Effect of clustered ion channels along an unmyelinated axon

Shangyou Zeng
College of Electronic Engineering, Guangxi Normal University, Guangxi 541004, People's Republic of China and Department of Physics, Xiangtan University, Hunan Province 411105, People's Republic of China

Yi Tang
Department of Physics, Xiangtan University, Hunan Province 411105, People's Republic of China

(Received 20 September 2008; revised manuscript received 16 June 2009; published 17 August 2009)

In most unmyelinated axons, ion channels are distributed uniformly along the axon to facilitate stable propagation of action potentials. In this case, the conduction in the axon is continuous, and the excitability along the membrane is constant. Some experimental papers show that ion channels also locate in clusters in some unmyelinated axons. In this paper, we investigate theoretically the effect of clustered ion channels along unmyelinated axon. We mainly focused on two aspects: the propagation efficiency and the propagation speed. Our results show that localization of potassium ion channels is beneficial for increasing propagation efficiency and propagation speed of action potentials; however, localization of sodium ion channels is advantageous to the propagation efficiency only when axonal parameters are in a specific range.

DOI: 10.1103/PhysRevE.80.021917 PACS number(s): 87.16.Uv

I. INTRODUCTION

In most unmyelinated axons, ion channels are distributed uniformly along the axon to facilitate stable propagation of action potentials. In this case, conduction in the axon is continuous, and excitability along the membrane is constant. Some experimental papers show that ion channels also locate in clusters in some unmyelinated axons. Widely dispersed clusters of potassium ion channels were observed in the axonal membrane of squid giant axons [1–3]. Punctuate domains of potassium ion channels were also observed in the axoplasm and are localized into (25–50)-μm-wide columns along the axon longitudinally [1–3]. In aplysia axonal membrane, sodium ion channels are localized in clusters, and the distance between clusters is on the order of 5–15 μm [4]. Sodium ion channel clusters are also observed in pyramidal cell dendrites of apteronotus [5] and frog sartorius muscle [6]. The distances between clusters in these two kinds of membranes are on the order of 5–15 and 10–20 μm respectively. Regional nodelike membrane specializations were also found in unmyelinated axons of rat retinal nerve fiber layer [7]. These experimental results demonstrate that conduction in some unmyelinated axons may occur in a nonuniform rather than in a continuous manner.

The mechanisms and the special functions of ion channel clusters along unmyelinated axons are unclear. In this paper, we investigate theoretically the effect of localization of ion channels along unmyelinated axons. Experimental papers show that half of the metabolic energy for the neural system is consumed by the pumps that exchange sodium and potassium ions across cell membranes [8–13]. We use the terminology "action potential propagation efficiency" to describe the energy consumption to propagate action potentials. If the energy consumption to propagate action potentials is decreased, the action potential propagation efficiency is increased, and vice versa. So for a specific potassium channel conductance, decreasing the minimal required sodium channel conductance for successful action potential propagation will increase the action potential propagation efficiency and decrease the metabolic energy consumption. We will focus on the effect of ion channel localization along an unmyelinated axon in two areas: the action potential propagation efficiency and the action potential propagation speed. Our results show that localization of potassium ion channels is beneficial for increasing propagation efficiency and propagation speed of action potentials; however, localization of sodium ion channels is advantageous to the propagation efficiency only when axonal parameters are in a specific range. The other aim of this paper is to try to find out how one can construct a more efficient axon. Our results show that increasing the cytoplasmic resistivity and the average potassium conductance is advantageous to the propagation efficiency due to localization of potassium ion channels; however, it is disadvantageous to the propagation efficiency due to localization of sodium ion channels. So in order to construct an efficient axon with localization of potassium ion channels and sodium ion channels, we should choose medial values of the cytoplasmic resistivity and the average potassium conductance.

II. METHODS

A. Deterministic Hodgkin-Huxley equations

Hodgkin and Huxley (HH) [14] first quantitatively formalized the electrical behavior of excitable nerve membrane. In HH equations, the voltage depending on the ion channel conductance is described by a set of deterministic nonlinear differential equations, and the electrical potential of neuron cell membrane is formalized by

$$C_m \frac{dV}{dt} = -g_L(V - V_L) - g_K(V - V_K) - g_{Na}(V - V_{Na}) + I, \tag{1}$$

where C_m is the specific capacitance of the membrane; V is the membrane potential; and V_L, V_K, and V_{Na} are the reversal potentials for the leakage current, the potassium ion channel

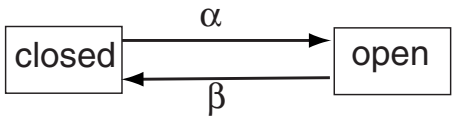

FIG. 1. Kinetic scheme of a two-state channel.

current, and the sodium ion channel current, respectively. The conductances g_L, g_K, and g_{Na} denote the specific conductances of the leakage current, the potassium ion channel, and the sodium ion channel. I is the specific injected current. For a specific membrane, g_L is constant; however, g_K and g_{Na} are voltage-dependent variables, which are described by a set of one-order differential equations.

Conductances for potassium and sodium ion channels are

$$g_K(V,t) = \bar{g}_K n^4,$$

$$g_{Na}(V,t) = \bar{g}_{Na} m^3 h,$$

where $\bar{g}_K$ and $\bar{g}_{Na}$ are the maximal conductances of potassium ion channels and sodium ion channels, respectively. The gating variables m, n, and h, with $0<m,n,h<1$ are voltage dependent and governed by the set of linear equations

$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n n,$$

$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m,$$

$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h h, \tag{2}$$

where α_n is the transition rate from close state to open state and β_n is the transition rate from open state to close state.

B. Stochastic Hodgkin-Huxley equations

If the number of ion channels is large, the dynamics of the m, the n, and the h gates can be described by first-order differential equations. If the number of ion channels is small, differential equations are not a good description due to the stochastic behavior of ion channels [15–17]. It is more accurate to use stochastic HH equations. To integrate Eq. (1), the numbers of open sodium and potassium channels have to be determined at each instant. It is assumed that the subunits of the sodium and the potassium channels are not cooperative and that they switch between the open and the closed states according to a Markovian process [18]. There are several methods to simulate the patch of ion channels. Each method has some advantages and disadvantages. We choose the simple stochastic method, which simulates the dynamics of each gate directly [19]. The method assumes that all gates open and close according to a two-state Markovian process with voltage-dependent opening and closing rates [19]. For example, the two-state Markovian process of a single gate is sketched in Fig. 1, where the transition rates α and β are the opening and the closing rates of the subunit. If the gate is closed at time t, it will open with the probability $\alpha\delta t$ and remain closed with the probability $1-\alpha\delta t$ in the time interval $(t,t+\delta t)$ for sufficiently small δt, i.e., $\delta t \ll 1/\alpha$. If the gate is open at time t, it will close with the probability $\beta\delta t$ and remain open with the probability $1-\beta\delta t$ in the time interval $(t,t+\delta t)$ for sufficiently small δt, i.e., $\delta t \ll 1/\beta$. We update the state of each gate by drawing a random number r from the unit interval from a uniform distribution. If the gate is closed at time t and $r>\alpha\delta t$, the gate remains closed while it opens if $r<\alpha\delta t$. Similarly, if the gate is open at time t and $r>\beta\delta t$, the gate remains open while it closes if $r<\beta\delta t$. If all the four n gates of one potassium channel open, the specific potassium channel opens; otherwise, it closes. If all the three m gates and the h gate of one sodium channel open, the specific sodium channel opens; otherwise, it closes. This method is obviously inefficient since each gate has to be simulated individually. It is, however, the most accurate methods since no other assumptions than the Markovian process have been made.

In this paper, the single-channel conductances of the sodium and the potassium channels are given by $\gamma_{Na}=\gamma_K=20$ pS [14]. Because we can keep track of the state of each ion channel using the stochastic method mentioned above, the total open numbers of sodium and potassium ion channels in the specific membrane can be calculated at each simulation step. If the area of the specific membrane is denoted as A and the open numbers of sodium and potassium channels are denoted as N_{Na} and N_K, the specific conductances of sodium and potassium ion channels of the specific membrane are given by $g_{Na}=N_{Na}\gamma_{Na}/A$ and $g_K=N_K\gamma_K/A$. Substituting the above expressions of the specific conductances of sodium and potassium ion channels into Eq. (1), we can get the formalization of the electrical potential of neuron cell membrane as the following equation:

$$C_m\frac{dV}{dt} = -g_L(V-V_L) - \frac{N_K\gamma_K}{A}(V-V_K) - \frac{N_{Na}\gamma_{Na}}{A}(V-V_{Na}) + I. \tag{3}$$

C. Compartmental model

In the compartmental model, a long heterogeneous axon is divided into small discrete compartments. Each compartment is small enough to be considered spatially uniform in properties. Then the continuous differential equation of the axon can be replaced with a set of ordinary differential equations. A chain of three cylindrical dendritic compartments is shown in Fig. 2(a). The three compartments are sufficiently small to be considered isopotential. The equivalent circuit of the three compartments is shown in Fig. 2(a). The mathematical expression of each compartment of the axon is an ordinary differential equation. Each equation is derived from Kirchhoff's current law. In the jth compartment, the net current i_{m_j} through the membrane equals the longitudinal current that enters the compartment minus the longitudinal current that leaves the compartment. Then the membrane current through the jth compartment is

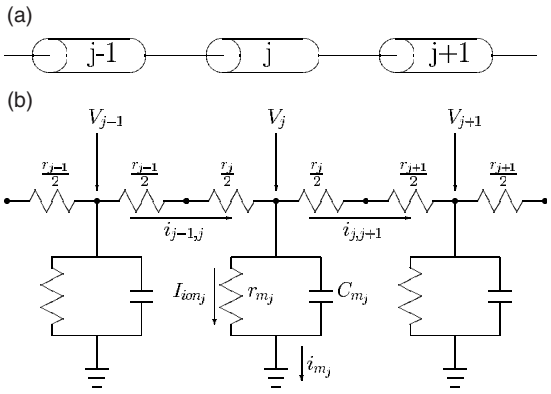

FIG. 2. (a) A chain of three cylindrical segments that are sufficiently short to be considered isopotential. (b) The equivalent circuit for the compartmental model of a chain of three successive small cylindrical segments of a passive dendritic membrane.

$$i_{m_j} = i_{j-1,j} - i_{j,j+1}, \tag{4}$$

where $i_{j-1,j}$ is the longitudinal current that flows from the $(j-1)$th to the jth compartment and $i_{j,j+1}$ is the longitudinal current that flows from the jth to the $(j+1)$th compartment.

For the jth compartment, the membrane current can be expressed as

$$i_{m_j} = c_{m_j}\frac{dV_j}{dt} + I_{ion_j}, \tag{5}$$

where V_j is the membrane potential, c_{m_j} is the membrane capacitance, and I_{ion_j} is the ionic current through the membrane. We can divide the voltage gradient between two nearby connected compartments by the axial resistance between the two compartments to get the longitudinal current approximately. Thus combining Eqs. (4) and (5), we can get the following equation:

$$c_{m_j}\frac{dV_j}{dt} + I_{ion_j} = \frac{V_{j-1} - V_j}{r_{j-1,j}} - \frac{V_j - V_{j+1}}{r_{j,j+1}} = (V_{j-1} - V_j)g_{j-1,j} - (V_j - V_{j+1})g_{j,j+1}, \tag{6}$$

where $r_{j,j+1}$ is the axial resistance between the jth and the $(j+1)$th compartments and $g_{j,j+1} = 1/r_{j,j+1}$ is the axial conductance between the jth and the $(j+1)$th compartments. We use d, Δx, C_m, and ρ_a to denote the diameter of the axon, the length of each compartment, the specific membrane capacitance, and the specific axoplasmic resistivity, respectively. If the geometrical and the electrical parameters of the axon are uniform, then we can get the following formulas: $c_{m_j} = \pi d\Delta x C_m$ and $g_{j-1,j} = g_{j,j+1} = \pi d^2/(4\rho_a \Delta x)$. If putting the above formula in Eq. (6), we can get the following equation:

$$\frac{dV_j}{dt} = -\frac{1}{\pi d\Delta x C_m} I_{ion_j} + \frac{d}{4\rho_a C_m \Delta x^2}(V_{j-1} - 2V_j + V_{j+1}). \tag{7}$$

The term I_{ion_j} can embody many types of channels in neural membrane including the leakage current, the sodium ion channel current, and the potassium ion channel current. The term can be expressed as

$$I_{ion_j} = g_L(V - V_L) + g_K(V - V_K) + g_{Na}(V - V_{Na}). \tag{8}$$

So, Eq. (6) can be rewritten as

$$\frac{dV_j}{dt} = -\frac{g_L(V_j - V_L) + g_K(V_j - V_K) + g_{Na}(V_j - V_{Na})}{\pi d\Delta x C_m} + \frac{d}{4\rho_a C_m \Delta x^2}(V_{j-1} - 2V_j + V_{j+1}). \tag{9}$$

III. RESULTS

We use the deterministic HH equations and the compartmental model to investigate this problem. The model has 101 compartments in total. External current is injected at the compartment one to initiate an action potential. The axonal parameters are listed in Table I.

A. Effect of potassium ion channel localization

How the potassium ion channel localization affects the action potential propagation efficiency is an interesting issue. We first delve into this issue. The axon diameter is 10 μm and the cytoplasmic resistivity is 70 Ω cm. Initially, potassium ion channels are distributed uniformly along the axon, with a conductance density of 20 $\mathrm{mS/cm^2}$. The minimal required conductance of sodium ion channels to support the stable action potential propagation is 23 $\mathrm{mS/cm^2}$. Then we keep the total potassium ion channel number constant, localize potassium ion channels gradually into clusters, and measure the minimal required sodium ion channel conductance to support a stable action potential propagation. There is one potassium ion channel cluster every five compartments. Potassium ion channels with lower densities are distributed uniformly between clusters. In order to demonstrate more clearly, we use formulas to define the potassium ion channel localization coefficient and the minimal required sodium ion channel ratio. For simplicity, we use C_l to denote the potassium ion channel localization coefficient, r_s to denote the minimal required sodium ion channel ratio, N_c to denote the number of potassium ion channels in clusters, and N_t to denote the total number of potassium ion channels. The minimal required sodium ion channel conductance when potassium ion channels are localized in clusters is denoted as S_l, and the minimal required sodium ion channel conductance when potassium ion channels are distributed uniformly is denoted as S_u. The potassium ion channel localization coefficient C_l and the minimal required sodium ion channel ratio r_s are expressed as the following formula:

$$C_l = \frac{N_c}{N_t}, \quad r_s = \frac{S_l}{S_u}.$$

As Fig. 3 shows, the potassium ion channel localization increases the propagation efficiency, and the minimal required sodium ion channel conductance can decrease by 15%.

TABLE I. Axonal parameters.

Compartment number	101
Compartment length	4 μm
Axon diameter [20]	10 μm
Cytoplasmic resistivity [21]	30–170 Ω cm
Membrane capacitivity [14]	1 μF/cm^2
Conductance of leakage current [14]	0.3 mS/cm^2
Reversal potential of sodium ion channel [14]	50.0 mV
Reversal potential of potassium ion channel [14]	−77.0 mV
Reversal potential of leakage current [14]	−54.4 mV
Transition rate of α_n [14]	$\frac{0.01(55+v)}{-\exp[-(55+v)/10]+1}$
Transition rate of β_n [14]	$0.125\exp[-(v+65)/80]$
Transition rate of α_m [14]	$\frac{0.1(v+40)}{-\exp[-(40+v)/10]+1}$
Transition rate of β_m [14]	$4.0\exp[-(v+65)/18]$
Transition rate of α_h [14]	$0.07\exp[-(v+65)/20]$
Transition rate of β_h [14]	$\frac{1.0}{\exp[(-35-v)/10]+1}$

The cytoplasmic resistivity of different neurons is not the same. It is interesting to test the effect of the cytoplasmic resistivity on the propagation efficiency. The axon diameter is 10 μm. The cytoplasmic resistivity ranges from 30 to 130 Ω cm. We test two cases and calculate the ratio of the minimal required sodium ion channel conductance of the two cases. In the localized case, 96% of potassium ion channels are localized in clusters; in the delocalized case, potassium ion channels are distributed uniformly along the axon. The results are shown in Fig. 4. As the cytoplasmic resistivity is increased, the localization of potassium ion channels has a more dramatic effect on the propagation efficiency. So in order to construct an efficient axon with localization of potassium ion channels, we should choose a large value of the cytoplasmic resistivity.

The next issue we will focus on is how the conductance of potassium ion channels affects the propagation efficiency. We vary the average potassium conductance from 20 to 50 mS/cm^2 [22]. We calculate the ratio of minimal required sodium ion channel conductances in the two cases. The two cases are the same as above. The axon diameter is 10 μm

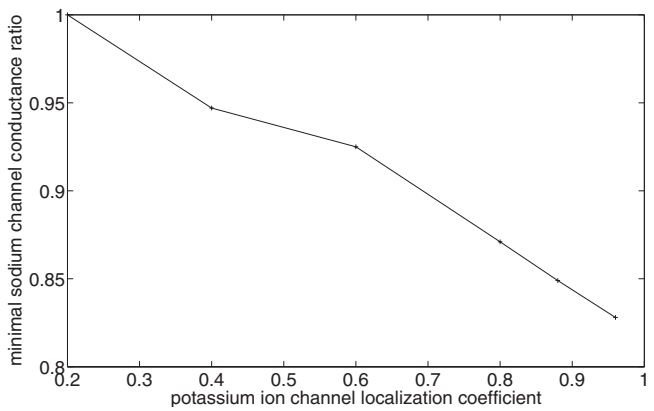

FIG. 3. The effect of potassium ion channel localization on propagation efficiency. The x axis represents the potassium ion channel localization coefficient, which is the number of potassium ion channels in clusters divided by the total number of potassium ion channels. The y axis represents the minimal required sodium ion channel ratio, i.e., the minimal required sodium ion channel conductance divided by the minimal required sodium ion channel conductance when potassium ion channels are distributed uniformly.

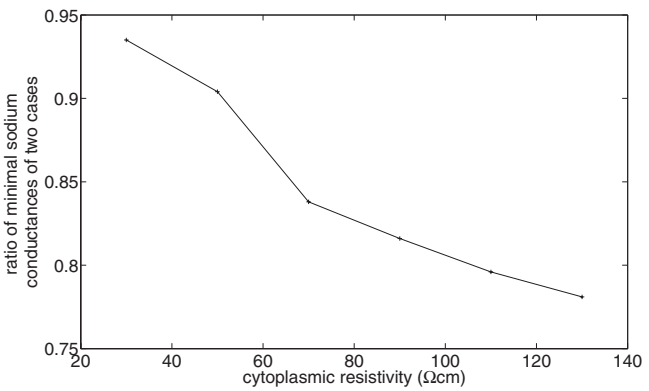

FIG. 4. The ratio of minimal required sodium ion channel conductances of two cases. In the localized case, 96% of the potassium ion channels are located in clusters. In the delocalized case, potassium ion channels are distributed uniformly along the axon. The average potassium ion channel conductance of the two cases is 20 mS/cm^2. The minimal required sodium ion channel conductance of the localized case is the numerator, and that of the delocalized case is the denominator.

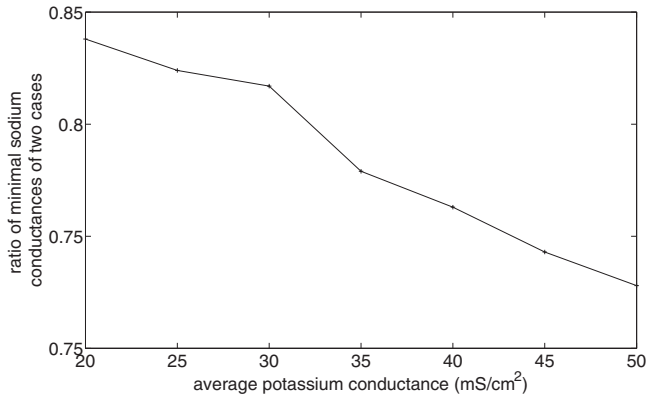

FIG. 5. The ratio of the minimal required sodium ion channel conductance in the two cases versus potassium ion channel conductance. The simulation condition is similar to that of Fig. 4 but with a different potassium ion channel density. In both cases, the average potassium ion channel conductance is the same.

and the cytoplasmic resistivity is 70 Ω cm. Figure 5 shows the ratio of the minimal required sodium ion channel conductance in the two cases. It shows that the effect of the potassium ion channel localization on the propagation efficiency is more dramatic as the potassium ion channel conductance is increased. So in order to construct an efficient axon with localization of potassium ion channels, we should choose a large value of the average potassium conductance.

The distance between two potassium ion channel clusters is another parameter affecting the propagation efficiency. We change the compartment number between potassium ion channel clusters then change the distance between two potassium ion channel clusters and calculate the ratio of the minimal required sodium conductance in the two cases. The two cases are again the same as above. The axon diameter is 10 μm and the cytoplasmic resistivity is 70 Ω cm. The average potassium ion channel conductance in the two cases is 20 mS/cm^2. The minimal required sodium ion channel conductance of the delocalized case is 23 mS/cm^2. Figure 6 shows that as one increases the distance between potassium ion channel clusters, the effect of the potassium ion channel localization on the propagation efficiency becomes large.

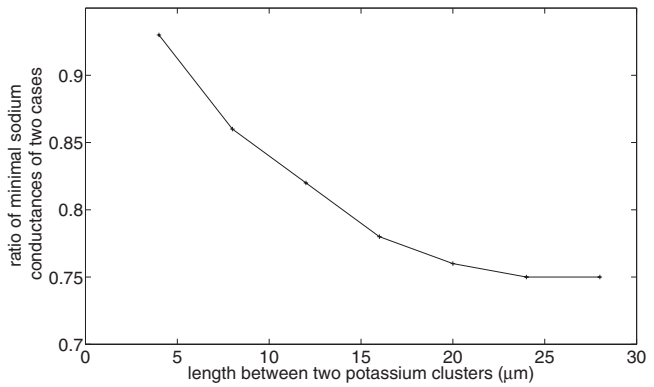

FIG. 6. The ratio of minimal required sodium ion channel conductance in the two cases versus the distance between potassium ion channel clusters. The simulation condition is similar to that of Fig. 4.

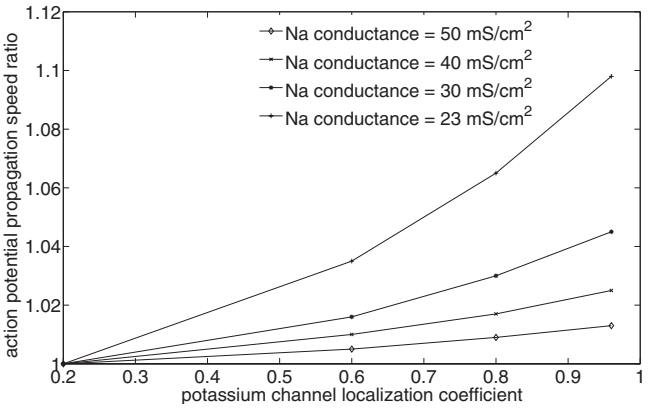

FIG. 7. The effect of potassium channel localization on propagation speed.

When the distance between potassium channel clusters reaches 24 μm, the ratio of the minimal required sodium conductance in the two cases reaches a minimal value.

Except investigating the effect of the potassium channel localization on the propagation efficiency, we also need to investigate the effect of the potassium channel localization on the action potential propagation speed. The axon diameter is 10 μm and the cytoplasmic resistivity is 70 Ω cm. The average potassium channel density is 20 mS/cm^2. We test four different sodium channel conductances: 23, 30, 40, and 50 mS/cm^2. For each sodium conductance, we first calculate the propagation speed for different potassium channel localizations, and then divide the results by the propagation speed when potassium channels are uniformly distributed to obtain the speed ratio. When potassium channels are uniformly distributed, the propagation speeds of the different sodium channel conductances 23, 30, 40, and 50 mS/cm^2 are 0.13, 0.16, 0.19, and 0.21 m/s, respectively. As shown in Fig. 7, the propagation speed increases for increasing potassium channel localization. As the sodium conductance is increased, the effect of the potassium channel localization on the propagation speed decreases.

B. Effect of sodium channel localization

After testing the effect of the potassium channel localization, we begin to test the effect of the sodium channel localization. The axon diameter is 10 μm and the cytoplasmic resistivity is 70 Ω cm. For different potassium conductances, we calculate the ratio of minimal required sodium conductances in two cases. In the localized case, there is one sodium channel cluster for every five compartments, and all the sodium channels are localized in the clusters. In the delocalized case, sodium channels are distributed uniformly along the axon. We vary the average potassium conductance from 20 to 50 mS/cm^2 [22]. The ratio of the minimal required sodium conductance is plotted in Fig. 8. As shown in Fig. 8, when the potassium conductance is low, the sodium channel localization will reduce the minimal required sodium conductance. When the potassium conductance is high, the sodium channel localization will increase the minimal required sodium conductance. Localization of sodium channels

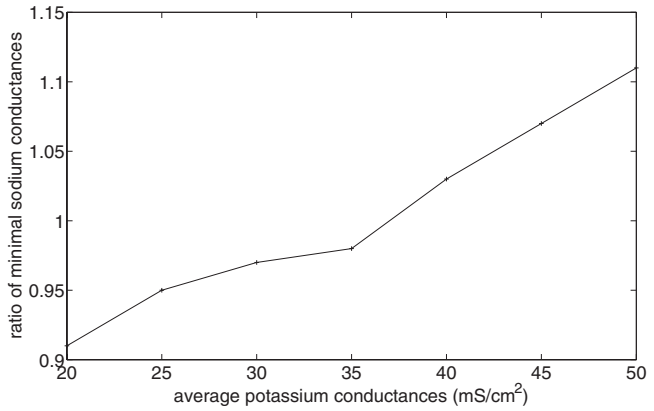

FIG. 8. The ratio of minimal required sodium conductances in two cases versus different potassium conductances. In the localized case, every fifth compartment has one sodium cluster, and all the sodium channels localize in the clusters. In the delocalized case, sodium channels distribute uniformly along the axon. The minimal required sodium conductance of the localized case is the numerator, and that of the delocalized case is the denominator.

is advantageous to the propagation efficiency only when the potassium conductance is low. So in order to construct an efficient axon with localization of sodium ion channels, we should choose a small value of the average potassium conductance.

In order to test the effect of the distance between sodium channel clusters on the propagation efficiency, we change the compartment number between two nearby sodium channel clusters. The axon diameter is 10 μm, the cytoplasmic resistivity is 70 Ω cm, and the potassium channel conductance is 20 mS/cm^2. The length of each sodium channel cluster is 4 μm. We calculate the ratio of the minimal required sodium conductance in both cases versus the distance between the two clusters. The two cases are the same as above. The result is shown in Fig. 9. As shown in Fig. 9, the ratio of the minimal required sodium conductance first decreases, reaches a minimal value, and then increases again for increasing distance between the clusters. There is an optimal distance in which the propagation efficiency is best.

Sodium cluster length may affect the ratio of the minimal required sodium conductance in both cases. In what follows,

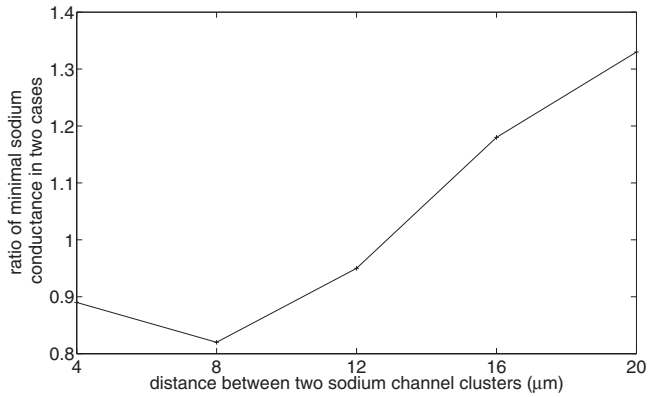

FIG. 9. The ratio of minimal required sodium conductances in two cases versus different distances between sodium channel clusters. The simulation condition is similar to that of Fig. 8.

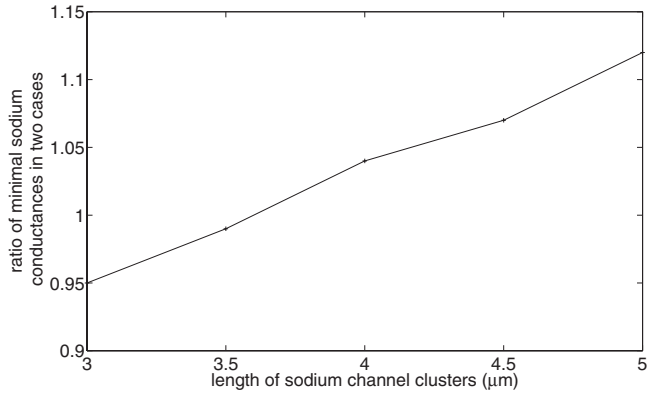

FIG. 10. The ratio of minimal required sodium conductances in two cases versus different sodium channel cluster lengths. The simulation condition is similar to that of Fig. 8.

we investigate the issue. The two cases are the same as above. The distance between sodium channel clusters is 10 μm, the axon diameter is 10 μm, the cytoplasmic resistivity is 70 Ω cm, and the potassium channel conductance is 20 mS/cm^2. The ratio of the minimal required sodium channel conductances is plotted in Fig. 10. As shown in Fig. 10, for increasing sodium channel cluster length, the ratio of minimal required sodium channel conductances increases. When the length of sodium channel clusters is less than 3.5 μm, localization of sodium channels is advantageous to the propagation efficiency; otherwise, localization of sodium channels is disadvantageous to the propagation efficiency.

The cytoplasmic resistivity is also another factor affecting the ratio of the minimal required sodium channel conductance in two cases. We will investigate this issue. The two cases are the same as above. The axon diameter is 10 μm and the potassium channel conductance is 20 mS/cm^2. The ratio of minimal required sodium channel conductances is plotted in Fig. 11. As shown in Fig. 11, with increasing cytoplasmic resistivity, the ratio of the minimal required sodium channel conductance increases. When the cytoplasmic resistivity is less than 120 Ω cm, localization of sodium channels is advantageous to the propagation efficiency; otherwise, localization of sodium channels is disadvantageous to the propagation efficiency. In order to construct an effi-

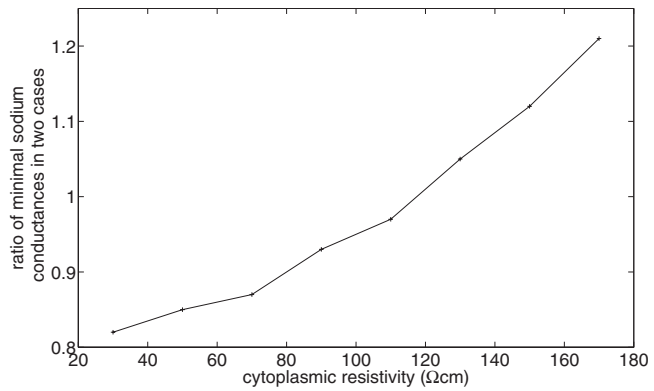

FIG. 11. The ratio of minimal required sodium conductances in two cases versus the cytoplasmic resistivity. The simulation condition is similar to that of Fig. 8.

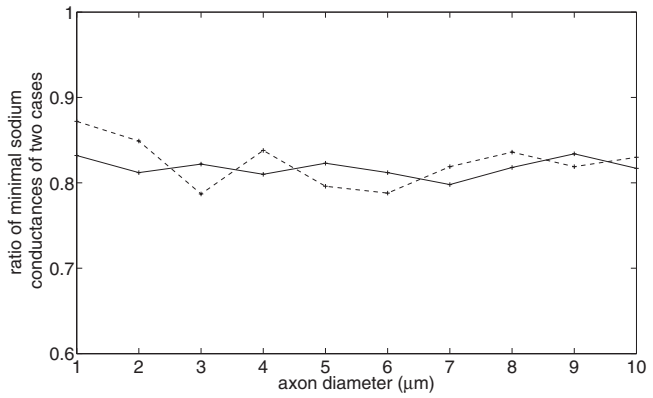

FIG. 12. The ratio of the minimal required sodium ion channel conductance in the two cases of two different methods versus axon diameter. The simulation condition is similar to that of Fig. 4. In both cases, the average potassium ion channel conductance is 30 mS/cm^2. The solid line is the result by deterministic HH equations, and the dashed line is the result by stochastic HH equations.

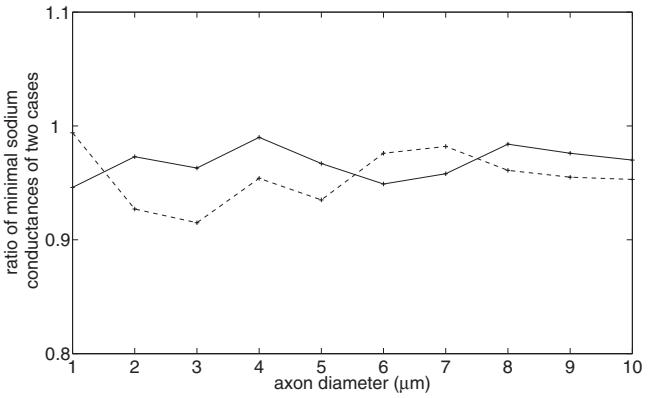

FIG. 13. The ratio of the minimal required sodium ion channel conductance in the two cases of two different methods versus axon diameter. The simulation condition is similar to that of Fig. 8. In both cases, the average potassium ion channel conductance is 30 mS/cm^2. The solid line is the result by deterministic HH equations, and the dashed line is the result by stochastic HH equations.

cient axon with localization of sodium ion channels, we should choose a small value of the cytoplasmic resistivity.

We have also tested the effect of sodium channel localization on the action potential propagation speed. Our results show that localization of sodium channels has only a weak effect on the action potential propagation speed.

C. Effect of ion channel noise

The axon diameter ranges usually from 1 to 20 μm [18,23]. If the axon diameter is small, the ion channel number in one compartment is small. Small ion channel cluster will induce ion channel noise [17,19]. We will investigate whether ion channel noise will affect the propagation efficiency adjusted by ion channel localization. In order to investigate the effect of ion channel noise, we use two different kinds of HH equations (deterministic and stochastic HH equations) to simulate the dynamics of sodium and potassium channels and compare the results of the two different methods. In order to suppress the contingency due to ion channel noise, we simulate 30 times of each specific axon diameter with 30 different random seeds by stochastic method and calculate the average propagation efficiency. We first investigate the case of potassium ion channel localization. The simulation condition is similar to that of Fig. 4. In both cases of each method, the average potassium ion channel conductance is 30 mS/cm^2. The ratio of the minimal required sodium ion channel conductance in the two cases of two different methods versus the axon diameter is plotted in Fig. 12. As shown in Fig. 12, the ratio versus the axon diameter by deterministic HH equations fluctuates within a narrow range, approximately 5%, so the axon diameter does not affect the propagation efficiency adjusted by potassium ion channel localization principally. We also can find that ion channel noise affects the propagation efficiency adjusted by potassium ion channel localization somehow. If the axon diameter is 10 μm, the ratio difference of the minimal required sodium ion channel conductance of two different HH equations is 2%. As the axon diameter decreases continually, the effect of ion channel noise increases gradually, and then the ratio difference of two different HH equations reaches 5% when the axon diameter is 1 μm. In general, the ratio versus the axon diameter by stochastic HH equations fluctuates within the range of 10%. Second, we investigate the case of sodium ion channel localization. The simulation condition is similar to that of Fig. 8. In both cases of each method, the average potassium ion channel conductance is 30 mS/cm^2. The ratio of the minimal required sodium ion channel conductance in the two cases of two different methods versus axon diameter is plotted in Fig. 13. As shown in Fig. 13, the ratio versus the axon diameter by deterministic HH equations fluctuates within a narrow range, approximately 5%, so the axon diameter does not affect the propagation efficiency adjusted by sodium ion channel localization principally. We also can find that ion channel noise affects the propagation efficiency adjusted by sodium ion channel localization somehow. If the axon diameter is 10 μm, the ratio difference of two different HH equations is 2%. As the axon diameter decreases continually, the effect of ion channel noise increases gradually, and then the ratio difference of two different HH equations reaches 5% when the axon diameter is 1 μm. In general, the ratio versus the axon diameter by stochastic HH equations fluctuates within the range of 10%. Above all, ion channel noise affects the propagation efficiency adjusted by ion channel localization somehow, and the propagation efficiency versus the axon diameter by stochastic HH equations fluctuates in the range of 10%. As the axon diameter decreases, the effect of ion channel noise on the propagation efficiency will increase gradually.

IV. CONCLUSION AND DISCUSSION

Localization of ion channels in myelinated axons is accompanied by the formation of myelin. The cells responsible for myelin formation are different for central nervous system (oligodendrocytes) and peripheral nervous system (Schwann cells). The thickening of myelin and Na channel localization

will increase the propagation speed of the action potential. But the mechanisms and the effects of ion channel localization in unmyelinated axon are unclear. In this paper, we investigated theoretically the effect of localization of ion channels along unmyelinated axons. We mainly focused on two aspects: the propagation efficiency and the propagation speed. Our results show that potassium channel localization is beneficial for increasing propagation efficiency and propagation speed of action potentials. Localization of sodium channels is advantageous to the propagation efficiency only when axonal parameters are in a specific range. Potassium ion channels have traditionally been considered to be electrically inexcitable and play a passive role in the electrical activity of the axon. So localization of potassium ion channels can increase the excitability of delocalized region in the axon, and then increase the propagation efficiency and the propagation speed of action potentials. Sodium ion channels have traditionally been considered to be electrically excitable and play an active role in the electrical activity of the axon. Localization of sodium ion channels can increase the excitability of the localized region in the axon; however, it can decrease the excitability of the delocalized region in the axon, so localization of sodium channels is advantageous to the propagation efficiency only when axonal parameters are in a specific range. The axon diameter ranges usually from 1 to 20 μm [18,23]. If the axon diameter is small, the ion channel number in one compartment is small. Small ion channel cluster will induce ion channel noise [17,19]. Our results show that ion channel noise affects the propagation efficiency adjusted by ion channel localization somehow, and the propagation efficiency versus the axon diameter by stochastic HH equations fluctuates in the range of 10%. As the axon diameter decreases, the effect of ion channel noise on the propagation efficiency will increase gradually.

Potassium ion channels play an important role in the modulation of excitability [22]. In their pioneering work on neuronal excitability, Hodgkin and Huxley [14] demonstrated that potassium ion channels play an important role in the repolarization of the action potential in the squid giant axon. There are two kinds of functions for internodal potassium ion channels in myelinated axons. One is that they stabilize the paranodal axolemma against nodal backfiring after a single impulse [24]. The other is to maintain a resting potential under the myelin [25,26]. Localization of potassium channels decreases the potassium conductance of the axon between potassium clusters and affects the repolarization of action potentials, the electrical stability at the resting potential of the axonal membrane, and the resting potential of the axonal membrane. In order to counterbalance the effect of potassium ion channel localization, it is necessary to decrease the sodium conductance of the axonal membrane between potassium channel clusters. Then localization of potassium ion channels and sodium ion channels at the same sites cannot only increase the propagation efficiency but also maintain the electrical stability of the axonal membrane.

According to the results of this paper, we can construct a better axon for better propagation efficiency with sufficient electrical stability. For the same potassium channel localization, increasing the cytoplasmic resistivity, the distance between potassium channel clusters, and the average potassium conductance all will increase the propagation efficiency. For the same sodium channel localization, increasing the cytoplasmic resistivity, the distance between sodium channel clusters, and the average potassium conductance will decrease the propagation efficiency. There are optimal values of the cytoplasmic resistivity, the distance between channel clusters, and the average potassium conductance to optimize the propagation efficiency and the electrical stability of unmyelinated axons with ion channel clusters. In future research, we will try to find the series of optimal values.

ACKNOWLEDGMENTS

This work was supported by Scientific Research Fund of Hunan Provincial Education Department (Contract No. 07B075), Xiangtan University Fund of Interactive Project (Contract No. 061ND09), and Xiangtan University Fund of initial scientific research of S.Z.

[1] J. R. Clay and A. M. Kuzirian, J. Neurobiol. **45**, 172 (2000).
[2] J. R. Clay and A. M. Kuzirian, Mol. Biol. Cell **10**, 1312 (1999).
[3] J. R. Clay and A. M. Kuzirian, Biophys. J. **76**, A223 (1999).
[4] H. Jahnsen and R. Llinas, J. Physiol. (London) **349**, 205 (1984).
[5] R. W. Turner *et al.*, J. Neurosci. **14**, 6453 (1994).
[6] W. Almers, P. R. Stanfield, and W. Stuhmer, J. Physiol. (London) **336**, 261 (1983).
[7] C. Hildebrand and S. G. Waxman, Brain Res. **258**, 23 (1983).
[8] S. Takahashi, B. F. Driscoll, M. J. Law, and L. Sokoloff, Proc. Natl. Acad. Sci. U.S.A. **92**, 4616 (1995).
[9] T. A. Churchill and B. J. Fuller, Transplantation **59**, 904 (1995).
[10] R. A. Edwards, P. L. Lutz, and D. G. Baden, Am. J. Physiol. Regulatory Integrative Comp. Physiol. **257**, 1354 (1989).
[11] M. Erecinska, F. Dagani, D. Nelson, J. Deas, and I. A. Silver, J. Neurosci. **11**, 2410 (1991).
[12] F. Dagani, R. Ferrari, and L. Canevari, Brain Res. **530**, 261 (1990).
[13] S. S. Kety, *Metabolism of the Nervous System* (Pergamon, London, 1957).
[14] A. L. Hodgkin and A. F. Huxley, J. Physiol. (London) **117**, 500 (1952).
[15] C. Chow and J. White, Biophys. J. **71**, 3013 (1996).
[16] E. Schneidman, B. Freedman, and I. Segev, Neural Comput. **10**, 1679 (1998).
[17] J. A. White, J. T. Rubinstein, and A. R. Kay, Trends Neurosci. **23**, 131 (2000).
[18] C. Koch, *Biophysics of Computation: Information Processing in Single Neurons* (Oxford University Press, New York, 1999).
[19] P. Jung and J. W. Shuai, EPL **56**, 29 (2001).

[20] S. Cullheim and B. Ulfhake, J. Comp. Neurol. **188**, 679 (1979).
[21] K. R. Foster, J. M. Bidinger, and D. O. Carpenter, Biophys. J. **16**, 991 (1976).
[22] B. Hille, *Ionic Channels of Excitable Membranes* (Sinauer Associates, Sunderland, MA, 1992).
[23] S. G. Waxman, J. D. Kocsis, and Peter K. Stys, *The Axon: Structure, Function, and Pathophysiology* (Oxford University Press, New York, 1995).
[24] S. Y. Chiu and J. M. Ritchie, J. Physiol. (London) **313**, 415 (1981).
[25] S. Y. Chiu and J. M. Ritchie, J. Physiol. (London) **322**, 485 (1982).
[26] S. Y. Chiu and J. M. Ritchie, Proc. R. Soc. London, Ser. B **220**, 415 (1984).