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Derivation of an Improved Hodgkin–Huxley Model for Potassium Channel by Means of the Fokker–Planck Equation

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This paper demonstrates the derivation of Hodgkin–Huxley-like equations from the Fokker–Planck equation. The primary result is that instead of the familiar $g_K = \hat{g}_K n^4$ equation expressing the potassium conductance as a function of the variable n which obeys a first order differential equation, the expression $g_K = g_o \exp[L^2 - (n-L)^2]$, where $L = 2.7$, is to be used. This form is obtained by solving analytically an approximate solution to a Fokker–Planck partial difference equation. Instead of the Hodgkin–Huxley interpretation as the probability of occupying the conducting state, the parameter $n(t)$ is now interpreted as the position of the "peak" of the population distribution function $P(N, t)$, which changes in time described by the Fokker–Planck equation.

This new approach enables close fitting of the experimental voltage clamp data for potassium conductance. In addition, the Cole–Moore shift paradox can be quantitatively explained in terms of the shift of the distribution function $P(N, t)$ by the initial clamped transmembrane potential V_i before the final clamped transmembrane potential V_f is applied, thus increasing the time necessary for the establishment of equilibrium.

KEY WORDS: Fokker–Planck equation; Gaussian distribution; Hodgkin–Huxley model; Cole–Moore shift.

1. INTRODUCTION

It is well known that although the Hodgkin–Huxley (HH) equations[1] are very successful in describing the behavior of ion conductances of the axon membrane in an electric field, the exact physical mechanism from which the

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equations are derived is still not understood. For example, to explain the sigmoidal behavior of the increase of potassium conductance, an ad hoc variable (n, which obeys first order kinetics) is raised to a 4th power so that the theory matches the experimental data. Furthermore, to explain the existence of the 4th power, four hypothetical particles controlling the opening of the gate of the potassium channel are introduced. Indeed, after Cole and Moore's discovery[2] which showed that the HH equations have difficulty in describing the voltage step response of the potassium channel conductance from a hyperpolarized state unless the power of the $n(t)$ variable is increased to 25, the validity of the particle interaction model has been seriously doubted. Many different models (Hoyt,[3] Goldman,[4] Tille,[5] Wobschall,[6] Moore and Cox,[7] Hille,[8] Lo,[9] Strandberg,[10] Liebovitch *et al.*,[11] and several works in Abbott *et al.*[12]) have been proposed in an attempt to improve the description of experimental data. Some involve complicated systems of intermediate chemical reactions which lead to systems of coupled differential equations, while some other represent the ion conductances as a convolution integral of the voltage with a kernel which absorbs the complicated underlying dynamics. Though these models fit equally the experimental data, their complicated equations do not provide an easy interpretation of the physical process governing the nature of the ion conductance channels.

The present work chooses to tackle this problem along the physical chemical line of approach which often plays a major role in biology as expressed by F. Crick, "Eventually one may hope to have the whole of biology explained in terms of the level below it... in terms of standard bonds of chemistry." No new assumptions or complicated reaction mechanisms will be introduced. The present theory is based on the fact that the ion conductance channel must necessarily be a macromolecule which can exist in many different geometrical configurations (Strandberg[13]). As each configuration has a specific conductance, the total ion conductance can be written as an ensemble average over the entire population of ion conductance channels. The present model thus reduces to a familiar problem in deformation kinetics of macromolecules under the influence of an external force which, in this case, is the electric field produced by the transmembrane potential $V(t)$.

2. APPLICATION OF DEFORMATION KINETICS

The formulation in this section follows closely Eyring's approach[14] to kinetics of plastic deformation. In his theory, the molecule to be studied is described by a certain reaction coordinate q and free energy $E(q)$ which characterizes a system of consecutive energy barriers. The magnitudes of

these energy barriers are determined by the molecular structure as well as the presence of external "forces" (e.g., an electric field or a mechanical strain) acting on the molecules and leading to their deformation. Standard reaction rate theory is used in formulating the dynamics of the system.

For the present application to ion conductance channel, let the reaction coordinate q range from $-\infty$ to ∞ and the free energy $E(q)$ be consisted of three terms:

1. A term $E_1(V)\sin^2(\pi q/D)$ which represents the energy barriers separated by the characteristic distance D (in reaction coordinate space). Here, $E_1(V)$ is the height of the potential barrier as a function of the membrane potential V.

2. A term $E_2(V)(q/D)^2$ which represents the elastic behavior of the macromolecule. $E_2(V)/D^2$ constitutes the proportionality constant.

3. A term $-2E_3(V)\,q/D$ which represents the effect of the transmembrane potential V on the free energy of the macromolecule.

The total energy $E(q)$ is hence given by

$$E(q) = E_1(V)\sin^2(\pi q/D) + E_2(V)(q/D)^2 - 2E_3(V)\,q/D. \tag{1}$$

In summary, the present model assumes by and large that each ion channel is described by a potential energy function consisting of three parts: a fine grained up and down varying part in the reaction coordinate to model the microscopic configuration energy, a Hooke's law term to model the energy change due to the elastic deformation of the channel macromolecule in reaction coordinate, and a linear term to account for the displacement in reaction coordinate of the minimum energy point as a result of the applied voltage. These assumed terms are quite standard. As will be shown later, they would produce a kinetics model capable of explaining the HH curves and the Cole–Moore shift. Figure 1 shows an example of the free energy $E(q)$ as a function of the reaction coordinate x for $D=1$, $E_1(V)=0.1$, $E_2(V)=0.005$, and $E_3(V)=-0.01$.

Kinetic equations similar to the HH equations can be derived using standard reaction rate theory with the above expression. Let $E_1(V)$, $E_2(V)$ and $E_3(V)$ be such that the curvature of $E(q)$ is dominated by the rapid oscillating term $\sin^2(\pi q/D)$. Hence, local minimums and maximums of $E(q)$ can be approximated to occur respectively at coordinates $q' = ND$, where $\sin^2(\pi q'/D)=0$, and at coordinates $q'' = ND + D/2$, where $\sin^2(\pi q''/D)=1$, with N being any positive or negative integer. A molecule passing from a local minimum state $q=ND$ to a neighboring minimum state $q=(N+1)D$ has to overcome the energy barrier between the two minimums at $q=(ND+D/2)$. According to reaction rate theory, this energy barrier then

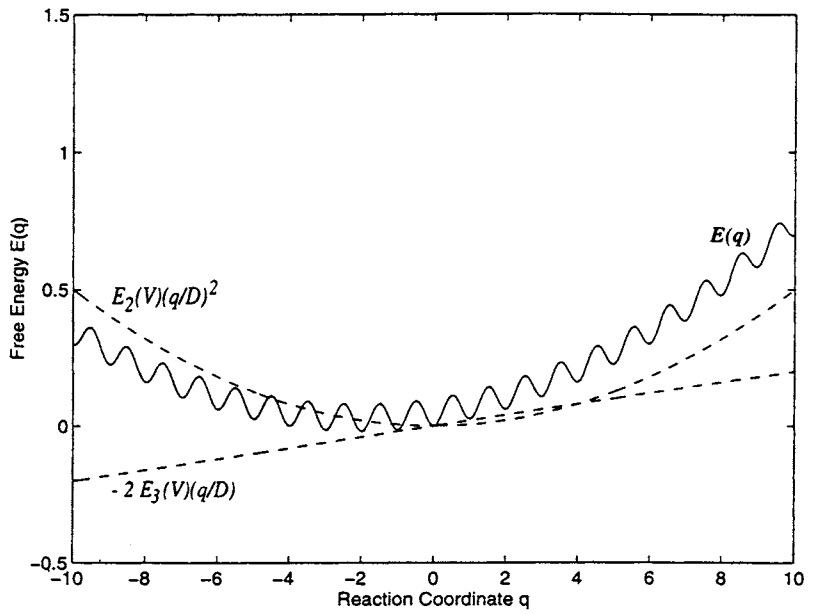

Fig. 1. Examples of $E_2(V)(q/D)^2$, $-2E_3(V)(q/D)$, and the Free Energy $E(q)$.

dictates the rate $k_+(ND)$ at which molecules at state $q=ND$ transform to state $q=(N+1)D$,

$$k_+(ND)=k_o e^{-[E(ND+D/2)-E(ND)]/k_BT} \tag{2}$$

Similarly, the rate $k_-(ND)$ at which molecules at the state at $q=ND$ transform to the state at $q=(N-1)D$ is given by

$$k_-(ND)=k_o e^{-[E(ND-D/2)-E(ND)]/k_BT} \tag{3}$$

In Eqs. (2) and (3), k_o is a proportionality constant, k_B is the Boltzman's constant, T is the temperature, and $E(ND+D/2)-E(ND)$ and $E(ND-D/2)-E(ND)$ are the respective heights of the barrier over which the molecule has to pass in order to transform from $q=ND$ to the neighboring states at $q=(N+1)D$ and $q=(N-1)D$. Equation (1) yields

$$\begin{aligned} E(ND+D/2)-E(ND) &= E_1(V)\sin^2(N\pi+\pi/2)-E_1(V)\sin^2(N\pi) \\ &\quad +E_2(V)(N+1/2)^2-E_2(V)N^2 \\ &\quad -2E_3(V)(N+1/2)+2E_3(V)N \\ &= E_1(V)+E_2(V)N-E_3(V), \end{aligned} \tag{4}$$

and

$$E(ND - D/2) - E(ND) = E_1(V) - E_2(V)N + E_3(V) \tag{5}$$

where the term $E_2(V)/4$ has been neglected as it is much smaller than $E_2(V)N$ for N appreciably larger than 1. Substituting Eqs. (4) and (5) into Eqs. (2) and (3) yields

$$k_+(ND) = K(V)\, e^{-[E_2(V)N - E_3(V)]/k_BT} = K(V)\, e^{-a(V)(N - G(V))} \tag{6}$$

and

$$k_-(ND) = K(V)\, e^{+a(V)(N - G(V))} \tag{7}$$

where

$$K(V) = k_o e^{-E_1(V)/k_BT} \tag{8}$$

$$a(V) = E_2(V)/k_BT \tag{9}$$

$$G(V) = E_3(V)/E_2(V). \tag{10}$$

The physical interpretation of Eqs. (6) and (7) is that the forward rate constant $k_+(ND)$ and backward rate constant $k_-(ND)$ are shifted exponentially by the quantity $G(V)$ for the transition. Here, $K(V)$, $a(V)$, $G(V)$ are functions of the transmembrane potential V, and $k_+(ND)$ and $k_-(ND)$ are functions of N and V. From now on $k_+(ND)$ will be denoted by $k_+(N, V)$ and $k_-(ND)$ by $k_-(N, V)$. Note that V may depend on t, i.e., $V = V(t)$.

Since the total number of molecules is conserved, the population distribution function $P(N, t)$ satisfies

$$\frac{d}{dt} P(N, t) = -[k_+(N, V) + k_-(N, V)]\, P(N, t) + k_+(N-1, V)\, P(N-1, t) + k_-(N+1, V)\, P(N+1, t) \tag{11}$$

The reader can easily identify this kinetic equation as the familiar Fokker–Planck equation encountered in many branches of statistical physics as well as chemistry. This partial difference equation describes how the population distribution function $P(N, t)$ evolves as the transmembrane potential $V(t)$ changes in time. A temporal change in $V(t)$ causes a change in the rate constant functions $k_+(N, V(t))$ and $k_-(N, V(t))$, and results in a re-distribution of the population of the macromolecules among the different

states N. In effect, the population distribution function $P(N, t)$ "adapts" to the change in $k_+(N, V(t))$ and $k_-(N, V(t))$ as $V(t)$ changes. The phenomenon can be visualized as a wave moving in the state space labeled by index N, seeking the equilibrium position as determined by the rate constants $k_+(N, V(t))$ and $k_-(N, V(t))$.

Substituting Eqs. (6) and (7) into Eq. (11) yields a modified form of the HH equations,

$$\begin{aligned} K(V)^{-1}\frac{d}{dt}P(N,t) = &-[e^{-a(V)(N-G(V))} + e^{a(V)(N-G(V))}]\,P(N,t) \\ &+ e^{-a(V)(N-G(V)-1)}P(N-1,t) \\ &+ e^{a(V)(N-G(V)+1)}P(N+1,t) \end{aligned} \tag{12}$$

In order to relate Eq. (12) to experimental data, the total conductance $g_K(t)$ is expressed as a sum of products of the population distribution function evaluated at state N and its corresponding conductance $g(N)$,

$$g_K(t) = \sum_{N=-\infty}^{+\infty} g(N)\,P(N,t) \tag{13}$$

The approach here then amounts to determination of $a(V)$, $G(V)$, $K(V)$, and $g(N)$, $-\infty < N < +\infty$, so that the resultant $g_K(t)$ from Eqs. (12) and (13) matches with the experimental conductances. It is important to emphasize that up to now except for the standard ones regarding the free energy $E(q)$, the present approach to the HH problem is completely general and free from any specific assumptions. In the next section, we will introduce some assumptions in order to obtain an approximate solution for the potassium channel.

3. APPROXIMATE SOLUTION FOR THE POTASSIUM CHANNEL

The first assumption in arriving an approximate solution for the potassium conductance is:

Assumption 1. The elastic behavior of the macromolecule is independent of the applied voltage, i.e., $E_2(V)$ and hence $a(V)$ are constant. Specifically, let

$$a(V) = a_o$$

With this assumption, Eq. (12) becomes

$$K(V)^{-1}\frac{d}{dt}P(N,t) = -[e^{-a_o(N-G(V))} + e^{a_o(N-G(V))}]\,P(N,t) + e^{-a_o(N-G(V)-1)}P(N-1,t) + e^{a_o(N-G(V)+1)}P(N+1,t) \tag{14}$$

the solution of which is now sought. Two special cases are examined first. When the transmembrane potential $V(t)$ is zero, there is no perturbation on the free energy of the macromolecule due to the electric field. The terms $E_3(V=0)$ and hence $G(V=0)$ are both zero. $P(N,t) = P_i(N) = P_o e^{-a_o N^2}$ is thus a particular solution of Eq. (14). P_o is the normalization constant such that the sum of $P(N,t)$ over N from $-\infty$ to $+\infty$ is equal to the total population P_{total} of macromolecules. P_{total} is an invariant quantity constant in time since the number of macromolecules are conserved in the process. When the potential is clamped, i.e., $V(t) = V_f$, the terms $E_3(V=V_f)$ and $G(V=V_f)$ are both constant, $P(N,t) = P_f(N) = P_o e^{-a_o(N-G_f)^2}$ is another particular solution of Eq. (14) where G_f is the constant value of $G(V=V_f)$. Hence, if the transmembrane potential is to vary from $V=0$ at time $t=0$ to some equilibrium value $V=V_f$ at time $t=\infty$, $P(N,t)$ would vary from $P_i(N)$ at $t=0$ to $P_f(N)$ at $t=\infty$. The question is: what about the intermediate $P(N,t)$?

We here postulate that the intermediate $P(N,t)$ remains very close to a Gaussian shape. The effective result then is that the "peak" of the postulated Gaussian distribution function $P(N,t)$ is being moved along by the potential V from the initial position of $N=0$ to the final position of $N=G_f$. With these observations, a general solution for Eq. (14) is sought which is of the form

$$P(N,t) = P_o e^{-a_o[N-f(t)]^2} \tag{15}$$

The equation of motion for $f(t)$ is found by substituting Eq. (15) into Eq. (14). After cancelling the common exponential factor,

$$\begin{aligned}
&2a_o K(V)^{-1}[N-f(t)]\frac{d}{dt}f(t) \\
&\quad = -e^{-a_o(N-G(V))} - e^{a_o(N-G(V))} + e^{-a_o[N-G(V)-1]-a_o[-2(N-f(t))+1]} \\
&\qquad + e^{a_o[N-G(V)+1]-a_o[2(N-f(t))+1]} \\
&\quad = 2\cosh[a_o(2f(t)-N-G(V))] - 2\cosh[a_o(N-G(V))] \\
&\quad = 4\sinh[a_o(f(t)-G(V)]\sinh[a_o(f(t)-N)]
\end{aligned}$$

Rearranging,

$$K(V)^{-1}\frac{d}{dt}f(t) = -\frac{2\sinh[a_o(f(t)-G(V))]\sinh[a_o(f(t)-N)]}{[a_o(f(t)-N)]} \tag{16}$$

Equation (15) expresses the population distribution function $P(N, t)$ in terms of a Gaussian function centered at $f(t)$ which evolves in time obeying Eq. (16). Further simplification to rid Eq. (16) of N is possible. Of all the states N ranging from $-\infty$ to $+\infty$, only those within close proximity of the moving "peak" are of interest since they are the ones with appreciable non-vanishing magnitudes of $P(N, t)$. Using the standard deviation $\sigma = 1/\sqrt{2a_0}$ of $P(N, t)$ as a "rough" measure of proximity, one proposes

Assumption 2. For practical interest,

$$|f(t)-G(V)| < 5\sigma, \qquad |f(t)-N| < 5\sigma \tag{17}$$

Assumption 2 basically states that the distance travelled by the Gaussian "peak" should be within a few (here we used 5, the number can actually be much larger depending on a_0) lengths of the standard deviation of $P(N, t)$, and that the range of interest for N should also be a within few standard deviations from the instantaneous "peak" location $f(t)$. Inequalities (17) can be further expressed as

$$|a_o(f(t)-G(V))| < \frac{5}{2\sigma}, \qquad |a_o(f(t)-N)| < \frac{5}{2\sigma} \tag{18}$$

Physically, the standard deviation σ of $P(N, T)$ is expected to be large. Hence,

$$|a_o(f(t)-G(V))| \ll 1, \qquad |a_o(f(t)-N)| \ll 1 \tag{19}$$

and the right hand side of Eq. (16) can be approximated by the first term of its Taylor series expansion,

$$K(V)^{-1}\frac{d}{dt}f(t) = 2a_o[G(V)-f(t)] \tag{20}$$

Equations (15) and (20) together constitute an approximate solution for Eq. (14). They yield the exact results $P(N, t) = P_i(N)$ and $P(N, t) = P_f(N)$ of Eq. (14) for the special cases of when $G(V=0)=0$ and $G(V=V_f)=G_f$. It is important to note that in general the functions $K(V)$ and $G(V)$ in Eq. (20) are actually implicit functions of the transmembrane potential $V(t)$. The transmembrane potential $V(t)$ determines the rate constant

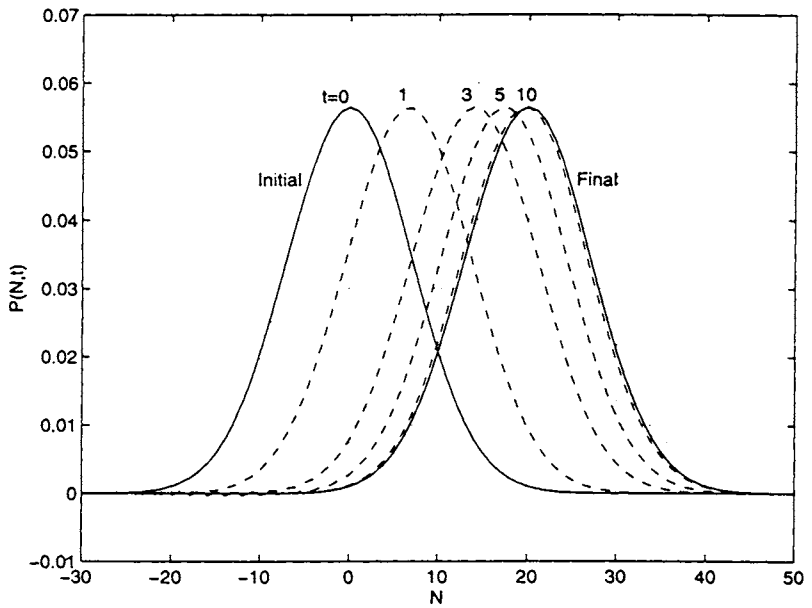

Fig. 2. Numerical solution of Eq. (14) at $t = 0$, 1, 3, 5, and 10 msec.

$K(V(t))$ and the "driving" function $G(V(t))$ which together gives the time dependent behavior $f(t)$ from which $P(N, t)$ is obtained by Eq. (15).

When assumption 2 is satisfied, the solution of Eqs. (15) and (20) constitutes very close approximation to the exact solution. As an example, Fig. 2 shows the solution to Eq. (14) obtained numerically using the Matlab (Version 4.2c) Toolbox command *ode*23 for the case where $a_o = 0.01$, $K(V = V_f) = 20000$, and $G(V = V_f) = G_f = 20$. It can be observed that the exact solution indeed takes the form of a moving Gaussian distribution as according to Eq. (15), and the instantaneous peak position of the Gaussian distribution is also predicted accurately by Eq. (20). Assumption 2 is satisfied in this example. It will be shown later that assumption 2 holds true for the experimental results as well, and hence the use of the approximate solution is well justified.

The last assumption in obtaining an approximate solution for the potassium channel concerns the conductance of the macromolecules.

Assumption 3. The conductance $g(N)$ of a macromolecule at state N is given by

$$g(N) = \bar{g}_K \left(\frac{r}{\pi}\right)^{1/2} e^{-r(N-N^*)^2} \tag{21}$$

Equation (21) specifies a band of conducting states as not all states are conducting. N^* is the state of maximum conductance and r is a constant governing the broadness of the conducting band. $\bar{g}_K$ is a proportionality constant. The factor $(r/\pi)^{1/2}$ is chosen so that the sum of $g(N)$ over N from $-\infty$ to $+\infty$ is equal to $\bar{g}_K$. Substituting Eqs. (15) and (21) into Eq. (13) yields

$$g_K(t) = \sum_{N=-\infty}^{+\infty} \bar{g}_K \left(\frac{r}{\pi}\right)^{1/2} e^{-r(N-N^*)^2} P_o e^{-a_o[f(t)-N]^2} \tag{22}$$

Taking the limit as an integral yields the following expression for $g_K(t)$,

$$g_K(t) = \bar{g}_K P_o [1 + (a_o/r)]^{-1/2} e^{-a_o[f(t)-N^*]^2/[1+(a_o/r)]} \tag{23}$$

The ratio (a_o/r) gives the relative broadness of the conducting band and the Gaussian distribution. If r approaches $+\infty$, i.e., $g(N)$ becomes a very narrow conducting band about N^*, then

$$g_K(t) = \bar{g}_K P_o e^{-a_o[f(t)-N^*]^2}$$

When the transmembrane potential V is zero, $f = G(V=0) = 0$. The potassium conductance g_o can therefore be obtained by simply letting $f = 0$ in Eq. (23),

$$g_o = \bar{g}_K P_o [1 + (a_o/r)]^{-1/2} e^{-a_o(N^{*2})/[1+(a_o/r)]} \tag{24}$$

Eliminating $\bar{g}_K$ from Eq. (23) with Eq. (24),

$$g_K(t) = g_o e^{a_o[N^{*2}-(f(t)-N^*)^2]/[1+(a_o/r)]} \tag{25}$$

Equations (20) and (25) can be put into a more convenient form by redefining and consolidating the variables and constants as follows,

$$L = a_o^{1/2}[1 + (a_o/r)]^{-1/2} N^*, \tag{26}$$

$$\bar{n}(V(t)) = a_o^{1/2}[1 + (a_o/r)]^{-1/2} G(V(t)), \tag{27}$$

$$n(t) = a_o^{1/2}[1 + (a_o/r)]^{-1/2} f(t), \tag{28}$$

$$T(V(t)) = \frac{1}{2a_o K(V(t))} \tag{29}$$

Then Eqs. (20) and (25) become

$$\frac{d}{dt}n(t) = [\bar{n}(V(t)) - n(t)]/T(V(t)) \tag{30}$$

$$g_K(t) = g_o e^{L^2 - [n(t) - L]^2} \tag{31}$$

The problem now is to determine g_o, L, and $\bar{n}(V(t))$ and $T(V(t))$ as functions of $V(t)$ such that Eqs. (30) and (31) match the experimental data for potassium conductance. Determination of these parameters will be presented in the next section.

4. PARAMETRIC MODEL FOR POTASSIUM CONDUCTANCE

(a) Voltage Clamp Data

The constants g_o, L, and functions $n(V)$, $T(V)$ can be determined from HH's voltage clamp data. In this case, at $t=0$, $V=0$, $f=0$, and $n(0)=0$, and Eq. (31) yields $g_K(0)=g_o$. The value for g_o is hence readily determined as the potassium conductance at $t=0$ which is 0.24 m.mho/cm^2. At $t>0$, $V(t)=V$, $T(V(t))=T(V)$, $\bar{n}(V(t))=\bar{n}(V)$, and Eq. (30) yields

$$n(t) = \bar{n}(V)(1 - e^{-t/T(V)}) \tag{32}$$

As t approaches ∞, $n(t=\infty)$ approaches asymptotically to $\bar{n}(V)$,

$$g_K(t=\infty) = g_o e^{L^2 - [\bar{n}(V) - L]^2} \tag{33}$$

and

$$\bar{n}(V) = L - \left[L^2 - \log\left(\frac{g_K(\infty)}{g_o}\right)\right]^{1/2} \tag{34}$$

L and $\bar{n}(V)$ can be found from the asymptotic potassium conductances corresponding to several clamp voltages. Table I shows the experimental data of V, $g_K(\infty)$, and τ_n from HH's paper (Table 1 from [1]). Note the sign change of the voltages V from HH's paper. The present work adopts the modern sign convention for transmembrane potentials: $V>0$ for depolarization and $V<0$ for hyperpolarization. The voltages are given in units of mV's and the time constants in msec's. Using the values of asymptotic potassium conductance $g_K(\infty)$ in the table and assuming

Table I. HH's Experimental Data

V (mV)	$g_K(\infty)$ (m.mho/cm^2)	τ_n (msec)
6	0.98	5.25
10	1.47	5.25
19	5.00	4.50
26	6.84	3.80
32	8.62	3.20
38	10.29	2.60
51	13.27	2.05
63	15.30	1.70
76	17.00	1.50
88	18.60	1.25
100	20.00	1.10
109	20.70	1.05

$L = 2.7$, one obtains from Eq. (34) a set of values for $\bar{n}(V)$ which can be approximated by the following functional relation,

$$\tilde{n}(V) = 0.63 \tanh\left(\frac{V}{15.5}\right) + 0.44 \tanh\left(\frac{V}{77.28}\right) \tag{35}$$

Figure 3 compares the values of $\bar{n}(V)$ as determined from the HH's data and the function $\tilde{n}(V)$. A very close fit of the $\bar{n}(V)$ data has been achieved. Note that $\tilde{n}(V)$ conveniently passes through the origin which is consistent with the fact that $n(t) = 0$ at $V = 0$. The choice of $L = 2.7$, and subsequently that of function $\tilde{n}(V)$, is not unique. By letting, say, $L = 3.0$, one would obtain a different set of values for $\bar{n}(V)$ and hence a different $\tilde{n}(V)$. The only constraint here on L is that L^2 has to be larger than the values of $\log(g_K(\infty)/g_o)$ in Eq. (34) to yield real numbers for $\bar{n}(V)$.

From Eq. (27), $a_o G(V) = \bar{n}(V) a_o^{1/2}[1 + (a_o/r)]^{1/2}$. With values of $\bar{n}(V)$ ranging from 0 to 1 here, assumption 2 is more or less satisfied with a_o smaller than 0.01. This corresponds to the Gaussian distribution function having a standard deviation of 7 or more. From a physical point of view, the actual standard deviation should be much larger than this. Assumption 2 is hence well justified. In this regards, the ratio (a_o/r) is not expected to contribute anything appreciable.

To determine $T(V)$, we note that in HH's paper [1] the values τ_n are determined by matching

$$g_K(t) = [g_K(\infty)^{1/4} - [g_K(\infty)^{1/4} - g_K(\infty)^{1/4}]\, e^{-t/\tau_n}] \tag{36}$$

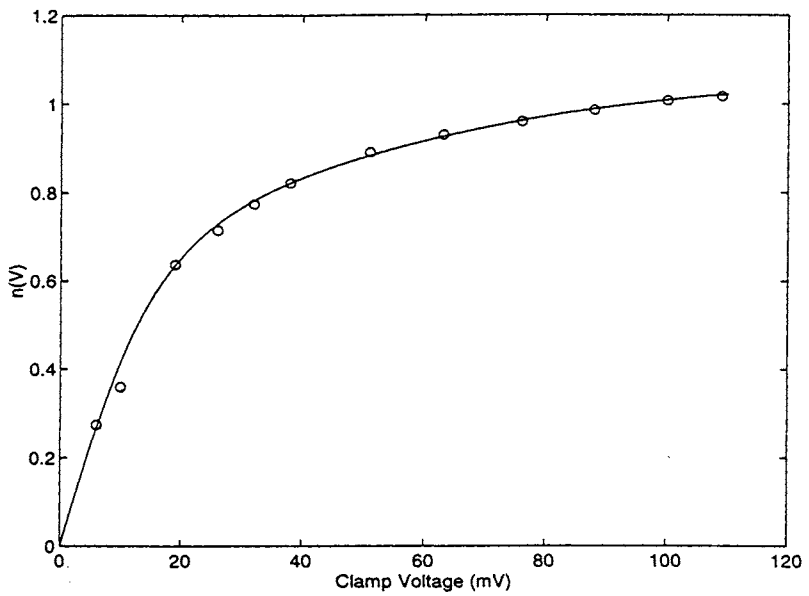

Fig. 3. $\tilde{n}(V)$ (circles) from HH data and the function $\tilde{n}(V)$.

with the rises of potassium conductances observed experimentally. Knowing that the curves as generated by HH constitute very good fits of the experimental data, we opt here to determine $T(V)$ by matching the rising conductance curves obtained with Eqs. (30) and (31) to those obtained with Eq. (36). The present approach could just as well determine $T(V)$ with the experimental data. As a result, a functional relation between $T(V)$ and V is obtained as:

$$\tilde{T}(V) = 0.1e^{-3V/10} + 2e^{-V^2/16000} + 3e^{-V^2/900} \tag{37}$$

Figure 4 compares the values of $T(V)$ determined by matching the HH curves and the function $\tilde{T}(V)$. Again, a very good fit of the $T(V)$ data is provided by $\tilde{T}(V)$. Note that the HH's voltage clamp data existed only for $V > 0$ and hence functions $\tilde{n}(V)$ and $\tilde{T}(V)$ as determined are valid for $V > 0$.

Figure 5 compares the rising conductance curves generated using the present approach with the functions $\tilde{n}(V)$ and $\tilde{T}(V)$ to those of the HH model. The two sets of curves agree closely with each other. Notice that their discrepancies, though small, can still be reduced if one goes back to Fig. 3 and refines the function $\tilde{n}(V)$ for a still better fit of the $\bar{n}(V)$ data.

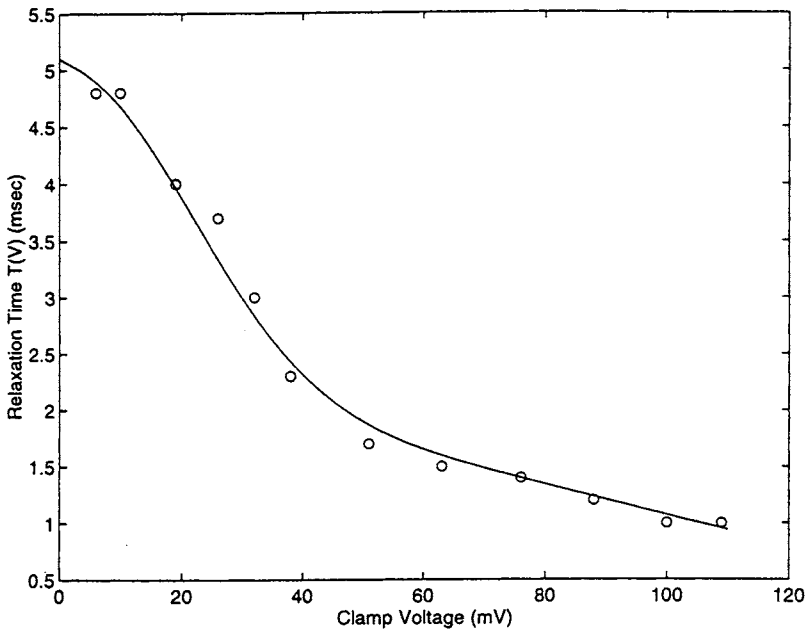

Fig. 4. $\bar{T}(V)$ (circles) from HH model and the function $\tilde{T}(V)$.

The same procedures here can be applied to matching the experimental results. Though not shown here, we have checked that the original HH data for potassium conductances are consistent with our equations. These include the familiar voltage clamp curves for potassium conductance as well as the curves for the decay of potassium conductance after the clamp potential has been removed.

Equations (30), (31), (35) and (37) form the fundamental equations for our theory of potassium conductance. These equations take the place of the HH equations. It is interesting to note the similarities and differences between the two different theories. Equation (30) is just the same as the HH equations for $n(t)$. Equation (31) takes the place of the quartic equation $g_K = \hat{g}_K n^4$ in the HH theory. Equations (35) and (37) are equivalent to the HH equations for the α and β variables which determine the n variable and the τ_n variable. In fact, besides using a different equation for g_K, the structure of the two theories is essentially the same. If HH had chosen the function $g_K = g_o e^{[L^2-(n-L)^2]} = (\text{Const})\, e^{-(n-L)^2}$ instead of the quartic equation to fit their monumental data they could have done their job just as comfortably as if they used their original quartic function. The history of the evolution of mathematical neurophysiology could have started this way.

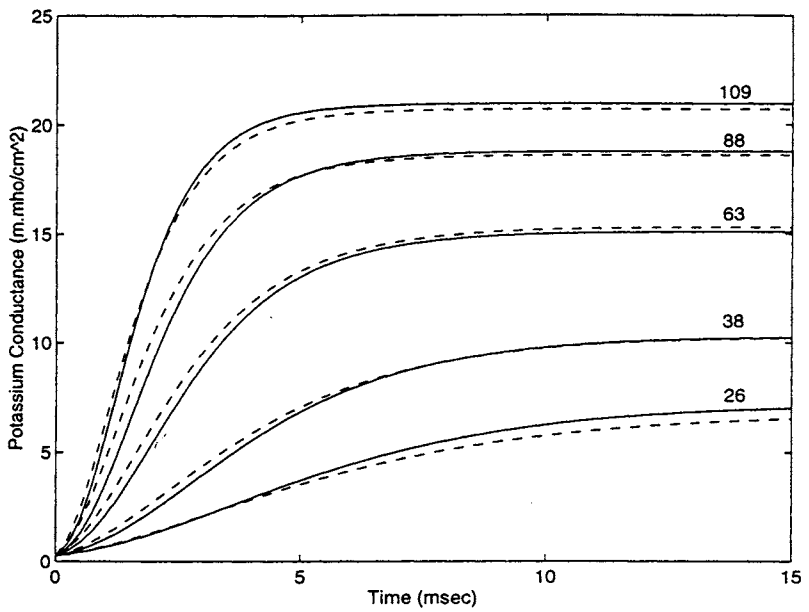

Fig. 5. Potassium conductances at different depolarization voltage (mV): the HH model (dash line), the present model (solid line).

(b) Cole–Moore Shift

The Cole–Moore shift [2] $T_{CM}(V_i, V_f)$ as a function of the initial clamped potential $V_i<0$ and the final clamped potential $V_f>0$ can be expressed in terms of $\bar{n}(V)$ and $T(V)$. Putting the solution of Eq. (30) in the following form:

$$\begin{aligned} n(t) &= \bar{n}(V_f) + [\bar{n}(V_i) - \bar{n}(V_f)]\, e^{-t/T(V_f)} \\ &= \bar{n}(V_f) + [\bar{n}(0) - \bar{n}(V_f)]\, e^{-(t - T_{CM}(V_i, V_f))/T(V_f)} \end{aligned} \tag{38}$$

one obtains

$$T_{CM}(V_i, V_f) = T(V_f) \log \left[\frac{(\bar{n}(V_f) - \bar{n}(V_i))}{(\bar{n}(V_f) - \bar{n}(0))} \right] \tag{39}$$

Equations (38) and (39) indicate a time delay of $T_{CM}(V_i, V_f)$ in the rising conductance curve for the $V_i<0$ case as compared to the $V=0$ case. Note that Eq. (30), and hence the derived expression $T_{CM}(V_i, V_f)$ of Eq. (39), is valid for both the HH theory and the present approach. The difference lies in the abilities of the two approaches to explaining the Cole–Moore data.

For over 30 years, the Cole–Moore shift has not been completely understood in terms of the HH equations. The inadequacy of the HH approach to account for a significant shift when the initial clamped potential is negative lies in the unjustified use of the quartic function $g_K = (\text{Const})n^4$. Introduction of this quartic function inherently restricts the magnitude of the $\bar{n}(V_i)$ variable for $V_i < 0$: if $\bar{n}(V_i < 0)$ is big, then according to Eq. (30) $n(t)$ would also be appreciable. This violates the interpretation that n is a probability of value between 0 and 1. Furthermore, a large $n(t)$ leads to appreciable conductance $g_K = (\text{Const})\, n(t)^4$ which contradicts experimental observation that the potassium conductance is very small for the hyperpolarized axon. Hence, $\bar{n}(V_i < 0)$ could not be appreciable and should be numerically close to $\bar{n}(0)$ in the HH formulation. Subsequently, the Cole–Moore shifts $T_{CM}(V_i, V_f)$ by Eq. (39) would be very small and not be able to fit the experimental data.

Utilization of a Gaussian function as a replacement for HH's quartic function in the present formulation places no limit on the value of $\bar{n}(V_i)$ consistent with the static ion conductance for $V_i < 0$. Here, $n(t)$ is not interpreted as a probability, but rather as the scaled (see Eq. (28)) instantaneous position of the "peak" of the population distribution function $P(N, t)$ which changes in time according to the Fokker–Planck equation. A large negative value for $n(t)$ would still result in a very small $g_K = (\text{Const})\, e^{-(n(t)-L)^2}$. This is the essential feature which distinguishes the present theory from the HH theory. The Gaussian function takes the burden away from $\bar{n}(V_i < 0)$ for making the potassium conductance small for negative static transmembrane potential, thus allowing $\bar{n}(V_i < 0)$ to be any large negative value necessary to match an appreciable Cole–Moore shift.

The present approach poses a distinct advantage in interpreting the Cole–Moore shift physically in terms of the population distribution function $P(N, t)$. Application of an initial negative transmembrane potential $V_i < 0$ shifts the equilibrium population distribution function in a direction opposite to the direction determined by the final positive transmembrane potential $V_f > 0$. Referring to Fig. 2, this means that the population distribution function would start with it's peak not at $N = 0$ but to the left at a position determined by $V_i < 0$. Therefore, extra time is needed for the population distribution function to converge to its final shape determined by V_f. The present theory hence provides a quantitative treatment for this time shift. In fact, for any given initial clamped voltage $V_i < 0$, a suitable $\bar{n}(V_i < 0)$ can always be found by solving Eq. (39) in terms of V_f and the experimental value of $T_{CM}(V_i, V_f)$,

$$\bar{n}(V_i < 0) = \bar{n}(V_f) + [\bar{n}(0) - \bar{n}(V_f)]\, e^{[T_{CM}(V_i, V_f)/T(V_f)]} \tag{40}$$

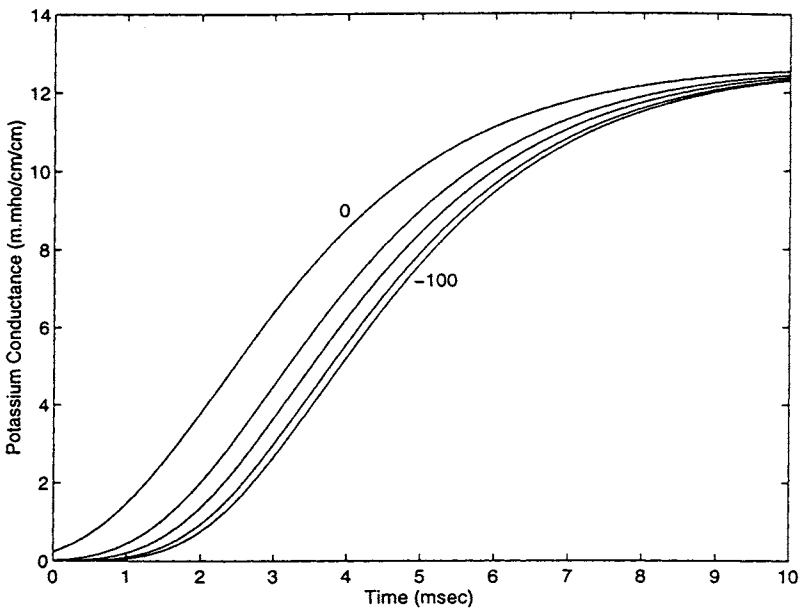

Fig. 6. Cole–Moore simulation using the present model with $V_f = 50$ mV and $V_i = 0, -10, -20, -50, -100$ mV for the upper through lower curves.

As $\bar{n}(V_i < 0)$ is not restricted to be a positive definite quantity here, the right hand side of Eq. (40) can always be evaluated and therefore the value of $\bar{n}(V_i < 0)$ will always exist for given V_f. The question of whether an unique $\bar{n}(V < 0)$ can be found such that Cole–Moore shifts of different V_f can be accounted for, however, still remains. Future additional tests of this important phenomenon are highly recommended. But as long as one is restricted to Cole–Moore shifts of a fixed final clamped transmembrane potential, as in all previous experiments, the present methodology will always fit the data perfectly using Eq. (39). In other words, the present approach sees no difficulties to fit the Cole–Moore curves. Rather, the Cole–Moore shifts are to determine the value of $\bar{n}(V)$ for negative V's!

As an example to show the sort of results obtained with the present approach, we assume that the function $\bar{n}(V)$ can be extrapolated to yield $\bar{n}(V_i < 0)$ and generate the conductance curves for $V_i = 0, -50, -100$ mV and $V_f = 50$ mV. The resulting curves are shown in Fig. 6. They qualitatively agree with those observed in the Cole–Moore experiments.[15, 16]

5. DISCUSSIONS

We like to bring out the following points regarding this work:

1. Although derivation of Eqs. (30) and (31) may be tedious, readers who are more interested in experimental neurophysiology instead of statistical mechanics could have skipped the entire derivation altogether. By assuming the Gaussian form of the conductance function (Eq. (31)) and a linear response of $n(t)$ (Eq. (30)), Eqs. (35) and (37) as well as the Cole–Moore shift analysis could be deduced.

2. The conductance function (Eq. (31)) derived here contains an infinite number of terms of powers of n while the quartic function in HH's theory contains only the 4th power. It can be shown that the quartic function closely approximates the present conductance function for $n > 0$ but not for $n < 0$. This explains why the HH's theory is capable of fitting the voltage clamp experimental data (which lies in the $n > 0$ regime) but not the Cole–Moore shift paradox (which lies in the $n < 0$ regime).

3. Numerical analysis has verified that the shape of the population distribution function remains largely unchanged during application of the transmembrane voltage. This indicates that time evolution of the macromolecular system may proceed in a state of quasi-equilibrium.

4. It is emphasized that not all approximations are needed to derive from Eq. (12) the HH like equations. However, such process is valuable as it makes the data analysis (e.g., choosing the correct equilibrium constants and functions) much easier and relates current electrophysiology with statistical mechanics.

5. Equation (21) assumes a Gaussian distribution for the conductance over the state N. One may point out that single channel recordings have shown that the channels are either completely open or completely closed. Hence the conductance may not vary in the way proposed here. Equation (21), however, may be interpreted as that each state N has specific open and close probabilities so that the net time averaged conductance has the assumed Gaussian distribution. Instead of a Gaussian distribution, one may also assume a band of uniform conductance for $g(N)$ in Eq. (21). In this case, Eq. (23) will involve the Error functions.

6. We acknowledged the fact that the present model has been applied to analyze only one set of experimental data, that of HH's. It is unclear whether the model will be supported or contradicted by other data. However, given that the present model work so well in the depolarization region ($V > 0$), we feel strongly that it can accommodate other experimental results previously supported by the HH model. The added advantage of the present model is, of course, it's purported validity for hyperpolarization region ($V < 0$). We would strongly encourage researchers in the field to apply the present model to their experimental results.

7. To arrive at the equations describing potassium conductance, the rate function $a(V)$ is assumed constant in Eq. (12). It is plausible that by letting $a(V)$ changes with voltage, equations describing the sodium inactivation phenomenon can be derived. This work is presently under investigation.

6. CONCLUSIONS

This paper shows from first principles derivation of a Fokker–Planck equation describing the potassium conductance macromolecular system. A close approximate solution to this equation is proposed and leads to a set of HH-like equations. The new equations have essentially the same structure as the HH theory but utilize a Gaussian function $g_K = (\text{Const})\, e^{-(n-L)^2}$ as a replacement for HH's quartic function $g_K = \hat{g}_K n^4$. Instead of being interpreted as a probability value in the HH theory, the variable $n(t)$ is now interpreted as the (scaled) instantaneous position of the "peak" of the population distribution function $P(N, t)$ which changes in time according to the Fokker–Planck equation. The new equations are physically more fundamental in the investigations of ion conductance macromolecular systems than the HH equations. They not only agree well with the HH's voltage clamp data but are also capable to quantitatively explaining the important Cole–Moore effect.

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