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EXTENSION OF COMPARTMENTAL PARAMETERS TO BLOCKS OF COMPARTMENTS WITH APPLICATION TO LIPOPROTEIN KINETICS

by

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ABSTRACT

Suppose that the compartments of a compartmental model are separated into blocks (sets of compartments). In general, the blocks can not be regarded as compartments but it may be possible to construct a "condensation model," the compartments of which correspond to the blocks, in such a fashion so as to retain certain salient properties of the blocks. Condensation is a way of formally summarizing a large model by presenting a smaller one in order to emphasize certain characteristics of the larger model. Suppose that the parameters to be retained are the mean residence times through the blocks. The paper deals with the construction of the condensation model, the properties of the condensation model, and possible applications of condensation to data analysis, particularly in regard to lipoprotein kinetics.

Introduction In theory, a compartmental system is a system which is made up of a finite number of macroscopic subsystems, called compartments or pools, each of which is homogeneous and well-mixed, and the compartments interact by exchanging material [1]. However, in practice it is often times difficult to determine the compartments of the system. As more data on a complex system become available, through improved experimental techniques, longer observation intervals, shorter spacing between samples, sampling more compartments, improved numerical methods, and etc., it frequently becomes apparant that one (or more) subsystem, once regarded as a compartment, is actually a block (subset) of compartments.

Now a compartment is described by parameters, (e.g., fractional transfer rates, residence times) which measure the kinetic response of the compartment to an input. These parameters may be utilized in a variety of ways, for instance to classify patient populations or drugs. When it becomes apparant that a subsystem is a block, instead of a compartment, then the block could be described through the parameters associated with compartments within the block. However such a description could be cumbersome, particularly if the block is large. Moreover, none of these compartmental measures describe the block as a single unit. Furthermore, the role of the old descriptors, i.e. those used to describe the block when it was thought to be a compartment, would be lossed.

One way of solving this problem is to define parameters on blocks as counterparts of compartmental parameters. However, such "block parameters" should not be chosen arbitrarily; the definitions of block parameters should be consistent with kinetic measures on compartments. To be more precise, a block parameter should satisfy the following criteria. First, the definition of a block parameter should extend the definition of a compartmental measure. For instance, suppose that the fractional transfer rate between two blocks is defined by a certain formula, say $A_{ij} = f_{ij}(a_{11}, a_{12}, \ldots, a_{nn})$, where the a_{ij} are the compartmental fractional transfer rates. In the event that the two blocks in question each consist of a single compartment, then A_{ij} should reduce to a_{ij}. Second, relations between compartmental parameters should be extended. Suppose that $g(c_1, c_2, \ldots, c_k) = 0$ is a relation between compartmental parameters c_i and C_i is the extension of c_i to blocks, $1 \le i \le k$. Then the corresponding block parameter relation, $g(C_1, C_2, \ldots, C_k) = 0$, should be satisfied.

The theory of compartmental parameters and the relations between these parameters is reviewed in Section 2. The main purpose of this paper is to extend this theory to block parameters in the manner described above. The development is particularly germane to the theory of lipoprotein kinetics [2], where the separation of a compartment into smaller units occurs with regularity. Examples are chosen from this field.

The extension of compartmental parameters to blocks carries other advantages. One of these concerns the problem of determining steady-state masses from steady-state inputs. The use of block parameters may greatly simplify the equations relating block masses to steady-state inputs. Block parameters are also useful for summarizing large models or for comparing competing models. These applications are illustrated in the examples.

2. Compartmental parameters A linear time-invariant n-compartmental model is defined by its fractional rate parameters a_{ij} where a_{ij} $(i \neq j)$ denotes the fractional transfer rate from compartment j to compartment i, and a_{0j} denotes the fractional excretion rate. The total fractional outflow rate is

$$a_{jj} = -\sum_{\substack{k=0 \\ k\neq j}}^{n} a_{kj}, \quad 1 \leq j \leq n \tag{2.1}$$

(the sign is negative because a_{jj} represents outflow). Its magnitude $|a_{jj}|$ is the turnover rate in compartment j. The compartmental matrix, defined by

$$\aleph = \{a_{ij}\}_{i,j=1}^{n},$$

is characterized by two properties. Its off-diagonal elements, i.e. the fractional transfer rates, are nonnegative and its column sums, i.e. the negatives of the fractional excretion rates, are nonpositive. It is to be assumed throughout that $\aleph$ is invertible, which is equivalent to the assumption that the system is without traps. (See [3] for the extension of this result to nonlinear systems.)

It has been noted by several authors ([4]-[18]) that a linear time-invariant compartmental system admits a stochastic interpretation. In fact, the compartmental matrix may be regarded as the infinitesimal generator of a Markovian process. With this interpretation,

$$T = -\aleph^{-1} \tag{2.2}$$

is the residence time matrix. It entries, t_{ij}, give the (mean) residence time that a particle spends in compartment i having initiated from compartment j ([2],[10],[11],[16],[17],[18]).

Several other parameters, which are related to these residence times, are given below.

The probability that a particle will enter compartment i, or the environment (i=0), upon its exit from compartment j is

$$q_{ij} = a_{ij}/|a_{jj}|,\ 0 \leq i \leq n,\ 1 \leq j \leq n,\ i \neq j. \qquad (2.3)$$

A particle may travel through several compartments upon its exit from compartment j before it enters compartment i. The probability that a particle enters compartment i after exiting from compartment j is denoted by r_{ij}. If compartment i is adjacent to compartment j, i.e. if $a_{ij} \neq 0$, then $r_{ij} = q_{ij}$; otherwise r_{ij} is obtained as a product of q_{km}'s along paths from compartment j to compartment i (as described in [16]) or the parameter may be obtained from the formula (see[16])

$$r_{ij} = t_{ij}/t_{ii},\ 1 \leq i,\ j \leq n. \qquad (2.4)$$

The matrix $\Omega = \{r_{ij}\}$ is the reachability matrix and formula (2.5) may be expressed in the matrix form

$$T = \text{diag}\ (T)\Omega, \qquad (2.5)$$

where diag (T) is the diagonal matrix formed from the diagonal entries of T.

A particle exiting compartment i may eventually return to this compartment by recycling through other compartments; the probability of returning to compartment i is [15,16]

$$p_j = \sum_{\substack{k=1 \\ k \neq j}}^{n} r_{jk}q_{kj},\ 1 \leq j \leq n. \qquad (2.6)$$

The (mean) first exit time (or turnover time) in compartment i is the residence time in the compartment without recycling and it is given by [15.16]

$$\tau_j = 1/|a_{jj}|,\ 1 \leq j \leq n. \qquad (2.7)$$

The total mean residence time that a particle spends in compartment j, having initiated in that compartment, can be found by summing the series [15], $\tau_j + e_j\tau_j + e_j\tau_j^2 + \ldots$, which converges to $\tau_j/(1 - p_j)$, but this time is t_{jj}.

Thus

$$t_{jj} = \tau_j / (1-p_j), \quad 1 \le j \le n. \tag{2.8}$$

The (mean) number of passages through the compartment, including the initial passage is ([15])

$$f_j = (1-p_j)^{-1} \tag{2.9}$$

and the (mean) number of cycles through the compartment is

$$f_j - 1 = \rho_j/(1-p_j). \tag{2.10}$$

The fractional catabolic rate for particles in compartment i is defined as

$$fcr_j = 1/t_{jj} = |a_{jj}| (1-p_j); \tag{2.11}$$

it is the fraction of particles lost per unit time irreversively from compartment j via all pathways [2].

3. Single-entrance blocks. In order to extend the definitions of the various parameters discussed above to blocks, in the manner described in Section 1, it is necessary to specify the manner in which material enters a block. It is convenient to begin with single-entrance blocks because the formulas can later be further generalized to include multi-entrance blocks.

Definition A subset of compartments in a compartmental model is said to be a single-entrance block if it contains a compartment e, called the entrance compartment, such that all material entering the block (including continuous or instantaeous inputs from external sources and transfers from external compartments) must enter through e.

It may be assumed, without loss of generality, that all compartments in the block are reachable from the entrance compartment, for a compartment in the block which is not reachable from e is vacuous and hence it does not play a role in the kinetics.

Consider a n-compartmental system which is partitioned into ν disjoint blocks, $\mathcal{B}_k$, with entrance compartments e_k, $1 \leq k \leq \nu$. The residence time in $\mathcal{B}_i$, T_{ij}, for a particle originating in $\mathcal{B}_j$ (i.e., in the entrance e_j of $\mathcal{B}_j$) is defined as the sum of all the residence times t_{ke_j} for compartments k in $\mathcal{B}_i$, i.e.,

$$T_{ij} = \sum_{k \in \mathcal{B}_i} t_{ke_j}, \quad 1 \leq i, j \leq \nu. \tag{3.1}$$

Next, the probability that a particle enters $\mathcal{B}_i$ from $\mathcal{B}_j$ (i.e., from the entrance e_j of $\mathcal{B}_j$) is defined as

$$R_{ij} = r_{e_i e_j}, \quad 1 \leq i, j \leq \nu. \tag{3.2}$$

It should be clear that if $\mathcal{B}_i$ and $\mathcal{B}_j$ each contain only one compartment, say $\mathcal{B}_i = \{i\}$, $\mathcal{B}_j = \{j\}$, (then $e_i = i$, $e_j = j$) then $T_{ij} = t_{ij}$ and $R_{ij} = r_{ij}$. Moreover, the extension of relation (2.4) holds, i.e.,

$$T_{ij} = T_{ii} R_{ij}, \quad 1 \leq i, j \leq \nu. \tag{3.3}$$

This formula is obtained by expressing $t_{ke_j} = t_{kk} r_{ke_j}$, which follows from formula (2.4). Since a particle must first enter e_i on its route from e_j to k in $\mathcal{B}_i$, $r_{ke_j} = r_{ke_i} r_{e_i e_j}$ and so $t_{ke_j} = t_{kk} r_{ke_i} R_{ij}$. Using formula (2.4) again, $t_{kk} r_{ke_i} = t_{ke_i}$. Thus $T_{ij} = \sum_{k \in \mathcal{B}_i} t_{ke_j} = \sum_{k \in \mathcal{B}_i} t_{ke_i} R_{ij} = T_{ii} R_{ij}$.

Setting $i = j$ in formula (3.1), gives

$$T_{jj} = \sum_{k \in \mathcal{B}_j} t_{ke_j}, \quad 1 \leq j \leq \nu. \tag{3.4}$$

which is the residence time in $\mathcal{B}_j$, having originated in $\mathcal{B}_j$, and allowing recycling through compartments exterior to $\mathcal{B}_j$. To obtain the first exit time, i.e. the residence time in $\mathcal{B}_j$, having originated in $\mathcal{B}_j$, and without recycling through exterior compartments, it is necessary to consider the submatrix

$$\aleph(\mathcal{B}_j) = \left\{a_{ik}\right\}_{i,k\in\mathcal{B}_j}. \tag{3.5}$$

It should not be difficult to verify that $\aleph(\mathcal{B}_j)$ is a compartmental matrix, i.e., its off-diagonal entries are nonnegative and its column sums are nonpositive. Moreover, it is the compartmental matrix which is associated with $\mathcal{B}_j$ when this block is "disconnected" from the rest of the system. The excretion rate for compartment i in $\mathcal{B}_j$, with respect to the system represented by $\aleph(\mathcal{B}_j)$ is

$$a_{0i}(\mathcal{B}_j) = a_{0i} + \sum_{k\notin\mathcal{B}_j} a_{kj}, \quad i \in \mathcal{B}_j. \tag{3.6}$$

It should be clear that since $\aleph$ (or rather the system associated with it) has no traps, neither has $\aleph(\mathcal{B}_j)$, and so $\aleph(\mathcal{B}_j)$ is invertible. The residence time matrix associated with $\aleph(\mathcal{B}_j)$ is

$$T(\mathcal{B}_j) = -\aleph(\mathcal{B}_j)^{-1}. \tag{3.7}$$

Its element $t_{ij}(\mathcal{B}_j)$ gives the residence time of a particle in compartment i of $\mathcal{B}_j$, having originated in compartment j of $\mathcal{B}_j$, prior to exiting $\mathcal{B}_j$. Consequently, the first exit time in $\mathcal{B}_j$, having originated in (the entrance e_j of) $\mathcal{B}_j$ is

$$\mathcal{T}_j = \sum_{k\in\mathcal{B}_j} t_{ke_j}(\mathcal{B}_j), \quad 1 \leq j \leq \nu. \tag{3.8}$$

The residence time T_{jj} (with recycling) is related to the residence time $\mathcal{T}_j$ (without recycling) by the formula

$$T_{jj} = \mathcal{T}_j/(1 - P_j), \quad 1 \leq j \leq \nu. \tag{3.9}$$

where P_j is the probability of returning to $\mathcal{B}_j$ after having exited this block. The derivation of formula (3.9) is essentially the same as the derivation of its compartmental analog, formula (2.8). Formulas (2.9) and (2.10) also have obvious extensions. The (mean) number of passages through block j, including the initial passage, is

$$F_j = (1 - P_j)^{-1}, \quad 1 \leq j \leq \nu \tag{3.10}$$

and

$$F_j - 1 = P_j/(1 - P_j), \quad 1 \leq j \leq \nu \tag{3.11}$$

is <u>the (mean) number of cycles through block j</u>. Notice that through formula (3.9), P_j is given by

$$P_j = 1 - T_j/T_{jj}, \quad 1 \leq j \leq \nu. \tag{3.12}$$

In analogy with compartmental formulas (2.7) and (2.11), the <u>total fractional outflow rate</u> from block j is defined as

$$A_{jj} = -T_j^{-1}, \quad 1 \leq j \leq \nu. \tag{3.13}$$

and the <u>fractional catabolic rate</u> is

$$FCR_j = T_{jj}^{-1} = |A_{jj}|(1 - P_j), \quad 1 \leq j \leq \nu. \tag{3.14}$$

The <u>turnover rate</u> in block j is $|A_{jj}|$.

Let Q_{ij} denote the probability that a particle enters block i upon its departure from block j, without passing through any other blocks, and let Q_{0j} be the probability that a particle enters the systems environment upon its departure from block j, without passing through any other blocks. Clearly,

$$\sum_{\substack{i=0 \\ i \neq j}}^{\nu} Q_{ij} = 1, \quad 1 \leq j \leq \nu. \tag{3.15}$$

The probability that a particle enters block k, $(k \neq j)$ upon departing from block j, and then returns to block j is $R_{jk}Q_{kj}$. The sum of these probabilities gives the probability of returning to block j, i.e.,

$$P_j = \sum_{\substack{k=1 \\ k \neq j}}^{\nu} R_{jk}Q_{kj}, \quad 1 \leq j \leq \nu. \tag{3.16}$$

The last formula is the analog of formula (2.6).

Next, one can represent R_{ij} as a sum of probabilities. Consider a particle which reaches block i from block j. The particles can enter i directly upon its exit from j; this event occurs with probability Q_{ij}. Or the particle can enter another (first) block k, before it reaches i; this event occurs with probability $R_{ij}Q_{kj}$. Consequently,

$$R_{ij} = Q_{ij} + \sum_{\substack{k=1 \\ k \neq i,j}}^{\nu} R_{ik}Q_{kj}, \quad 1 \leq i, \; j \leq \nu, \; i \neq j. \tag{3.17}$$

Notice that formula (3.15) constitutes $\nu(\nu-1)/2$ linear relations in the Q_{ij} $(i \neq j)$, which could be used to obtain these parameters, however it may be easier to obtain them more directly in terms of the q_{ij} parameters as indicated in Example 6.1 (below). The analog of formula (2.3) is formula (3.18), which is used to define the block fractional transfer rates and the block excretion rate.

$$A_{ij} = Q_{ij}|A_{jj}|, \quad 0 \leq i \leq \nu, \; 1 \leq j \leq \nu, \; i \neq j. \tag{3.18}$$

That is, A_{ij} is the turnover rate for block j for particles entering block i, immediately upon departure from block j. In view of identity (3.15),

$$A_{jj} = -\sum_{\substack{k=0 \\ k \neq j}}^{\nu} A_{kj}, \quad 1 \leq j \leq \nu, \tag{3.19}$$

in analogy with formula (2.1).

The block compartmental matrix is the matrix

$$[\aleph] = \{A_{ij}\}_{i,j=1}^{\nu}. \tag{3.20}$$

It should not be difficult to verify that $[\aleph]$ is in fact a compartmental matrix. The digraph (directed graph or flow diagram) of $[\aleph]$, $\mathcal{D}([\aleph])$, may be constructed from the digraph of $\aleph$, $\mathcal{D}(\aleph)$, as follows. A directed arc from block j to block i exists in $\mathcal{D}([\aleph])$ if and only if there is at least one directed arc in $\mathcal{D}(\aleph)$ from a compartment in block j to e_i, and a directed arc from block j to the environment exists in $\mathcal{D}([\aleph])$ if and only if there is at least one directed arc in $\mathcal{D}(\aleph)$ from a compartment in block j to the environment. From this construction one can see that $\mathcal{D}([\aleph])$ is without traps since $\mathcal{D}(\aleph)$ has no traps. Thus $[\aleph]$ is invertible.

The block residence time matrix is defined by

$$[T] = \{T_{ij}\}_{i,j=1}^{\nu}. \tag{3.21}$$

So far the relations involving block parameters were obtained either as definitions or as identities expressing the laws of probability (with the exception of relation (3.3) which was verified). One relation still remains to be proved.

<u>Theorem 3.1</u> Let $[\aleph]$ and $[T]$ denote the block compartmental and residence time matrices as defined by formulas (3.20) and (3.21), respectively. Then

$$[T] = -[\aleph]^{-1} \tag{3.22}$$

(in analogy with relation (2.2)).

<u>Proof</u> To obtain the inverse of $[\aleph]$, use formulas (3.18) and (3.13) to factor

$$[\aleph] = \begin{bmatrix} -1 & Q_{12} & Q_{13} & \cdot & \cdot & \cdot & Q_{1\nu} \\ Q_{21} & -1 & Q_{23} & \cdot & \cdot & \cdot & Q_{1\nu} \\ \cdot & & & & & & \\ \cdot & & & & & & \\ \cdot & & & & & & \\ Q_{\nu 1} & Q_{\nu 2} & Q_{\nu 3} & \cdot & \cdot & \cdot & -1 \end{bmatrix} \begin{bmatrix} T_1^{-1} & 0 & 0 & \cdot & \cdot & \cdot & 0 \\ 0 & T_2^{-1} & 0 & \cdot & \cdot & \cdot & 0 \\ \cdot & & & & & & \\ \cdot & & & & & & \\ \cdot & & & & & & \\ 0 & 0 & 0 & \cdot & \cdot & \cdot & T_\nu^{-1} \end{bmatrix}$$

$$= [Q]\mathrm{diag}(T_j^{-1}), \tag{3.23}$$

where the matrix [Q] is defined as the left factor in the above equation. Defining the matrix

$$[R] = \{R_{ij}\}_{i,j=1}^{\nu}, \tag{3.24}$$

relations (3.16) and (3.17) can be expressed by the matrix equation

$$[R][Q] = -\operatorname{diag}(1 - P_j) \tag{3.25}$$

(recall that $R_{jj} = 1$, $Q_{jj} = -1$, $1 \le j \le \nu$). So, from formulas (3.23),(3.25), and (3.9).

$$-[\aleph]^{-1} = \operatorname{diag}(T_j/(1-P_j))[R] = \operatorname{diag}(T_{jj})[R] \tag{3.26}$$

Finally, relation (3.3) in matrix form is

$$[T] = \operatorname{diag}(T_{jj})[R],$$

hence $-[\aleph]^{-1} = [T]$ and the proof is now complete.

The next result is motivated by Example 6.1 (below). Fig.s 6.2 and 6.4 are each block partitions of Fig. 6.1 but Fig. 6.4 may also be regarded as a block partition of Fig. 6.2, i.e. each "compartment" in Fig, 6.4 corresponds to a block in Fig. 6.2. As might be expected, it is possible to determine the block parameters in Fig. 6.4 from those in Fig. 6.2 by treating the blocks in Fig. 6.2 as compartments. To be precise, let $\aleph, [\aleph^{(1)}]$ and $[\aleph^{(2)}]$ be the block compartmental matrices for fig.s. 6.1, 6.2, and 6.4, respectively. Let $[[\aleph^{(1)}]]$ be the block compartmental matrix which results from block partitioning fig. 6.2 to form Fig. 6.4. Then $[[\aleph^{(1)}]] = [\aleph^{(2)}]$ the general result is given below.

<u>Theorem 3.2</u>. Consider a compartmental system, with compartmental matrix, $\aleph$. Suppose that $[\aleph^{(i)}]$, $i = 1,2$, are block compartmental matrices which result from partitioning the system in two ways. Suppose that each block in partition (2) is formed as a union of blocks in partition (1) so that partition

(2) results as further partition of partition (1). Let $[[\aleph^{(1)}]]$ be the block compartmental matrix which results from partitioning system (1) (regarded as a compartmental system) to form system (2). Then $[[\aleph^{(1)}]] = [\aleph^{(2)}]$.

<u>Proof.</u> In view of Theorem 3.2, it suffices to work with the residence time matrices. Let $T_{ij}^{(2)}$ be an element of $[T^{(2)}] = -[\aleph^{(2)}]^{-1}$, i.e. $T_{ij}^{(2)}$ is the residence time in block i (of system (2)) for particles originating in the entrance compartment e of block j (of system (2)). Now compartment e belongs to one (and only one) block of system (1); denote this block by $\mathcal{B}_j^{(1)}$. By definition, $T_{ij}^{(2)}$ $= \sum_{k\in\mathcal{B}_j^{(2)}} t_{ke} = \sum_{\mathcal{B}_s^{(1)}\subset\mathcal{B}_i^{(2)}} \sum_{k\in\mathcal{B}_s^{(1)}} t_{ke}$, where the latter equation is obtained by regrouping the sum according to the partitioning of $\mathcal{B}_i^{(2)}$ into blocks from system (1). Since compartment e is also the entrance of $\mathcal{B}_j^{(1)}$, the residence time in block s (of system (1)) for particles originating in the entrance e of block j (of system (1)) is $T_{sj}^{(1)} = \sum_{k\in\mathcal{B}_s^{(1)}} t_{ke}$. Consequently, $T_{ij}^{(2)} = \sum_{\mathcal{B}_s^{(1)}\subset\mathcal{B}_i^{(2)}} T_{sj}^{(1)}$. Now regarding, the blocks of system (1) as compartments in system (2), $\mathcal{B}_j^{(1)}$ is the entrance of $\mathcal{B}_j^{(2)}$, and the last formula gives the block residence time in terms of these compartments as defined in Formula (3.1). This completes the proof.

<u>4. Multi-entrance blocks</u> The theory which was developed above for single-entrance blocks may be extended to include blocks with multiple entrances, however the manner in which material enters the block must be prescribed in accordance with the following definition.

<u>Definition</u> Let $\mathcal{B}$ be a subset of compartments in an n-compartmental system. Consider a particle entering $\mathcal{B}$ and let σ_e denote the probability that the particle enters $\mathcal{B}$ at a particular compartment e in $\mathcal{B}$. Then $\mathcal{B}$ is said to be a multi-entrance block if σ_e is a constant which depends

only on e (and it is independent of time and the particular source (continuous inputs, instantaneous inputs, transfers from external compartments) of the entering particle), for all e in B.

As it was stated previously, it is assumed that there are no traps or vacuous compartments in the system, i.e., each compartment both reaches the environment and it is reachable from at least one input.

The case of a multi-entrance block is reducible to the single-entrance-block case by means of the following device. Suppose that B is a multi-entrance block. B may be modified by inverting into it an additional compartment, denoted by e and re-directing all inflows into the block to enter e. The fractional transfer rates from e to a compartment j in B is defined as $\gamma\sigma_j$ where γ is a positive constant; no transfers are defined from e to exterior compartments or to the environment. Note that γ is the turnover rate in compartment e. The modification of the block is illustrated in Fig. 4.1. The modification does effect the kinetics but only by increasing the residence time in the block by γ^{-1}. Thus as $\gamma \to \infty$ the original kinetics are regained. The parameters associated with a multi-entrance block are defined by modifying the block to a single-entrance block, as described above, calculating the parameters in the manner set forth in the previous section, and then taking the limit as the turnover rate, γ, of the inserted compartment tends to infinity.

The device introduced above extends the formulas in the preceeding section to multi-entrance blocks in a single stroke. However, block parameters may be obtained directly without modifying the system.

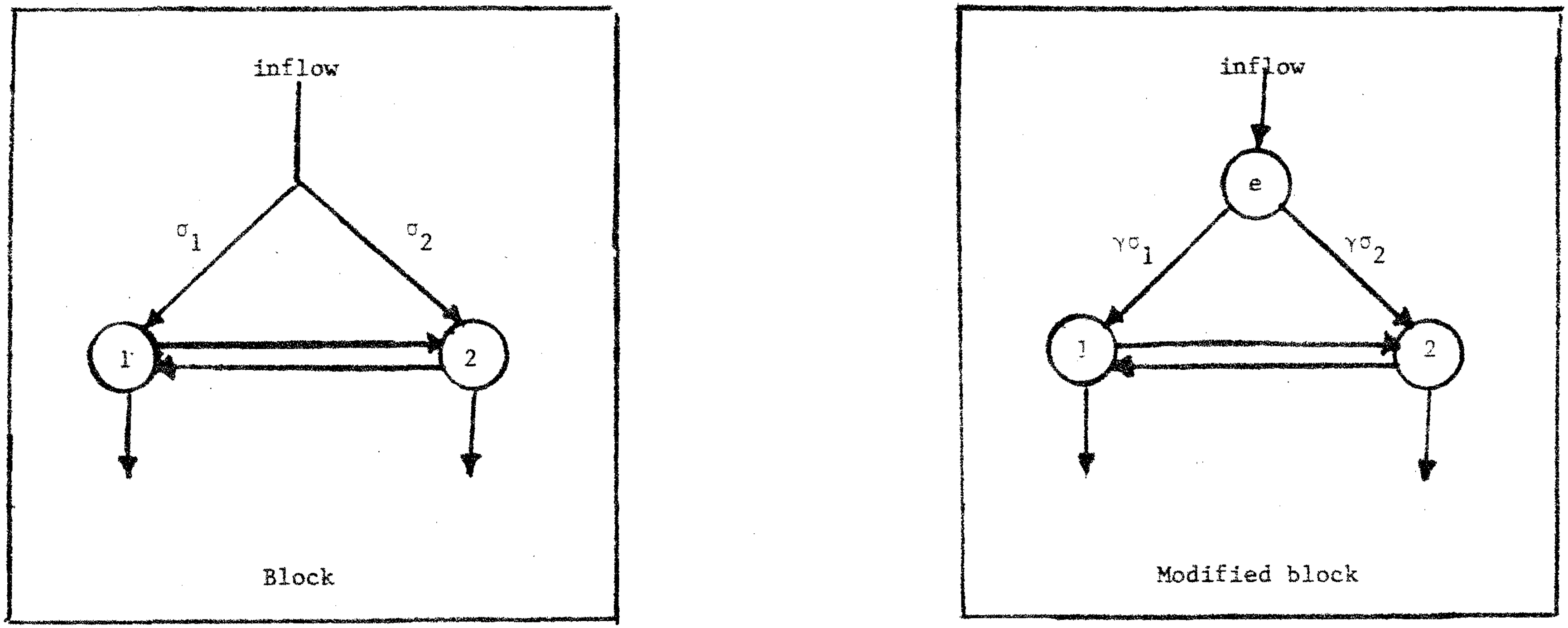


Figure 4.1 Modification of a multi-entrance block to form a single-entrance block.

Theorem 4.1 Let $\mathcal{B}_j$ be a multi-entrance block and let $\mathcal{B}_i$ be a disjoint block $(i \neq j)$ or let $\mathcal{B}_i$ be identical with $\mathcal{B}_j$ $(i=j)$. In either case the residence time in block i for a particular initiating in block j is

$$T_{ij} = \sum_{e \in \mathcal{B}_j} \sum_{k \in \mathcal{B}_i} t_{ke} \sigma_e^{(j)}, \qquad (4.1)$$

where $\{\sigma_e^{(j)}\}$ denotes the entering distribution associated with block j.

Proof First consider the case where $\mathcal{B}_i$ and $\mathcal{B}_j$ are disjoint blocks. The symbol "~" is used generically to distinguish the modified compartmental system which results by inserting an additional compartment e in block j. Now, by formulas (3.1) and (2.4),

$$\tilde{T}_{ij} = \sum_{i \in \mathcal{B}_i} \tilde{t}_{ie} = \sum_{i \in \mathcal{B}_i} \tilde{t}_{ii} \tilde{r}_{ie}. \qquad (4.2)$$

By the construction of the modified system, a particle must pass through a (first) compartment k in block j on its route to compartment i in $\mathcal{B}_i$ and this event occurs with probability $\sigma_k^{(j)}$. So $\tilde{r}_{ie} = \sum_{k \in \mathcal{B}_i} \tilde{r}_{ik} \sigma_k^{(j)}$, giving

$$\tilde{T}_{ij} = \sum_{i \in \mathcal{B}_i} \sum_{k \in \mathcal{B}_j} \tilde{t}_{ii} \tilde{r}_{ik} \sigma_k^{(j)} = \sum_{k \in \mathcal{B}_j} \sum_{i \in \mathcal{B}_i} \tilde{t}_{ik} \sigma_k^{(j)}. \qquad (4.3)$$

Moreover, the residence time in compartment i of block i, for a particle originating in compartment k in block j, is independent of e, i.e., $\tilde{t}_{ik} = t_{ik}$, so formulas (4.3) and (4.1) coincide.

Now consider the case $i = j$. By formula (3.1),

$$\tilde{T}_{ij} = \sum_{i \in \tilde{\mathcal{B}}_j} \tilde{t}_{ie} = \sum_{i \in \mathcal{B}_j} \tilde{t}_{ie} + \tilde{t}_{ee}, \qquad (4.4)$$

By the construction, $\tilde{t}_{ee} = \sigma^{-1}$, and arguing as before, $\tilde{t}_{ie} = \sum_{k \in \mathcal{B}_j} t_{ik} \sigma_k^{(j)}$. Consequently,

$$\tilde{T}_{jj} = \sum_{i \in \mathcal{B}_j} \sum_{k \in \mathcal{B}_j} t_{ik} \sigma_k^{(j)} + \gamma^{-1}, \qquad (4.5)$$

so, as $\gamma \to \infty$, one obtains the desired formula. This concludes the proof.

In a similar manner, the first exit time in a multi-entrance block j is found to be given by formula (4.6).

$$T_j = \sum_{k \in B_j} \sum_{e \in B_j} t_{ke}(B_j)\sigma_e^{(j)}, \tag{4.6}$$

where $t_{ke}(B_j)$ was defined in the paragraph preceding formula (3.8).

Remark 4.1 According to the definitions, a single-exit block, B, may be characterized as a special case of a multi-exit block, which contains a compartment e_j such that $\sigma_e^{(j)} = 1$ and $\sigma_k^{(j)} = 0$ for $k \neq e$. Notice that for a single-entrance block, formulas (4.1) and (4.6) reduce to their counterparts in Section 3.

Remark 4.2 Suppose that a compartmental system is partitioned into ν disjoint multi-entrance blocks. Then by means of formula (4.1) one obtains the block residence time matrix $[T]$. The block compartmental matrix may be obtained by $[K] = -[T]^{-1}$. The elements of this matrix are the block fractional transfer rates, which can be used to obtain all the remaining block parameters by means if the formulas in Section 2.

Remark 4.3 A subset of compartments may not qualify as a multi-entrance block because the entrance distribution may not be time-invariant. Suppose that B_j is a multi-entrance block and B_i is a subset of compartments which are exterior to B_j. Even though B_i may not qualify as a multi-entrance block, the residence time in B_i, for particles originating in B_j, may still be defined by formula (4.1), since this formula requires only that B_j have a time-invariant entrance distribution.

Remark 4.4 Suppose that B_j is a multi-entrance block which is embedded in a larger system. Even though it may not be possible to partition those compartments which are exterior to B_j into multi-entrance blocks, it is still possible to assign kinetic parameters to B_j. Formula (4.1), with $i = j$, defines the residence time T_j (without recycling). Block parameters P_j, F_j, A_{jj}, and FCR_j may then be obtained by means of formulas (3.12), (3.10), (3.13), and (3.14).

5. Steady State A major objective of compartmental studies is to determine the steady-state masses m_i of the various compartments from the constant steady-state inputs into these compartments (or vice-versa). These may be found by inverting the system

$$\underline{u} = -\aleph\, \underline{m} \,, \tag{5.1}$$

where $\underline{u}$ is the vector of inputs, $\underline{m}$ is the vector of masses, and $\aleph$ is the compartmental matrix [2]. The mass of a block B is then

$$M = \sum_{k \in B_j} m_k \,. \tag{5.2}$$

The calculation of M_j may be substantially simplified by using block parameters. Suppose that the model is partitioned into ν disjoint multi-entrance blocks, B_j, with steady-state masses M_j and constant steady-state inputs U_j (which enters B_j according to the block's entrance distribution).

Theorem 5.1 Let $\underline{M}$, $\underline{U}$, and $[\aleph]$ be the vector of block masses, the vector of block inputs, and the block compartmental matrix, respectively. Then

$$\underline{U} = -[\aleph]\, \underline{M} \tag{5.3}$$

Proof Multiplying in formula (5.1) by the block residence time matrix the formula becomes $\underline{m} = T\underline{u}$ or $m_k = \sum_{i=1}^{n} t_{ki} u_i$. Grouping the terms in the sum into blocks, $m_k = \sum_{j=1}^{\nu} \sum_{e\in B_j} t_{ke}u_e$. Since U_j enters B_j in accordance with its entrance distribution, $u_e = \sigma_e^{(j)}U_j$ for $e \in B_j$ and so $m_k = \sum_{j=1}^{\nu} \sum_{e\in B_j} t_{ke}\sigma_e^{(j)}U_j$. By formula (5.2), $M_i = \sum_{k\in B_i} \sum_{j=1}^{\nu} \sum_{e\in B_i} t_{ke}\sigma_e^{(j)}U_j =$ $\sum_{j=1}^{\nu}\left[\sum_{k\in B_i} \sum_{e\in B_j} t_{ke}\sigma_e^{(j)}\right]U_j = \sum_{j=1}^{\nu} T_{ij}U_j$. Thus $\underline{M} = [T]\underline{U}$, which, by Theorem 3.1, is equivalent to formula (5.3) and the proof is complete.

An important steady-state parameter is the production rate, pr_i, into compartment i. This includes direct entry from outside the system (u_i), and first time entries contributed through other compartments. More precisely,

$$pr_i = \sum_{j=1}^{n} r_{ij}u_j, \quad 1 \le i \le n \; . \tag{5.4}$$

An alternate formula for the production rate is [2]

$$p_{ri} = fcr_i m_i \cdot \; , \quad 1 \le i \le n. \tag{5.5}$$

These relations may be extended to blocks. The production rate into block i is defined as

$$PR_i = \sum_{j=1}^{\nu} R_{ij}U_j \; , \quad 1 \le i \le \nu. \tag{5.6}$$

<u>Theorem 6.2</u> Let PR_i, FCR_i, and M_i be the production rate, the fractional catabolic rate, and the mass of block i, respectively. Then

$$PR_i = FCR_i M_i, \quad 1 \le i \le \nu. \tag{5.7}$$

<u>Proof</u> The relation $M_i = \sum_{j=1}^{\nu} T_{ij}U_j$ was obtained in the proof of Theorem 5.1. Recall that $T_{ij} = T_{ii}R_{ij}$ and $FCR = T_{ii}^{-1}$, so $FCR_i M_i =$ $T_{ii}^{-1}\sum_{j=1}^{\nu} T_{ii}R_{ij}U_j = PR_i$, which concludes the proof.

The turnover rate in a block may be expressed as an average excretion rate weighted by the steady-state masses as shown below.

Theorem 5.3 Let $\mathcal{B}_j$ be a multi-entrance block which is embedded in a compartmental system. (It is not necessary to assume that the system is partitionable into disjoint blocks.) Let $a_{0i}(\mathcal{B}_j)$ be the fractional excretion rate of compartment i in $\mathcal{B}_j$ (as defined in formula (3.6)). Then the turnover rate in $\mathcal{B}_j$ is

$$|A_{jj}| = \sum_{i\in\mathcal{B}_j} a_{0i}(\mathcal{B}_j)m_i/M_j. \tag{5.8}$$

Proof According to relation (5.1), the steady-state equation for compartment i in $\mathcal{B}_j$ is

$$\sum_{k\in\mathcal{B}_j} a_{ik}m_k + v_i = 0, \tag{5.9}$$

where $v_i = \sum_{s\notin\mathcal{B}_j} a_{is}m_s + u$ is the steady-state rate of inflow into compartment i from other compartments and the external input. The total rate of inflow is then

$$V_j = \sum_{i\in\mathcal{B}_j} v_i = \sum_{i\in\mathcal{B}_j}\sum_{k\in\mathcal{B}_j} -(a_{ik}m_k). \tag{5.10}$$

Rearranging the sum and taking account of formulas (2.1) and (3.6) yields

$$V_j = \sum_{k\in\mathcal{B}_j}\left(-\sum_{i\in\mathcal{B}_j} a_{ik}\right)m_k = \sum_{k\in\mathcal{B}_j} a_{0k}(\mathcal{B}_j)m_k. \tag{5.11}$$

On the other hand, system (5.9) may be inverted to yield

$$m_i = \sum_{k\in\mathcal{B}_j} t_{ik}(\mathcal{B}_j)v_k. \tag{5.12}$$

Moreover, v_k is that proportion of V_j which enters compartment k, so $v_k = \sigma_k^{(j)}V_j$. Hence, by formulas (5.2), (5.12), (3.8), and (3.13),

$$M_j = \sum_{i\in\mathcal{B}_j}\sum_{k\in\mathcal{B}_j} t_{ik}(\mathcal{B}_j)\sigma_k^{(j)}V_j = T_jV_j = V_j/|A_{jj}|. \tag{5.13}$$

Substituting for V_j from formula (5.11) completes the proof.

Since $|A_{jj}|$ is a weighted average of the excretion rates it follows that

$$\min_{i \in B_j} a_{0i}(B_j) \leq |A_{jj}| \leq \max_{i \in B_j} a_{0i}(B_j). \qquad (5.14)$$

In applying the above inequalities it should be kept in mind that if there is a compartment which does not transfer directly to either the environment or to an exterior compartment then the term on the extreme left of relation (5.14) is zero.

6. Examples

Example 6.1 A model for the kinetics of Very Low Density Lipoprotein Triglycerides, which was first developed by Zech et al [19] and is discussed elsewhere ([2],[20]), is shown in Fig. 6.1. The VLDL-TG block, B, consisting of compartments 1,6,7,8, and 21, is of particular interest. It is a single-entrance block with entrance at compartment 1. To obtain parameters which are associated with the VLDL-TG block alone (see Remark 4.4) it is convenient to begin with the first exit time, T. Since there is no recycling within the block, $t_{k1}(B) = \tau_k r_{k1}$ for each compartment k in B and so $T = \tau_1 + \tau_6 r_{61} + \tau_7 r_{71} + \tau_8 r_{81} + \tau_{21} r_{211}$. The probability that a particle in compartment 1 exits the block irreversibly from compartment 8 (to enter the IDL range) is $Q_0 = q_{08}q_{87}q_{76}q_{61}$. The probability in that a particle in compartment 1 will enter compartment 4 (to form free glycerol) is therefore $r_{41} = 1 - Q_0$. The probability that a particle in compartment 1 is recycled is $P = r_{14}r_{41} = (q_{104}+q_{244})(1-Q_0)$.

These parameters may be evaluated from the fractional transfer rate values in Fig. 6.1. Other parameters may be determined from these by formulas (3.8)-(3.13) and the results of these calculations are presented in Table 1.

Table 1. VLDL-TG block parameters calculated from the fractional transfer rates in Fig. 6.1.

First exit time (no recycling), $\mathcal{T}$ = 5.88h

Residence time (with recycling), T = 5.91h

Turnover rate, $|A| = .170h^{-1}$

Fractional catabolic rate, $FCR = .169h^{-1}$

Probability of recycling, P = .00564

Mean number of recycles, F-1 = .00567

Probability of forming IDL, $Q_0 = .353$

Probability of reconverting to free glycerol, $r_{41} = .647$

Fig. 6.1 may be partitioned into four single-entrance blocks: GLYCEROL = $\{4,5\}$, SLOW CONVERSION = $\{24\}$, FAST CONVERSION = $\{10,11,12,13,14\}$ and VLDL-TG = $\{1,6,7,8,21\}$, as shown in Fig. 6.2. The simplest procedure for calculating the block fractional transfer rates is to first calculate the block first exit times (as indicated above for the VLDL-TG block). Next calculate the inter-block transfer probabilities Q_{ij}, which can be found in terms of the q_{ij}. Finally, use formulas (3.13) and (3.18) to obtain the A_{ij}. The results are given in Fig. 6.2.

It is interesting that Fig. 6.2 has been used as a reduced model for VLDL-TG kinetics (in place of Fig. 6.1) i.e., each of the four blocks was

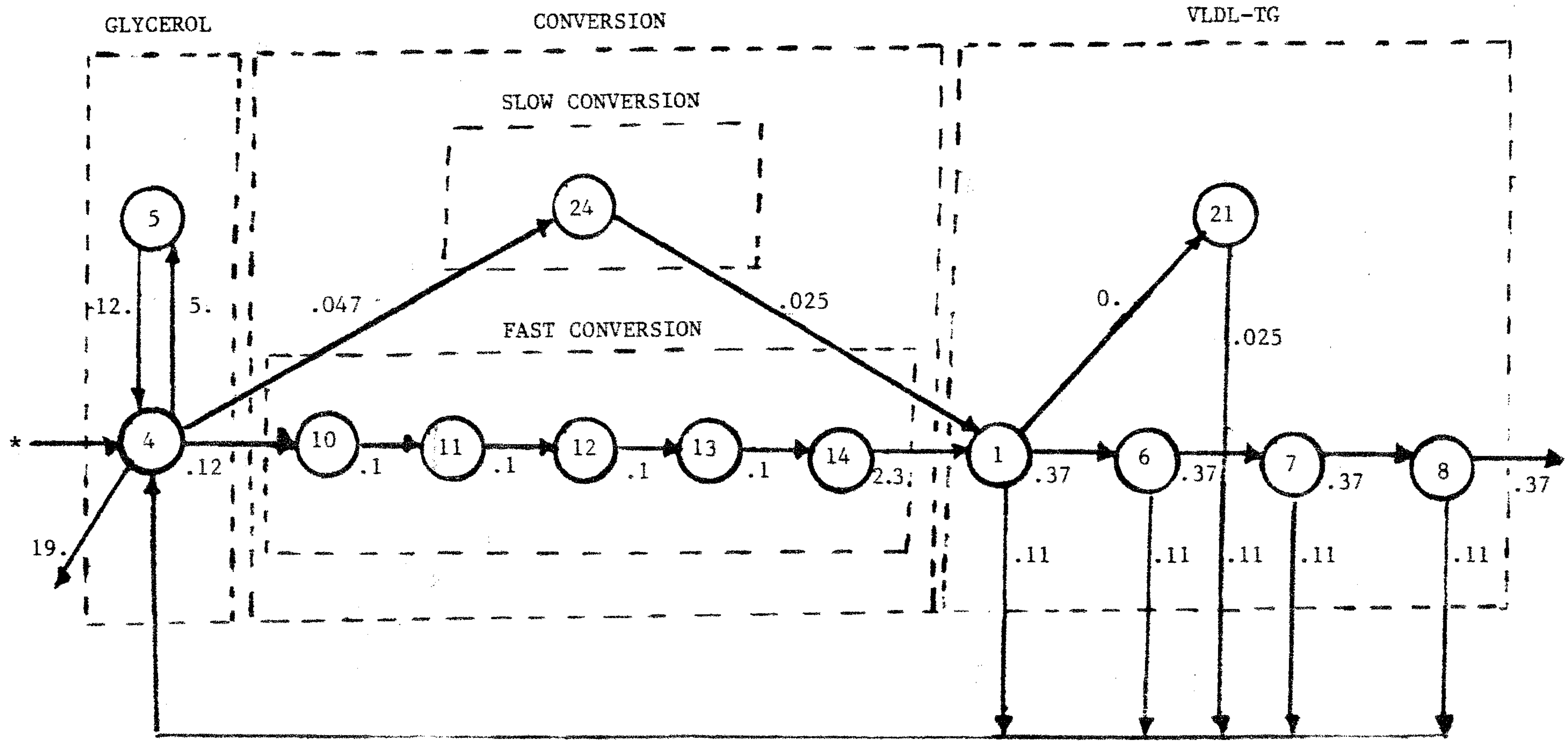


Figure 6.1 VLDL-TG Model. Tracer, indicated by "*" enters compartment 4. The fractional transfer rates (in units of reciprocal hours), are approximations for normal subjects as reported by Zech et al [19].

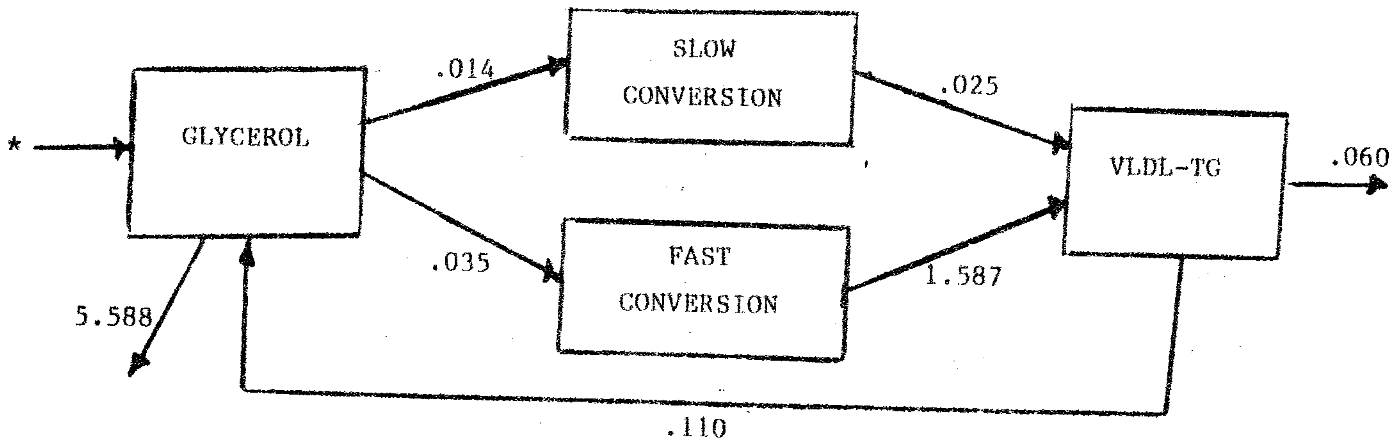


Figure 6.2 Partitioning of Fig. 6.1 by GLYCEROL, SLOW CONVERSION, FAST CONVERSION, and VLDL-TG blocks.

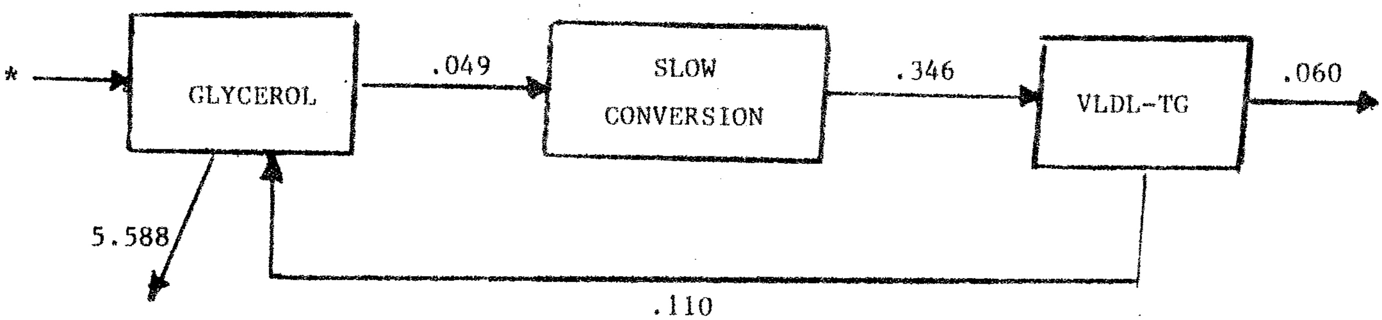


Figure 6.3 Partitioning of Fig. 6.1 by GLYCEROL, CONVERSION, and VLDL-TG blocks.

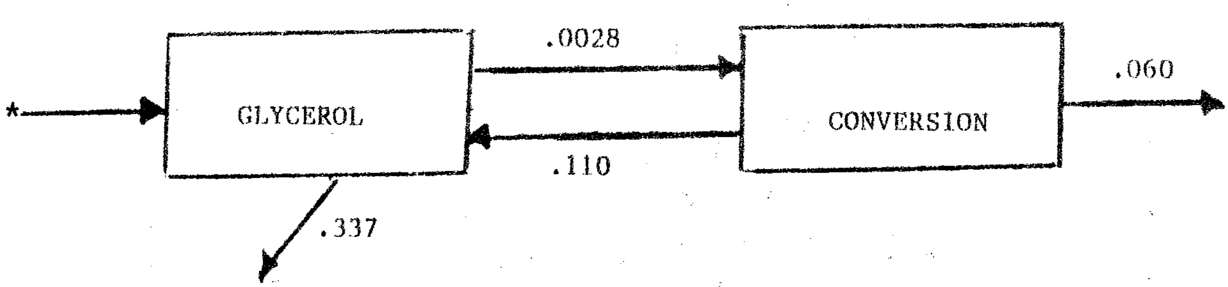


Figure 6.4 Partitioning of Figure 6.1 by SYNTHESIS and VLDL-TG blocks.

treated as if it were a single compartment (see [21]).

Fig. 6.1 may be partitioned into three blocks by combining SLOW CONVERSION and FAST CONVERSION into the CONVERSION block as shown in Fig. 6.3. Notice that CONVERSION is a multi-entrance block. Material enters this block by transfers from compartment 4 to compartments 10 and 24. The entrance distribution is given by $\sigma_{10} = a_{104}/(a_{104} + a_{244})$, $\sigma_{24} = a_{244}/(a_{104} + a_{244})$ and the remaining σ_k are zero. The block fractional transfer rates are shown in Fig. 6.3.

Finally, by combining the GLYCEROL and CONVERSION blocks, Fig. 6.1 is partitioned into two single-entrance blocks as shown in Fig. 6.4. Fig.s 6.2 - 6.4 serve to summarize Fig. 6.1; they should not be construed as reduced models.

Finally, since there are no steady-state inputs into the CONVERSION block, Fig. 6.4 may be exploited, in conjunction with Theorems 5.1 and 5.2, to simplify steady-state analyses.

Example 6.2 In the exploratory stages of modeling a physiological process, various possible models are considered, For instance, Fig. 6.5 presents four possible models for VLDL-B kinetics [2]. It is interesting to compare these models. Two models are comparable if they are block partitionable to topologically equivalent models. Model D may be compared to model C by combining the "delipidation chain" $\{11, 12, 13, 14\}$ into a (multi-entrance) block as shown as model F in Fig. 6.6. All four models in Fig. 6.5 may be compared by combining all the compartments in each model into a single block, T, as shown (as model F) in Fig. 6.6. It is interesting to compare these models

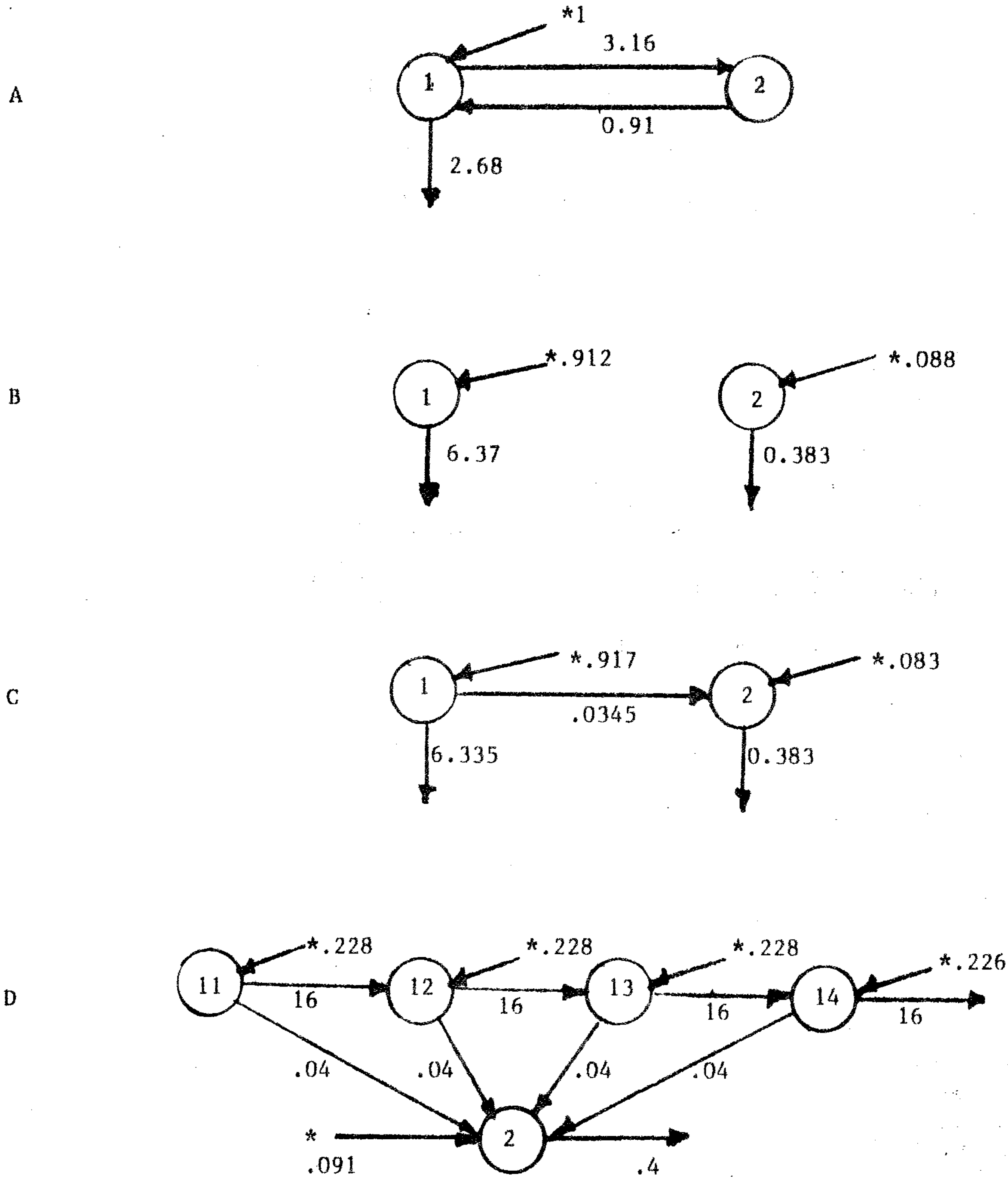
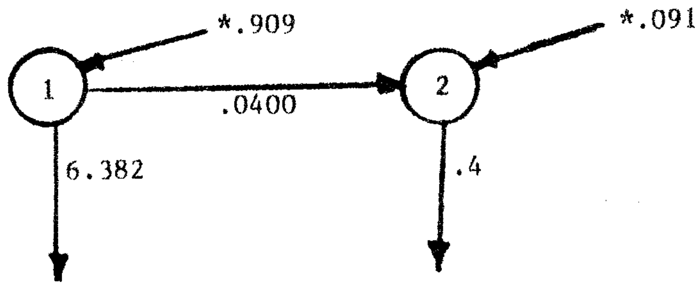


Figure 6.5 Four VLDL-B models [2]. "*" denotes the initial distribution of tracer. Compartment 1 (in models A, B, and C) denotes the plasma; it is replaced by the delipidation chain in model D. Compartemnt 2 is the extraplasma compartment in all four models. Time is measured in days.

E



F

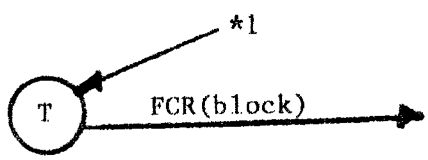


Figure 6.6 Block partitioned models. Model E is the partition of model D (in Fig. 6.5); block 1 represents the plasma compartments. Model F is the partition of models A, B, C, or D to a single block.

in terms of fractional catabolic rates since there are popular meaures in lipoprotein kinetics. The FCR for a block is defined in formula (3.14), however if the block consists of the entire system, as in model F, the block FCR is also the reciprical of the residence time in the system. The plasma fractional catabolic rate is the fcr for compartment 1 in the case of models A, B, and C, as defined in formula (2.11). In the case of model D, the plasma is represented by block 1 in model E and so the FCR is defined by formula (3.14). The extraplasma is compartment 2 in all four models. The values of the fractional catabolic rates for the four models are shown in Table 2.

Table 2. Fractional catabolic rates for VLDL-B models.

Model	A	B	C	D
FCR (block)	0.60	2.68	2.68	2.61
FCR (plasma)	2.68	6.37	6.37	6.42
FCR (extraplasma)	0.42	0.38	0.38	0.40

As might be expected, the models are less dissimilar when viewed through block parameters. The only striking difference occurs in FCR (block) and FCR (plasma) values in model A which is due to the recycling in this model, and this recycling does not exist in the other models.

7. Discussion The pertinent points of the paper may be summarized as follows. First, several relations between compartmental parameters were shown to carry over to their block counterparts. The block parameters, which were introduced as a means of measuring kinetic properties of block, also play a

role in steady-state analysis and summarizing and comparing models. The block residence times are defined in an obvious way by summing over the residence times in the interior compartments. However, the block turnover rates turn out to be weighted averages of certain functional transfer rates within the block as given in Theorem 5.3.

Partitioning of a compartmental system into disjoint blocks gives rise to the block compartmental system. This entity has the structural properties of a compartmental system, however it can not be viewed as a reduced model since the block parameters are determined from the original model.

It should be emphasized that the block parameters defined above apply only to situations in which the donor block has a time-invariant entrance distribution (see Remarks 4.3 and 4.4). Such situations occur often enough, but it would be nice to extend the theory to more general cases; this possibility will be explored in the near future.

Figure Captions

Figure 4.1 Modification of a multi-entrance block to form a single-entrance block.

Figure 6.1 VLDL-TG Model. Tracer, indicated by "*" enters compartment 4. The fractional transfer rates (in units of reciprical hours), are approximations for normal subjects as reported by Zech et al [19].

Figure 6.2 Partitioning of Fig. 6.1 by GLYCEROL, SLOW CONVERSION, FAST CONVERSION, and VLDL-TG blocks.

Figure 6.3 Partitioning of Fig. 6.1 by GLYCEROL, CONVERSION, and VLDL-TG blocks.

Figure 6.4 Partitioning of Figure 6.1 by SYNTHESIS and VLDL-TG blocks.

Figure 6.5 Four VLDL-B models [2]. "*" denotes the initial distribution of tracer. Compartment 1 (in models A, B, and C) denotes the plasma; it is replaced by the delipidation chain in model D. Compartment 2 is the extraplasma compartment in all four models. Time is measured in days.

Figure 6.6 Block partitioned models. Model E is the partition of model D (in Fig. 6.5); block 1 represents the plasma compartments. Model F is the partition of models A, B, C, or D to a single block.

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