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Computational Models for Nanoscale Fluid Dynamics and Transport Inspired by Nonequilibrium Thermodynamics¹

Traditionally, the numerical computation of particle motion in a fluid is resolved through computational fluid dynamics (CFD). However, resolving the motion of nanoparticles poses additional challenges due to the coupling between the Brownian and hydrodynamic forces. Here, we focus on the Brownian motion of a nanoparticle coupled to adhesive interactions and confining-wall-mediated hydrodynamic interactions. We discuss several techniques that are founded on the basis of combining CFD methods with the theory of nonequilibrium statistical mechanics in order to simultaneously conserve thermal equipartition and to show correct hydrodynamic correlations. These include the fluctuating hydrodynamics (FHD) method, the generalized Langevin method, the hybrid method, and the deterministic method. Through the examples discussed, we also show a top-down multiscale progression of temporal dynamics from the colloidal scales to the molecular scales, and the associated fluctuations, hydrodynamic correlations. While the motivation and the examples discussed here pertain to nanoscale fluid dynamics and mass transport, the methodologies presented are rather general and can be easily adopted to applications in convective heat transfer. [DOI: 10.1115/1.4035006]

1 Introduction

A common strategy in multiscale modeling involves systematically coarse-graining the atomistic description to build models with reduced representation at a larger length scale. Alternatively, a top-down approach may be employed, in which models are constructed based on governing equations at the mesoscale, which already have a reduced representation of the underlying microscopic dynamics. Bridging methods integrating these bottom-up and top-down methods have been achieved in two limits: (1) hierarchical bridging, which involves computing a property or a constitutive relationship at a smaller scale using a more-detailed model and employing the computed values in the other [1,2]; (2) domain decomposition bridging, which involves performing molecular scale modeling in a small domain and integrating it with continuum modeling in a larger domain [3]. An important application of nanoscale mass transport occurs in targeted drug delivery. In the following, we will use the targeted drug delivery problem for illustration purposes. In traditional modes of drug delivery, only a small fraction of injected drugs access the diseased tissue. Suboptimal drug delivery represents an acute challenge by limiting the efficacy of biotherapeutics. Strategies to address and overcome this challenge may be based on theoretical and computational approaches to iterate with innovative experimental methods. Targeted drug delivery using nanoparticles coated with specific targeting ligands is such an approach in therapeutic and diagnostic applications [3–5]. Targeted drug delivery is a multiscale problem, and in this case a large range of length and time scales are important to hydrodynamic, microscopic, and

molecular interactions mediating nanoparticle motion in blood-flow and cell binding. In drug delivery applications involving vascular targeting, for example, the molecular interactions (such as receptor–ligand bonds) and the hydrodynamic interactions (such as margination of the nanoparticle in blood) are equally significant [6–10]. Multiple macroscopic and microscopic time scales governing the problem include: (i) the inertial time-scale, (ii) the viscous relaxation time-scale, (iii) the hydrodynamic interaction timescale, (iv) the molecular interaction timescale, and (v) the Brownian diffusion time-scale. This simultaneous relevance of disparate length (and time scales) does not fit traditional multiscale methods. The challenge lies in integrating fluid motion and viscous memory for multiphase flow in complex geometries, while simultaneously including thermal and stochastic effects to simulate correctly the quasi-equilibrium distributions, in order to enable multivalent receptor–ligand binding at the physiological temperature. Similar examples may be cited for nanoscale heat transport. Nanocomposites synthesized as nanoparticle suspensions in viscous, viscoelastic, and elastic media have been proposed as functional materials for several technological applications for which characterizing the transport properties such as diffusion coefficient, viscosity, and thermal conductivity are of paramount importance. However, how the nanoparticle dispersion in the host medium influences these properties has been intensely debated in the literature [11–13].

2 Accurate Representation of Nanoparticle Dynamics: Stochastic and Hydrodynamic Effects Using Fluctuating Hydrodynamics (FHD) With Markovian Noise

For nanosized particles, to account for the thermal fluctuations in a mechanical system, one can add the thermal force terms to the governing equations of the system based on the theory of nonequilibrium statistical mechanics [14]. We adopt the fluctuating

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hydrodynamics (FHD) approach [15], which essentially adds stochastic stresses to the stress tensor in the fluid momentum equation. Direct numerical simulations (DNS) of fluctuating hydrodynamics (FHD) approach have been carried out by employing the finite volume method [16–19], the lattice Boltzmann method [20–26], the smoothed-particle method [27,28], and the stochastic Eulerian–Lagrangian method [29,30]. A comparison of these methods is described in Ref. [31]. In the following, we extend the work of Uma et al. [31] by employing arbitrary Lagrangian–Eulerian (ALE) finite element method (FEM) to account for the fluid–particle interaction. We note that a key feature and strength of the ALE method is that due to the adaptive mesh approach, it can resolve multiple hydrodynamic regimes such as bulk, near-wall, and lubrication amidst arbitrarily shaped boundaries.

We consider a spherical nanoparticle immersed in an incompressible Newtonian fluid in a circular tube, see Fig. 1. The inlet and outlet boundaries are denoted by Σ_i and Σ_o , respectively, Σ_w is the wall boundary, and the particle surface is denoted by Σ_p . The radius of the spherical particle is denoted by a , and the length and diameter of the circular tube are L and D , respectively. The center of mass of the particle is located either in terms of r , the separation with respect to the tube center, or h , the distance as measured from the wall boundary.

The fluid domain satisfies

$$\nabla \cdot \mathbf{u} = 0 \quad (1)$$

$$\rho \frac{D\mathbf{u}}{Dt} = \nabla \cdot \boldsymbol{\sigma} \quad (2)$$

where $\mathbf{u}$ and ρ are the velocity and density of the fluid, respectively, and $\boldsymbol{\sigma}$ is the stress tensor given by

$$\boldsymbol{\sigma} = -p\mathbf{J} + \mu[\nabla\mathbf{u} + (\nabla\mathbf{u})^T] + \mathcal{S} \quad (3)$$

Here, p is the pressure, $\mathbf{J}$ is the identity tensor, and μ is the dynamic viscosity. The random stress tensor $\mathcal{S}$ is assumed to be a Gaussian white noise that satisfies

$$\langle S_{ij}(\mathbf{x}, t) \rangle = 0 \quad (4)$$

$$\langle S_{ik}(\mathbf{x}, t) S_{lm}(\mathbf{x}', t') \rangle = 2k_B T \mu (\delta_{il} \delta_{km} + \delta_{im} \delta_{kl}) \delta(\mathbf{x} - \mathbf{x}') \delta(t - t') \quad (5)$$

where $\langle \cdot \rangle$ denotes an ensemble average, k_B is the Boltzmann constant, T is the absolute temperature, and δ_{ij} is the Kronecker delta.

Fig. 1 Schematic of the DNS computational domain and the FEM mesh representation

The Dirac delta functions $\delta(\mathbf{x} - \mathbf{x}')$ and $\delta(t - t')$ denote that the components of the random stress tensor are spatially and temporally uncorrelated. The mean and variance of the random stress tensor are chosen to be consistent with the fluctuation–dissipation theorem [32].

The translational and rotational motions of a rigid particle suspended in the fluid satisfy

$$m \frac{d\mathbf{U}}{dt} = \mathbf{G} - \int_{\Sigma_p} \boldsymbol{\sigma} \cdot \hat{\mathbf{n}} \, ds \quad (6)$$

$$\mathbf{I} \frac{d\boldsymbol{\Omega}}{dt} + \boldsymbol{\Omega} \times (\mathbf{I}\boldsymbol{\Omega}) = -\mathbf{R}^T \int_{\Sigma_p} (\mathbf{x} - \mathbf{X}) \times (\boldsymbol{\sigma} \cdot \hat{\mathbf{n}}) \, ds \quad (7)$$

where $\mathbf{U}$ and $\boldsymbol{\Omega}$ are the translational and rotational velocities of the particle, $\mathbf{X}$ denotes the position of its center of mass. The mass and the moments of inertia of the particle are, respectively, given by m and $\mathbf{I}$, and $\mathbf{G}$ represents a body force such as gravity. $\hat{\mathbf{n}}$ is the outward pointing unit normal to the particle surface. Here, the angular velocity $\boldsymbol{\Omega}$ and the moment of inertia $\mathbf{I}$ are defined with respect to the body frame attached to the particle—we denote the body frame by the tuples (x', y', z') . $\mathbf{R}$ is the rotational matrix that transforms the body frame quantities to the inertial frame (x, y, z) .

The initial conditions of the problem are

$$\mathbf{U}(t=0) = 0, \quad \boldsymbol{\Omega}(t=0) = 0, \quad \mathbf{u}(t=0) = 0 \quad (8)$$

in Σ , which represents the boundaries, see below

and the boundary conditions are given by

$$\mathbf{u} = \mathbf{u}_{\text{in}} \quad \text{on } \Sigma_i \quad (\text{inlet}) \quad (9)$$

$$\boldsymbol{\sigma} \cdot \hat{\mathbf{n}} = 0 \quad \text{on } \Sigma_o \quad (\text{outlet}) \quad (10)$$

$$\mathbf{u} = 0 \quad \text{on } \Sigma_w \quad (\text{wall boundary}) \quad (11)$$

$$\mathbf{u} = \mathbf{U} + \mathbf{R}\boldsymbol{\Omega} \times (\mathbf{x} - \mathbf{X}) \quad \text{on } \Sigma_p \quad (\text{particle surface}) \quad (12)$$

2.1 Numerical Generation of Random Stresses. We describe the important procedure to numerically generate the random stresses associated with an unstructured tetrahedral mesh. The random stress at each node on the computational domain depends on the volumes of the tetrahedrons associated with it. In particular, using the Peskin delta function approximation, $\delta(t)$ is approximated as $1/\Delta t$, where Δt is the timestep of integration, and $\delta(\mathbf{x})$ is approximated as $1/V_e$, where V_e is the Voronoi volume for a node in the bulk fluid. For a node on the surface of the particle, the Voronoi volume is only one-half represented by the fluid, with the other half falling in the solid. Hence, the Peskin delta function approximation for a surface node is given by $\delta(\mathbf{x}) = 2/V_e$, thereby causing the magnitude of the random stress on a surface node to be $\sqrt{2}$ times that of a node of equivalent Voronoi volume in the bulk. This consideration of the correct implementation of the Peskin delta function is critical to the adherence of thermal equipartition for translational and rotational degrees-of-freedom of particle motion, as indicated by Fig. 2.

2.2 Added Mass Consideration. The simulations in Fig. 2 are obtained from five different realizations, with each realization consisting of $N=20,000$ time-steps. The error bars have been plotted from standard deviations of the temperatures obtained with the different realizations, based on which the statistical error is established to be less than 5%. We note that due to the incompressibility assumption invoked in our model equations, the particle mass m is augmented by an added mass $m_0/2$, $M = m + m_0/2$, where m_0 is the mass of the displaced fluid and M is the virtual or added mass of the particle [31,33–36]; the added

mass correction is, in general, a function of distance from the wall, see, for example, Ref. [37].

2.3 Temperature Equilibration Consideration. It is evident from the close agreement with the Maxwell–Boltzmann distribution (MBD) displayed in Fig. 2 that the correct temperature T_0 is being realized for both translational and rotational degrees-of-freedom, panels (a) and (b), while simultaneously adhering to the correct temporal correlations, panels (c) and (d). Indeed, the particle (translational and rotational) diffusivities calculated from the linear velocity autocorrelation function (VACF) are consistent with those predicted from the Stokes–Einstein and Stokes–Einstein–Debye relationships; moreover, the method correctly captures the renormalization of the diffusivity as a function of separation from a bounding wall, see Ref. [31]. Other considerations, such as the effect of buoyancy, and that of a harmonic confining potential, have also been reported using this approach; for details, see Refs. [38] and [39].

3 Constructing a Thermostat Using Fluctuating Hydrodynamics With Non-Markovian Particle Equation

While the added mass correction has a physical basis (i.e., for the incompressible fluid, the displaced mass of the fluid is essentially translated along with the particle), the FHD approach has its limitations for defining free energy landscapes of reactions occurring on the nanoparticle surfaces when such reactions are coupled to nanoparticle transport. In nanoscale mass transport, such limitations arise, for example, during receptor–ligand mediated adhesion of nanocarriers to cells, in the presence of convective hemodynamic flow. Since the FHD simulations solve the stochastic Navier–Stokes equation, which includes the inertial time-scale, it captures the memory effects due to fluid inertia. Therefore, from the perspective of realizing a thermostat that maintains the particle at the correct temperature T_0 based on m (rather than M), one can view the nanoparticle motion as being described by a generalized Langevin equation (or GLE) which incorporates a memory function given by

$$m \frac{dU}{dt} = - \int_{-\infty}^t \zeta^{(i)}(t-t') U(t') dt' + R(t) \quad (13)$$

for the Brownian particle, where $\zeta^{(i)}(t)$ is the frictional force memory kernel. Here, the random force $R(t)$ is zero-centered that obeys the fluctuation–dissipation theorem (and hence can serve as a suitable thermostat to maintain a constant temperature T_0) [14,40]; namely

$$\langle R(t)R(t') \rangle = k_B T_0 \zeta^{(i)}(|t-t'|) \quad (14)$$

Therefore, a time correlated noise is added to the particle equations of motion: Eqs. (6) and (7) similar to that in the GLE (Eq. (13)) resulting in

$$m \frac{dU}{dt} = - \int_{\partial \Sigma_p} [-p\mathbf{J} + 2 \mu D[\mathbf{u}] + \mathbf{S}(\mathbf{x}, t)] \cdot \hat{\mathbf{n}} ds + \int_{-\infty}^t \xi(t') e^{-|t-t'|/\tau_1} dt' \quad (15)$$

$$\frac{d(\mathbf{I}\omega)}{dt} = - \int_{\partial \Sigma_p} (\mathbf{x} - \mathbf{X}) \times [(-p\mathbf{J} + 2 \mu D[\mathbf{u}] + \mathbf{S}(\mathbf{x}, t)) \cdot \hat{\mathbf{n}}] ds + \int_{-\infty}^t \boldsymbol{\mu}(t') e^{-|t-t'|/\tau_2} dt' \quad (16)$$

where the random force ξ and the torque $\boldsymbol{\mu}$ are given by

$$\xi(t') = \int_{\partial \Sigma_p} \mathbf{S}(\mathbf{x}', t') \cdot \hat{\mathbf{n}} ds \quad (17)$$

$$\boldsymbol{\mu}(t') = \int_{\partial \Sigma_p} (\mathbf{x}' - \mathbf{X}) \times (\mathbf{S}(\mathbf{x}', t') \cdot \hat{\mathbf{n}}) ds \quad (18)$$

The time integral in Eqs. (15) and (16) excludes the frictional force and torque at the time instant t since it has already been accounted for in the hydrodynamic force and torque terms, respectively. The characteristic timescales for memory for translational motion, i.e., τ_1 , and rotational motion, i.e., τ_2 , account for the history of the previous fluctuations, which not only directly impact the particle motion but also the fluid stresses due to the two-phase coupling of the weak formulation. The variables τ_1 and τ_2 are tuned in order to satisfy equipartition based on m (rather than on M) and $\mathbf{I}$. The methodology to compute these parameters is shown in Ref. [41], see also Ref. [42]. It is clear that in the limit of the characteristic memory times $\tau_1, \tau_2 \rightarrow 0$ (i.e., in the absence of memory), Eqs. (15) and (16) reduce to Eqs. (6) and (7), respectively, which correspond to the Markovian fluctuating hydrodynamics. The success and validity of this hybrid approach (i.e., by combining the Markovian fluctuating hydrodynamics for the fluid along with the non-Markovian Ornstein–Uhlenbeck noise in the equations of motion of the nanoparticle) in simulating the translational and rotational Brownian motion of a nanoparticle in an incompressible Newtonian stationary fluid medium is demonstrated in Ref. [41]; the results show that the hybrid approach can serve as an accurate thermostat without the need for the added mass correction, while simultaneously capturing the correct hydrodynamic correlations [41]. This denotes a major advance since it enables the accommodations of asymmetric carrier shapes in confined geometries with attendant wall effects.

4 Memory Function Approach to Coarse-Graining With Hydrodynamic Interactions Under Confinement

In the description of the dynamics of nanosized Brownian particles in an unbounded fluid domain in the inertial regime, the transition from exponential behavior of the VACF to algebraic behavior is attributed to influences of the fluid inertia; this is explicit in the asymptotic analysis of the linearized hydrodynamic equations for a Newtonian fluid by Hauge and Martin-Löf [32] and Zwanzig and Bixon [33]. However, in many technological applications, boundary effects and confining potentials are important, which make the evaluation of particle motion and associated transport much more complicated. The timescales of these motions overlap with the inertial timescale of the fluid, and as such, the temporal correlations in the inertial regime are strongly influenced by the confining boundaries and potentials. Theoretical analyses on this front are described in Refs. [43–47]. Collectively, these studies have investigated the dynamics of the motion of a spherical particle near the wall by confining the particle to different distances h from the wall. In the absence of an external potential, the parallel motion in the bulk-regime ($h/a \rightarrow \infty$) showing the $t^{-1.5}$ scaling of the VACF transitions to a $t^{-2.5}$ scaling with positive amplitude in the near-wall regime ($h/a > 1$), while for the perpendicular motion, a $t^{-3.5}$ scaling for the intermediate times is followed by a long-time tail that exhibits a $t^{-2.5}$ scaling with negative amplitude. In the presence of a confining potential, the VACF is characterized by a $t^{-3.5}$ scaling in the bulk regime and a $t^{-4.5}$ scaling in the near-wall regime. For a particle in the lubrication regime (where $(h-a)/a \rightarrow 0$), only the steady translational and rotational motions have been investigated: for example, for motion perpendicular to the wall, the spherical particle experiences a translational friction coefficient that is enhanced by a factor of $a/(h-a)$ [48]; for rotation around the axis perpendicular to the wall, the torque coefficient is augmented by a factor of $1.2 - 3(\pi^2/6 - 1)(h/a - 1)$ [49,50]. A detailed and consistent study of the hydrodynamic interactions in the lubrication layer and

important aspects of the wall effects in the lubrication and other hydrodynamic regimes are available in Ref. [51]. Also, for the majority of scaling relationships for VACF under various spatial and adhesion regimes that have been obtained through the asymptotic analysis of linear hydrodynamics, their validity through direct numerical simulations have been established in Ref. [51].

4.1 Incorporation of the Effects of Boundaries on Hydrodynamic Interactions. The equation of stochastic motion for each component of the velocity of a nanoparticle immersed in a fluid in an unbounded domain (in the limit of the linearized Navier–Stokes equation) takes the form of a GLE and is given by

$$M \frac{dU}{dt} = -6\pi\mu a U(x, t) + 3a^2 \sqrt{\pi\rho\mu} \int_{-\infty}^t |t-t'|^{-\frac{3}{2}} U(x, t') dt' - kx(t) + R(t) \quad (19)$$

Comparing Eqs. (13) and (19) yields $\zeta^{(t)}(t) = 12\pi\mu a \delta(t) - 3a^2 \sqrt{\pi\rho\mu} t^{-\frac{3}{2}}$, and $R(t) = R_w(t) + R_c(t)$, with a white noise correlation $\langle R_w(t)R_w(t') \rangle = 12\pi\mu a k_B T \delta(t-t')$, a colored noise correlation $\langle R_c(t)R_c(t') \rangle = -3a^2 \sqrt{\pi\rho\mu} k_B T |t-t'|^{-\frac{3}{2}}$, and $\langle R_w(t)R_c(t') \rangle = \langle R_w(t) \rangle \langle R_c(t') \rangle = 0$. Equation (19) representing a particle in an unbounded fluid domain can be extended to incorporate the effect of the boundaries on hydrodynamic interactions. In a recent study,

Fig. 2 The evolution of translational and rotational dynamics of a spherical particle ($a = 250$ nm) in the inertial regime, when immersed in a Newtonian fluid (with properties of water) and confined at the center of a cylindrical vessel ($D = 20$ μ m), simulated using the FHD approach at temperature $T_0 = 310$ K. (a) and (b) The probability distributions of the Cartesian components of the translational and rotational velocities showing the adherence to the corresponding Maxwell–Boltzmann distributions. (c) and (d) The short-time ($t \sim \tau_v = a^2/\nu$, where $\nu = \mu/\rho$ and ρ is the fluid density) evolution of the linear velocity autocorrelation function (VACF) and angular velocity autocorrelation function (AVACF) in the inertial regime showing the correct asymptotic transition from the exponential behavior ($\xi^{(tr)} = 6\pi\mu a$ and $\xi^{(rot)} = 8\pi\mu a^3$) for $t \rightarrow 0$ to algebraic behavior for $t > \tau_v$.

Yu et al. [37] formulated a composite GLE that explicitly encodes the transition from a bulk domain to a near-wall domain as the particle is approaching a confining boundary. This is accomplished by using a pertinent bridging function that transitions the GLE from that for the bulk regime at early times (when the momentum diffusion from the particle is yet to reach the boundary, i.e., $t \lesssim h^2/\nu$) to that for near-wall regimes for later times (when the reflected momentum wave from the boundary begins to impact the temporal velocity correlations of particle motion, i.e., $t \gtrsim h^2/\nu$). For perpendicular motion, the composite GLE for that case is given by

$$M \frac{dU_{\perp}}{dt} = -6\pi\mu a\beta U_{\perp}(x, t) - A_1(t) \int_{-\infty}^t |t-t'|^{-\frac{3}{2}} U_{\perp}(x, t') dt' - A_2(t) \int_{-\infty}^t |t-t'|^{-\frac{5}{2}} U_{\perp}(x, t') dt' - kx(t) + R(t) \quad (20)$$

where $\beta = (1 - (9a/8h))^{-1}$, $M = (3m/2)(1 - (a^3/8h^3))^{-1}$, $A_1(t) = -3a^2\sqrt{\pi\rho\mu}(e^{-\frac{t}{\tau_w}})$, and $A_2(t) = (9/8)am\sqrt{(\rho/\pi\mu)\beta^2(1 - e^{-\frac{t}{\tau_w}})}$ complements $A_1(t)$; here, $\tau_w = h^2/\nu$.

The random forces and force correlations consistent with the fluctuation-dissipation theorem are given by: $R(t) = R_w(t) + e^{-\frac{t}{\tau_w}} R_{c1}(t) + (1 - e^{-\frac{t}{\tau_w}}) R_{c2}(t)$ with $\langle R_w(t) R_w(t') \rangle = 12\pi\mu a\beta k_B T \delta(t-t')$, $\langle R_{c1}(t) R_{c1}(t') \rangle = -3a^2\sqrt{\pi\rho\mu} k_B T |t-t'|^{-\frac{3}{2}}$, $\langle R_{c2}(t) R_{c2}(t') \rangle = (9/8)am\sqrt{(\rho/\pi\mu)\beta} 2k_B T |t-t'|^{-\frac{5}{2}}$, and $\langle R_w(t) R_{c1}(t') \rangle = \langle R_w(t) R_{c2}(t') \rangle = \langle R_{c1}(t) R_{c2}(t') \rangle = 0$.

4.2 Deterministic Method for VACF and Angular Velocity Autocorrelation Function (AVACF) Calculations. For stochastic simulations, a large number of realizations are required to reach satisfactory statistics of the dynamical properties. Since $\zeta^{(t)}(t)$ is hydrodynamic in origin, the scaled relaxation of $U(t)$ can also be obtained in the absence of the random force $R(t)$. This procedure is known as the deterministic method. The deterministic method is based on the Onsager regression hypothesis, which states that the regression of microscopic thermal fluctuations at equilibrium follows the macroscopic law of relaxation of small nonequilibrium disturbances [52,53]. Mathematically, this yields $\langle \Delta U(t) \rangle / \langle \Delta U(0) \rangle = \langle \Delta U(t) \Delta U(0) \rangle / \langle \Delta U(0)^2 \rangle$, where $\Delta U(t) =$

$U(t) - \langle U(t) \rangle$. This provides the frame work for our employing the deterministic method for evaluating VACFs and AVACFs. Here, we also perform deterministic simulations in which the particle is driven initially by a weak impulse giving $U(0)$ in the absence of the $R(t)$. The correlation between a macroscopically driven $U(0)$ and the subsequent $U(t)$ would be equivalent to the calculated VACF (also denoted as $C_v(t)$) obtained from the stochastic simulations, according to Onsager's regression hypothesis [54].

In Fig. 3(a), for a non-neutrally buoyant Brownian particle at various distances from the wall, the deterministic numerical solutions to the composite GLE have been compared with the analytical solutions of the linearized Navier-Stokes equation for the same particle-wall system in a quiescent fluid. This shows excellent agreement between theory and simulations. In Fig. 3(b), the deterministic (i.e., without thermal noise) and the stochastic (i.e., with thermal noise) results for the composite GLE are compared to those from the FHD method for a particle in the lubrication regime and bound via a harmonic potential, again showing excellent agreement between the coarse-grained GLE approach [37] and the full-scale FHD/DNS simulations [51].

In Ref. [51], the dynamics and correlations in the presence of flow, wall-confinement, and adhesion interactions have been resolved by carrying out the FHD method in three different hydrodynamic regimes, namely, bulk ($(h-a)/a \gg 1$), near-wall ($(h-a)/a \sim 1$), and lubrication ($(h-a)/a \ll 1$) regimes. The formulation and results of that study provide a systematic approach for studying the temporal hydrodynamic correlations in the presence of a curved vessel wall, particle size, particle-fluid density variations, adhesive interactions (confining potential), and low Reynolds number flows, especially focusing on the lubrication regime. The significance of the DNS approach using FHD in terms of capturing the VACF of nanoparticle motion under a variety of confinement and flow conditions can be recognized in relation to the GLE formalism for nanoparticle motion. Indeed, the composite GLE framework [37] correctly captures the different hydrodynamic correlations at different time scales, when boundaries, confining potentials, and flow-fields are introduced. Therefore, the VACF determined by DNS provides a direct input to the GLE by defining the memory function. As demonstrated here, the GLE then represents a reduced dimensional and computationally efficient framework for encoding nanoparticle dynamics. We note that parallel approaches to bridge the molecular and hydrodynamic scales in pure fluids by combining molecular dynamics

Fig. 3 (a) Normalized VACF of a non-neutrally buoyant Brownian particle near an infinite plane wall in an incompressible, quiescent fluid medium for different separations from the wall. The symbols are the corresponding results from Ref. [47], and the lines are the predictions from the composite GLE simulations reported by Yu et al. [37]; here $\rho_p/\rho = 2.25$ with ρ_p being the density of the particle. (b) Normalized VACF of a neutrally buoyant Brownian particle in the lubrication regime with $h/a = 1.14$ in the presence of a harmonic spring (representing strong adhesion with $k = 1$ N/m) and comparison with DNS and FHD simulations.

simulations and linearized fluctuating hydrodynamics equations have been described by Chu and co-workers [55–58].

5 Generalized Langevin Equations for Bridging Colloidal and Molecular Scale Dissipation

In nanoscale mass transport, the adhesive dynamics of nanoparticles are governed by the binding interactions, which are more often than not, mediated by receptor–ligand complexes. The

example of a harmonic spring in Fig. 3(b) represents such an interaction at a coarse-grained level. The confining potential can have a range of values for the reactive compliance (or alternatively the stiffness) depending on the receptor–ligand pair, the use of spacers or tethers, the properties of the nanoparticle or the adhesive surface (e.g., flexible versus rigid); within the harmonic approximation, in which the adhesive potential is approximated as $V(x) = (1/2)kx^2$, the values for k typically fall in the range of $10^{-6} - 10$ N/m. Such potentials influence nanoparticle dynamics

Fig. 4 (a) Schematic of the coarse-grained model considered. The ligand-functionalized nanoparticle of radius a is attached to the wall through ligand–receptor binding interaction (first spring with the force constant k), including the relaxation of receptor internal dynamics subject to the conformational potential (second spring with the force constant k_s). The particle center of mass is located at h from the wall. The red dots from top to down: particle center-of-mass position x_p , ligand tip position x_l , receptor tip position x_r , and receptor tip position at equilibrium x_r^0 . (b) Normalized velocity autocorrelation functions for the nanoparticle for different conditions: in the bulk fluid predicted from the Stokes equation with $C_v(t) = (k_B T/M) \times \exp\{-6\pi\mu a t/M\}$ (thin solid), in the bulk fluid obtained from the Navier–Stokes equation (thin dashed), close to the wall predicted from the lubrication theory with $C_v(t) = (k_B T/M) \times \exp\{-6\pi\mu a^2 t/(M(h-a))\}$ (thick solid), close to the wall obtained from the Navier–Stokes equation (thick dashed), and attached to the vessel wall calculated from the current GLE simulations (dotted). (c) Normalized position autocorrelation functions for the receptor tip (dashed) and the nanoparticle (dotted) obtained from the current GLE simulations compared with the analytical solution for the free protein reported in Refs. [59] and [60] (solid). Simulated probability distributions of the relative positions of (top) the nanoparticle center of mass and (bottom) the receptor tip. The black curves are the equilibrium Boltzmann distributions for the harmonically bound nanoparticle position, with the gray lines denoting the 5% error about the MBD, panel (d), and the free receptor tip position, panel (e).

in an obvious way through influencing the energy landscape of adhesion, i.e., through $V(x)$. However, in the inertial timescale of $t \sim a^2/\nu$, which has been the main focus of this article, the internal dynamics of receptor–ligand complexes can also influence nanoparticle adhesion, independent of the energy landscape, $V(x)$. Single-molecule laser spectroscopy studies [59] have shown that fluctuations within a single protein exhibit wide relaxation spectrum characterizing a long-time memory, implying that the protein dynamics should also be described suitably by a GLE. Here, we present such an approach, where the colloidal hydrodynamics of a nanoparticle attached to a confining surface through a receptor–ligand bond, is coupled to the internal frictional relaxation (e.g., dissipation associated with solvent relaxation dynamics) of the receptor–ligand complex itself, see Fig. 4(a). If we consider the dimensions of the receptor–ligand complex (in the scale of $\sim 10^1$ nm), which are much smaller than the nanoparticle ($a \sim 10^2$ nm), the particle dynamics itself occurs in the lubrication regime (i.e., with $(h-a)/a \ll 1$). Therefore, in order to precisely encode the position-dependent, enhanced hydrodynamic drag when the particle binds to the surface in such a regime, and simultaneously account for the dynamical relaxation of the ligand–receptor pair, we formulate and simultaneously solve two coupled GLEs

$$M \frac{d^2 \bar{x}_p(t)}{dt^2} = - \int_{-\infty}^t \zeta_p^{(t)}(t-t') \frac{d\bar{x}_p}{dt'} dt' + k(x(t) - \bar{x}_p(t)) + R_p(t) \quad (21)$$

$$0 = - \int_{-\infty}^t \zeta_r^{(t)}(t-t') \frac{dx}{dt'} dt' - (k + k_s)x(t) + k\bar{x}_p(t) + R_r(t) \quad (22)$$

Equation (21) corresponds to the nanoparticle equation of motion subject to a strong lubrication force and adhesion, while Eq. (22) describes the receptor dynamics. $\bar{x}_p = x_p - a - l - x_r^0$ is the rescaled nanoparticle center-of-mass position, l is the ligand length, and x_r^0 is the equilibrium position of the receptor tip, $x = x_r - x_r^0$ is the instantaneous receptor tip position relative to its equilibrium value. The hydrodynamic memory function in Eq. (21), $\zeta_p^{(t)} = 2\zeta_{p,0}^{(t)}\delta(t-t')$ with $\zeta_{p,0}^{(t)} = 6\pi\mu a\{a/(h(t)-a)\}$, denotes the enhanced resistance of the nanoparticle in the lubrication layer. $\zeta_r^{(t)}(t-t') = \zeta_r^0(\lambda_r)|t-t'|^{-\lambda_r}$ in Eq. (22) is the memory function for receptor internal dynamics with ζ_r^0 being the fiction coefficient and λ_r being the power-law index. Following the fluctuation–dissipation theorem [14], the random forces of the particle (R_p) and receptor (R_r) are related to the frictional terms via $\langle R_p(t)R_p(t') \rangle = 2k_B T \zeta_{p,0}^{(t)}\delta(t-t')$ and $\langle R_r(t)R_r(t') \rangle = k_B T \zeta_r^{(t)}(t-t')$.

In Figs. 4(b)–4(d), we depict our results from the stochastic simulations of Eqs. (21) and (22) at $T = 310$ K for a nanoparticle ($a = 250$ nm) adhered to a planar wall (with equilibrium separation $x_r^0 = 19$ nm, $l = 15$ nm, and $k = 1$ N/m, see Ref. [37]). The conformational force constant $k_s = 1.88$ N/m, the friction coefficient $\zeta_r^0 = 1.32$ N s^{0.5} m^{−1}, and the power-law index $\lambda_r = 0.5$ for the receptor protein are taken from the measurements of Ref. [60].

In Figs. 4(b) and 4(c), we present the normalized velocity autocorrelation functions of the nanoparticle $C_v(t) = \langle U(t)U(0) \rangle$ and the normalized position autocorrelation functions of the nanoparticle ($C_x(t) = \langle x_p(t)x_p(0) \rangle$) and of the receptor tip ($C_x(t) = \langle x(t)x(0) \rangle$) as a function of the scaled time, t/τ_ν . It is evident that the nature of the velocity autocorrelation function for a bound nanoparticle (dotted) is completely distinct from that for an unbound nanoparticle either in the bulk fluid (thin lines) or close to the vessel wall (thick lines). For a free nanoparticle in the bulk, the analytical solution of the Stokes equation predicts an exponentially decaying $C_v(t)$ (thin solid), and the DNS of the Navier–Stokes equation [51] yields a $C_v(t)$ that exhibits a $t^{-3/2}$ long-time tail (thin dashed). When the particle moves to the proximity of the wall but not bound to the wall, the lubrication force

enhances the hydrodynamic resistance felt by the particle and leads to a faster decay of $C_v(t)$, where the steady-state lubrication theory predicts an exponential decay with an augmented drag coefficient (thick solid), and the long-time tail of the DNS solution is altered by the wall-induced vortex reflection (thick dashed). Once the particle is bound to the wall due to ligand–receptor interactions, the strong adhesion leads to oscillations in $C_v(t)$ that prevail in the hydrodynamic correlations. In the results for $C_x(t)$, the long-time decay for the bound nanoparticle (dotted) is consistent with that observed in $C_v(t)$. In terms of the receptor dynamics, the much faster-decaying $C_x(t)$ for the bound receptor tip (dashed) compared with the slowly decaying correlation for a free receptor (solid) indicates that the dynamical relaxation of the protein is strongly coupled with the instantaneous motion of the nanoparticle. In Figs. 4(d) and 4(e), the probability distributions of the nanoparticle center-of-mass position and the receptor tip position are presented. We find, not surprisingly, that the presence of ligand–receptor relaxation makes the nanoparticle distribution close to the Boltzmann distribution for a harmonically bound particle. However, the nanoparticle binding makes conformational distribution of the receptor highly constrained, as evidenced by the much narrower receptor tip distribution compared to the unbound receptor. These observations suggest that the fluctuations of the antibody–antigen complex indeed play a significant role in the nanoparticle binding and relaxation dynamics.

6 Conclusions

Validated multiscale models of nanoparticle dynamics that mechanistically handle events at multiple distinct scales (e.g., the macroscopic regime, the lubrication regime, and the adhesion regime) and which couple directly with the associated transport dynamics should be able to provide the algorithmic methodology for rapid and accurate determination of optimal nanoparticle design. However, due to competing hydrodynamic and adhesion forces at disparate length scale, traditional multiscale frameworks are not easily amenable for addressing the associated challenges. In this paper, we have primarily described and focused on Brownian motion of a nanoparticle and hydrodynamic interactions in the presence of flow-fields and hydrodynamic confinement. The fluctuating hydrodynamics, the generalized Langevin equations, the hybrid scheme, and the deterministic method have all been discussed in detail. Illustrative computations and results for VACF and AVACF at various regimes have been presented. In particular, the determination of the autocorrelation functions accurately for long times (compared to the inertial relaxation time) using the deterministic approach provides a direct route for computing transport properties using the appropriate Green–Kubo formulas [61]. Several works in the literature have reported calculations of transport properties for models of simple and complex fluids [62,63]. Encouraged by these studies which focussed on the molecular level, we propose that the Green–Kubo methodologies can be used to study the properties of suspensions of nanoparticles and nanocomposites at the mesoscopic scale, when combined with computational methods that resolve hydrodynamic interactions and thermal effects simultaneously, including the examples described in this article.

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Nomenclature

AVACF = angular velocity autocorrelation function
 CFD = computational fluid dynamics
 DNS = deterministic direct numerical simulations of the Navier–Stokes equation
 DNS = direct numerical simulations
 FEM = finite element method
 FHD = fluctuating hydrodynamics aka DNS stochastic
 GLE = generalized Langevin equation
 MBD = Maxwell–Boltzmann distribution
 VACF = linear velocity autocorrelation function

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