Proposal Review

Northeastern University

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Global identifiability
More definitions
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Basic examples

Control and Decision Making in Systems Biology

Northeastern University

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Committee: Dr. Irina Kareva
Prof. Mark Niedre
Prof. Carey Rappaport
Prof. Bahram Shafai

Outline

The objective of is to have an overview of what I have done during my PhD.

- ▶ Mahdiar Sadeghi (presenter).

- ▶ Prof. Eduardo Sontag (advisor).

- ▶ Dr. Irina Kareva

- ▶ Prof. Mark Niedre

- ▶ Prof. Carey Rappaport

- ▶ Prof. Bahram Shafai

Review of basic definitions.

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The basic definitions are from Miao et. al.[1], for a general system:

$$\dot{x}(t) = f(t, x(t), u(t), \theta), \tag{1a}$$
$$y(t) = g(x(t), u(t), \theta). \tag{1b}$$

- ▶ $x(t) \in R^n$ is a vector of state variables.
- ▶ $y(t) \in R^m$ is the measurement or output vector.
- ▶ $u(t) \in R^p$ is the known system input vector.
- ▶ $\theta \in R^q$ the parameter vector.
- ▶ θ is unknown and has to be estimated based on experimental data. Here we assume that the parameters are constant.

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[1]Hongyu Miao et al. "On identifiability of nonlinear ODE models and applications in viral dynamics". In: *SIAM review* 53.1 (2011), pp. 3–39.

Global identifiabilty

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▶ **Definition:** A system structure is said to be globally identifiable if for any θ within an open neighborhood of some point θ^* in the parameter space, $y(u, \theta_1) = y(u, \theta_2)$ holds if and only if $\theta_1 = \theta_2$.

▶ **Example:** The following model is globally identifiable.

$$\dot{x}(t) = ax(t) + bu(t), \tag{2a}$$
$$y(t) = x(t). \tag{2b}$$

▶ **Example:** The following model is not globally identifiable.

$$\dot{x}(t) = \frac{a}{c}x(t) + bu(t), \tag{3a}$$
$$y(t) = x(t). \tag{3b}$$

$y(t)$ of parameter sets $\theta_1 = (a, b, c) = (1, 2, 3)$ and $\theta_2 = (a, b, c) = (2, 2, 6)$ are the same.

More identifiabilty definitions

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- ▶ **Local identifiability:** A system structure is said to be locally identifiable if for any admissible input $u(t)$ and any two parameter vector θ_1 and θ_2 in the prameter space Θ, $y(u, \theta_1) = y(u, \theta_2)$ holds if an only if $\theta_1 = \theta_2$.

- ▶ **Local strong identifiability** (x_0-identifiability).

- ▶ **Structural identifiability.**

- ▶ **Algebric identifiability.**

- ▶ **Algebric identifiability with known initial conditions.**

- ▶ **Structural equivalence:** Given two systems in the form

$$\dot{x} = f(x(t, \theta)\theta) + u(t)g(x(t, \theta), \theta), \tag{4a}$$
$$y = h(x(t, \theta), \theta) \tag{4b}$$

If there exist two parameters $\theta_1, \theta_2 \in \Theta$ such that, for the same admissible input $u(t)$, the solution of the two systems exists for θ_1 and θ_2, respectively, and the corresponding system outputs are the same, the system with parameters θ_1 is said to be equivalent to the system with parameter θ_2.

Copy the following examples into Maple cloud app.

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Model (2) where the parameters and initial conditions should be locally and globally identifiable:

```
dx/dt = a*x + b*u(t)
y=x
```

Model (3) where a, and c are not identifiable:

```
dx/dt = a*x/c + b*u(t),
y=x
```

Tumor growth model[2].

The minimal version of the tumor growth model with $n = 2$:

$$\dot{x}_1(t) = \frac{\lambda_0 x_1(t)}{(1 + (\frac{\lambda_0 y(t)}{\lambda_1})^\Psi)^{\frac{1}{\Psi}}} - k_2 x_1(t)u(t), \tag{5a}$$

$$\dot{x}_2(t) = k_2 x_1(t)u(t) - k_1 x_2(t), \tag{5b}$$

$$y(t) = x_1(t) + x_2(t). \tag{5c}$$

Let's try SIAN with the following code.

```
dx1/dt = l0*x1/(1+(l0*y/l1)^P)^(1/P) - k2*x1*u(t),
dx2/dt = k2*x1*u(t) - k1*x2,
y = x1+x2
```

error message:StringTools:-RegMatch.
The solution is to use an equivalence form of the model. But why?

```
dx1/dt = x1*w-k2*u(t)*x1,
dx2/dt = k2*u(t)*x1-k1*x2,
dz/dt = psi*(x1*w-k1*x2)*z/y,
dw/dt = -(x1*w-k1*x2)*z*w/(y*(1+z)),
y= x1+x2
```

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[2]Monica Simeoni et al. "Predictive pharmacokinetic-pharmacodynamic modeling of tumor growth kinetics in xenograft models after administration of anticancer agents". In: *Cancer research* 64.3 (2004), pp. 1094–1101.

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In general, the algorithm does not allow noninteger powers and powers being parameters [3]

The solution is to define intermediate variables $z(t)$ and $w(t)$:

$$z(t) = \left(\frac{\lambda_0 y(t)}{\lambda_1}\right)^{\Psi}, \tag{6a}$$

$$w(t) = \frac{\lambda_0}{(1 + z(t))^{\frac{1}{\Psi}}}. \tag{6b}$$

Then dynamic can be rewritten in the following form.

$$\dot{x}_1(t) = x_1(t)w(t) - k_2 u(t)x_1(t), \tag{7a}$$

$$\dot{x}_2(t) = k_2 u(t)x_1(t) - k_1 x_2(t), \tag{7b}$$

$$\dot{z}(t) = \frac{\Psi z(t)}{y(t)}\dot{y}(t) = \frac{\Psi}{y(t)}(x_1(t)w(t) - k_1 x_2(t)), \tag{7c}$$

$$\dot{w}(t) = -\frac{w(t)\dot{z}(t)}{\Psi(1 + z(t))} = -\frac{w(t)z(t)}{y(t)(1 + z(t))}(x_1(t)w(t) - k_1 x_2(t)). \tag{7d}$$

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[3]https://github.com/pogudingleb/SIAN/issues/2

Profile likelihood

▶ Most useful to determine practical identifiability based on a given synthetic/expermental data.

▶ Practical identifiability $\Rightarrow$ structural identifiabiility.

▶ Structural identifiablity $\not\Rightarrow$ practical identifiablity.

▶ An open source software in MATLAB[4]:
https://github.com/Data2Dynamics/d2d.

▶ An open source software in Python[5]:
https://github.com/systemsmedicine/PDE_params.

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[4]Andreas Raue et al. "Data2Dynamics: a modeling environment tailored to parameter estimation in dynamical systems". In: *Bioinformatics* 31.21 (2015), pp. 3558–3560.

[5]César Parra-Rojas and Esteban A Hernandez-Vargas. "PDEparams: Parameter fitting toolbox for partial differential equations in python". In: *Bioinformatics* 36.8 (2020), pp. 2618–2619.

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