# Identifiability of Linear Compartmental Tree Models

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DART XI
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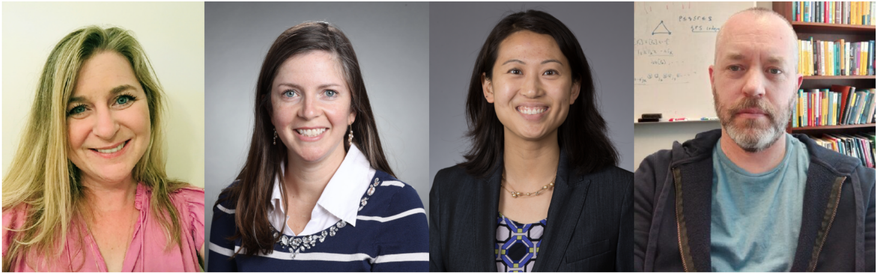
# Collaborators



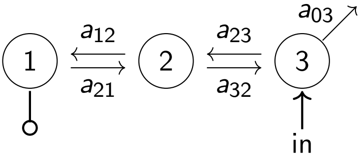
Dr. Elizabeth Gross
U. of Hawai'i at Mānoa

Dr. Nicolette Meshkat
Santa Clara University

Dr. Anne Shiu
Texas A&M University

Dr. Seth Sullivant
North Carolina State U.

# Motivating Example




**Linear Compartmental Model**

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

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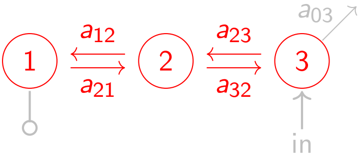


Directed Graph: $G = \mathrm{Cat}_3$

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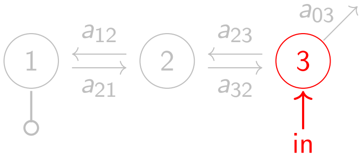


Input Compartment: $In = \{3\}$

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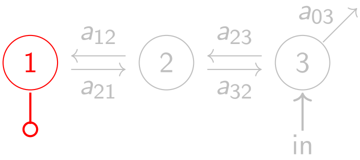


Measured Compartment: $Out = \{1\}$

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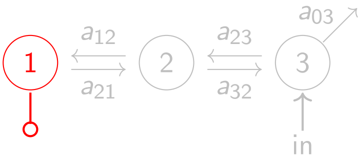


"Output" Compartment: $\mathit{Out} = \{1\}$

**Linear Compartmental Model**

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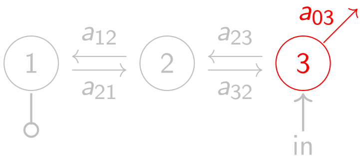


Leak Compartment: $Leak = \{3\}$

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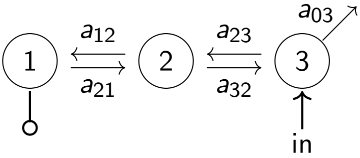


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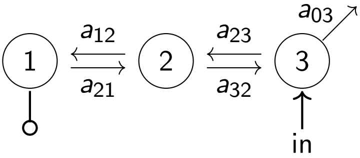


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## Motivating Question: Identifiability

Given information about the input and output compartment[s], can we **recover** all flow rate parameters?

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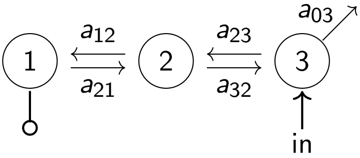


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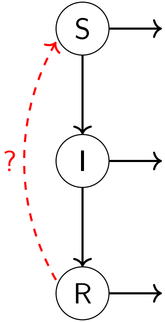
Given information about the input and output compartment[s], can we **identify** all flow rate parameters?

# Compartmental Models in the Wild

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



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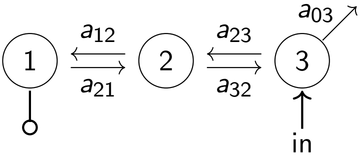


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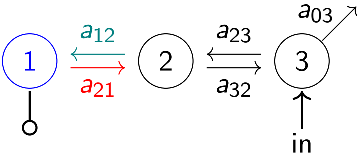


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ODEs in terms of concentrations $x_i(t)$, input $u_3(t)$, and output $y_1(t)$:

$$\dot{x_1} = -a_{21}x_1(t) \qquad +a_{12}x_2(t)$$

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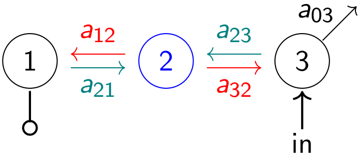


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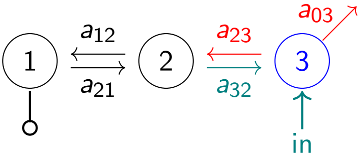


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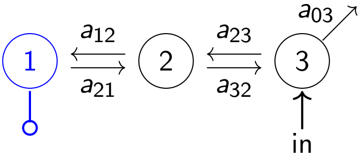


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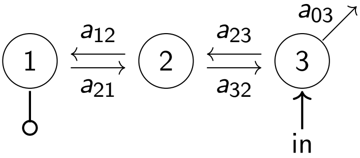


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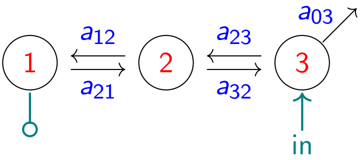


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<u>*Goal*</u>: *Identify the parameters $a_{ji}$ from the measurable variables.*

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$$\begin{pmatrix} \partial_t + a_{21} & -a_{12} & 0 \\ -a_{21} & \partial_t + a_{12} + a_{32} & -a_{23} \\ 0 & -a_{32} & \partial_t + a_{03} + a_{23} \end{pmatrix} \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ u_3(t) \end{pmatrix}$$

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via Cramer's Rule:

$$\det \begin{pmatrix} \partial_t + a_{21} & -a_{12} & 0 \\ -a_{21} & \partial_t + a_{12} + a_{32} & -a_{23} \\ 0 & -a_{32} & \partial_t + a_{03} + a_{23} \end{pmatrix} y_1(t)$$

$$= \det \begin{pmatrix} 0 & -a_{12} & 0 \\ 0 & \partial_t + a_{12} + a_{32} & -a_{23} \\ u_3(t) & -a_{32} & \partial_t + a_{03} + a_{23} \end{pmatrix}$$

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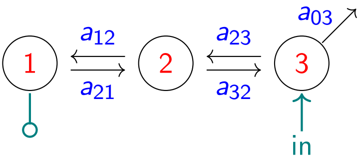


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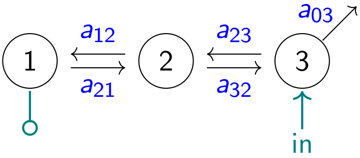
$$\det(\partial_t I - A) y_1 = \underbrace{\det(\partial_t I - A)^{(3,1)}}_{\text{remove row 3 and col 1}} u_3$$

by Cramer's Rule and substitution.

# Motivating Example: Input/Output Equation

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Via a substitution and application of Cramer's Rule:

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

an ODE in only the measurable variables and the parameters:

Input/Output Equation

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

# Identifiability Analysis: Structural vs. Practical

## Overview

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

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## Remark

Structural identifiability is a **necessary condition** for practical identifiability.

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## Structural Identifiability via the input-output equation

We consider structural identifiability as a two-step problem:

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## Goal

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

# Novel Input-Output Equation Characterization

**Theorem ($, Gross, Meshkat, Shiu, Sullivant [1])**

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

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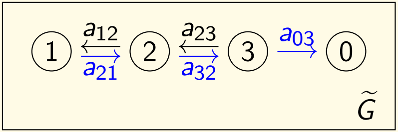
## Definitions

A directed graph $H$ is called an *incoming forest* if

- no vertex has more than one outgoing edge, and
- its underlying undirected graph is a forest

## 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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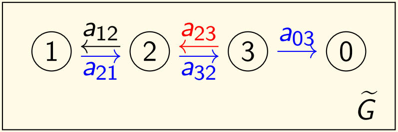

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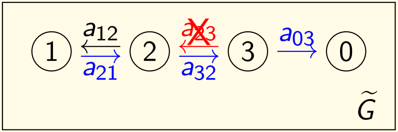

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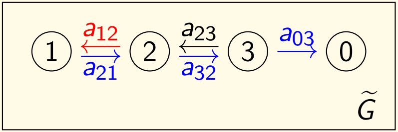
- its underlying undirected graph is a forest

## Example

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



# Novel Input-Output Equation Characterization

## Theorem ($, Gross, Meshkat, Shiu, Sullivant [1])

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

## Definitions

A directed graph $H$ is called an *incoming forest* if

- no vertex has more than one outgoing edge, and
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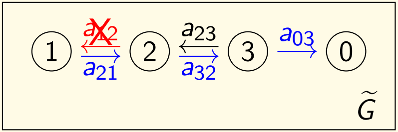
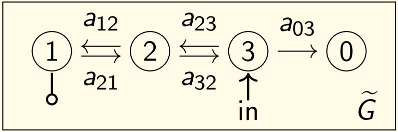


## Example

For $\mathcal{M} = (\mathrm{Cat}_3, \{3\}, \{1\}, \{3\})$:




The $k^{\text{th}}$ coefficient of LHS of the i-o equation is:

$$c_k = \sum_{F \in \mathcal{F}_{3-k}(\widetilde{G})} \pi_F$$

LHS coefficients: Incoming forests with 1 edge

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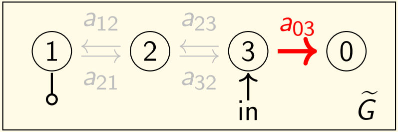


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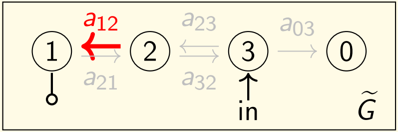


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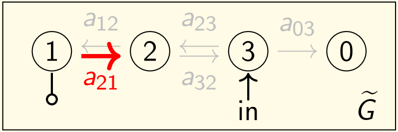


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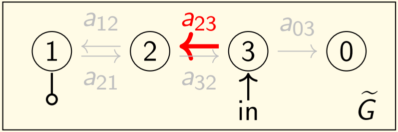


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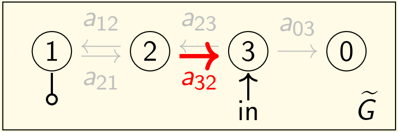


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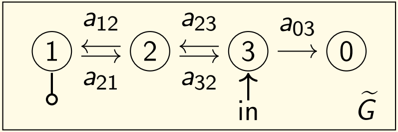


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LHS coefficients: Incoming forests with 2 edge

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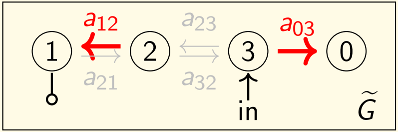


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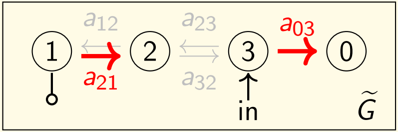


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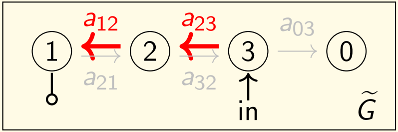


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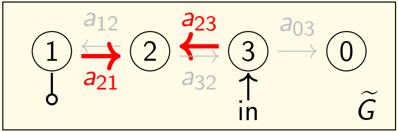


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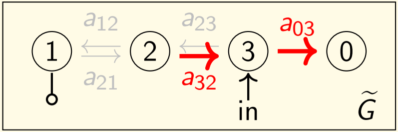


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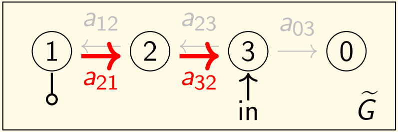


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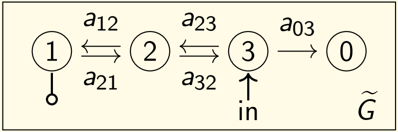


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LHS coefficients: Incoming forests with 3 edge

| Derivative | Coefficient |
|---|---|
| $y_1^{(3)}$ | 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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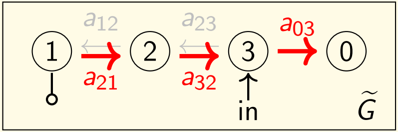


The $k^{\text{th}}$ coefficient of LHS of the i-o equation is:

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LHS coefficients: Incoming forests with 3 edge

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|---|---|
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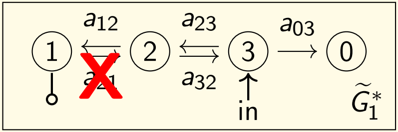


The $k^{\text{th}}$ coefficient of RHS of the i-o equation is:

$$d_k \;=\; \sum_{F \in \mathcal{F}^{3,1}_{3-k-1}(\widetilde{G}_1^*)} \pi_F$$

RHS coefficients:

| Derivative | Coefficient |
|---|---|
| $u_3^{(0)}$ | |

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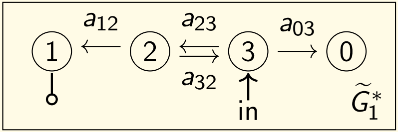


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RHS coefficients: Incoming forests with 2 edges AND a path from 3 to 1

| Derivative | Coefficient |
|---|---|
| $u_3^{(0)}$ | |

## Example

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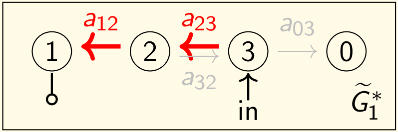


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RHS coefficients: Incoming forests with 2 edges AND a path from 3 to 1

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|---|---|
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# Number of Coefficients

## Corollary ($, Gross, Meshkat, Shiu, Sullivant [1])

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

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

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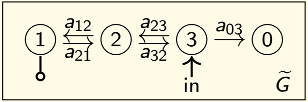
## Example

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

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




$\#$ on LHS $= 3$ (since $|Leak| = 1$)

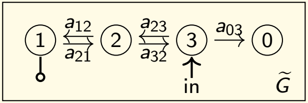
$\#$ on RHS $= 3 - \underbrace{\mathrm{dist}(3,1)}_{2} = 1$

# Example

## Example

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:

$$\phi_{\mathcal{M}} : \mathbb{R}^5 \to \mathbb{R}^4$$

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

# Identifiability

**Definition***

A model $(G, In, Out, Leak)$ with coefficient map $\phi$ is

- *locally identifiable* (identifiable) if, outside a set of measure zero, every point in $\mathbb{R}^{|E_G|+|Leak|}$ has an open neighborhood $U$ for which the restriction $\phi|_U : U \to \mathbb{R}^m$ is **one-to-one**; and
- *unidentifiable* if $c$ is generically **infinite-to-one**.

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**Proposition (Sufficient condition for unidentifiability)**

A model $\mathcal{M} = (G, In, Out, Leak)$ is *unidentifiable* if

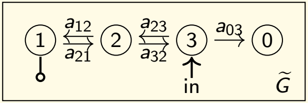
$$\underbrace{\#\text{ parameters}}_{|E_G|+|Leak|} > \#\text{ coefficients.}$$

# Example

## Example

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:

$$\phi_{\mathcal{M}} : \mathbb{R}^5 \to \mathbb{R}^4$$

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

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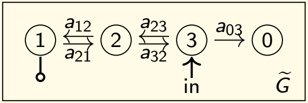


$\#$ on LHS $= 3$

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The coefficient map corresponding to $\mathcal{M}$ is:

$\phi_{\mathcal{M}} : \mathbb{R}^5 \to \mathbb{R}^4$ $\quad$ $\mathcal{M}$ is UNIDENTIFIABLE

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

# Unidentifiability

**Corollary ($, Gross, Meshkat, Shiu, Sullivant [1])**

Consider $\mathcal{M} = (G, \{in\}, \{out\}, Leak)$ where $G$ is strongly connected and $|V_G| = n$. Define $L$ and $d$ as follows:

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

Then $\mathcal{M}$ is **unidentifiable** if

$$\underbrace{|Leak| + |E_G|}_{\#\text{ parameters}} > \underbrace{2n - L - d}_{\#\text{ coefficients}}.$$

# The Jacobian

## Proposition

$\mathcal{M} = (G, \{i\}, \{j\}, Leak)$ is locally identifiable if and only if the rank of the Jacobian matrix of its coefficient map is equal to # parameters.

## Example

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

$$y_1^{(3)} + \underbrace{(a_{03} + a_{12} + a_{21} + a_{23} + a_{32})}_{c_2}\ddot{y}_1 + \underbrace{(a_{03}a_{12} + a_{03}a_{21} + a_{12}a_{23} + a_{21}a_{23} + a_{03}a_{32} + a_{21}a_{32})}_{c_1}\dot{y}_1$$

$$+ \underbrace{(a_{03}a_{21}a_{32})}_{c_0} y_1 = \underbrace{(a_{12}a_{23})}_{d_0} u_3$$

$$J(\phi_{\mathcal{M}}) = \begin{array}{c} \\ c_2 \\ c_1 \\ c_0 \\ d_0 \end{array} \begin{array}{c} \begin{array}{ccccc} a_{03} & a_{12} & a_{21} & a_{23} & a_{32} \end{array} \\ \begin{pmatrix} 1 & 1 & 1 & 1 & 1 \\ a_{12} + a_{21} + a_{32} & a_{03} + a_{23} & a_{03} + a_{23} + a_{32} & a_{12} + a_{21} & a_{03} + a_{21} \\ a_{21}a_{32} & 0 & a_{03}a_{32} & 0 & a_{03}a_{21} \\ 0 & a_{23} & 0 & a_{12} & 0 \end{pmatrix} \end{array}$$

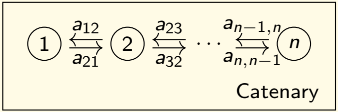
# Tree Models

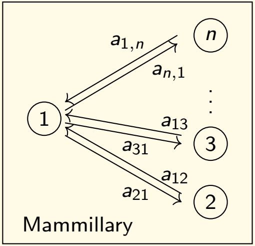
## Definition

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 [1])**

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: $|E_G| + |Leak| = 2n - 2 + |Leak|$

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Top-Left:

- # parameters $\geq 2n$ (since $|Leak| \geq 2$)
- # coefficients $= 2n - \underbrace{\mathrm{dist}(\mathrm{in}, \mathrm{out})}_{\geq 2}$

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Bottom-Right:

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

# Unidentifiability of Tree Models

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

*but that does* **not** *guarantee identifiability.*

# Building Identifiable Tree Models

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

- start with some base model that we know is identifiable (Prop*)
- from base model, *build* all tree models where $|Leak| \leq 1$ and $\mathrm{dist}(\mathrm{in}, \mathrm{out}) \leq 1$ and retain identifiability at each step

**Proposition* ($, Gross, Meshkat, Shiu, Sullivant [1])**

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

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

**Proposition (Gross, Harrington, Meshkat, Shiu [2])**

Let $\mathcal{M} = (G, In, Out, \emptyset)$ be strongly connected and identifiable. Then, the model $\mathcal{M}' = (G, In, Out, \{k\})$ is also identifiable.

# Moving the Input/Output

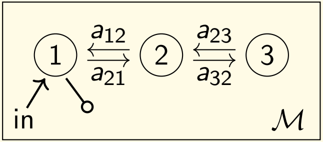
**Proposition ($, Gross, Meshkat, Shiu, Sullivant [1])**

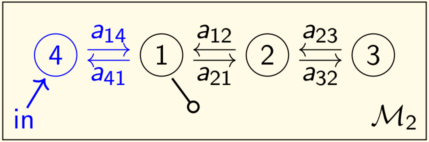
Let $\mathcal{M} = (G, \{i\}, \{i\}, \emptyset)$ be an identifiable tree model. Let $H$ be the graph $G$ with the added node $n$ and edges $i \to n$ and $n \to i$. Then following models are also identifiable:

- $\mathcal{M}_1 = (H, \{i\}, \{n\}, \emptyset)$
- $\mathcal{M}_2 = (H, \{n\}, \{i\}, \emptyset)$.

**Example**

Here, $\mathcal{M} = (\text{Cat}_3, \{1\}, \{1\}, \emptyset)$ and $\mathcal{M}_2 = (\text{Cat}_4^*, \{4\}, \{1\}, \emptyset)$:



# Proof of Moving the Input/Output

**Theorem ($, Gross, Meshkat, Shiu, Sullivant [1])**

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- $\mathcal{M}_1 = (H, \{i\}, \{n\}, \emptyset)$
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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 $\phi_{\mathcal{M}_1}$ to "find" the Jacobian of $\phi_{\mathcal{M}}$, which by assumption has full rank:

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

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

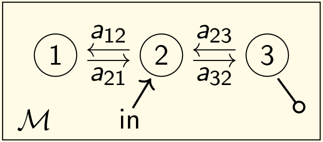
# Adding a Leaf

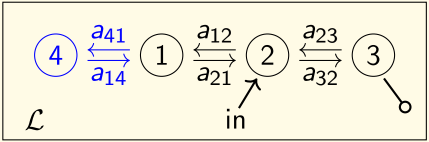
**Proposition ($, Gross, Meshkat, Shiu, Sullivant [1])**

Let $\mathcal{M} = (G, \{i\}, \{j\}, \emptyset)$ be an identifiable tree model. Define $\mathcal{L} = (H, \{i\}, \{j\}, \emptyset)$ where $H$ is the graph $G$ with the added node $n$ and edges $k \to n$ and $n \to k$ for some $k \in V_G$. Then, $\mathcal{L}$ is identifiable.

**Example**

Here, $\mathcal{M} = (\text{Cat}_3, \{2\}, \{3\}, \emptyset)$ and $\mathcal{L} = (\text{Cat}_4^*, \{2\}, \{3\}, \emptyset)$:



# Classification of Tree Models

**Theorem ($, Gross, Meshkat, Shiu, Sullivant [1])**

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

*Proof outline:*

- $\mathcal{M}$ is unidentifiable if either $\mathrm{dist}(\mathrm{in}, \mathrm{out}) > 1$ or $|Leak| > 1$
- $\mathcal{M}$ is identifiable if $in = out$ and $|Leak| = 0$
- $\mathcal{M}$ is identifiable if $\mathrm{dist}(\mathrm{in}, \mathrm{out}) = 1$ and $|Leak| = 0$
- if $\mathcal{M}$ is identifiable with $|Leak| = 0$, then it is identifiable with $|Leak| = 1$

# Example

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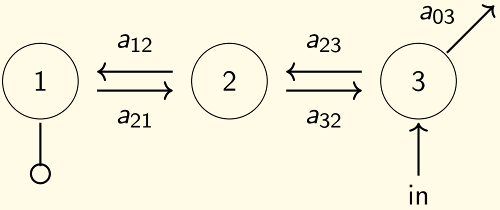

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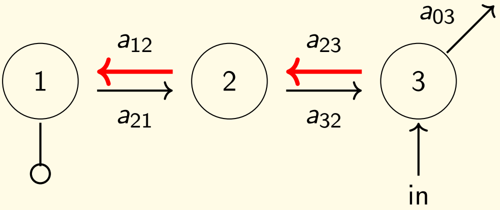


**UNIDENTIFIABLE**,

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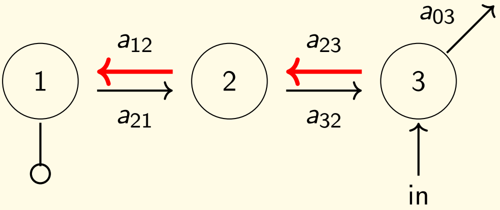


**UNIDENTIFIABLE**, since $\mathrm{dist}(3, 1) = 2 > 1$

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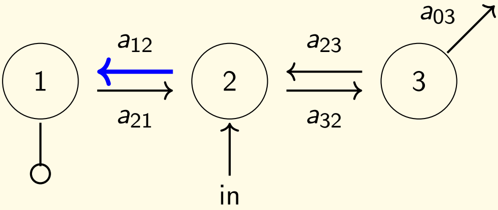

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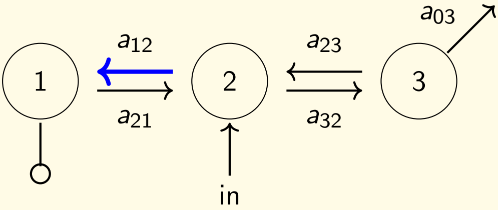
**Example**



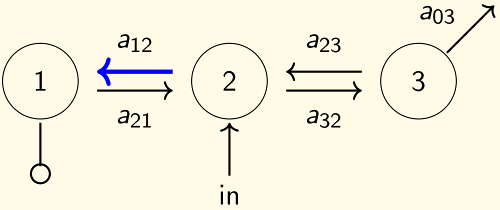

**IDENTIFIABLE**,

# Example

**Theorem ($, Gross, Meshkat, Shiu, Sullivant [1])**

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**




**IDENTIFIABLE**, since $\mathrm{dist}(2, 1) = 1 \leq 1$ 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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**Remark**

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

# Future Work

- generalize results on tree models to other linear compartmental models
- find more applications for new characterization of coefficients
  - consider *distinguishability*, i.e. the problem of determining whether two or more linear compartmental models fit a given set of measured data
  - look for patterns in the singular locus for *dividing edges*
  - consider identifiability versus observability relationship
- consider the problem of determining identifiability when multiple inputs/outputs are present

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# Thank you!!!