Identifiability, indistinguishability, and other problems in biological modeling

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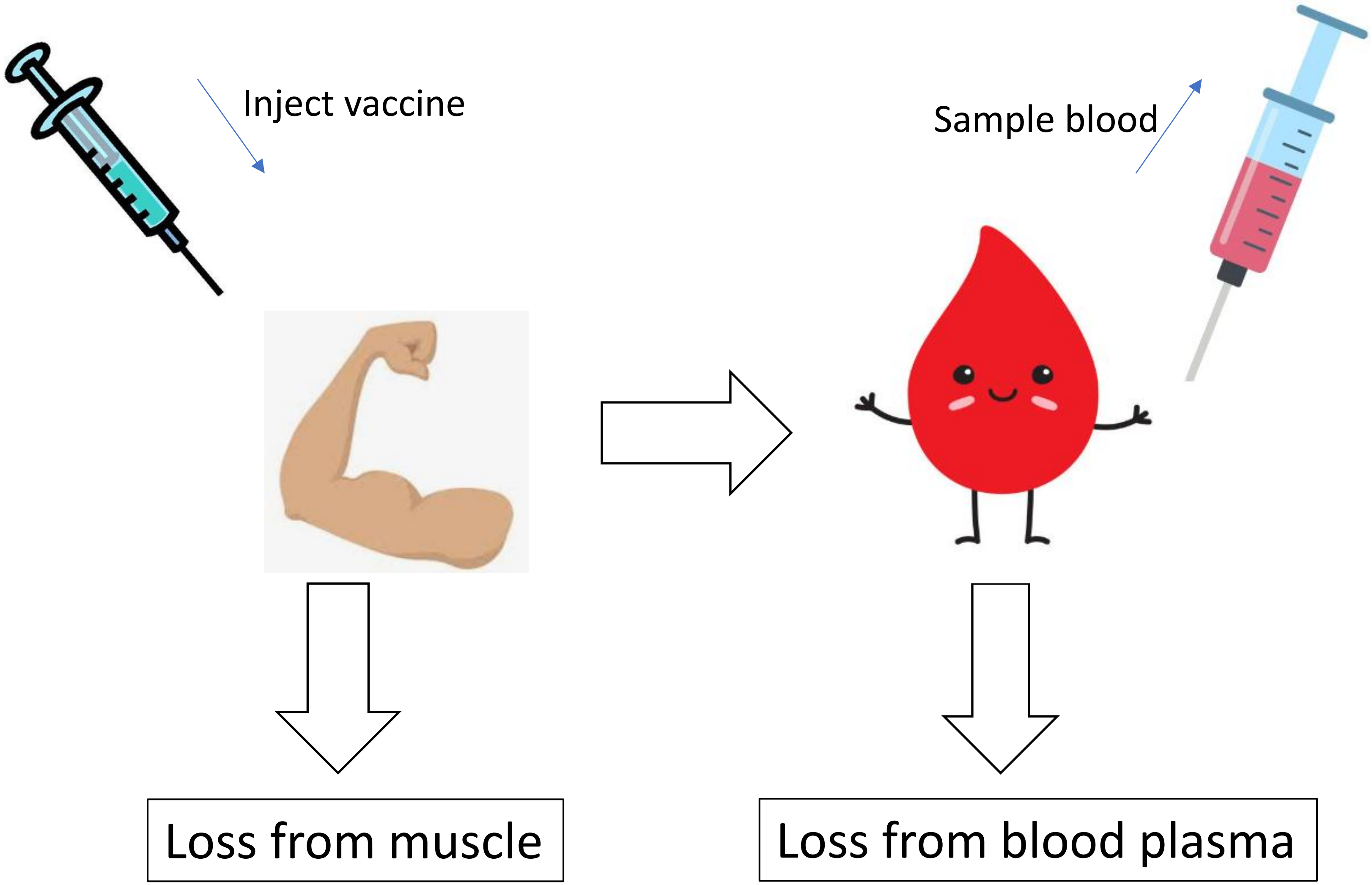
New Directions in Algebraic Statistics

July 22, 2025

Consider a vaccine injection model (IM)*:



Inject vaccine

Sample blood

Loss from muscle

Loss from blood plasma

*Example 13.6 from DiStefano, *Dynamics Systems Biology Modeling and Simulation*

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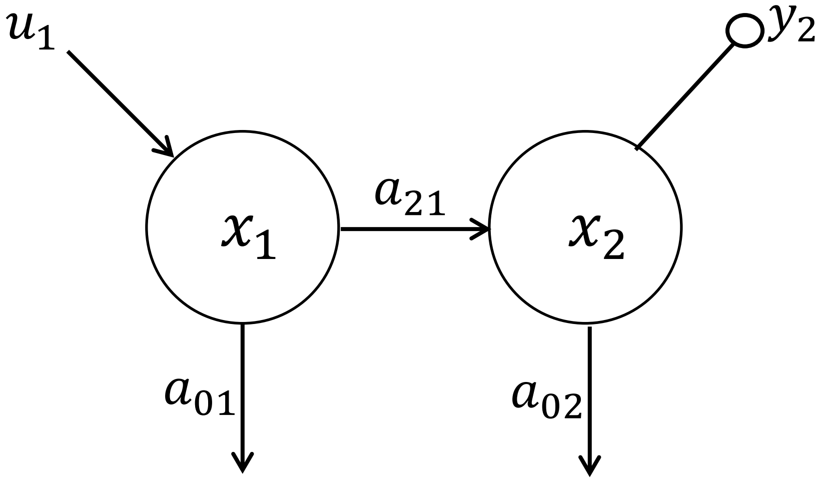

$$\dot{x}_1(t) = -(a_{01} + a_{21})x_1(t) + u_1(t)$$
$$\dot{x}_2(t) = a_{21}x_1(t) - a_{02}x_2(t)$$
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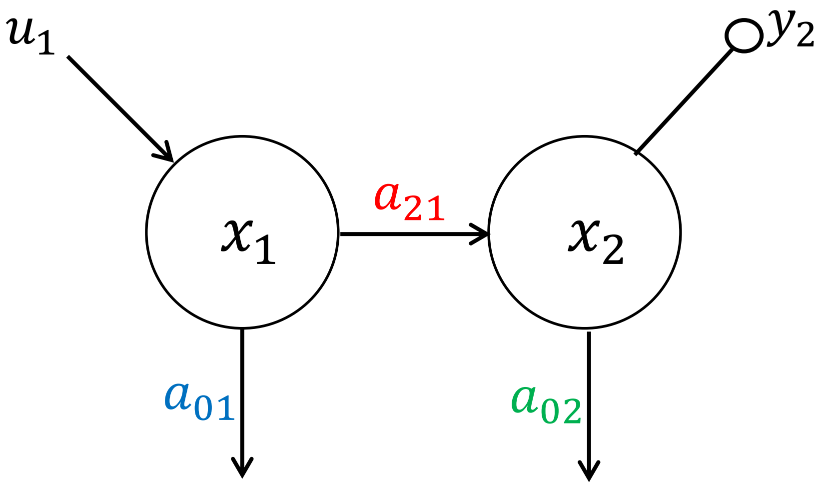

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- More generally, what can we say about classes of identifiable models? Submodels? Joined models? etc
- What do we do with an unidentifiable model?

How to test identifiability – Diff. alg. approach

- Have ODE model:

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

$$\dot{x}_2 = a_{21}x_1 - a_{02}x_2$$

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[Ollivier 1990, Ljung-Glad 1994]

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- Assuming perfect data, we know $\dot{u}_1, \dot{y}_2, \ddot{u}_1, \ddot{y}_2, \ldots$

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- Can we eliminate unknown variables $x_1, \dot{x}_1, x_2, \dot{x}_2$?
- Must determine *input-output equation* (in terms of $u_1, y_2, \dot{u}_1, \dot{y}_2, \ldots$)

[Ollivier 1990, Ljung-Glad 1994]

Determine input-output equations

Have system $\dot{x} = Ax + u, \quad y_2 = x_2$

Rewrite system as $(\partial I - A)x = u$, where $\partial = d/dt$

$$\begin{pmatrix} \partial + a_{01} + a_{21} & 0 \\ a_{21} & \partial + a_{02} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} u_1 \\ 0 \end{pmatrix}$$

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Then by Cramer's Rule:

$$x_2 = \frac{\det \begin{pmatrix} \partial + a_{01} + a_{21} & u_1 \\ a_{21} & 0 \end{pmatrix}}{\det \begin{pmatrix} \partial + a_{01} + a_{21} & 0 \\ a_{21} & \partial + a_{02} \end{pmatrix}}$$

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Thus $\ddot{y}_2 + (a_{01} + a_{02} + a_{21})\dot{y}_2 + (a_{01}a_{02} + a_{21}a_{02})y_2 = a_{21}u_1$

Obtain coefficient map

Assume we can uniquely determine coefficients from perfect data

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Extract coefficients from input-output equations to get coefficient map:

$$p \longmapsto c(p)$$

$$(a_{01}, a_{21}, a_{02}) \mapsto (a_{01} + a_{21} + a_{02},\ \ a_{01}a_{02} + a_{21}a_{02},\ \ \ a_{21})$$

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Model is (generically):

- Globally identifiable if c is generically one-to-one
- Locally identifiable if c is generically finite-to-one
- Unidentifiable if c is generically infinite-to-one

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Parameter a_{ij} is (generically):

- Globally identifiable if its value can be recovered uniquely
- Locally identifiable if its value can be recovered up to a finite set
- Unidentifiable if its value can't be recovered even up to a finite set

Obtain coefficient map

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$$a_{01} + a_{02} + a_{21} = a_{01}^* + a_{02}^* + a_{21}^*$$

$$a_{01}a_{02} + a_{21}a_{02} = a_{01}^*a_{02}^* + a_{21}^*a_{02}^*$$

$$a_{21} = a_{21}^*$$

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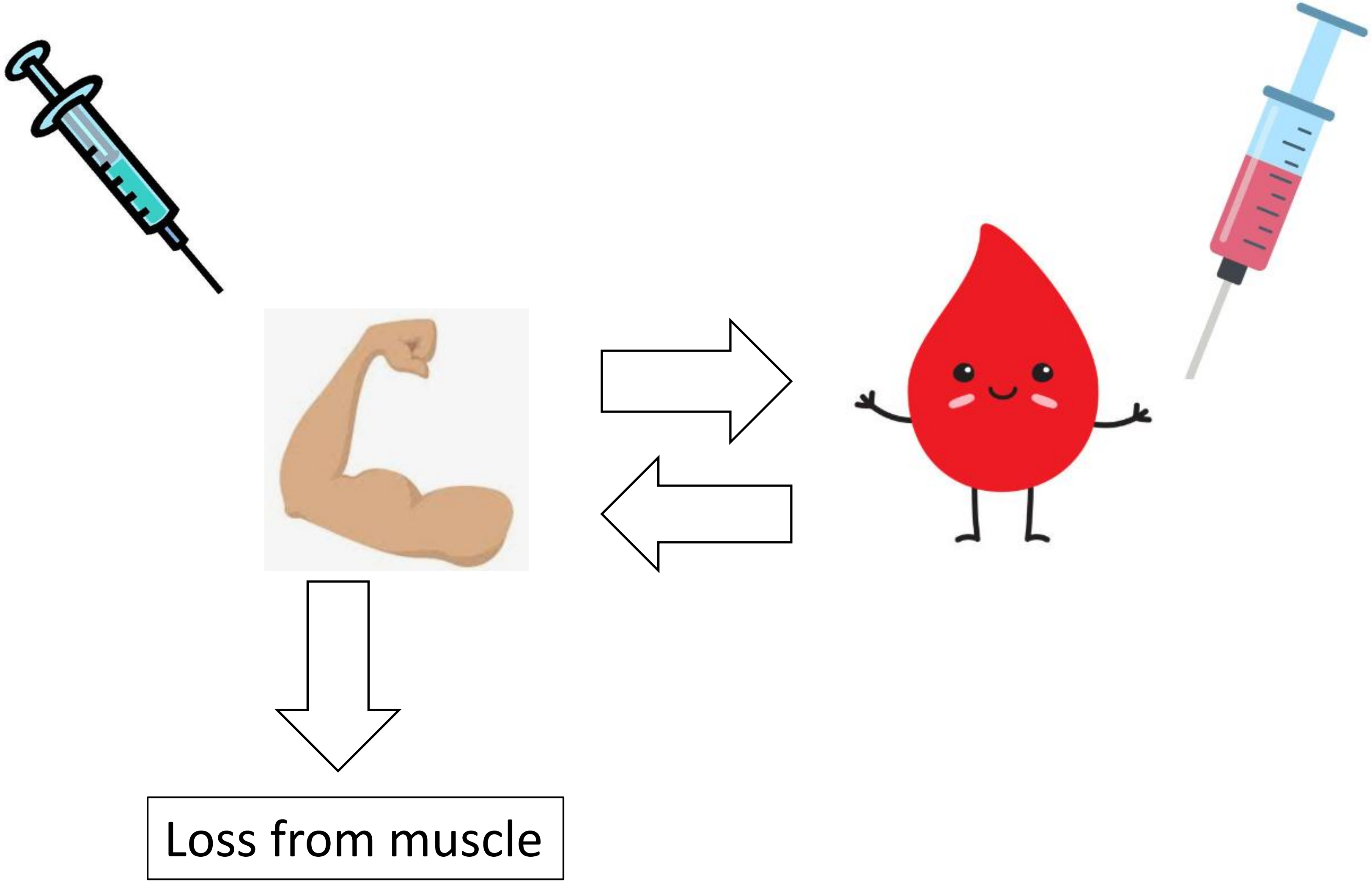
Model is globally identifiable

What if I change my model?



Loss from muscle

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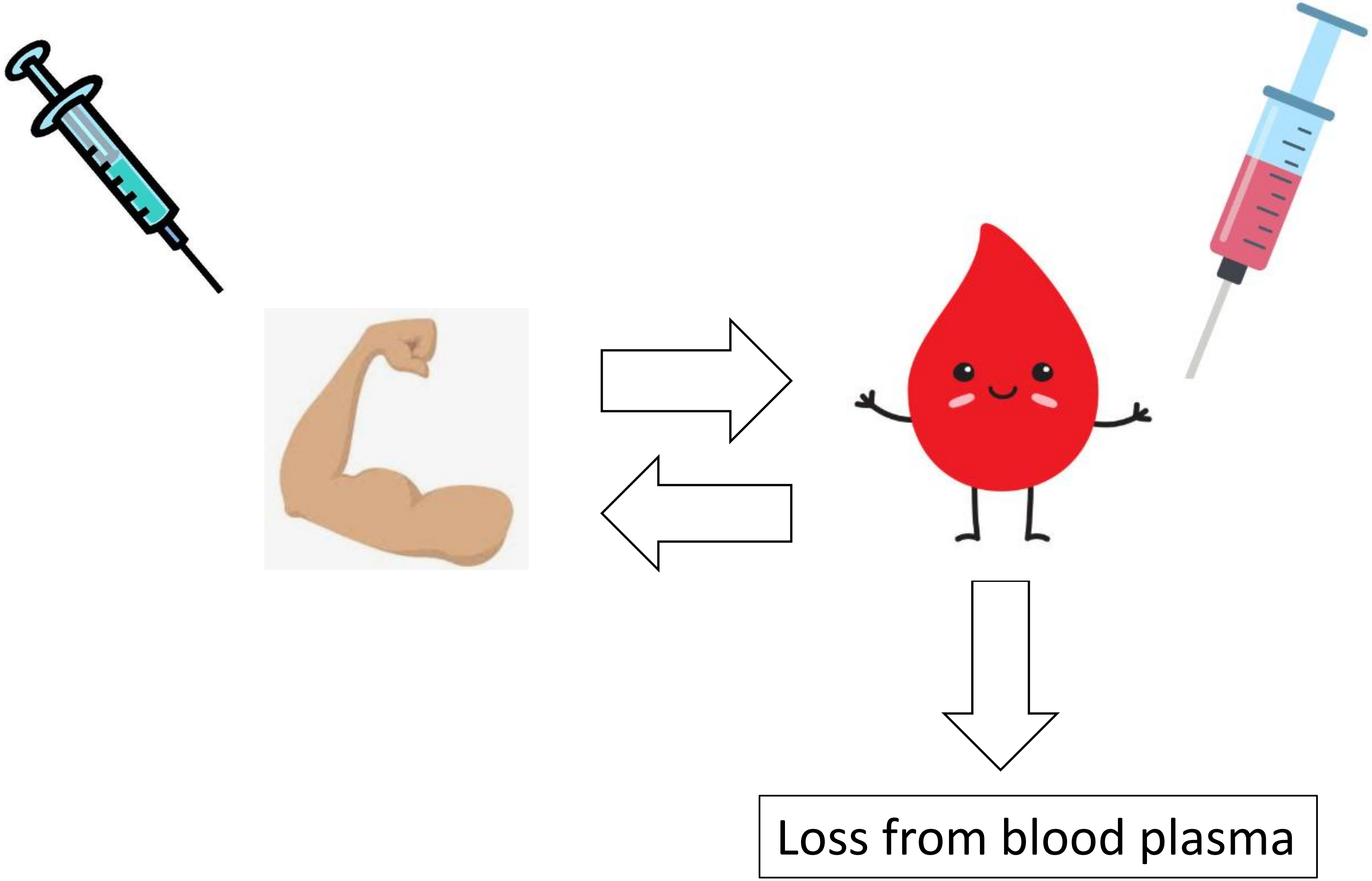
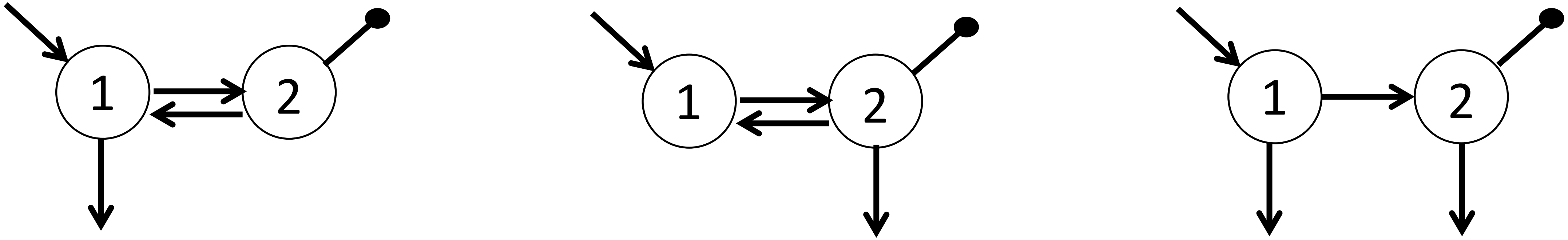


Loss from blood plasma

What if I change my model?



Are these the same models or different models?

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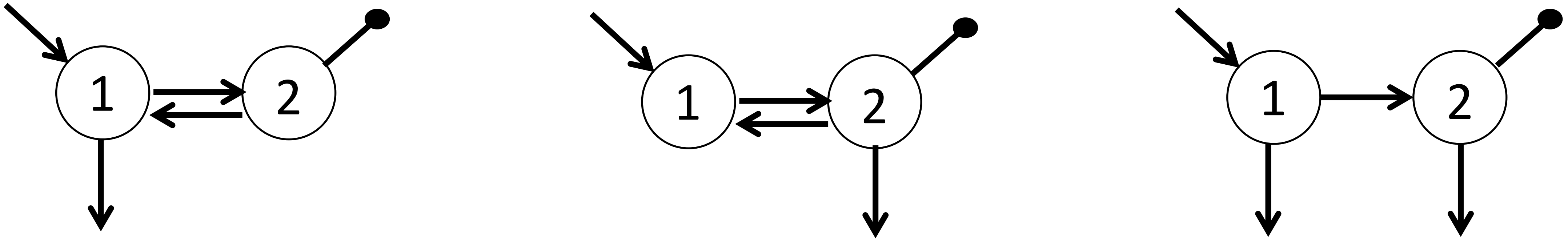

Are these the same models or different models?
(…what do we mean by “**same**”?)

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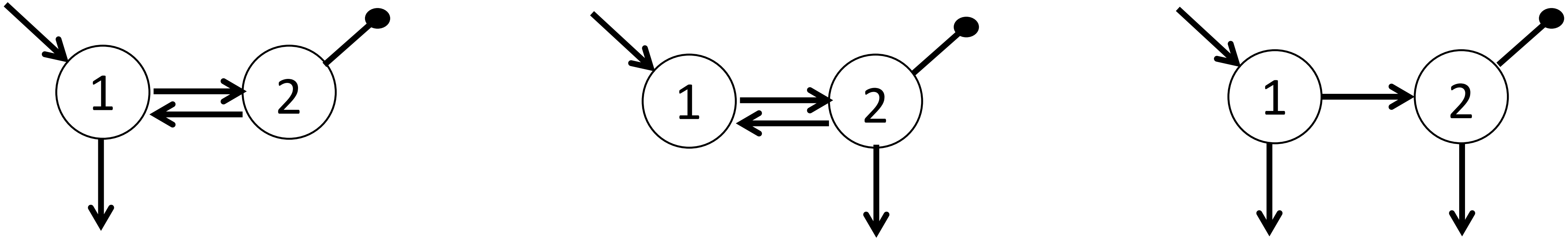

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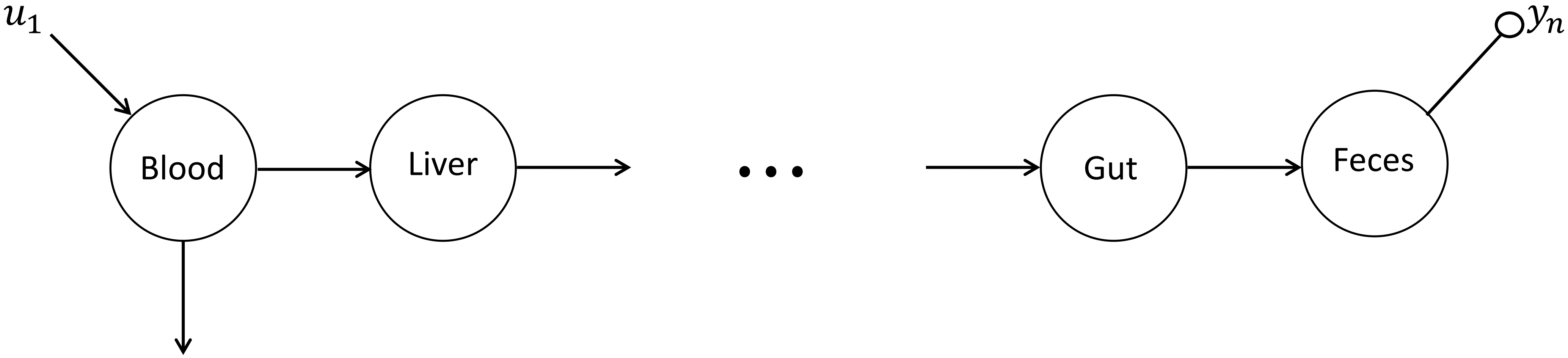
(…what do we mean by “**same**”?)

Not immediately obvious, let’s examine other models first…

Path models

Consider a one-way path with input on one end and output on other



Ex:

- metabolism model*
- time-delay model
- signal delay with attenuation

*Example 4.3 from DiStefano, *Dynamics Systems Biology Modeling and Simulation*

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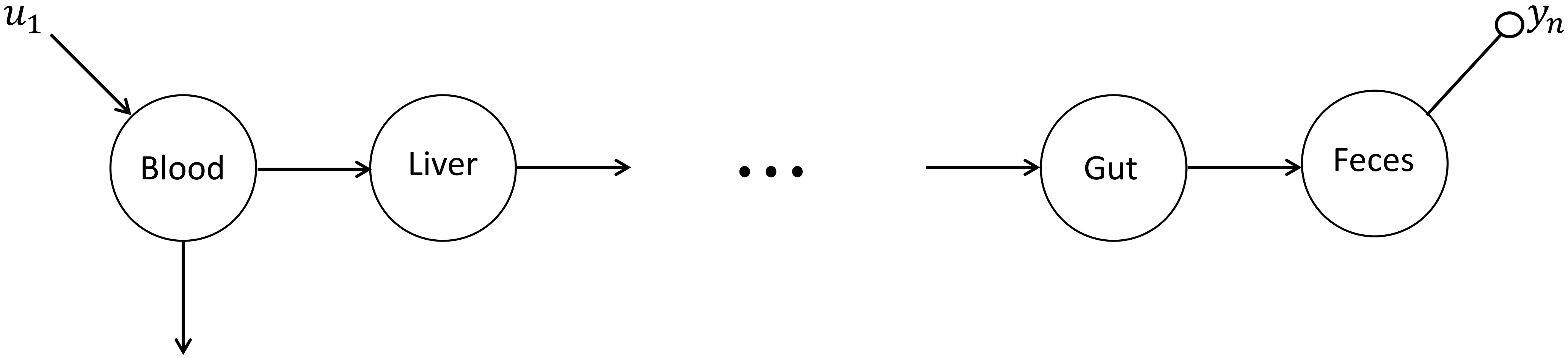

- locally identifiable

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Consider the following models:

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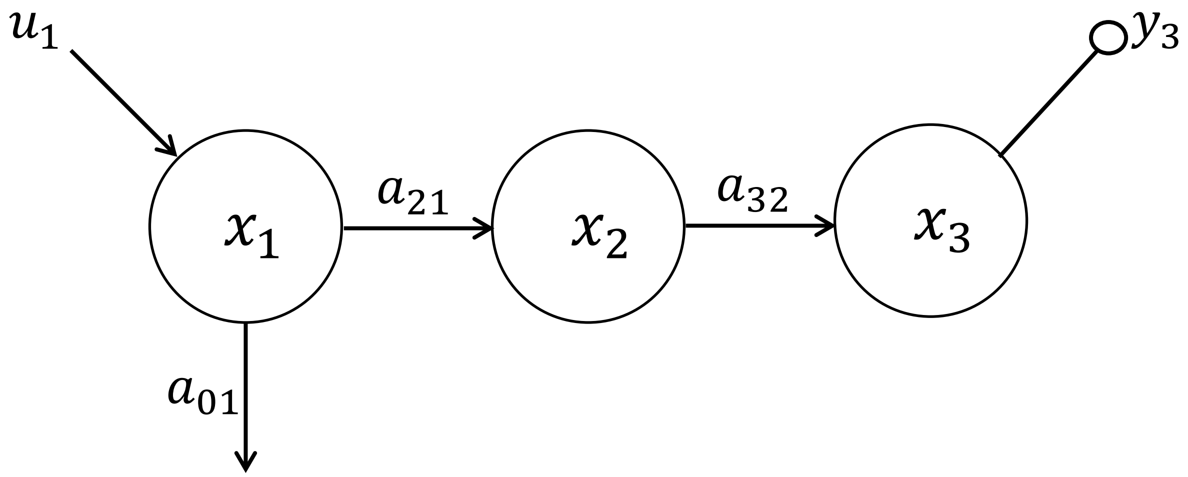
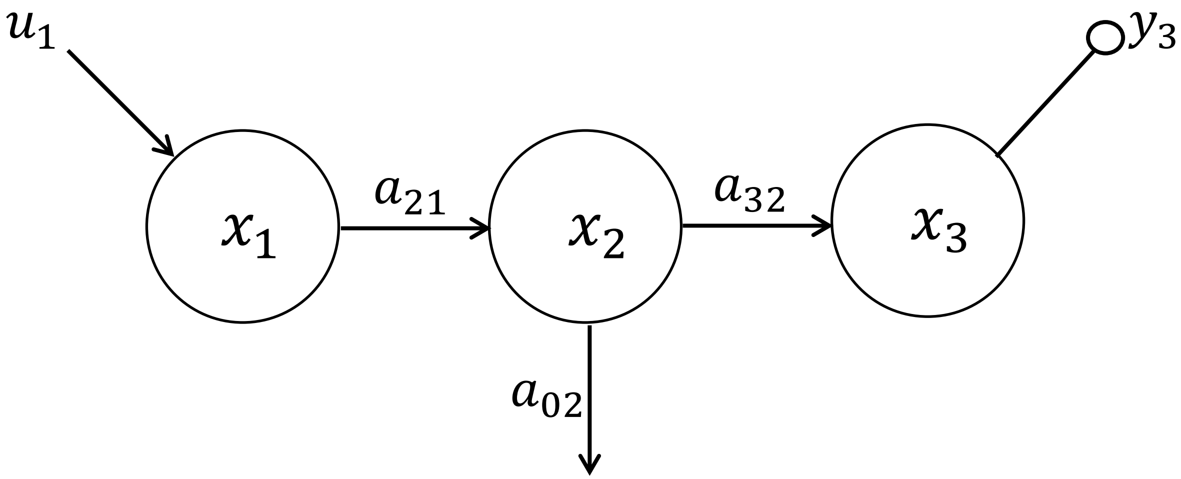


I/O eqn $\dddot{y}_3 + (a_{32} + a_{01} + a_{21})\ddot{y}_3 + (a_{01}a_{32} + a_{21}a_{32})\dot{y}_3 = a_{21}a_{32}u_1$

Consider the following models:

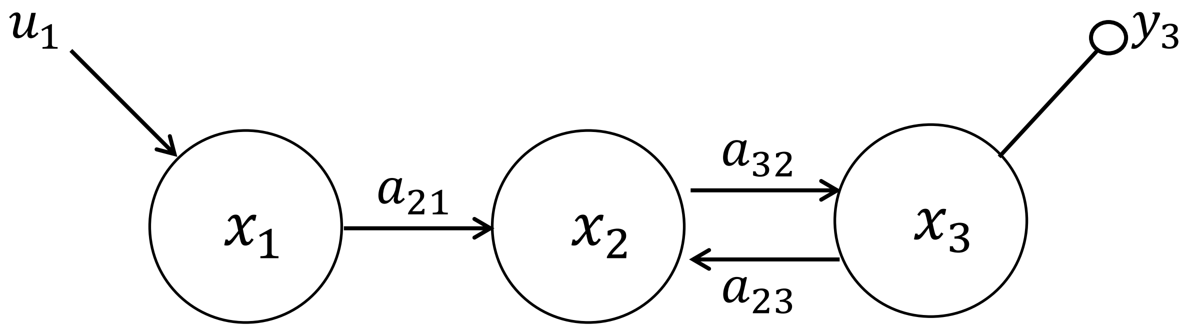
Model 2



I/O eqn $\dddot{y}_3 + (a_{21} + a_{02} + a_{32})\ddot{y}_3 + (a_{02}a_{21} + a_{32}a_{21})\dot{y}_3 = a_{32}a_{21}u_1$

Consider the following models:

Model 3



I/O eqn $\dddot{y}_3 + (a_{21} + a_{23} + a_{32})\ddot{y}_3 + (a_{23}a_{21} + a_{32}a_{21})\dot{y}_3 = a_{32}a_{21}u_1$

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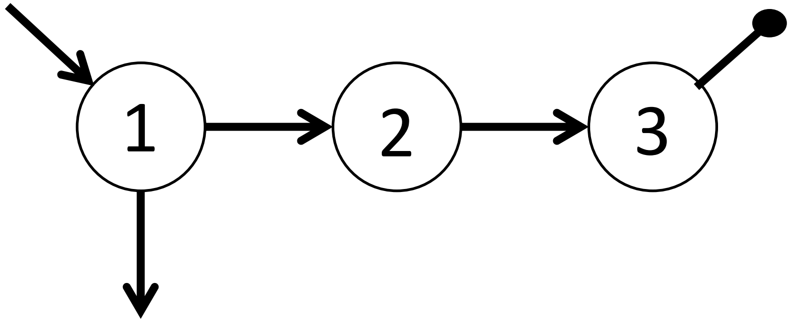

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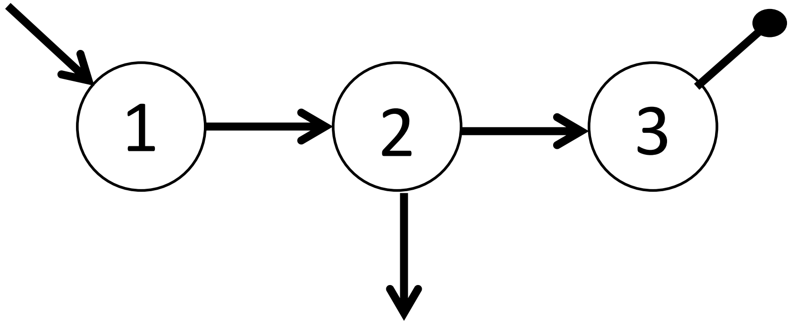

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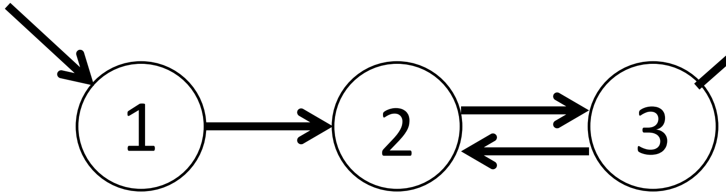

Coefficient maps:

$a_{32} + a_{01} + a_{21}$	$a_{21} + a_{02} + a_{32}$	$a_{21} + a_{23} + a_{32}$
$a_{01}a_{32} + a_{21}a_{32}$	$a_{02}a_{21} + a_{32}a_{21}$	$a_{23}a_{21} + a_{32}a_{21}$
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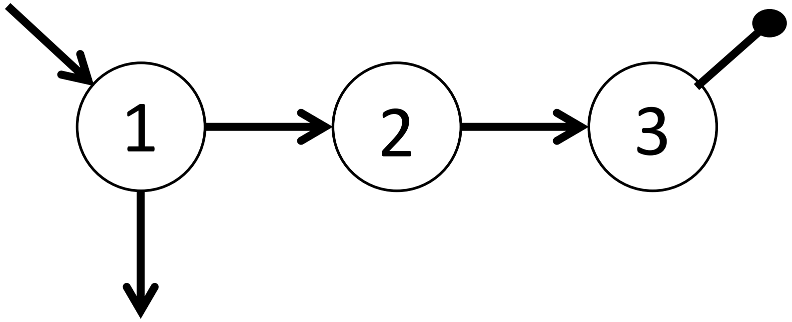
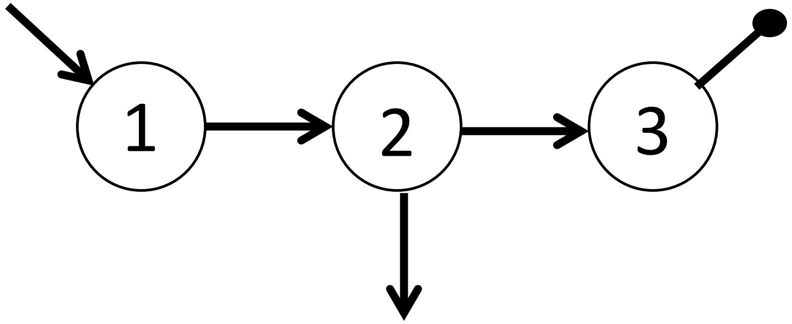


Model 2



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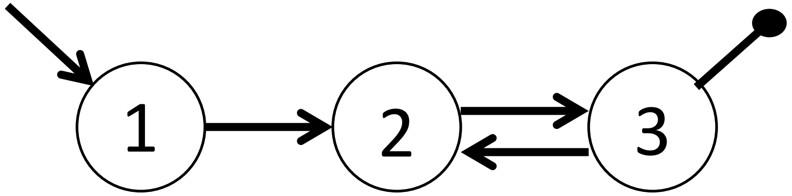

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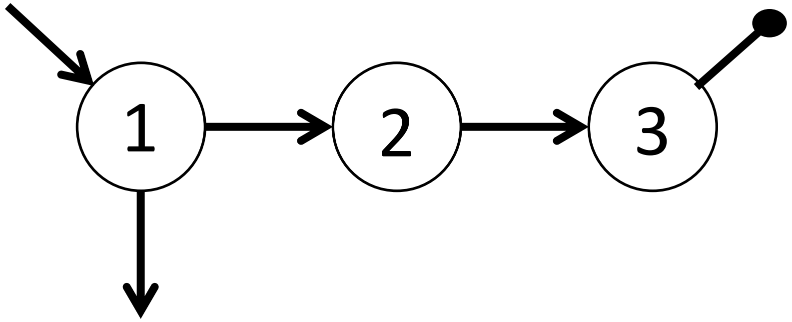
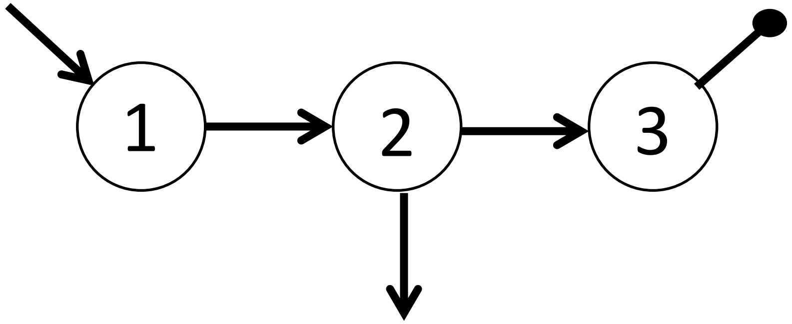


Model 2



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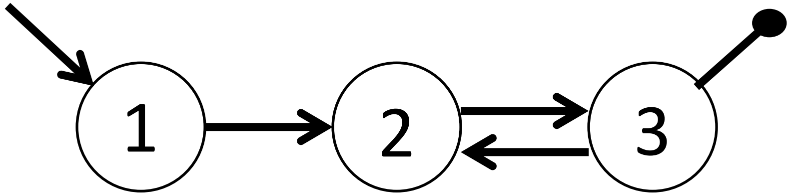

Coefficient maps:

$a_{32} \equiv a_{21} \equiv a_{21}$

$a_{01} \equiv a_{02} \equiv a_{23}$

$a_{21} \equiv a_{32} \equiv a_{32}$

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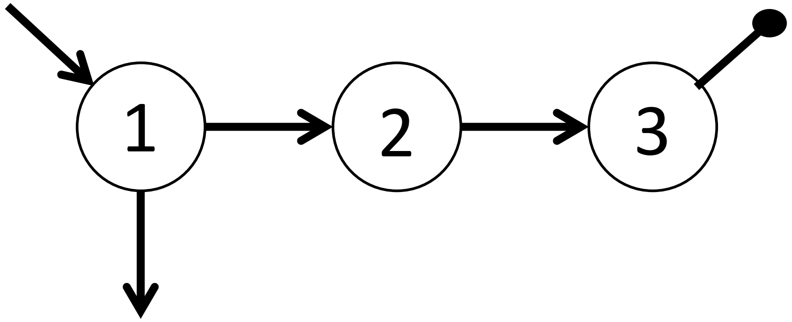

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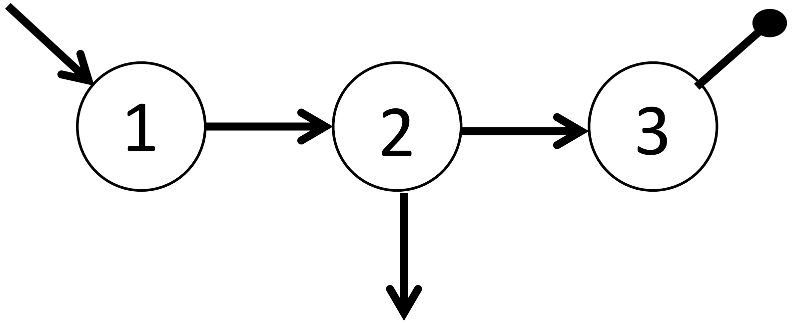

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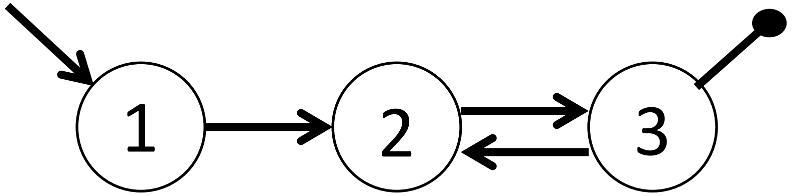

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$$a_{21} \equiv a_{32} \equiv a_{32}$$

Models are indistinguishable!

Indistinguishability

Two models are indistinguishable if for any choice of parameter values in the first model, there is a choice of parameter values in the second model that will yield the same dynamics, and vice versa

[Walter et al 1984]

Indistinguishability

Two models are <u>indistinguishable</u> if for any choice of parameter values in the first model, there is a choice of parameter values in the second model that will yield the same dynamics, and vice versa

Necessary conditions:

- Same input/output variables

[Walter et al 1984]

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Necessary conditions:

- Same input/output variables
- Same structure of I/O eqns, i.e. same u, y, $\dot{u}$, $\dot{y}$, … terms appearing

[Walter et al 1984]

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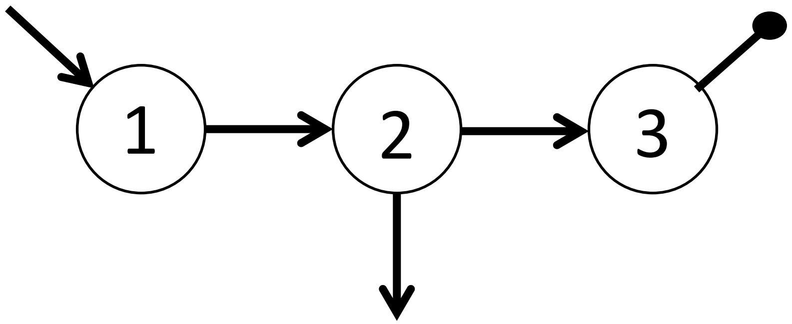
Necessary conditions:

- Same input/output variables
- Same structure of I/O eqns, i.e. same $u, y, \dot{u}, \dot{y}, \ldots$ terms appearing
- Coefficients must satisfy the same algebraic dependency relationships

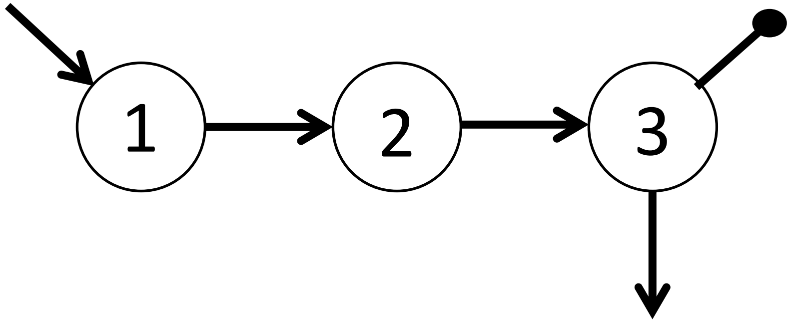
[Walter et al 1984]

Distinguishable models:

Model 2



Model 4



I/O eqn:

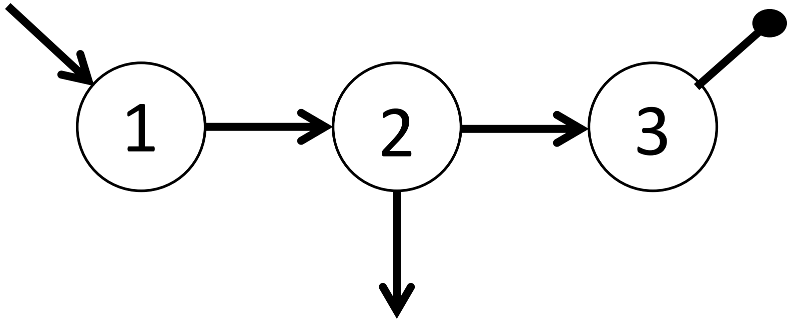
$$\begin{aligned}&\dddot{y}_3 + (a_{21} + a_{02} + a_{32})\ddot{y}_3\\ &+ (a_{02}a_{21} + a_{32}a_{21})\dot{y}_3\\ &\qquad = a_{32}a_{21}u_1\end{aligned}$$

$$\begin{aligned}&\dddot{y}_3 + (a_{21} + a_{03} + a_{32})\ddot{y}_3\\ &+ (a_{32}a_{21} + a_{32}a_{03})\dot{y}_3 + (a_{21}a_{32}a_{03})y_3\\ &\qquad = a_{32}a_{21}u_1\end{aligned}$$

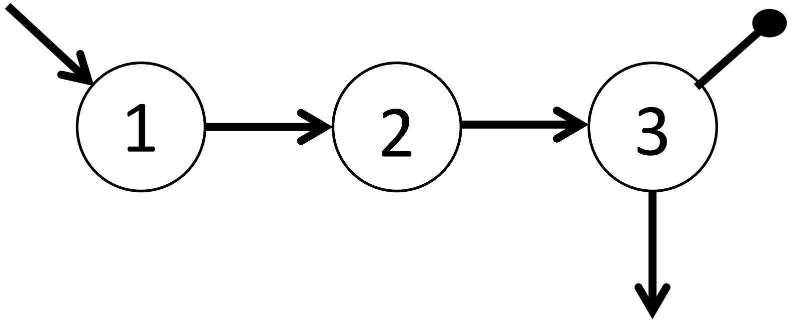
Not the same I/O eqn structure ⇒ Distinguishable!

Distinguishable models:

Model 2



Model 4



I/O eqn:

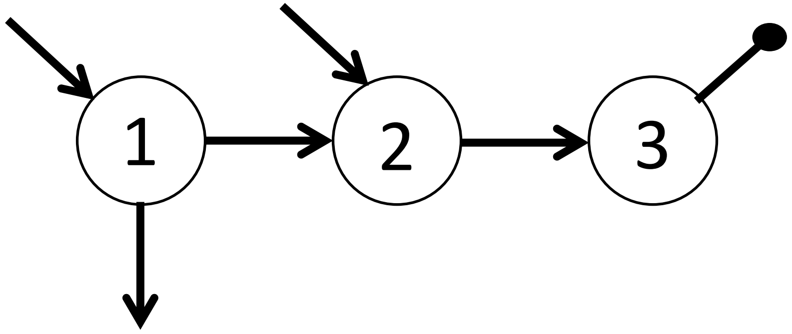
$$\dddot{y}_3 + (a_{21} + a_{02} + a_{32})\ddot{y}_3 + (a_{02}a_{21} + a_{32}a_{21})\dot{y}_3 = a_{32}a_{21}u_1$$

$$\dddot{y}_3 + (a_{21} + a_{03} + a_{32})\ddot{y}_3 + (a_{32}a_{21} + a_{32}a_{03})\dot{y}_3 + (a_{21}a_{32}a_{03})y_3 = a_{32}a_{21}u_1$$

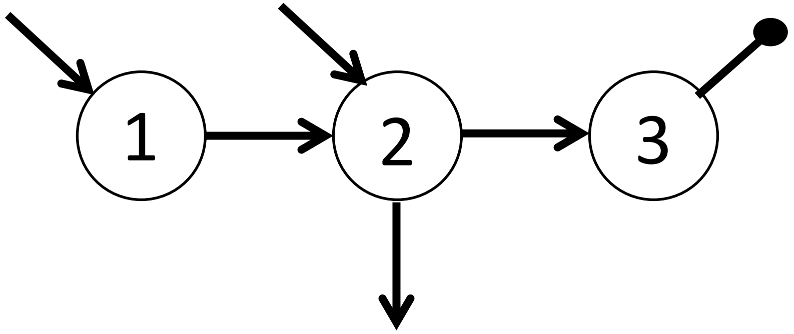
Not the same I/O eqn structure ⇒ Distinguishable!

Distinguishable models:

Model 1A



Model 2A



I/O eqn:

$$\dddot{y}_3 + (a_{32} + a_{01} + a_{21})\ddot{y}_3 + (a_{01}a_{32} + a_{21}a_{32})\dot{y}_3 = a_{21}a_{32}u_1 + a_{32}\dot{u}_2 + (a_{01}a_{32} + a_{21}a_{32})u_2$$

$$\dddot{y}_3 + (a_{21} + a_{02} + a_{32})\ddot{y}_3 + (a_{02}a_{21} + a_{21}a_{32})\dot{y}_3 = a_{21}a_{32}u_1 + a_{32}\dot{u}_2 + (a_{21}a_{32})u_2$$

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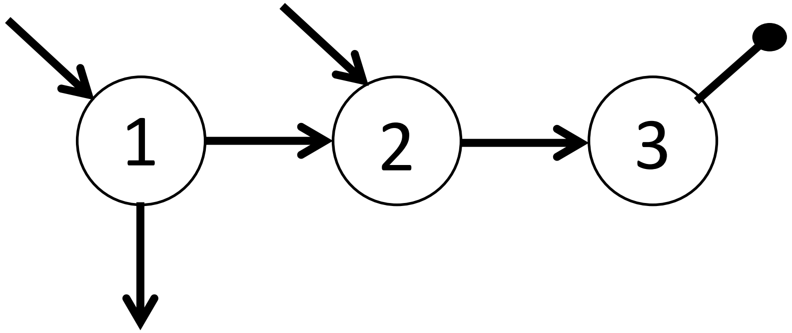
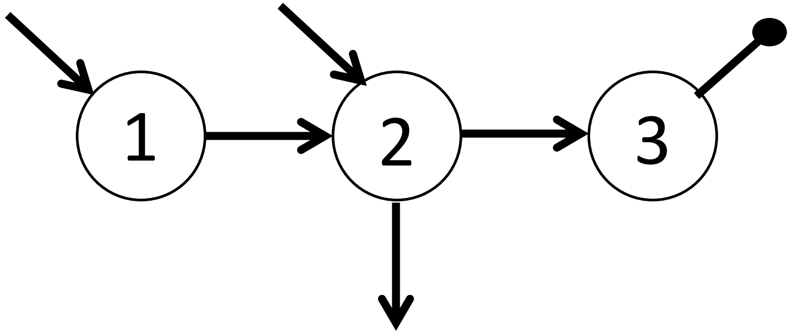


Model 2A



I/O eqn:

$$\dddot{y}_3 + (a_{32} + a_{01} + a_{21})\ddot{y}_3 + (a_{01}a_{32} + a_{21}a_{32})\dot{y}_3 = a_{21}a_{32}u_1 + a_{32}\dot{u}_2 + (a_{01}a_{32} + a_{21}a_{32})u_2$$

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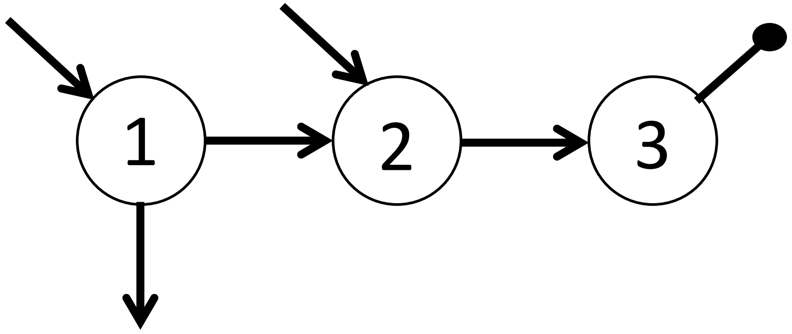
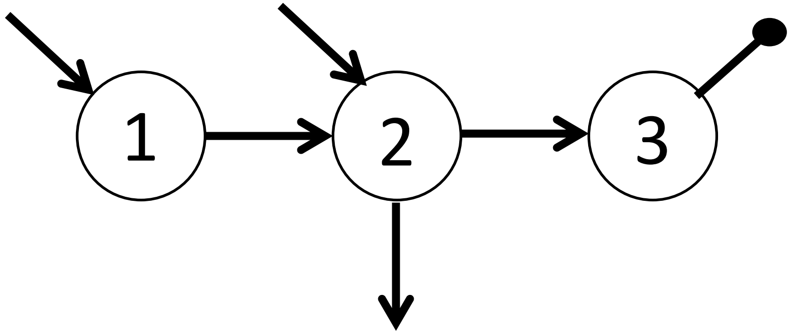


Model 2A



I/O eqn:

$$\dddot{y}_3 + (\overbrace{a_{32} + a_{01} + a_{21}}^{c_1})\ddot{y}_3 + (\overbrace{a_{01}a_{32} + a_{21}a_{32}}^{c_2})\dot{y}_3 = \overbrace{a_{21}a_{32}}^{c_3}u_1 +$$

$$\underbrace{a_{32}}_{c_4}\dot{u}_2 + (\underbrace{a_{01}a_{32} + a_{21}a_{32}}_{c_5})u_2$$

$$\dddot{y}_3 + (a_{21} + a_{02} + a_{32})\ddot{y}_3 + (a_{02}a_{21} + a_{21}a_{32})\dot{y}_3 = a_{21}a_{32}u_1 +$$

$$a_{32}\dot{u}_2 + (a_{21}a_{32})u_2$$

Distinguishable models:

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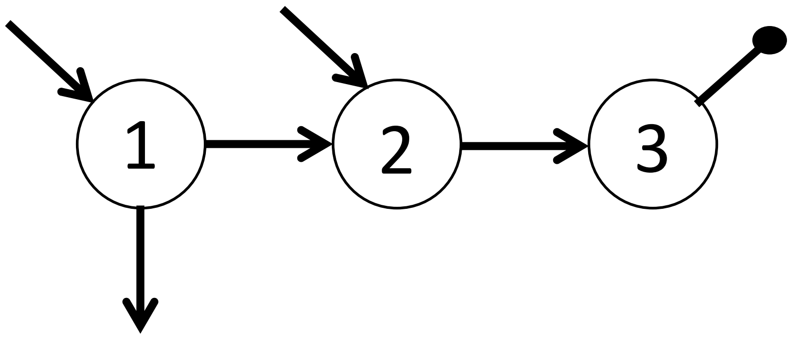
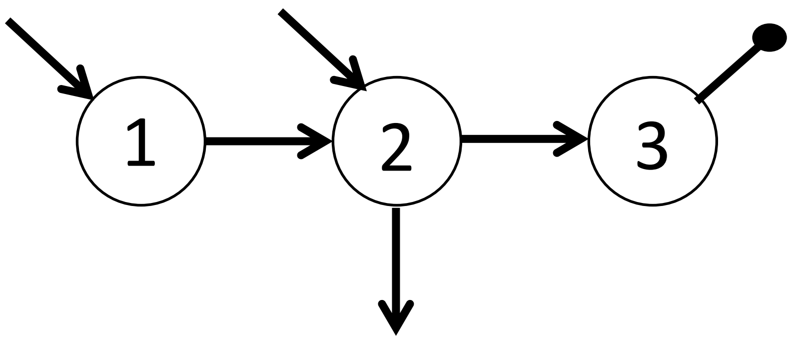


Model 2A



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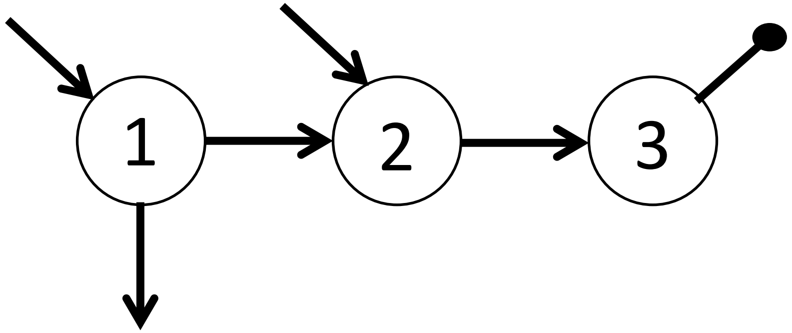
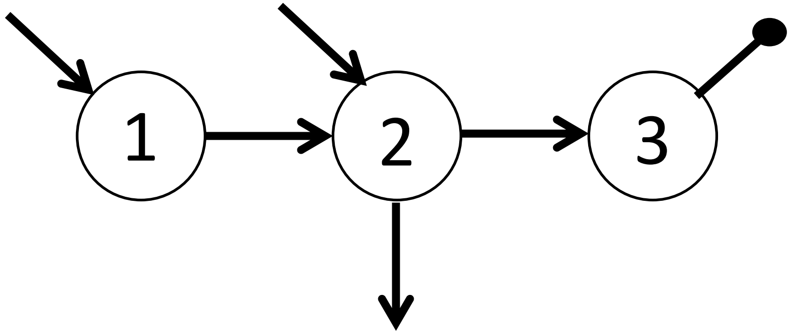


Model 2A



Algebraic dependency relationships:

Model 1: $c_2 - c_5 = 0, \quad c_1 c_4 - c_4^2 - c_5 = 0$

Model 2: $c_3 - c_5 = 0, \quad c_2 c_4^2 - c_1 c_4 c_5 + c_5^2 = 0$

$\Rightarrow$ Distinguishable!

Indistinguishability

Two models are indistinguishable if for any choice of parameter values in the first model, there is a choice of parameter values in the second model that will yield the same dynamics, and vice versa

Necessary conditions:

- Same input/output variables
- Same structure of I/O eqns, i.e. same u, y, $\dot{u}$, $\dot{y}$, … terms appearing
- Coefficients must satisfy the same algebraic dependency relationships

How to prove indistinguishability?

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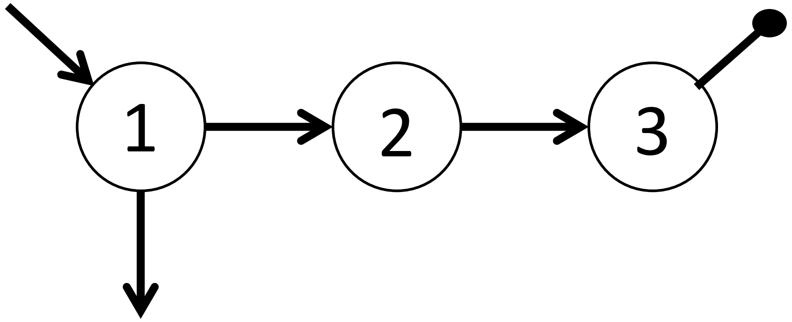
- Coefficients must satisfy the same algebraic dependency relationships

Sufficient: Check that images of coefficient maps are the same

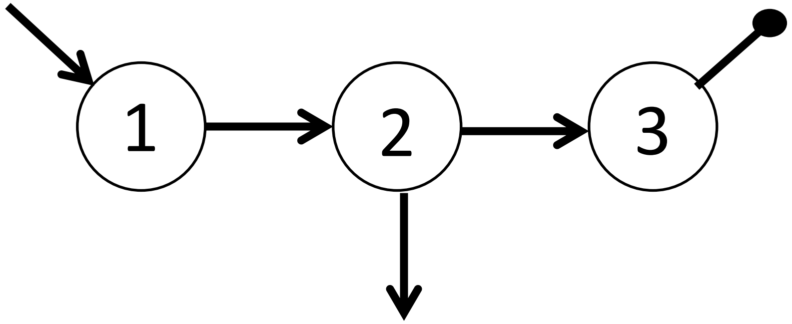
[M-Rosen-Sullivant 2018]

Consider the following models:

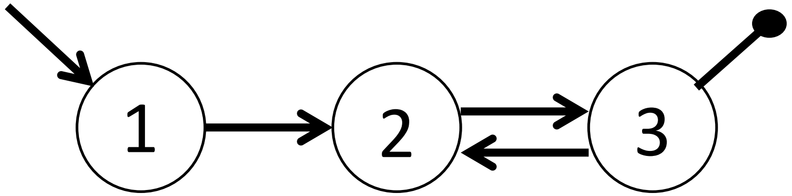
Model 1



Model 2



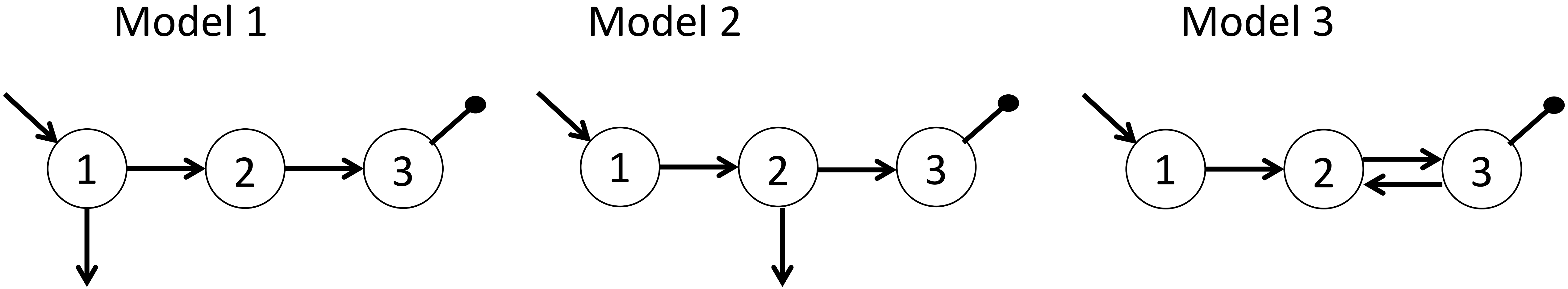
Model 3



Coefficient maps: all **surjective**

$a_{32} + a_{01} + a_{21}$	$a_{21} + a_{02} + a_{32}$	$a_{21} + a_{23} + a_{32}$
$a_{01}a_{32} + a_{21}a_{32}$	$a_{02}a_{21} + a_{32}a_{21}$	$a_{23}a_{21} + a_{32}a_{21}$
$a_{21}a_{32}$	$a_{32}a_{21}$	$a_{32}a_{21}$

Consider the following models:



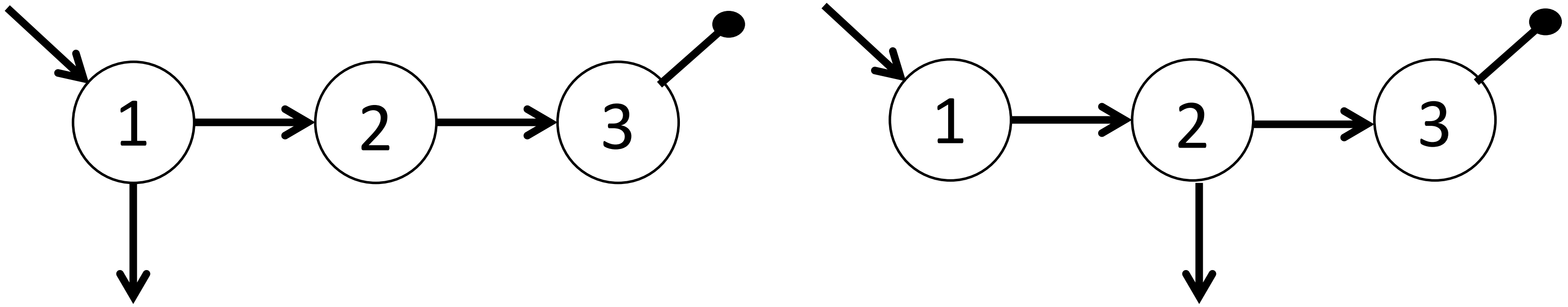
Coefficient maps: all **surjective**

How to tell without computation?

$a_{32} + a_{01} + a_{21}$	$a_{21} + a_{02} + a_{32}$	$a_{21} + a_{23} + a_{32}$
$a_{01}a_{32} + a_{21}a_{32}$	$a_{02}a_{21} + a_{32}a_{21}$	$a_{23}a_{21} + a_{32}a_{21}$
$a_{21}a_{32}$	$a_{32}a_{21}$	$a_{32}a_{21}$

Conditions on graph?

Consider Model 1 and Model 2:

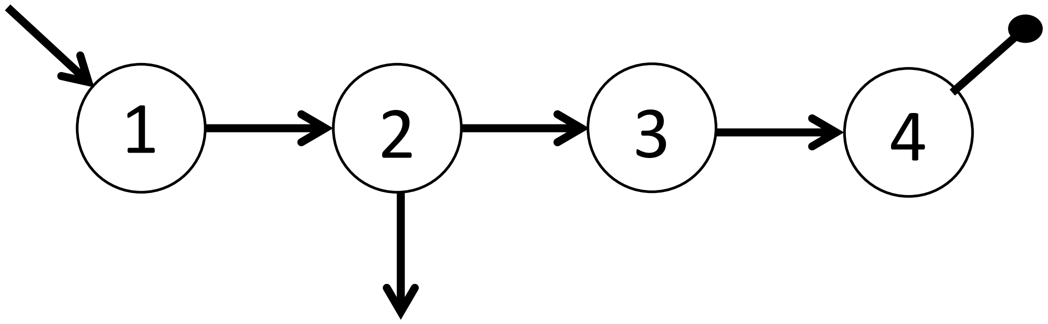


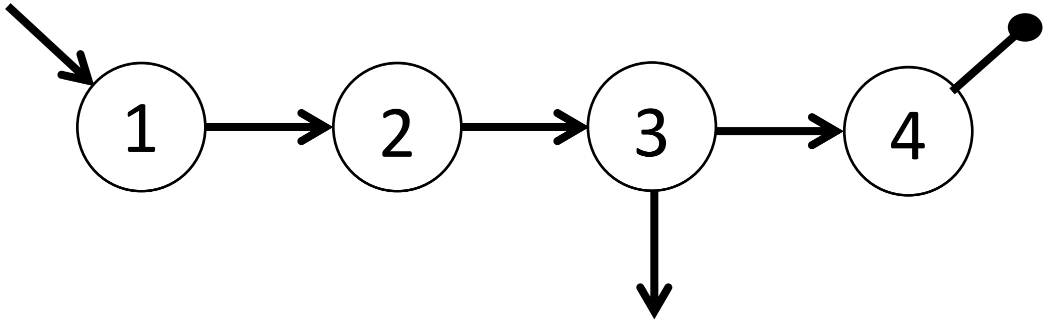
Noticed we “moved the leak down the path”

Can move leak in general

Consider path models with a leak:

- Leak can be in compartment $i = 1, \ldots, n - 2$





Then we can move the leak down the path

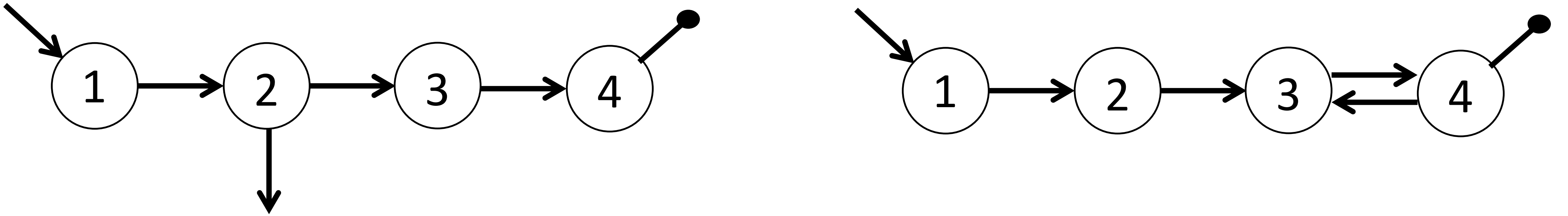
- Leak moves from i to $i + 1$

[Bortner-M 2024]

Can replace leak with backwards edge

Consider path models with a leak:

- Leak can be in compartment $i = 1, \ldots, n-1$



Then we can replace leak with backwards edge

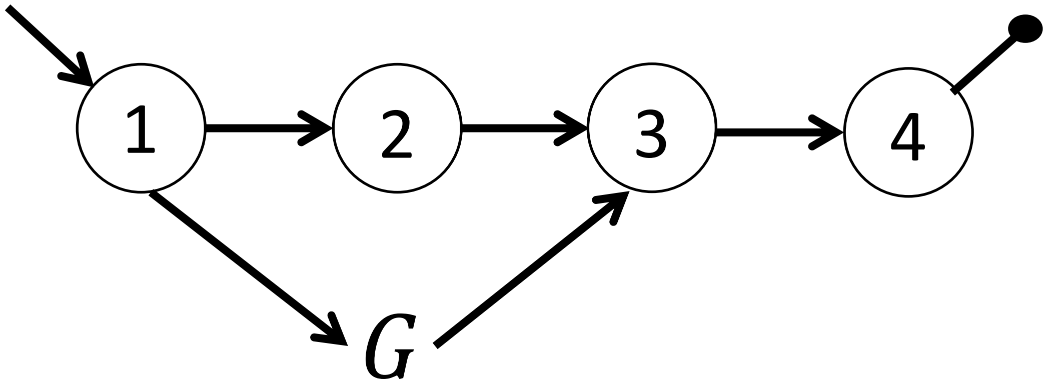
- Edge from compartment n to $n-1$

[Bortner-M 2024]

Detour indistinguishability

Consider path models with a "detour":

- exit and entry nodes i and j with outgoing and incoming edges connecting to graph G



[Bortner-M 2024]

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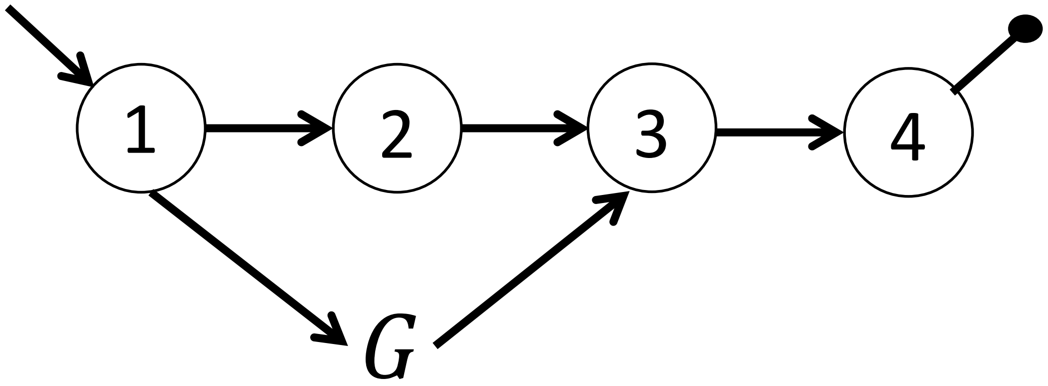

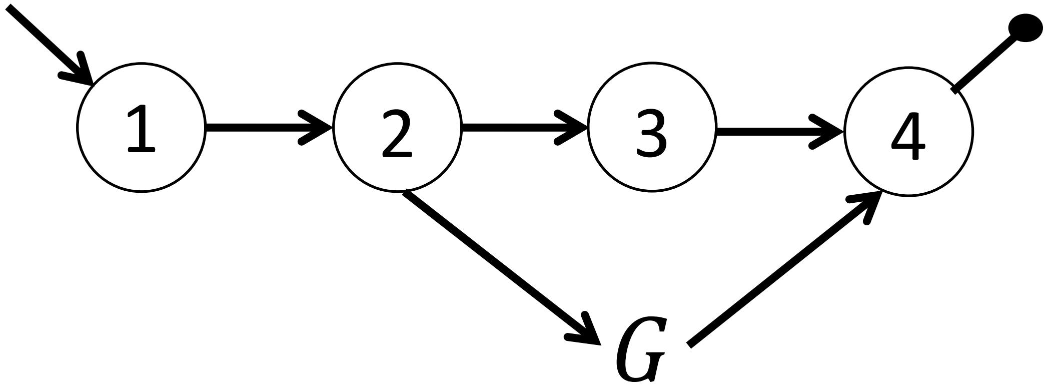

Then we can move the “detour” down the path:

- New exit and entry notes are $i + k$ and $j + k$

[Bortner-M 2024]

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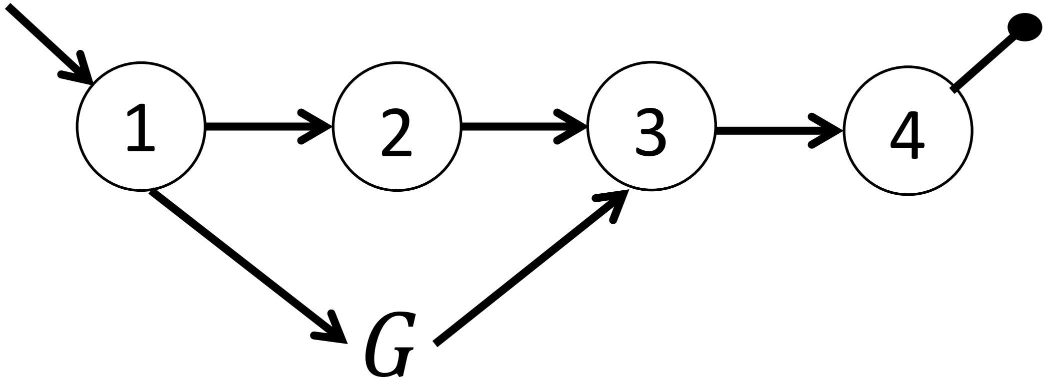

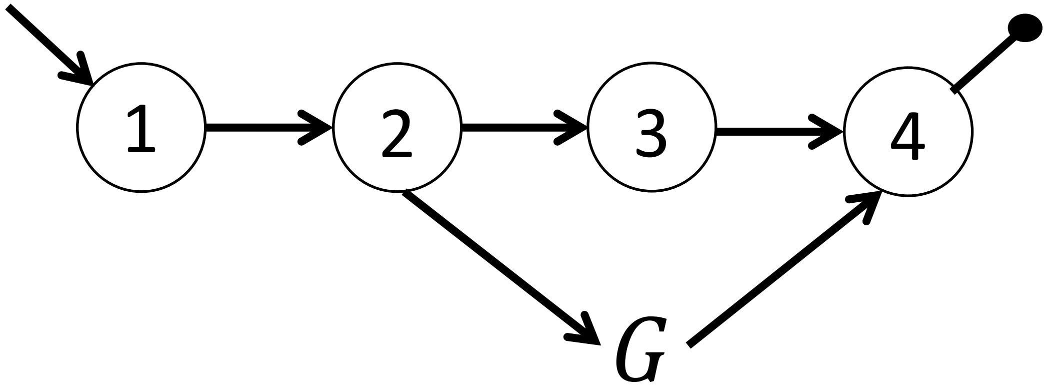

Then we can move the “detour” down the path:

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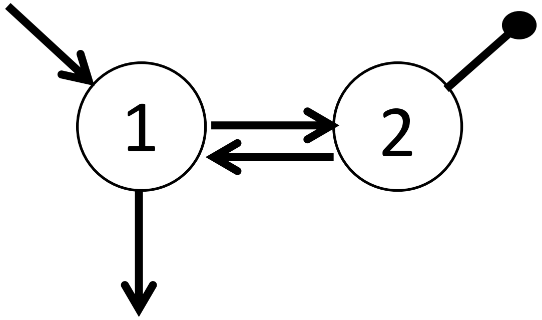
Other families of graphs?

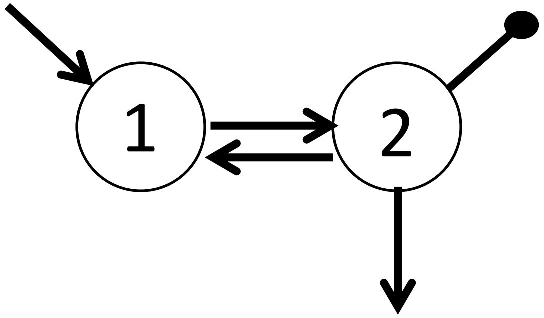
[Bortner-M 2024]

Recall our earlier vaccine models:

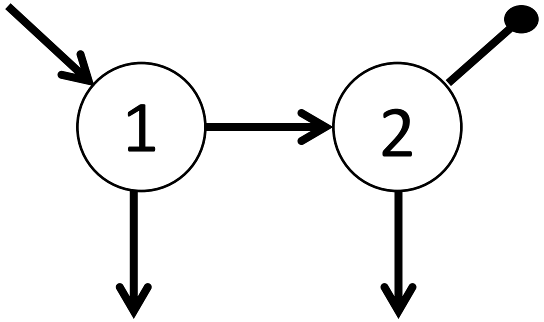
Model A



Model B



Model C



I/O eqn:

$$\ddot{y}_2 + (a_{01} + a_{12} + a_{21})\dot{y}_2 + a_{01}a_{12}y_2 = a_{21}u_1$$

$$\ddot{y}_2 + (a_{02} + a_{12} + a_{21})\dot{y}_2 + a_{02}a_{21}y_2 = a_{21}u_1$$

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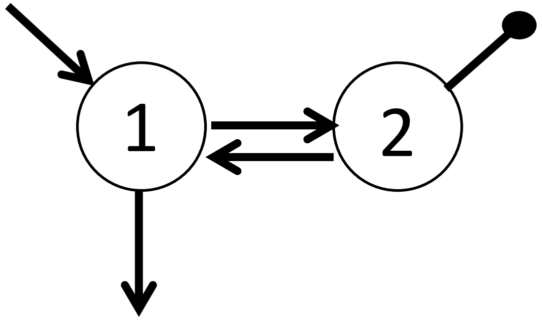

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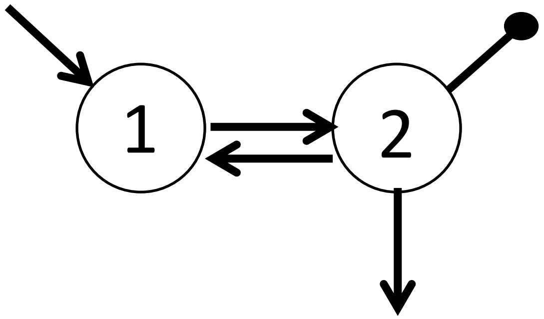

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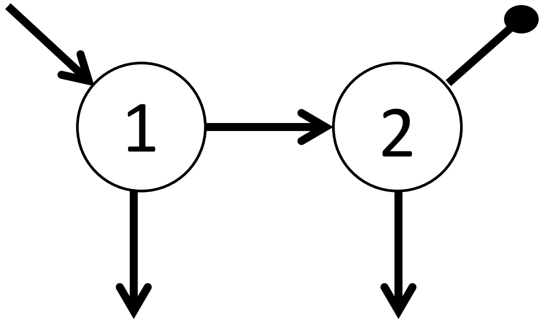

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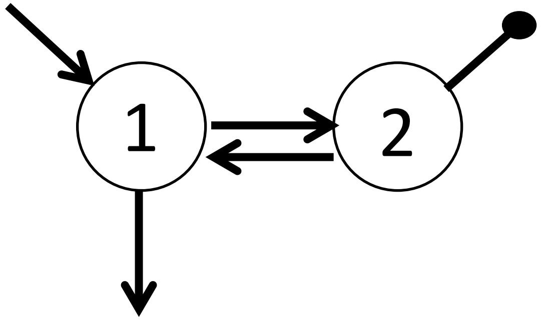

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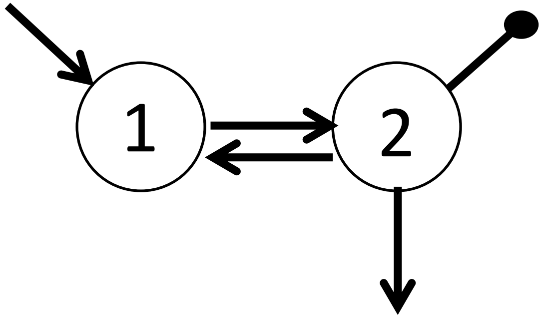

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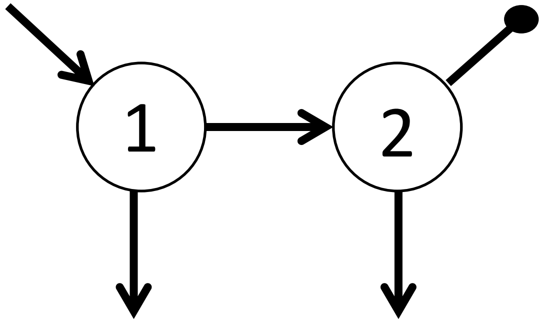

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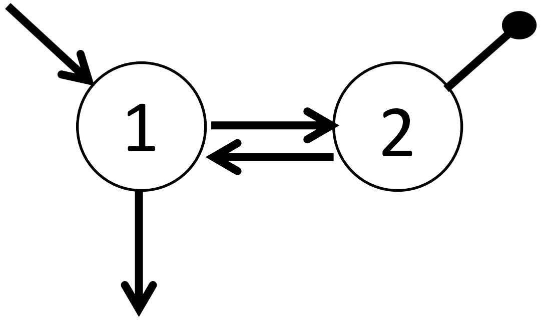
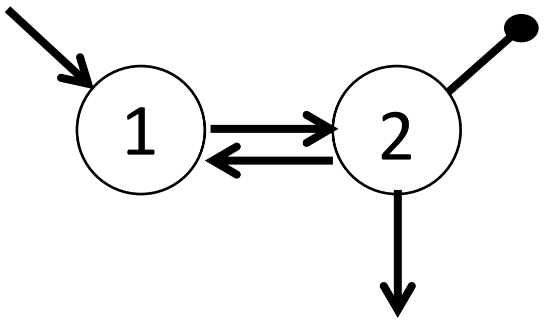
No renaming of parameters results in the same coefficients

Indistinguishable, but not from renaming:

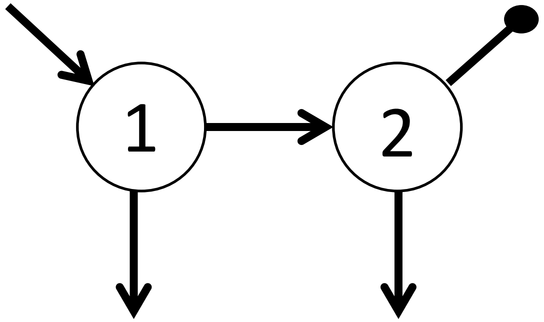
Model A



Model B



Model C



Coeff map: $(a_{01}, a_{12}, a_{21}) \mapsto (a_{01} + a_{12} + a_{21},\ \ a_{01}a_{12},\ \ a_{21})$

$$(a_{02}, a_{12}, a_{21}) \mapsto (a_{02} + a_{12} + a_{21},\ \ a_{02}a_{21},\ \ a_{21})$$

$$(a_{01}, a_{21}, a_{02}) \mapsto (a_{01} + a_{21} + a_{02},\ \ a_{01}a_{02} + a_{21}a_{02},\ \ \ a_{21})$$

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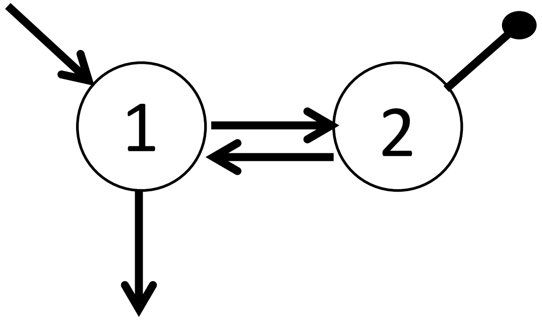
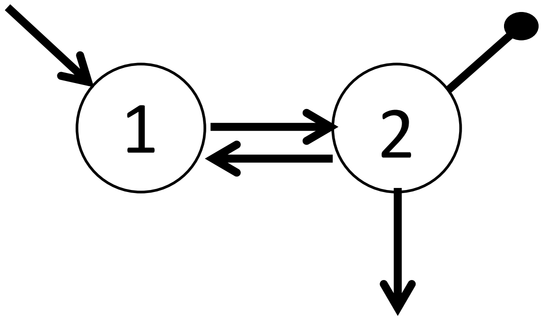


Model B



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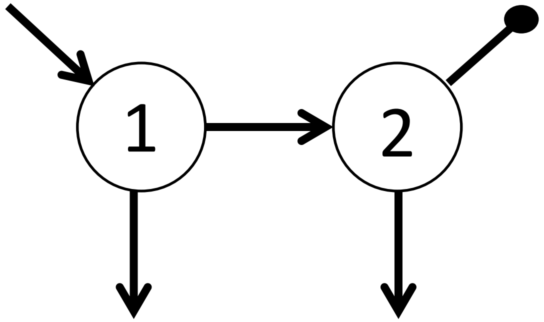

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$(a_{02}, a_{12}, a_{21}) \mapsto (a_{02} + a_{12} + a_{21},\ \ a_{02}a_{21},\ \ a_{21})$

$(a_{01}, a_{21}, a_{02}) \mapsto (a_{01} + a_{21} + a_{02},\ \ a_{01}a_{02} + a_{21}a_{02},\ \ a_{21})$

Identifiable and indistinguishable

Indistinguishable, but not from renaming:

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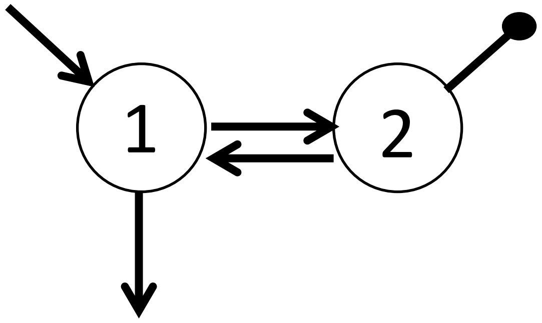
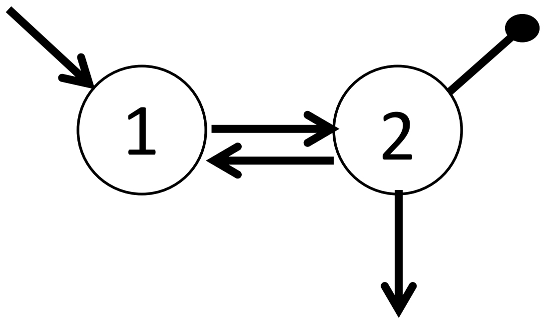
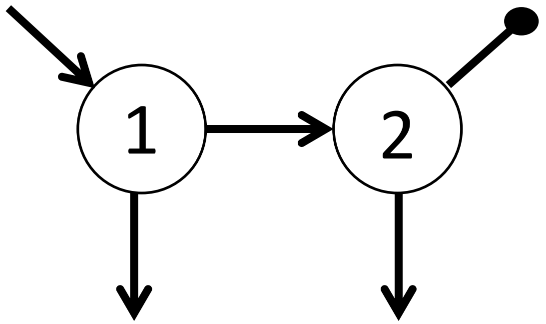


Model B



Model C



Coeff map: $(a_{01}, a_{12}, a_{21}) \mapsto (a_{01} + a_{12} + a_{21},\ \ a_{01}a_{12},\ \ a_{21})$

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$(a_{01}, a_{21}, a_{02}) \mapsto (a_{01} + a_{21} + a_{02},\ \ a_{01}a_{02} + a_{21}a_{02},\ \ a_{21})$

Special case: #params = #coeffs, identifiable ⟺ indistinguishable

So what does this all mean?

- Does it mean my original model is bad?

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- Does it mean my original model is bad?
  - No!
  - Just says with limited data, there's lots of models that can fit
- If a bunch of models work, is there a best one to choose?
  - Oftentimes, yes
  - Certain models may make more sense in terms of the rate constants to estimate

So what does this all mean?

- Do there exist models with:
  - specified inputs/outputs,
  - specified number of compartments, number of parameters

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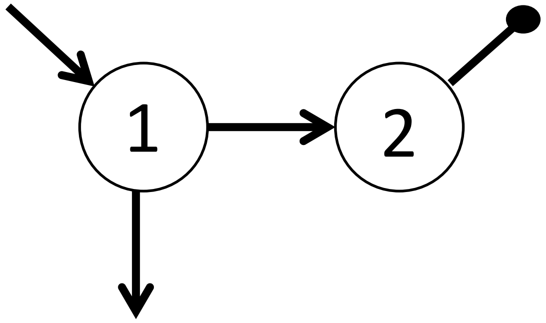
So what does this all mean?

- Do there exist models with:
  - specified inputs/outputs,
  - specified number of compartments, number of parameters

  that are distinguishable from all other models with those specs?
  - Yes!



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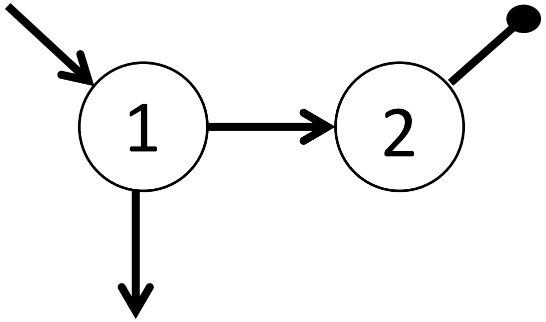
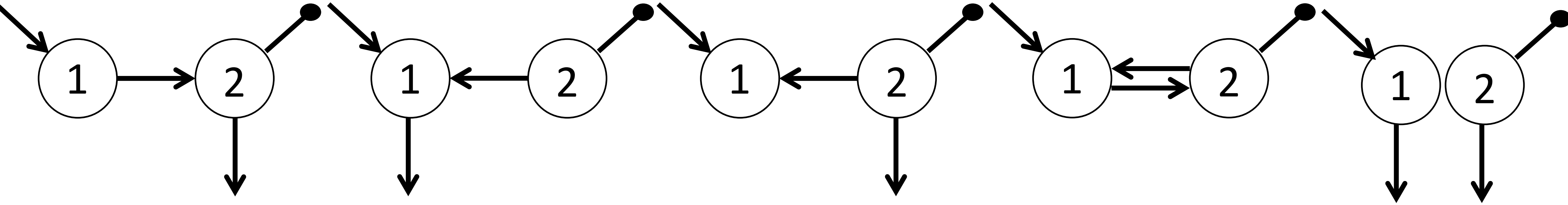
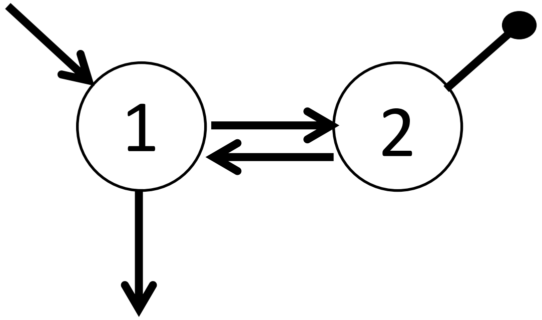


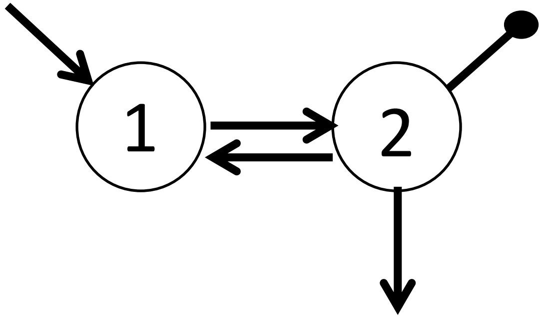
  - Distinguishable from



Back to Model A and Model B…

- Recall these models are identifiable

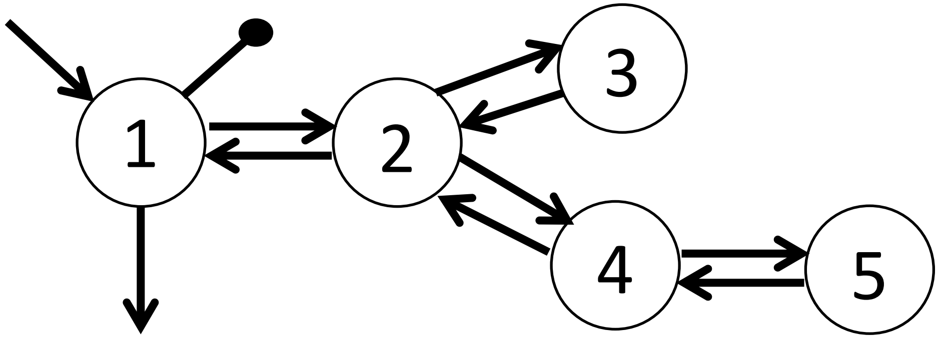




- Belong to the same “family” of models

What families of models are **identifiable**?

- Bidirectional tree models



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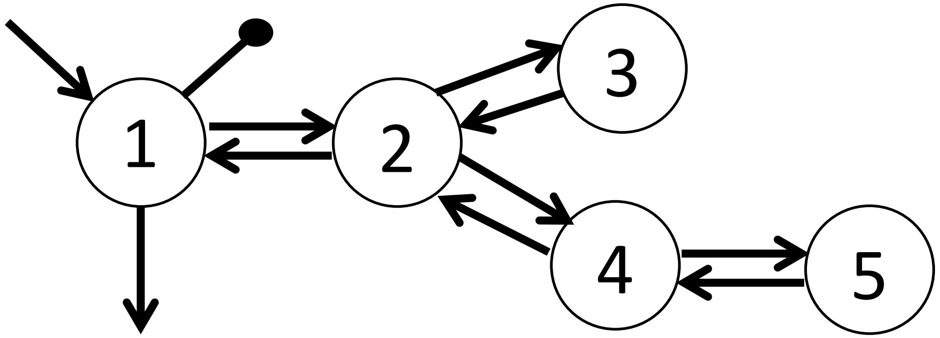

- <u>Theorem [Gross et al 2023]</u>: Let M be a bidirectional tree model with single input and output. M is locally identifiable ⇔ input and output are **at most 1 compartment away** and there is **at most 1 leak**.

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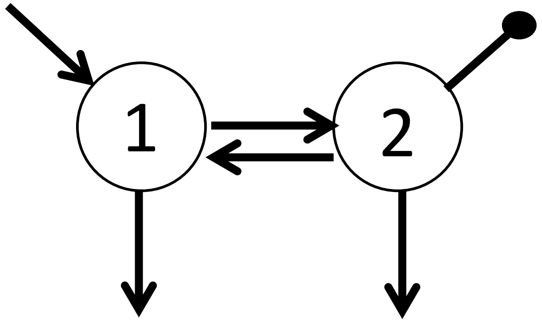

Unidentifiable

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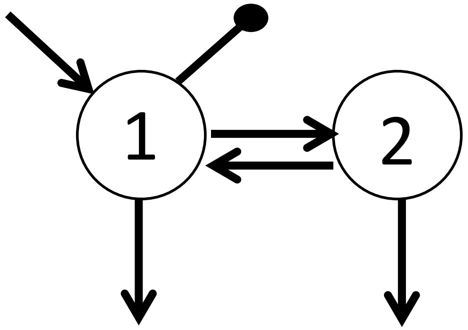

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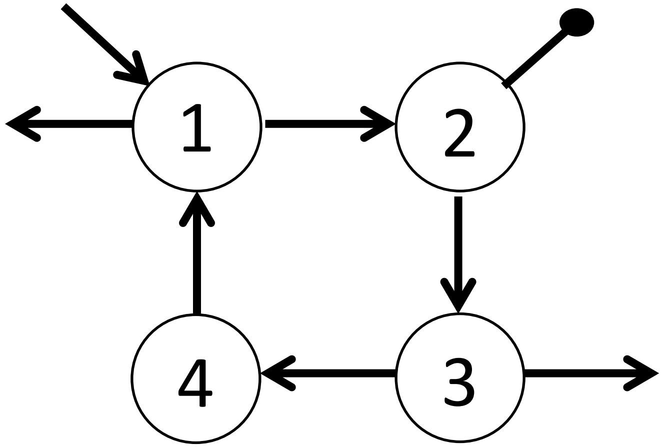
- Cycle models



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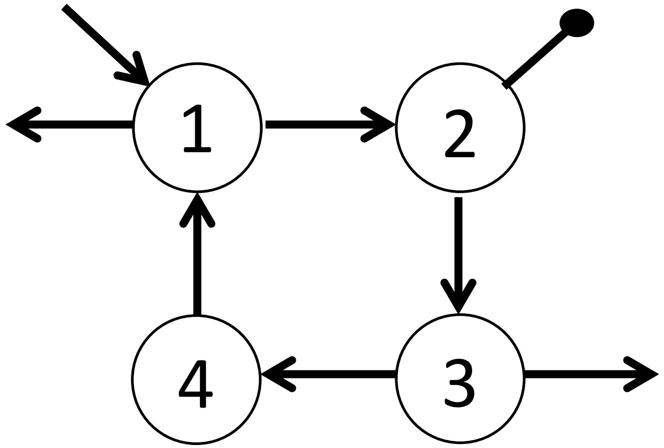
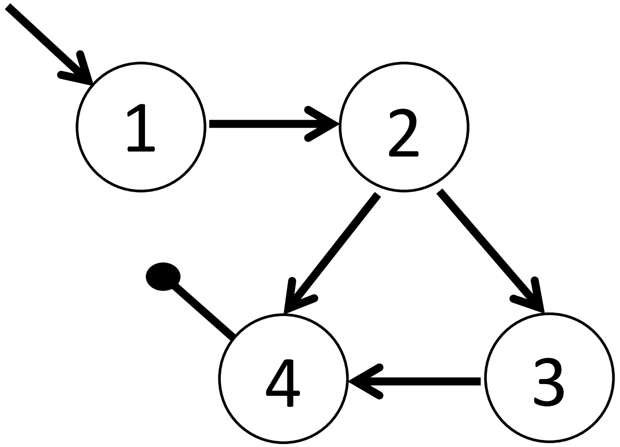


- <u>Theorem [Saber et al 2024]</u>: A directed-cycle model is locally identifiable ⇔ it is **leak-interlacing** (between any two leaks there is an input or output)

What families of models are **identifiable**?

- Acyclic models



What families of models are **identifiable**?

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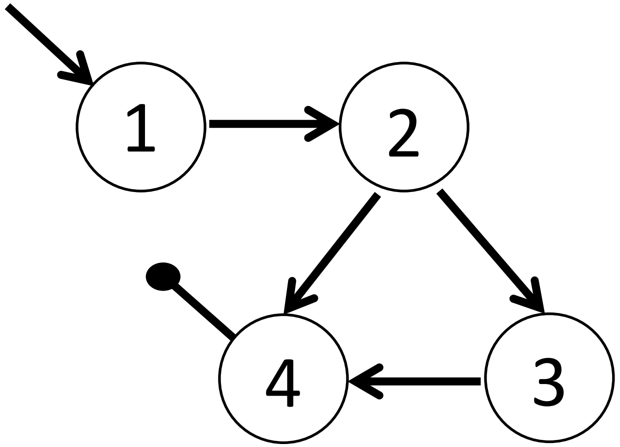
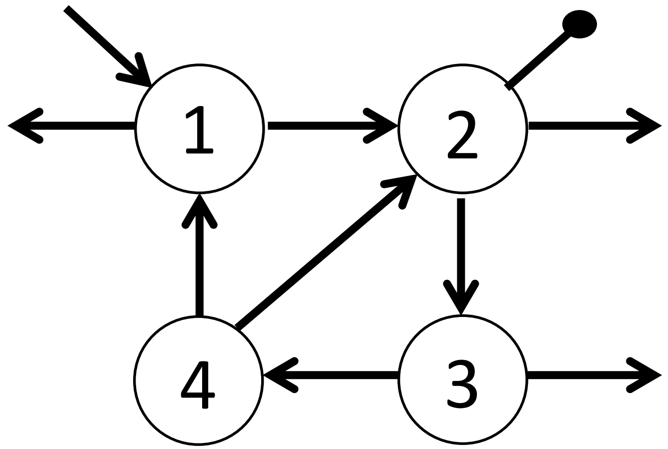


- <u>Theorem [Bortner-M, in progress]</u>: Let M be an acyclic model with a single input, single output, no leaks. M is locally identifiable $\Leftrightarrow$ it is **input-output connectable** (every vertex lies on a path from input to output) and has ≤ 1 vertex with > 1 outgoing edges

What families of models are **unidentifiable**?

- Strongly connected models w/ too many leaks



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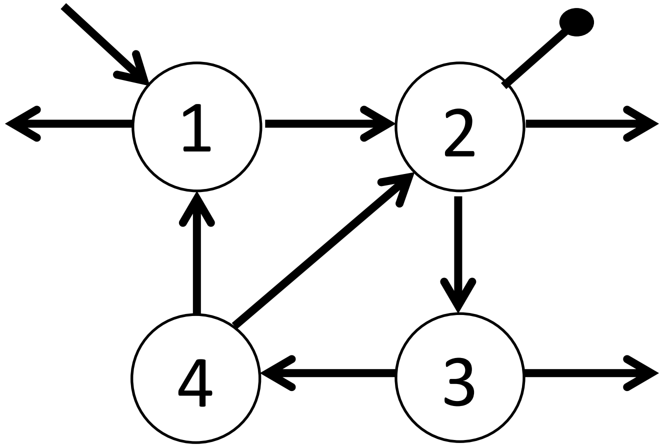
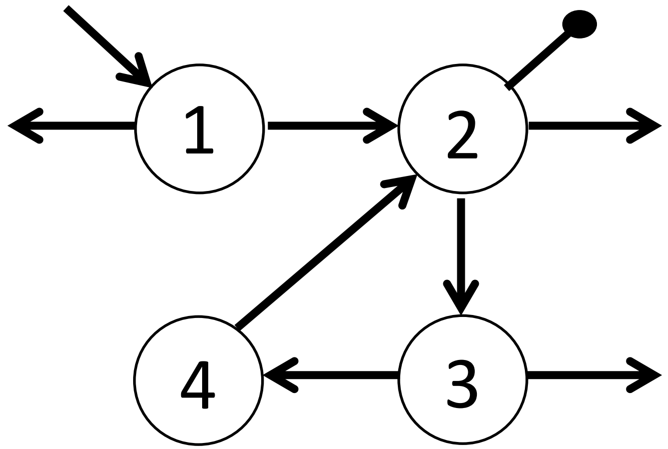


- Theorem [Bortner-M 2022]: Let G be strongly connected with one input. If the **number of leaks is greater than the number of I/O compartments**, then M is unidentifiable.

What families of models are **unidentifiable**?

- Strongly input-output connected models w/ too many leaks



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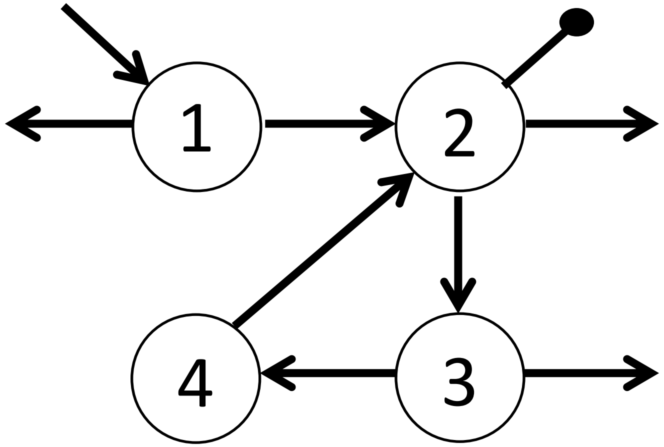
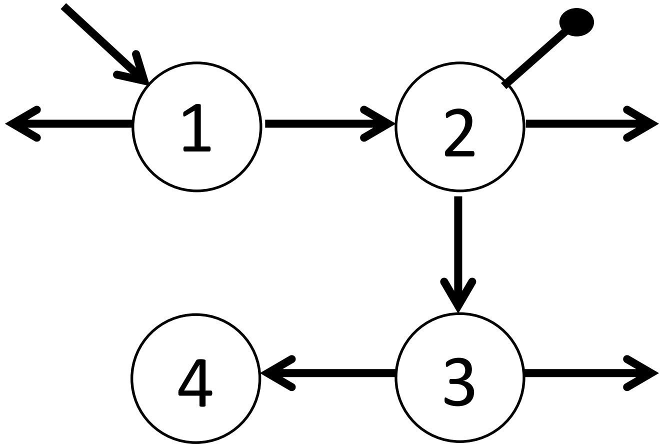


- <u>Theorem [Bortner-M 2022]</u>: Let G be strongly input-output connected with one output. If the **number of leaks is greater than the number of I/O compartments**, then M is unidentifiable.

What families of models are **unidentifiable**?

- Not output-connectable



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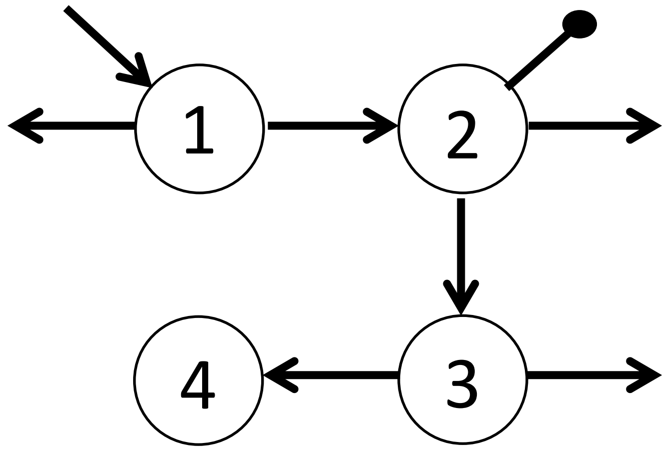
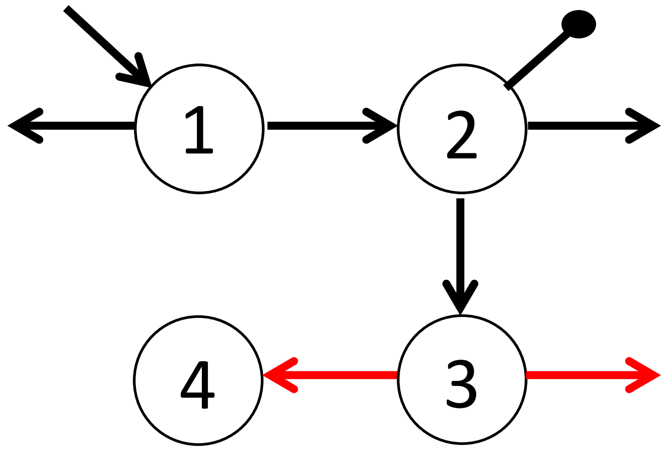


- <u>Theorem [Gross et al 2019]</u>: Let G be a graph that is **not output-connectable**. Then the model is unidentifiable.

What parameters are **unidentifiable**?

- Not in output-reachable subgraph



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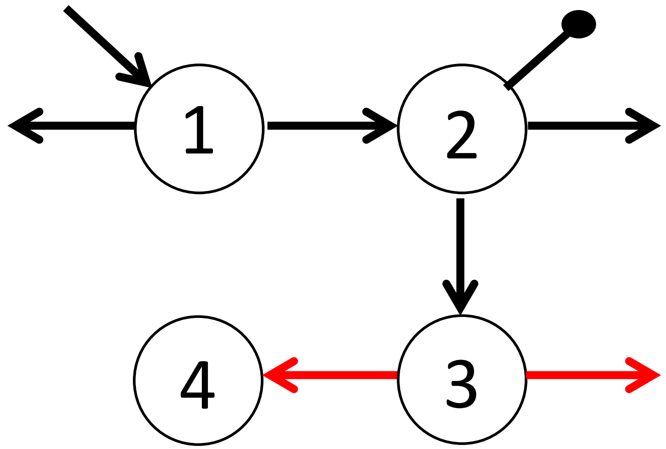
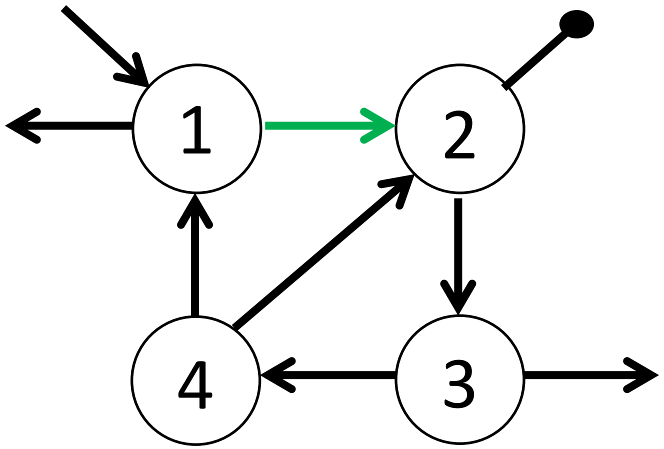


- Theorem [Gross et al 2019]: Let j be a compartment **not in the output-reachable subgraph**. Then the parameters a_{0j} , a_{kj} are unidentifiable (if they are nonzero).

What parameters are **globally identifiable**?

- Edge from input to output in strongly connected graph



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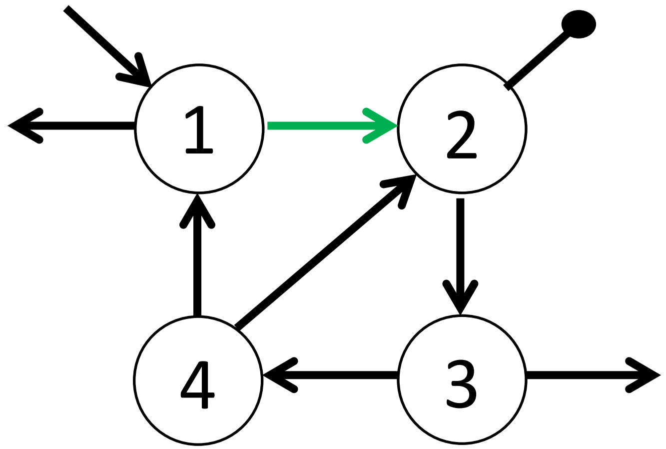
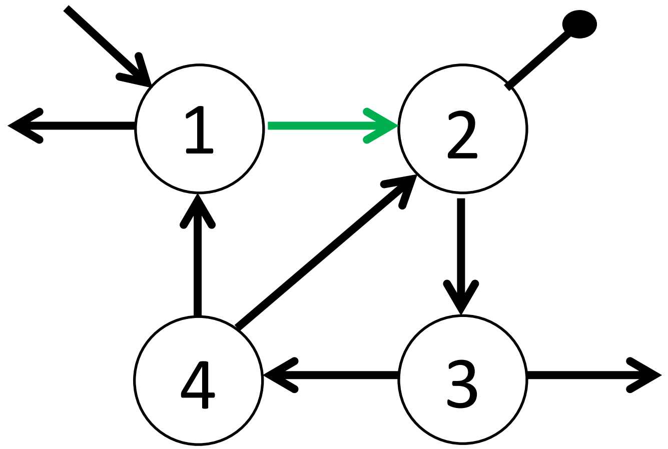


- Theorem [Clemens et al 2025]: Let G be a strongly connected graph with input in compartment i and output in compartment j. Then the edge a_{ji} is globally identifiable (if it is nonzero).

What parameters are **globally identifiable**?

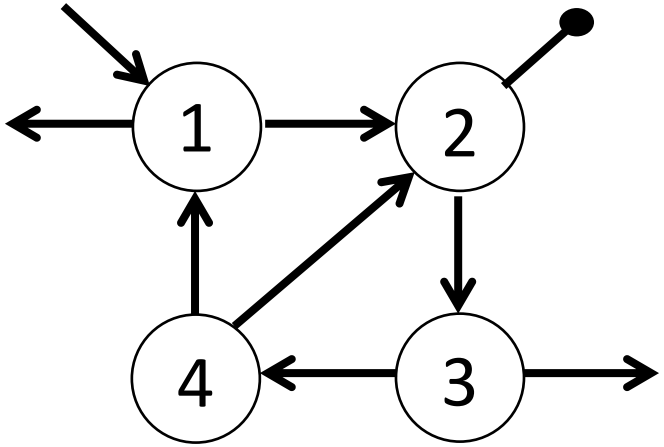
- Edge from input to output in strongly connected graph



- Theorem [Clemens et al 2025]: Let G be a strongly connected graph with input in compartment i and output in compartment j. Then the edge a_{ji} is globally identifiable (if it is nonzero).
- What about the full model itself?

The dream: is a given model identifiable?

- Model doesn’t satisfy previous assumptions



- Is this identifiable or unidentifiable?

The dream: is a given model identifiable?

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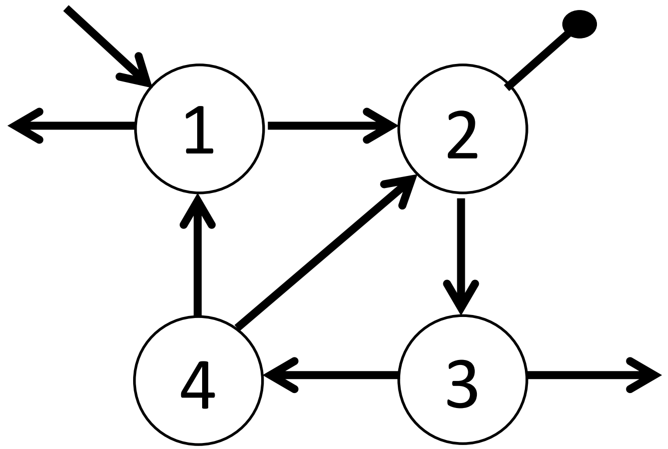
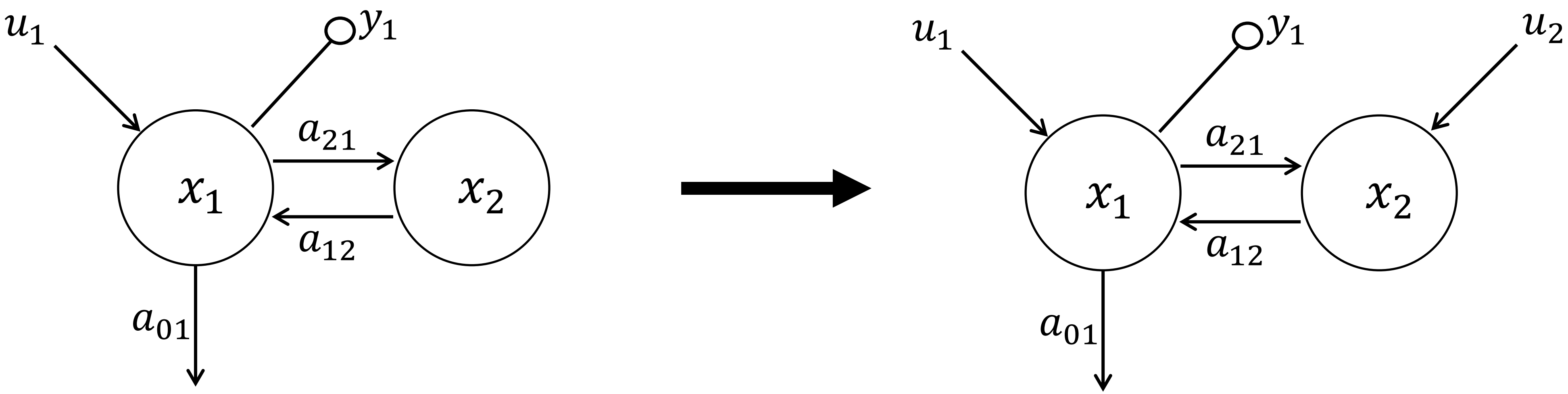


- Is this identifiable or unidentifiable?
- More on this in recent review paper [M-Shiu 2025]

Other interesting questions

Operations that preserve identifiability

- Adding inputs/outputs



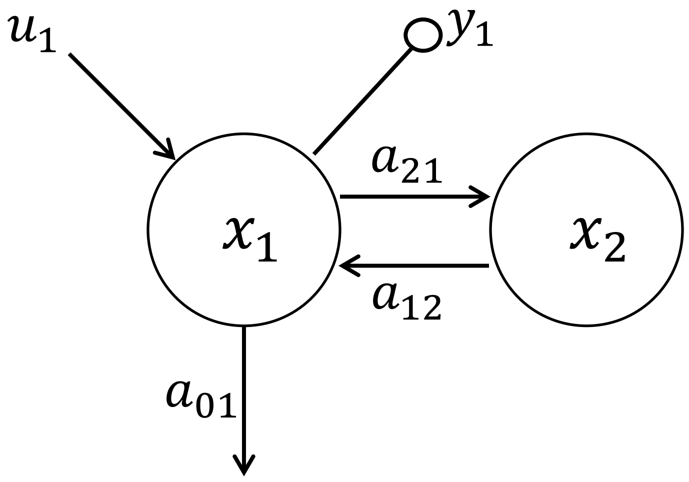
Identifiable

Identifiable

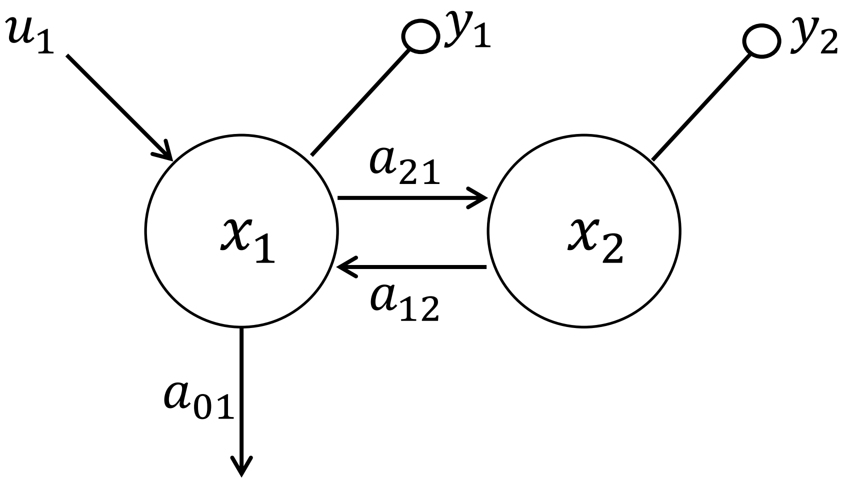
Other interesting questions

Operations that preserve identifiability

- Adding inputs/outputs



Identifiable

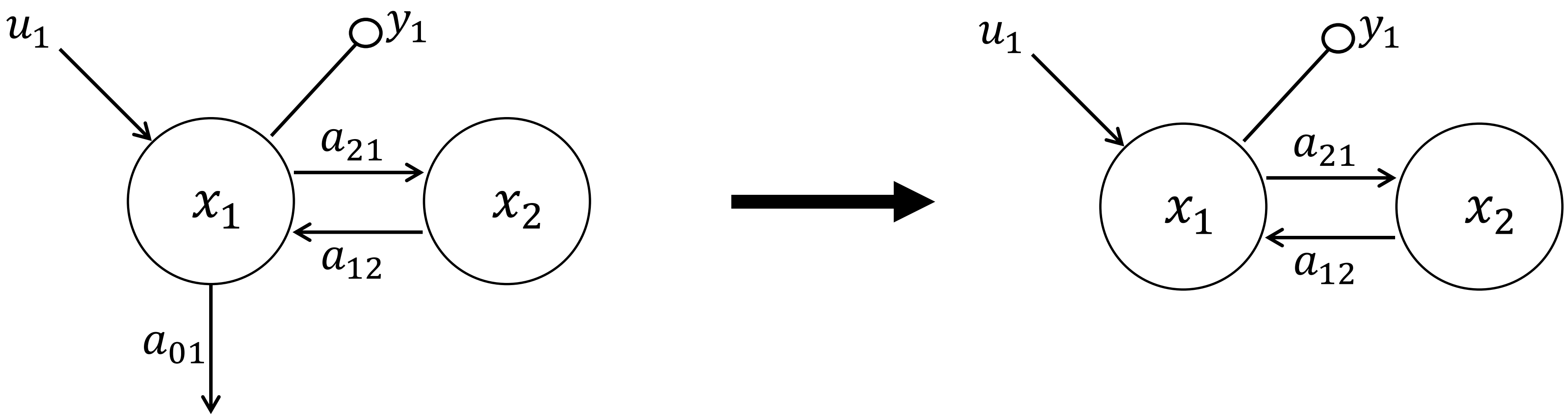


Identifiable

Other interesting questions

Operations that preserve identifiability

- Removing a leak from a strongly connected model w/ single input/output/leak in the same compartment [Gross et al 2019]



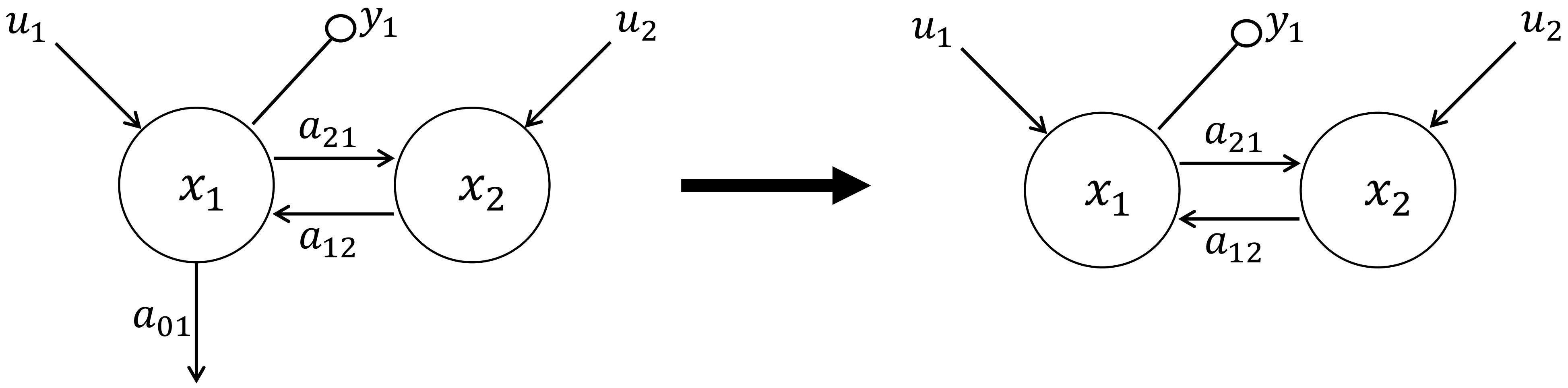
Identifiable

Identifiable

Other interesting questions

Operations that preserve identifiability

- Conjecture [Gross et al 2019]: For a strongly connected model with at least one input and output and exactly 1 leak, removing the leak preserves identifiability



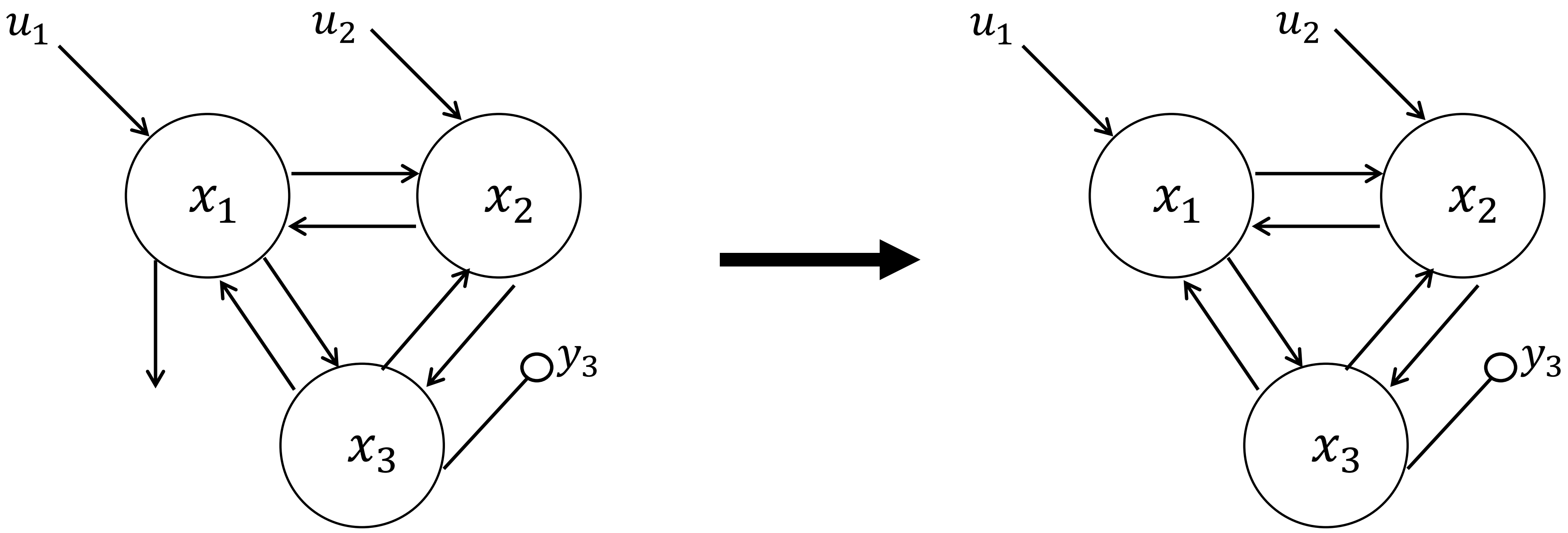
Identifiable

Identifiable

Other interesting questions

Operations that preserve identifiability

- Counterexample [Gogishvili 2024]:



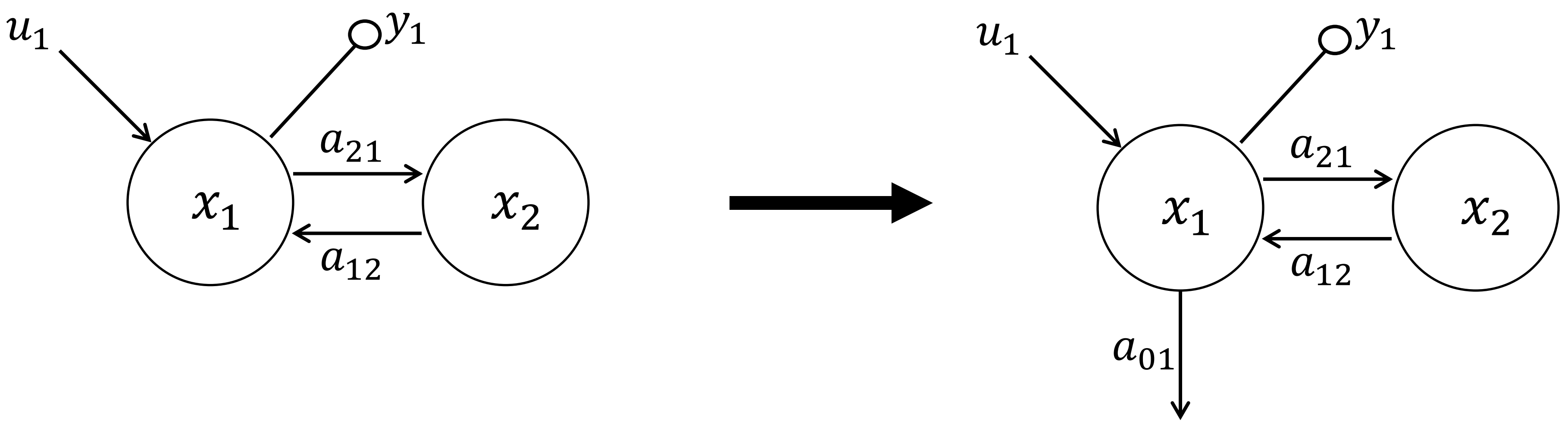
Identifiable

Unidentifiable

Other interesting questions

Operations that preserve identifiability

- Adding a leak to a strongly connected model w/o leaks [Gross et al 2019]



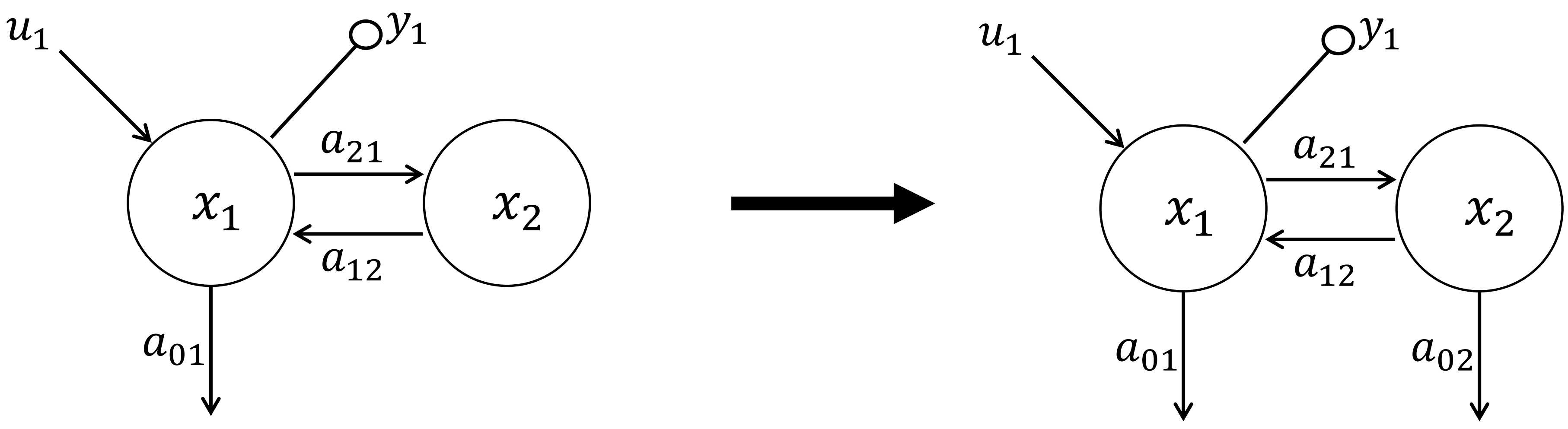
Identifiable

Identifiable

Other interesting questions

Operations that preserve identifiability

- Warning: having no leaks to begin with is necessary!

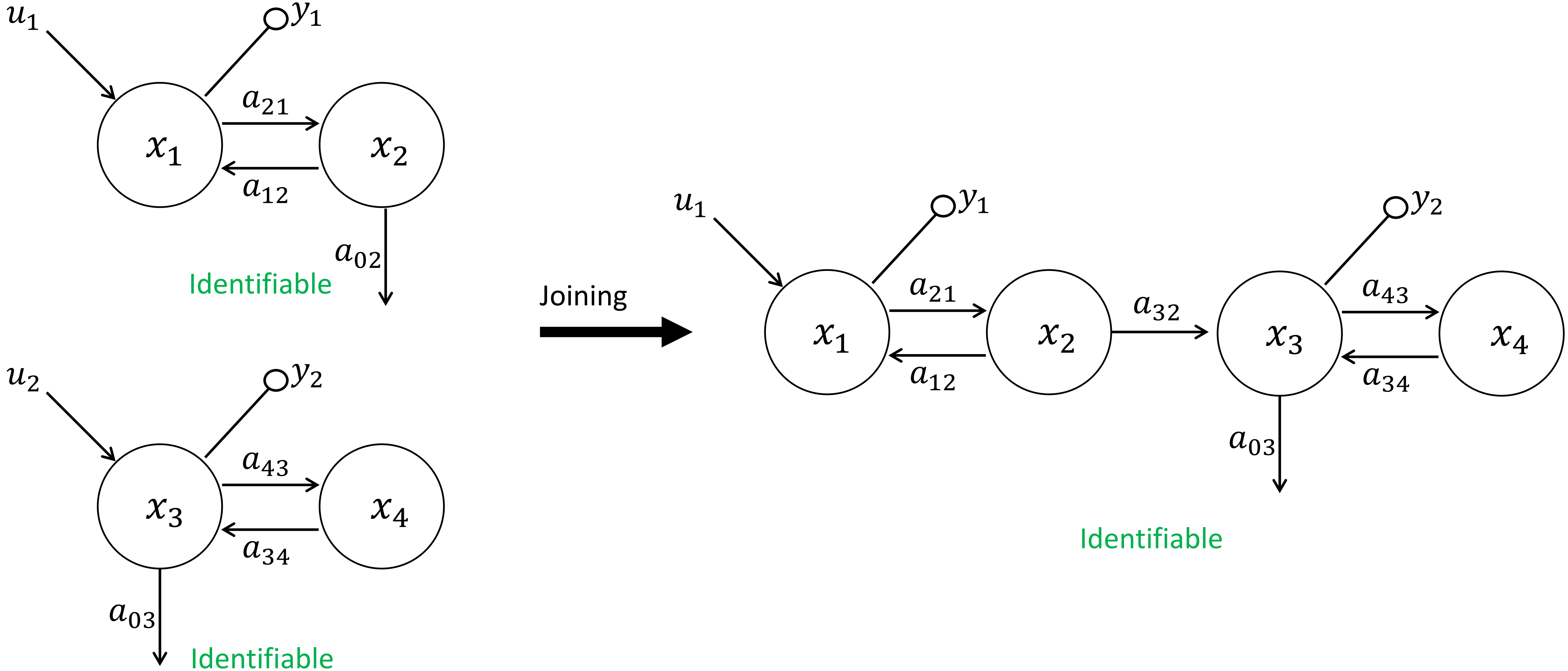


Identifiable

Unidentifiable

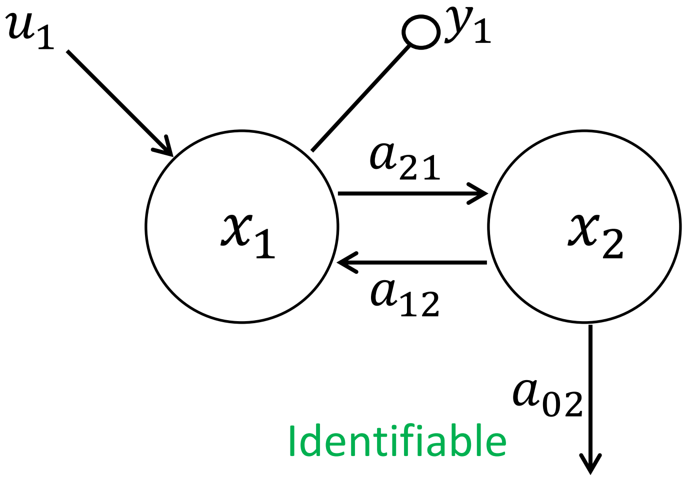
Other interesting questions

Joining/decomposing identifiable models

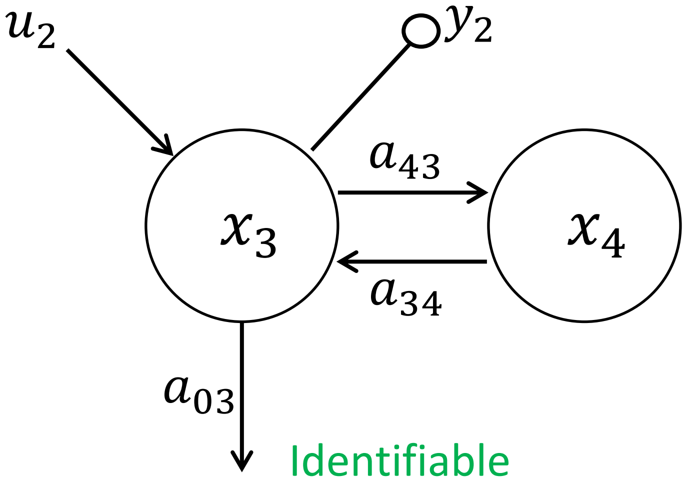


Other interesting questions

Joining/decomposing identifiable models

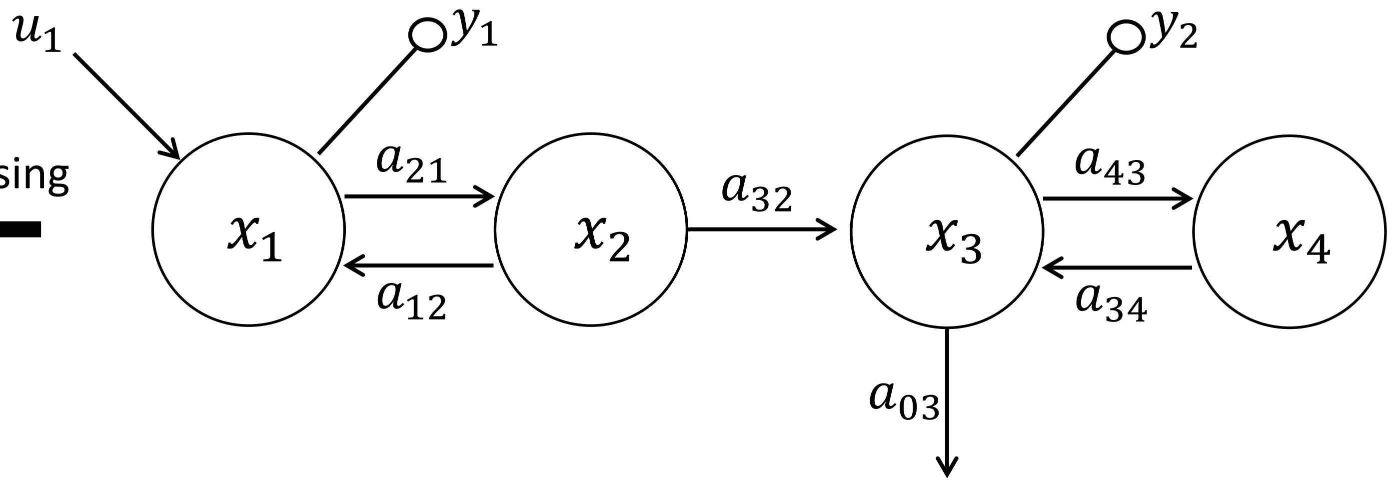


Identifiable



Identifiable

Decomposing

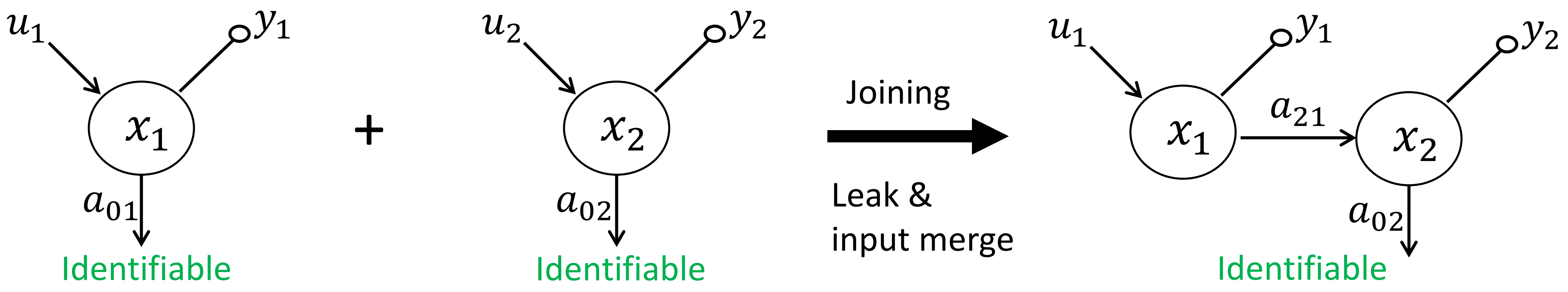


Identifiable

Other interesting questions

Joining strongly connected models [Gross et al 2020]

i.)



Identifiable

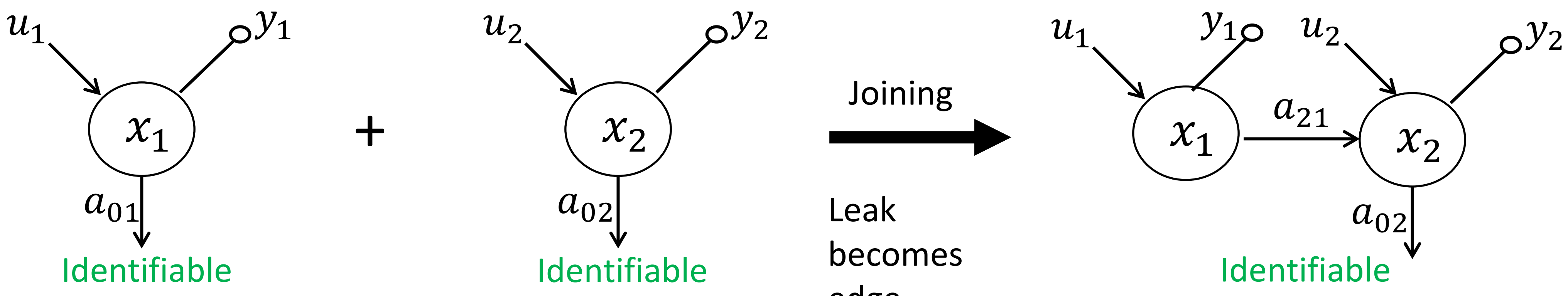
Identifiable

Joining

Leak & input merge

Identifiable

ii.)



Identifiable

Identifiable

Joining

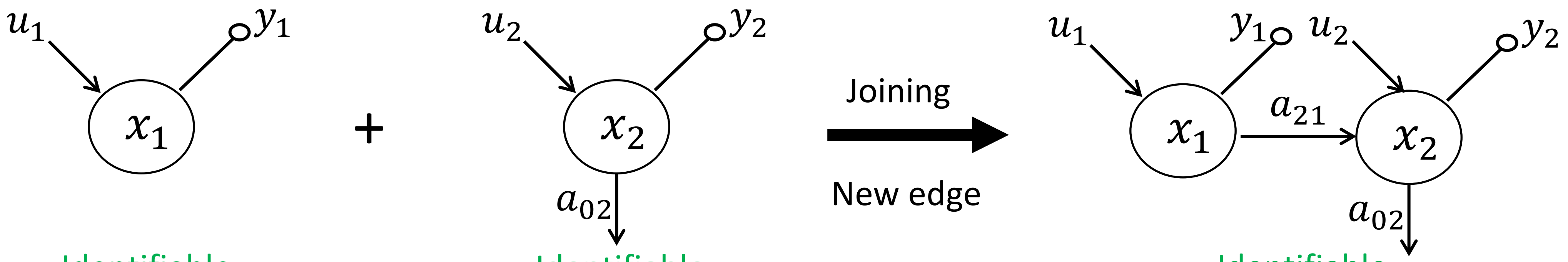
Leak becomes edge

Identifiable

Other interesting questions

Joining strongly connected models [Gross et al 2020]

iii.)

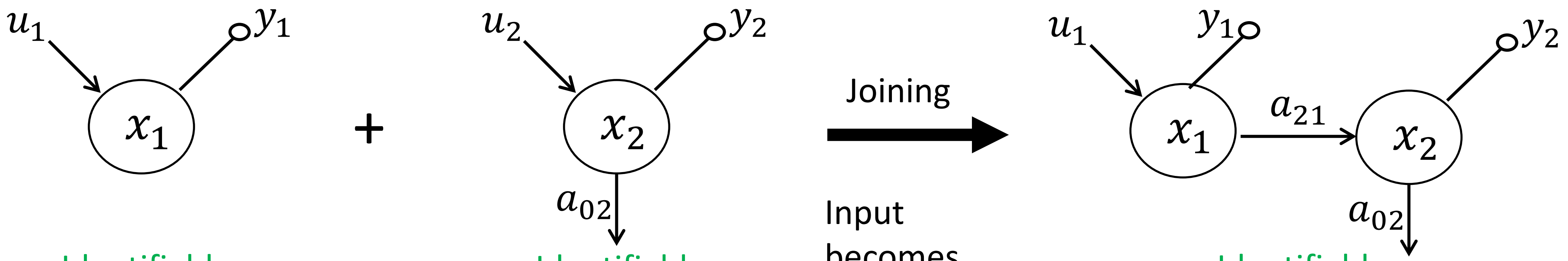


Joining

New edge

Identifiable Identifiable Identifiable

iv.)



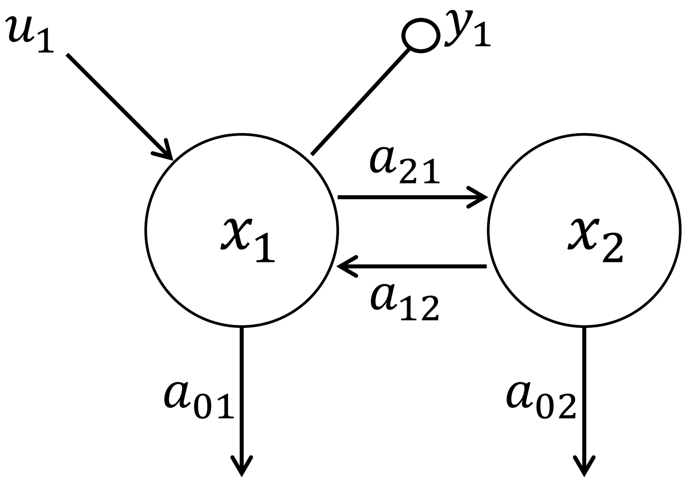
Joining

Input
becomes
edge

Identifiable Identifiable Identifiable

What to do with an unidentifiable model?

Recall model from earlier slide:



Unidentifiable

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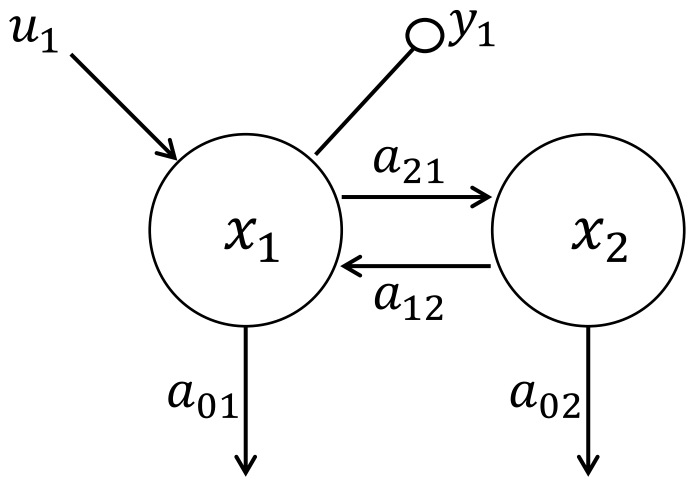

Unidentifiable

$$\ddot{y}_1 + (a_{01} + a_{02} + a_{12} + a_{21})\dot{y}_1 + (a_{01}a_{12} + a_{02}a_{21} + a_{01}a_{02})y_1 = \dot{u}_1 + (a_{02} + a_{12})u_1$$

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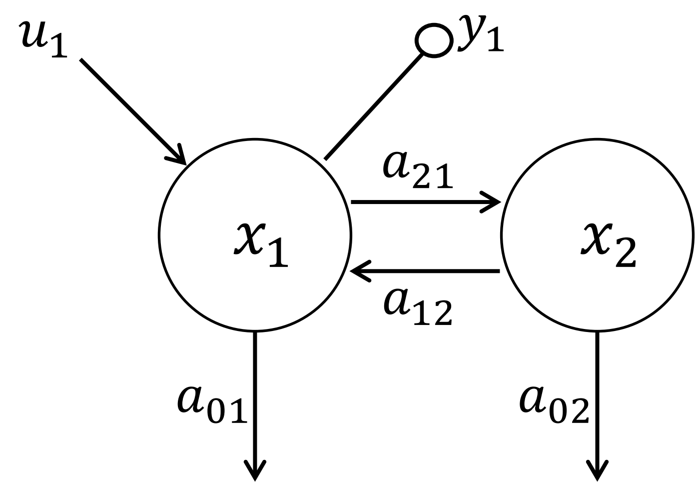

Unidentifiable

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- How do we fix this?

What to do with an unidentifiable model?

Some options:

- Add more data (increase the number of coefficients)

What to do with an unidentifiable model?

Some options:

- Add more data (increase the number of coefficients)
- Remove edges/leaks (decrease the number of parameters)

What to do with an unidentifiable model?

Some options:

- Add more data (increase the number of coefficients)
- Remove edges/leaks (decrease the number of parameters)
- Set parameters to known values (decrease the # of parameters)

What to do with an unidentifiable model?

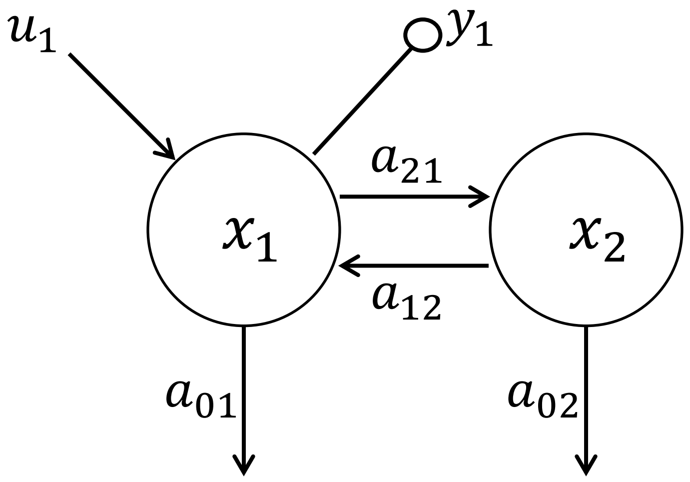
Some options:

- Add more data (increase the number of coefficients)
- Remove edges/leaks (decrease the number of parameters)
- Set parameters to known values (decrease the # of parameters)
- Reparametrize

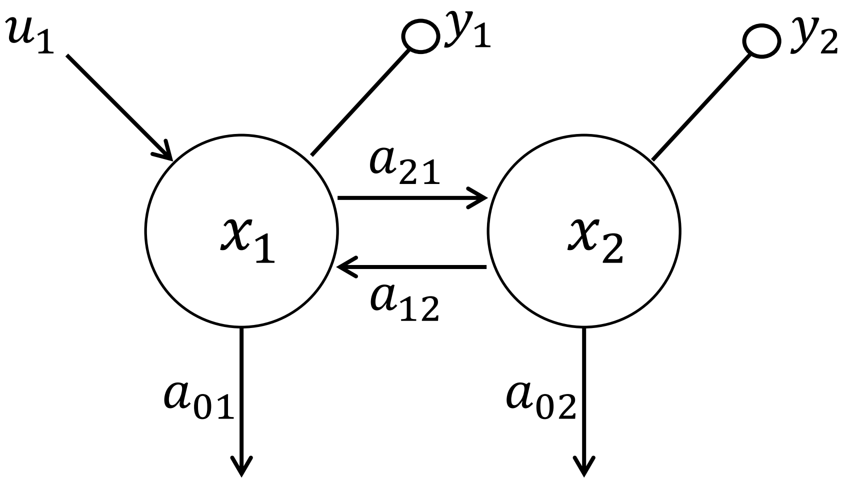
What to do with an unidentifiable model?

Option #1. Adjust model, if experimentally feasible

- Add inputs or outputs



Unidentifiable



Identifiable

What to do with an unidentifiable model?

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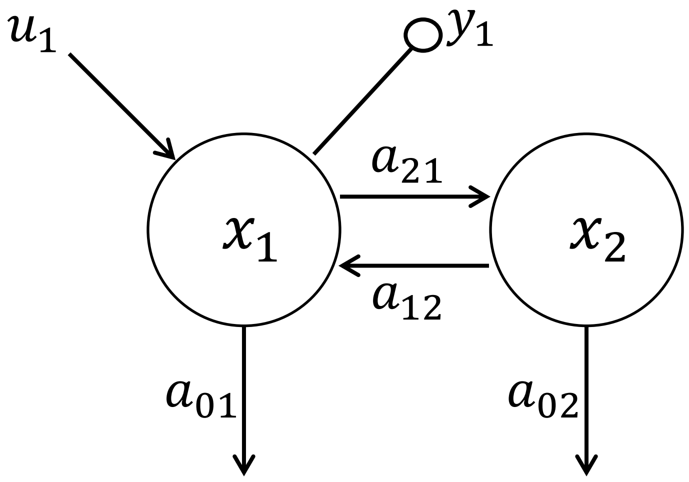
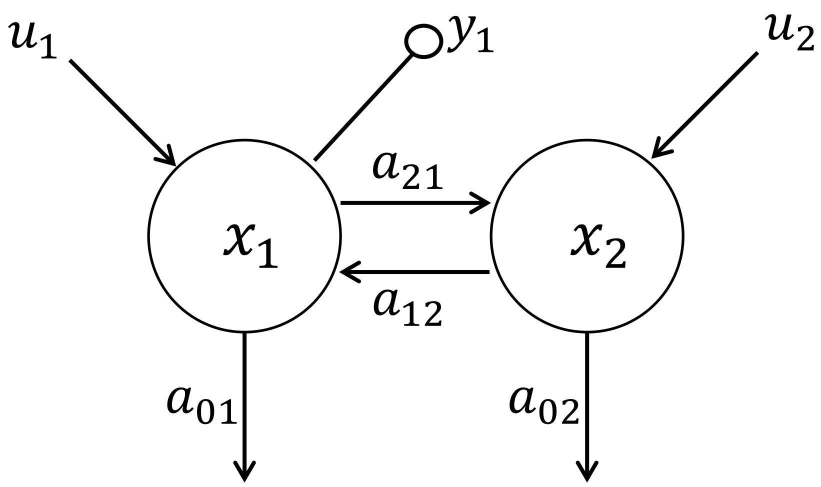


Unidentifiable

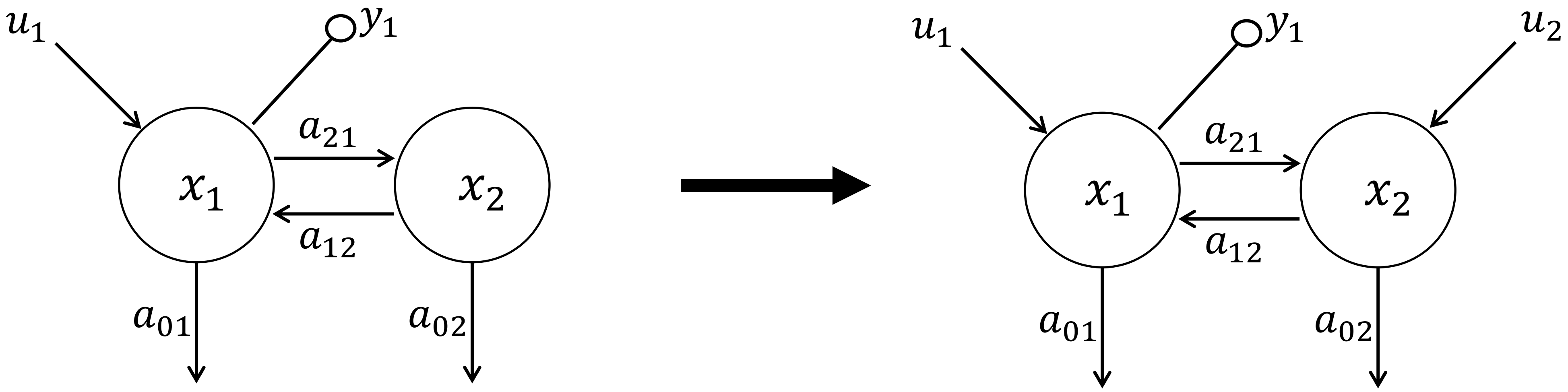


Identifiable

What to do with an unidentifiable model?

Option #1. Adjust model, if experimentally feasible

- Add inputs or outputs
- <u>Open</u>: What is a minimal set of inputs or outputs to obtain identifiability?



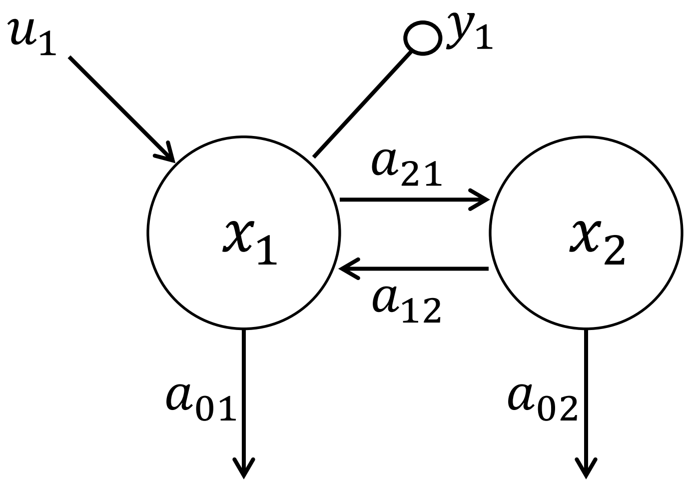
Unidentifiable

Identifiable

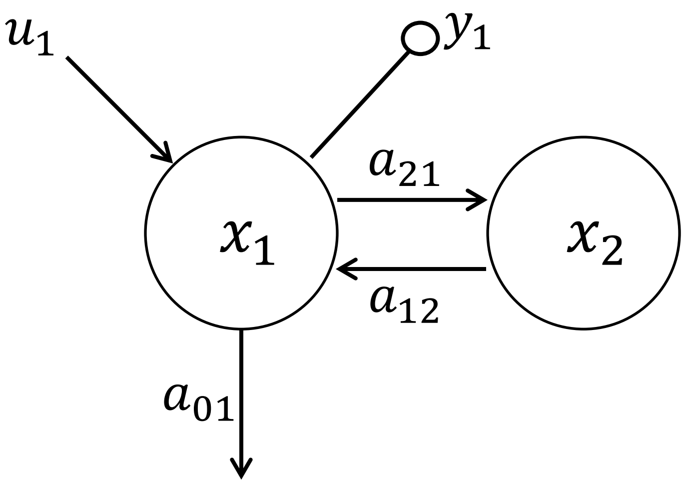
What to do with an unidentifiable model?

Option #2. Adjust model, if experimentally feasible

- Remove a leak or edge



Unidentifiable

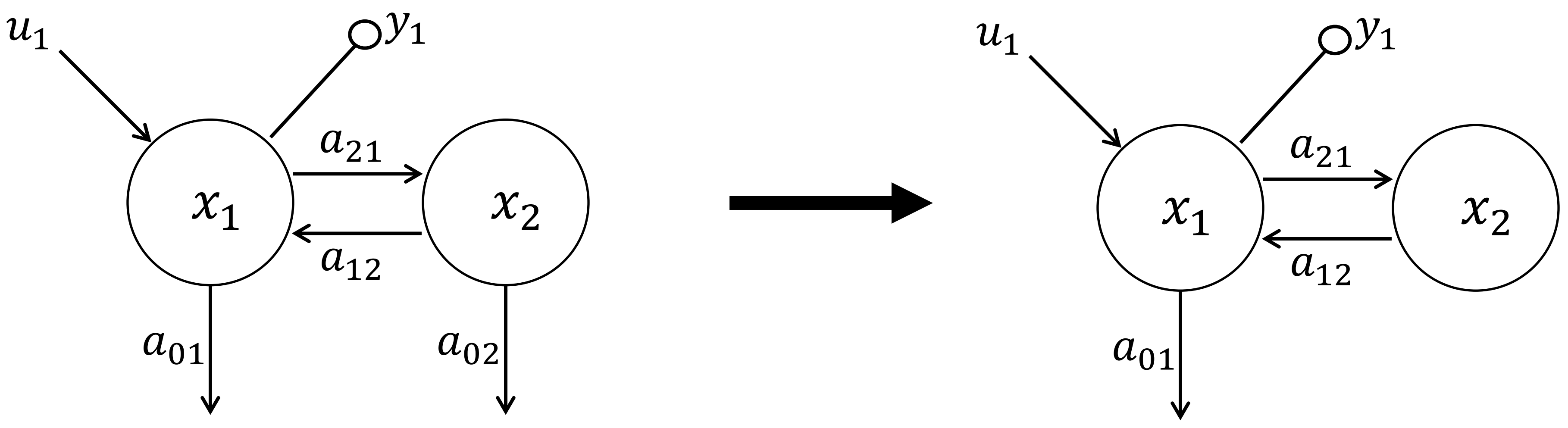


Identifiable

What to do with an unidentifiable model?

Option #2. Adjust model, if experimentally feasible

- Remove a leak or edge
- <u>Open</u>: Which edges or leaks should I remove to obtain identifiability?



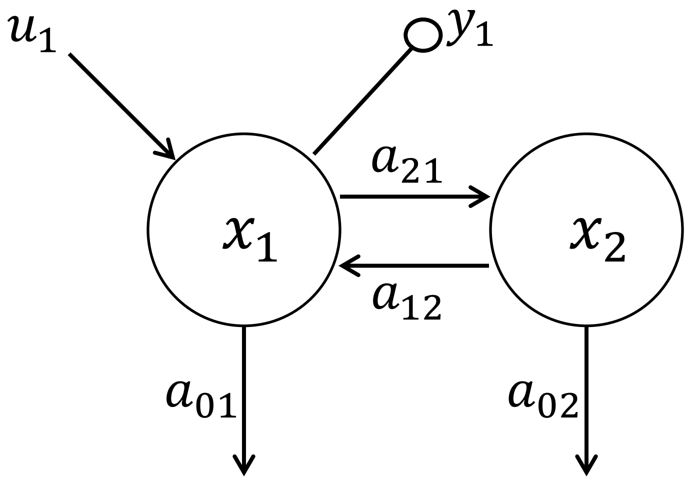
Unidentifiable

Identifiable

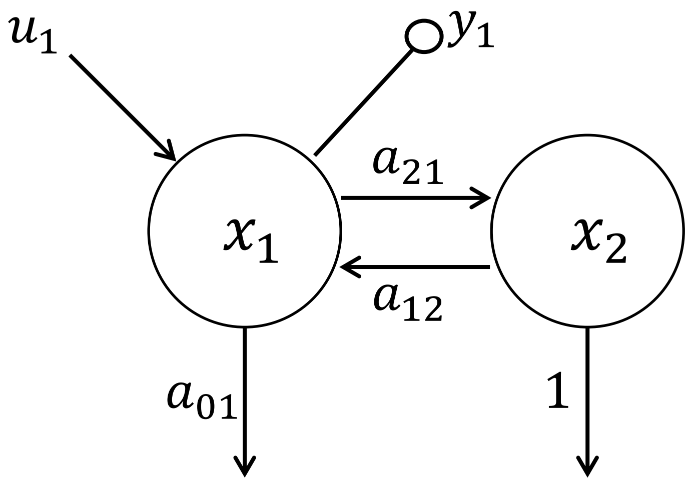
What to do with an unidentifiable model?

Option #3. Adjust model, if experimentally feasible

- Set parameter to known value



Unidentifiable



Identifiable

What to do with an unidentifiable model?

Option #4. Find an identifiable reparametrization

- How to do this? Find an appropriate scaling of the state variables [M-Sullivant 2014]:

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

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

$$y_1 = x_1$$

$$\underset{\substack{X_1 = x_1 \\ X_2 = a_{12}x_2}}{\longrightarrow}$$

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

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$$y_1 = X_1$$

Beyond linear

Can we answer these same types of questions for nonlinear models?

Ex: SIR Model

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

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

Un-id: $\beta=\beta^*$ $\gamma=\gamma^*$ $\mu = \mu^*$ $kN = k^*N^*$

Reparam: $S' = \frac{S}{N},$ $I' = \frac{I}{N},$ $R' = \frac{R}{N}$

Beyond linear

What to do with an unidentifiable model?

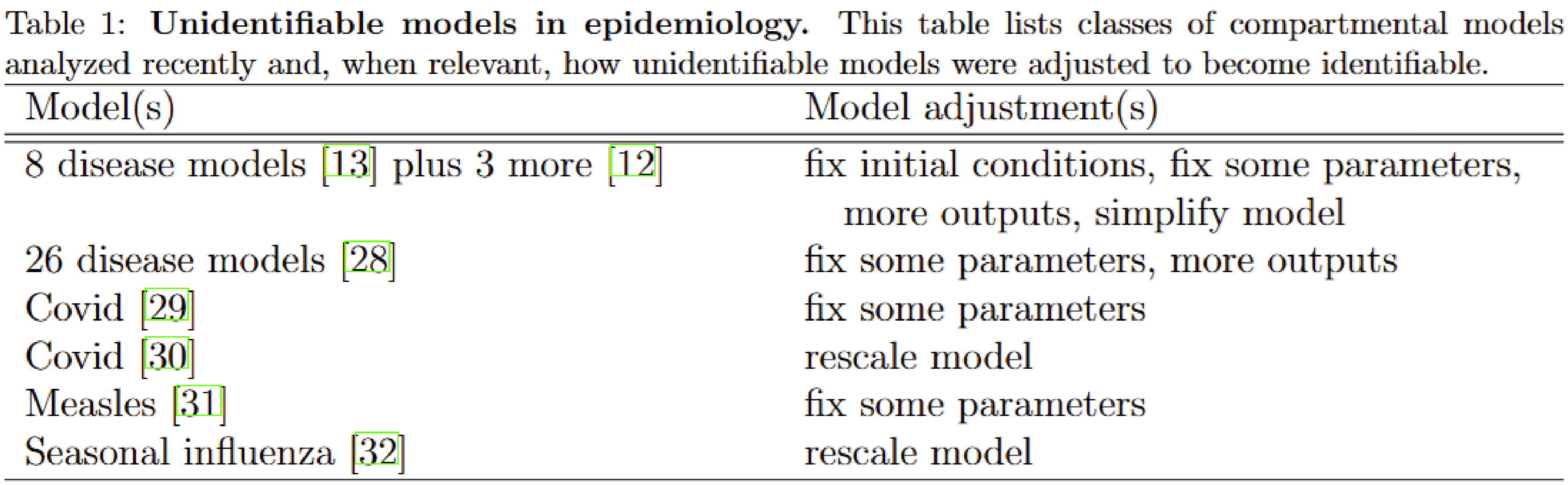

Table 1: **Unidentifiable models in epidemiology.** This table lists classes of compartmental models analyzed recently and, when relevant, how unidentifiable models were adjusted to become identifiable.

Model(s)	Model adjustment(s)
8 disease models [13] plus 3 more [12]	fix initial conditions, fix some parameters, more outputs, simplify model
26 disease models [28]	fix some parameters, more outputs
Covid [29]	fix some parameters
Covid [30]	rescale model
Measles [31]	fix some parameters
Seasonal influenza [32]	rescale model

[M-Shiu 2025]

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Generalization

Theorem (M-Sullivant-Eisenberg) Let $M = (G, In, Out, Leak)$ be a linear compartmental model with at least one input. Then the following equations are input-output equations for M for each $i \in Out$:

$$\det(\partial I - A)y_i = \sum_{j \in In} (-1)^{i+j} \det(\partial I - A)_{ij}\, u_1$$

Idea behind proofs

- Formula for input-output equation:

$$\ddot{y}_1 - \underbrace{(a_{11} + a_{22})}\dot{y}_1 + \underbrace{(a_{11}a_{22} - a_{12}a_{21})}y_1 = \dot{u}_1 \underbrace{- a_{22}}u_1$$

Coefficients of characteristic polynomial of A … of A_{11}

- Coefficients factor through cycles in graph

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

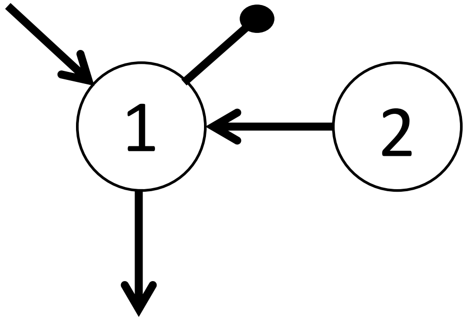
- Number of independent cycles in graph:

$$\underbrace{m - n + 1}_{\text{\# cycles}} + \underbrace{n}_{\text{\# self cycles}} = m + 1$$

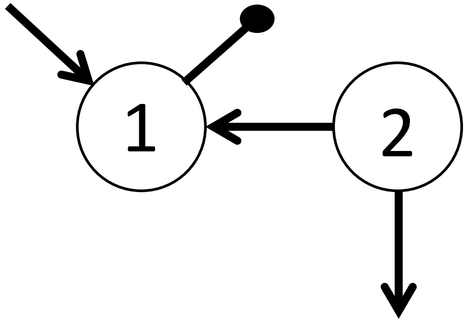
- Ident. reparam. $\Leftrightarrow$ $\dim(im(c))$ is maximal (=# independent cycles)

Distinguishable models:

Model 1



Model 2



I/O eqn:

$$\ddot{y}_1 + (a_{01} + a_{12})\dot{y}_1 + a_{01}a_{12}y_1$$
$$= \dot{u}_1 + a_{12}u_1$$

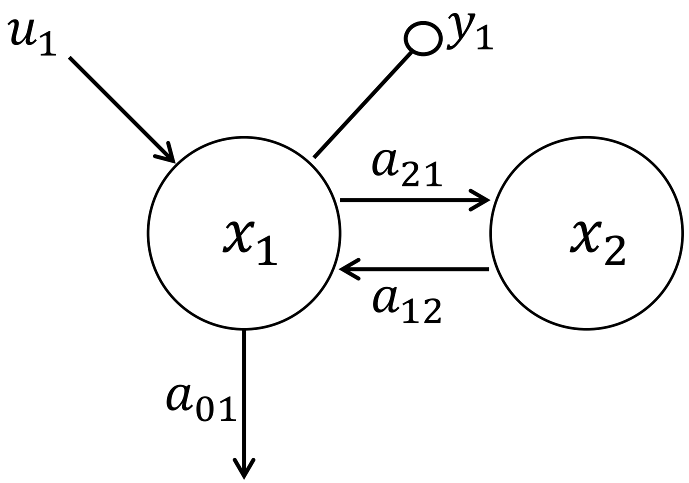
$$\ddot{y}_1 + (a_{02} + a_{12})\dot{y}_1$$
$$= \dot{u}_1 + (a_{02} + a_{12})u_1$$

Not the same I/O eqn structure ⇒ Distinguishable!

Can identifiability break down?

- Recall *generic* identifiability
- Can analyze singular locus:

$$\ddot{y}_1 + (a_{01} + a_{12} + a_{21})\dot{y}_1 + a_{01}a_{12}y_1 = \dot{u}_1 + a_{12}u_1$$



$$c(a_{01}, a_{12}, a_{21}) = (a_{01} + a_{12} + a_{21},\ a_{01}a_{12},\ a_{12})$$

$$Jac(c) = \begin{pmatrix} 1 & 1 & 1 \\ a_{12} & a_{01} & 0 \\ 0 & 1 & 0 \end{pmatrix}$$

Identifiable

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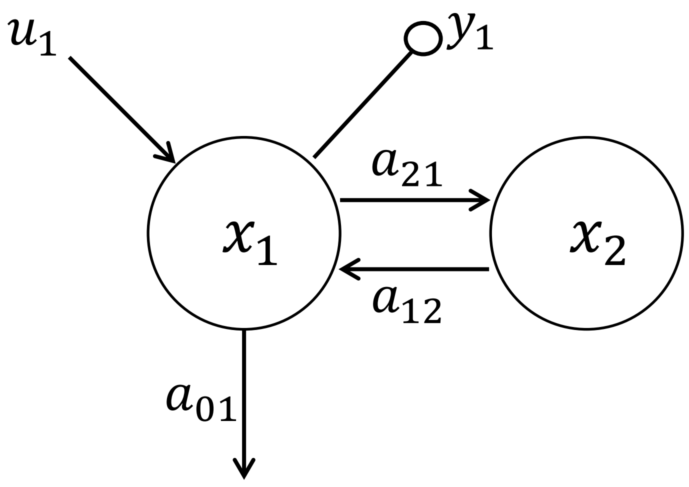

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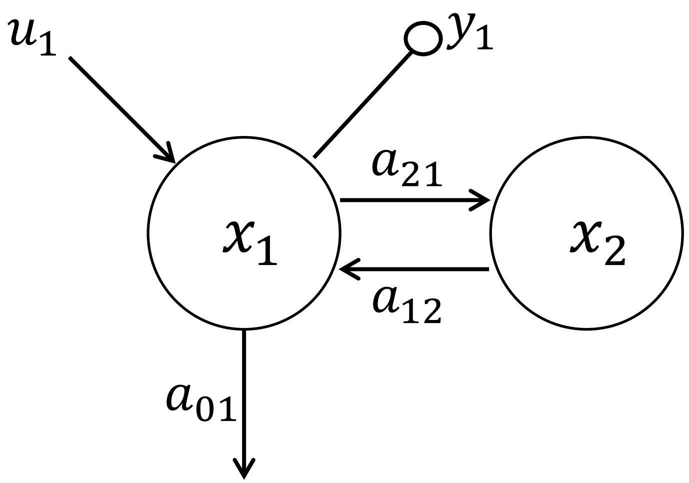

Identifiable

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$$Jac(c) = \begin{pmatrix} 1 & 1 & 1 \\ a_{12} & a_{01} & 0 \\ 0 & 1 & 0 \end{pmatrix}$$

$$\det\big(Jac(c)\big) = a_{12}$$

Identifiability holds as long as $a_{12} \neq 0$

Singular locus

- The singular locus is the subset of the parameter space where the Jacobian matrix of c has rank strictly less than the number of parameters.

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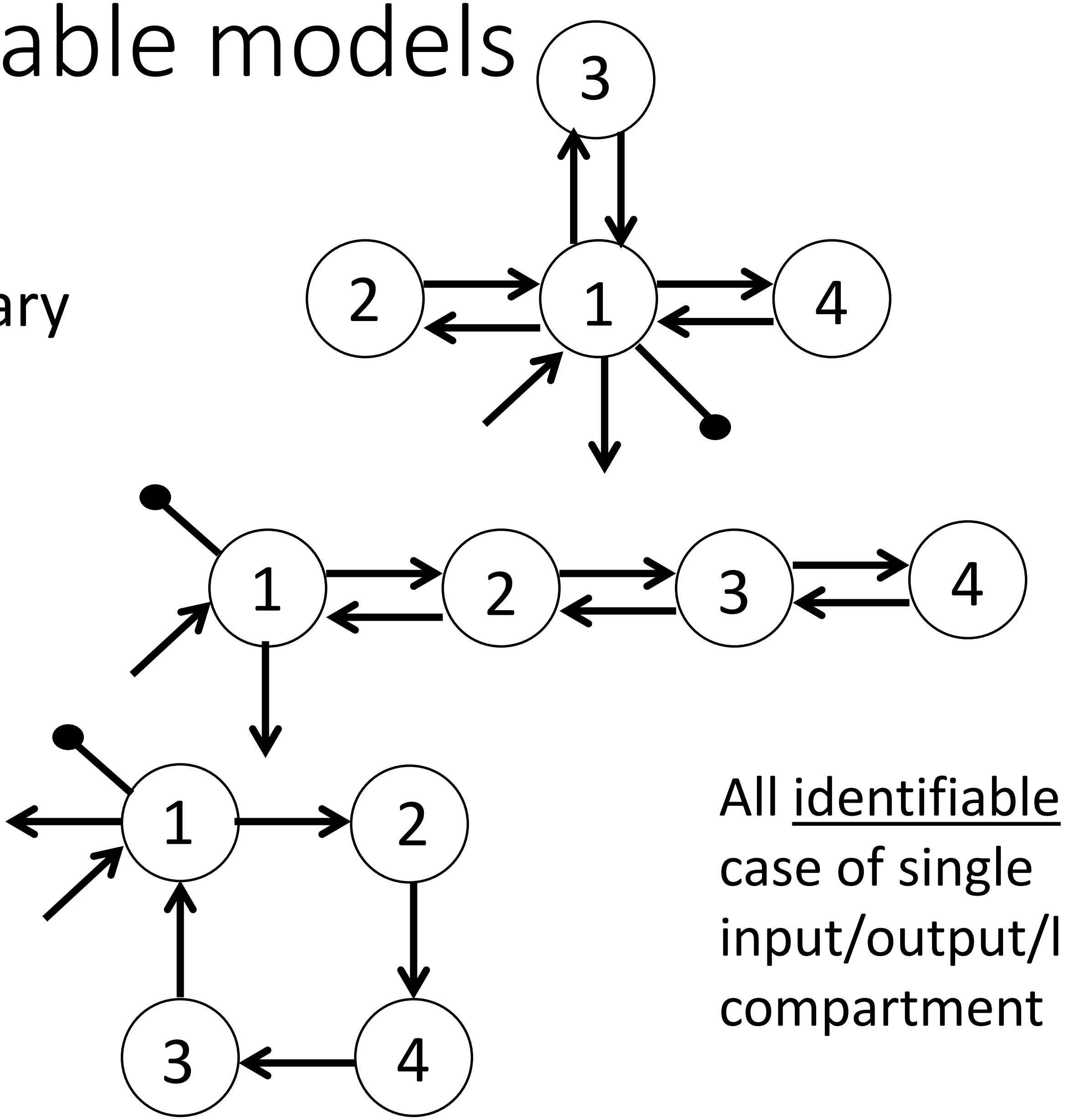
- Can we find formulas for singular locus equations?

Identifiable models

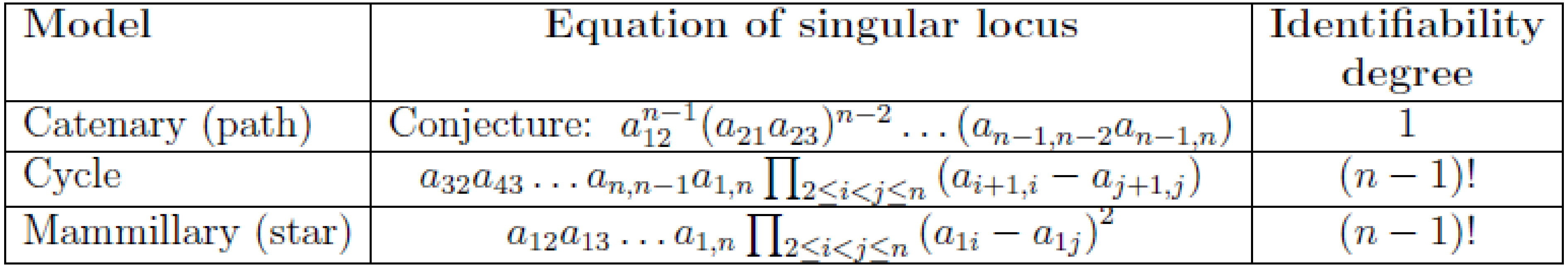


- Mammillary
- Catenary
- Cycle

All <u>identifiable</u> for the case of single input/output/leak in 1st compartment

[M-Sullivant-Eisenberg 2015]

Singular locus

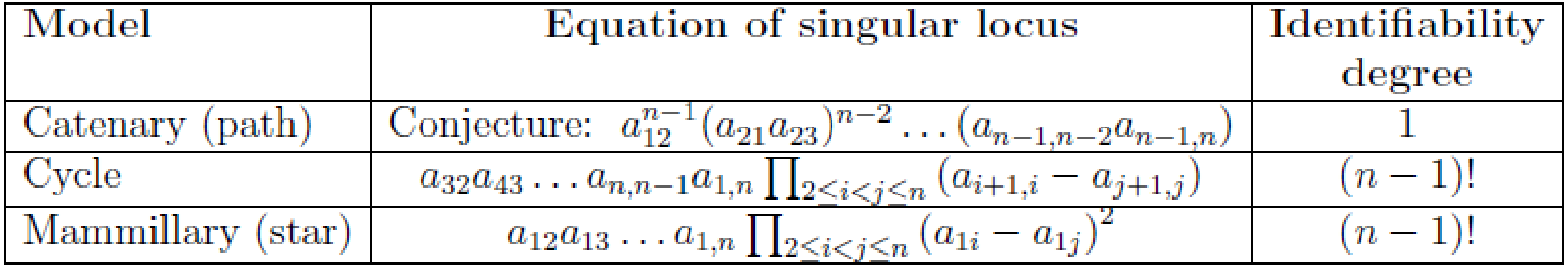


Model	Equation of singular locus	Identifiability degree
Catenary (path)	Conjecture: $a_{12}^{n-1}(a_{21}a_{23})^{n-2}\dots(a_{n-1,n-2}a_{n-1,n})$	1
Cycle	$a_{32}a_{43}\dots a_{n,n-1}a_{1,n}\prod_{2\leq i<j\leq n}(a_{i+1,i}-a_{j+1,j})$	$(n-1)!$
Mammillary (star)	$a_{12}a_{13}\dots a_{1,n}\prod_{2\leq i<j\leq n}(a_{1i}-a_{1j})^2$	$(n-1)!$

- What does this tell us?
  - For cycle and mammillary models, **nonzero** and **distinct** parameter values yield identifiability
  - For catenary models, **nonzero** parameter values yield identifiability

[Gross-M-Shiu 2021]

Singular locus



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- What does this tell us?
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Other families of graphs?

[Gross-M-Shiu 2021]

Application: identifiable submodels

- Theorem (Gross-M-Shiu 2021):
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Application: identifiable submodels

- Theorem (Gross-M-Shiu 2021):
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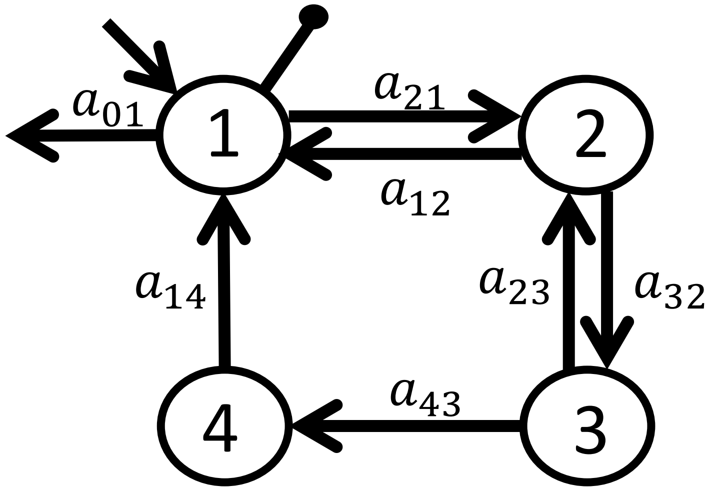
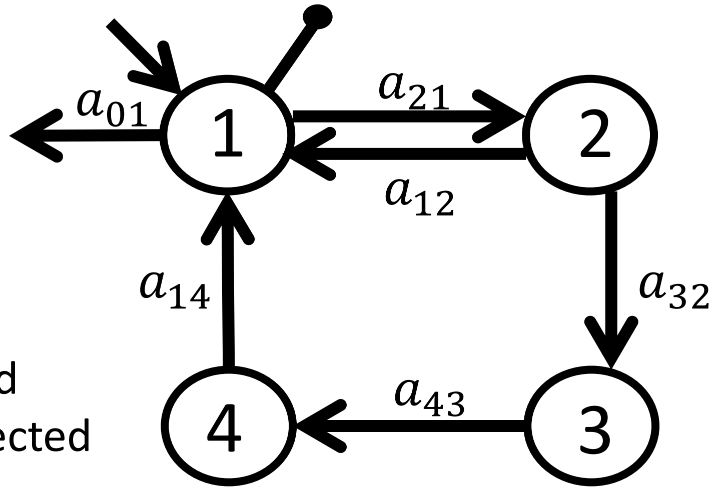
  - Ex: $a_{12}a_{14}a_{21}^2a_{32}(a_{12}a_{14} - a_{14}^2 - a_{12}a_{23} + a_{14}a_{23} + a_{14}a_{32} - a_{12}a_{43} + a_{14}a_{43} - a_{32}a_{43})(a_{12}a_{23} + a_{12}a_{43} + a_{32}a_{43})$



Identifiable

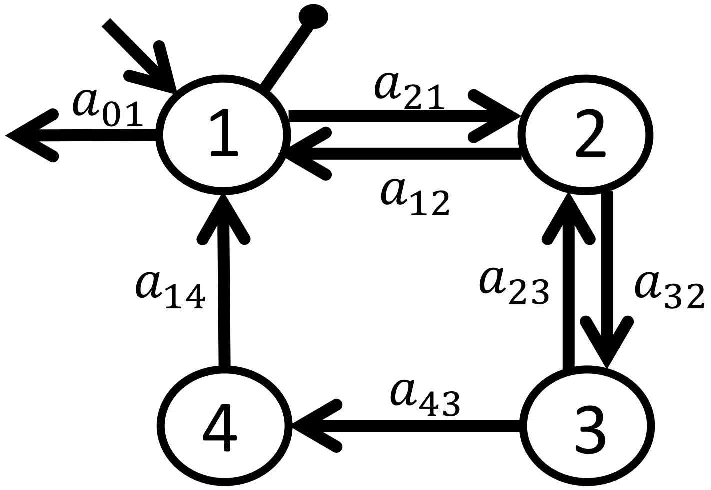
Not divisible by a_{23} and remains strongly connected when deleting a_{23}



Identifiable

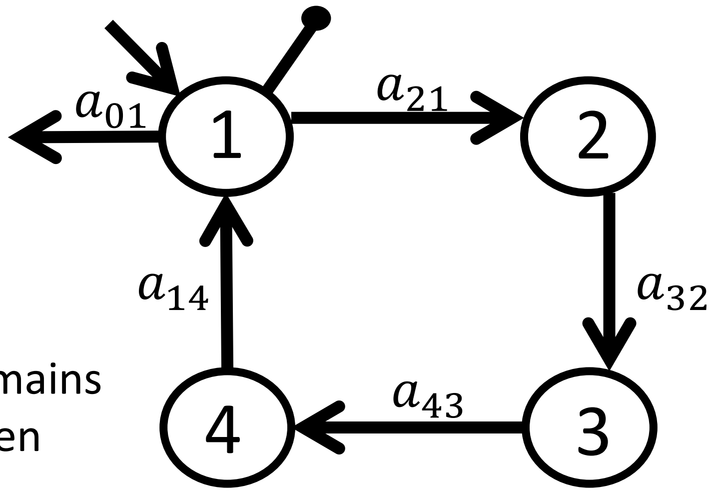
Application: identifiable submodels

- Converse doesn't hold:
  - Strongly connected models: If singular locus equation is divisible by a parameter, then delete parameter. If it remains strongly connected, then the submodel may be identifiable.
  - Ex: $a_{12}a_{14}a_{21}^2a_{32}(a_{12}a_{14} - a_{14}^2 - a_{12}a_{23} + a_{14}a_{23} + a_{14}a_{32} - a_{12}a_{43} + a_{14}a_{43} - a_{32}a_{43})(a_{12}a_{23} + a_{12}a_{43} + a_{32}a_{43})$



Identifiable

Divisible by a_{12} and remains strongly connected when deleting a_{12} and a_{23}



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

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$$\xrightarrow[\substack{X_1 = x_1 \\ X_2 = a_{12}x_2}]{}$$

$$\dot{X}_1 = q_1X_1 + X_2 + u_1$$

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$$y_1 = X_1$$

New map is 1-1 → $c(q_1, q_2, q_3) = (-q_1 - q_3,\ \ q_1q_3 - q_2,\ \ -q_3)$