Fractal scaling mechanisms in biomembranes

Oscillations in the lateral diffusion coefficient

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Abstract. A modified model of the Cohen-Turnbull free volume theory for lateral transport processes in biomembranes is presented. The model which is based on renormalization group theoretical concepts incorporates fractal rather than Markovian diffusion kinetics. It predicts harmonic oscillations in the lateral diffusion coefficient around a dominant power-law trend and clarifies, in addition, recently observed deviations from the Cohen-Turnbull exponential law.

Key words: Lipid-protein interactions, renormalization, Lévy distributions

I. Introduction

In recent years much interest has been focussed on the problem of molecular mobility in cell membranes. Detailed experiments now make it possible to test various theoretical models for the lateral diffusion coefficient of lipids or proteins in biological membranes. Lateral diffusion processes have been measured principally by two different experimental methods. The first method is fluorescence photo-bleaching recovery, and the second method is based on the excimer formation technique.

Theoretical models for lateral diffusion mechanisms of lipids in monolayer or bilayer systems are well described by hopping processes based on the Cohen-Turnbull free volume theory, which assumes that diffusion takes place in three steps (i) creation of a hole in the solvent by lateral density fluctuations, (ii) a molecule jumps into this hole, and (iii) the resulting void is filled by solvent molecules.

Cohen and Turnbull (1959) quantitatively considered the effect of free volume on diffusion in hard-sphere fluids. Other investigators (MacCarthy and Kozak 1982; O'Leary 1987) applied the Cohen-Turnbull idea in order to study the relationship of the lateral diffusion coefficient D to the free area a_F in a two-dimensional hard-disk fluid. The result of such a theory is an exponential dependence of the average diffusion coefficient $\langle D \rangle$ on $1/a_F$ given by

$$\langle D \rangle = D(r^*) \exp(-\gamma\, a_{\mathrm{HC}}/a_F), \tag{1}$$

where $a_{\mathrm{HC}} = \pi r^{*2}$ is the hard-core area of the diffusing molecule, r^* its hard-core radius, γ is a constant introduced by Cohen and Turnbull to compensate for the overlap of free volumen (or free area) and the pre-exponential factor $D(r^*)$ depends, in general, on temperature T, viscosity η etc. It is not within the scope of our current considerations to determine some functional forms for $D(r^*)$. We only mention that Vaz et al. (1984) discussed this problem recently. For our purpose it is sufficient to use the knowledge that $D(r^*)$ does not depend on the variable a_F but solely on system parameters like T and η, and on the hard-disk radius r^*. It has the status of a parameter in the Cohen-Turnbull theory.

An adaptation of the Cohen-Turnbull (CT) law (1) by Galla et al. (1979) is capable of fitting their experimental data. More recently, Peters and Beck (1983) demonstrated the range of validity of the CT-theory for dilauroylphosphatidylcholine monolayers by measuring the average lateral diffusion coefficient $\langle D \rangle$ as a function of $1/a_F$. The dependence of $\langle D \rangle$ on the free area a_F can be tested by assessing the linearity of a log $\langle D \rangle$ vs $1/a_F$ plot at constant temperature. The CT-theory predicts – according to Eq. (1) – a straight line in such a plot (Fig. 1)

$$\ln\left(\frac{\langle D \rangle}{D(r^*)}\right) = -\gamma\, a_{\mathrm{HC}}/a_F := \xi^*. \tag{2}$$

The best fit of the experimental data obtained by Peters and Beck (1983) is based on the parameter choices: $D(r^*) = 124\ \mu\mathrm{m}^2/\mathrm{s}$ and $\gamma\, a_{\mathrm{HC}} = 26.0\ \text{Å}^2$. However, significant deviations from the linear relation (2) are observed for large values of a_F. In Fig. 1 we have replotted the Peters and Beck data on a dimensionless scale.
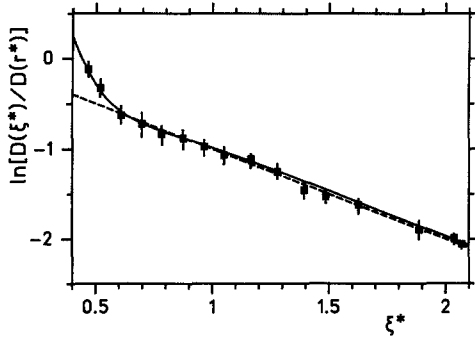
Fig. 1. A log-linear-plot shows deviations of the Cohen-Turnbull theory (*dashed straight line*) from experimental data (*squares*) for large a_F-values. Full curve represents the result of this study for the lateral diffusion coefficient. $\xi^* = \gamma\, a_{HC}/a_F$, parameters are taken from Peters and Beck (1983): $D(r^*) = 124\ \mu m^2/s$ and $\gamma\, a_{HC} = 26\ \text{Å}^2$

In a very recent investigation, O'Leary (1987) argued that these deviations are purely based on an improper normalization of the probability $P(r)$ for the hole formation in the CT-theory. In this paper, however, we will show that (i) the Cohen-Turnbull normalization is correct within the context of probability theory, and (ii) we propose a mechanism which not only clarifies the observed deviations from the Cohen-Turnbull law but which, in addition, predicts fractal scaling oscillations around a power-law trend of the average lateral diffusion coefficient.

II. Cohen-Turnbull theory for lateral protein diffusion

If the membrane contains proteins or domains of gel-phase lipid, diffusion will be obstructed, and as a consequence the (resultant) effective diffusion coefficient will be reduced. This effect has been incorporated into the CT-Theory very recently by O'Leary (1987). He started out with the probability distribution function $P(r)$ for hole formation in the solvent system

$$P(r) = \exp(-W(r)/kT), \tag{3}$$

where $W(r)$ is the work required to create a hole of radius r in the solvent, k is Boltzmann's constant and T is temperature. Then, in the spirit of scaled-particle theory, $W(r)$, with $r \geq 0$, is expanded into a Taylor series around $r = 0$ with the result (O'Leary 1987)

$$\frac{W(r)}{kT} = -\ln\left(1 - \sum_i \pi \varrho_i r_i^2\right) + \frac{2\pi \sum_i \varrho_i \bar{\gamma}_i r_i r}{1 - \pi \sum_i \varrho_i r_i^2} + 0(r^2) \tag{4}$$

leading to

$$P(r) = A\,\exp(-\beta r),\ r \geq 0. \tag{5}$$

Here, the following short-hand notations have been introduced:

$$A = 1 - \pi \sum_i \varrho_i r_i^2, \quad \beta = (\pi/A) \sum_i \varrho_i \gamma_i r_i, \quad \gamma_i = 2\bar{\gamma}_i, \tag{6}$$

Where ϱ_i is the number density of species i, r_i its radius, and γ_i are semiempirical constants (O'Leary 1987).

In addition, we have neglected (as done by O'Leary and others) the term of order r^2 indicated as $O(r^2)$ in Eq.(4), since this term is proportional to r^2 times the lipid lateral-spreading pressure, which is zero, because the pressure of the membrane is balanced by an equal external pressure (O'Leary 1987).

With the probability distribution $P(r)$ one can define (and calculate) average values. So, for instance, the average value for the lateral diffusion coefficient $D(r)$ is given by (Cohen and Turnbull 1959)

$$\langle D(r) \rangle := \int_0^\infty D(r)\, P(r)\, dr / \int_0^\infty P(r)\, dr.$$

Taking the normalized probability distribution

$$g(r) = \frac{\beta}{A}\, P(r) = \beta\, e^{-\beta r}, \quad \int_0^\infty g(r)\, dr = 1 \tag{7}$$

having moments

$$\langle r^n \rangle = \int_0^\infty r^n\, g(r)\, dr = n!\, \beta^{-n}, \tag{8}$$

where, particularly, the first moment is given by

$$\langle r \rangle = 1/\beta, \tag{9}$$

one can rewrite the average diffusion coefficient as

$$\langle D(r) \rangle = \int_0^\infty D(r)\, g(r)\, dr. \tag{10}$$

In the hard-area model, discussed here, diffusion can take place only if the "hole" created by fluctuations has a radius $r \geq r^*$, where r^* is the hard-core radius of the diffusing particle. For $r < r^*$ the hole created is not large enough to absorb a hard-core particle of radius r^* and diffusion cannot occur. This situation requires (Cohen and Turnbull 1959; O'Leary 1987)

$$D(r) = \begin{cases} D(r^*) & \text{for } r \geq r^* \\ 0 & \text{for } r < r^* \end{cases} \tag{11}$$

which, when inserted into (10), leads to

$$\langle D(r) \rangle = D(r^*) \int_{r^*}^\infty g(r)\, dr = D(r^*) \exp(-\beta r^*). \tag{12}$$

If there is only a single component

$$\varrho_i = \varrho = 1/a_L, \quad r_i = r^*, \quad \gamma_i = \gamma$$

one obtains

$$\beta r^* = \gamma \frac{a_{HC}}{a_F}, \qquad (13)$$

where $a_{HC} = \pi r^{*2}$ is the hard-core area of a lipid molecule of radius r^* and $a_F = a_L - a_{HC}$ is the free area per lipid molecule, and $a_L = 1/\varrho$ is the total area per lipid molecule. Inserting (13) into (12) we recover the conventional Cohen-Turnbull exponential law (1) for the average lateral diffusion coefficient as used by Galla et al. (1979) and by Peters and Beck (1983) for the interpretation of their experimental results.

Taking into account any number N of components $(i = 1, 2,..., N)$ Eq. (12) still holds and incorporates via β (as given in (6)) the effect of obstructed diffusion leading to a decrease in the average diffusion coefficient as discussed by O'Leary (1987), if the diffusing particles are proteins or other impurities with a radius much larger than that of a lipid molecule. O'Leary (1987) investigated this effect in two-component bilayers for various protein concentrations. His formula contains in comparison with our result, Eq. (12), besides $D(r^*)$ a second pre-exponential factor a_F/a_L due to a different normalization of the probability distribution $P(r)$. However, our objection is that the Cohen-Turnbull normalization, as used here, is absolutely correct, and we suggest that the conflict between the Peters and Beck experimental data for large values of a_F and the theoretical predictions based on the CT-law (2) cannot be resolved just by choosing a different normalization for $P(r)$ but by renormalization, as we will demonstrate in the next section.

Thus, we suppose that the observed deviations from the Cohen-Turnbull theory are a manifestation of the fact that the fluctuations responsible for the creation of a hole within the context of the CT-theory do not operate on a single characteristic scale but have many different length scales available ranging from molecular spacing up to correlation lengths of the size of the membrane system. A mathematical strategy for dealing with a problem with many different lengths scales is based on renormalization group theoretical concepts (Wilson 1979).

III. Renormalization group approach

An essential part of the renormalization group is to develop a strategy for dealing with problems that have multiple scales of length. The central concept of such a strategy is to break the main problem down into a sequence of subproblems, with each subproblem involving only a single characteristic length scale (Wilson 1979).

In order to demonstrate such a procedure for the problem under discussion we assume that the Cohen-Turnbull exponential distribution function, Eq. (7), i.e. $g(r) \, dr = \exp(-r/\langle r \rangle) \, d(r/\langle r \rangle) = g(\xi) d\xi$ with

$$g(\xi) = \exp(-\xi), \quad \xi := r/\langle r \rangle = \beta r \qquad (14)$$

is the basic probability distribution natural for the process of the formation of a hole of mean radius $\langle r \rangle$. In the next step there may be a certain probability $p_1(<1)$ that the fluctuations will operate on a different length scale creating a hole of mean value $\lambda_1 \langle r \rangle$, i.e. amplifying the original mean value $\langle r \rangle$ to $\lambda_1 \langle r \rangle$, with $\lambda_1 > 1$. Then the basic distribution $g(\xi) \, d\xi$ is converted to $g(\xi/\lambda_1) \, d(\xi/\lambda_1)$. Applying this process again to another subproblem, which may occur with a probability p_2, amplifying $\langle r \rangle$ to $\lambda_2 \langle r \rangle$, and converting $g(\xi) d\xi$ to $g(\xi/\lambda_2) d(\xi/\lambda_2)$, etc., one finally arrives at the "renormalized" or "amplified" probability distribution

$$G(\xi) \, d\xi = C \sum_{m=0}^{\infty} (p_m/\lambda_m) \, g \, (\xi/\lambda_m) \, d\xi$$

with $p_0 = \lambda_0 = 1$, $p_m < 1$, $\lambda_m > 1$ (for amplification processes), and C is a normalization constant. The choice $p_m = p^m$ and $\lambda_m = \lambda^m$ which has been taken by Montroll and Shlesinger (1982) within an economical context leads to

$$G(\xi) = C \sum_{m=0}^{\infty} (p/\lambda)^m \, g \, (\xi/\lambda^m), \qquad (15)$$

where the choice

$$C = 1 - p \qquad (16)$$

normalizes $G(\xi)$.

Of course, if no amplification process is present $(p = 0)$, then $G(\xi) = g(\xi)$. Replacing $\xi \to \xi/\lambda$ in (15) and multiplying this expression by p/λ one obtains the functional equation (renormalization group transformation)

$$G(\xi) = (p/\lambda) \, G \, (\xi/\lambda) + Cg(\xi). \qquad (17)$$

Because $g(\xi)$ is analytic, all singular behaviour is stored in the homogeneous part of this equation which has the asymptotic solution $G(\xi) \sim 1/\xi^{\mu+1}$ representing a stable Lévy distribution function if the exponent μ is restricted to the range

$$0 < \mu = \frac{\ln(1/p)}{\ln \lambda} \leq 2. \qquad (18)$$

Knowing $G(\xi)$ we can calculate "renormalized" average values taken with respect to $G(\xi)$ and denoted by an overbar (West et al. 1986)

$$\overline{D(\xi)} = \int_0^{\infty} D(\xi) \, G(\xi) \, d\xi. \qquad (19)$$

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Inserting (15) into (19) gives

$$\overline{D(\xi)} = C \sum_{j=0}^{\infty} (p/\lambda)^j \int_0^{\infty} D(\xi)\, g(\xi/\lambda^j)\, d\xi.$$

Taking $\xi = r/\langle r \rangle$, $D(\xi) = D(r^*)$ for $r \geq r^*$ and $D(\xi) = 0$ for $r^* < r$ (as above in Eq. (11)) we find (with $g(\xi/\lambda^j)$ given in Eq. (7))

$$\overline{D(\xi)} = C\, D(r^*) \sum_{j=0}^{\infty} p^j \exp(-\xi^*/\lambda^j) =: D(\xi^*) \qquad (20)$$

with $\xi^* = r^*/\langle r \rangle = \beta\, r^*$. For $p = 0$ only the first $(j = 0)$ term survives representing just the original Cohen-Turnbull law $D(\xi^*) = \langle D(r) \rangle$ as given in Eq. (1).

The series in (20) can be decomposed by adding and subtracting terms with $j = -1, -2, \ldots$, leading to

$$D(\xi^*)/D(r^*) = C(D_S(\xi^*) + D_r(\xi^*)) \qquad (21)$$

with

$$D_S(\xi^*) = \sum_{j=-\infty}^{\infty} p^j \exp(-\xi^*/\lambda^j) = \sum_{j=-\infty}^{\infty} p^{-j} \exp(-\xi^* \lambda^j)$$

and

$$D_r(\xi^*) = -\sum_{j=1}^{\infty} p^{-j} \exp(-\xi^* \lambda^j).$$

Making use of (18) the amplification probability p and normalization constant C can be rewritten in terms of the two scaling parameters μ and λ

$$p = \lambda^{-\mu}, \quad C = 1 - \lambda^{-\mu} \qquad (22)$$

which, when inserted into $D_S(\xi^*)$, gives

$$D_S(\xi^*) = \sum_{j=-\infty}^{\infty} \lambda^{\mu j} \exp(-\xi^* \lambda^j). \qquad (23)$$

This part of the average diffusion coefficient (21) satisfies the following homogeneous scaling relation:

$$D_S(\lambda \xi^*) = \lambda^{-\mu}\, D_S(\xi^*). \qquad (24)$$

For $D_r(\xi^*)$ we obtain

$$D_r(\xi^*) = -\sum_{j=1}^{\infty} \lambda^{\mu j} \exp(-\xi^* \lambda^j), \qquad (25)$$

satisfying the inhomogeneous scaling relation

$$D_r(\lambda \xi^*) = \lambda^{-\mu}(D_r(\xi^*) + \lambda^\mu \exp(-\lambda \xi^*)). \qquad (26)$$

The homogeneous scaling part $D_S(\xi^*)$ as given in Eq. (23), which stores all the singular behaviour of Eq. (17) in which we are interested in, can be transformed by applying Poisson's summation formula (Nonnenmacher 1988) to a power-law representation with the result

$$D_S(\xi^*) = A(\xi^*)/\xi^{*\mu}, \quad \xi^* = \beta r^* > 0, \qquad (27)$$

where

$$A(\xi^*) = (1/\ln\lambda) \qquad (28)$$
$$\left\{ \Gamma(\mu) + 2 \sum_{m=1}^{\infty} |\Gamma(\nu_m)| \cos(\arg\Gamma(\nu_m) + 2\pi m \ln\xi^*/\ln\lambda) \right\}$$

is a periodic function in $\ln\xi^*$ with period $\ln\lambda$, i.e. $A(\lambda\xi^*) = A(\xi^*)$, and $\Gamma(\nu_m)$ is the complex-valued Γ-function with $\nu_m = \mu - i\, 2\pi m/\ln\lambda$. The sum appearing in (28) converges rapidly, and for most practical applications it may be approximated well by taking into account only the first $(m = 1)$ term. Neglecting all the oscillations one obtains the power-law trend

$$D_S(\xi^*) = A_0/\xi^{*\mu} \quad \text{with} \quad A_0 = \Gamma(\mu)/\ln\lambda. \qquad (29)$$

In general, all singular behaviour of the average diffusion coefficient $D(\xi^*)$ coming from the renormalization group transformation (17) is contained in the relation

$$D(\xi^*)/D(r^*) = CD_S(\xi^*), \quad C = 1 - \lambda^{-\mu} \qquad (30)$$

with $D_S(\xi^*)$ given in Eq. (27).

IV. Comparison with experimental results

Peters and Beck (1983) measured the average diffusion coefficient for lipid diffusion in pure dilauroylphosphatidylcholine monolayers. For such a single-component membrane systeme ξ^* is given by Eq. (13): $\xi^* = \beta r^* = \gamma a_{HC}/a_F$.

The prediction of the Cohen-Turnbull theory according to Eq. (2) is represented by the broken line in Fig. 1. The full curve is calculated from Eq. (30) taking into account the first term $(m = 1)$ in Eq. (28) for $\mu = 1.9$ and $\lambda = 14$.

Because the function $A(\xi^*)$, Eq. (28), is periodic in $\ln\xi^*$, it is quite natural to look into the data on a log-log-plot, where $\log = \ln = $ logarithmus naturalis (to base e). Squares in Fig. 2 represent the Peters and Beck
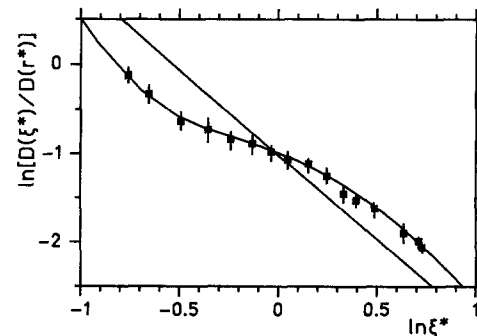

Fig. 2. Renormalization group theory predicts (in a log-log-plot) harmonic oscillations (*full curve*) around a power-law trend (*straight line*) in quantitative agreement with the Peters and Beck data (*squares*)

data. The straight line gives the dominant power-law trend calculated from Eq. (30) with $D_S(\xi^*)$ taken from Eq. (29) with $\mu = 1.9$ and $\lambda = 14$. The curve following closely the experimental data is the prediction of Eq. (30) with $D_S(\xi^*)$ from (27) for only one term ($m = 1$) of the sum in Eq. (28). This plot demonstrates clearly the cosine-oscillation (full curve) around the power-law trend (straight line) predicted by the renormalization group (homogeneous scaling) result (28) in quantitative agreement with the Peters and Beck data.

V. Discussion

In this paper we have derived, by using renormalization group theoretical considerations, a relation between the average lateral diffusion coefficient and the free area a_F. The derivation is based on the Cohen-Turnbull free volume theory, in which diffusion is supposed to take place by hopping processes of molecules into vacancies created by lateral density fluctuations. The renormalization group approach, used here, assumes that these fluctuations do not operate on a single characteristic scale but have multiple scales of length available. While O'Leary's scaled-particle diffusion model leads to the same functional form for the average diffusion coefficient as the original Cohen-Turnbull free volume theory, except for a pre-exponential factor, the model presented in this paper predicts fractal scaling oscillations in the diffusion coefficient.

The concept of fractal scaling, which has become a powerful strategy in physics during the last decade, includes exact self-similar and statistical self-similar scaling mechanisms as well. To describe exact self-similar processes one needs only one scaling parameter, the power-law exponent μ, which – in many cases – can be identified with the fractal dimension in the spirit of Mandelbrot (1983). For statistical self-similar and, particularly, for self-affine processes, however, the fractal dimension is not as easy to define as for exact self-similarity, and one has to take into account at least two scaling parameters: the power-law exponent μ and Weierstrass' spectral parameter λ which measures the period of the harmonic oscillations around the power-law trend as demonstrated in Fig. 2. It becomes evident by inspection of Fig. 2 that the experimental data show much more structure when being interpreted on the basis of our fractal scaling formula (30) than being stored in the conventional interpretation in a log-linear graph (Fig. 1) which clearly does not address the full dynamic range of phenomena evident in these data.

Finally we note that much more pronounced fractal scaling oscillations have already been observed in quite different biological patterns: The diameter-law for successive generations in the human bronchial tree has been reformulated very recently (West et al. 1986; Nonnenmacher and Nonnenmacher 1988) within the context of renormalization group theory. The resulting diameter-law predicts harmonic oscillations around a power-law trend as in the case of the lateral diffusion coefficient investigated in this paper.

From these investigations of quite different biological patterns like fractal scaling structures in the bronchial tree and in the lateral diffusion coefficient discussed here, we suggest that fractal scaling mechanisms will represent a unifying principle in morphogenetic scaling processes operating on many different scales instead of involving only a single characteristic scale of length for the underlying fluctuations. In any case, fractal scaling provides a mechanism for the description and interpretation of the design of complex, irregular but highly stable biological structures and pattern formations.

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