Diffusion on Membrane Tubes: A Highly Discriminatory Test of the Saffman−Delbruck Theory

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The efficient transport of membrane proteins is vital in maintaining life. In this work, we investigate the transport of such membrane proteins along long thin membrane tubes or tethers. We calculate the diffusion constant to leading order in the low Reynolds number regime to be $D = (4\pi\eta)^{-1} \log(r/a)$, with r and a being the tube and protein radii, respectively, and η being the membrane viscosity. Thus we propose an exact limiting form for the controversial logarithmic correction, such as originally introduced by Saffman and Delbruck, that involves the tube radius rather than some "frame size". Our work suggests a test of this logarithmic correction could be achieved by measuring diffusion on membrane tubes, exploiting the fact that the equilibrium tube radius can be controlled by the membrane tension and varied over several orders of magnitude. We analyze the time taken for a protein to transit a membrane tube between cells and find that this can vary by an order of magnitude over physiological tensions. This is a strong effect in biological terms and suggests a possible regulatory coupling between membrane tension and signaling.

Introduction

Our theoretical study of the motion of membrane proteins addresses a long outstanding controversy about their diffusion. This can be traced to Saffman and Delbruck's seminal paper on protein diffusion on flat membranes.[1] It was here that these authors first predicted a logarithmic dependence of the protein diffusion constant on the ratio of the size of the protein to the size of the membrane, a result of great relevance to membrane biophysics. This dependence still remains the subject of intense scientific interest and controversy since it has proved extremely difficult to verify. Indeed, Urbach and co-workers[2] recently presented evidence that calls this logarithmic dependence into question. Our work achieves two important goals. First, it analyzes a new way of verifying this logarithmic dependence. This does not involve measuring the diffusion of proteins of different sizes,[2] but rather involves changing the "size" of the membrane. This could now be achieved by controlling the force on a tubular membrane tether held in place by a laser tweezer focused on a conjugated bead. By controlling the membrane surface tension, one controls the tube radius, which we show to be the relevant "membrane size". Our calculations are directed at this new membrane geometry, that of long slender membrane tubes. A physiologically relevant and experimentally accessible range of membrane tensions gives rise to a huge change in the tube radius (perhaps approaching 2 orders of magnitude). In turn, this leaves a clear signal in the measurable diffusion constant of membrane proteins, which we suggest could be made to vary by about an order of magnitude. In this magnitude, we show how measurements of diffusion constants, for example, by FRAP, at various tether forces could provide a test of Saffman and Delbruck's predictions.

The formation of membrane tubes has received much recent interest.[3−13] These tubes can arise in biology due to the polymerization of actin fibers[14] or microtubules,[15] which may be coupled to molecular motor proteins.[14,15] Such tubular structures appear on or within cell membranes and neuronal growth cones,[14−16] as well as on vesicles observed in vitro.[11,17−24] Biological membranes that exist in the endoplasmic reticulum (ER) and the Golgi apparatus can also form complex and highly dynamical tubular structures.[25−33] Indeed, it has recently been reported experimentally[34] that long membrane tubes are involved

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in transport between membrane compartments such as the Golgi and ER, or between the plasma membranes of nearby cells.[35,59] It is thus important that we understand the mobility of small proteins that are free to diffuse on such tubular membrane networks. As we have stated, such tubular membrane geometries can be recreated in a highly controlled fashion by pulling a membrane-tethered bead from the surface of a cell or vesicle, for example, using a laser trap. In this way the axial force exerted by such membrane tethers can be measured, and this can be used to extract the membrane tension.[3,12]

Protein diffusion on *flat* biomembranes has been extensively studied experimentally in various biological contexts (see, e.g., refs 2 and 36−40). The theoretical approach to this problem has involved calculating the diffusion constant for a small protein on a large flat membrane, and various results already exist.[1,41−46] These share the feature of a logarithmic correction to the diffusion constant which, as discussed above, is difficult to test and somewhat experimentally controversial.[2] For the sake of completeness, we re-derive this result in the appendix via the theory outlined below, where we also discuss diffusion on a large spherical membrane. Throughout the present work we neglect the effect of flows in any surrounding fluid,[2,47] as we discuss further in the Conclusion.

In what follows, we aim to calculate the diffusion constant of a small protein on a long thin cylindrical membrane tube or tether. Our motivation is twofold: (1) to quantify the rate of transport of membrane proteins within and between cells and (2) to analyze a model geometry that may allow for a more rigorous test of the proposed logarithmic correction to the diffusion constant. This would be achieved by variation of the tube radius over several orders of magnitude through the controlled variation of either the membrane tension σ, or, equivalently, the axial "tether" force f_L required to hold the tube at constant length L,[48] which will be discussed further below. The membrane rigidity κ is usually assumed to remain constant. Additional contemporary interest in these problems is reflected in refs 13 and 20, for example.

Theory

We now proceed to calculate the diffusion constant of a small protein diffusing on a cell membrane tether or tube, via consideration of its low Reynolds number hydrodynamics.[49−52] We approximate the flow field $\mathbf{u}$ around a protein by that of a Stokeslet,[49−53] the flow due to a unit point force $\mathbf{f}$ at the protein's location. While other, more complicated theoretical hydrodynamic approaches exist in the literature[49−52] with their concomitantly much more difficult to implement boundary conditions, our use of Stokeslets should yield an accurate description on scales greater than the protein size $\sim a$, which we assume to be the case in what follows. The resulting linear relationship between the particle (Stokeslet) velocity $\mathbf{u}_0$ and force $\mathbf{f}$ will be used to obtain the diffusion constant as usual.[49−53] The hydrodynamic equations governing incompressible, low Reynolds number Stokes flow are

$$-\nabla p + \eta\nabla^2\mathbf{u} + \mathbf{f}\delta^2(x) = 0$$
$$\nabla\cdot\mathbf{u} = 0 \qquad (1)$$

where η characterizes the membrane viscosity, having units of viscosity multiplied by length (membrane thickness).

Using the incompressibility constraint, $\nabla\cdot\mathbf{u} = 0$, we can eliminate the pressure $p(x)$ (with units of surface pressure) from eq 1 via $-\nabla^2 p + \nabla\cdot\mathbf{f}\delta^2(x) = 0$. That is, at each point x, we choose a $p(x)$ such that fluid incompressibility is satisfied. This leads to the following solution for the flow field, which possesses the characteristic and well-known Oseen tensorial structure:[49−52]

$$\mathbf{u}^\alpha(x) = -\frac{\mathbf{f}^\beta}{\eta}(\delta^\alpha_\beta\nabla^2 - \nabla^\alpha\nabla_\beta)\int d^2x' G(x-x')G(x') \qquad (2)$$

In eq 2 we have introduced the useful Green function $G(x - x')$ which satisfies the relation $-\nabla^2 G(x - x') = \delta^2(x - x')$.[54] In addition, at the protein's location, $x = 0$ (no boundary "finite size" shape effects), we must satisfy the appropriate boundary condition $\mathbf{u}(0) = \mathbf{u}_0$, where $\mathbf{u}_0$ is the velocity of the protein. In this short-distance limit, as we approach the protein's location ($x \to 0$), we can use the well-known result[54] that $-\nabla^\alpha\nabla_\beta G(x - x') \approx 1/2\delta^\alpha_\beta\delta^2(x - x')$ as $(x - x') \to 0$. By utilizing the aforementioned properties of the Green function $G(x - x')$, and via careful inspection of eq 2, we can therefore see that all we require to complete our calculation is the $x \to 0$ limit of $G(x)$. This allows us to write directly from eq 2, using the well-known relation $\mathbf{f} = \zeta\mathbf{u}_0$,

$$D = \frac{k_B T}{\zeta} = \frac{k_B T}{2\eta}\, G(x)|_{x\to 0} \qquad (3)$$

using the limit $x \to 0$ at the protein's location. Here, D is the protein's diffusion constant, and ζ is its coefficient of friction. Typically, however, the Green function $G(x)$ diverges as $x \to 0$, so that we need to introduce a "cutoff", a, in order to give the protein a finite size. Note, therefore, that this simple result is valid as long as the size of the protein is small compared with the size of the membrane, which typically holds under physiological conditions.[15] Given this simplifying limit, and using the result obtained in eq 3, we can see that, with perfect generality, we can establish the protein diffusion constant (in whatever membrane geometry we choose) by investigating the short-distance properties of the Green function $G(x - x')$, as defined above.

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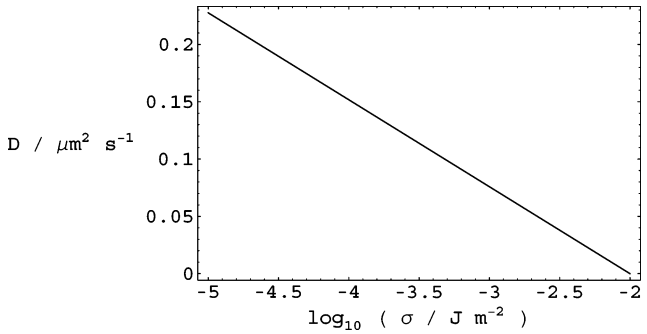

Figure 1. Plot of the diffusion constant D (in units of $\mu m^2\ s^{-1}$) for a protein diffusing along the surface of a membrane tether as a function of the membrane surface tension σ (in units of $J\ m^{-2}$). The absolute value of D depends on the precise values of η and a used (in our case, $\eta \approx 5 \times 10^{-9}\ J\ m^{-2}\ s$ and $a \approx 5$ nm). The large variation in D accessible, through changes in membrane tension, is a key predicition of the work presented here.

Membrane Tubes

In a cylindrical geometry corresponding to a tube of length L and radius r, the Green function is given,[54] in terms of Fourier variables, by

$$G(\Delta x) = \frac{1}{2\pi L r} \sum_{mn} \frac{1}{\mathbf{q}^2} \exp(2\pi i n \Delta z/L + im\Delta\phi) \qquad (4)$$

where $\mathbf{q} = q_z\hat{\mathbf{z}} + \mathbf{q}_\phi\hat{\phi}$, $q_z = 2\pi n/L$, and $q_\phi = m/r$. The Green function in eq 4 is given such that the flow field $\mathbf{u}$ dissipates for large separation in Δz while also respecting the necessary periodicity in $\Delta\phi$. Focusing on the biologically relevant case of long and thin membrane tethers, we can investigate, precisely as outlined above, the required short-distance limit $G(\Delta x)|_{\Delta x \to 0}$ of eq 4, in the long-length limit also of $L \to \infty$. This can be simply achieved by converting the sum over n into an integral. Then using the result of eq 3 from above, we thus obtain the diffusion constant as

$$D = \frac{k_B T}{4\pi\eta} \sum_{m=1}^{\infty} \frac{1}{m} \exp(-ma/r) \cos(ma/r)$$
$$= \frac{k_B T}{4\pi\eta} \left[\ln\left(\frac{r}{a}\right) + O(1) + O\left(\frac{a}{r}\right) + ... \right] \qquad (5)$$

This gives the leading order logarithmic behavior in the limit $r/a \gg 1$. In calculating eq 5, we have assumed that the protein shape (or size) is given implicitly by $\Delta z = a$ and $r\Delta\phi = a$. Changing the shape of the protein merely alters the order unity contribution in eq 5, and is therefore a subleading effect in the limit $r/a \gg 1$ of interest to us here. Heuristically, we can also understand, if we so wish, the logarithmic behavior of the diffusion constant with respect to membrane tube radius as arising due to the necessity of introducing a low-wavelength (long-distance) cutoff into the sum over all modes m, as arises in eq 5 for example.

Protein Diffusion on Membrane Tethers. It is well-known that, for a membrane tube (or tether) with surface tension σ and bending modulus κ, its equilibrium radius is given by $r = \sqrt{\kappa/2\sigma}$,[3] and the force required in order to maintain its equilibrium length L is given by $f_L = 2\pi\sqrt{2\kappa\sigma}$.[3] Using these results in eq 5, we obtain the following result for a surface protein diffusing along the length of a membrane tether (in the limit $L/r \gg 1$):

$$D = \frac{k_B T}{8\pi\eta} \ln\left(\frac{\kappa}{2\sigma a^2}\right)$$
$$= \frac{k_B T}{4\pi\eta} \ln\left(\frac{2\pi\kappa}{f_L a}\right) \qquad (6)$$

Figure 1 shows that, as the surface tension σ decreases, and therefore the radius of the membrane tether $r = \sqrt{\kappa/2\sigma}$ increases, the mobility of the diffusing surface protein increases. The total variation of σ shown in the figure is on the order of the physiological range, and *in vitro* experiments should allow the exploration of even larger regimes of σ. Additionally, utilizing the scaling relationship $L^2 = 2D\tau$ for one-dimensional diffusion, and our previous result for the diffusion constant D, we can find a characteristic time for a surface protein to diffuse along a membrane tether of length L (in the limit $L/r \gg 1$):

$$\tau = \frac{4\pi\eta L^2}{k_B T \ln\left(\frac{\kappa}{2\sigma a^2}\right)}$$
$$= \frac{2\pi\eta L^2}{k_B T \ln\left(\frac{2\pi\kappa}{f_L a}\right)} \qquad (7)$$

The variation of τ with σ follows from $\tau \sim 1/D$. The relation $j = -D\partial c/\partial z \approx D\Delta c/L$ for the flux on a unit sheet per unit length per time must be combined with the tube circumference (the relevant unit length) to obtain the steady-state flux of proteins per second along the surface of a biological tether (in the quasi-equilibrium limit):

$$J = \frac{k_B T \Delta c}{4\eta L} \sqrt{\frac{\kappa}{2\sigma}} \ln\left(\frac{\kappa}{2\sigma a^2}\right)$$
$$= \frac{k_B T \Delta c}{2\eta L} \sqrt{\frac{\kappa}{2\sigma}} \ln\left(\frac{2\pi\kappa}{f_L a}\right) \qquad (8)$$

where Δc is the protein concentration difference between the ends of the cell membrane tether. In contrast to the transit time τ, the flux J depends on a power of σ. In practice, it is therefore relatively insensitive to the logarithmic variation of the particle mobility with σ.

Comparison with Experiment. For a typical membrane tether, we have $\kappa \approx 10^{-19}\ J$ [3,12,14] and $\sigma \approx 10^{-4}\ J\ m^{-2}$,[3,12,14,55] such that $r \approx 20$ nm and $f_L \sim 10 - 100$ pN. Typical membrane tether lengths might be a few microns, while a typical plasma membrane has a viscosity of $\eta \approx 5 \times 10^{-9}\ J\ m^{-2}\ s$.[56,57] A typical protein has $a \approx 5$ nm, such that $2\pi r/a \gg 1$ is satisfied, validating the approximate theoretical approach used in this work, as outlined above. Inserting the appropriate values into eq 5, we find $D \approx 10^{-13}\ m^2\ s^{-1}$ for proteins diffusing on a membrane tether, which is experimentally reasonable.[14,15,59−61] Additionally, by inserting the appropriate values into eq 7, we find that $\tau \sim 10^{-3} - 10^3$ s for $L \sim 10$ nm $- 10\ \mu$m, respectively. This is consistent

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with timescales for passive biological transport,[2,36−40] while transport via "active" motors is also known to exist.[14,15]

Furthermore, we can quantitatively calculate the effect of varying the membrane surface tension σ on the mobility of a surface protein diffusing along the length of a membrane tether. Biologically, membrane tethers may be expected with surface tensions in the range of $\sigma \approx 10^{-2} - 10^{-5}$ J m^{-2}.[3,14] Thus the highest surface tensions that membranes can support are on the order of 10^{-2} J m^{-2} and correspond to very small tether radii, where the approximation $r \gg a$ may be starting to break down. Conversely, we see from Figure 1 that, for the lowest tensions, on the order of 10^{-5} J m^{-2}, we have $D \sim 10^{-1}$ μm^2/s. While the precise value depends on the size of the diffusing particle (protein) and the membrane viscosity, we can say that the diffusion constants at these extreme tensions differ by an order of magnitude (see Figure 1). From a biological perspective, this is a rather large effect. Moreover, it follows that a similar order of magnitude variation also exists for the time τ taken for such a particle to diffuse along a membrane tether.

Conclusion

We have calculated the diffusion constant of a small protein diffusing on a cell membrane tether or tube, via consideration of its Stokes flow and low Reynolds number hydrodynamics.[49−52] An exact form for the protein diffusion constant was found to depend logarithmically on the membrane surface tension or the applied axial tether force. In this work, we have used the well-known method of the Stokeslet[49−53] in order to model the flow around a small protein by treating it as arising from a point force at the same location. This approach gives the leading order variation of the protein coefficient of friction and is insensitive to the shape of the protein when the protein is small compared to the size of the membrane, as will usually be satisfied under typical physiological conditions.[1,14,52]

Our work is significant in that it suggests and quantifies a way of probing the controversial logarithmic variation of the diffusion constant with a characteristic membrane size, here identically the tube radius. Furthermore, our work has biological significance, given the interest in tubular structures within and connections between cells. It is interesting to speculate whether there exists a regulatory relationship between membrane tension and the exchange of cellular information along long thin membrane tubes or tethers in living cells.

Note that we do not discuss bulk dissipation in this work.[2,47,61] Rather, we study surface friction alone in order to propose a new test of Saffman and Delbruck's original theoretical predictions.[1] Moreover, bulk dissipation should be small for tube radii smaller than $r_c = a\ \eta_{memb}/\eta_{solvent}$, where $a = 5$ nm is the membrane thickness, and the viscosity ratio is perhaps $\eta_{memb}/\eta_{solvent} = 100$.[47] This suggests that bulk dissipation can be neglected for surface tensions down to 10^{-7} N/m, as is appropriate to the work presented here.[47]

Furthermore, we would like to point out that our result has a rather unique quality. To understand this simply, note that Saffman and Delbruck[1] originally introduced a large length scale logarithmic cutoff length for convenience. There is no real "frame size" for typical planar membranes, whereas, in our study, the membrane tube radius is (identically) this relevant length. Moreover, we see the main impact of our paper being that it provides a tool for testing Saffman and Delbruck's original predictions,[1] rather than simply providing new theoretical results.

Also note that the next order correction for the diffusion constant beyond the leading order in r/a logarithmic terms is non-universal, depending on the shape of the protein and, for example, whether it matches the curved shape of the tube for all tube radii. We choose to ignore such non-dominant, finite-size shape effects in this work, as they add little in the context of our study and would also probably be of limited general interest.

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Appendix

Flat Membranes. Although the result for the diffusion constant of a protein (of size a) on a flat membrane (of large radius R) is well-known,[1,41−46] we briefly reproduce it here (in the limit $R/a \gg 1$) for the sake of completeness. For the flat membrane case, we find (using a Fourier representation of the Green function for convenience)

$$G(\Delta x)|_{\Delta x \to 0} = \frac{1}{2\pi}\int_0^\infty \frac{dq}{q}\,(J_0(qa) - J_0(qR)) = \frac{1}{2\pi}\ln(R/a) \quad (9)$$

such that, by using eq 3, the protein diffusion constant on a flat membrane is given by $D = k_BT/4\pi\eta\ \ln(R/a)$. Reassuringly, this result agrees with that found in the literature[1] (for zero tangential stress), in the same limit of interest, namely, $R/a \gg 1$. Using the identity $R^2 = 2D\tau$, valid for one-dimensional diffusion, and our result for the diffusion constant D, we can also find the time taken for a protein to diffuse across a patch of flat membrane of size R: $\tau = 2\pi\eta R^2/k_BT\ \ln(R/a)$.

Membrane Spheres. For completeness, we also consider protein diffusion on spherical biological membranes. The appropriate Green function on a sphere is well-known[54,58] and is given by

$$G(\theta,\phi;\theta',\phi') = -\frac{1}{4\pi}\ln(1 - \cos\theta\cos\theta' - \sin\theta\sin\theta'\cos(\phi - \phi')) \quad (10)$$

In the short-distance limit, valid for small proteins, we must have $\theta - \theta' \approx (\phi - \phi')\sin\theta \approx a/\rho$, where a is the size of the protein and ρ is the radius of the sphere. Using eq 3, we therefore find that the diffusion coefficient for a small protein on a large membrane sphere is given by $D = k_BT/4\pi\eta\ \ln(\rho/a)$, in the limit $\rho/a \gg 1$. Using the identity $\rho^2 = 2D\tau$, valid for one-dimensional diffusion, and our result for the diffusion constant D, we find the time taken for a protein to traverse a membrane sphere of radius ρ via diffusion to be $\tau = 2\pi\eta\rho^2/k_BT\ \ln(\rho/a)$ to leading order in a/ρ.

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