社団法人　電子情報通信学会
THE INSTITUTE OF ELECTRONICS,
INFORMATION AND COMMUNICATION ENGINEERS

信学技報
TECHNICAL REPORT OF IEICE.
MBE2000-53 (2000-09)

Mathematical Method for Stochastic Approach for Biochemical Reactions.

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We introduced a method for analyzing the probabilistic behavior of a biochemical reaction. The target reaction was simplified to be composed of sufficient amount of substrate, enzyme, intermediate product and the final product. The random variables E(t), S(t), C(t) and P(t) represented the number of enzyme, substrate, intermediate complex and product molecules at time t. Let e, s, c and p denote integer values that these random variables can assume. The Kolmogorov forward equation was induced for the probabilistic behavior of the system. By defining the generator function of the system, we obtained the partial differential equation that the probability generating function satisfies. By expanding the generating function, we could obtain the mean (expected value) and the variance of the biochemical behaviors. The present method will be available for evaluating the stochastic behavior of the single component biochemical reaction.

Biochemical reaction. Probabilistic differential equation, Generator function. Kolmogorov equation.

生化学反応に対する確率的解析方法

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生化学反応を確率的に解析する方法を紹介した。反応系は基質１分子、生成物質１分子で構成される、最も単純な場合とした。基質は十分量存在し、生成物質は極端に大量ではなく逆方向解離は無視できるとした。確率変数によって酵素分子数、基質分子数、中間生成物質分子数、生成物質数を定義した。確率的にこれらの変数は整数値のみをとるとした。任意の時刻における酵素数と生成物質数を規定する状態確率に対するKolmogorov方程式を導出し、それに対して確率母関数を定義し、その方程式を偏微分方程式を解くことで求めた。求めた母関数を級数展開することで、反応系の期待値、定常偏差を決定することができた。　本研究は単一反応における確率的挙動を推定するうえで有用である。

生化学反応．確率微分方程式．Kolmogorov方程式．確率母関数．期待値、定常偏差

1. The Stochastic model.

We consider the general reaction

$$E+S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \underbrace{ES \rightleftharpoons EP}_{C} \underset{k_4}{\overset{k_3}{\rightleftharpoons}} E+P, \qquad (I)$$

where k1, k2, k3 and k4 are the rate constants for individual steps of the reaction. The random variables E(t), S(t), C(t) and P(t) represent the number of enzyme, substrate , intermediate complex and product molecules at time t. Let e, s, c and p denote integer values that these random variables can assume.

State	*Probability*
$e-1, s-1, c+1, p$	$k_1 es\Delta t+o(\Delta t)$
$e+1, s+1, c-1, p$	$k_2 c\Delta t+o(\Delta t)$
$e+1, s, c-1, p+1$	$k_3 c\Delta t+o(\Delta t)$
$e-1, s, c+1, p-1$	$k_4 ep\Delta t+o(\Delta t)$
e, s, c, p (no change)	$1-\begin{Bmatrix} k_1 es+k_4 ep \\ +k_2 c+k_3 c\end{Bmatrix}\Delta t+o(\Delta t),$

$$s+c+p=S_0$$
$$e+c=E_0,$$

the stochastic model can be described in the following way:

Transition in time Δt	*Probability*
$(e, p)\to(e-1, p)$	$k_1 S_0 e\Delta t+o(\Delta t)$
$(e, p)\to(e+1, p)$	$k_2(E_0-e)\Delta t+o(\Delta t)$
$(e, p)\to(e+1, p+1)$	$k_3(E_0-e)\Delta t+o(\Delta t)$
$(e, p)\to(e, p)$ (no change)	$1-[k_1 S_0 e+(k_2+k_3)(E-e)]\Delta t+o(\Delta t)$

where the probability of more than one molecular transition in the interval $(t, t+\Delta t)$ is $o(\Delta t)$.

3. The Joint Generating Function for *E* and *P*

Let

$$P^*_{e,p}(t)=Pr(E(t)=e, P(t)=p).$$

We proceed to derive the forward Kolmogorov equations for $P^*_{e,p}(t)$. We have,

$$\begin{aligned}P^*_{e,p}(t+\Delta t)=&[1-k_1S_0e\Delta t-(k_2+k_3)(E_0-e)\Delta t]P^*_{e,p}(t)\\ &+(1-\delta_{e,E_0})k_1S_0(e+1)P^*_{e+1,p}(t)\Delta t\\ &+(1-\delta_{e,0})k_2(E_0-e+1)P^*_{e-1,p}(t)\Delta t\\ &+(1-\delta_{e,0})(1-\delta_{p,0})k_3(E_0-e+1)P^*_{e-1,p-1}(t)\Delta t+o(\Delta t)\end{aligned} \qquad (1)$$

where $\delta_{j,k}$ is the Kronecker delta,

$$\delta_{j,k}=\begin{cases}1 \text{ if } j=k\\ 0 \text{ if } j\neq k,\end{cases}$$

and $0\leqq e\leqq E_0$, $0\leqq p\leqq S_0$. Then, upon transferring the term $P^*_{e,p}(t)$ to left-hand side of expression (1), dividing by Δt, and letting $\Delta t\to 0$, obtain the system of forward Kolmogorov equations,

$$\begin{aligned}\frac{d}{dt}P^*_{e,p}(t)=&-[k_1S_0e+(k_2+k_3)(E_0-e)]P^*_{e,p}(t)\\ &+(1-\delta_{e,E_0})k_1S_0(e+1)P^*_{e+1,p}(t)\\ &+(1-\delta_{e,0})k_2(E_0-e+1)P^*_{e-1,p}(t)\\ &+(1-\delta_{e,0})(1-\delta_{p,0})k_3(E_0-e+1)P^*_{e-1,p-1}(t),\end{aligned} \qquad (2)$$

$0\leqq e\leqq E_0$, $0\leqq p\leqq S_0$.

In order to deal with system (2) of difference-differential equations introduce the generating function

$$\phi(u, v, t)=\sum_{e=0}^{E_0}\sum_{p=0}^{S_0}u^ev^pP^*_{e,p}(t), \qquad (3)$$

$0\leqq u\leqq 1$, $0\leqq v\leqq 1$.

Then, upon multiplying (2) by u^ev^p and summing over the possible valu *e* and *p*, we obtain, after some algebra, the partial differential equation

$$\frac{\partial\phi}{\partial t}=[-(k_2+k_3v)u^2-(k_1S_0-k_2-k_3)u+k_1S_0]\frac{\partial\phi}{\partial u} \qquad (4)$$
$$-E_0[k_2+k_3-u(k_2+k_3v)]\phi.$$

Equation (4) can be solved by standard methods in the theory of differential equations (see Appendix). The solution is found to be

$$\phi(u, v, t)=\left[\frac{\{1-\exp(-k_1S_0t(\alpha(v)+\beta(v)))\}+u\{\alpha(v)+\beta(v)\exp(-k_1S_0t(\alpha(v)+\beta(v)))\}}{\alpha(v)+\beta(v)}\right]^{E_0} \qquad (5)$$
$$\times\exp(E_0t(k_1S_0\alpha(v)-k_2-k_3)),$$

where

$$\alpha(v)=\frac{2(k_2+k_3v)}{k_1S_0-k_2-k_3+[(k_1S_0-k_2-k_3)^2+4k_1S_0(k_2+k_3v)]^{\frac{1}{2}}},$$
$$\beta(v)=\frac{2(k_2+k_3v)}{-k_1S_0+k_2+k_3+[(k_1S_0-k_2-k_3)^2+4k_1S_0(k_2+k_3v)]^{\frac{1}{2}}}.$$

4. Distributions of the Components of the Reaction

Putting $v=1$, we have $\alpha(1)=(k_1S_0)^{-1}(k_2+k_3)$, $\beta(1)=1$, and from (5),

$$\begin{aligned}\phi(u, 1, t)=&\sum_{e=0}^{E_0}Pr(E(t)=e)u^e\\ =&\left[\frac{k_1S_0}{k_1S_0+k_2+k_3}\{1-\exp[-(k_1S_0+k_2+k_3)t]\}\right.\\ &\left.+\frac{u}{k_1S_0+k_2+k_3}\{k_2+k_3+k_1S_0\exp[-(k_1S_0+k_2+k_3)t]\}\right]^{E_0}.\end{aligned} \qquad (6)$$

The distribution of $E(t)$ is seen to be binomial and, upon expanding in (6),

$$\begin{aligned}Pr(E(t)=e)=&\binom{E_0}{e}\left[\frac{1}{k_1S_0+k_2+k_3}\right.\\ &\left.\times\{k_2+k_3+k_1S_0\exp[-(k_1S_0+k_2+k_3)t]\}\right]^e\\ &\times\left[\frac{k_1S_0}{k_1S_0+k_2+k_3}\{1-\exp[-(k_1S_0+k_2+k_3)t]\}\right]^{E_0-e}\end{aligned} \qquad (7)$$

$0\leqq e\leqq E_0$. The mean of $E(t)$ is then readily found to be

$$\begin{aligned}\mu_E=&\sum_{e=0}^{E_0}ePr(E(t)=e)\\ =&\frac{E_0}{k_1S_0+k_2+k_3}\left[k_2+k_3+k_1S_0\exp[-(k_1S_0+k_2+k_3)t]\right],\end{aligned} \qquad (8)$$

and the variance is

$$\begin{aligned}\sigma_E^2=&\sum_{e=0}^{E_0}e^2Pr(E(t)=e)-\left[\sum_{e=0}^{E_0}ePr(E(t)=e)\right]^2\\ =&\frac{k_1S_0E_0}{(k_1S_0+k_2+k_3)^2}\left[k_2+k_3+k_1S_0\exp\{-(k_1S_0+k_2+k_3)t\}\right]\\ &\times\left[1-\exp\{-(k_1S_0+k_2+k_3)t\}\right].\end{aligned} \qquad (9)$$

Next, putting $u=1$ in (5) and noting that

$$k_1S_0(\beta(v)-\alpha(v))=k_1S_0-k_2-k_3,$$

we have

t

$$\begin{aligned}\phi(1, v, t)=&\sum_{p=0}^{S_0}Pr(P(t)=p)\,v^p\\ =&\left[\frac{k_2+k_3-k_1S_0\exp\{-(k_2+k_3-k_1S_0+2k_1S_0\beta(v))t\}+k_1S_0\beta(v)(1+\exp\{-(k_2+k_3-k_1S_0+2k_1S_0\beta(v))\})}{k_2+k_3-k_1S_0+2k_1S_0\beta(v)}\right]^{E_0}\\ &\times\exp\{E_0k_1S_0t(\beta(v)-1)\}.\end{aligned} \qquad (10)$$

The mean, μ_P, and variance σ_P^2 of $P(t)$ are then found by tedious but strai forward calculations to be

$$\begin{aligned}\mu_P=&\sum_{p=0}^{S_0}pPr(P(t)=p)=\left[\frac{\partial\phi(1, v, t)}{\partial v}\right]_{v=1}\\ =&\frac{E_0k_1k_3S_0}{k_1S_0+k_2+k_3}\left[t-\frac{1}{k_1S_0+k_2+k_3}(1-\exp\{-(k_1S_0+k_2+k_3)t\})\right],\end{aligned} \qquad (11)$$

$$\begin{aligned}\sigma_P^2=&\sum_{p=0}^{S_0}p^2Pr(P(t)=p)-\left[\sum_{p=0}^{S_0}pPr(P(t)=p)\right]^2\\ =&\left[\frac{\partial^2\phi(1, v, t)}{\partial v^2}\right]_{v=1}+\left[\frac{\partial\phi(1, v, t)}{\partial v}\right]_{v=1}-\left\{\left[\frac{\partial\phi(1, v, t)}{\partial v}\right]_{v=1}\right\}^2\\ =&E_0\left[\frac{k_1k_3S_0t}{k_1S_0+k_2+k_3}+\frac{k_1^2k_3^2S_0^2}{(k_1S_0+k_2+k_3)^4}\right.\\ &\times\Big\{8(1-\exp\{-(k_1S_0+k_2+k_3)t\})\\ &-4(k_1S_0+k_2+k_3)t\exp\{-(k_1S_0+k_2+k_3)t\}\\ &\left.-(1-\exp\{-(k_1S_0+k_2+k_3)t\})^2-4(k_1S_0+k_2+k_3)t\Big\}\right].\end{aligned} \qquad (12)$$

The correlation between $E(t)$ and $P(t)$ is

$$\begin{aligned}\mathrm{corr}\,(E(t), P(t))=&\sigma_P^{-1}\sigma_E^{-1}\,\mathrm{cov}\,(E(t), P(t))\\ =&\sigma_P^{-1}\sigma_E^{-1}\left\{\left[\frac{\partial^2\phi}{\partial u\partial v}\right]_{u=1\ v=1}-\mu_P\mu_E\right\} \qquad (13)\\ =&-\sigma_P^{-1}\sigma_E^{-1}\frac{E_0k_1^2k_3S_0^2}{(k_1S_0+k_2+k_3)^3}\Big\{2t(k_1S_0+k_2+k_3) \qquad (13\\ &\times\exp\{-(k_1S_0+k_2+k_3)t\}\\ &-(1-\exp\{-2(k_1S_0+k_2+k_3)t\})\Big\},\end{aligned}$$

APPENDIX

A] Induction of equation (4)

Multiply $u^e v^p$ on both sides of (2)

$$d/dt \sum_{e=0}^{E0}\sum_{p=0}^{S0} u^e v^p P^{\cdot}_{e\cdot p}(t)$$

$$= \sum_{e=0}^{E0}\sum_{p=0}^{S0} k_1 S_0 e u^e v^p P^{\cdot}_{e\cdot p}(t) - \sum_{e=0}^{E0}\sum_{p=0}^{S0}(k_2+k_3)E_0 u^e v^p P^{\cdot}_{e\cdot p}(t)$$

$$+\sum_{e=0}^{E0}\sum_{p=0}^{S0}(k_2+k_3)e u^e v^p P^{\cdot}_{e\cdot p}(t) + \sum_{e=0}^{E0}\sum_{p=0}^{S0} k_1 S_0 (e+1) u^e v^p P^{\cdot}_{e+1\cdot p}(t)$$

$$+\sum_{e=0}^{E0}\sum_{p=0}^{S0} k_2 E_0 u^e v^p P^{\cdot}_{e-1\cdot p}(t) - \sum_{e=0}^{E0}\sum_{p=0}^{S0} k_2 (e-1) u^e v^p P^{\cdot}_{e-1\cdot p}(t)$$

$$+\sum_{e=0}^{E0}\sum_{p=0}^{S0} k_3 E_0 u^e v^p P^{\cdot}_{e-1\cdot p-1}(t) - \sum_{e=0}^{E0}\sum_{p=0}^{S0} k_3 (e-1) u^e v^p P^{\cdot}_{e-1\cdot p-1}(t)$$

Now we set $\phi(u,v,t) = \sum_{e=0}^{E0}\sum_{p=0}^{S0} u^e v^p P^{\cdot}_{e\cdot p}(t)$

Then,

$$\partial\phi/\partial u = \sum_{e=0}^{E0}\sum_{p=0}^{S0} e u^{e-1} v^p P^{\cdot}_{e\cdot p}(t)$$

$$= \sum_p \left[0\cdot u^{-1}\cdot P_0 + 1\cdot u^0\cdot P_1 + 2\cdot u\cdot P_2 + \cdots\right]v^p$$

$$= \sum_{e=0}^{E0}\sum_{p=0}^{S0} (e+1) u^e P_{e+1\cdot p}(t) \qquad : \text{ The 4th term}$$

$$u\cdot\partial\phi/\partial u = \sum_p \left[0\cdot u^0\cdot P_0 + 1\cdot u^1\cdot P_1 + 2\cdot u^2\cdot P_2 + \cdots\right]v^p$$

$$= \sum_{e=0}^{E0}\sum_{p=0}^{S0} e u^e P_{e\cdot p}(t) v^p$$

$$u\cdot\phi = \sum_{e=0}\sum_{p=0} u^{e+1} v^p P^*_{e\cdot p}$$

$$= \sum_{p=0} v^p\left[u\cdot P_0 + u^2 P_1 + u^3 P_2 + \cdots\right]$$

$$= \sum_{p=0} v^p\left[u^0\cdot P_{-1} + u\cdot P_0 + u^2\cdot P_1 + u^3\cdot P_2\cdots\right]$$

$$= \sum_{p=0} v^p \sum_{e=0} u^e P_{e-1p} \qquad : \text{ The 5 th term}$$

$$u\cdot v\cdot\phi = \sum_{p=0}\sum_{e=0} v^p u^e P_{e-1p-1} \qquad : \text{The 7 th term}$$

$$u^2\cdot\frac{\partial\phi}{\partial u} = \sum_{p=0}\sum_{e=0} e u^{e+1} v^p P_{e\cdot p}$$

$$= \sum_{p=0}\left[0\cdot u^1\cdot P_0 + 1\cdot u^2\cdot P_1 + 2\cdot u^3\cdot P_2 + 3\cdot u^4\cdot P_3\cdots\right]v^p$$

$$= \sum_{p=0}\left[(-1)\cdot u\cdot P_{-1} + 0\cdot u^1\cdot P_0 + 1\cdot u^2\cdot P_1 + 2\cdot u^3\cdot P_2 + 3\cdot u^4\cdot P_3 + \cdots\right]v^p$$

$$= \sum_{p=0}\sum_{e=0} (e-1) u^e\cdot P_{e-1p}\cdot v^p \qquad : \text{ The 6 th term}$$

Next we seek $\sum_{p=0}\sum_{e=0}(e-1)u^e\cdot v^p\cdot P^*_{e-1\cdot p-1}(t)$

$$v\cdot u^2\cdot\frac{\partial\phi}{\partial u} = \sum_{p=0}\sum_{e=0}(e-1)u^e\cdot P_{e-1\cdot p}\cdot v^{p+1}$$

$$= \sum_{e=0}(e-1)u^e\left[v^1\cdot P_0 + v^2\cdot P_1 + v^3\cdot P_2 + \cdots\right]$$

$$= \sum_{e=0}(e-1)u^e\left[v^0\cdot P_{-1} + v^1\cdot P_0 + v^2\cdot P_1 + v^3\cdot P_2\cdots\right]$$

$$= \sum_{e=0}(e-1)u^e \sum_{p=0} v^p\cdot P_{p-1\cdot e-1} \qquad : \text{The 8 th term}$$

Substitute these transformations to the right side

$$= -k_1 S_0\cdot u\cdot\partial\phi/\partial u - (k_2+k_3)\cdot E_0\cdot\phi$$
$$+ (k_2+k_3)\cdot u\cdot\partial\phi/\partial u + k_1 S_0\cdot\partial\phi/\partial u$$
$$+ k_2 E_0\cdot u\cdot\phi - k_2 u^2\cdot\partial\phi/\partial u$$
$$+ k_3 E_0\cdot u\cdot v\cdot\phi - k_3 v\cdot u^2\cdot\partial\phi/\partial u$$
$$= \left[-(k_1 S_0 - k_2 - k_3)u + k_1 S_0 - (k_2 + v k_3)u^2\right]\partial\phi/\partial u$$
$$- E_0\left[k_2 + k_3 - k_2 u - k_3 u\cdot v\right]\phi \qquad \text{------------ (4)}$$

B] Solution of the equation (4).

Setting

$$\varphi(u,v,t) = E_0^{-1}\cdot\log\phi(u,v,t)$$

We have

$$\frac{\partial\varphi}{\partial t} = E_0^{-1}\frac{\partial\log\phi}{\partial t} = \frac{1}{E_0}\frac{1}{\phi}\frac{\partial\phi}{\partial t}$$

$$\frac{\partial\varphi}{\partial u} = \frac{1}{E_0}\frac{1}{\phi}\frac{\partial\phi}{\partial u}$$

Hence,

$$E_0\cdot\phi\cdot\frac{\partial\varphi}{\partial t} = \left[-(k_1 S_0 - k_2 - k_3)u + k_1 S_0 - (k_2 + v k_3)u^2\right]E_0\phi\frac{\partial\varphi}{\partial u}$$
$$- E_0\left[k_2 + k_3 - k_2 u - k_3 u\cdot v\right]\phi$$

Eliminate $E_0\cdot\phi$ on both sides

$$\frac{\partial\varphi}{\partial t} = \left[-(k_1 S_0 - k_2 - k_3)u + k_1 S_0 - (k_2 + v k_3)u^2\right]\frac{\partial\varphi}{\partial u}$$
$$-\left[k_2 + k_3 - k_2 u - k_3 u\cdot v\right]$$

Putting $K_1 = k_1 S_0$ $\quad K_2 = k_2 + k_3$ we have

$$\frac{\partial\varphi}{\partial t} = \left[-(k_2 + v k_3)u^2 - (K_1 - K_2)u + K_1\right]\frac{\partial\varphi}{\partial u} - \left[K_2 - u(k_2 + v k_3)\right]$$

---------------(A2)

We solve above equation by Lagrange method.

The first term in the right side can be regarded as the quadratic equation.

$$(k_2 + v k_3)u^2 + (K_1 - K_2)u - K_1 = 0$$

$$u = \frac{-(K_1 - K_2) \pm \sqrt{(K_1 - K_2)^2 + 4(k_2 + v k_3)\cdot K_1}}{2(k_2 + v k_3)}$$

Hence

$$(k_2 + v k_3)u^2 + (K_1 - K_2)u - K_1 = K_1\left[\alpha(v)u + 1\right]\left[\beta(v)u - 1\right]$$

$$\frac{1}{\alpha(v)} = \frac{(K_1 - K_2) + \sqrt{(K_1 - K_2)^2 + 4K_1(k_2 + v k_3)}}{2(k_2 + v k_3)}$$

$$\frac{1}{\beta(v)} = \frac{(-K_1 + K_2) + \sqrt{(K_1 - K_2)^2 + 4K_1(k_2 + v k_3)}}{2(k_2 + v k_3)}$$

※

We seek

$$(k_2+vk_3)u^2+(K_1-K_2)u-K_1=K_1[\alpha(v)u+1][\beta(v)u-1]$$

the coefficients of $\alpha(v)$ and $\beta(v)$. Eliminate K_1 on the both sides and the right side is

$$=(\alpha\beta)u^2+(\beta-\alpha)u-1$$

and

$$\alpha\beta=(k_2+vk_3)/K_1$$
$$\beta-\alpha=(K_1-K_2)/K_1$$

We have

$$\alpha=\frac{(-K_1+K_2)\pm\sqrt{(K_1-K_2)^2+4K_1(k_2+vk_3)}}{2K_1}$$

$$\frac{1}{\alpha}=\frac{(K_1-K_2)+\sqrt{(K_1-K_2)^2+4K_1(k_2+vk_3)}}{2(k_2+vk_3)}$$

Similarly, we have

$$\beta=\frac{(K_1-K_2)\pm\sqrt{(K_1-K_2)^2+4K_1(k_2+vk_3)}}{2K_1}$$

$$\frac{1}{\beta}=\frac{-(K_1-K_2)+\sqrt{(K_1-K_2)^2+4K_1(k_2+vk_3)}}{2(k_2+vk_3)}$$

In addition, from another auxially equation in (A2)

$$u\cdot(k_2+k_3v)=u\cdot K_1\cdot\alpha\cdot\beta$$

Then, we have

$$\frac{dt}{1}=\frac{du}{K_1[\alpha(v)u+1][\beta(v)u-1]}=\frac{dv}{0}=-\frac{d\varphi}{K_2-K_1\alpha\cdot\beta\cdot u}$$

One integral is clearly

$$v=c$$

We use this to find another two solutions. We have

$$\frac{d\varphi}{du}=-\frac{(K_2-K_1\alpha(c)\beta(c)u)}{K_1[\alpha(c)u+1][\beta(c)u-1]}$$

By partial fractuation,

$$\frac{d\varphi}{du}=\frac{(K_1\beta+K_2)\alpha}{K_1(\alpha+\beta)}\frac{1}{(\alpha u+1)}+\frac{(K_1\alpha-K_2)\beta}{K_1(\alpha+\beta)}\frac{1}{(\beta u-1)}$$

$$=\frac{d}{du}\left[\frac{(K_1\beta+K_2)}{K_1(\alpha+\beta)}\log(\alpha u+1)+\frac{(K_1\alpha-K_2)}{K_1(\alpha+\beta)}\log(\beta u-1)\right]$$

From this we have

$\psi=(K1\ \beta+K2)/[(K1\ (\alpha+\beta)]\log(\alpha u+1)$
$+(K1\ \alpha-K2)[(K1(\alpha+\beta)]\log(\beta u-1)$

where α,β are functions of c

About the second solution

$$\varphi=\frac{(K_1\beta(v)+K_2)}{K_1(\alpha(v)+\beta(v))}\log(\alpha(v)u+1)+\frac{(K_1\alpha(v)-K_2)}{K_1(\alpha(v)+\beta(v))}\log(\beta(v)u-1)$$

Then, for the final combination, we have

$$\frac{dt}{1}=\frac{du}{K_1[\alpha u+1][\beta u-1]}$$

Therefreo, we have

$$K_1\frac{dt}{du}=\frac{1}{(\alpha+\beta)}\left[\frac{\beta}{(\beta u-1)}-\frac{\alpha}{(\alpha u+1)}\right]$$

$=1/(\alpha+\beta)\ d\,[\log[(\beta u-1)/(\alpha u+1)]]/du$

Then

$$K_1\cdot t=\frac{1}{[\alpha(v)+\beta(v)]}\log\left[\frac{\beta(v)\cdot u-1}{\alpha(v)\cdot u+1}\right]+c$$

Therefore, the general solution of (A2) is

$$\varphi(u,v,t)+\frac{(K_2-K_1\alpha(v))}{K_1[\alpha(v)+\beta(v)]}\log[\beta(v)u-1]$$
$$-\frac{(K_2+K_1\beta(v))}{K_1[\alpha(v)+\beta(v)]}\log[\alpha(v)u+1]$$
$$=\Phi\cdot\left[K1\cdot t-\frac{1}{(\alpha(v)+\beta(v))}\log\left[\frac{\beta(v)u-1}{\alpha(v)u+1}\right]\right]\text{-------(A3)}$$

Here, Φ is an unknown function. We determine this by using the initial conditon at $t=0$

$$\phi(u,v,0)=u_0^E$$

In another form,

$$\varphi(u,v,0)=\log u$$

Putting t=o (A－3), we have

$$\Phi\cdot\left[-\frac{1}{\alpha+\beta}\log\left(\frac{\beta u-1}{\alpha u+1}\right)\right]=\log u+\frac{(K_2-K_1\alpha)}{K_1(\alpha+\beta)}\log(\beta u-1)+\frac{(K_2+K_1\beta)}{K_1(\alpha+\beta)}\log(\alpha u+1)$$

$=\log u+\{(K2-K1\ \alpha)\log(\beta u-1)-(K2-K1\ \alpha$
$+K1\ \alpha+K1\ \beta)\ \log(\alpha u+1)\}/[K1(\alpha+\beta)]$

$$=\log u+\frac{(K_2-K_1\alpha)}{K_1(\alpha+\beta)}\log\left[\frac{\beta u-1}{\alpha u+1}\right]-\log(\alpha u+1)$$

Now, we set $\omega=-\frac{1}{\alpha+\beta}\cdot\log\left[\frac{\beta u-1}{\alpha u+1}\right]$

Then $u=\frac{1+e^{-(\alpha+\beta)\omega}}{\beta-\alpha\cdot e^{-(\alpha+\beta)\omega}}$

Substitute this to (A_4)

$$\Phi(\omega)=\log\left[\frac{u}{\alpha u+1}\right]+\frac{(K_2-K_1\alpha)}{K_1(\alpha+\beta)}\cdot\log\left[\frac{\beta u-1}{\alpha u+1}\right]$$
$$=\log\left[\frac{u}{\alpha u+1}\right]+(K_1\alpha-K_2)\frac{\omega}{K_1}$$

$$\alpha u+1=\frac{(\alpha+\beta)}{\beta-\alpha\cdot e^{-(\alpha+\beta)\omega}}$$

Therefore,

$$\log\left(\frac{u}{\alpha u+1}\right)=\log\left[\frac{1+e^{-(\alpha+\beta)\omega}}{\alpha+\beta}\right]$$

Associating them, we have

$$\Phi(\omega)=\log\left[\frac{1+e^{-(\alpha+\beta)\omega}}{\alpha+\beta}\right]+\left(\alpha-\frac{K_2}{K_1}\right)\omega\text{ ---------(A5)}$$

Consequently, (A_3) is

$$\varphi(u,v,t)=\frac{(K_2+K_1\beta)}{K_1(\alpha+\beta)}\log(\alpha u+1)-\frac{(K_2-K_1\alpha)}{K_1(\alpha+\beta)}\log(\beta u-1)$$
$$+\Phi\left[K_1 t-\frac{1}{(\alpha+\beta)}\log\left(\frac{\beta u-1}{\alpha u+1}\right)\right]$$

****

The functional form of $\Phi[\;]$ can be given by (A_5)

$$\omega=K_1 t-\frac{1}{(\alpha+\beta)}\log\left(\frac{\beta u-1}{\alpha u+1}\right)$$

Substitute this, we have

$$(\omega)=\log\left[\frac{1+e^{-(\alpha+\beta)\left[K_1 t-\frac{1}{(\alpha+\beta)}\log\left(\frac{\beta u-1}{\alpha u+1}\right)\right]}}{\alpha+\beta}\right]+\left(\alpha-\frac{K_2}{K_1}\right)\left[K_1 t-\frac{1}{(\alpha+\beta)}\log\left(\frac{\beta u-1}{\alpha u+1}\right)\right]$$

=log [{1 + exp((-(α+β)kt) *(β u-1)/(α u+1)}/(α+β)}
+ (α k1 -k2) t-(α - K2/K1)/(α+β) log[(β u-1)/(α u+1)]

$$=\log\left[\frac{\left(\alpha u+1+e^{-(\alpha+\beta)K_1 t}\cdot(\beta u-1)\right)}{(\alpha+\beta)(\alpha u+1)}\right]+(\alpha K_1-K_2)t$$
$$-\frac{(\alpha K_1-K_2)}{K_1(\alpha+\beta)}\left[\log(\beta u-1)-\log(\alpha u+1)\right]$$

Therefore

$$\varphi(u,v,t)=\frac{(K_2+K_1\beta)}{K_1(\alpha+\beta)}\log(\alpha u+1)-\frac{(K_2-K_1\alpha)}{K_1(\alpha+\beta)}\log(\beta u-1)$$
$$+\log\left[\frac{\left(\alpha u+1+e^{-(\alpha+\beta)K_1 t}\cdot(\beta u-1)\right)}{(\alpha+\beta)(\alpha u+1)}\right]+(\alpha K_1-K_2)t$$
$$-\frac{(\alpha K_1-K_2)}{K_1(\alpha+\beta)}\log(\beta u-1)+\frac{(\alpha K_1-K_2)}{K_1(\alpha+\beta)}\log(\alpha u+1)$$

=log [{(α u+1) + exp((-(α+β)kt) *(β u -1) }/(α+β)(α u+1)}] + (α k1 -k2) t
+ [K2+K1 β+α K1- K2)) log (α u+1)/(K1(α+β))

= log (α u+1)) + log [{(α u+1) + exp((-(α+β)kt) * (β u -1) }/(α+β)] - log (α u+1)} + (α k1 -k2) t

$$=\log\left[\frac{\left(\alpha u+1+e^{-(\alpha+\beta)K_1 t}\cdot(\beta u-1)\right)}{(\alpha+\beta)}\right]t\cdot\log e^{(\alpha K_1-K_2)t}$$

= log [{(α u+1) + exp((-(α+β)kt) * (β u -1) }/(α+β) }*exp(α K1 -K2)t)

$$=E_0^{-1}\cdot\log\phi$$

Then,we have the equation (5)

4. Distribution of the components of the reaction

At $v=1$ $\alpha(1)=\dfrac{(k_2+k_3)}{k_1 S_0}$ $\beta=1$

Then,

$$\phi(u,1,t)=\left[\frac{\left\{-e^{-k_1 S_0 t((k_2+k_3)/k_1 S_0+1)}\right\}+u\left\{\frac{k_2+k_3}{k_1 S_0}+e^{-k_1 S_0 t((k_2+k_3)/k_1 S_0+1)}\right\}}{\left\{(k_2+k_3)/k_1 S_0+1\right\}}\right]^{E_0}$$
$$\cdot e^{E_0\cdot t(k_1 S_0\cdot(k_2+k_3)/k_1 S_0-k_2-k_3)}$$
$$=\left[\frac{k_1 S_0}{(k_2+k_3+k_1 S_0)}\left[1-e^{-t(k_2+k_3+k_1 S_0)}\right]+\frac{u}{(k_2+k_3+k_1 S_0)}\left[k_2+k_3+k_1 S_0 e^{-t(k_2+k_3+k_1 S_0)}\right]\right]^{E_0}$$
$$=\sum_{e=0}^{E_0}P_\chi(E(t)=e)u^e$$

Putting
$$A=\frac{k_1 S_0}{(k_2+k_3+k_1 S_0)}\left[1-e^{-t(k_2+k_3+k_1 S_0)}\right]$$
$$B=\frac{\left(k_2+k_3+k_1 S_0 e^{-t(k_2+k_3+k_1 S_0)}\right)}{(k_2+k_3+k_1 S_0)}$$

We have

The left side $=[A+Bu]^{E_0}={}_{E_0}C_e(u\cdot B)^e\cdot A^{E_0-e}$

$$={}_{E_0}C_e\left[\frac{\left(k_2+k_3+k_1 S_0 e^{-t(k_2+k_3+k_1 S_0)}\right)}{(k_2+k_3+k_1 S_0)}\right]^e\cdot\left[\frac{k_1 S_0\left(1-e^{-t(k_2+k_3+k_1 S_0)}\right)}{(k_2+k_3+k_1 S_0)}\right]^{E_0-e}$$

Finally, we have the equation (7). From these,

The mean of $E(t)$ is obtained by differentiating (6) with respect to u and setting $u=1$

$$\mu_E=\sum_{e=0}^{E_0}P_\chi(E(t)=e)e\cdot u^{e-1}\;(u=1)$$
$$=\frac{\partial}{\partial u}[A+Bu]^{E_0}\;(u=1)$$
$$=E_0[A+Bu]^{E_0-1}\cdot B\;(u=1)=E_0(A+B)^{E_0-1}\cdot B$$
$$=E_0\left[\frac{k_1 S_0\left(1-e^{-t(k_2+k_3+k_1 S_0)}\right)}{(k_2+k_3+k_1 S_0)}+\frac{\left(k_2+k_3+k_1 S_0 e^{-t(k_2+k_3+k_1 S_0)}\right)}{(k_2+k_3+k_1 S_0)}\right]^{E_0-1}$$
$$\cdot\frac{\left(k_2+k_3+k_1 S_0 e^{-t(k_2+k_3+k_1 S_0)}\right)}{(k_2+k_3+k_1 S_0)}$$
$$=E_0[1]^{E_0-1}\cdot\frac{\left(k_2+k_3+k_1 S_0 e^{-t(k_2+k_3+k_1 S_0)}\right)}{(k_2+k_3+k_1 S_0)}\text{-----------}(8)$$

Variation

$$\sigma_E^2=\sum_{e=0}^{E_0}e^2\cdot\mathrm{Prob}(E(t)=e)-\left[\sum_{e=0}^{E_0}e\cdot\mathrm{Prob}(E(t)=e)\right]^2$$
$$\frac{\partial\phi}{\partial u}=\sum_{e=0}eu^{e-1}\cdot P_r$$
$$u\frac{\partial\phi}{\partial u}=\sum_{e=0}eu^e\cdot P_r$$
$$\frac{\partial}{\partial u}\left[u\cdot\frac{\partial\phi}{\partial u}\right]=\sum_{e=0}e^2u^{e-1}\cdot P_r$$

∴

$$\sum_{e=0}^{E_0}e^2\cdot P_r(E(t)=e)=\frac{\partial}{\partial u}\left[u\cdot\frac{\partial\phi}{\partial u}\right]_{u=1}$$

$$= \frac{\partial}{\partial u}\left[u \cdot \frac{\partial \left[A + u \cdot B\right]^{E_0}}{\partial u}\right]_{u=1}$$

$$= \frac{\partial}{\partial u}\left[u \cdot E_0\left(A + u \cdot B\right)^{E_0 - 1} \cdot B\right]_{=1}$$

$$= E_0 \cdot B\left[\left(A + u \cdot B\right)^{E_0-1} + u \cdot \left(E_0 - 1\right)\left(A + u \cdot B\right)^{E_0-2} \cdot B\right]_{=1}$$

$$= E_0 \cdot B \cdot \left(A + B\right)^{E_0-2} \cdot \left(A + E_0 B\right)$$

Therefore,

$$\sigma_E^2 = E_0 \cdot B \cdot \left(A + B\right)^{E_0-2} \cdot \left(A + E_0 B\right) - E_0^2\left(A + B\right)^{2E_0-2} B^2$$

$$= E_0 \cdot \frac{\left(k_2 + k_3 + k_1 S_0 e^{-t(k_2+k_3+k_1S_0)}\right)\left(k_1 S_0\right)\left(1 - e^{-(k_2+k_3+k_1S_0)t}\right)}{\left(k_1 S_0 + k_2 + k_3\right)^2} \qquad \text{--------------------------(9)}$$

5. Derivation of the equation (11)

Putting u=1 on the equation (5)

$$k_1 S_0\left(\beta(v) - \alpha(v)\right)$$

$$= k_1 S_0 \cdot 2\left(k_2 + v k_3\right) \cdot \left[\frac{1}{\left[\left(k_1 S_0 - k_2 - k_3\right)^2 + 4k_1 S_0\left(k_2 + k_3 v\right)\right]^{1/2} - \left(k_1 S_0 - k_2 - k_3\right)}\right.$$

$$\left. - \frac{1}{\left[\left(k_1 S_0 - k_2 - k_3\right)^2 + 4k_1 S_0\left(k_2 + k_3 v\right)\right]^{1/2} + \left(k_1 S_0 - k_2 - k_3\right)}\right]$$

$$= \frac{4k_1 S_0\left(k_2 + v \cdot k_3\right)\left(k_1 S_0 - k_2 - k_3\right)}{4k_1 S_0\left(k_2 + k_3 v\right)}$$

$$= \left(k_1 S_0 - k_2 - k_3\right)$$

Then,

$$\phi(u = 1, v, t) = \left[\frac{\left\{1 - e^{-k_1 S_0 t(\alpha+\beta)}\right\} + \left\{\alpha + \beta \cdot e^{-k_1 S_0 t(\alpha+\beta)}\right\}}{\alpha + \beta}\right]^{E_0} \cdot e^{E_0 t(k_1 S_0 \alpha - k_2 - k_3)}$$

Since

$k_1 S_0(\beta - \alpha) = k_1 S_0 - k_2 - k_3$. we have

$$\alpha + \beta = 2\beta + \left(k_2 + k_3\right)/\left(k_1 S_0\right) - 1$$

$$= \frac{2\beta \cdot k_1 S_0 + \left(k_2 + k_3\right) - \left(k_1 S_0\right)}{k_1 S_0}$$

By these relations

$$\phi(u = 1, v, t) = \left[\frac{\left\{1 - e^{-k_1 S_0 \cdot t\left(2\beta k_1 S_0 + k_2 + k_3 - k_1 S_0\right)/k_1 S_0}\right\} \cdot k_1 S_0}{\left(2\beta k_1 S_0 + k_2 + k_3 - k_1 S_0\right)}\right.$$

$$\left. + \frac{\left\{\beta + \left(k_2 + k_3\right)/\left(k_1 S_0\right) - 1 + \beta \cdot e^{-t\left(2\beta k_1 S_0 + k_2 + k_3 - k_1 S_0\right)}\right\} \cdot k_1 S_0}{\left(2\beta k_1 S_0 + k_2 + k_3 - k_1 S_0\right)}\right]^{E_0}$$

$$\cdot e^{E_0 \cdot t\left(k_1 S_0\right)\left(\beta - 1\right)}$$

$$= \left[\frac{k_2 + k_3 - k_1 S_0 e^{-t\left(2\beta k_1 S_0 + k_2 + k_3 - k_1 S_0\right)} + \beta \cdot k_1 S_0\left(1 + e^{-t\cdot\left(2\beta k_1 S_0 + k_2 k_3 - k_1 S_0\right)}\right)}{2\beta k_1 S_0 + k_2 + k_3 - k_1 S_0}\right]^{E_0}$$

$$\cdot e^{E_0 \cdot t \cdot k_1 S_0(\beta - 1)}$$

Differentiate this with respect to v. Taking into mind that β is a function of v, setting

$$k_2 + k_3 = f \quad , \quad k_2 + k_3 - k_1 S_0 = n \quad , \quad k_1 S_0 = g$$

$$\phi = \left[\frac{f - g \cdot e^{-t\cdot(2\beta g + n)} + \beta \cdot g \cdot \left(1 + e^{-t\cdot(2\beta g + n)}\right)}{2\beta g + n}\right]^{E_0} \cdot e^{E_0 t \cdot g(\beta - 1)}$$

We have differentiation by parts

$$① \frac{\partial \beta}{\partial v} = 2 \cdot \frac{\partial}{\partial v}\left[\frac{\left(k_2 + v \cdot k_3\right)}{\left[\left(k_1 S_0 - k_2 - k_3\right)^2 + 4k_1 S_0\left(k_2 + v k_3\right)\right]^{1/2} - \left(k_1 S_0 - k_2 - k_3\right)}\right]$$

$$= 2 \cdot \frac{\partial}{\partial v}\left[\frac{\left(k_2 + v \cdot k_3\right)}{\left[n^2 + 4g\left(k_2 + v k_3\right)\right]^{1/2} + n}\right]$$

$$= 2 \cdot \left[\frac{k_3\left\{\left[n^2 + 4g\left(k_2 + v k_3\right)\right]^{1/2} + n\right\} - 2 \cdot g \cdot k_3 \cdot \left[4g \cdot \left(k_2 + v k_3\right) + n^2\right]^{-1/2}\left(k_2 + v \cdot k_3\right)}{\left[\left[n^2 + 4g \cdot \left(k_2 + v k_3\right)\right]^{1/2} + n\right]^2}\right]$$

settin (v =1)

$$= 2 \cdot \left[\frac{k_3\left(n^2 + 4g\left(k_2 + k_3\right)\right)^{1/2} + k_3 n - 2 \cdot g \cdot k_3\left(4g\left(k_2 + k_3\right) + n^2\right)^{-1/2}\left(k_2 + k_3\right)}{\left(\left(n^2 + 4g\left(k_2 + k_3\right)\right)^{1/2} + n\right)^2}\right]$$

Since

$$n^2 + 4g\left(k_2 + k_3\right) = \left(f + g\right)^2$$

$$= 2 \cdot \left[\frac{k_3\left(f + g\right) + k_3 \cdot n - 2g \cdot k_3\left(f + g\right)^{-1} \cdot \left(k_2 + k_3\right)}{\left(\left(f + g\right) + n\right)^2}\right]$$

$$= \frac{k_3}{\left(k_2 + k_3 + k_1 S_0\right)}$$

$$② \frac{\partial e^{-t\cdot(2g\beta + n)}}{\partial v} = -2 \cdot t \cdot g \cdot \beta' \cdot e^{-t\cdot(2g\beta + n)}$$

$$③ \frac{\partial e^{E_0 t \cdot g(\beta - 1)}}{\partial v} = e^{E_0 \cdot t \cdot g \cdot (\beta - 1)} \cdot E_0 \cdot t \cdot g \cdot \beta'$$

$$④ \frac{\partial \phi}{\partial v}(v=1) = E_0\left[\frac{f - g \cdot e^{-t\cdot(2g\beta + n)} + \beta \cdot g \cdot \left(1 + e^{-t\cdot(2g\beta + n)}\right)}{2g\beta + n}\right]^{E_0 - 1}$$

$$\cdot \frac{\partial}{\partial v}\left[\frac{f - g \cdot e^{-t\cdot(2g\beta + n)} + \beta \cdot g \cdot \left(1 + e^{-t\cdot(2g\beta + n)}\right)}{2g\beta + n}\right] \cdot e^{E_0 t \cdot g(\beta - 1)}$$

$$+ \left[\frac{f - g \cdot e^{-t(2g\beta + n)} + \beta \cdot g \cdot \left(1 + e^{-t(2g\beta + n)}\right)}{2g\beta + n}\right]^{E_0} \cdot e^{E_0 t \cdot g(\beta - 1)} \cdot E_0 \cdot t \cdot g \cdot \beta'$$

$$⑤ \text{3term} = \frac{\left[\left\{-g \cdot e^{-t(2g\beta + n)}\right\}' + g\left\{\beta\left(1 + e^{-t\cdot(2g\beta + n)}\right)\right\}'\right] \cdot \left(2g\beta + n\right)}{\left(2g\beta + n\right)^2}$$

$$- 2g\beta' \frac{\left[f - g \cdot e^{-t\cdot(2g\beta + n)} + \beta \cdot g\left(1 + e^{-t(2g\beta + n)}\right)\right]}{\left(2g\beta + n\right)^2}$$

$$= \frac{\left[-g \cdot \left(-2tg\right)\beta' e^{-t\cdot(2g\beta + n)} + g\left\{\beta' \cdot \left(1 + e^{-t\cdot(2g\beta + n)}\right) + \beta\left(-2tg \cdot \beta' e^{-t(2g\beta + n)}\right)\right\}\right]}{\left(2g\beta + n\right)^2}$$

$$- 2g\beta' \left[f - g \cdot e^{-t\cdot(2g\beta + n)} + \beta \cdot g\left(1 + e^{-t(2g\beta + n)}\right)\right] \Big/ \left(2g\beta + n\right)^2$$

$$\beta\left(v = 1\right) = 1$$

$$= \frac{\left[2tg^2\cdot\beta' e^{-t(2g+n)} + g\cdot\beta'\left(1+e^{-t(2g+n)}\right) - 2tg^2\cdot\beta' e^{-t(2g+n)}\right]}{(2g+n)^2}$$

$$-2g\beta'\frac{\left[f - g\cdot e^{-t(2g+n)} + g\left(1+e^{-t(2g+n)}\right)\right]}{(2g+n)^2}$$

$$= g\cdot\beta'\frac{1}{(2g+n)^2}\left[(2g+n)+(2g+n)e^{-t(2g+n)} - 2(f+g)\right]$$

$$= g\cdot\beta'\frac{1}{(k_1S_0+k_2+k_3)^2}\left[-(k_1S_0+k_2+k_3)+(k_1S_0+k_2+k_3)e^{-t(k_1S_0+k_2+k_3)}\right]$$

$$= \beta'\frac{(k_1S_0)}{(k_1S_0+k_2+k_3)}\left[-1+e^{-t(k_1S_0+k_2+k_3)}\right]$$

⑥ $$\left[\frac{f - g\cdot e^{-t(2g\beta+n)} + \beta\cdot g\cdot\left(1+e^{-t(2g\beta+n)}\right)}{2g\beta+n}\right]_{v=1} = 1$$

⑦ $$\frac{\partial\phi}{\partial v}(u=1) = E_0\frac{\beta'(k_1S_0)}{(k_1S_0+k_2+k_3)}\left[-1+e^{-t(k_1S_0+k_2+k_3)}\right]e^{E_0\cdot t\cdot g\cdot(\beta-1)}$$
$$+ e^{E_0\cdot t\cdot g(\beta-1)}\cdot E_0\cdot t\cdot g\cdot\beta'$$

$$= E_0\frac{k_3(k_1S_0)}{(k_2+k_3+k_1S_0)}\left[t - \frac{\left(1-e^{-t(k_1S_0+k_2+k_3)}\right)}{k_1S_0+k_2+k_3}\right]$$

****

6. Derivation of the equation (12)

(12)

$$\frac{\partial^2\phi}{\partial v^2}(u=1,v,t)\,(u=1)$$

$$\phi(1,v,t) = \left[\frac{f - g\cdot e^{-t(2g\beta+n)} + g\cdot\beta\cdot\left(1+e^{-t(2g\beta+n)}\right)}{2g\beta+n}\right]^{E_0}\cdot e^{E_0 t g(\beta-1)}$$

$$= \left[G(v)\right]^{E_0}\cdot e^{E_0 t\cdot g(\beta-1)}$$

$$\phi'' = \frac{\partial^2\left[G(v)\right]^{E_0}}{\partial v^2}\cdot e^{E_0 t\cdot g(\beta-1)} + 2\frac{\partial G^{E_0}}{\partial v}\cdot\frac{\partial e^{E_0\cdot t\cdot g(\beta-1)}}{\partial v} + G^{E_0}\cdot\frac{\partial^2 e^{E_0 t\cdot g(\beta-1)}}{\partial v^2}$$

$$\frac{\partial G^{E_0}}{\partial v} = E_0\cdot G^{E_0-1}\cdot\frac{\partial G(v)}{\partial v}$$

$$\frac{\partial^2 G^{E_0}}{\partial v^2} = E_0\cdot\left[(E_0-1)G^{E_0-2}\cdot\frac{\partial G}{\partial v}\cdot\frac{\partial G}{\partial v} + G^{E_0-1}\frac{\partial^2 G}{\partial v^2}\right]$$

$v=1$ $\quad G(v)=1$

$$= E_0\cdot\left[(E_0-1)(G')^2 + G''\right]$$

①Hence, we first derive $G''(v)$ $(v=1)$

generally

$$\frac{\partial^2}{\partial v^2}\left(\frac{H}{J}\right) = \frac{\left[H''\cdot J^3 - HJ''\cdot J^2 - 2J^2J'H' + 2JH\cdot(J')^2\right]}{J^4}$$

The numerators of $G''(v)$ are

$$H = f - g\cdot e^{-t(2g\beta+n)} + g\cdot\beta\cdot\left(1+e^{-t(2g\beta+n)}\right)$$

$$H' = 2tg^2\cdot\beta' e^{-t(2g\beta+n)} + g\cdot\beta'\cdot e^{-t(2g\beta+n)} - 2tg^2\beta\cdot\beta' e^{-t(2g\beta+n)} + g\cdot\beta'$$

$$H'' = 2tg^2\left\{\beta'' e^{-t(2g\beta+n)} + \beta'(-2tg\beta')e^{-t(2g\beta+n)}\right\}$$

$$+ g\beta'' e^{-t(2g\beta+n)} + g\cdot\beta'\cdot(-2tg\beta')e^{-t(2g\beta+n)}$$
$$-2t\cdot g^2\left[(\beta')^2 e^{-t(2g\beta+n)} + \beta\beta'' e^{-t(2g\beta+n)} + \beta\beta'(-2tg\beta')e^{-t(2g\beta+n)}\right]$$
$$+ g\beta''$$

while at $v=1$ we have $\beta(v=1)=1$

$$= 2tg^2\left\{\beta'' - 2tg(\beta')^2\right\}e^{-t(2g+n)} + g\beta''$$
$$+ \left\{g\beta'' - 2tg^2(\beta')^2 - 2tg^2(\beta')^2 - 2tg^2\beta'' + 4t^2g^3(\beta')^2\right\}e^{-t(2g+n)}$$
$$= \left[g\cdot\beta'' - 4t\cdot g^2(\beta')^2\right]e^{-t(2g+n)} + g\cdot\beta''$$

and

$$H'(v=1) = g\cdot\beta'\left(1+e^{-t(2g+n)}\right)$$

$$H(v=1) = f - g\cdot e^{-t(2g+n)} + g\left(1+e^{-t(2g+n)}\right) = f+g$$

The components of the denominator are

$J = 2g\beta+n$ $\qquad J(v=1) = 2g+n$

$J' = 2g\beta'$ $\qquad J'(v=1) = 2g\beta'(v=1)$

$J'' = 2g\beta''$ $\qquad J''(v=1) = 2g\beta''(v=1)$

②In the second, we seek $\beta''(v=1)$

②−1

$$\frac{\partial\beta}{\partial v} = \frac{\partial}{\partial v}\left[\frac{2(k_2+v\cdot k_3)}{\left[(k_1S_0-k_2-k_3)^2+4k_1S_0(k_2+vk_3)\right]^{1/2} - (k_1S_0-k_2-k_3)}\right]$$

$$= \frac{\partial}{\partial v}\left[\frac{2(k_2+v\cdot k_3)}{\left[F(v)\right]^{1/2}+n}\right]$$

$$\frac{\partial F(v)^{1/2}}{\partial v} = \frac{1}{2}F(v)^{-1/2}\frac{\partial F}{\partial v} = \frac{4k_1S_0\cdot k_3}{2\left[(k_1S_0-k_2-k_3)^2+4k_1S_0(k_2+vk_3)\right]^{1/2}}$$

$$= 2\cdot\left[\frac{k_3\cdot\left(F^{1/2}+n\right) - (k_2+v\cdot k_3)\cdot\left(F^{1/2}\right)'}{\left[F^{1/2}+n\right]^2}\right]$$

at $v=1$ we have

$F^{1/2} = (k_2+k_3+k_1S_0)$ and

$$\left(F^{1/2}\right)' = 2k_1S_0\cdot k_3/(k_2+k_3+k_1S_0)$$

$$= 2\cdot\left[\frac{k_3\cdot(k_2+k_3+k_1S_0+k_2+k_3-k_1S_0) - (k_2+k_3)\cdot 2k_1S_0k_3/(k_2+k_3+k_1S_0)}{2^2(k_2+k_3)^2}\right]$$

$$= \frac{k_3}{(k_2+k_3+k_1S_0)}$$

②−2

$$\frac{\partial^2\beta}{\partial v^2} = \frac{\partial^2}{\partial v^2}\left[\frac{2(k_2+v\cdot k_3)}{\left[F^{1/2}\right]+n}\right]_{v=1}$$

Generaly

$$\frac{\partial^2}{\partial v^2}\left(\frac{H}{J}\right) = \frac{\left[H''\cdot J^3 - H\cdot J''\cdot J^2 - 2J^2J'H' + 2JH\cdot(J')^2\right]}{J^4}$$

and

$H = 2\cdot(k_2+v\cdot k_3)$, $\quad H(v=1) = 2(k_2+k_3)$

$H' = 2k_3$

$H'' = 0$

$$J = F^{1/2} + n \quad : J(v=1) = k_2 + k_3 + k_1S_0 + k_2 + k_3 - k_1S_0 = 2(k_2 + k_3)$$

$$J' = \frac{1}{2}\cdot F^{-1/2}\cdot F' = \frac{2k_1S_0k_3}{k_2 + k_3 + k_1S_0} = \frac{2k_1S_0k_3}{h}$$

$$J'' = \frac{1}{2}\cdot\left[-\frac{1}{2}\cdot F^{-3/2}(F')^2 + F^{-1/2}F''\right]_{v=1}$$

$$= \frac{1}{2}\cdot\left[-\frac{1}{2}(k_2 + k_3 + k_1S_0)^{-3}\cdot(4k_1S_0k_3)^2 + (k_2 + k_3 + k_1S_0)^{-1}\cdot 0\right]$$

$$= -\frac{4\cdot(k_1S_0k_3)^2}{(k_2 + k_3 + k_1S_0)^3}$$

Hence the numerator of β'' are

$$H''\cdot J^3 = 0$$

$$-H\cdot J''\cdot J^2 = \frac{-2(k_2 + k_3)\cdot(-4)\cdot(k_1S_0k_3)^2\cdot(2\cdot(k_2 + k_3))^2}{(k_2 + k_3 + k_1S_0)^3} = \frac{32\cdot(k_1S_0k_3)^2\cdot(k_2 + k_3)^3}{(k_2 + k_3 + k_1S_0)^3}$$

$$-2J^2\cdot J'\cdot H' = \frac{-32\cdot k_1S_0\cdot k_3^2\cdot(k_2 + k_3)^2}{(k_2 + k_3 + k_1S_0)}$$

$$2\cdot J\cdot H\cdot(J')^2 = 32\cdot\frac{(k_1S_0)^2\cdot k_3^2\cdot(k_2 + k_3)^2}{(k_2 + k_3 + k_1S_0)^2}$$

By these we have the numerator of (β'')

$$= 32\cdot\left[\frac{(k_1S_0k_3)^2(k_2 + k_3)^3}{(k_2 + k_3 + k_1S_0)^3} - \frac{k_1S_0k_3^2\cdot(k_2 + k_3)^2}{(k_2 + k_3 + k_1S_0)} + \frac{(k_1S_0)^2k_3^2(k_2 + k_3)^2}{(k_2 + k_3 + k_1S_0)^2}\right]$$

$$= -32\cdot\frac{(k_1S_0)\cdot k_3^2\cdot(k_2 + k_3)^4}{(k_2 + k_3 + k_1S_0)^3}$$

The denominator is

$$J^4 = 2^4\cdot(k_2 + k_3)^4$$

$$\therefore \frac{\partial^2\beta}{\partial v^2} = -2\cdot\frac{(k_1S_0)k_3^2}{(k_2 + k_3 + k_1S_0)^3} \qquad \frac{\partial\beta}{\partial v} = \frac{k_3}{k_2 + k_3 + k_1S_0}$$

Rearrange them in $\partial^2G/\partial v^2$

$$H = g\left[\beta'' - 4tg\cdot(\beta')^2\right]^{-t(2g+n)} + g\beta''$$

$$H' = g\cdot\beta'\left(1 + e^{-t(2g+n)}\right) \qquad H = f + g$$

$$J = 2g\beta + n \quad , \quad J' = 2g\beta' \quad , \quad J'' = 2g\beta''$$

all of them are determined by β, β''

$$\frac{\partial^2G}{\partial v^2} = \Big[g\cdot\left[\left(\beta'' - 4tg(\beta')^2\right)^{-t(2g+n)} + \beta''\right](2g+n)^3$$

$$-(f+g)\cdot 2g\beta''\cdot(2g+n)^2 - 2(2g+n)^2\cdot 2g\beta'\cdot g\beta'\left(1 + e^{-t(2g+n)}\right)$$

$$+ 2\cdot(2g+n)(f+g)(2g\beta')^2\Big]\Big/(2g+n)^4$$

Putting $2g + n = 2k_1S_0 + k_2 + k_3 - k_1S_0 = h$

$f + g = k_2 + k_3 + k_1S_0 = h$, we have

$$= \Big[g\cdot\beta''e^{-ht}\cdot h^3 - 4tg^2(\beta')^2e^{-ht}\cdot h^3 + g\beta''h^3$$

$$-2h\cdot g\cdot\beta''h^2 - 4h^2g^2(\beta')^2\left(1 + e^{-th}\right) + 2\cdot h^2 4g^2(\beta')^2\Big]$$

substitute $\beta'' = -2(k_1S_0)k_3^2/h^3 \qquad \beta' = k_3/h$

$$= g\cdot\frac{(-2)k_1S_0k_3^2e^{-ht}h^3}{h^3} - 4\frac{tg^2k_3^2e^{-ht}h^3}{h^2} + g\frac{(-2)(k_1S_0)k_3^2h^3}{h^3}$$

$$-2\frac{h^3g(-2)(k_1S_0)k_3^2}{h^3} - \frac{4h^2g^2k_3^2\left(1 + e^{-ht}\right)}{h^2} + \frac{8h^2\cdot g^2k_3^2}{h^2}$$

since $g = k_1S_0$

$$= -6(k_1S_0k_3)^2e^{-ht} - 4\cdot t\cdot(k_1S_0k_3)^2he^{-ht} + 6(k_1S_0k_3)^2$$

By these, we have

$$\frac{\partial^2G}{\partial v^2} = \frac{(k_1S_0k_3)^2}{h^4}\left[6 - 6e^{-ht} - 4t\cdot h\cdot e^{-ht}\right]$$

$$\text{while}\ \frac{\partial G}{\partial v} = \frac{(k_1S_0k_3)}{h^2}\left(-1 + e^{-ht}\right) \qquad (G')^2 = \frac{(k_1S_0k_3)^2}{h^4}\left(-1 + e^{-ht}\right)^2$$

As a result, $\left[e^{E_0\cdot t\cdot g(\beta-1)}\right]_{=1} = e^0 = 1$

$$\phi''_{(v=1)} = \frac{\partial^2G^{E_0}}{\partial v^2} + 2\cdot\frac{\partial G^{E_0}}{\partial v}\cdot\frac{\partial e^{E_0 t\cdot g(\beta-1)}}{\partial v} + G^{E_0}\frac{\partial^2e^{E_0tg(\beta-1)}}{\partial v^2}$$

$$= E_0\left((E_0 - 1)(G')^2 + G''\right) + 2E_0G^{E_0-1}G'\cdot e^{E_0tg(\beta-1)}\cdot E_0t\cdot g\cdot\beta'$$

$$+ G^{E_0}\frac{\partial}{\partial v}\left[E_0t\cdot g\cdot(\beta)'e^{E_0tg(\beta-1)}\right]$$

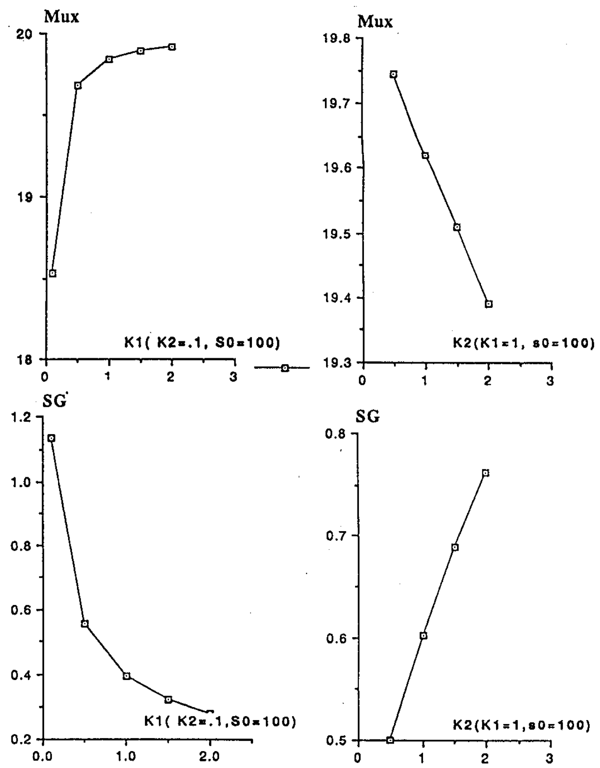
$$= E_0\left((E_0 - 1)(G')^2 + G''\right) + 2E_0^2G't\cdot g\cdot\beta'$$

$$+ E_0\cdot t\cdot g\left[\beta''e^{E_0tg(\beta-1)} + \beta'E_0tg\beta'e^{E_0tg(\beta-1)}\right]$$

$$= E_0^2(G')^2 - E_0(G')^2 + E_0G'' + 2E_0^2tgG'\beta'$$

$$+ E_0\cdot t\cdot g\cdot\beta'' + E_0^2t^2g^2(\beta')^2$$

Fig 1. Computed results of μx and σ as functions of K1, K2 and so.



3. Results and conclusion.

Fig 1 shows expected values (Mux) as functions of rate constants k1 and k2 while setting so=100. The lower part of Fig 1 shows standard deviation (SG) . These two quantities changed significantly as functions of biochemical parameters. The present method will be available for predicting the probabilistic behaviors of the biochemical reaction system.

3. Reference.

Heyde, C.C. J. Theoretical. Biology. vol 25. pp 159. 1969.