

Methods for Simulating Migration of Polymer Chains

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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.)

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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
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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.	
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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	
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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	
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	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
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	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
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	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
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	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
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	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
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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.

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

$$285 \quad F_j = \frac{Gr_i}{1 - (\frac{r}{r_0})^2} \quad (4)$$

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

290 Key Research Findings

291 Research in macromolecular transport using Brownian
 292 dynamics is either fundamental in that a parameterized
 293 class of fluid flow conditions is considered, or a particu-
 294 lar experiment is modeled with well-known geometric and
 295 fluid conditions.

296 In the study of molecular transport and conformation in
 297 simple flows, results suggest that the motion is not very
 298 simple. Many polymers have fairly complex shapes when
 299 in a quiescent fluid. They can be coiled, straight, curved
 300 or a combination of different shapes as seen in Fig 1.
 301 This tendency is important when discussing the transport
 302 in a shear flow. Both simulations and experiments produce
 303 molecular shapes described as coils, dumbbell, linked, half
 304 dumbbell, straight and folded, all in a single longitudi-
 305 nal shear flow. Moreover, for varying flow parameters, the
 306 shape can transition between the different forms, and the
 307 transition is unpredictable. Similarly, in linear shear flows,
 308 the motion can be characterized as longitudinal (perpen-
 309 dicular to the shear direction), tumbling, or globular. Tran-
 310 sition between flows can occur without changing flow
 311 parameters. The transition rate, however, is usually gov-
 312 erned by the strength of the shear.

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

316 the motion of a large number of molecules in a micro-
 317 fluidic system. Therefore, statistics are collected on a sin-
 318 gle molecule given a variety of initial conditions, for exam-
 319 ple. Then predictions about the average behavior of certain
 320 types of molecules in certain types of flows can be made.
 321 The non-dimensional Weissenberg number ($Wi = \dot{\gamma} \lambda$) is
 322 defined as the product of fluid strain rate ($\dot{\gamma}$) and the
 323 longest relaxation time of the polymer chain (λ). This
 324 number provides an approximation to the ratio of ability
 325 of the flow to stretch the polymer chain divided by the ten-
 326 dency of the chain to resist stretching. For large Wi , the
 327 flow generally results in stretching of the molecule; for
 328 small Wi , the molecule's conformation is dominated by
 329 Brownian motion.

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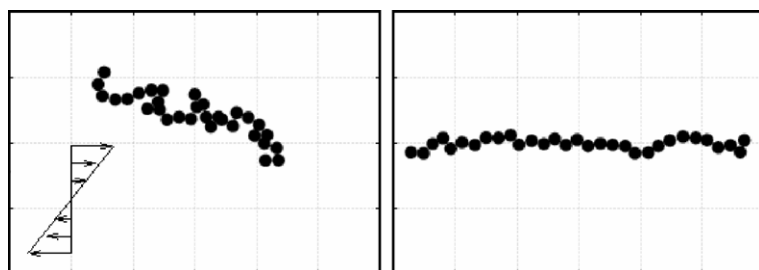
339 Future Directions for Research

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

345 In terms of fundamental studies, modeling of polymer
 346 chains is still in its infancy. Although there are plenty
 347 of instances where experiments and simulation converge,
 348 there is no general purpose, all-encompassing simula-
 349 tion approach that works universally. The primary diffi-
 350 culty arises from resolving the relative strengths of each
 351 force acting on the molecule. In isolation, each force can
 352 be described mathematically with a good deal of rigor.
 353 However, the relative magnitude of each force relies on
 354 difficult to characterize free parameters. Therefore, simu-
 355 lations still rely on experiments to provide data for accu-
 356 rate simulations. A first-principles simulation is simply not
 357 possible yet. Consequently, much of the current research
 358 is devoted to refining the force models to include more
 359 physics in simulations.

360 In terms of applied studies, different configurations are
 361 constantly being addressed to help analyze specific exper-
 362 imental studies and to help provide ranges for the free
 363 parameters associated with the forces.

364 To address both of these concerns, the following areas are
 365 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
 crucial and too large a step can result in physically unreal-
 istic motion. New methods to treat this artifact are needed
 to provide transport in confined channels.

DNA Hybridization

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

Cross References

- ▶ 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

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6 Methods for Simulating Migration of Polymer Chains

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Uncorrected Proof
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