Effects of fractal gating of potassium channels on neuronal behaviours*

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The classical model of voltage-gated ion channels assumes that according to a Markov process ion channels switch among a small number of states without memory, but a bunch of experimental papers show that some ion channels exhibit significant memory effects, and this memory effects can take the form of kinetic rate constant that is fractal. Obviously the gating character of ion channels will affect generation and propagation of action potentials, furthermore, affect generation, coding and propagation of neural information. However, there is little previous research on this series of interesting issues. This paper investigates effects of fractal gating of potassium channel subunits switching from closed state to open state on neuronal behaviours. The obtained results show that fractal gating of potassium channel subunits switching from closed state to open state has important effects on neuronal behaviours, increases excitability, rest potential and spiking frequency of the neuronal membrane, and decreases threshold voltage and threshold injected current of the neuronal membrane. So fractal gating of potassium channel subunits switching from closed state to open state can improve the sensitivity of the neuronal membrane, and enlarge the encoded strength of neural information.

Keywords: memory effects, fractal gating, neuronal spiking

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1. Introduction

Voltage-dependent ion channels mediate action potentials in excitable membranes, and play an important role in signal generation and propagation in neurons. The ionic mechanism underlying generation and propagation of action potentials in the neuronal system was well quantified in giant axon by Hodgkin and Huxley.[1−4] The classical models of voltage-gated ion channels[5,6] assumes that ion channels switch between a small number of conformational states with kinetic rate constants which only depend on the present state of the channels. In this Markov process,[7,8] the physical state of one ion channel at a certain time does not depend on its physical state at the earlier time. However, these assumptions may not be conformational changes in proteins. The protein consisting of thousands of amino acids is separated by small energy barriers.[9−17] Thus, a channel would be expected to have a continuum of many conformational states rather than a few discrete states, and significant dynamic processes with memory are exhibited. In the past twenty years, a bunch of experimental papers have shown that many voltage-gated ion channels do not activate as a pure Markov process, however exhibit significant memory effects.[18−26] This memory effects can take the form of kinetic rate constant being fractal.[22−26] The fractal model proposes that the effective rate constant has the form At^{1-D}, where A is the kinetic setpoint, t is the time that the channel has resided in the current state, and D is the fractal dimension. This form was chosen because many other physical systems display this type of scaling.[27−29]

Information generation, coding and propagation in neurons are through action potentials. An action potential is the transient alteration of membrane potential across an excitable membrane generated by activities of voltage-gated ion channels embedded in the membrane. Action potentials within neural systems are generally driven by ions through ion channels. The two main kinds of ion channels for action potentials are sodium ion channels and potassium ion channels. The inward sodium ion current through sodium ion channels is responsible for the depolarizing phase of

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an action potential, and the outward potassium ion current through potassium ion channels is responsible for the repolarizing phase of an action potential. It is well known that ion channels are critical for propagation of action potentials along mylinated and unmylinated axons. So ion channels are the basic elements to mediate generation and propagation of action potentials. Then it is obvious that gating character of ion channels will affect generation and propagation of action potentials, furthermore, affect generation, coding and propagation of neural information. As mentioned above, a bunch of experimental papers have shown that gating character of some ion channels is fractal rather than memoryless.[18−26] So it is reasonable to imagine that fractal gating of ion channels will affect generation and propagation of action potentials, furthermore, affect generation, coding and propagation of neural information. Although there are some theoretical papers on fractal gating of ion channels,[30−36] however, there is little previous research on the interesting and important subject we mentioned above. In this paper, we will investigate effects of fractal gating of ion channels on neuronal behaviours. Behaviour changes of a whole unit is usually due to behaviour changes of its components, so it is reasonable to deduce that fractal gating of one whole channels is due to fractal gating of its components, channel subunits. On the other hand, the cornerstone of modern neuroscience, the Hodgkin–Huxley (HH) equations formalize the dynamics of neuronal membranes by simulating the dynamics of channel subunits, so in our simulations, we simulate fractal gating of ion channels by simulating fractal gating of channel subunits. Although there are experimental papers to demonstrate fractal gating of some sodium channels,[20,37] in order to investigate this subject step by step, we first focus on fractal gating of potassium channels for the first step. In order to delve into this subject more clearly and gradually, in this paper we first consider fractal gating of potassium channels switching from closed state to open state. In the follow-up researches, we will investigate effects of fractal gating of potassium channels switching from open state to closed state and fractal gating of sodium channels. In this paper, we investigate the effects of fractal gating of potassium channels by investigating those of potassium channel subunits. Our research results show that fractal gating of potassium channel subunits switching from closed state to open state has important effects on neuronal behaviours, increases excitability, rest potential and spiking frequency of the neuronal membrane, and decreases threshold voltage and threshold injected current of the neuronal membrane. So fractal gating of potassium channel subunits switching from closed state to open state can improve the sensitivity of the neuronal membrane, and enlarge the encoded strength of neural information.

2. Methods

2.1. Deterministic HH model

The membrane dynamics formalized by the HH equations is given by the following equation[1−4]

$$C_m \mathrm{d}v/\mathrm{d}t = -g_{\mathrm{K}} n^4 (v - v_{\mathrm{K}}) - g_{\mathrm{Na}} m^3 h (v - v_{\mathrm{Na}}) - g_{\mathrm{l}} (v - v_{\mathrm{l}}) + I, \quad (1)$$

where c_m denotes the specific capacitance, g_{K} the maximal potassium conductance, g_{Na} the maximal sodium conductance, and g_{l} the leakage conductance of the neuronal membrane. The voltages v_{K}, v_{Na} and v_{l} denote the potassium, sodium and leakage reversal potentials respectively and I is the current injected into this membrane. The leakage conductance is a constant, however, the sodium and potassium conductances are voltage-dependent. The gating variables n, m and h represent the open probabilities of one n, m and h gate respectively and have a value between 0 and 1. We can assume that each potassium gate has two states, the open state and the closed state. If the open probability is n, then the closed probability is $1 - n$. The transition between the open state and the closed state is governed by first order kinetics, and the voltage-dependent transition rates from the closed state to the open state and from the open state to the closed state are α_n and β_n. It is similar for m and h gates in sodium channels. The gating variables n, m and h obey the following equations:

$$\mathrm{d}n/\mathrm{d}t = \alpha_n (1 - n) - \beta_n n, \quad (2)$$

$$\mathrm{d}m/\mathrm{d}t = \alpha_m (1 - m) - \beta_m m, \quad (3)$$

$$\mathrm{d}h/\mathrm{d}t = \alpha_h (1 - h) - \beta_h h, \quad (4)$$

where α_x and β_x $(x = n, m, h)$ are voltage-dependent opening and closing rates respectively and given in Table 1 with the other parameters used in the following simulations.[1−4]

Table 1. Parameters and rate functions used in our simulation.

c_m	specific membrane capacitance	1 μF/cm
$v_{\rm K}$	potassium reversal potential	-77 mV
$v_{\rm Na}$	sodium reversal potential	50 mV
$v_{\rm l}$	leakage reversal potential	-65 mV
$\gamma_{\rm K}$	single potassium channel conductance	20 pS
$\gamma_{\rm Na}$	single sodium channel conductance	20 pS
$g_{\rm K}$	potassium channel conductance	36 mS/cm^2
$g_{\rm Na}$	sodium channel conductance	120 mS/cm^2
$g_{\rm l}$	leakage conductance	1 mS/cm^2
$\rho_{\rm K}$	potassium channel density	20/μm^2
$\rho_{\rm Na}$	sodium channel density	60/μm^2
α_n		$\frac{0.01(V+55)}{1-{\rm e}^{-(V+55)/10}}$ ms^{-1}
β_n		$0.125\,{\rm e}^{-(V+65)/80}$ ms^{-1}
α_m		$\frac{0.1(V+40)}{1-{\rm e}^{-(V+40)/10}}$ ms^{-1}
β_m		$4\,{\rm e}^{-(V+65)/18}$ ms^{-1}
α_h		$0.07\,{\rm e}^{-(V+65)/20}$ ms^{-1}
β_h		$\frac{1}{1-{\rm e}^{-(V+35)/10}}$ ms^{-1}

2.2. Stochastic HH model

The dynamics of the n, m and h gates can be described by first-order differential equations when the number of ion channels is large. However, ion channels are random devices with stochastic gating character. When the number of ion channels is small, the stochastic effect becomes important in neuronal dynamics, and the deterministic differential equations are not a good description for neuronal dynamics. In stochastic HH equations, voltage variation of a neuronal membrane obeys the following equation:

$$\begin{aligned} {\rm d}v/{\rm d}t = & -(g_{\rm K}N_{\rm K}^{\rm open}/N_{\rm K}(v-v_{\rm K}) \\ & + g_{\rm Na}N_{\rm Na}^{\rm open}/N_{\rm Na}(v-v_{\rm Na}) \\ & + g_{\rm l}(v-v_{\rm l})) + I, \end{aligned} \tag{5}$$

where $N_{\rm K}^{\rm open}$ and $N_{\rm Na}^{\rm open}$ respectively represent the numbers of open potassium and sodium channels in the specific membrane, $N_{\rm K}$ and $N_{\rm Na}$ represent respectively the total numbers of potassium and sodium channels in the specific membrane. The parameters in Eq. (1) are independent of the membrane area, however the total numbers of potassium and sodium channels $N_{\rm K}$ and $N_{\rm Na}$ in Eq. (5) are proportional to the membrane area, and the numbers of open potassium and sodium channels $N_{\rm K}^{\rm open}$ and $N_{\rm Na}^{\rm open}$ in Eq. (3) are approximately proportional to the membrane area. The coefficient n^4 in Eq. (1) means that there are four n gates in one potassium channel. Only when all the four n gates are in the open state, does the potassium channel open. Similarly, the coefficient m^3h in Eq. (1) means that there are three m gates and one h gate in one sodium channel. Only when all the three m gates and the h gate are in the open state, does the sodium channel open. To integrate Eq. (5), the numbers of open sodium and potassium channels have to be determined at each instant, and one method called simple stochastic HH method was employed.[37–39] On one hand, subunits in ion channels are cooperative, one potassium channel consists of four n subunits and one sodium channel consists of three m subunits and one h subunit; on the other hand, each subunit in one ion channel switches between open and closed states independently with transition rate just depending on membrane voltage.[37–43] This means that all subunits open and close according to a two-state Markov process with voltage-dependent opening and closing rates.[37–41,44,45] Because there are four n subunits in one potassium channel, we need an $N_{\rm K}\times 4$ matrix to record the state of each potassium subunit. Similarly, we need an $N_{\rm Na}\times 4$ matrix to record the state of each sodium subunit. We first simulate the state of each potassium subunit according to the two-state Markov process at each instant. Secondly, according to the states of four certain potassium subunits in one potassium channel, we obtain the state of each potassium channel at each instant. Thirdly, according to the state of each potassium channel, we obtain the number of open potassium channels at each instant. Similarly, we can obtain the number of open sodium channels at each instant. When the numbers of open

sodium channels and open potassium channels are obtained, we can update the membrane voltage in Eq. (5) at each instant. The kinetic two-state Markov process of a single subunit is shown in Fig. 1, α and β are the opening and closing rates of the subunits. A very small time interval δt is chosen, for $\delta t \ll 1/\alpha$ and $\delta t \ll 1/\beta$. If the gate is closed at time t, it will open with probability $\alpha\delta t$ and remain closed with probability $1-\alpha\delta t$. If the gate is open at time t, it will close with probability $\beta\delta t$ and remain open with probability $1-\beta\delta t$. According to the assumption described above, a random number γ from a uniform distribution in each simulation step is employed. If the subunit is closed at time t and $\gamma > \alpha\delta t$, the subunit keeps in the closed state, while it switches to the open state if $\gamma < \alpha\delta t$. Similarly, if the subunit is open at time t and $\gamma > \beta\delta t$, the subunit remains open, while it switches to the closed state if $\gamma < \beta\delta t$.

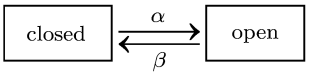


Fig. 1. Kinetic scheme of a two-state gate.

2.3. Fractal HH model

The gating behaviour of ion channels is memoryless in the popular Markov model. In contrast, this fractal gating method simulates ion channels gating with memory effects. The basic assumption of this method is that once the channel subunit closes, the reopening rate is dependent on the time spent in the closed state, so that the rate of reopening declines as the closed time increases. The reopening rate of one gate is set as $k(t)$:

$$c \xrightarrow{k(t)} o,$$

where $k(t)$ is time-dependent and given by

$$k(t) = At^{1-D}, \tag{6}$$

where A is the kinetic setpoint and D is the fractal dimension from 1 to 2.[20,23,26] In this paper, A is set as α_n, which is the transition rate of n gate in the Markov process. In order to avoid simulation divergence of Eq. (6), we also need to choose a small value τ.[36] In our simulation, for potassium channels of squid axon, we set $\tau = 1$ ms. When the dwell-time $t < \tau$, the Markov method is employed, and the kinetic rate only depends on membrane voltage. When the dwell-time $t > \tau$, the fractal method is employed, and the kinetic rates not only depend on membrane voltage, but also on dwell time t. In order to investigate effects of fractal gating step by step, we just simulate fractal gating of potassium channel subunits switching from closed state to open state. The switching process of potassium channel subunits from open state to closed state and the switching process of sodium channel subunits are chosen as Markov process. In the future research, we will investigate a series of fractal gating issues, including effects of fractal gating of potassium channel subunits switching from open state to closed state, the competitive behaviours between the two fractal gating mechanisms of potassium channel subunits, and effects of fractal gating of sodium channel subunits.

3. Results

In our simulations, we simulate fractal gating of ion channels by simulating fractal gating of channel subunits. In the closed state of potassium channels, there are four different kinds of sub-states, sub-state with four closed n gates, sub-state with three closed n gates, sub-state with two closed n gates and sub-state with one closed n gate. If the fractal dimension of single n gate is D, we can deduce that the fractal dimension of the sub-state with four closed n gates is approximately $4 \times (D-1) + 1$. Similarly, the fractal dimension of the sub-state with three closed n gates is approximately $3 \times (D-1) + 1$, the fractal dimension of the sub-state with two closed n gates is approximately $2 \times (D-1) + 1$, and the fractal dimension of the sub-state with one closed n gate is approximately $(D-1) + 1$. Furthermore, we can suppose approximately that the general fractal dimension of one potassium channel is the average of the fractal dimensions of four different sub-states, then the approximate fractal dimension of one potassium channel is $2.5 \times (D-1) + 1$. Actually, the deduction is not strict, we should use accurate simulation to obtain the fractal dimension D' of potassium channels. We use the methods in Refs. [22]–[26] to calculate the relationship between the fractal dimension D of potassium channel subunits and the fractal dimension D' of potassium channels, and the results are plotted in Fig. 2. In the simulation, we choose the membrane voltage as -65 mV, which is near the rest potential of the neuronal membrane. We find from Fig. 2 that D' is approximately $3.0 \times (D-1) + 1$, which is close to our approximate deduction result $2.5 \times (D-1) + 1$.

Because the experimental result of the fractal dimension D' of potassium channels is from 1 to 2,[20,23,26] according to the simulation result in Fig. 2, we can choose the fractal dimension D of potassium channel subunits from 1.0 to 1.3. Thus, in the following simulation, we choose D as 1.0, 1.1, 1.2 and 1.3.

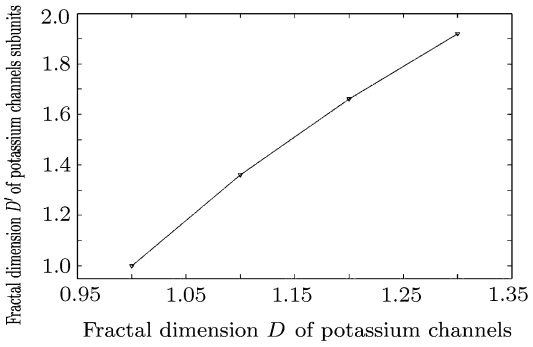


Fig. 2. The relationship between the fractal dimension D of potassium channel subunits and the fractal dimension D' of potassium channels.

3.1. Effects of fractal gating of potassium channels on large neuronal membrane

We first focus on the case of large neuronal membrane. If the area of the neuronal membrane is large, the ion channel number on the membrane is large, and then the effect of channel fluctuation is less. If the area of the neuronal membrane is large enough, we can neglect the effect of ion channel noise, and the specific membrane has a certain threshold voltage for initializing a spike. We choose the area of the neuronal membrane as 2000 μm^2, which is large enough to have a certain threshold voltage. In order to measure the threshold voltage, we inject external current pulse to the neuronal membrane, starting from a small value. In each step, computer will judge whether an action potential is generated or not and records the highest voltage of the neural membrane due to the external current pulse. If an action potential is not generated, the magnitude of the external current pulse will increase 0.01 mV, and the procedure is repeated again till an action potential is generated. Then we can obtain the threshold voltage of the neuronal membrane, which is the highest voltage of the preceding step. In order to eliminate the error due to ion channel noise, we choose 100 different random seeds in the simulations, repeat the whole procedure described above 100 times, and obtain the accurate threshold voltage by calculating the average of the results of 100 trials. The threshold voltage versus the fractal dimension D is plotted in Fig. 3. As shown in Fig. 3, increasing the fractal dimension D will decrease continuously the threshold voltage of the large neuronal membrane. It is well known that lower threshold voltage means higher excitability, so fractal gating of potassium channel subunits switching from closed state to open state increases excitability of the neuronal membrane, and makes the neuronal membrane easy to spike.

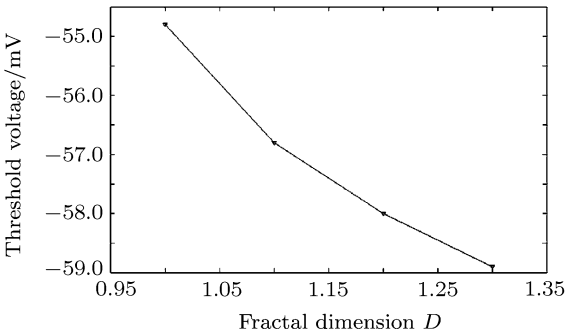


Fig. 3. Threshold voltage of the neuronal membrane versus the fractal dimension D.

Except threshold voltage, spiking frequency versus external injected current is another factor to measure excitability of the neuronal membrane. We also choose the area of the neuronal membrane as 2000 μm^2, which is large enough to neglect the effect of ion channel noise. The spiking frequency versus external injected current is plotted in Fig. 4. As shown in Fig. 4, increasing the fractal dimension D increases continuously the spiking frequency. It shows that fractal gating of potassium channel subunits switching from closed state to open state increases excitability of the neuronal membrane, and makes the neuronal membrane easy to spike.

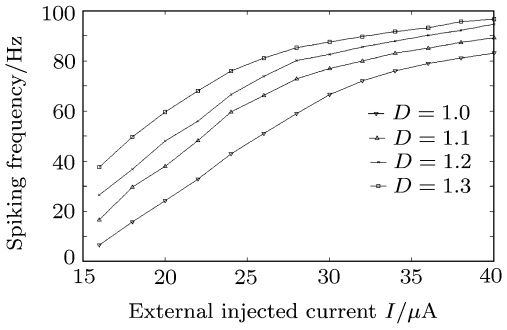


Fig. 4. Spiking frequency versus different injected current with different fractal dimension D.

Threshold injected current evoking stable and regular spikes is also an important parameter to measure excitability of the neuronal membrane. We

also choose the area of the neuronal membrane as 2000 μm^2. In order to measure the threshold injected current, we inject the constant external current to the neuronal membrane, starting from a small value. In each step, computer will judge whether the stable and regular spikes are generated or not. If not, the magnitude of external injected current will increase 0.01 μA, and the procedure is repeated again till the stable and regular spikes are generated. Then we obtain the threshold injected current. In order to eliminate the error due to ion channel noise, we choose 100 different random seeds in the simulations, repeat the whole procedure described above 100 times, and obtain the accurate threshold injected current by calculating the average of the results of 100 trials. The threshold injected current versus the fractal dimension D is plotted in Fig. 5. As shown in Fig. 5, increasing the fractal dimension D decreases continuously the threshold injected current. Lower threshold injected current means higher excitability of neuronal membrane, so fractal gating of potassium channel subunits switching from closed state to open state increases excitability of the neuronal membrane, and makes the neuronal membrane easy to spike.

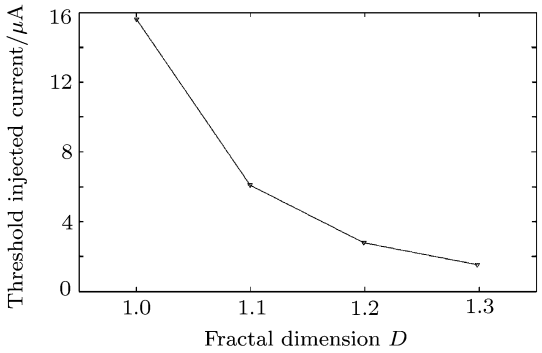


Fig. 5. Threshold injected current versus the fractal dimension D.

Rest potential is also a parameter to measure excitability of neuronal membrane. If the rest potential of the specific neuronal membrane is higher, the membrane is more excitable and easier to evoke action potentials, and *vice versa*. We also choose the area of the neuronal membrane as 2000 μm^2, which is large enough to neglect the spontaneous spiking due to ion channel noise. Rest potentials of the neuronal membrane versus the fractal dimension D are plotted in Fig. 6. As shown in Fig. 6, increasing the fractal dimension D increases continuously the rest potential of the neuronal membrane, so fractal gating of potassium channel subunits switching from closed state to open state increases excitability of the neuronal membrane, and makes the neuronal membrane easy to spike. Above all, in four aspects, threshold voltage, spiking frequency, threshold injected current and rest potential, we show that fractal gating of potassium channel subunits switching from closed state to open state increases excitability of the large neuronal membrane, and makes the large neuronal membrane easy to spike. Previous researches show that threshold voltage of the neuronal membrane decides excitability of the neuronal membrane and excitability of the neuronal membrane decides spiking frequency of the neuronal membrane.[46,47] So, threshold voltage is more fundamental to decide the electrical behaviours of the neuronal membrane than spiking frequency. The changing of threshold voltage induces the changing of spiking frequency. Decreasing threshold voltage will increase spiking frequency, and *vice versa*. In one word, threshold voltage is more fundamental, and the change of spiking frequency is the result of the change of voltage threshold.

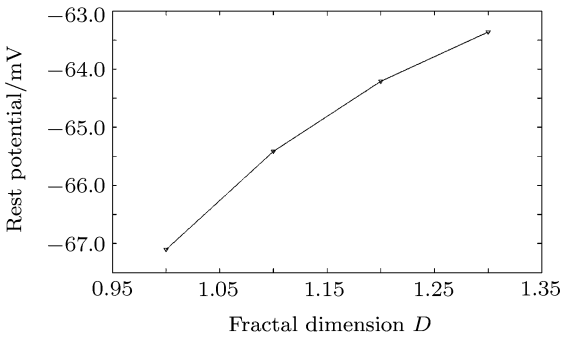


Fig. 6. Rest potential versus the fractal dimension D.

3.2. Effects of fractal gating of potassium channels on small neuronal membrane

Now, we focus on the case of small neuronal membrane. If the area of the neuronal membrane is small, and then the ion channel number on the neuronal membrane is also small. In the neuronal membrane with small number of ion channels, the effect of ion channel noise due to stochastic switching of ion channels is dramatic, and spontaneous spikes can be generated by ion channel noise.[37,38,48] We calculate the average interspike interval $\langle T \rangle$ of neuronal membranes with different sizes versus different fractal dimension D, and the results are shown in Fig. 7. In order to minimize the effect due to ion channel noise, we simulate

5000 spikes for each point in Fig. 7 and then obtain the accurate average interspike interval. As shown in Fig. 7, for a certain neuronal membrane, increasing the fractal dimension D, decreases continuously the average interspike interval $\langle T \rangle$ of spontaneous spikes. In other words, increasing the fractal dimension D decreases continuously the average spontaneous spiking frequency. It means that fractal gating of potassium channel subunits switching from closed state to open state increases excitability of the small neuronal membrane, and makes the small neuronal membrane easy to spike. We find from Fig. 7 that as a function of the membrane area, the average spontaneous interspike intervals do not increase monotonically. In Ref. [38], we explained the phenomenon in detail. In this paper, we introduce it briefly. When the membrane area is small, only one sodium channel opens, a spontaneous spike can be evoked. If the sodium channel number in a specific neuronal membrane increases, the probability of one sodium channel opening will increase. So when the membrane area is small, enlarging the membrane area will increase the spontaneous spiking frequency, and decrease the average spontaneous interspike interval. When the membrane area is large, opening of single sodium channel cannot trigger an action potential, a critical fraction of all available sodium channels is required to be open. It is well known that if ion channel number is large, when we increase the number of sodium channels, the effect of ion channel noise will be suppressed and decreased continuously. So if ion channel number in the neuronal membrane with large area increases, there will be increasing probability that the open fraction of all available sodium channels due to ion channel noise reaches the critical value, then the spontaneous spiking frequency will decrease and the average spontaneous interspike interval will increase.

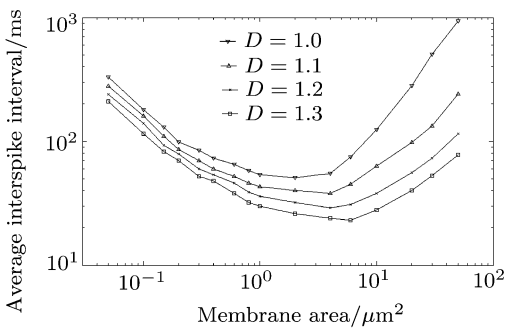


Fig. 7. Average interspike interval versus membrane area with different fractal dimension D.

3.3. Mechanism to induce the effects of fractal gating of potassium channel subunits

According to the research results of the two above subsections, fractal gating of potassium channel subunits switching from closed state to open state increases excitability of the neuronal membrane, and makes the neuronal membrane easy to spike. In order to explain the results, we can check Eq. (6). According to Eq. (6), the transition rate of potassium channel subunits switching from closed state to open state decreases when the dwell time of the specific potassium channel subunit in closed state increases. It means that the transition rate of ion channel subunits with fractal gating is less than that of ion channel subunit switching by Markov process. Smaller transition rate of the specific ion channel subunits means larger dwell time of the specific ion channel subunit in the original state, so fractal gating of potassium channel subunits switching from closed state to open state will increase the dwell time of potassium channel subunits in closed state, and then decrease activation of potassium ion channels. It is well known that activation of potassium ion channels is important to regulate excitability and rest potential of the neuronal membrane. If activation of potassium ion channels decreases, excitability and rest potential of the neuronal membrane will increase, and *vice versa*. Till now, we explain qualitatively why fractal gating of potassium channel subunits switching from closed state to open state can improve excitability of the neuronal membrane, and make the neuronal membrane easy to spike. Furthermore, we can use simulation results to show quantitatively that fractal gating of potassium channel subunits switching from closed state to open state can increase the average dwell time of potassium channel subunits in closed state, and then increase excitability of the neuronal membrane and make the neuronal membrane easy to spike. In order to calculate the average dwell time of a single potassium subunit in closed state, we track the state of a certain subunit in a certain potassium ion channel, and record the spans of the certain subunit in closed state. Then the average dwell time of a single potassium channel in closed state is the sum of the spans in closed state dividing by the number of the spans. In order to increase accuracy, the simulation time is as long as 10^6 ms. We first calculate the average dwell time of single potassium channel subunit at fixed membrane voltage versus different fractal di-

mension D. We change the fixed membrane voltage from -60 mV to 50 mV, and use four different D from 1.0 to 1.3. The results are plotted in Fig. 8. As shown in Fig. 8, when the fractal dimension D increases, at fixed membrane voltage, the average dwell time of single potassium subunit in closed state will increase correspondingly.

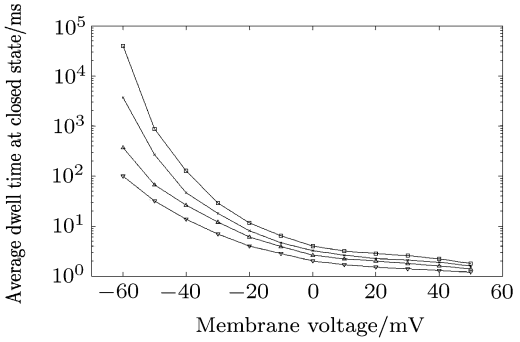


Fig. 8. Average dwell time of single potassium channel subunit in closed state versus membrane voltage with different fractal dimension D.

On the other hand, membrane voltage is not fixed at a certain value, however, changes from -80 mV to 50 mV according to different firing status of the neuronal membrane. So in the further step, we do not fix the membrane, and calculate the average dwell time of single potassium channel subunit over all the membrane voltage. Similarly, we calculate the average dwell time with four different fractal dimension D from 1.0 to 1.3 versus different membrane areas. The corresponding results are plotted in Fig. 9.

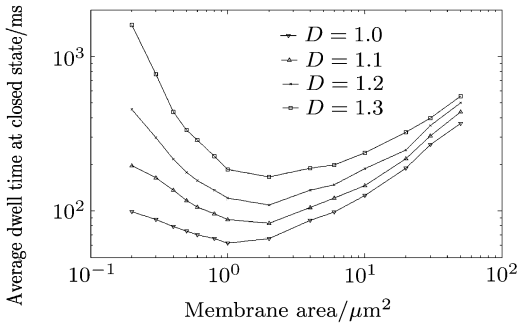


Fig. 9. Average dwell time of single potassium channel subunit in closed state versus membrane area with different fractal dimension D.

As shown in Fig. 9, increasing the fractal dimension D will increase correspondingly the average dwell time of single potassium subunit in closed state. From Fig. 9, we can find that as a function of membrane area, the average dwell time does not increase monotonically. The nonmonotonic behaviour of the average dwell time is due to that of the average spontaneous interspike interval. Above all, we show quantitatively that fractal gating of potassium channel subunits switching from closed state to open state can increase the average dwell time of one potassium channel subunit in closed state, decrease activities of the potassium channels, and then increase excitability of the neuronal membrane and make the neuronal membrane easy to spike.

4. Conclusion and discussion

Voltage-gated ion channels are the basic elements to mediate generation and propagation of action potentials, furthermore, mediate generation, coding and propagation of neural information. The classical model of voltage-gated ion channels assumes that transition rates of ion channels are memoryless and depend only on the present state of the specific channel. However, a bunch of experimental papers have shown that many voltage-gated ion channels do not activate as a pure Markov process, however exhibit significant memory effects.[18−26] In other words, switching character of ion channels is fractal rather than memoryless. It is obvious that changing the switching character of ion channels will affect the macroscopic behaviours of the excitable membrane. In this paper, we investigated the effects of fractal gating of ion channels on neuronal behaviours. In order to delve into this subject clearly and gradually, we first considered the fractal gating of potassium channel subunits switching from closed state to open state. The obtained results show that the fractal gating of potassium channel subunits switching from closed state to open state will increase excitability, rest potential and spiking frequency of the neuronal membrane, and decrease threshold voltage and threshold injected current of the neuronal membrane. It is well known that neurons use spiking frequency to encode stimulus strength.[46,47] In some neurons, the encoded strength of stimulus has linear relationship with spiking frequency. So fractal gating of potassium channel subunits switching from closed state to open state not only increases the sensitivity of neuronals membranes, but also enlarges the encoded strength of neural information.

It is well known that the activation of potassium ion channels is important to regulate excitability and rest potential of neuronal membranes.[1−4] If the activation of potassium ion channels decreases, excitabil-

ity and rest potential of the neuronal membrane will increase, and *vice versa*. Fractal gating of potassium channel subunits switching from closed state to open state will decrease the switching probability of potassium channel subunits from closed state to open state, increase the average dwell time of potassium channel subunits at closed state, reduce the activation of potassium channels, and then increase excitability of neuronal membrane and make neuronal membrane easy to spike. We also demonstrate quantitatively that fractal gating of potassium channel subunits switching from closed state to open state will increase the average dwell time of potassium channel subunits in closed state. We demonstrate this quantitatively in two aspects, fixed membrane voltage and variable membrane voltage. In the two aspects, we obtain the similar results that fractal gating of potassium channel subunits switching from closed state to open state will increase the average dwell time of potassium channel subunits in a closed state.

We have done some research on effects of fractal gating of potassium channel subunits switching from open state to closed state. Our preliminary results show that fractal gating of potassium channel subunits switching from open state to closed state has the opposite effects of fractal gating of potassium channel subunits switching from closed state to open state, will decrease excitability, rest potential and spiking frequency of the neuronal membrane, and increase threshold voltage and threshold injected current of the neuronal membrane. If we consider the two fractal gating mechanisms together, there are interesting competitive behaviours between the two fractal gating mechanisms. In addition to fractal gating of potassium channels, evidence for fractal gating of sodium channels has also been discovered. In the future research, we will investigate a series of fractal gating issues, including effects of fractal gating of potassium channel subunits switching from open state to closed state, the competitive behaviours between the two fractal gating mechanisms of potassium channel subunits, and effects of fractal gating of sodium channel subunits.

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