Parameter Estimation for Biochemical Reaction Networks

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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)
\[
\frac{d}{dt} c = N \cdot r(c, r, K), \quad y = h(c)
\]
- Reaction kinetics
  \[ r = \frac{r_1}{K_1^a + c^a} + \cdots + \frac{r_n}{K_n^a + c^a} \]
- Known: Reaction & Hill orders $a$ & $\eta$

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

Method
3 step approach to parameter estimation (2)

1. Model extension
Introduce new dynamic variables for
- Reactions rates (3)
  \[ \frac{d}{dt} \log(r) \Rightarrow \dot{r} = f_e(c, m, r) \]
- Denominators (Hill variables)
  \[ M := K^n + c^n \Rightarrow \dot{M} = f_0(c) \]
  \[
  \Rightarrow \text{Trajectories on manifold embedded in higher dimensional state space}
  \Rightarrow \text{Shape of manifold defined by parameters}
\
Extended system: Parameter independent & linear output

2. State reconstruction
Nonlinear high gain observer (4)
\[
x = f(x) \\
\dot{y} = \frac{y}{\dot{y}} \\
\dot{x} = \frac{\dot{y}}{y}
\]

Dynamic part: Equivalent extended system
- Trafo with observability map: $z = \phi(x)$
  - Consisting of linear integrator chains
  - Nonlinearity summarized in $\phi$

Static part: Trafo into original coordinates
- Inverse observability map

Caution: Bound $\phi$ & $\phi^{-1}$ if system not everywhere observable

3. Obtaining parameter values
Solve definition of extended states for parameters
\[
x(t) : \exists \epsilon(t), M(t), \phi(t)
\]
Def. $M$ & $r$
Estimated parameters

First Results
If system bounded and trajectory observable
- $^2$-convergence in observer canonical coordinates because nonlinearity bounded
- Guaranteed & accurate parameter estimation

Guarantees convergence

Example
Circadian rhythm in Neurospora (5)
- Oscillations: day-night cycle
- Dynamic gene regulation model
- 3 species concentrations, 3 mass action & 3 Hill reactions $\Rightarrow$ 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

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