

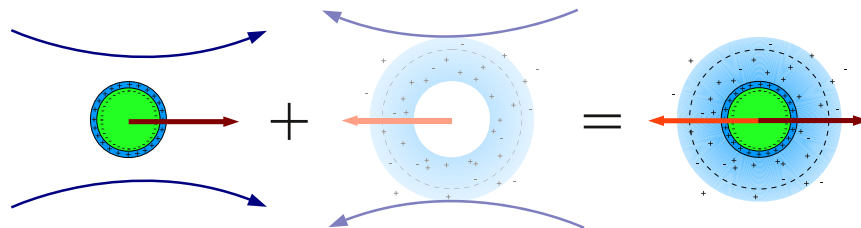


Fig. 2. The electric field pulls on the monomer and its ion sheath with equal and opposite force. To first order, the perturbation of the fluid due to the shear from the monomer is canceled by the shear due to the counter-ions. HI can only exist on length scales shorter than λ_D .

convective flow of a free-draining polymer superimposed with diffusive motion governed by a Stokes-like diffusion coefficient that scales like $1/R_H$ [7]. As a consequence, one cannot use a Nernst–Einstein equation to link the electrophoretic mobility μ to the diffusion coefficient D of a polyelectrolyte subjected to an electric field. The qualitatively different effects of electric and non-electric forces on the transport of polyelectrolytes in solution provide opportunities for novel methods for their separation. This will be the focus of much of this review.

3. Electro-hydrodynamic equivalence principle

The previous section presented a bleak picture for free-flow electrophoretic fractionation of long DNA fragments. However, if electric and non-electric forces act in concert, the picture is different. An electric force acts on both the polyelectrolyte and the surrounding ions, but a non-electric force $\vec{F}$ can be chosen to act only on the monomers. Under simultaneous action of the two forces, the resulting motion is, in the linear regime, a superposition of the two responses. The steady state drift velocity $\vec{v}$ is achieved when the drag force F_ξ balances the electric force F_E and the non-electric force $\vec{F}$ [2•]

$$0 = \vec{F} + \vec{F}_\xi + \vec{F}_E \quad (4)$$

$$= \vec{F} - \hat{\xi} \cdot (\vec{v} - \hat{\mu} \cdot \vec{E})$$

where $\hat{\xi}$ and $\hat{\mu}$ are the effective hydrodynamic friction and electrophoretic mobility tensors. Since the counter-ions are unaffected by $\vec{F}$, the total force on the ion sheath and on the chain no longer cancel and a long ranged hydrodynamic flow field ($\sim 1/r$) appears, which generates collective responses in the chain. The transport coefficients $\hat{\xi}$ and $\hat{\mu}$ are then explicitly dependent on the polyelectrolyte conformation and in principle have a tensorial character. In particular, the drift velocity $\vec{v}$ is, in general, a function of the polyelectrolyte's size N , in contrast to the universal plateau mobility μ_0 observed in free-solution. In other words, the polyelectrolyte is no longer free-draining [10] and size fractionation is possible.

The result of Eq. (4), first proposed for polymers in the seminal work of Long et al. [2•], suggests a *Principle of Electro-hydrodynamic Equivalence* [2•]. The term $\hat{\mu} \cdot \vec{E}$ can be thought of as an effective local velocity $\vec{v}_s$. In full, the equivalence principle states that when polyelectrolytes with small Debye lengths are acted on by a weak electric field $E \ll \zeta/\lambda_D$ and simultaneously by a mechanical force F , one can replace a consideration of the full electrostatics and hydrodynamics with an effective local flow which is simply the Smoluchowski slip velocity (Eq. (2)). The remainder of the review will be spent discussing examples of such non-electric forces in the context of electrophoresis problems.

4. Tethered polyelectrolytes and stall forces

To illustrate the power of the equivalence principle, we consider a tethered polyelectrolyte in an electric field [12]. The tension induced

by anchoring the polymer in place acts as the non-electric force and the net chain velocity is $\vec{v} = 0$. Thus, according to Eq. (4), we can identify a *stall force* [2•]

$$\vec{F}_{stall} = -\hat{\xi} \cdot (\hat{\mu} \cdot \vec{E}). \quad (5)$$

We note that as a direct consequence of this principle, $\vec{F}_{stall}$ is significantly less than the sum of the electrical forces on each monomer. In the frame of the tether, the electric field generates a flow of solvent due to its action on the free counter-ions in the Debye layer of the polyelectrolyte. The magnitude of this velocity is given by Eq. (2). In the frame of the solvent, however, it is the polymer that translates through the solvent at a rate given by Eq. (2). In either view, the polyelectrolyte experiences an effective conformation-dependent hydrodynamic drag $\hat{\xi}$ [2•] and it will deform under sufficiently strong electric forces due to the associated viscous forces. This creates an interesting self-consistent drag-conformation-velocity problem.

The conformations of tethered polymers in flows are well understood [13–15]. When the drag force $F_{flow} = \xi v$ is less than thermal forces, $F_{therm} \approx k_B T/R_H$, the polymer is an undeformed coil with hydrodynamic radius $R_H \sim N^{3/5}$; while if $F_{flow} > F_{therm}$, deformation occurs. The transition between these regimes takes place at the critical field

$$E^*(N) \approx \frac{k_B T}{\mu_0 \xi R_H} \sim N^{-6/5}. \quad (6)$$

For $E > E^*(N)$ the chain is deformed more rapidly by the flow than can be relaxed by internal diffusion, resulting in deformed steady-state conformations. The polymer then unfurls into the so-called *trumpet* regime in which the conformation is a series of increasingly large blobs. The blob size increases because chain tension decreases from a maximum value at the tethering point to zero at the free end of the polymer (see Fig. 3) [13,14]. When $E > N^{1/5} E^*$, a small fully-extended chain section appears near the tether point (the so-called *stem-flower* regime [13,14]), eventually leading to a fully extended chain for $E > N^{6/5} E^*$ [16].

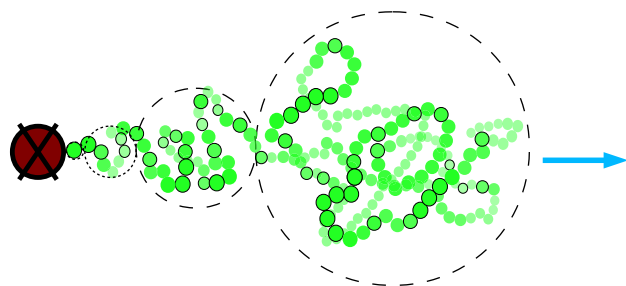


Fig. 3. The trumpet regime of a polyelectrolyte tethered to a stationary post in the presence of an electric field ($1 < E/E^* < N^{1/5}$) or a moderate flow field.

The equivalence principle has been verified for highly extended conformations both by explicit molecular dynamics simulations [20,21] and experimentally by fluorescence for dsDNA stained with ethidium bromide [12,19] and epifluorescence microscopy of YOYO-1 labeled λ -DNA [17•]. By tethering DNA to insulating elliptical posts (which do slightly perturb the otherwise uniform electric field), it has been demonstrated that tethered DNA is indeed not free-draining. In fact, comparison between extension by an electric field and extension by a flow field reproduced in Fig. 4 shows very nearly identical results and demonstrates that the equivalence principle is a very useful approximation. The slight systematic errors in Fig. 4 suggest that at high fields full electro-hydrodynamics are not completely linear and Eq. (4) is no longer strictly appropriate. Stigter and Bustamante [22] describe the mobility in this regime through a numerical theory that incorporates the alignment of DNA with the applied field. Polyelectrolytes are modeled as worm-like chains of ellipsoidal segments with HI. According to this *Stigter model*, the resulting extension produced by an electric field compared to a flow field given by Eq. (2) differs except at the smallest deformations. For a given stall force, flow fields stretch polyelectrolytes to a greater extent than electric fields demonstrating that strictly speaking the equivalence principle is only valid for small deformations [22]. However, as a working approximation it is quite sufficient.

5. End-labeled free-solution electrophoresis (ELFSE)

Tethering a polyelectrolyte to a post may be a good test of the equivalence principle but the practical potential of Eq. (4) lies in the idea that by frustrating the free-draining nature of polyelectrolytes, DNA can be separated based on size. In many ways tethering a polyelectrolyte to a neutral object (a *label* or *drag-tag*) that is free to convect is equivalent to polymers tethered to a post when viewed in the rest frame of the polymer. In fact, this theoretical framework can be used to study polyelectrolytes dragging an uncharged label (ELFSE) as well as charged labels pulling a neutral polymer (called *Free-Solution Conjugate Electrophoresis* [23–25]). The drag-tag can be a colloid [26], a micelle [27], a neutral polymer [28•] or any microscopic object that provides a drag force. Let us consider two types of drag-tag: (i) a hard sphere as shown in Fig. 5, and (ii) a second polymer (or polyelectrolyte) as in Fig. 6.

5.1. Spherical drag-tags

If we apply the equivalence principle to both objects independently (i.e., we assume that there is no hydrodynamic or electrostatic interactions between the drag-tag, which may be charged too, and the polyelectrolyte) then from Eq. (4) the forces on the polyelectrolyte

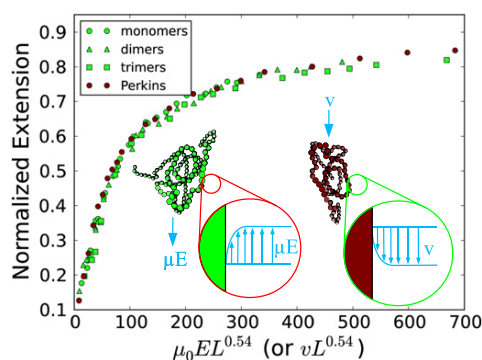


Fig. 4. The fractional extension of a λ -DNA fragment plotted against the combination $\mu_0 E L^{0.54}$ as measured by Ferree and Blanch [17•] compared to the extension by flow measured by Perkins et al. [18] (x-axis is now $v L^{0.54}$). A similar analysis was done by Long et al. [12,19]. Produced from data provided by S. Ferree and T.T. Perkins.

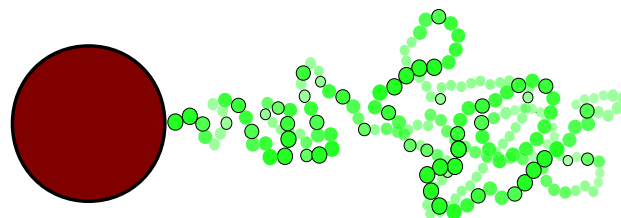


Fig. 5. The electrophoretic motion of a polyelectrolyte pulling a neutral colloidal particle.

(subscript p) and drag-tag label (L) are $F_p = \xi_p(v - \mu_p E)$ and $F_L = \xi_L(v - \mu_L E)$. For a spherical label of radius R and mobility μ_L , $\xi_L = 6\pi\eta R_L$. By balancing the forces, the mobility of the composite object is found to be

$$\mu_{ELFSE} = \frac{v}{E} = \frac{\xi_p \mu_p + \xi_L \mu_L}{\xi_p + \xi_L}. \quad (7)$$

This expression is deceptively simple since ξ_p is conformationally dependent and so is a function of the effective velocity of the fluid ($v - \mu_p E$) stretching the polymer, i.e. $\xi_p \rightarrow \xi_p(v - \mu_p E)$. The mobility must be solved self-consistently [1].

5.2. Diblock copolymer drag-tags

When the drag-tag is another polyelectrolyte, the difference isn't directly in Eq. (7) but rather in the form of the friction coefficient of the drag-tag [29]. In this case, the conformations (and so the friction coefficients) of both blocks are functions of their respective effective flows: $\xi_p \rightarrow \xi_p(v - \mu_p E)$ and $\xi_L \rightarrow \xi_L(v - \mu_L E)$. A key ingredient of the dynamics is that as the field induces elongation of the two polymers, ξ_p and ξ_L increase, which results in a reduction of the net velocity v . Again, we have a complicated self-consistent problem. Simulations using *dumb-bell models* of ELFSE complexes show that at high enough fields, this coupling can result in a nonmonotonic mobility as a function of electric field [30]. For the important case of uncharged drag-tags [31], the composite mobility reduces to

$$\frac{\mu_{ELFSE}}{\mu_p} = \frac{\xi_p}{\xi_p + \xi_L} = \frac{1}{1 + \xi_L/\xi_p}. \quad (8)$$

It has been implicitly assumed that the drag-tag and the DNA are hydrodynamically separated objects throughout this discussion but this is not necessarily true. This assumption is most suspect when the complex is not deformed by electrophoretic motion. In this case, there is no reason to assume that the drag-tag and the DNA occupy different space (most likely the label is immersed within the DNA conformation or vice-versa). Experiments [28•] and simulations [32] indicate that the field strengths normally applied are too small to induce segregation.

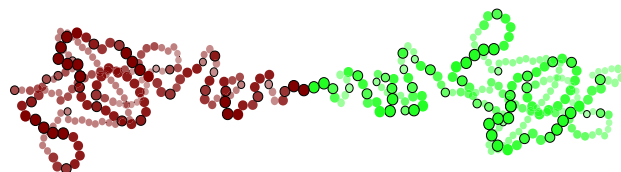


Fig. 6. A diblock copolymer as an ELFSE complex. As the electric forces move the charged block through the fluid, it must drag the other. Both chains deform in opposite directions and the mobility of the complex must be self-consistent with the conformation of the complex.

There is a subtle point here [33]: One may be tempted to argue that when the charged DNA engulfs the uncharged polymeric label the DNA double-layer ensures that the entire complex is free-draining (i.e., perhaps the drag-tag is free-draining too). This is not the case. The friction coefficients of the drag-tag and the DNA still depend explicitly on the conformation even when unsegregated and randomly mixed. The net electrophoretic mobility of random coil polyelectrolyte chains is highly dependent of the charge distribution but, when the Debye layer is small, it is essentially an average of the mobility of each monomer [33]. The ELFSE complex can be viewed as a di-polyampholyte. In this case, Eq. (8) is still applicable, but since the friction terms have different meanings, it is more practical to rewrite it as

$$\frac{\mu_{\text{ELFSE}}}{\mu_p} = \frac{1}{1 + \alpha/N} \quad (9)$$

where N is the number of DNA monomers and α is the number of bases contained in a DNA blob that has the same hydrodynamic radius as the drag-tag [34•]. Since α is a relative friction coefficient, it depends on the persistence length of DNA. This expression has been tested experimentally and was found to be in superb agreement with data. The value of α can actually be predicted with good accuracy from the basic physical properties of the DNA and its drag-tag [24,35].

Early experimental work on ELFSE showed that DNA with streptavidin drag-tags tethered to both ends were significantly slower than one would expect on the basis of the drag generated by a single streptavidin [36]. It wasn't until end-effects were looked at in detail that this enhancement was understood and identified as potentially useful [37]. In brief, charged end monomers contribute slightly more to the overall mobility of the complex because they are more likely to reside outside the core of the coil [34•]. Replacing an end-monomer by an uncharged label thus has an effect slightly larger than predicted by Eq. (9). Therefore, it was predicted that an ELFSE label of size $2\xi_L$ placed at one end of a DNA molecule would slow it down less than two labels of size ξ_L placed at the two ends. Experimental comparison of DNA with synthetic polypeptoid drag-tags at one or both ends confirmed the predictions of enhanced drag [38].

The improved understanding of ELFSE allows for the design of efficient drag-tags. Indeed, some engineered labels have been considered. For example, branched drag-tags [39] and soft micelles [40,41,27] both hold great potential for ELFSE because of their large hydrodynamic size [35].

6. Collisions with posts

Arrays of isolated posts have been investigated in recent years as a means of electrophoretic separation of DNA by length [42] (dense arrays are essentially similar to sieving gels). In this scenario, a polyelectrolyte chain that collides and catches on a post will have a residence time on the post before escaping that depends of the chain length. Intuitively, this process should be able to provide molecular separation if the collision frequency and system parameters are chosen properly.

In general, we may divide polymer-obstacle collisions into four stages: (i) free flow approach, (ii) deformation, (iii) unhooking escape, and (iv) partial or complete conformational relaxation before the next collision. Here we are most interested in regimes (ii) and (iii), when the post interacts with the chain. Since the post exerts a transient reaction force on the chain during collision and the subsequent escape, the equivalence principle holds during this process. So, the effective drag force on the chain while it is associated with the post depends on both chain length and conformation, just as was described above for end-tethered polyelectrolytes.

As shown in Fig. 7, there are several possible ways a polyelectrolyte can collide with a post. We will focus our attention on finite sized posts of diameter $D < R_g$. If the impact parameter between the

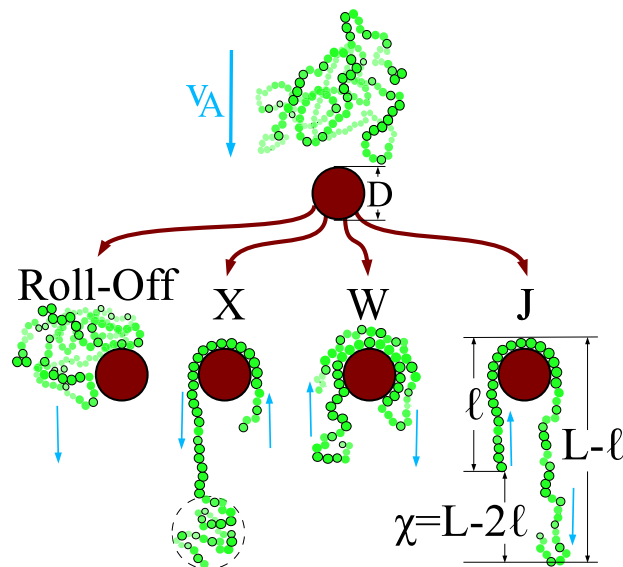


Fig. 7. A schematic description of the polymer-post collision process. The chain approaches the post relatively undeformed before it collides and either rolls off or deforms. The different arms compete to drag the polymer over the post until one side is chosen and the chain un-hooks. The hooked chains can be categorized as (i) J-collisions, (ii) W-collisions, and (iii) X-collisions.

post and the center of mass of the chain is less than R_g , then the probability of a collision event occurring is certain. However, as the impact factor becomes larger than R_g the probability of a collision quickly decays [43]. When a collision does occur, the polyelectrolyte can simply roll off the post (a possibility that is especially important if the driving field is too small to unravel the chain), or it can deform around the post and temporarily hook [44]. The propensity of the chain to either roll off or hook to the post is determined by the Deborah number $De = \tau_{\text{relax}}/\tau_A$, the ratio of the natural relaxation time of the polymer to the characteristic time scale of the shearing $\tau_A \approx D/\mu_0 E$. When $De < 10^0$, minimal stretching occurs and the polyelectrolyte rolls off the post. For $10^0 < De < 10^2$ hooking occurs with a probability that is highly dependent on De [44]. Finally, in the regime $De > 10^2$, the hooking probability as a function of impact parameter becomes independent of De , and the chain deforms significantly [44].

If the chain does hook to the post, it will adopt a transient pulley-like conformation in which each arm competes to escape. Such conformations are often categorized as being in one of the three states shown in Fig. 7: J-collisions, X-collisions, and W-collisions. Simple collisions that result in a single strand of polymer hooked around the post with stretched arms downstream are referred to as J-collisions. An X-collision is a very asymmetric variant of the J-collisions with a short, extended arm and a long, partially relaxed arm that forms a stem-flower conformation. In an X-collision, the chain unhooks before the long arm can fully extend. A W-collision is a relatively rare event in which a polymer is partially trapped on the post in a folded conformation with numerous strands in contact with the post. This is a metastable state that often becomes a J-collision during the escape process [45,46]. We refer readers interested in W- and X-collisions to the excellent review by Dorfman [42] who covers collisions in some detail. In the following, we focus our attention on the case of J-collisions.

J-collisions are conceptually simple because the arms can be treated as two extended threads. In the large force limit of $E \gg E^*$, both arms are fully stretched at all times t [47]. The pertinent lengths are defined in Fig. 7. The shorter arm has a length $l(t) < L/2$, where $L = Nb$ is the contour length of the polymer, and the longer one has a length $L - l(t)$. The difference between the two arms is $\chi(t) = L - 2l(t)$.

The two arms are competing so unhooking dynamics result from the balance of the forces on the two arms. The net force on the chain due to the electric field that results from the excess length χ is $\xi_\chi v_s$, where $v_s = \mu_0 E$ is the equivalent electrophoretic flow rate. As the chain unhooks at a rate $d\ell/dt$, it resists with an overall drag force $-\xi_j d\ell/dt$. Notice that ξ_χ is the friction coefficient of the excess length while ξ_j is the friction coefficient of the entire chain in the J-collision conformation. Thus, the unhooking process obeys the equation of motion

$$\frac{d\ell}{dt} = v_s \frac{\xi_\chi}{\xi_j}. \quad (10)$$

Assuming the equivalence principle applies, the friction coefficients for an extended, rod-like chain section of n monomers of size b and friction coefficient ξ_b , scales as $\xi_{\text{rod}} \sim n\xi_b/\ln n$. This provides estimates for both ξ_j and ξ_χ . Integrating Eq. (10) gives the length of the shorter arm $\ell(t)$ throughout the unhooking process. From this, the escape time τ_e can be found as the time at which $\ell(t = \tau_e) = 0$. Averaging the initial length $\ell(0)$ over all possible values $(0 - L/2)$ gives the mean unhooking time as [15]

$$\langle \tau_e \rangle = \left(\frac{Nb}{2\mu_0 E} \right) \times g(N) \quad (11)$$

where $g(N)$ is a weak (logarithmic) function of N that differs depending on the nature of the force applied and the role of the HI (in practice, $g \approx 1$). The collision process has been studied in detail for various situations by Kenward and Slater [48] using a theoretical framework that includes HI but excludes electrophoretic forces.

However, for weak electric field strengths the two arms of the J-conformation are not fully stretched, and this simple expression is no longer valid. Field strength actually plays a cardinal role in determining unhooking dynamics [47]. For moderate fields in the range $N^{1/5} < E/E^* < 10N^{1/5}$, there is a broad transition regime between extended arms (the case presented above) and undeformed coils. At these fields, the arms adopt the trumpet conformations discussed in Section 4. Early work on incorporating hydrodynamic interactions into the weak field regime applied the equivalence principle to each arm and predicted different scalings for the escape time of freely draining and hydrodynamically coupled chains [16]. To the best of our knowledge, these scaling laws have not been verified by experiments or simulations. A more recent model proposes an escape time similar in form to Eq. (11) but with E -dependence incorporated [45,46]. The unhooking time in moderate fields is

$$\tau_e = \frac{\mathcal{L}}{2\mu_0 E} \ln \left(\frac{\mathcal{L}}{\mathcal{L} - \ell} \right) \quad (12)$$

where $\mathcal{L}$ is the effective contour length of the stretched chain. The effective length goes as $\mathcal{L} \sim N^\gamma$ where the scaling γ is set by the field strength E and lies within the range $0.54 < \gamma < 0.75$ [45,18] for weak fields and $\gamma \rightarrow 1$ for the strong field limit discussed previously. The escape time has been verified many times using Brownian Dynamics simulations that neglect HI completely [47,49] and compared to experiment [46] but results that test the role of HI are lacking.

7. Confinement effects

7.1. Confinement between plates

Confining a polyelectrolyte in a narrow channel, capillary, or between closely spaced parallel walls sterically limits its possible conformations, inducing chain extension in the unconstrained dimensions. The confinement increases the probability of interaction between the monomers of the polyelectrolyte and the molecules of the interface,

thereby inducing a non-electric force during electrophoresis due to added friction of the monomers in transient contact with the wall. This non-electric frictional force is presumably an extensive quantity that increases linearly with the number of monomers in contact with the wall:

$$\vec{F} = \vec{F}_w \approx \omega N \xi_w \vec{v}. \quad (13)$$

where ξ_w is the monomer-wall friction factor, N is the degree of polymerization of the polyelectrolyte, and ω is the fraction of monomers in transient contact with the wall. The confining walls have a second effect in this scenario. The proximity of the walls screens the hydrodynamic interactions between monomers (by symmetry of the angular pre-averaging of the hydrodynamic interaction tensor [50,51]). Therefore, the friction coefficient of the chain is typical of a free-draining chain [52], $\vec{F}_\xi = N \xi_b \vec{v}$. Putting $\vec{F}_\xi$, $\vec{F}_w$ and $\vec{F}_E = N \xi_b \mu_0 \vec{E}$ into Eq. (4) gives

$$\mu = \frac{\mu_0}{1 + (\xi_w/\xi_b)\omega} \quad (14)$$

In the weak field limit ($E \leq 300$ V/cm), the electrophoretic mobility of λ -DNA confined between narrowly separated plates ($D \approx 19$ nm) is consistent with Eq. (14) for $\omega \sim N^{1/2}$ [53]. This result may be understood qualitatively by appealing to established scaling notions for confined polymers. For a polymer chain with contour length $L = Nb$ confined in one or more dimensions to a gap of size D , one might expect the fraction of monomers ω in contact with the wall to be an increasing function of the ratio L/D . Consider the case of a polymer confined in solution within a narrow gap, $D \ll R_g$, between parallel planar surfaces with a uniform distribution of adhesive sites. For gaps smaller than the persistence length of the polymer, $D < p$, the polymer adopts a quasi-2D self-avoiding conformation in good solvent conditions with lateral radius of gyration $R_{||} \sim N^{3/4}$. As each monomer is in the vicinity of the walls, the fraction of monomers in contact at any instant with adhesive sites on the wall scales as $\omega \sim \Theta R_{||}^2 / N \sim N^{1/2}$, where Θ is the surface number density of adhesive sites. A version of this argument has been previously proposed for larger gap sizes, $p \ll D \ll R_g$ [53], with the same conclusion. At even larger fields, λ -DNA continues to move through nanoslits in a stick-slip manner [54]. This suggests that the mean friction ξ_w may be field-dependent and a result of entropic or dielectrophoretic trapping.

7.2. Single adsorbing wall

In fact, it is possible to restrict the conformational freedom of a polyelectrolyte with only a single wall. Consider DNA near an adsorbing flat surface. The surface enacts a non-electric force on the polymer and the deformed DNA conformation is the net result of the competition between adsorption and the entropy loss due to confinement. The equivalence principle can thus be utilized and applying an electric field parallel to the surface can produce a molecular size dependent mobility.

This phenomenon was first reported by Pernodet et al. [55]. The additional friction between the surface and the (adsorbed) DNA appears to be responsible for the fact that DNA fractionation is now possible. Exactly how the mobility scales with contour length remains an unsettled issue. The earliest work found $\mu \sim N^{-\beta}$ where $\beta = 0.87$ for double-stranded DNA on Si wafers [55] and yet later investigations observed $\beta \approx 0.25$ [56,57]. A deterministic model has been proposed that indicates β may in fact be field dependent [58]. At the smallest fields this model predicts that $\beta = 1$ while at the largest fields it suggests β goes to zero and the mobility again becomes size independent.

Experiments of DNA electrophoresis along self-assembled, corrugated surfaces of nonporous silica beads indicated that surface friction rather than topology controls fractionation [56]. Engineering

complicated chemically nanopatterned surfaces can augment small changes in conformation (and presumably friction) improving performance [57,59–61].

8. Electro-hydrodynamics of Soft Interfaces

In this section we look at recent progress in the understanding of the use of polymer coatings for modulating the shear of a fluid at a solid–liquid interface. This field can be divided into two sub-topics: polymer coatings for modulating the electro-osmotic flow generated by an immobile charged surface (EOF) [62], and the electrophoresis of soft colloids [63]. In EOF researchers are interested in the fluid velocity far from the wall while in soft colloid electrophoresis researchers are interested in the mobility of the polymer grafted colloid. Understanding one gives insight into the other since the physics which governs the two is very similar. Below we connect recent advances in understanding of the modulation of EOF with parallel advances in the field of soft colloid electrophoresis.

Much of the theory of soft interfaces comes from the soft colloid electrophoresis community [63,64] and is based on continuum hydrodynamic and electrokinetic transport equations for particles with porous, compliant polymeric coatings. Alternative approaches have utilized scaling models from polymer physics [65] or coarse-grained simulation methods to study the response of polymer layers to EOF [66–70].

One prediction in both the soft colloid electrophoresis and soft interface EOF communities is that for a thick enough coating both the mobility of the colloid and the EOF mobility generated by the coating are simply the free-draining mobility of individual polymers, μ_0 . The reason for this is simply the fact that the polymers shear the fluid such that the difference in the velocity of the backbone and the nearby fluid is the Smoluchowski slip velocity. Thus for soft colloids being electrophoresed the polymers move $\mu_0 E$ faster than the fluid, while for grafted polymers the surrounding fluid is pumped with a velocity $-\mu_0 E$ as schematically shown in Fig. 8. The equivalence between EOF and the electrophoretic mobility was investigated in experimental studies utilizing heteropolymers of variable charge densities. Heteropolymers made of neutral and charged monomers were synthesized and the electrophoretic mobility of the polyelectrolytes was compared to the EOF produced when the same heteropolymer was used as a polymer coating [71]. The two values showed very close agreement, although the EOF mobility was slightly lower.

Efforts to model the effects of polymer coatings on EOF have focused on end-grafted polymers in the limit of thin Debye layers (the Smoluchowski limit) [65]. This scaling theory makes predictions for

EOF profiles within and outside of the polymer layers as a function of the grafting density, the degree of polymerization, electrophoretic mobility of the polymers, the electric field, and the electro-osmotic flow in an uncoated channel. Partial inhibition of EOF by neutral polymer layers on charged surfaces was predicted, and the implications of the electro-hydrodynamic equivalence principle were considered. In the limit of thicker Debye layers, there have been numerous theoretical studies of the electrophoresis of polymer-coated colloids [63,64]. As an example, for polyelectrolyte grafted colloids at low-to-moderate ζ -potentials, detailed predictions based on continuum electrokinetic transport analysis have been made for the deviation of the electrophoretic mobility from free-draining behavior [63]. In both cases the difference in the fluid velocity between the interface and the bulk approaches the Smoluchowski slip velocity as the coating becomes thicker, although the difference for thinner coatings differs. In addition, the fluid flow profile, while qualitatively similar, is quantitatively different in the two cases.

Recently, there has been increasing effort to develop accurate and efficient computer simulations of EOF near soft interfaces. For instance, predictions of the scaling approach of Harden et al. [65] for the dependence of the EOF mobility on grafting density and degree of polymerization has been confirmed by MD simulations for neutral chains grafted to a charged surface [66]. Other simulations of rod-like polymers fixed rigidly to a surface (to ensure uniform density as a function of height from the surface) focused on the fluid velocity profile near the wall [67], which agreed with theory [65]. When the polymers were allowed to stretch, a non-linear relationship between the EOF mobility and the applied electric field was observed, but with a different form from that predicted for flexible grafted chains [68]. While these studies all focused on neutral coatings new computational methods based on the equivalence principle [21,72] should allow for simulations of charged coatings.

As an example of the similarity between EOF near soft interfaces and soft colloid electrophoresis, one can consider the effect of solvent quality on the ability of neutral polymer coatings to quench EOF [68,69], and compare this to soft colloid electrophoresis experiments, which look at the temperature dependence of PNIPAM coated charged colloids [73]. Both approaches address how neutral polymers affect the shear of fluid at a charged surface as the solvent quality varies. In each case, there is significant slip at the interface when the solvent quality is poor and the polymer coating is collapsed on the surface. When the solvent quality is good and the polymers swell to form a thick layer, both approaches demonstrate that the slip is virtually eliminated. Moreover, both approaches show that the change in the height of the polymer layer is strongly correlated with a change in the slip at the

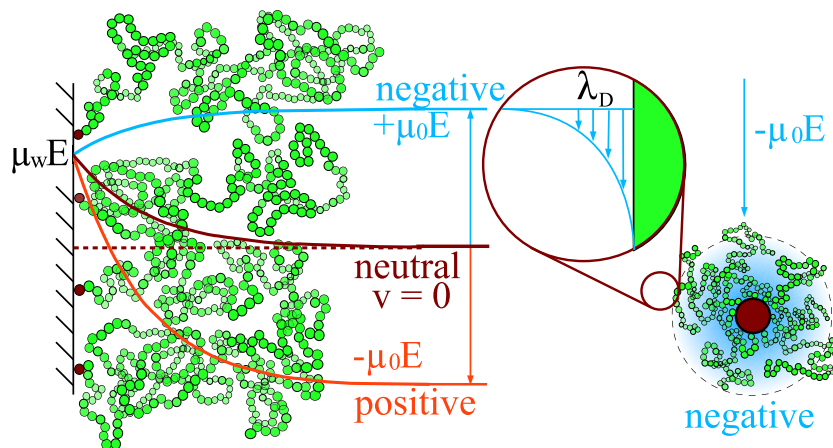


Fig. 8. A thick enough neutral coating will reduce the EOF from the bare wall value of $v_f = \mu_w E$ to zero outside of the polymer layer. A positively charged coating will cause the velocity to be reduced even further to $-\mu_0 E$, where μ_0 is the free-solution mobility of the polymer itself. On the other hand, a negatively charged layer will contribute to the EOF increasing the fluid velocity up to $\mu_0 E$. A soft colloid electrophoreses at the same velocity as the EOF produced by its brush.

interface. Similar results have been seen in experiments on the modulation of EOF with polymer coatings with varying degrees of hydrophilicity [70,74].

9. Future perspectives

Electro-hydrodynamics of polyelectrolytes is an important topic with numerous practical applications, most notably DNA fractionation. While long chains subject only to an electric field are free-draining, polyelectrolytes subject to both an electric field and a mechanical force are not—a fact not widely appreciated in the literature. In many such situations, the Principle of Electro-hydrodynamic Equivalence can be used to predict the mobility. This review covered several prototypical systems currently being studied but many more exist and inevitably new systems will emerge.

While not covered in this review, nanopores have received extensive attention; however, only recently have researchers recognized the importance of hydrodynamics. Grosberg and Rabin have discussed the role of the equivalence principle as molecules transition from the bulk solution into the nanopore [75]. During the translocation process itself, the stall force required to hold a polyelectrolyte fixed in the pore is indeed given by Eq. (5) [76–78]. On the other hand, hydrodynamics on the scale of the polymer coil do not appear to play an important role and in certain cases can be ignored.

Separation by confinement was discussed in this review but only between two parallel plates. Confining DNA to dimensions smaller than its persistence length is possible and such strongly confined systems exhibit markedly different behavior than that discussed here [79]. Current experiments focus on micro- or even nano-scale systems but still rely on relatively simple geometries due to the difficulty in manufacturing non-trivial patterns. Fabrication approaches continue to improve the ability to tailor device geometries, although it is unclear what complex structures will be best for the fractionation of DNA or other biologically relevant macromolecules (or even cells and organelles). Entropy-exploiting devices [80], nanopits [81], and future engineered surfaces are among the systems that will likely lead to superior separation potential.

While current devices have been designed based on purely physical intuition, in the near future device geometries and dimensions will be pre-optimized based on computer simulation results made possible by increases in computing power and new simulation techniques [82]. In particular, simulation methods based on the equivalence principle have emerged in recent years for several mesoscopic fluid models such as dissipative particle dynamics [72], Brownian dynamics [83], and lattice-Boltzmann [21] fluids, which have shown realistic behavior with drastically less computation time. These and other future developments should lead to crucial advancements in this important field.

Acknowledgments

This work was supported through NSERC Discovery Grants to G.W.S. and J.L.H. Financial support of O.A.H. and T.N.S. from the NSERC-CGS program is gratefully acknowledged. We would like to thank C. Holm, S. Ferree, and T.T. Perkins for generously granting permission to present their data. We would also like to thank A.E. Barron and M.V. Chubynsky for helpful discussions.

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Appendix C: Effective molecular diffusion coefficient in a two-phase gel medium

OA Hickey, JF Mercier, MG Gauthier, F Tessier, S Bekhechi, GW Slater. *The Journal of Chemical Physics* **124**, 204903 (2006)
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Effective molecular diffusion coefficient in a two-phase gel medium

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(Received 17 March 2006; accepted 29 March 2006; published online 22 May 2006)

We derive a mean-field expression for the effective diffusion coefficient of a probe molecule in a two-phase medium consisting of a hydrogel with large gel-free solvent inclusions, in terms of the homogeneous diffusion coefficients in the gel and in the solvent. Upon comparing with exact numerical lattice calculations, we find that our expression provides a remarkably accurate prediction for the effective diffusion coefficient, over a wide range of gel concentration and relative volume fraction of the two phases. Moreover, we extend our model to handle spatial variations of viscosity, thereby allowing us to treat cases where the solvent viscosity itself is inhomogeneous. This work provides robust grounds for the modeling and design of multiphase systems for specific applications, e.g., hydrogels as novel food agents or efficient drug-delivery platforms. © 2006 American Institute of Physics. [DOI: 10.1063/1.2198204]

I. INTRODUCTION

Controlling the formation of multiphase hydrogels unveils a vast landscape of material design prospects. The microstructure of the resulting gel medium, hence many of its physical properties, is ultimately determined by the concentration of the different phases, the relative rates of the concurrent gelation and phase separation phenomena, and a number of other processing variables.^{1–3} An archetypal instance of a two-phase hydrogel is shown in Fig. 1, and the biocompatibility of this particular gelatin/maltodextrin example immediately evokes biomedical applications, e.g., hydrogels tailored as vehicles for controlled drug release. For design purposes, however, a sound model predicting the physical properties of the microstructured material is needed. In this article we focus on the effective diffusion coefficient of small molecules in such two-phase systems, and suggest for it an analytical expression in terms of the microphase parameters. This generic problem has a long history,^{4,5} but the new expression we propose here discriminates between obstruction-limited and viscosity-limited transports, and its validity is demonstrated convincingly by comparison with *exact* numerical results.

In recent years, our group has developed a new microscopic approach to model the obstruction-limited transport of hard particles in two-dimensional (2D) and three-dimensional (3D) gels of various structures.^{6,7} In our lattice master equation approach, reviewed in Sec. II, we cast the steady-state transport problem in a system of coupled linear equations, the solution of which yields the normalized diffusion coefficient for a single particle through an arbitrary configuration of obstacles (representing gel fibers). Using a sparse matrix notation and a biconjugate gradient solver, we obtain results of a precision exceeding that of explicit Monte Carlo (MC) calculations by many orders of magnitude, in very short computing time (e.g., a precision of one part in

10^8 over a million site system requires a few minutes of computation on a modern desktop computer). After applying our method to predict the transport properties of molecules in a variety of sieving systems⁸ and to demonstrate the limitations of existing mean-field theories,^{8–10} we successfully extended it to treat flexible polymer molecules¹¹ and probe-fiber interactions.¹² We also showed that, in the continuum limit, results are independent of the lattice type and converge toward off-lattice simulation results.¹³

It is the objective of this article to explain how our lattice model is extended to treat the diffusion of a probe molecule in a phase-separated gel medium, and to include the contribution of viscosity-limited transport. We then show, in Sec. III, that a simple mean-field expression for the effective diffusion coefficient compares remarkably well with exact numerical results over a broad range of microstructure parameters.

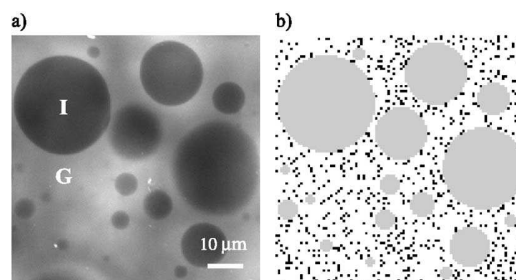


FIG. 1. (a) Confocal laser micrograph of a hydrogel (G) with viscous inclusions (I), obtained from a solution containing 10% gelatin and 12% maltodextrin, at pH 3. The concurrent phase-separation and gelation processes are controlled to yield well-separated, roughly spherical inclusions with a log-normal size distribution (image courtesy of S. Hodge). The viscosity inside the maltodextrin-rich inclusions is found to be significantly higher than in the gel phase. (b) Example of a 100×100 lattice representation for the hydrogel slice shown in the micrograph (we show a 2D example, but the extension to 3D is immediate). Inclusions are represented by spherical domains of viscous sites (gray), of total volume fraction ϕ_I , while gel fibers are modeled by a concentration c of impenetrable obstacles (black) in a zone of total volume fraction $(1 - \phi_I)$.

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II. LATTICE DIFFUSION MODEL

A. Diffusion through a matrix of obstacles

Consider a hypercubic lattice in d dimensions, of spacing a , size L^d , with periodic boundary conditions along all axes, as a discrete representation of a space in which a particle is set to diffuse. Let there be *free sites* (the solvent), which the particle may visit, and impenetrable *obstacle sites* (gel fibers), which it cannot (see Fig. 1). In a standard MC context, the effective diffusion coefficient D of the particle in such an obstacle matrix is extracted from its mean-square displacement $\langle r^2 \rangle$ for a long, N -step random walk (RW) over a long time $t = N\tau$ (with τ the unit time step) through the definition

$$D \equiv \lim_{t \rightarrow \infty} \frac{\langle r^2 \rangle}{2dt}. \quad (1)$$

We developed a powerful alternative to this traditional approach,^{6,7} which consists in considering the action of a small dimensionless external field ϵ on the particle, and obtain the diffusion coefficient parallel to the field direction $D_{\parallel}$ from the resulting velocity v , via the Nernst-Einstein relation,

$$\frac{D_{\parallel}}{D_0} = \lim_{\epsilon \rightarrow 0} \frac{v}{v_0}, \quad (2)$$

where $D_0 = 1/2$ and $v_0 = \epsilon/d$ are the free-solution diffusion coefficient and velocity, respectively (physical quantities in natural units are understood to be multiplied by the appropriate combination of a and τ). We can calculate v exactly from a master equation involving the single-step transition probabilities between free lattice sites. Under a small bias, the transition probabilities to free nearest neighbor sites along directions perpendicular to the field are $p_{\perp} = 1/2d$, while along the field axis they become, to first order in ϵ ,

$$p_{\pm} = \frac{1 \pm \epsilon}{2d}. \quad (3)$$

Given a total of M free sites, it is therefore possible to construct the lattice-specific $M \times M$ Markovian transition matrix $\mathbf{T}$, wherein the contribution of obstacles shows up as diagonal elements (the particle *bounces back* when hitting an obstacle, and remains on the same lattice site). The steady-state probability density of the particle on the free sites is independent of time, so it is given by the M -component normalized eigenvector $\mathbf{n}$, solution of

$$\mathbf{T}\mathbf{n} = \mathbf{n}. \quad (4)$$

Now consider the vector $\mathbf{v}$ giving the average velocity of a particle on each of the free sites: $\mathbf{v} = \mathbf{f}_{+}p_{+} - \mathbf{f}_{-}p_{-}$, where each component of $\mathbf{f}_{\pm}$ is equal to 1 or 0 whether the neighbor site in the $\pm$ direction is free or not, respectively. The overall velocity v is then given by the scalar product $\mathbf{v} \cdot \mathbf{n}$. Hence the diffusion problem is solved *exactly* upon solving Eq. (4) for $\mathbf{n}$ (to first order in ϵ). Indeed, the effective diffusion coefficient along the field direction can be written as

$$\frac{D_{\parallel}}{D_0} = \lim_{\epsilon \rightarrow 0} \frac{\mathbf{v} \cdot \mathbf{n}}{\epsilon/d}. \quad (5)$$

If the system is isotropic, we may take $D = D_{\parallel}$ in the foregoing development. This powerful numerical approach is well established, and we have expounded on explicit examples and optimization techniques in previous publications.^{6-10,13}

B. Viscosity

We now want to take the solvent viscosity into account in our lattice model: regardless of collisions with fixed obstacles, the dynamics of the diffusing particle should *slow down* in regions of higher viscosity. However, our master equation algorithm implies that the fundamental transition time step is the same for all the lattice sites. We must therefore modify the local transition probabilities to model site-specific viscosity. Indeed, we can endow any given site with an increased viscosity by adding a probability s of *staying* on that site. Given that v_i is proportional to $p_{\pm}$ and inversely proportional to the local viscosity η , we simply need to use the modified transition probabilities

$$p_{\perp} = \frac{1}{2d\eta}, \quad p_{\pm} = \frac{1 \pm \epsilon}{2d\eta}, \quad s = 1 - \frac{1}{\eta}, \quad (6)$$

which yields the correct free-solution velocity $v_0 = \epsilon/d\eta$. These new transition probabilities are easily included in our calculation method, and we are thus equipped to find the exact numerical value of D for any configuration of obstacles and viscous sites. We will use these numerical results to test the validity of our analytical expressions for D derived in Sec. III.

Note that by imposing a detailed balance condition between two neighboring sites i and j , that is, $n_i p_{i \rightarrow j} = n_j p_{j \rightarrow i}$, we find that the local occupation probability densities n_i and n_j of those two sites are related through

$$\frac{n_i}{n_j} = \frac{\eta_i}{\eta_j}. \quad (7)$$

Thus, when $\epsilon = 0$ and the diffusing particle can access all free sites, the normalized vector $\mathbf{n}$ is given by

$$n_i = \frac{\eta_i}{\sum_{j=1}^M \eta_j}. \quad (8)$$

This is a constraint of our lattice model and it is subject to some physical interpretation, as discussed in the concluding remarks below.

III. EFFECTIVE DIFFUSION COEFFICIENT

We want to derive an analytical approximation for the effective diffusion coefficient of a small molecule in a phase-separated system consisting of a gel comprising large, well-defined gel-free inclusions (as in Fig. 1). We also want our final expression to be amenable to inhomogeneous viscosity cases. We will tackle the problem of gel-free inclusions and viscosity separately, before bringing them into a single, final expression.

A. Gel-free domains, uniform viscosity

Assume for the moment that the viscosity of all free sites in the lattice is the same, but that there are large obstacle-free zones, or inclusions, occupying a volume fraction ϕ_I . The gel phase then occupies a volume fraction $(1 - \phi_I)$, and we write the free volume in the gel phase as

$$\phi_G \approx (1 - c)(1 - \phi_I), \quad (9)$$

where c denotes the concentration of obstacles (the gel *concentration*). This is an excellent approximation for a point-like particle and realistic values of c (for a finite-size particle, we must use the effective concentration c_{eff} ,⁸ for very high values of c , closed subdomains may form, which are then inaccessible to the probe molecule).

Our goal is to express the effective diffusion coefficient D in terms of the diffusion coefficients D_I and $D_G = D_G(c)$ in the individual homogeneous phases. In the spirit of mean-field theory, we can write the diffusion coefficient of a lattice random walker as $D = a^2/2d\langle\tau\rangle$, where $\langle\tau\rangle$ is the average time spent on a site between successful MC moves. In our two-phase system, we may take the space average

$$\langle\tau\rangle = \frac{\phi_I\tau_I + \phi_G\tau_G}{\phi_I + \phi_G}, \quad (10)$$

where $\tau_i = a^2/2dD_i$ is the mean-field residency time in phase i . We therefore have

$$D = \frac{a^2}{2d} \frac{\phi_I + \phi_G}{\phi_I\tau_I + \phi_G\tau_G} = \frac{\phi_I + \phi_G}{\phi_I(2d\tau_I/a^2) + \phi_G(2d\tau_G/a^2)}, \quad (11)$$

so we expect the effective diffusion coefficient to follow the approximation

$$D = D_0 \frac{\phi_I + \phi_G}{\phi_I\xi_I + \phi_G\xi_G}, \quad (12)$$

where we have defined $\xi_i \equiv D_0/D_i^*$ (the $\star$ here indicates that we disregard viscosity in the calculation of the diffusion coefficient; in the case of gel-free inclusions, we automatically have $\xi_I=1$). We expect this mean-field approximation to be accurate for spherical, isolated inclusions, provided that their characteristic size is significantly larger than the mean distance between gel fibers.

In Fig. 2, we plot the value of the normalized diffusion effective coefficient D/D_0 as a function of the gel-free inclusion volume fraction ϕ_I , for four values of gel concentration. The solid lines correspond to Eq. (12), with ϕ_G given by Eq. (9), while data points indicate the exact values obtained with the calculation method outlined in Sec. II. Both are seen to agree almost perfectly, except perhaps for high values of c and ϕ_I (which correspond to extreme experimental conditions). For the sake of efficiency, we used a 2D lattice with a single gel-free inclusion of volume fraction ϕ_I for most of our calculations, but for $c=20\%$ we verified that a using a collection of inclusions with a log-normal size distribution (or a random one, results not shown) does not affect the accuracy of Eq. (12).

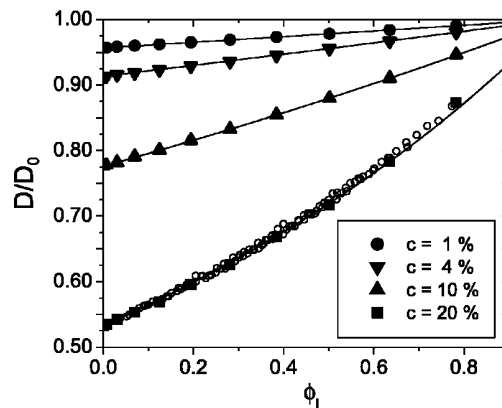


FIG. 2. Values of D/D_0 as a function of the gel-free inclusion volume fraction ϕ_I , for four different values of c . Solid data points are obtained from exact 2D lattice calculations with a single gel-free inclusion (lattice size is 100×100 , data points shown are an average over 50 independent realizations, and error bars are smaller than the symbol size). Open data points correspond to realizations where we used many gel-free inclusions (of total volume fraction ϕ_I) with a log-normal size distribution. Solid lines correspond to Eq. (12).

B. Viscous sites

The change in the diffusion coefficient due to local viscosity variations can be derived exactly, for any given lattice. Indeed, the addition of viscous sites in the system does not affect the RW trajectory of the particle, and the new value of D can therefore be obtained by a simple renormalization of the time spent on each site. Taking η_i as the viscosity of site i and $\langle\eta\rangle$ as the free-site average viscosity, we write, quite generally,

$$D = D_{\eta_0} \frac{\eta_0}{\langle\eta\rangle} = D_{\eta_0} \frac{\eta_0}{\frac{1}{M} \sum_{i=1}^M \eta_i}, \quad (13)$$

where D_{η_0} is the diffusion coefficient calculated when the viscosity is uniform and equal to a reference viscosity η_0 on all the free sites. We do not compare Eq. (13) with exact lattice calculations because it is exact, by construction.

C. Gel with viscous inclusions

As a practical example, we now combine the two preceding results to write a final analytical expression for the effective diffusion coefficient of a gel with viscous inclusions, i.e., in the specific case where viscosity zones coincide with the gel-free domains. Taking η_I and η_G as the respective viscosities inside the inclusion and inside the gel pores, and realizing that

$$\langle\eta\rangle = \frac{\phi_I\eta_I + \phi_G\eta_G}{\phi_I + \phi_G}, \quad (14)$$

we can use Eq. (13) with D_{η_0} given by Eq. (12), to obtain the effective value of D as a function of the microphase parameters ϕ , ξ , and η ,

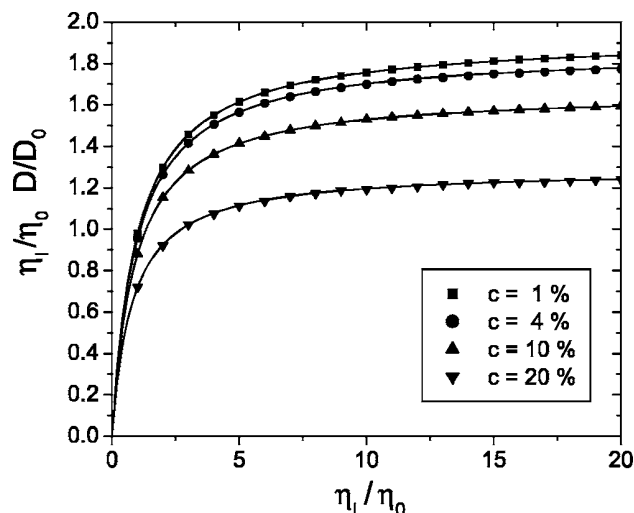


FIG. 3. Values of $\eta_i/\eta_0 \times D/D_0$ as a function of η_i/η_0 , in a 2D lattice with a gel-free inclusion of viscosity η_i and a fixed volume fraction $\phi_i = 50.25\%$, for four values of c . Data points are obtained from exact 2D lattice calculations (lattice size is 100×100 , data points shown are an average over 50 independent realizations, and error bars are smaller than the symbol size). Solid lines correspond to Eq. (15).

$$D = D_0 \eta_G \left(\frac{\phi_I + \phi_G}{\phi_I \xi_I + \phi_G \xi_G} \right) \left(\frac{\phi_I + \phi_G}{\phi_I \eta_I + \phi_G \eta_G} \right). \quad (15)$$

We immediately remark the symmetry between the two factors; however, keep in mind that the first one is a mean-field approximation valid in the limit of well-defined, isotropic inclusions, while the second factor is an exact result that is independent of the geometry of the viscous sites. In particular, the latter can be extended to account for any number of viscosity domains [as per Eq. (13)], whereas generalizing the first factor incurs additional errors for each additional phase. It should also be possible to consider gel inclusions (in other words, a mixture of two different gels) by taking ϕ_I as the free volume in the second gel phase, but we have not yet investigated this particular generalization in detail.

In Fig. 3 we plot the value of D/D_0 as a function of the viscosity η_i in the inclusion. Viscosity values are normalized with respect to the reference viscosity η_0 , and y-axis values are multiplied by η_i/η_0 to resolve the curves. It is not surprising to find that the agreement with Eq. (15) is again almost perfect here, since we already showed that Eq. (12) provides an excellent approximation of D/D_0 in a uniform viscosity situation, and that the addition of viscous domains is handled exactly.

IV. CONCLUDING REMARKS

We have derived an expression for the effective diffusion coefficient in a hydrogel comprising viscous inclusions. The gel-free inclusion aspect is treated in a mean-field approach,

while the viscosity aspect is treated explicitly. This expression is in remarkable agreement with exact 2D calculations performed with our lattice model, extended to take into account spatial variations in viscosity. The agreement is best at low gel concentrations, typical of real hydrogels, and we expect it to agree even better in 3D, because the formation of closed subdomains is then much less likely. We are looking forward to further extend our model to include local affinity effects and interfacial effects between the different phases.

We should comment briefly on Eq. (8), which indicates that, in an obstacle-free system, the local concentration is proportional to the local viscosity. Physically, this implies that underlying diffusion process can be modeled as a random walk with a *constant mean-free path* throughout the system, as explained most clearly by Schnitzer *et al.*^{14,15} This is a reasonable assumption in the case at hand, because the probe molecule mostly diffuses through water in either the gel or the MD regions, but the issue can only be settled conclusively from experimental measurements, which are not available at this time. It would be worthwhile to explore the generalization of our lattice algorithm to treat the different classes of microscopic diffusion processes.

ACKNOWLEDGMENTS

We thank Shane Hodge and Simon Vieth for providing Fig. 1(a) and details on the experimental setting, as well as Ivan L'Heureux for useful discussion. This research is supported by the Advanced Foods and Materials Network (AFMnet). We are also grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support and to the High Performance Virtual Computational Laboratory (HPCVL) for providing access to computational resources.

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Appendix D: The diffusion coefficient of a polymer in an array of obstacles is a non-monotonic function of the degree of disorder in the medium

OA Hickey, GW Slater. *Physics Letters A* **364**, 448-552 (2007)

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Physics Letters A 364 (2007) 448–452

PHYSICS LETTERS A

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The diffusion coefficient of a polymer in an array of obstacles is a non-monotonic function of the degree of disorder in the medium

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Received 27 July 2006; received in revised form 28 November 2006; accepted 6 December 2006

Available online 15 December 2006

Communicated by C.R. Doering

Abstract

Using Monte Carlo simulations, we have found that there is a surprising non-monotonic dependence of a polymer's diffusion coefficient upon the degree of disorder of the surrounding environment. Starting with a two-dimensional periodic lattice of obstacles, we randomly displace obstacles to create a quenched gel system with a tunable degree of disorder. Very small displacements increase the diffusion coefficient of polymers since they increase the width of the tube through which the polymer chains reptate. As we displace the obstacles further, however, entropic trapping is observed and the diffusion coefficient of the polymer decreases dramatically. This is a striking example of the delicate balance between entropic and frictional effects for a polymer diffusing in a dense system.

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PACS: 61.25.Hq; 78.55.Qr

Keywords: Entropic trapping; Diffusion; Polymer physics; Anomalous diffusion; Reptation

Entropic trapping (ET) of polymer chains in random gels or porous systems is a concept that was originally proposed by Muthukumar and Baumgartner in a seminal 1987 paper [1]. In ET, the spatial dependence of a chain's conformational entropy (or free energy) is equivalent to an external potential that tends to trap the chain in those regions of the gel where its entropy is maximized. Dense gel regions lower the conformational entropy of the chain, and are thus avoided. Empty regions, on the other hand, maximize the entropy and act as potential wells that trap the chain for extended periods of time. Long-time diffusion is thus limited by the time it takes to jump between large pores separated by dense regions (the latter then act as potential barriers). Evidence for ET has been reported, for example, in the case of DNA gel electrophoresis [2–4]. The concept of ET has also been used to create novel microfluidic devices [5,6]. Recently it has been suggested that ET might also be involved in binding in some biological systems [7].

We previously demonstrated that ET sometimes leads to surprising and counter-intuitive effects. Using the bond-fluctuation Monte Carlo algorithm [8,9], we examined a polymer chain diffusing in a two-dimensional array of periodically distributed obstacles. The dependence of the diffusion coefficient $D(C)$ on the fraction $1 - C$ of obstacles removed from the array was non-monotonic. The limiting cases were fully consistent with the Rouse ($C = 0$) and reptation ($C = 1$) models. As $1 - C$ increases (more obstacles are removed), one intuitively expects a monotonic increase of $D(C)$ since the removal of obstacles should obviously make it easier for the chain to diffuse. However, it was not the case for this model system. Starting with a perfectly periodic lattice of obstacles, removing a small percentage of the obstacles actually caused a considerable decrease in the diffusion coefficient [8,9]. This is due to entropic trapping in the voids left after obstacles are removed. These local entropic traps acted as potential wells, reducing the diffusion coefficient of polymers. The strongest trapping occurred when only $1 - C = 10\%$ of the obstacles were removed [9]. As more obstacles were removed, the traps became stronger, but also got larger, reducing the distance between traps. Eventually the traps

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all joined and they were no longer isolated: A percolating pathway was created and the diffusion coefficient rapidly increased towards the value $D(0)$ expected for a free chain.

This interesting non-monotonic transition between the reptation and Rouse limits is the non-trivial result of ET. However, one of the weaknesses of the previous study was that removing obstacles simultaneously increased both the degree of disorder in the array of obstacles and the free volume available to the chain. We now report a study of a similar system where we keep the number of obstacles constant and increase the amount of disorder by randomly moving the obstacles in the vicinity of their initial position. Due to the nature of the model we have a small decrease in the free volume available due to the creation of lakes (empty sites completely surrounded by obstacles), as well as channels which are too narrow (only one site wide) to allow a monomer to pass through. However, the change in the free volume is always less than seven percent. Thus, this model reduces the effect of changes in the obstacle density (concentration of the gel) and allows us a new look at the transition from a periodic distribution of obstacles (where polymer reptation is known to occur [10]) to a totally random distribution of obstacles (where ET is expected to dominate dynamics [11]).

The model used in our simulations is based on the two-dimensional Bond-Fluctuation Monte Carlo algorithm [12] (see Fig. 1) on a square lattice (whose mesh size is $a = 1$). This is the same model as used in previous simulation of entropic trapping done in our group, and has been described in detail in previous papers on this topic [9].

A polymer chain consists of N monomers (represented as one square plaquette on the lattice) which are linked by bonds which can vary between $2a$ and $\sqrt{13}a$ in length (this yields 36 possible bond vectors linking adjacent monomers). This, combined with the fact that two monomers cannot occupy the same

site on the lattice or touch one another, prevents bond crossing. A move consists of attempting to move a random monomer one site in the $\pm x$, or $\pm y$ direction. Monomer moves are accepted as long as the new bond lengths remain in the range $[2a, \sqrt{13}a]$ and there is no monomer or obstacle blocking the way. One Monte Carlo Step (MCS) consists of N such moves. The polymer is only added after the system of obstacles is properly prepared, so as to ensure that its presence does not affect the final obstacle layout.

Our obstacles are also represented as square plaquettes on the lattice that cannot overlap or touch one another. First, the obstacles are placed periodically to form a regular array with a simple square symmetry of periodicity $\lambda \geq 4a$. We make the lattice large enough (at least 5000 sites by 5000 sites, with periodic boundary conditions) that finite size effects are negligible.

We then add a tunable degree of randomness to the system by allowing each obstacle to move in the harmonic potential

$$U(r_i) = \frac{1}{2} K (\vec{r}_i - \vec{r}_{oi})^2 \quad (1)$$

about its initial position $\vec{r}_{oi}$, where K is the spring constant that controls the amount of disorder in the system. When $K \rightarrow \infty$, the obstacles do not move from their initial location and therefore remain periodic in space. The other extreme is when $K \rightarrow 0$: In this limit, the position of the obstacles take on a totally random (or disordered) distribution. Values of K between these two extremes will result in an intermediate amount of disorder in our obstacle distribution.

We displace the obstacles using monomer-like random moves that we accept, if there is no other obstacle blocking the move, with a probability given by a standard Metropolis test: $P = \exp\{-\frac{U(\vec{r}_{\text{new}}) - U(\vec{r}_{\text{current}})}{k_B T}\}$, where k_B is Boltzmann's constant and T is the temperature. The obstacles are prepared (or warmed up) for a total of 250 attempted moves per obstacle. The equilibrium distribution (neglecting volume exclusion) of the obstacles about their initial positions $\vec{r}_{oi}$ is given by the Boltzmann distribution

$$\rho(r) \sim \exp\left(-\frac{K r^2}{2k_B T}\right), \quad (2)$$

where $r^2 \equiv (\vec{r}_i - \vec{r}_{oi})^2$. Due to the finite number of attempted moves and volume exclusion effects between obstacles, our data does not fit this distribution perfectly, although it is very close (the $K = 0$ case is obviously special). Once we have completed this warm-up period, we quench the obstacles in place for the rest of the simulation. An approximate value (neglecting volume exclusion and the finite warm up time) for the root mean square obstacle displacement can easily be found by evaluating the simple Boltzmann sum

$$r_{\text{rms}} = \langle r^2 \rangle^{1/2} \approx \sqrt{\frac{\sum_{ij} r_{ij}^2 \exp(-\frac{K r_{ij}^2}{2k_B T})}{\sum_{ij} \exp(-\frac{K r_{ij}^2}{2k_B T})}}. \quad (3)$$

The difference between the values found using Eq. (3) and our simulations are tabulated in Table 1.

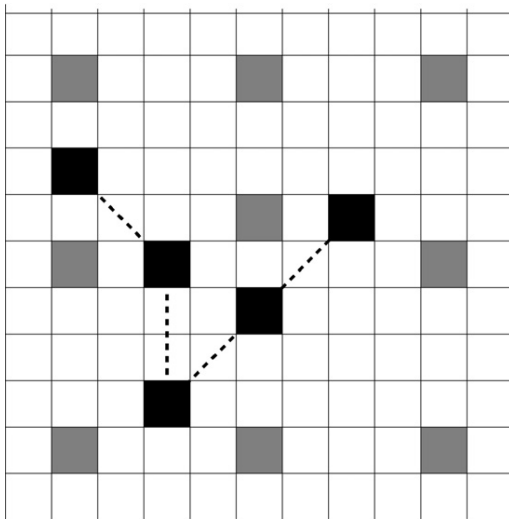


Fig. 1. A simple schematic representation of our simulation model. The grey boxes represent obstacles while the black boxes are monomers. The dotted lines show the bonds between adjacent monomers. The obstacles initially form a periodic array (here with a periodicity of 4). In this example, only the central obstacle was moved from its initial position in order to add some disorder in the system.

Table 1

Root mean square displacement of the obstacles: Here we show values of r_{rms} when $\lambda_0 = 4$ for various values of our disorder parameter K . The N stands for numerical results and are the exact solutions given by Eq. (3) for an obstacle in our harmonic potential, neglecting volume exclusion with the other obstacles and the finite warm up time. S stands for simulation and is the actual root mean square displacement observed in our simulations

K	40	20	10	9	8	7	6	5	4	3	2	1	0.5	0
N	9×10^{-5}	0.0135	0.163	0.209	0.266	0.338	0.425	0.532	0.656	0.801	0.999	1.41	2.00	∞
S	0	0.0138	0.164	0.209	0.265	0.338	0.425	0.532	0.655	0.799	0.982	1.33	1.85	12.1

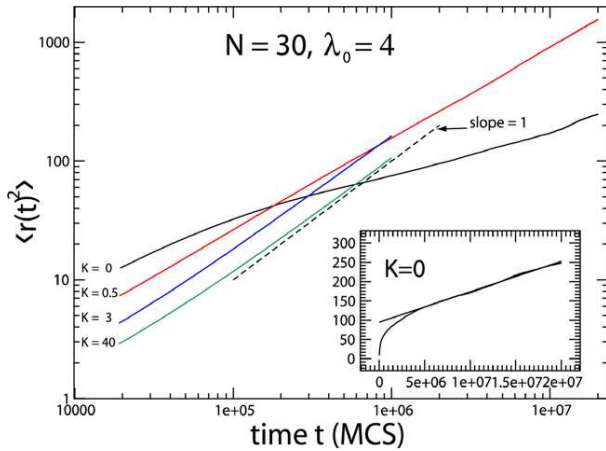


Fig. 2. Log-log plot of the mean squared displacement versus time. We observe anomalous diffusion (slope < 1) for short times when the array of obstacles is disordered. Inset: Cartesian graph showing the raw data for $K = 0$ together with the linear fit $\langle r^2 \rangle = a_0 + 4Dt$, giving the diffusion coefficient $D = 1.97 \times 10^{-6}$ and the correlation length $a_0 = 94.8$.

In most of our simulations, the initial separation between obstacles was set to $\lambda = 4a$. This is the smallest separation that will allow a polymer to be inserted in a periodic lattice. Placing the obstacles so close together causes them to strongly affect the diffusion of the polymer since the monomers will almost always be next to an obstacle. It is also the same separation that was chosen in previous studies mentioned above [8,9]. Larger values of λ gives similar results, but one requires longer polymer chains to observe significant entropic trapping. Note that we use non-dimensional units by expressing K in terms of $\frac{k_B T}{a^2}$, where $a = 1$ is the lattice step size. Similarly we non-dimensionalize the initial separation, λ , by setting $\lambda_0 \equiv \frac{\lambda}{a}$.

The quantity we will look at is the diffusion coefficient D , defined by

$$D = \lim_{t \rightarrow \infty} \frac{\langle [\vec{R}_{\text{cm}}(t) - \vec{R}_{\text{cm}}(0)]^2 \rangle}{4t}, \quad (4)$$

where $\vec{R}_{\text{cm}}(t)$ is the position of the center of mass of the chain at a time t . As reported previously [8,9,13], disordered systems produce anomalous diffusion for short times with the mean square displacement increasing as $\langle \Delta R_{\text{cm}}^2 \rangle \sim t^\beta$ and $\beta < 1$. As we can see in Fig. 2, this transient period can actually last for a long period of time and log-log graphs of $\langle [\vec{R}_{\text{cm}}(t) - \vec{R}_{\text{cm}}(0)]^2 \rangle$ versus t do not always allow us to clearly observe the asymptotic regime where the slope approaches one (see the $K = 0$ curve for example). For this reason, we instead calculate D by using the linear expression $\langle [\vec{R}_{\text{cm}}(t) - \vec{R}_{\text{cm}}(0)]^2 \rangle = 4Dt + a_0$ and restricting the fit to the long-time data (see inset of Fig. 2 for

an example). In order to identify the time scale over which normal diffusion occurs, we monitor the second derivative of the curve (it should be zero in the normal diffusion regime). The resulting value of the fitting parameter a_0 depends on both K and N , and represents the correlation length of the system, i.e. the distance over which the chain diffuses during the transient, anomalous regime.

In order to visualize the effect of ET let us consider the effective “entropic potential”, or free energy of the monomers. Let the probability of a monomer being at lattice site i be P_i . The entropic potential, in units of $k_B T$, of this site can then be defined as $W(i) = -\ln(P_i)$. Fig. 3 shows three free energy plots which compare where the monomers of a short chain ($N = 10$) spent their time during diffusion for three different values of the disorder parameter K . When $K = 8$ (which corresponds to a root mean square displacement $r_{\text{rms}} = 0.265$) (Fig. 3c), there is very little disorder in this small system and the monomers of the chain spent a fairly equal period of time on each site. When $K = 0$ (Fig. 3a), on the other hand, the system is almost completely disordered and very large spatial differences in the obstacle layout exist. In this case, the chain spent most of its time in a region with relatively few obstacles on the right side of the matrix, while avoiding the obstacle riddled area in the top left corner. In the intermediate $K = 4$ case ($r_{\text{rms}} = 0.655$), many obstacles are displaced by one or two lattice sites, but all the obstacles are still fairly localized about their initial positions, thereby not creating large obstacle free regions which would act as entropic traps. The result is apparently a percolating system of wider channels; the free energy plot (Fig. 3b) indicates that the chain has moved along these channels more frequently than through the thinner ones. Not surprisingly, these density plots will correspond to very different diffusion regimes.

Let us start our analysis of the diffusion data (Fig. 4) by looking at what happens when $K \gg 1$ (see also Fig. 3c). In this limit, the dynamics of the polymer chains is best described by the reptation model since the polymer chains migrate in a regular array of obstacles. However, since our chains are relatively short ($N \leq 30$), we expect strong finite-sized effects. It is interesting to note that the monomer free energy landscape is not completely flat (Fig. 3c). One can identify three types of sites here: Those in between two obstacles, those next to these sites, and finally the sites that are not adjacent to any obstacle. The three sites have roughly a 4 : 2 : 1 occupancy ratio. This purely geometric effect is an artifact of the algorithm chosen here (the lattice spacing $\lambda = 4a$ nearly matches the maximum bond length $\sqrt{13}a$ while lateral monomer motion is not allowed between two obstacles) and it is much weaker for $\lambda > 4a$ (not shown).

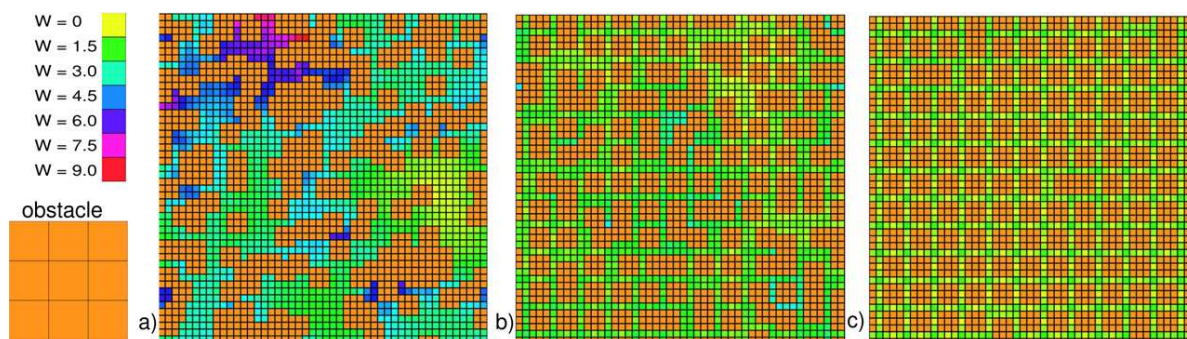


Fig. 3. Here we plot the entropic potential defined as $W = -\ln(P_i)$, where P_i is the probability of a monomer being at site i . For this example, we used a reduced lattice size (48 sites by 48 sites), and ran the simulation for 2.5×10^{10} MCS. This was enough time for our $N = 10$ polymer chain to fully explore the lattice several times. The three plots are for: (a) $K = 0$, (b) $K = 4$, and (c) $K = 8$. These values were chosen since they represent the three different regimes of diffusion seen in Fig. 4.

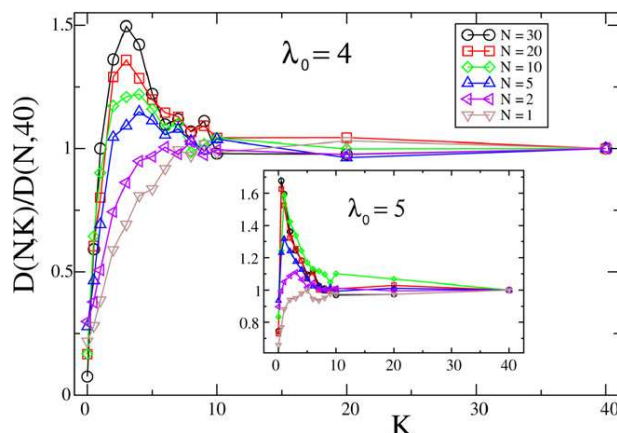


Fig. 4. Reduced diffusion coefficient $D(K)/D(K = 40)$ vs spring constant K for initial obstacle separation $\lambda_0 = 4$ and $\lambda_0 = 5$ (inset). The corresponding value of the root mean squared obstacle displacement for the main graph ($\lambda_0 = 4$) is shown in Table 1.

When “disorder” is added to our system (i.e., when K is reduced), we observe a remarkable and unexpected increase of the polymer’s diffusion coefficient D (Fig. 4). The maximum diffusion coefficient is observed around $K = 3$, which corresponds to root mean square obstacle displacement of order unity ($r_{\text{rms}} = 0.798$). We notice that the increase is larger for longer chains (reaching about 50% for $N = 30$), and that there is no increase for the monomer ($N = 1$) or the dimer ($N = 2$). Fig. 3b shows that this regime is characterized by wide channels that do not act as entropic traps because they are too small to house the whole polymer chain. Moreover, they form a highly connected (percolating) cluster that facilitate diffusion of long polymer chains over large distances. As usual, the free ends of the chain act like a probe biasing the diffusive motion to be through the more open areas. The wider tubes do not seem to affect the diffusion coefficient of smaller, non-reptating molecules. The increase in D is also partially due to a swelling in the radius of gyration which increases by about 7% for $N = 30$ (data not shown). The inset of Fig. 4 shows that when $\lambda_0 = 5$ this increase of D for intermediate amounts of disorder is of even greater magnitude.

Finally let us look at the ET regime, which occurs as K decreases further. In Fig. 4 we see that D drops for all values of N , including $N = 1$. The drop is slightly less significant for shorter chains. For our largest molecular size, $N = 30$, the diffusion coefficient drops by more than order of magnitude, a spectacular consequence of ET. In fact, both the magnitude of the increase in D around the critical value $K \approx 3$, and the magnitude of the subsequent drop at $K = 0$, increase with polymer size. It is somewhat surprising that the values of D at $K = 0$ for the longer polymer chains in the $\lambda_0 = 5$ case are only about 25% lower than those for the periodic lattice. However, the drop from the maximum value of D is still impressive and for longer chains we expect stronger ET. For the single monomer $N = 1$, the reduction of the diffusion coefficient is mostly due to the creation of dead-ends and the increased amount of tortuosity at low values of K . There is a small contribution due to the reduction of the free volume, but this change is insignificant compared to the change in D . The diffusion data is replotted in Fig. 5 as a function of N for various values of K ; similar to what was reported before [9], ET leads to a diffusion coefficient that decreases faster than what is predicted by the reptation theory ($D \sim N^{-3/2}$ in this case [14]). In the $K = 0$ case the data agrees roughly with a $D \sim N^{-5/2}$ power law as shown. Turning to Fig. 3a (which represents only a small system), we see that the free energy plot generated a strong entropic trap located on the right side of the lattice. The NW area, on the other hand, is long and narrow, giving chains in this region a very low conformational entropy; not surprisingly, the chain avoided this region.

In this Letter we looked at how randomly displacing obstacles from a periodic pattern affects the diffusion coefficient of a polymer chain with the help of the Bond-Fluctuation Monte Carlo algorithm. Like previous studies which looked at how the removal of obstacles from a perfectly periodic array of obstacles affected diffusion [8,9,13,14], we found that a disordered obstacle layout can cause a significant decrease in the diffusion coefficient.

The fact that slight perturbations of the obstacles on a periodic lattice create increased diffusion and cause a slower drop in the diffusion coefficient (see Fig. 5) as the chain length increases is an exciting new effect of weak disorder. There have

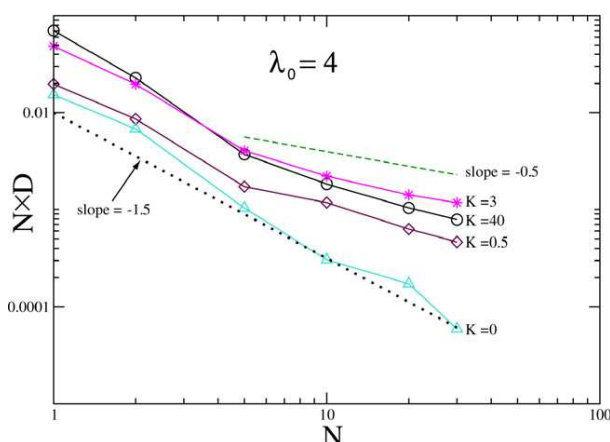


Fig. 5. Log-log plot of $D(N) \times N$ vs polymer size N . The dashed line shows the theoretical slope of -0.5 for polymer chains reptating in a fixed and periodic network of obstacles [14]. The dotted line gives an idea of the scaling of D with respect to N in the $K=0$ case (D appears to scale roughly as $N^{-5/2}$).

been many papers published about the dramatic reduction in the diffusion coefficient of polymers in disordered systems. Intuitively one would expect that as one transitions from a periodic array of obstacles to a random one there would be a monotonic decrease in D (or monotonic increase in ET). Here we demonstrated that in fact randomness caused by moving obstacles small distances actually increases the diffusion coefficient by increasing the width of the tube through which the polymer reptates. The competition between ET and increased tube widths

leads to a rather spectacular maximum in the diffusion coefficient as the amount of disorder is slowly increased.

Acknowledgements

This research was supported by an NSERC Discovery Grant to G.W.S. O.A.H. would like to acknowledge an entrance scholarship from the University of Ottawa as well as a scholarship from HPCVL. The latter also provided computational resources for this work. We would also like to thank the other members of our research group for helpful discussions and suggestions for this manuscript.

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