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Hierarchical organization of noise generates spontaneous signal in *Paramecium* cell

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ABSTRACT

In many cellular processes, spontaneous activities are often the basis for their functioning. *Paramecium* cells change their swimming direction under a homogeneous environment, which is induced by a spontaneous signal generation in the membrane electric potential. For such a spontaneous activity, a theoretical model has been proposed by Oosawa (2007) [Biosystems 88, 191–201.], in which intracellular noise is hierarchically organized from thermal fluctuations to spike-like large fluctuations, which induces a signal to change spontaneously the swimming direction. Our analysis of the model shows that the system is a kind of excitable media, in which a spike is induced by a stochastic fluctuation. We show conditions of channels properties to have a spike train.

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1. Introduction

Living cells respond to various kinds of stimuli from the environment by changing their behaviors. Such activities to induce behavioral changes also take place even without external stimuli. For example, *Paramecium* cells that is a group of unicellular ciliate protozoa swim straight with speed of about 2–3 mm/s and change their swimming direction spontaneously with frequency about $0.1\text{--}0.2\text{ s}^{-1}$ under homogeneous environment (Oosawa and Nakaoka, 1977). The directional change is induced by a transient reversal of the beating direction of cilia in a limited area on the cell surface. The time interval between successive directional changes is distributed approximately according to an exponential distribution (Toyotama, 1981), suggesting that a stochastic process underlines the spontaneous directional change (Nakaoka and Oosawa, 1977). *Paramecium* cells are known to exhibit tactic behavior for temperature gradient (thermotaxis). By modulating the frequency of directional change, cells generate directional movement up the gradient. Therefore, such a spontaneous activity is the basis for tactic responses to external stimuli.

The reversal of beating direction of cilia is initiated by a spontaneous electric signal in *Paramecium* cell (Machemer and Eckert, 1973). The electric potential inside the *Paramecium* cells is about from -20 to -30 mV on average. However, it is not stationary in time, but showing a random fluctuation with amplitude of one to a few mV (Majima, 1980; Moolenaar et al., 1976). The potential sometimes shows a spike-like abrupt change with potential about 5–10 mV. When such a spike is generated, the beat direction of cilia changes. Thus, the spontaneous change in swimming direction is induced by the membrane spike generation. The electric potentials are generated and sustained by ionic currents, such as sodium Na^+ , calcium Ca^{2+} , and potassium K^+ , through the cell membrane. In the normal condition, sodium Na^+ and calcium Ca^{2+} flow inward because of the higher extracellular concentrations, whereas potassium K^+ flows outward. In the case of *Paramecium* cells, the frequency of the reversal of beating direction of cilia is controlled by the concentration of intracellular calcium Ca^{2+} (Nakaoka et al., 1984; Iwadate and Nakaoka, 2008). The fluctuation of electric potential has been reported to be affected by the concentration of calcium Ca^{2+} and potassium K^+ (Majima, 1980; Moolenaar et al., 1976).

For the spontaneous signal generation, Oosawa (1990, 2001, 2007) proposed a theoretical model, in which intracellular noise plays an essential role, which is hierarchically organized from thermal fluctuations to spike-like large fluctuations. Recently, the role of such intracellular fluctuation or noise has been discussed (Shibata and Fujimoto, 2005; Shibata and Ueda,

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2008). The generation and amplification of fluctuation along a signaling cascade can also be studied experimentally (Korobkova et al., 2004; Miyanaga et al., 2007; Park et al., 2010). The model proposed by Oosawa (Oosawa model) consists of two steps: The first step is the fluctuation generated by stochastic processes of channels induced by thermal fluctuation. For the second step, such fluctuation is amplified to generate large spike-like fluctuations. We note that the first step is a natural extension of the general model of membrane potential with several kinds of ion channels (Keener and Sneyd, 2008) to include the effect of stochastic fluctuations. For the second step, the model simply assumes a membrane potential sensitive ion channel. Thus, this model is considered to be general and simplest for the study of the effect of fluctuations in membrane potential. The general aspects of this model can be applicable for other systems with some extension and modification. Therefore, this model is considered as a starting point to study the spontaneous signal generation based on the fluctuating membrane potential.

So far, however, any systematic analysis of this model has not been performed. Therefore, in the present paper, we study the mechanism and conditions of spontaneous spike generation in Oosawa model. We briefly review the model proposed by Oosawa in Section 2. In Section 3, we show spontaneous spike generation in Oosawa model by numerical simulation. In Section 4, we show that the model can exhibit a kind of excitable behavior with a large excursion of potential. For the spike generation, the fluctuation which is amplified to generate spikes plays an essential role. In Section 5, we study the dependence of the property of fluctuation on the spike generation. This paper ends in Section 6 with summary and discussion.

2. Oosawa model of spontaneous spike generation in *Paramecium* cells

Here, we briefly review the model of spontaneous signal generation proposed by Oosawa. In Oosawa model, a process of the fluctuation of intracellular electric potential consists of two steps. The first step is to produce a basic fluctuation. It requires two kinds of ion channels A and B for cations A^+ and B^+ , which generates the outward current when channel A opens, whereas channel B generates inward current (Fig. 1). These ion channels generate circulating current across the membrane. These channels show stochastic transitions between open and closed states by thermal fluctuation. As a result, the circulating current in the electric potential shows a basic fluctuation. The second step is to amplify the potential fluctuation and generate spikes at random intervals. For the amplification, the third ion channel C for cation C^+ is supposed, which generates an inward current (Fig. 1). Channel C is supposed to be voltage-sensitive with the open probability which is an increasing function of the electric membrane potential $V(t)$. See Oosawa (2001, 2007) for the derivation of the model in detail.

Oosawa model consists of four variables; the membrane potential $V(t)$, the numbers of open channels of A and B, $n_A(t)$ and $n_B(t)$,

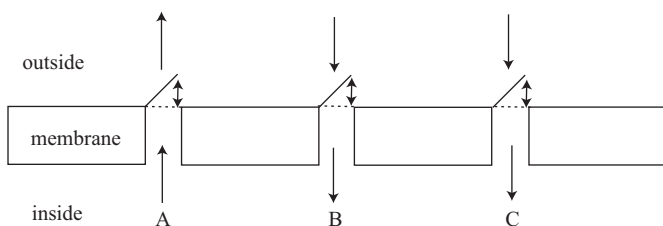


Fig. 1. A schematic diagram of the model of spontaneous signal generation proposed by Oosawa. Oosawa model consists of three kinds of channels, A, B and C. Channel A generates outward current, whereas channels B and C generate inward current.

and the probability that channel C is open, $P(t)$. The evolution equation for the deviation of the membrane potential $V(t)$ from its average $\bar{V}(t)$, $v(t) = V(t) - \bar{V}(t)$ is

$$C \frac{dv(t)}{dt} = -\bar{G}_0 v(t) + i_{AB}(t) + i_C(t) \quad (1)$$

where C is the membrane capacitance, \bar{G}_0 is the sum of the average of the conductance of channels A and B, $i_{AB}(t)$ is the current of channels A and B from its average, and $i_C(t)$ is the current generated by channel C. The current $i_{AB}(t)$ is given by

$$i_{AB}(t) = -I_0 \left(\frac{n_A(t)}{\bar{n}_A} - \frac{n_B(t)}{\bar{n}_B} \right) \quad (2)$$

where I_0 is the average value of the current of channels A or B, or the circulating current across the membrane, and \bar{n}_A and \bar{n}_B are the average numbers of open channels. For channels A and B, the transition rates from open to closed state are given by k_A^+ and k_B^+ , while from closes to open states, k_A^- and k_B^- . The total numbers of channels A and B are, respectively, N_A and N_B . The current $i_C(t)$ is given by

$$i_C(t) = I_C P(t) \quad (3)$$

where $I_C = -N_C g_C (\bar{V}(t) - V_C)$ is the maximum current with the number of channel C, N_C , their conductance g_C , and the equilibrium potential V_C . For channel C, the transition rates are supposed to depend on the electric membrane potential $v(t)$. Thus, the probability of the open state, $P(t)$, can be dependent on time. The evolution equation for $P(t)$ is thus given by

$$\frac{dP(t)}{dt} = -k_C^+(t)P(t) + k_C^-(t)(1-P(t)) \quad (4)$$

where $k_C^+(t)$ and $k_C^-(t)$ are the transition rates from open to closed states and its reverse, respectively. Consider a situation where the free energies of channels in each states depend on the potential fluctuating $v(t)$ (Oosawa, 2001, 2007, 1975). Thus, the transition rates are given by

$$k_C^+(t) = k_+^* \exp\left(-\frac{\beta}{d} v(t)\right), \quad k_C^-(t) = k_-^* \exp\left(+\frac{\beta}{d} v(t)\right) \quad (5)$$

where k_+^* , k_-^* , and β are constants and d is the thickness of the membrane. Since β is a positive constant, the open state becomes more favorable to a positive shift in the potential. If k_+^* is much larger than k_-^* , the probability of the open state P is nearly zero when the field has no fluctuating component. When the potential $v(t)$ exhibits a fluctuation with positive value, the transition rate to open state increases rapidly. The possible candidates for A and B could be potassium and sodium ions, whereas the voltage-sensitive channel could be of calcium ions (Oosawa, 2007).

3. Numerical result

Here, we first study the intracellular potential fluctuation in Oosawa model by numerical simulation. We consider the case that the ratio of open state of channel A generating outward flow is large (leak channels) and the ratio of closed state of channel B generating inward flow is larger than unity. As a result, the intracellular potential is negative. The voltage-sensitive channel C producing inward flow is responsible for generating large spike-like positive potential. The equilibrium of channel C is supposed to be close to the closed state. The potential fluctuation with positive value generated by channels A and B is amplified by collective shift of the equilibrium of channel C to open state so that large positive potential is expected to be produced transiently.

We first investigated the behavior of the electric membrane potential numerically and its dependence on the value of parameter I_C , the maximum current of channel C. Depending on the

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