Model for an enzymatic reaction-diffusion system realizing storage of graded information

Hiroshi Okamoto and Kazuhisa Ichikawa
Foundation Research Laboratory, Fuji Xerox Company Ltd., Kanagawa 243-04, Japan
(Received 14 March 1994)

An enzymatic reaction-diffusion system in a neuron is supposed for the modeling of synaptic storage of information. This system can encode and store the history of signal transmissions in a graded and cumulative fashion. This graduality appears to result from signal-induced changes in quantities that are held constant with time in the absence of signals.

PACS number(s): 87.10.+e, 87.22.Jb, 87.22.Me

I. INTRODUCTION

It is now generally believed that a use-dependent change in the transmission strength of a synapse (a plastic change in the synaptic weight) is an elementary process of information storage in the brain [1]. In 1985, Lisman proposed an enzymatic reaction scheme for theoretical modeling of molecular mechanisms of synaptic plasticity [2]. He postulated two enzymes in a postsynaptic spine: One enzyme undergoes an autocatalytic activation and the active form of this enzyme is responsible for synaptic enhancement; meanwhile, the other enzyme deactivates the former enzyme. In this paper, we will call the former and the latter enzymes an *enhancer* and an *inactivator,* respectively. This reaction system can work as a binary switch: A signal transferred through a synapse is encoded to a binary number by the "threshold" appearing in the enzymatic reactions, and then the synaptic weight is (not) enhanced if the signal intensity is above (below) this threshold. Since Lisman's scheme is a hypothetical but fairly plausible one [3], we can employ it as a basis for further discussion on molecular mechanisms of synaptic plasticity.

Consider a group of synapses formed on the same neuron and neighboring with each other. In the original Lisman model, the enzymatic reactions in each spine are assumed to proceed independently of those in the other spines. This assumption, however, can no longer be held if some of the enzymes are soluble in cytosol. Diffusional transportations of the soluble enzymes in cytosol between spines inevitably cause some kind of interaction between the signal-transduction processes at neighboring synapses. Such an interaction must modify the simple information-storage hypothesis in the original Lisman model.

Let the inactive enhancer, the active enhancer, and the inactivator be symbolized by E, E^*, and I, respectively. Each of them may be soluble or associated to membrane [4]. The cases to be theoretically examined are listed as follows: (i) E is soluble whereas E^* and I are membrane associated; (ii) E and I are soluble whereas E^* is membrane associated; (iii) I is soluble whereas E and E^* are membrane associated [5].

Recently, the present authors investigated the case (i) and found a pattern-encoding and storage hypothesis based on a phenomenon dubbed *synapse selection:* The weight of only one of neighboring synapses, which is the strongest at an initial time, is selected and enhanced, and the weights of the other synapses are returned to their basal levels in ascending order of their initial strength [6].

There still remained the cases (ii) and (iii) to be examined. The present authors have investigated these remaining cases to complete the series of examinations and, in the case (ii), found an interesting pattern-encoding and storage hypothesis based on a phenomenon quite different from synapse selection.

II. CONSTRUCTION OF A MODEL

The case we will examine in this paper is that E and I are soluble whereas E^* is membrane associated. A schematic drawing of our model is presented in Fig. 1. In each postsynaptic spine, E, E^*, and I obey the following reaction scheme [2]:

$$E^*+E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} E^*E \xrightarrow{k_2} E^*+E^* , \tag{2.1}$$

$$I+E^* \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} IE^* \xrightarrow{k_4} I+E , \tag{2.2}$$

where k_1, k_{-1}, k_2, k_3, k_{-3}, and k_4 are rate constants, and E^*E and IE^* symbolize intermediary metabolites. It is natural to assume that E^*E and IE^* are membrane associated because E^*, a part of these complexes, is bound by membrane.

Signal transmissions at synapses trigger conversion of E to E^* in each spine, which is additionally described by

$$E \xrightarrow{f_i(t)} E^* , \tag{2.3}$$

where $f_i(t)$ is the time-dependent rate constant whose amplitude defines the signal intensity at the ith synapse at time t.

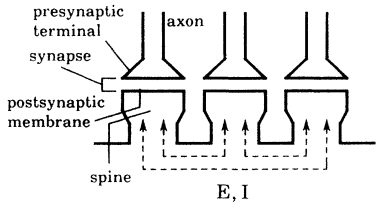

FIG. 1. A schematic drawing of our model.

The time evolution of the enzyme concentrations in the ith spine is then described by the following equations [6]:

$$\frac{d[E^*]_i}{dt}=f_i(t)[E]_i-k_1[E]_i[E^*]_i +(k_{-1}+2k_2)[E^*E]_i -k_3[E^*]_i[I]_i+k_{-3}[IE^*]_i \ , \tag{2.4}$$

$$\frac{d[E]_i}{dt}=-f_i(t)[E]_i-k_1[E]_i[E^*]_i +k_{-1}[E^*E]_i+k_4[IE^*]_i+\sum_{j=1}^{N}J_{E_{ij}} \ , \tag{2.5}$$

$$\frac{d[E^*E]_i}{dt}=k_1[E]_i[E^*]_i-(k_{-1}+k_2)[E^*E]_i \ , \tag{2.6}$$

$$\frac{d[I]_i}{dt}=-k_3[E^*]_i[I]_i+(k_{-3}+k_4)[IE^*]_i+\sum_{j=1}^{N}J_{I_{ij}} \ , \tag{2.7}$$

$$\frac{d[IE^*]_i}{dt}=k_3[E^*]_i[I]_i-(k_{-3}+k_4)[IE^*]_i \ . \tag{2.8}$$

In the above equations, $J_{E_{ij}}$ and $J_{I_{ij}}$ represent diffusional transportations of E and I in cytosol from the jth spine to the ith one, respectively; their exact forms are given by

$$J_{E_{ij}}=-k_E([E]_i-[E]_j) \ , \tag{2.9}$$

$$J_{I_{ij}}=-k_I([I]_i-[I]_j) \ , \tag{2.10}$$

where k_E and k_I are the mass transfer coefficients for E and I, respectively, and $i,j=1,\ldots,N$, with N being the number of neighboring synapses interacting with each other through cytosolic transportations of E and I.

From (2.4)–(2.8), one finds that

$$\sum_{i=1}^{N}([E]_i+[E^*]_i+2[E^*E]_i+[IE^*]_i)=NC_E \ , \tag{2.11}$$

$$\sum_{i=1}^{N}([I]_i+[IE^*]_i)=NC_I \ , \tag{2.12}$$

where C_E and C_I are constants. Equations (2.11) and (2.12) represent conservations of the total concentrations of all forms of the enhancer and the inactivator, respectively.

Following the preceding studies [2,6], we will postulate steady-state assumptions for intermediary metabolites [7] as follows:

$$\frac{d[E^*E]_i}{dt}=\frac{d[IE^*]_i}{dt}=0 \quad (i=1,\ldots,N) \ . \tag{2.13}$$

On the basis of these assumptions, one can simplify (2.4)–(2.8), (2.11), and (2.12) as follows:

$$\frac{dx_i}{ds}=\epsilon_i(s)x_i+\frac{x_iy_i}{\beta}-\frac{Nx_i}{\sum_{j=1}^{N}x_j+\gamma} \ , \tag{2.14}$$

$$\frac{dy_i}{ds}=-\epsilon_i(s)x_i-\frac{x_iy_i}{\beta}+\frac{Nx_i}{\sum_{j=1}^{N}x_j+\gamma}+\left[\sum_{j=1}^{N}y_j-Ny_i\right]\delta \ , \tag{2.15}$$

$$\sum_{i=1}^{N}(x_i+y_i)=N\alpha \ , \tag{2.16}$$

where x_i, y_i, s, α, β, γ, δ, and $\epsilon_i(s)$ are dimensionless variables and parameters defined as follows: $x_i=(k_2/V_I)[E^*]_i$; $y_i=(k_2/V_I)[E]_i$; $s=k_2t$; $\alpha=(k_2/V_I)\bar{C}_E$; $\beta=(k_2/V_I)K_A$; $\gamma=(k_2/V_I)K_I$; $\delta=k_E/k_2$; $\epsilon_i(s)=f_i(t)/k_2$, with $K_A=(k_{-1}+k_2)/k_1$, $K_I=(k_{-3}+k_4)/k_3$, $V_I=k_4C_I$, and $\bar{C}_E=C_E-(1/N)\sum_{i=1}^{N}(2[E^*E]_i+[IE^*]_i)$.

III. ANALYTICAL AND NUMERICAL INVESTIGATION OF THE MODEL

Our problem is now described by the nonlinear dynamical system (2.14)–(2.16). Therefore the dynamical behavior of the model can be elucidated by analyzing the mathematical structure of trajectories given by this dynamical system.

We will first examine the model in the absence of signals, and next consider the effects caused by signal transmissions. In the absence of signals, say $f_i(t)=0$ for $i=1,\ldots,N$, the dynamical system has equilibrium points whose coordinates are the solutions of

$$\frac{dx_i}{ds}=\frac{dx_i}{ds}=0 \quad (i=1,\ldots,N) \text{ with (2.16)} \ . \tag{3.1}$$

Let $P^{(\mathrm{eq})}$ be an equilibrium point. It can be easily proved that (i) when $\mu<0$, $P^{(\mathrm{eq})}$ is $P^{(+)}$ or P_0; (ii) when $\mu>0$ and $\nu>1$, $P^{(\mathrm{eq})}$ is $P^{(+)}$, $P^{(-)}$, or P_0; and (ii) when $\mu>0$ and $\nu<1$, $P^{(\mathrm{eq})}=P_0$. Here μ and ν are the order parameters defined by

$$\mu=N\beta-\alpha\gamma \ , \tag{3.2}$$

$$\nu=\frac{N[2N\beta-\alpha\gamma-2\sqrt{N\beta(N\beta-\alpha\gamma)}]}{\gamma^2} \ ; \tag{3.3}$$

$P^{(+)}$, $P^{(-)}$, and P_0 are the points whose coordinates are given by

$$x_i=v_i^{(+)}, \quad y_i=\frac{N\beta}{S^{(+)}+\gamma} \quad (i=1,\ldots,N) \ , \tag{3.4}$$

$$x_i=v_i^{(-)}, \quad y_i=\frac{N\beta}{S^{(-)}+\gamma} \quad (i=1,\ldots,N) \ , \tag{3.5}$$

and

$$x_i=0 \ , \quad y_i=\alpha \quad (i=1,\ldots,N) \ , \tag{3.6}$$

respectively, where $v_i^{(+)}$'s and $v_i^{(-)}$'s are arbitrary positive numbers satisfying

$$\sum_{i=1}^{N}v_i^{(+)}=S^{(+)} \ , \quad \sum_{i=1}^{N}v_i^{(-)}=S^{(-)} \tag{3.7}$$

where $S^{(+)}$ and $S^{(-)}$ are the larger and the smaller roots of the quadratic equation,

$$S^2-(N\alpha-\gamma)S+N(N\beta-\alpha\gamma)=0 \ . \tag{3.8}$$

Notice that the values of $v_i^{(+)}$'s and $v_i^{(-)}$'s cannot be uniquely determined only from (3.1). To determine them uniquely, we need additional criteria.

Now we will examine the stabilities of the equilibrium

points to know the asymptotic behavior of the dynamical system. Set $x_i = x_i^{(eq)} + \chi_i$ and $y_i = y_i^{(eq)} + \psi_i$ assuming that χ_i and ψ_i represent small fluctuations around an equilibrium point $(x^{(eq)}, y^{(eq)})$, and then linearize Eqs. (2.14) and (2.15) with respect to χ_i and ψ_i. From these linearized equations, we can derive the characteristic equation which determines the stability of each equilibrium point. When $P^{(eq)} = P^{(+)}$, the characteristic equation is

$$\lambda^N \left\{ \sum_{k=1}^{N} \frac{1}{N} \left[\lambda + \left[\frac{1}{\beta} - \frac{N^2}{(S^{(+)}+\gamma)^2} \right] v_k^{(+)} \right] \times \prod_{i=1, i\neq k}^{N} \left[\lambda + \frac{v_i^{(+)}}{\beta} + N\delta \right] \right\} = 0 ; \quad (3.9)$$

when $P^{(eq)} = P^{(-)}$

$$\lambda^N \left\{ \sum_{k=1}^{N} \frac{1}{N} \left[\lambda + \left[\frac{1}{\beta} - \frac{N^2}{(S^{(-)}+\gamma)^2} \right] v_k^{(-)} \right] \times \prod_{i=1, i\neq k}^{N} \left[\lambda + \frac{v_i^{(-)}}{\beta} + N\delta \right] \right\} = 0 ; \quad (3.10)$$

and when $P^{(eq)} = P_0$

$$\lambda^N \left[\lambda + \frac{N\beta - \alpha\gamma}{\beta\gamma} \right]^N = 0 . \quad (3.11)$$

The equations (3.9)–(3.11) yield $\lambda = 0$ as an N-multiple root. One finds that, when $\mu < 0$, or $\mu > 0$ and $\nu > 1$, the real parts of all the other roots of (3.9) are negative. Therefore, $P^{(+)}$ has marginal stability. When $\mu > 0$, (3.10) has at least one positive root, and accordingly $P^{(-)}$ is unstable. P_0 is unstable when $\mu < 0$ and stable when $\mu > 0$. These results are summarized in Table I.

From the above observations one can expect that (i) when $\mu < 0$, $P \to P^{(+)}$ as $s \to \infty$; (ii) when $\mu > 0$ and $\nu > 1$, $P \to P^{(+)}$ or $P \to P_0$; and (iii) when $\mu > 0$ and $\nu < 1$, $P \to 0$. We verified this expectation by numerically calculating the time evolutions of the dynamical system for various sets of the parameter values and the initial conditions. Typical results are shown in Fig. 2.

A surprising result we found in the above investigation is that, in the cases (i) and (ii), the final state of the dynamical system can depend on its initial state in a graded fashion. Figure 3(a) demonstrates this for the simplest case $N = 2$. Initial ends of trajectories in the figure are assigned the same values of α, β, γ, and δ. In spite of that, their final ends are different.

This strange phenomenon can be resolved as follows. The existence of the N-multiple root $\lambda = 0$ suggests that the dynamical system may have N hidden conservative

TABLE I. Equilibrium points of the dynamical system (2.14)–(2.16) and their stabilities. S and U represent stable and unstable, respectively.

		Case	Equilibrium points	Stability
$\mu < 0$		(i)	P_0	U
			$P^{(+)}$	S
$\mu > 0$	$\nu > 1$	(ii)	P_0	S
			$P^{(-)}$	U
			$P^{(+)}$	S
	$\nu < 1$	(iii)	P_0	S

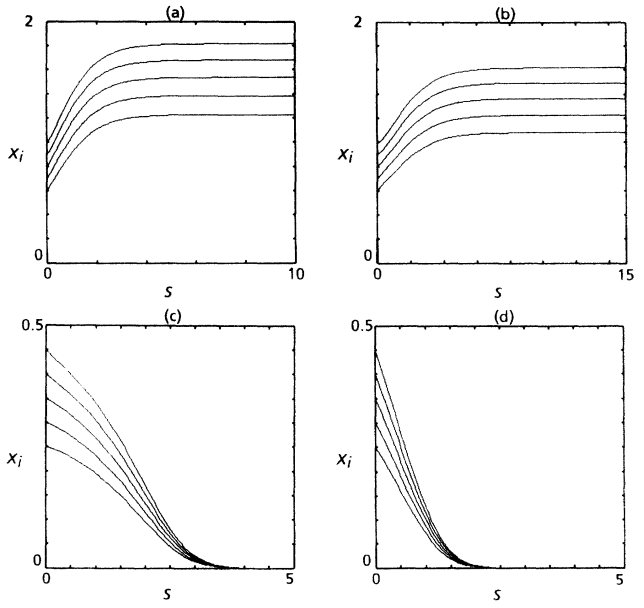

FIG. 2. The time evolutions of x_i's for $N = 5$. The parameter values are chosen in each figure as follows: In (a), $(\alpha, \beta, \gamma, \delta) = (2.0, 1.0, 3.0, 1.0)$, satisfying $\mu < 0$; in (b) and (c), $(\alpha, \beta, \gamma, \delta) = (2.0, 1.0, 1.0, 1.0)$, satisfying $\mu > 0$ and $\nu > 1$; in (d), $(\alpha, \beta, \gamma, \delta) = (2.0, 1.5, 1.0, 1.0)$, satisfying $\mu > 0$ and $\nu < 1$.

quantities, besides usual conservative quantities appearing in chemical-reaction systems such as the total concentrations of all forms of substances [see (2.11) and (2.12), or their reduced form (2.16)]. In fact, one can find the following N quantities that are held constant with time:

$$Q_i = x_i + y_i + \beta\delta \sum_{j=1}^{N} (\ln x_i - \ln x_j) \quad (i = 1, \ldots, N) . \quad (3.12)$$

Using (2.16), one has

$$\sum_{i=1}^{N} Q_i = N\alpha . \quad (3.13)$$

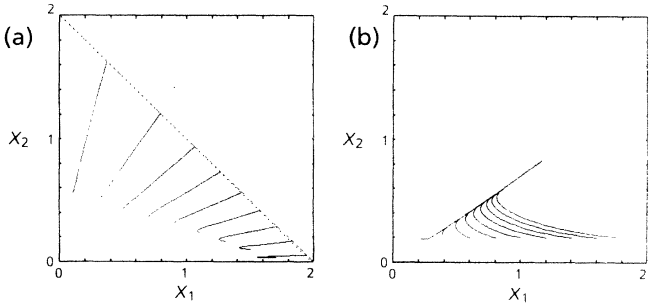

FIG. 3. The orthogonal projections of trajectories for $N = 2$ onto the x_1x_2 plane. (a) The orthogonal projections of trajectories starting from points giving different sets of Q_i's. The parameter values are chosen as $(\alpha, \beta, \gamma, \delta) = (2.0, 2.5, 3.0, 1.0)$ which satisfies $\mu < 0$. Notice that the final ends of the trajectories are all aligned along $x_1 + x_2 = S^{(+)}$ (dashed line), as obviously expected from (3.7). (b) The orthogonal projections of trajectories starting from different points but giving the same Q_i's. The same parameter values as in (a) are employed. The coordinates of the initial ends of the trajectories are chosen according to the formula $y_i = Q_i - x_i - \beta\delta \sum_{j=1}^{N} (\ln x_i - \ln x_j)$ to ensure that they all satisfy $(Q_1, Q_2) = (3.0, 1.0)$.

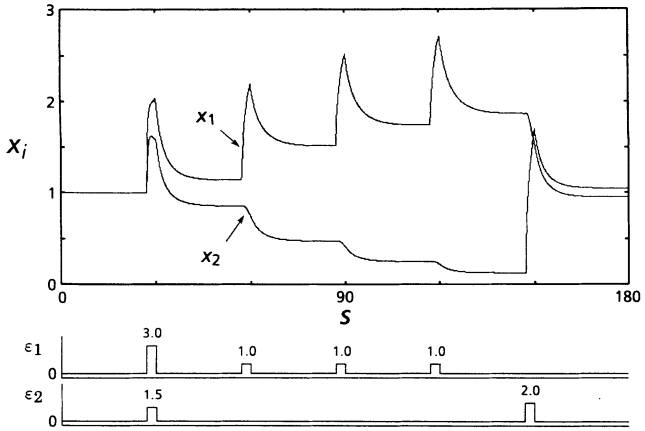

FIG. 4. The time evolutions of x_i's in the presence of synaptic stimulations. The same parameter values as in Fig. 3(a) are employed. The time courses of the amplitudes of $\epsilon_1(s)$ and $\epsilon_2(s)$ supposed in the calculation are illustrated at the bottom of the figure.

Given a set of Q_i's that satisfy (3.13) together with (3.1), the coordinates of $P^{(+)}$ and $P^{(-)}$ are uniquely determined. In other words, different sets of Q_i's can give the different coordinates of $P^{(+)}$ and $P^{(-)}$. The values of Q_i's are determined by the initial values of x_i's and y_i's through (3.12). Therefore, as the initial end of the trajectory is altered, its final end ($P^{(+)}$) is translocated in proportion to this alteration [Fig. 3(a)].

It is therefore expected that trajectories starting from different points but giving the same Q_i's end at the same point. We numerically verified this expectation [Fig. 3(b)].

Next we will discuss the effect of signal transmissions on the time evolution of the system. The appearance of nonzero $f_i(t)$'s still holds (2.16) but breaks the conservations of Q_i's. Suppose a series of intermittent signal transmissions and consider, for example, the case $\mu<0$ in which the state point always converges to $P^{(+)}$. $P^{(+)}$ is translocated by the first signal transmission and then the state point begins to migrate towards this translocated $P^{(+)}$. The next signal transmission further translocates $P^{(+)}$ towards which the state point migrates again. Succeeding signal transmissions drive further translocations of $P^{(+)}$ and following migrations of the state point. For $N=2$, the time evolution of x_i's in the presence of signal transmissions was numerically demonstrated in Fig. 4.

We can measure the weight of the ith synapse by the amplitude of x_i because, as formerly mentioned, x_i is a dimensionless variable proportional to $[E^*]_i$, and E^* is responsible for synaptic enhancement. Figure 4 shows a kind of synaptic plasticity: A signal transmission at a synapse results in enhancement of this synapse and depression of the other unstimulated synapses. To what extent the synapse is enhanced gradually depends upon the signal intensity, and repeated stimulations result in cumulative enhancement. The same results were obtained for $N>2$ (data not shown). Thus, the reaction-diffusion system in our model can encode and store the history of signal transmissions in a graded and cumulative manner.

IV. SUMMARY AND DISCUSSION

In our model, synaptic plasticity is realized as gradual and cumulative storage of the history of signal transmissions. This graduality results from signal-induced breaking of the conservations of Q_i's. It should be noticed that the appearance of these conservative quantities is due to the interaction between synapses mediated by diffusional transportations of the enzymes.

In addition, it is also noticeable that, when $\mu>0$ and $\nu>1$, the system functions as an on-off switch [Figs. 2(b) and 2(c)]. This is a consequence of our extension of the original Lisman scheme [3]. However, the switch in our extended scheme can perform much more complicated tasks than the simple binary switch by Lisman: It can remember the amplitude of the initial values of x_i's and their order.

In the parameter space, let $V^{(N)}$ be the subspace defined by $\mu>0$ and $\nu>1$. For given α, β, and γ, $V^{(N)}$ expands as N becomes larger. This indicates that the system functions as a switch under a wide range of the parameter values for large N. The original Lisman model was associated with a problem that the parameter range under which the system functions as a switch, given by setting $N=1$ in $\mu>0$ and $\nu>1$, is relatively narrow (see discussions in [2] and [6]). This difficulty, however, has thus been improved in our extended scheme.

In the present study, we have a relation $\sum_{i=1}^{N} x_i^{(\mathrm{eq})}=S^{(+)}$ [see (3.7)] at the chemical equilibrium; that is, the total of the synaptic weights does not change even though each of them can be gradually altered. This resembles the synaptic-weight-normalization procedure employed for the modeling of self-organization of orientation selective cells in the visual cortex [8].

[1] T. H. Brown, E. W. Kairiss, and C. L. Keenan, Annu. Rev. Neurosci. **13**, 475 (1990), and references therein.

[2] J. E. Lisman, Proc. Natl. Acad. Sci. U.S.A. **82**, 3055 (1985).

[3] Molecular mechanisms of synaptic plasticity have been extensively studied by experiment but yet are far from established. See T. V. P. Bliss and G. L. Collingridge, Nature **361**, 31 (1993), and references therein.

[4] There are a large number of enzymes in cells, and some of them are soluble in cytosol and others are associated to membrane. There are also many enzymes which are soluble or membrane associated in one state and change their solubility in another state.

[5] The cases that E^* is soluble are excluded from the list because of the following reasons. If E^* is soluble, the E^* concentration becomes flat at neighboring spines at the chemical equilibrium, and accordingly each synapse completely loses its use-dependent specificity.

[6] H. Okamoto and K. Ichikawa Phys. Rev. E **49**, 3412 (1994).

[7] See, for example, D. Voet and J. G. Voet, *Biochemistry* (Wiley, New York, 1990).

[8] C. von der Malsburg, Kybernetik **14**, 85 (1973).