Multiscale Modeling and optimization of nanocarrier targeting in drug delivery

R.Radhakrishnan*, P.S. Ayyaswamy**, David M. Eckmann*,***
*Department of Bioengineering
**Department of Mechanical Engineering and Applied Mechanics
***Department of Anesthesiology and Critical Care
University of Pennsylvania, Philadelphia, PA 19104

Abstract:

Targeted drug delivery using functionalized nanocarriers (i.e. carriers coated with specific targeting ligands) represents a promising approach in therapeutic applications. However, targeting of nanocarriers (NCs) to endothelial cells (ECs) remains an important design challenge in biomedical science. The use of functionalized NCs offers a range of tunable design parameters (i.e., size, shape, linkers, targeting ligand density, control of drug release, etc.) and a high-dimensional tunable parameter space needs to be spanned to determine optimal design. Challenges inherent to design include: (i) physical/chemical properties of nanocarrier, (2) molecular and geometric parameters surrounding receptor-ligand interactions and NCs, (iii) accurate characterization of hydrodynamics, (iii) physico-chemical barriers for NC uptake/arrest/internalization, and (iv) uncertainty in targeting environment, to name a few. The dynamic process of delivery involves several scales: a macroscopic scale where transport of the carrier occurs in the flowing fluid medium of the vessel (variable Reynolds number), a mesoscopic scale where the carrier approaches the endothelial cell and interacts with flow in the glycocalyx and a nanoscale where the ligands on the carrier actually bind with the receptors on the cell membrane. Clearly, an actual modeling of the NC transport, targeting, and drug release would require a simultaneous treatment of all these scales for a given concentration of targeted carriers. A systematic approach would entail the individual treatment of processes associated with each scale for carriers of various sizes and densities, and bridging algorithms to rigorously pass information and match boundary conditions across scales, in order to obtain a composite picture.

Here, we describe a numerical finite-element study on the macroscopic scale which involves the description of the carrier motion subject to hydrodynamic forces in the flow in conjunction with Brownian as well as adhesive interactions. This macroscopic modeling is carried out in two different ways, i.e. by employing fluctuating forces on the NC [1] as well as by employing fluctuating stresses on the fluid [2]. We report that a hybrid approach which incorporates essential elements from both these approaches is necessary to simultaneously preserve thermodynamic distribution functions as well as hydrodynamic correlations [3,4]. The results for the attainment of thermal equilibrium between the carrier and the surrounding medium, diffusivity for the carrier in the medium, effect of the presence of the confining vessel wall and adhesive (receptor-ligand) interactions on particle displacement and diffusivity will be discussed. As a bridging strategy, we note that either of these methods may be easily generalized to investigate the fluctuating motion of a NC and its interactions with red-blood cells and platelets in which the near-field interactions are resolved directly (by simulating the dynamics of NC and blood cells), and the far-field effects of the particulate suspension (hematocrit) are treated as dispersion in NC velocities due to athermal collisions with red-blood cells; in such an application, in addition to a preset temperature, a particulate temperature of the blood plasma is introduced [3]. The algorithm for resolving NC dynamics discussed above will be integrated with that for the evaluation of mass transport (this is currently underway). The outcome of this scale study will be bridged with methods for computing absolute binding free energies and for sampling transient reaction paths in order to enable direct comparison with experimental methods (in vitro cellular targeting, in vivo targeting in mice, and biophysical measurements via AFM and microscopy) methods as described in our recent work [5,6]; we

note that bridging to the molecular scale in order to incorporate the effects of varying epitopes of receptors and ligands on the efficacy of targeting is discussed in our recent study [7]. By predicting the kinematics, dynamics and binding of the NCs, we are able to guide their precise design for addressing disease-specific targeting requirements, in vivo. This entails investigations of parameter sensitivity, such as NCs of various radii, densities that contain various drugs in vessels of different sizes and flow rates.

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Keywords: Targeted drug delivery, Brownian motion, hydrodynamic interactions, fluctuating hydrodynamics, non-Markovian, generalized Langevin, Absolute Binding Free Energy

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