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

The topic I announced:

March Meeting Tutorial 23

Biological physics throughout the curriculum, and at all levels

Breaking out of the one-elective box, the one-department box, and even the one-university box

Phil Nelson, Univ Penn, pcn@upenn.edu

The topic I wanted to give:

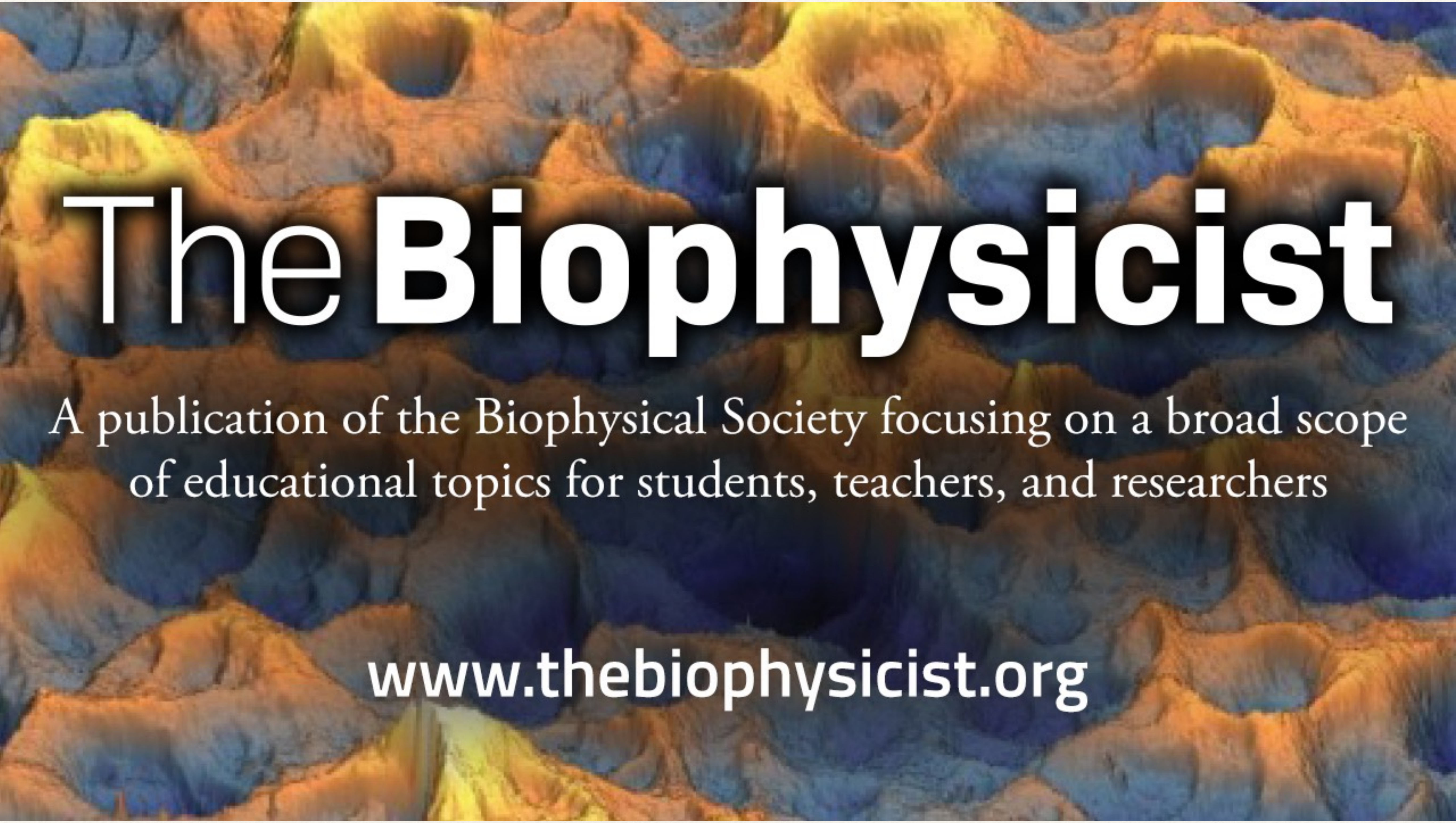
March Meeting Tutorial 23

"How could anything like that possibly happen at all?"

Getting and sustaining attention from demo, through analysis, to tech payoff.

Luckily they turned out to be the same topic.

But first: submit your own great ideas to



Hail to the incoming (editor-in-)Chief Padmini Rangamani

Phil Nelson

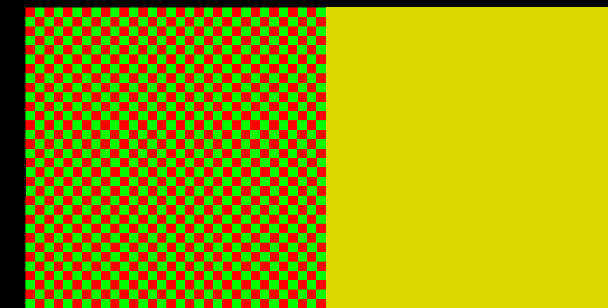
Plan

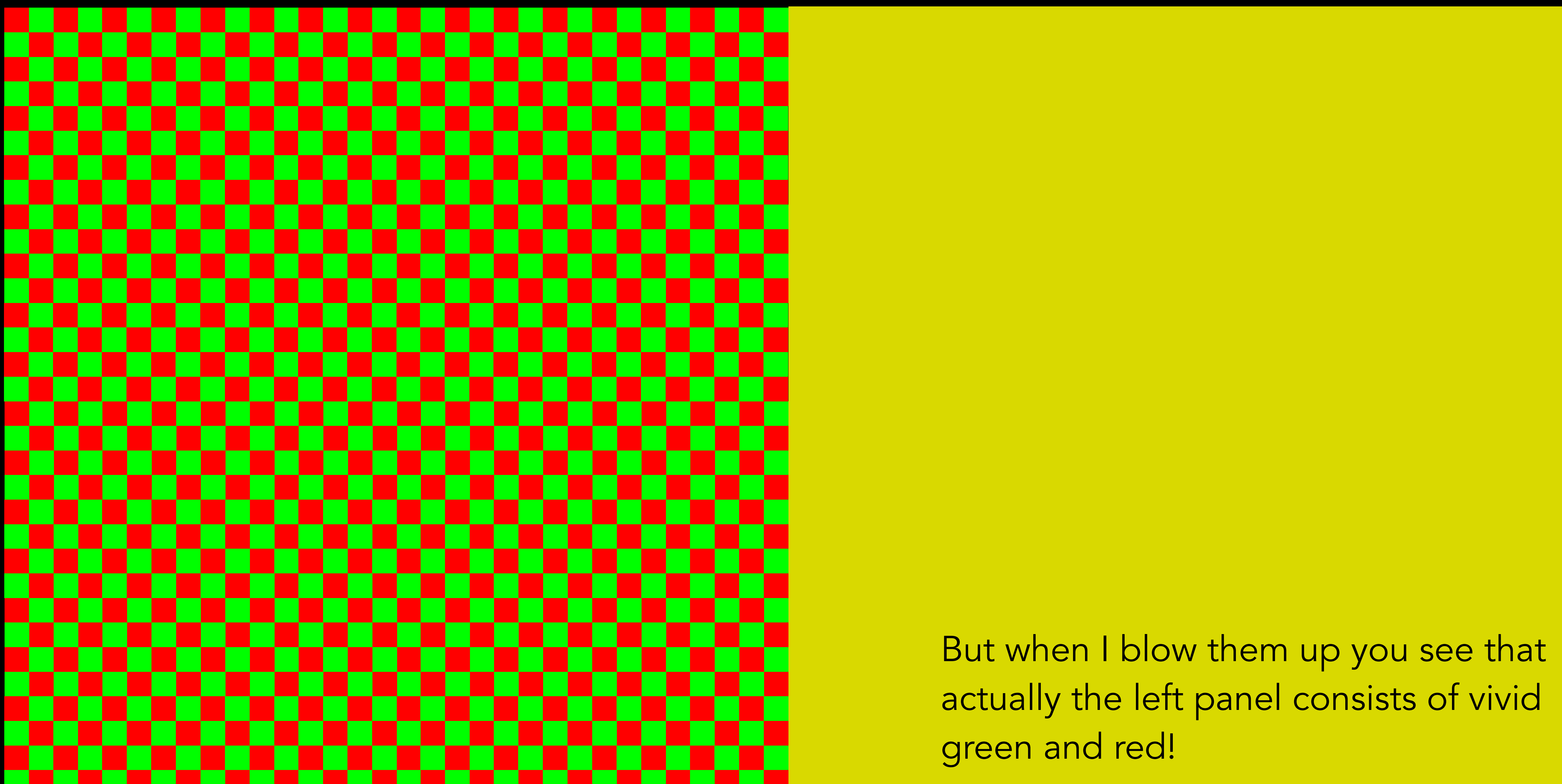
- Some physical reality
- Some institutional reality
- Some examples:
  - E&M
  - Quantum
  - "Modern" Physics
  - Analytical "Mechanics"
- Wrap

“What we want is a story that starts with an earthquake and works its way up to a climax.” — attr. to Samuel Goldwyn

Physicists love stories that are weird and upsetting but *true*.

These two panels may look similar in color, particularly if you’re sitting in back (or remove your glasses).





How could anything like that possibly happen at all?

I.e., How could your eyes be so bad that they can't even tell spectral yellow from red+green?

Some physical reality

"A paradox is the truth standing on its head to attract attention" - GK Chesterton

Today's earthquakes:

R+G=Y

UV laser pointer on quinine solution

Visible laser on diffraction slide.

Every time I see these things I'm thrilled all over again. I eventually learned to SAY that to my class.

Generally, Physics instruction (and textbooks) are pretty impoverished when it comes to *surprising raw phenomena.* But this is the essence of compelling narrative.

Grumpy old profs say

"Students just don't seem to have any scientific curiosity these days."

and

"They just want to know "the facts" so they can regurgitate them on command."

but

Crime fiction writers seem to know something useful about engagement.

so

Maybe an opportunity there. Maybe we could communicate our love for our subject better. Maybe that's not actually difficult.

All the modern pedagogy innovations will not make our courses compelling if we don't select compelling content.

Plan

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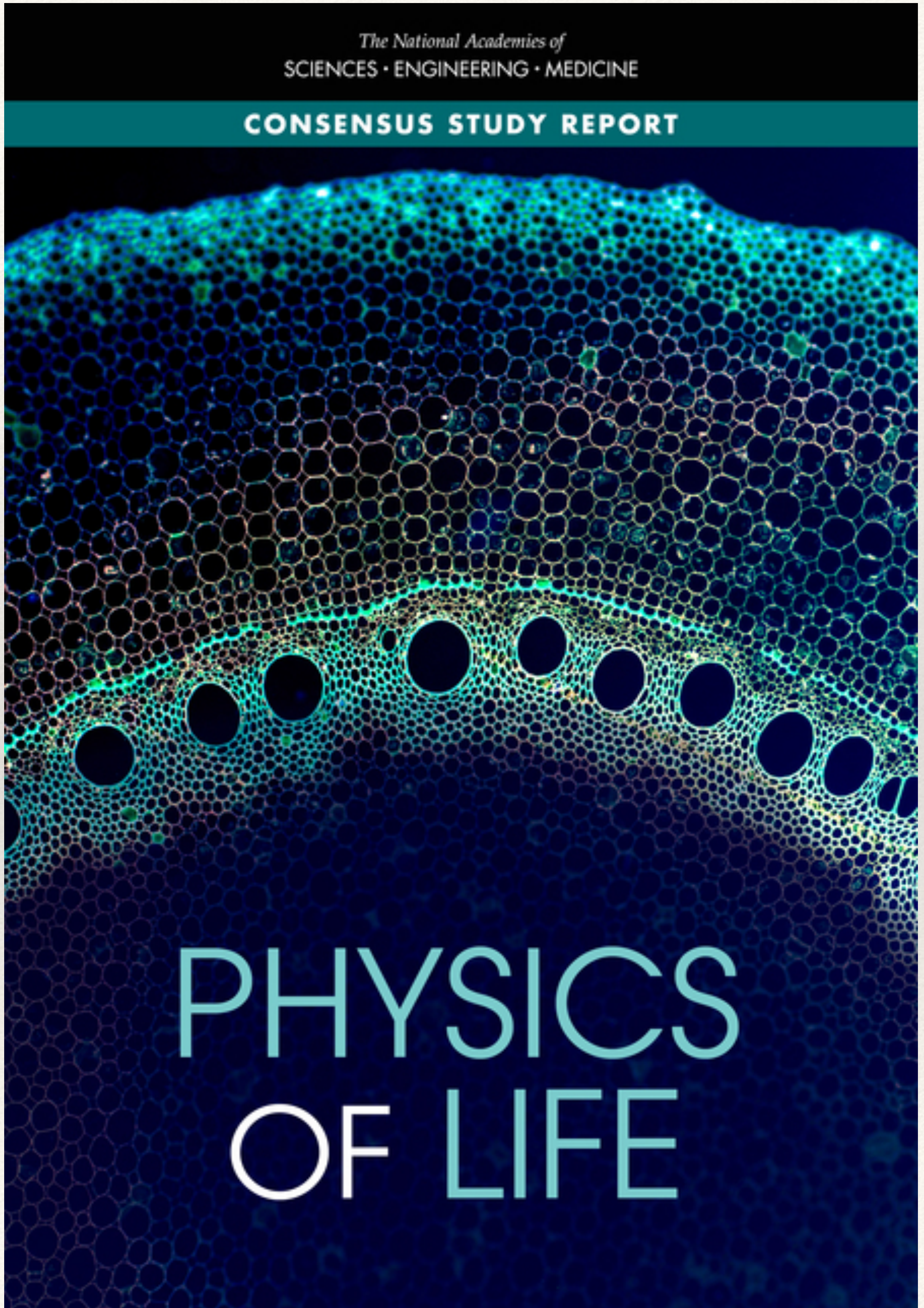
Some institutional reality

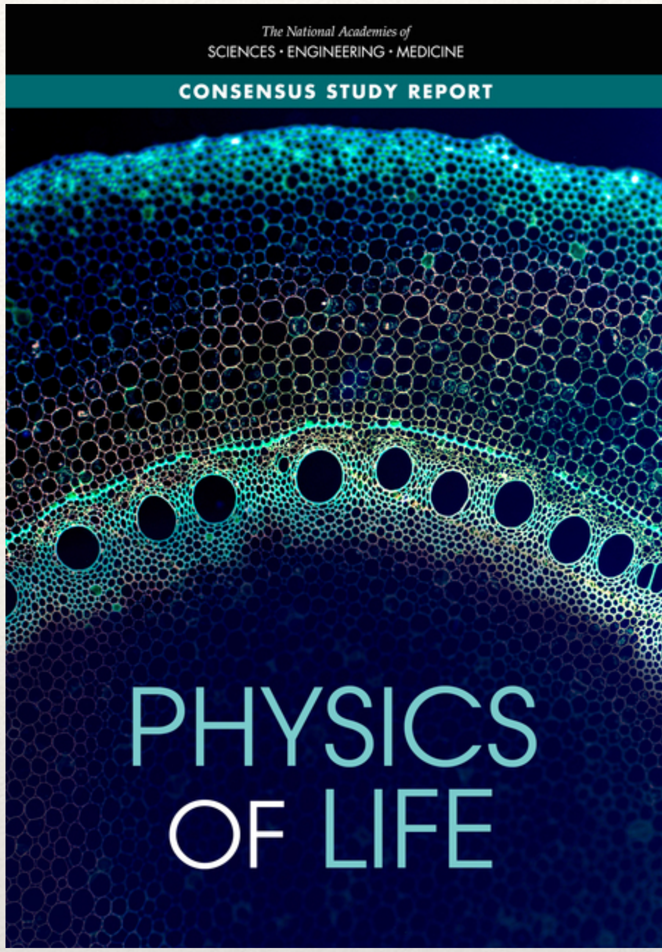
I love biological physics – you do too, apparently – but a new field needs some help if it is to thrive. Students have never heard of this discipline when they arrive at university. Most have still never heard of it when they graduate.

That means there's a category of student who could get interested but who (reasonably) decided after a year or two of college that Physics itself was a dead, historical subject and not something they could do for a living.



Institutional reality, II

The National Academies' report points out that this accidental secrecy stems in large part from the fact that BP is still largely confined to one elective course.



As a big, grown-up subfield, ***it should instead be marbled into every course at every level.***

[I would add "all the way up to our required PhD courses."]

Luckily, ***biological physics is the best framework to engage many students in even traditional Physics topics.***

But: **All the modern pedagogy innovations will not make our courses compelling if we don't select compelling content.**

Please use the file card to jot down some opportunities to do this that pop into your mind as I mention a few favorites of mine.

Plan

- Some physical reality
- Some institutional reality
- Some examples:
  - E&M
  - Quantum
  - "Modern" Physics
  - Analytical "Mechanics"
- Wrap

Every example to follow is available to you, developed in a textbook. These are all topics I have actually covered in a class.

Some examples

There is an art to choosing examples that:

- Address questions of genuine, independent biological interest *and*
- Address questions that are actually under discussion in students' life-science classes, *and*
- Can actually be convincingly connected to the physics that you can can cover at whatever level you are at.

To that second point: Physics profs are sometimes hurt that students don't seem to be interested in that brilliant discussion of blood pressure in giraffes. Remember that intro level life-science courses today are overwhelmingly focused on the *molecular level.* If you want to talk about physiology, remember that those students won't see any of that until their last year, *if even then.* So keep in mind that extra framing will be needed.

Lisa Lapidus. The Biophysicist 2021; 2(1).

Some examples: E&M

- Why is ATP a "high energy" molecule?
- Why do biochemists claim that macromolecules bind specifically by recognizing detailed patterns of charge? Why don't they mostly just see each others' *net* charge? How could anything like that possibly happen at all?

"Developing an understanding of how molecules interact with and dissociate from one another requires an appreciation of both the nature of intermolecular interactions and the processes that disrupt them, yet a survey of biology textbooks reveals that the mechanism of dissociation is (apparently) never explicitly discussed, while the factors that underlie the specificity and stability of molecular interactions (including entropic effects associated with the aqueous context of biological systems) are considered in a superficial manner."

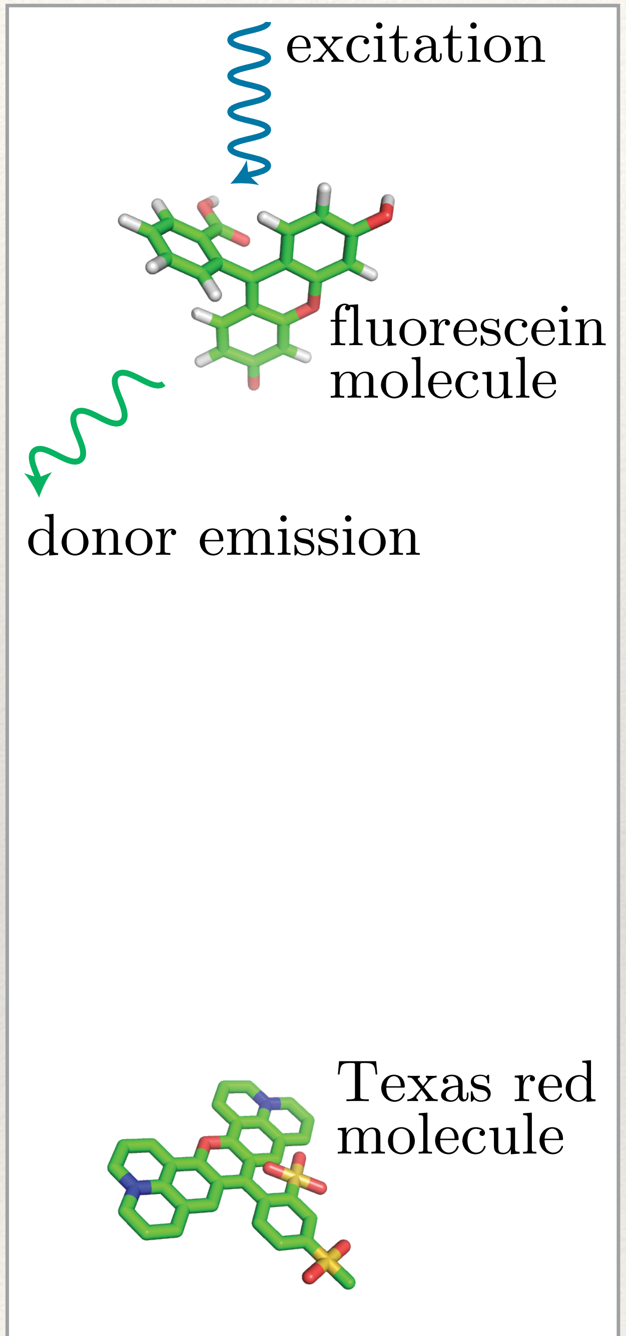
MW Klymkowsky, JD Rentsch, EBegovic, MM Cooper, CBE LIFE SCIENCES EDUCATION 2016.

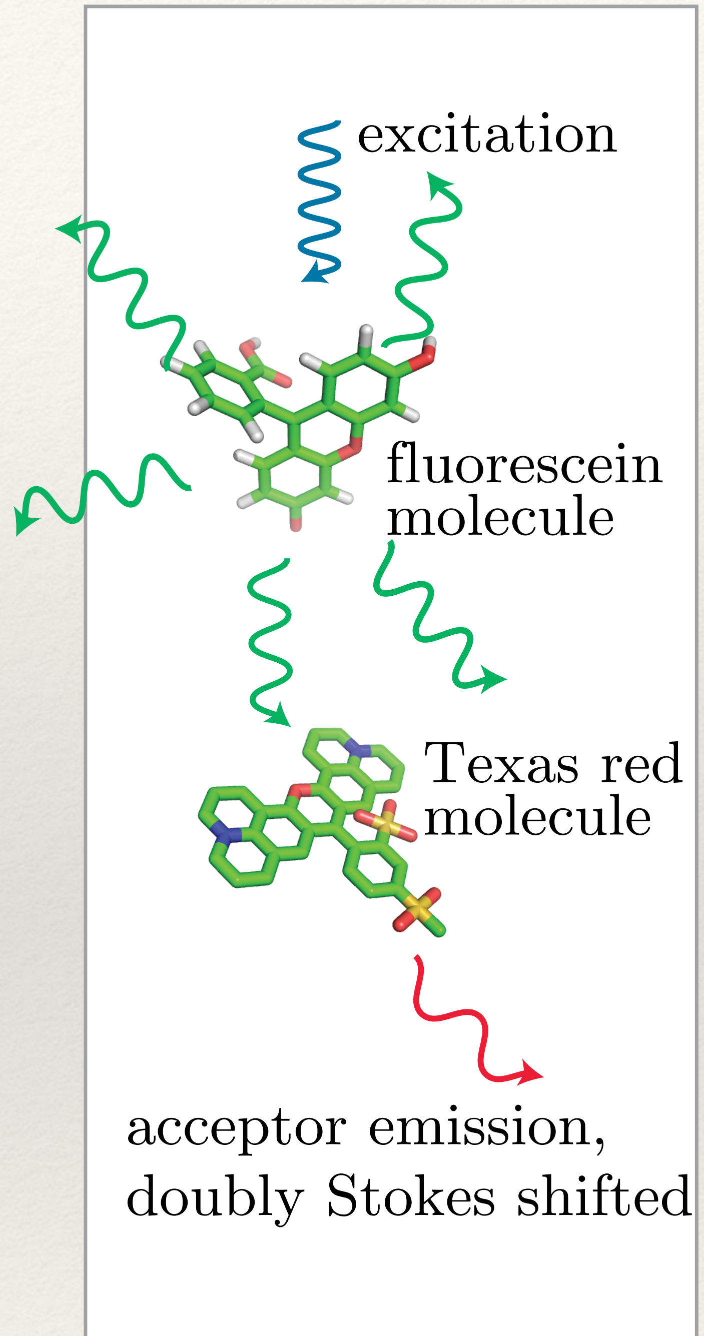
Some examples: E&M

- People often say "the brain is a computer, and neurons are its wires." But signals travel down a coax cable at $2 \cdot 10^8$m/s, or down a neuron at ~10 m/s."
- How did H Fricke establish the existence of nanometer-thick cell membranes long before the invention of electron microscopy? How did that resolve a bitter dispute between cell and non-cell adherents?

How could anything like that possibly happen at all?

Excitation transfer: Naïve picture





How could anything like that possibly happen at all?

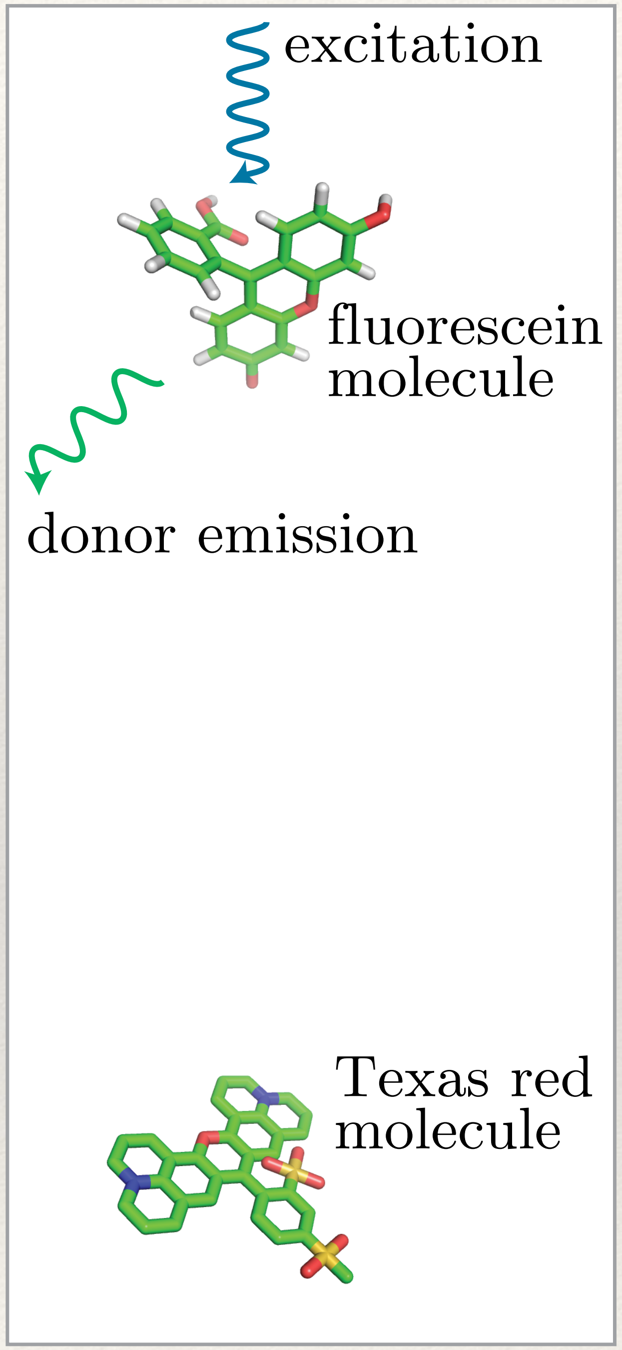
Much bigger than physical collision radius

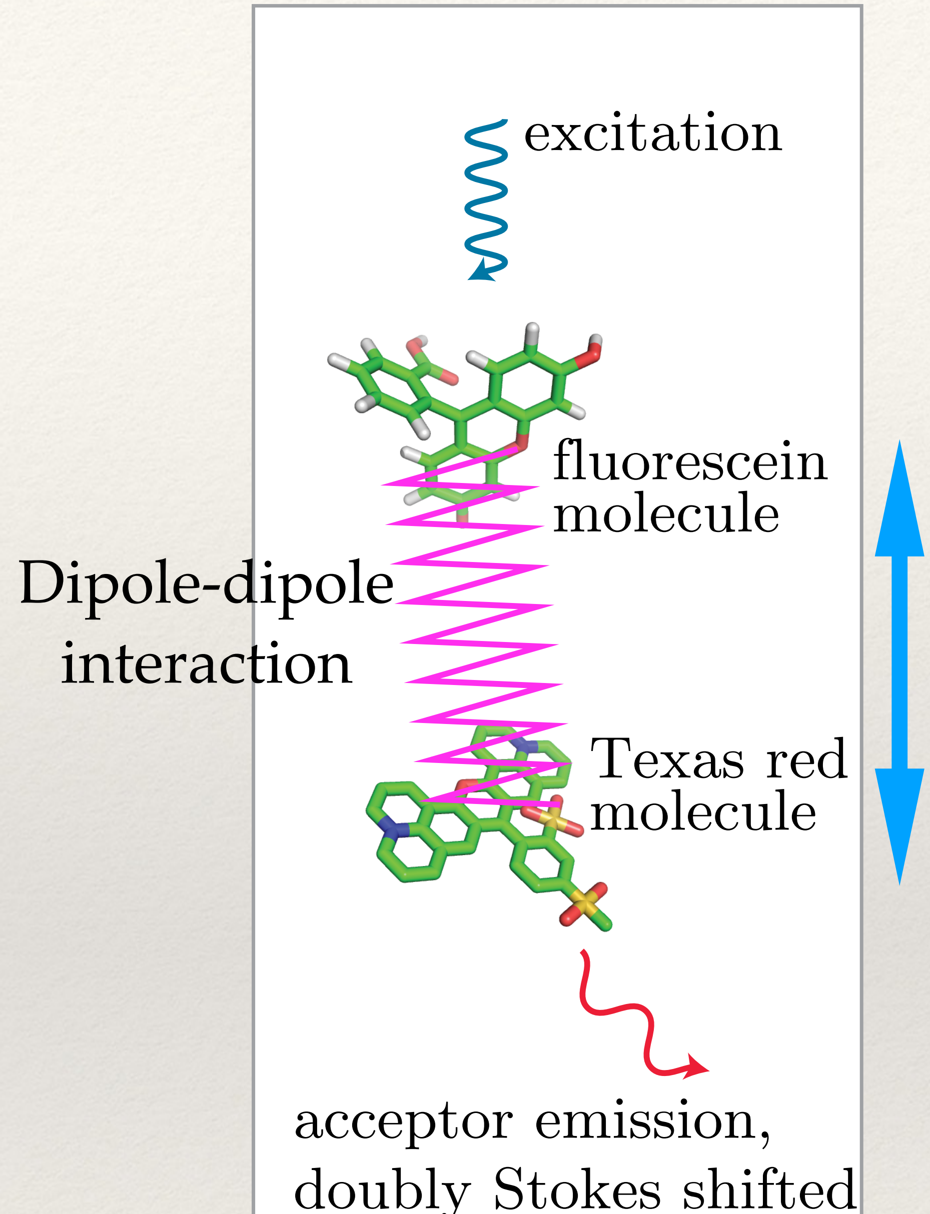
Cannot explain observed high transfer efficiency when donor and acceptor are well separated – most intermediate photons will ``miss."

P N, *From Photon to Neuron* (Princeton 2017).

Phil Nelson

Excitation transfer via dipole interaction





Much bigger than physical collision radius but much smaller than the wavelength of a photon with the appropriate energy

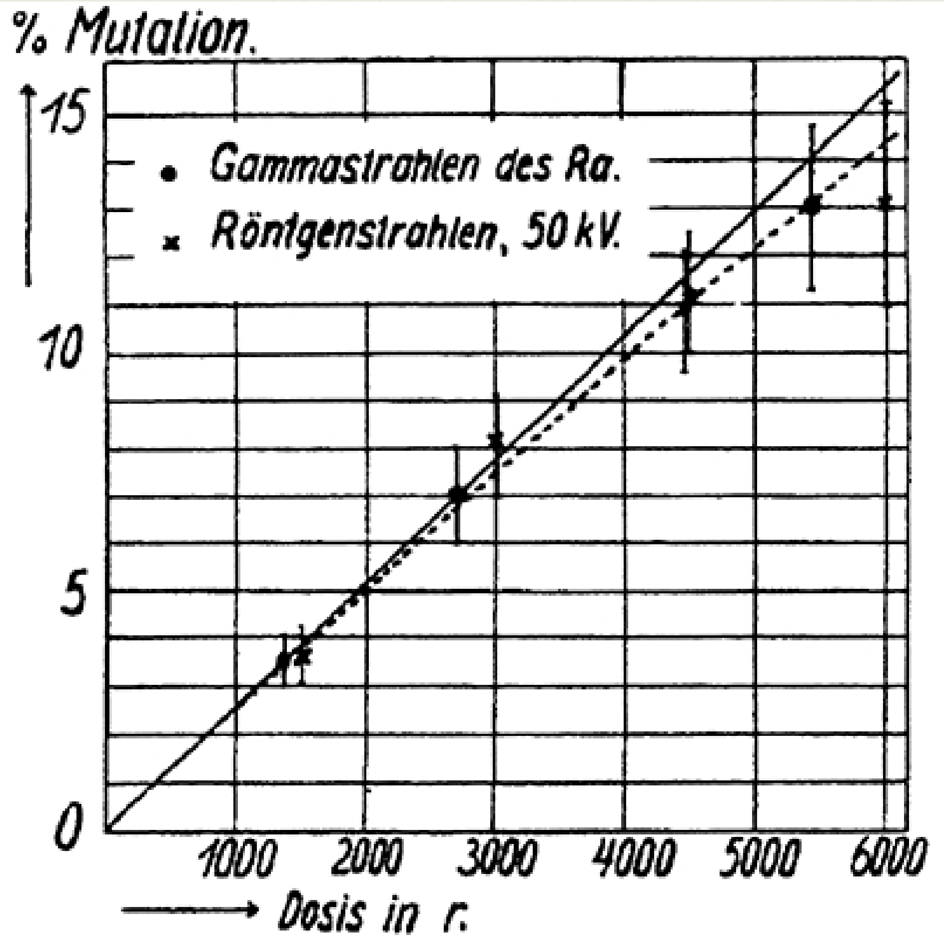
Dipole fields are very strong in the near-field region, potentially explaining how FRET can dominate over donor emission. The resonance idea potentially explains why the many other nearby molecules (e.g. water) don't get excited. Together, these observations can explain the high observed transfer efficiency.

P N, *From Photon to Neuron* (Princeton 2017).

Some examples: "Modern" physics

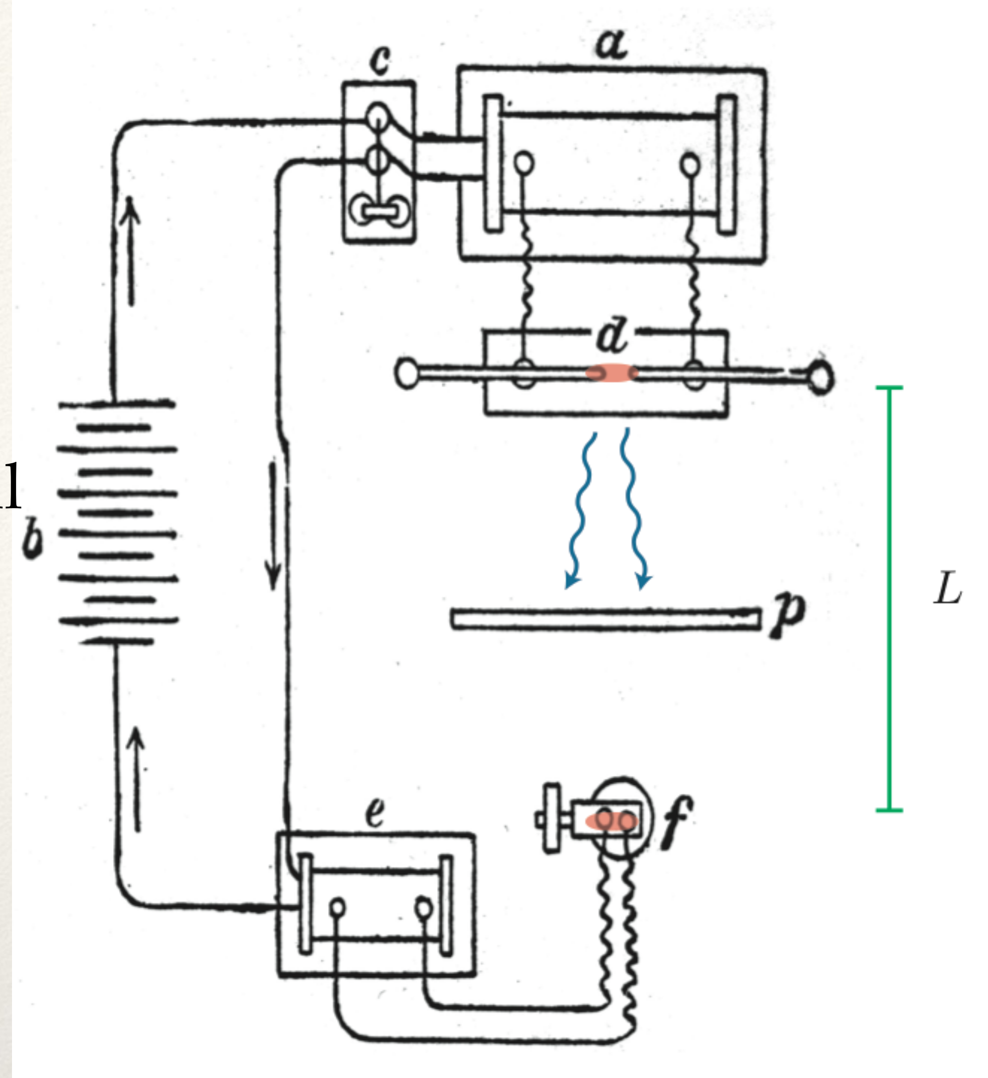
M Delbruck and colleagues deduced the existence of an information-carrying linear polymer long before x-ray crystallography established the structure of DNA – long before it was even established that the polymer even *was* DNA – and even the *existence* of polymers was controversial.

They did this by thinking carefully about x-ray mutagenesis, and by asking How could anything like the rules of heredity, and this graph, possibly happen at all?

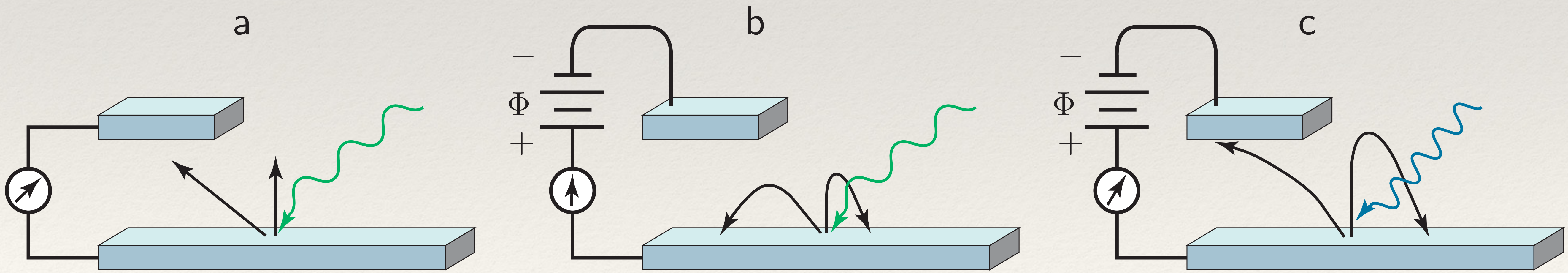


Photoelectric effect

Hertz's original diagram of his experiment:



Later experiments found a "stopping energy" that depends on incoming light frequency:



P N, *From Photon to Neuron* (Princeton 2017).

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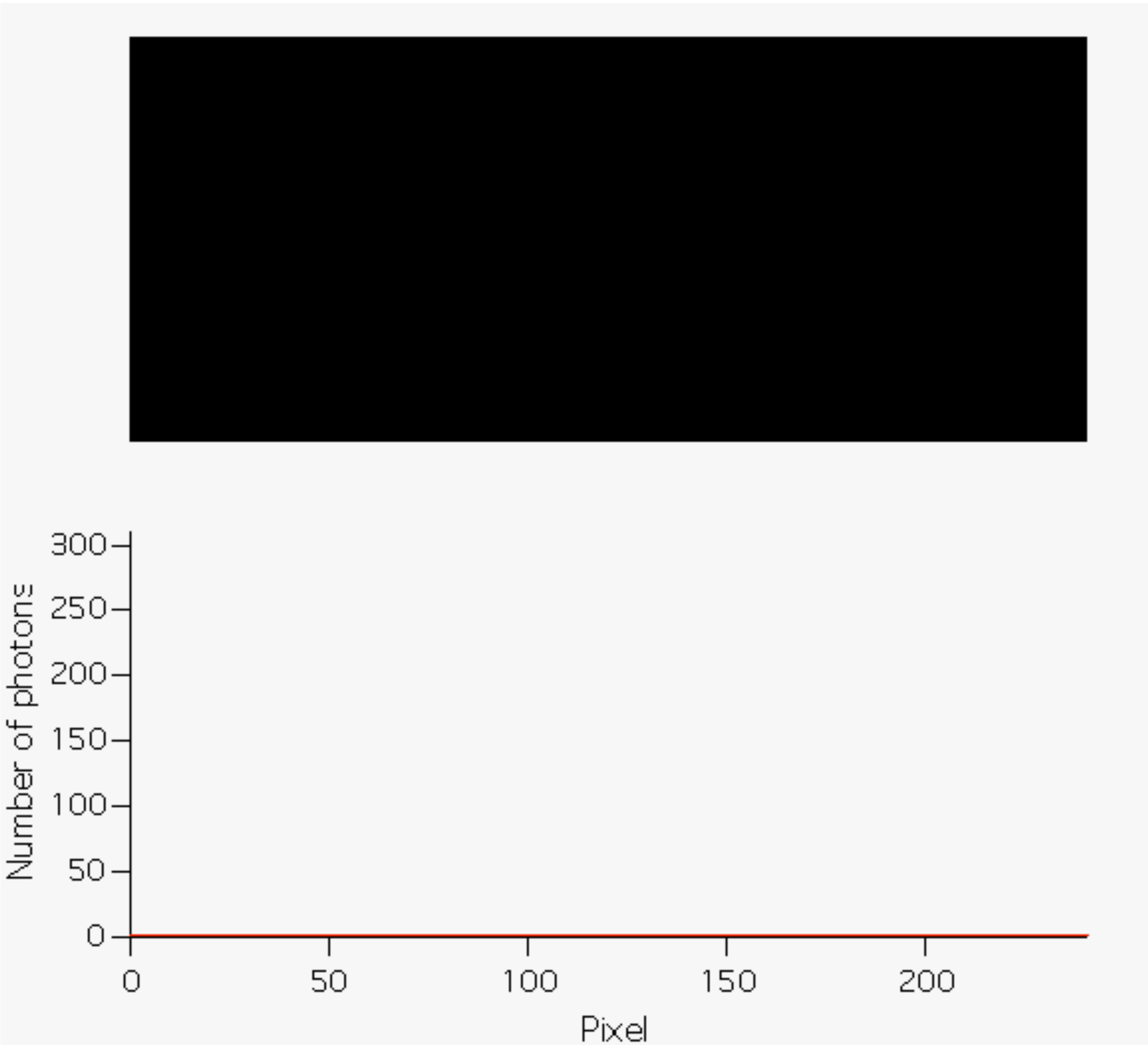
Even classic diffraction effects turned out to be particulate in character:



How could anything like that possibly happen at all?

Jean-François Roch
François Treussart
Philippe Grangier
http://www.physique.ens-cachan.fr/old/franges_photon/interference.htm

A vision about vision

The ink was barely dry on Einstein's paper when Lorentz asked, "Doesn't this imply an absolute limit to human visual sensitivity?"

“Lorentz’s suggestion really is quite astonishing. If correct, it would mean that the boundaries of our perception are set by basic laws of physics, and that we [nearly] reach the limits of what is possible. Further, if the visual system really is sensitive to individual light quanta, then some of the irreducible randomness of quantum events should be evident in our perceptions of the world around us, which is a startling thought.” – W Bialek, Biophysics

[Isn't this a more engaging road into quantum physics than black-body radiation?]

On quinine solution

A medium that doesn't absorb light may be transparent or turbid, depending on the length scale of the constituent objects.

and

That jug of fluid was transparent to visible light.

but

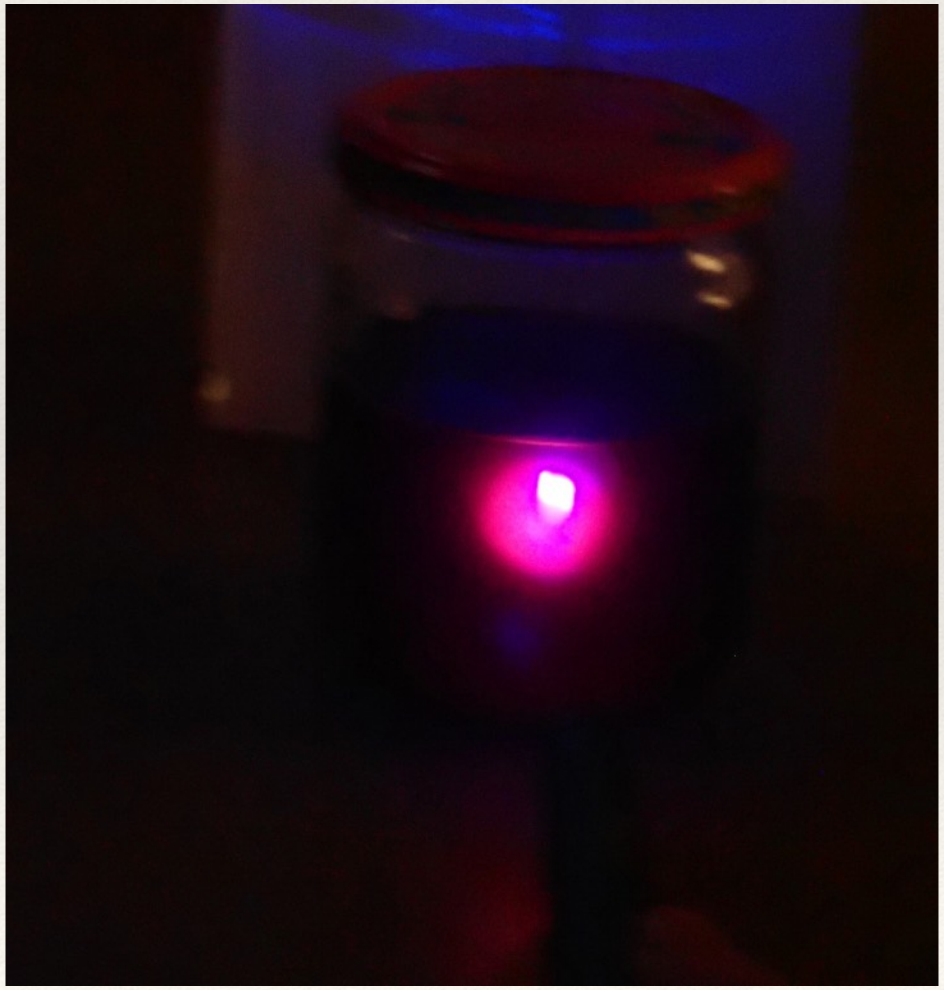
It seemed turbid to UV light, whose wavelength isn't much different from visible.

so

We have a problem. Resolving it takes us right to the heart of fluorescence microscopy, fluorescence polarization anisotropy, etc.

Weird+real = memorable

Blue laser spot, and what happens when you shine it on chlorophyll solution.



Weird+real = memorable

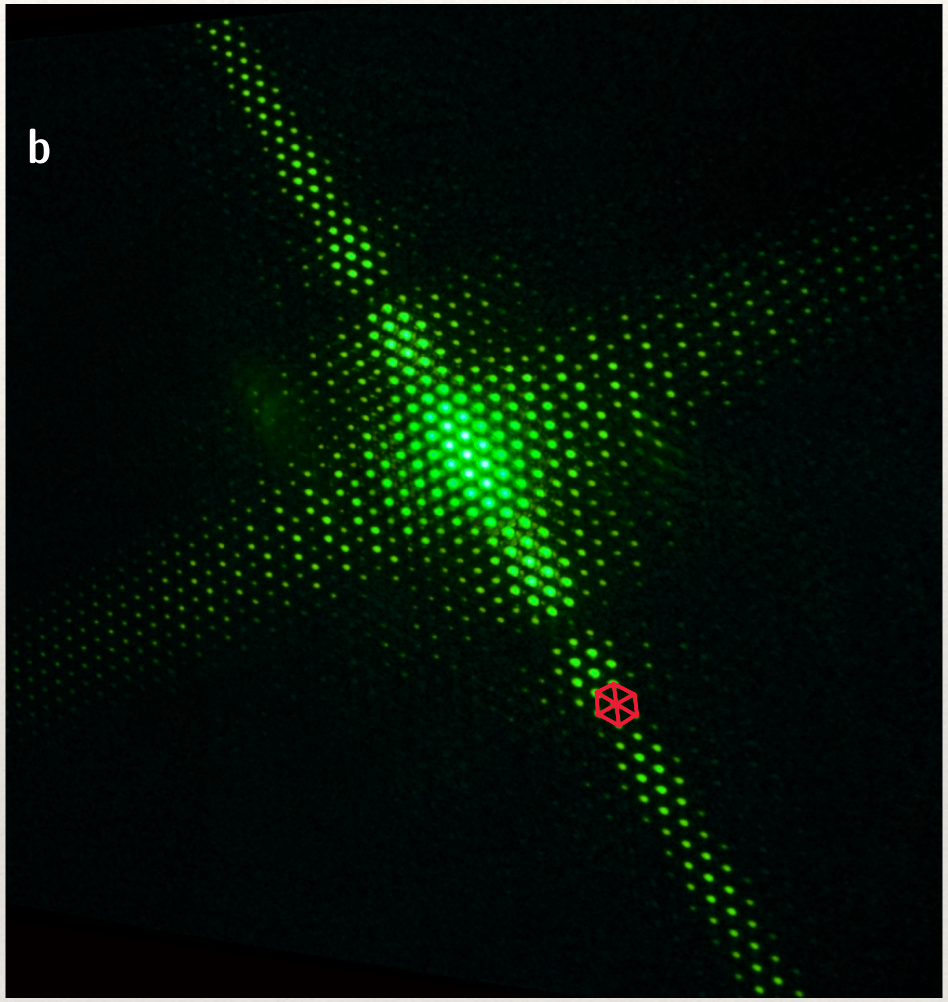
Especially after you remind the audience that there is nothing fake / virtual / digital / simulated here.

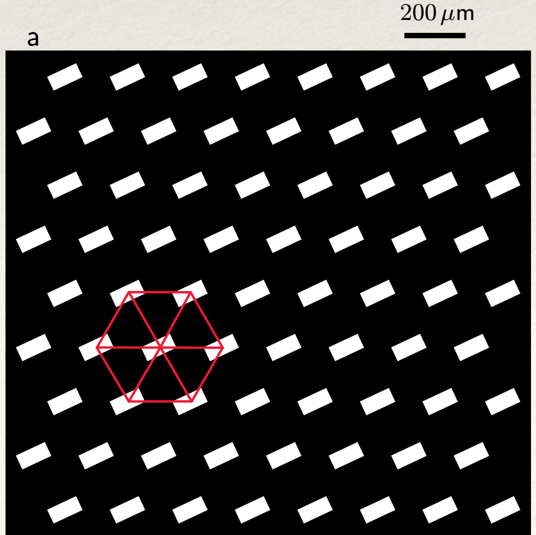
Some demos are also suitable for large audiences.

How could anything like that possibly happen at all?

Understanding this phenomenon goes right to the heart of structure determination by x-ray diffraction.

Diffraction pattern, and the mask that created it.





P N, *From Photon to Neuron* (Princeton 2017).

Some examples: Quantum

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Back to FRET

OK – FRET is useful. Many of its features make sense, at least qualitatively, when we invoke dipole-dipole coupling.

Umm…

(a) FRET is strongly quantum-mechanical because it deals with discrete energies and states;

but

FRET is strongly classical: Superpositions are not observed, and you can get the rate by a classical calculation.

(b) FRET follows first-order kinetics (fixed probability per time to make a one-way transition)

but

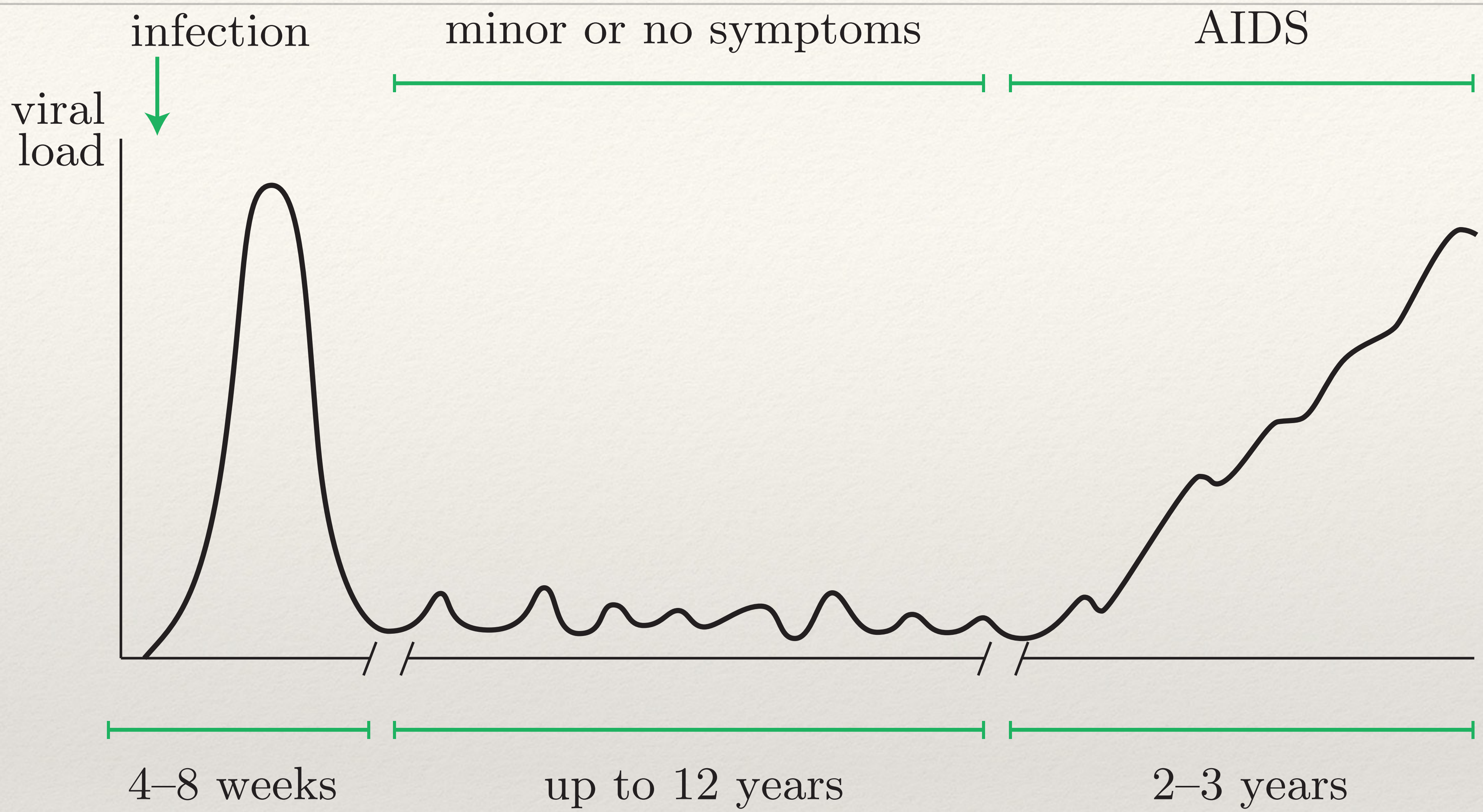
That's not what quantum mechanics (seems to) predict.

So

How could anything like that possibly happen at all?

P N, *From Photon to Neuron* (Princeton 2017).

Some examples: Analytical "Mechanics"



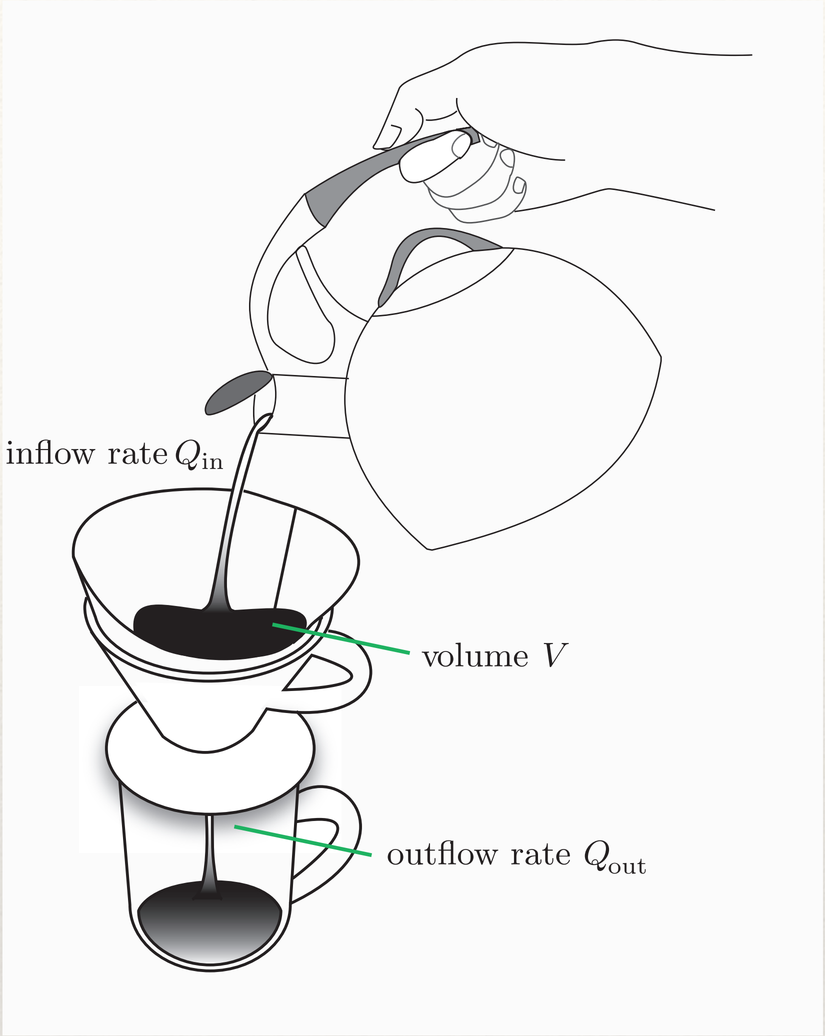
Left untreated, HIV infection seems not too serious for even a decade. *What is happening during that period?*

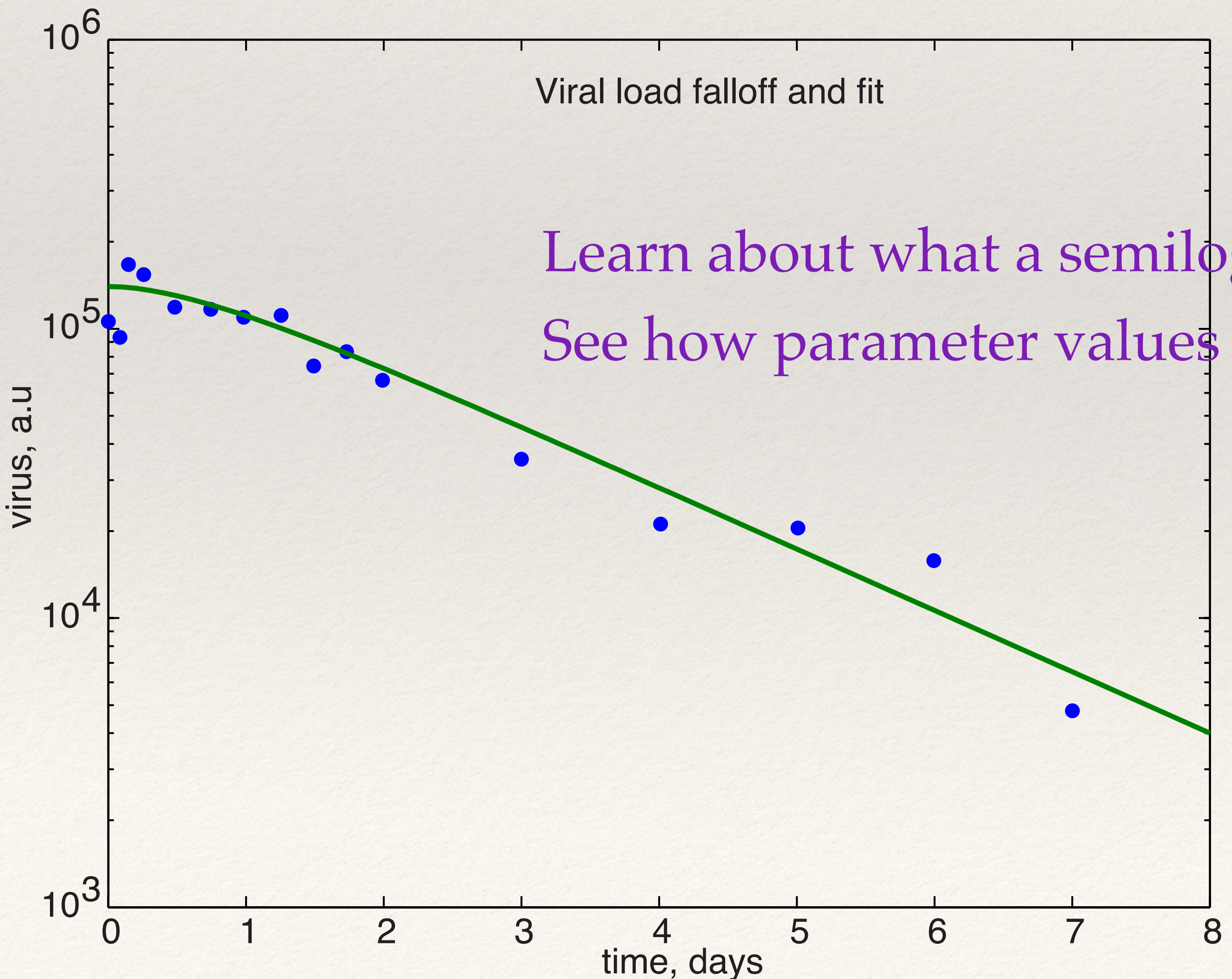
Once the first antiviral drugs were invented, each was effective for about a month, then failed. *Why? What to do?*

From PN, *Physical models of living systems 2nd ed*. (2022).

A simple physical model

Less is (sometimes) much more.





Learn about what a semilog plot shows.

See how parameter values affect the graph.

From PN, *Physical models of living systems 2nd ed*. (2022). Data from Perelson et al. 1995.

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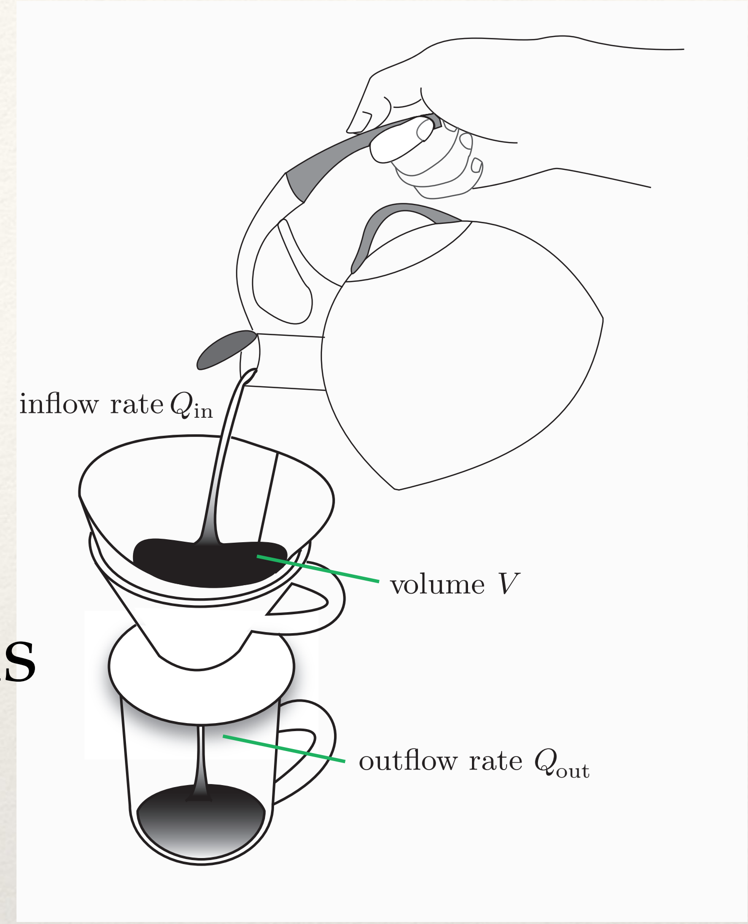
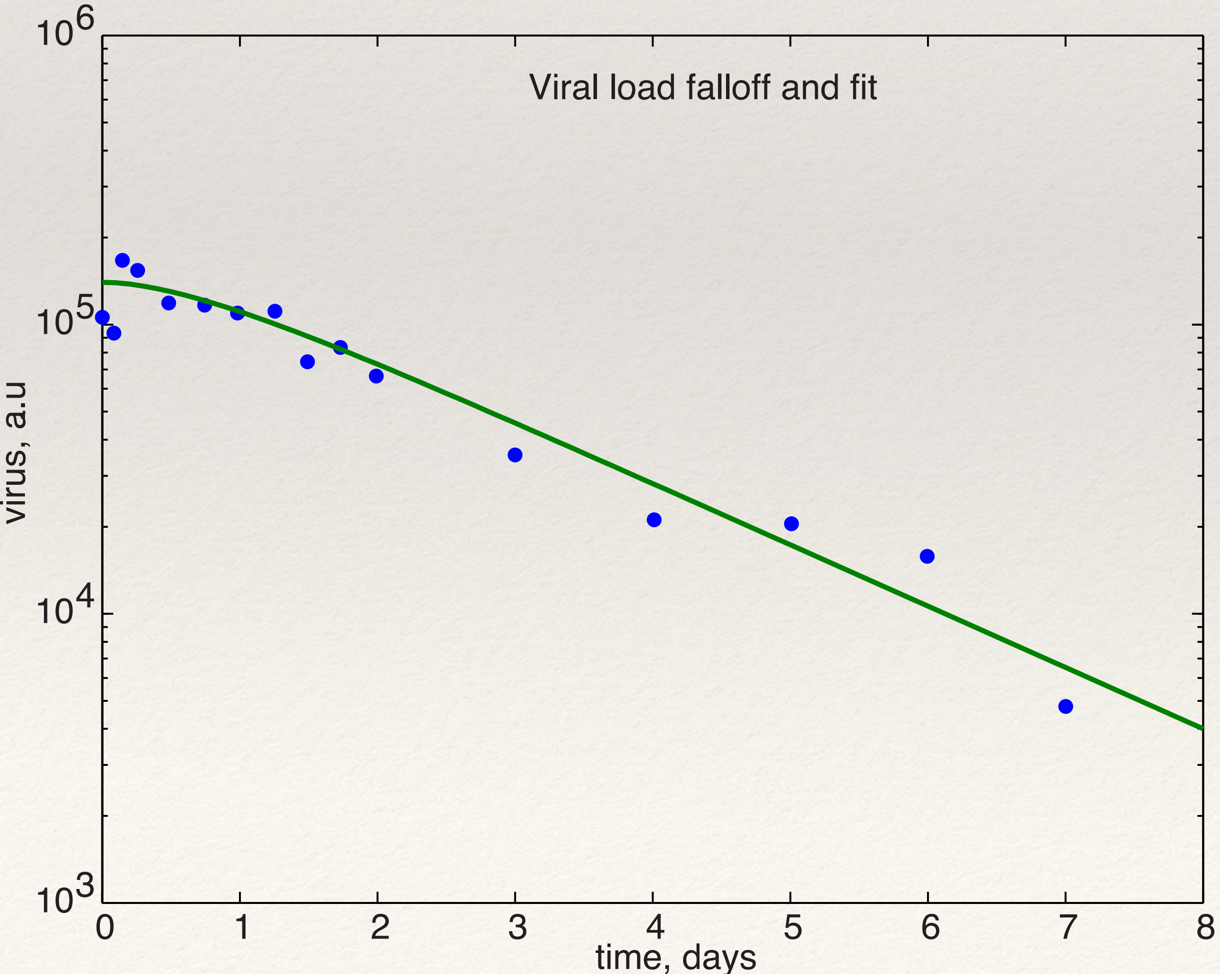
What math is really for

We want to know the rate of new T-cell infections. In 1995 this was not directly measurable; only the viral load was measurable. So we *embody the model in equations, solve and fit them, and extract the desired rate from the fit.*



The model, and its mathematical analysis, carries us *from what we can measure to what we wish to know.*



In this case, the model didn't just help with analysis of an experiment; it also helped the researchers *imagine* what experiment *was needed.*

From PN, *Physical models of living systems 2nd ed.* (2022). Data from Perelson et al. 1995.

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Feedback control: A biological problem

Cells in a frog embryo divide in synchrony.

And

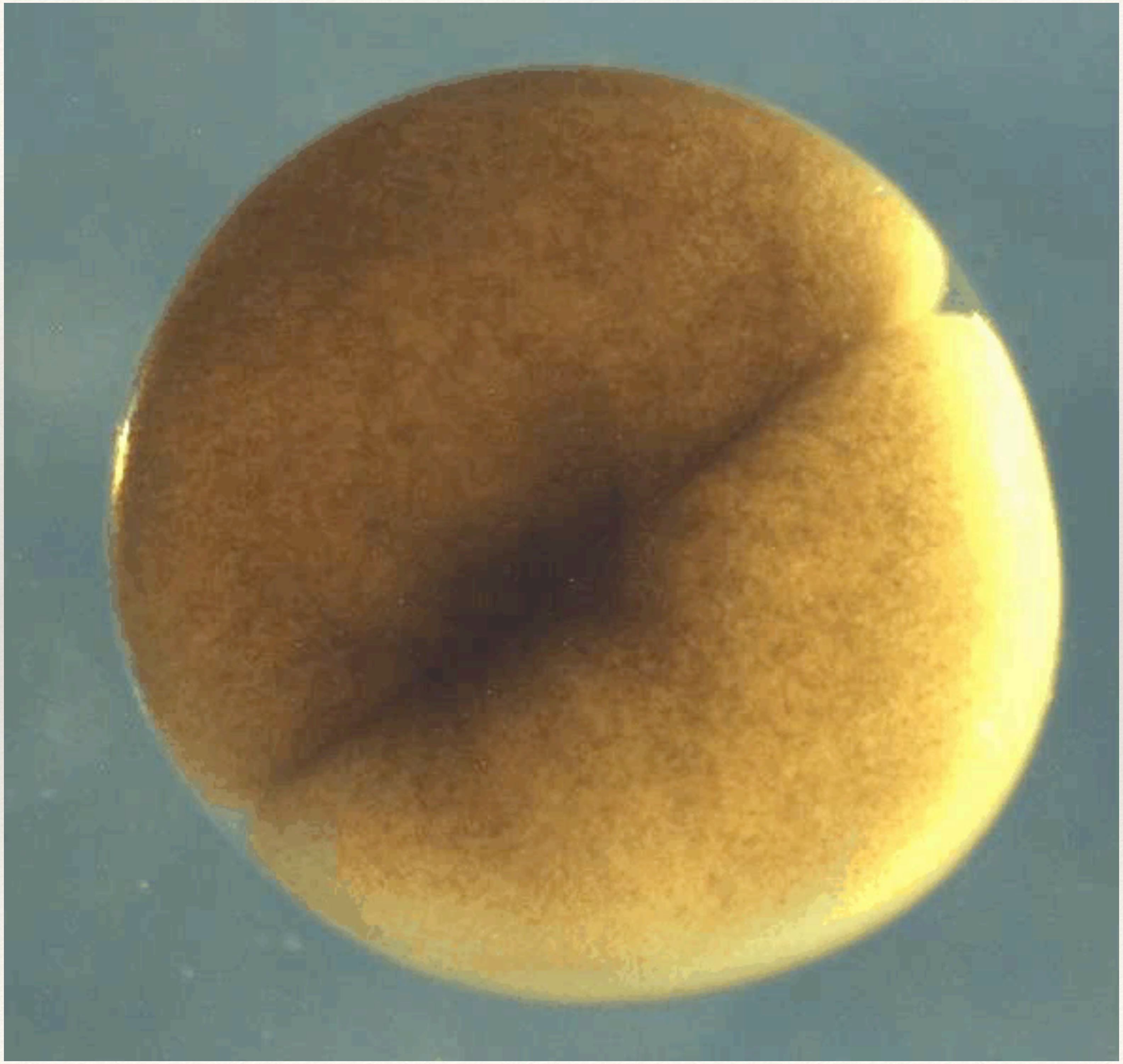
That's important for proper development

But

Those cells are not communicating; they stay in sync even if separated.

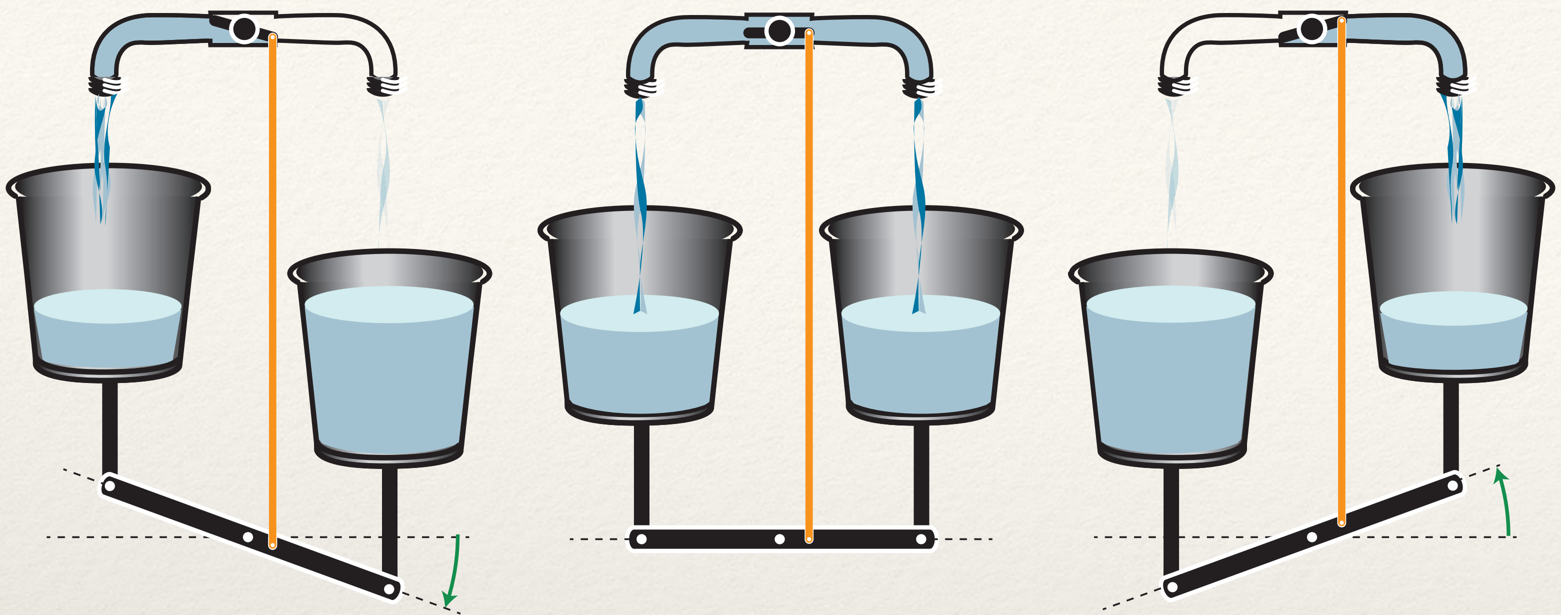
So

We need to understand robust oscillation in a single cell.



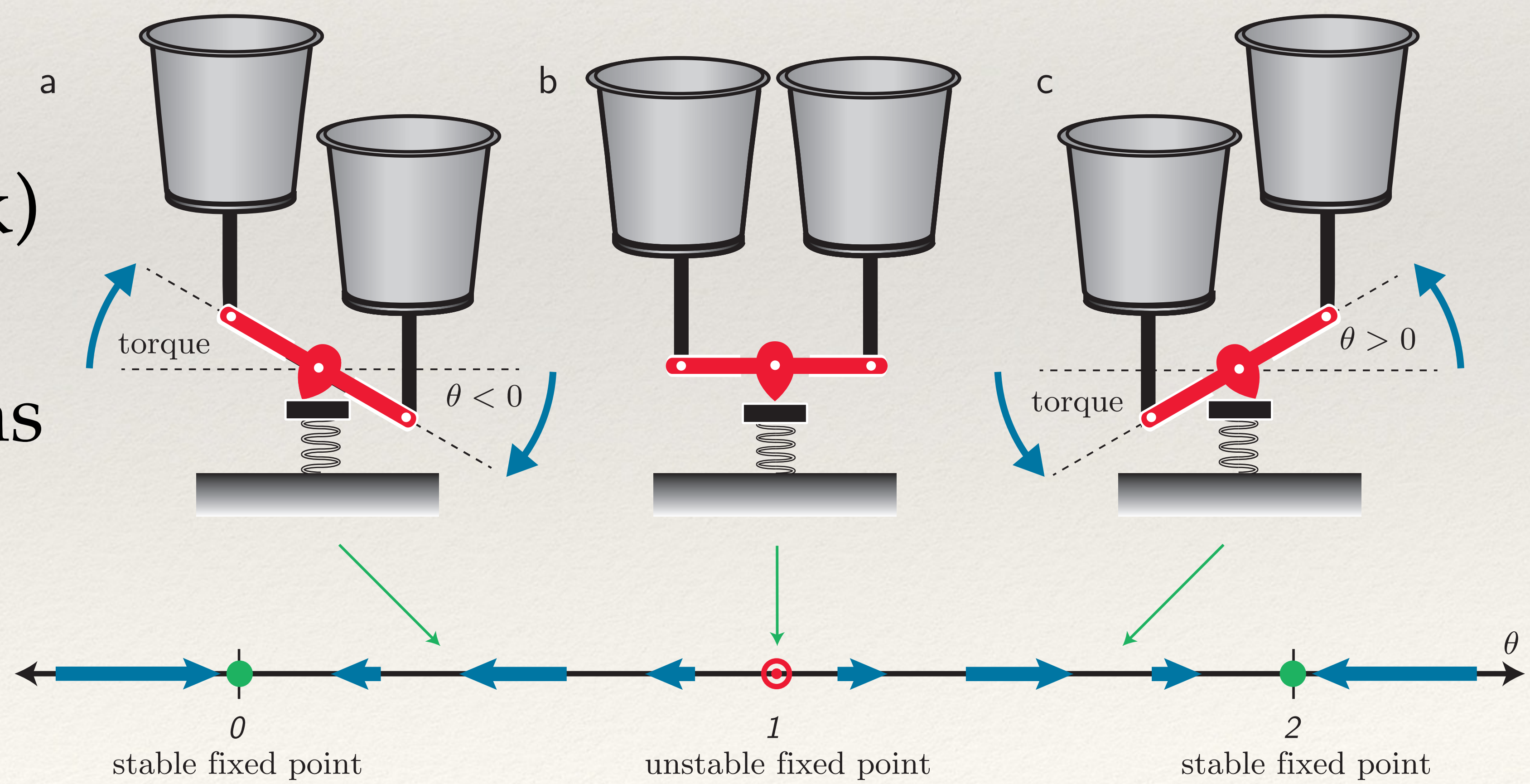
Video courtesy Tony Tsai.

Feedback: Mechanical analogy



This negative-feedback system oscillates, but not robustly.

Adding a toggle element (linked positive feedback) gives us a relaxation oscillator, which performs much better.



From PN, *Physical models of living systems 2nd ed*. (2022).

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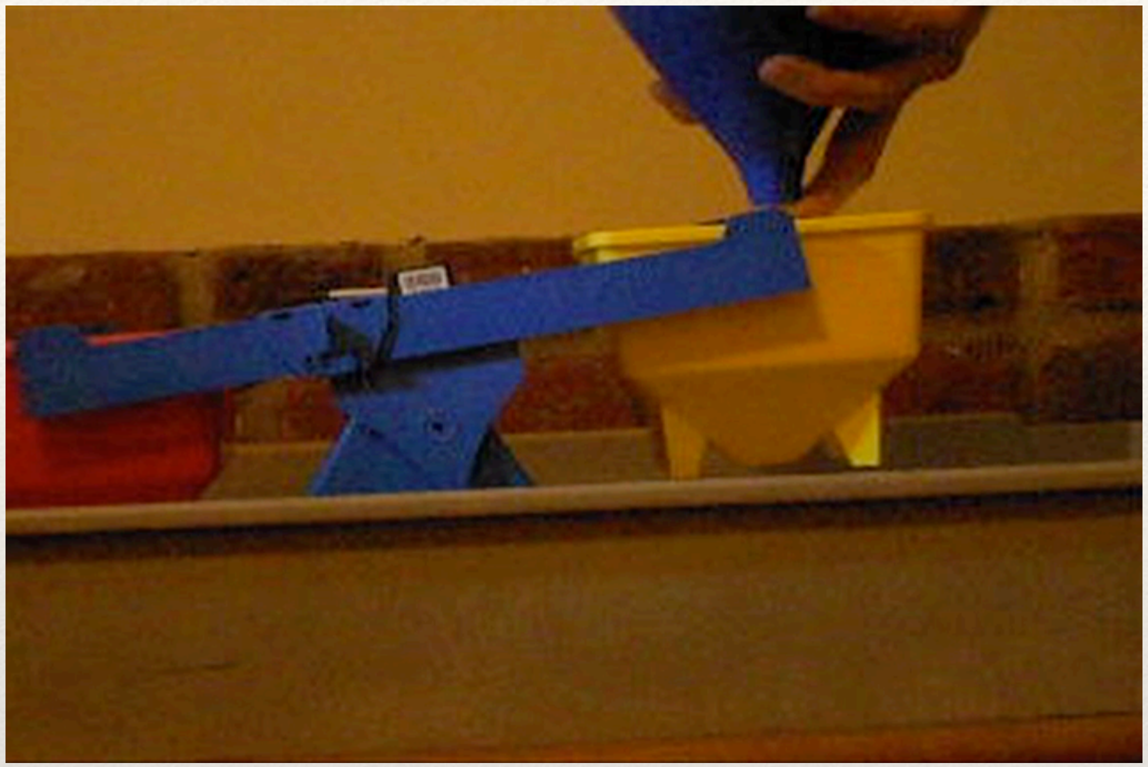
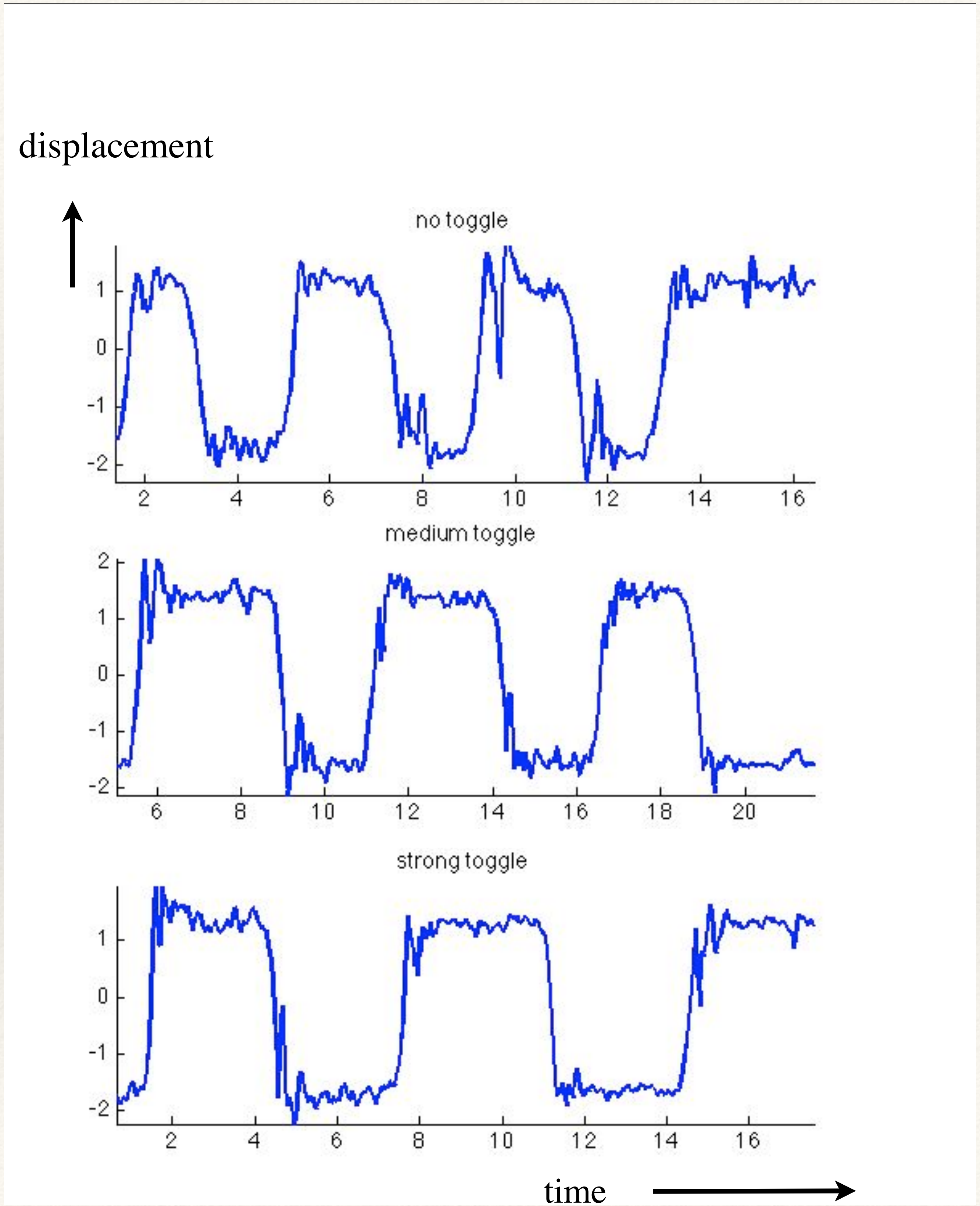
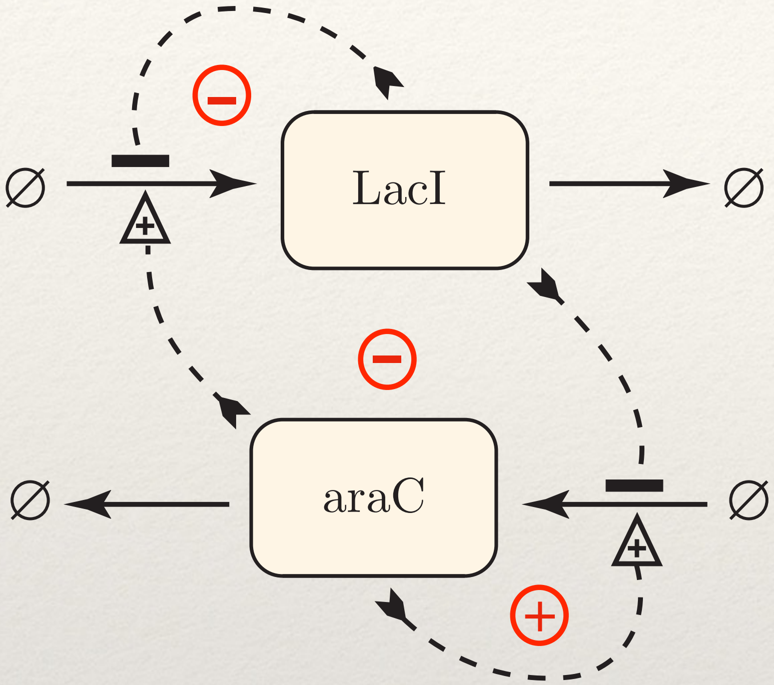
Feedback: Classroom realization

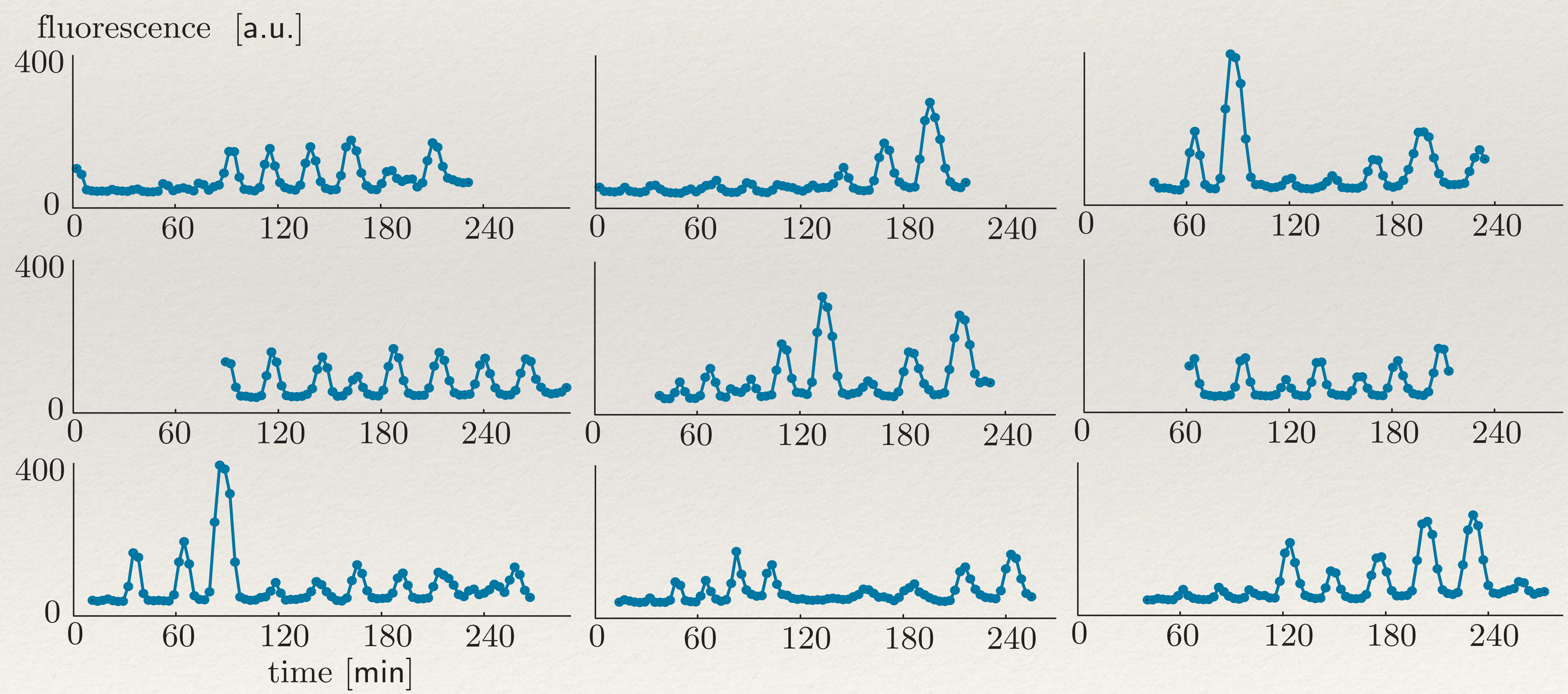




“Build it to understand it.”

Feedback: Realization in synthetic biology





From PN, *Physical models of living systems 2nd ed*. (2022). Data from: Stricker et al., Nature (2008).

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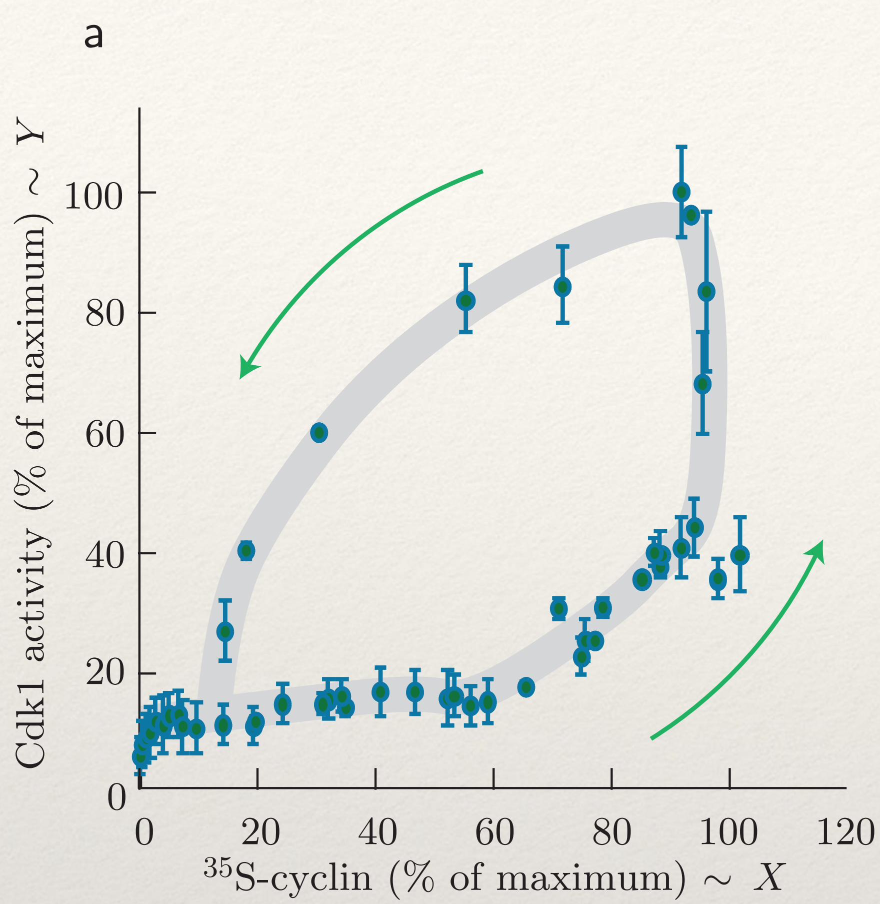
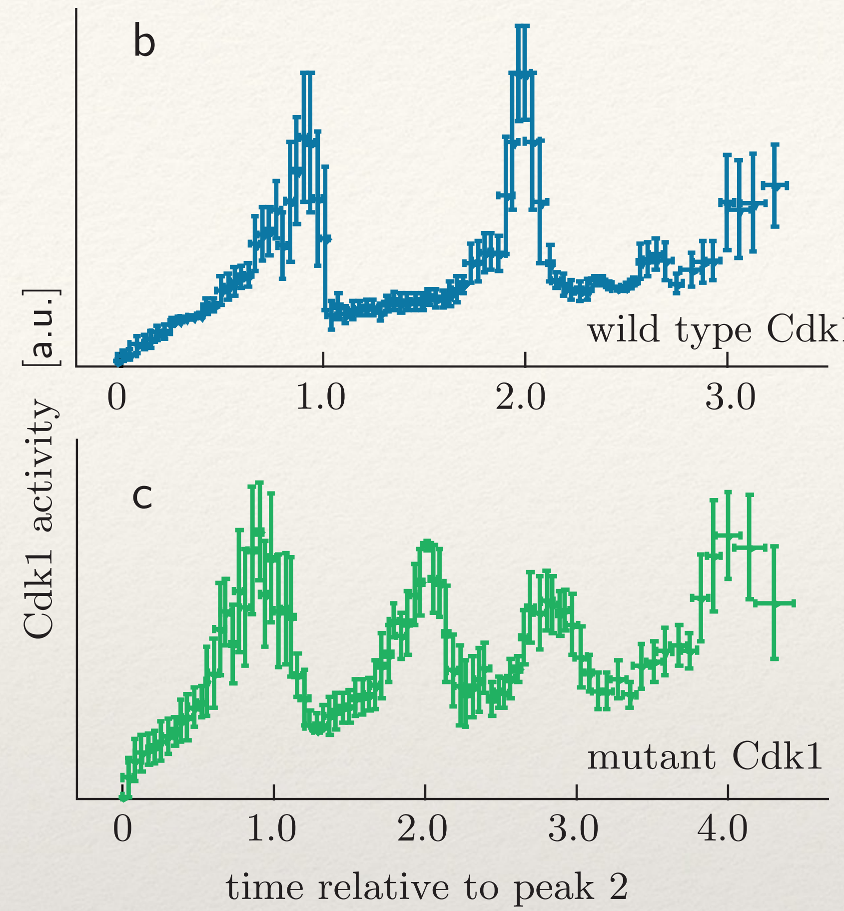
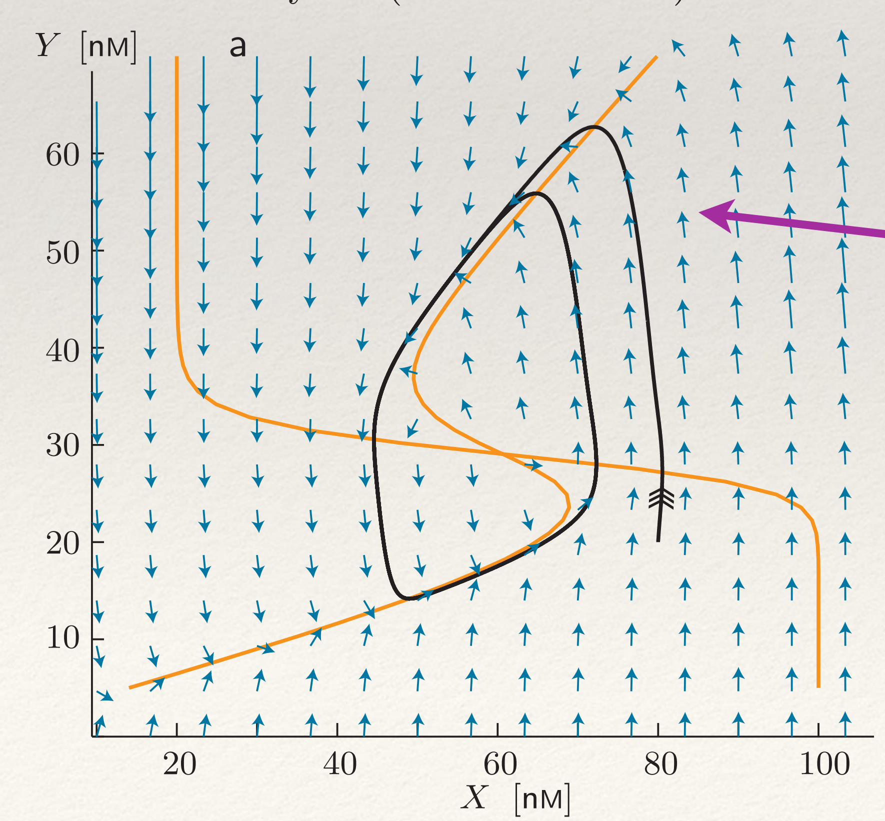
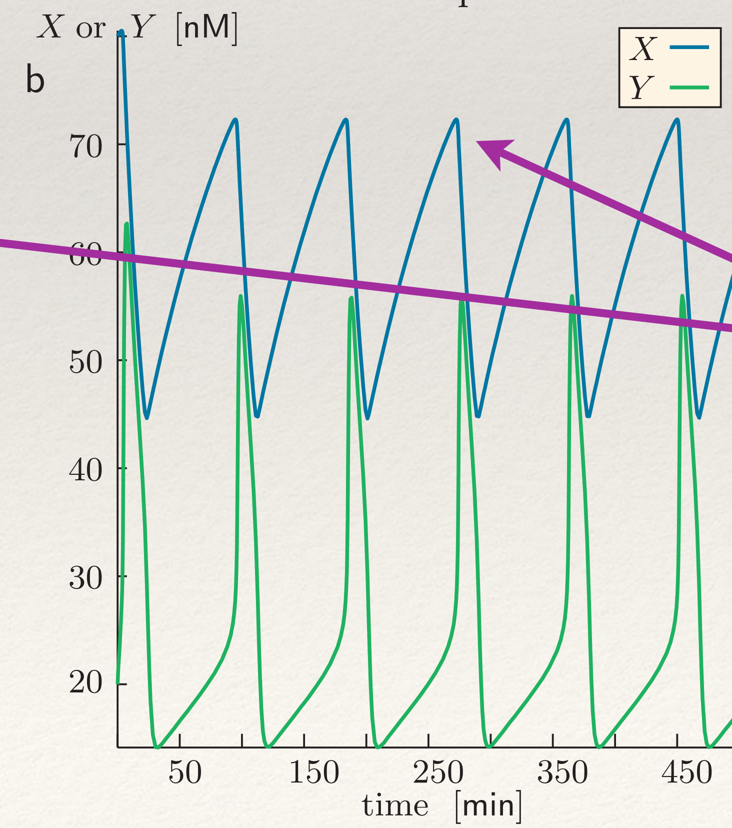
Feedback: Realization in frog embryo





A phase portrait tells us much of what we want to know about a dynamical system–without solving any equations.





Assignments students do

From PN, *Physical models of living systems*. Data from: Pomerening et al., Cell (2005).

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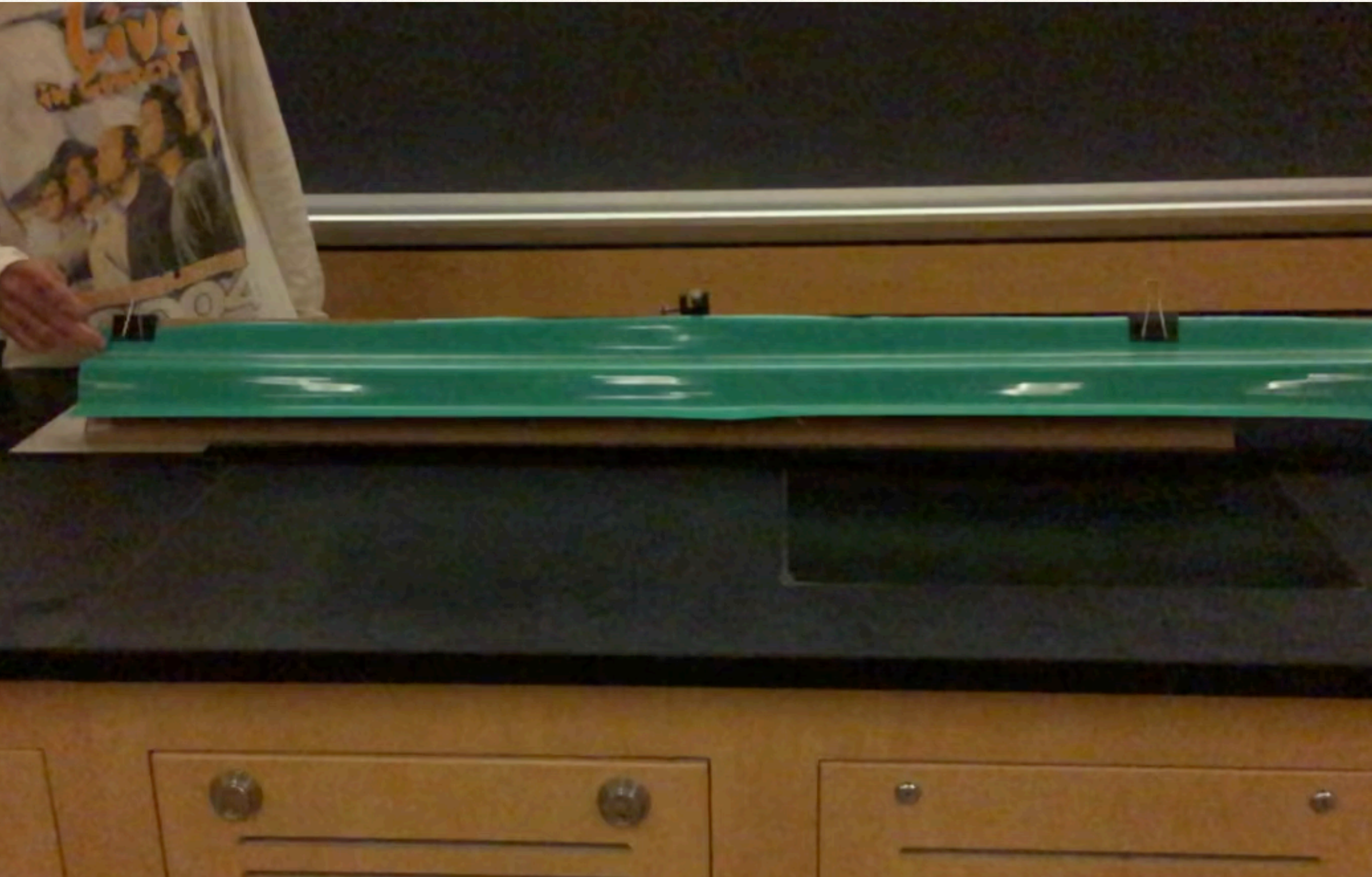
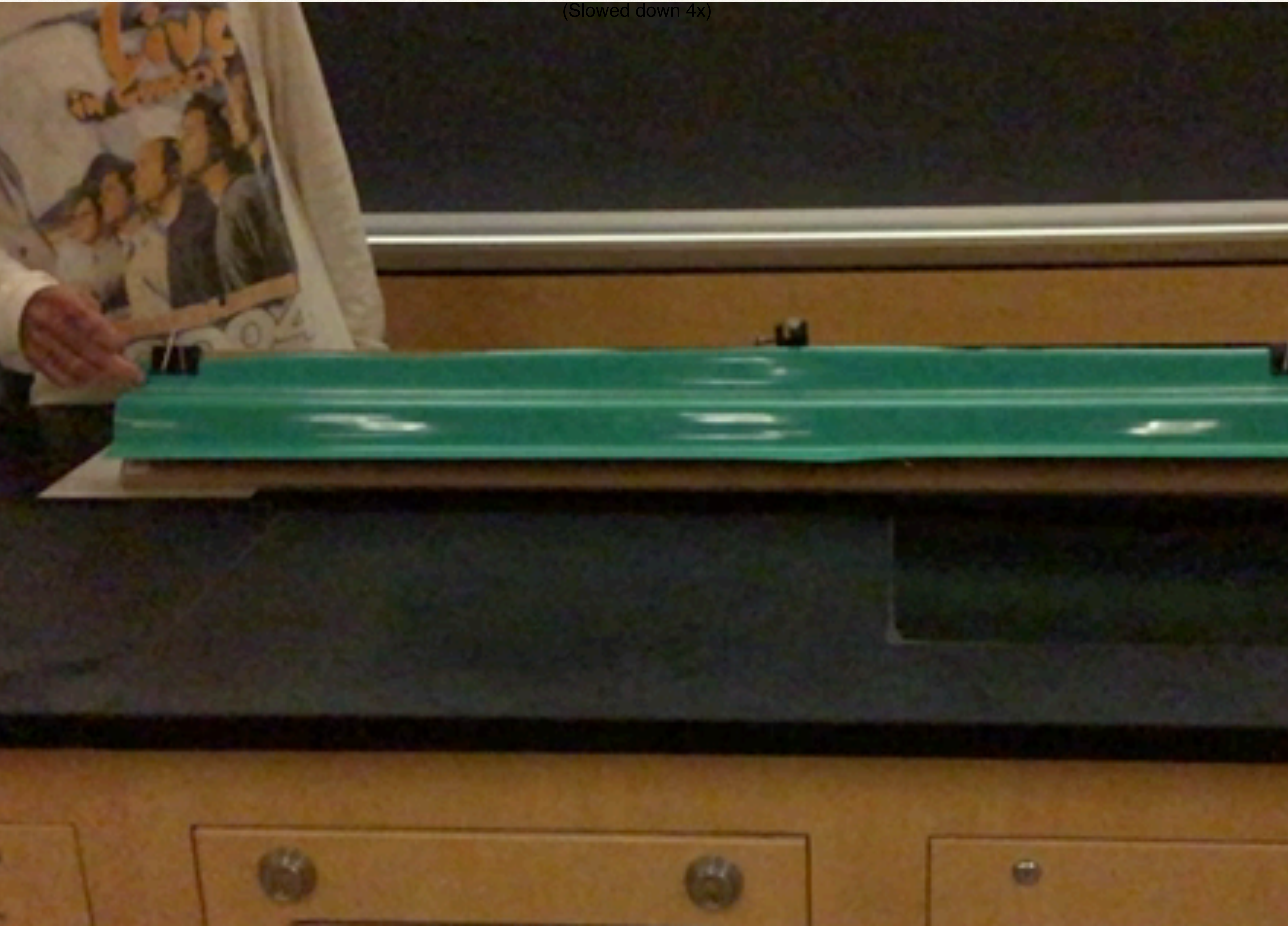
Action potential as a nonlinear traveling wave



(Slowed down 4x)

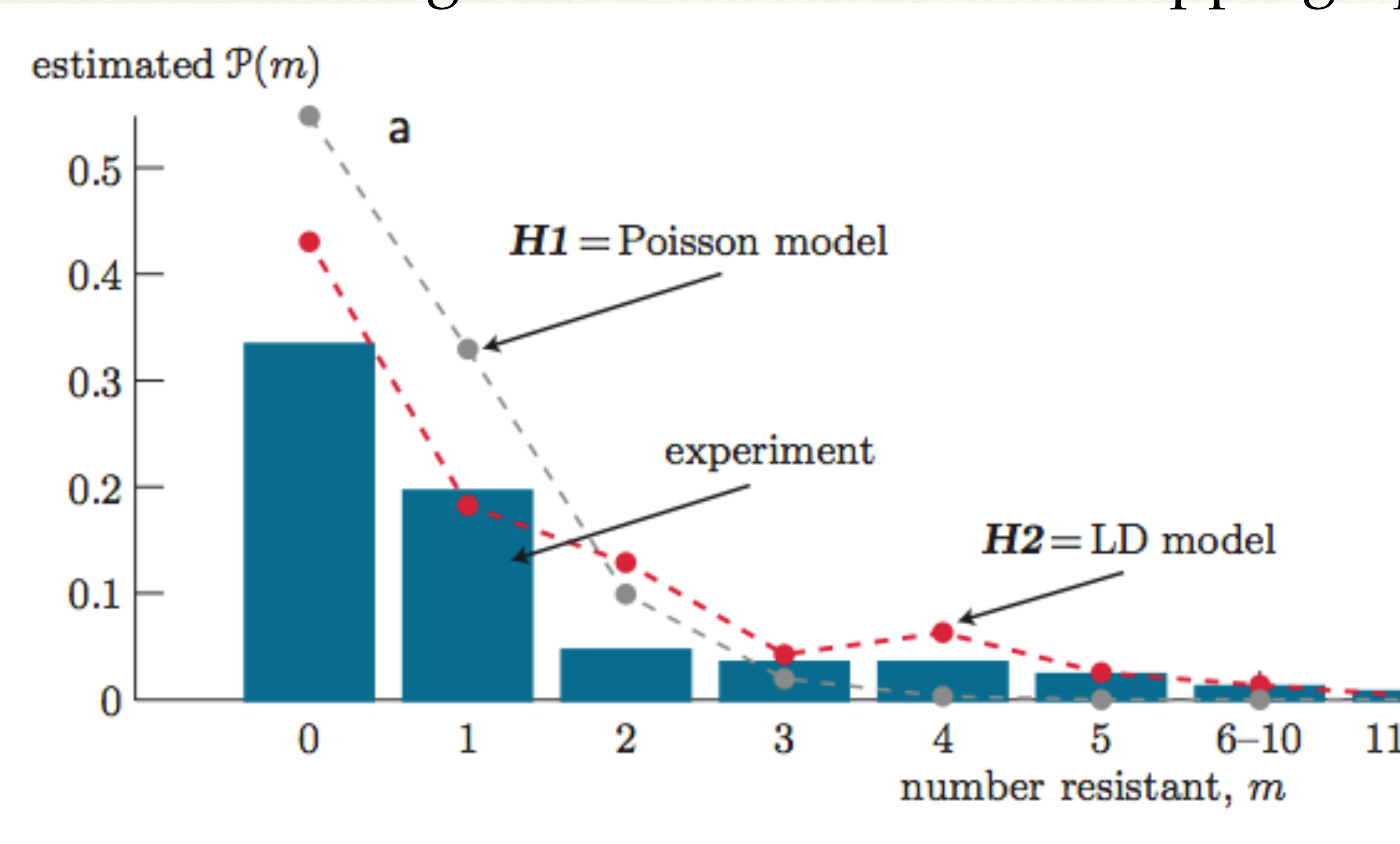


Some examples: Statistical

Cognitive dissonance is memorable

"Wait, I thought evolution took millions of years?!"

But here is drug resistance in bacteria cropping up in just 20 generations:



Luria says he got the idea after an encounter with real slot machines!

That was an old experiment, but fluctuation analysis is still in use today, e.g. for drug-resistance in cancer.

From PN, *Physical models of living systems*. Data from: Luria and Delbrück.

Phil Nelson

Things I want every student to know

Throughout my education, the attitude to fluctuations in data was:
"Take enough data to beat down the noise so you have believable mean value(s), then if needed do least-squares fitting."

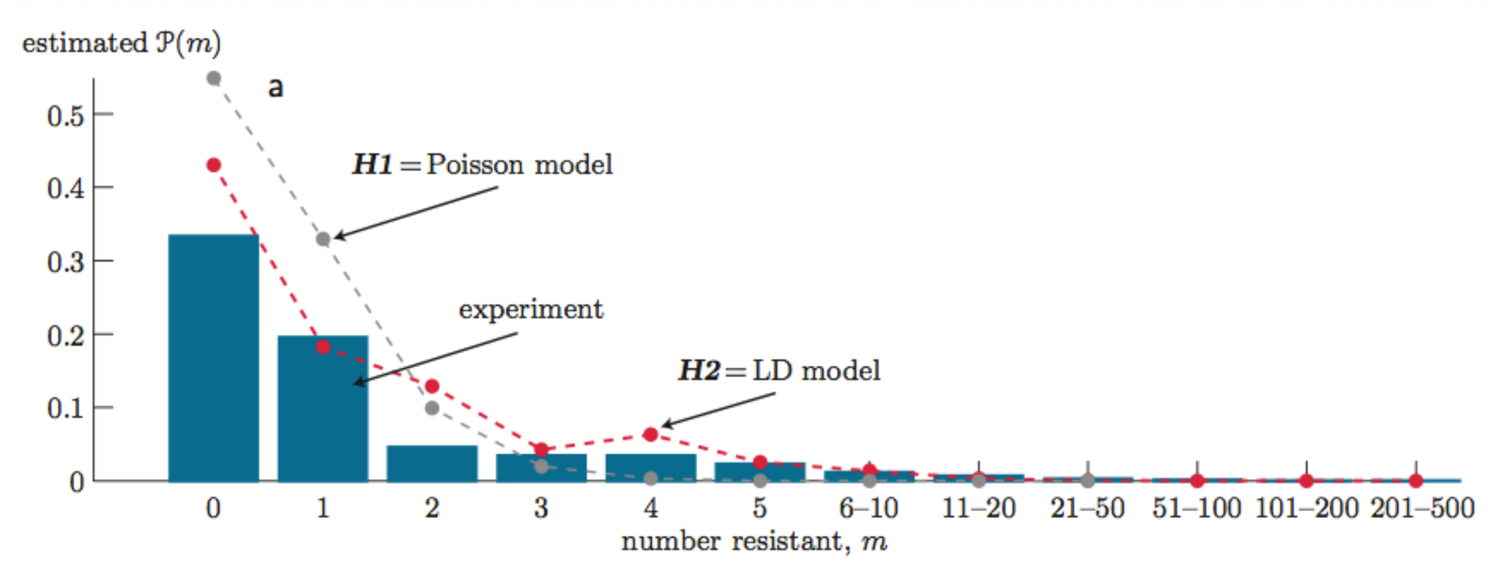
But:

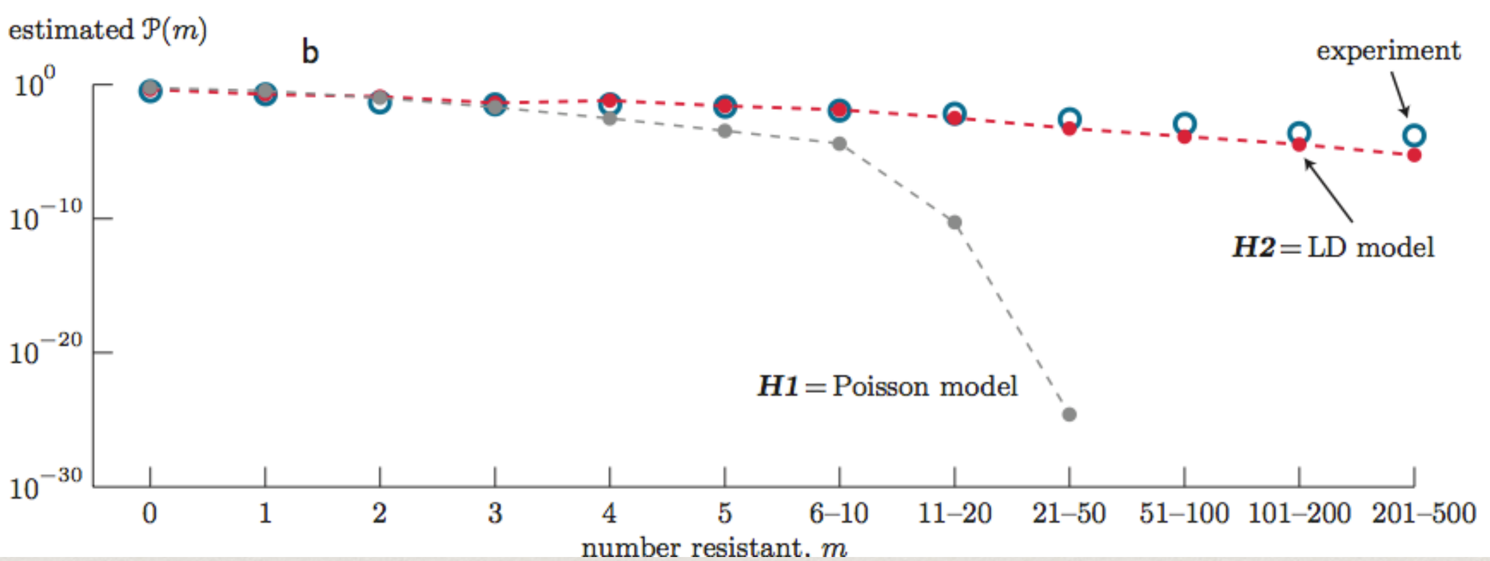
- Sometimes the fluctuations are the main story and you lose something when you neglect them.
- Sometimes the fluctuations are not Gaussian, as assumed by least-squares.
- Some distributions -- and not just pathological curiosities -- have long tails, so that you can NEVER BEAT DOWN THE NOISE by taking more data: They have no well-defined mean.
- Nevertheless, you can do science in such situations, that is, choose between competing models based on such data.

Skills/Frameworks: Visual representation of data

Here are best-fit predictions of two competing models. Each model has one fitting parameter.

The two models may appear equally successful when presented in this way.





Students make semilog plot; suddenly they see how badly the "Lamarckian" model of drug-resistance fails and how well the Luria-Delbrück model succeeds. Far from being an irritation to be minimized, ***fluctuations carry the key insight.***

Students also see, often for the first time, a ***long-tail distribution*** in a biologically important context.

Within each model, we also see which parameter value is best.

"Yikes! How can the *style of a graph* affect a *scientific conclusion?*" That's strong motivation to find a more objective approach.

From PN, *Physical models of living systems 2nd ed*. (2022). Data from: Luria and Delbrück.

Phil Nelson

When math lets you down

Where did those two competing theory results come from, by the way?

"Lamarckian" model predicts a Poisson distribution, which misses the long tail of the distribution.

For the "Darwinian" model, it very hard (not impossible) to predict analytically the distribution of survivors.

But it is *trivial* for undergraduates to *simulate* it in a few lines of code, a valuable lesson on the importance of having both tools in your toolbelt:

```
Double population.
Poisson distribution of new mutants in that
doubling, based on current population.
(Retain existing mutants from previous generations.)
Repeat.
```

Payoff

Back to the HIV problem, the researchers framed a *promising hypothesis* by *analogy* to a decades-old observation in a very different context (drug resistance in bacteria).

Physical reasoning suggested an experiment that might not have been done otherwise (measure viral load very frequently after administering antiviral).

Analysis of those data confirmed the hypothesis, *motivating* a new therapeutic approach (triple-drug cocktail).

Many people are alive today because of this breakthrough.

This approach will bear more fruit in the future.

Catch bonding in leukocytes

How could
anything &c?

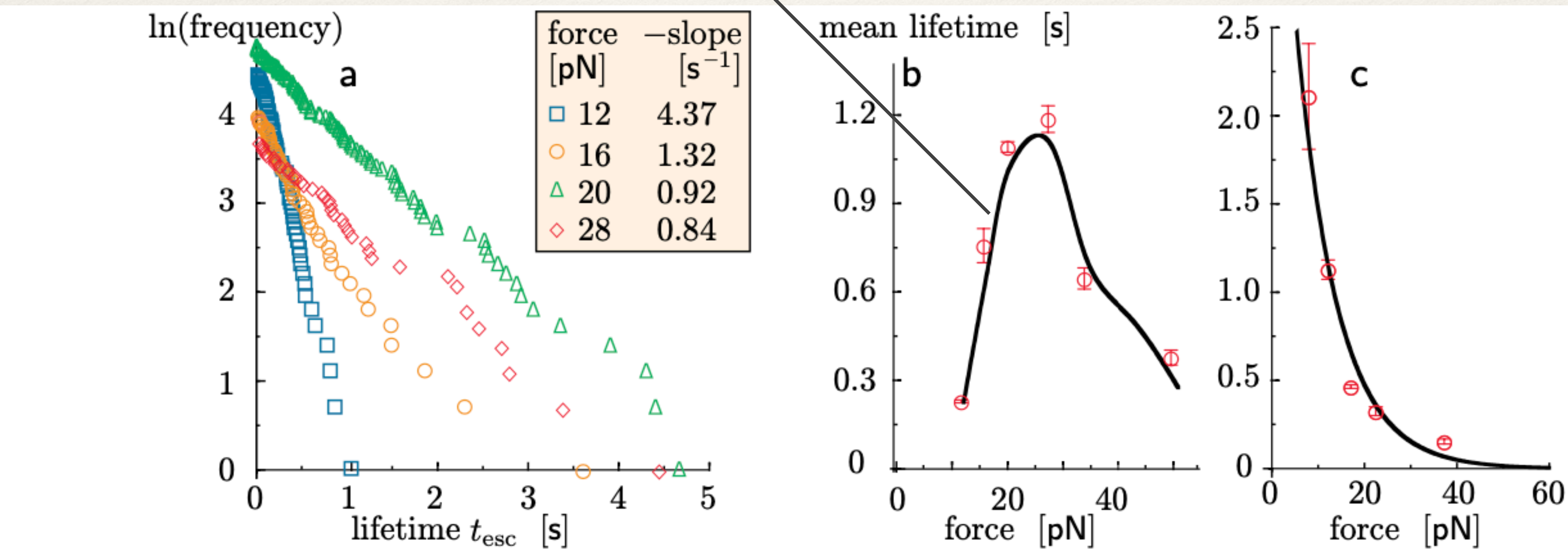


Figure 6.10: [Experimental data.] **Bond lifetimes in the experiment of Figure 6.9.** (a) Semilog plot of tl

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The Velcro effect

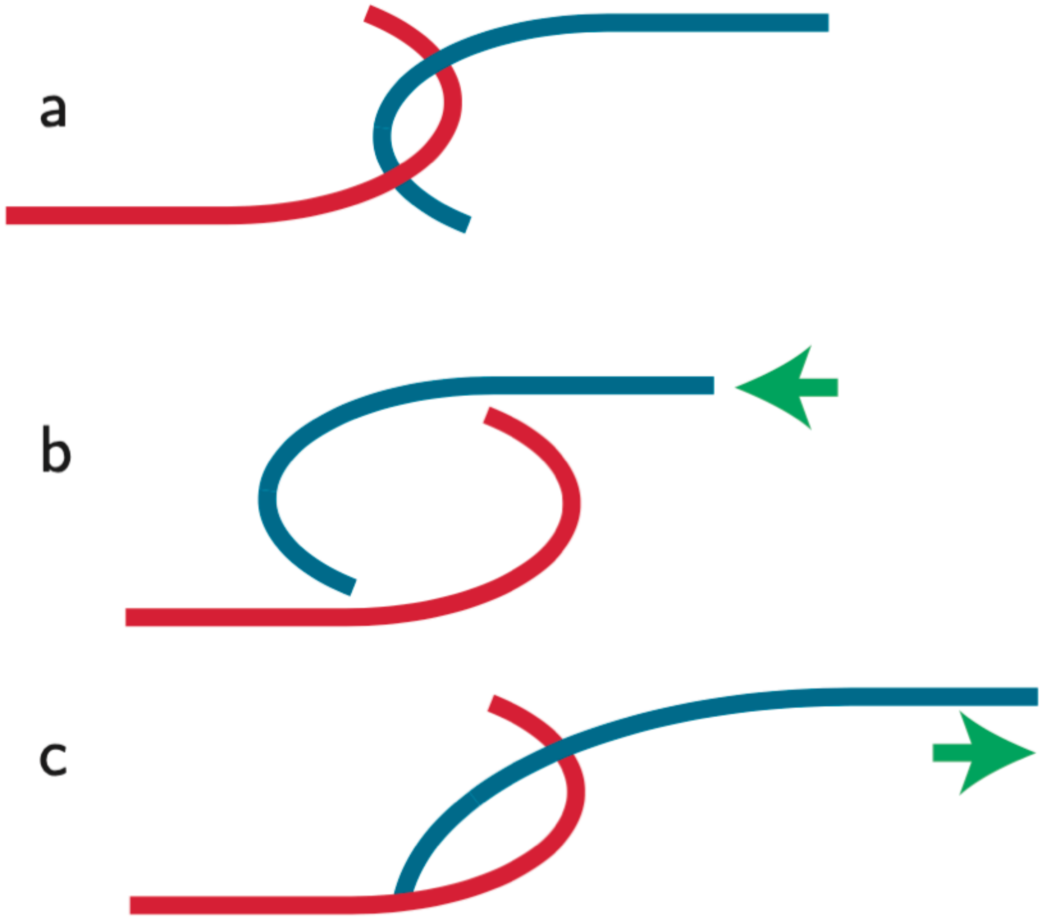


Figure 6.6: [Metaphor.] **Mechanical model of a catch bond.** (a) Two deformable hooks are linked. A weak spring keeps them under slight tension (*not shown*). (b) However, thermal agitation can move them together, against the weak spring, far enough to disengage. (c) An external pulling force can discourage that escape pathway. Then the hooks stay engaged unless the external force is so large as to straighten one or both of them (the alternate pathway to escape).

Phil Nelson

Two escape routes

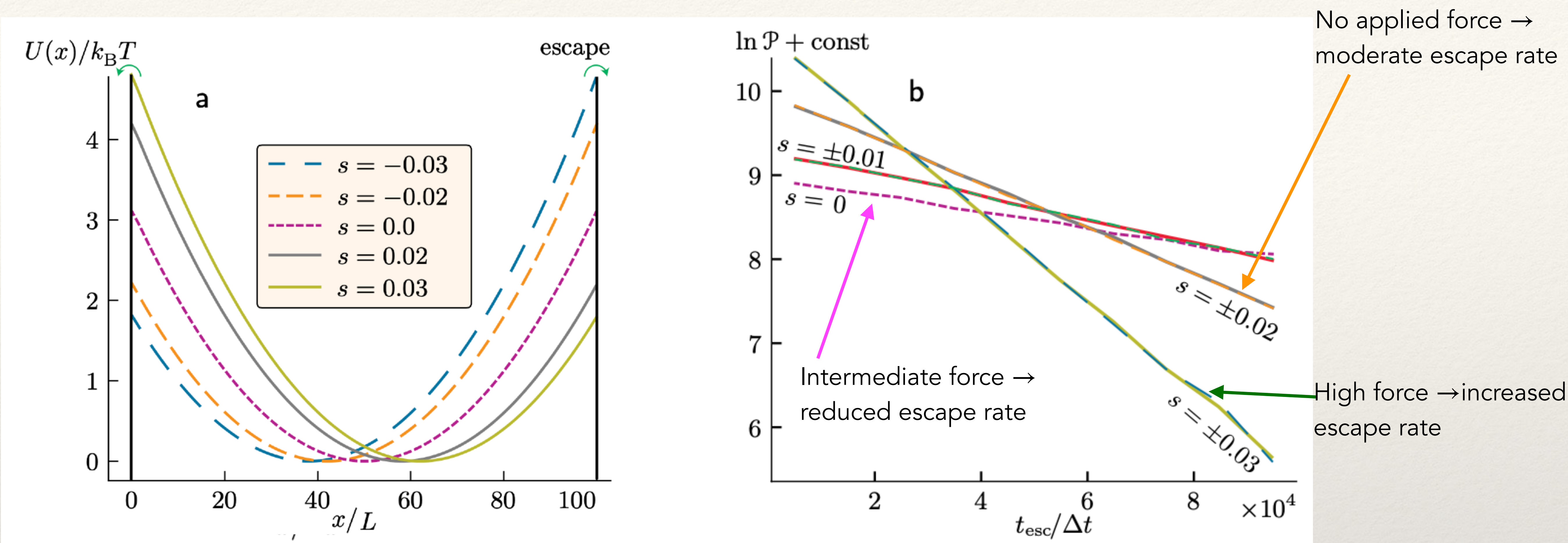
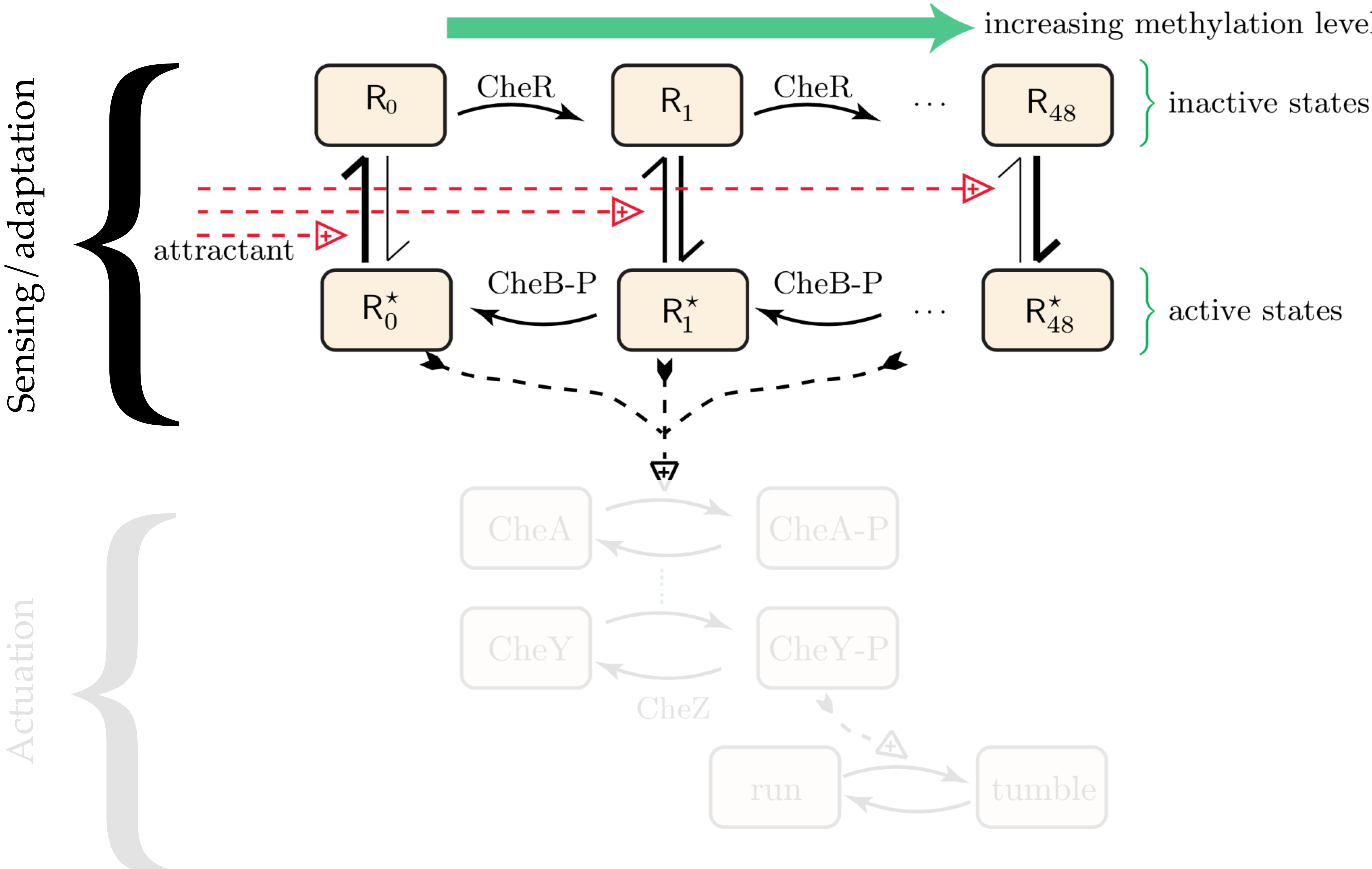


Figure 6.7: [Computer simulation.] **Multiple escape routes.** 80 000 walkers were again released, but this time they could "escape" either to the left or right side of the harmonic trap. (a) Potential energy functions. Negative values of s correspond to easier escape to the left; positive values correspond to easier escape to the right. (b) Semilog plot of the distribution of first-passage times.

Adaptation in sensing

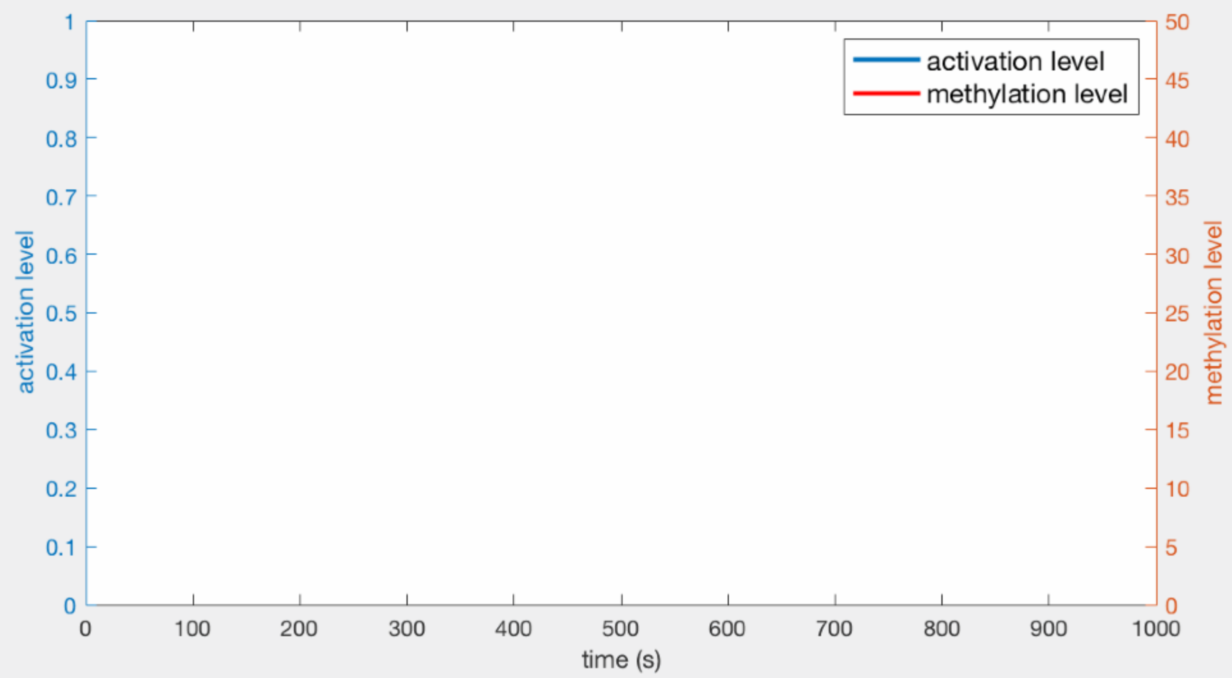
Any living organism gets an advantage if it can make decisions---Even single-cell organisms. But how can you make decisions without a brain? How could anything like that possibly happen at all?

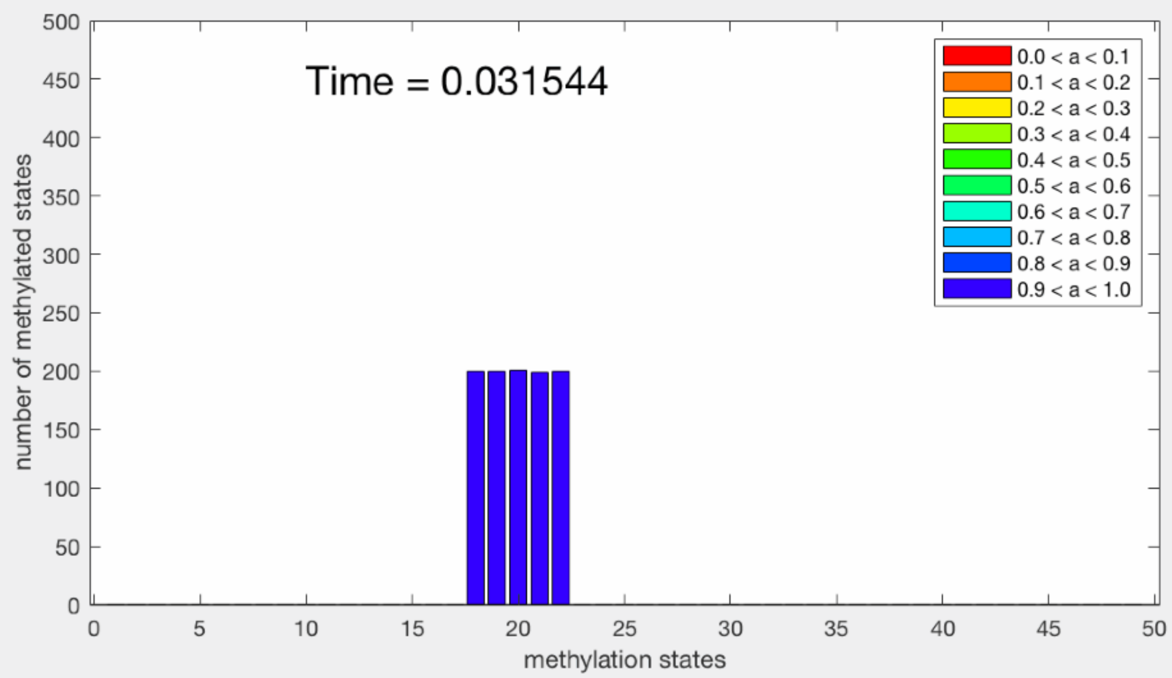


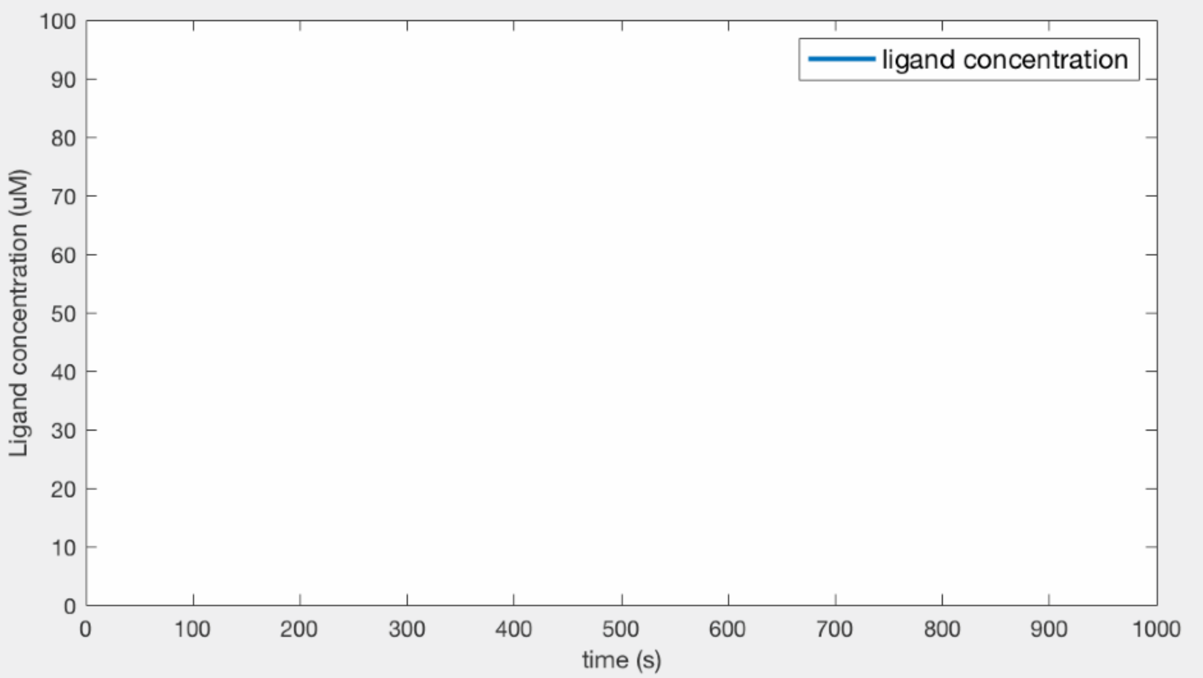
PN, *From photon to neuron*. The model was developed by Tom Shimizu, Yuhai Tu, Howard Berg, and coauthors.

Phil Nelson

Adaptation to steady attractant level





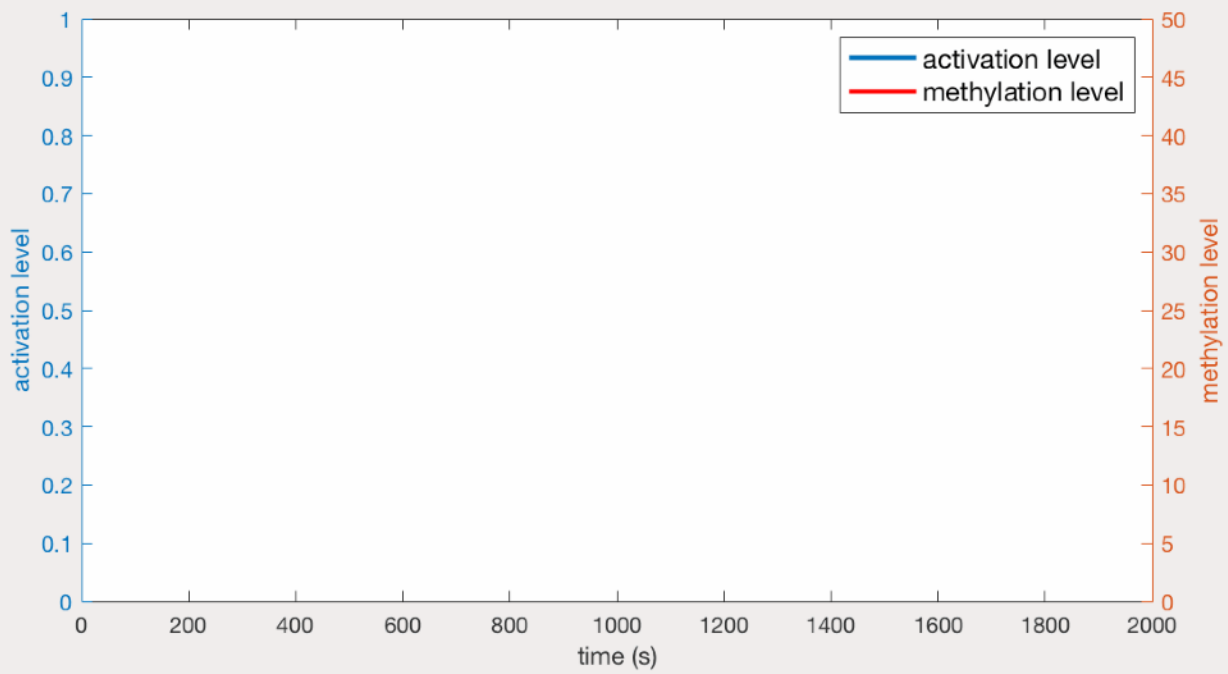


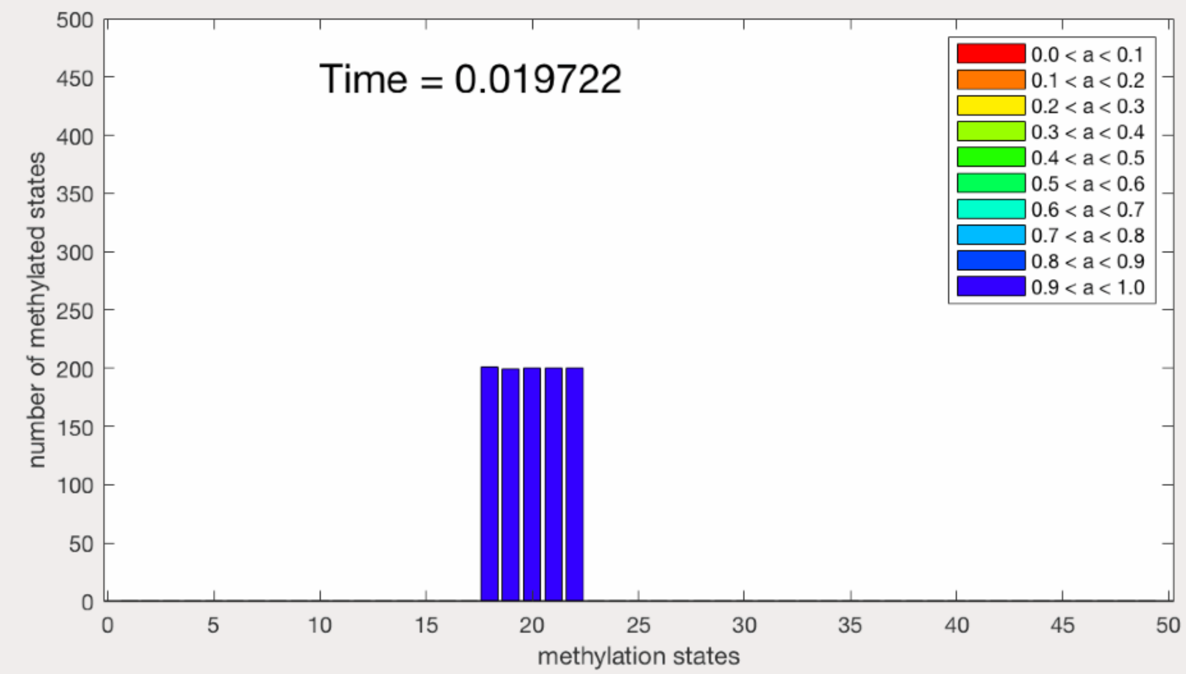
Here is a project that some real students did in one intense week.

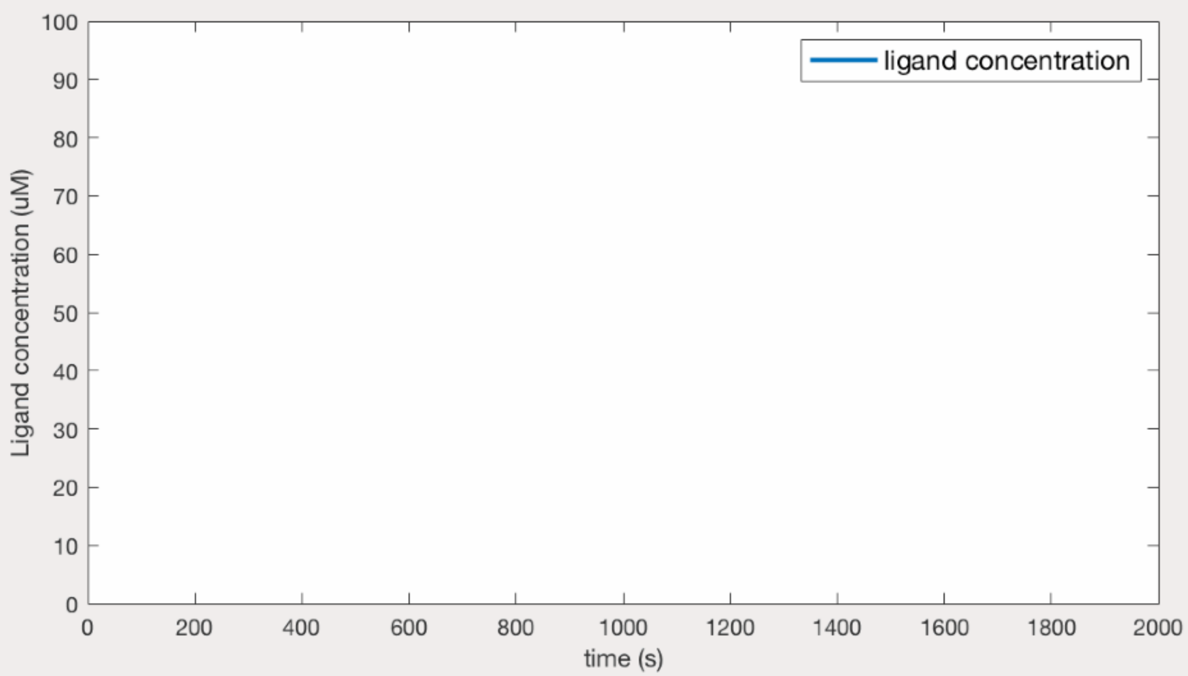
This sort of stochastic, yet purposeful, behavior is starting to feel "*lifelike*." Students are impressed to see it emerging from such simple ingredients.

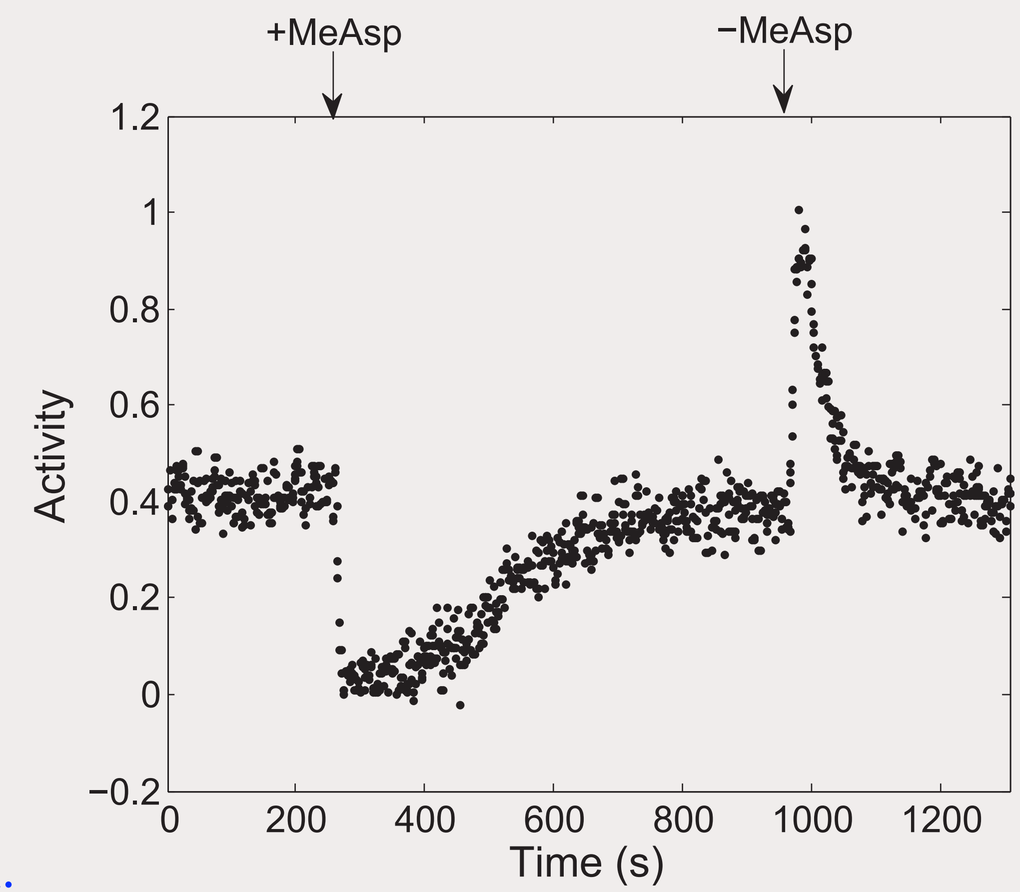
Tina Subic, Edita Bulovaite, and PN, unpublished.

Adaptation to a jump of attractant level









Simulation: Tina Subic, Edita Bulovaite, and PN, unpublished.
Experiment: J Yuan and HC Berg, Biophys. J 2012.

Phil Nelson

Plan

- Some physical reality
- Some institutional reality
- Some examples:
  E&M
  Quantum
  "Modern" Physics
  Analytical "Mechanics"
- Wrap

On being wrong

> "A student can get a degree without ever having the *unambiguous* experience of being wrong. Such an education dovetails with the pedagogical effects of the material culture inhabited by the well-to-do, which insulates them from failed confrontations with reality." – *Michael Crawford*

I guess he wasn't talking about Physics classes. We have the opposite problem: Students feel it's oppressive and stifling to be constantly told you're wrong. Try saying:

"Only in a field where you can be, and often are, objectively wrong can you sometimes be objectively *right*.

"And when you're objectively right it doesn't matter what the big-shot authorities say. *They, too, are often wrong*. Even a young person like you can overturn accepted results, and often the world notices *immediately*.

"If you were wrong this time, you can learn how to be right next time."

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

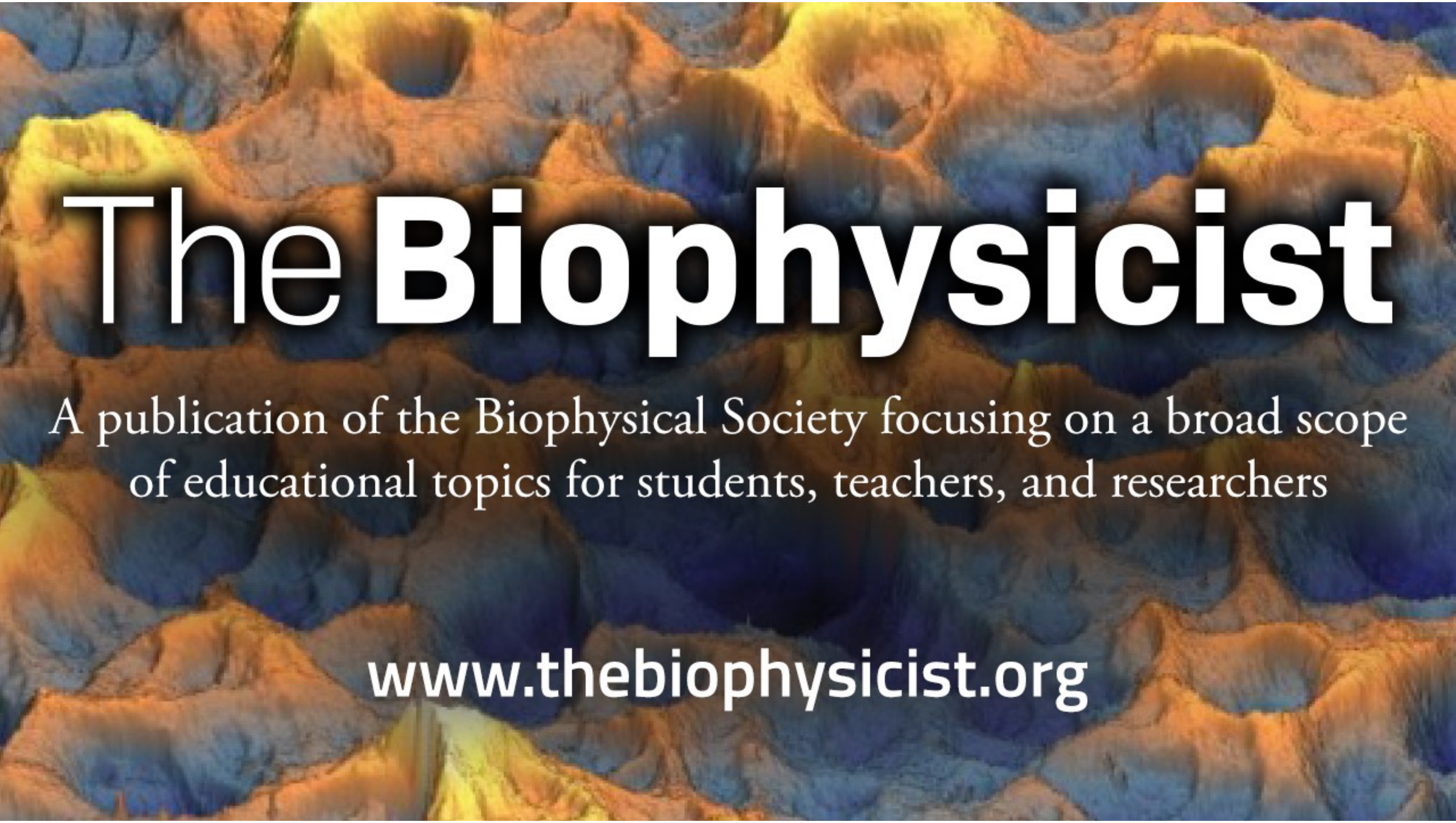
To tell them "The Facts"?
Um – facts are now free in infinite quantity.
To tell them the latest, most trustworthy facts?
Um – none of us can be as up to date as Wikipedia.

But – Possibly your students have not yet encountered Physics as a *clash* between our preconceptions and *phenomena* that stubbornly refuse to *fit*. Probably they heard about this happening in 1905 but don't realize it still happens *every day.* Probably they haven't seen it playing out in the context of things they *care about a lot.*

All the modern pedagogy innovations will not make our courses compelling if we don't select compelling content.

Your class, whatever it is, may be their last chance to see that and get excited before they wander away into finance etc.

Hey - no pressure.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A publication of the Biophysical Society focusing on a broad scope
of educational topics for students, teachers, and researchers
www.thebiophysicist.org

Reading

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

Houston, We Have a Narrative, by Randy Olson.

Physics of life, National Academies Press 2022.

Lisa Lapidus. The Biophysicist 2021; 2(1).

Thanks

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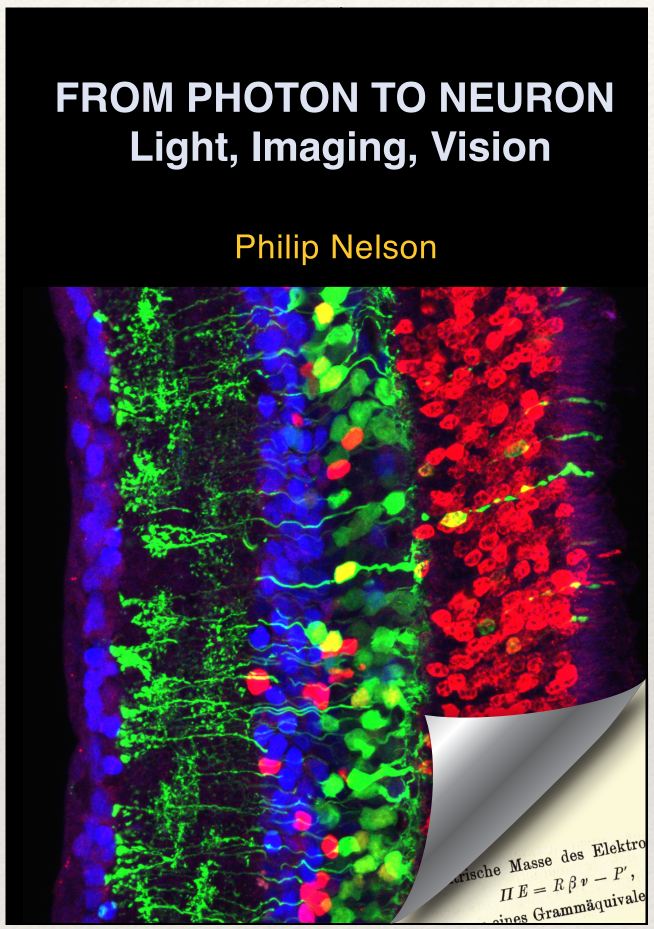

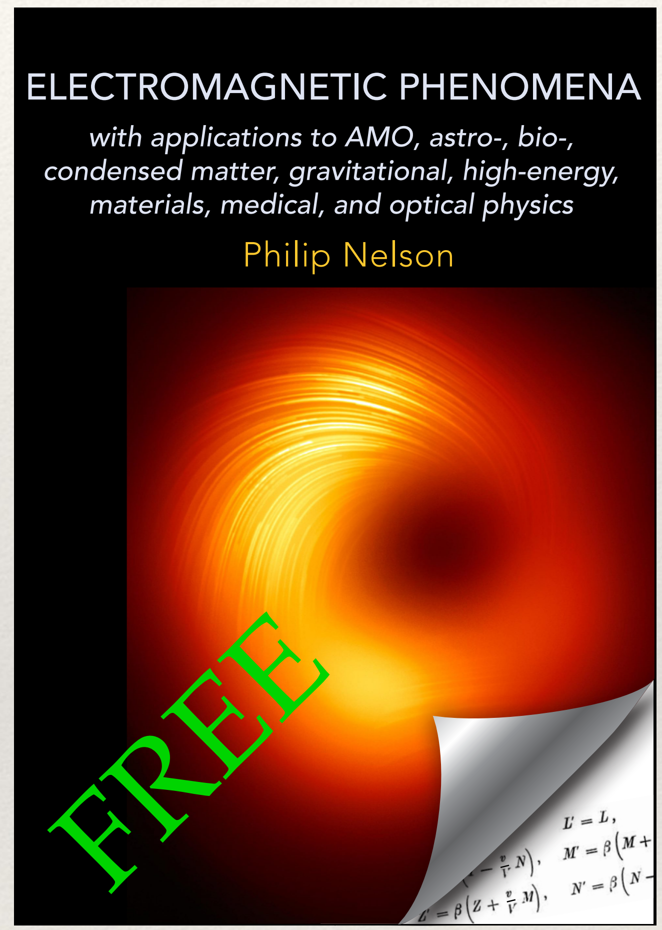

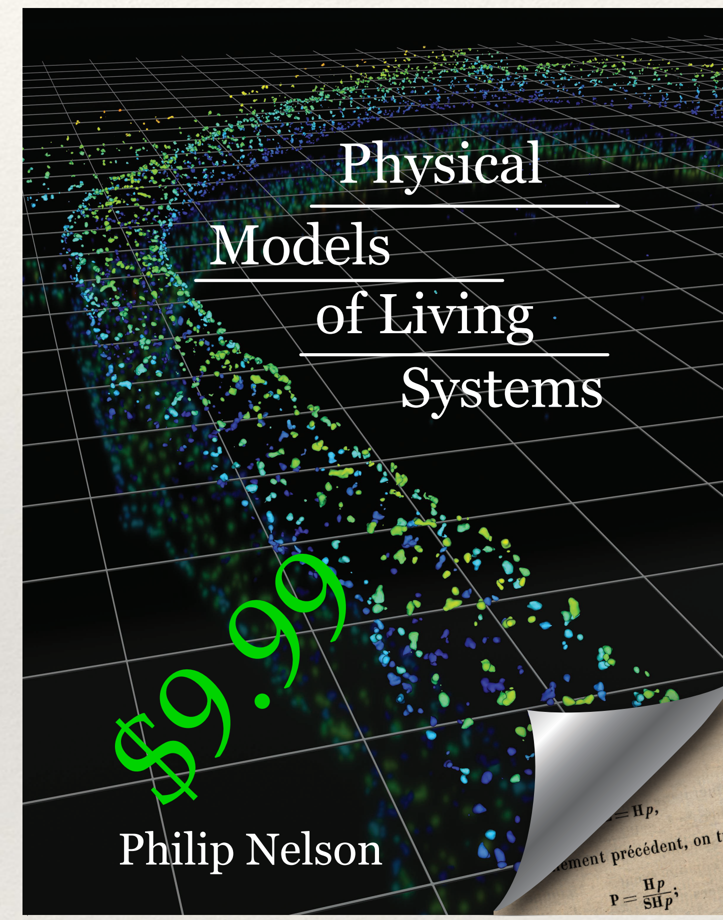

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