An overview of the use of hybrid models in biochemical networks

JOHN LYGEROS

Automatic Control Laboratory, ETH Zürich
WWW.CONTROL.ETHZ.CH
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The speakers

Konstantinos Koutroumpas

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Outline

1. Mathematical Modeling in Biology

2. Systems Biology

3. Hybrid Systems

4. Hybrid Systems Biology

5. Workshop Outline
Mathematical Modeling in Biology

- Long history, many levels
- Population dynamics
  - Single species
  - Predator-prey models
  - Ecosystems
- Epidemiology
Mathematical Modeling in Biology

- Organisms of parts thereof
  - Neurophysiology
  - Anesthesia
  - Exercise and rehabilitation
Mathematical Modeling in Biology

- Molecular level
  - Genes and protein coding
  - Protein-protein interactions
  - Signaling within the cell
  - Signaling between cells
Systems biology

- Here refers to mathematical modeling of biological processes at the molecular level
- Genes, proteins, and their interactions
- Field driven by abundance of data
  - Microarray
  - Imaging and microscopy
  - Reporter systems, micorarrays, bioinformatics, robotics
Systems biology

- Models based on biologists intuition
- Used to “correlate” large data sets
- Model predictions
  - Highlight “gaps” in understanding
  - Motivate new experiments
- Virtuous cycle
Example: DNA replication

- Microarray data:
  - Positions along genome
  - Efficiencies
  ~900 origins of replication
- Manual analysis impossible
- Develop stochastic model
- Monte-Carlo simulation
- Model predictions unrealistic
Example: DNA replication

- Predicted duration of DNA replication too long
- Many possible explanations
- Tested on the model
- Only two seem plausible
- New data will allow us to test one (hopefully!)
- Targeted experiments designed to test the other
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Hybrid systems

• Dynamical systems that involve interaction of discrete & continuous dynamics
• Systems with phased operation
  – Bouncing balls, walking robots
  – Systems controlled by valves, pumps, computers
  – Embedded systems
• Focus of interest for over a decade
Dynamical evolution

\[ \dot{x} \in F(q_3, x) \]

\[ x(0) \]

\[ R(q_3, q_2, x(t)) \rightarrow R(q_3, q_2, x(t')) \]

\[ \text{Continuous dynamics} \]

\[ \text{Discrete transition} \]

\[ \text{Guard} \]
Uncertainty

- Dynamical systems often deterministic: One solution for each initial condition
- Hybrid systems allow uncertainty in
  - Initial condition
  - Flow direction
  - Discrete & continuous state destinations
  - Choice between flowing and jumping
- “Traditionally” uncertainty worst case
- This may be too coarse for biological systems
- Stochastic hybrid systems: Probabilities
Hybrid Systems

Methods and computational tools
- Modeling & simulation
- Identification & observers
- Analysis & verification
- Controller design

Numerous successful applications
- Automotive & avionics
- Industrial processes
- Transportation
- Telecom & power networks
- Biochemical systems
Why hybrid systems biology?

Different modeling methods at molecular level

- Discrete: Finite states and their interactions
- Continuous: ODE, PDE
- Stochastic: Master equation, Markov chain
- Hybrid

Discrete models

Example: Directed and undirected graphs

Other examples: Bayesian & Boolean networks
Discrete models

• Advantages:
  – Easy to develop: Directly map biological intuition
  – Easy to analyze: Graph operations
  – Analysis can lead to interesting conclusions
    • Cycles suggest feedback relations
    • Sub-graphs suggest functional modules
    • Graph comparisons suggest evolutionary conserved mechanisms

• Disadvantages:
  – Somewhat coarse
  – No temporal variation or spatial information

• Alternative: Add continuous dynamics
Continuous models: ODE

- Model evolution of concentrations of RNA, proteins, etc.
- Chemical reactions, interdependencies lead to nonlinear differential equations
- Nonlinearities often due to sigmoidal activation functions

\[
\frac{d[CycB]}{dt} = k_1 - (k'_1 + k''_2 [Cdh1]) [CycB]
\]

\[
\frac{d[Cdh1]}{dt} = \frac{(k'_3 + k''_3 A)(1 - [Cdh1])}{J_3 + 1 - [Cdh1]} - \frac{k_4 m [CycB] [Cdh1]}{J_4 + [Cdh1]}.
\]

[CyclinB/Cdk dimers]

[Cdh1/APC complexes]

[Tyson & Novak, 1999]
Continuous models: ODE

• Advantages
  – Direct link to biochemical understanding
  – Standard nonlinear systems tools applicable (e.g. bifurcation analysis)

• Disadvantages
  – Model quickly becomes very complex
Continuous models: ODE

\[
\frac{d[CycB]}{dt} = k_1 - (k'_2 + k''_2 [Cdh1]) [CycB]
\]

\[
\frac{d[Cdh1]}{dt} = \frac{(k'_3 + k''_3 A)(1 - [Cdh1])}{J_3 + 1 - [Cdh1]} - \frac{k_4 m[CycB][Cdh1]}{J_4 + [Cdh1]}.
\]

[Tyson & Novak, 1999]

\[
\frac{d\text{Sic1}}{dt} = k_5 - k'_5 \text{Sic1} - k_6 \text{Sic1} + k_{pp} \text{Cdc14} \cdot \text{Sic1P} - k_j \text{Clb} \cdot \text{Sic1} + k_\mu \text{Tri} + k_{2c} \text{Tri}
\]

\[
\frac{d\text{Sic1P}}{dt} = k_p \text{Sic1} - k_{pp} \text{Cdc14} \cdot \text{Sic1P} - (k'_6 + k''_6)\text{Sic1P} - k_j \text{Clb} \cdot \text{Sic1P} + k_\mu \text{TriP} + k_{2c} \text{TriP}
\]

\[
\frac{d\text{Tri}}{dt} = k_j \text{Clb} \cdot \text{Sic1} - k_\mu \text{Tri} - k_{2c} \text{Tri} - k'_6 \text{Tri} - k_\mu \text{Tri} + k_{pp} \text{Cdc14} \cdot \text{TriP}
\]

\[
\frac{d\text{TriP}}{dt} = k_p \text{Tri} - k_{pp} \text{Cdc14} \cdot \text{TriP} + k_j \text{Clb} \cdot \text{Sic1P} - k_\mu \text{TriP} - k_{2c} \text{TriP} - (k'_6 + k''_6)\text{TriP}
\]

\[
\frac{d\text{Ctb}}{dt} = k_1 \text{mass} - k_j \text{Clb} \cdot \text{Sic1} + k_\mu \text{Tri} - k_j \text{Clb} \cdot \text{Sic1P} + k_\mu \text{TriP}
\]

\[
- k_2 \text{Ctb} + k'_6 \text{Tri} + (k''_6 + k''_6)\text{TriP}
\]

\[
\frac{d\text{Hct1}}{dt} = \frac{k_{hct}(1 - \text{Hct1})}{J_{hct} + 1 - \text{Hct1}} - \frac{k_{hct} \text{Hct1}}{J_{hct} + \text{Hct1}}
\]

\[
\frac{d\text{Cdc20}}{dt} = k_{as} \text{Ctb} - k_{as} \text{Cdc20} + k_{a1} \text{Cdc20} - k_{ad} \text{Cdc20}
\]

\[
\frac{d\text{Cdc20}_a}{dt} = k_{as} \text{Cdc20} - k_{as} \text{Cdc20}_a - k_{ad} \text{Cdc20}_a
\]

\[
\frac{d\text{INH}}{dt} = k_3 - k_1 \text{INH} \text{Cdc14} + k_4 \text{IC} - k_4 \text{Cdc20}_a \text{INH}
\]

\[
\frac{d\text{IC}}{dt} = k_1 \text{INH} \text{Cdc14} - k_4 \text{IC} - k_4 \text{Cdc20}_a \text{IC}
\]

\[
\frac{d\text{mass}}{dt} = \mu \text{mass}
\]

[Tyson & Novak 2001]
Continuous models: ODE

- **Advantages**
  - Direct link to biochemical understanding
  - Standard nonlinear systems tools applicable (e.g. bifurcation analysis)
- **Disadvantages**
  - Model quickly becomes very complex
  - Sensitivity w.r.t. parameter values
  - Concentration approximation often inaccurate
  - Deterministic
  - No spatial component
- **Alternative:** Abstract nonlinearities by switches
Continuous models: PDE

- Model evolution of concentrations
- But with a spatial component
- Reaction diffusion equations
- Can be model variations of concentrations
  - Between cells
  - Between different compartments in a cell
  - Between different areas in a nucleus
Continuous models: PDE

- Concentrations of chemicals, $x_i(t,l)$, $i=1, 2, \ldots, n$
- In parameterized by 1 dimension ($l$) + time ($t$)

\[ \frac{\partial x_i}{\partial t} = f_i(x) + d_i \frac{\partial^2 x_i}{\partial l^2} \]

- Reaction term (as for ODE)
- Diffusion term (spatial component)
Continuous models: PDE

- $n$ coupled PDE + boundary conditions
- Normally in 3 dimensions + time
- Disadvantages
  - Very difficult to solve
    - By hand for few chemicals, low dimension
    - Numerically?
  - Sensitivity w.r.t. parameter values
  - Concentration approximation often inaccurate
  - Deterministic
- Advantages
  - Fairly faithful representation of reality
  - Simplification often possible (eg. radial symmetry)
Stochastic master equations

- Treat every molecule separately
- State, $X$, number of molecules of chemicals
- Joint probability distribution $p(X, t)$
- Evolves according to $m$ reactions

$$\frac{\partial}{\partial t} p(X, t) = \sum_{j=1}^{m} [b_j - a_j p(X, t)]$$

Effect of reaction $j$
Stochastic master equations

• Advantages
  – Very faithful representation of reality
  – Can deal with few copies of molecules
  – Can be blended with/simplified to ODE models
  – Spatial component can be added

• Disadvantages
  – Very difficult to solve in general
  – Often resort to simplifications
  – Stochastic simulation
**Stochastic simulation [Gillespie]**

- Monte-Carlo type simulation
- State: Number of molecules of each chemical
- Algorithm
  1. Determine when next reaction will be (stochastic)
  2. Determine which reaction this will be (stochastic)
  3. Update system state according to reaction
  4. Repeat
- Complexity, efficient implementation
- Widely used in practice
- Spatial variation possible (e.g. step 1)
Why hybrid systems biology?

- Model exist to deal with discrete, continuous and stochastic aspects of the problem
- Often the interaction makes the difference
- Example: Cell cycle
Why hybrid systems biology?

• Example: Cell differentiation

Courtesy: J. Wittbrodt
Why hybrid systems biology?

- Time scale hierarchies
- Abstract nonlinearities by switches

\[
\dot{x}_i = k_i h(x_j, \theta_j, m) - l_i x_i
\]

Nonlinear

\[
\begin{cases} 
    k_i - l_i x_i & \text{if } x_j \geq \theta_j \\
    -l_i x_i & \text{else}
\end{cases}
\]

Piecewise affine
Why hybrid systems biology?

• PWA systems
  – Special type of hybrid systems
  – Not general nonlinear systems
  – Provide enough structure to allow some analysis

• Biological networks → special class of PWA
  – Dynamics decoupled
  – Switching boundaries aligned with the axes

• Special care is needed
  – Dynamics discontinuous
  – Sliding modes, pseudo equilibria
Stochastic hybrid systems

• In some cases stochastic terms central

• Examples:
  – Master equation, stochastic simulation
  – Cell cycle
  – Cell differentiation

• Stochastic hybrid models
  – Discrete states
  – Continuous states
  – Probabilistic representation of uncertainty
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Workshop overview

8.45 - 9.30 John Lygeros: An overview of hybrid models for biochemical systems
9:45 - 10.30 Zoe Lygerou: An introduction to information flows within the cell

11:00 - 11:45 Zoe Lygerou: Tools and approaches in modern biological science
12:00 - 12:45 Hidde de Jong: Qualitative analysis and verification of piecewise affine models of genetic regulatory networks

14:30 - 15.15 Delphine Ropers: Development and experimental validation of piecewise affine models of carbon starvation response in Escherichia coli
15:30 - 16:15 Giancarlo Ferrari-Trecate: Identification of deterministic piecewise affine models of genetic regulatory networks

16:45 - 17:30 John Lygeros: Stochastic hybrid models of DNA replication