Lateral diffusion of a protein on a fluctuating membrane

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Measurements of lateral diffusion of proteins in a membrane typically assume that the movement of the protein occurs in a flat plane. Real membranes, however, are subject to thermal fluctuations, leading to movement of an inclusion into the third dimension. We calculate the magnitude of this effect by projecting real three-dimensional diffusion onto an effective one on a flat plane. We consider both a protein that is free to diffuse in the membrane and one that also couples to the local curvature. For a freely diffusing inclusion the measured projected diffusion constant is up to 15% smaller than the actual value. Coupling to the curvature enhances diffusion significantly up to a factor of two.

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Introduction

During the last two decades significant progress has been made regarding novel microscopy techniques, that are mainly based on the observation of single or few molecules. With the aid of single particle tracking, photon force microscopy, or fluorescence-based single-molecule microscopy one is now capable of studying the dynamic properties of lipids or proteins in membranes with positional accuracies smaller than 40 nm and a time resolution that can be as small as tens of microseconds, see the review [1] and references therein. These techniques together with other methods like fluorescence correlation spectroscopy, reviewed in [2], have made it possible to measure lateral diffusion of single molecules in a membrane very accurately giving insight into the organisation of biomembranes. Although these high resolution methods have become standard practice, it is typically overlooked that a membrane is soft and therefore subject to thermal shape undulations. Diffusion coefficients extracted from experimental data usually correspond to projected diffusion in a flat plane. The fluctuations of the membrane, however, lead to a three-dimensional motion of the diffusing protein, but unlike free three-dimensional diffusion the particle is confined to the membrane. Since the fluctuation spectrum of the membrane can be affected by external parameters, like e.g. temperature, osmotic pressure or pH differences [3, 4], these high accuracy methods should make the apparent change in diffusion experimentally measurable.

In this paper, we are interested in how big the difference between the actual intramembrane and the measured projected diffusion constant is. We study both the case of a protein, which is free to diffuse [5, 6], and a curvature-coupled protein with (or inducing) a spontaneous curvature. Most studies of membrane-inclusions within various models, which include rigid inclusions of various shapes, or proteins with a large domain outside the membrane, analyse the static interaction with the membrane and/or the interaction between inclusions [7–11], and have not yet addressed the dynamical issue of diffusion.

Free diffusion

First, we regard the simplest case of a protein free to diffuse in the membrane. We assume that the diffusion is not influenced by the local shape of the membrane, therefore apart from the inclusion being confined to the membrane there are no interactions between membrane and protein. To describe diffusion on a curved surface, the Laplace operator in the diffusion equation for a plane needs to be replaced by the Laplace-Beltrami operator. We consider both a protein that is free to diffuse in the membrane and one that also couples to the local curvature. For a freely diffusing inclusion the measured projected diffusion constant is up to 15% smaller than the actual value. Coupling to the curvature enhances diffusion significantly up to a factor of two.

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First, we regard the simplest case of a protein free to diffuse in the membrane. We assume that the diffusion is not influenced by the local shape of the membrane, therefore apart from the inclusion being confined to the membrane there are no interactions between membrane and protein. To describe diffusion on a curved surface, the Laplace operator in the diffusion equation for a plane needs to be replaced by the Laplace-Beltrami operator. If the position of the surface \( r \) is expressed in the Monge representation, i.e. \( \tilde{r} = (r, y, h(x, y)) \), the resulting Smolouchovski equation is [5]

\[
\frac{\partial P(x, y, t)}{\partial t} = D \left\{(1 + h_y^2) \frac{\partial^2 P}{\partial x^2} + (1 + h_x^2) \frac{\partial^2 P}{\partial y^2} - 2h_x h_y \frac{\partial^2 P}{\partial x \partial y} \right. \\
- \frac{1}{g} \left[h_x h_y (1 + h_x^2) + h_y h_x (1 + h_y^2) - 2h_x h_y h_x^2 \right] \frac{\partial P}{\partial x} \\
- \frac{1}{g} \left[h_y h_x (1 + h_x^2) + h_x h_y (1 + h_y^2) - 2h_x h_y h_y^2 \right] \frac{\partial P}{\partial y} \right\} \tag{1}
\]

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with \( h_x = \partial h(x,y)/\partial x \) -- for the other subscripts accordingly -- and \( g = 1 + h_x^2 + h_y^2 \). \( D \) is the diffusion constant on the curved surface, \( P(x,y,t) \, dx \, dy \) is the probability to find the diffusing particle in the area element \( dx \, dy \) at point \( r \). The membrane is subject to thermal fluctuations. Similarly to the calculation of diffusion within the Zimm model \([13]\) we introduce a preaveraging approximation: Instead of using the prefactors, that contain \( h_x, h_y, h_x x, h_y y, h_x y \), and therefore explicitly depend upon position and time, we replace them by their thermal averages \((\ldots)\). This approximation is valid if the time scale of protein diffusion is much larger than that of membrane shape fluctuations. Due to their asymmetry averages like \( \langle h_x h_y/g \rangle \) and many others vanish. Only \( \langle h_x^2/g \rangle = \langle h_y^2/g \rangle \) are non-zero contributions. This considerably simplifies the diffusion equation

\[
\frac{\partial P(x,y,t)}{\partial t} = D \left\{ \left(1 - \frac{\langle h_x^2/g \rangle}{g} \right) \frac{\partial^2 P}{\partial x^2} + \left(1 - \frac{\langle h_y^2/g \rangle}{g} \right) \frac{\partial^2 P}{\partial y^2} \right\}. \tag{2}
\]

Average quantities of an isotropic membrane cannot be different for the \( x- \) or \( y- \) direction, and the effective diffusion constant \( D_{\text{proj}} \), that would be measured in the \( x-y \)-plane is rescaled to

\[
\frac{D_{\text{proj}}}{D} = \left(1 - \frac{\langle h_x^2/g \rangle}{g} \right) = \frac{1}{2} \left(1 + \frac{1}{g} \right). \tag{3}
\]

This relation has been derived previously by a slightly different approach \([6]\) but not evaluated.

We evaluate the rescaling factor \( D_{\text{proj}}/D \) using the classical Helfrich Hamiltonian \( \mathcal{H}_0 \) as a model for the membrane. It takes the following approximate form in the Monge representation (\( r \equiv (x,y), \nabla \equiv (\partial/\partial x, \partial/\partial y) \))

\[
\mathcal{H}_0[h(r,t)] = \int_A d^2r \frac{\kappa}{2} (\nabla^2 h)^2 + \frac{\sigma}{2} (\nabla h)^2, \tag{4}
\]

where \( \kappa \) is the bending rigidity of the membrane and \( \sigma \) an effective tension \([14]\). To calculate the expression \( \langle 1/g \rangle = \int_0^\infty d\alpha \exp[-\alpha g] \) we introduce the functional integral

\[
\tilde{Z}(\alpha) = \int \mathcal{D}[h] \exp \left[ -\alpha \int_{L^2} d^2r \frac{\kappa}{2} (\nabla^2 h)^2 + \left( \frac{\sigma}{2} + \frac{\alpha}{\beta L^2} \right) (\nabla h)^2 \right]. \tag{5}
\]

where \( L \) is the length of the system in the \( x- \) and \( y- \) direction and \( \beta = 1/(k_B T) \) the inverse temperature. The partition function \( Z \) of the membrane is given by \( \tilde{Z}(\alpha = 0) \) and therefore \( \langle \exp[-\alpha (\nabla h)^2] \rangle = \tilde{Z}(\alpha)/\tilde{Z}(0) \). Using a Fourier expansion of spatially varying variables the calculation of \( \tilde{Z}(\alpha) \) is straightforward and yields

\[
\langle \exp[-\alpha (\nabla h)^2] \rangle = \exp \left[ -\frac{1}{2} \sum_{x,y} \ln \left(1 + \frac{2\alpha L^2}{\beta} \frac{1}{\kappa k^2 + \sigma} \right) \right]. \tag{6}
\]

The cutoff wave number \( q_m \sim 1/a \) is given by the smallest length scale \( a \) present in the membrane. Because \( L q_m \gg 1 \) we replace the summation on the rhs by the integration over \( k \). The ratio of projected and intramembrane diffusion constant may then be written as

\[
\frac{D_{\text{proj}}}{D} = \frac{1}{2} + \frac{1}{2} \int_0^\infty d\alpha \exp \left[ -\alpha - \frac{1}{8\pi} \left\{ \frac{\beta \sigma / q_m^2 (L q_m)^2}{\beta \kappa} \ln \left( \frac{\beta \sigma / q_m^2}{\beta \kappa + \beta \sigma / q_m^2} \right) + (L q_m)^2 \times \ln \left(1 + \frac{2\alpha (L q_m)^2}{\beta \kappa + \beta \sigma / q_m^2} \right) + (L q_m)^2 \frac{2\alpha}{\beta \kappa} \right\} \right]. \tag{7}
\]

This integral is a function of three dimensionless quantities \( L q_m, \beta \kappa, \) and \( \beta \sigma / q_m^2 \). An analytic solution is not found, but the fast decay of the integrand facilitates the numerical evaluation.

For a numerical calculation of the scaling factor of the diffusion constant, we first need to analyse the size of the parameters \( \beta \kappa, \kappa, \beta, \sigma, L, q_m \), which go into eq. (7). Typical values of \( \beta \kappa \) for lipid bilayer membranes lie in the range between 5 and 50. The smallest length scale \( a \) of the system, that gives \( q_m \sim 1/a, \) is roughly the size of a lipid which is on the order of nanometres. The area \( L^2 \) of membranes studied in experiments can vary strongly from a few \( \mu \text{m}^2 \) to approximately 100,000 \( \mu \text{m}^2 \). For \( (L q_m)^2 \) we, therefore, regard the range from \( 10^6 \) to \( 10^{11} \). Typical values for the effective tension of a fluctuating membrane at room temperature are \( 10^{-6} \text{mJ/m}^2 \lesssim \sigma \lesssim 10^{-3} \text{mJ/m}^2 \), while rupture occurs for tensions on the order of \( \sigma \sim 1 \text{mJ/m}^2 \) \([14]\). The whole range we regard is \( 10^{-6} \lesssim \beta \sigma / q_m^2 \lesssim 10^{-1} \).

First, we analyse the case of vanishing effective tension \( \sigma = 0 \): In fig. [1] we show \( D_{\text{proj}}/D \) as a function of \( (L q_m)^2 \) for the given values of \( \beta \kappa \). Overall we see that in the parameter ranges, which correspond to experimental conditions, the projected
diffusion constant is reduced by up to \( \sim 15\% \). As was to be expected we also find that a more rigid membrane leads to weaker rescaling of the diffusion constant and that an increase in membrane size, which leads to stronger fluctuations, causes the scaling factor to decrease. In fig. 2 we display \( D_{\text{proj}}/D \) as a function of rigidity \( \beta \kappa \) for the given \( (Lq_m)^2 \). We find that an increase in \( \beta \kappa \) from 5 to 50 increases \( D_{\text{proj}}/D \) monotonically by approximately 0.1. For larger membranes, when the role of the fluctuations is more pronounced, \( D_{\text{proj}}/D \) is smaller and the rise with \( \beta \kappa \) stronger.

We now consider the influence of an effective tension. The larger \( \sigma \) the more expensive it is for the membrane to fluctuate, i.e. to build up gradients \( \nabla h \). As a consequence, an increase in \( \sigma \) will lead to a weaker reduction of \( D_{\text{proj}}/D \). This can be seen in fig. 3 where we display \( D_{\text{proj}}/D \) as a function of \( \beta \kappa \) and \( \beta \sigma/q_m^2 \) for \( (Lq_m)^2 = 10^7 \). For the smallest regarded effective tension and bending rigidity the reduction of the diffusion constant is the strongest with \( \sim 10\% \). An increase in \( \beta \kappa \) and \( \beta \sigma/q_m^2 \) leads to a decreased difference between the projected and actual diffusion constant. For larger effective tensions and smaller rigidity the lines of constant \( D_{\text{proj}}/D \) appear almost linear. This behaviour can be extracted analytically from eq. (7) in the limit of large systems

\[
D_{\text{proj}}/D \approx \left\{ 1 + \left[ 1 + \ln \left( 1 + \frac{\beta \kappa}{\beta \sigma/q_m^2} \right) \right] / (4 \pi \beta \kappa) \right\}^{-1} / 2, \tag{8}
\]

which may be a more convenient expression for future reference than the full expression (7).

Curvature-coupled diffusion

In this section we regard a protein that interacts with the fluctuating membrane. The exact mechanisms, how a protein couples to a bilayer membrane are not understood, however there are a large number of possibilities that have been explored in theoretical calculations and simulations [7, 8, 9, 10, 11, 12]. In this study we model a protein of radius \( a_p \) at position \( \mathbf{R} \equiv (X, Y) \) in the projected plane to couple to a local curvature \( C_p \) of the membrane via the elastic coefficient \( m \). This situation could be caused either by the shape of the protein alone, or by a protein with a large extramembrane domain, that induces a spontaneous curvature in the membrane [12]. The energy \( \mathcal{H}_1 \) of this interaction,

\[
\mathcal{H}_1[h(\mathbf{R})] = \frac{m}{2} \left( \nabla^2 h(\mathbf{R}) - C_p \right)^2 - \frac{\kappa}{2} \pi a_p^2 \left( \nabla^2 h(\mathbf{R}) \right)^2, \tag{9}
\]

needs to be added to the membrane energy \( \mathcal{H}_0 \) of eq. (4) to give the full energy \( \mathcal{H} = \mathcal{H}_0 + \mathcal{H}_1 \) of the system. The second term of eq. (9) accounts for the fact that there is no membrane where the protein is. If we are interested in the dynamics of the system we need to take the equations of motion both for the membrane and the particle into account. The dynamics of the membrane is expressed by

\[
\partial h(\mathbf{r})/\partial t = - \int d^2 r' \Lambda(\mathbf{r}, \mathbf{r}') \left( \delta \mathcal{H}_0/\delta h(\mathbf{r}') + \delta \mathcal{H}_1/\delta h(\mathbf{r}') \right) + \xi(\mathbf{r}) \tag{10}
\]

with the kinetic or Onsager coefficient \( \Lambda(\mathbf{r}, \mathbf{r}') \) and random fluctuations \( \xi \), which obey the fluctuation dissipation theorem. In Fourier space, the kinetic coefficient for a free, on average planar, membrane embedded in infinite space is given by \( \Lambda(k) = \frac{4}{\pi} k_0^2 \left( 1 + \kappa k^2 \right) \),
average energy equation (11), which corresponds to using only the dynamics time into eq. (13) and performing the two time integrals yields which we previously related to the intramembrane diffusion constant $h$ the dynamics of the system. If we regard eq. (10), it is clear that the solution will have two additive parts: the first is the result of the unperturbed membrane, while the second $h_0(r, t)$ is a correction caused by the protein-membrane interaction energy $H$. To calculate the full dynamics of the particle $h_0 + h_1$ is plugged into eq. (11). If, however, the interaction energy is much smaller than the unperturbed membrane energy, $H_1 \ll H_0$, we may use the first order approximation of the Langevin equation (11), which corresponds to using only the dynamics $h_0$ of an unperturbed membrane to calculate the protein dynamics.

This approximate form of eq. (11) is now used to calculate the diffusion constant of the curvature-coupled protein inclusion defined as $D_{\kappa} \equiv \lim_{t \to \infty} \langle \Delta R^2(t) \rangle / 4t$. $\Delta R^2$ is the projected squared distance in the $X$-$Y$-plane the particle has moved during time $t$. In the following we will drop the subscript of $\kappa$ and assume that it is the result of the unperturbed membrane. Using eq. (11) we write ($R(t = 0) = 0$)

$$
\langle \Delta R^2(t) \rangle = \int_0^t \int_{0}^{t'} dt' dr' \left\langle \frac{\partial R(\tau)}{\partial \tau} \frac{\partial R(\tau')}{\partial \tau'} \right\rangle
= \int_0^t \int_0^{t'} dt' dr' \mu_{\text{proj}}^2 \left\{ m^2 C_p^2 \langle \nabla^2 h(\tau) \rangle \langle \nabla^2 h(\tau') \rangle \right\} + O(h^4).
$$

For the last line we used eq. (12) and remembered that averages of uneven powers of $h$ vanish. Because contributions on the order of $O(h^4)$ are negligible, they are omitted in the following. To calculate the diffusion coefficient, we need the thermal average $\langle M \rangle \equiv \langle \nabla^2 h(t) \rangle / \langle \nabla^2 h(0) \rangle$). We introduce the function $Z(\alpha)$

$$
Z(\alpha) = \int D[h] \exp \left\{ -\beta \frac{1}{(2\pi)^2} \int \frac{d^2k}{2\pi} \left\{ \frac{E(k)}{2} - \frac{\alpha}{\beta L^2} k^6 \exp \left\{ -\Lambda(k) E(k) t \right\} \right\} h(k) \right\}.
$$

with $E(k) \equiv \kappa k^4 + \sigma k^2$. The desired quantity is then determined by $\langle M \rangle = \frac{1}{Z(0)} \frac{\partial Z(0)}{\partial \alpha}$. Inserting the evaluation of eq. (12) into eq. (13) and performing the two time integrals yields

$$
\langle \Delta R^2(t) \rangle = 4D_{\text{proj}} t + \mu_{\text{proj}}^2 m^2 C_p^2 \frac{1}{2\pi} \int_0^{\infty} dk \frac{2k^7}{\beta E^2(k) \Lambda(k)} \left\{ t + \frac{\exp[-\Lambda(k) E(k) t]}{\Lambda(k) E(k)} - 1 \right\},
$$

FIG. 3: Factor $D_{\text{proj}} / D$ as a function of $\beta \kappa$ and $\beta \sigma / q_m^2$ for $(q_m L)^3 = 10^7$. The reduction in diffusion constant is the weakest for stiff membranes at high effective tension.

FIG. 4: Ratio $D_{\kappa} / D$ of the diffusion constant of a curvature-coupled protein and intramembrane diffusion as a function of rigidity $\beta \kappa$ and effective tension $\beta \sigma / q_m^2$ for $(L q_m)^2 = 10^7$. 

$(4\pi k)^{-1}$ with the viscosity $\eta$ of the fluid surrounding the membrane [14]. The dynamics of the inclusion follows the Langevin equation

$$
\partial R / \partial t = -\mu_{\text{proj}} \nabla R H + \zeta = \mu_{\text{proj}} \left\{ m C_p (\kappa \pi a^2 - m) \nabla^2 h(R) \right\} \nabla R \left\{ \nabla^2 h(R) \right\} + \zeta,
$$

where $\zeta$ is a random force acting on the inclusion with

$$
\langle \zeta(t) \rangle = 0 \quad \text{and} \quad \langle \zeta(t) \zeta(t') \rangle = 2D_{\text{proj}} k \delta(t - t'),
$$

while $\mu_{\text{proj}}$ is a mobility, that is connected to the diffusion coefficient via the Einstein relation $k_B T \mu_{\text{proj}} = D_{\text{proj}}$. Because we are only regarding the movement of the particle in the projected plane we need to use the projected diffusion constant $D_{\text{proj}}$, which we previously related to the intramembrane diffusion constant $D$. The solution of the coupled eqs. (10) and (11) defines the dynamics of the system. If we regard eq. (10), it is clear that the solution will have two additive parts: the first is the result $h_0(r, t)$ of the membrane without inclusion, while the second $h_1(r, t)$ is a correction caused by the protein-membrane interaction energy $H$. To calculate the full dynamics of the particle $h_0 + h_1$ is plugged into eq. (11). If, however, the interaction energy is much smaller than the unperturbed membrane energy, $H_1 \ll H_0$, we may use the first order approximation of the Langevin equation (11), which corresponds to using only the dynamics $h_0$ of an unperturbed membrane to calculate the protein dynamics.
from which we derive the diffusion constant $D_{cc}$ for curvature-coupling as

$$D_{cc} = D_{proj} \left\{ 1 + \mu_{proj} m^2 C_p \frac{1}{\pi} \frac{\eta}{\kappa^2} \left[ 1 + \frac{1}{2 (1 + \frac{1}{2} \eta^2 q_m^2)} - \frac{3}{2} \frac{1}{\sqrt{\frac{\kappa}{\sigma} q_m}} \arctan \left( \frac{\sqrt{\frac{\kappa}{\sigma} q_m}}{q_m} \right) \right] \right\}. \quad (16)$$

Contrary to the last section, where we could give quantitative predictions for the relation between projected and free intramembrane diffusion, this expression is subject to more model parameters and is less universal. However, it is still instructive to make a semi-quantitative estimate to gain insight into the influence of curvature-coupled protein diffusion.

The factor $[\ldots]$ on the right of eq. (16), that contains only $\sqrt{\kappa / \sigma q_m^2}$, is always very close to one. Only towards the low end of the regarded range $10 \leq \sqrt{\kappa / \sigma q_m^2} \leq 10^4$ is this factor slightly reduced. Therefore, the prefactor of $[\ldots]$, which contains the elastic constant $\kappa$, the spontaneous curvature $C_p$, the rigidity $\kappa$, the cutoff wave number $q_m$, the viscosity $\eta$, and the mobility $\mu_{proj}$, determines the magnitude of the diffusion. Because this prefactor is obviously positive, the diffusion of a protein is generally enhanced for the considered coupling to local curvature.

The characteristic scale of the elastic constant $m$ is the bending rigidity $\kappa$ of the membrane times the area $\pi a_p^2$ occupied by the protein. Thus we can write $m = c_1 \kappa \pi a_p^2$ with a constant $c_1$ on order of unity. We choose $c_1 = 2$. An axisymmetric inclusion, whose area on one side of a membrane with width $d$ is twice that of the other side, produces a spontaneous curvature of $C_p = 4/3d$ [14]. A good estimate for the cutoff wave number is $q_m = \frac{2 \pi}{a_p}$. We further assume the radius of the protein to be $a_p = 8a$, and the width of the membrane $d = 5a$. These estimates ensure that the energy of the protein may still be regarded as a perturbation. Unlike the initial problem, where we could give the ratio $D_{proj} / D$, we now also need an estimate for the mobility $\mu_{proj} = \beta D_{proj}$. Saffman and Delbrück [15] derived this expression for the mobility within a flat two-dimensional liquid layer bound by a surrounding three-dimensional fluid with viscosity $\eta$

$$\mu' = [\ln (\nu d / (\eta a_p)) - \gamma] / (4 \pi \nu d). \quad (17)$$

In this equation, $\nu$ is the viscosity of the liquid layer, i.e. the membrane, and $\gamma \approx 0.577$ is the Euler number. This mobility is valid for $\nu d / \eta a_p >> 1$, which is the case for a typical lipid membrane. We use eq. (17) with the previously calculated rescaling, $\mu_{proj} = \mu' D_{proj} / D$, for the estimate of the diffusion constant $D_{cc}$. For a lipid membrane, the viscosity is on the order of $\nu \approx 1\text{erg sec/cm}^3$ and the viscosity of water is $\eta \approx 10^{-2}\text{erg sec/cm}^3$. This gives $\eta / \nu \approx 0.01$. If we neglect the effective tension and use our estimates in eq. (16), we find:

$$D_{cc}(\sigma = 0)/D \simeq D_{proj} / D \left\{ 1 + 0.81 D_{proj} / D \right\}. \quad (18)$$

For a typical ratio of $D_{proj} / D = 0.95$ we see that the diffusion of the protein is increased by $\approx 68\%$. This estimate reveals that a coupling to local curvature can lead to a significantly enhanced diffusion coefficient.

The ratio $D_{cc} / D$ for $\sigma > 0$ using $D_{proj} / D$ from eq. (7) is shown in fig. 4 as a function of $\beta \sigma / q_m$ and $\beta \kappa$ for $(L q_m)^2 = 10^7$. Surprisingly the weakest influence on the diffusion constant is found for small rigidity $\beta \kappa$ and small effective tension $\beta \sigma / q_m^2$.

In summary, we have found that thermal fluctuations of biomembranes have considerable influence on the diffusion of proteins. When the protein is free to diffuse within the membrane, the projected diffusion constant, which corresponds to the quantity typically measured, is up to $15\%$ smaller than that of the true intramembrane diffusion. The lower the bending rigidity or the effective tension and the larger the membrane, the stronger is this effect. Experimentally, it could be studied by observing the change in the projected diffusion constant upon osmotically induced swelling of an initially flaccid vesicle, which increases the effective tension [14]. To gain insight into the influence of protein-membrane interactions, we studied the diffusion of an inclusion with a spontaneous curvature and found that this enhances diffusion significantly. When the projected diffusion constant is measured this leads to an interesting interplay: on the one hand fluctuations can lead to enhanced intramembrane diffusion, while on the other hand stronger fluctuations lead to a smaller projected diffusion constant. It is therefore possible that the measurement of the diffusion coefficient at constant rigidity and increasing effective tension reveals a maximum for a
certain effective tension. Future experimental studies should analyse the effect of changing membrane fluctuations on the lateral diffusion of proteins, since they could shed light on the local coupling mechanisms between proteins and lipids.

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