Mathematical Tools for Systems Biology

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June 24, 2005
EMU
I = lac repressor
= protein which regulates transcription of lac mRNA (genes in blue)

Z = beta-galactosidase
= protein which cleaves lactose to produce glucose, galactose, and allolactose

Y = Lactose permease
= protein which transports lactose into the cell

A = Transacetylase (not used directly in lactose metabolism)

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Continuous Model for *lac* Operon

\[
\begin{align*}
\frac{dM}{dt} & = \alpha_M \frac{1 + K_1 (e^{-\mu \tau_M} A_{TM})^n}{K + K_1 (e^{-\mu \tau_M} A_{TM})^n} + \Gamma_0 - \tilde{\gamma}_M M \\
\frac{dB}{dt} & = \alpha_B e^{-\mu \tau_B} M_{TB} - \tilde{\gamma}_B B \\
\frac{dA}{dt} & = \alpha_A B \frac{L}{K_L + L} - 0_A B \frac{A}{K_A + A} - \tilde{\gamma}_A A \\
\frac{dL}{dt} & = \alpha_L P \frac{L_c}{K_{L_c} + L_c} - \beta_L P \frac{L}{K_{L_1} + L} - \beta_{L_2} B \frac{L}{K_{L_2} + L} - \tilde{\gamma}_L L \\
\frac{dP}{dt} & = \alpha_P e^{-\mu (\tau_P + \tau_B)} M_{TP + TB} - \tilde{\gamma}_P P
\end{align*}
\]

M = mRNA  
B = *beta*-galactosidase  
A = allolactose  
L = lactose (intracellular)  
P = permease

Yildrim and Mackey  
*Biophysical Journal* 84  
2003
Continuous Model with Dynamics

Steady-state values when $L_e = 8.0 \times 10^{-2}$ mM

$\bar{M} = 1.08 \times 10^{-3}$ mM
$\bar{B} = 7.35 \times 10^{-4}$ mM
$\bar{A} = 5.06 \times 10^{-1}$ mM
$\bar{P} = 1.51 \times 10^{-2}$ mM
### Discrete Model for \textit{lac} Operon

<table>
<thead>
<tr>
<th>Function</th>
<th>Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>( f_M )</td>
<td>( A )</td>
</tr>
<tr>
<td>( f_B )</td>
<td>( M )</td>
</tr>
<tr>
<td>( f_A )</td>
<td>( A \lor (L \land B) = A + LB + ALB )</td>
</tr>
<tr>
<td>( f_L )</td>
<td>( P \lor (L \land \neg B) = P + L(B + 1) + PL(B + 1) )</td>
</tr>
<tr>
<td>( f_P )</td>
<td>( M )</td>
</tr>
</tbody>
</table>

**Model assumptions**

- Transcription/translation = 1 time unit
- mRNA/protein degradation = 1 time unit
- Lactose always available
Discrete Model with Dynamics

(M, B, A, L, P)
Goals

• Construct other models of the lac operon.

• Discover 4 software packages for modeling and simulating biochemical networks.
Questions to Keep in Mind

• Purpose of each software?
• Does each accomplish its purpose?
• Benefits?
  – Life scientist
  – Computationalist
  – Theorist
• Limitations?
• Need for improvement? How?
Gepasi Biochemical Simulation

- Gepasi = Genetic pathway simulator
- Software for modeling biochemical systems
- Simulates kinetics of biochemical reactions
- Provides analytical tools to
  - fit models to data
  - optimize any function of the model
  - perform metabolic control, linear stability analysis
- Simplifies the task of model building

chemistry \rightarrow mathematics
(reactions) \rightarrow (matrices and diff eqs)
Biochemical Simulation

Model Definitions

• Define chemical **Reactions**.
• Define **Kinetics** (rules) for each reaction.
• Initialize **Metabolites**.

Tasks – **Run** simulation.

Plot – **Plot** the solutions.
Tasks

• Classify method as top-down and/or bottom-up.

• Change the number of time points run and sampled to zoom in.
  – Be sure to save as a new file.

• Increase the initial concentration of B.

• Change the kinetics on the synthesis of B.
Polynome • Polynome = set of discrete polynomial functions which describe a system

• Software for reverse engineering of biochemical networks

• Models = systems of polynomial functions
  – Each function gives dynamics of one variable

• Computes optimal model from time series
  – Data: wildtype or knockout time series
  – Uses computational algebra to
    • compute entire set of models that fit the data
    • selects the “minimal” model
Tasks

• Classify method as top-down and/or bottom-up.

• Create models for 1, 2, 3, 4 time series. Is there an improvement?

• Vary the variable order. How do models/dynamics change?
Discrete Visualizer of Dynamics

• Software for visualization of the dynamics of multi-state discrete models of biological networks.

• Models = systems of polynomial functions

• Computes
  – transition states from all possible initializations
  – statistics of the state space

• Graphs entire state space or a single trajectory
Tasks

• View different trajectories for a polynomial model. Are there fixed points or cycles?

- 0 0 0 0 0
- 0 1 0 0 0
- 0 0 0 1 0
- 2 2 2 2 2

• Choose an update schedule. Have the cycles/fixed points changed?

• View dependency graphs for two different models for the same data.

• Modify the functions to get cycles of different lengths.

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GINsim – Gene Interaction Network simulation

Software for modeling and simulation of genetic regulatory networks

Models = asynchronous, multivalued logical functions

Consists of a simulator of qualitative models of genetic regulatory networks based on a discrete, logical formalism

Simulates qualitative dynamical behavior
Qualitative analysis of regulatory graphs: a computational tool based on a discrete formal framework

Draw graph of the network.
*To save every time, first Edit ➔ Choose DTD, then save.*

Current Selection

- Add and define values of nodes.
- Add and define values of edges.

Logical Parameters

- Add interactions.
- Define value at which interaction occurs.

Actions ➔ Run simulation

- Initialize variables.
- Choose updating of variables.

Actions ➔ Layout Algorithms
Tasks

• Classify method as top-down and/or bottom-up.

• Compute the state space for the trajectory starting $0 0 0 0 0$.
  – Is there a stable steady state?
  – Is there an initialization with multiple steady states?

• Compare trajectories for both types of updating.
  – $2 1 2 0 1$
  – $1 1 1 1 1$
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