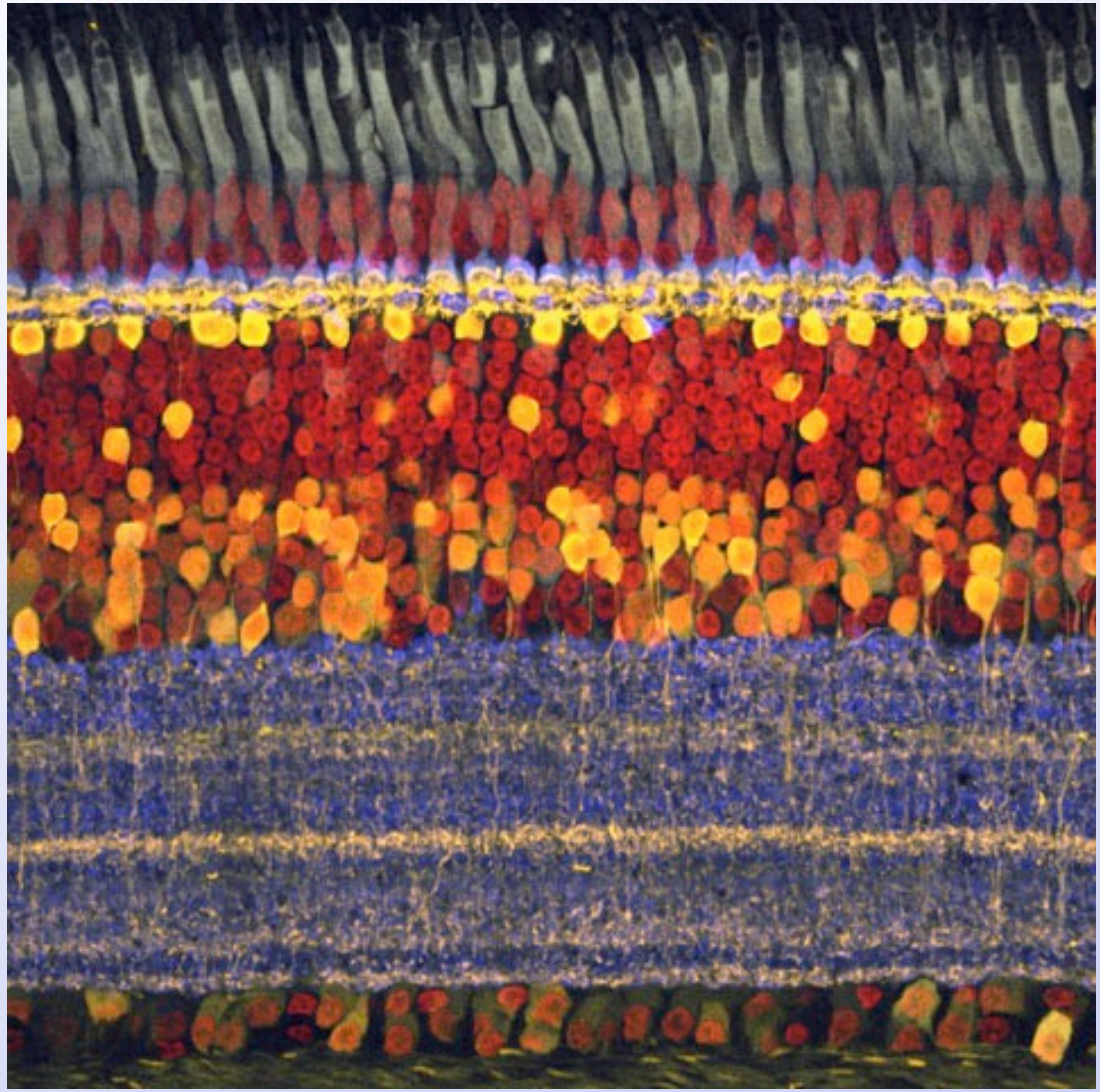
An intermediate-level course on physical models of living systems



Phil Nelson
University of Pennsylvania

Image of chick retina by Andy Fischer.

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

Plan

1. Indoctrination
2. Skill set
3. Feedback in natural and synthetic biology
4. Light, vision, and 21st century imaging
5. And now a word from our sponsor
6. Wrap

1.1: Why do we even have upper-level classes at all?

- **To tell them facts?**

  No -- facts are now free in infinite quantity.
- **To tell them the latest, most trustworthy facts?**

  No -- none of us can be as up to date as Wikipedia.

Well -- *skills and habits* still matter a lot. There is a big gap between information, for example that found on Wikipedia, and the competencies needed to obtain, integrate, and synthesize information, with the goal of making new knowledge that is relevant to important goals.

A class should help students get that -- in some specific context. ***Biological physics is an interesting context for that purpose***, regardless whether a student goes on in that field.

The interesting questions in science are those where we shake our heads and ask, ***"How could anything like that possibly happen at all?"*** Physics, including biophysics, is full of such questions. (Some have answers, too.)

1.2: Your students need an upper-level class

Michael asked about Joe’s talk: “How can anyone cover all that stuff?”

Of course you can’t cram it into a single intro course. But you’ve got to cover it, if you want to prepare students in the ways advocated by BIO2010, MCAT, etc. Also if you wish to prepare students to do research in the current century.

The good news is, it’s amazing how much you *can cover* in just one more semester. I’ll describe two different courses, each of which I teach to undergrads with only one year of intro physics/calculus as the prerequisite.

Kimberly: “Will students need all this if they’re not going to be researchers?”

First, 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*.
Second... (coming later).

1.3: Things I've heard this week

- Bob: Complex word problems with long statements ("passage questions")... You walk into a room with an unfamiliar problem, and you need to pull the right tool out of your bag... "Using content knowledge to reason about applications to living systems"
- Others will appear in the slides in green

2.1: Skills: Probabilistic thinking

Indoctrination
Skill set
Feedback in nat
Light, vision, ar
And now a wor
Wrap

Several speakers mentioned the "role of indeterminacy / probabilistic systems / statistical inference."

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.

2.2: Skills: What one does with data

- Students should be confronted with situations in which statistical variation is not just a nuisance to be minimized, but rather is telling us something quantitative and central to the hypotheses being confronted.
- Students should be exposed to statistical methods that they can actually understand and adapt for themselves, not just the incantations of authority figures or black-box buttons on canned software.
- Those methods should prepare students to evaluate others' work, and hence should include the Bayesian framework now sweeping through many fields.

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*.

2.3: An everyday question in clinical practice

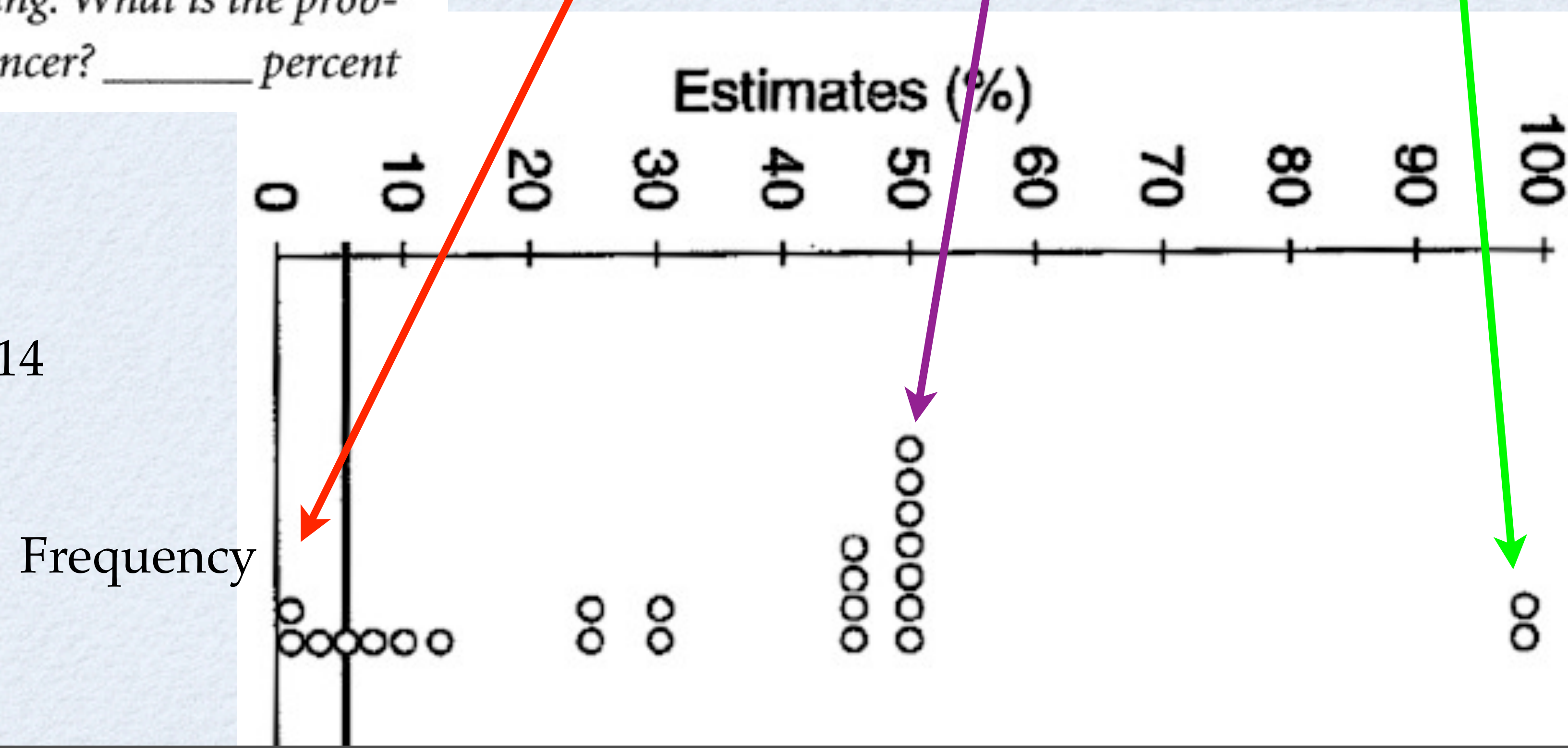
To diagnose colorectal cancer, the hemoccult test—among others—is conducted to detect occult blood in the stool. This test is used from a particular age on, but also in routine screening for early detection of colorectal cancer. Imagine you conduct a screening using the hemoccult test in a certain region. For symptom-free people over 50 years old who participate in screening using the hemoccult test, the following information is available for this region:

The probability that one of these people has colorectal cancer is 0.3 percent. If a person has colorectal cancer, the probability is 50 percent that he will have a positive hemoccult test. If a person does not have colorectal cancer, the probability is 3 percent that he will still have a positive hemoccult test. Imagine a person (over age 50, no symptoms) who has a positive hemoccult test in your screening. What is the probability that this person actually has colorectal cancer? ______ percent

After we work through the correct reasoning, then we see how the Bayes formula packages it into a simple procedure.

Back to Kimberly's question:

Here are the replies of 24 practicing physicians, who had an average of 14 years of professional experience:



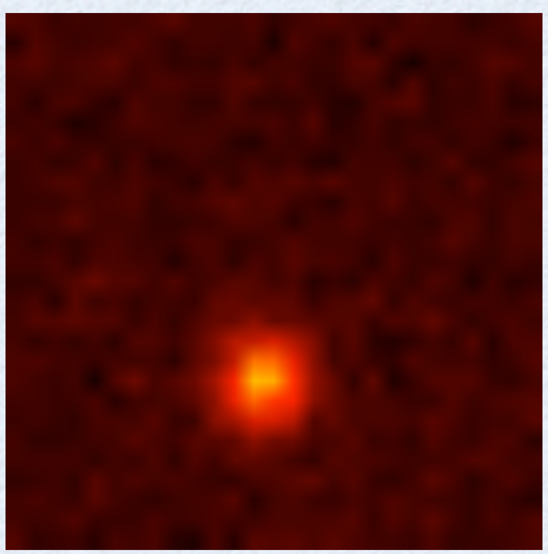
G. Gigerenzer, *Calculated risks*

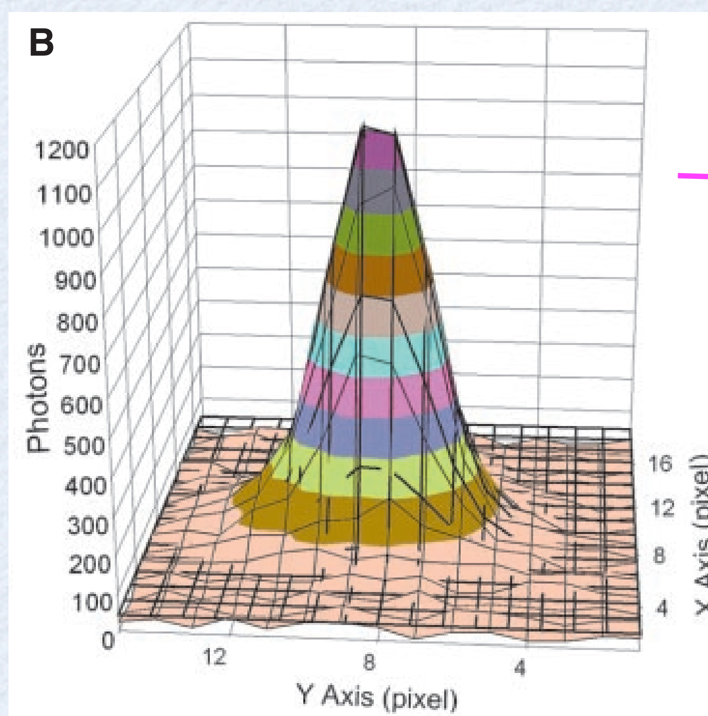
2.4: Beyond the diffraction limit

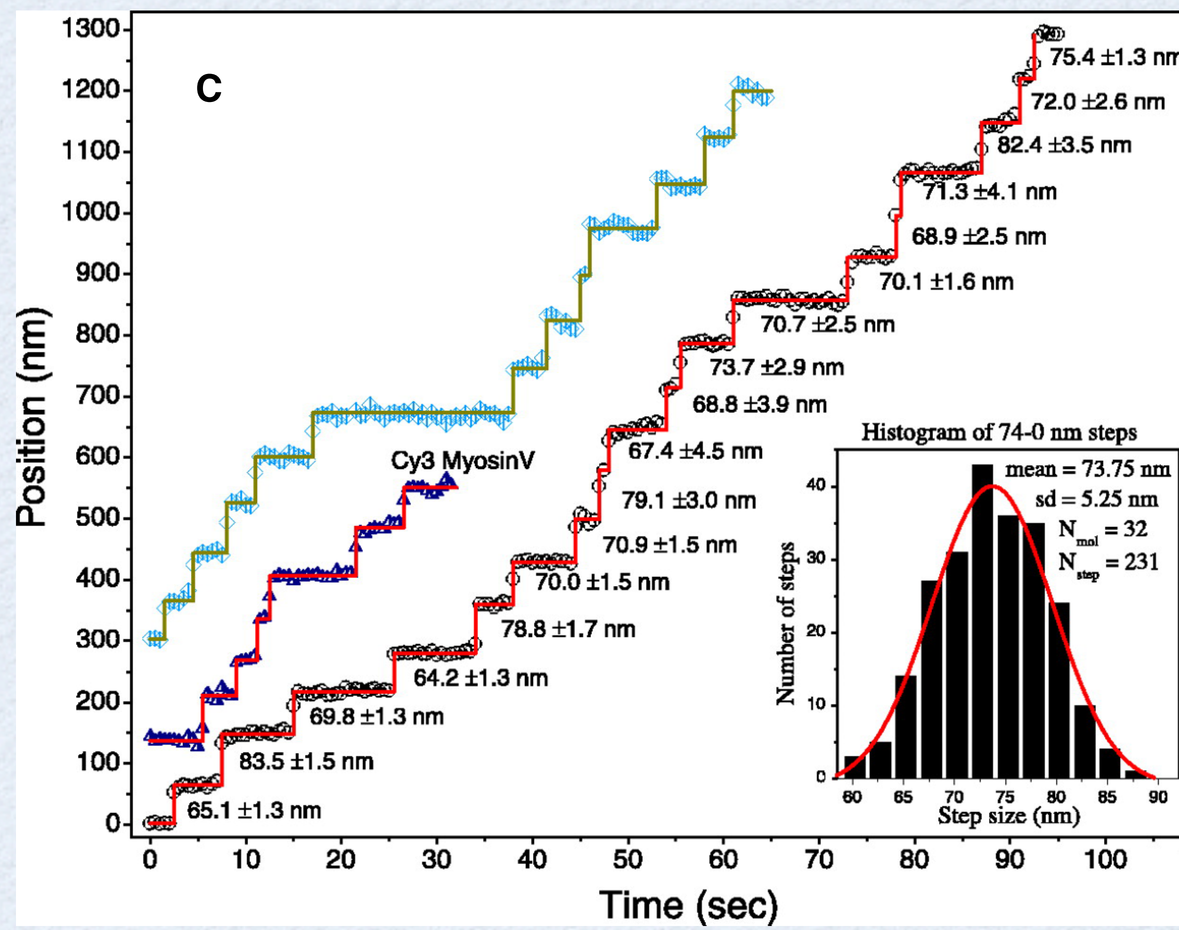
Framing: “How Life Does Those Tricks” -- that’s interesting. But “How Instruments Work” -- that’s interesting too.

Hey, how did Yildiz et al. measure the steps taken by a molecular motor using visible light? The diffraction-limited spot is at least 200 nm wide! In fact, *Everything interesting* in cells is below the diffraction barrier!

We must reimagine imaging as a problem of ***inference***. Where is that bead?







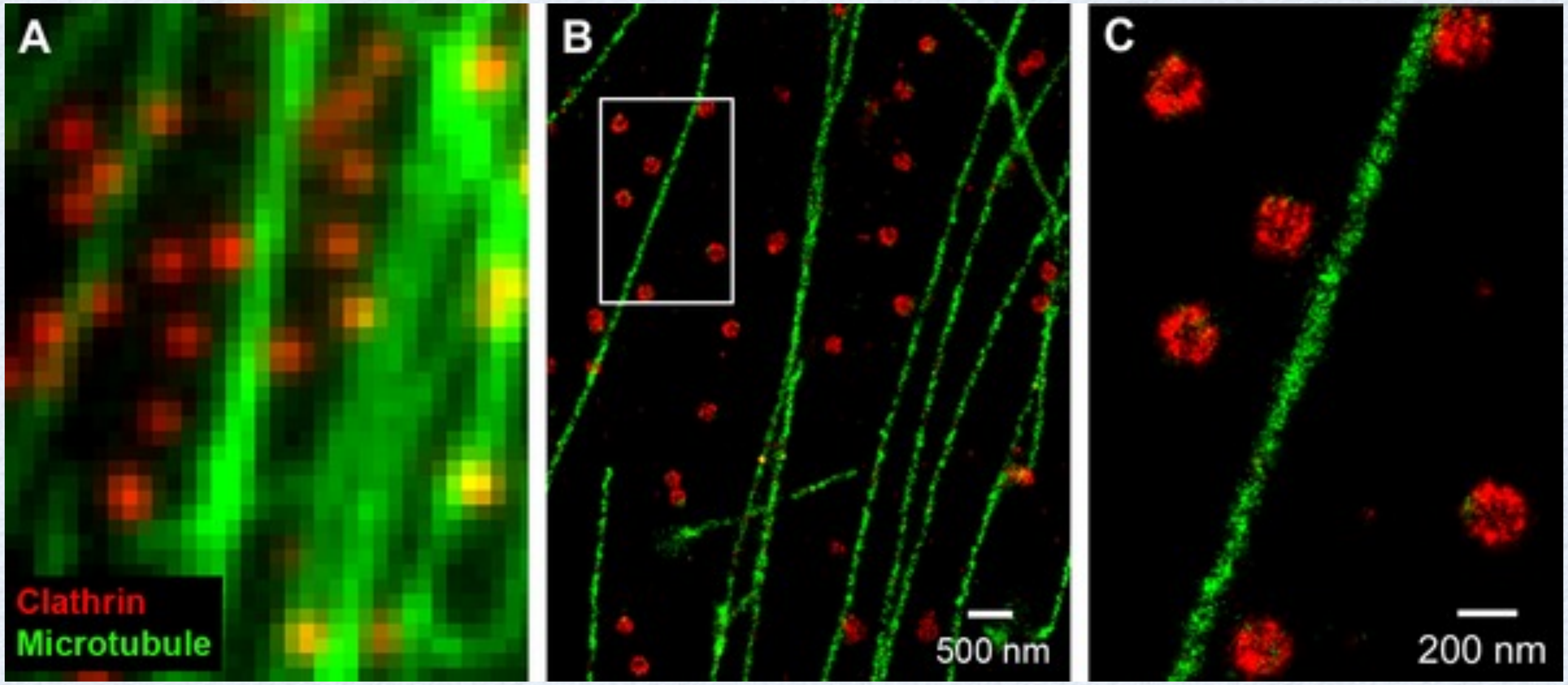
A Yildiz, J N Forkey, S A McKinney, T Ha, Y E Goldman, P R Selvin. Science (2003) **300**: 2061.

Is that all?

Is anything *newer* going on?"

Oh, yes. Here's a family of techniques that got named **"Method of the year 2008"** by *Nature Methods*:

Conventional: Superresolution: Detail:



Understanding the lumpy, statistical character of light has led to microscopy methods like PALM, fPALM, STORM, STED.

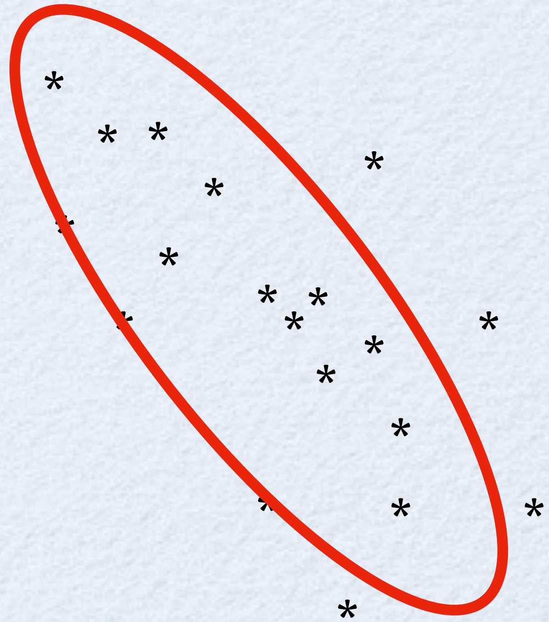
Catherine's students say, "Nobody in my lab knows about how this instrument works..."

Images: Bo Huang, Mark Bates, Xiaowei Zhuang. Annu Rev Biochem (2009) vol. 78 pp. 993-1016.

2.5: Teaching/research

In fact, the Bayes formula, and its variant maximum likelihood, lead to most of the statistical methods we need.
I've used the same thinking in my own work on molecular motors and on neuroscience. (**Lucky I had to teach it!**)

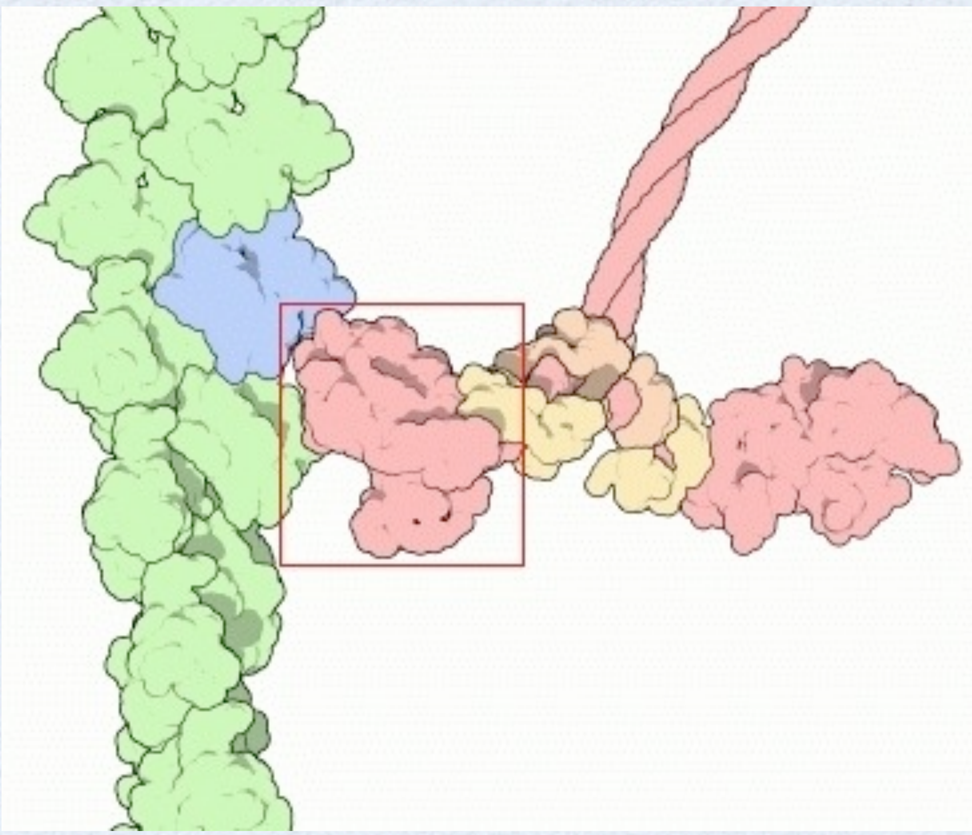
Just this week, Raghu asked me:
"I got a lot of blips on my CCD camera. I'm interested in finding the best determination of how that blob is oriented. I don't care where it's centered, nor how wide it is. And the answer should run fast, because I want to do this on a lot of video frames."

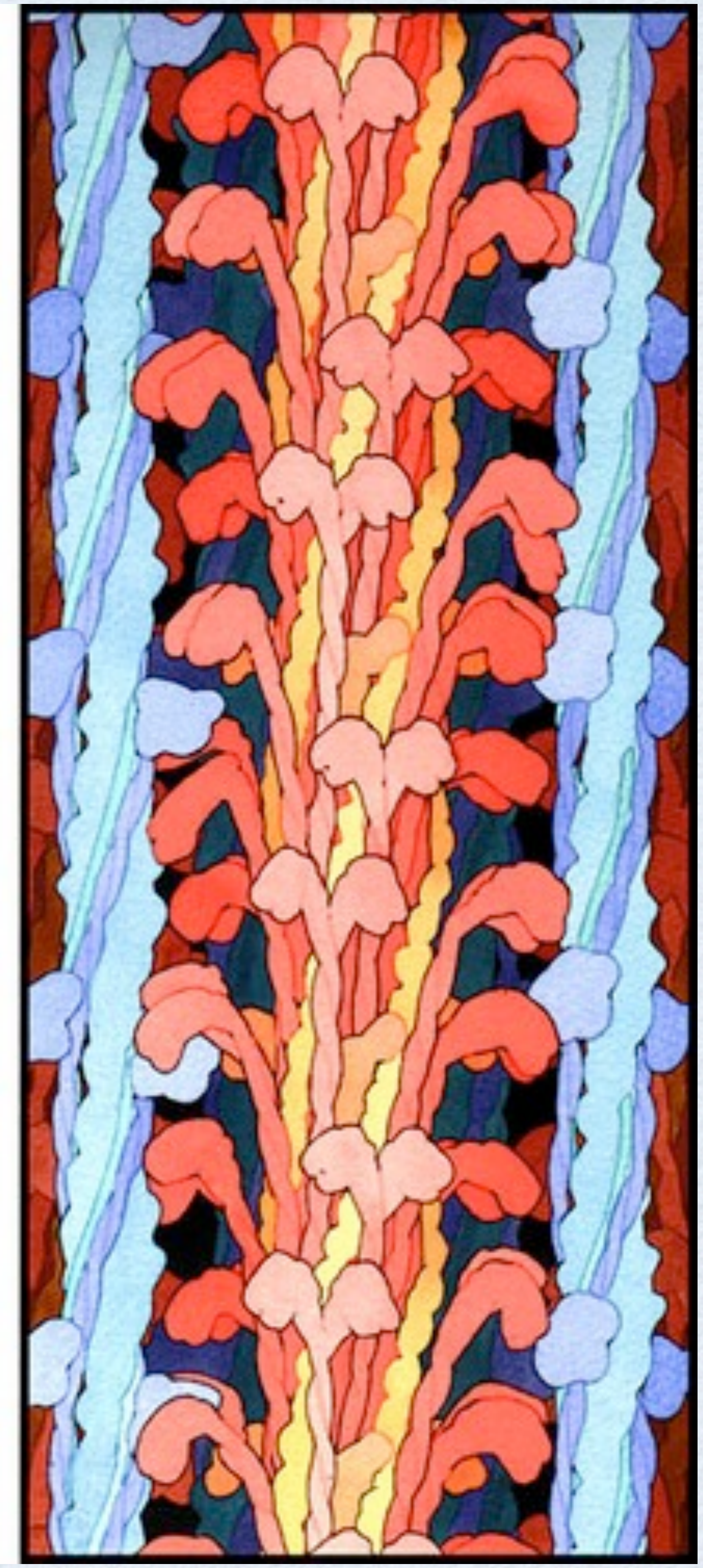


Well, you set up a likelihood function, then marginalize the uninteresting (nuisance) parameters. It's not too difficult, once you've got the framework.

2.6: Molecular machines

Myosin is a molecular motor that walks on actin filaments:





Framing: How can we get information about this invisibly small motor's mechanism?

Here is where a little probability goes a long way.

Students can test two hypotheses about the gait by analyzing the statistics of the motor's steps:

Images based on x-ray crystallography data by David Goodsell.

SCIENCE VOL 300 27 JUNE 2003

Myosin V Walks Hand-Over-Hand: Single Fluorophore Imaging with 1.5-nm Localization

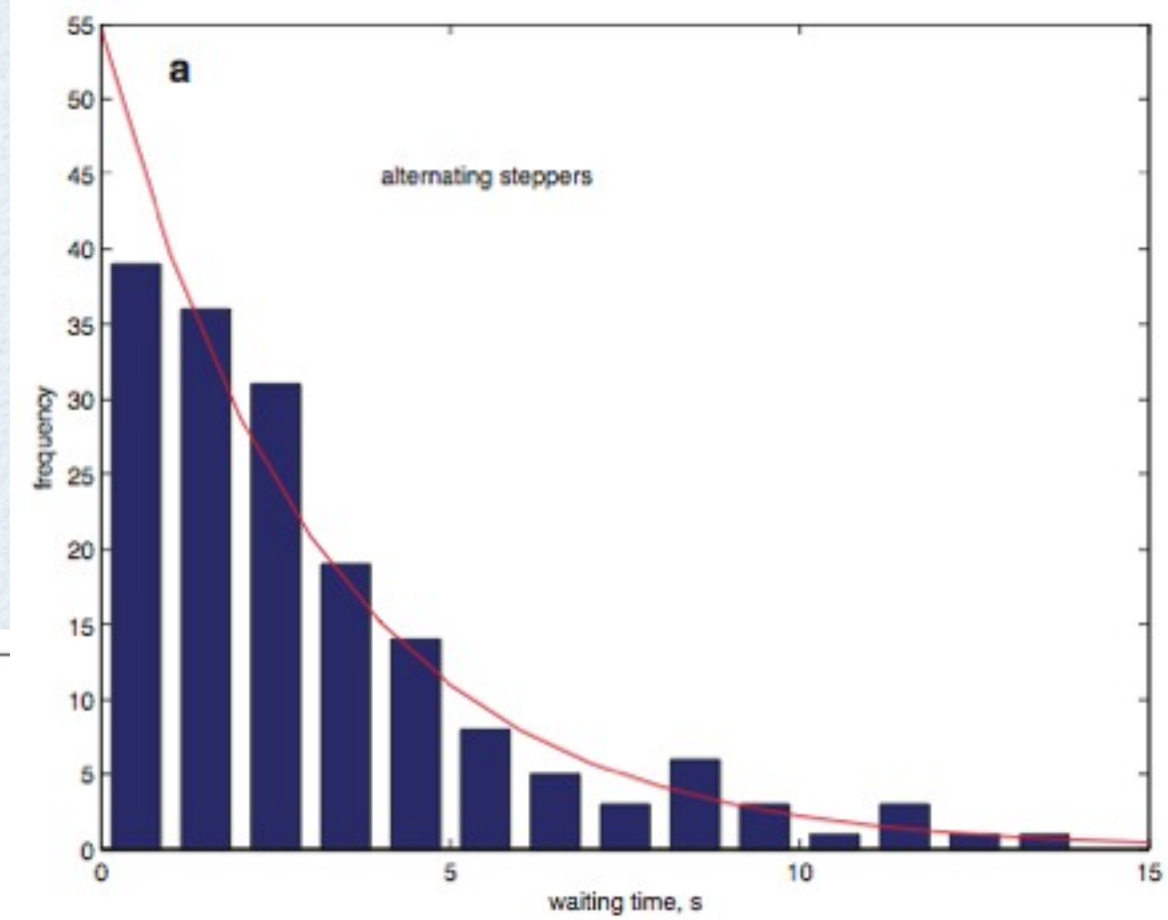
Ahmet Yildiz,[1] Joseph N. Forkey,[3] Sean A. McKinney,[1,2] Taekjip Ha,[1,2] Yale E. Goldman,[3] Paul R. Selvin[1,2*]

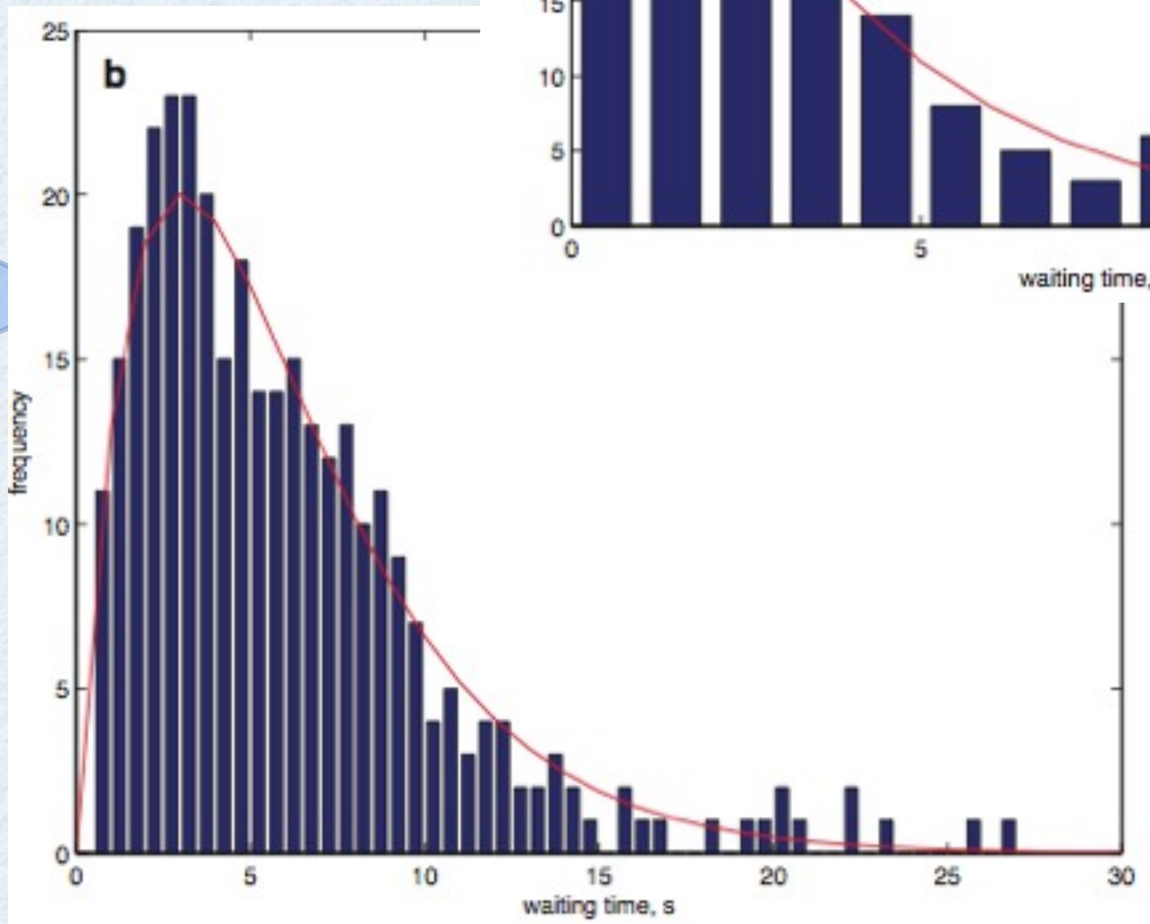
Second, we can also detect the 0-nm steps indirectly via a kinetic analysis. If the step rate of one head is k_1 (A → B, Fig. 1) and the step rate of the other head is k_2 (B → A′, Fig. 1), then the dwell time probability distribution function for the A → B transition is $f(t) = k_1 e^{-k_1 t}$ and for the B → A′ transition is $g(t) = k_2 e^{-k_2 t}$. In the 42-33 and 52-23 cases, the total probability of dwell times is the sum of two exponentials: $P(t) = (k_1 e^{-k_1 t} + k_2 e^{-k_2 t})/2$. If each head has the same stepping rate, $P(t)$ reduces to a single exponential $P(t) = k_1 e^{-k_1 t}$. In the 74-nm case, the observable is A → A′, which is the CONVOLUTION of two processes. If A → A′ takes t s, and A → B takes u s, then B → A′ will take $t - u$ s with $0 < u < t$. Integration over all possible values of u gives the convolution $P(t) =$

$$\int_0^t f(u) \cdot g(t-u)\,du = k_1 k_2 \cdot (e^{-k_1 t} - e^{-k_2 t})/(k_1 - k_2).$$

If the two rates are equal, then $P(t) = t k^2 e^{-kt}$. Note that $P(0) = 0$ and that $P(t)$ initially increases and then decreases for the 74-nm data if they contain hidden 0-nm steps, whereas the 42-33 or 52-23 data are expected to decay monotonically.

Dwell time distribution of the two stepping types of myosin X. Top: alternating steppers; Bottom: long-steppers.
These distributions tell a story, once students learn how to convert a hypothesis to a predicted distribution (curves).





Graphs from P Nelson, *Physical models of living systems* (WH Freeman, to appear).

2.7: Bacterial genetics

Framing: Drug resistance is a very big deal.

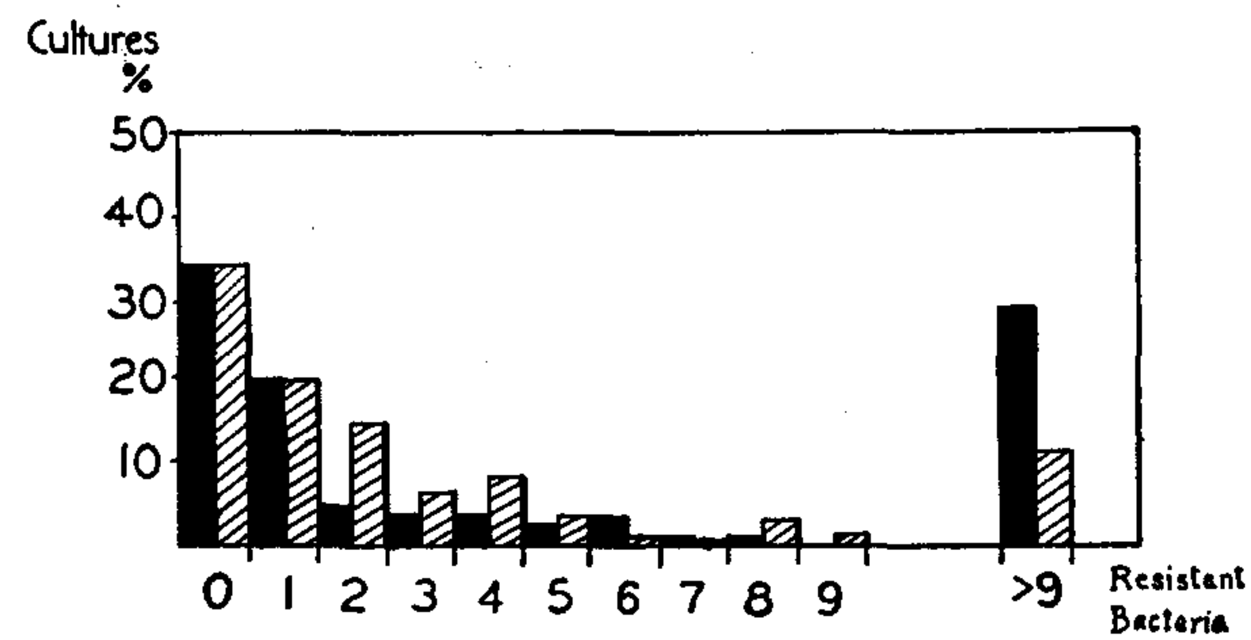


FIGURE 2.—Experimental (Experiment No. 23) and calculated distributions of the numbers of resistant bacteria in a series of similar cultures. Solid columns: experimental. Cross-hatched columns: calculated.

Luria & Delbruck, 1947

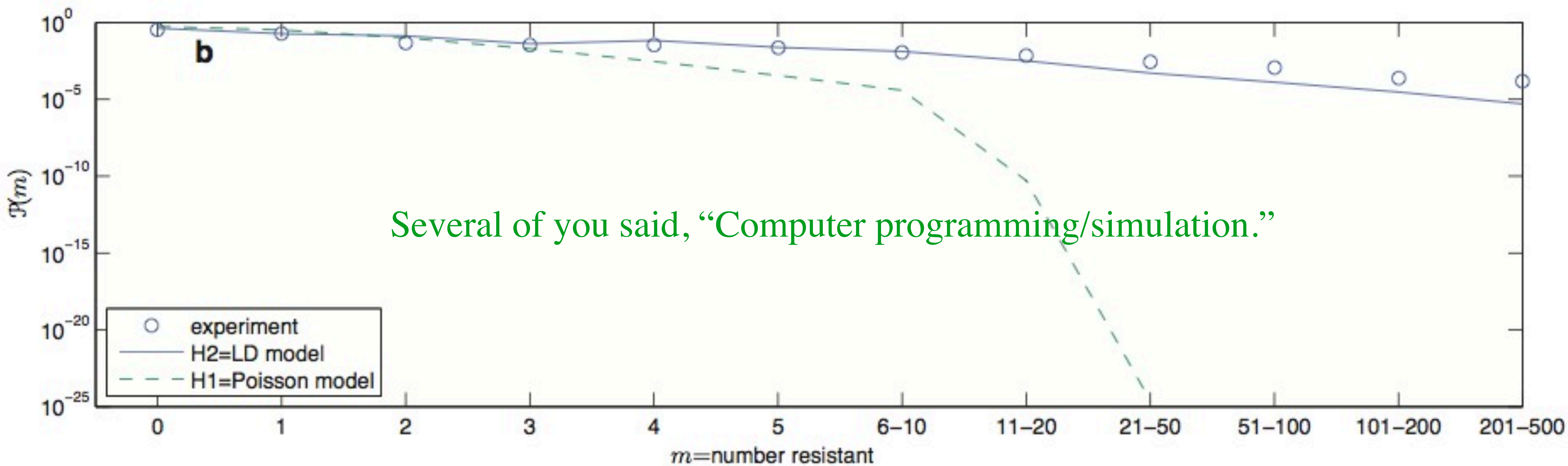
Luria and Delbruck noticed a statistical peculiarity in their data -- a huge "fat tail." They came up with a "Mendel, not Lamarck" model for drug resistance, and detailed quantitative predictions for such distributions that distinguished their model from the alternative.

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 in MATLAB.

Students can easily simulate the Luria--Delbruck model using Matlab:

Of 5000 simulated cultures, most have zero resistant mutants but a few have *very* many. This may be an ancient case history, but a lot of cutting-edge research is done on “fat-tail” distributions like this one. Biophysics is a good context for students to learn how to handle such things. In fact, many distributions arising in Biophysics have *infinite variance.*

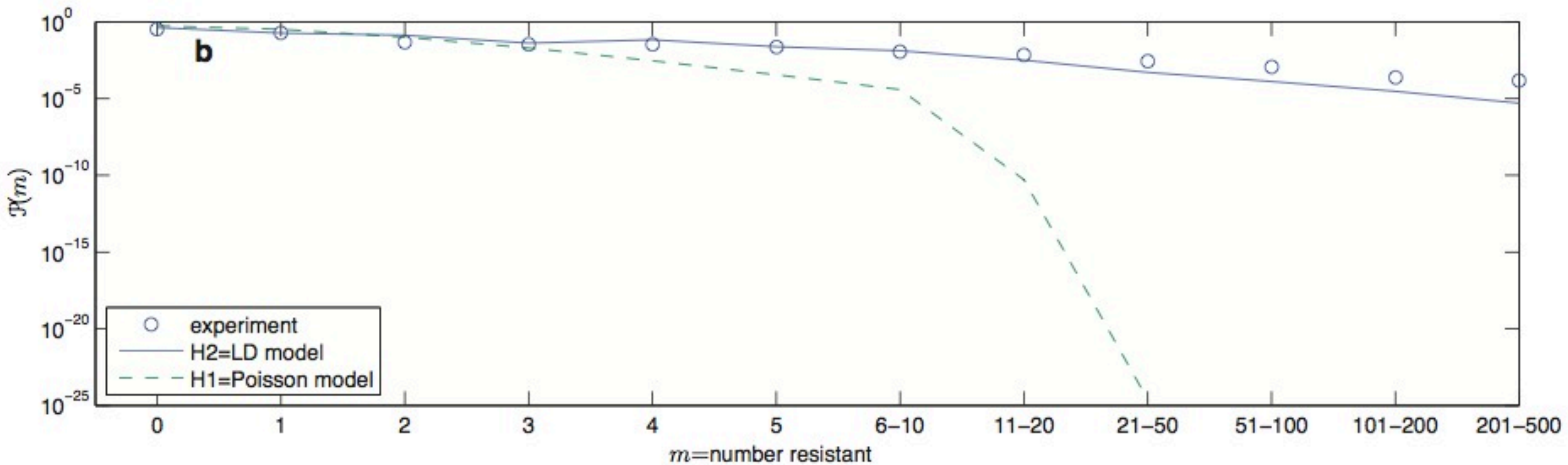


Several of you said, “Computer programming/simulation.”

And -- similar ideas are also illuminating when applied to retinoblastoma. ***A good physical model applies to problems beyond the one for which it was developed.***

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

Visual communication



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.

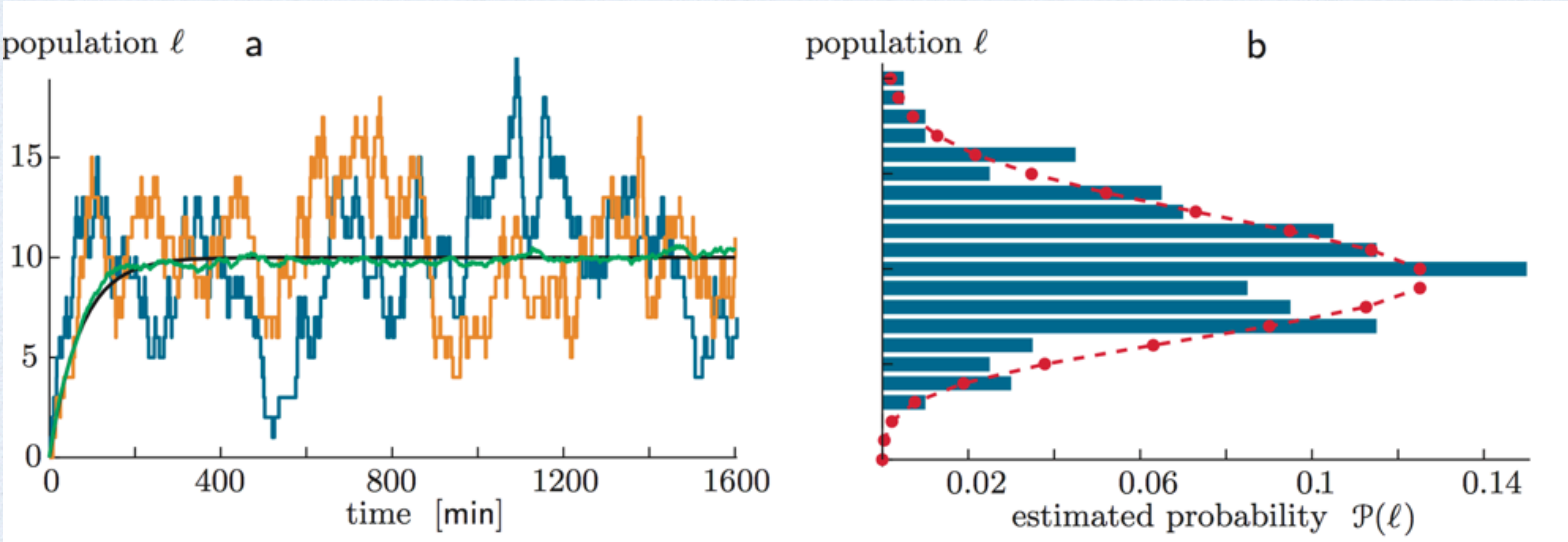
Barbara stressed "how to be a scientist" skills, including knowing what to do with data and scientific graphics that

2.6: From random quantities to random processes

Wonmuk said, "Stochastic simulation."

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.



3

Indoctrination

Skill set

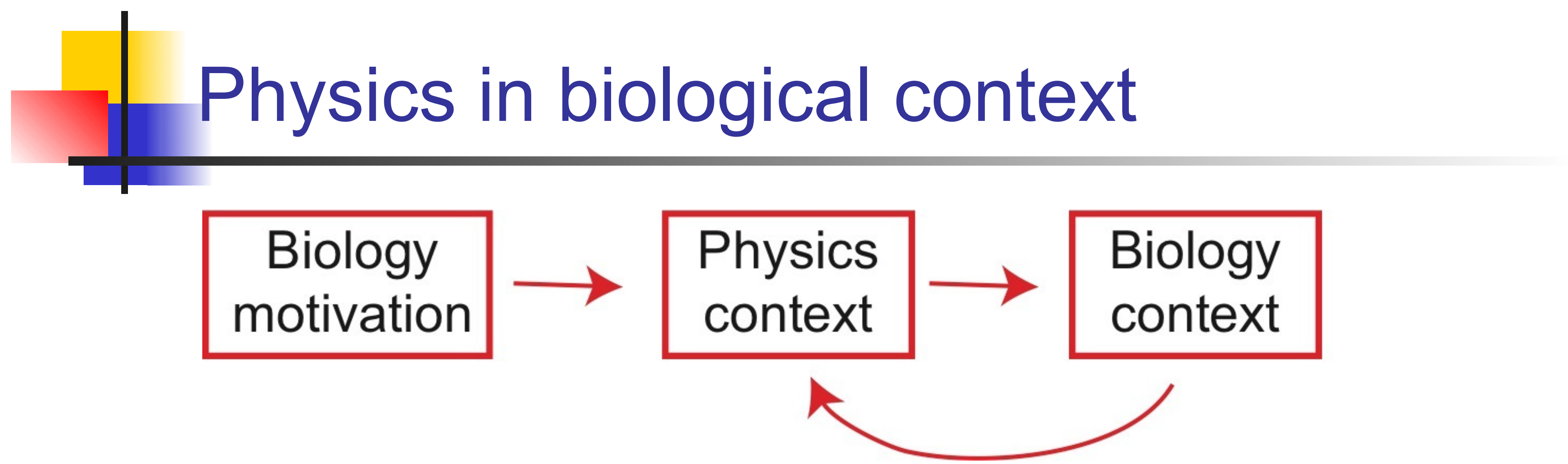
Feedback in natural and synthetic biology

Light, vision, and 21st C imaging

And now a word from our sponsor

Wrap

A lesson that Catherine told us:



SWARTHMORE

3: A new frontier

(Several speakers mentioned "systems behavior." BIO2010 says "dynamical networks")

- **Students are excited about synthetic biology, a 21st C science ("Build life to understand it").**
- **They are often unable to grasp some of the underpinnings of the field, however, because they have not yet been exposed to basic ideas about dynamical systems.**
- **Many of those ideas are rooted in mechanical and other physical metaphors that are no longer part of most students' general knowledge.**
- **Students, especially engineering students, like that.**
- **Natural living systems also employ feedback control.**
- **Out of the welter of zillions of articles, I chose *three* concepts. For each, I follow the same three steps:**
  - Introduce a *biological problem* cells face.
  - Find a *mechanical mechanism* that addresses an analogous problem.
  - Describe a *synthetic biology implementation* that is simple enough to admit a quantitative prediction.
  - Return to a natural example.

3.1 Biological problem: Homeostasis

Framing: Chemical reactions in cells are random. Environmental fluctuations are random. **How can a cell do anything organized in the face of all that randomness?**

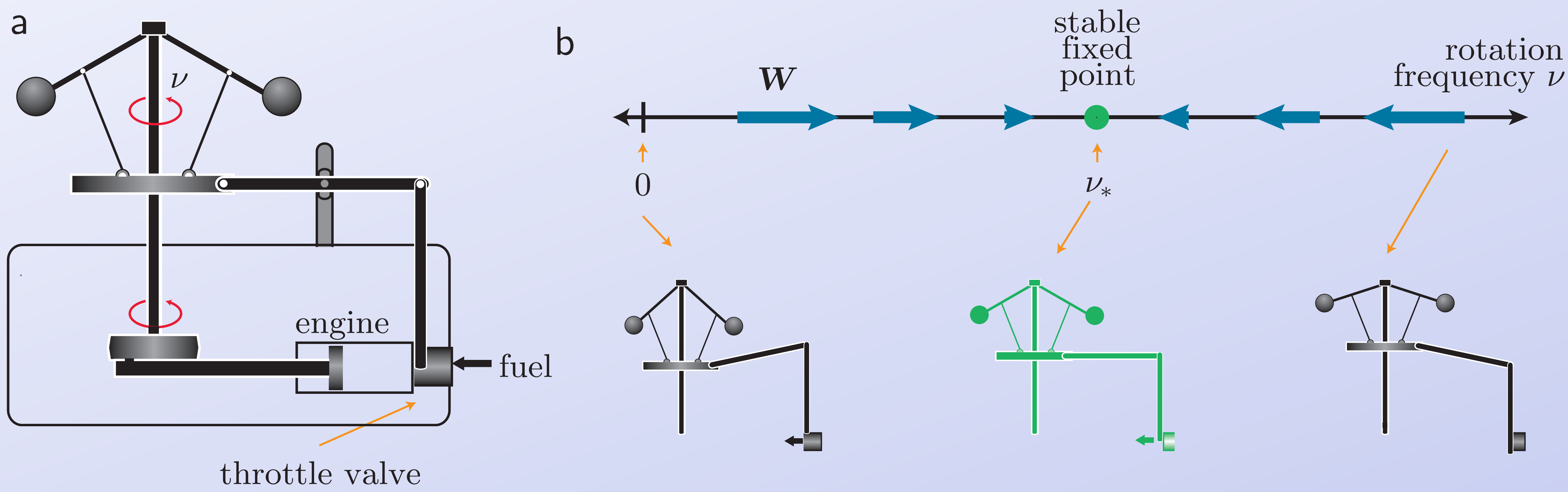
- **A cell does not have 6×10^{26} copies of each relevant molecule.** Fluctuations are significant.

- **Cells must also respond to variations of small numbers of external signal molecules.**

To get started, how does a cell even maintain a roughly constant composition (homeostasis)?

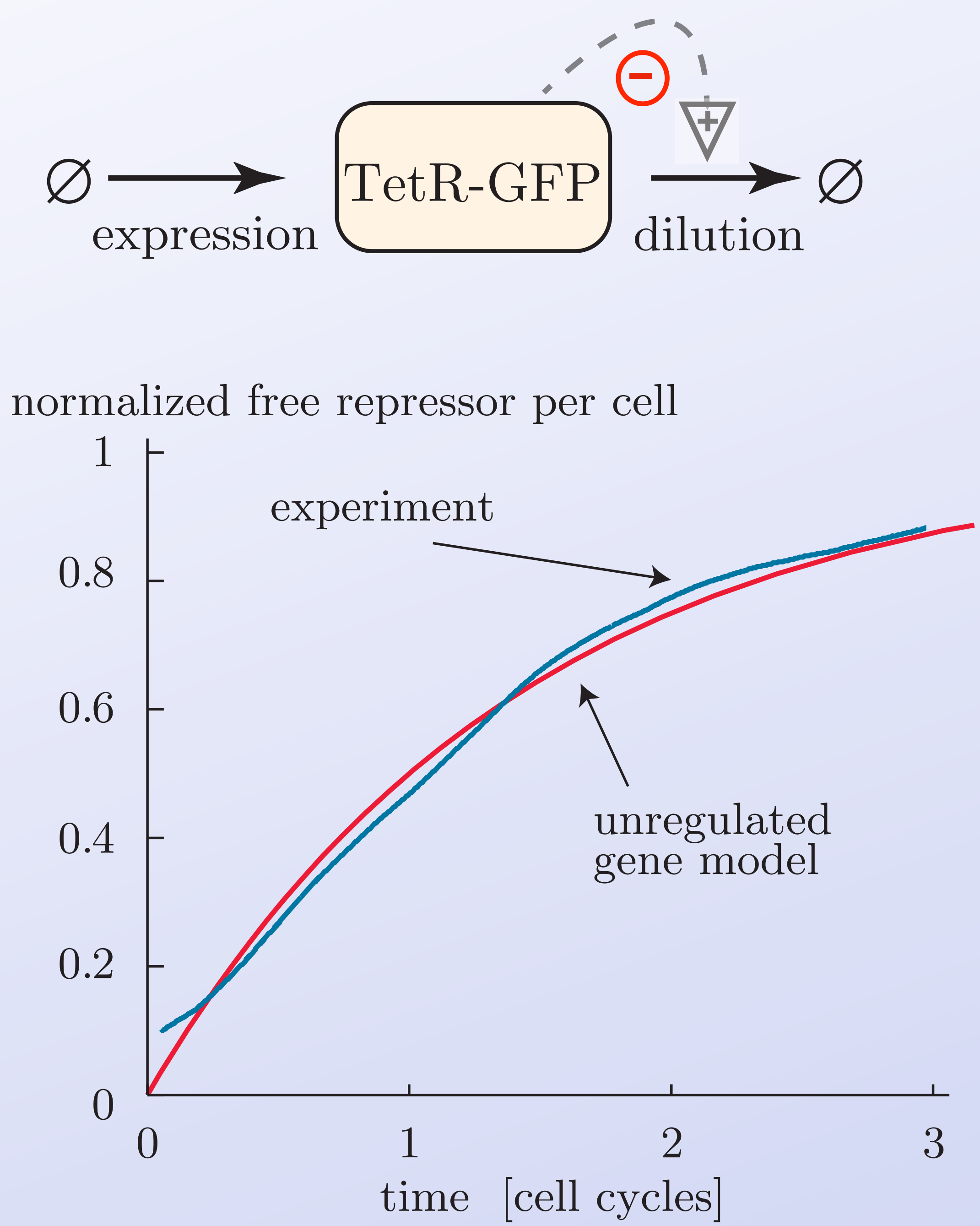
Biological problem I: Homeostasis

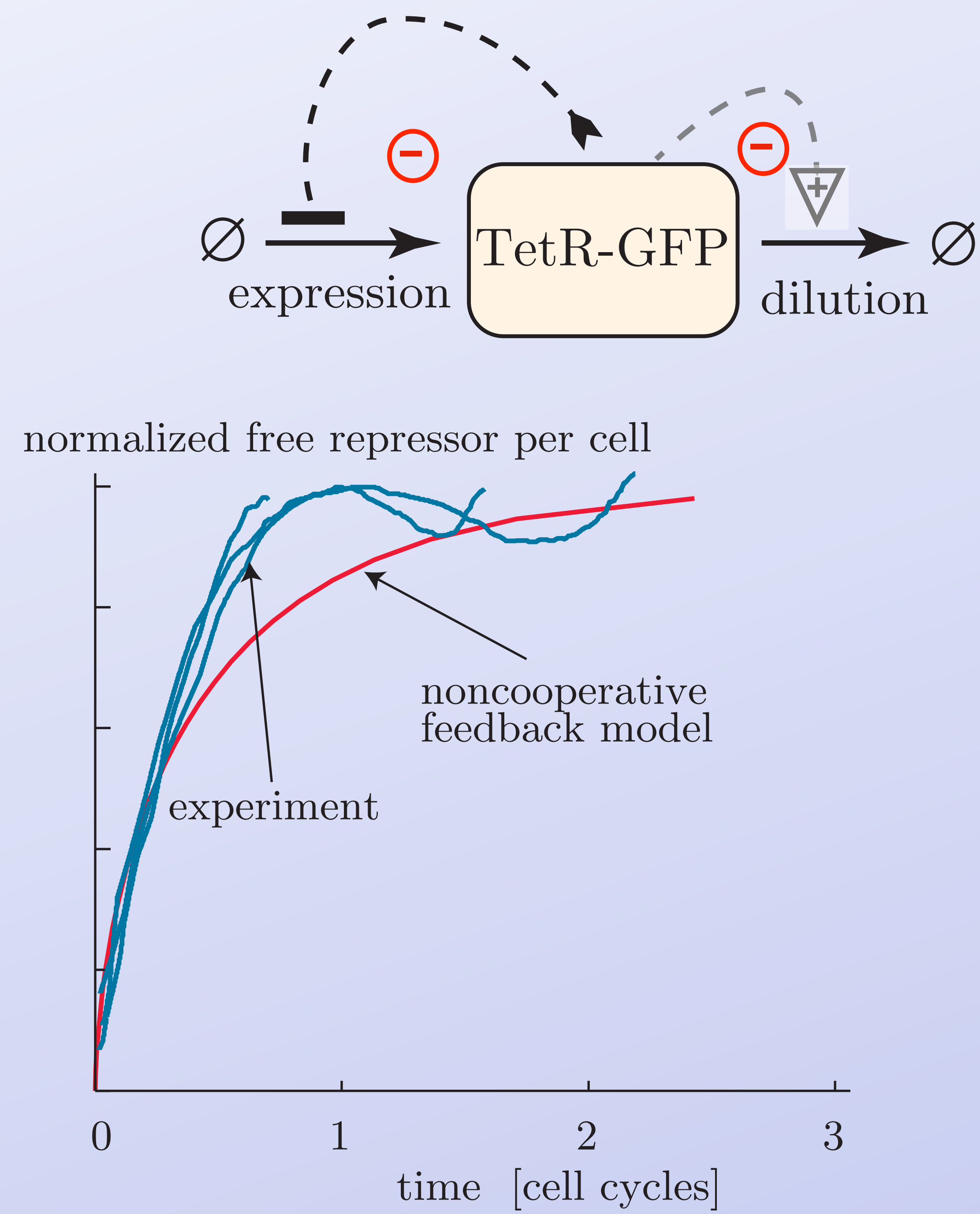
Mechanical analogy I: Governor



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

Biological problem I: Homeostasis
Mechanical analogy I: Governor
Synthetic biology I: Governor circuit





From P Nelson, *Physical models of living systems* (WH Freeman, to appear). Data from: N Rosenfeld et al. J Mol Biol (2002) vol. 323 (5) pp. 785-93

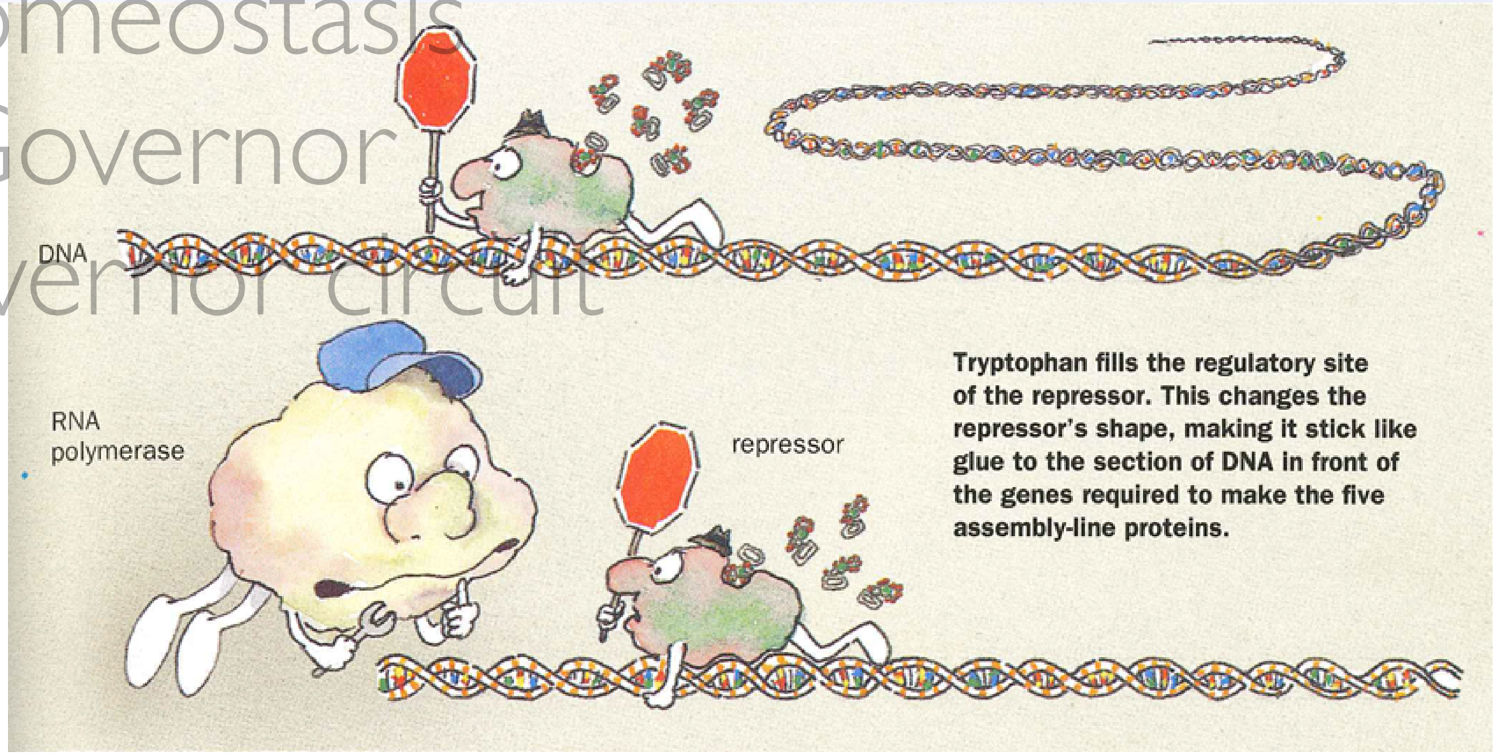
Biological problem I: Homeostasis

Mechanical analogy I: Governor

Synthetic biology I: Governor circuit

Natural realization I: *trp* regulation circuit

a



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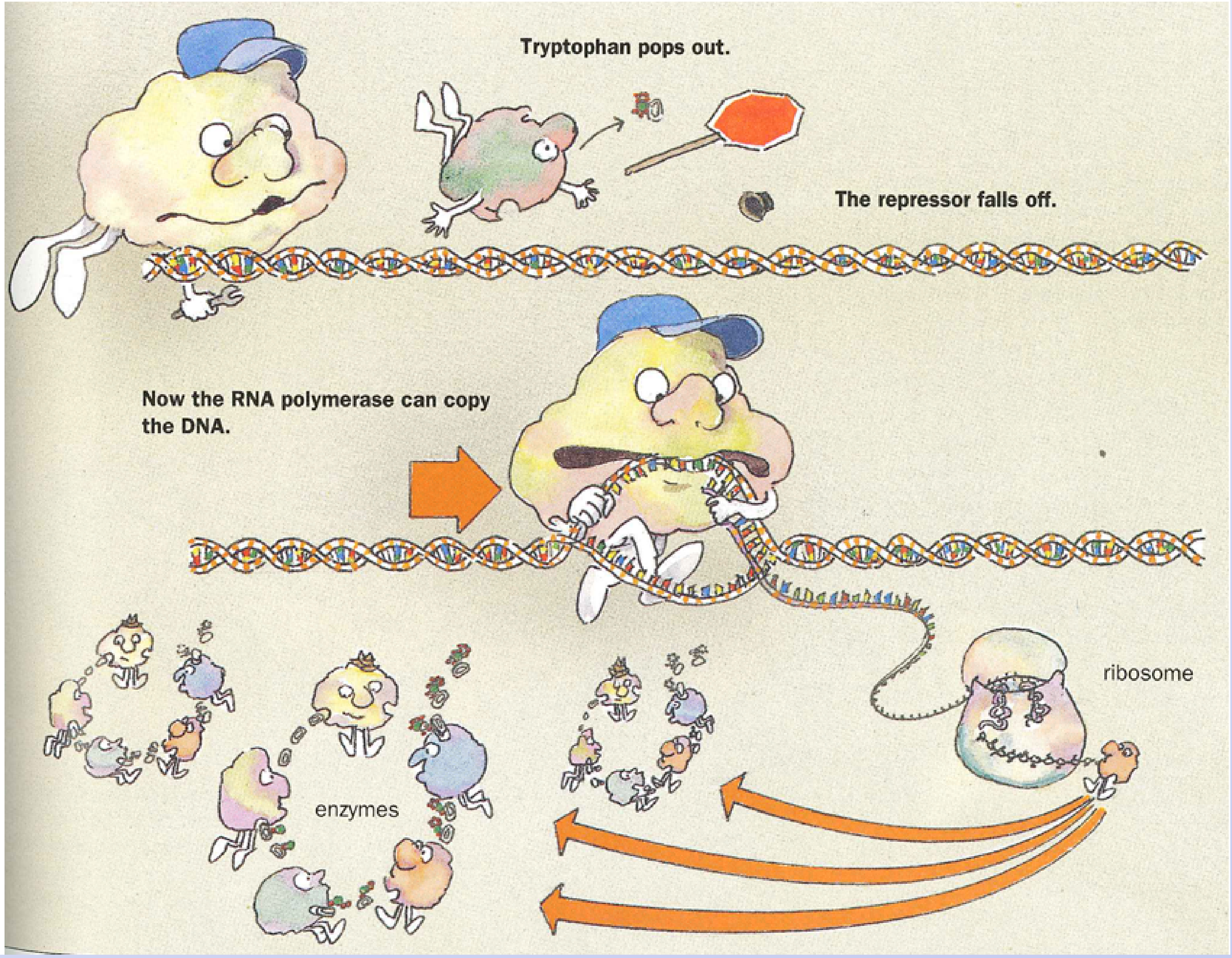
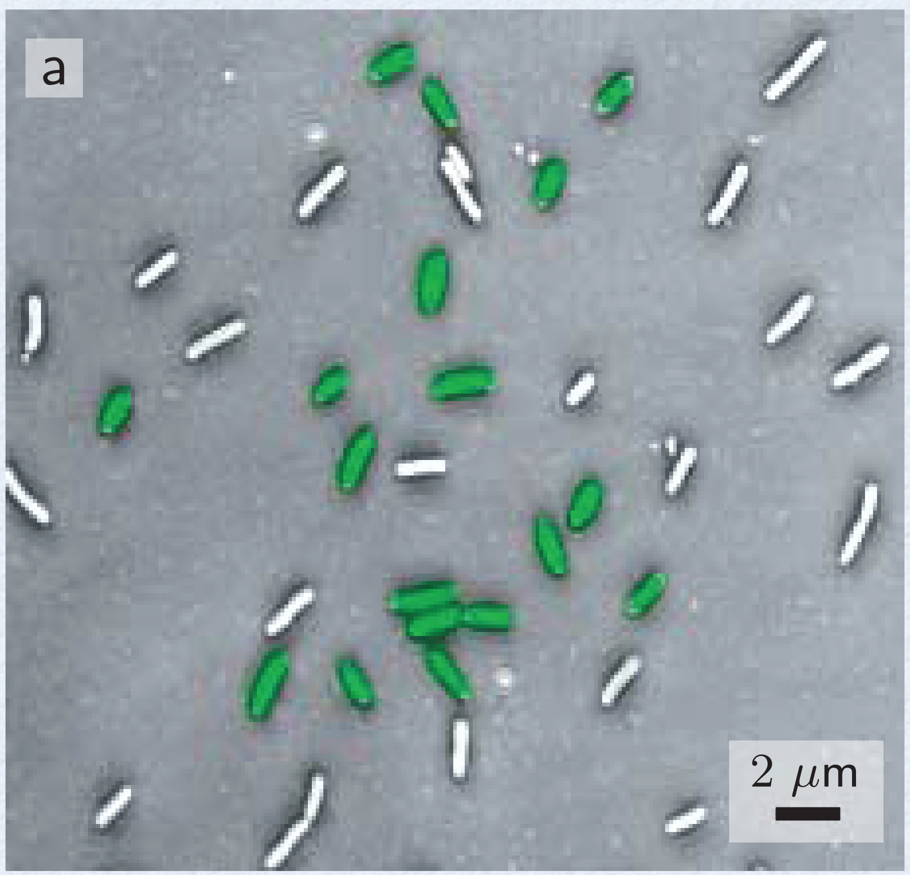
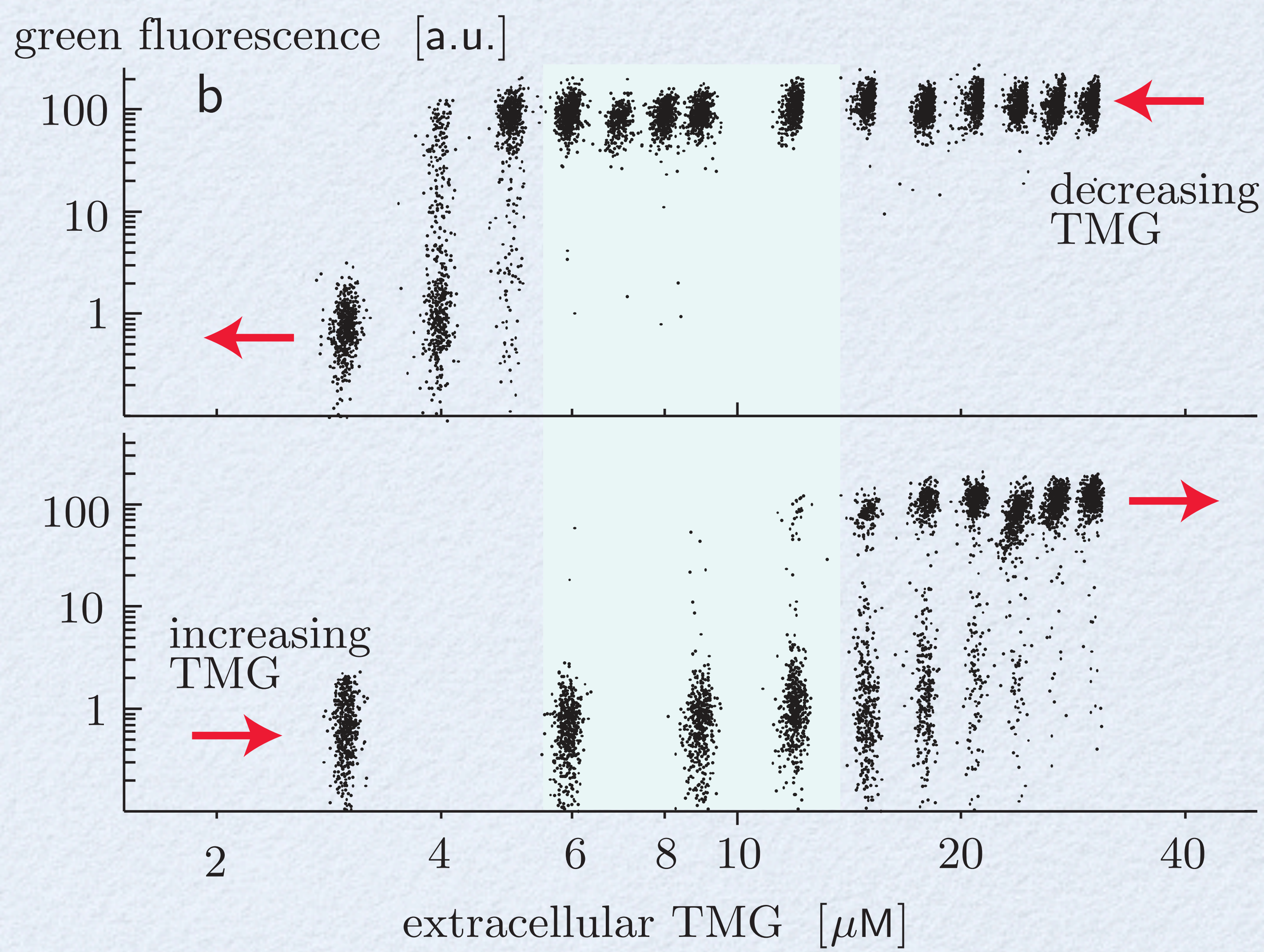


From Hoagland and Dodson, *The way life works*.

3.2 Biological problem: Switch response

Framing: How do you make decisions without a brain?

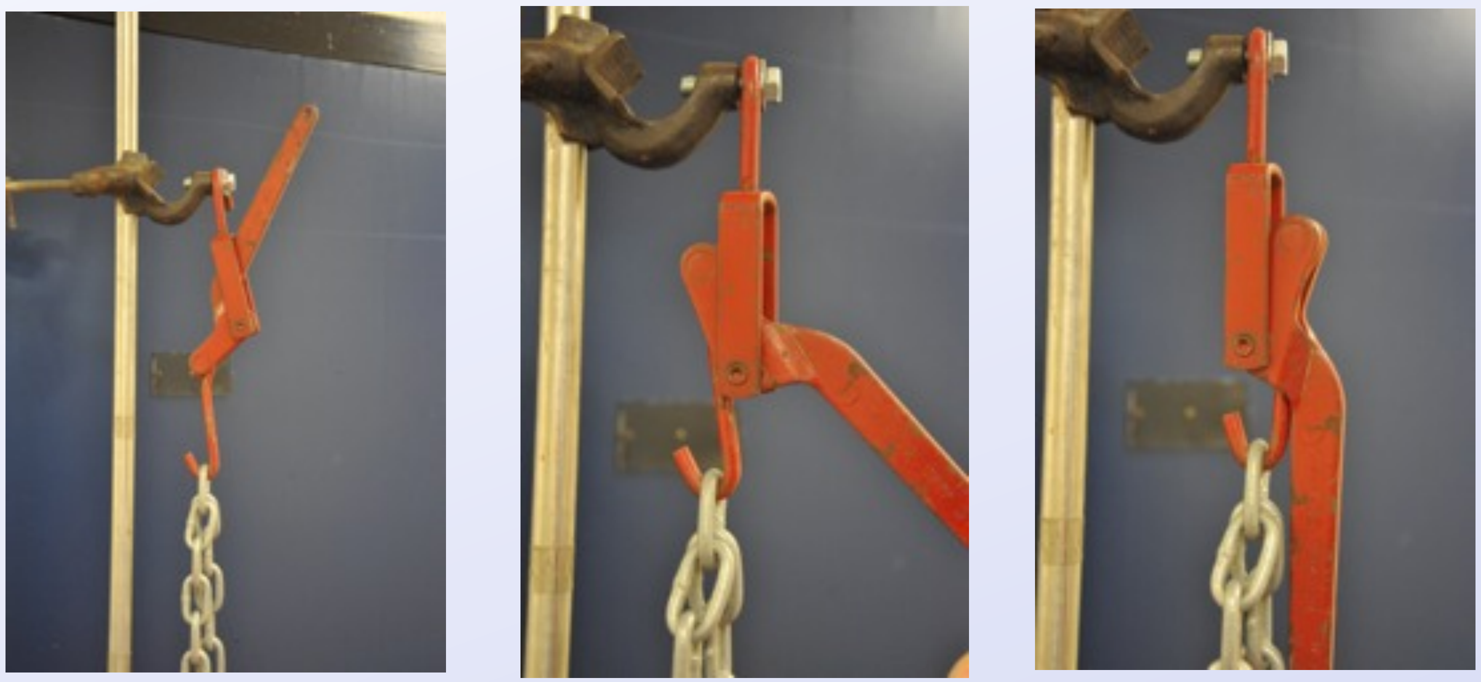


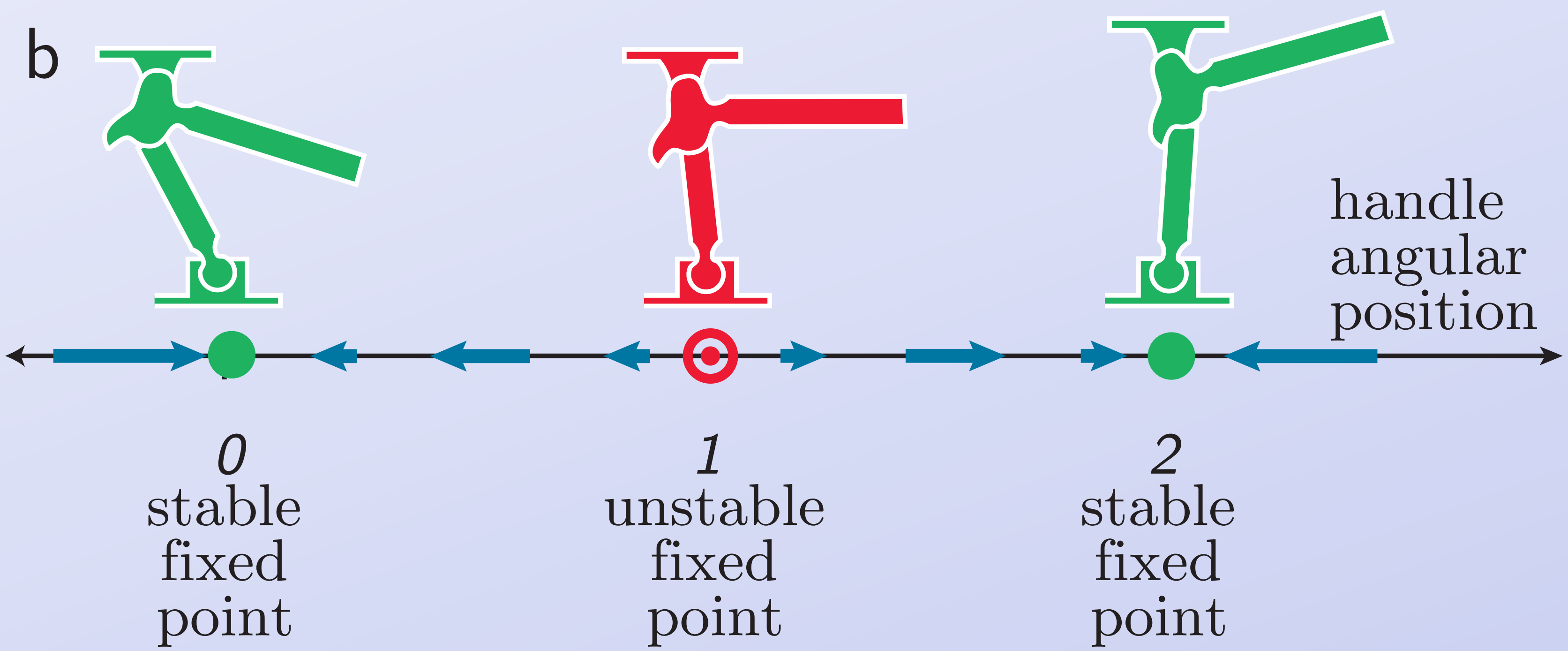


From P Nelson, *Physical models of living systems* (WH Freeman, to appear). Data and image from: Ozbudak et al., Nature (2004) vol. 427 (6976) pp. 737-740.

Biological problem 2: Switch response

Mechanical analogy 2: Toggle



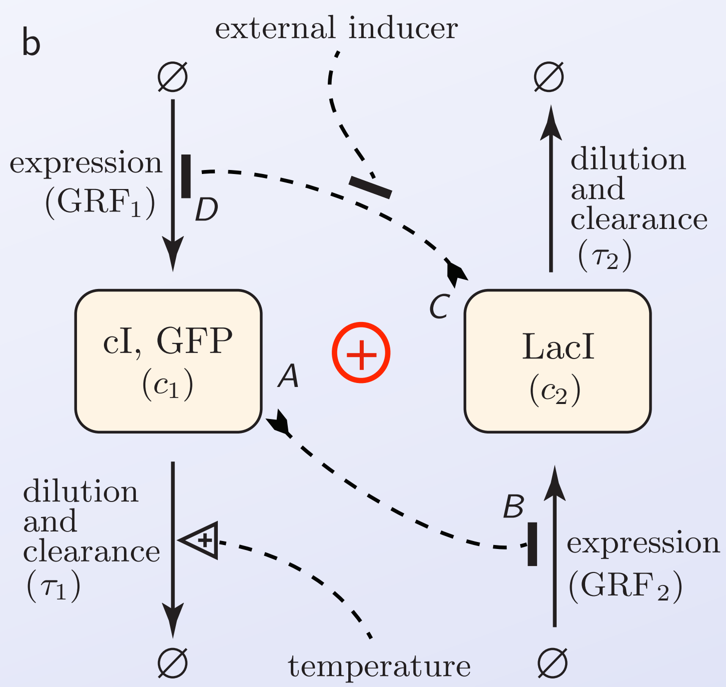


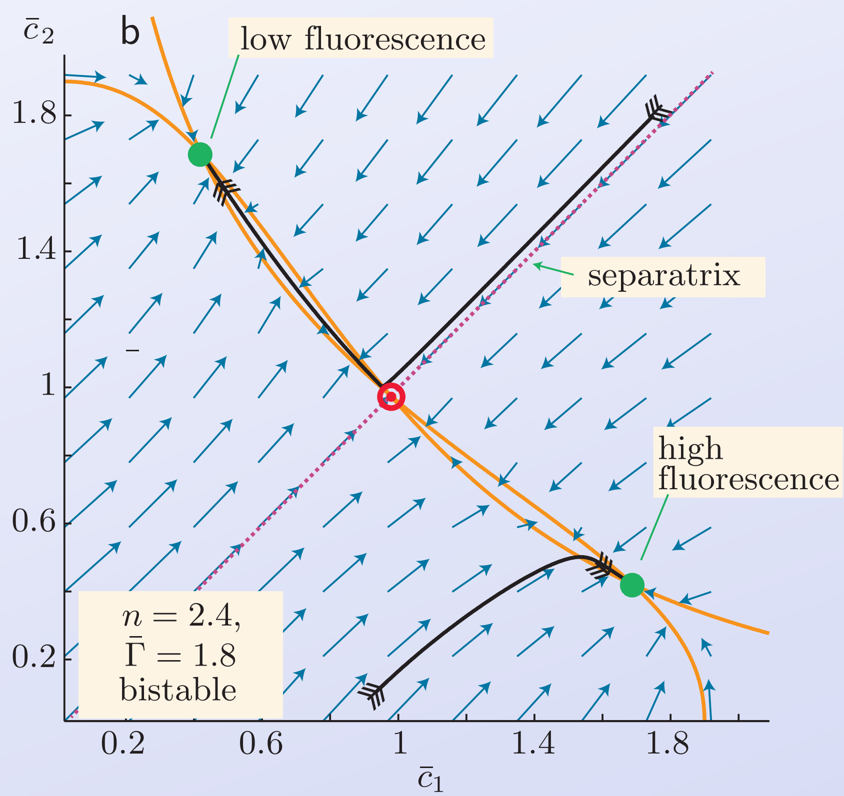
From P Nelson, *Physical models of living systems* (WH Freeman, to appear).

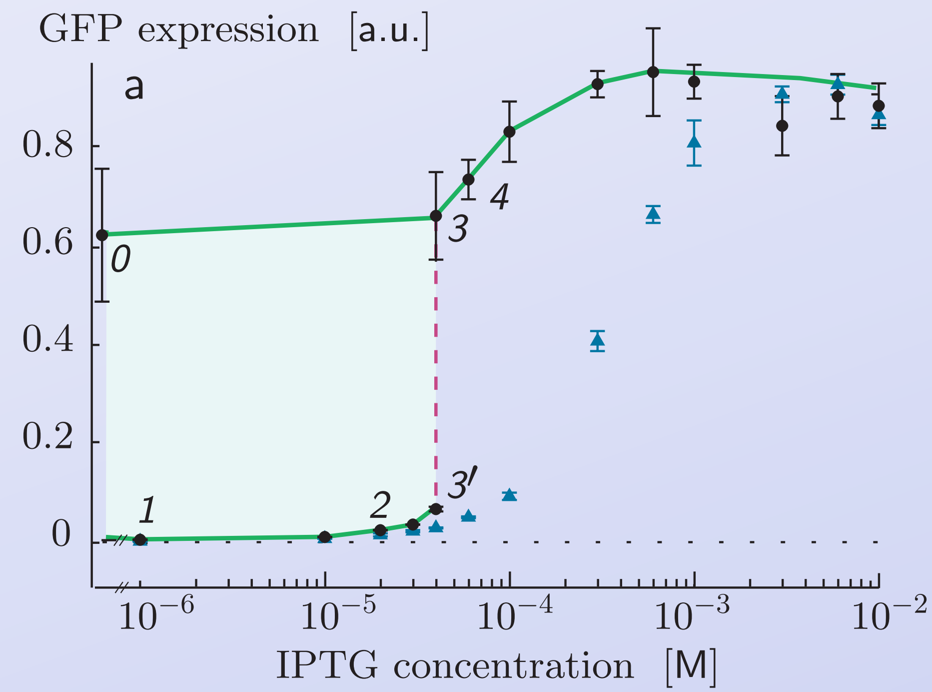
Biological problem 2: Switch response

Mechanical analogy 2: Toggle

Synthetic biology 2: Two-gene switch







Joe said, “How switches work”

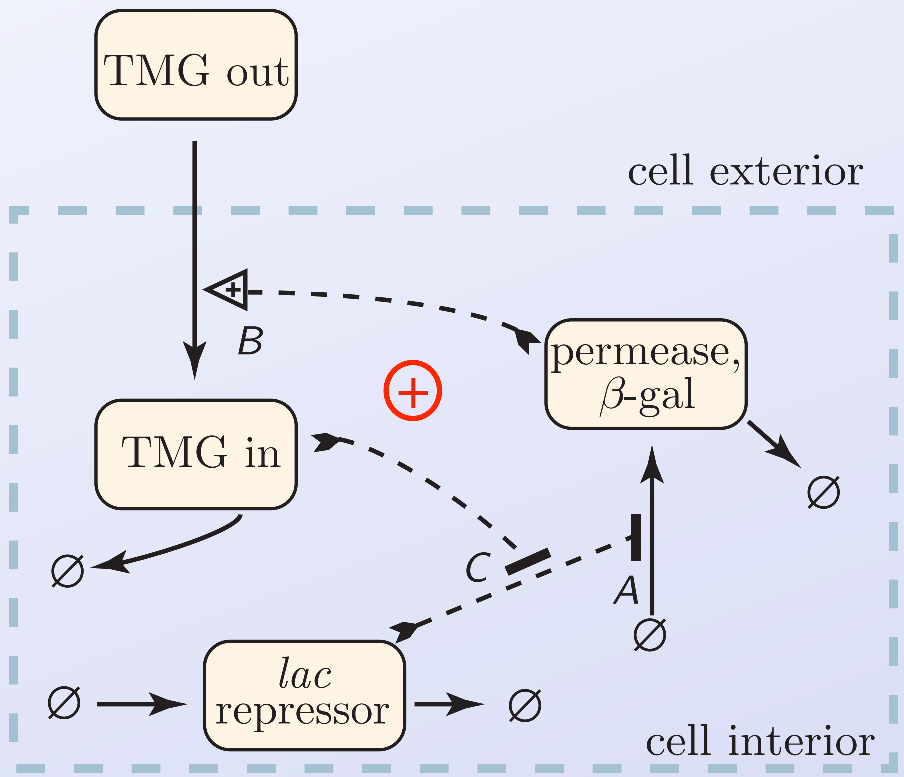
From P Nelson, *Physical models of living systems* (WH Freeman, to appear). Data from: Gardner et al., Nature (2000) vol. 403 (6767) pp. 339-42.

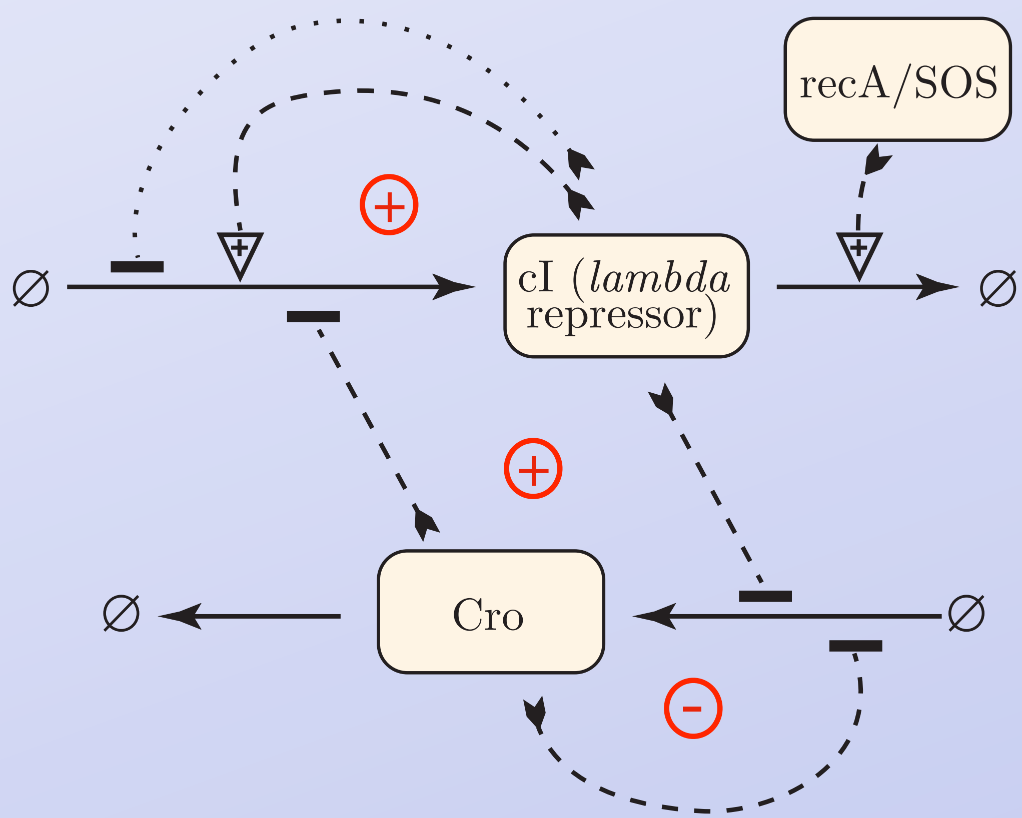
Biological problem 2: Switch response

Mechanical analogy 2: Toggle

Synthetic biology 2: Two-gene switch

Natural realization 2: *lac* and *lambda* switches

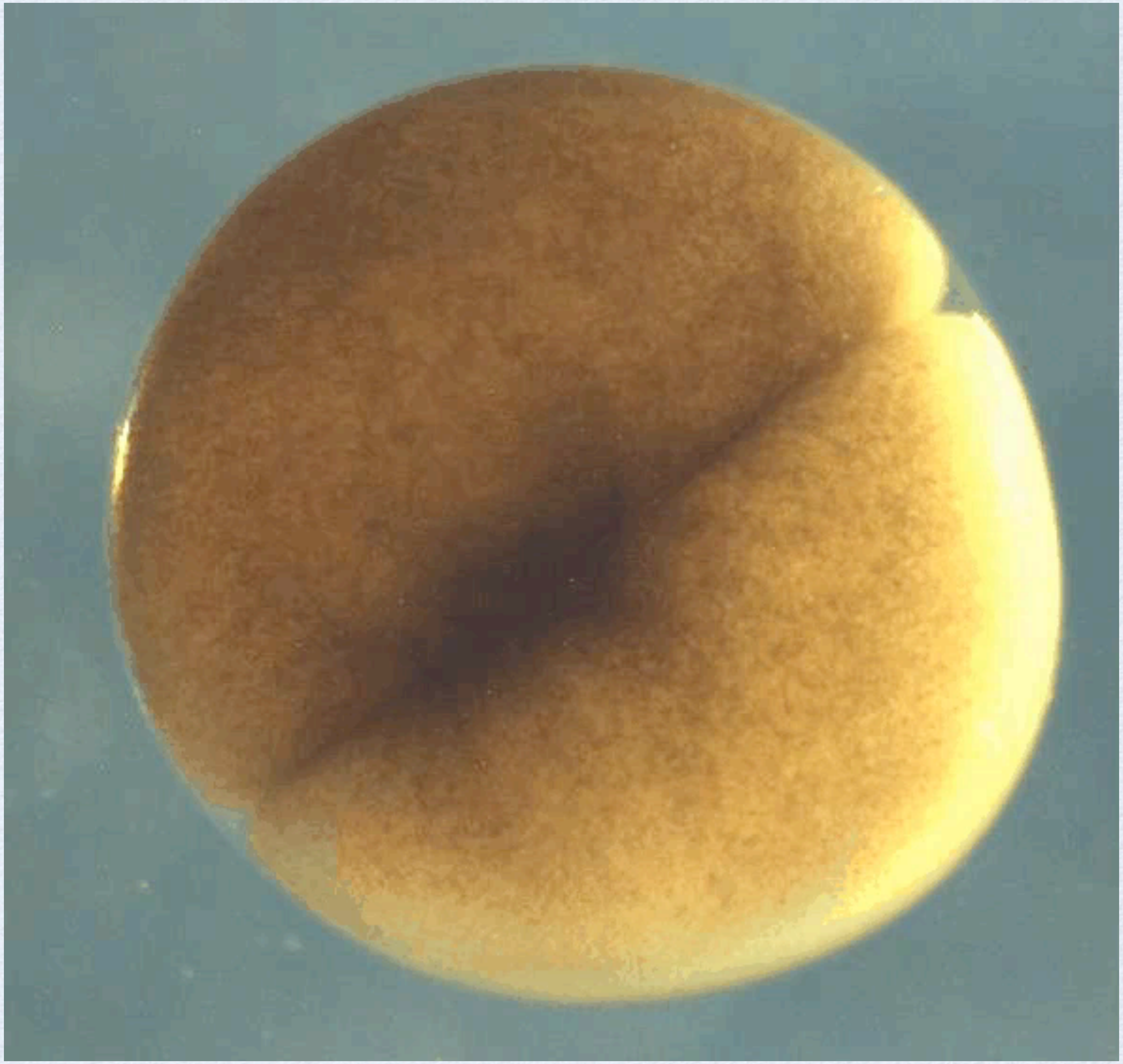




From P Nelson, *Physical models of living systems* (WH Freeman, to appear).

3.3 Biological problem: Periodic behavior

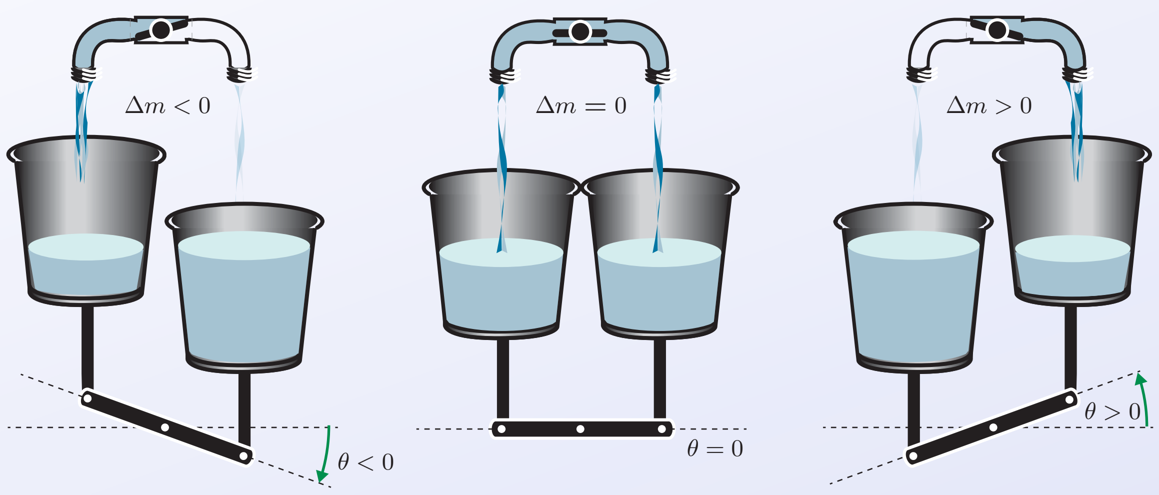
Framing: How do these dividing cells stay in sync without communicating?

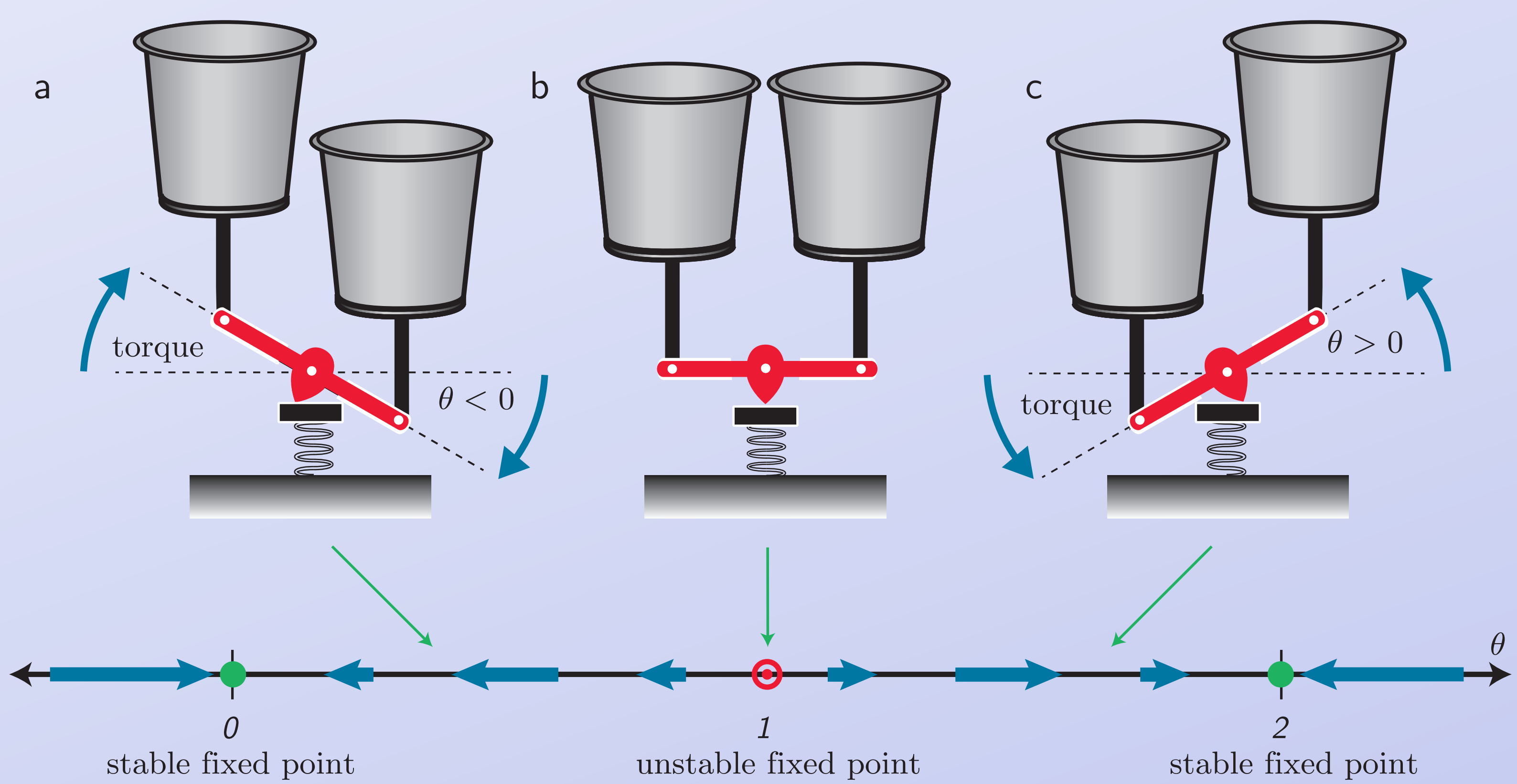


Video courtesy Tony Tsai.

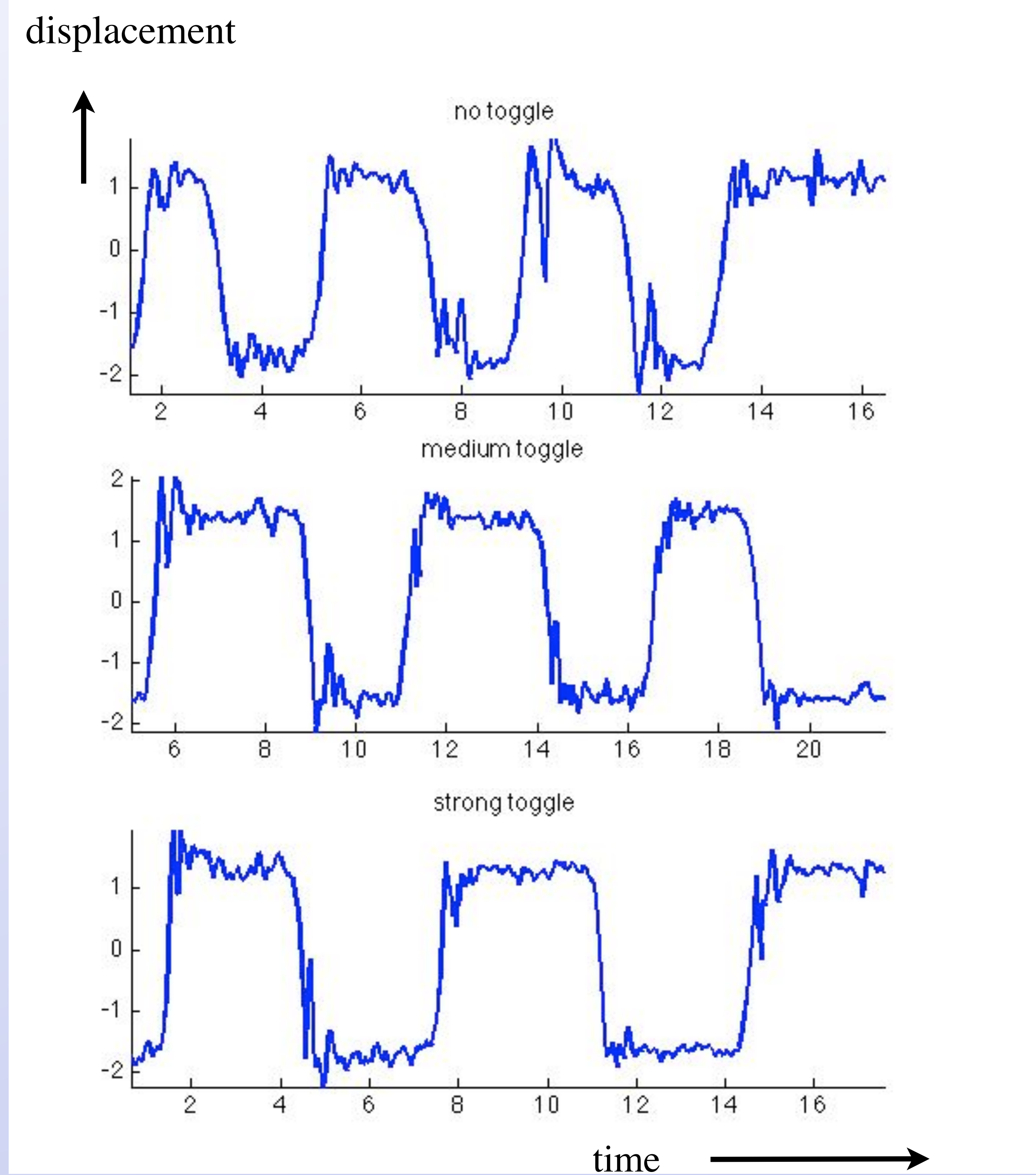
Biological problem 3: Periodic behavior

Mechanical analogy 3: Relaxation oscillator





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


displacement
no toggle
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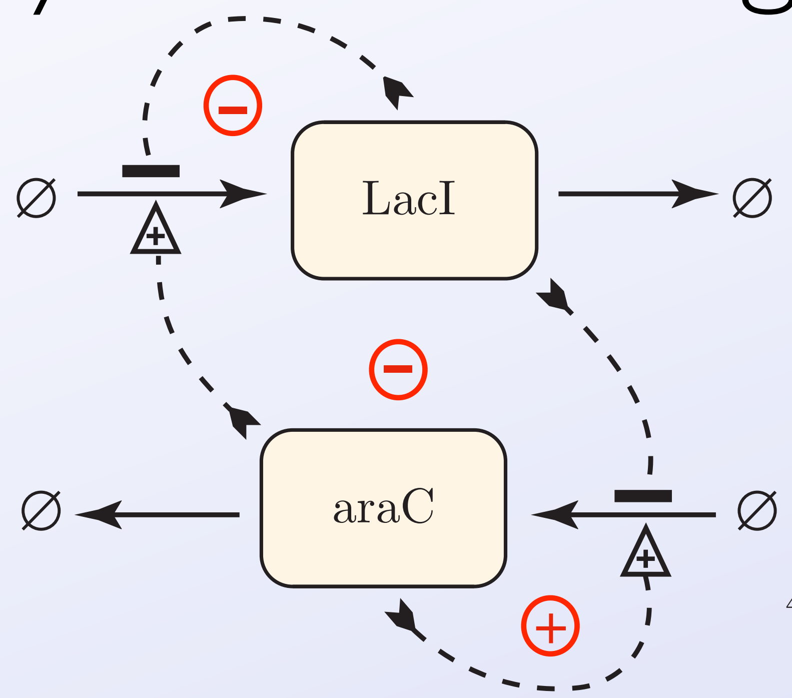
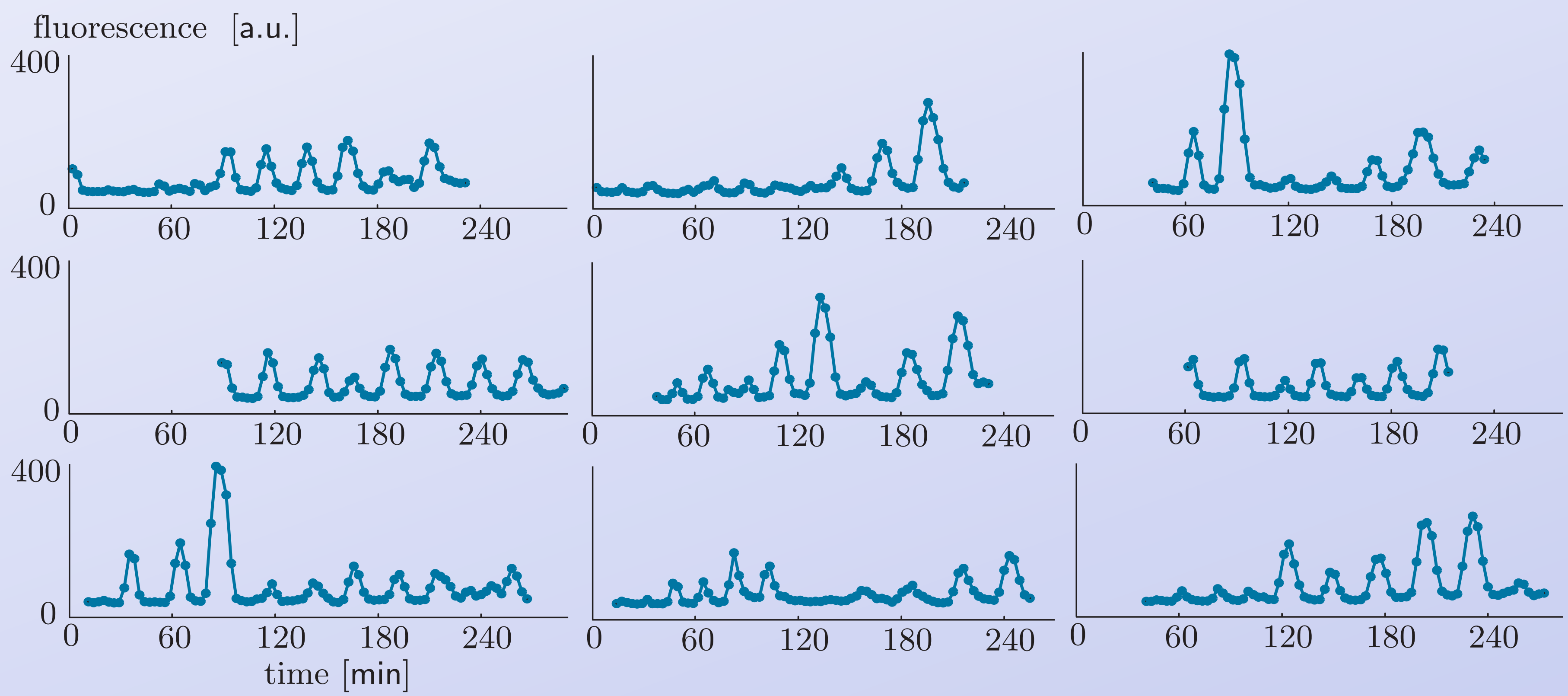
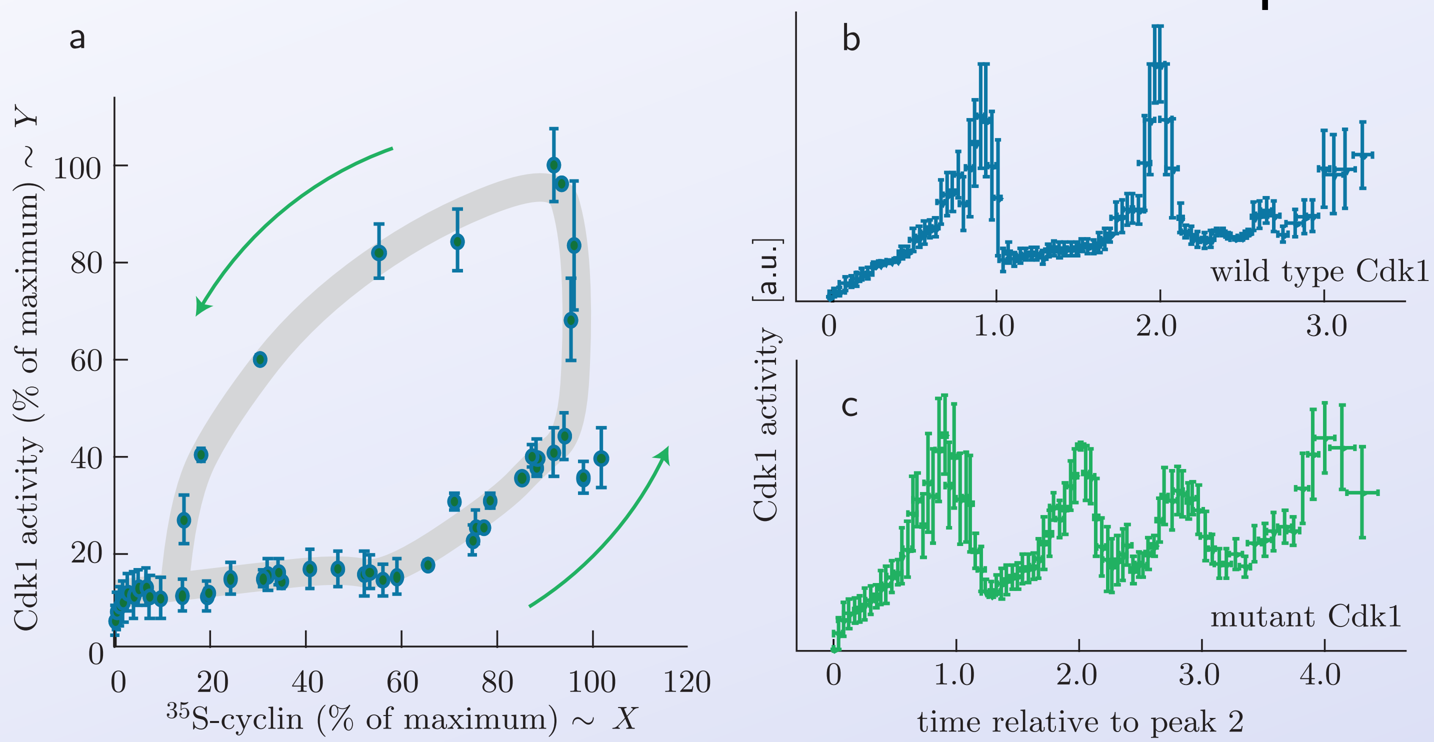
Biological problem 3: Periodic behavior
Mechanical analogy 3: Relaxation oscillator
Synthetic biology 3: Oscillation via linked +/- feedback loops

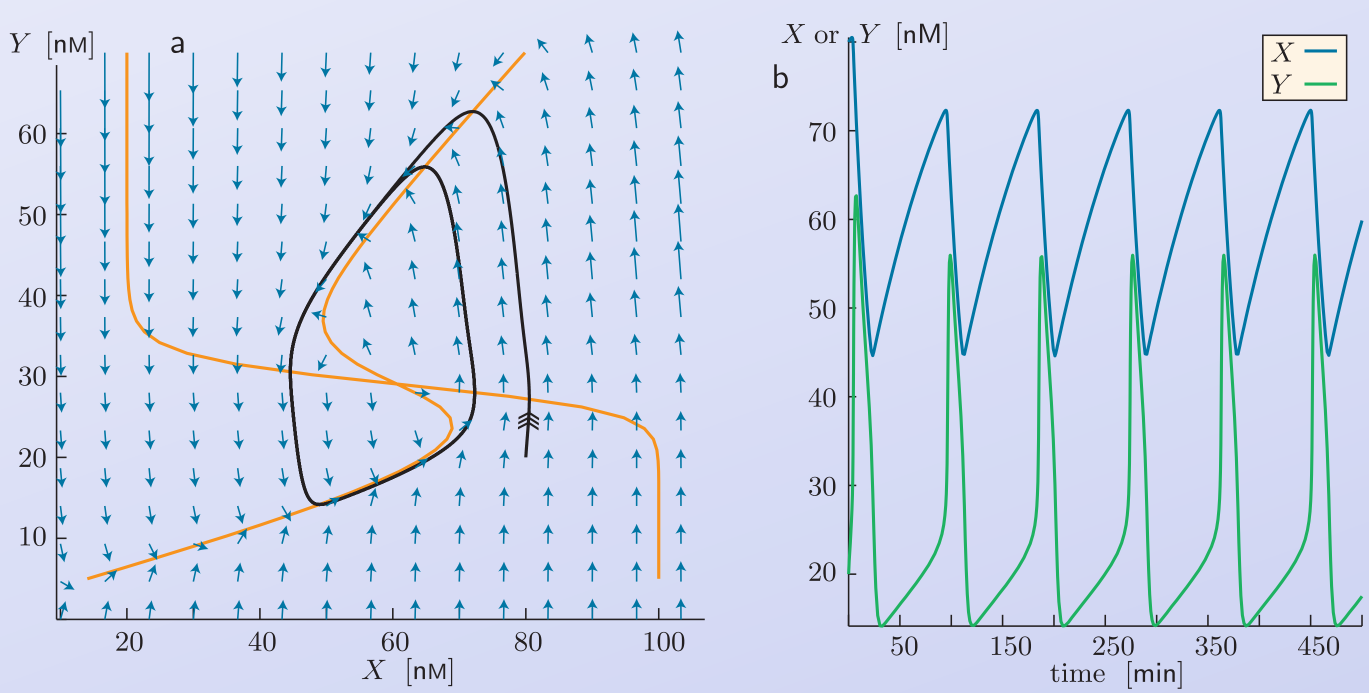




From P Nelson, *Physical models of living systems* (WH Freeman, to appear). Data from: Stricker et al., Nature (2008) vol. 456 (7221) pp. 516-519.

Biological problem 3: Periodic behavior
Mechanical analogy 3: Relaxation oscillator
Synthetic biology 3: Relaxation oscillator
Natural realization 3: Xenopus oocyte





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

Light, vision, and 21st C imaging

Subtext: **Biophysical problems are an interesting road into quantum physics with a lot of high-profile, current applications that can motivate students.**

(Are your life-science students really likely to take your department's regular quantum mechanics course?)

and: By the way, somehow **a good physical model** (in this case the sum over trajectories) **can apply to widely disparate problems.**

and: You won't understand much about single-molecule fluorescence, FRET, 2-photon imaging... if you don't know that light is particulate. **Understanding 21st C apparatus is another motivation for understanding fundamental physics.** Even the math-phobes can appreciate that.

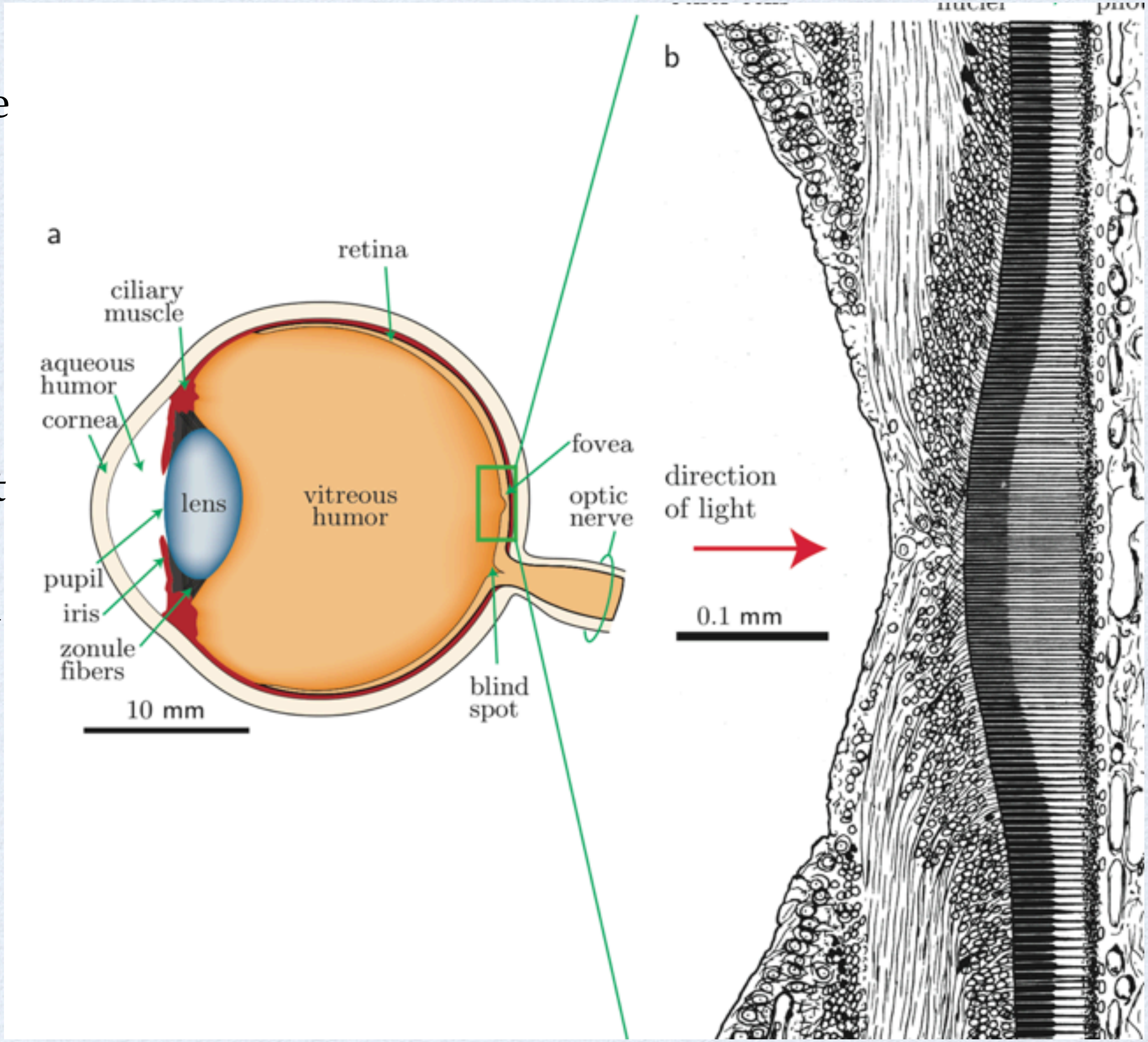
(Robert and others said, "quantum physics.")
(I realize Dave and Jenny said, "no quantum physics." But this is not the intro course.)

4.1 False sense of security

The human eye has a lens-based focusing system, in some ways like a camera. It seems to make sense in terms of Snell's Law, a consequence of the wave theory of light.

The finite size of our pupils limits the resolution we can get at the retina, due to diffraction. There's no point having a pixel size smaller than this resolution limit, and remarkably, *our photoreceptor cells really are about this size*.

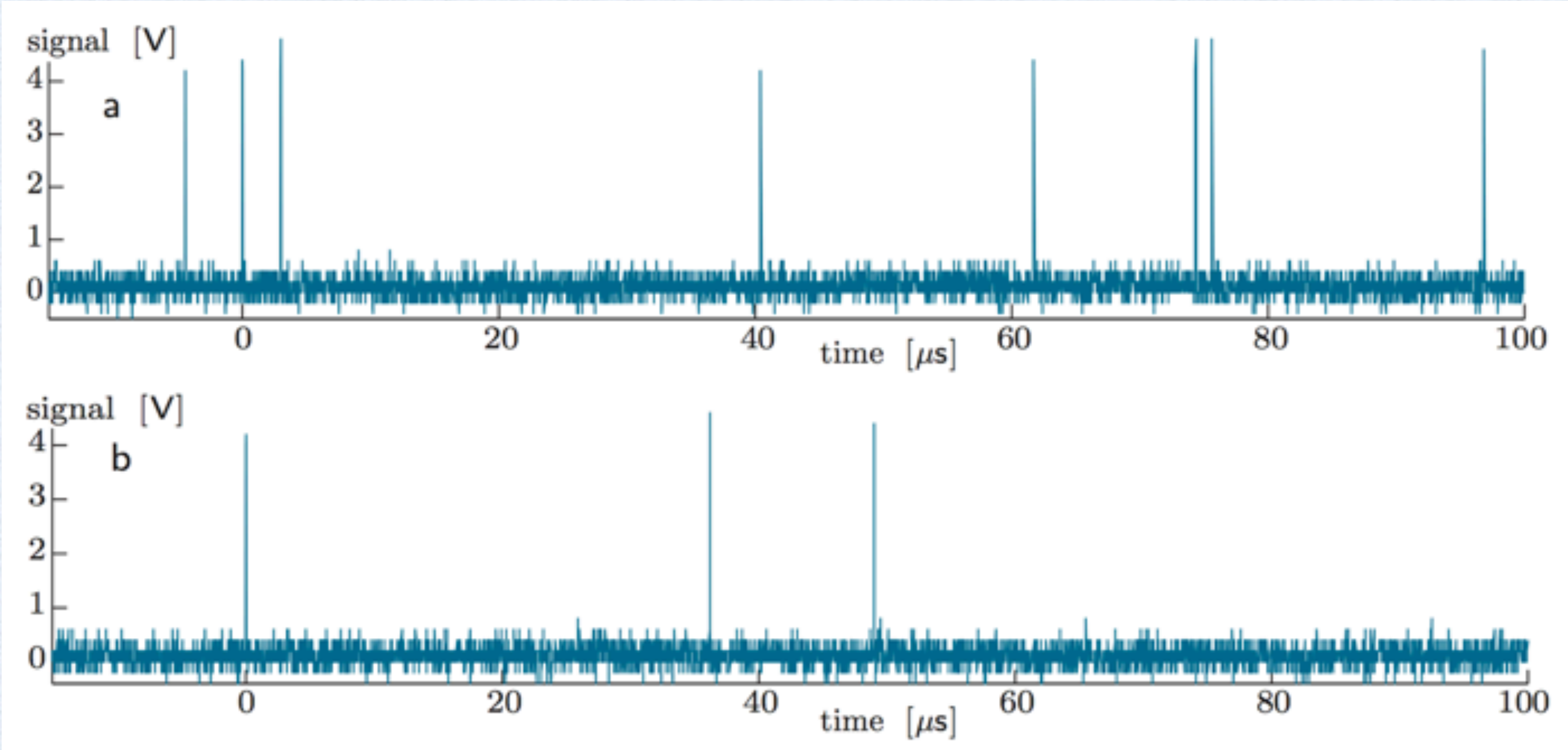
Looks like the wave theory of light explains everything.



4.2 Uh-oh

But what happens *next?* What happens in those photoreceptor cells that translates light into nerve impulses?

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



These are *not* uniformly spaced blips. Instead the clicks are *as random as possible* -- they are a "Poisson process." Something about light is intrinsically random.

click for uniform clicks audio

click for shot noise

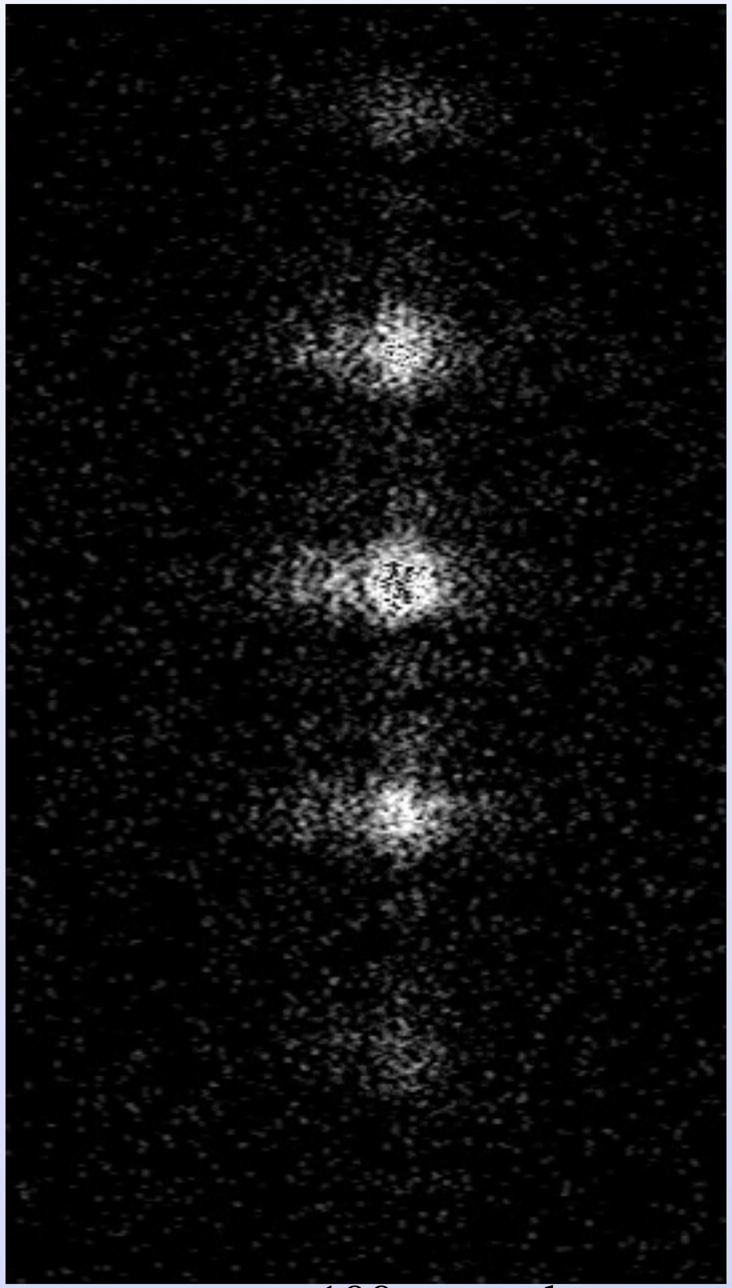
Moreover, when we shine dim light on *several* photodetectors, they *never respond in unison*: Each click comes from just *one* detector, even if the beam of light is spread out to cover them all.

Both digital and film cameras also expose one pixel at a time, at random:

Even classic diffraction effects turned out to be particulate in character.

33 msec

1 second



100 seconds

Einstein found he could only understand phenomena such as the photoelectric effect and thermal radiation by postulating that light consists of tiny *lumps* -- the “photon hypothesis.”

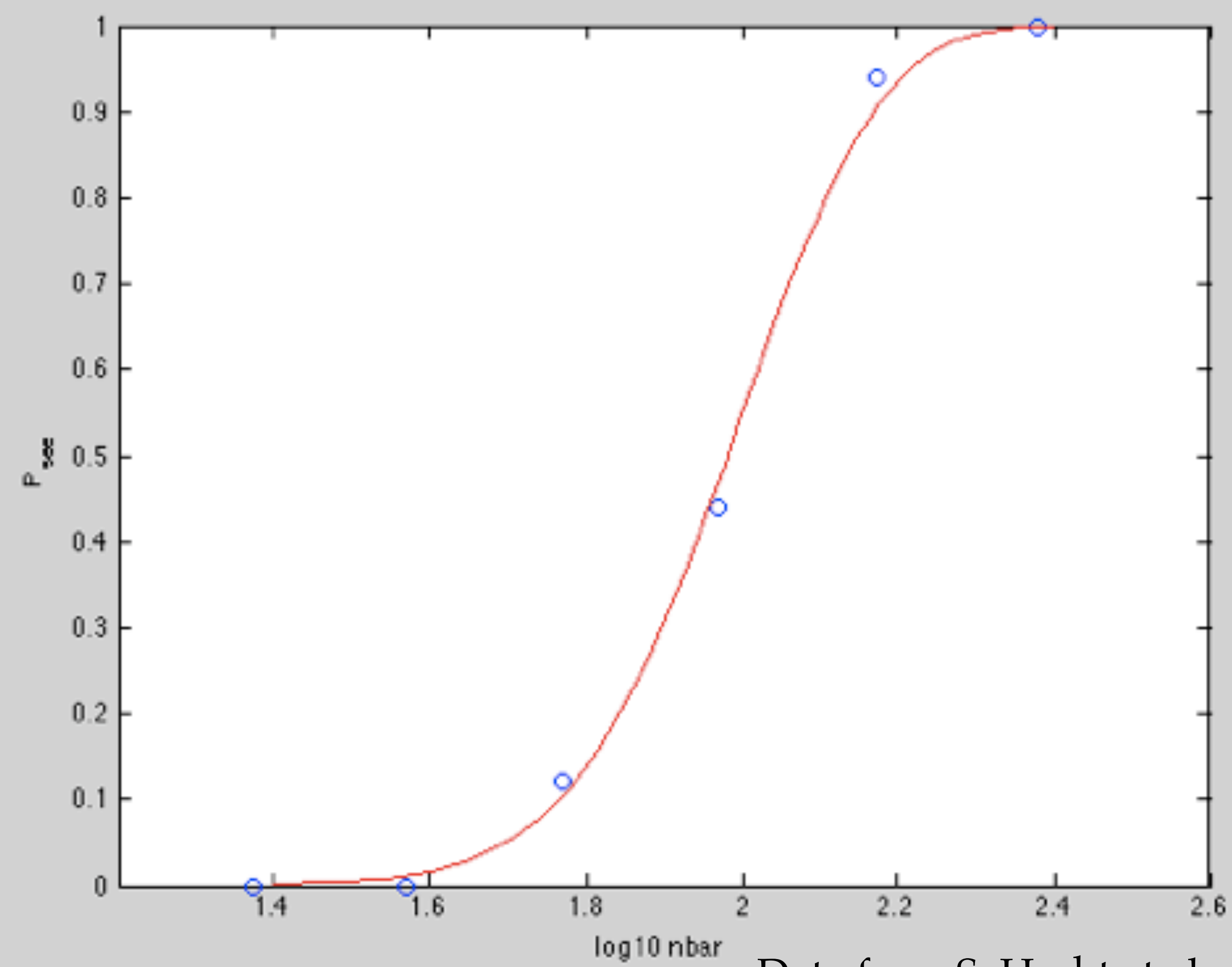
[Aside]

All this way-out stuff about quanta sounds a good tale, but what's it to do with Life? Students could be forgiven the suspicion that, like Calvin, we are taking a fundamental idea and found a naive/irrelevant application for it.

But on the contrary: If your competitor/threatening predator/prey has better night vision than you, that could be a problem. That's the mother of invention, big time. If there's a fundamental limit to vision, you want to *be there*.

4.2 Vision in dim light

Framing: "What's all that theoretical stuff got to do with *vision,* a real biological process? Surely vision is a terribly complex system, impossibly difficult to understand? Surely the inconceivably tiny energy in a single photon is irrelevant to a macroscopic organism like us?"



Data from S. Hecht et al

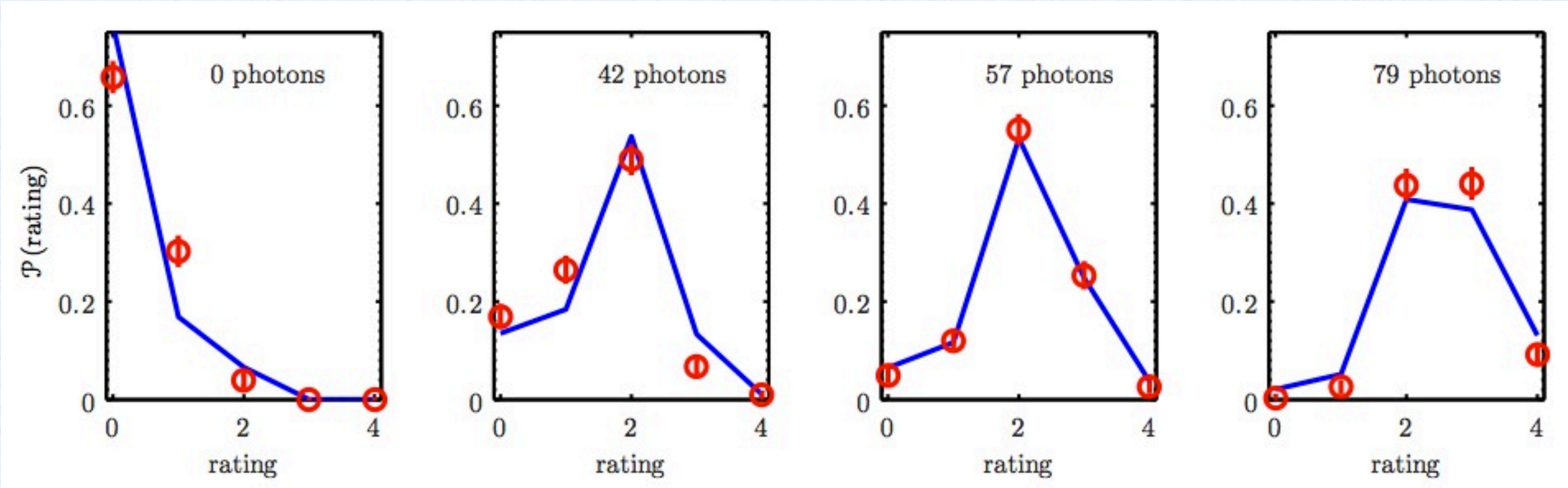
Joe discussed this curve: Hecht et al measured the probability for a human subject to see a flash, vs intensity. They found a simple **physical model** predicting the form of this "probability of seeing curve."

Then they were led from this information to the conclusion that a ***single photon absorption can excite a rod cell,*** and that a quorum of just a few simultaneous rod-cell firings is enough to register consciously.

More about dim light vision

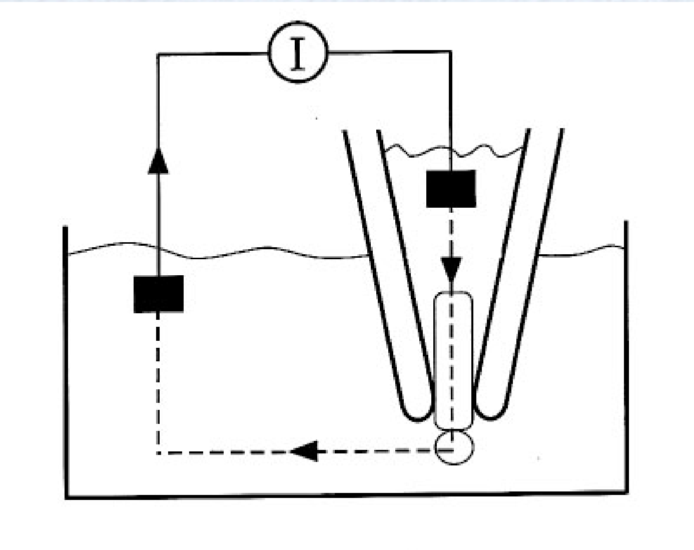
Actually, Hecht's model omitted something huge--the role of spontaneous isomerizations. Here is a 1-parameter fit to *a function of two variables,* the probability of a subject assigning a given rating to the strength of a flash as a function of that flash's nominal strength.

Simple fits like this one can be done from scratch without having to rely on big black-box packages.

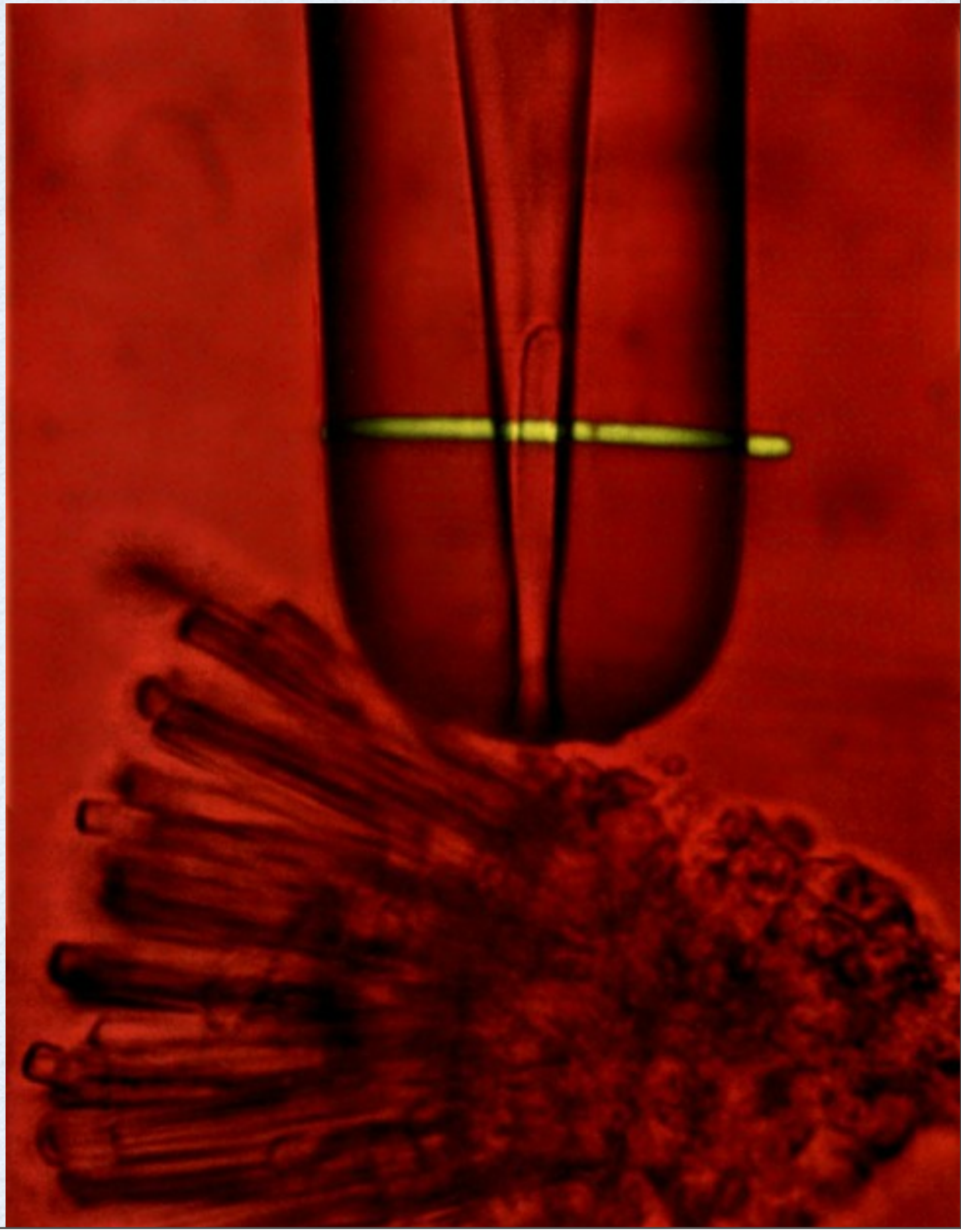


From P Nelson, *From photon to neuron* (WH Freeman, to appear). Data courtesy Heidi Hofer, following an experiment originally done by Barbara Sakitt.

4.3: Onward to single cells

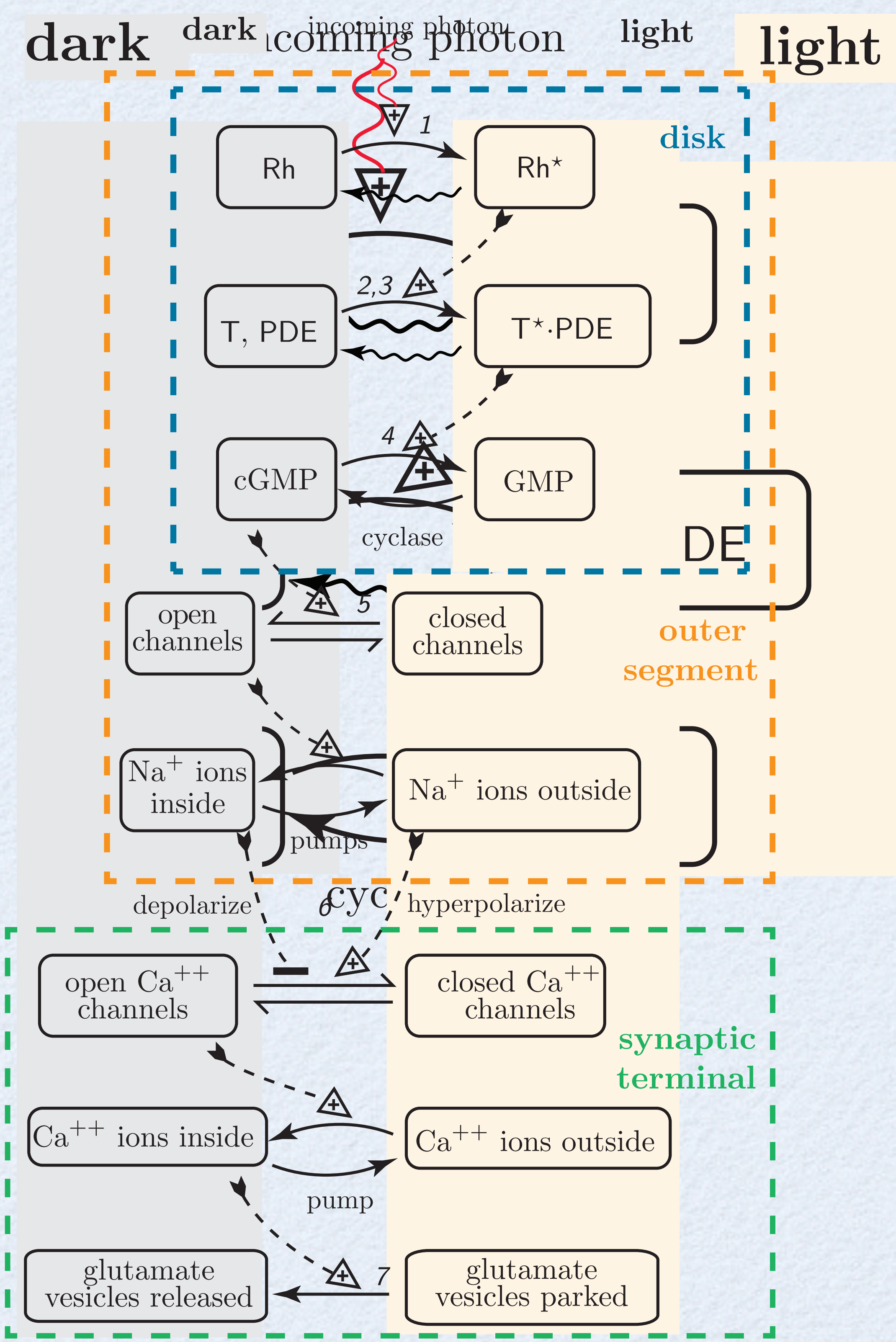


Direct measurements on single rod cells confirmed that they can respond to single photons, and that the response has inherent randomness.
An individual rod or cone cell's response can be measured by gently sucking its outer segment into a pipette electrode and stimulating it with 500 nm light (green).

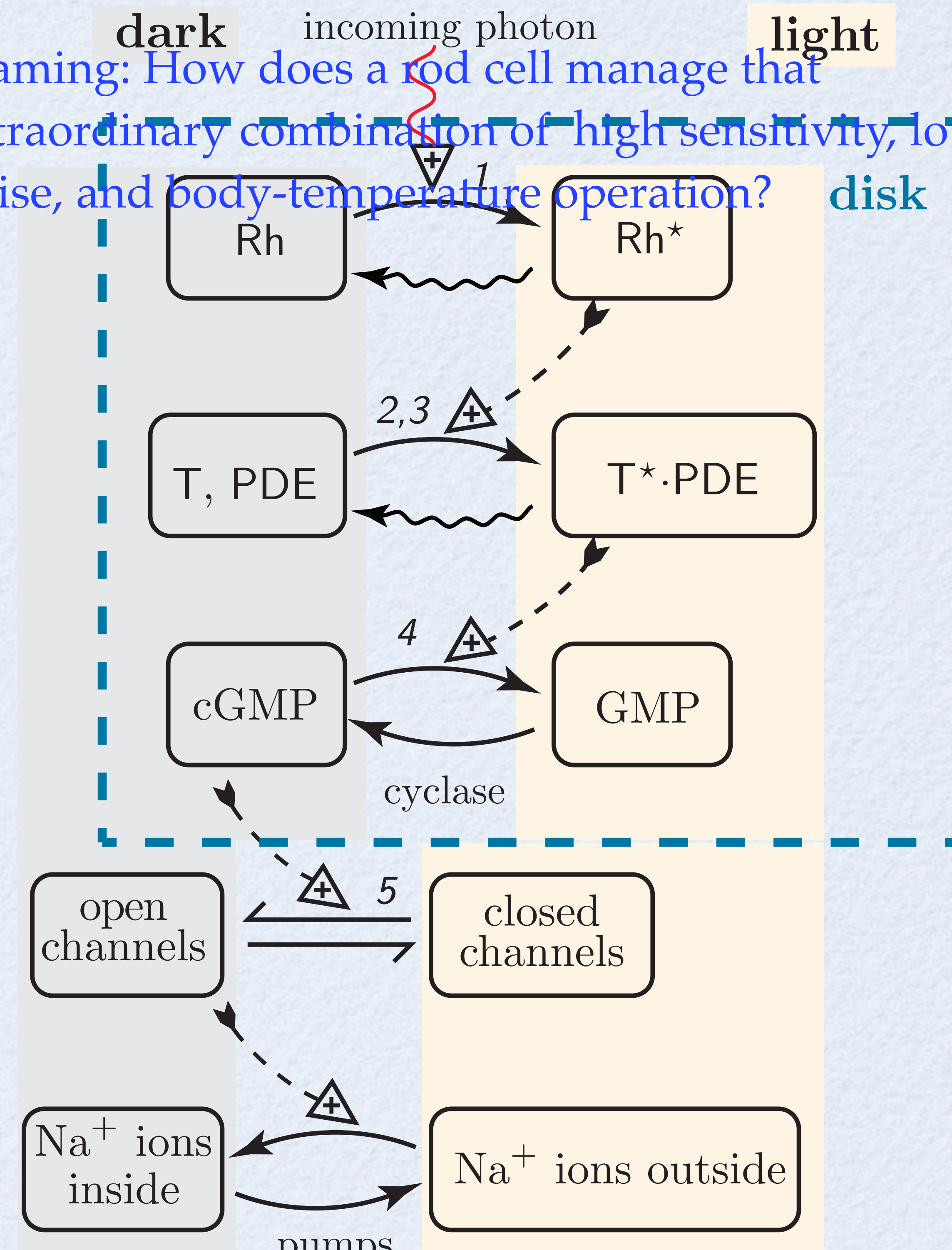


Images D. Baylor; F. Rieke and courtesy K-W Yau. Scale: outer diameter of pipette about 6 micrometers.

4.4: An extraordinary mechanism



Framing: How does a rod cell manage that extraordinary combination of high sensitivity, low noise, and body-temperature operation?



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

4.5: An intolerable contradiction

"OK, so light comes in tiny lumps. I'll write that down in my notes."

Wait! Light *also* shows many other properties long thought to be slam-dunk evidence of *wavelike* behavior, much of it critically important for the design of visual organs. How could any of that ***possibly happen at all*** in the particle picture? Einstein didn't know.

Now, in Physics we often put a box around a set of issues and say, "We can't understand that today," and move on. But this is an ***intolerable contradiction*****.** It's too big to put a box around it. We have to understand it before we have any business moving on.

Generally professors say, "You're not ready for that. You'll understand that some day."

(They really mean, "Shut up.")

Is that really an adequate response? Students would have to wait till they were halfway through a PhD in high-energy particle physics (which they're not going to do anyway) before we'd get around to telling them.

Can't we tell them something we actually believe is *true*? Can't we have them do a calculation *for themselves* that illuminates this apparent paradox?

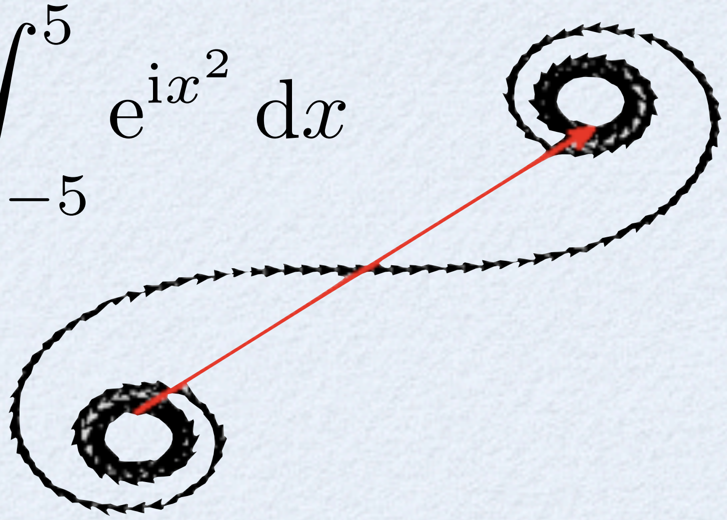
Reconciliation of wave/particle

``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.

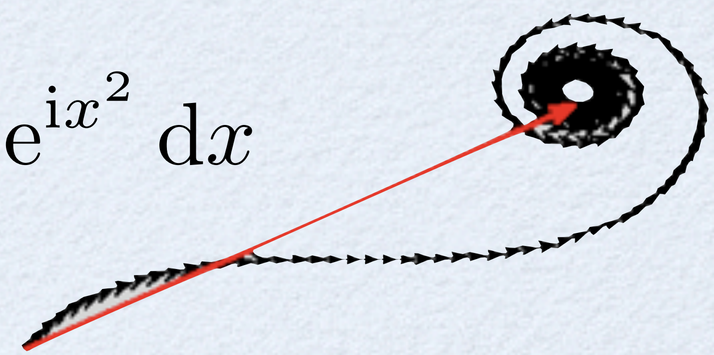
The key question is, ***Why does light (usually) (seem to) go on (pretty) straight lines?***
After all, a penny held in the sunlight casts a sharp shadow.

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.

$$\int_{-5}^{5} \mathrm{e}^{\mathrm{i}x^2}\,\mathrm{d}x$$

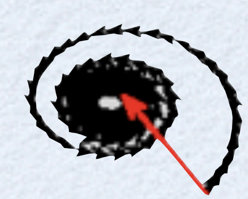


$$\int_{-1}^{9} \mathrm{e}^{\mathrm{i}x^2}\,\mathrm{d}x$$

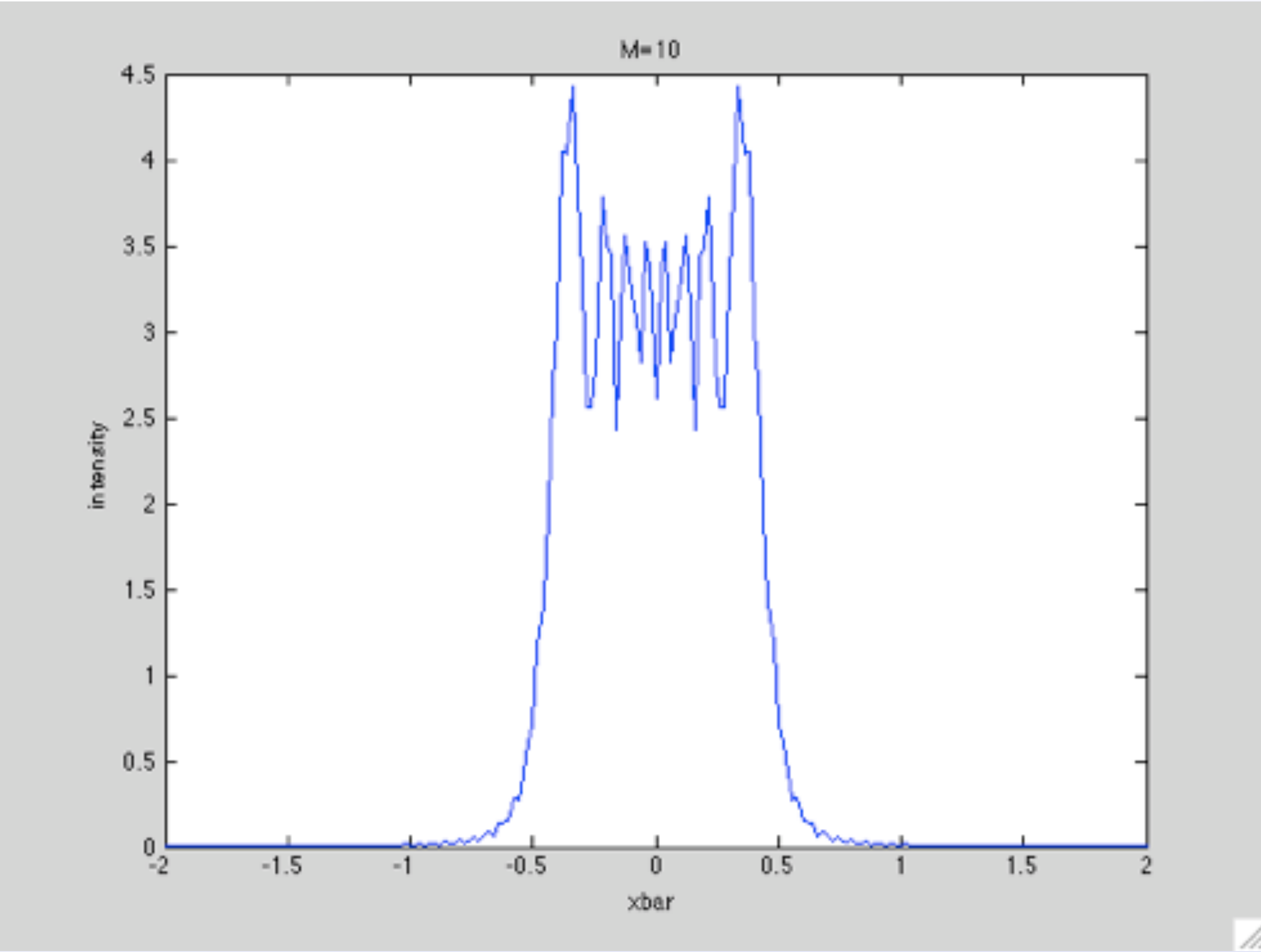


A similar integral whose range of integration contains *no* stationary-phase point will have a small total value:

$$\int_{1}^{11} \mathrm{e}^{\mathrm{i}x^2}\,\mathrm{d}x$$



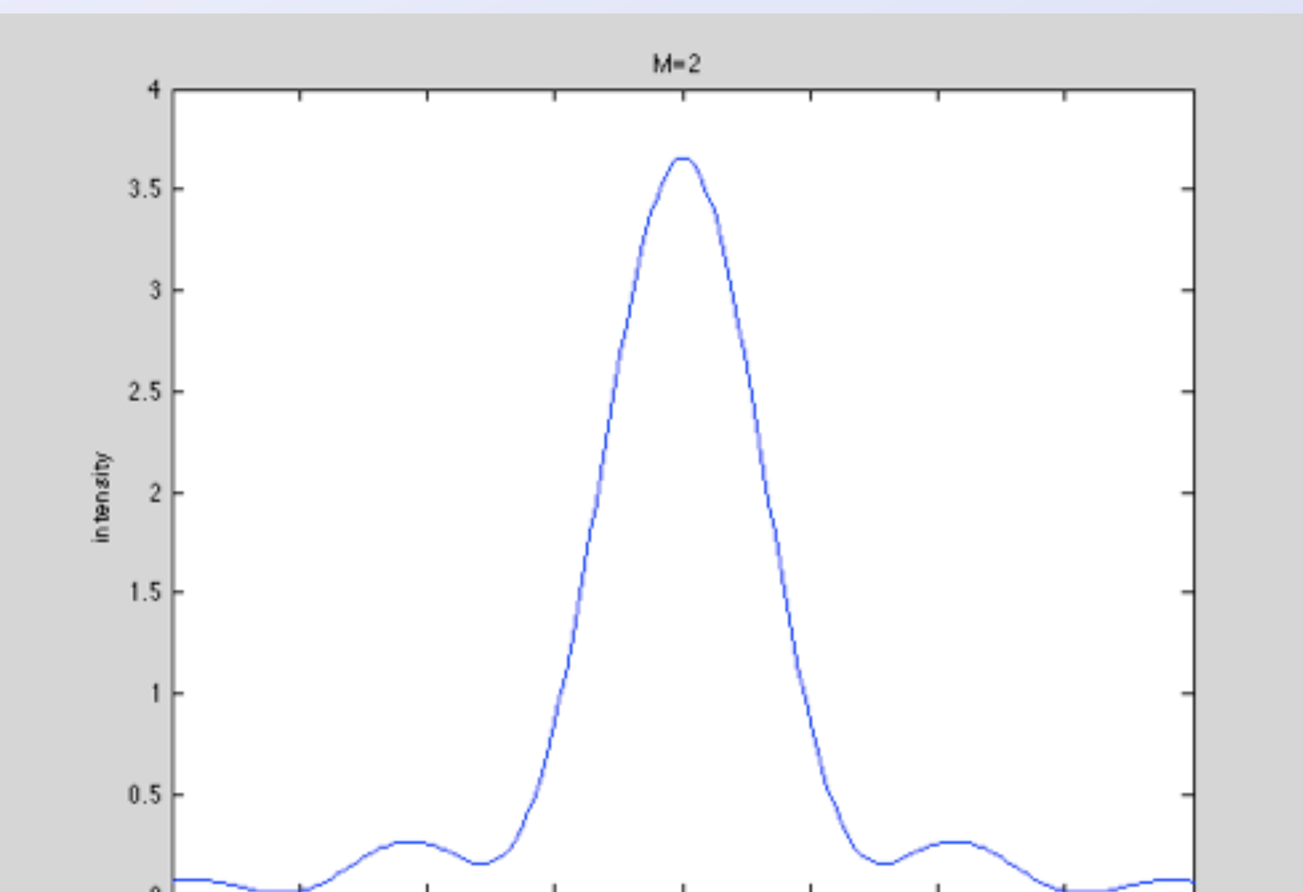
From P Nelson, *From photon to neuron* (WH Freeman, to appear).

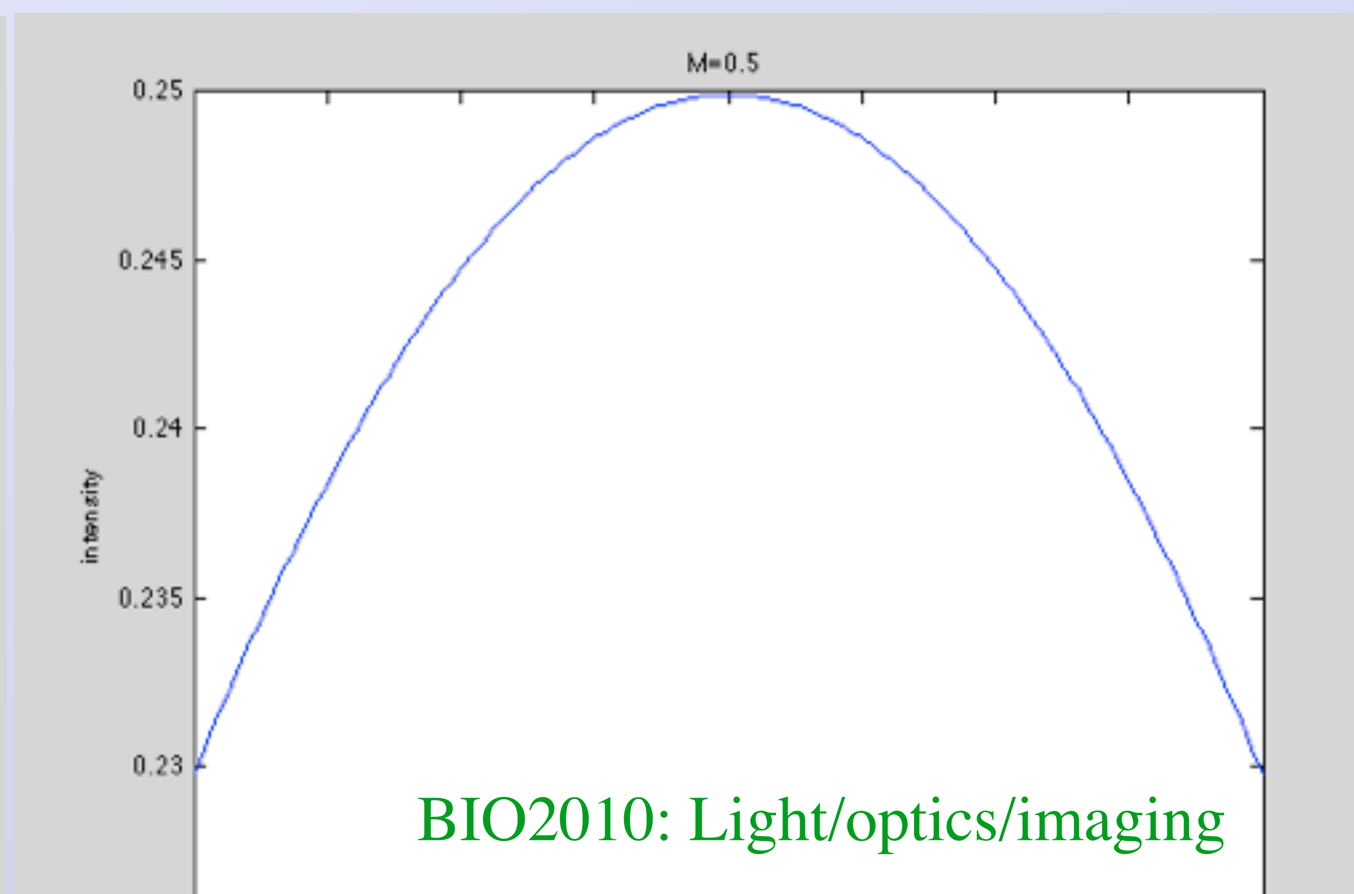


The concept we found -- “stationary phase” -- explains why shadows sometimes have sharp edges, other times not. Students can approximate the integrals in Matlab, then see the same phenomena live, with a laser.

Left: wide slit, sharp edges.
Lower left: medium slit, medium edges.
Lower right: narrow slit, fuzzy edges.

That gives us the “diffraction limit” on resolution (how well we can see) of an optical system. You can now understand other optical phenomena (like focusing) with similar principles.





Indoctrination
Skill set
Feedback in natural and synthetic biology
Light, vision, and 21st C imaging

And now a word from our sponsor

Wrap

These courses aren't for most premeds. But there is a growing cadre of mathematically adept premeds who can handle them. What will they get?

From Preview 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.**

6

Indoctrination
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Wrap

6.1 A small practical matter

Ahem. You have to convince your department to actually ***offer*** an upper-level course. That means committing staff (you) to it, which generally means discontinuing something else. **Nancy said, "We're short on staff already."** And doing it one-off isn't enough -- it needs to continue.

It's a serious concern. You can argue:

- We could cut some other, less essential course. (Is "Physics of music" really essential?)
- Everywhere Engineering departments are tired of paying for freshman Physics, and trying to wriggle out of having their students take it. *We need a product that our customers want.*
- Engineering departments, and their students, are keenly interested in life science.
- A course on Biophysics is also essential for a ***major*** in Biophysics. You can create such a major even without a corresponding academic department, or cross-list it in another department. Then the course gets a base.
- To avoid "that's not Physics", you need to make sure you ***keep the physics in Biophysics*** -- you need to include some top-drawer, indisputable Physics content. It can't all be about bioinformatics.
- Actually, even without a dedicated course I've found that biophysical examples make basic ideas come alive for students in any course, as I'll describe. So it's generally good to ***keep the biophysics in Physics.***
- ***If all else fails, convince your visiting committee to beat up on your colleagues.***

6.2: Excuse me

What is a “physical model” anyway?

What is “the role of the textbook?”

When will these books be available?

Textbooks

To come full circle, I claimed that it's important to inject 21st C content into our upper-level classes. If we're not telling our students things we ourselves were never taught, then we're giving them an obsolete product.

"Why not address this with a seminar course where they read original articles?" (But which 6 should we choose? What about the other 10^4? Are they ready to read papers in *Cell*?)

A textbook, like a class, attempts to carry students from an initial state to a different final state. It can also take account of the initial state of the instructor, offering a perspective that ties on to both her own, and the students', prior knowledge and offering enough resources for both to stretch.

Sorry if that sounds pompous. I can only say that *I didn't know any of these things myself ten years ago*, so I know a bit about where (some) readers are coming from.

If an author can keep fresh the painful personal memory of the frustration of trying to learn new things... maybe a useful book will result.

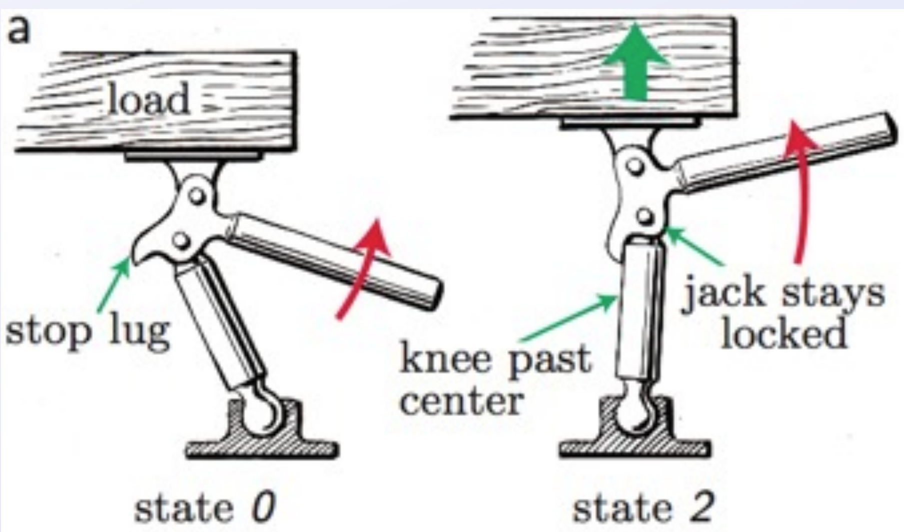
(Edit said: "Leave your comfort zone.")

Finally, an upper-level textbook can bring a lot of tough, yet doable, problems, which have been refined with the (unwilling) help of the author's own classes. It can also supply the instructor -- who has a *lot* of other commitments -- with their solutions.

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...

(Edit said: "Modeling.")

(Edit also said: "*Probabilistic* Modeling.")

Thanks

University of Pennsylvania

NSF BIO

W H Freeman and Co.

NSF NSEC

... And an amazingly large number of you for correspondence and suggestions. Please let me know if you'd like to review it for WHF.

For these slides see:

www.physics.upenn.edu/~pcn