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Determining identifiable parameter combinations using subset profiling

Marisa C. Eisenberg [a,b,*], Michael A.L. Hayashi [a,*]

[a] Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, United States
[b] Department of Mathematics, University of Michigan, Ann Arbor, United States

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ABSTRACT

Identifiability is a necessary condition for successful parameter estimation of dynamic system models. A major component of identifiability analysis is determining the identifiable parameter combinations, the functional forms for the dependencies between unidentifiable parameters. Identifiable combinations can help in model reparameterization and also in determining which parameters may be experimentally measured to recover model identifiability. Several numerical approaches to determining identifiability of differential equation models have been developed, however the question of determining identifiable combinations remains incompletely addressed. In this paper, we present a new approach which uses parameter subset selection methods based on the Fisher Information Matrix, together with the profile likelihood, to effectively estimate identifiable combinations. We demonstrate this approach on several example models in pharmacokinetics, cellular biology, and physiology.

1. Introduction

Identifiability analysis is a critical step in the parameter estimation process which addresses whether it is possible to uniquely recover the model parameters from a given set of data. For ordinary differential equation (ODE) models, this problem is typically broken into two broad and often overlapping categories: *practical identifiability*, which incorporates practical estimation issues that come with real data (such as noise and bias), and *structural identifiability*, which considers identifiability issues inherent to the model structure. This is often framed as a best-case scenario wherein the data are assumed to be known completely (i.e. smooth, noise-free and known for every time point). Structural identifiability is a necessary condition for parameter estimation with noisy data [1].

In the common case of model unidentifiability, a key concept in identifiability analysis is that of *identifiable combinations*, i.e. combinations of parameters which are identifiable even if the individual parameters are not [1–3]. These combinations give information on how to reparameterize a given model for identifiability and also give insight into what additional parameters can be experimentally measured to yield an identifiable model [2–6].

Many different analytical approaches to structural identifiability have been developed [1,5,7–9]. However, these methods are often restricted to specific classes of models, such as the Laplace transform approaches used in linear ODE models [1,10,11], and differential algebra methods used for rational function ODE models [3,7,12,13]. They may also be difficult to implement algorithmically, computationally intensive, or not guaranteed to terminate, making applications beyond relatively simple models more challenging [8,9,14,15].

In the case of unidentifiability, a range of analytical or symbolic approaches to determining identifiable combinations have been developed [3,5,6,13]. For example, the differential algebra approach can be used to uncover identifiable parameter combinations and reparameterizations of the model in terms of these combinations [3]. The differential algebra-based method in [3] uses Gröbner bases to find a 'simplest' set of combinations, denoted the canonical set. However, this can require the expensive calculation of large numbers of Gröbner bases [3]. A related approach to the one presented here involves using a Jacobian matrix and solving a set of partial differential equations to determine identifiable combinations and identifiable reparameterizations of a model [5,6,16]. This approach provides a quite general framework for determining structurally identifiable combinations, although it does require a level of expert knowledge as there are a range of different tools and possible approaches for applying these methods.

By contrast, while most numerical approaches to identifiability provide only local (rather than global) information about the parameters, they are often more computationally tractable [17].

* Corresponding authors. Address: Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, United States (M.C. Eisenberg).
E-mail addresses: marisae@umich.edu (M.C. Eisenberg), mhayash@umich.edu (M.A.L. Hayashi).

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Many of these methods have been used to address both structural and practical identifiability, often by using simulated data (either without noise or with a range of different noise assumptions, depending on whether structural or practical identifiability is considered) [18–20]. Techniques used for numerically evaluating both local structural identifiability and practical identifiability include the Fisher Information Matrix (FIM) [21–26] and the profile likelihood [18], among others [27–29]. However, development of numerical methods for finding identifiable combinations for nonlinear ODE models has received somewhat less attention [17,18].

For a more comprehensive review of the different approaches to identifiability analysis, the reader is referred to [30,31], which also provide some comparison of the computational speed, ease-of-use, and types of models to which each method is applicable.

In this paper, we propose a simple numerical approach to determining identifiable combinations. We make use of two established numerical tools in identifiability analysis: the FIM (and associated Cramer–Rao estimates of the covariance matrix), and the profile likelihood [18,21–24]. Individually, there are gaps in the applicability of each method (particularly for higher dimensional combinations) [18], as discussed further below. Instead, our approach builds on these two tools to determine local structurally identifiable combinations in nonlinear differential equation models.

2. Framework and definitions

2.1. Model structure

We begin by introducing the overall modeling framework and identifiability definitions used here. Let the model be given by

$$\begin{aligned}\dot{\mathbf{x}} &= f(\mathbf{x}, t, \mathbf{u}, \mathbf{p})\\ \mathbf{y} &= g(\mathbf{x}, t, \mathbf{p})\end{aligned} \tag{1}$$

where $\dot{\mathbf{x}}$ is a system of first order ODEs, with t representing time, and $\mathbf{u}$ the experimental input function(s), if any. The set of model parameters to be estimated are given by $\mathbf{p}$ (typically real-valued). The model output(s) are given by $\mathbf{y}$, which represents the measured variables—in our case assumed to be noise-free. We also let $\mathbf{x_0}$ represent the vector of initial conditions for $\mathbf{x}(t)$, some or all of which may also be unknown parameters to be estimated.

2.2. Identifiability

Identifiability analysis explores the question: given an input $\mathbf{u}$, model $\dot{\mathbf{x}} = f(\mathbf{x}, t, \mathbf{u}, \mathbf{p})$ and experimental output $\mathbf{y}$, is it possible to uniquely identify the parameters $\mathbf{p}$? Structural identifiability examines a 'best-case' version of this question in which we assume 'perfect' noiseless data. If parameter has a unique value p^* which yields a given output $\mathbf{y}^*$, it is considered *globally (or uniquely) structurally identifiable*; if there is a unique value p^* within a local neighborhood of parameter space yielding $\mathbf{y}^*$, it is considered *locally structurally identifiable*; and if there are a continuum of values of p which yield the output $\mathbf{y}^*$, the parameter is considered *unidentifiable*. A model is said to be globally structurally identifiable if all the parameters are globally structurally identifiable; if any parameters are locally structurally identifiable or unidentifiable, the model is also considered locally structurally identifiable or unidentifiable, respectively. In the case of model unidentifiability, the model parameters typically form *identifiable combinations*, i.e. combinations of parameters which are identifiable even though the individual parameters are unidentifiable.

More formally, structural identifiability can be thought of in terms of injectivity of the map $\Phi : \mathbf{p} \to \mathbf{y}$ given by viewing the model output $\mathbf{y}$ as a function of the parameters $\mathbf{p}$ [3,14]. We note that because there may be some 'special' or degenerate values for the parameter or initial conditions for which an otherwise identifiable model is unidentifiable (e.g. if all initial conditions are zero and there is no input to the model), structural identifiability is often defined for almost all parameter values and initial conditions [3,13,14].

Definition 2.1. For a given ODE model $\dot{\mathbf{x}} = f(\mathbf{x}, t, \mathbf{u}, \mathbf{p})$ and output $\mathbf{y}$, an individual parameter p is *globally (or uniquely) structurally identifiable* if for almost every point $\mathbf{p}^*$ and almost all initial conditions, the equation $\mathbf{y}(\mathbf{x}, t, \mathbf{p}^*) = \mathbf{y}(\mathbf{x}, t, \mathbf{p})$ implies $p = p^*$. Similarly, a model $\dot{\mathbf{x}} = f(\mathbf{x}, t, \mathbf{u}, \mathbf{p})$ is said to be *globally structurally identifiable* for a given choice of output $\mathbf{y}$ if every parameter is globally structurally identifiable, i.e. the equation $\mathbf{y}(\mathbf{x}, t, \mathbf{p}^*) = \mathbf{y}(\mathbf{x}, t, \mathbf{p})$ has only one solution, $\mathbf{p} = p^*$. Equivalently, a model is globally structurally identifiable for a given output if and only if the map Φ is injective almost everywhere, i.e. if there exists a unique set of parameter values $\mathbf{p}^*$ which yields a given trajectory $\mathbf{y}(\mathbf{x}, t, \mathbf{p}^*)$ almost everywhere.

Local structural identifiability can be defined in an analogous way as for global structural identifiability (substituting finitely many solutions for the unique solution in the definition above), but it is often instead evaluated in a local neighborhood of a particular point in parameter space (particularly for numerical approaches, e.g. as in [17,18,32]). We consider this form of local structural identifiability in this work.

Definition 2.2. For a given ODE model $\dot{\mathbf{x}} = f(\mathbf{x}, t, \mathbf{u}, \mathbf{p})$, input $\mathbf{u}$, and output $\mathbf{y}$, a parameter p is said to be *locally structurally identifiable* at p^* if within a local neighborhood of p^*, the equation $\mathbf{y}(\mathbf{x}, t, \mathbf{p}^*) = \mathbf{y}(\mathbf{x}, t, \mathbf{p})$ implies $p = p^*$. Similarly, a model is said to be *locally structurally identifiable* for a given choice of input and output if every parameter is locally structurally identifiable.

While structural identifiability is often treated as a formal or mathematical property and evaluated using analytical approaches, a range of numerical approaches have also been developed to investigate the structural identifiability properties of a model [17,18,21–24,28,29,33,34]. Commonly used tools in these approaches include parameter sensitivities [22–24], as well as profile likelihoods [17,18]. Many of these rely on the idea that if one uses sufficiently noise-free, frequently sampled simulated data (so that the data is effectively 'error-free') for parameter estimation, then any identifiability issues which arise must be due to structural rather than practical identifiability issues [18,20]. Numerical approaches to structural identifiability often only address local structural identifiability at a particular point in parameter space, since they typically require numerical values for the parameters to be used. However, this can often be partially mitigated by testing a wide range of parameter values.

Practical identifiability extends the notion of structural identifiability to deal with the case in which noisy/real data is used [18,22,35]. A structurally identifiable model may still be practically unidentifiable for a variety of reasons—for example, if the model identifiability is highly sensitive to measurement error in the data or if measurements are taken too sparsely and miss key features of the system dynamics. In some cases, practically identifiable combinations can be found, even within an otherwise structurally identifiable model (e.g. as seen in models of cholera in [20]).

2.3. Parameter graph

In examining the parameter identifiability structure, it is often convenient to consider a parameter graph of the identifiable combinations. While visualizing the parameter graph is not necessary for the method, it is often useful to illustrate features of the parameter