Structural Identifiability of Biological Models

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Motivation: Unidentifiable models

- 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: 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:

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

$$y = X_1$$

Outline

- Identifiable reparametrizations of linear compartment models
  - Scaling reparametrizations
  - Necessary and sufficient conditions
- Finding identifiable functions, in general
  - Using Gröbner Bases
  - Linear algebra techniques

Structural Identifiability Analysis

- Model:
  - x state variable
  - u input
  - y output
  - p parameter

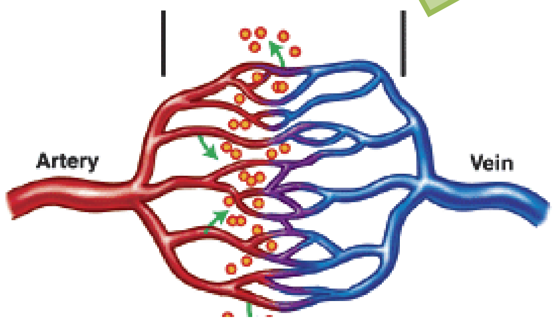
$$\dot{x}(t) = f(t, x(t), u(t), p)$$
$$y(t) = g(x(t), p)$$

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

Motivation: biological models

Drug input

Measured drug concentration

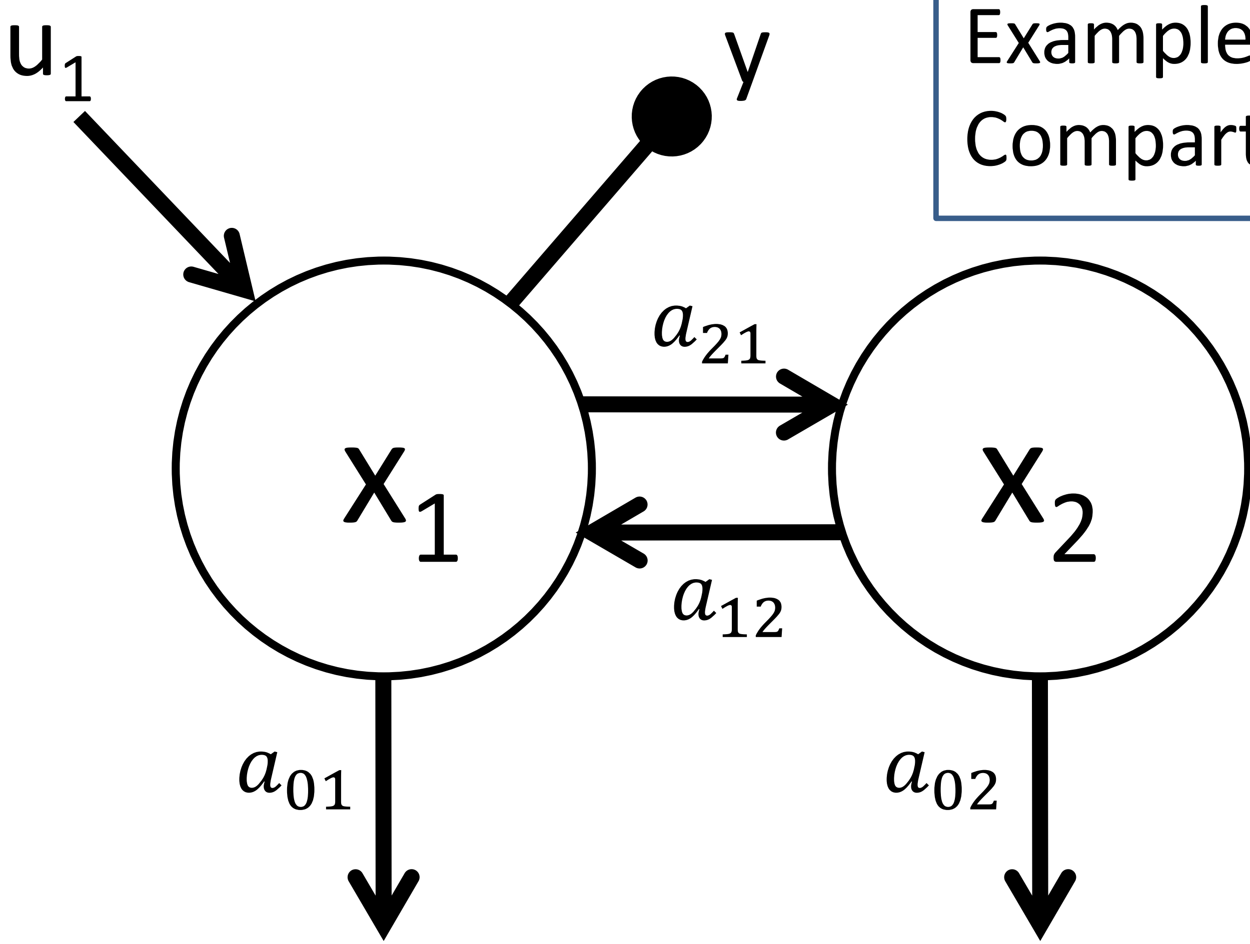


Drug exchange

Loss from blood

Loss from organ

Example: Linear 2-Compartment Model



Can we determine parameters $a_{01}, a_{02}, a_{12}, a_{21}$ from input-output data?

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

Linear Compartment Models

- Let $G = (V, E)$ be a directed graph with m edges and n vertices
- Model

$$\dot{x}(t) = A(G)x(t) + u(t)$$
$$y(t) = x_1(t)$$

- where $x \in \mathbb{R}^n$ is the state variable

  u is the input where $u = \begin{pmatrix} u_1 \\ 0 \\ \vdots \\ 0 \end{pmatrix}$

  y is the output

Assumption #1: Single input/output in first compartment

Linear Compartment Models

- Let $G = (V, E)$ be a directed graph with m edges and n vertices
- Model

$$\dot{x}(t) = A(G)x(t) + u(t)$$
$$y(t) = x_1(t)$$

- where $A(G)$ has the form:

$$A(G)_{ij} = \begin{cases} -a_{0i} - \sum_{k:\ i \to k \in E} a_{ki} & \text{if } i = j \\ a_{ij} & \text{if } j \to i \text{ is an edge of } G \\ 0 & \text{otherwise} \end{cases}$$

Assumption #2: Leaks from every compartment, so $a_{0i} \neq 0$ for all i

Linear Compartment Models

- Let $G = (V, E)$ be a directed graph with m edges and n vertices
- Model

$$\dot{x}(t) = A(G)x(t) + u(t)$$
$$y(t) = x_1(t)$$

- where $A(G)$ has the form:

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

Assumption #3: Strongly connected graph, with $m \leq 2n - 2$

Our class of models

- Assumptions:
  - I/O in first compartment
  - Leaks from every compartment
  - G strongly connected with at most $2n - 2$ edges

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

- Identifiability: Which parameters of model can be determined 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: $det(\partial I - A)\, y = det(\partial I - A_1)\, u_1$

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

Identifiability

- Can recover coefficients from data [Soderstrom & Stoica 1998]
- Identifiability: is it possible to recover the parameters of the original system, from the coefficients of I/O eqn? [Ljung & Glad 1994]
  - Two sets of parameter values yield same coefficient values?
  - Is coeff map 1-to-1?

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

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: globally identifiable

  finite-to-one: locally identifiable

  infinite-to-one: unidentifiable

- Concerned with *generic local identifiability*
  - Check dimension of image of coefficient map
    - If *dim im c = m+n,* then locally identifiable
    - If *dim im c* < *m+n*, then unidentifiable

Local identifiability vs. Unidentifiability

- Ex: 2-comp model

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

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

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

Jacobian has rank 3:

$\Rightarrow$ Unidentifiable!

$$\begin{pmatrix}-1 & 0 & 0 & -1\\ a_{22} & -a_{21} & -a_{12} & a_{11}\\ 0 & 0 & 0 & -1\end{pmatrix}$$

Unidentifiable models

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

  Ex: $a_{12} + a_{21}$ or $a_{12}a_{21}$

- A function $f: \mathbb{R}^{m+n} \to \mathbb{R}$ is called identifiable from *c* if $\mathbb{R}(f, c_1, \ldots, c_{2n-1})/\mathbb{R}(c_1, \ldots, c_{2n-1})$ is an algebraic field extension

Unidentifiable models

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

  Ex: $a_{12} + a_{21}$ or $a_{12}a_{21}$

- A function $f\colon \mathbb{R}^{m+n} \rightarrow \mathbb{R}$ is called identifiable from *c* if $f = \Phi(c)$

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:

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

- What do we do with identifiable functions?
- Any special meaning in original model?

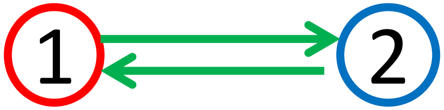
2-compartment model as graph

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}

Coeff map factors through cycles

- Coeff map *c* in terms of cycles of graph G

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

- Due to cyclic permutations in determinant (Leibniz formula)

$$\det(A) = \sum_{\sigma \epsilon S_n} sgn(\sigma) \prod_{i=1}^{n} a_{\sigma(i),i}$$

- Strongly connected?
- G is strongly connected: *m+1* independent cycles

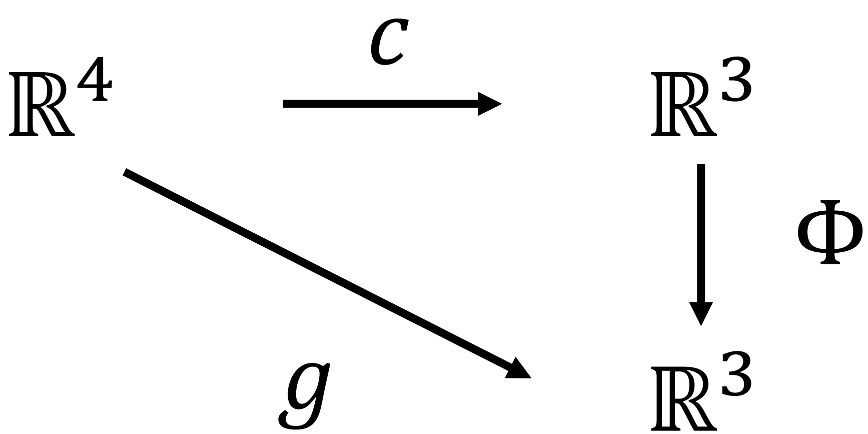
  (= *n* self-cycles + *m-n+1* cycles)

  Thus *dim im c* ≤ *m+1*

Why are cycles identifiable?

- Recall *dim im c = m+1 = 2+1 = 3*
- Let $g\colon \mathbb{R}^4 \to \mathbb{R}^3$ be the “cycle map”

  $(a_{11}, a_{22}, a_{12}, a_{21}) \longmapsto (a_{11}, a_{22}, a_{12}a_{21})$
- Commutative diagram:



Thus $g = \Phi(c)$

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. $-(a_{01} + a_{21}), -(a_{02} + a_{12}),\ a_{12}a_{21}$

- Reparametrize: 4 independent parameters $\rightarrow$ 3 independent parameters?

Identifiable reparametrization

Let $c\colon \mathbb{R}^{m+n} \to \mathbb{R}^{2n-1}$ be our coefficient map

An identifiable reparametrization of a model is a map $q\colon \mathbb{R}^{k} \to \mathbb{R}^{m+n}$ such that:

- $c \circ q\colon \mathbb{R}^{k} \to \mathbb{R}^{2n-1}$ 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

$$\frac{a_{ij} f_i(A)}{f_j(A)}$$

- Only graphs with at most 2n-2 edges

Identifiable scaling reparametrization

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

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

- 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

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

Identifiable scaling reparametrization

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

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

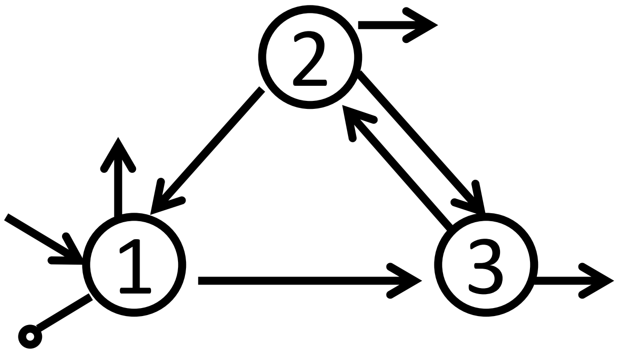
$$y = X_1$$

- Why useful?
  - Nondimensionalization of original model
  - New model: know qualitative behavior of X_1, X_2

- Worked for 2-comp model. Does this always work?

Motivation: Unidentifiable models

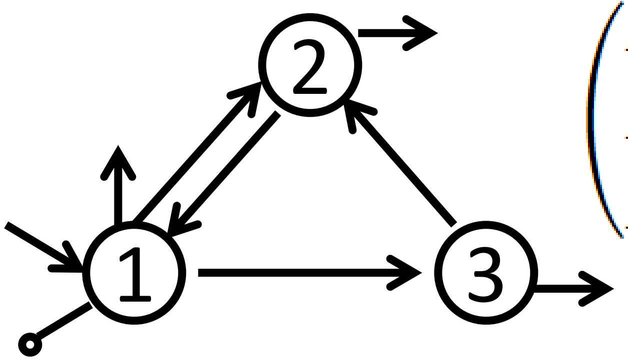
- Model 1: **No** ID scaling reparametrization!



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

$$y = x_1$$

- 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 models admit an identifiable scaling reparametrization?

Main result:

Theorem (M-Sullivant): The following are equivalent:

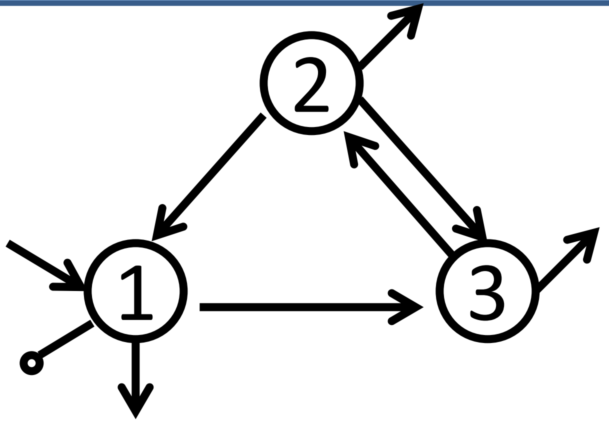
The model has an identifiable scaling reparametrization

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

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

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

Non-Example: Model 1



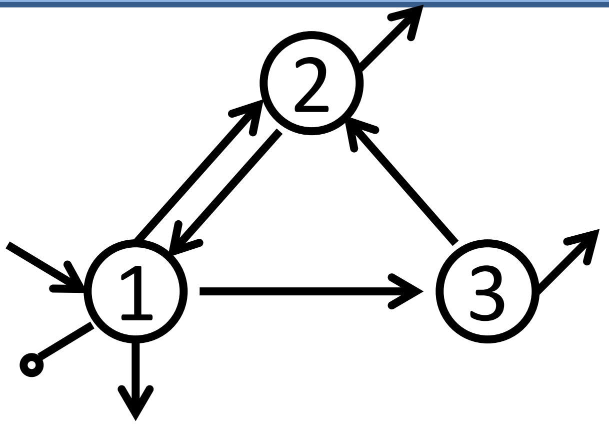
Model:

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

$$y = x_1$$

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

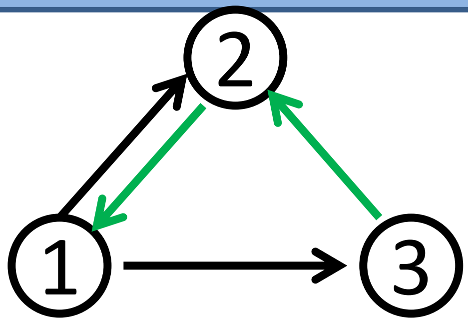
1) Form a spanning tree *T*
2) Form the directed incidence matrix *E(T)*:

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

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

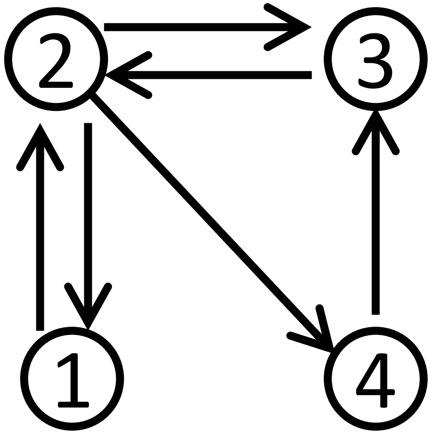
$$\begin{pmatrix} \dot{X}_1 \\ \dot{X}_2 \\ \dot{X}_3 \end{pmatrix} = \begin{pmatrix} a_{11} & 1 & 0 \\ a_{12}a_{21} & a_{22} & 1 \\ a_{12}a_{31}a_{23} & 0 & a_{33} \end{pmatrix} \begin{pmatrix} X_1 \\ X_2 \\ X_3 \end{pmatrix} + \begin{pmatrix} u_1 \\ 0 \\ 0 \end{pmatrix}$$

$$y = X_1$$

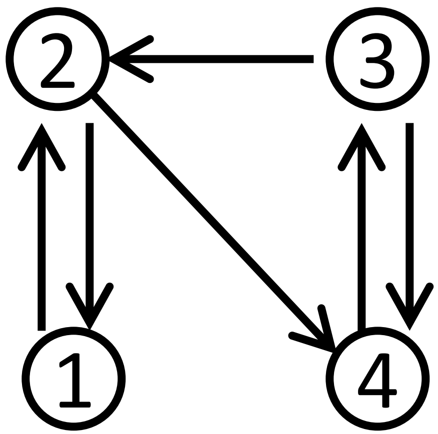
Which graphs have this property?

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

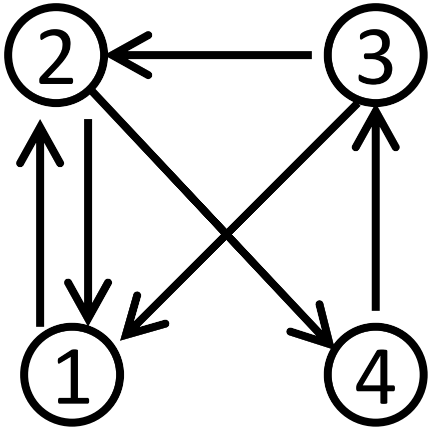
Good:



Bad:



- Not complete characterization:



Problem: Finding identifiable functions

- What if we have a different class of models?
  - How to find simplest identifiable functions?
- Problem: Given a field extension

$$\mathbb{R}(c_1, \dots, c_m)/\mathbb{R}$$

  find a "nice" transcendence basis
- In other words:
  - Let $d =$ number of algebraically independent functions among $c_1, \dots, c_m$
  - Find algebraically independent functions $f_1, \dots, f_d$ that are algebraic over $\mathbb{R}(c_1, \dots, c_m)$.

Gröbner Basis Heuristic to Find Identifiable Functions

- Consider the ideal
$$J = \langle c_1(p) - c_1(p^*), \ldots, c_m(p) - c_m(p^*) \rangle \in \mathbb{R}(p^*)[p]$$
- <u>Proposition</u>: If $f(p) - f(p^*) \in J$, then f is generically identifiable from c
- Try to find sparse polynomials like this in J by using elimination orderings

M, Eisenberg, and DiStefano 2009

Gröbner Basis Heuristic to Find Identifiable Functions

- Example: $c(p) - c(p^*) =$

$$(-a_{11} - a_{22} - (-a_{11}^* - a_{22}^*),$$
$$a_{11}a_{22} - a_{12}a_{21} - (a_{11}^*a_{22}^* - a_{12}^*a_{21}^*),$$
$$-a_{22} - (-a_{22}^*))$$

Gröbner basis for ordering $(a_{11}, a_{12}, a_{21}, a_{22})$ is

$$(\boldsymbol{a_{11}} - a_{11}^*,\ \boldsymbol{a_{12}a_{21}} - a_{12}^*a_{21}^*,\ \boldsymbol{a_{22}} - a_{22}^*)$$

So $a_{11}, a_{22}, a_{12}a_{21}$ are identifiable functions

Gröbner Basis Heuristic to Find Identifiable Functions

- Model 2:

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

$$y = x_1$$

- Gröbner basis of $c(p) - c(p^*)$ for ordering $(a_{23}, a_{31}, a_{12}, a_{21}, a_{33}, a_{22}, a_{11})$ is

$$(\boldsymbol{a_{11}} - a_{11}^*, \quad \boldsymbol{a_{22}^2} - \boldsymbol{a_{22}} a_{22}^* - \boldsymbol{a_{22}} a_{33}^* + a_{22}^* a_{33}^*,$$
$$\boldsymbol{a_{22}} + \boldsymbol{a_{33}} - a_{22}^* - a_{33}^*, \quad \boldsymbol{a_{12}} \boldsymbol{a_{21}} - a_{12}^* a_{21}^*,$$
$$a_{12}^* \boldsymbol{a_{21}} a_{21}^* \boldsymbol{a_{22}} - a_{12}^* \boldsymbol{a_{21}} a_{21}^* a_{22}^* + a_{12}^* a_{21}^* \boldsymbol{a_{23}} \boldsymbol{a_{31}}$$
$$- a_{12}^* \boldsymbol{a_{21}} a_{23}^* a_{31}^*,$$
$$a_{12}^* a_{21}^* \boldsymbol{a_{22}} - a_{12}^* a_{21}^* a_{22}^* + \boldsymbol{a_{12}} \boldsymbol{a_{23}} \boldsymbol{a_{31}} - a_{12}^* a_{23}^* a_{31}^*)$$

Testing for local identifiability

- Let $J(c)$ be the Jacobian matrix:

$$J = \begin{pmatrix} \frac{\partial c_1}{\partial p_1} & \cdots & \frac{\partial c_1}{\partial p_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial c_m}{\partial p_1} & \cdots & \frac{\partial c_m}{\partial p_n} \end{pmatrix}$$

- rank $J(c)$ (at a generic point) gives the dimension of image of c
- <u>Proposition</u>: Let n be the dimension of the parameter space. The model is locally identifiable if and only if rank $J(c) = n$.

M and Sullivant 2014

Testing for local identifiability of functions

- Proposition: A function f is locally identifiable from c if and only if $\nabla f \in rowspan\, J(c)$
- Example:

$$c(a_{11}, a_{12}, a_{21}, a_{22}) = (-a_{11} - a_{22}, a_{11}a_{22} - a_{12}a_{21}, -a_{22})$$

- Consider the function

$$f(a_{11}, a_{12}, a_{21}, a_{22}) = a_{12}a_{21}$$

- Then $\nabla f = (0 \quad a_{21} \quad a_{12} \quad 0)$

$$J(c) = \begin{pmatrix} -1 & 0 & 0 & -1 \\ a_{22} & -a_{21} & -a_{12} & a_{11} \\ 0 & 0 & 0 & -1 \end{pmatrix}$$

M and Sullivant 2014

Linear Algebra Heuristic to Find Identifiable Functions

- Proposition: Let $c: \mathbb{R}^n \to \mathbb{R}^m$ with $c_1, \dots, c_m$ homogeneous. Let v be a vector in the row span of $J(c)$ over $\mathbb{R}(c_1, \dots, c_m)$. Then $v \cdot p$ is a locally identifiable function.
- Example:

$$c(a_{11}, a_{12}, a_{21}, a_{22}) = (-a_{11} - a_{22}, a_{11}a_{22} - a_{12}a_{21}, -a_{22})$$

- We have:

$$J(c) = \begin{pmatrix} -1 & 0 & 0 & -1 \\ a_{22} & -a_{21} & -a_{12} & a_{11} \\ 0 & 0 & 0 & -1 \end{pmatrix} \to \text{Apply Gaussian Elimination}$$

$$\text{over the field } \mathbb{R}(c_1, \dots, c_m) \to \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & a_{21} & a_{12} & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

- Thus a_{11}, $2a_{12}a_{21}$, a_{22} are identifiable functions
- Nonhomogeneous?

M, Rosen, and Sullivant, in press, 2017

Linear Algebra Heuristic to Find Identifiable Functions

- Model 1:
  $c(a_{11}, a_{12}, a_{22}. a_{23}, a_{31}, a_{32}, a_{33}) = (-a_{11} - a_{22} - a_{33}, a_{11}a_{22} - a_{23}a_{32} + a_{11}a_{33} + a_{22}a_{33}, -a_{12}a_{23}a_{31} + a_{11}a_{23}a_{32} - a_{11}a_{22}a_{33}, -a_{22} - a_{33}, a_{22}a_{33} - a_{23}a_{32})$

- With respect to parameter ordering $(a_{11}, a_{22}, a_{23}, a_{32}, a_{33}, a_{12}, a_{31})$, we have:

$J(c) =$

$$\begin{pmatrix} -1 & -1 & 0 & 0 & -1 & 0 & 0 \\ a_{22} + a_{33} & a_{11} + a_{33} & -a_{32} & -a_{23} & a_{11} + a_{22} & 0 & 0 \\ a_{23}a_{32} - a_{22}a_{33} & -a_{11}a_{33} & -a_{12}a_{31} + a_{11}a_{32} & a_{11}a_{23} & -a_{11}a_{22} & -a_{23}a_{31} & -a_{12}a_{23} \\ 0 & -1 & 0 & 0 & -1 & 0 & 0 \\ 0 & a_{33} & -a_{32} & -a_{23} & a_{22} & 0 & 0 \end{pmatrix}$$

Linear Algebra Heuristic to Find Identifiable Functions

- Apply Gaussian Elimination over $\mathbb{R}(c_1, \ldots, c_m) \rightarrow$

$$\begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 & -1 & 0 & 0 \\ 0 & a_{33} & -a_{32} & -a_{23} & a_{22} & 0 & 0 \\ 0 & 0 & -a_{12}a_{31} & 0 & 0 & -a_{23}a_{31} & -a_{12}a_{23} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

- Thus a_{11}, $a_{22} + a_{33}$, $a_{22}a_{33} - a_{23}a_{32}$, $a_{12}a_{23}a_{31}$ are identifiable functions

Linear Algebra Heuristic to Find Identifiable Functions

- With respect to different parameter ordering $(a_{11}, a_{31}, a_{12}, a_{32}, a_{23}, a_{22}, a_{33})$, we have:

$$J(c) =$$

$$\begin{pmatrix} -1 & 0 & 0 & 0 & 0 & -1 & -1 \\ a_{22}+a_{33} & 0 & 0 & -a_{23} & -a_{32} & a_{11}+a_{33} & a_{11}+a_{22} \\ a_{23}a_{32}-a_{22}a_{33} & -a_{12}a_{23} & -a_{23}a_{31} & a_{11}a_{23} & -a_{12}a_{31}+a_{11}a_{32} & -a_{11}a_{33} & -a_{11}a_{22} \\ 0 & 0 & 0 & 0 & 0 & -1 & -1 \\ 0 & 0 & 0 & -a_{23} & -a_{32} & a_{33} & a_{22} \end{pmatrix}$$

Different column ordering

Linear Algebra Heuristic to Find Identifiable Functions

- Apply Gaussian Elimination over $\mathbb{R}(c_1, \dots, c_m) \rightarrow$

$$\begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -a_{12}a_{23} & -a_{23}a_{31} & 0 & -a_{12}a_{31} & 0 & 0 \\ 0 & 0 & 0 & -a_{23} & -a_{32} & a_{11}-a_{22} & a_{11}-a_{33} \\ 0 & 0 & 0 & 0 & 0 & -1 & -1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

- So a_{11}, $a_{12}a_{23}a_{31}$,

$$-\frac{a_{22}^2}{2} - \frac{a_{33}^2}{2} - a_{23}a_{32} + \frac{a_{11}a_{22}}{2} + \frac{a_{11}a_{33}}{2},$$

$$a_{22} + a_{33}$$

are identifiable functions

Linear Algebra Heuristic to Find Identifiable Functions

- Apply Gaussian Elimination over $\mathbb{R}(c_1, \ldots, c_m) \rightarrow$

$$\begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -a_{12}a_{23} & -a_{23}a_{31} & 0 & -a_{12}a_{31} & 0 & 0 \\ 0 & 0 & 0 & -a_{23} & -a_{32} & a_{11}-a_{22} & a_{11}-a_{33} \\ 0 & 0 & 0 & 0 & 0 & -1 & -1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

- So a_{11}, $a_{12}a_{23}a_{31}$,

$$-\frac{a_{22}^2}{2} - \frac{a_{33}^2}{2} - a_{23}a_{32} + \frac{a_{11}a_{22}}{2} + \frac{a_{11}a_{33}}{2},$$

$a_{22} + a_{33}$

are identifiable functions

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Thank you for your attention!