University of Strathclyde Engineering

Parameter estimation in biochemical reaction networks: An observer-based approach

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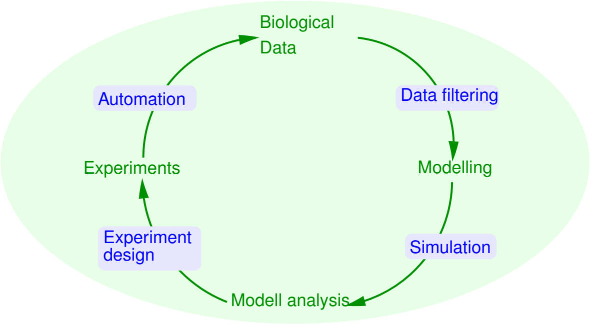
Outline

- **Introduction**
- Identification using Structural Information
- Summary and Outlook



Systems Biology Concept

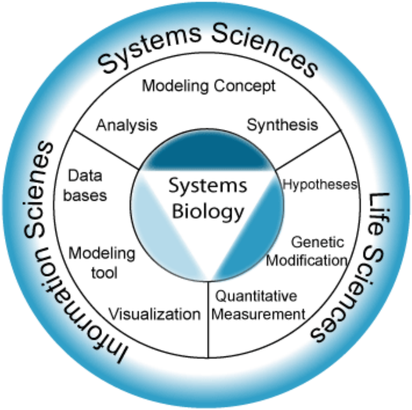
Quantitative, dynamical & spatial Biology
⇒ mathematical Modelling

Main Components

- quantitative, dynamical experiments
- Modelling
- Modell analysis
- Experiment design

Integrative Approach: Life sciences, natural sciences, math, engineering

- Experimenters
- Data analysts
- Modellers
- Model analysts



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Goal: better understanding of complex biological systems

Main Bottleneck: Experimental quantification of model parameters

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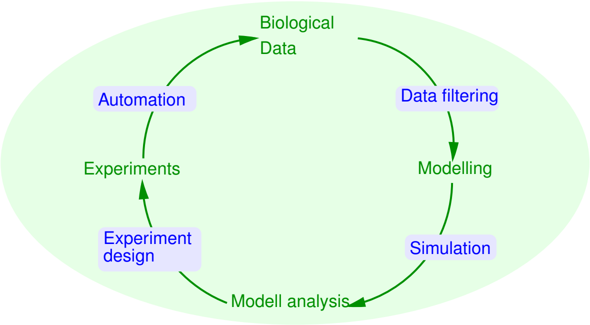


Motivation

- parameter estimation using dynamical data
- measurements often concentrations, fluxes
- mass action: system linear in parameters

Outputs: concentrations, fluxes
and their low order derivatives

Main idea

Extend system	$\dot{c} = Nv(c, p)$
by	$\dot{p} = 0$

and use appropriate coordinates

Identification of Biochemical Systems

Extended system

$$\begin{aligned} \dot{c} &= N \cdot v(c, p) \\ \dot{p} &= 0 \end{aligned} \qquad (1)$$

New extended system

$$\begin{aligned} \dot{c} &= N \cdot v \\ \dot{v} &= f(c, v) \end{aligned} \qquad (2)$$

Proposition — *Farina, Findeisen, Bullinger et al. (2006)*

For $c > 0$, $p > 0$, *there exists a diffeomorphism between systems* (1) *and* (2).

Advantages of new extended form (2)

- all states are (in principle) directly measurable
- only structural information needed
- assumptions often satisfied
- parameter values "hidden" in initial conditions
- c-dynamics linear
- Extendable to Hill kinetics $v_i = V_{\max} \frac{c_j^n}{K^n + c_j^n}$

Identifiability

Farina, Findeisen, Bullinger et al. (2006)

Extended system with measured concentrations

$$\dot{c} = N \cdot v$$
$$\dot{v} = f(c, v) \qquad (3)$$
$$y = H_c \cdot c.$$

Proposition

If along a trajectory $(\bar{c}, \bar{v}) = \big(\bar{c}(t), \bar{v}(t)\big)$ *the linearisation of system* (3) *is observable, then the nonlinear system is locally uniformly observable around the trajectory.*

Corollary

In steady state: observability only achievable if all concentrations measured

Dynamic information essential as rarely all states measured

Parameter Estimation via State Observer

Bullinger, Fey, Farina, Findeisen 2008

- Observability map: $\Phi(x) = \begin{bmatrix} y_1 & \dot{y}_1 & \dots & y_1^{(r_1)} & \dots & y_m^{(r_m)} \end{bmatrix}^T$
- Use observability map as coordinate transformation: $\xi = \Phi(x)$
  $\Rightarrow \frac{d^{r_i}}{dt^{r_i}} \hat{y}_i = \phi_i(x)$ and $\dot{\xi} = J\xi + B\phi_i(x)$
- Observer: Dynamical system estimating ξ

Problem

Observability map not everywhere invertible:
some singularities outside of manifold $\{x | \dot{p} = 0\}$

Solution

Special observers   e.g.: Event-based observer   *Vargas & Moreno, 2005*

- $\Rightarrow$ ϵ-approximation of extended state ξ
- Parameters directly obtainable from estimated extended state x

Event-based Observer

High-gain observer with saturated inverse observability map

Observer in observability canonical form

$$\frac{d^{r_i}}{dt^{r_i}}\hat{y}_i = \hat{\phi}_i(\hat{x})$$

$$\hat{\xi} = \Phi(\hat{x}) = \begin{bmatrix} \hat{y}_1 & \dot{\hat{y}}_1 & \cdots & \hat{y}_1^{(r_1)} & \cdots & \hat{y}_m^{(r_m)} \end{bmatrix}^T$$

$$\hat{\phi}_i(\hat{x}) = \begin{cases} \phi_i(\hat{x}) & \text{for } |\phi_i(\hat{x})| < \delta, \\ \delta \operatorname{sgn} \phi_i(\hat{x}) & \text{for } |\phi_i(\hat{x})| \geq \delta, \end{cases}$$

Event: time intervals with ill-conditioned Φ^{-1}

$$T_{\text{Event}} = \left\{ t : \left| \frac{\lambda_{\min} \frac{\partial \Phi}{\partial x}}{\lambda_{\max} \frac{\partial \Phi}{\partial x}} \right| < \epsilon \right\},$$

During event: no back transformation of observer states

Overview of Proposed Parameter Estimation

Applicable to

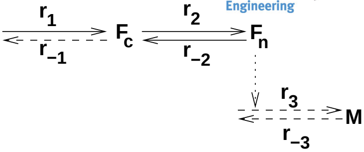
- biochemical systems with mass action and Hill kinetics
- ordinary differential equation models

Three steps

1. transform into parameter free extended system
2. estimate extended state
3. recover parameters

Illustrate with simple example

Simple Model of Circadian Rhythm



- three species
- six reactions (three Hill)
- exhibits autonomous oscillations (day-night cycle)

Leloup et al., 1999

$$
\begin{aligned}
\dot{M} &= r_3 - r_{-3} \\
\dot{F}_c &= r_1 - r_{-1} - r_2 + r_{-2} \\
\dot{F}_n &= r_2 - r_{-2}
\end{aligned}
$$

where

$$
\begin{aligned}
r_1 &= k_1 M & r_{-1} &= v_{-1}\frac{F_c}{K_{-1} + F_c} \\
r_2 &= k_2 F_c & r_{-2} &= k_{-2} F_n \\
r_3 &= v_3 \frac{K_3^4}{K_3^4 + F_n^4} & r_{-3} &= v_{-3}\frac{M}{K_{-3} + M}
\end{aligned}
$$

Simple Model: Extended System

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$$x = \begin{bmatrix} M & F_c & F_n & m_{r_{-1}} & m_{r_3} & m_{r_{-3}} & r_1 & r_{-1} & r_2 & r_{-2} & r_3 & r_{-3} \end{bmatrix}^T,$$

m_i : denominator of Hill kinetics

$$\frac{d}{dt}\left[\begin{array}{c} M \\ F_c \\ F_n \\ \hline m_{r_{-1}} \\ m_{r_3} \\ m_{r_{-3}} \\ \hline r_1 \\ r_{-1} \\ r_2 \\ r_{-2} \\ r_3 \\ r_{-3} \end{array}\right] = \left[\begin{array}{c} r_3 - r_{-3} \\ r_1 - r_2 + r_{-2} - r_{-1} \\ r_2 - r_{-2} \\ \hline r_1 - r_2 + r_{-2} - r_{-1} \\ 4F_n^3\left(r_2 - r_{-2}\right) \\ r_3 - r_{-3} \\ \hline r_1\left(r_3 - r_{-3}\right)/M \\ \left(r_1 - r_2 + r_{-2} - r_{-1}\right)\left(\frac{r_{-1}}{F_c} - \frac{r_{-1}}{m_{r_{-1}}}\right) \\ r_2\left(r_1 - r_2 + r_{-2} - r_{-1}\right)/F_c \\ r_{-2}\left(r_2 - r_{-2}\right)/F_n \\ -4r_3F_n^3\left(r_2 - r_{-2}\right)/m_{r_3} \\ r_{-3}(r_3 - r_{-3})\left(1/M - 1/m_{r_{-3}}\right) \end{array}\right].$$

Right-hand side: free of parameters

Simple Model: Output

Measure of species concentrations and outflow reactions

$$y = \begin{bmatrix} M & F_c & F_n & r_{-1} & r_{-3} \end{bmatrix}^T.$$

Limit order of derivatives:

- bad data
- minimise numerical errors
- simpler observer design

Observability map invertible, e.g. for

$$\Phi(x) = \begin{bmatrix} M & \dot{M} & \ddot{M} & F_c & \dot{F}_c & F_n & \dot{F}_n & \ddot{F}_n & r_{-1} & \dot{r}_{-1} & r_{-3} & \dot{r}_{-3} \end{bmatrix}^T.$$

Problem: Singular Points

Local observability lost if either

$$r_2 = r_{-2}$$
$$r_3 = r_{-3}$$
$$r_1 + r_{-2} = r_2 + r_{-1}$$
$$F_c(r_2 - r_{-2}) = F_n(r_1 + r_{-2} - r_2 - r_{-1}).$$

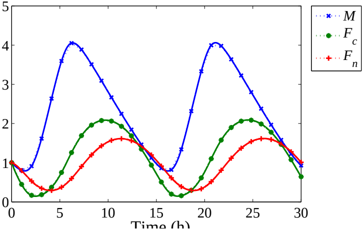
Then: Inverse of observability map (Φ^{-1})

- non-Lipschitz
- but continuous

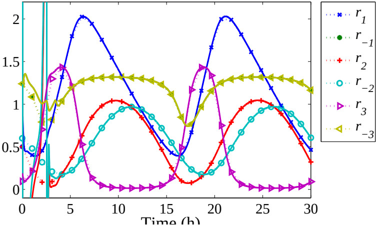
Use of event-based observer

- $\epsilon = 10^{-4}$, $\delta = 5$
- Parameter estimation possible at any time
  However, not recommended during event

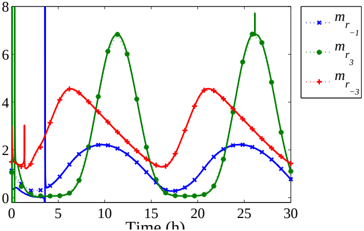
Simulation Results — States



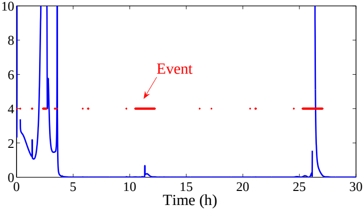
Concentrations



Reaction rates



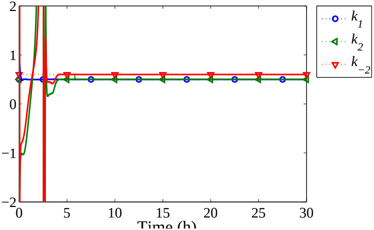
Hill variables



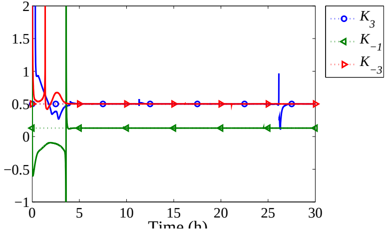
Estimation error

Good state estimation outside events

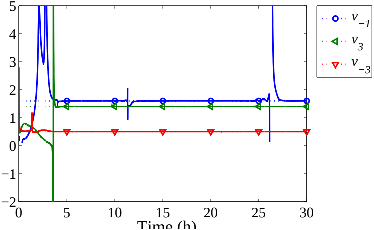
Simulation Results — Parameters



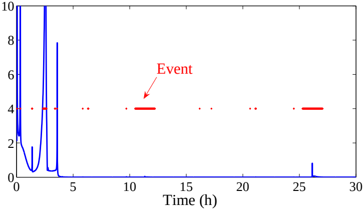
Rate constants



Hill constants



Maximal Hill rates



Estimation error

Good parameter estimation away from events

Summary

- Systems approach (modelling) allows
  - fusion of diverse data & hypotheses
  - analysis of key components
  - feedback to biology
  - main bottleneck: parameter estimation
- proposed new approach
  - suited especially for biochemical networks
  - uses structural information
  - three steps:
    - transform system in coordinate-free form
    - estimate extended state
    - recover parameters
- Outlook
  - better state estimation (optimisation-based)
  - analysis of noise and sampling

Thanks

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Thank you for your attention