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COMBOS: A Web Application  
for Finding Identifiable Parameter Combinations  
of Nonlinear Ordinary Differential Equation Models

A thesis submitted in partial satisfaction  
of the requirements for the degree Master of Science  
in Computer Science

by

Christine Er-zhen Kuo

2013

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2013

## ABSTRACT OF THE THESIS

### COMBOS: A Web Application for Finding Identifiable Parameter Combinations of Nonlinear Ordinary Differential Equation Models

by

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Master of Science in Computer Science  
University of California, Los Angeles, 2013  
Professor Joseph J. DiStefano III, Chair

Parameter identifiability problems can plague biomodelers when they reach the quantification stage of development, even for relatively simple models. Novice modelers often may not even recognize that identifiability properties of the model are the problem. This highly technical subject is also difficult to teach.

COMBOS is a user-friendly web app that addresses and solves key aspects of the structural identifiability (SI) problem for a practical class of nonlinear (and linear) ordinary differential equation (ODE) systems biology and other models. Given the ODE and measurement models (user input) of the form  $dx/dt = f(x,p,u)$  and  $y = g(x,p)$ , it provides not only a list of uniquely (globally) and non-uniquely (locally) SI model parameters, but also the combinations of parameters that are not individually SI. If locally SI, it also provides the number of solutions. The behind-the-scenes symbolic

differential algebra algorithm is based on computing Gröbner bases of model attributes established after some algebraic transformations and is currently run in the computer algebra system Maxima.

COMBOS was developed for facile instructional as well as research use. It has been validated for models of moderate dimensions with and without initial conditions. COMBOS includes several built-in examples, including linear 2 to 4-compartment models and a 4th-order nonlinear unidentifiable HIV dynamics model.

The thesis of Christine Er-zhen Kuo is approved.

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2013

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## INTRODUCTION

Structural identifiability analysis establishes which parameters of an ODE model are quantifiable from a given input-output experiment, with model of the general nonlinear ODE form  $dx/dt = f(x,p,u)$  and output  $y = g(x,p)$ . A model is structurally identifiable if all parameters have a unique or finitely many solutions, and is unidentifiable if some parameters have an uncountably infinite number of solutions. Quantifying parameter combinations is always possible when individual parameters are not identifiable. The ability to readily determine which parameter combinations are identifiable in a nonlinear model is especially pertinent, particularly for large nonlinear models that involve tens of state variables and hundreds of parameters (DiStefano 2010).

$$\begin{aligned} \frac{dx_1}{dt} &= -(k_{01} + k_{21})x_1 + k_{12}x_2 + u_1 \\ \frac{dx_2}{dt} &= k_{21}x_1 - (k_{02} + k_{12})x_2 \\ y_1 &= \frac{x_1}{V} \end{aligned}$$

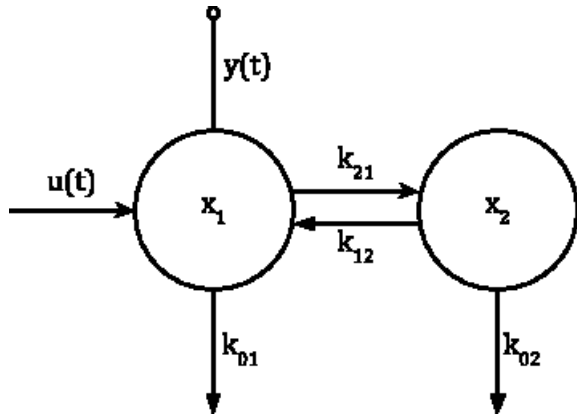


Figure 1 - 2-Compartmental Model

$$\begin{aligned} V &= V \\ p &= -k_{12}k_{21} \\ k_{11} &= k_{01} + k_{21} \\ k_{22} &= k_{02} + k_{12} \\ \frac{dx_1}{dt} &= k_{11}x_1 + x_2' + u_1 \\ \frac{dx_2'}{dt} &= px_1 - k_{22}x_2' \\ y_1 &= \frac{x_1}{V} \end{aligned}$$

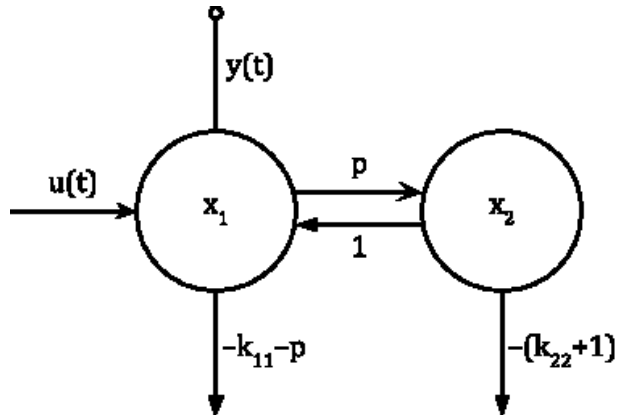


Figure 2 - Reparameterized Model

We illustrate this with a simple example. Figure 1 shows a general 2-compartment model and the ODEs describing it. There are five unknown parameters: the volume  $V$  of compartment 1 and four rate constants. The experiment shown has

one input and one output, both in compartment 1. This model is not structurally identifiable because none of the  $k_{ij}$ 's are quantifiable, even from ideal output data over some time interval.

Lack of structural identifiability poses a challenge for further quantitative analysis of the model. For example, without some parameter values, it cannot be simulated. This indeterminacy can be overcome by reparameterizing the model in terms of the identifiable combinations of parameters and computing solutions using combinations in the ODEs. Figure 2 shows one form of reparameterized model using the identifiable parameter combinations and the ODEs describing the new system. Note that the new compartmental model has one less parameter value, making it structurally identifiable. In light of this motivating example, it is evident that finding identifiable parameter combinations can help overcome roadblocks encountered in quantitative analysis of unidentifiable models.

We created a web application, COMBOS, that implements our algorithm for finding identifiable parameter combinations in nonlinear ODE systems (Meshkat et al. 2009, 2011). COMBOS serves as the interface between the user with a linear or nonlinear model and Maxima<sup>1</sup>, an open-source computer algebra software package we currently use to solve for identifiable parameter combinations.

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<sup>1</sup> Maxima is an open source computer algebra system. <http://maxima.sourceforge.net>

## METHODS

### User interface

The overall schematic of COMBOS is shown in Figure 3. Models can be entered into COMBOS for identifiability analysis in two ways: a fill-in form for adding math equations, entered using a standard markup language; and a text area for copy/paste with equations delimited by semicolons. This is preferred to file upload because it circumvents storing user input on the server, thereby minimizing security concerns. Equations are displayed in native math form as they are entered. The standardized syntax for both is further described below.

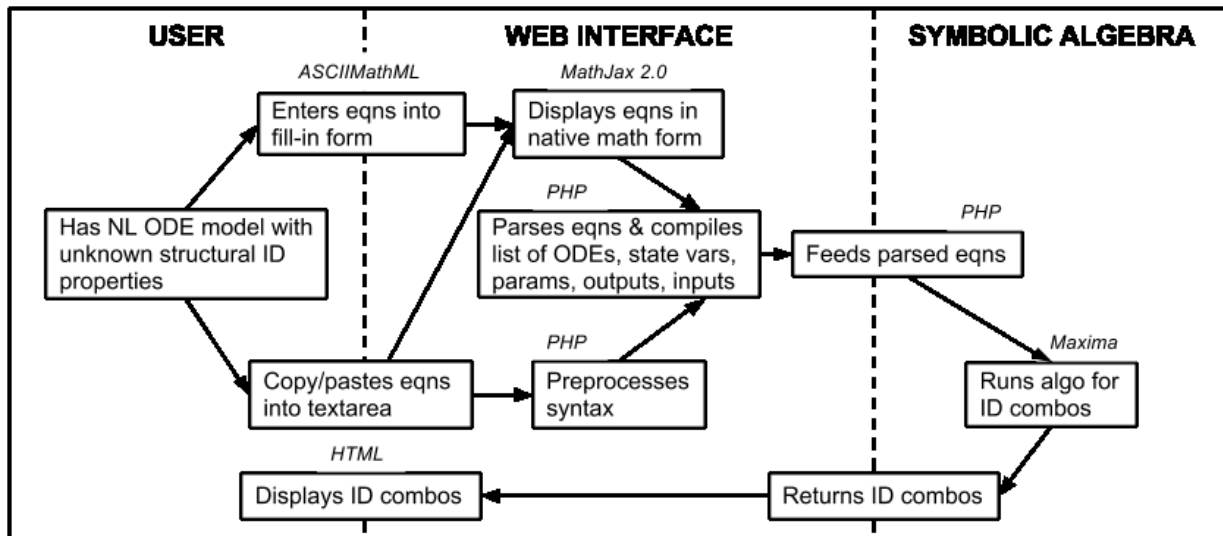


Figure 3 - COMBOS Flowchart

### Syntax & Naming Guidelines

Equations are entered using ASCII MathML<sup>2</sup> notation, chosen over its MathML and LaTeX counterparts for its simplicity, reduced character count and thus usability. Table 1 lists the naming guidelines for equations of the form  $dx/dt = f(x,p,y)$  and  $y = g(x,p)$  that users must adhere to.

<sup>2</sup> ASCII MathML is a mathematical expression library. <http://www1.chapman.edu/~jipsen/mathml/asciimath.html>

Time	MUST BE "t"	
State variables	MUST BE "x" followed by a number	x1
Initial conditions	CAN BE defined for any existing state variable and, if so, MUST BE expressed as a number or a function of the parameters	$x_2(0)=3*p_1$
Inputs	MUST BE "u" followed by a number	u2
Outputs	MUST BE "y" followed by a number	y3
Parameters	MUST BE any unreserved letter (NOT x,u,y,t) by itself or followed by any combination of letters, numbers, or commas	p p4 Vmax k12,34
Known constants	MUST BE entered as numerical values; otherwise, they will be treated as unknown parameters	
Operands	MUST BE separated by some combination of operators (+ - * / ^) and regular parentheses	$k_0, 1*x_1+u_1$

Table 1 - Syntax & Naming Guidelines

Certain features of COMBOS naming conventions should be noted. Numbering of state variables, inputs and outputs MUST start from 1 and be monotonically increasing. This means the numerical subscript of an input or output does not necessarily correspond to the compartment number indicated by a state variable. For instance, a system with a single output at compartment 2 is written  $y_1=x_2$ . In addition, common math function names (e.g. *sin*, *ln*) and constants (e.g. *pi*, *e*) are currently not recognized by the parser and would be incorrectly treated as parameters if encountered.

### *Initial Conditions*

The COMBOS interface provides a convenient way to enter any known initial conditions. Initial conditions may or may not be known for a given state variable, and knowledge of initial conditions does change the resulting structural identifiability of the parameters and parameter combinations. When known, initial conditions are

usually numbers, but COMBOS also allows them to be functions of the parameters, which can be useful in applications. When not known, initial conditions are simply treated as generic by default; we assume this is the majority case.

For each state variable, a subfield is added for entering the corresponding initial condition. Initial conditions are assumed unknown (generic) and hidden from view at the start, so as not to obscure the view and usability of the overall interface. The visibility of the subfield can be manually toggled so that it is displayed only if there are initial values to enter. Similarly, for the copy/paste method, users need only list values for known initial conditions. To test a model with some known initial conditions, we set those initial conditions arbitrarily to 1.

### *Technical Implementation*

The COMBOS web app is run on an Apache PHP web server<sup>3</sup>. The web app is written entirely in HTML/CSS, PHP and Javascript/JQuery. In COMBOS, equations are dynamically displayed in native math form with MathJax 2.0<sup>4</sup> and parsed with a PHP script. Maxima code is run on the parsed input, and the identifiability results are generated for the user.

The main parser is written in PHP. The PHP script is responsible for string parsing, executing scripts, and displaying HTML content. ODEs, output equations, and initial conditions are stored in separate arrays. The parser loops through the entries in the order listed, simultaneously extracting relevant information and constructing the syntax-appropriate input to Maxima. For each ODE and output equation, we use regular expressions to identify and record the state variables, inputs, outputs and parameters. Parameters are mapped from user-defined to general symbols to make further data

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<sup>3</sup> The Apache PHP web server <http://biocyb1.cs.ucla.edu> is a virtual server hosted by the UCLA Computer Science Department.

<sup>4</sup> MathJax 2.0 is an open-source Javascript library that displays ASCIIMathML, MathML, and LaTeX markup in native math form on all modern web browsers. <http://www.mathjax.org>

analysis more convenient. For each initial condition, we check that there are no references to undefined state variables, inputs, outputs, or parameters. After all entries are parsed into a complete Maxima command, the model is run in Maxima and the identifiability results are generated. Results displayed include the model with copy/paste equivalent, the parameter mapping table, the parsed input for processing with Maxima, and the SI parameters and parameter combinations computed from Maxima.

## RESULTS

### *Comparisons with DAISY*

To evaluate COMBOS functionality and accuracy, we compared COMBOS results with those from DAISY<sup>5</sup>, another algebraic biology software package for analyzing parameter identifiability. The following models run on COMBOS are taken from several DAISY publications (Saccomani et al. 2003, 2007, 2010, 2011). All models are given below in COMBOS-acceptable syntax.

In the first paper, the role of initial conditions in parameter identifiability is discussed in three examples (Saccomani et al. 2003). The first example is a 3-compartmental linear model with input in compartment 1 and output from compartment 2:

$$\begin{aligned}\frac{dx_1}{dt} &= p_{13}x_3 + p_{12}x_2 - p_{21}x_1 + u_1 \\ \frac{dx_2}{dt} &= -p_{12}x_2 + p_{21}x_1 \\ \frac{dx_3}{dt} &= p_{13}x_3 \\ y_1 &= x_2\end{aligned}$$

*Equation 1*

In DAISY, the initial condition  $x_3(0) = 0$  makes the model no longer globally identifiable, with  $p_{13}$  unidentifiable. COMBOS results are consistent and show that under generic initial conditions, all 3 parameters are uniquely identifiable. Upon adding initial condition  $x_3(0) = 0$ , only  $p_{12}$  and  $p_{21}$  remain uniquely identifiable, so  $p_{13}$  is unidentifiable, as in DAISY.

The second example is a nonlinear 2-compartmental model:

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<sup>5</sup> DAISY (Differential Algebra for Identifiability of SYstems) is a computer algebra software tool for global identifiability analysis. <http://www.dei.unipd.it/~pia>

$$\frac{dx_1}{dt} = -p_0 u_1 - p_2 x_1 - p_3 x_2$$

$$\frac{dx_2}{dt} = p_3 x_1 x_2 - p_1 x_1$$

$$y_1 = x_1$$

*Equation 2*

In DAISY, with no initial conditions given, the system is globally identifiable. For an initial condition  $x_2(0) = \frac{p_1}{p_3}$ , the system becomes inaccessible and  $p_3$  becomes unidentifiable. COMBOS confirms these results.

The third example tests a 3-compartmental model:

$$\frac{dx_1}{dt} = p_1 u_1 x_3$$

$$\frac{dx_2}{dt} = p_2 x_1$$

$$\frac{dx_3}{dt} = p_3 x_1 x_2$$

$$y_1 = x_1$$

$$y_2 = x_2$$

*Equation 3*

In DAISY analysis, when initial conditions are set to  $x_1(0) = 0, x_3(0) = 0$ , the model reduces to  $\left\{ y_1 = 0, \frac{dy_2}{dt} = 0 \right\}$  so all parameters are unidentifiable, but for all other initial conditions,  $p_2$  is uniquely identifiable. However, COMBOS results show that parameter  $p_2$  is always uniquely identifiable for all initial conditions. This contradiction indicates initial conditions are handled differently in DAISY and COMBOS (see Discussion).

In the second paper, DAISY is used to test global identifiability of three biological and physiological systems (Bellu et al. 2007). The first example is a 4-compartmental mamillary model:



$$\frac{dx_1}{dt} = -(k_{21} + k_{31} + k_{41} + k_{01})x_1 + k_{12}x_2 + k_{13}x_3 + k_{14}x_4 + u_1$$

$$\frac{dx_2}{dt} = k_{21}x_1 - k_{12}x_2$$

$$\frac{dx_3}{dt} = k_{31}x_1 - k_{13}x_3$$

$$\frac{dx_4}{dt} = k_{41}x_1 - k_{14}x_4$$

$$y_1 = x_1$$

Equation 4

In DAISY, with no initial conditions given, the model is locally identifiable. COMBOS results show that under the same conditions, one parameter  $k_{01}$  is uniquely identifiable while the others are all locally identifiable with 3 solutions. This confirms the overall model is locally identifiable. DAISY, on the other hand, does not indicate the number of local solutions. DAISY results also show that, when at least two initial conditions are known among  $x_2(0), x_3(0), x_4(0)$ , the model becomes globally identifiable. COMBOS results show that when initial conditions are set to  $x_2(0) = 1, x_3(0) = 1$ , all seven parameters become uniquely identifiable, so the model is globally identifiable.

The second example is a 2-compartmental model of drug kinetics in the blood and tissues with nonlinear Michaelis-Menten kinetics. Input of drug is delivered into blood and output is measured in tissues.

$$\frac{dx_1}{dt} = -\frac{V_{max}}{k_m + x_1}x_1 + u_1$$

$$\frac{dx_2}{dt} = \frac{V_{max}}{k_m + x_1}x_1 - p_1x_2$$

$$y_1 = x_2$$

Equation 5

Both DAISY and COMBOS results indicate the model is globally identifiable, i.e. all three parameters  $V_{max}, k_m, p_1$  are uniquely identifiable.

The third example is another nonlinear 2-compartmental model in an input-output experiment that samples outputs in both blood and tissues, with input in blood only:

$$\begin{aligned}\frac{dx_1}{dt} &= -\left(p_{21} + \frac{V_{max}}{k_m + x_1}\right)x_1 + p_{12}x_2 + u_1 \\ \frac{dx_2}{dt} &= p_{21}x_1 - p_{12}x_2 \\ y_1 &= x_1 \\ y_2 &= x_2\end{aligned}$$

*Equation 6*

Again, both DAISY and COMBOS results indicate the model is globally identifiable, i.e. all four parameters  $V_{max}, k_m, p_{12}, p_{21}$  are uniquely identifiable.

In the third paper, DAISY is used to test global identifiability of two more biological and biomedical models (Saccomani et al. 2010). The first example is a nonlinear polynomial model of antibody interaction with a tumor, with known constants  $a, b, d$ :

$$\begin{aligned}\frac{dx_1}{dt} &= -(k_3 + k_7)x_1 + k_4x_2 \\ \frac{dx_2}{dt} &= k_3x_1 - (k_4 + ak_5 + bdk_3)x_2 + k_6x_3 + k_6x_4 + k_5x_2x_3 + k_5x_2x_4 \\ \frac{dx_3}{dt} &= ak_5x_2 - k_6x_3 - k_5x_2x_3 \\ \frac{dx_4}{dt} &= bdk_5x_2 - k_6x_4 - k_5x_2x_4 \\ \frac{dx_5}{dt} &= k_7x_1 \\ y_1 &= x_5\end{aligned}$$

*Equation 7*

In DAISY, when initial condition  $x_1(0)$  is known and nonzero and the rest are set to zero, all parameters are uniquely identifiable. Interestingly, in this particular experiment, the model would be globally identifiable whether or not initial conditions are known. The COMBOS results confirm that with initial condition  $x_1(0)$  and known constants all set to 1, all four parameters are uniquely identifiable.

The second example is a 3-compartmental model that examines the effect of initial conditions on parameter identifiability:

$$\begin{aligned}\frac{dx_1}{dt} &= -p_1x_1 + p_2x_2 + u_1 \\ \frac{dx_2}{dt} &= p_3x_1 - p_4x_2 + p_5x_3 \\ \frac{dx_3}{dt} &= p_6x_1 - p_7x_3 \\ y_1 &= x_1\end{aligned}$$

*Equation 8*

In DAISY, with no initial conditions given, the model is unidentifiable. COMBOS results show that under the same conditions, parameter  $p_1$  and parameter combination  $p_2p_3$  are uniquely identifiable, while parameters  $p_4, p_7$  and parameter combination  $p_2p_5p_6$  are locally identifiable with 2 solutions. This confirms that the overall model is unidentifiable. DAISY results also show that when initial conditions are included, the model becomes locally identifiable. In COMBOS, when all initial conditions are set to 1,  $p_1, p_2, p_3$  become uniquely identifiable, and  $p_4, p_5, p_6, p_7$  become locally identifiable with 2 solutions. This confirms that the overall model becomes locally identifiable.

In the fourth paper, DAISY is used to analyze several nonlinear HIV/AIDS models (Saccomani et al. 2011). The first example is a nonlinear polynomial 4-

compartmental model that describes the dynamics of uninfected, latently infected and actively infected cells, along with the free virus particles:

$$\begin{aligned}\frac{dx_1}{dt} &= s - dx_1 - bx_4x_1 \\ \frac{dx_2}{dt} &= q_1bx_4x_1 - m_1x_2 - k_1x_2 \\ \frac{dx_3}{dt} &= q_2bx_4x_1 - k_1x_2 - m_2x_3 \\ \frac{dx_4}{dt} &= k_2x_3 - cx_4 \\ y_1 &= x_1 \\ y_2 &= x_4\end{aligned}$$

*Equation 9*

In DAISY, with no initial conditions given, the model is unidentifiable, with  $b, d, s$  uniquely identifiable and  $c, m_2$  locally identifiable. COMBOS results confirms that under the same conditions, parameters  $b, d, s$  are uniquely identifiable and  $c, m_2$  are locally identifiable with 3 solutions. It further finds that parameter combination  $q_2k_2$  is uniquely identifiable and  $k_1 + m_1, q_1k_1k_2$  are locally identifiable with 3 solutions. This confirms that the overall model is unidentifiable.

The second example is a nonlinear 4-compartmental model of viral fitness, with dual infection by mutant and wildtype viruses, and the assumption that the viral population densities are proportional to their corresponding infected cell densities:

$$\begin{aligned}\frac{dx_1}{dt} &= (r - k_m x_2 - k_w x_3 - k_R x_4) x_1 \\ \frac{dx_2}{dt} &= (r_m + k_m x_1 - q_m x_3) x_2 + p_m k_R x_4 x_1 \\ \frac{dx_3}{dt} &= (r_w + k_w x_1 - q_w x_2) x_3 + p_w k_R x_4 x_1 \\ \frac{dx_4}{dt} &= (r_{mw} + (1 - p_m - p_w) k_R x_1) x_4 + (q_m + q_w) x_3 x_2\end{aligned}$$

$$y_1 = x_1$$

$$y_2 = x_2$$

$$y_3 = x_3$$

$$y_4 = x_4$$

Equation 10

In DAISY, with all initial conditions assumed known, the model is globally identifiable. COMBOS results confirm that with all initial conditions set to 1, all eleven parameters are uniquely identifiable.

### *Benchmarking COMBOS*

Our primary benchmark for COMBOS is the computational capacity of the underlying symbolic algebraic program, i.e. dimensionality of the models it can handle. Currently, the COMBOS algorithm is implemented in Maxima. Following are five models benchmarked under generic initial conditions. (See Appendix for implementation details.)

Test-Model 1 is a linear ODE system with  $n^2$  parameters and no inputs:

For dimensions  $n \geq 2$

$$\frac{dx_i}{dt} = p_{i,1} x_1 + \dots + p_{i,n} x_n$$

$$y_i = x_i, \text{ for } i = 1 \text{ to } n$$

*Test-Model 1*

In COMBOS, results were generated up to dimension  $n = 5$  for Model 1 and successfully found all parameters globally identifiable. For dimensions  $n = 6$  and greater, the computations did not complete. (See Discussion for limitations of Maxima.)

Test-Model 2 is a linear system with one input and  $n - 1$  outputs:

$$\begin{aligned} &\text{For dimensions } n \geq 2 \\ &\frac{dx_1}{dt} = p_{1,1}x_1 + \dots + p_{1,n}x_n + u_1 \\ &\frac{dx_i}{dt} = p_{i,1}x_1 + \dots + p_{i,n}x_n, \text{ for } i = 2 \text{ to } n \\ &y_j = x_j, \text{ for } j = 1 \text{ to } n - 1 \\ &\textit{Test-Model 2} \end{aligned}$$

Test-Models 3, 4, 5 are three variations of the Test-Model 2 single-input system with different outputs defined. Test-Model 3 has a single output sampled in the same compartment as the input:  $y_1 = x_1$ . Test-Model 4 has a single output sampled in a different compartment from the input:  $y_1 = x_n$ . Test-Model 5 has two outputs sampled in separate compartments, with one sample in the same compartment as the input:  $y_1 = x_1$  and  $y_2 = x_n$ .

In COMBOS, results were generated up to dimension  $n = 4$  in Test-Model 2 and up to dimension  $n = 3$  in Test-Models 3, 4, 5. Above these dimensions, the system became too complex for the algorithm and/or Maxima to handle. All Test-Models 2, 3, 4, 5 were found unidentifiable. The results were consistent with the known identifiability properties of the model and, for the first time, provided the identifiable combinations of parameters that were not individually identifiable.

## DISCUSSION

COMBOS is a novel web application for complete identifiability analysis, especially for finding structurally identifiable parameter combinations in otherwise unidentifiable systems. In principle, given the ODE and input-output relations of the system, it finds all the parameters and parameter combinations that are uniquely identifiable or locally identifiable with the number of local solutions. All of this is limited by computational constraints of symbolic algebra.

### *Eliminating Infeasible Solutions*

It is important that COMBOS does not overstate or understate the number of feasible solutions in the results. A parameter combination is identifiable but infeasible if the expression implies that one or more parameter values are not both real and positive. To eliminate infeasible solutions, we add the constraint that all parameters must be positive before computing the results in Maxima.

### *Limitations of Maxima*

Results from testing different models in COMBOS reveal limitations in using Maxima for symbolic algebra. Maxima software is constrained by both the size of the argument list as well as the complexity of the system analyzed. For solutions with complex polynomial or rational functions as parameter combinations, computation in Maxima can take an indefinite amount of time, so we abort the process after a few hours.

Because of the apparent limitations of Maxima, further research can look into Macaulay2<sup>6</sup> and Singular<sup>7</sup>, other open source computer algebra systems that seem to be more computationally powerful than Maxima for computing Gröbner bases.

---

<sup>6</sup> Macaulay2 is a software system for research in algebraic geometry with core algorithms for handling Gröbner bases. <http://www.math.uiuc.edu/Macaulay2>

### *Other Issues*

In the current algorithm, Gröbner bases of model attributes are computed to find the identifiable parameters and parameter combinations of the model. While the accuracy of the algorithm has been validated for many compartmental and other biologically motivated models (see Results), a few issues require further investigation.

First, the algorithm does not always generate an algebraically independent set of identifiable parameter combinations for rational functions. It is able to successfully do so for polynomial functions but seems to have difficulty with combinations that are rational functions, despite an explicit check for algebraic independence.

The COMBOS implementation also appears to not handle initial conditions as rigorously as DAISY. When no initial conditions are given, COMBOS and DAISY results are consistent. In general, initial conditions are properly handled when the system state is accessible everywhere, as well as when the system state is non-accessible but easily solved by setting the right hand side of the equations to zero (see Equations 1 and 2). However, when non-accessibility is hard to determine, the algorithm does not handle initial conditions correctly, and thus the model may be found identifiable when in fact addition of initial conditions renders it unidentifiable (see Equation 3).

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<sup>7</sup> Singular is a computer algebra system for polynomial computations with core algorithms for handling Gröbner bases. <http://www.singular.uni-kl.de>



## APPENDIX

### Program Documentation

#### *Website*

The COMBOS web application is accessible online at

<http://biocyb1.cs.ucla.edu/combos/html>.

#### *List of scripts*

In the current directory:

- **index.php** is the main webpage that contains the HTML form where users enter equations and are displayed the results.
- **helper.js** contains the Javascript functions that enable addition and deletion of input fields, fills in corresponding input fields upon clicking the example links, toggles the visibility of the initial condition form fields, and calls on MathJax.js to display user input in native math form.
- **upload.php** is the PHP script executed on the webpage upon submitting the copy/pasted file contents. It preprocesses the text before calling the parser. Pre-processing includes separating entries into ODEs with inputs, output equations, and initial conditions by semicolons and adding the entries to the `$_POST` array.
- **parser.php** is the PHP script executed on the webpage upon form submission. It is either called directly by the fill-in form or indirectly by upload.php. The parser converts all input equations to Maxima markup; maps all user-defined parameters to general parameters `p`; creates separate lists for the differential equations, state variables, output variables, input variables, parameters, and initial conditions; runs the Maxima code on the lists; and displays Maxima results on the webpage.
- **MathJax.js** (v 2.0) is a third-party Javascript package that can display mathematical expressions written in AsciiMathML, LaTeX, and MathML markup in native math

form. The advantage of using MathJax over AsciiMathML directly is that MathJax is able to display output properly on all major browsers, whereas AsciiMathML only works in Mozilla Firefox. We desire to use AsciiMathML markup because the syntax is less verbose and easier for users to learn.

- **index.css** is the CSS stylesheet used on the main webpage.

In the examples directory:

- **JSON files** are on the path of the example links on the main webpage and contain the equations that will fill in the input fields when the example links are clicked.

In the ../maxima directory:

- **FindCombos.maxima** is the Maxima code developed by N. Meshkat for finding identifiable parameter combinations in a system of nonlinear ODEs.

#### *Benchmarking files*

In the ../benchmark directory:

- **daisy.php** is a PHP script that calls the copy/paste method in COMBOS on an array of example models taken from DAISY publications.
- **daisy.html** is the output file generated by daisy.php. It contains the COMBOS results for each example model.
- **test.sh** is a BASH shell script that executes the PHP scripts for benchmarking Models 1 to 5.
- **modelx.php** (for  $x = 1$  to 5) is a PHP script that calls the copy/paste method in COMBOS on a standard set of ODE systems (see Results: Benchmarking COMBOS).
- **modelx.html** (for  $x = 1$  to 5) is the output file generated by modelx.php using ODE systems from Model  $x$ . It contains the COMBOS results from each run.

### *Instructions for Further Development*

The code for the four main source files (index.php, helper.js, parser.php, and upload.php) has been commented in detail. Changes to the user interface and dynamic effects should be made in index.php and helper.js, while changes to the parsing and pre-processing should be made in parser.php and upload.php.

Future work in COMBOS include optimizing Maxima code for faster computation and more accurate handling of initial conditions, and perhaps switching to a more efficient program for symbolic algebra like Macaulay2, developing an algorithm to re-parameterize unidentifiable models based on identifiable parameter combinations, and building in a more comprehensive syntax checker for equations entered.

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