Features of action potential initiation in cortical neurons with multiple internal states

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Abstract

Analyzing the dynamics of action potential initiation in cortical neurons *in vitro*, some features of the initiation dynamics of cortical neuron action potentials are shown to be outside the range of behaviors described by the Hodgkin-Huxley formalism. We propose a new model which describes the dynamics of sodium channel, where we are based on the hypothesis that the gate subunits are interacting each other. This model can reproduce one of the features of action potential initiation in cortical neurons, variant onset potential.

1 Introduction

Hodgkin-Huxley formalism is a great guidepoint in physiology, because it showed that a mathematical study can contribute to understand the function of nerve for the first time. This formalism not only describe the electrical phenomena of nerve excitation well as data fitting but also describes nature of electrically excitable membrane. Hodgkin-Huxley formalism considers excitable membrane as a population of ionic channels, and provides us various insights about functional structures of ionic channels [1].

Hodgkin-Huxley formalism has several assumptions in the starting point of the consideration. Here we give three assumptions of those.

- The state of an ionic channel is determined by conformation of subunits called gates.
- A gate can be in either of two conformations which are uniquely determined by membrane potentials.
- Gates are independent of each other.

In terms of structure of channel, these assumptions means that channel is not fundamental element itself but is composed of more fundamental gate elements, the gate obeys to very simple rules, and the actions of the gates are affected by voltage sensor. Thus we see that these assumptions provide rigorous descriptions about structure of ionic channel. These descriptions have been verified by cloning or X-ray structure analysis [2, 3], but even now these are fundamental concepts in understanding ionic channel.

On the other hand, the phenomena which are not described by H-H formalism are also discussed. About twenty years ago, Matsumoto insisted that, in order to describe action potentials in squid axon, it is necessary to assume that the conformation changes of gates are not only determined by membrane potentials but also the time after onset [4]. Recently Naundorf *et al.* insisted that two characteristic features of action potential initiation in neurons in cat visual cortex *in vitro* and *in vivo*, rapid onset of action potential and variance of onset potential, cannot be described by H-H formalism [5]. As shown in Fig.(1), action potential initiation recorded from rat hippocampal CA3 pyramidal cell *in vitro* also shows variance of onset potential. Thus detailed analysis have revealed features that are impossible to be described by H-H formalism. How those features are are made by ionic channel, and how should we change our recognition of ionic channel? In this paper, we especially note on one of the features, variant onset potential. We propose that this variance can be produced by gates which interacts each other, while gates are assumed to be independent in the H-H formalism. With this proposition, we will see that ionic channel is not a simple but a complicated object which is composed of mutually communicating several subunits.

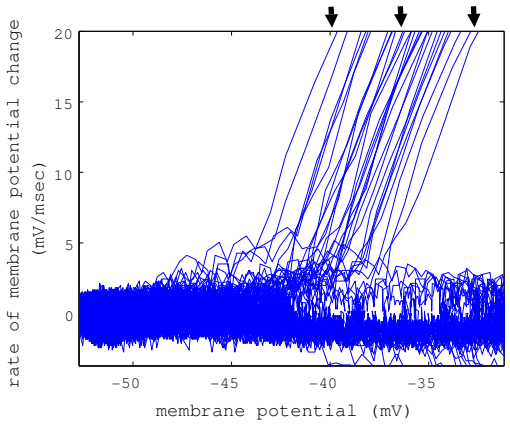

Figure 1: Phase plot (dV/dt versus V) of the action potential around the initial phase of the action potential in cortical neurons recorded *in vitro*. Arrows indicate three sample action potentials. The experimental data was provided by Hujisawa *et al.* [6].

2 Model

In order to understand the features of the action potential initiation, we consider a sodium channel composed of several gates that are not independent. (Here we call fundamental subunit which take two state "gate", even when it is not related to open-close of the channel.) This model is shown to be able to produce variation of onset potential.

The model is defined as following. We assume a sodium channel is composed of three types of gates, M, N, and H, and their gate variables are m, n, and h. Among these gates, M and H are activation and inhibition gates for each as given in the H-H formalism, and N is another gate that we introduce here. We assume that H gate does not work, that is $h = h_0(\text{const})$, in this paper.

Conformation changes of gates M and N are assumed to mutually catalyze as

$$\text{gate M} \quad : \quad S_0^M \underset{\beta_m(V,n)}{\overset{\alpha_m(V,n)}{\rightleftharpoons}} S_1^M \tag{1}$$

$$\text{gate N} \quad : \quad S_0^N \underset{\beta_n(V,m)}{\overset{\alpha_n(V,m)}{\rightleftharpoons}} S_1^N, \tag{2}$$

where catalytic relation is included in state dependence of transition rate of gate state. The rate equations of these reactions are given by

$$\frac{dm}{dt} = \alpha_m(V,n)(1-m) - \beta_m(V,n)m \tag{3}$$

$$\frac{dn}{dt} = \alpha_n(V,m)(1-n) - \beta_n(V,m)n \quad . \tag{4}$$

Now we restrict the catalytic reaction to first order, so that the transition rates become

$$\alpha_m(V,n) \simeq \alpha_m^0(V) + \alpha_m^1(V)(n-n_0), \tag{5}$$

$$\alpha_n(V,m) \simeq \alpha_n^0(V) + \alpha_n^1(V)(m-m_0), \tag{6}$$

$$\beta_m(V,n) \simeq \beta_m^0(V),\ \beta_n(V,m) \simeq \beta_n^0(V), \tag{7}$$

where m_0, n_0 are constants which imply gate states where catalytic function works well. Thus the rate equations are linearized as

$$\frac{dm}{dt} = \alpha_m^0(V)(1-m) - \beta_m^0(V)m + \alpha_m^1(V)(n-n_0) \tag{8}$$

$$\frac{dn}{dt} = \alpha_n^0(V)(1-n) - \beta_n^0(V)n + \alpha_n^1(V)(m-m_0) \tag{9}$$

The ionic current caused by the sodium channel is assumed to be affected gate M and N as

$$I_{Na} = -\overline{g}_{Na} m h_0 (V - V_{Na}). \tag{10}$$

Eqs.(8)(9)(10) and the balance equation between membrane potential and ionic current are taken as our model of action potential. In our numerical simulations, we assume that the transition rates takes following sigmoid forms,

$$\alpha_m^0(V) = \tau_{m0}^{-1}/(1+\exp(-(V-V_{m0})/k_{m0})) \tag{11}$$

$$\beta_m^0(V) = \tau_{m0}^{-1}/(1+\exp((V-V_{m0})/k_{m0})), \tag{12}$$

$$\alpha_n^0(V) = \tau_{n0}^{-1}/(1+\exp(-(V-V_{n0})/k_{n0})) \tag{13}$$

$$\beta_n^0(V) = \tau_{n0}^{-1}/(1+\exp((V-V_{n0})/k_{n0})), \tag{14}$$

$$\alpha_m^1(V) = -\tau_{m1}^{-1}/(1+\exp(-(V-V_{m1})/k_{m1})) \tag{15}$$

$$\alpha_n^1(V) = \tau_{n1}^{-1}/(1+\exp(-(V-V_{n1})/k_{n1})). \tag{16}$$

The concept of our model is illustrated in Fig.(2), but detailed explanation is given latter.

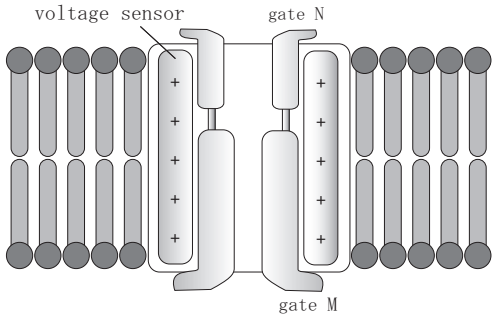

Figure 2: Illustration of the concept of the interacting gates model. Voltage sensor affects to the actions of gate M and gate N, while these gates interact each other.

3 Result

Now we investigate behavior of the model. In our simulation, values of the parameters are assigned referring parameters used in the H-H equations, except for the parameters used in Eqs. (11)∼(16). We used parameter values as $\tau_{m0} = 0.1$ms, $V_{m0} = -35$mV, $k_{m0} = 6$mV, $\tau_{n0} = 60$ms, $V_{n0} = 80$mV, $k_{n0} = 4$mV, $\tau_{m1} = \tau_{n1} = 0.1$ms, $V_{m1} = V_{n1} = -30$mV, $k_{m1} = k_{n1} = 6$mV. Phase plot that graph the rate of change of the membrane potential dV/dt against the instantaneous membrane potential V is shown in Fig.(3). Although the onset is seen to be slow compared to experimental data, we can see the variance of onset potential. (Note that it is necessary to consider another mechanism in order to get a rapid onset [5].) This variance of onset potential is considered to be

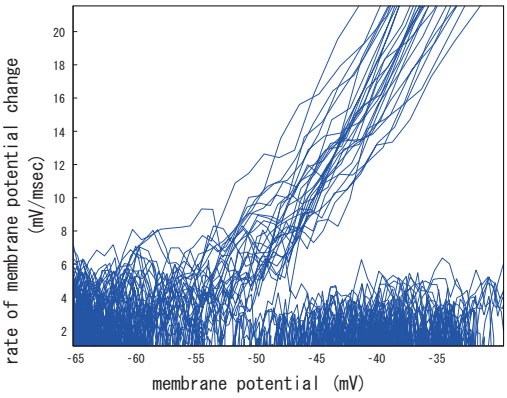

Figure 3: Phase plot calculated with the interacting gates model. Although the onset is seen to be slow compared to experimental data, the variant onset potential is seen.

made by internal dynamics of the state of the sodium channel. In Fig.(4), we show the orbit of the channel state (m, n). As we see, the channel is closed $(m = 0)$ and the value of n gradually decreases before action potential initiation, and excitation follows $(m > 0)$ afterward. Here we note that excitation happens not at a constant value of n but at various values of n. And we can show with Eq.(8) that the onset value of potential depends on the value of n. Thus it can be said that the channel with interacting gates as shown in Fig.(4) can produce the onset potential variation.

Lastly we say about relation between dynamical feature supposed in the interacting gates model and structure of ionic channel. In the H-H formalism, the action of voltage sensor is transmitted to each selective

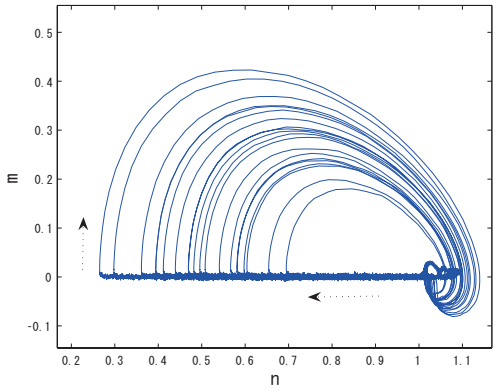

Figure 4: Orbit of the channel state (m, n). Excitation of gate M is not happened at constant value of gate variable n, but excitations can be initiated at various values of n.

filter (gate), and each selective filter independently open or close. In interacting gates model, voltage sensor affects to not only selective filter but also hidden gate component, and this hidden gate component mutually interacts with the selective filter (Fig.(2)). This might be related to paddle hypothesis recently proposed by MacKinnon *et al.* [3]. In the conventional idea, the action of voltage sensor affects only to local structure around sensor, while paddle hypothesis consider that voltage sensor can change global form of the channel. The change of global structure can be interpreted as the case that the local subunits are strongly correlated. In our study, we have seen that fluctuation of action potential includes features which does not emerge in the case that channel is a simple compound of local units. This would also imply that analysis of fluctuation is useful to generally consider structure and function of channel.

4 Summary

In order to understand the features of the action potential initiation, we proposed a new model which describes dynamics of sodium channel, where we assumed the channel is composed of several gates that are not independent. One of the features of action potential initiation, fluctuating onset potential, were shown to be able to be reproduced by this new model. This implies that the ionic channels are not simple compound of local units but global and complex object whose subunits are strongly correlated. This would

mean that analysis of fluctuation is useful to generally consider structure and function of channels.

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