Monte Carlo simulation for statistical mechanics model of ion-channel cooperativity in cell membranes

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Voltage-gated ion channels are key molecules for the generation and propagation of electrical signals in excitable cell membranes. The voltage-dependent switching of these channels between conducting and nonconducting states is a major factor in controlling the transmembrane voltage. In this study, a statistical mechanics model of these molecules has been discussed on the basis of a two-dimensional spin model. A new Hamiltonian and a new Monte Carlo simulation algorithm are introduced to simulate such a model. It was shown that the results well match the experimental data obtained from batrachotoxin-modified sodium channels in the squid giant axon using the cut-open axon technique.

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I. INTRODUCTION

Ion channels are a class of proteins that reside in the membranes of all biological cells and form conduction pores that regulate the transport of ions into and out of cells [1]. Not only are ion channels important in their biological purpose, they are also extremely interesting for their possible use in bioelectronics, more specifically as a component in a new class of biosensors. Different channels are classified by their gating mechanisms. Some are voltage gated; others are ligand gated (e.g., neurotransmitter gated channels) and yet other channels can be gated by heat or even mechanical stress. These gating mechanisms and different forms of cooperativity between ion channels are central issues in biological physics because of the dominant role channels played in the control of key cellular processes [2–4]. Cooperative behavior in ion channels arises from direct, energetic interactions between components of a system. Such interactions give rise to a sigmoidal dependence between the state of the system (e.g., ligand binding to a receptor) and the thermodynamic variables (e.g., ligand concentration). Two levels of interaction can take place in a system of ion channels: local cooperation between subunits of a macromolecular channel protein, and nonlocal cooperation between different channel proteins.

Many studies have considered the cooperative interactions between ligand-gated ion channels. Such interactions give rise to a sigmoidal dependence between the ligand binding to a receptor and ligand concentration. Ligand-gated channel current is usually derived in equilibrium and thermotropic-type models such as the Hill [5] and Langmuir [6] equations. Also, the Ising model of statistical mechanics and lattice-type theories employed in this field are of equilibrium and thermotropic with a chemical potential modified to accommodate for the dependence on ligand concentration [7]. In these works, local cooperativity was illustrated by the Hill equation and the contribution from short-range cooperativity to the Hill coefficient has also been evaluated in a nearest-neighbor interaction, Ising-type model. Contrary to the Hill, Langmuir, Ising, and other stationary type models, lyotropic, nonstationary, nonequilibrium, long-range interaction models were derived recently [8,9]. These models were based on the DNA replication and the cell cycle [10] and a comparison of their model results with an Ising-type model provided a methodology to obtain the nonequilibrium scaling dependence of Ising-type models on the reactant concentration. Besides these works, Guo and Levine [11] introduced a phenomenological model for the clustering which is due to an interaction between nearest-neighbor receptors. They described the clustering by the statistical mechanics of a simple lattice Hamiltonian and calculated a phase diagram. Zafar *et al.* [12] presented a statistical mechanics model for the interaction between the neurotransmitter and receptor ion channels. Based on the model, an equation for concentration response curves was derived and the model provided good fits to measured curves.

Voltage-sensitive membrane channels show also cooperative behavior as evident from electrophysiological experiments [13,14]. Using the principles of statistical mechanics, different approaches were proposed to account for the interchannel cooperativity. Ghosh and Mukherjee [15] have suggested a statistical mechanical approach for a microscopic analysis of these systems. They developed a model of the Zimm-Bragg type for a membrane with a large number of channels behaving cooperatively and tested their model with voltage-dependent conductance data for gap-junction channels in embryonic cells. Ghosh [16] extended their analysis for the relaxation of channels to deal with the time-dependent observations. Yang *et al.* [17] proposed a statistical mechanical model of cell membrane potassium and sodium ion channels in squid giant axon. The model incorporated interactions between the tissue electric field and the respective ion channels and was equivalent to the familiar lattice-gas model in statistical mechanics. Under a mean-field approximation, the maximum fractions of potassium and sodium channels were obtained by solving a self-consistent nonlinear equation. The model produced an excellent fit to experimental observations for maximum fractions of potassium and sodium conduction under a static external

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stimulus. Erdem and Ekiz [18] developed the Bethe lattice version of this model based on the recursion technique used for magnetic systems and showed the collective effects introduced by transmembrane voltage. Recently, Erdem [19] used the one-dimensional Ising-model formalism to study the collective equilibrium behavior of voltage-gated channels. In Ref. [19], effects of negative and positive cooperativity on the open probability of a batrachotoxin-modified (BTX) sodium channels were discussed. While there is vast literature devoted to statistical mechanics modeling of ion-channel cooperativity, these have not been adequately addressed using computational methods [11].

Computational studies can make meaningful contributions to our understanding of biological ion channels [20]. A wide variety of computational methods, such as molecular-dynamics simulations [21], kinetic rate models [22], continuum electrostatic Poisson-Boltzmann theory [23], and Brownian dynamics [24], provided a virtual route for interpreting experimental observations on relating a channel structure to its function. Besides these works, the Monte Carlo (MC) simulation technique was used to model the noise and stochastic resonance in voltage-gated ion channels [25]. Adair [25] took the Hodgkin-Huxley (HH) description of sodium and potassium channels in the squid giant axon as a basis of calculation and used relations from statistical mechanics when the channel states were separated by a Gibbs energy. In the HH formulation of the channel dynamics, the state of the domains depends only on the potential difference and not on the neighboring channel states [26]. Im *et al.* [27] combined the grand canonical MC simulations with the Brownian dynamics to simulate movement of ions in membrane channels. This approach provided a framework for simulating ion permeation in context of detailed microscopic models. Similarly, an algorithm in which kinetic lattice grand canonical MC simulations were combined with mean-field theory was presented to calculate ion currents in model ion-channel system by Hwang *et al.* [28].

On the other hand, the long-range coupling between ion channels in squid giant axons originates from specific distribution of sodium channels in the membrane [29] and also from global capacitance coupling [30]. Transmembrane voltage is a global membrane property determined in part by the membrane capacitance. Through their transition rates, it globally couples the independent ion channels. When the membrane channel number is small, the individual channels open and close independently, producing a very noisy transmembrane potential. As the membrane channel number increases, a transition to regular, collective behavior occurs. The regular behavior in globally coupled stochastic elements has been experimentally observed and analyzed by Sherman *et al.* [31]. The molecular origin of the spatial long-range interactions in squid giant axons arises from the specific distribution of sodium channels. These interactions are crucial to introduce Hopf bifurcation in squid axons and for the generation of action potentials [29].

Neurotoxins have played important role in understanding the molecular properties of sodium channels. A variety of different neurotoxins acts on the sodium channel to modify its gating so as to keep the channel open for longer. This leads to repetitive firing of neurons so that the nervous system no longer functions properly [32]. Nonpolar toxins are able to penetrate the lipid membrane and so can reach sodium channel sites that are embedded in it. They produce persistent activation by inhibiting inactivation and shifting the activation-voltage curve to more negative potentials [33]. Among various toxins studied the BTX (a toxin produced by the Colombian frogs of genera Phyllobates, in particular P. Aurotaenia) is one of the most potent and specific activators of sodium channels, causing them to remain open at the resting membrane potentials. It also decreases channel conductance and modifies ion selectivity [34,35]. Therefore, the BTX is able to induce profound changes in the behavior of nerve and muscle sodium channels. An increase in temperature speeds up the kinetics of these channels and decreases the probability of finding the channel open, i.e., they become closed with the increase in temperature.

The effects of BTX on sodium channels in hybrid neuroblastoma cells were studied by using voltage clamp method by Huang *et al.* [34]. BTX-modified sodium channels activated with first-order kinetics and, over most of the potential range, activated more slowly. Iwasa *et al.* [13] analyzed the current records from voltage-clamped membrane patches containing two BTX-modified sodium channels in hybrid neuroblastoma cells to determine whether these channels are identical and independent. Their results showed a clear discrepancy with binomial distribution and suggested that the explanation of this discrepancy was negative cooperativity between two channels in a patch. The negative cooperativity described in Ref. [13] was based on a slower rate of channel opening when the neighboring channel was open than it is closed and this was considered as a useful property to relate channel structure to channel function in future attempts. These cooperative interactions do not occur between every pair of channels and it is difficult to imagine interactions between channels separated by large distances. Of nine two-channel patches observed in Ref. [13] five patches contained clearly interacting channels, two patches contained two independent, identical channels, and the two patches showed a behavior consistent with either nonindependence or nonidentity. The interacting channels were the majority when a large number of two-channel patches were examined. The analysis of two-channel patches showed relatively simple kinetics involving two closed states and one open state. Despite the fact that ion permeation through the BTX-modified channels has received much attention [33–35], detailed reports on channel cooperativity for the squid axon sodium channels are scarce.

In this paper, we study the statistical mechanics model of cooperativity for the voltage-sensing BTX-modified sodium channels in squid giant axon systems using a MC simulation technique. In reality, these channels are found in outside-out patches of axolemma from squid giant axon and may be prepared experimentally by means of the cut-open axon technique [35]. The process of BTX modification of sodium channels in the squid axon is accelerated by holding the patch at hyperpolarized voltages and then applying depolarizing voltage pulses for short periods of time. The advantage of using the squid axon BTX-modified sodium channels to perform this kind of simulations is twofold. First, they have simple kinetics involving two states as open (O) or close (C). Second their steady-state activation contains our gating pa-

rameters (e.g., gating charge per channel and the midpoint values for the membrane potential), hence they are convenient for our simulation. Our study shows that there indeed exists a weak cooperativity between the BTX-modified sodium channels.

The paper is organized as follows: In Sec. II. We present the model with a Hamiltonian and suggest the simulation method to calculate the open probability of the BTX-modified sodium channels. Comparisons between MC simulation and experimental results obtained using cut-open axon technique and the effects of cooperative interactions on the simulation results are given in Sec. III. Finally in Sec. IV, our conclusions are summarized and discussed.

II. MODEL AND SIMULATION METHOD

We mentioned above that ion channels which have different biological and physicochemical structures with different gating mechanisms are located on the membrane surface as grown into the cell. These channels can be either open or closed. There is some structure or the property of the channel that is concerned with the transition between these two states, and the word *gate* is used to describe this concept. 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. On the other hand, *modulation* occurs when some substance or agent affects the gating of the channel in some way.

The behavior of a simple two-state channel is 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 this theoretical framework, in a population of N identical channels in the membrane, the number of channels in the closed and open states is 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 given by [32]

$$E = \sum_{i=1}^{2} n_i \varepsilon_i + z e_0 n_1 V, \tag{1}$$

where z is the number of charges on gating particle, e_0 is the elementary electronic charge, and V is the potential difference, also called the membrane potential. This expression of internal energy does not include interactions between ion channels. However, some theoretical models have supposed by many authors as including interactions between ion channels. At this point, we must remark that one of the most fascinating models is a statistical model based on spin systems [17]. By analogy between channel and spin systems it was considered [17–19] that membrane is a two-dimensional sheet and assume that the channels are located on a finite square lattice in the membrane with each channel having two states (open and closed) and incorporating the interactions between these states. In this context, the energy of the channel system was defined in the form,

$$E = -J \sum_{\langle ij \rangle}^{N} \sigma_i \sigma_j - z e_0 (V - V_0) \sum_{i=1}^{N} \sigma_i, \tag{2}$$

where σ_i can take the values 0 and 1 corresponding to C and O states, respectively, and N denotes total number of channels on the membrane surface. Also J represents the interaction energy between a pair of nearest-neighbor channels, denoted by $\langle ij \rangle$, and V_0 [equals to $-(\varepsilon_1-\varepsilon_2)/ze_0$] is the voltage at which half of the channels are open. In type of this study, open probability for interactive system has been obtained using mean-field approximation. In fact, it is shown that the mean-field solutions of theoretical models [17–19] with nearest-neighbor interacting states give compatible results with the experimental studies.

Indeed, a channel system can be represented by a spin system since a membrane is essentially a surface phenomenon and a channel has two possible states, and representing the distribution of channels over the cellular membrane on a two-dimensional array with each channel having two states and with interactions we are led to a generalized two-dimensional spin model. However, we have seen in this study that Eq. (2) is not a simulation model of channel systems. Meaningful results of Eq. (2) in the mean-field approximation are only obtained if spin variable σ_i takes on the values of 0 and +1 instead of −1 and +1. But simulation of Eq. (2) with spin $\sigma_i = \pm 1$ produces magnetization curve which changes in the interval $[-1, +1]$, and magnetization of a spin system does not correspond to open probability for a channel system. Therefore, in order to obtain open probability of a channel system, we here discuss a model based on spin system. Note that, in this model, we also visualize the membrane as a two-dimensional sheet, and we assume that the channels are located on a finite square lattice in the membrane with each channel having two states (open and closed) and incorporating the interactions between these states like in mean-field model, and we assume that, in a spin model with $\sigma_i = \pm 1$, the probability of inversion of a spin from −1 to +1 corresponds to the open probability P_O of a channel on the cell surface. Based on this assumption, we can simulate the spin system to obtain open probability of channels on the cell membrane. To simulate the open probability of such a channel system, a new Hamiltonian was introduced as

$$E = J \sum_{i=1}^{N} \sigma_i P_O + z e_0 (V - V_0) \sum_{i=1}^{N} \sigma_i, \tag{3}$$

where P_O is defined in terms of magnetization of spin system as

$$P_O = \left(\frac{1}{2} + \frac{\tilde{m}}{2}\right), \tag{4}$$

where $\tilde{m}$ is the average magnetization per spin, and it is given by

$$\tilde{m} = \frac{1}{N}\sum_{j}^{N} \sigma_j. \tag{5}$$

In these equations P_O represents open probability of channels, σ_i (and σ_j) can take the values +1 and −1 corresponding to O and C states, N denotes total number of spins on the lattice which corresponds to the number of channels on the membrane surface. Energy of a given channel system in this model in terms of overall probability, i.e., open probability P_O which is a global variable. Similarly, the energy of a single channel can be written depends on overall probability as

$$E_i = J\sigma_i P_O + ze_0(V - V_0)\sigma_i. \tag{6}$$

Since the interaction is of infinite range in Eq. (3), a global coupling between channels is introduced for the system. In the case $J=0.0$, the first term is absent in Eq. (3) this means that the global coupling disappears, hence open probability is calculated in terms of the second term. However, for $J \neq 0$ values, global coupling in the first term shows effects on the open probability. It will be shown in Sec. III that the energy proposed above, namely, Eq. (3), and its single-channel modification, Eq. (6), is a correct approximation for calculating the probability P_O.

We deal with the probability of flipping of down spins which corresponds to the open probability of close channels in this model. Therefore, during the simulation we focus only on the probability of flip instead of numerical difference between up and down spins, i.e., net magnetization. Here we will simulate the model described in Eq. (3) using a MC algorithm to calculate the open probability P_O since direct simulation of Eq. (2) with standard MC method is not suitable. Our simulation algorithm shows a few significant differences from standard Metropolis MC algorithm. Therefore, before we give our simulation algorithm steps, we remind briefly standard Metropolis MC algorithm steps.

It is known that, in the standard Metropolis MC algorithm, the Boltzmann probability function p is defined as $p \sim \exp(-\Delta E/kT)$, where ΔE indicates energy difference between initial and final configuration of a spin, on the other hand, k and T then are the Boltzmann constant and temperature values, respectively. The energy difference is then given by $\Delta E = E_f - Ei$ where E_f and E_i represent final and initial energy of a spin, respectively. The standard Metropolis MC Algorithm follows those steps: (i) initially all spins are randomly set, (ii) a trial configuration is made by sequentially choosing one spin, (iii) the energy of a choosing spin is calculated due to ΔE, (iv) if $\Delta E < 0$ then the new state of spin is accepted (i.e., choosing spin flips), otherwise, (v) a random number r in the unit interval is generated and the new state is only accepted if $r \leq \exp(-\Delta E/kT)$, otherwise, the previous state is retained, and finally, (vi) the value of desired quantities is determined. Whereas, in our simulation algorithm approach, we have modified the Boltzmann probability function as $p_i \sim \exp(-E_i/kT)$ where E_i represents initial energy of a spin i defined Eq. (6). After initially the probability P_O has been set as zero which indicates that there is no up spin (i.e., open channel) in the lattice, our method follows those steps: (i) all spins are initially set as down, i.e., all channels are closed, (ii) a trial configuration is made by sequentially choosing one spin, (iii) the energy of choosing spin is calculated due to Eq. (6). (iv) A random number r in the unit interval is generated and the new state is only accepted if $r \leq \exp(-E_i/kT)$, otherwise, the previous state is retained, and finally, (v) the value of desired quantities is determined. Using this modified algorithm, simulation of the above model has been performed on an $L \times L$ square lattice ($L=20$) with periodic boundary conditions. In the simulation k was set as unity, and the data were also generated with 5000 MC steps per site.

In this section lastly we must remark that our MC simulation algorithm is different from standard MC algorithm. The most important difference appears depend on acceptance rule. In the new simulation algorithm, a choosing spin (i.e., channel) flips only depends on probability with $p_i \sim \exp(-E_i/kT)$ where E_i is a function of open probability P_O. This indicates that in new simulation method trial moves (opening or closing of a channel) is that they are no longer completely random: the moves are biased in such a way that the channel to be inserted has an enhanced probability to fit into existing configuration. As a result the algorithm proposed in the present study is biased and hence ergodicity is broken. Such kind of biased MC methods was previously used in the research [36,37].

III. SIMULATION RESULTS

In our simulation we consider the BTX-modified Na+ channels in the squid giant axon [35]. The probability of channel opening (P_O) for noninteractive channel systems [32] is well described by a Boltzmann distribution of the form as a function of voltage and temperature,

$$P_O = \{1 + \exp[-ze_0(V - V_0)/kT]\}^{-1}, \tag{7}$$

where z (number of charges on gating particle) and V_0 (the voltage at which half of the channels are open) are called the Boltzmann parameters (or gating parameters), k is the Boltzmann constant, and T is the temperature of the system. The parameters z and V_0 are found from different single-channel experiments. A single Boltzmann distribution was considered to fit all the data available from experiments done at different temperatures and in different axons. Particularly, sigmoidal-shaped curves were obtained for the steady-state channel opening of the BTX-modified sodium channels by Correa *et al.* [35]. 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 values equal to −67.5, −63.9, −66.8, −61.2, and −57.6 mV, and z values equal to 3.7, 3.6, 3.6, 4.0, and 4.1 for temperatures 0, 3.4, 3.7, 8.5, and 14.3 °C, respectively.

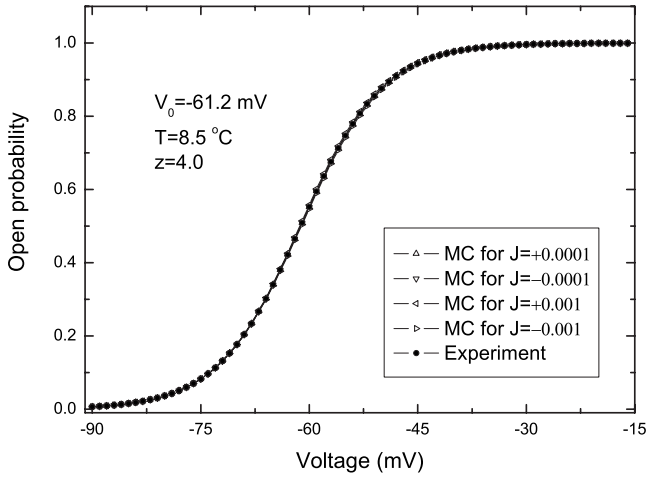

FIG. 1. Probability of channel opening (P_O) at $V_0=-61.2$ mV, $T=8.5$ °C, $z=4.0$, $J=\pm 0.0001$ and $J=\pm 0.001$ eV; open triangles: MC calculations; filled circle: experimental data Ref. [35].

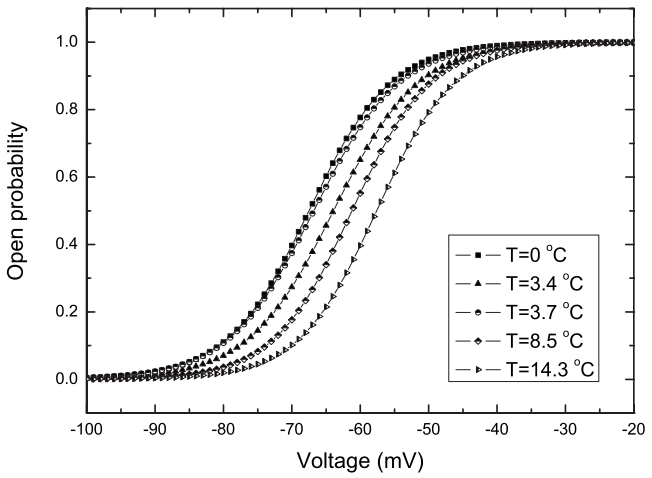

FIG. 2. Voltage dependence of the probability of opening (P_O) of a BTX sodium channel at several temperatures for the two-dimensional lattice with $J=0.0001$ eV. The curves are obtained using the same parameters of Ref. [35].

Figure 1 shows the P_O as a function of voltage for the case $T=8.5$ °C, $z=4.0$, $V_0=-61.2$ mV. To compare our MC results using these parameters with the experiment we also show the experimental data for the same parameters in Fig. 1. In this figure, the open triangles and filled circle correspond to MC simulation calculations and experimental measurement, respectively. In the case of weakly interacting channels (with $J=\pm 0.0001$ and $J=\pm 0.001$ eV), a matching of the theoretically computed data based on the MC simulation with the experimental observations is seen explicitly. It is found that the slope value of the sigmoidal curve at V_0 is exactly equal to its value at V_0 for the experimental curve. These results well agree with the two-dimensional model predictions for the ligand-gated ion channels [7]. In the two-dimensional model of ligand-gated ion channels, expression for the mean open probability, P_O, was derived from the grand partition function and interactions between neighboring open channels gave rise to sigmoidal P_O vs concentration curve. The same Hill slope was found in the model as the fit of the experimental data obtained from nicotine ACh receptor channels.

The dependence of the probability of being open state (P_O) on the membrane voltage is shown in Fig. 2 for a two-dimensional lattice, using the values of z, V_0, temperature (T) given in Ref. [35] with $J=0.0001$ eV. Analysis of the P_O data shows that the probability of being open vs voltage relation is also sigmoidal, that is the fraction of channels in open state rises to 1.0 from 0.0, as in the HH model [26]. From the figure one can see that increasing temperature causes P_O vs voltage 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 destabilizes the open configuration of the channel, because large depolarizing voltage is needed to obtain the same P_O. These results are in good agreement with the results reported in gating kinetics of BTX-modified sodium channels [35], and confirm that our model is correct in MC simulation framework to simulate open probability of BTX channels.

On the other hand, in Fig. 3, we demonstrated the simulation results for the temperature dependence of opening and closing probabilities of the channels. This figure represents the equilibrium behavior of ion channels on the membrane at different temperature. As seen from Fig. 3 opening probability P_O of ion channels exponentially decreases with increasing temperature from 0.00 to 0.20. Conversely, closing probability P_C of ion channels exponentially increases with increasing temperature. However, functional behavior of opening and closing probabilities obeys second-order exponential form as $P_{O,C}=\pm A_1 \exp(\mp T/\tau_1) \pm A_2 \exp(\mp T/\tau_2)$ with $A_1=0.45$, $A_2=0.07$ and $\tau_1=0.01$, $\tau_2=0.12$ for $J=\pm 0.0001$. At high temperatures, converging to 0.5 of the opening and closing probabilities indicates that this value is equilibrium value for ion channels. That is, at high temperatures, while the half of ion channels is approximately open, the other half is close, randomly. This is expected behavior for ion channels.

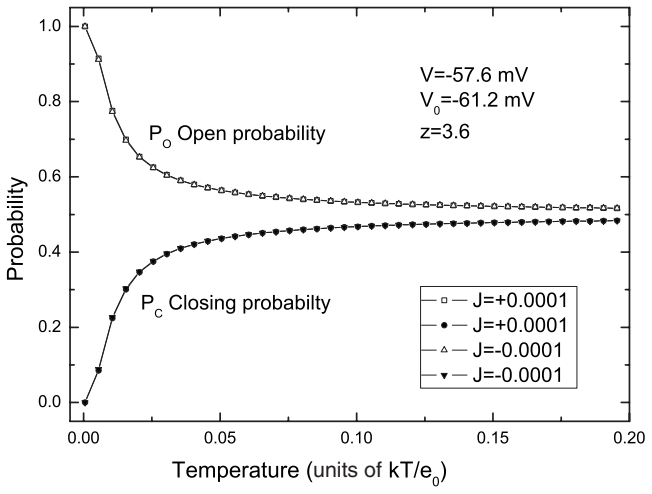

FIG. 3. Opening and closing probabilities of channels vs temperature kT/e_0 at $J=\pm 0.0001$, $V=-57.6$ mV, $V_0=-61.2$ mV, $z=3.6$.

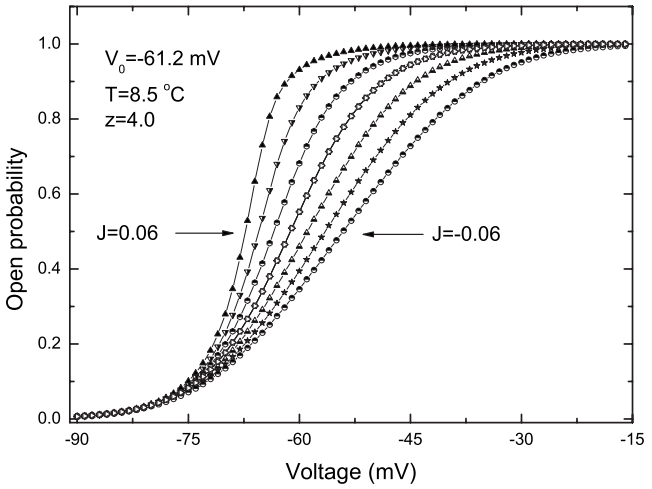

FIG. 4. MC results for different values of the energy of interaction (J) between adjacent open channels at $V_0=-61.2$ mV, $T=8.5$ °C, $z=4.0$ for $J=\pm 0.0001, \pm 0.02, \pm 0.04, \pm 0.06$ eV.

Finally, to assess the effects of strong cooperativity on P_O vs voltage variation we show the MC simulations for the dependence of open-channel probability on membrane potential for, $J=\pm 0.0001, \pm 0.02, \pm 0.04, \pm 0.06$ eV for fixed values of z, V_0, and T in Fig. 4. Two-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 voltage 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, seen in Fig. 4. Similar behaviors have also been observed in two-dimensional model predictions for the ligand-gated ion channels [7]. Positive cooperativity increased the slope at the midpoint of the P_O vs concentration curve, shifted the apparent binding affinity to lower concentrations. Negative cooperativity had the opposite effects. Thus, the present modified Hamiltonian and modified MC simulation algorithm may be useful approach to test the results reported in Ref. [7].

IV. SUMMARY AND CONCLUSION

In this study, we have presented the MC simulation for statistical mechanics model of cooperativity between voltage-sensitive ion channels in cell membranes. We have also discussed a Hamiltonian and a modified MC simulation algorithm for calculating the fraction of channels in open state, i.e., open probability at equilibrium for the channels. The Hamiltonian contains global coupling between the channels and the algorithm is an improvement over the standard metropolis MC algorithm. Since the global or long-range interactions among the sodium channels in squid giant axons are crucial for generation of action potentials and the BTX is able to induce profound changes in the behavior of nerve sodium channels, we have considered the BTX-modified sodium channels of squid giant axon in our simulation. Open probability for the BTX-modified sodium channels has been found for different voltage, temperature, and coupling strength to other channels (J). It was shown that in the case of weak cooperativity ($J\approx 0$) the results well match the experimental data using cut-open axon technique. On the other hand, in the case of strong cooperativity ($J>0$), the MC simulation predicted a different sort of voltage dependence for the open probability, i.e., a shift along the voltage axis and a change in slope at the midpoint potential. When compared with model curves for the ligand-gated channels the simulation results also well agree with the two-dimensional Ising-model predictions for the open probability versus concentration curves. This indicates that the present simulation method is applicable to the ligand gated channel systems.

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