Learning parameters in ODEs
Application to biological networks

Florence d’Alché-Buc

Joint work with Minh Quach and Nicolas Brunel
IBISC FRE 3190 CNRS, Université d’Évry-Val d’Essonne, France
Nonlinear State-Space Model based on ODEs

Continuous time ODE model
\[
\begin{align*}
\frac{dx(t)}{dt} &= f(x(t), u(t); \theta) \\
y(t) &= H(x(t), u(t); \theta) + \epsilon(t)
\end{align*}
\]

The augmented system at discrete-time points \( t_0, t_1, \ldots, t_{N-1} \) possibly irregularly spaced

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

with
\[
F(x(t_k), u; \theta_k) = x(t_k) + \int_{t_k}^{t_{k+1}} f(x(\tau), u(\tau); \theta_k) d\tau
\]

\( u(\cdot) \) is a control variable
The hidden process is no more noisy (for sake of simplicity)
Timepoints can be irregularly spaced due to the integration (numerical)
Even if $f(.; \theta)$ is linear, the hidden process is not linear
Parameter estimation

- According the nature of function $f$, the graph of interactions between components may be encapsulated in $f$ or not
- In the next slides, we assume that the graph structure is given
- Current work includes coupling parameter estimation algorithms with stochastic search for the graph of interactions

Hidden state estimation

- For instance in Michaelis-Menten equations and Hill kinetics, recover proteins concentrations from gene expression observation
Parameter and hidden variable estimation (2)

- Prior on $x(t_0)$ and prior on $\theta$
- Learning as filtering (or smoothing) with an augmented approach
- Random initializations
Nonlinear state-space models

Results

Repressilator

JAK-STAT signaling pathway

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Learning parameters in ODEs
**Estimation of parameters**

Table: \( T = 25 \) observations. Average with std for 100 samples, each used for 50 random initialisations: case of Repressilator

<table>
<thead>
<tr>
<th>Parameter</th>
<th>True Parameter</th>
<th>UKF estimation</th>
<th>UKS estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>( v_1 )</td>
<td>150</td>
<td>150.50 ( \pm ) 4.14</td>
<td>151.49 ( \pm ) 4.51</td>
</tr>
<tr>
<td>( v_2 )</td>
<td>80</td>
<td>76.80 ( \pm ) 4.91</td>
<td>81.45 ( \pm ) 4.09</td>
</tr>
<tr>
<td>( v_3 )</td>
<td>100</td>
<td>118.01 ( \pm ) 17.2</td>
<td>98.41 ( \pm ) 7.45</td>
</tr>
<tr>
<td>( k_{1,2} )</td>
<td>50</td>
<td>51.27 ( \pm ) 3.63</td>
<td>46.35 ( \pm ) 3.44</td>
</tr>
<tr>
<td>( k_{2,3} )</td>
<td>30</td>
<td>31.21 ( \pm ) 2.81</td>
<td>29.07 ( \pm ) 2.64</td>
</tr>
<tr>
<td>( k_{3,1} )</td>
<td>40</td>
<td>37.8 ( \pm ) 2.95</td>
<td>39.71 ( \pm ) 2.85</td>
</tr>
</tbody>
</table>
**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.
Nonlinear state-space models

Results

JAK-STAT signaling pathway

ODE:

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

Observed variables

\[
\begin{align*}
y_1 &= x_2 + 2x_3 \\
y_2 &= (x_1 + x_2 + 2x_3)
\end{align*}
\]

Experimental data: 16 time points

\(\theta = (a_1, a_3, a_4)^T\) is the parameters to be estimated
Convergence of the prediction error

**Fig. 11.** Convergence of the prediction error when applying multiple UKF sweeps over the data set
Fig. 12. Prediction of STAT5 phosphorylation and total amount of STAT5.
Fig. 13. The evolution of the true (dashed) and estimated (solid) concentrations of the four unobserved variables.
Challenges in (dynamical) modeling approaches

- Identifiability of dynamical models $\rightarrow$ simpler models: nonparametric models
- Prior knowledge
- Scaling to large networks by mixture models
- Non stationarity by switching models (see Xing’s team work in ISMB 2009 and ICML 2009, linear models)
- Coupling parameter and structure learning
- **coupled systems**: metabolic and regulatory networks, protein-protein interactions and regulatory network