Estimating Parameters and Hidden Variables in a Nonlinear State-space Model of Biological Networks

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Motivation
- Reverse Engineering of Biological Networks

Method
- Nonlinear State-Space Model
- Estimation algorithm

Results
- Repressilator
- JAK-STAT signaling pathway

Conclusion
1 Motivation
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4 Conclusion
**Motivation**

- Multi-scale
  - Regulatory networks
  - Metabolic networks
  - Signaling pathways
- Mathematical model
  - stochastic nature
  - dynamical systems
- Challenge
  - nonlinear
  - partially observed

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**Method**

**Results**

**Conclusion**

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**Reverse Engineering of Biological Networks**

**Biological networks**

- **Metabolic space**
  - Metabolite 1 → Metabolite 2
- **Protein space**
  - Protein 2 → Complex 3:4 → Protein 4
  - Protein 1 → Gene 2
- **Gene space**
  - Gene 1 → Gene 2, Gene 3 → Gene 4
Motivation

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Reverse Engineering of Biological Networks

Quantitative models of Biological Networks

System of ODE’s

\[ \frac{dx}{dt} = f(x(t), u(t); \theta) \]

- \( x(t) \): state variables at time \( t \)
  - protein concentrations
  - mRNA concentrations
  - metabolite concentrations

- \( f \): encodes the structure of the system
  - nonlinear function
  - Michaelis-Menten kinetics
  - Mass action kinetics
  - ...

- \( \theta \): parameter set (kinetic parameters, rate constants,...)

- \( u(t) \): input variables at time \( t \)
Reverse Engineering of Biological Networks

Given

- An ODE model:
  \[
  \frac{dx(t)}{dt} = f(x(t), u(t); \theta)
  \]

- A partially and noisy observation model:
  \[
  y(t) = H(x(t), u(t); \theta) + \epsilon(t)
  \]

  where \( H \) is a nonlinear observation function, \( \epsilon(t) \) is a i.i.d noise

- A sequence of observed data: \( y_{1:K} = \{y_1, ..., y_K\} \) at time \( t_1, t_2, ..., t_k \)

Goal

- Estimation of parameters \( \theta \)
- Estimation of states \( x(t) \)
Given

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Nonlinear State-Space Model

Continuous time ODE model

\[
\frac{dx(t)}{dt} = f(x(t), u(t); \theta) \\
y(t) = H(x(t), u(t); \theta) + \epsilon(t)
\]

The corresponding discrete-time state-space model

The system at discrete-time points \( t_1, ..., t_K \)

\[
x(t_{k+1}) = F(x(t_k), u; \theta) \\
y(t_k) = H(x(t_k), u(t_k); \theta) + \epsilon(t_k)
\]

with

\[
F(x(t_k), u; \theta) = x(t_k) + \int_{t_k}^{t_{k+1}} f(x(\tau), u(\tau); \theta) d\tau
\]
Nonlinear State-Space Model

Continuous time ODE model

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Conclusion
Given:
- Prior distribution over the initial state and parameters: \( p(x_1, \theta) \)
- A transition model: \( p(x_k|x_{k-1}, \theta) \)
- An observation model: \( p(y_k|x_k, \theta) \)
- A sequence of observations: \( y_{1:K} = \{y_1, ..., y_K\} \)

Estimating the posterior distributions
- The filtering distribution: \( p(x_k, \theta|y_{1:k}) \)
- The smoothing distribution: \( p(x_k, \theta|y_{1:K}) \)
Bayesian inference

Given:
- Prior distribution over the initial state and parameters: \( p(x_1, \theta) \)
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Estimating the posterior distributions
- The filtering distribution: \( p(x_k, \theta|y_{1:k}) \)
- The smoothing distribution: \( p(x_k, \theta|y_{1:K}) \)
Recursive Bayesian Filtering

Suppose that $\theta$ is known, recursively calculate the filtering distribution of the states $p(x_k|y_{1:k})$

Two steps

1. **Prediction:**
   
   $$p(x_{k+1}|y_{1:k}) = \int p(x_{k+1}|x_k)p(x_k|y_{1:k})dx_k$$

2. **Update:**
   
   $$p(x_{k+1}|y_{1:k+1}) = \frac{p(y_{k+1}|x_{k+1})p(x_{k+1}|y_{1:k})}{p(y_{k+1}|y_{1:k})}$$

   where:

   $$p(y_{k+1}|y_{1:k}) = \int p(y_{k+1}|x_{k+1})p(x_{k+1}|y_{1:k})dx_{k+1}$$

- Analytical solution obtained only when $F, H$ are linear and $p(x_1)$ and $\epsilon$ are Gaussian $\rightarrow$ Kalman Filter
- When $F, H$ are nonlinear, the integrals are usually intractable. Approximate solutions are needed!
Suppose that $\theta$ is known, recursively calculate the filtering distribution of the states $p(x_k|y_{1:k})$

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Two steps

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Nonlinear SSM → Approximate Solutions

- Gaussian Approximations:
  - Extended Kalman Filter [Jazwinski 1970]
  - Unscented Kalman Filter [Julier and Uhlmann 1995-2000]

  - Particle filters

Basic problem: Nonlinear transformation of a random variable:

\[ y = F(x) \]

- Given:
  \[ \bar{x} = E(x) \quad P_x = E \left[ (x - \bar{x})(x - \bar{x})^T \right] \]

- Find:
  \[ \bar{y} = E(y) \quad P_y = E \left[ (y - \bar{y})(y - \bar{y})^T \right] \]
### Nonlinear State-Space Model

#### Estimation algorithm

<table>
<thead>
<tr>
<th>EKF</th>
<th>UKF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linearize $F$: $A = \frac{\partial F}{\partial x}$</td>
<td>Compute sigma-points: ${X_i} = {\bar{x} + \gamma \sqrt{P_x}, \bar{x} - \gamma \sqrt{P_x}}$</td>
</tr>
<tr>
<td>$\bar{y} = F(\bar{x})$  $P_y = A^T P_x A$</td>
<td>Transform sigma-points: $Y_i = F(X_i)$</td>
</tr>
<tr>
<td></td>
<td>Reconstruct posterior statistics: $\bar{y} = \sum_i \alpha_i Y_i$  $P_y = \sum_i \alpha_i (Y_i - \bar{y})(Y_i - \bar{y})^T$</td>
</tr>
</tbody>
</table>
Unscented Kalman Filter

- Deterministic sampling method, number of sigma points is small → fast
- No need to calculate derivatives (Jacobians, Hessians, etc.)
- Exact to 2nd order of Taylor series expansion for both mean and covariance.
- Can be extended to capture higher-order statistics (skew, kurtosis, etc.)
Parameter Estimation

- Augmented state approach

\[
\begin{align*}
\theta_{k+1} &= \theta_k \\
x(t_{k+1}) &= F(x(t_k), u; \theta_k) \\
y(t_k) &= H(x(t_k), u(t_k); \theta_k) + \epsilon(t_k)
\end{align*}
\]

- Joint state and parameter estimation
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Repressilator

[Elowitz, Nature 2000]

\[
\frac{dr_1}{dt} = v_{1}^{\text{max}} \frac{k_{12}^{n}}{k_{12}^{n} + p_{2}^{n}} - k_{1}^{\text{mRNA}} r_1
\]

\[
\frac{dr_2}{dt} = v_{2}^{\text{max}} \frac{k_{23}^{n}}{k_{23}^{n} + p_{3}^{n}} - k_{2}^{\text{mRNA}} r_2
\]

\[
\frac{dr_3}{dt} = v_{3}^{\text{max}} \frac{k_{31}^{n}}{k_{31}^{n} + p_{1}^{n}} - k_{3}^{\text{mRNA}} r_3
\]

\[
\frac{dp_1}{dt} = k_{1} r_1 - k_{1}^{\text{protein}} p_1
\]

\[
\frac{dp_2}{dt} = k_{2} r_2 - k_{2}^{\text{protein}} p_2
\]

\[
\frac{dp_3}{dt} = k_{3} r_3 - k_{3}^{\text{protein}} p_3
\]

- mRNAs are observed, proteins are hidden
- mRNA and protein degradation rate constants are supposed to be known
- Estimate 9 parameters
Synthetic data
Fig. 4. Recursive estimation of the maximal rate of Michaelis-Menten kinetics through time for the case $S = 1$ and sampling time $\Delta_t = 0.2$ (corresponds to 100 data points). Dash lines: true parameters. Solid lines: Estimated parameters along with their confidence intervals.
Fig. 5. Recursive estimation of Michaelis constants $k_{12}, k_{23}, k_{31}$ through time.
Fig. 3. The evolution of the true (dashed) and estimated (solid) protein concentrations.
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**Repressilator**

**JAK-STAT signaling pathway**

[Swameye, PNAS 2003]

- **ODE:**
  \[
  \begin{align*}
  \dot{x}_1(t) &= -a_1 x_1(t)u(t) + 2a_4 x_4(t)1_{\{t \geq \tau\}} \\
  \dot{x}_2(t) &= a_1 x_1(t)u(t) - 2a_4 x_2^2(t) \\
  \dot{x}_3(t) &= -a_3 x_3(t) + x_2^2(t) \\
  \dot{x}_4(t) &= a_3 x_3(t) - a_4 x_4(t)1_{\{t \geq \tau\}}
  \end{align*}
  \]

- **Observed variables**
  \[
  y_1 = x_2 + 2x_3 \\
  y_2 = x_1 + x_2 + 2x_3
  \]

- Experimental data: 16 time points
- \(\theta = (a_1, a_3, a_4)^\top\) is the parameters to be estimated
Fig. 12. Prediction of STAT5 phosphorylation and total amount of STAT5.
Conclusion

- A general framework based on nonlinear state-space models for describing biological networks
- Bayesian inference based on UKF for estimating parameters and hidden states from noisy and partially observed data

Ongoing work

- Unscented Kalman smoothing
- Particle smoothing