# Nonlinear drift-diffusion model of gating in the fast Cl channel

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(Received 1 February 2007; published 30 July 2007)

The dynamics of the open or closed state region of an ion channel may be described by a probability density $p(x,t)$ which satisfies a Fokker-Planck equation. The closed state dwell-time distribution $f_c(t)$ derived from the Fokker-Planck equation with a nonlinear diffusion coefficient $D(x) \propto \exp(-\gamma x)$, $\gamma > 0$ and a linear ramp potential $U_c(x)$, is in good agreement with experimental data and it may be shown analytically that if $\gamma$ is sufficiently large, $f_c(t) \propto t^{-2-\nu}$ for intermediate times, where $\nu = U_c'/\gamma \approx -0.3$ for a fast Cl channel. The solution of a master equation which approximates the Fokker-Planck equation exhibits an oscillation superimposed on the power law trend and can account for an empirical rate-amplitude correlation that applies to several ion channels.

DOI: 10.1103/PhysRevE.76.011923 PACS number(s): 87.15.He, 05.10.Gg, 05.40.Jc, 87.16.Uv

## INTRODUCTION

Ion channels are macromolecules which permit the conduction of ions across the membrane and are essential for metabolic cellular processes and information processing in the nervous system. The transition of a channel from the closed to the open state is regulated by the motion of one or more helical molecules which may depend on the membrane potential or the binding of a neurotransmitter to a receptor [1,2]. The open and closed state dwell-time distributions 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 [3]

$$f(t) = \sum_{i=1}^{N} a_i k_i \exp(-k_i t). \quad (1)$$

The discrete state Markov model assumes that the rate constants $k_i$ and the amplitudes $a_i$ may be derived from the transition rates between a small number $N$ of distinct conformational substates that form the open or closed state, and has been successful in describing gating current and dwell-time distributions in ion channels with the transition rates usually assumed to be independent. However, by assuming that the amplitude $a_i$ and the rate $k_i$ satisfy an empirical correlation $a_i \propto k_i^p$ where $p \approx 0.5$ [4], the resulting $f(t)$ exhibits an oscillation superimposed on a power law which provides an approximate fit to the dwell-time distribution obtained from some ion channels [5].

By contrast to the discrete state Markov model, diffusion models assume that there are a large number of closed states, and are able to describe the approximate time course of gating currents [6,7], the intermediate power law behavior of the dwell-time distribution $f_c(t) \propto t^{-1.5}$ when the diffusion coefficient is constant [8–12], and $f_c(t) \propto t^{-2}$ when the approximately equal forward and backward transition rates between neighboring states decrease geometrically away from the open state [13,14]. An intermediate power law of the type $f_c(t) \propto t^{-2+\alpha/2}$, where $\alpha$ is the index of anomalous diffusion ($\alpha = 1$ for normal diffusion) may be derived from a fractional diffusion model of ion channel gating and is in qualitative agreement with the data from a locust Ca-dependent BK channel when $\alpha = 0.14$ [15].

The voltage dependence of the channel opening and closing rate functions may be derived from the mean state residence time for an interacting diffusion regime [11,12] or from an expression for the quasistationary diffusion current between the open and closed regions at each membrane surface, and in the latter case, the interaction between the open state probability and the membrane potential may be described by a Lagrangian (see the Appendix). It may be shown that the closed state dwell-time distribution $f_c(t)$ derived from a Fokker-Planck equation with a nonlinear diffusion coefficient $D(x) = D_c \exp(-\gamma x)$, $\gamma > 0$ and a linear potential $U_c(x)$ is in good agreement with experimental data from a K and nACh channel and for intermediate times, $f_c(t) \propto t^{-1.5}$ when $\nu = U_c'/\gamma = -0.5$ where $U_c' = \partial U_c(x) \partial x$ is a constant [16]. In this paper, it is shown analytically that if $\gamma$ is sufficiently large, the solution of the Fokker-Planck equation has an intermediate power law approximation $f_c(t) \propto t^{-2-\nu}$, and provides a good description of the data from a fast Cl channel when $\nu \approx -0.3$. The solution of the master equation approximation to the Fokker-Planck equation can also account for the empirical rate-amplitude correlation $a_i \propto k_i^p$ where $p \approx 0.65$ for a fast Cl channel.

## NONLINEAR DRIFT-DIFFUSION MODEL

The opening of voltage and ligand gated channels is dependent on the configuration of a sensor which is comprised of one or more helical molecules which may undergo rotation and translation between each surface of the membrane [2]. The states of the sensor are considered to form a linear chain and therefore, in a continuous model, each physical variable is a function of the one-dimensional reaction coordinate $x$. Positively charged residues on each sensor molecule are arranged in a regular array and interact with multiple charged chemical groups on adjacent structures and the electrostatic environment to generate a sequence of energy wells and barriers [17]. It is assumed that the open state region $R_o$ ($-d_o - d_m \leq x \leq -d_m$) is adjacent to the closed state region for the sensor which is comprised of $R_m$ ($-d_m \leq x$

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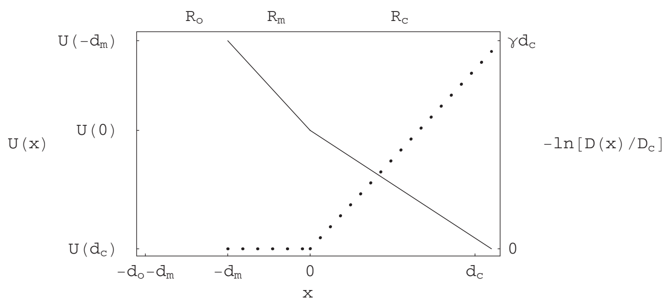


FIG. 1. The potential function $U(x)$ (solid line) and $-\ln[D(x)/D_c]$ (dotted line) for the Brownian dynamics of a channel sensor with reaction coordinate $x$ in the closed state regions $R_m$ and $R_c$.

$\leqslant 0$), where the diffusion coefficient $D(x)$ is a constant $D_m$, and $R_c$ $(0 \leqslant x \leqslant d_c)$ where the increase in barrier height between closed states in the direction away from the open state is represented by a nonlinear diffusion coefficient $D(x)$ (see Fig. 1). The continuous diffusion regime in $R_c$ may be approximated by discrete diffusion between a large number $N$ of states where the transition rates $g_i = g_1 \sigma^{1-i}$, $b_i = b_1 \sigma^{1-i}$ for $i = 2$ to $N-1$, $\sigma > 1$ (see Fig. 2), $D(x_i) \propto g_i$, $x_i = d_c(i-1)/(N-1)$ and therefore $D(x) \propto \exp(-\gamma x)$, $\gamma = (N-1)\ln \sigma / d_c > 0$. Qualitative agreement between gating current observed in K channels and that computed from a Fokker-Planck equation is obtained by assuming that the diffusion coefficient is dependent on the reaction coordinate [6].

The probability density $p(x,t)$ of states of the sensor satisfies a Fokker-Planck equation [18–20]

$$\frac{\partial p(x,t)}{\partial t} = -\frac{\partial j(x,t)}{\partial x} = \frac{\partial}{\partial x}\left[D(x)\left(\frac{\partial p(x,t)}{\partial x} + \frac{\partial U(x)}{\partial x}p(x,t)\right)\right], \tag{2}$$

where $j(x,t)$ is the probability current, and $U(x)$ is assumed to be a linear potential function, in units of $kT$ where $k$ is Boltzman's constant and $T$ is the absolute temperature. The Brownian motion of the sensor in $R_o$, $R_m$ and $R_c$ is a continuous generalization of thermally activated transitions between a finite number of closed states and an open state in discrete diffusion models of gating (see Figs. 1 and 2) [8,10,14]. An analytical solution of Eq. (2) has been presented when the diffusion coefficient $D(x)$ and the potential function $U(x)$ are independent of $x$ [11,12].

We shall assume that in the region $R_m$, $U_m(x)$ is dependent on the charge $Q$ transferred across $R_m$ and the potential difference $V$ across the membrane relative to the external medium, the diffusion time $\tau_m = d_m^2/D_m$ is small relative to the mean time that the sensor resides in $R_c$, and that $p(-d_m,t) = 0$ at the boundary between the open and closed regions. Therefore, the unidirectional probability current is quasistationary and may be approximated by the expression [18]

$$j_m(t) = -\frac{p(0,t)D_m}{\int_{-d_m}^{0}\exp[U_m(x) - U_m(0)]dx}. \tag{3}$$

The transitions between closed states in $R_c$ are confined by the inner surface of the membrane, and therefore a reflecting boundary is imposed at $x = d_c$ [4,10–12]

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

where $U_c'$ is a constant. The probability current at the interface between $R_m$ and $R_c$ is continuous and thus

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

where $j_m(t)$ is given by Eq. (3). It is assumed that, for each channel opening, the dwell time for the closed region begins when a sensor molecule is transferred across the region $R_m$ to the closed state at $x=0$ in $R_c$, and thus $p(x,0) = \delta(x)$.

In the region $R_c$, Eq. (2) may be expressed as

$$\frac{\partial n(z,t)}{\partial t} = D_c\left(\frac{\partial^2 n(z,t)}{\partial z^2} + \frac{1}{z}\frac{\partial n(z,t)}{\partial z} - \frac{n(z,t)(\nu+1)^2}{z^2}\right), \tag{6}$$

where $z = z_0 \exp(\gamma x/2)$, $z_0 = 2/\gamma$, $z_d = z_0 \exp(\gamma d_c/2)$, $\nu = U_c'/\gamma$, and $n(z,t) = z^{\nu-1}p(x,t)$. From the solution of Eq. (6) with the initial condition and the boundary conditions (4) and (5) using the method of Laplace transforms, it may be shown that the probability that the sensor is in the closed state region $R_c$ is

$$P_c(t) = \int_0^{d_c} p(x,t)dx = \sum_{i=1}^{\infty} a_i \exp(-\omega_i t), \tag{7}$$

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

$$\frac{S_\nu(\mu_i, z_0)}{C_\nu(\mu_i, z_0)} = \frac{r_c}{\mu_i(z_d - z_0)}, \tag{8}$$

$r_c = 2D_m[\exp(\gamma d_c/2) - 1]/\gamma D_c Y_m$, $Y_m = \int_{-d_m}^{0}\exp[U_m(x) - U_m(0)]dx$, $C_\nu(\mu_i,z)$, and $S_\nu(\mu_i,z)$ are defined in terms of Bessel functions of the first kind

$$C_\nu(\mu,z) = J_{-\nu}(\mu z_d)J_{\nu+1}(\mu z) + J_\nu(\mu z_d)J_{-\nu-1}(\mu z),$$

$$S_\nu(\mu,z) = J_{-\nu}(\mu z_d)J_\nu(\mu z) - J_\nu(\mu z_d)J_{-\nu}(\mu z),$$

$a_i = 2/[1 + h_1(\mu_i) + h_2(\mu_i)]$ and

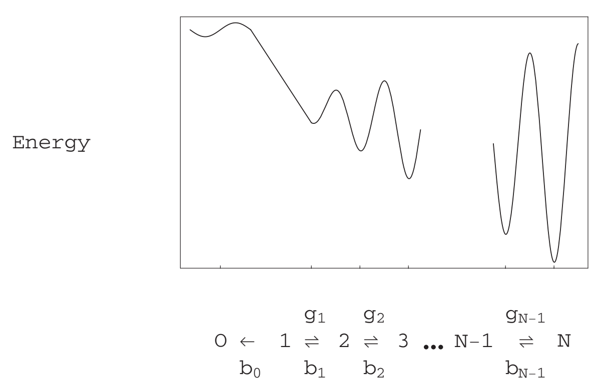


FIG. 2. Energy level diagram for a Markov chain of $N$ closed states of a channel sensor with increasing barrier height and decreasing energy away from the open state $O$.

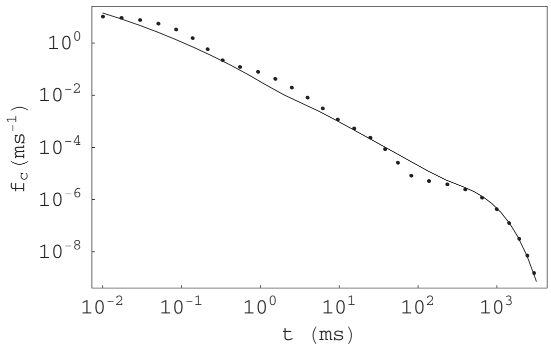


FIG. 3. The closed state dwell-time distribution function $f_c(t)$ for a fast Cl channel [22] (dotted line) and the nonlinear drift-diffusion model (solid line) where $\tau_c=1200$ ms, $r_c=228$, $\gamma=8/d_c$, and $\nu=-0.3$.

$$h_1(\mu)=\frac{\mu(z_d-z_0)}{r_cC_\nu(\mu,z_0)}\frac{d[\mu S_\nu(\mu,z_0)]}{d\mu}, \qquad (9)$$

$$h_2(\mu)=\frac{1}{C_\nu(\mu,z_0)}\frac{d[\mu C_\nu(\mu,z_0)]}{d\mu}.$$

When $\nu$ is an integer, the solution of Eq. (6) may be expressed in terms of Bessel functions of the first and second kind. If $r_c$ is sufficiently small, it may be shown from Eq. (9) that $a_1\approx 1$, $a_i\approx 0$ for $i>1$, the probability $P_c(t)\approx \exp(-\omega_1 t)$ where $\omega_1=D_mU_c'/Y_m[1-\exp(-U_c'd_c)]$, and therefore the solution accounts for the exponential distribution of closed times described in slow $K$ channels [21].

The distribution function $f_c(t)=-dP_c(t)/dt$ obtained from Eq. (7) is also in good agreement with the approximate power law distributions of closed times from a $K$ channel and a nACh channel when $\nu\approx-0.5$ [16], and a fast Cl channel when $\nu\approx-0.3$ (see Fig. 3). For $\gamma d_c\gg 1$, $r_c\gg 1$ and $-1<\nu<0$, the power law behaviour of $f_c(t)\propto t^{-2-\nu}$, for intermediate times, may be derived by adopting a small argument approximation for $J_\nu(\mu z_0)$ and a large argument approximation for $J_\nu(\mu z_d)$ [23],

$$h_1(\mu)\approx \mu^2(z_d-z_0)^2/r_c,$$

$$h_2(\mu)\approx \frac{r_c\Gamma(1+\nu)(\mu/\gamma)^{-1-2\nu}}{\theta\Gamma(-\nu)},$$

$$\theta\approx\frac{\cos[\mu z_d+\pi(\nu-0.5)/2]}{\cos[\mu z_d-\pi(\nu+1.5)/2]}.$$

There exists a positive integer $m$ such that for $i<m$, $h_2(\mu_i)\gg h_1(\mu_i)$ and hence for $t\gg 1/\omega_m$,

$$P_c(t)\approx\frac{2\pi A\tau_c^{\nu+1/2}}{\Gamma(1+\nu)}\sum_{i=1}^{\infty}y_i^{1+2\nu}\exp(-y_i^2t), \qquad (10)$$

where $A=\theta\Gamma(-\nu)[2\exp(\gamma d_c/2)]^{-1-2\nu}/r_c\pi$, $\tau_c=(z_d-z_0)^2/D_c$, and $y_i\approx\pi(i-0.5)/\sqrt{\tau_c}$. For large $\tau_c$, $\Delta y_i=y_{i+1}-y_i=2y_1\approx\pi/\sqrt{\tau_c}$ is small, and if $t\ll\tau_c$, the sum of the infinite series may be approximated by the integral

$$\frac{\sqrt{\tau_c}}{\pi}\int_0^\infty y^{1+2\nu}\exp(-y^2t)dy=\frac{\sqrt{\tau_c}\Gamma(1+\nu)t^{-1-\nu}}{2\pi}$$

and thus

$$P_c(t)\approx A\left(\frac{\tau_c}{t}\right)^{1+\nu}. \qquad (11)$$

When $\nu=-0.5$ this expression reduces to $P_c(t)\approx\sqrt{\tau_c/\pi t}/r_c$ which describes the power law approximation for a K and nACh ion channel [16] whereas for a fast Cl channel, $\nu\approx-0.3$ and $P_c(t)\approx 0.1(\tau_c/t)^{0.7}/r_c\pi$. If $t>\tau_c$, $P_c(t)\approx a_1\exp(-D_c\mu_1^2t)$ where $\mu_1$ is a solution of Eq. (8) and therefore the continuous diffusion model describes the exponential tail that is often observed in the closed-time distribution. However, the patch clamp procedure has limited resolution whereas the solution of the Fokker-Planck equation includes an infinite number of high frequency components and therefore the agreement between the small time behaviour of the continuous model and the histogram data is only approximate. If $\gamma d_c\ll 1$, adopting the large argument approximation for both $J_\nu(\mu z_0)$ and $J_\nu(\mu z_d)$, it may be shown that $P_c(t)\approx\sqrt{\tau_c/\pi t}/r_c$ for intermediate times, in agreement with the power law for the constant diffusion model ($\gamma=0$) [8,10–12].

The mean closed time for the ion channel is [3,24]

$$T_c=\int_0^\infty tf_c(t)dt=\int_0^\infty P_c(t)dt, \qquad (12)$$

and from the solution (7), when $U_m(x)=Q(V-V_f)(1+x/d_m)/kT$ and $V_f$ is a constant,

$$\frac{1}{T_c}=\frac{D_mQ(V-V_f)}{d_mkT(1-\exp[-Q(V-V_f)/kT])}\frac{U_c'}{1-\exp(-U_c'd_c)}, \qquad (13)$$

and is independent of the mathematical form of the ion channel closed-time distribution. Equation (13) may also be derived in the special case when a quasistationary state is attained in the closed region $R_c$ in a time $\ll T_c$ (see the Appendix), and if $U_c'\to 0$, the expression reduces to that obtained from the constant diffusion model [11]. The voltage dependence of the mean closed time determined from patch clamp data is generally in agreement with Eq. (13), but for some ion channels $T_c$ is only weakly dependent on $V$ [21,25].

Although the intermediate power law (11) may be derived from the Fokker-Planck equation, the solution does not satisfy a rate-amplitude law $a_i\propto k_i^p$. Therefore, assuming that the ion channel sensor has a finite number of closed states [2], we may consider a Markovian master equation which approximates Eq. (2). If the channel sensor is able to undergo thermally activated transitions between $N$ closed states and an open state (see Fig. 2), it may be assumed that the dynamics are described by a master equation

$$\frac{dp_1}{dt}=b_1p_2-(g_1+b_0)p_1,$$

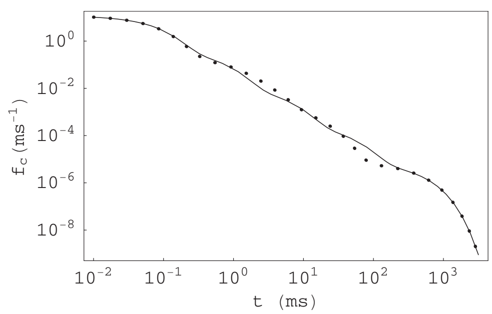

FIG. 4. The closed-time distribution function $f_c(t)$ for a fast Cl channel [22] (dotted line) and the master equation approximation to the nonlinear drift-diffusion model (solid line), where $N=5$, $b_0=3200$, $g_1=870.4$, $b_1=512$, and $\sigma_i=8$ for each $i$.

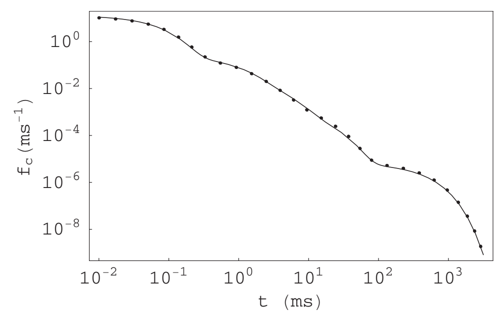

FIG. 5. The closed-time distribution function $f_c(t)$ for a fast Cl channel [22] (dotted line) and the master equation approximation to the nonlinear drift-diffusion model (solid line), where $N=5$, $b_0=3900$, $g_1=1200$, $b_1=380$, and $\sigma_i=(15,3.5,4.7,21)$.

$$\frac{dp_i}{dt} = g_{i-1}p_{i-1} + b_{i+1}p_{i+1} - (g_i + b_{i-1})p_i, \quad (1 < i < N),$$

$$\frac{dp_N}{dt} = g_{N-1}p_{N-1} - b_{N-1}p_N, \tag{14}$$

where $p_i(t)$ is the probability of occupying the $i$th closed state at time $t$, the transition rates are

$$g_i = g_{i-1}/\sigma_{i-1}, \quad b_i = b_{i-1}/\sigma_i \tag{15}$$

for $1<i<N$, $\sigma_1 \ldots \sigma_{N-1}$ are the transition rate ratios, and $b_0$ is the rate between the first closed state and the open state. The master equation model with the transition rates (15) is a more general form of discrete diffusion models where $g_1=b_1$, $\sigma_i=\sigma$ for each $i$ and either $\sigma=1$ [8] or $\sigma>1$ [14]. As the difference in reaction coordinate between states $\to 0$ and $N \to \infty$, the limit of the master equation when $\sigma_i=\sigma$ for each $i$, is a Fokker-Planck equation in the region $R_c$ [24,26].

The survival probability is given by

$$P_c(t) = \sum_{i=1}^{N} p_i(t), \tag{16}$$

and the closed-time distribution function $f_c(t)=-dP_c/dt$ may be obtained by solving Eq. (14) with the initial condition $p_1(0)=1$, $p_i(0)=0$ for $i>1$. The function $f_c(t)$ derived with uniform values for $\sigma_i$ provides a good fit to the data from a fast Cl channel (see Fig. 4), and exhibits an oscillation superimposed on the power law trend for intermediate times. However, a better fit to the experimental data may be obtained by choosing nonuniform values for $\sigma_i$ (see Fig. 5). The values of $a_i$ and $k_i$ that are derived from the solution are comparable to those obtained experimentally and satisfy an approximate rate-amplitude correlation $a_i \propto k_i^p$ [4] (see Fig. 6 where $p \approx 0.65$ for a fast Cl channel). The solution of the constant diffusion model ($\sigma_i=1$) does not satisfy a rate-amplitude correlation but for sufficiently large $N$, $f_c(t) \propto t^{-1.5}$ for intermediate times [8].

The rate-amplitude correlation and the intermediate power law that are observed for the closed-time distribution $f_c(t)$ of several types of ion channels [4] may be derived by considering Eq. (14) with $g_i=g_1\sigma^{1-i}$, $b_i=b_1\sigma^{1-i}$ for $i=2$ to $N-1$, $b_0=b_1\sigma$ where $\sigma>1$ is sufficiently large and $p=\ln(b_i/g_{i+1})/\ln \sigma$. Using matrix methods, it may be shown that $P_c(t)=\sum_{i=1}^{N} a_i \exp(-k_i t)$ where $a_i/a_{i+1} \approx b_i/g_{i+1}=\sigma^p$, $k_i/k_{i+1} \approx \sigma$, and hence $a_i \propto k_i^p$. For $t_i=1/k_i$,

$$f_c(t_i) \approx \frac{t_i^{-p-1}}{e\sum_{j=1}^{N} k_j}\left(1 + \sum_{j\neq i} T_j\right),$$

where $T_j=e(k_j/k_i)^{p+1}\exp(-k_j/k_i)$, $\sum_{j\neq i}T_j \ll 1$, and hence $f_c(t_i) \propto t_i^{-p-1}$ follows a general power law.

## DISCUSSION

Discrete diffusion models of ion channel gating have dwell-time distributions which may be approximated by the intermediate power law $t^{-3/2}$ when the transition rates are constant [8,10], and by $t^{-2}$ when the forward and backward transition rates between neighboring states decrease geometrically away from the open state [14]. In this paper, we have considered a Fokker-Planck equation which describes the dynamics of an ion channel sensor in the presence of a linear ramp potential $U_c(x)$ and an exponentially decreasing diffusion coefficient $D(x)=D_c\exp(-\gamma x)$, and is a more general form of discrete and continuous diffusion models [11,12]. The solution of the nonlinear diffusion model is dependent on the parameter $\nu=U_c'/\gamma$ and provides a good fit to the closed-time distribution function $f_c(t)$ for a delayed rectifier K channel and a nACh channel ($\nu \approx -0.5$) and a fast Cl

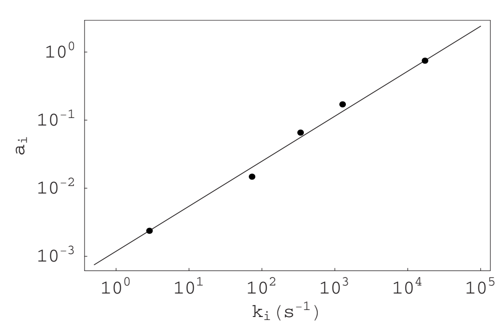

FIG. 6. The amplitudes $a_i$ and the rates $k_i$ that are calculated from the master equation model of a fast Cl channel (see Fig. 5) satisfy the equation $a_i \propto k_i^p$ where $p \approx 0.65$ (solid line).

ion channel ($\nu \approx -0.3$), and it may be shown analytically that for sufficiently large $\gamma$, $f_c(t) \propto t^{-2-\nu}$ for intermediate times.

Although the Fokker-Planck equation assumes a continuum of states, the ion channel sensor has a discrete structure and therefore the dynamics may be described by a Markovian master equation which approximates the nonlinear drift-diffusion equation. The distribution function $f_c(t)$ obtained from the solution to the master equation provides a good fit to the data from a fast Cl channel and exhibits an approximate rate-amplitude correlation $a_i \propto k_i^p$ where $p \approx 0.65$ [4]. Therefore, a variation in the energy of closed states and an increase in the barrier height away from the open state are important factors in the closed-state dynamics of several ion channels.

## APPENDIX

The channel opening and closing rate functions may be derived from an expression for the quasi-stationary diffusion current between the open and closed regions at each membrane surface when $p(-d_m,t) \propto P_o(t) = \int_{-d_m-d_0}^{-d_m} p(x,t)dx$ and $p(0,t) \propto P_c(t)$ (unpublished). If a quasistationary state is attained in the closed region $R_c$ in a time $\ll T_c$, and therefore corresponds to a small $r_c$ solution of the Fokker-Planck equation, from Eqs. (7) and (12), we may write

$$p(0,t) = \frac{P_c(t)}{\int_0^{d_c} \exp[U_c(0) - U_c(x)]dx} \tag{17}$$

and $dP_c/dt = -P_c/T_c$, where

$$\frac{1}{T_c} = \frac{D_m}{\int_{-d_m}^0 \exp[U_m(x) - U_m(0)]dx \int_0^{d_c} \exp[U_c(0) - U_c(x)]dx}. \tag{18}$$

Similarly, if a quasistationary state is attained in the open region $R_o$ in a time $\ll T_o$, where $T_o$ is the mean open time,

$$\frac{1}{T_o} = \frac{D_m}{\int_{-d_m}^0 \exp[U_m(x) - U_m(-d_m)]dx \int_{-d_m-d_0}^{-d_m} \exp[U_o(-d_m) - U_o(x)]dx}. \tag{19}$$

Therefore, each of the dwell-time distributions $f_c(t)$ and $f_o(t)$ is a single exponential function and in agreement with the data from slow K channels [21]. If $U_m(x) = Q(V-V_f)(1+x/d_m)/kT$ [1] and $U_c(x) = U_c(0) + U_c' x$, the mean closed time $T_c$ reduces to Eq. (13) and a similar expression may be obtained for $T_o$.

The probability current between the open and closed state regions may be approximated by the expression [18]

$$j_m(t) = -\frac{D_m[p(0,t)\exp U_m(0) - p(-d_m,t)\exp U_m(-d_m)]}{\int_{-d_m}^0 \exp U_m(x)dx} \tag{20}$$

when the diffusion time $\tau_m \ll T_c$ or $T_o$. Therefore, assuming that $P_o(t) \approx 1 - P_c(t)$ and $P_f = \alpha/(\alpha+\beta)$ is the stationary value of $P_o$, where $\alpha = 1/T_c$ is the mean opening rate, and $\beta = 1/T_o$ is the mean closing rate, from Eq. (17) and $p(-d_m,t) \propto P_o(t)$ we may write

$$\frac{dP_o(t)}{dt} = \alpha(1-P_f) - \beta P_f - (\alpha+\beta)[P_o(t) - P_f], \tag{21}$$

a rate equation that describes the variation of K conductance in slow K channels ($g_K \propto P_o$) [21], and in delayed rectifier K channels assuming that the opening of the channel is determined by four identical and independent subunits ($g_K \propto P_o^4$) [1].

If $I_m$ is the macroscopic membrane K current across a membrane when each K channel is open, the linear component of the ionic current is $I_m(P_o - P_f) = -C\dot{V}$. The nonlinear component of the K current and the other ionic currents through the membrane, such as Na, are considered to be perturbations to the membrane potential. The net flow of ions across a membrane is dependent on the K conductance which, in turn, is determined by the membrane potential. The voltage dependence of the rate functions (18) and (19) may also be derived from a Lagrangian $L$ and dissipation function $F$ which describes the interaction between the linear component of the ionic current and the quasistationary gating current between the closed and open region at each membrane surface

$$L = \frac{\lambda(C\dot{V})^2}{2I_m} - \frac{CD_m kT}{Q}\int \frac{1 - \exp[U_m(-d_m) - U_m(0)]}{Y_m} dV,$$

$$F = \frac{\lambda(C\dot{V})^2}{2I_m \tau},$$

where $Y_c = \int_0^{d_c} \exp[U_c(0) - U_c(x)]dx$, $Y_o = \int_{-d_m-d_o}^{-d_m} \exp[U_o(-d_m) - U_o(x)]dx$, $\lambda = (Y_c + Y_o)d_m kT/D_m Q$, $\tau = 1/(\alpha+\beta)$, the Lagrangian $L$ satisfies the equation

$$\frac{d}{dt}\left(\frac{\partial L}{\partial \dot{q}}\right) - \frac{\partial L}{\partial q} + \frac{\partial F}{\partial \dot{q}} = 0,$$

and the canonical coordinates $q = C(V - V_f)$ and $p = -\lambda(P_o - P_f)$.

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