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Identifiable reparametrizations of linear compartment models

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ABSTRACT

Structural identifiability concerns finding which unknown parameters of a model can be quantified from given input–output data. Many linear ODE models, used in systems biology and pharmacokinetics, are unidentifiable, which means that parameters can take on an infinite number of values and yet yield the same input–output data. We use commutative algebra and graph theory to study a particular class of unidentifiable models and find conditions to obtain identifiable scaling reparametrizations of these models. Our main result is that the existence of an identifiable scaling reparametrization is equivalent to the existence of a scaling reparametrization by monomial functions. We provide an algorithm for finding these reparametrizations when they exist and partial results beginning to classify graphs which possess an identifiable scaling reparametrization.

1. Introduction

Parameter identifiability analysis for dynamic system ODE models addresses the question of which unknown parameters can be quantified from given input–output data. This paper is concerned with structural identifiability analysis, that is whether the parameters of a model could be identified if perfect input–output data (noise-free and of any duration required) were available. If the parameters of a model have a unique or finite number of values given input–output data, then the model and its parameters are said to be *identifiable*. However, if some subset of the parameters can take on an infinite number of values and yet yield the same input–output data, then the model and this subset of parameters are called *unidentifiable*. In such cases, we attempt to reparametrize the model to render it identifiable.

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There have been several methods proposed to find these identifiable reparametrizations. Evans and Chappell (2000) use a Taylor Series approach, Chappell and Gunn (1998) use a similarity transformation approach, and both Ben-Zvi et al. (2004) and Meshkat et al. (2009) use a differential algebra approach to find identifiable reparametrizations of nonlinear ODE models (see Miao et al. (2011) for a survey of methods). However, as demonstrated in Evans and Chappell (2000), there is no guarantee that these reparametrizations will be rational. For practical applications, e.g. in systems biology, a rational reparametrization is desirable. The motivation for this paper is to address the following question for linear systems:

Question 1.1. For which linear ODE models does there exist a rational identifiable reparametrization?

In this paper, we focus on *scaling reparametrizations*, which are reparametrizations that are obtained by replacing an unobserved variable by a scaled version of itself, and updating the model coefficients accordingly. We will answer the above question and provide an algorithm (see Algorithm 6.1) which takes as its input a system of linear ODEs with parametric coefficients and gives as its output an identifiable scaling reparametrization, if it exists, or shows that no identifiable scaling reparametrization exists.

Our main result gives a precise characterization of when a scaling reparametrization exists, for a specific family of linear ODE models.

Theorem 1.2. *Consider the linear compartment model with associated strongly connected graph G, where the input and output are in the same compartment. The following conditions are equivalent for this model*:

(1) *The model has an identifiable scaling reparametrization.*
(2) *The model has an identifiable scaling reparametrization by monomial functions of the original parameters.*
(3) *The dimension of the image of the double characteristic polynomial map associated to G is equal to the number of linearly independent cycles in G.*

Note the two key features of the theorem: by part (2) we only need to consider monomial scaling reparametrizations of the model, and by part (3) checking for the existence of an identifiable monomial rescaling is equivalent to determining the dimension of the image of a certain algebraic map, the *double characteristic polynomial map*. Theorem 1.2 leaves open the problem of characterizing the graphs G which satisfy the necessary dimension requirements, but we provide a number of partial results, including upper bounds on the number of edges that can appear, and constructions of families of graphs which realize the dimension bound, and hence have identifiable reparametrizations by monomial rescalings.

The organization of the paper is as follows. The next section provides introductory material on compartment models, how to derive the input–output equation, identifiability, and reparametrizations. Section 2 also introduces the main algebraic object of study in this paper: the double characteristic polynomial map. Section 3 explains how the identifiability problem relates to the directed cycles in the graph G, and how the cycle structure gives bounds on the dimension of the image of the double characteristic polynomial map. Section 4 contains a proof of Theorem 1.2, which reduces the problem of characterizing the graphs which have a scaling reparametrization to the problem of calculating the dimension of the image of the double characteristic polynomial map. Section 5 includes various combinatorial constructions to achieve the correct dimension, as well as some necessary conditions. In particular, we show that all minimal inductively strongly connected graphs achieve the correct dimension, and hence have an identifiable scaling reparametrization. Section 6 summarizes our theoretical results with an algorithm for computing an identifiable scaling reparametrization (if one exists). Section 6 also includes the results of systematic computations for graphs with few vertices, and contains conjectures based on the results of those computations.