Fluctuation-induced hydrodynamic coupling in an asymmetric, anisotropic dumbbell

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We recently introduced a model of an asymmetric dumbbell made of two hydrodynamically coupled subunits as a minimal model for a macromolecular complex, in order to explain the observation of enhanced diffusion of catalytically active enzymes. It was shown that internal fluctuations lead to a negative contribution to the overall diffusion coefficient and that the fluctuation-induced contribution is controlled by the strength of the interactions between the subunits and their asymmetry. We develop the model by studying the effect of anisotropy on the diffusion properties of a modular structure. Using a moment expansion method we derive an analytic form for the long-time diffusion coefficient of an asymmetric, anisotropic dumbbell and show systematically its dependence on internal and external symmetry. The method provides a tractable, analytical route for studying the stochastic dynamics of dumbbell models. The present work opens the way to more detailed descriptions of the effect of hydrodynamic interactions on the diffusion and transport properties of biomolecules with complex structures.

I. INTRODUCTION

Understanding the dynamics of biomolecules is crucial to fully appreciate and potentially harness their functionalities in the search for biocompatible micro- and nanomachines. At the nano-scale, enzymes have been studied due to their prevalence and efficiency in performing very specific functions under conditions dominated by thermal fluctuations and viscous hydrodynamics [1], and a fundamental understanding of the effect of catalytic activity on enzyme dynamics could provide insight into the physical organisation of intracellular processes. All of this has promoted recent interest in the effect of the catalytic activity of a single enzyme molecule on its dynamics. In this context, interesting phenomena have been reported, most notably enhanced diffusion of a single enzyme when it is in the presence of substrate molecules [2–5].

Most physical explanations of this phenomenon were dependent on nonequilibrium mechanisms, relying on the speed and exothermicity of the catalysed chemical process [5–8]. There was then evidence to suggest that the non-equilibrium step of the catalytic cycle is in fact not a necessary condition for observing enzyme enhanced diffusion [9]. We proposed a model where binding and unbinding of substrate molecules to the enzyme could affect its internal fluctuations and therefore its overall diffusion coefficient, even in the absence of catalytic events. More precisely, we studied a minimal dumbbell model to investigate the effect of fluctuations of the internal degrees of freedom of the enzyme on its overall diffusion, on the basis that such fluctuations are modified by substrate binding [10].

The main theoretical challenges of studying the transport properties of macromolecules are the following, which are generic to suspensions of flexible objects: a large number of degrees of freedom in the phase space; the treatment of hydrodynamic interactions between the rigid bodies that make up the flexible object; and coupling between translational and rotational motions and internal and external motions [11]. The effect of hydrodynamic interactions on the dynamics of macromolecular suspensions is a long-standing problem of polymer physics, whose study requires approaches from statistical physics, low Reynolds number hydrodynamics and rheology. Models of flexible chains or dumbbells have been extensively studied and successfully used to model the dynamics of real macromolecules. Equilibrium-like averaging procedures, pioneered by Zimm [12] and subsequently refined [13, 14], have been proposed to account for hydrodynamic interactions. Numerical strategies allowing efficient sampling of the configurations of such model polymers were employed to study, for instance, the behaviour of chains and dumbbells under shear [15], their cyclisation dynamics [16, 17] or their diffusion properties. With our asymmetric dumbbell model, we investigated effects that were overlooked so far, such as the effect of internal asymmetries, which results in the coupling of translational and rotational motion and is inherent in real macromolecules, in particular in enzymes which bear an active site and therefore a built-in asymmetry, the effect of orientation fluctuations of the subunits that constitute the dumbbell and couple to the compressional degrees of freedom, and the effect of changes between the different conformational landscapes explored by the enzyme during its catalytic cycle [10]. Furthermore, our approach provides analytical results in a tractable way.

For the initial version of our model, hydrodynamic interactions were approximated by their isotropic part, which amounts to a pre-averaging of their orientation dependence, a common approximation in polymer dy-

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namics [18]. However, pre-averaging subunit orientations compromises knowledge of the effect of local anisotropy. In this paper, we go one step further in the determination of the diffusion coefficient of a generalized dumbbell by including hydrodynamic interactions due to anisotropy. We incorporate the orientations of the subunits with the aim of offering a consistent treatment of the orientation dependence. It is hoped that the analytical approach that is provided in what follows will inspire descriptions of the effect of hydrodynamic interactions on the transport properties of modular biomolecules beyond what is available from classical polymer dynamics theories.

II. THE MODEL

In order to study the effects of fluctuation-induced hydrodynamic coupling, we consider the simplest system, endowed with a minimal number of degrees of freedom, exhibiting this type of phenomenon. We consider a pair of rigid, unequal Brownian particles which are of arbitrary shape, suspended in a viscous, unbounded and incompressible fluid. The particles are coupled through long-range, solvent-mediated hydrodynamic interactions and through an interaction potential $U(\mathbf{x}^1, \mathbf{x}^2, \hat{\mathbf{u}}^1, \hat{\mathbf{u}}^2)$. We assume Stokes flow, so that the forces and torques exerted by the subunits on the fluid are linearly related to the instantaneous linear and angular velocities through hydrodynamic interactions [19, 20]. The positions $\mathbf{x}^\alpha$ and orientations $\hat{\mathbf{u}}^\alpha$ (with $\alpha = 1, 2$) of the individual subunits undergo thermal fluctuations around the equilibrium configuration (see fig. 1). As such, the system describes low Reynolds number flow around an asymmetric dumbbell which accesses different compressional and orientation modes in a fluctuation-dependent way.

We construct an interaction potential based on some generic structural observations that have been reported for enzymes. In [21], fluorescence emission spectrophotometry was used to detect conformational changes in the presence of substrates in the enzyme aldolase, with the observation of different spectra in the presence of each of the two different substrates of aldolase, suggesting the occurrence of different conformations and concentration dependence of the fluorescence spectra during substrate binding. The enzyme urease is known to have open and closed states, with transition between the states controlled by substrate binding, which drives the dynamics of a “flap” [22]. Such substrate-driven fluctuations of the orientations of an enzyme are incorporated in the coefficients of the interaction potential for the dumbbell. The interaction potential U is defined through the enabled modes of fluctuation: $\hat{\mathbf{u}}^1$ and $\hat{\mathbf{u}}^2$ are taken to be coplanar and only fluctuations in the plane containing these vectors are considered. Fluctuations out of the plane are neglected for simplicity. Hence, for small fluctuations, the interaction potential can be expanded in the fluctuation angles between the orientation vectors of the individual subunits $\hat{\mathbf{u}}^1$, $\hat{\mathbf{u}}^2$ and the orientation vector of the axis of the dumbbell $\hat{\mathbf{n}}$, given by $\mathbf{x} = \mathbf{x}^2 - \mathbf{x}^1 = x\hat{\mathbf{n}}$, as

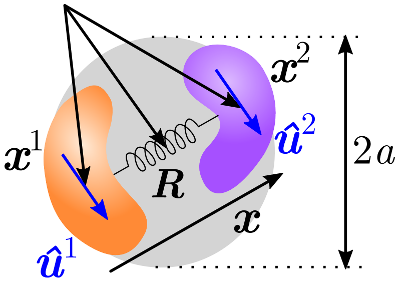

FIG. 1. The generalized dumbbell, which has typical size a and consists of two nonidentical subunits at positions $\mathbf{x}^\alpha$ and orientations $\hat{\mathbf{u}}^\alpha$ which are hydrodynamically coupled and also interact via some potential $U(\mathbf{x}^1, \mathbf{x}^2, \hat{\mathbf{u}}^1, \hat{\mathbf{u}}^2)$. The midpoint between the subunits (com) of the dumbbell is denoted by $\mathbf{R}$ and the elongation (*i.e.*, separation of the subunits) by $\mathbf{x}$. The subunits fluctuate about the equilibrium configuration due to thermal fluctuations.

$$U = V_0(x) + \sum_{\alpha=1}^{2} V_\alpha(x)\, \hat{\mathbf{n}} \cdot \hat{\mathbf{u}}^\alpha + V_{12}(x)\, \hat{\mathbf{u}}^1 \cdot \hat{\mathbf{u}}^2 \qquad (1)$$

to lowest order in $\hat{\mathbf{n}} \cdot \hat{\mathbf{u}}^\alpha$ and $\hat{\mathbf{u}}^1 \cdot \hat{\mathbf{u}}^2$. The expansion takes into account that the interaction fields are generated by fluctuations. $V_0(x)$ contributes only to the extension of the dumbbell, while $V_\alpha(x)$ and $V_{12}(x)$ in addition quantify the strength of the constraints on orientation fluctuations. For the majority of our analysis, the interaction functions are considered to be generic and distinct, and only in sect. VII are specific functions assigned to illustrate our findings. In application to real macromolecules, the specific functional forms will depend on the macromolecule being modelled and structural modifications due to substrate binding can be incorporated into the coefficients of (1) [10]. We leave this as a topic for future work.

III. SMOLUCHOWSKI EQUATION

We begin our analysis with the Smoluchowski equation for a pair of interacting Brownian particles. The probability $P(\mathbf{x}^1, \mathbf{x}^2, \hat{\mathbf{u}}^1, \hat{\mathbf{u}}^2; t)$ of finding subunit α at position $\mathbf{x}^\alpha$ and with orientation $\hat{\mathbf{u}}^\alpha$ at time t satisfies the following evolution equation:

$$\partial_t P = \mathcal{L}_{\mathrm{T}} P + \mathcal{L}_{\mathrm{R}} P, \qquad (2)$$

with

$$\mathcal{L}_{\mathrm{T}} P = \sum_{\alpha,\beta=1}^{2} \nabla_\alpha \cdot \mathsf{M}_{\mathrm{TT}}^{\alpha\beta} \cdot \left[(\nabla_\beta U) P + k_{\mathrm{B}} T \nabla_\beta P \right], \qquad (3)$$

$$\mathcal{L}_{\mathrm{R}} P = \sum_{\alpha,\beta=1}^{2} \Big\{ \nabla_\alpha \cdot \mathsf{M}_{\mathrm{TR}}^{\alpha\beta} \cdot \left[(\mathcal{R}^\beta U) P + k_{\mathrm{B}} T \mathcal{R}^\beta P \right]$$

$$+ \mathcal{R}^{\alpha} \cdot \mathsf{M}_{\mathrm{RR}}^{\alpha\beta} \cdot \left[(\mathcal{R}^{\beta} U) P + k_{\mathrm{B}} T \mathcal{R}^{\beta} P \right] \\ + \mathcal{R}^{\alpha} \cdot \mathsf{M}_{\mathrm{RT}}^{\alpha\beta} \cdot \left[(\nabla_{\beta} U) P + k_{\mathrm{B}} T \nabla_{\beta} P \right] \Big\} , \qquad (4)$$

where ∇_{α} and $\mathcal{R}^{\alpha} = \hat{\mathbf{u}}^{\alpha} \times \partial_{\hat{\mathbf{u}}^{\alpha}}$ are the gradient operator and rotational gradient operator [15], respectively, with respeect to the position vector of subunit α. The Smoluchowski equation (2)–(4) is known in polymer dynamics as the equation of motion for dilute polymer solutions as presented in the Zimm model [15], where it describes the dynamics of a chain of axisymmetric and equal particles.

The $\mathsf{M}_{\mathrm{AB}}^{\alpha\beta}$ are matrix elements of a generalized field tensor which couples the translational (T) and rotational (R) motion of the subunits. The tensor should be understood as the Green's function for the system, which relates the velocities of the subunits to the generating forces and torques through

$$\begin{pmatrix} \dot{\mathbf{x}}^1 \\ \dot{\mathbf{x}}^2 \\ \omega^1 \\ \omega^2 \end{pmatrix} = \begin{pmatrix} \mathsf{M}_{\mathrm{TT}}^{11} & \mathsf{M}_{\mathrm{TT}}^{21} & \mathsf{M}_{\mathrm{RT}}^{11} & \mathsf{M}_{\mathrm{RT}}^{21} \\ \mathsf{M}_{\mathrm{TT}}^{12} & \mathsf{M}_{\mathrm{TT}}^{22} & \mathsf{M}_{\mathrm{RT}}^{12} & \mathsf{M}_{\mathrm{RT}}^{22} \\ \mathsf{M}_{\mathrm{TR}}^{11} & \mathsf{M}_{\mathrm{TR}}^{21} & \mathsf{M}_{\mathrm{RR}}^{11} & \mathsf{M}_{\mathrm{RR}}^{21} \\ \mathsf{M}_{\mathrm{TR}}^{12} & \mathsf{M}_{\mathrm{TR}}^{22} & \mathsf{M}_{\mathrm{RR}}^{12} & \mathsf{M}_{\mathrm{RR}}^{22} \end{pmatrix} \begin{pmatrix} \mathbf{F}^1 \\ \mathbf{F}^2 \\ \mathbf{T}^1 \\ \mathbf{T}^2 \end{pmatrix} , \qquad (5)$$

where $\dot{\mathbf{x}}^{\alpha}$ and ω^{α} are the steady state linear and angular velocities of the subunits, and $\mathbf{F}^{\alpha}$ and $\mathbf{T}^{\alpha}$ are the driving forces and torques. The linearity of eq. (5) is the result of the low Reynolds number approximation. For $\alpha \neq \beta$, $\mathsf{M}_{\mathrm{AB}}^{\alpha\beta}$ describe the hydrodynamic coupling of the subunits. For $\alpha = \beta$, they are the response of the subunit to an external force or torque.

Finding the mobility tensor M_{AB} is nontrivial as hydrodynamic interactions have a complex nonlinear dependence on the positions and geometries of the interacting particles. Exact expressions exist for interacting spheres [20], and the tensor can be reduced with simpliflying approximations. For example, in the Oseen approximation the particles are assumed to be well-seperated point forces in the fluid. If the interacting particles are identical, their finite sizes are accounted for in the Rotne-Prager-Yamakawa approximation, where the mobility tensor is symmetric positive definite [15, 23]. For nonidentical particles, there are numerical methods for computing hydrodynamic interactions [24, 25] and methods for modelling more complex geometries, typically by extension of the bead models developed by Kirkwood, Riseman and Bloomfield [26], which have been used for hydrodynamic calculations of bacterial viruses [27]. Specific macromolecules may have additional symmetry properties that may reduce the number of independent components of the hydrodynamic tensor [19]. For the purpose of our analytical considerations, at this stage, we do not specify a functional form for the hydrodynaimc interactions as this would require futher approximations but leave this as a topic for future work.

We emphasise that the strength of our approach is to provide analytical results for the effect of internal fluctuations within a tractable and general formalism, and starting from a minimal model of only two coupled subunits. Considering a more realistic structure for an enzyme would require us to consider the coupling between even more subdomains. This would result in a much more involved calculation, without necessarily providing any further insight into the fluctuation-induced effects.

Due to its asymmetry and extensibility, it is not a priori obvious which point on the dumbbell should be chosen for its position in the bulk. Since physical quantities must necessarily be independent of this choice in the long-time limit, we choose to locate the dumbbell position by the centre-of-mass (com). In the com $\mathbf{R} = (\mathbf{x}^1 + \mathbf{x}^2)/2$ and separation $\mathbf{x}$ coordinates, eqs. (3) and (4) become

$$\mathcal{L}_{\mathrm{T}} P = \frac{1}{4} \nabla_{\mathbf{R}} \cdot (\mathsf{M} \cdot k_{\mathrm{B}} T \nabla_{\mathbf{R}} P) + \frac{1}{2} \nabla_{\mathbf{x}} \cdot (\Gamma \cdot k_{\mathrm{B}} T \nabla_{\mathbf{R}} P) \\ + \frac{1}{2} \nabla_{\mathbf{R}} \cdot \{ \Gamma \cdot [k_{\mathrm{B}} T \nabla_{\mathbf{x}} P + (\nabla_{\mathbf{x}} U) P] \} \\ + \nabla_{\mathbf{x}} \cdot \{ \mathsf{W} \cdot [k_{\mathrm{B}} T \nabla_{\mathbf{x}} P + (\nabla_{\mathbf{x}} U) P] \} , \qquad (6)$$

$$\mathcal{L}_{\mathrm{R}} P = \sum_{\alpha,\beta=1}^{2} \Bigg\{ \frac{1}{2} \mathcal{R}^{\alpha} \cdot \left(\Phi^{(\alpha)} \cdot k_{\mathrm{B}} T \nabla_{\mathbf{R}} P \right) \\ + \frac{1}{2} \nabla_{\mathbf{R}} \cdot \left\{ \Phi^{(\alpha)} \cdot [k_{\mathrm{B}} T \mathcal{R}^{\alpha} P + (\mathcal{R}^{\alpha} U) P] \right\} \\ + (-1)^{\alpha} \nabla_{\mathbf{x}} \cdot \left\{ \Lambda^{(\alpha)} \cdot [k_{\mathrm{B}} T \mathcal{R}^{\alpha} P + (\mathcal{R}^{\alpha} U) P] \right\} \\ + (-1)^{\alpha} \mathcal{R}^{\alpha} \cdot \left\{ \Lambda^{(\alpha)} \cdot [k_{\mathrm{B}} T \nabla_{\mathbf{x}} P + (\nabla_{\mathbf{x}} U) P] \right\} \\ + \mathcal{R}^{\alpha} \cdot \left\{ \Psi^{\alpha\beta} \cdot \left[k_{\mathrm{B}} T \mathcal{R}^{\beta} P + (\mathcal{R}^{\beta} U) P \right] \right\} \Bigg\} . \qquad (7)$$

Using the symmetry property $\mathsf{M}_{\mathrm{AB}}^{\alpha\beta} = \mathsf{M}_{\mathrm{BA}}^{\beta\alpha}$ (which follows from the Lorentz reciprocal theorem [19, 20]), we have defined new hydrodynamic tensors which are linear combinations of the old ones, such that: $\mathsf{M} = \mathsf{M}_{\mathrm{TT}}^{11} + \mathsf{M}_{\mathrm{TT}}^{22} + 2\mathsf{M}_{\mathrm{TT}}^{12}$, $\mathsf{W} = \mathsf{M}_{\mathrm{TT}}^{11} + \mathsf{M}_{\mathrm{TT}}^{22} - 2\mathsf{M}_{\mathrm{TT}}^{12}$ and $\Gamma = \mathsf{M}_{\mathrm{TT}}^{22} - \mathsf{M}_{\mathrm{TT}}^{11}$ are composed of the translation tensors; $\Psi^{\alpha\beta} = \mathsf{M}_{\mathrm{RR}}^{\alpha\beta}$ the rotation tensors and; $\Lambda^{(1)} = \mathsf{M}_{\mathrm{TR}}^{11} - \mathsf{M}_{\mathrm{TR}}^{21}$, $\Lambda^{(2)} = \mathsf{M}_{\mathrm{TR}}^{22} - \mathsf{M}_{\mathrm{TR}}^{12}$, $\Phi^{(1)} = \mathsf{M}_{\mathrm{TR}}^{11} + \mathsf{M}_{\mathrm{TR}}^{21}$ and $\Phi^{(2)} = \mathsf{M}_{\mathrm{TR}}^{22} + \mathsf{M}_{\mathrm{TR}}^{12}$ consist of the coupling tensors. The new hydrodynamic tensors are the configuration-dependent transport coefficients for the asymmetric dumbbell. In the limit of the orientations of the dumbbell being locked, its dynamics is described by eq. (6), and M, W and Γ are respectively the translation, rotation and translation-rotation coupling tensors. With the inclusion of orientation dynamics, $\Phi^{(\alpha)}$ is the tensor coupling rotations of subunit α to translations of the com, $\Lambda^{(\alpha)}$ is the tensor coupling rotations of subunit α to rotations of the vector $\hat{\mathbf{n}}$ and $\Psi^{\alpha\beta}$ are the rotation tensors for the orientations of the subunits.

IV. AVERAGING PROCEDURE

The solution of the hydrodynamic equations (6) and (7) gives the full probability density for trajectories in the phase space, including a description of the conformational evolution. However, calculating the long-time effective diffusion coefficient requires only a coarse-grained description, where the dependence on microscopic coordinates has been averaged out. The effective diffusion coefficient of the dumbbell can be determined from its relation to the mean-square com displacement

$$D_{\text{eff}} = \lim_{t\to\infty} \frac{1}{6}\frac{\mathrm{d}}{\mathrm{d}t} \int_{\mathbf{R}}\int_{\mathbf{x}}\int_{\hat{\mathbf{u}}^1}\int_{\hat{\mathbf{u}}^2} \mathbf{R}^2 P, \tag{8}$$

where subscripts denote integration with respect to the variable. Naive integration of (6) and (7) leads to a hierarchy of equations with increasingly higher–order correlation functions of the external and internal degrees of freedom, owing to the difference in characteristic time scales. The hierarchy is closed by eliminating the dependence on internal coordinates. In ref. [11], the phase space is divided into two orthogonal subspaces consisiting of *local* and *global* coordinates, which are bounded and unbounded respectively, the so–called *generalized Taylor dispersion theory.* We adopt the method introduced in ref. [10], where the hierarchy is closed through the definition of an averaging procedure which eventually leads to a closed expression after a suitable truncation approximation.

A well-defined averaging procedure is motivated by the identification of a separation of the time scales in the dynamics of the dumbbell. We identify three time scales: two of which are associated with the relaxation time of internal degrees of freedom, and the third, the characteristic time scale of diffusion, the slowest of the three. Given a potential that can be Taylor expanded around the minimum, the quadratic term gives the effective spring constant of the potential (k) and the time scale for $x = |\mathbf{x}|$ to return to its equilibrium value, $\tau_{\text{s}} = \xi/k$, where ξ is the friction coefficient of the enzyme. The rotational diffusion time of the enzyme τ_{r}, which determines the rate of loss of memory of orientation through$\langle \hat{\mathbf{n}}(t)\cdot\hat{\mathbf{n}}(0)\rangle = \exp(-|t|/\tau_{\text{r}})$, is of the order $\xi a^2/k_{\text{B}}T$. The ratio of the two times $\tau_{\text{s}}/\tau_{\text{r}}$ goes as $k_{\text{B}}T/ka^2 \sim \delta x/a$, the relative deformation of the enzyme due to thermal fluctuations, and is therefore bounded by unity. The rotational diffusion time of each subunit (*i.e.*, the relaxation times associated to the variables $\hat{\mathbf{u}}^1$ and $\hat{\mathbf{u}}^2$) is also of the order of τ_r if the size of the subunits is comparable to that of the dumbbell as a whole. With this consideration, we can average over the separation of the subunits assuming $\hat{\mathbf{n}}$, $\hat{\mathbf{u}}^1$ and $\hat{\mathbf{u}}^2$ to be fixed. The average is defined as $\langle\cdot\rangle = \frac{1}{\mathcal{P}}\int \mathrm{d}x\, x^2\cdot P$, where $\mathcal{P} = \int \mathrm{d}x\, x^2 P$.

The average over the separation x of the Smoluchowski equation requires expressions for the gradients of the interaction potential, $\nabla_{\mathbf{x}}U$ and $\mathcal{R}^\alpha U$. Applying $\nabla_{\mathbf{x}} = \hat{\mathbf{n}}\partial_x - \frac{1}{x}\hat{\mathbf{n}}\times\mathcal{R}$ and $\mathcal{R}^\alpha$ to eq. (1) gives

$$\nabla_{\mathbf{x}}U = \hat{\mathbf{n}}U' + \mathsf{Q}_{\hat{\mathbf{n}}}\cdot\left(\frac{V_1(x)}{x}\hat{\mathbf{u}}^1 + \frac{V_2(x)}{x}\hat{\mathbf{u}}^2\right), \tag{9}$$

$$\mathcal{R}^\alpha U = \sum_{\beta=0}^{2} V_{\alpha\beta}(x)(\hat{\mathbf{u}}^\alpha\times\hat{\mathbf{u}}^\beta), \tag{10}$$

introducing the notation $\hat{\mathbf{u}}^0 \equiv \hat{\mathbf{n}}$, $V_{\alpha 0} \equiv V_\alpha$ and $\mathsf{Q}_{\hat{\mathbf{n}}} = (1-\hat{\mathbf{n}}\hat{\mathbf{n}})$. For a hydrodynamic tensor A, $\nabla_{\mathbf{x}}\cdot\mathsf{A} = \nabla_{\mathbf{x}}\cdot[\hat{\mathbf{n}}\hat{\mathbf{n}}\cdot\mathsf{A} + \mathsf{Q}_{\hat{\mathbf{n}}}\cdot\mathsf{A}]$, has just one contribution, $-(\hat{\mathbf{n}}\times\mathcal{R})\cdot\mathsf{Q}_{\hat{\mathbf{n}}}\cdot\mathsf{A}/x$, after averaging over the separation. The full expression for the evolution of the separation-averaged distribution $\mathcal{P}(\mathbf{R},\hat{\mathbf{n}},\hat{\mathbf{u}}^1,\hat{\mathbf{u}}^2;t)$ is given by the sum of the following

$$\begin{aligned}
\mathcal{L}_{\text{T}}\mathcal{P} = \frac{1}{2}\nabla_{\mathbf{R}}\cdot\Bigg[&\frac{1}{2}\langle\mathsf{M}\rangle\cdot k_{\text{B}}T\nabla_{\mathbf{R}}\mathcal{P}\\
&+\sum_{\alpha=1}^{2}\mathsf{Q}_{\hat{\mathbf{n}}}\cdot\left\langle\frac{\mathsf{\Gamma}\,V_\alpha(x)}{x}\right\rangle\cdot\hat{\mathbf{u}}^\alpha\mathcal{P}\\
&-\hat{\mathbf{n}}\times\mathcal{R}\cdot\left(\left\langle\frac{\mathsf{\Gamma}}{x}\right\rangle k_{\text{B}}T\mathcal{P}\right)+\left\langle\hat{\mathbf{n}}\times\mathcal{R}\cdot\frac{\mathsf{\Gamma}}{x}\right\rangle k_{\text{B}}T\mathcal{P}\Bigg]\\
&-\hat{\mathbf{n}}\times\mathcal{R}\cdot\Bigg[\mathsf{Q}_{\hat{\mathbf{n}}}\cdot\frac{1}{2}\left\langle\frac{\mathsf{\Gamma}}{x}\right\rangle\cdot k_{\text{B}}T\nabla_{\mathbf{R}}\mathcal{P}\\
&+\mathsf{Q}_{\hat{\mathbf{n}}}\cdot\sum_{\alpha=1}^{2}\left\langle\frac{\mathsf{W}\,V_\alpha(x)}{x^2}\right\rangle\cdot\hat{\mathbf{u}}^\alpha\mathcal{P}\\
&-\hat{\mathbf{n}}\times\mathcal{R}\cdot\left(\mathsf{Q}_{\hat{\mathbf{n}}}\cdot\left\langle\frac{\mathsf{W}}{x^2}\right\rangle k_{\text{B}}T\mathcal{P}\right)\\
&+\mathsf{Q}_{\hat{\mathbf{n}}}\cdot\left\langle\hat{\mathbf{n}}\times\mathcal{R}\cdot\frac{\mathsf{W}}{x^2}\right\rangle k_{\text{B}}T\mathcal{P}\Bigg],
\end{aligned} \tag{11}$$

$$\begin{aligned}
&\mathcal{L}_{\text{R}}\mathcal{P} =\\
&\sum_{\substack{\alpha,\beta=1\\ \gamma=0}}^{2}\mathcal{R}^\alpha\cdot\Bigg\{k_{\text{B}}T\left[\mathcal{R}^\beta\cdot\left(\left\langle\mathsf{\Psi}^{\alpha\beta}\right\rangle\mathcal{P}\right)-\left\langle\mathcal{R}^\beta\cdot\mathsf{\Psi}^{\alpha\beta}\right\rangle\mathcal{P}\right]\\
&+\left\langle\mathsf{\Psi}^{\alpha\beta}V_{\beta\gamma}\right\rangle\cdot(\hat{\mathbf{u}}^\beta\times\hat{\mathbf{u}}^\gamma)\mathcal{P}+\frac{1}{2}\left\langle\mathsf{\Phi}^{(\alpha)}\right\rangle\cdot k_{\text{B}}T\nabla_{\mathbf{R}}\mathcal{P}\\
&+(-1)^\alpha\mathsf{Q}_{\hat{\mathbf{n}}}\cdot\left\langle\frac{\mathsf{\Lambda}^{(\alpha)}V_\beta}{x}\right\rangle\cdot\hat{\mathbf{u}}^\beta\mathcal{P}\\
&-(-1)^\alpha\hat{\mathbf{n}}\times\mathcal{R}\cdot\left(\left\langle\frac{\mathsf{\Lambda}^{(\alpha)}}{x}\right\rangle k_{\text{B}}T\mathcal{P}\right)\\
&+(-1)^\alpha\left\langle\hat{\mathbf{n}}\times\mathcal{R}\cdot\frac{\mathsf{\Lambda}^{(\alpha)}}{x}\right\rangle k_{\text{B}}T\mathcal{P}\Bigg\}\\
&+\frac{1}{2}\nabla_{\mathbf{R}}\cdot\sum_{\substack{\alpha,\beta=1\\ \gamma=0}}^{2}\Bigg\{\langle\mathsf{\Phi}^{(\alpha)}V_{\alpha\beta}\rangle\cdot(\hat{\mathbf{u}}^\alpha\times\hat{\mathbf{u}}^\beta)\mathcal{P}\\
&+k_{\text{B}}T\left[\mathcal{R}^\alpha\cdot\left(\left\langle\mathsf{\Phi}^{(\alpha)}\right\rangle\mathcal{P}\right)-\left\langle\mathbf{R}^\alpha\cdot\mathsf{\Phi}^{(\alpha)}\right\rangle\mathcal{P}\right]\Bigg\}\\
&-\sum_{\substack{\alpha=1\\ \beta=0}}^{2}(-1)^\alpha\hat{\mathbf{n}}\times\mathcal{R}\cdot\Bigg\{\mathsf{Q}_{\hat{\mathbf{n}}}\cdot\left\langle\frac{\mathsf{\Lambda}^{(\alpha)}V_{\alpha\beta}}{x}\right\rangle\cdot(\hat{\mathbf{u}}^\alpha\times\hat{\mathbf{u}}^\beta)\mathcal{P}\\
&+\mathcal{R}^\alpha\cdot\left(\mathsf{Q}_{\hat{\mathbf{n}}}\cdot\left\langle\frac{\mathsf{\Lambda}^{(\alpha)}}{x}\right\rangle k_{\text{B}}T\mathcal{P}\right)\\
&-\mathsf{Q}_{\hat{\mathbf{n}}}\cdot\left\langle\mathcal{R}^\alpha\cdot\frac{\mathsf{\Lambda}^{(\alpha)}}{x}\right\rangle k_{\text{B}}T\mathcal{P}\Bigg\}.
\end{aligned} \tag{12}$$

We have used the relation

$$\langle U'\phi(x)\rangle = k_{\text{B}}T\left\langle\phi'(x)+2\,\frac{\phi(x)}{x}\right\rangle, \tag{13}$$

which is valid for any function ϕ of the separation coordinate and after a sufficient amount of time so that the distribution has reached a Boltzmann-like equilibrium in the x-dependence, such that $P \propto \mathrm{e}^{-U/k_{\mathrm{B}}T}$. Note that there are no terms with the coefficient V_{12} in the expression for $\mathcal{L}_{\mathrm{T}}\mathcal{P}$, as such terms are due to the action of the rotation gradient operator $\mathcal{R}^{\alpha}$ on the interaction potential.

V. MOMENT EXPANSION

In the next step of the calculation we focus on the orientations of the dumbbell. Analytic studies of low Reynolds number dynamics typically involve a description of the continuum equations and following previous work [28–31], we turn to a macroscopic description of the system where we consider the evolution of the probability density, $\rho(\mathbf{R};t) = \int_{\hat{\mathbf{n}},\hat{\mathbf{u}}^1,\hat{\mathbf{u}}^2} \mathcal{P}$, defined as the zeroth moment of the probability distribution. The density $\rho(\mathbf{R};t)$ and polarities $\mathbf{p}(\mathbf{R};t) = \int_{\hat{\mathbf{n}},\hat{\mathbf{u}}^1,\hat{\mathbf{u}}^2} \hat{\mathbf{n}}\mathcal{P}$ and $\mathbf{p}^{\alpha}(\mathbf{R};t) = \int_{\hat{\mathbf{n}},\hat{\mathbf{u}}^1,\hat{\mathbf{u}}^2} \hat{\mathbf{u}}^{\alpha}\mathcal{P}$, are constant over time scales that are large compared to the time scale of fluctuations, and lengths that are large on the scale of the typical size of the dumbbell, and are thus appropriate quantities for describing diffusion of the com [29]. However, the evolution equation for the density is not closed and involves polarisations $\mathbf{p}$ and $\mathbf{p}^{\alpha}$ —inevitably, the equations satisfied by the polarisations are also not closed and involve higher-order moments, which must be re-expressed in terms of the density and polarisations.

A discussion on the role of orientation on the dynamics of the dumbbell requires a statement on the functional dependence of the hydrodynamic tensors on orientations. With the orientation-pre-averaging approximation, where hydrodynamic tensors were approximated as isotropic, and written $\mathsf{A} \simeq a_0 \mathsf{1}$, we had previously described a coarse-grained dynamics [10]. We now consider anisotropic hydrodynamic interactions.

As previously stated, the hydrodynamic tensors in eqs. (11) and (12) will be nonlinear functions of the geometric properties of the dumbbell, such as the subunit separation, but an explicit form of the dependence is not required for our analysis so we make no further speculation here. Rather, we approximate the mobility functions, smilarly to (1), by an expansion in the fluctuation angles:

$$\mathsf{A} \simeq \left[a_0(x) + \sum_{\alpha=1}^{2} a_{\alpha}(x)\hat{\mathbf{u}}^{\alpha}\cdot\hat{\mathbf{n}} + a_{12}(x)\hat{\mathbf{u}}^1\cdot\hat{\mathbf{u}}^2 \dots\right] \mathsf{1}, \tag{14}$$

again to lowest order in the fluctuation angle. In addition to assuming planar motion, we have also made the diagonal approximation [18] so that motion in different axes is decoupled. This approximation has been widely used in polymer dynamics [12] and is exact for certain geometries [18, 24]. A is any of the mobility tensors M, W, $\mathsf{\Gamma}$, $\mathsf{\Lambda}^{(\alpha)}$, $\mathsf{\Phi}^{(\alpha)}$ and $\mathsf{\Psi}^{(\alpha\beta)}$, $a_0 = m_0, w_0, \gamma_0, \lambda_0, \phi_0^{(\alpha)}, \psi_0^{(\alpha\beta)}, \psi_0^{(\alpha)}$, $a_{\alpha} = m_{\alpha}, w_{\alpha}, \gamma_{\alpha}, \lambda_{\alpha}, \phi_{\alpha}^{(\alpha)}, \psi_{\alpha}^{(\alpha\beta)}, \psi_{\alpha}^{(\alpha)}$ and $a_{12} = m_{12}, w_{12}, \gamma_{12}, \lambda_{12}, \phi_{12}^{(\alpha)}, \psi_{12}^{(\alpha\beta)}, \psi_{12}^{(\alpha)}$, after renaming $\mathsf{\Psi}^{(11)} = \mathsf{\Psi}^{(1)}$ and $\mathsf{\Psi}^{(22)} = \mathsf{\Psi}^{(2)}$.

With the inclusion of anisotropy in the hydrodynamic tensors, the zero– and first–order moments of the separation–averaged Smoluchowski equation give the following dynamical equations for the density and polarisations:

$$\begin{aligned}\partial_t\rho = {}& \frac{k_{\mathrm{B}}T}{4}\left\langle m_0\right\rangle \nabla_{\mathbf{R}}^2\rho + k_{\mathrm{B}}T\left\langle\frac{\gamma_0}{x}\right\rangle \nabla_{\mathbf{R}}\cdot\mathbf{p} \\ &+ \frac{1}{3}\sum_{\alpha\neq\beta=1}^{2}\left\{\left\langle\frac{\gamma_0 V_{\alpha}}{x}\right\rangle \nabla_{\mathbf{R}}\cdot\mathbf{p}^{\alpha} + \frac{1}{3}\left\langle\frac{\gamma_{12}V_{\alpha}}{x}\right\rangle \nabla_{\mathbf{R}}\cdot\mathbf{p}^{\beta}\right\},\end{aligned} \tag{15}$$

$$\begin{aligned}\partial_t\mathbf{p} = {}& -\frac{k_{\mathrm{B}}T}{3}\left\langle\frac{\gamma_0}{x}\right\rangle \nabla_{\mathbf{R}}\rho - 2k_{\mathrm{B}}T\left\langle\frac{w_0}{x^2}\right\rangle \mathbf{p} \\ &- \frac{2}{3}\sum_{\alpha\neq\beta=1}^{2}\left\{\left\langle\frac{w_0 V_{\alpha}}{x^2}\right\rangle \mathbf{p}^{\alpha} + \frac{1}{3}\left\langle\frac{w_{12}V_{\alpha}}{x^2}\right\rangle \mathbf{p}^{\beta}\right\},\end{aligned} \tag{16}$$

$$\begin{aligned}\partial_t\mathbf{p}^{\alpha} = {}& \frac{1}{9}\left[\left\langle\frac{\gamma_0 V_{\alpha}}{x}\right\rangle + \frac{1}{3}\left\langle\frac{\gamma_{12}V_{\beta}}{x}\right\rangle\right]\nabla_{\mathbf{R}}\rho \\ &- \frac{2}{3}\left[\left\langle\psi_0^{(\alpha)}V_{\alpha}\right\rangle + \frac{1}{3}\left\langle(\psi_{\beta}^{(\alpha)} - \psi_{\beta}^{(\alpha\beta)})V_{12}\right\rangle\right. \\ &+ \left.\frac{1}{3}\left\langle\psi_{12}^{(\alpha\beta)}V_{\beta}\right\rangle\right]\mathbf{p} \\ &- \frac{2}{3}\left[\left\langle(\psi_0^{(\alpha)} - \psi_0^{(\alpha\beta)})V_{12}\right\rangle - \frac{1}{3}\left\langle\psi_{\alpha}^{(\alpha\beta)}V_{\beta}\right\rangle\right. \\ &+ \left.k_{\mathrm{B}}T\left\langle\psi_{12}^{(\alpha\beta)}\right\rangle\right]\mathbf{p}^{\beta} - 2k_{\mathrm{B}}T\left\langle\psi_0^{(\alpha)}\right\rangle\mathbf{p}^{\alpha}.\end{aligned} \tag{17}$$

where we have kept terms up to the lowest order in spatial derivatives ($\nabla_{\mathbf{R}}^2\rho$, $\nabla_{\mathbf{R}}\cdot\mathbf{p}$ and $\nabla_{\mathbf{R}}\cdot\mathbf{p}^{\alpha}$), and rewritten higher-order moments according to the expressions in appendix A, keeping only the traceless symmetric part of the corresponding tensors as we expand around an isotropic geometry [29]. From eq. (15) we see that all the corrections to the diffusion equation contain the coefficient $\mathsf{\Gamma}$, hence all corrections to the effective diffusion coefficient are driven by the hydrodynamic coupling of translational and rotational motion. As the tensor $\mathsf{\Gamma}$ is only nonvanishing for asymmetric bodies, we note that the hydrodynamic equations are not closed because of the asymmetry of the dumbbell. However, the hierarchy can be truncated by a closure scheme which yields a closed set of dynamical equations for the density and polarisations. Finally, we note the absence of the tensors $\mathsf{\Phi}^{(\alpha)}$ and $\mathsf{\Lambda}^{(\alpha)}$, respectively the coupling tensors of rotations of subunit to translations of the dumbbell and rotations of subunit to rotations of the dumbbell. Such couplings will be produced if the system is given a feature which breaks the corresponding chiral symmetry such as a macroscopic constraint [32].

VI. CLOSURE APPROXIMATION AND THE DIFFUSION EQUATION

A. Closure scheme

By assuming time scales that are large compared to the relaxation time of fluctuations, we can assume $\partial_t \mathbf{p} = 0$ and $\partial_t \mathbf{p}^\alpha = 0$ in eqs. (16) and (17), and find expressions for the polarisations that are linear in the density. The polarisation of the dumbbell is given by

$$\mathbf{p} = \left[S_0 + S_2 + S_3 + \mathcal{O}(4)\right] \nabla_{\mathbf{R}} \rho, \tag{18}$$

where the S_i are due to the difference in mobility between the subunits:

$$S_0 = -\frac{1}{6} \frac{\langle \gamma_0 / x \rangle}{\langle w_0 / x^2 \rangle}, \tag{19}$$

$$S_2 = -\frac{1}{6(3k_{\mathrm{B}}T)} \frac{1}{\langle w_0/x^2 \rangle} \sum_{\alpha \neq \beta} g_\alpha \left\langle \frac{w_0 V_\alpha}{x^2} \right\rangle, \tag{20}$$

$$\begin{aligned} S_3 = &-\frac{1}{18(3k_{\mathrm{B}}T)} \frac{1}{\langle w_0/x^2 \rangle} \sum_{\alpha \neq \beta} \left\{ \left\langle \frac{w_0 V_\alpha}{x^2} \right\rangle \right. \\ &\times \left[g_{12,\beta} + \frac{1}{3k_{\mathrm{B}}T} \frac{\langle \gamma_0 / x \rangle}{\langle w_0 / x^2 \rangle} \frac{\left\langle (\psi_\beta^{(\alpha)} - \psi_\beta^{(\alpha\beta)}) V_{12} \right\rangle}{\left\langle \psi_0^{(\alpha)} \right\rangle} \right. \\ &\left. - \frac{g_\beta}{k_{\mathrm{B}}T} \frac{\left\langle \left(\psi_0^{(\alpha)} - \psi_0^{(\alpha\beta)}\right) V_{12} \right\rangle + k_{\mathrm{B}}T \left\langle \psi_{12}^{(\alpha\beta)} \right\rangle}{\left\langle \psi_0^{(\alpha)} \right\rangle} \right] \\ &\left. + g_\beta \left\langle \frac{w_{12} V_\alpha}{x^2} \right\rangle \right\}, \end{aligned} \tag{21}$$

and for the polarisation of the subunits

$$\mathbf{p}^\alpha = \left[T_1 + T_2 + T_3 + \mathcal{O}(4)\right] \nabla_{\mathbf{R}} \rho, \tag{22}$$

where

$$T_1 = \frac{1}{6} g_\alpha, \tag{23}$$

$$\begin{aligned} T_2 = &\frac{1}{18} \left[g_{12,\beta} + \frac{1}{3k_{\mathrm{B}}T} \frac{\langle \gamma_0 / x \rangle}{\langle w_0 / x^2 \rangle} \frac{\left\langle (\psi_\beta^{(\alpha)} - \psi_\beta^{(\alpha\beta)}) V_{12} \right\rangle}{\left\langle \psi_0^{(\alpha)} \right\rangle} \right. \\ &\left. - \frac{g_\beta}{k_{\mathrm{B}}T} \frac{\left\langle \left(\psi_0^{(\alpha)} - \psi_0^{(\alpha\beta)}\right) V_{12} \right\rangle + k_{\mathrm{B}}T \left\langle \psi_{12}^{(\alpha\beta)} \right\rangle}{\left\langle \psi_0^{(\alpha)} \right\rangle} \right], \end{aligned} \tag{24}$$

$$T_3 = \frac{1}{6(3k_{\mathrm{B}}T)^2} \frac{1}{\langle w_0/x^2 \rangle} \frac{\left\langle \psi_0^{(\alpha)} V_\alpha \right\rangle}{\left\langle \psi_0^{(\alpha)} \right\rangle} \sum_\gamma \left\langle \frac{w_0 V_\gamma}{x^2} \right\rangle g_\gamma. \tag{25}$$

The dimensionless coefficients

$$g_\alpha = \frac{1}{3k_{\mathrm{B}}T} \left[\frac{\langle \gamma_0 V_\alpha / x \rangle}{\left\langle \psi_0^{(\alpha)} \right\rangle} + \frac{\langle \gamma_0 / x \rangle}{\langle w_0 / x^2 \rangle} \frac{\left\langle \psi_0^{(\alpha)} V_\alpha \right\rangle}{\left\langle \psi_0^{(\alpha)} \right\rangle} \right], \tag{26}$$

$$g_{12,\beta} = \frac{1}{3k_{\mathrm{B}}T} \left[\frac{\langle \gamma_{12} V_\beta / x \rangle}{\left\langle \psi_0^{(\alpha)} \right\rangle} + \frac{\langle \gamma_0 / x \rangle}{\langle w_0 / x^2 \rangle} \frac{\left\langle \psi_{12}^{(\alpha\beta)} V_\beta \right\rangle}{\left\langle \psi_0^{(\alpha)} \right\rangle} \right], \tag{27}$$

give the scale for polarisation of subunit α at leading order and next to leading order, respectively. The equivalent quantity for the complex is the ratio of the coupling and rotation coefficients, $\langle \gamma_0/x \rangle / \langle w_0/x^2 \rangle$, at leading order. The difficulty in computing g_α and $g_{12,\beta}$ for nonspherical geomtries is inherited from the mobility functions, however, numerical evaluations are possible [26] and will be the subject of future work.

The index of the coefficients S_i and T_i gives their order in the joint expansion of the potential and hydrodynamic tensors. The effect of anisotropy is seen in the coefficients S_3 and T_2, that is, at second order in the polarisation of a subunit and at third order in the polarisation of the complex.

B. The diffusion equation

Using the results of the previous section, we finally get the closed diffusion equation $\partial_t \rho = D_{\mathrm{eff}} \nabla^2_{\mathbf{R}} \rho$, with the asymptotic effective diffusion coefficient

$$\begin{aligned} D_{\mathrm{eff}} = &\frac{k_{\mathrm{B}}T}{4} \langle m_0 \rangle \\ &- \frac{k_{\mathrm{B}}T}{6} \left[\frac{\langle \gamma_0 / x \rangle^2}{\langle w_0 / x^2 \rangle} - \sum_{\alpha \neq \beta} \left(\delta D_2^{\alpha\alpha} + \delta D_3^{\alpha\beta} \right) \right] + \mathcal{O}(4). \end{aligned} \tag{28}$$

The first term is the usual thermal average of contributions from translational modes of the dumbbell. The leading-order fluctuation-induced correction is due to coupling of the translational and rotational motion, and hence the internal asymmetry of the dumbbell. To obtain a physical intuition for the result, consider the force dipole created by the dumbbell on the fluid. If this fluctuating dipole has a nonvanishing average, the asymmetry of the dumbbell couples the dipole to a net drift velocity. Considering, for instance, the force experienced by the second subunit over the time scale when the separation coordinate has equilibrated but the orientation of the dumbbell is frozen, $\langle \mathbf{F}^2 \rangle = -\langle U' \rangle \hat{\mathbf{n}}$, we notice that a nonzero average dipole will result provided $\langle U' \rangle \neq 0$. Assuming that the average at the relevant time scale is taken with the weight $\mathrm{e}^{-U/k_{\mathrm{B}}T}$, it is easy to see that $\langle U' \rangle$ does not vanish in any dimension other than one (even though $U'|_{x=x_{\mathrm{eq}}} = 0$, where x_{eq} is the equilibrium separation of the subunits) due to the entropic contributions to sampling of the configuration space when using radial coordinates. The resulting contribution to the diffusion coefficient is proportional to $-\langle U' \rangle^2$, which highlights a similarity to dispersion forces [33].

Subsequent corrections, labelled $\delta D_i^{\alpha\beta}$, are the fluctuation-induced corrections of order i in the moment expansion, the first two of which are

$$\delta D_2^{\alpha\alpha} = h_\alpha g_\alpha, \tag{29}$$

$$\begin{aligned}\delta D_3^{\alpha\beta} &= \frac{1}{3}\left[g_{12,\beta}h_\alpha + g_\beta h_{12,\alpha}\right] \\ &- \frac{1}{3k_\mathrm{B}T}h_\alpha\left[g_\beta\frac{\left\langle\left(\psi_0^{(\alpha)} - \psi_0^{(\alpha\beta)}\right)V_{12}\right\rangle + k_\mathrm{B}T\left\langle\psi_{12}^{(\alpha\beta)}\right\rangle}{\left\langle\psi_0^{(\alpha)}\right\rangle}\right. \\ &\left.-\frac{1}{3}\frac{\langle\gamma_0/x\rangle^2}{\langle w_0/x^2\rangle}\frac{\left\langle(\psi_\beta^{(\alpha)} - \psi_\beta^{(\alpha\beta)})V_{12}\right\rangle}{\left\langle\psi_0^{(\alpha)}\right\rangle}\right],\end{aligned} \tag{30}$$

where g_α and $g_{12,\beta}$ are given by (26) and (27), and we have defined the quantities

$$h_\alpha = \frac{1}{3k_\mathrm{B}T}\left[\left\langle\frac{\gamma_0 V_\alpha}{x}\right\rangle - \frac{\langle\gamma_0/x\rangle}{\langle w_0/x^2\rangle}\left\langle\frac{w_0 V_\alpha}{x^2}\right\rangle\right], \tag{31}$$

$$h_{12,\alpha} = \frac{1}{3k_\mathrm{B}T}\left[\left\langle\frac{\gamma_{12} V_\alpha}{x}\right\rangle - \frac{\langle\gamma_0/x\rangle}{\langle w_0/x^2\rangle}\left\langle\frac{w_{12} V_\alpha}{x^2}\right\rangle\right]. \tag{32}$$

The coefficients h_α and $h_{12,\alpha}$ are comparable to the separation averaged coupling tensor $\langle\gamma_0/x\rangle$ at the first and second order in the moment expansion. The correction $\delta D_2^{\alpha\alpha}$, previously reported in ref. [10], is of order one and is estimated to be positive for harmonic-like potentials. From eq. (28) we see that the motion of the dumbbell is retarded by asymmetry through hydrodynamic interactions between its subunits. The magnitude of the fluctuation-induced correction depends on the constraint functions V_α and V_{12} (see (29) and (30)): It is at maximum if there is no constraint from the internal potential, decreasing as the amount of constraining increases. Correspondingly, the correction is observed at a time scale governed by the separation relaxation time (a detailed calculation is given in [10]). Lastly, anisotropy is first seen at third order in D_eff, signifying that it is a higher-order effect.

In summary, since reduction in the diffusion coefficient is driven by asymmetry, any decrease in asymmetry will lead to a positive contribution to D_eff. With our assumption of an unbounded quiescent fluid environment, the symmetry properties of eq. (28) are intrinsic to the dumbbell. In the case that the external symmetry is broken, the effect of symmetry breaking on the diffusion coefficient can be determined by recalculating the polarisation fields with an appropriate expansion for the hydrodynamic tensors to replace (14). The equilibrium model proposed in ref. [10] for a catalytically active enzyme is an application of the case with changing internal symmetry.

We emphasise that the regime we have considered is a first approximation. Although, within the closure scheme, no new terms are introduced in (15)-(17) if terms of higher order in the fluctuation angles are included in (1) and (14). Their contribution would only change the numerical coefficients of the terms already in (15)-(17).

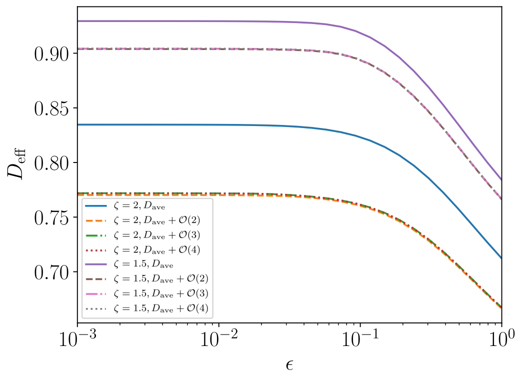

FIG. 2. The effective diffusion coefficient of two axisymmetric dumbbells with asymmetries $\zeta = 2$ and $\zeta = 1.5$ as a function of relative fluctuations ϵ, with $v_1 = 0.1$, $v_2 = 0.13$, $v_{12} = 0.15$ and $a_1/a = 0.3$. D_ave is the first term of D_eff; $D_\mathrm{ave} + \mathcal{O}(2)$ is the sum of the first two terms; $D_\mathrm{ave} + \mathcal{O}(3)$ includes $\delta D_2^{\alpha\alpha}$; and $D_\mathrm{ave} + \mathcal{O}(4)$ includes $\delta D_3^{\alpha\beta}$.

VII. EXAMPLE: AN AXISYMMETRIC DUMBBELL

In order to provide a more quantitative analysis of the role of the internal interaction potential on D_eff, we consider the example of an axisymmetric dumbbell composed of rigid spherical subunits with radii a_1 and a_2 with $a_2 > a_1$ that interact interact via a potential U that has harmonic x-dependence so that $U = \frac{1}{2}k(x - a)^2\left[1 + \sum_{\alpha=1,2} v_\alpha\, \hat{\mathbf{n}}\cdot\hat{\mathbf{u}}^\alpha + v_{12}\, \hat{\mathbf{u}}^1\cdot\hat{\mathbf{u}}^2\right]$ for $x > a_1 + a_2$ and ∞ otherwise, where a is the typical size of the dumbbell and v_α and v_{12} are the constraint parameters such that $v_\alpha, v_{12} \ll 1$ which are independent of x. The mobility functions for interacting particles are widely known for such axisymmetric geometries. We provide some plots of D_eff which were made using the mobility functions from ref. [34] for widely separated spheres (expressions for the leading-order contributions are given in appendix C). We have defined the dimensionless numbers $\epsilon = \sqrt{k_\mathrm{B}T/ka^2}$, a measure of fluctuations of the dumbbell around its equilibrium, $\zeta = a_2/a_1$, the geometric asymmetry and the ratio a_1/a.

Figure 2 shows the relation between D_eff and relative fluctuations of the dumbbell. As expected, the diffusion coefficient of the dumbbell is lowered when its asymmetry is increased. Furthermore, D_eff increases with the stiffness of the potential and its maximum value is attained in the limit of a rigid potential.

Figure 3(a) shows the dependence of D_eff on the constraint parameter v_1, with constant v_2 and v_{12}. There is a clear reduction in the effective diffusion upon the inclusion of the fluctuation-induced corrections, particularly $\delta D_2^{\alpha\alpha}$— even at small relative deformations. In the far-field limit where the separation of the subunits is much greater than the typical size of the dumbbell, the mobility functions are given by a series expansion

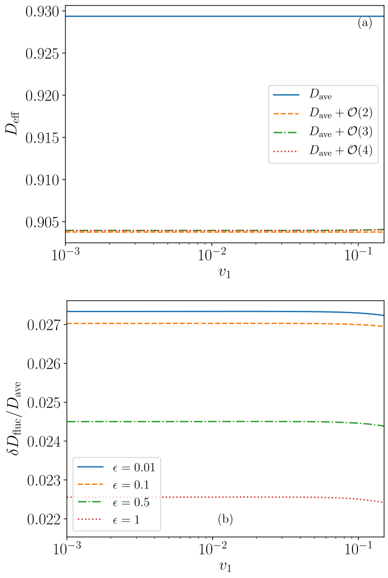

FIG. 3. In both figures, $\zeta = 1.5$, $v_2 = 0.1$, $v_{12} = 0.15$ and $a_1/a = 0.3$. (a) The effective diffusion coefficient of an axisymmetric dumbbell as a function of the constant constraint parameter v_1, with $\epsilon = 0.01$. (b) Relative decrease in diffusion coefficient for different values of ϵ. See sect. VII for definitions.

in $1/x$ so that a small deformation in the dumbbell can have significant contributions to the diffusion coefficient. In fig. 3(b) it can be seen that the relative decrease in the diffusion coefficient due to fluctuation-induced corrections $\delta D_{\rm fluc}/D_{\rm ave}$ increases with the stiffness of the potential, where

$$D_{\rm ave} = \frac{k_{\rm B}T}{4}\langle m_0\rangle \tag{33}$$

and

$$\delta D_{\rm fluc} = \frac{k_{\rm B}T}{6}\left[\frac{\langle \gamma_0/x\rangle^2}{\langle w_0/x^2\rangle} - \sum_{\alpha\neq\beta}\left(\delta D_2^{\alpha\alpha} + \delta D_3^{\alpha\beta}\right)\right]. \tag{34}$$

VIII. CONCLUSION

We have proposed a new theoretical framework for understanding the effect of internal hydrodynamic interactions on the stochastic translational motion of modular structures in a fluid environment under low Reynolds number conditions. In an asymmetric modular structure, such interactions (here caused by thermal fluctuations) result in a decrease in the diffusion coefficient of the object, hence there is a fluctuation-induced correction to the diffusion coefficient. We show that this correction is driven by an interplay between internal and external asymmetry. Although the full result is presented for a general dumbbell, where anisotropy is a relevant measure, we consider the case of an axisymmetric dumbbell (for which the hydrodynamic functions are well known) to provide a quantitative example.

We have shown that the hydrodynamic equations which describe the evolution of moments of the distribution function of the generalized dumbbell are not closed, but with a careful consideration of the motion of such an object, one is able to close these equations at any order.

The present work then gives an insight into the effect of internal fluctuations and asymmetries on the effective diffusion coefficient of a model modular macromolecule. The ideas presented here are very generic, and could be specified to different real systems. In particular, it would be of interest to study more complex structures that reproduce faithfully the structure of specific enzyme molecules. This could be achieved using extensive numerical simulations that would include both stochastic dynamics and hydrodynamic interactions, and could be the topic of future work.

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Appendix A: Traceless symmetric tensors

The moment expansion is equivalent to a multipole expansion of the distribution function, where instead of spherical harmonics, the expansion is in terms of irreducible tensors in three dimensions, which are equivalent to the spherical harmonics, with components that are polynomials in the unit vectors $\hat{\mathbf{u}}^1$, $\hat{\mathbf{u}}^2$, and $\hat{\mathbf{n}}$ [29]. In the definitions of the irreducible tensors parentheses denotes symmetry in the isolated subscripts and the tensors are traceless on contraction of those indices. The sum over Greek letters runs over 0, 1 and 2, where we have used the notation $\hat{\mathbf{u}}^0 = \hat{\mathbf{n}}$.

Starting with the second-order nematic tensor

$$Q_{ij}^{\alpha\beta} = \int_{\hat{\mathbf{n}},\hat{\mathbf{u}}^1,\hat{\mathbf{u}}^2}\left(u_i^\alpha u_j^\beta - \frac{1}{3}\delta_{ij}\delta^{\alpha\beta}\right)\mathcal{P}, \tag{A1}$$

at third-order

$$\begin{aligned} Q_{ijk}^{\alpha(3)} = \int_{\hat{\mathbf{n}},\hat{\mathbf{u}}^1,\hat{\mathbf{u}}^2}\Big[&u_i^\alpha u_j^\alpha u_k^\alpha \\ &- \frac{1}{5}(\delta_{ij}u_k^\alpha + \delta_{ik}u_j^\alpha + \delta_{jk}u_i^\alpha)\Big]\mathcal{P}, \end{aligned} \tag{A2a}$$

$$Q_{(ij)k}^{\alpha\beta\gamma(3)} = \int_{\hat{\mathbf{n}},\hat{\mathbf{u}}^1,\hat{\mathbf{u}}^2}\left[u_i^\alpha u_j^\beta u_k^\gamma - \frac{1}{3}u_k^\gamma\delta_{ij}\delta^{\alpha\beta}\right]\mathcal{P}, \tag{A2b}$$

at order four

$$Q^{\alpha(4)}_{ijkl} = \int_{\hat{\mathbf{n}},\hat{\mathbf{u}}^1,\hat{\mathbf{u}}^2} \left[u^\alpha_i u^\alpha_j u^\alpha_k u^\alpha_l - \frac{1}{15} T_{ijkl} \right] \mathcal{P}, \tag{A3a}$$

$$Q^{\alpha\beta\gamma\delta(4)}_{(ij)(kl)} = \int_{\hat{\mathbf{n}},\hat{\mathbf{u}}^1,\hat{\mathbf{u}}^2} \left[u^\alpha_i u^\beta_j u^\gamma_k u^\delta_l - \frac{1}{9} \delta_{ij}\delta_{kl}\delta^{\alpha\beta}\delta^{\gamma\delta} \right] \mathcal{P}, \tag{A3b}$$

where we have defined the fourth-rank tensor $T_{ijkl} = \delta_{ij}\delta_{kl} + \delta_{ik}\delta_{jl} + \delta_{il}\delta_{jk}$. Finally at order five,

$$\begin{aligned} Q^{\alpha(5)}_{ijklm} = & \int_{\hat{\mathbf{n}},\hat{\mathbf{u}}^1,\hat{\mathbf{u}}^2} \Big\{ u^\alpha_i u^\alpha_j u^\alpha_k u^\alpha_l u^\alpha_m \\ & - \frac{1}{35} \big[u^\alpha_m T_{ijlk} + u^\alpha_l T_{ijkm} + u^\alpha_k T_{ijlm} \\ & + u^\alpha_j T_{iklm} + u^\alpha_i T_{jklm} \big] \Big\} \mathcal{P}, \end{aligned} \tag{A4a}$$

$$\begin{aligned} Q^{\alpha\beta\gamma\delta\epsilon(5)}_{(ijkl)m} = & \int_{\hat{\mathbf{n}},\hat{\mathbf{u}}^1,\hat{\mathbf{u}}^2} \Big[u^\alpha_i u^\beta_j u^\gamma_k u^\delta_l u^\epsilon_m \\ & - \frac{1}{15} u^\epsilon_m T_{ijkl} \delta^{\alpha\beta\gamma\delta} \Big] \mathcal{P}, \end{aligned} \tag{A4b}$$

$$Q^{\alpha\beta\gamma\delta\epsilon(5)}_{(ijk)(lm)} = \int_{\hat{\mathbf{n}},\hat{\mathbf{u}}^1,\hat{\mathbf{u}}^2} \Big[u^\alpha_i u^\beta_j u^\gamma_k u^\delta_l u^\epsilon_m \tag{A4c}$$

$$- \frac{1}{15} (u^\gamma_k \delta_{ij} + u^\beta_j \delta_{ik} + u^\alpha_i \delta_{ik}) \delta_{lm} \delta^{\alpha\beta\gamma} \delta^{\delta\epsilon} \Big] \mathcal{P}, \tag{A4d}$$

$$\begin{aligned} Q^{\alpha\beta\gamma\delta\epsilon(5)}_{(ij)(kl)m} = & \int_{\hat{\mathbf{n}},\hat{\mathbf{u}}^1,\hat{\mathbf{u}}^2} \Big[u^\alpha_i u^\beta_j u^\gamma_k u^\delta_l u^\epsilon_m \\ & - \frac{1}{9} u^\epsilon_m \delta_{ij}\delta_{kl}\delta^{\alpha\beta}\delta^{\gamma\delta} \Big] \mathcal{P}, \end{aligned} \tag{A4e}$$

the highest order encountered in our moment expansion.

Appendix B: Higher order moments

To illustrate the consistency of the moment expansion in sect. V, we consider the translational motion of an axisymmetric dumbbell, for which the hydrodynamic tensors can be decomposed into isotropic and directional parts as $\mathsf{A} = A_I(x)\mathbb{1} + A_D(x)\hat{\mathbf{n}}\hat{\mathbf{n}}$. For this example the separation-averaged Smoluchowski equation (11) is

$$\begin{aligned} \mathcal{L}_\mathrm{T}\mathcal{P}(\mathbf{R},\hat{\mathbf{n}};t) = & \frac{k_\mathrm{B}T}{4} \nabla_\mathbf{R} \cdot [\langle\mathsf{M}\rangle \cdot \nabla_\mathbf{R}\mathcal{P}] \\ & - k_\mathrm{B}T \left\langle \frac{\Gamma_\mathrm{I}}{x} \right\rangle \nabla_\mathbf{R} \cdot [(\hat{\mathbf{n}} \times \mathcal{R}\mathcal{P}) + \hat{\mathbf{n}}\mathcal{P}] \\ & + k_\mathrm{B}T \left\langle \frac{\mathrm{W_I}}{x^2} \right\rangle \mathcal{R}^2 \tilde{\rho}_{12}. \end{aligned} \tag{B1}$$

The first four moments satisfying the following euqtions

$$\begin{aligned} \partial_t \rho(\mathbf{R};t) = & \frac{k_\mathrm{B}T}{4} \left(\langle \mathrm{M_I} \rangle + \frac{1}{3} \langle \mathrm{M_D} \rangle \right) \nabla^2_\mathbf{R} \rho \\ & + \frac{k_\mathrm{B}T}{4} \langle \mathrm{M_D} \rangle \partial_{R_i}\partial_{R_j} Q_{ij} + k_\mathrm{B}T \left\langle \frac{\Gamma_\mathrm{I}}{x} \right\rangle \nabla_\mathbf{R} \cdot \mathbf{p}, \end{aligned} \tag{B2}$$

$$\begin{aligned} \partial_t \mathbf{p}(\mathbf{R};t) = & \frac{k_\mathrm{B}T}{4} \left(\langle \mathrm{M_I} \rangle + \frac{1}{5} \langle \mathrm{M_D} \rangle \right) \nabla^2_\mathbf{R} \mathbf{p} \\ & + \frac{k_\mathrm{B}T}{4} \langle \mathrm{M_D} \rangle \left[\frac{2}{5} \nabla_\mathbf{R}(\nabla_\mathbf{R} \cdot \mathbf{p}) + \partial_{R_j}\partial_{R_k} Q^{(3)}_{ijk} \mathbf{e}_i \right] \\ & - k_\mathrm{B}T \left\langle \frac{\Gamma_\mathrm{I}}{x} \right\rangle \partial_{R_j} \left[\frac{1}{3} \rho \mathbf{e}_j - 2 Q_{ij} \mathbf{e}_i \right] - 2k_\mathrm{B}T \left\langle \frac{\mathrm{W_I}}{x^2} \right\rangle \mathbf{p}, \end{aligned} \tag{B3}$$

$$\begin{aligned} \partial_t Q_{ij}(\mathbf{R};t) = & \frac{k_\mathrm{B}T}{4} \langle \mathrm{M_I} \rangle \nabla^2_\mathbf{R} Q_{ij} - 6k_\mathrm{B}T \left\langle \frac{\mathrm{W_I}}{x^2} \right\rangle Q_{ij} \\ & + \frac{k_\mathrm{B}T}{4} \langle \mathrm{M_D} \rangle \Big[\partial_{R_k}\partial_{R_l} Q^{(4)}_{ijkl} - \frac{1}{3} \partial_{R_k}\partial_{R_l} Q_{kl} \delta_{ij} \\ & - \frac{2}{15} \left(\frac{1}{3} \nabla^2_\mathbf{R} c \delta_{ij} - \partial_{R_i}\partial_{R_j} c \right) \Big] \\ & + k_\mathrm{B}T \left\langle \frac{\Gamma_\mathrm{I}}{x} \right\rangle \Big[3\partial_{R_k} Q^{(3)}_{ijk} + \frac{4}{15} \nabla_\mathbf{R} \cdot \mathbf{p} \delta_{ij} \\ & - \frac{2}{5} \left(\partial_{R_i} p_j + \partial_{R_j} p_i \right) \Big], \end{aligned} \tag{B4}$$

and

$$\begin{aligned} \partial_t Q^{(3)}_{ijk}(\mathbf{R};t) = & \frac{k_\mathrm{B}T}{4} \langle \mathrm{M_I} \rangle \nabla^2_\mathbf{R} Q^{(3)}_{ijk} + \frac{k_\mathrm{B}T}{4} \langle \mathrm{M_D} \rangle \\ & \times \Big\{ \partial_{R_l}\partial_{R_m} \Big[Q^{(5)}_{ijklm} \\ & - \frac{1}{5} \left(Q^{(3)}_{lmi} \delta_{jk} + Q^{(3)}_{lmj} \delta_{ik} + Q^{(3)}_{lmk} \delta_{ij} \right) \Big] \\ & - \frac{2}{175} \left(\nabla^2_\mathbf{R} p_i + 2\partial_{R_i}(\nabla_\mathbf{R} \cdot \mathbf{p}) \right) \delta_{jk} \\ & - \frac{2}{175} \left(\nabla^2_\mathbf{R} p_j + 2\partial_{R_j}(\nabla_\mathbf{R} \cdot \mathbf{p}) \right) \delta_{ik} \\ & - \frac{2}{175} \left(\nabla^2_\mathbf{R} p_k + 2\partial_{R_k}(\nabla_\mathbf{R} \cdot \mathbf{p}) \right) \delta_{ij} \\ & + \frac{2}{35} \left(\partial_{R_i}\partial_{R_j} p_k + \partial_{R_i}\partial_{R_k} p_j + \partial_{R_j}\partial_{R_k} p_i \right) \Big\} \\ & \times \Big\{ \partial_{R_l} \Big[4Q^{(4)}_{ijkl} - \frac{2}{5} \left(Q_{il}\delta_{jk} + Q_{jl}\delta_{ik} + Q_{kl}\delta_{ij} \right) \Big] \\ & - \left(\partial_{R_i} Q_{jk} + \partial_{R_j} Q_{ik} + \partial_{R_k} Q_{ij} \right) \Big\} \\ & + k_\mathrm{B}T \left\langle \frac{\Gamma_\mathrm{I}}{x} \right\rangle - 12k_\mathrm{B}T \left\langle \frac{\mathrm{W_I}}{x^2} \right\rangle Q^{(3)}_{ijk}, \end{aligned} \tag{B5}$$

using the following properties of the rotational gradient operator:

$$\mathcal{R}_i n_j = \epsilon_{ikj} n_k, \tag{B6a}$$

$$\mathcal{R}_k(n_i n_j) = \epsilon_{kli} n_l n_j + \epsilon_{klj} n_l n_i, \tag{B6b}$$

$$\begin{aligned} \mathcal{R}_l(n_i n_j n_k) = & \epsilon_{lmi} n_m n_j n_k \\ & + \epsilon_{lmj} n_m n_i n_k + \epsilon_{lmk} n_m n_i n_j, \end{aligned} \tag{B6c}$$

$$\begin{aligned} \mathcal{R}_m(n_i n_j n_k n_l) = & \epsilon_{mni} n_n n_j n_k n_l + \epsilon_{mnj} n_n n_i n_k n_l \\ & + \epsilon_{mnk} n_n n_i n_j n_l + \epsilon_{mnl} n_n n_i n_j n_k, \end{aligned} \tag{B6d}$$

$$\mathcal{R}^2 n_i = -2n_i, \tag{B6e}$$

$$\mathcal{R}^2(n_i n_j) = -6\left(n_i n_j - \frac{1}{3}\delta_{ij}\right), \tag{B6f}$$

$$\mathcal{R}^2(n_i n_j n_k) = -12\Big[n_i n_j n_k - \frac{1}{6}\left(n_k\delta_{ij} + n_j\delta_{ik} + n_i\delta_{jk}\right)\Big]. \tag{B6g}$$

It is straightforward to see that none of the terms in the stationary values of Q and $Q^{(3)}$ survive the closure scheme.

Appendix C: Expressions for hydrodynamic tensors

In the Oseen approximation, where the subunits are spherical with radii a_1 and a_2, and their typical sizes are small compared to the distance, x, between them, the mobility functions can be approximted as

$$m_0 \simeq \frac{1}{6\pi\eta}\left(\frac{1}{a_1} + \frac{1}{a_2}\right) + \frac{1}{4\pi\eta x}, \tag{C1}$$

$$w_0 \simeq \frac{1}{6\pi\eta}\left(\frac{1}{a_1} + \frac{1}{a_2}\right) - \frac{1}{4\pi\eta x}, \tag{C2}$$

$$\gamma_0 = \frac{1}{6\pi\eta}\left(\frac{1}{a_2} - \frac{1}{a_1}\right), \tag{C3}$$

$$\psi_0^{(\alpha)} \simeq \frac{1}{8\pi\eta a_\alpha^3}, \tag{C4}$$

$$\chi_0^{\alpha\beta} \simeq \frac{1}{16\pi\eta x^3}, \tag{C5}$$

where η is the viscosity of the suspending fluid.

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