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The Transport Properties of the Cell Membrane Ion Channels in Electric Fields: Bethe Lattice Treatment

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Abstract The interactive two-state model of cell membrane ion channels in an electric field is formulated on the Bethe lattice by means of the exact recursion relations. The probability of channel opening or maximum fractions of open potassium and sodium channels are obtained by solving a non-linear algebraic equation. Using known parameters for the conventional mean-field theory the model gives a good agreement with the experiment both at low and high trans-membrane potential values. For intermediate voltages, the numerical results imply that collective effects are introduced by trans-membrane voltage.

Keywords Bethe lattice · Trans-membrane conductance · Potassium and sodium ion channels

1 Introduction

The cell membrane is the outer layer of a cell with a typical thickness of 10 nm. It consists of a lipid bi-layer whose typical thickness is 3 nm and is responsible, along with the cell wall, for maintaining a balance between the outside world and the inside the cell. The cell membrane is a selectively permeable barrier that allows some substances to pass through to the inside of the cell while keeping others out. In order to understand how the cell membrane functions to regulate flow into and out of a cell, it is important to understand the structure of a typical membrane. A cell membrane has several key features that are present throughout all cells with a membrane. First of all, most cell membranes are composed of two layers of lipids or fats. Each layer is composed of individual lipid molecules that have two distinct regions. The head of the lipid likes to be near water and the tail region does not like water. As a result of this disposition toward water the lipid molecules pack to form an external layer

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with their head toward the exterior and their tails within the two layers of the membrane. Cellular membranes are fluid, which means that the lipids are able to move within the layers.

Another important component of membranes, that are also able to move within the lipid layer and between layers is proteins. They give the membrane much of its ability to selectively allow some substances out while allowing others in. Proteins can act as transport molecules which actively carry molecules or ions across the membrane, or they can simply provide a channel for molecules of a certain size to pass freely through. There is a structure of protein molecules called ion channels which provides conduction pathways for specific ions to transverse the membrane and thus constitutes a fundamental element for electrical signaling in nerve muscle and synapse. Ion channels are embedded across the membrane and form gateways for ions moving into and out of the cell [1]. These embedded transmembrane proteins allow the formation of a concentration gradient between the extracellular and intracellular contents. These ion channels are said to be 'gated' if they can be opened or closed. There are three types of gated ion channels: Ligand-gated, Mechanically gated, and Voltage-gated. Ligand-gated channels open or close in response to the binding of a small signaling molecule or "ligand". Some ion channels are gated by extracellular ligands; some by intracellular ligands. In both cases, the ligand is not the substance that is transported when the channel opens. The binding of neurotransmitter acetylcholine opens sodium channels in certain synapses. Mechanically gated channels are beyond the scope of this work, but stretch receptors, opening channels to create nerve impulses form one such example. Voltage-gated channels are found in neurons and muscle cells. They open or close in response to changes in the charge (measured in volts) across the membrane. For example, as an impulse passes down a neuron, the reduction in the voltage opens sodium channels in the adjacent portion of the membrane. This allows the influx of sodium ions into the neuron and thus the continuation of the nerve impulse.

The first detailed quantitative measurements of the ionic currents through the voltage-gated channels were performed by Hodgkin and Huxley in the early 1950s [2–6]. By using the voltage- clamp technique (VCT) they were able to measure the kinetics of potassium and sodium ionic currents in squid giant axon. This led them to a set of differential equations that describe the dynamics of the action potential. The predictions of their model turned out to be in remarkably good agreement with the experimental observations. In the model introduced by Hodgkin and Huxley (HH) [2], ion channels are treated as independent entities and the transport of ions through these channels is modeled phenomenologically by first-order rate equations. Various properties of the HH model have been studied so far [7–11].

Similar to HH model, noninteractive two-state models for ion channel kinetics have been proposed and studied recently [12–16]. In these models, each channel is opened by a movement of single gating particle which carries a charge and transport of ions through these channels is modeled by a first-order rate equations with voltage and temperature dependent rates of transition. In these equations, the transition rates have been obtained by the statistical mechanical approach [13, 14, 16]. The results for the noninteractive model agreed with the measurements by cut-open axon technique in the squid giant axon [17]. On the other hand, the possibility of interactions between neighboring channels with the state of one channel affecting the states of its neighbors and vice versa exists. These cooperative effects have been mooted over the years as possible mechanisms of interaction at the cellular membrane level [18, 19]. If the cell is exposed to an electric field the depolarization and hyperpolarization caused by the ion flow across the membrane creates a change in the interaction energy with the field. By the laws of statistical physics these changes in energy will result in changes in the probabilities of the states of the ion channels. A statistical mechanical model for the interacting ion channels in the presence of electric fields has been proposed by Yang et al.

[20]. The model was based on the conventional type of mean field approximation (MFA) and conceptually is quite different from the conventional HH Cable model theories [21, 22]. In this approximation, as formalized by Landau [23], they introduced an order parameter but neglected the correlations between fluctuating channel states at different sites and did not distort the lattice geometry. The numerical results gave excellent agreement with the VCT experimental measurements for potassium and sodium trans-membrane conductance using some choices of parameter values. Conventional mean-field theories are not always trustworthy. Recent advances in molecular biology and electrophysiological techniques have shown that the trans-membrane voltage introduces nontrivial correlations among the fluctuating channels and macroscopic voltage fluctuations lead to collective effects in ion channel proteins [24–27]. To gain insight into this problem, in a recent study, interacting potassium and sodium channel states with pair correlation have also been formulated by using the pair approximation (PA) of the cluster variation method by us [28]. Our work presented qualitative results but did not give a correct explanation of the experimental data.

For a more reliable theory including correlations among the channels the lattice may be approximated by a (Cayley) tree [29] and the resulting problem is solved exactly. Gujrati [30] demonstrated that the behavior on the Bethe or Bethe-like lattices are qualitatively correct even when conventional mean-field theories fail and argued that mean-field theories are more reliable if derived on a Bethe lattice (BL). Our purpose in this paper is to formulate and study a new statistical mechanical model for cell membrane ion channels based on recursive calculations on a tree. In the model, we assume that the channels are located on the BL and interact with each other by a repulsive interaction as well as external electric field. A Bethe lattice or a Cayley tree is the simplest possible branching medium which has no closed loops [31]. It can serve as an approximation to a real lattice for studying the transport properties. In recent years, the Bethe lattice has been extensively used to study various models such as spin glasses [32], Ising models [33–37], Hubbard model [38], tight-binding models [39, 40], etc.

The paper is organized as follows: In Sect. 2, the model and its mean-field formulation are given in detail. In Sect. 3, we formulate the interactive two-state model for ion channels on the Bethe lattice with a general coordination number q, and obtain the recursion relations. The procedure of investigation of transport properties based on these relations is described and discussed in Sect. 4. Finally some concluding remarks are presented in the last section.

2 The Model and Mean-Field Formulation

In the interacting ion channel model, there are two driving forces for ions flowing through the channels: electrical and osmotic. The osmotic forces can be represented electrically as the so-called Nernst potential V due to concentration difference of ions across the membrane [41, 42]. When the membrane is in its resting state where the channels are mostly closed, the trans-membrane potential difference is V_0. When the cell is exposed to a uniform electric field (E), the maximum induced trans-membrane potential change occurs where the field is normal to the cell surface. As the channels open, the ions flow out of the cell. This creates a local hyperpolarization around the channel. The effective dipole moment change around the channel will cause a change of interaction energy with the induced trans-membrane electric field (E'). Taking the positive direction of E' as pointing to outside of the cell, the associated interaction energy with the induced electric field in the membrane is $-E'Ql/\varepsilon_r$, where l is the thickness of the lipid bilayer, ε_r is the permittivity and Q is the local electrical charge

transfer per channel given by

$$Q = \frac{c|V - V_0|}{\rho}. \tag{1}$$

In (1) c is the membrane capacitance per unit area and ρ is the density of channels on the membrane. Thus, the energy change is given by

$$\gamma = \mu - \frac{Q}{\varepsilon_r}\bar{V}, \tag{2}$$

where $\bar{V} = lE'$ is the induced trans-membrane potential and μ is the chemical potential of a channel, i.e. the energy difference between an isolated open and closed channel in the absence of induced trans-membrane electric field. The total energy of such a channel system for a 'configuration' $\{\sigma\} = (\sigma_1, \sigma_2, \ldots, \sigma_N)$ can be

$$\xi\{\sigma\} = J\sum_{\langle ij\rangle}\sigma_i\sigma_j + \gamma\sum_{i=1}^{N}\sigma_i, \tag{3}$$

where $\sigma_i = 0, 1$ and correspond to closed and open channel states, respectively, N is the total number of exposed ion channels and J represents the interaction energy between a pair of nearest neighbor channels, denoted by $\langle ij\rangle$. The positive values of J imply repulsive interactions between neighboring channels. Equation (3) is the well known and much studied lattice-gas model in statistical mechanics.

In equilibrium statistical mechanics where the external field is constant or static, the probability of a particular 'configuration' $\{\sigma\}$ is given by the Gibbs canonical distribution

$$P\{\sigma\} = \frac{1}{Z}\exp\left(-\frac{\xi\{\sigma\}}{kT}\right), \tag{4}$$

where k is the Boltzmann constant and T is the absolute temperature. The normalization constant, or canonical partition function Z is defined by

$$Z = \sum_{\{\sigma\}}\exp\left(-\frac{\xi\{\sigma\}}{kT}\right). \tag{5}$$

The sum in (5) is over all (2^{N_K} and $2^{N_{Na}}$) configurations of potassium and sodium ion channels. The mean or average fraction of open activated channels (or probability of gate opening) are defined by

$$P_O = \left\langle \frac{1}{N}\sum_{i=1}^{N}\sigma_i \right\rangle = \sum_{\{\sigma\}}\left(\frac{1}{N}\sum_{i=1}^{N}\sigma_i\right)P\{\sigma\}. \tag{6}$$

For the mean-field version of the model, it is assumed that each channel interacts with a 'mean-field' generated by other channels which is proportional to P_O defined by (6). That is we take the first term of (3) to be $JP_O\sum_{i=1}^{N}\sigma_i$. The total energy, (3) can thus be expressed in the form

$$\xi\{\sigma\} = (JP_O + \gamma)\sum_{i=1}^{N}\sigma_i. \tag{7}$$

In order for the model to be self-consistent, the mean-field P_O in $JP_O \sum_{i=1}^{N} \sigma_i$, must agree with P_O calculated from (6). Some straightforward calculations yield the self-consistent, or mean-field equation

$$P_O = \left\{1 + \exp\left[\frac{JP_O + \gamma}{kT}\right]\right\}^{-1}. \tag{8}$$

Equation (8) is well known in statistical mechanics and has also found applications to ion-protein binding where it is commonly known as the Scatchard equation.

When a potassium channel opens the potassium ions flow out of the cell. On the other hand, a sodium channel is different from a potassium channel in that it effectively has two 'gates': the activation and the inactivation gates [43]. When an activation gate opens, the sodium ions flow into the cell. When a Na channel opens the Na flow is cut off by the inactivation gate. The transition from the maximum Na conduction state to the asymptotic or equilibrium state is assumed to be determined by the inactivation gate. Thus, $P_O^{(\mathrm{K})}$ is the mean fraction of open potassium channels and $P_O^{(\mathrm{Na})}$ denotes the mean fraction of closed inactivation gates for sodium channels. In other words, $P_O^{(\mathrm{Na})}$ is the change in mean fraction of open sodium channels due to the inactivation process as the system approaches to equilibrium. By solving (8) the maximum trans-membrane conductance is calculated for potassium and sodium channels in the squid giant axon [20]. The MFA model is tested with the Hodgkin and Huxley's classic works on squid axons by the VCT experiments [2–6] and produces an excellent fit to observations for maximum K and Na conduction under a static external stimulus. The model also predicts repulsive interactions between neighboring channels [2–6]. This suggests that when a K channel opens, the opening probability of neighboring K channels is reduced. Similarly, when the inactivation gate of a Na channel closes, the closing probability of neighboring Na inactivation gate is reduced. It should be mentioned that the MFA agreement to the experiment is due to the lack of voltage fluctuations and corresponding correlations of channels in the case of VCT observations. A VCT system in its original form measures current flow through an area of membrane no smaller than several hundred square micrometers and usually rather larger than this. The currents recorded are the summed currents of several hundred or more channels, so they are sometimes called 'macroscopic' currents. The electrical activity of single channels is not accessible by this means. Three further extensions of the VCT were developed for investigating single channel activity: fluctuation analysis, the use of artificial lipid bilayers, and the patch-clamp technique (PCT) [1].

3 Model Formulation on the Bethe Lattice

For the Bethe lattice formulation of the model, we assume that ion channels in cell membranes are located on the Bethe lattice in a two-dimensional sheet. The Bethe lattice shown in Fig. 1 is characterized by the coordination number q (the number of the neighbors of each site) and can be thought of as being built in a recursive manner by attaching to a central site on which there is a channel and q channels interacting with the central site. Then to each of these q channels are attached $q - 1$ channels. One continues in this manner ad infinitum to construct the full Bethe lattice. The partition function of the system is given by

$$Z = \sum_{\sigma} P_r(\sigma), \tag{9}$$

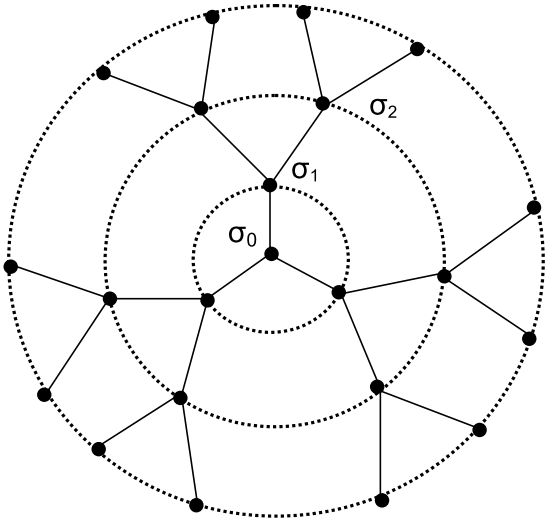

Fig. 1 Bethe lattice with coordination number $q = 3$. σ_0 is the value of the channel at the central site

where

$$P_r(\sigma) = \exp\left[-\beta\left\{J\sum_{\langle i,j\rangle}\sigma_i\sigma_j + \gamma\sum_i \sigma_i\right\}\right], \tag{10}$$

with $\beta = 1/kT$. The first summation in (10) is over all edges of the graph, the second over all sites. The $P_r(\sigma)$ can be thought of as an unnormalized probability distribution: in particular, if σ_0 is the ion channel at the central site 0, then the mean number of open channels or the probability of being open state for a single channel is

$$P_O = \langle\sigma_0\rangle = \frac{1}{Z}\sum_\sigma \sigma_0 P_r(\sigma). \tag{11}$$

From Fig. 1 it is apparent that if the Bethe lattice is cut at 0, then it splits up into q identical disconnected pieces. Each of these is a rooted tree (with root 0). This implies that (10) factors:

$$P_r(\sigma) = e^{-\beta\gamma\sigma_0}\prod_{j=1}^{q} Q_n(\sigma_0|\sigma_j), \tag{12}$$

where σ_j denotes all the ion channels (other than the central ion channel σ_0) on the jth sub-tree, and

$$Q_n(\sigma_0|\sigma_j) = \exp\left[-\beta\left\{J\sum_{\langle i,j\rangle}\sigma_i\sigma_j + J\sigma_0\sigma_1 + \gamma\sum_i \sigma_i\right\}\right], \tag{13}$$

σ_i being the ion channel on site i of the sub-tree. Site 1 is the site adjacent to 0, as in the upper sub-tree of Fig. 1. The first summation in (13) is over all edges of the sub-tree other than $(0, 1)$; the second is over all sites other than 0. The suffix n denotes the fact that the sub-tree has n shells, i.e. n steps from the root to the boundary sites. Further if the upper sub-tree in Fig. 1 is cut at the site 1 adjacent to 0, then it too decomposes into q pieces: one

being the trunk (0, 1), the rest being identical branches. Each of these branches is a sub-tree like the original, but with only $n-1$ shells. Thus,

$$Q_n(\sigma_0|\sigma_j) = e^{-\beta(J\sigma_0\sigma_1+\gamma\sigma_1)} \prod_{j=1}^{q-1} Q_{n-1}(\sigma_1|\sigma_j), \tag{14}$$

where σ_j denotes all the ion channels (other than σ_1) on the jth branch of the sub-tree. These factorization relations (see (12) and (14)) make it easy to calculate the open probability for the channels (P_O). We define

$$r_n(\sigma_0) = \sum_{\sigma} Q_n(\sigma_0|\sigma), \tag{15}$$

and then from (9) and (10),

$$Z = \sum_{\sigma_0} e^{-\beta\gamma\sigma_0}[r_n(\sigma_0)]^q. \tag{16}$$

Similarly, from (11) and (12), the probability of being open state is written as

$$P_O = \frac{1}{Z}\sum_{\sigma_0} \sigma_0 e^{-\beta\gamma\sigma_0}[r_n(\sigma_0)]^q. \tag{17}$$

Since all the ion channels can have the values $\sigma = 1$ and 0, the partition function can be calculated using (9), (10) and (16) as

$$Z = [r_n(0)]^q + e^{-\beta\gamma}[r_n(1)]^q. \tag{18}$$

The mean number of open channels (P_O) can be written by using (11), (12) and (17) as

$$P_0 = \frac{1}{Z}(e^{-\beta\gamma})[r_n(1)]^q = \frac{e^{-\beta\gamma}[r_n(1)]^q}{[r_n(0)]^q + e^{-\beta\gamma}[r_n(1)]^q}. \tag{19}$$

In order to calculate P_O in terms of recursion relations we need to sum (15) over all σ and σ_1 to find

$$r_n(\sigma_0) = \sum_{\sigma_1} e^{-\beta(J\sigma_0\sigma_1+\gamma\sigma_1)}[r_{n-1}(\sigma_1)]^{q-1}. \tag{20}$$

Since σ_0 and σ_1 take two possible values, i.e. 1 and 0, one can obtain two different $r_n(\sigma_0)$ for two possible values of σ_0. If the central channel is open ($\sigma_0 = 1$), then

$$r_n(1) = \sum_{\sigma_1} e^{-\beta(J\sigma_1+\gamma\sigma_1)}[r_{n-1}(\sigma_1)]^{q-1} = [r_{n-1}(0)]^{q-1} + e^{-\beta(J+\gamma)}[r_{n-1}(1)]^{q-1}, \tag{21}$$

and the central channel is closed ($\sigma_0 = 0$), then

$$r_n(0) = \sum_{\sigma_1} e^{-\beta\gamma\sigma_1}[r_{n-1}(\sigma_1)]^{q-1} = [r_{n-1}(0)]^{q-1} + e^{-\beta\gamma}[r_{n-1}(1)]^{q-1}. \tag{22}$$

Let us introduce the following variable x_n:

$$x_n = \frac{r_n(1)}{r_n(0)}. \tag{23}$$

From (21–23), we can easily obtain the following recursion relation:

$$x_n = \frac{1 + e^{-\beta(J+\gamma)} x_{n-1}^{q-1}}{1 + e^{-\beta\gamma} x_{n-1}^{q-1}}. \tag{24}$$

Through x_n, we can express the average number of open or the mean fraction of open channels by

$$P_O = \frac{e^{-\beta\gamma} x_n^q}{1 + e^{-\beta\gamma} x_n^q}, \tag{25}$$

or

$$P_O = \frac{1}{1 + x_n^{-q} \exp(\beta\gamma)}. \tag{26}$$

In order to investigate the transport properties of the system, it is necessary to solve the recursion relation given in (24) iteratively for $J > 0$ and $\mu > 0$ and substitute (24) into (26). Thus we can examine the voltage variation of P_O. Assuming that the trans-membrane conductance is proportional to the average number of open channels, the value of $P_O^{(\mathrm{K})}$ as calculated from (26) is proportional to the asymptotic or maximum trans-membrane potassium conductance. For sodium channels, $P_O^{(\mathrm{Na})}$ is proportional to the trans-membrane conductance difference between the peak and the equilibrium or the asymptotic value. Given that the equilibrium or the asymptotic trans-membrane conductance is much smaller than the peak value [41], $P_O^{(\mathrm{Na})}$ is approximately proportional to the maximum trans-membrane sodium conductance.

4 Results and discussion

An interactive two-state model for cell membrane K and Na ion channels in electric fields has been proposed and studied based on the recursion technique used for Ising models of magnetic systems. In the model, the K or Na channels are regarded as residing on a Bethe lattice in two-dimensions, an infinitely branching tree with all sites having the same coordination number, and interactions between the neighboring channels and the tissue electric field are incorporated. Using the recursion relations obtained on that lattice we derived explicit expressions for the maximum fractions of open K and Na ion channels (P_O). For a comparative analysis of present approach and the conventional MFA predictions, we consider the normalized maximum potassium and sodium conductance data measured experimentally using a voltage clamp method [2–6]. The experiment was carried out using several axons and under different temperatures (T). The sodium conductance was measured at 6 °C and 8.5 °C. For potassium conductance, the experimental temperatures were 6 °C, 8.5 °C, 11 °C and 22 °C. The normalized maximum conductance was observed to be insensitive to the temperature. For the squid giant axon, the K and Na channel densities are $\rho_{\mathrm{K}} \cong 1.8 \times 10^{13}$ m^{-2} and $\rho_{\mathrm{Na}} \cong 3 \times 10^{14}$ m^{-2} [20, 44–46]. The Nernst potentials across the membrane for K and Na ions are estimated to be $V_{\mathrm{K}} = -74.7$ mV and $V_{\mathrm{Na}} = 54.2$ mV, respectively, and the resting membrane potential value is $V_0 = -68$ mV [37]. The membrane capacitance per unit area is $c = 1$ μF and the relative permittivity of the lipid bi-layer is $\varepsilon_r \cong 3$ [42]. The predicted values of chemical potentials and channel-channel interaction energies for the K channels were $\mu_{\mathrm{K}} = 0.106, 0.107, 0.108, 0.111$ eV and $J_{\mathrm{K}} = 0.453, 0.451, 0.449, 0.441$ eV corresponding to $T = 6$ °C, 8.5 °C, 11 °C, 22 °C, respectively. Similarly, these values were

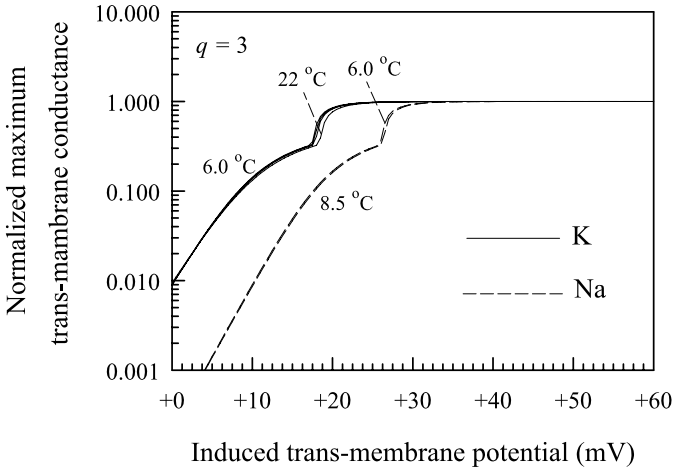

Fig. 2 Maximum trans-membrane potassium (K) and sodium (Na) ion conductance vs. induced trans-membrane potential ($\bar{V}$) at several temperatures for $q = 3$

predicted for the Na channels as $\mu_{Na} = 0.191, 0.193$ eV and $J_{Na} = 0.319, 0.316$ eV for temperatures $T = 6\,^{\circ}$C, 8.5 °C, respectively [20, 28].

The normalized maximum trans-membrane conductance for the K and Na ion channels as a function of the induced trans-membrane potential ($\bar{V}$) are plotted in Fig. 2, using the above values of T, ρ, V, V_0, c, ε_r, μ and J. In the figure, the solid curves are for K channels and the dashed curves for Na channels and the numbers on the curves represent the values of temperature. The model calculations for the K conductance are normalized to 1 at $\bar{V} = 42.35, 42.75, 43.15, 44.65$ mV voltage values corresponding to the temperatures $T = 6\,^{\circ}$C, 8.5 °C, 11 °C, 22 °C, respectively. Similarly, the normalized values for the Na conductance are found to be $\bar{V} = 48.75$, and 49.2 mV, corresponding to 6 °C and 8.5 °C temperature values, respectively. These potential values for the normalized ion conductances are greater than our previous PA calculations [28] while less than the MFA results which are $\bar{V} = 100$ mV reported by Yang et al. [20]. As with experimental measurements and the MFA and PA model predictions, the Bethe lattice calculations for the normalized conductances are insensitive to the temperature variations, i.e. calculations with different temperatures used in experiments produce the same theoretical curves.

Figure 3 illustrates the normalized K and Na ion conductance vs. induced trans-membrane voltage curves for $q = 3$ at $T = 8.5\,^{\circ}$C with $J_K = 0.451$ eV, $\mu_K = 0.107$ eV, $J_{Na} = 0.316$ eV, $\mu_{Na} = 0.193$ eV. In Fig. 3, the solid curves are the BL model calculations and the dashed curves are the VCT measurements reported in Ref. [3]. In this case, the BL results with $q = 3$ give the same values as the VCT measurements at low induced potentials and at very high $\bar{V}$ values, seen in Figs. 3(a) and 3(b). In other words, the BL trans-membrane conductance data well agree with the VCT measurements at small $\bar{V}$ values, but a disagreement with the experiment occurs at larger voltages below $\bar{V} = 100$ mV, i.e. there is a moderately sharp increase in conductance above some threshold. These discrepancies at the intermediate voltages reveal that induced trans-membrane voltage introduces correlations among the fluctuating channels and displays the existence of collective effects in the system [24–27]. Occurrence of a sharp change in our model conductance data above a certain induced voltage is qualitatively well agree with the voltage dynamics in ensembles of a single type voltage-gated potassium-selective ion channels using the PCT [25, 26] and with

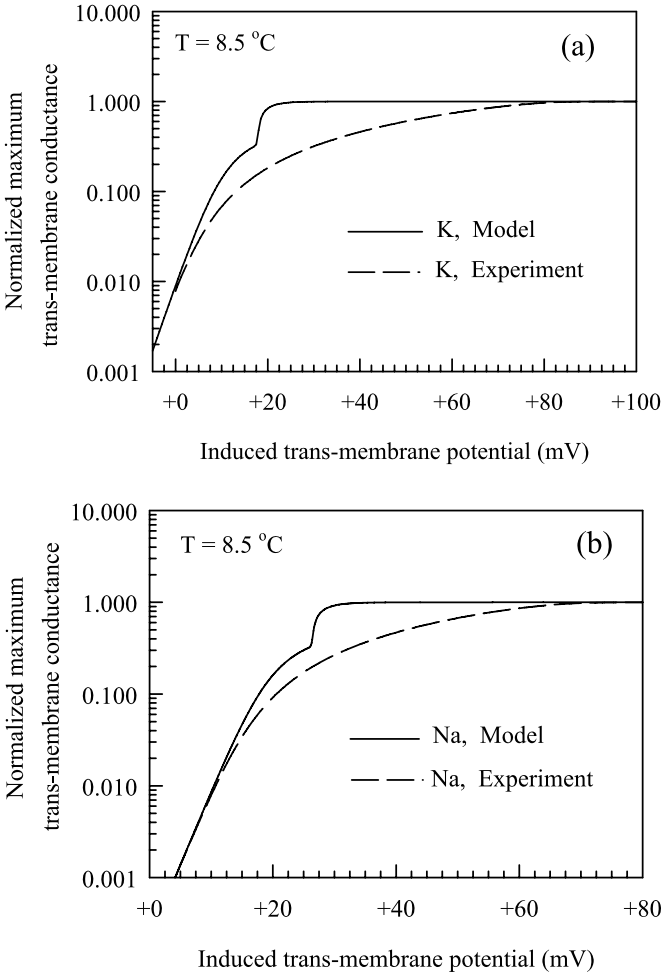

Fig. 3 **a** Maximum trans-membrane potassium conductance as a function of $\bar{V}$ for $T = 8.5\,^{\circ}\mathrm{C}$; *solid curve*: Bethe lattice calculations with $q = 3$; *dashed curve*: VCT measurements taken from Ref. [3]. (**b**) Same as (**a**) but for the sodium channels

the current clamp analysis of selective voltage-gated delayed-rectifier potassium channels in detached patch configuration [47]. For the model system used in the PCT experiments, with single-type potassium channels, a direct connection between the channel's kinetics and the transmembrane potential or the mechanism of membrane potential stabilization was dominated by a sharp change in the probability of potassium channels to open above a threshold value. Above a certain characteristic number of channels, the steady-state transmembrane voltage almost saturates around this threshold value. This characteristic number of channels depends on the various parameters of the system, especially the leak conductance. The sharp drop in potential for small numbers of channels and its saturation for large numbers of channels is a direct consequence of the voltage-dependent kinetics of the system. Similarly, the current clamp experimental observations suggested that the density and kinetics of voltage gated potassium channels, in the model system studied by Marom et al. [47], are major fac-

tors that determine both the mean and stability of membrane potential at a negative value and many potassium channels demonstrated a characteristic knee of their open probability-voltage curve at that voltage value. These experimental observations support the choice of a BL to model the distribution of ion channels on the cell membrane and calculations on the recursive structure provide us with a opportunity to study the coupling between the state of the channels and the induced transmembrane voltage which leads to a collective effect.

5 Conclusion

In this work, we have presented the Bethe lattice version of interacting model for potassium and sodium ion channels in electric fields proposed by Yang et al. [20]. We have also given a direct method for calculating the potassium and sodium trans-membrane conductances using exact recursion relations. These conductances are found by solving the non-linear algebraic equations for the probability of channel opening and must satisfy all the requirements of membrane electrophysiology. The advantage of Bethe or similar recursive lattice is apparent. By a proper choice of these lattices, it is possible to study the coupling between the microscopic state of the channels and the macroscopic voltage fluctuations, which are usually lost in conventional mean-field calculations, because of the lack of correlations. These correlations are present on the Bethe lattices, even though very weak and ensure that we obtain realistic results. In our calculations, the MFA predictions of chemical potentials (μ) and channel-channel interaction energies (J) for potassium and sodium channels have been used. When compared with the MFA and PA model curves, the model calculations transforms to the MFA results (or voltage-clamp measurements) at low voltage values and to the PA results at high trans-membrane potentials ($\bar{V}$). This indicates that the BL agreement to the voltage-clamp measurements is fairly good while the MFA agreement to experiment is excellent. The main feature of the voltage-clamp observations that require us to go beyond the usual mean-field theory to the BL approximation is that the VCT is not sensitive to detect the correlations and collective effects in the channel systems. These features are achieved by studying the trans-membrane voltage as a dynamical variable using standard patch-clamp technique which is invented recently. Thus, the formulation of ion channels on the Bethe lattice gives us new ways to analyze the patch-clamp conductance data and provide new insight into the physical or electrophysiological properties of the channel proteins in cell membranes.

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