Introduction to Biological Modeling

Lecture 2: Modeling dynamics
Sept. 29, 2010

Steve Andrews

Brent lab, Basic Sciences Division, FHCRC

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
Tyson, Chen, and Novak "Sniffers, buzzers, toggles, and blinkers: dynamics of regulatory and signaling pathways in the cell" *Current Opinion in Cell Biology* 15:221-231, 2003.

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

Proc. Natl. Acad. Sci. USA
Vol. 88, pp. 7328–7332, August 1991
Cell Biology

Modeling the cell division cycle: cdc2 and cyclin interactions

(maturation promoting factor/metaphase arrest/*wee1*/*cdc25*)

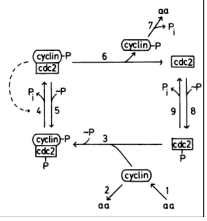
JOHN J. TYSON

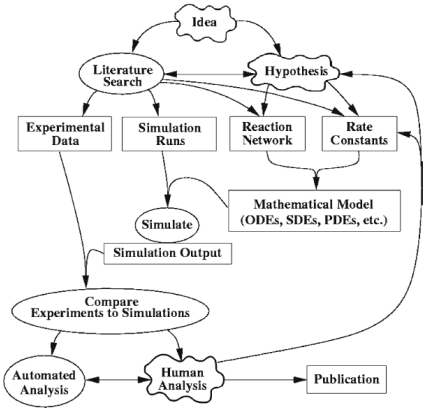
Department of Biology, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061

Communicated by David M. Prescott, May 20, 1991 (received for review January 23, 1991)

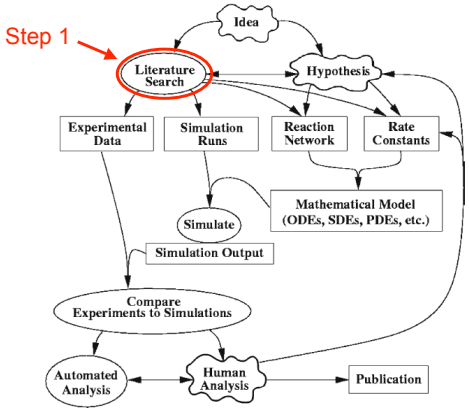
ABSTRACT **The proteins cdc2 and cyclin form a heterodimer (maturation promoting factor) that controls the major events of the cell cycle. A mathematical model for the interactions of cdc2 and cyclin is constructed. Simulation and analysis of the model show that the control system can operate in three modes: as a steady state with high maturation promoting factor activity, as a spontaneous oscillator, or as an excitable switch. We associate the steady state with metaphase arrest in unfertilized eggs, the spontaneous oscillations with rapid division cycles in early embryos, and the excitable switch with growth-controlled division cycles typical of nonembryonic cells.**

Passage through the cell cycle is marked by a temporally organized sequence of events including DNA replication, mitosis, and the appearance of certain cell-cycle specific



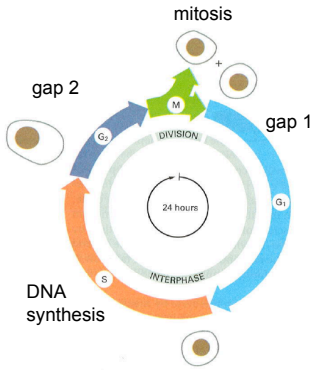


Credit: Shaffer et al., *Methods in Molecular Biology, Systems Biology,* (Maly, ed.) 500:81, 2009.



Credit: Shaffer et al., *Methods in Molecular Biology, Systems Biology,* (Maly, ed.) 500:81, 2009.

Eukaryotic cell cycle



Cycle times

8 min. in fly embryo

30 min. in *Xenopus* early embryo

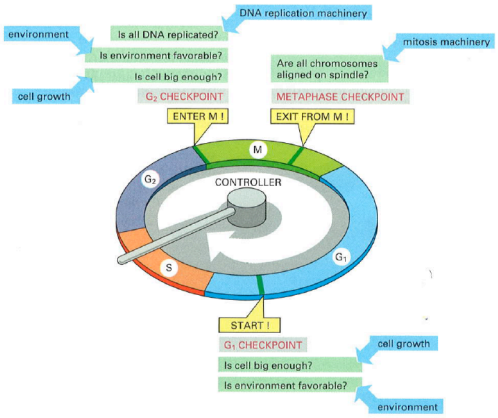
12 hours in fast growing mammalian tissues

year or longer in mammalian liver

stopped in human neurons and skeletal muscles

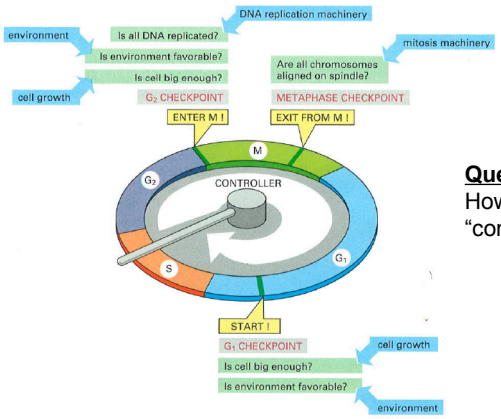
Credit: Alberts, et al. *Molecular Biology of the Cell*, 3rd ed., 1994.

Cell cycle checkpoints



Credit: Alberts, et al. *Molecular Biology of the Cell*, 3rd ed., 1994.

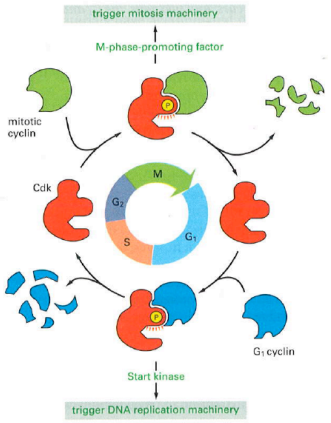
Cell cycle checkpoints



Question
How does the "controller" work?

Credit: Alberts, et al. *Molecular Biology of the Cell*, 3rd ed., 1994.

Cyclins and Cdk



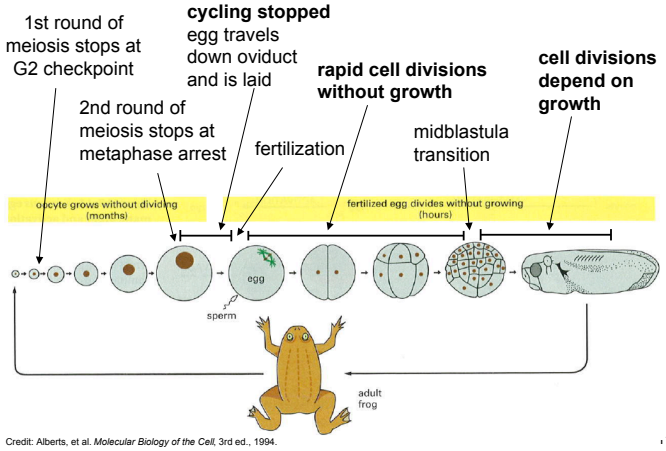
Cdk =
cyclin dependent kinase
p34, from mol. weight
Cdc28 in budding yeast
Cdk1 in human
cdc2 in fission yeast

cyclin
lots of different cyclins

Cdk + cyclin =
"Start kinase"
MPF

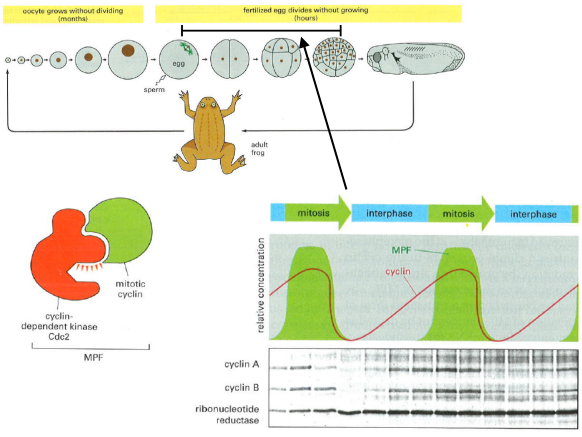
Credit: Alberts, et al. *Molecular Biology of the Cell*, 3rd ed., 1994.

Xenopus life cycle

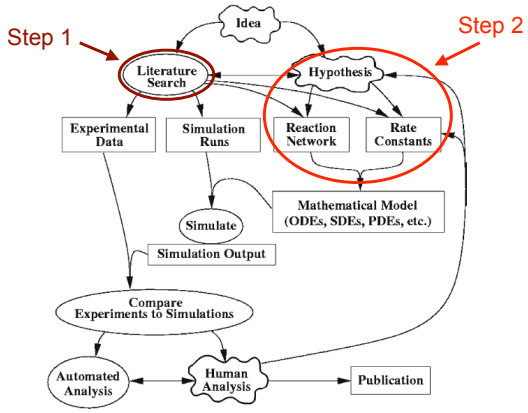


Credit: Alberts, et al. *Molecular Biology of the Cell*, 3rd ed., 1994.

MPF and cyclin in early embryo

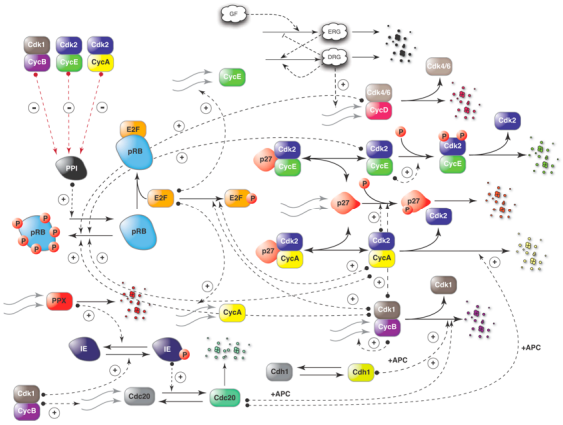


Credit: Alberts, et al. *Molecular Biology of the Cell*, 3rd ed., 1994.



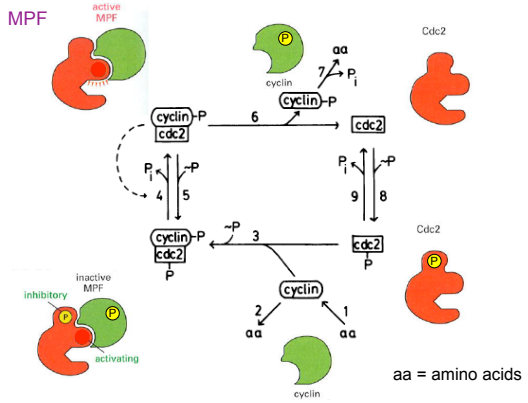
Credit: Shaffer et al., *Methods in Molecular Biology, Systems Biology,* (Maly, ed.) 500:81, 2009.

Cell cycle network



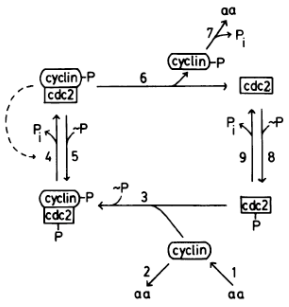
Credit: http://satyaprakashnayak.com/Projects.html, which says it's from Tyson and Novak.

Tyson's model (1991)



Credit: Alberts, et al. *Molecular Biology of the Cell,* 3rd ed., 1994; Tyson, *Proc. Natl. Acad. Sci. USA* 88:7328, 1991.

Tyson's model (1991)



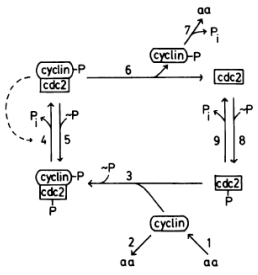
includes
- core cdc2-cyclin interactions

ignores
- cdc2 phosphorylation at T167
- attributes cyclin degradation to phosphate, not ubiquitin
- MPF enhancement of cyclin degradation
- cell size control, wee1, and cdc25
- downstream effects

assumptions
- total amount of cdc2 is fixed
- phosphorylation in rxn 3 is much faster than dimerization
- several parameter relations ...

Credit: Tyson, *Proc. Natl. Acad. Sci. USA* 88:7328, 1991.

Tyson's model (1991)

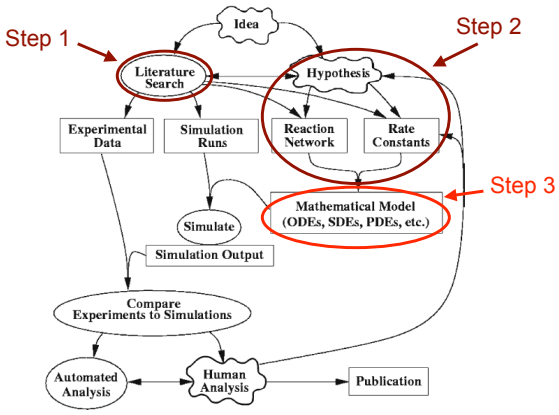


Parameter	Value
k_1[aa]/[CT]	0.015 min^{-1}
k_2	0
k_3[CT]	200 min^{-1}
k_4	10–1000 min^{-1} (adjustable)
k_4'	0.018 min^{-1}
k_5[~P]	0
k_6	0.1–10 min^{-1} (adjustable)
k_7	0.6 min^{-1}
k_8[~P]	>>k_9
k_9	>>k_6

* [CT] = total cdc2

Note
- Many parameters don't matter, and so are set to 0, or >>k_2
- Fewer parameters are needed by grouping multiple unknowns together, e.g. k_1[aa]/[CT]
- The model is explored with respect to the adjustable parameters.

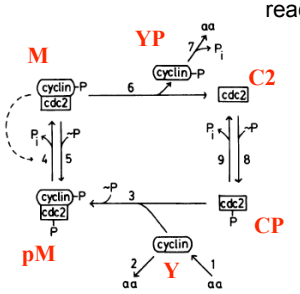
Credit: Tyson, *Proc. Natl. Acad. Sci. USA* 88:7328, 1991.



Credit: Shaffer et al., *Methods in Molecular Biology, Systems Biology,* (Maly, ed.) 500:81, 2009.

From reactions to equations

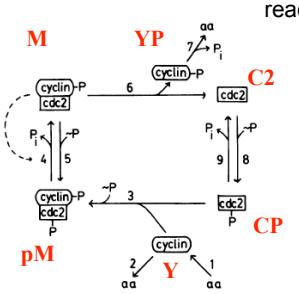
Mass action kinetics:
reaction rate ~ reactant concentrations



$$d[C2]/dt = k_6[M] - k_8[\sim P][C2] + k_9[CP]$$

From reactions to equations

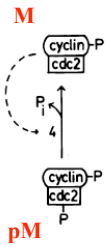
Mass action kinetics:
reaction rate ~ reactant concentrations



$$d[C2]/dt = k_6[M] - k_8[\sim P][C2] + k_9[CP]$$
$$d[CP]/dt = -k_3[CP][Y] + k_8[\sim P][C2] - k_9[CP]$$
$$d[pM]/dt = k_3[CP][Y] - [pM]F([M]) + k_5[\sim P][M]$$
$$d[M]/dt = [pM]F([M]) - k_5[\sim P][M] - k_6[M]$$
$$d[Y]/dt = k_1[aa] - k_2[Y] - k_3[CP][Y]$$
$$d[YP]/dt = k_6[M] - k_7[YP]$$

All straight-forward,
except reaction 4

Reaction 4: positive feedback



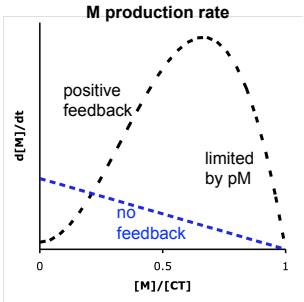
No feedback

$$\frac{d[M]}{dt} = k_4[pM]$$

With feedback

$$\frac{d[M]}{dt} = [pM]F([M])$$

$$F([M]) = k_4' + k_4\left(\frac{[M]}{[CT]}\right)^2$$

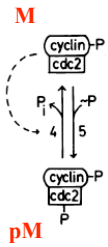


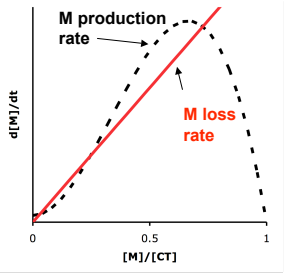
* [CT] = total cdc2, which is constant in this model

Positive feedback can cause bistability

Add in reaction 5

$$\frac{d[M]}{dt} = [pM]\left(k_4' + k_4\left(\frac{[M]}{[CT]}\right)^2\right) - k_5[\sim P][M]$$

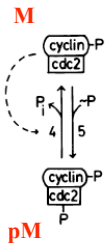


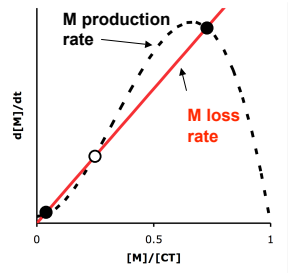


Positive feedback can cause bistability

Add in reaction 5

$$\frac{d[M]}{dt} = [pM]\left(k_4' + k_4\left(\frac{[M]}{[CT]}\right)^2\right) - k_5[\sim P][M]$$



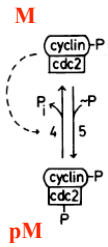


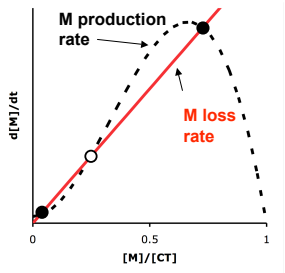
fixed points
production rate = loss rate
$d[M]/dt = 0$

Positive feedback can cause bistability

Add in reaction 5

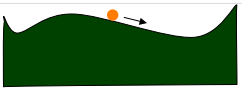
$$\frac{d[M]}{dt} = [pM]\left(k_4' + k_4\left(\frac{[M]}{[CT]}\right)^2\right) - k_5[\sim P][M]$$



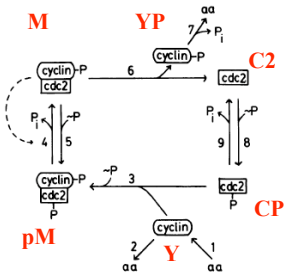


fixed points
production rate = loss rate
$d[M]/dt = 0$

2 stable points,
1 unstable point



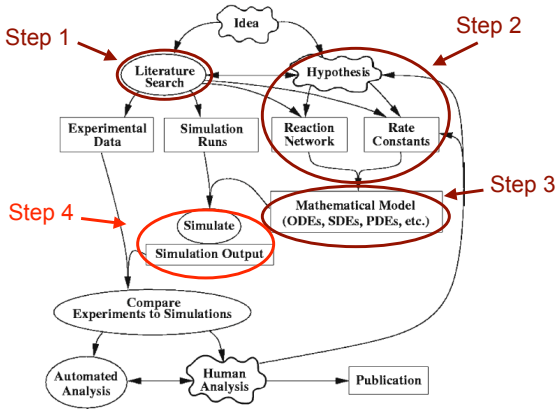
The mathematical model



Parameter	Value
k_1[aa]/[CT]	0.015 min^{-1}
k_2	0
k_3[CT]	200 min^{-1}
k_4	10–1000 min^{-1} (adjustable)
k_4'	0.018 min^{-1}
k_5[~P]	0
k_6	0.1–10 min^{-1} (adjustable)
k_7	0.6 min^{-1}
k_8[~P]	>>k_9
k_9	>>k_6

$$d[C2]/dt = k_6[M] - k_8[\sim P][C2] + k_9[CP]$$
$$d[CP]/dt = -k_3[CP][Y] + k_8[\sim P][C2] - k_9[CP]$$
$$d[pM]/dt = k_3[CP][Y] - [pM]F([M]) + k_5[\sim P][M]$$
$$d[M]/dt = [pM]F([M]) - k_5[\sim P][M] - k_6[M]$$
$$d[Y]/dt = k_1[aa] - k_2[Y] - k_3[CP][Y]$$
$$d[YP]/dt = k_6[M] - k_7[YP]$$

Credit: Tyson, *Proc. Natl. Acad. Sci. USA* 88:7328, 1991.



Credit: Shaffer et al., *Methods in Molecular Biology, Systems Biology*, (Maly, ed.) 500:81, 2009.

Simulation tools

Excel - surprisingly good for very simple models, $

MatLab - excellent multi-purpose tool, lots of extensions, $$

Mathematica - also excellent; better for analytical work, $$

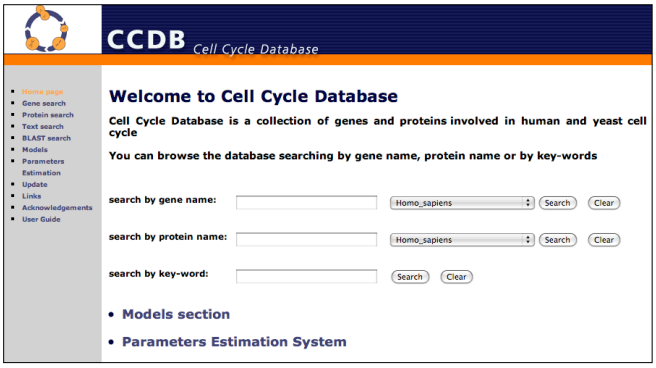
Copasi - designed for cell biology simulations, has GUI

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/
Lots of good cell cycle information



Cell cycle database models

Models section has
- 26 cell cycle models
- 14 in SBML
- 12 "simulable" modules

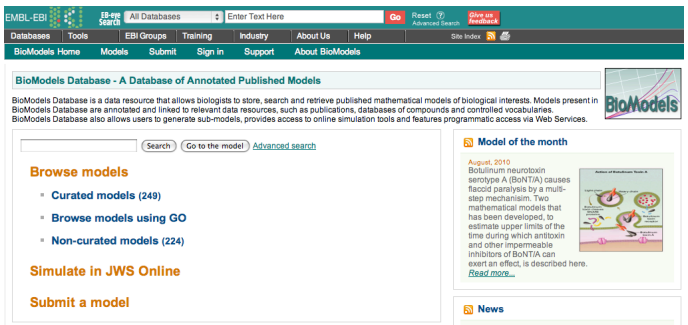
SBML
- Systems Biology Markup Language
- XML language
- A computer-readable standard language that many simulators use.

```
<reaction metaid="_000011" id="Reaction2" name="cdc2k
phosphorylation" reversible="false">
<listOfReactants>
<speciesReference species="C2"/>
</listOfReactants>
<listOfProducts>
<speciesReference species="CP"/>
</listOfProducts>
<kineticLaw>
<math xmlns="http://www.w3.org/1998/Math/MathML">
<apply>
<times/>
<ci> cell </ci>
<ci> C2 </ci>
<ci> k8notP </ci>
</apply>
</math>
<listOfParameters>
<parameter metaid="_840213" id="k8notP" value="1000000"/>
</listOfParameters>
</kineticLaw>
</reaction>
```


BioModels database

http://www.ebi.ac.uk/biomodels-main/

lots of published models, all written in SBML

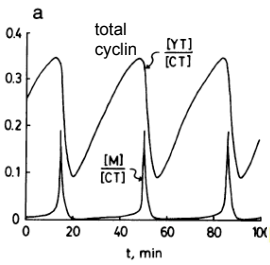


Get the model from either Cell Cycle Database and simulate its “simulable” module, or get it from BioModels and simulate it with Copasi.

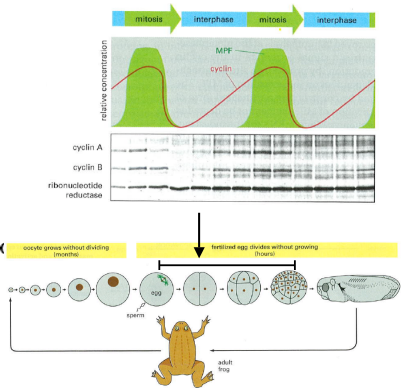
Simulation results

stable oscillations

k_4 = 180 min^{-1}, k_6 = 1 min^{-1}



similar to early embryo oscillations

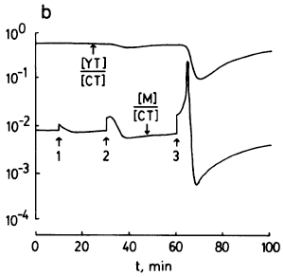


Credit: Alberts, et al. *Molecular Biology of the Cell*, 3rd ed., 1994; Tyson, *Proc. Natl. Acad. Sci. USA* 88:7328, 1991.

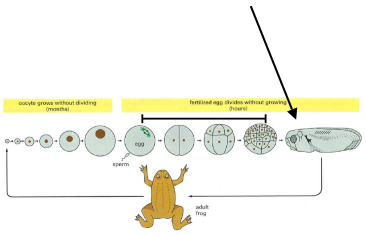
Simulation results

stable steady-state, but excitable

k_4 = 180 min^{-1}, k_6 = 2 min^{-1}



similar to late embryo growth-limited cell cycle;

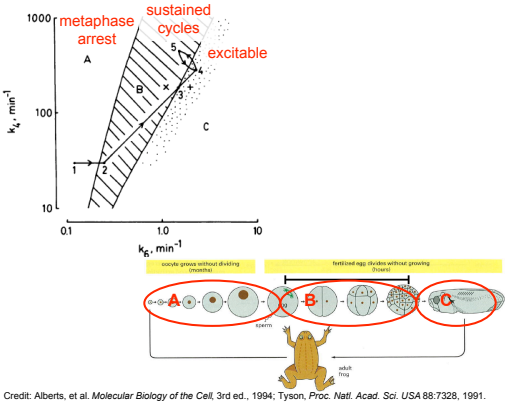


a large enough perturbation triggers excitation

Credit: Alberts, et al. *Molecular Biology of the Cell*, 3rd ed., 1994; Tyson, *Proc. Natl. Acad. Sci. USA* 88:7328, 1991.

Simulation results

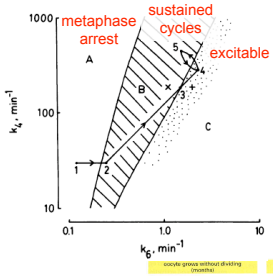
Phase diagram for system behaviors



Credit: Alberts, et al. *Molecular Biology of the Cell*, 3rd ed., 1994; Tyson, *Proc. Natl. Acad. Sci. USA* 88:7328, 1991.

Simulation results

Phase diagram for system behaviors

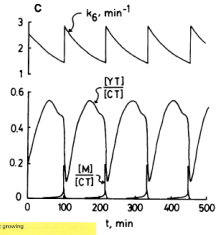


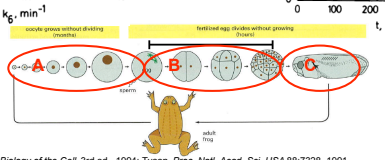
Growth-limited cycles

cell volume increase lowers k_6

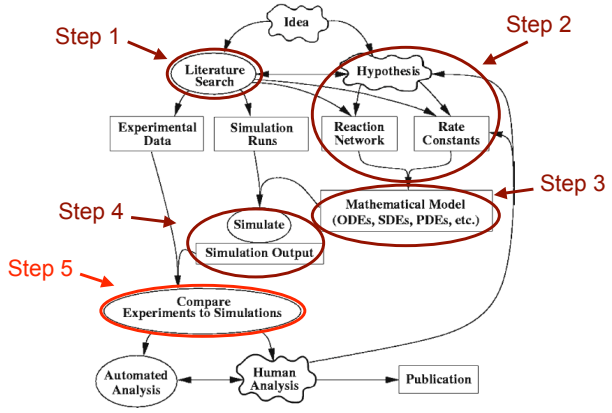
lower k_6 triggers mitosis

DNA replication doubles k_6



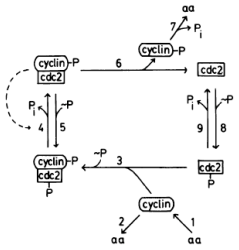


Credit: Alberts, et al. *Molecular Biology of the Cell*, 3rd ed., 1994; Tyson, *Proc. Natl. Acad. Sci. USA* 88:7328, 1991.



Credit: Shaffer et al., *Methods in Molecular Biology, Systems Biology*, (Maly, ed.) 500:81, 2009.

Summary of model results



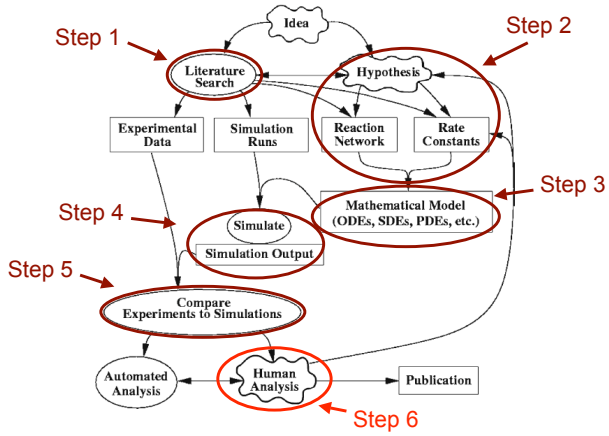
Good aspects

- 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

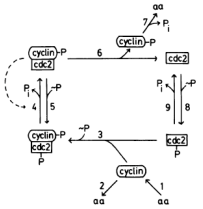
Credit: Tyson, *Proc. Natl. Acad. Sci. USA* 88:7328, 1991.

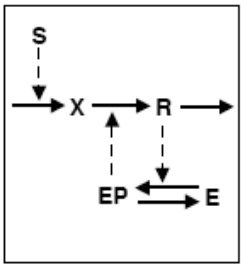


Credit: Shaffer et al., *Methods in Molecular Biology, Systems Biology,* (Maly, ed.) 500:81, 2009.

A substrate-depletion oscillator

"Sniffers, buzzers, toggles, and blinkers" interpretation

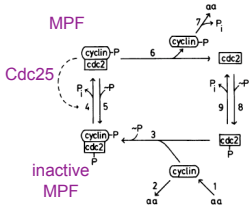


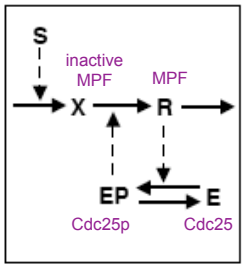


Credit: Tyson, *Proc. Natl. Acad. Sci. USA* 88:7328, 1991; Tyson *et al. Current Opinion in Cell Biology* 15:221, 2003.

A substrate-depletion oscillator

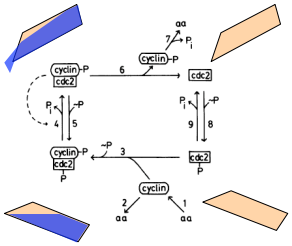
"Sniffers, buzzers, toggles, and blinkers" interpretation





Credit: Tyson, *Proc. Natl. Acad. Sci. USA* 88:7328, 1991; Tyson *et al. Current Opinion in Cell Biology* 15:221, 2003.

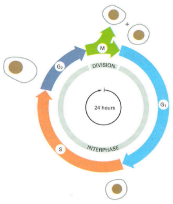
A substrate-depletion oscillator



Credit: http://www.aspencountry.com/product.asp?dept_id=460&pfid=35192; Tyson, *Proc. Natl. Acad. Sci. USA* 88:7328, 1991.

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
- Generalizing results



Homework

Copasi

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

Read

Covert, Schilling, Famili, Edwards, Goryanin, Palsson, “Metabolic modeling of microbial strains *in silico*” *TRENDS in Biochemical Sciences* 26:179, 2001.