A design principle in biochemical reaction networks based on realization theory

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Outline

- Some special features of the differential equations of biochemical reaction networks
- Why are there so many reactant species?
- Possible connection with a nonlinear realization problem
- A conjecture and a problem formulation
- A hack for the solution

Some features of the equations

- Biochemical reaction networks seem to always contain *terms with special forms*

- Many reactant species, but *“function” appears to be described by a small subset*

- e.g. Circadian Oscillation in Drosophila:

$$\begin{aligned}
\dot{x}_4 &= v_{3p}\,\frac{x_3}{k_{3p} + x_3} - v_{4p}\,\frac{x_4}{k_{4p} + x_4} - k_3\, x_4 x_8 + k_4\, x_9 \\
&\quad - v_{dp}\,\frac{x_4}{K_{dp} + x_4} - k_d\, x_4 \\
\dot{x}_5 &= K_{iT}^n\,\frac{v_{st}}{K_{iT}^n + x_{10}^n} - v_{mt}\,\frac{x_5}{k_{mt} + x_5} - k_d\, x_5
\end{aligned}$$

- Each special form $\Longleftrightarrow$ Specific biochemical reaction mechanism

A model reduction question

Given a biochemical reaction network, say

$$\frac{d}{dt}\begin{bmatrix} x_1 \\ \vdots \\ x_{30} \end{bmatrix} = f\left(x_1, \ldots, x_{30}\right) \tag{1}$$

If function is described by a small number of states,

say $x_1,\ x_{12}$

does there exist a reduced model

$$\frac{d}{dt}\begin{bmatrix} x_1 \\ x_{12} \end{bmatrix} = g\left(x_1, x_{12}\right) \tag{2}$$

such that *behavior of (x_1, x_{12}) in (1)* $\Longleftrightarrow$ *behavior of (x_1, x_{12}) in (2)*

A Similar Question in Reverse

Given a low order system

$$\dot{z} \;=\; g(z),$$

z: *small number of variables*, g: *possibly complicated function*,

can this system be imbedded in

$$\dot{X} \;=\; F(X),$$

X: possibly *large number of variables*, F has *special form*?

$$\{z_1, \ldots, z_r\} \;\subset\; \{X_1, \ldots, X_n\}$$

embedded: Every trajectory of z is part of a trajectory of X

A nonlinear realization problem

Implementation with *Linear* Elements: Carleman Linearization

Example: $\dot{z} = g(z) = z^2$

Define: $X_1 := z, \quad X_2 := z^2, \quad , \cdots , \; X_n := z^n, \quad \cdots$

$$\frac{d}{dt}\begin{bmatrix} X_1 \\ X_2 \\ X_3 \\ X_4 \\ \vdots \end{bmatrix} = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 & \\ 0 & 0 & 2 & 0 & 0 & \cdots \\ 0 & 0 & 0 & 3 & 0 & \\ 0 & 0 & 0 & 0 & 4 & \\ & & \vdots & & & \ddots \end{bmatrix} \begin{bmatrix} X_1 \\ X_2 \\ X_3 \\ X_4 \\ \vdots \end{bmatrix}, \qquad \text{i.e.} \qquad \dot{\mathcal{X}} = \mathcal{A}\mathcal{X}$$

The original system is imbedded in this linear system

Easily generalizable to vector z and analytic g using

$$X_{(i_1,\ldots,i_n)} := z^{i_1} \ldots z^{i_n}$$

Implementation with *Quadratic* Elements

Consider: $\dot{z} = g(z)$,

Can embed in a larger system

$$\dot{\mathcal{X}} = \mathcal{Q}(\mathcal{X})$$

where $\mathcal{Q}$ is Quadratic

g polynomial $\Rightarrow$ $\mathcal{X}$ finite

$\mathcal{X}$, $\mathcal{Q}$ non-unique

(Starkl & del Re, ACC, CDC '03)

Note:

- Can approximate any system with $\mathcal{Q}$ a neural network
- Many other possibilities for the building blocks of $\mathcal{Q}$

Implementation with *Quadratic* Elements (cont.)

Example: $\dot{z} = z^4$

Define $x_i := z^i$

$$
\begin{aligned}
\dot{x}_1 &= x_4 \\
\dot{x}_4 &= 4z^3\dot{z} = 4z^3z^4 = 4x_3x_4 \\
\dot{x}_3 &= 3z^2z^4 = 3x_2x_4 = 3x_3^2 \\
\dot{x}_2 &= 2z\ z^4 = 2x_1x_4
\end{aligned}
$$

Choice of Z and RHS are non-unique!

Procedure terminates in finite number of steps

Realization (Implementation) Issues

Goal: Realize given dynamics $\dot{z} = g(z)$
with a given set of motifs (building blocks)

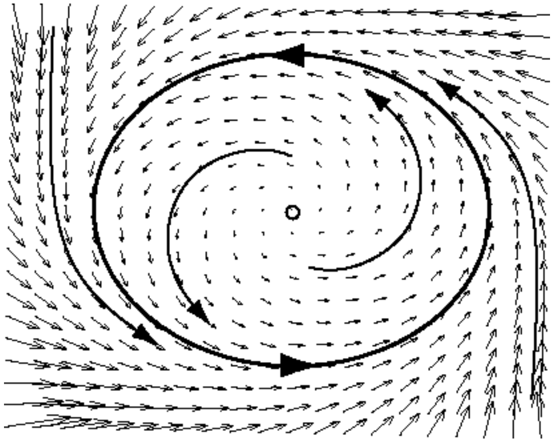
- Choice of new intermediate variables
  - Monomials ($x_i := z^i$)
  - Orthogonal Polynomials ($x_i := J_i(z)$)
  - $\cdots$

- Available building blocks, e.g.
  - Quadratic terms ($k_{ij} x_i x_j$, restrictions on reaction rates k_{ij})
  - Hill terms $\frac{x_i}{K + x_i}$

- Original dynamics are an invariant manifold of $\dot{z} = g(z)$
  - for implementation: must be a *stable* invariant manifold

A Design Principle

- Design dynamics for prescribed function,
  e.g. as p increases, oscillator $\longrightarrow$ bistable switch



  - Design vector field f for dynamics $\dot{z} = f(z, p)$
  - Can generally be done with 2 or 3 states.
  - but f is not realizable with given motifs

- Apply an expansion procedure to imbed dynamics in a larger system

$$\dot{z} \;=\; g(z, p)$$

  - g constructed from available motifs

A Conjecture

Why so many intermediate reactant species?

One answer:
To realize function using building blocks available with biochemistry

In other words:
Biological function may be easily described by $\dot{z} = g(z)$, w/ small z

But g *may contain terms not realizable with biochemical reactions*

The Reverse Embedding Problem in General

Given a large system

$$\dot{x} \;=\; f(x),$$

with specified building blocks (allowable reaction terms).

Did it arise from the "expansion" of a smaller system

$$\dot{z} \;=\; g(z),$$

where z a subset of x?

Possibly much more interesting than forward embedding problems which are hard to employ

A Hack for the Embedding Problem

- Start with original large system

$$\dot{x} = f(x)$$

- Simulate to produce trajectories “representative” of typical bio-function

- Identify a subset of states (relabel them z) that describe bio-function

- Use simulation data to fit a model

$$\dot{z} = g(z),$$

where g is parametrized, e.g. polynomial of some order.

Reformulation as Linear Regression

For polynomial g, fitting can be made into linear regression. Define

$$\begin{aligned} z^{(1)} &= z \\ z^{(2)} &= z \otimes z \\ z^{(3)} &= z \otimes z^{(2)} \\ &\vdots \end{aligned} \tag{3}$$

Then

$$g(z) = G\, Z,$$

$$Z := [1\ z'\ z^{(2)\prime} \ldots z^{(m)\prime}]',$$

Coefficients of polynomial g are entries of matrix G

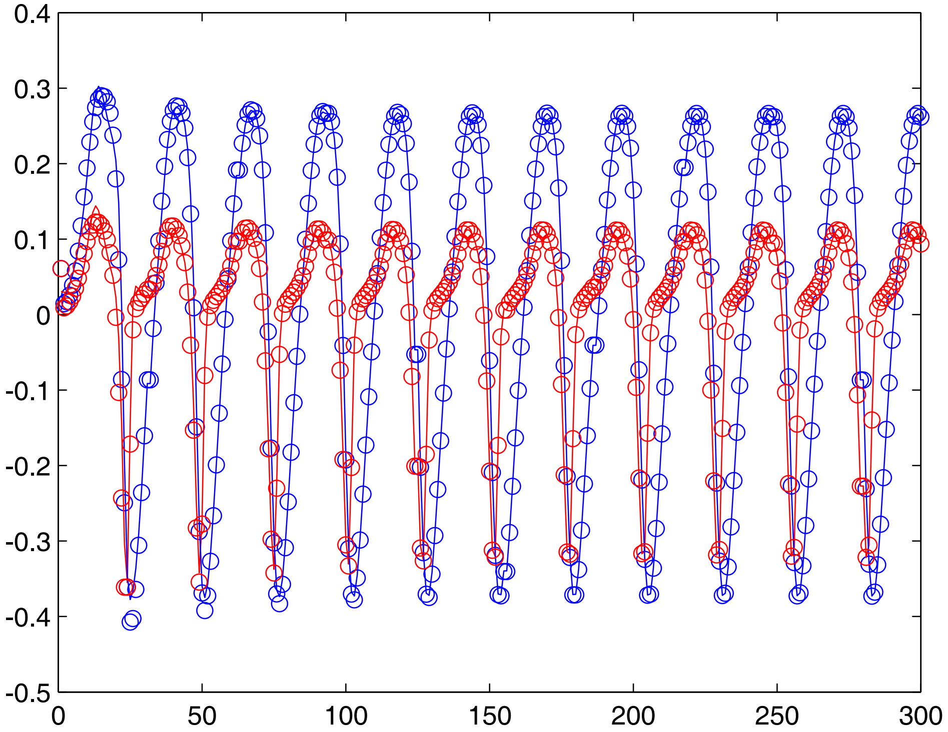
Fitting trajectories to $\dot{z} = GZ \quad \Leftrightarrow \quad$ Linear regression for entries of G

Example: Circadian Oscillation in Drosophila

Original model has 10 species

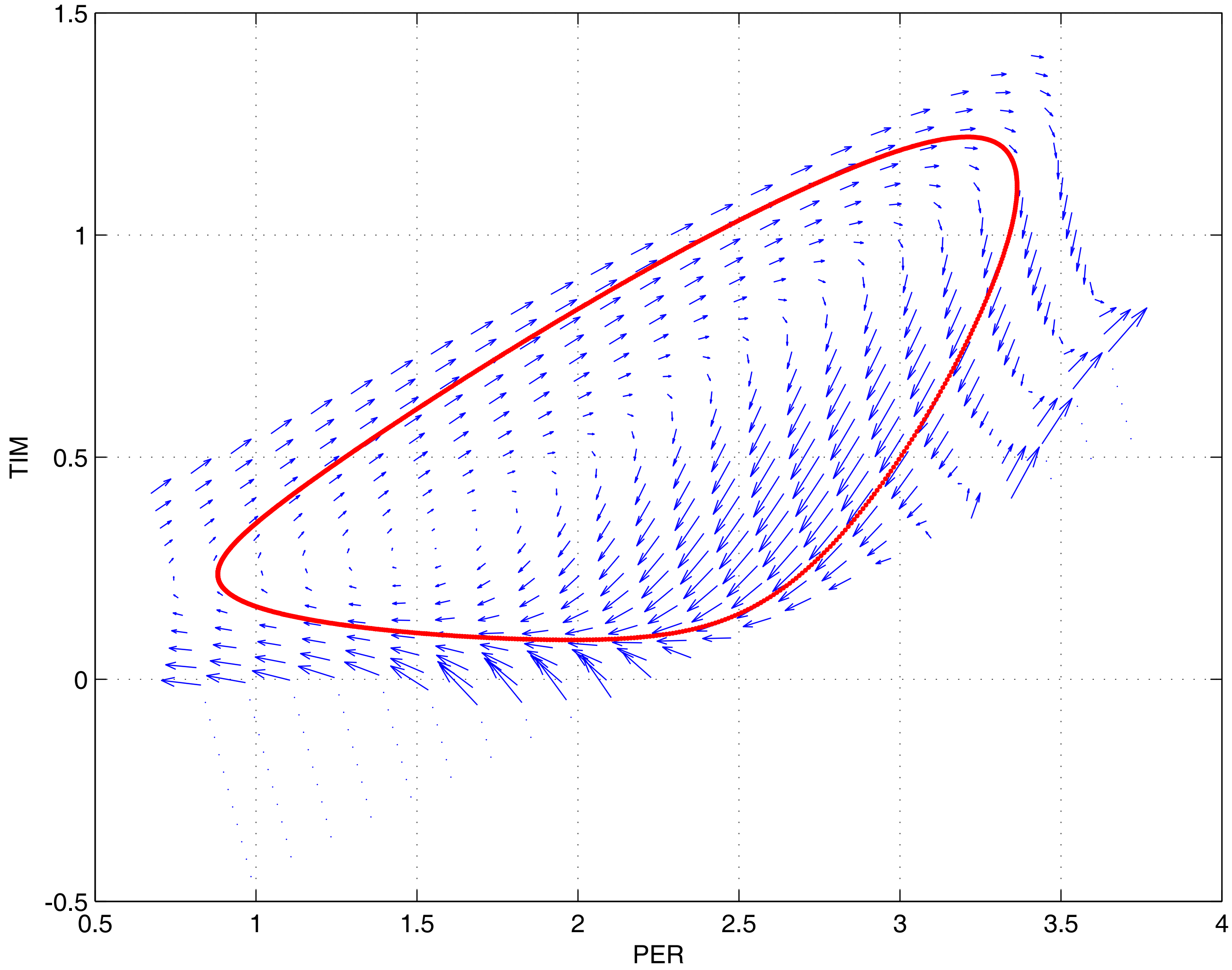
Function is described by 2: PER & TIM

Reduced model in example shown: 2 states, g of degree 5



Original PER/TIM (solid)
Reduced PER/TIM (dots)

Example: Circadian Oscillation in Drosophila (Cont.)



Vector field of the reduced model

Limit cycle trajectory of original system (Bamieh & Giarre, ACC ’07)

Comments

- Hack is easily generalizable to include parameters and/or inputs

$$\dot{z} = g(z, p, u)$$

- Difficult to compare reduced and original model
- Need better quantification of reduction error or comparison of behavior of original and reduced
- The original forward and reverse mathematical problems are open