Identifiability of Leak Parameters in Linear Compartmental Models

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REU in Algebraic Methods in Computational Biology
Texas A&M University, Summer 2025

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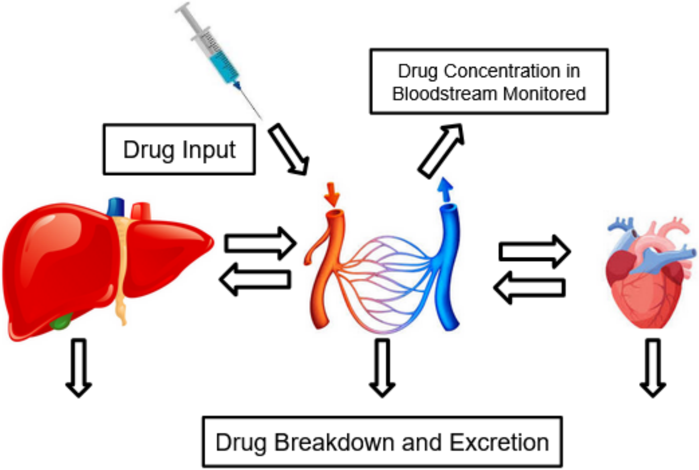
Motivation



Images taken from Google Images

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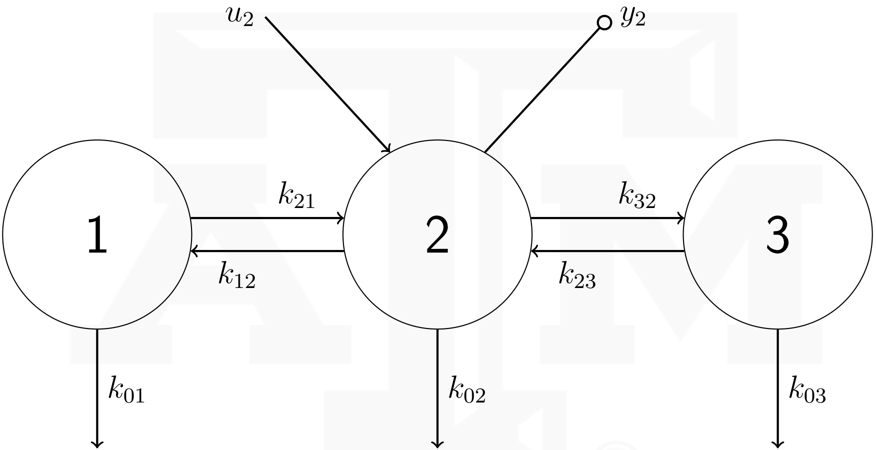

Model Properties

Compartmental Matrix [2]

The **compartmental matrix** of a linear compartmental model $\mathcal{M}$ is given by $A = (a_{ij})$, where

$$a_{ij} := \begin{cases} -\sum_{m:i \to m \in E_G} k_{mi}, & i = j, i \notin Leak \\ -k_{0i} - \sum_{m:i \to m \in E_G} k_{mi}, & i = j, i \in Leak \\ k_{ij}, & i \neq j, (j,i) \in E_G \\ 0, & i \neq j, (j,i) \notin E_G \end{cases}$$

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We use this matrix to write a system of ODEs as $\frac{dx}{dt} = Ax + u$.

$$A = \begin{pmatrix} -k_{01} - k_{21} & k_{12} & 0 \\ k_{21} & -k_{02} - k_{12} - k_{32} & k_{23} \\ 0 & k_{32} & -k_{03} - k_{23} \end{pmatrix}$$

Input-Output Equations

The **input-output equations** for a compartmental matrix A are the system of equations

$$det(\partial I - A)y_j = \sum_{i \in Inputs} (-1)^{i+j} det((\partial I - A)_{i,j}) u_i$$

where $j \in Outputs$, ∂ is a derivative operator and, $((\partial I - A)_{i,j})$ is the submatrix formed by removing the i^{th} row and j^{th} column from $(\partial I - A)$.
[1, Proposition 2.10]

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Rewrite as polynomials in ∂

$$[c_n \partial^n + \cdots + c_1 \partial + c_0] y_j = \sum_{i \in Inputs} [d_{i,n-1} \partial^{n-1} + ... + d_{i,1} \partial + d_{i,0}] u_i$$

where each coefficient c_k and $d_{i,k}$ is a rational function of the rate parameters in the system.

Model Properties

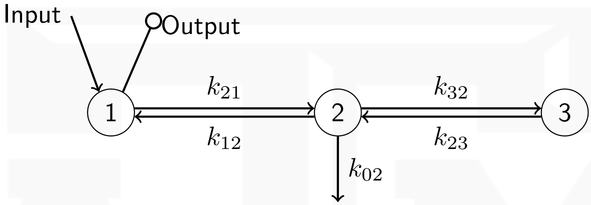
Coefficient Map

Given input-output equations for a model, we define a **coefficient map** $\bar{\boldsymbol{c}} : \mathbb{R}^{L+E} \to \mathbb{R}^m$ mapping the model's set of parameters to the vector

$$\begin{pmatrix} c_n \\ \vdots \\ c_0 \\ d_{1,n-1} \\ \vdots \\ d_{k,0} \end{pmatrix}$$

where k is the number of inputs and m is the dimension of the vector formed by the coefficients, omitting entries of 0, 1, or other redundant coefficients.

Example



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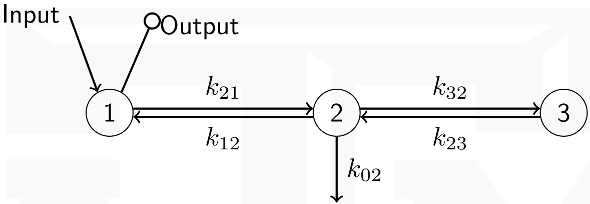

$$A = \begin{pmatrix} -k_{21} & k_{12} & 0 \\ k_{21} & -k_{02} - k_{12} - k_{32} & k_{23} \\ 0 & k_{32} & -k_{23} \end{pmatrix}$$

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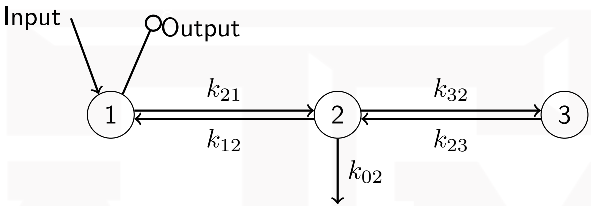

$$A = \begin{pmatrix} -k_{21} & k_{12} & 0 \\ k_{21} & -k_{02}-k_{12}-k_{32} & k_{23} \\ 0 & k_{32} & -k_{23} \end{pmatrix}$$

$$[\partial^3 + (k_{02}+k_{12}+k_{21}+k_{23}+k_{32})\partial^2 + (k_{02}k_{21}+k_{02}k_{23}+k_{12}k_{23}+k_{21}k_{23}+k_{21}k_{32})\partial$$
$$+(k_{02}k_{21}k_{23})]y_1 = [\partial^2 + (k_{02}+k_{12}+k_{23}+k_{32})\partial + (k_{02}k_{23}+k_{12}k_{23})]u_1$$

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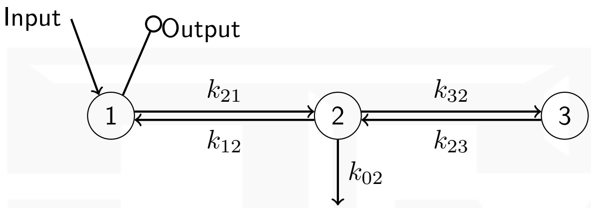

$$[\partial^3 + (k_{02}+k_{12}+k_{21}+k_{23}+k_{32})\partial^2 + (k_{02}k_{21}+k_{02}k_{23}+k_{12}k_{23}+k_{21}k_{23}+k_{21}k_{32})\partial + (k_{02}k_{21}k_{23})]y_1 = [\partial^2 + (k_{02}+k_{12}+k_{23}+k_{32})\partial + (k_{02}k_{23}+k_{12}k_{23})]u_1$$

$$\bar{\boldsymbol{c}} : \begin{pmatrix} k_{02} \\ k_{12} \\ k_{21} \\ k_{23} \\ k_{32} \end{pmatrix} \mapsto \begin{pmatrix} k_{02}+k_{12}+k_{21}+k_{23}+k_{32} \\ k_{02}k_{21}+k_{02}k_{23}+k_{12}k_{23}+k_{21}k_{23}+k_{21}k_{32} \\ k_{02}k_{21}k_{23} \\ k_{02}+k_{12}+k_{23}+k_{32} \\ k_{02}k_{23}+k_{12}k_{23} \end{pmatrix} = \begin{pmatrix} c_2 \\ c_1 \\ c_0 \\ d_1 \\ d_0 \end{pmatrix}$$

Useful Definitions

Identifiability

A parameter is **identifiable** if it can be retrieved to a finite number of solutions using only the entries in the coefficient map of its model. If a parameter is not identifiable, then it is called **unidentifiable** [4, Definition 2.4].

Identifiability Degree

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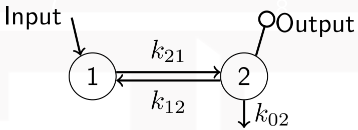
Identifiability Degree

The **identifiability degree** of a parameter is the number of possible solutions for the parameter.

- If a parameter can be determined uniquely, it is **globally identifiable**
- If a parameter can be determined with multiple possible solutions, it is **locally identifiable**
- Otherwise, a parameter is **unidentifiable**

Example of Identifiability Degree



For this model we have

$$(k_{02}, k_{12}, k_{21}) \mapsto \bar{c} = (k_{02} + k_{21} + k_{12}, k_{21}k_{02}, k_{21})$$

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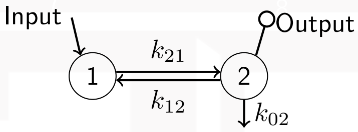

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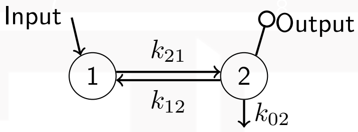

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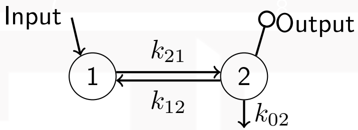

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k_{12} is globally identifiable for similar reasoning.

Main Result: Identifiability of Leaks

Global Leak Theorem

If a model is strongly connected with one input and output and a leak at the same compartment as the output, then that leak parameter is globally identifiable.

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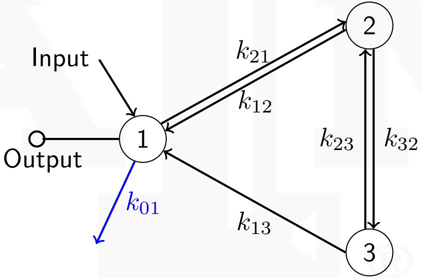
Global Leak Theorem

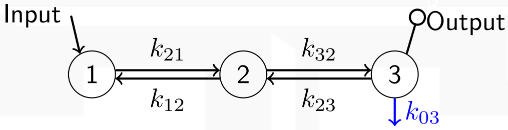
If a model is strongly connected with one input and output and a leak at the same compartment as the output, then that leak parameter is globally identifiable.

This means that if there exists a directed path from each compartment to every other compartment, then a leak at the output compartment (k_{01}) is going to have 1 possible solution.



By computing the coefficient map for this model, we can find that $k_{01} = \frac{c_3}{c_5}$. This means k_{01} is globally identifiable, as expected from the Global Leak Theorem.

Global Leak Example 1

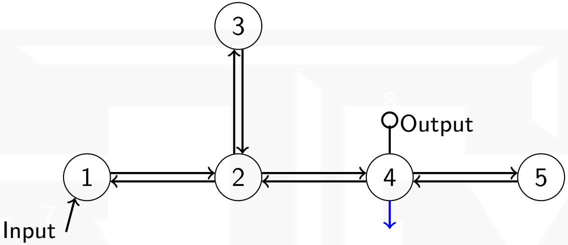


This model produces the following coefficient map:

$$\begin{pmatrix} c_1 \\ c_2 \\ c_3 \\ c_4 \end{pmatrix} = \begin{pmatrix} k_{03} + k_{12} + k_{21} + k_{23} + k_{32} \\ k_{03}(k_{12} + k_{21} + k_{32}) + k_{12}k_{23} + k_{21}k_{23} + k_{21}k_{32} \\ k_{03}k_{21}k_{32} \\ k_{21}k_{32} \end{pmatrix}$$

It is clear to see that $k_{03} = \frac{c_3}{c_4}$, so k_{03} is globally identifiable, as expected from the Global Leak Theorem.

Global Leak Example 2



This model produces the following coefficients:

$$c_5 = k_{04}k_{21}k_{23}k_{42}k_{45}$$

$$c_8 = k_{21}k_{23}k_{42}k_{45}$$

Since $k_{04} = \frac{c_5}{c_8}$, k_{04} is globally identifiable, as expected from the Global Leak Theorem.

Strongly Connected

It is necessary to include the condition of a *strongly connected* model because

- we understand more about these graphs as linear compartmental models[1]
- it is typically more applicable to biology and real-world scenarios

[1] Ovchinnikov *et al.* 2022 [5]

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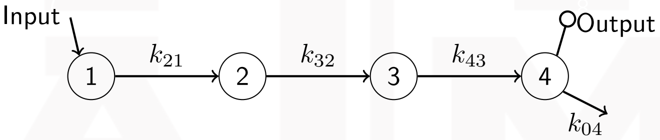
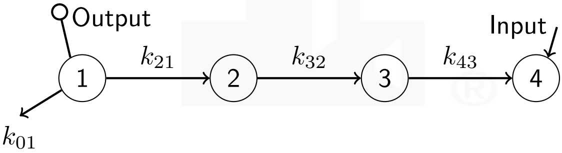
For example, the Global Leak Theorem generalizes to this model:



but not for this model:



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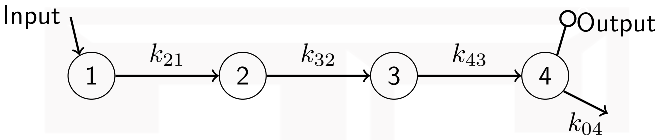

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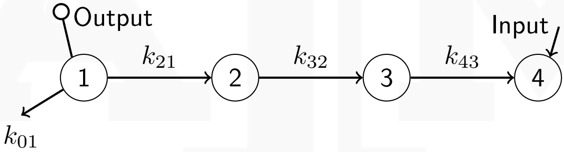

Conjecture

The Global Leak Theorem holds if every compartment has a directed path to the output.

Identifiability Preservation

Preservation of Identifiability Conjecture

If a leak is introduced at the same compartment as the output, then the identifiability degree of the non-leak parameters does not change.

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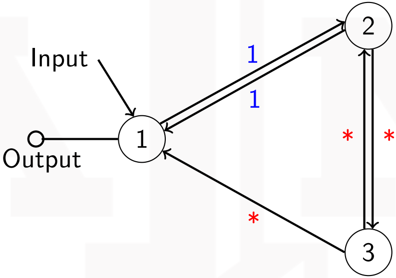

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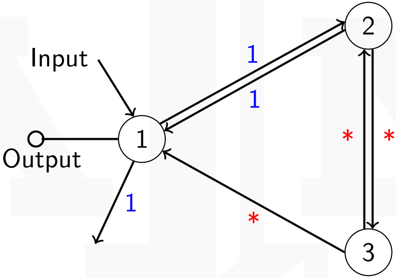

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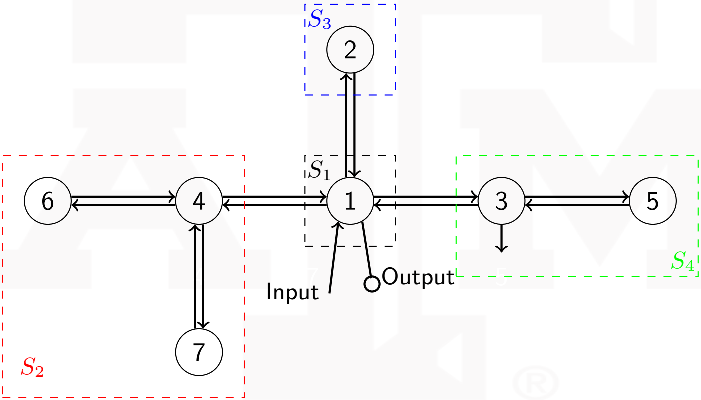
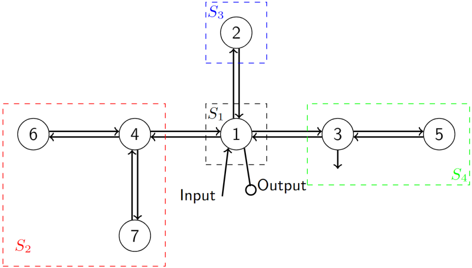
The model below is a **tree model** (a model that can be separated into subsystems S_i). In this case, there are subsystems S_1, S_2, S_3, and S_4.



Cobelli *et al.*'s Formula



Cobelli's Formula (Cobelli *et al.* 1979)

$$D = \frac{(n-1)!}{n_2!n_3!n_4!}2!$$

where D is the identifiability degree and n is the number of compartments.[3]

In this case, $n_2 = 3$, $n_3 = 1$, and $n_4 = 2$ because those are the sizes of the subsystems off of 1, the input and output compartment. According to this formula, $D = 120$ for this model.

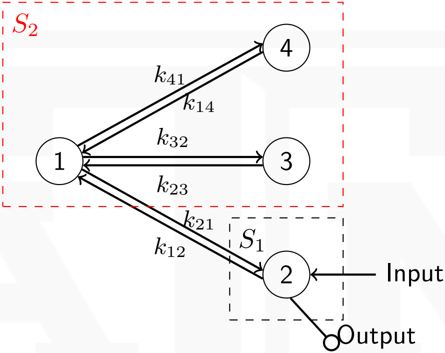
Generalization of Cobelli *et al.*'s Conjecture

For a tree model M_t, the identifiability degree D is given by

$$D = \frac{(n-1)!}{n_2!n_3!...n_N!} \prod_{i=2}^{N} q_i!$$

where
q_i is the number of bidirected edges with symmetry (edges that can be switched without changing the system) within a subsystem,
n is the total number of compartments,
n_i is the number of compartments in a subsystem,
and N is the number of subsystems.

Example of Cobelli *et al.*'s Conjecture



Here,

$$D = \frac{(n-1)!}{n_2!} \prod_{i=2}^{2} q_i! = \frac{3!}{3!} 2! = 2$$

which we can calculate using the coefficient map.

Future Directions

- Further generalize Global Leak Theorem
- Investigate preservation of identifiability of non-leak parameters
- Prove Cobelli *et al.*'s Conjecture

Acknowledgements

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[3] Claudio Cobelli, Alfredo Lepschy, and Gianni Romanin Jacur. "Identifiability Results on Some Constrained Compartmental Systems". In: *Mathematical Biosciences* 47 (1979), pp. 173–195.

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[5] Alexey Ovchinnikov, Gleb Pogudin, and Peter Thompson. "Input-output equations and identifiability of linear ODE models". In: *IEEE Transactions on Automatic Control* (2022).

Thank You!