Noise-induced drift in two-dimensional anisotropic systems

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(Received 14 June 2017; revised manuscript received 18 September 2017; published 17 October 2017)

We study the isothermal Brownian dynamics of a particle in a system with spatially varying diffusivity. Due to the heterogeneity of the system, the particle's mean displacement does not vanish even if it does not experience any physical force. This phenomenon has been termed "noise-induced drift," and has been extensively studied for one-dimensional systems. Here, we examine the noise-induced drift in a two-dimensional anisotropic system, characterized by a symmetric diffusion tensor with unequal diagonal elements. A general expression for the mean displacement vector is derived and presented as a sum of two vectors, depicting two distinct drifting effects. The first vector describes the tendency of the particle to drift toward the high diffusivity side in each orthogonal principal diffusion direction. This is a generalization of the well-known expression for the noise-induced drift in one-dimensional systems. The second vector represents a novel drifting effect, not found in one-dimensional systems, originating from the spatial rotation in the directions of the principal axes. The validity of the derived expressions is verified by using Langevin dynamics simulations. As a specific example, we consider the relative diffusion of two transmembrane proteins, and demonstrate that the average distance between them increases at a surprisingly fast rate of several tens of micrometers per second.

DOI: 10.1103/PhysRevE.96.042141

I. INTRODUCTION

Recent advances in single particle tracking methods and force measurement techniques have led to renewed interest in the problem of isothermal Brownian motion in inhomogeneous systems [1]. A prominent example is diffusion of a colloidal particle near a surface, in which case due to hydrodynamic interactions, the diffusion coefficients parallel and perpendicular to the boundary are (i) different from each other, and (ii) increase with the particle-wall distance [2,3]. Another example is diffusion in liquid-crystalline systems where the orientation of the media is heterogeneous [4,5]. Closely related is the problem of Brownian motion of nonspherical particles, e.g., ellipsoids whose diffusion coefficients along the long and short axes are different [6,7].

A common feature in the above examples of Brownian motion with state-dependent diffusion is the *anisotropic* nature of the dynamics, i.e., the fact it is direction dependent. Such problems arise only in two and higher dimensions. Current theoretical understanding of the topic of heterogeneous diffusion, however, is based on studies of one-dimensional systems where a particle moves in a medium with coordinate-dependent diffusion coefficient $D(x)$ (see recent review [8], and many references therein). The dynamics of a freely diffusing particle (i.e., experiencing no potential energy gradient) in a one-dimensional isothermal system, can be described by Langevin's equation [9]

$$m\frac{dv}{dt} = -\alpha(x)v + \beta[x(t)], \tag{1}$$

where m and $v = dx/dt$ denote, respectively, the mass and the velocity of the particle. This is Newton's second law of motion where the contact with the heat bath is realized via the action of two effective forces: A friction force, $-\alpha v$, proportional to the velocity with a coordinate-dependent friction coefficient $\alpha(x) > 0$, and a stochastic force $\beta(t)$ that can be modeled as a multiplicative Gaussian noise with zero mean $\langle\beta(t)\rangle = 0$ and δ-function autocorrelation $\langle\beta(t)\beta(t')\rangle = 2\alpha[x(t)]k_BT\delta(t-t')$, where k_B is Boltzmann's constant and T is the temperature of the system. These statistical properties ensure that the fluctuation-dissipation theorem is obeyed, which is necessary for achieving correct Fickian dynamics [10]. The state-dependent diffusion coefficients $D(x)$ and $\alpha(x)$ are related to each other via Einstein's relation [11]

$$\alpha(x) = k_BT/D(x). \tag{2}$$

The trajectory of the particle can be calculated by numerically integrating Langevin's equation in time. From an ensemble of stochastic trajectories, the probability distribution function (PDF), $P(x,t)$, of finding the particle at coordinate x at time t can be determined for a given initial distribution $P(x,0)$. In heterogeneous systems with spatially varying friction coefficient $\alpha(x)$, Langevin's equation must be supplemented with a convention for choosing the value $\alpha(x)$ at each integration time step dt. The ambiguity about the appropriate convention rule is known in the literature as the Itô-Stratonovich dilemma [12]. In the "overdamped" limit of Langevin's equation, which is when the inertial term on the left-hand side of Eq. (1) is set identically to zero, different conventions lead to different dynamics and, consequently, different PDFs [13]. Keeping the inertial term in Eq. (1), on the other hand, ensures that the correct PDF is obtained when the integration time step $dt \to 0$, regardless of the interpretation of the stochastic calculus [14]. This remarkable difference between the underdamped and overdamped Langevin equations is directly related to the most striking feature of heterogeneous Brownian dynamics—the noise-induced drift.

The term "noise-induced drift" refers to the phenomenon that a particle, freely diffusing in a medium with a coordinate-dependent friction coefficient $\alpha(x)$, tends to drift toward the less viscous side of the system [1]. By "freely" we mean in the absence of external forces, concentration, or temperature

gradients. The presence of a diffusion coefficient gradient allows for a drift in the position of an individual particle *without a net particle current*—a rather counterintuitive equilibrium effect. The drift originates from the fact that when the particle moves in the less viscous direction, it suffers less dissipation and therefore travels longer distances [14]. The drifting effect is countered by the tendency of the particle to diffuse more slowly and get trapped for longer durations at the more viscous part of the system. In a closed system, the consequence of the opposite "drifting" and "trapping" effects is the proper uniform equilibrium distribution [15]. We notice, however, that the drift is an inertial effect taking place at short time scales $t \lesssim \tau = m/\alpha$ during which Langevin's dynamics is ballistic in nature. This effect is missing in the overdamped version of Eq. (1) which, therefore, must be written with an additional term to correctly account for the drifting effect. The magnitude of this so-called "spurious drift" term depends on the chosen interpretation [13]. The term spurious drift is, of course, misleading as the drift is a very real physical phenomenon.

In dimensions higher than one, the system is characterized by a symmetric diffusion matrix that can be diagonalized along the principal diffusion directions. It is expected to observe noise-induced drift toward lower viscosity along each of these principal directions, since the multidimensional dynamics decouples into independent one-dimension problems. This, however, is true only if the directions of the principal axes are fixed. If, on the other hand, the principal directions are themselves spatially dependent, the noise-induced drift may be also affected by their rotation. In this work we derive an expression for the noise-induced drift in two-dimensional anisotropic systems [Eq. (13)]. The derivation indeed reveals a new term representing an additional novel contribution to the noise-induced drift arising from spatial variations in the directions of the principal axes. The magnitude of the new term is proportional to the difference between the the principal diffusion coefficients and the rate of spatial change of the principal unit vectors (curvature). The newly derived expression for the noise-induced drift is tested and validated by using Langevin dynamics simulations of model systems with anisotropic diffusion tensor. To demonstrate the importance of the drift effect, we use the derived expression to evaluate the variations in the relative distance between two transmembrane proteins, and find the noise-induced effect to be surprisingly large.

The paper is organized as follows. In Sec. II, we present our derivation for the noise-induced drift. Section III presents the results of computer simulations of Langevin dynamics in two-dimensional anisotropic systems. In Sec. IV we apply the newly derived expression to the case study of pair diffusion of membrane proteins. Finally, in Sec. V, we discuss the results and explain why the variations of the principal diffusion axes induce an additional component to the noise-induced drift.

II. DERIVATION

A. Noise-induced drift in one dimension

The displacement, Δx, of a particle initially located at $x = x_0$ can be calculated by integrating the full (underdamped) Langevin equation (1) over the time interval from $t = 0$ to $t = \Delta t$, and taking the average of the different terms with respect to all possible noise realizations and all possible values of the initial velocity (or, equivalently, over an ensemble of particles). This yields the following equation:

$$\left\langle \int_{x_0}^{x_0+\Delta x} \alpha(x)dx \right\rangle = -\langle m\Delta v\rangle + \left\langle \int_0^{\Delta t} \beta(t)dt \right\rangle. \tag{3}$$

Both terms on the right-hand side of Eq. (3) vanish for the following reasons: The first term is the average momentum change of the particles, which are moving at constant temperature and experience no deterministic force due to a potential gradient. Their momentum distribution function, therefore, remains unchanged and is given by the symmetric Maxwell-Boltzmann equilibrium distribution. The second term represents the average momentum change due to the thermal noise. It vanishes because the ensemble average at each time instance and coordinate $\langle\beta(x(t)\rangle = 0$ [11,14]. (It is the noise variance rather than the mean that depends on the coordinate x.) We thus conclude that

$$\left\langle \int_{x_0}^{x_0+\Delta x} \alpha(x)dx \right\rangle = 0. \tag{4}$$

Assuming that $\alpha(x)$ is a smooth function which does not change considerably during the time interval Δt, one can use the truncated Taylor expansion $\alpha(x) \simeq \alpha(x_0) + \alpha'(x_0)(x - x_0)$ in (4) to arrive at the following relation:

$$\langle\Delta x\rangle = -\frac{\alpha'(x_0)}{2\alpha(x_0)}\left\langle(\Delta x)^2\right\rangle \tag{5}$$

between the mean displacement and the mean-squared displacement (MSD). Further assuming that the time interval of interest Δt is much larger than the ballistic time $\tau \sim m/\alpha(x_0)$, the MSD on the right-hand side of Eq. (5) can be approximated to leading order by $\langle(\Delta x)^2\rangle \simeq 2D(x_0)\Delta t$ which, together with Einstein's relation (2), yields

$$\langle\Delta x\rangle \simeq D'(x_0)\Delta t. \tag{6}$$

From Eq. (6) we identify the drift velocity $v^{\text{drift}} \equiv \langle\Delta x\rangle/\Delta t$ as being equal to the gradient of the diffusion coefficient, $D'(x)$.

B. Multidimensional systems

In dimensions higher than one, Langevin's equation takes the tensorial form [16]

$$m\frac{dv_i}{dt} = -\alpha(\{x_k\})_{ij}v_j + \beta_i[\{x_k(t)\}], \tag{7}$$

where the subscripts i, j, and k denote Cartesian coordinates and Einstein's summation rule over repeated indices is assumed. The components of the friction tensor, α_{ij}, may depend on all the space coordinates, $\{x_k\}$, and the noise satisfies $\langle\beta_i(t)\rangle = 0$, and $\langle\beta_i(t)\beta_j(t')\rangle = 2\alpha_{ij}k_BT\delta(t - t')$. The space-dependent diffusion tensor, $D_{ij}(\{x_k\})$, is related to α_{ij} via Einstein's relation (2), which in dimensions higher than one reads $\alpha_{ik}D_{kj} = k_BT\delta_{ij}$, where δ_{ij} is the Kronecker's delta (identity matrix) [16]. The drift can be calculated by repeating the derivation outlined above for one-dimensional systems.

This leads to the generalized form of Eq. (5)

$$\alpha_{ij}\langle\Delta x_j\rangle = -\frac{\partial\alpha_{ij}}{\partial x_k}\left\langle\int [x_k - x_k(0)]dx_j\right\rangle \simeq -\frac{\partial\alpha_{ij}}{\partial x_k}\left\langle\frac{\Delta x_k\Delta x_j}{2}\right\rangle \simeq -\frac{\partial\alpha_{ij}}{\partial x_k}D_{kj}\Delta t. \quad (8)$$

From Einstein's relation we deduce that $(\partial\alpha_{ij}/\partial x_k)D_{kj} + \alpha_{ij}(\partial D_{kj}/\partial x_k) = 0$, and by using this result in (8), we arrive at

$$\langle\Delta x_i\rangle \simeq \left.\frac{\partial D_{ij}(\{x_k\})}{\partial x_j}\right|_0 \Delta t, \quad (9)$$

which generalizes Eq. (6) for d-dimensional ($d > 1$) systems.

Since α_{ij} is a real symmetric matrix at each point in space, it can be diagonalized. Along the *local* principal axes, the friction tensor reads $\alpha_{ij} = \alpha_j\delta_{ij}$ (Einstein's summation convention is suppressed henceforth), where $\alpha_j(\{x_k\}) = k_BT/D_j(\{x_k\})$ is the coordinate-dependent eigenvalue of the matrix α_{ij} that is associated with the jth principal direction, and D_j is the corresponding, space-dependent eigenvalue of the diffusion matrix. We now consider the Brownian motion of a particle in a two-dimensional anisotropic system with $D_1(x_1,x_2) \neq D_2(x_1,x_2)$, where the Cartesian axes of the laboratory frame, $\hat{x}_1$ and $\hat{x}_2$, are chosen to lie in the *initial* principal directions. The diffusion tensor of the system, $D(x_1,x_2)$, is given by

$$\begin{pmatrix} D_1\cos^2\theta + D_2\sin^2\theta & \Delta D\sin 2\theta \\ \Delta D\sin 2\theta & D_1\sin^2\theta + D_2\cos^2\theta \end{pmatrix}, \quad (10)$$

where $\Delta D\,(x_1,x_2) = D_1 - D_2$, and $\theta\,(x_1,x_2)$ is the angle between the laboratory frame axes and the local principal directions [$\theta(t=0) = 0$]. We note that the same form Eq. (10) is also used to study the Brownian motion of an ellipsoid in a homogeneous medium [7]. However, in the latter example, the diffusion tensor does not depend on the center-of-mass coordinates of the particle as in the present study, but on the instantaneous orientation of the (nonspherical) Brownian particle. This implies an important difference between the two problems. In the case of diffusion of particles with anisotropic shapes, the translational and orientational degrees of freedom are decoupled and, therefore, at sufficiently long times the motion must become isotropic. In the case discussed herein of diffusion in anisotropic medium, the changes in the orientation of the diffusion tensor depend on the position of the particle, which introduces a strong coupling between the translational diffusion and the orientational variations.

Using Eq. (10) in Eq. (9) yields the following expressions for drift velocity, $v_i^{\rm drift} = \langle\Delta x_i\rangle/\Delta t$:

$$v_1^{\rm drift} = \frac{\partial D_1}{\partial x_1} + \Delta D\frac{\partial\theta}{\partial x_2}, \quad (11)$$

$$v_2^{\rm drift} = \frac{\partial D_2}{\partial x_2} + \Delta D\frac{\partial\theta}{\partial x_1}. \quad (12)$$

The second terms on the right-hand sides of Eqs. (11) and (12) can be reexpressed in a more illuminating form as follows. The unit vectors $\hat{x}_1$ and $\hat{x}_2$ in the local principal directions define an orthogonal curvilinear coordinate system, as exemplified in Fig. 1. The partial derivatives of θ, appearing in Eqs. (11) and (12), give the curvatures c_1 and c_2 of the coordinate curves $x_1 = x_1(0)$ and $x_2 = x_2(0)$, respectively: $c_i = \partial\theta/\partial x_i$. In vector notation (see Fig. 1): $\vec{c}_1 = (\partial\theta/\partial\hat{x}_1) = -c_1\hat{x}_2$, and $\vec{c}_2 = (\partial\theta/\partial\hat{x}_2) = c_2\hat{x}_1$, which allows writing Eq. (9) in the following vectorial form:

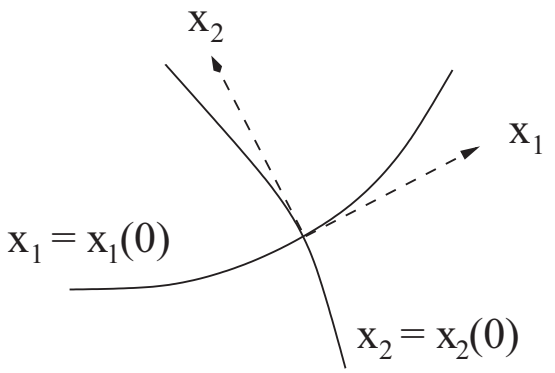

FIG. 1. The local principal directions define an orthogonal curvilinear coordinate system with unit vectors $\hat{x}_i$ ($i = 1,2$) that are tangent to the coordinate curves $x_i = x_i(0) = \text{const}$.

$$\begin{pmatrix} v_1^{\rm drift} \\ v_2^{\rm drift} \end{pmatrix} = \begin{pmatrix} \partial D_1/\partial x_1 \\ \partial D_2/\partial x_2 \end{pmatrix} + \begin{pmatrix} (D_1 - D_2)c_2 \\ (D_2 - D_1)c_1 \end{pmatrix}, \quad (13)$$

which constitutes the main result of this paper.

III. LANGEVIN DYNAMICS SIMULATIONS

The two vectors on the right-hand side of Eq. (13) depict two distinct drifting effects. The former represents the d-dimensional generalization of the one-dimensional equation (6) for the drift in the direction of increasing diffusivity. Its validity can be tested by considering an example where the principal directions of the diffusion tensor are fixed, in which case the angle θ is constant and the second vector is null. This is illustrated in Fig. 2, which shows results for $\langle\Delta x_1\rangle$ and $\langle\Delta x_2\rangle$ vs time in an anisotropic two-dimensional

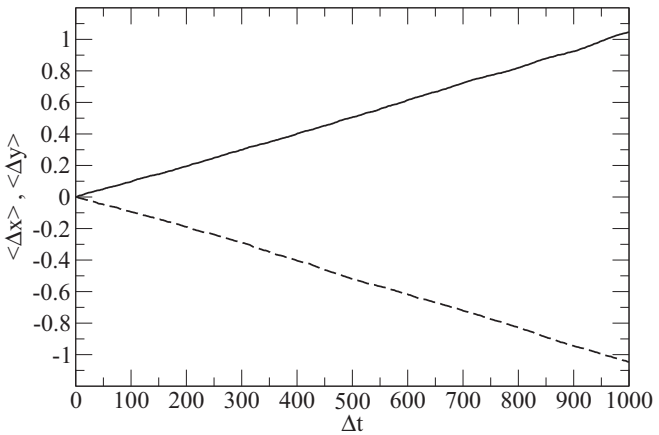

FIG. 2. The mean displacements $\langle\Delta x_1\rangle$ (solid line) and $\langle\Delta x_2\rangle$ (dashed line) as a function of time, computed from Langevin dynamics simulations of 5×10^5 stochastic trajectories of a particle moving in an anisotropic system with $D_1 = 10x_1/(x_2)^2$ and $D_2 = 10/x_2$, and starting at $x_1 = x_2 = 100$.

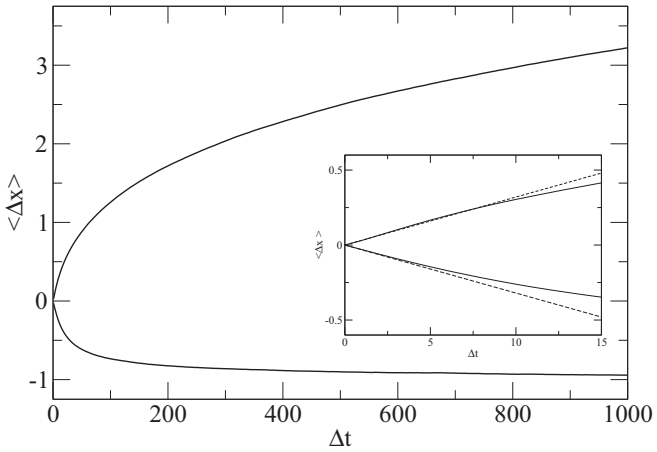

FIG. 3. The mean displacement in the x direction, $\langle \Delta x \rangle$, as a function of time. The monotonically increasing (decreasing) curve depicts results for a particle starting at $(x,y) = (1,0)$ and moving in an anisotropic system with $D_r = 1/25$, and $D_\theta = 1/125$ ($D_r = 1/125$ and $D_\theta = 1/25$). The inset shows a magnification of the initial region $\Delta t \leqslant 15$, where the tangent dashed lines depict the asymptotic behavior $\langle \Delta x \rangle \sim \pm(4/125)\Delta t$, expected from Eq. (13).

system with $D_1 = 10x_1/(x_2)^2$ and $D_2 = 10/x_2$. The results are based on inertial Langevin dynamics simulations of 5×10^5 trajectories of a particle of unity mass ($m = 1$) at constant temperature ($k_B T = 1$) starting at $(x_1,x_2) = (100,100)$. The trajectories are computed with $dt = 10^{-4}$ (which is three orders of magnitude smaller than the ballistic time), using a method based on the robust Grønbech-Jensen and Farago (G-JF) Langevin thermostat [17,18] and the novel "inertial" convention for assigning the values of the friction function at each time step [11]: $\alpha_i^{\text{inertial}} \equiv [\alpha_i(\{x_k(t)\}) + \alpha_i(\{x_k(t) + v_k(t)dt\})]/2$. From Eq. (13), we expect the drift velocities in this case to be $v_1^{\text{drift}} \simeq \partial_{x_1} D_1(100,100) = 10^{-3}$ and $v_2^{\text{drift}} \simeq \partial_{x_2} D_2(100,100) = -10^{-3}$, which is in agreement with the data in Fig. 2.

The second vector on the right-hand side of Eq. (13) depicts a different drifting effect, namely, the one which is associated with the spatial variations in the principal directions of the diffusion tensor. In order to focus on this contribution to the mean displacement of the particle, we consider a system with constant diffusion coefficients D_1 and D_2 ($D_1 \neq D_2$), in which case the first vector is null. As examples, we consider two radially symmetric systems: one with diffusion coefficients $D_1 = D_r = 1/25$ and $D_2 = D_\theta = 1/125$, in the radial and tangential directions, respectively, and the other with $D_1 = D_r = 1/125$ and $D_2 = D_\theta = 1/25$. Using a method similar to that employed in Fig. 2 (see Ref. [19]), we compute 5×10^5 trajectories, each of which start at $(x,y) = (1,0)$. Figure 3 depicts the mean displacement along the x axis, which is the initial radial direction, as a function of time. The monotonically increasing curve shows the mean displacement of the particle in the system where $D_r = 1/25$ and $D_\theta = 1/125$, whereas the decreasing curve corresponds to the system with $D_r = 1/125$ and $D_\theta = 1/25$. In the former case, the particle drifts outward ($\langle \Delta x \rangle > 0$), which is in agreement with Eq. (13) for $D_r = D_1 > D_2 = D_\theta$. Conversely, the particle moves inward for $D_r = D_1 < D_2 = D_\theta$, which is indeed observed in the simulations. Notice that in the latter case, the displacement $\langle \Delta x \rangle \to -1$ for $\Delta t \to \infty$, which is anticipated since this is exactly the initial distance of the particle from the symmetry center of the system. At small times (i.e., when the particle is still close to the point of origin), we expect the drift velocity v_1^{drift} to converge to the asymptotic values of $(D_1 - D_2)c_2 = \pm(4/125)$ [see Eq. (13)]. This result is captured by the simulations, as demonstrated in the inset to Fig. 3 by the tangent dashed lines depicting the asymptotic behavior $\langle \Delta x \rangle \sim \pm(4/125)\Delta t$. For both systems (data not shown), the mean displacement along the initial angular direction $\langle \Delta y \rangle = 0$, which is expected from symmetry arguments, and is also consistent with Eq. (13) considering that the curvature c_1 of r lines is zero.

IV. PAIR DIFFUSION OF TRANSMEMBRANE PROTEINS

A particularly interesting example of two-dimensional diffusion with radial symmetry is the relative pair diffusion between two transmembrane proteins. This, and other closely related setups, have attracted considerable attention because the lateral diffusion of membrane proteins and lipid domains is an important biophysical factor in controlling the dynamics and functioning of the cell membrane (see reviews [20,21], and references therein). Let us consider two membrane inclusions with cylindrical cross sections of radius a, and denote by $\vec{r}$ the vector distance between them ($r = |\vec{r}| \gg a$). The temporal evolution of $\vec{r} = (r,\theta)$ is diffusive, and the associated diffusion coefficients vary with r because of the hydrodynamic interactions between the proteins. Explicitly, the radial and tangential diffusion coefficients of the vector $\vec{r}$ are given by [22]

$$D_r(r) = \frac{k_B T}{2\pi\eta_m}[\ln(r/a) - 3/2 + \kappa r/3], \tag{14}$$

$$D_\theta(r) = \frac{k_B T}{2\pi\eta_m}[\ln(r/a) - 1/2 - \kappa r/3], \tag{15}$$

where κ^{-1} is the Saffman-Delbrück length given by the ratio between the two-dimensional membrane viscosity η_m and twice the three-dimensional viscosity of the embedding fluid η_f: $\kappa^{-1} = \eta_m/2\eta_f$. For lipid bilayers $\eta_m \sim 10^{-10}$–10^{-9} Pa s m, implying that $\kappa^{-1} \sim 0.1$–1 μm. Using expressions (14) and (15) in Eq. (13) gives the average velocity at which the inclusions are moving away from each other: $v_r^{\text{drift}} = k_B T\kappa/(2\pi\eta_m) \sim 1$–$10^2$ μm/s, which is (i) independent of r, and (ii) surprisingly large considering that the linear size of cellular membranes is typically $\sim$10 μm. There are obviously many other factors that produce an inhomogeneous diffusion environment for a membrane protein, most notably the presence of viscous raft domains and the cytoskeleton meshwork that generates corrals in which the protein may be localized [23,24]. Nevertheless, the magnitude of the noise-induced drift (as indicated by the above calculation of v_r^{drift}) appears to be quite large, which suggests that the hydrodynamic interactions between the proteins cannot be neglected when studying their lateral diffusion in an inhomogeneous membrane. We remind one here (see earlier discussion) that in isothermal systems, the drifting effect is countered by an opposite trapping effect

in regions of low diffusivity. Therefore, when two proteins come within close vicinity to each other, they would tend to remain closely separated [25], and this tendency is likely to be intensified by shorter range attractive interactions, for instance, van der Waals and membrane-mediated interactions [26].

We note that expressions (14) and (15) hold in the regime where $r \ll \kappa^{-1}$. For $r \gg \kappa^{-1}$, the radial and azimuthal diffusion coefficients are given by [22]

$$D_r(r) = \frac{k_B T}{2\pi\eta_m}[\ln(2/\kappa a) - \gamma - 2/(\kappa r)], \tag{16}$$

$$D_\theta(r) = \frac{k_B T}{2\pi\eta_m}[\ln(2/\kappa a) - \gamma - 2/(\kappa r)^2], \tag{17}$$

where $\gamma \simeq 0.58$ is Euler's constant. Using these expressions in Eq. (13), we arrive at $v_r^{\rm drift} = k_B T/(\pi\eta_m \kappa^2 r^3)$, for the noise-induced radial drift velocity at large separations.

V. DISCUSSION

In this paper we studied the problem of single particle diffusion in multidimensional systems with space-dependent diffusion coefficient, focusing on the noise-induced drift in two dimensions. By following the derivation for the drift in one-dimensional systems [Eq. (6)], we arrive at the generalized form (9) in higher dimensions. This expression is further analyzed in two dimensions by considering a coordinate system that aligns along the local principal diffusion axes. This analysis yields Eq. (13), where the noise-induced drift vector is expressed as the sum of two terms representing two distinct noise-induced drifting effects. The first effect, which arises also in the one-dimensional case, originates from the fact that the ballistic distance grows proportionally to the local diffusion coefficient and, therefore, the particle moves more persistently ("makes larger steps") in the direction of increasing diffusivity. The second effect is a novel one, existing only in dimensions larger than one. It stems from the gradual rotation of the principal diffusion directions $\hat{x}_1$ and $\hat{x}_2$ occurring during the motion of the particle, and can be understood as follows. At very large times, after the particle moves to distant regions and the memory of the initial principal directions is lost, the dynamics becomes isotropic, and is characterized by the average diffusion coefficient $(D_1 + D_2)/2$. Assuming (without loss of generality) that $D_1 > D_2$, this implies that as the particle diffuses away from its initial position, the effective diffusion coefficient in the initial $\hat{x}_1$ direction decreases, $D_1^{\rm eff} < D_1$, while the diffusion along the initial $\hat{x}_2$ direction occurs with an effectively increasing diffusion coefficient, $D_2^{\rm eff} > D_2$. *The origin of the drift lies in the fact that the rate of rotation is spatially dependent.* It is larger in the direction where the curvature of the x_1 and x_2 curves increases, which explains the form of the second vector in expression (13) for the two-dimensional noise-induced drift velocity.

We used the newly derived expression to estimate the drift velocity of a pair of membrane proteins, and found it to be surprisingly large. The actual diffusive dynamics of membrane proteins is obviously more complex. It takes place in a highly crowded environment, which implies that many-body effects are important. Nevertheless, our study clearly highlights the fact that hydrodynamic interactions between proteins (which are the origin of the diffusivity spatial variations here) are likely to be key factors.

ACKNOWLEDGMENTS

I thank Haim Diamant for helpful discussions on diffusion of membrane inclusions and for critical reading of the manuscript. This work was supported by the Israel Science Foundation (ISF) through Grant No. 1087/13.

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