Kinetic parameter estimation in biochemical reaction networks using observability extensions

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Introduction

Accurate & reliable **parameter estimation** [1]

- Vital part of mathematical modeling
- Bottleneck in systems biology
- Becoming feasible (better measurements)

Problem statement

Kinetic reaction model (ode's)

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

- Measurement $\boldsymbol{y}$
  - Some reaction rates $\boldsymbol{r_i}$
  - Some species concentrations $\boldsymbol{c_i}$
- Reaction kinetics

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

- Known: Reaction & Hill-term orders ν & η

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

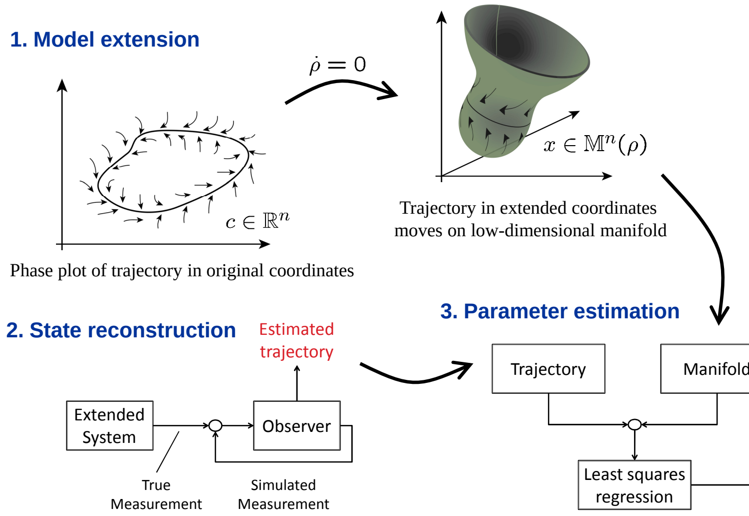
Method

1. **Model extension** [2]
   Introduce new dynamic variables for
   - Reactions rates
     $\frac{d}{dt}\log(r) \Rightarrow \dot{r} = f(c, m, r)$
   - Denominators (Hill variables)
     $m = K^\eta + c^\eta \Rightarrow \dot{m} = f(c)$

   ⇒ Extended system:
   Parameter independent & linear output
   $\dot{x} = f(x), \quad y = C \cdot x$

   ⇒ Initial conditions ≙ parameters
2. **State reconstruction** [3]
   Use measurement to estimate new states
   - Non-linear observer with *error*-gain L
     $\dot{\tilde{x}} = f(\tilde{x}) + L(y - \tilde{y}), \quad \tilde{y} = h(\tilde{x})$
   - **Caution:** L ill-conditioned if not well observable
3. **Parameter estimation**
   Use definition of extended variables
   - Reaction rates ⇒ nominal rates $\hat{r}$
   - Hill variables ⇒ Hill constants K

Illustration of the method



Model extension
- Higher dimensional space

⇒ Trajectory on manifold

Shape of manifold
- Defined by parameters
- According definition extended variables

Regression on observed trajectory

⇒ Identifies parameters

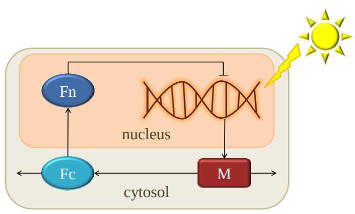
Example

Circadian rhythm in neurospora

- Oscillations according to day-night cycle

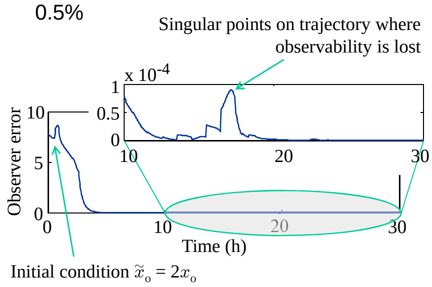
Model [3]

- Dynamic gene regulation model
- 3 species, 3 mass action & 3 Hill reactions ⇒ **9 unknown parameters**



Results

- Observer converged
- Parameter estimate accurate, error < 0.5%



Important Advantages

- **Decoupling** of state & parameter estimation
- *Identifiability* can be analyzed in terms of *observability*
- Measurement of all states (species concentrations) **not** generally **necessary**

Conclusion

- Allows us to identify models & experiments for which the estimation is possible
- Very accurate estimation under noise free conditions

Parameter estimation can benefit from observability based approach

Outlook

- Application to models of metabolic pathways, signal transduction and gene regulation
- Hybrid observer design:
  Continuous simulation & discrete updates
- Treating noise:
  e.g. Kalman Filters, error propagation, …

References

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