Spatial curvature effects on molecular transport by diffusion

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For a substance diffusing on a curved surface, we obtain an explicit relation valid for very small values of the time, between the local concentration, the diffusion coefficient, the intrinsic spatial curvature, and the time. We recover the known solution of Fick's law of diffusion in the flat space limit. In the biological context, this result would be useful in understanding the variations in the diffusion rates of integral proteins and other molecules on membranes.

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I. INTRODUCTION

Transport of enzymes, charged ions, and metabolic substances within biological cells and tissues and across cell membranes is one of the major processes which sustains and guides life. Indeed, extracellular and intracellular transport of substances can well be considered to be the most important and pervasive among all the life-supporting biological activities.

Molecular transport across cell membranes by passive diffusion or in accordance with Fick's law is a well-studied area. However in the available literature on the subject, no mention has been made of how the local curvature of the cell plays a part, if at all, in this process. Molecules released at a specific location on the cell surface or on the nuclear membrane diffuse along the curved membrane surface to another location.

It is known that thermal agitation permits lateral diffusion of phospholipid and glycolipid molecules within a leaflet of planar phospholipid bilayers of biological membranes. A lipid molecule can diffuse several micrometers per second at a temperature of 37°C. It has also been established experimentally that many important proteins freely float within the plane of the membrane.

Measurements have shown that the rates of diffusion of proteins in biomembranes are considerably lower than those seen in artificial membranes [1,2]. The physical structure and the dynamical changes occurring on a membrane surface would well be expected to play an important role in determining the lateral mobility of molecules on its surface.

The metabolism and synthesis of fatty acids and phospholipids occur in the smooth endoplasmic reticulum, and the rough endoplasmic reticulum is a site of protein synthesis. It is well known that in many cells these extensively curved and folded membrane vesicles are continuous with the nuclear and cell membranes. In the cytosol also, these folds distort the homogeneity in the spatial distribution of the cytosolic fluid. Transport of a substance by diffusion should therefore be described by a corrected form of Fick's law, modified to take into account the local curvature of the surface through which it moves. In this paper we discuss how to take care of curvature effects and also give for transient phenomena, an explicit expression relating the concentration of the diffusing substance, the intrinsic spatial curvature experienced by it, the diffusion coefficient and the time.

II. DIFFUSION ON CURVED SURFACES

Consider diffusion of a substance described by its concentration $C(x,t)$ from a spatial point x where it has been released on the cell, to another point x'. For a particular time slice, the line element ds between each pair of neighboring points on the spatial surface is given by

$$ds^2=\sum_{i,j=1}^{n} g_{ij}(x)dx^i dx^j, \tag{1}$$

where dx^k denote the coordinate differences between neighboring points, n is the spatial dimension, and g_{ij} denotes the metric. We choose to work with a Riemannian signature for the metric.

The usual form of Fick's law relates the current density or the flux of material per unit area, $j(x,t)$ to its concentration gradient in flat space,

$$j_i(x,t)=-D\partial_i C(x,t), \tag{2}$$

where D denotes the diffusion coefficient, ∂_i denotes the gradient operator, and $C(x,t)$ is the field variable denoting the concentration. It is assumed here that the diffusion coefficient is independent of the concentration of the diffusing substance.

In curved space, while formulating the problem, one must incorporate the effects of the intrinsic spatial curvature of the surface on which the substance is diffusing. We make the simplifying assumption that in the infinitesimal neighborhood of any point, the diffusion properties are the same in all directions and that D does not depend upon the position and the concentration of the diffusing material.

Transport of the substance by diffusion into and out of the invariant volume element $\sqrt{g}d^n x$ surrounding the point x is given by the conservation equation,

$$[\partial C(x,t)]/\partial t=-\nabla_i j^i(x,t), \tag{3}$$

where ∇_i denotes the covariant derivative and includes the Christoffel connection $\Gamma^k{}_{il}$, $\nabla_i j^k=\partial_i j^k+\Gamma^k{}_{il}j^l$, and we have considered a *parametric* dependence of C on the time t.

Performing a covariant differentiation of Eq. (2) with respect to x, and substituting Eq. (3) into it we then obtain the correct form of Fick's second law of diffusion,

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$$[\partial C(x,t)]/\partial t = -D\Box C(x,t), \tag{4}$$

where we have used $\Box$ to denote the n-dimensional Laplace-Beltrami operator. For flat three-dimensional space, $\Box$ reduces to the usual three-dimensional Laplacian.

It was shown in Ref. [3] that at least in mitochondrial inner membranes, the diffusion coefficient D of intramembrane particles shows an inverse correlation with their concentration, implying that the proper form of Fick's law reflecting the concentration dependence of D should be studied, rather than Eq. (4). In our work, however, we consider only the simplest form of Fick's law with a concentration-independent diffusion coefficient, in order to see how far just the spatial curvature effects could modify the known result.

It becomes particularly interesting to learn about the configuration of the released substance during the initial infinitesimal time intervals to see how the intrinsic curvature of the cell would influence diffusive transport on the membrane surface, and hence its configuration at later times.

In order to solve Eq. (4), we rescale the time parameter by: $t \to Dt$, so that Eq. (4) now reads

$$[\partial C(x,t)]/\partial t = \Box C(x,t) - \eta C(x,t), \tag{5}$$

and the parameter t now has the dimensions of length squared. We have introduced a drag term ηC with $\eta > 0$ which can be thought to account for negative concentration changes due to possible frictional effects on the motion of the molecules. We have introduced it here just for the sake of mathematical convenience, and at the end of the calculations it can be set to zero.

In the actual physical situation, of course, the drag term is very much present, and receives contributions from the drag arising from the pericellular matrix viscosity, from steric effects, and from transient binding to relatively immobile structures [1]. Also in the actual situation, the η term is not constant and has a coupling with the concentration gradient. We have, however, restricted ourselves to $\eta = 0$ for the sake of simplicity in this paper.

We assume that the molecules diffuse freely on the surface without interacting or binding with any other molecules. We write Eq. (5) in a point-separated form as

$$[\partial C(x,x',t)]/\partial t = (\Box_x - \eta) C(x,x',t), \tag{6}$$

where the biscalar $C(x,x',t)$ is subject to the condition

$$\lim_{x' \to 0} C(x,x',t) = C(x,t) \tag{7}$$

and to the physical boundary condition

$$\lim_{t \to 0} C(x,x',t) = \delta(x,x'). \tag{8}$$

This enables us to obtain a well-defined explicit solution for $C(x,t)$ which is valid for small values of t, in terms of the spatial curvature. The solution to Eq. (6) is well known [4–6],

$$C(x,x',t) = \frac{1}{(4\pi t)^{n/2}} e^{-\eta t} e^{-\sigma(x,x')/2t} \Delta^{1/2}(x,x') \Omega(x,x',t), \tag{9}$$

where the biscalar $\sigma(x,x')$ equals half the square of the geodesic distance between x and x' and $\Delta(x,x')$ is the VanVleck–Morette determinant

$$\Delta(x,x') = -(g(x))^{-1/2} \det[-\partial_i \partial_{j'} \sigma(x,x')] (g(x'))^{-1/2}. \tag{10}$$

This is a biscalar quantity which reduces to unity in flat space.

In curved space, one can expand $\Delta(x,x')$ in a series expansion in powers of the curvature by working in Riemann normal coordinates y which define a locally inertial system in the neighborhood of the point x'. In these coordinates [7], with origin at x', $\Delta(x,x') = (g(x))^{-1/2}$, so that

$$\Delta^{1/2}(x,x') = (g(x))^{-1/4} = 1 + \tfrac{1}{12} R_{\alpha\beta} y^\alpha y^\beta + O(y^3), \tag{11}$$

where x is regarded as a function of the Riemann normal coordinates y, such that $x \to x'$ as $y \to 0$. In the coincidence limit, and for our purposes, it is only the first term on the right hand side of Eq. (11) which is relevant for the calculations.

The function $\Omega(x,x',t)$ has a series expansion in the coincidence limit $x' \to x$,

$$\lim_{x' \to x} \Omega(x,x',t) = \sum_{k=0}^{\infty} t^k E_k(x), \tag{12}$$

valid in the limit $t \to 0$, where $E_k(x)$ are known coefficients known in the literature as Gilkey coefficients [4–7]:

$$E_0 = I, \quad E_1 = \frac{R}{6} - \eta, \quad E_2 = \frac{1}{2}\left(\frac{R}{6} - \eta\right)^2 - \frac{1}{180} R_{\mu\nu} R^{\mu\nu} + \frac{1}{180} R_{\mu\nu\rho\sigma} R^{\mu\nu\rho\sigma} + \frac{1}{30} \Box R - \frac{1}{6} \Box \eta,$$

$$E_3 = \frac{1}{7!}[18\Box^2 R + 17 R_{;\mu} R^{;\mu} - 2 R_{\mu\nu;\rho} R^{\mu\nu;\rho} - 4 R_{\mu\nu;\rho} R^{\mu\rho;\nu} + 9 R_{\mu\nu\rho\sigma;\tau} R^{\mu\nu\rho\sigma;\tau} + 28 R \Box R - 8 R_{\mu\nu} \Box R^{\mu\nu}$$

$$+ 24 R_{\mu\nu} R^{\mu\rho;\nu}{}_{\rho} + 12 R_{\mu\nu\rho\sigma} \Box R^{\mu\nu\rho\sigma} + \tfrac{35}{9} R^3 - \tfrac{14}{3} R R_{\mu\nu} R^{\mu\nu} + \tfrac{14}{3} R R_{\mu\nu\rho\sigma} R^{\mu\nu\rho\sigma} - \tfrac{208}{9} R_{\mu\nu} R^{\mu}{}_{\rho} R^{\nu\rho}$$

$$+\tfrac{64}{3}R_{\mu\nu}R_{\rho\sigma}R^{\mu\rho\nu\sigma}-\tfrac{16}{3}R_{\mu\nu}R^{\mu}{}_{\rho\sigma\tau}R^{\nu\rho\sigma\tau}+\tfrac{44}{9}R_{\mu\nu\rho\sigma}R^{\mu\nu\alpha\beta}R^{\rho\sigma}{}_{\alpha\beta}+\tfrac{80}{9}R_{\mu\nu\rho\sigma}R^{\mu\alpha\rho\beta}R^{\nu\sigma}{}_{\alpha\beta}]$$

$$-\tfrac{1}{60}\Box^2\eta+\tfrac{1}{12}\eta\Box\eta+\tfrac{1}{12}(\Box\eta)\eta+\tfrac{1}{12}\eta_{;\mu}\eta^{;\mu}-\tfrac{1}{6}\eta^3-\tfrac{1}{36}R\Box\eta-\tfrac{1}{90}R^{\alpha\beta}\eta_{;\alpha\beta}-\tfrac{1}{30}R_{;\mu}\eta^{;\mu}+\tfrac{1}{12}\eta^2R$$

$$-\tfrac{1}{30}\eta R^2+\tfrac{1}{180}\eta R_{\mu\nu}R^{\mu\nu}-\tfrac{1}{180}\eta R_{\mu\nu\rho\sigma}R^{\mu\nu\rho\sigma}. \tag{13}$$

Here I denotes the identity matrix, R stands for the Ricci scalar, and the semicolon denotes a covariant differentiation. Although the fourth Gilkey coefficient has also been calculated in the literature, we have displayed above only terms up to third order in the Riemann curvature.

Now rescaling t back to Dt, we obtain the solution we seek for diffusion of molecules in the presence of a drag term in n spatial dimensions for transient times:

$$C(x,t)=\frac{1}{(4\pi Dt)^{n/2}}e^{-\eta Dt}e^{-\sigma(x,0)/2Dt}\Delta^{1/2}(x,0)\sum_{k=0}^{\infty}(Dt)^kE_k(x). \tag{14}$$

For the standard diffusion equation without the η term, and in flat space, the only Gilkey coefficient which contributes is E_0, and in this case we recover the known result

$$C(x,t)=1/[(4\pi Dt)^{n/2}]\,e^{-x^2/4Dt}. \tag{15}$$

In a recent paper [8], Gompper and Goos suggested that the diffusion of amphiphilic molecules within a monolayer at the oil-water interface of the microemulsion phase in an oil-water-amphiphile mixture can be used to measure the average Gaussian curvature of the monolayer. They considered surfaces of constant curvature. Result (14), discussed here for the concentration, is also valid for surfaces of varying curvature.

In fact, from Eq. (14) it is an easy matter to obtain a general solution to the diffusion equation for n-dimensional spaces with arbitrary constant curvature K for which the value of the Riemann curvature depends neither on the coordinate x nor on the planar direction at x. For such spaces, the Riemann curvature is given in terms of their metric g_{ij} by

$$R_{ijkl}=K(g_{ik}g_{jl}-g_{il}g_{jk}) \quad (\text{for} \quad n\geqslant 3), \tag{16}$$

from which the Gilkey coefficients turn out to be

$$E_0=1,$$

$$E_1=\frac{n(n-1)}{6}K, \quad E_2=\frac{n(n-1)(3n+1)}{360}K^2, \tag{17}$$

$$E_3=\frac{n(n-1)}{9\times 7!}\{7(n-1)^3(5n-1)+61(n-1)^2+68n+28\}K^3.$$

We then find that expression (14) for the concentration of the diffusing substance has the following dependance on the Gaussian curvature K:

$$C(x,t)=\frac{1}{(4\pi Dt)^{n/2}}e^{-x^2/4Dt}\times\left(1+\frac{n(n-1)}{6}KDt+\frac{n(n-1)(3n+1)}{360}(KDt)^2+\frac{n(n-1)}{9\times 7!}[7(n-1)^3(5n-1)+61(n-1)^2+68n+28](KDt)^3+\cdots\right). \tag{18}$$

$K>0$ corresponds to the spherical surfaces, while surfaces with $K<0$ correspond to hyperboloid ones—$K=0$ are flat Euclidean surfaces.

It is shown in Ref. [8] that the structure of a microemulsion can be quantified in terms of a quantity which depends upon the Euler characteristic χ_E of the surface within which the amphiphile molecules diffuse. χ_E is obtained from the Gaussian curvature using the Gauss-Bonnet theorem

$$\int dSK=2\pi\chi_E, \tag{19}$$

where the integral is over a closed surface S. It should therefore be possible, in the case of surfaces of approximately constant area, to express result (18) in terms of the topological invariants characterizing them, after appropriately scaling them. However, this exercise is beyond the scope of this paper. Because of their enormous complexity, biological cells and membranes do not in general have isotropic and homogeneous compositions, and the membrane surfaces are more often than not of varying curvature; in these situations, one needs to use Eqs. (13) and (14) rather than Eq. (18).

For the specific case of diffusion in two dimensions such as on membranes, the coefficients in Eq. (13) simplify considerably because in these dimensions both the Riemann tensor R_{ijkl} and the Ricci curvature scalar R have only one component, and both the Riemann tensor and the Ricci tensor R_{ij} can be expressed in terms of the curvature scalar R:

$$R_{ijkl}=\tfrac{1}{2}R(g_{ik}g_{jl}-g_{il}g_{jk}) \tag{20}$$

and

$$R_{ij}=\tfrac{1}{2}Rg_{ij}. \tag{21}$$

It must be borne in mind that in our treatment, we have regarded time as a *parameter* and the indices $i,j,k,l,\mu,\nu,\alpha,\beta$, etc. label spatial dimensions only, for we are working on a particular time slice at each instant of time.

We consider the simplest example of diffusion of a substance on the surface of a sphere of constant radius r. For a 2

sphere, the Ricci curvature scalar is

$$R=\frac{2}{r^2}.$$

In fact, in this case, the Gaussian curvature $K=1/r^2$. Substituting this value of R into Eqs. (13), (20), and (21), or by simply using Eq. (17), the Gilkey coefficients reduce for this example to

$$E_0=1, \quad E_1=\frac{1}{3r^2}, \quad E_2=\frac{1}{15r^4}, \quad E_3=\frac{4}{315r^6}, \quad (22)$$

giving the following result for the concentration of the diffusing substance of an initial unit amount, at a point distant x from the point of its release on the surface of the sphere, at a time t:

$$C(x,t)=\frac{1}{(4\pi Dt)}e^{-x^2/4Dt}\left[1+\frac{Dt}{3r^2}+\frac{1}{15}\left(\frac{Dt}{r^2}\right)^2 +\frac{4}{315}\left(\frac{Dt}{r^2}\right)^3+\cdots\right]. \quad (23)$$

The result obtained in Ref. [8] for the mean square displacement of a particle diffusing on a sphere is essentially equivalent to the leading and next to leading order terms in Eq. (23).

In the series expansion in Eqs. (14), (18), and (23), valid for very small t values, it is assumed that the curvature terms are small in comparison with the flat space result. Care must be taken before applying the actual values of t, D, and r to these expressions to ensure that this assumption is satisfied.

For a substance having a D value of 10^{-6} $\mathrm{cm^2\,s^{-1}}$ released on the surface of a spherical cell of radius 1 μm, diffusing through a distance of 0.5 μm in time 1 ms, one obtains a calculated value of 4259.4751×10^4 per $\mathrm{cm^2}$ for its concentration, using the usual expression [Eq. (15)] for flat space diffusion, while the improved solution [Eq. (23)] gives an additional correction of 0.034 per $\mathrm{cm^2}$ to this—a difference of 3.4% from the flat space result, and a deviation of 0.33% from the flat space results for a time duration of 10^{-4} s, while for a D value of 10^{-7} $\mathrm{cm^2\,s^{-1}}$, the deviations from the flat space result for time durations of 1 and 0.1 ms are 0.33% and 0.033% respectively.

The experimentally measured values of the concentrations, of course, correspond to the corrected values and the curvature-corrected Fick's law [Eq. (14)], since the diffusing molecules have already traversed over the curved surface of the cell. However, it must be borne in mind that the diffusion times measured and calculated, in fact, calibrate distances different from the flat space distances, when one makes a comparison between diffusion rates on different cells and on membranes whose curvatures differ from point to point and from one another. What we intend to point out here is that one must remember that flat space methods must not be applied when one is talking about biological membranes and surfaces which are very curved, or even for surfaces with varying curvature, for which one must apply the coefficients in Eq. (13). We have not included realistic effects such as drag terms arising from the viscosity of the cytosolic fluid, and we have considered also only lateral (two-dimensional) diffusion in this work.

It is seen that curvature effects considerably modify the solution of the diffusion problem. In a biological context, it is well known that depending upon the cell type, between 30% and 90% of all integral proteins in the plasma membrane are freely mobile, and, among these, the lateral diffusion rate of a protein in an intact membrane is around 10–30 times lower than that of the same protein embedded in synthetic liposomes [1,2,9]. It has been suggested that this could be because the mobility of the proteins might be hampered by interactions with the rigid submembrane cytoskeleton.

In arriving at those diffusion rates, these authors considered only the normal form of Fick's law for flat space. Use of the correct form of Fick's law, taking into account the varying curvatures of the membranes on which the protein molecules diffuse, must be made when seeking to explain such theories.

III. DISCUSSION

We have shown how the curvature of the surface through which molecules diffuse modify the usual form of Fick's law, and the relation between the concentration of the diffusing molecules, the diffusion constant and the time. Many intramembrane particles are electrically charged, and, when they are subjected to an external electric field, move from their original random distribution to a more ordered distribution. It would be interesting to see the effect of external electromagnetic fields on molecules which are electrically charged, diffusing on curved surfaces.

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