

An electrophysiological model of chemotactic response in *Paramecium*

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Abstract—In order to survive in complex natural environments, living organisms have been genetically acquiring various algorithms. *Paramecium*, for example, exhibits an avoiding reaction when it senses repellent chemicals on the anterior part of the cell. Also, on sensing attractants, it accelerates its swimming velocity and remains in the area. Such a chemotactic response is called chemotaxis.

In this paper, we propose the computer model of *Paramecium* based on biological knowledge. And, we report the simulation experiments that the computer model can reproduce the characteristics of the actual organism.

I. INTRODUCTION

With the great progress that has been made in micro-processing technology, it has been possible to realize micromachines of submillimeter size, and there are increasing expectations to use these as medical robots which can operate *in vivo*. However, it is very difficult to resolve problems such as control and energy supply, and therefore, a new approach has been proposed in which protozoans are utilized as a kind of micromachine, and a number of studies that attempt to control protozoans as one of the microelectromechanical systems (MEMS) have been reported [1], [2].

Protozoans show specific reactions to various stimuli in the environment. The mechanism is called taxis and is one of the keys to survival in various environments. The protozoan receives many kinds of external stimuli, such as light, temperature and chemical material, as well as mechanical stimuli. The research that uses protozoans as MEMS has focused on their response to the electrical potential of the environment [1], [2].

Many protozoans show galvanotaxis, swimming to the cathode in an environment with an electrical potential. However, it is very hard to control living things like bacteria because the influence of Brownian movement is strong. Therefore, in the research that uses protozoans as MEMS, *Paramecium* is especially useful as its size is large enough to avoid such environmental artifacts. The behavior of protozoans to an electrical stimulus has been observed, and a control law has been proposed on the basis of the statistical data [2]. However, experiments to collect data need a lot of time, and also the control law based on the data cannot always be applied to the actual control because the intracellular characteristics of the protozoan are determined corresponding to the various ion concentrations in the environment. If a computer model can be constructed to realize the behavior based on the intracellular change

corresponding to the environmental conditions, an effective control law for the protozoan could be derived.

Some models have been proposed which focused on the internal processing system of living organisms. The model called E-CELL [3] has been developed by Tomita et al. to simulate the behavior of the entire cell based on the chemical reaction, and another model has been developed by Bray and Lay [4] and Hauri and Ross [5] to simulate part of the internal processing of *E. coli* bacteria.

Our research group has also developed the *E. coli* model based on the chemical equation of the internal processing system, and has applied it to mobile robot control [6], [7], [8]. Furthermore, the authors focused on *Paramecium*, and proposed the model [9] which realizes the change in the membrane potential for the mechanical stimuli under specific environmental conditions by using the differential equation proposed by Hodgkin and Huxley [10]. However, the membrane potential in *Paramecium* varies according to the Ca^{2+} and K^{+} concentrations in the environment [11]. Also, the rapid changes in Ca^{2+} and K^{+} concentrations in the environment can be considered as a kind of chemotactic stimuli. The previous model [9] has not considered the above-mentioned mechanism. Therefore, in this paper, a new model for the internal processing system in *Paramecium* is proposed to explain the change in the membrane potential corresponding to the Ca^{2+} and K^{+} concentrations in the environment in addition to the motor control model.

This paper is organized as follows: In Section 2, the relationship between chemotaxis and the electric phenomena of the membrane in *Paramecium* is explained. In Section 3, a model of chemotactic response of *Paramecium* is described in detail. In Section 4, the effectiveness of this model is verified through a series of computer simulations using the proposed model. The simulation results are compared with results using the actual organisms.

II. CHARACTERISTICS OF AN ELECTRIC MEMBRANE AND TAXIS

Paramecium forms a discoid shape of about 250 μm length and about 50 μm width, and with a uniform covering of cilia on the surface. The direction of ciliary beat is modified by environmental triggers. For example, *Paramecium* shows an avoiding response if it senses a high temperature area in front of the cell (see Fig. 1(a)). Also, an escape response is shown by increasing ciliary beat frequency as *Paramecium* senses touch by the feeler of a predator on the posterior part of the cell (see Fig. 1(b)). The behavior that protects a body appropriately from the danger elements in the environment is called taxis.

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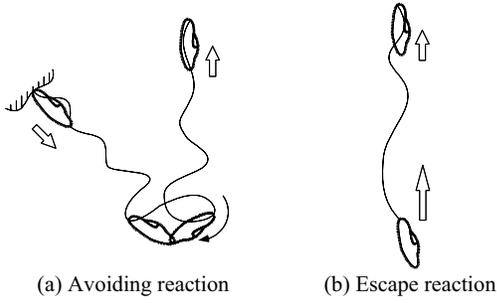


Fig. 1. Avoiding and escape reactions of *Paramecium*

Paramecium processes information by electrophysiological phenomena. Ion channels and ion pumps reside in the membrane, these proteins play an important role in maintaining the ionic connection between the interior and the exterior of the cell. In the cell, the Ca^{2+} concentration is maintained at a level lower than that of the external environment, while the K^+ concentration is maintained at a higher level. In a standard salt solution, the membrane potential is maintained at approximately 30 mV lower than that of the external environment when *Paramecium* does not receive the stimuli from the environment. When *Paramecium* receives a stimulus, the ion channels open and ionic flow occurs between the interior and the exterior of the cell. The membrane potential is then depolarized or hyperpolarized by the ionic flow. We consider that the depolarization of membrane potential occurs when *Paramecium* senses danger in the new environment; on the other hand, the hyperpolarization of membrane potential can be considered to occur when *Paramecium* senses that the new environment is safe. The ciliary movement is determined based on the information processed by the cell.

III. MODEL OF CHEMOTACTIC RESPONSE OF *Paramecium*

The proposed model comprises three units, namely, the sensory unit, information processing unit, and motor control unit. In this section, we describe the detail of each unit.

A. Sensory unit

Fig. 2 illustrates the relationship between the change in membrane potential and environmental changes. It can be considered that a compulsory electrical change in membrane potential, similar to that in the voltage-clamp experiments [11], is generated when the ionic composition of the environment changes (see Fig. 2). For instance, the resting membrane potential rises when the K^+ concentration in the environment increases, and then the potential difference generated between the environment and the interior of the cell decreases (see Fig. 2 A \rightarrow B). An early current is generated as shown in Fig. 2B, when the cell of *Paramecium* is considered as a capacitor. Then, the sensory unit determines the probability of the aperture rate of ion channels that are opened by changed in the environmental conditions.

First, in the sensory unit, the resting membrane potential E_{leak} , which depends on $[\text{Ca}^{2+}]_o$ and $[\text{K}^+]_o$, is calculated

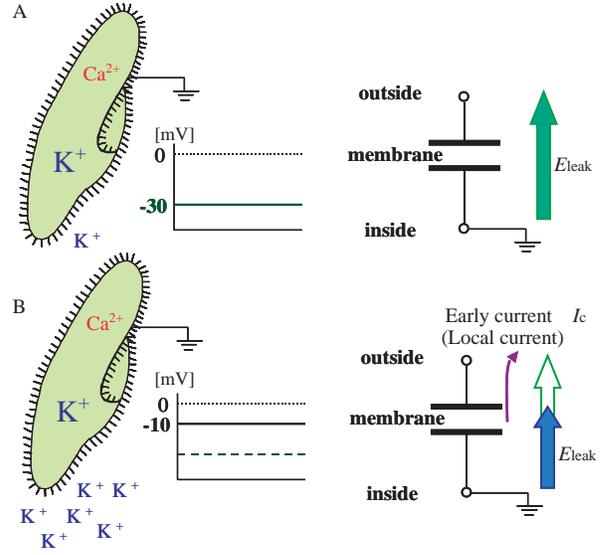


Fig. 2. Depolarization mechanism of *Paramecium*

by using the Goldman-Hodgkin-Katz equation [11]:

$$E_{\text{leak}} = \frac{\alpha_{\text{Ca}} E_{\text{Ca}} + \alpha_{\text{K}} E_{\text{K}}}{\alpha_{\text{Ca}} + \alpha_{\text{K}}}, \quad (1)$$

where α_{Ca} and α_{K} are the existence ratios of the Ca^{2+} and K^+ channels, respectively. Also, E_{Ca} and E_{K} are the equilibrium potentials which are generated by the difference in the concentration of ions inside and outside the cell. These are calculated using the following equation [11]:

$$E_{\text{ion}} = \frac{RT}{cF} \ln \frac{[\text{ion}]_o}{[\text{ion}]_i} \quad (\text{ion} \in \{\text{Ca}^{2+}, \text{K}^+\}), \quad (2)$$

where c is the ionic valency, F the Faraday constant, R the gas constant, and T the absolute temperature. Also, $[\text{ion}]_o$ is the ionic concentration of the environment, and $[\text{ion}]_i$ the intracellular ionic concentration.

Then, the early current $I_c(t)$ is calculated by:

$$I_c(t) = \frac{1}{R_m} (E_{\text{leak}}(t) - V(t)), \quad (3)$$

where R_m is the input resistance of the membrane in *Paramecium*, and $V(t)$ the membrane potential. A positive value of $I_c(t)$ means outflow of current. In this study, it is assumed that the early aperture rate of each ion channel is proportional to the size of $I_c(t)$. The early aperture ratios of the Ca^{2+} channel and the K^+ channel are calculated as follows:

$$O_{\text{Ca}} = \begin{cases} b_{\text{Ca}} I_c & (I_c \geq \text{Th}_1) \\ 0 & (I_c < \text{Th}_1), \end{cases} \quad (4)$$

$$O_{\text{K}} = \begin{cases} 0 & (I_c > \text{Th}_2) \\ -b_{\text{K}} I_c & (I_c \leq \text{Th}_2), \end{cases} \quad (5)$$

where b_{Ca} , b_{K} , Th_1 , and Th_2 are constants. The early aperture rate O_{Ca} of the Ca^{2+} channel increases when the early current is larger than the threshold Th_1 and flows

outwards ($I_c \geq Th_1 > 0$). Conversely, the early aperture rate O_K of the K^+ channel increases when the early current is smaller than the threshold Th_2 and flows inwards ($I_c \leq Th_2 < 0$). Thus, the early aperture rate of each ion channel is determined corresponding to the change in the environmental conditions.

B. Information processing unit

In this unit, the change in membrane potential and the Ca^{2+} concentration in cilia are calculated by the input of the sensory unit. The characteristics of this model can be expressed by the electric circuit as shown in Fig. 3, where the cell membrane and the ion channels are considered as a condenser and active resistive elements, respectively. Fig. 3 illustrates the relationship between the change in membrane potential and current flow into a cell, in which the ion channels are affected by the membrane potential.

First, the electrical characteristics of *Paramecium* are modeled as follows:

$$\dot{V}(t) = \frac{1}{C_m} [I_c(t) - I_{Ca}(t, V) - I_K(t, V) - I_{leak}(t, V)] \quad (6)$$

where $V(t)$ is the membrane potential, $I_c(t)$ is the early current, and C_m is the membrane capacity. The Ca^{2+} current $I_{Ca}(t, V)$, the K^+ current $I_K(t, V)$, and the leakage current $I_{leak}(t, V)$ are given by the following equations [9]:

$$I_{Ca}(t, V) = \bar{g}_{Ca} m^5 \{1 - (1 - h)^5\} (V(t) - E_{Ca}), \quad (7)$$

$$I_K(t, V) = \bar{g}_K n (V(t) - E_K), \quad (8)$$

$$I_{leak}(t, V) = g_{leak} (V(t) - E_{leak}), \quad (9)$$

where \bar{g}_{Ca} , \bar{g}_K , and g_{leak} are the maximum values of the ion conductance for Ca^{2+} , K^+ and leakage ion channels, respectively. Equilibrium potentials for Ca^{2+} , K^+ and leakage ions are expressed as E_{Ca} , E_K and E_{leak} , respectively. Also, m , h and n are the activation probabilities of each ion channel. Activation probabilities, $x \in \{m, h, n\}$, of each channel are calculated based on the Hodgkin-Huxley equations [10] as follows:

$$\begin{aligned} \dot{m}(t, V, O_{Ca}) &= \alpha_m(V, O_{Ca}) \cdot (1 - m(t, V, O_{Ca})), \\ &\quad -\beta_m(V) \cdot m(t, V, O_{Ca}) \end{aligned} \quad (10)$$

$$\begin{aligned} \dot{h}(t, V, O_{Ca}) &= \alpha_h(V, O_{Ca}) \cdot (1 - h(t, V, O_{Ca})), \\ &\quad -\beta_h(V) \cdot h(t, V, O_{Ca}) \end{aligned} \quad (11)$$

$$\begin{aligned} \dot{n}(t, V, O_K) &= \alpha_n(V, O_K) \cdot (1 - n(t, V, O_K)) \\ &\quad -\beta_n(V) \cdot n(t, V, O_K). \end{aligned} \quad (12)$$

O_{Ca} and O_K are the initial open ratios of the Ca^{2+} channel and the K^+ channel calculated by the sensory unit. The complicated change in depolarization is realized by the above mechanism.

Next, the Ca^{2+} concentration in cilia is calculated. Deciliated *Paramecium* whose cilia are removed by chemical treatment is utilized in order to formulate the electrical characteristic of only the cell body. The change in membrane

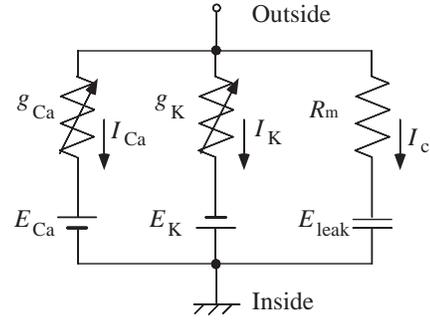


Fig. 3. Electric circuit model for *Paramecium*

potential is given as:

$$\dot{V}(t) = \frac{1}{C_m} [I_c(t) - I_{Ca(cell)}(t, V) - I_K(t, V) - I_{leak}(t, V)], \quad (13)$$

where $I_{Ca(cell)}$ is the current in the cell of the deciliated *Paramecium*, and is defined by the following equation:

$$I_{Ca(cell)} = \bar{g}_{Ca(cell)} m_{(cell)}^5 \{1 - (1 - h_{(cell)})^5\} (V(t) - E_{Ca}), \quad (14)$$

where $\bar{g}_{Ca(cell)}$ is the maximum value of the ion conductance for the Ca^{2+} channel in the cell, and $x_{(cell)}$ ($x \in \{m, h\}$) is the activation probability in only the cell body defined by:

$$\begin{aligned} \dot{x}_{(cell)}(t, V, O_{Ca}) &= \alpha_{x_{(cell)}}(V, O_{Ca}) \\ &\quad \cdot (1 - x_{(cell)}(t, V, O_{Ca})) \\ &\quad - \beta_{x_{(cell)}}(V) \cdot x_{(cell)}(t, V, O_{Ca}). \end{aligned} \quad (15)$$

By using both $I_{Ca(cell)}$ and the Ca^{2+} current I_{Ca} in the whole *Paramecium*, the Ca^{2+} current in cilia $I_{Ca(cilia)}$ is expressed as:

$$I_{Ca(cilia)} = I_{Ca} - I_{Ca(cell)}. \quad (16)$$

Thus, the ionic flow of Ca^{2+} in the cell body and that in cilia can be separated. Finally, the Ca^{2+} concentration in cilia is calculated as follows [12]:

$$\frac{d[Ca^{2+}]_{in}}{dt} = -\frac{1}{2F} [I_{Ca(cilia)} + (I_p)_{Ca}], \quad (17)$$

$$(I_p)_{Ca} = 2F \frac{(\bar{J}_p)_{Ca}}{1 + \left(\frac{K_m}{[Ca^{2+}]_{in}}\right)^3}, \quad (18)$$

where $[Ca^{2+}]_{in}$ is the Ca^{2+} concentration in cilia, F the Faraday constant, $(\bar{J}_p)_{Ca}$ the maximum active Ca^{2+} extrusion, and K_m the $[Ca^{2+}]_{in}$ at which the active Ca^{2+} extrusion is at half its maximum value. Also, $(I_p)_{Ca}$ is the current produced by the Ca^{2+} pump which discharges Ca^{2+} to the exterior of the cell, and it is assumed that $(I_p)_{Ca}$ is included in I_{leak} calculated by Eqs. (9) for simplicity.

C. Motor control unit

The swimming condition of *Paramecium* depends on the ciliary beat direction and its frequency. It is easy to understand the direction of the ciliary beat of *Paramecium* by considering the front of *Paramecium* as the direction of 12 o'clock on an analog clock as shown in Fig. 4(a) [11]. As *Paramecium* senses stimuli, the direction of the ciliary beat changes between half past six and 12 o'clock, while it is half past four in the normal condition (see Fig. 4(a)). The swimming velocity increases when the ciliary beat direction approaches 6 o'clock. Also, *Paramecium* goes backwards as the ciliary beat direction approaches 12 o'clock. The ciliary beat direction is regulated by the Ca^{2+} concentration in cilia [13]. Therefore, the ciliary beat direction $\phi([\text{Ca}^{2+}]_{in})$ is modeled as the following functions of $[\text{Ca}^{2+}]_{in}$:

$$\begin{aligned} \phi([\text{Ca}^{2+}]_{in}) &= \pi \left(\frac{1}{A_\phi \log_{10}([\text{Ca}^{2+}]_{in})} - 0.5 \right) \\ &\quad (A_\phi = A_{\phi 1} \quad ([\text{Ca}^{2+}]_{in} < C_\phi)) \\ &\quad (A_\phi = A_{\phi 2} \quad ([\text{Ca}^{2+}]_{in} \geq C_\phi)), \end{aligned} \quad (19)$$

where $A_{\phi 1}$ and $A_{\phi 2}$ are constants that determine the direction of the ciliary beat, and C_ϕ is the concentration value of $[\text{Ca}^{2+}]_{in}$ when the direction of the ciliary beat approaches 3 o'clock.

The ciliary beat frequency is regulated by the membrane potential. Although the steady-state frequency of the ciliary beat is 10-20 Hz, it is increased to about 50 Hz corresponding to the change in membrane potential [14], [15]. In addition, the ciliary beat frequency decreases when the Ca^{2+} concentration increases to more than $10^2 \mu\text{M}$ [11]. Therefore, the ciliary beat frequency, $f(V, [\text{Ca}^{2+}]_{in})$, is modeled as the following equations of the membrane potential:

$$f(V, [\text{Ca}^{2+}]_{in}) = f(V) - f([\text{Ca}^{2+}]_{in}), \quad (20)$$

$$f(V) = f_0 + A_{f1} (|A_{f req} - V(t)|)^{A_{f2}}, \quad (21)$$

$$f([\text{Ca}^{2+}]_{in}) = \left(\frac{f_{max}}{1 + \exp(A_{f3} \log_{10}(A_{f4} [\text{Ca}^{2+}]_{in}))} \right), \quad (22)$$

where A_{fi} ($i = 1, 2, 3, 4$) are constants, f_0 the steady-state value of ciliary beat frequency, f_{max} the maximal value, and $A_{f req}$ the membrane potential value during the resting beat frequency. The driving force F is calculated as follows:

$$F = a_0 f(V, [\text{Ca}^{2+}]_{in}), \quad (23)$$

where a_0 is the coefficient which transforms the ciliary beat frequency into the driving force F in *Paramecium*. On the other hand, the driving force parallel to the longitudinal axis of the body is calculated by $f_f = F \sin \phi([\text{Ca}^{2+}]_{in})$, and the driving force perpendicular to the axis is $f_s = F \cos \phi([\text{Ca}^{2+}]_{in})$ (see Fig. 4(b)). The velocity of *Paramecium* is calculated by:

$$v_i = -a_1 f_i \quad (i \in f, s), \quad (24)$$

where v_f is the velocity in the longitudinal direction of the body, v_s that in the perpendicular direction, and the coefficient a_1 which transforms the driving forces into velocity.

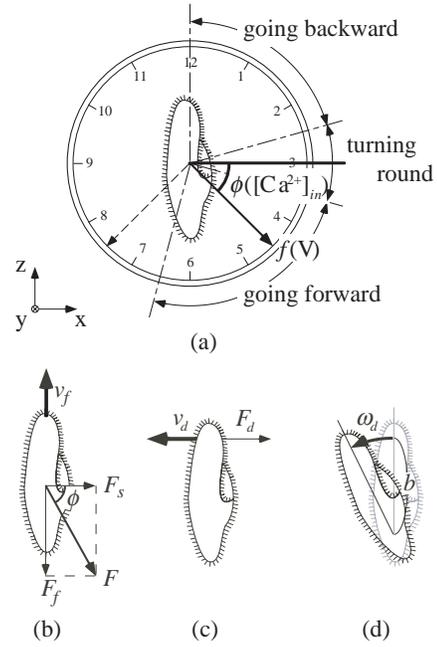


Fig. 4. Ciliary beat direction and ciliary beat frequency [11]

Also, when *Paramecium* is regarded as an ellipsoid, the rotational angular velocity, ω_s , is given by:

$$\omega_s = \frac{v_s}{r}, \quad (25)$$

where the central axis is the longitudinal axis of the body and the radius is r .

In addition to the ciliary beat, the particular ciliary movement around the peristome also generates the force f_d , which is perpendicular to the longitudinal axis as shown in Fig. 4(c). The velocity v_d , which is perpendicular to the longitudinal axis, and the turning angle velocity ω_d by v_d are given by the following equations:

$$v_d = -a_2 f_d, \quad (26)$$

$$\omega_d = \frac{v_d}{b}, \quad (27)$$

where a_2 is a coefficient which transforms f_d into v_d , and b is the distance between the fulcrum of rotation and the point of application of f_d (see Figure 5(d)). The motion of *Paramecium* can be calculated by v_f , ω_s and ω_d .

As described above, a model for the internal information transmission from the reception of the external stimulus to the motion of *Paramecium* has been produced.

IV. SIMULATION OF CHEMOTACTIC RESPONSE

A. Determination of parameters

The parameters were set in order to carry out the computer simulation with the proposed chemotactic model for *Paramecium*. First, the parameters included in Eqs. (1) to (4) were determined based on Reference[11] as follows: $[\text{K}^+]_i = 20 \text{ mM}$, $[\text{Ca}^{2+}]_i = 10^{-8} \text{ M}$. The intracellular concentrations of Ca^{2+} and K^+ in standard salt solution can be calculated by Eq. (2) from the value of the equilibrium potential described

in Reference[11]. The parameters R_m , b_{Ca} and b_K were set by trial and error as follows: $R_m = 10^9 \Omega$, $b_{Ca} = 0.721$, $b_K = 1.0$. Also, the parameters included in Eqs. (6) to (18) were determined based on the measurements by Naito[11], [9]. The ciliary beat direction $\phi([Ca^{2+}]_i)$ and the parameters for the driving force by the ciliary beat frequency $f(V)$, $A_{\phi 1}$, $A_{\phi 2}$, A_{freq} , and f_0 were determined by both the video of the motion of *Paramecium* and References[13], [11] as follows: $A_{\phi 1} = 0.35$, $A_{\phi 2} = 10^6$, $A_{freq} = -30.0\text{mV}$, $f_0=15.0$. Also, $r = 25 \mu\text{m}$ because the width of *Paramecium* is about $50 \mu\text{m}$.

B. Characteristics of the membrane potential in *Paramecium*

Simulation experiments were executed to verify the characteristics of membrane potential when the value of $[K^+]_o$ was changed. Fig. 5(a) show the resting membrane potential (●) and the maximum value of the saturation at depolarization (○) of actual *Paramecium* when the K^+ concentration of the environment was changed [17]. Fig. 5(b) show the relationship between the change in the resting membrane potential (●) and the maximum value of the saturation at depolarization (○) of the proposed model. The full line in each figure was calculated by the least-squares method. From Fig. 5, it was confirmed that the actual characteristics of the membrane potential can be approximately realized by the proposed model.

C. Behavior of *Paramecium* depending on the K^+ concentration in environment

Next, the behavior of the proposed model to the change in ion composition in environment was examined. The experiments were carried out on *Paramecium* according to the following procedures.

- 1) The silicon seat of about 1 mm in thickness is turned over like a rectangle of 1 mm in length and 10 mm in width. The left side is filled with test solution, and the right side is filled with standard salt solution ($[K^+]_o = 4 \text{ mM}$).
- 2) *Paramecium* that adapted to the standard salt solution in advance is transferred onto the right area with the dropper.
- 3) The behaviors in the test solution and the boundary of two solutions are observed.

The left side of Fig. 6(a) to (c) shows the trajectories of *Paramecium*, and the right side shows the time course of swimming velocities for the test solution. Fig. 6(c) is an experimented result after the individual in Fig. 6(b) collided with the wall at the left end. Since the movements in three-dimensional space were observed in the horizontal plane, a true swimming velocity of *Paramecium* could not be measured. Then, the swimming velocity was calculated from the amount of movement in the center of gravity in the two-dimensional video image data, where the difference between forward and backward movements was not considered.

Fig. 6(a) shows the escape reaction of *Paramecium* from the area where the K^+ concentration is higher than the standard salt solution. Also, *Paramecium* showed accelerated swimming velocity where the K^+ concentration was lower

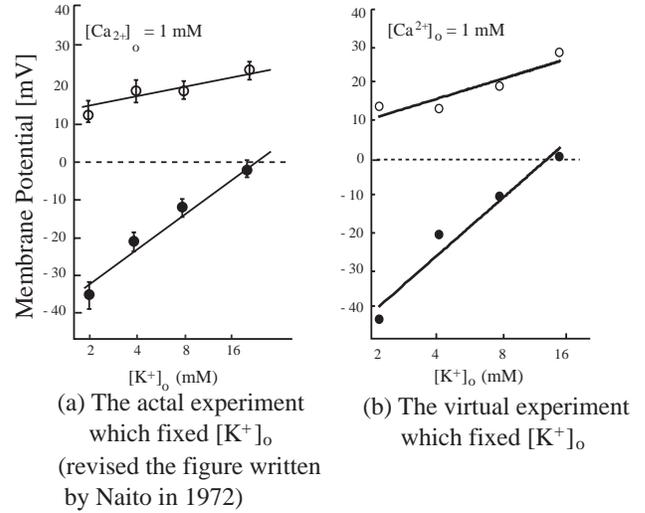


Fig. 5. Characteristics of the membrane potential toward Ca^{2+} and K^+ in the environment

than the standard salt solution (see Fig. 6(b)). Furthermore, in Fig. 6(c), the escape reaction to the area of standard salt solution is shown after swimming in the environment with low K^+ concentration for a while.

The computer simulation was carried out to confirm that the behavior of actual *Paramecium* can be realized by the proposed model. The results when K^+ concentrations of the stimulation solution were set to 8 mM and 0.5 mM are shown in Fig. 7(a) and (b), respectively. The swimming velocity of the model was calculated in the motor control unit, and the negative velocity means backward movement. The escape reaction was observed to the area where the K^+ concentration was higher. Also, it was confirmed that the swimming velocity increased in the area where the K^+ concentration was higher than the standard salt solution, and *Paramecium* tries to stay in the area. From the above results, it can be stated that the proposed model was able to realize the behavior based on the internal processing system.

V. CONCLUSION

The characteristics of the membrane potential in *Paramecium* are varied by the Ca^{2+} and K^+ concentrations in environment, and the rapid change in Ca^{2+} and K^+ concentrations in environment act as a trigger for the chemotactic response of *Paramecium*. In this paper, a new model for the internal processing system in *Paramecium* is proposed to realize the change in membrane potential corresponding to the Ca^{2+} and K^+ concentrations in environment. Also, the motor control unit controlled by the internal processing system was proposed. It was confirmed that the actual characteristics of the membrane potential and behavior can be approximately realized by the proposed model. It may be necessary to include other ions as well as Ca^{2+} and K^+ in the membrane model. Future research will be directed to propose a more detailed model that considers electrical

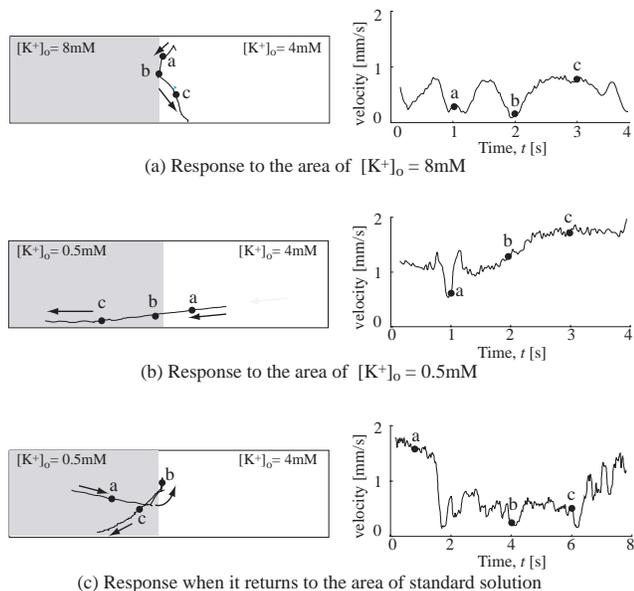


Fig. 6. Chemotactic responses of actual *Paramecium* to the change in K^+ concentration in the environment

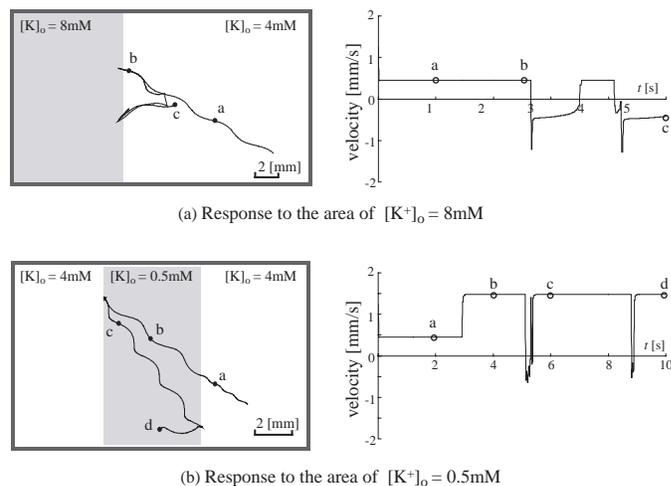


Fig. 7. Chemotactic responses of the proposed model to the change in K^+ concentration in the environment

stimuli from various ions. Then it is aimed to develop a response simulator of *Paramecium* not only to chemicals but also to electric field stimulation.

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