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Mechanical behaviour of DNA molecules - elasticity and migration

M. Benke, E. Shapiro, D. Drikakis
Fluid Mechanics and Computational Science (FMaCS)
School of Engineering, Cranfield University
Bedfordshire, Cranfield, MK43 0AL, UK

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Abstract

A novel multi-scale simulation method developed to describe mesoscale phenomena occurring in biofluidic devices is presented. The approach combines the macro-scale modelling of the carrier fluid and the micro-scale description of the transported macro-molecules or compounds. Application of the approach is demonstrated through mesoscale simulations of DNA molecules. The investigated phenomena include elastic relaxation of dsDNA molecules and migration of ssDNA molecules in a microchannel flow. The results of the first study demonstrate that the elastic behaviour of the DNA molecules can be captured sucessfully. The second study proves that the migration of ssDNA in pressure driven microchannel flows can be explained by the hydrodynamic interaction with the carrier liquid.

1 Introduction

Micro- and nanofluidic devices offer numerous advantages compared to macro-scale systems, including enhanced reaction control, reduced operating volumes and throughput time. As a result, these devices are increasingly used

in biomedical engineering ([1, 2]) with applications including mixing [3], filtering and separation [4] and bio-detection [5]. The ability to manipulate complex molecules with liquid flow in micro- and nano devices is required in many biomedical applications, which propmts the development of modelling tools capable of resolving the physical processes involved.

Micro- and nanofluidic systems are characterised by physical phenomena occuring at a range of scales. Interaction between macromolecules and the molecules of the carrier liquid occur on atomistic length and time scale, however transport of macromolecules and their mechanical behaviour is determined by the macroscopic flow field of the carrier liquid. Conventional modelling methods are designed to describe phenomena relevant to a limited range of scales. Molecular modelling techniques can capture the properties of a single macromolecule at timescale of several nanoseconds and are widely used to describe nano-scale DNA behaviour [6], molecule-molecule interactions [7] and structural changes [8]. However the computational resource requirements make molecular techniques inefficient for meso- and macroscopic phenomena. The motion of the liquid flow at scales of up to $\sim$ 10nm can be adequately described with the conventional continuum fluid dynamics techniques. The challenge associated with the development of models capable of resolving DNA motion in fluid flow is that of coupling the macroscopic motion of the carrier fluid with the microscopic model of the DNA molecule.

This aim can be accomplished by introducing a simplified mechnical model of a DNA molecule. The idea behind simplified mechanical models

is similar to that of coarse-graining models originating from the molecular dynamics studies (e.g. [9]). For example, Brownian Dynamics (BD) approach based on mechanical representation of DNA molecules as bead-rod or bead-spring structures [10] has been developed to cover considerably longer time scales than molecular modelling (e.g. [11]). BD has been extensively used to determine macroscopic properties of dilute polymer solutions [12], model dynamics of DNA molecules [13] and migration of macromolecules [14]. Drawbacks of the approach include the implicit treatment of the solvent and omitted inertial forces. These simplifications can limit the applicability of BD, especially when for complex and unsteady carrier liquid flows.

An alternative meta-modelling approach has been developed recently [15, 16]. The approach is closely related to BD, since it relies on a mechanical representation of macromolecules, however, the carrier liquid flow is modelled explicitly using Computational Fluid Dynamics (CFD) and the acceleration terms are kept in the equations of motion of the DNA. In this paper, the application of this approach to the dsDNA relaxation process is presented followed by a study of the ssDNA migration phenomenon.

2 Meta-modelling approach

The meta-modelling approach is based on the continuum level modelling of the carrier liquid coupled with the motion of the mechanical bead-rod or bead-spring structures representing DNA molecules. The motion of the me-

chanical structures is determined by the hydrodynamic and inter-molecular forces acting on individual beads. Motion of the bead n with mass m_n and position vector $\boldsymbol{r}_n$ is described by the Langevin equation

$$m_n \frac{d^2 \boldsymbol{r}_n}{dt^2} = m_n \gamma_n \left(\boldsymbol{u}(\boldsymbol{r}_n) - \boldsymbol{v}_n \right) + \boldsymbol{\phi}_n + \boldsymbol{\psi}_n + \boldsymbol{\varphi}_n(t), \tag{1}$$

where $m_n \gamma_n = 6\pi\eta b_n$ is the friction coefficient arising from the Stokes drag of a sphere with radius b_n, in a fluid with a dynamic viscosity η. $\boldsymbol{u}(\boldsymbol{r}_n)$ is the fluid velocity; $\boldsymbol{v}_n$ denotes the particle velocity; $\boldsymbol{\phi}_n$ represents the sum of all non-hydrodynamic forces; $\boldsymbol{\psi}_n$ incorporates additional hydrodynamic forces relevant to polymer migration phenomena including the Saffman lift force and the Faxen correction (e.g. [17]). $\boldsymbol{\varphi}_n(t)$ is the random Brownian force, modelling the effect of the carrier liquid molecules stochastically colliding with the beads and exchanging momentum. It is worth noting that bead-rod or bead-spring models provide an equivalent mechanical behaviour with respect to elastic and transport properties. However they do not necessarily resolve the conformation of the macromolecule.

Governing equations of the incompressible carrier liquid are given by

$$\frac{\partial \boldsymbol{u}}{\partial t} + (\boldsymbol{u} \cdot \nabla)\boldsymbol{u} = -\frac{1}{\rho}\nabla p + \nu \Delta \boldsymbol{u} + \frac{1}{\rho}\boldsymbol{F}, \tag{2}$$

$$\nabla \cdot \boldsymbol{u} = 0, \tag{3}$$

where ρ, p, ν and $\boldsymbol{u}$ denote density, pressure, kinematic viscosity and ve-

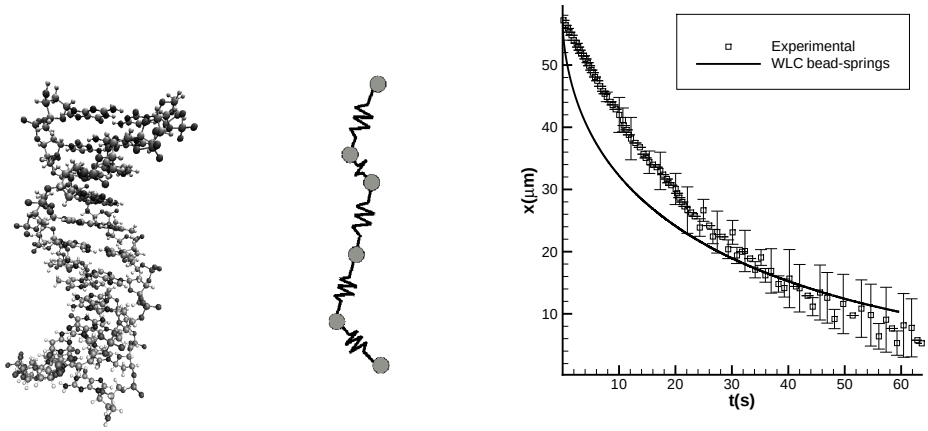
locity respectively and $\boldsymbol{F}$ on the right-hand side of the momentum equation represents the force arising due to the presence of macromolecules. The forcing term $\boldsymbol{F}$ is equal in magnitude and opposite in the direction to the force exerted by the fluid on the macromolecule. Further details of the numerical implementation of the forcing term can be found in [22].

The coupled system of Equations (1)-(3) is solved numerically. The flow field was calculated using the in-house finite volume artificial compressibility solver, with inviscid fluxes approximated using the characteristics-based method (e.g. [18, 20, 19, 21]) combined with the third order variables reconstruction [18, 20]. Viscous fluxes were computed using the second order central approximation. The integration in pseudo-time for the artificial compressibility formulation was performed using the fourth-order Runge-Kutta method (e.g. [18, 20]).

3 Applications

3.1 Modeling elastic response of dsDNA

Smith et al. [23] performed a series of measurements to determine the elastic response of dsDNA, when subjected to external stretching forces. In order to represent this behaviour, a mechanical model of dsDNA can be constructed using the bead-spring approximation. The non-hydrodynamic force in the



(a) molecular model of dsDNA (courtesy of M. Lai, Cranfield University)

(b) elastic model

(c) end-to-end distance during relaxation

Figure 1: Dynamic simulation of a 164 kbp dsDNA molecule

Equation (1) is then defined as

$$\begin{aligned} \boldsymbol{\phi}_n &= -F\big(\boldsymbol{r}_{n-1}(t), \boldsymbol{r}_n(t)\big) \cdot \boldsymbol{e}(t)_{n-1,n} + \\ &\quad + F\big(\boldsymbol{r}_n(t), \boldsymbol{r}_{n+1}(t)\big) \cdot \boldsymbol{e}(t)_{n,n+1}, \end{aligned} \tag{4}$$

where $F\big(\boldsymbol{r}_{n-1}(t), \boldsymbol{r}_n(t)\big)$ is the magnitude and $\boldsymbol{e}(t)_{n-1,n}$ is the direction of the elastic force. Elastic forces acting on dsDNA molecules can be approximated by the following formula

$$F = \frac{k_B T}{\lambda_p} \left(\frac{1}{4(1 - x/l)^2} - \frac{1}{4} + x/l \right), \tag{5}$$

suggested by Bustamante et al. [24]. Here k_B is Boltzmann's constant, T is temperature and λ_p is the persistence length of the molecule. x denotes the extension of a single spring and l is the fully extended length of the spring.

To evaluate the complete model, the experimental study of Wong et al. [25] has been simulated. In this study relaxation of labeled 164 kbp T2 DNA molecules in a solution with viscosity $\eta = 21.5\,\mathrm{cP}$ has been investigated under no-flow conditions. In the simulations, a bead-spring chain model containing 53 springs has been used to represent the dsDNA molecule. The coarse graining parameters were selected following the study of Underhill and Doyle [26]. The total mass of the molecule was uniformly distributed along the beads, resulting in $m_n = 3.6384 \cdot 10^{-21}\,\mathrm{kg}$. The drag coefficient of the molecule was approximated by Batchelor's formula [27], which resulted in the hydrodynamic bead radius of $b_n = 33.7\,\mathrm{nm}$. The simulation results presented in Figure 1 are in good overall agreement with the experiment. While the discrepancy observed in the beginning of the relaxation process indicates that the fit of the elastic force given by the Equation (4) over-predicts the actual force. The end-to-end distance of dsDNA obtained at later stages is well within the stochastic variation in the experiment, represented by the error bars.

3.2 Simulation of DNA migration

Migration of macromolecules across streamlines in fluid flows has been observed by various researchers (e.g. [28]). The phenomenon results in the

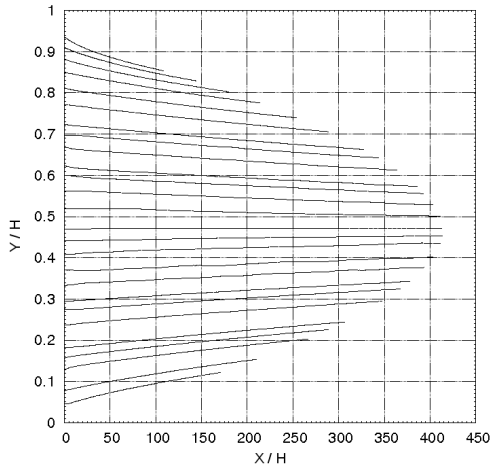
focusing of the macromolecule concentration field, which leads to decrease of the near-wall molecule concentration. This process occurs on relatively long time scales.

The modelling approach described in the previous section allows us to develop a hydrodynamic explanation of this phenomenon. The spherical particles in a non-uniform flow experience a number of additional hydrodynamic forces in addition to the drag force. Taking into account Saffman lift force together with Faxen drag correction leads to the following expression for the hydrodynamic force in Equation (1)

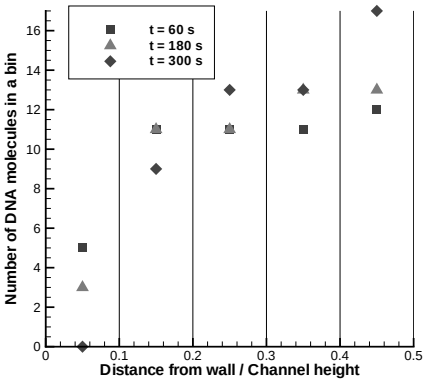
$$\boldsymbol{\psi}_n = -\eta\pi b_n^3 \left(\frac{2\boldsymbol{u}_{max}}{H^2}\right) + \frac{1.615\,(2b_n)^2\sqrt{\rho\eta}\;(\boldsymbol{u}(\boldsymbol{r}_n) - \boldsymbol{v}_n)\times\boldsymbol{\omega}}{\sqrt{\omega}}, \qquad (6)$$

where $\boldsymbol{u}_{max}$ is the maximum flow velocity, H denotes the channel height and $\boldsymbol{\omega}$ is the vorticity vector.

Migration of single-stranded DNA molecules has been investigated in fully developed pressure driven channel flow at Reynolds number 0.075, based on the bulk velocity and channel height of 75μm. Water at room temperature was assumed as the carrier liquid, resulting in the dynamic viscosity and density of 10^3Pas and 10^3kg/m^3 respectively. At the inlet, 100 ssDNA molecules were distributed uniformly along the height of the microchannel. The mechanical behaviour of ssDNA is better represented by the bead-rod model (e.g. [29]). The resulting structure consisted of 160 beads with parameters obtained from the mesoscopic model of a 48kbp ssDNA molecule leading to



(a) DNA center-of-mass trajectories



(b) Variation of DNA number density

Figure 2: Migration results for 48kbp ssDNA molecules in channel Poiseuille flow

bead radius and rod length of 6.47nm and 86.57nm respectively.

Figure 2 illustrates center-of-mass trajectories of a subset of several ssDNA molecules and the variation of the concentration profile along the channel length. In order to obtain the concentration profile, the channel height was divided into 10 bins and the distribution of ssDNA molecules was computed according to the position of the centre of mass. The results demonstrate that the number of molecules present in the near wall region is decreasing and the number of molecules in the channel mid-plane is increasing with time, in agrement with the experimental observations.

4 Conclusions

An overview of a novel multi-scale simulation method developed for mesoscopic processes relevant to biofluidic applications has been presented. The strength of the approach lies in the ability to incorporate both microscopic and macroscopic effects. The results presented for the dsDNA relaxation study validate the approach and demonstrate its capability to resolve the dynamics of elastic dsDNA behaviour in liquid. Modelling of the ssDNA motion in a pressure-driven microchannel flow demonstrates that the experimentally observed DNA migration phenomenon can be explained by hydrodynamic forces acting on the macromolecules.

Further research is required to develop robust multiscale modelling tools. In particular molecular techniques and targeted experiments are required to provide information necessary to determine parameters of the equivalent mechanical representation. However the results presented here indicate that the modelling approach presented in this paper shows promise and can become an essential design tool for micro and nano-fluidics design in biomedical industry.

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Benke, Matyas; Shapiro, Evgeniy; Drikakis, Dimitris

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