**A multiscale model for predicting margination effects and transport of nanogels in blood vasculature: comparison of Dynamical Density Functional Theory and Monte Carlo based approaches**

David M. Eckmann3,4

Coauthors: Zahera Jabeen,1 Hsiu-Yu Yu,2 Portonovo S. Ayyaswamy,1 Ravi Radhakrishnan4,5

1Department of Mechanical Engineering and Applied Mechanics, University of Pennsylvania, Philadelphia, PA 19104, USA.

2Department of Chemical Engineering, National Taiwan University, Taipei 10617, Taiwan.

3Department of Anesthesiology and Critical Care, University of Pennsylvania, Philadelphia, PA 19104, USA

4Department of Bioengineering, University of Pennsylvania, Philadelphia, PA 19104, USA

5Department of Chemical and Biomolecular Engineering, University of Pennsylvania, Philadelphia, PA 19104, USA

Vascular targeted drug delivery is emerging as a promising therapeutics and diagnostic approach in many diseases. However, the percentage of drug-carriers which reach the targeted site via transport through the complex vasculature is a minuscule number (~0.01%) owing to hydrodynamic and other physiological barriers such as glycocalyx. When the drug carriers are injected into the blood stream, they face a heterogeneous environment in which the red blood cells form a cell-rich core in the middle and a cell-free layer near the walls of the capillaries. The process of margination of the drug-carriers, in which they escape to the near wall-region close enough to bind with the endothelium, depends on the design of the drug-carrier, namely shape, size and flexibility, and its hydrodynamic interactions with the blood flow and the vasculature. Nanogels synthesized with tunable cross-linking density represent a viable drug-carrier for vascular delivery applications [1] with the hope that the barriers can be surmounted. As a class of nanocarriers, the nanogel has the added benefit of finely tunable degree of flexibility (by controlling the crosslinking density) and deformability to ellipsoidal or spheroidal shapes under flow and confinement. The open challenge is to exploit these properties to enhance drug delivery efficiency. Towards this end, it is desired to simultaneously yield efficient margination of these nanogels to increase the encounter with the vessel wall, as well as enhanced adhesion mediated through multivalent receptor ligand bonds between the proteins functionalized on the nanogels and the receptors on the cell surface; these will lead to an enhanced binding to, and subsequent uptake by, the endothelial cells.

Here, we aim to study the margination effect and the dependence on flow rate, vessel diameter, and hematocrit density. In our multiscale model, we define and compute a composite interaction potential which includes the hydrodynamic interactions of the nanogel with blood flow and the vasculature. Towards this end, we utilize analytical techniques like Dynamical Density Functional Theory [2] and computational approaches comprising of a combination of finite element based direct numerical simulations (DNS) [3] and Monte Carlo (MC) simulations [4]. As proof of principle, we have been successful in implementing DDFT for flow-driven particulate suspensions modeled as hardspheres confined in a cylindrical vessel, and experiencing a lift-force due to hydrodynamic interactions with the confining wall. The density distribution of the particulates as a function of RePe (product of Re: Reynolds and Pe: Peclet numbers), vessel diameters, and particulate density obtained from DDFT was validated using Monte Carlo simulations. Consistent with previous studies, we observe inhomogenous density distributions in the radial direction. In addition, we see increased spatial correlations at higher flow rates. A margination potential due to this density distribution will act on smaller particles (also modeled as hard spheres) to influence their margination to the wall. These calculations can be exploited in predicting the behavior of nanocarrier margination amidst red blood cell (RBC) laden flow in blood vessels.

Current work is focused on extending the computational model to include hydrodynamic interactions due to pair-wise collisions, incorporate shape and deformability effects (by modeling the RBCs as discoids [5] and nanogels as ellipsoids [6] interacting via Gay-Berne potential). The shape anisotropies of the RBCs and nanogels as well as the deformability of both RBCs and nanogels will be mapped to the shape parameters and interaction energies of the Gay-Berne discoids and ellipsoids respectively. The lift force on the RBCs and nanogels will be estimated using ALE-based DNS, and incorporated in the model [7,8,9]. As discussed in [3], our multiscale framework will utilize the computation of hydrodynamic interactions using rigorous and computationally demanding methods like DNS and perform MC and generalized Langevin equation (GLE) simulations to predict margination of NCs in physiological blood flow conditions.

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