Identifiability of Linear Compartmental Tree Models

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New Directions in Algebraic Statistics
Institute for Mathematical and Statistical Innovation
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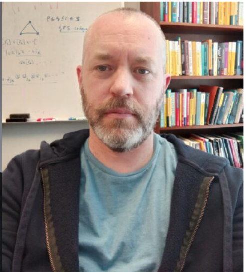
Collaborators



Dr. Elizabeth Gross
U. of Hawai'i at Mānoa

Dr. Nicolette Meshkat
Santa Clara University

Dr. Anne Shiu
Texas A&M University

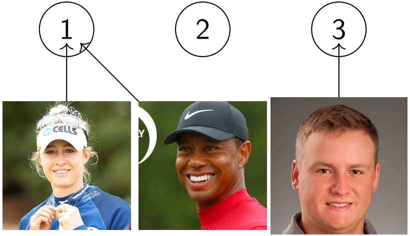
Dr. Seth Sullivant
North Carolina State U.

Motivating Example

"Compartments"

1 := Good Golfers
2 := Average Golfers
3 := Bad Golfers

Motivating Example



Nelly Korda   Tiger Woods   Not Nelly or Tiger

1 := Good Golfers
2 := Average Golfers
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Motivating Example

1 := Good Golfers
2 := Average Golfers
3 := Bad Golfers

Moving between compartments

Motivating Example

$1 :=$ Good Golfers
$2 :=$ Average Golfers
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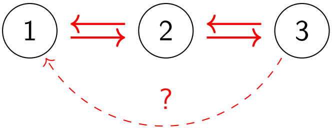
Moving between compartments

Motivating Example



Moving between compartments

1 := Good Golfers
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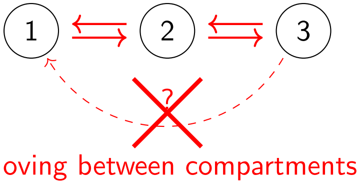
Motivating Example



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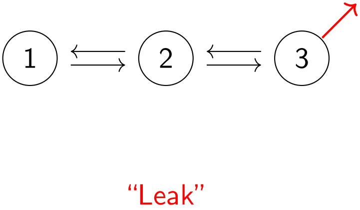

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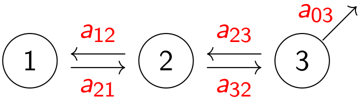

1 := Good Golfers
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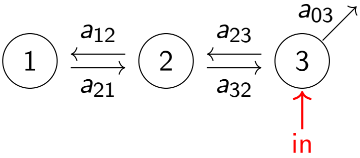
"Flow Rate Parameters"

$a_{(destination)(source)}$

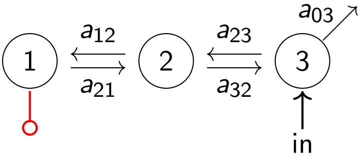
Motivating Example



"Input into the system"

1 := Good Golfers
2 := Average Golfers
3 := Bad Golfers

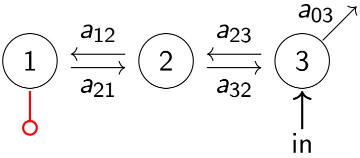
Motivating Example



"Measured Compartment"

1 := Good Golfers
2 := Average Golfers
3 := Bad Golfers

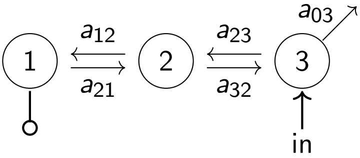
Motivating Example



"**Output** Compartment"

1 := Good Golfers
2 := Average Golfers
3 := Bad Golfers

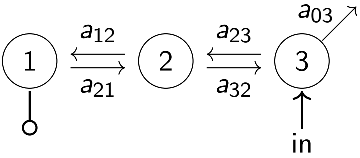
Motivating Example



Linear Compartmental Model

$$\mathcal{M} = (G, In, Out, Leak)$$
$$= (\mathrm{Cat}_3, \{3\}, \{1\}, \{3\}).$$

Motivating Example



Linear Compartmental Model

$$\mathcal{M} = (G, In, Out, Leak)$$
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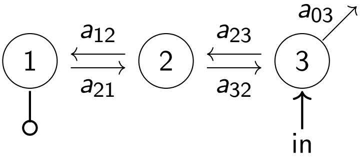
Motivating Question: Identifiability

Given information about the input and output compartment, can we **find** all flow rate parameters?

Motivating Example



Linear Compartmental Model

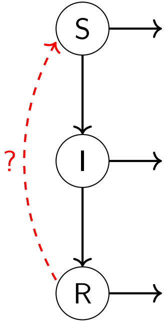
$$\mathcal{M} = (G, In, Out, Leak)$$
$$= (\text{Cat}_3, \{3\}, \{1\}, \{3\}).$$

Motivating Question: Identifiability

Given information about the input and output compartment, can we **identify** all flow rate parameters?

Compartmental Models in the Wild

- SIR Model for spread of a virus in Epidemiology
- SIV Model for vaccine efficiency in Epidemiology
- Modeling Pharmacokinetics for absorption, distribution, metabolism, and excretion in the blood
- Modeling different biological systems

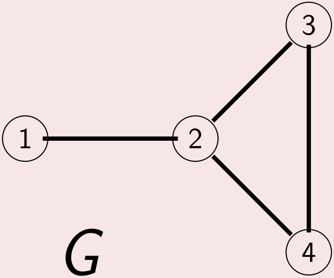


Background - Graph Theory

Definition (by Example)

An *undirected graph* $G = (V, E)$ consists of two sets:

- vertices V, e.g. $\{1, 2, 3, 4\}$
- edges E, e.g. $\underbrace{\{\{1, 2\}, \{2, 3\}, \{2, 4\}, \{4, 3\}\}}_{\text{unordered pairs of vertices}}$



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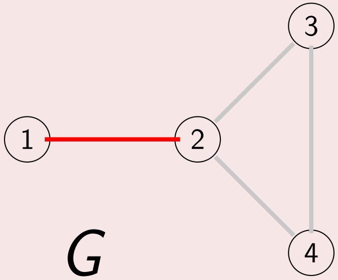

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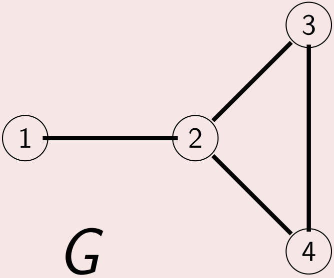
An undirected graph $G = (V, E)$ is a *forest* if it contains no cycles, i.e. a path starting and ending at the same vertex without using an edge twice.



Does this graph contain a cycle?

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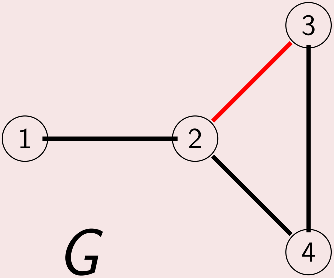

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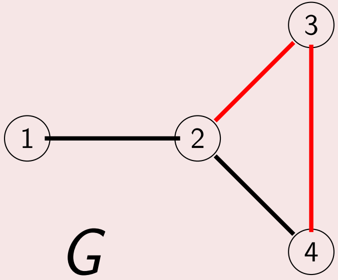

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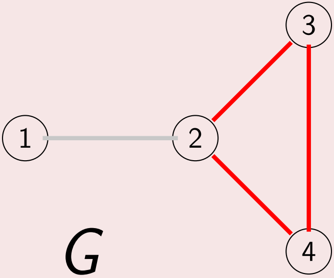

Does this graph contain a cycle?

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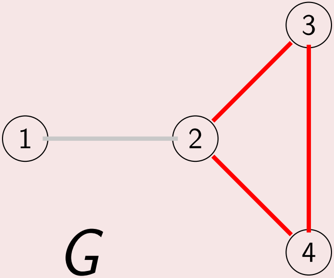

Does this graph contain a cycle? YES!

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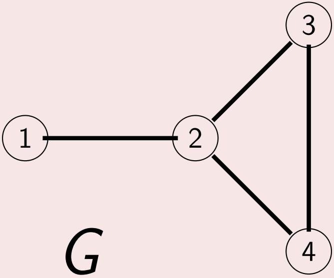

How could we make this graph a forest?

Background - Graph Theory

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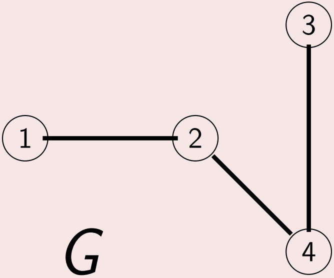

How could we make this graph a forest? Remove {2,3}

Background - Graph Theory

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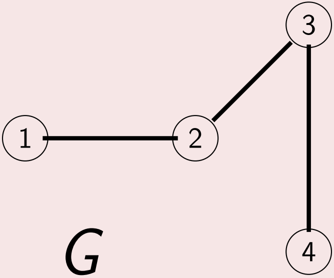

How could we make this graph a forest? Remove {2,4}

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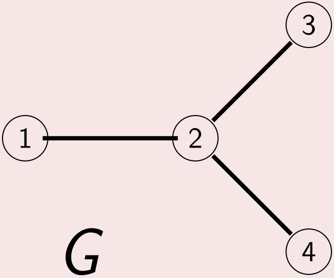

How could we make this graph a forest? Remove {4,3}

Background - Graph Theory

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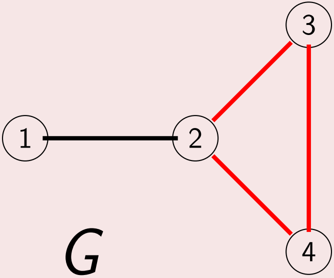
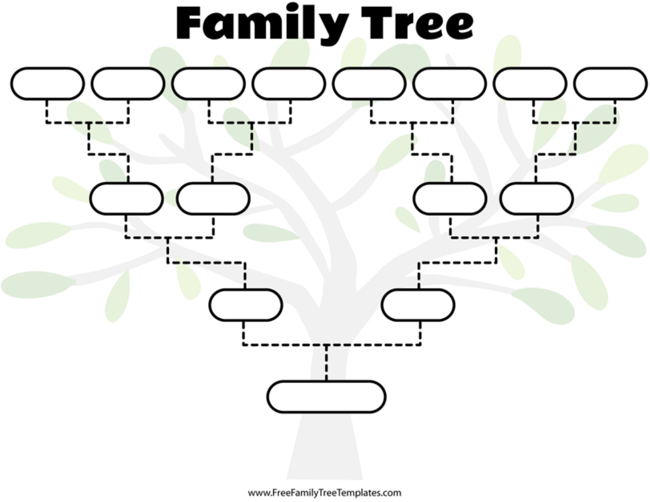
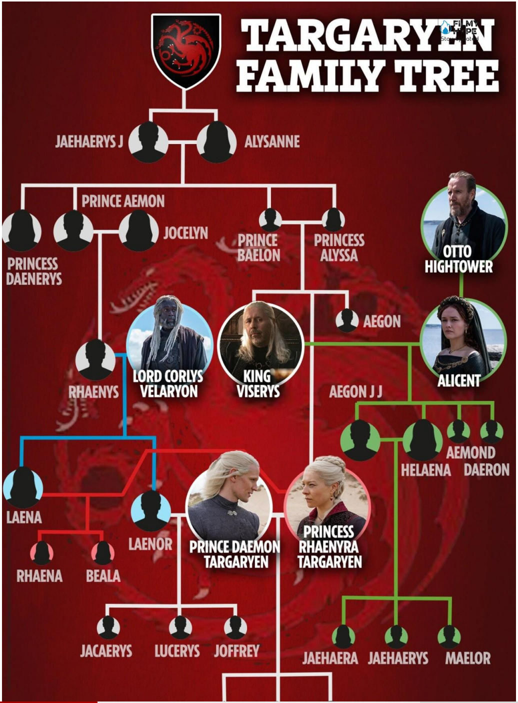


Note: A forest is a collection of trees (connected graph with no cycles)!

Family Trees




TARGARYEN FAMILY TREE
JAEHAERYS J
ALYSANNE
PRINCE AEMON
JOCELYN
PRINCESS DAENERYS
PRINCE BAELON
PRINCESS ALYSSA
OTTO HIGHTOWER
AEGON
RHAENYS
LORD CORLYS VELARYON
KING VISERYS
ALICENT
AEGON J J
AEMOND
HELAENA
DAERON
LAENA
LAENOR
PRINCE DAEMON TARGARYEN
PRINCESS RHAENYRA TARGARYEN
RHAENA
BEALA
JACAERYS
LUCERYS
JOFFREY
JAEHAERA
JAEHAERYS
MAELOR

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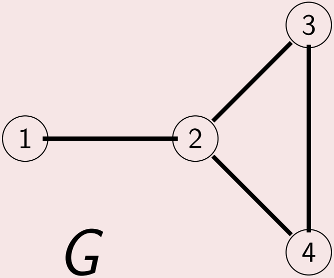

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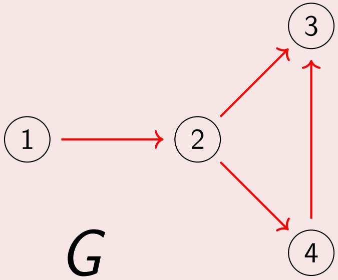

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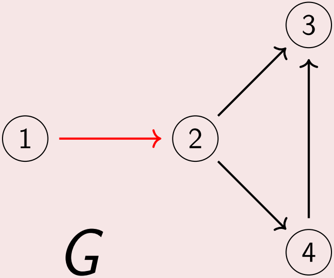
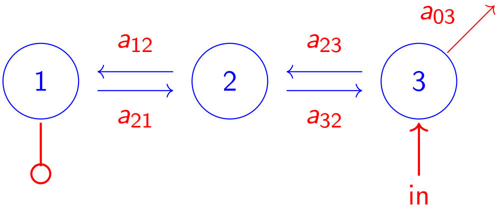


Motivating Example



$$\begin{aligned}\mathcal{M} &= (G, In, Out, Leak) \\ &= (\mathrm{Cat}_3, \{3\}, \{1\}, \{3\}).\end{aligned}$$

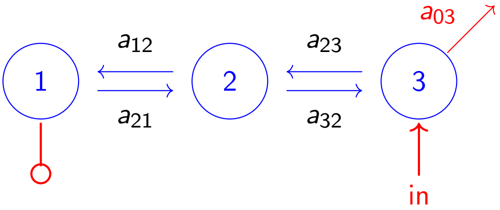
Motivating Example

$$\mathcal{M} = (G, In, Out, Leak)$$
$$= (\mathrm{Cat}_3, \{3\}, \{1\}, \{3\}).$$

With

$$\mathrm{Cat}_3 = (\{1, 2, 3\}, \{(1, 2), (2, 1), (2, 3), (3, 2)\})$$

Motivating Example

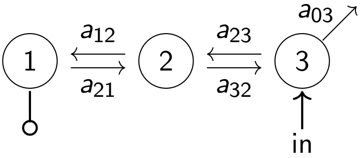


$$\mathcal{M} = (G, In, Out, Leak) = (\text{Cat}_3, \{3\}, \{1\}, \{3\}).$$

With

$$\text{Cat}_3 = (\{1,2,3\}, \{(1,2),(2,1),(2,3),(3,2)\})$$

Motivating Example



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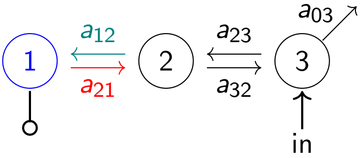
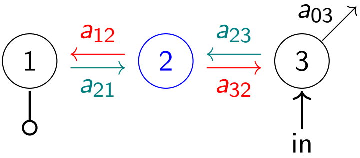


$$\mathcal{M} = (G, In, Out, Leak) = (\text{Cat}_3, \{3\}, \{1\}, \{3\}).$$

ODEs in terms of concentrations $x_i(t)$, input $u_3(t)$, and output $y_1(t)$:

$$x_1'(t) = -a_{21}x_1(t) \qquad +a_{12}x_2(t)$$

Motivating Example



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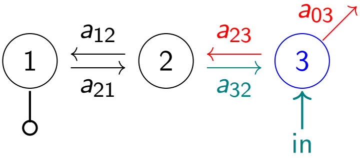
$$\begin{aligned} x_1'(t) &= -a_{21}x_1(t) + a_{12}x_2(t) \\ x_2'(t) &= a_{21}x_1(t) - (a_{12} + a_{32})x_2(t) + a_{23}x_3(t) \end{aligned}$$

Motivating Example



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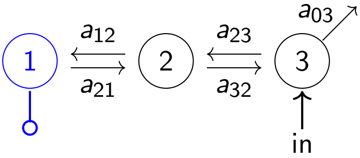
\end{aligned}$$

Motivating Example



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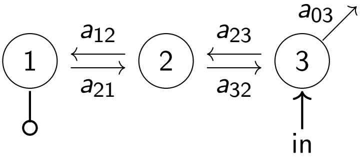
\end{aligned}$$

with

$$y_1(t) = x_1(t).$$

Motivating Example



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ODEs in terms of concentrations $x_i(t)$, input $u_3(t)$, and output $y_1(t)$:

$$\begin{pmatrix} x_1'(t) \\ x_2'(t) \\ x_3'(t) \end{pmatrix} = \underbrace{\begin{pmatrix} -a_{21} & a_{12} & 0 \\ a_{21} & -a_{12} - a_{32} & a_{23} \\ 0 & a_{32} & -a_{03} - a_{23} \end{pmatrix}}_{\text{compartmental matrix } A} \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \\ u_3(t) \end{pmatrix}$$

with

$$y_1(t) = x_1(t).$$

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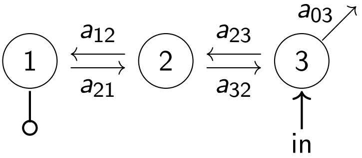

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with

$$y_1(t) = x_1(t).$$

Goal: Identify the parameters a_{ji} from the measurable variables.

Linear Compartmental Model Motivating Example

Goal: Identify the parameters a_{ji} from the measurable variables.

Differential Substitution/Elimination:

$$
\begin{aligned}
\underline{x_1'(t)} &= -a_{21}\underline{x_1(t)} + a_{12}x_2(t) \\
x_2'(t) &= a_{21}\underline{x_1(t)} - (a_{12} + a_{32})x_2(t) + a_{23}x_3(t) \\
x_3'(t) &= a_{32}x_2(t) - (a_{03} + a_{23})x_3(t) + u_3(t)
\end{aligned}
$$

with

$$\underbrace{\underline{y_1(t) = x_1(t)}}_{y_1'(t) = x_1'(t)}$$

Linear Compartmental Model Motivating Example

Goal: Identify the parameters a_{ji} from the measurable variables.

Differential Substitution/Elimination:

$$\begin{aligned}
y_1'(t) &= -a_{21}y_1(t) && +a_{12}\underline{x_2(t)} \\
x_2'(t) &= \quad a_{21}y_1(t) && -(a_{12}+a_{32})x_2(t) && +a_{23}x_3(t) \\
x_3'(t) &= && \quad a_{32}x_2(t) && -(a_{03}+a_{23})x_3(t) && +u_3(t)
\end{aligned}$$

with

$$\underbrace{y_1(t) = x_1(t)}_{y_1'(t)=x_1'(t)}$$

Linear Compartmental Model Motivating Example

Goal: Identify the parameters a_{ji} from the measurable variables.

Differential Substitution/Elimination:

$$
\begin{aligned}
x_2(t) &= \frac{1}{a_{12}} y_1'(t) + \frac{a_{21}}{a_{12}} y_1(t) \\
\underline{x_2'(t)} &= a_{21} y_1(t) - (a_{12} + a_{32}) \underline{x_2(t)} + a_{23} x_3(t) \\
x_3'(t) &= a_{32} \underline{x_2(t)} - (a_{03} + a_{23}) x_3(t) + u_3(t)
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\underbrace{y_1(t) = x_1(t)}_{y_1'(t) = x_1'(t)}
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$$x_2(t) = \frac{1}{a_{12}}y_1'(t) + \frac{a_{21}}{a_{12}}y_1(t)$$

$$\frac{1}{a_{12}}y_1''(t) + \frac{a_{21}}{a_{12}}y_1'(t) = a_{21}y_1(t) - (a_{12}+a_{32})\left(\frac{1}{a_{12}}y_1'(t) + \frac{a_{21}}{a_{12}}y_1(t)\right) + a_{23}\underline{x_3(t)}$$

$$x_3'(t) = a_{32}\left(\frac{1}{a_{12}}y_1'(t) + \frac{a_{21}}{a_{12}}y_1(t)\right) - (a_{03}+a_{23})x_3(t) + u_3(t)$$

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\underline{x_3'(t)} &= \frac{a_{32}}{a_{12}} y_1'(t) + \frac{a_{21}a_{32}}{a_{12}} y_1(t) - (a_{03} + a_{23}) \underline{x_3(t)} + u_3(t)
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Linear Compartmental Model Motivating Example

Goal: Identify the parameters a_{ji} from the measurable variables.

Differential Substitution/Elimination:

$$y_1^{(3)} + (a_{03} + a_{12} + a_{21} + a_{23} + a_{32})y_1'' + (a_{03}a_{12} + a_{03}a_{21} + a_{12}a_{23} + a_{21}a_{23} + a_{03}a_{32} + a_{21}a_{32})y_1' + (a_{03}a_{21}a_{32})y_1 = (a_{12}a_{23})u_3.$$

an ODE in only the measurable variables and the parameters:

Input/Output Equation

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Input/Output Equation

Theorem (Meshkat, Sullivant, Eisenburg, 2015)

Can also be done via Cramer's rule:

$$\det(\partial I - A)y_1 = \overbrace{\det(\partial I - A)^{3,1}}^{\text{remove row 3, col. 1}} u_3$$

Linear Compartmental Model Motivating Example

Goal: Identify the parameters a_{ji} from the measurable variables.

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

$$\begin{aligned}
y_1^{(3)}(t_1) + c_2 y_1''(t_1) + c_1 y_1'(t_1) + c_0 y_1(t_1) &= d_0 u_3(t_1) \\
y_1^{(3)}(t_2) + c_2 y_1''(t_2) + c_1 y_1'(t_2) + c_0 y_1(t_2) &= d_0 u_3(t_2) \\
y_1^{(3)}(t_3) + c_2 y_1''(t_3) + c_1 y_1'(t_3) + c_0 y_1(t_3) &= d_0 u_3(t_3) \\
&\vdots \\
y_1^{(3)}(t_m) + c_2 y_1''(t_m) + c_1 y_1'(t_m) + c_0 y_1(t_m) &= d_0 u_3(t_m)
\end{aligned}$$

and recover each coefficient c_2, c_1, c_0, d_0 uniquely.

Linear Compartmental Model Motivating Example

Goal: Identify the parameters a_{ji} from the measurable variables.

Consider the injectivity (invertibility) of the coefficient map:

Example (Continued)

For $\mathcal{M} = (\text{Cat}_3, \{3\}, \{1\}, \{3\})$, the input/output equation is:

$$y_1^{(3)} + (a_{03} + a_{12} + a_{21} + a_{23} + a_{32})y_1'' + (a_{03}a_{12} + a_{03}a_{21} + a_{12}a_{23} + a_{21}a_{23} + a_{03}a_{32} + a_{21}a_{32})y_1' + (a_{03}a_{21}a_{32})y_1 = (a_{12}a_{23})u_3.$$

The *coefficient map* corresponding to $\mathcal{M}$ is the map from the space of parameters to the space of coefficients of the input-output equation:

$$\phi \colon \mathbb{R}^5 \to \mathbb{R}^4$$

$$\begin{pmatrix} a_{03} \\ a_{12} \\ a_{21} \\ a_{23} \\ a_{32} \end{pmatrix} \mapsto \begin{pmatrix} a_{03} + a_{12} + a_{21} + a_{23} + a_{32} \\ a_{03}a_{12} + a_{03}a_{21} + a_{12}a_{23} + a_{21}a_{23} + a_{03}a_{32} + a_{21}a_{32} \\ a_{03}a_{21}a_{32} \\ a_{12}a_{23} \end{pmatrix}$$

Identifiability Analysis: Structural vs. Practical

Overview

We want to recover (identify) parameters of ODE models from measured variables.

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Structural Identifiability Analysis: A two part problem

Structural Identifiability via the input-output equation

We consider structural identifiability as a two-step problem:

1. Find an **input/output equation** of the ODE system in terms of measurable variables in a way that's <u>intuitive</u> from the graph
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Goal

We want to classify identifiability by the underlying **graph structure**.

Novel Input-Output Equation Characterization

Theorem ($, Gross, Meshkat, Shiu, Sullivant, [2023])

The coefficients of the input-output equation of an LCM $(G, In, Out, Leak)$ can be generated by *incoming forests* on graphs related to G.

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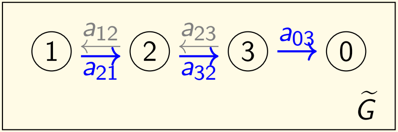
Example

The set of incoming forests with 3 edges on $\widetilde{G}$: $\mathcal{F}_3(\widetilde{G}) = \{\{1 \to 2, 2 \to 3, 3 \to 0\}\}$



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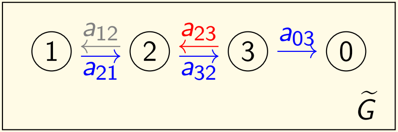

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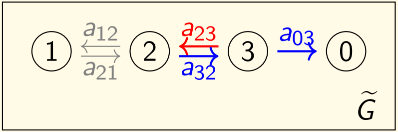

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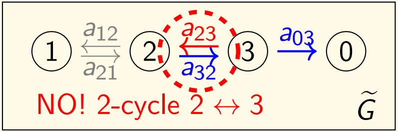

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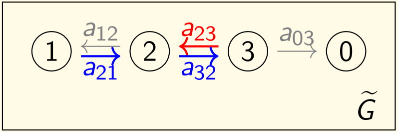

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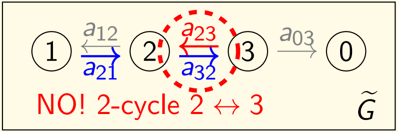

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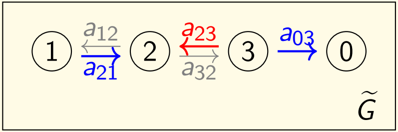

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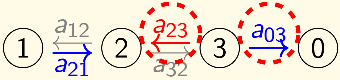
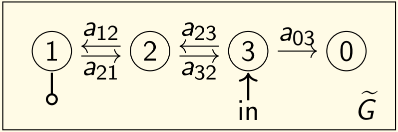


NO! double outgoing from 3 $\widetilde{G}$

Example

For $\mathcal{M} = (G, \{3\}, \{1\}, \{3\})$, we have



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LHS coefficients: $y_1^{(2)}$: Incoming forests with 1 edge

Derivative	Coefficient
$y_1^{(3)}$	1
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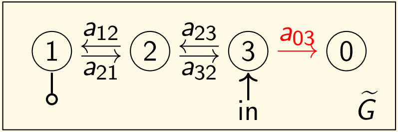

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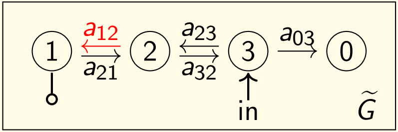

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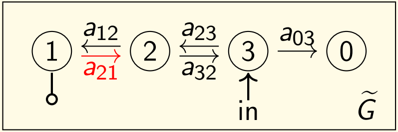

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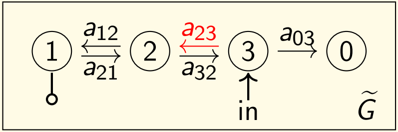

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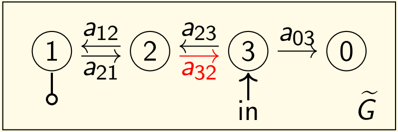

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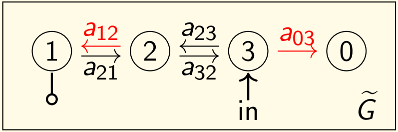

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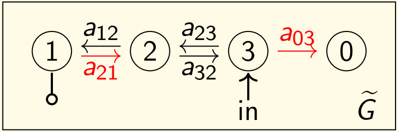

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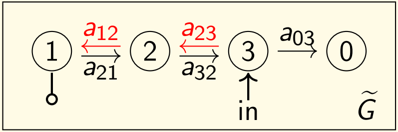

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LHS coefficients: $y_1^{(1)}$: Incoming forests with 2 edges

Derivative	Coefficient
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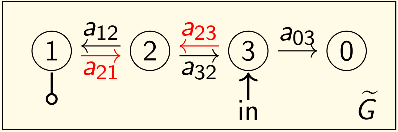

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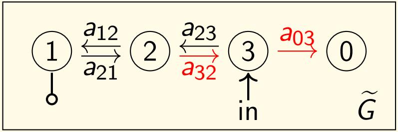

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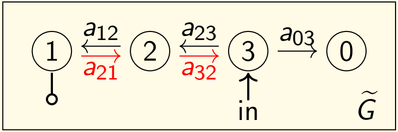

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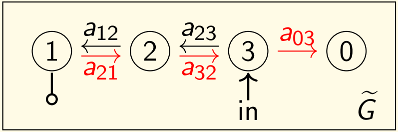

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LHS coefficients: $y_1^{(0)}$: Incoming forests with 3 edges

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$y_1^{(3)}$	1
$y_1^{(2)}$	$a_{03} + a_{12} + a_{21} + a_{23} + a_{32}$
$y_1^{(1)}$	$a_{03}a_{12} + a_{03}a_{21} + a_{12}a_{23} + a_{21}a_{23} + a_{03}a_{32} + a_{21}a_{32}$
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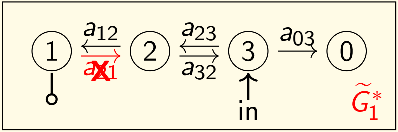

$\widetilde{G}_1^*$: Remove all edges **leaving** the output $\{1\}$.

RHS coeff:

Derivative	Coefficient
$u_3^{(0)}$	

Example

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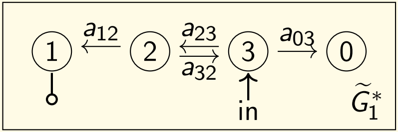

Incoming Forests:

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RHS coeff: Incoming forests with 2 edges AND a path from $\underbrace{in}_{3}$ to $\underbrace{out}_{1}$

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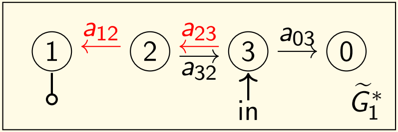

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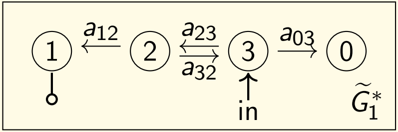

Incoming Forests:

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RHS coefficients: Incoming forests with **1 edge** AND a path from 3 to 1?

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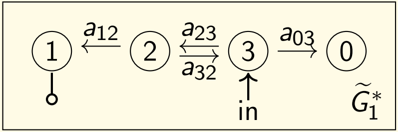

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RHS coefficients: Incoming forests with **3 edges** AND a path from 3 to 1?

Derivative	Coefficient
$u_3^{(0)}$	$a_{12}a_{23}$

Number of Coefficients

Corollary ($, Gross, Meshkat, Shiu, Sullivant, [2023])

Consider $\mathcal{M} = (G, \{in\}, \{out\}, Leak)$ where G is strongly connected and $|V_G| = n$. Then the **number of coefficients** in the input/output equation:

$$\#\text{ on LHS} = \begin{cases} n & \text{if } \#\text{Leaks} \geq 1 \\ n-1 & \text{if } \#\text{Leaks} = 0 \end{cases}, \quad \#\text{ on RHS} = \begin{cases} n-1 & \text{if } in = out \\ n - \mathrm{dist}(\mathrm{in}, \mathrm{out}) & \text{if } in \neq out. \end{cases}$$

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For $\mathcal{M} = (G, \{3\}, \{1\}, \{3\})$, the input/output equation is:

$$y_1^{(3)} + (a_{03} + a_{12} + a_{21} + a_{23} + a_{32})y_1'' + (a_{03}a_{12} + a_{03}a_{21}$$
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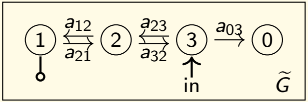

$|Leak| = 1$

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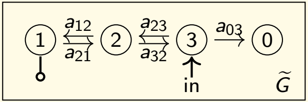

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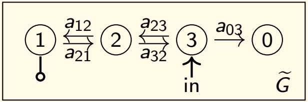

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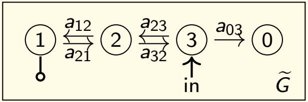


$|Leak| = 1 \Rightarrow \#$ on LHS $= 3$

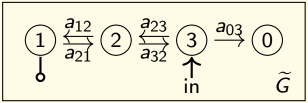
$\mathrm{dist}(3,1) = 2 \Rightarrow \#$ on RHS $= 3-2 = 1$

Example

Example (Continued)

For $\mathcal{M} = (\text{Cat}_3, \{3\}, \{1\}, \{3\})$, the input/output equation is:

$$y_1^{(3)} + (a_{03} + a_{12} + a_{21} + a_{23} + a_{32})\ddot{y}_1 + (a_{03}a_{12} + a_{03}a_{21} + a_{12}a_{23} + a_{21}a_{23} + a_{03}a_{32} + a_{21}a_{32})\dot{y}_1 + (a_{03}a_{21}a_{32})y_1 = (a_{12}a_{23})u_3.$$



on LHS = 3

on RHS = 1

The *coefficient map* corresponding to $\mathcal{M}$ is the map from the space of parameters to the space of coefficients of the input-output equation:

$$\phi\colon \mathbb{R}^5 \to \mathbb{R}^4$$

$$\begin{pmatrix} a_{03} \\ a_{12} \\ a_{21} \\ a_{23} \\ a_{32} \end{pmatrix} \mapsto \begin{pmatrix} a_{03} + a_{12} + a_{21} + a_{23} + a_{32} \\ a_{03}a_{12} + a_{03}a_{21} + a_{12}a_{23} + a_{21}a_{23} + a_{03}a_{32} + a_{21}a_{32} \\ a_{03}a_{21}a_{32} \\ a_{12}a_{23} \end{pmatrix}$$

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A model is

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Consider $\mathcal{M} = (G, \{in\}, \{out\}, Leak)$ where G is *strongly connected* and

$$L = \begin{cases} 0 & \text{if } \#Leak = 0 \\ 1 & \text{if } \#Leak \geq 1 \end{cases} \quad \text{and} \quad d = \begin{cases} 1 & \text{if } \mathrm{dist}(\mathrm{in}, \mathrm{out}) = 0 \\ \mathrm{dist}(\mathrm{in}, \mathrm{out}) & \text{if } \mathrm{dist}(\mathrm{in}, \mathrm{out}) \neq 0. \end{cases}$$

Then $\mathcal{M}$ is **unidentifiable** if $\underbrace{|Leak| + |E_G|}_{\#\text{ parameters}} > \underbrace{2|V_G| - L - d}_{\#\text{ coefficients}}$.

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Remark [not a necessary condition]

There are models that with $\#$parameters $\leq$ $\#$coefficients that are still unidentifiable!

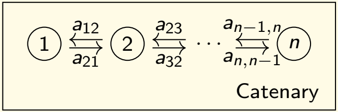
Tree Models

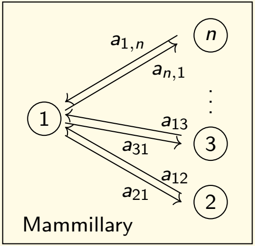
Definition

A (bidirectional) *tree model* $\mathcal{M} = (G, In, Out, Leak)$ has properties

- the edge $i \to j \in E_G$ if and only if the edge $j \to i \in E_G$
- underlying undirected graph of G a [double] tree*

Examples





Unidentifiability of Tree Models

Theorem ($, Gross, Meshkat, Shiu, Sullivant, [2023])

A tree model $\mathcal{M} = (G, \{in\}, \{out\}, Leak)$ is unidentifiable if

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Proof idea: Let $n = |V_G|$.

- # parameters: $\underbrace{|E_G|} + |Leak| = \underbrace{2n - 2} + |Leak|$
  since a *tree* always has $n - 1$ edges,' a *double tree* as $2(n - 1)$ edges!

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- $\#$ coefficients:

	$\|Leak\| \geq 2$	$\|Leak\| = 1$	$\|Leak\| = 0$
$\mathrm{dist}(\mathrm{in}, \mathrm{out}) \geq 2$	$2n - \mathrm{dist}(\mathrm{in}, \mathrm{out})$	$2n - \mathrm{dist}(\mathrm{in}, \mathrm{out})$	$2n - \mathrm{dist}(\mathrm{in}, \mathrm{out}) - 1$
$\mathrm{dist}(\mathrm{in}, \mathrm{out}) = 1$	$2n - 1$	$2n - 1$	$2n - 2$
$\mathrm{dist}(\mathrm{in}, \mathrm{out}) = 0$	$2n - 1$	$2n - 1$	$2n - 2$

Unidentifiability of Tree Models

Theorem ($, Gross, Meshkat, Shiu, Sullivant, [2023])

A tree model $\mathcal{M} = (G, \{in\}, \{out\}, Leak)$ is unidentifiable if

$$\mathrm{dist}(\mathrm{in}, \mathrm{out}) \geq 2 \text{ or } |\mathrm{Leak}| \geq 2.$$

Proof idea: Let $n = |V_G|$.

- # parameters: $|E_G| + |Leak| = 2n - 2 + |Leak| \geq 2n - 2 + 2 = 2n$
- # coefficients:

	$\lvert Leak\rvert \geq 2$	$\lvert Leak\rvert = 1$	$\lvert Leak\rvert = 0$
$\mathrm{dist}(\mathrm{in}, \mathrm{out}) \geq 2$			
$\mathrm{dist}(\mathrm{in}, \mathrm{out}) = 1$			
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- # coefficients:

	$\lvert Leak\rvert \geq 2$	$\lvert Leak\rvert = 1$	$\lvert Leak\rvert = 0$
$\mathrm{dist}(\mathrm{in}, \mathrm{out}) \geq 2$	$2n - \mathrm{dist}(\mathrm{in}, \mathrm{out})$	$2n - \mathrm{dist}(\mathrm{in}, \mathrm{out})$	$2n - \mathrm{dist}(\mathrm{in}, \mathrm{out}) - 1$
$\mathrm{dist}(\mathrm{in}, \mathrm{out}) = 1$	$2n - 1$	$2n - 1$	$2n - 2$
$\mathrm{dist}(\mathrm{in}, \mathrm{out}) = 0$	$2n - 1$	$2n - 1$	$2n - 2$

- five red cases have # parameters > # coefficients

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- five red cases have # parameters > # coefficients $\implies$ unidentifiability

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- five red cases have # parameters > # coefficients $\Longrightarrow$ unidentifiability
- four blue cases have # parameters = # coefficients

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- five red cases have # parameters > # coefficients $\Longrightarrow$ unidentifiability
- four blue cases have # parameters = # coefficients,

but that does not guarantee identifiability.

Can we find a counterexample?

Is there an unidentifiable tree model with $\mathrm{dist}(\mathrm{in}, \mathrm{out}) < 2$ and $|Leak| < 2$?

*Brought to you by Cursor

Building [Locally] Identifiable Tree Models

Plan for showing that # parameters = # coefficients implies identifiability:

1. start with some base model that we know is identifiable

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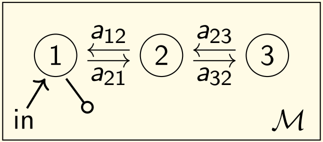
Proposition ($, Gross, Meshkat, Shiu, Sullivant, [2023])

The tree model $\mathcal{M} = (G, \{i\}, \{i\}, \emptyset)$ is *locally* identifiable.

Example

$\mathcal{M} = (\text{Cat}_3, \{1\}, \{1\}, \emptyset)$ is locally identifiable:



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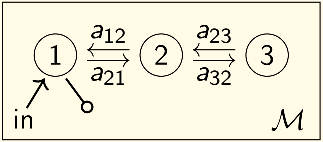
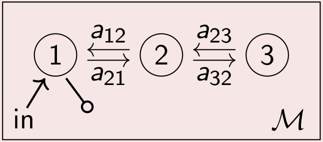


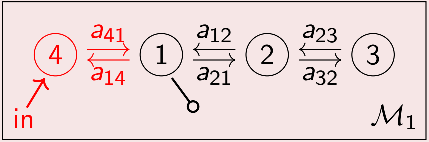
2. from base model, *build* all tree models where $|Leak| \leq 1$ and $\text{dist}(\text{in}, \text{out}) \leq 1$ and **retain local identifiability at each step**

Legal Moves: 1) Moving Input or Output

Prop: Moving the Input or Output

$\mathcal{M} = (G, \{1\}, \{1\}, \emptyset)$ identifiable $\implies$ $\mathcal{M}_1 = (H, \{4\}, \{1\}, \emptyset)$ identifiable:





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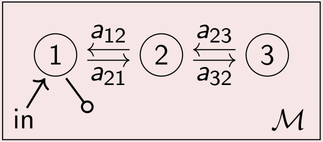

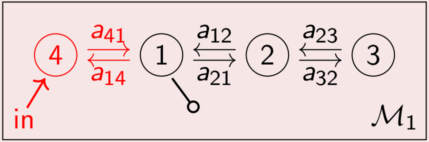

Proof idea:

Theorem (Inverse Function Theorem)

If a function $\varphi\colon \mathbb{R}^n \to \mathbb{R}^n$ has Jacobian with (generically) nonzero determinant, then that function is locally injective.

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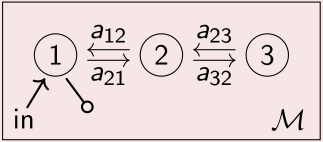
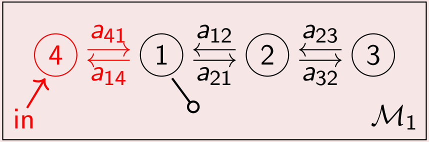




Proof idea:

- write the coefficients of $\mathcal{M}_1$ in terms of $\mathcal{M}$ and the new parameters
- manipulate the Jacobian of $\mathcal{M}_1$ to "find" the Jacobian of $\mathcal{M}$, which by assumption has full rank:

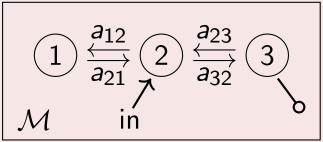
$$J(\mathcal{M}_1) = \begin{pmatrix} J(\mathcal{M}) & 0 \\ * & C \end{pmatrix}$$

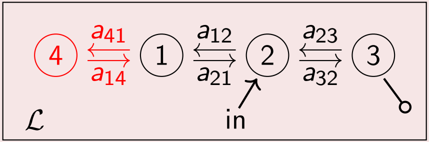
- show that C has full rank using properties of the graph

Legal Moves: 2) Adding Leaves

Prop: Adding Leaves

$\mathcal{M} = (G, \{2\}, \{3\}, \emptyset)$ identifiable $\implies$ $\mathcal{L} = (H, \{2\}, \{3\}, \emptyset)$ identifiable:

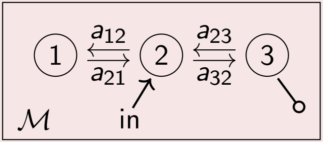


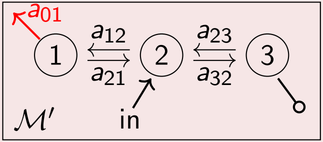


Legal Moves: 3) Adding a Leak

Prop: Adding a Leak

$\mathcal{M} = (G, \{2\}, \{3\}, \emptyset)$ identifiable $\Longrightarrow \mathcal{M}' = (G, \{2\}, \{3\}, \{1\})$ identifiable:





Classification of Tree Models

Theorem ($, Gross, Meshkat, Shiu, Sullivant, [2023])

A tree model $\mathcal{M} = (G, \{in\}, \{out\}, Leak)$ is identifiable **if and only if** $\mathrm{dist}(\mathrm{in}, \mathrm{out}) \leq 1$ and $|Leak| \leq 1$.

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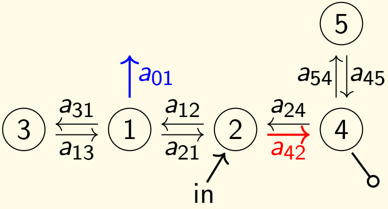

$(G, \{2\}, \{4\}, \{1\})$

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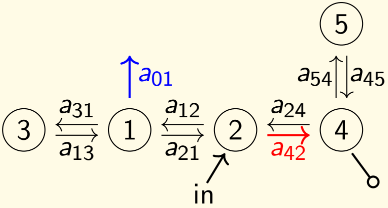

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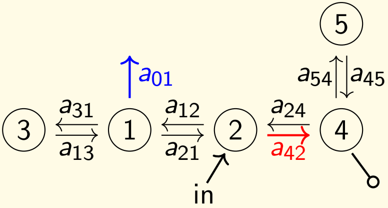

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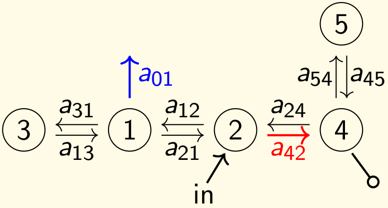

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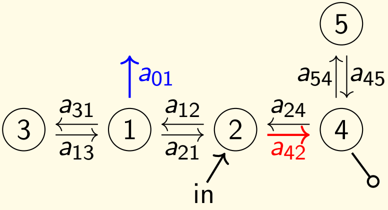

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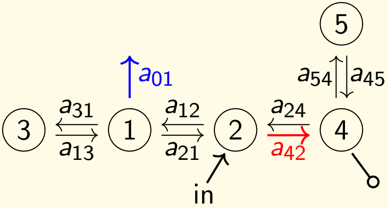

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- $\text{dist}(\underbrace{2}_{\text{In}}, \underbrace{4}_{\text{Out}}) = 1 \leq 1$
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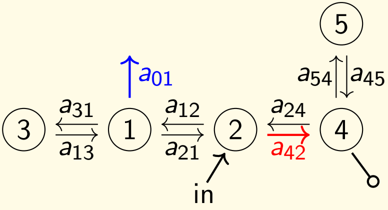

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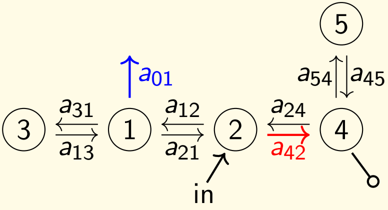

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- $\mathrm{dist}(\underbrace{2}_{\text{In}}, \underbrace{4}_{\text{Out}}) = 1 \leq 1$
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YES!

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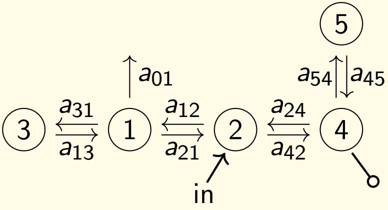

$(G, \{2\}, \{4\}, \{1\})$

a. Identifiable base model:
$$(\underbrace{G_0}_{\text{graph}}, \underbrace{\{i\}}_{\text{In}}, \underbrace{\{i\}}_{\text{Out}}, \underbrace{\emptyset}_{\text{Leak}})$$
b. Move the input/output
c. Add "leaves"
d. Add a single leak

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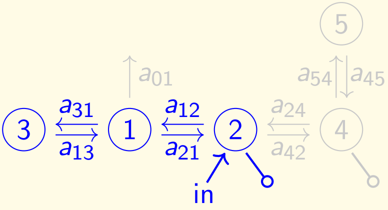

$(\mathrm{Cat}_3, \{2\}, \{2\}, \emptyset)$

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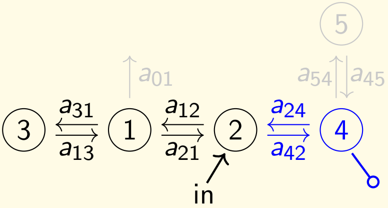

$(G_4, \{2\}, \{4\}, \emptyset)$

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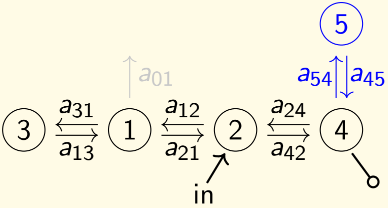

$(G_5, \{2\}, \{4\}, \emptyset)$

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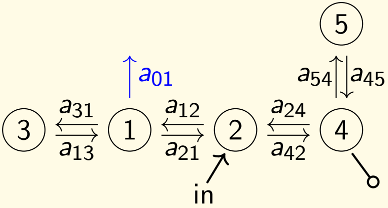

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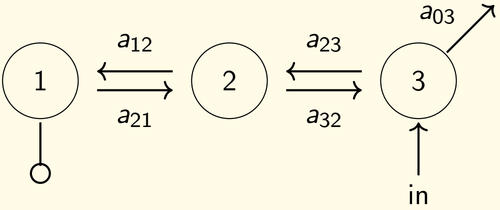

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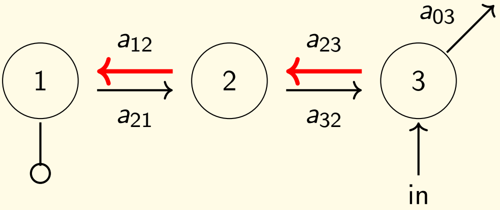

UNIDENTIFIABLE,

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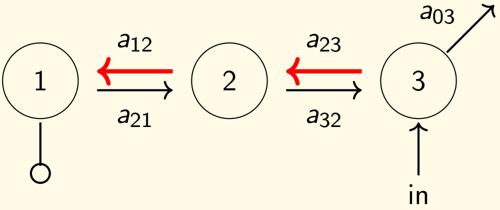

UNIDENTIFIABLE, since $\mathrm{dist}(3, 1) = 2 > 1$

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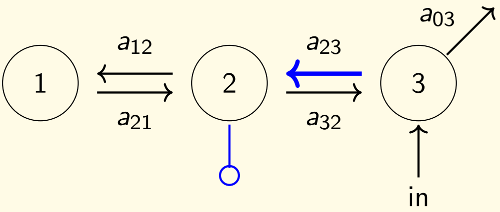

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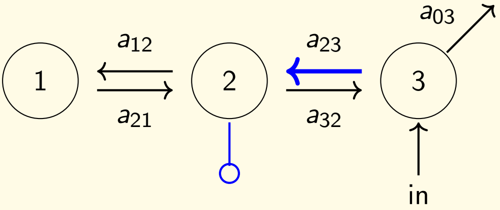
A tree model $\mathcal{M} = (G, \{in\}, \{out\}, Leak)$ is identifiable **if and only if** $\mathrm{dist}(\mathrm{in}, \mathrm{out}) \leq 1$ and $|Leak| \leq 1$.

Example $(\mathrm{Cat}_3, \{3\}, \{2\}, \{3\})$



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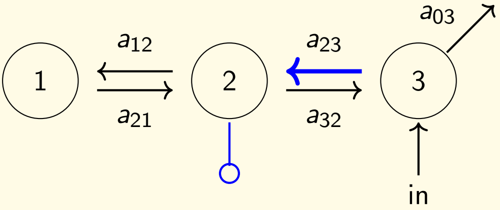

IDENTIFIABLE, since $\mathrm{dist}(3, 2) = 1 \leq 1$ and $|Leak| = 1 \leq 1$.

Conclusion

Theorem

For **ALL** linear compartmental models*, we can generate defining input-output equations from the underlying graph.

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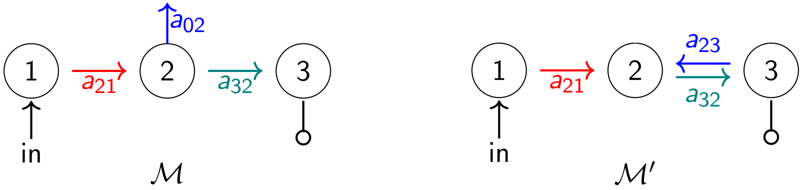
Takeaway

Biologists/modelers can use this information to design models which are structurally identifiable in the hope that they are practically identifiable.

Future Work/Open Problems

- generalize results on tree models to other linear compartmental models (classify identifiability of other families by their graphs)
- consider the problem of determining identifiability when multiple inputs/outputs are present
- expand to *global* identifiability
- find more applications for new characterization of coefficients
  - look for patterns in the singular locus for *dividing edges*
  - expand *indistinguishability* ($-Meshkat, [2024]), i.e. the problem of determining whether two or more linear compartmental models fit a given set of measured data

Motivating Example: Indistinguishability



$$\mathcal{M} : y_3^{(3)} + (a_{21} + a_{02} + a_{32})\ddot{y}_3 + (a_{02}a_{21} + a_{21}a_{32})\dot{y}_3 = (a_{21}a_{32})u_1$$

$$\mathcal{M}' : y_3^{(3)} + (a_{21} + a_{23} + a_{32})\ddot{y}_3 + (a_{23}a_{21} + a_{21}a_{32})\dot{y}_3 = (a_{21}a_{32})u_1$$

Renaming:

$$a_{21} \leftrightarrow a_{21}$$

$$a_{02} \leftrightarrow a_{23}$$

$$a_{32} \leftrightarrow a_{32}$$

Skeletal Path Moves: Walking the Leak

Question

What "*leak moves*" can you perform on a basic skeletal path model resulting in an indistinguishable model?

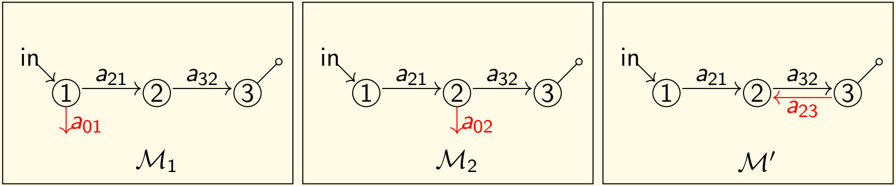
Skeletal Path Moves: Walking the Leak

Theorem ($ & Meshkat [2024]; $, Gilliana, Patel, & Tamras [2025*])

The following skeletal path models are indistinguishable:

- $\mathcal{M}_i = (\overrightarrow{P_n}, \{1\}, \{n\}, \{i\})$ for any $i \in \{1, 2, 3, \ldots, n-1\}$
- $\mathcal{M}' = (\overrightarrow{P_n} \cup \{n \to n-1\}, \{1\}, \{n\}, \emptyset)$.

Example



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Proof idea 1: Left-hand side of the input/output equation of $\mathcal{M}_i$ given by:

$$\det(\partial I - A_i) y_n = \det \begin{pmatrix} \partial + a_{21} & 0 & \cdots & \cdots & 0 & 0 \\ -a_{21} & \ddots & \ddots & \ddots & \vdots & \vdots \\ 0 & \ddots & \partial + a_{0i} + a_{i(i-1)} & \ddots & \vdots & \vdots \\ \vdots & \ddots & -a_{i(i-1)} & \ddots & 0 & 0 \\ 0 & \cdots & \ddots & \ddots & \partial + a_{n(n-1)} & 0 \\ 0 & \cdots & \cdots & 0 & -a_{n(n-1)} & \partial \end{pmatrix} y_n$$

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Proof idea 2:

- Under a renaming of the parameters, the incoming forests of each $\mathcal{M}_i$ are exactly the same as the incoming forests of each $\mathcal{M}_j$ (and $\mathcal{M}'$).

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Proof idea 2:

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- Thus, each of the coefficients of the respective input/output equations are indistinguishable.

Acknowledgments and References

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- Cashous Bortner and Nicolette Meshkat.
  Graph-based sufficient conditions for the indistinguishability of linear compartmental models.
  SIAM Journal on Applied Dynamical Systems, 23(3):2179–2207, 2024.

Thank you!!! - cbortner@csustan.edu

arXiv Link