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Brownian Diffusion of Ion Channels in Different Membrane Patch Geometries

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We asymptotically calculate the spatially averaged mean first passage time (MFPT) of a diffusing channel protein in a finite membrane patch containing a small absorbing anchor site. Different two-dimensional membrane geometries are considered including a circular, a square-shaped, a rectangular and a cylindrical domain. The asymptotic expressions are found to be in excellent agreement with results from Monte-Carlo simulations if the radius of the diffusing protein is sufficiently small. For a larger radius a simple correction to the asymptotic expressions is proposed. We show that the average MFPT for a circle and a square-shaped domain of the same area are approximately equal as long as the anchor site is close to the center of the domain. We also discuss how the average MFPT depends on the aspect ratio of a rectangular and a cylindrical domain. Among such domains with a fixed area a minimal MFPT is obtained for the square-shaped domain.

Keywords: Mean first passage time, Ion channel, Brownian diffusion, IP₃R, Neumann function

I. INTRODUCTION

Cytosolic calcium ions (Ca²⁺) play a crucial role in the regulation of various physiological phenomena, such as exocytosis, enzyme control, gene regulation, cell growth and proliferation, and apoptosis [1]. A common source of cytosolic Ca²⁺ in many cells is the release of Ca²⁺ through the inositol 1,4,5-trisphosphate receptor (IP₃R) from intracellular stores, e.g. the endoplasmic reticulum (ER), in response to the second messenger inositol trisphosphate (IP₃) [2]. Thus, the spatial distribution of IP₃Rs can be important for the local delivery of Ca²⁺ to specific sites within the cell to regulate Ca²⁺-dependent subcellular functions [3, 4].

In many cell types IP₃R is diffusible within the ER membrane, and it can dynamically migrate upon cell stimulation. For example, long term agonist stimulation in the smooth muscle cell line A7r5 leads to a global redistribution of type-1 IP₃Rs [5]. In addition to the global movements of IP₃Rs, it has been observed that local clustering of IP₃Rs can occur, for example, in the basophilic cell line RBL-2H3 where IP₃R clustering can be rapidly triggered by activation of the Ca²⁺ signalling cascade [6], and IP₃R clustering is not dependent on changes in the structure of the ER [7]. Also, the maturation of oocytes before fertilization leads to IP₃R clustering [8].

The biological consequences of IP₃R clustering are not clear yet. Clustered IP₃Rs show a strong stochastic open/close dynamics causing a noisy Ca²⁺ signal.

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Within a lattice model it has been shown that channel clusters can generate a stochastic backfiring pattern [9]. Other simulations suggest that the clustering distribution of IP₃Rs may improve the periodicity of local Ca²⁺ signals [10] and enhance the sensitivity of global Ca²⁺ signals responding to a weak IP₃ stimulus [11]. Based on global spiking data of four cell types, it was suggested that Ca²⁺ spikes are caused by random wave nucleation events with a regular regime arising from the array enhanced coherence resonance effect of IP₃R clusters [12].

The dynamical regulation of IP₃R clustering has been investigated only recently. First, it was suggested that Ca²⁺ triggered the clustering of IP₃Rs [6]. Theoretical analysis showed that a periodic (Ca²⁺) signal could lead to an oscillatory or to a quasi-stationary cluster size distribution [13]. Later, it was shown that a conformational change in the IP₃R, evoked by IP₃, was sufficient to induce clustering [14]. Further experiments indicated that the depletion of the Ca²⁺ store may facilitate the clustering of IP₃Rs [15]. More recently, with patch-clamp recordings from the outer nuclear envelope of DT40 cells expressing rat IP₃R1 or IP₃R3, it was shown that IP₃ causes IP₃R rapidly and reversibly to aggregate into small clusters of about four IP₃Rs [16]. However, another study indicated that puff sites represent preestablished stable clusters of IP₃Rs and that functional IP₃Rs are not readily diffusible within the ER membrane in SH-SY5Y, Hela and astrocyte cells [17].

These experiments clearly demonstrate the need to reliably estimate the time scale on which clustering occurs. In general, one can expect an effect of IP₃R clustering on the Ca²⁺ dynamics when the time scale for clustering and the time scale for the open/closing dynamics of individual IP₃R channels are comparable. To estimate the time scale of IP₃R clustering we assume that IP₃Rs undergo
Brownian motion on an ER membrane patch containing an anchor site. This could be, for example, a fixed cytoskeletal structure which traps and fixes the IP₃,R channels upon encounter. The relevant time scale for clustering is given by the mean first passage time (MFPT) [18], i.e. the average time it takes an IP₃,R channel to reach a given target site on the membrane for the first time. In the case that clustering is a purely diffusion-limited process the MFPT can be calculated in the framework of the Smoluchowski theory [19].

The MFPT arises in many applications, but explicit results were mostly restricted to one-dimensional geometries [20–23]. Recently, first results were given for the MFPT in more complex geometries including microdomains [24], two- and three dimensional domains containing small exit sites [25–28, 30], as well as for regular lattices [31] and complex networks [32, 33]. Specifically, in a bounded two-dimensional domain containing a circular trapping region the MFPT can be expressed in terms of the Neumann function \( G_N \) as [28, 29]

\[
T_{x_0}(x) = -\frac{1}{D} G_N(x; x_0)
\]  

(1)

where \( x \) and \( x_0 \) denote the starting point for the random walk inside \( \Omega \) and the center of the trapping region, respectively. \( |\Omega| \) and \( D \) correspond to the area of the domain and the diffusion coefficient, respectively.

In two dimensions the Neumann function has the general form

\[
G_N(x; x_0) = -\frac{1}{2\pi} \ln |x - x_0| + R_N(x; x_0)
\]  

(2)

where \( R_N \) represents the regular part of \( G_N \) at \( x_0 \) which is uniquely determined by the boundary value problem

\[
\Delta G_N = \frac{1}{|\Omega|} - \delta(x - x_0), \quad x \in \Omega
\]

\[
\partial_n G_N = 0, \quad x \in \partial \Omega
\]

\[
\int_{\Omega} dx G_N = 0.
\]

(3)

Here, \( \Delta \) denotes the Laplace operator in two dimensions and \( \partial_n \) denotes the derivative in the direction of the outward normal of the respective domain. The spatially averaged MFPT (\( \bar{T} \)) of Eq. 1 is then given in terms of \( R_N(x; x_0) \) as

\[
\bar{T}_{x_0} = \frac{|\Omega|}{D} \left( \frac{1}{2\pi} \ln \frac{L_c}{\varepsilon} + \lim_{x \to x_0} R_N(x; x_0) \right)
\]  

(4)

where \( L_c \) denotes a characteristic length scale of the domain \( \Omega \) and \( \varepsilon \) is the effective radius of the trapping region. It accounts for the fact that the diffusing ion channel (radius \( r_{ch} \)) is immediately absorbed upon the first contact with the anchor site (radius \( r_{an} \)). Thus \( \varepsilon = r_{ch} + r_{an} \). Note that in the continuum description the diffusing channel is treated as a point particle.

Often, the leading order term in Eq. 4 is sufficient to estimate the order of magnitude for the average MFPT, and it only requires knowledge of three parameters: The total surface area \( |\Omega| \), the diffusion coefficient \( D \) and the effective radius of the trapping region relative to the characteristic length scale of the domain \( \varepsilon/L_c \). Thus the leading order term is insensitive to geometrical details of the underlying domain. If more than one length scale is required to characterize the shape of the domain, such as the aspect ratio of a rectangular domain, then the \( O(1) \) term, involving the regular part of the Neumann function, can become important especially in highly asymmetric domains [26].

Strictly speaking, the expressions in Eqs. 1, 3 and 4 are valid only in the asymptotic limit \( \varepsilon \ll L_c \), but comparison with numerical solutions of the respective partial differential equations gave excellent agreement up to values of \( \varepsilon/L_c = 0.2 \) [26, 28]. In the present work, we compare the asymptotic expression for the spatially averaged MFPT (Eq. 4) with direct Monte Carlo simulations of a Brownian particle (IP₃,R channel) in different two-dimensional domains. We study in detail its dependence on the size of IP₃,R channel, the size and the position of the anchor site, the size of the ER membrane patch, and different membrane shapes.

We find excellent agreement between the asymptotic expression in Eq. 4 and stochastic simulations if the \( O(1) \) term is taken into account and the radius of the diffusing channel \( (r_{ch}) \) is sufficiently small. For a larger channel radius a simple correction to Eq. 4 is proposed which is in very good agreement with the results of stochastic simulations. We also investigate how the average MFPT depends on the aspect ratio of a rectangular and a cylindrical domain. Among such domains with a fixed area a minimal MFPT is obtained for a square-shaped domain.

II. SIMULATION METHOD

We consider Brownian diffusion of an IP₃,R channel in different two-dimensional ER membrane geometries including a circular, a square-shaped, a rectangular and a cylindrical domain. For the first three domains we use reflecting boundary conditions while the cylindrical domain is modelled as a rectangular domain with periodic boundary conditions along the \( y \)-axis and reflecting boundary conditions along the \( x \)-axis.

The IP₃,R is represented as a small particle with a radius of \( r_{ch} \) that diffuses within the ER membrane with diffusion coefficient \( D \). Based on electron microscopy and single particle analysis of purified IP₃,Rs, the radius of a channel was estimated in the range 9 nm to 18 nm [34]. Using fluorescence recovery after photobleaching it was suggested that IP₃,Rs diffusion within ER membranes is with a diffusion coefficient \( D \) of 0.03–0.04 \( \mu \text{m}^2/\text{s} \) [35] or 0.45 \( \mu \text{m}^2/\text{s} \) [36].

In the simulation, the IP₃,R channel undergoes a Brownian random walk in both \( x \) and \( y \) directions. Their positions are updated at time steps \( \Delta t \) by adding random numbers drawn from a Gaussian distribution with zero
mean [17]. The width (standard deviation) of the Gaussian is \( \sqrt{2D\Delta t} \). In the simulation, we chose the time step \( \Delta t = 5 \times 10^{-5} \) s. Different time steps have been tested giving the same results.

We also consider an anchor site or absorbing region with radius \( r_{an} \) in the patch representing a fixed cytoskeletal structure to trap the channels. The fixed anchor site is designated as IP3R channel trap location. Here we assume \( r_{an} \) is of order of 10 nm [17]. An IP3R channel moving within a distance of \( \varepsilon = r_{ch} + r_{an} \) will become trapped at the anchor site. To remain compatible with the assumptions for the derivation leading to Eq. 4, we assume that trapped channels will neither affect the trap diameter nor its location. When the channel reaches the patch boundary within a distance which is less than \( r_{ch} \), reflecting boundary conditions will be used for the mobile IP3R.

In the simulation, the IP3R channel is located in the patch randomly at the beginning. Then the channel undergoes a Gaussian random walk with diffusion coefficient \( D \). The random diffusing time of the channel before colliding with the anchor site is calculated. A spatially averaged MFPT is defined as the average of the diffusion times obtained from 500,000 trials starting at arbitrary positions in the patch.

### III. RESULTS

**A. IP3R diffusion in a circular patch**

We consider a diffusing particle in a circular domain of radius \( R \) containing a small absorbing circular region of effective radius \( \varepsilon \) at the center. The diffusion coefficient of the particle is \( D \). Then the MFPT required for the particle to hit the absorbing region at the center when starting at an arbitrary position inside the annulus \( \varepsilon < r < R \) is determined by the simple boundary value problem

\[
\begin{align*}
\Delta T &= -\frac{1}{D}, \quad \varepsilon < r < R \\
T &= 0, \quad r = \varepsilon \\
\partial_r T &= 0, \quad r = R
\end{align*}
\]

Due to the spherical symmetry the problem can be solved analytically. We include it here for didactical purpose since it will serve as a benchmark for more complicated geometries considered later. The solution of Eqs. 5 gives the MFPT as

\[
T(r) = \frac{\varepsilon^2 - r^2}{4D} + \frac{R^2}{2D} \ln \frac{r}{\varepsilon}.
\]

Then the spatially averaged MFPT is computed as

\[
\bar{T}_{circ} = \frac{1}{\pi} \frac{1}{(R^2 - \varepsilon^2)} \int_0^{2\pi} d\varphi \int_{\varepsilon}^{R} T(r)rdr
\]

\[
= \frac{R^2}{2D} \ln \frac{R}{\varepsilon} - \frac{3}{8} \frac{R^2}{D} + O\left(\frac{\varepsilon^2}{R^2} \ln \frac{R}{\varepsilon}\right).
\]

In typical applications the contact radius \( \varepsilon \) is in the nanometer range whereas diffusion occurs in membrane patches with a typical length scale in the micrometer range. In that case terms of \( O((\varepsilon^2/R^2)\ln(R/\varepsilon)) \) and smaller can be neglected in Eq. 7 and the spatially averaged MFPT is well approximated by

\[
\bar{T}_{circ} \approx \frac{R^2}{2D} \ln \frac{R}{\varepsilon} - \frac{3}{8} \frac{R^2}{D}.
\]

To compare this expression with the general form of the average MFPT shown in Eq. 4, we rewrite Eq. 8 as

\[
\bar{T}_{circ} \approx \frac{\pi R^2}{D} \left( \frac{1}{2\pi} \ln \frac{R}{\varepsilon} - \frac{3}{8\pi} \right)
\]

which shows that the regular part of the Neumann function for a circular domain with a singularity at the origin is given by \( R_{N,circ}(0) = -3/8\pi [37] \).

Now with the Brownian random walk simulation, we consider a diffusing IP3R channel in a circular domain of radius \( R_{circ} \) with a reflecting boundary and containing a small absorbing circular region of radius \( r_{an} \) at the center. The radius of the channel is \( r_{ch} \) and its diffusion coefficient is \( D \).

First we discuss the first passage time (FPT) for the channel starting at a given distance \( r \). As shown in Figure 1A the FPTs exhibit an exponential distribution with a time constant of \( T = 41.7s \) at \( r = 1\mu m \) corresponding to the MFPT. For the exponential distribution, the standard deviation of the FPTs is equal to its mean and Eq. 6 yields \( T = 42.1s \) with \( \varepsilon = r_{an} + r_{ch} \) and \( R = R_{circ} \). Figure 1B shows excellent agreement of the MFPT between the stochastic simulation and Eq. 6 as function of the distance \( r \).

In the following, we focus on the discussion of the spatially averaged MFPT for a channel starting at arbitrary positions in the patch. As shown in Figure 1C the FPT still exhibits an exponential distribution with a time constant of \( \bar{T} = 40.6s \) corresponding to the spatially averaged MFPT. For the example given in Figure 1C, using only the leading order term in Eq. 8 yields a spatially averaged MFPT of \( \bar{T} = 49.1s \), while taking into account the contribution from the second order term in Eq. 8 significantly improves the result to 40.7s.

Figure 2 shows the results of stochastic simulations for the dependence of the spatially averaged MFPT on several parameters such as the diffusion coefficient \( D \) (Fig. 2A), the patch radius \( R_{circ} \) (Fig. 2B), the anchor radius \( r_{an} \) (Fig. 2C), and the channel radius \( r_{ch} \) (Fig. 2D), together with the asymptotic result in Eq. 8 with \( R = R_{circ} \). For comparison we have also plotted the leading order term alone (dashed line) in Figure 2. Figs. 2A-C clearly demonstrate the importance of the \( O(1) \) term in Eq. 4 (\( \sim R_{N} \)) to achieve full agreement between the results from stochastic simulations and the two-term approximation in Eq. 8 even in the case \( \varepsilon/R = (r_{ch} + r_{an})/R \ll 1 \).

Figure 2D shows marked deviations between the results of the stochastic simulation and the asymptotic result.
(red curve) in Eq. 8 with \( R = R_{\text{circ}} \) as the radius \( (r_{ch}) \) of the diffusing channel protein increases. However, when the true radius of the domain \( R \) is replaced by an effective radius \( R = R_{\text{circ}} - r_{ch} \), we again find excellent agreement (green curve) between the results of the stochastic simulation and the asymptotic result in Eq. 8. This suggests the following interpretation: In contrast to the derivation of the asymptotic result, the diffusing channel in the stochastic simulations is not treated as a point particle. Due to the reflecting boundary condition, it only samples an area with an effective radius of \( R_{\text{circ}} - r_{ch} \) since it never penetrates the boundary region \( [R_{\text{circ}} - r_{ch}, R_{\text{circ}}] \). As Figure 2 D shows this finite size effect becomes noticeable already for comparably small values of \( r_{ch}/R_{\text{circ}} \approx 0.01 \).

\[ \Delta T = -\frac{1}{D} \left( \frac{1}{2} \ln \frac{L}{\varepsilon} + \frac{1}{12} - \frac{1}{2\pi \ln \pi} \right). \]

\[ T(x, y) = -\frac{4L^2}{D} G_N(x, y) + T_{sq} \]

where \( G_N \) is the Neumann function for the unit square and the average MFPT is given by

\[ T_{sq} = \frac{4L^2}{D} \left( \frac{1}{2\pi \ln \pi} \right). \]

Here we have used the known result for the regular part of the Neumann function for the unit square [26]

\[ \lim_{(x,y)\to(0,0)} R_{N,\text{sq}}(x, y) \approx \frac{1}{12} - \frac{1}{2\pi \ln \pi}. \]

Figure 3 shows the results of Monte Carlo simulations for the average MFPT of an IP3R channel diffusing in a square patch of length \( L_{sq} \) with an anchor site in the center and reflecting boundary condition. We investigate the
Next we compare the average MFPT for a circular and a square patch having the same total area. For this purpose we set $L = R \sqrt{\pi}/2$ in Eq. 9 and obtain

$$T_{sq} = \frac{\pi R^2}{D} \left( \frac{1}{2\pi} \ln \sqrt{\pi R / 2\varepsilon} + \frac{1}{12} - \frac{1}{2\pi} \ln \pi \right)$$

$$= \frac{\pi R^2}{D} \left( \frac{1}{2\pi} \ln \frac{R}{\varepsilon} \frac{3}{8\pi} \frac{2}{3} \ln (4\pi) - \frac{2\pi}{9} \right)$$

$$\simeq T_{circ}$$

since $(2/3) \ln (4\pi) - 2\pi/9 \approx 1$. Hence, with respect to the $O(1)$ expansions in Eqs. 8 and 9 the average MFPT for a circular and a square domains of the same total area are basically indistinguishable. We have confirmed this result by stochastic simulations of the average MFPT for varying domain sizes as shown in Fig. 4.

**C. IP$_3$R diffusion in a cylindrical patch**

Biologically, the ER is more like a complex tubular network of small interconnected cylindrical membrane patches. Therefore, we consider now diffusion of IP$_3$R channels on a cylindrical domain of height $2H$ and radius $R_C$. However, in the simulations we neglect the curvature of the membrane since the size of an IP$_3$R channel is much smaller than the length and the circumference of the cylinder. Consequently, the membrane is assumed to be locally flat which can be modeled as a rectangular domain with periodic boundary conditions at $x = \pm \pi R_C$ and reflecting boundary conditions at the top and bottom of the cylinder at $y = \pm H$.

To obtain an expression for the average MFPT for a cylindrical domain we only have to replace the regular part of the Neumann function for the square in Eq. 9 with that for a cylindrical domain (height $2H$ and circumference $2\pi R_C$). In Ref. [26] we have derived two (alternative) expressions for this quantity given by

$$R_{N,cyl}(0,0) = \frac{1}{2\pi} \left( \frac{H}{6R_C} - \ln \frac{H}{R_C} \right)$$

$$- \frac{1}{\pi} \sum_{n=1}^{\infty} \ln \left(1 - e^{-n\pi R_C/2H}\right)$$

(10)

or

$$R_{N,cyl}(0,0) = \frac{1}{2\pi} \left( \frac{\pi^2 R_C}{6H} - \ln \pi \right)$$

$$- \frac{1}{\pi} \sum_{n=1}^{\infty} \ln \left(1 - e^{-n\pi^2 R_C/2H}\right).$$

(11)

As we have shown in Ref. [26] both expressions represent the same function. However, the infinite sums posses a different speed of convergence. While the infinite sum in Eq. 10 rapidly converges for $H \gg R_C$ the infinite sum in Eq. 11 converges rapidly in the opposite limit.
Specifically, for $H \gg R_C$, the infinite sum in Eq. 10 can be neglected and the average MFPT for the cylindrical domain can be approximated as

$$\bar{T}_{cyl} \approx \frac{4\pi R_C H}{2\pi D} \left( \ln \frac{H}{\varepsilon} + \frac{H}{6R_C} - \ln \frac{H}{R_C} \right) \quad (12)$$

Note that this expression reduces to Eq. 9 if $H/R_C = \pi$ while keeping $H = L$ fixed. Hence, the average MFPT for a square-shaped domain and that of an equally sized cylindrical domain should be equal. This was confirmed by the stochastic simulations (star symbols) shown in Fig. 3 where we used $H_{cyl} = \pi R_C = L_{sq}$.

Next we discuss how the average MFPT depends on the aspect ratio $x = H/\pi R_C$ of the cylindrical domain. Therefore, the total surface area $A_{cyl}$ is kept constant. Note that for a fixed area and a given aspect ratio the height $H$ and radius $R_C$ are given by

$$H = \frac{\sqrt{A_{cyl} x}}{2} \quad \text{and} \quad R_C = \frac{1}{2\pi} \sqrt{\frac{A_{cyl}}{x}},$$

which allows to rewrite the average MFPT as

$$\bar{T}_{cyl} = \frac{A_{cyl}}{2\pi D} \left( \ln \frac{\sqrt{A_{cyl} x}}{2\varepsilon} + \frac{\pi x}{6} - \ln(\pi x) \right)$$

$$- \frac{A_{cyl}}{\pi D} \sum_{n=1}^{\infty} \ln \left( 1 - e^{-2\pi n x} \right) \quad (13)$$

using Eq. 10 or

$$\bar{T}_{cyl} = \frac{A_{cyl}}{2\pi D} \left( \ln \frac{\sqrt{A_{cyl} x}}{2\varepsilon} + \frac{\pi}{6x} - \ln(\pi) \right)$$

$$- \frac{A_{cyl}}{\pi D} \sum_{n=1}^{\infty} \ln \left( 1 - e^{-2\pi n / x} \right) \quad (14)$$

using Eq. 11. Note that these expressions for the average MFPT are symmetric under the inversion $x \rightarrow 1/x$. Indeed, changing $x$ to $1/x$ in Eq. 13 yields the expression in Eq. 14 and vice versa. For a quantitative comparison of these expressions with the results from numerical simulations we used a different number of terms ($n_{\text{max}}$) from the infinite sum in Eq. 13 to correctly reproduce the behavior of the average MFPT for $x \ll 1$.

As shown in Fig. 5 a minimal average MFPT is obtained for $x = 1$, i.e. for $H = \pi R_C$ corresponding to a square-shaped cylindrical domain. In general, we see a moderate dependence of the average MFPT on the aspect ratio. For example, increasing (or decreasing) the aspect ratio by a factor of 3 increases the average MFPT by approximately 13%. The asymptotic expression in Eq. 13 nicely fits the results of Monte-Carlo simulations given by the black symbols.

Since the Neumann function for a rectangular domain with reflecting walls and that for a cylindrical domain is the same as long as the singularity is located at the origin the average MFPT for both domains should also be equal.

To confirm this we plot in Fig. 5 the dependence of the average MFPT on the ratio between the width and the length of a rectangular domain with reflecting boundary conditions. Similarly as for the cylindrical domain, a minimal average MFPT is obtained when the aspect ratio equals one, i.e. for a square-shaped domain.

D. The case of an off-center anchor site

In the cases investigated so far the anchor site was always located at the center of the domain. Now we consider the situation when the anchor site is shifted away from the center by a distance $d$.

In principle, all one has to know is the regular part of the Neumann function for the respective domain, but with the singular point $x_0$ (cf. Eq. 3) shifted off the center. However, already for the case of a rectangular domain the explicit expression for the Neumann function with an off-center singularity is very clumpy [38]. Therefore, to illustrate the general procedure we consider only the case of a circular domain with an off-center absorbing region. In that case the Neumann function (for the unit disk) has the explicit representation [37]

$$G_N(x, x_0) = \frac{1}{2\pi} \left( - \ln |x - x_0| - \ln \left| x \frac{x_0}{|x_0|} - x_0 \right| \right)$$

$$+ \frac{1}{2\pi} \left( \frac{1}{2} (|x|^2 + |x_0|^2) - \frac{3}{4} \right).$$

Here, $x$ denotes the normalized distance by $R$. The reg-
ular part of $G_N$ is defined as (cf. Eq. 2)
\[
R_N(x, x_0) = G_N(x, x_0) + \frac{1}{2\pi} \ln |x - x_0|^2 - x_0 |x_0|^2 - \frac{3}{4} \right].
\]
Hence, the average MFPT for an anchor site at an arbitrary point inside a circular domain becomes
\[
\bar{T}_{\text{circ}}(x_0) = \frac{\pi R^2}{D} \left( \frac{1}{2\pi} \ln \frac{R}{\varepsilon} + \lim_{x \to x_0} R_N(x, x_0) \right)
= \frac{R^2}{2D} \left( \ln \frac{R}{\varepsilon} + \frac{3}{4} + \ln \left| x_0 |x_0| - \frac{x_0}{|x_0|} - |x_0|^2 \right) \right).
\]
Without loss of generality we assume that anchor site is shifted along the $x$-axis, i.e. $x_0 = (a,0) = (d/R,0)$. Then the expression for the average MFPT simplifies to
\[
\bar{T}_{\text{circ}}(a) = \frac{R^2}{2D} \left( \ln \frac{R}{\varepsilon} + \frac{3}{4} - \left( \ln |a^2 - 1| - a^2 \right) \right) \tag{15}
\]
which reduces to Eq. 8 in the limit $a \to 0$.

The results of the stochastic simulations in Figure 6 show very good agreement with Eq. 15. For comparison we have also performed simulations in a square-shaped domain with reflecting boundary conditions and in a domain with cylindrical topology where $L_{\text{cyl}} = \pi R_C$, all having the same area. They indicate that the average MFPT becomes sensible for the shape of the domain as the absorbing anchor site is shifted towards the domain boundary. Specifically, marked deviations between the average MFPT for the circular and the square-shaped domain occur when $d/L_{sq} > 0.6$.

IV. DISCUSSION AND CONCLUSIONS

In this paper we combine asymptotic analytical methods with Monte Carlo simulations to discuss the Brownian movement of calcium ion channels (IP$_3$Rs) on a membrane patch of the endoplasmic reticulum (ER) containing a small absorbing anchor site to trap the channel. We find excellent agreement between the asymptotic expression and stochastic simulations if the $O(1)$ in Eq. 4, coming from the regular part $R_N$ of an associated Neumann function, is taken into account and the radius of the diffusing channel ($r_{ch}$) is sufficiently small.

As the channel radius increases one has to take into account that the diffusing channel only samples an effective area when reflecting boundary conditions are applied. Based on this observation we suggest a simple correction to the asymptotic expression for the average MFPT when the channel radius increases. Specifically, at large channel radius, the characteristic length of the domain $L_c$ should be replaced by the effective length $L_c - r_{ch}$ in

\[
T(\bar{R}, L_{sq}) = \frac{2}{\pi} \ln \frac{\bar{R}}{\varepsilon} - \frac{3}{4} + \frac{1}{2} \left( |x|^2 + |x_0|^2 - 3 \right). \tag{15}
\]

FIG. 6: (Color online) Dependence of the average MFPT on the distance $d$ of the anchor site from the patch center for different domain shapes. Red circles represent simulation data for the circle patch with $R = 1.69 \mu$m; black squares represent simulation data for the square patch (all boundaries reflecting) with $L_{sq} = 1.5 \mu$m; green stars represent simulation data for the cylindrical patch with $L_{cyl} = 1.5 \mu m = \pi R_C$. Here $r_{ch} = 9$ nm, $r_{an} = 10$ nm and $D = 0.1 \mu m^2/s$.

Eq. 4 keeping the functional form of the expression for the average MFPT the same. Both asymptotic results and Monte Carlo simulations show that the average MFPT for a circular and a square-shaped domain of the same total area are indistinguishable if the anchor site remains within half a characteristic length scale from the domain center (Fig. 6). This suggests that in symmetric domains, which are characterized by only one length scale, the average MFPT is insensitive to the particular shape of the domain boundary if the trapping site is sufficiently close to the domain center.

However, when the domain is asymmetric, as in the case of a rectangular or a cylindrical domain, the average MFPT depends on the aspect ratio between the characteristic length scales of the respective domain. As a result, one can observe a difference in the average MFPT, compared to a square-shaped domain of the same area, even when the anchor site is located at the origin. Changing the aspect ratio can only increase the average MFPT compared to a square-shaped domain of the same area for which the average MFPT assumes a minimum.

In the present study we focused on the spatially averaged MFPT of a small diffusing channel protein towards a small absorbing anchor site in different two-dimensional geometries which was motivated by the observed clustering of IP$_3$R calcium channels diffusing within a finite ER membrane patch. However, we would like to mention that our results may also be useful to estimate the average MFPT of channel proteins or receptor molecules on other membrane structures or quasi two-dimensional cellular organelles. The inverse of the average MFPT can be used as an estimate for the diffusion-limited rate constant to describe the association between a diffusing channel protein and a preestablished static trapping site such as an IP$_3$R cluster.
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VI. REFERENCES