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Extending existing structural identifiability analysis methods to mixed-effects models

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ABSTRACT

The concept of structural identifiability for state-space models is expanded to cover mixed-effects state-space models. Two methods applicable for the analytical study of the structural identifiability of mixed-effects models are presented. The two methods are based on previously established techniques for non-mixed-effects models; namely the Taylor series expansion and the input-output form approach. By generating an exhaustive summary, and by assuming an infinite number of subjects, functions of random variables can be derived which in turn determine the distribution of the system's observation function(s). By considering the uniqueness of the analytical statistical moments of the derived functions of the random variables, the structural identifiability of the corresponding mixed-effects model can be determined. The two methods are applied to a set of examples of mixed-effects models to illustrate how they work in practice.

1. Introduction

Structural identifiability analysis tests if the parameters in a given model structure can be uniquely determined with a given input design together with noise-free, continuous output function(s). If there exists a unique set of parameters for the output solution then the model is called *structurally globally identifiable*, if there exists a countable number of sets of parameters for an output the model is called *structurally locally identifiable* and if there exist uncountable numbers of parameter sets for a model output the model is called *structurally unidentifiable* [1,2].

Several methods have been developed for performing structural identifiability analysis including the Taylor series approach [3], the Laplace transformation approach [4], the similarity transformation approach [5], the Exact Arithmetic Rank (EAR) approach [6], differential algebra based approaches [7], input-output approaches [8], and the profile likelihood approach [9]. These methods were originally developed to study structural identifiability in systems of ordinary differential equations with no statistical element included. Additional important publications regarding structural identifiability include [10–15].

An area where mathematical modelling and simulation plays an important role is in drug discovery and development in the pharmaceutical industry. One of the motivations for using modelling in drug discovery and development is to detect and quantify variations in both pharmacokinetics in a population, i.e., how the drug is distributed in the body, and in pharmacodynamics, i.e., what effect the drug has on the body. This is essential for instance when finding personalised dosing regimens and optimal dosing for different subgroups in the population. It is not uncommon that the pharmacokinetic properties and the pharmacodynamic response for a particular treatment varies between different patients, or groups of patients with different covariates (sex, age, weight, etc), or even between different treatment occasions. In order to predict such future scenarios with confidence having a structurally identifiable model is central. To model this, a so called mixed-effects framework is commonly used [16]. In such a framework, all subjects in a population share the same structural model and parametrisation, but not the same parameter values. By postulating the form of the distribution of the model parameters in a statistical model, the inference problem is expanded to include variance parameters as well as the structural parameters.

However, the addition of a statistical model means that existing structural identifiability methods are not directly applicable to mixed-effects models. Although there has been some work done on the problem of structural identifiability in mixed-effects models including [17–20] and [21], the main efforts of developing methods to analyse structural identifiability have so far been focused on non-mixed-effects, or fixed-effects systems. The two methods presented in this paper are related to the Laplace transform approach for mixed-effects system

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presented in [21] via the generation of the exhaustive summary explained below. However, the Laplace transform for mixed-effects systems presented in [21] is only applicable to linear systems whereas the two approaches presented in this paper are applicable to nonlinear system as well.

In this paper, we first define what we mean by structural identifiability in systems of ordinary differential equations and mixed-effects systems, respectively. Then, we present two existing structural identifiability analysis methods and how they can be extended to mixed-effects models. Lastly, we apply these methods to a set of mixed-effects models to illustrate how the methods work in practice.

2. Structural identifiability

2.1. State-space model

Consider a model written in the following state-space form

$$\begin{aligned} \dot{\boldsymbol{x}}(t,\theta) &= \boldsymbol{f}(\boldsymbol{x}(t,\theta),\boldsymbol{u}(t),\theta) \quad \boldsymbol{x}(t_0)=\boldsymbol{x}_0(\theta) \\ \boldsymbol{y}(t,\theta) &= \boldsymbol{h}(\boldsymbol{x}(t,\theta),\boldsymbol{u}(t),\theta) \end{aligned} \tag{1}$$

where $\boldsymbol{x}(t,\theta)\in\mathbb{R}^n$ is the state vector, $\boldsymbol{u}(t)\in\mathbb{R}^q$ is the input vector, $\theta\in\mathbb{R}^p$ is the vector of the model parameters, $\boldsymbol{y}(t,\theta)\in\mathbb{R}^m$ is the output vector, t denotes time and $\boldsymbol{f}$ and $\boldsymbol{h}$ are smooth functions.

Let the generic parameter vector $\boldsymbol{\theta}$ belong to a feasible parameter space $\boldsymbol{\Theta}$, i.e., $\boldsymbol{\theta}\in\boldsymbol{\Theta}$. Let $\boldsymbol{y}(t,\boldsymbol{\theta})$ be the output function from the state-space model (1). Further, consider a parameter vector $\bar{\theta}$ where $\boldsymbol{y}(t,\theta)=\boldsymbol{y}(t,\bar{\theta})$ for all t. If this equality, in a neighbourhood $N\in\boldsymbol{\Theta}$ of $\boldsymbol{\theta}$, implies that $\theta=\bar{\theta}$ then the model is *structurally locally identifiable*. If $N=\boldsymbol{\Theta}$ then the model is *structurally globally identifiable*. For a structurally unidentifiable parameter, θ_i, every neighbourhood N around θ_i has a parameter vector $\bar{\theta}$ where $\theta_i\neq\bar{\theta}_i$ that gives rise to identical input-output relations [1].

2.2. Mixed-effects state-space model

By a mixed-effects state-space model, subsequently denoted mixed-effects model, we mean a system written in the following form

$$\begin{aligned} \dot{\boldsymbol{x}}_i(t,\boldsymbol{\phi}_i) &= \boldsymbol{f}(\boldsymbol{x}_i(t,\boldsymbol{\phi}_i),\boldsymbol{u}_i(t),\boldsymbol{\phi}_i) \quad \boldsymbol{x}_i(t_0)=\boldsymbol{x}_0(\boldsymbol{\phi}_i) \\ \boldsymbol{y}_i(t,\boldsymbol{\phi}_i) &= \boldsymbol{h}(\boldsymbol{x}_i(t,\boldsymbol{\phi}_i),\boldsymbol{u}_i(t),\boldsymbol{\phi}_i) \end{aligned} \tag{2}$$

where $\boldsymbol{\phi}_i=g(\theta,\boldsymbol{\eta}_i,\mathbf{C}_i)$ are the parameters for the ith subject, $\boldsymbol{\eta}_i\sim N(\boldsymbol{0},\boldsymbol{\Omega})$ are the random effects where N denotes a normal distribution, $\boldsymbol{\Omega}$ is the covariance matrix of the random effects $\boldsymbol{\eta}_i$, $\boldsymbol{\theta}$ is a vector of the population parameters and $\mathbf{C}_i$ are the covariates vector for the different subjects in the population.

As mixed-effects models give individual trajectories, the structural identifiability concept needs to be extended from considering the uniqueness of model parameters given a set of output signals to considering the uniqueness of model parameters given a set of distributions of the output signals, i.e., whether different parameter values may result in different or identical distributions of the same given output signal(s).

Let $p(\boldsymbol{y}_{\{\boldsymbol{\theta},\,\boldsymbol{\Omega}\}},t)$ denote the distribution of the output signals $\boldsymbol{y}$ at time t. Let the generic parameter vector and matrix $\{\boldsymbol{\theta},\boldsymbol{\Omega}\}$ belong to a feasible parameter space $\{\boldsymbol{\theta},\boldsymbol{\Omega}\}\subset\boldsymbol{\Theta}$, and consider the following two sets of parameters $\{\boldsymbol{\theta},\boldsymbol{\Omega}\}$ and $\{\bar{\theta},\bar{\boldsymbol{\Omega}}\}$. If $p(\boldsymbol{y}_{\{\theta,\Omega\}},t)=p(\boldsymbol{y}_{\{\bar{\theta},\bar{\Omega}\}},t)$ for all t implies that $\{\theta,\boldsymbol{\Omega}\}=\{\bar{\theta},\bar{\boldsymbol{\Omega}}\}$ in a neighbourhood $N\subset\boldsymbol{\Theta}$ then the model is *structurally locally identifiable*, and if $N=\boldsymbol{\Theta}$ the model is *structurally globally identifiable*. For a *structurally unidentifiable* parameter, θ_i, or ω_i, every neighbourhood N around θ_i, or ω_i, has a parameter vector/matrix $\bar{\theta}$, or $\bar{\boldsymbol{\Omega}}$, where $\theta_i\neq\bar{\theta}_i$, or $\omega_i\neq\bar{\omega}_i$, that gives rise to the same distribution of identical input-output relations.

3. Methods

In this section two structural identifiability analysis methods that were originally developed for non-mixed-effects state-space systems will be presented. It will be shown how these methods can be extended to also study structural identifiability in mixed-effects models by considering functions of random variables.

In a structural identifiability analysis the model structure itself is analysed to see whether it allows for unique parameter estimates or otherwise. In such an analysis, assumptions on having ideal experimental conditions are made. For a fixed-effects state-space model, such ideal experimental conditions include noise-free and continuous-time data. In a mixed-effects system, ideal experimental conditions also include having data from an infinite number of subjects. In some sense, this concept is similar to the parallel experiment approach presented in [11] since each subject could be viewed as a single experiment resulting in an infinite number of parallel experiments. As a consequence, the output signal(s) are continuous both in time as well as their distribution at all time points. The distribution of the output signal(s) depends on the distribution of the model parameters. Therefore, in order to study the structural identifiability of a mixed-effects model, the distributions of the model parameters must be studied analytically.

3.1. Functions of random variables

In this paper we relate the structural identifiability problem in mixed-effects systems to functions of random variables $Z_k(\boldsymbol{\theta},\boldsymbol{\eta})$.

Let $\boldsymbol{Z}(\theta,\boldsymbol{\eta})=(Z_1(\theta,\boldsymbol{\eta}),Z_2(\theta,\boldsymbol{\eta}),\cdots)^T$ be a vector of functions of random variables. In our analysis we assume full knowledge of all of the statistical moments and covariances of $\boldsymbol{Z}(\boldsymbol{\theta},\boldsymbol{\eta})$. We are interested in whether the statistical moments and covariance matrix of $\boldsymbol{Z}(\boldsymbol{\theta},\boldsymbol{\eta})$ determines $\{\boldsymbol{\theta},\boldsymbol{\Omega}\}$ uniquely, or otherwise. By calculating different orders m of the statistical moments and covariance of $\boldsymbol{Z}(\boldsymbol{\theta},\boldsymbol{\eta})$, introducing alternative parameters $\{\bar{\theta},\bar{\boldsymbol{\Omega}}\}$, equating these such that

$$\mathbb{E}[\boldsymbol{Z}^m(\theta,\boldsymbol{\eta})] = \mathbb{E}[\boldsymbol{Z}^m(\bar{\theta},\bar{\boldsymbol{\eta}})] \tag{3}$$

$$\mathrm{Cov}(\boldsymbol{Z}(\theta,\boldsymbol{\eta})) = \mathrm{Cov}(\boldsymbol{Z}(\bar{\theta},\bar{\boldsymbol{\eta}})) \tag{4}$$

and solving for $\boldsymbol{\theta}$ and $\boldsymbol{\Omega}$ the uniqueness or otherwise of the parameters can be determined. By $\mathbb{E}[\boldsymbol{Z}^m(\theta,\boldsymbol{\eta})]$ we mean the mth statistical moment element-wise in $\boldsymbol{Z}(\boldsymbol{\theta},\boldsymbol{\eta})$.

As an example, consider the case of two functions of random variables $\boldsymbol{Z}$. To ensure positivity both functions are lognormally distributed. The associated covariance matrix $\boldsymbol{\Omega}$ is full. We therefore have the following:

$$\boldsymbol{Z}=\begin{pmatrix} Z_1 \\ Z_2 \end{pmatrix}=\begin{pmatrix} \theta_1 e^{\eta_1} \\ \theta_2 e^{\eta_2} \end{pmatrix} \tag{5}$$

$$\boldsymbol{\eta}\sim N(\boldsymbol{0},\boldsymbol{\Omega}) \qquad \boldsymbol{\Omega}=\begin{pmatrix} \omega_1 & \omega_{12} \\ \omega_{12} & \omega_2 \end{pmatrix} \tag{6}$$

with unknown parameter vector $\theta=(\theta_1,\theta_2,\omega_1,\omega_2,\omega_{12})$. The first moment for $\boldsymbol{Z}$ is

$$\mathbb{E}[\boldsymbol{Z}]=\begin{pmatrix} \theta_1 e^{\frac{\omega_1}{2}} \\ \theta_2 e^{\frac{\omega_2}{2}} \end{pmatrix}. \tag{7}$$

The covariance matrix for $\boldsymbol{Z}$ is given by

$$\begin{aligned} \mathrm{Cov}(\boldsymbol{Z}) &= \mathbb{E}[\boldsymbol{Z}\boldsymbol{Z}^T]-\mathbb{E}[\boldsymbol{Z}]\mathbb{E}[\boldsymbol{Z}]^T \\ &= \begin{pmatrix} \mathbb{E}[Z_1^2]-\mathbb{E}[Z_1]^2 & \mathbb{E}[Z_1Z_2]-\mathbb{E}[Z_1]\mathbb{E}[Z_2] \\ \mathbb{E}[Z_1Z_2]-\mathbb{E}[Z_1]\mathbb{E}[Z_2] & \mathbb{E}[Z_2^2]-\mathbb{E}[Z_2]^2 \end{pmatrix} \end{aligned}$$

where the diagonal elements, i.e., the variances of Z_1 and Z_2, are given