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A physical model of sodium channel gating

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Abstract. Most current models of membrane ion channel gating are abstract compartmental models consisting of many undefined states connected by rate constants arbitrarily assigned to fit the known kinetics. In this paper is described a model with states that are defined in terms of physically plausible real systems which is capable of describing accurately most of the static and dynamic properties measured for the sodium channel of the squid axon. The model has two components. The *Q*-system consists of charges and dipoles that can move in response to an electric field applied across the membrane. It would contain and may compose the gating charge that is known to transfer prior to channel opening. The *N*-system consists of a charged group or dipole that is constrained to move only in the plane of the membrane and thus does not interact directly with the trans-membrane electric field but can interact electrostatically with the *Q*-system. The *N*-system has only two states, its resting state (channel closed) and its excited state (channel open) and its response time is very short in comparison with that of the *Q*-system. On depolarizing the membrane the the *N*-system will not make a transition to its open state until a critical amount of *Q*-charge transfer has occurred. Using only four adjustable parameters that are fully determined by fitting the equilibrium properties of the model to those of the sodium channel in the squid axon, the model is then able to describe with some accuracy the kinetics of channel opening and closing and includes the Cole and Moore delay. In addition to these predictions of the behaviour of assemblies of channels the model predicts some of the individual channel properties measured by patch clamp techniques.

Key words: Gating, model, sodium channel, electrostatic

Introduction

In this paper is described a simple but physically plausible model that is capable of simulating many of the measured static and kinetic properties associated with current gating of the trans-membrane ion channels in excitable tissue. As an example the model predictions are compared in detail with those exhibited by the sodium channel of the squid giant axon for which there exists good experimental data (Keynes and Kimura 1983).

There are at least two motives for the construction of models of physical systems. The first is to simulate accurately the response of a given system in order to incorporate this output in a model of a larger assembly. The second is to construct models with real physical components in the hope of pointing the direction to a better understanding of the actual processes that underlie the operation of the system. The Hodgkin and Huxley (1952) m^3 model of sodium channel gating is an example of the first type of model and was constructed in order to simulate accurately the form of the action potential. Although later researchers have tried to put flesh on the model by associating real physical entities with the *m* particles this was not the viewpoint of the originators who wrote in their paper "It was pointed out in Part II of this paper that certain features of our equations were capable of a physical interpretation, but the success of the equations is no evidence in favour of the mechanism of permeability change that we tentatively had in mind when the formulated them."

Most of the currently used models of sodium current gating are of the first type referred to above (Fishman 1985). For example, a recently quoted model (Armstrong 1981) involves a linear sequence of six states, five representing closed states and the sixth the open state. Each of the states are connected to their neighbours by forward and backward transitions with assigned rate constants. Varying amounts of charge are supposed to transfer as the system passes between the five closed states and these precede the attainment of the sixth and open state. It is entirely plausible that the complicated statics and kinetics of the conduction of the sodium channel can be represented by a model with this number of assigned constants. However this type of compartmental model contains no information about the processes that underlie channel gating other than the fact that the output can to some accuracy be represented by a set (in this case five) of simultaneous linear differential equations.

Here an attempt will be made to construct a model of the second kind so that each state of the model is associated with a well defined and physically plausible state of the channel complex.

The model

The model has two components. The first is an assembly of charges or electric dipoles (the *Q*-system) that respond to the voltage applied across the membrane and which would form part of the experimentally measured gating charge transfer detected when excitable channels are switched as described in detail for example by Almers (1978), Goldman (1976) or Keynes (1983). The second (the *N*-system) is a charge or electric dipole that moves in the plane of the membrane and is thus silent as far as the measurement of gating charge transfer is concerned. For simplicity the *N*-system is assumed to have only two states represented by $n = 0$ as the ground state which represents a channel closed to the conduction of ions and $n = 1$ as the excited state which represents a channel that is open and hence conducting ions across the membrane.

There are at least two types of experiment that support the existence of an electrically silent late stage in excitable channel gating. The first is that if the squid axon is deuterated by the substitution of D_2O for H_2O, the rise of the sodium current is delayed by a factor of about 1.4 (Conti and Palmieri 1968) whereas the gating charge transfer is not changed (Meves 1974). Similar effects in the axons of Mixycola have been measured by Schauf and Bullock (1979). This argues for an electrically silent late stage in the gating process which is slowed by deuteration. The second type of experiment involves the pressure dependence of the sodium current (Conti et al. 1982) and the gating charge transfer (Conti et al. 1984) in the squid axon. These authors conclude that a final and electrically silent rate-limiting step in the opening of the sodium channel has an activation volume about twice as large as the preceding steps which contribute to the trans-membrane charge transfer.

One possibility for the *Q* and *N* systems required for the model is shown in Fig. 1 a. The *Q* system is represented by a cylindrical region spanning the membrane which contains charges that are free to move from one side of the membrane to the other under the influence of any electric field applied across it. The *N*-system is represented by a single charged particle that interacts electrostatically with the charges of the *Q*-system but, because it is only free to move in the plane of the membrane and not transverse to it, does not interact with the electric field applied across the membrane. The two systems are depicted on the left side of Fig. 1 a in the ground or resting state. The *Q* charges are mostly near the inner face of the membrane reflecting the fact that the axon rests with its interior negatively charged relative to its exterior. The *N*-particle is assumed to rest in the $n = 0$ state closest to the cylindrical region in which the *Q*-charges move due to fixed charges in its region. If now the inside of the axon is suddenly made more positive some of the *Q*-charges will move with a relaxation time characteristic of their transfer across the membrane. The repulsion between the positive *Q*-charges near the outer face of the membrane and the positive *N*-particle will result in an increasing tendency for the *N*-particle to transfer from its resting $n = 0$ state depicted at the left hand side of Fig. 1 a to its conducting $n = 1$ state depicted on the right side of the figure. A central assumption of the model is that the characteristic time for the motion of the *N*-particle is much shorter that that which characterizes the approach to equilibrium of the *Q*-charges so that the *N*-system can at all times be considered to be in equilibrium with the instantaneous state of the *Q*-system. In the centre of Fig. 1 a is depicted an intermediate state in which some of the *Q*-charges have transferred but not a sufficient number to force the *N*-particle to move from its resting state.

Many of the features of the model may be understood from this simple description without the need of the detailed mathematical model given below. It clearly depends upon a threshold phenomenon in which a critical amount of *Q*-charge transfer must occur before the probability of an *N*-particle transfer is likely. This ties in with the known fact that much of the measured gating charge transfer precedes in time the channel opening and it also gives rise to the observed sigmoid current switch-on characteristic of the sodium current when plotted against time. A feature of the model is that the charge transfer represented by the *Q*-system can consist of many components such as hydrophobic ions moving in the lipid phase, rotation of the dipole moments of water molecules in the aqueous core of the channel or the motion of charged groups tethered to the membrane spanning proteins that define the sodium channel. It is the electrostatic effect of the cumulative Q-charge transfers that increases the probability of an N-particle transfer and there is no need for any of the Q-charges to be attached to specific molecular groups in order for the N-particle to transfer and for the channel to open. It is clear that the model is exactly the same if the Q-charges are positive and the N-particle is positive and near the outer surface of the membrane or if the Q-charges are negative and the N-particle is negative and located at the inner face of the membrane.

In Fig. 1b are depicted the equivalent three states of another realization of the model that is physically more probable. Here the Q-system is represented by a polarizable channel core and the N-particle is a neighbouring alpha-helical section of a membrane protein with its known large electric dipole moment. With the Q-system polarized inward in its resting state the dipole moments of the Q and N systems attract each other. However when, under the influence of the trans-membrane electric field the dipole moment of the Q-system has reversed in direction sufficiently, the Q and N systems repel each other and the N-system makes an electrically silent sideways movement that leads to channel opening. Note that the Q-system, which is supposed to consist of many small electric dipoles and mobile charges, reverses the direction of its dipole moment but that the alpha-helical dipole does not reverse. I have previously described such a gating mechanism and attempted by simple calculation to show that it is physically viable (Edmonds 1985) so that I will not describe it further here. Figure 1c depicts yet another possible physical realization of the model in which the Q-system is as described above but the N-system consists of a pair of contiguous and oppositely directed alpha-helices that are free to rotate about a common axis parallel the their length. When the Q-system is in its ground state the N-system exists in its $n = 0$ state with the dipole moment of the helix nearest to the Q-system pointing outward due to the attraction of the oppositely directed helix dipoles. In the $n = 1$ conducting state, in which the direction of the Q-system dipole moment is reversed, the attraction of oppositely directed helix dipoles has resulted in the rotation of the pair of helices about their common axis to open the channel. The rapid fall with distance R of the force of attraction of two antiparallel dipoles (approximately R^{-4}) ensures that the electrostatic interaction between the dipole moment of the Q-system and the nearest helix dipole dominates over that with the further helix dipole. I have previously described a model of a membrane ion counter-port based on such a pair of contiguous alpha-helical electric dipoles (Edmonds 1986).

The energy of the N-particle in its two positions may be written as

$$E(n = 0) = |e| * (-VN/2 + q * VNQ)$$

and

$$E(n = 1) = |e| * (+VN/2),$$

where $|e|$ is the proton charge and $|e| * VN$ is the excess in energy of the state $n = 1$ over that of the state $n = 0$ due to the static charges in its vicinity but not including the Q-system. $|e| * q * VNQ$ represents the contribution to the excess in energy of the state $n = 0$ over the state $n = 1$ due to the interaction between the Q-system and the N-particle where q is a parameter between 0 and 1 which characterizes the completeness of the Q-system transfer. In equilibrium, the probability n that the N-system finds

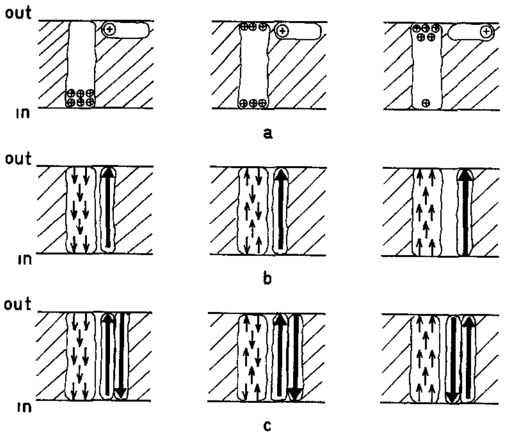

Fig. 1 a, b and c. In **a** is sketched one particularly simple realization of the model with the Q-system consisting of charges that move across the membrane and the N-system consists of a charged particle constrained to move in the plane of the membrane. At the left is shown the model in its resting state and on the right is shown the model when, in response to a positive voltage applied across the membrane, sufficient of the Q-charges have transferred to force the N-particle to make its transition to its excited state causing channel opening. The central sketch shows an intermediate state. In **b** the Q-system consists more generally of a polarizable portion of the channel complex and the N-system is a neighbouring alpha-helical part of the supporting protein with its considerable electric dipole moment. The three states depicted correspond to those shown in **a** with channel opening caused by the sideways translation of the helix. In **c** the Q-system is as in **b** but the N-system consists of a pair of neighbouring alpha-helices with oppositely directed dipole moments and the opening of the channel is caused by the rotation of the pair of helices about an axis parallel to their length in response to their electrostatic coupling to the Q-system itself in the state characterized by $n = 1$ is given by

$$n(q) = \exp(-E(n=1)/kT)/$$
$$\cdot (\exp(-E(n=1)/kT) + \exp(-E(n=0)/kT)),$$

where k is the Boltzmann constant and T is the absolute temperature. This can be simply written as

$$n(q) = 1/(1 + \exp((+VN - q * VNQ)/VT), \qquad (1)$$

where $VT = kT/|e|$. $n(q)$ is correctly identified with the mean value of n for an assembly of identical N-systems maintained at a temperature T when the Q-variable has the value q. Any individual N-system will always be either in state $n = 0$ or state $n = 1$ and, particularly near the threshold for transition, may rapidly fluctuate between these two definite states under the influence of the ambient thermal fluctuations.

In order to compare the model with experiment it is necessary to include a particular form for the variable q which reflects the charge transfer in the Q-system. We will identify q, which varies between 0 and 1, with the normalized total voltage dependent gating charge transfer measured experimentally, and write the equilibrium value of q at a membrane voltage $VM = V_{\text{in}} - V_{\text{out}}$ as $q\,e(VM)$ given by

$$q\,e(VM) = 1/(1 + \exp(-ZQ * (VM - VQ)/VT)), \qquad (2)$$

where ZQ is the "effective valence" of the Q-changes and VQ is the membrane voltage at which $q = 0.5$. This is the result that would be obtained for an assembly of non-interacting identical Q-charges each of valence ZQ and each traversing the total voltage VM applied across the membrane. Here we need not rely on any such specific model for $q\,e(VM)$ but use ZQ and VQ as parameters to obtain a curve of total gating charge against membrane voltage that agrees with experiment. The kinetics of the Q-system is represented at any value of VM by a single relaxation time constant $TQ(VM)$ so that at any time t the value of q is given by $q\,t(VM)$. If we start at an initial membrane voltage VMi at which the value of $q\,e(VMi) = q\,i$ and suddenly change VM to a final value of VMf at which the value of $q\,e(VMf) = q\,f$ then we will assume that the time variation of $q\,t(VMf)$ is given by

$$q\,t(VMf) = q\,i + (q\,f - q\,i) * (1 - \exp(-t/TQ)). \qquad (3)$$

We will further assume that the variation of TQ with VM is given by

$$TQ(VM) = 2 * TQ_0/(\exp(-ZQ * (VM - VQ)/VT)$$
$$+ \exp(ZQ * (VM - VQ)/VT)), \qquad (4)$$

where TQ_0 is the maximum relaxation time attained at a membrane voltage of VQ. Equations (3) and (4) are those that would result from non-interacting identical Q-charges each of valence ZQ moving across an energy barrier of height B between two states of energy

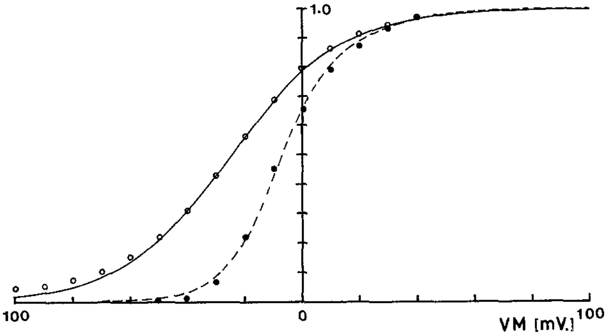

Fig. 2. The *open circles* show experimental results for the total gating charge transfer for the sodium channel of the squid giant axon when plotted against membrane voltage. The *full line* is that predicted by the model assuming simple exponential behaviour for the Q-system with $ZQ = 1.33$ and $VQ = -25$ mV. The *filled circles* are the values of the normalized sodium ion conductance of an assembly of channels in the same axon determined experimentally and the *broken line* is the model prediction assuming $VN = 145.4$ mV and $VNP = 192.4$ mV. The source of the experimental data is described in the text

$$E(q=0) = ZQ * (VM - VQ)/2 \quad \text{and}$$
$$E(q=1) = -ZQ * (VM - VQ)/2$$

where $2 * TQ_0 = \exp(+B/kT)$. Once again we will make no such assumption but merely use Eqs. (2), (3) and (4) to attempt to fit the experimental data for the gating charge transfer.

In Fig. 2 is shown as open circles the smoothed values of the total (unfractionated) gating charge as measured by Prof. R. D. Keynes and collaborators. I am most grateful to him for providing me so freely with such data. The full line through the points is the prediction of Eq. (2) with $ZQ = 1.33$ and $VQ = -25$ mV, chosen to obtain a reasonably close fit to the data. Also in Fig. 2 is shown as filled circles the experimental values of the average sodium channel conductance, normalized to 1, obtained by the same group. The solid line through these points is the value of the change in $n(q)$ predicted by the model using the values of q obtained above substituted into Eq. (1) with $VN = 145.2$ mV and $VNQ = 192.4$ mV. The predicted shape of the equilibrium sodium conductance characteristic is seen to be in good agreement with experiment and fitting the curve determines the only two adjustable parameters of the model. With the model fully determined by the static characteristic, the kinetic predictions of the model may now be compared with experiment.

Because we assume that the N-particle motion is characterized by a time constant very short com-

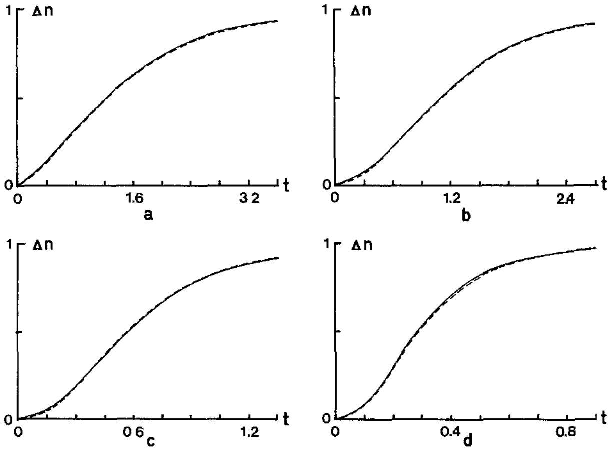

Fig. 3 a – d. The *full lines* in the figures **a** to **d** show the predictions of the model for the change in n with time, starting from a resting membrane voltage of −50 mV and making sudden changes of membrane voltage to −25 mV, 0 mV, 25 mV and 50 mV respectively. In each case the total change in n has been normalized to unity. The *broken curves* are the best fits to the full curves using a m^3 model by varying the relaxation time TM and the time delay d

pared to that of the Q-system, there is only one effective time constant (TQ_0) that determines the kinetics of the model. In this paper we choose $TQ_0 = 1$ and all times predicted by the model will simply scale with this value. In Fig. 3 are displayed as full curves the model predictions for the time variation of the average number of channels that are open, which is given by the change of n in Eq. (1) with the time variation of q determined by Eq. (3), when the membrane is held at −50 mV and then suddenly changed to various more positive membrane voltages. The curves are seen to display the sigmoid shape that is observed experimentally.

In their comprehensive measurement of sodium channel conductance Keynes and Kimura (1983) fitted their data to a Hodgkin and Huxley model as given below by

$$m = m\,i + (m\,f - m\,i) * (1 - \exp(-t/TM))$$

and

$$GNa = m^X,$$

where TM is a relaxation time, GNa is the normalized sodium conductance and X is a number determined by fitting the data. Eliminating m between these equations as having little meaning here, the m^X law may be conveniently written as

$$GNa = (GNa\,i^{1/X} + (GNa\,f^{1/X} - GNa\,i^{1/X}) * (1 - \exp(-t/TM)))^X, \qquad (5)$$

where $GNa\,i$ and $GNa\,f$ are the initial and final equilibrium values of the normalized sodium conductance GNa. They found that for various depolarizing pulses from various holding membrane voltages that the data could be well represented with a fixed value of X for each transient and that the values of X obtained varied between 2.9 and 4.4 with an average value of 3.5. This is in agreement with many investigations in the past including the pioneer work of Hodgkin and Huxley (1952) who obtained values close to 3. However, Keynes and Kimura (1983) and other investigators in the past (Keynes and Rojas 1976; Taylor and Bezanilla 1983) have found that there exists an appreciable delay in the sodium conductance time variation which increases with more negative starting membrane voltages and is greatest for depolarizations to less positive voltages. This is often called the Cole and Moore delay after the investigators who first detected the effect for the potassium channel of the squid axon (Cole and Moore 1960). In order to test whether the model leads to Cole and Moore time shifts and relaxation time constants TM similar to those found experimentally, the predictions of the model were compared with the predictions of Eq. (5) with t replaced by $t - d$ where d is a time delay. In particular the predictions of the model were regarded as the experimental data and a least squares computer fit to these data was made by comparison with Eq. (5) by fixing $X = 3$ and allowing both TM and d to vary in order to minimize the difference between the two curves. The broken lines in Fig. 3 were the result and to the accuracy of the plot they are identical with the model prediction over much of the curves. The root mean square deviation between the full and broken curves in Figs. 3a to d are 0.0065, 0.0063, 0.0079 and 0.0083 respectively. The resultant values of d and TM for a variety of conditions are plotted in Fig. 4 as full lines.

In Fig. 4a it is seen that the model predictions, when interpreted by an m^3 analysis, do give rise to Cole and Moore shifts which are negligible at membrane voltages more positive than about −25 mV and that the delay grows as the starting voltage is made more negative for a fixed final voltage. The delay saturates at extreme negative starting voltages and depolarizing to more positive final voltages tends to diminish the delay found. Each of these features is found in a comparison of experimental data with a m^3 model. As to the magnitude of the effect, Keynes and Rojas (1976) in their Fig. 5 show a delay when pulsing to −10 mV growing from a negligible amount at a starting voltage of −50 mV to about 140 μs (28% of the maximum TM) at a starting voltage of −150 mV. For pulses to −10 mV the model predicts a negligible delay when starting from −25 mV, growing to a delay of 12.4% of

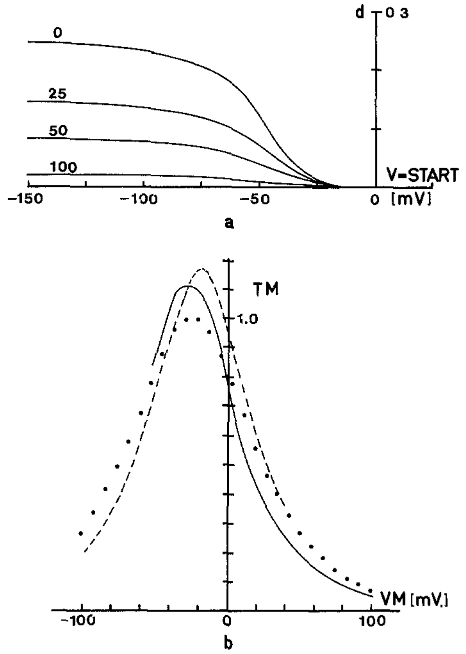

Fig. 4. In **a** are shown the values of the delay *d* obtained by fitting the model predictions using a m^3 model, plotted against the starting or resting membrane voltage. The numbers beside the curves give the fixed final voltage in millivolts of the membrane for that curve. In **b** are shown the values of the relaxation time TM obtained by fitting a m^3 model to the predictions of the model for positive depolarizing pulses (*full line*) and for negative polarizing pulses (*broken line*). The dotted line gives the values for TQ(VM) predicted by Eq. (4) with $TQ_0 = 1$, included for comparison

TM(max) at a starting voltage of -50 mV and to 24.5% of TM(max) at a starting voltage of -150 mV which is of a comparable magnitude.

The full line in Fig. 4b gives the values of TM obtained by this analysis of the model predictions while the dotted line gives the values for $TQ(VM)$ predicted by Eq. (4) for comparison purposes. It is seen that when the model predictions are compared with the Hodgkin and Huxley m^3 model a bell shaped curve for TM is obtained which is close to but not identical with the $TQ(VM)$ curve. The value of TM obtained depends only on the final voltage after the sudden depolarization and does not for example depend upon the starting voltage. Such a bell shaped curve with TM, dependent upon the final voltage but not the initial voltage is also obtained when experiment is compared with the m^3 model.

In addition to such data obtained by means of positive depolarizing pulses Keynes and Kimura (1983) obtained data by pulsing to a positive voltage until the sodium conductance had risen to near its maximum and then applying a negative repolarizing pulse to measure the subsequent decaying tail current. When this tail current was fitted using the full m^3 model described by Eq. (5), values of TM were obtained that agreed substantially with the curve of TM plotted against VM obtained by using depolarizing pulses. It is to be emphasized that the full m^3 model predicts tail current decay containing components with the three time constants TM, $TM/2$ and $TM/3$. The model predictions for the changes in n subsequent to a sudden negative change in membrane voltage from an initial positive starting voltage, when analysed using the m^3 model as described above, yielded the values of TM shown by the broken line in Fig. 4b. These can be seen to lie approximately but not exactly on the curve of TM obtained for depolarizing pulses (full line).

Conclusions

Einstein is credited with the remark that a model should be as simple as possible, but certainly no simpler. The extent to which this particularly simple model for excitable channel gating will stand direct comparison with experiment belongs in the future. From my doubtless partisan viewpoint it has the following attractive features:

(1) It is very simple as described by Eq. (1) and in particular much simpler than the m^3 model usually employed.

(2) Unlike the m^3 model it is readily interpretable in terms of a plausible physical system.

(3) It is able to predict the form of the static sodium current conductance as a function of membrane voltage of an assembly of channels (Fig. 2); connecting it to the gating charge transfer curve using only two adjustable constants.

(4) Using no further adjustable constants it is able to reproduce the sigmoid channel conductance characteristic that would result from a sudden positive change in the membrane voltage.

(5) The general bell shape of the TM versus VM curve for both polarizing and depolarizing membrane voltage excursions and the voltage dependences and magnitude of the Cole and Moore time delays obtained by interpreting the model predictions using a m^3 model are similar to those obtained by the interpretation of experimental data using the same means.

(6) Besides the statistical predictions for assemblies of channels listed above, the model predicts that a single channel would open and shut rapidly due to the fast response assumed for the N-system. Following a depolarizing pulse from a resting membrane voltage the model predicts that an individual channel would experience a variable delay before abruptly opening. The delay is determined by the

thermally-activated statistical fluctuations in the accommodation of the Q-system to the applied voltage. Also the N-system would rapidly fluctuate between its open $n = 1$ and closed $n = 0$ states, particularly if the membrane voltage resulted in the Q-system being near to its threshold value. All these properties are known to characterize single channels as measured using the patch clamp technique (Sigworth and Neher 1980).

One area in which the model is certainly oversimplified is in the treatment of the Q-system. It is well established (Khodorov 1979; Peganov 1979; Greef et al. 1982) that the gating charge that transfers when the sodium channel of the squid axon is depolarized is not homogeneous and contains at least two components. The two components have different kinetics and for example the maximum in the bell shaped dependence of the relaxation times of the components peak at different membrane voltages. Thus although the total equilibrium gating charge transfer is well represented by Eq. (2) as shown in Fig. 2, the kinetics of the transfer differ in detail from the simple form assumed in Eqs. (3) and (4). Such changes will change the details of the sodium conductance kinetics predicted by the model through the dependence of n on q. Prof. R. D. Keynes and myself have jointly made some progress in modelling some aspects of the heterogeneous gating charge transfer which we hope to report soon.

No mention of inactivation has been included in this paper in order to present the essentials of the new model as clearly as possible. However inactivation may easily be included by postulating a charged or dipolar inactivating system, so that the probability of inactivation is markedly increased by the additional electrostatic interactions between the inactivating system and the Q-system that result from the transfer of the Q-charges in a manner similar to that described previously (Edmonds 1983). Inactivation may then have a membrane voltage dependence or not depending on whether the inactivating system changes its energy in the applied trans-membrane electric field or is electrically silent like the N-system of the present model. The attractive electrostatic interaction between the inactivating system and the transferred Q-charges can also explain the negative shift in applied membrane voltage of the equilibrium inactivating characteristic relative to the equilibrium activation characteristic again as described before (Edmonds 1983).

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