Simulation guided design of a microfluidic device for electrophoretic stretching of DNA

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(Received 22 August 2012; accepted 10 October 2012; published online 24 October 2012)

We have used Brownian dynamics-finite element method (BD-FEM) to guide the optimization of a microfluidic device designed to stretch DNA for gene mapping. The original design was proposed in our previous study [C. C. Hsieh and T. H. Lin, *Biomicrofluidics* **5**(4), 044106 (2011)] for demonstrating a new pre-conditioning strategy to facilitate DNA stretching through a microcontraction using electrophoresis. In this study, we examine the efficiency of the original device for stretching DNA with different sizes ranging from 48.5 kbp (λ -DNA) to 166 kbp (T4-DNA). The efficiency of the device is found to deteriorate with increasing DNA molecular weight. The cause of the efficiency loss is determined by BD-FEM, and a modified design is proposed by drawing an analogy between an electric field and a potential flow. The modified device does not only regain the efficiency for stretching large DNA but also outperforms the original device for stretching small DNA. © 2012 American Institute of Physics. [<http://dx.doi.org/10.1063/1.4763559>]

INTRODUCTION

With the development of microfluidics, numerous microfluidic devices have been created for various purposes,² and many of them are for biomedical applications.³ In general, these devices use flow or electric field to manipulate biomolecules for specific purposes, including concentration,^{4,5} separation,⁶ and detection.⁷ Most microfluidic devices in the literatures are prototypes to demonstrate new ideas. These devices are often primitive and need to be optimized if they are for the practical use. However, microfluidic systems are very complicated because intrinsically they have non-trivial geometry and are filled with aqueous solution and biomolecules. As a result, simply applying rational ideas to perform device optimization may not necessarily lead to a better design, and a more sophisticated approach for device optimization is needed. With the advance of computer, using numerical modeling to facilitate the design process is now a common approach in many engineering fields. Influenced by this trend, numerical simulations have been gradually emerging in the design process of microfluidic devices.^{1,8–10}

To use computer modeling as a design tool, it is necessary that the employed models are able to predict qualitatively or even quantitatively the key physical phenomena involved. For problems concerning large time and length scales, computational fluid dynamics (CFD)¹¹ has become a necessary tool in any serious design. For problems concerning small time and length scales, molecular dynamics has also been used as a prescreening tool for drug discovery¹² and for material design.¹³ However, the optimization of a microfluidic device that usually involves both large and small scale phenomena requires special concerns. In a biomicrofluidic system with solvents and biomolecules, the solvent molecules are small and relax fast while the biomolecules such as DNA and proteins are large and relax slow. The separation between the physical scales of large and small molecules posts great difficulty in modeling their behavior. On the other hand, also due to the separation of physical scales, solvents and the biomolecules may be simulated using models at different scales. One solution is using the so called mesoscale

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simulations¹⁴ that use coarse-grained molecular models to treat both solvents and biomolecules. For example, DNA as biomolecules are usually modeled by a bead-spring model¹⁵ or a bead-rod model^{16,17} while the solvents are modeled by mesoscale models such as lattice Boltzmann method,¹⁸ dissipative particles dynamics,¹⁹ and stochastic rotational dynamics.²⁰ However, the mesoscale simulations are still expensive in computer time, especially when one is more interested in the behavior of biomolecules.

A more economical approach is to treat the solvents as a continuum and to simulate biomolecules with a coarse-grained molecular model. In this way the flow field is solved by standard computational fluid dynamics, and biomolecules are described by a coarse-grained model with Brownian dynamics (BD).²¹ In BD, the collective motions of the solvents affect biomolecules through the Brownian force and the drag force obtained from CFD. The combination of computational fluid dynamics and Brownian dynamics can be characterized as the BD-CFD method. Based on the numerical methods used for CFD, possible variations of BD-CFD include finite difference method (BD-FDM), finite element method (BD-FEM),^{22,23} and boundary element method (BD-BEM).²⁴ BD-CFD was initially used as a tool for researchers to understand experimental results,²⁵ but as the simulations become more accurate, recent studies have started to use BD-CFD as a predictive tool for device design.^{1,26}

In this study, we aim to use the BD-FEM method to test the limit of an existing microfluidic device and to improve the original design to achieve better performance. The microfluidic devices to test and their design parameters are shown in Fig. 1. Fig. 1(a) is a microfluidic device with a simple contraction. It is the most popular geometry to perform DNA stretching for high throughput gene mapping.^{27–31} DNA molecules in buffer solutions are driven through the device either by electrophoresis or by pressure-driven flow. When DNA molecules pass the contraction funnel, they will be stretched by the strong electric/flow field gradient. At the place where DNA reaches its maximum extension, the positions of fluorescently labeled genome sequence on DNA are detected, and the identity of DNA can be identified. Although the device

FIG. 1. The schematic diagram of the testing devices: (a) case I, (b) case II. The design parameters are listed below: $w_1 = 200 \mu\text{m}$, $w_2 = 3.8 \mu\text{m}$, $w_3 = 10 \mu\text{m}$, $l_1 = 250 \mu\text{m}$, $l_2 = 250 \mu\text{m}$, $l_3 = 50 \mu\text{m}$, the contraction length $l_c = 80 \mu\text{m}$, $a = 140 \mu\text{m}$, $b = 95 \mu\text{m}$, $f_1 = \frac{w_1}{2 \left(\frac{w_1}{w_2} - 1 \right) + 1}$; $f_2 = 100 - b \sqrt{1 - \frac{(190-x)^2}{a^2}}$. The height of both devices is set to $2 \mu\text{m}$ in z direction (not shown). The contour length of λ -, 2λ -, and T4-DNA are displayed in (a) for reader's reference. When the devices operate, DNA molecules are driven from the inlet (right) to the outlet (left) by electrophoresis and will be stretched in the contraction.

like the one in Fig. 1(a) has been used to demonstrate the application for gene mapping,^{27,31} its efficiency for stretching DNA is not high. To improve the device, the design shown in Fig. 1(b) was proposed in our previous study¹ as a modification to the simple contraction. The modified device consists of two parts: an expansion for “pre-conditioning” DNA and a contraction for stretching DNA. In the following discussion, we denote the devices in Figs. 1(a) and 1(b) as case I and case II, respectively. In our previous study,¹ DNA in both devices were driven by electrophoresis, and we have shown that case II outperforms case I using λ -DNA as the target DNA. The success of case II relies on an extension-rotation motion of DNA between the expansion and the contraction. This motion allows DNA to be pre-stretched before they enter the contraction to experience a second stretching.

In this study, we want to exam the ability of the two devices in Fig. 1 to stretch DNA with different molecular weights because this is a common situation to happen in reality. For this purpose, we chose λ -DNA (48.5 kbp), λ -DNA dimer (2λ -DNA, 97 kbp), and T4-DNA (166 kbp) as the model DNA. Among these DNA, the longest one is T4-DNA that has a contour length about $71.4 \mu\text{m}$ after stained. We do not test DNA longer than T4-DNA because the length of the contraction is $80 \mu\text{m}$. Any DNA longer than the contraction cannot be efficiently stretched. An illustrative comparison between the length of the contraction funnel and the contour lengths of the three model DNA is given in Fig. 1(a), where all DNA have their heads aligned with the end of the contraction. We note that all these DNA are experimentally available, so our prediction is possible to be tested experimentally in the future.

SIMULATION METHODS

The finite element method and Brownian dynamics simulations are used together as our design tools. Since we want to create a microfluidic device to stretch DNA by electric field, we first use the finite element method to solve the electric field in the testing geometry. The governing equation and boundary conditions for electric potential ϕ are set by

$$\nabla^2 \phi = 0 \quad \text{in } \Omega, \quad (1)$$

$$\phi = \phi_{\text{given}} \quad \text{or} \quad \frac{\partial \phi}{\partial \mathbf{n}} = 0 \quad \text{on } \partial\Omega, \quad (2)$$

where Ω is the problem domain, $\partial\Omega$ is the boundary of the domain, and $\mathbf{n}$ denotes the unit vector normal to the boundary. The boundary condition $\phi = \phi_{\text{given}}$ is imposed on the outlet and inlet of the device. ϕ_{given} is set to be zero at the outlet while its value at the inlet is determined so that the resulting electric field gradient matches the desired Deborah number (De). Since microfluidic devices are typically made of glass or PDMS, the boundary condition $\frac{\partial \phi}{\partial \mathbf{n}} = 0$ is set on the wall of the device to reflect the insulating nature of these materials. We note that the governing equation and boundary conditions for electric potential are the same as those for potential flow in hydrodynamics. Thus, we can consider the influence of device geometry to the electric field using the concepts developed from potential flow. This similarity is very helpful when we consider how the electric field would change when the shape of the device is modified. Once the electric potential is solved, the electric field $\mathbf{E}$ is calculated from $\mathbf{E} = -\nabla \phi$ and is fed into Brownian dynamics simulations for evaluating the electric force on DNA. The connection between FEM data and BD simulations is established with an efficient searching algorithm developed in our previous study.

We then employ the Brownian dynamics with bead-spring model to describe the conformation and dynamics of DNA. In the model, a DNA is discretized into N beads connected by N_s ($=N-1$) springs. The evolution of DNA conformation can be obtained from the force balance at each bead

$$\frac{d\mathbf{r}_i}{dt} = \mu^b \mathbf{E}(\mathbf{r}_i) + \frac{1}{\zeta} [\mathbf{F}_i^B(t) + \mathbf{F}_i^S(t) + \mathbf{F}_i^{EV}(t)], \quad (3)$$

where $\mathbf{r}_i$ is the position of the i -th bead, μ^b is the electrophoretic mobility of a bead, $\mathbf{E}(\mathbf{r}_i)$ is the electric field at $\mathbf{r}_i$, ζ is the drag coefficient of a bead, $\mathbf{F}_i^B$ is the Brownian force, $\mathbf{F}_i^S$ is the sum of the spring forces acting on the i -th bead, and $\mathbf{F}_i^{EV}$ is the sum of the excluded volume force between beads. To construct Eq. (3), we invoke the theory of electro-hydrodynamic equivalence³² so that the effect of electric force on DNA can be modeled by a hydrodynamic flow field equal to $\mu^b \mathbf{E}$. The effect of electro-osmosis is not considered here because in such experiments polyvinylpyrrolidone^{28,30,33,34} is usually used to dynamically coat the microchannel walls to eliminate electro-osmotic flow. We also note that hydrodynamic interaction is neglected because the height of the testing devices is very close to or smaller than the natural size of DNA simulated.^{35–37} A more detailed explanation is given later in the discussion section. During the simulations, if any bead moves across the boundary, it is moved back to the nearest wall.³⁸

To perform the BD simulations, Eq. (3) is made dimensionless with the following dimensionless variables:

$$\hat{\mathbf{r}} \equiv \frac{\mathbf{r}}{l}, \quad \hat{t} \equiv \frac{t}{\zeta l^2 / k_B T}, \quad \hat{\mathbf{E}} \equiv \frac{\mathbf{E}}{E_0}, \quad \hat{\mathbf{F}}(\hat{\mathbf{r}}) \equiv \frac{\mathbf{F}(\mathbf{r}) l}{k_B T}, \quad (4)$$

where l is the maximum extension of a spring ($=L/N_s$), $k_B T$ is the thermal energy, and E_0 is set to be the electric field at the inlet of case I. Based on the definitions in Eq. (4), the dimensionless force balance equation is

$$\frac{d\hat{\mathbf{r}}_i}{d\hat{t}} = Pe \hat{\mathbf{E}}(\hat{\mathbf{r}}_i) + \hat{\mathbf{F}}_i^B + \hat{\mathbf{F}}_i^S + \hat{\mathbf{F}}_i^{EV}, \quad (5)$$

where $Pe = \mu^b E_0 l / D$ is the bead Peclet number and D is the diffusivity of a bead ($=k_B T / \zeta$). The dimensionless Brownian force term $\hat{\mathbf{F}}_i^B$ is described by

$$\hat{\mathbf{F}}_i^B = \sqrt{\frac{6}{\delta t}} \mathbf{R}_i, \quad (6)$$

where $\mathbf{R}_i$ is a vector with each of the three component uniformly distributed between 1.0 and -1.0 . The spring force between bead i and j , $\hat{\mathbf{f}}_{ij}^S$, is described by a modified Marko-Siggia spring law derived by Underhill and Doyle³⁹

$$\hat{\mathbf{f}}_{ij}^S = \frac{v}{\lambda} \left\{ \hat{r}_{ji} - \frac{1}{4} + \frac{1}{4(1 - \hat{r}_{ji})^2} \right\} \frac{\hat{\mathbf{r}}_j - \hat{\mathbf{r}}_i}{\hat{r}_{ji}}, \quad (7)$$

where $\hat{r}_{ji}$ is the dimensionless distance between beads i and j , $v(\equiv l/A_p)$ is the number of the true persistence length A_p per spring, and $\lambda(\equiv A_{eff}/A_p)$ is the ratio of the effective persistence length A_{eff} to the true DNA persistence length. The modified Marko-Sigga spring law is employed so the additional flexibility caused by the discretization of a DNA into a bead-spring chain can be offset. The value of A_p is taken from experimental value and set to be $0.053 \mu\text{m}$.⁴⁰ The values of l , v , A_{eff} , and λ depend on the degree of discretization of a chain, and they are listed in Table I. We maintain the maximum spring length very close for all three different DNA, and thus their values of l , v , A_{eff} , and λ are also very similar. Because each bead can be

TABLE I. The simulation parameters for DNA.

DNA	L (μm)	N	N_s	l (μm)	A_{eff} (μm)	v	$R_{g,bulk}$ (μm)
λ -DNA	20.5	19	18	1.1389	0.07345	21.488	0.70
2λ -DNA	41.0	37	36	1.1389	0.07345	21.488	1.06
T4-DNA	71.4	64	63	1.1333	0.07354	21.384	1.47

connected by either one or two springs, the total spring force acting on bead i is calculated from

$$\hat{\mathbf{F}}_i^S = \begin{cases} \hat{\mathbf{f}}_{i,i+1}^S & i = 1 \\ \hat{\mathbf{f}}_{i,i+1}^S + \hat{\mathbf{f}}_{i,i-1}^S & 1 < i < N_b \\ \hat{\mathbf{f}}_{i,i-1}^S & i = N_b \end{cases} \quad (8)$$

The dimensionless excluded volume force between beads $\hat{\mathbf{F}}_i^{EV}$ is modeled by a soft potential expressed as follows:⁴¹

$$\hat{\mathbf{F}}_i^{EV} = - \sum_{j=1 (j \neq i)}^{N_b} \frac{9}{2} \hat{v}^{EV,p} \left(\frac{3}{4\sqrt{\pi}} \right)^3 v_j^2 \exp \left(\frac{-9v_j^2}{4} \right) \hat{\mathbf{r}}_{ji}, \quad (9)$$

where $\hat{v}^{EV,p} (= v^{EV,p}/l^3)$ is the dimensionless excluded volume parameter, and the dimensional value of $v^{EV,p}$ is set to $0.0004 \mu\text{m}^3$. This potential has been shown to produce correct dependence between DNA contour length and its equilibrium size under good solvent condition. The simulated bulk radius of gyration ($R_{g,\text{bulk}}$) of DNA is also given in Table I. Finally, we stress that the BD-FEM used here is not a truly coupled calculation. The results of FEM are fed into BD as input data while the results of BD are not fed back to FEM to refine the calculation.

In our simulations, the DNA extension, L_{ex} , is defined by the distance between the maximum coordinates (x_{max}, y_{max}) and the minimum coordinates (x_{min}, y_{min}) of the DNA chain. Thus, L_{ex} is not the exact DNA extension measured along its contour but an approximation adapted from experiments²⁸ for easier measurement. The exact and the approximated DNA extension will converge when DNA is fully stretched. We also note that the De reported in this study is a nominal De in the contraction funnel. It is defined by $De = \tau \dot{\epsilon}_x = \tau \mu^b E_1 / l_c$, where $\mu^b E_1$ is the electrophoretic velocity at the outlet of the contraction ($x/l_c = -1$). To account for the “molecular individualism,”⁴² all the ensemble averaged results are obtained from 300 independent runs starting with different equilibrium conformations and different initial positions randomly distributed along the y direction at the inlet of the devices. The BD simulations were performed by integrating Eq. (5) with an explicit Euler’s method. The dimensionless time step $\delta \hat{t}$ is fixed to be 10^{-5} for $De \leq 10$. The time step size is adjusted by a factor $10/De$ for $De > 10$.

RESULTS AND DISCUSSIONS

As we have focused on stretching λ -DNA in our previous study, here we exam the efficiency of the same devices for stretching DNA with higher molecular weight. Since the devices are the same as those studied in our previous study, we do not discuss the field kinematics here again. We refer Figs. 4(a), 4(b), 4(d), and 4(e) of our previous study¹ for the discussion of the field kinematics in these devices. We show in Fig. 2 the evolution of the ensemble averaged relative extension of DNA $\langle L_{ex}/L \rangle$ at $De = 23$ for λ -, 2λ -, and T4-DNA in (a) case I and (b) case II, respectively. In addition to the simulation results, the dotted line is given to indicate the maximum possible DNA extension. It is estimated using a dumbbell model at a homogeneous field (infinite strain),⁴³ and the result is independent of the molecular weight of DNA.

From Fig. 2(a), the evolution of DNA extension is found similar for DNA with different molecular weights. For $x/l_c > 0$, De is nearly zero. Thus, the values of $\langle L_{ex}/L \rangle$ over this regime represent the equilibrium values of the relative DNA extension ($L_{ex,eq}/L$). At $x/l_c \approx 0$, DNA starts to extend and eventually reaches a maximum extension around $x/l_c \approx -1$ where the contraction ends. It is found that larger DNA reaches a lower degree of maximum extension. This is because the device provides a fixed amount of strain, but a larger DNA has a smaller value of ($L_{ex,eq}/L$) to start with. We also observe from Fig. 2(a) that the location of the maximum DNA extension gradually shifts downstream from $x/l_c \approx -1$ for λ -DNA to $x/l_c \approx -1.2$ for

FIG. 2. The ensemble averaged relative extension of DNA as a function of x for λ -, 2λ -, and T4-DNA at $De = 23$ in (a) case I and in (b) case II. The dotted line represents the steady-state relative DNA extension estimated in a homogeneous field.

T4-DNA. This may seem strange because De has become zero for $x/l_c < -1$. In fact, the chain could continue to stretch due to the difference in electrophoretic velocity between its head and tail. This is the so called non-local effect²⁶ that only becomes prominent when the contour length of DNA is about or larger than the contraction length. Since the funnel length is $80 \mu\text{m}$, this effect becomes apparent only for T4-DNA (contour length = $71.4 \mu\text{m}$). Comparing Fig. 2(b) with Fig. 2(a), we find that the shift of the location of the maximum DNA extension also exists. As can be seen in Fig. 2(b), DNA molecules in case II are pre-stretched at the expansion and reach higher maximum extension than those in case I. The advantage of case II over case I is obvious for λ -DNA, but not as much for T4-DNA. The preconditioning effect of case II appears to weaken with increasing DNA molecular weight.

Fig. 3 compares the maximum ensemble averaged relative extension $\langle L_{ex,max} \rangle / L$ for λ -, 2λ -, and T4-DNA at different De in (a) case I and (b) case II, respectively. As can be seen, the relative maximum extension of T4-DNA is significantly lower than those of λ - and 2λ -DNA in both cases. Comparing Fig. 3(a) with Fig. 3(b), we find that case II outperforms case I in stretching all different lengths of DNA. Moreover, the comparison also confirms the trend that the preconditioning effect of case II is weakened as the molecular weight of DNA increases. We also find from Figs. 3(a) and 3(b) that DNA extension starts to saturate at $De \sim 20$. Since increasing De often leads to more error in detection, the optimal De for operating these devices would be around 20.

FIG. 3. The maximum ensemble averaged relative DNA extension for λ -, 2λ -, and T4-DNA at $De = 7, 14, 23$, and 50 in (a) case I and in (b) case II. The dotted line represents the steady-state relative DNA extension estimated in a homogeneous field.

Because a given device can only provide a fixed amount of strain, it is expected that these devices perform better in stretching smaller DNA. However, the declining of the pre-conditioning effect of case II is rather unexpected. To determine its cause, we analyze the snapshots of λ - and T4-DNA taken when they pass case II in Fig. 4. To also reveal the influence of

FIG. 4. The snapshots of DNA conformation in case II at $De = 23$ for λ -DNA (a)-(c) and T4-DNA (d)-(f). The initial y position of the center of mass of DNA is $3.5 \mu\text{m}$ (a),(d), $1 \mu\text{m}$ (b),(e), and $0 \mu\text{m}$ (c),(f), respectively.

the local field kinematics on DNA, we set the initial y position of DNA as $y = 3.5 \mu\text{m}$ (Figs. 4(a) and 4(d)), $y = 1 \mu\text{m}$ (Figs. 4(b) and 4(e)), and $y = 0 \mu\text{m}$ (Figs. 4(c) and 4(f)). It is easily seen from Fig. 4 that T4-DNA behaves very similarly to λ -DNA for any given initial position. In either case, DNA molecules moving off the center axis are found undergoing an extension-rotation motion at the expansion. On the other hand, DNA molecules moving along the center axis are stretched and then compressed at the expansion. It has been found that the pre-conditioning effect of case II relies on two key steps:¹ (1) DNA is pre-stretched at the expansion (2) DNA rotates to align with the funnel direction before it enters the contraction. However, the later step is absent for DNA molecules that pass near the axis of the device. This is because DNA passing this regime often has its segments on both sides of the axis. Due to the symmetry of the field, the rotational motion of DNA seen in Figs. 4(a), 4(b), 4(d), and 4(e) will not happen, and DNA molecules are prone to fold (see Fig. 4(f)) at the entrance of the contraction. As a result, DNA molecules passing this region do not benefit from any the pre-conditioning effect. Moreover, a larger DNA suffers more from this problem (comparing Figs. 4(c) and 4(f)) because the width of this regime is about the size of the DNA extension. Thus, the overall efficiency of the device to stretch DNA decreases with the molecular weight of DNA.

To improve the device's efficiency in dealing with larger DNA, we need to modify its design to avoid DNA folding. A straightforward way is to prevent DNA from flowing through the region near the axis. However, the modified device should preserve the extension-rotation motion that has been shown to pre-condition DNA for easier stretching. Achieving both could be very difficult because any modification to the device may alter the field kinematics that is critical to the extension-rotation motion. To come up with a better design, we consider the nature of the electric field. Since the governing equation for the electric potential is the Laplace equation which is also the governing equation for the potential flow in fluid mechanics, we can use the analogy between the electric field and potential flow field⁴⁴ to help our consideration. Using this analogy, electricity lines can be considered as streamlines. It is well known that any streamline of a potential flow can be replaced with a no-penetration boundary without altering the rest of flow field. Similarly, each electricity line can be replaced with an insulated boundary without affecting the rest electric field. On the other hand, although introducing an insulating boundary posts no effect on the rest electric field, it introduces an excluded volume effect that prevents DNA from penetrating the boundary and thus effectively forbids the presence of some DNA conformation. Following this thought, we propose an alternative design called case III that is derived from case II by cutting case II along its center axis. This modification should leave the rest electric field unchanged but prevent DNA from passing the axial region where the rotational motion of DNA is absent.

The shape and the representative electricity lines in cases II and III are shown in Figs. 5(a) and 5(b), respectively. It is easily seen that the electricity lines in case III are identical to those in case II. The introduction of the wall along the axis should prevent the formation of the conformations like the one shown in Fig. 4(f). We qualitatively examine our prediction using Fig. 6 which shows the snapshots of DNA conformation in case III at $De = 23$ for T4-DNA. The initial y position of the center of mass of DNA is (a) $3.5 \mu\text{m}$ and (b) $1 \mu\text{m}$, respectively. As can be seen, DNA molecules in Fig. 6 behave similarly to those shown in Figs. 4(d) and 4(e), implying that the modification to the device does not affect the behavior of DNA flowing outside of the center regime.

To quantitatively determine the difference between case II and case III, we plot in Fig. 7 the DNA population distribution and their averaged relative extension as a function of the y -component of their center of mass at the inlet of the contraction ($x/l_c = 0$) at $De = 23$. As can be seen, the averaged DNA extension is nearly the same for cases II and III over different positions. This observation is consistent with our expectation since the field kinematic is unaffected. However, the DNA population distribution is very different in two devices. For case II, the density of DNA population is a decreasing function of y , and nearly half of the DNA population passes the region very close to the center axis. This population distribution results from the excluded volume effect of the device wall. For case III, the excluded volume effect also

FIG. 5. Comparison of the electric field lines in cases II and III. The shape of case III is just a half of that of case II. Due to the insulated wall boundary conditions and the harmonic governing equation of the electric potential, cutting case II along the center axis will not change the electric field in the rest part.

appears along $y = 0$, and therefore it results in a peak in DNA population distribution at a moderate y position.

We compare in Fig. 8 the ensemble averaged relative T4-DNA extension as a function of their x position for cases I, II, and III at $De = 23$. Consistent with the previous analysis, case III is more efficient than case II despite the fact that the average DNA extension in both cases is very close at the inlet of the contraction. More importantly, the maximum relative extension is about 86% in case III, close to the estimated theoretical limit (94%) and much higher than those in case I (75%) and case II (79%). Finally, we compare in Fig. 9 the maximum ensemble averaged relative extension $\langle L_{ex,max}/L \rangle$ for λ -, 2λ -, and T4-DNA at different De in case III. From the figure, the values of $\langle L_{ex,max}/L \rangle$ for three different DNA have become very close to each other. The small difference may be attributed to the fact that larger DNA has smaller $(L_{ex,eq}/L)$. Comparing Fig. 9 with Fig. 3, we conclude that although larger DNA benefit more from the modification made to the device, case III outperforms cases I and II for stretching all different DNA tested here. More importantly, case III has been proved to work equally well for DNA with different contour length ranging from $20\ \mu\text{m}$ to $70\ \mu\text{m}$.

Finally, we discuss the possible limitation to our design. First, the hydrodynamic interaction was not included in our simulations because of the excessive computational cost. However,

FIG. 6. The snapshots of T4-DNA conformation in case III at $De = 23$. The initial y position of the center of mass of DNA is (a) $3.5\ \mu\text{m}$ and (b) $1\ \mu\text{m}$, respectively.

FIG. 7. The averaged relative T4-DNA extension (symbols and lines) and the population distribution (bars) as functions of the y -component of their center of mass at the inlet of the contraction ($x/l_c = 0$) at $De = 23$ for cases II and III.

we note that the DNA motion caused by the electric field does not induce hydrodynamic interaction due to the compensating motion of the counterions on DNA.^{23,45} This is also why DNA of different size cannot be separated by free solution electrophoresis. The hydrodynamic interaction due to nonelectrical forces still exists, but it is much diminished³⁵ because of the presence of the confinement. Thus, neglecting hydrodynamic interaction should have very limited influence to our results. On the other hand, more serious deviation might stem from the simplified treatment to the charged nature of DNA. In our simulations, the electric properties of DNA are only accounted for by the phenomenon of electrophoresis. However, other phenomena related to the electric properties of DNA may become important in certain situations. For example, recent experiments show that DNA coil can adapt a compressed conformation in a uniform but strong DC field.⁴⁶ Moreover, electric field gradient at the expansion and contraction of the proposed devices might induce dielectrophoresis effect that could polarize DNA and result in unpredictable influence to DNA behavior.^{43,47}

To summarize, in order to have an affordable but useful prediction, we use coarsened-grained models that hopefully preserve the most important physics but only leave away the unimportant ones. From the reasonable agreement between the previous experiments^{28,33} and simulations,^{26,48} the FEM-BD simulations used here should be capable to catch the behavior of the

FIG. 8. The evolution of the ensemble averaged relative extension of T4-DNA as a function of x at $De = 23$ in cases I, II, III, and homogeneous field.

FIG. 9. The maximum ensemble averaged relative DNA extension for λ -, 2λ -, and T4-DNA at $De = 7, 14, 23$, and 50 for case III. The dotted line represents DNA extension estimated in a homogeneous field.

DNA in microfluidic devices. If future experimental tests reveal significant discrepancy from our predictions, the results of this study can at least serve as a base case for comparison to identify the important factors that should be considered in future studies.

CONCLUSIONS

We have demonstrated how computer simulations with a coarse-grained molecular model and a continuum calculation are used to improve a microfluidic device designed for stretching DNA. Using the computer simulations, detailed information about the DNA behavior in a microfluidic device is predicted, and it enables us to develop a rational strategy to improve the device. This study was motivated by the recent trend in many engineering fields that computer simulations are used to refine primitive design before experiments. Comparing to the development of simulation guided design in continuum and molecular level, the situation we face in developing biomicrofluidic devices is more challenging because of the presence of both large and small molecules. However, with the growing power of computer we believe that simulation guided design will become an essential process in the future development of biomicrofluidic devices. We hope that this work could inspire more studies to participate and to accelerate the development of this field.

ACKNOWLEDGMENTS

The authors thank the National Science Council of Taiwan for supporting this research under the Grant No. NSC 100-2628-E-002-029-MY2.

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