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Receptor-ligand diffusion-limited reaction rates on curved membranes

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ABSTRACT

We provide an expression for the diffusion-limited reaction rate on a curved surface, or membrane, in the perturbative deformation regime. This result is applied to the specific case of calculating the receptor-ligand association rate at membrane deforming, transmembrane receptor proteins, or inclusions. The dynamics of mechanochemical coupling between chemical activity and local membrane curvature is further investigated, and the effect of thermal membrane fluctuations is also discussed. It is found for transmembrane proteins, or inclusions, that their concomitant receptor-ligand reaction rates can be typically reduced by as much as 20% due to the effect of locally induced membrane curvature or geometry.

1. Introduction

Receptor-ligand reaction rates associated with membrane embedded molecules, such as transmembrane proteins or inclusions, are vital to many physiological processes required in order to preserve life, such as regulating ion transport, maintaining cellular adhesion, signal transduction, and chemoreception [1–3]. Moreover, it is thought that the rates of such biomolecular reactions on cell membranes are strongly dependent on diffusion-limited encounters [1–6].

Much previous work has been carried out on calculating receptor-ligand diffusion-limited reaction rates on two-dimensional, planar, non-curved, or flat surfaces or membranes [4–7,14,15,8,12,13,9–11,16–18]. In this work, we firstly provide an expression for the diffusion-limited reaction rate on a weakly curved, or non-planar, surface or membrane. Secondly, we apply our derived result to the biophysically relevant and important specific case of the association rate between surface diffusing ligands and a membrane deforming receptor protein, or transmembrane inclusion. As a consequence, for receptor-ligand systems, we are naturally led to further investigate potential dynamical aspects of the mechanochemical coupling between chemical activity and locally induced membrane curvature. We also briefly discuss how chemical activity on membranes is affected by thermal membrane fluctuations.

The simplified physical setup we wish to describe is sketched in Fig. 1. Consider dividing up the entire cell membrane (with an average inclusion density $\overline{\rho}_{\mathrm{inc}}$) into many, smaller, lipid bilayer area 'patches'. Each membrane bilayer area patch contains (on average) a single, large, membrane bound receptor or inclusion (as depicted in Fig. 1.), of radius a. The membrane embedded receptor protein induces a local curvature in the membrane, characterised by the deformation angle β at the location of the inclusion. The numerous randomly distributed, and smaller, membrane bound ligands (with an average ligand density $\overline{\rho}_{\mathrm{lig}}$) diffuse along the membrane, and ultimately react with the receptor protein at a β dependent reaction rate k. Note, when $\beta = 0$, the membrane remains globally flat, and the receptor-ligand reaction rate reverts to its flat membrane value, k_0.

We should mention that, due to the essentially two-dimensional nature of the problem, rather subtle issues are already well known to arise in the context of consistently defining a steady-state reaction rate on a planar surface or flat membrane [7–11]. Such theoretical issues, however, can be straightforwardly ameliorated by several methods, including taking into account adsorption and desorption of diffusing molecules from the bulk [5,6,12,13], incorporating activated processes [5,6], or by utilising a 'closed cell', or mean-field, type approach as considered in [14–18]. Whichever method is used moreover, as is commonly found in two-dimensional settings, in the physically relevant limit one inevitably comes across the presence of logarithmic terms involving an effective long-distance cut-off, r_{max}. As we shall see below, by using for example the 'closed cell', or mean-field, type approach of [14–18], we are able to provide a corresponding, and physically well motivated, value for r_{max} in the work presented here.

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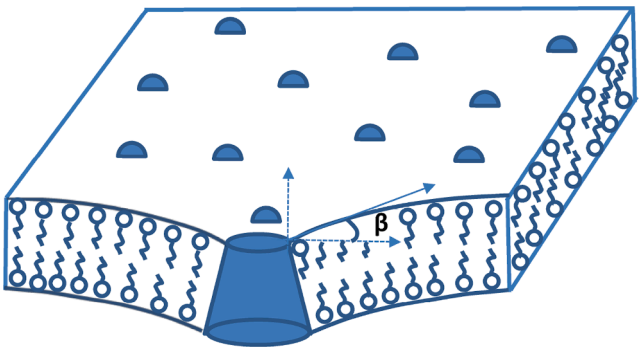

Fig. 1. Sketch of a cross-section through a lipid membrane bilayer patch. The large membrane bound receptor or inclusion (shown as a truncated cone) induces a local curvature in the membrane, characterised by the deformation angle β at the location of the receptor. The smaller membrane bound ligands (shown as randomly distributed hemispheres) diffuse along the membrane and ultimately react with the receptor protein at a β dependent reaction rate k.

2. Methods

2.1. Diffusion limited reactions on curved surfaces

We firstly concentrate on a single receptor centered at the origin of our membrane coordinates. Due to the intrinsically curved nature of the surfaces considered in this work, we are unavoidably and inevitably led to using the mathematical apparatus of differential geometry, and associated metric tensors (see e.g. [19] for further mathematical details). For ease of use, we choose to express membrane curvature in terms of the radially symmetric Monge representation (see e.g. [19–22] for more details), where the membrane shape is given perturbatively via a height function $h(r)$, in terms of the radial coordinate, or distance from the inclusion centre, r. Using conventional notation [19,21], and using for shorthand $h'(r) = \frac{\partial h(r)}{\partial r}$, the required metric components become: $g_{rr} = 1 + h'^2$ and $g_{\phi\phi} = r^2$ such that $\sqrt{g} = r(1+h'^2)^{1/2}$. The proper distance along the curved membrane is as usual given by $ds^2 = g_{rr}\,dr^2 + g_{\phi\phi}\,d\phi^2$ [19,21]. Note that for a flat membrane, or surface, $h' = 0$.

As is customary, and for the sake of simplicity, we assume radial symmetry in what follows. The radially symmetric ligand diffusion equation [23,24], with ligand density $\rho_{\text{lig}}(r)$, intrinsic surface diffusion constant D and metric tensor g [19–21], on a general curved surface, or membrane, is written as:

$$\frac{\partial \rho_{\text{lig}}}{\partial t} = \frac{D}{r\sqrt{1+h'^2(r)}}\frac{\partial}{\partial r}\left(\frac{r}{\sqrt{1+h'^2(r)}}\frac{\partial \rho_{\text{lig}}}{\partial r}\right) \tag{1}$$

where we tacitly assume, for simplicity, that our (much smaller, and hence quicker) diffusing ligands do not appreciably alter the local membrane curvature, but rather simply propagate on a given, fixed, background surface geometry as prescribed by the presence of a (much larger, and relatively immobile) membrane deforming embedded receptor protein, or transmembrane inclusion.

For the calculation of the steady-state, diffusion-limited reaction rate, we require the time independent, radially symmetric ligand density, $\rho_{\text{lig}}(r)$, which satisfies by simplifying Eq. (1) [4–7,14,15,8,12,13,9–11,16–18], via the use of a constant α:

$$\frac{r}{\sqrt{1+h'^2(r)}}\frac{\partial \rho_{\text{lig}}(r)}{\partial r} = \alpha \tag{2}$$

Integrating Eq. (2) from the minimum allowed distance a (given by the radius of the receptor), to the maximum allowed distance $r_{\max}$ (mentioned above), we get:

$$\overline{\rho}_{\text{lig}} = \alpha\int_a^{r_{\max}}\frac{dr}{r}\sqrt{1+h'^2(r)} \tag{3}$$

Note that in writing Eq. (3), we have utilised the following boundary conditions: $\rho(r_{\max}) = \overline{\rho}_{\text{lig}}$ (corresponding to a constantly maintained average ligand density reservoir), and $\rho(a) = 0$ (a perfectly absorbing receptor). The diffusion limited reaction rate k can then be shown to be given by the diffusive flux at a, such that [4–7,14,15,8,12,13,9–11,16–18]:

$$k = 2\pi D\alpha = 2\pi D\overline{\rho}_{\text{lig}}\Big/\int_a^{r_{\max}}\frac{dr}{r}\sqrt{1+h'^2(r)} \tag{4}$$

Evaluating the integral in Eq. (4) perturbatively in $h(r)$, we finally obtain the contribution Δk to the reaction rate due to locally induced curvature, of:

$$\Delta k/k_0 = -\frac{1}{\ln\left(r_{\max}^2/a^2\right)}\int_a^{r_{\max}}\frac{dr}{r}h'^2(r) \tag{5}$$

where we have defined for convenience: $\Delta k/k_0 = (k-k_0)/k_0$. Note that k_0, straightforwardly given by $k_0 = 4\pi D\overline{\rho}_{\text{lig}}/\ln\left(r_{\max}^2/a^2\right)$, corresponds to the well known flat surface reaction rate, in the absence of any membrane curvature [4–7,14,15,8,12,13,9–11,16–18].

Eq. (5) represents the main result of this paper for the diffusion-limited reaction rate on a curved surface, or membrane, in the perturbative deformation regime.

3. Results

3.1. Receptor-ligand reaction rate at a membrane bound inclusion

In order to describe the required membrane profile, we use the following well known Hamiltonian H of membrane elasticity [20,21]:

$$H = \frac{1}{2}\int 2\pi r dr\left(\kappa\left(\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial}{\partial r}h(r)\right)\right)^2 + \sigma\left(\frac{\partial}{\partial r}h(r)\right)^2\right) \tag{6}$$

which contains surface tension (σ), and rigidity (κ) controlled terms. The membrane shape [20,21] is again written in the Monge representation, via a radially symmetric height function $h(r)$.

A transmembrane receptor, or membrane bound inclusion, of size a typically constrains the shape $h(r)$ of the membrane at the inclusion, such that the membrane gradient $h'(r)$ at a becomes: $h'(a) = \left.\frac{\partial h(r)}{\partial r}\right|_{r=a} = \beta$. Minimising H in Eq. (6) w.r.t $h(r)$, subject to this boundary condition, it can be straightforwardly shown (see e.g. [22] for further details) that the radially symmetric membrane shape is given in terms of a modified Bessel function by: $h(r) = -\beta r_0 K_0(r/r_0)/K_1(a/r_0)$, where $r_0 = \sqrt{\kappa/\sigma}$. Using this membrane characteristic length scale, r_0, we can see that for distances far from the locally curvature inducing inclusion, or transmembrane receptor protein (such that $r \gg r_0$), the membrane becomes essentially flat.

Inserting this derived expression for $h(r)$ into Eq. (5), and carrying out the required integral we have:

$$\Delta k/k_0 = -\frac{\beta^2}{2\ln(1/\pi\overline{\rho}_{\text{inc}}a^2)} \tag{7}$$

where we have taken the physically meaningful limits $a^2/r_0^2 \ll 1$ and $a^2/r_{\max}^2 \ll 1$.

Additionally, in writing Eq. (7), we have replaced the rather *ad hoc, long-distance cut-off* $r_{\max}$ *by taking into account the more physically motivated scenario of a system of many receptors distributed randomly over the cell membrane surface. This can be accomplished via the 'closed cell', or*

mean-field type, boundary condition [14–18]: $\pi\overline{\rho}_{\rm inc}r_{\rm max}^2=1$. Thus, additionally, k_0 now becomes: $k_0=4\pi D\overline{\rho}_{\rm lig}/\ln\left(1/\pi\overline{\rho}_{\rm inc}a^2\right)$, where $\overline{\rho}_{\rm inc}$ is the average inclusion, or receptor, density over the entire cell membrane surface, and $\overline{\rho}_{\rm lig}$ is the analogous average ligand density. In this way, as is typical of mean-field type approximations, a system of many receptors can be reduced to an effectively single receptor problem, and we treat the effect of all the other receptors by providing an average density, $\overline{\rho}_{\rm inc}$, over the entire membrane surface [5,6]. Moreover, we consistently assume that $r_0/r_{\rm max}$ is sufficiently small that the mean-field, or single effective membrane inclusion approximation considered here remains valid, with negligible curvature overlap between neighbouring regions associated with individual transmembrane receptors.

3.2. Mechanochemical feedback mechanism

Eq. (7) above demonstrates the effect of a curvature inducing receptor protein, or membrane deforming inclusion, via the shape β, on the receptor-ligand diffusion-limited reaction rate k. Moreover, the binding of ligands to a receptor typically induces a conformational change in the receptor [25–28]. We are thus naturally led to further ask what effect the reaction rate could have back on the membrane shape. It is known [25–28] that analogous mechanochemical coupling processes are required for regulation of cell signalling, mechanosensitive channels, and in order for cells to sense their environment.

Assuming, for simplicity, that the membrane receptor, or inclusion, shape, β, depends on the number of attached ligands present, N, via $\beta\sim N$, we can then see that $\frac{\partial\beta}{\partial t}\sim\frac{\partial N}{\partial t}$, which goes as $\sim k$. Introducing a constant of proportionality, μ, which determines the strength of mechanocoupling present, we are thus led to write:

$$\frac{\partial\beta}{\partial t}=\mu k=\mu k_0\left(1-\frac{\beta^2}{2\ln(1/\pi\overline{\rho}_{\rm inc}a^2)}\right) \tag{8}$$

Solving Eq. (8) perturbatively in β gives:

$$\beta(t)=\mu k_0 t\left(1-\frac{(\mu k_0 t)^2}{6\ln(1/\pi\overline{\rho}_{\rm inc}a^2)}\right) \tag{9}$$

From Eq. (9) we can observe that the effect of an existing feedback mechanism on the receptor, or inclusion, shape via the diffusion limited reaction rate of binding to ligands, leads to a telltale, or signature, deviation of the growth of $\beta(t)$ from the purely linear behaviour expected where such a feedback mechanism is absent. Naturally, the analysis presented here assumes that the rate of change of membrane inclusion shape occurs on time scales much slower than the time necessary for the diffusing species, or ligands, to produce a steady-state reaction rate. Such a negative feedback mechanism driven by a diffusive flux, as quantified in this work, could potentially be important for describing the regulation of chemical processes via local membrane geometry or curvature in real cells.

3.3. Estimate of the effect of membrane fluctuations on reaction rates

Using our main result given above by Eq. (5), we can additionally approximately estimate the possible role of thermal membrane fluctuations on the receptor-ligand association rate, in the case of transmembrane inclusions which do *not* deform the membrane (i.e. $\beta=0$). The purely fluctuating membrane gradient correlation function, $\langle h'^2(r)\rangle$, can be estimated from the Hamiltonian of Eq. (6) straightforwardly via the use of a wavevector q Fourier Transform as (see e.g. [22,21] for more calculational details):

$$\left\langle h'^2(r)\right\rangle\approx\int\frac{qdq}{2\pi}\frac{1}{\kappa q^2+\sigma} \tag{10}$$

Carrying out the Fourier wavevector integral over q in Eq. (10), we can obtain $\langle h'^2(r)\rangle$ as:

$$\left\langle h'^2(r)\right\rangle\approx\frac{1}{8\pi\kappa}\ln(\sigma_{\rm max}/\sigma) \tag{11}$$

where $\sigma_{\rm max}=\kappa q_{\rm max}^2$, and $q_{\rm max}$ is the wavevector associated with the shortest wavelength membrane undulation that can plausibly be modelled by the membrane Hamiltonian. Note that due to translation invariance, $\langle h'^2(r)\rangle$ does not depend on the radial position r, as expected, and therefore the integral required in Eq. (5) can be trivially carried out to give:

$$\Delta k/k_0\approx-\frac{1}{16\pi\kappa}\ln(\sigma_{\rm max}/\sigma) \tag{12}$$

which now depends logarithmically on the membrane tension σ, with k_0 as given above, and typically we have $\sigma_{\rm max}/\sigma\gg1$. Note that we tacitly assume that the membrane fluctuations estimated here occur on timescales much faster than the typical timescales required for ligand diffusion.

4. Discussion

We have theoretically demonstrated in this work how receptor-ligand chemical activity on surfaces, or membranes, explicitly depends on membrane induced local geometry or curvature (in the perturbative regime). Moreover, we have shown quantitatively how geometric or curvature properties of typical biological membranes affect local concentration gradients, and hence regulate biomolecular reaction rates.

By firstly deriving the diffusion-limited reaction rate for a weakly curved, or non-planar, surface, we can proceed to apply this result in the specific context of membrane bound ligands associating with a locally curvature inducing, transmembrane receptor or inclusion. The additional influence of purely thermal membrane fluctuations on membrane bound receptor-ligand chemical activity is also briefly explored.

Arising out of this work, we further describe the effect of diffusion-limited receptor-ligand reaction rates on the rate of growth of locally induced membrane curvature. The subtle interplay between receptor shape, membrane curvature, and ligand binding rate, via a negative feedback loop as outlined in this work, may represent a potentially important example of the known mechanochemical coupling between chemical activity and local membrane geometry present in real cells.

For typical membrane inclusions [1–3,5,17,18,29–34] we have: $a\approx5{\rm nm}$,$\overline{\rho}_{\rm inc}\approx1-10^3\mu{\rm m}^{-2}$. In order for the perturbative regime considered in this work to remain valid, we must have for the deformation angle: $\beta\lesssim1$. These physiologically relevant values give a contribution to the diffusion limited reaction rate of: $|\Delta k|/k_0\sim5-20\,\%$; which potentially represents a substantial effect.

Correspondingly, for thermal membrane fluctuations [2,21,35], we typically have a value of $\sigma_{\rm max}\approx1{\rm Jm}^{-2}$. Assuming the physiologically relevant values of $\sigma\approx10^{-5}{\rm Jm}^{-2}$, and $\kappa\approx20{\rm k_BT}$, we get a contribution to $|\Delta k|/k_0\sim$ of a few %. Despite this seemingly insubstantial effect due to membrane fluctuations, we should mention that analogous few % changes with varying membrane tension, albeit in membrane area, are routinely observed experimentally [36,37].

Given the work presented here, further applications to additional membrane geometries of interest should prove straightforward. It would also be particularly interesting to see if the particular mechanochemical coupling effect described here could be measured experimentally in the near future by possibly utilising artificial, reconstituted, or *in vitro protein-membrane systems.*

We only consider here a perfectly absorbing boundary condition for the diffusing species at the membrane bound inclusion. The extension of the results obtained in this work to the interesting, and potentially biologically important, case of a radiation type boundary condition at the membrane receptor, will be addressed in an additional future

publication.

The impact of ligand shape/size, electrostatics, van der Waals interactions, and binding site local curvature on the receptor-ligand association rate represent potentially important and subtle effects which would require careful additional consideration, in various explicit and specific biochemical contexts. The detailed inclusion of such additional considerations is well beyond the scope of this letter, which we plan to address in future, lengthier, publications.

Some related differential geometry-based approaches for biomolecular systems, that offer somewhat different perspectives, can be found in the work of [38,39]. Naturally, the full nonperturbative regime (for the membrane shape and diffusion equations) can clearly only be accessed numerically. Such detailed nonperturbative considerations will be left to future work.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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