Identifiability of Linear Compartmental Tree Models

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Outline

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Identifiability Analysis: A two part problem

Overview

Structural identifiability is the problem of determining if the parameters of a model can be recovered from the measurable variables of the model under perfect conditions.
Note: Structural identifiability is a necessary condition for practical identifiability.

- Structural identifiability can be carried out in two phases:
  1. Find the input/output equation[s] of the ODE system in terms of observable variables
  2. Determine injectivity of coefficient map defined by input/output equation[s] often via the computing the rank of the Jacobian

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LCM Motivating Example

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

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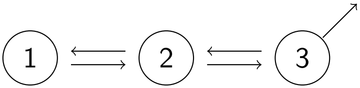

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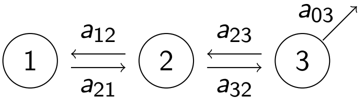

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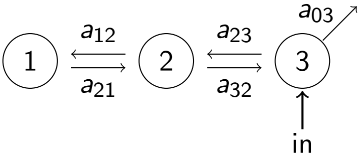

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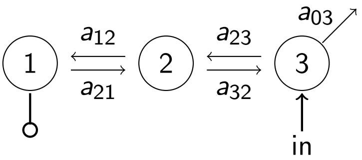

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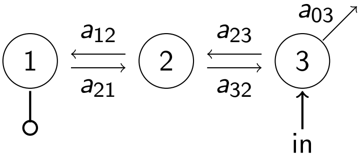

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$$= (\mathrm{Cat}_3, \{3\}, \{1\}, \{3\}).$$

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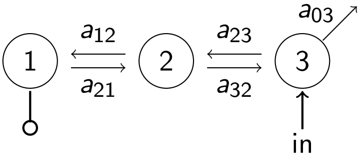


$$\begin{aligned}\mathcal{M} &= (G, In, Out, Leak)\\ &= (\mathrm{Cat}_3, \{3\}, \{1\}, \{3\}).\end{aligned}$$

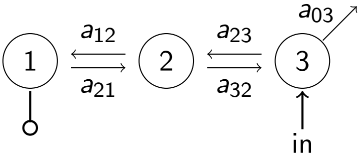
ODE in terms of concentrations $x_i(t)$, input $u_3(t)$, and output $y_1(t)$:

$$\begin{aligned}\dot{x}_1(t) &= -a_{21}x_1(t) + a_{12}x_2(t)\\ \dot{x}_2(t) &= a_{21}x_1(t) - (a_{12} + a_{32})x_2(t) + a_{23}x_3(t)\\ \dot{x}_3(t) &= a_{32}x_2(t) - (a_{03} + a_{23})x_3(t) + u_3(t)\end{aligned}$$

with

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

LCM Motivating Example



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

$$\begin{pmatrix} \dot{x}_1(t) \\ \dot{x}_2(t) \\ \dot{x}_3(t) \end{pmatrix} = \underbrace{\begin{pmatrix} -a_{21} & a_{12} & 0 \\ a_{21} & -a_{12} - a_{32} & a_{23} \\ 0 & a_{32} & -a_{03} - a_{23} \end{pmatrix}}_{\text{compartmental matrix A}} \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \\ u_3(t) \end{pmatrix}$$

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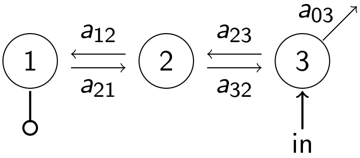
LCM Motivating Example: Input/Output Equation



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

Via a simple 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

Input/Output Equation

Proposition

Consider $\mathcal{M} = (G, In, Out, Leak)$ with $n = |V_G|$ and $|In| \geq 1$. Define ∂I to be the $n \times n$ diagonal matrix where the diagonal entries are the differential operator d/dt. Then, the following equations are input/output equations of $\mathcal{M}$:

$$\det(\partial I - A)y_j = \sum_{i \in In} (-1)^{i+j} \det\left((\partial I - A)^{i,j}\right) u_i \qquad \text{for } j \in Out .$$

Remark

This characterization of the input/output equation is difficult to relate to the Jacobian for later identifiability analysis.

Input/Output Equation via G ($in = out$)

Theorem (Gross, Meshkat, Shiu [4])

Consider $\mathcal{M} = (G, In, Out, Leak)$ with G strongly connected, $In = Out = \{1\}$ and $|Leak| \geq 1$. If $n = |V_G|$, then an input/output equation of $\mathcal{M}$ is

$$y_1^{(n)} + c_{n-1} y_1^{(n-1)} + \cdots + c_1 y_1' + c_0 y_1 \; = \; u_1^{(n-1)} + d_{n-2} u_1^{(n-2)} + \cdots + d_1 u_1' + d_0 u_1$$

with coefficients:

$$c_i = \sum_{F \in \mathcal{F}_{n-i}(\widetilde{G})} \pi_F \quad \text{for } i = 0, 1, \ldots, n-1, \quad \text{and}$$

$$d_i = \sum_{F \in \mathcal{F}_{n-i-1}(\widetilde{G}_1)} \pi_F \quad \text{for } i = 0, 1, \ldots, n-2.$$

Input/Output Equation via G

Theorem (B., Gross, Meshkat, Shiu, Sullivant [1])

Consider $\mathcal{M} = (G, In, Out, Leak)$ with $|In| \geq 1$ and $n = |V_G|$. Then an input/output equation (for some $j \in Out$) for $\mathcal{M}$ is

$$y_j^{(n)} + c_{n-1} y_j^{(n-1)} + \cdots + c_1 y_j' + c_0 y_j \ = \ \sum_{i \in In} (-1)^{i+j} \left(d_{i,n-1} u_i^{(n-1)} + \cdots + d_{i,1} u_i' + d_{i,0} u_i \right) .$$

with coefficients:

$$c_k \ = \ \sum_{F \in \mathcal{F}_{n-k}(\widetilde{G})} \pi_F \qquad \text{for } k = 0, 1, \ldots, n-1 \ , \quad \text{and}$$

$$d_{i,k} \ = \ \sum_{F \in \mathcal{F}^{i,j}_{n-k-1}(\widetilde{G}_j^*)} \pi_F \qquad \text{for } i \in In \text{ and } k = 0, 1, \ldots, n-1 \ .$$

Graph Definitions

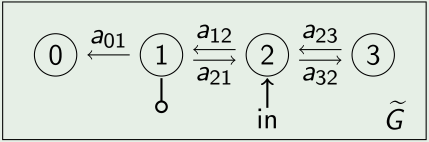
Definitions

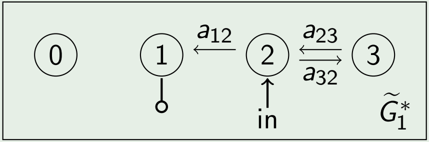
For a model $\mathcal{M} = (G, In, Out, Leak)$

- $\widetilde{G}$ is the graph $G \cup \{0\}$ where for each $i \in Leak$, we add the edge $i \to 0$ with edge weight a_{0i}
- $\widetilde{G}_k^*$ is the graph $\widetilde{G}$ where we remove every edge leaving node k

Example

For $\mathcal{M} = (G, \{2\}, \{1\}, \{1\})$ where $G = \text{Cat}_3$, we have





Incoming Forests

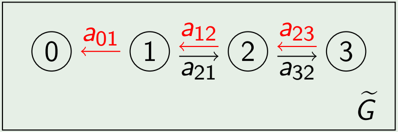
Definitions

For a directed graph H

- H is called an *incoming forest* if its underlying undirected graph is a forest, and no vertex has more than one outgoing edge
- $\mathcal{F}_k(H)$ is the set of all incoming forests on H with k edges
- $\mathcal{F}_k^{i,j}(H)$ is the set of all incoming forests on H with k edges containing a directed path from i to j
- π_H is the product of edge weights of the edges of H

Example

- $\mathcal{F}_3(\widetilde{G}) = \{\{3 \to 2, 2 \to 1, 1 \to 0\}\}$
- $\mathcal{F}_2^{2,1}(\widetilde{G}) = \{\{2 \to 1, 3 \to 2\}, \{2 \to 1, 1 \to 0\}\}$
- $\pi_{\widetilde{G}} = a_{01} a_{12} a_{21} a_{23} a_{32}$.



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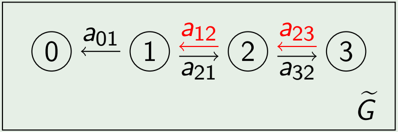

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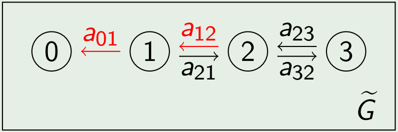

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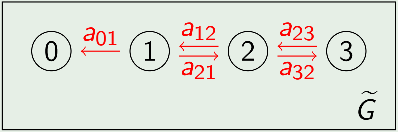

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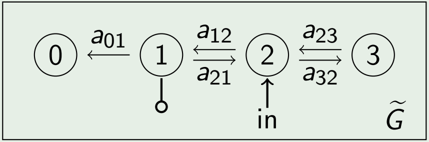

The k^{th} coefficient of LHS of the i-o equation is:

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

LHS coefficients:

Derivative	Coefficient
$y_1^{(3)}$	1
$y_1^{(2)}$	$a_{01} + a_{12} + a_{21} + a_{23} + a_{32}$
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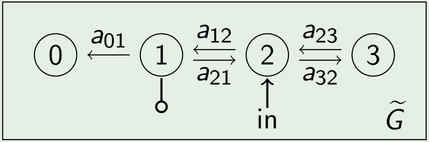

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LHS coefficients: Incoming forests with 1 edge

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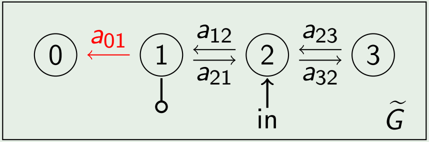

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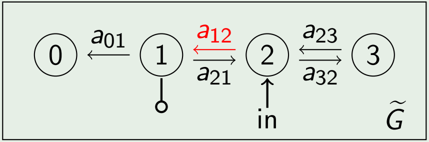

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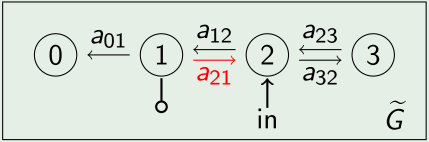

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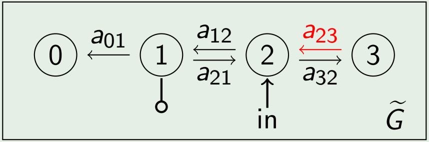

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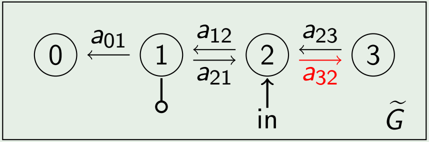

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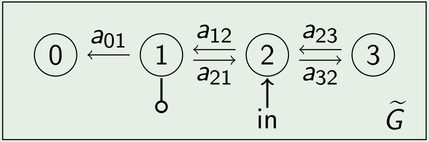

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LHS coefficients: Incoming forests with 2 edges

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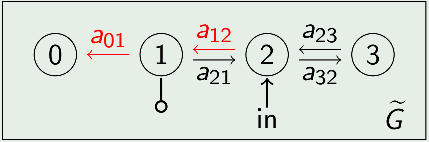

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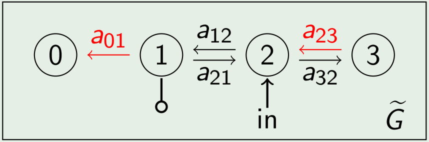

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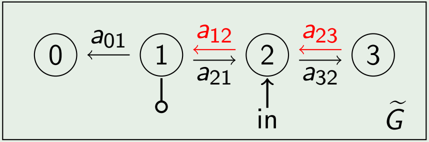

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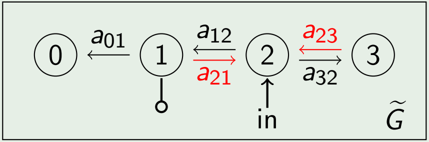

The k^{th} coefficient of LHS of the i-o equation is:

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

LHS coefficients: Incoming forests with 2 edges

Derivative	Coefficient
$y_1^{(3)}$	1
$y_1^{(2)}$	$a_{01} + a_{12} + a_{21} + a_{23} + a_{32}$
$y_1^{(1)}$	$a_{01}a_{12} + a_{01}a_{23} + a_{12}a_{23} + a_{21}a_{23} + a_{01}a_{32} + a_{21}a_{32}$
$y_1^{(0)}$	$a_{01}a_{12}a_{23}$

Example

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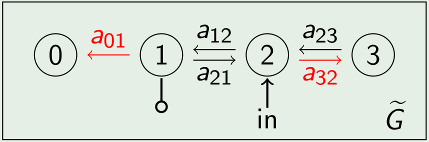

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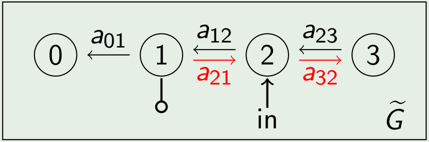

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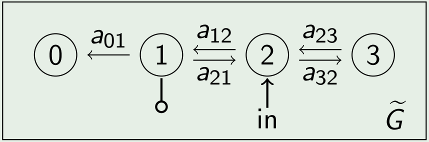
Example

For $\mathcal{M} = (G, \{2\}, \{1\}, \{1\})$, we have



The k^{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 3 edges

Derivative	Coefficient
$y_1^{(3)}$	1
$y_1^{(2)}$	$a_{01} + a_{12} + a_{21} + a_{23} + a_{32}$
$y_1^{(1)}$	$a_{01}a_{12} + a_{01}a_{23} + a_{12}a_{23} + a_{21}a_{23} + a_{01}a_{32} + a_{21}a_{32}$
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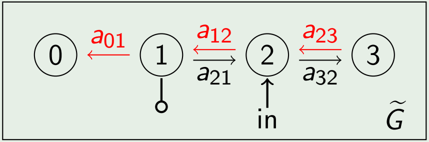
Example

For $\mathcal{M} = (G, \{2\}, \{1\}, \{1\})$, we have



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

LHS coefficients: Incoming forests with 3 edges

Derivative	Coefficient
$y_1^{(3)}$	1
$y_1^{(2)}$	$a_{01} + a_{12} + a_{21} + a_{23} + a_{32}$
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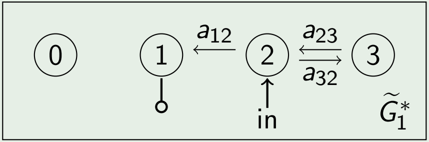
Example

For $\mathcal{M} = (G, \{2\}, \{1\}, \{1\})$, we have



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

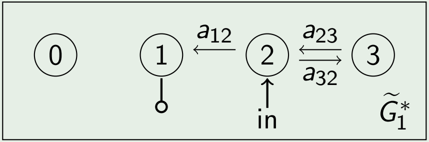
$$d_k = \sum_{F \in \mathcal{F}^{2,1}_{3-k-1}(\widetilde{G}_1^*)} \pi_F$$

RHS coefficients:

Derivative	Coefficient
$u_2^{(1)}$	a_{12}
$u_2^{(0)}$	$a_{12}a_{23}$

Example

For $\mathcal{M} = (G, \{2\}, \{1\}, \{1\})$, we have



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

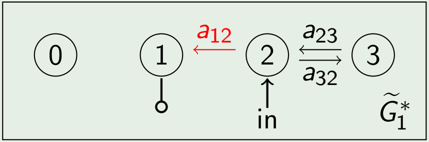
$$d_k = \sum_{F \in \mathcal{F}^{2,1}_{3-k-1}(\widetilde{G}_1^*)} \pi_F$$

RHS coefficients: Incoming forests with 1 edge and the edge from 2 to 1

Derivative	Coefficient
$u_2^{(1)}$	a_{12}
$u_2^{(0)}$	$a_{12}a_{23}$

Example

For $\mathcal{M} = (G, \{2\}, \{1\}, \{1\})$, we have



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RHS coefficients: Incoming forests with 1 edge and the edge from 2 to 1

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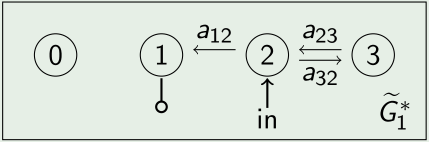
Example

For $\mathcal{M} = (G, \{2\}, \{1\}, \{1\})$, we have



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

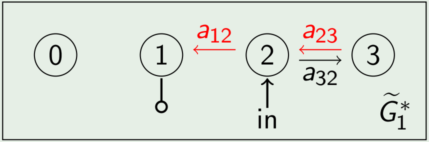
$$d_k = \sum_{F \in \mathcal{F}^{2,1}_{3-k-1}(\widetilde{G}_1^*)} \pi_F$$

RHS coefficients: Incoming forests with 2 edges and the edge from 2 to 1

Derivative	Coefficient
$u_2^{(1)}$	a_{12}
$u_2^{(0)}$	$a_{12}a_{23}$

Example

For $\mathcal{M} = (G, \{2\}, \{1\}, \{1\})$, we have



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RHS coefficients: Incoming forests with 2 edges and the edge from 2 to 1

Derivative	Coefficient
$u_2^{(1)}$	a_{12}
$u_2^{(0)}$	$a_{12}a_{23}$

Proof structure: Induction on $|E_G|$

Theorem (B., Gross, Meshkat, Shiu, Sullivant [1])

The RHS of the input/output equation of $\mathcal{M} = (G, \{in\}, \{out\}, Leak)$ with $in \neq out$ has coefficients $d_k = \sum_{F \in \mathcal{F}_{n-k-1}^{in,out}(\widetilde{G}_{out}^*)} \pi_F$

Proof idea: Induction on $|E_G|$

- Base case: $|E_G| = 0$
  - $\mathcal{F}_{n-k-1}^{in,out} = \emptyset$ so all d_k are zero
  - $(\partial I - A)_{i,j} = 0$ for all $i \neq j$, therefore $\det((\partial I - A)^{in,out}) = 0$
- Inductive step
  - Laplacian expansion down the *in* column, i.e. all edges leaving *in*

$$\det((\partial I - A)^{in,out}) = \sum_{in \to j \in E_G} (-1)^{in+j} a_{j(in)} \underbrace{\det((\partial I - A)^{\{in,j\},\{in,out\}})}_{\text{RHS of model with less edges}}$$

Proof structure: Induction on $|E_G|$

Theorem (B., Gross, Meshkat, Shiu, Sullivant [1])

The RHS of the input/output equation of $\mathcal{M} = (G, \{in\}, \{out\}, Leak)$ with $in \neq out$ has coefficients $d_k = \sum_{F \in \mathcal{F}_{n-k-1}^{in,out}(\widetilde{G}_{out}^{*})} \pi_F$

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- Base case: $|E_G| = 0$
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- Inductive step
  - Laplacian expansion down the *in* column, i.e. all edges leaving *in*

$$\det((\partial I - A)^{in,out}) = \sum_{in \to j \in E_G} (-1)^{in+j} a_{j(in)} \underbrace{\det((\partial I - A^{*})^{j,out})}_{\text{RHS of model with less edges}}$$

Number of Coefficients

Corollary (B., Gross, Meshkat, Shiu, Sullivant [1])

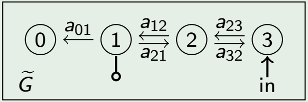
Consider $\mathcal{M} = (G, \{in\}, \{out\}, Leak)$ where G is strongly connected and $|V_G| = n$. Then the numbers of non-constant coefficients on the left-hand and right-hand sides of the input/output equation are:

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

Example

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

$$y_1^{(3)} + (a_{01} + a_{12} + a_{21} + a_{23} + a_{32})\ddot{y}_1 + (a_{01}a_{12} + a_{01}a_{23} + a_{12}a_{23} + a_{21}a_{23} + a_{01}a_{32} + a_{21}a_{32})\dot{y}_1 + (a_{01}a_{12}a_{23})y_1 = (a_{12}a_{23})u_2.$$



$\#$ on LHS $= 3$

$\#$ on RHS $= 1$

Identifiability

Definitions

- Let ϕ be the *coefficient map* from the parameter space of a model to the coefficient space of its input/output equation
- A model is said to be *generically locally structurally identifiable* (identifiable) if, outside a set of measure zero, every point in the parameter space has an open neighborhood U for which $\phi|_U$ is one-to-one

Proposition (Sufficient condition for unidentifiability)

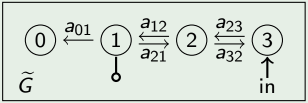
A model $\mathcal{M} = (G, In, Out, Leak)$ is *unidentifiable* if

$$\# \text{ parameters} > \# \text{ coefficients}.$$

Example

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

$$y_1^{(3)} + (a_{01} + a_{12} + a_{21} + a_{23} + a_{32})\ddot{y}_1 + (a_{01}a_{12} + a_{01}a_{23}$$
$$+a_{12}a_{23} + a_{21}a_{23} + a_{01}a_{32} + a_{21}a_{32})\dot{y}_1 + (a_{01}a_{12}a_{23})y_1 = a_{12}a_{23}u_2.$$



$\#$ on LHS $= 3$

$\#$ on RHS $= 1$

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

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

$$\begin{pmatrix} a_{01} \\ a_{12} \\ a_{21} \\ a_{23} \\ a_{32} \end{pmatrix} \mapsto \begin{pmatrix} a_{01} + a_{12} + a_{21} + a_{23} + a_{32} \\ a_{01}a_{12} + a_{01}a_{23} + a_{12}a_{23} + a_{21}a_{23} + a_{01}a_{32} + a_{21}a_{32} \\ a_{01}a_{12}a_{23} \\ a_{12}a_{23} \end{pmatrix}$$

Unidentifiability

Corollary (B., 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:

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

Then $\mathcal{M}$ is unidentifiable if

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

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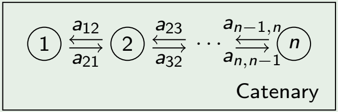
Tree Models

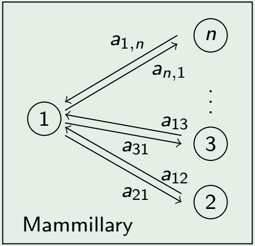
Definition

A *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 tree*

Examples





Unidentifiability of Tree Models

Theorem (B., 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 in $\mathcal{M}$ is $|E_G| + |Leak| = 2n - 2 + |Leak|$
- in all five cases, $\#$ parameters $>$ $\#$ coefficients

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

Note: The four cases in blue have $\#$ parameters $=$ $\#$ coefficients, but that does not guarantee identifiability.

Building Identifiable Tree Models

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

- start with some base model that we know is identifiable (Theorem*)
- 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

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

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

Theorem (Gross, Harrington, Meshkat, Shiu [3])

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

The Jacobian

Theorem

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

Example

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

$$y_1^{(3)} + (\underbrace{a_{01} + a_{12} + a_{21} + a_{23} + a_{32}}_{c_2})\ddot{y}_1 + (\underbrace{a_{01}a_{12} + a_{01}a_{23} + a_{12}a_{23} + a_{21}a_{23} + a_{01}a_{32} + a_{21}a_{32}}_{c_1})\dot{y}_1 + (\underbrace{a_{01}a_{12}a_{23}}_{c_0})y_1 = (\underbrace{a_{12}a_{23}}_{d_0})u_3$$

$$J(\phi) = \begin{array}{c} \\ c_2 \\ c_1 \\ c_0 \\ d_0 \end{array} \begin{array}{c} \begin{array}{ccccc} a_{01} & a_{12} & a_{21} & a_{23} & a_{32} \end{array} \\ \begin{pmatrix} 1 & 1 & 1 & 1 & 1 \\ a_{12} + a_{23} + a_{32} & a_{01} + a_{23} & a_{23} + a_{32} & a_{01} + a_{12} + a_{21} & a_{01} + a_{21} \\ a_{12}a_{23} & a_{01}a_{23} & 0 & a_{01}a_{12} & 0 \\ 0 & a_{23} & 0 & a_{12} & 0 \end{pmatrix} \end{array}$$

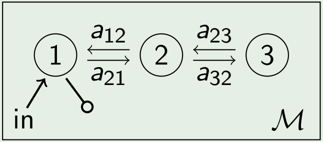
Theorem (B., Gross, Meshkat, Shiu, Sullivant [1])

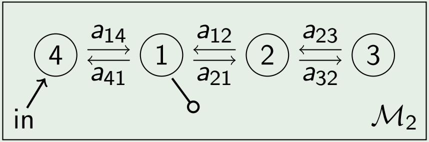
Let $\mathcal{M} = (G, \{i\}, \{i\}, \emptyset)$ be an identifiable tree model with $|V_G| = n - 1$. Let H be the graph G with the added node n and edges $i \to n$ and $n \to i$. Then following models are also identifiable:

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

Example

Here, $\mathcal{M} = (G, \{1\}, \{1\}, \emptyset)$ and $\mathcal{M}_2 = (H, \{4\}, \{1\}, \emptyset)$:





Proof of Moving the Input/Output

Theorem (B., Gross, Meshkat, Shiu, Sullivant)

Let $\mathcal{M} = (G, \{i\}, \{i\}, \emptyset)$ be an identifiable tree model with $|V_G| = n - 1$. 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:

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

Proof idea:

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

$$J(\phi_k) = \begin{pmatrix} J(\phi) & 0 \\ * & C \end{pmatrix}$$

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

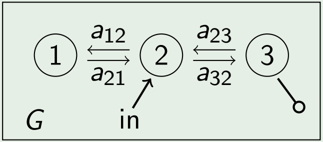
Adding a Leaf

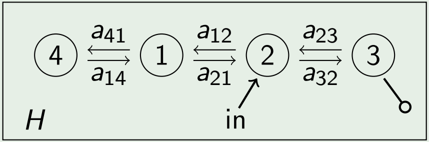
Theorem (B., Gross, Meshkat, Shiu, Sullivant [1])

Let $\mathcal{M} = (G, \{i\}, \{j\}, \emptyset)$ be an identifiable tree model with $|V_G| = n-1$. 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, $\mathcal{M} = (G, \{2\}, \{3\}, \emptyset)$ and $\mathcal{L} = (H, \{2\}, \{3\}, \emptyset)$:





Proof of Adding a Leaf

Theorem (B., Gross, Meshkat, Shiu, Sullivant [1])

Let $\mathcal{M} = (G, \{i\}, \{j\}, \emptyset)$ be an identifiable tree model with $|V_G| = n - 1$. 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.

Proof idea:

- Define weight $\omega \in \mathbb{Q}_{\geq 0}^{\# \text{ parameters}}$ so that the initial form of most coefficients does not contain a_{nk} or a_{kn}, define $\phi_{\mathcal{L},\omega}$
- We know that $\text{Rank}(J(\phi_{\mathcal{L},\omega})) \leq \text{Rank}(J(\phi_{\mathcal{L}}))$
- We can write $J(\phi_{\mathcal{L},\omega}) = \begin{pmatrix} J(\phi_{\mathcal{M}}) & 0 \\ * & C \end{pmatrix}$
  - show C has maximal rank using properties of the graph
  - this implies that $\text{Rank}(J(\phi_{\mathcal{L},\omega})) = \max\{\text{Rank}(J(\phi_{\mathcal{L}})\}$

Classification of Tree Models

Theorem (B., 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 idea:

- $\mathcal{M}$ 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 $|Leak| = 1$

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 the problem of determining identifiability when multiple inputs/outputs are present

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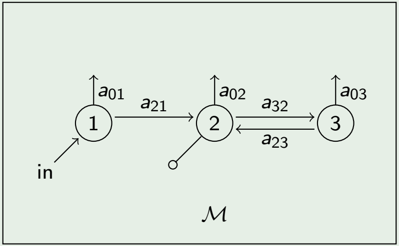
Identifiable Path/Cycle Model Motivating Example

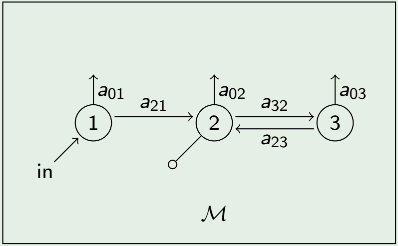
Example



- The model $\mathcal{M} = (G, \{1\}, \{2\}, V_G)$ is not identifiable:
  - $\#$ parameters $= 6$
  - max $\#$ coefficients $= 5$
- Maybe we can recover combinations of parameters

Identifiable Path/Cycle Model Motivating Example

Example



$$A = \begin{pmatrix} -a_{01} - a_{21} & 0 & 0 \\ a_{21} & -a_{02} - a_{32} & a_{23} \\ 0 & a_{32} & -a_{03} - a_{23} \end{pmatrix}$$

Input/Output Equation:

$$y_2^{(3)} + (a_{01} + a_{02} + a_{03} + a_{21} + a_{23} + a_{32})\ddot{y_2} + (a_{01}a_{02} + a_{01}a_{03} + a_{02}a_{03}$$
$$+a_{02}a_{21} + a_{03}a_{21} + a_{01}a_{23} + a_{02}a_{23} + a_{21}a_{23} + a_{01}a_{32} + a_{03}a_{32} + a_{21}a_{32})\dot{y_2}$$
$$+(a_{01}a_{02}a_{03} + a_{02}a_{03}a_{21} + a_{01}a_{02}a_{23} + a_{02}a_{21}a_{23} + a_{01}a_{03}a_{32} + a_{03}a_{21}a_{32})y_2 = (a_{21})\dot{u_1} + (a_{21}a_{03} + a_{21}a_{23})u_1$$

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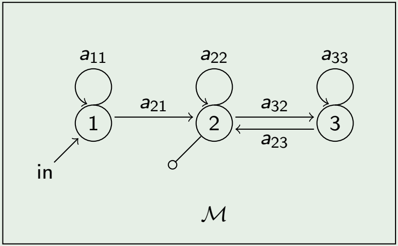

$$A = \begin{pmatrix} a_{11} & 0 & 0 \\ a_{21} & a_{22} & a_{23} \\ 0 & a_{32} & a_{33} \end{pmatrix}$$

Input/Output Equation:

$$y_2^{(3)} + (-a_{11} - a_{22} - a_{33})\ddot{y_2} + (a_{11}a_{22} - a_{23}a_{32} + a_{11}a_{33} + a_{22}a_{33})\dot{y_2} + (a_{11}a_{23}a_{32} - a_{11}a_{22}a_{33})y_2 = (a_{21})\dot{u_1} + (a_{21}a_{03} + a_{21}a_{23})u_1$$

This model is an *identifiable path/cycle model* with identifiable functions

$$a_{11},\ a_{22},\ a_{33},\ a_{21},\ a_{23}a_{32}.$$

Results (Preprint [2])

- Stated necessary and sufficient conditions for a model to be an identifiable path/cycle model based on graph
- Stated results relating identifiable path/cycle models to identifiable models based on reducing the number of leaks
- Expanded several previous result on *identifiable cycle models* [5, 6]
  - Again, the identifiable cycle models all have $in = out$

Acknowledgments and References I

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Cramer's Rule

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

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

$$\begin{pmatrix} \dot{x}_1(t) \\ \dot{x}_2(t) \\ \dot{x}_3(t) \end{pmatrix} = \underbrace{\begin{pmatrix} -a_{21} & a_{12} & 0 \\ a_{21} & -a_{12} - a_{32} & a_{23} \\ 0 & a_{32} & -a_{03} - a_{23} \end{pmatrix}}_{\text{compartmental matrix A}} \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \\ u_3(t) \end{pmatrix}$$

with

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

yields

$$\left(\begin{pmatrix} d/dt & 0 & 0 \\ 0 & d/dt & 0 \\ 0 & 0 & d/dt \end{pmatrix} - \begin{pmatrix} -a_{21} & a_{12} & 0 \\ a_{21} & -a_{12} - a_{32} & a_{23} \\ 0 & a_{32} & -a_{03} - a_{23} \end{pmatrix} \right) \begin{pmatrix} y_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ u_3(t) \end{pmatrix}$$

Cramer's Rule Continued

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

$$\begin{pmatrix} \lambda + a_{21} & -a_{12} & 0 \\ -a_{21} & \lambda + a_{12} + a_{32} & -a_{23} \\ 0 & -a_{32} & \lambda + a_{03} + a_{23} \end{pmatrix} \begin{pmatrix} y_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ u_3(t) \end{pmatrix}$$

Applying Cramer's Rule

$$y_1(t) = \frac{\det \begin{pmatrix} 0 & -a_{12} & 0 \\ 0 & \lambda + a_{12} + a_{32} & -a_{23} \\ u_3(t) & -a_{32} & \lambda + a_{03} + a_{23} \end{pmatrix}}{\det \begin{pmatrix} \lambda + a_{21} & -a_{12} & 0 \\ -a_{21} & \lambda + a_{12} + a_{32} & -a_{23} \\ 0 & -a_{32} & \lambda + a_{03} + a_{23} \end{pmatrix}}$$

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

Proof structure: Induction on $|E_G|$

Theorem

The RHS of the input/output equation of $\mathcal{M} = (G, \{in\}, \{out\}, Leak)$ with $in \neq out$ has coefficients $d_k = \sum_{F \in \mathcal{F}_{n-k-1}^{in,out}(\widetilde{G}_i^*)} \pi_F$

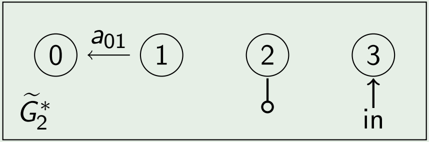
Proof idea: Induction on $|E_G|$

- Base case: $|E_G| = 0$
  - $\mathcal{F}_{n-k-1}^{in,out} = \emptyset$ so all the d_k above are zero
  - $(\lambda I - A)_{i,j} = 0$ for all $i \neq j$, therefore $\det((\lambda I - A)^{in,out}) = 0$

Example

Consider $\mathcal{M} = (G, \{3\}, \{2\}, \{1\})$.

$$\lambda I - A = \begin{pmatrix} \lambda + a_{01} & 0 & 0 \\ 0 & \lambda & 0 \\ 0 & 0 & \lambda \end{pmatrix}$$



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- Inductive step
  - Laplacian expansion down the *in* column, i.e. all edges leaving *in*

$$\det((\lambda I - A)^{in,out}) = \sum_{in \to j \in E_G} (-1)^{in+j} a_{j(in)} \underbrace{\det((\lambda I - A)^{\{in,j\},\{in,out\}})}_{\text{RHS of model with less edges}}$$

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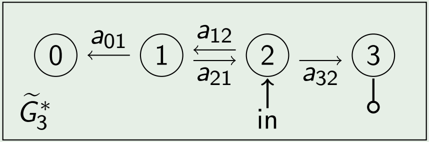
Consider $\mathcal{M} = (G, \{2\}, \{3\}, \{1\})$.

$$\lambda I - A = \begin{pmatrix} \lambda + a_{01} + a_{21} & a_{12} & {\color{red}0} \\ {\color{red}a_{21}} & {\color{red}\lambda + a_{12} + a_{32}} & {\color{red}0} \\ 0 & a_{32} & {\color{red}\lambda} \end{pmatrix}$$



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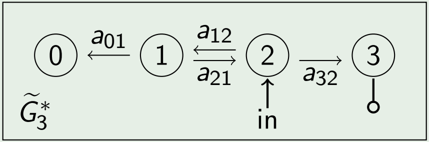
Example

Consider $\mathcal{M} = (G, \{2\}, \{3\}, \{1\})$.

$$(\lambda I - A)^{2,3} = \begin{pmatrix} \lambda + a_{01} + a_{21} & a_{12} \\ 0 & a_{32} \end{pmatrix}$$



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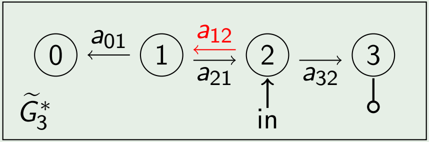

$$\det((\lambda I - A)^{2,3}) = (-1)^{1+2} a_{12} \det(0) + (-1)^{2+2} a_{32} \det(\lambda + a_{01} + a_{21})$$

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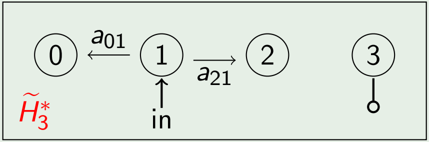

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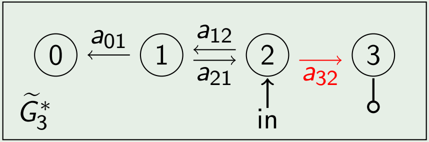

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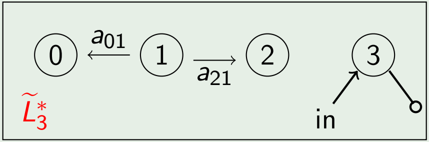

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