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The Concept of "Conformation" and the "Combinatorial Approach" for Parameter Estimation in a Multi-compartment Model System

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We have developed a systematic method of pharmacokinetic parameter estimation based on the "law of product" and the "law of sum," just as in the theory of probability. We named this method the "combinatorial approach," for this approach plays an essential role in the handling of our "combinatorial model scheme" (Kurita *et al.*, *J. Pharm. Sci.*, submitted). First we defined the concept of "conformation" and "subconformation." In any complicated system, simple relations hold among the transfer function or the availability for subconformations. For example we have proved that for any conformation, $F(C_1)+F(C_2)=F(C_1+C_2)$ and $F(C_1 * C_2)=F(C_1)\times F(C_2)$ hold, where $F(C)$ stands for the availability of conformation C and C_1+C_2 is the combination in parallel and $C_1 * C_2$ is the combination in series. We have introduced the "principle of replacement" and the "principle of substitution" as a concrete method of calculation, and explained how they work using several examples. In steady-state kinetics we have defined the concepts of "upstream" conformation and "downstream" conformation for each compartment. By these availabilities, the concentration ratio between the concentration of the inlet and that of the outlet is determined and these concentrations satisfy additive relations in a log scale just as in a cascade. The combinatorial approach in pharmacokinetics is available to estimate the pharmacokinetic parameters in an intuitive and straightforward manner in a complicated multicompartment model system.

Keywords——pharmacokinetics; combinatorial approach; combinatorial conformation; replacement; substitution; compartment; combinatorial model

Introduction

For analysis in multi-compartment systems, especially for the linear case, the linear algebraic method has been well developed.[1-4] However, in a case where the number of compartments is large, the parameter can not always be predicted in an intuitively clear fashion.

We have recently proposed a new scheme named the "combinatorial model system" for hepatic elimination kinetics where we can handle the parameter estimation in an arithmetical way.[5] Therefore we introduce here a different approach from the conventional methods such as those to solve mass balance differential equations concretely or to utilize the linear algebraic tools, and explain how we can carry out the parameter estimation in our combinatorial model scheme. This method allows strightforward parameter estimation based on the model structure using the idea of calculating probability along the routes from the inlet to the outlet of the system.

Theory

The Concept of Conformation

In order to handle the complicated compartmental model system in a consistent manner,

it is convenient to introduce the concept which satisfies the following conditions. (1) It is a multi-compartment system. (2) It has a single inlet (we allow the situation where substances are divided into multiple compartments through ramifications of the blood flow from the single inlet). (3) It has a single route of outlet. A typical example which satisfies these conditions is a conventional perfusion system where the drug flows into through a single inlet and flows out through a single outlet. We define the system which satisfies the above three conditions as a "combinatorial conformation" or simply a "conformation" and we adopt the notation "C" or "C_i". A single multi-compartmental system can contain multiple conformations. The most simple example of the conformation is a single compartment system which has one inlet and one outlet as well as one secretion route. Sometimes one conformation contains another conformation. If C_1 is contained in C_2 we say C_1 is a "subconformation" of C_2 and describe it as $C_1 < C_2$.

The set of conformations satisfies the "order relation",[6] that is to say, (1) if $C_1 < C_2$ and $C_2 < C_3$ then $C_1 < C_3$, and (2) if $C_1 < C_2$ and $C_1 > C_2$ then $C_1 = C_2$. If conformation C is composed of subconformations C_1, C_2, $\cdots$, and C_n, we denote it as

$$C=[C_1, C_2, \cdots, C_n] \tag{1}$$

and we call each C_i a "component" of C.

Two conformations are combined to make a new conformation by connecting the inlets and/or the outlets. If C_1 and C_2 are combined in series, that is, if the outlet of C_1 is the inlet of C_2, we call the resulting conformation the "product" of C_1 and C_2,[5] and we denote it as

$$C=C_1 * C_2 \tag{2}$$

If C_1 and C_2 are combined in parallel we call the resulting conformation the "sum" of C_1 and C_2, and denote it as

$$C=C_1+C_2 \tag{3}$$

Most systems can be generated by finite repetitions of sums and products, but there is a system which can not be generated by the combination of compartments in series and in parallel as will be shown later. Notice that even in such a case the resulting system is a conformation. If a conformation C is generated by the repeated products of subconformations C_1, C_2, $\cdots$, and C_n, that is, if

$$C=C_1 * C_2 * \cdots * C_n \tag{4}$$

holds, then we call this expression the "product decomposition" of conformation C.

Availability, Extraction Ratio, and Clearance

In the following section we restrict our concern to the conformations. Nevertheless, almost all the pharmacokinetic models are included. Note also that the generalized linear mammilary system[7,8] is included. We begin with the fundamental definitions of the pharmacokinetic parameters.[5] For a conformation C, the amount of drug recovered (or the probability that we find the drug) at the outlet after unit dose of drug is administered at the inlet of the system is defined as the "availability" of C, denoted as "$F(C)$". We call "$1-F(C)$" the "extraction ratio", denoted as "$E(C)$". In most pharmacokinetic situations there is a flow Q from the inlet to the outlet, and we call $Q \times E(C)$ the "tissue clearance" of C, denoted as $CL(C)$.

We will now explain the method based on the combinatorial approach. To begin with, as the simplest situation, we handle the two-compartment systems which are the "product" or the "sum" of two compartments. In case of the product, the drug is divided into two directions as it goes through each compartment. The probability of such subdivision is q_1 and

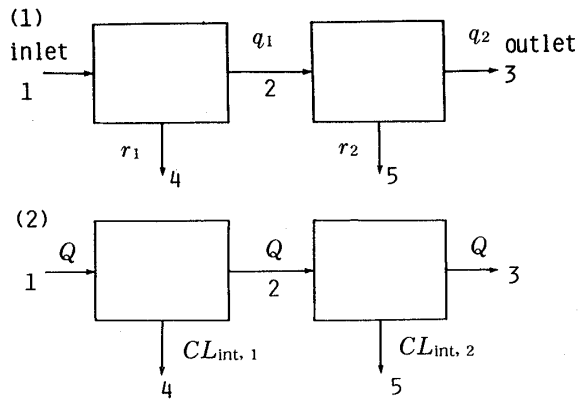

Fig. 1. Model Systems

(1) The "product" (combination in series) of two compartments with a single inlet and a single outlet. "1, 2, 3, 4, and 5" stand for the reference spots for defining the routes of drug transfer. r_1 and r_2 are the transfer coefficients along the elimination routes and q_1 and q_2 are those along the outflow routes, respectively. (2) The same model as in (1). Q; blood flow, $CL_{int,1}$ and $CL_{int,2}$; the intrinsic clearance for each compartment.

r_1 ($q_1+r_1=1$) in the left compartment of Fig. 1(1). In this case, q_1 and r_1 are the transfer coefficients of the compartment system. Here we denote the probability of passing through the route from i to j as $P_{i,j}$. In the situation of Fig. 1(1), the transitional probability of the drug from the inlet to the outlet is divided by the "law of product" as in the theory of probability into the sum of the product of probabilities along the two routes 1-2 and 2-3. Thus

$$P_{1,3}=P_{1,2}\times P_{2,3} \tag{5}$$

If this compartment is the conventional "well-stirred" compartment[9] such as in Fig. 1(2), where Q is the blood flow, and $CL_{int,1}$ and $CL_{int,2}$ are the respective intrinsic clearances, $P_{1,2}$ corresponds to $q_1=Q/(Q+CL_{int,1})$, and $P_{2,3}$ corresponds to $Q/(Q+CL_{int,2})$, so

$$P_{1,3}=Q/(Q+CL_{int,1})\times Q/(Q+CL_{int,2}) \tag{6}$$

and this is equal to the availability of the conformation which is the product of two compartments. By similar consideration we get the availability F for the product of n compartments,

$$F=\prod_{i=1}^{n} Q/(Q+CL_{int,i}) \tag{7}$$

The clearance of the product conformation is obtained from two different viewpoints. One is the indirect method utilizing the availability,

$$\begin{aligned} CL&=Q(1-F)\\ &=Q[1-Q/(Q+CL_{int,1})\times Q/(Q+CL_{int,2})] \end{aligned} \tag{8}$$

Another approach is the direct method to evaluate the respective routes of drug elimination one by one. For example, in Fig. 1(1), there are two routes of elimination. One is the route 1-4 and

$$P_{1,4}=CL_{int,1}/(Q+CL_{int,1}) \tag{9}$$

As for the route 1-5, this is subdivided by the "law of product" into two routes 1-2 and 2-5, and then

$$\begin{aligned} P_{1,5}&=P_{1,2}\times P_{2,5}\\ &=Q/(Q+CL_{int,1})\times CL_{int,2}/(Q+CL_{int,2}) \end{aligned} \tag{10}$$

Therefore considering that the events through the two routes are "exclusive phenomena" with respect to each other, we get the extraction ratio E as follows:

$$\begin{aligned} E&=P_{1,4}+P_{1,5}\\ &=CL_{int,1}/(Q+CL_{int,1})+Q/(Q+CL_{int,1})\times CL_{int,2}/(Q+CL_{int,2}) \end{aligned} \tag{11}$$

The clearance is easily obtained by the definition $CL=Q\times E$

The above two expressions for the extraction ratio seem to be different at a glance, but should be equal. This is obvious from the relation:

$$r_1+q_1r_2=(1-q_1)+q_1(1-q_2)$$
$$=1-(1-r_1)(1-r_2) \tag{12}$$

Similarly in the case of the product conformation of n compartments as in Fig. 2(1), the extraction ratio E is on the one hand

$$E=r_1+q_1r_2+q_1q_2r_3+\cdots+q_1q_2\cdots q_{n-1}r_n \tag{13}$$

and on the other hand, as the availability is $q_1q_2\cdots q_{n-1}q_n$,

$$E=1-q_1q_2\cdots q_n \tag{14}$$

Thus, the clearance of product conformation of n compartments is

$$CL=Q[1-Q/(Q+CL_{\text{int},1})\times Q/(Q+CL_{\text{int},2})\times\cdots\times Q/(Q+CL_{\text{int},n})] \tag{15}$$

Now we introduce a simpler expression. Let

$$R=CL_{\text{int}}/Q \tag{16}$$

This is the so-called "efficiency number" in chemical engineering.[10,11] Now in general the probability of the division through the compartment is rewritten as follows.

$$q_1=Q/(Q+CL_{\text{int}})=1/(1+CL_{\text{int}}/Q)=1/(1+R) \tag{17}$$

$$r_1=CL_{\text{int}}/(Q+CL_{\text{int}})=R/(1+R) \tag{18}$$

Then in Fig. 1(2)

$$F=1/[(1+R_1)\times(1+R_2)] \tag{19}$$

$$E=1-1/[(1+R_1)\times(1+R_2)] \tag{20}$$

$$CL=Q[1-1/(1+R_1)/(1+R_2)] \tag{21}$$

Generally in Fig. 2(1)

$$F=\prod_{i=1}^{n}1/(1+R_i) \tag{22}$$

$$E=1-\prod_{i=1}^{n}1/(1+R_i) \tag{23}$$

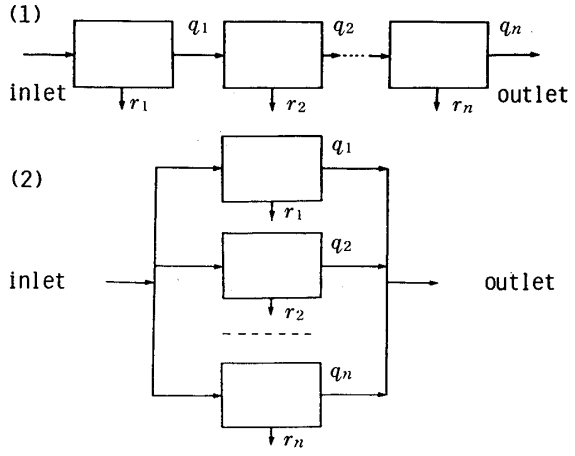

Fig. 2. Model Systems

(1) The "product" (combination in series) of n compartments, in which $r_1, r_2, \cdots$, and r_n are the transfer coefficients along the elimination routes and $q_1, q_2, \cdots$, and q_n are those along the outflow routes, respectively. (2) The "sum" (combination in parallel) of n compartments, in which $r_1, r_2, \cdots, r_n, \cdots$, and q_n are the same as in (1).

$$CL=Q\left[1-\prod_{i=1}^{n} 1/(1+R_i)\right] \tag{24}$$

Now we consider the conformation which consists of the sum of the compartments as in Fig. 2(2). This conformation is described as $C=C_1+C_2+\cdots+C_n$. As the drug is at first subdivided in proportion to the ratio of blood flows $q_1:q_2:\cdots:q_n$ and then it goes through the respective compartment, considering the n routes from the inlet to the outlet, we obtain the availability;

$$\begin{aligned} F(C)&=\sum_{i=1}^{n}(\text{the probability through the route of } i\text{-th line})\\ &=\sum_{i=1}^{n} q_i\times F(C_i)\\ &=\sum_{i=1}^{n} q_i/(1+R_i) \end{aligned} \tag{25}$$

Extraction ratio is the total sum of the probability of the eliminated drug at each compartment C_i;

$$\begin{aligned} E(C)&=\sum_{i=1}^{n} p_i\times E(C_i)\\ &=\sum_{i=1}^{n} p_i\times R_i/(1+R_i) \end{aligned} \tag{26}$$

Where p_i is the ratio of the total blood flow Q and the local blood flow Q_i flowing through C_i, that is $p_i=Q_i/Q$. Therefore

$$CL(C)=Q\left[1-\sum_{i=1}^{n} p_i\times R_i/(1+R_i)\right] \tag{27}$$

The sum of $F(C)$ and $E(C)$ is naturally equal to 1. The clearance is rewritten by $p_iQ=Q_i$ as

$$CL(C)=Q-\sum_{i=1}^{n} Q_i\times CL_{\text{int},i}/(Q+CL_{\text{int},i}) \tag{28}$$

The above discussion about the product conformation and the sum conformation can be generalized to all situations in the following manner. For the availability, we pick up all the routes from the inlet to the outlet which are "exclusive" to each other, then add up the availability along the respective routes. For example in the situation in Fig. 3(1) there are three routes 1-2-U_4, 1-2-U_5, and 1-4. We add up the results along each route after multiplying

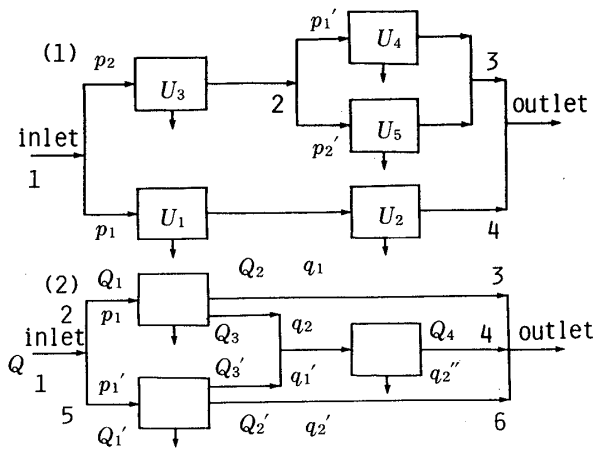

Fig. 3. Model Systems

(1) An example of "conformation" which is composed of both the product and the sum of "conformations." U_1, U_2, $\cdots$, and U_n are the compartments. $p_1:p_2$ $(p_1+p_2=1)$ and $p_{1'}:p_{2'}$ $(p_{1'}+p_{2'}=1)$; the blood flow fraction at each ramified point. 1, 2, 3 and 4; the reference spots. (2) An example of conformation which cannot be obtained by the repetition of the sum and the product. 1, 2, 3, $\cdots$, and 6; the reference spots. Q, Q_1, $Q_{1'}$, Q_2, $Q_{2'}$, Q_3, $Q_{3'}$, Q_4, $Q_{4'}$; the blood flow. p_1, $p_{1'}$, q_1, $q_{1'}$, q_2, $q_{2'}$, and $q_{2''}$; transfer coefficients along the routes.

by the blood flow fraction p_i;

$$F=p_1F(U_1)F(U_2)+p_2F(U_3)p_{1'}F(U_4)+p_2F(U_3)p_{2'}F(U_5) \tag{29}$$

The above discussion suggests that in general if $C=C_1{*}C_2$, *i.e.*, C is the combined conformation in series, the product of availability of each component C_i gives the availability of C. This is because the probability from the inlet of C_1 (spot 1) to the outlet of C_2 (spot 3) through the outlet of C_1 (*i.e.*, the inlet of C_2) (spot 2) is the product of $P_{1,2}$ and $P_{2,3}$ by the "law of product" irrespective of the complexity of C_1 or C_2. Therefore for any conformation C_1 and C_2.

$$F(C_1{*}C_2)=F(C_1)\times F(C_2) \tag{30}$$

If C_1 and C_2 are combined in parallel the availability of the resultant conformation becomes the sum of each availability with the weight of blood flow fraction. This is because there are two "exclusive" routes from the inlet to the outlet and the sum of the probability along each route is the total availability due to the "law of sum". Therefore for any conformations C_1 and C_2 if the ratio of blood flow fraction is $p_1:p_2$,

$$F(C_1+C_2)=p_1F(C_1)+p_2F(C_2) \tag{31}$$

holds. The extraction ratio and the clearance can be easily derived from the value of availability.

In a general conformation we can use the above two equations repeatedly to calculate the parameters. Notice also that there is a conformation which cannot be constructed only from combinations in series and in parallel, as we have pointed out already. Even then, we can easily calculate the parameters by using the combinatorial approach to add up the probabilities along the "exclusive" routes from the inlet to the outlet. For example in Fig. 3(2) there are four routes 1-2-3, 1-2-4, 1-5-4, and 1-5-6. Then write down the probability along each route and add them up;

$$F=p_1q_1+p_1q_2q_{2''}+p_1q_{1'}q_{2''}+p_{1'}q_{2'} \tag{32}$$

Rewrite this under the condition $Q=Q_1+Q_{1'}$, $Q_1=Q_2+Q_3$, $Q_{1'}=Q_{2'}+Q_{3'}$, then

$$\begin{aligned}F=&Q_1/Q\times[1/(1+R_1)]+Q_1/Q\times[1/(1+R_1)]\times Q_3/Q_1\times[1/(1+R_2)]\\&+Q_{1'}/Q\times[1/(1+R_{1'})]\times Q_{3'}/Q_{1'}\times[1/(1+R_2)]\\&+Q_{1'}/Q\times[1/(1+R_{2'})]\times Q_{2'}/Q_{1'}\end{aligned} \tag{33}$$

is easily obtained.

The System with Loops and the "Loop Correction"

Here we handle the case with some loops along the routes from the inlet to the outlet. Even in this case we can essentially apply the same rules. In Fig. 4(1) there is the route from the spot 1 to the spot 4 through the spot 3, and this route can be "exclusively" subdivided into the routes which go around the loop n times. If we denote the probability along the routes which go around n times as $P_{1,4}(n)$, as the decrease rate of drug corresponding to one cycle along the loop is qs, the availability of the conformation in Fig. 4(1) is;

$$\begin{aligned}F(C)&=\sum_{n=1}^{\infty}P_{1,4}(n)=p+(qs)p+(qs)^2p+\cdots+(qs)^np+\cdots\\&=p/(1-qs)\end{aligned} \tag{34}$$

i.e. if a loop is contained along the route we should correct the value by dividing by the difference between 1 and the probability of decrease corresponding to the one cycle along the

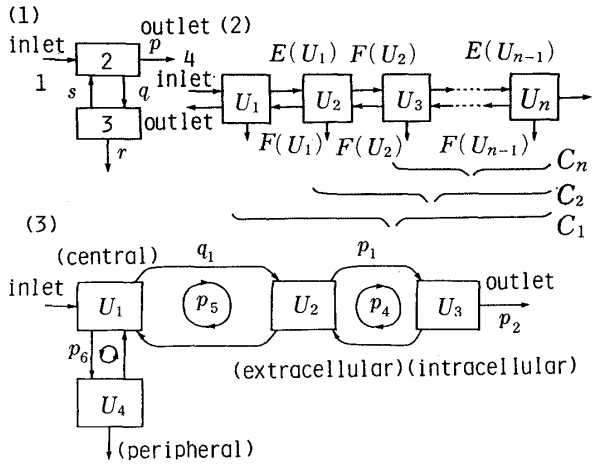

Fig. 4. Model Systems

(1) Two-compartment with a loop. p, q, r, and s; transfer coefficients along respective route. (2) An n-compartment model with multiple loops. $E(U_i)$ and $F(U_i)$; the extraction ratio and the availability for the corresponding compartment U_i. We consider that C_i's in the figure form a sequence of "conformations." (3) A 4-compartment model with three loops. p_4, p_5, and p_6; probabilities for decrease along each loop. p_1, p_2 and q_1; transfer coefficients along each route. U_1, the central compartment; U_2, the extracellular space of the liver; U_3, the intracellular space of the liver; U_4, the peripheral space.

loop. We call this procedure the "loop correction".

We introduce the "principle of replacement" and the "principle of substitution" in a more complicated case. The former is a method to look upon a subconformation in a complicated system as just like a single compartment, and the latter is a method to substitute the expression for a complicated conformation into the expression for a single compartment. Thus these two methods are complementary to each other. For example, in Fig. 4-2, we consider the sequence of conformations $C_1 > C_2 > \cdots > C_n$ as illustrated in the figure. First we look upon C_1 as the single compartment, denoting the availability by $F(C_1)$. Then we look upon C_1 as the combination of U_1 and C_2 by the principle of replacement. As U_1 undergoes the loop correction for the loop between the U_1 and C_2,

$$F(C_1)=F(U_1)/(1-P_1) \tag{35}$$

where P_1 is the drug decrease rate corresponding to the one cycle along the loop. The probability of the drug transfer from U_1 to C_2 is $E(U_1)$ and that from C_2 to U_1 is $F(C_2)$, therefore

$$P_1=E(U_1)F(C_2) \tag{36}$$

and

$$F(C_1)=F(U_1)/[1-E(U_1)F(C_2)] \tag{37}$$

Similarly, by looking upon C_k as the combination of U_k and C_{k+1} by the principle of replacement,

$$F(C_k)=F(U_k)/[1-E(U_k)F(C_{k+1})] \tag{38}$$

By substituting these equations successively (by the principle of substitution), we obtain;

$$F(C_1)=F(U_1)/(1-E(U_1)/(1-E(U_2)/\cdots/(1-E(U_{n-1})/F(U_n))\cdots) \tag{39}$$

Such calculation is convenient when a complicated recirculation system or successive diffusion process exists. For example we consider the situation in Fig. 4(3) where drug is transferred from the central compartment to the extracellular one from which the drug is taken into the intracellular compartment. Let p_4, p_5 and p_6 stand for the probabilities of decreasing ratio along the respective loops in Fig. 4(3). The probability for straightforward outflow is $P=q_1p_1p_2$. By the "loop correction" for the peripheral loop between U_1 and U_2 we get $P'=P/(1-p_6)$. By the "loop correction" for the recirculation between U_1 and U_2 we get $P''=P'/(1-p_5/(1-p_6))$ considering again the "loop correction" for the connected loop between U_1 and U_4. By the "loop correction" for the loop between U_2 and U_3 we get

$P=P''/(1-p_4/(1-p_5/(1-p_6)))$ considering again the "successive loop correction" for the successively connected two loops. Thus we reach the final availability;

$$F=P/(1-p_6)/(1-p_5/(1-p_6))/(1-p_4/(1-p_5/(1-p_6)))$$
$$=P/(1-p_4-p_5-p_6-p_4p_6) \tag{40}$$

Generalization to the Formula for Transfer Functions

The relations between the availabilities of conformations can be generalized to obtain the relations between the transfer functions for the conformations.

For the product C of the two compartment model U_1 and U_2, it is well known that

$$Tr(C)=Tr(U_1)\times Tr(U_2) \tag{41}$$

holds. For the sum C of two compartment models

$$Tr(C)=q_1Tr(U_1)+q_2Tr(U_2) \tag{42}$$

holds. Here $Tr(C)$ stands for the Laplace transform which is defined by the relation

$$Tr(C)=Tr(v(t))/Tr(u(t)) \tag{43}$$

for the Laplace transform of the input function $u(t)$ and that of the output function $v(t)$ for the conformation C. If we let s equal 0, then the relations of availabilities can be derived,[12] because in the Eq. 43

$$\lim_{s\to 0} Tr(u(t))=AUC(u(t)) \tag{44}$$

$$\lim_{s\to 0} Tr(v(t))=AUC(v(t)) \tag{45}$$

and the ratio $AUC(v(t))/AUC(u(t))$ is equal to the ratio $v(t)/u(t)$ at the steady state, and this ratio is the availability of the conformation.

For the Laplace transformations we can also apply the combinatorial approach, because the "law of product" and the "law of sum" are also valid for the "Laplace operator". Thus, the "principle of substitution" is also applicable. For example consider the situation in Fig. 5(1) where there are multiple loops. Let "$T_{io}(U)$" stand for the transfer function from the inlet of compartment U to the outlet of U, and let "$T_{ie}(U)$" stand for the transfer function from the inlet to the elimination site. If L_k stands for the k-th loop in Fig. 5(1), we call $T_{ie}(U_k)T_{io}(U_{k+1})$ the "transfer function along the loop" L_k, denoting "T_k" for the respective k. We first write down the transfer function $T_{io}(U_1)$ along the route from the inlet of U_1 to the outlet of U_1 (the "principle of replacement"). Then we apply the procedure of "loop correction" by $1-T_1$, and T_1 is corrected by $1-T_2$, *etc.* (successive application of the law of

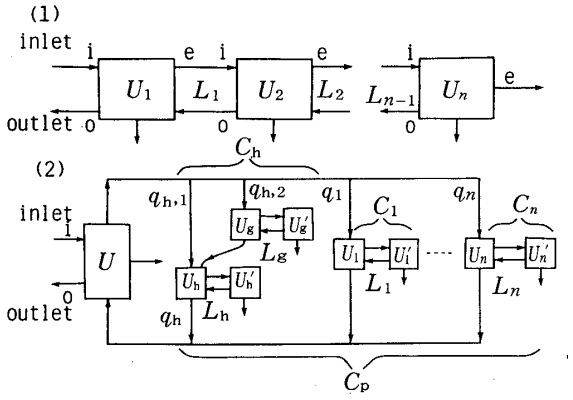

Fig. 5. Model Systems

(1) Similar model to that in Fig. 4(2). (1) "i", "o", and "e"; the inlet, the outlet, and the elimination site, respectively. L_i; the i-th loop. (2) Complicated pharacokinetic model with conformations which are combined in parallel. U, U_1, $\cdots$, and U_h, *etc.*: compartments. C_p, C_h, C_1, C_2, $\cdots$, and C_n: conformations.

substitution). Thus the final result is

$$T(U_1)/(1-T_2/(1-T_3/\cdots/(1-T_{n-1}))\cdots) \tag{46}$$

where $T_k=T_{ie}(U_k)T_{ie}(U_{k+1})$.

The above two principles are also used in cases with parallel loops. First we replace the peripheral conformation by the single compartment U_p (the "principle of replacement"). Then carry out the loop correction by $1-T$ where T is the transfer function along the loop for the single peripheral compartment and is denoted as $T=T_{ie}(U)T_{io}(U_p)$ if the central compartment is denoted as U, then substitute T by $T_{io}=q_1T_{io}(U_1)+q_2T_{io}(U_2)+\cdots+q_nT_{io}(U_n)$ where $T_{io}(U_k)$ is the transfer function from the inlet of compartment U_k to the outlet of U_k which forms the parallel peripheral loops with blood flow fraction q_k.

In this way by applying the "principle of substitution" and the "principle of replacement" we can easily write down the transfer function for the complicated compartmental model system in a straightforward manner. The situation in Fig. 5(2) is easily expressed as

$$T=T_{io}(U)/[1-T_{ie}(U)T_{io}(C_p)] \tag{47}$$

where C_p stands for the conformation which forms the peripheral system, and

$$T_{io}(C_p)=q_hT_{io}(C_h)+q_1T_{io}(C_1)+\cdots+q_nT_{io}(C_n) \tag{48}$$

where $T_{io}(C_h)$, $T_{io}(C_1)$, $\cdots$ are the transfer functions from the inlet to the outlet of the conformation with the blood flow fractions q_h, q_1, $\cdots$, q_n as in Fig. 5(2), and

$$T_{io}(C_h)=[q_{h,1}-q_{h,2}T_{io}(U_g)/[1-T_{ie}(U_g)T_{io}(U_{g'})]] \times T_{io}(U_h)/[1-T_{ie}(U_h)T_{io}(U_{h'})] \tag{49}$$

$$T_{io}(C_1)=T_{io}(U_1)/(1-T_{ie}(U_1)T_{io}(U_{1'}) \tag{50}$$

In each process we apply the principle of replacement repeatedly. By substituting the latter expressions into the former we obtain the final result. And, of course, by letting $s=0$, we immediately obtain the expression for the availability. We can replace C_h or C_i of this system by more complicated subconformations as in Fig. 6(1) and/or Fig. 6(2). In Fig. 6(1), we consider the situation where enterohepatic circulation exists. Here U_b, $U_{b'}$ and $U_{b''}$ stand for the sequence of bile tree compartments, and the drug passes into the gastroenteric compartment $U_{g'}$. The transfer function for C_h is;

$$T(C_h)=q_{h,1}T(C_{h,1})+q_{h,2}T(C_{h,2}) \quad \text{[the law of sum]} \tag{51}$$

where $C_{h,1}$ is the conformation along the hepatic artery and $C_{h,2}$ is the conformation along U_g and U_h. Notice that both $C_{h,1}$ and $C_{h,2}$ have three loops of different types. For $C_{h,1}$;

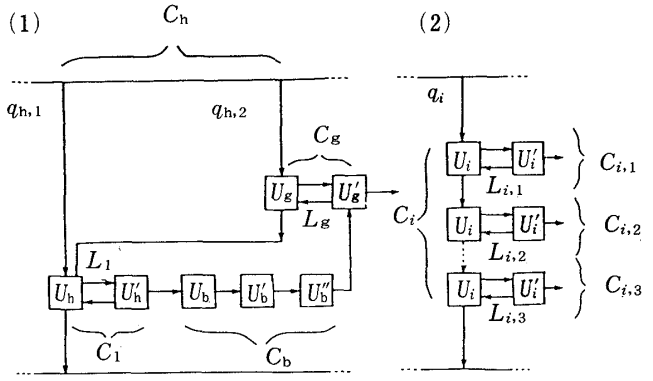

Fig. 6. Model System

(1) The substitution for the conformation C_h in Fig. 5(1). There are three loops in this conformation and the largest loop forms the enterohepatic circulation. (2) The substitution for the conformation C_i in Fig. 5(2). This conformation is subdivided into three subconformations combined in series.

$$T(C_{h,1}) = T(C_1)/[1 - T_{ie}(C_1) \times T(C_b) \times T(C_g)]$$

[the loop correction, and the principle of replacement]

$$= T_{io}(U_h)/[1 - T_{ie}(U_h)T_{io}(U_{h'})]/[1 - T_{io}(U_h)/[1 - T_{ie}(U_h)T_{io}(U_{h'})]$$
$$\times T(U_b)T(U_{b'})T(U_{b''})T_{io}(U_{g'}) \times T_{io}(U_g)/[1 - T_{ie}(U_g)T_{io}(U_{g'})]] \quad (52)$$

[the law of product and the principle of substitution, *etc.*]

For $C_{h,2}$;

$$T(C_{h,2}) = T(C_g)T(C_1)/[1 - T_{ie}(C_1) \times T(C_b) \times T(C_g)]$$

[the law of product, the loop correction, and the principle of replacement]

$$= T_{io}(U_g)/[1 - T_{ie}(U_g)T_{io}(U_{g'})] \times T_{io}(U_h)/[1 - T_{ie}(U_h)T_{io}(U_{h'})]/[1 - T_{io}(U_h)$$
$$/[1 - T_{ie}(U_h)T_{io}(U_{h'})] \times T(U_b)T(U_{b'})T(U_{b''})$$
$$\times T_{ie}(U_{g'})T_{io}(U_g)/[1 - T_{ie}(U_{g'})T_{ie}(U_g)]] \quad (53)$$

[the law of product, the loop correction, and the principle of substitution]

In a similar way if the conformation C_i in Fig. 5(2) is replaced by the conformation in Fig. 6(2), the transfer function to be substituted is;

$$q_i T(C_i) = q_i T(C_{i,1} {}^*C_{i,2} {}^*C_{i,3}) \quad \text{[the principle of replacement]}$$
$$= q_i T(C_{i,1})T(C_{i,2})T(C_{i,3}) \quad \text{[the law of product]}$$
$$= q_i T_{io}(U_i)/[1 - T(L_{i,1})]T_{io}(U_i)/[1 - T(L_{2,i})]T_{io}(U_i)/[1 - T(L_{3,i})]$$
[the loop correction]
$$= q_i[T_{io}(U_i)/[1 - T_{ie}(U_i)T_{ie}(U_{i'})]]^3 \quad \text{[the law of substitution]} \quad (54)$$

In this way the combinatorial approach is generalized as an arithmetical method to obtain the transfer function by (1) finding the subconformation structure along the "exclusive" routes in the complicated compartmental models, (2) using the "law of sum," and/or the "law of product", (3) considering the subconformation as a single compartment (the "principle of replacement"), and (4) substituting the transfer function for the subconformation or conformation loop (the "principle of substitution").

Concentration Cascade at the Steady State

Among three-compartment systems as in Fig. 7(1), the mass balance of the drug should hold in the steady state. The drug quantity entering the compartment U_k is $Q \times c_{k-1}$, and the

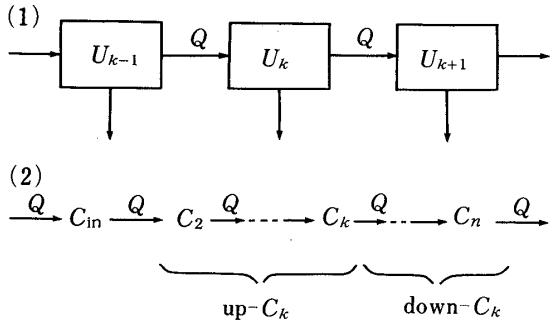

Fig. 7. Model System

(1) The sequence of three compartments. (2) The concepts of "upstream" up-C_k and the "downstream" down-C_k of the compartment C_k. In this sequence of compartments the concentration gradient between each compartment forms a kind of "cascade" on a log scale.

drug quantity going out is $Q \times c_k$, where c_k stands for the concentration of U_k. The ratio of these two values is by definition the availability F_k for the compartment U_k;

$$Q \times c_k/(Q \times c_{k-1}) = F_k . \tag{55}$$

Therefore

$$c_k = F_k \times c_{k-1} \tag{56}$$

Now consider the conformation sequence $C = C_{in} * C_2 * \cdots * C_{n-1} * C_{out}$, where each C_i stands for a compartment. If we follow the chain of conformations, c_{in} and c_{out} are connected by these concentration chains;

$$Q \times c_{in} \times F(C_2) = Q \times c_2 \tag{57}$$

$$Q \times c_2 \times F(C_3) = Q \times c_3 \tag{58}$$

$$\cdots, Q \times c_{n-1} \times F(C_{out}) = Q \times c_{out} \tag{59}$$

Thus

$$c_{out} = c_{in} \times F(C_2) \times F(C_3) \times \cdots \times F(C_{n-1}) \times F(C_{out}) \tag{60}$$

Let us call the conformation $C_2 * C_3 * \cdots * C_k$ which forms the route from C_2 to C_k the "upstream" of C_k, denoted as "up-C_k" (Fig. 7(2)). The reason why we use the term "upstream is to introduce here the local point of view. As the ratio of the drug quantity which enters from C_{in} and that which leaves C_k is the availability of up-C_k by definition,

$$Q \times c_{in} \times F(\text{up-}C_k) = Q \times c_k \tag{61}$$

that is,

$$c_{in} \times F(\text{up-}C_k) = c_k \tag{62}$$

On the other hand if we call the subconformation $C_{k+1} * \cdots * C_{out}$ the "downstream" of C_k, denoted as "down-C_k" (Fig. 7(2)), as the ratio of the drug quantity entering from C_k and that leaving C_{out} is the availability of down-C_k, we have

$$Q \times c_k \times F(\text{down-}C_k) = Q \times c_{out} \tag{63}$$

therefore we get

$$c_k \times F(\text{down-}C_k) = c_{out} \tag{64}$$

If we consider the logarithmic value of the concentration, these relations can be treated in an additive way, and the concentration difference between the two compartments satisfies additivity just as in a "cascade", that is to say, we define the "height" of the respective compartment U by $\log[F(\text{down-}U)]$. This consideration supports the validity of taking the "mean value" of the concentrations as the mean value of the logarithmic values of concentration.

Thus, in a conformation which is decomposed into the product $C = C_1 * C_2 * \cdots * C_n$, if each $F(C_k)$ is equal to each other (we denote this simply as F), we obtain

$$c_k = c_1 \times F^{k-1} \tag{65}$$

This means that the decrease of concentration behaves like a geometric progression. In semi-log scale the concentrations are plotted on a straight line, and thus we know that an exponentially decreasing concentration gradient holds along the decomposed compartmental system.

Conclusion

The concept of "conformation" and its availability, extraction ratio, and clearance are very convenient to derive the parameter value intuitively in a complicated compartment model system. The "law of sum", the "law of product", the "principle of replacement" and the "principle of substitution" are useful tools to write down the parameter expression in a straightforward manner. The concept of "upstream" or "downstream" of the conformation is useful to describe the concentration relations at the steady state in the situation of a "concentration cascade". If the compartment has a product decomposition with homogeneous compartments, the concentration gradient behaves in an exponential manner.

In our combinatorial approach the estimation of parameters can be performed simply by following certain procedures of looking at the arrangement of compartments without relying on the method of linear algebra. Thus, it is possible to understand how the structure or arrangement of the compartments affects the parameter value in a concrete and intuitive manner. Our combinatorial approach should be useful to investigate the arithmetical relation between the model structure and the metabolic parameters.

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