Collective Equilibrium Behaviour of Ion Channel Gating in Cell Membranes: An Ising Model Formulation

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Abstract A statistical mechanical model for voltage-gated ion channels in cell membranes is proposed using the transfer matrix method. Equilibrium behavior of the system is studied. Representing the distribution of channels over the cellular membrane on a one-dimensional array with each channel having two states (open and closed) and incorporating channel–channel cooperative interactions, we calculate the fraction of channels in the open state at equilibrium. Experimental data obtained from batrachotoxin-modified sodium channels in the squid giant axon, using the cut-open axon technique, is best fit by the model when there is no interaction between the channels.

Keywords Statistical mechanics · Ising model · Transfer matrix method · Squid giant axon · Voltage-gated ion channels · Channel–channel cooperative interactions

Ion channels are a class of proteins embedded in cell membranes, and form conduction pores that regulate the transport of ions into and out of cells. These pore proteins are present in all living organisms and play a crucial role in many biological functions, including electrical signaling in the nervous system, hormone secretion, and heart and muscle contraction [1]. The voltage-dependent switching of these channels between conducting and nonconducting states is a major factor in controlling the transmembrane voltage. Mathematical models have been developed to study the kinetics of such channels and the corresponding excitability in a variety of nerve cells [2, 3]. The classical Hodgkin–Huxley mathematical model (or HH model) [4, 5] is obtained via theoretical insight and curve fitting rather than derived from fundamental principles. According to the HH model, the kinetics of the ion channels being open or closed is described by first-order nonlinear differential equations (HH equations) for the transmembrane voltage. In the HH equations, the gating variables that govern the activation and inactivation of the channels and experimentally-determined voltage transition rates are included [4].

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Using the principles of statistical mechanics, different approaches have been proposed to address the mechanism of voltage sensing and gating in ion channels. Roux [5] developed a rigorous statistical mechanical formulation of the equilibrium properties of selective ion channels incorporating the influence of the membrane potential, as well as multiple occupancy and saturation effects. Yang et al. [6] presented a statistical mechanical model for interactive ion channels in the presence of electric fields. They obtained the maximum fractions of open potassium and sodium channels by solving a self-consistent nonlinear algebraic equation under a mean-field approximation (MFA) with the important constraint of a static, not time-varying, electric field. We recently proposed and studied the pair approximation (PA) version of the interactive model [7]. The PA model results qualitatively agreed with the MFA results for the potassium and sodium transmembrane conductance reported in [6]. We also used the MFA and PA methods in order to incorporate the effects related to ion transport through the noninteracting ion channels [8–10]. In these works [8, 10], the dynamics of the system were investigated and the kinetic rate constants were found using two different statistical mechanical treatments, namely path probability and path integral methods. The results were tested with experimental data obtained with cut-open axon technique (COAT) for batrachotoxin-modified sodium channels [11].

In the present paper, we propose and study a new statistical mechanical approach for voltage-gated ion channels in cell membranes using the transfer matrix method (TMM). The TMM was first introduced by Kramers and Wannier [12]. It worked with immediate success in the one-dimensional Ising model and became the first method to treat successfully the field-free Ising model in two dimensions [13]. As a channel has two possible states (open and closed), the Ising model formalism has been applied to the one-dimensional voltage sensitive channel ensembles. Representing the distribution of channels over the cellular membrane on a one-dimensional array with each channel having two states, and incorporating the interactions between these states, we calculate the fraction of channels in the open state at equilibrium. This type of calculation for ion channels was first performed by Ghosh and Mukherjee [14]. They studied the co-operative behavior of voltage-sensitive membrane channels from electrophysiological experiments and suggested a statistical mechanical approach based on a Zimm–Bragg type model [15]. They also tested the model with voltage-dependent conductance data for gap-junction channels in embryonic cells. Ghosh [16] created the same problem for the relaxation of membrane channels. Besides these works, Liu and Dilger [17] applied the one-dimensional Ising model to the study of cooperative phenomena between ligand-gated ion channels and derived the expressions for the mean open channel probability and the variance from the grand partition function. The one-dimensional model based on the TMM has also been extensively applied to cooperative biological systems [18–20].

Ion channels can be either open (O) or closed (C). The word *gate* is used to describe the structure or the property of the channel that is concerned with the transition between these two states. When the gate is open, the ions flow through the channel, and when it is closed they cannot. Gating is the process whereby the gate is opened and closed. There may be a number of different closed and open states, so the gating processes may involve a number of different sequential or alternative transitions from one state of the channel to another. *Modulation* occurs when some substance or agent affects the gating of the channel in some way. The behavior of our simple two-state channel can first be described by a simple two-state system in which each channel is opened by the movement of a single gating particle which carries a charge. At any moment the particle is in one of two positions, 1 and 2, and these are associated with closed and open states, respectively. The positions 1 and 2

correspond to two wells in an energy profile, and there is a single energy barrier between them.

In a population of n identical channels in the membrane, the number of channels in the closed and open states will be indicated by n_1 and n_2 , respectively. n_1 is the occupation number of gating particles in position 1 with energy ε_1 , and n_2 is the occupation number of gating particles in position 2 with energy ε_2 , so that $n_1 + n_2 = n$. A simple expression for the internal energy of such a system in the presence of a membrane potential is

$$E = \sum_{i=1}^2 n_i \varepsilon_i + ze_0 n_1 V, \quad (1)$$

where z is the number of charges on gating particle, e_0 is the elementary electronic charge and V is the potential difference across the cell membrane, also called the membrane potential. If we retain only nearest-neighbour interactions between channels, the energy of the system can be written in the form

$$E = -J \sum_{\langle ij \rangle} \sigma_i \sigma_j - h \sum_{i=1}^n \sigma_i, \quad (2)$$

where J represents the energy associated with the cooperative interaction between a pair of nearest-neighbour channels, denoted by $\langle ij \rangle$, and σ_i can take the values 0 and 1 corresponding to C and O states, respectively. The second term is analogous to the external magnetic field in the original formulation of the Ising model and defined by $h = ze_0(V - V_0)$ where V_0 [equals to $-(\varepsilon_1 - \varepsilon_2)/ze_0$] is the voltage at which half of the channels are open. Models in which ion channels are located on a one-dimensional lattice are not novel. In fact, more general lattice models than that given below have been studied [21–23]. However, the previous studies concerned mainly the overall channel interactions on the membranes; local distribution of the channels were not studied. In the present study, we study only a simple case, but several interesting properties of the model are obtained exactly. For simplicity, we consider the classical model and introduce channel–channel interactions via a one-dimensional array.

The one-dimensional model is a chain of n channels; each channel has two nearest neighbors. Here we shall follow the TMM, first introduced by Kramers and Wannier [12]. To apply this method, we replace the actual lattice by one having the topology of a closed, endless structure. Therefore, we impose the periodic boundary condition $\sigma_{n+1} = \sigma_1$, making the topology of the chain that of a circle. The partition function is

$$Z(V, T) = \sum_{\{\sigma_i=0,1\}} \exp \left[\frac{1}{kT} \sum_{i=1}^n (J\sigma_i\sigma_{i+1} + h\sigma_i) \right], \quad (3)$$

where k is the Boltzmann constant and T is the temperature of the system. The partition function can be expressed in terms of matrices. Let us write

$$Z(V, T) = \sum_{\{\sigma_i=0,1\}} \exp \left\{ \frac{1}{kT} \sum_{i=1}^n \left[J\sigma_i\sigma_{i+1} + \frac{1}{2}h(\sigma_i + \sigma_{i+1}) \right] \right\}, \quad (4)$$

which is equivalent to (3) by virtue of periodic boundary condition. Let a 2×2 matrix $\mathbf{W}$ be so defined that its matrix elements are given by

$$\langle \sigma | W | \sigma' \rangle = \exp \left\{ \frac{1}{kT} \left[J\sigma\sigma' + \frac{1}{2}h(\sigma + \sigma') \right] \right\}, \quad (5)$$

where σ and σ' may independently take on the values 0 and 1. An explicit representation for $\mathbf{W}$ is

$$W = \begin{bmatrix} 1 & e^{B/2} \\ e^{B/2} & e^{A+B} \end{bmatrix}, \quad (6)$$

where $A = J/kT$ and $B = h/kT$. By an easy calculation we find that the two eigenvalues $\lambda_{0,1}$ are

$$\lambda_{0,1} = \frac{1}{2} \left\{ (1 + e^{A+B}) \mp \sqrt{(1 - e^{A+B})^2 + 4e^B} \right\}. \quad (7)$$

The partition function can be calculated easily from the trace of W^n as

$$Z(V, T) = \text{Tr} \begin{bmatrix} 1 & e^{B/2} \\ e^{B/2} & e^{A+B} \end{bmatrix}^n = \text{Tr} \begin{bmatrix} \lambda_0^n & 0 \\ 0 & \lambda_1^n \end{bmatrix} = \lambda_0^n + \lambda_1^n. \quad (8)$$

Hence, the mean fraction of channels in the open state, or the a channel's probability of being in the open state, p_o , is given by

$$\begin{aligned} p_o = \langle \sigma_i \rangle &= \frac{1}{n} \frac{\partial \ln Z}{\partial h} \\ &= \frac{1}{2\lambda_1} \left\{ e^{A+B} - \frac{(1 - e^{A+B})e^{A+B}}{\sqrt{(1 - e^{A+B})^2 + 4e^B}} + \frac{2e^B}{\sqrt{(1 - e^{A+B})^2 + 4e^B}} \right\}. \end{aligned} \quad (9)$$

In our calculations, we consider the batrachotoxin-modified sodium channels in the squid giant axon [11]. In [11], the Boltzmann parameters, i.e., the values for the equivalent number of gating particles, z , and the voltage at which the channel is open 50% of the time, V_0 , are found from different single-channel experiments. A single Boltzmann distribution was considered to fit all the data available from experiments performed at different temperatures and in different axons. A sigmoidal-shaped curve were obtained for the steady-state channel opening of the batrachotoxin-modified sodium channels by Correa et al. [11]. They determined p_o from experimental recordings made at the bath temperatures 0, 3.4, 3.7, 8.5, 14.3°C. For each temperature, recordings at different voltages were made after the bath temperature had stabilized. The fits to Boltzmann distributions gave V_0 values equal to -67.5, -63.9, -66.8, -61.2, -57.6 mV and z values equal to 3.7, 3.6, 3.6, 4.0, 4.1 for temperatures 0, 3.4, 3.7, 8.5, 14.3°C, respectively.

The dependence of the probability of being open (p_o) on the membrane voltage (V) is shown in Fig. 1 for a one-dimensional lattice, using the above values of V_0 , z and T with $J=0.0$ eV. Analysis of the p_o data shows that p_o vs. voltage relation is also sigmoidal, that is, the fraction of channels in the open state rises to 1.0 from 0.0, as in the HH model [4, 5]. From the figure, one can see that increasing the temperature causes the p_o vs. V curve to shift to the right along the voltage axis without changing the voltage dependence. The direction of the shift implies that an increase in temperature stabilizes the closed, or

Fig. 1 Voltage dependence of the probability of opening (p_o) of a batrachotoxin-modified sodium channel at several temperatures for the one-dimensional lattice with $J=0.0$ eV. The curves are obtained using the same parameters of [11] in Eq. 9 of the present paper

destabilizes the open, configuration of the channel, because a larger depolarizing voltage is need to obtain the same p_o . These results are in good agreement with the results reported for the gating kinetics of batrachotoxin-modified sodium channels by COAT [11].

Figure 2 illustrates p_o as a function of voltage for the case $T=8.5^\circ\text{C}$, $z=4.0$, $V_0=-61.2$ mV. To compare our model results using these parameters with the experiment, we also show the experimental data for the same parameters in Fig. 2a. In this figure, the solid and dashed curves correspond to model calculations and experimental measurements, respectively. In the case of noninteracting channels (or without cooperative interactions between the channels, $J=0.0$ eV), the two curves are virtually indistinguishable. It is found that the slope value of the sigmoidal curve at V_0 is equal to its value at V_0 for the experimental curve. These model results agree well with the one-dimensional model predictions for the ligand-gated ion channels [17]. In the one-dimensional model of ligand-gated ion channels, the expression for the mean open probability, p_o , was derived from the grand partition function, and interactions between neighbouring open channels gave rise to a sigmoidal p_o vs. concentration curve. The same Hill slope was found in the model as in the fit of the experimental data obtained from nicotinic ACh receptor channels. On the other hand, to assess the effects of cooperativity on p_o vs. V variation, we show the predictions of (9) for the dependence of open channel probability on membrane potential for $J=0, \pm 0.02, \pm 0.04, \pm 0.06$ eV in Fig. 2b. The one-dimensional model predicts that both the position and shape of the curves are different when the interaction energy (J) between the channels is changed; e.g., when open channels exhibit positive cooperativity ($J<0$), p_o vs. V curve is shifted to lower voltages and the slope at V_0 becomes steeper. When $J>0$, the curve is shifted to higher voltages and the slope becomes less steep. In the case of strong negative cooperativity, the proposed model predicts a different sort of voltage dependence for p_o , i.e., the p_o versus V curve flattens near $p_o=0.5$, as seen in Fig. 2b. Similar behaviours have also been observed in one-dimensional model predictions for ligand-gated ion channels [17]. Positive cooperativity increased the slope at the midpoint of the p_o vs. concentration curve, shifting the apparent binding affinity to lower concentrations. Negative cooperativity had the opposite effects. Thus, the present TMM technique may be a useful approach to test the results reported in [17].

Fig. 2 **a** Probability of channel opening (p_o) at $V_0 = -61.2$ mV, $T = 8.5^\circ\text{C}$, $z = 4.0$, $J = 0.0$ eV; *solid curve*: model calculations; *dashed curve*: experimental data taken from [11] and reproduced with the permission of the authors and the publisher. **b** Model predictions for different values of the energy of interaction (J) between adjacent open channels. $V_0 = -61.2$ mV, $T = 8.5^\circ\text{C}$, $z = 4.0$

In conclusion, we have presented a model for cell membrane ion channels using the transfer matrix method. Similar to the MFA and PA approximation techniques, the TMM model is based on the principles of statistical mechanics and is quite different from conventional theories. In the model, we assume that an ion channel is located on a lattice site in one-dimensional chain and can either be in an open or a closed state. The significant advantage in using TMM is that it assumes cooperative interactions (J) between the channels. In other words, since ion channels mutually interact, there is a need either for cyclic boundary conditions, or in the TMM, to calculate the statistical sums for the partition function of the system. Using the energy of the system in a symmetrical form with a boundary condition, the fraction of channels in the open state at equilibrium is calculated for the batrachotoxin-modified sodium channels in the squid giant axon. The model, which is mathematically equivalent to the one-dimensional Ising model for magnetic systems, produces a strong agreement with the experimental measurements for the open probability of sodium channels under no interactions ($J=0$) between the neighbouring channel states. Since a membrane is

essentially a surface phenomenon, a two-dimensional version of the proposed model for the voltage-gated channels may be developed incorporating interactions between ion channels and external electric fields [6, 7]. The present theory also develops a possible approach to the problem of channels that are not voltage-gated, using ideas from [17].

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