Identifiability of linear compartmental models

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Parameter Estimation Workshop – NCSU
August 9, 2014
78 slides

Structural Identifiability Analysis

- Linear Model:
  - x state variable
  - u input
  - y output
  - A, B, C matrices with unknown parameters

$$\boxed{\begin{gathered}\dot{x}(t) = Ax(t) + Bu(t)\\ y(t) = Cx(t)\end{gathered}}$$

- Finding which unknown parameters of a model can be quantified from given input-output data

But why linear compartment models?

- Used in many biological applications, e.g. pharmacokinetics
- Very often unidentifiable!
- Nice algebraic structure
  - Can actually prove some *general* results!

Unidentifiable Models

- Question 1: Can we always “reparametrize” an unidentifiable model into an identifiable one?

Motivation: Question 1

- Model 1:

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{pmatrix} = \begin{pmatrix} a_{11} & a_{12} & 0 \\ 0 & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} + \begin{pmatrix} u_1 \\ 0 \\ 0 \end{pmatrix}$$

$$y = x_1$$

- Model 2:

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{pmatrix} = \begin{pmatrix} a_{11} & a_{12} & 0 \\ a_{21} & a_{22} & a_{23} \\ a_{31} & 0 & a_{33} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} + \begin{pmatrix} u_1 \\ 0 \\ 0 \end{pmatrix}$$

$$y = x_1$$

Motivation: Question 1

- Model 1: **No** ID scaling reparametrization!

$$\xcancel{\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{pmatrix} = \begin{pmatrix} a_{11} & a_{12} & 0 \\ 0 & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} + \begin{pmatrix} u_1 \\ 0 \\ 0 \end{pmatrix}}$$

$$y = x_1$$

- Model 2: ID scaling reparametrization:

$$\begin{pmatrix} \dot{X}_1 \\ \dot{X}_2 \\ \dot{X}_3 \end{pmatrix} = \begin{pmatrix} a_{11} & 1 & 0 \\ a_{12}a_{21} & a_{22} & 1 \\ a_{12}a_{31}a_{23} & 0 & a_{33} \end{pmatrix} \begin{pmatrix} X_1 \\ X_2 \\ X_3 \end{pmatrix} + \begin{pmatrix} u_1 \\ 0 \\ 0 \end{pmatrix}$$

$$y = X_1$$

Unidentifiable Models

- Question 1: Can we always “reparametrize” an unidentifiable into an identifiable one?

- Question 2: If a reparametrization exists, can we instead modify the original model to make it identifiable?

Motivation: Question 2

- Model 2:

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{pmatrix} = \begin{pmatrix} a_{11} & a_{12} & 0 \\ a_{21} & a_{22} & a_{23} \\ a_{31} & 0 & a_{33} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} + \begin{pmatrix} u_1 \\ 0 \\ 0 \end{pmatrix}$$

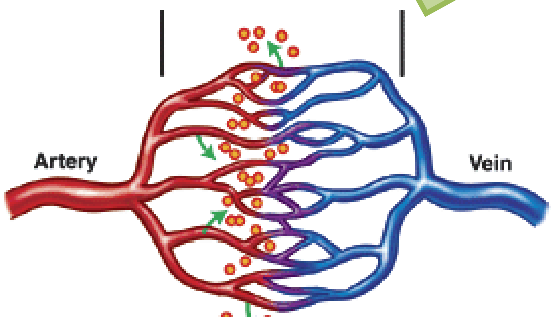
$$y = x_1$$

- Starting with Model 2, how should we adjust model to obtain identifiability?
  - Decrease # of parameters?
  - Add input/output data?

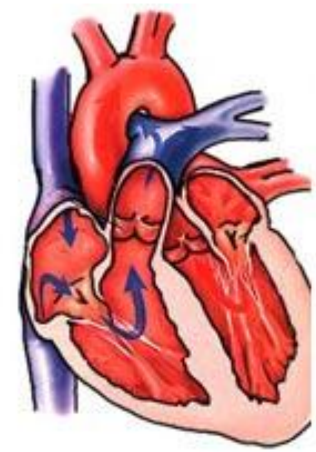
Motivation: biological models

Drug input

Measured drug concentration



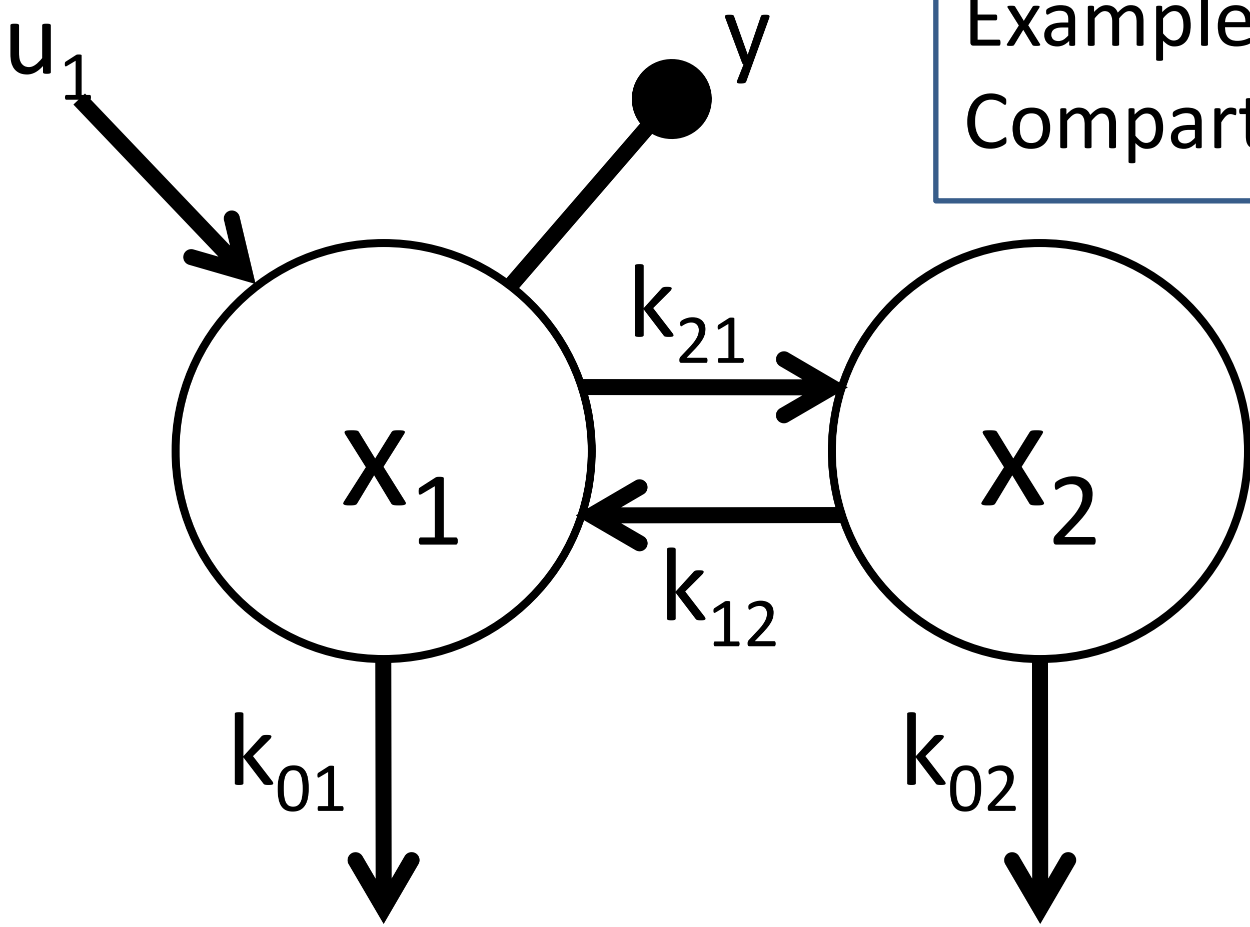
Drug exchange



Loss from blood

Loss from organ

Example: Linear 2-Compartment Model



$$\dot{x}_1 = -(k_{01} + k_{21})x_1 + k_{12}x_2 + u_1$$
$$\dot{x}_2 = k_{21}x_1 - (k_{02} + k_{12})x_2$$
$$y = x_1$$

Linear Compartment Models

- <u>System equations</u>:

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix} = \begin{pmatrix} -(k_{01} + k_{21}) & k_{12} \\ k_{21} & -(k_{02} + k_{12}) \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} + \begin{pmatrix} u_1 \\ 0 \end{pmatrix}$$

$$y = x_1$$

- Can change to form $\dot{x} = Ax + u$

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix} = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} + \begin{pmatrix} u_1 \\ 0 \end{pmatrix}$$

$$y = x_1$$

Larger class of models to investigate

- Assumptions:
  - I/O in first compartment
  - Leaks from every compartment

$$\dot{x} = Ax + u$$
$$y = x_1$$

where $u = \begin{pmatrix} u_1 \\ 0 \\ \vdots \\ 0 \end{pmatrix}$ and diagonal elements = a_{ii}

Useful tool: Directed Graph

- A directed graph G is a set of:
  - Vertices
  - Edges
- Ex 1:
  - Vertices: {1, 2}
  - Edges: {1→2, 2→1}

$$1 \rightleftarrows 2$$

Useful tool: Directed Graph

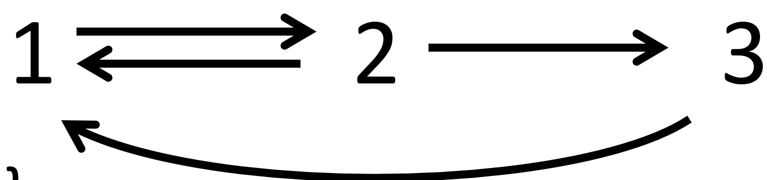
- A directed graph G is a set of:
  - Vertices
  - Edges
- Ex 2:

$$1 \rightleftarrows 2 \longrightarrow 3$$

  - Vertices: {1, 2, 3}
  - Edges: {1→2, 2→1, 2→3}
- A graph is *strongly connected* if there exists a path from each vertex to every other vertex

Useful tool: Directed Graph

- A directed graph G is a set of:
  - Vertices
  - Edges
- Ex 3:



  - Vertices: {1, 2, 3}
  - Edges: {1→2, 2→1, 2→3, 3→1}
- A graph is *strongly connected* if there exists a path from each vertex to every other vertex

Convert to graph

- Let G be directed graph with m edges, n vertices
- Associate a matrix A to the graph G:

$$A(G)_{ij} = \begin{cases} a_{ii} & if\ i = j \\ a_{ij} & if\ j \rightarrow i\ is\ an\ edge \\ 0 & otherwise \end{cases}$$

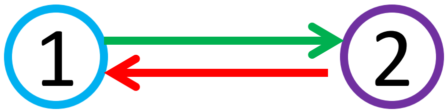
  where each a_{ij} is an independent real parameter
- Look only at strongly connected graphs

2-compartment model as graph

Model: $$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix} = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} + \begin{pmatrix} u_1 \\ 0 \end{pmatrix}$$

$$y = x_1$$

Graph:



- Cycle: $a_{12}a_{21}$
- "Self" cycles: a_{11}, a_{22}

Identifiability Analysis

- Model: $\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix} = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} + \begin{pmatrix} u_1 \\ 0 \end{pmatrix}$

$$y = x_1$$

- Unknown parameters: $\{a_{11}, a_{12}, a_{21}, a_{22}\}$

- Identifiability: Which parameters of model can be quantified from given input-output data?
  - Must first determine *input-output equation*

Find Input-Output Equation

- Rewrite system eqns as $(\partial I - A)x = u$
- Cramer's Rule:

$$A = \begin{pmatrix} a_{11} & \cdots & a_{1n} \\ \vdots & \ddots & \vdots \\ a_{n1} & \cdots & a_{nn} \end{pmatrix} \qquad A_1 = \begin{pmatrix} a_{22} & \cdots & a_{2n} \\ \vdots & \ddots & \vdots \\ a_{n2} & \cdots & a_{nn} \end{pmatrix}$$

$$x_1 = \frac{det(\partial I - A_1)u_1}{det(\partial I - A)}$$

- I/O eqn: $det(\partial I - A)y = det(\partial I - A_1)u_1$

$$\boxed{\begin{aligned} y^{(n)} + c_1 y^{(n-1)} + \cdots + c_n y \\ = u_1^{(n-1)} + c_{n+1} u_1^{(n-2)} + \cdots + c_{2n-1} u_1 \end{aligned}}$$

Identifiability

- Can recover coefficients from data
- Identifiability: is it possible to recover the parameters of the original system, from the coefficients of I/O eqn?
  - Two sets of parameter values yield same coefficient values?
  - Is coeff map 1-to-1?

$$y^{(n)} + c_1 y^{(n-1)} + \cdots + c_n y = u_1^{(n-1)} + c_{n+1} u_1^{(n-2)} + \cdots + c_{2n-1} u_1$$

2-compartment model

- I/O eqn

$$\ddot{y} - (a_{11} + a_{22})\dot{y} + (a_{11}a_{22} - a_{12}a_{21})y$$
$$= \dot{u}_1 - a_{22}u_1$$

- Coefficient map $c: \mathbb{R}^4 \to \mathbb{R}^3$

$$(a_{11},\ a_{12},\ a_{21},\ a_{22})$$
$$\mapsto (-(a_{11} + a_{22}),\ a_{11}a_{22} - a_{12}a_{21}, -a_{22})$$

- <u>Identifiability</u>: Is the coefficient map 1-to-1?

No!

Identifiability from I/O eqns

- Question of injectivity of the coefficient map

$$c: \mathbb{R}^{m+n} \to \mathbb{R}^{2n-1}$$

- If *c* is one-to-one: <u>globally identifiable</u>

  finite-to-one: <u>locally identifiable</u>

  infinite-to-one: <u>unidentifiable</u>

One-to-one Example

- Map $c: \mathbb{R}^2 \longrightarrow \mathbb{R}^2$

$$(p_1, p_2) \longmapsto (p_1 + p_2,\ p_1 - p_2)$$

- 2 equations:

$$\begin{aligned} p_1 + p_2 &= p_1^* + p_2^* \\ p_1 - p_2 &= p_1^* - p_2^* \end{aligned}$$

- One-to-one:

$$p_1 = p_1^* \qquad p_2 = p_2^*$$

Finite-to-one Example

- Map $c: \mathbb{R}^2 \longrightarrow \mathbb{R}^2$

$$(p_1, p_2) \longmapsto (p_1 + p_2,\ p_1 p_2)$$

- 2 equations:

$$p_1 + p_2 = p_1^* + p_2^*$$
$$p_1 p_2 = p_1^* p_2^*$$

- Finite-to-one:

$$p_1 = p_1^* \qquad p_2 = p_2^*$$

or

$$p_1 = p_2^* \qquad p_2 = p_1^*$$

Our example

- 3 equations:

$$a_{11} + a_{22} = a_{11}^* + a_{22}^*$$

$$a_{11}a_{22} - a_{12}a_{21} = a_{11}^* a_{22}^* - a_{12}^* a_{21}^*$$

$$a_{22} = a_{22}^*$$

- Infinite-to-one!

$$a_{11} = a_{11}^* \qquad a_{22} = a_{22}^* \qquad a_{12} = \frac{a_{12}^* a_{21}^*}{a_{21}}$$

Our example

- 3 equations:

$$a_{11} + a_{22} = a_{11}^* + a_{22}^*$$

$$a_{11}a_{22} - a_{12}a_{21} = a_{11}^* a_{22}^* - a_{12}^* a_{21}^*$$

$$a_{22} = a_{22}^*$$

- Infinite-to-one!

$a_{11} = a_{11}^*$ $a_{22} = a_{22}^*$ $a_{12}a_{21} = a_{12}^* a_{21}^*$

Testing identifiability in practice

- Check dimension of image of coefficient map

$$c\colon \mathbb{R}^{m+n} \to \mathbb{R}^{2n-1}$$

- If *dim im c = m+n,* then locally identifiable
- If *dim im c* < *m+n*, then unidentifiable
- Linear Ex: $c\colon \mathbb{R}^2 \longrightarrow \mathbb{R}^2$

$$(p_1, p_2) \longmapsto (p_1 + p_2,\ p_1 - p_2)$$

- Jacobian has rank 2: $\begin{pmatrix} 1 & 1 \\ 1 & -1 \end{pmatrix}$

Testing identifiability in practice

- Check dimension of image of coefficient map

$$c: \mathbb{R}^{m+n} \to \mathbb{R}^{2n-1}$$

- If *dim im c = m+n,* then locally identifiable
- If *dim im c* < *m+n*, then unidentifiable
- Our Ex: $c: \mathbb{R}^4 \to \mathbb{R}^3$

$$(a_{11}, a_{12}, a_{21}, a_{22}) \mapsto (-(a_{11}+a_{22}), a_{11}a_{22} - a_{12}a_{21}, -a_{22})$$

- Jacobian has rank 3: $\begin{pmatrix} -1 & 0 & 0 & -1 \\ a_{22} & -a_{21} & -a_{12} & a_{11} \\ 0 & 0 & 0 & -1 \end{pmatrix}$

Unidentifiable models

- Cannot determine individual parameters, but can we determine some combination of the parameters?

  Ex: $p_1 + p_2$ or $p_1 p_2$

- A function f: $\mathbb{R}^{m+n} \to \mathbb{R}$ is called identifiable from *c* if $f = \Phi(c_1, \dots, c_{2n-1})$

Identifiable functions

- Coefficients:

$$c_1 = -(a_{11} + a_{22})$$
$$c_2 = a_{11}a_{22} - a_{12}a_{21}$$
$$c_3 = -a_{22}$$

- Identifiable functions (cycles):

$$a_{11} = -(c_1 - c_3)$$
$$a_{22} = -c_3$$
$$a_{12}a_{21} = (c_1 - c_3)c_3 - c_2$$

- Coefficients can be written in terms of identifiable functions:

$$(a_{11},\, a_{12},\, a_{21},\, a_{22}) \mapsto (-(a_{11} + a_{22}),\, a_{11}a_{22} - a_{12}a_{21}, -a_{22})$$

Unidentifiable model

- Model $$\begin{pmatrix}\dot{x}_1\\ \dot{x}_2\end{pmatrix} = \begin{pmatrix}a_{11} & a_{12}\\ a_{21} & a_{22}\end{pmatrix}\begin{pmatrix}x_1\\ x_2\end{pmatrix} + \begin{pmatrix}u_1\\ 0\end{pmatrix}$$
$$y = x_1$$

- Identifiable functions $a_{11},\ a_{22},\ a_{12}a_{21}$
  i.e. $-(k_{01} + k_{21}), -(k_{02} + k_{12}), k_{12}k_{21}$
- Reparametrize: 4 independent parameters $\rightarrow$ 3 independent parameters?

Identifiable reparametrization

Let $c\colon \mathbb{R}^{m_1} \to \mathbb{R}^{m_2}$ be a coefficient map

An identifiable reparametrization of a model is a map $q\colon \mathbb{R}^{m_3} \to \mathbb{R}^{m_1}$ such that:

- $c \circ q\colon \mathbb{R}^{m_3} \to \mathbb{R}^{m_2}$ has the same image as c
- $c \circ q$ is identifiable (finite-to-one)

Scaling reparametrization

- Choice of functions $f_1, \dots, f_n \colon \mathbb{R}^{m+n} \to \mathbb{R}$ where we replace $x_1, \dots, x_n$ with

$$X_i = f_i(A)x_i$$

- Set $f_1 = 1$ since $y = x_1$ is observed
- Since model is $\dot{x} = Ax + u$, each parameter a_{ij} is replaced with $\dfrac{a_{ij} f_i(A)}{f_j(A)}$
- Only graphs with at most 2n-2 edges

Reparametrize original model

- Use scaling: $X_1 = x_1 \quad X_2 = a_{12}x_2$

$$\begin{pmatrix}\dot{X}_1\\ \dot{X}_2\end{pmatrix} = \begin{pmatrix} a_{11} & 1 \\ a_{12}a_{21} & a_{22}\end{pmatrix}\begin{pmatrix}X_1\\ X_2\end{pmatrix} + \begin{pmatrix}u_1\\ 0\end{pmatrix}$$
$$y = X_1$$

- Re-write:

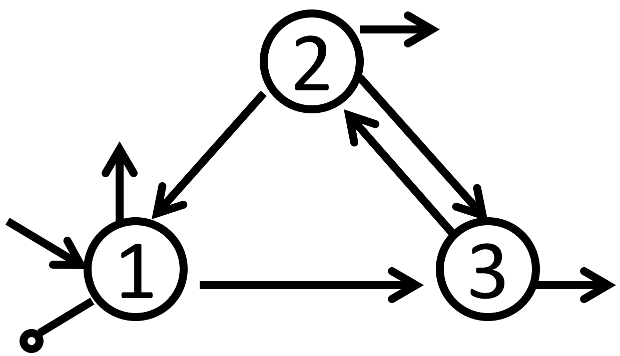
$$\begin{pmatrix}\dot{X}_1\\ \dot{X}_2\end{pmatrix} = \begin{pmatrix} q_{11} & 1 \\ q_{21} & q_{22}\end{pmatrix}\begin{pmatrix}X_1\\ X_2\end{pmatrix} + \begin{pmatrix}u_1\\ 0\end{pmatrix}$$
$$y = X_1$$

- Map $c \circ q$ has same image as c and is 1-to-1

$$(q_{11}, q_{21}, q_{22}) \\ \mapsto (-(q_{11} + q_{22}), q_{11}q_{22} - q_{21}, -q_{22})$$

Motivation: Unidentifiable models

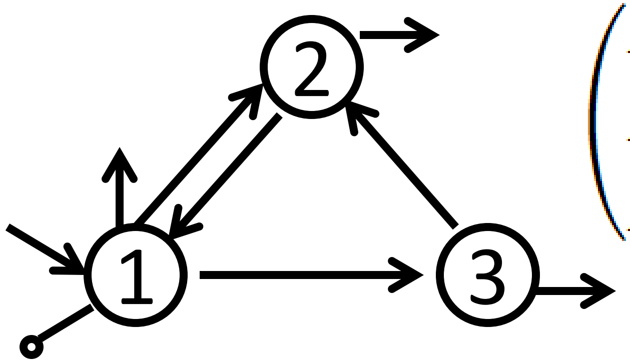
- Model 1: **No** ID scaling reparametrization!



$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{pmatrix} = \begin{pmatrix} a_{11} & a_{12} & 0 \\ 0 & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} + \begin{pmatrix} u_1 \\ 0 \\ 0 \end{pmatrix}$$

$$y = x_1$$

- Model 2: ID scaling reparametrization:



$$\begin{pmatrix} \dot{X}_1 \\ \dot{X}_2 \\ \dot{X}_3 \end{pmatrix} = \begin{pmatrix} a_{11} & 1 & 0 \\ a_{12}a_{21} & a_{22} & 1 \\ a_{12}a_{31}a_{23} & 0 & a_{33} \end{pmatrix} \begin{pmatrix} X_1 \\ X_2 \\ X_3 \end{pmatrix} + \begin{pmatrix} u_1 \\ 0 \\ 0 \end{pmatrix}$$

$$y = X_1$$

Main question:

Which graphs with $\leq 2n-2$ edges admit an identifiable scaling reparametrization?

Main result[1] :

<u>Let G be a strongly connected graph. Then TFAE:</u>

The model has an identifiable scaling reparametrization

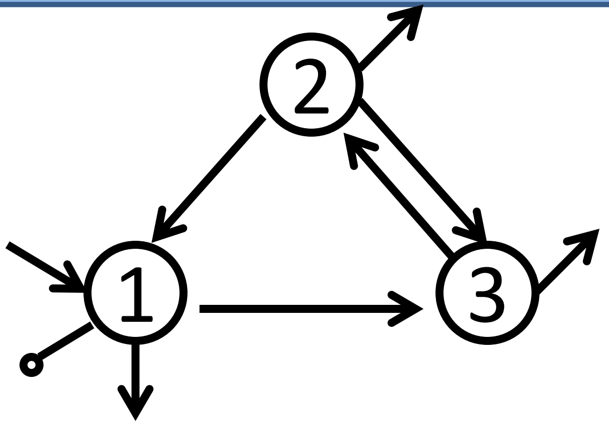
$\Leftrightarrow$ The model has an identifiable scaling reparametrization by monomial functions of the original parameters

$\Leftrightarrow$ All the monomial cycles in G are identifiable functions

$\Leftrightarrow$ $\mathit{dim\ im\ c} = m+1$

[1] N. Meshkat and S. Sullivant, Identifiable reparametrizations of linear compartment models, Journal of Symbolic Computation 63 (2014) 46-67.

Non-Example: Model 1



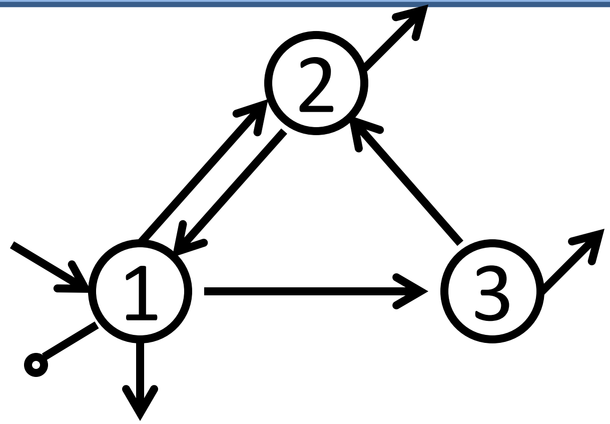
Model:

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{pmatrix} = \begin{pmatrix} a_{11} & a_{12} & 0 \\ 0 & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} + \begin{pmatrix} u_1 \\ 0 \\ 0 \end{pmatrix}$$

$$y = x_1$$

dim im c = 4, so no ID scaling reparametrization!

Example: Model 2



Model:

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{pmatrix} = \begin{pmatrix} a_{11} & a_{12} & 0 \\ a_{21} & a_{22} & a_{23} \\ a_{31} & 0 & a_{33} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} + \begin{pmatrix} u_1 \\ 0 \\ 0 \end{pmatrix}$$

$$y = x_1$$

Identifiable cycles: $a_{11},\ a_{22},\ a_{33},\ a_{12}a_{21},\ a_{12}a_{31}a_{23}$

Algorithm to find identifiable reparametrization

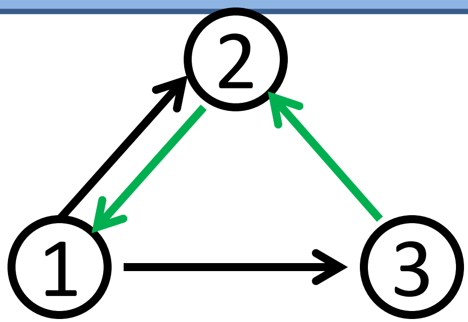
1) Form a spanning tree *T*
2) Form the directed incidence matrix *E(T)*:

$$E(T)_{i(j,k)} = \begin{cases} 1 & if\ i = j \\ -1 & if\ i = k \\ 0 & otherwise \end{cases}$$

3) Let *E* be *E(T)* with first row removed
4) Columns of E^{-1} are exponent vectors of monomials $f_i(A)$ in scaling $X_i = f_i(A)x_i$

Identifiable reparametrization

- Spanning tree



$$E(T) = \begin{pmatrix} -1 & 0 \\ 1 & -1 \\ 0 & 1 \end{pmatrix} \qquad E^{-1} = \begin{pmatrix} 1 & 1 \\ 0 & 1 \end{pmatrix}$$

- Rescaling:

$$X_1 = x_1 \qquad X_2 = a_{12}x_2 \qquad X_3 = a_{12}a_{23}x_3$$

- Identifiable scaling reparametrization

$$\begin{pmatrix} \dot{X}_1 \\ \dot{X}_2 \\ \dot{X}_3 \end{pmatrix} = \begin{pmatrix} a_{11} & 1 & 0 \\ a_{12}a_{21} & a_{22} & 1 \\ a_{12}a_{31}a_{23} & 0 & a_{33} \end{pmatrix} \begin{pmatrix} X_1 \\ X_2 \\ X_3 \end{pmatrix} + \begin{pmatrix} u_1 \\ 0 \\ 0 \end{pmatrix}$$

$$y = X_1$$

Main result

- A model with
  - I/O in first compartment
  - n leaks
  - Strongly connected graph G

  has an identifiable scaling reparametrization

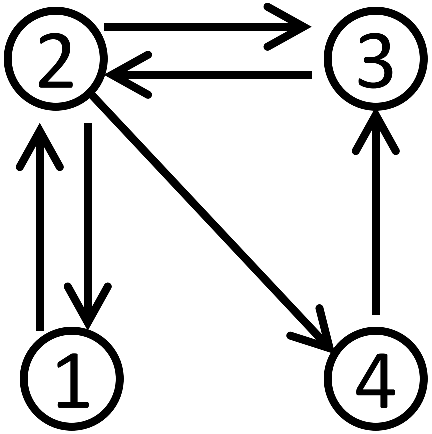
  $\Leftrightarrow$ all the monomial cycles are identifiable

  $\Leftrightarrow$ $\boxed{\mathit{dim}\ \mathit{im}\ c = m+1}$

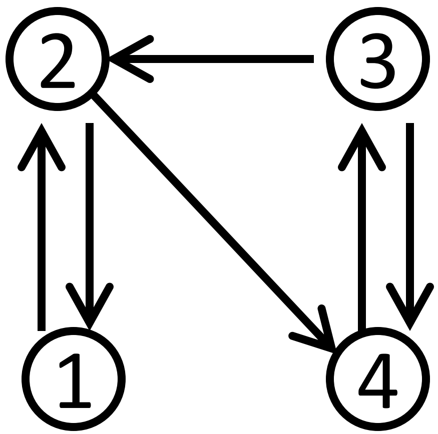
Which graphs have this property?

- Inductively strongly connected graphs when m=2n-2

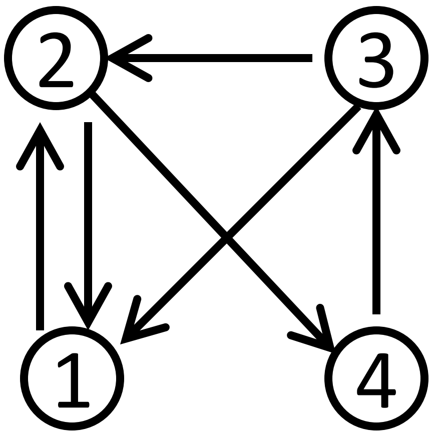
Good:



Bad:



- Not complete characterization:

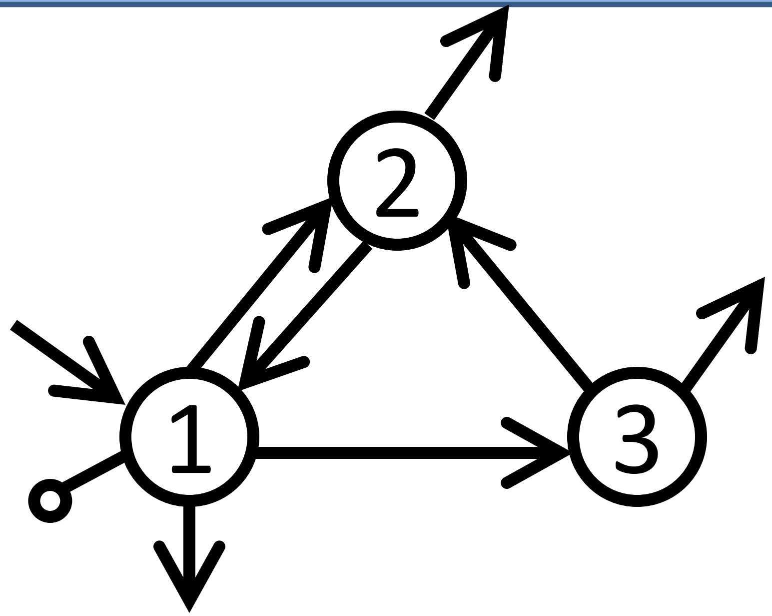


Unidentifiable Models

- Question 1: Can we always “reparametrize” an unidentifiable into an identifiable one?

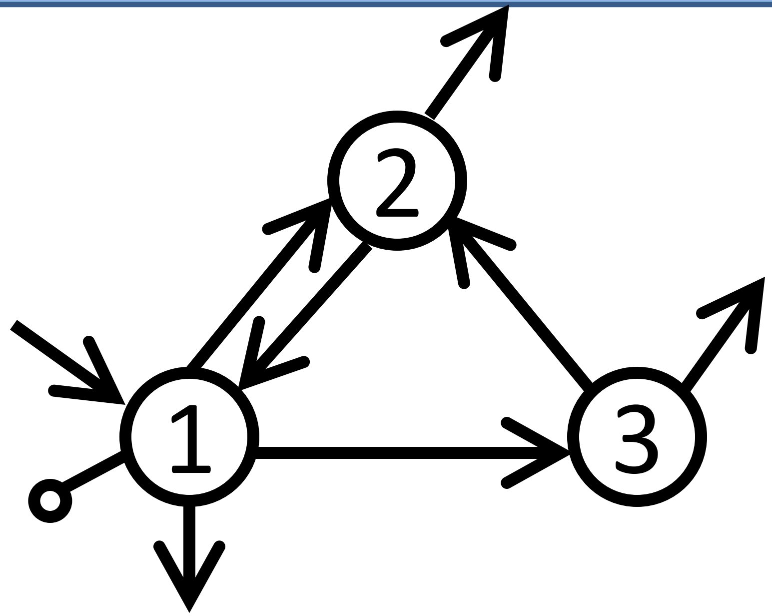
- Question 2: If a reparametrization exists, can we instead modify the original model to make it identifiable?

Model 2



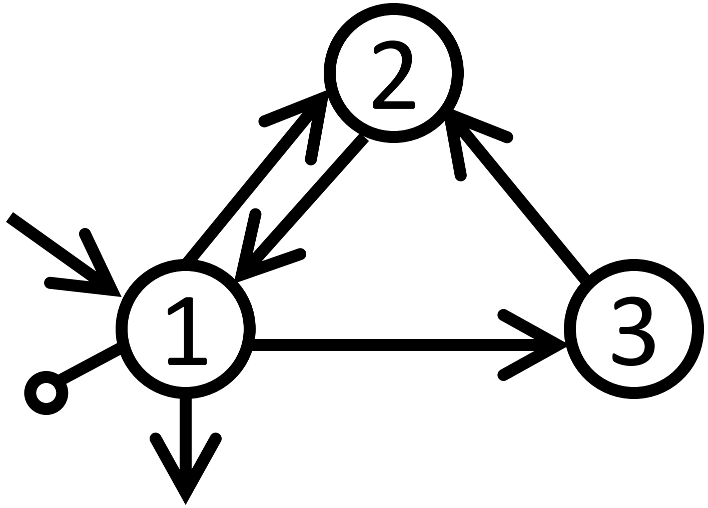
- Input/Output in compartment 1
- Leaks from every compartment
- *dim im c* = m+1 = 5
- Identifiable cycles $a_{11},\ a_{22},\ a_{33},\ a_{12}a_{21},\ a_{12}a_{31}a_{23}$

Obtaining Identifiability



- Starting with Model 2, how should we adjust model to obtain identifiability?
- Two options: Remove leaks or add input/output

Removing leaks



- Remove 2 leaks

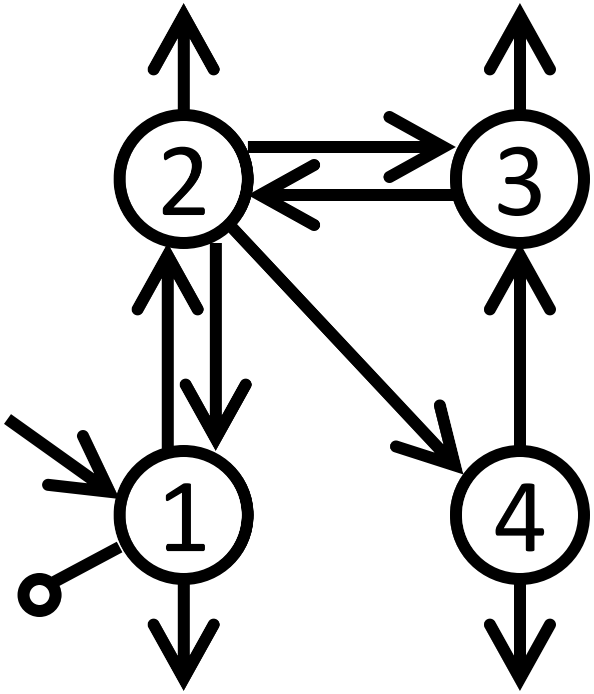
$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{pmatrix} = \begin{pmatrix} a_{11} & a_{12} & 0 \\ a_{21} & -a_{12} & a_{23} \\ a_{31} & 0 & -a_{23} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} + \begin{pmatrix} u_1 \\ 0 \\ 0 \end{pmatrix}$$

$$y = x_1$$

- *dim im c* = 5

Theorem on Removing leaks [2]

- Starting with a model with:
  - I/O in first compartment
  - n leaks
  - Strongly connected graph G
  - *dim im c* = m+1
- Remove n-1 leaks $\Longrightarrow$ Local identifiability
- Ex:



[2] N. Meshkat, S. Sullivant, and M. Eisenberg, Identifiability results for several classes of linear compartment models, In preparation.

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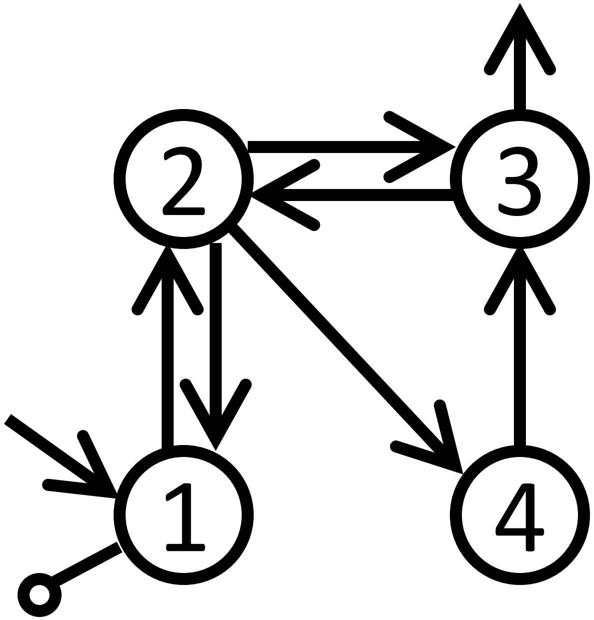
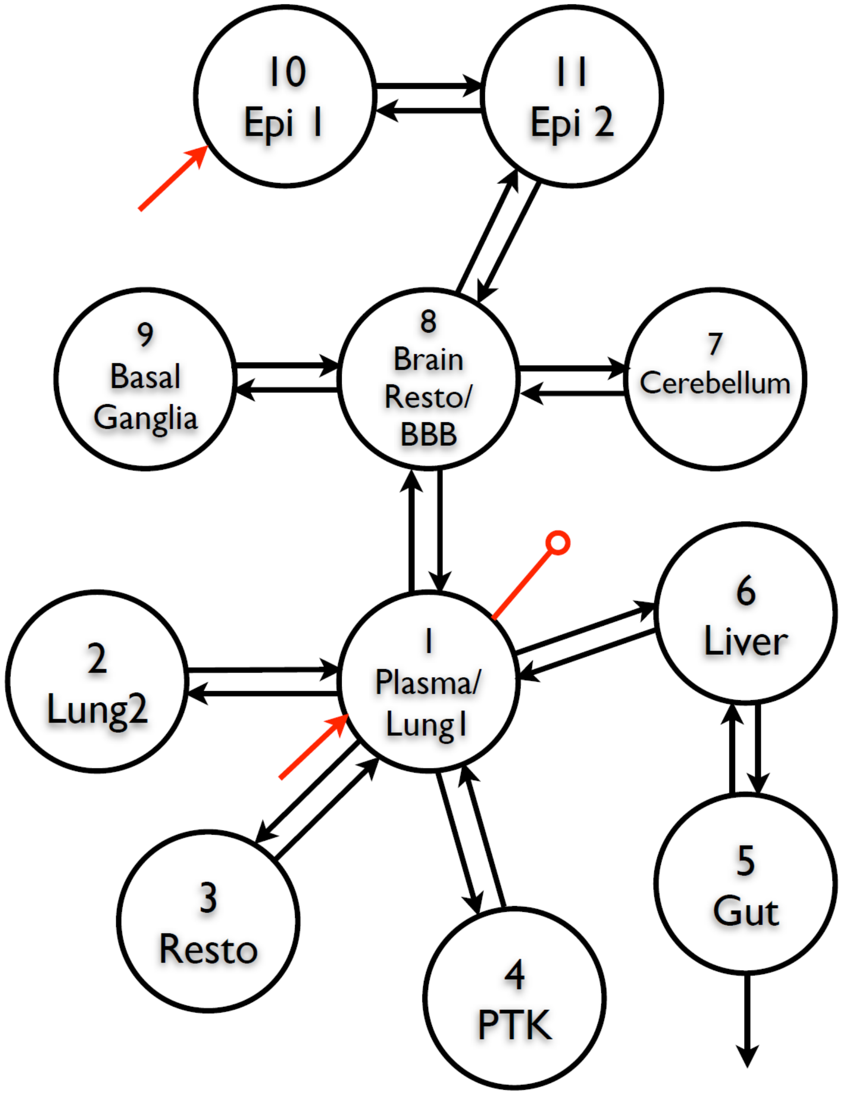


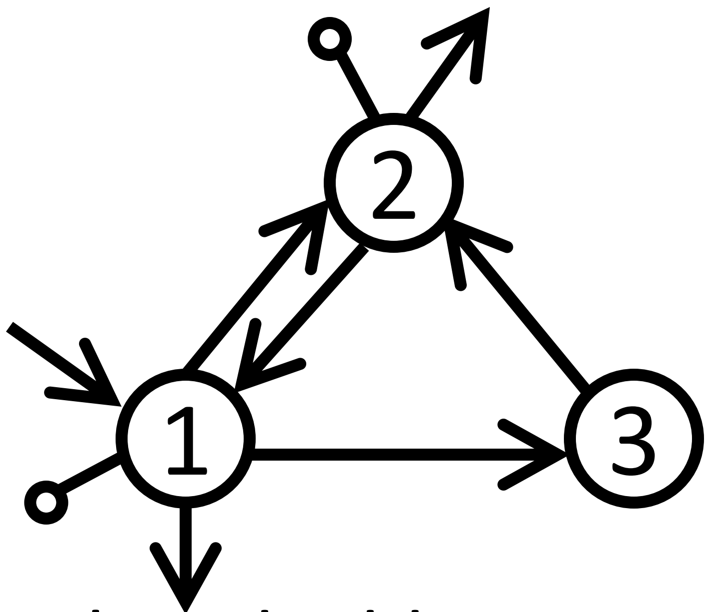
[2] N. Meshkat, S. Sullivant, and M. Eisenberg, Identifiability results for several classes of linear compartment models, In preparation.

Example: Manganese Model [3]



[3] P. K. Douglas, M. S. Cohen, and J. J. DiStefano III, Chronic exposure to Mn inhalation may have lasting effects: A physiologically-based toxico-kinetic model in rats, Toxicology and Environmental Chemistry 92 (2) (2010) 279-299.

Adding output to leak compartment



- Remove 1 leak and add 1 output to leak compartment

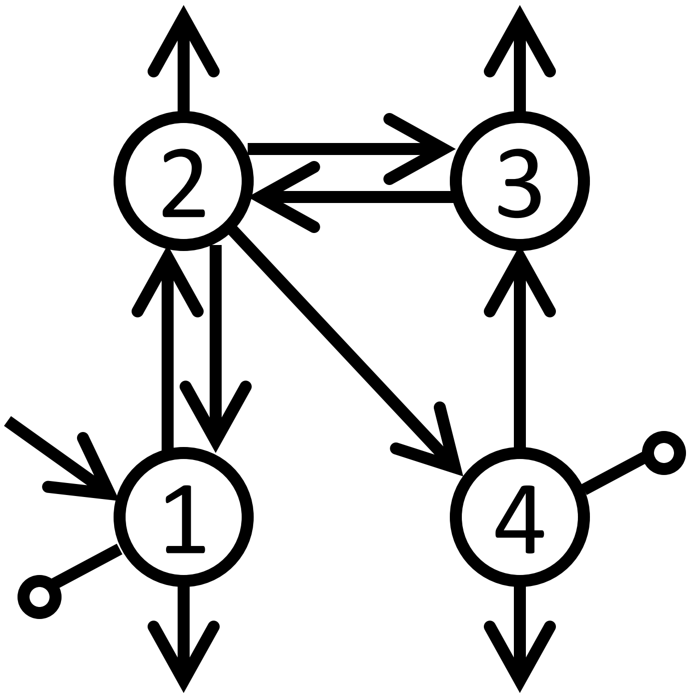
$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{pmatrix} = \begin{pmatrix} a_{11} & a_{12} & 0 \\ a_{21} & a_{22} & a_{23} \\ a_{31} & 0 & -a_{23} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} + \begin{pmatrix} u_1 \\ 0 \\ 0 \end{pmatrix}$$

$$y_1 = x_1$$
$$y_2 = x_2$$

- *dim im c* = 6

Thm: Removing leaks and adding inputs/outputs

- Starting with a model with:
  - I/O in first compartment
  - n leaks
  - Strongly connected graph G
  - *dim im c* = m+1
- Remove a subset of leaks so that every leak compartment has either input or output $\Longrightarrow$ Local identifiability
- Ex:



Thm: Removing leaks and adding inputs/outputs

- Starting with a model with:
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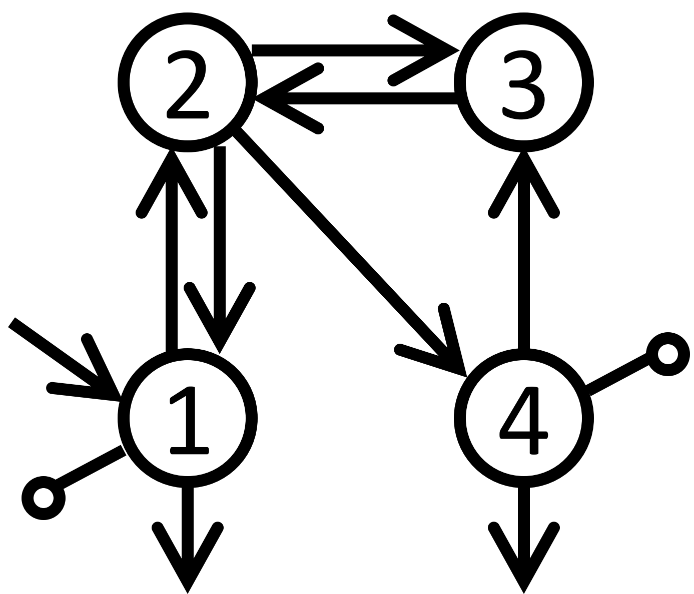
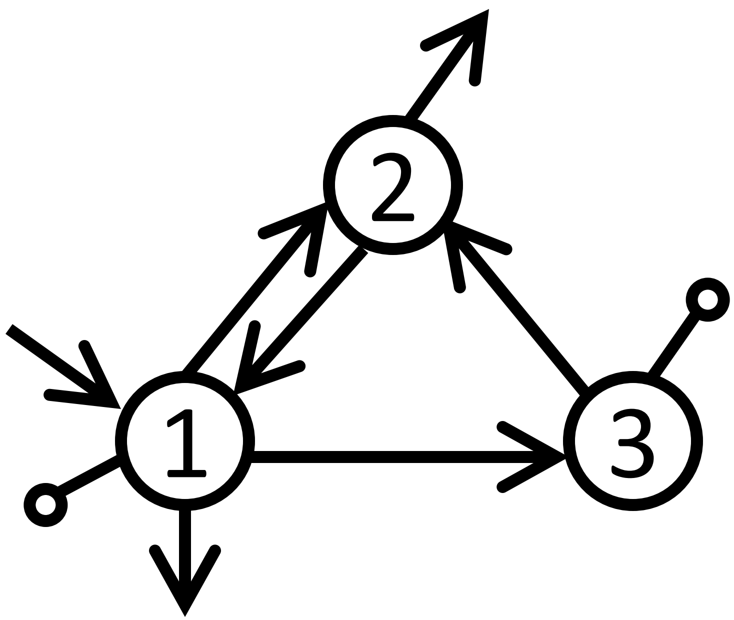


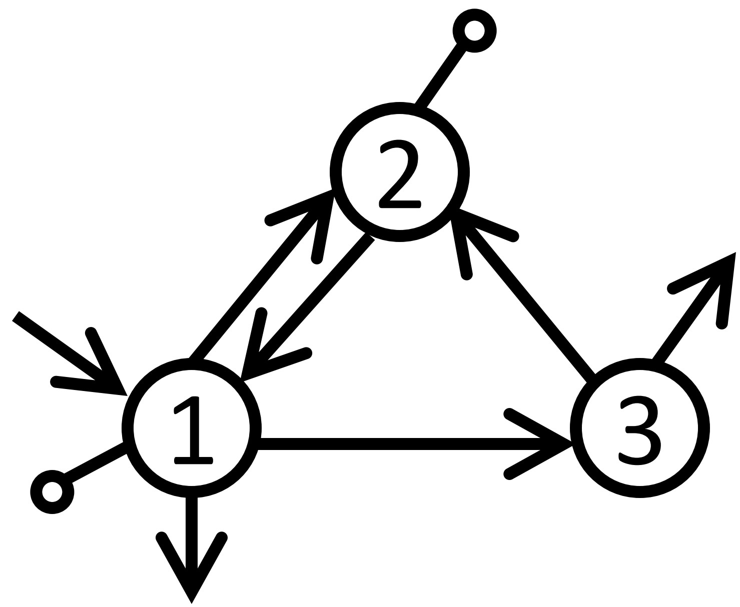
Sufficient, not necessary

- Harder to find *general* conditions if I/O not in leak compartment

Identifiable

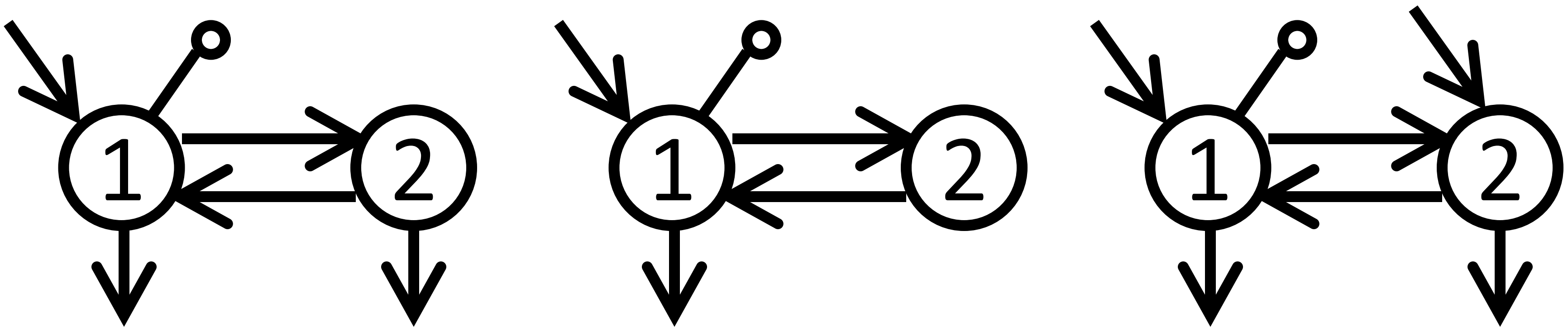


Not identifiable



Quiz!

- Which of the following models are identifiable?



(A) (B) (C)

- Answer: B and C

Identifiability Problem for Nonlinear Models

- What is our model is nonlinear?
- Same process:
  - Find I/O equations
  - Test injectivity of coefficient map

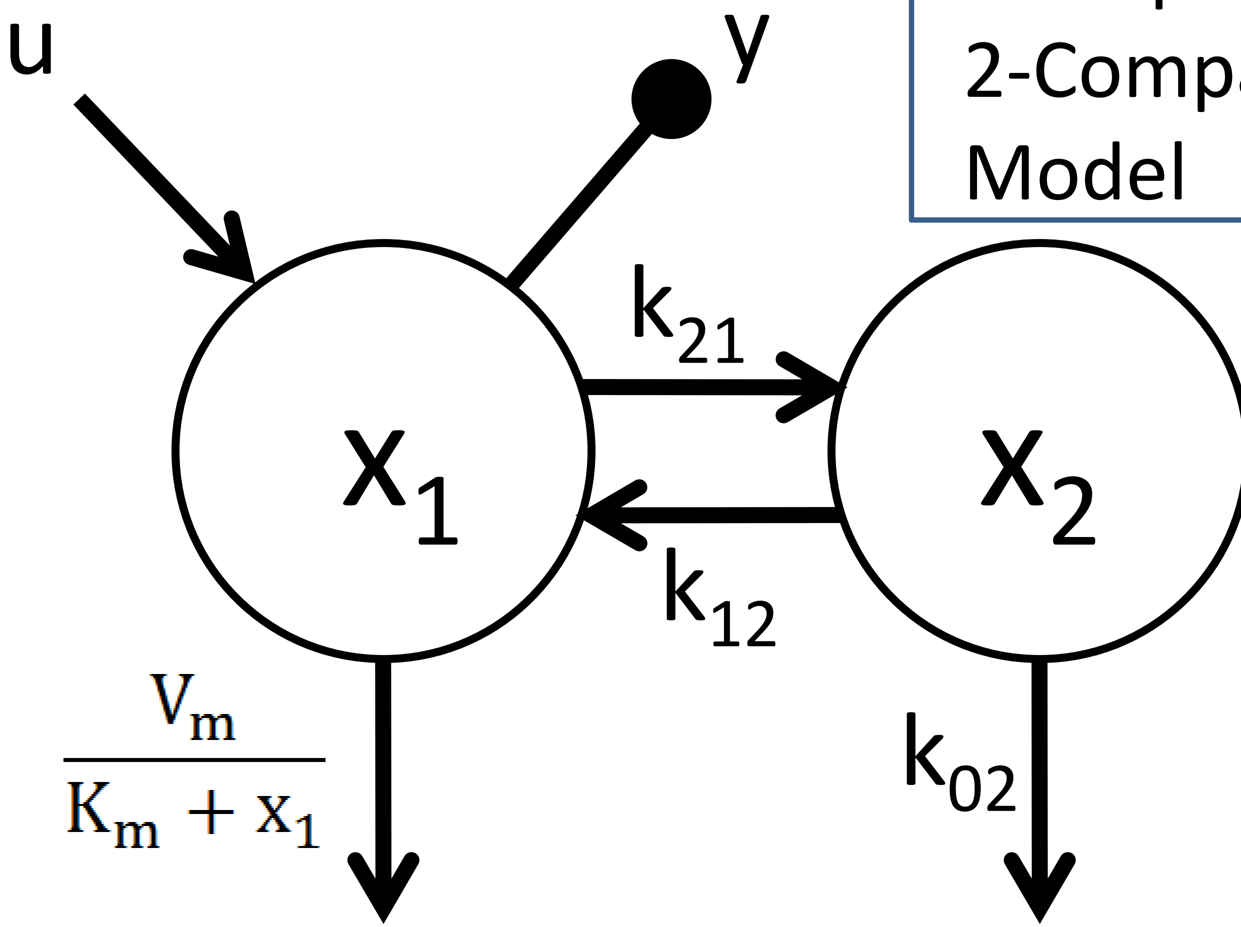
$$\boxed{F_j(u, \dot{u}, \ddot{u}, \dots, y, \dot{y}, \ddot{y}, \dots, p) = 0}$$

Identifiability Problem for Nonlinear Models

- What is our model is nonlinear?
- Same process:
  - Find I/O equations
  - Test injectivity of coefficient map

$$\sum_i c_{ji}(p)\psi_{ji}(u, \dot{u}, \ddot{u}, \ldots, y, \dot{y}, \ddot{y}, \ldots) = 0$$

Example: Nonlinear 2-Compartment Model



$$\dot{x}_1 = -\left(k_{21} + \frac{V_M}{K_M + x_1}\right)x_1 + k_{12}x_2 + u$$

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

$$y = x_1$$

Nonlinear 2-compartment model

- I/O eqn

$$
\begin{aligned}
-K_M^2\dot{u} - 2K_M\dot{u}y - \dot{u}y^2 + K_M^2\ddot{y} + 2K_M\ddot{y}y + \ddot{y}y^2& \\
+ (k_{02}K_M^2 + k_{12}K_M^2 + k_{21}K_M^2 + K_MV_M)\dot{y}& \\
+ (2k_{02}K_M + 2k_{12}K_M + 2k_{21}K_M)\dot{y}y& \\
+ (k_{02} + k_{12} + k_{21})\dot{y}y^2 - (k_{02}K_M^2 + k_{12}K_M^2)u& \\
- (2k_{02}K_M + 2k_{12}K_M)uy - (k_{02} + k_{12})uy^2& \\
+ (k_{02}k_{21}K_M^2 + k_{02}K_MV_M + k_{12}K_MV_M)y& \\
+ (2k_{02}k_{21}K_M + k_{02}V_M + k_{12}V_M)y^2 + k_{02}k_{21}y^3& \\
= 0&
\end{aligned}
$$

Nonlinear 2-compartment model

- I/O eqn

$$
\begin{aligned}
-K_M^2\dot{u} - 2K_M\dot{u}y - \dot{u}y^2 + K_M^2\ddot{y} + 2K_M\ddot{y}y + \ddot{y}y^2 \\
&+ (k_{02}K_M^2 + k_{12}K_M^2 + k_{21}K_M^2 + K_MV_M)\dot{y} \\
&+ (2k_{02}K_M + 2k_{12}K_M + 2k_{21}K_M)\dot{y}y \\
&+ (k_{02} + k_{12} + k_{21})\dot{y}y^2 - (k_{02}K_M^2 + k_{12}K_M^2)u \\
&- (2k_{02}K_M + 2k_{12}K_M)uy - (k_{02} + k_{12})uy^2 \\
&+ (k_{02}k_{21}K_M^2 + k_{02}K_MV_M + k_{12}K_MV_M)y \\
&+ (2k_{02}k_{21}K_M + k_{02}V_M + k_{12}V_M)y^2 + k_{02}k_{21}y^3 \\
&= 0
\end{aligned}
$$

- Globally identifiable

Nonlinear 2-compartment model

- I/O eqn

$$
\begin{aligned}
&-K_M^2\dot{u} - 2K_M\dot{u}y - \dot{u}y^2 + K_M^2\ddot{y} + 2K_M\ddot{y}y + \ddot{y}y^2 \\
&\quad + (k_{02}K_M^2 + k_{12}K_M^2 + k_{21}K_M^2 + K_MV_M)\dot{y} \\
&\quad + (2k_{02}K_M + 2k_{12}K_M + 2k_{21}K_M)\dot{y}y \\
&\quad + (k_{02} + k_{12} + k_{21})\dot{y}y^2 - (k_{02}K_M^2 + k_{12}K_M^2)u \\
&\quad - (2k_{02}K_M + 2k_{12}K_M)uy - (k_{02} + k_{12})uy^2 \\
&\quad + (k_{02}k_{21}K_M^2 + k_{02}K_MV_M + k_{12}K_MV_M)y \\
&\quad + (2k_{02}k_{21}K_M + k_{02}V_M + k_{12}V_M)y^2 + k_{02}k_{21}y^3 \\
&\quad = 0
\end{aligned}
$$

- Globally identifiable

Nonlinear 2-compartment model

- I/O eqn

$$
\begin{aligned}
-K_M^2\dot{u} - 2K_M\dot{u}y - \dot{u}y^2 + K_M^2\ddot{y} + 2K_M\ddot{y}y + \ddot{y}y^2 \\
+ (k_{02}K_M^2 + k_{12}K_M^2 + k_{21}K_M^2 + K_M V_M)\dot{y} \\
+ (2k_{02}K_M + 2k_{12}K_M + 2k_{21}K_M)\dot{y}y \\
+ ({\color{blue}k_{02} + k_{12}} {\color{red}+ k_{21}})\dot{y}y^2 - (k_{02}K_M^2 + k_{12}K_M^2)u \\
- (2k_{02}K_M + 2k_{12}K_M)uy - ({\color{blue}k_{02} + k_{12}})uy^2 \\
+ (k_{02}k_{21}K_M^2 + k_{02}K_M V_M + k_{12}K_M V_M)y \\
+ (2k_{02}k_{21}K_M + k_{02}V_M + k_{12}V_M)y^2 + k_{02}k_{21}y^3 \\
= 0
\end{aligned}
$$

- Globally identifiable

Nonlinear 2-compartment model

- I/O eqn

$$\begin{aligned}
-K_M^2\dot{u} - 2K_M\dot{u}y - \dot{u}y^2 + K_M^2\ddot{y} + 2K_M\ddot{y}y + \ddot{y}y^2 \\
+ (k_{02}K_M^2 + k_{12}K_M^2 + k_{21}K_M^2 + K_M V_M)\dot{y} \\
+ (2k_{02}K_M + 2k_{12}K_M + 2k_{21}K_M)\dot{y}y \\
+ (k_{02} + k_{12} + k_{21})\dot{y}y^2 - (k_{02}K_M^2 + k_{12}K_M^2)u \\
- (2k_{02}K_M + 2k_{12}K_M)uy - (k_{02} + k_{12})uy^2 \\
+ (k_{02}k_{21}K_M^2 + k_{02}K_M V_M + k_{12}K_M V_M)y \\
+ (2k_{02}k_{21}K_M + k_{02}V_M + k_{12}V_M)y^2 + k_{02}k_{21}y^3 \\
= 0
\end{aligned}$$

- Globally identifiable

Nonlinear 2-compartment model

- I/O eqn

$$
\begin{aligned}
-K_M^2\dot{u} - 2K_M\dot{u}y - \dot{u}y^2 + K_M^2\ddot{y} + 2K_M\ddot{y}y + \ddot{y}y^2 \\
&+ (k_{02}K_M^2 + k_{12}K_M^2 + k_{21}K_M^2 + K_MV_M)\dot{y} \\
&+ (2k_{02}K_M + 2k_{12}K_M + 2k_{21}K_M)\dot{y}y \\
&+ (k_{02} + k_{12} + k_{21})\dot{y}y^2 - (k_{02}K_M^2 + k_{12}K_M^2)u \\
&- (2k_{02}K_M + 2k_{12}K_M)uy - (k_{02} + k_{12})uy^2 \\
&+ (k_{02}k_{21}K_M^2 + k_{02}K_MV_M + k_{12}K_MV_M)y \\
&+ (2k_{02}k_{21}K_M + k_{02}V_M + k_{12}V_M)y^2 + k_{02}k_{21}y^3 \\
&= 0
\end{aligned}
$$

- Globally identifiable

Nonlinear 2-compartment model

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$$
\begin{aligned}
-K_M^2\dot{u} - 2K_M\dot{u}y - \dot{u}y^2 + K_M^2\ddot{y} + 2K_M\ddot{y}y + \ddot{y}y^2 \\
&+ (k_{02}K_M^2 + k_{12}K_M^2 + k_{21}K_M^2 + K_M V_M)\dot{y} \\
&+ (2k_{02}K_M + 2k_{12}K_M + 2k_{21}K_M)\dot{y}y \\
&+ (k_{02} + k_{12} + k_{21})\dot{y}y^2 - (k_{02}K_M^2 + k_{12}K_M^2)u \\
&- (2k_{02}K_M + 2k_{12}K_M)uy - (k_{02} + k_{12})uy^2 \\
&+ (k_{02}k_{21}K_M^2 + k_{02}K_M V_M + k_{12}K_M V_M)y \\
&+ (2k_{02}k_{21}K_M + k_{02}V_M + k_{12}V_M)y^2 + k_{02}k_{21}y^3 \\
&= 0
\end{aligned}
$$

- Globally identifiable

Differential algebra

- How to find I/O equations for nonlinear models?
- Differential elimination
  - Differentiation + Gröbner Basis
  - Differential Gröbner Basis
    - Rosenfeld-Gröbner in Maple
  - Ritt’s pseudo-division

Example on Lotka-Volterra

- Equations:

$$\dot{x}_1 = ax_1 - bx_1x_2$$
$$\dot{x}_2 = -cx_2 + dx_1x_2$$
$$y = x_1$$

- Commands in Maple:

$with(DifferentialAlgebra)$

$sys := [-diff(x1(t), t) + a \cdot x1(t) - b \cdot x1(t) \cdot x2(t), -diff(x2(t), t) + d \cdot x1(t) \cdot x2(t) - c \cdot x2(t), y(t) - x1(t)]$

$R := DifferentialRing(blocks = [x1, x2, y], derivations = [t])$

$G := RosenfeldGroebner(sys, R)$

Example on Lotka-Volterra

- Equations:

$$\dot{x}_1 = ax_1 - bx_1x_2$$
$$\dot{x}_2 = -cx_2 + dx_1x_2$$
$$y = x_1$$

- Rosenfeld-Gröbner gives:

$$\left[x1(t) = y(t), x2(t) = -\frac{\frac{\mathrm{d}}{\mathrm{d}t} y(t) - y(t)\, a}{y(t)\, b}, \frac{\mathrm{d}^2}{\mathrm{d}t^2} y(t) = \frac{1}{y(t)} \left(\left(\frac{\mathrm{d}}{\mathrm{d}t} y(t) \right)^2 + \left(\frac{\mathrm{d}}{\mathrm{d}t} y(t) \right) y(t)^2\, d - \left(\frac{\mathrm{d}}{\mathrm{d}t} y(t) \right) y(t)\, c - y(t)^3\, a\, d + y(t)^2\, a\, c \right) \right]$$

Example: Nonlinear HIV Model [4]

- Model equations:

$$\dot{x}_1 = -bx_1x_4 - dx_1 + s$$

$$\dot{x}_2 = bq_1x_1x_4 - k_1x_2 - m_1x_2$$

$$\dot{x}_3 = bq_2x_1x_4 + k_1x_2 - m_2x_3$$

$$\dot{x}_4 = -cx_4 + k_2x_3$$

$$y_1 = x_1$$

$$y_2 = x_4$$

- Parameter vector:

$$\boldsymbol{p} = \{b, d, s, m_2, c, m_1, k_1, q_1, k_2, q_2\}$$

[4] X. Xia and C. H. Moog, Identifiability of nonlinear systems with application to HIV/AIDS models, *IEEE Trans Autom Contr* 48 (2003), 330-336.

Input-Output equations

- Rosenfeld-Gröbner gives two equations:

$$\dot{y}_1 + by_1y_2 + dy_1 - s = 0$$

$$\dddot{y}_2 + (c + k_1 + m_1 + m_2)\ddot{y}_2 - bq_2k_2\dot{y}_2y_1 +$$
$$(ck_1 + cm_1 + cm_2 + k_1m_2 + m_1m_2)\dot{y}_2 +$$
$$b^2q_2k_2y_1y_2^2 + bk_2(dq_2 - k_1q_1 - k_1q_2 - m_1q_2)y_1y_2 +$$
$$(-bq_2k_2s + ck_1m_2 + cm_1m_2)y_2 = 0$$

- Coefficient map $c: \mathbb{R}^{10} \to \mathbb{R}^9$
  - Unidentifiable!

How to find identifiable functions?

- Injectivity test: If $\boldsymbol{c}(\boldsymbol{p}) = \boldsymbol{c}(\boldsymbol{p}^*)$, does $\boldsymbol{p} = \boldsymbol{p}^*$?
- Amounts to solving a system of polynomial equations
- Find Gröbner Basis of $\boldsymbol{c}(\boldsymbol{p}) - \boldsymbol{c}(\boldsymbol{p}^*) = \boldsymbol{0}$
  – Gives system of equations $\boldsymbol{c}(\boldsymbol{p}) = \boldsymbol{c}(\boldsymbol{p}^*)$ in "triangular form"
    - Analogous to Gaussian elimination for systems of linear equations
  – Must give an "ordering" of parameters to do the elimination

Example of Gröbner Basis

- Set up $\boldsymbol{c}(\boldsymbol{p}) - \boldsymbol{c}(\boldsymbol{p}^*)$, for

$$\boldsymbol{p} = \{m_1, k_1, m_2, q_1, k_2, q_2, b, d, s, c\} \qquad \boldsymbol{p}^* = \{\zeta, \eta, \delta, \theta, \rho, \kappa, \alpha, \lambda, \gamma, \epsilon\}$$

$$\begin{pmatrix} b - \alpha \\ d - \lambda \\ -s + \gamma \\ -b\, k2\, q2 + \alpha\, \kappa\, \rho \\ b^2\, k2\, q2 - \alpha^2\, \kappa\, \rho \\ c\, k1\, m2 + c\, m1\, m2 - b\, k2\, q2\, s - \delta\, \epsilon\, \zeta - \delta\, \epsilon\, \eta + \alpha\, \gamma\, \kappa\, \rho \\ c + k1 + m1 + m2 - \delta - \epsilon - \zeta - \eta \\ -b\, k1\, k2\, q1 + b\, d\, k2\, q2 - b\, k1\, k2\, q2 - b\, k2\, m1\, q2 + \alpha\, \eta\, \theta\, \rho + \alpha\, \zeta\, \kappa\, \rho + \alpha\, \eta\, \kappa\, \rho - \alpha\, \kappa\, \lambda\, \rho \\ c\, k1 + c\, m1 + c\, m2 + k1\, m2 + m1\, m2 - \delta\, \epsilon - \delta\, \zeta - \epsilon\, \zeta - \delta\, \eta - \epsilon\, \eta \end{pmatrix}$$

- Gröbner basis for $\boldsymbol{p} = \{m_1, k_1, m_2, q_1, k_2, q_2, b, d, s, c\}$

$$\begin{pmatrix} -(c - \delta)\, (c - \epsilon)\, (c - \zeta - \eta) \\ -s + \gamma \\ d - \lambda \\ b - \alpha \\ -\alpha\, (k2\, q2 - \kappa\, \rho) \\ -c^2 - c\, m2 - m2^2 + c\, \delta + m2\, \delta + c\, \epsilon + m2\, \epsilon - \delta\, \epsilon + c\, \zeta + m2\, \zeta - \delta\, \zeta - \epsilon\, \zeta + c\, \eta + m2\, \eta - \delta\, \eta - \epsilon\, \eta \\ -\alpha\, (q2\, \eta\, \theta - k1\, q1\, \kappa + c\, q2\, \kappa + m2\, q2\, \kappa - q2\, \delta\, \kappa - q2\, \epsilon\, \kappa)\, \rho \\ \alpha\, (k1\, k2\, q1 - \eta\, \theta\, \rho - c\, \kappa\, \rho - m2\, \kappa\, \rho + \delta\, \kappa\, \rho + \epsilon\, \kappa\, \rho) \\ c + k1 + m1 + m2 - \delta - \epsilon - \zeta - \eta \end{pmatrix}$$

Algorithm [5]

- Find Gröbner Bases of $\boldsymbol{c}(\boldsymbol{p}) - \boldsymbol{c}(\boldsymbol{p}^*)$ for different orderings of the parameter vector $\boldsymbol{p}$
- Look for elements of the form $f(\boldsymbol{p}) - f(\boldsymbol{p}^*)$ in Gröbner Basis
- Implies $f(\boldsymbol{p})$ is identifiable
- Must find *N* identifiable functions in order to reparametrize, where *N = dim im c*

[5] N. Meshkat, M. Eisenberg, and J. J DiStefano III, An algorithm for finding globally identifiable parameter combinations of nonlinear ODE models using Groebner Bases, *Math. Biosci.* 222 (2009)

Examine Gröbner Bases

$$\boldsymbol{p} = \{m_1, k_1, m_2, q_1, k_2, q_2, b, d, s, c\}$$

$$\begin{pmatrix}
-(c-\delta)\,(c-\epsilon)\,(c-\zeta-\eta) \\
-s+\gamma \\
d-\lambda \\
b-\alpha \\
-\alpha\,(k2\,q2-\kappa\,\rho) \\
-c^2 - c\,m2 - m2^2 + c\,\delta + m2\,\delta + c\,\epsilon + m2\,\epsilon - \delta\,\epsilon + c\,\zeta + m2\,\zeta - \delta\,\zeta - \epsilon\,\zeta + c\,\eta + m2\,\eta - \delta\,\eta - \epsilon\,\eta \\
-\alpha\,(q2\,\eta\,\Theta - k1\,q1\,\kappa + c\,q2\,\kappa + m2\,q2\,\kappa - q2\,\delta\,\kappa - q2\,\epsilon\,\kappa)\,\rho \\
\alpha\,(k1\,k2\,q1 - \eta\,\Theta\,\rho - c\,\kappa\,\rho - m2\,\kappa\,\rho + \delta\,\kappa\,\rho + \epsilon\,\kappa\,\rho) \\
c + k1 + m1 + m2 - \delta - \epsilon - \zeta - \eta
\end{pmatrix}$$

$$\boldsymbol{p} = \{m_2, q_1, k_2, q_2, b, d, s, c, m_1, k_1\}$$

$$\begin{pmatrix}
(k1+m1-\delta)\,(k1+m1-\epsilon)\,(k1+m1-\zeta-\eta) \\
-c^2 - c\,k1 - k1^2 - c\,m1 - 2\,k1\,m1 - m1^2 + c\,\delta + k1\,\delta + m1\,\delta + c\,\epsilon + k1\,\epsilon + m1\,\epsilon - \delta\,\epsilon + c\,\zeta + k1\,\zeta + m1\,\zeta - \delta\,\zeta - \epsilon\,\zeta + c\,\eta + k1\,\eta + m1\,\eta - \delta\,\eta - \epsilon\,\eta \\
-s+\gamma \\
d-\lambda \\
b-\alpha \\
-\alpha\,(k2\,q2-\kappa\,\rho) \\
-\alpha\,(q2\,\eta\,\Theta - k1\,q1\,\kappa - k1\,q2\,\kappa - m1\,q2\,\kappa + q2\,\zeta\,\kappa + q2\,\eta\,\kappa)\,\rho \\
\alpha\,(k1\,k2\,q1 - \eta\,\Theta\,\rho + k1\,\kappa\,\rho + m1\,\kappa\,\rho - \zeta\,\kappa\,\rho - \eta\,\kappa\,\rho) \\
c + k1 + m1 + m2 - \delta - \epsilon - \zeta - \eta
\end{pmatrix}$$

$$\boldsymbol{p} = \{q_1, k_2, q_2, b, d, s, c, m_1, k_1, m_2\}$$

$$\begin{pmatrix}
-(m2-\delta)\,(m2-\epsilon)\,(m2-\zeta-\eta) \\
-k1^2 - 2\,k1\,m1 - m1^2 - k1\,m2 - m1\,m2 - m2^2 + k1\,\delta + m1\,\delta + m2\,\delta + k1\,\epsilon + m1\,\epsilon + m2\,\epsilon - \delta\,\epsilon + k1\,\zeta + m1\,\zeta + m2\,\zeta - \delta\,\zeta - \epsilon\,\zeta + k1\,\eta + m1\,\eta + m2\,\eta - \delta\,\eta - \epsilon\,\eta \\
c + k1 + m1 + m2 - \delta - \epsilon - \zeta - \eta \\
-s+\gamma \\
d-\lambda \\
b-\alpha \\
-\alpha\,(k2\,q2-\kappa\,\rho) \\
-\alpha\,(q2\,\eta\,\Theta - k1\,q1\,\kappa - k1\,q2\,\kappa - m1\,q2\,\kappa + q2\,\zeta\,\kappa + q2\,\eta\,\kappa)\,\rho \\
\alpha\,(k1\,k2\,q1 - \eta\,\Theta\,\rho + k1\,\kappa\,\rho + m1\,\kappa\,\rho - \zeta\,\kappa\,\rho - \eta\,\kappa\,\rho)
\end{pmatrix}$$

Identifiable Functions

- ID parameters: $\{c\,,s\,,d\,,b,\ m_2\}$
  - Globally identifiable (one solution)

    $$\{s\,,d\,,b\}$$

  - Locally identifiable (three solutions)

    $$\{c\ ,\ m_2\}$$

- ID parameter combinations: $\{q_2k_2\,,q_1k_1k_2\,,m_1+k_1\}$
  - Globally identifiable (one solution)

    $$\{q_2k_2\}$$

  - Locally identifiable (three solutions)

    $$\{q_1k_1k_2\,,m_1+k_1\}$$

Identifiable Reparametrization

- Identifiable: $\{c\,, s\,, d\,, b\,, q_2k_2\,, m_2\,, q_1k_1k_2\,, m_1 + k_1\}$
- Use scaling: $X_2 = k_1k_2x_2 \quad X_3 = \dfrac{x_3}{q_2}$

$$\dot{x}_1 = -bx_1x_4 - dx_1 + s$$

$$\dot{X}_2 = b(q_1k_1k_2)x_1x_4 - (m_1 + k_1)X_2$$

$$\dot{X}_3 = bx_1x_4 + \frac{X_2}{q_2k_2} - m_2X_3$$

$$\dot{x}_4 = -cx_4 + q_2k_2X_3$$

$$y_1 = x_1$$

$$y_2 = x_4$$

Implementation: COMBOS

- Collaboration with Christine Kuo, Joe DiStefano III (UCLA)
- Finds identifiable combinations for unidentifiable models
- http://biocyb1.cs.ucla.edu/combos

Available software to test identifiability

- Differential Algebra Methods:
  - DAISY
    - Available online at http://www.dei.unipd.it/~pia
  - COMBOS
    - Soon available at http://biocyb1.cs.ucla.edu/combos
- Other methods:
  - GenSSI
    - Available online at http://www.iim.csic.es/~genssi/

Acknowledgements

- Collaborators:
  - Seth Sullivant (NCSU)
  - Marisa Eisenberg (Univ. of Michigan)
  - Joe DiStefano III (UCLA)
  - Christine Kuo (Harvard)

Summary

- Nec. and suff. for identifiable scaling reparam
- Suff. conditions for obtaining identifiability
- Algorithm to find identifiable functions in nonlinear models using Gröbner Bases
- COMBOS

Thank you for your attention!