Nanoparticle Diffusion in Microvessels

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Keywords: Blood flow, Red blood cell, Nanoparticle, Diffusion, Brownian motion

Nanoparticle (NP) diffusion in microvessels is influenced by both the RBC-enhanced shear-induced diffusion (RESID) and the Brownian diffusion (BD). We numerically investigate the NP radial diffusivity dependence on the hemorheological properties via a multiscale and multimodal complex blood solver. The NP radial diffusivity is found to peak at low hematocrit (5%) and level off at high hematocrit (>20%) under fixed WSR. Smaller vessel confines the suspension flow leading to lower diffusivity compared to larger vessels. BD and RESID follow simple superposition within the parameter ranges of this study. This work provides insights to the NP diffusion mechanisms in complex blood flow in micro-vessels.

1. Introduction

Nanotherapeutics is an emerging therapy technique that uses intravascularly injected NP systems to deliver drugs to biological targets such as tumor. Investigating the mechanisms of NP dispersion in vasculatures is of fundamental significance to the development of nano-drug systems with high bioavailability. Computational analysis of such complex multimodal suspension problem remains challenging due to the large length-scale discrepancy between NP ~O(10 nm) and RBC ~O(10 μm) and the complication of nanoscale particle suspension dynamics, shown in Figure 1. Here, we apply a recently developed multiscale and multimodal complex blood solver [1, 2] to investigate the NP radial diffusivity mechanism across a wide range of hemorheological and particle characteristics.

Figure 1. Multimodal cellular blood flow with various constitutive components, primarily including RBCs (red), platelets (white), nanoparticles (yellow) and proteins (green).

2. Methods

2.1 Lattice-Boltzmann method

The method for the fluid phase with suspended particle interaction is based on the three-dimensional LB method developed by Aidun et al. [3-5]. The LB method solves the discretized Boltzmann equation in velocity space through the propagation of the fluid “particle” along the discrete lattice velocities and the collision of the local fluid “particle” to be relaxed to the equilibrium distribution. The collision term is linearized by the single-relaxation-time Bhatnagar, Gross, and Krook (BGK) operator [6]. The LB method is extensively validated [5, 7, 8] and proved to be suitable for the direct numerical simulation (DNS) of dense suspensions of both rigid and deformable particles in complex flows with high efficiency and scalability [3, 9].

2.2 Langevin-dynamics approach

The multiscale particle and polymer dynamics are resolved with high efficiency and accuracy through a coupled LB-LD approach that has been extensively verified [1, 2, 10] and successfully applied to particle transport in cellular blood flow [2, 10-14]. This approach allows for capturing the dynamics of particle ranging from nanoscale to microscale without refining the Eulerian lattice resolution. The LD particles are coupled to the LB fluid in a two-way fashion with both the Brownian effect and many-body hydrodynamics interactions fully resolved at linear scales. The particle dynamics can be described by

\[ m_i \frac{d^2x_i}{dt^2} = c_i \mathbf{P}_i + \mathbf{P}_n + \mathbf{S}_i, \]  

where \( m_i \) is the mass of particle \( i \). The conservative force, \( c_i \mathbf{P}_i \), specifies interparticle or particle-surface interaction forces including the Lennard-Jones potential to account for the van der Waals force and particle volume-exclusion effect and the Morse potential for particle-cell interactions. The frictional force \( \mathbf{F}_n^i \) is assumed to be proportional to the particle relative velocity with respect to the local fluid [15]. The stochastic force term, \( \mathbf{S}_i \), satisfies the fluctuation dissipation theorem (FDT) [16] and gives rise to the Brownian effect.

2.3 Spectrin-link method

Modelling of RBC membrane is done through the coupling of a coarse-grained SL approach [17, 18] with the LB method, which has been extensively validated with experimental results and proved to be a successful tool to capture both single RBC dynamics and rheology of suspensions of RBCs at physiological concentrations [3, 19, 20]. In the SL model, the Helmholz free energy of the RBC network system \( E(x_a) \), including plane components and constraint potentials to conserve membrane area and cell volume, is given by

\[ E(x_a) = E_{in-plane} + E_{bending} + E_{volume} + E_{area}. \]  

The forces due to the SL method are determined by the spatial derivative of \( E(x_a) \) with respect to the triangulation link vectors. Each of the vertices that combine to form the triangulated RBC membrane surface advances per the set of Newton’s equations of motion. The coupling between the membrane and fluid is done through the simple bounce-back method [5]. The cell-cell interactions are resolved through sub-grid models [21, 22].

3. Results

Below we report the dependences of NP radial diffusivity in microvessels on the hemorheological properties given the page limit. A variation of hematocrit, \( \text{Ht} = 0-30\% \), is considered to show the hematocrit dependence. The effect of confinement ratio, \( d_p/d_v \), is studied by considering two sizes of vessel diameter, \( d_v = 20 \mu m \) and \( 40 \mu m \). A fixed wall shear rate (WSR) \( \dot{\gamma}_w = 2000 s^{-1} \) matching typical physiological WSR in arterioles is applied to all cases. NP size is fixed to be 100 nm for all cases. The severity of the particle Brownian effect is determined by a Pelet number, \( Pe = 3\pi \eta_w d_p^2/(4k_BT) \), and RBC deformability is quantified by a Capillary number, \( \text{Ca}_G = \mu \dot{\gamma}_w d_p/(2G) \), where \( \mu \) is the plasma dynamics viscosity, \( G \) is the RBC moduli and \( d_p \) is the RBC disk diameter.

Figure 2 (A) depicts the NP-RBC binary suspension flow in a 40 μm vessel at equilibrium state. The RBC phase has a 20% hematocrit; the NP number concentration is \( 1 \times 10^5/ml \) resulting in 10,000 NPs in the periodic tube section. Figure 2 (B) presents
the normalized site-specific NP radial diffusivity, \( D_{r\tau} = D_{rr}/(\Delta t^2) \), where the particle radial diffusivity, \( D_{rr} \), is evaluated by measuring mean-squared radial displacement (MSRD) of each particle. It is shown that \( D_{r\tau} \) exhibits a "donut" shape distribution, i.e., the radial diffusivity appears to be axisymmetric with low diffusivity occurs at the axial and near-wall regions. This non-monotonic distribution of \( D_{r\tau} \) along radius follows the pattern of the platelet cross-stream velocity fluctuation distribution in a microchannel reported by Zhao and Shaqfeh [23], which suggests that the anisotropic distribution of the \( D_{r\tau} \) can be attributed to the velocity fluctuations induced by the RBC phase as well as the vessel wall. 

**Figure 2** (C) summarizes the ensemble-averaged particle radial diffusivity, \( \langle D_{r\tau} \rangle = \langle D_{rr} \rangle / \langle \Delta t^2 \rangle \), at different \( Ht \) within a 20 \( \mu \)m or 40 \( \mu \)m vessel. The apparent diffusivity, \( \langle D_{rr} \rangle \), defined as the diffusivity when BD and RESID co-exist, is shown to peak at low \( Ht \) and saturate at \( Ht > 20\% \) under a constant pressure drop. The trend of the \( \langle D_{r\tau} \rangle \) is shown to be determined by RESID, \( \langle D_{rr} \rangle \), while BD, \( \langle D_{rr}^B \rangle \), is almost added to RESID, given the superimposed diffusivity \( \langle D_{rr}^{TBP} \rangle = \langle D_{rr} \rangle + \langle D_{rr}^B \rangle \) matches well with \( \langle D_{rr} \rangle \) from computation. The decrease of the diffusivity at high \( Ht \) may be correlated to the bluntness of the velocity profile at high \( Ht \) shown in **Figure 2** (D), suggesting a decreased local shear rate due the Fahraeus-Lindqvist effect [24]. Besides, \( \langle D_{r\tau} \rangle \) increases as the confinement ratio. This can be explained by noticing the drop of \( \langle D_{rr} \rangle \) near the wall shown in **Figure 2** (B); the larger the tube the less prominent the reduction of \( \langle D_{rr} \rangle \) due to the wall effect.

![Figure 2](image)

**Figure 2.** The decomposition and variation of the normalized particle radial diffusivity under different hemorheological conditions. (A) A well-dispersed RBC-NP binary suspension flow in a 40 \( \mu \)m vessel at 20\% hematocrit, \( Pe = 3.3 \) and \( C_{aq} = 1.52 \); (B) the distribution of the NP normalized radial diffusivity corresponding to (A) scenario; (C) the normalized NP radial diffusivity variation about different hematocrit and confinement ratio; (D) the flow axial velocity profile under different hematocrit.

4. Conclusions

The dependence of the NP radial diffusivity on hemorheological properties is investigated quantitatively. The NP apparent diffusivity is shown to peak at low hematocrit and saturate at high hematocrit under fixed WSR. Smaller vessel confines the suspension flow leading to lower NP radial diffusivity. The interplay between BD and RESID is shown to follow simple superposition.

Sandia National Laboratories is a multimission laboratory managed and operated by National Technology and Engineering Solutions of Sandia LLC, a wholly owned subsidiary of Honeywell International Inc. for the U.S. Department of Energy’s National Nuclear Security Administration under contract DE-NA0003525.

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