Ion channel gating: a first passage time analysis of the Kramers type

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ABSTRACT. The opening rate of voltage-gated potassium ion channels exhibits a characteristic, knee-like turnover where the common exponential voltage-dependence changes suddenly into a linear one. An explanation of this puzzling crossover is put forward in terms of a stochastic first passage time analysis. The theory predicts that the exponential voltage-dependence correlates with the exponential distribution of closed residence times. This feature occurs at large negative voltages when the channel is predominantly closed. In contrast, the linear part of voltage-dependence emerges together with a non-exponential distribution of closed dwelling times with increasing voltage, yielding a large opening rate. Depending on the parameter set, the closed-time distribution displays a power law behavior which extends over several decades.

Introduction

Voltage-dependent ion channels of biological membranes are formed by pore-like single proteins which poke through the cell membrane. They provide the conducting pathways for the ions of specific sorts. Such potassium K$^+$ and sodium Na$^+$ channels participate in many important processes occurring in living cells. For example, these are crucial for the phenomenon of neural excitability.

Two features are important for the biological function of these naturally occurring nanotubes. First, they either are dwelling in open conformations, allowing for the ion flow to pass through, or are resting in closed, non-conducting conformations. Between these two conformation types the ion channel undergoes spontaneous, temperature driven transitions – the so-called gating dynamics – which can be characterized by the residence time distributions of open, $f_o(t)$, and closed, $f_c(t)$, states, respectively. The mean open and closed residence times, $\langle T_{o(c)} \rangle := \int_0^\infty f_{o(c)}(t)dt$ are prominent quantifiers of the gating dynamics. In particular, they determine the mean opening (closing) rates $k_{o(c)} := \langle T_{o(c)} \rangle^{-1}$. The second important feature refers to the fact that the gating dynamics is voltage-dependent. This provides a mechanism for a mutual coupling among otherwise independent ion channels. This very mechanism is realized through the common membrane potential. Both ingredients are central for the seminal model of neuronal activity put forward by Hodgkin and Huxley in 1952.

The dichotomous character of gating transitions yields a bistable dynamics of the Kramers type. Therefore, a priori one expects that both, the opening and the closing gating rates will expose an exponential, Arrhenius-like dependence on voltage and temperature. Indeed, the closing rate of many K$^+$ channels follows such a pattern; in clear contrast, however, the opening rate usually does not. To explain the experimental voltage-dependence of the relaxation time of the potassium current for a giant squid axon Hodgkin and Huxley postulated that the gating behavior of a potassium channel is determined by four independent, voltage-sensitive gates, each of which undergoes a two-state Markov dynamics with a functional form in Eq. 1:

$$k_o(V) = \frac{a_c(V - V_c)}{1 - \exp[-b_c(V - V_c)]}$$  \[1\]

for the opening rate, which is commonly used in neurophysiology. In Eq. 1 $a_c, b_c, V_c$ are some experimental parameters. Notwithstanding that in their work this kind of dependence has been used for a single gate, the opening rate of the whole K$^+$ channel can also be fitted by Eq. 1, see e.g. in. The same modeling for a whole channel is used also for dendritic K$^+$ channels in neocortical pyramidal neurons.

Note that in Eq. 1 the voltage-dependence of the opening rate changes in a knee-like manner from an exponential behavior into a linear one, cf. Fig. 1. This typical, experimentally observed behavior of delayed rectifier K$^+$ channels presently lacks an explanation in physical terms. A qualitative explanation of this gating dynamics has briefly been mentioned in recent work. However, a definite analysis leading to the functional form in Eq. 1 is not available. A first main
The complex structure of the multi-dimensional conformational space of proteins implies an intricate kinetics despite an apparently simple bistability that is observed (19). Two popular theoretical approaches
have been developed to cope with this complexity. A first one uses a simple bistable dynamics as a basis. To model the complexity of the observed kinetics this dynamics is amended by using an additional stochastic time-dependence of the energy profile, or kinetic constants. Such an approach is nowadays commonly known under the label of “fluctuating barriers” [21]. Alternatively, one can attempt to model the complexity of the energy profile itself in the simplest possible way. Our strategy is to find such a minimal model of the second kind which does allow for a rigorous analysis and does reproduce some nontrivial features of the gating dynamics.

Let us assume that the conformational stochastic dynamics between the open and closed states can be described in terms of a one-dimensional reaction coordinate dynamics $x(t)$ in a conformational potential $U(x)$, Figs. 2,3. Since the distribution of open residence time intervals assumes typically a single-exponential [5], in the following we rather shall focus on the behavior of the closed residence time intervals. In order to evaluate the distribution of closed residence time intervals it suffices to restrict our analysis to the subspace of closed states by putting an absorbing boundary at the interface, $x = b$, between the closed and open conformations, see Fig. 3. We next assume that the gating dynamics is governed by two gates: an inactivation gate and an activation gate. The inactivation gate corresponds to the manifold of voltage-independent closed substates. It is associated with the flat part, $-L < x < 0$, of the potential $U(x)$ in Fig. 3. In this respect, our modeling resembles that in [21]. The mechanism of inactivation in potassium channels is quite sophisticated and presently not totally established [4]. It is well known that inactivation can occur on quite different time scales [4]. The role of a fast inactivation gate in Shaker $K^+$ channels is taken over by the channel’s extended N-terminus which is capable to plug the channel’s pore from the cytosol part while diffusing towards the pore center [22]. The slow inactivation apparently is due to a conformational narrowing of the channel pore in the region of selectivity filter [4]. In both cases, no net gating charge translocation occurs and the inactivation process does not depend on voltage. When the inactivating plug is outside of the pore, or the selectivity filter is open ($x > 0$ in Fig. 3) the channel can open only if the activation barrier is overcome.

The dynamics of the activation gate occurs on the linear part of the ramp of the potential $U(x)$; i.e. on $0 < x < b$ in Fig. 3, like in [4]. Note that for $0 < x < b$, the inactivating plug diffuses outside of the channel’s pore and the selectivity filter is open. During the activation step a gating charge $q$ moves across the membrane, this feature renders the overall gating dynamics voltage-dependent. The channel opens when the reaction coordinate reaches the location $x = b$ in Fig. 3. This fact is accounted for by putting an absorbing boundary condition at $x = b$. Moreover, the channel closes immediately when the inactivation gate closes ($x \leq 0$), or when the activation gate closes. To account for this behavior in extracting the closed residence time distribution we assume that the channel is reset into the state $x = 0$ after each closure (see below).

The diffusional motion of the inactivated gate is restricted in conformational space. We characterize this fact by the introduction of a conformational diffusion length $L$ (Fig. 3) and the diffusion constant $D \sim k_BT$ that are combined into a single parameter – the conformational diffusion time

$$\tau_D = L^2/D. \quad [2]$$

This quantity constitutes an essential parameter for the theory. We assume that the activation barrier height $U_0$ is linearly proportional to the voltage bias $V$ [4], i.e. in terms of the gating charge $q$ we have

$$U_0 = -q(V - V_c). \quad [3]$$

Moreover, $U_0$ is positive for negative voltages, i.e. for $V < V_c$, vanishes at $V = V_c$, and becomes negative for $V > V_c$. Thus, for $V > V_c$ the channel “slips” in its open state, rather than overcomes a barrier. In addition, the fraction $\xi$ of the voltage-dependent substates in the whole manifold of the closed states should be

![Kramers Type Model](image-url)

**Figure 3:** Studied model and its diffusion counterpart.
very small, implying that
\[ \xi = b/L \ll 1. \]  

**Analytical solution.** The corresponding Fokker-Planck equation for the probability density of closed states \( P(x,t) \) reads
\[ \frac{\partial P(x,t)}{\partial t} = D \frac{\partial}{\partial x} \left( \frac{\partial}{\partial x} + \beta \frac{\partial U(x)}{\partial x} \right) P(x,t), \]  
where \( \beta = 1/(k_B T) \). In order to find the distribution of closed residence times \( f_c(t) \), we solve Eq. 5 with the initial condition \( P(x,0) = \delta(x) \), in combination with a reflecting boundary condition \( \frac{dP(x,t)}{dx}|_{x=-L} = 0 \), and an absorbing boundary condition, \( P(x,t)|_{x=b} = 0 \) \(^3\). The closed residence time distribution then follows as
\[ f_c(t) = \frac{\Phi_c(t)}{dt}, \]  
where \( \Phi_c(t) = \int_{-L}^b P(x,t)dx \) is the survival probability of the closed state.

By use of the standard Laplace transform method we arrive at the following *exact* solution:
\[ \hat{f}_c(s) = \frac{A(s)}{B(s)}, \]  
where
\[ A(s) = \exp(-\beta U_0/2)\sqrt{\beta^2 U_0^2 + 4\xi^2 \tau_D s} \]  
\[ B(s) = \sqrt{\beta^2 U_0^2 + 4\xi^2 \tau_D s} \]  
\[ \times \cosh \left( \frac{\sqrt{\beta^2 U_0^2 + 4\xi^2 \tau_D s}}{2} \right) \]  
\[ + \left( 2\xi \sqrt{\tau_D s} \tanh \sqrt{\tau_D s} - \beta U_0 \right) \]  
\[ \times \sinh \left( \frac{\sqrt{\beta^2 U_0^2 + 4\xi^2 \tau_D s}}{2} \right). \]

The explicit result in Eq. 8 allows one to find all moments of the closed residence time distribution. In particular, the mean closed residence time \( \langle T_c \rangle = \lim_{s \to 0}[1 - \hat{f}_c(s)]/s \) reads
\[ \langle T_c \rangle = \tau_D \xi \frac{\beta U_0(e^{\beta U_0} - 1 - \xi) + \xi(e^{\beta U_0} - 1)}{\beta^2 U_0^2}. \]  

This very same result \(^11\) can be obtained alternatively if we invoke the well-known relation for the mean first-passage time \( \langle T_c \rangle = \frac{1}{\beta} \int_0^b dx e^{\beta U(x)} \int_{-L}^b dy e^{-\beta U(y)} \) \(^3\). This alternative scheme provides a successful validity check for our analytical solution in Eq. 8.

**Elucidation of the voltage dependence in Eq. 7.** Upon observing the condition \(^4\) Eq. 10 by use of \(^3\) reads in leading order of \( \xi \)
\[ k_o = \frac{1}{\langle T_c \rangle} \approx \frac{\beta q \sqrt{V - V_c}}{\xi \tau_D \frac{1}{1 - \exp[-\beta q(V - V_c)]}}. \]  

With the parameter identifications
\[ b_c = \frac{q}{k_B T} \]  
and
\[ a_c = \frac{q}{\xi \tau_D k_B T}. \]  

the result in Eq. 11 precisely coincides with Eq. 7. The fact that our novel approach yields the puzzling voltage dependence in Eq. 7 constitutes a first prime result of this work.

Let us next estimate the model parameters for a Shaker IR K\(^+\) channel from Ref. \(^3\). In \(^3\), the voltage-dependence of \( k_o(V) \) at \( T = 18 \) °C has been parameterized by Eq. 7 with the parameters given in the caption of Fig. 1. Then, from Eq. 12 the gating charge can be estimated as \( q \approx 20e \) (e is the positive valued, elementary charge). As to the diffusion time \( \tau_D \), we speculate that it corresponds to the time scale of inactivation; the latter is in the range of seconds and larger \(^6\). Therefore, we use \( \tau_D = 1 \) sec as a lower bound for our estimate. The fraction of voltage-dependent states \( \xi \) is then extracted from Eq. 13 to yield, \( \xi \approx 0.0267 \). This value, indeed, is rather small and thus proves our finding in Eq. 11 to be consistent.

**Analysis for the closed residence time distribution.** The exact results in Eqs. 7-8 appear rather entangled. To extract the behavior in real time one needs to invert the Laplace transform numerically. With \( \xi < < 1 \), however, Eqs. 7-9 are formally reduced to
\[ \hat{f}_c(s) = \frac{1}{1 + (k_o \tau_D)^{-1} \sqrt{\tau_D s} \tanh \sqrt{\tau_D s}}. \]

This prominent leading order result can be inverted *analytically* in terms of an infinite sum of exponentials, yielding:
\[ f_c(t) = \sum_{n=1}^{\infty} c_n \lambda_n \exp(-\lambda_n t), \]  
where the rate constants \( 0 < \lambda_1 < \lambda_2 < \ldots \) are solutions of the transcendental equation
\[ \tan \sqrt{\lambda_n \tau_D} = \frac{k_o \tau_D}{\sqrt{\lambda_n \tau_D}} \]  
and the expansion coefficients \( c_n \), respectively, are given by
\[ c_n = \frac{2}{1 + k_o \tau_D + \lambda_n/k_o}. \]  

Note from Eq. 8 that the set \( c_n \) is normalized to unity, i.e. \( \sum_{n=1}^{\infty} c_n = 1 \).

The analytical approximation, Eqs. 15-17, is compared in Fig. 4 with the precise numerical inversion
Kramers model — diffusion model ....
$V = -45$ mV
$\tau_D = 1$ sec

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4}
\caption{Closed residence time distribution for a diffusion-limited case. The exact numerical result (full line) is compared with the analytical approximation in Eqs. (15)–(17) (broken line). The latter one coincides with the exact solution of the diffusion model by Millhauser et al. in the scaling limit.}
\end{figure}

\begin{equation}
\tau_D = 1 \text{ sec}
\end{equation}

Figure 4: Closed residence time distribution for a diffusion-limited case. The exact numerical result (full line) is compared with the analytical approximation in Eqs. (15)–(17) (broken line). The latter one coincides with the exact solution of the diffusion model by Millhauser et al. in the scaling limit.

The numerical inversion has been performed with the Stehfest algorithm [23]. As can be deduced from Fig. (4), for $t > 10$ msec the agreement is very good indeed. A serious discrepancy occurs only in the range $0.01 \text{ msec} < t < 0.1$ msec which lies outside the range of the patch clamp experiments ($t > 0.1$ msec). Moreover, the agreement is improving with increasing $\tau_D$ (not shown).

**Origin of the power law distribution.** The features displayed by the closed residence time distribution $f_c(t)$ depend sensitively on the applied voltage $V$. When $V > V_c$, e.g. $V = -45$ mV, as in Fig. 4, the activation barrier towards the channel opening disappears and the opening dynamics becomes diffusion-limited. In this case, the diffusion time $\tau_D = 1$ sec largely exceeds the mean closed residence time $\langle T_c \rangle \approx 18.4$ msec. Put differently, $\tau_D \gg \langle T_c \rangle$ and the closed residence time distribution exhibits an intricate behavior with three distinct regions, see in Fig. 4. Most importantly, for the intermediate time scale

\begin{equation}
\frac{\langle T_c \rangle^2}{\tau_D} \ll t \ll \tau_D
\end{equation}

we find from Eq. (14) (by considering the limit $\tau_D \to \infty$) that the closed residence time distribution obeys a power law; reading

\begin{equation}
f_c(t) \approx \frac{1}{2(\pi \tau_D)^{1/2} k_o t^{3/2}}.\end{equation}

This type of behavior is clearly detectable in Fig. 4 where it covers about two decades of time. As follows from Eq. (15) an increase of $\tau_D$ by one order of magnitude (while keeping $\langle T_c \rangle$ fixed) extends the power law region by two orders of magnitude. This conclusion is fully confirmed by our numerics (not shown). This power law dependence, which extends over four orders of magnitude, has been seen experimentally for a $K^+$ channel in NG 108-15 cells [11]. On the contrary, for channels, where $\tau_D$ is smaller, the power law region shrinks and eventually disappears, whereas the mean opening rate defined via Eq. (10) still exhibits a steep dependence on the voltage. Thus, our model is capable to describe for different channels both, the emergence of power law as well as its absence.

On the time scale $t \geq \tau_D$ the discussed power law distribution crosses over into the exponential tail; the latter is fully described by the smallest exponent $\lambda_1$ in Eq. (18), i.e., by

\begin{equation}
f_c(t) \approx c_1 \lambda_1 \exp[-\lambda_1 t].\end{equation}

This feature is clearly manifest in Fig. 4. The transition towards the exponential tail in the closed residence time-interval distribution can be used to estimate the diffusion time $\tau_D$ on pure experimental grounds!

Finally, let us consider the opposite limit, $\tau_D \ll \langle T_c \rangle$, for $V \ll V_c$. For the considered set of parameters this occurs, e.g., for $V = -55$ mV when the channel is predominantly closed. Then, the diffusion step in the opening becomes negligible and in the experimentally relevant range of closed residence times, defined by $\langle T_c \rangle$, the corresponding distribution can be approximated by a single exponential [20]. A perturbation theory in Eq. (16) yields $\lambda_1 \approx k_o (1 - (k_o \tau_D)/3)$. For the used parameters we have $\lambda_1 \approx 0.96 k_o$ and, from Eq. (17), $c_1 \approx 0.95$. This result is in a perfect agreement with the precise numerics obtained from Eqs. (15–17). Thus, the distribution of closed residence times is single-exponential to a very good degree. Consequently, one and the same channel can exhibit both, an exponential and a power-law distribution of closed residence times, as a function of the applied transmembrane voltage. With an increase of $\tau_D$ the voltage range of the exponential behavior shifts towards more negative voltages, $V < V_c$, and vice versa.

**Reduction to a diffusion model.** Let us relate our model to that introduced previously by Millhauser et al. [12]. The latter one is depicted with the lower part in Fig. 3. It assumes a discrete number $N$ of closed substates with the same energy. The gating particle jumps with the equal forward and backward rates $k$ between the adjacent states which are occupied with probabilities $p_n(t)$. At the right edge of the chain of closed states the ion channel undergoes transition into the open state with the voltage-dependent rate constant $\gamma$. To calculate the closed residence time distribution $f_c(t)$ one assumes $p_0(0) = 1$, $p_n(0) = 0$ and $d\Phi_n(t)/dt = -\gamma p_n(t)$, where $\Phi_n(t) = \sum_{n=0}^{N} p_n(t)$ is
the survival probability \([22, 13]\).

We consider the continuous diffusion variant of this model \([22]\) in a scaling limit: we put \(\Delta x \to 0, k \to \infty, \gamma \to \infty, N \to \infty\) keeping the diffusion length \(L = N\Delta x\), the diffusion constant \(D = k(\Delta x)^2\), and the constant \(k_o = \gamma/N\) all finite. The latter one has the meaning of mean opening rate, see below. Note that in clear contrast with our approach, the rate parameter \(k_o\) in the diffusion model is of pure phenomenological origin. The problem of finding the closed residence time distribution is reduced to solving the diffusion equation

\[
\frac{\partial P(x, t)}{\partial t} = D \frac{\partial^2 P(x, t)}{\partial x^2}\]  

with the initial condition \(P(x, 0) = \delta(x - 0_-)\), the reflecting boundary condition \(\left. \frac{\partial P(x, t)}{\partial x} \right|_{x = -L} = 0\) and the radiation boundary condition \([22]\)

\[
\left. \frac{\partial P(x, t)}{\partial x} \right|_{x = 0} = -\frac{L k_o}{D} P(0, t). \]  

We emphasize that the radiation boundary condition \([22]\) is not postulated, but is rather derived from the original discrete model in the considered scaling limit. Using the Laplace transform method we solved this problem exactly and obtained the result in Eq. \([14]\). In conclusion, our approximate result in Eqs. \([14, 17]\) provides the exact solution of the diffusion model \([14, 15]\) in the scaling limit! This exact analytical solution is obtained here for the first time. Note, however, that this so obtained diffusion model is not able to resolve the puzzling voltage dependence in Eq. \([1]\).

### Synopsis and Conclusions

With this work we put forward a unifying generalization of the diffusion theory of ion channel gating by Millhauser et al. \([12, 13]\). Our novel theory reproduces for the first time the functional form of the puzzling voltage-dependence in Eq. \([1]\). The latter has been postulated almost fifty years ago in the pioneering paper by Hodgkin and Huxley \([8]\) and is commonly used in the neurophysiology up to now. The proposed model of the Fokker-Planck-Kramers type explains the origin of steep voltage-dependence in Eq. \([1]\) within a clear physical picture which seemingly is consistent with both our current understanding of the physics of proteins and basic experimental facts. Our study furthermore reveals the connection between the voltage dependence of the opening rate and the intricate behavior for the closed residence time distribution in corresponding voltage regimes. A particularly appealing feature of our approach is that our model contains only four voltage-independent physical parameters: the diffusion time \(\tau_D\), the fraction of voltage-dependent substates \(\xi\), the gating charge \(q\) and the threshold voltage \(V_c\). Several experimental findings could be described consistently while still other ones call for an experimental validation.

In particular, when (i) the activation barrier is very high, i.e., \(V > V_c\), the activation step determines completely the opening rate: the distribution of closed residence times is nearly exponential, as well as the voltage-dependence of the opening rate. The channel is then predominantly closed. We remark that the opening rate should exhibit an exponential dependence on temperature as well. This conclusion follows from Eqs. \([11, 12]\) and the fact that in accord with our model the parameter \(\alpha_c\) in Eq. \([1]\) is temperature independent. Indeed, with the diffusion time \(\tau_D\) being inversely proportional to the temperature, i.e. \(\tau_D \sim 1/D \sim 1/(k_B T)\), yielding \(\alpha_c \sim 1/(\tau_D k_B T)\), cf. Eq. \([13]\). In contrast, when (ii) the activation barrier vanishes, i.e. the voltage shifts towards the positive direction, the closed residence time distribution becomes non-exponential. On the intermediate time scale given in Eq. \([18]\) this distribution exhibits a power law behavior, \(f_c(t) \propto t^{-3/2}\), which crosses over into an exponential one at \(t > \tau_D\). The emergence of the exponential tail can be used to determine the conformational diffusion time \(\tau_D\) experimentally. When (iii) the activation barrier assumes negative values at voltages \(V < V_c\), our result for the opening rate exhibits a linear dependence on voltage and, consequently, see Eq. \([11]\), it no longer depends on temperature. The weak temperature dependence will emerge however when we renormalize the diffusion coefficient \(D\) due to the roughness of random energy landscape (cf. Fig. 2). Assuming uncorrelated Gaussian disorder one gets \(D \sim k_B T \exp(-\langle \delta U^2 \rangle/(k_B T)^2)\) \([9, 20]\), where \(\langle \delta U^2 \rangle\) is the mean-squared height of the barrier between substates. Then, \(k_o \sim \exp(-\langle \delta U^2 \rangle/(k_B T)^2)\), and since \(\sqrt{\langle \delta U^2 \rangle} \sim k_B T\) this non-Arrhenius dependence is weak at room temperatures. This result has a clear thermodynamic interpretation: when the activation barrier vanishes the closed-to-open transition is entropy dominated and thus the opening rate will only weakly depend on temperature. In accord with our model this type of behavior correlates with a non-exponential kinetics.

The temperature behavior of the opening rate (or, equivalently, the mean closed time) presents a true benchmark result of our theory. The authors are looking forward to seeing this feature being tested experimentally.

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