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Robust global identifiability theory using potentials—Application to compartmental models

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ABSTRACT

This paper presents a global practical identifiability theory for analyzing and identifying linear and nonlinear compartmental models. The compartmental system is prolonged onto the potential jet space to formulate a set of input–output equations that are integrals in terms of the measured data, which allows for robust identification of parameters without requiring any simulation of the model differential equations. Two classes of linear and non-linear compartmental models are considered. The theory is first applied to analyze the linear nitrous oxide (N_2O) uptake model. The fitting accuracy of the identified models from differential jet space and potential jet space identifiability theories is compared with a realistic noise level of 3% which is derived from sensor noise data in the literature. The potential jet space approach gave a match that was well within the coefficient of variation. The differential jet space formulation was unstable and not suitable for parameter identification. The proposed theory is then applied to a nonlinear immunological model for mastitis in cows. In addition, the model formulation is extended to include an iterative method which allows initial conditions to be accurately identified. With up to 10% noise, the potential jet space theory predicts the normalized population concentration infected with pathogens, to within 9% of the true curve.

1. Introduction

The approach of *in silico* trials is very useful for testing new algorithms and models before implementation in a clinical environment and helps to generate novel predictions and hypotheses that enhance understanding of complex pharmacological systems [15]. A number of parameters characterizing the behavior of these systems are generally not accessible to direct measurement. Their values are thus approximated indirectly as a parameter identification problem [6]. Many biological, physiological and pharmacological systems are adequately described using first order, non-linear differential equations models describing the internal structure of the systems. A commonly used approximation that often suffices to capture the underlying dynamics is linear compartmental models [29].

Structural identifiability is an important prerequisite for the parameter estimation. If the models are not identifiable, any numerical optimization approach that seeks to find the parameters from measured data will be ill-conditioned and will not give physiologically consistent and accurate answers. Thus, the resulting estimate would not be reliable for *in silico* experiments. However, identifiability analyses can provide insight into the design of suitable experiments to provide unique identifiability and combined with *in silico* testing can provide guidelines or protocols for expensive or difficult *in vivo* experiments [7,24].

Identifiability analyses have been formalized by Bellman and Astrom for linear compartmental models [9]. The early theories of identifiability analyses concentrate on the similarity transform of the state matrix, and testing the rank of this transform [20,39]. Other approaches have used the Laplace transform of the input and output for identifiability [19,40,43].

Different approaches to the non-linear identifiability problem have been proposed in the literature, for example the Pohjanpalo Taylor series method [34], and the differential algebra based method [5,10,27,30,32]. Sedoglavic [37] constructs the variational system from the differential equation model to compute the required Jacobians to test for local algebraic observability. Karlsson [27] developed an efficient method for local structural identifiability analysis of very large scale systems, through a computation of random integer coefficient power series. The differential algebra based method is becoming more widely used due to its usefulness in addressing global as well as local models. Algorithms have been successfully developed and implemented in a range of available software packages [2,10,27,30]. In addition, probabilistic approaches have been developed and implemented [35,36]. Once structural identifiability has been determined, algorithms for parameter estimation in models of dynamical systems

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given discrete time measurement data can be applied. A survey on such algorithms is given in Ref. [44].

The current linear and non-linear global differential identifiability theories only address the existence of a unique set of parameters that match any given data set described by the model. In other words, the theory used to prove global identifiability gives no means to identify the parameters once the model is shown to be identifiable. The major problem is that differentials are very sensitive to noise so the formulation cannot be applied to real data [11]. Note that the profile likelihood approach developed by Raue *et al.* [35] provides a method to identify confidence interval estimates of the parameters from measured data, but only proves local identifiability and requires numerous computations in the solution domain.

This work presents a practical implementable approach to global identifiability theory by prolongation of the original compartmental differential equation models onto the potential jet space. This method allows the input–output equations to be formulated entirely in terms of integrals, so that measured data can be transformed on to the potential jetspace surface and parameter identification achieved without requiring any numerical solution of the underlying model. In other words, all computations are performed on the potential jet space which is highly efficient computationally and robust to noise. For the special case of the first order, minimal model of glucose–insulin dynamics, the method provides the mathematical foundation behind the previously developed integral method which has been used extensively in critical care [22]. The proposed theory is applied to a number of compartmental systems and provides both a theory for identifiability and a direct method for system identification. This method is shown to be robust to noise and thus suitable for practical modeling and experimental design.

2. Methodology

2.1. Differential Jet space

Differential equations, from a group transformations point of view, act on the space co-ordinatized by the dependent and independent variables. These group transformations give rise to the differential jet space, which forms the basis of most of the current approaches of identifiability analysis, since their actions are essentially the prolongation of the set of differential equations onto the differential jet space. This section gives an overview of the transformations and functions as well as the definition of the differential jet space [33].

A simple system of differential equation involves one independent variable t (time) on T, and q dependent variables (states) $x = (x_1, \ldots, x_q)$ as coordinates on $X \simeq \mathbb{R}^q$. The total space is the Euclidean space $E = T \times X \simeq \mathbf{R}^{1+q}$ coordinatized by the independent and dependent variables.

Definition 1. The total space $E = T \times X \simeq \mathbb{R}^1 \times \mathbb{R}^q$ the nth differential jet space $J^n = J^nE = T \times X^{(n)}$ is the Euclidean space of dimension $1 + q^{(n)} = 1 + q\binom{1+n}{n}$, whose co-ordinates consist of the time t, the q dependent variables x_α, and the derivative co-ordinates defined:

$$x_\alpha^J = \frac{d}{dt^\alpha} f^\alpha(t), \quad \alpha = 1, \ldots, q. \tag{1}$$

Definition 2. A smooth function $x = f(t)$ from T to X has nth prolongation $x^{(n)} = f^{(n)}(t)$, which is a function from T to $X^{(n)}$ obtained by evaluating all derivatives of f up to order n. The individual coordinate function of $f^{(n)}(t)$ is given by Eq. (1).

As an example, consider a simple map $f : T \to X, t \mapsto x = f(t)$, which maps the T axis onto the X axis. A 0-jet is given simply by its graph $(t, f(t))$. A 1-jet is given by the co-ordinate $(t, f(t), \dot{f}(t))$. A 2-jet is given by $(t, f(t), \dot{f}(t), \ddot{f}(t))$, and so on up to the n-jet. The set of all k-jets from T to X is called the k-jet space.

Formally, in terms of equivalence classes of section s in smooth vector bundle π, defined by $[s]_t^k$, the k-jet space is defined [25]:

$$J^k(\pi) = \{[s]_t^k : t \in T, s \in \Gamma(\pi)\} \tag{2}$$

The k-jet space is endowed with a smooth manifold structure, which is called the manifold of k-jets of sections of π and the following maps defined:

$$\pi_k : J^k(\pi) \to T, \quad [s]_t^k \to t \tag{3}$$

$$\pi_{k,l} : J^k(\pi) \to J^l(\pi), \quad [s]_t^k \to [s]_t^l, \quad k \geq l \tag{4}$$

are smooth fiber bundles. Eqs. (3) and (4) make it possible to write a given differential equation on sections of a bundle in an invariant form [25]. Most of the analyses of jet spaces focus on the case where $k = \infty$, that is, the space of $J^\infty(\pi)$, which is understood to be the limit of the chain:

$$\cdots \to J^{k+1}(\pi) \overset{\pi_{k+1,k}}{\to} J^k(\pi) \to \cdots \to J^1(\pi) \overset{\pi_{1,0}}{\to} J^0(\pi) \tag{5}$$

2.1.1. Geometric interpretation of the differential jet space

As an aid to understanding the differential jet space, this section gives numerical examples to demonstrate the geometric aspects in the differential jet space.

Consider the first order differential equations defined:

$$\dot{y} - y = 0, \quad y(0) = 1 \tag{6}$$

$$\dot{y} + y^2 = 0 \quad y(0) = 1 \tag{7}$$

The analytical solutions of Eqs. (6) and (7) are defined:

$$y(t) = \exp(t) \tag{8}$$

$$y(t) = \frac{1}{t+1} \tag{9}$$

Eqs. (6) and (7) represent a plane and parabolic surface respectively in the 1-jet space $(t, y, \dot{y})$ and are plotted in Figs. 1 and 2. The solutions of Eqs. (8) and (9) for a given initial condition are plotted as blue dashed curves on the (t, y) plane and their corresponding prolongation to the 1-jet space are the 3D space curves denoted by black lines. In theory, any measured data could be represented on the surfaces of Figs. 1 and 2 without having to solve the equations, but requires differentiation, which is sensitive to noise. The 1-jet space surfaces consist of the prolongated solutions of Eqs. (8) and (9) for all initial conditions $y(0) \in$

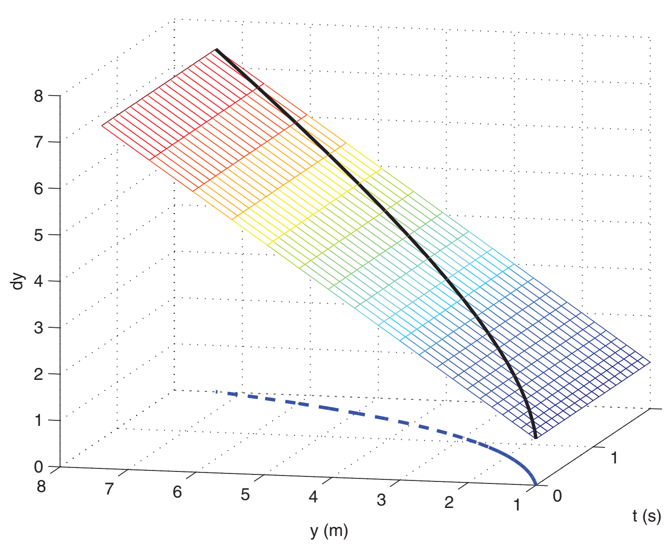

Fig. 1. 3D surface visualization for the differential jet space of Eq. (6) including the solution curve (blue dashed lines) and prolonged solution space curve (black solid lines).(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)