Parameter Estimation for Biochemical Reaction Networks

Dirk Fey and Eric Bullinger

Industrial Control Centre, Electronic and Electrical Engineering

dirk.fey@eee.strath.ac.uk

University of Strathclyde Engineering

Problem

Accurate & reliable **parameter estimation** (1)

- Vital part of mathematical modelling
- Bottleneck in systems biology
- Becoming more and more feasible (better measurements)

Kinetic reaction model (ode's)

$$\frac{d}{dt}c = N \cdot r(c;\, \hat{r}, K), \quad y = h(c)$$

- Reaction kinetics

$$r = \hat{r}\frac{c_1^{\nu_1}}{K_1^{\eta_1} + c_1^{\eta_1}} \cdot \ldots \cdot \frac{c_n^{\nu_n}}{K_n^{\eta_n} + c_n^{\eta_m}}$$

- Known: Reaction & Hill orders ° & η

Aim: Infer the parameters K & $\hat{r}$ based on measurement y (output)

Method

3 step approach to parameter estimation (2)

1. Model extension

Introduce new dynamic variables for

- Reactions rates (3)

  $\frac{d}{dt}\log(r) \Rightarrow \dot{r} = f_r(c, m, r)$

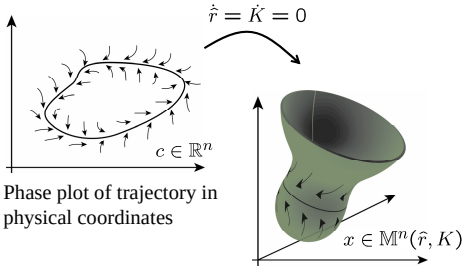
- Denominators (Hill variables)

  $M := K^\eta + c^\eta \Rightarrow \dot{M} = f_M(c)$

⇒ Trajectories on manifold embedded in higher dimensional state space

⇒ Shape of manifold defined by parameters

Extended system: Parameter independent & linear output

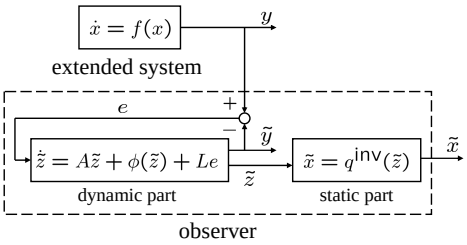


Phase plot of trajectory in physical coordinates

Trajectory in extended coordinates lies in a higher state space on a low-dimensional manifold

2. State reconstruction

Nonlinear high gain observer (4)



Dynamic part: *Equivalent extended system*

Trafo with observability map: $z = q(x)$

- Consisting of linear integrator chains
- Nonlinearity summarized in Á

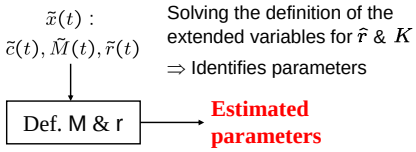
Static part: *Trafo into original coordinates*

- Inverse observability map

Caution: Bound Á & q^{inv} if system not everywhere observable

3. Obtaining parameter values

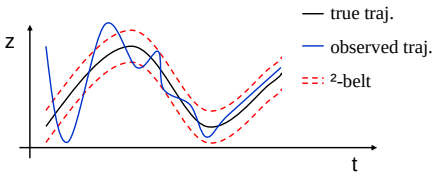
Solve definition of extended states for parameters



First Results

If system bounded and trajectory observable

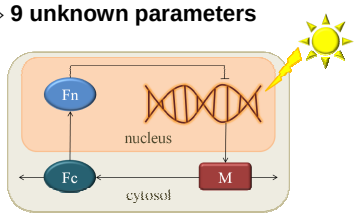
- **²-convergence** in observer canonical coordinates because nonlinearity bounded
- **Guaranteed** & accurate parameter estimation



Example

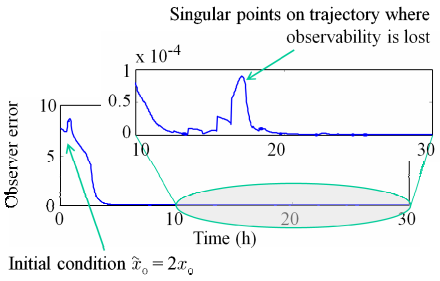
Circadian rhythm in neurospora (5)

- Oscillations: day-night cycle
- Dynamic gene regulation model
- 3 species concentrations, 3 mass action & 3 Hill reactions
  ⇒ **9 unknown parameters**



Result

Estimation accurate and reliable



Conclusion & Advantages

- Combined state & parameter estimation
- *Identifiability* can be analyzed in terms of *observability*
- Measurement of all states generally **not necessary**

Guarantees convergence

Future Work

- Application: metabolic pathways, signal transduction, gene regulation…
- Hybrid observer design: Continuous simulation with discrete measurement updates
- Dealing with noise: Kalman Filters, error propagation, …

References

(1) Peifer, M & Timmer, J, *IET Syst Biol*, 1(2):78–88 (2007)

(2) Fey, D, Findeisen, R, Bullinger, E, *Proc. 17th IFAC WC*, accepted (2008)

(3) Farina, M, Findeisen, R, Bullinger et al., *45th IEEE CDC*, 2104–2109 (2006)

(4) Vargas, A & Moreno, JA, *Int J Contr*, 78:247–253 (2005)

(5) Leloup, JC, Gonze, D, & Goldbeter, A, *J Biol Rhythms*, 14(6):433–444 (1999)