Structural parameter identifiability with a view towards model theory

Gleb Pogudin

LIX, CNRS, École Polytechnique,
Institut Polytechnique de Paris, France

Plan

- Intro to identifiability
- Approach via input-output equations and subtleties
- Through the lens of model theory: subtleties $\to$ features
- Open problems

Intro to identifiability

What is identifiability: toy examples

Example

In the model described by $\dot{x} = kx$

- x can measured in an experiment
  and, therefore, its derivatives can be estimated,
- k is an unknown scalar parameter.

What is identifiability: toy examples

Example

In the model described by $\dot{x} = kx$

- x can measured in an experiment
  and, therefore, its derivatives can be estimated,
- k is an unknown scalar parameter.

$$k = \frac{\dot{x}}{x} \quad \Longrightarrow \quad k \text{ is identifiable.}$$

What is identifiability: toy examples

Example

In the model described by $\dot{x} = kx$

- x can measured in an experiment
  and, therefore, its derivatives can be estimated,
- k is an unknown scalar parameter.

$$k = \frac{\dot{x}}{x} \quad \Longrightarrow \quad k \text{ is identifiable.}$$

Example

In the model described by $\dot{x} = x + k_1 + k_2$

- x can measured in an experiment
  and, therefore, its derivatives can be estimated,
- k_1 and k_2 are unknown scalar parameters.

What is identifiability: toy examples

Example

In the model described by $\dot{x} = kx$

- x can measured in an experiment
  and, therefore, its derivatives can be estimated,
- k is an unknown scalar parameter.

$$k = \frac{\dot{x}}{x} \implies k \text{ is identifiable.}$$

Example

In the model described by $\dot{x} = x + k_1 + k_2$

- x can measured in an experiment
  and, therefore, its derivatives can be estimated,
- k_1 and k_2 are unknown scalar parameters.

$$\text{Impossible to find } k_1 \text{ and } k_2 \implies k_1 \text{ and } k_2 \text{ are non-identifiable.}$$

Identifiability: Motivation

Common problem: more than one parameter value fits the data.

Identifiability: Motivation

Common problem: more than one parameter value fits the data.

There are different options

Cause		**Remedy**
Noisy data	$\Longrightarrow$	More measurements or better equipment

Identifiability: Motivation

Common problem: more than one parameter value fits the data.

There are different options

Cause		**Remedy**
Noisy data	$\Longrightarrow$	More measurements or better equipment
Non-identfiability	$\Longrightarrow$	Another model or new equipment

Identifiability: Motivation

Common problem: more than one parameter value fits the data.

There are different options

Cause		**Remedy**
Noisy data	$\Longrightarrow$	More measurements or better equipment
Non-identfiability	$\Longrightarrow$	Another model or new equipment

Verifying identifiabilty allows a modeller to find the cause and choose the correct remedy.

Is this really an issue?

J Math Chem (2008) 44:244–259
DOI 10.1007/s10910-007-9307-x

ORIGINAL PAPER

Identifiability of chemical reaction networks

Gheorghe Craciun · Casian Pantea

Received: 20 June 2007 / Accepted: 14 August 2007 / Published online: 21 September 2007
© Springer Science+Business Media, LLC 2007

Abstract We consider the dynamics of chemical reaction networks under the assumption of mass-action kinetics. We show that there exist reaction networks $\mathcal{R}$ for which the reaction rate constants are not uniquely identifiable, even if we are given

Is this really an issue?

SIAM Review
Vol. 53, No. 1, pp. 3–39

© 2011 Society for Industrial and Applied Mathematics

On Identifiability of Nonlinear ODE Models and Applications in Viral Dynamics*

Hongyu Miao[†]
Xiaohua Xia[‡]
Alan S. Perelson[§]
Hulin Wu[†]

Abstract. Ordinary differential equations (ODEs) are a powerful tool for modeling dynamic processes with wide applications in a variety of scientific fields. Over the last two decades, ODEs have also emerged as a prevailing tool in various biomedical research fields, especially in infectious disease modeling. In practice, it is important and necessary to determine unknown parameters in ODE models based on experimental data. Identifiability analysis is the first step in determining unknown parameters in ODE models and such analysis techniques for nonlinear ODE models are still under development. In this article, we review identifiability analysis methodologies for nonlinear ODE models developed in the past couple of decades, including structural identifiability analysis, practical identifiability

Is this really an issue?

Animal (2018), **12:4**, pp 701–712 © The Animal Consortium 2017
doi:10.1017/S1751731117002774

animal

Review: To be or not to be an identifiable model. Is this a relevant question in animal science modelling?

R. Muñoz-Tamayo[1†], L. Puillet[1], J. B. Daniel[1,2], D. Sauvant[1], O. Martin[1], M. Taghipoor[3] and P. Blavy[1]

[1]UMR Modélisation Systémique Appliquée aux Ruminants, INRA, AgroParisTech, Université Paris-Saclay, 75005 Paris, France; [2]Trouw Nutrition R&D, P.O. Box 220, 5830 AE Boxmeer, The Netherlands; [3]PEGASE, AgroCampus Ouest, INRA, 35590 Saint-Gilles, France

(Received 4 May 2017; Accepted 24 September 2017; First published online 3 November 2017)

What is a good (useful) mathematical model in animal science? For models constructed for prediction purposes, the question of model adequacy (usefulness) has been traditionally tackled by statistical analysis applied to observed experimental data relative to model-predicted variables. However, little attention has been paid to analytic tools that exploit the mathematical properties of the model equations. For example, in the context of model calibration, before attempting a numerical estimation of the model parameters, we might want to know if we have any chance of success in estimating a unique best value of the model parameters from available measurements. This question of uniqueness is referred to as structural identifiability; a mathematical property that is defined on the sole basis of the model structure within a hypothetical ideal experiment determined by a setting of model inputs (stimuli) and observable variables (measurements). Structural identifiability analysis applied to dynamic models described by

Relaxation of the problem: local identifiability

On this slide

- x can be measured in an experiment
  and, therefore, its derivatives can be estimated
- k_1 and k_2 are unknown scalar parameters

Equation	What happens	Identifiable?
$\dot{x} = x + k_1$	$k_1 = \dot{x} - x$	**YES**
$\dot{x} = x + {k_1}^2$	$k_1 = \pm\sqrt{\dot{x} - x}$	**NO**
$\dot{x} = x + k_1 + k_2$	Infinitely many values for k_1 and k_2	**NO**

Relaxation of the problem: local identifiability

On this slide

- x can be measured in an experiment
  and, therefore, its derivatives can be estimated
- k_1 and k_2 are unknown scalar parameters

Equation	What happens	Identifiable?
$\dot{x} = x + k_1$	$k_1 = \dot{x} - x$	**Globally**
$\dot{x} = x + {k_1}^2$	$k_1 = \pm\sqrt{\dot{x} - x}$	**Locally**
$\dot{x} = x + k_1 + k_2$	Infinitely many values for k_1 and k_2	**NO**

Local identifiability: state of the art

- **Jacobian test**: *Hermann and Krener* (1977)

Local identifiability: state of the art

- **Jacobian test**: *Hermann and Krener* (1977)

- **Efficient software**:
  - ObservabilityTest (2002)
  - IdentifiabilityAnalysis (2012)
  - STRIKE-GOLDD (2016)

Local identifiability: state of the art

- **Jacobian test**: *Hermann and Krener* (1977)

- **Efficient software**:
    - ObservabilityTest (2002)
    - IdentifiabilityAnalysis (2012)
    - STRIKE-GOLDD (2016)

- **Criteria for systems of special form:**
    - *Meshkat, Sullivant, Eisenberg* (2015)
    - *Meshkat, Rosen, Sullivant* (2016)
    - *Baaijens, Draisma* (2016)
    - *Gross, Meshkat, Shiu* (2018)

The importance of being globally identifiable

- Local identifiability does not guarantee the uniqieness of the parameter value.

The importance of being globally identifiable

- Local identifiability does not guarantee the uniqieness of the parameter value.
- Lack of global identifiability is hard to detect using numeric methods.

The importance of being globally identifiable

- Local identifiability does not guarantee the uniqieness of the parameter value.
- Lack of global identifiability is hard to detect using numeric methods.
- It happens!

It happens: epidemiology (SEIR model)

$$\begin{cases} S' = -\beta \frac{SI}{N}, \\ E' = \beta \frac{SI}{N} - \eta E, \\ I' = \eta E - \alpha I, \\ R' = \alpha R, \\ N = S + E + I + R, \\ \\ \end{cases}$$

Susceptible

$\downarrow$

Exposed

$\downarrow$

Infectious

$\downarrow$

Recovered

It happens: epidemiology (SEIR model)

$$\begin{cases} S' = -\beta \frac{SI}{N}, \\ E' = \beta \frac{SI}{N} - \eta E, \\ I' = \eta E - \alpha I, \\ N' = 0, \end{cases}$$

Susceptible
$\downarrow$
Exposed
$\downarrow$
Infectious
$\downarrow$
Recovered

It happens: epidemiology (SEIR model)

$$\begin{cases} S' = -\beta \frac{SI}{N}, \\ E' = \beta \frac{SI}{N} - \eta E, \\ I' = \eta E - \alpha I, \\ N' = 0, \\ y_1 = N, \\ y_2 = \kappa I. \end{cases}$$

Susceptible

$\downarrow$

Exposed

$\downarrow$

Infectious

$\downarrow$

Recovered

It happens: epidemiology (SEIR model)

$$\begin{cases} S' = -\beta \frac{SI}{N}, \\ E' = \beta \frac{SI}{N} - \eta E, \\ I' = \eta E - \alpha I, \\ N' = 0, \\ y_1 = N, \\ y_2 = \kappa I. \end{cases}$$

Susceptible
↓
Exposed
↓
Infectious
↓
Recovered

Turns out:

Only locally identifiable: α, η,

Nonidentifiable: β, κ.

It happens: epidemiology (SEIR model)

$$\begin{cases} S' = -\beta \frac{SI}{N}, \\ E' = \beta \frac{SI}{N} - \eta E, \\ I' = \eta E - \alpha I, \\ N' = 0, \\ y_1 = N, \\ y_2 = \kappa I. \end{cases}$$

Susceptible
$\downarrow$
Exposed
$\downarrow$
Infectious
$\downarrow$
Recovered

Turns out:

Only locally identifiable: α, η,

Nonidentifiable: β, κ.

Furthermore:

An unordered pair $\{\alpha, \eta\}$ is identifiable.

Will see similar in *slow-fast ambiguity* later.

Global identifiability: state of the art

Taylor series method	Theory: *Ponjanpalo*, 1978 Software: GenSSI 2.0, 2017 Termination criterion only for special cases
Differential elimination for parameters	Theory: *Diop, Fliess, Ljung, Glad*, 1993 Tackles only small examples
Input-output equations	Theory: *Ollivier*, 1990 Software: DAISY, 2007; COMBOS, 2014 In a few minutes!
Prolongations + symbolc sampling	Theory: *Hong, Ovchinnikov, P., Yap*, 2019 Software: SIAN, 2019

Input-output equations

Specification: what we are after

Input

System

$$\begin{cases} \dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, \mathbf{k}), \\ \mathbf{y} = \mathbf{g}(\mathbf{x}, \mathbf{k}), \end{cases}$$

where

- $\mathbf{x}$ are unknown *state variables*;
- $\mathbf{k}$ are unknown scalar *parameters*;
- $\mathbf{y}$ are *outputs* measured in experiment.

Specification: what we are after

Input

System

$$\begin{cases} \dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, \mathbf{k}), \\ \mathbf{y} = \mathbf{g}(\mathbf{x}, \mathbf{k}), \end{cases}$$

where

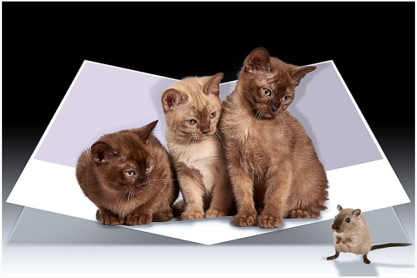
- $\mathbf{x}$ are unknown *state variables*;
- $\mathbf{k}$ are unknown scalar *parameters*;
- $\mathbf{y}$ are *outputs* measured in experiment.

Output

Generators of the field of identifiable rational functions in $\mathbf{k}$.

Running example: predator-prey model

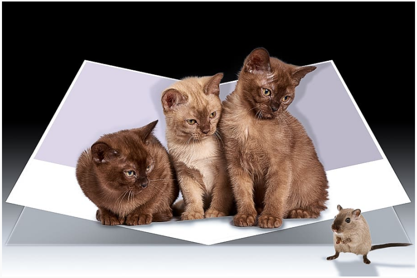
$$\begin{cases} \dot{x}_1 = k_1 x_1 - k_2 x_1 x_2, \\ \dot{x}_2 = -k_3 x_2 + k_4 x_1 x_2, \\ y = x_1. \end{cases}$$



- x_1 - prey
- x_2 - predators

Running example: predator-prey model

$$\begin{cases} \dot{x}_1 = k_1 x_1 - k_2 x_1 x_2, \\ \dot{x}_2 = -k_3 x_2 + k_4 x_1 x_2, \\ y = x_1. \end{cases}$$



- x_1 - prey
- x_2 - predators

Globally identifiable: k_1, k_3, k_4
Nonidentifiable: k_2
Identifiable functions: $\mathbb{C}(k_1, k_3, k_4)$.

Step 1: Eliminate

Whereof one cannot speak, thereof one must be silent

Step 1: Eliminate

Whereof one cannot speak, thereof one must be silent

Idea: we cannot measure $x_2 \implies$ let us eliminate it!

Step 1: Eliminate

Whereof one cannot speak, thereof one must be silent

Idea: we cannot measure $x_2 \implies$ let us eliminate it!

$$\begin{cases} \dot{x}_1 = k_1 x_1 - k_2 x_1 x_2, \\ \dot{x}_2 = -k_3 x_2 + k_4 x_1 x_2, \\ y = x_1. \end{cases} \implies y\ddot{y} - \dot{y}^2 - k_4 y^2 \dot{y} - k_3 y \dot{y} + k_1 k_4 y^3 - k_1 k_3 y^2 = 0$$

Step 1: Eliminate

Whereof one cannot speak, thereof one must be silent

Idea: we cannot measure $x_2 \implies$ let us eliminate it!

$$\begin{cases} \dot{x}_1 = k_1 x_1 - k_2 x_1 x_2, \\ \dot{x}_2 = -k_3 x_2 + k_4 x_1 x_2, \\ y = x_1. \end{cases} \implies y\ddot{y} - \dot{y}^2 - k_4 y^2 \dot{y} - k_3 y \dot{y} + k_1 k_4 y^3 - k_1 k_3 y^2 = 0$$

Input-output equation - the “minimal” differential equation for y with coefficients in parameter.

Step 2: Extract coefficients

Idea: evaluations of $y \implies$ linear equations on the coefficients

$$y\ddot{y} - \dot{y}^2 - k_4 y^2 \dot{y} - k_3 y \dot{y} + k_1 k_4 y^3 - k_1 k_3 y^2 = 0$$

Step 2: Extract coefficients

Idea: evaluations of $y \implies$ linear equations on the coefficients

$$y\ddot{y} - \dot{y}^2 - k_4 y^2 \dot{y} - k_3 y \dot{y} + k_1 k_4 y^3 - k_1 k_3 y^2 = 0$$

$$\begin{aligned}
y(t_1)\ddot{y}(t_1) - \dot{y}(t_1)^2 &= k_4 y(t_1)^2 \dot{y}(t_1) + k_3 y(t_1)\dot{y}(t_1) - k_1 k_4 y(t_1)^3 + k_1 k_3 y(t_1)^2, \\
y(t_2)\ddot{y}(t_2) - \dot{y}(t_2)^2 &= k_4 y(t_2)^2 \dot{y}(t_2) + k_3 y(t_2)\dot{y}(t_2) - k_1 k_4 y(t_2)^3 + k_1 k_3 y(t_2)^2, \\
&\vdots \\
y(t_N)\ddot{y}(t_N) - \dot{y}(t_N)^2 &= k_4 y(t_N)^2 \dot{y}(t_N) + k_3 y(t_N)\dot{y}(t_N) - k_1 k_4 y(t_N)^3 + k_1 k_3 y(t_N)^2.
\end{aligned}$$

Step 2: Extract coefficients

Idea: evaluations of $y \implies$ linear equations on the coefficients

$$y\ddot{y} - \dot{y}^2 - k_4 y^2 \dot{y} - k_3 y \dot{y} + k_1 k_4 y^3 - k_1 k_3 y^2 = 0$$

$$\begin{aligned}
y(t_1)\ddot{y}(t_1) - \dot{y}(t_1)^2 &= k_4 y(t_1)^2 \dot{y}(t_1) + k_3 y(t_1)\dot{y}(t_1) - k_1 k_4 y(t_1)^3 + k_1 k_3 y(t_1)^2, \\
y(t_2)\ddot{y}(t_2) - \dot{y}(t_2)^2 &= k_4 y(t_2)^2 \dot{y}(t_2) + k_3 y(t_2)\dot{y}(t_2) - k_1 k_4 y(t_2)^3 + k_1 k_3 y(t_2)^2, \\
&\vdots \\
y(t_N)\ddot{y}(t_N) - \dot{y}(t_N)^2 &= k_4 y(t_N)^2 \dot{y}(t_N) + k_3 y(t_N)\dot{y}(t_N) - k_1 k_4 y(t_N)^3 + k_1 k_3 y(t_N)^2.
\end{aligned}$$

Assume nonsingular: (identifiable $\iff$ rational in $k_4, k_3, k_1 k_4, k_1 k_3$)

Step 2: Extract coefficients

Idea: evaluations of $y \implies$ linear equations on the coefficients

$$y\ddot{y} - \dot{y}^2 - k_4 y^2 \dot{y} - k_3 y \dot{y} + k_1 k_4 y^3 - k_1 k_3 y^2 = 0$$

$$\begin{aligned}
y(t_1)\ddot{y}(t_1) - \dot{y}(t_1)^2 &= k_4 y(t_1)^2 \dot{y}(t_1) + k_3 y(t_1)\dot{y}(t_1) - k_1 k_4 y(t_1)^3 + k_1 k_3 y(t_1)^2, \\
y(t_2)\ddot{y}(t_2) - \dot{y}(t_2)^2 &= k_4 y(t_2)^2 \dot{y}(t_2) + k_3 y(t_2)\dot{y}(t_2) - k_1 k_4 y(t_2)^3 + k_1 k_3 y(t_2)^2, \\
&\vdots \\
y(t_N)\ddot{y}(t_N) - \dot{y}(t_N)^2 &= k_4 y(t_N)^2 \dot{y}(t_N) + k_3 y(t_N)\dot{y}(t_N) - k_1 k_4 y(t_N)^3 + k_1 k_3 y(t_N)^2.
\end{aligned}$$

Assume nonsingular: (identifiable $\iff$ rational in $k_4, k_3, k_1 k_4, k_1 k_3$)

Remarks

- Assumption is not always true
- Coefficients are called canonical base in model theory language

Subtlety: the assumption does not always hold

Subtlety: the assumption does not always hold

Not yet an example (twisted harmonic oscillator)

$$\begin{cases} \dot{x}_1 = (\omega + \alpha) x_2, \\ \dot{x}_2 = -\omega x_1, \\ y = x_2 \end{cases}$$

Subtlety: the assumption does not always hold

Not yet an example (twisted harmonic oscillator)

$$\begin{cases} \dot{x}_1 = (\omega + \alpha) x_2, \\ \dot{x}_2 = -\omega x_1, \\ y = x_2 \end{cases} \implies \ddot{y} + \omega(\omega + \alpha) y = 0$$

Subtlety: the assumption does not always hold

Not yet an example (twisted harmonic oscillator)

$$\begin{cases} \dot{x}_1 = (\omega + \alpha)x_2, \\ \dot{x}_2 = -\omega x_1, \\ y = x_2 \end{cases} \implies \ddot{y} + \omega(\omega + \alpha)y = 0$$

Example

Assume that α is known

$$\begin{cases} \dot{x}_1 = (\omega + x_3)x_2, \\ \dot{x}_2 = -\omega x_1, \\ \dot{x}_3 = 0, \\ y_1 = x_2,\ y_2 = x_3 \end{cases}$$

Subtlety: the assumption does not always hold

Not yet an example (twisted harmonic oscillator)

$$\begin{cases} \dot{x}_1 = (\omega + \alpha) x_2, \\ \dot{x}_2 = -\omega x_1, \\ y = x_2 \end{cases} \implies \ddot{y} + \omega(\omega + \alpha) y = 0$$

Example

Assume that α is known

$$\begin{cases} \dot{x}_1 = (\omega + x_3) x_2, \\ \dot{x}_2 = -\omega x_1, \\ \dot{x}_3 = 0, \\ y_1 = x_2,\ y_2 = x_3 \end{cases} \implies \ddot{y}_1 + \omega^2 y_1 + \omega y_1 y_2 = 0,\ \dot{y}_2 = 0$$

Looks like ω is identifiable, but it is NOT.

Subtlety: the assumption does not always hold

Not yet an example (twisted harmonic oscillator)

$$\begin{cases} \dot{x}_1 = (\omega + \alpha) x_2, \\ \dot{x}_2 = -\omega x_1, \\ y = x_2 \end{cases} \implies \ddot{y} + \omega(\omega + \alpha) y = 0$$

Example

Assume that α is known

$$\begin{cases} \dot{x}_1 = (\omega + x_3) x_2, \\ \dot{x}_2 = -\omega x_1, \\ \dot{x}_3 = 0, \\ y_1 = x_2,\ y_2 = x_3 \end{cases} \implies \ddot{y}_1 + \omega^2 y_1 + \omega y_1 y_2 = 0,\ \dot{y}_2 = 0$$

Looks like ω is identifiable, but it is NOT.
Only $\omega(\omega + \alpha), \alpha$ known $\implies$ quadratic equation in ω

Why do we care about this method then?

Why do we care about this method then?

- Used in practice (software: DAISY, COMBOS)

Why do we care about this method then?

- Used in practice (software: DAISY, COMBOS)
- If the assumption is true, finds all identifiable functions

Why do we care about this method then?

- Used in practice (software: DAISY, COMBOS)
- If the assumption is true, finds all identifiable functions
- Not a bug but a feature (in a few minutes)!

Model theory

joint with A. Ovchinnikov, A. Pillay, and T. Scanlon

Setup

- Language $\mathcal{L} = \{0, 1, +, \cdot, '\}$.

Setup

- Language $\mathcal{L} = \{0, 1, +, \cdot, '\}$.
- Axioms, part 1 (*differential field*):
  - axioms of fields
  - $(a + b)' = a' + b'$ and $(ab)' = a'b + ab'$

Setup

- Language $\mathcal{L} = \{0, 1, +, \cdot, '\}$.
- Axioms, part 1 (*differential field*):
  - axioms of fields
  - $(a+b)' = a' + b'$ and $(ab)' = a'b + ab'$
- Axioms, part 2 (*differentially closed field*):
  there could be a solution $\implies$ there is one

Setup

- Language $\mathcal{L} = \{0, 1, +, \cdot, '\}$.
- Axioms, part 1 (*differential field*):
  - axioms of fields
  - $(a+b)' = a' + b'$ and $(ab)' = a'b + ab'$
- Axioms, part 2 (*differentially closed field*): there could be a solution $\implies$ there is one
- Fix such a very big field K

Dictionary: types

Type over $A \subset K$ is a satisfiable set of formulas in $\mathcal{L} \cup A$.

Realization of a type is an element of K satisfying the formulas.

Dictionary: types

Type over $A \subset K$ is a satisfiable set of formulas in $\mathcal{L} \cup A$.

Realization of a type is an element of K satisfying the formulas.

Predator-prey

Let $A = \{k_1, k_2, k_3, k_4\}$ (K is big, a lot of transendental constants over $\mathbb{C}$)

Dictionary: types

Type over $A \subset K$ is a satisfiable set of formulas in $\mathcal{L} \cup A$.

Realization of a type is an element of K satisfying the formulas.

Predator-prey

Let $A = \{k_1, k_2, k_3, k_4\}$ (K is big, a lot of transendental constants over $\mathbb{C}$)

solution

$$\varphi_1(x_1, x_2, y) = (x_1' = k_1 x_1 - k_2 x_1 x_2),$$
$$\varphi_2(x_1, x_2, y) = (x_2' = -k_3 x_2 + k_4 x_1 x_2),$$
$$\varphi_3(x_1, x_2, y) = (y = x_1);$$

Dictionary: types

Type over $A \subset K$ is a satisfiable set of formulas in $\mathcal{L} \cup A$.

Realization of a type is an element of K satisfying the formulas.

Predator-prey

Let $A = \{k_1, k_2, k_3, k_4\}$ (K is big, a lot of transendental constants over $\mathbb{C}$)

solution $\varphi_1(x_1, x_2, y) = (x_1' = k_1 x_1 - k_2 x_1 x_2)$,
$\varphi_2(x_1, x_2, y) = (x_2' = -k_3 x_2 + k_4 x_1 x_2)$,
$\varphi_3(x_1, x_2, y) = (y = x_1)$;

output $\psi(y) = \exists x_1, x_2\; \varphi_1(x_1, x_2, y) \,\&\, \varphi_2(x_1, x_2, y) \,\&\, \varphi_3(x_1, x_2, y)$

Dictionary: types

Type over $A \subset K$ is a satisfiable set of formulas in $\mathcal{L} \cup A$.

Realization of a type is an element of K satisfying the formulas.

Predator-prey

Let $A = \{k_1, k_2, k_3, k_4\}$ (K is big, a lot of transendental constants over $\mathbb{C}$)

solution $\varphi_1(x_1, x_2, y) = (x_1' = k_1 x_1 - k_2 x_1 x_2)$,
$\varphi_2(x_1, x_2, y) = (x_2' = -k_3 x_2 + k_4 x_1 x_2)$,
$\varphi_3(x_1, x_2, y) = (y = x_1)$;

output $\psi(y) = \exists x_1, x_2\ \varphi_1(x_1, x_2, y) \,\&\, \varphi_2(x_1, x_2, y) \,\&\, \varphi_3(x_1, x_2, y)$

generic solution **solution** + negations of equations that are not consequences of $\varphi_1, \varphi_2, \varphi_3$

Dictionary: types

Type over $A \subset K$ is a satisfiable set of formulas in $\mathcal{L} \cup A$.

Realization of a type is an element of K satisfying the formulas.

Predator-prey

Let $A = \{k_1, k_2, k_3, k_4\}$ (K is big, a lot of transendental constants over $\mathbb{C}$)

solution $\varphi_1(x_1, x_2, y) = (x_1' = k_1 x_1 - k_2 x_1 x_2)$,
$\varphi_2(x_1, x_2, y) = (x_2' = -k_3 x_2 + k_4 x_1 x_2)$,
$\varphi_3(x_1, x_2, y) = (y = x_1)$;

output $\psi(y) = \exists x_1, x_2 \; \varphi_1(x_1, x_2, y) \,\&\, \varphi_2(x_1, x_2, y) \,\&\, \varphi_3(x_1, x_2, y)$

generic solution **solution** + negations of equations that are not consequences of $\varphi_1, \varphi_2, \varphi_3$

generic output **output** + negations of all nonconsequences

Dictionary: definability

Definition

Let $B \subset K$, $a \in K$.

a is *definable* over B iff, for every automorphism $\alpha\colon K \to K$:

$$\big(\forall b \in B\ \alpha(b) = b\big) \implies \alpha(a) = a.$$

Dictionary: definability

Definition

Let $B \subset K$, $a \in K$.

a is *definable* over B iff, for every automorphism $\alpha\colon K \to K$:

$$\big(\forall b \in B\ \alpha(b) = b\big) \implies \alpha(a) = a.$$

Example

Let $a \in K$ - constant, and x - generic solution of $x' = ax$.

Dictionary: definability

Definition

Let $B \subset K$, $a \in K$.

a is *definable* over B iff, for every automorphism $\alpha\colon K \to K$:

$$\big(\forall b \in B\ \alpha(b) = b\big) \implies \alpha(a) = a.$$

Example

Let $a \in K$ - constant, and x - generic solution of $x' = ax$.

$$\alpha(x) = x \implies \alpha(a) = \alpha\left(\frac{x'}{x}\right) = \frac{\alpha(x')}{\alpha(x)} = \frac{x'}{x} = a$$

Dictionary: definability

Definition

Let $B \subset K$, $a \in K$.

a is *definable* over B iff, for every automorphism $\alpha\colon K \to K$:

$$\big(\forall b \in B\ \alpha(b) = b\big) \implies \alpha(a) = a.$$

Example

Let $a \in K$ - constant, and x - generic solution of $x' = ax$.

$$\alpha(x) = x \implies \alpha(a) = \alpha\left(\frac{x'}{x}\right) = \frac{\alpha(x')}{\alpha(x)} = \frac{x'}{x} = a$$

Fact

In differentially closed fields

$$a \text{ definable over } B \quad \implies \quad a = f(B, B', B'', \ldots)$$

Dictionary: canonical base

Example

Type over $A = \{k_1, k_2, k_3, k_4\}$ of generic solution of

$$y\ddot{y} - \dot{y}^2 - k_4 y^2 \dot{y} - k_3 y \dot{y} + k_1 k_4 y^3 - k_1 k_3 y^2 = 0$$

Dictionary: canonical base

Example

Type over $A = \{k_1, k_2, k_3, k_4\}$ of generic solution of

$$y\ddot{y} - \dot{y}^2 - k_4 y^2 \dot{y} - k_3 y \dot{y} + k_1 k_4 y^3 - k_1 k_3 y^2 = 0$$

(generic output of the predator-prey model)

Dictionary: canonical base

Example

Type over $A = \{k_1, k_2, k_3, k_4\}$ of generic solution of

$$y\ddot{y} - \dot{y}^2 - k_4 y^2 \dot{y} - k_3 y \dot{y} + k_1 k_4 y^3 - k_1 k_3 y^2 = 0$$

(generic output of the predator-prey model)

A canonical base: $k_4,\ k_3,\ k_1 k_4,\ k_1 k_3$

Dictionary: canonical base

Example

Type over $A = \{k_1, k_2, k_3, k_4\}$ of generic solution of

$$y\ddot{y} - \dot{y}^2 - k_4 y^2 \dot{y} - k_3 y \dot{y} + k_1 k_4 y^3 - k_1 k_3 y^2 = 0$$

(generic output of the predator-prey model)

A canonical base: $k_4,\ k_3,\ k_1 k_4,\ k_1 k_3$

Generate the same field $\implies$ a canonical base as well, e.g. k_1, k_3, k_4.

Translation

Identifiability

Model theory

Translation

Identifiability

(1) coefficients of the IO-equation

Model theory

(1) canonical base of the output

Translation

Identifiability

(1) coefficients of the IO-equation

(2) α is identifiable

Model theory

(1) canonical base of the output

(2) α is definable over output

Translation

Identifiability

(1) coefficients of the IO-equation
(2) α is identifiable
(3) α is rational in the coefficients of the IO-equation

Model theory

(1) canonical base of the output
(2) α is definable over output
(3) α is definable over the canonical base

Translation

Identifiability

(1) coefficients of the IO-equation
(2) α is identifiable
(3) α is rational in the coefficients of the IO-equation
(4) Assumption: (2) $\iff$ (3)

Model theory

(1) canonical base of the output
(2) α is definable over output
(3) α is definable over the canonical base

Translation

Identifiability

(1) coefficients of the IO-equation

(2) α is identifiable

(3) α is rational in the coefficients of the IO-equation

(4) Assumption: (2) $\iff$ (3)

Model theory

(1) canonical base of the output

(2) α is definable over output

(3) α is definable over the canonical base

(4) type of output "is" **one-based**

Translation

Identifiability

(1) coefficients of the IO-equation

(2) α is identifiable

(3) α is rational in the coefficients of the IO-equation

(4) Assumption: (2) $\iff$ (3)

Model theory

(1) canonical base of the output

(2) α is definable over output

(3) α is definable over the canonical base

(4) type of output "is" **one-based**

One?

Are there two-based, three-based, etc?

From one to many

Defintion

Type is n-*based* $\iff$ canonical base is definable from n independent realizations

From one to many

Defintion

Type is n-*based* $\iff$ canonical base is definable from n independent realizations

In other words

The coefficients of the input-output equation are identifiable from n experiments with *different initial conditions*.

From one to many

Defintion

Type is *n-based* $\iff$ canonical base is definable from n independent realizations

In other words

The coefficients of the input-output equation are identifiable from n experiments with *different initial conditions*.

Theorem

The following are equal

(1) the field generated by the coefficient of the IO-equations;

(2) the set of rational functions in parameter identifiable from *sufficiently many experiments*.

From one to many

Defintion

Type is *n-based* $\iff$ canonical base is definable from n independent realizations

In other words

The coefficients of the input-output equation are identifiable from n experiments with *different initial conditions*.

Theorem

The following are equal

(1) the field generated by the coefficient of the IO-equations;

(2) the set of rational functions in parameter identifiable from *sufficiently many experiments*.

Corollary

The IO-equations method solves *the multiexperimental identifiability problem*.

Example: Twisted harmonic oscillator

$$\begin{cases} \dot{x}_1 = (\omega + x_3)x_2, \\ \dot{x}_2 = -\omega x_1, \\ \dot{x}_3 = 0, \\ y_1 = x_2,\ y_2 = x_3 \end{cases}$$

Example: Twisted harmonic oscillator

$$\begin{cases} \dot{x}_1 = (\omega + x_3)x_2, \\ \dot{x}_2 = -\omega x_1, \\ \dot{x}_3 = 0, \\ y_1 = x_2,\ y_2 = x_3 \end{cases}$$

Canonical base: ω.

Example: Twisted harmonic oscillator

$$\begin{cases} \dot{x}_1 = (\omega + x_3)x_2, \\ \dot{x}_2 = -\omega x_1, \\ \dot{x}_3 = 0, \\ y_1 = x_2,\ y_2 = x_3 \end{cases}$$

Canonical base: ω. From a single experiment, we find $c := \omega(\omega + y_2)$.

Example: Twisted harmonic oscillator

$$\begin{cases} \dot{x}_1 = (\omega + x_3)x_2, \\ \dot{x}_2 = -\omega x_1, \\ \dot{x}_3 = 0, \\ y_1 = x_2,\ y_2 = x_3 \end{cases}$$

Canonical base: ω. From a single experiment, we find $c := \omega(\omega + y_2)$.
After two experiments:

$$\begin{cases} c_1 = \omega(\omega + y_{2,1}), \\ c_2 = \omega(\omega + y_{2,2}). \end{cases}$$

Example: Twisted harmonic oscillator

$$\begin{cases} \dot{x}_1 = (\omega + x_3)x_2, \\ \dot{x}_2 = -\omega x_1, \\ \dot{x}_3 = 0, \\ y_1 = x_2,\ y_2 = x_3 \end{cases}$$

Canonical base: ω. From a single experiment, we find $c := \omega(\omega + y_2)$.
After two experiments:

$$\begin{cases} c_1 = \omega(\omega + y_{2,1}), \\ c_2 = \omega(\omega + y_{2,2}). \end{cases}$$

We can cancel ω^2 and get a linear equation in ω.

Example: Twisted harmonic oscillator

$$\begin{cases} \dot{x}_1 = (\omega + x_3)x_2, \\ \dot{x}_2 = -\omega x_1, \\ \dot{x}_3 = 0, \\ y_1 = x_2, \ y_2 = x_3 \end{cases}$$

Canonical base: ω. From a single experiment, we find $c := \omega(\omega + y_2)$.
After two experiments:

$$\begin{cases} c_1 = \omega(\omega + y_{2,1}), \\ c_2 = \omega(\omega + y_{2,2}). \end{cases}$$

We can cancel ω^2 and get a linear equation in ω.
The type of output is two-based, ω is 2-experimental identifiable.

Example: slow-fast ambiguity

Example: slow-fast ambiguity

Chemical reaction

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

Example: slow-fast ambiguity

Chemical reaction

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

Equations

$$\begin{cases} \dot{x}_A = -k_1 x_A, \\ \dot{x}_B = k_1 x_A - k_2 x_B, \\ \dot{x}_C = k_2 x_C, \end{cases}$$

Example: slow-fast ambiguity

Chemical reaction

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

Equations

$$\begin{cases} \dot{x}_A = -k_1 x_A, \\ \dot{x}_B = k_1 x_A - k_2 x_B, \\ \dot{x}_C = k_2 x_C, \\ \\ y_1 = x_C, \\ y_2 = \varepsilon_A x_A + \varepsilon_B x_B + \varepsilon_C x_C, \end{cases}$$

Example: slow-fast ambiguity

Chemical reaction

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

Equations

$$\begin{cases} \dot{x}_A = -k_1 x_A, \\ \dot{x}_B = k_1 x_A - k_2 x_B, \\ \dot{x}_C = k_2 x_C, \\ \dot{\varepsilon}_A = 0, \\ y_1 = x_C, \\ y_2 = \varepsilon_A x_A + \varepsilon_B x_B + \varepsilon_C x_C, \\ y_3 = \varepsilon_A \end{cases}$$

Example: slow-fast ambiguity

Chemical reaction

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

- From one experiment: $k_1 + k_2,\ k_1 k_2,\ \varepsilon_C$

Equations

$$\begin{cases} \dot{x}_A = -k_1 x_A, \\ \dot{x}_B = k_1 x_A - k_2 x_B, \\ \dot{x}_C = k_2 x_C, \\ \dot{\varepsilon}_A = 0, \\ y_1 = x_C, \\ y_2 = \varepsilon_A x_A + \varepsilon_B x_B + \varepsilon_C x_C, \\ y_3 = \varepsilon_A \end{cases}$$

Example: slow-fast ambiguity

Chemical reaction

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

Equations

$$\begin{cases} \dot{x}_A = -k_1 x_A, \\ \dot{x}_B = k_1 x_A - k_2 x_B, \\ \dot{x}_C = k_2 x_C, \\ \dot{\varepsilon}_A = 0, \\ y_1 = x_C, \\ y_2 = \varepsilon_A x_A + \varepsilon_B x_B + \varepsilon_C x_C, \\ y_3 = \varepsilon_A \end{cases}$$

- From one experiment: $k_1 + k_2,\ k_1 k_2,\ \varepsilon_C$
- Canonical base: $k_1, k_2, \varepsilon_B, \varepsilon_C$

Example: slow-fast ambiguity

Chemical reaction

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

Equations

$$\begin{cases} \dot{x}_A = -k_1 x_A, \\ \dot{x}_B = k_1 x_A - k_2 x_B, \\ \dot{x}_C = k_2 x_C, \\ \dot{\varepsilon}_A = 0, \\ y_1 = x_C, \\ y_2 = \varepsilon_A x_A + \varepsilon_B x_B + \varepsilon_C x_C, \\ y_3 = \varepsilon_A \end{cases}$$

- From one experiment: $k_1 + k_2,\ k_1 k_2,\ \varepsilon_C$
- Canonical base: $k_1, k_2, \varepsilon_B, \varepsilon_C$
- Two experiments are sufficient

Summary

- Structural identifiability: important problem
  Naturally connected to algebra

Summary

- Structural identifiability: important problem
  Naturally connected to algebra
- Computational differential algebra and algebraic geometry: algorithms to tackle this problem

Summary

- Structural identifiability: important problem
  Naturally connected to algebra
- Computational differential algebra and algebraic geometry: algorithms to tackle this problem
- Model theory:
  understanding what these algorithms are actually doing
  (and design new; tell you next time)

Open problems

Role of the initial conditions

Example: why different

$\dot{x} = ax$ with x *generic* $\implies$ a is identifiable as $a = \frac{\dot{x}}{x}$.

Role of the initial conditions

Example: why different

$\dot{x} = ax$ with x *generic* $\implies$ a is identifiable as $a = \frac{\dot{x}}{x}$.

But if $x(0) = 0$, then $x(t) = 0 \implies$ no information about a

Role of the initial conditions

Example: why different
$\dot{x} = ax$ with x *generic* $\implies$ a is identifiable as $a = \frac{\dot{x}}{x}$.

But if $x(0) = 0$, then $x(t) = 0 \implies$ no information about a

Question
Given fixed initial conditions, is it decidable whether a parameter is identifiable?

Role of the initial conditions

Example: why different
$\dot{x} = ax$ with x *generic* $\implies$ a is identifiable as $a = \frac{\dot{x}}{x}$.

But if $x(0) = 0$, then $x(t) = 0 \implies$ no information about a

Question
Given fixed initial conditions, is it decidable whether a parameter is identifiable?

Theorem (Hong, Ovchinnikov, P., Yap)
Let there are n state variables and ℓ parameters. Then

(1) parameter k is identifiable **iff**

(2) k is a rational function of $n + \ell + 1$ derivatives of outputs at $t = 0$.

Role of the initial conditions

Example: why different
$\dot{x} = ax$ with x *generic* $\implies$ a is identifiable as $a = \frac{\dot{x}}{x}$.

But if $x(0) = 0$, then $x(t) = 0 \implies$ no information about a

Question
Given fixed initial conditions, is it decidable whether a parameter is identifiable?

Theorem (Hong, Ovchinnikov, P., Yap)
Let there are n state variables and ℓ parameters. Then

(1) parameter k is identifiable **iff**

(2) k is a rational function of $n + \ell + 1$ derivatives of outputs at $t = 0$.

Not true for fixed initial conditions
Let $\dot{x} = 1 + ax^{100},\ y = x,\ x(0) = 0,$

Role of the initial conditions

Example: why different

$\dot{x} = ax$ with x *generic* $\implies$ a is identifiable as $a = \frac{\dot{x}}{x}$.

But if $x(0) = 0$, then $x(t) = 0 \implies$ no information about a

Question

Given fixed initial conditions, is it decidable whether a parameter is identifiable?

Theorem (Hong, Ovchinnikov, P., Yap)

Let there are n state variables and ℓ parameters. Then

(1) parameter k is identifiable **iff**

(2) k is a rational function of $n + \ell + 1$ derivatives of outputs at $t = 0$.

Not true for fixed initial conditions

Let $\dot{x} = 1 + ax^{100},\ y = x,\ x(0) = 0,$

Then $\dot{x}(0) = 1$, $\ddot{x}(0) = \ldots = x^{(99)}(0) = 0$, but $x^{(100)}(0) = 100!a$.

Role of the initial conditions

Example: why different
$\dot{x} = ax$ with x *generic* $\implies$ a is identifiable as $a = \frac{\dot{x}}{x}$.

But if $x(0) = 0$, then $x(t) = 0 \implies$ no information about a

Question
Given fixed initial conditions, is it decidable whether a parameter is identifiable?

Theorem (Hong, Ovchinnikov, P., Yap)
Let there are n state variables and ℓ parameters. Then

(1) parameter k is identifiable **iff**

(2) k is a rational function of $n + \ell + 1$ derivatives of outputs at $t = 0$.

Not true for fixed initial conditions
Let $\dot{x} = 1 + ax^{100},\ y = x,\ x(0) = 0,$

Then $\dot{x}(0) = 1$, $\ddot{x}(0) = \ldots = x^{(99)}(0) = 0$, but $x^{(100)}(0) = 100!a$.

Question
Is there a bound in terms of, for example, degrees?

$\mathbb{R}$ vs. $\mathbb{C}$

State-of-the-art

- To the best of my knowledge, all algorithms for global identifiability work over $\mathbb{C}$;

$\mathbb{R}$ vs. $\mathbb{C}$

State-of-the-art

- To the best of my knowledge, all algorithms for global identifiability work over $\mathbb{C}$;
- It is not clear how to define identifiability over $\mathbb{R}$: might be several typical behaviours

$\mathbb{R}$ vs. $\mathbb{C}$

State-of-the-art

- To the best of my knowledge, all algorithms for global identifiability work over $\mathbb{C}$;
- It is not clear how to define identifiability over $\mathbb{R}$: might be several typical behaviours

Why $\mathbb{C}$ matters?

- Identifiable over $\mathbb{C} \implies$ "identifiable" over $\mathbb{R}$;
- Nonidentifiability over $\mathbb{C}$ indicates hidden symmetries;

$\mathbb{R}$ vs. $\mathbb{C}$

State-of-the-art

- To the best of my knowledge, all algorithms for global identifiability work over $\mathbb{C}$;
- It is not clear how to define identifiability over $\mathbb{R}$: might be several typical behaviours

Why $\mathbb{C}$ matters?

- Identifiable over $\mathbb{C} \implies$ "identifiable" over $\mathbb{R}$;
- Nonidentifiability over $\mathbb{C}$ indicates hidden symmetries;

Questions

- How to define and assess identifiability over $\mathbb{R}$?
- Parameter k is nonidentifiable over $\mathbb{C} \overset{?}{\Rightarrow}$ nonidentifiable over $\mathbb{R}$ on an open subset?

Reparametrization

Example: predator-prey

$$\begin{cases} \dot{x}_1 = k_1 x_1 - k_2 x_1 x_2, \\ \dot{x}_2 = -k_3 x_2 + k_4 x_1 x_2, \\ y = x_1. \end{cases}$$

Reparametrization

Example: predator-prey

$$\begin{cases} \dot{x}_1 = k_1 x_1 - k_2 x_1 x_2, \\ \dot{x}_2 = -k_3 x_2 + k_4 x_1 x_2, \\ y = x_1. \end{cases}$$

Make a change of variables: $z_2 := k_2 x_2$, then:

$$\begin{cases} \dot{x}_1 = k_1 x_1 - x_1 z_2, \\ \dot{z}_2 = -k_3 z_2 + k_4 x_1 z_2. \end{cases}$$

Reparametrization

Example: predator-prey

$$\begin{cases} \dot{x}_1 = k_1 x_1 - k_2 x_1 x_2, \\ \dot{x}_2 = -k_3 x_2 + k_4 x_1 x_2, \\ y = x_1. \end{cases}$$

Make a change of variables: $z_2 := k_2 x_2$, then:

$$\begin{cases} \dot{x}_1 = k_1 x_1 - x_1 z_2, \\ \dot{z}_2 = -k_3 z_2 + k_4 x_1 z_2. \end{cases}$$

All parameters are identifiable now!

Questions

- How to search for such reparametrizations?

Reparametrization

Example: predator-prey

$$\begin{cases} \dot{x}_1 = k_1 x_1 - k_2 x_1 x_2, \\ \dot{x}_2 = -k_3 x_2 + k_4 x_1 x_2, \\ y = x_1. \end{cases}$$

Make a change of variables: $z_2 := k_2 x_2$, then:

$$\begin{cases} \dot{x}_1 = k_1 x_1 - x_1 z_2, \\ \dot{z}_2 = -k_3 z_2 + k_4 x_1 z_2. \end{cases}$$

All parameters are identifiable now!

Questions

- How to search for such reparametrizations?
- Can one always write a system of ODEs with coefficients being identifiable (or in canonical base) with the same input-output equations?

Support

The work was supported by

- National Science Foundation
- City University of New York
- National Security Agency

I would also like to thank the American Institute of Mathematics and M.Eisenberg and N.Meshkat for organizing workshop “Identifiability problems in systems biology ”.