Identifiable Paths and Cycles in Linear Compartmental Models

Cash Bortner [1] Nicolette Meshkat [2]

[1]North Carolina State University

[2]Santa Clara University

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Outline

1. Background
   - Linear Compartmental Models
   - Identifiability and the Input/Output Equation
2. Identifiable Path/Cycle Models
3. Tree Models

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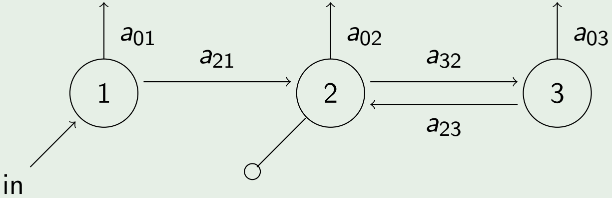
Linear Compartmental Models

- $\mathcal{M} = (G,\ In,\ Out, Leak)$ where $In, Out, Leak \subseteq V$

Example

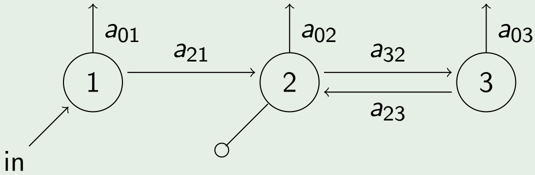


$$\mathcal{M} = (G,\ \{1\},\ \{2\},\ \{1,2,3\})$$

Linear Compartmental Model ODE's

Example

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



$$\begin{aligned}
\dot{x}_1(t) &= -(a_{01}+a_{21})x_1(t) && && + u_1(t)\\
\dot{x}_2(t) &= a_{21}x_1(t) && -(a_{02}+a_{32})x_2(t) && + a_{23}x_3(t)\\
\dot{x}_3(t) &= && a_{32}x_2(t) && -(a_{03}+a_{23})x_3(t)
\end{aligned}$$

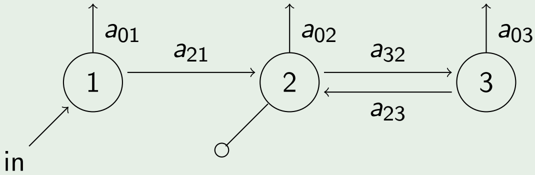
with

$$y_2(t) = x_2(t).$$

Linear Compartmental Model ODE's

Example

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



$$\begin{pmatrix} \dot{x}_1(t) \\ \dot{x}_2(t) \\ \dot{x}_3(t) \end{pmatrix} = \underbrace{\begin{pmatrix} -a_{01} - a_{21} & 0 & 0 \\ a_{21} & -a_{02} - a_{32} & a_{23} \\ 0 & a_{32} & -a_{03} - a_{23} \end{pmatrix}}_{\text{compartmental matrix}} \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} + \begin{pmatrix} u_1(t) \\ 0 \\ 0 \end{pmatrix}$$

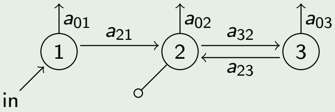
with

$$y_2(t) = x_2(t).$$

LCM Input/Output Equation

- Eliminate the state variables $x_i(t)$ from the system of ODE's to get an *input/output equation*

Example



$\mathcal{M} = (G, \{1\}, \{2\}, V)$

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

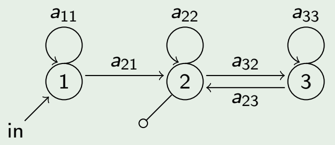
Input/Output Equation:

$$y_2^{(3)} + (a_{01} + a_{02} + a_{03} + a_{21} + a_{23} + a_{32})\ddot{y}_2 + (a_{01}a_{02} + a_{01}a_{03} + a_{02}a_{03}$$
$$+a_{02}a_{21} + a_{03}a_{21} + a_{01}a_{23} + a_{02}a_{23} + a_{21}a_{23} + a_{01}a_{32} + a_{03}a_{32} + a_{21}a_{32})\dot{y}_2$$
$$+(a_{01}a_{02}a_{03} + a_{02}a_{03}a_{21} + a_{01}a_{02}a_{23} + a_{02}a_{21}a_{23} + a_{01}a_{03}a_{32} + a_{03}a_{21}a_{32})y_2 = (a_{21})\dot{u}_1 + (a_{21}a_{03} + a_{21}a_{23})u_1$$

LCM Reparameterized Input/Output Equation

- When every compartment has a leak, reparameterize the "diagonal elements" as a_{ii}

Example



$\mathcal{M} = (G, \{1\}, \{2\}, V)$

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

Input/Output Equation:

$$y_2^{(3)} + (-a_{11} - a_{22} - a_{33})\ddot{y}_2 + (a_{11}a_{22} - a_{23}a_{32} + a_{11}a_{33} + a_{22}a_{33})\dot{y}_2 + (a_{11}a_{23}a_{32} - a_{11}a_{22}a_{33})y_2 = (a_{21})\dot{u}_1 + (-a_{21}a_{33})u_1$$

Identifiability

Definition

- 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 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

Note: Look at the Jacobian of ϕ for local identifiability!

Proposition (Sufficient condition for unidentifiability)

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

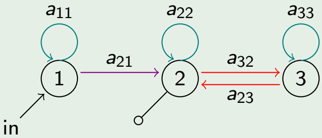
$$\# \text{ parameters} > \# \text{ coefficients.}$$

Input/Output Coefficient Map

Proposition (Meshkat, Sullivant, Eisenberg)

Let $\mathcal{M} = (G, In, \{j\}, V)$ such that G is output connectable. The coefficient map factors through the cycles, self-cycles, and paths from input to output.

Example

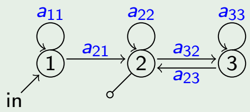


$\mathcal{M} = (G, \{1\}, \{2\}, V)$

$$\phi : \begin{pmatrix} a_{11} \\ a_{22} \\ a_{33} \\ a_{21} \\ a_{23} \\ a_{32} \end{pmatrix} \mapsto \begin{pmatrix} -a_{11} - a_{22} - a_{33} \\ a_{11}a_{22} - a_{23}a_{32} + a_{11}a_{33} + a_{22}a_{33} \\ a_{11}a_{23}a_{32} - a_{11}a_{22}a_{33} \\ a_{21} \\ -a_{21}a_{33} \end{pmatrix}$$

Identifiable Path/Cycle Model Motivating Example

Example



$\mathcal{M} = (G, \{1\}, \{2\}, V)$

$$y_2^{(3)} + (-a_{11} - a_{22} - a_{33})\ddot{y}_2 + (a_{11}a_{22} - a_{23}a_{32} + a_{11}a_{33} + a_{22}a_{33})\dot{y}_2 + (a_{11}a_{23}a_{32} - a_{11}a_{22}a_{33})y_2 = (a_{21})\dot{u}_1 + (-a_{21}a_{33})u_1$$

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

Definition

For a function $\phi \colon \mathbb{R}^{|E|+|Leak|} \to \mathbb{R}^k$, a function $f \colon \mathbb{R}^{|E|+|Leak|} \to \mathbb{R}$ is locally identifiable from ϕ if there is a finitely multivalued function $\psi \colon \mathbb{R}^k \to \mathbb{R}$ such that $\psi \circ \phi = f$.

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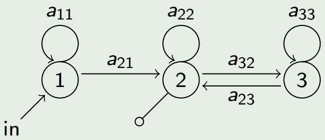
Identifiable Path/Cycle Model

Definition

$\mathcal{M} = (G, In, Out, V)$ is an *identifiable path/cycle model* if

- all of the independent monomial cycles and monomial paths from input to output are locally identifiable, and
- each parameter is contained in such a cycle or path

Example



$$\mathcal{M} = (G, \{1\}, \{2\}, V)$$

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

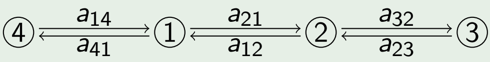
$$a_{11},\ a_{22},\ a_{33},\ a_{21},\ a_{23}a_{32}.$$

$$y_2^{(3)} + (-a_{11} - a_{22} - a_{33})\ddot{y}_2 + (a_{11}a_{22} - a_{23}a_{32} + a_{11}a_{33} + a_{22}a_{33})\dot{y}_2 + (a_{11}a_{23}a_{32} - a_{11}a_{22}a_{33})y_2 = (a_{21})\dot{u}_1 + (-a_{21}a_{33})u_1$$

Definition

G is *inductively strongly connected* w.r.t vertex 1 if each of the induced subgraphs $G_{\{1,\ldots,i\}}$ is strongly connected for $i = 1, \ldots, n$ for some ordering of the vertices

Example



$G = G_{\{1,2,3,4\}}$

G is inductively strongly connected w.r.t. 1 by the order 1, 2, 3, 4.

Graph Definitions

Definition

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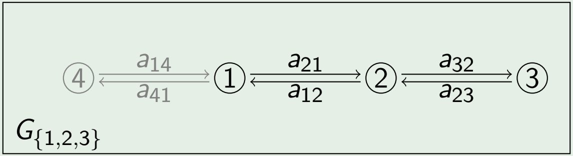

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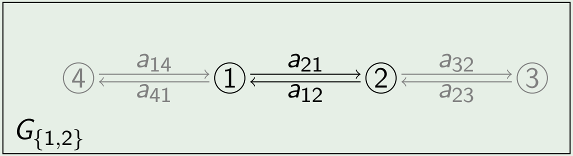

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Graph Definitions

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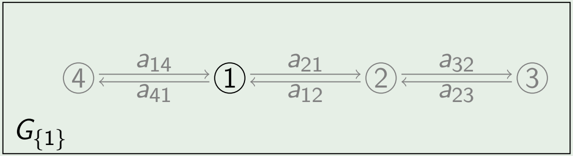


G is inductively strongly connected w.r.t 1 by the order 1, 2, 3, 4.

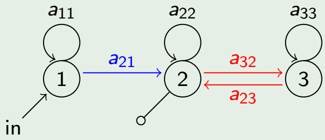
Graph Definitions ctd.

Definition

G is *strongly input-output connected* (w.r.t $In, Out \subseteq V$) if

- it is connected
- and every edge is contained in a cycle or path from input to output

Example



$$\mathcal{M} = (G, \{1\}, \{2\}, V)$$

G is strongly input-output connected since every edge is part of a cycle or a path from 1 to 2.

Sufficient Condition for Identifiable Path/Cycle Model

Theorem (B., Meshkat)

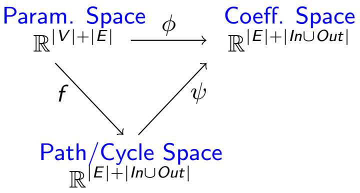
Let $\mathcal{M} = (G, In, Out, V)$ such that

(i) *G is strongly input-output connected and $|Out| = 1$ or*

(ii) *G is strongly connected and $|In| = 1$.*

If the image of the coefficient map ϕ has dimension $|E| + |In \cup Out|$, then the model is an identifiable path/cycle model.

Proof idea:



- Factor the coefficient map through the "path/cycle space" which as a result of (i) and/or (ii) has dimension $|E| + |In \cup Out|$
- ψ must be invertible if $\dim(\mathrm{im}(\phi)) = |\mathrm{E}| + |\mathrm{In} \cup \mathrm{Out}|$, so $f = \psi^{-1} \circ \phi$, so f is ident. from ϕ

Sufficient Condition for Identifiable Path/Cycle Model

Theorem (B., Meshkat)

Let $\mathcal{M} = (G, \{i\}, \{j\}, V)$ *such that*

- *G strongly input-output connected*
- $|E| = 2|V| - \mathrm{dist}(\mathrm{i}, \mathrm{j}) - 2$
- *G has no path from j to i*
- *G becomes inductively strongly connected by adding an edge from j to i*

then $\mathcal{M}$ *is an identifiable path/cycle model.*

Sufficient Condition for Identifiable Path/Cycle Model

Theorem (B., Meshkat)

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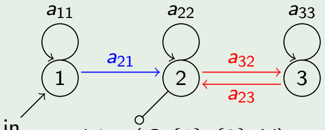
Example



$\mathcal{M} = (G, \{1\}, \{2\}, V)$

G is strongly input-output connected as it is connected and the edges are either in a cycle or path from input to output

Sufficient Condition for Identifiable Path/Cycle Model

Theorem (B., Meshkat)

Let $\mathcal{M} = (G, \{i\}, \{j\}, V)$ such that

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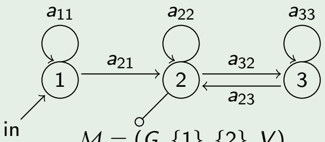
Example



$\mathcal{M} = (G, \{1\}, \{2\}, V)$

$|E| = |V| = 3$ and $\mathrm{dist}(1,2) = 1$ so

$$|E| = 2|V| - \mathrm{dist}(1,2) - 2$$

$$3 = 2(3) - 1 - 2.$$

Sufficient Condition for Identifiable Path/Cycle Model

Theorem (B., Meshkat)

Let $\mathcal{M} = (G, \{i\}, \{j\}, V)$ such that

- *G strongly input-output connected*
- $|E| = 2|V| - \mathrm{dist(i,j)} - 2$
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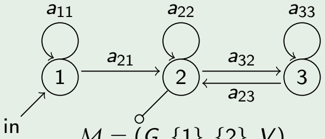
then $\mathcal{M}$ is an identifiable path/cycle model.

Example



$\mathcal{M} = (G, \{1\}, \{2\}, V)$

There is no path from 2 to 1.

Sufficient Condition for Identifiable Path/Cycle Model

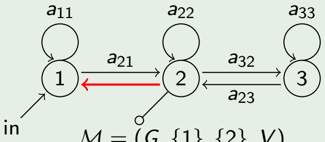
Theorem (B., Meshkat)

Let $\mathcal{M} = (G, \{i\}, \{j\}, V)$ *such that*

- G *strongly input-output connected*
- $|E| = 2|V| - \mathrm{dist(i,j)} - 2$
- G *has no path from* j *to* i
- G *becomes inductively strongly connected by adding an edge from* j *to* i

then $\mathcal{M}$ *is an identifiable path/cycle model.*

Example



$\mathcal{M} = (G, \{1\}, \{2\}, V)$

With the added edge $2 \to 1$, G becomes inductively strongly connected via the ordering $1, 2, 3$.

Sufficient Condition for Identifiable Path/Cycle Model

Theorem (B., Meshkat)

Let $\mathcal{M} = (G, \{i\}, \{j\}, V)$ *such that*

- *G strongly input-output connected*
- $|E| = 2|V| - \mathrm{dist(i,j)} - 2$
- *G has no path from j to i*
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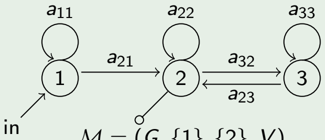
then $\mathcal{M}$ is an identifiable path/cycle model.

Example



$\mathcal{M} = (G, \{1\}, \{2\}, V)$

Thus, $\mathcal{M}$ is an identifiable path/cycle model!

Identifiable from Identifiable Path/Cycle

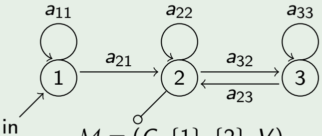
Theorem (B., Meshkat)

For $\mathcal{M} = (G, In, Out, V)$ and $\widetilde{\mathcal{M}} = (G, In, Out, L)$ with $L = In \cup Out$ and one of

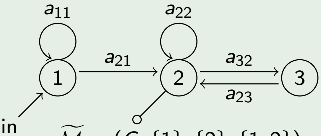
- *G strongly input-output connected and $|Out| = 1$ or*
- *G strongly connected and $|In| = 1$*

then $\widetilde{\mathcal{M}}$ is locally identifiable if and only if $\mathcal{M}$ is an identifiable path/cycle model.

Example



$\mathcal{M} = (G, \{1\}, \{2\}, V)$



$\widetilde{\mathcal{M}} = (G, \{1\}, \{2\}, \{1, 2\})$

As $\mathcal{M}$ is an identifiable path/cycle model, then $\widetilde{\mathcal{M}}$ is identifiable.

Why Identifiable Path/Cycle Models?

- Previous work has focused on models $\mathcal{M} = (G, \{i\}, \{i\}, Leak)$

Theorem (Meshkat, Sullivant)

For $\mathcal{M} = (G, \{i\}, \{i\}, V)$ an identifiable cycle model, there exists an identifiable scaling reparameterization in terms of monomial functions of the original parameters.

- This work focuses on models $\mathcal{M} = (G, \{i\}, \{j\}, Leak)$ where $i \neq j$, and generalizations with more than one input or output

Conjecture

For identifiable path/cycle model $\mathcal{M} = (G, \{i\}, \{j\}, V)$, there exists an identifiable scaling reparameterization in terms of monomial functions of the original parameters.

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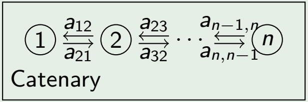
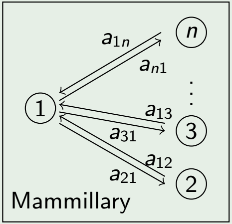
Classification of Identifiable Tree Models

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

A (bidirectional) tree model $\mathcal{M} = (G, \{i\}, \{j\}, Leak)$ *is generically locally identifiable if and only if* $\mathrm{dist}(\mathrm{i}, \mathrm{j}) \leq 1$ *and* $|Leak| \leq 1$*.*

Example





Classification of Identifiable Tree Models

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

A (bidirectional) tree model $\mathcal{M} = (G, \{i\}, \{j\}, Leak)$ *is generically locally identifiable if and only if* $\mathrm{dist(i,j)} \leq 1$ *and* $|Leak| \leq 1$.

Proof idea:

- (Necessary) Show that if $|Leak| > 1$ or $\mathrm{dist(i,j)} > 1$, then $\mathcal{M}$ cannot be identifiable as # parameters > #coefficients
- (Sufficient) Start with a known identifiable model with $i = j$ and perform "moves" which retain identifiability to inductively generate every tree model with $\mathrm{dist(i,j)} \leq 1$ and $|Leak| \leq 1$.

Acknowledgments and References I

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