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On the Transition between Stable Steady States in a Model of Biochemical System with Positive Feedback

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The transition from one stable steady state branch to another stable steady state branch in a simple metabolic system with positive feedback is discussed with the aid of the bimodal Gaussian probability distribution method. Fluctuations lead to transitions from one stable steady state branch to the other, so that the bimodal Gaussian evolves to a new distribution. We also obtain the fractional occupancies in the two stable steady states in terms of a parameter characterizing conditions of the system.

Introduction

Biochemical reactions with feedback mechanisms may show the interesting phenomena of multiple steady states, such as hysteresis due to transition among the branches of steady states and oscillation.[1-3] The multiple steady states which result from the use of homogeneous macroscopic equations have been observed in a variety of systems, especially in superconductor, in van der Waals gases, and etc.[4] Many authors have studied the existence of multiple steady states and hysteresis in chemical and biochemical systems.[2,5,7,8] These behaviors are exhibited due to nonlinearity of the kinetic equation involved. There exist simple kinetic models consisted of many dimensional ordinary differential equations for the concentrations of the metabolites in a biochemical system.[3,7] Even though they are simplified, they are at least comparable with the experimental results qualitatively.

The purpose of the present paper is to investigate the transition between branches of stable steady states of a biochemically reacting system which is controlled by a positive feedback mechanism.[7-10]. At first, we obtained the steady state values from the deterministic equations which describe the instability for a biochemical reaction model with positive feedback. With the aid of the Fokker-Planck equation corresponding to the Langevin equation which describes fluctuations from the steady state due to the random forces (diffusion),[5,6] we obtain the bimodal Gaussian distribution in the region of multiple steady states. The bimodal Gaussian distribution should evolve to a new distribution by fluctuations. Thus, in order to discuss transitions between stable steady states due to fluctuations we obtain the fractions which describes a new Gaussian distribution at stable steady states in terms of the parameter which characterizes conditions of the system.

Theory

A kinetic equation for a model of metabolic control circuit with positive feedback is given as[1,7]

$$\frac{d}{dt}X_1 = f(X_n, u) - k_1 X_1 \tag{2.1}$$

$$\frac{d}{dt}X_j = X_{j-1} - k_j X_j, \quad (2 \leq j \leq n)$$

where X_j and k_j are the dimensionless concentration and the rate constant of the j-th component, respectively, and

$$f(X_n, u) = \frac{u + X_n^p}{1 + X_n^p}. \tag{2.2}$$

Here, p is the cooperativity of the positive feedback system and u is the controllable parameter depending on temperature and concentrations and etc.

Under the steady state approximation, the steady state value, X_n^o, is the solution of the following equation:

$$f(X_n^o, u) - \varphi X_n^o = 0, \tag{2.3}$$

with $\varphi = \prod_{i=1}^{n} k_i$. The steady state value X_n^o is discontinuous at the marginal stability point u_t. As the parameter u is slowly increased, the system reaches a marginal stability point. Further increase in the parameter causes the system to change to another stable branch. As the parameter is decreased, the system evolves to another marginal stability

point. Also, further decrease in the parameter brings about a transition to stable branch. The system has multiple steady states between lower marginal stability point u_l^l and higher marginal stability point u_l^h.

For simplicity let us consider that the cooperativity (p) and the feedback length (n) are both 2 and all kinetic constants are equal to k. In the region of multiple steady states, the stability of the steady states is determined by the linear stability analysis.[11] When there exist three steady states, the lower and higher steady states are stable but the intermediate one is unstable. When the system in a stable steady state is disturbed by random forces, it will be driven away from its state. In terms of the deviation from the steady state value, $x_i = X_i - X_i^0$, the Langevin equation is given as

$$\frac{d}{dt}\begin{pmatrix}\chi_1\\ \chi_2\end{pmatrix} = \begin{pmatrix}-k & h\\ 1 & -k\end{pmatrix}\begin{pmatrix}\chi_1\\ \chi_2\end{pmatrix} + \begin{pmatrix}\zeta_1\\ \zeta_2\end{pmatrix}, \tag{2.4}$$

where

$$h_i = f'(X_n^{0\,i}). \tag{2.5}$$

and i denotes the higher or the lower steady state value. The random forces, ζ_i's, are assumed to satisfy the following Gaussian conditon:

$$\langle \zeta_i(t)\rangle = 0,\ \langle \zeta_i(t)\zeta_j(t')\rangle = 2D_{ij}\delta_{ij}\delta(t-t'), \tag{2.6}$$

where the brackets denote an ensemble average over the fluctuations of the random forces, D_{ij} is the diffusion coefficient, δ_{ij} is the Kronecker delta, and $\delta(t-t')$ is the Dirac delta function.

With the aid of the normalized left and right eigenvectors corresponding to eigenvalue $-\lambda_i$ of the matrix in Eq. (2.4) denoted by $\underset{\sim}{\Psi}^i$ and Ψ^i, respectively, the Langevin equation can be diagonalized. Then, the Fokker–Planck equation for the transition probability is given as[6,10]

$$\frac{\partial}{\partial t}P(y_1, y_2, t\,|\,y_1^0, y_2^0) = \sum_{i,j=1}^{2}\left(\lambda_i\frac{\partial}{\partial y_i}y_i - d_{ij}\frac{\partial^2}{\partial y_i\partial y_j}\right) \times P(y_1, y_2, t\,|\,y_1^0, y_2^0), \tag{2.7}$$

where

$$y_i = \underset{\sim}{\Psi}^i\cdot\underset{\sim}{x},\quad \zeta_i' = \underset{\sim}{\Psi}^i\cdot\underset{\sim}{\zeta}$$
$$2d_{ij}\delta(t-t') = \langle\zeta_i'(t)\zeta_j'(t')\rangle. \tag{2.8}$$

The initial condition for the transition probability is assumed to be the Dirac delta distribution.

Let us define the Fourier transform with respect to the variables q_1 and q_2 as follows.

$$P(y_1, y_2, t\,|\,y_1^0, y_2^0) = (2\pi)^{-2}\int dq_1dq_2\exp[i(q_1y_1+q_2y_2)] \times \widetilde{P}(q_1, q_2, t\,|\,y_1^0, y_2^0). \tag{2.9}$$

Substituting Eq. (2.9) into Eq. (2.7), we obtain the following equation:

$$\frac{\partial}{\partial t}\widetilde{P} = \sum_{i,j=1}^{2}\left(-\lambda_i q_i\frac{\partial}{\partial q_j} - d_{ij}q_iq_j\right)\widetilde{P}_i \tag{2.10}$$

Thus, we may express the solution for $\widetilde{P}(q_1, q_2, t|y_1^0, y_2^0)$ as

$$\widetilde{P} = \prod_{i,j=1}^{2}\exp\{-iq_iM_i'(t) - \frac{1}{2}q_iq_jC_{ij}'(t)\} \tag{2.11}$$

where $M_i'(t)$ and $C_{ij}'(t)$ are the first moment and the variance with respect to the variables y_i's, respectively. It can be shown that the time derivatives of $M_i'(t)$ and $C_{ij}'(t)$ satisfy the following equations,

$$\dot{M}_i'(t) = -\lambda_iM_i'$$
$$\dot{C}_{ij}'(t) = -\delta_{ik}\lambda_kC_{kj}'(t) - C_{ik}'(t)\lambda_k\delta_{kj} + 2d_{ij} \tag{2.12}$$

where the dots denote differentiations with respect to time. Since d_{ij} and $C_{ij}'(t)$ are symmetric, the solutions are

$$M_i'(t) = \exp(-\lambda_it)y_i$$
$$C_{ij}'(t) = 2\frac{1-\exp(-\lambda_i-\lambda_j)t}{\lambda_i+\lambda_j}d_{ij} \tag{2.13}$$

where we have neglected the initial value of $C_{ij}'(t)$. Rewriting y_i and d_{ij} in terms of the original variables with the aid of Eq. (2.8), we may express the probability distribution at a steady state as

$$P_{st}(\chi_1, \chi_2) = P(\chi_1, \chi_2, \infty\,|\,x_1^0, x_2^0, 0) = \frac{1}{2\pi\sqrt{\det C}}\exp\{-\frac{1}{2}([C^{-1}(\infty)]_{11}\chi_1^2 + 2[C^{-1}(\infty)]_{12}\chi_1\chi_2 + [C^{-1}(\infty)]_{22}\chi_2^2)\} \tag{2.14}$$

The expressions of the variance for the system at the steady state are written as

$$C_{11}(\infty) = \frac{2D_{11}}{(\lambda_2-\lambda_1)^2}\{\frac{(k-\lambda_2)^2}{2\lambda_1} + \frac{(k-\lambda_1)^2}{2\lambda_2} - \frac{2(k-\lambda_1)(k-\lambda_2)}{\lambda_1+\lambda_2}\} + 2D_{22}(\frac{(k-\lambda_1)(k-\lambda_2)}{\lambda_2-\lambda_1})^2\{\frac{1}{2\lambda_1} + \frac{1}{2\lambda_2} - \frac{2}{\lambda_1+\lambda_2}\},$$

$$C_{12}(\infty) = \frac{2D_{11}}{(\lambda_2-\lambda_1)^2}\{-\frac{k-\lambda_2}{2\lambda_1} - \frac{k-\lambda_1}{2\lambda_2} + \frac{2k-\lambda_1-\lambda_2}{\lambda_1+\lambda_2}\} - 2D_{22}\frac{(k-\lambda_1)(k-\lambda_2)}{(\lambda_2-\lambda_1)^2}\{\frac{k-\lambda_1}{2\lambda_1} + \frac{k-\lambda_2}{2\lambda_2} - \frac{2k-\lambda_1-\lambda_2}{\lambda_1+\lambda_2}\}, \tag{2.15}$$

$$C_{22}(\infty) = \frac{2D_{11}}{(\lambda_2-\lambda_1)^2}\{\frac{1}{2\lambda_1} + \frac{1}{2\lambda_2} - \frac{2}{\lambda_1+\lambda_2}\} + \frac{2D_{22}}{(\lambda_2-\lambda_1)^2}\{\frac{(k-\lambda_2)^2}{2\lambda_1} + \frac{(k-\lambda_1)^2}{2\lambda_2} - \frac{2(k-\lambda_1)(k-\lambda_2)}{\lambda_1+\lambda_2}\}$$

where

$$\lambda_1 = k+\sqrt{h},\quad \lambda_2 = k-\sqrt{h} \tag{2.16}$$

We assume that the diffusion coefficient of each component is equal, $D_{11} = D_{22} = D$. Then, the inverse and the determinant of the covariance matrix at the steady state are given as

$$[C(\infty)^{-1}]_{11}=\frac{2k(2k^2-h+1)}{D\{4k^2+(h-1)^2\}},$$

$$[C(\infty)^{-1}]_{12}=-\frac{2k^2(h+1)}{D\{4k^2+(h-1)^2\}}, \quad (2.17)$$

$$[C(\infty)^{-1}]_{22}=\frac{2k(2k^2-h^2-h)}{D\{4k^2+(h-1)^2\}},$$

$$det\{C(\infty)\}=\frac{D^2}{4}\{\frac{4k^2+(h-1)^2}{k^2(k^2-h)}\}.$$

Under the condition that the system has three steady states, the upper and lower steady states are stable and the intermediate one is unstable. The probability distribution is the bimodal Gaussian peaked around X_n^{ol} and X_n^{oh}, where X_n^{ol} is the lower concentration steady state and X_n^{oh} is the higher one. It is well known that an arbitrary initial distribution may be expressed as the bimodal Gaussian[5],

$$P_{st}(x_1^\circ, x_2^\circ)=f_h P_{st}^h(x_1^\circ, x_2^\circ)+f_l P_{st}^l(x_1^\circ, x_2^\circ), \quad (2.18)$$

where f_h and f_l are the fractions of the ensemble initially concentrated on the domains of attraction of the steady states X_n^{ol} and X_n^{oh}. For the macroscopic system, the existence of the bimodal Gaussian implies that hysteresis can be observed and the steady state distribution is governed by the initial distribution. The distribution should evolve to a new distribution due to fluctuations. That evolution results in the change of the fraction

$$\Delta f_h=g_l f_l-g_h f_h, \quad (2.19)$$

where g_h is the value of the normalized X_i^{oh} Gaussian below the unstable steady state X_i^* and g_l is the value of the normalized X_i^{ol} Gaussian above X_i^*. When this evolution takes place during a time interval τ, a kinetic equation for the fractional occupancies becomes

$$\frac{d}{dt}f_h=-(f_h-\bar{f}_h)/\bar{\tau}, \quad (2.20)$$

where $\bar{\tau}$ is a new relaxation time given by

$$\bar{\tau}=\tau/(g_l+g_h) \quad (2.21)$$

and $\bar{f}_h$ and $\bar{f}_l$ are the steady state fractions in the two stable steady states:

$$\bar{f}_h=\frac{g_l}{g_l+g_h} \quad \text{and} \quad \bar{f}_l=\frac{g_h}{g_l+g_h}. \quad (2.22)$$

The values of g_l and g_h are obtained by

$$g_l=\int_{x_1^*}^{\infty}\int_{x_2^*}^{\infty}P_{st}^l(x_1, x_2)\,dx_1\,dx_2$$

$$=\frac{1}{4}erfc[\alpha_l(X_1^*-X_1^{\circ l})\,erfc[\beta_h(X_2^*-X_2^{\circ l})] \quad (2.23)$$

and

Table 1. The Ratio of $\bar{f}_l$ and $\bar{f}_h$ for the Parameter u when $\varphi=0.5$ and $D=0.1$ in the System

u	0.01	0.02	0.03	0.04	0.05	0.06	0.07
$\bar{f}_l$	0.978	0.920	0.774	0.519	0.254	0.092	0.022
$\bar{f}_h$	0.022	0.080	0.226	0.481	0.746	0.908	0.978

Table 2. The Ratio of $\bar{f}_l$ and $\bar{f}_h$ for the Parameter u when $\varphi=0.53$ and $D=0.1$ in the System

u	0.055	0.060	0.065	0.070	0.075	0.080	0.085
$\bar{f}_l$	0.948	0.858	0.718	0.530	0.337	0.177	0.065
$\bar{f}_h$	0.052	0.142	0.282	0.470	0.663	0.822	0.935

$$g_h=\int_{-\infty}^{x_1^*}\int_{-\infty}^{x_2^*}P_{st}^h(x_1, x_2)\,dx_1\,dx_2$$

$$=\frac{1}{4}erfc[\alpha_h(X_1^{\circ h}-X_1^*)]\,erfc[\beta_h(X_2^{\circ h}-X_2^*)] \quad (2.24)$$

where α_r and β_r are given as

$$\alpha_r(X_1^{\circ r})=(\frac{C_{22}^r}{2\,det\,C^r}) \quad \text{and} \quad \beta_r(X_2^{\circ r})=(\frac{1}{2C_{22}^r}) \quad (2.25)$$

and $erfc(z)$ is the complementary error function. In Eq. (2.25), r denotes either h or l.

The bimodal Gaussian distribution should evolve to a new distribution by fluctuations. Thus, using the fractions $\bar{f}_h$ and $\bar{f}_l$, we may discuss transitions between stable steady states due to fluctuations. The relaxation to the distribution is governed by $\bar{f}_h$ and $\bar{f}_l$. The values of g_l and g_h are very small except around the critical values (marginal stability points) of u.

Results and Discussion

Multiple steady states in biochemical systems with positive feedback mechanism have been observed.[3] One of the important problems is whether or not phase separation into two stable steady states occurs. If such a phase separation occurs, it is unlikely that it would be at the Maxwell-type construction. The analogue to phase separation in nonequilibrium systems is caused by nonuniformities and the Maxwell construction gives only an approximation to this phenomena. A stochastic diffusion process for which the probability satisfies the Fokker-Planck equation gives bimodal Gaussian probability for the two phases. It is not necessary to equate the probability distributions between the two phases, because the amounts of the two phases can be calculated.

Transition between branches of stable steady states of a biochemically reacting system which is controlled by the positive feedback mechanism represents a change in the parameter of the system. The bimodal Gaussian depends on the fractions of $\bar{f}_l$ and $\bar{f}_h$ as shown in Tables 1 and 2. In the case that $\varphi=0.5$, the values of u_t^h and u_t^l are 2/27 and 0, respectively, and when $\varphi=0.53$ the lower and higher marginal stability points are about 0.053 and 0.086. Near the parameter u_t^h the fraction is $\bar{f}_h \gg \bar{f}_l$ and near u_t^l the value of $\bar{f}_h$ is

very smaller than the value of $\bar{f}_t$. This means that a gradual change of the steady state from one dominated by X^{ol} concentration at u_t^l to one of X^{oh} concentration at u_t^h will be observed. There is a discontinuous change from X^{ol} Gaussian to X^{oh} Gaussian at that value of $u = u_m$ satisfying Maxwell-type construction ($\bar{f}_l/\bar{f}_h = 1$). The ratio depends on the value of the parameter u. For $u < u_m$ the lower steady state is dominant whereas for $u > u_m$, the higher one becomes dominant. This is expected for a large system when observations are made on a time scale far longer than the kinetic processes occurring in the system. Otherwise, the hysteresis will be observed.

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Inter- and Intra-granular Critical Current in $Bi_{1.4}Pb_{0.6}Sr_2Ca_2Cu_{3.6}O_x$ Superconducting Oxide

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A.c. susceptibility for $Bi_{1.4}Pb_{0.6}Sr_2Ca_2Cu_{3.6}O_x$ superconductor is measured as a function of temperature at different value of a.c. magnetic field amplitude. Two transition steps are attributed to the intergranular and intragranular properties. Based on Bean's critical state model, intergranular critical current density, J_c^{gb} (11 A/cm^2 at 77 K) and intragranular critical current density, J_c^g (7×10^3 A/cm^2 at 100 K) are estimated. The low values of J_c^{gb} and J_c^g reflect a poor nature of coupling between grains and the low pinning force density of intragrain in $Bi_{1.4}Pb_{0.6}Sr_2Ca_2Cu_{3.6}O_x$ superconductor.

Introduction

Recently, a new superconducting Bi-Sr-Ca-Cu-O system with high critical temperature was discovered.[1] The Bi-Sr-Ca-Cu-O system mainly contains two superconducting phases, $Bi_2Sr_2Ca_2Cu_3O_x$ (2223 phase) and $Bi_2Sr_2Ca_1Cu_2O_x$ (2212 phase) with T_c of 110 K and 80 K, respectively. Partial substitution of Bi by Pb was found to increase the volume fraction of the 2223 phase.[2] Furthermore, it has been reported that addition of Pb prevents stacking faults of the layer structure and promotes crystallization of the 2223 phase.[3]

In this work, the magnetic and current transport properties of the Bi-Pb-Sr-Ca-Cu-O system are studied by a.c. magnetic susceptibility ($\chi = \chi' - i\chi''$) measurements. The changes of the real part signal χ' and the imaginary part signal χ'' with respect to the temperature are caused by induced shielding current and hysteresis losses, respectively,[4,5] which are related to the critical current density, J_c. The purpose of this study is to estimate the critical current density of $Bi_{1.4}Pb_{0.6}Sr_2Ca_2Cu_{3.6}O_x$ superconductor and to describe the nature of coupling between grains and the intrinsic superconducting property.

Experimental

The 2223 phase was prepared by solid state reactions of a mixture of Bi_2O_3, $PbCO_3$, $SrCO_3$, $CaCO_3$ and CuO with the nominal composition of $Bi_{1.4}Pb_{0.6}Sr_2Ca_2Cu_{3.6}O_x$. The mixed powder was pressed into pellets, and then calcined at 810 °C for 24 hr in air. The resulting pellet was reground, pelletized and finally sintered at 855 °C for 160 hr in air then slowly cooled down to room temperature.

The product was characterized by powder X-ray diffraction with Ni-filtered Cu-K_α radiation. The temperature dependence of electrical resistivity was measured with a conventional four probe method. The microstructure was observed by scanning electron microscope (SEM).