Kinetic model based on molecular mechanism for action potential

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Abstract: The Hodgkin-Huxley model for action potential has been widely used which were not built on a microscopic description of the neuronal membrane. By molecular dynamics simulations, the molecular mechanism of the channel currents is becoming clear. However, the quantitative link between molecular mechanism and action potential remains to be elucidated. Here, a kinetic model for action potential based on the molecular mechanism of the channel currents is proposed. Using it, the experimental observations about action potential are reproduced quantitatively and explained from molecular mechanism. We find that the accumulation of Na^+ ions near exit of the electivity filter is the dominant event to cause the refractory period of the Na^+ channel and the types of the channel currents depend on its rate constants. The channel inductance represents the inertia of the channel to remain certain ions binding state, the channel resistances include ones against state transition and charge transfer.

Key words: action potential, kinetic model, molecular mechanism, channel inductance, circuit model

1. Introduction

Neurons process and encode information by generating sequences of action potentials. It has been more than 50 years since Hodgkin and Huxley proposed a mechanistic model by which such action potentials are generated in an electrically excitable membrane. The Hodgkin-Huxley (H-H) model[1] for action potential generation has been widely and successfully used[2-6]. It is the closest that neurophysiologists have to Newton's laws of motion, and it underpins almost all modern models of how neurons work. However, the H-H equations were written on an empirical basis and were not built on a microscopic description of the excitable neuronal membrane grounded on the opening and closing of ionic channels. This led to an incorrect prediction of inactivation kinetics of the Na^+ channel[7-9]. In the model, there are several empirical functions and some variables without exact physical sense.

To elucidate the microscopic mechanism of the action potential, exploration of the molecular properties of voltage-gated ion channels began thirty years ago with report of the discovery of the sodium channel protein by neurotoxin labeling method[10-11]. A major breakthrough is that the crystallographic structure of the KcsA K^+ channel was determined by X-ray analysis with data to 3.2 angstroms[12]. Based on the X-ray structure of the K^+ channel, the molecular dynamics free energy simulations were performed[13]. From the X-ray structure of the KcsA K^+ channel, cryo-electron microscopy[14] and the molecular models[15-16] of the sodium channels, the Brownian dynamics simulations for the Na^+ channel are also done[17]. Now, the molecular mechanism of the sodium and potassium channel currents is becoming clear, but the quantitative link between the molecular mechanism and the action potential remains to be elucidated and some performance of the action potential should be

explained at molecular level.

In this paper, the Author proposes a novel kinetic model of the action potential based on the molecular mechanism of the sodium and potassium channel currents. In the model, the channel currents are considered as the function of the membrane voltage, channel states and the ion concentrations. Here, all of the functions and coefficients have exact physical sense and the link between the molecular mechanism and the action potential is created. From the model, the experimental observations about the action potential are reproduced quantitatively and explained from molecular mechanism. From the model, the occurrence mechanics of the refractory period is elucidated, the electrochemical impedances of the sodium and potassium ion channels are analyzed, the existence of the channel inductance is illustrated and its physical sense is explained, the novel insight and results about the channel resistances are given, the occurrence mechanics of the different sodium and potassium currents is elucidated. Based on analyzing electrochemical impedances, a simplified circuit model for the action potential is introduced in which the channel resistance, the channel inductance, and the positive feedback link of the sodium channel are included. From it, the analytical solutions can be given easily and the effects of the static magnetic field on the action potential are explained successfully.

2. The molecular mechanism and kinetic model of action potential

The X-ray structure of the KcsA K^+ channel revealed that it comprises a wide, nonpolar cavity of 16 A on the intracellular side, leading up on the extracellular side to a narrow pore of 12 A. This region of the pore acts as a "selectivity filter" by allowing only the passage of K^+ ions across the cell membrane[12]. The molecular dynamics simulations show that K^+ ions conduction involves transitions between two main states, with two and three K^+ ions occupying the electivity filter, respectively. The channel can hold two K^+ ions in stable equilibrium in the selectivity filter. As the third K^+ ion binds to the electivity filter from the intracellular side, the central energy barrier is lowered, and the first ion can cross in its random motions. The translocation of K^+ ions in single file through the selectivity filter is the rate-limiting step[13].

Brownian dynamics simulations for the sodium channel show that the molecular mechanism of the sodium channel current is identical to one of the potassium channel[17]. The difference is that the sodium ions bind to the selectivity filter from extra-cellular side, and leave from the intercellular side.

Based on the molecular mechanism of the sodium and potassium channel currents, the Author proposes the kinetic models for the state transition of the sodium and potassium channels (see Fig.1).

We denote by E_{i2} and E_{i3} the channel states with two and three ions, respectively (here, i=Na for Na^+ channel, i=K for K^+ channel). From the model, the kinetic equations for ions conduction of the sodium or potassium channel can be given

$$\begin{cases} d[E_{i2}]/dt = k_{il}[E_{i3}] + k_{-ib}[E_{i3}] - k_{ib}[i^+][E_{i2}] & \text{(1-a)} \\ d[E_{i3}]/dt = k_{ib}[i^+][E_{i2}] - k_{il}[E_{i3}] - k_{-ib}[E_{i3}] & \text{(1-b)} \end{cases}$$

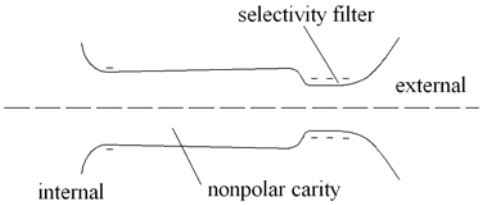
where $[E_{i2}]$ and $[E_{i3}]$ is the density of Na^+ or K^+ channel at the states with two and three ions, respectively($[E_{i2}]+[E_{i3}]=[E_{i0}]$, $[E_{i0}]$ is the total density of Na^+ or K^+ channel). $[i^+]$ is Na^+ concentration near Na^+ channel outside the membrane, or K^+ concentration near K^+ channel inside the membrane. k_{ib} is the binding rate constant for Na^+ or K^+ ions to the binding site on the selectivity filter, k_{-ib} is the corresponding dissociation rate constant. k_{il} is the dissociation rate constant for Na^+ or K^+ ions from the opposite side of the selectivity filter.

The steady-state approximation is applied to Eq.(1), the sodium or potassium channel current can be given

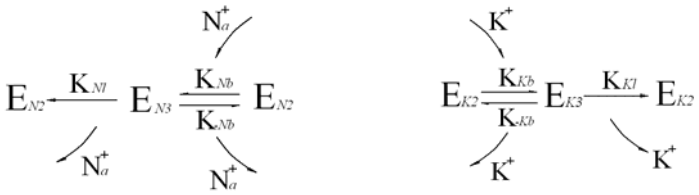
$$I_i = \lambda k_{il} / (1 + K_i) \qquad (2)$$

where $K_i = (k_{il} + k_{-ib}) / (k_{ib}[i^+])$, λ is the ratio of the current intensity to the reaction rate.

The binding or dissociation rates for Na^+ or K^+ ions to the binding site on the selectivity filter depend on the voltage across membrane. The resting membrane voltage is approximately -60mV inside versus outside, it is favorable for K^+ ions to bind to the selectivity filter inside the membrane, and unfavorable for Na^+ ions to bind to the selectivity filter outside the membrane. As the depolarization occurs, the K^+ binding rate drops and the Na^+ binding rate grows. The binding or dissociation rate constants for Na^+ and K^+ ions can be given by $k_{Nb} = k_{N1} e^{\alpha_N' \delta (V + V_{Ns})}$, $k_{-Nb} = k_{N1} e^{-\beta_N' \delta (V + V_{Ns})}$, $k_{kb} = k_{k1} e^{-\alpha_K' \delta (V - V_{Ks})}$ and $k_{-kb} = k_{k1} e^{\beta_K' \delta (V - V_{Ks})}$ (here $\delta = F/RT$, F is Faraday's constant, R the gas constant, T the temperature in Kelvin, α_N', α_K', β_N' and β_K' are the transfer factors of the electric pole reaction, $\alpha_N' + \beta_N' = 1$, $\alpha_K' + \beta_K' = 1$, V the membrane voltage, V_{Ns} and V_{ks} the standard electrode potentials for Na^+ or K^+ ions to bind to the selectivity filter, respectively).



(a)



(b) (c)

Fig.1 Na^+ and K^+ channels, and their kinetic models for state transition (a) Na^+ or K^+ channel, (b) kinetic model for Na^+ channel, (c) kinetic model for K^+ channel

The concentration $[Na^+]$ near Na^+ channel outside the membrane depends on the average Na^+ concentration $[Na^+]_a$ outside the membrane and the membrane voltage, $[Na^+]=[Na^+]_a e^{\delta V}$. The concentration $[K^+]$ near K^+ channel inside the membrane depends on the average K^+ concentration $[K^+]_a$ inside the membrane and the membrane voltage, $[K^+]=[K^+]_a e^{-\delta V}$. The dissociation rate for Na^+ or K^+ ions from the opposite side of the selectivity filter depends on the electrochemical potential difference across membrane. The rate constants can be given by $k_{Nl} = k_{N2}(e^{\alpha_N \delta(V_N - V)} - 1)$ and $k_{kl} = k_{k2}(e^{\alpha_k \delta(V - V_K)} - 1)$ (here, V_N and V_K are Na^+ or K^+ reversal potentials, respectively; α_N and α_k the transfer factors of the electrode reaction for Na^+ or K^+ leaving from the opposite side).

Eq.(2) can give the steady-state sodium or potassium currents at the different membrane voltages. As the voltage changes from one value to another, changes of the channel currents with the time can be determined from related rate equation. From $k_{Nl} = k_{N2}(e^{\alpha_N \delta(V_N - V)} - 1)$, we know $dk_{Nl}/dt = -\alpha\delta V_t(k_{Nl} + 1)$ (here, $V_t = dV/dt$, t is the time). So, the constant k_{Nl} as a function of the time can be given by $k_{Nl} = (k_{Nl0} - k_{Nl\infty})e^{-\alpha_N \delta \bar{V}_t t} + k_{Nl\infty}$ (here, k_{Nl0} is the initial value of k_{Nl}, $k_{Nl\infty}$ is its stable value, $\bar{V}_t$ is the time average of dV/dt). In a same manner, other rate constants as the time function can be determined.

The circuit equation for nerve membrane is given by

$$I_K + I_{Na} + I_c = I_A \tag{3}$$

where I_A is the applied current, I_c is the capacitance current, $I_c = C_m \frac{dV}{dt}$, C_m is membrane capacitance per unit area(here, the leakage current is neglected).

Eq.(3) is identical to the circuit equation for nerve membrane widely used currently. However, I_N and I_K is determined by Eq.(2). If I_A is an impulsive current, Eq.(3) can be replaced by the initial-value problem: $I_K + I_{Na} + I_c = 0$, $V(0)=V_0$. Combining Eqs.(2), (3) and the rate constant equations, the membrane potentials as a function of time for various initial voltages can be given by numerical technique.

Using the parameter values listed in Table 1, the sodium and potassium currents as the function of the membrane voltage(Fig.2(a) and (b)) and the membrane voltage as the function of time for various initial voltages (Fig.2(c)) are given. Results shows that the model can reproduce the experimental observations from Hodgkin and Huxley(1952)[1]. From the model, some new insight about channel currents and action potential can be given:

At the resting state(V=-60mV), both sodium current and potassium one are quite small, and equal to each other. As the depolarization occurs, two currents grow, but the K^+ current is above Na^+ current as the voltage V is below initial threshold voltage. Below it, the sub-threshold response occurs, else the action potential occurs.

At the resting voltage, the electrochemical potential for Na^+ ions to flow through the Na^+ channel is large, but the Na^+ concentration near Na^+ channel outside the membrane is low. Less Na^+ ions bind to the selectivity filter. Most of sodium channels are in the close state with two Na^+ ions. So, the sodium current is small. At $V=V_N$ (55mV), the Na^+ concentration near Na^+ channel outside the membrane is large, but the electrochemical potential for Na^+ ions to flow is zero(dissociation rate of the Na^+ ions from the internal side of the selectivity filter reduces to zero). Thus, most of sodium channels are still in close state with two Na^+ ions. Only at a moderate membrane voltage, the sodium current is large.

At the resting voltage, K^+ concentration near K^+ channel inside the membrane is large, but the electrochemical potential for K^+ ions to flow through K^+ channel is small. That limits the dissociation rate for K^+ ions from the outer side of the selectivity filter. So, the potassium current is small. As the depolarization grows, the electrochemical potential for K^+ ions to flow through K^+ channel grows. As

soon as the membrane voltage is above zero, the dissociation rate for K^+ ions grows quickly with the voltage(more potassium channels can change into the open state with three K^+ ions). It causes the obvious increase of the K^+ current.

If the initial voltage is below initial threshold voltage, the K^+ current plays a governing role($I_N < I_K$) and a minus feedback process occurs(see case V_0=-50mv). If the initial voltage is above the initial threshold voltage, the Na^+ current plays a governing role($I_N > I_K$) and the membrane potential grows gradually(a positive feedback process begins). As the membrane voltage gets to another threshold voltage, the Na^+ current grows suddenly and the action potential occurs(see cases V_0=-40mv and V_0=-45mv, the threshold voltage for action potential is -45mv). From it, we know that there are two thresholds: one is for membrane potential increase, another for the action potential. As the membrane voltage is near equilibrium potential for sodium ions, another minus feedback process occurs. The large electrochemical gradient drives K^+ ions to run out of the membrane quickly and the membrane potential returns to the equilibrium potential for K^+ ions. The action potential is a coupled positive-minus feedback process. If the initial voltage is much larger than the threshold for action potential, most of sodium channels can change into the open state with three Na^+ ions rapidly and the action potential occurs quickly(see case V_0=20mv).

Immediately after generation of an action potential, another action potential usually cannot be generated regardless of the amount of current injected into the axon. This period is called the refractory period which is considered to be caused by the inactivation of Na^+ channel.

The activation of Na^+ channel needs two conditions: a) the electivity filter of the Na^+ channel can change into the state with three Na^+ ions(the central energy barrier in the electivity filter can be lowered obviously); b) the Na^+ ions in the energy well have enough large random motions. If one of the two conditions is removed, the inactivation of Na^+ channel occurs. The possible events removing above conditions include: i) the conformational changes of the trans-membrane segments for the Na^+ channel, its N terminus or the C terminus near electivity filter (it can change the energy well in the electivity filter); ii) the membrane voltage change(it influences not only on the overall energy field across the membrane, but also on the Na^+ concentration near entrance of the electivity filter to change the local energy well in the electivity filter); iii) some toxins occupy the binding site on the electivity filter and the third Na^+ ion can not bind to the electivity filter. iv) the accumulation of Na^+ ions near exit of the electivity filter as the action potential occurs(it can change the local energy well in the electivity filter

and makes the electivity filter remain at close state with two Na^+ ions though a large membrane voltage is applied). Only after the Na^+, K^+-ATPase ionic pump drive the Na^+ ions out of the membrane, and the membrane potential returns to the resting potential, the electivity filter of the Na^+ channel can be changed into open state with three Na^+ ions again. The accumulation of Na^+ ions near exit of the electivity filter may be the dominant event to cause the refractory period of the Na^+ channel.

Table 1 Employed parameter values for kinetic model based on molecular mechanism

Faraday's constant (C/mol):	F=9.64867×10^4
gas constant(J/mol.K)	R=8.314
temperature(K)	T=298
extracellular Na^+ concentration(mM)	$[Na^+]_a$=460
intracellular K^+ concentration(mM)	$[K^+]_a$=410
reversal potentials (mV)	V_{Na}=55 V_K=-72
transfer factors of the electric pole reactions	α_N=0.9 α_K=0.7 α'_N=0.9 α'_K=0.5
the ratio λ (mA/cm^2)	1.5×10^{-7}
standard electrode potential(mV)	V_{Ns}=0 V_{ks}=180
rate constants	k_{N1}=1×10^4 M^{-1}s^{-1} k_{K1}=1×10^4 M^{-1}s^{-1} k_{N2}=2×10^3 s^{-1} k_{K2}=1.5×10^2 s^{-1}

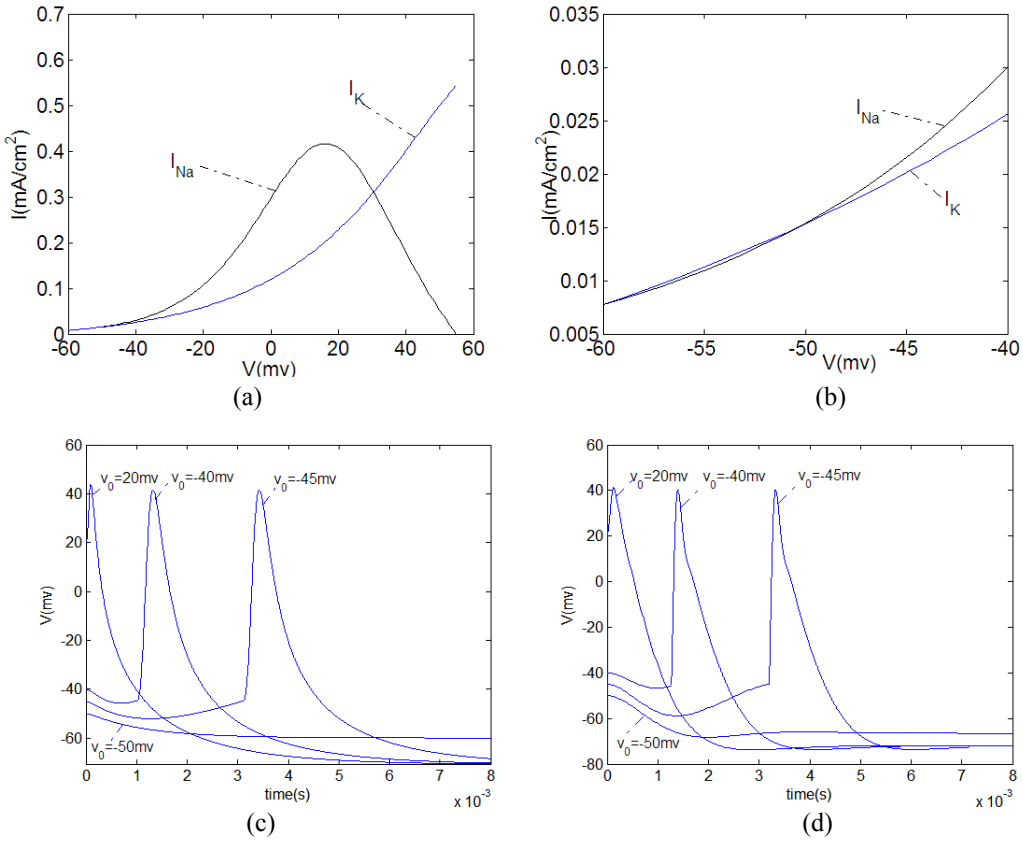


Fig.2 The channel currents and the space-clamped membrane potential (a) changes of the currents with voltage(universe figure) (b) changes of the currents with voltage(local figure) (c) space-clamped membrane potential for various initial voltages from kinetic model (d) space-clamped membrane potential for various initial voltages from simplified circuit model

3. Electrochemical impedances of Na^+ and K^+ channels

The occurrence of the sodium or potassium channel currents is an electro-chemical coupled process. Hodgkin and Huxley considered the channels as the nonlinear electric resistances. However, from the kinetic model based on molecular mechanism, we can know more details about them.

We take the membrane voltage V and the density $[E_{i3}]$ of the sodium or potassium channel at the state with three ions as state variables. Neglecting high order terms, the increment of the channel current can be written by $\Delta I_i = \frac{\partial I_i}{\partial V}\Delta V + \frac{\partial I_i}{\partial E_{i3}}\Delta E_{i3}$. From it, Faraday admittance can be given as[18]

$$g = \frac{\Delta I_i}{\Delta V} = \frac{\partial I_i}{\partial V} + \frac{\partial I_i}{\partial E_{i3}}\frac{\partial E_{i3}}{\partial V} = \frac{1}{R_t} + \frac{B}{a + j\omega} \tag{4}$$

where R_t is the charge transfer resistance, $1/R_t = \partial I_i / \partial V$; a=- $\partial \dot{E}_{i3} / \partial E_{i3}$, $\dot{E}_3$ is the change rate of the density $[E_{i3}]$ relative to the time; B= mb , $m = \partial I_i / \partial E_{i3}$, $b = \partial \dot{E}_{i3} / \partial V$.

In Eq.(4), R_t and a are positive. If B is negative, the equivalent circuit of the channel can be expressed as a series circuit consisting of a resistance R_t and a compound element formed by parallel of a resistance R_a and a capacitance C_a. The impedance of the channel can be given by $R_t + \frac{R_a}{1 + j\omega R_a C_a}$, here $R_a = \frac{R_t^2 |B|}{a - R_t |B|}$ and $C_a = \frac{1}{R_t^2 |B|}$. If B is positive, the equivalent circuit of the channel can be expressed as a parallel circuit consisting of a resistance R_t and a compound element formed by series of a resistance R_a and an inductance L. The impedance of the channel is given by $R_t + 1/(R_a + j\omega L)$, here $R_a = a/B$ and $L = 1/B$.

For Na^+ channel, $a = -\partial \dot{E}_{N3} / \partial E_{N3} = k_{Nb}[Na^+] + k_{Nl} + k_{-Nb}$, and

$$B = \frac{\lambda k_{Nl}}{(1 + K_N)^2}\frac{\delta}{k_{Nb}[Na^+]}[\alpha_N k_{N2} + (1 + \alpha_N + \alpha_N^{'})k_{Nl} + 2k_{-Nb}][k_{Nb}[Na^+] + k_{Nl} + k_{-Nb}] > 0$$

Hence, the equivalent circuit of the Na^+ channel is a parallel circuit consisting of a resistance R_t and a compound element formed by series of a resistance R_a and an inductance L_N(see Fig.3(a)). Thus,

$$R_a = \frac{a}{B} = \frac{(1 + K_N)^2 k_{Nb}[Na^+]}{[\alpha_N k_{N2} + (1 + \alpha_N + \alpha_N^{'})k_{Nl} + 2k_{-Nb}]\lambda k_{Nl}\delta} \tag{5-a}$$

$$L=\frac{1}{B}=\frac{(1+K_N)^2}{\lambda k_{Nl}}\frac{k_{Nb}[Na^+]}{\delta}\frac{1}{[\alpha_N k_{N2}+(1+\alpha_N+\alpha_N^{'})k_{Nl}+2k_{-Nb}][k_{Nb}[Na^+]+k_{Nl}+k_{-Nb}]} \quad (5\text{-b})$$

$$\frac{1}{R_t}=\frac{\partial I_N}{\partial V}=\frac{\lambda}{(1+K_N)^2}\frac{\delta}{k_{Nb}[Na^+]}[(1+\alpha_N^{'})k_{Nl}^2+2k_{Nl}k_{-Nb}-\alpha_N(k_{N2}+k_{Nl})(k_{-Nb}+k_{Nb}[Na^+])] \quad (5\text{-c})$$

For K^+ channel, $a=-\partial\dot{E}_{k3}/\partial E_{k3}=k_{kb}[K^+]+k_{kl}+k_{-kb}$, and

$$B=-\frac{\lambda k_{kl}}{(1+K_K)^2}\frac{\delta}{k_{kb}[K^+]}[\alpha_k k_{k2}+(1+\alpha_K+\alpha_K^{'})k_{kl}+2k_{-kb}][k_{kb}[K^+]+k_{kl}+k_{-kb}]<0$$

Hence, the equivalent circuit of the K^+ channel is a series circuit consisting of a resistance R_t and a compound element formed by parallel of a resistance R_a and a capacitance C_a(see Fig.3(b)). From the resistance R_t, coefficients a and B, the resistance R_a and capacitance C_a can be given easily. The resistance R_t is

$$\frac{1}{R_t}=\frac{\partial I_K}{\partial V}=\frac{\lambda}{(1+K_K)^2}\frac{\delta}{k_{kb}[K^+]}[(1+\alpha_k^{'})k_{kl}^2+2k_{kl}k_{-kb}-\alpha_k(k_{k2}+k_{kl})(k_{-kb}+k_{kb}[K^+])] \quad (6)$$

Eqs.(5)-(6) give the electrochemical impedances of the Na^+ and K^+ channels as the functions of the membrane voltage(see Fig.4). It shows:

For Na^+ channel, the conductance g_a (=$1/R_a$) and g_t (=$1/R_t$), and the reciprocal $1/L_N$ of the inductance, grow obviously, get to a maximum value, and then drop with the membrane voltage. The conductance g_t is much smaller than g_a. So, the Na^+ channel can be simplified as a series circuit consisting of a resistance R_a and an inductance L_N(see Fig.3c). For K^+ channel, the conductance g_a is much larger than g_t. It shows that the resistance R_a can be considered as a conducting wire approximately. The total K^+ channel can be simplified as a resistance R_t (see Fig.3d). As the membrane voltage grows, the conductance g_t first grows slowly, and then grows quickly for V above zero.

We find that the Na^+ and K^+ channels not only include dissipative elements(electric resistances), but also include inertial elements(inductance or capacitance). The inductance or capacitance represents the inertia of the channel to remain certain ions binding state. It means that not only the driving potential but also the time are required to change Na^+ or K^+ channels from the state with two ions to the one with three ions.

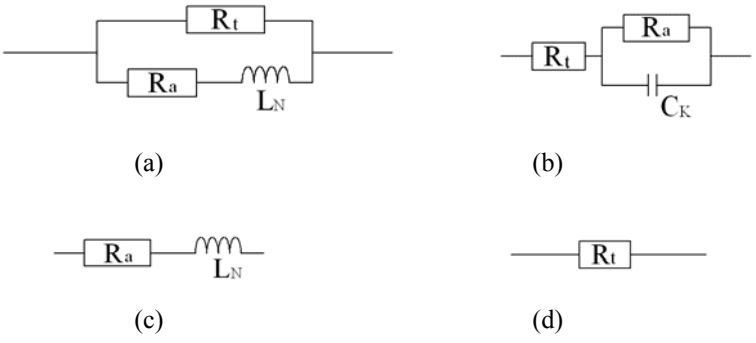
The electric resistances represent resistance of the channel against ions moving through it. From our model, it is known that ions motion through the channel is coupled to its state transition. So, the electric resistances include resistance against state transition of the channel plus resistance against charge transfer.

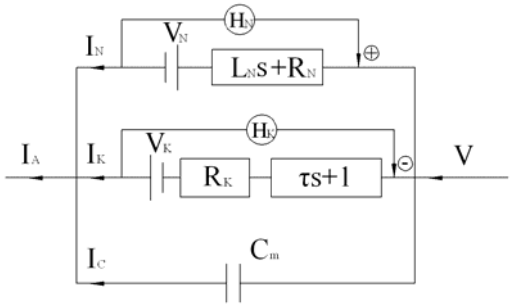
As above stated, two resistances are parallel in sodium channel. The resistance against charge transfer is quite large and the conductance g_t is small which grows slightly and then reduces to zero rapidly with membrane voltage. Hence, the conductance of the sodium channel depends on state transition conductance g_a mainly. In potassium channel, two resistances are in series. The resistance against state transition is quite small. Hence, the conductance of the potassium channel depends on charge transfer conductance g_t mainly.

At $V=V_{Na}$, dissociation rate of the Na^+ ions from the internal side of the selectivity filter reduces to zero, and the sodium conductance reduce to zero (see g_a in Fig.4(a)). The result is different from one widely accepted currently in which the sodium conductance gets to the maximum at $V=V_{Na}$.

Up to till, the sodium conductance has been determined by the equation $I_{Na}/(V-V_{Na})$. As the membrane voltage is near V_{Na}, the denominator V-V_{Na} becomes quite small, so calculated sodium conductance becomes large at $V=V_{Na}$. Actually, the equation $I_{Na}/(V-V_{Na})$ is appropriate only for calculating sodium conductance near the rest potential.

Our model shows that the sodium current changes along with potential difference V-V_{Na} in exponential function. Only near the rest potential, the sodium current can be approximated as the linear function of the potential difference V-V_{Na}. The sodium conductance should be given by differentiating sodium current with respect to the membrane voltage V.





(e)

Fig.3 The equivalent circuits for Na^+ and K^+ channels and simplified circuit model for action potential
(a) equivalent circuit for Na^+ channel (b) equivalent circuit for K^+ channel (c) simplified equivalent circuit for Na^+ channel (d) simplified equivalent circuit for K^+ channel (e) simplified circuit model for action potential

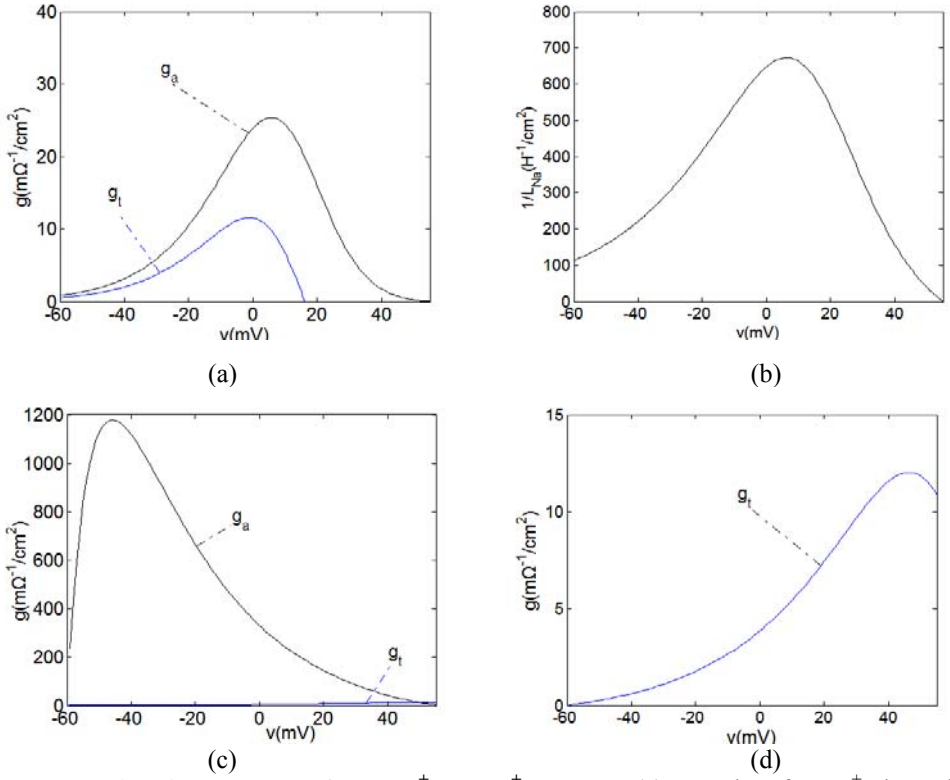


Fig.4 The electrochemical impedances of the Na^+ and K^+ channels (a) g_t and g_a for Na^+ channel (b) L_N for Na^+ channel (c) g_t and g_a for K^+ channel (d) g_t for K^+ channel

For many different types of vertebrate neurons, depolarization results not only in the activation of the rapidly activating and inactivating Na^+ current but also in the activation of the Na^+ current that does not inactivate(known as the persistent Na^+ current)[22].

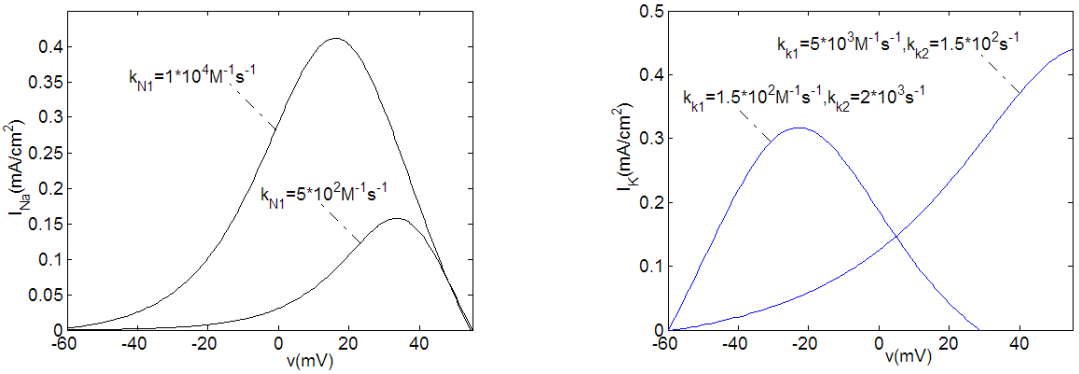
Our model shows that the types of the Na^+ currents depend on the rate constants of the Na^+ channels. As Na^+ binding rate constant to the binding site on the selectivity filter is much larger than its dissociation rate constant from the opposite side, the dissociation of Na^+ ions from the opposite side is the rate limit step(see the case of $K_{N1}=1\times10^4M^{-1}s^{-1}$ and $K_{N2}=2\times10^3s^{-1}$ in Fig.5(a)). Here, the

accumulation of Na^+ ions near exit of the electivity filter occurs during the action potential. It makes the electivity filter remain at close state with two Na^+ ions until these Na^+ ions diffuse and go out of the membrane.

When Na^+ binding rate constant to the binding site is smaller than its dissociation rate constant from the opposite side, the Na^+ channel current is small and grows slowly with the membrane voltage. Here, Na^+ binding to the binding site is the rate limit step(see the case of $K_{N1}=5\times10^2M^{-1}s^{-1}$ and $K_{N2}=2\times10^3s^{-1}$ in Fig.5(a)). As soon as a Na^+ ion binds to the binding site on the electivity filter, the Na^+ ion on the opposite side of the electivity filter escapes and it has enough time to diffuse and leave from exit of the electivity filter(Na^+ ions do not accumulate near exit of the electivity filter). The local energy well in the electivity filter is not changed and most of the electivity filter remains at open state with three Na^+ ions all along. Therefore, the Na^+ channel does not inactivate and the persistent Na^+ current occurs. The Na^+ channel with persistent current has smaller conductance and larger inductance. The conductance and inductance grow slowly with the membrane voltage. It shows that the Na^+ channel with persistent current has large inertia to remain certain ions binding state.

The persistent Na^+ current plays an important regulatory function in the control of the functional responsiveness of the neuron to synaptic inputs and may contribute to the dynamic coupling of the dendrites to the soma[22]. So, it is possible that the Na^+ channels at dendrites or synapse have large electric resistance and inductance with small membrane voltage sensitivity.

The simplest K^+ current is that rapidly activates on depolarization and does not inactivate. Some K^+ currents activate with depolarization but also inactivate with time(known as the transient K^+ current)[23].



(a) (b)

Fig.5 Changes of the channel currents along with their rate constants (a) sodium currents($K_{N2}=2\times10^3s^{-1}$) (b) potassium currents

We find that the rate constants of the K^+ channels govern the types of the K^+ channel currents. When K^+ binding rate constant to the binding site on the selectivity filter is much larger than its dissociation rate constant from the opposite side, the K^+ dissociation from the opposite side is the rate limit step(see the case of $K_{K1}=5\times10^3M^{-1}s^{-1}$ and $K_{K2}=1.5\times10^2s^{-1}$ in Fig.5(b)). Here, the K^+ current grows slowly with the membrane voltage and the persistent K^+ current occurs. When K^+ binding rate constant to the binding site on the selectivity filter is much smaller than its dissociation rate constant from the opposite side, K^+ binding to the binding site is the rate limit step(see the case of $K_{K1}=1.5\times10^2M^{-1}s^{-1}$ and $K_{K2}=2\times10^3s^{-1}$ in Fig.5(b)). Near the selectivity filter inside the membrane, the K^+ concentration first grows and then drops rapidly with the membrane voltage. It makes most of the K^+ channels change from open state into close state. So, the transient K^+ current occurs. The K^+ channel with transient current has the channel conductance sensitive to the membrane voltage. It first grows and then drops rapidly with the membrane voltage.

4. Simplified circuit model for action potential

Based on analyzing electrochemical impedances of the Na^+ and K^+ channels, the simplified circuit model for action potential can be given. For Na^+ channel, the sodium current can cause increase of the Na^+ concentration inside the membrane. In many cases, impulse activity has been believed to be of slight significance to the intracellular $[Na^+]$. However, neuronal processes such as axons and nerve endings constitute spatially restricted volumes and greater changes in intracellular $[Na^+]$ may be expected in these regions[19]. It will cause decrease of the reversal potential V_N. It is equivalent to increase of the membrane potential at a constant V_N. This is a positive feedback process. So, a positive feedback loop is added in the equivalent circuit for Na^+ channel.

For K^+ channel, the potassium current may cause increase of the K^+ concentration outside the membrane and cause increase of the reversal potential V_K. It is equivalent to decrease of the membrane potential at a constant V_K. This is a negative feedback process. Thus, a negative feedback loop is added in the equivalent circuit for K^+ channel. Of course, because of large space outside the membrane relative to intracellular compartment, the changes in extra-cellular $[K^+]$ are quite small and can be neglected.

Besides it, we know from Fig.2 that relative to Na^+ current, K^+ current has certain delay. It is equivalent to add a delay link. According to Hodgkin and Huxley's model, the reversal potentials V_N and V_K are considered as the DC sources. Thus, the simplified circuit model for action potential can be

given(see Fig.3(e)). From Fig.3(e), the circuit equations for the sodium and potassium channels can be given by

$$V_N/s - V - H_N I_N = I_N(L_N s + R_N)$$

$$V_K/s + V - H_K I_K = I_K R_K(\tau s + 1)$$

Substituting the feedback links $H_N = 1/(C_N s)$ and $H_K = 1/(C_K s)$ into above equations, yields

$$V_N/s - V = I_N(L_N s + R_N + 1/(C_N s)) \quad (7\text{-a})$$

$$V_K/s + V = I_K(R_K \tau s + R_K + 1/(C_K s)) \approx I_K R_K(\tau s + 1) \quad (7\text{-b})$$

C_K is much larger than C_N because of large space outside the membrane relative to intracellular compartment, so $1/(C_K s)$ is neglected. Substituting Eq.(7) and the current $I_C = C_m s V$ into Eq.(3), yields

$$V = \frac{i_A}{Gs} + \frac{V_N}{Gg_N s} - \frac{V_K}{Gg_K s} \quad (8)$$

where $G = C_m + \frac{1}{g_N} + \frac{1}{g_K}$, $g_N = L_N s^2 + R_N s + \frac{1}{C_N}$, $g_K = R_K s(\tau s + 1)$.

Eq.(8) is the simplified circuit equation for action potential. It can be used to determine not only action potential, but also sub-threshold responses. From Fig.4, the average values of the related resistance and inductance for close or open states can be estimated. Substituting them into Eq.(8), the membrane potentials as a function of time for various initial voltages can be given(see Fig.2(d), the parameter values employed are given in Table 2). Fig.2(d) can reproduce the results from Fig.2(c). It shows that the simplified circuit model is successful.

Table 2 Employed parameter values for simplified circuit model

Membrane capacitance (μF/cm^2)	C_m=1
Reversal potentials (mV)	V_{Na}=55, V_K=-72
Na^+ channel resistances (Ω cm^2)	R_N=12000 (below initial threshold at close state) R_N=1200 (above initial threshold at close state) R_N=60 (at open state)
Na^+ channel inductances (Hcm^2)	L_N=6.25 (below initial threshold at close state) L_N=5 (above initial threshold at close state) L_N=0.0025 (at open state)
Na^+ channel feedback capacitance (μF/cm^2)	C_N=5
K^+ channel resistances (Ω cm^2)	R_K=600 (at close state) R_K=120 (at open state)
K^+ channel delay time constant (ms)	τ=0. 5

The simplified circuit model is simple and its analytical solution can be given. It is used to study the effects of the static magnetic field on the action potential successfully.

When the nerve cells are exposed to a small static magnetic field, the action potential was not influenced. If the magnetic field is relatively large, the amplitude and propagation velocity of the action potential are reduced slightly. Explanation about the features of the action potential is quite different and remains debated[20-21]. Using our model, the features are explained as below:

When the nerve cells are exposed to a magnetic field, Hall effect occurs. As the ions run, a Hall electric potential is produced by the ions accumulating on the cell membrane under magnetic force. The Hall electric potential can be expressed as $V_H = R_H I_i B_m /(2a)$ (here, B_{m} is the magnetic induction intensity, a the radius of the nerve fiber, R_H Hall coefficient). Thus, the equation of the sodium channel circuit can be changed into

$$V_N = V + L_N \frac{dI_N}{dt} + R_N I_N + \frac{1}{C_N}\int I_N dt + V_H = V + L_N \frac{dI_N}{dt} + R_{vN} I_N + \frac{1}{C_N}\int I_N dt$$

where $R_{vN} = R_N + R_H B/(2a)$, it is equivalent resistance considering effect of the magnetic field.

As the nerve cells are exposed to a magnetic field, it is equivalent to increase channel resistance of the nerve membrane. It means that the resistance against Na^+ dissociation from the selectivity filter inside the membrane grows. Thus, the amplitude and propagation velocity of the action potential should be reduced. However, the Hall coefficient R_H is small, and the effects of the magnetic field are so small that it can be neglected as the magnetic induction intensity is small. If a large magnetic field is applied, the effects of the magnetic field become perceptible, but they are still small. Hence, the amplitude and propagation velocity of the action potential are reduced slightly. We can predict that the amplitude and propagation velocity of the action potential will be reduced obviously when a static magnetic field with quite large magnetic induction intensity is applied to the nerve membrane. When the magnetic field is removed, the ions accumulating on the membrane will diffuse and return to the internal medium of the nerve cell. However, the diffusion will take some time. Hence, the effects of the magnetic field on the action potential will persist for some time after the field is removed. Usually, the Hall coefficient is sensitive to temperature. That may explain effects of the temperature change on relationship between the action potential and the magnetic field.

5 Conclusions

In this paper, the Author proposes a novel kinetics model for action potential based on the molecular mechanism. Here, all of the functions and coefficients have exact physical sense. It can be simplified as a simplified circuit model. The model is a generalized model which can be used to analyze the action potential and the sub-threshold response. Using the model, the experimental observations about the action potential are reproduced quantitatively and explained from the molecular mechanism. The main conclusions are summarized as below:

(1) At the resting state, Na^+ concentration near Na^+ channel is low and most of Na^+ channels are in the close state with two Na^+ ions which causes small sodium current. At Na^+ reversal potential, Na^+ concentration near Na^+ channel is high, but the electrochemical potential for Na^+ ions to flow through the channel is zero and the dissociation rate of the Na^+ ions from the selectivity filter reduces to zero. So, most of sodium channels are still in the close state and the sodium current reduces to zero. Only at a moderate membrane voltage, large sodium current occurs.

(2) The accumulation of Na^+ ions near exit of the electivity filter is the dominant event to cause the refractory period of the Na^+ channel. The accumulation of Na^+ ions near exit of the electivity filter during action potential can change the local energy well of the electivity filter and makes it remain at close state though a large membrane voltage is applied. Only after the Na^+, K^+-ATPase ionic pump drive Na^+ ions out of the membrane and the membrane potential returns to the resting potential, the Na^+ channel can be changed into open state with three Na^+ ions again.

(3) Na^+ and K^+ channels include not only dissipative elements: electric resistances, but also inertial elements: inductance or capacitance. The electric resistances represent resistance of the channel against ions motion through it which includes resistance against state transition of the channel plus resistance against charge transfer. At Na^+ reversal potential, the sodium conductance reduce to zero which is different from one widely accepted currently. The inductance or capacitance represents the inertia of the channel to remain certain ions binding state. The Na^+ channel with persistent current has large inertia to remain certain ions binding state. The K^+ channel with transient current has the channel resistance sensitive to the membrane voltage. The types of the channel currents depend on the rate constants of the ion channels.

(4) The initial threshold voltage corresponds to the voltage under which the sodium and potassium currents are equal to each other. Below it, the sub-threshold response occurs, else the action potential

will occur. The sub-threshold response is a minus feedback process. The action potential is a coupled positive-minus feedback process.

(5) From the kinetics model, a simplified circuit model of the action potential is introduced in which the channel resistance and the channel inductance are included. From it, we know that increase of the resistance against Na^+ dissociation from the selectivity filter causes decrease of the amplitude and propagation velocity of the action potential when the nerve membrane is exposed to a magnetic field.

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