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# Predicting the vascular adhesion of deformable drug carriers in narrow capillaries traversed by blood cells

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ABSTRACT

In vascular targeted therapies, blood-borne carriers should realize sustained drug release from the luminal side towards the diseased tissue. In this context, such carriers are required to firmly adhere to the vessel walls for a sufficient period of time while resisting force perturbations induced by the blood flow and circulating cells. Here, a hybrid computational model, combining a Lattice Boltzmann (LBM) and Immersed Boundary Methods (IBM), is proposed for predicting the strength of adhesion of particles in narrow capillaries (7.5 $\mu$m) traversed by blood cells. While flowing down the capillary, globular and biconcave deformable cells (7 $\mu$m) encounter 2 $\mu$m discoidal particles, adhering to the vessel walls. Particles present aspect ratios ranging from 0.25 to 1.0 and a mechanical stiffness varying from rigid (Ca = 0) to soft (Ca = $10^{-3}$). Cell–particle interactions are quantitatively predicted over time via three independent parameters: the cell membrane stretching $\delta p$; the cell-to-particle distance $r$, and the number of engaged ligand–receptor bonds $N_L$. Under physiological flow conditions (Re = $10^{-2}$), rigid particles are detached and displaced away from the wall by blood cells. This is associated with a significant cell membrane stretching (up to 10%) and rapid breaking of molecular bonds (t $u_{max}$/H <1). Differently, soft particles deform their shape as cells pass by, thus reducing force perturbations and extending the life of molecular bonds. Yet, only the thinnest deformable particles (2 ×0.5 $\mu$m) firmly adhere to the walls under all tested configurations. These results suggest that low aspect ratio deformable particles can establish long-lived adhesive interactions with capillary walls, enabling *de facto* vascular targeted therapies.



## 1. Introduction

Targeting the diseased vasculature is an attractive strategy for the diagnosis and treatment of a variety of pathologies. In cancer, endothelial cells express unique receptor molecules, such as integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$, tumor endothelial markers, vascular epidermal growth factor receptors, and so on (Neri and Bicknell (2005) and Atukorale et al. (2017)). In cardiovascular and chronic inflammatory diseases, the endothelium presents inflammatory molecules, such as P- and E-selectins, ICAM and VCAM-1, higher densities as compared to the normal vasculature (Libby, 2002; Ta et al., 2018; Soriano et al., 2000). Even, within the white adipose tissue, specific receptors are exposed on the surface of endothelial cells (Kolonin et al., 2004; Daquinag et al., 2011; Anselmo and Mitragotri, 2017). Although some of these receptors could be directly used as targets for small therapeutic molecules, most of them would serve as docking sites for blood-borne, vascular targeted particles (Kolhar

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et al., 2013; Decuzzi and Ferrari, 2008). Engineered micro- and nano-carriers for the precise delivery of multiple agents are entering clinical trials for the diagnosis and treatment of a variety of diseases, including cancer, cardiovascular and neurological (Peer et al., 2007; Mulder et al., 2014). These carriers are realized using different techniques where attributes such as the size, the composition, the surface properties and, more recently, the shape and mechanical stiffness can be finely and independently tuned (Euliss et al., 2006; Godin et al., 2012; Muro et al., 2008; Palange et al., 2017; Palomba et al., 2018; Anselmo et al., 2015). Vascular targeted carriers can deposit at the luminal side large amounts of imaging and therapeutic molecules whose controlled release towards the diseased tissue can be triggered via a number of mechanisms, including chemical and mechanical stimuli (Mura et al., 2013).

Several reports have investigated the vascular transport of micro and nano-carriers in the attempt to identify the optimal configuration that could favor their deposition on endothelial walls. For instance, the works of Liu and collaborators showed that red blood cells would favor the lateral drifting and vascular binding of sufficiently large nanoparticles (Tan et al., 2011). Similarly, the authors demonstrated that the contribution of red blood cells is mostly amplified for micron-sized particles over conventional 100 nm nanoparticles (Lee et al., 2013). A more comprehensive analysis was provided by Vahidkhah and Bagchi, who considered the vascular transport and adhesion of spherical, prolate and oblate spheroids with differ aspect ratios (Vahidkhah and Bagchi, 2015). Their numerical results confirmed that oblate spheroids with moderate aspect ratios would more efficiently marginate and adhere to the wall, as compared to spherical particles and prolate spheroids. Beyond size and shape, the effect of particle deformability on margination dynamics was documented in the work of Muller et al. (2016). These authors confirmed that micrometer carriers marginate better than their sub-micrometer counterparts and that deformable carriers are less prone to marginate as compared to rigid particles and demonstrated, in complex whole blood flow, that 2D and 3D simulations of red blood cells tend to return qualitatively similar results. Fish M. B. and colleagues explored the ability of micro- and nanosized particles to identify and bind to diseased endothelium, confirming that microcarriers outperforms nanoconstructs in margination and adhesive properties (Fish et al., 2017). In particular, rigid particles show improved adhesive abilities for large shear rate, while soft particles for low shear rates. 3D blood flow modeling and the accurate description of the viscoelastic properties of red blood cells (RBCs) has allowed the scientific community at large to learn more about molecular, nano and microscale transport within capillary networks, under physiological and pathological conditions (Fedosov et al., 2010; Ahmed et al., 2018; Li et al., 2017). Nonetheless, 2D models can still be very effective in dissecting some basic mechanisms regulating the interaction between deformable RBCs and nano/micro-particles. For instance, a recently published paper used a 2D blood flow model to predict the dispersion of nanoparticles, as a function of the RBC motion and deformation, in good agreement with experimental data (Tan et al., 2016). Despite these seminal works, at authors' knowledge, no study has ever systematically analyzed the interaction between particles deposited onto a wall and circulating blood cells.

Carrier margination and adhesion are necessary but not sufficient conditions for fully realizing drug delivery through vascular targeting. Indeed, carriers should adhere to the vessel walls for sufficiently long times, without being dislodged away by hemodynamic forces and circulating cells, in order to support the continuous and controlled release of therapeutic agents towards the diseased tissue. In this work, the authors propose a hybrid computational scheme, combining an Immersed-Boundary (IBM) and a Lattice Boltzmann–BGK (LBM) method, for studying cell–particle interactions in narrow capillaries. While the IBM serves to characterize the capillary transport of deformable objects (cells and particles), the LBM provides an Eulerian description of the fluid evolution (Coclite et al., 2016). While flowing within a narrow capillary, 7 $\mu$m deformable cells encounter particles adhering to the wall, which act as partial occlusions. Cell and particle dynamics are predicted under different conditions, including four cell shapes, resembling leukocytes and erythrocytes; four aspect ratios for the adhering particles; two values of particle affinity with the vascular walls and two different values of the mechanical stiffness of the particles. Three parameters are introduced for quantitatively described the physical problem, namely the stretching ratio of the cell; relative distance between particles and cells; and adhesive strength of the particles to the wall.

## 2. Computational method

### 2.1. The lattice Boltzmann method

The evolution of the fluid is defined in terms of a set of N discrete distribution functions $\{f_i\}, (i = 0, \ldots, N-1)$, which obey the dimensionless Boltzmann equation

$$f_i(\boldsymbol{x} + \boldsymbol{e_i}\Delta t, t + \Delta t) - f_i(\boldsymbol{x}, t) = -\frac{\Delta t}{\tau}\left[f_i(\boldsymbol{x}, t) - f_i^{eq}(\boldsymbol{x}, t)\right], \tag{1}$$

in which $\mathbf{x}$ and t are the spatial and time coordinates, respectively; $[\boldsymbol{e}_i], (i = 0, \ldots, N-1)$ is the set of discrete velocities; $\Delta$t is the time step; and $\tau$ is the relaxation time given by the unique non-null eigenvalue of the collision term in the BGK-approximation (Bhatnagar et al., 1954). The kinematic viscosity of the flow is strictly related to the single relaxation time $\tau$ as $\upsilon = c_s^2\left(\tau - \frac{1}{2}\right)\Delta t$ being $c_s = \frac{1}{\sqrt{3}}\frac{\Delta x}{\Delta t}$ the reticular speed of sound. The moments of the distribution functions define the fluid density $\rho = \sum_i f_i$, velocity $\boldsymbol{u} = \sum_i f_i \boldsymbol{e_i}/\rho$, and the pressure $p = c_s^2\rho = c_s^2\sum_i f_i$. The local equilibrium density functions $[f_i^{eq}]\,(i = 0, \ldots, N-1)$ are expressed by the Maxwell–Boltzmann distribution

$$f_i^{eq}(\boldsymbol{x}, t) = \omega_i\rho\left[1 + \frac{1}{c_s^2}(\boldsymbol{e_i}\cdot\boldsymbol{u}) + \frac{1}{2c_s^4}(\boldsymbol{e_i}\cdot\boldsymbol{u})^2 - \frac{1}{2c_s^2}\boldsymbol{u}^2\right]. \tag{2}$$