Structural Identifiability in Mixed-Effects Models: Two different approaches ⋆

D. Janzén [*,**,***] **M. Jirstrand** [**] **N. D. Evans** [***] **M. Chappell** [***]

[*] *Department of Systems and Data Analysis, Fraunhofer-Chalmers Centre, Chalmers Science Park, SE-412 88 Gothenburg, Sweden (e-mail: D.L.I.Janzen@warwick.ac.uk, mats.jirstrand@fcc.chalmers.se).*
[**] *AstraZeneca RD, SE-431 83 Mölndal, Sweden (e-mail: D.L.I.Janzen@warwick.ac.uk)*
[***] *School of Engineering, University of Warwick, Coventry, CV4 7AL, United Kingdom, (e-mail: D.L.I.Janzen@warwick.ac.uk, neil.evans@warwick.ac.uk, M.J.Chappell@warwick.ac.uk)*

Abstract: Structural identifiability analysis is a theoretical concept that ascertains whether unknown model parameters can be uniquely determined for a given experimental setup. If this condition is not fulfilled numerical parameter estimates will be meaningless and the model prediction may not necessarily be reliable. Therefore, structural identifiability should be considered a prerequisite in any project where model predictions are a part of the decision making process. For models defined by ordinary differential equations, there are several methods developed both for the linear and nonlinear cases. In systems pharmacology pharmaceutical drug development projects there is, apart from an interest in understanding the biological mechanisms, also an interest in subject variability. For this, mixed-effects models are typically used. However, despite the wide use of mixed-effects models and being a part of the decision making process in pharmaceutical drugs projects, very little has been done on developing methods for structural identifiability analysis of mixed-effects models. In this paper, we propose and compare two methods for performing such an analysis. The first method is based on applying a set of established statistical theorems while in the second method the system is augmented to yield a random differential equation system format followed by subsequent analysis.

Keywords: Systems Pharmacology, Structural Identifiability, Observability, Mixed-Effects models, Random Differential Equations, Statistics

1. INTRODUCTION

Systems pharmacology is a sub-field of the more broader concept of mathematical modelling of biological systems. More specifically, in systems pharmacology efforts are focused on understanding the underlying biological mechanisms using modelling as a way of developing effective pharmaceutical drugs more efficiently. According to Vicini and van der Graaf (2013), the idea behind having a more systems approach to drug development, is to be able to better develop optimal and translatable pharmacological pathway interventions, scalable to humans. Systems pharmacology is an emerging field, and its importance and application in drug development will most likely continue to increase.

For a systems pharmacology model to be truly useful, the concept of *identifiability* must always be considered, i.e. whether the unknown model parameters can be estimated in a meaningful way. There are two types of problems associated with identifiability *i) Structural identifiability,* where assumption of perfect experimental conditions is made, i.e. continuous-time and noise-free input and output functions. This assumption allows an analysis of whether or not the actual model structure itself with a given observation function allows estimation of unique parameter estimates. *ii) Practical identifiability,* which concerns how the amount and quality of information in the experimental data are translated into the model parameter uncertainty. A model can be structurally identifiable, but still be practically unidentifiable due to poor data quality, e.g. bad signal-to-noise ratio, or sparse sampling. Conversely, if a model is structurally unidentifiable then it is always practically unidentifiable. Therefore, a structural identifiability analysis should always be performed prior to a practical identifiability analysis. In this paper, we will only consider structural identifiability analysis.

A great deal of effort has been made on developing methods for structural identifiability analysis of deterministic systems. These methods include the Taylor series expansion introduced by Pohjanpalo (1978), the Laplace trans-

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formation approach by Bellman and Astrom (1970), a differential algebra approach by Ljung and Glad (1994), the software DAISY which also is based on differential algebra algorithms presented in Bellu et al. (2007), the Exact Arithmetic Rank approach by Karlsson et al. (2012), rewriting the model on an input-output form presented in Evans et al. (2013), a numerical approach called Profile-Likelihood by Raue et al. (2011) and the Similarity Transformation outlined in Vajda (1982).

In a pharmaceutical drug development project it is, alongside having a good understanding of the underlying biological mechanisms, also important to have knowledge about patient variability in terms of efficacy and toxicity. For this, mixed-effects modelling has been widely used. However, the structural identifiability analysis methods mentioned above can only be applied to deterministic models. Apart from a few results, e.g. Wang (2013) which is applicable for linear mixed-effects models and Shivva et al. (2013) which is based on numerical approaches, very little has been performed on structural identifiability for mixed-effects models. In this paper we propose and compare two approaches for such an analysis together with examples.

2. STRUCTURAL IDENTIFIABILITY

In this section we introduce structural identifiability first with an conceptual example of using simulations from a structurally unidentifiable model. We then formally define structural identifiability.

Consider the well known one-compartment absorption model

$$\dot{x}(t) = -k_a x(t) \quad x(0) = FDose \tag{1}$$

$$\dot{c}(t) = \frac{k_a x(t)}{V} - \frac{CL}{V} c(t) \quad c(0) = 0 \tag{2}$$

$$y(t) = c(t) \tag{3}$$

where k_a is the absorption rate, F is the bioavailability, $Dose$ is the administered dose, CL is the clearance of the drug and V is the volume of distribution and $c(t)$ is the concentration of the drug in the plasma which is measured. It has previously been shown, for instance in Cheung et al. (2013), that the model parameters $\{CL, F, V\}$ are structurally unidentifiable but the ratios of the model parameters $\{\frac{CL}{F}, \frac{V}{F}\}$ are structurally identifiable.

In Figure 1, simulations using three different parameters sets are shown. The values used for the different parameters sets are summarized in Table 1.

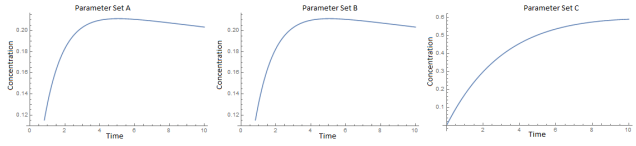

Fig. 1. The simulations using parameter set A and B are identical while the simulation using parameter set C has a different profile.

Note in Table 1 that the ratios for parameter set A and B are the same while one of the ratios in parameter set C is different. These numerical results are consistent with previous symbolic results followed from structural identifiability analysis.

Table 1. Parameter values used for simulations.

Parameter Set	k_a	CL	F	V	$\frac{CL}{V}$	$\frac{V}{F}$
A	0.01	0.9	1	1	0.9	1
B	0.01	0.45	0.5	0,5	0.9	1
C	0.01	0.3	1	1	0.3	1

Now follows a more formal definition of structural identifiability.

Let the generic parameter vector $\mathbf{p}$ belong to a feasible parameter space $\mathbf{\Omega}$ such that $\mathbf{p} \in \mathbf{\Omega}$. Let $y(t, \mathbf{p})$ be the observable output function from a state space model. Further consider a parameter vector $\bar{\mathbf{p}}$ where $y(t, \mathbf{p}) = y(t, \bar{\mathbf{p}})$ for t. If this equality, in a neighbourhood $N \in \mathbf{\Omega}$, implies that $\mathbf{p} = \bar{\mathbf{p}}$ the model is *structurally locally identifiable*. If $N = \mathbf{\Omega}$ then the model is *globally structurally identifiable*. However, if $y(t, \mathbf{p}) = y(t, \bar{\mathbf{p}})$ implies $\mathbf{p} \neq \bar{\mathbf{p}}$ then the model is *structurally unidentifiable*.

For mixed-effects models there are, in addition to the model parameters, also statistical parameters describing the model parameter distributions in the population. The concept of structural identifiability in a mixed-effects model context then expands to determining whether the distribution of the model parameters is uniquely determined by the statistical parameters. For instance, if the parameters $P_1 \in N(\mu_1, \omega_1)$ and $P_2 \in N(\mu_2, \omega_2)$ then the statistical parameters $\{\mu_1, \mu_2, \omega_1, \omega_2\}$ are structurally unidentifiable if only the sum $p_{sum} = P_1 + P_1$ is estimated since $P_{sum} \in N(\mu_1 + \mu_2, \sqrt{\omega_1^2 + \omega_2^2})$.

3. METHODS

In this section the general mixed-effects model structure is defined together with two different approaches to structural identifiability analysis applicable to such model structures.

3.1 Mixed-effects models

Before introducing the mixed-effects model structure we first introduce the deterministic model

$$\dot{\mathbf{x}}(t) = f(\mathbf{x}(t), \mathbf{u}(t), \boldsymbol{\theta}) \quad \mathbf{x}(t_0) = \mathbf{x}_0 \tag{4}$$

$$\mathbf{y}(t) = h(\mathbf{x}(t), \mathbf{u}(t), \boldsymbol{\theta}) \tag{5}$$

where $\mathbf{x}(t) \in \mathbf{R}^m$ is the state, $\mathbf{u}(t) \in \mathbf{R}^n$ is the input, $\boldsymbol{\theta} \in \mathbf{R}^d$ are the model parameters and $\mathbf{y}(t) \in \mathbf{R}^w$ is the output.

In contrast to the deterministic model, in mixed-effects modelling framework individual estimates of each subject's parameters are obtained. This is done by defining *fixed effects*, which are related to a population, and *random effects*, which are related to individuals within that population. In the inference problem, the random effects are assumed to belong to a postulated distribution which allows sharing of information between all subjects in a simultaneous estimation of all subject;s parameters. The mixed-effects model has the following general form

$$\dot{\mathbf{x}}_i(t) = f(\mathbf{x}_i(t), \mathbf{u}_i(t), \boldsymbol{\phi}_i) \quad \mathbf{x}_i(t_0) = \mathbf{x}_0(\boldsymbol{\phi}_i) \tag{6}$$

$$\mathbf{y}_i(t) = h(\mathbf{x}_i(t), \mathbf{u}_i(t), \boldsymbol{\phi}_i) \tag{7}$$

$$\tag{8}$$

where $\boldsymbol{\phi}_i = g(\boldsymbol{\theta}, \boldsymbol{\eta}_i, \mathbf{C}_i)$ are the parameters for the ith subject, $\boldsymbol{\eta}_i \in N(\mathbf{0}, \boldsymbol{\Sigma})$ are the random effects where $\boldsymbol{\Sigma}$ is the variance-covariance matrix, $\boldsymbol{\theta}$ are the population parameters and $\mathbf{C}_i$ are covariates. In systems pharmacology, most parameters are typically assumed to belong to a log-normal distribution $\boldsymbol{\phi}_i = \boldsymbol{\theta} e^{\boldsymbol{\eta}_i}$ to ensure positivity.

3.2 Repeated measurement approach

In a structurally unidentifiable model, it is still common to have structurally identifiable combinations of parameters, e.g. products, sums or ratios. The main idea behind the repeated measurement approach is to consider what happens to models where such parameter combinations exist in terms of structural identifiability in a mixed-effects framework, i.e. how the parameters belonging to a distribution, which may or may not be correlated with each other, affect whether they are structurally identifiable or not.

To state the problem more formally, consider

$$\mathbf{Z} = w(\boldsymbol{\Phi}) \tag{9}$$

where $\boldsymbol{\Phi} = [\boldsymbol{\phi}_i]$ is a vector of containing a subset of the model parameters with postulated parametrised distributions and $\boldsymbol{\Phi} \in \mathbf{R}^p$, $\mathbf{Z} \in \mathbf{R}^q$, $q < p$ and $w(\cdot)$ being in general a nonlinear function, e.g. products, sums or ratios of two or more parameters. The repeated measurement approach is to determine under what conditions the original parametrised distributions of $\boldsymbol{\Phi}$ are determined by a lower dimensional distribution of $\mathbf{Z}$. Several theorems will be presented below that can help in answering this question.

Theorem 1. (Radhakrishna (1971)) Suppose P_1, P_2 and P_3 are three independent real-valued random variables. Consider the two linear forms:

$$Z_1 = a_1 P_1 + a_2 P_2 + a_3 P_3 \tag{10}$$

$$Z_2 = b_1 P_1 + b_2 P_2 + b_3 P_3 \tag{11}$$

such that $a_i : b_i \neq a_j : b_j$ for $i \neq j$. If the characteristic function of (Z_1, Z_2) does not vanish, then the joint distribution of (Z_1, Z_2) determines the distribution of P_1, P_2 and P_3 up to a change of location.

Theorem 2. (Radhakrishna (1971)) In an extension of Theorem 1, consider p linear functions Z_i, $1 \leq i \leq p$, of n independent variables P_i. The smallest number p of linear functions $\mathbf{Z}_i$, $1 \leq i \leq p$ such that the joint distribution specifies the distribution of each random variable P_i, $1 \leq i \leq n$, can be calculated from the following relation

$$\frac{p(p-1)}{2} < n \leq \frac{p(p+1)}{2} \tag{12}$$

Theorem 3. (Rao (1992)) Suppose P_1, P_2 and P_3 are three independent positive random variables. Let

$$Z_1 = \frac{P_1}{P_3} \tag{13}$$

$$Z_2 = \frac{P_2}{P_3} \tag{14}$$

If the characteristic function of (log Z_1, log Z_2) does not vanish then the distribution of (Z_1, Z_2) determines the distributions of P_1, P_2 and P_3 up to a change of scale.

Theorem 4. (Szekely and Rao (2000)) Let P_1, P_2,..., P_n be independent random variables. Given the moments $E[P_j^s]$ where $s = 1,2,...,\ m$ and $j = 1,2,...,\ n$ the joint distribution function of the linear forms

$$Z_i = \sum_{j=1}^{n} a_{ij} P_i, i = 1, 2, ...k \tag{15}$$

with an arbitrary nonvanishing joint characteristic function uniquely determines the distributions of P_1, P_2,..., P_n if and only if

$$n \leq \binom{k+m}{m+1}. \tag{16}$$

Theorems 1-4 provide some general conditions how the parameters belonging to a distribution affects structural identifiability. In Example 1 below Theorem 1 is applied to show preciously how the repeated measurement approach can be used.

3.3 Augmented system approach

The second approach deals with augmenting the original system in such as way that the model parameters in the original system are differential equations with a zero-derivative and a random variable as initial condition in the augmented system, i.e. the augmented system is a random differential equation system where the randomness enters only through the initial conditions.

Theorem 5. (Soong (1973)) Consider the random system described by

$$\dot{\mathbf{X}}(t) = \mathbf{f}(\mathbf{X}(t), t) \tag{17}$$

$$\mathbf{X}(t_0) = \mathbf{X}_0 \tag{18}$$

where the initial condition $\mathbf{X}_0$ are random variables. The general solution takes the form

$$\mathbf{X}(t) = \mathbf{h}(\mathbf{X_0}, t) \tag{19}$$

If $\mathbf{h}(\cdot)$ is continuous in $\mathbf{X_0}$, has continuous partial derivatives with respect to $\mathbf{X_0}$ and defines a one-to-one mapping, the inverse transform can then be written as

$$\mathbf{X}_0 = \mathbf{h}^{-1}(\mathbf{X}, t) \tag{20}$$

The joint density function $p(\mathbf{x}, t)$ of $\mathbf{X}(t)$ is then given by

$$f(\mathbf{x}, t) = p_0[\mathbf{x}_0 = \mathbf{h}^{-1}(\mathbf{x}, t)] \mid J \mid \tag{21}$$

where $f_0(\mathbf{x}_0)$ is the joint density function of the initial condition $\mathbf{X}_0$ and $J = \left| \frac{\partial \mathbf{x}_0}{\partial \mathbf{x}} \right|$.

Problem formulation: In the augmented system the structural identifiability problem becomes a question of whether the joint distribution function $p(\mathbf{x}, t)$ of the states $\mathbf{X}(t)$ is uniquely determined by (21) in Theorem 5.

One way of connecting the output function $\mathbf{y}(t)$ with the model structure and the density function for the random initial conditions is to consider the moments of the output function $\mathbf{y}(t)$. The nth moment of the ith component of the state vector $\boldsymbol{X}(t)$, here denoted as $X_i(t)$, is given by

$$E[X_i^n(t)] = \int_{-\infty}^{\infty} h_i^n(\boldsymbol{x}_0, t) p_0(\boldsymbol{x}_0) d\boldsymbol{x}_0 \tag{22}$$

Assume for some arbitrary model that we have $y(t) = x_1(t)$. From eq. 22 we have, using $E[y^n(t)] = E[X_1^n(t)] = \int_{-\infty}^{\infty} h_1^n(\boldsymbol{x}_0, t) p_0(\boldsymbol{x}_0) d\boldsymbol{x}_0$ for some number n, a set of n equations describing the n different moments of $\mathbf{y}(t)$ in terms of the statistical parameters $\{\mu, \omega, \rho\}$ (expected value, variance, correlation) and the model structure. The

assumption here is that we have, apart from noise free, continuous data, an infinite number of subjects/patients. The task is now to show that the different moments of our observation $\mathbf{y}(t)$ are uniquely determined by the statistical parameters. Note that in this way the output can be any arbitrary function e.g. a sum, products etc. of several states. For instance if $y(t) = x_1 + x_2$, then $E[y^n(t)] = E[X_1^n(t)] + E[X_2^n(t)]$.

4. EXAMPLES

In this section two examples of structural identifiability analysis will be given using the approaches presented in the previous section.

4.1 Example 1: Simple tumour growth model

Consider the two following simple tumour growth models

$$\dot{q}_A(t) = (P_1 - P_3)q_A(t) = Z_1 q_A(t) \tag{23}$$

$$q_A(0) = q_{A0} \tag{24}$$

$$y_1(t) = q_A(t) \tag{25}$$

and

$$\dot{q}_B(t) = (P_2 - P_3)q_B(t) = Z_2 q_B(t) \tag{26}$$

$$q_B(0) = q_{B0} \tag{27}$$

$$y_2(t) = q_B(t) \tag{28}$$

where $P_i = e^{\eta_i}$ and $\eta_i \in N(0, \sigma_i)$, P_1 and P_2 are the growth rate of the tumour with no drug present and with drug present respectively, P_3 is the natural cell death, $q_A(t), q_B(t)$ are the tumour sizes. Note that the parameter P_3 is shared between the two models. If we estimate all model parameters simultaneously we can apply Theorem 1 to show that the variances of the model parameters σ_1, σ_2 and σ_3 are structurally identifiable even though the model parameters in the deterministic case are structurally unidentifiable.

From Theorem 1 we have

$$Z_1 = P_1 - P_3 \tag{29}$$

$$Z_2 = P_2 - P_3 \tag{30}$$

This means that if the model parameters in (23)-(28) are estimated in parallel, i.e. if the joint distribution (Z_1, Z_2) is estimated, the variance σ_i of the individual parameters is structurally identifiable. However, the population parameters are structurally unidentifiable.

4.2 Example 2

Consider the following model with only one state and one normally distributed dose parameter Z_{Dose}

$$\dot{x}_1(t) = -x_1(t) \quad x_1(0) = Z_{Dose} \tag{31}$$

$$y(t) = x_1(t) \quad p_0(Z_{Dose}) = \frac{e^{-\frac{(Z_{Dose}-\mu_{Dose})^2}{2\omega_{Dose}^2}}}{\sqrt{2\pi}\omega_{Dose}} \tag{32}$$

with the solution $y(t) = Z_{Dose}e^{-t}$. The first and second moment of the observation function $y(t)$ is, using eq. 22,

$$E[y(t)] = E[x_1(t)] \tag{33}$$

$$= \int_{-\infty}^{\infty} Z_{Dose}e^{-t}\frac{e^{-\frac{(Z_{Dose}-\mu_{Dose})^2}{2\omega_{Dose}^2}}}{\sqrt{2\pi}\omega_{Dose}}dZ_{Dose} \tag{34}$$

$$= \frac{e^{-t}\mu_{Dose}}{\sqrt{\frac{1}{\omega_{Dose}^2}}\omega_{Dose}} \tag{35}$$

$$E[y^2(t)] = E[x_1^2(t)] \tag{36}$$

$$= \int_{-\infty}^{\infty} (Z_{Dose}e^{-t})^2\frac{e^{-\frac{(Z_{Dose}-\mu_{Dose})^2}{2\omega_{Dose}^2}}}{\sqrt{2\pi}\omega_{Dose}}dZ_{Dose} \tag{37}$$

$$= \frac{e^{-2t}\left(\mu_{\text{Dose}}^2 + \omega_{Dose}^2\right)}{\sqrt{\frac{1}{\omega_{Dose}^2}}\omega_{Dose}} \tag{38}$$

To show that the first two moments of the output signal $y(t)$ are determined uniquely by the statistical parameters we can equate $E[y_\theta^n(t)] = E[y_{\bar{\theta}}^n(t)]$ where $n = 1, 2$ and $\theta = \{\mu_{Dose}, \omega_{Dose}\} and \bar{\theta} = \{\bar{\mu}_{Dose}, \bar{\omega}_{Dose}\}$ is an alternative parameter vector. If this equation system implies that $\theta = \bar{\theta}$ then the statistical parameters are structurally identifiable. This yields

$$\frac{e^{-t}\mu_{\text{Dose}}}{\sqrt{\frac{1}{\omega_{\text{Dose}}^2}}\omega_{\text{Dose}}} = \frac{e^{-t}\bar{\mu}_{\text{Dose}}}{\sqrt{\frac{1}{\bar{\omega}_{\text{Dose}}^2}}\bar{\omega}_{\text{Dose}}} \tag{39}$$

$$\tag{40}$$

and

$$\frac{e^{-2t}\left(\mu_{\text{Dose}}^2 + \omega_{\text{Dose}}^2\right)}{\sqrt{\frac{1}{\omega_{\text{Dose}}^2}}\omega_{\text{Dose}}} = \frac{e^{-2t}\left(\bar{\mu}_{\text{Dose}}^2 + \bar{\omega}_{\text{Dose}}^2\right)}{\sqrt{\frac{1}{\bar{\omega}_{\text{Dose}}^2}}\bar{\omega}_{\text{Dose}}} \tag{41}$$

for which the only solutions are $\mu = \bar{\mu}$ and $\omega = \bar{\omega}$. The mixed-effect model (31)-(32) is therefore structurally uniquely identifiable.

Observability

Observability is an important concept in systems modelling in general. A system such as (4)-(5) is said to be observable if and only if, given an input-output map, the initial conditions x_0 can be determined, see Hermann and Krener (1977). Observability is strongly related to structural identifiability since observability may be regarded as a generalisation of structural identifiability. If a system, written in an extended state-space form, i.e. the model parameters are defined as state variables, but with zero time-derivative, is shown to be observable then it follows directly that the system also is structurally identifiable.

In the augmented system approach presented in this paper, the system is rewritten on such an extended state-space form. Therefore, although no explicit approach is presented here, it is still worth mentioning that an alternative to considering the moments of the output function $y(t)$ is to instead combine existing observability tests such as the *Observability Rank Criterion* together with the joint density function of the initial conditions $p_0(\boldsymbol{x}_0)$ to determine whether the system is observable or not and therefore determining whether the system is structurally identifiable or otherwise.

5. DISCUSSION

Both of the two methods presented have been shown to be applicable to study structural identifiability in mixed-effects models. However, there are a few obvious differences between the methods worth mentioning.

The repeated measurement approach and Theorems 1-4 rely on certain structures or combinations of model parameters appearing in the model. In models where these structures do not exist this method cannot be used to study structural identifiability. It is also necessary that the parameter estimation includes parallel models with some parameters shared such as in Example 1. In modelling patient variability, another scenario could for instance be a difference in the distribution of the bioavailability parameter F between males/females while the remaining model parameters belong to the same distribution for males/females. Finally, Theorems (1)-(4) assumes that the random variables are independent and therefore offer no insight on how to deal with covariance between the model parameters.

Augmenting the original system form to a random differential equation system form is in some sense a more general approach to the structural identifiability problem for mixed-effects models. This is due to the following three reasons: *i)* in the augmented system the problem of structural identifiability can instead be regarded as an observability problem. If the augmented system is observable, the original system is structurally identifiable since all model parameters are included in the initial conditions. *ii)* In contrast to the repeated measurement approach, any model structure may be considered. This includes any covariance between any two model parameters. *iii)* In contrast to the repeated measurement approach, if the model structure is unidentifiable this approach still informs on which parameters are identifiable/unidentifiable and also the parameter combinations that are structurally identifiable. However, it is worth noting that, even for very simple model structures, the expression to be evaluated quickly grows in complexity. In addition, this method requires finding the system solution $h(\cdot)$ which may become very computationally expensive.

6. CONCLUSION

Two methods for structural identifiability analysis in mixed-effects models have been proposed. The two methods have different advantages and disadvantages. While the approach using functions of random variables requires minimal computation it requires a certain structure of the equations in order to be applicable. In addition, the method does not give any information about combinations of parameters that are structurally identifiable.

The other proposed approach, which involves augmenting the original system to a random differential equation system, is much more general in the sense that any arbitrary model structure, including covariance, can theoretically be analysed. With this approach it is also possible to determine structurally identifiable parameter combinations in the case of a structurally unidentifiable model. However, at present the latter method suffers from expensive computation even for relatively simple models.

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