Identifiability and observability of biological models using algebraic matroids

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Joint work with Zvi Rosen and Seth Sullivant

Virtual seminar on algebraic matroids and rigidity theory

September 17, 2020

Outline

- What is structural identifiability? What to do with an unidentifiable model?
    - How can we use matroids?
- What is observability?
    - How can we use matroids?
- Open questions

Structural Identifiability

ODE Model:

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

$x(t)$ state variable vector
$u(t)$ input vector
$y(t)$ output vector
p parameter vector

Structural Identifiability

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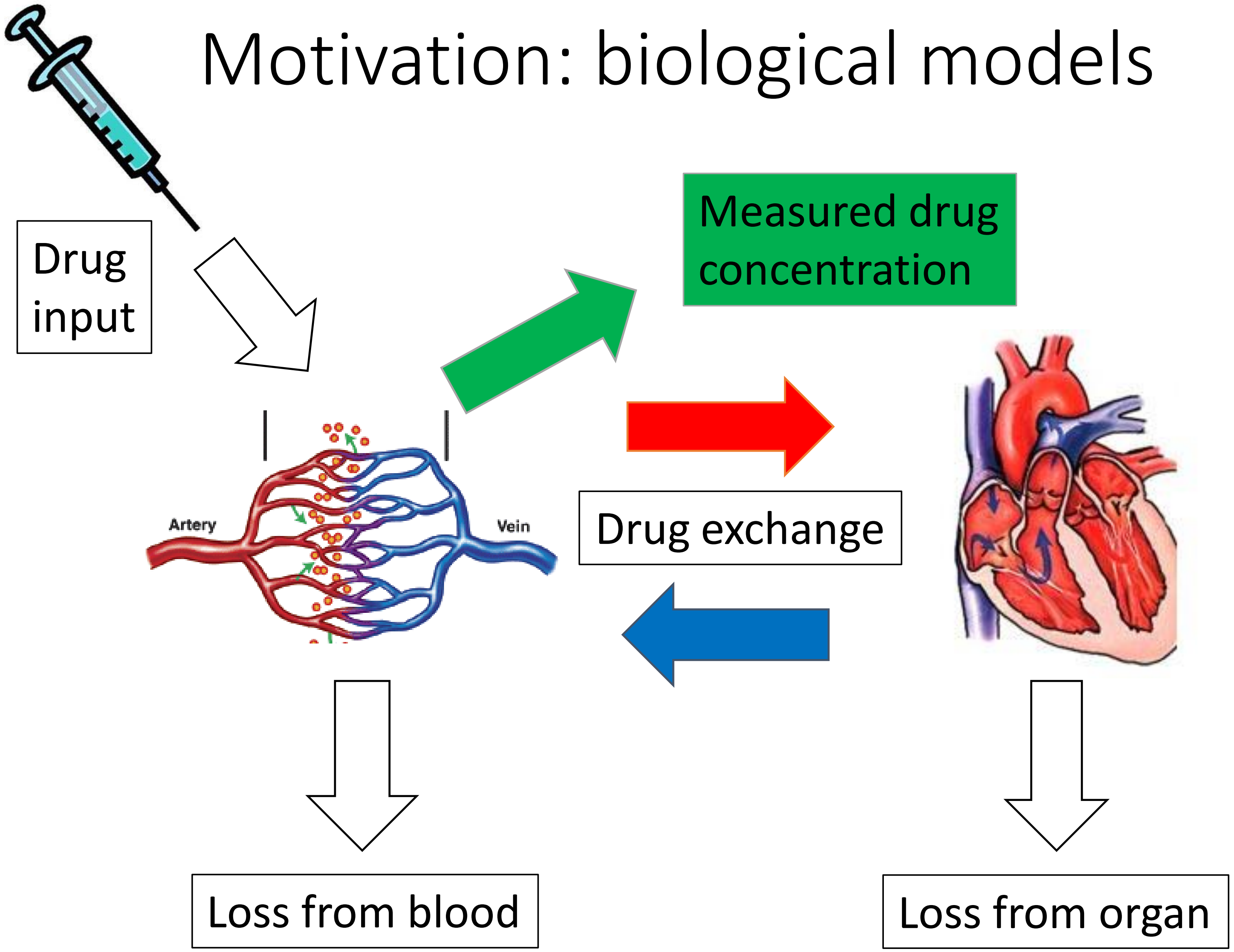
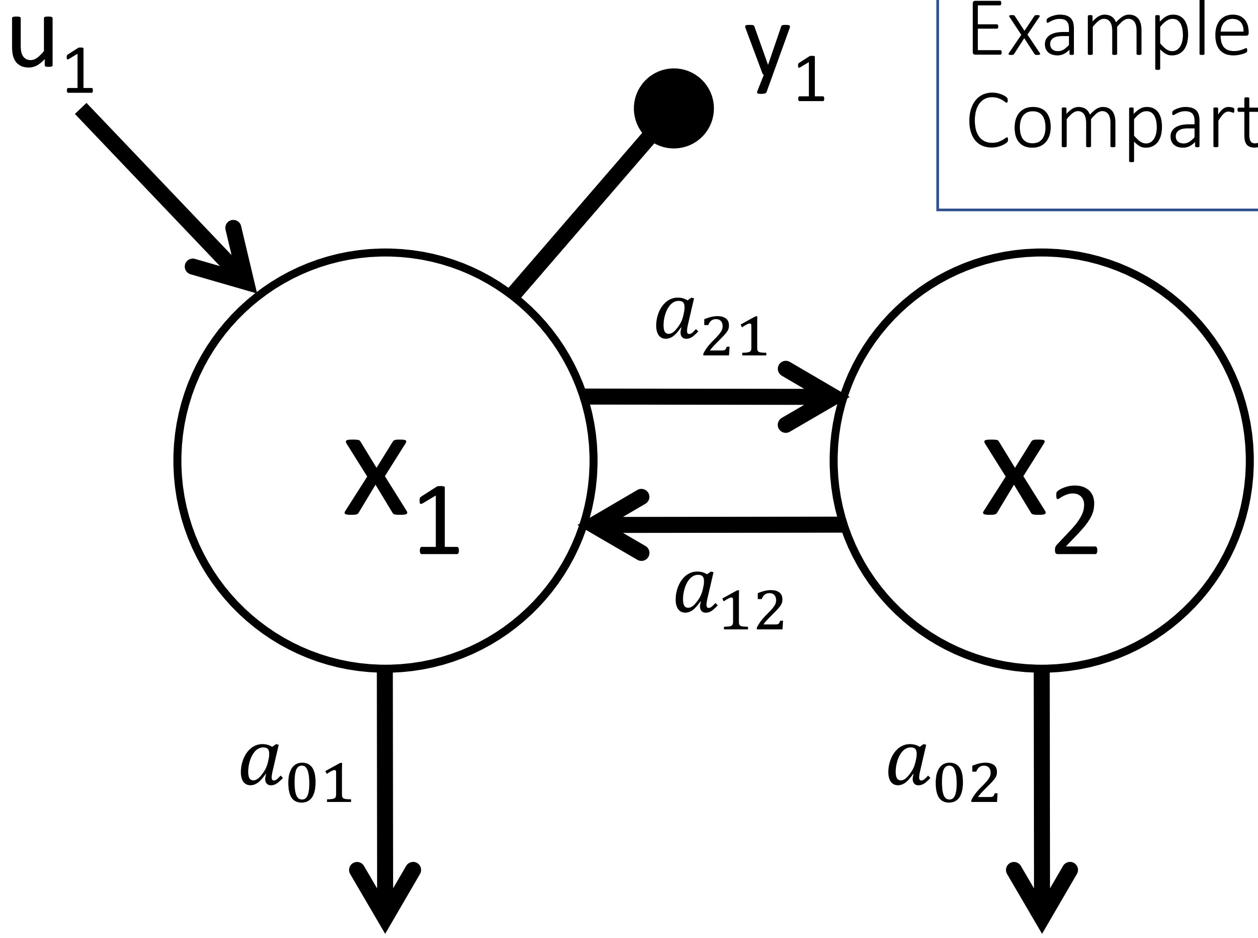
Structural identifiability: which unknown parameters can be determined from known input/output data?

Motivation: biological models



Example: Linear 2-Compartment Model



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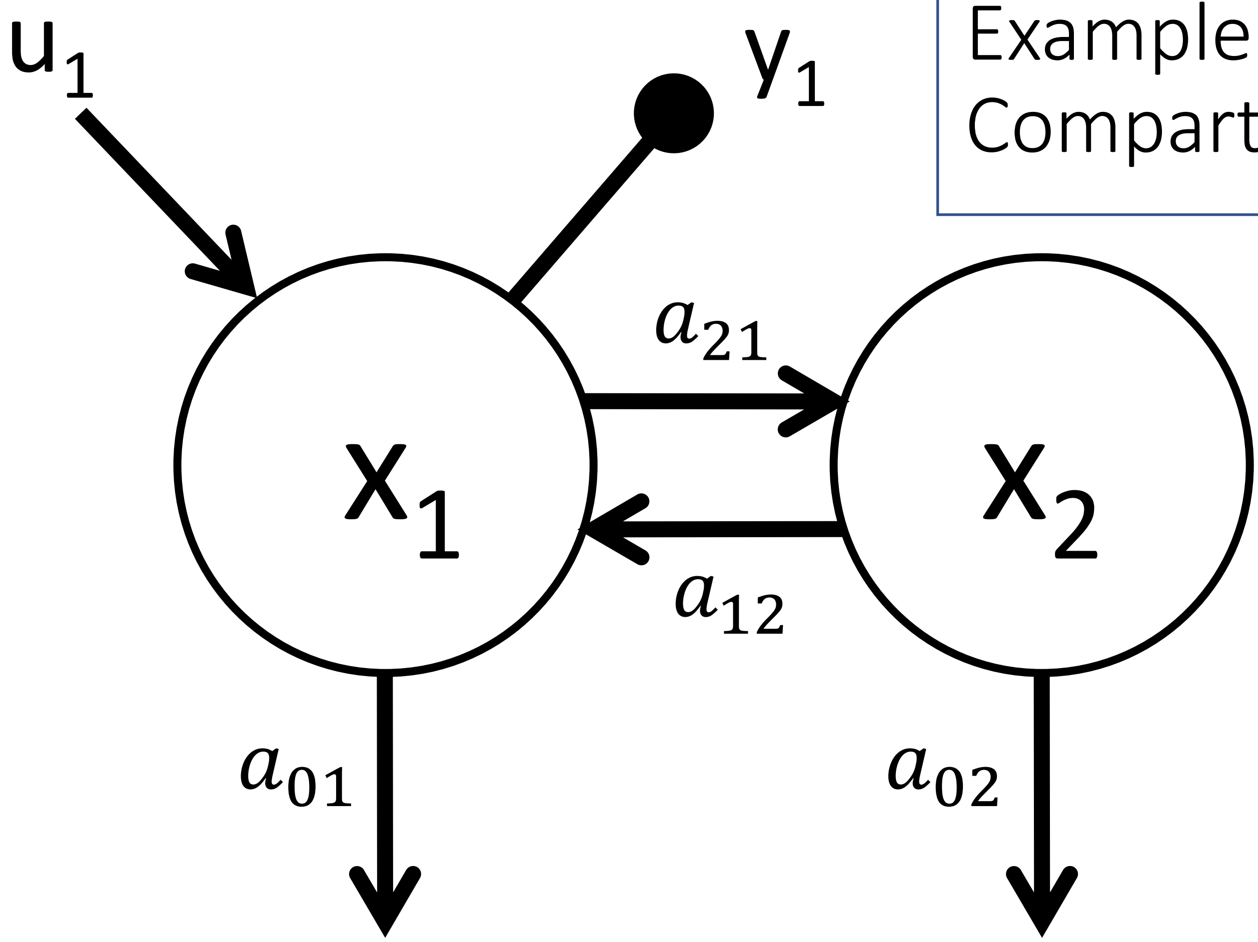

Can we determine parameters $a_{01}, a_{02}, a_{12}, a_{21}$ from input-output data?

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How to test identifiability

- Have ODE model:

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- Have known variables: u_1, y_1
- Can we eliminate unknown variables $x_1, \dot{x}_1, x_2, \dot{x}_2$?
  - Must determine *input-output equation* (in terms of $u_1, y_1, \dot{u}_1, \dot{y}_1, \ldots$)

Structural Identifiability

- Differential algebra method (Ollivier 1990, Ljung-Glad 1994)
    - Determine input-output equations using differential elimination
    - Obtain coefficient map
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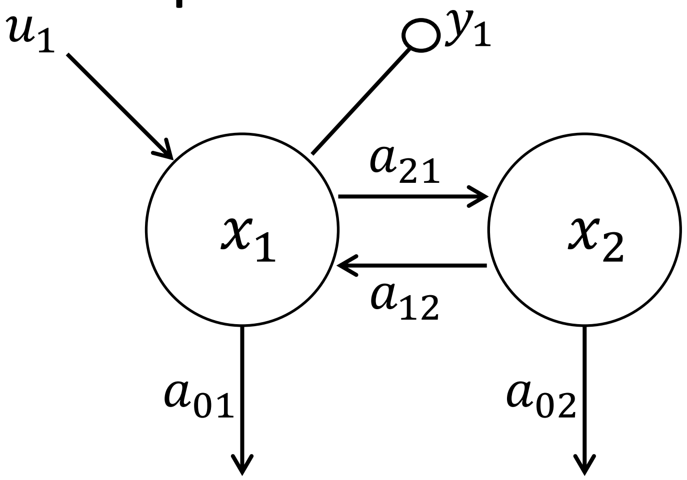

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Obtain coefficient map

Assume we can uniquely determine coefficients from perfect data

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Evaluate at many time instances: $t_1, t_2, t_3, \ldots$

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Extract coefficients to get coefficient map $c: \mathbb{R}^4 \to \mathbb{R}^3$

$$p \longmapsto c(p)$$

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So our model is unidentifiable!

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- Get:

a_{01}, a_{02}, a_{12} in terms of free parameter a_{21} and $a_{01}^*, a_{02}^*, a_{12}^*, a_{21}^*$

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- Find Jacobian of coefficient map and check rank at generic point:

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$$J(c) = \begin{pmatrix} 1 & 1 & 1 & 1 \\ a_{02} + a_{12} & a_{01} + a_{21} & a_{01} & a_{02} \\ 0 & 1 & 1 & 0 \end{pmatrix}$$

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1. Adjust model, if experimentally feasible
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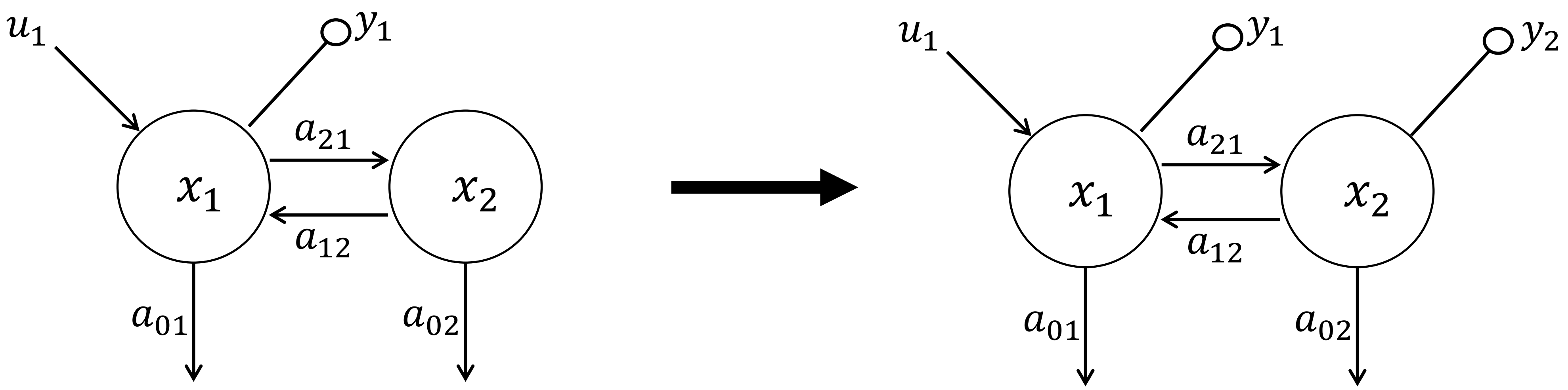

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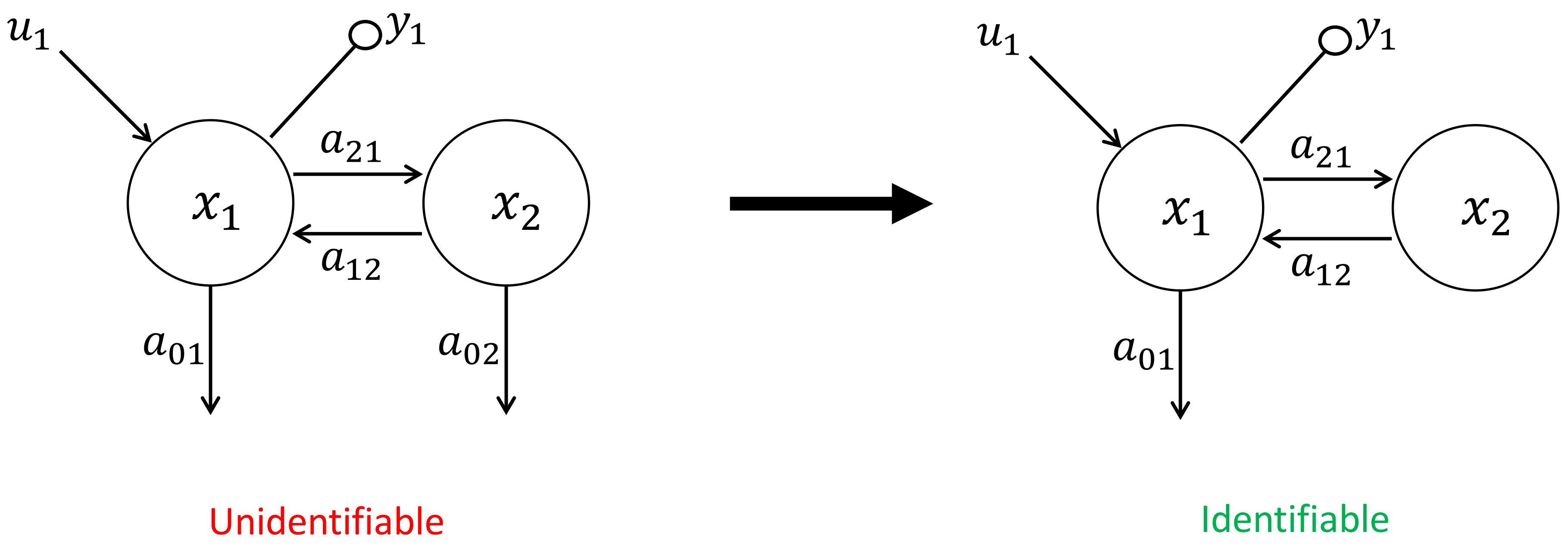

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$$c_1 = a_{01} + a_{02} + a_{12} + a_{21}$$
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$$a_{01} + a_{21} = c_1 - c_3$$
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→

$$X_1 = x_1$$

$$X_2 = a_{12}x_2$$

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Goal: try to reparametrize model over identifiable functions of parameters by finding an appropriate scaling of the state variables:

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

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Is this useful???
Does this always work???

Ex: Susceptible-Infected-Recovered (SIR) Model

$$\dot{S} = \mu N - \beta SI/N - \mu S$$
$$\dot{I} = \beta SI/N - (\mu + \gamma)I$$
$$\dot{R} = \gamma I - \mu R$$
$$y = kI$$

- $S(t)$ = number of susceptible individuals
- $I(t)$ = number of infected individuals
- $R(t)$ = number of recovered individuals
- $\mu =$ birth/death rate
- $\beta =$ transmission parameter
- $\gamma =$recovery rate
- $k =$proportion of infected population which is measured/observed
- $N =$ total population size
- $y(t)$ denotes the subset of the infected population we are measuring

Capasso 1993

Ex: Susceptible-Infected-Recovered (SIR) Model

$$\dot{S} = \mu N - \beta S I / N - \mu S$$
$$\dot{I} = \beta S I / N - (\mu + \gamma) I$$
$$\dot{R} = \gamma I - \mu R$$
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- $S(t)$ = number of susceptible individuals
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Capasso 1993

Identifiability analysis

- SIR Model Eqns

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- Input-output equation:

$$(-\beta\mu + \mu^2 + \mu\gamma) y^2 + \frac{(\beta\mu + \beta\gamma)}{kN} y^3 + \mu y \dot{y} + \frac{\beta}{kN} y^2 \dot{y} - \dot{y}^2 + y \ddot{y} = 0$$

SIR Model

- Identifiability test:

$$-\beta\mu + \mu^2 + \mu\gamma = -\beta^*\mu^* + {\mu^*}^2 + \mu^*\gamma^*$$

$$\frac{\beta\mu + \beta\gamma}{kN} = \frac{\beta^*\mu^* + \beta^*\gamma^*}{k^*N^*}$$

$$\mu = \mu^*$$

$$\frac{\beta}{kN} = \frac{\beta^*}{k^*N^*}$$

- Solution:

β=β^* γ=γ^* $\mu = \mu^*$ $kN = k^*N^*$

Capasso 1993

SIR Model

- Idenfiable combinations β, γ, μ, kN
- Reparametrize $s = \frac{S}{N},\ i = \frac{I}{N},\ r = \frac{R}{N}$
- New model eqns:

$$\dot{s} = \mu - \beta s i - \mu s$$
$$\dot{i} = \beta s i - (\mu + \gamma) i$$
$$\dot{r} = \gamma i - \mu r$$
$$y = kNi$$

$$(\beta, \gamma, \mu, kN) \mapsto \left(-\beta\mu + \mu^2 + \mu\gamma, \frac{\beta\mu + \beta\gamma}{kN}, \mu, \frac{\beta}{kN} \right)$$

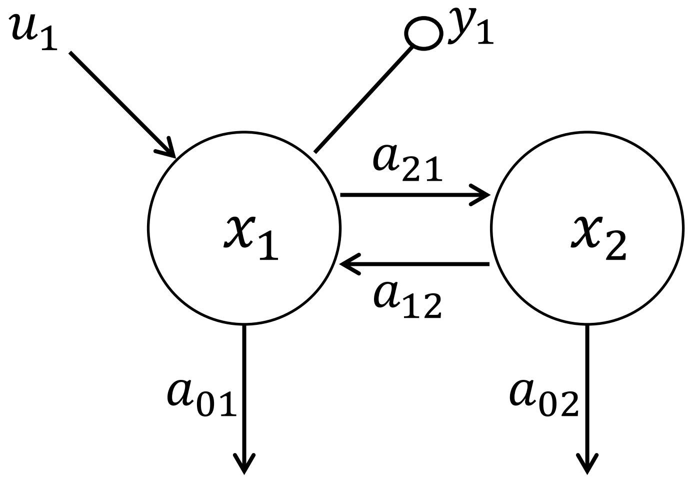
When can we do this?

Capasso 1993

Identifiable scaling reparametrization

Looked at special class of linear models:

- Strongly connected
- Single input/output in same compartment
- Leaks from every compartment
  - Can re-write diagonal elements as a_{ii}



<u>Ex:</u>

$$\dot{x}_1 = a_{11}x_1 + a_{12}x_2 + u_1$$

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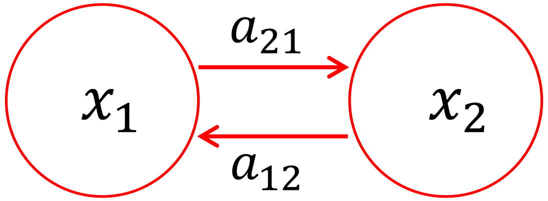

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$$\dot{x} = A(G)x + u$$

Graph G with m edges and n vertices

Cycles $a_{11},\ a_{22},\ a_{12}a_{21}$

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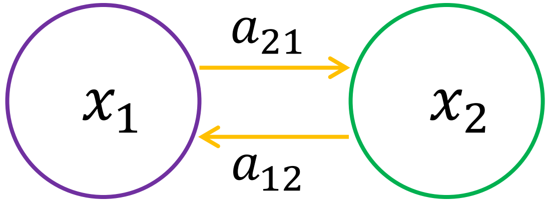

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Identifiable functions $-(a_{01} + a_{21}) = a_{11}$, $a_{12}a_{21}$, $-(a_{02} + a_{12}) = a_{22}$ are cycles in graph!

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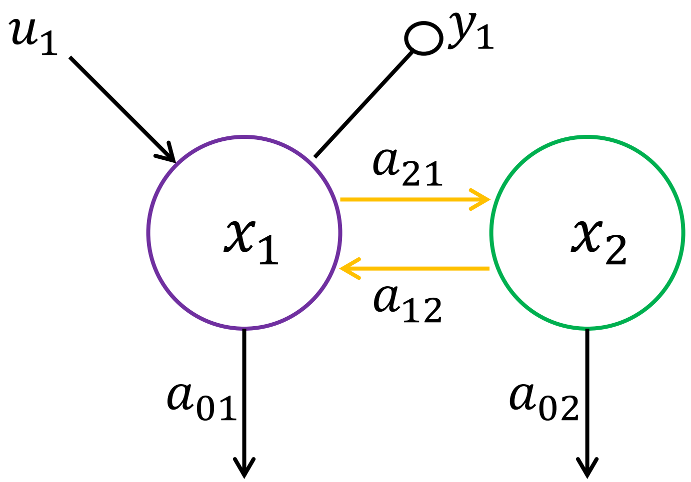


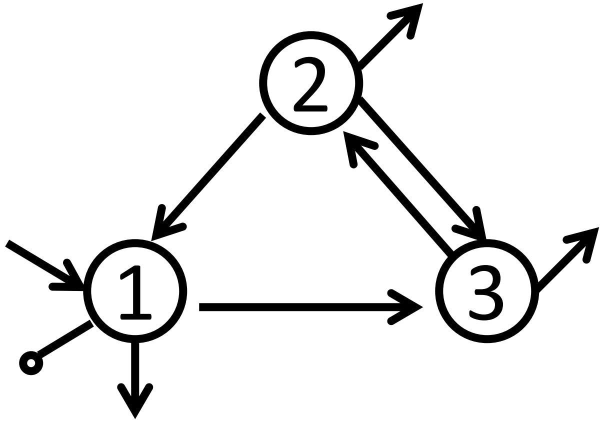
<u>Theorem (M-Sullivant 2014)</u>: Model with above assumptions has an identifiable scaling reparametrization

$$\Leftrightarrow \dim(im(c)) = m + 1$$

$\Leftrightarrow$ cycles in graph are identifiable

Examples

Model 1



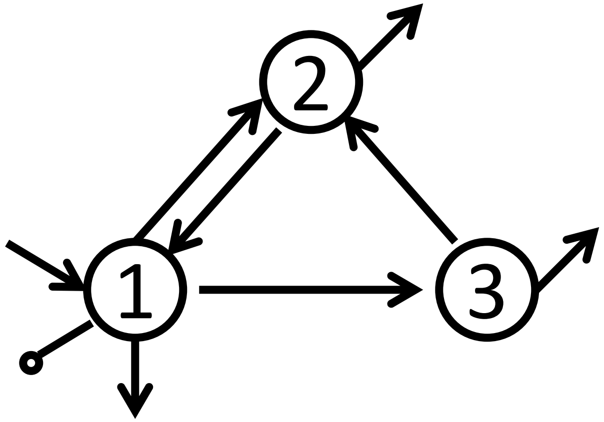
$$\begin{pmatrix}\dot{x}_1\\ \dot{x}_2\\ \dot{x}_3\end{pmatrix} = \begin{pmatrix}a_{11} & a_{12} & 0\\ 0 & a_{22} & a_{23}\\ a_{31} & a_{32} & a_{33}\end{pmatrix}\begin{pmatrix}x_1\\ x_2\\ x_3\end{pmatrix} + \begin{pmatrix}u_1\\ 0\\ 0\end{pmatrix}$$

$$y_1 = x_1$$

$$\dim\big(im(c)\big) = 4$$

No identifiable scaling reparametrization!

Model 2



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$$y_1 = x_1$$

$$\dim\big(im(c)\big) = 5$$

Has an identifiable scaling reparametrization

What about other models?

- Linear compartmental models with more inputs and outputs?
  Nonlinear models?

  - How do we find identifiable functions of parameters?

  - Do they have an identifiable scaling reparametrizations?

How to find identifiable functions in general?

- Ad hoc methods:
  - Find Gröbner bases of $\{c(p) - c(p^*)\}$ for different orderings of p

M-DiStefano-Eisenberg 2009, M-Rosen-Sullivant 2018, Bates-Hauenstein-M 2019

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- Can we somehow use algebraic matroids?

M-DiStefano-Eisenberg 2009, M-Rosen-Sullivant 2018, Bates-Hauenstein-M 2019

How to involve matroids

- <u>Theorem 6.7.1 [Oxley]</u>: Suppose $\mathbb{K}$ is an extension field of a field $\mathbb{F}$ and E is a finite subset of $\mathbb{K}$. Then the collection I of subsets of E that are algebraically independent over $\mathbb{F}$ is the set of independent sets of a matroid on E. The resulting matroid is called an *algebraic matroid.*

- Ex: 2-compartment model

  $E = \{a_{11}, a_{22}, a_{12}, a_{21}\}$ and $\mathbb{F} = \mathbb{R}\big(c_1(p), c_2(p), c_3(p)\big)$ where

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

  Then $I = \big\{\emptyset, \{a_{12}\}, \{a_{21}\}\big\}$ and $C = \big\{\{a_{11}\}, \{a_{22}\}, \{a_{12}, a_{21}\}\big\}$

How to involve matroids

- Mapping $p \mapsto \big(c_1(p), c_2(p), c_3(p)\big)$
- Variety V of interest is the pre-image of a point $\hat{c} = (\widehat{c_1}, \widehat{c_2}, \widehat{c_3})$ under the map c, which has a trivial vanishing ideal.
- Point $\hat{c}$ can be taken to be a generic point of $\mathbb{R}^3$ by setting $\{\widehat{c_1}, \widehat{c_2}, \widehat{c_3}\}$ to be algebraically independent over $\mathbb{R}$.
- So the only algebraic constraints on the p-variables come from the equations $\{c(p) = \hat{c}\}$.

How to involve matroids

- Ideal $P = \langle c_1(p) - \widehat{c_1}, c_2(p) - \widehat{c_2}, c_3(p) - \widehat{c_3} \rangle$ which contains the polynomials in $\mathbb{R}(\hat{c})[p] = \mathbb{R}(\widehat{c_1}, \widehat{c_2}, \widehat{c_3})[a_{11}, a_{22}, a_{12}, a_{21}]$.
- Ideal P is prime, therefore computation of the algebraic matroid modulo P is well-defined.

How to involve matroids

Prop 2.14 [Király-Rosen-Theran 2013]: Let $P = \langle f_1, \ldots, f_m \rangle$ be a prime ideal contained in $\mathbb{F}[x_1, \ldots, x_n]$. Define the Jacobian matrix $J(P)$ as:

$$\left(\frac{\partial f_i}{\partial x_j} : 1 \leq i \leq m, 1 \leq j \leq n\right)$$

This matrix, when considered as a matroid with columns as the ground set and linear independence over $\mathrm{Frac}(\mathbb{F}[x]/\, P)$ defining independent set I represents the dual matroid to $M(P)$. The transpose of the matrix spanning the kernel gives the matroid $M(P)$.

How to involve matroids

- Ex: Let c be the map $p \mapsto \big(c_1(p), c_2(p), c_3(p)\big)$ from linear 2-compartment model. Jacobian $J(c)$ is given by:

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

A basis for the kernel of this matrix is given by $(0, 0, a_{12}, -a_{21})^T$.

Here, linear independence is taken over $\mathrm{Frac}(\mathbb{F}[x]/\,P) \cong \mathbb{R}(\hat{c})(a_{12}, a_{21})$.

How to involve matroids

Thus, a vector matroid is given by:

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

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Dependency relationship? Find a Gröbner basis to get $a_{12}a_{21} = (\widehat{c_1} - \widehat{c_3})\widehat{c_3} - \widehat{c_2}$

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Does not tell us if polynomial can be decoupled in a_{12}, a_{21} and $\hat{c}$!
$a_{12}a_{21} - (\widehat{c_1} - \widehat{c_3})\widehat{c_3} - \widehat{c_2}$ vs. $a_{12} - (\widehat{c_1} - \widehat{c_3})\widehat{c_3} - a_{21}\widehat{c_2}$

Observability

- The state variable x_i is *observable* if it can be recovered from observation of the input and output alone
  - i.e. how well internal states of a system can be inferred from knowledge of external inputs/outputs

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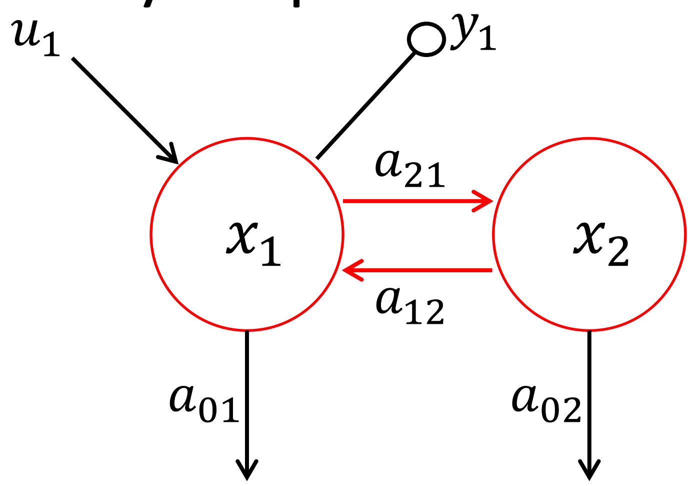
$$x_2 = (\dot{y}_1 + (a_{01} + a_{21})y_1 - u_1)/a_{12}$$

Observability

- For linear compartmental models, can translate this to a graphical condition:
- <u>Thm [Godfrey&Chapman 1990]</u>: A model is observable ⟺ it is *output connectable* for every output.



- For nonlinear models, do not have easy to check criteria based on model structure

Observability

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  - *generically unobservable* if there are **infinitely many** trajectories for x_i compatible with given input-output trajectory.
  - *rationally observable* if there is a **rational function** F such that the trajectory $x_i(t)$ satisfies $x_i(t) = F(y, y', \dots, u, u', \dots, p)$.

Observability

<u>Prop 6.3 [M-Rosen-Sullivant 2018]</u>: Consider state space model with 1 output y. Consider ideal $P =$

$$\left\langle x' - f(x,u,p), \ldots, x^{(n-1)} - \frac{d^{n-2}}{dt^{n-2}} f(x,u,p), \right.$$

$$\left. \underbrace{y - g(x,p)}_{\text{Original system}}, \ldots, y^{(n-1)} - \frac{d^{n-1}}{dt^{n-1}} g(x,p) \right\rangle$$

Original system

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Derivatives of system, where $n =$ # state variables

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$$\left. y - g(x,p), \dots, y^{(n-1)} - \frac{d^{n-1}}{dt^{n-1}} g(x,p) \right\rangle$$

Consider an elimination ordering $<$ with three blocks of variables: $\{x, x', \dots, x^{(n-1)}\} \backslash \{x_i\} > \{x_i\} > \{y, u, y', u', \dots, y^{(n-2)}, u^{(n-2)}, y^{(n-1)}\}$

Then a Gröbner basis for P with respect to $<$ will contain a polynomial in $x_i, y, y', \dots, u, u', \dots$ if it exists. Otherwise, no such polynomial exists.

Observability of 2-comp model

- $P = \langle a_{11}x_1 + a_{12}x_2 + u_1 - x_1', \quad a_{21}x_1 + a_{22}x_2 - x_2',$
  $x_1 - y_1, \quad x_1' - y_1' \rangle$
  contains polynomials in the ring $\mathbb{R}(p)[x_1, x_2, x_1', x_2', u_1, y_1, y_1']$

- Find Gröbner basis with elimination order $<$, we have:

$$a_{11}y_1 + a_{12}x_2 + u_1 - y_1'$$
$$x_1 - y_1$$

are two polynomials of the desired form.

Observability of 2-comp model

- $P = \langle a_{11}x_1 + a_{12}x_2 + u_1 - x_1', \quad a_{21}x_1 + a_{22}x_2 - x_2',$
  $x_1 - y_1, \quad x_1' - y_1' \rangle$
  contains polynomials in the ring $\mathbb{R}(p)[x_1, x_2, x_1', x_2', u_1, y_1, y_1']$

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$$a_{11}y_1 + a_{12}x_2 + u_1 - y_1'$$
$$x_1 - y_1$$

  are two polynomials of the desired form.

- So the model is rationally observable. Is this overkill?

Observab’ty of 2-comp model using matroids

- $$P = \langle a_{11}x_1 + a_{12}x_2 + u_1 - x_1', \quad a_{21}x_1 + a_{22}x_2 - x_2', \quad x_1 - y_1, \quad x_1' - y_1' \rangle$$
  contains polynomials in the ring $\mathbb{R}(p)[x_1, x_2, x_1', x_2', u_1, y_1, y_1']$

- Instead of applying a Gröbner basis to find desired polynomials, we can examine the algebraic matroid associated to the system. The ground set $E = \{x_1, x_2, x_1', x_2', u_1, y_1, y_1'\}$.

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- Look for circuits including x_1, x_2 while excluding x_1' and x_2'.

Observab’ty of 2-comp model using matroids

- $P = \langle a_{11}x_1 + a_{12}x_2 + u_1 - x_1', \quad a_{21}x_1 + a_{22}x_2 - x_2',$
  $x_1 - y_1, \quad x_1' - y_1' \rangle$
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- Instead of applying a Gröbner basis to find desired polynomials, we can examine the algebraic matroid associated to the system. The ground set $E = \{x_1, x_2, x_1', x_2', u_1, y_1, y_1'\}$.

- Look for circuits including x_1, x_2 while excluding x_1' and x_2'.

- Find circuits: $\{x_1, y_1\}, \{x_2, u_1, y_1, y_1'\}$, and $\{x_1, x_2, u_1, y_1'\} \Rightarrow$ x_1, x_2 locally observable

Observability of SIR model using matroids

- $P = \left\langle S' + \mu S + \frac{\beta SI}{N} - \mu N, S'' + \mu S' + \frac{\beta SI'}{N} + \frac{\beta S' I}{N}, I' + (\mu + \gamma) I - \frac{\beta SI}{N}, I'' + (\mu + \gamma) I' - \frac{\beta S' I}{N} - \frac{\beta SI'}{N}, R' + \mu R - \gamma I, R'' + \mu R' - \gamma I', y - kI, y' - kI', y'' - kI'' \right\rangle$
  contains polynomials in the ring $\mathbb{R}(p)[S, I, R, S', I', R', S'', I'', R'', y, y', y'']$

- Ground set $E = \{S, S', S'', I, I', I'', R, R', R'', y, y', y''\}$.

Observability of SIR model using matroids

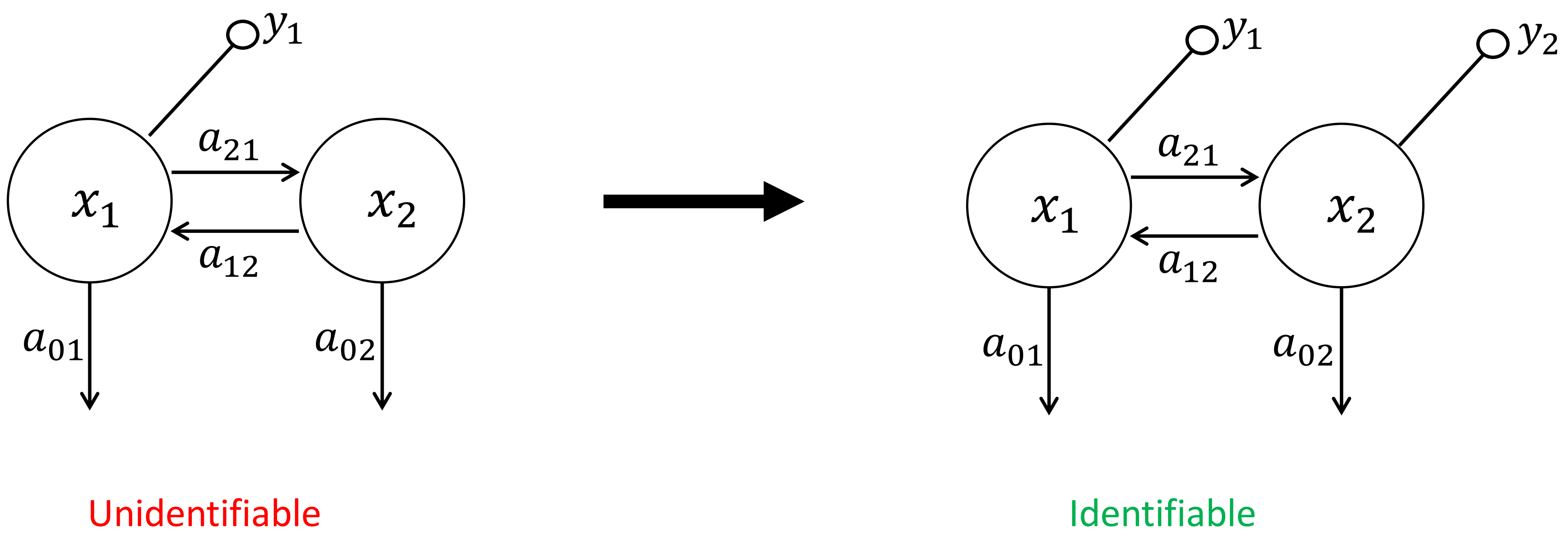
- $P = \left\langle S' + \mu S + \frac{\beta S I}{N} - \mu N, S'' + \mu S' + \frac{\beta S I'}{N} + \frac{\beta S' I}{N}, I' + (\mu + \gamma) I - \frac{\beta S I}{N}, I'' + (\mu + \gamma) I' - \frac{\beta S' I}{N} - \frac{\beta S I'}{N}, R' + \mu R - \gamma I, R'' + \mu R' - \gamma I', y - kI, y' - kI', y'' - kI'' \right\rangle$
  contains polynomials in the ring $\mathbb{R}(p)[S, I, R, S', I', R', S'', I'', R'', y, y', y'']$
- Ground set $E = \{S, S', S'', I, I', I'', R, R', R'', y, y', y''\}$.
- Circuits including S, I, R while excluding their derivatives: $\{S, y, y'\}, \{S, y, y''\}, \{S, y', y''\}, \{I, y\}, \{I, y', y''\} \Rightarrow S, I$ locally observable

Observability of SIR model using matroids

- $P = \left\langle S' + \mu S + \frac{\beta S I}{N} - \mu N, S'' + \mu S' + \frac{\beta S I'}{N} + \frac{\beta S' I}{N}, I' + (\mu + \gamma) I - \frac{\beta S I}{N}, I'' + (\mu + \gamma) I' - \frac{\beta S' I}{N} - \frac{\beta S I'}{N}, R' + \mu R - \gamma I, R'' + \mu R' - \gamma I', y - kI, y' - kI', y'' - kI'' \right\rangle$
  contains polynomials in the ring $\mathbb{R}(p)[S, I, R, S', I', R', S'', I'', R'', y, y', y'']$
- Ground set $E = \{S, S', S'', I, I', I'', R, R', R'', y, y', y''\}$.
- Circuits including S, I, R while excluding their derivatives: $\{S, y, y'\}, \{S, y, y''\}, \{S, y', y''\}, \{I, y\}, \{I, y', y''\} \Rightarrow S, I$ locally observable
- Any relation including *one* of $\{R, R', R''\}$ must include at least two $\Rightarrow$ R unobservable

Open questions

1. Determining minimal sets of inputs/outputs to obtain identifiability
   - Can we use matroids???



Open questions

2. Identifiable functions of parameters in general
   - Can we use matroids???

Recall dependency relationships:

$a_{12}a_{21} - (\widehat{c_1} - \widehat{c_3})\widehat{c_3} - \widehat{c_2}$ vs. $a_{12} - (\widehat{c_1} - \widehat{c_3})\widehat{c_3} - a_{21}\widehat{c_2}$

"Decoupled" vs. "Coupled"

Open questions

3. Identifiable scaling reparametrizations in general
    - Can we use matroids???

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

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

$$y_1 = x_1$$

$\longrightarrow$

$$\dot{X}_1 = -(a_{01} + a_{21})X_1 + X_2 + u_1$$

$$\dot{X}_2 = a_{12}a_{21}X_1 - (a_{02} + a_{12})\,X_2$$

$$y_1 = X_1$$

Thank you!

Questions?