Samaneh Farokhirad

Department of Chemical and Biomolecular
Engineering,
University of Pennsylvania,
Philadelphia, PA 19104
e-mail: samaneh@seas.upenn.edu

N. Ramakrishnan

Department of Cancer Biology,
University of Pennsylvania,
Philadelphia, PA 19104
e-mail: ramn@seas.upenn.edu

David M. Eckmann

Department of Anesthesiology and Critical Care,
Department of Bioengineering,
University of Pennsylvania,
Philadelphia, PA 19104
e-mail: David.Eckmann@uphs.upenn.edu

Portonovo S. Ayyaswamy

Department of Mechanical Engineering and
Applied Mechanics,
University of Pennsylvania,
Philadelphia, PA 19104
e-mail: ayya@seas.upenn.edu

Ravi Radhakrishnan

Department of Chemical and Biomolecular
Engineering,
Department of Bioengineering,
University of Pennsylvania,
Philadelphia, PA 19104
e-mail: rradhak@seas.upenn.edu

Nanofluid Dynamics of Flexible Polymeric Nanoparticles Under Wall Confinement

Describing the hydrodynamics of nanoparticles in fluid media poses interesting challenges due to the coupling between the Brownian and hydrodynamic forces at the nanoscale. We focus on multiscale formulations of Brownian motion and hydrodynamic interactions (HI) of a single flexible polymeric nanoparticle in confining flows using the Brownian Dynamics method. The nanoparticle is modeled as a self-avoiding freely jointed polymer chain that is subject to Brownian forces, hydrodynamics forces, and repulsive interactions with the confining wall. To accommodate the effect of the wall, the hydrodynamic lift due to the wall is included in the mobility of a bead of the polymer chain which depends on its proximity to the wall. Using the example of a flexible polymeric nanoparticle, we illustrate temporal dynamics pertaining to the colloidal scale as well as the nanoscale. [DOI: 10.1115/1.4043014]

1 Introduction

Nanoparticles (NPs) have been the subject of extensive theoretical and experimental investigations due to their importance in numerous industrial and medical applications [1–3]. Due to their tunable physicochemical properties, such as the size, shape, rigidity, structure, and surface chemistry, a multitude of applications have been identified for NP-mediated delivery of diagnostic and therapeutic agents. Examples include targeted delivery to an inflamed cell and tissue-specific delivery of imaging agents for disease diagnosis. In general, NPs can be classified into nondeformable (or rigid) and deformable (or flexible) categories. While theoretical and computational works have extensively analyzed for the impact of size and shape of rigid NPs on their targeting efficiency [3–20], the role of carriers' flexibility on enhanced drug delivery has been explored to a far lesser extent, and the potential benefits of tuning nanoparticle elasticity are not clear. As such, similar treatment of flexible NPs offers a lot of exciting challenges and opportunities and recent research efforts have focused on how flexibility can be leveraged to tune the biological function and fate of nanoparticles. Polymeric NPs serve well as a delivery system for drugs and as model systems for understanding the mechanisms of the biological effects of nanomaterials. Among polymeric NPs, core-shell polymer-based NPs consisting of a lysozyme rich core with a dextran-rich corona have shown to be very good candidates for drug delivery, because of their low

cytotoxicity and their tunable properties such as shape, size, and rigidity which in turn is controlled by the cross-linking (CL) density [21].

The importance of developing multiscale computational methods to study NP interactions and transport can be readily recognized by considering an important example of nanoscale mass transport which is the study of the motion of NPs (1–100 nm) in an external fluid medium, namely nanoscale fluid dynamics (NFD). Nanofluids and NFD have been found to provide a considerable heat transfer and viscosity enhancement in comparison to conventional solid-liquid suspensions. Their novel properties such as diffusion coefficient, viscosity, and thermal conductivity make them potentially useful in almost all areas of engineering. On the application of nanofluids, targeted NPs filled with therapeutics or imaging agents that are directed to precise locations through a micron-scale blood vessel in the body to deliver the drug to the intended target such as an endothelial cell surface on an inflamed tissue is thus a multiscale problem which covers a large range of length and time scales for hydrodynamic interactions (HI) (such as margination of the nanoparticle in blood), microscopic, and molecular interactions (such as receptor-ligand bonds) mediating nanoparticle motion in blood flow and cell binding. We will use the targeted drug delivery problem in this study for illustration purposes.

The effect of the solvent can be considered differently among coarse-grained molecular dynamics (CG-MD) models. In the case of NFD where both fluid mechanics and thermal effect have equal importance, the solvent effect has to be considered either explicitly such as dissipative particle dynamics or implicitly by including hydrodynamic interactions. In this article, we use the

Contributed by the Heat Transfer Division of ASME for publication in the JOURNAL OF HEAT TRANSFER. Manuscript received September 8, 2018; final manuscript received February 22, 2019; published online March 27, 2019. Assoc. Editor: Debjyoti Banerjee.

Langevin or Brownian dynamics (BD) method, based on the later approach, to mimic friction, random collisions, and hydrodynamic interactions in our model for CG polymeric NPs.

How the NP dispersion in the host medium affects thermophysical properties remains rather debated [22,23]. However, it is believed that factors such as the large surface-to-volume ratio of nanoparticles, liquid–solid interfacial layers [24], Brownian motion of the nanoparticles [25,26], the nature of the proximity-dependent interaction of a NP with a confining boundary, and the temperature of the base fluid [27] influence the enhancement of fluid thermal conductivity.

2 Coarse-Grained Solution for the Motion of Flexible Nanoparticles in an External Fluid Medium, While Preserving Hydrodynamic Effects

The overall goal of this section is to describe the CG-MD or BD method to study the mechanism of flow-induced conformational change in flexible polymeric NPs.

2.1 Computational Method and Implementation. In the BD simulation technique, explicit solvent molecules are replaced by a stochastic force and the hydrodynamic forces mediated by them are accounted for through a hydrodynamic interaction kernel. The trajectories and interactions between the coarse-grained molecules are calculated using a stochastic differential equation which is integrated forward in time, allowing for the study of the temporal evolution and the dynamics of complex fluids, such as polymers and colloids. BD simulations are particularly suitable to study the structure and rheology of simple and complex fluids in hydrodynamic flows and other nonequilibrium conditions [28–33].

The flexibility of a polymer chain is determined by the ratio of L/l_p , where l_p is the persistence length, and L is the contour length of the polymer. Flexible polymers have $L/l_p \gg 1$, whereas this ratio for semiflexible chains is about 1. The choice of the model for a polymeric NP of interest depends on its chemical and mechanical properties. The simulation objectives decide the level of molecular detail that is needed to be retained. The most common coarse-grained model that captures the essential physics required to simulate the dynamic of flexible polymers is the freely jointed chain bead-spring model [34,35]. Here, the polymer chain is replaced by a set of beads connected to each other by a Kuhn spring and the springs represent the internal degrees-of-freedom of the polymer associated with stretching a subsection of the chain [34]. In order to model the conformational dynamics of cross-linked core–shell polymer-based NPs, far away from any boundary or subjected to any confinement, we consider a topology where a fixed number of strands are attached to a core to mimic an experimentally inferred architecture for this material [36], and each arm of the NP is modeled as connected segments of freely jointed chains. In the aforementioned core–shell polymer construct, the NP consists of a rigid lysozyme core with a fluidic and soft dextran corona and thus by regulating the fluid content of dextran brushes via modifications to internal structure, it is straightforward to tune their flexibility. Varying the CL density is a well-established method to control the softness of the NP assembly. We keep the same type of bonds for CL and measure the number of cross-links as a percentage based on the ratio of number of CLs to number of beads. The CLs are introduced based on a simulated annealing protocol to mimic the experimental reactions for CL [37]. NPs with large degree of CL will relax like a hard sphere [37] of equivalent radius of gyration, and the corresponding relaxation rate is smaller than that for star polymers.

The molecular weight of a dextran monomer is 162 Da. The initial microstructure for a molecular weight of 70 kDa of the dextran polymer chain is considered as an arm of the star polymer that contains a total of 25 arms attached to the lysozyme core. Each arm attached to the lysozyme core is represented by four coarse-

grained beads which in turn are interconnected by four Kuhn springs in series. Following the experimental estimates of Ref. [36], the core radius is set to $a = 10$ nm and the size of each bead is set to be the same as that of the core, i.e., $a = 10$ nm. The equilibrium distance and the stiffness of each spring are determined using the freely jointed chain model [38,39], i.e., $k_s = (3k_B T)/(N_K b_K)$ with N_K being the number of Kuhn's segments per bead and $b_K = 0.44$ nm [38] being the size of each Kuhn's segment, respectively. If b is the size of each monomer and N is the number of monomers per bead, i.e., $b = 1.5$ nm, and $N = 70,000/(4 \times 162)$, then we can impose $N_K b_K = Nb$ [37] to calculate the stiffness of the link between beads.

In the bead spring model consisting of N_b beads connected by flexible springs, the governing equations in the inertia free limit are obtained by a force balance on each bead

$$\mathbf{F}_i^{\text{HD}} + \mathbf{F}_i^{\text{HI}} + \mathbf{F}_i^B + \mathbf{F}_i^{\text{nHD}} = 0, \quad i = 1, 2, 3, \dots, N_b \quad (1)$$

where the subscript i refers to the bead number and $\mathbf{F}_i^{\text{HD}}$, $\mathbf{F}_i^{\text{HI}}$, $\mathbf{F}_i^B$ and $\mathbf{F}_i^{\text{nHD}}$ are the hydrodynamic drag force, hydrodynamic force due to interbead hydrodynamic interactions, Brownian forces due to random collisions of the solvent with the particle, and all non-hydrodynamic forces, respectively. This total nonhydrodynamic force includes any external body forces, any spring forces, and any excluded volume interactions.

The hydrodynamic drag force is the friction force experienced by a polymeric NP due to relative motion with respect to the solvent and is given by [40]

$$\mathbf{F}_i^{\text{HD}} = -\zeta \left(\frac{d\mathbf{r}_i}{dt} - \mathbf{v}_i \right) \quad (2)$$

where $\zeta = 6\pi\mu a$ is the friction factor, $\mathbf{r}_i$ is the position of the bead i , and $\mathbf{v}_i$ is the unperturbed velocity field evaluated at $\mathbf{r}_i$. By assuming that the NP will not change the flow field, $\mathbf{v}_i$ can be defined as the solvent velocity, i.e., $\mathbf{v}_i = \mathbf{r}_i \cdot \nabla \mathbf{u}$, where $\nabla \mathbf{u}$ is the velocity gradient tensor from external forces and hence $\mathbf{F}_i^{\text{HD}} = -\zeta((d\mathbf{r}_i/dt) - \mathbf{r}_i \cdot \nabla \mathbf{u})$.

The differential equation governing the motion of the NP then becomes

$$\frac{d\mathbf{r}_i}{dt} = \mathbf{r}_i \cdot \nabla \mathbf{u} + \frac{1}{\zeta} (\mathbf{F}_i^{\text{HI}} + \mathbf{F}_i^B + \mathbf{F}_i^{\text{nHD}}) \quad (3)$$

and is commonly called Brownian dynamics. This is a stochastic differential equation, because the Brownian force is taken from a random distribution and fluctuates extremely rapidly and integrating this equation forward in time a Brownian dynamic simulation can be performed. In order to satisfy the fluctuation–dissipation theorem, the average of the random force over a long-time scale should tend to zero and a relationship between Brownian motion and the drag must exist [41], which are given by

$$\langle \mathbf{F}_i^B(t) \rangle = \mathbf{0} \quad (4)$$

$$\langle \mathbf{F}_i^B(t) \mathbf{F}_j^B(t') \rangle = 6k_B T \zeta \delta_{ij} \delta(t - t') \mathbf{I} \quad (5)$$

where k_B is the Boltzmann's constant, T is the temperature, δ_{ij} is the Kronecker delta, $\delta(t - t')$ is the Dirac delta function, and $\mathbf{I}$ is the unit second-order tensor. The stochastic nature here means that many independent trajectories must be produced and averaged together to produce the time evolution of an ensemble-averaged property.

2.1.1 Hydrodynamic Interactions. Hydrodynamic interactions between beads mediated by the solvent is very important to accurately model the dynamics of the polymeric NP [42,43]. As a bead of a polymeric NP moves, it exerts a force on the solvent which changes the velocity field from its unperturbed value and as a

result changes the hydrodynamic drag force exerted on other beads. This velocity disturbance is a linear function of the hydrodynamic drag force and is considered by including interactions of the image of beads of the periodic system, which is conceived as a two-dimensional lattice system of identical cells of volume V , through the Ewald sum method described by Beenakker [44]. Each image cell is denoted by an index l and contains the same number of beads N_b . The resultant velocity experienced by bead i due to the Brownian and systematic forces acting on bead j is computed using Ewald summation as

$$\mathbf{v}'_i = \sum_{j=1}^{N_b} \sum_{\mathbf{l}} \mathbf{M}_{ij}^{\text{HI}}(\mathbf{r}_{ij}^{\mathbf{l}}) \cdot (\mathbf{F}_j^{\text{B}} + \mathbf{F}_j^{\text{nHD}}) \quad (6)$$

where $\mathbf{M}_{ij}^{\text{HI}}$ is the pairwise hydrodynamic mobility tensor, $\mathbf{r}_{ij}^{\mathbf{l}}$ is the distance between the periodic images of beads i and j in box $\mathbf{l}$, and $\mathbf{l}$ is comprised of components of two-dimensional lattice vectors expressed as $\mathbf{l} = (l_1 L, l_2 L)$, and L is the length of the simulation box. The pairwise hydrodynamic mobility tensor in Eq. (6) is described by adopting the Rotne–Prager–Yamakawa tensor [45,46]

$$\begin{aligned} \mathbf{M}_{ij}^{\text{HI}} &= \frac{1}{6\pi\mu a} \mathbf{I} \text{ for } i = j \\ &= \frac{1}{8\pi\mu r_{ij}} \left[\left(1 + \frac{2a^2}{3r_{ij}^2}\right) \mathbf{I} + \left(1 - \frac{2a^2}{r_{ij}^2}\right) \frac{\mathbf{r}_{ij}\mathbf{r}_{ij}}{r_{ij}^2} \right] \text{ for } i \neq j, r_{ij} \geq \sigma \\ &= \frac{1}{6\pi\mu a} \left[\left(1 - \frac{9r_{ij}}{32a}\right) \mathbf{I} + \frac{3r_{ij}}{32a} \frac{\mathbf{r}_{ij}\mathbf{r}_{ij}}{r_{ij}^2} \right] \text{ for } i \neq j, r_{ij} < \sigma \end{aligned} \quad (7)$$

where, $\sigma = 2a$ is the interparticle distance, $\mathbf{r}_{ij} = \mathbf{r}_i - \mathbf{r}_j$ is the relative position vector between beads i and j , $r_{ij} = |\mathbf{r}_{ij}|$, while $((\mathbf{r}_{ij}\mathbf{r}_{ij})/r_{ij}^2)$ is the product of normalized vectors. Because of the long range of the mobility tensor, i.e., $r \gg a$, Eq. (7) decays slowly as $1/r$. To include the effect of other beads in the mobility of a test bead, we adopt a quasi-two-dimensional Ewald sum of the mobility tensor shown by Bleibel [47]. The pair-wise mobility tensor is then defined by

$$\begin{aligned} 6\pi\mu a \mathbf{v}^i &= 6\pi\mu a \sum_{j=1}^{N_b} \mathbf{M}_{ij}^{\text{HI}}(\mathbf{r}_{ij}) \cdot (\mathbf{F}_j^{\text{B}} + \mathbf{F}_j^{\text{nHD}}) \\ &+ \left(1 - \frac{3}{2}\pi^{-1/2}a\alpha - \frac{2}{3}\pi^{-1/2}a^3\alpha^3\right) (\mathbf{F}_i^{\text{B}} + \mathbf{F}_i^{\text{nHD}}) \\ &+ \sum_{\mathbf{l} \neq 0} \sum_{j=1}^{N_b} \mathbf{M}^{(1)}(\mathbf{r}_{ij} + \mathbf{l}) \cdot (\mathbf{F}_j^{\text{B}} + \mathbf{F}_j^{\text{nHD}}) \\ &+ \frac{1}{V} \sum_{\mathbf{k} \neq 0} \sum_{j=1}^{N_b} \mathbf{M}^{(2)}(\mathbf{k}) \cos(\mathbf{k} \cdot \mathbf{r}_{ij}) \cdot (\mathbf{F}_j^{\text{B}} + \mathbf{F}_j^{\text{nHD}}) \end{aligned} \quad (8)$$

which includes hydrodynamic interactions and contribution from image-replicas. Here, $M^{(1)}$ and $M^{(2)}$ are contributions from periodic images along “1” and “2” directions and are functions of the interbead distance, defined in Ref. [47]. The sum in Eq. (8) is only valid for $r > \sigma$, and hence, to introduce the effect of overlapping beads, the term shown in Eq. (7) for $r < \sigma$ is added to keep the Rotne–Prager–Yamakawa tensor ($\mathbf{M}_{ij}$) positive-definite for all configurations [48]. We numerically check the convergence of the mobility tensors to determine the number of boxes and the value of convergence parameter α .

2.1.2 Effect of Wall Confinement. In many technological applications, boundary effects and confining potentials are

important, which make the evaluation of particle motion and associated transport much more complicated. In targeted drug delivery applications, the beads of polymeric NPs exhibit an anisotropic hindered Brownian motion due to hydrodynamic effects, particularly near the vessel wall [19,37]. The modified diffusion coefficient, in the directions parallel and normal to the wall surface, is expressed in terms of their respective mobilities. We account for the effect of hydrodynamic interactions on the NP near a wall via decreased mobility of beads of the NP and increased drag due to the presence of other NPs. The effect of the wall is thus translated to the self-mobility shown in Eq. (7). Faxen and Angew [49] showed that a spherical particle, moving parallel to a rigid planar wall, experiences a decrease in mobility by a factor

$$\beta_{\parallel} = 1 - \frac{9}{16} \left(\frac{a}{y}\right) + \frac{1}{8} \left(\frac{a}{y}\right)^3 - \frac{45}{256} \left(\frac{a}{y}\right)^4 - \frac{1}{16} \left(\frac{a}{y}\right)^5 \quad (9)$$

where y is the perpendicular coordinate of the center of the bead and $(a/y) > 2$. For the present case study due to repulsion from the wall, the distance between beads and the wall will be always larger than $2a$. Wakiya [4] showed that using the method of reflections as applied to two spherical particles in the presence of a planar wall, a spherical particle moving toward the wall experiences an increased drag which is given by

$$\beta_{\perp} = 1 - \frac{9}{8} \left(\frac{a}{y}\right) + \frac{1}{2} \left(\frac{a}{y}\right)^3 - \frac{2}{8} \left(\frac{a}{y}\right)^5 \quad (10)$$

It must be noted that in our simulations, the hydrodynamic interactions between one bead and the wall are considered through the use of Eqs. (9) and (10) and the simultaneous effect of HI between multiple beads, and the wall is presently ignored, as the size of the bead is smaller than the instantaneous distance of its center from the wall.

2.1.3 Nonhydrodynamic Interactions. In addition to Brownian forces, the beads of the NP experience some non-Brownian forces, due to the intermolecular interactions from all other beads, including bead–bead interaction and spring–spring repulsion. Following Ref. [37], the interaction between adjacent connected beads is considered through a harmonic potential

$$U^s(r_{ij}) = \frac{1}{2} k^s (r_{ij} - r_{\text{eq}})^2 \quad (11)$$

where r_{eq} is the equilibrium bond distance and is set to $2a$. The spring restoring forces (F^s) are derived by taking the spatial derivative of the segmental chain free energy. The bond stiffness for the cross-links are kept the same as that of the stiffness of the inter bead springs.

Excluded volume accounts for the steric interaction between beads when they approach each other and the Weeks–Chandler–Anderson potential [50] is used to model this interaction

$$U^{\text{WCA}}(r_{ij}) = 4\epsilon \left[\left(\frac{\sigma}{r_{ij}}\right)^{12} - \left(\frac{\sigma}{r_{ij}}\right)^6 + \frac{1}{4} \right] \quad (12)$$

where $\epsilon = 0.7k_B T$ is the interaction strength, and σ is the excluded volume radius. The cut-off radius for Weeks–Chandler–Anderson potential is set to $r_c = 2^{1/6}\sigma$.

Since the concentration of the beads can change in the direction normal to the wall surface, $\mathbf{r}_i \cdot \nabla \mathbf{u}$ is nonzero along the perpendicular direction. Following Ermak and McCammon [51] $\mathbf{r}_i \cdot \nabla \mathbf{u}$ can be approximated to $\sum_j \partial D_{ij} / \partial r_{ij}$ for $t \gg (m/\zeta)$. We now modify Eq. (3) using the mobility tensor shown in Eq. (9) which replaces the mobility tensor in the Stokes flow limit, i.e., $(1/\zeta)$, for all

nonhydrodynamic forces such as spring restoring force ($\mathbf{F}_i^s$) and force due to excluded volume effect ($\mathbf{F}_i^{\text{WCA}}$)

$$\frac{d\mathbf{r}_i}{dt} = \sum_{j=1}^{N_b} \mathbf{M}_{ij} \cdot \mathbf{F}_i^{\text{HD}} + \sqrt{2k_B T / \Delta t} \sum_{j=1}^{N_b} \mathbf{B}_{ij} \cdot \mathbf{n}_j(t) \quad (13)$$

Here, Δt is the time-step of integration, and $\mathbf{n}$ is a random vector chosen from a Gaussian distribution of zero mean and unit variance. $\mathbf{B}$ is a weight factor and is computed from the Rotne–Prager–Yamakawa tensor by the decomposition of $\mathbf{M}$, i.e., $\mathbf{M} = \mathbf{B} \cdot \mathbf{B}^T$, and following the Cholesky decomposition.

We scale time t with relaxation time of diffusion (a^2/D_0) (where D_0 is the unconstrained diffusivity of a Brownian particle given by $(k_B T / \zeta)$), r with a , F with $k_B T / a$ and $\mathbf{M}$ with $(D_0 / k_B T)$. The configurations are then subjected to Brownian dynamics simulations and carefully calibrated bead-spring chain model of flexible NP enables us to explore the accessible time and length scales in numerical simulations. In the context of drug delivery, the dynamics of flexible polymeric NPs as nanocarriers functionalized with targeting antibodies in a confined environment, such as in a narrow blood vessel, is governed by a complex interplay between the Brownian forces, hydrodynamic interactions, margination effects due to the presence of larger particulates in the blood such as red blood cell, as well as adhesive interactions of ligand-receptor near the vessel wall. The individual magnitude of these multitude of interactions are influenced by several physiological factors such as antibody density, the expression levels of the antigen molecules and hydrodynamic factors such as the hematocrit density, the flow rate and the vessel size. These effects must be addressed as other nonBrownian forces into the governing stochastic differential equation (Eq. (13)). However, the focus here is on the effect of wall-confinement and hydrodynamic interactions on the deformation and transport properties of the flexible NPs and the role of other physiological factors on the diffusivity of such NPs close to wall-confinement will be the subject of future study.

2.2 Transport and Equilibrium Properties of Deformable Nanoparticle. In this section, we evaluate the effects of the confining boundary and flexibility of the NP on the NP microstructure and transport properties. The stochastic and inter-bead hydrodynamic forces are included to model the internal segmental motion of these deformable carriers taking into account the hydrodynamic interactions. The detailed parameter sets used in the simulation of deformable cross-linked polymer-based NPs subjected to wall-confinement using BD methods are summarized in Table 1. The initial model of uncross-linked arms represents an NP of 0% CL. Cross-links between beads are added [37] to create NP models with varying CL densities of 0%, 20%, 60%, 100%, and 160%. For each configuration, we perform at least three independent simulations with different initial conditions and repeat these steps for

four independent configurations (replicas with varying internal structures). Overall the position vectors of the beads are recorded for 10^{12} time steps. The computations for a typical trajectory noted above require three central processing unit-weeks on a single core of an Intel Xeon 2.7 GHz workstation.

To characterize the net spatial movement and microstructure of a flexible NP, we calculate the mean squared displacement (MSD) over time as well as equilibrium shape of NP, respectively. We write the MSD of the nanocarrier along direction m as

$$\langle [r_i^m(t) - r_i^m(0)]^2 \rangle = 2D_s^m t \quad (14)$$

where r_i^m represents the absolute position of bead i along direction m , D_s^m is the self-diffusivity of the NP along direction m , and t is the trajectory time. Here, the ensemble average is taken over all the beads and we use dimensionless quantities, i.e., MSD_m/a^2 and $D_{s,m}/D_0$. From the bead trajectories, we evaluate the diffusion coefficient of NPs using least squares fits of the mean square displacement as a function of time. We show the perpendicular and horizontal components of MSD and self-diffusivity as MSD_p , MSD_h , D_p , and D_h , respectively. The shape factor (a measure of shape anisotropy) of the NP can be estimated by computing the eigenvalues of the radius of gyration (R_g) matrix (λ_i ($i = 1, 3$)), defined in terms of bead positions, and is given by

$$S = \frac{27 \left\langle \prod_i^3 (\lambda_i - \bar{\lambda}) \right\rangle}{\left\langle \left(\sum_i^3 \lambda_i \right)^3 \right\rangle} \quad (15)$$

where $\bar{\lambda} = \frac{1}{3}(\sum_i^3 \lambda_i)$. Bishop [52] have showed that S varies from -0.25 to 2 , where the change in sign from “-ve” to “+ve” signifies an oblate to a prolate shape change.

It has been shown that Ref. [53] the mean squared displacement (diffusion at any correlation time) decreases with diameter of a solid sphere. For deformable bodies in an unbounded fluid domain the perpendicular mean squared displacement decreases with radius of gyration (shown in Ref. [37]). To test this hypothesis, we investigate the Brownian motion of the deformable NPs with different CL density and in presence of wall confinement. Figure 1(a) shows the perpendicular mean squared displacement as a function of scaled time for five different cross link densities. It may be noted that at any correlation time MSD is found to be smaller for NP with higher density of CL. Figure 1(b) demonstrates that the radius of gyration of the NP decreases with increasing the CL density. It has also been shown that Ref. [37] when there is no confinement effect, the radius of gyration of the NP decreases with increasing density of CL. This limit holds when the NP is at a distance $h \gg O(a)$ (from the wall) and in this regime, the NP remains spherical as noted by the computed values of the shape factor S (Fig. 1(c)) for all CL densities. Although the shape distortion of the NP is negligible, the CL density influences the diffusivity of NPs in both parallel and perpendicular directions as shown in Figs. 1(d) and (e). While the diffusivity of the NP is reduced in parallel direction, its perpendicular diffusivity is increased with increasing the size of the NP.

3 Conclusions

In this paper, we have described and focused on Brownian motion of cross-linked polymer-based nanoparticles and hydrodynamic interactions in the presence of hydrodynamic confinement. The CG-MD or BD method that involves interactions with surrounding fluid molecules or the so-called hydrodynamic interactions has been discussed in detail. Illustrative computations and results for polymeric nanoparticles has been presented to explore the effects of wall-confinement, hydrodynamic interactions, and NP synthesis factors such as the density of CL on NP microstructure (shape and deformation) and transport properties such as

Table 1 Details of the coarse-grained solutions using Brownian dynamics for flexible NPs

Property	Symbol	Value
Number of cores	N_c	1
Bead radius	a	10 nm
Number of beads in an arm	N_b	4
Number of arms attached to a core	f	25
Molecular weight of dextran monomer	M_{monomer}	162 Da
Molecular weight of dextran polymer	M_{polymer}	70 kDa
Size of each Kuhn segment	b_k	0.44 nm
Size of monomer	b	1.5 nm
Number of monomers per bead	N	108
Number of Kuhn segments	N_k	368
Stiffness of spring between beads	k_s	1.74329×10^{-4} J/m ²
System temperature	T	300 K
Dynamic viscosity of plasma	η	1.3 mPa

Fig. 1 (a) MSD perpendicular to the wall as a function of scaled time; the MSD_p is nondimensionalized with the square of radius of the beads and the inset shows the logarithmic plot of MSD_p against the scaled time. (b) Radius of gyration as a function of CL density and (c) shape factor as a function of R_g obtained at different CL densities; the radius of gyration is nondimensionalized with the radius of the beads. (d) and (e) Diffusivity of NPs against the radius of gyration, R_g ; D_h denotes the horizontal self-diffusivity of NPs along the 1 and 3 directions and D_p is the perpendicular self-diffusivity along the 2 direction.

diffusion coefficient. Due to the presence of the confining wall, the NP undergoes deformation. We quantified the effect of deformation by comparing the horizontal and perpendicular diffusivities and the radius of gyration tensor of the NP. Our results show that while the extent of deformation is not significantly influenced by the density of CL, the CL and wall hydrodynamic interactions do alter the radius of gyration and the diffusion coefficient.

Acknowledgment

We thank Arijit Sarkar for helpful discussions on the results and methods, Carme Coll Ferrer and Russell Composto for discussions on the experimental aspects of synthesis of polymeric NPs. We acknowledge support from the National Institutes of Health through Grant Nos. 1R01EB006818, U01EB016027, and 1U54CA193417. Computational resources were provided in part by the Penn's School of Engineering and Applied Sciences (SEAS), Penn MRSEC and by the Extreme Science and Engineering Discovery Environment (XSEDE) Grant No. MCB060006.

Funding Data

- National Institutes of Health (Grant Nos. 1R01EB006818 and 1U54CA193417; Funder ID: 10.13039/1000000054).
- National Institute of Biomedical Imaging and Bioengineering (Grant Nos. U01EB016027; Funder ID: 10.13039/1000000070).
- Extreme Science and Engineering Discovery Environment (XSEDE) (Grant No. MCB060006; Funder ID: 10.13039/501100008982).

Nomenclature

BD = Brownian dynamics
 CG-MD = coarse-grained molecular dynamics
 CL = cross-linking
 MD = molecular dynamics
 MSD = mean squared displacement
 NFD = nanoscale fluid dynamics

References

- [1] Wei, L., Cai, C., Lin, J., and Chen, T., 2009, "Dual-Drug Delivery System Based on Hydrogel/Micelle Composites," *Biomaterials*, **30**(13), pp. 2606–2613.

- [2] Ahmed, E., 2015, "Hydrogel: Preparation, Characterization, and Applications: A Review," *J. Adv. Res.*, **6**(2), pp. 105–121.
- [3] Radhakrishnan, R., Yu, H. Y., Eckmann, D. M., and Ayyaswamy, P. S., 2016, "Computational Models for Nanoscale Fluid Dynamics and Transport Inspired by Nonequilibrium Thermodynamics," *ASME J. Heat Transfer*, **139**(3), p. 033001.
- [4] Wakiya, S., 1957, "Viscous Flows Past a Spheroid," *J. Phys. Soc. Jpn.*, **12**(10), pp. 1130–1141.
- [5] Sugihara-Seki, M., 1996, "The Motion of an Ellipsoid in Tube Flow at Low Reynolds Number," *J. Fluid Mech.*, **324**(1), pp. 287–308.
- [6] Glowinski, R., Pan, T. W., Hesla, T. I., Joseph, D. D., and Périoux, J., 2001, "A Fictitious Domain Approach to the Direct Numerical Simulation of Incompressible Viscous Flow Past Moving Rigid Bodies: Application to Particulate Flows," *J. Comput. Phys.*, **169**(2), pp. 363–426.
- [7] Swaminathan, T. N., Mukundakrishnan, K., and Hu, H. H., 2006, "Sedimentation of an Ellipsoid Inside an Infinitely Long Tube at Low and Intermediate Reynolds Numbers," *J. Fluid Mech.*, **551**(1), pp. 357–385.
- [8] Hsu, R., and Gnanatos, P., 1989, "The Motion of a Rigid Body in a Viscous Fluid Bounded by a Plane Wall," *J. Fluid Mech.*, **207**(1), pp. 29–72.
- [9] Ding, E. J., and Aidun, C., 2000, "The Dynamics and Scaling Law for Particles Suspended in Shear Flow With Inertia," *J. Fluid Mech.*, **423**, pp. 317–344.
- [10] Xia, Z., Connington, K. W., Rapaka, S., Yue, P., Feng, J. J., and Chen, S., 2009, "Flow Patterns in the Sedimentation of an Elliptical Particle," *J. Fluid Mech.*, **625**, pp. 249–272.
- [11] Huang, H., Yang, X., and Lu, X. Y., 2014, "Sedimentation of an Ellipsoidal Particle in Narrow Tubes," *Phys. Fluids*, **26**(5), p. 053302.
- [12] Sharma, N., and Patankar, N. A., 2004, "Direct Numerical Simulation of the Brownian Motion of Particles by Using Fluctuating Hydrodynamic Equations," *J. Comput. Phys.*, **201**(2), pp. 466–486.
- [13] Donev, A., Vanden-Eijnden, E., Garcia, A., and Bell, J., 2010, "On the Accuracy of Finite Volume Schemes for Fluctuating Hydrodynamics," *Commun. Appl. Math. Comput. Sci.*, **5**(2), pp. 149–197.
- [14] Ladd, A. J. C., 1993, "Short-Time Motion of Colloidal Particles: Numerical Simulation Via a Fluctuating Lattice-Boltzmann Equation," *Phys. Rev. Lett.*, **70**(9), pp. 1339–1342.
- [15] Ladd, A. J. C., 1994, "Numerical Simulations of Particulate Suspensions Via a Discretized Boltzmann Equation—Part 1: Theoretical Foundation," *J. Fluid Mech.*, **271**, pp. 285–309.
- [16] Ladd, A. J. C., 1994, "Numerical Simulations of Particulate Suspensions Via a Discretized Boltzmann Equation—Part 2: Numerical Results," *J. Fluid Mech.*, **271**, pp. 311–339.
- [17] Atzberger, P. J., 2011, "Stochastic Eulerian Lagrangian Methods for Fluid-Structure Interactions With Thermal Fluctuations," *J. Comput. Phys.*, **230**(8), pp. 2821–2837.
- [18] Uma, B., Swaminathan, T. N., Radhakrishnan, R., Eckmann, D. M., and Ayyaswamy, P. S., 2011, "Nanoparticle Brownian Motion and Hydrodynamic Interactions in the Presence of Flow Fields," *Phys. Fluids*, **23**(7), p. 073602.
- [19] Ramakrishnan, N., Wang, Y., Ayyaswamy, P. S., Ayyaswamy, P. S., and Radhakrishnan, R., 2017, "Motion of a Nano-Spheroid in a Cylindrical Vessel Flow: Brownian and Hydrodynamic Interactions," *J. Fluid Mech.*, **821**, p. 117.
- [20] Radhakrishnan, R., Ramakrishnan, N., Eckmann, D. M., and Ayyaswamy, P. S., 2019, "Nanoscale Fluid Dynamics," *21st Century Nanoscience Book*, K. Sattler, ed., Taylor and Francis, New York.

- [21] Eckmann, D. M., Composto, R. J., Tsourkas, A., and Muzykantov, V. R., 2014, "Nanogel Carrier Design for Targeted Drug Delivery," *J. Mater. Chem. B*, **2**(46), pp. 8085–8097.
- [22] Koblinski, P., Prasher, R., and Eapen, J., 2008, "Thermal Conductance of Fluids: Is the Controversy Over," *J. Nanopart. Res.*, **10**(7), pp. 1089–1097.
- [23] Prasher, R., Song, D., Wang, J., and Phelan, P., 2006, "Measurements of Nanofluid Viscosity and Its Implications for Thermal Applications," *Appl. Phys. Lett.*, **89**(13), p. 133108.
- [24] Frenkel, D., and Smit, B., 1996, *Understanding Molecular Simulation: Algorithms to Applications*, Academic Press, Cornwall, UK.
- [25] Prasher, R., Bhattacharya, P., and Phelan, P. E., 2006, "Brownian-Motion-Based Convective-Conductivity Model for the Effective Thermal Conductivity of Nanofluids," *ASME J. Heat Transfer*, **128**(6), pp. 588–595.
- [26] Jang, S. P., and Choi, S. U. S., 2004, "Role of Brownian Motion in the Enhanced Thermal Conductivity of Nanofluids," *App. Phys. Lett.*, **84**(21), pp. 4316–4318.
- [27] Kumar, D. H., Patel, H. E., Kumar, V. R. R., Sundararajan, T., Pradeep, T., and Das, S. K., 2004, "Model for Heat Conduction in Nanofluids," *Phys. Rev. Lett.*, **93**(14), pp. 144301–144304.
- [28] Waigh, T. A., 2005, "Microrheology of Complex Fluids," *Rep. Prog. Phys.*, **68**(3), pp. 685–742.
- [29] Cicuta, P., and Donald, A. M., 2007, "Microrheology: A Review of the Method and Applications," *Soft Matter*, **3**(12), p. 1449.
- [30] Squires, T. M., and Mason, T. G., 2010, "Fluid Mechanics of Microrheology," *Annu. Rev. Fluid Mech.*, **42**(1), pp. 413–438.
- [31] Squires, T. M., and Mason, T. G., 2010, "Tensorial Generalized Stokes-Einstein Relation for Anisotropic Probe Microrheology," *Rheol. Acta*, **49**(11–12), pp. 1165–1177.
- [32] Gómez-González, M., and Álamo, J. C. D., 2016, "Two-Point Particle Tracking Microrheology of Nematic Complex Fluids," *Soft Matter*, **12**(26), pp. 5758–5779.
- [33] Kailasham, R., Chakrabarti, R., and Prakash, J. R., 2018, "Rheological Consequences of Wet and Dry Friction in a Dumbbell Model With Hydrodynamic Interactions and Internal Viscosity," *J. Chem. Phys.*, **149**(9), p. 094903.
- [34] Doi, M., and Edwards, S. F., 1986, *The Theory of Polymer Dynamics*, Oxford The Clarendon Press, New York.
- [35] Peterlin, A., 1966, "Hydrodynamics of Macromolecules in a Velocity Field With Longitudinal Gradient," *J. Polym. Sci.*, **4**(4), pp. 287–291.
- [36] Ferrer, M. C., Robert, C. J., Eckmann, D. M., and Composto, R. J., 2015, "A Facile Route to Synthesize Nanogels Doped With Silver Nanoparticles," *J. Nanopart. Res.*, **15**, pp. 1–7.
- [37] Sarkar, A., Eckmann, D. M., Ayyaswamy, P. S., and Radhakrishnan, R., 2015, "Hydrodynamic Interactions of Deformable Polymeric Nanocarriers and the Effect of Crosslinking," *Soft Matter*, **11**(29), pp. 5955–5969.
- [38] Liu, Y., Lipowsky, R., and Dimova, R., 2012, "Concentration Dependence of the Interfacial Tension for Aqueous Two-Phase Polymer Solutions of Dextran and Polyethylene Glycol," *Langmuir*, **28**(8), pp. 3831–3839.
- [39] Pelton, R., Zhang, J., Chen, N., and Moghaddamzadeh, A., 2003, "The Influence of Dextran Molecular Weight on the Dry Strength of Dextran-Impregnated Paper," *Tappi J.*, **2**, pp. 15–18.
- [40] Bird, R. B., 1997, *Dynamics of Polymeric Liquids*, Wiley, Hoboken, NJ.
- [41] Larson, R. G., 2005, "The Rheology of Dilute Solutions of Flexible Polymers: Progress and Problems," *J. Rheol.*, **49**(1), pp. 1–70.
- [42] Alexander-Katz, A., 2006, "Shear-Flow-Induced Unfolding of Polymeric Globules," *Phys. Rev. Lett.*, **98**(13), p. 138101.
- [43] Miao, L., Young, C. D., and Sing, C. E., 2017, "An Iterative Method for Hydrodynamic Interactions in Brownian Dynamics Simulations of Polymer Dynamics," *J. Chem. Phys.*, **147**(2), p. 024904.
- [44] Beenakker, C. W. J., 1986, "Ewald Sum of the Rotne-Prager Tensor," *J. Chem. Phys.*, **85**(3), pp. 1581–1582.
- [45] Rotne, J., and Prager, S., 1969, "Variational Treatment of Hydrodynamic Interaction in Polymers," *J. Chem. Phys.*, **50**(11), pp. 4831–4837.
- [46] Yamakawa, H., 1970, "Transport Properties of Polymer Chains in Dilute Solution: Hydrodynamic Interaction," *J. Chem. Phys.*, **53**(1), pp. 436–443.
- [47] Bleibel, J., 2012, "Ewald Sum for Hydrodynamic Interactions With Periodicity in Two Dimensions," *J. Phys. A: Math. Theor.*, **45**(22), p. 225002.
- [48] Zhou, T., and Chen, S. B., 2006, "Computer Simulations of Diffusion and Dynamics of Short-Chain Polyelectrolytes," *J. Chem. Phys.*, **124**(3), p. 034904.
- [49] Faxen, H., and Angew, Z., 1927, "Die Geschwindigkeit Zweier Kugeln, Die Unter Einwirkung Der Schwere in Einer Zähnen Flüssigkeit Fallen," *Math. Mech.*, **7**, pp. 79–80.
- [50] Weeks, J. D., Chandler, D., and Andersen, H. C., 1971, "Role of Repulsive Forces in Determining the Equilibrium Structure of Simple Liquids," *J. Chem. Phys.*, **54**(12), pp. 5237–5247.
- [51] Ermak, D. L., and McCammon, J. A., 1978, "Brownian Dynamics With Hydrodynamic Interactions," *J. Chem. Phys.*, **69**(4), p. 1352.
- [52] Bishop, M., 1986, "Polymer Shapes in Three Dimensions," *J. Chem. Phys.*, **85**(10), pp. 5961–5962.
- [53] Brenner, H., 1961, "The Slow Motion of a Sphere Through a Viscous Fluid Towards a Plane Surface," *Chem. Eng. Sci.*, **16**, pp. 242–251.