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Nanoparticle transport in cellular blood flow

Zixiang Liu[a], Yuanzheng Zhu[a], Rekha R. Rao[b], Jonathan R. Clausen[b], Cyrus K. Aidun[a,*]

[a] George W. Woodruff School of Mechanical Engineering, Georgia Institute of Technology, Atlanta, GA 30332, USA
[b] Sandia National Laboratories, Albuquerque, NM 87185, USA

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ABSTRACT

The biotransport of the intravascular nanoparticle (NP) is influenced by both the complex cellular flow environment and the NP characteristics. Being able to computationally simulate such intricate transport phenomenon with high efficiency is of far-reaching significance to the development of nanotherapeutics, yet challenging due to large length-scale discrepancies between NP and red blood cell (RBC) as well as the complexity of nanoscale particle dynamics. Recently, a lattice-Boltzmann (LB) based multiscale simulation method has been developed to capture both NP–scale and cell–level transport phenomenon at high efficiency. The basic components of this method include the LB treatment for the fluid phase, a spectrin-link method for RBCs, and a Langevin dynamics (LD) approach to capturing the motion of the suspended NPs. Comprehensive two-way coupling schemes are established to capture accurate interactions between each component. The accuracy and robustness of the LB–LD coupling method are demonstrated through the relaxation of a single NP with initial momentum and self-diffusion of NPs. This approach is then applied to study the migration of NPs in micro-vessels under physiological conditions. It is shown that Brownian motion is most significant for the NP distribution in 20 μm venules. For 1 ~ 100 nm particles, the Brownian diffusion is the dominant radial diffusive mechanism compared to the RBC-enhanced diffusion. For ~ 500 nm particles, the Brownian diffusion and RBC-enhanced diffusion are comparable drivers for the particle radial diffusion process.

1. Introduction

Analysis of whole blood flow has been demonstrated through direct numerical simulation (DNS) of the major constituents of blood including the plasma, red blood cells (RBCs) (~45%), and other cells (~0.7%) such as white blood cells (WBCs) and platelets [1-5]. Both single RBC dynamics [1,3,6] and rheological properties of dense suspensions of RBCs [7-10] have been computationally resolved, showing promising agreements with experimental results. Particularly, the lattice-Boltzmann (LB) method for the fluid phase coupled with the Spectrin-Link (SL) analysis of the RBC membrane as a hybrid mesoscopic method (LB–SL) has shown to be both efficient and accurate [3].

Owing to the success of DNS for whole blood, the mechanisms of migration and margination of microscale particles in blood flow have been understood to a considerable extent. In the study of hemostasis and platelet-rich thrombi formation, the mechanism of platelet margination has been investigated and shown its dependence on hemodynamics and cell properties [11-13]. For micro-sized particles of high rigidity (such as platelets, WBCs and stiffened RBCs under pathological conditions) suspended in non-dilute RBC suspensions, the propensity of particle margination is found to be mainly driven by the RBC-enhanced diffusion in the RBC-laden region as well as the sink-like effect of the RBC-depleted layer [14-16]. Based on these complex margination mechanisms, a continuum model has been proposed to bridge the DNS capability with the patient-specific applications [17].

In contrast, analysis of the transport of NPs in cellular blood flow remains challenging due to the large length-scale discrepancy between NPs ~O(10 nm) and RBCs ~ O(10 μm), as shown in Fig. 1. Moreover, further complexities come from the intricate NP dynamics, which highly depend on the particle Brownian effect, inter-particle hydrodynamic interactions (HI) mediated through the fluid, and particle–RBC interactions. Because of the rapid development of the nanotherapeutics field, more attention has been drawn to understand the NP transport in blood vessels.

To study the influence of RBCs on NP transport in microcirculation, Tan et al. [18] apply a simplified Brownian dynamics approach for NPs and an immersed finite-element (FE) method for both RBC deformation and fluid flow, showing substantial margination behavior for 100 nm particles. Although the Brownian effect is included in the method, particles are only treated as passive tracers without including the effect of HI. It is shown that HI has a

* Corresponding author.
E-mail address: cyrus.aidun@me.gatech.edu (C.K. Aidun).

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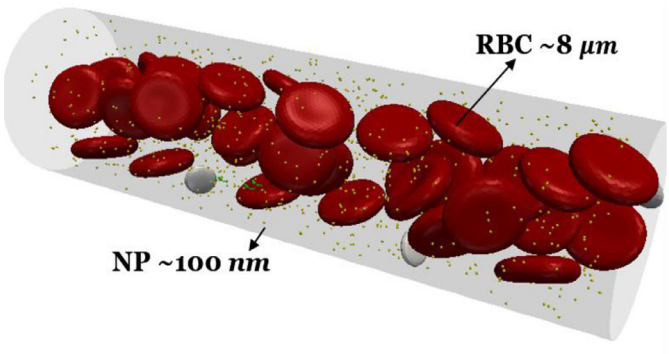

Fig. 1. NPs (yellow dots) transport in a cellular blood vessel with various constitutive components of large length-scale discrepancies. RBC (red) is about 8 μm; platelet (white) is 2 – 3 μm; the monomers of certain proteins, e.g. Von Willebrand factors (VWFs), can be as small as ~60 nm; and NPs are generally in the range of 0 – 500 nm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

significant effect on the microstructure and rheological properties of colloidal/non-colloidal suspensions [19,20]. A similar hydrodynamic approach is applied by Lee et al. [21] with all constituents (including NPs) resolved directly using FE grids. In their simulation, a dispersion factor defined as the ratio between the calculated radial diffusivity and theoretical Brownian diffusivity is introduced to quantify the severity of particle margination, which falls short of describing the actual total diffusivity of the particle. A rather insignificant NP margination is observed in their study, which is contradictory to the margination behaviors observed by Tan et al. [18]. Viewing the inefficiency of the current three-dimensional whole blood flow solvers, Tan et al. [22] apply two-dimensional simulations to obtain parametric behaviors of NP transport in cellular blood flow, which provides limited understanding on the actual three-dimensional NP migration behaviors; although some efforts have been made by Muller et al. [23] to try to connect the two-dimensional particle margination behavior with the three-dimensional counterparts.

One explanation for the above contradictory prediction of NP distribution in vessels may be overlooking the Brownian effect on the NP dynamics, given none of the studies above have provided solid verification or detailed analysis of the NP Brownian motion. However, the effect of thermal fluctuation on NPs suspended in blood is fundamentally important. For example, NP of diameter 50 – 100 nm suspended in a 20 μm vessel under typical wall shear rate $\dot{\gamma}_w = 500\ s^{-1}$ yields a Péclet number, $Pe = 3\pi\mu\dot{\gamma}_w d_p^3/(4k_BT)$, in the range of 0.04 – 0.3, indicating the significance of NP Brownian effect. Therefore, it is paramount to correctly resolve the NP Brownian motion in order to predict the accurate NP biodistribution in cellular vessels.

Given the multiscale nature of NP transport in cellular blood flow, hybrid approaches that combine NP dynamics and mesoscale hydrodynamic approach may be the key to realize accessible three-dimensional parametric studies with large variable space. Ahlrichs and Dünweg [24] couples a fluctuating LB method [25] with a Molecular dynamics (MD) approach for point particles through a friction term, exhibiting promising efficacy in dealing with solvent-polymer systems. Compared with the typical Brownian dynamics approach that addresses HI by dealing with an expensive mobility matrix, this hybrid LB–MD approach scales linearly with the number of particles; however, it requires an empirical rescaling of the prescribed friction coefficient to produce the theoretical Brownian diffusivity. Recently, Mynam et al. [26] showed that the empirical modification of the friction coefficient is due to extra mobility introduced by the fluctuating LB method. By removing the fluctuation in the fluid phase, a particle Brownian diffusivity is correctly determined without any artificial rescaling. Previous hybrid approaches for particle–solvent systems [24,26-28] require sub-iterations to maintain numerical stability while solving the Langevin equation (LE) coupled with the LB method, reducing overall computational efficiency.

Here, an efficient three-dimensional multiscale LB–LD approach for the NP-solvent system coupled with the well-established LB–SL method for RBC suspension [3] is proposed to fully resolve the NP transport in cellular blood flow. Two-way coupling between the NP and fluid phase is achieved by introducing an LB forcing source term [29] to account for the momentum exchange between the LB and LD system. The framework of this multiscale computational approach is depicted in Fig. 2, where all modules in different scales are included. The entire system is advanced in LB time scale without the necessity of introducing sub-time steps.

In Section 2, the basic elements of this computational approach are presented, namely the LB method for the fluid phase, the coarse-grained SL method to capture the RBC membrane dynamics, the LD approach for NPs, and the comprehensive two-way coupling schemes that bridge the entire computational framework. In Section 3, the accuracy and robustness of this approach are demonstrated through multiple benchmark cases. Then in Section 4, this approach is applied to study the NP migration in a micro–vessel with a physiological concentration of RBCs. In Section 5, this work is concluded with some remarks and an outlook to the future work.

2. Methodology

2.1. Lattice-Boltzmann method

The method used to solve for the fluid-phase is based on the three-dimensional LB method developed by Aidun et al. [2,30,31]. The LB method relies on propagating the fluid particles with discrete velocities, $\boldsymbol{e}_i$, resulting in the formation of a lattice space. A collision step relaxes the particle distribution function (PDF), f_i, toward a local equilibrium PDF, $f_i^{(eq)}$, causing a diffusion of momentum. With the collision term linearized by the single-relaxation-time Bhatnagar, Gross, and Krook (BGK) operator [34], the time evolution of the PDF takes the form of

$$f_i(\boldsymbol{r} + \Delta t_{LB}\boldsymbol{e}_i,\ t + \Delta t_{LB}) = f_i(\boldsymbol{r},\ t) - \frac{1}{\tau}\left[f_i(\boldsymbol{r},t) - f_i^{(eq)}(\boldsymbol{r},t)\right] + f_i^S(\boldsymbol{r},t), \tag{1}$$

where τ is the normalized single relaxation time, and f_i^S is a forcing source PDF based on the method of He et al. [29] to account for the external force effect. This method has a pseudo-sound-speed of $c_s = \frac{\Delta r_{LB}}{\sqrt{3}\Delta t_{LB}}$, and a kinematic viscosity of $\nu_{LB} = (\tau - \frac{1}{2})c_s^2\Delta t_{LB}$ [35], where the LB time step, Δt_{LB}, and lattice unit distance, Δr_{LB}, are set equal to 1. At low Mach number, i.e., small $\frac{u}{c_s}$, the LB equation recovers the incompressible Navier-Stokes equation [36] with the equilibrium PDF determined by local macroscopic variables as

$$f_i^{(eq)}(\boldsymbol{r},t) = \omega_i\rho_{LB}\left[1 + \frac{1}{c_s^2}(\boldsymbol{e}_i\cdot\boldsymbol{u}) + \frac{1}{2c_s^4}(\boldsymbol{e}_i\cdot\boldsymbol{u})^2 - \frac{1}{2c_s^2}(\boldsymbol{u}\cdot\boldsymbol{u})\right], \tag{2}$$

where ρ_{LB} and $\boldsymbol{u}$ are the macroscopic fluid density and velocity given by moments of the equilibrium distribution functions, i.e., $\rho_{LB} = \sum_{i=1}^{\mathbb{N}} f_i^{(eq)}$ and $\boldsymbol{u} = \frac{1}{\rho_{LB}}\sum_{i=1}^{\mathbb{N}} f_i^{(eq)}\boldsymbol{e}_i$. The lattice weights, ω_i, are determined by the LB stencil in use. For the D3Q19 stencil used in this study, $\mathbb{N}$ is equal to 19, and ω_i is 1/3, 1/18, and 1/36 for the rest, nondiagonal, and diagonal directions, respectively [2]. The LB method is extensively validated [31,37,38] and proved to be suitable for DNS of dense suspension of particles and capsules [2,4].

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