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A theoretical model of LDL-receptor trapping on a spherical cell

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Abstract

The kinetics of the trapping of LDL-receptor complexes by coated pits on the surface of fibroblasts is examined in this paper. We have recently developed a mathematical formalism to extend Keizer's non-linear, non-equilibrium fluctuation–dissipation theory to the kinetics of chemical systems constrained to a spherical surface. Keizer's theory is ideally suited to the study of open biological systems. In the past it has been used to investigate endocytosis on fibroblasts. However, these applications have modeled the cell membrane with an infinite plane. As such, the finite size of the cellular membrane, as well as its precise symmetry, could not be incorporated into the previous studies. Thus in this paper we use our recently developed methodology to reexamine the trapping step in endocytosis on spherical cells. For cell surface processes, the theoretical consideration of a spherical symmetry or an infinite plane, in model calculations, will depend on the experimental or *in vivo* conditions of the processes of interest. For a spherical symmetry, we find that the finite size of the cell surface does not significantly affect the rate of the trapping step given the empirically determined values for the relevant parameters on fibroblasts. This result supports the approximation used in the previous investigation. However, this and other analyses indicate that the finitie size of the biological surface probably is an important parameter for processes which occur on smaller biological surfaces such as those found on organelles.

Keywords: LDL-receptor complexes; Fibroblasts; Keizer's theory

1. Introduction

Almost all biological processes occur away from equilibrium. They are maintained at an essentially stable steady-state by external fluxes of reactants, products, and by-products. In this way, metabolites are replaced as they are consumed, wastes are removed as they are produced, etc. As such, the study of open systems kept away from equilibrium is of central importance in biophysical chemistry.

The study of these systems is complicated by several factors. In the first place, biochemical reactions occur almost exclusively in aqueous solution. The viscosity of water is high enough to significantly impede the motion of the reactant species. Under this condition, fluctuations in reactant density become an important factor which

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can significantly impact upon the observed behavior of the system under investigation. In other words, processes in open biological systems are stochastic processes which must be described by stochastic equations. The second complicating factor results from the already mentioned necessity that biological systems function away from equilibrium. This prevents the application of most traditional stochastic methods because these methods apply only to stochastic systems either moving towards or at equilibrium. Finally, most biological processes can be described as chemical reactions with second-order elementary steps. This implies that such systems are non-linear. In order to account for these complexities, our research relies on a theoretical approach developed by Keizer [1] which can describe non-linear stochastic systems away from equilibrium.

Of the various open biological systems which require investigation, our research is principally interested in the transport of macromolecules across cell membranes. In this paper, we study the kinetics of one step in receptor-mediated endocytosis. Our purpose here is the application of Keizer's theory to the step during endocytosis in which a receptor–ligand complex is trapped by a coated pit. Using Keizer's non-equilibrium method, the kinetics of this step have been investigated by one of us [2,3]. However, these investigations model the cell membrane as an infinite plane. Although this approximation is perhaps a good one, the actual effect of the cell membrane's finite size on the trapping rate is unknown. In this paper, we assume that the cell membrane has spherical symmetry. Since this geometry better approximates the geometry of actual cell membranes, we consider our new results results to be more meaningful. Furthermore, we believe that these results can eventually be generalized to biological processes which occur on organelles where the effect of surface size is probably significant.

In receptor-mediated endocytosis, proteins embedded in the cell membrane, called receptors, are able to diffuse throughout the cell surface and bind to specific macromolecules also known as ligands. The receptor–ligand complexes also diffuse until they become trapped in specific regions which are termed coated pits. The coated pits then envaginate, thereby transporting the receptors and ligands inside the cell.

We begin our analysis by describing the trapping of a receptor–ligand complex by a coated pit with the following reaction equation:

$$A + S \xrightarrow{k^+} S, \tag{1}$$

where A is the receptor–ligand complex, S is the coated pit, and k^+ is the rate coefficient. Next, we simplify the model assuming that the coated pit is a permanent trap. Thus, we are neglecting the finite lifetime of the coated pit. This simplification allows us to focus on the non-equilibrium technique to study processes on spherical surfaces. The inclusion of the finite lifetime of the pit and other relevant kinetic steps for endocytosis will be addressed elsewhere. The ultimate goal of this analysis is to calculate the rate coefficient, k^+, for eq. (1) on spheres of various sizes given appropriate values of other relevant parameters. The first step in calculating the rate coefficient is postulating that the rate coefficient is given by the following expression [4,5]:

$$k^+ = \int_0^\infty k^\circ(r)\, g_{AS}(r) r^2 \, dr, \tag{2}$$

here k° is the intrinsic chemical reactivity, which, in the case of chemical reactions, can be obtained using semiclassical and/or quantum mechanical methods, and $g_{AS}(r)$ is the radial distribution function [6] of A receptors around a central pit, S. The reactivity used here is given by the Smoluchowski reactivity which stipulates that the reaction occurs only when r is equal to the encounter radius, d_R

$$k^\circ(r) = \frac{k^\circ}{4\pi r^2} \delta(r - d_R), \tag{3}$$

in which $\delta(r - d_R)$ is Dirac's delta function. Using the Smoluchowski reactivity, eq. (2) reduces to

$$k^+ = k^\circ g_{AS}(d_R). \tag{4}$$

Because the fluctuating forces [1] can be represented essentially as Markov processes, one expects that the information needed to construct

the radial distribution function is contained in the density–density correlation function,

$$\langle \delta n_A(r, t)\delta n_S(r', t')\rangle = \sigma(r, r')\delta(t - t') \quad (5)$$

where δn is the fluctuation in number density around the macroscopic average, $\bar{n}$, and the r's represent positions. Consistent with this expectation, one can equate the radial distribution function, $g(r)$, and the density–density correlation function, $\sigma(r)$, using a well-known relation from the theory of fluids [7]

$$g_{ij}(r) = 1 - \delta(r)\frac{\delta_{ij}}{\bar{n}_i} + \frac{\sigma_{ij}(r)}{\bar{n}_i\bar{n}_j}, \quad (6)$$

where r is now the distance between two particles, δ_{ij} is Kronecker's delta, and $\bar{n}_i$ is the macroscopic number density of the ith species. Thus $g_{ij}(r)$ can be determined once $\sigma_{ij}(r)$ is known.

For the purpose of deriving an expression for $\sigma_{ij}(r)$, we use Keizer's fluctuation–dissipation (F–D) theory [1]. This theory is a statistical nonequilibrium thermodynamic approach based in part on fundamental remarks by Onsager [8] which relate the strength of the fluctuating and dissipating forces present in a stochastic system to the density–density correlation function. Keizer's theory allows us to describe the dynamics of density fluctuations using a system of linear stochastic differential equations and then to use these results to study the effect of these fluctuations on the density–density correlation function away from equilibrium.

Before proceeding any further it is helpful to pause and outline the presentation which follows. In Section 2 of this paper, we derive expressions for the density–density correlation function, $\sigma(r)$, the radial distribution function, $g_{AS}(r)$, and the rate coefficient, k^+, for the trapping process using Keizer's theory. The results obtained are discussed in Section 3. Section 4 is a synopsis of the overall effort.

2. Trapping of receptor–ligand complex by stationary coated pits

In this section we apply the F–D theory to the bimolecular process described by eq. (1). We are concerned only with the rate coefficient, k^+, in a stationary ensemble corresponding to an asymptotically stable steady-state which develops in a system homogeneous in both temperature and all number densities. The only molecular processes that we include in our analysis are bimolecular trapping and translational diffusion.

The first task is to write the stochastic partial differential equation for the density–density correlation function, $\sigma(r)$. Equation (5) suggests that a possible avenue of approach to this problem involves writing a Langevin-type equation for the fluctuations in number density

$$\frac{\partial}{\partial t}\begin{pmatrix}\delta n_A\\ \delta n_S\end{pmatrix} = \mathbf{H}\begin{pmatrix}\delta n_A\\ \delta n_S\end{pmatrix} + f. \quad (7)$$

In this equation, which establishes the agonistic relation between the fluctuating and dissipating forces, $\mathbf{H}$ is the relaxation matrix (associated with the dissipative forces) and f is the fluctuating force vector.

Next, we determine the dissipation matrix, $\mathbf{H}$. This can be done in the following way. Onsager first postulated [8] that fluctuations in a system dissipate at a rate equivalent to the first-order variations in the canonically determined transport rate. Taking this into consideration, one must first write the canonical transport equation for the system in question in order to specify the dissipative forces pointed to by Onsager. The mass action laws for the trapping process under the conditions specified previously can be written as

$$\frac{\partial}{\partial t}\begin{pmatrix}\bar{n}_A\\ \bar{n}_S\end{pmatrix} = \begin{pmatrix}-k^+\bar{n}_S\bar{n}_A + \mathscr{R}\\ 0\end{pmatrix}, \quad (8)$$

[1] The term *force* perhaps requires explanation. A stochastic system is not static. Instead, it is constantly pushed away from the macroscopic average by fluctuations which then dissipate. The first stochastic system extensively analyzed was the Brownian motion of a free particle. In this case, the stochastic variable was velocity. As such, it was natural to term the agent which caused fluctuations and dissipations in velocity a *force*. This term, although not ideally suited for stochastic analyses of chemical reactions, is carried over for lack of a better substitute.

where $\mathscr{R}$ is a homogeneous external flux needed to achieve a steady state away from equilibrium. The first-order variations in the transport rate arise immediately from a Taylor expansion of the instantaneous number density, $n(t)$, around the macroscopic average $\bar{n}$. Additionally, one must also consider that fluctuations, which represent a local gradient in the number density of a given species, can also dissipate through translational diffusion. The diffusion component of the dissipation matrix simply assumes that fluctuations will dissipate according to Fick's Second Law of diffusion. Combination of dissipation through chemical reaction and translational diffusion give the relaxation matrix as

$$\mathbf{H} = \begin{pmatrix} D_A \nabla^2 - k^+ \bar{n}_S & -k^+ \bar{n}_A \\ 0 & D_S \nabla^2 \end{pmatrix}, \tag{9}$$

where the D's are diffusion coefficients.

Turning our attention to the fluctuating force vector, f, and the influence the form of the force vector has on the problem as a whole, we note that f has the following characteristics. It is composed exclusively of random terms representing Markov processes. As such, these terms approximate white noise and have a time-average of zero, even over short spans. This property indicates that eq. (7) can be solved formally. Doing this, one can arrive at meaningful expressions for the moments of the number densities and the covariance between number densities at different times. This can be seen in the following way. If one assumes, as we already have implicitly, that $\mathbf{H}$ is a local operator [9,10], operation on eq. (5) by $\partial/\partial t$, subsequent substitution of eq. (7) into this result, and several algebraic manipulations, yield the following equation for the density–density correlation function [9,10]:

$$\frac{\partial}{\partial t}\boldsymbol{\sigma}(\Omega, \Omega') = \mathbf{H}\boldsymbol{\sigma}(\Omega, \Omega') + \boldsymbol{\sigma}(\Omega, \Omega')\mathbf{H}^{\mathsf{T}} + \boldsymbol{\gamma}(\Omega, \Omega'; \bar{n}_i). \tag{10}$$

The $\boldsymbol{\gamma}$ term [2] is the covariance of the fluctuating force vector (Ω, Ω') which is given using the F–D theory as [1]

$$\begin{aligned}\boldsymbol{\gamma}(\Omega, \Omega'; \bar{n}_i) &= \langle f(\Omega, r; t) f^{\mathsf{T}}(\Omega', r'; t')\rangle \\ &= \begin{pmatrix} k^+ \bar{n}_A \bar{n}_S - 2D_A \bar{n}_A \nabla^2 & 0 \\ 0 & -2D_S \bar{n}_S \nabla^2 \end{pmatrix} \\ &\quad \times \delta(r - R)\frac{\delta(\Omega - \Omega')}{R^2}\delta(t - t'),\end{aligned} \tag{11}$$

where R is the distance from the center of the sphere.

Now we solve eq. (10) at a stable steady state using the appropriate eigenfunction method. Specifically, eq. (10) is expanded as a double Laplace series of spherical harmonics [9,10]

$$G(\Omega, \Omega') = \sum_{l=0}^{\infty}\sum_{l'=0}^{\infty}\sum_{m=-1}^{l}\sum_{m'=-l'}^{l'} \hat{G}_{l,l'}^{m,m'} Y_l^m(\Omega) Y_{l'}^{m'*}(\Omega') \tag{12}$$

where Y_l^m and $Y_{l'}^{m'}$ are spherical harmonics, and $\hat{G}_{l,l'}^{m,m'}$ is given by the integral transform

$$\hat{G}_{l,l'}^{m,m'} = \iint Y_l^m(\Omega) Y_{l'}^{m'*}(\Omega') G(\Omega, \Omega')\, d\Omega\, d\Omega'. \tag{13}$$

Some simplifications are possible since the reaction is restricted to a spherical surface. Because of the spherical symmetry, $\boldsymbol{\sigma}$ is a not a function of the position of the particles on the sphere. Instead, $\boldsymbol{\sigma}$ is only a function of the arc distance between the two vectors, (θ, ϕ) and (θ', ϕ'), namely

$$\begin{aligned}\boldsymbol{\sigma}((\theta, \phi), (\theta', \phi'); t)\delta(r - r') &= \boldsymbol{\sigma}(\alpha; t)\delta(r - r'),\end{aligned} \tag{14}$$

where α is the angle between r and r'. By using the addition theorem of spherical harmonics $\hat{\boldsymbol{\sigma}}$ can now be rewritten as [9,10]

$$\hat{\boldsymbol{\sigma}}_{l,l'}^{m,m'} = \frac{4\pi}{2l+1}\hat{\boldsymbol{\sigma}}_l \delta_{l,l'}\delta_{m,m'}\frac{\delta(r - r')}{R^2}, \tag{15}$$

[2] A justification of this form of the γ-matrix is in progress.

where $\hat{\sigma}_l$ is given by the Legendre transform

$$\hat{\sigma}_l = \frac{2l+1}{2}\int_{-1}^{1} P_l(\cos\alpha)\sigma(\cos\alpha)\,\mathrm{d}(\cos\alpha). \tag{16}$$

The transformation of eq. (10) yields a simple algebraic equation which is solved in Appendix A. In the limit where D_S goes to zero, the Legendre transform of the density–density correlation function, $\hat{\sigma}_{AS,l}$, is given by:

$$\lim_{D_S\to 0}\hat{\sigma}_{AS,l} = \bar{n}_A^{SS}(R\xi)^2\left[\frac{1}{l(l+1)+(R\xi)^2}\right]\frac{2l+1}{4\pi R^2}, \tag{17}$$

where

$$\xi^{-1}\sqrt{D_A/k^+\bar{n}_S^{SS}} \tag{18}$$

is the coherence length, and R is the radius of the sphere. The inverse transformation of eq. (17) gives

$$\sigma_{AS}(\alpha) = -\delta(r-r')\frac{\bar{n}_A^{SS}\bar{n}_S^{SS}k^+}{4\pi D_A} \times\sum_{l=0}^{\infty}\left[\frac{2l+1}{l(l+1)+(R\xi)^2}\right]P_l(\cos\alpha). \tag{19}$$

Finally, substitution of eq. (19) into eq. (6) gives the radial distribution function, $g_{AS}(\alpha)$ as

$$g_{AS}(\alpha) = 1-\frac{k^+}{4\pi D_A}\sum_{l=0}^{\infty}\left[\frac{2l+1}{l(l+1)+(R\xi)^2}\right]P_l(\cos\alpha). \tag{20}$$

After a series of algebraic manipulations [9,10], eq. (18) can be written as a definite integral

$$g_{AS}(\alpha) = 1-\frac{k^+}{2\pi D_A} \times\int_0^{\infty}\frac{\mathrm{e}^{-x/2}\cos\left[x/2\sqrt{4(R\xi)^2-1}\right]\mathrm{d}x}{\sqrt{1-2\cos\alpha\,\mathrm{e}^{-x}+\mathrm{e}^{-2x}}}. \tag{21}$$

Notice that

$$\cos\left[\frac{x}{2}\sqrt{4(R\xi)^2-1}\right] = \cosh\left[\frac{x}{2}\sqrt{1-4(R\xi)^2}\right]$$

when

$$4(R\xi)^2-1<0.$$

In order to compare this results with previous results obtained on a flat surface, we take the limit of eq. (21) as R goes to infinity. In this case the behavior of the reaction on the sphere is identical to the behavior on a plane. One can easily show that

$$\lim_{R\to\infty}\left[1-g_{AS}(\alpha)\right] = \frac{k^+}{2\pi D_A}\int_0^{\infty}\frac{\cos[R\alpha\xi]\,\mathrm{d}x}{\sqrt{x^2+1}} = \frac{k^+}{2\pi D_A}K_0(R\alpha\xi), \tag{22}$$

where K_0 is the Associated Bessel function of order zero and $R\alpha = d_R$, the reaction distance. This result is consistent with other nonequilibrium studies of this reaction on an infinite plane [2,3]. Finally, substitution of eq. (21) into eq. (4) gives the following transcendental equation:

$$k^+ = k^0\left[1-\frac{\tilde{k}}{\frac{1}{2}N_S}\int_0^{\infty}\frac{\mathrm{e}^{-x/2}\cos\left(\frac{x}{2}\sqrt{4\tilde{k}-1}\right)\mathrm{d}x}{\sqrt{1-\cos\alpha\,\mathrm{e}^{-x}+\mathrm{e}^{-2x}}}\right], \tag{23}$$

where $\tilde{k} = (R\xi)^2$ and N_S is the number of sinks.

Equation (23) is the principle result of this section, and it can be solved numerically for the rate coefficient, k^+. Once a value of k^+ is obtained, it can be substituted into eq. (21). The integral in eq. (21) can then be evaluated using numerical methods for a sequence of angles, α, to give the radial distribution function, $g_{AS}(\alpha)$, of receptor–ligand complexes around coated pits. Note that the radial distribution function plays a pivotal role in studies of endocytosis in that it is this function, and not the rate coefficient itself, which can be determined by experiments. As such, it is through the radial distribution function that one can verify experimentally our theoretical result.

Before proceeding to a discussion between our results, some comments concerning our approach are in order. Earlier studies of reactions of a pair of particles on a spherical surface have used the Sano–Tachiya [11] equation, which is derivable from the Smoluchowski equation for the survival probability of a pair of particles. In this approach, Sano and Tachiya obtain an expression for the mean reaction time as a function of radii and diffusion coefficients. Although it is a useful approach, it is not clear how it can be applied to open stochastic systems which are not moving towards equilibrium. One of the advantages of our present approach is that it has been designed precisely to describe the dynamics of non-equilibrium stochastic systems. Also, it is unclear how the earlier approach using the Sano–Tachiya equation can be used to determine either the effect of concentration on the rate coefficient [12–14] or the limiting behavior of a spherical system as it approaches the topology of an infinite plane. Both of these factors can be analyzed naturally during the course of our discussion based on Keizer's theory.

3. Results

Since the transcendental equation given by eq. (23) is difficult to solve analytically for an arbitrary intrinsic reactivity, k°, we restrict ourselves to analyze diffusion-controlled processes. The assumption of the diffusion-controlled limit greatly simplifies eq. (23) principally because the semiclassical and/or quantum mechanical calculations required to obtain the intrinsic reactivity are circumvented. Moreover, since no experimental evidence has been reported on the real nature of the rate limiting step in receptor trapping by coated pits, the diffusion-controlled limit is justified because the diffusion of the receptor–ligand complex through the highly viscous membrane could be a reasonable rate limiting step for the trapping process. In the diffusion-controlled limit, eq. (23) becomes

$$\tilde{k}^{-1} = \frac{2}{N_S}\int_0^{\infty} \frac{e^{-x/2}\cos\left(\frac{x}{2}\sqrt{4\tilde{k}-1}\right)\,dx}{\sqrt{1-\cos\alpha\, e^{-x}+e^{-2x}}} \qquad (24)$$

where

$$\tilde{k} = R^2\frac{k^{+}\bar{n}_S^{SS}}{D_A}. \qquad (25)$$

For diffusion-controlled trapping, eq. (24) has been solved for the rate coefficient, k^{+}, using MATHEMATICA™ on a Sun 3/50 work station.

When considering trapping on cell surfaces, the value of the relevant parameters, such as reactant concentrations and diffusion constants, are all interrelated. In other words, they are not free to vary independently. As a result, the best way to select a possible set of parameters is to use empirically determined values. For our analysis, we use values observed for fibroblasts [15] and LDL receptors [16] which are found in Table 1. Working within this constraint, the effect of the size of the spherical surface on k^{+} is the natural object of study. Our analysis seeks to elucidate this calculations show that, at these radii with the concentration of pits held steady at 0.31 pits $(\mu m)^{-2}$, the effect of sphere size on the rate coefficient is insignificant. This result verifies the hypothesis used to justify the earlier model which assumed an infinite planar geometry. However, this and other analyses [9,10] point to an interdependence between sphere size and concentration such that, as the radius or concentration decrease, the effect of sphere size becomes more pronounced. This further suggests that the size of the reactive surface might play a very significant role when biological processes on smaller surfaces, such as organelles, are considered. Since the values of the relevant parameters must be determined empirically, we cannot look

Table 1

Characteristic parametes for LDL receptors on human fibroblasts

Parameter	Symbol	Value	Reference source
Radius of coated pits	R	0.10 μm	[15]
Receptor diffusion constant	D_A	$4.5\ 10^{-3}\ \mu m^2/s$	[16]
Steady-state density of coated pits (37°C)	n_S^{SS}	0.31 μm^{-2}	[15]

Table 2

Effect of sphere size on k^+ for a fixed receptor concentration

Radius of sphere (μm)	$k^+/2\pi D_A$
5	0.1663
10	0.1674
15	0.1676
20	0.1677
25	0.1677
30	0.1677
35	0.1677
40	0.1677
45	0.1677
50	0.1677

into this interesting development in this paper. Future exploration of this question awaits new experimental data.

Additionally, and in keeping with the idea that the radial distribution function is subject to experimental verification, we plot the radial distribution function for the observed parameters. In this case, we use the solution of the transcendental equation for 10 μm (see Table 2), substitute in eq. (21) and integrate for different values of the angle between the points on the sphere. These plots are shown in Figs. 1(a) and 1(b). As these figures show, the radial distribution functions are practically identical on spheres of radius 10 μm and on an infinite plane.

4. Summary and conclusions

In this paper we have used Keizer's non-equilibrium, non-linear statistical thermodynamic approach to study the trapping step in endocytosis of fibroblasts. Improving on previous studies of this phenomenon, this analysis is able to investigate the trapping process using a model which accounts for the finite size of the membrane surface and more accurately mimicks the symmetry of cell membranes. These advances are made possible by implementing the mathematical formalism on a spherical surface instead of on an infinite plane. The results obtained here both confirm and go beyond the prior findings. These findings had been based on the assumption that, since the cell membrane is so much larger than the receptor–ligand complex and the coated pit, one could approximate the cell membrane with an infinite plane. The validity of this assumption has been borne out by the present analysis in that calculations assuming a spherical geometry conclusively indicate that the finite size and geometry of the spherical surface does not appreciably affect the rate of the trapping process for the given empirically determined values of the relevant parameters on fibroblasts. However, this and other studies indicate that processes which occur

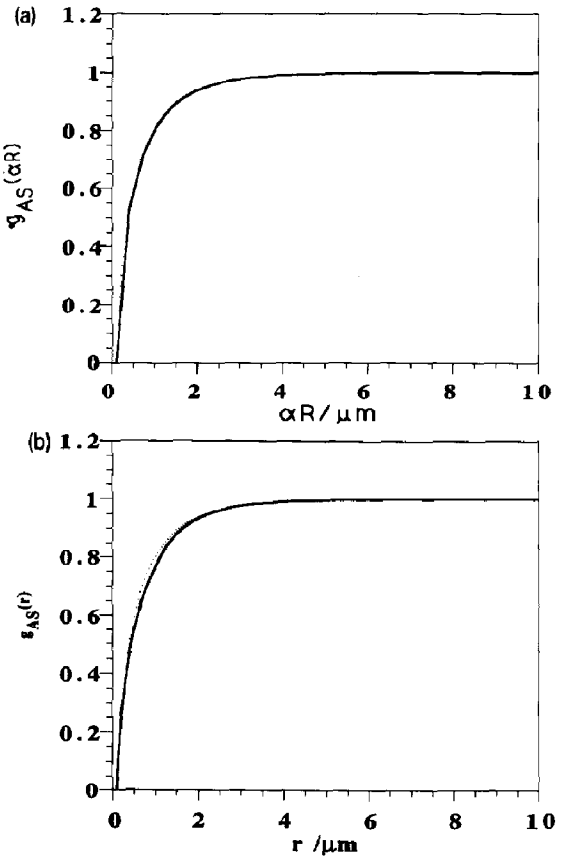

Fig. 1. (a) Plot of the radial distribution function, $g_{AS}(\alpha R)$, on a sphere with a radius of 10 μm. The product, αR, represents the arc distance between the two particles (where α is the angle between the two particles and R is the radius of the sphere). (b) Plot of the radial distribution function, $g_{AS}(r)$, on an infinite plane where r is the distance between the two particles. A comparison between the two plots verifies at a glance that the differences between the two radial distribution functions are negligible when $R = 10$ μm.

on smaller biological surfaces, such as process which occur on organelles, might be significantly influenced by the size of these smaller bodies. Since the values for the relevant parameters, such as diffusion constants and concentrations, are heavily interrelated, exploration of this interesting possibility is not viable until empirically determined values are available.

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Appendix A

The dissipation-fluctuation theorem for an isotropic system at a stationary state is given by the following equation:

$$\int \mathbf{H}(r; r'')\sigma(r''-r')\,dr'' + \int \sigma(r-r'')\mathbf{H}^{\mathsf{T}}(r''; r')\,dr'' = -\gamma(r)\delta(r-r'). \tag{A.1}$$

From eq. (7), the relaxation matrix $\mathbf{H}$ has the following structure:

$$\mathbf{H}(r; r') = \mathbf{H}(r)\delta(r-r'). \tag{A.2}$$

Consequently, eq. (A.1) reduces to a local version, i.e.

$$\mathbf{H}(r)\sigma(r-r') + \sigma(r-r')\mathbf{H}^{\mathsf{T}}(r') = -\gamma(r)\delta(r-r'). \tag{A.3}$$

A double spherical harmonic transformation on (A.3), i.e.,

$$\iint Y_l^m(\Omega)[\mathbf{H}(r)\sigma(r-r') + \sigma(r-r')\mathbf{H}^{\mathsf{T}}(r')]Y_{l''}^{m'*}(\Omega')\,d\Omega\,d\Omega' = -\iint Y_l^m(\Omega)[\gamma(r)\delta(r-r')] \times Y_{l''}^{m'*}(\Omega')\,d\Omega\,d\Omega' \tag{A.4}$$

reduces eq. (A.2) to

$$\mathbf{H}_l^m \iint \{Y_l^m(\Omega)[\sigma(r-r')]Y_{l''}^{m'*}(\Omega')\,d\Omega\,d\Omega'\} + \iint \{Y_l^m(\Omega)[\sigma(r-r')] \times Y_{l''}^{m'*}(\Omega')\,d\Omega\,d\Omega'\}\mathbf{H}_{l''}^{m'} = -\gamma_l^m \left\{ \iint Y_l^m(\Omega)[\delta(\Omega-\Omega')] \times Y_{l''}^{m'*}(\Omega)\,d\Omega\,d\Omega' \right\} \frac{\delta(r-r')}{r^2} \tag{A.5}$$

For processes constrained to a spherical surface, the density–density correlation function is a function of the angle between the two points on the sphere, namely

$$\sigma(r-r') = \sigma(\cos\alpha)\delta(r-r'), \tag{A.6}$$

where α is the angle between r and r' and satisfies the following relation:

$$\cos\alpha = \sin\phi\,\sin\phi' + \cos\phi\,\cos\phi'\,\cos(\theta-\theta'). \tag{A.7}$$

In this case, we can expand σ using a Legrendre series, namely

$$\sigma(\cos\alpha) = \sum_{l''=0}^{\infty} \sigma_{l''} P_{l''}(\cos\alpha) = \sum_{l''=0}^{\infty} \sigma_{l''} \frac{4\pi}{2l''+1} \sum_{\mu''=-l''}^{l''} Y_{l''}^{m''*}(\Omega) Y_{l''}^{m''}(\Omega'), \tag{A.8}$$

where we have defined

$$\sigma_l = \frac{2l+1}{2} \int_{-1}^{1} \sigma(\cos\alpha) P_l(\cos\alpha)\,d(\cos\alpha). \tag{A.9}$$

Therefore

$$\sigma_{l,l''}^{m,m'} \equiv \iint Y_l^m(\Omega) Y_{l''}^{m'*}(\Omega')\sigma(r-r')\,d\Omega\,d\Omega' = \frac{4\pi\delta(r-r')}{2l+1}\sigma_l \delta_{l,l''}\delta_{m,m'}. \tag{A.10}$$

Using this expression, one can reduce eq. (A.5)

$$\frac{4\pi}{2l+1}\left[H_l^m\sigma_l+\sigma_l H_l^{m\mathrm{T}}\right]\delta_{l,l'}\delta_{m,m'}\delta(r-r') = -\gamma_l^m\delta_{l,l'}\delta_{m,m'}\frac{\delta(r-r')}{r^2}. \quad \text{(A.11)}$$

Therefore the F–D theorem reduces to

$$\mathbf{H}_l^m\boldsymbol{\sigma}_l+\boldsymbol{\sigma}_l\mathbf{H}_l^{m\mathrm{T}} = -\boldsymbol{\gamma}_l^m\frac{1}{2}\frac{2l+1}{4\pi}. \quad \text{(A.12)}$$

From eqs. (7)–(9), we get

$$\mathbf{H}_l^m = \begin{bmatrix} -D_{\mathrm{A}}\dfrac{l(l+1)}{R^2}-k^+\bar{n}_{\mathrm{S}} & -k^+\bar{n}_{\mathrm{A}} \\ 0 & -D_{\mathrm{S}}\dfrac{l(l+1)}{R^2} \end{bmatrix} \quad \text{(A.13)}$$

$$\boldsymbol{\gamma}_l^m = \begin{bmatrix} 2\bar{n}_{\mathrm{A}}D_{\mathrm{A}}\dfrac{l(l+1)}{R^2}+k^+\bar{n}_{\mathrm{A}}\bar{n}_{\mathrm{S}} & 0 \\ 0 & 2\bar{n}_{\mathrm{S}}D_{\mathrm{S}}\dfrac{l(l+1)}{R^2} \end{bmatrix} \quad \text{(A.14)}$$

Solving for $\sigma_{\mathrm{AS},l}$, one gets

$$\hat{\sigma}_{\mathrm{AS},l} = -\bar{n}_{\mathrm{A}}^{\mathrm{SS}}\bar{n}_{\mathrm{S}}^{\mathrm{SS}}\frac{k^+}{D_{\mathrm{A}}}\frac{2l+1}{4\pi R^2} \times\left\{\frac{1}{\left(1+\dfrac{D_{\mathrm{S}}}{D_{\mathrm{A}}}\right)\left[\dfrac{l(l+1)}{R^2}+\dfrac{k^+\bar{n}_{\mathrm{S}}^{\mathrm{SS}}}{D_{\mathrm{A}}}\right]}\right\} \quad \text{(A.15)}$$

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