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System theory and system identification of compartmental systems

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Chapter 1

Introduction

1.1 Motivation

It is well known that the environment is changing to a state that may be harmful to humans, animals, and plants. At many places the water, ground, and air are polluted, with all its consequences. One of the problems concerns the effect of the pollution on human beings. Which substances are toxic and to what extent are they toxic?

At the RIVM (Rijksinstituut voor Volksgezondheid en Milieuhygiëne/National Institute of Public Health and Environmental Protection), Bilthoven, The Netherlands, investigations are performed to support policy makers in the field of public health and environment. Government decisions concerning storage of nuclear waste, control of sulphite-emissions, and control of toxic substances in food and industrial products are studied here. These decisions may be based on the evaluation of control measures by mathematical models. Examples of such mathematical models are the transport and diffusion of radioactive material in layers of the earth, of transport and diffusion of SO_2 in the atmosphere and its effect on the biosphere, and the effect of toxic substances on human beings. To determine the effect of for example toxic substances on human beings, it should be investigated how these substances are processed by the body. Therefore a need exists for mathematical models in public health and environment protection, for procedures to obtain the parameters of such models from scarce data, and for procedures to use these models for evaluation of planned governmental measures.

Compartmental systems are mathematical systems that are frequently used

in biology and mathematics. A compartmental system consists of several compartments with more or less homogeneous amounts of material. The compartments interact by processes of transportation and diffusion. Compartmental systems consist of inputs (inflows), states (amounts or concentrations of the substance in the compartments), and outputs (observations). These variables are positive. Systems with this property are in system theory called positive systems. Compartmental systems form a subclass of positive systems, since they also have to satisfy mass balance laws. The dynamic behaviour of the concentrations involved may often in a first approximation be taken as linear. Then linear compartmental systems are obtained. Hence the resulting models form a subclass of the positive linear systems.

Questions posed by public health and environmental protection can be translated into questions for the class of compartmental systems. Possible questions include the following. How to obtain from possibly scarce data a system in the class of compartmental systems that is both realistic and not too complex? How can such a system be used for prediction and control?

A special class of compartmental systems is formed by the Physiologically Based Pharmacokinetic (PBPK) models [90]. These models are used to describe the effect of toxic substances on human beings and animals. The body is modelled as an interconnection of several compartments. The relations between these compartments are described physiologically such as by flow rates and absorption coefficients. The behaviour of the compartments can be measured only indirectly. The parameter values have a natural variability between organs within a subject and between subjects. A characteristic of these models is that the parameters have a direct physiological interpretation. This class of models allows extrapolation of conclusions from animals to other animals and to human beings. It is highly relevant for the investigation of the effect of the environment on public health.

Examples of PBPK models are those of dioxins and of benzo(a)pyrene in the body. The dioxin model describes the dispersion of dioxin in a rat [153]. The intention of the RIVM is, by extrapolating the conclusions of the research from animals to human beings, to determine the maximal tolerable daily intake (TDI) of dioxin, which is defined as the exposure level (g/kg/day) to which the *general* population may *chronically* be exposed without developing adverse toxic effects. It is already known that a very small amount of dioxin is carcinogenic for animals. For human beings it is only assumed to be carcinogenic. For adults the exposure to dioxins occurs mainly via the food. Taking variation in consumption habits into account the TDI is not exceeded at any age starting at one year. However, a quite different situation emerges in the case of sucklings. Breast-fed babies may be exposed to fairly high amounts of dioxin via mother's milk. During the first months of life, the exposure level exceeds the current TDI 10- to 20-fold. Though in excess of the TDI, the toxic effects of the exposure of sucklings to dioxins from mother's milk are unknown and cannot be addressed by experimental means. Therefore the toxic risk associated with the exposure to dioxins from mother's milk has to be estimated by the interspecies extrapolation of dioxin from animals to human beings. To model the disper-

sion of dioxin in a rat, an internal experiment is performed. In the model five compartments are considered: blood, liver, slowly perfused tissue (representing muscles, gastro-intestinal tract), richly perfused tissue (representing lungs, kidney), and fat. The amount of dioxin in the liver can be measured and the metabolism takes place in the liver.

The benzo(a)pyrene model is a simulation model of intravenous injection of benzo(a)pyrene (BaP) to a rat. Actually, the motivation is to test for human beings the importance of the metabolism of the lung at the exposure of metabolites and unchanged benzo(a)pyrene. Benzo(a)pyrene is a substance that can enter the body through food or the air. The model both describes the amount of BaP and the amount of metabolites in several compartments: lung, liver, fat, bile, richly perfused tissue, slowly perfused tissue and blood. For the experiment a solution of benzo(a)pyrene is injected intravenously. Metabolism takes place in the liver and the lung. The metabolites may cause cancerous tumours in the liver. The concentration of unchanged benzo(a)pyrene in the blood and the concentration of the metabolites in the blood and the bile can be measured.

All problems studied in this thesis arise from one general problem, that of system identification of positive linear systems, in particular of linear compartmental systems. This problem includes a study of modelling by compartmental systems, of realization, of parameter estimation, and of validation. These terms will be explained in the next section. The system identification problem is roughly to determine, given input-output data, a system within a prescribed class of dynamic systems such that this system approximates the given data as good as possible, according to a criterion. An algorithm for this problem allows one to obtain an estimate of the parameters of a system representation.

1.2 Approach

The problems mentioned in Section 1.1 will be approached with concepts and tools of system and control theory. The approach to the subject of system identification of compartmental systems is to follow the procedure for system identification of finite-dimensional systems [93]. The difference between system identification of compartmental systems and that of finite-dimensional linear systems and Gaussian systems is that a compartmental system is a finite-dimensional *positive* linear system. In a positive linear system the input, state, and output are positive. Therefore positive linear algebra [11] instead of ordinary linear algebra is the main tool for positive linear dynamic systems. Positive linear algebra has not been as far developed as linear algebra. Many aspects of the theory still has to be elaborated.

A procedure for system identification of finite-dimensional systems involves the following steps. The corresponding diagram is shown in Figure 1.1.

Procedure for system identification. Assume a phenomenon to be modelled has been specified, together with the purpose of the model.

1. Model class Select a class of mathematical models from which a model for

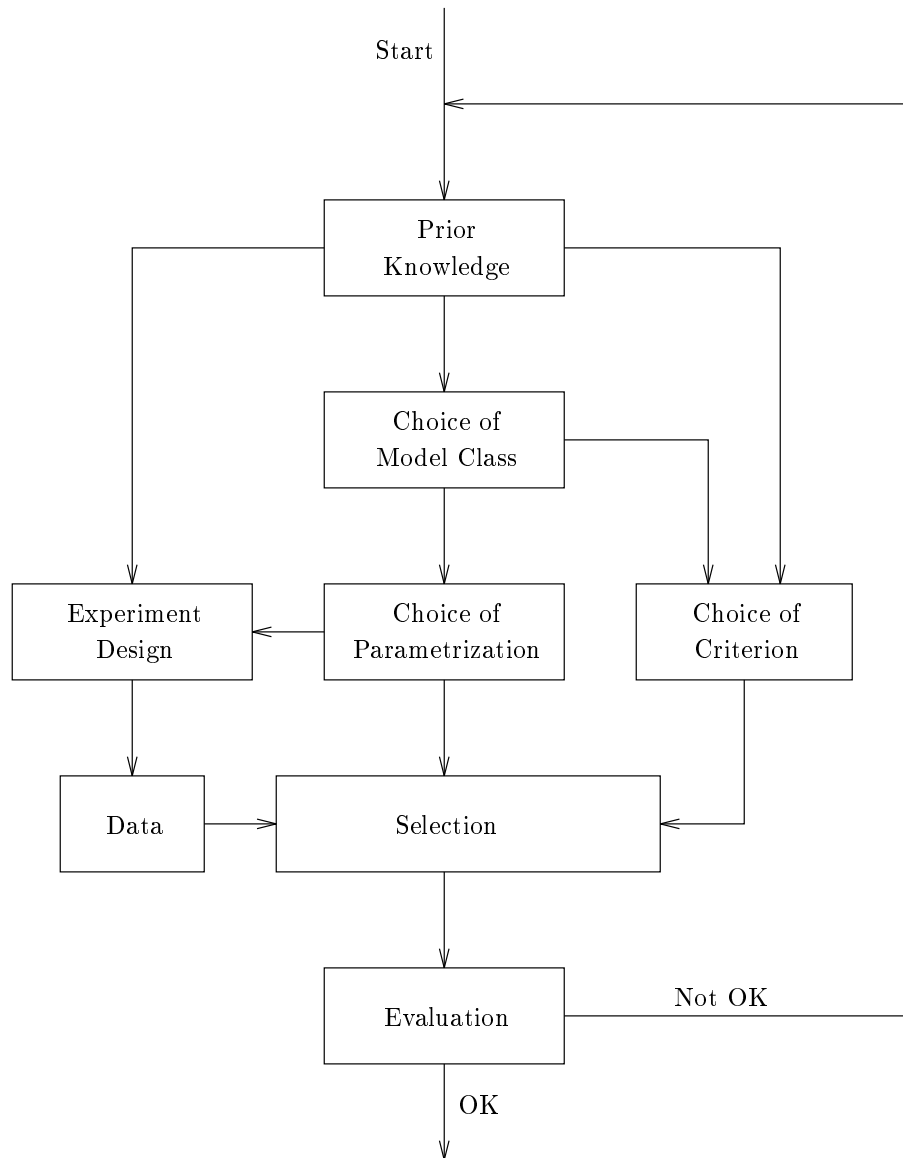


Figure 1.1: Diagram of the system identification procedure.

the phenomenon may be chosen.

2. **Experimentation** Design an experiment, select inputs, and, if possible, perform the experiment, and collect data on the phenomenon.
3. **Realization and parametrization** Describe the classes of observationally equivalent models and select a parametrization.
4. **Selection** Select a model in the model class on the basis of the experimental data and a criterion such that this model is realistic and not too complex.
5. **Evaluation** Evaluate the selected model according to additional criteria (different from the one in the selection step) and if the model is not satisfactory, adjust the options of this procedure such as the model class and repeat the necessary steps of this procedure.

Step 1 is the modelling, which depends mainly on the application of the model. It involves the choice of the character of the model, i.e., linear or nonlinear, the model order, and the model structure. The models that will be studied in this thesis are linear compartmental systems, which form a subclass of linear dynamic systems. Compartmental systems depend on the prior physical information, which imposes a certain structure on the system. This structure can be incorporated into the system by a parametrization. This is the topic of Step 3. Sometimes the systems have a special structure, such as a catenary or mammillary structure. In those cases general results can be derived. The restriction to the class of linear dynamic systems can be justified by the argument that many physical and biological relations may be approximated by dynamic systems in this class. Most of the system identification literature deals with this class of systems. But for the special class of compartmental systems, or, more generally, of positive linear systems, no literature on system identification is available. Another question to be posed is whether the model should be continuous-time or discrete-time. This depends on the prior information and the available observations. Often the prior information asks for a continuous-time model, whereas the observations are discrete-time. In this case the option would be to sample the continuous-time model, according to the observation intervals, since it is very difficult to model it in discrete-time.

The design of an experiment, mentioned in Step 2, is an important step. It includes the selection of an input from the class of admissible inputs, choosing sampling intervals, and selecting the to be measured objects and the to be collected number of data. Sometimes data are already available before a model class is chosen, that is, before the procedure of system identification is started. In this case the data might not be informative enough to estimate the model uniquely. Of course, it is not always possible to influence the experiment, and in that case one can only hope that the data are informative enough. But if inputs can be chosen, they have to be selected in such a way that the data are as informative as possible, subject to possible input constraints. This selection will depend on the parametrization chosen in Step 3. Experiments performed

at RIVM or at other laboratories should be set up in cooperation with the modeller, because of the considerations above.

The concept of parametrization of a class of dynamic models in Step 3 is the major point for the system identification problem. An important issue in this context is to construct a parametrization of a class of dynamic systems such that all systems are parametrized and systems having identical input-output behaviour have the same parameter values. This is the structural identifiability problem. Environmental modelling requires consideration of structural identifiability conditions for dynamic systems structured by physical laws. Intuitively, structural identifiability is whether the parameter values can uniquely be determined from the observations of inputs and outputs. Structural identifiability has been introduced by Bellman and Åström in [9]. Since then structural identifiability of linear and nonlinear structured systems has been studied by many authors. Often it is sufficient to test structural identifiability on the parametrization of the system, since many and long experiments can be performed. Theoretically, this is the structural identifiability from the Markov parameters. However, free and long-term experimentation is usually not possible for animals and human beings. Therefore 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. Because of that, also a test on the data is necessary for structural identifiability. This has not been performed in the existing literature. It involves aspects on whether the data set is informative enough to distinguish between non-equal systems. Theoretically, this is the structural identifiability from the input-output data.

The test for structural identifiability from the Markov parameters is based on realization theory, see for example [133]. For time-invariant finite-dimensional linear systems the realization problem has been solved. From these results equivalent conditions for structural identifiability may be formulated. However, for other classes of dynamic systems, such as positive linear systems, the realization problem is still open. Conditions for structural identifiability may not be known for these classes. In 1977 a paper by H. Maeda, S. Kodama, and F. Kajiya appeared on the realization problem for compartmental systems [99]. Afterwards, in the 1980's, a number of papers appeared on the realization of positive linear systems [98, 109, 110, 112, 147, 150]. However, their approach is different from the approach followed in this thesis in that they concentrate on the step from ordinary linear systems to positive linear systems and on the eigenvalues of the realizations. The minimality of positive linear systems is neither studied in these papers, nor by L. Farina and others in the papers [1, 43, 44, 45] and the book [121], which appeared in the 1990's. The realization problem for positive linear systems is closely related to the stochastic realization problem for finite-valued processes. This problem has been studied by G. Picci and J.H. van Schuppen [114, 117, 129] and M. Fliess [47]. In the literature this latter problem is also known as the realization problem for the hidden Markov model, or for a partially observed Markov chain, or for a finite stochastic system. Earlier results on the characterization of finite state pro-

cesses that can be realized as functions of a finite state Markov chain appeared in [49, 67].

The approximation problem is to select a compartmental system in a specified class such that the external behaviour of this system fits the given data, according to a criterion. This is the topic of Step 4. If the set of candidate systems has been selected, the class has been parametrized using a parameter vector, and the parametrization is structurally identifiable, then the selection of the best system within the set becomes a problem of estimating the parameter vector. First the identification criterion has to be chosen. In general the maximum likelihood method and the least-squares method are used. The question is whether these methods are also useful for positive linear systems. The methods assume that the error is Gaussian, which cannot be the case for positive linear systems. Indeed, Gaussian errors may result in negative values of the output. The use of these methods may result in systems of which the state or the output is not positive. Therefore other methods should be searched for.

1.3 Overview of the thesis

The organization of this thesis is as far as possible in accordance with the procedure of system identification. Chapter 2 describes the model class of compartmental systems. Properties relevant for this thesis are presented. Most of these properties already appeared in the literature. By means of a graphical representation the classes of catenary and mammillary systems are introduced.

Chapter 3 deals with the problem of structural identifiability. Tests for the structural identifiability of linear compartmental systems are proposed. The method is based on the similarity transformation approach. This approach uses realization theory of time-invariant finite-dimensional linear systems. Unfortunately it only tests structural identifiability from the Markov parameters, which is sufficient in case of free and long-term experimentation. But for some problems, like the problems faced with in this thesis or economic problems, this unrestricted experimentation is not possible from moral or economical points of view. Therefore structural identifiability from Markov parameters has to be extended to structural identifiability from input-output data. This also involves the initial condition response, which could be neglected in case of a long horizon. The approach is split into discrete-time and sampled continuous-time linear dynamic systems. Also conditions for structural identifiability of structured positive linear systems are presented, but these are only sufficient. To obtain sufficient and necessary conditions for structural identifiability of structured positive linear systems, the realization problem for positive linear systems has to be solved first. This is the subject of Chapter 5.

In Chapter 4 the positive linear algebra, necessary for the realization of positive linear systems, is studied. A main problem in the positive linear algebra is the factorization problem for positive matrices. This requires the concept of positive rank. A factorization of positive matrices will be associated with an extremal factorization. A matrix factorization of an extremal factoriza-

tion can then be associated with a prime in the positive matrices. Therefore, in Section 4.2 and Section 4.3, the theory of primes in the class of positive matrices, of doubly stochastic matrices, and of doubly stochastic circulants is presented. These classes are monoids with respect to multiplication. Primes in these classes are matrices that are neither units nor can be factorized into two non-unit matrices in the considered class. A partial classification of primes in the three classes is presented, in particular in the class of doubly stochastic circulants. It is shown that the classification of a prime in the doubly stochastic circulants is equivalent to the solvability of a linear equation over a doubly stochastic circulant. Also a representation of doubly stochastic circulants as polynomials in the quotient semi-ring of $R_+[z]$ is presented. The interest for primes in the doubly stochastic circulants is motivated by the fact that Hankel matrices are closely related to circulants, i.e., Hankel matrices are upward circulants in the single-input-single-output case. Moreover, some primes in the doubly stochastic circulants are also primes in the doubly stochastic matrices, or even primes in the positive matrices. In Section 4.4 and Section 4.5 the relation between polyhedral cones and positive matrices is indicated. The factorization of positive matrices is equivalent to the construction of a polyhedral cone that contains a specified polyhedral cone. In this perspective extremal cones are defined. These cones turn out to be closely related to primes in the positive matrices. Parallel to the concept of rank in linear algebra, the concept of positive rank has been defined in the positive linear algebra. A procedure is suggested to determine the positive rank of a positive matrix. However, a complete algorithm cannot be given yet. The idea of the procedure is to search for extremal cones that contain the cone corresponding to the positive matrix.

The realization problem for positive linear systems is treated in Chapter 5. Given a positive impulse response function, the positive realization problem is to find a positive linear system, i.e., a positive linear state space system, such that its impulse response function equals the given one. Four steps can be considered in this problem: existence, characterization of minimality, classification, and the relation between realizations. A positive realization of an impulse response function is said to be minimal if the state space as a vector space over the positive real numbers is of minimal dimension. The results depend largely on Chapter 4. For the existence of a positive realization necessary and sufficient conditions are presented in terms of polyhedral cones. In distinction with similar conditions for ordinary linear systems, these conditions are phrased only as an inclusion relation and not as an equality. For the characterization of minimality a sufficient condition in terms of positive rank has been proposed. This condition turns out to be weaker than the reachability/observability condition for ordinary linear systems. In order to get a condition that is both necessary and sufficient, the notion of positive system rank is introduced. Furthermore, for a special class of impulse response functions all minimal positive realizations are classified. This indicates a way of treating the problem of classification in general. It also shows that there may exist different equivalence classes of minimal positive realizations of the same impulse response function. For ordinary linear systems only one equivalence class exists. The results above mainly re-

fer to discrete-time positive linear systems. Finally, it is shown in Section 5.6 that results for continuous-time positive linear systems can be derived from the discrete-time case via a transformation.

In Chapter 6 positive linear observers for linear compartmental systems are derived. As in linear system theory, the state x can be approximated by \hat{x} . The observer should be such that the error, $\hat{x}(t) - x(t)$, converges to zero. Above that, for positive linear systems, the observer should be chosen in such a way, that the approximation of the state, $\hat{x}(t)$, is positive, like the state, $x(t)$, itself. Necessary and sufficient conditions on the system matrices of a compartmental system, called positive detectability, are presented for the existence of a positive linear observer satisfying the above specifications. It turns out that the conditions depend mainly on the structure of the compartmental system. The continuous-time case and the discrete-time case are treated separately.

In Chapter 7 a solution to the approximation problem is proposed. The approximation problem is to select a system in the model class such that the input and output of this system fit the observations as well as possible. Use will be made of an approximation criterion. For time-invariant finite-dimensional linear systems the least squares criterion is a common criterion. Related to this criterion is the likelihood criterion, used for a stochastic system with Gaussian observation noise. For system identification of positive linear systems the least squares criterion seems in general not appropriate. A special nonlinear criterion is developed for positive linear systems. It is motivated by a stochastic system with an inverted gamma distributed observation noise. The underlying nonlinear function is strictly convex. An algorithm is presented based on this criterion and a positive linear observer for positive linear systems, which has been developed in Chapter 6. An example illustrates some of the results.

In Chapter 8 the structural identifiability of three compartmental systems used at RIVM is considered. Two of them, the nitrate model and the benzo(a)-pyrene model, are developed at RIVM. Also a general class of compartmental systems is studied. This is the class of mammillary systems. The methods from Chapter 3 are used to decide whether the models are structurally identifiable or not. Moreover, indications are given for the selection of the inputs in order to obtain data that are informative enough to estimate the parameters. The conditions for the structural identifiability of the three real examples are checked using the symbolic manipulation package Maple V. The procedures and the sessions are included in the appendix of the chapter.

Finally, in Chapter 9 concluding remarks are made and directions for further research are indicated.

Most of the results of this thesis are based on manuscripts which appeared as report and/or have been submitted for publication to journals. Chapter 2 and Chapter 6 are based on [70]. Chapter 3 is based on [73]. Sections 4.2 and 4.3 list some results from [115], but are mainly based on [116]. Section 4.4 and Section 4.5 contain preliminaries from [68], [69], and [72]. Chapter 5 presents the results on positive realization from [68, 69, 71, 72]. Finally, Chapter 8 presents the case studies from [73] and the model from [74].