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J.M. van den Hof

Department of Operations Reasearch, Statistics, and System Theory

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CWI
P.O. Box 94079
1090 GB Amsterdam
The Netherlands

Structural Identifiability from Input-Output Observations of Linear Compartmental Systems

J.M. van den Hof
CWI
P.O. Box 94079, 1090 GB Amsterdam, The Netherlands

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 tests for the structural identifiability of linear compartmental systems are proposed. The method is based on the similarity transformation approach. New contributions in the theory are the conditions for structural identifiability of structured positive linear systems. In addition, structural identifiability from the Markov parameters is extended to structural identifiability from the input-output data, in which the initial condition is (partially) unknown and non negligible. Finally, conditions are presented for structural identifiability of a sampled continuous-time linear dynamic system.

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1. Introduction

Mathematical systems that are frequently used in biology and mathematics are compartmental systems. Such a system consists of several compartments with more or less homogeneous concentrations of material. The compartments interact by processes of transportation and diffusion.

In this paper we shall study linear compartmental systems consisting of inputs, states, and outputs. These variables are positive, so these systems are in system theory called positive linear systems. In biology we often have some prior knowledge on the structure of the model. Therefore we also fit compartmental systems in the class of structured linear systems, in which the parameters of the system depend on a parameter vector.

Before estimating the parameters, we should 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 [10, 26]. If a system is locally identifiable, it may be the case that a countable number of solutions exist, so the parameters cannot uniquely be estimated from the data. If a parameter is locally identifiable but not globally, then the input-output data can be represented by at least two different parameter estimates for this system. So we cannot decide which solution is a good estimate. In this paper attention is therefore focused on global identifiability. There are several methods to test local identifiability, but only a few of these can test *global* identifiability. These include the Laplace transform approach, described in for example [1, 9, 13, 22], the Taylor series expansion approach, in for example [9, 22], and the exhaustive modeling or similarity transformation approach, see for example [3, 8, 9, 13, 17]. The last two approaches can also be applied, in an adapted version, to nonlinear systems, see [4, 27]. In [21] a method using differential algebra is given. In this paper we mean *global* structural identifiability, when we speak of structural identifiability.

It is difficult to predict a priori which approach will involve the least computational effort, but we decided to use the similarity transformation approach for linear systems. A reason for this choice is that the set of equations we have to solve consists of polynomials of smaller order than the sets of equations appearing in most other approaches. According to Lecourtier and Raksanyi, in [17], the similarity transformation approach is one of the most powerful when tested through symbolic computation packages.

Because free and long-term experimentation is usually not possible, the estimation and identifiability of the parameters of systems for human beings and animals involve more problems than for e.g. electrical or mechanical systems, due to the scarcity of data. In many cases the initial condition is (partially) unknown and non negligible. New in this paper is that the structural identifiability from the Markov parameters is extended via structural identifiability from both the Markov parameters and the initial condition response to structural identifiability from input-output data, for both discrete-time and sampled continuous-time linear dynamic systems. Also sufficient conditions for structural identifiability of structured positive linear systems are given. These aspects are not treated explicitly in the literature of system identification of compartmental systems. The main results of this paper are Proposition 2.10 and the results in Section 3.

In this paper we shall discuss the structural identifiability of three models. Two of them have been developed at the RIVM (Rijksinstituut voor Volksgezondheid en Milieuhygiëne, National Institute of Public Health and Environmental Protection), Bilthoven, The Netherlands. At the RIVM investigations are performed to support policy makers in decision making on areas of public health and environment. Decisions are based on the evaluation of control measures by mathematical systems. The structural identifiability of a more general compartmental model has been discussed in [29].

This paper is organized as follows. In Section 2 the definitions and the theory for the test of structural identifiability from the Markov parameters and the initial parameters are given. In Section 3 the structural identifiability from the input-output data is treated. The three models are examined in Section 4, 5, and 6, respectively.

2. Definitions and problem formulation

In this section formal definitions are given and the problem is posed.

2.1 Linear systems

We shall start with a general definition of a linear dynamic system. A dynamic system is a mathematical description for a phenomenon that arises in economy, technology, environment, etc. It consists of inputs, states, outputs, and relations between these variables.

The notation we use is as follows. $Z_+ = \{1, 2, \ldots\}$, $Z_n = \{1, 2, \ldots, n\}$, $N = \{0, 1, 2, \ldots\}$, R is the set of real numbers, R^n is the n-dimensional vector space over R, and $R^{n\times m}$ is the set of $n \times m$ matrices with elements in R. $R_+ = [0, \infty)$ is the set of positive real numbers. Denote by R_+^n the set of n-tuples of the positive real numbers.

Definition 2.1 A *linear dynamic system (continuous-time, time-invariant linear dynamic system* in *state space form)* is a dynamic system in which the state, input, and output space are $X = R^n$, $U = R^m$, $Y = R^k$, respectively, the time index set is $T \subseteq R$. The state, input, and output function are related by

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

where $A \in R^{n\times n}$, $B \in R^{n\times m}$, $C \in R^{k\times n}$, $D \in R^{k\times m}$. Denote the system by σ and the class of linear dynamic systems by $\mathrm{L}\Sigma$. The indices n, m, k, the matrices A, B, C, D, and the initial state x_0 are called the *system parameters.* Denote these system parameters by

$$\mathrm{L\Sigma P}(n,m,k) = R^{n\times n}\times R^{n\times m}\times R^{k\times n}\times R^{k\times m}\times R^{n},\quad (A,B,C,D,x_0)\in \mathrm{L\Sigma P}(n,m,k).\quad \Box$$

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 structural information in linear dynamic systems by the following definition.

Definition 2.2 A *structured linear dynamic system* is a linear dynamic system together with a *parameter set* $P \subset R^r$ for some $r \in \mathbf{N}$ and maps

$$A: P \to R^{n\times n},\quad B: P\to R^{n\times m},\quad C: P\to R^{k\times n},\quad D: P\to R^{k\times m},\quad x_0: P\to R^n.$$

The dynamic system will be represented by the equations

$$\begin{aligned}\dot{x}(t) &= A(p)x(t)+B(p)u(t),\quad x(t_0)=x_0(p),\\ y(t) &= C(p)x(t)+D(p)u(t).\end{aligned}\tag{2.2}$$

Denote

$$\mathrm{SL\Sigma P}(n,m,k) = \{(A(p),B(p),C(p),D(p),x_0(p))\in \mathrm{L\Sigma P}(n,m,k)\mid p\in P\}$$

and let $f: P\to \mathrm{SL\Sigma P}(n,m,k)$ be the *parametrization map*

$$f(p) = (A(p),B(p),C(p),D(p),x_0(p)).\quad \Box$$

From now on, f is assumed to be a polynomial map, unless stated otherwise. For most problems this is not a restriction, since if f is not a polynomial map, a re-parametrization will give a polynomial map, as can be seen in the case studies in Section 4, 5, and 6. In practice also the initial condition is often (partially) unknown. Therefore the definition has been extended by the map

$$x_0: P\to R^n,\quad x(t_0)=x_0(p).$$

Definition 2.3 Consider a subset $\mathrm{L\Sigma_1}$ of the set of linear dynamic systems $\mathrm{L\Sigma}$, and denote the corresponding set of parameters by $\mathrm{L\Sigma P_1}$ and $\mathrm{L\Sigma P}$. A *parametrization* of the set $\mathrm{L\Sigma P_1}$ is a tuple (P,f), for a set $P\subset R^r$ and a map $f: P\to \mathrm{L\Sigma P_1}$ that is onto or surjective. P is said to be the *parameter set* and f the *parametrization map*. $\Box$

The key property of a parametrization, say (P,f) of $\mathrm{L\Sigma P_1}$, is that it is onto: every element of $\mathrm{L\Sigma P_1}$ is the image of an element in P under f.

The relation between inputs and outputs of a linear dynamic system in state space form is given by the external behaviour of the linear dynamic system (2.1):

$$y(t) = Ce^{A(t-t_0)}x(t_0) + \int_{t_0}^{t} W(t-s)u(s)ds + Du(t),$$

in which $W: T\to R^{k\times m}$ is the function

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

W will be extended at $t=0$ to $W(0)=D$. The function W is called the *impulse response function* of the system. It can completely be characterized by *Markov parameters*, defined as follows:

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

We can view the Markov parameters $M(0), M(1), M(2),\ldots$ as a function $M: \mathbf{N}\to R^{k\times m}$. Denote by $\mathbf{M}(k,m)$ the set of Markov parameters $M:\mathbf{N}\to R^{k\times m}$. Define the map that associates the system parameters of a linear dynamic system with the Markov parameters $g: \mathrm{L\Sigma P}(n,m,k)\to \mathbf{M}(k,m)$ by

$$g((A,B,C,D,x_0))(j) = \begin{cases} D, & j=0, \\ CA^{j-1}B, & j=1,2,\ldots. \end{cases} \tag{2.3}$$

The function $V : T \to R^k$, defined by

$$V(t) = Ce^{A(t-t_0)}x(t_0), \quad t \geq t_0,$$

is called the *initial condition response function* of the system. This function can be characterized by the *initial parameters*, defined as follows:

$$\begin{aligned} N(0) &= 0, \\ N(j) &= \frac{d^{j-1}}{dt^{j-1}}V(t)|_{t\downarrow t_0} = \frac{d^{j-1}}{dt^{j-1}}Ce^{A(t-t_0)}x(t_0)|_{t=t_0} = CA^{j-1}x_0, \quad j=1,2,\ldots. \end{aligned}$$

The initial parameters $N(0), N(1), N(2), \ldots$ can be viewed as a function $N : \boldsymbol{N} \to R^k$. Denote by $\mathcal{N}(k)$ the set of initial parameters $N : \boldsymbol{N} \to R^k$. Define the map that associates the system parameters of a linear dynamic system with the initial parameters $g_1 : \mathrm{L\Sigma P}(n,m,k) \to \mathcal{N}(k)$ by

$$g_1((A,B,C,D,x_0))(j) = \begin{cases} 0, & j=0, \\ CA^{j-1}x_0, & j=1,2,\ldots. \end{cases} \tag{2.4}$$

The other way around: in the literature (A,B,C,D) is called a realization of the impulse response function $W(t)$, and it is called a minimal realization if the dimension of the state space is as small as possible [24]. In this paper the concept of realization is extended, as defined below.

Definition 2.4 Consider the set $\mathbf{M}(k,m) \times \mathcal{N}(k)$. A *realization* of $\{(M(j),N(j)), j \in \boldsymbol{N}\} \in \mathbf{M}(k,m) \times \mathcal{N}(k)$ is a quintuple

$$(A,B,C,D,x_0) \in \mathrm{L\Sigma P}(n,m,k),$$

such that

$$\begin{aligned} M(0) &= D, \\ M(j) &= CA^{j-1}B, \quad j=1,2,\ldots, \\ N(0) &= 0, \\ N(j) &= CA^{j-1}x_0, \quad j=1,2,\ldots. \end{aligned}$$

A realization is said to be *minimal* if there exists no $n_1 \in \boldsymbol{N}$, $n_1 < n$, for which there exists a realization in $\mathrm{L\Sigma P}(n_1,m,k)$. The realization is called *weakly reachable* if

$$\mathrm{rank}\begin{pmatrix} B & AB & \cdots & A^{n-1}B & x_0 & Ax_0 & \cdots & A^{n-1}x_0 \end{pmatrix} = n,$$

and then the pair $(A,(B \;\; x_0))$ is called a *reachable pair.* □

It can easily be seen that reachability of the realization, i.e. the pair (A,B) is reachable, implies weak reachability of the realization.

Proposition 2.5 *The quintuple* $(A,B,C,D,x_0) \in \mathrm{L\Sigma P}(n,m,k)$ *is a minimal realization of the associated* $\{(M(j),N(j)), j \in \boldsymbol{N}\}$ *if and only if it is weakly reachable and observable, i.e.*

$(A,(B \;\; x_0))$ *is a reachable pair*

and

(A,C) *is an observable pair.*

Proof. Define $\tilde{B} = (B \;\; x_0) \in R^{n\times(m+1)}$ and $\tilde{D} = (D \;\; 0) \in R^{k\times(m+1)}$. Then $\tilde{M}(\cdot)$ can be defined as follows:

$$\begin{aligned}\tilde{M}(0) &:= \tilde{D} = (D \;\; 0) = \begin{pmatrix} M(0) & N(0) \end{pmatrix},\\ \tilde{M}(j) &:= CA^{j-1}\tilde{B} = \begin{pmatrix} CA^{j-1}B & CA^{j-1}x_0 \end{pmatrix} = \begin{pmatrix} M(j) & N(j) \end{pmatrix}, \quad j = 1,2,\ldots.\end{aligned}$$

The result follows from the known result in realization theory of time-invariant finite-dimensional linear systems: $(A, \tilde{B}, C, \tilde{D})$ is a minimal realization of the associated $(\tilde{M}(j), j \in \mathbb{N})$ if and only if $(A, \tilde{B})$ is a reachable pair and (A, C) is an observable pair. □

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 positive linear systems is formed by the *linear compartmental systems*. For a general text on this class of systems, see [13]. 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 $A = (a_{ij})_{i,j=1,\ldots,n}$, we have

$$a_{ij} \geq 0, \qquad i,j \in \{1,\ldots,n\},\; i \neq j,$$

$$a_{ii} \leq -\sum_{j=1, j\neq i}^{n} a_{ji}, \text{ or } \sum_{j=1}^{n} a_{ji} \leq 0, \quad i \in \{1,\ldots,n\}.$$

The models studied in this paper belong to this class of systems.

2.2 Structural Identifiability from Markov parameters and initial parameters

The problem in this paper is whether the parameters of a structured linear system are structurally identifiable. This concept is defined below. 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. Consider a structured linear dynamic system of the form (2.2) with corresponding Markov parameters

$$M_p(j) = \begin{cases} D(p), & j = 0,\\ C(p)A(p)^{j-1}B(p), & j = 1,2,\ldots, \end{cases} \tag{2.5}$$

and corresponding initial parameters

$$N_p(j) = \begin{cases} 0, & j = 0,\\ C(p)A(p)^{j-1}x_0(p), & j = 1,2,\ldots. \end{cases} \tag{2.6}$$

In the literature the following assumptions are made for structural identifiability.

Assumption 2.6 *Conditions required for the use of structural identifiability from the Markov parameters of a structured linear dynamic system.*

1. *The dynamic system is stable;*
2. *The time horizon of the experiment is long relative to the dynamics of the system;*
3. *The possibility exists to experiment freely with the input function.*

If assumptions 1 and 2 are satisfied, then the effect of the initial conditions may be neglected as time proceeds. The resulting map from inputs to outputs is then

$$y(t) = \int_{t_0}^{t} W_p(t-s)u(s)ds + W_p(0)u(t),$$

where $W_p : T \to R^{k\times m}$ is defined by

$$W_p(t) = \begin{cases} D(p), & t = 0, \\ C(p)e^{A(p)t}B(p), & t > 0. \end{cases}$$

Moreover, if also assumption 3 is satisfied, then it is possible to obtain the Markov parameters $M_p(k)$ from the observations of inputs and outputs. Therefore knowledge of the inputs and outputs is equivalent, under the conditions stated above, to knowledge of the Markov parameters. Then identifiability of the parameters of a structured linear dynamic system may be phrased in terms of the Markov parameters. For linear dynamic systems derived from biological models, the assumptions 2 and 3 are in general not satisfied. Free and long-term experimentation on human beings and animals is usually not possible. Therefore the effect of the initial conditions cannot be neglected. So, in this subsection, not only structural identifiability from the Markov parameters is treated, but also structural identifiability from the initial parameters. Also the knowledge of the Markov parameters and the initial conditions cannot just be derived from the inputs and outputs. The structural identifiability from the input-output data will be considered in Section 3.

In the following we use terminology of algebraic geometry, see [16, X,§2,3]. A property is said to be *generic* if it holds for all $p \in P \subset R^r$ outside an algebraic set, and if there exists at least one $p \in P$ for which it holds. An *algebraic set* is defined by a finite set of polynomials according to

$$\{p \in P \quad | \quad f_1(p) = 0, \ldots, f_\kappa(p) = 0\},$$

where $f_i : P \to R, \quad i = 1, \ldots, \kappa$ are polynomials. Intuitively, a property is generic if it holds everywhere except at the zeros of some polynomials.

Definition 2.7 Consider a structured linear dynamic system in state space form

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

with parametrization (P, f), $f : P \to \mathrm{SL\Sigma P}_1(n,m,k)$. Let $g : \mathrm{SL\Sigma P}_1(n,m,k) \to \mathbf{M}(k,m)$ be as defined in (2.3). Let $g_1 : \mathrm{SL\Sigma P}_1(n,m,k) \to \mathcal{N}(k)$ be as defined in (2.4). The parametrization (P, f) is said to be *structurally identifiable from the Markov parameters and the initial parameters* if the map

$$(g, g_1) \circ f : P \to \mathbf{M}(k,m) \times \mathcal{N}(k), \qquad \text{i.e.} \qquad (g \circ f(p), g_1 \circ f(p)) = (M_p, N_p),$$

see (2.5) and (2.6), is injective for all $p \in P$ outside an algebraic set. □

Note that in general the map $(g, g_1) \circ f$ is not onto, the image of P under $(g, g_1) \circ f$ is a proper subset of $\mathbf{M}(k,m) \times \mathcal{N}(k)$. If there is no initial condition response, i.e. x_0 is negligible, then $g_1 \equiv 0$ and (P, f) is said to be structurally identifiable from the Markov parameters if $g \circ f : P \to \mathbf{M}(k,m)$ is injective for all $p \in P$ outside an algebraic set. On the other hand, if there is no input, i.e. $u = 0$ and $B = 0$, then $g \equiv 0$ and (P, f) is said to be structurally identifiable from the initial parameters if the map $g_1 \circ f : P \to \mathcal{N}(k)$ is injective for all $p \in P$ outside an algebraic set. Both cases can be seen as special cases of Definition 2.7, so only the general case is treated. This general case is new in the theory of structural identifiability. In most of the literature only structural identifiability from Markov parameters has been considered.

The similarity approach for the test of structural identifiability is based on realization theory, see for example [24]. For time-invariant finite-dimensional linear systems the realization problem has been solved. From the solution of this realization problem, the realization of $\{(M(j), N(j)), j \in N\}$ can easily be derived, by setting $\tilde{B} = (B \quad x_0)$ and $\tilde{D} = (D \quad 0)$. 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 [28, 30]. The necessary and sufficient conditions for structural identifiability, to be derived in the sequel, may be calculated with the aid of a symbolic calculation program.

Definition 2.8 Consider the structured linear dynamic system

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

with parametrization (P, f), $f : P \to \mathrm{SL\Sigma P}_1(n, m, k)$.

a This system is called *structurally weakly reachable* if, for all $p \in P$ outside an algebraic set,

$$\operatorname{rank}\begin{pmatrix} B(p) & A(p)B(p) & \cdots & A(p)^{n-1}B(p) & x_0(p) & A(p)x_0(p) & \cdots & A(p)^{n-1}x_0(p) \end{pmatrix} = n.$$

In this case one says that $(A(\cdot), (B(\cdot) \quad x_0(\cdot))$ is a *structurally reachable pair.*

b This system is called *structurally observable* if, for all $p \in P$ outside an algebraic set,

$$\operatorname{rank}\begin{pmatrix} C(p) \\ C(p)A(p) \\ \vdots \\ C(p)A(p)^{n-1} \end{pmatrix} = n.$$

In this case one says that $(A(\cdot), C(\cdot))$ is a *structurally observable pair.*

c This system is called *structurally minimal* if, for all $p \in P$ outside an algebraic set, it is a minimal realization of its Markov parameters and its initial parameters. □

Theorem 2.9 *Consider the structured linear dynamic system*

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

with parametrization (P, f), $f : P \to \mathrm{SL\Sigma P}_1(n, m, k)$.

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

b *Assume that the system is structurally minimal. Then this parametrization is structurally identifiable from the Markov parameters and the initial 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*

$$A(p) = TA(q)T^{-1}, \;\; B(p) = TB(q), \;\; C(p) = C(q)T^{-1}, \;\; D(p) = D(q), \;\; x_0(p) = Tx_0(q), \quad (2.7)$$

imply that $p = q$. Under the assumption stated and for all $q \in P$ outside an algebraic set, the system of equations (2.7) for the pair $(p, T) \in P \times R^{n \times n}$, with T nonsingular, has the unique solution $(p, T) = (q, I)$.

Proof. Setting $\tilde{B}(p) = (B(p), x_0(p))$, this result follows directly from the main result of realization theory for time-invariant finite-dimensional linear systems, since

$$\tilde{M}_p(j) := C(p)A(p)^{j-1}\tilde{B}(p) = \begin{pmatrix} C(p)A(p)^{j-1}B(p) & C(p)A(p)^{j-1}x_0(p) \end{pmatrix} = \begin{pmatrix} M_p(j) & N_p(j) \end{pmatrix},$$

for $j = 1, 2, \ldots$. For references see [2, 14, 15, 24]. □

To obtain equations that are not too complex, we will rewrite Condition (2.7) as follows:

$$A(p)T = TA(q), \quad B(p) = TB(q), \quad C(p)T = C(q), \quad D(p) = D(q), \quad x_0(p) = Tx_0(q). \tag{2.8}$$

Then we obtain polynomial equations that are linear in the elements of T, which are easier to handle, see the subsection before Section 4.

Examples presented in [31] show that structural identifiability is not equivalent to structural reachability, structural observability, and Condition (2.7). The point is that the parametrization of a structured linear system may be structurally identifiable but not structurally reachable. For modelling reasons, it is preferred to deal with systems that are structurally minimal. The modelling procedure used in mathematical biology can produce an interconnection of linear compartmental systems each of which is a minimal realization, but this interconnection is not be a minimal realization of its Markov parameters.

For positive linear systems, i.e., with input, state, and output positive, the conditions given in Theorem 2.9 are only sufficient, not necessary.

Proposition 2.10 *Consider the structured positive linear system*

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

with parametrization (P, f), $f : P \to \mathrm{SL\Sigma P}_1(n, m, k)$. *The parametrization* (P, f) *is structurally identifiable from the Markov parameters and the initial parameters if the following conditions are satisfied:*

1. *this system is structurally weakly reachable and structurally observable in the sense of Definition 2.8;*
2. *Condition (2.7) 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. □

3. Structural identifiability from input-output observations

In Subsection 2.2 a solution has been presented for the problem of structural identifiability of the parameters from the Markov parameters and the initial parameters. In this section the problem of structural identifiability from the input-output observations will be solved. Since observations usually appear in discrete-time, first the discrete-time case will be treated in Subsection 3.1, and in Subsection 3.2 the continuous-time case will be considered in case of discrete sampled data.

3.1 Discrete time

In this subsection, linear dynamic systems in discrete-time, represented by

$$\begin{aligned} x(t+1) &= Ax(t) + Bu(t), \quad x(t_0) = x_0, \\ y(t) &= Cx(t) + Du(t), \end{aligned} \tag{3.1}$$

where $x \in R^n$, $y \in R^k$, $u \in R^m$, $t \in T \subset Z$, are considered. The Markov parameters and the initial parameters for the discrete-time case are defined analogously to the continuous-time case:

$$M(0) = D,$$

$$\begin{aligned} M(j) &= CA^{j-1}B, \quad j = 1, 2, \ldots, \\ N(0) &= 0, \\ N(j) &= CA^{j-1}x_0, \end{aligned}$$

and the set of such parameters is also denoted by $\mathbf{M}(k,m)$, $\mathcal{N}(k)$, respectively. As Liu and Suen in [20], we will use the following notation. From (3.1) we obtain

$$Y(l,i,j) = R(i)X(l,1,j) + P(i)U(l,i,j) \tag{3.2}$$

with

$$\begin{aligned} R(i) &= \begin{pmatrix} C \\ CA \\ \vdots \\ CA^{i-1} \end{pmatrix}, \quad P(i) = \begin{pmatrix} D & 0 & 0 & \cdots & 0 \\ CB & D & 0 & \cdots & 0 \\ CAB & CB & D & \cdots & 0 \\ \vdots & & & \ddots & \vdots \\ CA^{i-2}B & CA^{i-3}B & CA^{i-4}B & \cdots & D \end{pmatrix}, \\ Y(l,i,j) &= \begin{pmatrix} y(l) & y(l+1) & \cdots & y(l+j-1) \\ y(l+1) & y(l+2) & \cdots & y(l+j) \\ \vdots & \vdots & & \vdots \\ y(l+i-1) & y(l+i) & \cdots & y(l+i+j-2) \end{pmatrix}, \end{aligned}$$

and $U(l,i,j)$ and $X(l,i,j)$ are defined similarly to $Y(l,i,j)$. In this subsection we take $t_0 = 1$.

In the paper of Liu and Suen [20], Corollary 3 is not correct. A corrected version is given by the same authors in [25]. Another version is given in the following proposition.

Proposition 3.1 *Let a length N input-output sequence be 'identifiable by systems of dimension n' (in the sense of [20]) and let $\Sigma(n) = (A,B,C,D)$ be a representation for some initial state $x(1)$, such that (3.1) is satisfied for the considered input-output sequence. Then*

1. *(A,C) is an observable pair;*
2. *$x(1)$ is uniquely determined by $\Sigma(n)$;*
3. *$(A,(B \ \ x(1)))$ is a reachable pair.*

Proof. 1. This follows from Theorem 2 in [20].
2. Since (A,C) is observable, $x(1)$ can uniquely be determined from the length N input-output sequence, by definition of observability.
3. Suppose $(A,(B \ \ x(1)))$ is not reachable. Define $\tilde{B} = (B \ \ x(1))$. Then there exists a nonsingular matrix $L \in R^{n \times n}$ such that

$$\begin{aligned} LAL^{-1} &= \begin{pmatrix} A_{11} & A_{12} \\ 0 & A_{22} \end{pmatrix}, \quad A_{11} \in R^{n_1 \times n_1}, \quad n1 < n, \\ L\tilde{B} &= L\begin{pmatrix} B & x(1) \end{pmatrix} = \begin{pmatrix} B_1 & x_1(1) \\ 0 & 0 \end{pmatrix}, \\ CL^{-1} &= \begin{pmatrix} C_1 & C_2 \end{pmatrix}. \end{aligned}$$

It follows that $\Sigma(n_1) = (A_{11}, B_1, C_1, D)$ is another representation with initial state $x_1(1) \in R^{n_1}$, contradicting Corollary 2 in [20]. So $(A,(B \ \ x(1)))$ is a reachable pair. □

To adapt the terminology of Liu and Suen to the terminology in this paper, the following proposition is stated.

Proposition 3.2 *An input-output sequence is 'identifiable by systems of dimension n' (in the sense of [20]) if and only if the Markov parameters and the initial parameters can uniquely be determined from the input-output sequence considered.*

Proof. An m-input-k-output sequence is 'identifiable by systems of dimension n' (in the sense of [20]) if and only if (by definition) there exists a representation $(A_1, B_1, C_1, D_1, x_1(1)) \in \mathrm{L\Sigma P}(n, m, k)$ satisfying (3.1) for the considered input-output sequence, and any other representation of dimension n satisfying (3.1) for the input-output sequence is isomorphic to $(A_1, B_1, C_1, D_1, x_1(1))$, i.e., $(A_2, B_2, C_2, D_2, x_2(1)) \in \mathrm{L\Sigma P}(n, m, k)$ is another representation satisfying (3.1) for the input-output sequence, if and only if there exists a $T \in R^{n\times n}$, nonsingular, such that

$$(A_2, B_2, C_2, D_2, x_2(1)) = (TA_1T^{-1}, TB_1, C_1T^{-1}, D_1, Tx_1(1)).$$

For all those isomorphic representations, the Markov parameters and the initial parameters are exactly the same, so $(A_1, B_1, C_1, D_1, x_1(1))$ and its isomorphisms are realizations of these Markov parameters and initial parameters. From Proposition 3.1 it follows that $(A_1, (\, B_1 \quad x_1(1)\,))$ is a reachable pair and (A_1, C_1) is an observable pair, so $(A_1, B_1, C_1, D_1, x_1(1))$ and its isomorphisms are exactly all *minimal* realizations of these Markov parameters and initial parameters.

On the other hand, the Markov parameters and the initial parameters can uniquely be determined from the input-output sequence if and only if there exists a minimal quintuple $(A, B, C, D, x(1)) \in \mathrm{L\Sigma P}(n, m, k)$, which is unique up to an isomorphism, such that (3.1) is satisfied for the considered input-output sequence. This proves the proposition. □

Proposition 3.3 *Consider a discrete-time linear dynamic system*

$$\begin{aligned} x(t+1) &= Ax(t) + Bu(t), \quad x(1) = x_0, \\ y(t) &= Cx(t) + Du(t), \end{aligned} \tag{3.3}$$

where $x \in R^n$, $y \in R^k$, $u \in R^m$, $t = 1, 2, 3, \ldots$. Assume (A, C) is an observable pair. Let q be the smallest integer for which $\mathrm{rank}(R(q)) = \mathrm{rank}(R(n))$. Let $S(q)$ be the sequential selector matrix associated with $R(n)$ as defined in [20]. The Markov parameters and the initial parameters can uniquely be determined from a length N input-output sequence associated with a linear dynamic system of the form (3.3) if and only if

$$\mathrm{rank}\begin{pmatrix} U(1, q+1, N-q) \\ Y(1, q, N-q) \end{pmatrix} = n + m(q+1). \tag{3.4}$$

Moreover, necessary conditions are

$$\mathrm{rank}(U(1, q+1, N-q)) = m(q+1), \tag{3.5}$$

and

$$N \geq n + m(q+1) + q. \tag{3.6}$$

Before proving Proposition 3.3, the following lemma will be proved.

Lemma 3.4 *Consider a discrete-time linear dynamic system of the form (3.3). Assume (A, C) is an observable pair. Let q be the smallest integer for which $\mathrm{rank}(R(q)) = \mathrm{rank}(R(n))$. Let $S(q)$ be the sequential selector matrix associated with $R(n)$ as defined in [20]. Then*

$$\mathrm{rank}\begin{pmatrix} U(1, q+1, N-q) \\ S(q)Y(1, q, N-q) \end{pmatrix} = \mathrm{rank}\begin{pmatrix} U(1, q+1, N-q) \\ Y(1, q, N-q) \end{pmatrix}. \tag{3.7}$$

Proof of Lemma 3.4. Note that the numbers within the square brackets of the citation refer to the corresponding numbers of the equations in [20]. Using

$$U(1,q,N-q) = \begin{pmatrix} I & 0 \end{pmatrix} U(1,q+1,N-q), \tag{3.8}$$

with $I \in R^{mq \times mq}$ and $0 \in R^{mq \times m}$, we have

$$\begin{aligned}
\begin{pmatrix} U(1,q+1,N-q) \\ S(q)Y(1,q,N-q) \end{pmatrix} &= \begin{pmatrix} U(1,q+1,N-q) \\ S(q)\{R(q)X(1,1,N-q) + P(q)U(1,q,N-q)\} \end{pmatrix} \\
&= \begin{pmatrix} U(1,q+1,N-q) \\ S(q)\{R(q)X(1,1,N-q) + P(q)\begin{pmatrix} I & 0 \end{pmatrix} U(1,q+1,N-q)\} \end{pmatrix} \\
&= \begin{pmatrix} I & 0 \\ S(q)P(q)\begin{pmatrix} I & 0 \end{pmatrix} & I \end{pmatrix} \begin{pmatrix} U(1,q+1,N-q) \\ S(q)R(q)X(1,1,N-q) \end{pmatrix}.
\end{aligned}$$

The first equality follows from (3.2) and the second equality follows from (3.8). Hence we obtain

$$\begin{aligned}
\operatorname{rank}\begin{pmatrix} U(1,q+1,N-q) \\ S(q)Y(1,q,N-q) \end{pmatrix} &= \operatorname{rank}\begin{pmatrix} U(1,q+1,N-q) \\ S(q)R(q)X(1,1,N-q) \end{pmatrix} \\
&= \operatorname{rank}\begin{pmatrix} U(1,q+1,N-q) \\ R(q)X(1,1,N-q) \end{pmatrix},
\end{aligned}$$

where the second equality follows from [20, (9)]. Again due to (3.8) above, we have

$$\begin{aligned}
\begin{pmatrix} U(1,q+1,N-q) \\ R(q)X(1,1,N-q) \end{pmatrix} &= \begin{pmatrix} U(1,q+1,N-q) \\ Y(1,q,N-q) - P(q)U(1,q,N-q) \end{pmatrix} \\
&= \begin{pmatrix} I & 0 \\ -P(q)\begin{pmatrix} I & 0 \end{pmatrix} & I \end{pmatrix} \begin{pmatrix} U(1,q+1,N-q) \\ Y(1,q,N-q) \end{pmatrix},
\end{aligned}$$

so

$$\operatorname{rank}\begin{pmatrix} U(1,q+1,N-q) \\ R(q)X(1,1,N-q) \end{pmatrix} = \operatorname{rank}\begin{pmatrix} U(1,q+1,N-q) \\ Y(1,q,N-q) \end{pmatrix}.$$

This proves the lemma. □

Proof of Proposition 3.3. The first part follows immediately from Theorem 7 of [20] and Proposition 3.2, using Lemma 3.4. For the second part, note that the matrix in the left hand side of (3.7) has $\operatorname{rank}(S(q)) + m(q+1)$ rows, which is equal to $n + m(q+1)$, since (A, C) is observable. So a necessary condition for (3.4) is that $U(1, q+1, N-q)$ has full row-rank, i.e. $\operatorname{rank}(U(1, q+1, N-q)) = m(q+1)$. The matrix

$$\begin{pmatrix} U(1,q+1,N-q) \\ Y(1,q,N-q) \end{pmatrix}$$

has $N - q$ columns, so for (3.4) also $N - q \geq n + m(q+1)$, or $N \geq n + m(q+1) + q$, is a necessary condition. □

Remark 3.5 Structural identifiability from discrete-time Markov parameters and initial parameters is defined analogously to the continuous-time case, described in Subsection 2.2. Definition 2.7 and 2.8 and the conditions in Theorem 2.9 and Proposition 2.10 can directly be transferred to the discrete-time case. □

For a given input-output sequence the following theorem can be used to decide whether the parameter p can uniquely be determined or not.

Theorem 3.6 *Consider a discrete-time structured linear dynamic system of the form*

$$\begin{aligned}
x(t+1) &= A(p)x(t) + B(p)u(t), \quad x(1) = x_0(p), \\
y(t) &= C(p)x(t) + D(p)u(t),
\end{aligned} \tag{3.9}$$

with parametrization (P, f), $f : P \to \mathrm{SL\Sigma P}(n, m, k)$. *Assume that a length* N *input-output sequence,*

$$u(1), u(2), \ldots, u(N),$$
$$y(1), y(2), \ldots, y(N),$$

associated with the dynamic system (3.9), is given. If

1. *the system is structurally weakly reachable and structurally observable;*
2. *for all* $p, \tilde{p} \in P$ *outside an algebraic set* S_1 *and for all* $T \in R^{n\times n}$, *nonsingular, the equations*

   $$A(p)T = TA(\tilde{p}), \quad B(p) = TB(\tilde{p}), \quad C(p)T = C(\tilde{p}), \quad D(p) = D(\tilde{p}), \quad x_0(p) = Tx_0(\tilde{p}),$$

   imply that $p = \tilde{p}$;
3. $$\operatorname{rank}\begin{pmatrix} U(1, q+1, N-q) \\ Y(1, q, N-q) \end{pmatrix} = n + m(q+1),$$

   in which q *is the smallest integer such that* $\operatorname{rank}(R(q)) = \operatorname{rank}(R(n))$ *for all* $p \in P$ *outside an algebraic set* S_2;

then the parameter p *can uniquely be determined from the considered input-output sequence, provided* $p \in P \setminus (S_1 \cup S_2)$. *Also for structured positive linear systems the result holds true.*

Proof. From Proposition 3.3 it follows that the Markov parameters and initial parameters can uniquely be determined from the length N input-output sequence if and only if

$$\operatorname{rank}\begin{pmatrix} U(1, q+1, N-q) \\ Y(1, q, N-q) \end{pmatrix} = n + m(q+1).$$

So, from Condition 1 and 3 it follows that the Markov parameters and the initial parameters can uniquely be determined from the considered length N input-output sequence for $p \in P \setminus S_2$. From Condition 1 and 2, it follows that the parametrization (P, f) is structurally identifiable from the Markov parameters and the initial parameters, i.e., the parameter p can uniquely be determined from the Markov parameters and the initial parameters, provided $p \in P \setminus S_1$. Conclusion: under the conditions stated, the parameter p can uniquely be determined from the considered length N input-output sequence for $p \in P \setminus (S_1 \cup S_2)$. □

Below an algorithm is given to determine the Markov parameters and the initial parameters from a length N input-output sequence for which (3.4) holds. First some terminology is introduced. For $k, m \in Z_+$, let $Q(k, m) = \mathbf{M}(k, m) \times \mathcal{N}(k)$, and denote by $Q(k, m, n) \subset Q(k, m)$ the set of Markov parameters and initial parameters in $Q(k, m)$ that admit a minimal realization of state space dimension n. For $(M(j), N(j), j \in \boldsymbol{N}) \in Q(k, m, n)$, let $(A, B, C, D, x_0) \in \mathrm{L\Sigma P}(n, m, k)$ be a minimal realization of the Markov parameters $M(j)$ and the initial parameters $N(j)$. Define $\tilde{M}(j) = (M(j) \;\; N(j))$, for $j \in \boldsymbol{N}$, and $\tilde{B} = (B \;\; x_0)$. For $r, p \in Z_+$, consider the Hankel matrix

$$H(r,p) = \begin{pmatrix} \tilde{M}(1) & \tilde{M}(2) & \cdots & \tilde{M}(p) \\ \tilde{M}(2) & \tilde{M}(3) & \cdot & \vdots \\ \vdots & \cdot & & \vdots \\ \tilde{M}(r) & \cdots & \cdots & \tilde{M}(p+r-1) \end{pmatrix}.$$

Algorithm 3.7 Consider an unknown discrete-time linear dynamic system of the form (3.3), where $x \in R^n$, $y \in R^k$, $u \in R^m$, $t = 1, 2, 3, \ldots$. Assume n, m, and k are known and it is given that $(A, \tilde{B})$ is a reachable pair and (A, C) is an observable pair. Let a length N input-output sequence of this system be given.

Step 1 Construct q and $S(q)$ with the MD algorithm in [20].

Step 2 If rank $\begin{pmatrix} U(1,q+1,N-q) \\ Y(1,q,N-q) \end{pmatrix} = n + m(q+1)$ goto step 3, else stop.

Step 3 Calculate $T_j \in R^{k\times m}$, for $j = 0,1,\ldots,q$, and $K_1 \in R^{k\times n}$ with

$$\begin{pmatrix} T_q & \cdots & T_0 & K_1 \end{pmatrix} = \begin{pmatrix} y(q+1) & \cdots & y(N) \end{pmatrix} \begin{pmatrix} U(1,q+1,N-q) \\ S(q)Y(1,q,N-q) \end{pmatrix}^{-*},$$

in which $R^{-*} = R^T(RR^T)^{-1}$, a right-inverse of R.

Step 4 Calculate

$$M(0) = T_0, \tag{3.10}$$

$$M(j) = T_j + K_1 S(q) \begin{pmatrix} 0 \\ M(j-1) \\ \vdots \\ M(0) \end{pmatrix}, \quad \text{with } 0 \in R^{k(q-j)\times m}, \quad \text{for } j = 1,\ldots,q, \tag{3.11}$$

$$M(q+j) = K_1 S(q) \begin{pmatrix} M(j) \\ \vdots \\ M(q+j-1) \end{pmatrix} \quad \text{for } j = 1,\ldots,N-q, \tag{3.12}$$

$$\begin{pmatrix} N(1) \\ \vdots \\ N(q) \end{pmatrix} = \begin{pmatrix} y(1) \\ \vdots \\ y(q) \end{pmatrix} - P(q) \begin{pmatrix} u(1) \\ u(2) \\ \vdots \\ u(q) \end{pmatrix}, \tag{3.13}$$

$$N(q+j) = K_1 S(q) \begin{pmatrix} N(j) \\ \vdots \\ N(q+j-1) \end{pmatrix} \quad \text{for } j = 1,\ldots,N-q. \tag{3.14}$$

Proposition 3.8 *Consider an unknown discrete-time linear dynamic system of the form (3.3), where $x \in R^n$, $y \in R^k$, $u \in R^m$, $t = 1,2,3,\ldots$. Assume n, m, and k are known and it is given that $(A, \tilde{B})$ is a reachable pair and (A, C) is an observable pair. Let a length N input-output sequence of this system be given. If (3.4) holds, Algorithm 3.7 constructs uniquely the Markov parameters and the initial parameters for the considered length N input-output sequence.*

Proof. See Appendix A. □

What can be said about the structural identifiability of the parametrization (P, f) from a length N input-output sequence?

First, notation is introduced. U^{Z_N} and Y^{Z_N} denote the set of sequences of length N with elements in U and Y, respectively. Define the map $G_{f,\bar{u}} : P \to Y^{Z_N}$ as follows. Define $F_f : P \to Q(k,m)$ by $F_f = (g, g_1) \circ f$, with $(g, g_1) \circ f$ as defined in Definition 2.7.

Let $H_{\bar{u}} : Q(k,m) \to Y^{Z_N}$ for $\bar{u} = (u(1),\ldots,u(N)) \in U^{Z_N}$ be the map from the set of Markov parameters and initial parameters to the length N output sequences $(y(1), y(2),\ldots,y(N)) \in Y^{Z_N}$, such that

$$y(t) = \sum_{s=1}^{t} M(t-s)u(s) + N(t), \quad t = 1,2,\ldots,N,$$

in which $M(j)$ and $N(j)$, for $j \in \boldsymbol{N}$, denote the Markov parameters and initial parameters, respectively. Now define $G_{f,\bar{u}} : P \to Y^{Z_N}$ by $G_{f,\bar{u}} = H_{\bar{u}} \circ F_f$.

Definition 3.9 Consider a discrete-time structured linear dynamic system of the form (3.9) with parametrization (P, f), $f : P \to \mathrm{SL\Sigma P}(n, m, k)$. The parametrization (P, f) is said to be *structurally identifiable at* $\bar{u} \in U^{Z_N}$ *from the length* N *output sequence* $\bar{y} \in Y^{Z_N}$ associated with the dynamic system (3.9) for input $\bar{u}$ if

$$G_{f,\bar{u}} : P \to Y^{Z_N}$$

is injective for all $p \in P$ outside an algebraic set, with $G_{f,\bar{u}}$ defined above. □

The following theorem gives conditions under which the to be performed experiment will give enough information to estimate the unknown parameters uniquely.

Theorem 3.10 *Consider the discrete-time structured linear dynamic system of the form (3.9), with parametrization* (P, f), $f : P \to \mathrm{SL\Sigma P}(n, m, k)$. *Consider a length* N *input sequence,*

$$\bar{u} = (u(1), u(2), \ldots, u(N)).$$

If

1. *the system is structurally weakly reachable and structurally observable;*
2. *for all* $p, \tilde{p} \in P$ *outside an algebraic set and for all* $T \in R^{n \times n}$, *nonsingular, the equations*

   $$A(p)T = TA(\tilde{p}), \quad B(p) = TB(\tilde{p}), \quad C(p)T = C(\tilde{p}), \quad D(p) = D(\tilde{p}), \quad x_0(p) = Tx_0(\tilde{p}),$$

   imply that $p = \tilde{p}$;
3. $N \geq q + m(q+1) + n$, *in which* q *is the least integer such that* $\mathrm{rank}(R(q)) = \mathrm{rank}(R(n))$ *for all* $p \in P$ *outside an algebraic set;*
4. $\mathrm{rank}(U(1, q+1, N-q)) = m(q+1)$;

then the parametrization (P, f) *is structurally identifiable at* $\bar{u} = (u(1), u(2), \ldots, u(N))$ *from the length* N *output sequence* $\bar{y} \in Y^{Z_N}$ *associated with the dynamic system (3.9) for input* $\bar{u}$.
For a structured positive linear system the same conditions imply structural identifiability at $\bar{u}$ *from the length* N *output sequence* $\bar{y} \in Y^{Z_N}$ *associated with the positive linear system (3.9) for input* $\bar{u}$.

Proof. Because of Condition 1 and 2, $F_f : P \to Q(k, m)$ is injective for all $p \in P$ outside an algebraic set. Because of Condition 1, F_f maps P into $Q(k, m, n)$. The map $H_{\bar{u}}$ defined above, restricted to $Q(k, m, n)$, is generically injective, since the Markov parameters and initial parameters, i.e. $M(0), M(1), \ldots, M(q), N(1), N(2), \ldots, N(q)$, and K_1 can uniquely be determined if Condition 3 holds and if

$$\mathrm{rank} \begin{pmatrix} U(1, q+1, N-q) \\ S(q)Y(1, q+1, N-q) \end{pmatrix} = n + m(q+1),$$

which holds generically if Condition 4 holds. It follows that the map $G_{f,\bar{u}} = H_{\bar{u}} \circ F_f : P \to Y^{Z_N}$ is generically injective, i.e. injective for all $p \in P$ outside an algebraic set. □

3.2 Continuous time

In the previous subsection the problem of structural identifiability from input-output observations is solved for systems in discrete-time. However, most compartmental models are continuous-time, whereas the observations are discrete-time. Therefore the system has to be sampled with a sufficient small sampling time Δ. Before stating the main result, some preliminaries must be discussed. Suppose the input is constant over the sampling interval Δ:

$$u(t) = u_\Delta(j) = u(j\Delta), \quad j\Delta \le t < (j+1)\Delta.$$

Then the system (2.1) can be written in discrete-time as follows, with $x_\Delta(t) = x(t\Delta)$, $u_\Delta(t) = u(t\Delta)$, and $y_\Delta(t) = y(t\Delta)$. Assume $t_0 = \Delta$, such that $x(t_0) = x_\Delta(t_0/\Delta) = x_\Delta(1)$,

$$\begin{aligned} x_\Delta(t+1) &= \hat{A}x_\Delta(t) + \hat{B}u_\Delta(t), \quad x_\Delta(1) = x_0, \\ y_\Delta(t) &= Cx_\Delta(t) + Du_\Delta(t), \end{aligned} \tag{3.15}$$

$t = 1, 2, 3, \ldots$, where

$$\begin{aligned} \hat{A} &= e^{A\Delta}, \\ \hat{B} &= \int_0^\Delta e^{A\tau} B d\tau. \end{aligned}$$

Define $h_\Delta : Q(k,m) \to Q(k,m)$ as the map that associates the Markov parameters and the initial parameters in the continuous-time case with the Markov parameters and the initial parameters in the discrete-time case as follows. Let $((M(j), N(j)), j \in \boldsymbol{N}) \in Q(k,m)$ be the Markov parameters and the initial parameters in the continuous-time case, and let $(A, B, C, D, x_0) \in \mathrm{L\Sigma P}(n_1, m, k)$ for $n_1 \in \boldsymbol{N}$ be a minimal realization. Defining $\hat{A}$ and $\hat{B}$ as above, and

$$\begin{aligned} \hat{M}(0) &= D, \\ \hat{M}(j) &= C\hat{A}^{j-1}\hat{B}, \quad j = 1, 2, \ldots, \\ \hat{N}(0) &= 0, \\ \hat{N}(j) &= C\hat{A}^{j-1}x_0, \quad j = 1, 2, \ldots, \end{aligned}$$

then h_Δ is defined by

$$h_\Delta(M(j), N(j)) = (\hat{M}(j), \hat{N}(j)), \quad j = 0, 1, 2, \ldots.$$

Since h_Δ does not dependent on the choice of the minimal realization (A, B, C, D, x_0), it is well defined. Indeed, if another minimal realization $(A_1, B_1, C_1, D_1, x_0^1) = (TAT^{-1}, TB, CT^{-1}, D, Tx_0)$ is considered, with $T \in R^{n_1 \times n_1}$, nonsingular, then

$$\begin{aligned} C_1\hat{A}_1^j\hat{B}_1 &= CT^{-1}e^{TAT^{-1}j\Delta}\int_0^\Delta e^{TAT^{-1}\tau}TBd\tau \\ &= CT^{-1}Te^{Aj\Delta}T^{-1}\int_0^\Delta Te^{A\tau}T^{-1}TBd\tau \\ &= Ce^{Aj\Delta}\int_0^\Delta e^{A\tau}Bd\tau \\ &= C\hat{A}^j\hat{B}, \end{aligned}$$

and

$$C_1\hat{A}_1^j x_0^1 = CT^{-1}e^{TAT^{-1}j\Delta}Tx_0 = Ce^{Aj\Delta}x_0 = C\hat{A}^j x_0,$$

for $j = 0, 1, 2, \ldots$.

Let $\sigma(A)$ denote the spectrum of A and $\mathrm{Im}(\lambda)$ the imaginary part of λ. Let $W \subset R^{n\times n}$ be such that the set

$$K(W) = \{\mathrm{Im}(\lambda) \in R \mid \lambda \in \sigma(A),\ A \in W\}$$

is bounded. Define $r(W)$ as follows.

$$r(W) = \frac{\pi}{\sup K(W)} \quad \text{if } \sup K(W) > 0, \quad \text{else } r(W) = \infty.$$

Note that $r(W)$ is strictly positive, since $K(W)$ is bounded. Denote by $Q_W(k,m,n) \subset Q(k,m,n)$ the set of Markov parameters and initial parameters in $Q(k,m,n)$ that admit a minimal realization (A,B,C,D,x_0) of state space dimension n with state transition matrix $A \in W$.

Lemma 3.11 *Let the map h_Δ and the set W be as defined above. If $0 < \Delta < r(W)$, then*

1. *h_Δ is injective on $Q_W(k,m,n)$;*
2. *h_Δ maps $Q_W(k,m,n)$ into $Q(k,m,n)$.*

Proof. See the Appendix B. □

A still open question is whether

$$\operatorname{rank}(R(q)) = \operatorname{rank}\begin{pmatrix} C \\ \vdots \\ CA^{q-1} \end{pmatrix} = n \quad \text{implies} \quad \operatorname{rank}(\hat{R}(q)) = \begin{pmatrix} C \\ C\hat{A} \\ \vdots \\ C\hat{A}^{q-1} \end{pmatrix} = n.$$

This problem is not solved yet. What is known is the following. From Lemma 3.11 it follows that $\operatorname{rank}(R(q)) = \operatorname{rank}(R(n)) = n$ implies $\operatorname{rank}(\hat{R}(n)) = n$. This can be weakened to $\operatorname{rank}(\hat{R}(r)) = n$, with $r = n + 1 - \operatorname{rank}(C)$, see [15]. Note that $q \le r \le n$, for $C \ne 0$. If a sampled length N input-output sequence is given, q can be determined with the MD algorithm in [20]. For a given input-output sequence the following theorem can be used to decide whether the parameter p can uniquely be determined or not. $U_\Delta(l,i,j)$ and $Y_\Delta(l,i,j)$ are defined similarly to $U(l,i,j)$ and $Y(l,i,j)$ in the previous subsection, but with $u_\Delta(\cdot)$ and $y_\Delta(\cdot)$ instead of $u(\cdot)$ and $y(\cdot)$.

Theorem 3.12 *Consider a continuous-time structured linear dynamic system of the form (2.2), with parametrization (P,f), $f : P \to \mathrm{SL\Sigma P}(n,m,k)$, in which P is such that for the set*

$$W_P = \{A(p) \in R^{n\times n} \mid p \in P\},$$

the set

$$K(W_P) = \{\operatorname{Im}(\lambda) \in R \mid \lambda \in \sigma(A),\ A \in W_P\}$$

is bounded. Assume that a sampled length N input-output sequence

$$u_\Delta(1), u_\Delta(2), \ldots, u_\Delta(N),$$
$$y_\Delta(1), y_\Delta(2), \ldots, y_\Delta(N),$$

associated with the sampled version of (2.2) is given, and let $t_0 = \Delta$. Let the integer q be constructed with the MD algorithm in [20]. If

1. *the system is structurally weakly reachable and structurally observable;*
2. *for all $p, \tilde{p} \in P$ outside an algebraic set S and for all $T \in R^{n\times n}$, nonsingular, the equations*

   $$A(p)T = TA(\tilde{p}), \quad B(p) = TB(\tilde{p}), \quad C(p)T = C(\tilde{p}), \quad D(p) = D(\tilde{p}), \quad x_0(p) = Tx_0(\tilde{p}),$$

   imply that $p = \tilde{p}$;
3. $\operatorname{rank}\begin{pmatrix} U_\Delta(1,q+1,N-q) \\ Y_\Delta(1,q,N-q) \end{pmatrix} = n + m(q+1);$
4. *the sample time Δ has been chosen so small that*

$$0 < \Delta < r(W_P);$$

5. *the continuous-time input is constant over each sampling interval* Δ*:*

$$u(t) = u_\Delta(j), \quad j\Delta \le t < (j+1)\Delta;$$

then the parameter p *can uniquely be determined from the considered sampled input-output sequence, provided* $p \in P \setminus S$*. Also for structured positive linear systems the result holds true.*

Proof. From Proposition 3.3 it follows that the discrete-time Markov parameters and initial parameters can uniquely be determined from the sampled length N input-output sequence if and only if

$$\text{rank}\begin{pmatrix} U_\Delta(1, q+1, N-q) \\ Y_\Delta(1, q, N-q) \end{pmatrix} = n + m(q+1).$$

So, from Condition 1 and 3 it follows that the discrete-time Markov parameters and initial parameters can uniquely be determined from the considered sampled length N input-output sequence. The map h_Δ is injective on $Q_{W_P}(k, m, n)$, because of Condition 4 and 5, so the continuous-time Markov parameters and initial parameters can uniquely be determined from the discrete-time Markov parameters and initial parameters. From Condition 1 and 2, it follows that the parametrization (P, f) is structurally identifiable from the continuous-time Markov parameters and initial parameters, i.e., the parameter p can uniquely be determined from the continuous-time Markov parameters and initial parameters, provided $p \in P \setminus S$. Conclusion: under the conditions stated, the parameter p can uniquely be determined from the considered sampled length N input-output sequence for $p \in P \setminus S$. □

For the structural identifiability of the parametrization (P, f) from the data, let $\hat{G}_{f,\bar{u}_\Delta} : P \to Y^{Z_N}$ be defined as follows. Let the maps $F_f : P \to Q(k, m)$ and $H_{\bar{u}_\Delta} : Q(k, m) \to Y^{Z_N}$ be as defined in Subsection 3.1. Let $h_\Delta : Q(k, m) \to Q(k, m)$ be the map defined at the beginning of this subsection. Now define $\hat{G}_{f,\bar{u}_\Delta} : P \to Y^{Z_N}$ by $\hat{G}_{f,\bar{u}_\Delta} = H_{\bar{u}_\Delta} \circ h_\Delta \circ F_f$.

Definition 3.13 Consider a continuous-time structured linear dynamic system of the form (2.2), with parametrization (P, f), $f : P \to \text{SL}\Sigma\text{P}(n, m, k)$. The parametrization (P, f) is said to be *structurally identifiable at a sampled* $\bar{u}_\Delta \in U^{Z_N}$ *from a sampled length* N *input-output sequence* $\bar{y}_\Delta \in Y^{Z_N}$ associated with the sampled version of the dynamic system (2.2) for input $\bar{u}_\Delta$ if

$$\hat{G}_{f,\bar{u}_\Delta} : P \to Y^{Z_N}$$

is injective for all $p \in P$ outside an algebraic set, with $\hat{G}_{f,\bar{u}_\Delta}$ defined above. □

The following theorem gives conditions under which the to be performed experiment will give enough information to estimate the unknown parameters uniquely.

Theorem 3.14 *Consider the continuous-time structured linear dynamic system of the form (2.2), with parametrization* (P, f)*,* $f : P \to \text{SL}\Sigma\text{P}(n, m, k)$*, in which* P *is such that for the set*

$$W_P = \{A(p) \in R^{n \times n} \mid p \in P\},$$

the set

$$K(W_P) = \{\text{Im}(\lambda) \in R \mid \lambda \in \sigma(A),\ A \in W_P\}$$

is bounded. Let $\text{rank}(C(p)) = c$ *for all* $p \in P$ *outside an algebraic set. Consider a sampled length* N *input sequence,*

$\bar{u}_\Delta = (u_\Delta(1), u_\Delta(2), \ldots, u_\Delta(N)),$

in which $\Delta \in (0, \infty)$ *is the sampling interval, and let* $t_0 = \Delta$. *If*

1. *the system is structurally weakly reachable and structurally observable;*
2. *for all* $p, \tilde{p} \in P$ *outside an algebraic set and for all* $T \in R^{n \times n}$, *nonsingular, the equations*

   $$A(p)T = TA(\tilde{p}), \quad B(p) = TB(\tilde{p}), \quad C(p)T = C(\tilde{p}), \quad D(p) = D(\tilde{p}), \quad x_0(p) = Tx_0(\tilde{p}),$$

   imply that $p = \tilde{p}$*;*
3. $N \geq r + m(r+1) + n$, *in which* $r = n + 1 - c$.
4. $\text{rank}(U_\Delta(1, r+1, N-r)) = m(r+1)$;
5. *the sample time* Δ *has been chosen so small that*

   $$0 < \Delta < r(W_P);$$
6. *the continuous-time input is constant over each sampling interval* Δ:

   $$u(t) = u_\Delta(j), \quad j\Delta \leq t < (j+1)\Delta;$$

then the parametrization (P, f) *is structurally identifiable at* $\bar{u}_\Delta$ *from the sampled length* N *output sequence* $\bar{y}_\Delta \in Y^{Z_N}$ *associated with the sampled version of the dynamic system (2.2) for input* $\bar{u}_\Delta$. *For a structured positive linear system the same conditions imply structural identifiability at* $\bar{u}_\Delta$ *from the sampled length* N *output sequence* $\bar{y}_\Delta \in Y^{Z_N}$ *associated with the sampled version of the positive linear system (2.2) for input* $\bar{u}_\Delta$.

Proof. Because of Condition 1 and 2, $F_f : P \to Q(k, m)$ is injective for all $p \in P$ outside an algebraic set. Because of Condition 1, F_f maps P into $Q(k, m, n)$, actually into $Q_{W_P}(k, m, n) \subset Q(k, m, n)$, for $W_P = \{A(p) \mid p \in P\}$. With Lemma 3.11, it follows that $h_\Delta : Q(k, m) \to Q(k, m)$ is injective on $Q_{W_P}(k, m, n)$, because of Condition 5 and 6, so h_Δ is injective on the range of F_f. Let q be the least integer such that

$$\text{rank}(\hat{R}(q)) = \text{rank} \begin{pmatrix} C(p) \\ C(p)\hat{A}(p) \\ \vdots \\ C(p)\hat{A}(p)^{q-1} \end{pmatrix} = \text{rank} \begin{pmatrix} C(p) \\ C(p)\hat{A}(p) \\ \vdots \\ C(p)\hat{A}(p)^{r-1} \end{pmatrix} = n.$$

Note that $q \leq r$. From Condition 4, which says that $U_\Delta(1, r+1, N-r)$ has full row-rank, it follows that the sub-matrix $U_\Delta(1, q+1, N-r)$ has full row-rank, i.e.,

$$\text{rank}(U_\Delta(1, q+1, N-r)) = m(q+1),$$

which implies that also

$$\text{rank}(U_\Delta(1, q+1, N-q)) = m(q+1).$$

So the discrete-time Markov parameters and initial parameters can uniquely be determined if Condition 3 holds and if for a sequential selector matrix $S(q)$

$$\text{rank} \begin{pmatrix} U_\Delta(1, q+1, N-q) \\ S(q)Y(1, q+1, N-q) \end{pmatrix} = n + m(q+1).$$

The latter condition holds generically if Condition 4 holds. It follows that $G_{f,\bar{u}_\Delta} = H_{\bar{u}_\Delta} \circ h_\Delta \circ F_f : P \to Y^{Z_N}$ is generically injective, i.e. injective for all $p \in P$ outside an algebraic set. □

Introduction to the case studies

Before starting with the case studies, we will first consider in this subsection the practical side of checking the conditions, mentioned in Subsection 2.2.

For the test of structural (weak) reachability (and structural observability, which is the dual of structural reachability) several methods are available. Lin [19] used a graph theoretic approach for the single-input case. Shields and Pearson [23], Glover and Silverman [7], and Davison [6] extended this to the multi-input case in terms of matrix algebra. But we can not use these theories, because the parameters in the case studies are in general not independent, which is a necessary condition for applying these methods. If a parameter appears twice in the matrices $A(p)$, $B(p)$, $C(p)$, and $D(p)$, then the independence assumption may not be satisfied. We can check the structural reachability and structural observability of the case studies by the method of Gröbner basis, using the symbolic manipulation package MAPLE, [5], with the theory of Habets [11].

To check the Conditions (2.8) by the method of Gröbner basis, using MAPLE is quite complicated. For systems with state space dimension $n \leq 3$ it will work fast, but for larger systems it turns out to be very time consuming. Sometimes the MAPLE function *'solve'* will give solutions (q, T) for the Conditions (2.8), but this is not always possible. In some cases the object is too large to be solved by the MAPLE function *'solve'*.

4. Case study 1: Nitrate model

The first case study concerns a model for the uptake and dispersion of nitrate in the human body, developed at RIVM, [32]. Four compartments are considered: nitrate (NO_3^-) in the stomach, the body pool, and the saliva, and nitrite (NO_2^-) in the saliva, as shown in Figure 1.

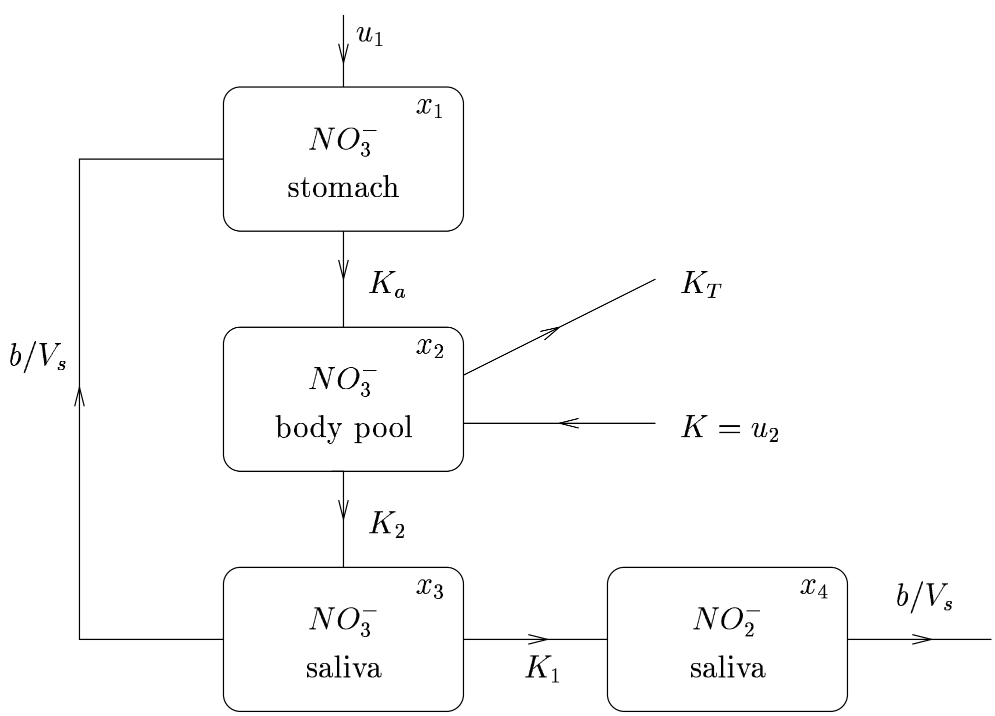

Figure 1: Nitrate model

The model may be described by the following differential equations:

$$\begin{aligned}
\dot{x}_1 &= -K_a x_1 + \frac{b}{V_s} x_3 + u_1, \\
\dot{x}_2 &= K_a x_1 - (K_2 + K_T) x_2 + K, \\
\dot{x}_3 &= K_2 x_2 - (K_1 + \frac{b}{V_s}) x_3, \\
\dot{x}_4 &= K_1 x_3 - \frac{b}{V_s} x_4,
\end{aligned}$$

in which x_1, x_2, and x_3 denote the amount of NO_3^- in the stomach, the body pool, and the saliva, respectively, and x_4 denotes the amount of NO_2^- in the saliva. u_1 denotes the uptake of nitrate.

K_a	:	absorption rate constant;
b	:	saliva production;
V_s	:	volume of saliva compartment;
K_2	:	excretion rate constant for NO_3^- from body pool into saliva;
K_T	:	excretion rate constant;
K_1	:	rate constant for conversion of NO_3^- into NO_2^-;
K	:	endogenous NO_3^- synthesis rate;
V_d	:	NO_3^- distribution volume.

We assume the constants K, K_T, and V_d to be known. The unknown parameters are K_a, K_2, K_1, b, V_s, and the initial condition x_0. We can observe the concentration of NO_3^- in the body pool and the saliva, and the concentration of NO_2^- in the saliva, i.e., we can observe $x_2/V_d, x_3/V_s$, and x_4/V_s. Using the following re-parametrization

$$\alpha = K_a, \quad \beta = K_2, \quad \gamma = K_1, \quad \delta = \frac{b}{V_s}, \quad \varepsilon = \frac{1}{V_s},$$

which is a bijection for the unknown parameters, for $V_s \neq 0$, defining

$$h_1 = K_T, \quad h_2 = \frac{1}{V_d}.$$

and taking as input vector $u = \begin{pmatrix} u_1 & K \end{pmatrix}^T$, we obtain the following structured linear system,

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

with $x = \begin{pmatrix} x_1 & x_2 & x_3 & x_4 \end{pmatrix}^T$, $p = (\alpha, \beta, \gamma, \delta, \varepsilon, \varphi_1, \varphi_2, \varphi_3, \varphi_4)$,

$$A(p) = \begin{pmatrix} -\alpha & 0 & \delta & 0 \\ \alpha & -\beta - h_1 & 0 & 0 \\ 0 & \beta & -\gamma - \delta & 0 \\ 0 & 0 & \gamma & -\delta \end{pmatrix}, \quad B(p) = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ 0 & 0 \\ 0 & 0 \end{pmatrix},$$

$$C(p) = \begin{pmatrix} 0 & h_2 & 0 & 0 \\ 0 & 0 & \varepsilon & 0 \\ 0 & 0 & 0 & \varepsilon \end{pmatrix}, \quad x_0(p) = \begin{pmatrix} \varphi_1 \\ \varphi_2 \\ \varphi_3 \\ \varphi_4 \end{pmatrix}.$$

Formally this system is parametrized by the parametrization (P, f), with

$$\begin{aligned}
P &= \{(\alpha, \beta, \gamma, \delta, \varepsilon, \varphi_1, \varphi_2, \varphi_3, \varphi_4) \in R_+^9 \subset R^9\}, \\
f(p) &= (A(p), B(p), C(p), x_0(p)) \quad \text{for } p \in P.
\end{aligned}$$

Note that f is a polynomial map, thanks to the re-parametrization.

Proposition 4.1 *The parametrization (P, f) of the structured linear dynamic system described above is structurally identifiable from the Markov parameters and the initial parameters as a positive linear system.*

Proof. Because this system is a positive linear system, Proposition 2.10 is used to check structural identifiability. We start with structural minimality of the system seen as an ordinary linear dynamic system. For structural weak reachability, we have to check whether

$$\text{rank}\big(B(p) \quad A(p)B(p) \quad A(p)^2B(p) \quad A(p)^3B(p) \quad x_0(p) \quad A(p)x_0(p) \quad A(p)^2x_0(p) \quad A(p)^3x_0(p)\big) = 4$$

outside an algebraic set. Using [11] and MAPLE, [5], the pair $(A(p), B(p))$ turns out to be structurally reachable, so also $(A(p), (\,B(p) \quad x_0(p)\,))$ is a structurally reachable pair. Calculation by hand gives the same conclusions.

For the structural observability, we use the same method as for the structural reachability, and we conclude that $(A(p), C(p))$ is structurally observable. Calculations by hand give the same conclusions, both for structural weak reachability and structural observability.

Now we may check structural identifiability by the similarity approach. For $p \in R^9$, find all $T \in R^{4\times4}$ and $\tilde{p} \in R^9$ such that

$$C(p)T = C(\tilde{p}), \tag{4.1}$$
$$B(p) = TB(\tilde{p}), \tag{4.2}$$
$$A(p)T = TA(\tilde{p}), \tag{4.3}$$
$$x_0(p) = Tx_0(\tilde{p}). \tag{4.4}$$

When we solve this set of equations with the help of the MAPLE function *'solve'*, we obtain the solution $(\tilde{p}, T) = (p, I)$. Also the calculation by hand gives this unique solution, with algebraic set $S = \{(\alpha, \beta, \gamma, \delta, \varepsilon, \varphi_1, \varphi_2, \varphi_3, \varphi_4) \in R^9 \mid \beta\gamma = 0\}$. This choice follows from the calculations. For the nitrate model the exclusion of S is not restricting. Indeed, $\beta = 0$ or $\gamma = 0$ would give $K_2 = 0$ or $K_1 = 0$, but then there would be no flow of nitrate from the body pool into the saliva or no conversion of NO_3^- into NO_2^-.

With Theorem 2.9 and Proposition 2.10 it follows that the parametrization is structurally identifiable as a positive linear system. □

Remark 4.2 It may be proven that the parametrization is also structurally identifiable if we only have observations of y_1 and y_3, or of y_2 and y_3. □

To determine the discrete-time Markov parameters and initial parameters from the observations of u and y, appearing in discrete-time, we observe that $m = 2$ and $r = 4 + 1 - \text{rank}(C(p)) = 2$ outside an algebraic set. Note that $2 \le q \le r$, so also $q = 2$. So the condition from Theorem 3.12 is

$$\text{rank}\begin{pmatrix} U(1,3,N-2) \\ Y(1,2,N-2) \end{pmatrix} = 4 + 2(2+1) = 10, \tag{4.5}$$

for which necessary conditions are $\text{rank}(U(1,3,N-2)) = 6$ and $N \ge 12$. If Condition (4.5) is satisfied, and the continuous-time input is constant over the sampling interval T, i.e. $u(t) = u_T(j)$ for $jT \le t < (j+1)T$, with $0 < T < r(W_P)$, where P is such that $K(W_P)$ is bounded, then all conditions of Theorem 3.12 are satisfied, so the parameters can uniquely be determined from the observations of u and y. But in reality it turns out that the second input, u_2, is a constant input, on which no control is possible. So $u_2(t) = K$, for all $t \in R$. Now Condition 4 of Theorem 3.14 is not satisfied, since for all $N \ge 12$ and for all discrete-time $u_1(1), u_1(2), \ldots, u_1(N)$,

$$\text{rank}(U(1,3,N-2)) = \text{rank}\begin{pmatrix} u_1(1) & u_1(2) & \cdots & u_1(N-2) \\ K & K & \cdots & K \\ u_1(2) & u_1(3) & \cdots & u_1(N-1) \\ K & K & \cdots & K \\ u_1(3) & u_1(4) & \cdots & u_1(N) \\ K & K & \cdots & K \end{pmatrix} \le 4.$$

So the sufficient conditions of Theorem 3.14 are not satisfied, and still nothing can be said about structural identifiability from the observations of u and y. From Proposition 3.3 it follows that the Markov parameters and the initial parameters cannot be uniquely determined. How to deal with this problem is not clear yet.

5. Case study 2: PB-PK modeling of dioxin

The second case study concerns a Physiologically Based Pharmaco Kinetic model of dioxin, (to be precise, 2,3,7,8-tetrachlorodibenzodioxin or TCDD), describing the dispersion of TCDD in a rat, [18]. In this model five compartments are considered: blood, liver, slowly perfused tissue, richly perfused tissue, and fat, as shown in Figure 2.

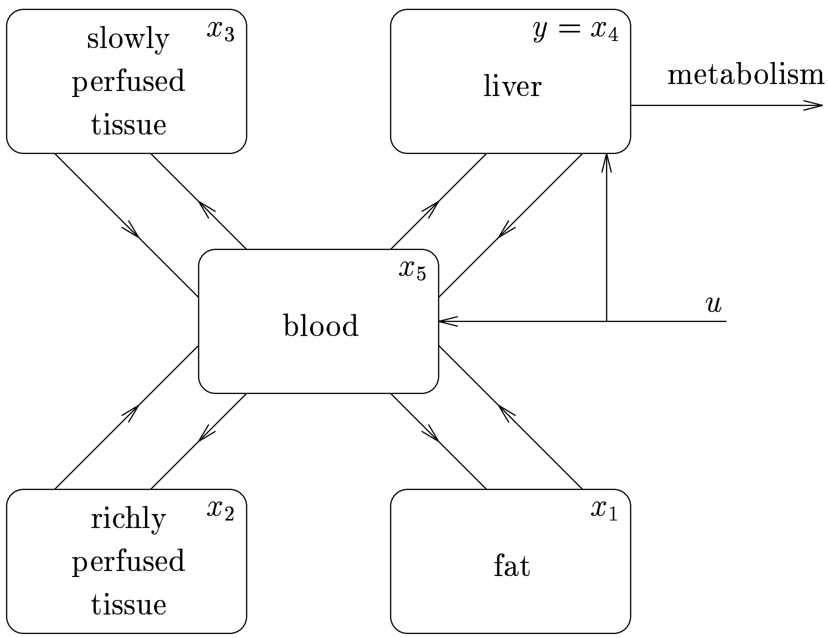

Figure 2: PB-PK model of dioxin in a rat

The model is described by the following differential equations:

$$
\begin{aligned}
\dot{x}_1 &= \frac{Q_f^c Q}{V_b(1+K_{ab})} x_5 - \frac{Q_f^c Q}{V_f P_f} x_1, \\
\dot{x}_2 &= \frac{Q_r^c Q}{V_b(1+K_{ab})} x_5 - \frac{Q_r^c Q}{V_r P_r} x_2, \\
\dot{x}_3 &= \frac{Q_s^c Q}{V_b(1+K_{ab})} x_5 - \frac{Q_s^c Q}{V_s P_s} x_3, \\
\dot{x}_4 &= \frac{Q_l^c Q}{V_b(1+K_{ab})} x_5 - \left(\frac{Q_l^c Q}{V_l P_l} + \frac{K_{fc}}{BW^{(1-c_a)} P_l} \right) x_4 + \frac{1}{1+K_{ab}} u, \\
\dot{x}_5 &= \frac{Q_f^c Q}{V_f P_f} x_1 + \frac{Q_r^c Q}{V_r P_r} x_2 + \frac{Q_s^c Q}{V_s P_s} x_3 + \frac{Q_l^c Q}{V_l P_l} x_4 - \frac{Q}{V_b(1+K_{ab})} x_5 + \frac{K_{ab}}{1+K_{ab}} u,
\end{aligned}
$$

in which x_1, x_2, x_3, x_4, and x_5 is the amount of dioxin in the fat (f), the richly perfused tissue (r), the slowly perfused tissue (s), the liver (l), and the blood (b), respectively. The function u denotes the uptake of dioxin.

Q	:	cardiac output;
$Q_f^c, Q_r^c, Q_s^c, Q_l^c$	:	blood flows to f, r, s, and l, respectively as fraction of Q;
V_f, V_r, V_s, V_l, V_b	:	volumes of f, r, s, l, and b, respectively;
P_f, P_r, P_s, P_l	:	blood partition coefficients of f, r, s, and l, respectively;
K_{ab}	:	dissociation constant for the binding of dioxin to blood constituents;
K_{fc}	:	first order elimination rate constant;
BW	:	body weight;
c_a	:	allometric scaling coefficient;

Note that we have $Q_f^c + Q_r^c + Q_s^c + Q_l^c = 1$. We assume the blood flows $(Q_f^c, Q_r^c, Q_s^c, Q_l^c, Q)$ to be known, as well as the organ volumes $(V_f, V_r, V_s, V_l, V_b)$, the bodyweight (BW), and the allometric scaling coefficient (c_a). The unknown parameters are $P_f, P_r, P_s, P_l, K_{fc}, K_{ab}$, and the initial condition x_0. Re-parametrize the system by defining:

$$\alpha = \frac{Q_f^c Q}{V_f P_f}, \qquad \beta = \frac{Q_r^c Q}{V_r P_r}, \qquad \gamma = \frac{Q_s^c Q}{V_s P_s},$$
$$\delta = \frac{Q_l^c Q}{V_l P_l}, \qquad \varepsilon = \frac{K_{fc}}{BW^{(1-c_a)} P_l}, \qquad \xi = \frac{1}{1 + K_{ab}},$$

and define

$$h_1 = \frac{Q_f^c Q}{V_b}, \quad h_2 = \frac{Q_r^c Q}{V_b}, \quad h_3 = \frac{Q_s^c Q}{V_b}, \quad h_4 = \frac{Q_l^c Q}{V_b}.$$

Note that α, β, γ, δ, ε, and ξ give a bijection in the unknown parameters. Then we can write the differential equations in the following form:

$$\begin{aligned}
\dot{x}_1 &= -\alpha x_1 + h_1 \xi x_5, \\
\dot{x}_2 &= -\beta x_2 + h_2 \xi x_5, \\
\dot{x}_3 &= -\gamma x_3 + h_3 \xi x_5, \\
\dot{x}_4 &= -(\delta + \varepsilon) x_4 + h_4 \xi x_5 + \xi u, \\
\dot{x}_5 &= \alpha x_1 + \beta x_2 + \gamma x_3 + \delta x_4 - \sum_{i=1}^{4} h_i \xi x_5 + (1 - \xi) u.
\end{aligned}$$

The amount of dioxin in the liver can be measured, i.e., observations are available for x_4. Taking these observations as output y, the system can be stated in the compact form of a structured linear system as follows:

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

with $x = \begin{pmatrix} x_1 & x_2 & x_3 & x_4 & x_5 \end{pmatrix}^T$, $p = (\alpha, \beta, \gamma, \delta, \varepsilon, \xi, \varphi_1, \varphi_2, \varphi_3, \varphi_4, \varphi_5)$,

$$A(p) = \begin{pmatrix} -\alpha & 0 & 0 & 0 & h_1\xi \\ 0 & -\beta & 0 & 0 & h_2\xi \\ 0 & 0 & -\gamma & 0 & h_3\xi \\ 0 & 0 & 0 & -\delta-\varepsilon & h_4\xi \\ \alpha & \beta & \gamma & \delta & -\sum_{i=1}^4 h_i\xi \end{pmatrix}, \quad B(p) = \begin{pmatrix} 0 \\ 0 \\ 0 \\ \xi \\ 1-\xi \end{pmatrix}, \quad x_0(p) = \begin{pmatrix} \varphi_1 \\ \varphi_2 \\ \varphi_3 \\ \varphi_4 \\ \varphi_5 \end{pmatrix},$$

$C(p) = \begin{pmatrix} 0 & 0 & 0 & 1 & 0 \end{pmatrix}$. Note that the values of h_1, h_2, h_3, and h_4 are known. We assume that these values are mutually unequal and nonzero. Formally this system is parametrized by the parametrization (P,f), with

$$\begin{aligned} P &= \{(\alpha,\beta,\gamma,\delta,\varepsilon,\xi,\varphi_1,\varphi_2,\varphi_3,\varphi_4,\varphi_5)\in R_+^{11}\subset R^{11}\}, \\ f(p) &= (A(p),B(p),C(p),x_0(p)) \quad \text{for } p\in P. \end{aligned}$$

The problem is whether this parametrization is structurally identifiable from the Markov parameters and the initial parameters.

Proposition 5.1 *The parametrization (P,f) of the structured linear dynamic system described above is structurally identifiable from the Markov parameters and the initial parameters as a positive linear system.*

Proof. Using Proposition 2.10 we will check structural identifiability. First we will check for structural weak reachability and structural observability for the system seen as an ordinary linear dynamic system. Again, using [11] and MAPLE, [5] $(A(p),B(p))$ is shown to be a structurally reachable pair, so also $(A(p),(\,B(p)\quad x_0(p)\,))$ is a structurally reachable pair. Calculation by hand gives the same conclusions. Also $(A(p),C(p))$ turns out to be a structurally observable pair.

Now we may check structural identifiability by the similarity approach. For $p\in R^{11}$, find all $T\in R^{5\times 5}$ and $\tilde{p}\in R^{11}$ such that

$$\begin{aligned} C(p)T &= C(\tilde{p}), && (5.1)\\ B(p) &= TB(\tilde{p}), && (5.2)\\ A(p)T &= TA(\tilde{p}), && (5.3)\\ x_0(p) &= Tx_0(\tilde{p}). && (5.4) \end{aligned}$$

Solving this set of equations for $(\tilde{p},T)$ with the MAPLE function *'solve'* is not possible. The object is too large to be solved by the MAPLE function *'solve'*. Therefore we will solve it by hand. We take $S=\{(\alpha,\beta,\gamma,\delta,\varepsilon,\xi,\varphi_1,\varphi_2,\varphi_3,\varphi_4,\varphi_5)\in R^{11}\mid(\alpha-\beta)(\alpha-\gamma)(\beta-\gamma)\alpha\beta\gamma\xi=0\}$ for the algebraic set. This choice follows from the calculations below. For the dioxin model the exclusion of S is not restricting. If for example $\alpha=0$, then $\frac{Q_f^c Q}{V_f P_f}=0$, so $Q_f^c Q=0$. Then also $h_1=0$, so the fat compartment could be eliminated. The same holds for β and γ. Since $\xi=1/(1+K_{ab})$, $\xi=0$ is not possible. Now assume $\alpha=\beta$. Then the flow of dioxin from the fat and the richly perfused tissue to the blood will have the same rate constant, which is not very realistic. The same can be said for $\alpha=\gamma$ and $\beta=\gamma$.

From (5.1) it immediately follows that T has the following form:

$$T=\begin{pmatrix} t_{11} & t_{12} & t_{13} & t_{14} & t_{15}\\ t_{21} & t_{22} & t_{23} & t_{24} & t_{25}\\ t_{31} & t_{32} & t_{33} & t_{34} & t_{35}\\ 0 & 0 & 0 & 1 & 0\\ t_{51} & t_{52} & t_{53} & t_{54} & t_{55} \end{pmatrix}.$$

(5.2) gives the following equations

$$\begin{aligned} 0 &= t_{14}\tilde{\xi}+t_{15}(1-\tilde{\xi}),\\ 0 &= t_{24}\tilde{\xi}+t_{25}(1-\tilde{\xi}),\\ 0 &= t_{34}\tilde{\xi}+t_{35}(1-\tilde{\xi}),\\ \xi &= \tilde{\xi},\\ 1-\xi &= t_{54}\tilde{\xi}+t_{55}(1-\tilde{\xi}). \end{aligned}$$

Because $\tilde{\xi}=\xi$, we have for the last equation

$$1-\xi=t_{54}\xi+t_{55}(1-\xi). \qquad (5.5)$$

From the first three equations we have that if $t_{i5} \neq 0$ and $\tilde{\xi} \neq 0$, then $\frac{t_{i4}}{t_{i5}} = \frac{\tilde{\xi}-1}{\tilde{\xi}}$, if $t_{i5} = 0$ then $t_{i4} = 0$, for $i = 1,2,3$. So, even if $t_{i5} = 0$,

$$t_{i4}t_{j5} = t_{j4}t_{i5}, \text{ for } i,j = 1,2,3. \tag{5.6}$$

The fourth row of (5.3) gives the following equations

$$\begin{aligned} h_4\xi t_{51} &= 0 & \Rightarrow t_{51} = 0, \\ h_4\xi t_{52} &= 0 & \Rightarrow t_{52} = 0, \\ h_4\xi t_{53} &= 0 & \Rightarrow t_{53} = 0, \\ -(\delta+\varepsilon) + h_4\xi t_{54} &= -(\tilde{\delta}+\tilde{\varepsilon}), & \\ h_4\xi t_{55} &= h_4\tilde{\xi}. & \end{aligned} \tag{5.7}$$

The implications hold outside the set S, so if $\xi \neq 0$. From the last equation it follows, together with $\tilde{\xi} = \xi$, that $t_{55} = 1$. Then, with (5.5), we have $t_{54} = 0$. So, from (5.7), it follows that $\tilde{\delta} + \tilde{\varepsilon} = \delta + \varepsilon$.

Let's consider the first three entries of the fourth column of (5.3).

$$\begin{aligned} -\alpha t_{14} &= -(\tilde{\delta}+\tilde{\varepsilon})t_{14} + \tilde{\delta}t_{15}, \\ -\beta t_{24} &= -(\tilde{\delta}+\tilde{\varepsilon})t_{24} + \tilde{\delta}t_{25}, \\ -\gamma t_{34} &= -(\tilde{\delta}+\tilde{\varepsilon})t_{34} + \tilde{\delta}t_{35}. \end{aligned}$$

Let $\sigma_1 = \alpha$, $\sigma_2 = \beta$, and $\sigma_3 = \gamma$. Multiplying the ith equation with t_{j5}, the jth with t_{i5}, and subtract, we obtain

$$(\sigma_i - \sigma_j)t_{j4}t_{i5} = 0, \quad i,j = 1,2,3, \quad i \neq j,$$

using (5.6). Outside S, $\sigma_i - \sigma_j \neq 0$. So we have $t_{i4}t_{j5} = t_{j4}t_{i5} = 0$, for $i,j = 1,2,3$, $i \neq j$. It follows that two pairs of the pairs (t_{i4}, t_{i5}), $i = 1,2,3$, are zero. Looking at the fifth entry of the fifth column of (5.3), i.e.

$$\alpha t_{15} + \beta t_{25} + \gamma t_{35} - \sum_{i=1}^{4} h_i\xi = -\sum_{i=1}^{4} h_i\tilde{\xi} \quad (= -\sum_{i=1}^{4} h_i\xi),$$

we see that $\alpha t_{15} + \beta t_{25} + \gamma t_{35} = 0$. Since there are two entries of (t_{15}, t_{25}, t_{35}) equal to zero also the third one is equal to zero outside S. It follows that $t_{i5} = t_{i4} = 0$ for $i = 1,2,3$. From the fifth entry of the fourth column of (5.3) it now follows that $\tilde{\delta} = \delta$, so also $\tilde{\varepsilon} = \varepsilon$.

Up till now we have obtained the following form for T:

$$T = \begin{pmatrix} t_{11} & t_{12} & t_{13} & 0 & 0 \\ t_{21} & t_{22} & t_{23} & 0 & 0 \\ t_{31} & t_{32} & t_{33} & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix} = \begin{pmatrix} T_1 & 0 \\ 0 & I \end{pmatrix}.$$

Considering the first column of (5.3), the subsequent nontrivial equations follow:

$$\begin{aligned} -\alpha t_{11} &= -\tilde{\alpha}t_{11}, \\ -\beta t_{21} &= -\tilde{\alpha}t_{21}, \\ -\gamma t_{31} &= -\tilde{\alpha}t_{31}, \\ \alpha t_{11} + \beta t_{21} + \gamma t_{31} &= \tilde{\alpha}. \end{aligned}$$

Outside the algebraic set S, only one of $\{t_{11}, t_{21}, t_{31}\}$ can be nonzero, the other two are zero. If we add these four equations, we obtain $0 = \tilde{\alpha}(1 - t_{11} - t_{21} - t_{31})$, so $t_{11} + t_{21} + t_{31} = 1$. So, exactly one out of $\{t_{11}, t_{21}, t_{31}\}$ is equal to one, the others are equal to zero. Equivalently, from the second and third column of (5.3), it follows that exactly one out of $\{t_{12}, t_{22}, t_{32}\}$ and exactly one out of $\{t_{12}, t_{23}, t_{33}\}$ is equal to one, the others are zero. Because T is nonsingular, it follows that T_1 has to be a permutation matrix. Now the first entry of the fourth column gives:

$$h_1 = t_{11}h_1 + t_{12}h_2 + t_{13}h_3.$$

Because T_1 is a permutation, only one out of $\{t_{11}, t_{12}, t_{13}\}$ is equal to one, the other two are zero. If $t_{12} = 1$, we would have $h_1 = h_2$. If $t_{13} = 1$, we would have $h_1 = h_3$. Both cases are impossible, because we assumed that h_1, h_2, h_3, h_4 are mutually different. So $t_{11} = 1$ and $t_{12} = t_{13} = 0$. Equivalently, from the second and the third entry of the fourth column, we obtain $t_{22} = t_{33} = 1$. It follows that $T = I$, and $\tilde{\alpha} = \alpha$, $\tilde{\beta} = \beta$, $\tilde{\gamma} = \gamma$, and from (5.4) it follows that $\tilde{\varphi}_i = \varphi_i$, for $i = 1, 2, \ldots, 5$, i.e., $\tilde{p} = p$. From Theorem 2.9 it follows that the parametrization is structurally identifiable as parametrization of an ordinary structured linear system. Moreover, using Proposition 2.10, the parametrization is also structurally identifiable as positive linear system. □

We have now solved the problem of structural identifiability of the parameters from the Markov parameters and the initial parameters, but can we identify the Markov parameters and the initial parameters from the observations of u and y, appearing in discrete-time? Since $\text{rank}(C) = 1$, we have $q = r = n = 5$, so the condition from Theorem 3.12 is

$$\text{rank}\begin{pmatrix} U(1, 6, N-5) \\ Y(1, 5, N-5) \end{pmatrix} = n + m(q+1) = 2n + 1 = 11, \tag{5.8}$$

since $m = 1$. For this condition, we need $\text{rank}(U(1, 6, N-5)) = 6$ and $N \geq 16$. Again, if Condition (5.8) is satisfied, and the continuous-time input is constant over the sampling interval, i.e. $u(t) = u_T(j)$ for $jT \leq t < (j+1)T$, with $0 < T < r(W_P)$, where P is such that $K(W_P)$ is bounded, then all conditions of Theorem 3.12 are satisfied, so the parameters can uniquely be determined from the observations of u and y.

6. Case study 3: Benzo(a)pyrene model

The third case study concerns that of a Benzo(a)pyrene model, developed at RIVM. It is a simulation model of intravenous injection of benzo(a)pyrene (BaP) to a bile duct cannulated rat. The model both describes the amount of BaP and the amount of metabolites in several compartments. We will only treat the model that describes the amount of BaP. This model consists of six compartments: lung, liver, fat, richly perfused tissue, slowly perfused tissue and blood, as shown in Figure 3.
The system is given by the following differential equations,

$$\begin{aligned}
\dot{x}_1 &= \frac{Q_l}{V_b}x_6 - \left(\frac{Q_l}{V_l P_l} + K_l\right)x_1, \\
\dot{x}_2 &= \frac{Q_{li}}{V_b}x_6 - \left(\frac{Q_{li}}{V_{li} P_{li}} + K_{li}\right)x_2, \\
\dot{x}_3 &= \frac{Q_f}{V_b}x_6 - \frac{Q_f}{V_f P_f}x_3, \\
\dot{x}_4 &= \frac{Q_r}{V_b}x_6 - \frac{Q_r}{V_r P_r}x_4, \\
\dot{x}_5 &= \frac{Q_s}{V_b}x_6 - \frac{Q_s}{V_s P_s}x_5, \\
\dot{x}_6 &= \frac{Q_l}{V_l P_l}x_1 + \frac{Q_{li}}{V_{li} P_{li}}x_2 + \frac{Q_f}{V_f P_f}x_3 + \frac{Q_r}{V_r P_r}x_4 + \frac{Q_s}{V_s P_s}x_5 - \frac{Q_c}{V_b}x_6 + I_t C_{inf},
\end{aligned}$$

in which x_1, x_2, x_3, x_4, x_5, and x_6, is the amount of BaP in the lung (l), the liver (li), the fat (f), the richly perfused tissue (r), the slowly perfused tissue (s), and the blood (b), respectively.

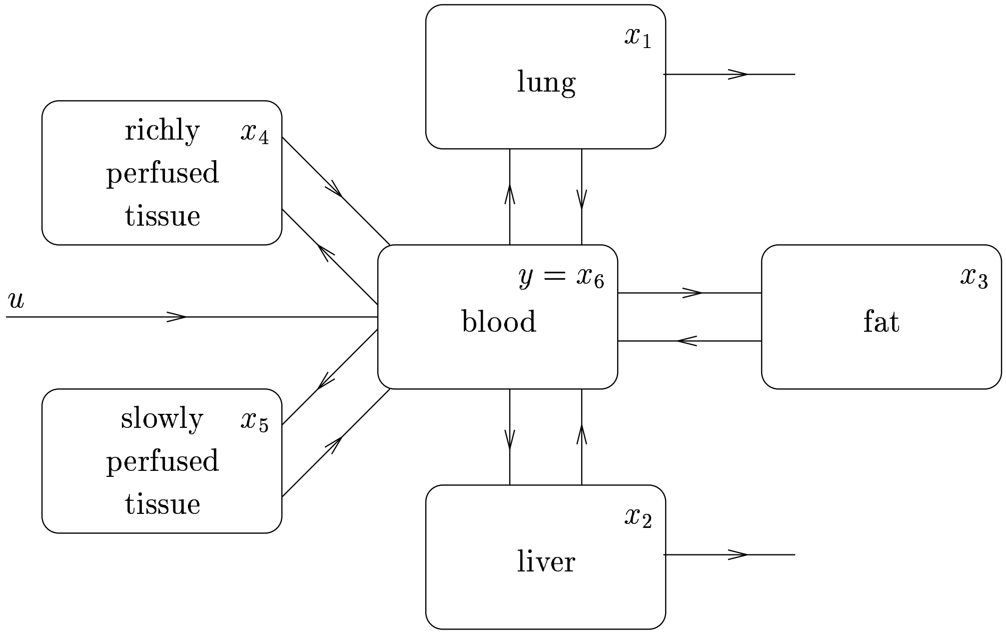

Figure 3: Benzo(a)pyrene model

Q_c	:	cardiac output;
$Q_l, Q_{li}, Q_f, Q_r, Q_s$	:	blood flows to l, li, f, r, and s, respectively;
$V_l, V_{li}, V_f, V_r, V_s, V_b$	:	volumes of l, li, f, r, s, and b, respectively;
$P_l, P_{li}, P_f, P_r, P_s$	:	partition coefficients of l, li, f, r, and s, respectively;
K_l, K_{li}	:	metabolic degradation rates of l and li, respectively;
I_t	:	infusion rate (ml/min);
C_{inf}	:	concentration infusion.

Note that we have $Q_l + Q_{li} + Q_f + Q_r + Q_s = Q_c$. We assume to be known the blood flows $(Q_l, Q_{li}, Q_f, Q_r, Q_s, Q_c)$, the organ volumes $(V_l, V_{li}, V_f, V_r, V_s, V_b)$, and the infusion (I_t, C_{inf}). The unknown parameters are $P_l, P_{li}, P_f, P_r, P_s, K_l, K_{li}$ and the initial condition x_0. Let us use the following bijection:

$$(P_l, P_{li}, P_f, P_r, P_s, K_l, K_{li}) \mapsto (\alpha, \beta, \gamma, \delta, \varepsilon, \xi, \rho),$$

with

$$\alpha = \frac{Q_l}{V_l P_l}, \qquad \beta = \frac{Q_{li}}{V_{li} P_{li}}, \qquad \gamma = \frac{Q_f}{V_f P_f},$$
$$\delta = \frac{Q_r}{V_r P_r}, \qquad \varepsilon = \frac{Q_s}{V_s P_s}, \qquad \xi = K_l, \qquad \rho = K_{li},$$

and define

$$h_1 = \frac{Q_l}{V_b}, \quad h_2 = \frac{Q_{li}}{V_b}, \quad h_3 = \frac{Q_f}{V_b}, \quad h_4 = \frac{Q_r}{V_b}, \quad h_5 = \frac{Q_s}{V_b}, \quad h_6 = \frac{Q_c}{V_b}.$$

Then we can write the differential equations in the following form:

$$
\begin{aligned}
\dot{x}_1 &= -(\alpha+\xi)x_1 + h_1 x_6,\\
\dot{x}_2 &= -(\beta+\rho)x_2 + h_2 x_6,\\
\dot{x}_3 &= -\gamma x_3 + h_3 x_6,\\
\dot{x}_4 &= -\delta x_4 + h_4 x_6,\\
\dot{x}_5 &= -\varepsilon x_5 + h_5 x_6,\\
\dot{x}_6 &= \alpha x_1 + \beta x_2 + \gamma x_3 + \delta x_4 + \varepsilon x_5 - h_6 x_6 + I_t C_{inf}.
\end{aligned}
$$

We will take the infuse as input: $u(t) = I_t C_{inf}$. There are measurements in the blood, i.e., we can observe x_6. We take this observation as output y. Now we can write the system in the compact form of a structured linear system:

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

with $x = \begin{pmatrix} x_1 & x_2 & x_3 & x_4 & x_5 & x_6 \end{pmatrix}^T$, $p = (\alpha, \beta, \gamma, \delta, \varepsilon, \xi, \rho, \varphi_1, \varphi_2, \varphi_3, \varphi_4, \varphi_5, \varphi_6)$,

$$
A(p) = \begin{pmatrix}
-\alpha-\xi & 0 & 0 & 0 & 0 & h_1\\
0 & -\beta-\rho & 0 & 0 & 0 & h_2\\
0 & 0 & -\gamma & 0 & 0 & h_3\\
0 & 0 & 0 & -\delta & 0 & h_4\\
0 & 0 & 0 & 0 & -\varepsilon & h_5\\
\alpha & \beta & \gamma & \delta & \varepsilon & -h_6
\end{pmatrix}, \quad
B(p) = \begin{pmatrix} 0\\0\\0\\0\\0\\1 \end{pmatrix}, \quad
x_0(p) = \begin{pmatrix} \varphi_1\\ \varphi_2\\ \varphi_3\\ \varphi_4\\ \varphi_5\\ \varphi_6 \end{pmatrix},
$$

$C(p) = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$. Note that we know the values of h_1, h_2, h_3, h_4, h_5, and h_6. We assume these values to be mutually unequal and nonzero. Formally, this system is parametrized by the parametrization (P, f), with

$$
\begin{aligned}
P &= \{(\alpha, \beta, \gamma, \delta, \varepsilon, \xi, \rho, \varphi_1, \phi_2, \varphi_3, \varphi_4, \varphi_5, \varphi_6) \in R_+^{13} \subset R^{13}\},\\
f(p) &= (A(p), B(p), C(p), x_0(p)) \quad \text{for } p \in P.
\end{aligned}
$$

Proposition 6.1 *The parametrization (P, f) of the structured linear dynamic system described above is* not *structurally identifiable from the Markov parameters and the initial parameters as a positive linear system.*

Proof. Using Proposition 2.10 we will check structural identifiability. First we will check for structural reachability and structural observability for the system seen as an ordinary linear dynamic system. Again, using [11] and MAPLE, [5] $(A(p), B(p))$ is shown to be a structurally reachable pair, so also $(A(p), (\,B(p) \quad x_0(p)\,))$ is a structurally reachable pair, and $(A(p), C(p))$ is a structurally observable pair.

Now we may check structural identifiability by the similarity approach. Using the MAPLE function *'solve'*, we obtain for the set of equations

$$
\begin{aligned}
C(p)T &= C(\tilde{p}), && (6.1)\\
B(p) &= TB(\tilde{p}), && (6.2)\\
A(p)T &= TA(\tilde{p}), && (6.3)\\
x_0(p) &= Tx_0(\tilde{p}), && (6.4)
\end{aligned}
$$

two solutions for $(\tilde{p}, T)$, with $p = (\alpha, \beta, \gamma, \delta, \varepsilon, \xi, \rho, \varphi_1, \varphi_2, \varphi_3, \varphi_4, \varphi_5, \varphi_6)$:

$$
\tilde{p} = (\beta\frac{h_2}{h_1}, \alpha\frac{h_1}{h_2}, \gamma, \delta, \varepsilon, \rho + \beta - \beta\frac{h_2}{h_1}, \xi + \alpha - \alpha\frac{h_1}{h_2}, \frac{h_1}{h_2}\varphi_2, \frac{h_2}{h_1}\varphi_1, \varphi_3, \varphi_4, \varphi_5, \varphi_6),
$$

$$T = \begin{pmatrix} 0 & \frac{h_1}{h_2} & 0 & 0 & 0 & 0 \\ \frac{h_2}{h_1} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix},$$

and $\tilde{p} = p$, $T = I$. We have found a nonsingular $T \neq I$ and a $\tilde{p} \neq p$ such that (6.1), (6.2), and (6.3) hold, so the parametrization is not structurally identifiable. Also as a positive linear system the parametrization is not structurally identifiable if $\rho+\beta-\beta\frac{h_2}{h_1}$, and $\xi+\alpha-\alpha\frac{h_1}{h_2}$ are positive. □

In a specific case it may be assumed that the partition coefficients P_l, P_{li}, P_f, P_r, and P_s are already known, nonzero, and mutually unequal. So the only unknowns are K_l and K_{li}, and the initial conditions. This system is parametrized by the parametrization (P_1, f_1), with

$$\begin{aligned} P_1 &= \{(\xi, \rho, \varphi_1, \varphi_2, \varphi_3, \varphi_4, \varphi_5, \varphi_6) \in R^8_+ \subset R^8\}, \\ f_1(p) &= (A(p), B(p), C(p), x_0(p)) \quad \text{for } p \in P_1. \end{aligned}$$

$S = \{(\xi, \rho, \varphi_1, \varphi_2, \varphi_3, \varphi_4, \varphi_5, \varphi_6) \in R^8 \mid (\alpha+\xi-\beta-\rho)(\alpha+\xi-\gamma)(\alpha+\xi-\delta)(\beta+\rho-\gamma)(\beta+\rho-\delta) = 0\}$ is taken to be the algebraic set. The MAPLE function *'solve'* gives the unique solution $(\tilde{p}, T) = (p, I)$. It follows that the parametrization (P_1, f_1) of the system is structurally identifiable from the Markov parameters and the initial parameters, and this also holds for the positive linear system.

To determine the discrete-time Markov parameters and initial parameters from the observations of u and y, we observe that $r = 6$, and also $q = 6$. From Proposition 6.1, it follows that in the case that the partition coefficients, the initial conditions, and K_l and K_{li} are unknown, the parametrization is not structurally identifiable from the Markov parameters and the initial conditions, therefore nothing can be said about the structurally identifiable from the observations. In the case the partition coefficients are known, the following can be said. The condition from Theorem 3.12 is

$$\operatorname{rank}\begin{pmatrix} U(1,7,N-6) \\ Y(1,6,N-6) \end{pmatrix} = 6 + 1(6+1) = 13, \tag{6.5}$$

for which necessary conditions are $\operatorname{rank}(U(1,7,N-6)) = 7$ and $N \geq 19$. If Condition (6.5) is satisfied, and the continuous-time input is constant over the sampling interval T, i.e. $u(t) = u_T(j)$ for $jT \leq t < (j+1)T$, with $0 < T < r(W_P)$, where P is such that $K(W_P)$ is bounded, then all conditions of Theorem 3.12 are satisfied, so the parameters are structurally identifiable from the observations of u and y.

7. Conclusions

Methods to test the structural identifiability of linear compartmental systems have been given, not only the structural identifiability from the Markov parameters and the initial parameters, but also from the input-output data. Those methods have been applied to test the structural identifiability of the parametrization of three models.

Another problem involving the class of linear compartmental systems is that this class is a subclass of positive linear systems. Necessary and sufficient conditions for structural identifiability of positive linear systems depend on the realization problem of positive linear systems, which is not completely solved yet.

Acknowledgement
The author acknowledges the useful suggestions received on the problem of this paper from J.H. van Schuppen.

A. Proof of Proposition 3.8

Since it is given that $(A, \tilde{B})$ is a reachable pair and (A, C) is an observable pair, there exists a minimal realization $(A, B, C, D, x_0) \in \text{L}\Sigma\text{P}(n, m, k)$ of the considered input-output sequence, with n, m, k known. Let the integer q and the sequential selector matrix $S(q)$ be constructed from the given input-output sequence by the MD algorithm in [20]. If

$$\text{rank}\begin{pmatrix} U(1, q+1, N-q) \\ S(q)Y(1, q, N-q) \end{pmatrix} < n + m(q+1),$$

then the Markov parameters and initial parameters cannot uniquely be determined, else with Lemma 2 in [20] it follows that for every realization $(A, B, C, D, x_0) \in \text{L}\Sigma\text{P}(n, m, k)$, satisfying the input-output sequence,

$$\text{rank}(S(q)R(q)) = \text{rank}(R(q)) = \text{rank}(S(q)) = n,$$

so, with $\tilde{B} = (B \;\; x_0)$,

$$\text{rank}(S(q)H(q, n)) = \text{rank}(S(q)R(q)(\tilde{B} \;\; \cdots \;\; A^{n-1}\tilde{B})) = n.$$

The matrix $S(q)H(q, n)$ has exactly n rows, say $r_1, r_2, \ldots, r_n$, so those are mutually linearly independent. Because also $\text{rank}(H(q+1, n)) = n$, the $(qk+1)$th row p_1 up to the $(qk+k)$th row p_k of $H(q+1, n)$ are linearly dependent on $r_1, r_2, \ldots, r_n$, i.e., there exist unique α_{ij}, $i = 1, \ldots, k$, $j = 1, \ldots, n$, such that

$$p_i = \sum_{j=1}^{n} \alpha_{ij} r_j, \quad \text{for } i = 1, \ldots, k.$$

Define

$$K_1 = \begin{pmatrix} \alpha_{11} & \cdots & \alpha_{1n} \\ \vdots & & \vdots \\ \alpha_{k1} & \cdots & \alpha_{kn} \end{pmatrix}.$$

It follows that for the Markov parameters and initial parameters there holds

$$M(q+l) = K_1 S(q) \begin{pmatrix} M(l) \\ \vdots \\ M(q+l-1) \end{pmatrix}, \tag{A.1}$$

$$N(q+l) = K_1 S(q) \begin{pmatrix} N(l) \\ \vdots \\ N(q+l-1) \end{pmatrix}, \tag{A.2}$$

for $l \in Z_+$.

For the input-output sequence there holds

$$y(t) = \sum_{s=1}^{t} M(t-s)u(s) + N(t), \quad \text{for } t = 1, 2, \ldots, N. \tag{A.3}$$

This gives for $i = 1, \ldots, q+1$, and $j = 2, 3, \ldots, N-q$,

$$y(i) = \begin{pmatrix} M(i-1) & \cdots & M(0) \end{pmatrix} \begin{pmatrix} u(1) \\ \vdots \\ u(i) \end{pmatrix} + N(i), \tag{A.4}$$

$$y(q+j) = \begin{pmatrix} M(q+j-1) & \cdots & M(q+1) \end{pmatrix} \begin{pmatrix} u(1) \\ \vdots \\ u(j-1) \end{pmatrix} + \begin{pmatrix} M(q) & \cdots & M(0) \end{pmatrix} \begin{pmatrix} u(j) \\ \vdots \\ u(q+j) \end{pmatrix} + N(q+j).$$

Now the following calculations can be performed, with $P(\cdot)$ as defined at the beginning of Subsection 3.1, and $K := K_1 S(q)$.

$$\begin{aligned} y(q+1) - K \begin{pmatrix} y(1) \\ \vdots \\ y(q) \end{pmatrix} &= \\ \begin{pmatrix} M(q) & \cdots & M(0) \end{pmatrix} \begin{pmatrix} u(1) \\ \vdots \\ u(q+1) \end{pmatrix} &+ N(q+1) K P(q) \begin{pmatrix} u(1) \\ \vdots \\ u(q) \end{pmatrix} - K \begin{pmatrix} N(1) \\ \vdots \\ N(q) \end{pmatrix} \\ &= \begin{pmatrix} -K & I \end{pmatrix} P(q+1) \begin{pmatrix} u(1) \\ \vdots \\ u(q) \\ u(q+1) \end{pmatrix}, \end{aligned}$$

applying (A.2) for $l = 1$, and for $j = 2, 3, \ldots, N-q$,

$$\begin{aligned} y(q+j) - K \begin{pmatrix} y(j) \\ \vdots \\ y(q+j-1) \end{pmatrix} &= \\ \begin{pmatrix} M(q+j-1) & \cdots & M(q+1) \end{pmatrix} \begin{pmatrix} u(1) \\ \vdots \\ u(j-1) \end{pmatrix} &+ \begin{pmatrix} M(q) & \cdots & M(0) \end{pmatrix} \begin{pmatrix} u(j) \\ \vdots \\ u(q+j) \end{pmatrix} \\ +N(q+j) - K \begin{pmatrix} M(j-1) & \cdots & M(1) \\ \vdots & & \vdots \\ M(q+j-2) & \cdots & M(q) \end{pmatrix} \begin{pmatrix} u(1) \\ \vdots \\ u(j-1) \end{pmatrix} &- KP(q) \begin{pmatrix} u(j) \\ \vdots \\ u(q+j-1) \end{pmatrix} \\ -K \begin{pmatrix} N(j) \\ \vdots \\ N(q+j-1) \end{pmatrix} & \\ &= \begin{pmatrix} -K & I \end{pmatrix} P(q+1) \begin{pmatrix} u(j) \\ \vdots \\ u(q+j-1) \\ u(q+j) \end{pmatrix}, \end{aligned}$$

applying (A.1) for $l = j-1, j-2, \ldots, 1$ respectively, (A.2) for $l = j$, and using the definition of $P(q+1)$ and $P(q)$. Define

$$T = \begin{pmatrix} -K & I \end{pmatrix} P(q+1), \tag{A.5}$$

then

$$\begin{pmatrix} y(q+1) & \cdots & y(N) \end{pmatrix} = \begin{pmatrix} T & K_1 \end{pmatrix} \begin{pmatrix} U(1,q+1,N-q) \\ S(q)Y(1,q,N-q) \end{pmatrix}$$

implies

$$\begin{pmatrix} T & K_1 \end{pmatrix} = \begin{pmatrix} y(q+1) & \cdots & y(N) \end{pmatrix} \begin{pmatrix} U(1,q+1,N-q) \\ S(q)Y(1,q,N-q) \end{pmatrix}^{-*},$$

in which $R^{-*} = R^T(RR^T)^{-1}$. Now it follows that, for $T = \begin{pmatrix} T_q & \cdots & T_0 \end{pmatrix}$ and $K = K_1 S(q)$, (3.10) and (3.11) follow from (A.5) by writing out $P(q+1)$, and (3.12) follows from (A.1) for $l = 1, 2, \ldots N-q$. Finally, (3.13) follows from (A.4) and (3.14) from (A.2). The uniqueness of the Markov parameters and initial parameters follows from Proposition 3.3. □

B. Proof of Lemma 3.11

1. From the definition of $\hat{A}$ and $\hat{B}$ it follows that h_Δ is injective on $Q_W(k,m,n)$ if the map $k_\Delta : W \to R^{n\times n}$, defined by $k_\Delta(A) = e^{A\Delta}$, is injective and if

$$\int_0^\Delta e^{A\tau} d\tau \tag{B.1}$$

is nonsingular for all $A \in W$. To prove that k_Δ is injective on W, consider $A \in W$. A can be written as $A = T\Lambda T^{-1}$, with

$$\Lambda = \begin{pmatrix} J_1 & & 0 \\ & \ddots & \\ 0 & & J_s \end{pmatrix},$$

in which $J_1, J_2, \ldots, J_s$ are Jordan blocks. k_Δ is injective on W if and only if the map $J \mapsto e^{J\Delta}$ is injective for Jordan blocks J with eigenvalue $\lambda \in \Omega(W)$, in which

$$\Omega(W) = \{\lambda \in C \in \sigma(A) \mid A \in W\}.$$

Consider the Jordan block $J_0 \in R^{p\times p}$,

$$J_0 = \begin{pmatrix} \lambda_0 & 1 & \cdots & 0 \\ 0 & \ddots & \ddots & \vdots \\ \vdots & & \ddots & 1 \\ 0 & \cdots & 0 & \lambda_0 \end{pmatrix} \in R^{p\times p}.$$

Then

$$e^{J_0\Delta} = e^{\lambda_0\Delta} \begin{pmatrix} 1 & \Delta & \frac{\Delta^2}{2!} & \cdots & \frac{\Delta^{l-1}}{(l-1)!} \\ 0 & \ddots & \ddots & \ddots & \vdots \\ \vdots & & \ddots & \ddots & \frac{\Delta^2}{2!} \\ \vdots & & & \ddots & \Delta \\ 0 & \cdots & \cdots & 0 & 1 \end{pmatrix}.$$

All solutions $J \in R^{p\times p}$ of $e^{J\Delta} = e^{J_0\Delta}$ are of the form

$$J\Delta = \begin{pmatrix} \lambda_0\Delta & 0 & \cdots & 0 \\ 0 & \ddots & & \vdots \\ \vdots & & \ddots & 0 \\ 0 & \cdots & 0 & \lambda_0\Delta \end{pmatrix} + \begin{pmatrix} 2\pi i n & \Delta & \cdots & 0 \\ 0 & \ddots & \ddots & \vdots \\ \vdots & & \ddots & \Delta \\ 0 & \cdots & 0 & 2\pi i n \end{pmatrix}$$

$$= \begin{pmatrix} \lambda_0 + \frac{2\pi in}{\Delta} & 1 & \cdots & 0 \\ 0 & \ddots & \ddots & \vdots \\ \vdots & & \ddots & 1 \\ 0 & \cdots & 0 & \lambda_0 + \frac{2\pi in}{\Delta} \end{pmatrix} \Delta,$$

for $n \in Z$. So

$$J = \begin{pmatrix} \lambda & 1 & \cdots & 0 \\ 0 & \ddots & \ddots & \vdots \\ \vdots & & \ddots & 1 \\ 0 & \cdots & 0 & \lambda \end{pmatrix}$$

with $\lambda = \lambda_0 + 2\pi in/\Delta$, for $n \in Z$. But for $\lambda, \lambda_0 \in \Omega(W)$, with $\mathrm{Re}(\lambda) = \mathrm{Re}(\lambda_0)$, in which $\mathrm{Re}(\lambda)$ denotes the real part of λ, we have

$$-\frac{2\pi}{\Delta} < -\frac{2\pi}{r(W)} = -2\sup K(W) \le \mathrm{Im}(\lambda - \lambda_0) \le 2\sup K(W) = \frac{2\pi}{r(W)} < \frac{2\pi}{\Delta}. \tag{B.2}$$

It follows that $\lambda - \lambda_0 \neq 2\pi in/\Delta$ for $n \in Z \setminus \{0\}$, so $\lambda - \lambda_0 = 2\pi in/\Delta$ for $n = 0$, i.e. $\lambda - \lambda_0 = 0$, and the only solution is $J = J_0$. It is proven that k_Δ is injective on W.

To prove that (B.1) is nonsingular, observe that for $A \in W$,

$$\begin{aligned} \int_0^\Delta e^{A\tau} d\tau \qquad & \text{is nonsingular, if and only if} \\ \int_0^\Delta e^{\Lambda\tau} d\tau \qquad & \text{is nonsingular, if and only if} \\ \int_0^\Delta e^{\lambda_j\tau} d\tau \neq 0, \qquad & \text{for all } \lambda_j \in \sigma(A), \text{ if and only if} \\ \frac{1}{\lambda_j}(e^{\lambda_j\Delta} - 1) \neq 0, \qquad & \text{for all } \lambda_j \in \sigma(A) \setminus \{0\}. \end{aligned} \tag{B.3}$$

Indeed, if $\lambda_j = 0$, then

$$\int_0^\Delta e^{\lambda_j\tau} d\tau = \Delta \neq 0.$$

Further, (B.3) holds if and only if $e^{\lambda_j\Delta} \neq 1$, for all $\lambda_j \in \sigma(A) \setminus \{0\}$, if and only if $\lambda_j\Delta \neq 2\pi ni$, for all $n \in Z, n \neq 0$, and for all $\lambda_j \in \sigma(A) \setminus \{0\}$. Since for $\lambda_j \in \Omega(W_P)$, with $\mathrm{Re}(\lambda_j) = 0$,

$$-\frac{2\pi n}{\Delta} < -\frac{\pi}{\Delta} < -\frac{\pi}{r(W)} \le \mathrm{Im}(\lambda_j) \le \frac{\pi}{r(W)} < \frac{\pi}{\Delta} < \frac{2\pi n}{\Delta}, \quad \text{for all } n \in Z_+,$$

and for $\lambda_j \in \Omega(W_P)$, with $\mathrm{Re}(\lambda_j) \neq 0$, $\lambda_j\Delta \neq 2\pi ni$, for all $n \in Z$, we have $\lambda_j\Delta \neq 2\pi ni$ for all $n \in Z$, for all $\lambda_j \in \sigma(A) \setminus \{0\}$.

2. If $0 < \Delta < r(W)$, then h_Δ maps $Q_W(k,m,n)$ into $Q(k,m,n)$. Indeed, from [12] it follows that if (A, B, C, D, x_0) is a minimal realization of its Markov parameters and initial parameters $(M(j), N(j))$, $j \in \mathbf{N}$, then also $(\hat{A}, \hat{B}, C, D, x_0)$ is a minimal realization of its Markov parameters and initial parameters $(\hat{M}(j), \hat{N}(j)), j \in \mathbf{N}$ if

$$(\lambda - \mu)\Delta \neq 0 \pmod{2\pi i} \quad \text{for } \lambda, \mu \in \sigma(A),\ \lambda \neq \mu. \tag{B.4}$$

For all $\lambda, \mu \in \Omega(W)$, with $\mathrm{Re}(\lambda) = \mathrm{Re}(\mu)$, (B.4) follows from (B.2), and it trivially holds for $\lambda, \mu \in \Omega(W)$, with $\mathrm{Re}(\lambda) \neq \mathrm{Re}(\mu)$. □

References

1. R. Bellman and K. J. Åström. On structural identifiability. *Math. Biosciences*, 7:329–339, 1970.
2. F. M. Callier and C. A. Desoer. *Linear System Theory.* Springer Texts in Electrical Engineering. Springer-Verlag, New York, 1991.
3. M. J. Chapman and K. R. Godfrey. On structural equivalence and identifiability constraint ordering. In E. Walter, editor, *Identifiability of parametric models*, pages 32–41, Oxford, 1987. Pergamon Press.
4. M. J. Chappell, K. R. Godfrey, and S. Vajda. Global identifiability of the parameters of nonlinear systems with specified inputs: A comparison of methods. *Math. Biosciences*, 102:41–73, 1990.
5. B. W. Char, K. O. Geddes, G. H. Gonnet, B. L. Leong, M. B. Monagan, and S. M. Watt. *First Leaves: A Tutorial Introduction to Maple V.* Springer-Verlag, New York, 1992.
6. E. J. Davison. Connectability and structural controllability of composite systems. *Automatica*, 13:109–123, 1977.
7. K. Glover and L. M. Silverman. Characterization of structural controllability. *IEEE Trans. Automatic Control*, 21:534–537, 1976.
8. K. Glover and J. C. Willems. Parametrizations of linear dynamical systems: Canonical forms and identifiability. *IEEE Trans. Automatic Control*, 19:640–645, 1974.
9. K. R. Godfrey and J. J. DiStefano III. Identifiability of model parameters. In E. Walter, editor, *Identifiability of parametric models*, pages 1–20, Oxford, 1987. Pergamon Press.
10. M. S. Grewal and K. Glover. Identifiability of linear and nonlinear dynamical systems. *IEEE Trans. Automatic Control*, 21:833–837, 1976.
11. L. C. G. J. M. Habets. *Algebraic and computational aspects of time-delay systems.* PhD thesis, Eindhoven University of Technology, 1994.
12. M. L. J. Hautus. Controllability and observability conditions of linear autonomous systems. *Indag. Math.*, 31, 1969.
13. J. A. Jacquez. *Compartmental Analysis in Biology and Medicine.* The University of Michigan Press, Ann Arbor, 1985.
14. R. E. Kalman. Mathematical description of linear dynamical systems. *Journal SIAM on Control*, 1:152–192, 1963.
15. R. E. Kalman, P. L. Falb, and M. A. Arbib. *Topics in mathematical systems theory.* McGraw-Hill Book Co., New York, 1969.
16. S. Lang. *Algebra.* Addison-Wesley Publ. Co., Reading, MA, 1971.
17. Y. Lecourtier and A. Raksanyi. The testing of structural properties through symbolic computation. In E. Walter, editor, *Identifiability of parameter models*, pages 75–84, Oxford, 1987. Pergamon Press.
18. H.-W. Leung. Development and utilization of physiologically based pharmacokinetic models for toxicological applications. *J. of Toxicology and Environmental Health*, 32:247–267, 1991.
19. C.-T. Lin. Structural controllability. *IEEE Trans. Automatic Control*, 19:201–208, 1974.
20. R. Liu and L. C. Suen. Minimal dimension realization and identifiability of input-output sequences. *IEEE Trans. Automatic Control*, 22:227–232, 1977.
21. L. Ljung and T. Glad. On global identifiability for arbitrary model parametrizations. *Automatica*, 30:265–276, 1994.

22. J. P. Norton. An investigation of the sources of nonuniqueness in deterministic identifiability. *Math. Biosciences*, 60:89–108, 1982.

23. R. W. Shields and J. B. Pearson. Structural controllability of multiinput linear systems. *IEEE Transactions on Automatic Control*, 21:203–212, 1976.

24. E. D. Sontag. *Mathematical Control Theory.* Number 6 in Texts in Applied Mathematics. Springer-Verlag, Berlin, 1990.

25. L. C. Suen and R. Liu. Minimal dimension realization versus minimal realization and a correction to "Minimal dimension realization and identifiability of input-output sequences". *IEEE Trans. Automatic Control*, 23:99–100, 1978.

26. S. Vajda. Deterministic identifiability and algebraic invariants for polynomial systems. *IEEE Trans. Automatic Control*, 32:182–184, 1987.

27. S. Vajda, K. R. Godfrey, and H. Rabitz. Similarity transformation approach to identifiability analysis of nonlinear compartmental models. *Math. Biosciences*, 93:217–248, 1989.

28. J. M. van den Hof. Realization of positive linear systems. Preprint, Submitted to a journal, 1994.

29. J. M. van den Hof. Structural identifiability of linear mamillary compartmental systems. Report BS-R9512, CWI, Amsterdam, 1995.

30. J. M. van den Hof and J. H. van Schuppen. Realization of positive linear systems using polyhedral cones. In *Proceedings of the 33rd Conference on Decision and Control*, pages 3889–3893. IEEE, 1994.

31. E. Walter. *Identifiability of state space models*, volume 46 of *Lecture Notes in Biomathematics.* Springer-Verlag, Berlin, 1982.

32. M. J. Zeilmaker and W. Slob. Physiologically based toxicokinetic modeling of nitrate and nitrite: Implications for setting toxicity standards. Report (in preparation) 619105.002, RIVM, Bilthoven, 1994.