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Dynamic Interactions of Targeted Nanocarriers with Endothelium

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Extended Abstract

The vascular administration of targeted nanocarriers enables precise delivery of drugs to diseased or inflamed endothelial cells. The primary therapeutic goal we are pursuing is to optimize endothelial delivery of antioxidant and anti-inflammatory agents for alleviation of acute pulmonary inflammation and oxidative stress through multiscale modeling with validating experimentation. A wide range of length and time scales are required for describing the physics of hydrodynamic and microscopic molecular interactions mediating nanocarrier motion in blood flow and endothelial cell binding in targeted vascular drug delivery. We incorporate features of nanocarrier design and optimization for clinical applications, including nanocarrier dimension, deformability, concentration and density of targeting molecules into computational models. We are conducting experiments and developing computational techniques required to understand binding interactions and hydrodynamics governing nanocarrier transport and cellular adhesion. Our modeling has been validated through synergistic molecular mechanics, cell culture and animal experiments of binding of selectively developed nanocarriers (Liu et al., 2010).

In this work, we have extended our computational framework to incorporate nanocarrier adhesion to live cells, where membrane compliance and fluidity play dominant roles. In particular, we investigate the explicit effects of membrane stiffness, deformation, local curvature, and excess area on the nanocarrier adhesion landscape. At the cellular length scales, the energy of the membrane is determined by relevant membrane properties namely bending rigidity, surface tension, membrane curvature, and excess surface area. The undulating membrane is modelled as a thin elastic sheet that is evolved computationally by simulating key degrees of freedom: thermal undulations and fluidity. All nanocarrier, receptor, and ligand degrees of freedom are also considered explicitly. The nanocarrier binding is quantified by computing the multivalency, spatial bond distribution, extent of membrane deformation etc., as a function of the afore-mentioned physical variables, which collectively reflect the physiological state of the target cell. We further quantify our results by computing the free energy landscape of adhesion; this also yields the computational analog of the experimentally measured binding avidity.

We also consider deformable gel-based nanocarriers, for which we have developed a Brownian dynamics framework incorporating hydrodynamic interactions to model cross-linked lysozyme-core/dextran-shell nanogels exposed to hydrodynamic shear forces. This work is motivated by our recent development of dextran-lysozyme nanogels (Coll Ferrer et al., 2013) and their recent application in targeted anti-inflammatory drug delivery to pulmonary endothelium in an endotoxin-induced murine experimental model of pulmonary inflammation, which we will describe. For our computational approach, we use Brownian dynamics simulations and theoretical models based on the hypothesis that molecular motion, polymer melt reptations, and entanglement density dominate the nanogel structure and dynamics. We specify an entanglement density and use simulated annealing to mimic the initial structure of the nanogels. We compute equilibrium and steady shear rheological

properties and entanglement density in presence of hydrodynamic interactions. We show that entanglements resist volume deformation under shear, which enhances the nanogel's role as a drug carrier. We also resolve internal and inhomogeneous/anisotropic stresses and strains, incorporating boundary effects, and combining this model with the functionalized NC model of adhesive interactions discussed above.

The computational approaches described here serve as powerful tools to fine-tune nanocarrier design for further clinical consideration. Development of such models, coupled with experiments, is essential to gain useful insights that can be translated into the optimal design of nanocarriers for endothelial targeting in vascular drug delivery.

References

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