Modeling the motion of a nanocarrier for targeted drug delivery

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Abstract:

Targeted drug delivery often uses nanocarries laden with drugs in blood vessels for transport. The dynamic process of delivery involves three separate scales - a macroscopic scale where transport of the carrier occurs in the flowing fluid medium of the vessel (variable Reynolds number), a second scale where the carrier approaches the endothelial cell (Stokes flow regime / porous media flow in the glycocalyx) and a nanoscale where the ligands on the carrier actually bind with the receptors on the cell membrane (binding energy and kinetics). A complete model of the transport requires simultaneous treatment of all these scales for a given concentration of targeted carriers, which is prohibitively complex. A systematic alternative entails the individual treatment of processes associated with each scale for carriers of various sizes and densities, and then match and merge them to obtain a composite picture. This has been our approach.

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 interactions. This macroscopic modeling may be carried out in two different ways: (a) solve the momentum equation including random stresses due to Brownian interactions, or, (b) employ the generalized Langevin equation together with non-Markovian processes. We have chosen to model the study in both ways [1,2] in order to evaluate the suitability and efficacy of any particular procedure for future comprehensive evaluations.

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 blood vessel wall on particle displacement and diffusivity are provided herein, using both procedures. Effects of carrier size, carrier density and vessel size have been investigated. Our numerical results show that the calculated temperature of the Brownian particle (a = 250 nm) in a quiescent fluid satisfies the equipartition theorem. For the range of fluid velocities considered, the temperature of the Brownian particle also satisfies the equipartition theorem for Poiseuille flow. Over long times, the decay of the velocity autocorrelation function captures algebraic tails for the translational ($t^{-3/2}$) and rotational ($t^{-5/2}$) motions of the nanoparticle. At short times, translational and rotational mean square displacement of the particle in quiescent fluid is proportional to $t^{1/2}$, and in the diffusive regime, it agrees with the Einstein's theory of Brownian motion. The hydrodynamic wall effects on the diffusivity of the particle agrees with the Stokes-Einstein diffusion relation with Brenner's correction. In the non-Markovian Langevin approach, for long times, an appropriate choice of colored noise was required to show the power-law decay in the velocity autocorrelation function. In regard to biological applications, it is noted that either of these two methods may be used to investigate the fluctuating motion of a nanocarrier in a particulate suspension where the dispersion in nanocarrier velocities are athermal in origin caused by collisions with red-blood cells. In such an application, the preset temperature must be replaced by a particulate temperature of blood plasma. In this case, we have shown that a hybrid scheme combining the Langevin approach with the fluctuating hydrodynamics approach enables the pre-programming of dynamic

correlations in the nanoparticle while simultaneously preserving hydrodynamic interactions in order to mimic the collisions of the nanoparticles with the cellular elements of blood [3].

The understanding of the dynamics obtained will now be incorporated for the evaluation of mass transport. Eventually, the outcome of this scale study will be merged with those described in our earlier papers concerning binding kinetics [4-6]. This is the bridging concept that will be invoked. By predicting the kinematics, dynamics and binding of the carrier, we will be able to "inversely" optimize design of suitable carrier(s) for addressing specific requirements. This would entail investigations of a number of carriers of various sizes and densities containing different drugs in vessels of a range of sizes over physiological flow rates.

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