IMFEM Framework for Drug Delivery in Microvasculature

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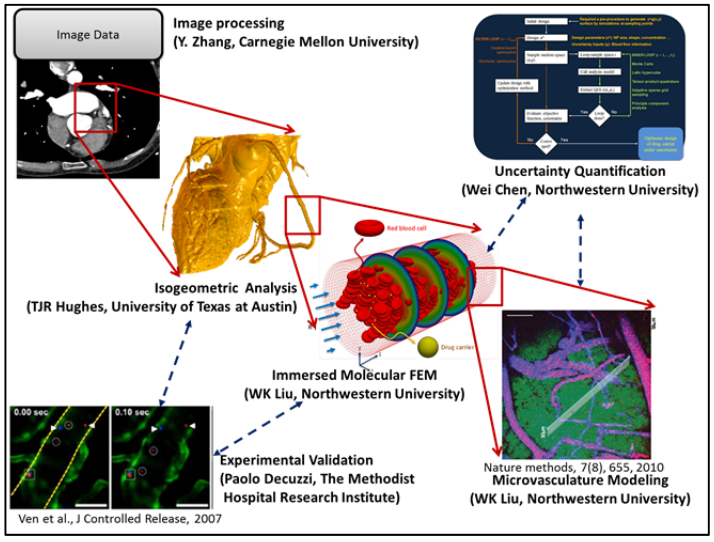
Emerging integrated multiscale experiments, models, and simulations opened the door for endless medical applications. One of the most promising among these is the targeted delivery of drugs and imaging agents using drug carrier-based platforms. Such drug delivery systems can now be made from a range of different materials, in a number of different shapes, coated with an array of different ligands, all leading to enhancements in delivery efficiency and specificity compared to previous delivery methods. Although the transport of these agents through the circulatory system is crucial to the successful targeting of specific regions of the body, characterizing drug carrier dynamics through the vasculature has remained a difficult task. The complex, multiscale nature of the vascular network as well as blood itself makes prediction of particle dispersion throughout the network prone to large errors, greatly hindering the rational design of delivery platforms. To this end, we propose a hierarchical multiscale framework for drug delivery through microvasculature that is capable of evaluating the effects of drug carrier design parameters on macroscale transport and delivery efficiency by using isogeometric analysis. At the microscale, the immersed molecular finite element method (IMFEM) is used to model the interactions between red blood cells (RBC), plasma, and drug carriers. IMFEM explicitly models both the RBCs and drug carriers with a Lagrangian mesh immersed in an Eulerian plasma domain. By explicitly accounting for the RBCs and drug carriers, the complex interactions that lead to Non-Newtonian blood rheology as well as phase separation and nanoparticle margination are captured. Information regarding the pressure-flow relation of the blood and drug carrier velocities is passed from the IMFEM simulations to a network model for the microvasculature. The network geometry can be specified based on in vivo images or through analytical branching-tree models. Transport through the network is fully specified by a pressure-flow relationship between nodes and a bifurcation law at each node. The margination dynamics calculated in the IMFEM simulations allows distributions of RBCs and drug carriers across the vesicle cross-section to be tracked and propagated correctly at bifurcation points, thus allowing for skimming effects of heterogeneous branching to be accurately modeled. The results of both the IMFEM simulations and network model can be readily compared to experiments. A Bayesian calibration method is used to update the uncertain multiscale computational model parameters so the model becomes more predictive. The Bayesian approach computes posterior distributions of the uncertain parameters by combining data from physical experiments and Gaussian process surrogates of the expensive simulation. In addition, a method for design under uncertainty is used on the updated model to systematically design drug carriers, aided by in vivo microvasculature data near tumors. The methodology presented here is capable of illuminating fundamental properties of suspended particles flowing thorough complex networks and, in addition, provides a robust framework for the rational design of drug delivery platforms.



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