Identifiability of linear compartment models: the singular locus

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Kolchin Seminar in Differential Algebra
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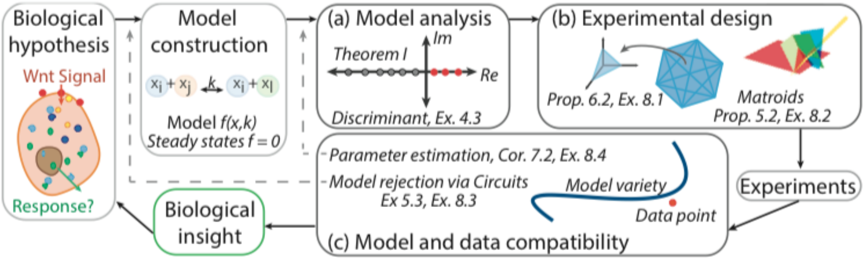


From *Algebraic Systems Biology: A Case Study for the Wnt Pathway*

(Elizabeth Gross, Heather Harrington, Zvi Rosen, Bernd Sturmfels 2016).

Outline

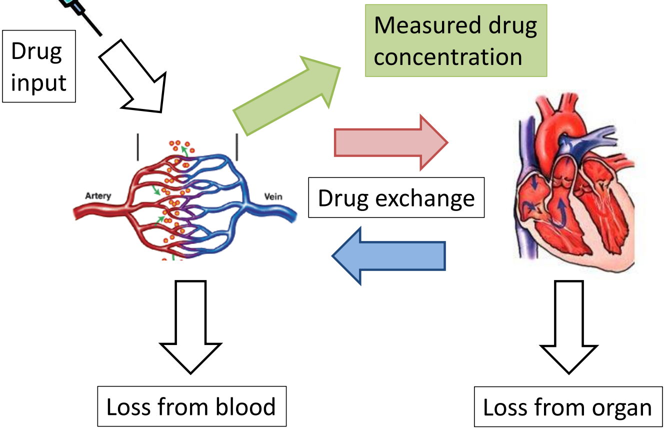
- Introduction: Linear compartment models
- Identifiability (via differential algebra)
- The singular locus

Joint work with
Elizabeth Gross and Nicolette Meshkat

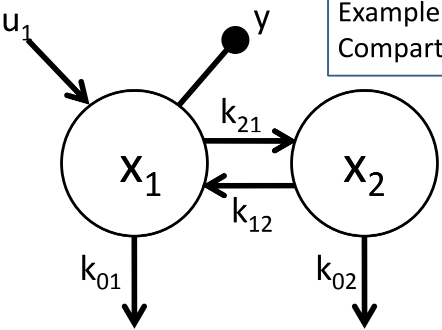
`arXiv:1709.10013`

Introduction

Motivation: biological models



Compartment model



Example: Linear 2-Compartment Model

$$\dot{x}_1 = -(k_{01} + k_{21})x_1 + k_{12}x_2 + u_1$$
$$\dot{x}_2 = k_{21}x_1 - (k_{02} + k_{12})x_2$$
$$y = x_1$$

Structural identifiability: Recover parameters k_{ij} from perfect input-output data $u_1(t)$ and $y(t)$? (Bellman & Astrom 1970)

IDENTIFIABILITY VIA DIFFERENTIAL ALGEBRA[1]: *Which models are identifiable?*

[1] Ljung and Glad 1994

Input-output equations

- *Setup:* a linear compartment model
- Let m = number of compartments
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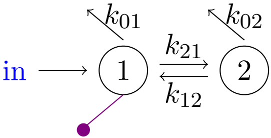

$$y_1^{(2)} + (k_{01} + k_{02} + k_{12} + k_{21})\, y_1' + (k_{01}k_{12} + k_{01}k_{02} + k_{02}k_{21})\, y_1 = (k_{02} + k_{12})\, u_1$$

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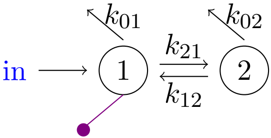
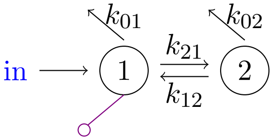


$$y_1^{(2)} + (k_{01} + k_{02} + k_{12} + k_{21})\, y_1' + (k_{01}k_{12} + k_{01}k_{02} + k_{02}k_{21})\, y_1 \;=\; (k_{02} + k_{12})\, u_1$$

- *Input-output equations* come from the elimination ideal:

$$\langle \text{ differential eqns. },\ \text{output eqns. } y_i = x_j\ ,\ \text{their } m \text{ derivatives } \rangle$$
$$\cap\ \mathbb{C}(k_{ij})[u_i, y_i]$$

Input-output equations, continued

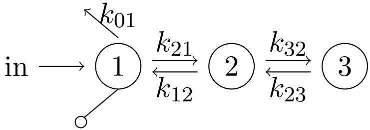


$$A = \begin{pmatrix} -k_{01} - k_{21} & k_{12} \\ k_{21} & -k_{02} - k_{12} \end{pmatrix} \qquad x'(t) = Ax(t) + u(t)$$

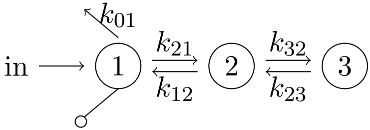
- **Proposition** (Meshkat, Sullivant, Eisenberg 2015): Consider a linear compartment model that is strongly connected, has an input and output in compartment-1 only, and has ≥ 1 leak. Then the input-output equation is:

$$\det(\partial I - A) y_1 = \det\left((\partial I - A)_{11}\right) u_1 \ .$$

Input-output equations, continued



Input-output equations, continued

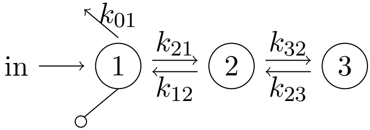


$$\det(\partial I - A) y_1 \;=\; \det\left((\partial I - A)_{11}\right) u_1$$

$$\det \begin{pmatrix} d/dt + k_{01} + k_{21} & -k_{12} & 0 \\ -k_{21} & d/dt + k_{12} + k_{32} & -k_{23} \\ 0 & -k_{32} & d/dt + k_{23} \end{pmatrix} y_1$$

$$= \;\det \begin{pmatrix} d/dt + k_{12} + k_{32} & -k_{23} \\ -k_{32} & d/dt + k_{23} \end{pmatrix} u_1$$

Input-output equations, continued



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$$= \;\det \begin{pmatrix} d/dt + k_{12} + k_{32} & -k_{23} \\ -k_{32} & d/dt + k_{23} \end{pmatrix} u_1$$

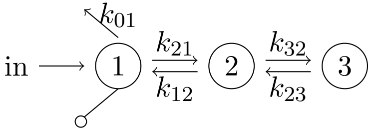
... expands to the *input-output equation*:

$$\begin{aligned} & y_1^{(3)} + (k_{01} + k_{12} + k_{21} + k_{23} + k_{32})\, y_1^{(2)} \\ & \quad + (k_{01}k_{12} + k_{01}k_{23} + k_{01}k_{32} + k_{12}k_{23} + k_{21}k_{23} + k_{21}k_{32})\, y_1' + (k_{01}k_{12}k_{23})\, y_1 \\ & \qquad = u_1^{(2)} + (k_{12} + k_{23} + k_{32})\, u_1' + (k_{12}k_{23})\, u_1 \;. \end{aligned}$$

PROOF OF $\det(\partial I - A)y_1 = \det((\partial I - A)_{11})\, u_1$

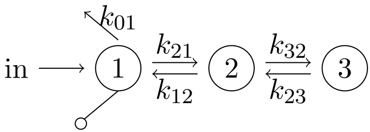
- $$x'(t) = Ax(t) + u(t) \quad \Leftrightarrow \quad (\partial I - A)x = u$$
- By Cramer's Rule,
$$y_1 = x_1 = \frac{\det(\partial I - A)_{\text{col. 1 replaced by } u}}{\det(\partial I - A)}$$
- Compute numerator by Laplace expansion along column 1

Coefficients of input-output equations



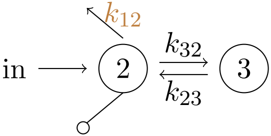
$$\begin{aligned} y_1^{(3)} &+ (k_{01} + k_{12} + k_{21} + k_{23} + k_{32})\, y_1^{(2)} \\ &+ (k_{01}k_{12} + k_{01}k_{23} + k_{01}k_{32} + k_{12}k_{23} + k_{21}k_{23} + k_{21}k_{32})\, y_1' + (k_{01}k_{12}k_{23})\, y_1 \\ &= u_1^{(2)} + (k_{12} + k_{23} + k_{32})\, u_1' + (k_{12}k_{23})\, u_1 \ . \end{aligned}$$

Coefficients of input-output equations



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

- coefficient of $y_1^{(i)}$ corresponds to forests with $(3-i)$ edges and ≤ 1 outgoing edge per compartment
- coefficient of $u_1^{(i)}$ corresponds to $(n-i-1)$-edge forests:



- **Thm 1**: The coefficients correspond to forests in model.

Identifiability

$$
\begin{aligned}
y_1^{(3)} &+ (k_{01} + k_{12} + k_{21} + k_{23} + k_{32})\, y_1^{(2)} \\
&+ (k_{01}k_{12} + k_{01}k_{23} + k_{01}k_{32} + k_{12}k_{23} + k_{21}k_{23} + k_{21}k_{32})\, y_1' + (k_{01}k_{12}k_{23})\, y_1 \\
&\quad = \; u_1^{(2)} + (k_{12} + k_{23} + k_{32})\, u_1' + (k_{12}k_{23})\, u_1 \; .
\end{aligned}
$$

- (Generic, local) *identifiability*: can the parameters k_{ij} be recovered from coefficients of input-output equations?

Identifiability

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$$\mathbb{R}^5 \to \mathbb{R}^5$$
$$(k_{01}, k_{12}, k_{21}, k_{23}, k_{32}) \mapsto (k_{01} + k_{12} + k_{21} + k_{23} + k_{32}, \ \ldots \ )$$

- Solve directly or use ...
- **Prop.** Identifiable $\Leftrightarrow$ Jacobian matrix of coefficient map has (full) rank = number of parameters

Identifiability

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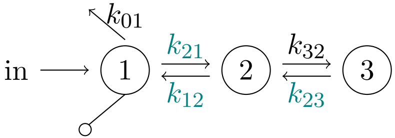
- Solve directly or use ...
- **Prop.** Identifiable ⇔ Jacobian matrix of coefficient map has (full) rank = number of parameters *generically*

The singular locus

Definition

- The **singular locus** is the set of non-identifiable parameters: when Jacobian matrix of coefficient map is rank-deficient.
- Example, continued:



The equation of the singular locus is:

$$\det \mathrm{Jac} \;=\; k_{12}^2 k_{21} k_{23} \;=\; 0\ .$$

Identifiable submodels

- *Motivation*: drug targets
- **Thm 2**: Let $\mathcal{M}$ be an identifiable linear compartment model, with singular-locus equation f. Let $\widetilde{\mathcal{M}}$ be obtained from $\mathcal{M}$ by deleting edges $\mathcal{I}$.
  If $f \notin \langle k_{ji} \mid (i,j) \in \mathcal{I} \rangle$, then $\widetilde{\mathcal{M}}$ is identifiable.

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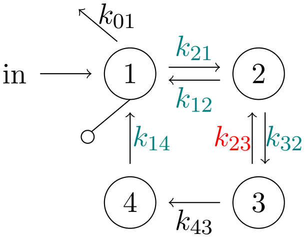

$$f = k_{12}k_{14}k_{21}^2k_{32}(k_{12}k_{14} - k_{14}^2 - \dots)(k_{12}k_{23} + k_{12}k_{43} + k_{32}k_{43}) .$$

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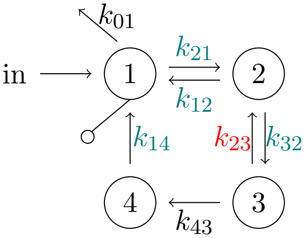

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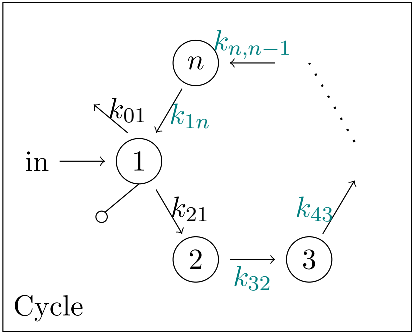
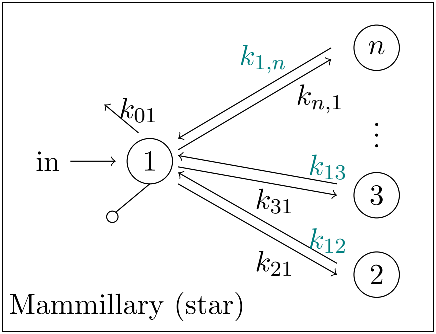
- *Converse is false*: deleting k_{12} and k_{23} is identifiable!

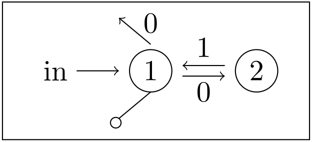
Cycle and mammillary models

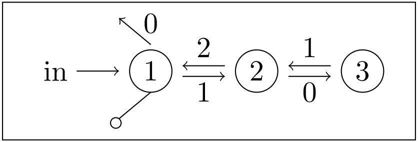


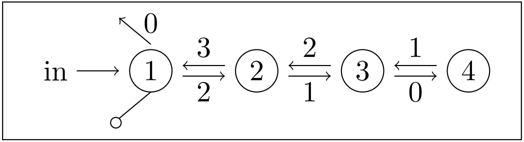


- **Thm 3**:
  - The singular-locus equation for the Cycle model is $k_{32}k_{43}\dots k_{n,n-1}k_{1,n}\prod_{2\leq i<j\leq n}(k_{i+1,i}-k_{j+1,j})$.
  - The singular-locus equation for the Mammillary model is $k_{12}k_{13}\dots k_{1,n}\prod_{2\leq i<j\leq n}(k_{1i}-k_{1j})^2$.

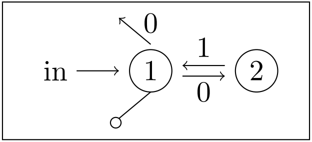
Catenary (path) models

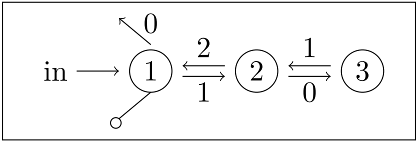


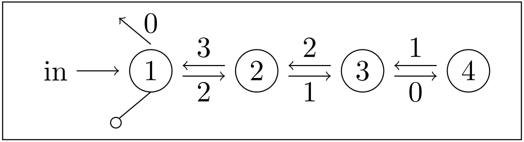




Catenary (path) models

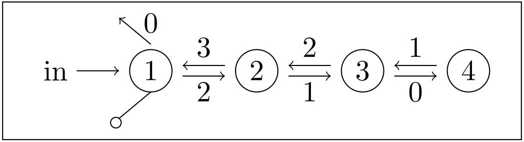


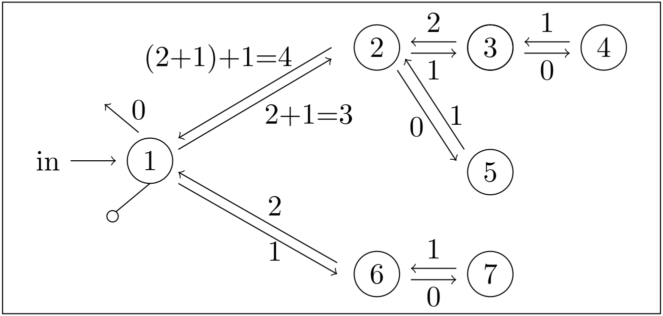




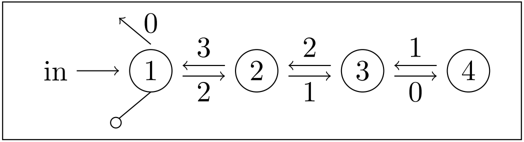
Conjecture: For **catenary models**, the exponents in the singular-locus equation generalize the pattern above.

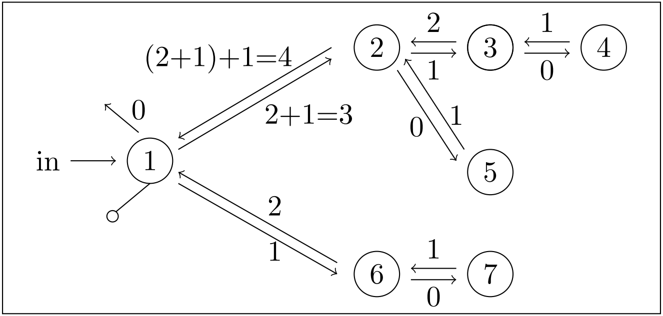
Tree conjecture





Tree conjecture





Conj.: (Hoch, Sweeney, Tung) For **tree models**, the exponents in the singular-locus equation generalize the pattern above.

Identifiability degree

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- **Proposition** (Cobelli, Lepschy, Romanin Jacur 1979)

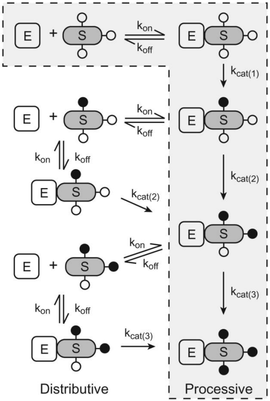
Model	**Identifiability degree**
Catenary (path)	1
Mammillary (star)	$(n-1)!$

- **Thm 4**

Model	**Identifiability degree**
Cycle	$(n-1)!$

Future work

Nonlinear models



From Processive phosphorylation: mechanism and biological importance, Patwardhan and Miller, *Cell Signal.* 2007.

Summary

The **singular locus** is an interesting mathematical object that can help us answer the question, *which linear compartment models are identifiable?*

Thank you.