Position-dependent stochastic diffusion model of ion channel gating

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A position-dependent stochastic diffusion model of gating in ion channels is developed by considering the spatial variation of the diffusion coefficient between the closed and open states. It is assumed that a sensor which regulates the opening of the ion channel experiences Brownian motion in a closed region R_c and a transition region R_m, where the dynamics is described by probability densities $p_c(x,t)$ and $p_m(x,t)$ which satisfy interacting Fokker-Planck equations with diffusion coefficient $D_c(x)=D_c \exp(\gamma_c x)$ and $D_m(x)=D_m \exp(-\gamma_m x)$. The analytical solution of the coupled equations may be approximated by the lowest frequency relaxation, a short time after the application of a depolarizing voltage clamp, when $D_m \ll D_c$ or the diffusion parameter γ_m is sufficiently large. Thus, an empirical rate equation that describes gating transitions may be derived from a stochastic diffusion model if there is a large diffusion (or potential) barrier between open and closed states.

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I. INTRODUCTION

Voltage and ligand gated channels play an important role in initiating and modulating the subthreshold response and the action potential in nerve and muscle membranes [1]. For many years the dynamics of the transition between the closed and open states of voltage-dependent channels have been described by an empirical rate equation,

$$\frac{dP_o(t)}{dt} = \alpha - (\alpha + \beta)P_o(t), \tag{1}$$

where α and β are opening and closing transition rates and $P_o(t)$ is the open state probability [2]. The dwell-time distribution for the open state of a nicotinic acetylcholine (nACh) ion channel is also an exponential function $f_o(t)$ and is associated with the decay of the muscle endplate current [3]. If the ion channel sensor has multiple closed states and an open state, it is assumed that the dynamics of the system is described by a master equation. Although the discrete state Markov model has been successful in describing ionic and gating currents across the membrane, and closed and open dwell-time distributions in ion channels [1,4,5], it does not take account of the Brownian motion of large protein molecules in the energy landscape [6].

The open or closed state dwell-time distribution $f(t)$ obtained from the patch clamp recording of stochastic current pulses in ion channels may be represented by a finite sum of exponential functions of time, and for several ion channels, $f(t)$ may be approximated by a power law t^{-p-1} for intermediate times [7,8]. In order to account for multiple relaxation times and the emergence of a power-law approximation to the dwell-time distribution, both discrete [9–12] and continuous [13–16] diffusion models have been proposed, and if it is further assumed that there is an increasing barrier height and decreasing energy away from the open state, general power laws and a rate-amplitude correlation may be derived [17,18]. For a Ca-dependent K channel, the non-Markovian character of the current fluctuations and the dwell-time distribution power-law behavior [19,20] may be described by a fractional diffusion model of ion channel gating [21].

A numerical solution to a Smoluchowski equation for a voltage-dependent channel has shown that a large potential barrier between states ensures that the closed state is Markovian with a well-defined escape rate. The gating current has been computed for an energy landscape with potential barriers and a spatially inhomogeneous diffusion coefficient and is in qualitative agreement with experimental data [22]. The objective of the paper is to derive an analytical solution of the interacting Fokker-Planck equations for a closed region R_c and transition region R_m in response to a depolarizing voltage clamp, and to show that the solution has a single dominant relaxation time when $D_m \ll D_c$ or the diffusion parameter γ_m is sufficiently large.

II. STOCHASTIC DIFFUSION MODEL OF ION CHANNEL GATING

The opening of ligand and voltage activated ion channels is dependent on the conformation of a sensor which is comprised of, in general, several macromolecules which may undergo rotation and translation between each surface of the membrane [1,23]. It is assumed that the sensor experiences Brownian motion in a closed state region $R_c(-d_c \leqslant x \leqslant 0)$, and a transition region $R_m(0 \leqslant x \leqslant d_m)$, adjacent to the open state, with the dynamics described by the probability densities $p_c(x,t)$ and $p_m(x,t)$ which satisfy Fokker-Planck (or Smoluchowski) equations [24,25],

$$\frac{\partial p_c(x,t)}{\partial t} = \frac{\partial}{\partial x}\left[D_c(x)\left(\frac{\partial p_c(x,t)}{\partial x} + \frac{\partial U_c(x)}{\partial x}p_c(x,t)\right)\right], \tag{2}$$

$$\frac{\partial p_m(x,t)}{\partial t} = \frac{\partial}{\partial x}\left[D_m(x)\left(\frac{\partial p_m(x,t)}{\partial x} + \frac{\partial U_m(x)}{\partial x}p_m(x,t)\right)\right], \tag{3}$$

where $U_c(x)$ and $U_m(x)$ are potential functions. The diffusion coefficient $D_c(x)=D_c \exp(\gamma_c x)$, $D_m(x)=D_m \exp(-\gamma_m x)$, γ_c and γ_m are constants, and either $D_c=D_m$ or there is a discontinuity at the interface between R_c and R_m (see Fig. 1). For Markovian ion channels, the power-law approximation to the

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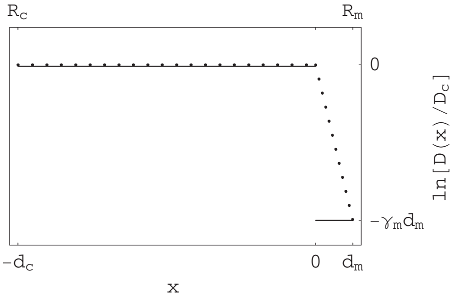

FIG. 1. The diffusion coefficient $D(x)$ within R_c and R_m may be continuous (dotted line) or there may be a discontinuity at the interface $x=0$ (solid line).

dwell-time distribution is dependent on the variation in barrier height between closed states [18], and therefore we may consider the effect of the diffusion parameters D_m and γ_m in the transition region on the gating dynamics of an ion channel.

The diffusion in the region R_c is confined by the inner surface of the membrane, and therefore a reflecting boundary is imposed at $x=-d_c$,

$$\frac{\partial p_c(x,t)}{\partial x} + U_c' p_c(x,t) = 0, \tag{4}$$

where $\partial U_c(x)\partial x$ is assumed to be a constant U_c'. Only unidirectional transitions from the closed to the open state are considered and therefore $p_m(d_m,t)=0$. It may be assumed that the probability current and the probability density are continuous at the interface between R_m and R_c,

$$j_c(0,t) = j_m(0,t), \tag{5}$$

$$p_c(0,t) = p_m(0,t). \tag{6}$$

The dwell time for each region is $T_c=\int_0^\infty P_c(t)dt$ and $T_m=\int_0^\infty P_m(t)dt$ where the survival probabilities $P_c(t)=\int_{-d_c}^0 p_c(x,t)dx$ and $P_m(t)=\int_0^{d_m} p_m(x,t)dx$ [5]. The ion channel is initially in a hyperpolarized state $[P_c(0)=1]$ and hence the initial condition may be specified as $p_c(x,0)=\delta(x)$ and $p_m(x,0)=0$, and we may assume that the ion channel is depolarized to a membrane clamp potential of $V=V_f$ for which $U_c(x)$ and $U_m(x)$ are independent of x.

The relative amplitude of the multiple relaxation times may be determined by solving Eqs. (2) and (3) with the initial and boundary conditions using the method of Laplace transforms. Defining $z=z_0\exp(-\gamma_c x/2)$, $z_0=2/(\gamma_c\sqrt{D_c})$, $z_d=z_0\exp(\gamma_c d_c/2)$, $y=y_0\exp(\gamma_m x/2)$, $y_0=2/(\gamma_m\sqrt{D_m})$, $y_d=y_0\exp(\gamma_m d_m/2)$, $p_c(x,t)=zu_c(z,t)$, and $p_m(x,t)=yu_m(y,t)$, Eqs. (2) and (3) may be expressed as Bessel differential equations, and it may be shown that the probability that the sensor is in the region R_c and R_m is

$$P_{cm}(t) = \int_{-d_c}^{d_m} p(x,t)dx = \sum_{i=1}^{\infty} a_i \exp(-\omega_i t), \tag{7}$$

where $\omega_i=\mu_i^2, \mu_i(<\mu_{i+1})$ is a solution of the eigenvalue equation

$$\frac{S_0(\mu_i,z_0,z_d)S_1(\mu_i,y_0,y_d)}{C_0(\mu_i,z_0,z_d)C_0(\mu_i,y_d,y_0)} = \sqrt{\frac{D_m}{D_c}}, \tag{8}$$

$C_0(\mu_i,z_0,z_d)$ and $S_\nu(\mu_i,z_0,z_d)$ for $\nu=0$ or 1 are defined in terms of Bessel functions of the first and second kinds,

$$C_0(\mu_i,z_1,z_2) = J_1(\mu_i z_1)Y_0(\mu_i z_2) - Y_1(\mu_i z_1)J_0(\mu_i z_2),$$

$$S_\nu(\mu_i,z_1,z_2) = J_\nu(\mu_i z_1)Y_\nu(\mu_i z_2) - Y_\nu(\mu_i z_1)J_\nu(\mu_i z_2),$$

with similar definitions for the parameters y_1 and y_2,

$$a_i = \frac{2C_0(\mu_i,y_d,y_d)}{C_0(\mu_i,y_d,y_0)[h_1(\mu_i)+h_2(\mu_i)+h_3(\mu_i)+h_4(\mu_i)]},$$

$$h_1(\mu) = \frac{1}{S_0(\mu,z_0,z_d)}\frac{d[\mu S_0(\mu,z_0,z_d)]}{d\mu},$$

$$h_2(\mu) = \frac{1}{S_1(\mu,y_0,y_d)}\frac{d[\mu S_1(\mu,y_0,y_d)]}{d\mu},$$

$$h_3(\mu) = -\frac{1}{C_0(\mu,z_0,z_d)}\frac{d[\mu C_0(\mu,z_0,z_d)]}{d\mu},$$

$$h_4(\mu) = -\frac{1}{C_0(\mu,y_d,y_0)}\frac{d[\mu C_0(\mu,y_d,y_0)]}{d\mu}. \tag{9}$$

Adopting a small argument approximation for the Bessel functions [26], from the solution (7)

$$T_c = \frac{d_c[\exp(\gamma_m d_m)-1]}{D_m\gamma_m}. \tag{10}$$

From Eqs. (7) and (8), if γ_c and γ_m are sufficiently small it may be shown that $\omega_1\approx D_m/d_c d_m\approx 1/T_c$ and

$$\frac{1}{a_1} \approx \frac{1}{2}\frac{\sin\sqrt{\tau_m/T_c}}{\sqrt{\tau_m/T_c}}\left[1+\frac{\tau_m}{T_c}+\frac{\tau_m}{T_c}\frac{\cos^2\sqrt{\tau_m/T_c}}{\sin^2\sqrt{\tau_m/T_c}}\left(1+\frac{\tau_c}{T_c}\right)\right], \tag{11}$$

where $\tau_m=d_m^2/D_m$ and $\tau_c=d_c^2/D_c$. Therefore $P_{cm}(t)$ may be approximated by the lowest frequency component with opening rate $\alpha\approx 1/T_c$ when $\tau_c\ll T_c$ and $\tau_m\ll T_c$ or equivalently

$$\frac{D_m}{D_c} \ll \frac{d_m}{d_c} \ll 1, \tag{12}$$

and is in good agreement with the survival probability of the slow closed state for a delayed rectifier K channel, after eliminating the fast closed component with a low frequency filter [27] (see Fig. 2). The relation $d_m\ll d_c$ may be obtained from the voltage dependence of the mean closed time for an interacting diffusion regime [15] or from the requirement that the probability current in the transition region is quasistationary [18], and $\tau_c\ll T_c$ is also satisfied when there is a large potential barrier in the region R_m. A short time after the application of the voltage clamp, the spatial variation of the probability density $p(x,t)$ is approximately linear in the region R_m (see Fig. 3) and therefore the probability current is constant within the transition region.

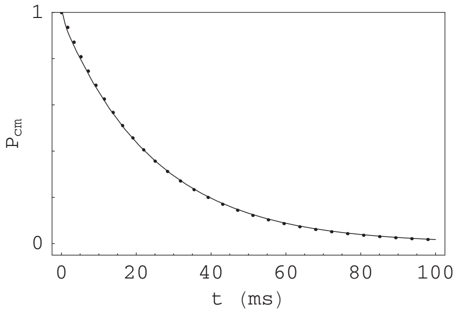

FIG. 2. The survival probability of the slow closed state for a delayed rectifier K channel [27] (dotted line) and the analytical solution $P_{cm}(t)$ (solid line) where $d_m/d_c=0.15$, $D_m/D_c=0.0225$, $\tau_c=3.4$ ms, γ_c, $\gamma_m\to 0$, $a_i=(0.977,0.130,-0.103,\dots)$, and $\omega_i=(0.040,2.26,3.62,\dots)$.

By assuming that $D_c(x)=D_m(x)=D$ and $d_m\ll d_c$, it follows that $T_c=\tau_c d_m/d_c\ll\tau_c$, and the dwell-time distribution for intermediate times may be described by a power law (see Fig. 4) [9,11,15], as observed in several types of ion channels for the closed states accessible from the open state during a depolarizing patch clamp. However, it should be noted that the closed states associated with a power-law approximation to the dwell-time distribution are, generally, not the same as those in the activation sequence [28].

If $D_m=D_c$, $\gamma_c d_c\ll 1$, and $\gamma_m d_m\gg 1$, adopting a small argument approximation in R_m and large argument approximation in R_c [26], it may be shown from Eqs. (7) and (8) that

$$\frac{1}{\omega_1}\approx\frac{d_c[\exp(\gamma_m d_m)-1]}{D_m\gamma_m}\approx T_c, \tag{13}$$

$$\frac{1}{a_1}\approx 1+\frac{\gamma_m d_c}{2[\exp(\gamma_m d_m)-1]}, \tag{14}$$

and thus $a_1\approx 1$ and $a_i\approx 0$ for $i>1$ when

$$\frac{\gamma_m d_m}{\exp(\gamma_m d_m)-1}\ll\frac{d_m}{d_c}, \tag{15}$$

or from Eq. (10), $\tau_c\ll T_c$. Therefore, when γ_m is sufficiently large, $P_{cm}(t)\approx\exp(-\omega_1 t)$, and in agreement with the data from a delayed rectifier channel [27] (see Fig. 5).

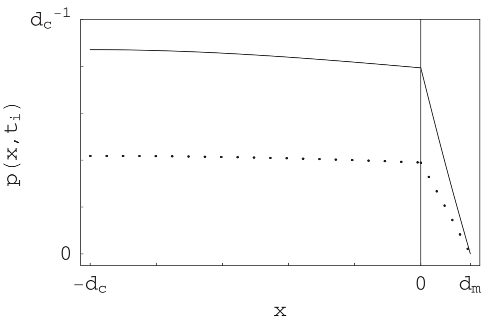

FIG. 3. The probablility density $p(x,t)$ in the region $R_c(-d_c\leqslant x\leqslant 0)$ and $R_m(0\leqslant x\leqslant d_m)$ for $t_1=2$ ms (solid line) and $t_2=20$ ms (dotted line) where $d_m/d_c=0.15$, $D_m/D_c=0.0225$, $\tau_c=3.4$ ms, γ_c, $\gamma_m\to 0$.

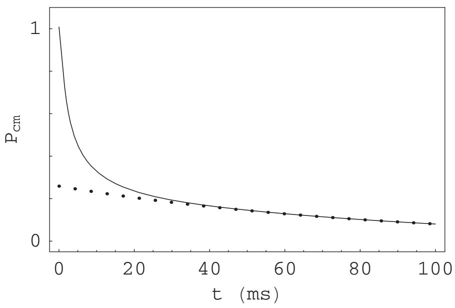

FIG. 4. The survival probability $P_{cm}(t)$ (solid line) and the lowest frequency component $a_1\exp(-\omega_1 t)$ (dotted line) where $d_m/d_c=0.15$, $D_c=D_m$, $T_c=24$ ms, γ_c, $\gamma_m\to 0$, $a_i=(0.259,0.245,0.218,\dots)$, and $\omega_i=(0.012,0.105,0.292,\dots)$.

III. DISCUSSION

Gating in voltage or ligand activated ion channels is regulated, in general, by several macromolecules which experience Brownian motion in the closed and open regions, where the dynamics may be described by probability densities which satisfy interacting Fokker-Planck equations. We have shown that a single dominant relaxation time may be derived from a position-dependent stochastic diffusion model when there is a discontinuity in the diffusion coefficient at the interface between the regions R_m and R_c with $D_m\ll D_c$, and the width of the transition region (d_m) is much less than the width of the closed region (d_c). These conditions ensure that $\tau_c\ll T_c$ and $\tau_m\ll T_c$, and therefore the Brownian motion in the closed and transition regions may be described as quasistationary. The small relative value of d_m is consistent with recent experimental data that indicate that each $S4$ sensor has a translation of the order of 6 Å across a focused electric field [29]. If $D_m(x)=D_m\exp(-\gamma_m x)$, the response of the system to a depolarizing voltage clamp may also be approximated by the lowest frequency relaxation when the diffusion parameter γ_m is sufficiently large.

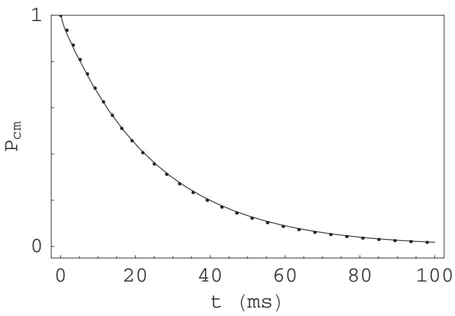

FIG. 5. The survival probability of the slow closed state for a delayed rectifier K channel [27] (dotted line) and the analytical solution $P_{cm}(t)$ (solid line) where $d_m/d_c=0.15$, $\gamma_c\to 0$, $\gamma_m d_m=6$, $\tau_c=2.2$ ms, $a_i=(0.984,0.055,-0.030,\dots)$, and $\omega_i=(0.04,3.5,7.48,\dots)$.

If the opening of the ion channel is determined by m identical and independent subunits and the conductance of the channel is expressed as $g \propto P_o(t)^m$ [2], a rate equation may be derived for each subunit when there is a large diffusion or potential barrier between the closed and open configurations of each sensor molecule. When the closed state dwell-time distribution obtained from a patch clamp recording has a finite number of relaxation times, the closed states may be represented as energy wells between potential or diffusion barriers within an energy landscape, and the resulting system of interacting Fokker-Planck equations may be approximated by a Markovian master equation.

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