

# Control and Decision Making in Systems Biology

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# Presentation outline

The objective of this study is to give a few examples of which numerical analysis can benefit applications of systems biology.

1. Background
2. Chemotherapy
3. Immunotherapy
4. Epidemics
5. Acknowledgement

Outline

Review

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Basic examples

# Review of basic definitions.

The basic definitions are from Miao et. al.<sup>1</sup>, for a general system:

$$\dot{x}(t) = f(t, x(t), u(t), \theta), \quad (1a)$$

$$y(t) = g(x(t), u(t), \theta). \quad (1b)$$

- ▶  $x(t) \in R^n$  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.
- ▶  $\theta$  is unknown and has to be estimated based on experimental data. Here we assume that the parameters are constant.

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

- **Definition:** A system structure is said to be globally identifiable if for any  $\theta$  within an open neighborhood of some point  $\theta^*$  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.

$$\dot{x}(t) = ax(t) + bu(t), \quad (2a)$$

$$y(t) = x(t). \quad (2b)$$

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

$$\dot{x}(t) = \frac{a}{c}x(t) + bu(t), \quad (3a)$$

$$y(t) = x(t). \quad (3b)$$

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

# More identifiability definitions

- ▶ **Local identifiability:** A system structure is said to be locally identifiable if for any admissible input  $u(t)$  and any two parameter vector  $\theta_1$  and  $\theta_2$  in the parameter space  $\Theta$ ,  $y(u, \theta_1) = y(u, \theta_2)$  holds if and only if  $\theta_1 = \theta_2$ .
- ▶ **Local strong identifiability** ( $x_0$ -identifiability).
- ▶ **Structural identifiability.**
- ▶ **Algebraic identifiability.**
- ▶ **Algebraic identifiability with known initial conditions.**
- ▶ **Structural equivalence:** Given two systems in the form

$$\dot{x} = f(x(t, \theta), u(t), \theta), \quad (4a)$$

$$y = h(x(t, \theta), u(t), \theta) \quad (4b)$$

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  $\theta_1$  and  $\theta_2$ , respectively, and the corresponding system outputs are the same, the system with parameters  $\theta_1$  is said to be equivalent to the system with parameter  $\theta_2$ .

Copy the following examples into Maple cloud app.

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

$$\begin{aligned}dx/dt &= a*x + b*u(t) \\ y &= x\end{aligned}$$

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

$$\begin{aligned}dx/dt &= a*x/c + b*u(t), \\ y &= x\end{aligned}$$

# Tumor growth model<sup>2</sup>.

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

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

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

$$y(t) = x_1(t) + x_2(t). \quad (5c)$$

Let's try SIAN with the following code.

```
dx1/dt = 10*x1/((1+(10*y/11)^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
```

<sup>2</sup>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.

In general, the algorithm does not allow noninteger powers and powers being parameters <sup>3</sup>

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

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

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

Then dynamic can be rewritten in the following form.

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

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

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

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

<sup>3</sup><https://github.com/pogudingleb/SIAN/issues/2> 



- ▶ Most useful to determine practical identifiability based on a given synthetic/experimental data.
- ▶ Practical identifiability  $\Rightarrow$  structural identifiability.
- ▶ Structural identifiability  $\nRightarrow$  practical identifiability.
- ▶ An open source software in MATLAB<sup>4</sup>:  
<https://github.com/Data2Dynamics/d2d>.
- ▶ An open source software in Python<sup>5</sup>:  
[https://github.com/systemsmedicine/PDE\\_params](https://github.com/systemsmedicine/PDE_params).

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

<sup>5</sup>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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