The Time Correlation Function between Fluctuating Concentrations in the Metabolic System with Negative Feedback

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The explicit form of time correlation function between fluctuating concentrations is obtained for the model of metabolic system with negative feedback near a stable(or marginally stable) steady state.

Introduction

The metabolic mechanism is a complex network of enzyme catalyzed reactions which transform substrate molecules into a variety of products. One kind of the most interesting metabolic mechanisms is that which shows a biochemical oscillation. Even though such mechanisms are very complex, Goodwin[1] has proposed a simple model of a biochemical metabolic oscillation for protein synthesis. The generalized model of metabolic system with negative feedback was given by Griffith[2] and Tyson and Othmer[3].

The purpose of the present paper is to obtain the time correlation functions between fluctuating concentrations near a stable(especially, marginally stable) steady state for the model of metabolic system with negative feedback.

In the next section we diagonalize the Langevin equation with a suitable eigenvector[4] and obtain the corresponding linear Fokker-Planck equation. Introducing a function and using the creation and annihilation operators, the probability distribution may be expressed in terms of the coupled Hermite polynomials.[5-6] Then, we may obtain the explicit form of the time correlation functions, which is easily applicable to any metabolic system near a stable (or marginally stable) steady state.

Theory

The concentration X_i of a substance S_i in a negative feedback system is assumed to satisfy a Langevin equation as follows[7-8]

$$\begin{aligned}\frac{d}{dt}X_1&=\frac{C_o}{1+KX_n^{\nu}}-k_1X_1+\xi_1,\\ \frac{d}{dt}X_i&=k_{i-1}X_{i-1}-k_iX_i+\xi_i,\quad (i=2,\cdots,n),\end{aligned}\tag{1}$$

where C_o is the rate constant of the initial substance S_l in the absence of the product S_n; ν is the cooperativity of the feedback inhibition; k_i's are the rate constants; K is the equilibrium constant of the following reaction which yields inactive S

$$E+\nu S_n \rightleftharpoons S. \tag{2}$$

Here E denotes the enzyme. The random force ξ_i is assumed to satisfy the Gaussian condition, that is,

$$<\xi_i>=0,<\xi_i(t)\,\xi_j(t')>=2D_i\delta_{ij}\delta(t-t'), \tag{3}$$

where D_i is the diffusion coefficient of the ith species, δ_{ij} the Kronecker delta and $\delta(t-t')$ the Dirac delta function. Since the magnitudes of the rate constants are arbitrary, we shall assume that all the rate constants are equal to k. Let X_i^o be the steady state value of X_i. Expanding Eq.(1) in terms of $x_i = X_i - X_i^o$ and linearizing it, we have

$$\frac{d}{dt}x=Mx+\xi, \tag{4}$$

where

$$x=(x_1,x_2,\cdots,x_n)^T,\ \xi=(\xi_1,\ \xi_2,\cdots,\ \xi_n)^T,$$

$$M=\begin{pmatrix} -k, & 0, & 0, & \cdots, & -h \\ k, & -k, & 0, & \cdots, & 0 \\ 0, & k, & -k, & \cdots, & 0 \\ \cdot & \cdot & \cdot & \cdots, & 0 \\ \cdot & \cdot & \cdot & \cdots, & 0 \\ \cdot & \cdot & \cdot & \cdots, & 0 \\ 0, & 0, & 0, & k, & -k \end{pmatrix}, \tag{5}$$

$$h=k\nu\left(\frac{c-1}{c}\right),\quad c=1+K(X_n^o)^{\nu}.$$

The Fokker-Planck equation corresponding to Eq.(4) is

$$\begin{aligned}&\frac{\partial}{\partial t}P(x_1,x_2,\cdots,x_n,t)=\Xi P(x_1,x_2,\cdots,x_n,t);\\ &\Xi=-\sum_{i=1}^{n}\frac{\partial}{\partial x_i}\left[\Xi_i-D_i\frac{\partial}{\partial x_i}\right],\end{aligned}\tag{6}$$

where Ξ_i is the ith row vector of the drift term in Eq.(4).

Let the eigenvalue of M and its corresponding right and left eigenvectors be $-\lambda_\alpha$, Ψ^α and $\bar{\Psi}^\alpha$, respectively. Then, we obtain 4

$$\lambda_m=k\left\{1-\left(\nu\frac{c-1}{c}\right)^{\frac{1}{n}}\exp i\left[(2m+1)\frac{\pi}{n}\right]\right\},$$

$$\bar{\Psi}^m = (1, \frac{k-\lambda_m}{k}, \cdots, (\frac{k-\lambda_m}{k})^{n-1}), \tag{7}$$

$$\Psi^m = \frac{1}{n}(1, \frac{k}{k-\lambda_m}, \cdots, (\frac{k}{k-\lambda_m})^{n-1})^T, \ (m=0,1,\cdots,n-1).$$

The stability of the system depends on the parameters ν, c and n.[9] When $\nu(c\text{-}1)/c < \sec^n(2m+1)\pi/n$, the system is stable, while it is unstable in the opposite sign. If $\nu(c\text{-}1)/c = \sec^n(2m+1)\pi/n$, the system shows the sustained oscillation.

With the aid of Eq.(7), Eq.(4) may be rewritten as follows

$$\frac{d}{dt}y_j = -\lambda_{j-1}y_j + \xi'_j, \ (j=1,2,\cdots,n), \tag{8}$$

where

$$y_j = \sum_{i=1}^{n} \bar{\Psi}_i^{j-1}x_i, \ \xi'_j = \sum_{i=1}^{n} \bar{\Psi}_i^{j-1}\xi_i. \tag{9}$$

The Fokker-Planck equation equivalent to Eq.(8) is

$$\frac{\partial}{\partial t}P(y_1, y_2, \cdots, y_n, t) = \Xi P(y_1, y_2, \cdots, y_n, t)$$
$$= -\lambda P(y_1, y_2, \cdots, y_n, t); \tag{10}$$

$$\Xi = \sum_{i,j=1}^{n} [\lambda_{j-1}\frac{\partial}{\partial y_j} + d_{ij}\frac{\partial^2}{\partial y_i \partial y_j}],$$

where

$$d_{ij} = <\xi'_i(t)\,\xi'_j(t)>. \tag{11}$$

In order to obtain a general solution of the Fokker-Planck equation let us introduce a new function defined as

$$\bar{P}(z_1, z_2, \cdots, z_n, t) = \exp(\frac{1}{4}\sum_{j=1}^{n} z_j^2)\,P(y_1, y_2, \cdots, t). \tag{12}$$

where

$$z_j = (\frac{\lambda_{j-1}}{d_{jj}})^{1/2}y_j. \tag{13}$$

Using Eq.(12), Eq.(11) reduces to

$$\frac{\partial}{\partial t}\bar{P} = \Xi_o\bar{P} = -\lambda\bar{P};\ \Xi_o = \exp(\frac{1}{4}\sum_{j=1}^{n} z_j^2)\,\Xi\exp(-\frac{1}{4}\sum_{j=1}^{n} z_j^2). \tag{14}$$

The creation and annihilation operators with respect to z_i are defined as[6]

$$b_i = \frac{\partial}{\partial z_i} + \frac{1}{2}z_{i'},\ \hat{b}_i^+ = -\frac{\partial}{\partial z_i} + \frac{1}{2}z_i. \tag{15}$$

The operators satisfy the following commutation relations

$$[\hat{b}_i, \hat{b}_j^+] = \delta_{ij},\ [\hat{b}_i, \hat{b}_j] = 0,\ [\hat{b}_i^+, \hat{b}_j^+] = 0. \tag{16}$$

Let the eigenfunction of $\hat{b}_i^+\hat{b}_j$ be $\bar{P}_{N_i}(z_i)$. Then, we have

$$\hat{b}_i\bar{P}_{N_i}(z_i) = N_i^{1/2}\bar{P}_{N_i}(z_i),\quad \hat{b}_i^+\bar{P}_{N_i}(z_i) = (N_i+1)^{1/2}\bar{P}_{N_i}(z_i), \tag{17}$$

where N_i is zero or positive integer and the eigenfunction is expressed in terms of the Hermite polynomials

$$\bar{P}_{N_i}(z_i) = \frac{1}{[N_j(2\pi)^{1/2}]^{1/2}}\exp(-\frac{1}{4}z_i^2)\,H_{N_i}(z_i/2^{1/2});\tag{18}$$

$$H_{N_i}(z_i) = (-1)^{N_i}\exp(\frac{1}{2}z_i^2)\ \frac{d^{N_i}}{dz_i^{N_i}}\exp(-\frac{1}{2}z_i^2).$$

The operator in Eq.(14) is given as

$$\Xi_o = -\sum_{j>1=1}^{n}[\lambda_i\hat{b}_i^+\hat{b}_i - \rho_{ij}\hat{b}_i^+\hat{b}_j^+];\ \rho_{ij} = 2(\frac{d_{ij}^2\lambda_{i-1}\lambda_{j-1}}{d_{ii}d_{jj}})^{1/2}. \tag{19}$$

A general solution of Eq.(14) may be expressed as

$$\bar{P}(z_1, z_2, \cdots, z_n, t) = \sum_{\{N_i\}}^{\infty} C_{\{N_i\}}\exp(-\lambda t)\,\bar{P}_{N_1}(z_1)\cdots\bar{P}_{N_n}(z_n), \tag{20}$$

where the summation notation and $C_{\{N_i\}}$ are

$$\sum_{\{N_i\}}^{\infty} = \sum_{N_1=0}\sum_{N_2=0}\cdots\sum_{N_n=0},\quad C_{\{N_i\}} = C_{N_1, N_2, \cdots, N_n} \tag{21}$$

The above solution indicates that the eigenfunctions are coupled each other through $C_{\{N_i\}}$ and eigenvalue.

Let $N = N_1 + N_2 + \cdots + N_n$ to obtain the eigenvalue. Then, Eq.(20) may be rewritten as

$$\bar{P}(z_1, z_2, \cdots, z_n, t) = \sum_{N=0}^{\infty}\sum_{\{N_i\}}^{N}{}' \ C'^{N}_{\{N_i\}}\exp(-\lambda t)\prod_{i=1}^{n}\bar{P}_{N_i}(z_1), \tag{22}$$

where $N \geq N_i \geq 0$ and the prime in the sum and $C_{\{N_i\}}$ means that one of the N_i's is omitted. Substitution of Eq.(22) into Eq.(16) leads to

$$\sum_{N=0}\sum_{\{N_i\}}^{N}{}' \ \{(\lambda_i N_i - \lambda)\,C'^{N}_{\{N_i\}}\prod_{i=0}^{n}\bar{P}_{N_i}(z_i) - \rho_{ij}[(N_i+1)\ (N_j+1)]^{1/2}$$
$$C'^{N+2}_{N_1,\cdots,N_i+1,\cdots,N_j+1,\cdots,N_n}\cdot\bar{P}_{N_i+1}(z_i)\,\bar{P}_{N_j+1}(z_j)$$
$$\prod_{\substack{s=1\\ s=i,j}}^{n}\bar{P}_{N_s}(z_s)\} = 0. \tag{23}$$

From the above equation we may obtain the recurrence formula for the eigenvalue

$$(\sum_{i=0}\lambda_{i-1}N_i - \lambda)\,C'^{N}_{\{N_i\}} = 0,\ \text{when}\ N=0\ \text{or}\ 1, \tag{24a}$$

$$(\sum_{i=0}\lambda_{i-1}N_i - \lambda)\,C'^{N}_{\{N_i\}} - \sum_{j>i=1}^{n}\rho_{ij}[(N_i+1)\ (N_j+1)]^{1/2}$$
$$\times C_{N_1,\cdots,\cdots N_i+1,\cdots,N_j+1,\cdots,N_n} = 0,\text{if}\ N \geqq 2. \tag{24b}$$

In Eq.(24a) $N = 0$ describes the steady state of the system.

Now, let us define the time correlation function between x_i and x_l near a steady state[4]

$$G_{x_ix_1}(t) = <x_i\exp(\Xi t)\,x_1>_\sigma \tag{25}$$

where $<\cdots>_o$ denotes the average over the probability distribution at a steady state. With the aid of Eqs.(9) and (13) we have

$$x_i = \frac{1}{|\bar{\Psi}|}\sum_{j=1}^{n}(\frac{d_{ii}}{\lambda_{i-1}})^{1/2}|\bar{\Psi}|_j^{i-1}z_{j'} \tag{26}$$

where $|\bar{\Psi}|$ is the determinant of the matrix consisted of the eigenvectors $\bar{\Psi}^{j\text{-}1}$ ($j = 1,2,\cdots,n$) and $|\bar{\Psi}|_j^{i\text{-}1}$ is the cofactor of the element $\bar{\Psi}_j^{i\text{-}1}$ in the determinant $|\bar{\Psi}|$. Using Eqs.(17), (22), (24a) and (26), the correlation function betwen x_l and x_p becomes

$$G_{x_ix_p}(t) = G_{x_px_i}(t) = \frac{1}{|\bar{\Psi}|^2}\sum_{k=1}^{n}|\bar{\Psi}|_k^{i-1}|\bar{\Psi}|_k^{p-1}(\frac{d_{kk}}{\lambda_{k-1}})$$
$$\times\exp(-\lambda_{k-1}t). \tag{27}$$

The above result holds unless the state is unstable. The relaxation time is defined as the inverse of real part of $\lambda_{k\text{-}1}$, which is, in general, complex. At the marginally stable steady state the relaxation time becomes infinite. This means that the system at the marginal state does not relax to the stable steady state but always oscillates on the closed trajectory.

In a forthcoming paper we shall apply the general result to a specific model, that is, the Goodwin model for protein synthesis[1] and then in detail discuss the physical and biological meanings of the results.

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Facile Reduction of Carboxylic Acid Salts to Aldehydes by Boron Hydrides, Thexylbromoborane-Dimethyl Sulfide and 9-Borabicyclo[3.3.1]nonane[†]

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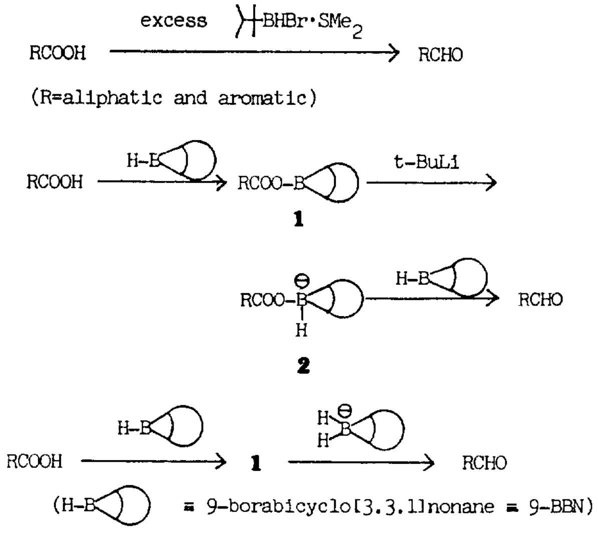
New methods for the reduction of carboxylic acid salts to aldehydes with 2 equiv of thexylbromoborane-dimethyl sulfide ($ThxBHBr{\cdot}SMe_2$) or 9-borabicyclo[3.3.1]nonane (9-BBN) are described. Both these reagents provide the corresponding aldehydes from various sodium and lithium salts of carboxylic acids in high yields both at room temperature. Such facile reductions are explained as the simple substitution for the bromo group of ThxBHBr by a carboxylate to form thexyl(acyloxy)borane followed by reduction with excess reagent and the formation of an ate complex followed by reduction with excess 9-BBN.

Introduction

Transformation of carboxylic acid derivatives, such as esters, amides, acid chlorides, nitriles, etc., to the corresponding aldehydes is of great importance because of their versatile utility in organic synthesis. Various useful methods for preparation of aldehydes from carboxylic acid derivatives have been developed[1], however there have been no report for the direct conversion of metal salts of carboxylic acid to aldehydes. Very recently, we have reported that thexylbromoborane-dimethyl sulfide ($ThxBHBr{\cdot}SMe_2$)[2] and 9-borabicyclo-[3.3.1]nonane (9-BBN)[3] can achieve the direct conversion of carboxylic acids to the corresponding aldehydes in high yields (eqs 1-3). This result intrigued us. Consequently, we have investigated to find out the new methodology for the direct conversion of carboxylic acid salts to aldehydes using such unique reducing agents.



(1)

(2)

(3)

In this paper, we describe details of such apparently first development for the direct conversion of sodium and lithium salts of carboxylic acids to aldehydes, which have already reported in a forn of communication[2a,4], including the mechanistic considerations as well as the isolation method of aldehyde products.

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