

Narrow escape time to a structured target located on the boundary of a microdomain

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The forward binding rate of chemical reactions is the reciprocal of the mean time for a Brownian molecule to hit its molecular target. When the target is embedded in the surface of a microdomain, this time is known as the narrow escape time, and it has been computed for various geometries. However, for large targets that extend from the surface far into the cytosol the classical computations do not apply and new ones are needed. In this work we generalize the narrow escape time formula to a three-dimensional spine attached to the boundary. We treat in detail the case of an ellipsoidal spine and validate our analysis by Brownian simulations. Finally, we compute the narrow escape time when the spine is uniformly covered by small partially absorbing disks and estimate the homogenized trapping rate of such a patchy surface. © 2009 American Institute of Physics. [DOI: 10.1063/1.3081633]

I. INTRODUCTION

Diffusion is a key regulator of the rate of chemical interactions: in chemoreception, the ability of a cell to sense and respond to external cues^{1–4} is controlled by diffusion of ligands to receptors. Numerous cell processes rely on the rate at which diffusing molecules hit a small target site, which can underlie higher cell function such as sensing, smell, and many others. This rate has been studied in various contexts, such as the trapping of diffusing particles in patchy surfaces,^{2,5} the resident time of receptors at synapses,^{6,7} the mean time for a DNA carrier to reach a small nuclear pore,⁸ or the hydrolysis rate of second messengers in the early cascade of phototransduction.⁹ In general, the mean time for a diffusible ligand to reach its target protein in a confined environment is often a limiting step that determines the forward binding rate.^{10–14}

The narrow escape time (NET) (Ref. 15) is the spatially averaged mean time for a diffusing particle, uniformly distributed, to hit a small target embedded in the surface. The NET was computed analytically and simulated for various geometries,^{15–18} and these computations were extended to several interacting targets¹⁹ and to stochastic dynamics in a potential well.^{7,20,21} However, previous works do not account for an extended three-dimensional target attached to a surface. Membrane proteins such as ionic channels, receptors, transporters, or nuclear pores are often not entirely embedded into the surface, but a large part of the proteins lives in the cytosol. This is the case for nicotinic acetylcholine receptors,²² TRPV1 channels (transient receptor potential family of ion channels),²³ metabotropic glutamate

receptors,^{24,25} the human epidermal growth factor family of receptors important in cancer therapy,²⁶ and others. For example, a nicotinic acetylcholine receptor has a transmembrane width around 20–30 Å and protrudes around 65 and 20 Å from the extracellular and intracellular membrane surfaces, respectively, and a TRPV1 channel has a transmembrane width around 50 Å and protrudes around 110 Å from the intracellular membrane. In addition to these structural examples, the need to consider a large cytosolic domain surrounding the target can also be the consequence of long ranged electrochemical interactions between ligands and targets (a large reaction radius). To derive accurate expressions for the reaction rate of such targets with diffusing ligands, we consider the mean time for diffusible molecules to reach the boundary of the effective cytosolic volume, referred to as a small spine attached to the surface. The analysis is based on the well known analogy between the NET and electrostatics, and one of the main results here is formula (30), which gives an explicit expression for the NET to an ellipsoidal spine. Finally, we compute the NET to a spine uniformly covered by small partially absorbing patches. This analysis extends and completes results derived in Refs. 1, 2, 5, and 27. As an application, we use this to estimate the uniform effective trapping rate of patchy surfaces.

II. NET TO A SMALL SPINE ATTACHED TO THE SURFACE

To compute the NET, we consider the mean first passage time (MFPT) $\tau(y)$ for a Brownian particle with diffusion constant D starting at position y in a confined volume V to hit an absorbing spine S , located on the complement of the otherwise reflecting surface ∂V_r . In our model the diffusing

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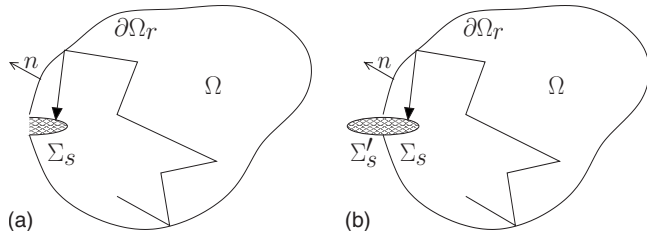


FIG. 1. (a) Domain Ω with an absorbing spine Σ_s located on the surface. A diffusing Brownian particle is reflected on the surface $\partial\Omega_r$, and it is absorbed on the spine surface $\partial\Sigma_s$. (b) The domain Σ'_s lies outside Ω and smoothly complements the spine Σ_s to the closed domain $\Sigma = \Sigma_s + \Sigma'_s$.

particles are punctual; however, at first order, their size can be taken into account by adjusting the extension of the spine. $\tau(\mathbf{y})$ satisfies²⁸

$$D\Delta\tau(\mathbf{y}) = -1, \quad \mathbf{y} \in V, \quad (1)$$

$$\tau(\mathbf{y}) = 0, \quad \mathbf{y} \in \partial S, \quad (2)$$

$$\frac{\partial}{\partial n}\tau(\mathbf{y}) = 0, \quad \mathbf{y} \in \partial V_r. \quad (3)$$

We introduce the small scaling parameter a that characterizes the extension of the spine and further assume that all other length scales are large compared to a , such that $a \ll |V|^{1/3}$ holds [see Fig. 1(a) drawn using scaled variables]. Using the dimensionless variable $x = y/a$ and the scaled domain and spine $\Omega = V/a^3$ and $\Sigma_s = S/a^3$, the scaled MFPT,

$$\hat{\tau}(\mathbf{x}) = \frac{aD}{|V|}\tau(\mathbf{y}), \quad (4)$$

is solution of

$$\Delta\hat{\tau}(\mathbf{x}) = -\frac{1}{|\Omega|}, \quad \mathbf{x} \in \Omega, \quad (5)$$

$$\hat{\tau}(\mathbf{x}) = 0, \quad \mathbf{x} \in \partial\Sigma_s, \quad (6)$$

$$\frac{\partial}{\partial n}\hat{\tau}(\mathbf{x}) = 0, \quad \mathbf{x} \in \partial\Omega_r. \quad (7)$$

Equation (5) can be interpreted as the electrostatic potential generated by a uniform charge density $|\Omega|^{-1}$ in Ω . We search for a solution of the form

$$\hat{\tau}(\mathbf{x}) = u(\mathbf{x}) + v(\mathbf{x}) + \kappa, \quad (8)$$

where κ is a constant, and $u(\mathbf{x})$ and $v(\mathbf{x})$ are functions that will be specified later, but anticipating their properties, in the limit $a \ll |V|^{1/3}$ (equivalently $|\Omega| \gg 1$) we have

$$\frac{1}{|\Omega|} \int_{\Omega} u(\mathbf{x}) d\mathbf{x} \approx 0, \quad \frac{1}{|\Omega|} \int_{\Omega} v(\mathbf{x}) d\mathbf{x} \approx 0 \quad \text{for } |\Omega| \gg 1. \quad (9)$$

As we will see, $u(\mathbf{x})$ is the electrostatic potential of a charged and conducting spine with surface potential $-\kappa$, and $v(\mathbf{x})$ can be neglected for large Ω . Using Eqs. (8) and (9), the NET, which is defined as the spatial average of $\hat{\tau}(\mathbf{x})$, is given by

$$\tau = \frac{|V|}{aD} \frac{1}{|\Omega|} \int_{\Omega} \hat{\tau}(\mathbf{x}) d\mathbf{x} = \frac{|V|}{aD} \kappa, \quad |\Omega| \gg 1. \quad (10)$$

III. DERIVATION OF $u(\mathbf{x})$ AND κ

To estimate $u(\mathbf{x})$, we complement the spine Σ_s smoothly by a domain Σ'_s located outside Ω [see Fig. 1(b)]. Σ_s and Σ'_s form together the closed volume Σ . The shape of Σ'_s is such that the equipotential lines of the charged and conducting surface $\partial\Sigma$ intersect the surface $\partial\Omega_r$ perpendicularly in the neighborhood of the spine. The extent of the neighborhood is approximately defined by the region where the flux originating from $u(\mathbf{x})$ is not negligible, which in dimensional units typically corresponds to distances of a few times a . Hence, the form of Σ'_s depends on the spine shape and on the geometry of the surface $\partial\Omega_r$ next to the spine. Since the scaling parameter a is small, $\partial\Omega_r$ in the vicinity of the spine will in most cases be well approximated by a plane, and then Σ'_s is just the mirror image of Σ_s with respect to this plane. However, if the spine is located in a cusp or a corner, then the shape of Σ'_s is more complicated and no longer obvious (see also Ref. 29).

The electrostatic potential $u(\mathbf{x})$ of the charged and conducting surface Σ that vanishes at large distances and has surface potential $-\kappa$ satisfies

$$\Delta u(\mathbf{x}) = 0, \quad \mathbf{x} \text{ outside } \Sigma, \quad (11)$$

$$u(\mathbf{x}) = -\kappa, \quad \mathbf{x} \in \partial\Sigma. \quad (12)$$

$u(\mathbf{x})$ depends via Σ on the spine shape and the local geometry of the boundary $\partial\Omega_r$ in the vicinity of the spine but not on the global shape of Ω .

The potential $-\kappa$ depends on the total charge Q located on $\partial\Sigma$ and the surface capacitance C . The charge Q is given by (the unit normal n points inwards Σ)

$$Q = \int_{\partial\Sigma} \frac{\partial u(\mathbf{x})}{\partial n} dS = \int_{\partial\Sigma_s} \frac{\partial u(\mathbf{x})}{\partial n} dS + \int_{\partial\Sigma'_s} \frac{\partial u(\mathbf{x})}{\partial n} dS. \quad (13)$$

By integrating Eq. (5) we find that the total charge in Ω is -1 . We therefore impose the charge located on the spine surface $\partial\Sigma_s$ to be -1 , which gives the condition

$$\int_{\partial\Sigma_s} \frac{\partial u(\mathbf{x})}{\partial n} dS = -1. \quad (14)$$

Because the surface $\partial\Sigma$ is conducting, condition (14) uniquely determines the value of Q in Eq. (13). By definition of the capacitance C , we obtain for the surface potential

$$\kappa = -\frac{Q}{C}. \quad (15)$$

In general, Q depends on the shapes of $\partial\Sigma_s$ and $\partial\Sigma'_s$. However, if the boundary $\partial\Omega_r$ next to the spine is planar, then Σ'_s is just the mirror image of Σ_s and the charges situated on $\partial\Sigma_s$ and $\partial\Sigma'_s$ are equal. We find from Eqs. (13) and (14) that $Q = -2$, and from this

$$\kappa = \frac{2}{C}. \quad (16)$$

IV. PROPERTIES OF $v(\mathbf{x})$

Because $\hat{\tau}(\mathbf{x}) = u(\mathbf{x}) + v(\mathbf{x}) + \kappa$ is solution of Eq. (5) using that $u(\mathbf{x})$ is solution of Eq. (11), $v(\mathbf{x})$ satisfies

$$\Delta v(\mathbf{x}) = -\frac{1}{|\Omega|}, \quad \mathbf{x} \in \Omega, \quad (17)$$

$$v(\mathbf{x}) = 0, \quad \mathbf{x} \in \partial\Sigma_s \quad (18)$$

$$\frac{\partial v(\mathbf{x})}{\partial n} = -\frac{\partial u(\mathbf{x})}{\partial n}, \quad \mathbf{x} \in \partial\Omega_r. \quad (19)$$

Contrary to $u(\mathbf{x})$, the function $v(\mathbf{x})$ depends on the global shape of Ω . By integrating Eq. (17) over Ω and using the boundary conditions we obtain

$$\int_{\partial\Sigma_s} \frac{\partial v(\mathbf{x})}{\partial n} dS - \int_{\partial\Omega_r} \frac{\partial u(\mathbf{x})}{\partial n} dS = -1. \quad (20)$$

Similarly, integrating Eq. (11) over Ω and using Eq. (14) yields

$$\int_{\partial\Omega_r} \frac{\partial u(\mathbf{x})}{\partial n} dS = 1. \quad (21)$$

Altogether, Eqs. (19) and (21) lead to the conditions

$$\int_{\partial\Omega_r} \frac{\partial v(\mathbf{x})}{\partial n} dS = -1, \quad (22)$$

$$\int_{\partial\Sigma_s} \frac{\partial v(\mathbf{x})}{\partial n} dS = 0. \quad (23)$$

We now use the conditions determining $v(\mathbf{x})$ to show that $v(\mathbf{x})$ vanishes asymptotically for large Ω : First, the source term for $v(\mathbf{x})$ in Eq. (17) converges to zero as $|\Omega|$ goes to infinity. Second, by definition [condition (18)], $v(\mathbf{x})$ is zero on the spine surface. Third, because the flux $\partial u(\mathbf{x})/\partial n$ through $\partial\Omega_r$ in a neighborhood of the spine vanishes, by using relation (19), it follows that $\partial v(\mathbf{x})/\partial n = 0$ in that region. Fourth, the total flux of $v(\mathbf{x})$ through the spine boundary $\partial\Sigma_s$ is zero [see Eq. (23)]. Fifth, the flux $\partial u(\mathbf{x})/\partial n$ at $\partial\Omega_r$ away from the spine and $\partial v(\mathbf{x})/\partial n$ [using Eq. (19)] converge to zero like $O(1/|x|^2)$. Since the solution of Eq. (17) is unique, we conclude that $v(\mathbf{x})$ vanishes for large Ω . When $|\Omega|$ increases to a half-plane, v converges to the bounded solution of the Laplace equation with zero boundary condition on the spine and Neumann boundary condition on the half-plane, and this solution is zero.

V. NET IN THE LARGE Ω LIMIT

We first determine the expression for the positional MFPT $\tau(\mathbf{y})$ when the spine is small compared to the micro-domain V , $a \ll |V|^{1/3}$ (equivalently $|\Omega| \gg 1$). Since $v(\mathbf{x})$ vanishes for large Ω , we obtain the result

$$\tau(\mathbf{y}) = \frac{|V|}{aD} \left[u\left(\frac{\mathbf{y}}{a}\right) + \kappa \right]. \quad (24)$$

Equation (24) shows that $u(\mathbf{x})$ determines the behavior of $\tau(\mathbf{y})$ in the boundary layer of the spine. Moreover, because

far away from the spine $u(\mathbf{x})$ is the potential of the point charge Q , by using Eq. (15) and the expression for the Newtonian potential, we obtain the asymptotic formula

$$\tau(\mathbf{y}) = \frac{|V|}{aD} \left(\frac{aQ}{4\pi|\mathbf{y}|} - \frac{Q}{C} \right), \quad |\mathbf{y}|/a \gg 1, \quad (25)$$

where $|\mathbf{y}|$ is the distance to the spine.

From our previous analysis we can now justify that the spatial average of $u(\mathbf{x})$ and $v(\mathbf{x})$ converges to zero for large Ω [see Eq. (9)]: first, $v(\mathbf{x})$ vanishes in this limit, and second, $u(\mathbf{x})$ is the potential of a clustered charge distribution whose spatial average vanishes as the volume increases. Thus, using Eq. (15), the NET τ defined in Eq. (10) is

$$\tau = \frac{|V|}{aD} \kappa = -\frac{|V|}{aD} \frac{Q}{C}. \quad (26)$$

When the spine is located on a planar surface, this general formula simplifies with $Q = -2$ to

$$\tau = \frac{|V|}{aD} \frac{2}{C}. \quad (27)$$

VI. NET TO AN ELLIPSOIDAL SPINE

We now treat the case of an ellipsoidal spine with transversal axes $a_2 \geq a_1$ and height a_3 . For the scaling parameter we can choose $a = a_1$. When the spine is located on a planar surface, Σ is an ellipsoid with scaled axes $\alpha_1 = a_1/a$, $\alpha_2 = a_2/a$, and $\alpha_3 = a_3/a$ and capacitance³⁰

$$C = \frac{8\alpha_1}{K(e, f)}, \quad (28)$$

with the eccentricity $e = \sqrt{1 - \alpha_1^2/\alpha_2^2}$, $f = a_3/a_1$, and the elliptic integral

$$K(e, f) = \frac{2}{\pi} \int_0^\pi \frac{d\theta}{\sqrt{(1 - e^2 \sin^2 \theta)(1 + f^2 \tan^2 \theta)}}. \quad (29)$$

Inserting C into Eq. (27) yields for the NET

$$\tau = \frac{|V|}{4a_1D} K(e, f). \quad (30)$$

From this expression we recover the known results for flat spines as special cases: For $a_1 = a_2$ and $a_3 = 0$ ($e = 0$ and $f = 0$) the ellipsoid reduces to a circle, and using that $K(0, 0) = 1$, we recover the narrow escape formula $\tau = |V|/(4a_1D)$.^{16,17,31} For $a_3 = 0$ ($f = 0$) the spine shrinks to an ellipse, and Eq. (30) reduces to the expression given in Ref. 31. For a spine that is a hemisphere of radius a_1 ($a_1 = a_2 = a_3$) we obtain

$$\tau = \frac{|V|}{2\pi a_1 D}, \quad (31)$$

where we used $K(0, 1) = 2/\pi$. Formula (31) differs from what was derived in Ref. 21 by a factor of 2. Finally, the NET to a rodlike spine with $a_1 = a_2$ and $f = a_3/a_1$ is

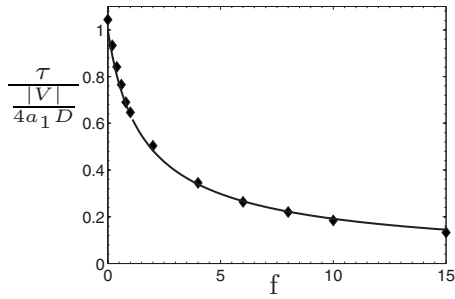


FIG. 2. MFPT for uniformly distributed particles to reach a rodlike spine with transversal axis $a_1=a_2$ and height a_3 ($f=a_3/a_1$). The spine is located on the surface of a large sphere with radius $r=30a_1$. The continuous curve given by Eq. (32) is in excellent agreement with the mean times obtained from Brownian simulations (each data point is obtained by averaging over 10 000 particles).

$$\tau = \frac{|V|}{2\pi a_1 D} \begin{cases} \frac{\arccos f}{\sqrt{1-f^2}}, & f \leq 1, \\ \frac{\operatorname{arccosh} f}{\sqrt{f^2-1}}, & f \geq 1. \end{cases} \quad (32)$$

For $f \gg 1$ we have the approximation $\tau \approx (|V|/2\pi a_1 D) \times [\ln(2f)/f]$. In Fig. 2 we compare the analytical formula (32) with Brownian simulations.

$$f(\sigma) = \begin{cases} 1 & [\text{Berg and Purcell (Ref. 1)}] \\ 1 - \sigma & [\text{Zwanzig (Ref. 2)}] \\ \sigma/F(\sigma) = \frac{1 - \sigma}{1 + 3.8\sigma^{1.25}} & [\text{Berezhkovskii et al. (Ref. 5)}]. \end{cases} \quad (34)$$

The approximation $f(\sigma)=1-\sigma$ is valid up to $\sigma \sim 0.1$ and $f(\sigma)=\sigma/F(\sigma)$ at least up to $\sigma \sim 0.5$.⁵ Finally, using Eqs. (27) and (33), we obtain the expression

$$\tau_{\text{ps}} = \frac{|V|}{aD} \frac{2N\hat{s} + f(\sigma)\tilde{C}}{\tilde{C}}. \quad (35)$$

For an ellipsoidal spine, using Eq. (28), we get

$$\tau_{\text{ps}} = \frac{|V|}{4a_1 D} \frac{K(e, f)Ns + f(\sigma)a_1}{Ns}. \quad (36)$$

If the spine is a hemisphere of radius r , formula (36) reduces to

$$\tau_{\text{ps}} = \frac{|V|}{2\pi r D} \frac{2Ns + f(\sigma)\pi r}{2Ns}. \quad (37)$$

Finally, for a spine that degenerates into a flat disk of radius r , we obtain

VII. NET FOR A REFLECTING SPINE UNIFORMLY COVERED BY N ABSORBING DISKS

To derive the NET τ_{ps} for a reflecting spine located on a planar surface and uniformly covered with N small absorbing disks of radius s , we first estimate the capacitance C of the insulated surface $\partial\Sigma$ covered with $2N$ (since $\partial\Sigma$ is twice the spine surface $\partial\Sigma_s$) disks of radius $\hat{s}=s/a$, where a is the scaling parameter. The disk capacitance is $4\hat{s}$ (only the outer disk side is charged), and thus [see Eq. (A7) in the Appendix]

$$C = \tilde{C} \frac{8N\hat{s}}{8N\hat{s} + f(\sigma)\tilde{C}}, \quad (33)$$

where $\tilde{C}$ is the capacitance of a conducting surface $\partial\Sigma$, σ is the fraction of the spine surface covered with the absorbing disks, and $f(\sigma)$ is a function that depends on the coverage σ and may also depend on the shape of $\partial\Sigma$. The asymptotic value of C when σ is close to zero (1) is $8N\hat{s}$ ($\tilde{C}$) and using that $\tilde{C} \gg 4\hat{s}$, it follows that the corresponding asymptotic value of $f(\sigma)$ has to be 1 (0). Furthermore, numerical simulations for a spherical and planar spine⁵ suggest that the function f does not vary much with the spine shape. By comparing our expression for C in Eq. (33) with the results in Refs. 1, 2, and 5 we find that $f(\sigma)$ is approximated by

$$\tau_{\text{ps}} = \frac{|V|}{4rD} \frac{Ns + f(\sigma)r}{Ns}. \quad (38)$$

We point out that Eq. (35) can be generalized to noncircular disks by replacing $4\hat{s}$ with the appropriate disk capacitance C_d (see also the Appendix).

VIII. NET FOR A REFLECTING SPINE UNIFORMLY COVERED BY N PARTIALLY ABSORBING DISKS

We now generalize the previous section and estimate the NET τ_{ps} for a reflecting spine located on a planar surface and uniformly covered with N small and partially absorbing disks. The radiation boundary condition for the disk surface is

$$D \frac{\partial \tau}{\partial n} = \kappa \tau. \quad (39)$$

Because the spatially averaged NET is the reciprocal of the steady state flux into the absorbing surface, we start by studying the flux expressions.

Using Eq. (33), the normalized flux J (normalized by the constant concentration far away from the absorbing surface) into the reflecting surface $\partial\Sigma$ uniformly covered by N absorbing disks is

$$J = \tilde{J}_\Sigma \frac{N\tilde{J}_d}{N\tilde{J}_d + f(\sigma)\tilde{J}_\Sigma}, \quad (40)$$

where $\tilde{J}_\Sigma = D\tilde{C}_\Sigma$ is the normalized flux into a perfectly absorbing surface $\partial\Sigma$ and $\tilde{J}_d = D\tilde{C}_d$ is the normalized flux into a perfectly absorbing disk. The straightforward generalization of this equation to a surface $\partial\Sigma$ uniformly covered with N partially absorbing disks is

$$J = J_\Sigma(\kappa) \frac{NJ_d(\kappa)}{NJ_d(\kappa) + f(\sigma, \kappa)J_\Sigma(\kappa)}, \quad (41)$$

where $J_\Sigma(\kappa)$ and $J_d(\kappa)$ are the normalized fluxes when the surfaces have the uniform trapping rate κ and a function $f(\sigma, \kappa)$ that now depends as well on κ . In order that Eq. (41) reduces to Eq. (40) for $\kappa \rightarrow \infty$, $f(\sigma, \kappa)$ has to converge toward $f(\sigma)$ [defined in Eq. (34)] in this limit. However, for finite κ , $f(\sigma, \kappa)$ and $f(\sigma)$ will be different in general. The asymptotic value of J for $\sigma \rightarrow 0$ ($\sigma \rightarrow 1$) requires that the corresponding asymptotic value of $f(\sigma, \kappa)$ is 1 (0).

To further evaluate Eq. (41) we need the expressions for $J_\Sigma(\kappa)$ and $J_d(\kappa)$. When Σ is a sphere of radius r and the disks are circles of radius s we have³

$$J_{\text{sph}}(\kappa) = \tilde{J}_{\text{sph}} \frac{\kappa}{\kappa + \frac{\tilde{J}_{\text{sph}}}{A_{\text{sph}}}}, \quad J_{\text{cd}} = \tilde{J}_{\text{cd}}(\kappa) \frac{\kappa}{\kappa + \frac{\tilde{J}_{\text{cd}}}{A_{\text{cd}}}}, \quad (42)$$

with $\tilde{J}_{\text{sph}} = D\tilde{C}_{\text{sph}}$ is the flux into an absorbing sphere, $A_{\text{sph}} = 4\pi r^2$ is the sphere surface, $\tilde{C}_{\text{sph}} = 4\pi r$ the sphere capacitance, $\tilde{J}_{\text{cd}} = D\tilde{C}_{\text{cd}}$, $A_{\text{cd}} = \pi s^2$, and $\tilde{C}_{\text{cd}} = 4s$. By combining Eq. (42) with Eq. (41) we obtain for the reciprocal flux J [we use $\sigma = A_{\text{sph}}/(NA_{\text{cd}})$]

$$\frac{1}{J} = \frac{1}{\tilde{J}_{\text{sph}}} + \frac{f(\sigma, \kappa)}{N\tilde{J}_{\text{cd}}} + \frac{1}{\kappa A_{\text{sph}}} \left(1 + \frac{f(\sigma, \kappa)}{\sigma} \right) \quad (43)$$

$$= \frac{1}{D4\pi r} + \frac{f(\sigma, \kappa)}{ND4s} + \frac{1}{\kappa 4\pi r^2} \left(1 + \frac{f(\sigma, \kappa)}{\sigma} \right), \quad (44)$$

which is a generalization of the result derived by Zwanzig and Szabo [see Eq. (17) in Ref. 3]. Equation (42) together with Eq. (41) can be used to derive a uniform effective trapping rate κ_{eff} by requiring that

$$J_\Sigma(\kappa_{\text{eff}}) = J_\Sigma(\kappa) \frac{NJ_d(\kappa)}{NJ_d(\kappa) + f(\sigma, \kappa)J_\Sigma(\kappa)}. \quad (45)$$

For a sphere covered by partially absorbing circular disks we obtain

$$\frac{1}{\kappa_{\text{eff}}} = \frac{1}{\kappa} \left(1 + \frac{f(\sigma, \kappa)}{\sigma} \right) + \frac{f(\sigma, \kappa) A_{\text{cd}}}{\sigma \tilde{J}_{\text{cd}}} \quad (46)$$

$$= \frac{1}{\kappa} \left(1 + \frac{f(\sigma, \kappa)}{\sigma} \right) + \frac{f(\sigma, \kappa) \pi s}{\sigma 4D}, \quad (47)$$

which generalizes the expressions for κ_{eff} suggested in Refs. 3 and 5. For $\sigma \rightarrow 1$ we have $\kappa_{\text{eff}} = \kappa$, as it should, and for $\sigma \rightarrow 0$ we recover the Zwanzig–Szabo expression³

$$\frac{1}{\kappa_{\text{eff}}} = \frac{1}{\sigma} \left(\frac{1}{\kappa} + \frac{\pi s}{4D} \right). \quad (48)$$

Expression (47) generalizes the formula

$$\frac{1}{\kappa_{\text{eff}}} = \frac{1}{\sigma \kappa} + \frac{f(\sigma)}{\sigma} \frac{\pi s}{4D} \quad (49)$$

proposed by Berezhkovskii *et al.*⁵ The numerical simulations results given in Ref. 5 for various κ and σ can be used to fit $f(\sigma, \kappa)$. Because the simulations were well explained by Eq. (49), equating Eq. (47) with Eq. (49) yields an approximation to $f(\sigma, \kappa)$:

$$f(\sigma, \kappa) = f(\sigma) + \frac{4D}{\pi s \kappa} \frac{1 - \sigma - f(\sigma)}{1 + \frac{4D}{\pi s \kappa}}. \quad (50)$$

The above expression has the correct asymptotic properties $f(0, \kappa) = 1$, $f(1, \kappa) = 0$, and $f(\sigma, \kappa) \rightarrow f(\sigma)$ for $\kappa \rightarrow \infty$.

If the surface $\partial\Sigma$ and the disks are such that Eq. (42) can be generalized to

$$J_\Sigma(\kappa) = \tilde{J}_\Sigma \frac{\kappa}{\kappa + \frac{\tilde{J}_\Sigma}{A_\Sigma}}, \quad J_d = \tilde{J}_d(\kappa) \frac{\kappa}{\kappa + \frac{\tilde{J}_d}{A_d}}, \quad (51)$$

we obtain the generalized formulas

$$\frac{1}{J} = \frac{1}{\tilde{J}_\Sigma} + \frac{f(\sigma, \kappa)}{N\tilde{J}_d} + \frac{1}{\kappa A_\Sigma} \left(1 + \frac{f(\sigma, \kappa)}{\sigma} \right), \quad (52)$$

$$\frac{1}{\kappa_{\text{eff}}} = \frac{1}{\kappa} \left(1 + \frac{f(\sigma, \kappa)}{\sigma} \right) + \frac{f(\sigma, \kappa) A_d}{\sigma \tilde{J}_d}. \quad (53)$$

Using this expression for J , the NET τ_{ps} to a reflecting spine located on a planar surface and uniformly covered by N partially absorbing disks is

$$\tau_{ps} = \frac{1}{\frac{1}{2} \frac{1}{|V|} J} = 2 \frac{|V|}{D} \left(\frac{1}{\tilde{C}_\Sigma} + \frac{f(\sigma, \kappa)}{2N\tilde{C}_d} + \frac{D}{\kappa A_\Sigma} \left(1 + \frac{f(\sigma, \kappa)}{\sigma} \right) \right). \quad (54)$$

As an example, for a hemispherical spine of radius r uniformly covered by N partially absorbing circular disks of radius s we have

$$\tau_{ps} = \frac{|V|}{D} \left(\frac{2Ns + f(\sigma, \kappa)\pi r}{4N\pi rs} + \frac{D}{\kappa} \frac{Ns^2 + f(\sigma, \kappa)2r^2}{2N\pi r^2 s^2} \right), \quad (55)$$

which reduces to Eq. (37) for completely absorbing disks ($\kappa \rightarrow \infty$). When the spine is a flat circular disk of radius r we get

$$\tau_{ps} = \frac{|V|}{D} \left(\frac{Ns + f(\sigma, \kappa)r}{4Nrs} + \frac{D}{\kappa} \frac{Ns^2 + f(\sigma, \kappa)r^2}{N\pi r^2 s^2} \right), \quad (56)$$

which reduces to Eq. (38) for $\kappa \rightarrow \infty$. In the limit of small and large coverages σ we have the asymptotic results

$$\tau_{ps} = \begin{cases} \frac{|V|}{ND} \left(\frac{1}{4s} + \frac{D}{\kappa\pi s^2} \right), & \sigma \rightarrow 0, \\ \frac{|V|}{D} \left(\frac{1}{4r} + \frac{D}{\kappa\pi r^2} \right), & \sigma \rightarrow 1. \end{cases} \quad (57)$$

IX. SUMMARY AND CONCLUSION

We investigated here the NET for a Brownian particle to hit a three-dimensional target attached to the surface. The expressions in Eqs. (27) and (30), respectively, allow to derive precise values of the forward binding rates to membrane proteins with extended cytosolic active domains. Equation (54) estimates the NET to a reflecting spine uniformly covered by N small and partially absorbing disks, which can be used to compute the rate by which diffusing ligands activate receptors clustered in particularly shaped surface regions. This formula is also relevant to obtain the rate by which ligands bind to multiple active sites located on large membrane proteins, such as the four binding sites of cyclic guanosine monophosphate (cGMP) channels or the four subunits of AMPA receptors. And finally, formula (53) estimates the homogenized trapping rate of a patchy surface, which can be used as an effective parameter in a more coarse grained model.

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APPENDIX: DERIVATION OF THE CAPACITANCE OF A PATCHY SURFACE

We derive here the formula for the capacitance C of a closed insulating surface $\partial\Sigma$ uniformly covered with N small conducting disks of capacitance C_d (the disks are charged only on the outer side). As an example, for circular disks with radius s we have $C_d = 4s$.³⁰ Let σ be the fraction of the surface $\partial\Sigma$ covered with absorbing disks, q_k ($1 \leq k \leq N$) the charge situated on the k th disk, and ϕ the uniform surface

potential (to ensure that all disks have the same potential, we can assume that they are connected via tiny wires). In the first approximation, the potential of the k th disk can be decomposed as the potential ϕ_{kk} generated by the charge q_k and the sum of all the potentials ϕ_{kj} generated by the other disk;¹ thus

$$\phi = \phi_{kk} + \sum_{\substack{j=1 \\ j \neq k}}^N \phi_{kj}. \quad (A1)$$

When the disks are well separated, such that the electrostatic interactions between neighboring disks are small, then $\phi_{kk} \approx q_k/C_d$. By averaging over all the disks we obtain

$$\phi = \frac{1}{N} \sum_{k=1}^N \frac{q_k}{C_d} + \frac{1}{N} \sum_{k=1}^N \sum_{\substack{j=1 \\ j \neq k}}^N \phi_{kj} = \frac{Q}{NC_d} + \frac{1}{N} \sum_{k=1}^N \sum_{\substack{j=1 \\ j \neq k}}^N \phi_{kj}, \quad (A2)$$

where $Q = \sum_{k=1}^N q_k$ is the total charge. The second term in Eq. (A2) is an average potential generated by all the disks, and in the first approximation we can write

$$\frac{1}{N} \sum_{k=1}^N \sum_{\substack{j=1 \\ j \neq k}}^N \phi_{kj} \approx \frac{Q}{\tilde{C}}, \quad (A3)$$

where $\tilde{C}$ is the capacitance of the conducting surface $\partial\Sigma$. Equation (A3) is a valid approximation for a disk coverage σ close to 1. We obtain for the capacitance

$$\frac{1}{C} = \frac{\phi}{Q} = \frac{1}{NC_d} + \frac{1}{\tilde{C}}. \quad (A4)$$

Clearly, Eq. (A4) is only a crude estimation because the two terms are valid approximation for opposite limits: $1/NC_d$ is reasonable when σ is close to zero, whereas $1/\tilde{C}$ is justified when σ approaches 1. When Σ is a sphere of radius r covered with N circular disks of radius s , Eq. (A4) yields ($\tilde{C} = 4\pi r$ and $C_d = 4s$)

$$C = 4\pi r \frac{Ns}{Ns + \pi r}, \quad (A5)$$

which is exactly the formula derived by Berg and Purcell.¹ A general form of Eq. (A4) is

$$\frac{1}{C} = \frac{f_1(\sigma)}{NC_d} + \frac{f_2(\sigma)}{\tilde{C}}, \quad (A6)$$

where $f_1(\sigma)$ and $f_2(\sigma)$ are functions that may depend on $\partial\Sigma$ and on the disks. From Eq. (A5) we obtain our main result,

$$C = \tilde{C} \frac{NC_d}{NC_d + f(\sigma)\tilde{C}}. \quad (A7)$$

where $f(\sigma) = f_1(\sigma) + (C_d/\tilde{C})(f_2(\sigma) - 1)$. When σ is close to zero (1) the asymptotic value for C is NC_d ($\tilde{C}$). Using $\tilde{C} \gg C_d$, it follows from Eq. (A7) that the corresponding asymptotic value of $f(\sigma)$ has to be 1 (0). A first approximation that fulfills both conditions $f(0)=1$ and $f(1)=0$ is $f(\sigma) = 1 - \sigma$, and indeed, when Σ is a sphere of radius r covered

with N circular disks of radius s , this is exactly the result derived by Zwanzig.² The more accurate approximation $f(\sigma)=\sigma/F(\sigma)$ can be found by comparing Eq. (A7) with the numerical results of Berezhkovskii *et al.*⁵ In general, $f(\sigma)$ depends on the shapes of $\partial\Sigma$ and that of the disks. However, the numerical results presented in Ref. 5 show that $f(\sigma)$ is very similar for a spherical and planar spine, which suggests that $f(\sigma)$ may be a quite universal function. Nevertheless, it remains for future work to explore the exact dependency of $f(\sigma)$ on the spine and disk shapes.

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