Generalizing the differential algebra approach to input-output equations in structural identifiability

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Abstract

Structural identifiability for parameter estimation addresses the question of whether it is possible to uniquely recover the model parameters assuming noise-free data, making it a necessary condition for successful parameter estimation for real, noisy data. One established approach to this question for nonlinear ordinary differential equation models is via differential algebra, which uses characteristic sets to generate a set of input-output equations which contain complete identifiability information for the model. This paper presents a generalization of this method, proving that identifiability may be determined using more general solution methods such as ad hoc substitution, Gröbner bases, and differential Gröbner bases, rather than via characteristic sets. This approach is used to examine the structural identifiability of several biological model systems using different solution methods (characteristic sets, Gröbner bases, differential Gröbner bases, and ad hoc substitution). It is shown that considering a range of approaches can allow for faster computations, which makes it possible to determine the identifiability of models which otherwise would be computationally infeasible.

1 Introduction

Identifiability analysis addresses the question of whether it is possible to uniquely recover the parameters from a given set of data. This problem can be broken into two broad (and sometimes overlapping) categories—practical or numerical identifiability identification, which incorporates the practical estimation issues of noise and bias, and structural identifiability, which considers a best-case scenario when 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, and can yield information about how to reparameterize the model when it is unidentifiable.

Many different approaches to structural identifiability analysis have been developed [1-4]. However, the computational intensity of many methods makes applications beyond relatively simple
models more challenging \[5\]. For linear models, identifiability can be determined globally via a transfer function approach and other linear algebra methods \[3, 6, 7\]. One successful approach to identifiability for polynomial and rational function ordinary differential equation (ODE) models is via differential algebra \[1, 5, 8\], which can be used to determine not only the overall identifiability of the model, but in the case of model unidentifiability, also uncovers identifiable parameter combinations and reparameterizations of the model in terms of these combinations \[9\]. In general these combinations are not unique and can be found in a range of different forms, although using Gröbner bases one can find a ‘simplest’ set of combinations denoted the canonical set \[9\].

The algebraic approach is based on using characteristic sets \[10\] (a method of solving/reducing differential polynomial systems) to generate a monic set of equations in terms of only the known or measured variables and the parameters, called the input-output equations, whose solutions are the set of all input-output pairs for the model. The coefficients of the input-output equations can then be used to test identifiability of the model \[5, 11, 12\]. One of the major limitations of this approach is that for more complex models it can become computationally intractable \[5\]. However, intuitively what makes the input-output equations informative about model identifiability is not that they are generated by characteristic sets, but rather that their solutions are the solution trajectories of the measured variables of the original system. It would therefore seem natural to extend this approach to more general methods of generating input-output equations.

Indeed, an initial foray in this direction has been made by Meshkat et al. \[13\], who show that Gröbner bases provide an alternative to Ritt’s pseudodivision in generating input-output equations. In this paper, we show that the input output equations contain complete identifiability information regardless of how they are generated, and moreover both Gröbner bases (shown independently of \[13\]) and the differential Gröbner bases of Mansfield \[14\] yield a set of input-output equations. Using this more general approach allows more flexible calculations for testing structural identifiability, which can speed up computation and make tractable models which would otherwise be computationally infeasible for the differential algebra approach. We then present examples and comparisons of the different solution methods, and show how choosing alternative solutions methods may allow the differential algebra approach to identifiability to be feasible for more complicated, nonlinear models.

2 Identifiability

We begin by introducing the identifiability framework used here. Let the model be given by

\[
\begin{align*}
\dot{x} &= f(x, t, u, p) \\
y &= g(x, t, p)
\end{align*}
\]

where \(\dot{x}\) is a system of first order ordinary differential equations (ODEs), with \(t\) representing time, and \(u\) the experimental input function(s), if any. The model parameters are given by the \(n_p\) dimensional vector \(p \in \mathbb{R}^{n_p}\) (the complex numbers \(\mathbb{C}\) may also sometimes be considered, depending on the model). We will occasionally refer to individual parameters within \(p\) as \(p\) (without bold-face), and refer to an arbitrary point in parameter space (\(\mathbb{R}^{n_p}\)) as \(p^*\). The measured data/output(s) are given by \(y\), which represents the the \(n_y\)-dimensional vector of output(s) without any measurement error. We also let \(x_0\) represent the vector of initial conditions for \(x(t)\). As in \[1, 11, 14\], we assume that \(f\) and \(g\) are rational polynomial functions of their arguments, and that \(u, x,\) and \(y\) are arbitrarily
differentiable. We also assume that constraints reflecting known relationships among parameters, variables, inputs, and outputs are already included in the model equations, as these are known to affect identifiability properties \[3, 7, 9\]. Alternatively, the equality constraints among parameters or variables can also be appended to the model equations without affecting the results given here.

Structural identifiability analysis explores the question: given an input \(u\), model \(\dot{x} = f(x, t, u, p)\) and experimental output \(y\), is it possible to uniquely identify the parameters \(p\), assuming “perfect” noiseless data? Mathematically, this can be thought of in terms of injectivity of the map \(\Phi : p \rightarrow y\) given by viewing the model output \(y\) as a function of the parameters \(p\) \[5, 9\]. We note that because there may be some ‘special’ or degenerate parameter values 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 \[5, 9, 11\].

**Definition 2.1.** For a given ODE model \(\dot{x} = f(x, t, u, p)\) and output \(y\), an individual parameter \(p\) is uniquely (or globally) structurally identifiable if for almost every value \(p^*\) and almost all initial conditions, the equation \(y(x, t, p^*) = y(x, t, p)\) implies \(p = p^*\). A parameter \(p\) is said to be non-uniquely (or locally) structurally identifiable if for almost any \(p^*\) and almost all initial conditions, the equation \(y(x, t, p^*) = y(x, t, p)\) implies that \(p\) has a finite number of solutions.

**Definition 2.2.** Similarly, a model \(\dot{x} = f(x, t, u, p)\) is said to be uniquely (respectively non-uniquely) structurally identifiable for a given choice of output \(y\) if every parameter is uniquely (respectively non-uniquely) structurally identifiable, i.e. the equation \(y(x, t, p^*) = y(x, t, p)\) has only one solution, \(p = p^*\) (respectively finitely many solutions). Equivalently, a model is uniquely structurally identifiable for a given output if and only if the map \(\Phi\) is injective almost everywhere, i.e. if there exists a unique set of parameter values \(p^*\) which yields a given trajectory \(y(x, t, p^*)\) almost everywhere.

The equivalence classes generated by \(\Phi\) are precisely the sets of parameter values yielding the same output, so that if the fibers of \(\Phi\) contain finitely many elements, the model is locally (non-uniquely) identifiable, and if the fibers of \(\Phi\) contain infinitely many elements, the model is termed unidentifiable.

### 3 Algebra and differential algebra background

In this section, we present a very brief overview of the differential and computational algebra concepts needed for this paper. For full details on the fundamentals of differential and computational algebra methods, the reader is referred to \[10, 14, 15\]. Let \(R\) be a ring in the usual algebraic sense, and \(x\) a set of indeterminates. For our applications, \(R\) will represent the field of coefficients for an ODE model, so that we will typically consider \(R\) to be either the real or complex numbers, depending on the model. We use the usual notation \(R[x]\) to represent the polynomial ring in \(x\), and \(R(x)\) to represent the field of rational functions of \(x\) with coefficients in \(R\).

A **differential ring** is simply a ring in the usual algebraic sense, together with a differentiation operation which obeys the usual linear and product rule properties for derivatives. For ODE models, we typically extend \(R[x]\) to form a differential ring with derivatives in time \(t\), denoted \(R\{x\}\), by adding an additional derivative operation, in this case the usual polynomial derivative where we take derivatives from the ring of constants \(R\) to be zero. Elements of \(R\{x\}\) can be
thought of as elements of \( R[x, x', x'', \ldots] \), where \( x' \) represents the set of derivatives of elements of \( x \) with respect to \( t \) (where \( x \) is our set of variables). We note that for convenience we will often view a particular differential polynomial in \( x \) as an element of \( R[x, x', \ldots, x^{(n)}] \), where \( n \) is the highest derivative of \( x \) appearing in the polynomial.

Typically when working with differential polynomial rings, a ranking on the variables is chosen, in our case a ranking of the form \( u < \dot{u} < \ddot{u} < \cdots < y < \dot{y} < \ddot{y} < \cdots < x < \dot{x} < \ddot{x} < \cdots \) given in [11]. This makes allows one to determine leading terms, make polynomials monic, etc. The leader of a differential polynomial is defined as the highest ranking derivative of that polynomial (which can be a derivative of order 0). Choosing a ranking allows us allows us to fix the coefficients of the input-output equations uniquely, by dividing by the coefficient of the leading term to make the polynomials monic [11, 9].

Let \( S \) be a set of differential polynomials in \( R\{x\} \). The set of all polynomials that can be formed from elements of \( S \) by addition, multiplication by elements of \( R\{x\} \), and differentiation is called a differential ideal generated by \( S \), which we write as \( \{S\} \). For a given set of polynomials \( S \) (or differential polynomials, where we simply view the derivatives of variables as additional indeterminates), the variety \( V(S) \) is defined in the usual way as the set of points for which all polynomials in \( S \) are zero. A differential ideal \( I \) is called prime if \( ab \in I \) implies that either \( a \in I \) or \( b \in I \) and is called perfect if \( a^k \in I \) implies \( a \in I \) (i.e. a perfect ideal coincides with its radical).

There are several methods for manipulating systems of polynomials and differential polynomials, including the Gröbner basis and characteristic set methods discussed here, as well as methods of resolvents, among others [14, 16]. The usual method used to generate the input-output equations in identifiability for ODE models is the characteristic set [10]. A characteristic set of a set of polynomials is defined to be a chain of minimal rank in the differential ring, where chains of polynomials are formed by using pseudoreduction [10] to reduce the rank of the polynomials compared to one another, until a minimal, autoreduced set is reached. For details on characteristic sets and their uses in identifiability, see [11, 8, 11, 17].

Gröbner bases are one of the most common tools in computational algebra, and hence are a natural generalization of the characteristic set approach for generating input-output equations, as numerous fast methods for calculating Gröbner bases have been developed (e.g. Faugere algorithm [18], Gröbner walk methods [19]). A Gröbner basis of an ideal \( I \) is a generating set for that ideal such that the remainder of any element of ring yields zero if and only if that element is an element of \( I \). Form more information on Gröbner bases, the reader is referred to [15]. When applying Gröbner bases to differential polynomials in \( x \), we typically work in \( R[x, x', \ldots, x^{(n)}] \) (where \( n \) is the highest order derivative appearing in our set of polynomials), where we treat derivatives of \( x \) as new indeterminates.

It would be natural to extend Gröbner basis theory to the differential case, and indeed there have been two major formulations of differential Gröbner bases [14, 16, 20]. Part of the difficulty in extending the Gröbner bases to the differential case is in incorporating the differential structure of the ring, which lends itself to pseudoreduction rather than conventional reduction as is done in algebraic Gröbner bases [14, 16]. Mansfield Gröbner bases [14] surmount this difficulty by developing a pseudoreduction formulation of differential Gröbner bases, and so we use this formulation here. A Mansfield differential Gröbner basis of a differential ideal \( I \) is a generating set of \( I \) such that full pseudoreduction of any element of \( I \) yields zero. Details and comparisons of Mansfield and algebraic Gröbner bases can be found in Mansfield’s thesis [14].
4 Generalized differential algebra approach to identifiability

Next, we introduce the basic differential algebra method, and give a few results which generalize the usual approach. As discussed above, the larger goal of the differential algebra method is to use algebraic manipulation to yield a monic set of \( n_y \) equations only in the input variables \( u \), output variables \( y \) and parameters \( p \), denoted the input-output equations [8], for which solutions are precisely the allowed input-output pairs of the system. In this case, every solution trajectory for the model \( (x, u, y) \) yields a solution \( (u, y) \) for the input-output equations, and every solution to the input-output equations corresponds to at least one model solution.

In the usual differential algebra approach the input-output equations are generated as part of a characteristic set [11,17], but in principle input-output equations could be generated by a range of methods, e.g. simply by ad hoc substitution and differentiation, using Gröbner bases (provided we add sufficient derivatives to generate enough equations), or via differential Gröbner bases. Indeed, we show below that the coefficients of the input-output equations in general are identifiable, and that these coefficients yield complete identifiability information for the model, regardless of how they are generated. This may allow us to simplify and speed up the identifiability analysis process, as we can more flexibly tailor our methods to the system at hand.

**Theorem 4.1.** The parameters of a rational function ODE model \( x(t, u, p) \), \( y(x, u, p) \) are globally (respectively locally) structurally identifiable if and only if the map \( c(p) \) from the parameters to the coefficients of a set of input-output equations is injective (respectively, the fibers contain finitely many elements), regardless of how the input-output equations are generated.

**Proof.** Let \( \Psi(u, y, p) \) be the monic input-output equations of our system, with each \( \Psi_j(u, y, p) := \sum_i c_i(p) \psi_i(u, y) = 0 \), where the \( \psi_i \) are distinct monomials in the inputs, outputs, and their derivatives, with the coefficient of the highest ranking term of each \( \psi_i \) equal to one. We refer to the complete set of coefficients of \( \Psi \) as \( c(p) \).

Let \( \Psi_{CS} \) be a set of input output equations generated using the characteristic set approach of [3,11]. Then if \( \hat{p} \) and \( p^* \) both yield the same trajectory \( \hat{y} \), the characteristic set approach tells us that the coefficients of \( \Psi_{CS} \) satisfy \( c_{CS}(\hat{p}) = c_{CS}(p^*) \). Additionally, the results of Diop [21] and Saccomani [5] (with some algebraic manipulation) give us that the differential ideal generated by \( \Psi_{CS} \) is prime, so that it coincides with its radical. As \( \Psi \) and \( \Psi_{CS} \) are both sets of input output equations, they have the same input-output solution pairs (i.e. the same variety). Then \( \Psi \) is contained in the differential ideal generated by \( \Psi_{CS} \) (by Seidenberg’s differential nullstellensatz, or by Hilbert’s nullstellensatz after appending sufficiently many derivatives of \( \Psi_{CS} \)). Then as \( \hat{p} \) and \( p^* \) both generate the same coefficients for \( \Psi_{CS} \), which in turn generates \( \Psi \), we know \( \hat{p} \) and \( p^* \) must both generate the same coefficients for \( \Psi \), i.e. \( c(\hat{p}) = c(p^*) \). Then any solutions to the map \( \Phi: p \rightarrow y \) are also solutions to \( c(p) \), i.e. we have the forward implication that if \( c(p) \) is injective (respectively has finite fibers), then the model is globally (locally) identifiable, i.e. the map \( \Phi: p \rightarrow y \) is injective (respectively has finite fibers).

To prove the converse, we need to show that if \( c(p) \) is not injective then neither is \( \Phi \), and if \( c(p) \) has infinitely many solutions, so does \( \Phi(p) \). One way to show this is to show that if \( p \) and \( p^* \) satisfy \( c(p) = c(p^*) \), then \( p \) and \( p^* \) also satisfy \( \Phi(p) = \Phi(p^*) \) (in other words, that \( p \) and \( p^* \) both yield the same input-output pair, and so are indistinguishable). However, this follows from the definition of \( c(p) \), as if \( c(p) = c(p^*) \), then by definition \( p \) and \( p^* \) yield the same trajectory.
This means that solutions to the model for both \( p \) and \( p^* \) yield the same input-output pair, i.e. \( \Phi(p) = \Phi(p^*) \).

This confirms that input-output equations contain complete identifiability information, which seems natural, as all the information obtainable from the known inputs and outputs (data) are present in the input-output equations. Next, we show that both Mansfield differential Gröbner bases and Gröbner bases (with sufficiently many derivatives of the model equations added in order to eliminate all non-observed variables) will yield a set of input-output equations. For this, we use the elimination theorem [14] and differential elimination theorem of Mansfield [14]. This may restrict the type of ordering used, as Mansfield proved the differential elimination theorem using lexicographic order while Cox considers a broader range of possible orderings for the non-differential version (see [15] for more details). However, this is not a problem for identifiability analysis as lexicographic ordering is typically used [1, 5].

**Theorem 4.2.** Both Mansfield differential Gröbner bases and Gröbner bases (with sufficiently many derivatives of the model equations added) of a rational function ODE model \( \dot{x}(t, u, p) = f(x, t, u, p), y(x, u, p) = g(x, t, p) \) contain a complete set of input-output equations.

**Proof.** Let us first show this for differential Gröbner bases. Let \( \tilde{f} = \dot{x}(t, u, p) - f(x, t, u, p) \), and \( \tilde{g} = y(x, u, p) - g(x, t, p) \), so that the model is given by \( \tilde{f} = 0, \tilde{g} = 0 \). Let \( mgb(\tilde{f}, \tilde{g}) \) be a Mansfield differential Gröbner basis of the model (clearing denominators of model as needed), taking a lexicographic ordering with \( u < \dot{u} < \cdots < y < \dot{y} < \cdots < x < \dot{x} < \cdots \) (as given in [11]). Then \( \{mgb\} = \{\tilde{f}, \tilde{g}\} \), so \( V(\{mgb\}) = V(\{\tilde{f}, \tilde{g}\}) \) and we have that solutions to \( mgb \) are precisely the allowed trajectories of the model. We also know that the characteristic set \( \text{char}(\tilde{f}, \tilde{g}) \subset \{\tilde{f}, \tilde{g}\} = \{mgb\} \). We note that the characteristic set has been shown to contain a set of input output equations [8 [11] 17], so that \( \{\tilde{f}, \tilde{g}\} \cap R\{y, u\} \neq \emptyset \). Then by the differential elimination theorem of Mansfield [14], we have that \( mgb \cap R\{y, u\} \) is a Mansfield Gröbner basis for the ideal \( \{\tilde{f}, \tilde{g}\} \cap R\{y, u\} \), i.e.

\[
\{mgb \cap R\{y, u\}\} = \{\tilde{f}, \tilde{g}\} \cap R\{y, u\}.
\]

Moreover, because solutions of \( \{\tilde{f}, \tilde{g}\} \cap R\{y, u\} \) are precisely the allowed input-output trajectories, and \( mgb \cap R\{y, u\} \) generates this ideal, then \( V(\{mgb \cap R\{y, u\}\}) \) is precisely all input-output trajectories. Thus \( mgb \) contains a complete set of input output equations. A very similar argument shows that the same is true for algebraic Gröbner bases, provided we begin by taking sufficiently many derivatives of the model equations to include all the differential variables needed to generate the characteristic set (and use the usual Gröbner basis elimination theorem [15] rather than the differential version). The algebraic Gröbner basis result has also been shown independently in [13], with more details given there on the number of derivatives needed to generate the input output equations. \qed
5 Examples

Next, we give some example applications of these results, and compare three of the methods for generating the input-output equations discussed here—characteristic sets, differential Gröbner bases, and \textit{ad hoc} substitution. All examples were implemented in Mathematica Version 8 [22]. It must be emphasized that the speed of any of these methods depends heavily on the details of its implementation, so that results of speed tests such as these may vary widely. These examples are only intended to demonstrate that using different approaches can in some cases significantly improve the speed of the identifiability computations.

**Example 1: Linear 2-compartment Model**. To begin, we introduce the linear 2-compartment model, which is frequently used in pharmacokinetics, and has been shown previously by several methods to be unidentifiable [9, 11]:

\[
\begin{align*}
\dot{x}_1 &= u(t) + k_{12}x_2 - (k_{01} + k_{21})x_1 \\
\dot{x}_2 &= k_{21}x_1 - (k_{02} + k_{12})x_2 \\
y &= \frac{x_1}{V}
\end{align*}
\]  

(2)

where \(x_1\) represents the mass of a substance in the blood (e.g. a hormone or drug), and \(x_2\) represents the mass of the substance in the tissue. The drug exchanges between blood and tissues, and is degraded/lost in both compartments, at the rates given by the \(k_{ij}\)'s above. The function \(u(t)\) represents a known input of the drug into the blood. The model output \(y = x_1/V\) is the blood concentration of the drug, where \(V\) is the blood volume. The \(k_{ij}\)'s and \(V\) are unknown parameters to be estimated.

To examine the identifiability of (2), we start by generating a set of input-output equations. By Theorem 4.1 we need not use characteristic sets, so we will instead use \textit{ad hoc} substitution to generate the input-output equations. We start by replacing \(x_1\) with \(x_1 = yV\), to give:

\[
\begin{align*}
\dot{y}V &= u(t) + k_{12}x_2 - (k_{01} + k_{21})yV \\
\dot{x}_2 &= k_{21}yV - (k_{02} + k_{12})x_2.
\end{align*}
\]
Next, we solve the first equation for $x_2$, to yield $x_2 = \frac{-u(t) + k_{01}V_y + k_{21}V_y + V\dot{y}}{k_{12}}$, which we plug into the second equation (differentiating to give $\dot{x}_2$) to yield:

$$k_{12}k_{21}V_y + (k_{02} + k_{12})(u(t) - V(k_{01} + k_{21})y + V\dot{y}) + \dot{u}(t) - V(k_{01} + k_{21})\dot{y} + V\ddot{y}$$

Collecting terms and making the polynomial monic (by dividing by the coefficient of the leading term $\dot{y}$) yields the input output equation:

$$- \frac{k_{02} + k_{12}}{V} u(t) - \frac{\dot{u}(t)}{V} + (k_{01}k_{02} + k_{01}k_{12} + k_{02}k_{21})y + (k_{01} + k_{02} + k_{12} + k_{21})\dot{y} + \ddot{y}. \quad (3)$$

We note that this is the same input-output equation that would be achieved via a characteristic set, but requires fewer steps than the characteristic set algorithm (in part because the characteristic set maintains a set of three equations, each with different leaders, which must all be reduced with respect to one another, rather than focusing on just the input-output equation). However, this example is simple enough that both approaches take similar amounts of computational time (the substitution approach took slightly less time than the characteristic set, but the improvement was basically insignificant).

In calculating the input-output equation, the differential Gröbner basis approach took 0.022579 seconds of CPU time in Mathematica, the substitution approach took 0.028624 seconds, and the characteristic set approach took 0.029163 seconds. Using a standard Gröbner basis to calculate the input-output equations took significantly longer, at 0.339387 seconds of CPU time.

By Theorem 4.1, the coefficients to (3) are identifiable. Then to test the identifiability of the individual parameters $(k_{01}, k_{02}, k_{12}, k_{21}, V)$, we must test injectivity of the map $c(p)$. Thus, suppose we have an alternative set of parameters $(a_1, a_2, a_3, a_4, a_5)$ which also yield the same output. As the coefficients for the input output equation are identifiable, we have that:

$$- \frac{k_{02} + k_{12}}{V} = -a_2 + a_3$$

$$- \frac{1}{V} = -a_5$$

$$k_{01}k_{02} + k_{01}k_{12} + k_{02}k_{21} = a_1a_2 + a_1a_3 + a_2a_4$$

$$k_{01} + k_{02} + k_{12} + k_{21} = a_1 + a_2 + a_3 + a_4$$

Solving for $(k_{01}, k_{02}, k_{12}, k_{21}, V)$ following the algorithm in [11] reveals that the model is unidentifiable, with identifiable combinations $k_{01} + k_{21}, k_{02} + k_{12}, k_{12}k_{21}$ and one identifiable parameter, $V$ (as also shown in [11]).

**Example 2: Nonlinear 2-compartment Model.** A common variant of the two compartment model is the following nonlinear version:

$$\dot{x}_1 = u(t) + k_{12}x_2 - \left(\frac{V_{\text{max}}}{K_m + x_1} + k_{21}\right)x_1$$

$$\dot{x}_2 = k_{21}x_1 - (k_{02} + k_{12})x_2$$

$$y = \frac{x_1}{V}. \quad (4)$$
Figure 2: Nonlinear 2-compartment model.

The input-output equation for this model is given by:

\[
\begin{align*}
- \frac{V(k_{02} + k_{12})}{K_m^2} u y^2 - \frac{2(k_{02} + k_{12})}{K_m} u y - \frac{k_{02} + k_{12}}{V} u - \frac{V y^2 u}{K_m^2} - \frac{2y u}{V} - \frac{\dot{u}}{V} + \frac{k_{02} k_{21} V^2 y^3}{K_m^2} \\
+ \left( \frac{k_{02} V^2 + k_{12} V^2 + k_{21} V^2}{K_m^2} \right) y^2 y + \frac{V^2 y^2 \dot{y}}{K_m^2} + \left( \frac{2k_{02} k_{21} V + k_{02} V V_{\text{max}} + k_{12} V V_{\text{max}}}{K_m^2} \right) y^2 + \frac{2V y \dot{y}}{K_m} \\
+ \left( \frac{2k_{02} V + 2k_{12} V + 2k_{21} V}{K_m} \right) y \dot{y} + \left( k_{02} k_{21} + \frac{k_{02} V_{\text{max}} + k_{12} V_{\text{max}}}{K_m} \right) y + \left( k_{02} + k_{12} + k_{21} + \frac{V_{\text{max}}}{K_m} \right) y \dot{y} + \ddot{y}
\end{align*}
\]

Solving for the parameters using the coefficients shows that the model is globally structurally identifiable. The timings for the calculation of the input-output equation for each of the different methods were: 0.013182 seconds CPU time in Mathematica for the differential Gröbner basis approach, 0.164781 seconds for the substitution approach, 0.214768 seconds CPU time for the characteristic set approach, and 3.06737 seconds CPU time using Gröbner bases.

6 Conclusions

In this work, we have extended the characteristic set-based differential algebra approach to structural identifiability \[8, 11, 17\] to incorporate more general differential polynomial solution methods. We show that the input output equations for a rational function ODE model, regardless of how they are generated, contain complete identifiability information for the model. In particular, we also show that Mansfield differential Gröbner bases and algebraic Gröbner bases can both be used to generate a set of input-output equations. These results may help to address one of the major criticisms of the differential algebra approach to identifiability—the computational complexity of the calculations required is often prohibitive for more complicated models \[11\].

For example, this is the case for the SIWR model examined in \[23\], where the characteristic set approach was computationally infeasible, but using ad hoc substitution, the identifiability of a disease model used for cholera was able to be established. Indeed, in both examples here, the
substitution approach performed quite well (second fastest), suggesting that incorporating this into a more rigorous algorithm might improve computation time for identifiability. The substitution approach used here has the disadvantage that it is non-algorithmic (and so not general for other models), but it does allow one to fine tune calculations and speed up computation for a particular model.

In the two examples given here, the differential Gröbner basis approach gave the shortest computation time. The improvement in speed of differential Gröbner bases over the algebraic Gröbner basis approach may be due to the fact that algebraic Gröbner bases do not take explicit advantage of the differential structure of the ring, making them less computationally efficient than the differential Grobner basis. However, as noted above, it must be emphasized that the details of the implementation for the Grobner basis algorithm may change these results significantly. Nonetheless, this suggests that efficient algorithms for Mansfield differential Gröbner basis calculation along the same line as those for algebraic Grobner bases (e.g. the Gröbner walk [19]) might be a viable approach to improving the speed of identifiability calculations in practice.

Acknowledgments
This work was supported by National Science Foundation Award 0635561. Many thanks to Joseph Tien, Suzanne Robertson, Jeff Dunworth, and Tony Nance (Ohio State University) for their helpful comments.

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