Dynamic Simulation of a Polymer Molecule Using COMSOL Multiphysics: DNA Separation in a Microchannel

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Introduction

DNA separation is used in a wide array of applications such as DNA characterization, fingerprinting, diagnosis and genome sequencing. Separating DNA by traditional methods, such as gel electrophoresis, can be time consuming and inefficient. Using microfluidic devices for DNA separation has been studied and deemed a more efficient separation method. However, the design and fabrication of such devices by trial-and-error can be time-consuming and costly. There have been computational studies finding the optimal design and investigating separation mechanisms within these devices. However, to the best of our knowledge, there hasn't been any application using commercial software to perform simulations of these systems. This is the first trial, where COMSOL Multiphysics® is used to simulate polymer dynamics [1]. This simulation study will open a new page for the application of COMSOL Multiphysics to the field of polymer dynamics and microfluidic device design. This study will also have an impact on biomedical applications involving the manipulation of biopolymer molecules. Among the many types of DNA separation methods, we focus on the separation of DNA by entropic traps. This type of separation consists of an array of structured microfluidic channels through which polymer molecules flow [2, 3].

Background

It was found that DNA molecules can be separated based on their chain length using a series of structured microchannels with periodically different channel heights, also known as entropic trap arrays, where the narrow channel gap is much smaller than the gyration diameter ($2R_g$) of a DNA molecule, as depicted in **Figure 1**.

When negatively charged DNA molecules are driven through the narrow and wide channels by electrophoretic forces, the interactions between the DNA molecules and the channel causes length-dependent elution times. It was observed that longer DNA molecules usually had a larger mobility (faster elution) than smaller DNA molecules. This is opposite to the behavior exhibited by free-draining DNA molecules. The reason behind this counter-intuitive separation mechanism was investigated. It was found that longer DNA molecules have a higher probability of being sucked into the small channels, instead of stagnating in the larger channels, due to the longer molecules occupying more surface area [2, 3].

Figure 1. A 2D schematic view of an array of entropic traps. A DNA molecule in a wide channel is flowing into a narrow channel.

Many simulations have been performed to study the details of this separation mechanism. A simulation study by Streek et al. discovered a corner diffusion mechanism for the slower elution of a shorter DNA molecule: If the diffusivity of a DNA molecule is strong relative to the field strength, it tends to stay trapped in the corner of the wider channel [4]. There were simulation studies using the Dissipative Particle Dynamics simulation, which investigated the separation mechanism in 3D simulation and discussed the effect of hydrodynamic interactions [5]. Additionally, various entropic trap designs continue to be created. [6-15].

Governing Equations / Numerical Model

In this study, a Brownian dynamics (BD) simulation was performed using a coarse-grained bead-spring model to represent the semi-flexible dynamic nature of a λ-DNA molecule in the entropic trap channel. A coarse-grained model of a λ-DNA molecule consists of N_b beads and $N_b - 1$ springs. The bead-spring

model is a well-known model for polymer dynamics and has been commonly used to study DNA dynamics in various type of microfluidic devices [1, 16]. The bead positions are determined by calculating sum of imposed forces on the beads at each time step. This is shown in equation (1).

$$\frac{d\left(m_p \frac{dr_i}{dt}\right)}{dt} = F_i^D + F_i^B + F_i^S + F_i^E + F_i^V \qquad (1)$$

Here, m_p represents the mass of a bead, the subindex i denotes each bead, and r_i is the position of the bead at the corresponding time-step. F_i^D is the friction force which can be calculated using Stoke's drag law:

$$F_i^D = \zeta \frac{dr_i}{dt} \qquad (2)$$

where ζ is a drag coefficient which represents the fluid friction exerted on the bead, i, which is moving through the solvent. For the case of spherical objects:

$$\zeta = 6\pi\mu r_p \qquad (3)$$

In equation (3), μ is the dynamic viscosity of the fluid and r_p is the bead radius. F_i^B is the Brownian force. F_i^S is the net spring force. F_i^E is the electrophoretic force exerted on the charged beads. F_i^V is excluded volume force of the bead that prevents the beads from overlapping in the simulation.

The Brownian force is derived for spherical beads by considering the fluctuation-dissipation theory:

$$F_i^B = \sqrt{\frac{6k_B T \zeta}{\Delta t}} w_i(t) \qquad (4)$$

where k_B is Boltzmann constant, T is the absolute temperature in Kelvin, and $w_i(t)$ is a random vector of a uniform distribution with a mean of 0 and a variance of 1. Each bead represents 4850 base pair long segment of the chain. Bead diameters are fixed to be $a = 77\ nm$ and the Worm-Like Chain (WLC) model springs, located between beads, follow the Marko-Siggia force rule:

$$F_{ij}^S = \frac{k_B T}{2b_k}\left[\left(1 - \frac{|r_j - r_i|}{N_{k,s} b_k}\right)^{-2} - 1 + \frac{4|r_j - r_i|}{N_{k,s} b_k}\right]\frac{r_j - r_i}{|r_j - r_i|} \qquad (5)$$

where b_k is the Kuhn length for λ-DNA. $N_{k,s}$ is the number of Kuhn lengths in a spring, which is 20 for our simulation. Note here that the WLC model for spring forces is the most commonly used model in dynamic DNA simulations [17, 18].

The force exerted by electrical field can be expressed by:

$$F_i^E = qeE \qquad (6)$$

where q is the charge number for each bead, e is electron charge, and E is the electrical field. q was calculated by a method explained in a previous work by Tessier et al. [8], and is -178 for each bead.

The interaction between the beads is described by the Lenard-Jones pairwise repulsion model and simulates the excluded volume of the beads:

$$F_i^V = \frac{24\varepsilon}{\sigma}\left[2\left(\frac{\sigma}{|r_j - r_i|}\right)^{13} - \left(\frac{\sigma}{|r_j - r_i|}\right)^7\right]\left(\frac{r_j - r_i}{|r_j - r_i|}\right) \qquad (7)$$

In equation (7), σ is the bead diameter and ε is repulsion energy. By substituting equations (2-5) into equation (1), the empirical model for the DNA chain is created and the DNA conformation through time can be derived. In our simulation, walls are assumed to be bouncy and bead interactions are defined by:

$$v_i = v_i^{old} - 2(\mathbf{n} \cdot v_i^{old})\mathbf{n} \qquad (8)$$

where v_i is a bead's velocity.

Simulation

The geometry of this device was defined in an earlier work [6] and it is shown in **Figure 2**. The length of each period was $L = 10\mu m$, and ratio of the wide channel length to that of the narrow channel was 1.0. Height of the wide region and narrow region were respectively, $H_L = 1.0\ \mu m$ and $H_s = 90\ nm$. H_s is much smaller than the gyration diameter of a typical λ-DNA molecule (around $760\ nm$). This fulfills an entropic array structural requirement mentioned earlier in this paper.
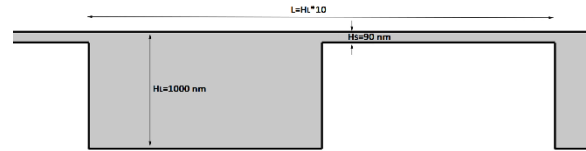

Figure 2. Channel structures used in simulations.

The Electric Currents Physics of the AC/DC module was chosen to calculate the steady state electric field across the channel, of which governing equation can be described as:

$$\nabla^2 \Phi = 0 \qquad (9)$$

Here, the electric field of potential is denoted by Φ. The mesh was selected to be extremely fine considering the large height difference between the wide and narrow channels. While the time needed to calculate simulation results can be adversely affected by increasing the sensitivity of the mesh used, in this case it did not. The electrical field was created by applying a potential of V_0 and $-V_0$ at the two ends of the channel, while the rest of the walls were assumed to be insulated walls.

The Laminar Flow Physics of the Fluid Flow module and the Particle Tracking for Fluid Flow Physics of the Particle-Tracing module were selected to simulate a DNA molecule as a bead-spring model within a Newtonian fluid. The beads are represented as particles and are connected to each other by spring forces. There was no inlet or outlet fluid flow to the channel because DNA is moved only by the electric field, not by flow. Therefore, no slip boundary condition was given to all the walls. Particles, or beads, were assumed to be reflecting whenever they collided with the wall borders. This was done by selection the bounce option in the Settings for the wall. Brownian and drag forces were added to the module setting from the force options provided by the module. To couple the existing electrical field with the main

equation of the charged beads, the Electric Force was added to the forces acting on the beads.

Spring force effect was defined by adding a custom Particle-Particle interaction to the settings. Particle-Particle Interactions are effective for all present beads. Therefore, the software does not discriminate between the beads and connects all existing beads with springs. To avoid this, a custom condition was added to the equation that made the software recognize the beads within its vicinity. **Figure 3** summarizes how the custom forces were implemented.

Another custom Particle-Particle interaction was added to the settings to represent the excluded volume force between the beads. A sort of modified Lennard-Jones equation was employed in a package, the second term on the right-hand side of equation (7) was removed to prevent the beads from collapsing into each other during simulation.

The absolute error tolerance is a tricky parameter to define. Very large values will result in weak and inaccurate results (abs_err: 1e-6 – 1e-7), while choosing very small values for absolute error tolerance drastically extends the simulation time (abs_err< 2e-8).
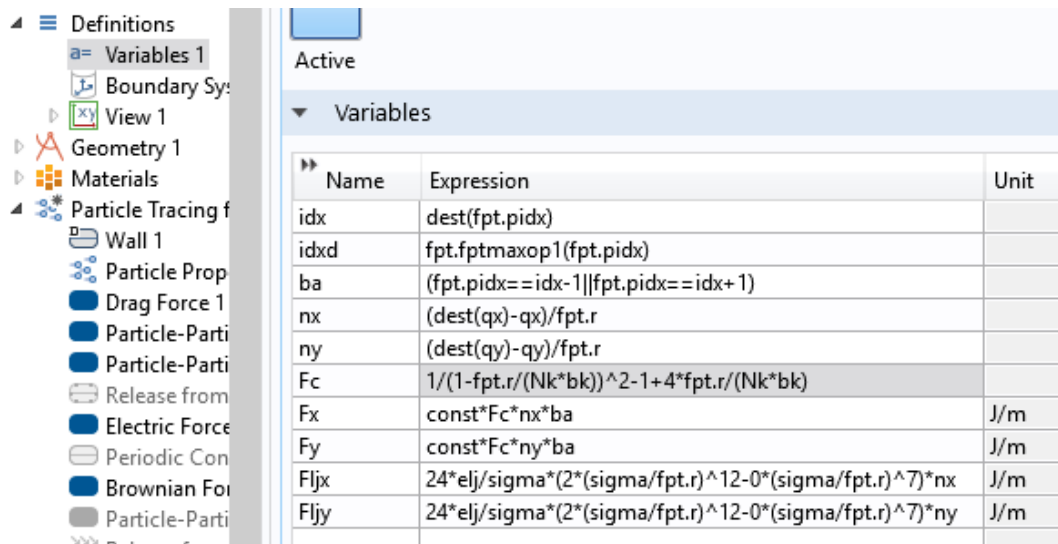

Figure 3. Screen capture of the Particle-Particle Interaction custom force definition. (Fx and Fy are spring force, Fljx and Fljy are excluded volume force).

Experimental Results / Simulation Results / Discussion

A nonuniform electrical field was calculated by solving equation (9) using FEM method. **Figure 4** shows qualitative point vectors of the solved electrical field.

We simulated the center-of-mass trajectory of N_b=2, 4 and 16 bead long DNA molecules flowing in the periodically constricted channel. The simulated trajectories of those DNA molecules traveling the same distance in the channel (from entering and exiting a larger channel) are shown in **Figure 5**. As expected from the electric field line in **Figure 4**, DNAs are moving faster in the narrow channels. As the DNA molecules are longer (more beads) the molecule moves faster. It is also observed that shorter (less beads) DNA molecules have nosier trajectories due to their stronger diffusivity. This indicates that the stronger diffusivity (Brownian force) of shorter DNA molecules slows their flowing through entropic trap channels by moving them off electric field lines.

Figure 6 compares the snapshots of a short (N_b=2) and a long (N_b=16) DNA flowing into and out of a wide channel in an entropic trap channel. It can be seen that the larger the surface area of a DNA molecule the more likely the molecule will be dragged into the smaller channel. These findings from our simulation agree with the findings observed in the study by Han et al. [2].
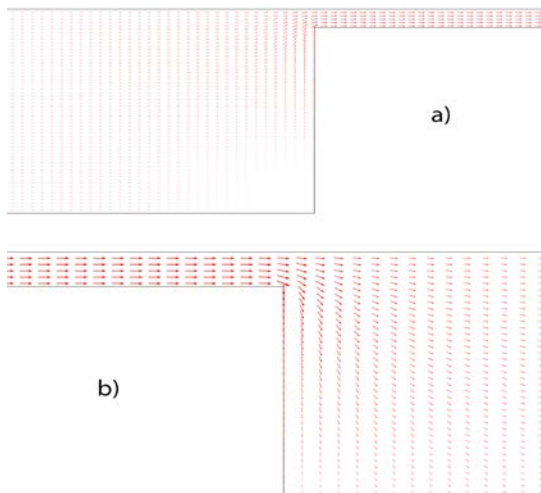

Figure 4. Simulated results of the electrical field flux vectors in **(a)** the right corner and **(b)** the left corner of a wide channel.
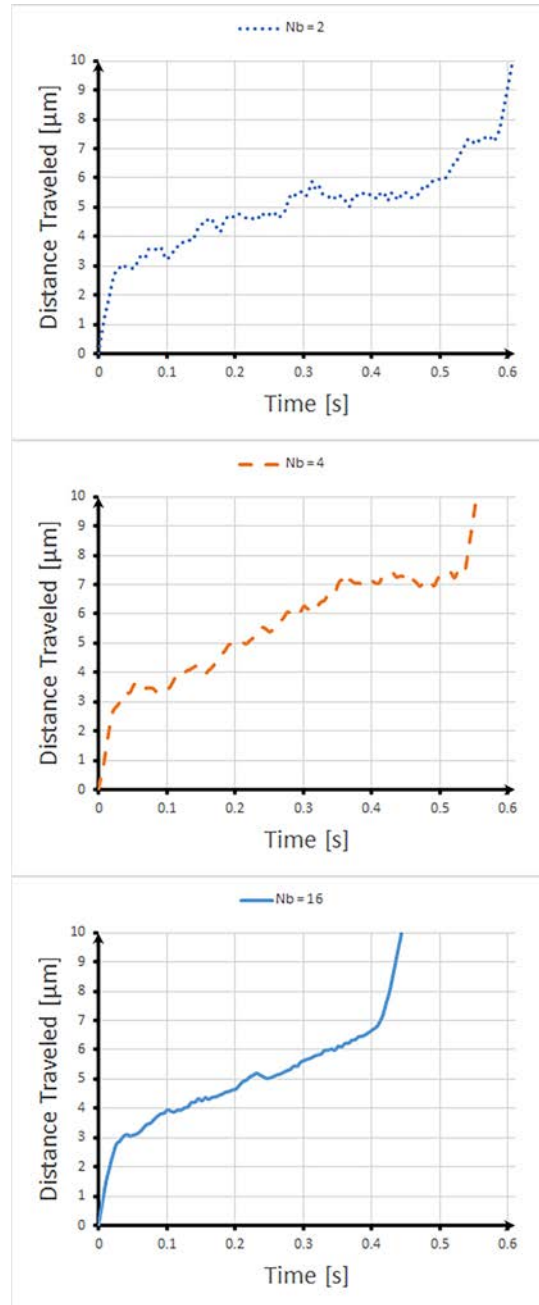

Figure 5. Simulated center-of-mass trajectories of DNA with N_b=2,4 and 16. The starting position and time is set when the center-of-mass of a DNA is passing at the center of a narrow channel.
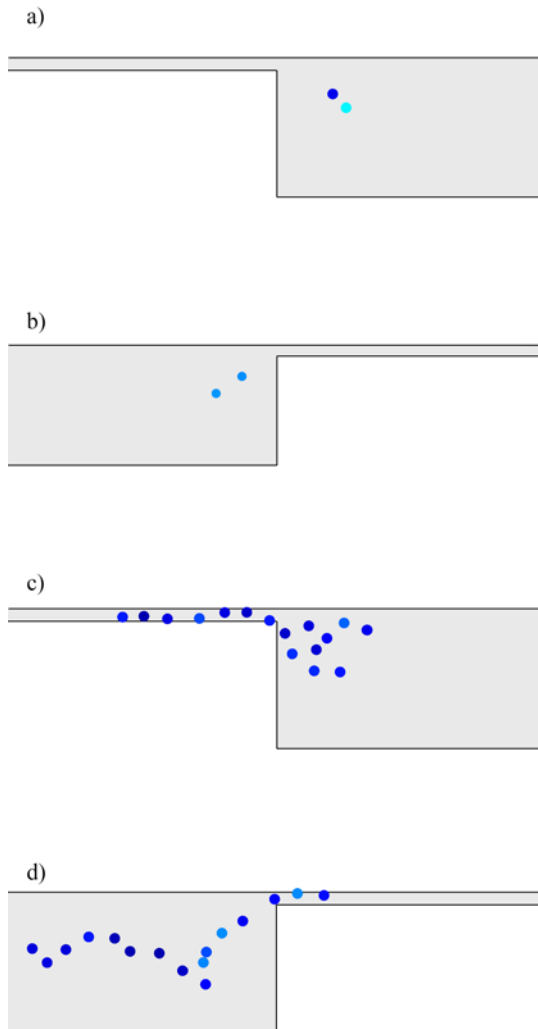
Figure 6. Snapshots of a shorter DNA molecule with N_b=2 and a longer DNA molecule with N_b=16, flowing into and out of a wide channel in an entropic trap channel: **a)** $N_b = 2$ at $t = 0.040$s, **b)** $N_b = 2$ at $t = 0.55$s, **c)** N_b =16 at t =0.025s, and **d)** $N_b = 16$ at $t = 0.38$s.

Conclusions

We successfully performed a Brownian coarse-grained bead-spring simulation of a λ-DNA molecule with various contour lengths in a periodically constricted channel using COMSOL Multiphysics®. The simulation results show good agreement with the previous results found by other researchers. To our knowledge, this is the first time that a DNA molecule or a single polymer molecule has been simulated using COMSOL Multiphysics®. It is expected that the computational time is expected to take much longer for BD simulation of DNA with more beads. However,

due to COMSOL's user-friendly graphic user interface and the easy analysis tools, we believe that our simulation can be a good example to be disseminated to the DNA dynamics research communities. Moreover, nonuniform field calculations in complex geometries can be easily calculated using COMSOL. This tends to be a time-consuming process in many other software programs.

The equation of motion of the beads provided in the module contains the inertial term $\frac{d(m_p v_i)}{dt}$, which is often neglected in typical microfluidic simulations. Therefore, our simulation result is more accurate in a sense that the inertial effect is considered and an extended simulation study for investigating the inertial effect can be possible.

Despite the good agreement of our results with previous results, there are some aspects that can be improved. The inclusion of hydrodynamic interaction effects is still challenging in FEM-based simulation [1]; including these forces would lead to a more accurate simulation. The bead-wall collision force is based on the distance from the center of the bead to the nearest wall surface. This needs to be improved to include the distance between the bead surface and the wall. Finally, finding a way to include the attractive force in the Leonard-Jones potential without making the model collapse within itself should be investigated. [2].

Acknowledgements

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