STRUCTURAL IDENTIFIABILITY OF BIOLOGICAL COMPARTMENTAL SYSTEMS.
Digital Computer Implementation of a Testing Procedure

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1. Introduction

The most widely treated problem in compartmental analysis of biological systems [1,2,3] concerns the choice of the compartmental structure of the system (identification of the compartments and of their relationships: compartmentalization)and the evaluation of the system parameters via a suitable input-output experiment (identification of the transfer rate constants: estimation).

However, prior to actually performing the identification experiment, the following problem has to be considered: can the chosen experiment provide the desired information about the system? i.e., can all parameters characterizing the adopted compartmental model be estimated from the chosen experiment? (identifiability problem: [4]).

This problem is particularly important in the study of "in vivo" phenomena as the experiment is often non repeatable because of induced harm, high cost, troubles etc. (e.g., radioactive tracer experiments). The problem is to be answered, therefore, after the compartmentalization but before the estimation. In such a way the problem can be characterized as the a priori structural identifiability problem because it has to be faced only with reference to assumptions about the model structure and not about the values of its parameters (values which can be obtained only through the planned experiment); the a posteriori identifiability, on the contrary, refers to the actually estimated values of the parameters and it is connected to the statistical evaluation of the reliability of the estimates.

In this paper the structural identifiability problem is considered for multi-input multi-output compartmental systems of any structure, where each input enters one compartment only and each output is re lated to one compartment. A testing procedure for the identifiability of such systems is presented and a description of the techniques employed for a digital computer implementation of the whole procedure is given. Finally we apply the above procedures to a compartmental model of copper metabolism.

2. Some concepts on compartmental systems

It seems useful to review some general concepts about compartmental systems.

A compartment is a quantity of material which kinetically behaves in a characteristic and homogeneous way. It must be emphasized that a compartment may or may not coincide with a physiologically realizable region of space.

A compartmental system consists of interconnected compartments which exchange material either by physical transport or by chemical reaction. A compartmental system is therefore characterized by compartments and intercompartmental relations.

The differential equations describing the dynamical behaviour of a compartmental system are obtained from the mass balance equation for each compartment:

$$\dot{q}_i = \sum_{\substack{j\neq i\\ j\neq 0}} f_{ij} + m_i + u_i - \sum_{\substack{j\neq i\\ j\neq 0}} f_{ji} - f_{oi} \qquad i=1,n \qquad (1)$$

where:

q_i is the amount of material of the i-th compartment;

m_i is the net rate of production of material by metabolism (internal input);

u_i is the rate at which material enters the i-th compartment from the environment external to the system (external or perturbation input);

f_{oi} is the excretion flow from the i-th compartment to the environment;

f_{ji} is the transfer flow from the i-th to the j-th compartment;

f_{ij} is the transfer flow from the j-th to the i-th compartment.

The classical compartment theory assumes linearity and time-invariance of the system; therefore eq.(1) can be written is the form:

$$\dot{q}_i = \sum_{\substack{j\neq i\\ j\neq 0}} k_{ij}\, q_j + m_i + u_i - \sum_{\substack{j\neq i\\ j\neq 0}} k_{ji}\, q_i - k_{oi}\, q_i \qquad (2)$$

where:

k_{ij} is the (non negative) rate constant from the j-th to the i-th compartment;

k_{oi} is the (non negative) rate constant from the i-th compartment to the environment.

In <u>steady state</u> m_i is assumed to be constant, the perturbation external input u_i is equal to zero, the rate of change of q_i is zero by definition and each q_i assumes a constant steady state value q_{is}.

With reference to the (small) deviations $x_i = q_i - q_{is}$ caused by u_i, equation (2) can be rewritten in the form:

$$\dot{x}_i = \sum_{\substack{j \neq i \\ j \neq 0}} k_{ij}\, x_j + u_i - \sum_{\substack{j \neq i \\ j \neq 0}} k_{ji}\, x_i - k_{oi}\, x_i \tag{3}$$

For a tracer, equation (3) also holds under the following assumptions:

i) the system is in steady state;

ii) the injected tracer has a metabolic fate identical to the fate of the non-labeled substance;

iii) the mixing of the injected tracer with the non-labeled substance within each compartment is complete and rapid in comparison with transfer rates of the substance between compartments;

iv) the amount of the injected tracer is negligible in comparison with the size of the compartment; the steady state is not altered by the injection;

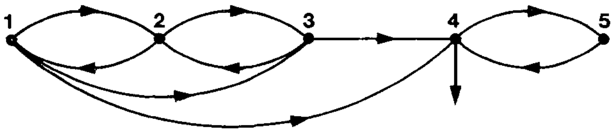
v) there is no isotopic fractionation for radioactive tracer.

For an n compartmental system, the k_{ij} rate constants can be grouped into a square, n order matrix K, the main diagonal of which is null, and the k_{oi} rate constants into an n order row matrix K_o.

As far as the structural identifiability problem is concerned, we must observe that matrices K and K_o are not yet known (as no estimation has been performed), but we know which of their entries are nonzero, as this derives from compartmentalization. Namely, we know only matrices H and H_o, obtained from K, K_o through the following statement:

$$\begin{cases} h_{rs}=0 & \text{if} \quad k_{rs}=0 \\ h_{rs}=1 & \text{if} \quad k_{rs}\neq 0 \end{cases} \qquad \text{with} \quad \begin{cases} r=0,n \\ s=1,n \end{cases} \tag{4}$$

Matrix H may be viewed as the connection matrix of a directed graph with nodes corresponding to compartments and branchesto the rate constants (fig.1).



$$H = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 & 1 \\ 0 & 0 & 0 & 1 & 0 \end{bmatrix} \qquad H_o = \begin{bmatrix} 0 & 0 & 0 & 1 & 0 \end{bmatrix}$$

Figure 1 - Directed graph of a compartmental system and corresponding H and H_o matrices.

For what follows it is useful to know whether a given compartment i can influence compartment j: with reference to the above graph, it corresponds to the existence of a path from compartment i to compartment j. As is well known, this problem may be solved by checking wether the ij entry of one of the successive powers of H is nonzero; the order of the first power of H in which such element is nonzero is equal to the number of branches of the minimum path from i to j. A system is said to be strongly connected when every compartment can be reached from every other compartment; in such a case matrix $R = \sum_{l=1}^{n} H^l$ has all nonzero entries. A system is said to be open (closed) when there is some exchange (no exchange) with the environment; the corresponding condition is $H_o \neq 0$ ($H_o \equiv 0$).

The variables x_i in (3) can be clearly considered as components of the state vector x of a dynamical, linear, time invariant system:

$$\dot{x} = Ax + Bu \qquad (5)$$

$$y = Cx \tag{6}$$

where $u = u_i$ is the input and y is the output formed by the measured variables.

It can be easily seen that the elements of A are related to the elements of K and K_o by:

$$a_{ij} = k_{ij} \qquad i \neq j \tag{7}$$

$$a_{ii} = -k_{oi} - \sum_{j=1}^{n} k_{ji} \tag{8}$$

Matrix A is therefore diagonally dominant and consequently its eigenvalues cannot be purely imaginary and have a non positive real part [7] ; usually however they are real and negative.

3. Statement of the problem

As previously said, in this paper we consider multi input - multi output compartmental systems of any structure where each input enters one compartment only and each output is related to one compartment.

The assumption about the structure is completely general (previous work in this field considers only strongly connected system [8,5] ; the general case is treated also in [6]); as a consequence no restrictions have to be made on matrix K (non-negativity of its entries is the only assumption).

The assumption about the inputs corresponds to the more usual case in tracer experiments. If we label the r_b inputs ($r_b \leq n$) with index j, ($j=1,r_b$), for the ($n \times r_b$) matrix B the following condition holds:

$$b_{il} = \begin{cases} 1 & \text{if input 1 enters the i-th compartment} \\ 0 & \text{otherwise} \end{cases} \tag{9}$$

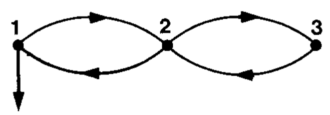
The assumption about the outputs corresponds to a large class of practical cases of tracer experiments. If we label the r_c outputs ($r_c \leq n$) with index k, ($k=1,r_c$), for the ($r_c \times n$) matrix C the following condition holds:

$$c_{mi} = \begin{cases} 1 & \text{if output m is taken from compartment i} \\ 0 & \text{otherwise} \end{cases} \tag{10}$$

The most general input-output configuration where the input can fraction into several compartments and the output is related to more than one compartment (the observed output variable y_r is a linear combination of some state variables x_s) is now under study.

As far as the identifiability problem is concerned, it must be noted that if the aim of identification is to have a model of the system, by which either the response to a given input or the input causing a desired response may be computed, than any equivalent realization (A,B, C) is acceptable. In such a case, as is well known, necessary and sufficient condition for identifiability is that the system be controllable and observable; all the required information about the system is included in the transfer function matrix.

In the case of biomedical applications, however, identification has diagnostic aims, and determining the transfer function matrix of the system (i.e. one of the equivalent (A,B,C) triples) may be insufficient, while it is necessary to evaluate all the transfer rate constants k_{rs}, which are of immediate physiological significance. In the latter case controllability and observability of the system are only necessary conditions; moreover the number of mutually independent coefficients of the transfer functions is to be at least equal to the number of nonzero k_{rs} transfer rate constants. In fig.2 this situation is clearly illustrated: the system is controllable and observable, but is not structurally identifiable as only four rate constants can be uniquely estimated.



$$B = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} \qquad\qquad C = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix}$$

Figure 2 - Example of a controllable, observable but non structurally identifiable compartmental system.

4. Outline of the procedure

With reference to what has been discussed in section 3, testing the structural identifiability of a compartmental system by a given input-output experiment (namely when the topological structure of input-state-output connection is completely known) consists of:

1) testing wether the necessary conditions for controllability and observability are satisfied with respect to the system structure (i.e. independently on the numerical values of nonzero k_{ij} parameters);

2) comparing (again with respect to the system structure and therefore independently on the numerical values) the number of not yet determined nonzero parameters of K and K_o matrices, and the number of mutually independent coefficients in the numerator and denominator polynomials of the $r_b \times r_c$ input-output transfer functions.

As far as topic 1 is concerned, as seen above, the problem is to be faced independently on the numerical values taken by the entries of A; therefore it seems not suitable to refer to usual controllability and observability criteria, based on the ranks of respectively controllability matrix P (constructed on the basis of the pair A,B) and observability matrix Q (constructed with A,C). On the contrary, it is useful to consider the following theorems [6] , which make use only of connection matrices H and H_o.

Theorem 1: The existence of at least one path reaching every uncontrolled compartment from a controlled one is a necessary condition for a compartmental system to be CC; the existence of at least one path from every unobserved compartment to an observed one is a necessary condition for a compartmental system to be CO.

Theorem 2.1: A compartmental system is CC in a structural sense if every uncontrolled compartment is reachable from at least a controlled one along any path.

Theorem 2.2: A compartmental system is CO in a structural sense if there is at least one path from every unobservable compartment to an observed one.

As far as topic 2 is concerned, the subject is somewhat complex and the discussion may be developed as follows.

From input and output behavior, the identification will allow one to determine, for instance, the values of numerator and denominator polynomials of the transfer functions related to every input-output pair (as controllability and observability have already been tested, the transfer function matrix uniquely corresponds to any minimal realization of the system). As seen above, the problem consists in checking wether the number of obtainable mutually independent coefficients is equal or less than the number of nonzero parameters k_{ij} of the considered compartmental model. Even if the relations between coefficients and k_{ij} are not linear, yet the given condition brings to the solvability of the problem.

Getting the analytical expressions of the numerator and denominator polynomial coefficients as functions of k_{ij} is extremely cumbersome; even if it may be used in the numerical estimation, if the system results to be identifiable, it is clearly more suitable to adopt a criterion which simply allows one to test whether the system is identifiable or not without computing the functions of k_{ij}. This is particularly useful if the systems turn out to be not identifiable and either a different experiment is to be planned, or a simpler model (identifiable through the planned experiment) is to be adopted.

For this purpose, the authors have suggested some test procedures [6], and here a new one is presented.

Consider the following expression for the transfer function matrix $\underline{G}(s)$ (cf [6] for computational details):

$$\underline{G}(s) = \frac{C.\mathrm{adj}\ (sI-A).B}{\det(sI-A)} = \frac{1}{\det(sI-A)}\Big\{ CB\left(s^{n-1}+\alpha_1 s^{n-2}+..+\alpha_{n-1}\right) + \\ + CAB\left(s^{n-2}+\alpha_1 s^{n-3}+..+\alpha_{n-2}\right) +..+ CA^{n-2}B(s+\alpha_1)+CA^{n-1}B\Big\} \tag{11}$$

$$\text{where}\quad \det(sI-A) = s^n+\alpha_1 s^{n-1}+ \alpha_2 s^{n-2}+..+\alpha_n \ .$$

$[\underline{G}(s)]_{ml}$ can be computed via (11) by taking $[CB]_{ml}, [CAB]_{ml}, ..., [CA^{n-1}B]_{ml}$ instead of the corresponding matrices.

In all we have $r_b r_c$ transfer functions $[\underline{G}(s)]_{ml} = N_{ml}/D$ from every input l to every output m.

Polynomial D, which is common to all transferences, is characterized by n coefficients $\alpha_1,..,\alpha_n$, and therefore it allows to write n equations in the parameters k_{ij}.

Analogously, the $r_b r_c$ numerators N_{ml} are characterized by $r_b r_c(n-1)$ coefficients; in fact the coefficient of s^{n-1} is 1 if the polynomial is of degree n-1. A knowledge of them allows one to write at most as many equations. However this number of equations must be reduced if the following situations occur:

1) N_{ml} has degree $p=n-1-v<n-1$;
2) N_{ml} has a w-th degree factor in common with D ;
3) N_{ml} has a z-th degree factor in common with one or more other numerators.

Hence it must be checked wether these situations occur and, in this case, v, w and z are to be evaluated. This purpose may be reached only by operations on the structure of the graph representing the system. In fact:

- situation 1) corresponds to the case in which in (11) all products $C A^i B$, i=0, 1...v-1 are null, which is easy to check on the graph, on the basis of the length (number of branches) of the shortest path from l to m; this length is v.
- situation 2) corresponds to the case where the subsystem controllable from l and observable from m does not coincide with the whole system as w compartments are not included (which is easily checked on the graph). In fact the reduced transfer function is a ratio of polynomials, where the denominator polynomial D' has degree n-w; if the transference is presented in standard form, with denominator polynomial D, then the numerator necessarily includes the factor D/D'.
- situation 3) corresponds to the case where the subsystem ml has a common cascade part (c.c.p.) with another subsystem m'l' which may be checked on the graph if there exist two nodes f, g such that: i) each node of c.c.p. is reachable from l and l' only through a path entering f and reaches m and m' through a path outgoing from g; ii) each node of c.c.p. can reach outer nodes only through g and can be reached from outer nodes only through f; the value of z is equal to the lowest power such that $[A^z]_{fg} \neq 0$ (see fig.3).

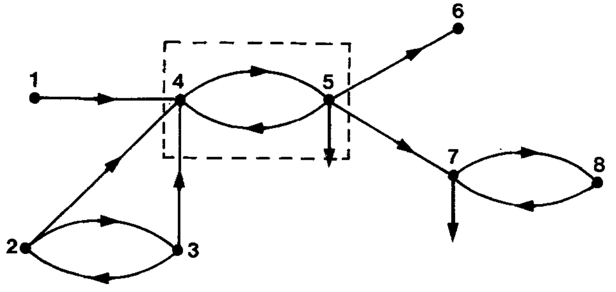
The number of independent equations in the k_{ij} system parameters is:

$$N = n + r_b \cdot r_c (n-1) - \sum_i v_i - \sum_j w_j - \sum_k (t_k - 1) z_k \qquad (12)$$

where, as seen above, the first addendum is related to the denominator, the second one is the maximum number of equations obtainable from the numerators, which is reduced by the terms indicated in the three sums, corresponding respectively to situations 1), 2), 3); the first sum refers to all numerators having degree less then n-1, the second one to numerators having some factors in common with the denominator and the third one to all cascade parts which are common to more ml subsystems; t_k is the number of m l subsystems having the same k-th cascade part.

N is to be compared with the total number N_k of the non zero k_{ij} to be determined. If $N < N_k$ the system is not identifiable by the chosen experiment and it is necessary either to modify the experiment or to adopt another model of simpler structure.

If $N \geq N_k$ the system is identifiable; if $N > N_k$ the system can be identified by a simpler experiment or the planned experiment allows one to identify a more complex model; however if the chosen experiment and the adopted model are used, it is possible either to utilize all equations to improve the estimates, or to delete $N-N_k$ equations to have a simpler computation (for this purpose we may eliminate either those equations which have complex analytical structure, or those which correspond to the most noisy channels, or those with highest parametric sensitivity).



$$B = \begin{bmatrix} 1 & 0 \\ 0 & 1 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \end{bmatrix} \quad ; \quad C = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

Figure 3 - Compartments 4 and 5 form the common cascade part between the four subsystems.

5. Flow chart

As seen in section 3 and 4 controllability and observability are necessary conditions for structural identifiability.

Referring to theorems 2.1, 2.2 and to matrix $R_1=R+I$, matrices R_1B and CR_1 can be used to test controllability and observability in a structural sense: $[R_1B]_{il}\neq 0$ denotes compartment i reachable from input l and $[CR_1]_{mi}\neq 0$ denotes compartment i observable from output m. The system is CC and CO if each row of R_1B and each column of CR_1 have at least one positive non zero entry. Note that controllability and observability always hold for strongly connected systems (see [5]).

Once controllability and observability have been tested, identifiability analysis can be performed following the line described in section 4. As the number of parameters obtainable from the denominator is always n, the numerators are considered. Putting matrices R_1B and CR_1 in boolean form, $(R_1B)_b$ and $(CR_1)_b$ respectively, their product $T=(CR_1)_b \times (R_1B)_b$ is computed. Each entry $[T]_{ml}$ represents the number of compartments controllable and observable from input l and output m. From T and A,B,C (see (12)) it is possible to know the number of parameters obtainable from the numerators, provided there are no common cascade parts. Note that for strongly connected compartmental systems each entry of T is equal to n, therefore T needs no computation (see above and section 2).

Given two subsystems ml and m'l', the possible common cascade part is a set of compartments S such that:

i) $[R_1B]_{il} > 0 \quad ; \quad [R_1B]_{il'} > 0 \quad ;$

$[CR_1]_{mi} > 0 \quad ; \quad [CR_1]_{m'i} > 0 \qquad \forall i \in S$

ii) $k_{ij} = 0 \quad \forall i \in S \quad , \forall j \notin S \quad$ except $i=f$;

$k_{ji} = 0 \quad \forall i \in S \quad , \forall j \notin S \quad$ except $j=g$.

If a common cascade part is found, a further simplification must be performed. Note that for strongly connected systems there are no common cascade parts due to their peculiar structure.
In fig.4 a general flow chart of the whole procedure is presented.

6. Example

The above presented procedure for testing identifiability was ap-

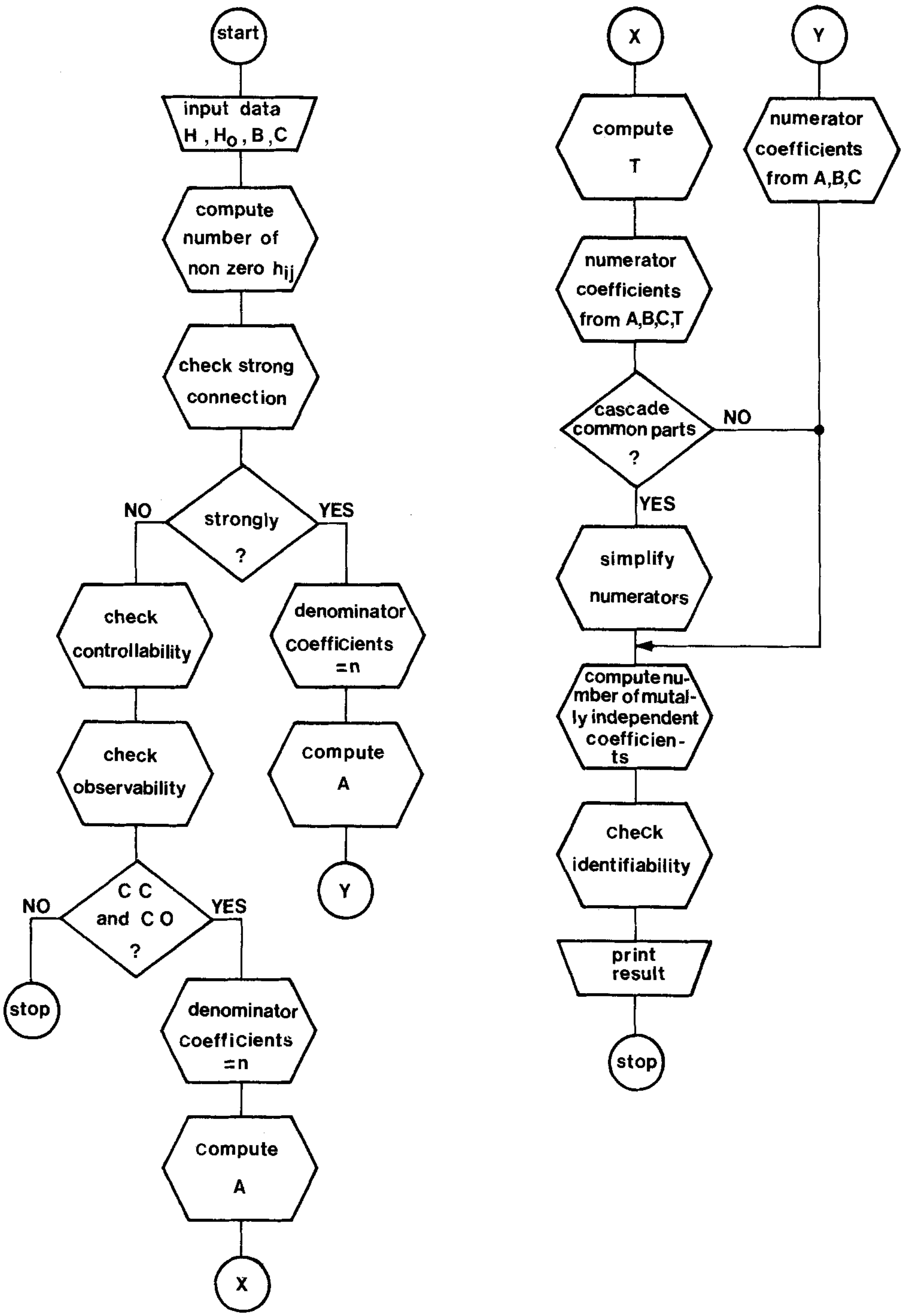


Figure 4 - The general flow chart of the procedure

plied to a compartmental model of copper metabolism, currently under investigation at the Istituto di Biologia Animale of the University of Padova. The model is shown in fig.5.

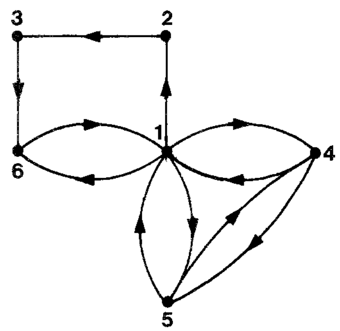


Figure 5 - A compartmental model of copper metabolism. Legend of compartments: 1- Plasma copper ; 2- Liver copper; 3- Copper-Ceruloplasmin ; 4- Copper-Albumin; 5- Copper in red blood cells; 6- Tissue copper.

Input-output tracer experiments can be performed with inputs in 1,5 and outputs in 1,3,4,5 variously combined. Structural identifiabi̲lity was analyzed with the program described above on an IBM 370/158 computer through a batch terminal. Results are reported in table 1. The system is strongly connected and is therefore always CC and CO.

Remark also that the simplest input-output configurations with input and output in compartment 1 and with input in 5 and output in 1 do not allow to identify the adopted model.

Table 1

Input(s) in compartments	Output(s) in compartments	Result
1	1	Not identifiable with 1 degree of freedom
1	1,3	Identifiable with 3 redundant equations
1	1,4	" " 4 " "
1	1,5	" " 4 " "
1	1,3,4	" " 8 " "
1	1,3,4,5	" " 13 " "
5	1	Not identifiable with 1 degree of freedom
5	1,3	Identifiable with 2 redundant equations
5	1,4	" " 4 " "
5	1,5	" " 4 " "
5	1,3,4	" " 7 " "
5	1,3,4,5	" " 12 " "
1,5	1	" " 4 " "
1,5	1,3	" " 11 " "
1,5	1,4	" " 14 " "
1,5	1,5	" " 14 " "
1,5	1,3,4	" " 21 " "
1,5	1,3,4,5	" " 31 " "

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