Old news and new news about single-photon sensitivity

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

Image of chick retina by Andy Fischer.

Plan

1. Indoctrination
2. Light
3. Vision
4. And now a word from our sponsor
5. Wrap

Plan

1. Indoctrination
2. Light
3. Vision
4. And now a word from our sponsor
5. Wrap

Challenge/opportunity

Challenge/opportunity

I love Q-bio–so do you–but If we want q-bio to flourish, to grow to the status of an independent field, we need to train a generation or two of young, new q-bio-ists.

Challenge/opportunity

I love Q-bio–so do you–but If we want q-bio to flourish, to grow to the status of an independent field, we need to train a generation or two of young, new q-bio-ists.

- 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.

Challenge/opportunity

I love Q-bio–so do you–but If we want q-bio to flourish, to grow to the status of an independent field, we need to train a generation or two of young, new q-bio-ists.

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

Challenge/opportunity

I love Q-bio–so do you–but If we want q-bio to flourish, to grow to the status of an independent field, we need to train a generation or two of young, new q-bio-ists.

- To a large extent, undergraduate physical-science curricula remain *firmly rooted in pencil-and-paper calculation,* despite the fact that most research is done with computers.
- To a large extent, undergraduate life-science curricula remain *firmly rooted in descriptive approaches,* despite the fact that much current research involves quantitative modeling.
- (Don't get me started on math curricula.)

Challenge/opportunity

I love Q-bio–so do you–but If we want q-bio to flourish, to grow to the status of an independent field, we need to train a generation or two of young, new q-bio-ists.

- To a large extent, undergraduate physical-science curricula remain *firmly rooted in pencil-and-paper calculation,* despite the fact that most research is done with computers.
- To a large extent, undergraduate life-science curricula remain *firmly rooted in descriptive approaches,* despite the fact that much current research involves quantitative modeling.
- (Don't get me started on math curricula.)

All those blue-ribbon panels haven't yet changed reality on the ground. (Maybe a little.)

Challenge/opportunity

I love Q-bio–so do you–but If we want q-bio to flourish, to grow to the status of an independent field, we need to train a generation or two of young, new q-bio-ists.

- To a large extent, undergraduate physical-science curricula remain *firmly rooted in pencil-and-paper calculation,* despite the fact that most research is done with computers.
- To a large extent, undergraduate life-science curricula remain *firmly rooted in descriptive approaches*, despite the fact that much current research involves quantitative modeling.
- (Don't get me started on math curricula.)

All those blue-ribbon panels haven't yet changed reality on the ground. (Maybe a little.)

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

What kind of skills and frameworks?

What kind of skills and frameworks?

- **Randomness is inescapable in the physical world, and yet conclusions can nevertheless be drawn with the help of ideas from probability.** The Bayesian viewpoint now sweeping many branches of science is important to learn early and often.

What kind of skills and frameworks?

- **Randomness is inescapable in the physical world, and yet conclusions can nevertheless be drawn with the help of ideas from probability.** The Bayesian viewpoint now sweeping many branches of science is important to learn early and often.
- **The basics of computer programming, in any general-purpose platform, are now easy enough to cover in a small fraction of a semester.** Incorporating it into any class is probably more important than whatever else you were going to do with those two weeks. That's what students told me, in some cases several years after taking the course.

(Admission)

(I realize that many of the people in this room could give a different, and equally good, talk on this subject. This is just a report on my own experience.)

Plan

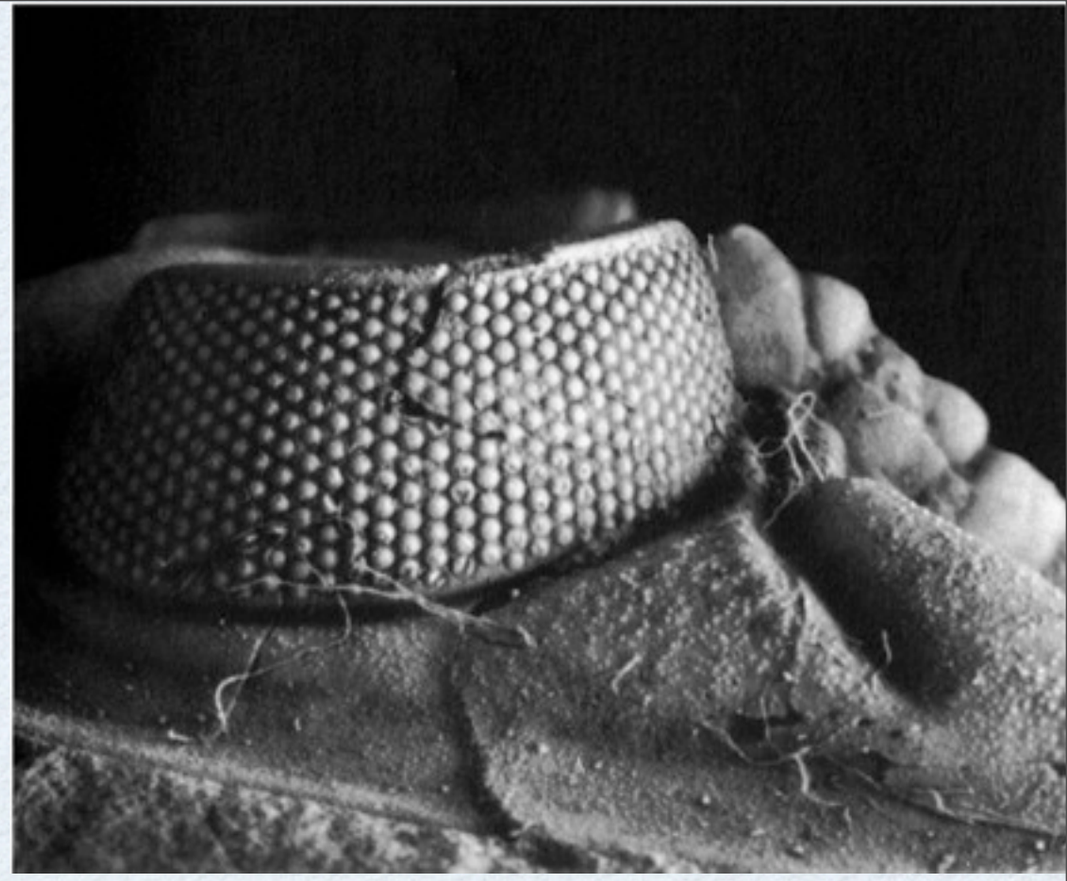
1. Indoctrination
2. Light
3. Vision
4. And now a word from our sponsor
5. Wrap

Eyes

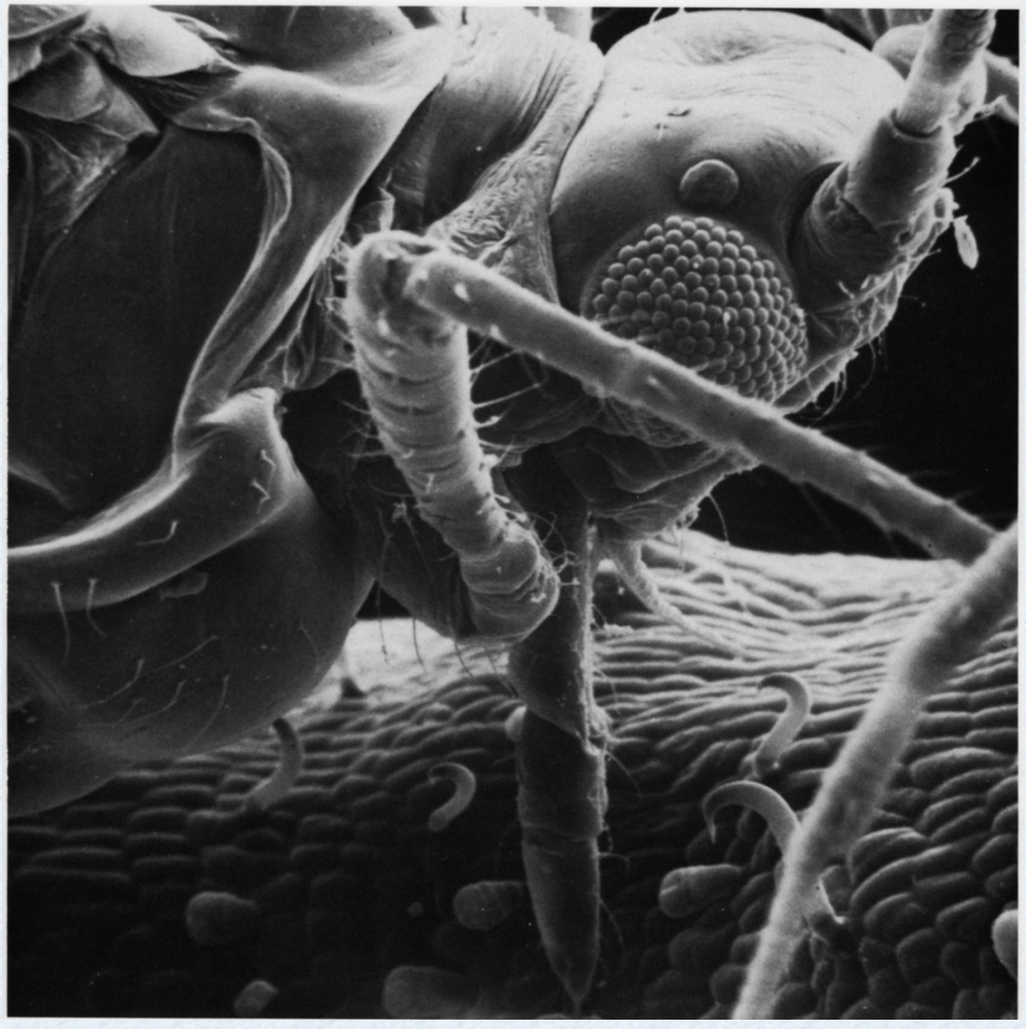
Eyes are an ancient invention: Here is Trilobite, half a billion years old.

Eyes

Eyes are an ancient invention: Here is Trilobite, half a billion years old.

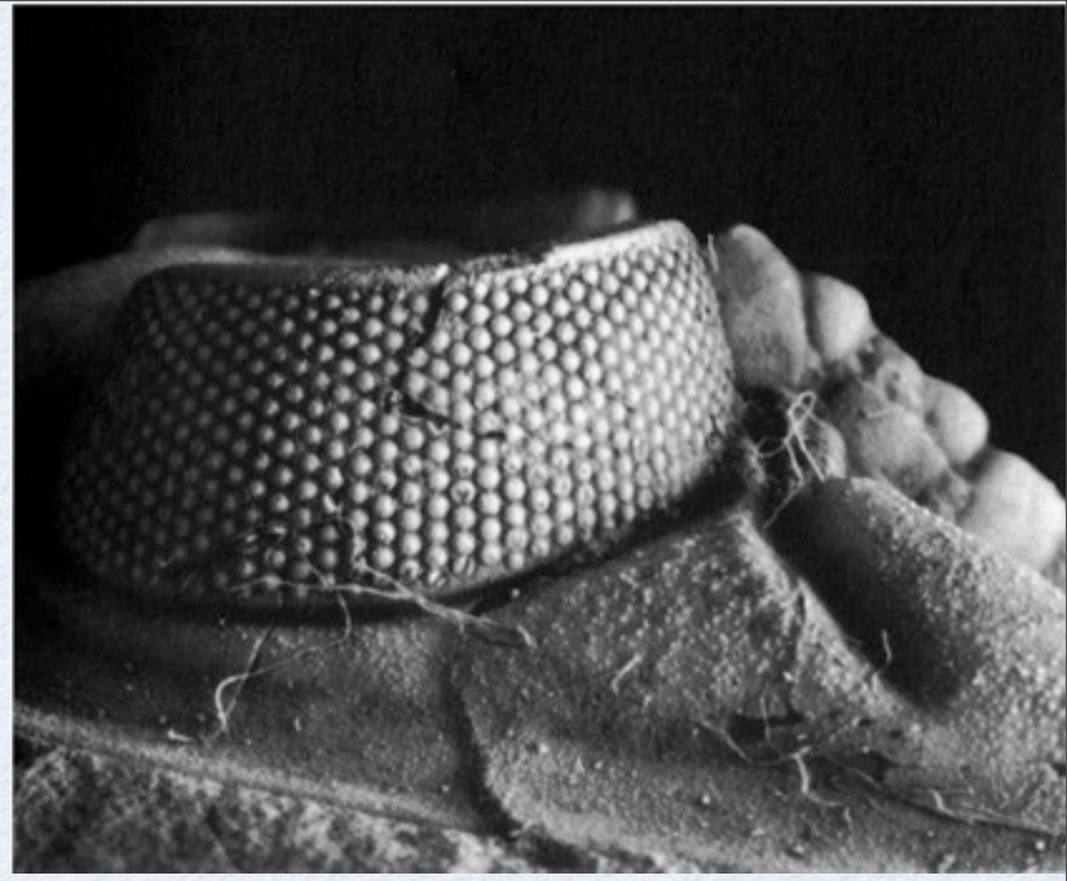


That design was successful: Here is a modern aphid.

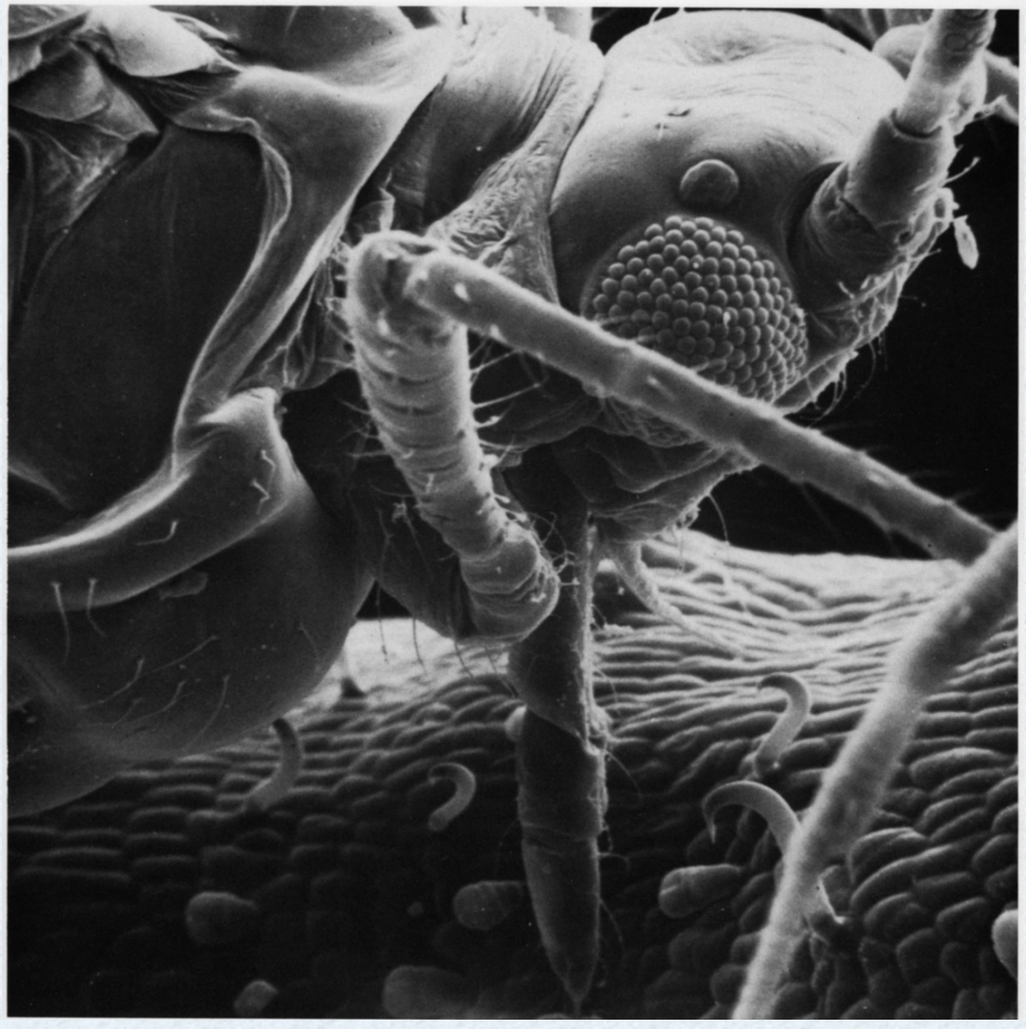


Eyes

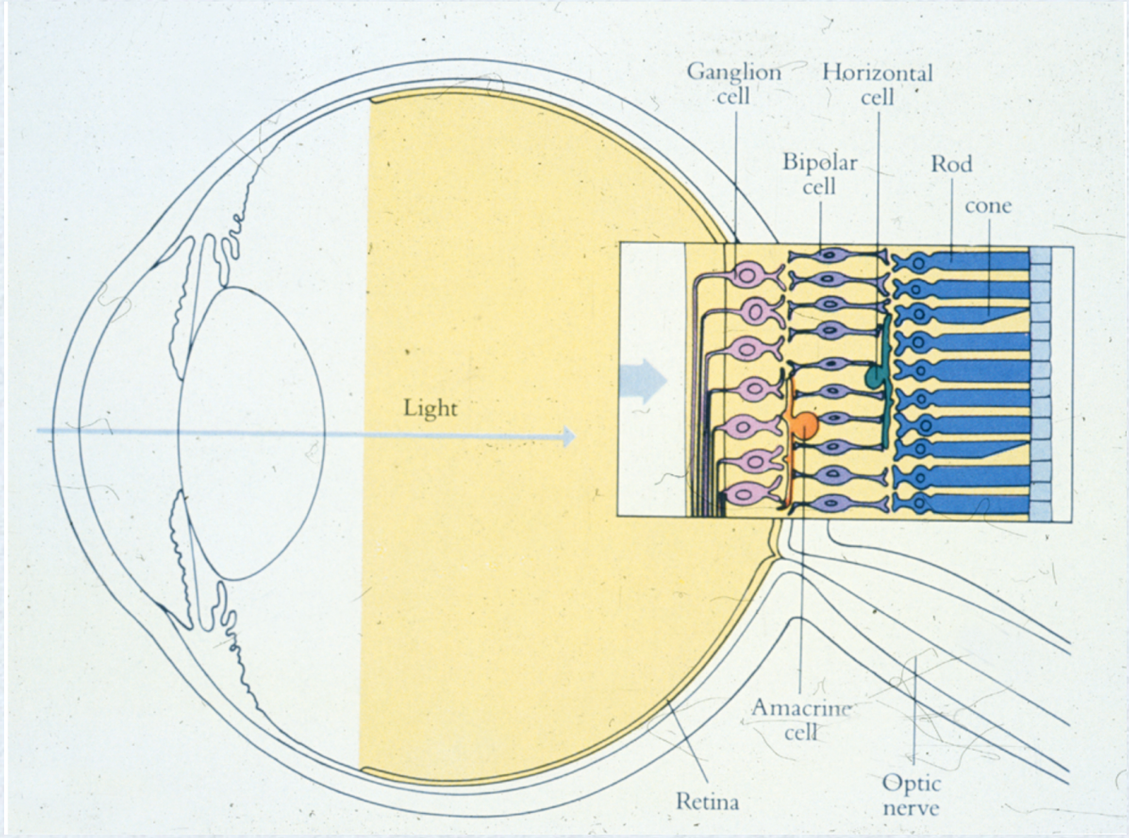
Eyes are an ancient invention: Here is Trilobite, half a billion years old.



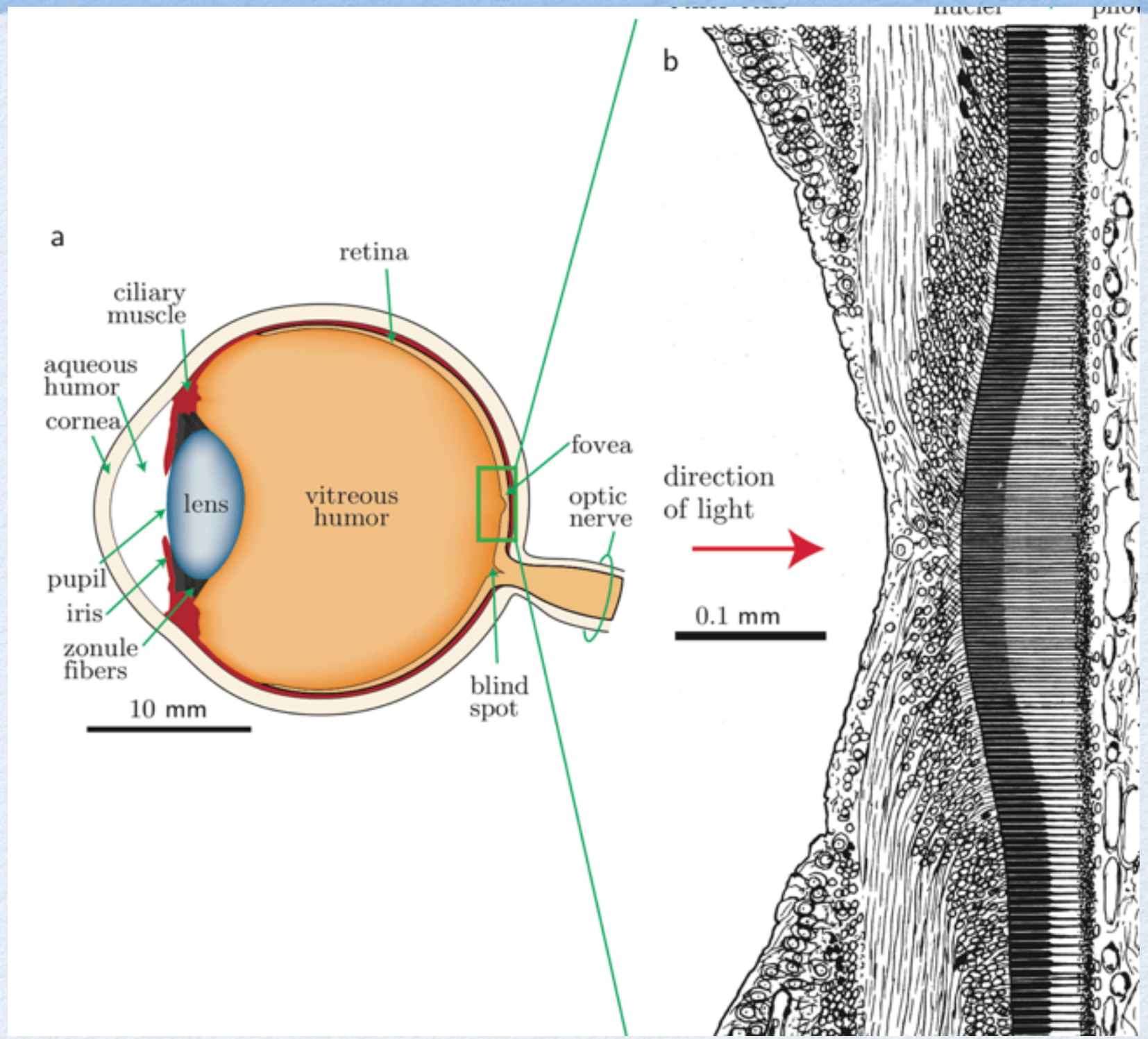
That design was successful: Here is a modern aphid.



But if you can afford to carry more weight around, here is a better design:



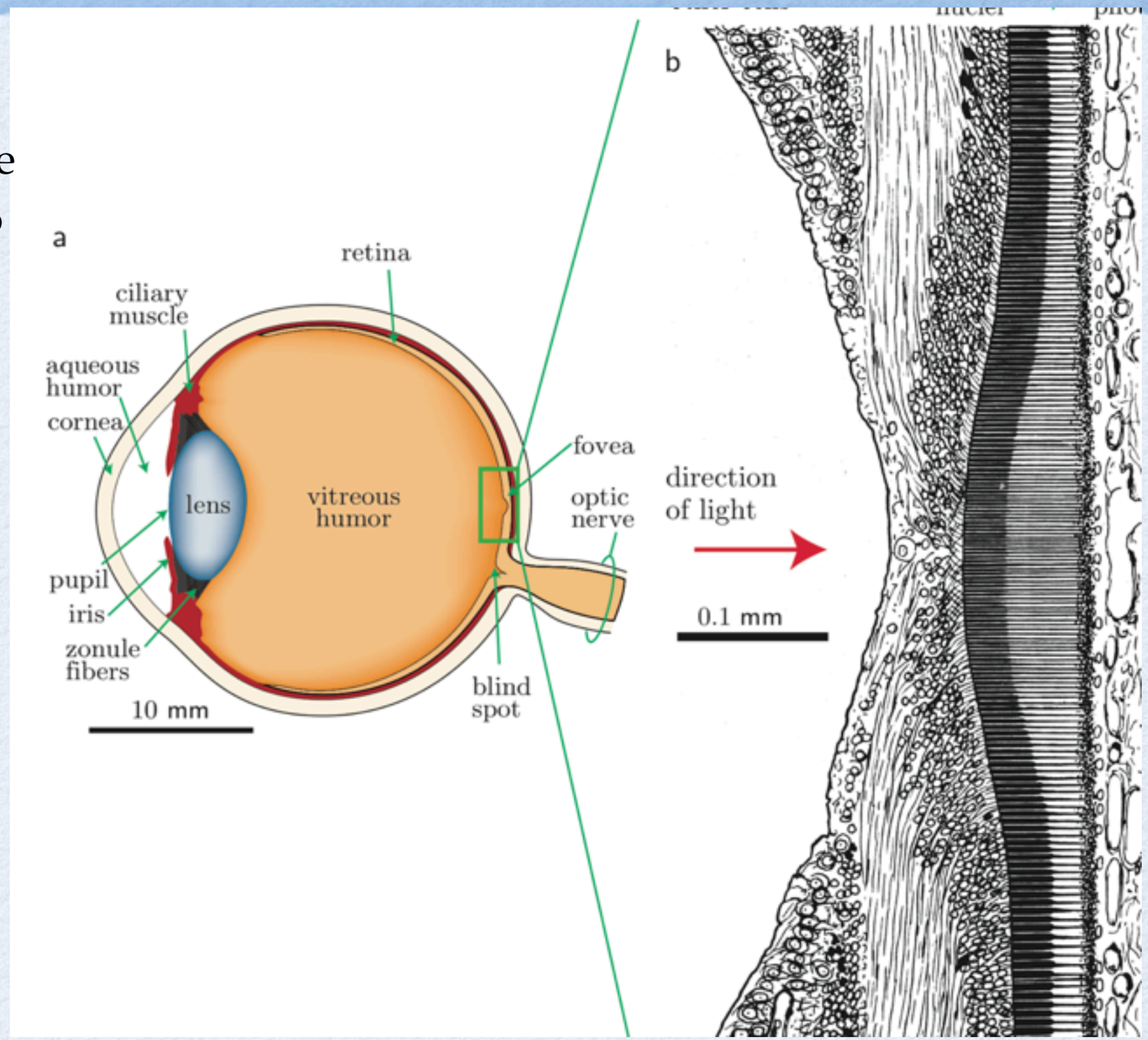
False sense of security



From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation).

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.

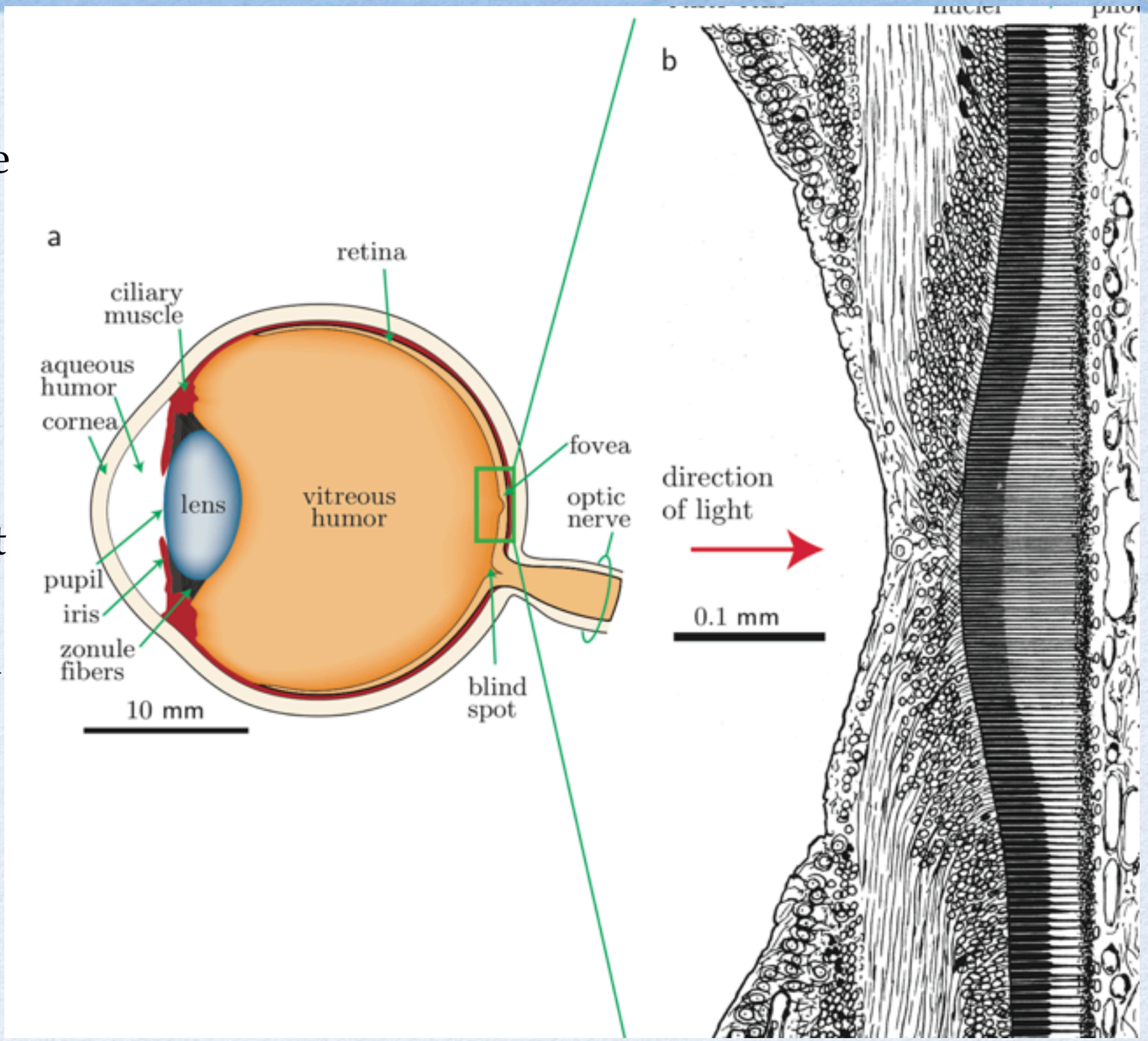


From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation).

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*.



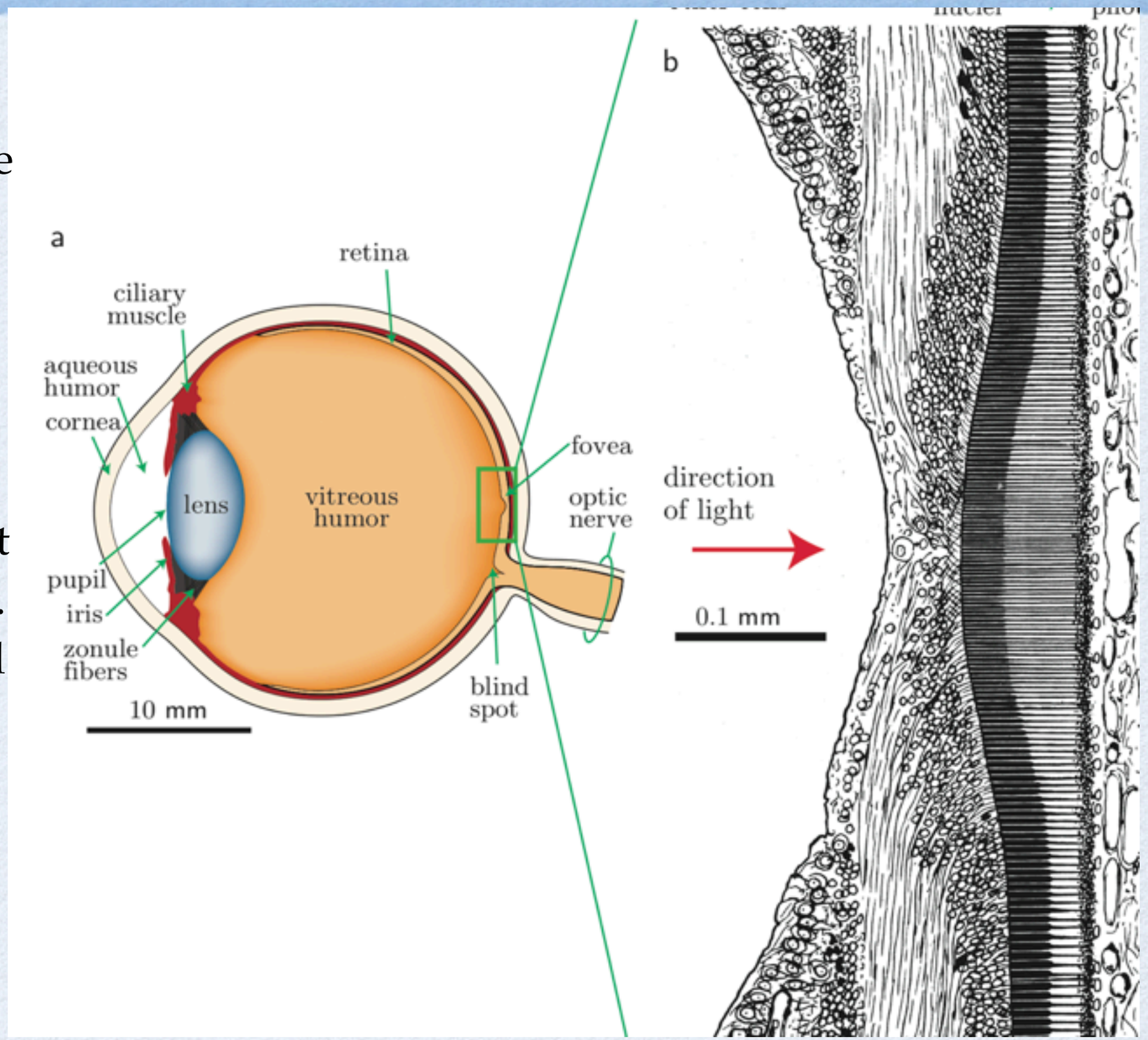
From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation).

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.

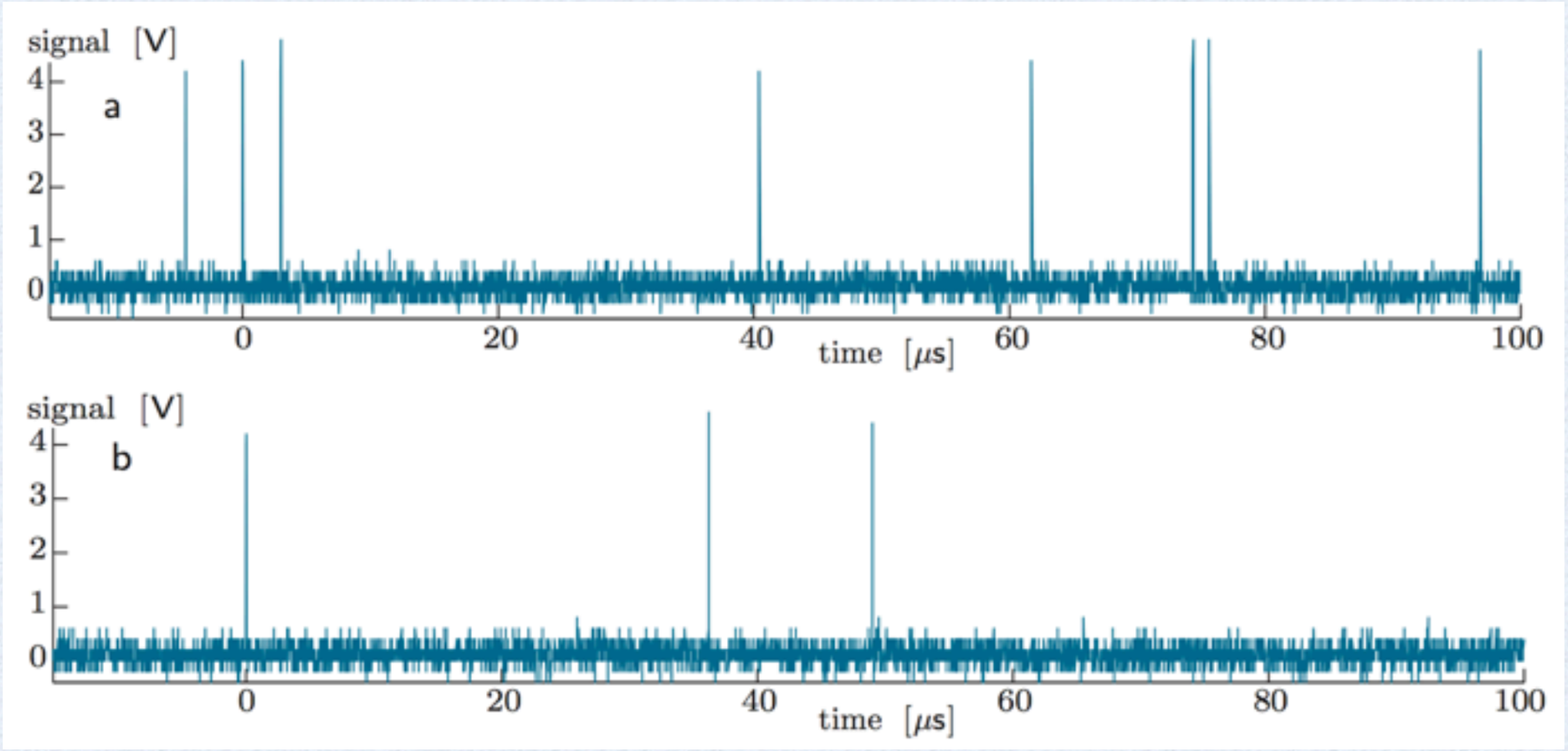


From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation).

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.

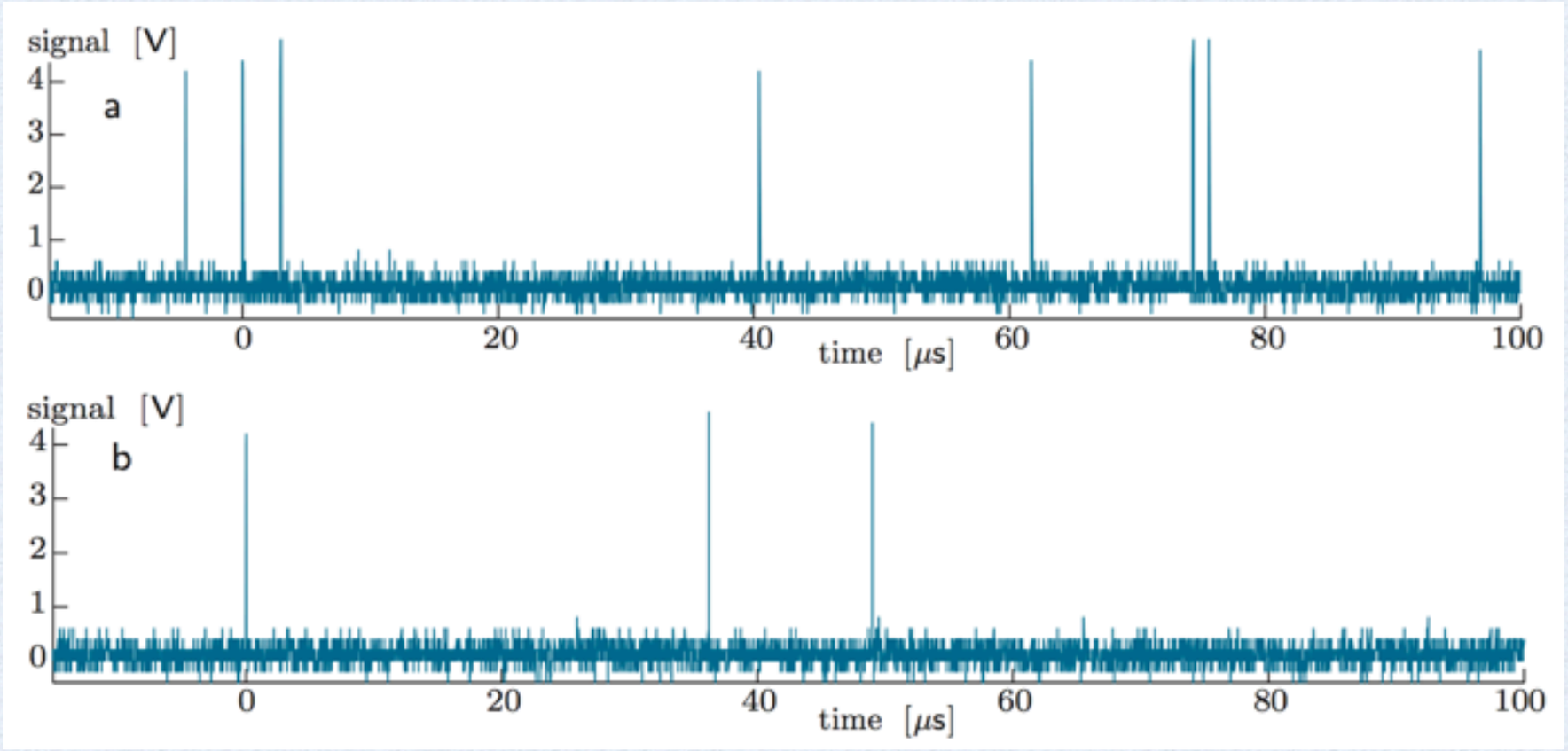
click for uniform clicks audio *click for shot noise*

From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation).

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.

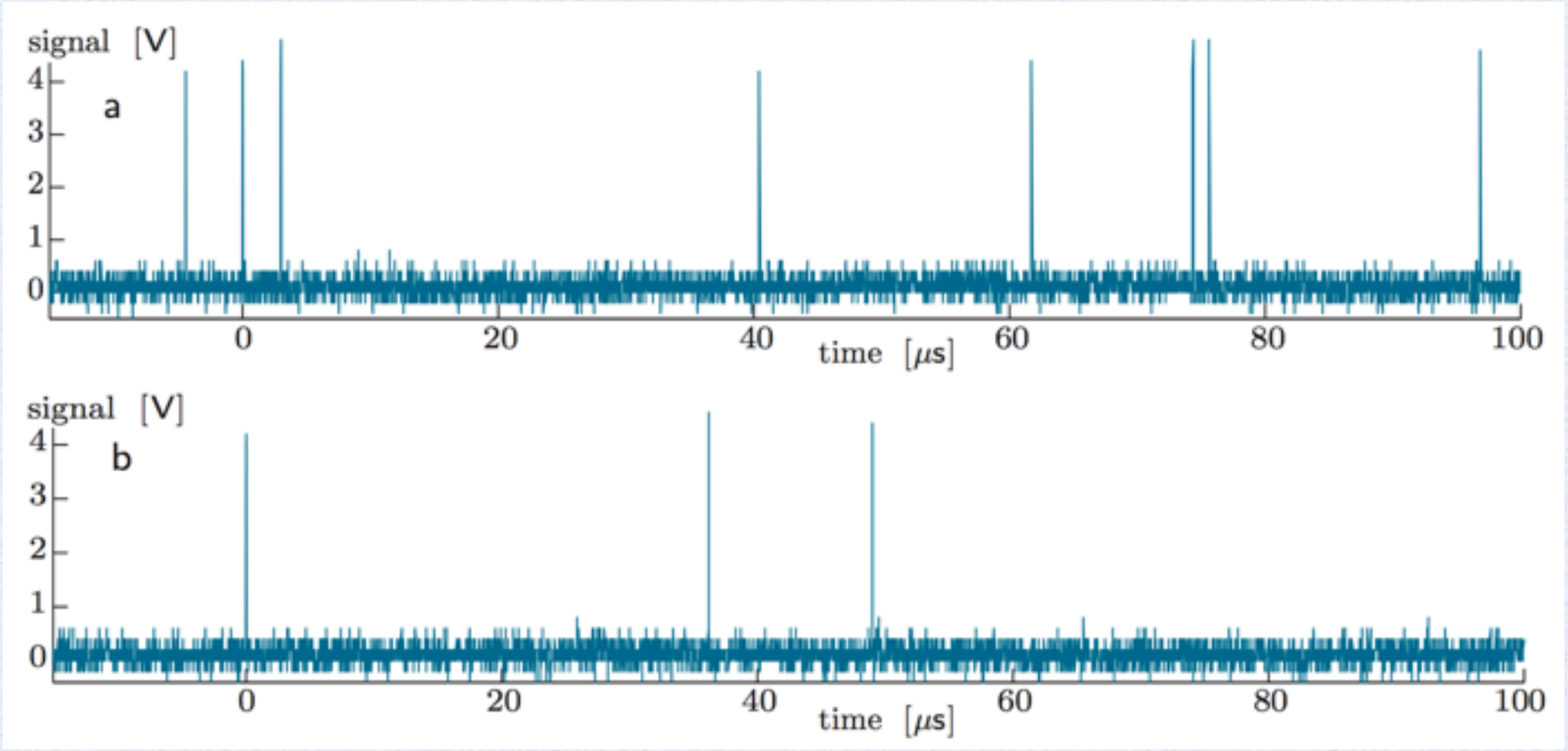
click for uniform clicks audio *click for shot noise*

From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation).

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.

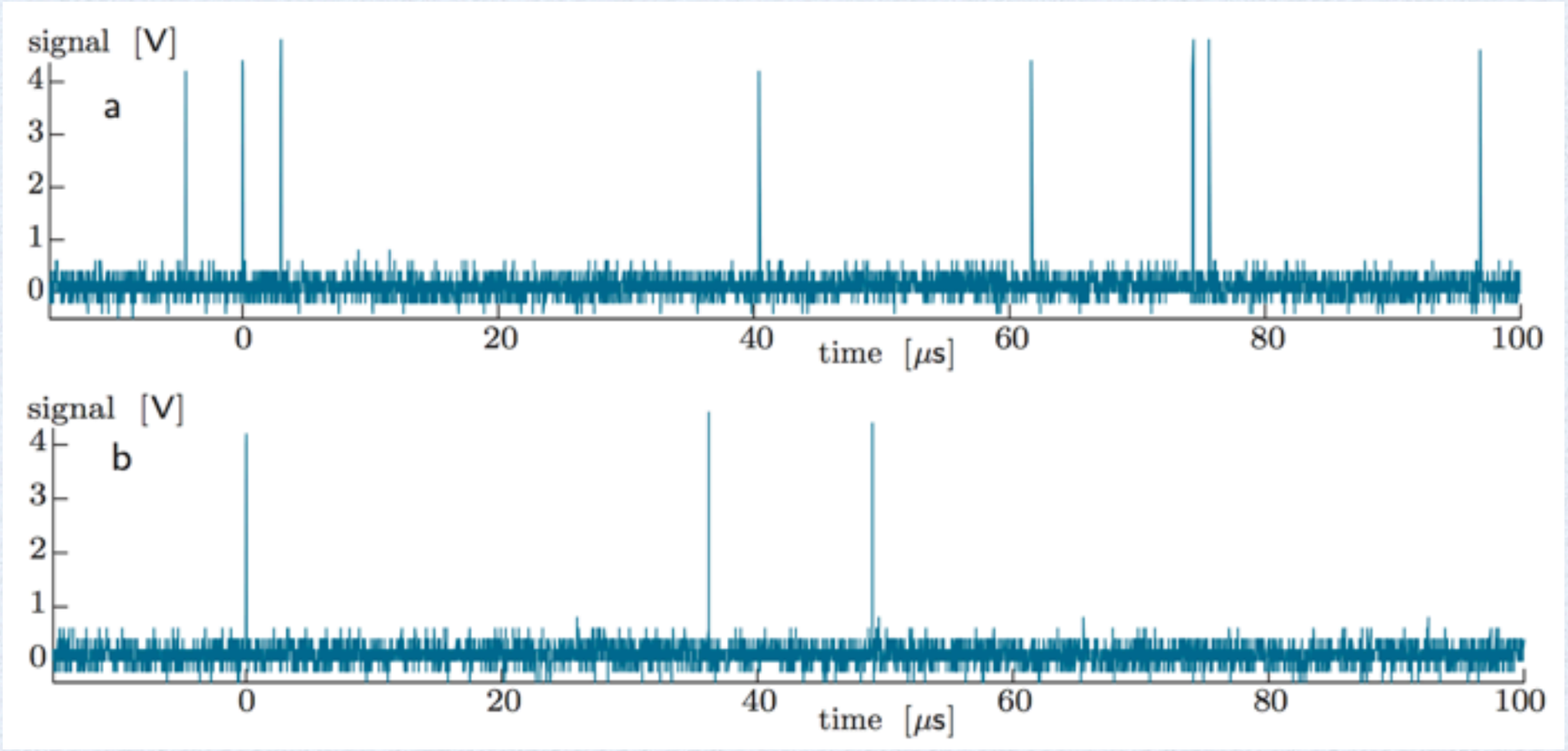
click for uniform clicks audio *click for shot noise*

From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation).

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.*



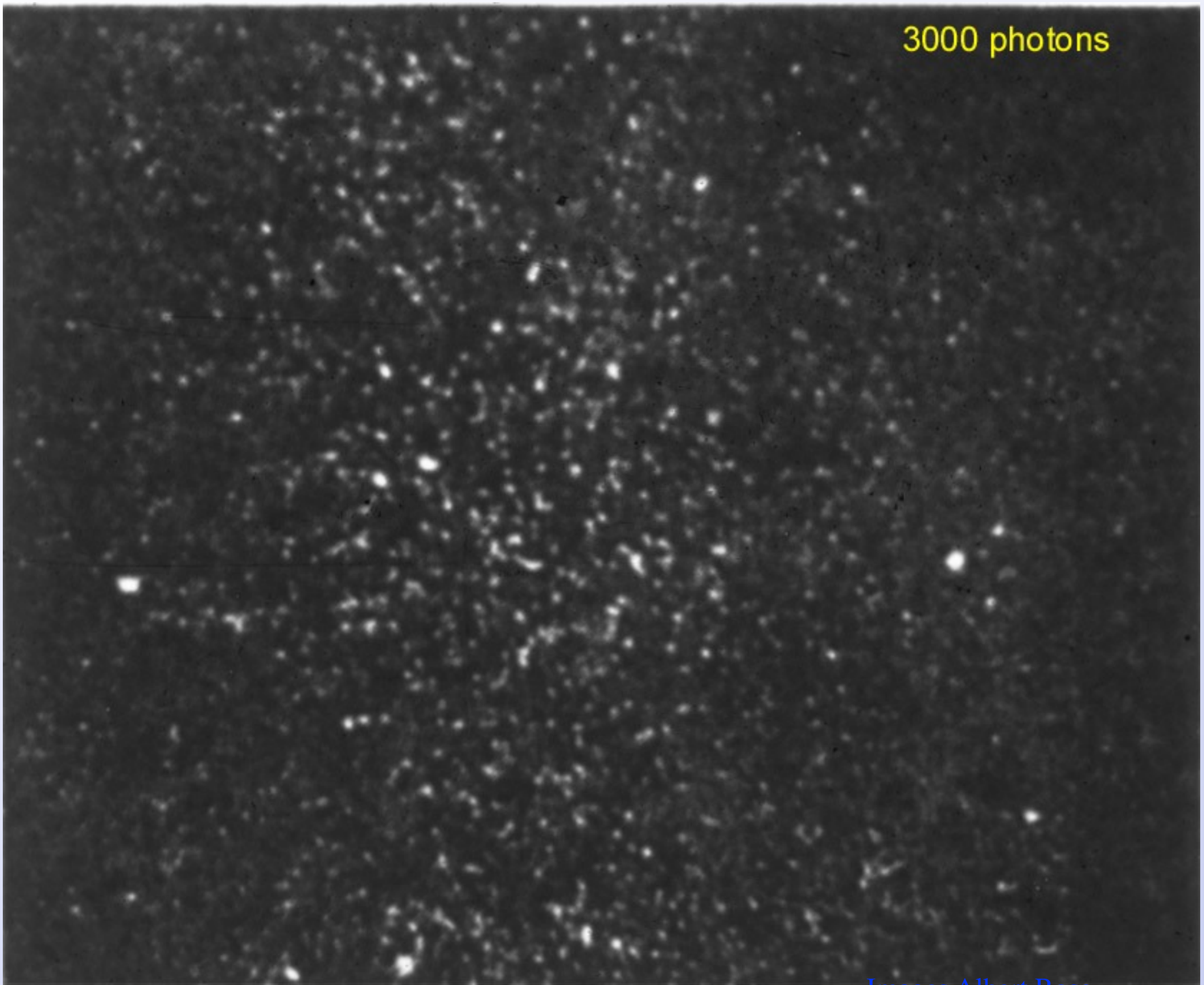
These are *not* uniformly spaced blips. Instead the clicks are *as random as possible* -- they are a "Poisson process." Something about light is intrinsically random.

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.

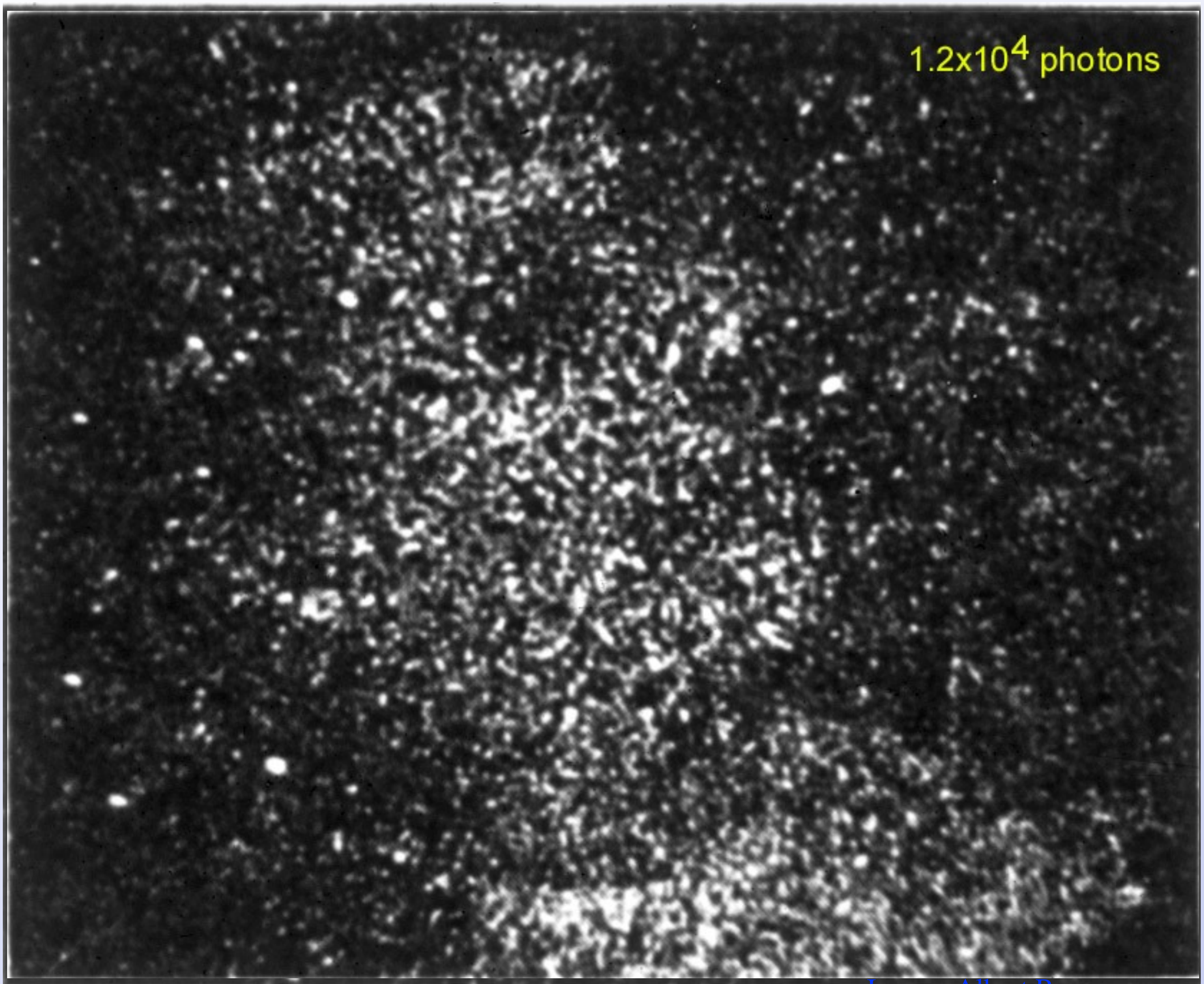
From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation).

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



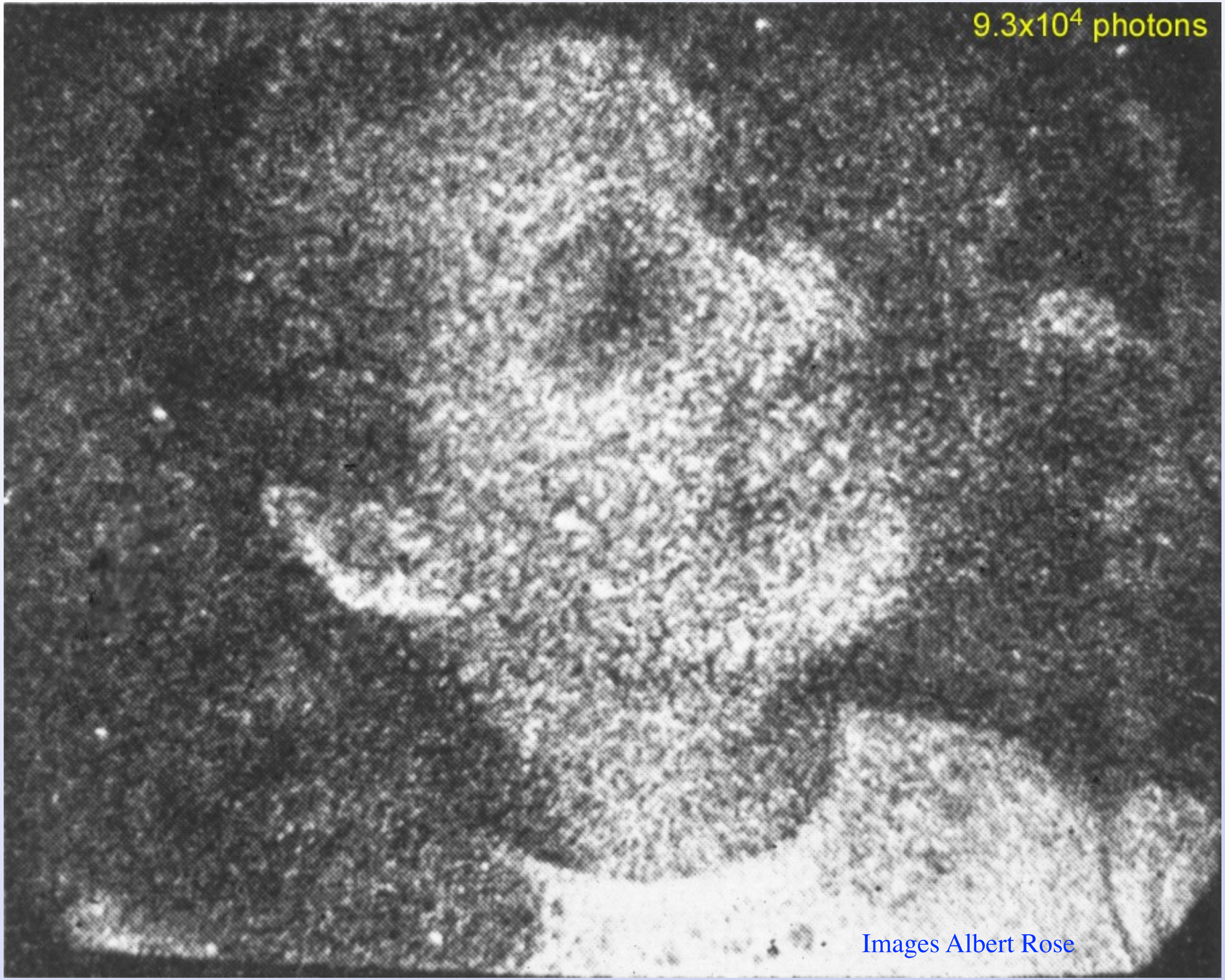
Images Albert Rose

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



Images Albert Rose

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



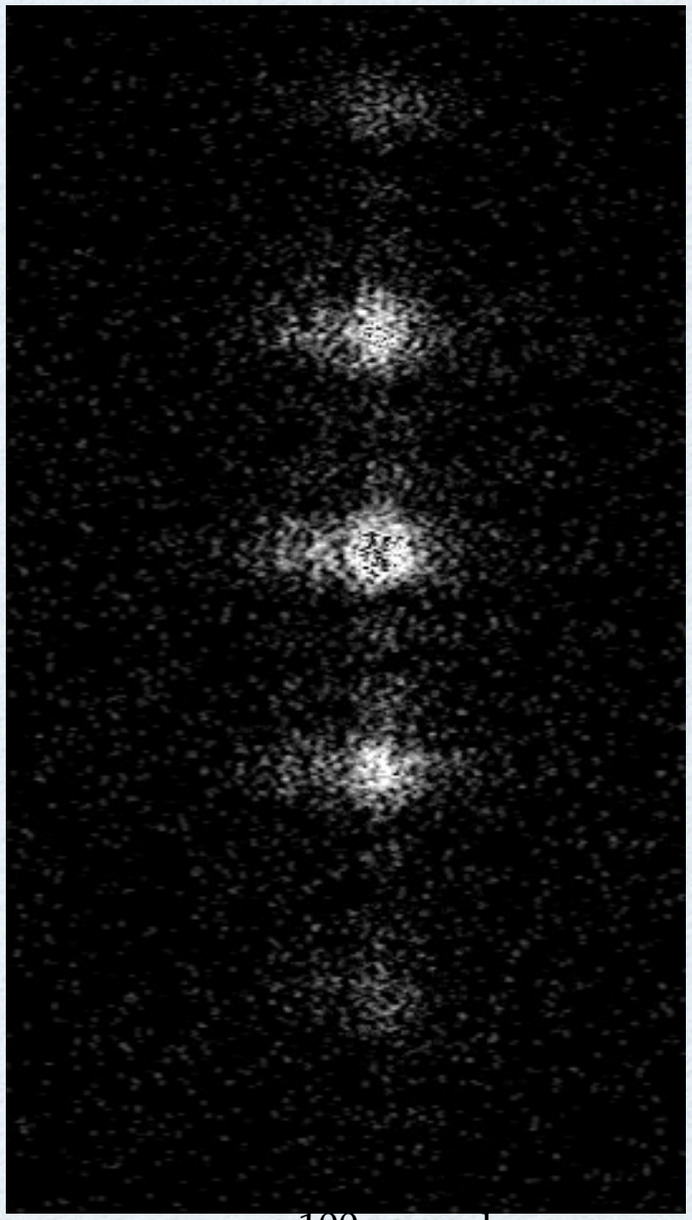
Both digital and film cameras also expose one pixel at a time, at random:

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

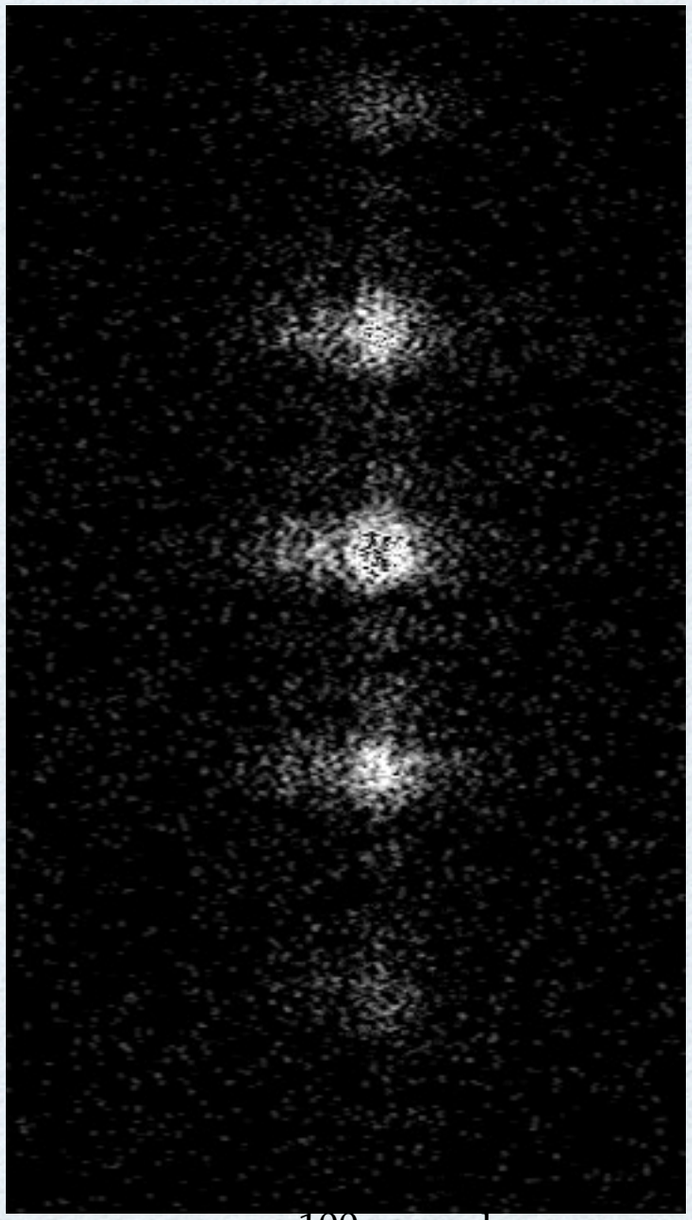


100 seconds

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 *lump*s -- the "photon hypothesis."

Plan

1. Indoctrination
2. Light
3. Vision
4. And now a word from our sponsor
5. Wrap

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 me?"

Image Edith Widder

[Aside]


NEXT WE'LL NEED TO ATTACH THOSE INPUT AND OUTPUT STRINGS AND A GROUNDING STRING.
WHY A GROUNDING STRING?
IT'S LIKE A LIGHTNING ROD FOR BRAINSTORMS ..I WANT TO KEEP MY IDEAS GROUNDED IN REALITY.

[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 finding a naive/irrelevant application for it.

[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 finding a naive/irrelevant application for it.

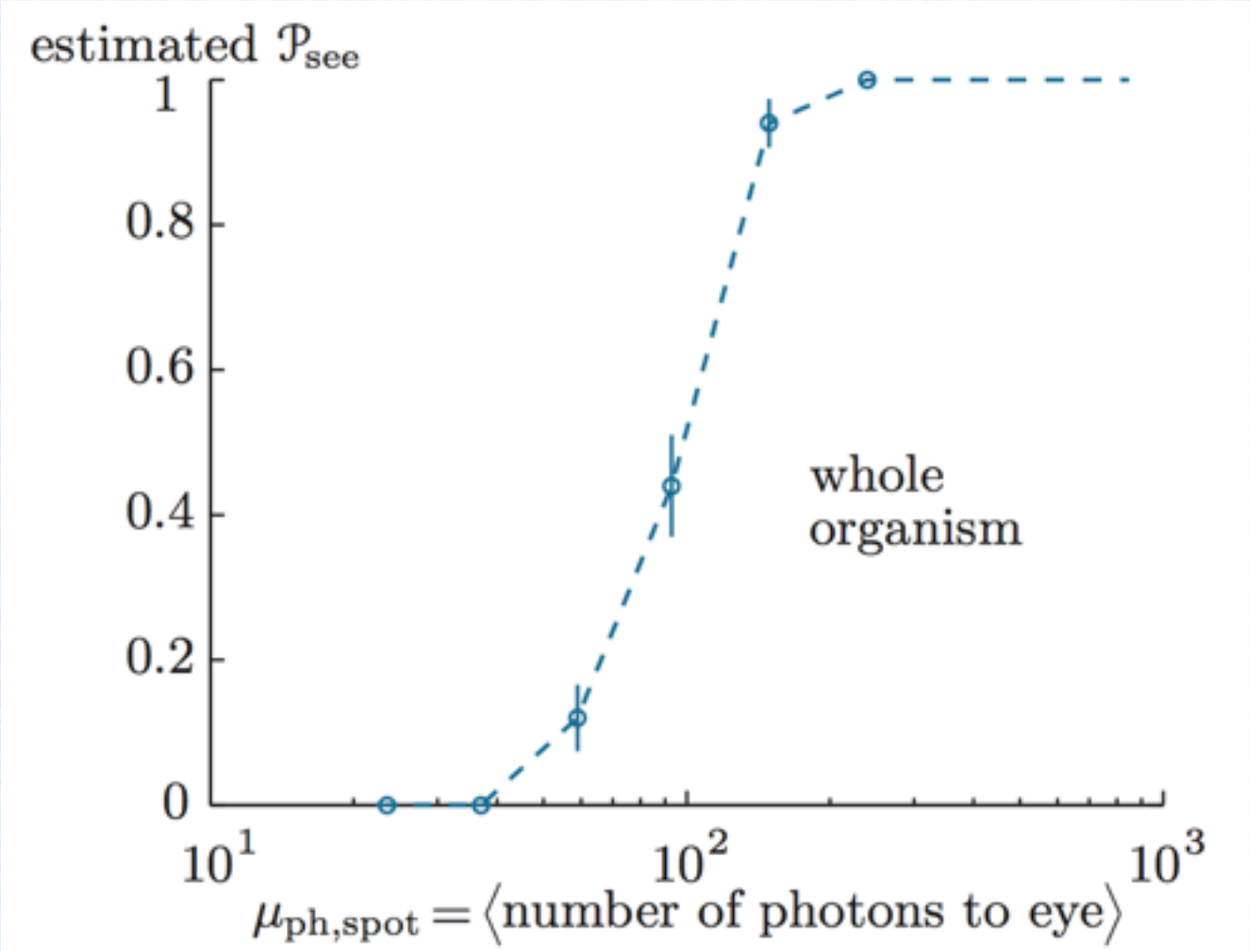
But on the contrary: If your competitor/threatening predator/prey has better night vision than you, that could be a problem. That's the mother of invention, big time. If there's a fundamental limit to vision, you need to *be there*.

[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 finding a naive/irrelevant application for it.

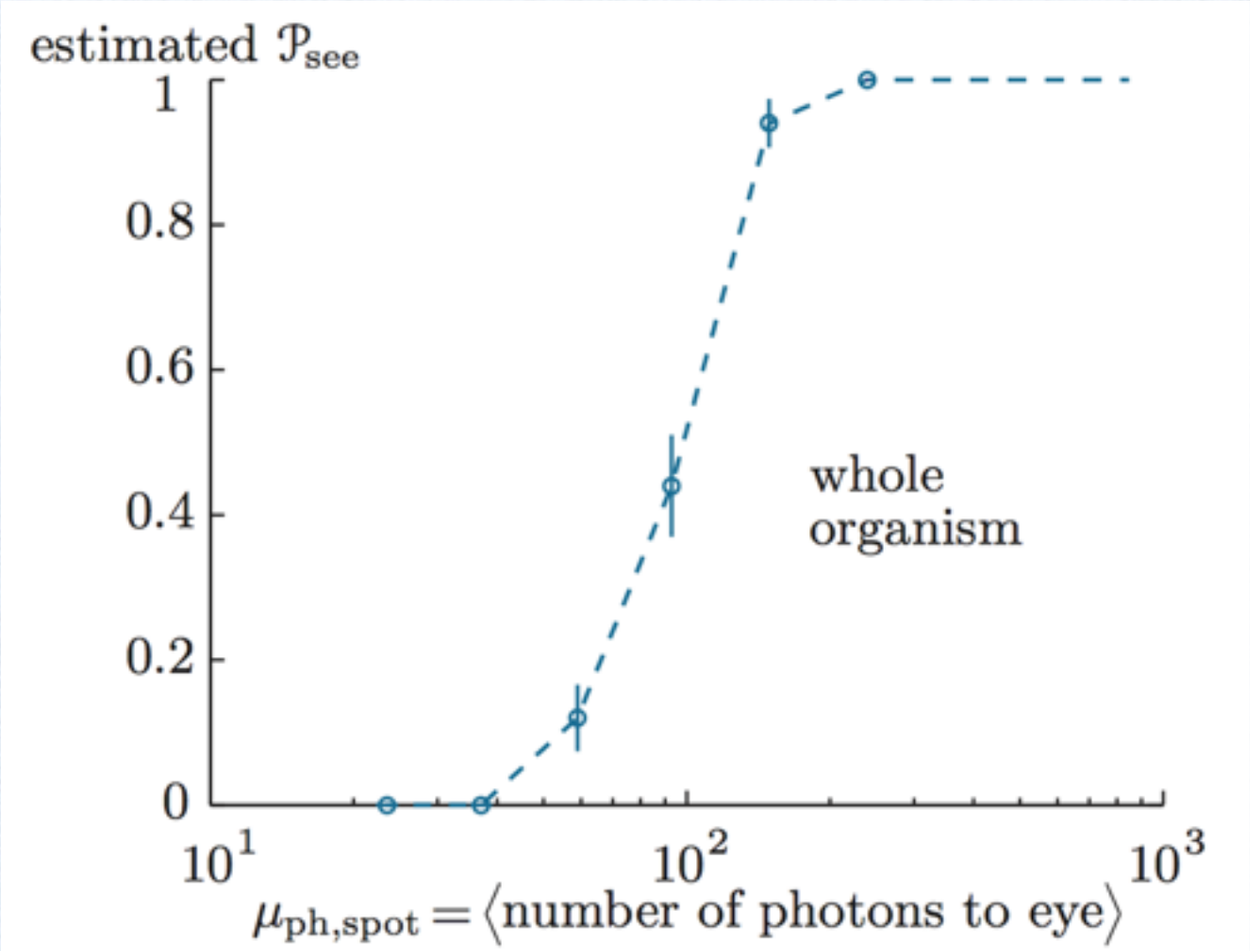
But on the contrary: If your competitor/threatening predator/prey has better night vision than you, that could be a problem. That's the mother of invention, big time. If there's a fundamental limit to vision, you need to *be there*.

The old news



From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation).

The old news



Hecht et al measured the probability for a human subject to see a flash, vs intensity. They found that, at the lowest detectable flash intensities, seeing is *probabilistic*, with a probability that follows a sigmoidal curve. What can we conclude?

From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation).

Sometimes simple is too simple

Sometimes simple is too simple

One often hears the takehome from that experiment expressed as “Our remarkable eyes can detect a single photon.” Unfortunately that won’t do:

Sometimes simple is too simple

One often hears the takehome from that experiment expressed as "Our remarkable eyes can detect a single photon." Unfortunately that won't do:

- Hecht data on previous slide shows that, for reliable seeing, we need to present about ***100*** photons to the eye–not ***1***. Why that number?

Sometimes simple is too simple

One often hears the takehome from that experiment expressed as "Our remarkable eyes can detect a single photon." Unfortunately that won't do:

- Hecht data on previous slide shows that, for reliable seeing, we need to present about ***100*** photons to the eye–not ***1***. Why that number?
- Quantum theory tells us that no laser, no filament, not shutter placed in front of the Sun, can deliver exactly 100, or any other exact number of photons–you always get a Poisson-distributed random variable.

Sometimes simple is too simple

One often hears the takehome from that experiment expressed as "Our remarkable eyes can detect a single photon." Unfortunately that won't do:

- Hecht data on previous slide shows that, for reliable seeing, we need to present about ***100*** photons to the eye–not ***1***. Why that number?
- Quantum theory tells us that no laser, no filament, not shutter placed in front of the Sun, can deliver exactly 100, or any other exact number of photons–you always get a Poisson-distributed random variable.

So yes, our eyes are remarkable, but what's the precise statement of *how* remarkable? Only when we've got that can we start to discard some hypotheses about what's going on and retain others.

More about dim light vision

From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation). Data Barbara Sakitt (1972).

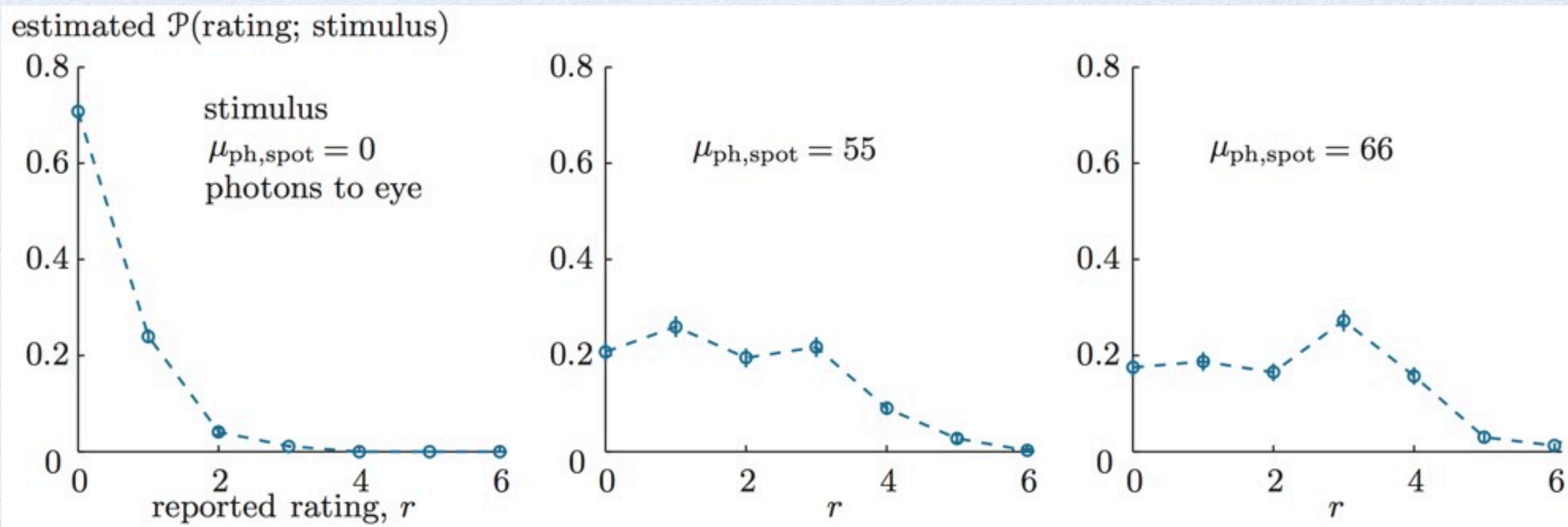
More about dim light vision

Actually, Hecht's model omitted something huge--the role of spontaneous isomerizations. Barlow proposed that fake photon signals, indistinguishable from the real thing, are folded into each rod cell's output at some fixed rate. Sakitt then performed a better psychophysics experiment than Hecht's: She measured *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:

From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation). Data Barbara Sakitt (1972).

More about dim light vision

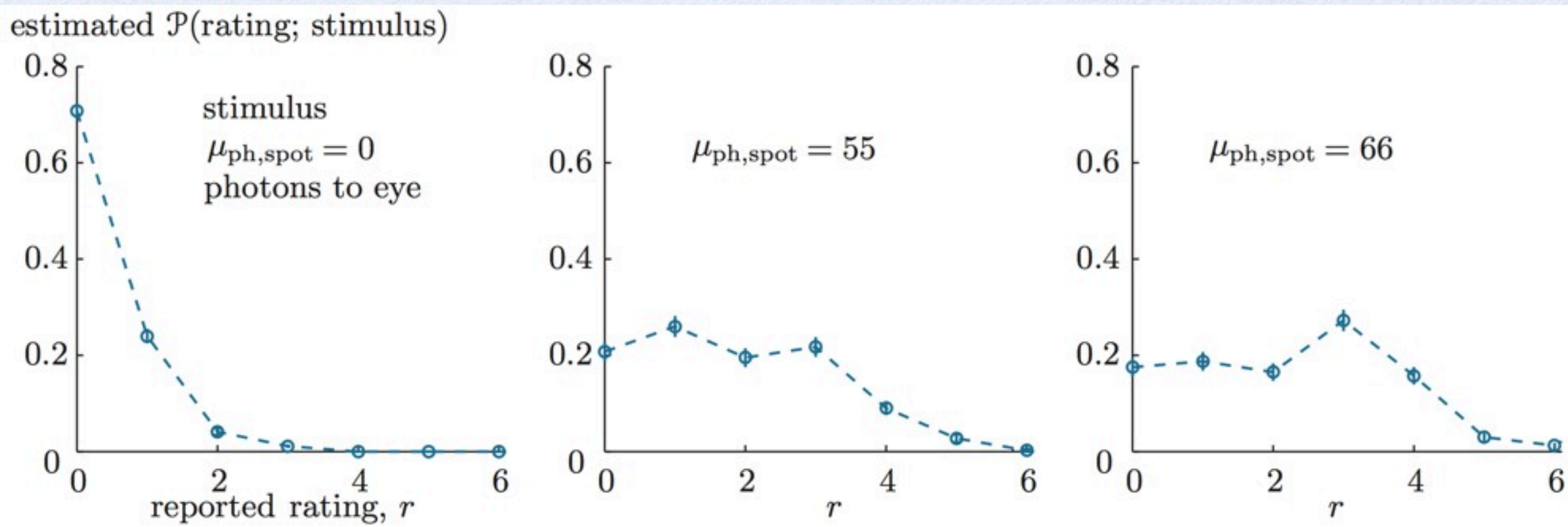
Actually, Hecht's model omitted something huge--the role of spontaneous isomerizations. Barlow proposed that fake photon signals, indistinguishable from the real thing, are folded into each rod cell's output at some fixed rate. Sakitt then performed a better psychophysics experiment than Hecht's: She measured *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:



From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation). Data Barbara Sakitt (1972).

More about dim light vision

Actually, Hecht's model omitted something huge--the role of spontaneous isomerizations. Barlow proposed that fake photon signals, indistinguishable from the real thing, are folded into each rod cell's output at some fixed rate. Sakitt then performed a better psychophysics experiment than Hecht's: She measured *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:



So great–all we need is to find a model that fits these data, right? Unfortunately these data greatly underdetermine the model (Fred Rieke). We need to get closer to the first step of transduction.

From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation). Data Barbara Sakitt (1972).

Onward to single cells

An individual rod or cone cell's response can be measured by gently aspirating its outer segment into a pipette electrode and stimulating it with 500 nm light (*green streak*).

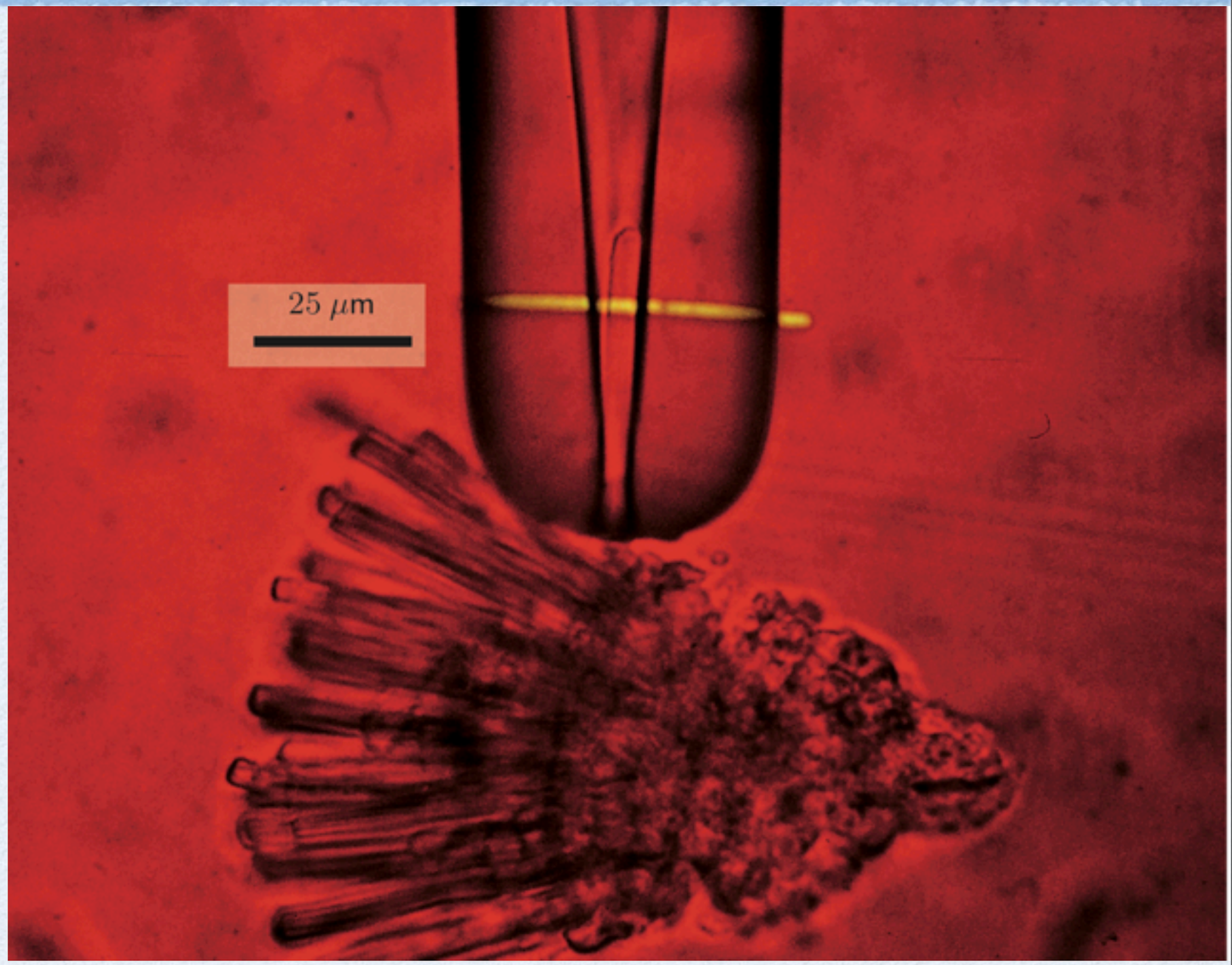
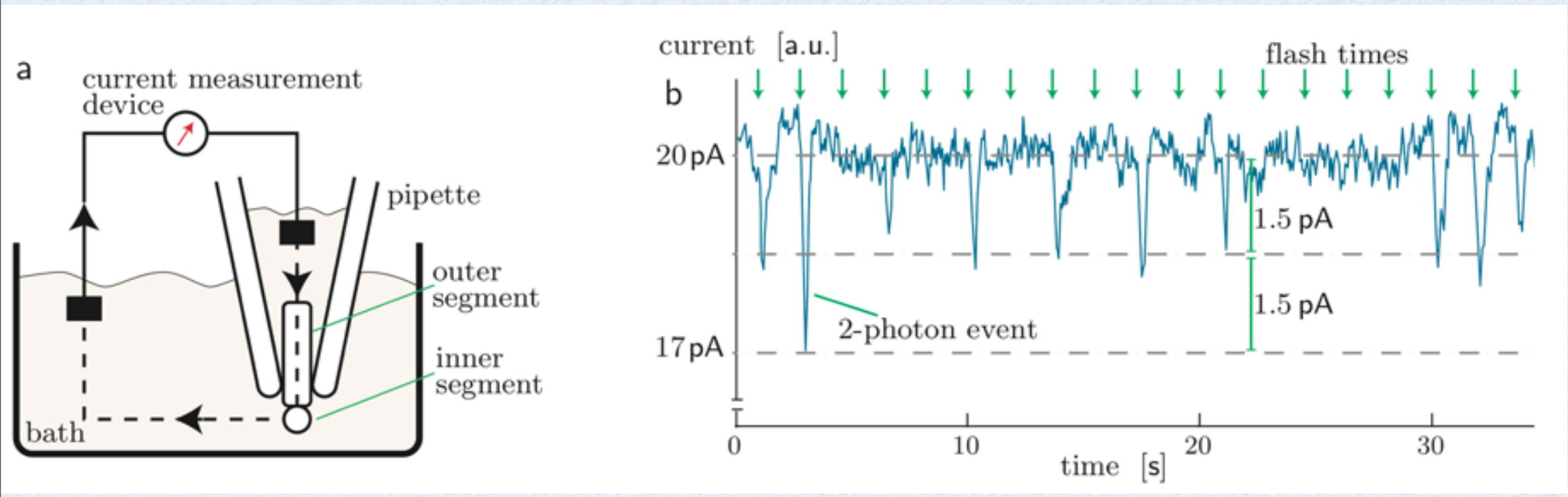


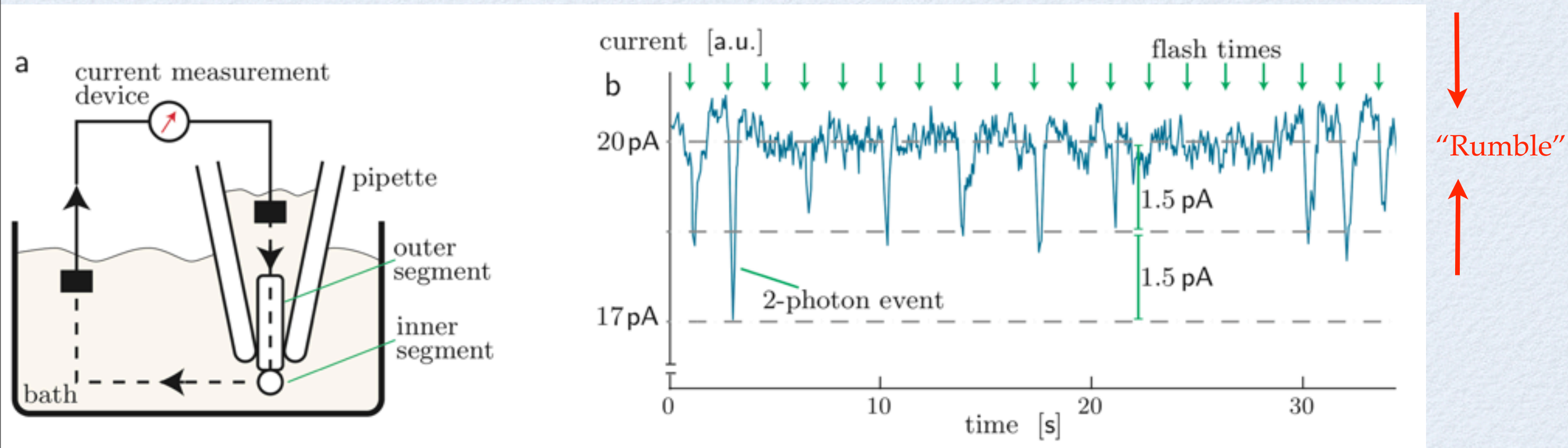
Image courtesy K-W Yau (1979).

Single-cell data



From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation). Data courtesy Greg Field (2008).

Single-cell data



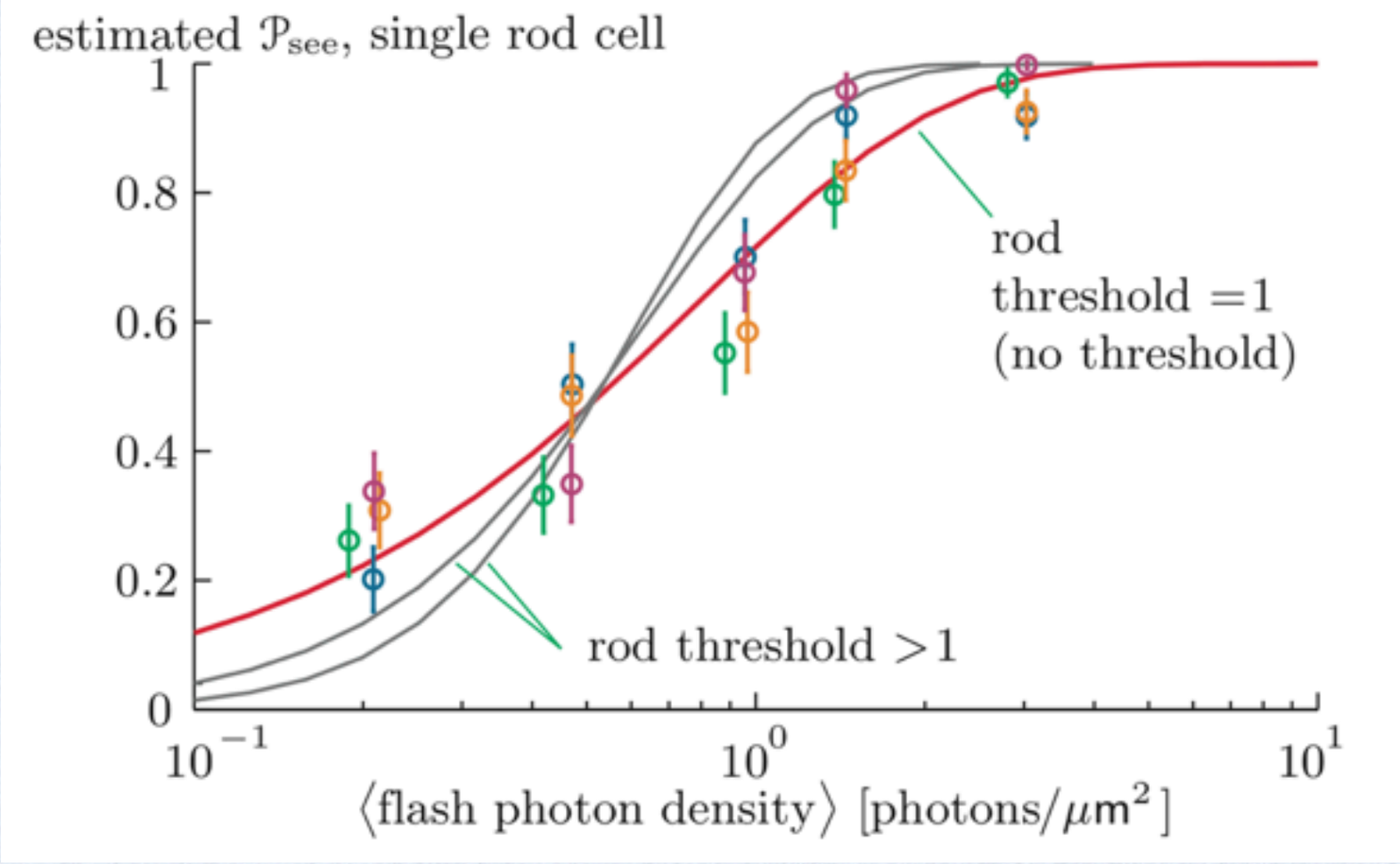
From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation). Data courtesy Greg Field (2008).

Now that's Q-bio

Baylor et al. found the probability of "seeing" curve for single rods. They knew the density of rhodopsin, its absorption cross-section, the rod cell dimensions. So from this data they obtained a meaningful (if partial) characterization of how good our visual apparatus is:

- *Most photon absorptions by rhodopsin are productive.*
- *A single productive absorption suffices to trigger a discrete signal.*
- *The false positive rate, though not zero, is small.*

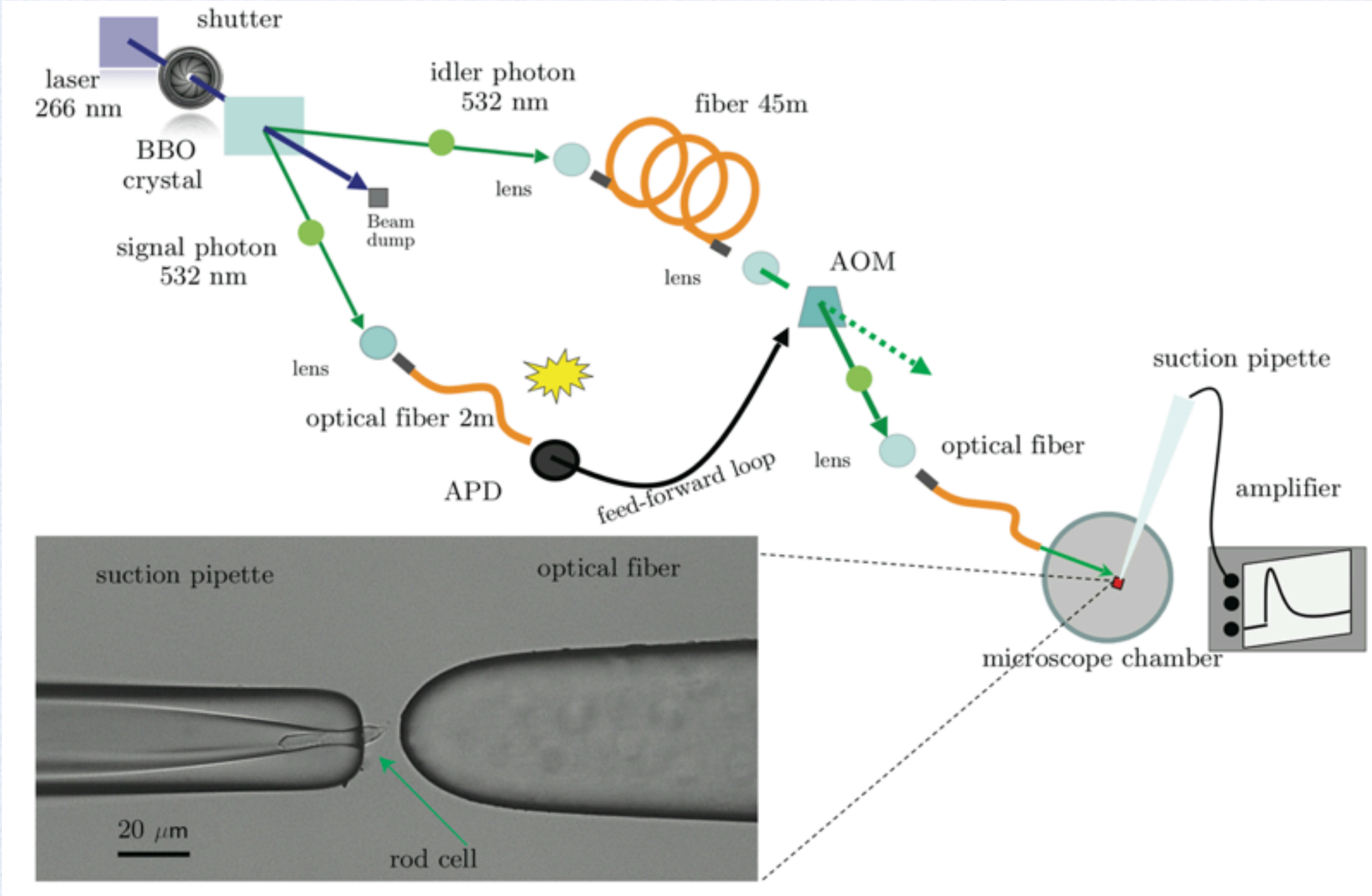
It's a great example of indirect reasoning:
There's no way to fit it to a model in which individual rods have a threshold of >1 photon for response, *even though there was no way to say how many photons were in any given flash.*



From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation). Data from Baylor, Lamb, Yau (1979).

Now that's P-bio

Very recently, high-tech experiments confirmed that conclusion directly:



Phan, Krichevskiy, et al PRL 2014.

A Q-bio challenge

OK. Now we have a handle on how remarkable rod cells are. But there's a long way to go between rod cells and verbal reports!

A Q-bio challenge

OK. Now we have a handle on how remarkable rod cells are. But there's a long way to go between rod cells and verbal reports!

I've outlined two very different approaches: Psychophysics collects verbal reports. Single-cell physiology just examines the earliest steps of transduction. There's a *lot* of processing in between those levels! Should we even attempt any synthesis that embraces them both?

A Q-bio challenge

OK. Now we have a handle on how remarkable rod cells are. But there's a long way to go between rod cells and verbal reports!

I've outlined two very different approaches: Psychophysics collects verbal reports. Single-cell physiology just examines the earliest steps of transduction. There's a *lot* of processing in between those levels! Should we even attempt any synthesis that embraces them both?

Well, it is definitely a challenge:

A Q-bio challenge

OK. Now we have a handle on how remarkable rod cells are. But there's a long way to go between rod cells and verbal reports!

I've outlined two very different approaches: Psychophysics collects verbal reports. Single-cell physiology just examines the earliest steps of transduction. There's a *lot* of processing in between those levels! Should we even attempt any synthesis that embraces them both?

Well, it is definitely a challenge:

- Single-cell physiology sets a *lower* bound on the visual system's loss and randomness.

A Q-bio challenge

OK. Now we have a handle on how remarkable rod cells are. But there's a long way to go between rod cells and verbal reports!

I've outlined two very different approaches: Psychophysics collects verbal reports. Single-cell physiology just examines the earliest steps of transduction. There's a *lot* of processing in between those levels! Should we even attempt any synthesis that embraces them both?

Well, it is definitely a challenge:

- Single-cell physiology sets a *lower* bound on the visual system's loss and randomness.
- The incredibly good dim-light vision of an entire animal sets an *upper* bound.

A Q-bio challenge

OK. Now we have a handle on how remarkable rod cells are. But there's a long way to go between rod cells and verbal reports!

I've outlined two very different approaches: Psychophysics collects verbal reports. Single-cell physiology just examines the earliest steps of transduction. There's a *lot* of processing in between those levels! Should we even attempt any synthesis that embraces them both?

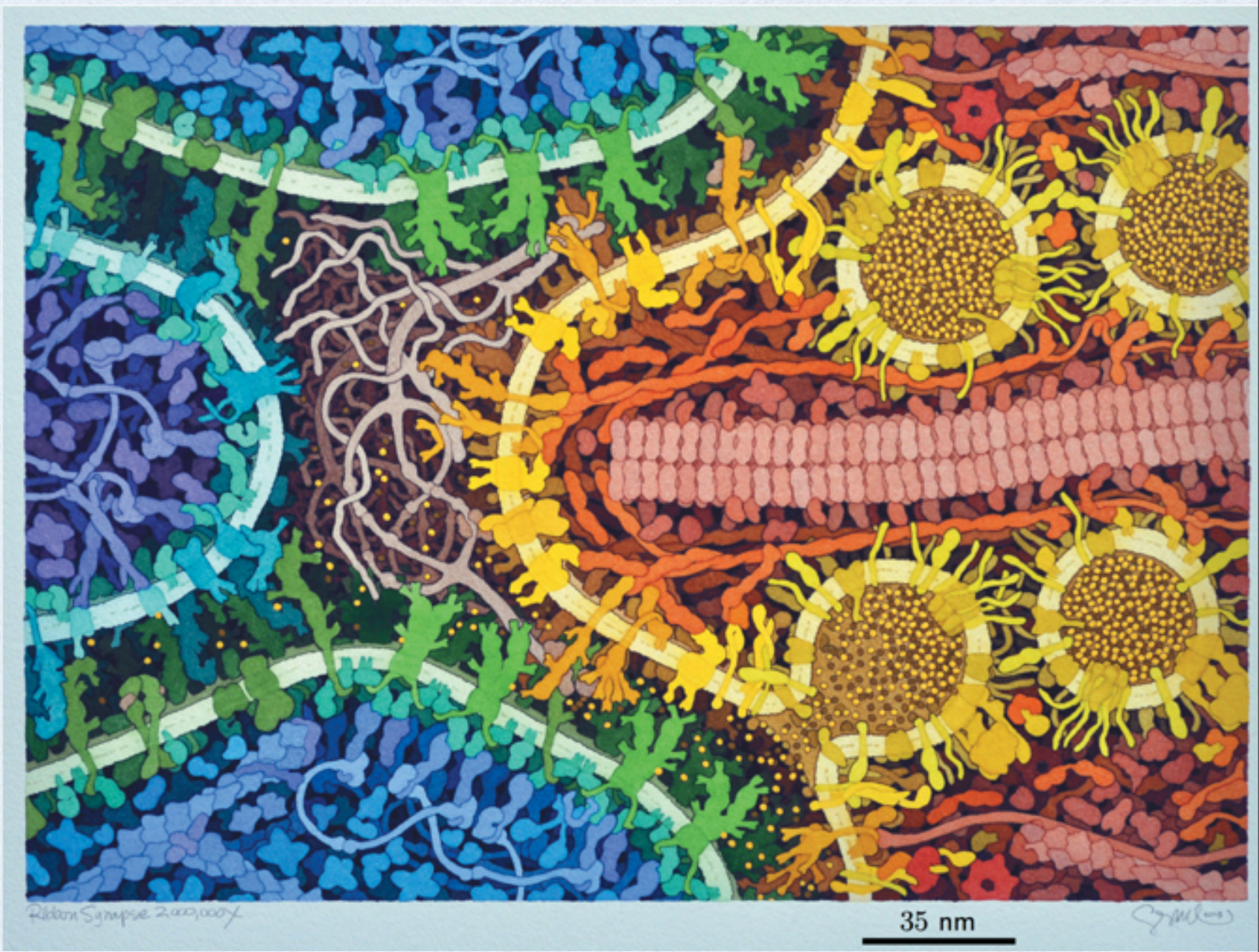
Well, it is definitely a challenge:

- Single-cell physiology sets a *lower* bound on the visual system's loss and randomness.
- The incredibly good dim-light vision of an entire animal sets an *upper* bound.

Is there any room between these bounds, and if so, how much? Even if our model of the intermediate processing is naive, finding one model that works would establish a baseline for others.

The first synapse

Baylor et al also had a prescient insight: The very first synapse must discard some genuine photon signals. That's a great example of being *way ahead of your time* by using Q-bio: Indeed, recent work pegs that loss at 50%? That thresholding eliminates nearly all the "rumble" noise, mostly spontaneous activation of phosphodiesterase.



From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation). Painting by David Goodsell.

Beyond the first synapse

Even after dealing with the subthreshold "rumble," there are still some false-positives, due to thermal isomerization, that are totally indistinguishable from real photon-induced isomerizations. Barlow realized that (a) some later stage of processing must enforce a threshold before alerting the conscious mind, and (b) that threshold may be programmable based on training, and (c) human subjects may even be able to implement *multiple* such thresholds. Let's try a model:

Beyond the first synapse

Even after dealing with the subthreshold "rumble," there are still some false-positives, due to thermal isomerization, that are totally indistinguishable from real photon-induced isomerizations. Barlow realized that (a) some later stage of processing must enforce a threshold before alerting the conscious mind, and (b) that threshold may be programmable based on training, and (c) human subjects may even be able to implement *multiple* such thresholds. Let's try a model:

- Each rod cell has a measured quantum catch and a measured rate of generating false positives.

Those numbers are *not fit parameters*.

Beyond the first synapse

Even after dealing with the subthreshold "rumble," there are still some false-positives, due to thermal isomerization, that are totally indistinguishable from real photon-induced isomerizations. Barlow realized that (a) some later stage of processing must enforce a threshold before alerting the conscious mind, and (b) that threshold may be programmable based on training, and (c) human subjects may even be able to implement *multiple* such thresholds. Let's try a model:

- Each rod cell has a measured quantum catch and a measured rate of generating false positives. Those numbers are *not fit parameters*.
- Each rod cell imposes no "quorum" (minimal number of catches before signaling).

Beyond the first synapse

Even after dealing with the subthreshold "rumble," there are still some false-positives, due to thermal isomerization, that are totally indistinguishable from real photon-induced isomerizations. Barlow realized that (a) some later stage of processing must enforce a threshold before alerting the conscious mind, and (b) that threshold may be programmable based on training, and (c) human subjects may even be able to implement *multiple* such thresholds. Let's try a model:

- Each rod cell has a measured quantum catch and a measured rate of generating false positives. Those numbers are *not fit parameters*.
- Each rod cell imposes no "quorum" (minimal number of catches before signaling).
- About half of all rod signals are lost at the first synapse. Again: *not a fit parameter.*

Beyond the first synapse

Even after dealing with the subthreshold "rumble," there are still some false-positives, due to thermal isomerization, that are totally indistinguishable from real photon-induced isomerizations. Barlow realized that (a) some later stage of processing must enforce a threshold before alerting the conscious mind, and (b) that threshold may be programmable based on training, and (c) human subjects may even be able to implement *multiple* such thresholds. Let's try a model:

- Each rod cell has a measured quantum catch and a measured rate of generating false positives. Those numbers are *not fit parameters*.
- Each rod cell imposes no "quorum" (minimal number of catches before signaling).
- About half of all rod signals are lost at the first synapse. Again: *not a fit parameter.*
- Thus, the total number of rod signals follows a *known Poisson distribution* determined by the flash strength.

Beyond the first synapse

Even after dealing with the subthreshold "rumble," there are still some false-positives, due to thermal isomerization, that are totally indistinguishable from real photon-induced isomerizations. Barlow realized that (a) some later stage of processing must enforce a threshold before alerting the conscious mind, and (b) that threshold may be programmable based on training, and (c) human subjects may even be able to implement *multiple* such thresholds. Let's try a model:

- Each rod cell has a measured quantum catch and a measured rate of generating false positives. Those numbers are *not fit parameters*.
- Each rod cell imposes no "quorum" (minimal number of catches before signaling).
- About half of all rod signals are lost at the first synapse. Again: *not a fit parameter.*
- Thus, the total number of rod signals follows a *known Poisson distribution* determined by the flash strength.
- Barlow's model assumes that later processing effectively pools (sums) the signals (both real and false) from a few thousand rods over about 200ms. *Not fit parameters.*

Beyond the first synapse

Even after dealing with the subthreshold "rumble," there are still some false-positives, due to thermal isomerization, that are totally indistinguishable from real photon-induced isomerizations. Barlow realized that (a) some later stage of processing must enforce a threshold before alerting the conscious mind, and (b) that threshold may be programmable based on training, and (c) human subjects may even be able to implement *multiple* such thresholds. Let's try a model:

- Each rod cell has a measured quantum catch and a measured rate of generating false positives. Those numbers are *not fit parameters*.
- Each rod cell imposes no "quorum" (minimal number of catches before signaling).
- About half of all rod signals are lost at the first synapse. Again: *not a fit parameter.*
- Thus, the total number of rod signals follows a *known Poisson distribution* determined by the flash strength.
- Barlow's model assumes that later processing effectively pools (sums) the signals (both real and false) from a few thousand rods over about 200ms. *Not fit parameters.*
- Sakitt proposed that later neural processing then applies a quorum requirement that must be met to report a rating of "1", and similarly for each other rating. The observer responds with the highest rating whose threshold has been met.

Beyond the first synapse

Even after dealing with the subthreshold "rumble," there are still some false-positives, due to thermal isomerization, that are totally indistinguishable from real photon-induced isomerizations. Barlow realized that (a) some later stage of processing must enforce a threshold before alerting the conscious mind, and (b) that threshold may be programmable based on training, and (c) human subjects may even be able to implement *multiple* such thresholds. Let's try a model:

- Each rod cell has a measured quantum catch and a measured rate of generating false positives. Those numbers are *not fit parameters*.
- Each rod cell imposes no "quorum" (minimal number of catches before signaling).
- About half of all rod signals are lost at the first synapse. Again: *not a fit parameter.*
- Thus, the total number of rod signals follows a *known Poisson distribution* determined by the flash strength.
- Barlow's model assumes that later processing effectively pools (sums) the signals (both real and false) from a few thousand rods over about 200ms. *Not fit parameters.*
- Sakitt proposed that later neural processing then applies a quorum requirement that must be met to report a rating of "1", and similarly for each other rating. The observer responds with the highest rating whose threshold has been met.

Is there any increasing sequence of four small integers (thresholds) that can fit the data (a function of two variables)?

Beyond the first synapse

Even after dealing with the subthreshold "rumble," there are still some false-positives, due to thermal isomerization, that are totally indistinguishable from real photon-induced isomerizations. Barlow realized that (a) some later stage of processing must enforce a threshold before alerting the conscious mind, and (b) that threshold may be programmable based on training, and (c) human subjects may even be able to implement *multiple* such thresholds. Let's try a model:

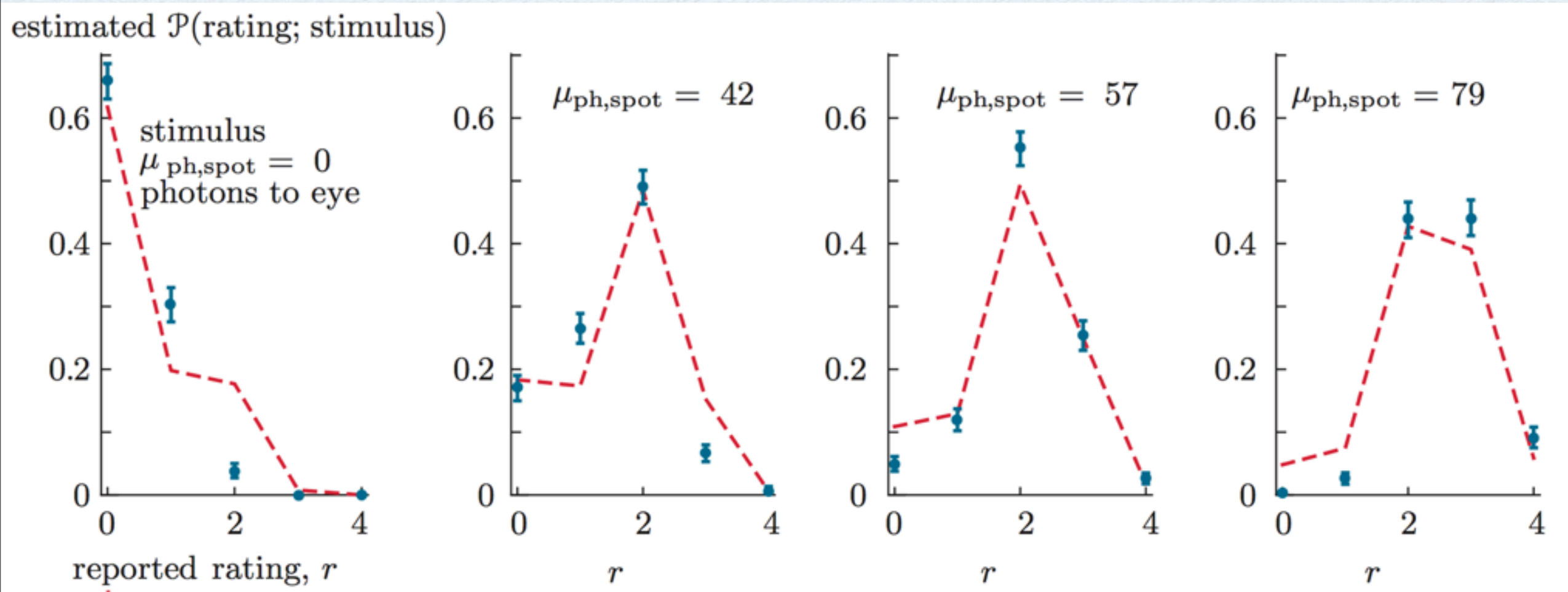
- Each rod cell has a measured quantum catch and a measured rate of generating false positives. Those numbers are *not fit parameters*.
- Each rod cell imposes no "quorum" (minimal number of catches before signaling).
- About half of all rod signals are lost at the first synapse. Again: *not a fit parameter.*
- Thus, the total number of rod signals follows a *known Poisson distribution* determined by the flash strength.
- Barlow's model assumes that later processing effectively pools (sums) the signals (both real and false) from a few thousand rods over about 200ms. *Not fit parameters.*
- Sakitt proposed that later neural processing then applies a quorum requirement that must be met to report a rating of "1", and similarly for each other rating. The observer responds with the highest rating whose threshold has been met.

Is there any increasing sequence of four small integers (thresholds) that can fit the data (a function of two variables)?
How low is the first of those thresholds?

Well, yes.

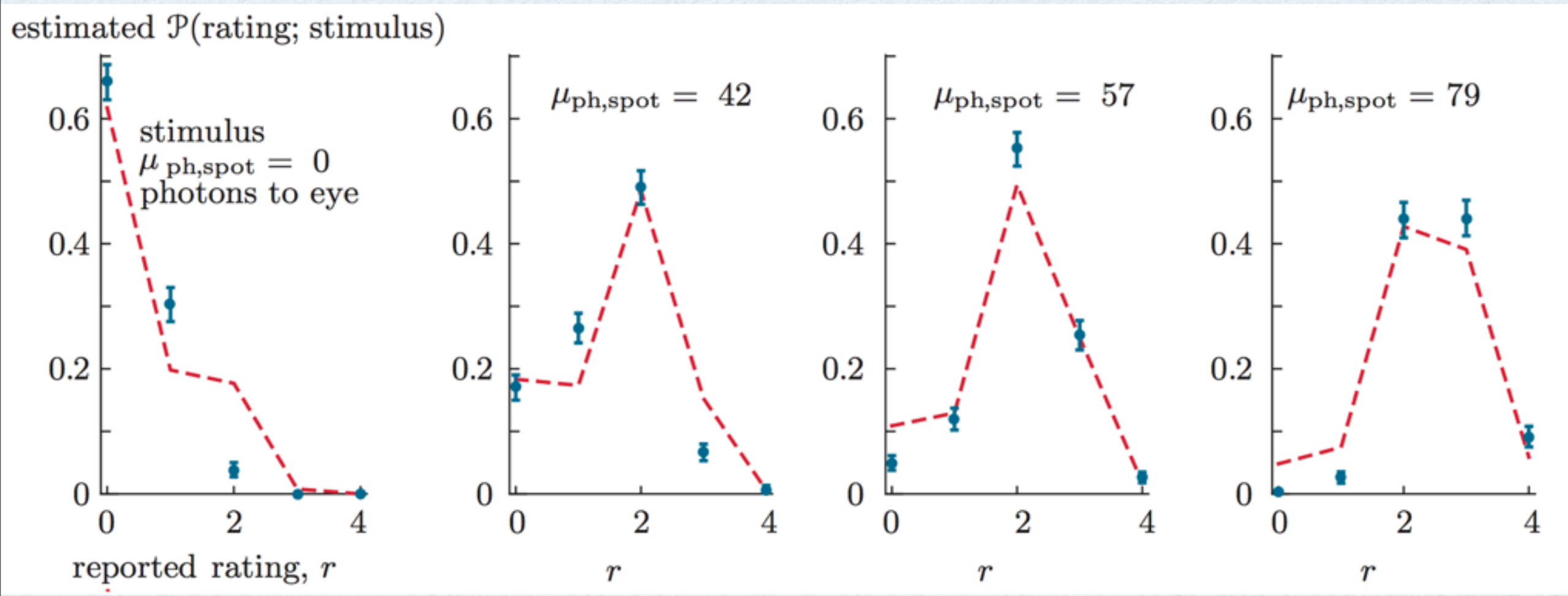
From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation). Data courtesy Heidi Hofer (2011).

Well, yes.



From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation). Data courtesy Heidi Hofer (2011).

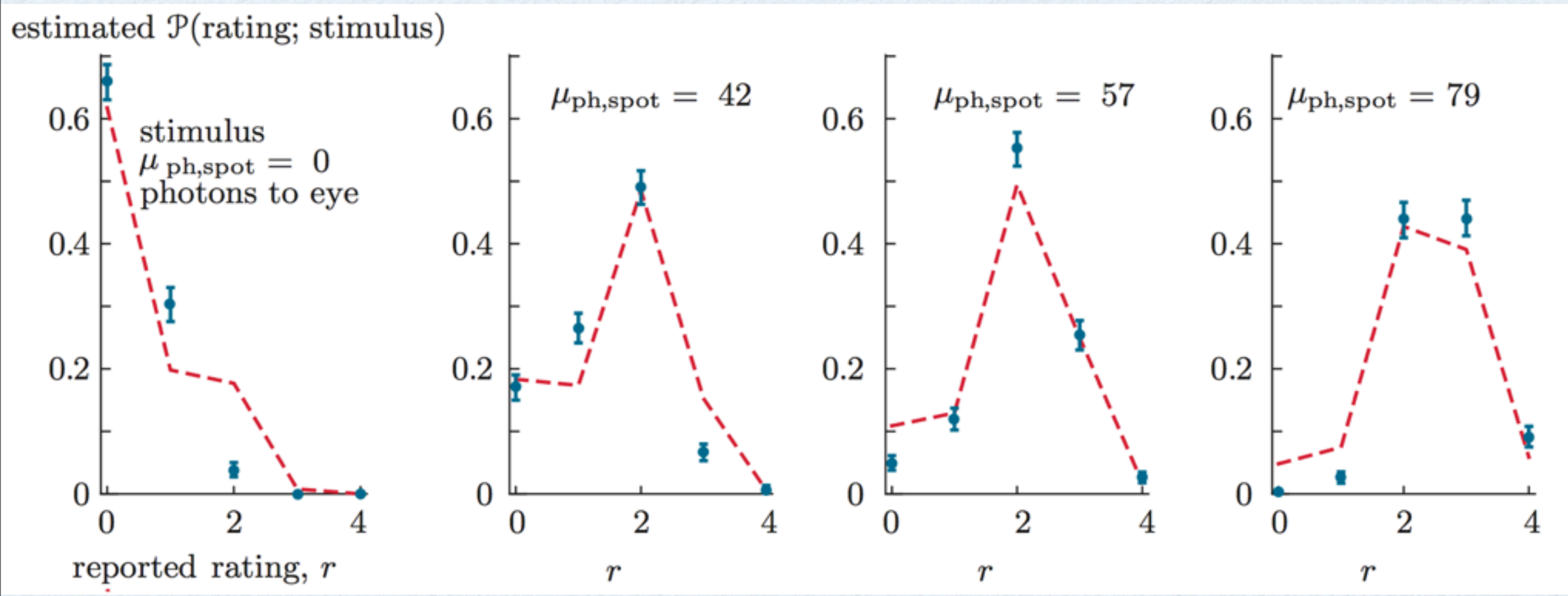
Well, yes.



For this subject the best fit gives the first threshold as ***just three*** signals. (Other subjects fit better with four.) That's enough to get a statistically measurable change in behavior.

From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation). Data courtesy Heidi Hofer (2011).

Well, yes.

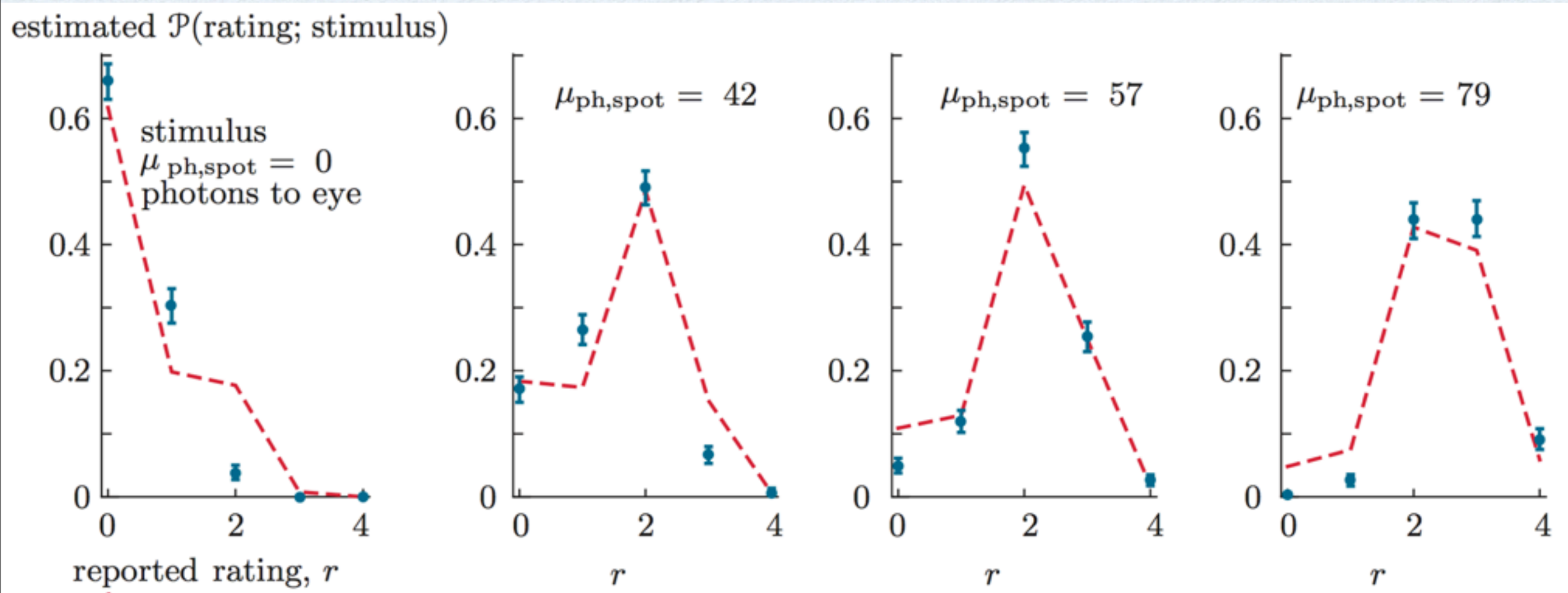


For this subject the best fit gives the first threshold as ***just three*** signals. (Other subjects fit better with four.) That's enough to get a statistically measurable change in behavior.

Moreover, ***no fit is possible*** if we change the model to add significant loss/noise after the first synapse. Everything beyond that point must be nearly perfect.

From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation). Data courtesy Heidi Hofer (2011).

Well, yes.



For this subject the best fit gives the first threshold as ***just three*** signals. (Other subjects fit better with four.) That's enough to get a statistically measurable change in behavior.

Moreover, ***no fit is possible*** if we change the model to add significant loss/noise after the first synapse. Everything beyond that point must be nearly perfect.

Understanding how that is possible is the ***next*** challenge/opportunity.

From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation). Data courtesy Heidi Hofer (2011).

Plan

1. Indoctrination
2. Light
3. Vision
4. And now a word from our sponsor
5. Wrap

This course isn't for most premeds. But there is a growing cadre of mathematically adept premeds who can handle it. What will they get?

Hilborn. Physics and the revised Medical College Admission Test. Am. J. Phys. (2014) vol. 82 (5) pp. 428-433

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.**

Skill 4: Data-based and Statistical Reasoning

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

General Mathematical Concepts and Techniques

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

A small practical matter

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 may mean discontinuing something else. And doing it one-off isn't enough -- it needs to continue.

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 may mean discontinuing something else. And doing it one-off isn't enough -- it needs to continue.

It's a serious concern. You can argue:

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 may mean discontinuing something else. 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."

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 may mean discontinuing something else. 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."
- "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."*

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 may mean discontinuing something else. 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."
- "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 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 may mean discontinuing something else. 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."
- "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 create a concentration within you department. Then the course gets a base.

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 may mean discontinuing something else. 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."
- "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 create a concentration within you department. Then the course gets a base.
- "At Penn, the course attracts >50% women."

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 may mean discontinuing something else. 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."
- "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 create a concentration within you department. Then the course gets a base.
- "At Penn, the course attracts >50% women."

- ***If all else fails, convince your visiting committee to beat up on your colleagues.***

A few results

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

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

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

A few results

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

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

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

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

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

4. Completing this course benefited my work in later courses

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

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

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

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

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

80 anonymous respondents, survey response rate about 80%.

Plan

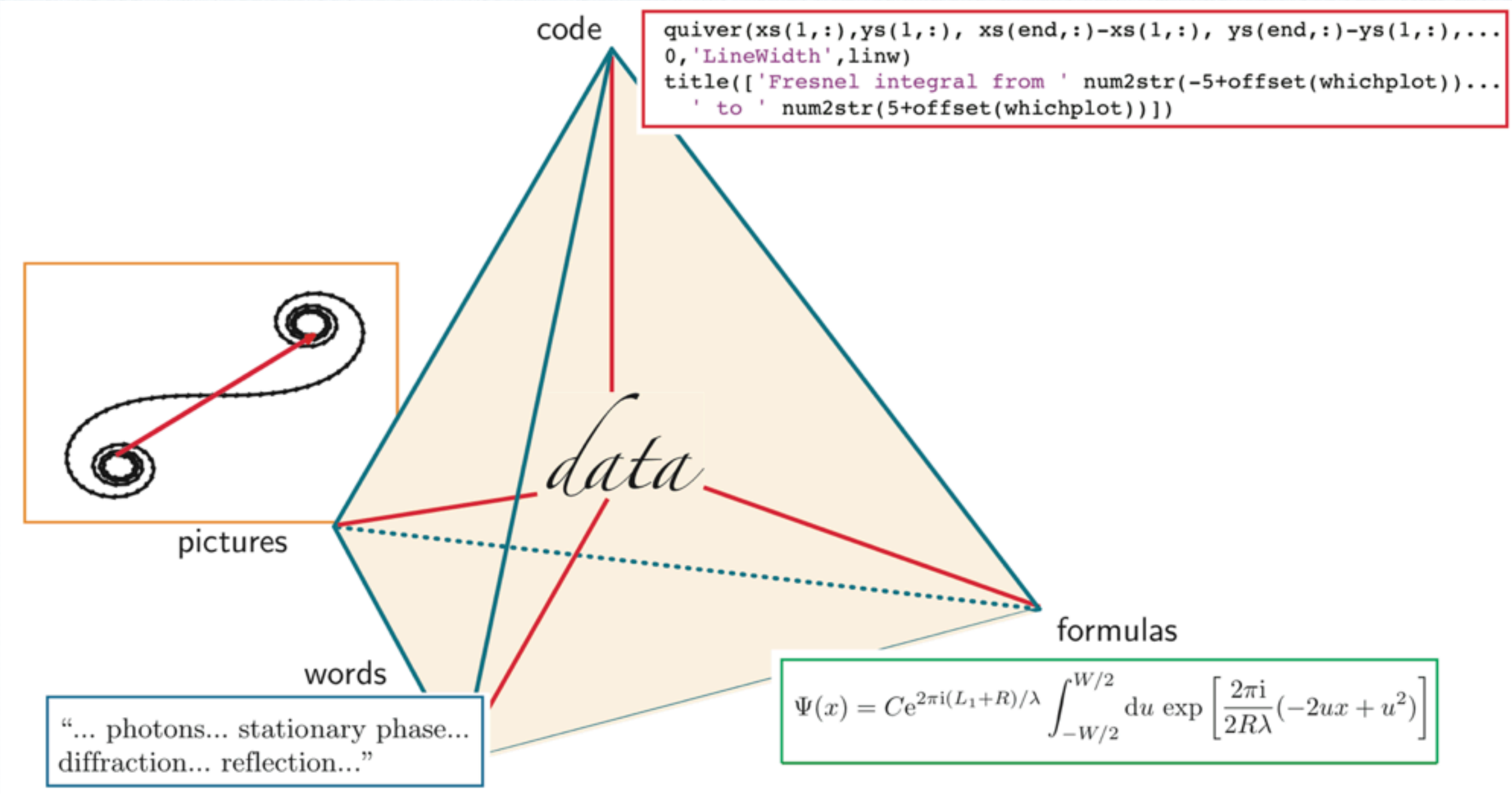
1. Indoctrination
2. Light
3. Vision
4. And now a word from our sponsor
5. Wrap

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

It's a Tetrahedron:

From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation).

What is modeling, anyway? Don't want to get all philosophical on you. I say,
It's a Tetrahedron:



From P. Nelson, ***From Photon to Neuron: Light, Imaging, Vision*** (in preparation).

Thanks

For these slides see:
www.physics.upenn.edu/~pcn
(or just google me)

University of Pennsylvania

Also see:

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

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

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

NSF BIO

NANO / BIO INTERFACE CENTER

NSF NSEC