



Centrum voor Wiskunde en Informatica

REPORTRAPPORT

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BS-R9512 1995

Report BS-R9512
ISSN 0924-0659

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SMC is sponsored by the Netherlands Organization for Scientific Research (NWO). CWI is a member of ERCIM, the European Research Consortium for Informatics and Mathematics.

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Structural Identifiability of Linear Mamillary Compartmental Systems

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Abstract

In biology and mathematics compartmental systems are frequently used. System identification of systems based on physical laws often involves parameter estimation. Before parameter estimation can take place, we have to examine whether the parameters are structurally identifiable. In this paper we propose a test for the structural identifiability of linear mamillary compartmental systems. The method is based on the similarity transformation approach.

AMS Subject Classification (1991): 93B30, 93B15

Keywords and Phrases: system identification, compartmental systems, structural identifiability, positive linear systems, realization.

Note: This paper will appear in the Proceedings of the *Third European Control Conference, ECC95, Rome, September, 1995.*

1. INTRODUCTION

In this paper we shall investigate the structural identifiability of a certain class of compartmental systems, the so-called mamillary systems.

The class of compartmental systems is a frequently used class of models in biology and mathematics. Such a system consists of several compartments with more or less homogeneous concentrations of material. The compartments interact by processes of transportation and diffusion. Linear compartmental systems consist of inputs, states, and outputs, which are positive, so these systems are in system theory called positive linear systems. In many models we can use some prior knowledge on the system parameters, derived from physical laws and, in biological systems, from anatomical structure, biochemistry, and physiology. We can incorporate this structure in a system and obtain a class of *structured linear dynamic systems*.

Before estimating the parameters, we have to examine whether the parameters are structurally identifiable, i.e., whether we can in principle determine the parameters *uniquely* from the data. In much of the literature on identifiability only *local* identifiability is treated, see [9, 18]. There are several methods to test local identifiability, but only a few can test *global* identifiability. These include the Laplace transform approach, described in for example [1, 8, 11, 15], the Taylor series expansion approach, in for example [8, 15], and the exhaustive modeling or similarity transformation approach, see for example [3, 7, 8, 11, 14]. The last two approaches can also be applied, in an adapted version, to nonlinear systems, see [4, 19]. In this paper we mean *global* structural identifiability, when we speak about structural identifiability.

The outline of this paper is as follows. In section 2 the problem is formulated and the theorems we need are given. In section 3 the results for a class of mamillary systems are given.

2. DEFINITIONS AND PROBLEM FORMULATION

In this section the problem is posed. We shall use the notation and definitions given in [17, section 3], but we will consider the continuous-time case, which can easily be derived from the discrete-time version.

For linear dynamic systems of the form

$$\begin{aligned} \dot{x}(t) &= Ax(t) + Bu(t), & x(t_0) &= x_0, \\ y(t) &= Cx(t) + Du(t), \end{aligned} \quad (2.1)$$

with $A \in R^{n \times n}$, $B \in R^{n \times m}$, $C \in R^{k \times n}$, $D \in R^{k \times m}$, the impulse response function W is defined by

$$W(t) = Ce^{At}B, \quad t > 0,$$

and will be extended at $t = 0$ to $W(0) = D$. It can completely be characterized by the *Markov parameters*, defined as follows:

$$\begin{aligned} M(0) &= D, \\ M(j) &= \frac{d^{j-1}}{dt^{j-1}}W(t)|_{t=0} = CA^{j-1}B, \quad j = 1, 2, \dots \end{aligned}$$

We can view the Markov parameters $M(0), M(1), M(2), \dots$ as a function $M : N \rightarrow R^{k \times m}$. The set of Markov parameters $M : N \rightarrow R^{k \times m}$ will be denoted by $\mathbf{M}(k, m)$. Let $\text{LSP}(n, m, k) = R^{n \times n} \times R^{n \times m} \times R^{k \times n} \times R^{k \times m}$ consist of the elements (A, B, C, D) , i.e. the system parameters, as defined above. Define the map that associates the system parameters of a linear dynamic system with the Markov parameters $g : \text{LSP}(n, m, k) \rightarrow \mathbf{M}(k, m)$ by

$$g((A, B, C, D))(j) = \begin{cases} D, & j = 0, \\ CA^{j-1}B, & j > 0. \end{cases} \quad (2.2)$$

Structured linear dynamic systems are linear dynamic systems in which the system parameters A , B , C , and D are polynomial maps, defined on a parameter set $P \subset R^r$. In this paper the initial condition x_0 is assumed to be zero or known. In practice x_0 is often (partially) unknown. This problem is much more complicated, and is treated in [21], together with structural identifiability from the input-output observations.

A subclass of the linear dynamic systems is formed by the *positive linear systems*. Positive linear systems are linear dynamic systems in which the state, input, and output space are $X = R_+^n$, $U = R_+^m$, $Y = R_+^k$, respectively. A special class of structured positive linear dynamic systems is formed by the *linear compartmental systems*. For a general text on this class of systems, see [11]. Linear compartmental systems are positive linear systems of the form (2.1), for which conservation of mass holds. This corresponds with the following requirements on the matrices of continuous-time linear systems.

- all elements of B , C , and D are nonnegative;
- for $A = (a_{ij})_{i,j=1,\dots,n}$, we have

$$\begin{aligned} a_{ij} &\geq 0, & i, j \in \{1, \dots, n\}, & i \neq j, \\ a_{ii} &\leq - \sum_{j=1, j \neq i}^n a_{ji}, & \text{or } \sum_{j=1}^n a_{ji} &\leq 0, & i \in \{1, \dots, n\}. \end{aligned}$$

The model studied in this paper belongs to this class of systems.

The problem in this paper is whether the parameters of a structured linear system are structurally identifiable. For the definition of this concept we refer to [17, section 4]. Intuitively, structural

identifiability is whether we can uniquely determine the parameter values from the observations of inputs and outputs. Structural identifiability has been introduced by Bellman and Åström in [1]. Since then structural identifiability of linear and nonlinear structured systems has been studied by many authors.

The similarity approach for the test of structural identifiability is based on realization theory. For time-invariant finite-dimensional linear systems the realization problem has been solved. Hence equivalent conditions for structural identifiability may be formulated. For other classes of dynamic systems, such as positive linear systems, the realization problem is still open, so conditions for structural identifiability may not be known. For the realization of positive linear systems, see [20, 22].

Theorem 2.1 *Consider the structured linear dynamic system*

$$\begin{aligned}\dot{x}(t) &= A(p)x(t) + B(p)u(t), & x(t_0) &= x_0, \\ y(t) &= C(p)x(t) + D(p)u(t),\end{aligned}$$

with parametrization (P, f) , $f : P \rightarrow \text{SL}\Sigma P_1(n, m, k)$, $p \mapsto (A(p), B(p), C(p), D(p))$.

a *This system is structurally minimal if and only if it is structurally reachable and structurally observable.*

b *Assume that the system is structurally minimal. Then this parametrization is structurally identifiable from the Markov parameters if and only if for all $p, q \in P$ outside an algebraic set and $T \in R^{n \times n}$, nonsingular, the equations*

$$A(p) = TA(q)T^{-1}, \quad B(p) = TB(q), \quad C(p) = C(q)T^{-1}, \quad D(p) = D(q), \quad (2.3)$$

imply that $p = q$. Under the assumption stated and for all $q \in P$ outside an algebraic set, the system of equations (2.3) for the pair $(p, T) \in P \times R^{n \times n}$, with T nonsingular, has the unique solution $(p, T) = (q, I)$.

Proof. This result follows directly from the main result of realization theory for time-invariant finite-dimensional linear systems. For references see [2, 12, 13, 16].

Remark 2.2 A structured linear dynamic system is structurally reachable (structurally observable) if it is reachable (observable) for all $p \in P$ outside an algebraic set.

To obtain equations that are not too complex, we will rewrite condition (2.3) as follows:

$$A(p)T = TA(q), \quad B(p) = TB(q), \quad C(p)T = C(q), \quad D(p) = D(q). \quad (2.4)$$

Then we obtain polynomial equations that are linear in the elements of T , which are easier to handle.

For positive linear systems, i.e., with input, state, and output positive, the conditions given in Theorem 2.1 are only sufficient, not necessary.

Proposition 2.3 *Consider the structured positive linear system*

$$\begin{aligned}\dot{x}(t) &= A(p)x(t) + B(p)u(t), & x(t_0) &= x_0, \\ y(t) &= C(p)x(t) + D(p)u(t),\end{aligned}$$

with parametrization (P, f) , $f : P \rightarrow \text{SL}\Sigma P_1(n, m, k)$. *The parametrization (P, f) is structurally identifiable from the Markov parameters if the following conditions are satisfied:*

1. *this system is structurally reachable and structurally observable in the sense of ordinary linear dynamic systems;*
2. *Condition (2.3) implies $p = q$ for all $p, q \in P$, outside an algebraic set, and $T \in R^{n \times n}$, nonsingular.*

Proof. If a linear dynamic system is structurally minimal as an ordinary linear system, it is definitely minimal as a positive linear system. \square

3. A GENERAL MAMILLARY SYSTEM

In this section we shall derive results on the structural identifiability of a class of compartmental systems, in which there is a central compartment and only exchange between this central compartment and the other compartments. In the literature this kind of system is called a *mamillary* system, and the central compartment the *mother* compartment. In [5] also results on identifiability of mamillary systems are given, but these only concern local identifiability. The reason that the system in this section is globally identifiable, is that there is some prior knowledge about some parameter values. We will study the following mamillary system, in which there is an input u in the mother compartment and we can take measurements in the mother compartment, as shown in Figure 1. There is excretion to the environment from only one non-mother compartment, say, without loss of generality, from compartment x_1 .

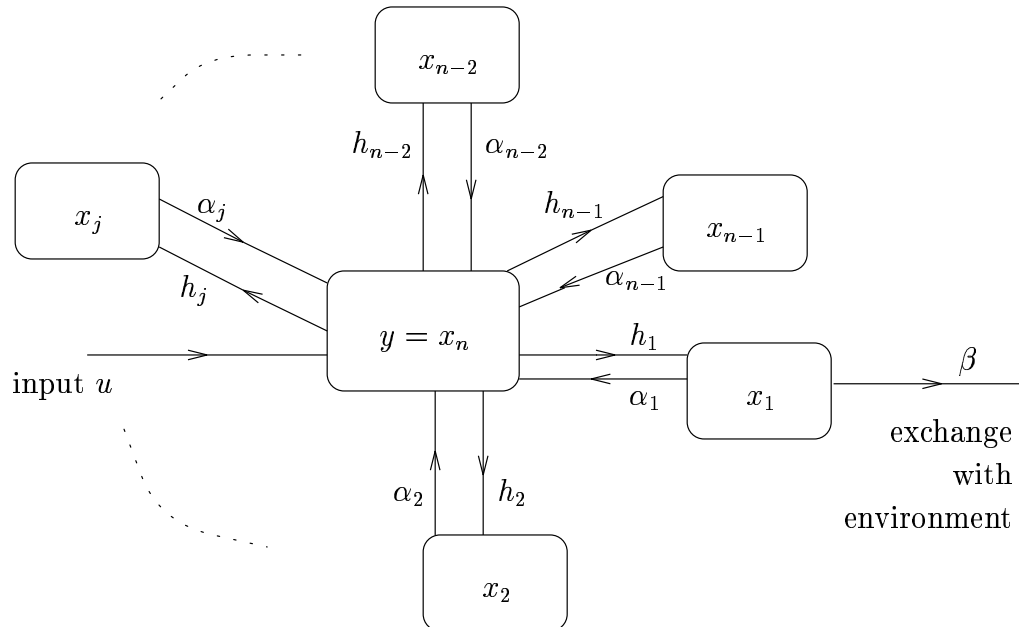


Figure 1: General mamillary model

The model is given by the following differential equations.

$$\begin{aligned}
 \dot{x}_1 &= -(\alpha_1 + \beta)x_1 + h_1x_n, \\
 \dot{x}_2 &= -\alpha_2x_2 + h_2x_n, \\
 \dot{x}_3 &= -\alpha_3x_3 + h_3x_n, \\
 &\vdots \\
 \dot{x}_{n-1} &= -\alpha_{n-1}x_{n-1} + h_{n-1}x_n, \\
 \dot{x}_n &= \sum_{i=1}^{n-1} \alpha_i x_i - h_n x_n + u,
 \end{aligned}$$

in which x_i denotes the concentration or amount of a substance in compartment i , α_i denotes the rate of exchange of the substance from compartment i into the mother compartment, β is the excretion rate, and h_i , for $i = 1, \dots, n - 1$, is the rate of exchange from the mother compartment

into compartment i . Finally, $h_n = \sum_{i=1}^{n-1} h_i$. The values of h_1, h_2, \dots, h_n are assumed to be known, which is realistic: we have several examples for which this assumption holds. We assume these values h_i to be nonzero and mutually unequal. The unknown parameters are $\alpha_1, \alpha_2, \dots, \alpha_{n-1}$, and β .

If we write the system in the compact form of a structured linear system, we will obtain

$$\begin{aligned} \dot{x} &= A(p)x + B(p)u, & x(t_0) &= x_0, \\ y &= C(p)x, \end{aligned} \tag{3.1}$$

with $x = (x_1 \ x_2 \ \dots \ x_n)^T$, $p = (\alpha_1, \alpha_2, \dots, \alpha_{n-1}, \beta)$,

$$A(p) = \begin{pmatrix} -\alpha_1 - \beta & 0 & \dots & 0 & h_1 \\ 0 & -\alpha_2 & \dots & 0 & h_2 \\ \vdots & & \ddots & & \vdots \\ 0 & 0 & \dots & -\alpha_{n-1} & h_{n-1} \\ \alpha_1 & \alpha_2 & \dots & \alpha_{n-1} & -h_n \end{pmatrix}, \quad B(p) = \begin{pmatrix} 0 \\ 0 \\ \vdots \\ 0 \\ 1 \end{pmatrix},$$

$C(p) = (0 \ \dots \ 0 \ 1)$. Formally, this system is parametrized by the parametrization (P, f) , with

$$\begin{aligned} P &= \{(\alpha_1, \alpha_2, \dots, \alpha_{n-1}, \beta) \in R_+^n \subset R^n\} \\ f(p) &= (A(p), B(p), C(p)) \quad \text{for } p \in P. \end{aligned}$$

Theorem 3.1 *The parametrization (P, f) of the structured linear dynamic system described above is structurally identifiable from the Markov parameters as a positive linear system.*

For the proof of Theorem 3.1 we need the following lemma.

Lemma 3.2 *Consider the linear dynamic system*

$$\begin{aligned} \dot{x} &= Ax + Bu, & x(t_0) &= x_0, \\ y &= Cx, \end{aligned} \tag{3.2}$$

with $x \in R^n$, $u \in R$, $y \in R$,

$$A = \begin{pmatrix} \alpha_1 & 0 & \dots & 0 & \gamma_1 \\ 0 & \alpha_2 & \dots & 0 & \gamma_2 \\ \vdots & & \ddots & & \vdots \\ 0 & 0 & \dots & \alpha_{n-1} & \gamma_{n-1} \\ \beta_1 & \beta_2 & \dots & \beta_{n-1} & \delta \end{pmatrix}, \quad B = \begin{pmatrix} 0 \\ 0 \\ \vdots \\ 0 \\ 1 \end{pmatrix},$$

$C = (0 \ \dots \ 0 \ 1)$. Then

1. (A, B) is reachable if and only if $\begin{cases} \gamma_i \neq 0, & i = 1, \dots, n-1, \\ \alpha_i \neq \alpha_j, & i, j = 1, \dots, n-1, \quad i \neq j. \end{cases}$
2. (A, C) is observable if and only if $\begin{cases} \beta_i \neq 0, & i = 1, \dots, n-1, \\ \alpha_i \neq \alpha_j, & i, j = 1, \dots, n-1, \quad i \neq j. \end{cases}$

Proof of Lemma 3.2. We will use the reachability condition of Hautus, [10]:

$$(A, B) \text{ is reachable if and only if } \text{rank}(\lambda I - A \ B) = n, \quad \text{for all } \lambda \in C.$$

1. For (3.2) we have

$$\begin{aligned} \text{rank}(\lambda I - A \ B) &= \text{rank} \begin{pmatrix} \lambda - \alpha_1 & 0 & \cdots & 0 & -\gamma_1 & 0 \\ 0 & \lambda - \alpha_2 & \cdots & 0 & -\gamma_2 & 0 \\ \vdots & & \ddots & & \vdots & \vdots \\ 0 & 0 & \cdots & \lambda - \alpha_{n-1} & -\gamma_{n-1} & 0 \\ -\beta_1 & -\beta_2 & \cdots & -\beta_{n-1} & -\delta & 1 \end{pmatrix} \\ &= \text{rank}(D_\lambda) + 1, \end{aligned}$$

with

$$D_\lambda := \begin{pmatrix} \lambda - \alpha_1 & 0 & \cdots & 0 & -\gamma_1 \\ 0 & \lambda - \alpha_2 & \cdots & 0 & -\gamma_2 \\ \vdots & & \ddots & & \vdots \\ 0 & 0 & \cdots & \lambda - \alpha_{n-1} & -\gamma_{n-1} \end{pmatrix} \in R^{(n-1) \times n}.$$

(\Leftarrow) For $\lambda \neq \alpha_i$, $i = 1, \dots, n-1$, we have $\text{rank}(D_\lambda) = n-1$. For $\lambda = \alpha_i$, we have

$$\left. \begin{array}{l} \gamma_i \neq 0, \quad i = 1, \dots, n-1, \\ \alpha_j \neq \alpha_i, \quad i, j = 1, \dots, n-1, \quad j \neq i \end{array} \right\} \text{ imply } \text{rank}(D_\lambda) = n-1.$$

(\Rightarrow) Assume $\gamma_i = 0$. Then, for $\lambda = \alpha_i$, the i th row of D_λ is equal to zero, so $\text{rank}(D_\lambda) < n-1$. Assume $\alpha_i = \alpha_j$ for some $i, j = 1, \dots, n-1$, $i \neq j$. Then, for $\lambda = \alpha_i$, the i th and the j th column of D_λ are equal to zero, so $\text{rank}(D_\lambda) < n-1$.

It follows that (A, B) is reachable if and only if $\left\{ \begin{array}{l} \gamma_i \neq 0, \quad i = 1, \dots, n-1, \\ \alpha_i \neq \alpha_j, \quad i, j = 1, \dots, n-1, \quad i \neq j. \end{array} \right.$

2. This follows from the fact that (A, C) is observable if and only if (A^T, C^T) is reachable. \square

Remark 3.3 The system (3.2) is an example of a general input-output hierarchical system, defined by Davison [6]. In that paper Davison proves that such a system is controllable and observable for almost all interconnection gains (in Lemma 3.2 the β_i and γ_i) and almost all output gain matrices (in Lemma 3.2 the α_i and δ). But this does not say anything about what happens if for example $\alpha_j = \beta_j$ for some j . This can just be the exception which lies in the algebraic set, or the hyper-surface in [6].

Proof of Theorem 3.1. For the problem of structural identifiability we will look at this positive linear system as an ordinary linear system. For Theorem 2.1, we first have to check structural reachability and structural observability. From Lemma 3.2 it follows that $(A(p), B(p))$ is reachable if and only if

$$\left\{ \begin{array}{l} h_i \neq 0, \quad i = 1, 2, \dots, n-1, \\ \alpha_i \neq \alpha_j, \quad i, j = 2, 3, \dots, n-1, \quad i \neq j, \\ \alpha_1 + \beta \neq \alpha_i, \quad i = 2, 3, \dots, n-1, \end{array} \right.$$

and $(A(p), C(p))$ is observable if and only if

$$\left\{ \begin{array}{l} \alpha_i \neq 0, \quad i = 1, 2, \dots, n-1, \\ \alpha_i \neq \alpha_j, \quad i, j = 2, 3, \dots, n-1, \quad i \neq j, \\ \alpha_1 + \beta \neq \alpha_i, \quad i = 2, 3, \dots, n-1, \end{array} \right.$$

It follows that the system will be structurally reachable and structurally observable, if we take for the algebraic set

$$S = \left\{ (\alpha_1, \alpha_2, \dots, \alpha_{n-1}, \beta) \in \mathbb{R}^n \mid \alpha_1 \prod_{i=2}^{n-1} \{(\alpha_1 + \beta - \alpha_i) \alpha_i \prod_{j=i+1}^{n-1} (\alpha_j - \alpha_i)\} = 0 \right\}.$$

Now we may check structural identifiability by the similarity approach. For $p \in \mathbb{R}^n$, find all $\tilde{p} \in \mathbb{R}^n$ and $T \in \mathbb{R}^{n \times n}$, such that

$$C(p)T = C(\tilde{p}), \quad (3.3)$$

$$B(p) = TB(\tilde{p}), \quad (3.4)$$

$$A(p)T = TA(\tilde{p}). \quad (3.5)$$

From (3.3) and (3.4) it immediately follows that T has the following form:

$$T = \begin{pmatrix} t_{11} & \cdots & t_{1,n-1} & 0 \\ \vdots & & \vdots & \vdots \\ t_{n-1,1} & \cdots & t_{n-1,n-1} & 0 \\ 0 & \cdots & 0 & 1 \end{pmatrix}. \quad (3.6)$$

The first row of (3.5) gives the following equations

$$\begin{aligned} -(\alpha_1 + \beta)t_{11} &= -t_{11}(\tilde{\alpha}_1 + \tilde{\beta}), \\ -(\alpha_1 + \beta)t_{1k} &= -t_{1k}\tilde{\alpha}_k, \quad k = 2, 3, \dots, n-1, \end{aligned} \quad (3.7)$$

and

$$h_1 = \sum_{j=1}^{n-1} t_{1j}h_j. \quad (3.8)$$

For $i = 2, 3, \dots, n-1$, the i th row of (3.5) gives the following equations

$$\begin{aligned} -\alpha_i t_{i1} &= -t_{i1}(\tilde{\alpha}_1 + \tilde{\beta}), \\ -\alpha_i t_{ik} &= -t_{ik}\tilde{\alpha}_k, \quad k = 2, 3, \dots, n-1, \end{aligned} \quad (3.9)$$

and

$$h_i = \sum_{j=1}^{n-1} t_{ij}h_j. \quad (3.10)$$

Outside S , $\alpha_1 + \beta, \alpha_2, \alpha_3, \dots, \alpha_{n-1}$ are mutually unequal, so in every column of T there is at most one nonzero element. Indeed, assume t_{ik} and t_{jk} , $i \neq j$, are both nonzero. To make notation easier, we take $i, j, k \in \{2, 3, \dots, n-1\}$, but for $i, j, k \in \{1, 2, \dots, n-1\}$ the same reasoning holds. Then (3.9) gives $\alpha_i t_{ik} = t_{ik}\tilde{\alpha}_k$ and $\alpha_j t_{jk} = t_{jk}\tilde{\alpha}_k$, from which it follows that $\alpha_i = \alpha_j$. Contradiction. Moreover, from the non-singularity of T it follows that exactly one element in every row and every column of T is nonzero.

Assume $t_{ij} \neq 0$ for some $i, j \in \{2, 3, \dots, n-1\}$. Then it follows from (3.9), $-\alpha_i t_{ij} = -t_{ij}\tilde{\alpha}_j$, that $\tilde{\alpha}_j = \alpha_i$, and from the j th entry of the n th row of (3.5) that $\alpha_i t_{ij} = \tilde{\alpha}_j$. So $t_{ij} = 1$. But then (3.10) gives $h_i = h_j$, which, by assumption on the h_i being different, is only possible if $i = j$. Consequently we have $t_{22} = t_{33} = \cdots = t_{n-1,n-1} = 1$, $t_{ij} = 0$ for $i, j \in \{1, 2, \dots, n-1\}$, $i \neq j$, and therefore $t_{11} \neq 0$. Now (3.8) gives $h_1 = t_{11}h_1$, which implies $t_{11} = 1$. So $T = I$ and $\tilde{p} = p$. With Theorem 2.1 and Proposition 2.3 it follows that the parametrization is structurally identifiable as a positive linear system. \square

Assume there is not only excretion from compartment x_1 to the environment, but also from a non-mother compartment, say, compartment x_j , for some $j \in \{2, 3, \dots, n-1\}$. Then in the matrix $A(p)$ the j, j -entry is $-\alpha_j - \gamma$ with γ unknown. With Lemma 3.2 the system is structurally reachable and structurally observable, but the parametrization is not structurally identifiable. Indeed, T , with $t_{11} = t_{jj} = 0$, $t_{1j} = h_1/h_j$, $t_{j1} = h_j/h_1$, and the other elements as above, satisfies (3.3), (3.4),

and (3.5) for a suitable \tilde{p} . So it is necessary to restrict to only one non-mother compartment with excretion to the environment.

At the other hand, if there is besides from compartment x_1 also excretion from the mother compartment, x_n , to the environment, we obtain the following structured linear system,

$$\begin{aligned}\dot{x} &= A(p)x + B(p)u, & x(t_0) &= x_0, \\ \dot{y} &= C(p)x,\end{aligned}$$

with x as above, $p = (\alpha_1, \alpha_2, \dots, \alpha_{n-1}, \beta, \gamma)$,

$$A(p) = \begin{pmatrix} -\alpha_1 - \beta & 0 & \cdots & 0 & h_1 \\ 0 & -\alpha_2 & \cdots & 0 & h_2 \\ \vdots & & \ddots & & \vdots \\ 0 & 0 & \cdots & -\alpha_{n-1} & h_{n-1} \\ \alpha_1 & \alpha_2 & \cdots & \alpha_{n-1} & -h_n - \gamma \end{pmatrix},$$

and $B(p)$ and $C(p)$ as above. Formally, this system is parametrized by the parametrization (P_1, f_1) , with

$$\begin{aligned}P_1 &= \{(\alpha_1, \alpha_2, \dots, \alpha_{n-1}, \beta, \gamma) \in R_+^{n+1} \subset R^{n+1}\} \\ f_1(p) &= (A(p), B(p), C(p)) \quad \text{for } p \in P_1.\end{aligned}$$

Theorem 3.4 *The parametrization (P_1, f_1) of the structured linear dynamic system described above is structurally identifiable from the Markov parameters as a positive linear system.*

Proof. Because in Lemma 3.2 there exist no restrictions on δ , which is equivalent to $-h_n - \gamma$ in the case of the parametrization (P_1, f_1) above, the pair $(A(p), B(p))$ will be reachable and $(A(p), C(p))$ will be observable outside S defined in the proof of Theorem 3.1. Now we may check structural identifiability by the similarity approach. For $p \in R^{n+1}$, find all $\tilde{p} \in R^{n+1}$ and $T \in R^{n \times n}$, such that

$$C(p)T = C(\tilde{p}), \tag{3.11}$$

$$B(p) = TB(\tilde{p}), \tag{3.12}$$

$$A(p)T = TA(\tilde{p}). \tag{3.13}$$

From (3.11) and (3.12) it immediately follows that T is of the form (3.6). Now the n th entry of the n th row of (3.13) gives

$$-h_n - \gamma = -h_n - \tilde{\gamma},$$

so $\tilde{\gamma} = \gamma$. The remaining part of the proof is equivalent to the proof of Theorem 3.1. \square

4. CONCLUSIONS

For mamillary systems with input and observations in the mother compartment and excretion only from one non-mother compartment, it is shown that the unknown parameters are (globally) structurally identifiable from the Markov parameters. Also some results on structural reachability and structural observability are given.

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