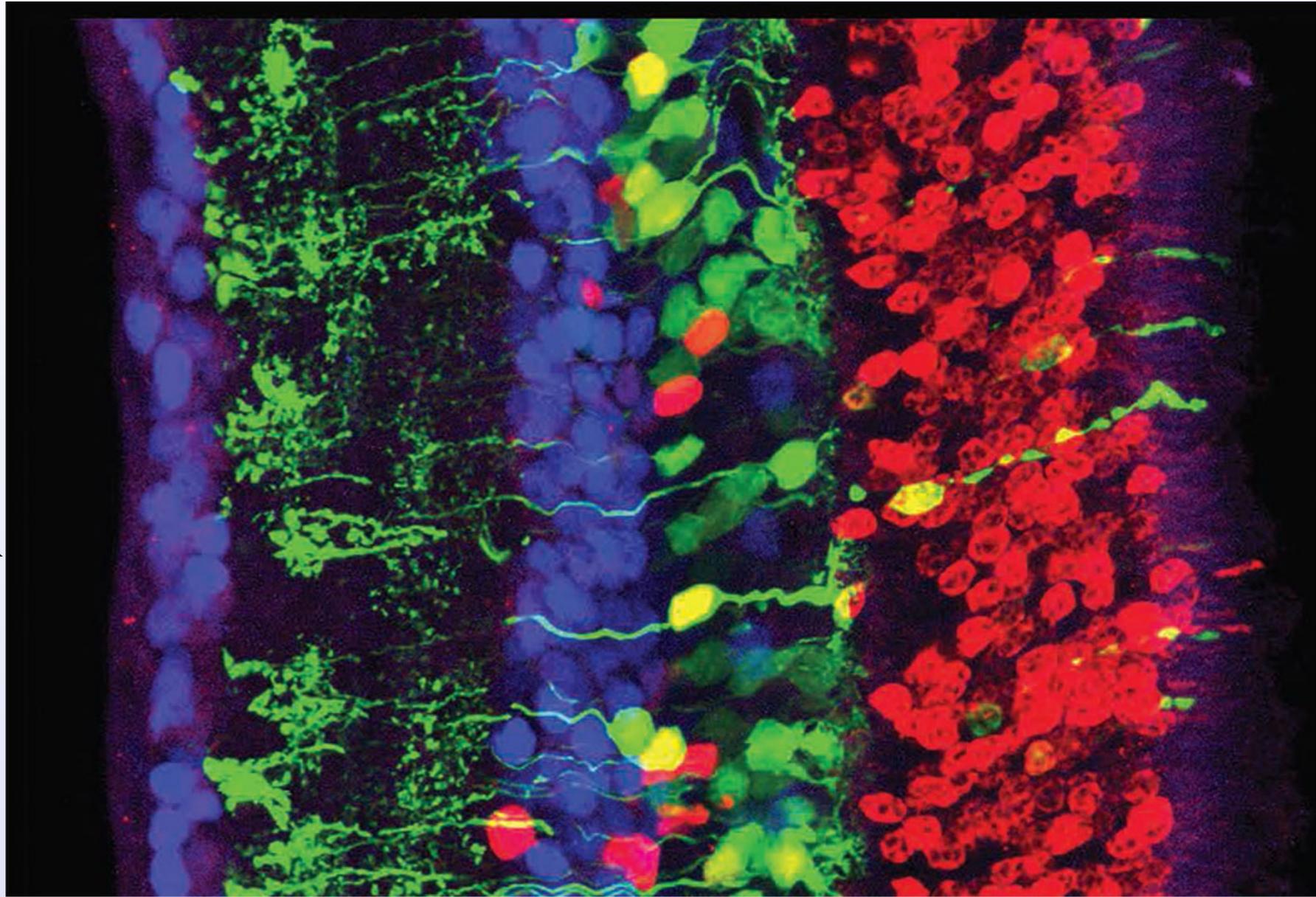


An  
intermediate-  
level course  
and textbook  
on light,  
imaging, and  
vision



**Phil Nelson**  
**University of Pennsylvania**

These slides will appear at  
[www.physics.upenn.edu/~pcn](http://www.physics.upenn.edu/~pcn)

Image of mouse retina courtesy  
Sui Wang and Constance Cepko

# Plan

1. Indoctrination
2. Skill set
3. Light, vision, and 21st century imaging
4. And now a word from our sponsor

# I: Is this your situation?

“I’m interested in biological physics.

*and*

So are many students in my university.

*but*

My department doesn’t want to assign me to a new course, and they’re not too sure this stuff is physics anyway.”

**My message today is:**

There has been a *revolution* in optical methods.

*and*

It’s still *ongoing*.

*and*

You need a lot of *physics* to understand it.

*and*

I’m talking about *cool* physics, not traditional first-year material.

*and*

It brings in *non-majors* who would otherwise not have taken another physics course.

*and*

Now there’s a new *textbook* about exactly that, so you don’t need to invent it from scratch.

*so*

**Of course your department should let you offer it!**

# 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 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 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.

## 2: Skills: Probabilistic and algorithmic thinking

Indoctrination

**Skill set**

Light, vision, a

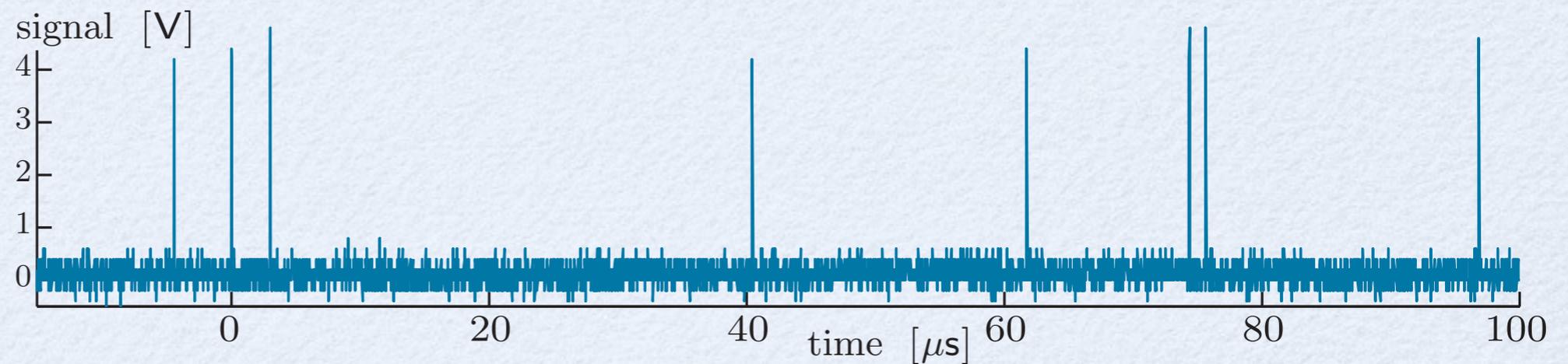
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**Biophysical problems are an interesting road into probability theory with high-profile, current applications that can motivate students.**

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.



Here's an extremely important example: Light arrives as blips in a Poisson process. If you thin a Poisson process by randomly discarding some fraction of the blips, the result is *still a Poisson process*. This is way more fun and memorable to show with a simulation – a few lines of code – than as a theorem.

# 3:

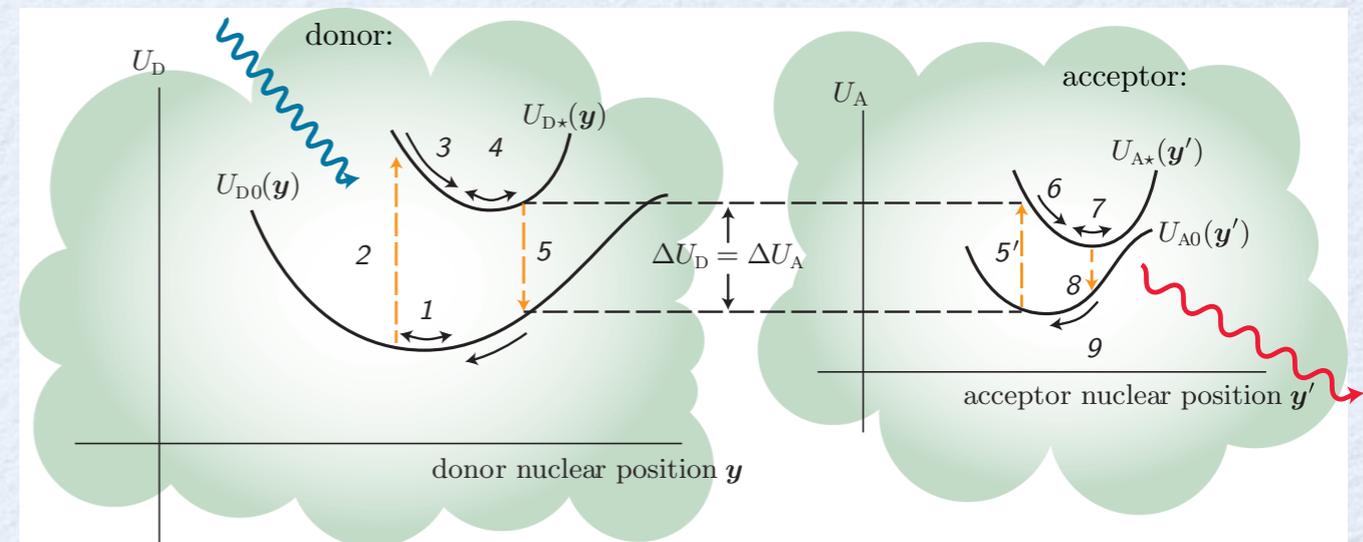
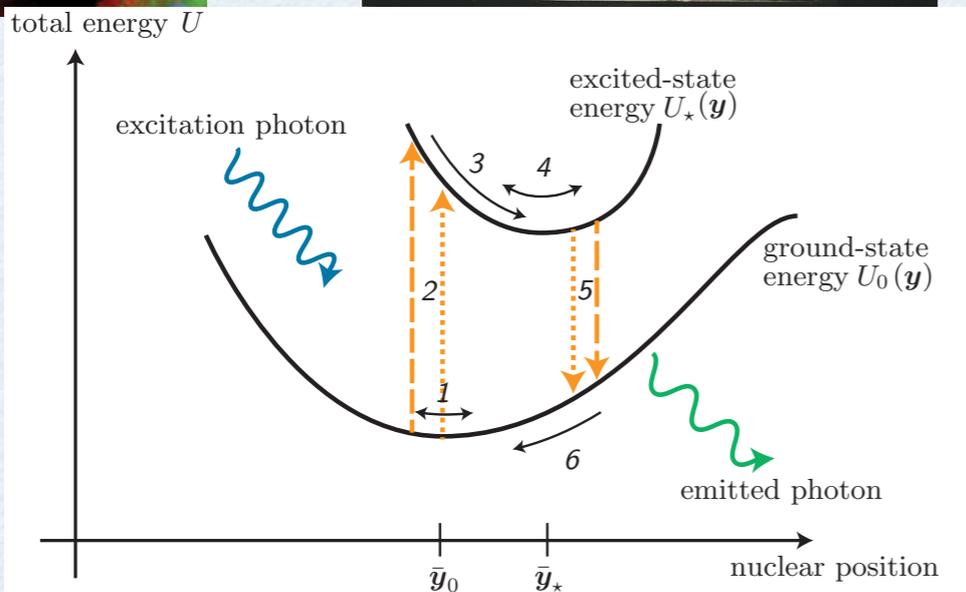
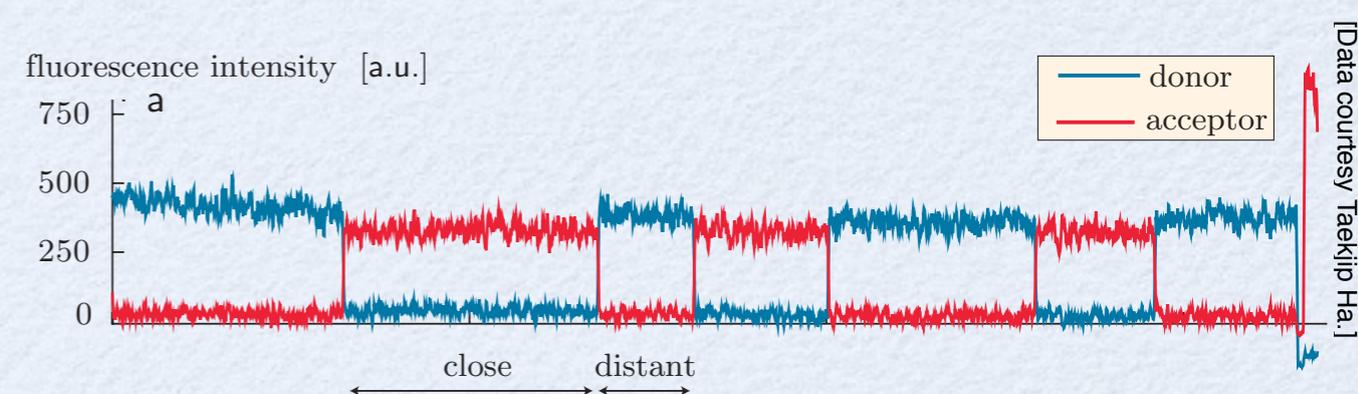
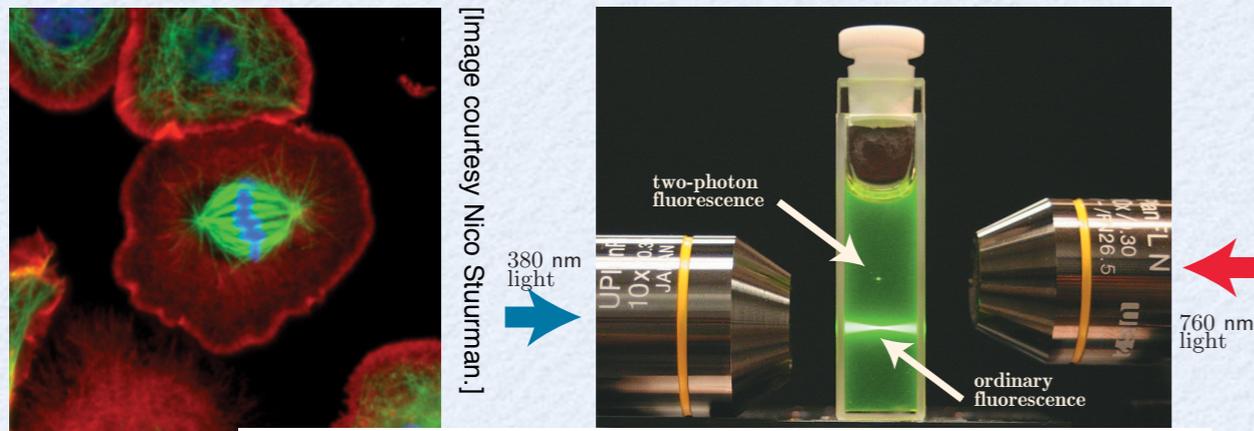
indocyanine

Skill set

## Light, vision, and 21st C imaging

And now a word from our sponsor

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.



**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? Did they really understand much when they took p-chem?)

# 3.1: 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.”

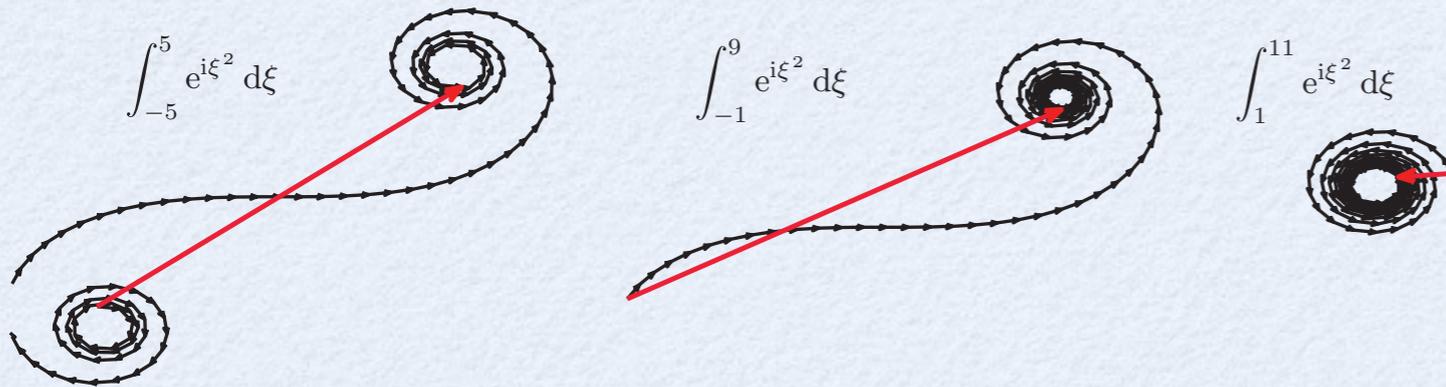
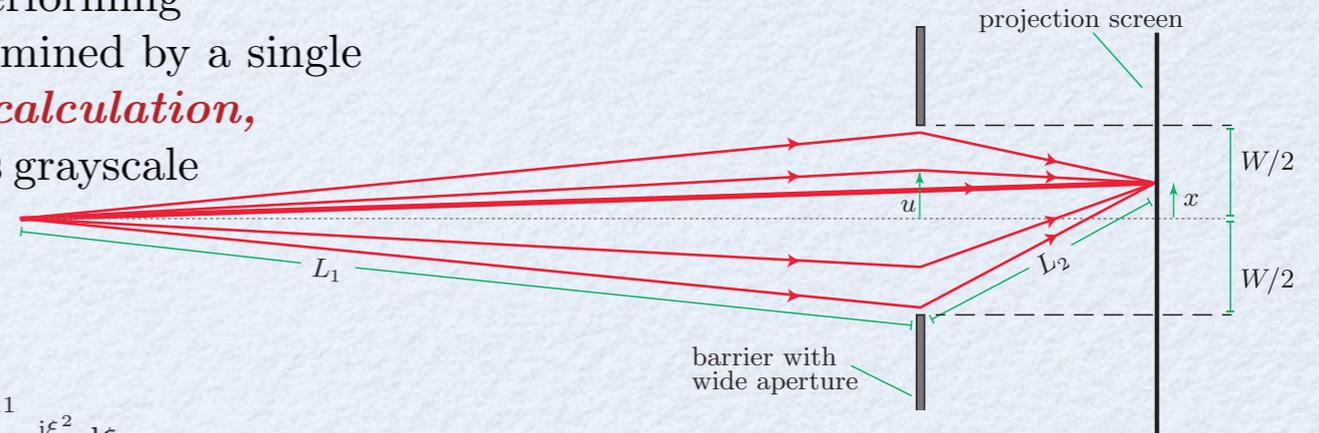
(They really mean, “Shut up.”)

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.

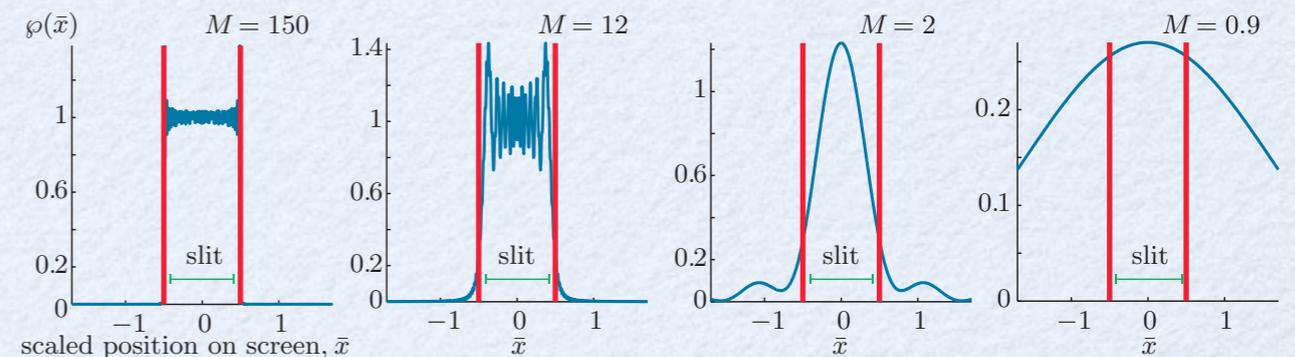
**Can’t we tell them something we actually believe is *true*? Can’t we have them do a calculation *for themselves* that illuminates this apparent paradox?**

# 3.2: Light also has wavelike aspects

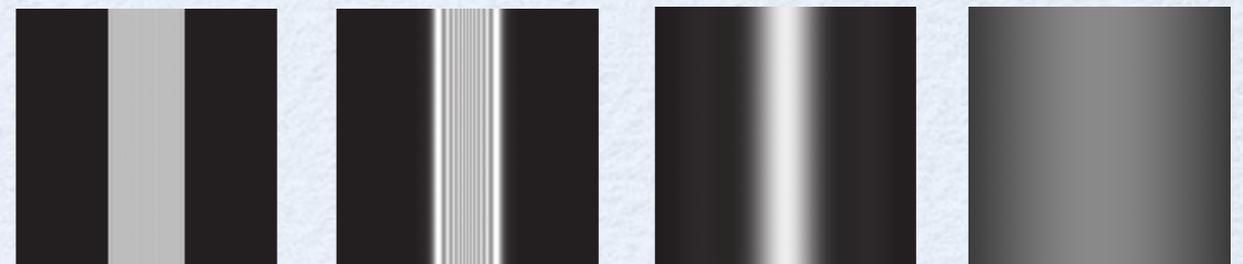
Students can understand qualitatively the crossover between rectilinear and diffractive propagation of light through a finite-width slit. Performing the sum over paths numerically yields both regimes, as determined by a single dimensionless parameter, here called  $M$ . *Students do the calculation, and visualize the answer*, both as traditional graphs and as grayscale images they can connect to an actual classroom demo.



The key to the ray-optics regime is the *principle of stationary phase*: If the aperture is wide, then it makes a big difference whether or not there's any stationary-phase path. If it's narrow, then there isn't much difference.



This one calculation contains the seeds of many important optical phenomena, for example the diffraction limit on resolution in a lens system.

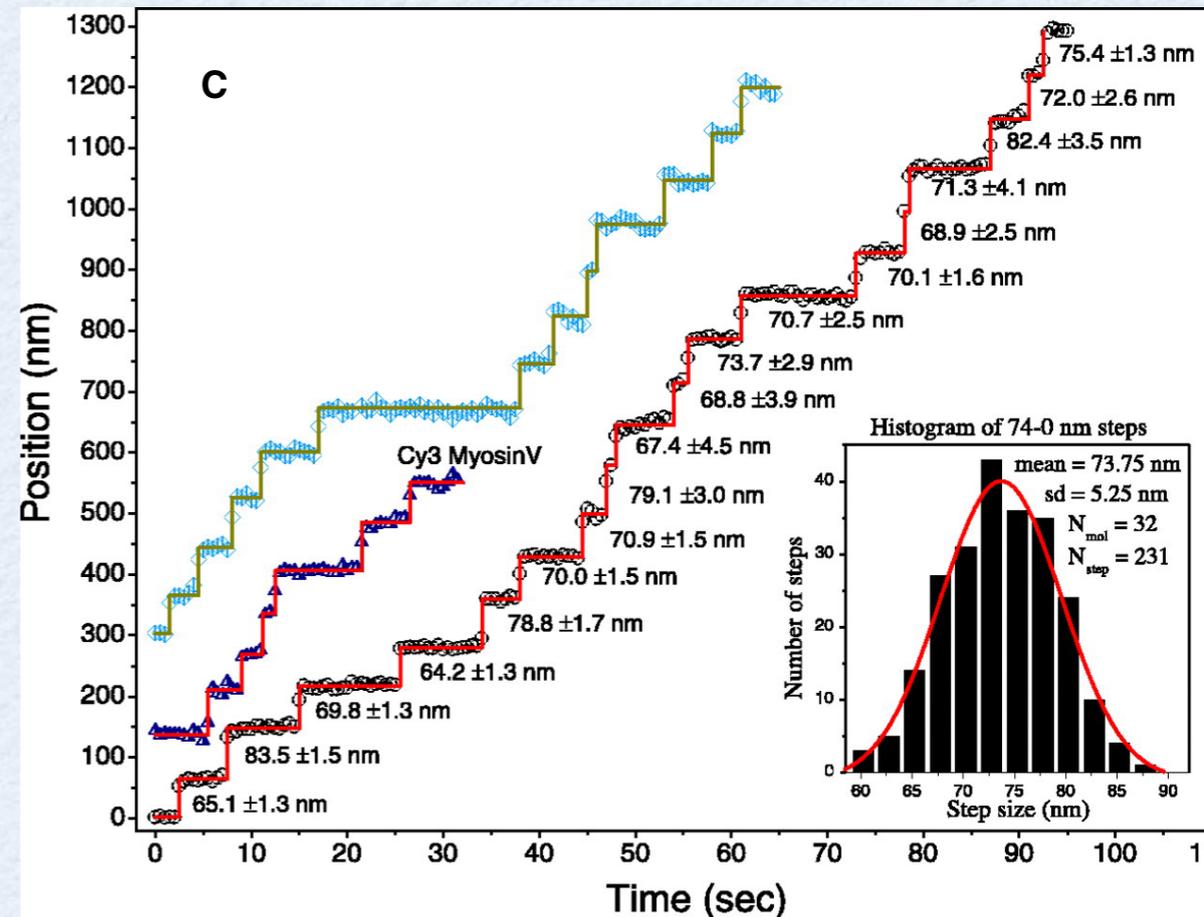
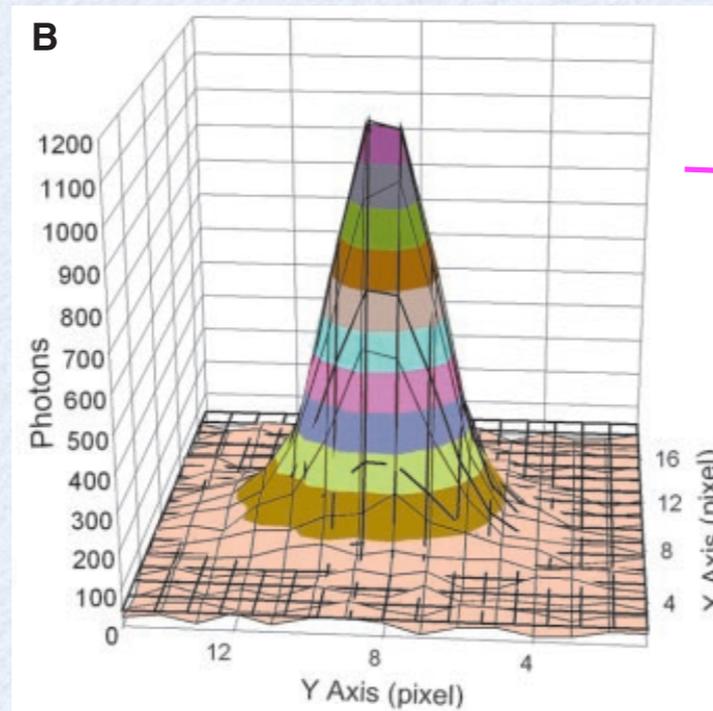
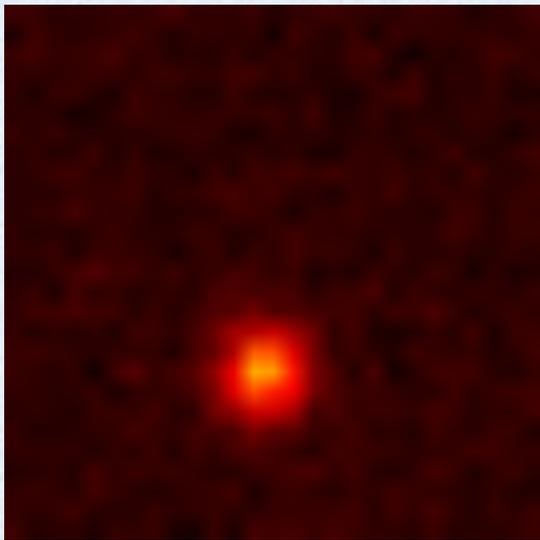


# 3.3: Beyond the diffraction limit

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

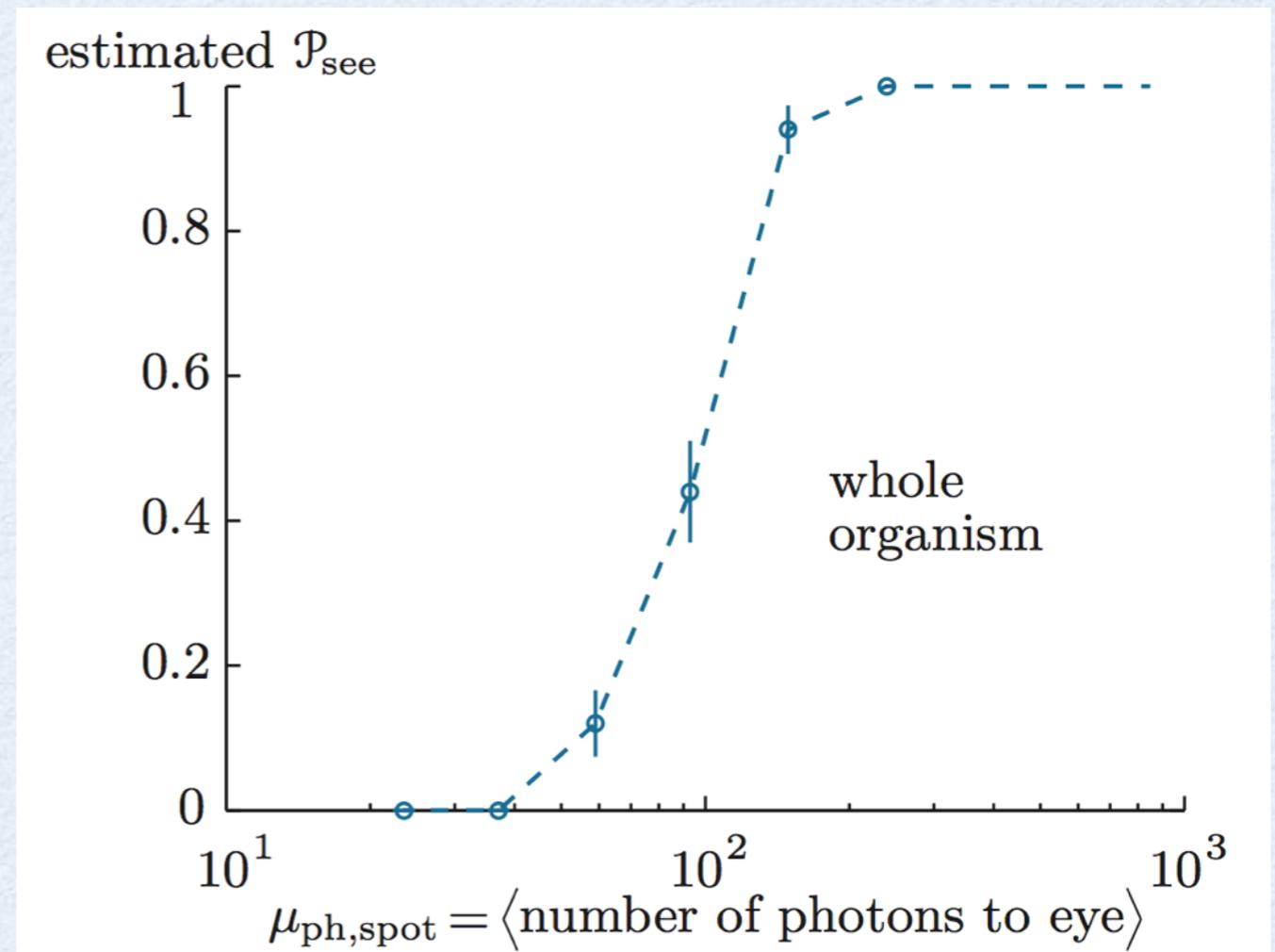
Hey, how did Yildiz et al. measure the steps taken by a molecular motor using visible light? The diffraction-limited spot is at least 200 nm wide! In fact, *Everything interesting in cells is below the diffraction barrier!*

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



# 3.4: Vision in dim light

Framing: “What’s all that theoretical stuff got to do with *my own body*, for example *vision*? 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?”

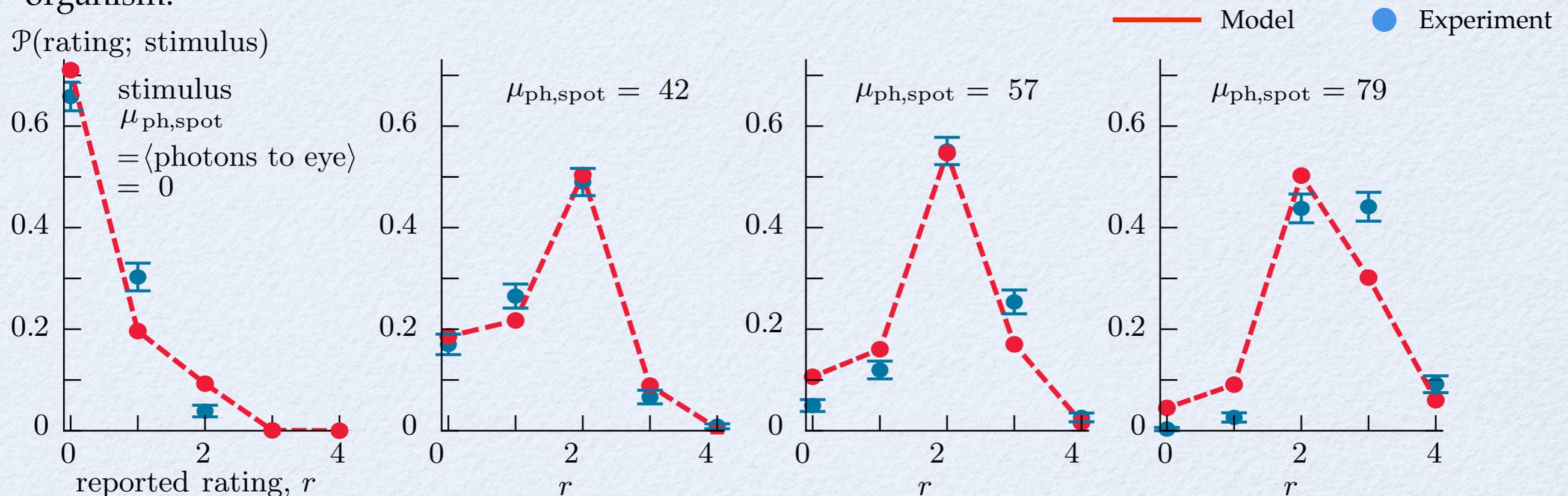


Hecht et al measured the probability for a human subject to see a flash, vs intensity. They found a simple **physical model** predicting the form of this “probability of seeing curve.” Then they were led from this information to the conclusion that a *single photon absorption can excite a rod cell*, and that a quorum of just a few simultaneous rod-cell firings is enough to register consciously.

# 3.5: More about dim light vision

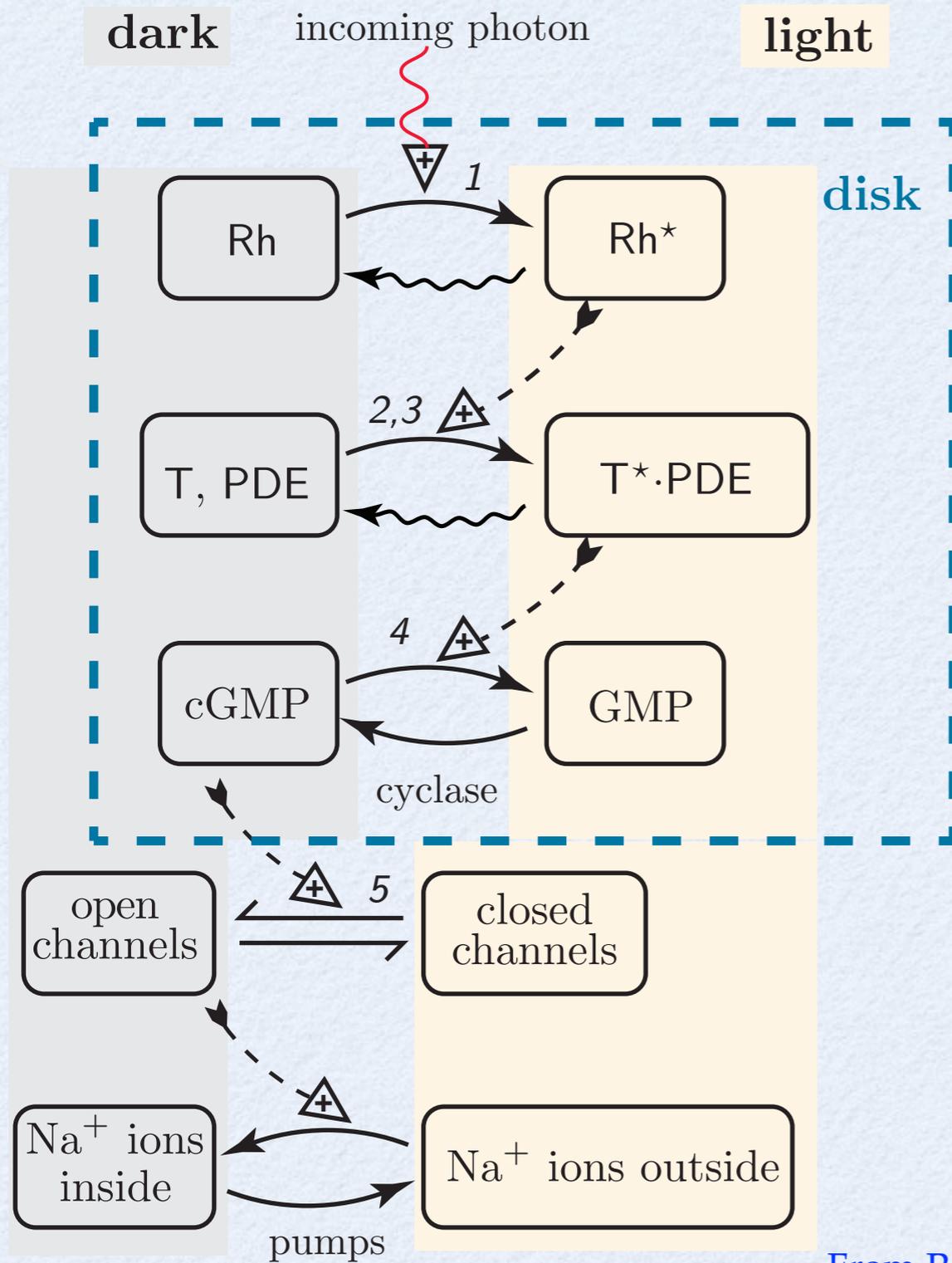
Actually, Hecht's model omitted something huge--the role of spontaneous isomerizations. Here is a 1-parameter fit to *a function of two variables*, the probability of a subject assigning a given rating to the strength of a flash as a function of that flash's nominal strength.

Simple fits like this one can be done from scratch without having to rely on big black-box packages. This exercise *brings all the threads together* (probabilistic reasoning, quantum character of light, etc.) into a remarkable insight into the performance of an entire complex organism.



From P Nelson, *From photon to neuron* (Princeton, 2017). Data courtesy Heidi Hofer, following an experiment originally done by Barbara Sakitt.

# 3.6: 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: Light, Imaging, Vision* (Princeton, 2017).

# 4

Indoctrination

Skill set

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 Official Guide for the MCAT<sup>2015</sup> 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 4:

**4D. How light interacts with matter**

- **Concept of Interference; Young Double-slit Experiment**
- **Thin films, diffraction grating, single-slit diffraction**
- **Other diffraction phenomena, X-ray diffraction**
- **Polarization of light**
- **Thin lenses: o Converging and diverging lenses; o Use of formula  $1/p + 1/q = 1/f$  o Lens strength**
- **Combination of lenses**
- **Lens aberration**
- **Optical Instruments, including the human eye**

# 5: Wrap

Indoctrination  
Skill set  
Light, vision,  
And now a w

## Wrap

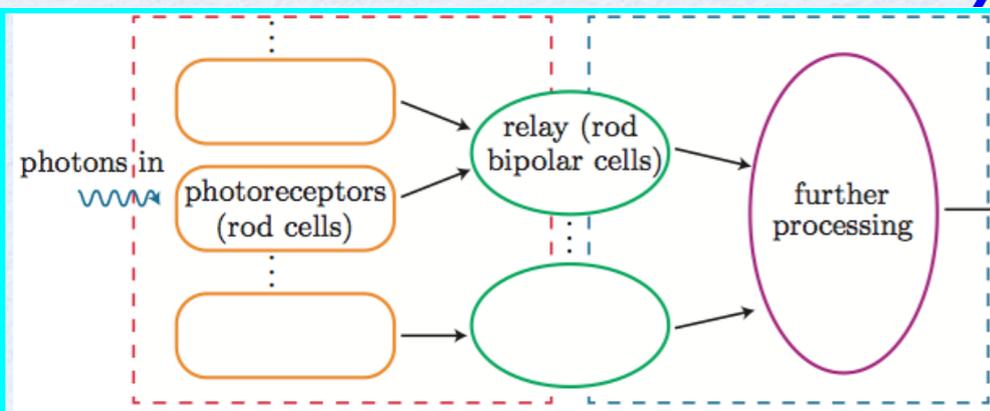
Excuse me... everybody says “modeling is super important.” But...

*What is a “physical model” anyway? Is it distinct from a “mathematical model”?*

# 5.1: What is physical modeling?

Don't want to get all philosophical on you. I say, *It's a Tetrahedron*. Today I applied this approach to dim-light vision, but 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
```



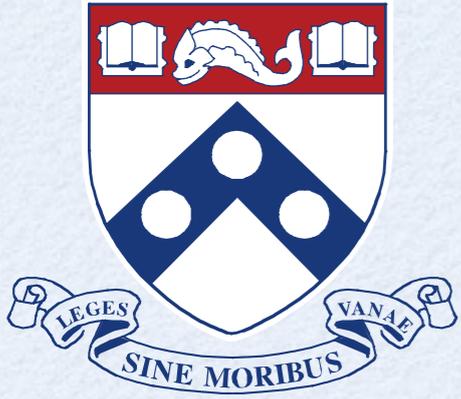
*data*

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

“Yadda, yadda... photons, yadda,...  
cumulative Poisson distribution...”

From P. Nelson, *From Photon to Neuron: Light, Imaging, Vision* (Princeton, 2017).

# Thanks



University of Pennsylvania

This material is the subject of a new textbook ([www.physics.upenn.edu/biophys/PtN](http://www.physics.upenn.edu/biophys/PtN)); **come to Princeton Press, booth 219.**



Let's take a moment to remember Kamal Shukla, NSF BIO

Also see:

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

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

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



For these slides see:  
[www.physics.upenn.edu/~pcn](http://www.physics.upenn.edu/~pcn)