Assessing the two-body diffusion tensor calculated by the bead models

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The diffusion tensor of complex macromolecules in Stokes flow is often approximated by the bead models. The bead models are known to reproduce the experimental diffusion coefficients of a single macromolecule, but the accuracy of their calculation of the whole multi-body diffusion tensor, which is important for Brownian dynamics simulations, has not been closely investigated. As a first step, we assess the accuracy of the bead model calculated diffusion tensor of two spheres. Our results show that the bead models produce very accurate diffusion tensors for two spheres where a reasonable number of beads are used and there is no bead overlap. © 2013 Author(s). All article content, except where otherwise noted, is licensed under a Creative Commons Attribution 3.0 Unported License. [<http://dx.doi.org/10.1063/1.4807590>]

I. INTRODUCTION

Calculating the diffusion tensor of the macromolecules is an essential step in their Brownian dynamics simulations.¹ An analytical form of the diffusion tensor of macromolecules based on their exact complex structure is impossible to obtain and the tensor is commonly approximated numerically by the bead models. The bead model was inspired by Kirkwood's fundamental works on the hydrodynamic properties of macromolecules.²⁻⁴ Its initial form was proposed by Bloomfield *et al.*,⁵⁻⁷ and later it was extensively studied and implemented in scientific software packages by the García de la Torre group.⁸⁻¹²

The bead model belongs to the type of diffusion tensor calculation methods that approximate the complex structure of macromolecules by smaller geometrically simple frictional elements for which an exact or approximate analytical diffusion tensor is available. And then these methods tackle the solvable frictional element-level hydrodynamic problems in place of the analytically unsolvable macromolecule-level problem. We summarize that all of the bead models have two key components: the way the macromolecules are approximated by a collection of beads, which we call the bead representation, and the way in which one formulates the diffusion tensor between beads. We also want to point out that the frictional elements can be points as in Kirkwood's model, spherical beads as in the bead models, triangular patches as in a boundary element method,¹³ or possibly other geometrical shapes. Here we study the bead model because it is more widely used in Brownian dynamics simulations than the boundary element method and it gives more accurate results than Kirkwood's "point model."

Generally, the bead models can be applied to two types of Brownian dynamics simulations. The first type is the Brownian dynamics simulation of one macromolecule,^{14,15} where

the macromolecule is set to be at least partly flexible. Each (bio)chemical unit, which can be an atom, amino acid, or even a protein domain, is approximated as one bead, and only the bead-level diffusion tensor needs to be calculated. The second type is the Brownian dynamics simulation of the diffusional association of multiple macromolecules,¹⁶⁻¹⁸ where the macromolecules are modeled as rigid bodies and (preferably) beads are packed on the surface of the macromolecules without considering their chemical structures.¹¹ Aside from calculating the bead-level diffusion tensor, an extra step is needed to convert the bead-level diffusion tensor into the diffusion tensor of the macromolecules. Note that the above two types of simulations can be combined with one another and do not necessarily have to incorporate the bead models or any kind of diffusion tensor calculations. The hydrodynamic interactions of the macromolecules are often ignored in order to save computational time.

The calculation of the one-body diffusion coefficients, i.e., the diagonal elements of the diffusion tensor, using the bead models has been shown to be computationally manageable and accurate.^{11,12,19} However, the performance of the bead models in calculating the diffusion coefficients and the off-diagonal elements of the diffusion tensors for two or more bodies has not been closely investigated.

In this work, we focus on the application of the bead models in the diffusional association type of Brownian dynamics simulations. As a first step, we assess the accuracy of the bead model calculation of the whole diffusion tensor of two spheres. We chose the two-sphere system because first, it is the simplest two-body system and each sphere represents one of the two biomolecules in a two-body diffusional association process. Second, the analytical and series solution of the diffusion tensor for the two-sphere system exists,²⁰ to which we can easily compare our bead model calculation results. Specifically, to build our bead models, we chose a type of bead representation called the shell (S)

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representation,^{5,10} which uses a shell of beads to represent the surface of the spheres. The bead-level diffusion tensor was then calculated by the popular modified Rotne-Prager (RP) tensor.^{8,21,22} From here on, “bead model” and “SRP model” both refer to the bead models consisting of the shell representation and the RP tensor.

II. THE MATHEMATICAL FORMULATION OF THE BEAD MODEL

A. The two-sphere diffusion tensor $\mathbb{D}$

The system studied here is two rigid non-overlapping equal-sized spheres in Stokes flow. The velocities/angular velocities of the spheres and the external forces/torques acting on the spheres are related to each other through the diffusion tensor $\mathbb{D}$ and the resistance tensor $\mathbb{R}$,

$$\mathbf{V} = \mathbb{D} \cdot \mathbf{F}, \quad (1)$$

$$\mathbf{F} = \mathbb{R} \cdot \mathbf{V}, \quad (2)$$

$$\mathbb{D} = \begin{bmatrix} \mathbb{D}_{11}^{tt} & \mathbb{D}_{12}^{tt} & \mathbb{D}_{11}^{tr} & \mathbb{D}_{12}^{tr} \\ \mathbb{D}_{21}^{tt} & \mathbb{D}_{22}^{tt} & \mathbb{D}_{21}^{tr} & \mathbb{D}_{22}^{tr} \\ \mathbb{D}_{11}^{rt} & \mathbb{D}_{12}^{rt} & \mathbb{D}_{11}^{rr} & \mathbb{D}_{12}^{rr} \\ \mathbb{D}_{21}^{rt} & \mathbb{D}_{22}^{rt} & \mathbb{D}_{21}^{rr} & \mathbb{D}_{22}^{rr} \end{bmatrix}, \quad (3)$$

$$\mathbf{F} = [\mathbf{F}_1 \quad \mathbf{F}_2 \quad \mathbf{T}_1 \quad \mathbf{T}_2]^T, \quad (4)$$

$$\mathbf{V} = [\mathbf{V}_1 \quad \mathbf{V}_2 \quad \boldsymbol{\Omega}_1 \quad \boldsymbol{\Omega}_2]^T. \quad (5)$$

Both $\mathbb{D}$ and $\mathbb{R}$ are in the form of symmetric 12 by 12 matrices. $\mathbb{D}$ is the inverse of $\mathbb{R}$ and vice versa. Each sub-matrix in Eq. (3) is itself a 3 by 3 (x, y, z by x, y, z) matrix. The subscripts 1 and 2 refer to spheres 1 and 2, the superscripts t and r refer to the translational and rotational motions. In Eqs. (4) and (5), $\mathbf{F}_i$, $\mathbf{T}_i$, $\mathbf{V}_i$, and $\boldsymbol{\Omega}_i$ are the external force, external torque, velocity, and angular velocity of sphere i , $i \in \{1, 2\}$. Except for the 12 diagonal elements in $\mathbb{D}$, the element on the column i and the row j in $\mathbb{D}_{cd}^{ab}$, $i, j \in \{x, y, z\}$, $a, b \in \{r, t\}$, $c, d \in \{1, 2\}$, models the coupling between the a motion of sphere c along the i -axis and the b motion of sphere d along the j -axis. The diagonal elements are not coupling terms, they model the translational or rotational motion of a sphere along an axis.

We define a “block” of the diffusion tensor to be an arbitrary group of terms in the tensor (the locations of those terms in the tensor do not have to form a connected rectangular block); for example, the tt block refers to all terms with the superscript tt . In Sec. IV, we assess the accuracy of the whole tensor and its different blocks separately.

The analytical and series expressions of the terms in $\mathbb{D}$ and $\mathbb{R}$ for two spheres have been derived over the years and are summarized in a paper by Jeffrey and Onishi (JO).²⁰ Here, we call it the JO solution set; it will be considered to give the exact values for $\mathbb{D}$ and all of our SRP model calculation results will be compared against it to assess the model’s accuracy.

B. The bead-level diffusion tensor $\mathbf{D}$

One of the two key components of a bead model is the way in which one formulates the diffusion tensor between beads. In this work, for a two-sphere system, we always use the same number of spherical beads for each sphere. If each sphere is represented by N beads and the system contains $2N$ beads in total, then the grand diffusion tensor $\mathbf{D}$ and the grand resistance tensor $\mathbf{R}$ for all of the beads are

$$\mathbf{v} = \mathbf{D} \cdot \mathbf{f}, \quad (6)$$

$$\mathbf{f} = \mathbf{R} \cdot \mathbf{v}, \quad (7)$$

$$\mathbf{D} = \begin{bmatrix} \mathbf{D}_{11} & \dots & \mathbf{D}_{1,2N} \\ \vdots & \ddots & \vdots \\ \mathbf{D}_{2N,1} & \dots & \mathbf{D}_{2N,2N} \end{bmatrix}. \quad (8)$$

Similar to Eqs. (4) and (5), $\mathbf{f}$ and $\mathbf{v}$ are the force/torque and velocity/angular velocity vectors of all of the beads. Theoretically, in this coupled $2N$ -body system, each $\mathbf{D}_{ij}$ is a 6 by 6 matrix containing four blocks with superscripts tt , tr , rt , rr , and depends on the coordinates and sizes of all of the beads. Unfortunately, such a complicated grand diffusion tensor is unsolvable. To make the calculations feasible, we only use approximate diffusion tensors for the many-bead system. Particularly, in the modified RP tensor,^{8,21,22} only the two-body hydrodynamic interactions are taken into account to the 3rd order of the inverse of the inter-bead distances. The rotational motions of the beads are also ignored. The form of the RP tensor is as follows:

When $i = j$,

$$\mathbf{D}_{ii} = \frac{1}{6\pi\mu a_i} \mathbf{I}. \quad (9)$$

When $i \neq j$,

$$\begin{aligned} \mathbf{D}_{ij} = & \frac{1}{8\pi\mu r_{ij}^3} \left[(r_{ij}^2 \mathbf{I} + \mathbf{r}_{ij} \otimes \mathbf{r}_{ij}) \right. \\ & \left. + \frac{a_i^2 + a_j^2}{r_{ij}^2} \left(\frac{r_{ij}^2}{3} \mathbf{I} - \mathbf{r}_{ij} \otimes \mathbf{r}_{ij} \right) \right], \\ & (a_i + a_j \leq r_{ij}), \end{aligned} \quad (10)$$

$$\begin{aligned} \mathbf{D}_{ij} = & \frac{1}{6\pi\mu a} \left[\left(1 - \frac{9}{32} \frac{r_{ij}}{a} \right) \mathbf{I} \right. \\ & \left. + \frac{3}{32} \frac{\mathbf{r}_{ij} \otimes \mathbf{r}_{ij}}{a r_{ij}} \right], \\ & (a_i + a_j > r_{ij}), \end{aligned} \quad (11)$$

where a_i is the radius of bead i , $a = (a_i + a_j)/2$, $\mathbf{r}_{ij}$ is the vector pointing from the center of bead i to the center of bead j , r_{ij} is the length of $\mathbf{r}_{ij}$, $\otimes$ represents outer product, μ is the solvent viscosity, and $\mathbf{I}$ is a 3 by 3 identity matrix. Note that Eq. (11) only applies to beads with the same radius.

Aside from the RP tensor we use here, there is the lower order Oseen tensor,²³ the higher order Reuland-Felderhof-Jones,²⁴ Mazur-van Saarloos,²⁵ Goldstein²⁶ tensors, and the JO solution set (not exact for the many-bead system). However, the RP tensor appears to be the best compromise between accuracy and computational power and it is the most commonly used diffusion tensor in Brownian dynamics simulations of biomolecules. So in this work, we use only the RP tensor to calculate the bead-level diffusion tensors.

C. From $\mathbf{D}$ to $\mathbb{D}$

To apply the bead models to the diffusional association of rigid macromolecules, $\mathbb{D}$ needs to be calculated from $\mathbf{D}$. During the $\mathbf{D}$ to $\mathbb{D}$ calculation procedure, all of the inter-bead hydrodynamic interactions are summed up to get the total hydrodynamic interaction between the two spheres. One of the steps is the inversion of $\mathbf{D}$. The computational complexity of the conventional matrix inversion operation for a n by n matrix is $O(n^3)$, making it the most time-consuming step in the bead model diffusion tensor calculations. The calculation procedure can be found in previous works.^{8,27,28} Here we used an equivalent but slightly different approach described below.

We first define a “12-case” velocity matrix, $\mathbf{V}^{12\text{-case}}$, for the two-sphere system. The 12 cases correspond to the 12 degrees of freedom of the system; in order they are: the translation of sphere 1 along x -, y -, and z -axis, the translation of sphere 2 along x -, y -, and z -axis, the rotation of sphere 1 about x -, y -, and z -axis, the rotation of sphere 2 about x -, y -, and z -axis. In the i th case, we let the system move by unit speed/angular speed only along its i th degree of freedom. From the 12 cases, we obtain 12 velocity/angular velocity vectors of the system; together we write them into $\mathbf{V}^{12\text{-case}}$ and it is numerically equal to an identity matrix,

$$\mathbf{V}^{12\text{-case}} = [\mathbf{V}^{\text{case } 1} \quad \dots \quad \mathbf{V}^{\text{case } 12}]_{12 \times 12} = \mathbf{I}, \quad (12)$$

and then from Eq. (2),

$$\begin{aligned} \mathbb{R} \cdot \mathbf{V}^{12\text{-case}} &= \mathbf{F}^{12\text{-case}}, \\ \mathbb{R} &= \mathbf{F}^{12\text{-case}}, \\ \mathbb{D} &= (\mathbf{F}^{12\text{-case}})^{-1}, \end{aligned} \quad (13)$$

where $\mathbf{F}^{12\text{-case}}$ is the matrix that contains the forces and torques experienced by the two spheres in the 12 cases. $\mathbb{R}$ and $\mathbf{F}^{12\text{-case}}$ are only numerically identical; matrix $\mathbf{I}$ is not explicitly written out in Eq. (13) but it bears units.

Having obtained Eq. (13), the next step is to calculate $\mathbf{F}^{12\text{-case}}$, invert it and get $\mathbb{D}$. Since the two spheres are rigid, for each case, we can easily calculate the velocity vector, $\mathbf{v}^{\text{case } i}$, of all the beads given the velocity/angular velocity vector, $\mathbf{V}^{\text{case } i}$, of the spheres. Note that since we use the RP tensor, the angular velocities of the beads do not

enter $\mathbf{v}^{\text{case } i}$,

$$\mathbf{v}^{\text{case } i} = \begin{bmatrix} \mathbf{V}_1^{\text{case } i} + \boldsymbol{\Omega}_1^{\text{case } i} \times \mathbf{r}_1 \\ \vdots \\ \mathbf{V}_1^{\text{case } i} + \boldsymbol{\Omega}_1^{\text{case } i} \times \mathbf{r}_N \\ \mathbf{V}_2^{\text{case } i} + \boldsymbol{\Omega}_2^{\text{case } i} \times \mathbf{r}_{N+1} \\ \vdots \\ \mathbf{V}_2^{\text{case } i} + \boldsymbol{\Omega}_2^{\text{case } i} \times \mathbf{r}_{2N} \end{bmatrix}, \quad (14)$$

where $\mathbf{r}_i$ is the vector that starts at the center of the sphere that bead i is on and ends at the center of bead i . After calculating the twelve $\mathbf{v}^{\text{case } i}$, we write them together as $(\mathbf{v}^{12\text{-case}})_{6N \times 12}$. The grand resistance tensor $\mathbf{R}$ is the inverse of the grand diffusion tensor $\mathbf{D}$, which is calculated by the RP tensor, and we have

$$\begin{aligned} \mathbf{f}^{12\text{-case}} &= \mathbf{R} \cdot \mathbf{v}^{12\text{-case}} \\ &= \mathbf{D}^{-1} \cdot \mathbf{v}^{12\text{-case}}. \end{aligned} \quad (15)$$

Here we obtain $\mathbf{f}^{12\text{-case}}$, which stores the twelve force vectors of the beads in the twelve cases. For each case, we can calculate the force/torque vector $\mathbf{F}^{\text{case } i}$ of the spheres from force vector $\mathbf{f}^{\text{case } i}$ of the beads by

$$\mathbf{F}^{\text{case } i} = \begin{bmatrix} \sum_{j=1}^N \mathbf{f}_j^{\text{case } i} \\ \sum_{j=N+1}^{2N} \mathbf{f}_j^{\text{case } i} \\ \sum_{j=1}^N \mathbf{r}_j \times \mathbf{f}_j^{\text{case } i} \\ \sum_{j=N+1}^{2N} \mathbf{r}_j \times \mathbf{f}_j^{\text{case } i} \end{bmatrix}, \quad (16)$$

where subscript j is the index of the beads. This way we obtain $\mathbf{F}^{12\text{-case}}$ from $\mathbf{f}^{12\text{-case}}$. And last, we obtain $\mathbb{D}$ as the numerical inverse of $\mathbf{F}^{12\text{-case}}$.

III. GENERATING BEAD REPRESENTATIONS FOR SPHERES

The other key component of the bead models is the way in which one approximates the macromolecules by a collection of spherical beads, or as we call it, a bead representation. There are several types of bead representations.¹⁰ Here we work with one type of bead representation only, the shell representation (most literature calls it “shell model,” but to avoid ambiguity, we call it the “shell representation” here). It only assigns beads to the surface of the spheres and it best represents the physical picture of the hydrodynamics of the rigid nonporous spheres because hydrodynamic interactions are fully screened in the interior of the spheres.

A. Building the shell representations

To build a N -bead shell representation for a single sphere, we restrict the N beads to be tangential to the sphere surface

FIG. 1. The shell representation for two spheres. Both spheres are placed along the vector (1,1,1), the dashed line, at an equal distance from the origin. In this example, both spheres have the same radius and each sphere surface consists of 50 beads.

from the inside and apply a pseudo-repulsive force between all pairs of beads. We iteratively minimize the pseudo-potential energy of the system and adjust the bead radius (which is same for all of the beads) such that no beads overlap and at least one pair of beads is tangential to each other.

The shell representation we use here is different from the commonly seen shell representations.^{5,29} In our shell building method, the surface of the sphere is roughly evenly divided by the beads, the shell of beads is smooth, and we can build a shell representation with an arbitrary number of beads. We believe that such shell representation will more evenly account for the hydrodynamic interactions at every part of the sphere surface. A view of our shell representation for the two-sphere system is shown in Fig. 1. We put the two spheres along vector (1,1,1) instead of an axis to avoid zero entries in the JO solution set calculated diffusion tensor and so the accuracy of all of the entries in the diffusion tensor can be assessed.

B. Calibrating the shell representations

Before attempting to calculate the two-sphere diffusion tensor using the bead models we made, we want to make sure that they can be used to calculate the single-sphere (ss) diffusion tensor accurately. The single-sphere diffusion tensor follows Stokes' law; its unitless form is

$$\mathbb{D}_{ss} = \mathbf{I}, \quad (17)$$

where $\mathbf{I}$ is a 6 by 6 identity matrix. The diagonal elements of the $\mathbb{D}_{ss}$ calculated by our bead models that use the shell representations built in Sec. III A are all bigger than 1. And the off-diagonal coupling terms are non-zero; but they have very small magnitudes ($<10^{-5}$). This is because, according to the way we build the shell representations, there are holes in between the beads and the bead centers are located on the inside of the sphere. These two factors lead to underestimated frictional forces experienced by the sphere.

FIG. 2. The values of the scaling factors for the bead models with different shell representations. The scaling factors calibrate the bead model calculated single-sphere diffusion tensors to be as close to the Stokes' law as possible. When a larger number of beads are used, the shell representation requires less scaling (scaling factor closer to 1), and therefore a smaller degree of calibration. Scaling factors c_t , c_r , and c_{opt} are as described in the text. Their values are calculated for 23 bead models and plotted with respect to N , the number of beads in a bead model. The R is the radius of the sphere, set to be 10 unit length here.

We calibrate the bead models calculated $\mathbb{D}_{ss}$ to be as close to the Stokes' law as possible by scaling the shell representations. According to Eqs. (9)–(11), the grand diffusion tensor, Eq. (8), is inversely proportional to the length scale of the shell representation, as such, we can shrink or stretch the shell representation of a bead model by multiplying a scaling factor c to all of the bead coordinates and radii to make its calculated $\mathbb{D}_{ss}$ as close to $\mathbf{I}$ as possible.

We first define the optimized scaling factor, c_{opt} , which scales the bead model calculated $\mathbb{D}_{ss}$ to have the smallest standard deviation from $\mathbf{I}$. For comparison, we also defined another two scaling factors, c_t and c_r , that, respectively, scales the calculated average translational and rotational diffusion coefficients to 1.

The values of the scaling factors only depend on two parameters, the number of beads used, N , and the sphere radius, R (Fig. 2). The value of c_{opt} falls between c_t and c_r and all three scaling factors are very close to each other at all N . After scaling with c_{opt} , for all 23 bead models used Fig. 2, the average diffusion coefficient is less than 2% different from the Stokes' law. We can also see that, when more beads are used (larger N), less scaling, therefore less calibration, is needed (scaling factors closer to 1, 1 means no scaling). This means that the bead models with more beads give more accurate $\mathbb{D}_{ss}$ without scaling.

According to our original shell representation building approach, for the two-sphere system, no bead overlap occurs as long as the spheres do not overlap. However, after scaling, the shell representations get stretched out (all the scaling factors are bigger than 1). The beads on different spheres will overlap when the two spheres are close. The smaller the number of beads used, the more the overlap when the two spheres are nearly touching.

In Sec. IV, all of the bead models used are scaled by c_{opt} .

IV. NUMERICAL RESULTS

For all of the test cases shown in this section, the two-sphere diffusion tensor was calculated by both the JO solution set and the SRP model, and we denote the two differently calculated diffusion tensors as $\mathbb{D}_{JO}$ and $\mathbb{D}_{SRP}$. Then, we measured the accuracy of the diffusion tensor by Frobenius norm and Pearson's correlation coefficient. Note that all of the lengths and tensors calculated are converted to be unitless for easy comparison.²⁰

First, we want to compare the differences between the magnitudes of $\mathbb{D}_{JO}$ and $\mathbb{D}_{SRP}$. The magnitude of individual tensors can be calculated from their Frobenius norm, see Eq. (18). Likewise the magnitude of the difference between $\mathbb{D}_{JO}$ and $\mathbb{D}_{SRP}$ can be calculated from the Frobenius norm of the difference of the two tensors. We standardize the magnitude difference by the norm percent deviation (NPD), see Eq. (19), to make the difference comparable across different system configurations,

$$\|\mathbb{D}\| = \sqrt{\sum_{i,j=1}^{12} d_{ij}^2}, \quad (18)$$

$$\text{NPD} = \frac{\|\mathbb{D}_{SRP} - \mathbb{D}_{JO}\|}{\|\mathbb{D}_{JO}\|}, \quad (19)$$

where d_{ij} denotes the element in the diffusion tensor and $\text{NPD} \in [0, +\infty)$. NPD tells us the average accuracy of the elements in $\mathbb{D}_{SRP}$, but it does not say anything about the accuracy of the individual elements. To address whether the accuracies of the individual elements in $\mathbb{D}_{SRP}$ are similar, we calculate the Pearson's correlation coefficient (PCC) between the two tensors. PCC measures the degree of linear correlation, or proportionality, between $\mathbb{D}_{SRP}$ and $\mathbb{D}_{JO}$ and is defined by Eq. (20),

$$\text{PCC} = \frac{\sum_{i,j=1}^{12} ((d_{JO})_{ij} - \bar{d}_{JO}) ((d_{SRP})_{ij} - \bar{d}_{SRP})}{\sqrt{\sum_{i,j=1}^{12} ((d_{JO})_{ij} - \bar{d}_{JO})^2} \sqrt{\sum_{i,j=1}^{12} ((d_{SRP})_{ij} - \bar{d}_{SRP})^2}}, \quad (20)$$

where $\bar{d}_{JO}$ and $\bar{d}_{SRP}$ denote the mean of the elements in $\mathbb{D}_{JO}$ and $\mathbb{D}_{SRP}$ and $\text{PCC} \in [-1, 1]$. When $\text{PCC} = 0$, the two tensors have no linear correlation and the accuracies of the elements in $\mathbb{D}_{SRP}$, i.e., the differences between each element in $\mathbb{D}_{SRP}$ and its corresponding element in $\mathbb{D}_{JO}$, have large standard deviation. When $\text{PCC} = \pm 1$, $\mathbb{D}_{SRP} = \pm \alpha \mathbb{D}_{JO}$ and $\text{NPD} = |\mp \alpha|$, α is a positive constant, the accuracies of the elements in $\mathbb{D}_{SRP}$ are the same, despite the fact that they can be equally high or equally low. Note that the signs in the diffusion tensor have physical meanings, any $\text{PCC} \leq 0$ indicates a wrongly calculated $\mathbb{D}_{SRP}$. An accurate bead model calculation should give a NPD value close to 0 and a PCC value close to 1. Note that both the NPD and PCC values can be calculated for any block of $\mathbb{D}_{SRP}$ with respect to the corresponding block of $\mathbb{D}_{JO}$.

A. The whole tensor

We first assessed the accuracy of the whole diffusion tensor calculated by six different bead models at various sphere separations (Fig. 3). We see that as the two spheres get further apart or as more beads are used in the calculation, the NPD value gets closer to 0 and the PCC value gets closer to 1 consistently, meaning an increasing accuracy of the bead model calculated diffusion tensors. However, the degree of improvement of the NPD and PCC values also gets smaller at the same time.

In Fig. 3, for all of the bead models used, when there are bead overlaps ($d <$ the sphere separations marked by the filled dots), the NPD values are much bigger than 0 and the PCC values are less close to 1, meaning a poor accuracy of the bead model calculated diffusion tensors. Also, with overlaps, the NPD and PCC curves show irregular behaviors, e.g., the 50-bead model curve crossing over the 100-bead model curve in both Figs. 3(a) and 3(b). But as the sphere separation gets larger, the NPD and PCC values sharply tend towards 0 and 1. When the gap between the bead shells fits exactly one bead

FIG. 3. The accuracy of different bead models at different sphere separations. The bead model calculated diffusion tensor becomes more accurate (the NPD value approaches 0 and the PCC value approaches 1) as the distance between the spheres increases or as more beads are used in the calculation. The sphere separation, d , is the distance between the centers of two spheres. The two spheres here both have a radius of 10 in unit length. For each bead model, the filled dots mark the distance at which the gap between the outer surfaces of the two bead shells is 0. The filled triangles mark the distance at which the gap between the outer surfaces of the two bead shells can fit exactly one bead.

FIG. 4. The accuracy of the different blocks of the bead model calculated diffusion tensor. The NPD values of the tensor blocks of the 50-bead model calculated diffusion tensors in Fig. 3 are plotted (the filled dots and triangles here have the same meanings as in Fig. 3). For each type of motion coupling (*tt*, *rr*, and *tr/rt*), the bead model always calculates the coupling between the motions of different spheres more accurately than the coupling between the motions of the same sphere. Consequently, the 12/21 sub-blocks always achieve lower NPD values than the non-diagonal 11/22 sub-blocks. The NPD values of the non-diagonal 11/22 sub-blocks, marked with plus signs in the legends, never converge and keep increasing as d increases.

(d = the sphere separations marked by the filled triangles), the NPD and PCC values have basically converged.

As a side note here, since none of the shell representations for the sphere is symmetric along all the lines that pass through the sphere center, different orientations of the shell representation for each bead model lead to slightly different $\mathbb{D}_{\text{SRP}}$ tensors. For each bead model calculation in Fig. 3, we took 10 random orientations of the bead model to calculate the NPD and PCC values. However, the standard deviations of the 10 NPD and the 10 PCC values for the 20-bead model when the two bead shells are exactly touching are only 0.0002 and 0.000004. For models with more beads and at larger separations, the standard deviations are essentially zero. Since different orientations give little differences in most cases, from here on, we will only use one orientation for each bead model calculation.

B. Different tensor blocks

Here, we used the 50-bead model for the investigation of the accuracy of different tensor blocks. In Fig. 4, we present only the NPD values because, similar to Fig. 3, the NPD and PCC values change with d according to the same trend; presenting both of them would be repetitive.

In Fig. 4, the tensor blocks are sorted by the type of motion coupling, the coupling between the translational motions (*tt*), the coupling between the rotational motions (*rr*), and the coupling between the translational and the rotational motions (*tr/rt*). For each type of motion coupling, the bead model always calculates the coupling between the motions of different spheres more accurately than the coupling between the motions of the same sphere. For example, in Fig. 4(a), the tensor block consists of $\mathbb{D}_{12}^{tt}$ and $\mathbb{D}_{21}^{tt}$ achieves lower NPD values than the tensor block consists of the off-diagonal elements of $\mathbb{D}_{11}^{tt}$ and $\mathbb{D}_{22}^{tt}$. Aside from this observation, the NPD value of the $\mathbb{D}_{12}^{tt}, \mathbb{D}_{21}^{tt}$ block converges to near 0 at large d , while the NPD value of the off-diagonal $\mathbb{D}_{11}^{tt}, \mathbb{D}_{22}^{tt}$ block keeps increasing as d increases, meaning that the elements in the block only get more and more different from the exact solution as d increases. Similar results are seen in Figs. 4(b) and 4(c).

The NPD values of the diagonal elements in $\mathbb{D}$ are presented separately because they model the translational or rotational motions of the single spheres, not the couplings between the motions. The accuracy of the bead model calculated diagonal elements falls between the accuracies of the couplings terms between spheres and the couplings terms within each sphere, as can be seen from their median NPD values in Figs. 4(a) and 4(b). The NPD values of the whole tensor $\mathbb{D}$ are also plotted in Fig. 4 as a reference.

In Fig. 4, bead overlaps again lead to inaccuracies (large NPD values) and irregular NPD trends. However, except for the NPD values of the off-diagonal 11/22 sub-blocks, the NPD values of the tensor blocks improve and converge quickly as d increases and bead overlaps disappear.

V. DISCUSSION

In this paper, we assess the accuracy of the whole diffusion tensor calculated by the bead models through the calculation of NPD and PCC values instead of assessing the accuracy of only the diagonal elements of the tensor.^{11,12} In the Brownian dynamics simulations that take hydrodynamics into account, the whole diffusion tensor should be used,¹ therefore it is important to assess the accuracy of all its entries.

The presented NPD and PCC measurements have direct physical meanings. In Brownian dynamics simulations, a NPD value closer to 0 means a more accurate average propagation speed of the system by $\mathbb{D}_{\text{SRP}}$; a PCC value closer to 1 means a more accurate shape of the propagation path generated by $\mathbb{D}_{\text{SRP}}$. If we perform Brownian dynamics simulations of the same system with the same sequence of random kicks, but two different diffusion tensors $\mathbb{D}_{\text{SRP}}$ and $\mathbb{D}_{\text{JO}}$ and we obtain two trajectories, when $\text{NPD} = 0$ and $\text{PCC} = 1$, $\mathbb{D}_{\text{SRP}} = \mathbb{D}_{\text{JO}}$ and the two trajectories can be exactly superimposed onto each other. When $\text{NPD} > 0$ and $\text{PCC} = 1$, $\mathbb{D}_{\text{SRP}} = \alpha \mathbb{D}_{\text{JO}}$ and $\text{NPD} = |1 - \alpha|$. For this case, the two trajectories will have the same shape, but the $\mathbb{D}_{\text{JO}}$ trajectory needs to be enlarged/shrunk by a factor of α to be superimposed onto the $\mathbb{D}_{\text{SRP}}$ trajectory; this is because the system propagated by $\mathbb{D}_{\text{SRP}}$ will move a factor of α faster/slower than the

system propagated by $\mathbb{D}_{JO}$. When $NPD = 0$ and $PCC < 1$, on average the systems in the two trajectories move at the same speed, but they follow two different propagation paths that cannot be superimposed onto each other by simple enlarging or shrinking.

The accuracy of the bead model calculated diffusion tensors gets better when more beads are used in the calculation. The reason for this is that when more beads are used, the bead model becomes equivalent to the boundary element method,¹³ which becomes equivalent to the exact solution to the Stokes equations as the boundary elements become infinitesimally small. The accuracy also gets better when the two spheres are further apart. Because the RP tensor was derived for well-separated beads and as the spheres get further apart, the beads on different spheres get further apart, the bead configuration fits more into the regime where the RP tensor was derived.

The magnitude accuracy (reflected by the NPD values) and proportionality accuracy (reflected by the PCC values) improve and decline according to the same trend. This means that, e.g., in simulations, the two-sphere system trajectory generated by the bead models with more beads will follow a more accurate path with a more accurate speed. In Fig. 3, all six bead models acquired a less than 2% difference between the magnitudes of $\mathbb{D}_{SRP}$ and $\mathbb{D}_{JO}$, and a PCC value bigger than 0.9998, meaning that all of the $\mathbb{D}_{SRP}$ are nearly proportional to $\mathbb{D}_{JO}$. This is a quite satisfying result, because, even with a small number of beads (20 beads), the $\mathbb{D}_{SRP}$ is still fairly accurate.

The hydrodynamic interactions between the beads on the same sphere are always more poorly accounted for than those between the beads on different spheres. In the two-sphere system, the hydrodynamic interactions between the different degrees of freedom of the same sphere should diminish quickly as the two spheres move apart. But because of the intrinsic asymmetry of the shell representations, these hydrodynamic interactions never disappear. And this leads to the big inaccuracy of the off-diagonal elements with subscripts 11 or 22 at large sphere separation. Fortunately, these elements are usually small enough that they do not contribute significantly to the overall error of $\mathbb{D}_{SRP}$. The RP tensor does not predict the hydrodynamic interactions between non-overlapping, but closely placed, beads as accurately as those of distantly placed beads, primarily because the derivation of the RP tensor assumes that the beads are well separated.

It has been reported that the bead models using the RP tensor do not produce rotational diffusion coefficients accurate enough because the rotational motion is only accounted for at the center of the beads.^{19,28,30} Our bead models with scaling greatly improved the accuracy of the rotational tensor block and the whole tensor. The term $0.031(4\pi R^2/(N + 12))^{1/2}$ in the fitted formula of the scaling factor shown in Fig. 2 makes up for the unaccounted hydrodynamic interactions due to the holes between the beads on a sphere surface of area $4\pi R^2$ and the unaccounted bead volumes. Note that when using scaling in our calculations, the ranking of the average accuracy of the three types of coupling terms, tt , rr , and tr/rt , depends on the choice of the scaling factor. We chose c_{opt} in our calculations because it optimizes the average accuracy of all terms in $\mathbb{D}$. On the other hand, e.g., c_t optimizes

the average accuracy of the tt terms only and leaves the rr and tr/rt terms less accurate.

For a two-sphere system, the bead models give consistent accuracy except for at small sphere separations. In general, for any bead model used here, when the bead shells of the two spheres overlap, the accuracy of $\mathbb{D}_{SRP}$ is always fairly low (Fig. 3), and the accuracies of different tensor blocks show irregular improvements and declinations (Fig. 4). Using the RP tensor on overlapping beads requires extra precaution,³¹ and it may lead to unexpected results as shown here. Avoiding the bead overlapping situation helps us calculate more accurate diffusion tensors. In the diffusional association Brownian dynamics simulations of two proteins modeled by beads, one could use less beads at large separations to save computation times and more beads at small separations to avoid overlaps.

The method of Brownian dynamics simulations with hydrodynamics calculated by the bead models was first developed more than 30 years ago.¹ Until today, the full hydrodynamics of the simulated biomolecules is still often ignored due to the size and complexity of the biomolecules. Usually, only the diagonal elements of the bead model calculated diffusion tensors are used. And in terms of the diffusional association simulations, the diffusion tensors are often pre-calculated for isolated biomolecules instead of calculated on-the-fly for the whole simulation system involving multiple biomolecules. This is mainly due to the challenge of quickly inverting and decomposing the diffusion tensors for large simulation systems. Both the conventional matrix inversion operation in the bead model calculations and the matrix decomposition operation in the Brownian dynamics simulations scale as $O(N^3)$, where N is the number of frictional elements in the system. Significant computational power is required to improve the bead model accuracy. Faster matrix operation methods exist³² and should be applied in the Brownian dynamics simulations with the bead models for practical reasons.

VI. CONCLUSIONS

In general, our bead models produce very accurate two-sphere diffusion tensors when the bead shells do not overlap and a reasonable number of beads are used (more than around 20 beads for each sphere). Through this work, we gained confidence in the accuracy of the bead model calculated diffusion tensors for two bodies with simple geometry. Tests with realistic globular biomolecules should be performed as the next investigation on the capability of the bead models. Continuous efforts are being made in developing faster matrix operation algorithms for diffusion tensors, as well as more accurate ways to calculate diffusion tensors from the bead models. We believe that, with these efforts, we can eventually use the bead models to calculate realistic diffusion tensors in the Brownian dynamics simulations of biomolecules.

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- ¹D. L. Ermak and J. A. McCammon, "Brownian dynamics with hydrodynamic interactions," *J. Chem. Phys.* **69**, 1352–1360 (1978).
- ²J. G. Kirkwood and J. Riseman, "The intrinsic viscosities and diffusion constants of flexible macromolecules in solution," *J. Chem. Phys.* **16**, 565–573 (1948).
- ³J. G. Kirkwood, "The statistical mechanical theory of irreversible processes in solutions of flexible macromolecules: Visco-elastic behavior," *Recl. Trav. Chim. Pays-Bas* **68**, 649–660 (1949).
- ⁴J. G. Kirkwood, "The general theory of irreversible processes in solutions of macromolecules," *J. Polym. Sci.* **12**, 1–14 (1954).
- ⁵V. A. Bloomfield, K. E. Van Holde, and W. O. Dalton, "Frictional coefficients of multisubunit structures. I. Theory," *Biopolymers* **5**, 135–148 (1967).
- ⁶V. A. Bloomfield, K. E. Van Holde, and W. O. Dalton, "Frictional coefficients of multisubunit structures. II. Application to proteins and viruses," *Biopolymers* **5**, 149–159 (1967).
- ⁷D. P. Filson and V. A. Bloomfield, "Shell model calculations of rotational diffusion coefficients," *Biochemistry* **6**, 1650–1658 (1967).
- ⁸J. García de la Torre and V. A. Bloomfield, "Hydrodynamic properties of macromolecular complexes. I. Translation," *Biopolymers* **16**, 1747–1763 (1977).
- ⁹J. García de la Torre, S. Navarro, M. C. López Martínez, F. G. Diaz, and J. J. López Cascales, "HYDRO: A computer program for the prediction of hydrodynamic properties of macromolecules," *Biophys. J.* **67**, 530–531 (1994).
- ¹⁰B. Carrasco and J. García de la Torre, "Hydrodynamic properties of rigid particles: Comparison of different modeling and computational procedures," *Biophys. J.* **76**, 3044–3057 (1999).
- ¹¹J. García de la Torre, M. L. Huertas, and B. Carrasco, "Calculation of hydrodynamic properties of globular proteins from their atomic-level structure," *Biophys. J.* **78**, 719–730 (2000).
- ¹²A. Ortega, D. Amorós, and J. García de la Torre, "Prediction of hydrodynamic and other solution properties of rigid proteins from atomic- and residue-level models," *Biophys. J.* **101**, 892–898 (2011).
- ¹³S. Aragon, "A precise boundary element method for macromolecular transport properties," *J. Comput. Chem.* **25**, 1191–1205 (2004).
- ¹⁴R. C. Wade, M. E. Davis, B. A. Luty, J. D. Madura, and J. A. McCammon, "Gating of the active site of triose phosphate isomerase: Brownian dynamics simulations of flexible peptide loops in the enzyme," *Biophys. J.* **64**, 9–15 (1993).
- ¹⁵C. E. Chang, T. Y. Shen, J. Trylska, V. Tozzini, and J. A. McCammon, "Gated binding of ligands to hiv-1 protease: Brownian dynamics simulations in a coarse-grained model," *Biophys. J.* **90**, 3880–3885 (2006).
- ¹⁶S. H. Northrup, S. A. Allison, and J. A. McCammon, "Brownian dynamics simulation of diffusion-influenced bimolecular reactions," *J. Chem. Phys.* **80**, 1517–1524 (1984).
- ¹⁷R. Gabbouline and R. Wade, "Simulation of the diffusional association of barnase and barstar," *Biophys. J.* **72**, 1917–1929 (1997).
- ¹⁸G. A. Huber and J. A. McCammon, "BrownDye: A software package for Brownian dynamics," *Comput. Phys. Commun.* **181**, 1896–1905 (2010).
- ¹⁹B. Carrasco and J. García de la Torre, "Improved hydrodynamic interaction in macromolecular bead models," *J. Chem. Phys.* **111**, 4817–4826 (1999).
- ²⁰D. J. Jeffrey and Y. Onishi, "Calculation of the resistance and mobility functions for two unequal rigid spheres in low-Reynolds-number flow," *J. Fluid Mech.* **139**, 261–290 (1984).
- ²¹J. Rotne and S. Prager, "Variational treatment of hydrodynamic interaction in polymers," *J. Chem. Phys.* **50**, 4831–4837 (1969).
- ²²H. Yamakawa, "Transport properties of polymer chains in dilute solution: Hydrodynamic interaction," *J. Chem. Phys.* **53**, 436–443 (1970).
- ²³C. W. Oseen, *Hydrodynamik* (Akademische Verlag, Leipzig, 1927).
- ²⁴P. Reuland, B. Felderhof, and R. Jones, "Hydrodynamic interaction of two spherically symmetric polymers," *Physica A* **93**, 465–475 (1978).
- ²⁵P. Mazur and W. van Saarloos, "Many-sphere hydrodynamic interactions and mobilities in a suspension," *Physica A* **115**, 21–57 (1982).
- ²⁶R. F. Goldstein, "Macromolecular diffusion constants: A calculational strategy," *J. Chem. Phys.* **83**, 2390–2397 (1985).
- ²⁷J. M. García Bernal and J. García de la Torre, "Transport properties and hydrodynamic centers of rigid macromolecules with arbitrary shapes," *Biopolymers* **19**, 751–766 (1980).
- ²⁸J. García de la Torre and V. Rodes, "Effects from bead size and hydrodynamic interactions on the translational and rotational coefficients of macromolecular bead models," *J. Chem. Phys.* **79**, 2454–2460 (1983).
- ²⁹J. García de la Torre, "Building hydrodynamic bead-shell models for rigid bioparticles of arbitrary shape," *Biophys. Chem.* **94**, 265–274 (2001).
- ³⁰J. García de la Torre, G. del Rio Echenique, and A. Ortega, "Improved calculation of rotational diffusion and intrinsic viscosity of bead models for macromolecules and nanoparticles," *J. Phys. Chem. B* **111**, 955–961 (2007).
- ³¹B. Carrasco, J. García de la Torre, and P. Zipper, "Calculation of hydrodynamic properties of macromolecular bead models with overlapping spheres," *Eur. Biophys. J.* **28**, 510–515 (1999).
- ³²R. R. Schmidt, J. G. Hernández Cifre, and J. García de la Torre, "Comparison of Brownian dynamics algorithms with hydrodynamic interaction," *J. Chem. Phys.* **135**, 084116 (2011).