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6 **NONEQUILIBRIUM RATE THEORY FOR CONDUCTION**
 7 **IN OPEN ION CHANNELS**

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28 We present a nonequilibrium reaction rate model of the ionic transition through an
 29 open ion channel, taking account of the interaction between an ion at the entrance of
 30 the channel and an ion at the binding site in a self-consistent way. The electrostatic
 31 potential is calculated by solution of the Poisson equation for a channel modeled as a
 32 cylindrical tube. The transition rate, and the binding site occupancy as a function of
 33 the left bulk concentration are compared to 1D Brownian dynamics simulations. The
 34 analysis is performed for a single binding site of high-affinity, with the exit rate influenced
 35 by barrier fluctuations at the channel exit. The results are compared with experimental
 36 data for the permeation of the Na⁺ ion through the Gramicidin A channel, with which
 37 they are shown to be in good agreement.

38 *Keywords:* Ion channels; permeation; nonequilibrium rate; stochastic dynamics; fluctu-
 39 ating barrier.

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1. Introduction

Ion channels are pathways down the centres of proteins embedded into the membranes of biological cells [1, 2], facilitating the diffusion of ions across the membranes. They are complicated devices [3], built of thousands of atoms, flexible, and filled with ions and water dipoles that coordinate their movements to allow ions to pass one by one across the membrane. To support life, channels have to be precise often selecting between similar ions with an accuracy of 1:1000 [4], yet able to deliver millions of ions per second, i.e., almost at the rate of free diffusion. In recent years impressive progress has been achieved both in understanding the structure of ion channels [3] and in modeling their properties [5]. Yet the mechanism that enables channels to be highly selective while still passing millions of ions per second remains a tantalizing paradox.

Channels displaying counter-intuitive behavior of this kind often have one singly occupied selectivity site [6] with a high affinity for a specific type of ion. The fact that a satisfactory explanation of the paradox has yet to be found, even in the most clearly characterized cases [7] of channel conduction, suggests that some basic physical phenomenon has been overlooked. The difficulties in modeling the system stem from the presence of the long-range Coulomb interaction and regions with low- and high-dielectric constants. The stochastic dynamics of ionic motion needs to be solved simultaneously with the Poisson equation for all the charges, which often results in strongly nonequilibrium stochastic dynamics. Therefore, only an approximate semi-analytic treatment of the problem is possible.

The simplifying assumptions that are frequently made to overcome these difficulties are sometimes not entirely self-consistent. First note that, in traditional [7–9] reaction rate theory (RRT), transitions of an ion from state i to state j associated with a potential barrier E_{ji} are assumed to proceed at thermal equilibrium with constant rate k_{ji}

$$k_{ji} = \kappa_0 \exp\left(-\frac{E_{ji}}{k_B T}\right), \quad (1)$$

equal to the product of the frequency factor κ_0 and the Arrhenius factor $\exp(-\frac{E_{ji}}{k_B T})$, where k_B is the Boltzmann constant and T is the temperature. At the same time to account for the Born self-energy it is often postulated [10] that an ion can only enter an empty channel: the effect of inter-ion interactions on the escape probabilities is ignored. Second, we note that the description of the current of ions through an open ion channel is often described by equilibrium Poisson–Nernst–Planck (PNP) theory, which also neglects the ion–ion interaction. The discrepancy between the PNP results and the results of Brownian dynamics (BD) simulations has been the subject of vigorous discussion [11, 12]. Yet to explain large ion fluxes through the channels with single high-affinity binding sites, the assumption of multiple-occupancy of the channel is sometimes made [13], ignoring the Born dielectric self-energy altogether. Although the assumptions mentioned may be valid in specific limits of physiological parameters, and helpful in explaining

1 some of the observed experimental data, they are not mutually self-consistent. Being
 2 just postulated, rather than related to the channel parameters, they may even be
 3 misleading where a different range of physiological parameters is to be considered.

4 In standard RRT, ion channels are modeled as a sequence of energy barriers over
 5 which the ion must jump. The physical basis of the standard three-well model of an
 6 ion channel is based on Eyring's transition state theory. The binding sites model
 7 postulates that ions pass through channels by binding with one or more particular
 8 sites in the channel pore [10]. Lauger went a step further than the Eyring analysis
 9 by allowing for the phenomenon of saturation to be observed in his rate theory
 10 analysis of the transport [14]. In the binding site model, the net unidirectional flux
 11 can be calculated, taking into account the probability that the binding site well is
 12 occupied. An ion can enter the well only if it is not already occupied by another
 13 ion, and an ion can only leave a well if it is there already, i.e., if the well is occupied.
 14 Knowing the probability for the occupied and unoccupied wells is therefore enough
 15 to characterize the current.

16 In this paper we introduce a modified RRT that takes into account the depende-
 17 nce of the escape probabilities on the ion-ion interaction. The theory also illu-
 18 minates the relation between the PNP and BD results. The electrostatic potential
 19 is calculated using the solution of the Poisson equation for a channel modeled as
 20 a cylindrical tube. The transition rate and the binding site occupancy as a func-
 21 tion of the left bulk concentration are compared to 1D BD simulations, taking into
 22 account particle injection. The analysis is performed for a single binding site of
 23 high-affinity, with the exit rate governed by barrier fluctuations. We will compare
 24 the model results with experimental measurements of the permeation of Na⁺ ions
 25 through the Gramicidin A channel, with which we will show that they are in good
 26 agreement.

27 **2. Rate Model Description**

28 We consider an archetypal model [1, 10] of an ion channel with a single high-affinity
 29 binding site, as shown in Fig. 1. It is considered as a 30 A long cylinder of radius
 30 2 A with a negatively charged ring at its center. Assuming cylindrical symmetry
 31 of the channel, the potential energies for a Na⁺ ion moving along the channel axis
 32 for the two state configurations are calculated by solution of Poisson's equation.
 33 The transition of an ion e.g., from the left to the right can be described within this
 34 model via the following steps (cf. [10]). To be able to enter the channel, an ion must
 35 arrive at the channel mouth. It does so with an arrival rate j_{ar}^l that is a function of
 36 the bulk concentration on the left C_l , and can be expressed as the average number
 37 of arrivals per unit time.

38 The probability of the ion being in the potential well must be connected to the
 39 probability of gaining entrance to the channel when it is empty. This is found by
 40 connecting the ion's arrival at the channel mouth to the probability of penetrating
 41 the empty channel. An estimate of the arrival time at the channel mouth, assuming

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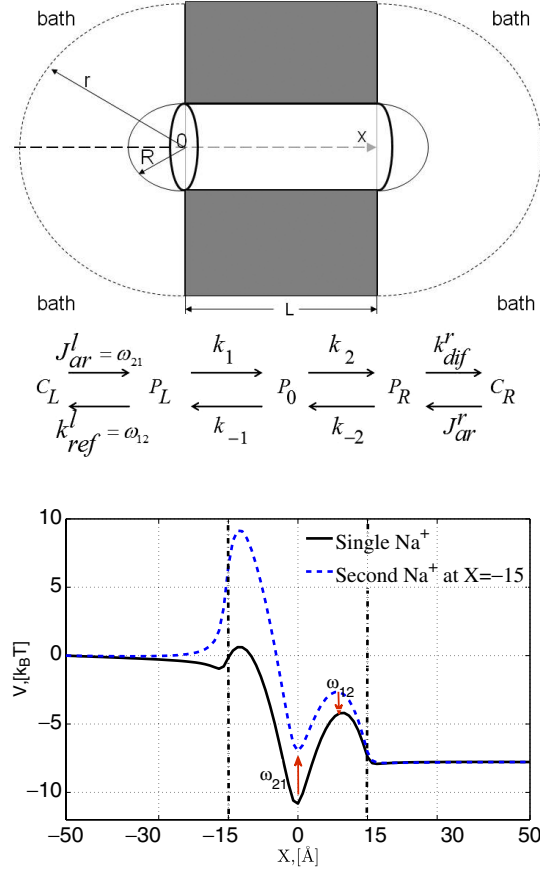


Fig. 1. Top panel: Geometry of the model system under consideration. It is comprised of a cylindrical channel with hemispheres at its left- and right-hand mouths. There is a fixed ring of negative charged (not shown) at its middle. This was the geometry used to solve Poisson's equation. Bottom: Potential energy along the channel axis, for 200 mV applied voltage. The full black line is the potential of a single Na^+ ion moving along the channel axis. This corresponds to State-1. The dashed line is the potential acting on a Na^+ ion moving along the channel axis when there is one Na^+ ion at the mouth of the channel, corresponding to State-2. The rate of jumping from state-1 to state-2 is $\omega_{21} = J_{ar}^l$, and the rate of jumping from state-2 to state-1 is $\omega_{12} = k_{dif}^r$.

- 1 charge neutrality and no applied field, can be obtained by considering pure diffusion
- 2 of ions through an imaginary hemisphere at the mouth of the channel of radius equal
- 3 to that of the channel. This problem is thus reduced to the determination of the ionic
- 4 flux through a hemispherical sink at the channel entrance where all ions arriving
- 5 at the boundary immediately vanish such that the ion concentration there goes to
- 6 zero. A first approximation of the rate of arrival at the channel mouth is given by
- 7 the Smoluchowski rate $1/\tau_{arrival} = 2\pi CDR$, where C is the bulk concentration far
- 8 away from the channel mouth, D is the ion diffusion coefficient and R is the radius
- 9 of the channel.

Nonequilibrium Rate Theory for Conduction in Open Ion Channels

The bulk concentration is introduced into the model using the injection rate. The fluctuations in the potential energy barrier are the result of ion-ion interactions. We are specifically interested in mechanisms of strong modulation of the potential energy barrier that do not require conformational changes. The rate of barrier modulation is directly related to the rate of ion arrival at the channel mouth. From the left mouth the ion can either diffuse away at diffusion rate k_{dif}^l , or bind to the binding site with the rate k_1 . Finally, the ion at the binding site can either return to the left compartment with the rate k_{-1} , or exit to the right compartment with the rate k_2 . Similarly, the ion transition from the right to the left is characterized by the set of rates $\{J_{\text{ar}}^r, k_{\text{dif}}^r, k_2, k_{-2}, k_{-1}\}$ and concentration C_r . The formulation is completed by providing a model for the transition rates and writing a set of kinetic equations, which can readily be solved under conditions of steady current. Therefore, the kinetic equations for the current are given by:

$$\frac{dP_l}{dt} = J_{\text{ar}}^l - k_{\text{ref}}^l P_l - k_1 P_l (1 - P_0) + k_{-1} P_0, \quad (2)$$

$$\frac{dP_0}{dt} = k_1 P_l (1 - P_0) - (k_{-1} + k_2) P_0 + k_{-2} P_r (1 - P_0), \quad (3)$$

$$\frac{dP_r}{dt} = J_{\text{ar}}^r - k_{\text{dif}}^r P_r + k_2 P_0 - k_{-2} P_r (1 - P_0), \quad (4)$$

1 where $J_{\text{ar}}^{l,r}$ are the constant arrival rates at which ions are injected respectively
 2 into the left and right volumes located at the mouths of the channel. $P_{l,r}$ are
 3 respectively the occupation probabilities of these volumes. P_0 is the probability of
 4 occupation of the charged binding site in the middle of the channel. k_{ref}^l and k_{dif}^r
 5 are respectively the diffusive reflection rates on the left and right of the channel.
 6 From Eqs. (2) and (4), the currents to the right and to the left of the channel are
 7 given respectively by $J = k_1 P_l (1 - P_0) - k_{-1} P_0$ and $J = k_2 P_0 - k_{-2} P_r (1 - P_0)$. We
 8 are interested in the steady-state current.

9 The ion injection rate on the left is given by: $J_{\text{ar}}^l = 2\pi R C_l D$, where C_l is the
 10 concentration in the left bulk. The diffusive and reflection rates at the left and right
 11 mouths, k_{dif}^r and k_{ref}^l , are calculated from the stationary solution when the channel
 12 is closed ($J = 0$). Therefore, the occupation probability of the left hemisphere at the
 13 channel mouth is given by $P_l = 2\pi R^3 C_l / 3$; corresponding to the number of ions in
 14 the left hemisphere. Similar expressions can be written for the ion injection rate and
 15 occupation probability of the right mouth, leading to $k_{\text{ref}}^l = k_{\text{dif}}^r = 3D/R^2$. P_0 is
 16 calculated by combining elements of the steady-state equations. The corresponding
 17 equation for P_0 is quadratic. We are interested in the case of small k_2 parameters
 18 or, in other words in the case when $J \ll J_{\text{ar}}^l$. The current can then be calculated
 19 from:

$$J = \frac{k_1(1 - P_0)J_{\text{ar}}^l - k_{\text{ref}}^l k_{-1} P_0}{k_{\text{ref}}^l + k_1(1 - P_0)}. \quad (5)$$

21 Considering the case of a unidirectional current, the concentration on the right-
 22 hand side of the channel is set to $C_r = 0$. Since there is no backflow from the right

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1 bulk to the left bulk, we set $k_{-2} = 0$. The occupation probability at the channel
2 binding site is given by:

$$3 \quad P_0 = \frac{k_1 J_{\text{ar}}^l}{k_1 J_{\text{ar}}^l + (k_2 + k_{-1}) k_{\text{ref}}^l}. \quad (6)$$

4 The corresponding current is therefore reduced to $J = k_2 P_0$. For a permeating ion
5 of charge ze , the current is given by $I = zeJ$. The occupation probabilities of the
6 left and right mouth of the channel are given respectively by $P_l = (J_{\text{ar}}^l - J)/k_{\text{ref}}^l$
7 and $P_r = J/k_{\text{dif}}^r$. Next, we calculate the rate k_2 of escape from the single binding
8 site within the framework of fluctuating barrier theory.

9 **2.1. The ion–ion interaction**

10 The PNP approach [15, 16] has shed light on how an ion permeates the channel.
11 Nevertheless, being an equilibrium approach, it ignores the ion–ion interaction. To
12 take this into account we consider the changes in potential profile for the ion at
13 the binding site induced by the presence of a second ion at the channel mouth. In
14 this approximation the ion–ion interaction enters the dynamics of the ion inside the
15 channel in the form of a Markovian dichotomous noise. The proposed reaction rate
16 model introduces the rate k_2 calculated for the case when the barrier fluctuates
17 between two states due to ion–ion interactions. Once the first ion is trapped at the
18 binding site, conduction may occur when a second positive ion arrives at the channel
19 mouth and the system switches to State-2. The latter corresponds to the reduced
20 barrier needing to be overcome by the trapped ion in order to exit to the right bath.

21 Thus, as the second ion arrives at the channel mouth, the first ion initially at
22 the binding site will have a higher chance of crossing the small barrier and exiting
23 to the right-hand side of the channel, and a much smaller chance of diffusing back
24 to the left bath. Hence the net transport to the right is caused directly by the
25 random (fluctuational) arrival of ions at the left mouth of the channel. To a good
26 approximation, no backflow of ions need be considered and we therefore calculate
27 the unidirectional current.

28 To describe the two-state potential model, we consider the equation of a pul-
29 sating ratchet

$$30 \quad m\gamma \frac{dx}{dt} = -\frac{dV(x, \zeta(t))}{dx} + \sqrt{2m\gamma k_B T} \xi(t). \quad (7)$$

We thus consider the overdamped unidirectional motion of a Na^+ ion of mass m ,
with a friction coefficient γ which is related to its diffusion coefficient through the
fluctuation dissipation relation. The thermal energy of the particle is $k_B T$. The
potential $V(x, \zeta(t))$ in this approximation is obtained by solving Poisson's equa-
tion. It takes account of the following three contributions: (i) the potential of the
Coulomb interaction with ions in the bulk; (ii) the electrostatic potential induced
by interaction with the protein; (iii) the potential of the Coulomb interaction with
the wall charge at the selectivity site. This mixed (hybrid) process is governed by

$\zeta(t)$; a dichotomous, stationary, Markovian noise and $\xi(t)$; a normalized white noise. For each state of the noise $\zeta(t)$ there corresponds a potential V_i . The system can be described by the probability distribution $P_i(x, t)$, which is the joint probability density for the position x of the particle and the state of the potential i . The corresponding Chapman–Kolmogorov equation for this distribution is:

$$\frac{\partial P_i(x, t)}{\partial t} = \frac{\partial}{\partial x} \left(\left[\frac{1}{m\gamma} \frac{dV_i}{dx} + \frac{k_B T}{m\gamma} \frac{\partial}{\partial x} \right] P_i(x, t) \right) + \sum_j (\omega_{ij} P_j(x, t) - \omega_{ji} P_i(x, t)), \quad (8)$$

1 where ω_{ij} are the transition rates between states j and i , given respectively by
2 $\omega_{21} = J_{\text{ar}}^l$ and $\omega_{12} = k_{\text{ref}}^l$. For the two states 1 and 2, Eq. (8) is reduced to:

$$3 \quad \frac{\partial}{\partial t} \begin{pmatrix} P_1(x, t) \\ P_2(x, t) \end{pmatrix} = \begin{pmatrix} \widehat{L}_1 - \omega_{21} & \omega_{12} \\ \omega_{21} & \widehat{L}_2 - \omega_{12} \end{pmatrix} \begin{pmatrix} P_1(x, t) \\ P_2(x, t) \end{pmatrix}, \quad (9)$$

where the operators \widehat{L}_i are given by $\widehat{L}_i = \frac{1}{m\gamma} \partial_x \frac{dV_i}{dx} + \frac{k_B T}{m\gamma} \partial_x^2$. The particle starts at the bottom of the potential (corresponding to the channel binding site $x = x_0$), with probability $P_i(x, 0) = \delta(x - x_0)$. Reflecting boundary conditions are chosen at the bottom of the potential ($x = x_0$) and absorbing boundary conditions at its top ($x = x_1$): $\frac{\partial P_i}{\partial x}(x = x_0, t) = 0$; $P_i(x = x_1, t) = 0$. Following the standard method described in Gardiner [17–19], the system of first-order ordinary differential equations giving the mean first passage time (MFPT) can be written:

$$\begin{cases} \frac{dT_1}{dx} = S_1 \\ \frac{k_B T}{m\gamma} \frac{dS_1}{dx} = \frac{1}{m\gamma} \frac{dV_1}{dx} S_1 + \omega_{21}(T_1 - T_2) - 1 \\ \frac{dT_2}{dx} = S_2 \\ \frac{k_B T}{m\gamma} \frac{dS_2}{dx} = \frac{1}{m\gamma} \frac{dV_2}{dx} S_2 + \omega_{12}(T_2 - T_1) - 1, \end{cases} \quad (10)$$

4 with the boundary conditions $\frac{dT_i}{dx}(x = x_0, t) = 0$; $T_i(x = x_1, t) = 0$.

5 **2.2. Solution of the boundary value problem**

6 The system Eq. (10) obtained from the fluctuating barrier model is solved numerically as a boundary value problem. The advantages of this method are that it
7 does not require linear approximation of the potential energy and it can easily be
8 extended to a larger number of states; specifically, one needs five states for two
9 types of ions at each side of the channel. Each of the states corresponds to a different
10 potential energy conformation. It is an approach that was not discussed earlier,
11 and one that is easily accessible to a broad audience of potential users.
12

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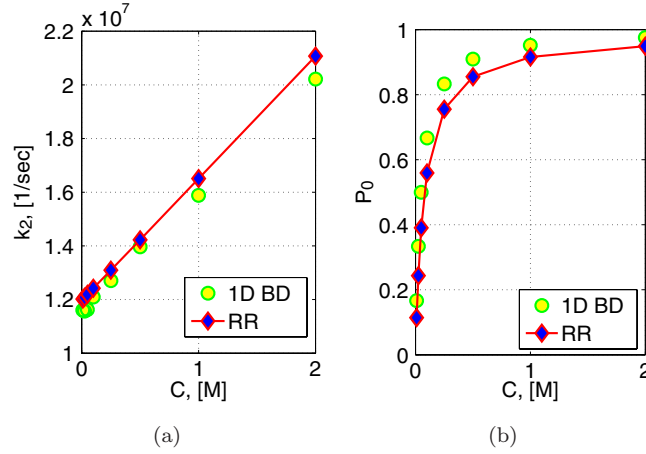


Fig. 2. (a) Escape rate as a function of bulk concentration. The circles are obtained using 1D BD simulation for a Na^+ inside the channel with particle injection at the channel's left mouth. The lozenges are calculated using fluctuating barrier theory. (b) Channel binding site occupancy as a function of bulk concentration. The lozenges are calculated using the modified reaction rate (RR) theory and the circles are obtained from a 1D BD simulation with ion injection at the channel's left mouth.

1 The MFPT for a particle that starts from the bottom at $x = x_0$ is $T =$
 2 $\sum_{i=1}^2 p^{(i)} T_i(x = x_0)$ [20], where $p^{(i)}$ is the occupation probability of the state (i),
 3 such that $\sum_{i=1}^2 p^{(i)} = 1$. The rate of escape from the channel binding site to the
 4 right bath is given by $k_2 = 1/T$.

5 3. Current Concentration Characteristics

6 We have calculated the modified rate k_2 as a function of the left bulk concentration
 7 for comparison with the rate obtained from direct BD simulations, taking into
 8 account particle injection at the mouth of the channel with the same Smoluchowski
 9 rate. As shown in Fig. 2(a), the two rates follow a similar linear dependence as
 10 a function of the concentration and are in reasonable agreement (cf. the Kramers
 11 rate over a nonfluctuating energy barrier which is independent of the concentration).
 12 The channel occupancy is also calculated and compared to that obtained from BD
 13 simulations: see Fig. 2(b). We compare the results with Andersen's experimental
 14 data [21] for the current of Na^+ ions in a gA channel in Fig. 3; we used the rates
 15 $k_1 = 3.3 \times 10^{10} \text{s}^{-1}$, $k_{-1} = 1.2 \times 10^7 \text{s}^{-1}$ as fitting parameters and a diffusion
 16 coefficient of $D = 1.17 \times 10^{-9} \text{m}^2 \text{s}^{-1}$ for the Na^+ ion.

17 4. Summary and Perspectives

18 We have introduced a nonequilibrium rate model of the ionic transition through
 19 an open ion channel within a self-consistent framework. The method takes explicit
 20 account of the interaction between an ion at the left mouth and an ion at the channel

Nonequilibrium Rate Theory for Conduction in Open Ion Channels

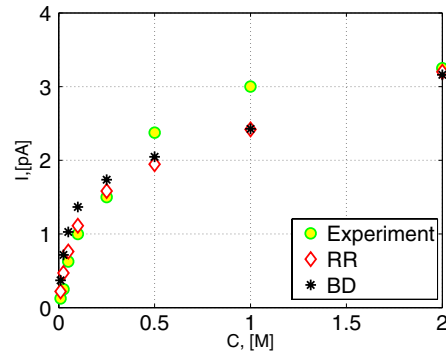


Fig. 3. Current as a function of concentration for a Na^+ ion in the gA channel. The circles are experimental data from Andersen *et al.* [21]. The lozenges represent the results of calculations based on the modified rate model. The stars are obtained from a 1D BD simulation for a Na^+ inside the channel with particle injection at the channel left mouth.

1 binding site. These ion–ion interactions result in fluctuations of the potential energy
 2 barrier of an ion at the binding site calculated from the channel structure by solving
 3 Poisson’s equation. We calculated the transition rate and binding site occupancy of
 4 an Na^+ ion as a function of the left bulk concentrations, and compared the result
 5 with 1D BD simulations using ions injection at the channel mouth. The model was
 6 applied to experimental permeation rate data for Na^+ ions in the Gramicidin A
 7 channel, yielding satisfactory agreement. Note that, in the case of Gramicidin, the
 8 ion–ion interaction is not particularly important, so that equilibrium PNP theory
 9 may be sufficient. We expect, however, that the effect will be of crucial importance
 10 in channels that display both high conductivity and high selectivity, e.g., the K^+
 11 and Ca^{2+} channels. These will be analyzed in our future work. Note also that the
 12 boundary value technique used for solution of the MFPT system of equations can
 13 readily be extended to encompass a larger number of states. This feature will be
 14 needed e.g., for the case when there are ions at both channel mouths, which five
 15 states will require.

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