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Characterization of nanoparticle binding dynamics in microcirculation using an adhesion probability function

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ABSTRACT

Quantitative understanding of nanoparticles transport and adhesion dynamic in microcirculation is very challenging due to complexity of fluid dynamics and imaging setup. In-vitro experiments within microfluidic channels showed the significant influence of shear rate, carrier size, particle-substrate chemistry and vessel geometry on particle deposition rate. However, there are few theoretical models that can accurately predict experimental results. We have developed a numerical model to predict nanoparticle transport and binding dynamics and verified with our previous *in-vitro* tests results. A binding probability function is used to simplify the carrier attachment and detachment processes. Our results showed that due to the complex dynamics of particle transport and adhesion mechanism, the correlation between binding probability and actual deposition rate is not linear. Using experimental data, it is shown that the binding probability of small particles changes slightly with shear rate whereas the chance of binding for big particles decreases exponentially with shear. Our particulate model also captured some phenomena that cannot be achieved by continuum approach such as accumulation of drug particles in close vicinity of vessel wall. In addition, the effects of channel geometry and antibody density on particle binding are discussed extensively. The results from our particulate approach agrees well with experimental data suggesting that it can be used as a simple, yet efficient predictive tool for studying drug carrier binding in microcirculation.

1. Introduction

Nanoparticles have been widely studied as potential multifunctional carrier platforms for therapeutic drug delivery and imaging applications (Chauvierre et al., 2003; Farokhzad and Langer, 2006; Nasongkla et al., 2006; Roney et al., 2005; Zhou et al., 2016). To deliver drugs to target diseased site, carriers of various sizes and shapes are needed to circulate in the body for a sufficient period of time. They need to laterally drift toward the vascular wall, interact with the receptors expressed on the vascular wall, and finally bind at the diseased region. Particle sizes can range from a few tens/hundreds of nanometers, such as dendrimers, micelles, nano-shells and polymeric spheres (Allen and Cullis, 2004; Duncan, 2006; Hirsch et al., 2003; Peer et al., 2007), to a few microns, such as lipid and silica-based microspheres (Tasciotti et al., 2008; Slowing et al., 2008). Furthermore, their shape can also vary from spheroidal to cylindrical, discoidal (Xu et al., 2009; Rolland et al., 2005; Champion et al., 2007) and nanopolypods (Ren and Tilley, 2007). The biodistribution of drug carriers in a vascular network will depend on many parameters such as particle size, shape, and local flow conditions (Sohrabi et al., 2014; Tan et al., 2016). For instance, several studies have demonstrated that particle binding is inversely correlated with shear rates (Lin et al., 2010; Blackwell et al., 2001). The adhesion of nanocarriers also depends on targeting antibodies' affinity and surface density (Muzykantov et al., 2012). Moreover, junctions and bifurcations in microvasculature largely influence particle binding (Prabhakarpandian et al., 2008; Tousi et al., 2010).

The size of particle significantly influences drug targeting specificity and efficacy. For instance, targeting capabilities and uptake of small nano-particles (NP) are enhanced by their larger surface to volume ratio. On the other hand, bigger drug carriers can carry higher payloads when used in vascular targeting. Drug carriers bigger than 20 nm are eliminated from circulation mainly by liver, spleen and lymphatic nodes (Leucuta, 2013; Fraley and Papahadjopoulos, 1982) and particles larger than ~500 nm generally have higher chance of depositing in capillaries (Shuvaev et al., 2011). Furthermore, carriers of radius under 100 nm are reported to migrate toward the vessel wall and interact

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with the endothelium more easily (Decuzzi et al., 2005). The deposition of spherical particles was shown to reduce monotonically as their diameter increase from 700 nm to 3 μm (Decuzzi et al., 2010). Also, it is observed that 3–4 μm particles are more likely to be permanently trapped into the open circulation of the spleen (Chen, 1978).

Due to complex physiological conditions and bioethical regulations, it is very challenging to quantify the drug delivery *in vivo*. Therefore, most of experimental studies are carried out in flow channels (Haun and Hammer, 2008; Kona et al., 2012). For example, Thomas et al. (Thomas et al., 2014) performed an in-vitro study in a microfluidic chip mimicking microvasculature. They showed that particle binding density decreases with increased shear rates for 200 nm and 2 μm particles and reported 10% higher binding at branching regions compared to straight sections. In that study, specificity in targeting is introduced by applying ligand-receptor chemistry on targeted region. Their biomimetic chip was coated with intercellular adhesion molecule 1 (ICAM-1) protein to study the influence of antibody density on binding.

Numerical models have been extensively used to study drug particle behavior in blood flow. Liu et al. (Liu et al., 2010) combined Monte Carlo and weighted histogram analysis method to study the nanocarrier binding affinities. Lee et al. (Lee et al., 2009) used immersed finite element method to simulate a nanoparticle focusing lens in a microfluidic channel. Gentile et al. (Gentile et al., 2008) investigated the effect of vessel permeability and blood rheology on the transport of nanoparticles. Longest et al. (Longest and Kleinstreuer, 2003) simulated the blood particle deposition process in a non-parallel flow. Decuzzi and Ferrari (Decuzzi and Ferrari, 2006) studied the ligand-receptor binding dynamics of non-spherical particles and proposed a simple formula for binding probability incorporating several factors such as hemodynamic forces, receptor and ligand density. However, there is no generalized model which could link nano-scale adhesion dynamic to measurable total deposition densities. Such a model should be benchmarked with the existing experimental data and can serve as a predictive tool in drug deliver studies.

In this paper, a numerical approach is developed to study drug particle deposition in a branched micro-channel under various shear rates. This model captures the complex dynamics of carrier transport and binding as well as their effect on actual deposition rate. Direct comparison with our previous in-vitro testing results (Thomas et al., 2014) is performed for particles of different sizes and surface chemistries. Our particulate approach helps capture phenomena which cannot be achieved by continuum models. In what follows, model geometry and parameters are first introduced. After discussing the complex correlation between binding probability and actual deposition, the effects of shear, antibody density, and geometry on particle binding are studied and discussed in detail.

2. Computational model

In our previous in-vitro experiments of NP binding (Thomas et al., 2014), ligand-receptor chemistry is applied on a microfluidic platform. The substrate of the biomimetic chip is coated with intercellular adhesion molecule 1 (ICAM-1) protein with density of 121 ± 12 sites/μm^2. The fabrication process of microfluidic device as well as coating/characterization of particles with ICAM-1 and substrate with anti-ICAM-1 are described in our prior work (Thomas et al., 2014) where the binding densities of 200 nm and 2 μm particles were reported under various shear rates. Following the experimental conditions, we performed numerical simulations with mean inlet velocity of 0.05 to 0.4 m/s which correspond to physiologically relevant shear rates of 200 to 1600 s^{-1} observed in the microvessels (Nagaoka and Yoshida, 2006; Nigro et al., 2011). The kinematic viscosity of the buffer solution is 1 cP.

In this study, the flow in microfluidic channel is assumed to be laminar and Newtonian. The steady state flow field is solved using conventional discretized form of Navier-Stokes equation (Sohrabi et al., 2014). Trajectories of discrete phase particles are calculated by integrating the force balance on the particle using Velocity Verlet algorithm in a Lagrangian reference frame. The particle velocity can be expressed as:

$$\frac{du_p}{dt} = \frac{18\mu}{\rho_p d_p^2}\left(\vec{u} - \vec{u}_p\right) + F_{b_i} \tag{1}$$

where $\vec{u}$ is the fluid phase velocity, $\vec{u}_p$ is the particle velocity, ρ_p is the density of the particle, d_p is the particle diameter, μ is the viscosity of the fluid and F_{b_i} is the Brownian force. The amplitudes of the Brownian force components are of the form

$$F_{b_i} = \zeta_i\sqrt{\frac{\pi S_0}{\Delta t}};\ S_0 = \frac{216\upsilon k_B T}{\pi^2\rho d_p^5\left(\frac{\rho_p}{\rho}\right)^2} \tag{2}$$

where ζ_i are zero-mean, unit-variance-independent Gaussian random number, and Δt is the calculation time step. T is the absolute temperature of the fluid, υ is the kinematic viscosity and k_B is the Boltzmann constant. The detail description about how particles react as they hit the microchannel boundaries and how binding probability function integrated into model are discussed in the next section.

A setup similar to experiments is used in our computational model as shown in Fig. 1a. The particle binding density is measured at the center section of the bottom channel surface. The width and height of channels are both 100 μm. The sampling regions of parent and daughter vessels are located far from inlet and bifurcation, respectively. The

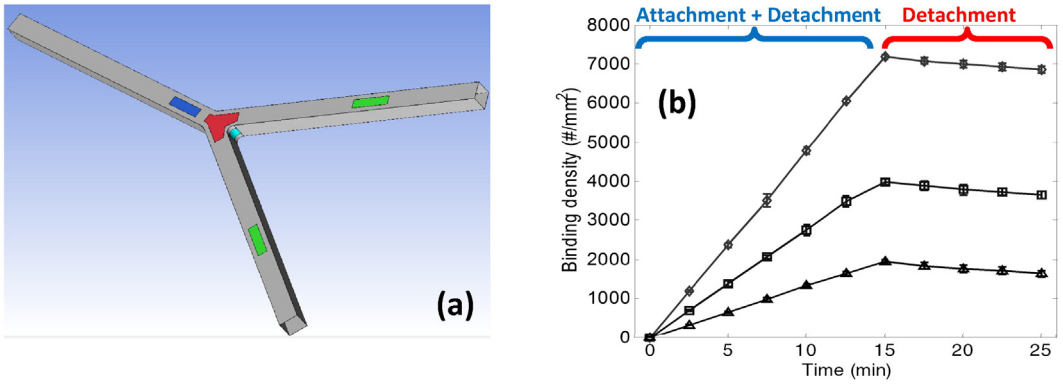

Fig. 1. (a) Sampling regions: Dark blue, red, light blue and green color regions correspond to parent, branching, bifurcation and daughter sampling regions, respectively. (a) Time history of binding density for 200 nm particles for three anti-ICAM-1 densities (Thomas et al., 2014). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)