Asymmetry and External Noise-Induced Free Energy Transduction

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PNAS 1987;84;729-733
doi:10.1073/pnas.84.3.729

Proc. Natl. Acad. Sci. USA
Vol. 84, pp. 729–733, February 1987
Biophysics

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(fluctuations/cycle diagrams/cycles/free energy transduction)

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Communicated by Terrell L. Hill, September 29, 1986

ABSTRACT **The effect of fluctuations in rate constants on the kinetic behavior of cyclic reacting systems, caused by a fluctuating external parameter, is studied. It is shown (*i*) that the stochastic properties of the system can be analyzed analytically by using the usual master equation approach when the external parameter is fluctuating with discrete square pulses and (*ii*) that the system is equivalent to an expanded chemical kinetic system with no fluctuation in rate constants. When applied to a linear four-state cyclic enzyme system, the formalism can be used to prove analytically the finding that an enzyme can extract the free energy from an externally applied fluctuating membrane potential and perform active free energy transduction. The formalism also can be used to assess the asymmetry constraints imposed on the values of the rate constants in order for the model to work.**

In a recent paper (1), it has been demonstrated by model calculations that enzymes undergoing cyclic reactions inside a membrane may be able to absorb free energy from an oscillating electric field applied externally across the membrane and transduce that energy into chemical or transport work. That is, the cyclic reactions of the enzymes can be made to prefer one direction over the other so that a net flux around the cycle is produced, even against a load, by oscillating the external parameter of the system. The conditions sufficient for the enzyme to work are: (*i*) some of the rate constants of the reactions must be dependent on the potential, and (*ii*) the stability of the enzyme states involved must be asymmetric (see below). For example, if the enzymes are charged (positive or negative) and their binding and dissociation with ligands from the bathing solutions are not symmetric at the two sides of the membrane, they are able to pump the ligand across the membrane against a gradient under an externally applied oscillating membrane potential (see ref. 1 or below). The study was motivated by the experimental and theoretical studies of Tsong and his colleagues (2–4) that active transport of Rb^+ ions across erythrocyte membranes with Na^+/K^+-ATPase could be achieved by applying a regularly alternating electric field across the membranes.

For the cases studied in ref. 1, the oscillation of the field (or potential) across the membrane was "regular" or "periodic" in that it was either a sine (or cosine) function of time or a train of alternating square pulses with a constant pulse duration. In this and the parallel paper (5), studies are reported on the case that the oscillations of membrane potential are not regular but random. The main purpose is to examine whether external random fluctuations (noise) in membrane potential can also be used to do work. In ref. 5, we have demonstrated that this is indeed the case when the same model as studied in ref. 1 is used with the same set of asymmetric rate constants. In this paper, I examine the fundamental questions of why asymmetric rate constants are required and what are the necessary and sufficient asymmetry conditions for a model to have noise-induced free energy transductions.

The paper is divided into two main parts. The first part deals with the study of stochastic properties of an arbitrary chemical reacting system in the presence of external parameters that are not constant but are fluctuating between discrete levels. The purpose is to show that the system can be treated as an expanded, nonfluctuating chemical system so that its kinetic properties can be studied analytically. The second part deals with the application of the formalism to the study of necessary conditions for a linear four-state model to have noise-induced free energy transductions. I shall show that there are many sets of asymmetric rate constants other than that used in ref. 1 that are sufficient to make the model work.

STOCHASTIC PROPERTIES OF EXTERNAL NOISE INFLUENCED KINETIC SYSTEMS

In this section, we study the master equation of an arbitrary kinetic system whose rate constants are not constant but randomly fluctuating between discrete levels, caused by discrete fluctuations in external parameters. For simplicity, we shall consider the case that the external parameter is fluctuating between two levels only (the dichotomous noise). That is, the parameter $\mathcal{V}$ can take two finite values (Δ and $-\Delta$), and the time of being in Δ or $-\Delta$ is a random variable. A random dichotomous $\mathcal{V}$ can be represented by a first-order process as

$$\mathcal{V}(\Delta) \underset{\gamma}{\overset{\gamma}{\rightleftarrows}} \mathcal{V}(-\Delta) \qquad [1]$$

in which γ^{-1} is the mean time of being in Δ or $-\Delta$.

Let us consider a kinetic system containing $A_1, A_2, \ldots, A_x$ species (or states) of molecules undergoing a total of s elementary reactions:

$$\nu_{r1}A_1 + \nu_{r2}A_2 + \ldots + \nu_{rx}A_x \underset{k'_r}{\overset{k_r}{\rightleftarrows}} \nu'_{r1}A_1 + \nu'_{r2}A_2 + \ldots + \nu'_{rx}A_x \qquad [2]$$

$$(r = 1, 2, \ldots, s),$$

where ν_{ri} and ν'_{ri} ($i = 1, 2, \ldots, x$) are the stoichiometric coefficients, and k_r and k'_r are the forward and the backward rate constants; k_r and k'_r are functions of $\mathcal{V}$. Let $\mathbf{N}(t)$ be the column matrix of the number of molecules of all species in the system at time t. In the absence of external fluctuations, the relaxation of the ensemble-averaged mean values, $\langle \mathbf{N}(t) \rangle$, toward their steady-state (or equilibrium) values, $\langle \mathbf{N} \rangle_{ss}$, follows the differential equation

$$\frac{d\langle \mathbf{N}(t) \rangle}{dt} = -\mathbf{M} \cdot (\langle \mathbf{N}(t) \rangle - \langle \mathbf{N} \rangle_{ss}), \qquad [3]$$

where $\mathbf{M}$ is the phenomenological relaxation matrix of the system (see ref. 6).

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In the presence of a fluctuating parameter with a dichotomous distribution, the variables that characterize the kinetic system are the set $\mathbf{N}(=N_1, N_2, \ldots, N_x)$ plus the parameter state (Δ or $-\Delta$). Thus, let $P(\mathbf{N}, \Delta, t)$ be the probability of finding the system with N_1 in state 1, N_2 in state 2, . . ., N_x in state x, and $\mathcal{V}$ in Δ at time t, and $P(\mathbf{N}, -\Delta, t)$ be that with $\mathcal{V}$ in $-\Delta$. Then, the master equation for these two probability functions can be expressed as

$$\frac{\partial P(\mathbf{N}, \Delta, t)}{\partial t} = \sum_{\mathbf{N}'} P(\mathbf{N}', \Delta, t)\cdot Q^+(\mathbf{N}; \mathbf{N}') - P(\mathbf{N}, \Delta, t)\cdot Q^+(\mathbf{N}'; \mathbf{N}) + P(\mathbf{N}, -\Delta, t)\cdot\gamma - P(\mathbf{N}, \Delta, t)\cdot\gamma, \quad [4]$$

$$\frac{\partial P(\mathbf{N}, -\Delta, t)}{\partial t} = \sum_{\mathbf{N}'} P(\mathbf{N}', -\Delta, t)\cdot Q^-(\mathbf{N}; \mathbf{N}') - P(\mathbf{N}, -\Delta, t)\cdot Q^-(\mathbf{N}'; \mathbf{N}) + P(\mathbf{N}, \Delta, t)\cdot\gamma - P(\mathbf{N}, -\Delta, t)\cdot\gamma, \quad [5]$$

where $Q^+(\mathbf{N}; \mathbf{N}')$ and $Q^-(\mathbf{N}; \mathbf{N}')$ are the transition probabilities from $\mathbf{N}'$ to $\mathbf{N}$ per unit time at $\mathcal{V} = \Delta$ and $\mathcal{V} = -\Delta$, respectively. The last two terms on the right-hand side of Eqs. **4** and **5** represent the transitions due to the parameter $\mathcal{V}$. Multiplying by $\mathbf{N}$ and taking summation over $\mathbf{N}$ on both sides of Eqs. **4** and **5**, we get (see ref. 6 for derivations)

$$\frac{d}{dt}\begin{pmatrix}\langle\mathbf{N}^+(t)\rangle\\ \langle\mathbf{N}^-(t)\rangle\end{pmatrix} = -\begin{pmatrix}\mathbf{M}^+ + \gamma\mathbf{E} & -\gamma\mathbf{E}\\ -\gamma\mathbf{E} & \mathbf{M}^- + \gamma\mathbf{E}\end{pmatrix}\cdot\begin{pmatrix}\langle\mathbf{N}^+(t)\rangle - \langle\mathbf{N}^+\rangle_{ss}\\ \langle\mathbf{N}^-(t)\rangle - \langle\mathbf{N}^-\rangle_{ss}\end{pmatrix} \quad [6]$$

where $\mathbf{M}^+$ and $\mathbf{M}^-$ are the phenomenological relaxation matrices of the system at $\mathcal{V} = \Delta$ and $\mathcal{V} = -\Delta$, respectively, and

$$\langle\mathbf{N}^+(t)\rangle = \sum_{\mathbf{N}} \mathbf{N}P(\mathbf{N}, \Delta, t) \quad [7]$$

$$\langle\mathbf{N}^-(t)\rangle = \sum_{\mathbf{N}} \mathbf{N}P(\mathbf{N}, -\Delta, t). \quad [8]$$

The $\langle\mathbf{N}^+\rangle_{ss}$ and $\langle\mathbf{N}^-\rangle_{ss}$ are the steady-state ($t = \infty$) values of $\langle\mathbf{N}^+(t)\rangle$ and $\langle\mathbf{N}^-(t)\rangle$, and $\mathbf{E}$ is a unity matrix.

By comparing with Eq. **3**, it becomes obvious that Eqs. **6** are exactly the phenomenological relaxation equations of the kinetic system that contain the following elementary reactions:

$$\nu_{r1}\mathrm{A}_1^+ + \nu_{r2}\mathrm{A}_2^+ + \ldots + \nu_{rx}\mathrm{A}_x^+ \underset{k_r^+}{\overset{k_r^+}{\rightleftarrows}} \nu'_{r1}\mathrm{A}_1^+ + \nu'_{r2}\mathrm{A}_2^+ + \ldots + \nu'_{rx}\mathrm{A}_x^+ \quad [9]$$

$$\nu_{r1}\mathrm{A}_1^- + \nu_{r2}\mathrm{A}_2^- + \ldots + \nu_{rx}\mathrm{A}_x^- \underset{k_r^-}{\overset{k_r^-}{\rightleftarrows}} \nu'_{r1}\mathrm{A}_1^- + \nu'_{r2}\mathrm{A}_2^- + \ldots + \nu'_{rx}\mathrm{A}_x^- \quad [10]$$

$$(r = 1, 2, \ldots, s),$$

$$\mathrm{A}_j^+ \underset{\gamma}{\overset{\gamma}{\rightleftarrows}} \mathrm{A}_j^- \qquad (j = 1, 2, \ldots, x), \quad [11]$$

where k_r^+ and k_r^- are the forward rate constants of reaction (2) at $\mathcal{V} = \Delta$ and $\mathcal{V} = -\Delta$, respectively. In other words, a chemical kinetic system in the presence of a dichotomous fluctuation in an external parameter can be represented by an expanded kinetic system with nonfluctuating rate constants. As a result, the calculation of kinetic and stochastic properties of the system can be carried out easily (see below).

THE MODEL AND THE ASYMMETRY CONDITIONS

As shown in Fig. 1 *Left*, the model system studied in ref. 1 consists of a membrane placed between two bathing solutions that contain an uncharged ligand designated L. Inside the membrane are a number of negatively charged enzyme molecules that can undergo four-state cyclic reactions. The kinetic diagram of the system at a constant transmembrane potential is also shown in Fig. 1 *Right*. The k_{12}, k_{14}, . . ., etc., are the rate constants of the reactions at $V = 0$ (V is the membrane potential, the potential in bath 1 relative to that in bath 2). c_1 and c_2 are the concentrations of ligand in the two bathing solutions. For each complete forward (+) cycle, a molecule of L is transported from bath 1 to bath 2. The ϕ^α and ϕ^β take into account the effect of transmembrane potential on the rate constants involved. ϕ is defined as

$$\phi = \exp(\Delta E(V)/RT), \quad [12]$$

where $\Delta E(V)$ is the change (increase or decrease) of free energy of state 1 or state 2 due to the presence of a transmembrane potential V (see Fig. 2). (Note that the ϕ here is equal to the square of the ϕ in ref. 1.) The change in the activation energy between state 1 and state 4 is equal to $\alpha\cdot\Delta E(V)$ and equal to $\beta\cdot\Delta E(V)$ between state 2 and state 3. The value of $\Delta E(V)$ is negative when $V = \Delta$ and positive when $V = -\Delta$, because the enzyme is negatively charged.

Since the condition of detailed balance must be obeyed at equilibrium ($c_1 = c_2$), the rate constants k_{12}, k_{21}, . . ., etc., should obey the Wegscheider relation (7):

$$k_{12}k_{23}k_{34}k_{41} = k_{21}k_{32}k_{43}k_{14}. \quad [13]$$

If V is finite and constant (no fluctuation), ϕ is a constant, and the kinetic equations describing the relaxation of the means can be represented by the diagram in Fig. 1 *Right*. No net transport of ligands will be observed at $c_1 = c_2$ because the product of rate constants in the forward (+) direction is

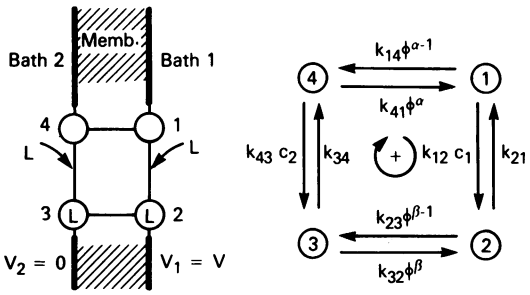

FIG. 1. (*Left*) The enzyme-mediated ligand-transport model studied in ref. 1. L is the ligand and V is the potential across the membrane (the potential in bath 1 relative to that in bath 2). The enzyme is negatively charged so that the translocation rate constants between states 1 and 4 and between 2 and 3 are voltage-dependent. (*Right*) The biochemical cycle diagram at a constant membrane potential. The voltage-dependent part of the translocation rate constants is explicitly expressed by the ϕ defined in Eq. **12**. α is the ratio of change in free energy of the activated state between state 1 and 4 to that of state 1 caused by the membrane potential (see Fig. 2). β is the corresponding ratio between states 2 and 3. The plus sign indicates that ligand L is transported from bath 1 to bath 2.

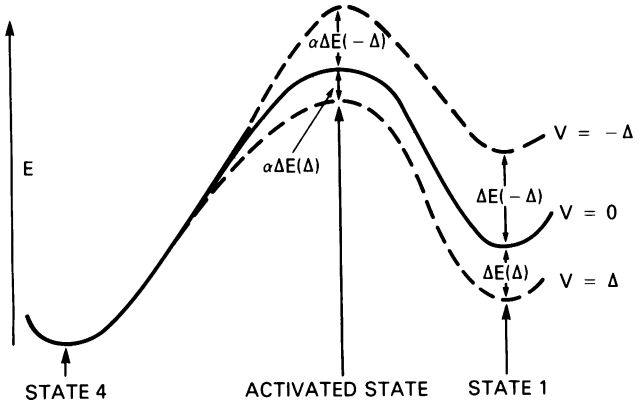

FIG. 2. The effect of membrane potential V on the free-energy profile of the reaction path from state 4 to state 1.

equal to that in the reverse direction according to Eq. **13**.

When V is fluctuating between two fixed values (Δ and $-\Delta$), according to the formalism discussed in the previous section the combined system (the kinetic system plus the fluctuating V) can be represented by the diagram in Fig. 3 in which the superscripts (or subscripts) + and − indicate whether V is positive or negative. In general, $\Delta E(\Delta)$ can be different from $\Delta E(-\Delta)$. Therefore, ϕ_+ may not be equal to $1/\phi_-$ (see Fig. 2).

From Fig. 3, one can see immediately that some of the cycles in the diagram do not have a Wegscheider relation (the product of rate constants in one direction is not equal to that in the reverse direction) even at $c_1 = c_2 = c$ and, therefore, would produce a net flux around that cycle at steady state. For example, the products of rate constants in the two directions of the cycle ($1^+ \to 2^+ \to 2^- \to 3^- \to 3^+ \to 4^+ \to 1^+$) are:

$$\Pi_+ = k_{12}\cdot c\cdot\gamma\cdot k_{23}\cdot\phi_-^{\beta-1}\cdot\gamma\cdot k_{34}\cdot k_{41}\cdot\phi_+^{\alpha}, \quad [14]$$

$$\Pi_- = k_{21}\cdot\gamma\cdot k_{32}\cdot\phi_-^{\beta}\cdot\gamma\cdot k_{43}\cdot c\cdot k_{14}\cdot\phi_+^{\alpha-1}. \quad [15]$$

Thus,

$$\frac{\Pi_+}{\Pi_-} = \frac{\phi_+}{\phi_-} \neq 1. \quad [16]$$

This implies a net transport of ligand from bath 1 to bath 2 within this cycle. That is, the fluctuating membrane potential serves as a free energy driving source for this particular cycle with a driving force equal to

$$X = RT\ln(\phi_+/\phi_-). \quad [17]$$

However, this result does not necessarily imply the existence of a net transport flux for the entire system because some other cycles may have the opposite net flux. Thus, we must examine all of the cycles before we can determine the existence of a noise-induced transport flux.

There are a total of 28 cycles for this system. But 12 of them have no net contribution to the transport of ligand L (e.g., see the cycles $1^+ \to 2^+ \to 2^- \to 1^- \to 1^+$ and $1^+ \to 2^+ \to 3^+ \to 3^- \to 2^- \to 1^- \to 1^+$). The 16 cycles that can contribute to the transport of ligands are shown in Fig. 4. Among these, 8 (numbers 9–16 in the figure) are driven by the chemical-potential gradient of the ligand and should have no contribution to the total flux at $c_1 = c_2$. Furthermore, the force X defined in Eq. **17** drives the transport of ligand from bath 1 to bath 2 in cycles 1–4 and from bath 2 to bath 1 in cycles 5–8. The total transport flux of the system at $c_1 = c_2 = c$ is the sum of these 8 cycle fluxes:

$$\begin{aligned} J = \Sigma^{-1}\,\Pi\,\gamma^2\,(\phi_-^{-1} - \phi_+^{-1}) \\ \times \{(\phi_+^{\alpha}\phi_-^{\beta} - \phi_+^{\beta}\phi_-^{\alpha})\,(2\gamma + k_{21} + ck_{12}) \\ \times (2\gamma + k_{34} + ck_{43}) \\ + (2\gamma + k_{34} + ck_{43})\cdot[k_{14}\phi_+^{\alpha}\phi_-^{\alpha}(\phi_-^{\beta-1} - \phi_+^{\beta-1}) \\ + k_{23}\phi_+^{\beta}\phi_-^{\beta}(\phi_+^{\alpha-1} - \phi_-^{\alpha-1})] \\ + (2\gamma + k_{21} + ck_{12})\cdot[k_{32}\phi_+^{\beta}\phi_-^{\beta}(\phi_+^{\alpha} - \phi_-^{\alpha}) \\ + k_{41}\phi_+^{\alpha}\phi_-^{\alpha}(\phi_-^{\beta} - \phi_+^{\beta})] \\ + \phi_+^{\alpha+\beta}\phi_-^{\alpha+\beta}\,(\phi_-^{-1} - \phi_+^{-1})\cdot(k_{32}k_{14} - k_{23}k_{41})\} \quad [18] \end{aligned}$$

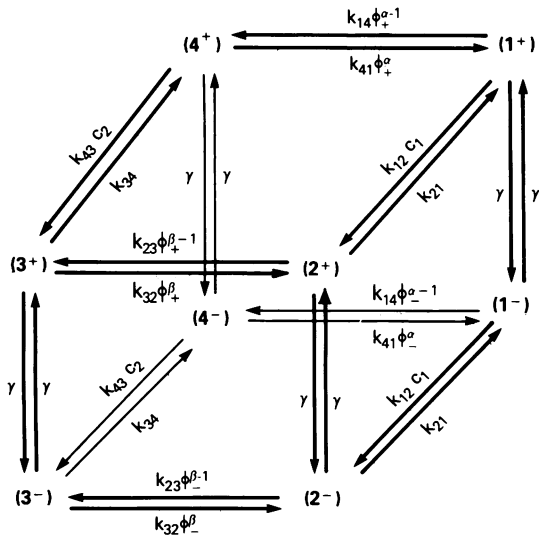

FIG. 3. The biochemical (cycle) diagram of the model when the membrane potential is fluctuating between two square pulses (+Δ and −Δ). The plus sign means that $V = +\Delta$, and the minus sign means that $V = -\Delta$. For example, $\phi_+ = \exp(\Delta E(\Delta)/RT)$ and $\phi_- = \exp(\Delta E(-\Delta)/RT)$.

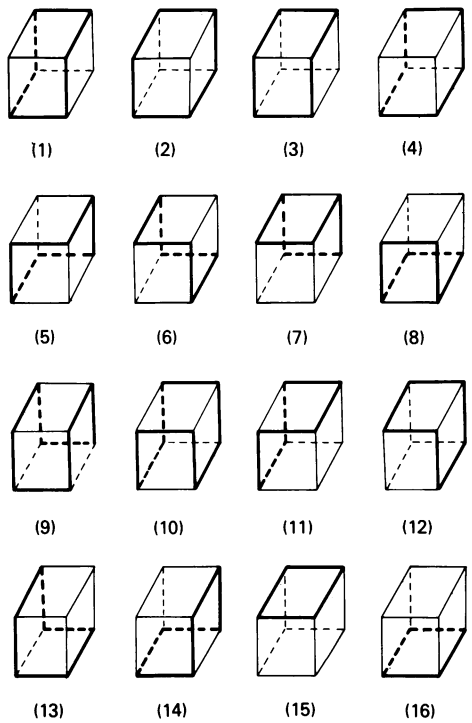

FIG. 4. Cycles for the diagram in Fig. 3 with nonzero forces for ligand transport. Cycles numbered 1–8 contain both X (Eq. **17**) and X_L [$= RT\ln(c_2/c_1)$] and are responsible for the fluctuation-induced active transport of ligand L. Cycles numbered 9–16 involve only X_L and are responsible for the passive transport of ligand L.

where Σ is the sum of all directional diagrams of the system (8), and Π is the product of the four rate constants shown on either side of Eq. **13**. Both Σ and Π are positive quantities. Thus, in order to have a net transport flux ($J \neq 0$), the quantity inside the braces must be nonzero. As one can see easily from Eq. **18**, J becomes zero independent of γ if $\alpha = \beta$, $k_{14} = k_{23}$, and $k_{41} = k_{32}$. This implies that, in order for the model to carry out free energy transduction, the "translocation" rate constants of the model must be asymmetrical between liganded and nonliganded enzyme molecules. In the following treatment, we will assess the general asymmetry conditions needed for the model to work.

Asymmetry Can Be Completely Absent from the Voltage-Independent Part of the Rate Constants. For simplicity, let us consider the case that all of the voltage-independent rate constants are equal to unity (completely symmetrical). Then, the J in Eq. **18** becomes

$$J = \Sigma^{-1}\Pi\,\gamma^2(\phi_-^{-1} - \phi_+^{-1})\,(2\gamma + c + 1) \times \{(2\gamma + c + 1)\,(\phi_+^{\alpha}\phi_-^{\beta} - \phi_+^{\beta}\phi_-^{\alpha}) + \phi_+^{\alpha}\phi_-^{\alpha}(\phi_-^{\beta} + \phi_-^{\beta-1} - \phi_+^{\beta} - \phi_+^{\beta-1}) + \phi_+^{\beta}\phi_-^{\beta}(\phi_+^{\alpha} + \phi_+^{\alpha-1} - \phi_-^{\alpha} - \phi_-^{\alpha-1})\}. \quad [19]$$

From this equation, it can be shown that the only way to make this J identically zero at all values of γ is to let α be equal to β. Thus, as long as α is not equal to β, J can become nonzero. That is, noise-induced free energy transduction can be achieved by the model, if the interaction between the potential and the activated state (see Fig. 2) is different for liganded and unliganded enzyme molecules. Since enzymes with and without ligands are expected to be in different conformations, it should not be too uncommon for them to have different α and β values.

Asymmetry Can Be Partially Absent from the Voltage-Independent Rate Constants Even When $\alpha = \beta$. Next, let us consider the case that asymmetry is absent between α and β. With $\alpha = \beta$, Eq. **18** becomes

$$J = \Sigma^{-1}\Pi\,\gamma^2\,(\phi_-^{-1} - \phi_+^{-1}) \times \{\phi_+^{\alpha}\phi_-^{\alpha}(\phi_-^{\alpha-1} - \phi_+^{\alpha-1})\,(2\gamma + k_{34} + ck_{43})\,(k_{14} - k_{23}) + \phi_+^{\alpha}\phi_-^{\alpha}(\phi_+^{\alpha} - \phi_-^{\alpha})\,(2\gamma + k_{21} + ck_{12})\,(k_{32} - k_{41}) + \phi_+^{2\alpha}\phi_-^{2\alpha}(\phi_-^{-1} - \phi_+^{-1})\,(k_{32}k_{14} - k_{23}k_{41})\}. \quad [20]$$

Table 1. Asymmetry requirement on rate constants for the generation of fluctuation-induced free energy transduction

Voltage-dependent part	Voltage-independent part
$\alpha \neq \beta$	No asymmetry in this part is required.
$\alpha = \beta \neq \alpha^{*\dagger}$	$k_{14} \neq k_{23}$, $k_{41} \neq k_{32}$; no additional asymmetry is required.
$\alpha = \beta = \alpha^*$	$k_{14} \neq k_{23}$, $k_{41} \neq k_{32}$, and at least one of the asymmetry sets: $k_{12} \neq k_{43}$, $k_{21} \neq k_{34}$, or $k_{14} \neq k_{41}$, $k_{23} \neq k_{32}$.

$^{\dagger}\alpha^*$ is the solution of the equation $\phi_-^{\alpha-1} + \phi_-^{\alpha} - \phi_+^{\alpha-1} - \phi_+^{\alpha} = 0$ at given ϕ_+ and ϕ_- values; when $\phi_+ = 1/\phi_-$, $\alpha^* = 1/2$.

It is obvious from this equation that J becomes zero as long as $k_{14} = k_{23}$ and $k_{41} = k_{32}$. Thus, for the model to produce transport flux at $c_1 = c_2 = c$, the enzyme must have different translocation rate constants for the liganded and the unliganded enzyme molecules at $V = 0$ ($k_{14} \neq k_{23}$, $k_{41} \neq k_{32}$).

If $k_{14} = k_{41}$, $k_{23} = k_{32}$, $k_{12} = k_{43}$, and $k_{21} = k_{34}$ (but $k_{14} \neq k_{23}$ and $k_{41} \neq k_{32}$), Eq. **20** becomes

$$J = \Sigma^{-1}\Pi\,\gamma^2\,(\phi_-^{-1} - \phi_+^{-1})\,\phi_+^{\alpha}\phi_-^{\alpha}\,(2\gamma + k_{34} + ck_{43})\,(k_{14} - k_{23}) \times (\phi_-^{\alpha-1} + \phi_-^{\alpha} - \phi_+^{\alpha-1} - \phi_+^{\alpha}). \quad [21]$$

It can be shown that, with given ϕ_+ and ϕ_-, there is one and only one α value (denoted as α^*) that will make the J in Eq. **21** equal to zero at any value of γ. For example, when $\phi_+ = 1/\phi_-$, α is equal to 1/2. For the case that $\phi_+ \neq 1/\phi_-$, the value of α^* will depend on the values of ϕ_+ and ϕ_-. As a result, if $\alpha(= \beta) \neq \alpha^*$, no asymmetry requirement is needed other than $k_{14} \neq k_{23}$ and $k_{41} \neq k_{32}$. On the other hand, if $\alpha = \beta = \alpha^*$, asymmetry must exist either in the binding reactions (k_{12} vs. k_{43} and k_{21} vs. k_{34}) or in the translocation reactions (k_{14} vs. k_{41} and k_{23} vs. k_{32}) as shown in Table 1.

For illustration, some numerical calculations are shown in Figs. 5 ($\alpha = \beta$) and 6 ($\alpha \neq \beta$). As one can see from the figures, any model whose rate constants satisfy any of the conditions in Table 1 can produce a net transport of ligand from bath 1 to bath 2 at $c_1 = c_2$. For comparison, a few flux curves for the case $c_2 > c_1$ are also included in the figures.

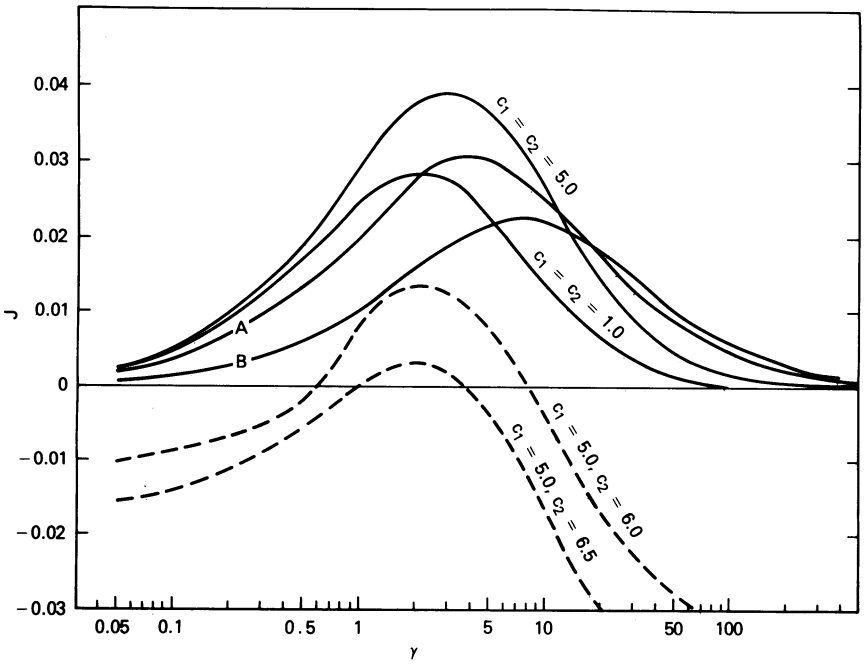

FIG. 5. Ligand transport flux calculated as a function of γ for models with $\alpha = \beta$. The solid curves are for equilibrium cases ($c_1 = c_2$), and the dashed curves are for $c_1 \neq c_2$. The rate constants of curves A and B are: A, $k_{12} = k_{21} = k_{34} = k_{43} = 1$, $k_{41} = 4$, $k_{14} = 16$, $k_{23} = 4$, $k_{32} = 1$, $\alpha = \beta = 0.5$ ($\alpha = \beta = \alpha^*$ case with symmetry in the binding steps); B, $k_{12} = k_{21} = k_{23} = k_{32} = k_{34} = k_{43} = 1$, $k_{14} = k_{41} = 5$, $\alpha = \beta = 0.2$ ($\alpha = \beta \neq \alpha^*$ case). The rate constants for the other four curves are: $k_{12} = k_{21} = k_{23} = k_{32} = 1$, $k_{14} = k_{41} = 5$, $k_{34} = k_{43} = 10$, and $\alpha = \beta = 0.5$ ($\alpha = \beta = \alpha^*$ case with symmetry in the translocation steps). In all cases, $k_{14} \neq k_{23}$ and $k_{41} \neq k_{32}$ as required (see the text and Table 1).

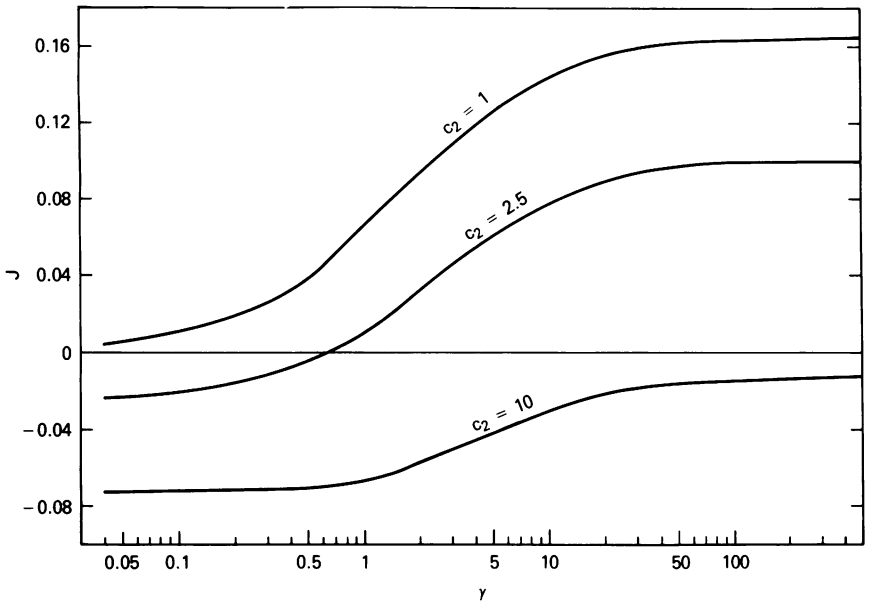

FIG. 6. Ligand transport flux calculated as a function of γ for the case $\alpha \neq \beta$. The rate constants used are all equal to unity. α = 0.8, β = 0.2, and c_1 = 1.0.

DISCUSSION

The main purpose of this paper is 2-fold. First, I show that a chemical kinetic system in the presence of a fluctuating external parameter can be represented by an expanded chemical kinetic system with constant (nonfluctuating) rate constants when the fluctuation of the external parameter is of the random square pulse type. As a result, both the kinetic and stochastic properties of the system can be studied easily by using existing theories for pure chemical kinetic systems. Second, I show that the noise-induced free energy transduction in linear cyclic kinetic systems can be studied analytically based on this formalism and the diagram method of Hill (8). As a result, I can explain (see also ref. 5) why fluctuations in membrane potential can induce a net ligand transport in the four-state enzyme model studied in ref. 1 and why the model needs asymmetric rate constants to do that. Also we are able to find out the basic necessary asymmetry condition(s) for the model to work.

As discussed in this paper and in ref. 5, in the presence of a fluctuating external parameter, some of the cycles of the corresponding kinetic diagram do not satisfy the Wegscheider relation (the product of rate constants in one direction of the cycle does not equal that in the other direction). This implies that a cyclic kinetic system initially at equilibrium can be changed into a nonequilibrium cycling system by fluctuations of the external parameter(s) that affects the rate constants of the system. As a result, ligands can be transported between the two baths. However, fluctuations in the external parameter induce not only cycles that transport ligand from bath 1 to bath 2 but also cycles that transport ligand from bath 2 to bath 1. The combined flux can become nonzero only when some kind of asymmetry exists in the rate constants of the model. As shown in Table 1, there are many ways to satisfy the asymmetry requirements. The set used in refs. 1 and 5 is just a special one of them. The most basic asymmetry condition for the model to work is found to be in the "translocation" rate constants of liganded and unliganded enzyme molecules.

I emphasize that all of the findings discussed above are based on the special case that the external parameter is fluctuating between two square pulses (dichotomous noise). But, I expect the results to be equally applicable to cases with more complicated fluctuations or with regular oscillations.

Finally, it should be pointed out that noise-induced phenomena in kinetic systems have been studied for a long time (9–17). However, only the effect of noise on stabilities and phase transitions between stable and unstable states of nonlinear kinetic systems has been considered. This paper and the parallel one (ref. 5) represent initial studies on the effect of external noise on cycling fluxes. So far we have considered only (membrane) potential fluctuations. In a paper to be published elsewhere, the study of active transport induced by fluctuations in ligand concentrations will be discussed. One interesting result of that study is the finding that asymmetric rate constants are not required by the model.

I thank Drs. Hans V. Westerhoff, Dean Astumian, and Terrell L. Hill for valuable discussions.

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