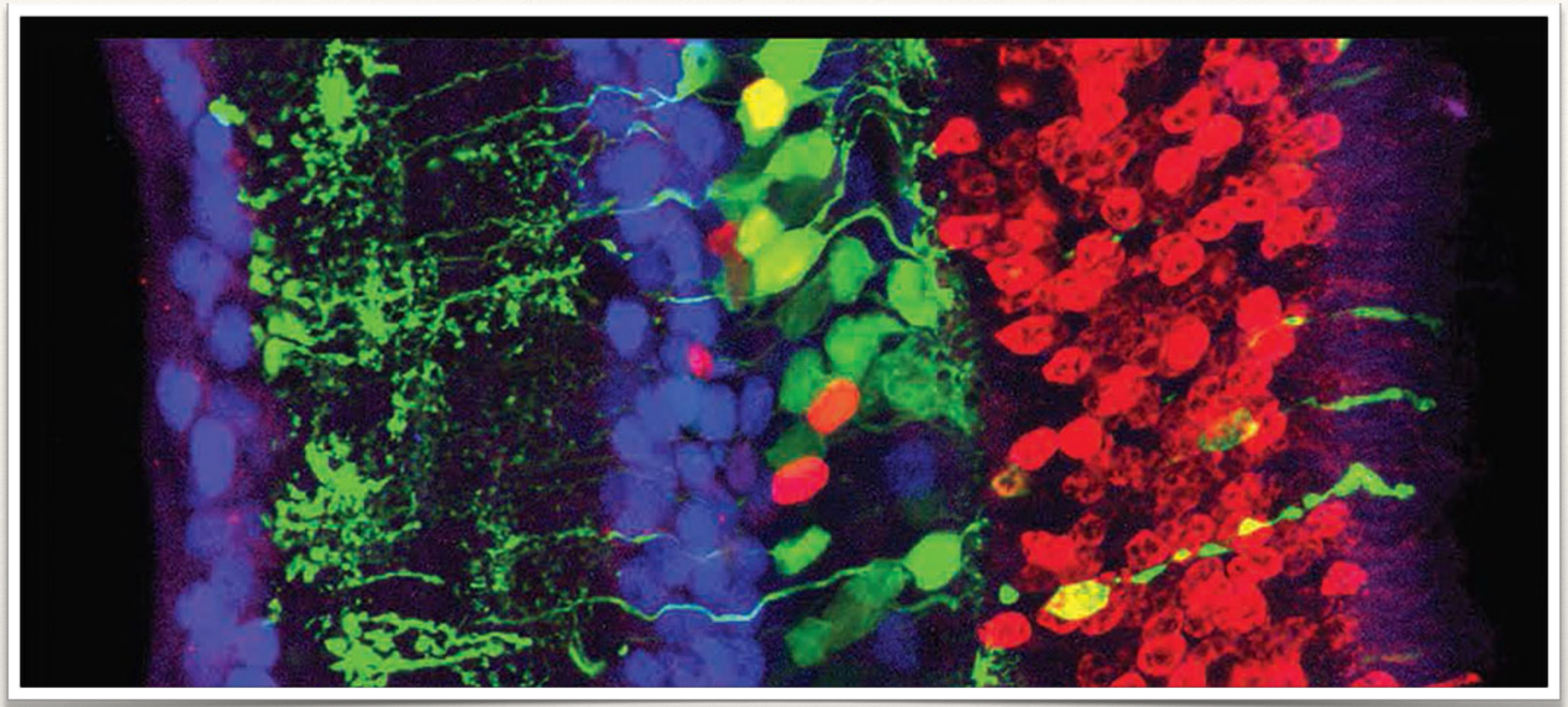
These slides will appear at
www.physics.upenn.edu/~pcn

Image of mouse retina courtesy Sui Wang and Constance Cepko



From Probability, Dynamics, and Modeling To Biology, Physics, and Instrumentation

Constructing an Upper-Division Course That Majors and Nonmajors Actually Take

Phil Nelson, Univ. Pennsylvania

Plan

1. Indoctrination *What do I cover?*
2. What we bring
3. The beautiful gift of being wrong
4. What is physical modeling?

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 – skills and habits still matter a lot. There is a big gap between raw information, or even the form 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 human needs.

So: A class should help students get that – in some specific context. If we tell students on Day One that this is the goal, they'll know whether they want it and why you're making them do certain things.

Biological physics is an interesting context for this kind of growth, regardless whether a student goes on in that field.

Challenge/opportunity: Majors

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 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: Nonmajors

- 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.
- Our introductory courses are also firmly rooted in ***deterministic models of continuous variables***. That doesn't feel very lifelike–everything in a cell is ***discrete and stochastic.***
- On the other hand, 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 spurious barriers 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 *quantitative modeling:* computation, simulation, and data visualization. It was once a huge hassle to overcome the barriers to having students do these things for themselves. Not any more.

The problem of free will

1: There's no Canon (no "Halliday and Resnick").

There's no GRE to teach to. No straitjacket of history.

Thus you have *free rein* to make it interesting, up to date, and useful. (No need to cover Atwood's machine et al.)

You can even make it different every time. That much free will terrifies me!

"***OMG!*** So what *do* I cover?"

That's the subject of this talk. But first:

2: In an elective course, there's also the problem that the *students* also have free will.

"***OMG!*** What if nobody enrolls?"

Ans: At my institution, lots of Engineering students enroll. Enrollment has never been a problem. BE is our fastest-growing major. Reach out to them, because they know they want this.

Top down, not bottom up

People who write murder mysteries know something important.

Consider starting with some juicy scientific revolution in progress right now, and the quantitative experiments that underpin it. Announce it on Day One. Point out that this revolution was wrought by a team that included at least one or two card-carrying physicists. Then ask, "*What classic (old) ideas will we need to arrive at that destination?*"

- Single-molecule manipulation and interrogation **[physics]**:
  - Concept of free energy can be applied to single molecules via **probability** ideas.
- Synthetic **biology**:
  - Phase portrait and other basic **dynamical** systems concepts are important.
- Superresolution and other 21st century microscopies **[instrumentation]**:
  - The wavelike and particle-like **models** of light are both crucial in the same instrument (iPALM).
- Optogenetics
- Cryo-EM... Cryo-electron tomography...
- Cancer immunotherapy...
- Machine learning for medical imaging...
- Earth System science:
  - This, too, is a kind of physiology, replete with feedback mechanisms.

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

The particulate character of light was an earthquake, way back in the 20th century.

It's still weird, upsetting, misunderstood when students first encounter it today.

But physicists love stories that are weird and upsetting but *true*.

It's also *indispensable for understanding the ongoing revolution in imaging*.

Plan

1. Indoctrination
2. What we bring *What subtexts behind the overt content?*
3. The beautiful gift of being wrong
4. What is physical modeling?

What math is really for

"Remember that in physics it has taken great scientists to discover simple things. They are very great names indeed which we couple with the explanation of the path of a stone, the droop of a chain, the tints of a bubble, the shadows in a cup." – *D'Arcy Thompson*

"Why must we have all this math?"

The job of math is to strip away the contingent so that we can see the hidden connections between phenomena. Sometimes we find that the problem we want to solve is *already solved* elsewhere.

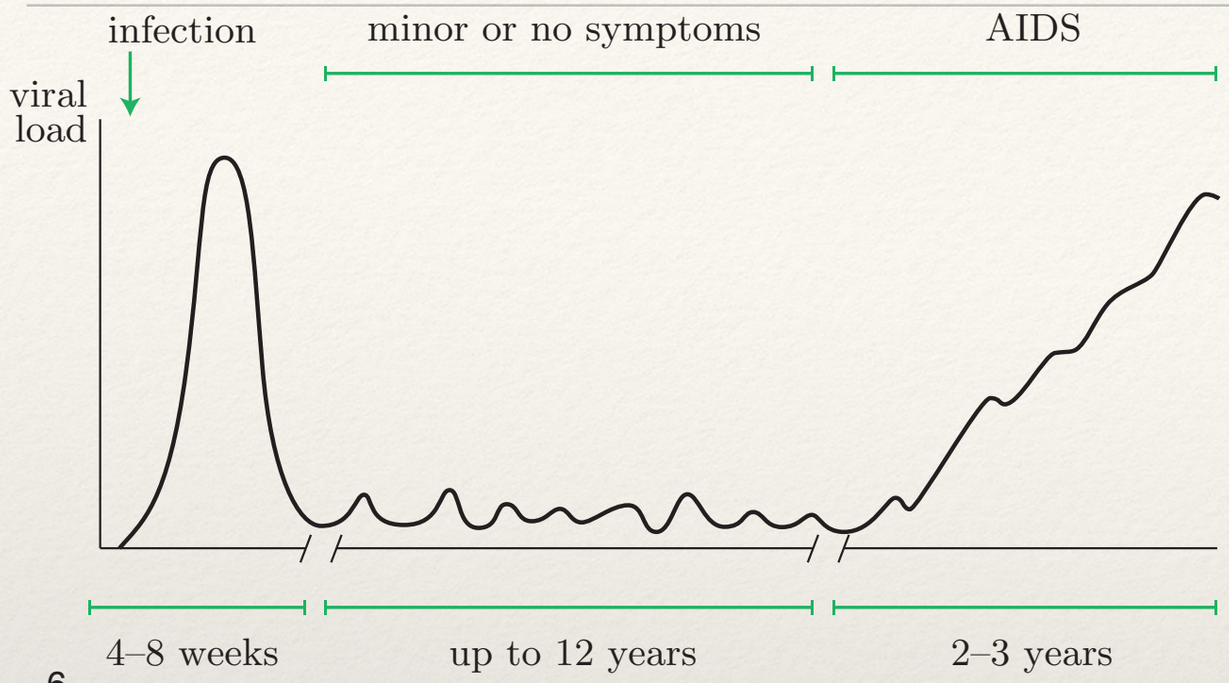
But we don't want to inhabit a *wholly* abstract world–that's why we're not (pure) mathematicians. Our interest is the phenomena, finding more effective ways to understand them eventually with the goal of accomplishing something in the world.

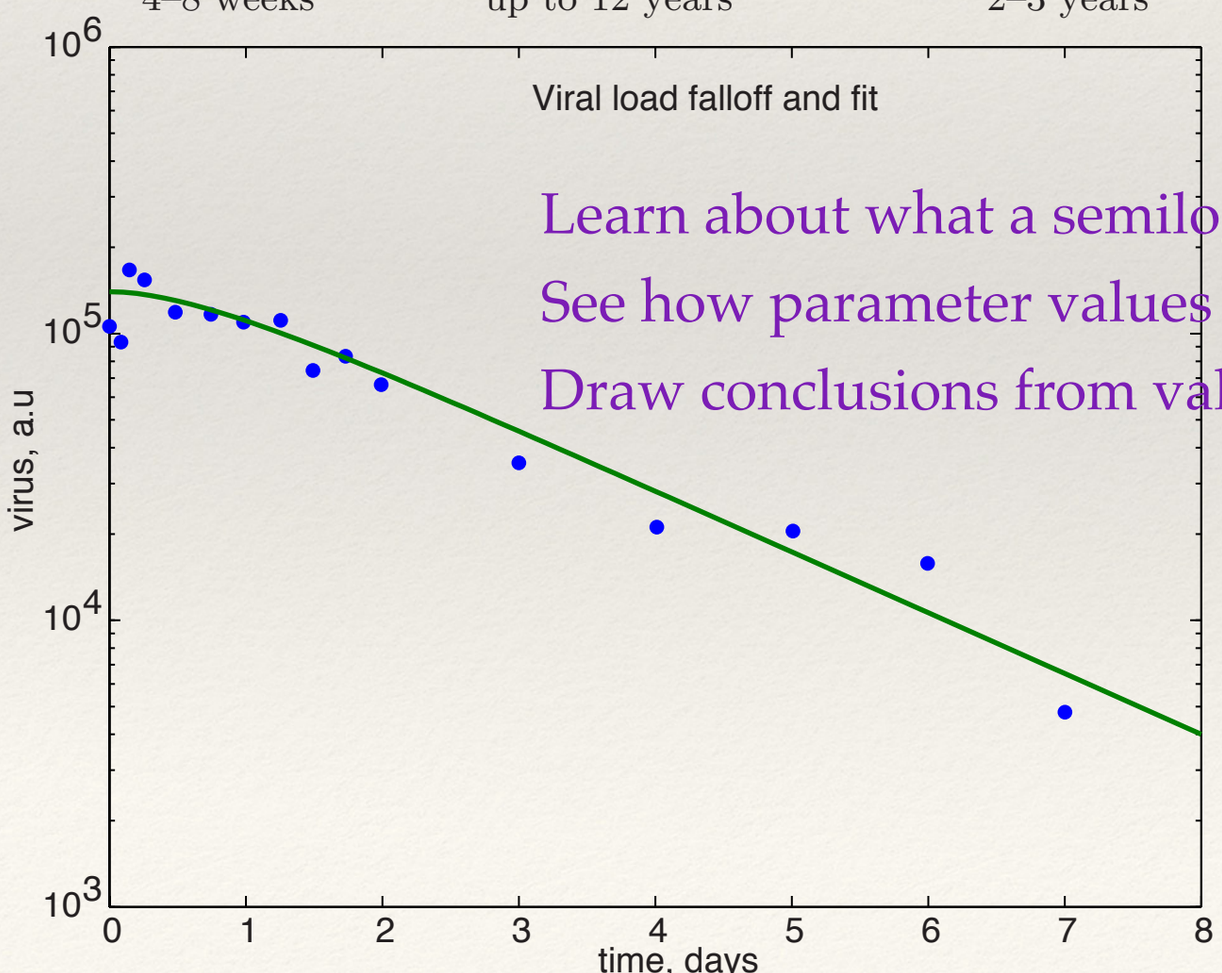
Make connections

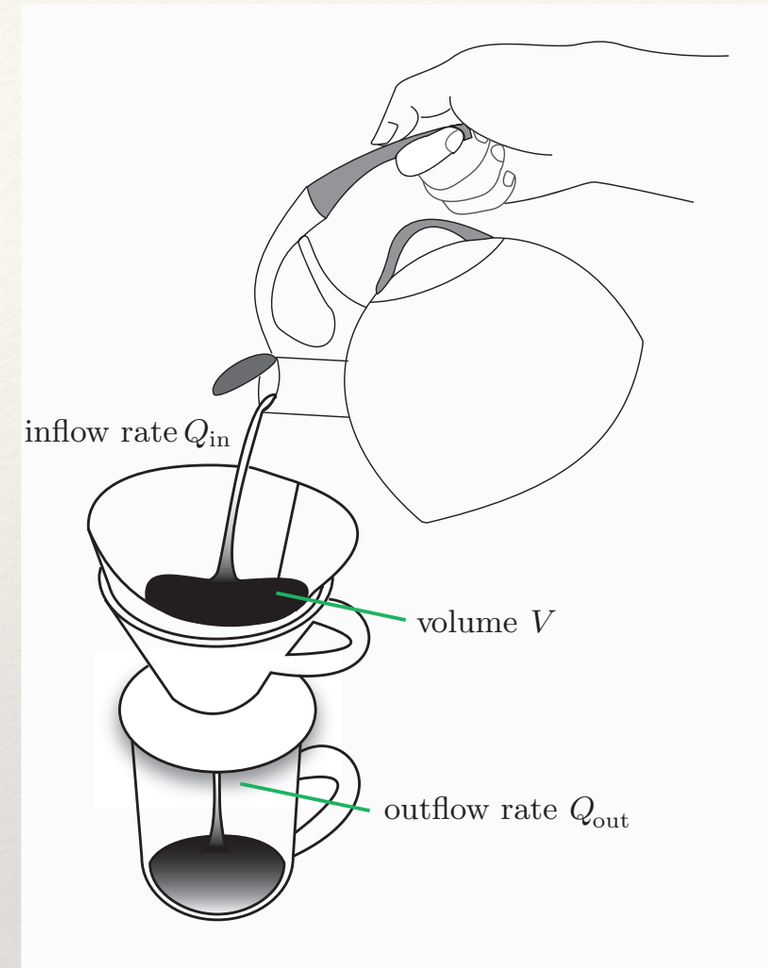
Again: "The same equations will have the same solutions."

- Electrostatic problems involve the same Laplace equation as steady diffusion, leading to an unintuitive and hugely important insight into chemoreception.
- Heat transport, nonsteady diffusion, signal transport on a cable all have essentially similar equations, so we learn about electrotonus by studying either of the other two problems.
- A fluctuating elastic rod (DNA in solution) has a partition sum that resembles the path integral for a quantum mechanical top, so the latter's solution gives us the former.
- Electrostatics in solution has the same Poisson equation as in vacuum, so we learn about electrocardiogram.
- Many more examples. *This is something we bring,* so draw attention to it.

Less is (sometimes) much more







Learn about what a semilog plot shows.

See how parameter values affect the graph.

Draw conclusions from values of fit parameters.

From PN, *Physical models of living systems*.

Phil Nelson

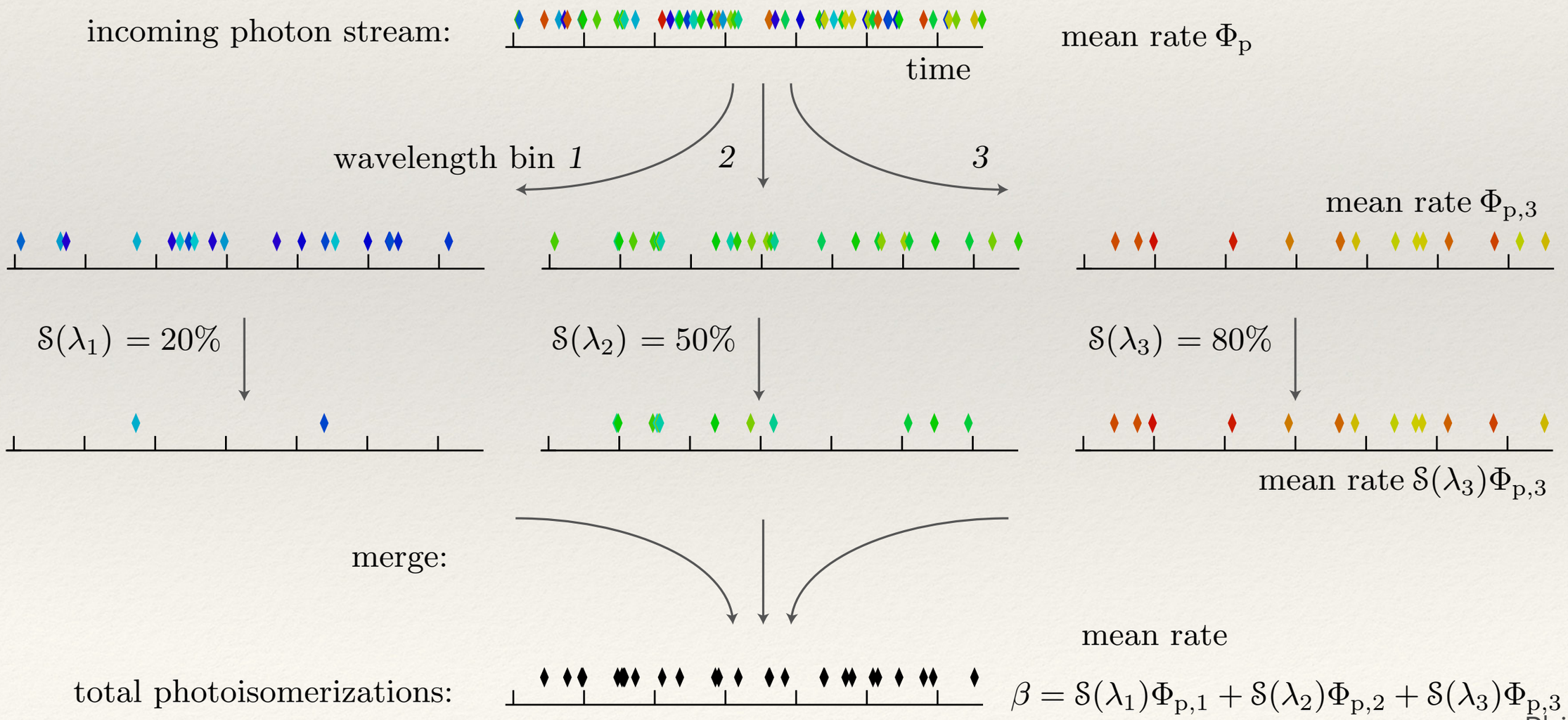
Analogies can be more than analogies

Imagine an air-hockey game. The puck is floating on a thin layer of air. It can move without friction in two directions. We apply a force $\boldsymbol{F}$ to the puck and see that it obeys Newton's law: $\boldsymbol{a}_\perp = \boldsymbol{F}_\perp/m$. Let Π denote the projection operation to the xy plane. Then:

Two forces are equivalent if $\Pi(\boldsymbol{F}) = \Pi(\boldsymbol{F}')$.

Remarkably, this mechanical notion of equivalence has all the same properties as the *color matching functions* of human subjects (Grassmann laws)! Light spectra play the role of $\boldsymbol{F}$.

Is this just some coincidence? Other fields of science don't usually supply such *precise, quantitative* analogies.



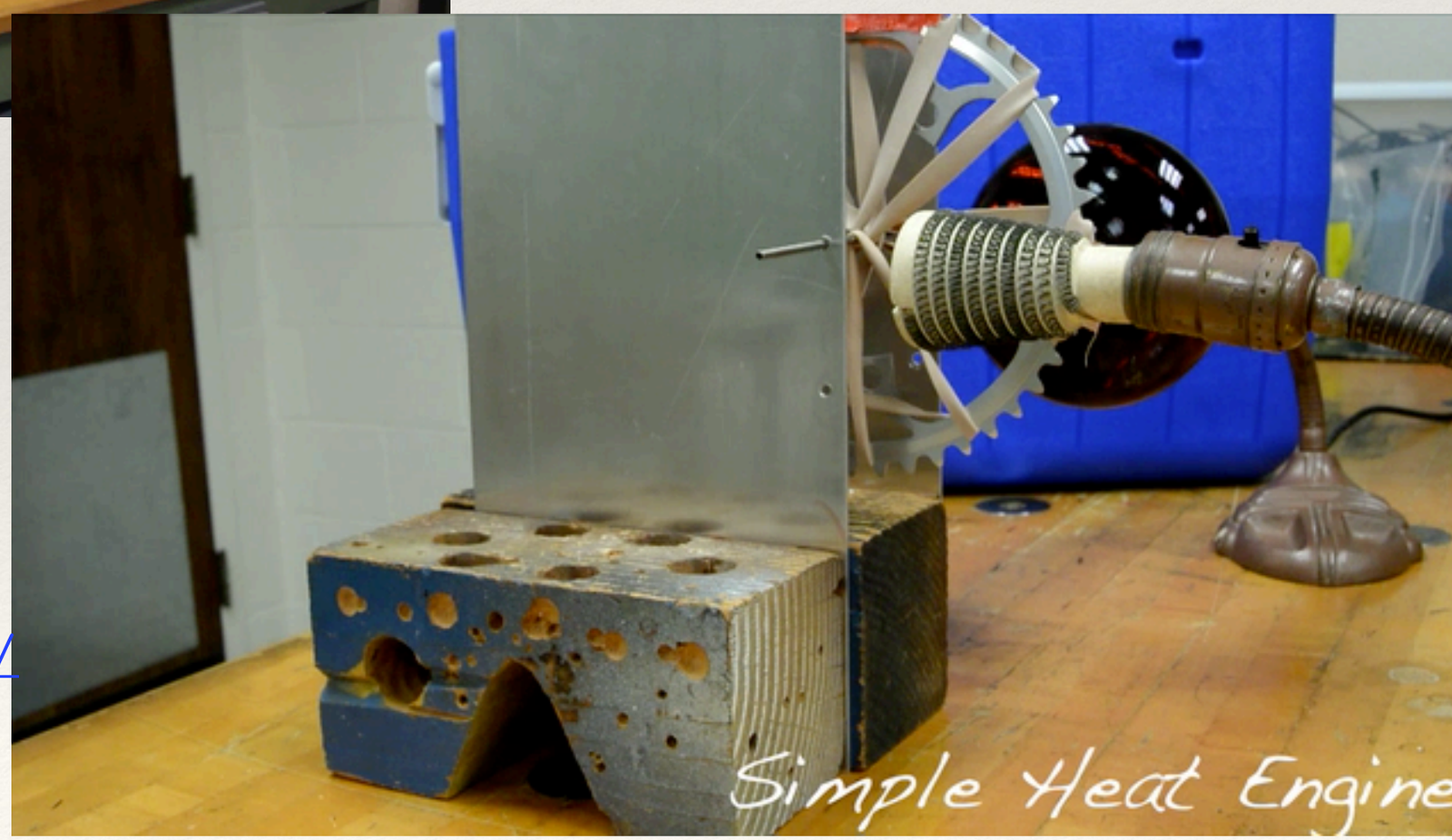
PN, *From Photon to Neuron.*

Phil Nelson

Demos: Weird+real = memorable

It's our great privilege that we can bring in a piece of apparatus, made from everyday materials, and show something crazy, yet explicable using a few big ideas.

youtu.be/EIHaqOxDzG8



PN and W Berner, *Activities & Classroom Demonstrations in Biological Physics: A Resource Document* (repository.upenn.edu/physics_papers/646/)

Skills/Frameworks: Dimensional analysis

Yes, it's good to help you make fewer mistakes on exams.

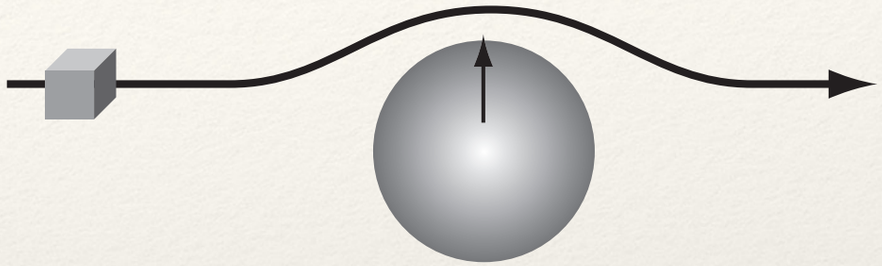
But it's much more: A *shortcut to insight:*

- If you believe there's a universal relation between viscous drag, diffusion, and thermal energy, then that relation can have *only one possible form* (Einstein relation).
- If you believe there's a universal spectrum of radiation from a hot black body, then that relation must *contain a previously unsuspected universal constant* of Nature (Planck constant).
- If you believe that electron charge and mass determine atomic structure, then there are *predictions about the scales* of atomic size and energy levels.

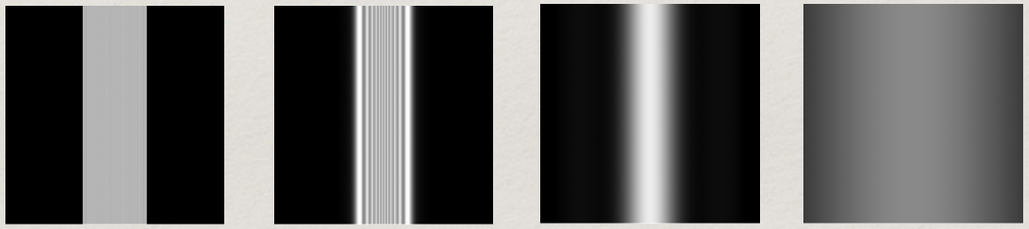
There is no heuristic with this much power in other fields of science. It's *something we bring.*

Skills/Frameworks: Dimensionless parameters

- Reynolds number demarcates inertial from noninertial regimes of fluid flow.
  - Crucial for swimming, foraging...



- A single combination of parameters demarcates diffractive from nondiffractive light propagation.
  - Crucial for microscopy.

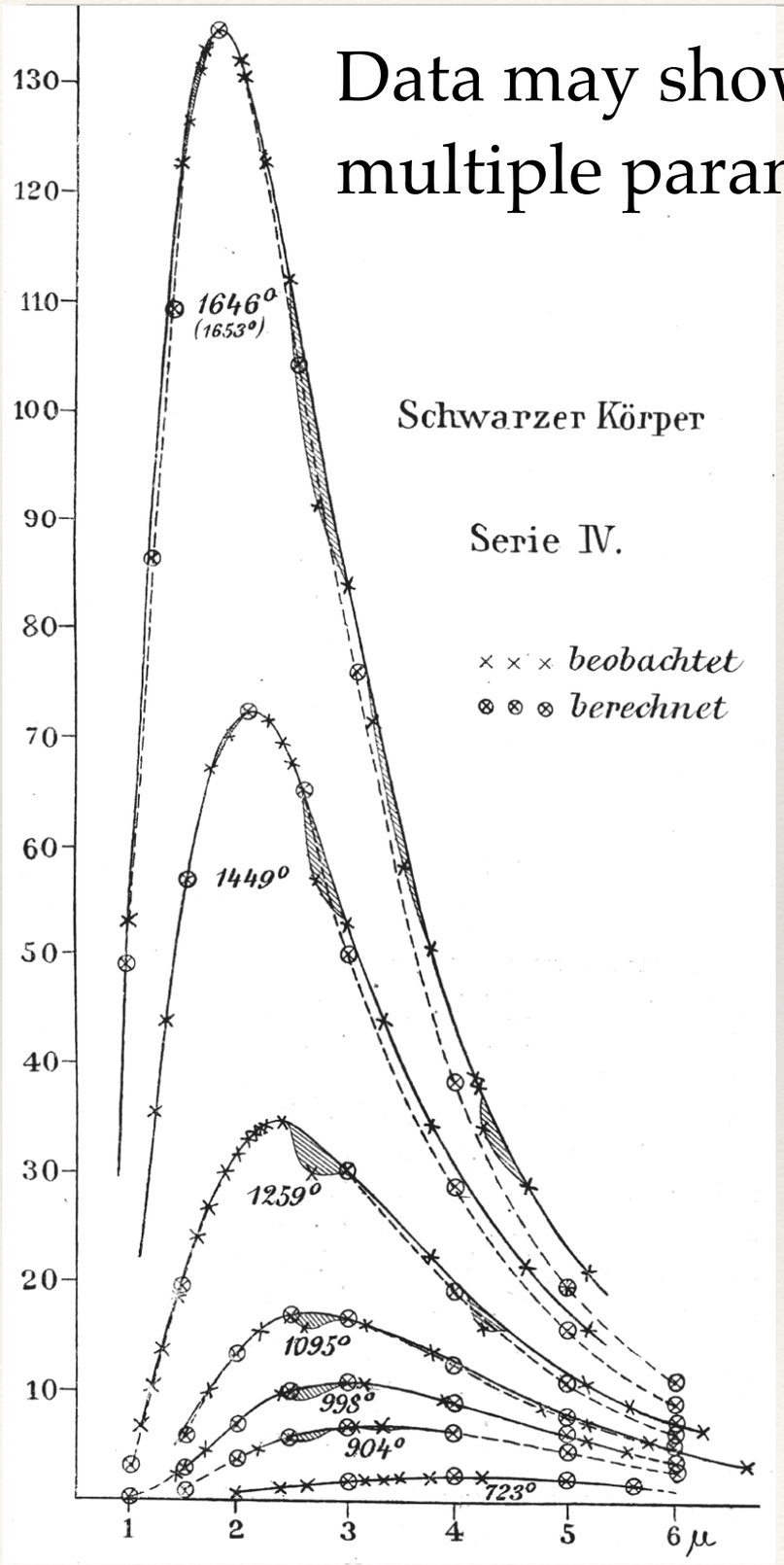


- Many more examples.

This much classification power from such simple insight–*something we bring.*

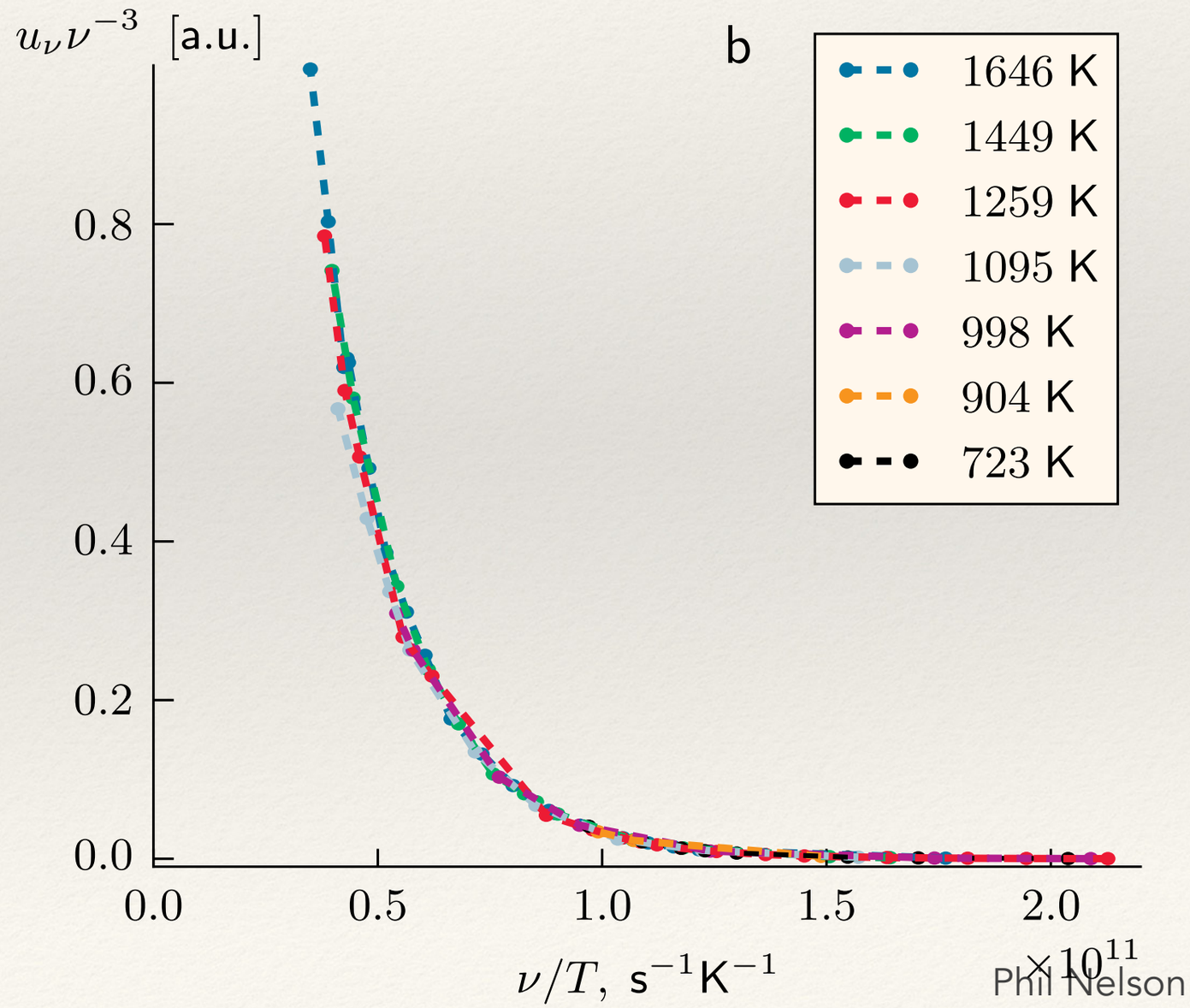
Phil Nelson

Skills/Frameworks: Data collapse



Data may show a complicated dependence on multiple parameters...

but an insightful model may show that they only enter in a few simple combinations:



PN, *From Photon to Neuron.*

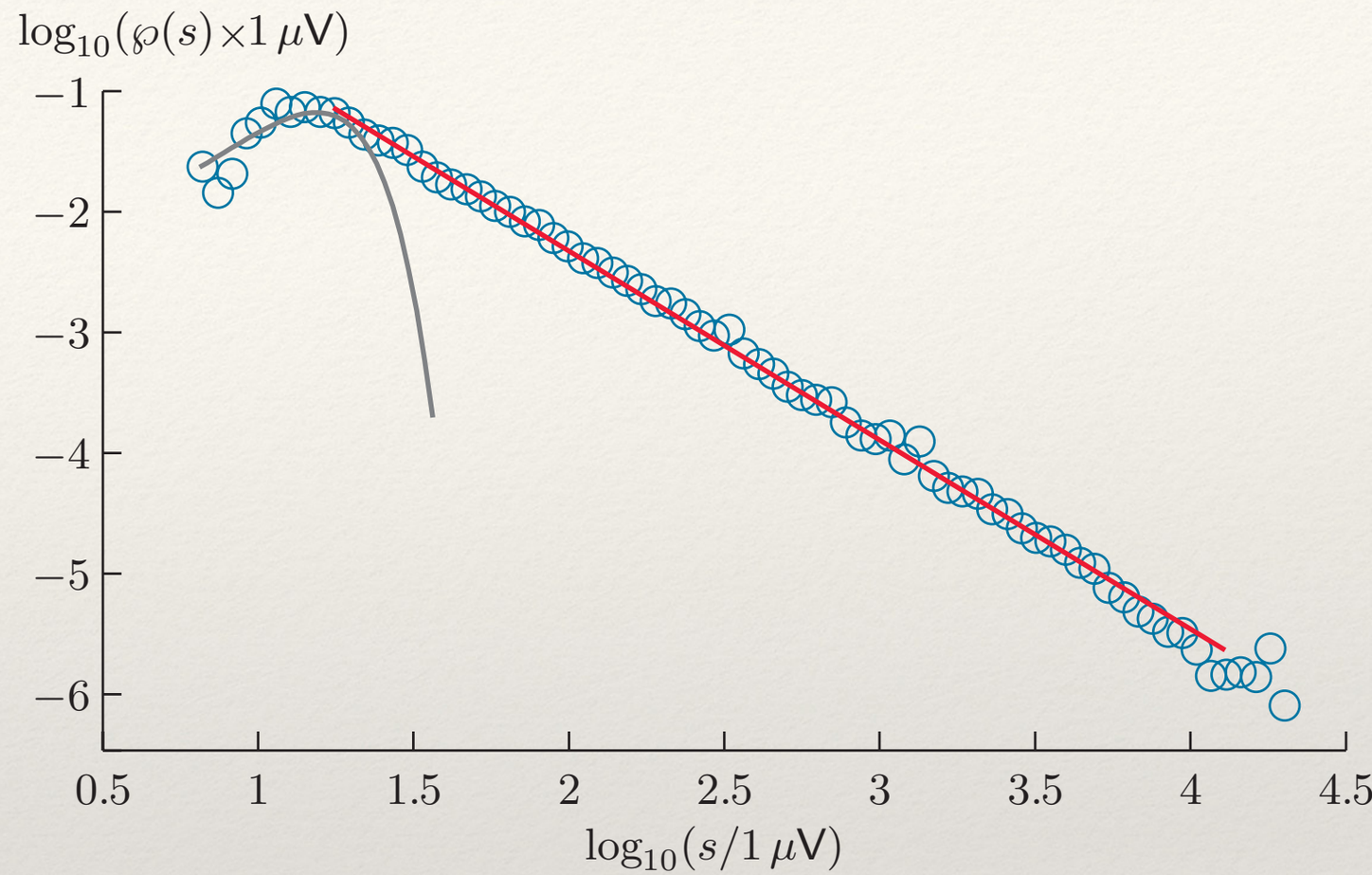
Phil Nelson

Skills/Frameworks: Randomness

Random-seeming signals often contain valuable information.

Even students who took a whole course on "biostatistics" generally think that every distribution is a Gaussian. They are surprised, intrigued, even shocked to find that many interesting quantities–covering an enormous range of phenomena–are instead all *power-law distributed.*

Where does that universality come from?



Students can make a histogram of the magnitudes of bursts of neural activity in brain slice.

From PN, *Physical Models of Living Systems*. (Data E D Gireesh and D Plenz.)

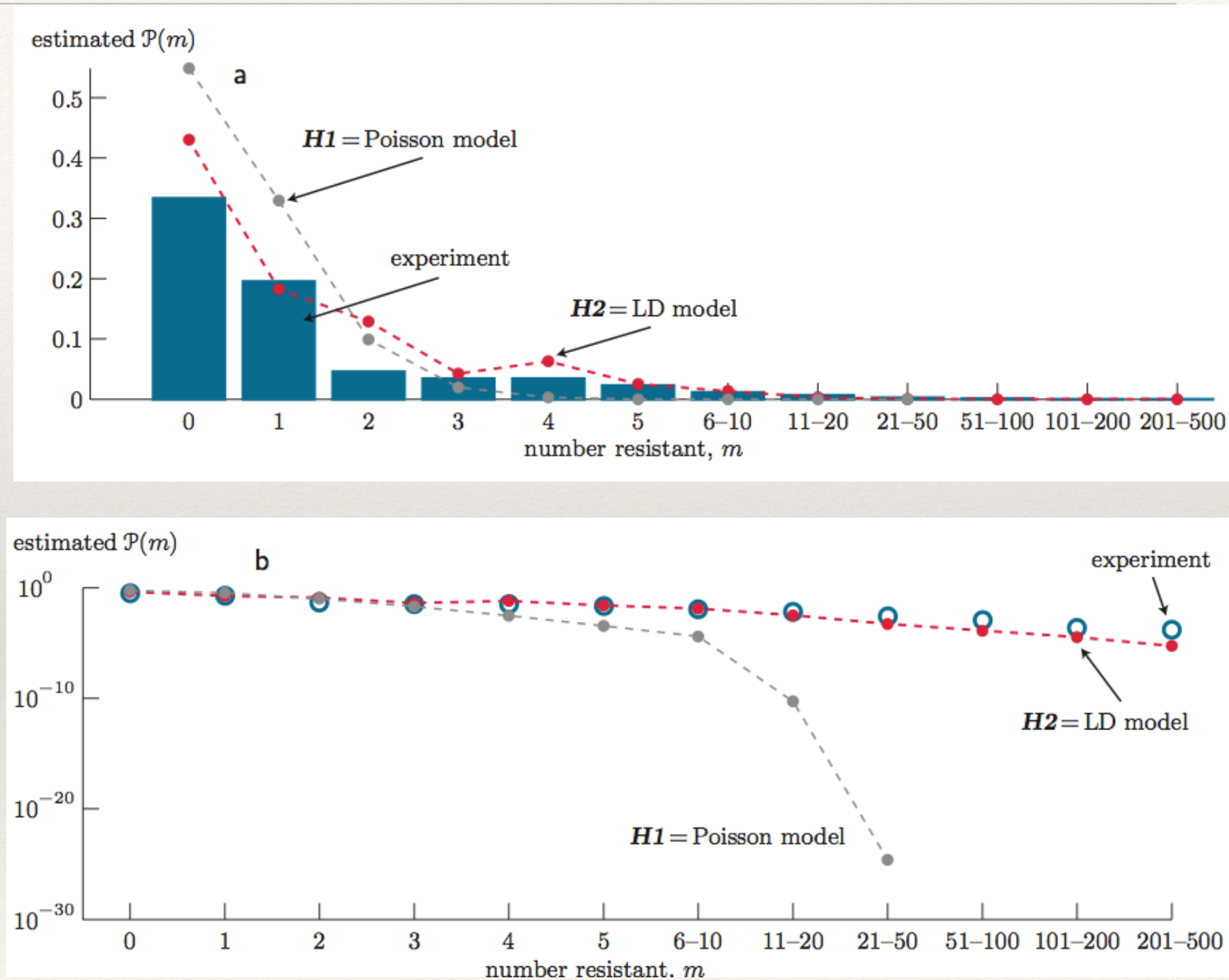
Skills/Frameworks: Visual representation of data

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

The two models look 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.
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*. Data from: Luria and Delbrück.

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Skills/Frameworks: Inference

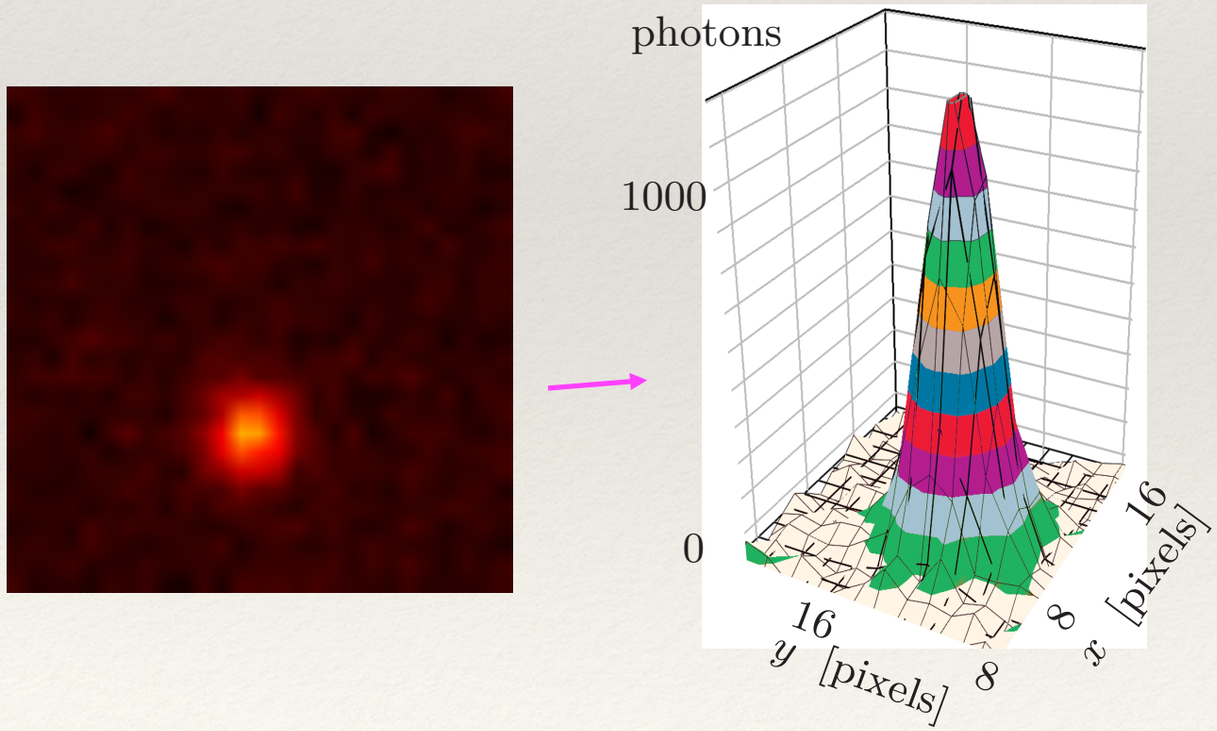
Students are keenly interested in the hot new *instruments* that keep getting invented.

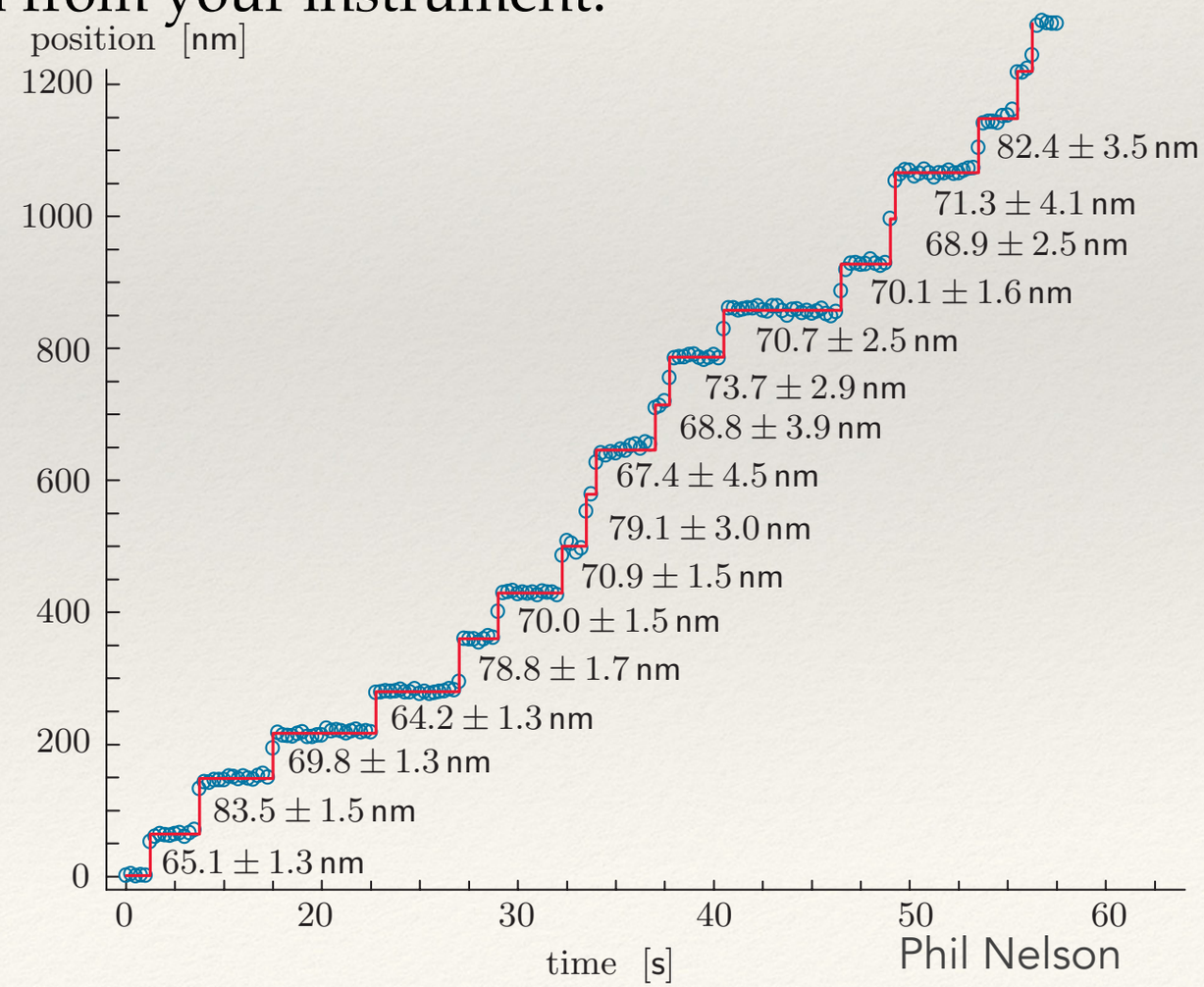
Most of them could only have been invented by people with *physical* insights.

But there is another ingredient: An instrument seeks to learn about a situation from some accessible stream of data. That is, it requires *inference*. And inference is a science.

Students are also well aware that this science is revolutionizing everything around them, so let's see it at work in the context of biophysics.

But data science alone is not enough! You need physics as the substrate, the "prior" that your inference will integrate with the raw data from your instrument.





PN, *From Photon to Neuron*. Data: A Yildiz, J N Forkey, S A McKinney, T Ha, Y E Goldman, P R Selvin. Science (2003).

Phil Nelson

Feedback control: A biological problem

Cells in a frog embryo divide in synchrony.

And

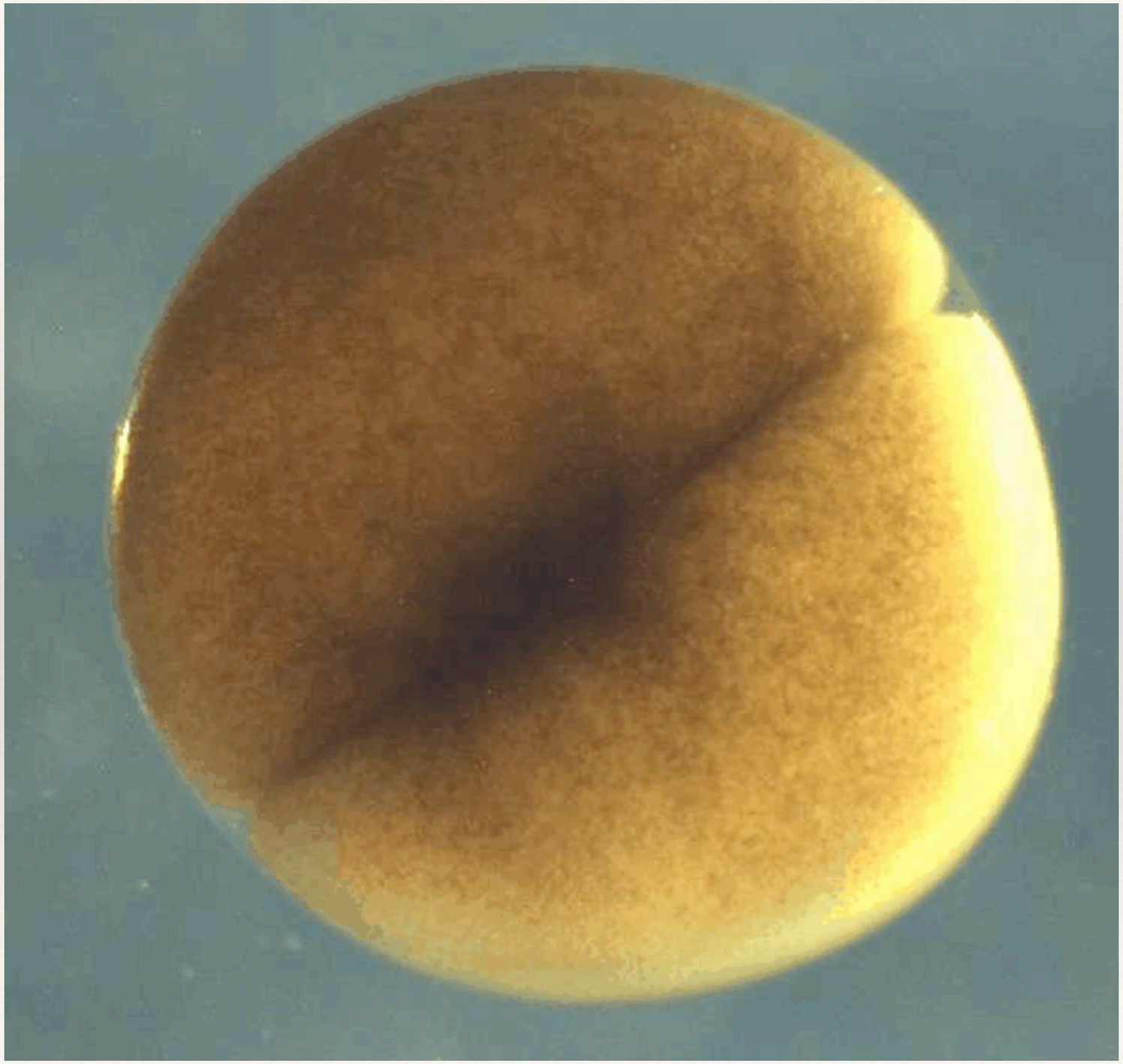
That's important for proper development

But

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

So

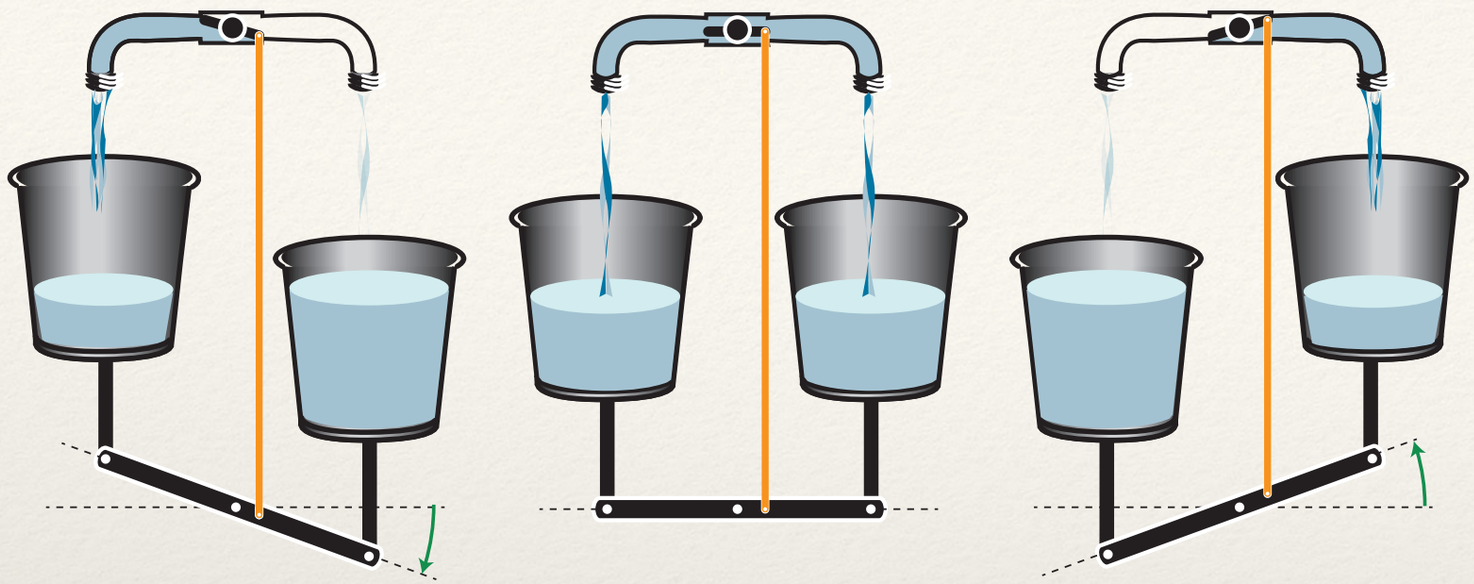
We need to understand robust oscillation in a single cell.



Video courtesy Tony Tsai.

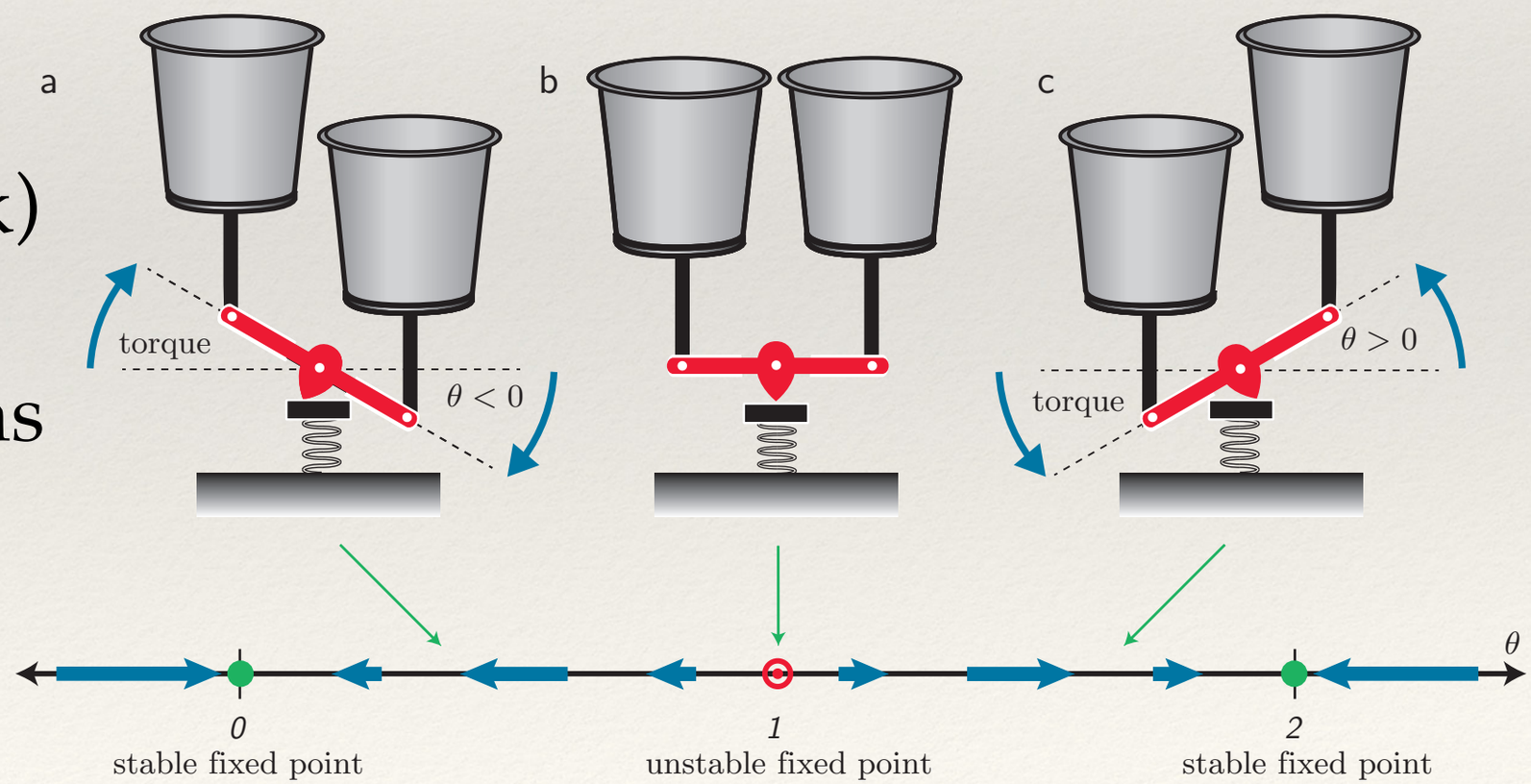
Phil Nelson

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*.

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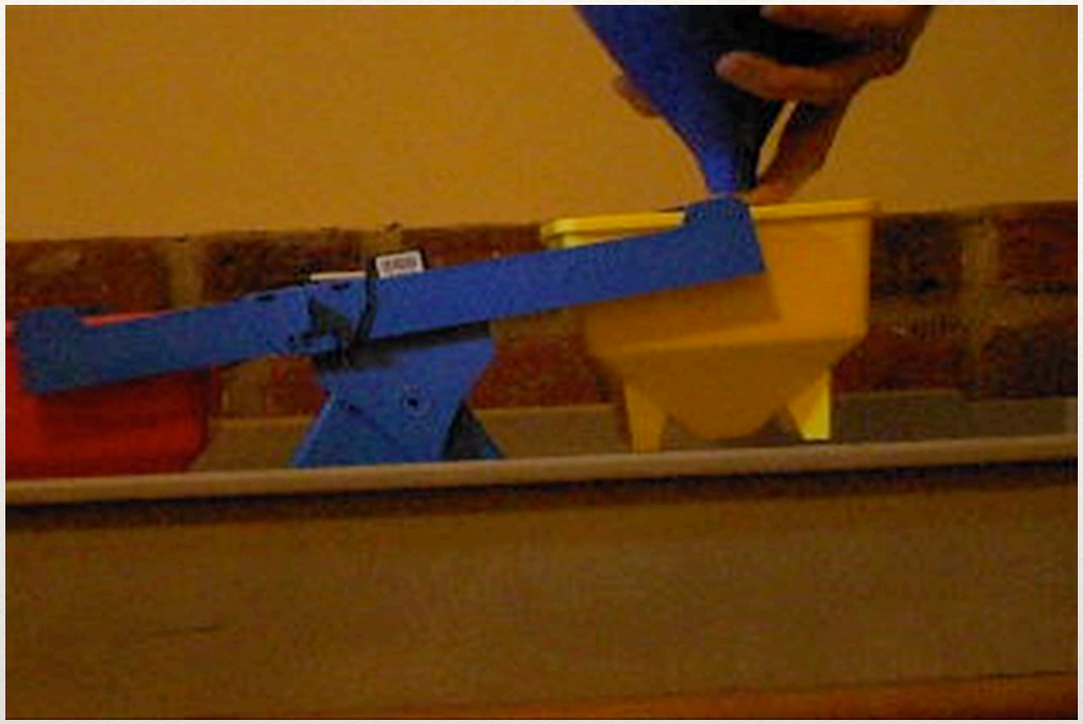
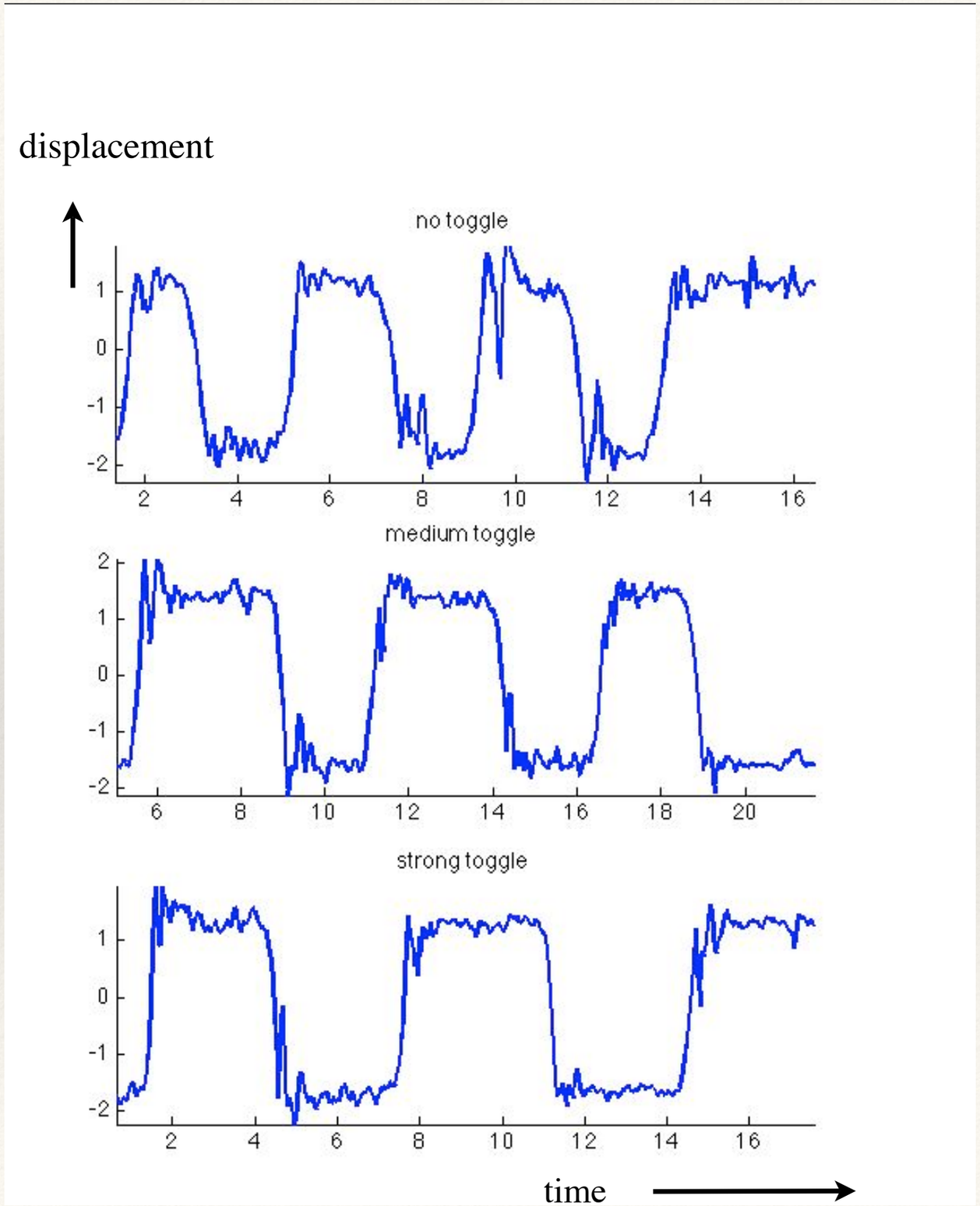
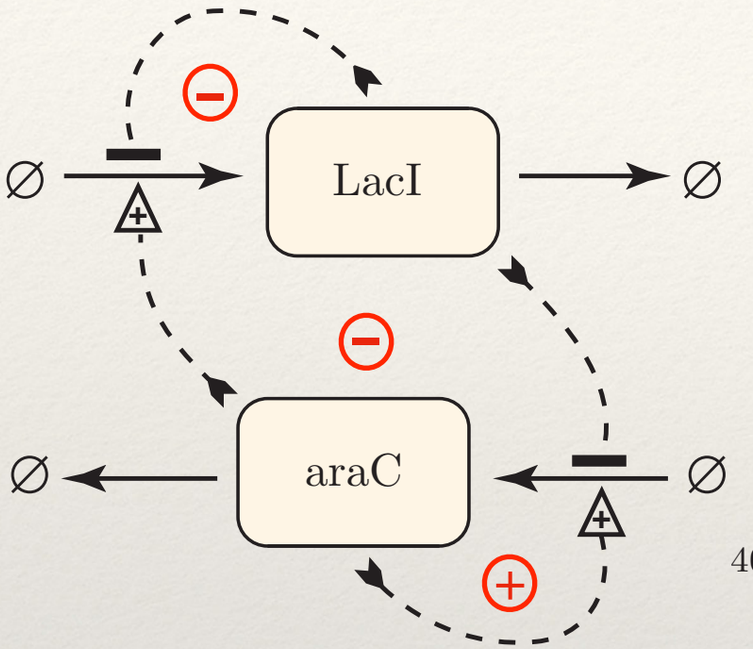
Feedback: Classroom realization

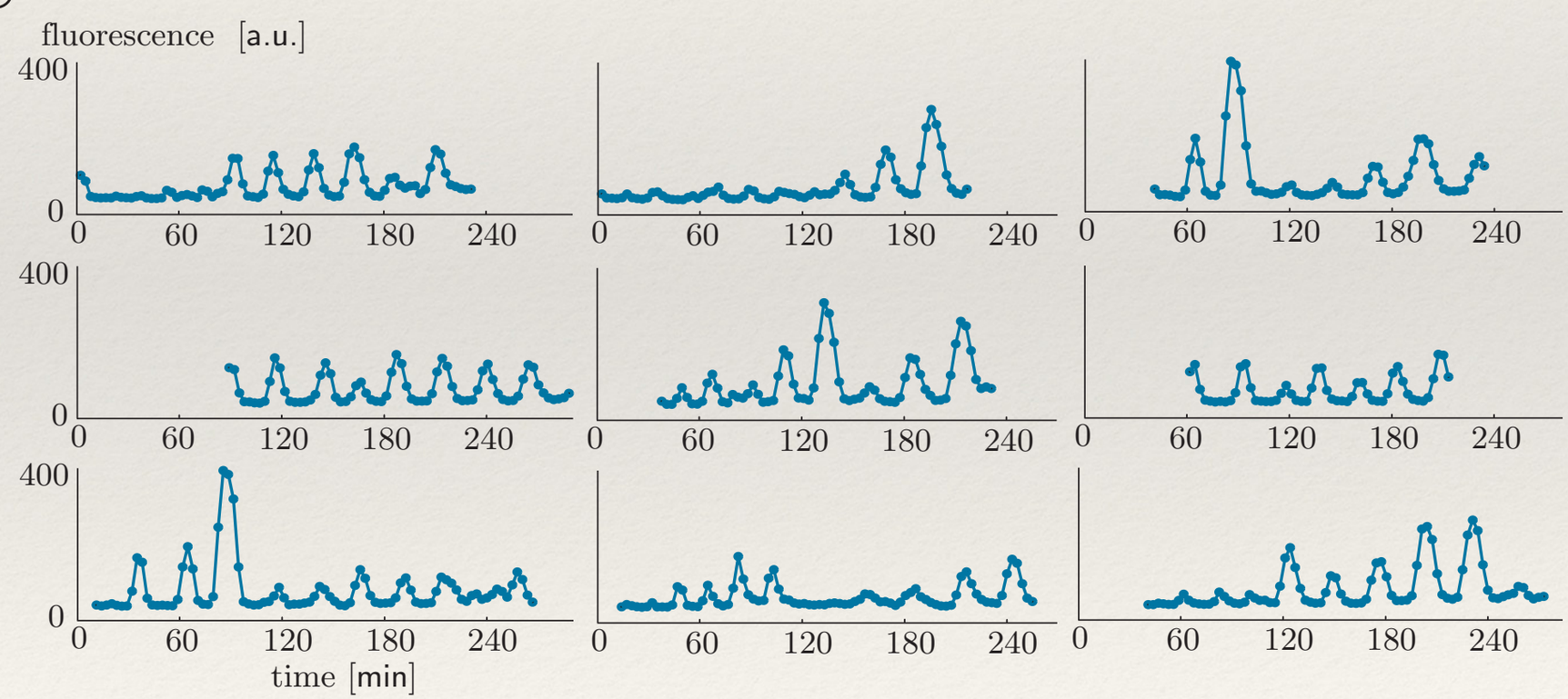


“Build it to understand it.”



Feedback: Realization in synthetic biology





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

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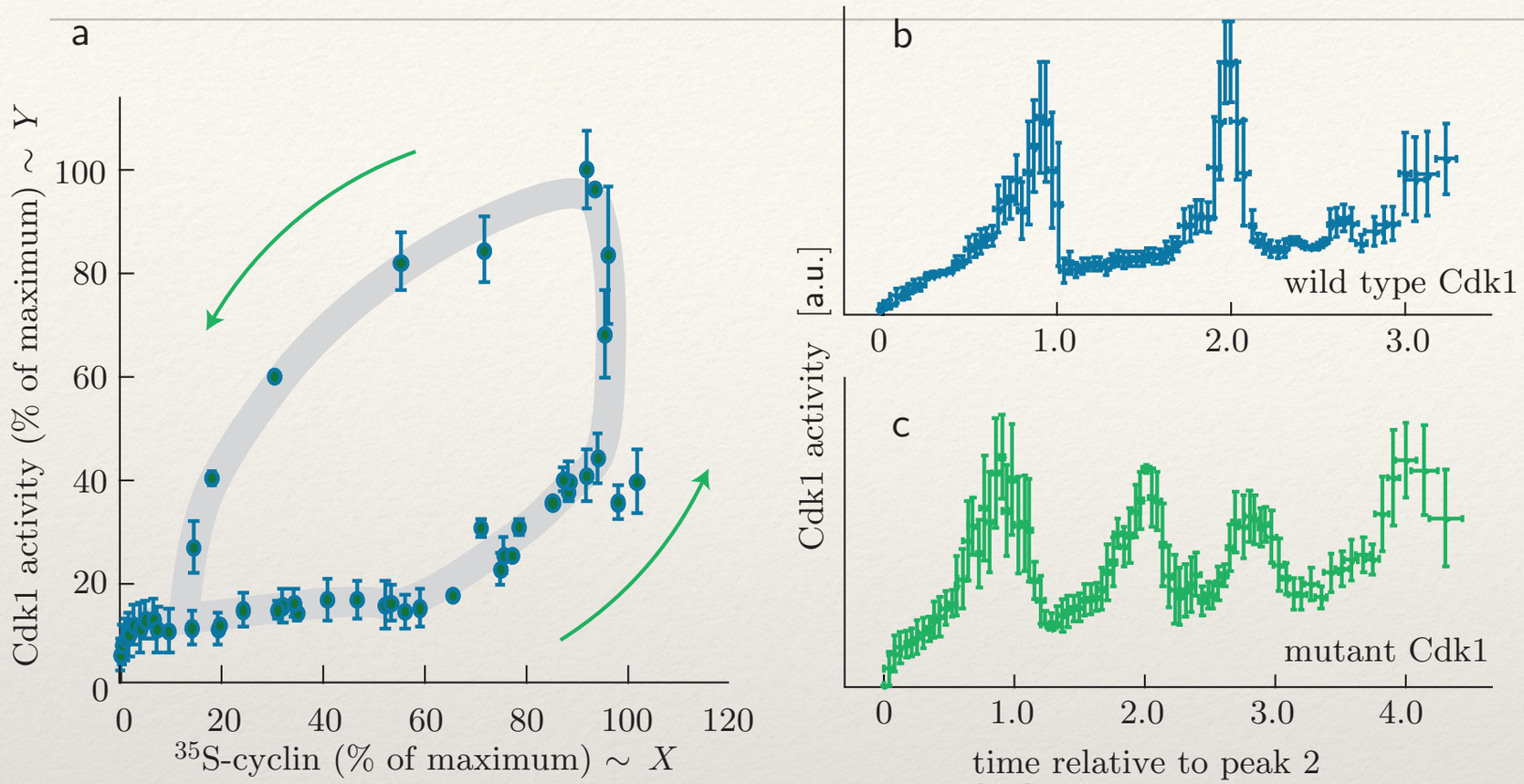
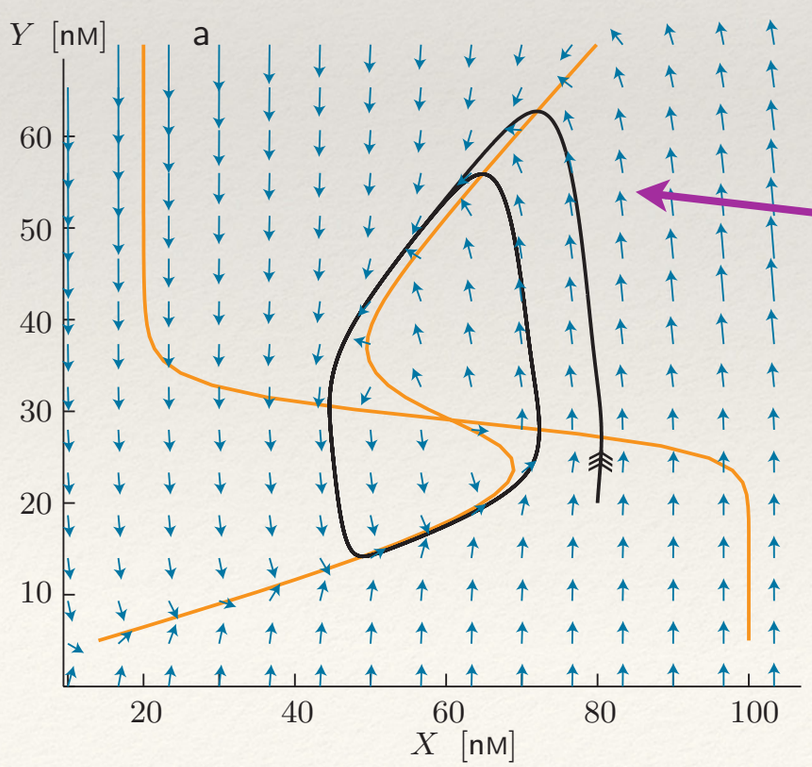
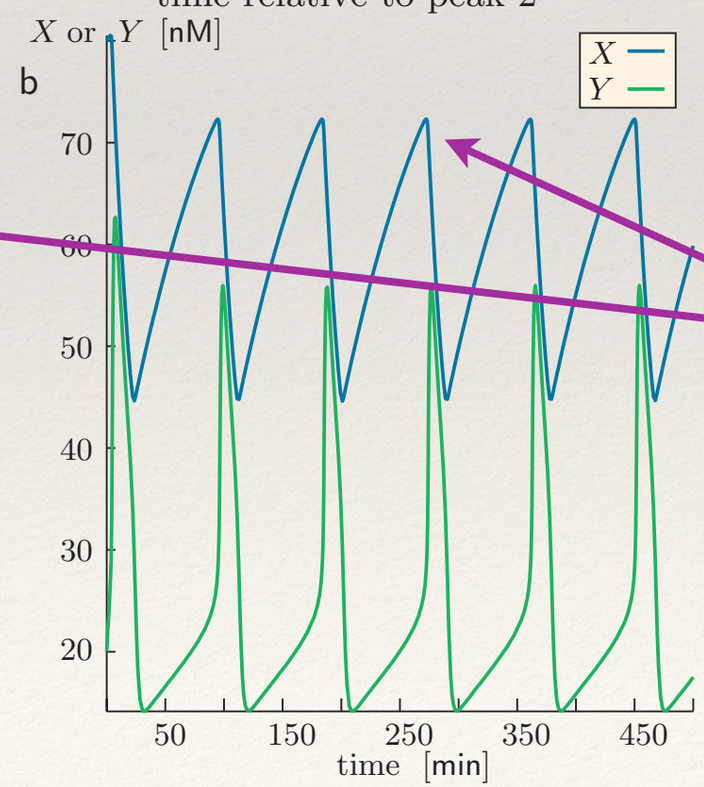
Feedback: Realization in frog embryo



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).

Phil Nelson

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3. The beautiful gift of being wrong *What could that mean?*
4. What is physical modeling?

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*.

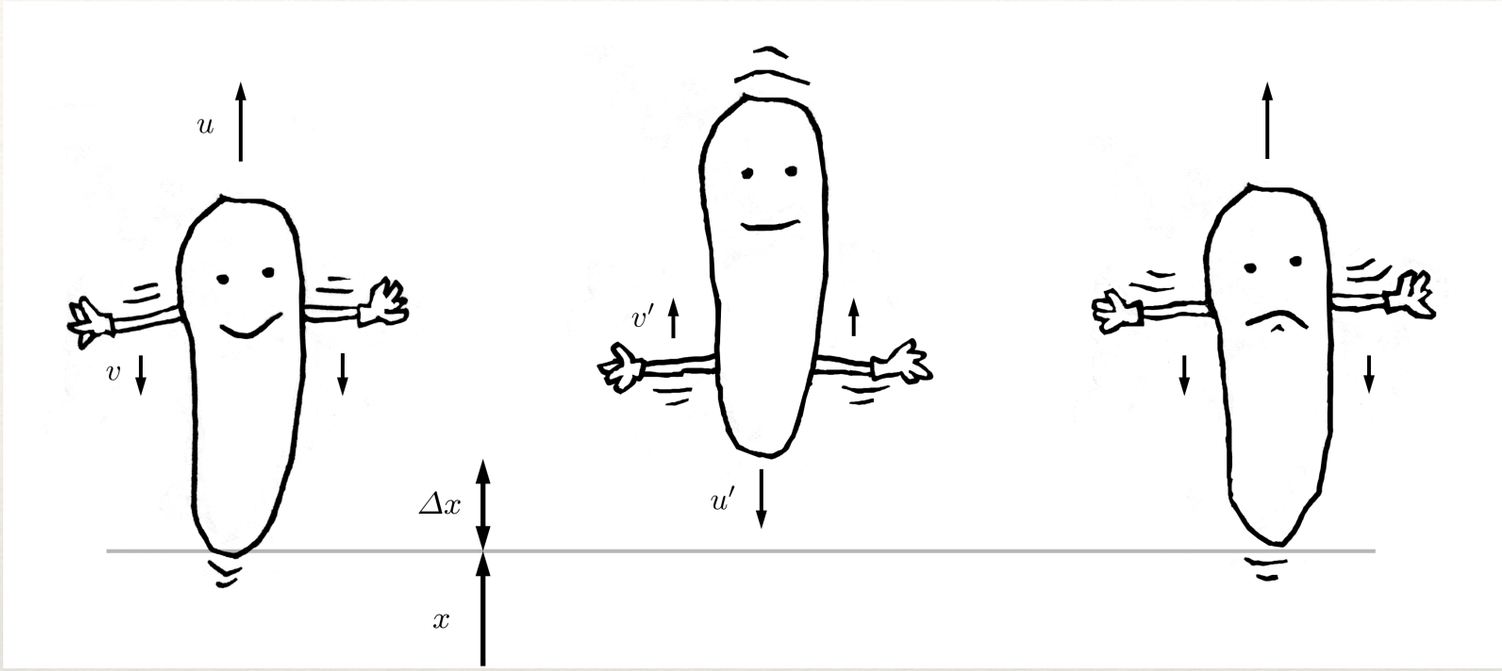
"And when you're objectively right it doesn't matter what the big-shot authorities say. *They, too, are often wrong*. Even a young person like you can overturn accepted results, and often the world notices *immediately*.

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

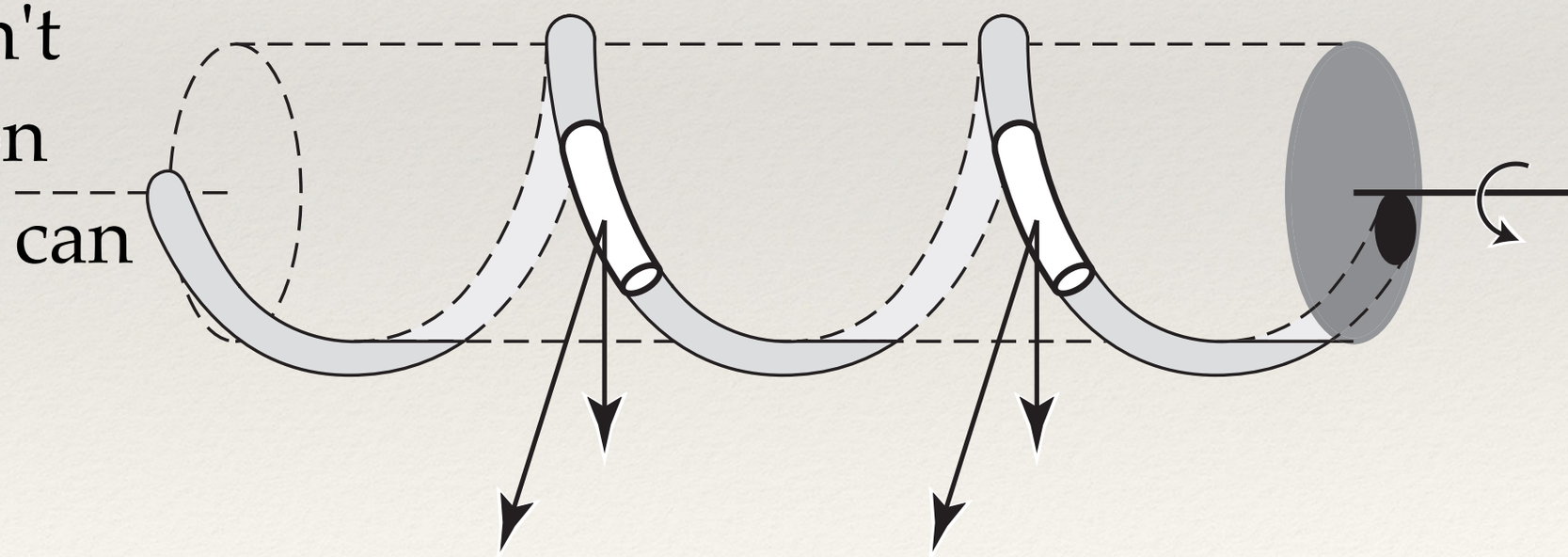
Phil Nelson

On being wrong: your beautiful idea may be impossible a priori due to a symmetry

Some ideas don't even need to be tested experimentally, which lets us focus our precious experimental effort on *promising* ideas.



Seeing that an idea can't work also focuses us on *why not*, which in turn can guide our search for a *better* idea.



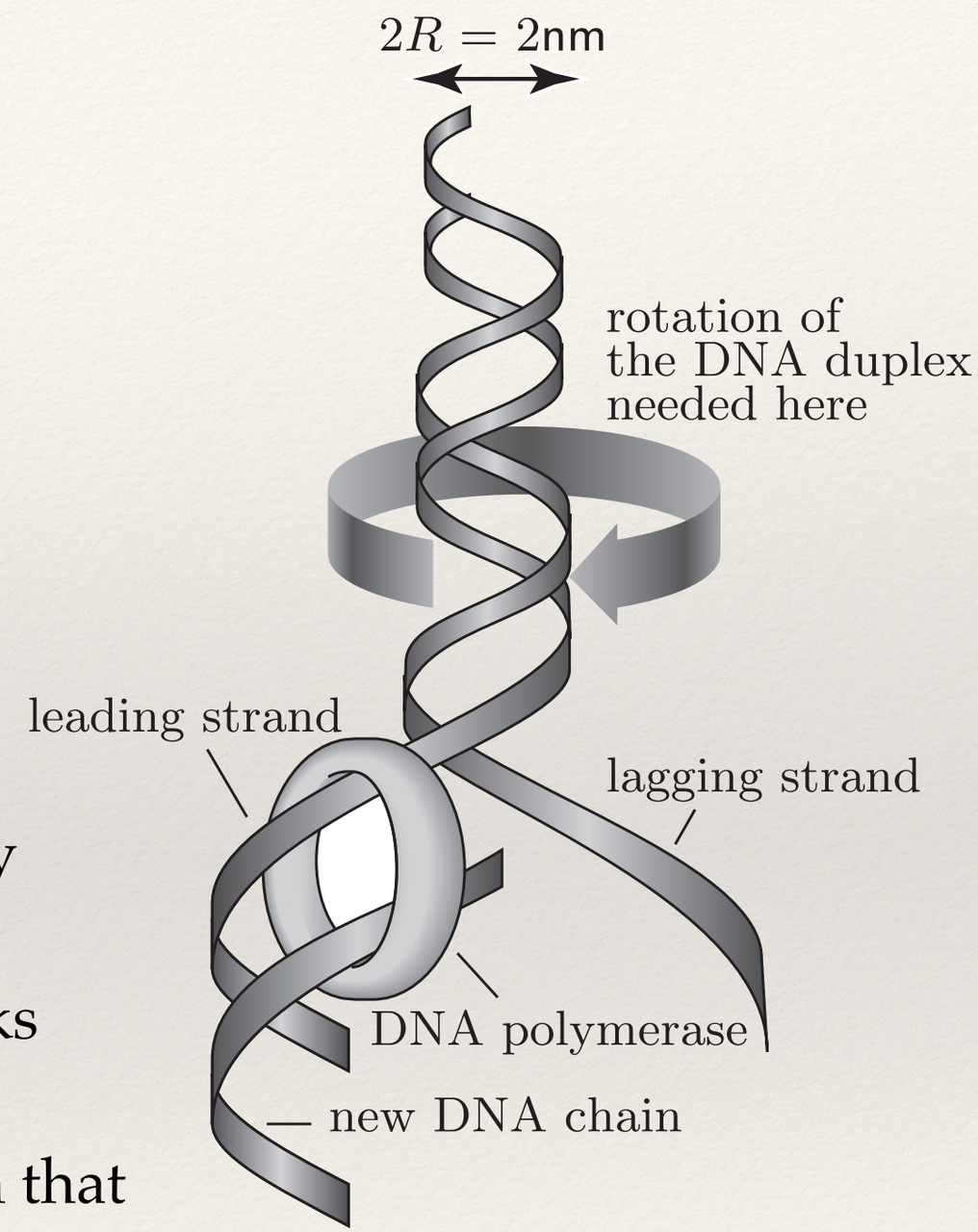
From PN, *Biological Physics*.

Phil Nelson

On being wrong: If the numbers don't work, then the idea doesn't work

An impossible amount of torsional drag would result from unwinding the double helix to replicate it.

Again: The same insight can guide our search for the resolution that Nature has found.



"At the time that I first saw the DNA structure many people might have said, 'You've got to unwind the chains to be able to copy the structure, and that looks impossible.' And they might have eliminated the Watson-Crick structure.... One plausible mechanism that we postulated for unwinding the two DNA strands is that there will be enzymes to do it. Which of course there are." – *Sydney Brenner*

From PN, *Biological Physics*.

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From Probability, Dynamics, and Modeling to Biology, Physics, and Instrumentation: Constructing an Upper-Division Course That Majors and Nonmajors Actually Take

How it's gonna be

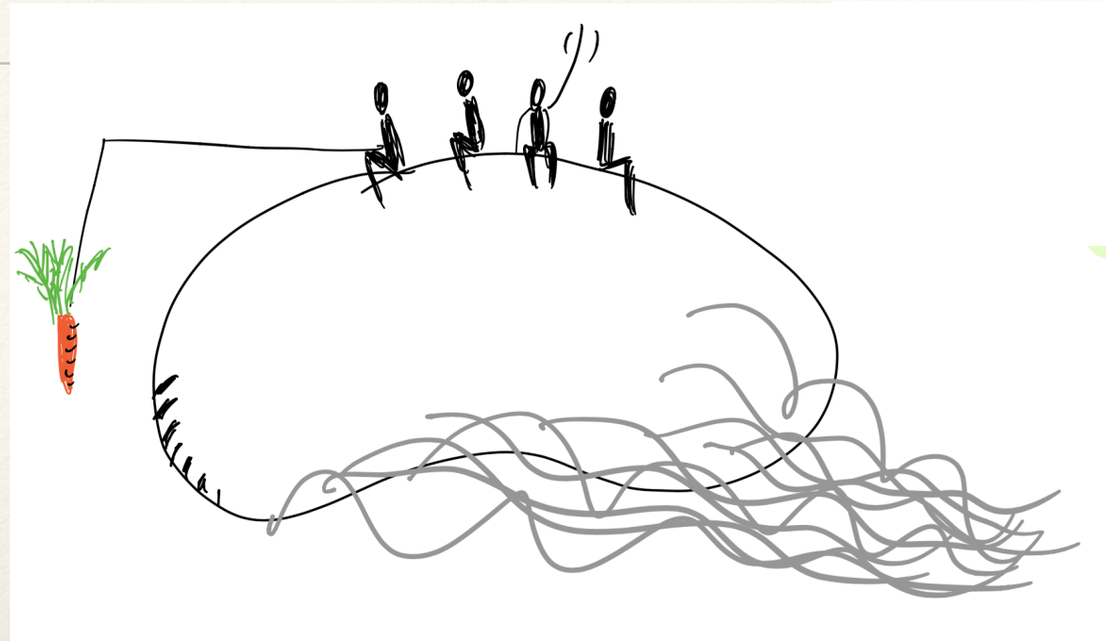
We hear a lot about the importance of training STEM students to work well in teams, and certainly that's true.

But there is another kind of team that will be critical for our students' future, one that's much less talked about: 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 that writing code from scratch, in a general-purpose programming language, to ***model reality,*** 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 you 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 their subsequent classes and beyond.

A case study: Adaptation in chemotaxis



"Biochemical binding interactions typically have a sweet spot covering less than a 100-fold range of concentrations.

And yet

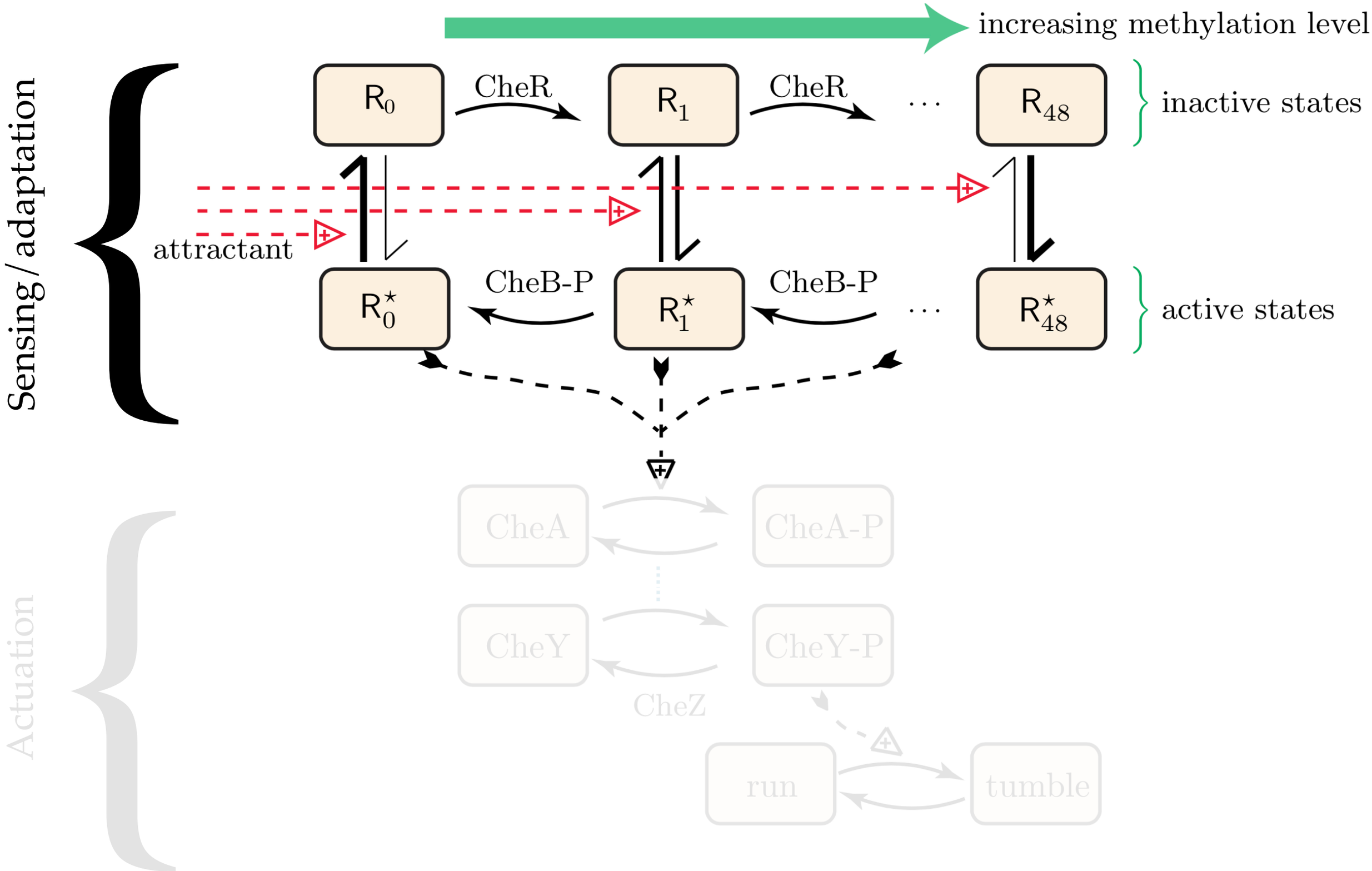
E. coli can follow gradients of food concentration over a 100000-fold dynamic range!

So

How is that possible?"

There's an answer embodied in a model. But it's complex enough that we can't immediately see its implications. A simple ***Gillespie simulation*** is valuable to get the qualitative behavior. A *movie* of the unfolding dynamics is a particularly vivid way to grasp what is happening.
Creating such a movie is now easy enough for students to do using modern computing platforms.

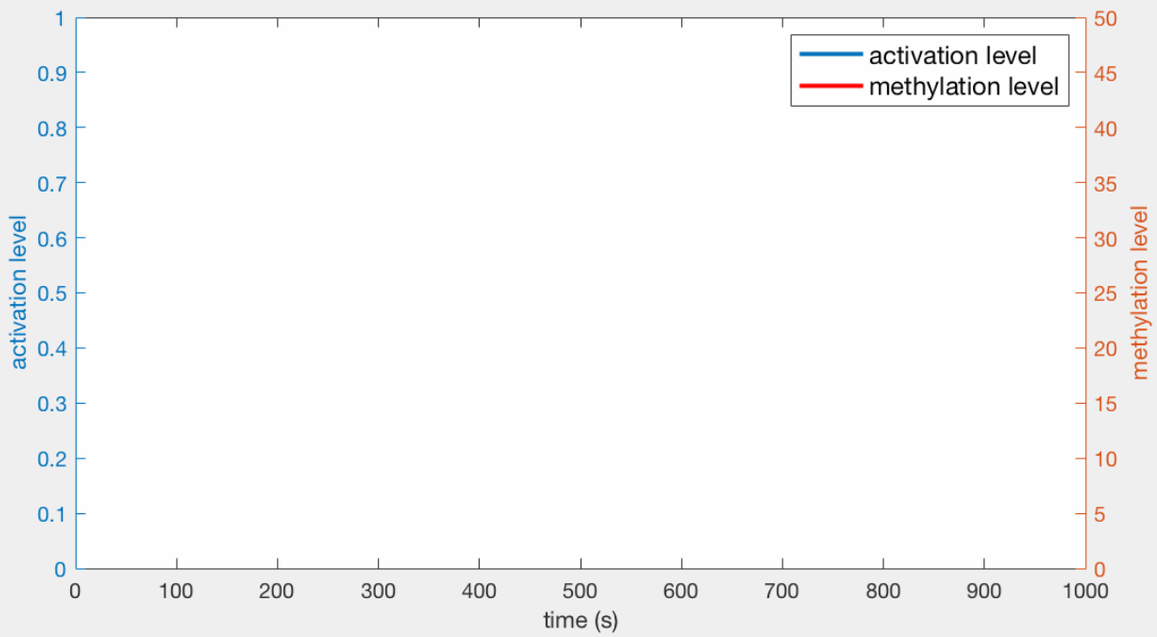
Cartoon: Tina Subic

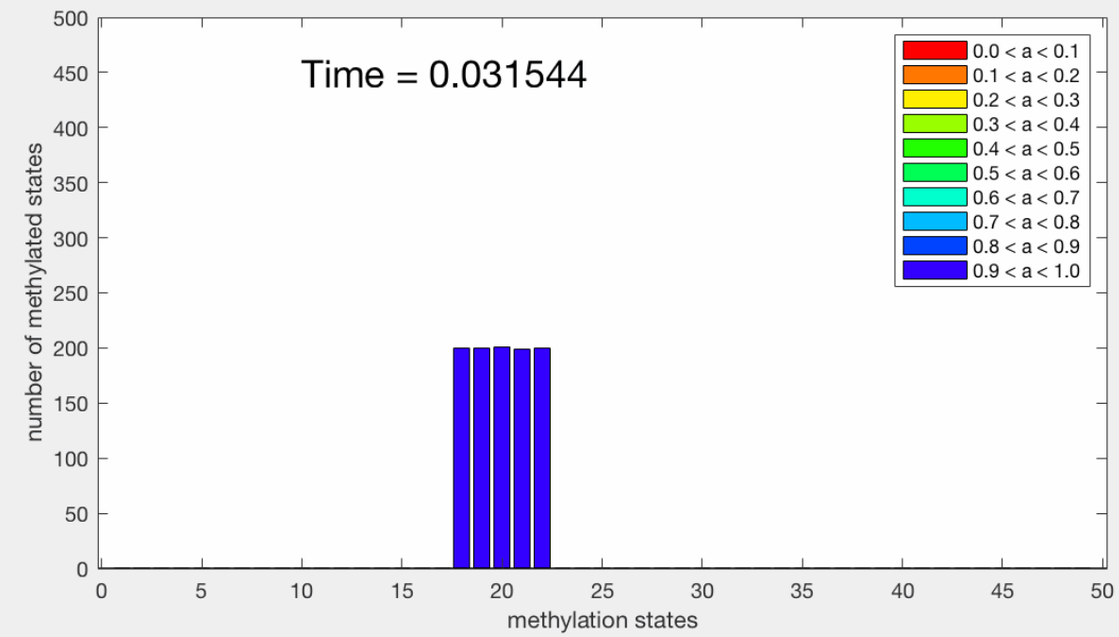


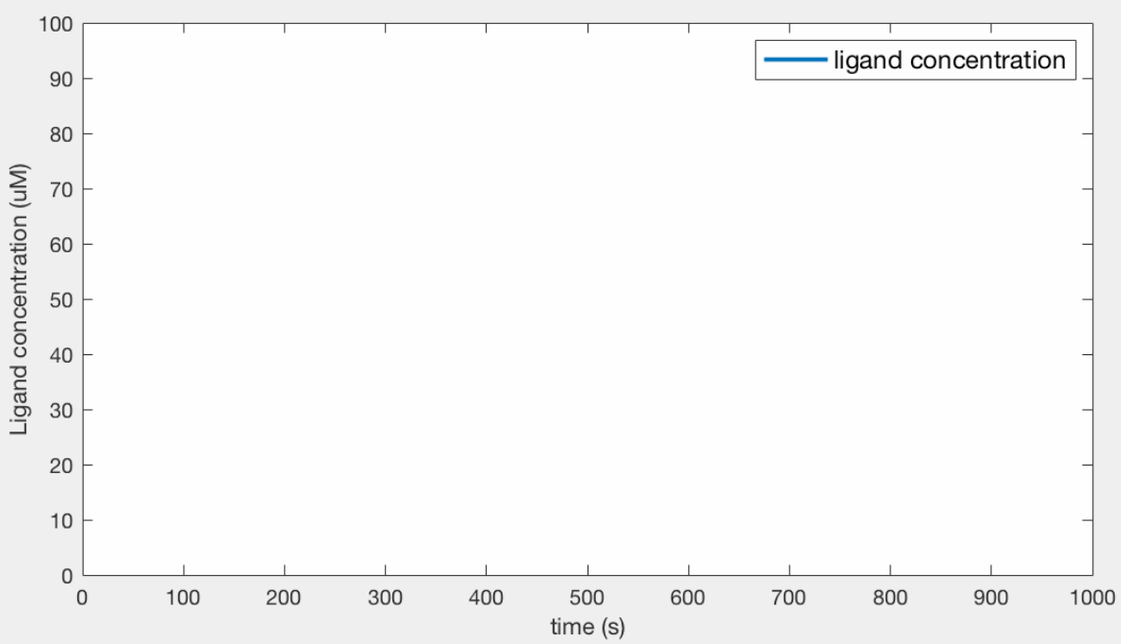
PN, *From photon to neuron*. The model was developed by Tom Shimizu, Yuhai Tu, Howard Berg, and coauthors.

Phil Nelson

Adaptation to steady attractant level







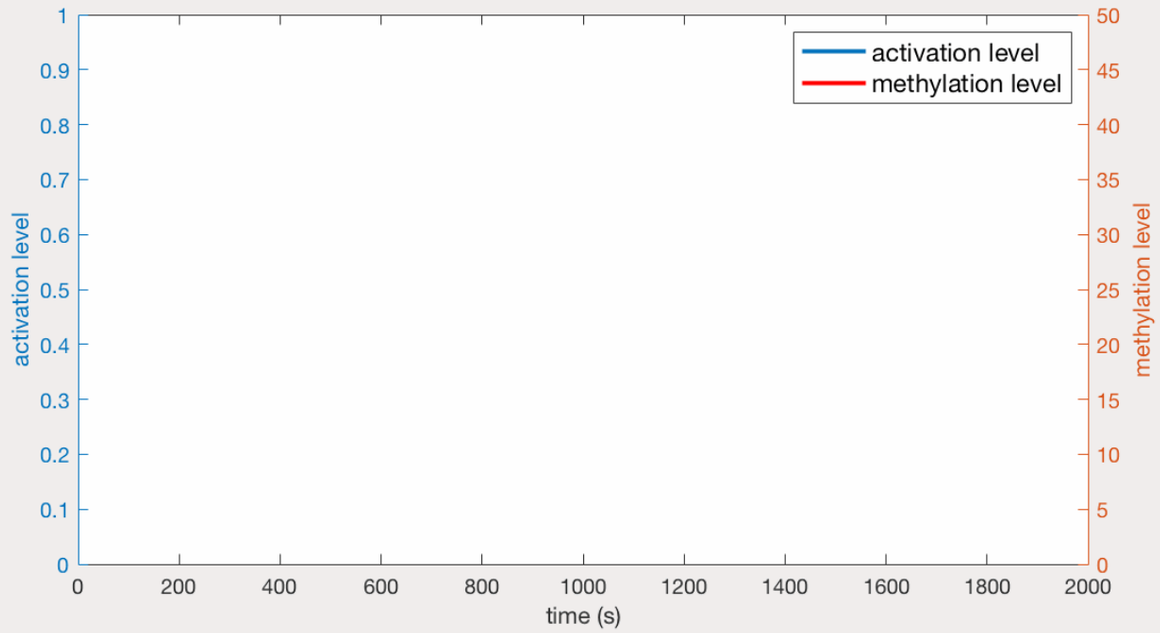
Tina Subic, Edita Bulovaite, and PN, unpublished.

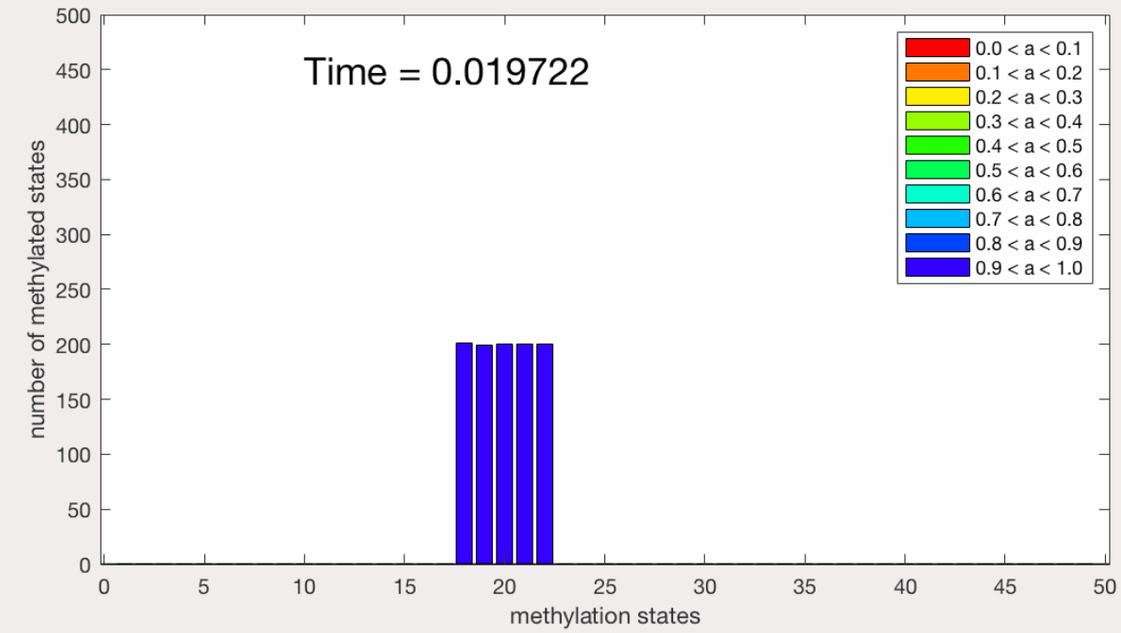
Here is a project that some real students did in one intense week.

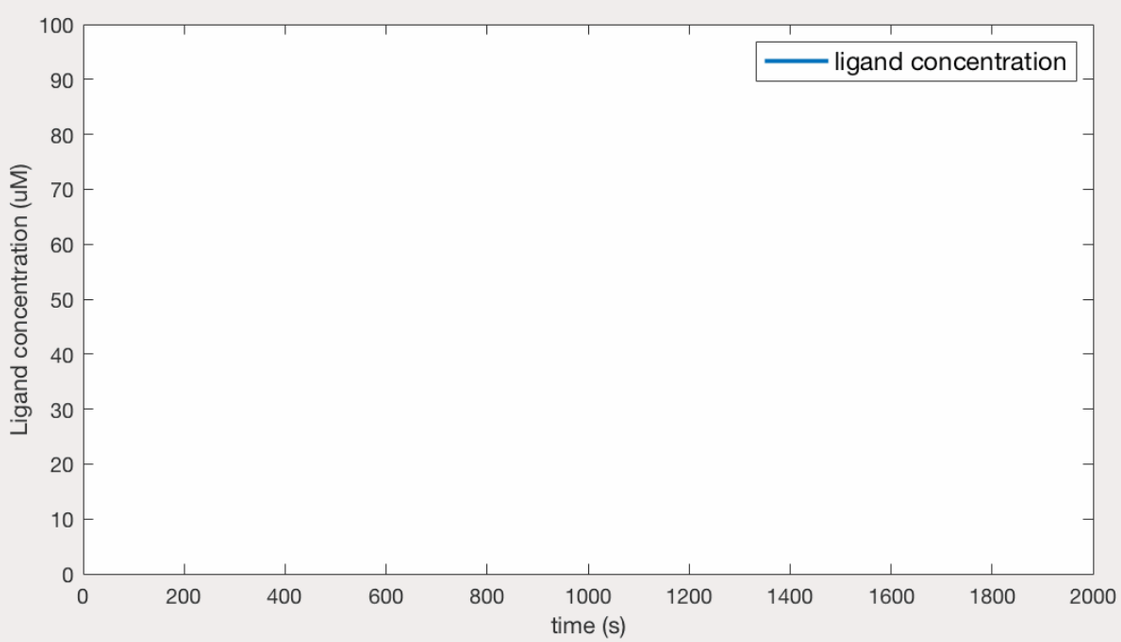
This sort of stochastic, yet purposeful, behavior is starting to feel "*lifelike*." Students are impressed to see it emerging from such simple ingredients.

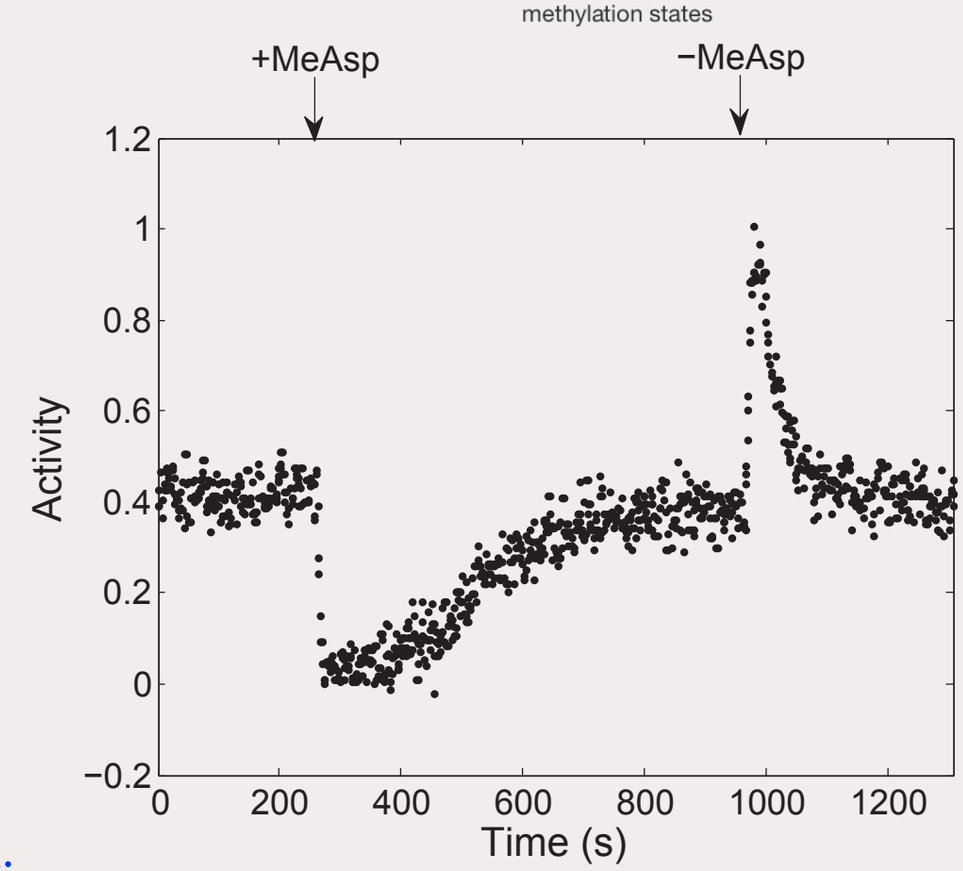
Meet me at my poster on Weds: L70.00343

Adaptation to a jump of attractant level









Simulation: Tina Subic, Edita Bulovaite, and PN, unpublished.

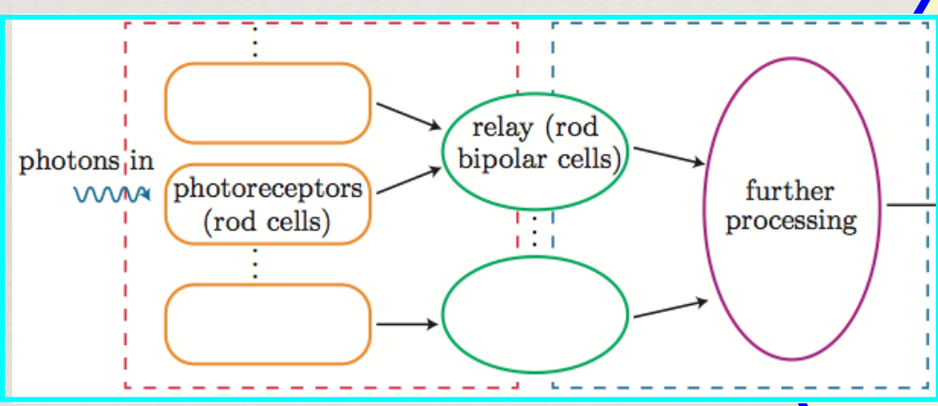
Experiment: J Yuan and HC Berg, Biophys. J 2012.

What is physical modeling?

I don't want to get all philosophical on you. I say, ***It's a Tetrahedron.*** It's useful to think of any modeling challenge in this way:

```
for j=1:46,
   photons=20+5*j;
   mbar=q*photons;
   total=0;
   for i=mstar:50
      total=total+exp(-mbar)*(mbar^i)/factorial(i);end
```

Students are keenly interested; they know they need this skill–they're just not sure what it is.



data

$$\mathcal{P}_{\text{see}}(\mu_{\text{ph,rod}}) = 1 - e^{-Q_{\text{rod,side}}\mu_{\text{ph,rod}}}$$

"Yadda, yadda... photons, yadda,... cumulative Poisson distribution...

PN, *From Photon to Neuron: Light, Imaging, Vision.*

Thanks

University of Pennsylvania

PHYS, BIO

This material is the subject of a two recent textbooks:

P Nelson, ***From photon to neuron*** (Princeton University Press, 2017) (www.physics.upenn.edu/biophys/PtN/).

P Nelson, ***Physical models of living systems*** (W H Freeman and Co, 2015) (www.physics.upenn.edu/biophys/PMLS).

Also see ***Activities and classroom demonstrations in biological physics: A resource document*** (repository.upenn.edu/physics_papers/646/).

Jesse Kinder and P Nelson, ***A student's guide to Python for physical modeling*** (Princeton University Press, 2018).

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

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