

Vascular transport and adhesion of nanocarriers in targeted drug delivery: bridging spatial and temporal scales using dynamical density functional theory and generalized Langevin equations

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Vascular targeting of functionalized nanocarriers (100 nm-1 μ m in size) to endothelial cells is a promising and viable therapeutic strategy in systems pharmacology. The efficiency of drug delivery using such nanocarriers is influenced by various physicochemical factors. These include: (1) the effect of hematocrit and flow field in determining the margination probability of the nanocarrier in the red blood cell (RBC)-free layer close to the vessel wall; (2) hydrodynamic interactions due to the wall; (3) thermal fluctuations; (4) glycocalyx resistance; (5) specific ligand-receptor binding interactions. Owing to the wide spectrum of time and length scales involved in this dynamical process, a unified theoretical framework bridging microscale many-body hydrodynamic interactions among the RBCs and nanocarriers, and the nanoscale adhesive dynamics for nanocarrier binding incorporating the receptor protein internal dynamics, would provide useful insight into the tailored design of functionalized nanocarriers for specific physiological environments, *in vivo*. To this end, we present a coarse-grained theoretical model for studying nanocarrier-cell adhesive dynamics in the presence of RBCs using a combined framework of generalized Langevin equations (GLEs) and dynamical density-functional theory (DDFT). The functionalized spherical nanoparticle is modeled with surface-tethered ligands that interact with the receptors on the endothelial cells. At the microscale within the vessel tube, using DDFT we obtain the RBC distribution and RBC-driven marginating potential for various vessel diameters, hematocrit densities, and blood flow rates through minimization of the RBC free energy functional under flow with respect to spatially varying RBC density. At the nanoscale close to the cell surface on the vessel wall, we formulate and simultaneously solve a set of GLEs for nanocarrier motion and ligand-receptor pair relaxation in the presence of the marginating potential, glycocalyx resistance, particle-wall hydrodynamic interactions, and Brownian interactions. We analyze the velocity and position autocorrelation functions along suitable coordinates (nanocarrier center of mass translation, ligand-receptor bond distance, and tether coordinates) to elucidate how the various interactions determine the relaxation dynamics of the nanocarrier. Complementing the free energy landscape of nanocarrier binding to cells [1], the autocorrelation functions quantify the effects of the physiological variables on the nanocarrier attachment and detachment (on- and off-) rates. In order to validate our model, the predicted time correlation functions for nanocarrier motion in a fluid close to a boundary (vessel-wall) are verified by direct numerical simulations of the Navier-Stokes equations using the finite element method for different particle separations from the vessel wall [2]. Our model results will assist in the optimal design of the nanocarrier for targeted drug delivery applications. We acknowledge support from NIH through grant NIH 1R01EB006818-05.

References:

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