Identifiability of Linear Compartmental Model Parameter Subsets

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Background: Linear Compartmental Model

Linear Compartmental Model (Gerberding, Obatake, Shiu 2020)

A **linear compartmental model** consists of a directed graph G=(V,E) where three sets, *In, Out, Leak* $\subseteq$ V , which are the Input, Output, and Leak compartments and $i \in$ V is a vertex representing a compartment. Each edge $j \rightarrow i$ in E represents the flow or transfer of material from the jth compartment to the ith compartment, with associated parameter (rate constant) k_{ij} .

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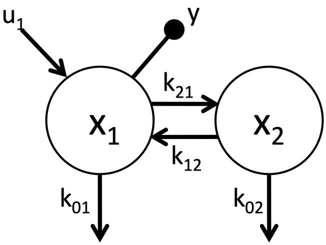

[Meshkat, 2014]

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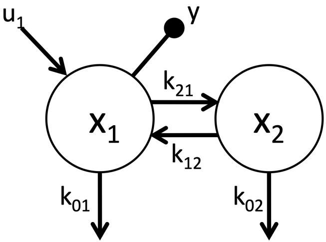

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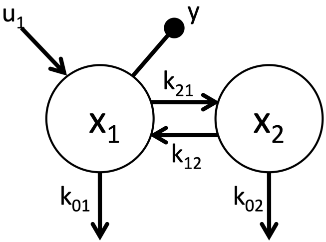

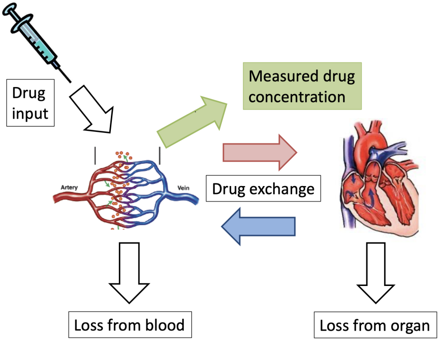

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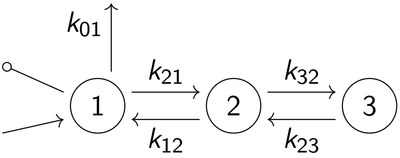
Background: Identifiable

Definition

A model M is **identifiable** if its parameters k_{ij} can be recovered from the coefficients of its input-output equation.

Model:



Input-Output Equations

Definition

An **Input-Output Equation** is an equation that holds along any solution of the ordinary differential equations defined by the model using only the input variables u_j, parameters k_{ij}, output variables y_i, and their derivatives.

Input-Output Equation:

$$y_1^{(3)} + (k_{01} + k_{12} + k_{21} + k_{23} + k_{23})y_1^{(2)} + (k_{01}k_{12} + k_{01}k_{23} + k_{01}k_{32} + k_{12}k_{23} + k_{21}k_{23} + k_{21}k_{32})y_1' + (k_{01}k_{12}k_{23})y_1 = u_1^{(2)} + (k_{12} + k_{23} + k_{32})u_1' + (k_{12}k_{23})u_1$$

Motivation

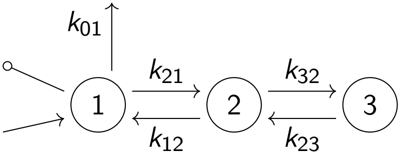
We know if a model M is identifiable there are certain operations that you can apply to it to obtain a new model M' such that M' is also identifiable.

Goal

When given a model M with only a subset of the parameters being identifiable, if M' is obtained by one of those same operations, then how is the subset of identifiable parameters of M' affected?

Operations

- Add/Delete Leak
- Add/Delete Edge
- Add/Delete Input
- Add/Delete Output



Theorem (Gross, Harrington, Shiu, Meshkat 2019)

Adding a leak to a strongly connected, identifiable model with no leaks preserves identifiability.

Example

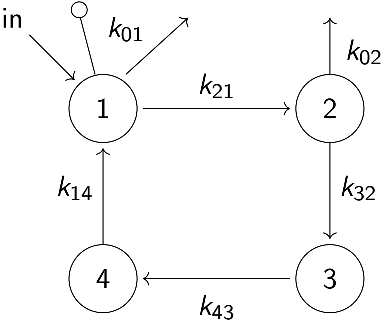


Figure: A cycle model

Example

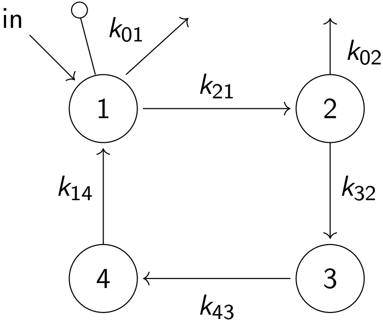
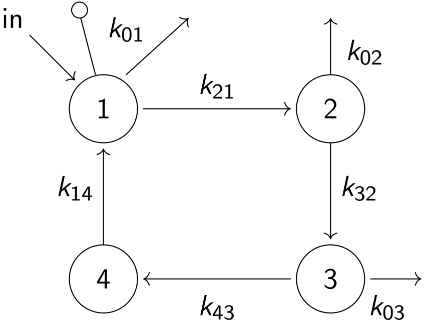


Figure: A cycle model

Model	Identifiable	Unidentifiable
Original	k_{14}, k_{43}	k_{01}, k_{02}, k_{21}, k_{32}

Example



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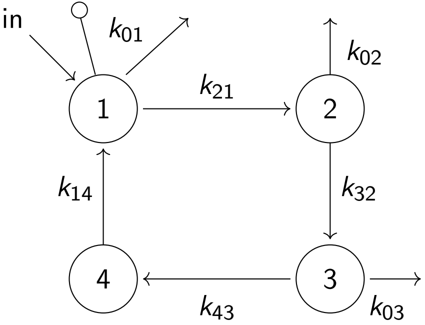


Figure: A cycle model

Model	Identifiable	Unidentifiable
Original	k_{14}, k_{43}	$k_{01}, k_{02}, k_{21}, k_{32}$
Leak from 3	k_{14}	$k_{01}, k_{02}, k_{21}, k_{32}, k_{43}, k_{03}$

Cycle Coefficients

Prop. 3.8: (Gerberding, Obatake, Shiu 2020)

Assume $n \leq 3$. Let M be an n-compartment cycle model with $In = \{1\}, Out = \{p\}$ (for some $1 \leq p \leq n$), and Leak$=\{i_1, i_2, \ldots, i_t\} \neq \emptyset$.

Then the coefficient map $c : \mathbb{R}^{n+t} \to \mathbb{R}^{2n-p+1}$ is given by $(k_{21}, k_{32}, \ldots, k_{1,n}, k_{0,i_1}, k_{0,i_2}, \ldots, k_{0,i_t}) \longmapsto (\mathrm{e}_1, e_2, \ldots, e_{n-1}, e_n - \prod_{i=1}^{n} k_{i+1,i}, k, e_1^*, \ldots, e_{n-p}^*)$

where $k := \prod_{i=2}^{p} k_{i,i-1}$,

and e_j and e_j^* denote the jth elementary symmetric polynomial on the sets

$E = \{k_{\ell+1,\ell} | \ell \in \{1, \ldots, n\} \setminus Leak\} \cup \{k_{\ell+1,\ell} + k_{0,\ell} | \ell \in Leak\}$ and $E^* = \{k_{\ell+1,\ell} | p+1 \leq \ell \leq n, \ell \notin Leak\} \cup \{k_{\ell+1,\ell} + k_{0,\ell} | p+1 \leq \ell \leq n, \ell \in Leak\}$, respectively.

Elemetary Symmetric Polynomials

Elementary Symmetric Polynomials

Let $x_1, ..., x_n$ be real numbers. $e_i(x_1, ..., x_n) = \sum_{1 \le j_1, <..., < j_i \le n} x_{j_1} x_{j_2} ... x_{j_i}$

$1 \le i \le n$

Example: Let $\mathrm{X} = \{x_1, x_2, x_3, x_4\}$

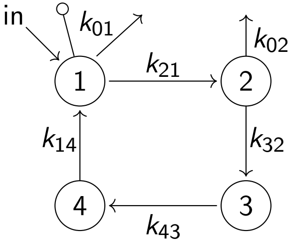
$e_1 = x_1 + x_2 + x_3 + x_4$

$e_2 = x_1x_2 + x_1x_3 + x_1x_4 + x_2x_3 + x_2x_4 + x_3x_4$

$e_3 = x_1x_2x_3 + x_1x_2x_4 + x_1x_3x_4 + x_2x_3x_4$

$e_4 = x_1x_2x_3x_4$

Right Hand Coefficients



$$(k_{21}, k_{32}, \ldots, k_{1,n}, k_{0,i_1}, k_{0,i_2}, \ldots, k_{0,i_t}) \longmapsto (\ldots,\ \mathrm{k},\ \mathrm{e}_1^* k, \ldots, e_{n-p}^* k)$$

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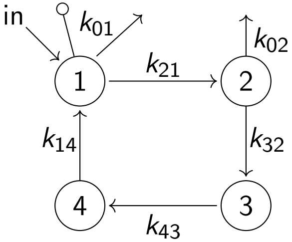

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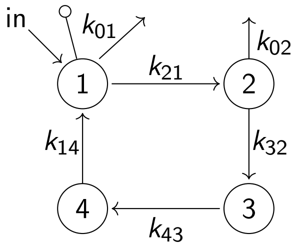
$(k_{21}, k_{32}, k_{43}, k_{14}, k_{01}, k_{02}) \longmapsto (\ldots, \mathrm{k}, \mathrm{e}_1^* k, \ldots, e_3^* k)$

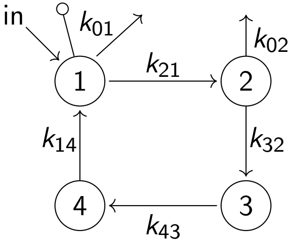
Right Hand Coefficients



$(k_{21}, k_{32}, \ldots, k_{1,n}, k_{0,i_1}, k_{0,i_2}, \ldots, k_{0,i_t}) \longmapsto (\ldots,\ k,\ e_1^* k, \ldots, e_{n-p}^* k)$
$(k_{21}, k_{32}, k_{43}, k_{14}, k_{01}, k_{02}) \longmapsto (\ldots, k, e_1^* k, \ldots, e_3^* k)$

where $k := \prod_{i=2}^{p} k_{i,i-1}$,

Right Hand Coefficients



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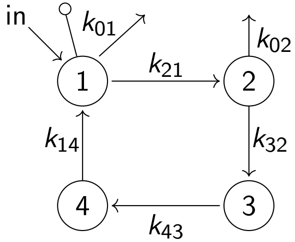
where $k := \prod_{i=2}^{p} k_{i,i-1}$,
$k := \prod_2^1 k_{1,0} = 1$

Right Hand Coefficients



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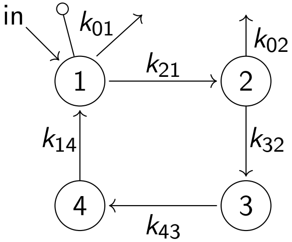
$E^* = \{k_{\ell+1,\ell} | p+1 \leq \ell \leq n, \ell \notin Leak\} \cup \{k_{\ell+1,\ell} + k_{0,\ell} | p+1 \leq \ell \leq n, \ell \in Leak\}$

Right Hand Coefficients



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$E^* = \{k_{43}, k_{14}\} \cup \{(k_{32} + k_{02})\}$

Example Cont.

$(k_{21}, k_{32}, k_{43}, k_{14}, k_{01}, k_{02}) \longmapsto (\ldots,\mathrm{k},\mathrm{e}_1^* k, \ldots, \mathrm{e}_{4-1}^* k)$
$k := \prod_2^1 k_{1,0} = 1$
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$d_1 = e_1^* =$

Example Cont.

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$d_1 = e_1^* = k_{43} + k_{14} + k_{32} + k_{02}$
$d_2 = e_2^* =$

Example Cont.

$(k_{21}, k_{32}, k_{43}, k_{14}, k_{01}, k_{02}) \longmapsto (\ldots, k, e_1^* k, \ldots, e_{4-1}^* k)$
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$d_3 = e_3^* =$

Example Cont.

$$(k_{21}, k_{32}, k_{43}, k_{14}, k_{01}, k_{02}) \longmapsto (\ldots,\mathrm{k},\mathrm{e}_1^* k, \ldots, e_{4-1}^* k)$$
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$$d_3 = e_3^* = k_{43} k_{14}(k_{32} + k_{02})$$

Lemma Motivation

$$d_1 = k_{43} + k_{14} + k_{32} + k_{02}$$
$$d_2 = k_{43}(k_{14} + (k_{32} + k_{02})) + k_{14}(k_{32} + k_{02})$$
$$d_3 = k_{43}k_{14}(k_{32} + k_{02})$$

$$E^{**} = \{k_{14}\} \cup \{(k_{32} + k_{02})\}$$
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$$d_1 = k_{43} + e_1^{**}$$
$$d_2 = k_{43}(e_1^{**}) + e_2^{**}$$
$$d_3 = k_{43}(e_2^{**})$$

Lemma 1.1

RHS coefficients of (1,1) cycles can be written as

$d_1 = k + e_1^{**}$

$d_2 = k(e_1^{**}) + e_2^{**}$

$\vdots$

$d_{n-p} = k(e_{n-p-1}^{**})$

where $k \in E^*$ and $E^{**} = E^* \setminus k$

Lemma 1.2

If M is a (1,1) cycle model, $k \in \{k_{\ell+1,\ell} | p+1 \leq \ell \leq n, \ell \notin Leak\}$ then the value of k can be determined by the following formula:

$0 = k^{(n-p)} - k^{(n-p-1)} d_1 + k^{(n-p-2)} d_2 \ldots \pm d_{n-p}$

Adding a Leak

Theorem

Let A be the set of identifiable parameters of an unidentifiable cycle model M with $In = 1, Out = 1$. After adding a leak to compartment j to create a new model M‘, A$\backslash k_{j+1,j}$ is the new set of identifiable parameters.

Pf: All compartments without leaks in model M still have no leaks in model M‘ except compartment j. Therefore, by Lemma 1.2, those compartments remain identifiable.

Other Findings & Future Research

Proposition: After adding a leak to compartment j in model M to create model M', the input-output equations of model M' can be obtained by swapping $k_{j+1,j}$ with $(k_{j+1,j} + k_{0j})$ and adding a product $k_{0j} \prod_{i=1}^{n} k_{i+1,i}$ where $i \neq j$ to coefficient C_n.

Theorem: Let M be a cycle model with some identifiable parameters and M' be that same model with a leak added to compartment j. If the formula to determine the value of an identifiable parameter in model M doesn't require the identifiability of $k_{j+1,j}$ and doesn't use the coefficient C_n, then it will remain identifiable in M'.

Conjecture: Let M be a cycle model with two leaks k_{0i} and k_{0j} where $i < j$. Adding an input or output to compartment j will make the entire model identifiable.

Thank You!