

Mathematical Method for the Time Minimum Optimal Control for the Cycling Reactions in Two Step Enzyme Reactions.

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We proposed a mathematical method for analyzing the time minimum optimal control strategy for the cycling reactions in the two enzymes system. The reaction system consisted of 2 substrates which interacts through the first enzyme. The first step produces two intermediate products. These are again utilized by the second enzyme system to produce the final products. By assuming the time minimum control, we set Hamiltonian function. By the partial differentiation, we get the optimized differential equations for the co-state variables. By the numerical method, the substrates and the intermediate products in the first step decreased rapidly while the intermediate and the final products in the second reaction increased significantly. The present method will be available for evaluating the time optimal nature of the cycling reactions in the biochemical systems.

Cycling reaction, Time minimum optimal control, Non linear differential equations, Intermediate

酵素反応系におけるCycling 反応 に対する最短時間制御

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酵素反応系におけるCycling reaction に対する最短時間制御の数学的解析方法を提唱した。反応系は2種類の基質が第1番目の酵素と反応して2種類の生成物質をつくるが、生成された2つの物質はおよびほかの基質と第2番目の酵素を介して反応する。系は20個の非線形微分方程式で記述した。この場合、基質も時間変量とした。これに対して最短時間で反応する場合を想定して、ハミルトニアンを設定した。相応する補助状態変数を設定し、それらに対する偏微分をおこない、最短時間で生化学的反應における各物質の濃度の時間経過を数値計算した。基質および、第1番目の酵素反応による中間代謝産物は反応開始とともに急速に減少した。一方第2番目の酵素による反応系の中間代謝物および最終生成物質は増加した。本研究を発展させれば複雑な酵素反応系の最短時間制御の解析に有用である。

酵素反応系. Cycling reaction. 最短時間制御. 非線形微分方程式. 中間代謝産物. 基質

1. Introduction.

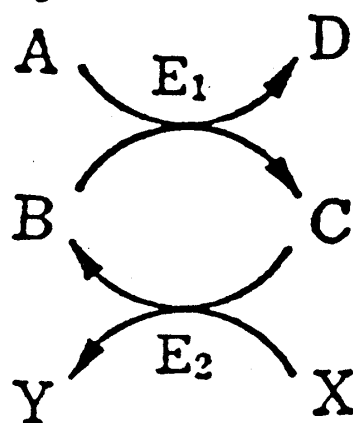
Recent advance in technology of biochemical experiments disclosed a lot of biochemical reactions. We can, however, find any attempt to evaluate how fast the reaction proceeds to achieve the final product. This links to define the purpose for evoking any given reaction. Fig 1 shows a typical example of the Coupling reaction to produce citrate from oxaloacetate. There may be some critical circumstances to produce any final product as fast as possible. Citrate is one of the most important species in the Crebs's TCA cycle to preserve the cellular function. When any circumstance change required to produce the Citrate as soon as possible, the reaction system may operate in the shortest time reaction. The basic strategy behind this reaction is the time optimal control.

In the present study, we propose a mathematical method for evaluating the time minimum optimal control for the Cycling reaction system.

Fig1. Cycling reaction through Acetyl-phosphate to Citrate.

Fig 2. Generalized schema for Cycling reaction.

Fig 2



[E1AB, E1CD]

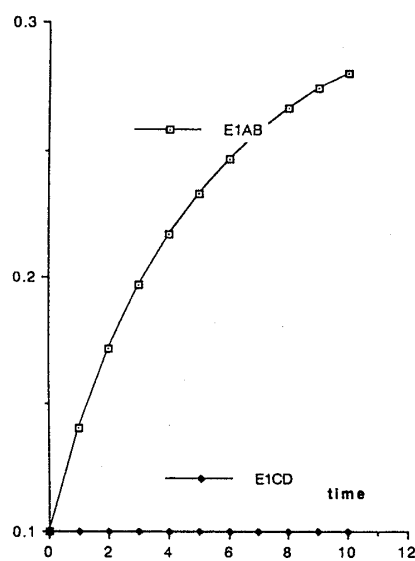


Fig 3

[E2X, E2Y, E2CX, E2BY]

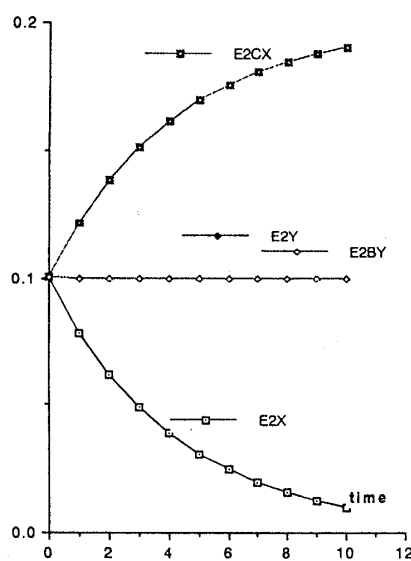
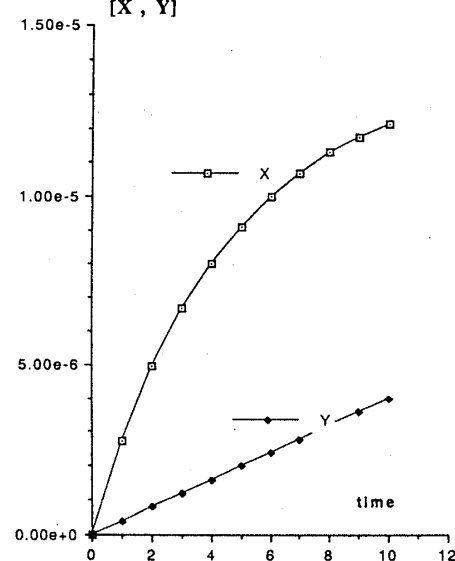


Fig 3

[X , Y]



2. Mathematical Method.

Fig 1 shows an example of actual Cycling reaction. Acetyl-phosphate and CoA (cofactor A) react through the enzyme E1 to produce acetyl-CoA and phosphate. Phosphate is a first step final produce that is not utilized any more. Acetyl CoA on the other hand is utilized in combination with oxaloacetate through the enzyme E2 to produce citrate which is the final product and CoA which again is utilized in the E1 reaction system. For the generalized case, we set substrates A, B, C and X as shown in Fig 2. (Hayashi and Sakamoto 1986) The

Fig 1.

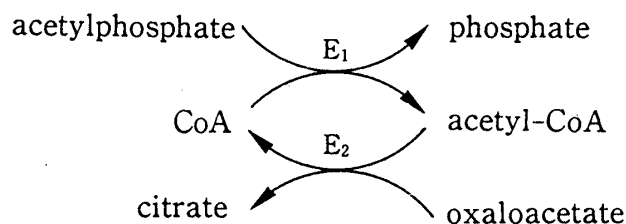
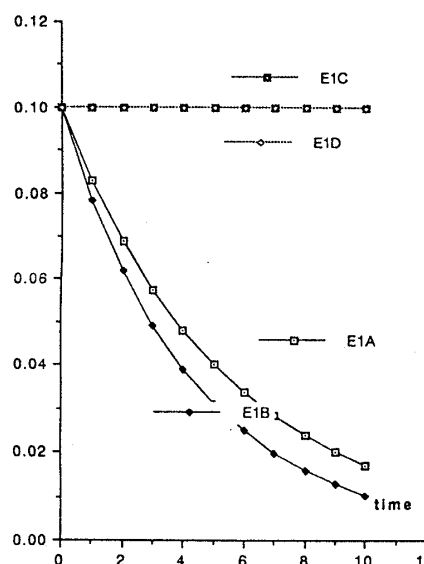
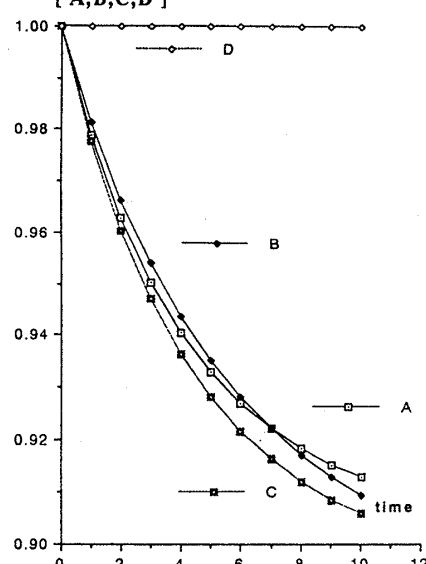


Fig 3.

[E1A, E1B, E1C, E1D]



[A,B,C,D]



4. Discussion.

The rate constants may change depending on the progress of the reaction which in turn alters the chemical properties of the enzymes E1 and E2. Hence, the rate constants have to be set as functions of the concentrations of the species. More over, to evaluate the validity and availability of the present method, strong comparison with controlled biochemical experiments is absolutely required.

5. Conclusion.

A mathematical method for the time minimum optimal control of Cycling reaction will be available for evaluating the rapid reaction of the biochemical systems.

6. Reference.

- Hayashi K and Sakamoto N. Dynamic Analysis of Enzyme Systems. Springer Verlag, 1986.

[APPENDIX 0]

The statement of the time-optimal problem.

Problem 6-1b. Time-optimal control to a moving target set. Given the system

$$\begin{aligned} \dot{x}'(t) &= f[x(t), t] + \sum_{j=1}^n b_{ij}[x(t), t] u_j(t), \quad i=1, 2, \dots, n \text{ or} \\ \dot{x}'(t) &= f[x(t), t] + B[x(t), t] u(t) \end{aligned} \quad (6-35)$$

Assume that

- $f[x(t), t]$ and $b_{ij}[x(t), t]$ are continuous in $x(t)$ and t .
- $\partial f[x(t), t] / \partial x_k(t)$, $\partial b_{ij}[x(t), t] / \partial t$, $\partial b_{ij}[x(t), t] / \partial x_k(t)$ and $\partial b_{ij}[x(t), t] / \partial t$ are continuous in $x(t)$ and t for $i, k = 1, 2, 3, \dots, n$ and $j = 1, 2, 3, \dots, r$.

- The components $u_1(t), u_2(t), \dots, u_r(t)$ are continuous in magnitude by the relation

$$u(t) \in \Omega \text{ or } |u_j(t)| \leq 1, \quad j=1, 2, \dots, r \text{ for all } t \quad (6-36)$$

Given a smooth target set S

$$g_\alpha[x, t] = 0 \quad \alpha=1, 2, 3, \dots, n-\beta \quad (6-37)$$

Assume that

- $g_\alpha[x, t]$, $\partial g_\alpha[x, t] / \partial x$, $\partial g_\alpha[x, t] / \partial t$ are continuous in x and t .
- The gradient vector $\partial g_\alpha[x, t] / \partial x$ are linearly independent for all $(x, t) \in S$. Let t_0 is a given initial time, $x(t_0)$ be a given initial state of the system 6-35. Given the cost function

$$J(u) = \int_{t_0}^T dt = T - t_0 : T \text{ free} \quad (6-38)$$

Then, determine the control $u(t)$ that :

- Satisfies the constraints 6-36
- Forces the state $x(t_0)$ of the system (6-35) to the target set S and
- Minimizes the cost function $J(u)$ of 6-38.

- The cost function to be minimized is

$$J(u) = \int_{t_0}^T L[x(t), u(t), t] dt \quad (6-43)$$

For the time optimal problem, we set

$$L[x(t), u(t), t] = 1 \quad (6-44)$$

to obtain the $J(u)$ given by the equation (6-34). Since t_0 is known and since the quantity $T - t_0$ is to be minimized, T must be free. Also the function $L[x(t), u(t), t] = 1$ satisfies all the continuity and differentiability requirements. The Hamiltonian function $H[x(t), p(t), u(t), t]$ for the system (6-35) and the cost function (6-38) is given by using matrix notation

$$H[x(t), p(t), u(t), t] = 1 + \langle p(t), f[x(t), t] + B[x(t), t] u(t) \rangle$$

$$\begin{aligned} &= \langle p(t), f[x(t), t] \rangle + \langle p(t), B[x(t), t] u(t) \rangle \\ &= \langle f[x(t), t], p(t) \rangle + \langle u(t), B[x(t), t] p(t) \rangle \end{aligned} \quad (6-45)$$

where $p(t)$ is the co-state vector. The Hamiltonian can be written in terms of vector form

$$\begin{aligned} H &= H[x(t), p(t), u(t), t] \\ &= 1 + \sum_{i=1}^n f_i[x(t), t] p_i(t) + \sum_{j=1}^r u_j(t) \left\{ \sum_{i=1}^n b_{ij}[x(t), t] p_i(t) \right\} \end{aligned} \quad (6-46)$$

Suppose that $u^*(t)$ is a time-optimal control that $x^*(t)$ is the resultant time optimal trajectory and that T^* is the minimum time. By definition, the optimal quantities must satisfy the relations

$$|u_j^*(t)| \leq 1, \quad j=1, 2, 3, \dots \quad (6-47)$$

$$x^*(t_0) = x(t_0) \quad (6-48)$$

$$x^*(T^*) \in S \quad (6-49)$$

Equation 6-49 implies (in view of 3-7) that

$$g[x^*(T^*), T^*] = 0 \quad (6-50)$$

Step1.

The optimal control theory implies that there is an optimal co-state $p^*(t)$ corresponding to the optimal control $u^*(t)$ and the optimal trajectory $x^*(t)$. The existence of $p^*(t)$ is a necessary condition. It is also necessary that the components $x_k^*(t)$ and $p_k^*(t)$, $k=1, 2, 3, \dots, n$ satisfies the canonical equations

$$\begin{aligned} \partial x_k^*(t) / \partial t &= \partial H[x^*(t), p^*(t), u^*(t), t] / \partial p_k^*(t) \\ \partial p_k^*(t) / \partial t &= -\partial H[x^*(t), p^*(t), u^*(t), t] / \partial x_k^*(t) \end{aligned} \quad (6-51)$$

for $k=1, 2, \dots, n$. On the other hand, from (4-6), we find that

$$\begin{aligned} H[x^*(t), p^*(t), u^*(t), t] \\ = 1 + \sum_{i=1}^n f_i[x^*(t), t] p_i^*(t) + \sum_{j=1}^r u_j^*(t) \left\{ \sum_{i=1}^n b_{ij}[x^*(t), t] p_i^*(t) \right\} \end{aligned} \quad (6-52)$$

and the canonical equations (6-51) reduce to

$$dx_k^*(t) / dt = f_k[x^*(t), t] + \sum_{j=1}^r b_{kj}[x^*(t), t] u_j^*(t) \quad (6-53)$$

$$dp_k^*(t) / dt = - \sum_{i=1}^n \left[\partial f_i[x^*(t), t] / \partial x_k^*(t) \right] p_i^*(t)$$

$$- \sum_{j=1}^r u_j^*(t) \sum_{i=1}^n \left\{ \partial b_{ij}[x^*(t), t] / \partial x_k^*(t) \right\} p_i^*(t) \quad (6-54)$$

for $k=1, 2, 3, \dots, n$. It is also necessary that

$$x_k^*(t) = x_k(t_0) \quad (6-55)$$

We have the following observation

Remark-1. The differential equation satisfied by $p^*(t)$ is linear in $p^*(t)$. It follows that if $p^*(t)$ satisfies the differential equation (6-54), then so does the vector $C p^*(t)$ where C is an arbitrary constant

From the optimal principle for $t \in [t_0, T^*]$,

$$H[x^*(t), p^*(t), u^*(t), t] = \min_{u(t) \in \Omega} H[x^*(t), p^*(t), u(t), t] \quad (6-56)$$

$H[x^*(t), p^*(t), u^*(t), t] \leq H[x^*(t), p^*(t), u(t), t]$ (6-57) for all $u(t) \in \Omega$ and $t \in [t_0, T^*]$. Viewing (6-52), we deduce that the equation (6-56) is converted to

$$\begin{aligned} 1 + \sum_{i=1}^n f_i[x^*(t), t] p_i^*(t) + \sum_{j=1}^r u_j^*(t) \left\{ \sum_{i=1}^n b_{ij}[x^*(t), t] p_i^*(t) \right\} \\ \leq 1 + \sum_{i=1}^n f_i[x^*(t), t] p_i^*(t) + \sum_{j=1}^r u_j(t) \left\{ \sum_{i=1}^n b_{ij}[x^*(t), t] p_i^*(t) \right\} \end{aligned} \quad (6-58)$$

Since the first two terms are the same on both sides

$$\sum_{j=1}^r u_j^*(t) \sum_{i=1}^n b_{ij} [x^*(t), t] p_i^*(t) \leq \sum_{j=1}^r u_j(t) \sum_{i=1}^n b_{ij} [x^*(t), t] p_i^*(t) \quad (6-59)$$

for all $u(t) \in \Omega$ and $t \in [t_0, T^*]$.

Remark-2. If $p^*(t)$ satisfies the equation (6-59), then so does the vector $C p^*(t)$ where C is an arbitrary constant.

The statement of the optimal principle is

$$H[x^*(T^*), p^*(T^*), u^*(T^*), T^*] \\ n-\beta \quad \partial g_\alpha [x^*(T^*), T^*] \quad \partial g_\alpha [x^*(T^*), T^*] \\ = \sum_{\alpha=1}^n c_\alpha \frac{\partial T^*}{\partial T^*} = \langle c \rangle \quad (6-60)$$

where c is an $n-\beta$ vector with components $c_1, c_2, \dots, c_{n-\beta}$. From the equations of 6-60 and 6-52, we have

$$1 + \sum_{i=1}^n f_i[x^*(T^*), T^*] p_i^*(T^*) \\ + \sum_{j=1}^r u_j^*(T^*) \left\{ \sum_{i=1}^n b_{ij} [x^*(T^*), T^*] p_i^*(T^*) \right\} \\ n-\beta \\ = \sum_{\alpha=1}^n c_\alpha \left[\partial g_\alpha [x^*(T^*), T^*] / \partial T^* \right] \quad (6-61)$$

Remark-3. If the target set S is not a function of time,

$$\partial g_\alpha [x^*(T^*), T^*] / \partial T^* = 0 \quad (6-62)$$

for $\alpha = 1, 2, \dots, n-\beta$, and the equation 6-11 reduces to

$$1 + \sum_{i=1}^n f_i[x^*(T^*), T^*] p_i^*(T^*) \\ + \sum_{j=1}^r u_j^*(T^*) \left\{ \sum_{i=1}^n b_{ij} [x^*(T^*), T^*] p_i^*(T^*) \right\} = 0 \quad (6-63)$$

Remark-4. If $p^*(T^*)$ satisfies the equation (6-61) or (6-63), then the vector $C p^*(T^*)$ where C is an arbitrary constant does not satisfy either equation (6-61) or (6-63). This is in consistinction to Remark 6-1 and 6-3.

From the optimal principle, the vector $p^*(T^*)$ must be normal to the target set S at $t = T^*$. The target set S at $t = T^*$ is specified by the $n-\beta$ equations

$$g_1(x, T^*) = 0 \\ g_2(x, T^*) = 0 \\ g_3(x, T^*) = 0 \\ * * * * * \\ g_{n-\beta}(x, T^*) = 0 \quad (6-64)$$

Now, let $h_1(x, T^*), h_2(x, T^*) \dots, h_{n-\beta}(x, T^*)$ denote the gradient vectors each having n components, we have

$$h_\alpha [x, T^*] = \partial g_\alpha [x, T^*] / \partial x, \quad \alpha = 1, 2, \dots, n-\beta \quad (6-65)$$

Then, it is necessary that the vector $p^*(T^*)$ be some linear combination of these gradient vectors at $x^*(T^*)$,

$$p^*(T^*) = \sum_{\alpha=1}^{n-\beta} k_\alpha h_\alpha [x^*(T^*), T^*] \quad (6-66)$$

where $k_1, k_2, \dots, k_{n-\beta}$ are arbitrary constants.

Remark-5. If $p^*(T^*)$ satisfies equation (6-66), so does the vector $C p^*(T^*)$ where C is a constant.

Step. 2

In this step, we derive an equation which relates $u^*(t)$ to $x^*(t)$ and $p^*(t)$ for $t \in [t_0, T^*]$ from equation (6-59). We then, eliminate the optimal control from all the equations. Let define functions $q_1^*(t), q_2^*(t) \dots q_r^*(t)$

$$q_j^*(t) = \sum_{i=1}^n b_{ij} [x^*(t), t] p_i^*(t) \quad j = 1, 2, \dots, r \quad (6-67)$$

$$q^*(t) = B' [x^*(t), t] p^*(t) \quad (6-68)$$

The vector $q^*(t)$ is thus, obtained by a linear transformation which matrix is $B' [x^*(t), t]$ on the vector $p^*(t)$. Using $q_j^*(t)$, the equation (6-59) becomes

$$\sum_{j=1}^r u_j^*(t) q_j^*(t) \leq \sum_{j=1}^r u_j(t) q_j^*(t) \quad (6-69)$$

for all $|u_j(t)| \leq 1, j = 1, 2, 3, \dots, r$ and $t \in [t_0, T^*]$. This equation means that the function

$$\phi[u(t)] = \sum_{j=1}^r u_j(t) q_j^*(t) \quad (6-70)$$

attains its absolute minimum at

$$u_j(t) = u_j^*(t) \quad (6-71)$$

$$\min_{u(t) \in \Omega} \phi[u(t)] = \min_{u(t) \in \Omega} \sum_{j=1}^r u_j(t) q_j^*(t) = \sum_{j=1}^r \min_{|u_j(t)| \leq 1} u_j(t) q_j^*(t) \quad (6-72)$$

Remark-6.

We can interchange the "min" operator and the " \sum " operator because the functions $u_1(t), u_2(t) \dots u_r(t)$ are constrained independently. In other words, if we have $u_1(t) = +1$, then all other controls $u_2(t) \dots u_r(t)$ can attain any values consistent with the magnitude constraints.

Now, it is easy that

$$\min_{|u_j(t)| \leq 1} \{ u_j(t) q_j^*(t) \} = -|q_j^*(t)| \quad (6-73)$$

The control $u_j^*(t)$ will minimize the function $u_j(t) q_j^*(t)$. It follows in viewing equation (6-73) that $u_j^*(t)$ must be the following function of $q_j^*(t)$

$$u_j^*(t) = +1 \quad \text{if } q_j^*(t) < 0 \\ u_j^*(t) = -1 \quad \text{if } q_j^*(t) > 0 \\ u_j^*(t) \text{ indeterminate} \quad \text{if } q_j^*(t) = 0 \quad (6-74)$$

We use the signum function to describe equation (6-74)

$$u_j^*(t) = -\text{sgn} \{ q_j^*(t) \} = -\text{sgn} \left\{ \sum_{i=1}^n b_{ij} [x^*(t), t] p_i^*(t) \right\} \quad (6-75)$$

for $j = 1, 2, 3, \dots, r$ and $t \in [t_0, T^*]$.

Equation (6-75) relates the components of the time-optimal control $u^*(t)$ to the state $x^*(t)$ and to the co-state $p^*(t)$. We note that if $p^*(t)$ is such that the equation (6-75) holds, then equation (6-75) also holds for any vectors $C p^*(t)$ provided that C is positive because $\text{sgn}[C] = +1$.

Now, we have Theorems

Theorem 1. The Bang-Bang Principle

Let $u^*(t)$ be a time optimal control for and let $x^*(t)$ and $p^*(t)$ be the corresponding state trajectory and co-state. If the problem is normal (there is a countable set of times $t_{1j}, t_{2j}, t_{3j} \dots$, such that $q_j^*(t) = \sum_{i=1}^n b_{ij} [x^*(t), t] p_i^*(t) = 0$ at $t = t_{\gamma j}$ and $\neq 0$ at $t \neq t_{\gamma j}$), then the components $u_1^*(t), u_2^*(t) \dots, u_r^*(t)$ must be defined by the relation for $t \in [t_0, T^*]$.

$$u_j^*(t) = -\text{sgn} \left\{ \sum_{i=1}^n b_{ij} [x^*(t), t] p_i^*(t) \right\} \quad j = 1, 2, \dots, r \quad (6-79)$$

$$u^*(t) = -\text{SNG} \{ q^*(t) \} = -\text{SNG} \{ B' [x^*(t), t] p^*(t) \}$$

Thus, if the problem is normal, the components of the time optimal control are piecewise constant functions of time.

Theorem 1. Reduced Necessary Conditions.

Let $u^*(t)$ be a time optimal control. Let $x^*(t)$ be the state on the time-optimal trajectory and let $p^*(t)$ be the corresponding co-state. Let T^* be the minimum time. If the problem is normal, then it is necessary that

1. the Theorem 1 be satisfied,

2. the state $\mathbf{x}^*(t)$ and co-state $\mathbf{p}^*(t)$ satisfy the reduced canonical equations

$$\begin{aligned} d\mathbf{x}^*(t)/dt &= \mathbf{f}[\mathbf{x}^*(t), t] - \sum_{j=1}^n \mathbf{b}_{kj} [\mathbf{x}^*(t), t] * \\ &\quad * \text{sgn} \left\{ \sum_{i=1}^n \mathbf{b}_{ij} [\mathbf{x}^*(t), t] \mathbf{p}_i^*(t) \right\} \quad \text{--(6-81)} \\ d\mathbf{p}^*(t)/dt &= - \sum_{i=1}^n \frac{\partial \mathbf{f}_i [\mathbf{x}^*(t), t]}{\partial \mathbf{x}^k(t)} \mathbf{p}_i^*(t) * \end{aligned}$$

$$\begin{aligned} &\sum_{j=1}^r \text{sgn} \left\{ \sum_{i=1}^n \mathbf{b}_{ij} [\mathbf{x}^*(t), t] \mathbf{p}_i^*(t) \right\} \sum_{i=1}^n \frac{\partial \mathbf{f}_i [\mathbf{x}^*(t), t]}{\partial \mathbf{x}^k(t)} \mathbf{p}_i^*(t) \\ &\quad \text{--(6-82)} \end{aligned}$$

For $k=1, 2, \dots, n$ and for $t \in [t_0, T^*]$. and
3. The Hamiltonian (6-52) along the time- optimal trajectory is given by the equation

$$\begin{aligned} H[\mathbf{x}^*(t), \mathbf{p}^*(t), \mathbf{u}^*(t), t] &= 1 + \sum_{i=1}^n \mathbf{f}_i [\mathbf{x}^*(t), t] \mathbf{p}_i^*(t) \\ &- \sum_{j=1}^r \sum_{i=1}^n \mathbf{b}_{ij} [\mathbf{x}^*(t), t] \mathbf{p}_i^*(t) \quad \text{for } t \in [t_0, T^*]. \end{aligned}$$

4. At the terminal time T^* , the following (see 6-61) holds

$$\begin{aligned} 1 + \sum_{i=1}^n \mathbf{f}_i [\mathbf{x}^*(T^*), T^*] \mathbf{p}_i^*(T^*) - \sum_{j=1}^r \sum_{i=1}^n \mathbf{b}_{ij} [\mathbf{x}^*(T^*), T^*] \mathbf{p}_i^*(T^*) \\ = \sum_{\alpha=1}^{n-\beta} \mathbf{c}_\alpha [\partial g_\alpha [\mathbf{x}^*(T^*), T^*] / \partial T^*] \quad \text{--(6-84)} \end{aligned}$$

5. At the initial time t_0 , $\mathbf{x}^*(t_0) = \mathbf{x}(t_0)$ --(6-85).

At the terminal time, T^* ,

$$g_\alpha(\mathbf{x}^*, T^*) = 0, \quad \alpha=1, 2, \dots, n-\beta \quad \text{--(6-86)}$$

$$\mathbf{p}^*(T^*) = \sum_{\alpha=1}^{n-\beta} k_\alpha [\partial g_\alpha [\mathbf{x}^*(T^*), T^*] / \partial \mathbf{x}^*(T^*)] \quad \text{(6-87)}$$

Step 3. In the step 1 and step 2, we stated relations that must be satisfied by the time optimal control $\mathbf{u}^*(t)$, the resulting state $\mathbf{x}^*(t)$, the corresponding co-state $\mathbf{p}^*(t)$ and the minimum time T^* . In the following steps, we use these steps to find the time-optimal control.

Step3-a. Formation of the Hamiltonian.

The Hamiltonian is (6-45 or 6-46)

$$H[\mathbf{x}(t), \mathbf{p}(t), \mathbf{u}(t), t] = 1 + \langle \mathbf{f}[\mathbf{x}(t), t], \mathbf{p}(t) \rangle + \langle \mathbf{u}(t), \mathbf{B}'[\mathbf{x}(t), t] \mathbf{p}(t) \rangle$$

where

$$\mathbf{x}'(t) = \mathbf{f}[\mathbf{x}(t), t] + \mathbf{B}[\mathbf{x}(t), t] \mathbf{u}(t) \quad \text{and the cost function}$$

$$J(\mathbf{u}) = \int_{t_0}^T 1 \, dt$$

Step 3-b. Minimization of the Hamiltonian

The Hamiltonian function $H[\mathbf{x}(t), \mathbf{p}(t), \mathbf{u}(t), t]$ depends on $2n + r + 1$ variables. Here we hold $\mathbf{x}(t)$, $\mathbf{p}(t)$ and t constants and we examine the behavior of the Hamiltonian which is now a function of $\mathbf{u}(t)$ only. Now, we define an H - minimum control as The admissible control $\mathbf{u}_o(t)$ is called H-minimal if it satisfies the relation

$$H[\mathbf{x}(t), \mathbf{p}(t), \mathbf{u}_o(t), t] \leq H[\mathbf{x}(t), \mathbf{p}(t), \mathbf{u}(t), t] \quad \text{--(6-89)}$$

for all $\mathbf{u}(t) \in \Omega$, all $\mathbf{x}(t)$ and all $\mathbf{p}(t)$ and all t . If we mimic the development presented in the step2, $\mathbf{u}_o(t)$ is

$$\mathbf{u}_o(t) = -\text{sgn} \left\{ \sum_{i=1}^n \mathbf{b}_{ij} [\mathbf{x}(t), t] \mathbf{p}_i(t) \right\}, \quad j=1, 2, \dots, r \quad \text{--(6-90)}$$

$$\mathbf{u}_o(t) = -\text{SGN} \{ \mathbf{B}'[\mathbf{x}(t), t] \mathbf{p}(t) \} \quad \text{--(6-91)}$$

Substitute the H-minimal control $\mathbf{u}_o(t)$ into (6-88),

$$H[\mathbf{x}(t), \mathbf{p}(t), \mathbf{u}_o(t), t] = 1 + \langle \mathbf{f}[\mathbf{x}(t), t], \mathbf{p}(t) \rangle$$

$$- \langle \text{SGN} \{ \mathbf{B}'[\mathbf{x}(t), t] \mathbf{p}(t) \}, \mathbf{B}'[\mathbf{x}(t), t] \mathbf{p}(t) \rangle \quad \text{--(6-92)}$$

and hence

$$H[\mathbf{x}(t), \mathbf{p}(t), \mathbf{u}_o(t), t] = 1 + \sum_{i=1}^n \mathbf{f}_i [\mathbf{x}(t), t] \mathbf{p}_i(t)$$

$$- \sum_{j=1}^r \sum_{i=1}^n \mathbf{b}_{ij} [\mathbf{x}(t), t] \mathbf{p}_i(t) \quad \text{--(6-93)}$$

The right side is only a function of $\mathbf{x}(t), \mathbf{p}(t)$ and t . For this reason, we define the function $H_o[\mathbf{x}(t), \mathbf{p}(t), t]$ by

$$H_o[\mathbf{x}(t), \mathbf{p}(t), t] = \min_{\mathbf{u}(t) \in \Omega} H[\mathbf{x}(t), \mathbf{p}(t), \mathbf{u}(t), t] \quad \text{--(6-94)}$$

These equations do not involve explicitly the trajectories nor the optimal quantities.

Step 3C. Restricting $\mathbf{x}(t)$ and $\mathbf{p}(t)$.

Let demand that the vectors $\mathbf{x}(t)$ and $\mathbf{p}(t)$ satisfy

$$\mathbf{x}'(t) = \frac{\partial H_o[\mathbf{x}(t), \mathbf{p}(t), t]}{\partial \mathbf{x}(t)} \quad \text{--(6-95)}$$

$$\mathbf{p}'(t) = - \frac{\partial H_o[\mathbf{x}(t), \mathbf{p}(t), t]}{\partial \mathbf{p}(t)} \quad \text{--(6-96)}$$

or

$$\mathbf{x}k'(t) = \mathbf{f}[\mathbf{x}(t), t] - \sum_{j=1}^r \mathbf{b}_{kj} [\mathbf{x}(t), t] \text{sgn} \left\{ \sum_{i=1}^n \mathbf{b}_{ij} [\mathbf{x}(t), t] \mathbf{p}_i(t) \right\}$$

$$\mathbf{p}k'(t) = - \sum_{i=1}^n \frac{\partial \mathbf{f}_i [\mathbf{x}(t), t]}{\partial \mathbf{x}^k(t)} \mathbf{p}_i(t)$$

$$\begin{aligned} &+ \sum_{j=1}^r \text{sgn} \left\{ \sum_{i=1}^n \mathbf{b}_{ij} [\mathbf{x}(t), t] \mathbf{p}_i(t) \right\} \sum_{i=1}^n \frac{\partial \mathbf{b}_{ij} [\mathbf{x}(t), t]}{\partial \mathbf{x}^k(t)} \mathbf{p}_i(t) \\ &\quad \text{--(6-97,98)} \end{aligned}$$

for $k=1, 2, \dots, n$. We note that

$$\frac{\partial H_o[\mathbf{x}(t), \mathbf{p}(t), t]}{\partial \mathbf{p}(t)} = \frac{\partial H[\mathbf{x}(t), \mathbf{p}(t), \mathbf{u}(t), t]}{\partial \mathbf{p}(t)} \quad \text{(} \mathbf{u}(t) = \mathbf{u}_o(t) \text{)} \quad \text{--(6-99)}$$

$$\frac{\partial H_o[\mathbf{x}(t), \mathbf{p}(t), t]}{\partial \mathbf{x}(t)} = \frac{\partial H[\mathbf{x}(t), \mathbf{p}(t), \mathbf{u}(t), t]}{\partial \mathbf{x}(t)} \quad \text{(} \mathbf{u}(t) = \mathbf{u}_o(t) \text{)} \quad \text{--(6-100)}$$

[APPENDIX 1]

The standardized state variables.

We set the concentrations of the species for the state variables as

E1	$x_1 (10 \cdot 10^{-6})$	E1 A B	x11
E2	$x_2 (10 \cdot 10^{-6})$	E1 C D	x12
A	$x_3 (5 \cdot 10^{-3})$	E2 C	x13
B	x_4	E2 X	x14
C	$x_5 (20 \cdot 10^{-6})$	E2 Y	x15
D	x_6	X (5 \cdot 10^{-3})	x16
E1 A	x_7	Y	x17
E1 B	x_8	E2 C X	x18
E1 C	x_9	E2 B Y	x19
E1 D	x_{10}	E2 B	x20

$$\begin{aligned} dydx_1 &= -k_1 x_1 x_3 + km_1 x_7 - k_2 x_1 x_4 + km_2 x_8 \\ &\quad + k_8 x_{10} - km_8 x_1 x_6 + k_9 x_9 - km_9 x_1 x_5; \end{aligned}$$

$$\begin{aligned} dydx_2 &= -k_{10} x_2 x_5 + km_{10} x_{13} - k_{11} x_2 x_{16} \\ &\quad + km_{11} x_{14} + k_{17} x_{15} - km_{17} x_2 x_{17} + k_{18} x_{20} \\ &\quad - km_{18} x_2 x_4; \end{aligned}$$

$$\begin{aligned} dydx3 = & k1 \ x1 \ x3 + km1 \ x7 - k4 \ x8 \ x3 + km3 \ x11 \\ & + k15 \ x19 - km15 \ x15 \ x4 + k18 \ x20 \\ & - km18 \ x2 \ x4; \end{aligned}$$

$$\begin{aligned} dydx4 = & -k2 \ x1 \ x4 + km2 \ x8 - k3 \ x7 \ x4 + km3 \ x11 \\ & + k15 \ x19 - km15 \ x15 \ x4 + k18 \ x20 \\ & - km18 \ x2 \ x4; \end{aligned}$$

$$\begin{aligned} dydx5 = & k6 \ x12 - km6 \ x10 \ x5 + k9 \ x9 - km9 \ x1 \ x5 \\ & - k10 \ x2 \ x5 + km10 \ x13 - k13 \ x14 \ x5 \\ & + km13 \ x18; \end{aligned}$$

$$dydx6 = k7 \ x12 - km7 \ x9 \ x6 + k8 \ x10 - km8 \ x1 \ x6;$$

$$dydx7 = k1 \ x1 \ x3 - km1 \ x7 - k3 \ x7 \ x4 + km3 \ x11;$$

$$dydx8 = k2 \ x1 \ x4 - km2 \ x8 - k4 \ x8 \ x3 + km4 \ x11;$$

$$dydx9 = k7 \ x12 - km7 \ x9 \ x6 - k9 \ x9 + km9 \ x1 \ x5;$$

$$dydx10 = k6 \ x12 - km6 \ x10 \ x5 - k8 \ x10 + km8 \ x1 \ x6;$$

$$\begin{aligned} dydx11 = & k3 \ x7 \ x4 - km3 \ x11 + k4 \ x8 \ x3 - km4 \ x11 \\ & - k5 \ x11 + km5 \ x12; \end{aligned}$$

$$\begin{aligned} dydx12 = & k5 \ x11 - km5 \ x12 - k6 \ x12 + km6 \ x10 \ x5 \\ & - k7 \ x12 + km7 \ x9 \ x6; \end{aligned}$$

$$\begin{aligned} dydx13 = & k10 \ x2 \ x5 - km10 \ x13 - k12 \ x16 \ x13 \\ & + km12 \ x18; \end{aligned}$$

$$\begin{aligned} dydx14 = & k11 \ x2 \ x16 - km11 \ x14 - k13 \ x14 \ x5 \\ & + km13 \ x18; \end{aligned}$$

$$\begin{aligned} dydx15 = & k15 \ x19 - km15 \ x4 \ x15 - k17 \ x15 \\ & + km17 \ x2 \ x17; \end{aligned}$$

$$\begin{aligned} dydx16 = & -k11 \ x2 \ x16 + km11 \ x14 - k12 \ x16 \ x13 \\ & + km12 \ x18; \end{aligned}$$

$$\begin{aligned} dydx17 = & k16 \ x19 - km16 \ x20 \ x17 + k17 \ x15 \\ & - km17 \ x2 \ x17; \end{aligned}$$

$$\begin{aligned} dydx18 = & k12 \ x16 \ x13 - km12 \ x18 + k13 \ x14 \ x5 \\ & - km13 \ x18 - k14 \ x18 + km14 \ x19; \end{aligned}$$

$$\begin{aligned} dydx19 = & k14 \ x18 - km14 \ x19 - k15 \ x19 + km15 \ x15 \ x4 \\ & - k16 \ x19 + km16 \ x20 \ x17; \end{aligned}$$

$$\begin{aligned} dydx20 = & k16 \ x19 - km16 \ x20 \ x17 - k18 \ x20 \\ & + km18 \ x2 \ x4; \end{aligned}$$

[APPENDIX II]

The optimized differential equations for the co-state variables are

$$\begin{aligned} \lambda 1' = & - \frac{\partial H}{\partial x1} = - [\lambda 1 (-k1 \ x3 - k2 \ x4 - k8 \ x6 - k9 \ x5) \\ & + \lambda 2 (0) + \lambda 3 (k1 \ x3) + \lambda 4 (-k2 \ x4) \\ & + \lambda 5 (-k9 \ x5) + \lambda 6 (-k8 \ x6) \\ & + \lambda 7 (k1 \ x3) + \lambda 8 (k2 \ x4) + \lambda 9 (k9 \ x5) \\ & + \lambda 10 (k8 \ x6) + \lambda 11 (0)] \end{aligned}$$

$$\begin{aligned} \lambda 2' = & - \frac{\partial H}{\partial x2} = - [\lambda 2 (-k10 \ x5 - k11 \ x16 - k17 \ x17 \\ & - k18 \ x4) + \lambda 4 (-k18 \ x4) \\ & + \lambda 5 (-k10 \ x5) + \lambda 13 (k10 \ x5) \\ & + \lambda 14 (k11 \ x16) + \lambda 15 (k17 \ x17) \\ & + \lambda 16 (-k11 \ x16) + \lambda 17 (-k17 \ x17) \\ & + \lambda 20 (k18 \ x4)] \\ = & - [k10 \ x5 (-\lambda 2 - \lambda 5 + \lambda 13) \\ & + k11 \ x16 (-\lambda 2 - \lambda 14 - \lambda 16) \\ & + k17 \ x17 (-\lambda 2 + \lambda 15 - \lambda 17) \\ & + k18 \ x4 (-\lambda 2 - \lambda 4 + \lambda 20)] \\ = & - [k2 \ x1 (-\lambda 1 - \lambda 4 + \lambda 8) \\ & + k18 \ x2 (-\lambda 2 - \lambda 4 + \lambda 20) \\ & + k3 \ x7 (-\lambda 4 - \lambda 7 + \lambda 11) \\ & + k15 \ x15 (-\lambda 4 - \lambda 15 + \lambda 19)] \end{aligned}$$

$$\begin{aligned} \lambda 3' = & - \frac{\partial H}{\partial x3} = - [\lambda 1 (-k1 \ x1) + \lambda 3 (k1 \ x1 - k4 \ x8) \\ & + \lambda 7 (k1 \ x1) + \lambda 8 (-k4 \ x8) \\ & + \lambda 11 (k4 \ x8)] \\ = & - [k1 \ x1 (-\lambda 1 + \lambda 3 + \lambda 7) \\ & + k4 \ x8 (-\lambda 3 - \lambda 8 + \lambda 11)] \end{aligned}$$

$$\begin{aligned} \lambda 4' = & - \frac{\partial H}{\partial x4} = - [\lambda 1 (-k2 \ x1) + \lambda 2 (-k18 \ x2) \\ & + \lambda 4 (-k2 \ x1 - k3 \ x7 - k15 \ x15 - k18 \ x2) \\ & + \lambda 7 (-k3 \ x7) + \lambda 8 (k2 \ x1) \\ & + \lambda 11 (k3 \ x7) + \lambda 15 (-k15 \ x15) \\ & + \lambda 19 (k15 \ x15) + \lambda 20 (k18 \ x2)] \end{aligned}$$

$$\begin{aligned} \lambda 5' = & - \frac{\partial H}{\partial x5} = - [\lambda 1 (-k9 \ x1) + \lambda 2 (-k10 \ x2) \\ & + \lambda 5 (-k6 \ x10 - k9 \ x1 - k10 \ x2 - k13 \ x14) \\ & + \lambda 9 (k9 \ x1) + \lambda 10 (-k6 \ x10) \\ & + \lambda 12 (k6 \ x10) + \lambda 13 (k10 \ x2) \\ & + \lambda 14 (-k13 \ x14) + \lambda 18 (k13 \ x14)] \\ = & - [k9 \ x1 (-\lambda 1 - \lambda 5 + \lambda 9) \\ & + k10 \ x2 (-\lambda 2 - \lambda 5 + \lambda 13) \\ & + k6 \ x10 (-\lambda 5 - \lambda 10 + \lambda 12) \\ & + k13 \ x14 (-\lambda 5 - \lambda 14 + \lambda 18)] \end{aligned}$$

$$\begin{aligned} \lambda 6' = & - \frac{\partial H}{\partial x6} = - [\lambda 1 (-k8 \ x1) + \lambda 6 (-k7 \ x9 - k8 \ x1) \\ & + \lambda 9 (-k7 \ x9) + \lambda 10 (k8 \ x1) \end{aligned}$$

$$+ \lambda_{12} (k_7 x_9)] \\ = - [k_8 x_1 (-\lambda_1 - \lambda_6 + \lambda_{10}) \\ + k_7 x_9 (-\lambda_6 - \lambda_9 + \lambda_{12})]$$

$$\lambda_7' = - \frac{\partial H}{\partial x_7} = - [\lambda_1 (k_1) + \lambda_3 (k_1) \\ + \lambda_4 (-k_3 x_4) + \lambda_7 (-k_1 - k_3 x_4) \\ + \lambda_{11} (k_3 x_4)]$$

$$\lambda_8' = - \frac{\partial H}{\partial x_8} = - [\lambda_1 (k_2) + \lambda_3 (-k_4 x_3) \\ + \lambda_4 (k_2) + \lambda_8 (-k_2 - k_4 x_3) \\ + \lambda_{11} (k_4 x_3)] \\ = - [k_2 (\lambda_1 + \lambda_4 - \lambda_8) \\ + k_4 x_3 (-\lambda_3 - \lambda_8 + \lambda_{11})]$$

$$\lambda_9' = - \frac{\partial H}{\partial x_9} = - [\lambda_1 (k_9) + \lambda_5 (k_9) \\ + \lambda_6 (-k_7 x_6) + \lambda_9 (-k_7 x_6 - k_9) \\ + \lambda_{12} (k_7 x_6)] \\ = - [k_9 (\lambda_1 + \lambda_5 - \lambda_9) \\ + k_7 x_6 (-\lambda_6 - \lambda_9 + \lambda_{12})]$$

$$\lambda_{10}' = - \frac{\partial H}{\partial x_{10}} = - [\lambda_1 (k_8) + \lambda_5 (-k_6 x_5) \\ + \lambda_6 (k_8) + \lambda_{10} (-k_6 x_5 - k_8) \\ + \lambda_{12} (k_6 x_5)] \\ = - [k_8 (\lambda_1 + \lambda_6 - \lambda_{10}) \\ + k_6 x_5 (-\lambda_5 - \lambda_{10} + \lambda_{12})]$$

$$\lambda_{11}' = - \frac{\partial H}{\partial x_{11}} = - [\lambda_3 (k_4) + \lambda_4 (k_3) + \lambda_7 (k_3) \\ + \lambda_8 (k_4) + \lambda_{11} (-k_3 - k_4 - k_5) \\ + \lambda_{12} (k_5)] \\ = - [k_4 (\lambda_3 + \lambda_8 - \lambda_{11}) \\ + k_3 (\lambda_4 + \lambda_7 - \lambda_{11}) \\ + k_5 (-\lambda_{11} + \lambda_{12})]$$

$$\lambda_{12}' = - \frac{\partial H}{\partial x_{12}} = - [\lambda_5 k_6 + \lambda_6 k_7 + \lambda_9 k_7 \\ + \lambda_{10} k_6 + \lambda_{11} k_5 \\ + \lambda_{12} (-k_5 - k_6 - k_7) \\ = - [k_6 (\lambda_5 + \lambda_{10} - \lambda_{12}) \\ + k_7 (\lambda_6 + \lambda_9 - \lambda_{12}) \\ + k_5 (\lambda_{11} - \lambda_{12})]$$

$$\lambda_{13}' = - \frac{\partial H}{\partial x_{13}} = - [\lambda_2 (k_{10}) + \lambda_5 (k_{10}) \\ + \lambda_{13} (-k_{10} - k_{12} x_{16}) \\ + \lambda_{16} (-k_{12} x_{16}) + \lambda_{18} (k_{12} x_{16})] \\ = - [k_{10} (\lambda_2 + \lambda_5 - \lambda_{13}) \\ + k_{12} k_{16} (-\lambda_{13} - \lambda_{16} + \lambda_{18})]$$

$$\lambda_{14}' = - \frac{\partial H}{\partial x_{14}} = - [\lambda_2 (k_{11}) + \lambda_{14} (-k_{11} - k_{13} x_5) \\ + \lambda_5 (-k_{13} x_5) + \lambda_{16} (k_{11}) \\ + \lambda_{18} (k_{13} x_5)] \\ = - [k_{11} (\lambda_2 - \lambda_{14} + \lambda_{16}) \\ + k_{13} k_5 (-\lambda_{14} + \lambda_{18} - \lambda_5)]$$

$$\lambda_{15}' = - \frac{\partial H}{\partial x_{15}} = - [\lambda_2 (k_{17}) + \lambda_4 (-k_{15} x_4) \\ + \lambda_{15} (-k_{15} x_4 - k_{17}) + \lambda_{17} (k_{17}) \\ + \lambda_{19} (k_{15} x_4)] \\ = - [k_{17} (\lambda_2 - \lambda_{15} + \lambda_{17}) \\ + k_{15} x_4 (-\lambda_4 - \lambda_{15} + \lambda_{19})]$$

$$\lambda_{16}' = - \frac{\partial H}{\partial x_{16}} = - [\lambda_2 (-k_{11} x_2) + \lambda_{13} (-k_{12} x_{13}) \\ + \lambda_{14} (k_{11} x_2) + \lambda_{16} (-k_{11} x_2 - k_{12} x_{13}) \\ + \lambda_{18} (k_{12} x_{13})] \\ = - [k_{11} x_2 (-\lambda_2 + \lambda_{14} - \lambda_{16}) \\ + k_{12} k_{13} (-\lambda_{13} - \lambda_{16} + \lambda_{18})]$$

$$\lambda_{17}' = - \frac{\partial H}{\partial x_{17}} = - [\lambda_2 (-k_{17} x_2) + \lambda_{15} (k_{17} x_2) \\ + \lambda_{17} (-k_{16} x_{20} - k_{17} x_2) \\ + \lambda_{19} (k_{16} x_{20}) \\ + \lambda_{20} (-k_{16} x_{20})] \\ = - [k_{17} x_2 (-\lambda_2 + \lambda_{15} - \lambda_{17}) \\ + k_{16} x_{20} (-\lambda_{17} + \lambda_{19} - \lambda_{20})]$$

$$\lambda_{18}' = - \frac{\partial H}{\partial x_{18}} = - [\lambda_5 (k_{13}) + \lambda_{13} (k_{12}) \\ + \lambda_{14} (k_{13}) + \lambda_{16} (k_{12}) \\ + \lambda_{18} (-k_{12} - k_{13} - k_{14}) \\ + \lambda_{19} (k_{14})] \\ = - [k_{13} (\lambda_5 + \lambda_{14} - \lambda_{18}) \\ + k_{12} (\lambda_{13} + \lambda_{16} - \lambda_{18}) \\ + k_{14} (-\lambda_{18} + \lambda_{19})]$$

$$\lambda_{19}' = - \frac{\partial H}{\partial x_{19}} = - [\lambda_4 (k_{15}) + \lambda_{15} (k_{15}) \\ + \lambda_{17} (k_{16}) + \lambda_{18} (k_{14}) \\ + \lambda_{19} (-k_{14} - k_{15} - k_{16}) \\ + \lambda_{20} (k_{16})] \\ = - [k_{15} (\lambda_4 + \lambda_{15} - \lambda_{19}) \\ + k_{16} (\lambda_{17} - \lambda_{19} + \lambda_{20}) \\ + k_{14} (-\lambda_{18} - \lambda_{19})]$$

$$\lambda_{20}' = - \frac{\partial H}{\partial x_{20}} = - [\lambda_2 k_{18} + \lambda_4 k_{18} + \lambda_{17} (-k_{16} x_{17}) \\ + \lambda_{19} (k_{16} x_{17}) \\ + \lambda_{20} (-k_{16} x_{17} - k_{18})] \\ = - [k_{18} (\lambda_2 + \lambda_4 - \lambda_{20}) \\ + k_{16} x_{17} (-\lambda_{17} + \lambda_{19} - \lambda_{20})]$$