A necessary condition for non-monotonic dose response

Polly Y. Yu
(Joint work with Eduardo Sontag)

NSF–Simons Center for Mathematical and Statistical Analysis of Biology, Harvard
Department of Mathematics, University of Illinois Urbana–Champaign

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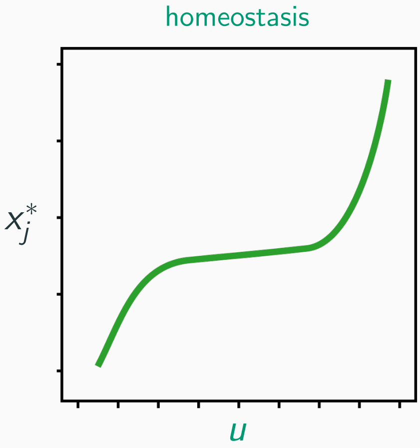
Slides:

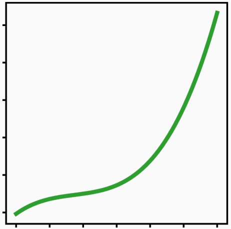
Dose response curve

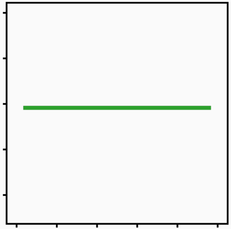
- ODE $\dfrac{d\vec{\boldsymbol{x}}}{dt} = \vec{\boldsymbol{f}}(\vec{\boldsymbol{x}}; u)$
- steady state curve $\vec{\boldsymbol{x}}^*(u)$
- shape of $\vec{\boldsymbol{x}}^*(u)$



Homeostasis, biphasic response, perfect adaptation

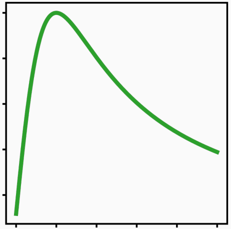
quasi-adaptation
(infinitesimal homeostasis)

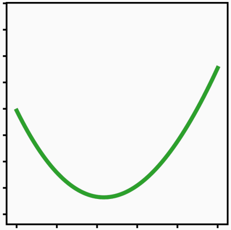




perfect adaptation

(stable) biphasic





A claim of necessary condition?

RESEARCH ARTICLE | APPLIED MATHEMATICS

Architecture of a minimal signaling pathway explains the T-cell response to a 1 million-fold variation in antigen affinity and dose

Melissa Lever, Hong-Sheng Lim, Philipp Kruger, +5, and Omer Dushek Authors Info & Affiliations

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Oversimplifying:

> Finally, models without an incoherent feed-forward loop but with negative feedback, although able to produce oscillations of P in time, cannot produce a bell-shaped dose–response (Fig. 4*D* and *SI Appendix*, Fig. S5; see also *SI Appendix* for a mathematical proof).

Mathematical setup

Assumptions

- For now, ODE $\dfrac{d\vec{\boldsymbol{x}}}{dt} = \vec{\boldsymbol{F}}(\vec{\boldsymbol{x}}, u) := \vec{\boldsymbol{f}}(\vec{\boldsymbol{x}}) + \hat{\mathbf{e}}_1 g(u)$
- Jacobian matrix $\mathbf{J}(\vec{\boldsymbol{x}}, u)$ with constant signs & negative diagonal
- Steady state curve $\vec{\boldsymbol{x}}^*(u) \quad \forall u \in I$
- $\mathbf{J}^* := \mathbf{J}(\vec{\boldsymbol{x}}^*(u), u)$ non-singular
- Output variable x_j

Graph representation

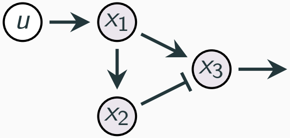
J-graph

- $(x_1, x_2, x_3 \geq 0)$

$$\dot{x}_1 = u - x_1$$
$$\dot{x}_2 = x_1^2 - x_2$$
$$\dot{x}_3 = 3x_1 + x_1^3 - 3x_2 - x_3$$

- $$\mathbf{J} = \begin{pmatrix} -1 & 0 & 0 \\ 2x_1 & -1 & 0 \\ 3 + 3x_1^2 & -3 & -1 \end{pmatrix} = \begin{pmatrix} -a_{11} & 0 & 0 \\ a_{21} & -a_{22} & 0 \\ a_{31} & -a_{32} & -a_{33} \end{pmatrix}$$

- Self-loops not drawn

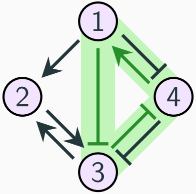


J-graph of **J**

J-graph of ODE

Feedback & feedforward loops

- **feedback loop**: cycle of length ≥ 2
  - **positive** (**PFBL**) if (product of) sign > 0



Feedback & feedforward loops

- **feedback loop**: cycle of length ≥ 2
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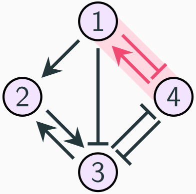
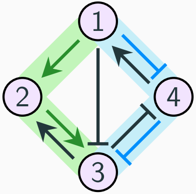
  - **negative** (**NFBL**) if (product of) sign < 0



Feedback & feedforward loops

- **feedback loop**: cycle of length ≥ 2
  - **positive** (**PFBL**) if (product of) sign > 0
  - **negative** (**NFBL**) if (product of) sign < 0
- **feedforward loop**: paths with same origin and destination
  - **coherent** (**CFFL**) if same signs



Feedback & feedforward loops

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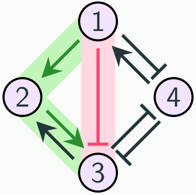
  - **incoherent** (**IFFL**) if opposite signs



Feedback & feedforward loops

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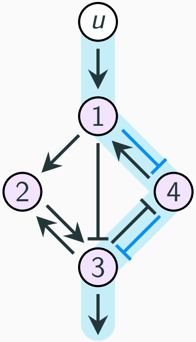
  - **incoherent** (**IFFL**) if opposite signs
- **input-output path**



Results

Summary

arXiv:2403.13862 (q-bio)

A necessary condition for non-monotonic dose response, with an application to a kinetic proofreading model -- Extended version

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- Algebraic condition (Cramer's rule):

$$\frac{\partial x_j^*}{\partial u} = \frac{(-1)^j}{\det \mathbf{J}^*} \mathbf{J}^*[\hat{1}, \hat{j}]$$

- Graph-theoretical condition for no mixed signs in minors

$$\mathbf{J}[\hat{1}, \hat{1}], \quad \mathbf{J}[\hat{1}, \hat{n}]$$

- Graph-theoretical condition for when stable branch $x_j^*(u)$ is monotonic

Summary

$$\begin{array}{ccc} \text{Quasi-adaptive} & \Longrightarrow & \text{IFFL}^1 \text{ or PFBL}^2 \\ \Uparrow & & \\ \text{Biphasic} & & \\ \Uparrow & & \\ \text{Stable biphasic} & \Longrightarrow & \text{IFFL}^1 \text{ or NFBL}^3 \end{array}$$

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$$\text{Stable biphasic} \Longrightarrow \text{IFFL}^1 \text{ or } (\text{PFBL}^2 \ \&\ \text{NFBL}^3)$$

[1] from u to output
[2] if $j = 1$, disjoint from x_1; if $j \neq 1$, vertex-disjoint from an input-output path
[3] reachable from input and to output

Mixed signs in principal minor

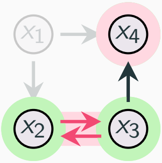
Input = Output

Let G be the J-graph of a signed symbolic matrix $\mathbf{J}$ with negative diagonal.

Let $G(\hat{1})$ be G without the node x_1 and incident edges.

Then $\mathbf{J}[\hat{1}, \hat{1}]$ has mixed signs $\iff$ $G(\hat{1})$ has PFBL.

$$\mathbf{J} = \begin{pmatrix} -a_{11} & 0 & 0 & 0 \\ a_{21} & -a_{22} & a_{23} & 0 \\ 0 & a_{32} & -a_{33} & 0 \\ a_{41} & 0 & a_{43} & -a_{44} \end{pmatrix}$$



$$\mathbf{J}[\hat{1}, \hat{1}] = a_{44}(a_{22}a_{33} - a_{23}a_{32})$$

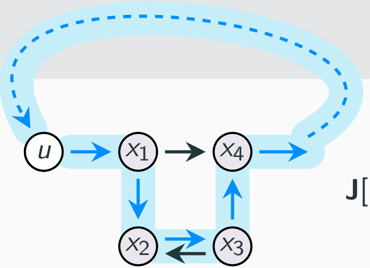
Mixed signs in non-principal minor

Input $1 \neq$ Output n

Let G be the J-graph of a signed symbolic matrix $\mathbf{J}$ with negative diagonal.

1. Then $\mathbf{J}[\hat{1}, \hat{n}] \equiv 0 \quad \iff \quad G$ has no input-output path.

$$\mathbf{J} = \begin{pmatrix} -a_{11} & 0 & 0 & 0 \\ a_{21} & -a_{22} & a_{23} & 0 \\ 0 & a_{32} & -a_{33} & 0 \\ a_{41} & 0 & a_{43} & -a_{44} \end{pmatrix} \quad (0 \to \pm 1)$$



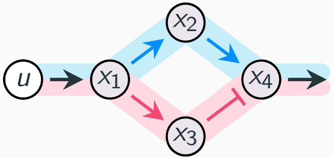
$$\mathbf{J}[\hat{1}, \hat{1}] = a_{41}(a_{22}a_{33} - a_{23}a_{32}) + a_{21}a_{32}a_{43}$$

Mixed signs in non-principal minor

Input $1 \neq$ **Output** n

Let G be the J-graph of a signed symbolic matrix $\mathbf{J}$ with negative diagonal.

1. Then $\mathbf{J}[\hat{1}, \hat{n}] \equiv 0 \iff G$ has no input-output path.
2. $\mathbf{J}[\hat{1}, \hat{n}]$ has mixed signs $\iff G$ has either an IFFL, or a PFBL vertex-disjoint from an input-output path.

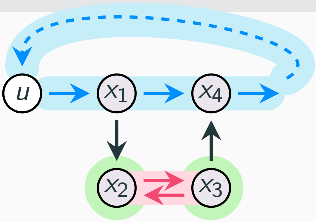


$$\mathbf{J}[\hat{1}, \hat{4}] = a_{33}a_{21}a_{42} - a_{22}a_{31}a_{43}$$

Input $1 \neq$ **Output** n

Let G be the J-graph of a signed symbolic matrix $\mathbf{J}$ with negative diagonal.

1. Then $\mathbf{J}[\hat{1}, \hat{n}] \equiv 0 \iff G$ has no input-output path.
2. $\mathbf{J}[\hat{1}, \hat{n}]$ has mixed signs $\iff G$ has either an IFFL, or a PFBL vertex-disjoint from an input-output path.



$$\mathbf{J}[\hat{1}, \hat{4}] = a_{21}a_{32}a_{43} + a_{41}(a_{22}a_{33} - a_{23}a_{32})$$

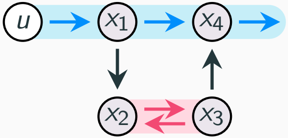
So far...

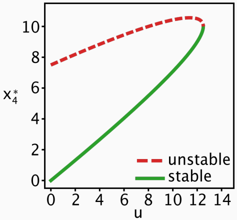
Necessary condition for quasi-adaptation

Biphasic $\implies$ quasi-adaptation $\implies$ mixed sign in minor

- $\mathbf{J}[\hat{1}, \hat{1}] \implies$ PFBL
- $\mathbf{J}[\hat{1}, \hat{n}] \implies$ IFFL, or PFBL

- algebraic property
- what about stable branch?





Stable biphasic

Based on monotone systems theory

For the system $\dot{\vec{\boldsymbol{x}}} = \vec{\boldsymbol{f}}(\vec{\boldsymbol{x}}) + \hat{\mathbf{e}}_1 g(u)$ with output x_j, assume

- signed Jacobian matrix $\mathbf{J}(\vec{\boldsymbol{x}}, u)$ with negative diagonal,
- Hurwitz along steady state $\vec{\boldsymbol{x}}^*(u)$, convergence to $\vec{\boldsymbol{x}}^*(u)$.

If $x_j^*(u)$ is *not* monotonic, then the J-graph either has an IFFL from u to x_j, or a NFBL that is reachable from u and to x_j.

Summary

$$\begin{array}{ccc} \text{Quasi-adaptive} & \Longrightarrow & \text{IFFL}^1 \text{ or PFBL}^2 \\ \Uparrow & & \\ \text{Biphasic} & & \\ \Uparrow & & \\ \text{Stable biphasic} & \Longrightarrow & \text{IFFL}^1 \text{ or NFBL}^3 \end{array}$$

$$\text{Stable biphasic} \Longrightarrow \text{IFFL}^1 \text{ or } (\text{PFBL}^2 \text{ \& NFBL}^3)$$

[1] from u to output
[2] if $j = 1$, disjoint from x_1; if $j \neq 1$, vertex-disjoint from an input-output path
[3] reachable from input and to output

Extensions & future directions

Extensions & future directions

- $\frac{d\vec{\boldsymbol{x}}}{dt} = \vec{\boldsymbol{F}}(\vec{x}, \vec{\boldsymbol{u}})$ for only $\frac{\partial x_j^*}{\partial u_i}$ — What about $\nabla_{\vec{\boldsymbol{u}}}\, x_j^*$?
- meaning of $\longrightarrow$, $\dashv$
  - $(X) \longrightarrow (Y)$ means **activation**: $Y_{\text{inact}} \rightleftharpoons Y \qquad X + Y_{\text{inact}} \longrightarrow X + Y$
  - $(X) \dashv (Y)$ means **inhibition**: $Y_{\text{inact}} \rightleftharpoons Y \qquad X + Y \longrightarrow X + Y_{\text{inact}}$

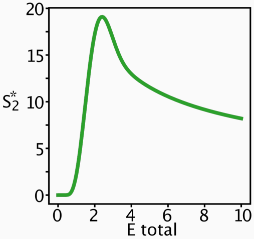
  — What about general conservation laws?

Example with conservation laws:

- Example:

$$S_0 + E \underset{1}{\overset{20}{\rightleftharpoons}} C_1 \xrightarrow{50} S_1 + E \underset{1}{\overset{20}{\rightleftharpoons}} C_2 \xrightarrow{5} S_2 + E$$

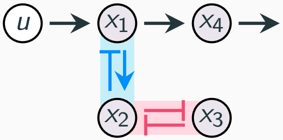
$$S_2 + F \underset{1}{\overset{10}{\rightleftharpoons}} D_1 \xrightarrow{50} S_1 + F \underset{1}{\overset{10}{\rightleftharpoons}} D_2 \xrightarrow{5} S_0 + F$$



$$S_{\text{total}} = 100, \; F_{\text{total}} = 25$$

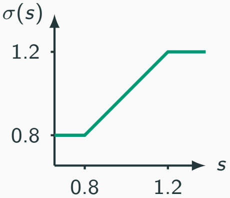
— relation to “ACR”-like property?

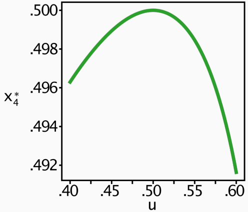
Example of stable biphasic & no IFFL:



$$\dot{x}_1 = h(x_2) - 2x_1 + u$$
$$\dot{x}_2 = h(x_3) - x_2 + x_1$$
$$\dot{x}_3 = f(x_2) - x_3$$
$$\dot{x}_4 = x_1 - x_4$$

$$h(s) = \frac{1}{2} e^{2(1-\sigma(s))}$$
$$f(s) = e^{1-\sigma(s)}$$





Not mass-action

— a mass-action example?

— DSR graph condition for kinetics systems?

Thank you!

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"Part II" – in progress

Slides

Additional slides

Examples