Introduction to Biological Modeling

Lecture 2: Modeling dynamics
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Last week
• Why model biology?
• Example: E. coli chemotaxis
• Typical modeling progression

Think about
What aspects of your research are ready for modeling?
What might you learn from it?

Reading

Dynamic cells

All cell systems are dynamic
• cell cycle
• circadian rhythms
• signaling
• development
• cell motility
• apoptosis
• metabolism*

Tyson, 1991
• initial “good” model of eukaryotic cell cycle
**Eukaryotic cell cycle**

*Cycle times*
- 8 min. in fly embryo
- 30 min. in *Xenopus* early embryo
- 12 hours in fast growing mammalian tissues
- Year or longer in mammalian liver stopped in human neurons and skeletal muscles

**Cell cycle checkpoints**

*Question*
How does the “controller” work?

**Cyclins and Cdk**

*Cdk* = cyclin dependent kinase
- p34, from mol. weight
- Cdc28 in budding yeast
- Cdk1 in human
- cdc2 in fission yeast

Cyclin
- Lots of different cyclins

Cdk + cyclin = “Start kinase” MPF

**Xenopus life cycle**

1st round of meiosis stops at G2 checkpoint
- Cycling stopped
- Egg travels down oviduct and is laid
- Rapid cell divisions without growth
- Cell divisions depend on growth
- Fertilization
- Fertilized egg divides without growing
- Sperm cell group without dividing
- Midblastula transition
- Egg
- Adult frog

2nd round of meiosis stops at metaphase arrest

**MPF and cyclin in early embryo**

*MPF* = M phase promoting factor
- Cyclin and Cdk
- Midblastula transition
- Cdk A, B, and C
- Cyclin
- Cyclin dependent kinase
- MPF
- Cdk1 and cyclin A
- Interphase
- Metaphase
- Anaphase
- Telophase
Step 1

Step 2

Step 3


Credit: http://www.satyaprakashnayak.com/Projects.html, which says it’s from Tyson and Novak.


Mass action kinetics: reaction rate ~ reactant concentrations

\[ \frac{d[M]}{dt} = k_{M}M - k_{M}P[M] \]

M production rate = loss rate
\[ \frac{d[M]}{dt} = 0 \]

2 stable points, 1 unstable point

From reactions to equations

All straight-forward, except reaction 4

Positive feedback can cause bistability

Add in reaction 5

\[ \frac{d[M]}{dt} = -k_{M}P[M] + k_{M}P[M] \]

Positive feedback can cause bistability

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The mathematical model

Parameter | Value
---|---
$k_{\text{C2}(\text{CT})}$ | 0.015 min$^{-1}$
$k_{y}$ | 6
$k_{\text{CT}}$ | 200 min$^{-1}$
$k_{y}$ | 0
$k_{\text{CP}}$ | 0.018 min$^{-1}$
$k_{\text{CP}}$ | 0
$k_{x}$ | 0.1–10 min$^{-1}$ (adjustable)
k_{x}$ | 0.6 min$^{-1}$
$k_{\text{P}}$ | $>4k_{y}$
$k_{\text{M}}$ | $>4k_{x}$

$d[C2]/dt = k_{\text{C2}(\text{CT})} - k_{\text{CP}}[C2] + k_{\text{CP}}[\text{CP}]
\text{d}[\text{CP}]/dt = -k_{\text{CP}}[\text{CP}][\text{Y}] + k_{\text{P}}[\text{P}][\text{C2}] - k_{\text{CP}}[\text{CP}]
\text{d}[\text{P}]/dt = k_{\text{CP}}[\text{P}][\text{Y}] - k_{\text{P}}[\text{P}][\text{M}] + k_{\text{P}}[\text{P}][\text{M}]
\text{d}[\text{M}]/dt = k_{\text{P}}[\text{P}][\text{M}] - k_{\text{P}}[\text{P}][\text{M}] + k_{\text{M}}[\text{M}]
\text{d}[\text{Y}]/dt = k_{\text{P}}[\text{P}][\text{M}] + k_{\text{P}}[\text{P}][\text{M}]
\text{d}[\text{Y}]/dt = k_{\text{P}}[\text{P}][\text{M}]

Simulation tools

Excel - surprisingly good for very simple models, $\$
MatLab - excellent multi-purpose tool, lots of extensions, $$
Mathematica - also excellent; better for analytical work, $$
Copasi - designed for cell biology simulations, has GUI
SBW - Systems Biology Workbench, front end to lots of simulators.
lots of others ...

Getting the Tyson 1991 model

Cell Cycle Database: [http://www.itb.cnr.it/cellcycle/](http://www.itb.cnr.it/cellcycle/)
Lots of good cell cycle information

BioModels database

[http://www.ebi.ac.uk/biomodels-main/](http://www.ebi.ac.uk/biomodels-main/)
Lots of published models, all written in SBML
Get the model from either Cell Cycle Database and simulate its "simulable" module, or get it from BioModels and simulate it with Copasi.

Simulation results

stable steady-state, but excitable

\[ k_4 = 180 \text{ min}^{-1}, \quad k_6 = 2 \text{ min}^{-1} \]

similar to late embryo growth-limited cell cycle;

A large enough perturbation triggers excitation

Phase diagram for system behaviors

Step 2

Growth-limited cycles

cell volume increase lowers \( k_6 \), lower \( k_6 \) triggers mitosis

DNA replication doubles \( k_6 \)

Step 1

Experimental Data

Simulation

Step 3

Mathematical Model (ODEs, SDEs, PDEs, etc.)

Step 4

Simulate

Step 5

Simulation Output

Automated Analysis

Human Analysis

Publication
Summary of model results

**Good aspects**
- Biology is basically correct.
- Represents all 3 Xenopus cell cycle stages: metaphase arrest, early embryo, and growth-limited cycling.
- MPF and cyclin curves qualitatively agree with experiment.

**Bad aspects**
- Roles of cdc25 and wee1 are not clear.
- Positive feedback \( F(M) \) is ad hoc.
- \( k_6 \) oscillation in growth-limited cycling is speculative.

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**A substrate-depletion oscillator**

“Sniffers, buzzers, toggles, and blinkers” interpretation

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**Summary**

Cell cycle overview
Model development
Model equations from reactions
- Mass action kinetics
Positive feedback
- Can cause bistability
Parameter choices
- Few matter, group as possible, explore some
Databases
- Cell cycle database, BioModels
Simulation tools
- Copasi
Tyson’s model results
- Metaphase arrest, early embryo, growth-limited cycling
Homework

Copasi
Download Copasi (Google for "copasi download" and explore some of the examples that come with it.

Read