Effect of the slow transient phenomenon of a synaptic modification on vestibulo-ocular reflex adaptation

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According to the experimental studies, the duration of the transient phenomenon of the synaptic modification involved in vestibulo-ocular reflex (VOR) adaptation lasts considerably long after the synaptic inputs. In the present article, effect of the transient phenomenon on VOR adaptation is studied by incorporating the transient phenomenon into the cerebellar model proposed by Fujita. In the present extended model, it is assumed that the synaptic modification is a modification of the concentrations of reactants and products for a certain reaction. The synaptic efficacy is given by the concentration of products. The model of reaction includes the supply of reactants and flux of reactants and products out of the reaction system. The supply of reactants is induced by correlation between two different types of input signals, which has been considered to be proportional to the amount of the synaptic modification at the moment. The flux produces natural recovery of the synaptic modification, which was observed in experiments. The simulation results suggest that VOR adaptation takes two types of courses according to the efficiency of the reactant supply to the synaptic inputs under the slow transient phenomenon of the synaptic modification. The present extended model gives approaches to control mechanisms of VOR adaptation. [S1063-651X(98)06005-X]

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I. INTRODUCTION

The vestibulo-ocular reflex (VOR) produces eye movements compensatory for head rotation, stabilizing retinal images of the visual surround. A schematic diagram of the neural circuit for the VOR is shown in Fig. 1. The semicircular canals sense head rotation and send output signals proportional to the head angular velocity. The output signals are carried to the eye muscles via the vestibular nucleus and move the eyeballs in the opposite direction to head rotation. When there is retinal image slip, VOR adaptation is induced to reduce the retinal image slip. VOR adaptation is considered to be induced by synaptic modifications of parallel fiber-Purkinje cell transmission in the cerebellar cortex [1]. Purkinje cells in the cerebellar cortex receive the signals from the semicircular canals via parallel fibers and the information of retinal image slip via climbing fibers, and then send inhibitory signals to the vestibular nucleus; the cerebellar cortex forms a side path to the VOR arc. The correlation between the parallel fiber input and the climbing fiber input induces the synaptic modification of parallel fiber-Purkinje cell transmission.

Based on these facts, Fujita proposed an adaptive filter model of the cerebellum and applied it to VOR adaptation [2,3]. In this model, the cerebellum performs a filtering action of a phase lead or lag compensator to the output signal, and has a learning capability to realize an optimum filtering function. It was shown that characteristics of VOR adaptation were successfully simulated, using the adaptive filter model, except for such problems as we discuss in the present article.

On the other hand, the previous experimental data on the modification of the parallel fiber-Purkinje cell synapse indicate that the transient phenomenon of the synaptic modification lasts several tens of minutes after the synaptic inputs [4,5]. This time is much longer than the time duration of the synaptic inputs required for the synaptic modification: the synaptic modifications in the experiments by Sakurai were induced by conjunctive climbing fiber-parallel fiber stimulation at 4 Hz for 25 s or parallel fiber stimulation at 4 Hz for 25 s [5]. Accordingly, the input signals continue to arrive at the synapse in the middle of the transient phenomenon of the synaptic modification. Thus, it seems that the information about the synaptic efficacy in the middle of the transient phenomenon has important an effect on the process of VOR adaptation. However, Fujita's model of the synaptic modification disregards the transient phenomenon. The present study will attempt to incorporate the transient phenomenon into Fujita's model and consider its effect on VOR adaptation.

II. METHODS

To begin with, Fujita's adaptive filter model is described [2,3]. Neuronal signals are represented by deviations of dis-

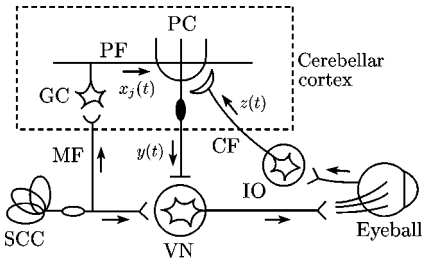

FIG. 1. Schematic diagram of the neural circuit for the VOR. SCC: semicircular canals, VN: vestibular nucleus, MF: mossy fiber, GC: granule cell, PF: parallel fiber, PC: Purkinje cell, CF: climbing fiber, IO: inferior olive, $x_j(t)$: parallel fiber input signal (the subscript j represents one of many parallel fiber inputs to a single Purkinje cell), $y(t)$: Purkinje cell output signal, $z(t)$: climbing fiber input signal.

charge rates from the spontaneous discharge rates. The Purkinje cell output (at time t) $y(t)$ is assumed to be a linear weighted summation of its parallel fiber inputs $x_j(t)$:

$$y(t)=\sum_{j=1}^{L} w_j(t)x_j(t), \tag{1}$$

where $w_j(t)$ is the efficacy of the jth parallel fiber-Purkinje cell synapse and L represents the number of parallel fiber-Purkinje cell synapses. The model includes a single Purkinje cell and so $y(t)$ has no subscript. The modification of the parallel fiber–Purkinje cell synapse is described as

$$\frac{dw_j(t)}{dt}=-\epsilon z(t)[x_j(t)+x_0], \tag{2}$$

where ϵ is a sufficiently small positive constant, $z(t)$ is the climbing fiber input, and x_0 denotes the spontaneous discharge rate of the parallel fiber. In practical computations, the changes in $w_j(t)$ are calculated at regular intervals (represented by T):

$$w_j(t)-w_j(nT-\Delta t)=0 \quad \text{for } t=nT, \tag{3}$$

$$w_j(t)-w_j(nT-\Delta t)=-\epsilon\int_{(n-1)T}^{nT} z(t')[x_j(t')+x_0]dt'$$

$$\text{for } nT<t<(n+1)T, \tag{4}$$

where n denotes an integral number and $0<\Delta t<T$. The climbing fiber input $z(t)$ is defined by

$$z(t)=y(t)-c(t), \tag{5}$$

where $c(t)$ is the Purkinje cell output to perfectly stabilize the retinal image. This model involves no recovery of the synaptic efficacy change, whereas the recovery was observed in experiments [4,5].

If the angular velocity of horizontal head rotation $\omega_H(t)$ is sinusoidal (with the normalized amplitude):

$$\omega_H(t)=\mathrm{Re}[e^{i\omega t}]$$

$$\equiv \mathrm{Re}[H(\omega,t)], \tag{6}$$

where ω denotes the angular frequency of the sinusoidal head rotation and $H(\omega,t)$ denotes the complex representation of the sinusoidal head angular velocity: $H(\omega,t)=\exp(i\omega t)$, then $x_j(t)$, $y(t)$, $c(t)$ and the angular velocity of eye rotation $\omega_E(t)$ are expressed as

$$x_j(t)=\mathrm{Re}\left[\frac{1}{2}\left(a_j-\frac{2}{2+i\omega T_g}\right)G_c(\omega)H(\omega,t)\right], \tag{7}$$

$$y(t)=\mathrm{Re}\left[\frac{1}{2}G_f(\omega)G_c(\omega)H(\omega,t)\right], \tag{8}$$

$$c(t)=\mathrm{Re}\left[\left(\frac{1}{2}G_c(\omega)-\frac{1}{G_1(\omega)}\right)H(\omega,t)\right], \tag{9}$$

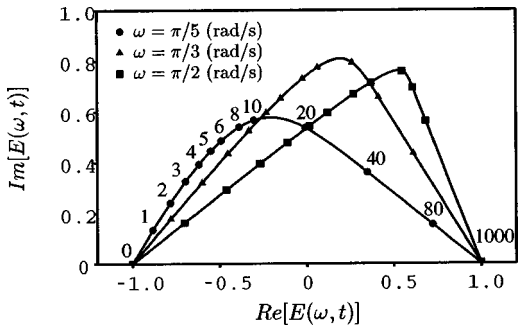

FIG. 2. Simulation results of VOR adaptation associated with left-right reversing prisms by Fujita's model. $\epsilon TL/4=0.1$. The numbers at data points in $\omega=\pi/5$ (rad/s) indicate the times from the starting point (unit T). The times of data points in $\omega=\pi/3$ (rad/s) and $\omega=\pi/2$ (rad/s) are the same as the corresponding data points in $\omega=\pi/5$ (rad/s). The initial ratio of the attenuation of VOR gain to the phase decrease increases with ω.

$$\omega_E(t)=\mathrm{Re}\left[-\frac{1}{2}G_1(\omega)G_c(\omega)[1-G_f(\omega)]H(\omega,t)\right], \tag{10}$$

where

$$G_c(\omega)=\frac{i\omega T_c}{1+i\omega T_c}, \tag{11}$$

$$G_f(\omega)=\sum_{j=1}^{L} w_j(t)\left(a_j-\frac{2}{2+i\omega T_g}\right), \tag{12}$$

$$G_1(\omega)=\left(1-\frac{kA}{1+i\omega T_o}\right)^{-1}, \tag{13}$$

$T_g=4$ (s), $T_c=5.7$ (s), $T_o=7$ (s), $k=0.96$, $A=0.8$, and a_j's are constants and take values from 0.4 to 1.6. For horizontal sinusoidal head rotation, the perfect VOR has a gain (eye angular velocity amplitude/head angular velocity amplitude) of 1.0 and a phase (of eye angular velocity relative to head angular velocity) of π (rad). VOR gain and phase will be expressed by the complex representation $E(\omega,t)$: $E(\omega,t)=-1$ in this case. From Eq. (10), $E(\omega,t)$ is defined by

$$E(\omega,t)=-\tfrac{1}{2}G_1(\omega)G_c(\omega)[1-G_f(\omega)]. \tag{14}$$

When vision is horizontally reversed by wearing left-right reversing prisms, the normal perfect VOR causes retinal image slip twice the head angular velocity and consequently VOR adaptation is induced. In this case $c(t)$ is expressed as

$$c(t)=\mathrm{Re}\left[\left(\frac{1}{2}G_c(\omega)+\frac{1}{G_1(\omega)}\right)H(\omega,t)\right]. \tag{15}$$

The improved perfect VOR, the VOR when adaptation to vision reversal is complete, has a gain of 1.0 and a phase of 0 (rad): $E(\omega,t)=1$. With subsequent removal of the prisms VOR gain and phase return to the normal value; in the readaptation process $c(t)$ is expressed as Eq. (9). In the following, we will mainly take up the adaptation process while wearing the prisms. Figure 2 shows the simulation results of VOR adaptation associated with the prisms by Fujita's

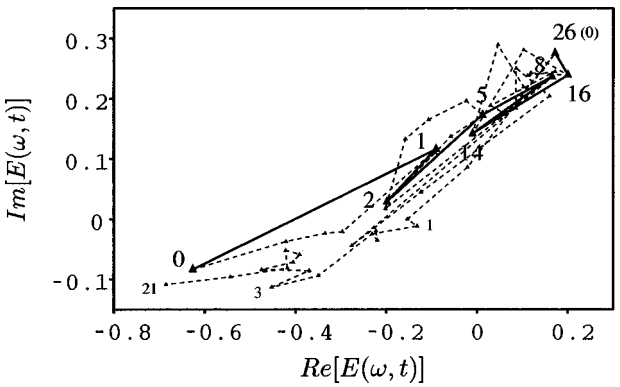

FIG. 3. Experimental data of the VOR gain and phase changes during adaptation to left-right reversing prisms and readaptation after removal of the prisms, reconstructed from Table I of Gonshor and Melvill Jones [6] by the author. $\omega=\pi/3$ (rad/s). The broken line shows all the original data, and the solid line is presented to make it easy to see the characteristics of the adaptation to the prisms. The large numbers at data points indicate the numbers of days spent after wearing the prisms and the small ones indicate the numbers of days after removal of the prisms. The large numbers 0, 1, 2, 5, 8, 14, 16, and 26 (small number 0) correspond to 2*A*(day)/11(time), 3*A*/10, 4/10, 7*A*/10, 10*A*/10, 16*B*/17, 18/11, and 28*B*/15 and the small ones 1, 3, and 21 to 29*A*/14, 31*B*/17, 49/13 in Table I.

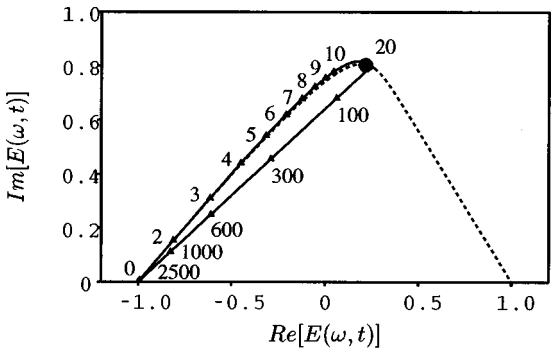

FIG. 4. Simulation result of the recovery of the VOR after adaptation to left-right reversing prisms by the present extended model. $\omega=\pi/3$ (rad/s), $\epsilon' T' L/4=0.1$, $k_{pr}T'=2$, $k_{rp}T'=k_r T'=k_p T'=0.002$. The numbers at data points indicate the times from the starting point (unit T'). The closed circle at time 20 indicates the arrival point of VOR adaptation to the prisms. Beyond that point $x_j(t)=z(t)=0$. The broken line represents the adaptation course with $\omega=\pi/3$ (rad/s) in Fig. 2.

model, and Fig. 3 shows the experimental data of the VOR gain and phase changes during adaptation to the prisms and readaptation after removal of the prisms by Gonshor and Melvill Jones [6]. In the simulations, it is assumed that the time required for VOR adaptation is much longer than the signal period and phases of $x_j(t)$'s relative to $\omega_H(t)$ are uniformly distributed between their minimum and maximum and, for simplicity, gains of $x_j(t)$'s relative to $\omega_H(t)$ are replaced with 1. The phase and the gain are given, from Eq. (7), by $\arg\{[a_j-2/(2+i\omega T_g)]G_c(\omega)/2\}$ and $|[a_j-2/(2+i\omega T_g)]G_c(\omega)/2|$, respectively. The initial attenuation and the following recovery of gain with decreasing phase in Fig. 2 are in good agreement with Fig. 3. However, the improved perfect VOR as in Fig. 2 has not been observed [6–9], and also the simulation by using Fujita's model cannot reproduce the recovery of the adaptively modified VOR observed when the subject's head was immobilized in the dark [7,8].

Then, we incorporate the transient phenomenon into Fujita's model of the synaptic modification. In order to simplify modeling, let us consider the synaptic modification to be a modification of the concentrations of reactants and products for a certain reaction. The concentrations of reactants and products of the jth synapse are designated by $C_j(t)$ and $C'_j(t)$, respectively. The synaptic efficacy $w_j(t)$ is proportional to $C'_j(t)$:

$$\alpha w_j(t)\equiv C'_j(t), \tag{16}$$

where α is a formal constant for the connection between the synaptic efficacy and the concentration of products. It is assumed that the reactants are supplied at T' intervals by the correlation between the parallel fiber input $x_j(t)$ and the climbing fiber input $z(t)$, such that

$$\Delta C_j(nT')\equiv -\alpha\epsilon'\int_{(n-1)T'}^{nT'} z(t')[x_j(t')+x_0]dt' \quad \text{for } n=1,\ldots, \tag{17}$$

where $\Delta C_j(nT')$ denotes the amount of concentration change of reactants by supply at $t=nT'$, α is the above formal constant, and ϵ' denotes efficiency of the reactant supply to the synaptic inputs. $t=0$ is the starting point for the synaptic modification. Furthermore, it is assumed that the reaction includes flux of reactants and products out of the reaction system. For simplicity, we assume that the flux at time t is proportional to the difference in concentrations between t and the beginning, which is similar in form to diffusion through a thin membrane.

Biological bases of the present extended model are as follows. Recent experiments suggest that Ca^{2+} inflow into the Purkinje cell, which is evoked by the climbing fiber input, would trigger the synaptic modification [10,11]. One possibility to link the Ca^{2+} inflow to the synaptic modification on the basis of current knowledge of synaptic transmission is that the Ca^{2+} inflow enhances the cGMP level in the Purkinje cell and the transmitter receptors at parallel fiber-Purkinje cell synapses will be desensitized under conjoint influences of cGMP from the inside and the transmitters from the outside [11]. On these bases, we could consider the reactants as the mixture of Ca^{2+} ions and the transmitters and the products as the changed receptors; the flux of the reactants could be considered as the diffusion of Ca^{2+} ions through membrane pumps, etc. and that of the transmitters out of the synapse. Whereas the products, that is, the changed receptors, might have no flux, this alteration would make no essential change to the present results.

The flux of the reactants or the products naturally produces the recovery of the synaptic modification, therefore, that of the VOR after adaptation to the prisms. The condition that the subject's head is immobilized in the dark corresponds to $x_j(t)=z(t)=0$ in the present model. Hence, $\Delta C_j(t)=0$ during the recovery period. Figure 4 shows the simulation result of the recovery of the adaptively modified

VOR obtained by the present extended model. After the VOR gain and phase changes up to the closed circle with adaptation to the prisms, it recovers straight to the original level. The straight recovery is due to a characteristic of the present model that the flux of reactants or products is proportional to a deviation of the concentration from the initial concentration. The rate equations of the present reaction are given by

$$\frac{dC_j(t)}{dt} = -(k_{pr}+k_r)[C_j(t)-C_j(0)]+k_{rp}[C'_j(t)-C'_j(0)] + F(t), \tag{18}$$

$$\frac{dC'_j(t)}{dt} = k_{pr}[C_j(t)-C_j(0)]-(k_{rp}+k_p)[C'_j(t)-C'_j(0)], \tag{19}$$

$$F(t) \equiv \sum_{k=1}^{n} \delta(t-kT')\Delta C_j(kT') \quad \text{for } nT' \leq t < (n+1)T', \tag{20}$$

where $C_j(0)$ and $C'_j(0)$ are the initial values of $C_j(t)$ and $C'_j(t)$, k_{pr} is a forward reaction rate constant, k_{rp} is a reverse reaction rate constant, $k_r[C_j(t)-C_j(0)]$ and $k_p[C'_j(t)-C'_j(0)]$ are the magnitudes of the flux of reactants and products, and $\delta(\cdot)$ is the Dirac delta function.

When $k_{rp}=k_r=k_p=0$, Eqs. (18) and (19) reduce to

$$\frac{dC_j(t)}{dt} = -k_{pr}[C_j(t)-C_j(0)]+F(t), \tag{21}$$

and

$$\frac{dC'_j(t)}{dt} = k_{pr}[C_j(t)-C_j(0)]. \tag{22}$$

From Eqs. (21) and (20) we derive

$$C_j(t)-C_j(0) = \sum_{k=1}^{n} \theta(t-kT')e^{-k_{pr}(t-kT')}\Delta C_j(kT'), \tag{23}$$

where $\theta(\cdot)$ is the Heaviside step function. Inserting Eq. (23) into Eq. (22) and using Eqs. (16) and (17) we obtain

$$\begin{aligned} w_j(t)-w_j(nT'-\Delta t) &= -\epsilon' \sum_{k=1}^{n} \theta(t-kT')(1-e^{-k_{pr}(t-kT')}) \\ &\times \int_{(k-1)T'}^{kT'} z(t')[x_j(t')+x_0]dt' \\ &+ \epsilon' \sum_{k=1}^{n-1} \theta(nT'-kT'-\Delta t)(1-e^{-k_{pr}(nT'-kT'-\Delta t)}) \\ &\times \int_{(k-1)T'}^{kT'} z(t')[x_j(t')+x_0]dt', \end{aligned} \tag{24}$$

where $0<\Delta t<T'$. Taking the limit of $k_{pr}\to\infty$ we find

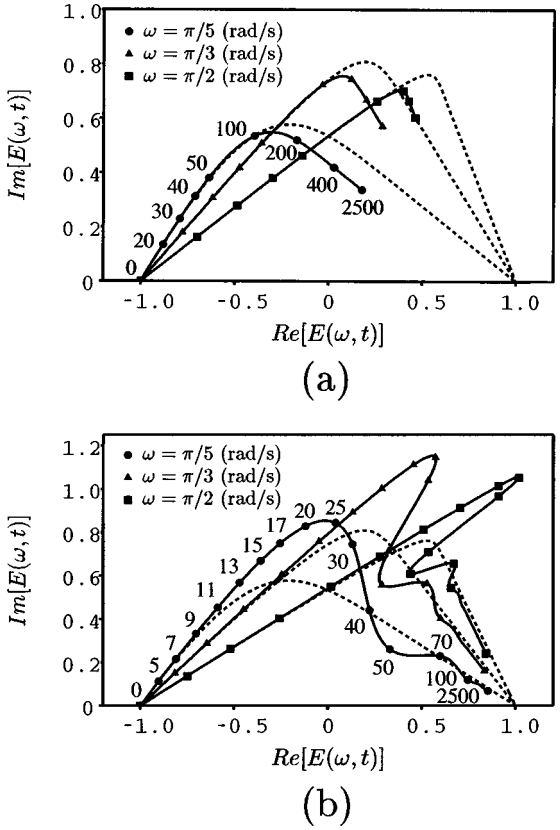

FIG. 5. Simulation results of VOR adaptation associated with left-right reversing prisms by the present extended model. (a) $\epsilon' T' L/4=0.01$, $k_{pr}T'=0.1$, $k_{rp}T'=k_rT'=k_pT'=0.002$. (b) $\epsilon' T' L/4=0.1$, $k_{pr}T'=0.1$, $k_{rp}T'=k_rT'=k_pT'=0.002$. The numbers at data points in $\omega=\pi/5$ (rad/s) indicate the times from the starting point (unit T'). The times of data points in $\omega=\pi/3$ (rad/s) and $\omega=\pi/2$ (rad/s) are the same as the corresponding data points in $\omega=\pi/5$ (rad/s). The broken lines represent the adaptation courses in Fig. 2.

$$w_j(t)-w_j(nT'-\Delta t)=0 \quad \text{for } t=nT', \tag{25}$$

$$w_j(t)-w_j(nT'-\Delta t) = -\epsilon' \int_{(n-1)T'}^{nT'} z(t')[x_j(t')+x_0]dt' \quad \text{for } nT'<t<(n+1)T'. \tag{26}$$

This result is equivalent to Eqs. (3) and (4). Thus, we can conclude that the present extended model returns to Fujita's model as $k_{rp}=k_r=k_p=0$ and $k_{pr}\to\infty$.

III. RESULTS

We are now concerned with the case where the transient phenomenon of the synaptic modification is much longer than the signal period: $\omega/k_{pr}>2\pi$ (rad). In this case, the simulation results of VOR adaptation can be divided into two types according to the magnitude of ϵ': the efficiency of the reactant supply to the synaptic inputs. Figures 5(a) and 5(b) show the two typical results for adaptation to left-right reversing prisms. As ϵ' becomes greater, the simulation result transforms from the *a* type into the *b* type. In the simulations, it is assumed that T' is much longer than the signal period, that is, the reactant supply requires the synaptic in-

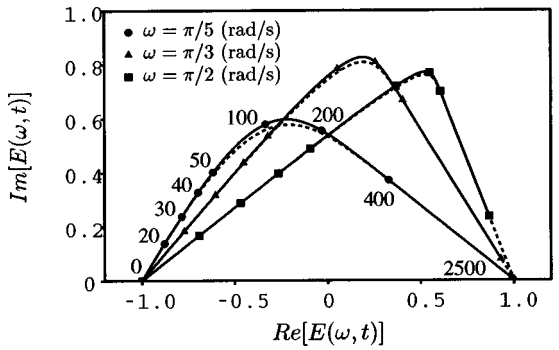

FIG. 6. Simulation results of VOR adaptation associated with left-right reversing prisms by the present extended model when ϵ' is sufficiently small and the flux of reactants and products does not exist. $\epsilon' T'L/4=0.01$, $k_{pr}T'=0.1$, $k_{rp}T'=0.002$, $k_rT'=k_pT'=0$. The numbers at data points in $\omega=\pi/5$ (rad/s) indicate the times from the starting point (unit T'). The times of data points in $\omega=\pi/3$ (rad/s) and $\omega=\pi/2$ (rad/s) are the same as the corresponding data points in $\omega=\pi/5$ (rad/s). The broken lines represent the adaptation courses in Fig. 2.

puts of much longer duration than the signal period. This assumption can be a good approximation because variation of the synaptic efficacy with time is sufficiently slow. While the adaptation process in Fig. 5(b) ends off on the way with oscillation, that in Fig. 5(a) ends off on the way without oscillation. The oscillation is caused by the accumulation of an extra supply of reactants, induced by the slow transient phenomenon of the synaptic modification. This effect disappears as ϵ' becomes smaller. On the other hand, it is due to the reverse reaction and the flux of reactants or products that the adaptation process ends off on the way. Especially, the adaptation course with the flux deviates inside that reachable to the improved perfect VOR. The adaptation course without the flux is along that reachable to the improved perfect VOR, as Fig. 6 shows. The tendency in Figs. 5 and 6 for the initial ratio of the attenuation of VOR gain to the phase decrease to increase with ω is the same as Fig. 2.

IV. DISCUSSION

As Fujita himself stated [3], one problem of Fujita's adaptive filter model is that Eq. (2) contains no natural attenuation property. The present extended model provides one prescription for this problem and produces natural recovery of the adaptively modified VOR. In addition, the model gives the following vision of VOR adaptation. If the adaptation course has oscillation, it might be because the efficiency of the reactant supply to the synaptic inputs is high. Whereas there is no satisfactory evidence of the oscillation, it was reported that a VOR phase fluctuates throughout the adaptation course [6,8,9]. On the other hand, if the adaptation course has no oscillation, it might suggest that the efficiency of the reactant supply to the synaptic inputs is controlled to be so low as to mask the effect of the slow transient phenomenon of the synaptic modification, that is, the accumulation of extra supply of reactants. The evidence for such a control mechanism as masks extra information and extracts only meaningful one was discovered in the primary visual cortex [12].

The adaptive processes by Fujita's model certainly reach maximum adaptation, but maximum adaptation to the prisms was not observed in previous experiments [6–9]. According to the present model, the reverse reaction and the flux of reactants or products stop the adaptive change associated with the prisms on the way, and the latter deviates the adaptation course inside that reachable to the improved perfect VOR. These give new ways to understand that the maximum adaptation was not observed and the adaptation processes seem to have stopped in the low-gain state [6–9]. The difference between the effect of the reverse reaction and that of the flux of reactants or products is distinguishable, as mentioned above. On the other hand, the readaptation course with normal vision is along that reachable to the normal perfect VOR owing to the form of $C_j(t)-C_j(0)$ and $C'_j(t)-C'_j(0)$ in Eqs. (18) and (19). The readaptation process with the flux always reaches the normal perfect VOR.

It was reported that adaptation rapidly acquired rebounded during periods without visual-vestibular activity, as Fig. 4 shows, but after long-term adaptive regulation this rebound disappeared and the adaptation appeared relatively permanent [7,8]. If the adaptation becomes really permanent, it would implicate that $C_j(0)$ and $C'_j(0)$ in Eqs. (18) and (19) must be replaced with the values for the permanent state or k_r and k_p in Eqs. (18) and (19) must be replaced with 0. These seem to produce further adaptation and eventually the improved perfect VOR. To resolve this problem, further experiments are needed.

Previous experimental data show the transition of $E(\omega,t)$ during readaptation to normal vision is faster than that during adaptation to reversed vision [6,9]. Fujita suggested that ϵ may have varied in above two cases [3]. On the other hand, the present extended model suggests two possibilities. One is that the efficiency of the reactant supply to the synaptic inputs (ϵ') or the reaction rate (k_{pr}, k_{rp}, k_r, k_p) varies in the above two cases. The other is that the flux accelerates the readaptation process.

It was reported that the adaptive changes in VOR gain and phase after wearing of the prisms were very sensitive to ω [8]. After 3 weeks both the gain and the phase lag relative to the normal perfect VOR decreased with ω, and after 7 weeks the gain decreased but the phase lag increased with ω. However, the present simulation results, including those by Fujita's model, do not show such dependences on ω. This discrepancy may be because the factors such as the efficiency of the reactant supply to the synaptic inputs vary according to ω, but it may be due to nonlinear properties of the VOR. In fact, the VOR has been known to be nonlinear and the relationship between the eye velocity and the head velocity is generally nonlinear [13]. However, we have not discussed the nonlinearities in the present article. Future studies are expected to consider those.

V. CONCLUSIONS

The present extended model gives the following vision of VOR adaptation. If the efficiency of the reactant supply to the synaptic inputs, involved in the synaptic modification, is sufficiently high, the adaptation course would oscillate due to extra information by the slow transient phenomenon of the synaptic modification. However, if the efficiency is con-

trolled to be so low to mask the extra information, the adaptation course would not oscillate.

On the other hand, if the mechanism of synaptic modification involves the reverse reaction and the flux of reactants or products, the adaptive change associated with left-right reversing prisms would end off on the way, and the adaptation course with the flux would deviate inside that reachable to the improved perfect VOR. These give new ways to understand that the maximum adaptation was not observed in previous experiments.

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