Title: Generalized Langevin Dynamics for Functionalized Nanocarrier Adhesion to Cell Surfaces in the Presence of Hydrodynamic Interactions

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PAVascular delivery of antibody-functionalized nanocarriers (50 nm-1 mm in size) to selectively bind targeted surface receptors expressed by endothelial cells is a viable therapeutic strategy in systems pharmacology. However, optimal nanocarrier design involves the appropriate selection of their size, shape, and antibody density on their surface. Additionally, the choice of appropriate tethers/linkers bridging the antibodies to the nanocarrier surface depends on the physiological microenvironment, including hemodynamics and rheological properties of blood flow in the microvasculature as well as the state of the endothelial cells (which governs expression of targeted receptors such as intracellular adhesion molecule-1, ICAM-1). We have recently shown that a model-based optimization of this design can be used to guide the achievement of targeting selectivity and specificity in vivo [1,2]. Here we address the important aspects of nanocarrier adhesive dynamics in terms of how they impact binding selectivity and specificity. The main hypothesis of this work is that the efficiency of vascular targeted drug delivery using functionalized nanoparticles is affected simultaneously by both biophysical and biochemical factors, including the margination probability of the nanocarrier towards the red blood cell-free layer, hydrodynamic interactions due to the wall and the near-wall flow field, thermal fluctuations, and the specific ligand-receptor (or antibody-antigen) binding interactions. A complete description of hydrodynamic interactions for the system can be achieved by direct numerical simulations of the fluctuating hydrodynamic equations, which simultaneously resolve the velocities and the stresses of the fluid medium and the particles [3-5]. Such a model can be pursued only for simple geometries for small systems such as short capillary segments not much longer than a few diameters of the blood cells, but it is not realistic for a pharmacological model considering nanocarrier margination and binding in a vascular network tree. With the objective of developing a coarse-grained description of the hydrodynamics in complex geometries, we present a generalized Langevin dynamics aiming to capture the adhesive dynamics of the nanocarrier close to the vessel wall in the presence of RBC-driven marginating potential, hydrodynamic interactions and Brownian forces. The functionalized nanoparticle is modeled as a hard or soft sphere with surface-grafted tethered ligands (antibodies) that interact with the receptors (e.g., ICAM-1) on the endothelial cell surface. To incorporate the memory effects of the nanocarirer due to coupling with the locally confined fluid and the relaxation of the ligand-receptor pair, a set of non-Markovian, generalized Langevin equations [6] for the nanocarrier motion (translational and rotational motion about the center of mass) and the stretching for each ligand tether as well as antibody-antigen pair are solved simultaneously. The space-time dependent memory functions are obtained from independent experiments [7], microscopic simulations [8], or analytical theories [9]. We analyze the nanocarrier velocity autocorrelation function along suitable coordinates (center of mass translation/rotation, ligand-receptor bond, and tether coordinates) to characterize nanocarrier adhesive dynamics and the potential of mean force along a specified reaction coordinate to quantify the binding affinity [1] in the presence of various hydrodynamic couplings.

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