

Methods for Simulating Migration of Polymer Chains

1 D.G. WALKER

2 Department of Mechanical Engineering, Vanderbilt

3 University, Nashville, USA

4 greg.walker@vanderbilt.edu

5 Synonyms

6 Macromolecular transport; Active particle flows; Brownian dynamics

8 Definitions

9 Polymer chains are long flexible molecules usually associated with organic molecules such as DNA. Their transport is important to many medical screening applications and can be described using Monte Carlo or molecular dynamics approaches.

14 Overview

15 The motion of large molecules in microfluidic flows is important because the trajectories of particles in shear flows do not always follow the local flow field. Therefore, a knowledge of the fluid dynamics is not sufficient to completely describe the motion of the particles. When a suspended particle does not track the flow, the particle is said to be active as opposed to passive. The dynamics of active particles are particularly interesting in microfluidic devices because the molecules of polymer chains can approach – and even exceed – the characteristic lengths of the device. Consequently, the deviations between the particle/molecular motion and the fluid motion can be significant.

28 While active particle dynamics can address the motion of any suspended particle in a fluid, microfluidic researchers are usually interested in polymer chains because these structures in general do not follow the fluid flow, have a high degree of flexibility, and model important biological subsystems such as DNA and many types of proteins. If we want to track or manipulate different polymer chains in a microfluidic system, we need to understand their dynamics relative to the fluid flow. However, not only will the bulk motion deviate from what the fluid is doing, but also their conformation or shape can change, which alters the transport properties. In other words, as polymer chains travel in a fluid system, the inherent flexibility of the chains allow them to bunch up, stretch out or tumble in the flow. As the shape of the chain changes, the fluid forces imposed on the chain will also change. As a result, the motion of

a flexible chain will vary even if the flow field remains constant. For microfluidic systems designed to sequence or hybridize DNA, for example, the conformation can be as important as the trajectory of bulk motion of the molecule.

Basic Methodology

The adjective *macromolecular* is often used to describe transport of molecules in systems as opposed to transport within a molecule. This distinction can be important because some of the same methods can be used to treat both systems. Depending on the size of the system, two general methods could be used to describe molecular motion in a fluid.

1. Molecular dynamics is a fundamental approach that requires only the knowledge of forces between individual atoms. This approach is useful only for the smallest microfluidic systems because modern computational architectures can only handle a few million atoms and a single nanoliter of water contains over 10^{16} atoms.
2. Brownian dynamics approximates a molecule as a structure with limited degrees of freedom and with continuum forces.

This approach is useful for multi-scale simulations, which are characteristic of the vast majority of microfluidic systems. With this approach we no longer have to simulate each individual atom, but approximate the force due to a large group of atoms.

Molecular Dynamics

Molecular motion can theoretically be described using molecular dynamics. In this context, molecular dynamics describes the motion of a molecule in a fluid by accurately characterizing the force between any two atoms in the system including the molecules of the surrounding fluid. All forces in the system are summed and Newton's law is applied to each atom to deduce its individual motion. The motion of the molecule is deduced from the motion of its constituent atoms. Because of its fundamental nature, a molecular dynamics approach is often considered *ab initio* or "from first principles", meaning that there are virtually no fitting parameters required to obtain a physical solution. Nevertheless, the force between atoms, or interatomic potential, arises from a variety of chemical interactions (Van der Waals' force, chemical bonding, electrostatic) and in general, is difficult to characterize. (Discussion of the different potential fields and their application is beyond the scope of this article, but it should be noted that inter-atomic potentials often contain approximations and non-physical fitting parameters, so the *ab initio* designation is not always appropriate.)

TS1 Please note that the pagination is not final; in the print version an entry will in general not start on a new page.

TS2 Please keep in mind that all figures are to be printed in greyscale. Only the online version will be colored.

2 Methods for Simulating Migration of Polymer Chains

92	Applications for molecular dynamics in microfluidic systems include, for example, protein folding in solution, transport of amino acids in ion channels, and locally driven electro-osmotic flows with rigid particles. However, these applications do not involve the bulk motion of a fluid and are extremely small, specialized systems. In general, the systems that microfluidic researchers consider are multi-scale in that they require knowledge of the bulk fluid motion, far-field boundary conditions, interactions with other molecules, walls and fluid structures, and other experimental conditions. Consequently, the molecular dynamics approach is rarely feasible or even necessary for multi-scale systems. Instead, researchers and analysts rely on coarse-graining techniques to reduce the degrees of freedom, where tractable solutions are more accessible.	141
93		142
94		143
95		
96		
97		
98		
99		
100		
101		
102		
103		
104		
105		
106		
107	Coarse-Grained Models	
108	By coarse-graining, the molecular system is discretized and treated as a bead/spring system or bead/rod system. In the case of the bead/spring system, the molecule is treated as a series of beads with mass and size connected by springs. In the case of the bead/rod model, the molecule is treated a series of massless beads connected by rigid rods. The bead/spring system is simpler, but can allow the molecule to cross, which is unphysical, and is susceptible to computationally unstable solutions. The bead/rod model is mathematically and computationally more difficult, but the motion is often more realistic. In either case, the discretization or the number of beads used to model the chain is somewhat arbitrary but is chosen so that the behavior of the chain in a flow matches observations of the motion of actual chains. In the case of DNA, each base pair could be treated as a bead, but even this level of coarse-graining is usually far too fine to yield reasonable computational times and unnecessary to achieve accurate results. Instead, most simulations use anywhere from 5 to 20 sections depending on the complexity of the flow and resulting motion of the molecule that needs to be captured. Besides the reduction in the problem size, another advantage of coarse-graining is that the forces on the beads or rods can be described by continuum mechanics instead of requiring inter-atomic potentials. The forces common to most simulations include the following.	
109		
110		
111		
112		
113		
114		
115		
116		
117		
118		
119		
120		
121		
122		
123		
124		
125		
126		
127		
128		
129		
130		
131		
132		
133		
134	Drag	
135	Drag forces arise from the difference between a bead or rod's velocity $\dot{\mathbf{r}}_i$ and the local velocity field of the fluid \mathbf{u}_i , with the difference scaled by the drag coefficient ζ , giving	
136		
137		
138	$F_D = -\zeta(\dot{\mathbf{r}}_i - \mathbf{u}_i)$.	
139	The drag coefficient depends on the size of the bead. In the case of rods, the local flow field may not be uniform across	
140		
	the rod, which gives rise to moments on the object as well. Because the motion of a rod involves an additional angular acceleration, the computations are often more involved.	141
		142
		143
	Internal	144
	The internal forces for coarse-grained models can be considered elastic (bead/spring) or rigid (bead/rod). Regardless of the method, the force connecting adjacent beads does not represent inter-atomic forces, but merely constricts the distance between adjacent beads. In general, the effect of a shear flow is to stretch the molecule, so an attractive force is applied to keep the molecule intact. For the spring-like model, several non-linear forms of for the attractive force have been proposed. For more information about the types and physical basis for the mathematical form of these forces, the reader is referred to [1, 2]. Although the rigid model (bead-rod chains) introduces an added level of complexity due to constraints on the motion, the results obtained using the bead-rod model are more accurate for a fewer number of beads. Furthermore, for more complex situations such as electric field induced motion and obstacle navigation, the bead/rod formalism is often considered more robust.	145
		146
		147
		148
		149
		150
		151
		152
		153
		154
		155
		156
		157
		158
		159
		160
		161
		162
	Electrostatic	163
	A myriad of conditions could give rise to non-uniform charge distributions in the fluid. For example, electroosmotic flows or solutions of electrolytes are often used to manipulate microfluidic flows. In these situations, the macromolecule may be subject to Coulomb forces. There is no general expression to account for these forces, but they will depend on the location and strength of the charge distribution the fluid as well as along the molecule.	164
		165
		166
		167
		168
		169
		170
		171
	Image	172
	The force of the wall is modeled as a steep potential near a physical barrier. The force is called an image potential because the magnitude is derived from a phantom particle that is placed on the perpendicular to the wall and the particle near the wall. The phantom particle is exactly the same as the particle being repulsed, and the repulsive force is the force between two neighboring particles (instead of the wall). This approach allows one to consider variations in forces that arise from the particles without having to treat the wall differently.	173
		174
		175
		176
		177
		178
		179
		180
		181
		182
	Brownian	183
	All other forces are essentially continuum forces, i. e. they would be present for a large-scale strand of beads and are not specific to molecules. The Brownian force, on the other	184
		185
		186

187 hand, is only present for very small objects. This force
 188 is the result of individual atoms and other molecules in
 189 the flow bumping into the macromolecule to change its
 190 conformation. In the continuum limit, enough momentum
 191 exchange occurs in all directions so that the net force is
 192 zero. For small objects, the net force is some non-zero ran-
 193 domly oriented force that goes to zero over long times.
 194 However, in some non-equilibrium situations such as near
 195 walls, the Brownian force can be non-uniform.

196 Hydrodynamic

197 Objects in the wake regions of other objects are known to
 198 experience different flow characteristics compared to the
 199 bulk motion of fluid. Therefore, some beads in a macro-
 200 molecule do not sample the bulk fluid, but a modified ver-
 201 sion of the bulk fluid because of the proximity of other
 202 beads in the flow. A great deal of research has gone into
 203 developing techniques and approximations to attempt to
 204 include this effect with varying degrees of success. The
 205 difficulty lies in the attempt to invent a general solution
 206 to a problem that is dependent on geometry, discretiza-
 207 tion of the molecule and flow characteristics. Discussion
 208 of these details are beyond the scope of this article. Instead
 209 the reader is referred to [3].

210 Other External

211 Many other forces could conceivably be important in
 212 macromolecule flows. For example,

- 213 1. magnetic forces could arise when dealing with mag-
 214 netized particles in conjunction with macromolecules,
 215 which is often done in drug delivery and targeting.
- 216 2. Gravitational forces may be important if transport
 217 occurs in a centrifuge.
- 218 3. Many experiments also track macromolecules with flu-
 219 orescent dyes. If the dye molecule is of the order of the
 220 transported molecule, then the dye can introduce addi-
 221 tional drag.
- 222 4. Hybridization of DNA can provide a force at the ends
 223 of the macromolecules that tether the molecule to a sur-
 224 face.
- 225 5. Van der Waals forces can arise between polar objects.
 226 Once the forces acting on the molecule are known, two
 227 approaches can be used to solve for the dynamics behav-
 228 ior of the particles. Boltzmann-based models (also called
 229 Fokker–Planck systems) can predict average quantities
 230 through calculation of a distribution function.

$$\begin{aligned} \frac{\partial f}{\partial t} &= \sum_i \left(m_i^{-1} p_i \frac{\partial f}{\partial r_i} + F_j \frac{\partial f}{\partial p_i} \right) \\ &= \sum_i \sum_j \frac{\partial}{\partial p_i} \zeta_{ij} \left(m_j^{-1} p_j f + kT \frac{\partial f}{\partial p_j} \right). \end{aligned} \quad (1) \quad 231$$

232 Moments of f result in an average displacement field. This
 233 approach has largely been supplanted by non-averaging
 234 techniques because of molecular individualism [3]. In
 235 other words, instead of calculating average displacements,
 236 the behavior of individual molecules are of more interest
 237 in modern macromolecule transport.

238 To determine specific molecular motions, the Langevin
 239 approach is relatively straightforward and involves inte-
 240 grating Newton's second law

$$\sum_i F_{ij} = m_j a_j = m_j \frac{d^2 x_j}{dt^2} \quad (2) \quad 241$$

242 over time to calculate the displacement (motion) of each
 243 bead. In equation 1, i indexes each force acting on a bead
 244 and j indexes the beads in the simulation. Tractable solu-
 245 tions to this motion are only possible when time is dis-
 246 cretized into tiny steps. Over each time step, the forces
 247 and acceleration are assumed constant. The integration
 248 scheme varies with the discretization of the molecule
 249 and type and magnitude of the forcing functions that are
 250 present. However, most generally applicable schemes are
 251 second-order accurate and involve some leap-frog tech-
 252 nique where velocities are calculated at the half-time step.
 253 The two primary difficulties are including the Brownian
 254 force and the hydrodynamic interactions because these
 255 two forces are not independent of the solution resulting
 256 in a non-linear system of equations. If we assume that
 257 the momentum relaxation is much faster than the posi-
 258 tion relaxation of the Brownian particles, then the result-
 259 ing equations can be simplified with a diffusion tensor that
 260 represents the influence of the Brownian force on average
 261 displacement [1].

$$\langle \Delta r_i \rangle = \sum_j \left(\frac{\partial D_{ij}^0}{\partial r_j} + \frac{D_{ij}^0}{kT} F_j^0 \right) t, \quad (3) \quad 262$$

263 where the summation index spans the particles in three-
 264 dimensional space. In the foregoing expression, the time
 265 is assumed to be greater than the momentum relaxation,
 266 i. e. $t \gg \tau^0 = mD/kT$. The Oseen tensor is often used for
 267 D_{ij} [2], but appropriate expression of this diffusion com-
 268 ponent is the subject of a great deal of research.

The prediction of molecular motion is only as good as the effective forces that act between beads or rods. In the case of rigid rods connected by rotating joints, Kramer's bead chain rod system is the prevailing model. In this approach, the total length of the polymer is fixed, which may not be physically realistic in many cases. Yet, this model prevents the molecular strand from crossing itself, which is also physically unrealistic. The displacement of the beads is usually predicted from an optimization using the inter-bead distance as an internal constraint. For the bead-spring, models several different forms of inter-bead potentials have been used. The simplest model has a linear spring between each bead. This model tends to allow too much displacement, so an inverse Langevin model is used to stiffen the spring for larger displacements, which can be approximated as

$$F_j = \frac{Gr_i}{1 - (\frac{r}{r_0})^2} \quad (4)$$

where G is the spring constant and r_0 is the relaxed molecule length. For DNA molecules, a worm-like chain model has proven remarkably successful, which has several forms that can be useful.

Key Research Findings

Research in macromolecular transport using Brownian dynamics is either fundamental in that a parameterized class of fluid flow conditions is considered, or a particular experiment is modeled with well-known geometric and fluid conditions.

In the study of molecular transport and conformation in simple flows, results suggest that the motion is not very simple. Many polymers have fairly complex shapes when in a quiescent fluid. They can be coiled, straight, curved or a combination of different shapes as seen in Fig 1. This tendency is important when discussing the transport in a shear flow. Both simulations and experiments produce molecular shapes described as coils, dumbbell, linked, half dumbbell, straight and folded, all in a single longitudinal shear flow. Moreover, for varying flow parameters, the shape can transition between the different forms, and the transition is unpredictable. Similarly, in linear shear flows, the motion can be characterized as longitudinal (perpendicular to the shear direction), tumbling, or globular. Transition between flows can occur without changing flow parameters. The transition rate, however, is usually governed by the strength of the shear.

These results suggest that control of a single polymer chain in a flow is difficult because of the unpredictability of any specific molecule. However, we are usually interested in

the motion of a large number of molecules in a microfluidic system. Therefore, statistics are collected on a single molecule given a variety of initial conditions, for example. Then predictions about the average behavior of certain types of molecules in certain types of flows can be made. The non-dimensional Weissenberg number ($Wi = \dot{\gamma} \lambda$) is defined as the product of fluid strain rate ($\dot{\gamma}$) and the longest relaxation time of the polymer chain (λ). This number provides an approximation to the ratio of ability of the flow to stretch the polymer chain divided by the tendency of the chain to resist stretching. For large Wi , the flow generally results in stretching of the molecule; for small Wi , the molecule's conformation is dominated by Brownian motion.

Other studies of polymer transport focus on how long molecules behave in a complex flow in the presence of obstacles. For example, one group has examined how DNA migrates through a field of posts where the strands straddle the obstacle. Simulations of this type are useful to help predict the resident time of DNA in a particular region. This might be important to researchers who are using micro-fluidic chambers to produce chemical reactions with DNA, for example.

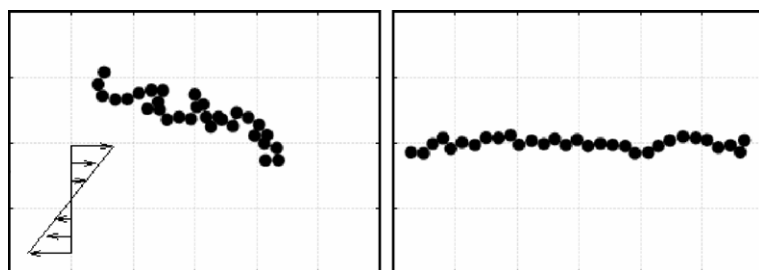
Future Directions for Research

Two research directions emerge from existing studies and needs in the community. (1) Fundamental studies focus on the physics governing the relationship between the forces acting on the beads. (2) Applied studies focus on how molecules behave in different systems.

In terms of fundamental studies, modeling of polymer chains is still in its infancy. Although there are plenty of instances where experiments and simulation converge, there is no general purpose, all-encompassing simulation approach that works universally. The primary difficulty arises from resolving the relative strengths of each force acting on the molecule. In isolation, each force can be described mathematically with a good deal of rigor. However, the relative magnitude of each force relies on difficult to characterize free parameters. Therefore, simulations still rely on experiments to provide data for accurate simulations. A first-principles simulation is simply not possible yet. Consequently, much of the current research is devoted to refining the force models to include more physics in simulations.

In terms of applied studies, different configurations are constantly being addressed to help analyze specific experimental studies and to help provide ranges for the free parameters associated with the forces.

To address both of these concerns, the following areas are suggested as immediate research areas where substantial



Methods for Simulating Migration of Polymer Chains, Figure 1 Conformation of a 30-bead chain in a linear shear flow at different times. The chain shown will exhibit a periodic tumbling motion if observed for long periods of time

366 contributions can be made.

367 Complex Flows

368 Most fundamental simulations examine simple flow situations such as elongation and linear shear flows. These
369 flows appear in many micro-fluidic structures, and include
370 a wide range of effects that molecules might experience.
371 In addition, the flow solution is simple and can be reliably
372 produced in the lab. Therefore, there is continued need
373 to investigate these configurations. However, these simple
374 flows do not represent all situations seen in modern
375 micro-fluidic devices. For example, stagnation point flow
376 into a stationary wall, flow around corners and flow mixing
377 are all complex phenomena that affect polymer chain
378 transport and conformation.
379

380 Overlap Models

381 Although the bead spring model appears adequate for
382 many situations, more complex flows can cause interaction
383 of a molecule with itself. For bead-spring models, this
384 can be treated by introducing strong, short-range potentials.
385 Because of the large gradients, however, simulations
386 are prone to exaggerated motion when beads non-
387 adjacent beads approach each other. The bead-rod model
388 attempts to account for the interaction by preventing the
389 coarse-grained model of the chain from crossing itself.
390 This approach can be relatively complex and a universally
391 agreed upon approach has not been established.

392 Wall Interaction

393 Typically a wall is modeled with an image potential. In this
394 case, a virtual particle that is located at the mirror location
395 to the real particle provides an interaction potential.
396 As such there is often an artificial buffer that prevents the
397 bead from contacting the wall and migration away from
398 surfaces is possible. Even though these interaction potentials
399 have a short range, they can be strong to prevent beads

from penetrating walls. As a results time stepping becomes
400 crucial and too large a step can result in physically unreal-
401 istic motion. New methods to treat this artifact are needed
402 to provide transport in confined channels.
403

DNA Hybridization 404

405 In the case of DNA transport, the researcher is often inter-
406 ested in hybridization, which is a reaction that changes
407 the characteristics of the chain or causes additional forces.
408 Motion in the presence of interaction particles is complex
409 and has not received much attention.

Cross References 410

- ▶ Brownian Motion and Diffusion 411
- ▶ Dielectrophoretic Motion of Particles and Cells 412
- ▶ Dissipative Particle Dynamics 413
- ▶ Electrokinetic Flow and Ion Transport in Nanochannels 414
- ▶ Electroosmotic Flow 415
- ▶ Multiscale Modeling and Numerical Simulations 416
- ▶ Molecular Dynamics Simulation Method 417
- ▶ Polymer Synthesis Within Microfluidic Reactor 418
- ▶ Van der Waals Interaction Forces 419

References 420

1. Ermak DL, McCammon JA (1978) Brownian dynamics with hydrodynamics interactions. *J Chem Phys* 69(4):1352–1360 421
2. Yamakawa H (1971) *Modern Theory of Polymer Solutions*. Harper and Row, New York 422
3. de Gennes PG (1997) *Polymer Physics: Molecular Individualism*. *Science* 276(5321):1999–2000 423
4. Marko JF, Siggia ED (1995) Stretching DNA. *Macromol* 28(26):8759–8770 424
5. Hur JS, Shaqfeh ESG, Babcock HB, Chu S (2002) Dynamics and Configurational Fluctuations of single DNA Molecules in Linear Mixed Flows. *Phys Rev E* 66(011915) **TS3** 425

TS3 Please check page range.

6 Methods for Simulating Migration of Polymer Chains

- 432 6. Schroeder CM, Shaqfeh ESG, Chu S (2004) Effect of Hydro-
433 dynamic Interactions on DNA Dynamics in Extensional Flow:
434 Simulation and Single Molecule Experiment. *Macromolecules*
435 37:9242–9256

Uncorrected Proof
2007-11-09