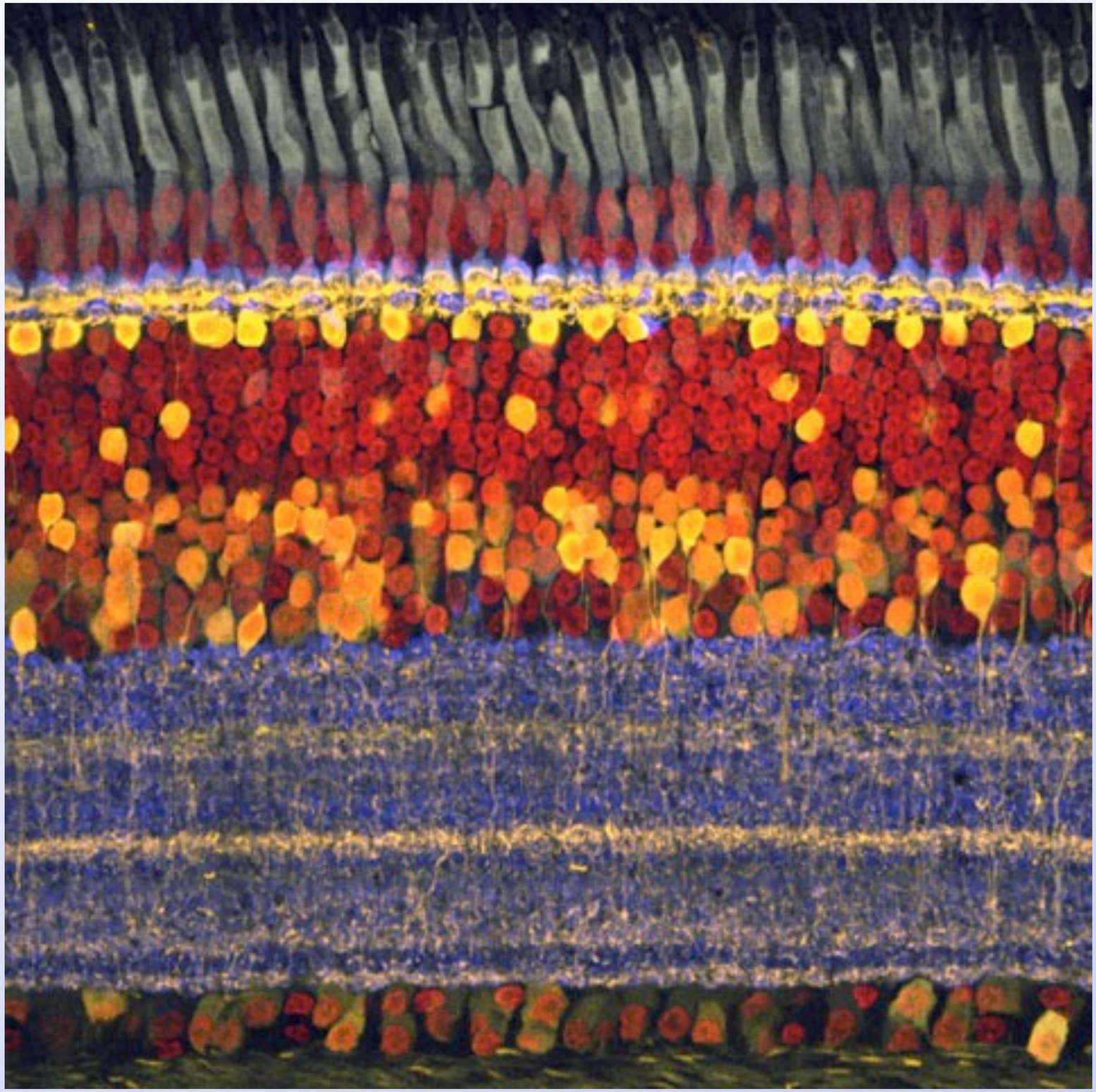
Learning physical biology via modeling and simulation–an intermediate-level class



Phil Nelson
University of Pennsylvania

These slides will appear at
www.physics.upenn.edu/~pcn

Image of chick retina by Andy Fischer.

Plan

1. Indoctrination
2. Skill set
3. Case studies
4. Outcomes
5. Wrap

1. Challenge/opportunity

I love Physics–so do you–but if we want Physics to flourish, we need to recruit new physicists.

Our instruction must account for what skills and concepts are already in the students' heads before they arrive. Often, what's in their heads includes a lot of life science. Instead of moaning about how they lack certain mathematical skills, can we work with this ***strength?***

In fact, let me propose to turn standard thinking on its head: In addition to the usual:

- ✳ "Physics is so important for understanding biology etc." (which is of course true)

I've also observed that for many students,

- ✳ Life science is an ideal ***context*** in which to teach ***serious physics***.

For these students, the subject *comes alive only when developed with a scientific motivation that they find compelling.*

Challenge/opportunity 2

- To a large extent, undergraduate physical-science curricula remain *firmly rooted in* ***pencil-and-paper calculation,*** despite the fact that most research is done with computers.
- To a large extent, undergraduate life-science curricula remain ***firmly rooted in descriptive approaches,*** despite the fact that much current research involves quantitative modeling.

Not only does our pedagogy not reflect current reality; it also creates a spurious barrier between the fields, reinforcing the narrow silos that prevent students from connecting them. *How ironic*, when we know how similar the fields are at the research level!

What *all sciences* have in common today is complete reliance on computation *and data visualization*. It was once a huge hassle to overcome the barriers to having students do their own computation and visualization. Not any more.

But students do need a lot of daily experience before this unnatural activity begins to feel natural.

Skill set

1. Indoctrination
2. Skill set
3. Case studies
4. Outcomes
5. Wrap

2. How it's gonna be

We hear a lot about the importance of training STEM students to work well in teams, and certainly that's true.

But there is another skill set that will be critical for our students' future, one that's much less talked about but that jumped out at me as I read ***Average is Over*** by Tyler Cowen: In many areas, even beyond STEM, the successful professionals are going to be the ones who can integrate with machines to ***do things that neither humans nor computers can do by themselves***. We may not want to hear this, but as artificial intelligence takes over more and more routine white-collar work there will be an ever-increasing premium on this skill set.

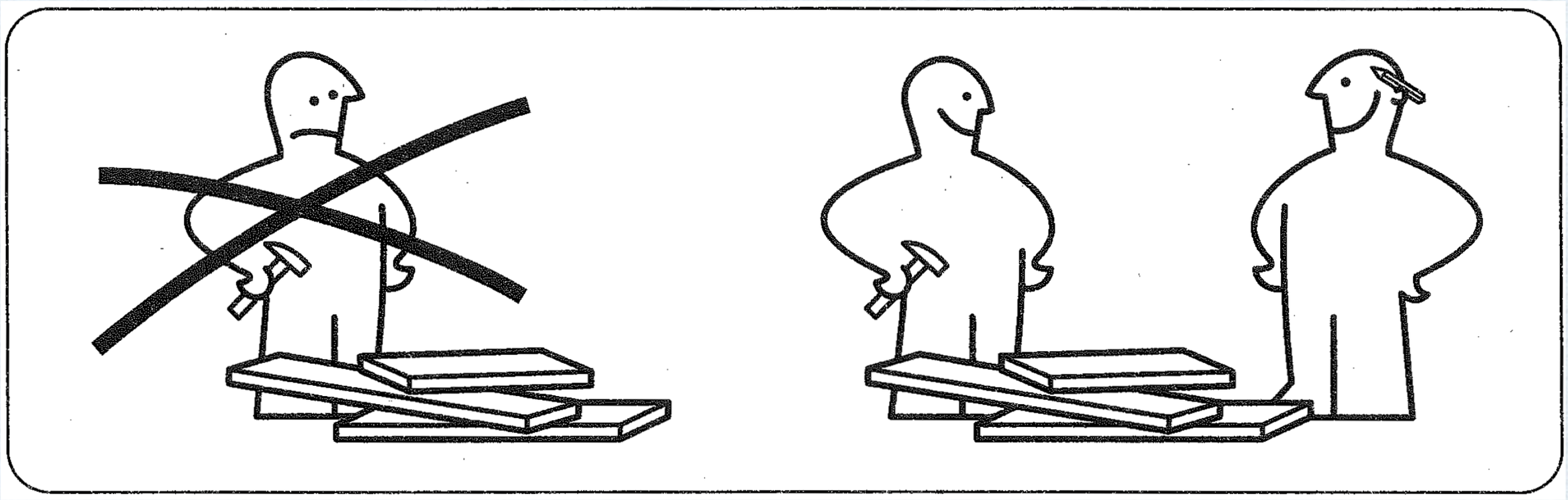
My message here is instead that writing code from scratch, in a general-purpose programming language, is a skill that

- Many of even our best students have not yet acquired;
- Is central to most kinds of current scientific research;
- Represents an entirely new mode of mental activity distinct from the other things we teach students to do;
- Enables an instructor to assign much more interesting and real-world problems;
- Gets many students excited and gives them a toolkit that they can and do carry over into all their subsequent classes and beyond.

How to get there on time

- On Day 1 of the class, I tell the students where to get a ***free download*** of the Python language, and I distribute installation instructions. I tell them they need to come to class *on Day 2* with a laptop, with this system installed and running. I pass out and collect a questionnaire.
- The questionnaire asks students for their general experience level with any computer math system. I use the responses to make teams of two students each. I ***assign partners*** so that a student from the lower self-evaluation levels is paired with one from the higher. I send everybody an e-mail with their partner's contact, saying "even if you're an expert, you must come to support your partner."
- On Day 2 of class I say, "Figure out if you or your partner has more computer experience; then that person should be ***advising, not touching*** the computer." I talk a little, show some things on the big screen, then stop and let the students try some things in the First Computer Lab section of the book. I walk around troubleshooting, along with 1 or 2 grad students. After maybe 10 minutes, I interrupt them and talk a little more, repeating till the class ends.
- Then we have some regular classes, followed by a second computer lab structured the same way but with ***different assigned partners,*** covering some new skills.
- After that I say, "If you liked either of your assigned partners, keep working together, but from now on work with whomever you like."

This is all the explicit programming instruction I do. From then on, I spend a little class time introducing some new syntax needed for that week's homework, and lots of instruction goes on in office hours. ***There's still room for a lot of physics.***



Your community should extend beyond your roommate, lab partner, or cat.

Case studies

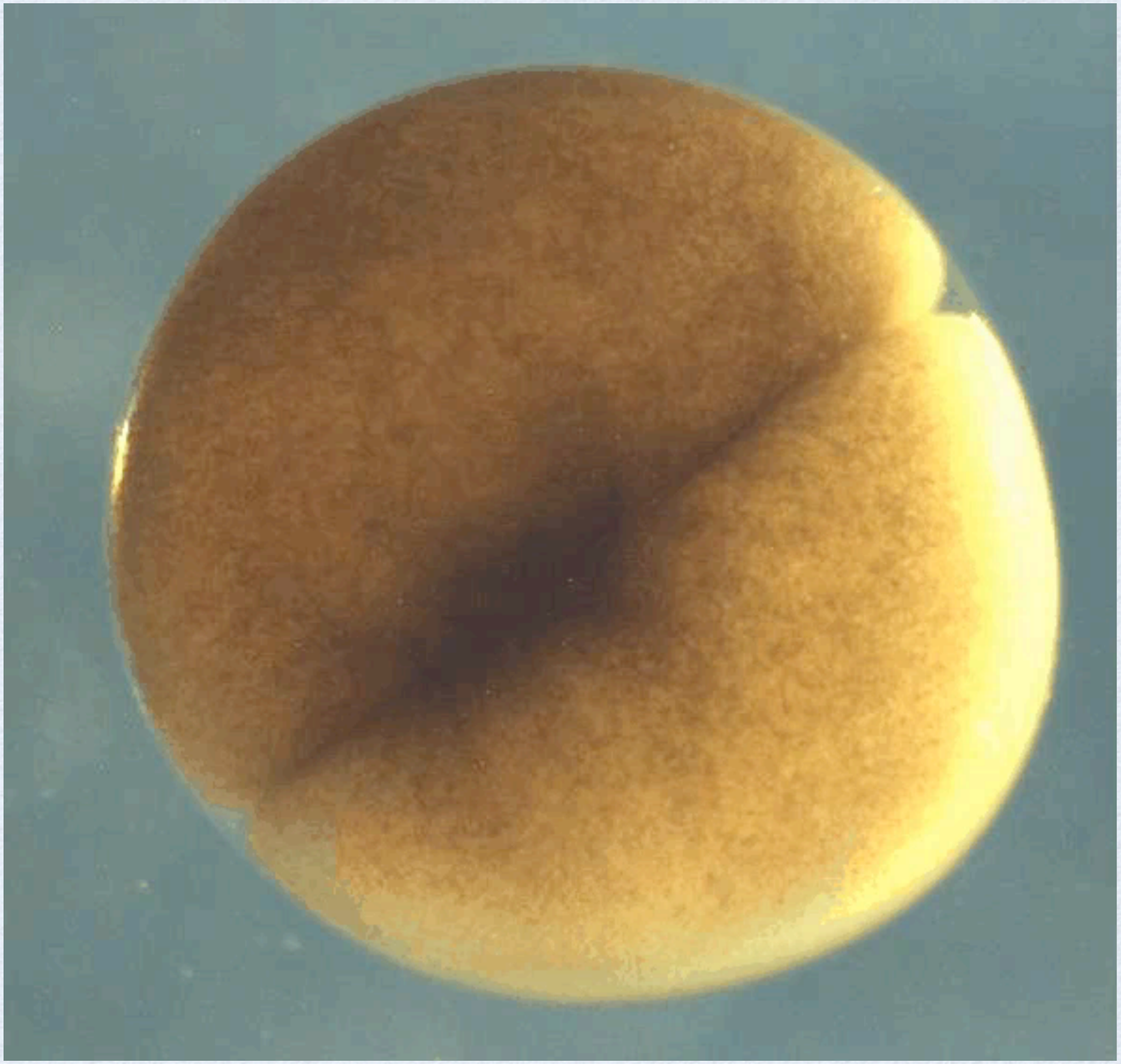
1. Indoctrination
2. Skill set
3. Case studies
4. Outcomes
5. Wrap

3.1 Control in cells

Molecular inventories are state variables.
They interact in ways that can be described by systems of ODEs.
The qualitative behavior of such a system can be predicted from its phase portrait.
You Can Do This Yourself.

Biological problem: Periodic behavior

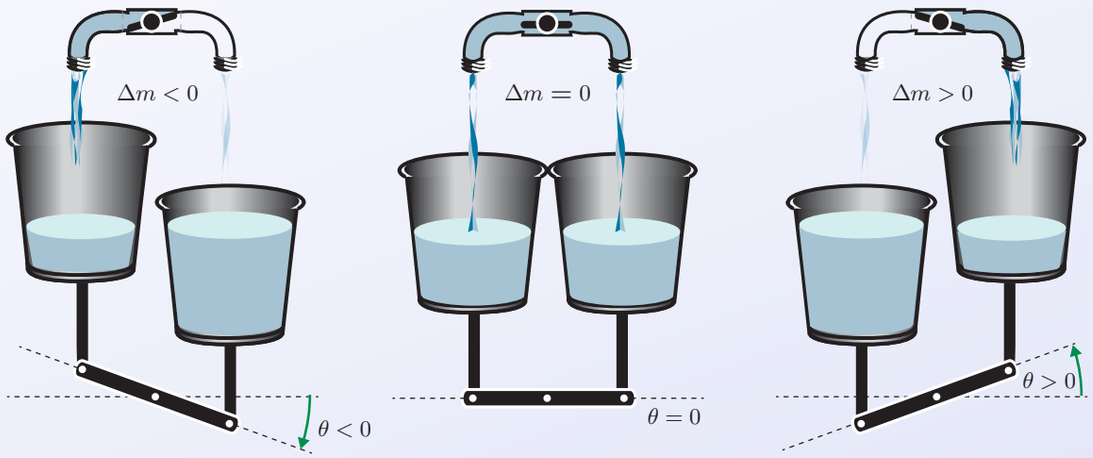
Framing: How do these dividing cells stay in sync without communicating?

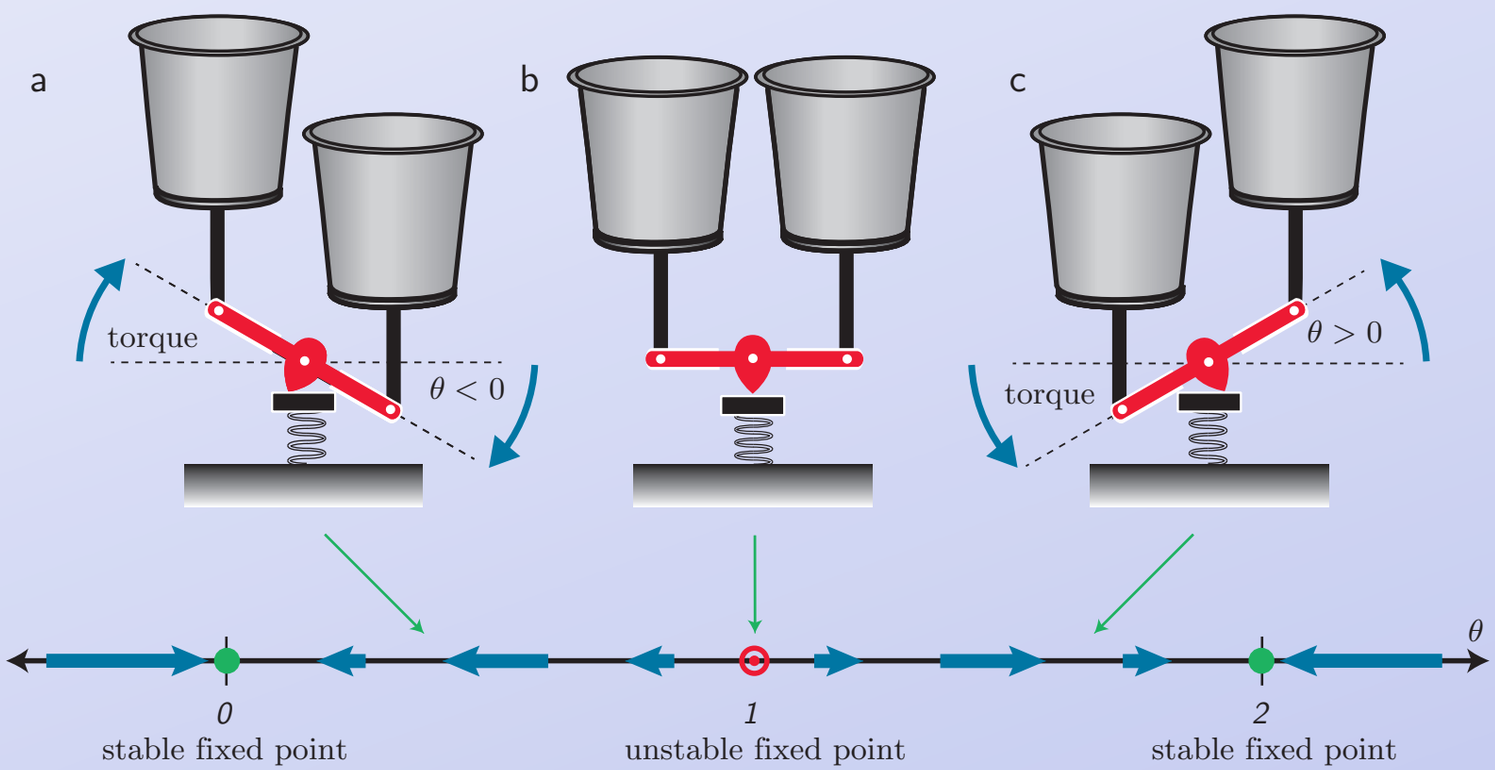


Video courtesy Tony Tsai.

Biological problem: Periodic behavior

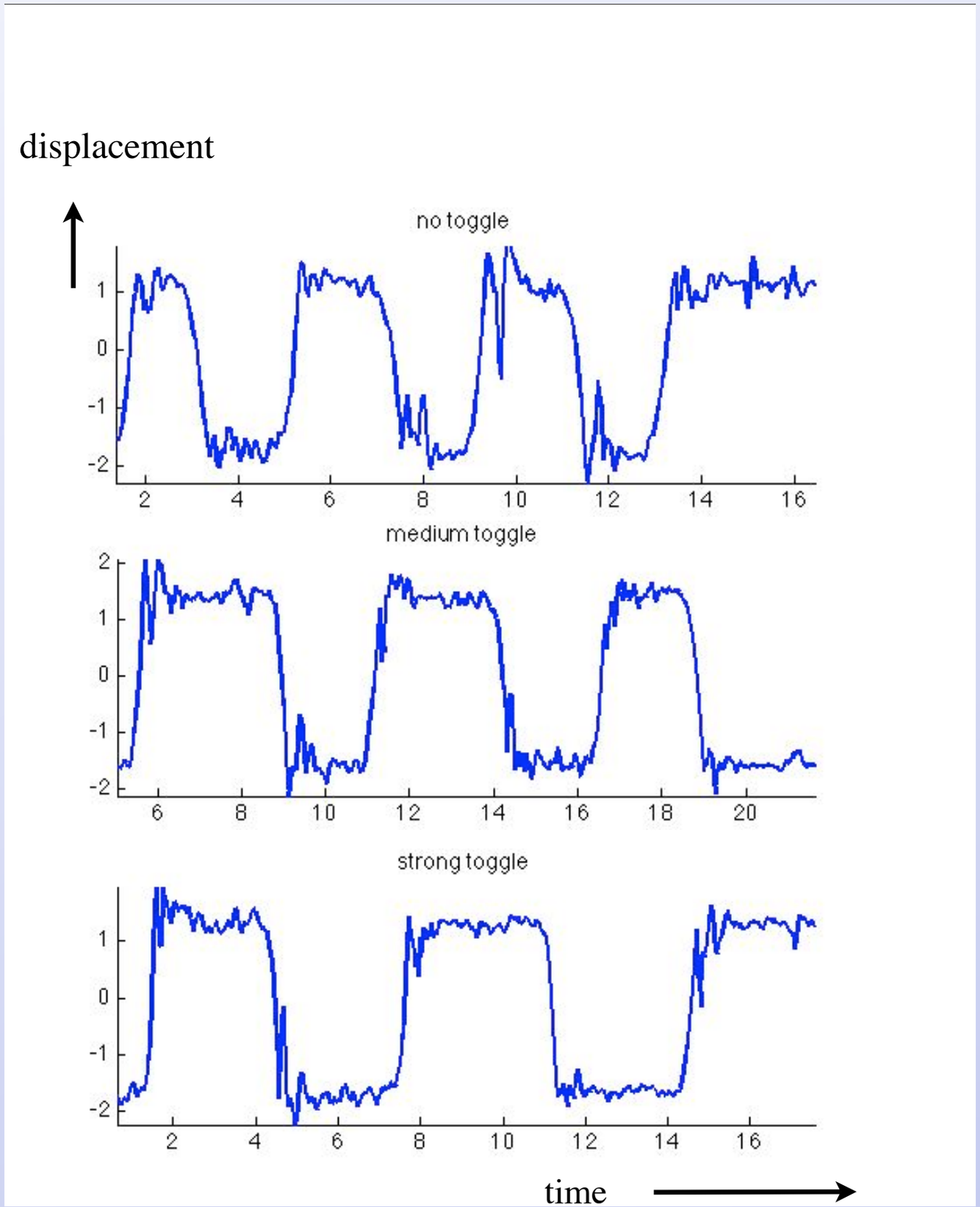
Mechanical analogy: Relaxation oscillator



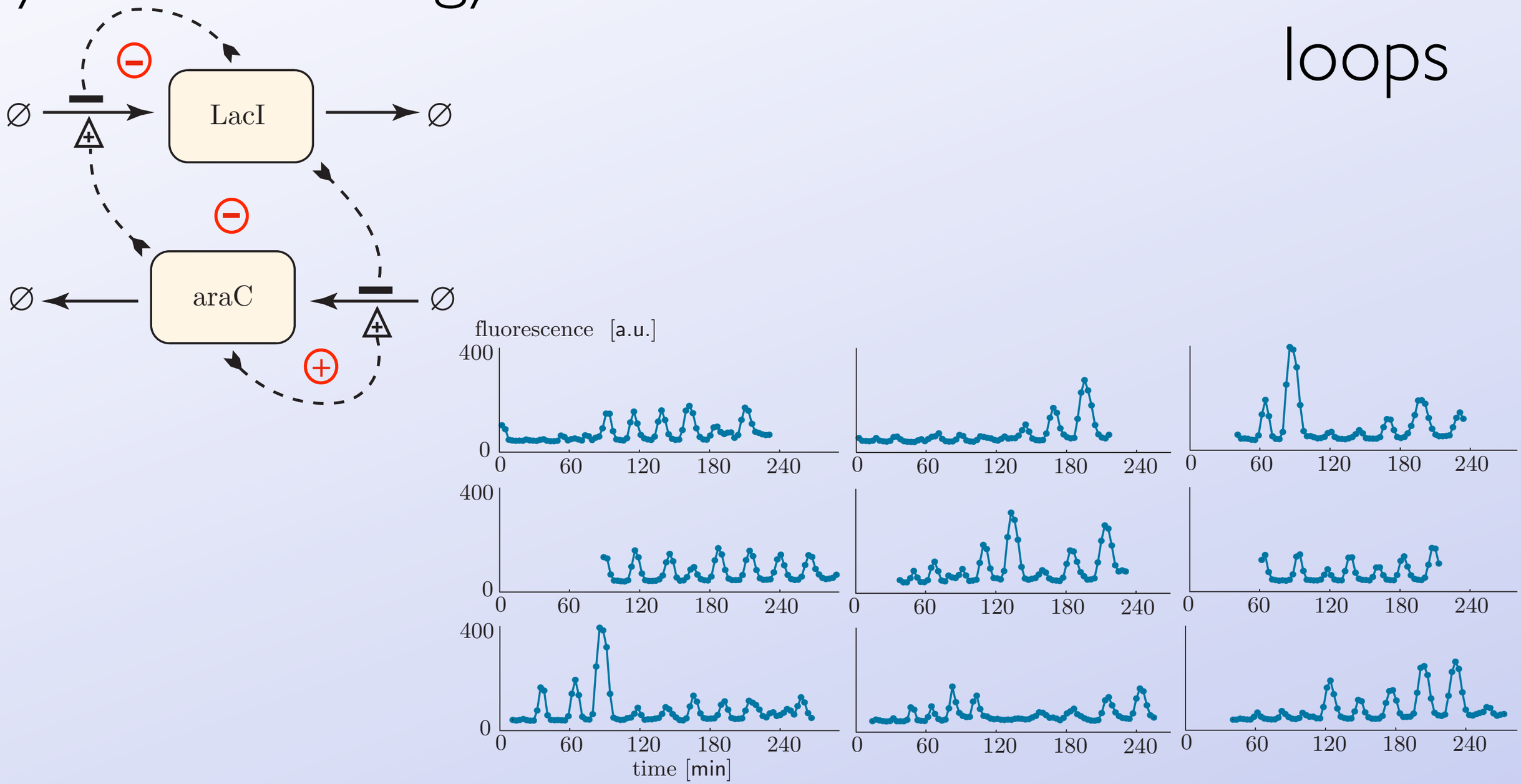


From P Nelson, *Physical models of living systems* (WH Freeman, 2015).

“Build it to understand it.”



Biological problem: Periodic behavior
Mechanical analogy: Relaxation oscillator
Synthetic biology: Oscillation via linked feedback loops



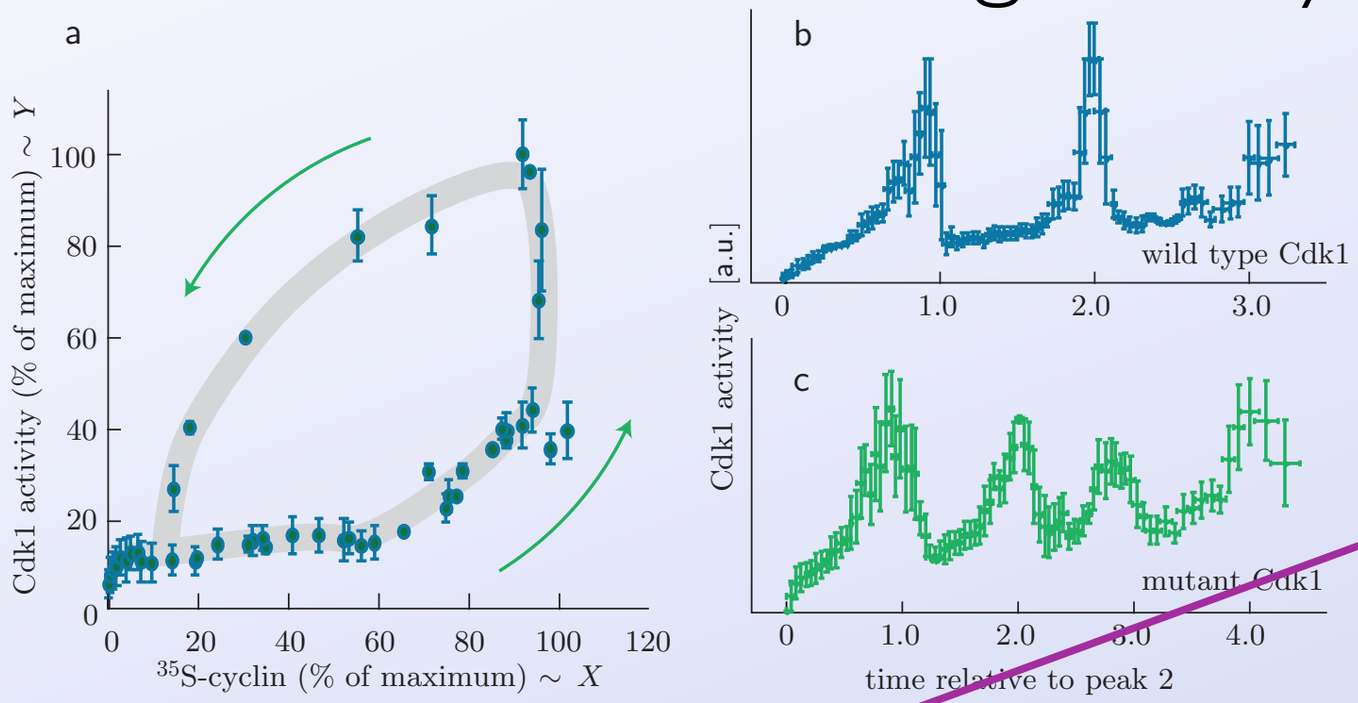
From P Nelson, *Physical models of living systems* (WH Freeman, 2015). Data from: Stricker et al., Nature (2008) vol. 456 (7221) pp. 516-519.

Biological problem: Periodic behavior

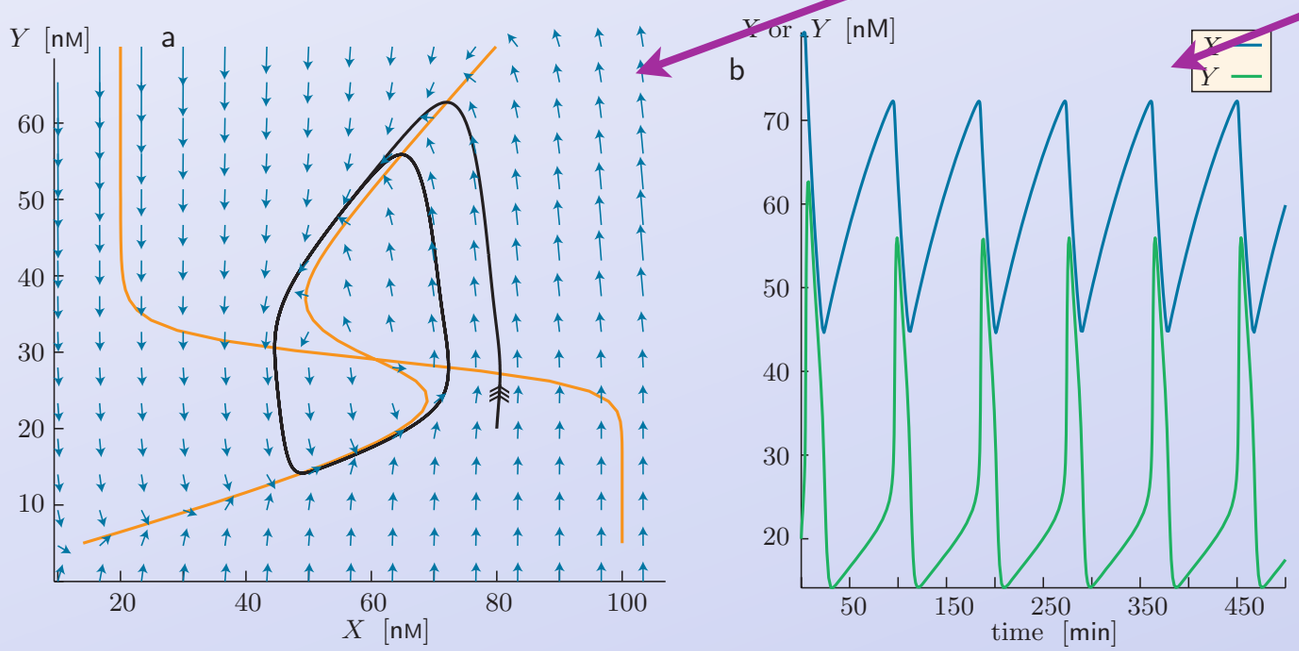
Mechanical analogy: Relaxation oscillator

Synthetic biology: Relaxation oscillator

Natural realization: frog embryo



Assignments students do



From P Nelson, *Physical models of living systems* (WH Freeman, 2015). Data from: Pomerening et al., Cell (2005) vol. 122 (4) pp. 565-78.

3.2 Probabilistic inference

Often the prediction of a model is a probability distribution.
Nevertheless such models can be falsified.
You Can Do This Yourself.

Skills: Probabilistic thinking

Students at this level have all completed two or more terms of calculus, so they are familiar with a mathematical world in which everything is continuous and deterministic.

They generally dislike calculus. ***Could that be*** because *everything in cell biology is* ***discrete and stochastic***?? No *wonder* they feel a disconnect!

Most, moreover, have little or no experience in algorithmic thinking. That's a pity, because just writing a few lines of code can give students infinitely more insight into basic probability than all the long theorems in all the long books.

Biophysical problems are an interesting road into probability theory with high-profile, current applications that can motivate students.

(Do your life-science students really understand it when they take their department's biostatistics course?)

Example: What is a "fit?" Could jiggle till they look good... could hit the "fit" button on our canned software... or we could maximize the *likelihood*.

Bacterial genetics

Framing: Drug resistance is a very big deal.

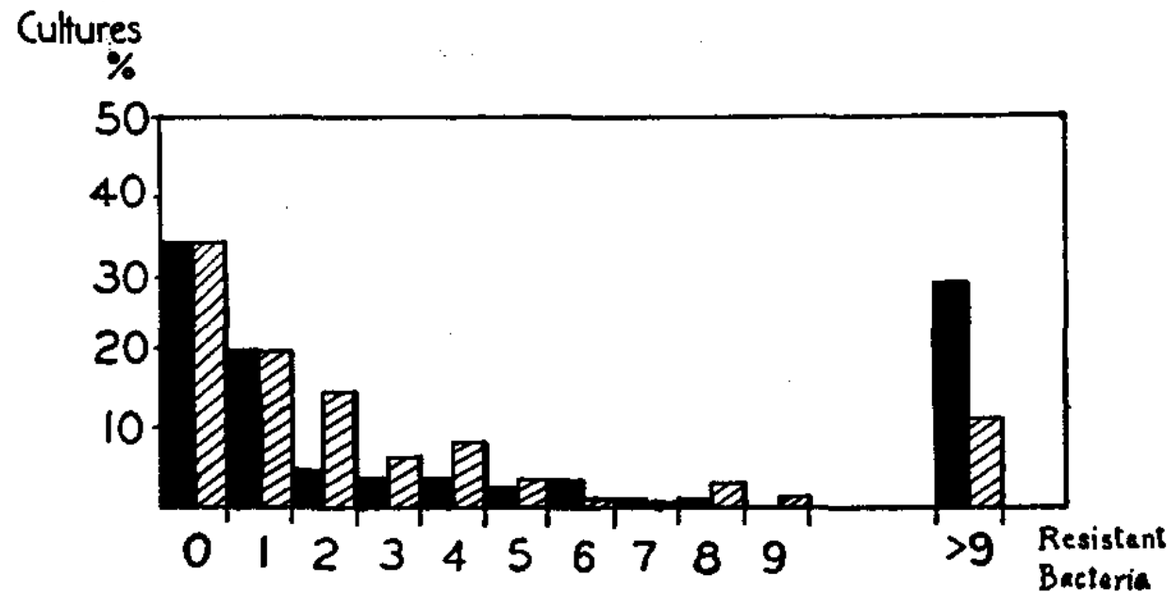


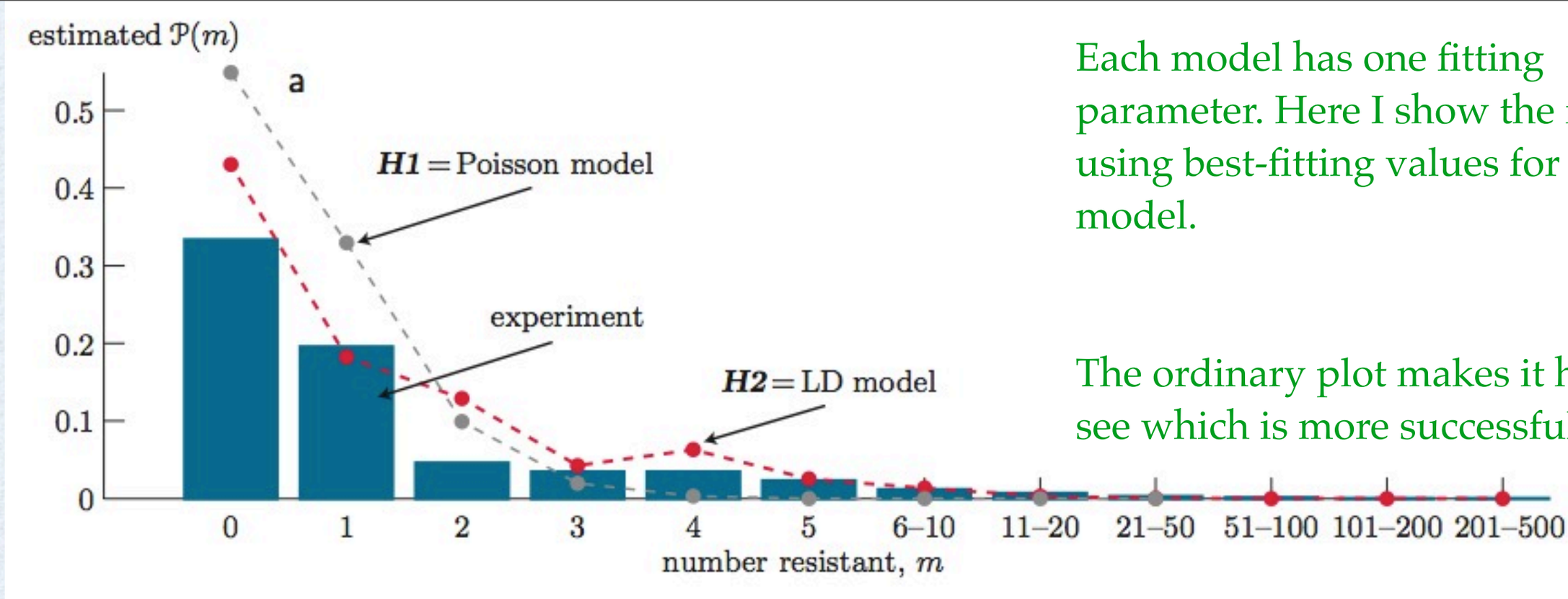
FIGURE 2.—Experimental (Experiment No. 23) and calculated distributions of the numbers of resistant bacteria in a series of similar cultures. Solid columns: experimental. Cross-hatched columns: calculated.

Luria & Delbruck, 1947

Luria and Delbruck noticed a statistical peculiarity in their data -- a huge "fat tail." They came up with a "Mendel, not Lamarck" model for drug resistance, and detailed quantitative predictions for such distributions that distinguished their model from the alternative.

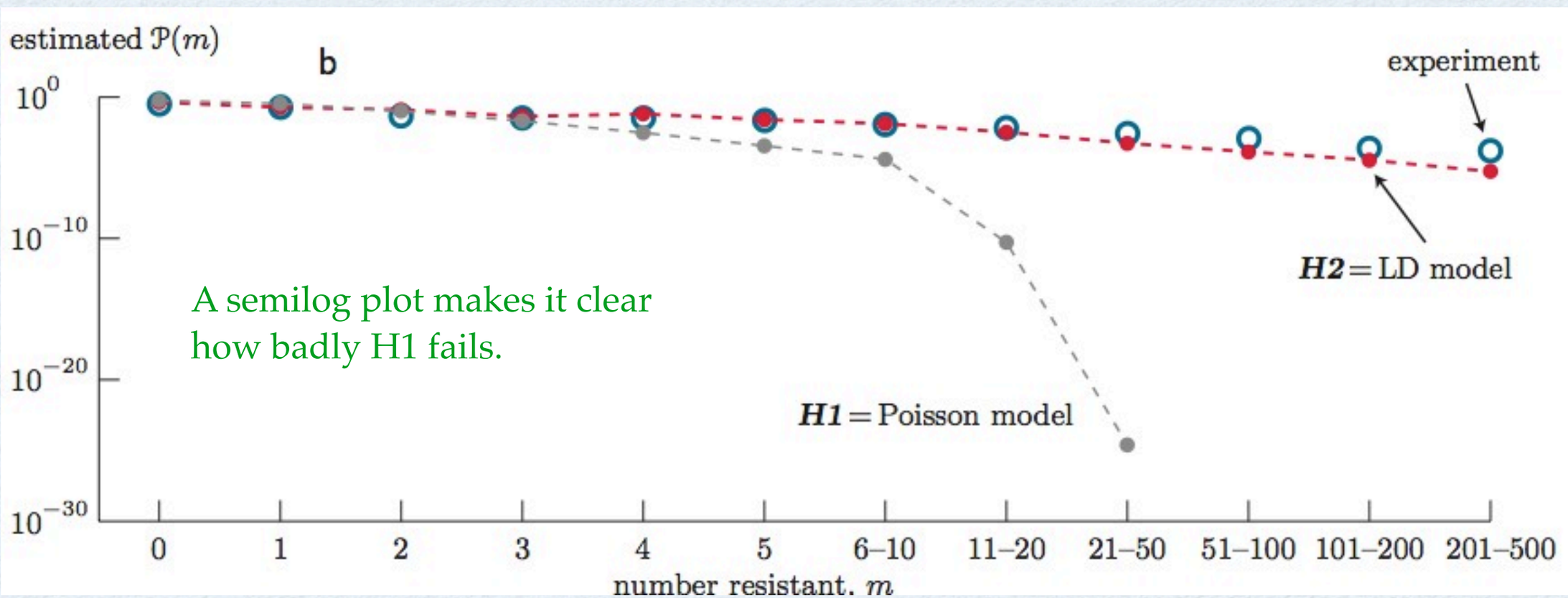
This is huge: The falsifiable prediction of their model was a ***probability distribution.***

They had to do very hard math. But now it's trivial for students to simulate on a laptop.



Each model has one fitting parameter. Here I show the results using best-fitting values for each model.

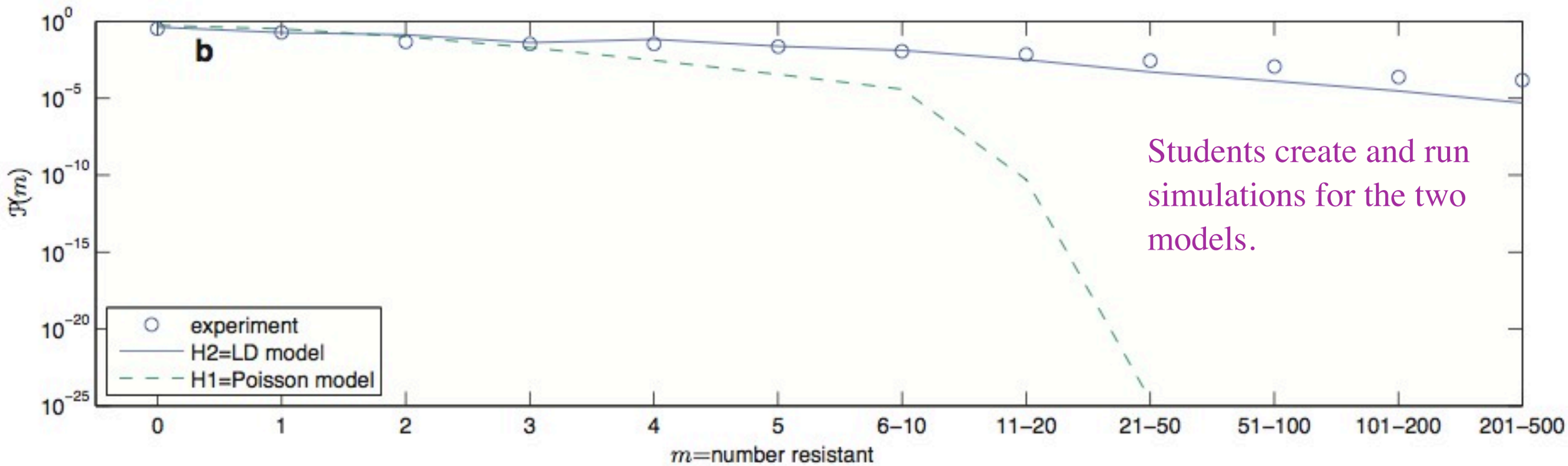
The ordinary plot makes it hard to see which is more successful.



A semilog plot makes it clear how badly H1 fails.

Yikes! How can the *style of a graph* affect a *scientific conclusion*? We'd better find a more objective approach.

Skills: Visual communication



Students create and run simulations for the two models.

Students must also become adept at extracting conceptual information from graphical representations of data and models. One way to do this is to become expert at *creating such representations themselves*. Here, again, general-purpose computer tools are the key. Students find them frustrating at first, but immensely empowering once they have a few successes.

This problem motivates us to invent a likelihood test; students evaluate competing models to decide objectively which model wins.

From P Nelson, *Physical models of living systems* (WH Freeman, 2015).

3.3: Random processes

Combining the two preceding themes, molecular inventories interact in ways controlled by random variables, and sometimes it matters in living cells.

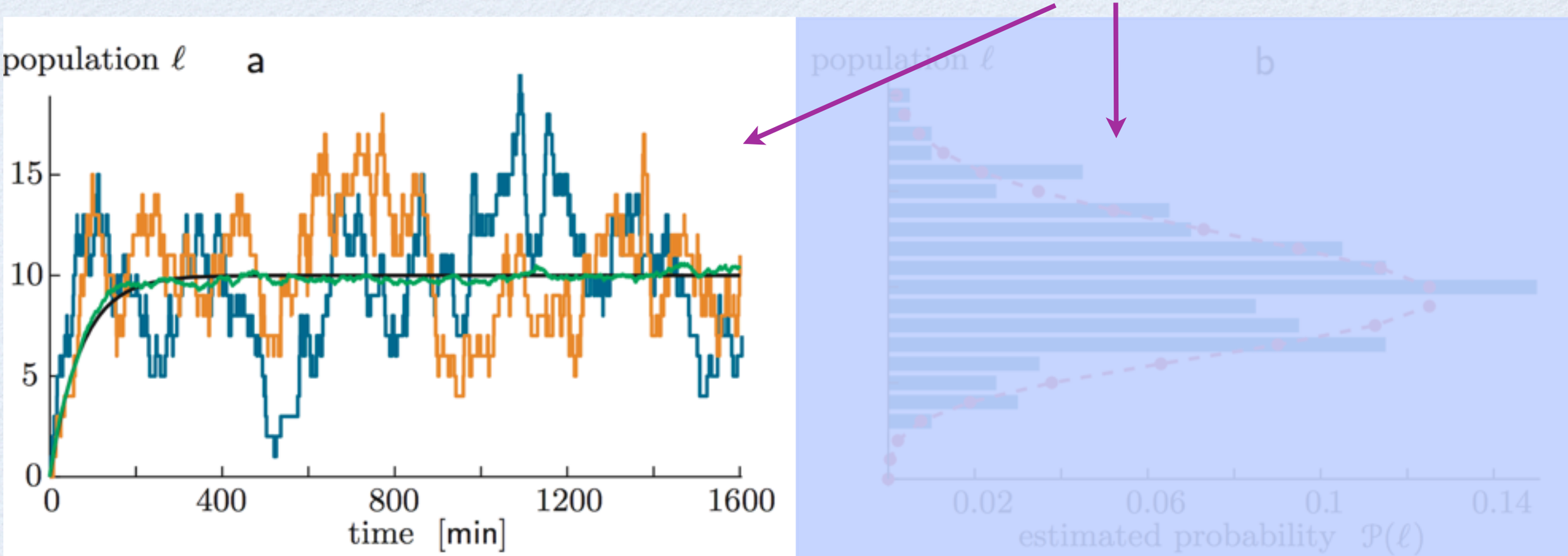
You Can Do This Yourself.

From random quantities to random processes

Simulations that they create for themselves can also foster critical attitudes about when continuous, deterministic approximations are useful.

Just a few lines of code suffice to simulate a birth-death process resembling transcription. For small molecule numbers, it doesn't look deterministic at all, but for larger numbers it does settle down. That's a key insight.

Assignments students do



From P Nelson, *Physical models of living systems* (WH Freeman, 2015).

3.4 The nature of light

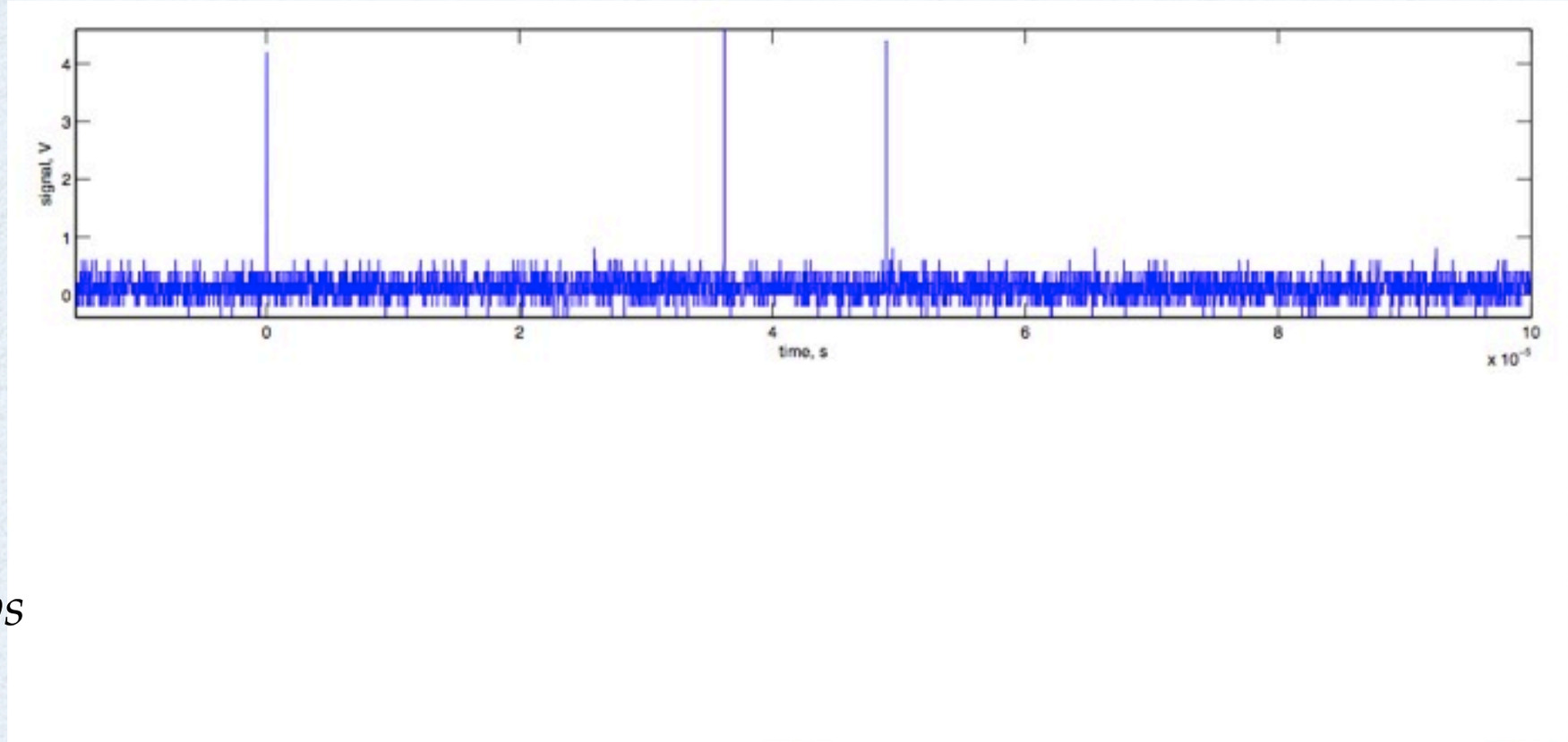
At the single-photon level light behaves randomly in space and in time.

Nevertheless, we can make probabilistic predictions.

You Can Do This Yourself.

We can detect very dim light with a photomultiplier tube or avalanche photodiode. Either way, light causes discrete clicks in the detector. ***Dimmer light gives equally big clicks, just less frequent***:

Dim illumination:



Slightly brighter (still very dim):

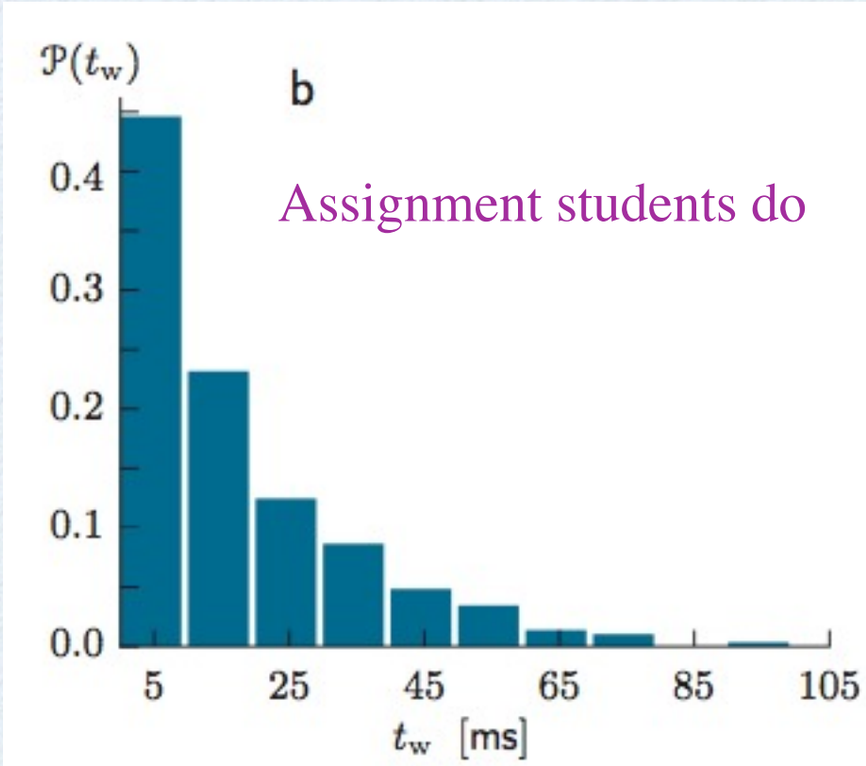
click for uniform blips

click for actual data

Experimental data courtesy J. F. Beausang.

How can we learn anything from "just noise?" To get a handle on what's going on, notice that the absolute times of individual clicks aren't very significant, but the *intervals* between successive clicks are:

Hmm. That looks familiar. Could that stupid Geometric distribution have anything to do with the cosmic mystery of light? Which bugged Einstein all his life?



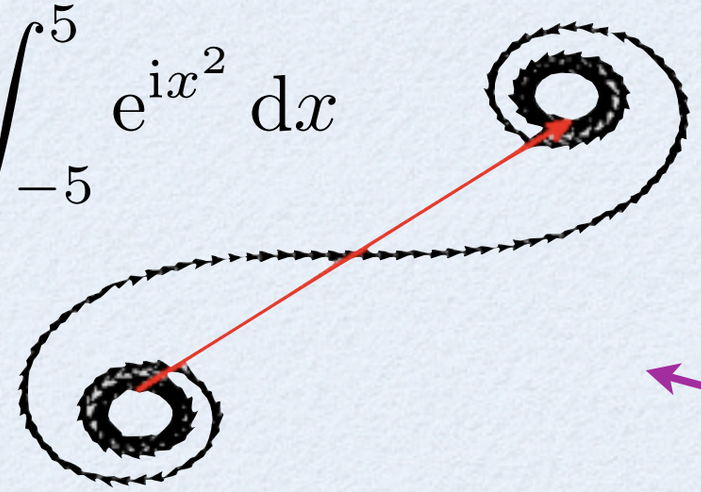
Reconciliation of wave/particle

``If light is a stream of particles, then what about all of the familiar classical optics results, including focusing by the lens of the eye?"
It's incredible, but we can reproduce all of those phenomena from the photon point of view.

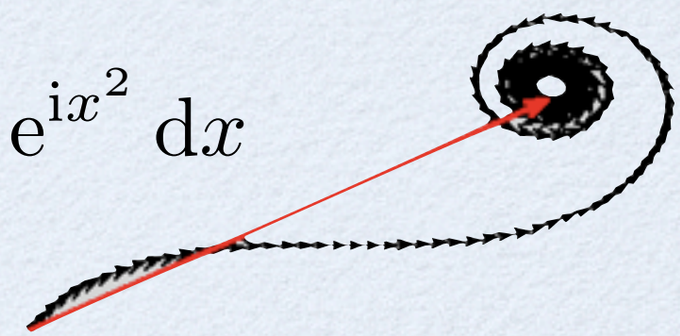
The key question is, ***Why does light (usually) (seem to) go on (pretty) straight lines?***
After all, a penny held in the sunlight casts a sharp shadow.

To answer that question, **students can approximate the Feynman integral in Matlab** as sums, drawing little arrows to represent each term in the sum. The full integral (red arrow) is the vector from one end of the chain to the other end, times dx.

$$\int_{-5}^{5} e^{ix^2}\,dx$$



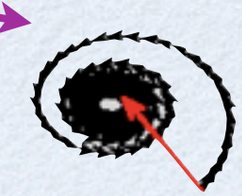
$$\int_{-1}^{9} e^{ix^2}\,dx$$



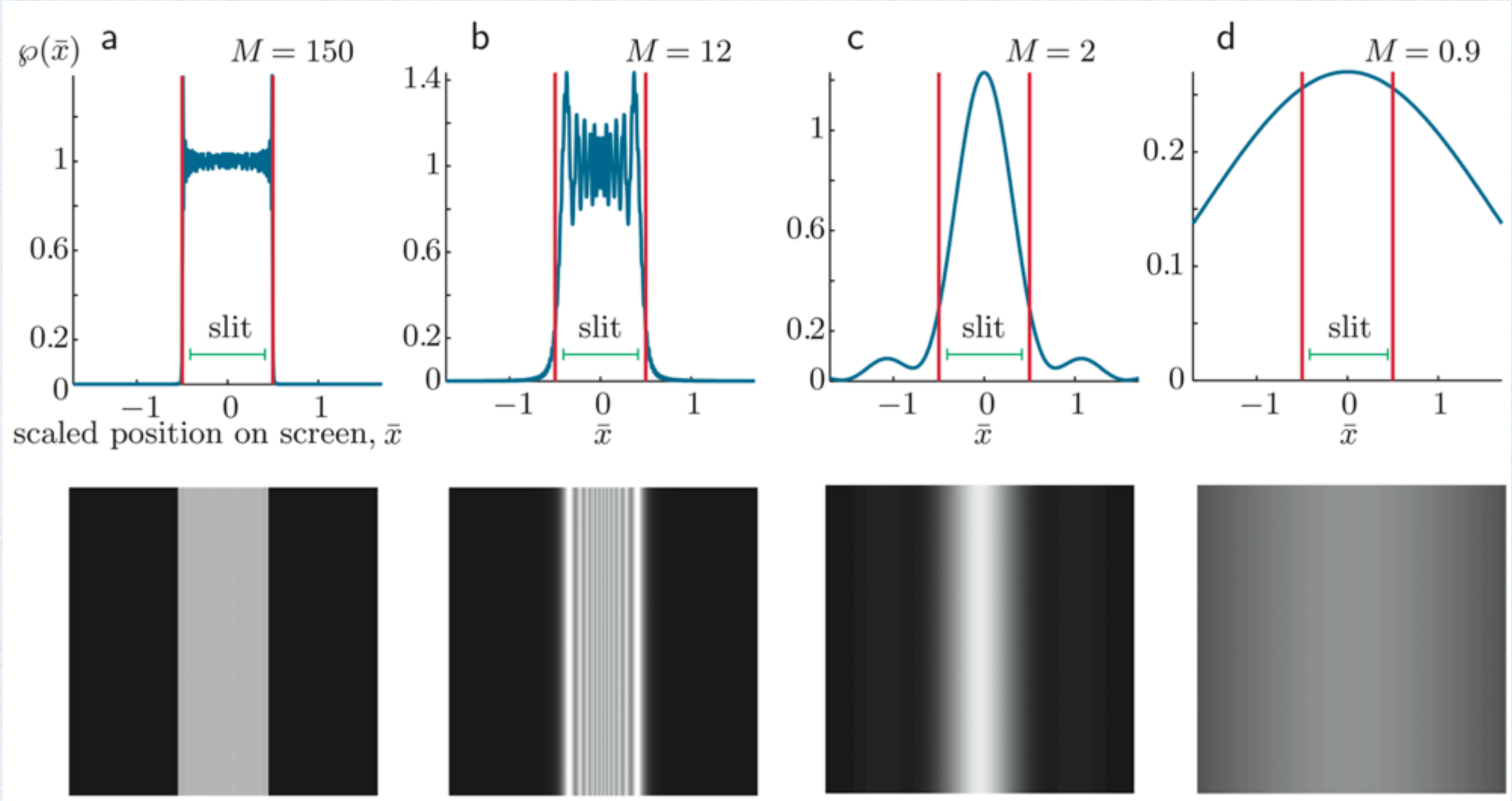
A similar integral whose range of integration contains *no* stationary-phase point will have a small total value:

Assignments

$$\int_{1}^{11} e^{ix^2}\,dx$$



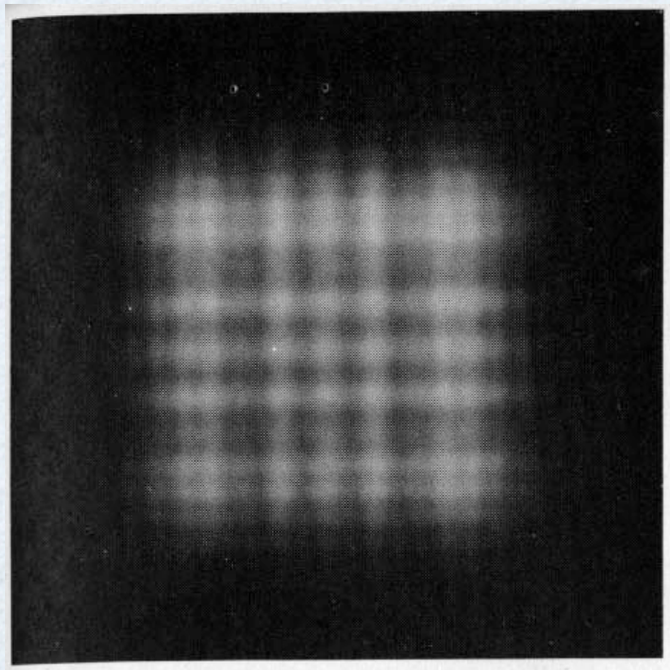
From P Nelson, *From photon to neuron* (to appear).



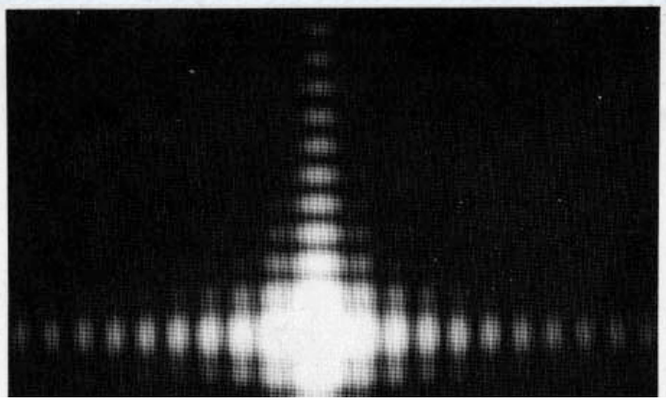
It's not too hard to learn how to do such calculations, and present them in these complementary ways. But...

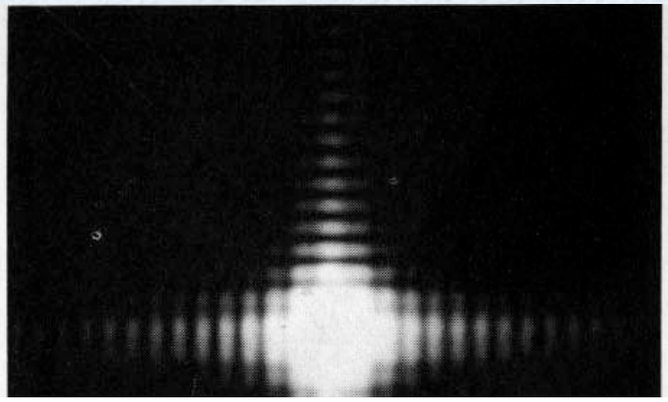
From P Nelson, *From photon to neuron* (to appear).

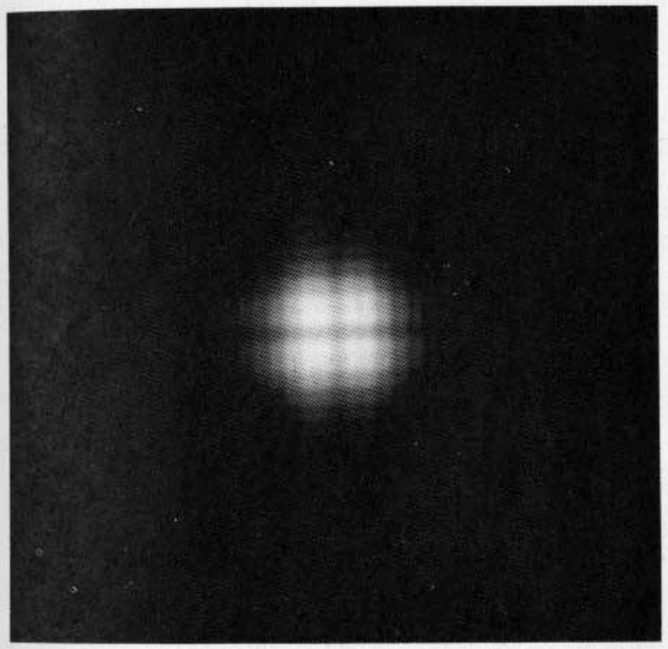
Beyond slits to more interesting apertures:



(a)



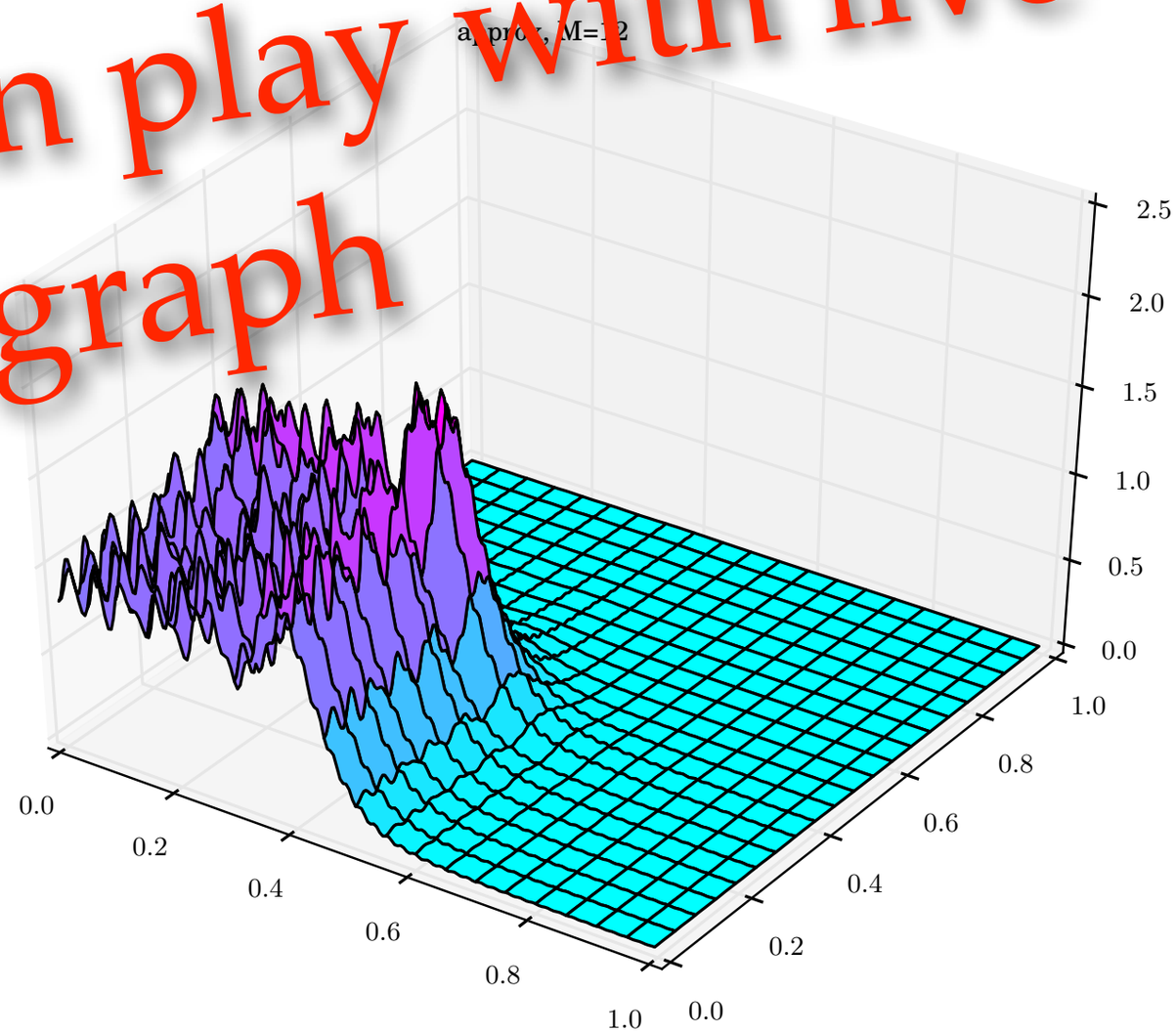




(d)

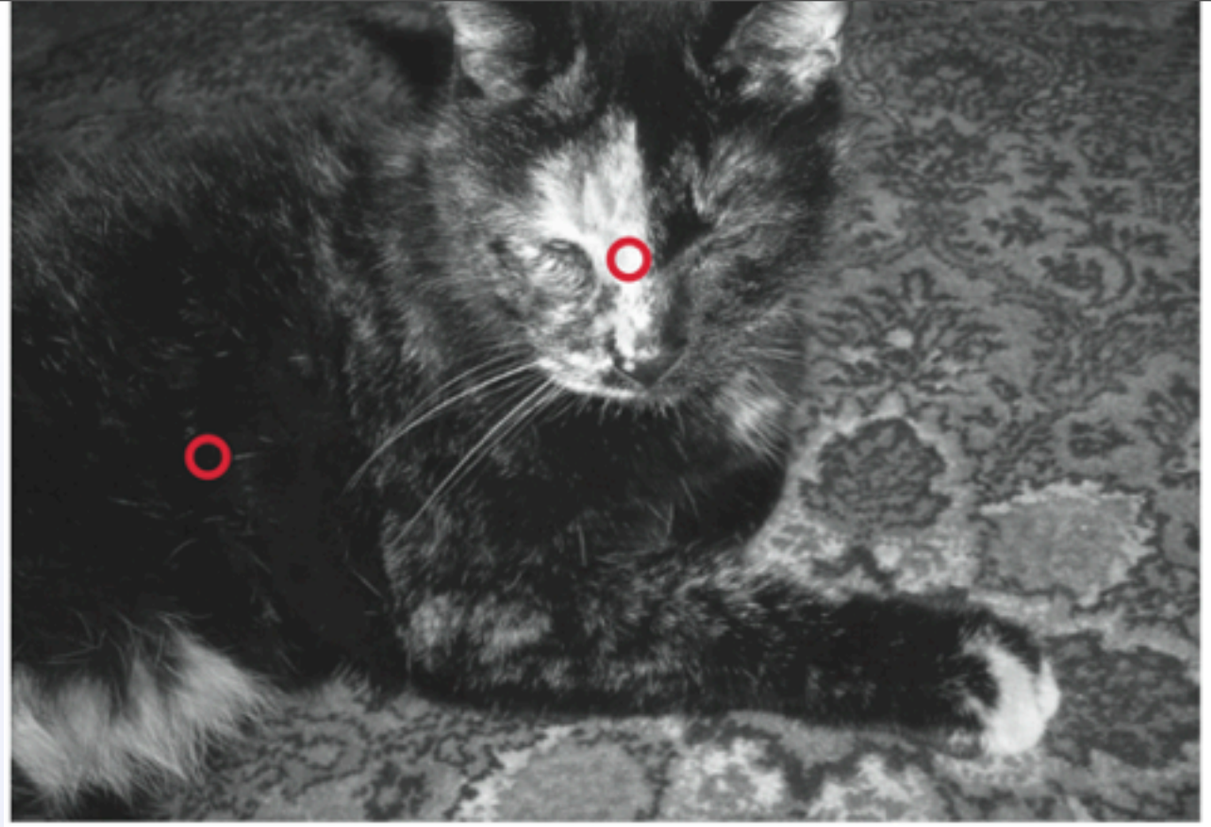
Figure 10.62 (a) A typical Fresnel pattern fo
(b)–(f) A series of Fresnel patterns for increasi
under identical conditions. Note that as the h

Then play with live 3D graph



3.5: Image analysis

An “image” is just a particular kind of dataset.
Mathematical operations on such a dataset correspond to transformations of the image.
Animals–*us*–use such transformations, e.g. to reduce bandwidth requirement on the optic nerve.
You Can Do This Yourself.



From P Nelson, *From photon to neuron* (to appear).

Assignments

Some outcomes

1. Indoctrination
2. Skill set
3. Case studies
4. Outcomes
5. Wrap

4: Is it worthwhile?

"Will students need all this if they're not going to be researchers?"

Many students *don't know yet* if they're going to be researchers. They are wondering, "is science interesting, and can I do it? They'll never know if you don't *make them stretch*.

"These courses are too mathematical for most premeds." Maybe, but there is a growing cadre of mathematically adept premeds who can handle them. What will they get?

From **Guide for the MCAT 2015 Exam**

The *Biological and Biochemical Foundations of Living Systems* and the *Chemical and Physical Foundations of Biological Systems* sections are designed to:

- target **basic research methods and statistics concepts** described by many baccalaureate faculty as important to success in introductory science courses; and
- require you to demonstrate your scientific inquiry and reasoning, research methods, and statistics skills as applied to the natural sciences.

Understanding the processes unique to living organisms, such as growing and reproducing, **maintaining a constant internal environment, acquiring materials and energy, sensing and responding to environmental changes, and adapting,** is important to the study of medicine.

Foundational Concept 2*B*. ***The structure, growth, physiology, and genetics of prokaryotes and viruses***

Foundational Concept 3: **Complex systems of tissues and organs sense the internal and external environments of multicellular organisms, and through integrated functioning, maintain a stable internal environment within an ever-changing external environment**

Foundational Concept 4: ***Complex living organisms transport materials, sense their environment,***
process signals, and respond to changes using processes understood in terms of physical principles.
4D. How light interacts with matter
4E. Atoms, nuclear decay, electronic structure, and atomic chemical behavior

Skill 1: Knowledge of Scientific Concepts and Principles

- Recognizing correct scientific principles
- Identifying the relationships among closely-related concepts
- Identifying the **relationships between different representations of concepts (e.g., verbal, symbolic, graphic)**
- Identifying examples of observations that illustrate scientific principles
- **Using mathematical equations to solve problems**

Skill 2: Scientific Reasoning and Problem-solving

- Reasoning about scientific principles, theories, and models
- Analyzing and evaluating scientific explanations and predictions
- Evaluating arguments about causes and consequences
- Bringing together theory, observations, and evidence to draw conclusions
- Recognizing scientific findings that challenge or invalidate a scientific theory or model

Skill 3: Reasoning about the Design and Execution of Research

- Identifying the role of theory, past findings, and observations in scientific questioning
- **Identifying testable research questions and hypotheses**
- **Distinguishing between samples and populations and results that support generalizations about populations**
- Identifying independent and dependent variables
- Reasoning about the features of research studies that suggest associations between variables or causal relationships between them (e.g., temporality, random assignment)
- Identifying conclusions that are supported by research results
- Determining the implications of results for real-world situations

Skill 4: Data-based and Statistical Reasoning

- **Using, analyzing, and interpreting data in figures, graphs, and tables**
- **Evaluating whether representations make sense for particular scientific observations and data**
- **Using measures of central tendency (mean, median, and mode) and measures of dispersion (range, inter-quartile range, and standard deviation) to describe data**
- **Reasoning about random and systematic error**
- **Reasoning about statistical significance and uncertainty (i.e., interpreting statistical significance levels, interpreting a confidence interval)**
- **Using data to explain relationships between variables or make predictions**
- **Using data to answer research questions and draw conclusions**

General Mathematical Concepts and Techniques

- **Recognize and interpret linear, semilog, and log-log scales and calculate slopes from data found in figures, graphs, and tables**
- **Demonstrate a general understanding of significant digits and the use of reasonable numerical estimates in performing measurements and calculations**
- **Use metric units, including conversion of units within the metric system, conversions between metric and English units (conversion factors will be provided when needed); dimensional analysis (using units to balance equations)**
- **Demonstrate a general understanding (Algebra II-level) of exponentials and logarithms (natural and base ten), solving simultaneous equations**
- **Demonstrate a general understanding of the following trigonometric concepts: definitions of basic (sine, cosine, tangent) and inverse (sin-1, cos-1, tan-1) functions; sin and cos values of 0°, 90°, and 180°; relationships between the lengths of sides or right triangles containing angles of 30°, 45°, and 60°**
- **Demonstrate a general understanding of vector addition and subtraction.**

A few outcomes

Incredibly, 80 responses including students who took the course up to 7 years ago. See details at http://www.physics.upenn.edu/biophys/PMLS/pdf/141130survey_Report.pdf

2. My level of computer-math experience prior to taking this course was

#	Answer	Bar
1	1 = No prior experience	
2	2	
3	3	
4	4 = Extensive prior experience	

3. My level of computer-math facility after finishing this course was

#	Answer	Bar
1	1 = Inadequate for needs I encountered later	
2	Click to write Choice 2	
3	Click to write Choice 3	
4	4 = Adequate for needs I encountered later	

4. Completing this course benefited my work in later courses

#	Answer	Bar
1	1 = Not really	
2	Click to write Choice 2	
3	Click to write Choice 3	
4	4 = Significantly	

6. Completing this course led me to take more advanced science course(s) that I might not otherwise have considered

#	Answer	Bar
1	1 = Not really	
2	Click to write Choice 2	
3	Click to write Choice 3	
4	4 = Really	

8. Completing this course conferred skills that made me more attractive to research labs and/or graduate programs

#	Answer	Bar
1	1 = I don't think so	
2	Click to write Choice 2	
3	Click to write Choice 3	
4	4 = I think so	

80 anonymous respondents, survey response rate about 80%.

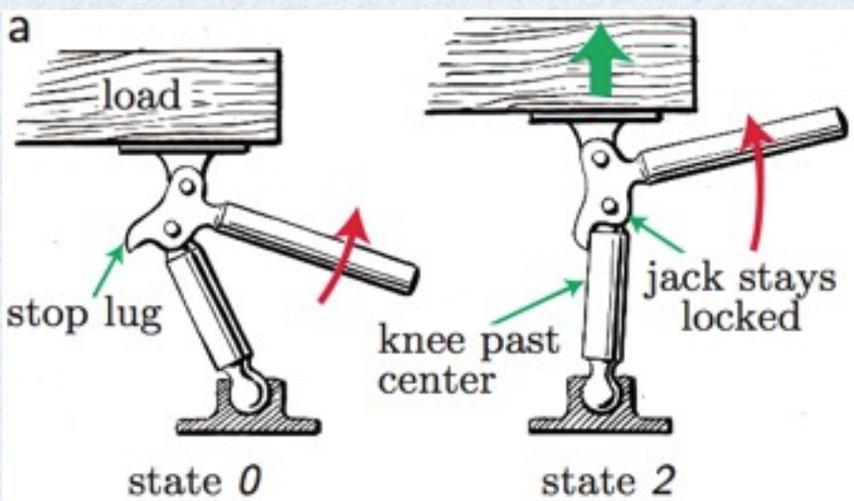
Wrap

1. Indoctrination
2. Skill set
3. Case studies
4. Outcomes
5. Wrap

What is modeling? Don't want to get all philosophical on you. I say,

It's a Tetrahedron:

```
Nf1=figure(1);
quiver(dm,theta,dmdot.*scaling,thetadot.*scalin
g,1);
% nullclines
hold on;
smalltg = [-1.2:.02:1.2];
```



data

$$\frac{dc_1}{dt} = -\frac{c_1}{\tau_1} + \frac{\Gamma_1/V}{1+(c_2/K_{d,2})^{n_1}}$$
$$\frac{dc_2}{dt} = -\frac{c_2}{\tau_2} + \frac{\Gamma_2/V}{1+(c_1/K_{d,1})^{n_2}}$$

"Yadda, yadda... feedback, yadda... bistability, hysteresis, yadda,... bifurcation...

From P Nelson, *Physical models of living systems* (WH Freeman).

Thanks

University of Pennsylvania

NSF BIO, PHYS

NSF NSEC

These slides will appear soon at:
www.physics.upenn.edu/~pcn
(or just google me)

Also see:

Physical models of living systems by PN (WH Freeman and Co., 2015) (www.physics.upenn.edu/biophys/PMLS).

A student's guide to MATLAB for physical modeling by Tom Dodson and PN (**free** at www.physics.upenn.edu/biophys/PMLS).

A student's guide to Python for physical modeling by Jesse Kinder and PN (Princeton University Press, 2015).

From photon to neuron: Light, Imaging, Vision by PN (2017).

(www.physics.upenn.edu/biophys/PtN).