Introduction to Biological Modeling

Lecture 1: Introduction
Sept. 22, 2010

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Brent lab, Basic Sciences Division, FHCRC

About me

- Background: experimental chemical physics
- Changed to computational biology in 2001
- Focusing on spatial simulations of cellular systems
- Joined Hutch last year

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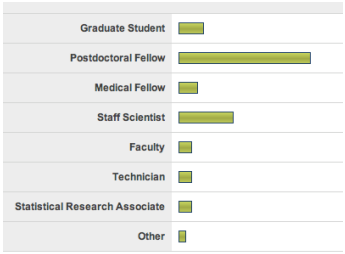
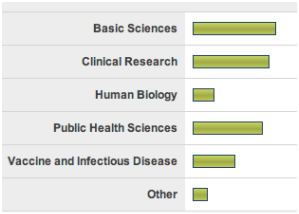
About you

https://www.surveymonkey.com/s/biologicalmodeling

You are ...



Your divisions are ...



Backgrounds include: genetics, proteomics, epidemiology, molecular biology, biochemistry, etc.

~ 25% of you have modeling experience

About you

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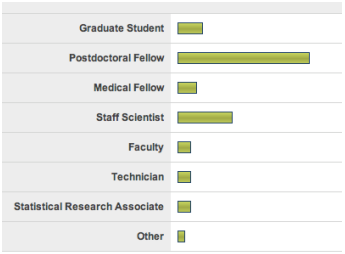
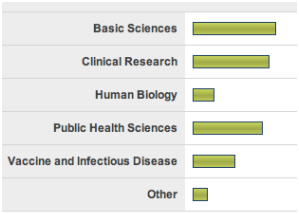


Your divisions are ...



Backgrounds include: genetics, proteomics, epidemiology, molecular biology, biochemistry, etc.

~ 25% of you have modeling experience

Please ask questions and share your knowledge in this class!

About this class

Introduction to Biological Modeling

Broad Scope
dynamics
metabolism
gene networks
stochasticity
development
mechanics
cancer

primary focus is systems within cells
(not tissues, physiology, epidemiology, ecology ...)

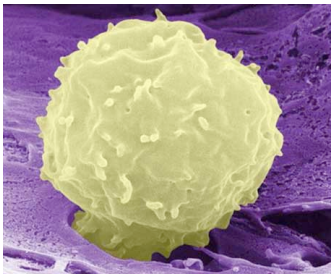
today's class
(not statistics, bioinformatics,...)

Why model biology?

Example: *E. coli* chemotaxis

Typical modeling progression

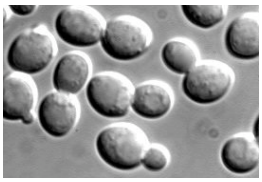
A cell is like a clock



closed compartment, complex internal machinery,
does interesting things

Credits: guardian.co.uk, January 8, 2009; http://www.faqs.org/photo-dict/phrase/409/alarm-clock.html

Make a simplified model system ...

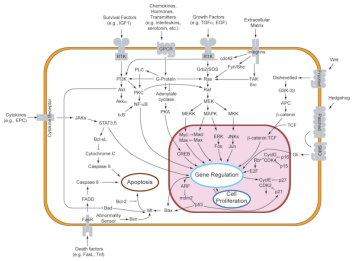


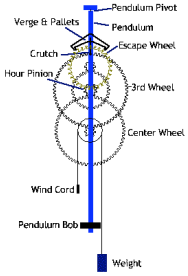
Credits: http://www.acad.carleton.edu/curricular/BIOL/faculty/szweifelindex.html; http://retrotoys.com/index.php

... experiment on it ...

Credits: Edyta Zielinska, *The Scientist* 21: 36, 2007; http://www.thinkgeek.com/geek-kids/3-7-years/c1de/

... and summarize what we know





Cartoons convey basic concepts,
but we still don't fully understand

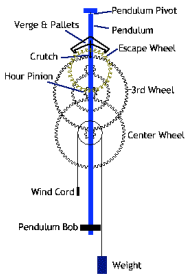
Credits: Wikipedia, public domain; http://www.woodenworksclocks.com/Design.htm

To understand, we need to create a model that:

- is precise
- accounts for the important facts
- ignores the unimportant facts
- allows us to explore the system dynamics
  ... and build an understanding

We don't truly understand until
we can make accurate predictions

A clock model



Pendulum period: $T = 2\pi\sqrt{\frac{l}{g}}$

Gear ratio: $\frac{\text{seconds}}{\text{revolution}} = \frac{T \cdot EW \cdot G_1 \cdot G_2}{P_1 \cdot P_2}$

This model is a hypothesis that
allows quantitative predictions

Credits: http://www.woodenworksclocks.com/Design.htm

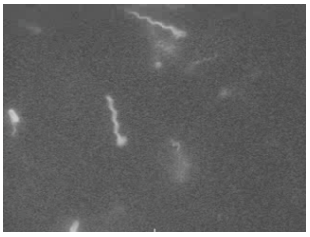
Why model biology?

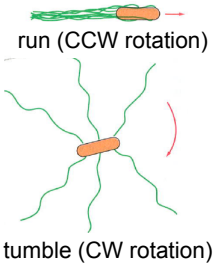
Example: *E. coli* chemotaxis

Typical modeling progression

E. coli swimming

E. coli cells "run" and "tumble"

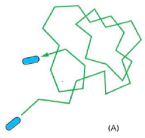




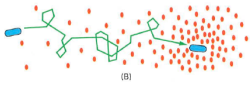
Credits: http://www.rowland.harvard.edu/labs/bacteria/showmovie.php?mov=fluo_fil_leave;
Alberts, Bray, Lewis, Raff, Roberts, and Watson, *Molecular Biology of the Cell, 3rd ed.* Garland Publishing, 1993.

E. coli chemotaxis

no attractant
⟶ unbiased random walk



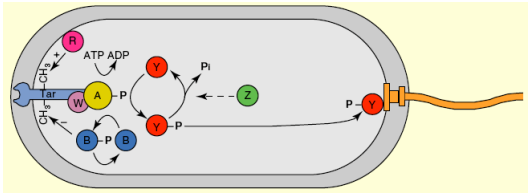
with attractant
⟶ biased random walk



If attractant concentration increases, cells *run longer*
If attractant concentration decreases, cells *tumble sooner*

Credit: Alberts, Bray, Lewis, Raff, Roberts, and Watson, *Molecular Biology of the Cell, 3rd ed.* Garland Publishing, 1993.

E. coli chemotaxis signal transduction



Signal transduction causing tumble

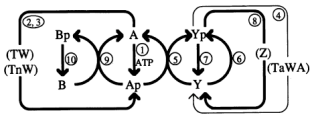
1. Tar (receptor) activates CheA
2. CheA autophosphorylates
3. CheA phosphorylates CheY
4. CheYp diffuses and binds to motor
5. Motor switches to CW, causing tumble
6. CheZ dephosphorylates CheY

Attractant binding decreases activities, suppressing tumbles

Credit: Andrews and Arkin, Curr. Biol. 16:R523, 2006.

First chemotaxis signal transduction model

Bray, Bourret, and Simon, 1993



Simple model:
- only addressed phospho-relay (no adaptation)
- *no* spatial, stochastic, or allostery detail
- 8 proteins, 18 reactions
- many guessed parameters

Credit: Bray, Bourret, Simon, Mol. Biol. Cell 4:469, 1993.

Model predictions vs. mutant data

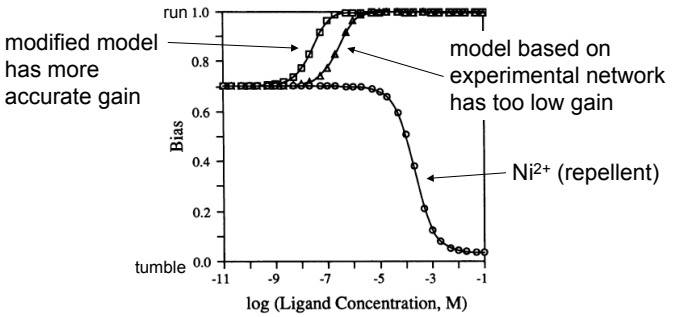
Table 5. Comparison of simulated and observed chemotactic behavior of mutant bacteria

Genotype	Bias: Simulated	Bias: Observed	Interpretation in terms of *bct 1.1* model	References
Single null mutants				
T^{-} [b]	sm	sm	Most Yp made by TW-stimulated A	Liu and Parkinson (1989)
B^{-}	tm	tm	More p flows to Y in absence of B	Parkinson (1978)
W^{-}	sm	sm	Most Yp made by TW-stimulated Y	Parkinson (1978)
A^{-}	sm	sm	No Yp	Parkinson (1978)
Y^{-}	sm	sm	No Yp	Parkinson (1978)
Z^{-}	tm	tm	Yp increases in absence of Z	Parkinson (1978)
Multiple null mutants				
$T^{-}Z^{-}$	wt	wt	Unstimulated A makes enough Yp in absence of Z	Liu and Parkinson (1989)
$B^{-}Z^{-}$	tm	?	More p flows to Y in absence of B and Z	
$T^{-}B^{-}Z^{-}$	tm	?	More p flows to Y in absence of B and Z	
$W^{-}Z^{-}$	wt	wt	Unstimulated A makes enough Yp in absence of Z	Liu and Parkinson (1989)
$T^{-}W^{-}Z^{-}$	wt	wt	Unstimulated A makes enough Yp in absence of Z	Liu and Parkinson (1989)
$A^{-}Z^{-}$	sm	sm	No Yp, even in absence of Z	Liu and Parkinson (1989)
$Y^{-}Z^{-}$	sm	sm	No Yp	Liu and Parkinson (1989)
$B^{-}Y^{-}Z^{-}$	sm	sm	No Yp	Wolfe *et al.* (1987)
Overproduction mutants				
T^{2+} [b]	sm[c]	sm	T overproduction sequesters A and TA complex	Liu and Parkinson (1989)
B^{2+}	sm	sm	B removes phosphate from A, thus reducing Yp	Stewart *et al.* (1988)
W^{2+}	sm	sm	W overproduction sequesters A in AW complex	Liu and Parkinson (1989), Sanders *et al.* (1989)
A^{2+}	tm[d]	sm	A overproduction leads to more Yp	Stewart *et al.* (1988)
Y^{2+}	tm	tm	Y overproduction leads to more Yp	Clegg and Koshland (1984)
Z^{2+}	sm	sm	Z stimulates loss of Yp	Kuo and Koshland (1987)

47 comparisons:
33 agreed, 8 differed, 6 had no experimental data

Quantitative model exploration

Dose-response curve for motor bias after adding different amounts of ligand



Credit: Bray, Bourret, Simon, Mol. Biol. Cell 4:469, 1993.

Model summary

Successes
- agreed with most mutant data
- qualitative trends agree with experiment

Failures
- failed for some mutant data
- some parameters had to be way off from experiment
- insufficient sensitivity and gain

Conclusions
- pathway is basically correct
- sensitivity and gain are wrong

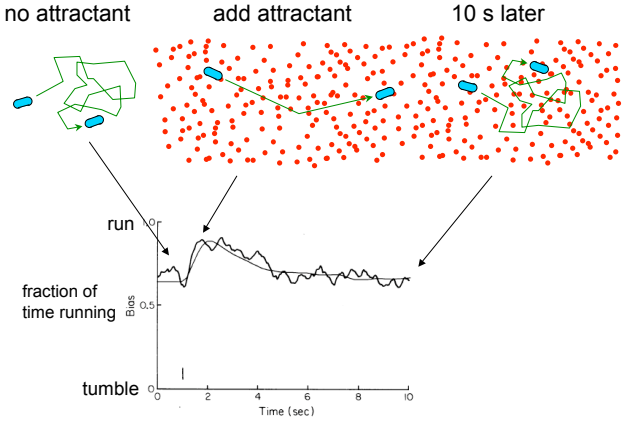
Why model biology?

How was modeling used to better understand *E. coli* chemotaxis?

Why model biology?

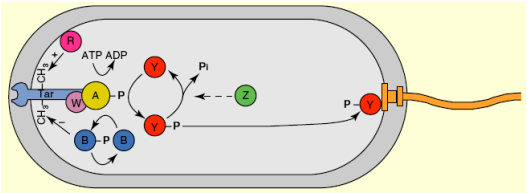
- Create a precise description of the system
  - focus on important aspects
  - highlight poorly understood aspects
  - a description that we can communicate
- Explore the system
  - test hypotheses
  - make predictions
  - build intuition
  - identify poorly understood aspects

E. coli adaptation



Credit: Segall, Block, Berg, *Proc. Natl. Acad. Sci. USA* 83:8987, 1986.

E. coli chemotaxis signal transduction



Signal transduction to tumble
1. Tar activates CheA
2. CheA autophosphorylates
3. CheA phosphorylates CheY
4. CheYp diffuses and binds to motor
5. Motor switches to CW -> tumble
6. CheZ dephosphorylates CheY

Attractant binding decreases activities, suppressing tumbles

Adaptation
1. CheR methylates Tar
2. CheA phosphorylates CheB
3. CheBp demethylates Tar

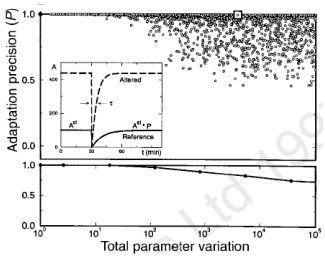
Methyl groups bound to Tar increase signaling activity

Credit: Andrews and Arkin, Curr. Biol. 16:R523, 2006.

Modeling adaptation

Barkai and Leibler, 1997

Postulated: CheB only demethylates active receptors



Specific results:
1. perfect adaptation
2. adaptation robust to variable protein concentrations

General results:
1. Robustness may be common in biology
2. Robustness can arise from network architecture

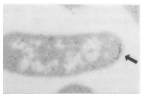
Credit: Barkai and Leibler, *Nature*, 387:913, 1997.

Model for gain and sensitivity

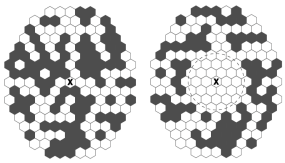
Problem
Experimental aspartate detection range: 2 nM to 100 mM.

From receptor K_D, detection range: 220 nM to 0.7 mM.

Experimental result
receptors cluster at poles (Maddock and Shapiro, 1993)



Bray, Levin, and Morton-Firth, 1998
Postulate: receptor activity spreads in the cluster



black = active receptor
white = inactive receptor
x = ligand

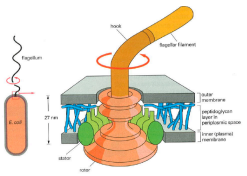
Credit:Maddock and Shapiro, *Science*, 259:1717, 1993; Bray, Levin, and Morton-Firth, *Nature* 393:85, 1998.

Model for gain and sensitivity

Specific results
Clustering leads to:
- increased sensitivity
- early saturation

Prediction
- some receptors are clustered, and some unclustered
- clustering decreases with adaptation to high attractant

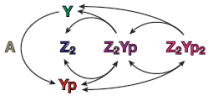
General results
- Many proteins form extended complexes; perhaps they have similar purposes.

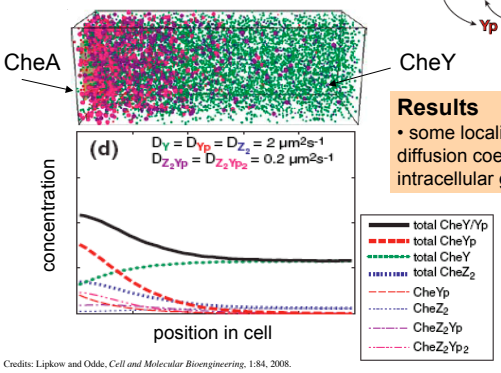


Credit: Alberts, Bray, Lewis, Raff, Roberts, and Watson, *Molecular Biology of the Cell, 3rd ed.* Garland Publishing, 1993.

Spatial chemotaxis model

Lipkow and Odde, 2008
Made spatial chemotaxis model
Included CheY-CheZ interactions

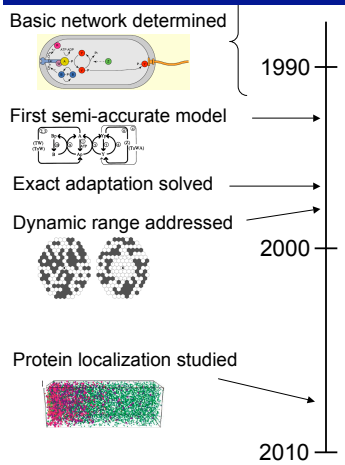




Results
- some localization + different diffusion coefficients can create intracellular gradients

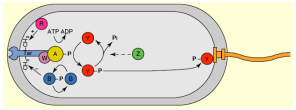
Credits: Lipkow and Odde, *Cell and Molecular Bioengineering*, 1:84, 2008.

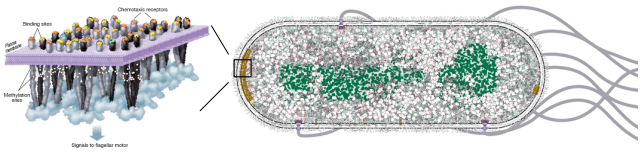
Chemotaxis summary



Good review
Tindall *et al.*, *Bulletin of Mathematical Biology*, 70:1525, 2008.

A new understanding of *E. coli*





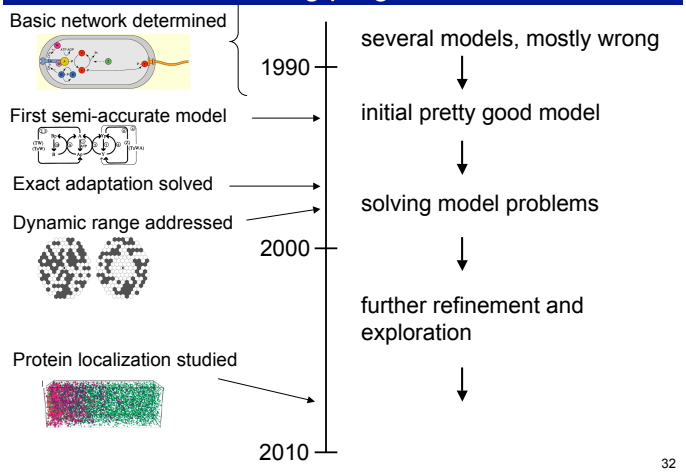
Credit: Andrews and Arkin, Curr. Biol. 16:R523, 2006; Bray, *Science* 229:1189, 2003; Bray, personal communication.

Why model biology?

Example: *E. coli* chemotaxis

Typical modeling progression

Modeling progression



More modeling progression

System is mapped out

Too complex for qualitative reasoning

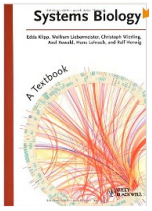
Initial models		Later models
simple	→	detailed
low accuracy	→	good accuracy
core network	→	large network
specific	→	general

Class details

class web page on LibGuide: http://campus.fhcrc.org
lists class topics, readings, homework

Registration
https://www.surveymonkey.com/s/biologicalmodeling

Textbook: *Systems Biology* by Klipp *et al.*
(at library or $85 from Amazon)



Homework

Things to 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.

(link will be on the LibGuides page, http://campus.fhcrc.org)

Workflow for building a model