Analysis of the Temporal Behaviors of the Carrier-Mediated Membrane Transport by Optimal Control Theory

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Theoretical analysis was performed on the carrier-mediated solute transport across the biological membrane based on optimal control principle that minimizes the rate of changes in concentrations of the species in combination with energy to drive the system. Experimental data for temporal change in carrier mediated transport could be simulated by the present model with regulating weighting coefficients. Changes in concentrations of the species due to the increase in rate constants could be explained by the compensatory action of the optimal control mechanism. The present study must be available for evaluation of the optimality in carrier mediated membrane transport.

key words : Membrane, Carrier, Transport, Solute, Optimal Control, Performance Function

1. Introduction

In biological systems, many materials are transported into intra cellular space through the biological membrane. There are three mechanisms of the transport across the membrane⁽¹⁾,

- (1) Passive transport : simple diffusion, diffusion through selective channel and facilitated diffusion⁽²⁾⁽³⁾.
- (2) Active transport : the primary active transport such as Ion transport, carrier protein dependent transport, secondary active transport such as co-transport or symport of Ions, anti port and exchange transport⁽⁴⁾⁽⁵⁾ and
- (3) Group trans location

Regardless of these mechanisms, ultimately they are performed by a solute specific carrier protein. Once, the solute has connected with the carrier protein and formed a complex, conformational changes occur in the carrier protein. As a result, a solute is transported across the membrane as a solute-carrier complex.

Considerable amounts of investigations have been accumulated and minute mechanisms are disclosed. However, there has been any study for the control strategy of membrane transport particularly from the stand point of economical operation.

In the present investigation, we propose a mathematical model of carrier mediated membrane transport based the optimal control mechanism. The fundamental concept is that the solute is transported across the membrane upon minimizing the energy and achieving the least change state without retention or depletion of all the participated species at any step of the transport process.

We show successful simulation for biological experimental result, the optimized time courses of concentrations of carrier-solute complexes and the influences of elevated rate constants.

2. Mathematical modeling

2.1 Modeling of the carrier-mediated transport across the membrane

A generalized model of the carrier mediated transport across the biological membrane is shown in fig. 1. The model consists of 4 steps of transport⁽⁶⁾ as followings :

- (1) The solutes in the extra cellular space (S_1) bind to the free carriers (C_1) on the outer surface of the membrane facing to the extra-cellular space.

- (2) The carrier-solute complex (CS_1) moves from the outer surface of the membrane to the inner surface of

Fig. 1. The schema of model of carrier-mediated membrane transport.

the membrane (CS_2) facing to the cellular plasma.

(3) The carrier-solute complex (CS_2) on the inner surface of the membrane releases the solutes to the cellular plasma.

(4) The solute free carriers (C_2) on the inner surface of the membrane return to the outer surface of the membrane (C_1). This process expresses the recycling phase of the carrier.

where

$[S_1]$: the concentration of the solute per unit volume of the extra-cellular space.

$[S_2]$: the concentration of the solute per unit volume of the cellular plasma.

$[C_1]$: the concentration of free carrier per unit area of the outer surface of the membrane.

$[C_2]$: the concentration of free carrier per unit area of the inner surface of the membrane.

$[CS_1]$: the concentration of the solute-carrier complex per unit area of the outer surface of the membrane.

$[CS_2]$: the concentration of the solute-carrier complex per unit area of the inner surface of the membrane.

kn is a rate constant of the reaction per unit time per unit area of the membrane. k_1, k_3, k_5 and k_7 are those when the solutes are carried into the cellular plasma. k_2, k_4, k_6 and k_8 are those of transport in the reverse direction. The instantaneous changes of the concentrations of the species are

$$\frac{d[C_1]}{dt} = k_2[CS_1] + k_7[C_2] - k_8[C_1] - k_1[C_1][S_1] + U_1 \quad (1)$$

$$\frac{d[CS_1]}{dt} = k_1[C_1][S_1] + k_4[CS_2] - k_3[CS_1] - k_2[CS_1] + U_2 \quad (2)$$

$$\frac{d[CS_2]}{dt} = k_3[CS_1] + k_6[C_2] - (k_4 + k_5)[CS_2] + U_3 \quad (3)$$

$$\frac{d[C_2]}{dt} = k_5[CS_2] + k_8[C_1] - (k_7 + k_6)[C_2] + U_4 \quad (4)$$

$$\frac{d[S_2]}{dt} = k_5[CS_2] \quad (5)$$

where U_n ($n=1, 2, 3, 4$) are the control inputs. The solutes in the extra-cellular space exist in sufficient amount. So we set $[S_1]$ as a constant. By the law of conservation,

$$[C_t] = [C_1] + [C_2] + [CS_1] + [CS_2] \quad (6)$$

where C_t is the total concentration of the carrier per unit area of the membrane. By converting the concentrations of these species to state variables,

$$[C_1] = X_1 \quad (7a)$$

$$[CS_1] = X_2 \quad (7b)$$

$$[CS_2] = X_3 \quad (7c)$$

$$[C_2] = X_4 \quad (7d)$$

and

$$[C_t] = X_0 \quad (7e)$$

Substituting $X_3 = X_0 - X_1 - X_2 - X_4$ into the equation (2), (3) and (4) the following are achieved:

$$\frac{dX_1}{dt} = X_1(-k_8 - k_1[S_1]) + k_2X_2 + k_7X_4 + U_1 \quad (8)$$

$$\frac{dX_2}{dt} = k_1[S_1]X_1 + (-k_2 - k_3)X_2 + k_4(X_0 - X_1 - X_2 - X_4) + U_2 \quad (9)$$

$$\frac{dX_4}{dt} = k_5X_1 + (k_5 - k_7 - k_6)(X_0 - X_1 - X_2 - X_4) + U_4 \quad (10)$$

$$\frac{dX_3}{dt} = -\frac{dX_1}{dt} - \frac{dX_2}{dt} - \frac{dX_4}{dt} \quad (11)$$

2.2 Setting the control inputs and their biological significance

U_1 is the control input for production of carrier protein. Because production of the carrier protein, C_1 has to be controlled economically to achieve the optimal transport state. This process is ultimately the result of the translation and protein synthesis on the messenger RNA. Its over production reduces the economical transport because of the unbalance of demand (solute that has to be carried) and supply (carrier production). On the contrary, its insufficient production makes the solute to accumulate abnormally in the extra cellular space

which in turn disturbs the physiological cellular function. Thus, we set U_1 as the control input that has to be controlled optimally.

U_3 is the control input for releasing the solutes at the inner surface of the membrane from the carrier-solute complex CS_2 . Essentially, this process relates to phosphorylation which is controlled by many humoral factors such as adrenalin.

U_2 is the control input for transporting the carrier-solute complex CS_1 across the membrane to the inner surface of the membrane. For this transportation, certain amount of biological energy is required to overcome the electro-chemical potential gradient across the cellular membrane⁽²⁾⁽⁶⁾⁽⁷⁾. When the solutes have charges, the energy for the transport is expressed by

$$\Delta\mu_s = RT \ln([S]_{in}/[S]_{out}) + nF\Delta\phi \quad \dots\dots\dots (12)$$

where

$\Delta\mu_s$: the electro chemical potential gradient of the solutes across the membrane,

R : the Gas coefficient, T : the absolute temperature, F : the Farady coefficient, $\Delta\phi$: the difference of the electrical potential across the membrane,

n : the valent of an electron and

$[S]_{in}$ $[S]_{out}$: the concentrations of the solutes in cellular plasma and extra cellular space.

To transport charged solutes by the carriers, this amount of energy has to be supplied. The most typical example is the active transport system of ions by ATP (Adenosine Tri Phosphate) -ase⁽⁸⁾. The carriers transport ions against the chemical gradient by utilizing the energy described above by hydrolysis of ATP. Therefore, utilizing the energy derived from ATP per unit time per unit area of the membrane was set as the control input, U_2 for the transport across the membrane. A similar explanation is given for U_4 .

2.3 Setting the cost function for evaluating performance of the transport

We propose the equation(13) for the cost function to evaluate the performance of the carrier mediated transport.

$$J = \int_0^{te} \left[\sum_{n=1}^4 \partial_n (\partial X_n / \partial t)^2 + \sum_{n=1}^4 \gamma_n (X_n - A_n)^2 + \sum_{n=1}^4 \beta_n U_n^2 \right] dt \quad \dots\dots\dots (13)$$

We assert that the optimal carrier-mediated transport is achieved when this cost function has been minimized during $[0, te]$. The significance of the cost function⁽¹¹⁾⁽¹²⁾ are

(1) The first 4 terms describe to minimize the rates of temporal changes in the concentrations of species,

$[C_1], [C_2], [CS_1], [CS_2]$

(2) The second 4 terms describe to minimize the deviations from the target concentrations, A_n ($n=1, 2, 3$ and 4) for the species, $[C_1], [C_2], [CS_1], [CS_2]$ and

(3) The last 4 terms express to minimize the consumption of the control inputs to drive the system.

The most important aspect of the transport is to carry the solutes smoothly without abnormal congestion (over functioning) nor depletion (in the vacant state) of solute, carrier and / or carrier-solute complex at any step in the transport process.

Minimizing the rates of temporal changes in concentrations prevents excessive rapid accumulation of solutes and / or carrier-solute complex and results in a smooth transport. If any one of these 4 species increased excessively or depleted completely, economical transport would be disturbed.

For example, if CS_1 increased rapidly to an excess amount, CS_1 would accumulate wastefully on the outer surface of the membrane unless control input works optimally so as to transport the surplus CS_1 rapidly to the inner surface. As a result, the solutes and the carriers would congest abnormally. These surplus CS_1 would be obstacles for free carriers to link with solute to form the complex CS_1 . Moreover, excess CS_1 will drive the reaction of $C_1 + S_1 \rightarrow CS_1$ to reverted direction and surplus CS_1 would be dissociated to C_1 and S_1 . Thus, minimizing the rates of the temporal changes in the concentrations of the components is an important condition for achieving economical transport.

The second four terms indicate the space in the membrane which solutes, carriers and carrier-solute complexes can occupy per unit area of the membrane has their limitations.

Minimizing the control inputs U_n ($n=1, 2, 3, 4$) is vital, because the carriers have to be produced economically (demand and supply matching) and the transport across the membrane against the electro chemical potential gradient has to utilize biological energy from ATP (adenosine tri phosphate) effectively. Thus, saving the energy derived from ATP results in an economical operation of the transport.

The weighting coefficients α_n , β_n and γ_n ($n=1, 2, 3$ and 4) measure the relative magnitude of minimizing the changes of components timed by those weighting coefficients.

2.4 The optimal solution

Substituting the equations (8) to (11) into the cost function and rearranging, we have Hamiltonian

$$\begin{aligned}
H = & d_1 X_1^2 + d_2 X_2^2 + d_3 X_4^2 + d_4 U_1^2 + d_5 U_2^2 \\
& + d_6 U_3^2 + d_7 U_4^2 + d_8 X_1 X_2 + d_9 X_1 X_4 \\
& + d_{10} X_2 X_4 + d_{11} X_1 U_1 + d_{12} X_2 U_2 \\
& + d_{13} X_4 U_1 + d_{14} X_1 U_2 + d_{15} X_2 U_3 \\
& + d_{16} X_4 U_2 + d_{17} X_1 U_3 + d_{18} X_2 U_4 \\
& + d_{19} X_4 U_3 + d_{20} X_1 U_4 + d_{21} X_2 U_4 \\
& + d_{22} X_4 U_4 + d_{23} X_1 + d_{24} X_2 + d_{25} X_4 \\
& + d_{26} U_2 + d_{27} U_3 + d_{28} U_4 \\
& + p_1(a_1 X_1 + a_2 X_2 + a_3 X_4 + U_1) \\
& + p_2(a_4 X_1 + a_5 X_2 + a_6 X_4 + a_7 + U_2) \\
& + p_4(a_{12} X_1 + a_{13} X_2 + a_{14} X_4 + a_{15} + U_4)
\end{aligned}
\tag{14}$$

where d_n , a_n are constants composed of the system parameters and the weighting coefficients. p_1 , p_2 and p_4 are the adjoint variables for X_1 , X_2 and X_4 . The optimal control is obtained by differentiating Hamiltonian function with respect to U_n .

$$\partial H / \partial U_n = 0 \tag{15}$$

Thus,

$$\partial H / \partial U_1 = 2d_4 U_1 + d_{11} X_1 + d_{12} X_2 + d_{13} X_4 + p_1 \tag{16 a}$$

$$\partial H / \partial U_2 = 2d_5 U_2 + d_{14} X_1 + d_{15} X_2 + d_{16} X_4 + d_{26} p_2 \tag{16 b}$$

$$\partial H / \partial U_3 = 2d_6 U_3 + d_{17} X_1 + d_{18} X_2 + d_{19} X_4 + d_{27} \tag{16 c}$$

$$\partial H / \partial U_4 = 2d_7 U_4 + d_{20} X_1 + d_{21} X_2 + d_{22} X_4 + d_{28} p_3 \tag{16 d}$$

The optimal U_n are

$$U_1 = d_{29} X_1 + d_{30} X_2 + d_{31} X_4 + d_{32} p_1 \tag{17 a}$$

$$U_2 = d_{33} X_1 + d_{34} X_2 + d_{35} X_4 + d_{36} p_2 + d_{37} \tag{17 b}$$

$$U_3 = d_{38} X_1 + d_{39} X_2 + d_{40} X_4 + d_{41} \tag{17 c}$$

$$U_4 = d_{42} X_1 + d_{43} X_2 + d_{44} X_4 + d_{45} p_3 + d_{46} \tag{17 d}$$

The optimal differential equations for the state variables are modified to

$$X_1' = a_1 X_1 + a_2 X_2 + a_3 X_4 + d_{29} X_1 + d_{30} X_2 + d_{31} X_4 + d_{32} p_1 \tag{18 a}$$

$$X_2' = a_4 X_1 + a_5 X_2 + a_6 X_4 + d_{33} X_1 + d_{34} X_2 + d_{35} X_4 + d_{36} p_2 + d_{37} \tag{18 b}$$

$$X_3' = a_{12} X_1 + a_{13} X_2 + a_{14} X_4 + d_{42} X_1 + d_{43} X_2 + d_{44} X_4 + d_{45} p_3 + d_{46} \tag{18 c}$$

The differential equations for the co-state variables are obtained by differentiating Hamiltonian with respect to individual state variable.

$$\begin{aligned}
p_1' = & -\partial H / \partial X_1 \\
= & h_1 X_1 + h_2 X_2 + h_3 X_4 + h_4 p_1 + h_5 p_2 + h_6 p_4 + h_7
\end{aligned}
\tag{19 a}$$

$$\begin{aligned}
p_2' = & -\partial H / \partial X_2 \\
= & h_8 X_1 + h_9 X_2 + h_{10} X_4 + h_{11} p_1 + h_{12} p_2 + h_{13} p_4 + h_{14}
\end{aligned}
\tag{19 b}$$

$$\begin{aligned}
p_3' = & -\partial H / \partial X_3 \\
= & h_{14} X_1 + h_{15} X_2 + h_{16} X_4 + h_{17} p_1 + h_{18} p_2 + h_{19} p_4
\end{aligned}
\tag{19 d}$$

Consequently, we have six simultaneous linear differential equations.

2.5 Setting system parameters

A carrier protein has at least two subunits for binding to solutes⁽¹⁾⁽²⁾. Lied and Stein⁽¹⁴⁾ proposed a model of a carrier protein which consisted of two subunits. Thus, probabilistically, the rate constant can be 0.5. Experimental analysis⁽¹⁵⁾ of glucose accumulation by an H ion-coupled active transport revealed that in a stable state, the fraction of co-transporter intermediates (corresponding to solute-carrier complexes) ranged from 0.01 to 0.78. In the facilitated diffusion of vehicles⁽¹⁶⁾, rate constant ranged 0.5 to 0.8. Therefore, the rate constant differs among the different kind of transport and materials. The present study, however, analyzes a general case and not a special one. For the convenience, we assumed that the transport starts from the steady and completely balanced state that had been achieved aprior. This means that species have distributed evenly at all the sides of membrane when the transport starts to operate. This feature is characterized by the equivocal initial condition (equation 17a). Thus, we set $k_1 = k_3 = k_5 = k_7 = 0.5$ ⁽¹⁷⁾.

We analyze the situation when the import exceeds the export, so we set $k_2 = k_4 = k_6 = k_8 = 0.01$. The target concentrations of the species were set to A_n ($n=1, 2, 3$ and 4) = 0.5. Because we have assumed the complete equilibrium state at the onset of new transport cycle, the final concentrations of all the species ($X_n(te)$) have to be equal to the target concentrations (A_n). The total amount of the solutes and carriers are set to $S_1 = 5.0$ and $C_t = 5.0$ for the simplicity.

The weighting coefficients were set to be unity $\alpha_n = \beta_n = \gamma_n = 1.0$ ($n=1, 2, 3, 4$) at the standard state and being regulated to simulate the experimental data. Consequently, the initial and final concentrations of the components were set⁽¹⁷⁾ as

$$X_n(0) = 0.01 \tag{20 a}$$

$$X_n(te) = 0.5 \quad (n=1, 2, 4) \tag{20 b}$$

The non zero conditions are indispensable for evoking the transport. For, example, Sodium-Potassium pump operates only when certain initial amounts of Na and K exist⁽³⁾⁽⁴⁾. The terminal states $X_n(te)$ were set to equivalent to the target concentration A_n because the inconsistency between the terminal and target concentrations indicates that the system can not achieve the object of the transport.

Mathematically, the present problem can be reduced to a two points boundary values problem. This formalization is important to describe the recycling nature of the carrier transport. This process is achieved particularly by setting the terminal condition which links to an initial for subsequent new transport cycle. For the simplicity, we set $te=1.0$.

Optimal time courses of X_1 , X_2 and X_4 were obtained by solving equations (18) and (19) under the boundary conditions (20) by numerical method.

3. Results

3.1 Simulation of the reported experimental data

Fig. 2. shows simulating the reported experimental data for transient changes of the concentrations of C_1 , CS_1 and C_2 of Na/glucose co-transport⁽¹⁸⁾. The parameters used for the simulation were shown in Table 1.

Table 1. Parameters for simulation.

1. Rate Constants	
$k_1=120, k_2=23, k_3=k_4=0.9,$	
$k_5=40, k_6=3.9, k_7=8.9, k_8=1.45$	
2. Weighting Coefficients	
$\alpha_1=1.0 \quad \alpha_2=500 \quad \alpha_3=1.0 \quad \alpha_4=200$	
$\beta_1=10 \quad \beta_2=1 \quad \beta_3=20 \quad \beta_4=30$	
$\gamma_1=1 \quad \gamma_2=1 \quad \gamma_3=4 \quad \gamma_5=1$	
3. Initial Conditions	
$C_1(0)=0.1 \quad CS_1(0)=0.2 \quad C_2(0)=0.2$	
4. Terminal Conditions	
$C_1(te)=0.01 \quad CS_1(te)=0.1 \quad C_2(te)=0.63$	

There were inevitable discrepancies with experimental data.

3.2 Influences of increased rate constants on the optimized temporal changes in concentrations of the species

The rate constants, k_3 , k_5 and k_7 were increased ten folds while k_1 was two fold. With increases in k_5 and k_7 , C_1 increased rapidly [Fig. 3(a)]. Increases in these coefficients accelerate the transport of CS_2 and C_2 . As a result, CS_2 and C_2 would be depleted rapidly. Thus, to compensate such reductions of CS_2 and C_2 , C_1 must be supplied as soon as possible. As a result, C_1 ($: X_1$) was controlled to increase. This reaction can be attributed to the operation of the optimal control that prevent C_1 from abnormal decreasing. Similar pattern could be observed for CS_1 ($: X_2$) but lesser effect by k_7 which locates away from CS_1 . The increase in k_1 reduced C_1 . This was due to an enhanced linkage of C_1 to CS_1 . The reduction of CS_1 ($: X_2$) [Fig. 3(b)] as a response to increase in k_1 and C_2 ($: X_4$) [Fig. 3(c)] as response to increase in k_5 were interesting. One possible explanation is that the optimal control operates to avoid the rapid changes in concentrations of CS_1 and C_2 induced by an accelerated transportations toward CS_1 and C_2 . As a result, they have been reduced rather than being increased. For CS_1 [Fig. 3(b)], increase in k_5 induced rapid increase. This must also be the compensatory operation of the optimal control mechanism to minimize

Simulation was performed by regulating the weighting coefficients and using reported experimental data of rate constants. The time courses of concentrations of C_1 , CS_1 and C_2 of reported experimental data were denoted by Ex-C1, Ex-CS1 and Ex-C2 and those without Ex are the theoretical results obtained by the optimized model.

Fig. 2. Simulation of experimental data.

Fig. 3. The optimized time courses of concentrations of X_1 ($=[C_1]$), X_2 ($=[CS_1]$), and X_4 ($=[C_2]$) at the standard level of rate constants k_n (sd in figures, $k_3=k_5=k_7=0.5$ and $k_2=k_4=k_6=k_8=0.01$). Rate constants were increased isolatedly and the time course of elevated rate constants were indicated by k_3 , k_5 , $k_7=5.0$, $k_6=1.0$. All other rate constants were set to the standard level. The transporting time is normalized to 1.0.

the reduction of CS_2 due to enhanced conversion to C_2 . There was, however, little effect by k_7 on CS_1 . Similar patterns could be observed in C_2 [Fig. 3(c)] with less obvious effects by k_n .

4. Discussion

The present paper proposed a generalized model of carrier mediated transport across the biological membrane. Particular emphasizes have been put on

(1) It is based on the optimal control principle. There has been no strategic investigation although we intuitively understood that the biological system prefer to work in the least change state, namely Homeostasis.

(2) Recycling nature to recruit free carrier on the inner surface of the membrane to free carrier on the outer surface. This property can be expressed by the two points boundary value problem.

We have shown that the present theory can describe the physiological carrier mediated transport by presenting successful simulation of experimental data.

The rate constant is one of the most critical factor that determines the temporal behaviors of the transport across the membrane. From experimental results⁽¹⁹⁾⁽²⁰⁾, association-dissociation reactions on membrane surfaces were faster than the transport across the membrane. However, data on the transport of L-Leucine into human erythrocytes at 25°C showed⁽¹⁷⁾ that at a stable state, the carrier is equally distributed at any site of the

membrane. Since we analyze the steady state in which the transport is stable, we set k_1 , k_3 , k_5 and k_7 equal to 0.5.

There are many other biological features of the rate constant, for example, the rate of the binding of solutes to the carriers enhances the rate of the transport across the membrane⁽¹⁷⁾, saturation phenomenon⁽²⁾, competition of binding sites with antagonist⁽²⁾ and voltage dependent co-transport with ions⁽¹⁷⁾. Such functional settings make the present problem insolvable⁽¹³⁾, we set the present rate constants as independent ones.

5. Conclusion

(1) A theoretical model of carrier-mediated transport across the biological membrane based on the optimal control principle can reconstruct physiological experimental data for membrane transport.

(2) The increase of rate of transfer at the contra lateral side for the inward transport augmented the rate of change in concentration of each component. The corresponding changes in the optimal control showed a variety of changes.

(3) Present investigation must be available for evaluation of the optimality in carrier mediated membrane transport.

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