Searching for Principles

Opportunities in Biological Physics
American Physical Society Meeting
Baltimore, Maryland
Sunday, 12 March, 2006

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http://www.princeton.edu/~wbialek/wbialek.html

Physics and biology were not always so separate ...

Helmholtz

the great figures of 19th century physics moved freely among subjects we would now distinguish as physics, biology, and even psychology

theory of sound -- theory of hearing
theory of resonance -- mechanics of the inner ear
optics -- design of the eye
absorption spectra -- color vision

more deeply:
the senses as our instruments to observe the physical world

are there "laws" of perception?
what sets the limits?
how do we learn about our world?

Rayleigh

portraits from http://scienceworld.wolfram.com/biography/

Some possible principles ...

Maximally reliable function in the presence of noise

- Photon counting in vision (by way of introduction)
- Molecule counting in bacterial chemotaxis
- Reliability vs noise in the regulation of gene expression
- Extracting reliable percepts from noisy sense data (many examples)
- Kinetic proofreading, active filtering, ...
- Exploration and stochastic optimization

No fine tuning: Robust function despite parameter variation

- Sequence ensembles and protein folding
- Ion channel densities and the computational function of neurons
- Adaptation in biochemical networks
- Long time scales
- Associatvity and generalization
- Reproducibility in embryonic development

Efficient representation of information relevant for function

- Is the genetic code efficient? (e.g., codon usage vs tRNA levels)
- Positional information in development and the dynamic range of transcriptional regulation
- Efficiency in the neural code
- Gathering information, learning rules, making predictions

http://www.princeton.edu/~wbialek/PHY562/PHY562_home.html

Where vision begins (at night):
Rod photoreceptor cells

images from MJ Berry & FM Rieke

outer segment:
packed with ~ 1 billion
molecules of rhodopsin

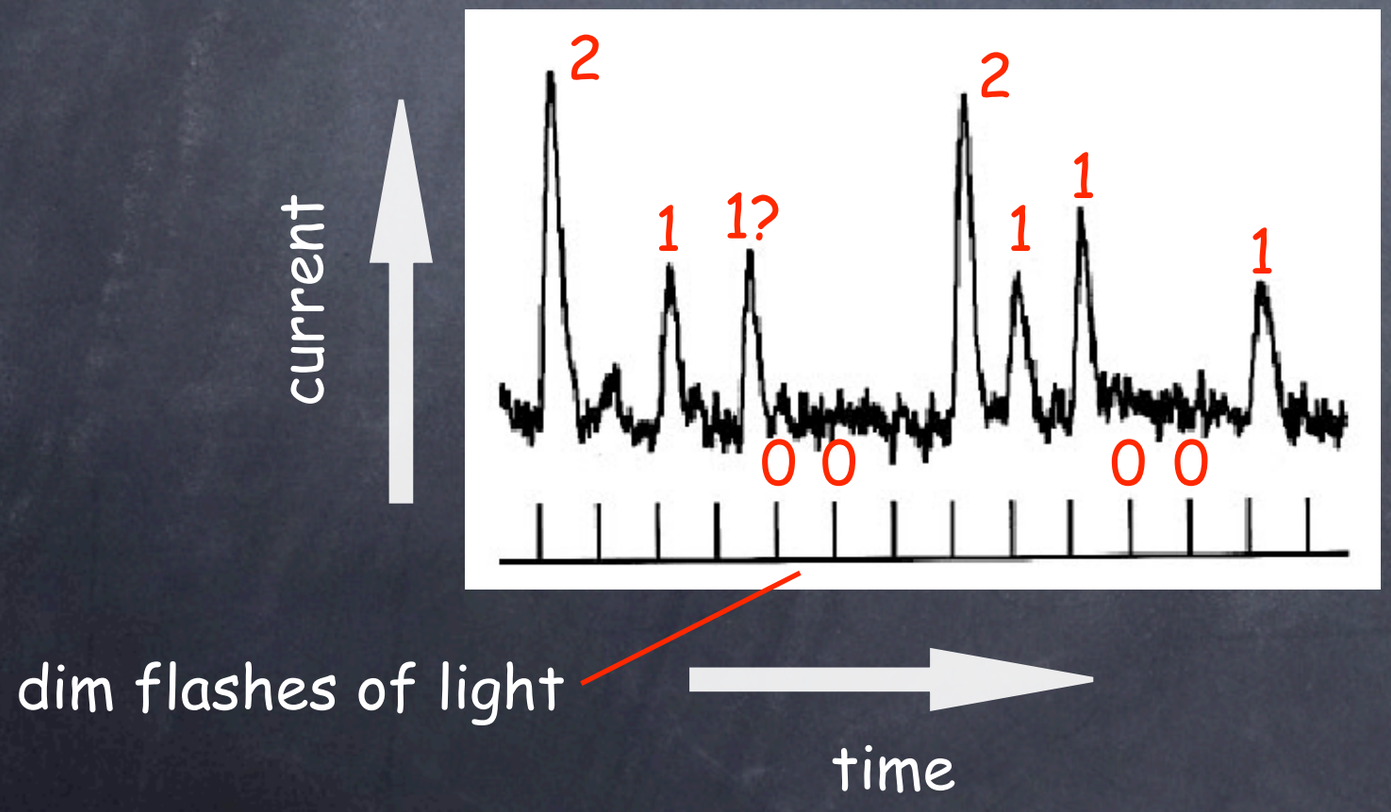
outer segment membrane:
ion channels close in
response to light,
electrical current is decreased

inner segment
membrane:
current is shaped
into a voltage signal

~ 30 microns

inner segment:
basic biology of the cell

synaptic ending:
connect to other cells,
voltage causes release
of neurotransmitter



responses to 0, 1, 2 photons
small background "rumbling" noise
spontaneous events (1?)

Single photon detection by the rod cells of the retina.
FM Rieke & DA Baylor,
Revs Mod Phys 70, 1027-1036 (1998).

noise problems at many levels:

- rhodopsin itself
- amplification/transduction network
- *retinal processing
- learning

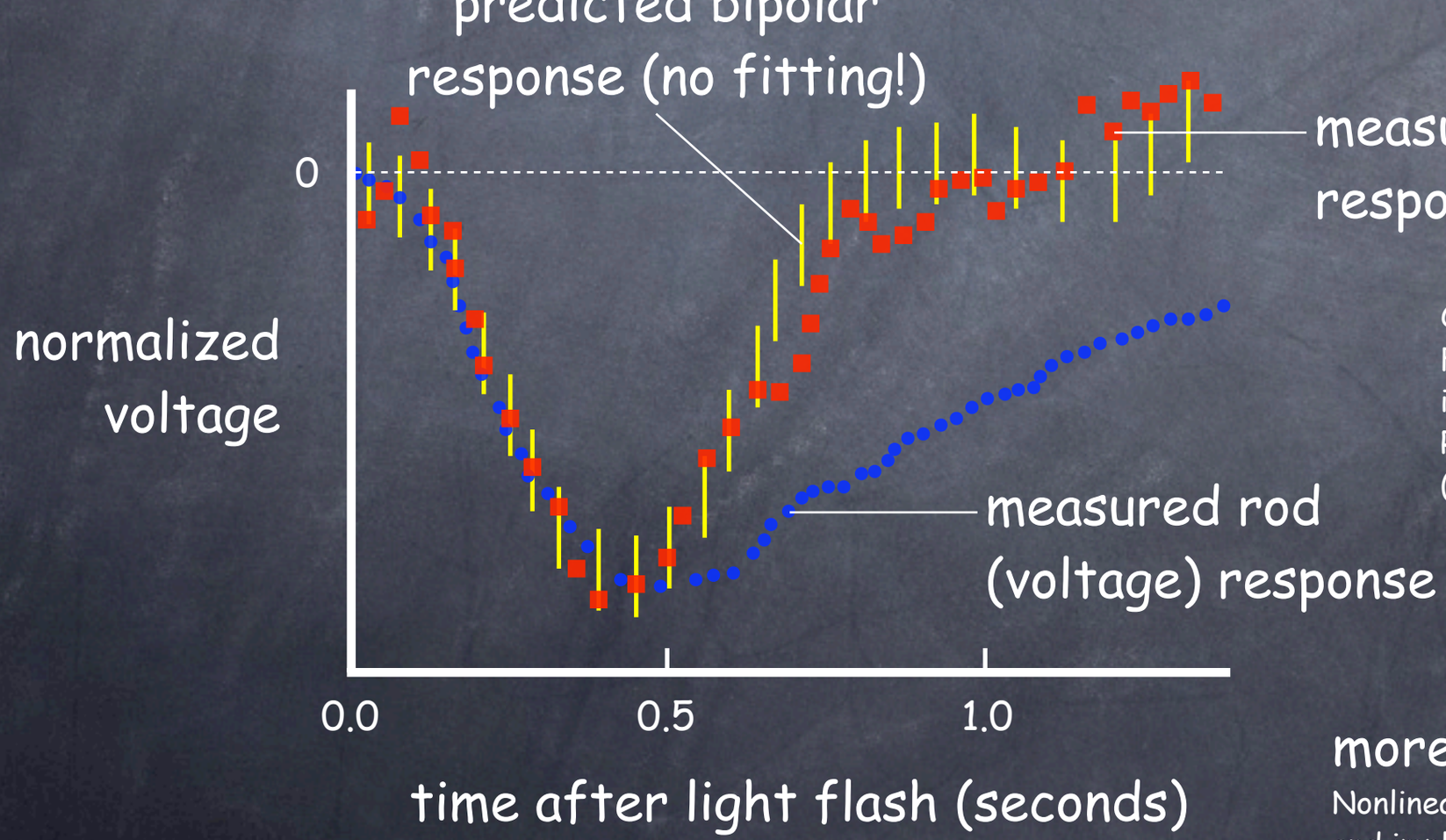
At low signal-to-noise ratios processing simplifies because $P[r(t)|I(t)]$ depends only a filtered version of the current.

The filter is "matched" to the single photon pulse $I_0(t)$ and the noise spectrum $N(\omega)$

$$\tilde{F}(\omega) = \frac{\tilde{I}_0^*(\omega)}{N(\omega)}$$

Temporal filtering in retinal bipolar cells:
Elements of an optimal computation?
W Bialek & WG Owen, Biophys J 58, 1227-1233 (1990).

implement this filter at first stage of processing: synapse from rod to bipolar cell

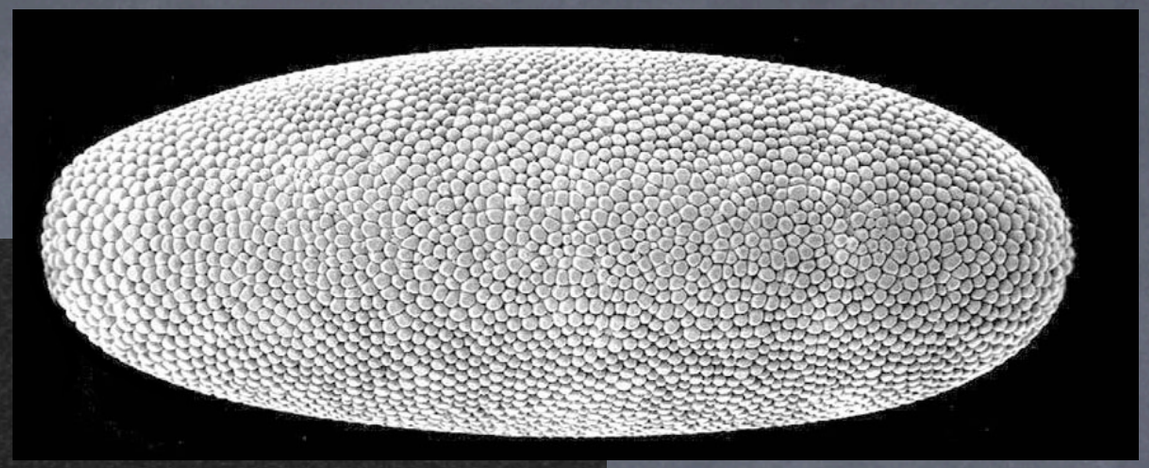


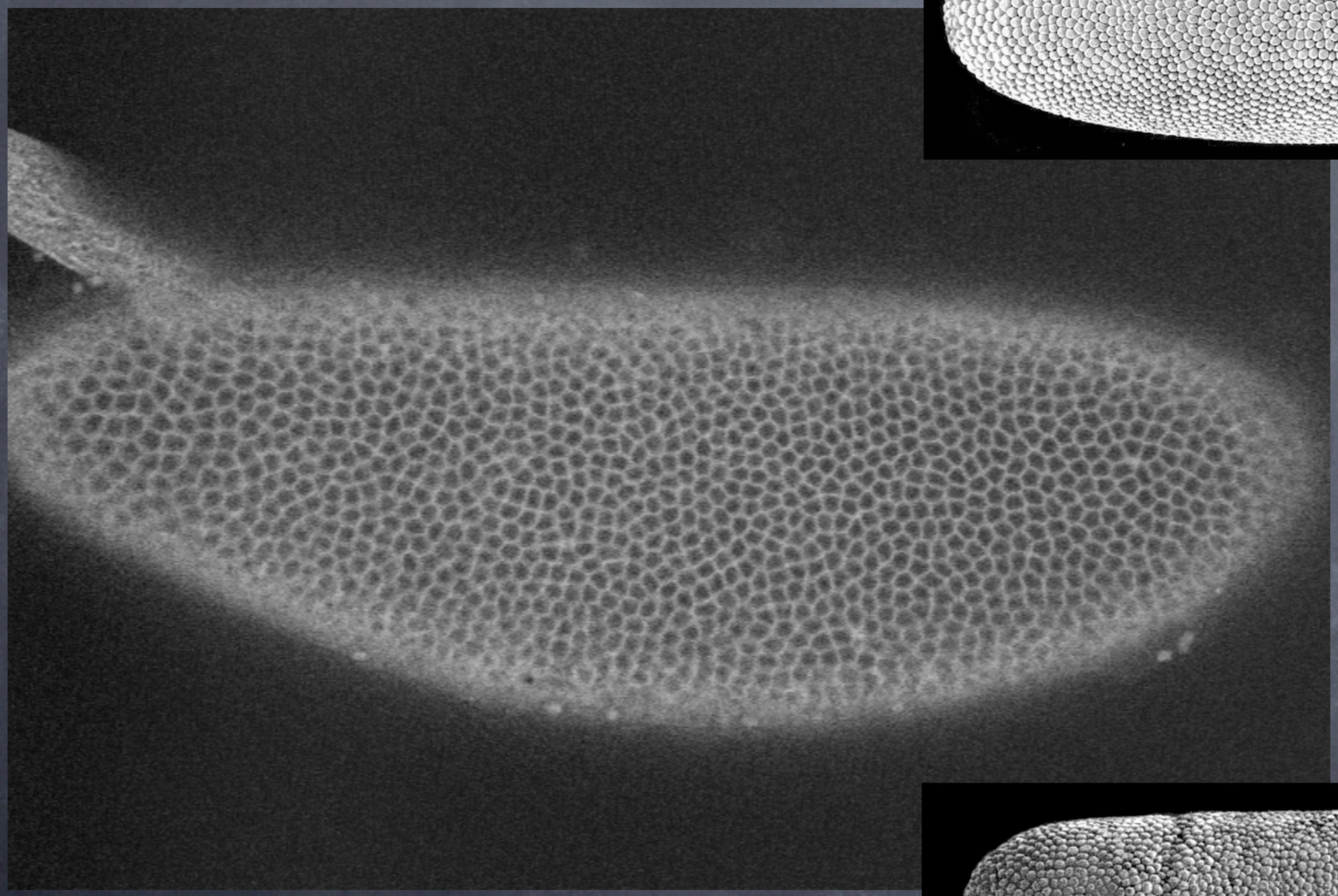
Optimal filtering in the salamander retina.
F Rieke, WG Owen & W Bialek,
in Advances in Neural Information Processing 3,
R Lippman, J Moody & D Touretzky, eds, pp 377-383
(Morgan Kaufmann, San Mateo CA, 1991).

more to say about this synapse ...

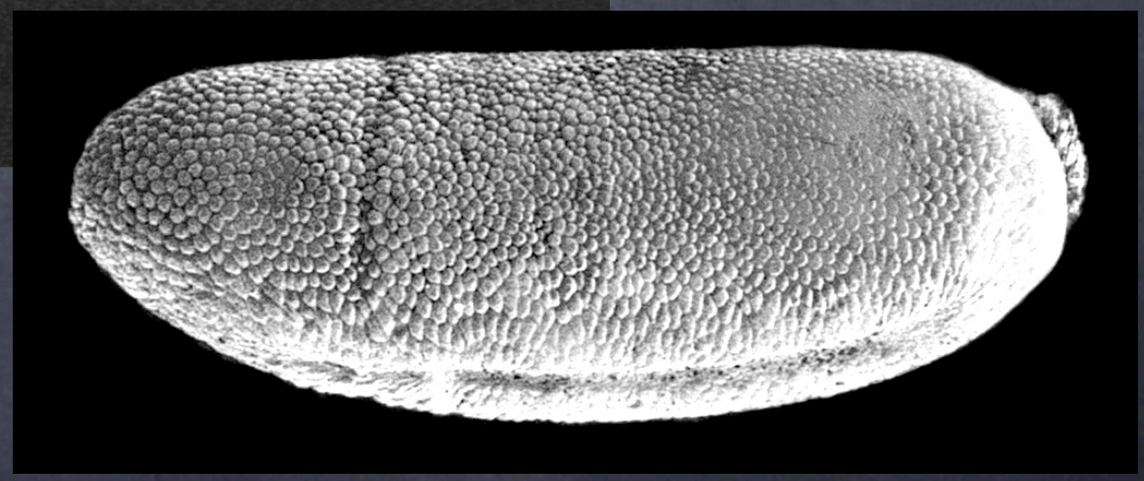
Nonlinear signal transfer from mouse rods to bipolar cells and implications for visual sensitivity.
GD Field & F Rieke, Neuron 34, 773-785 (2002).

A critical moment in a fly's life (and yours too)





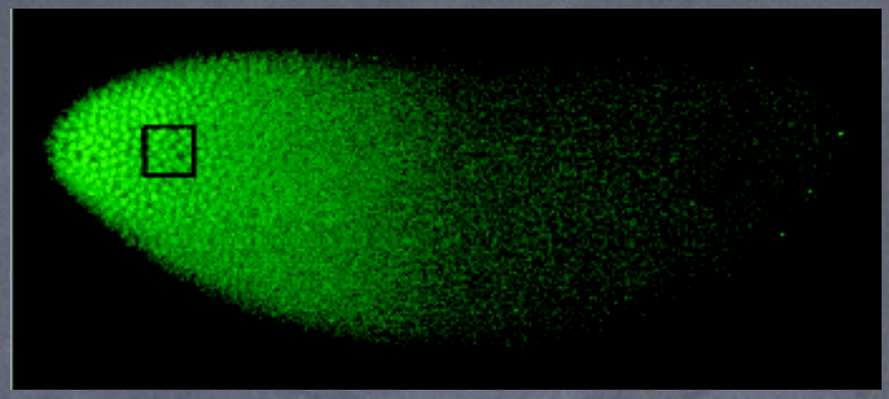
~15 minutes of real time



spatial structure in the adult organism results from spatial patterns of gene expression

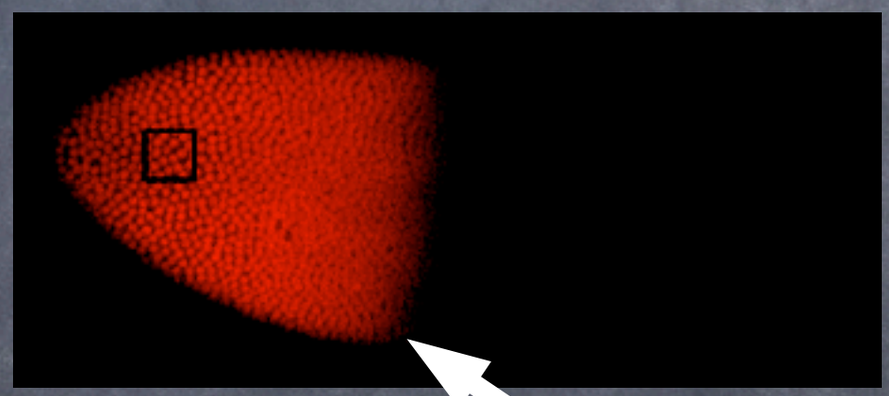
mother puts messenger RNA for bicoid at (future) head of the embryo

stain for bicoid protein



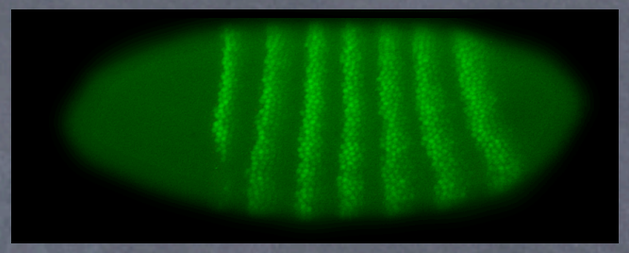
bicoid acts as a transcription factor to activate expression of hunchback

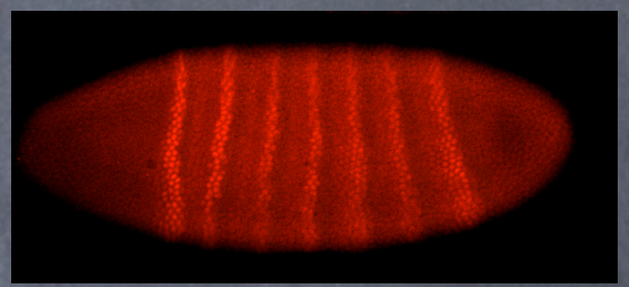
stain for hunchback protein

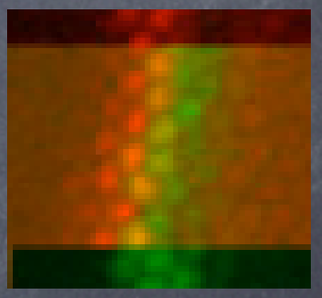


this boundary is the first step in making the "segments" of the fly's body

bicoid and hunchback cooperate to activate other genes in more complex patterns







how accurately can the boundaries be drawn?

or, how precisely can the system measure bicoid concentration?

what are the physical limits to counting bicoid molecules?

An intuitive picture ...

If sensors are of size a, and molecules are at concentration c, we will "count" $N \sim ca^3$ molecules and make relative errors $\sim 1/N^{1/2}$

If we average for a time T, we can make $K \sim T/t$ measurements, where $t \sim a^2/D$ is the time to "clear" via diffusion ... fractional error reduced by $1/K^{1/2}$

Limiting precision of concentration sensing:

$$\frac{\delta c}{c} \sim \frac{1}{\sqrt{cDaT}}$$

Physics of chemoreception.
HC Berg & EM Purcell,
Biophys J 20, 193-219 (1977).

Remarkably, the "sensor size" a could be ~nm (a single receptor)
or ~μm (the whole bacterium)

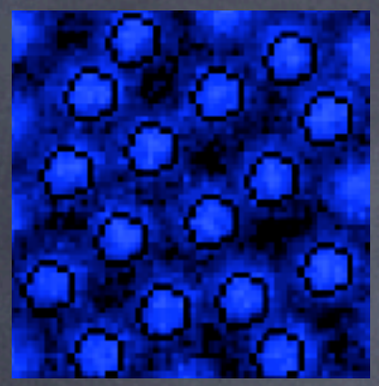
Can we make this rigorous?

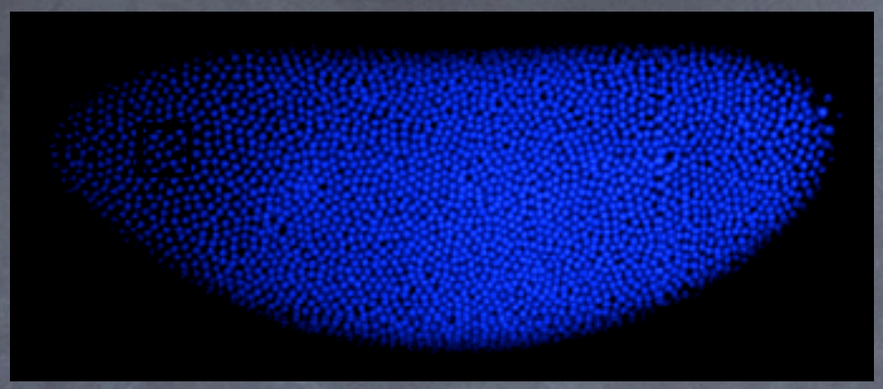
Where are the details of ligand-receptor kinetics?
(maybe the absence of details is good news!)
Are correlations among receptors treated correctly?
(and what happens with real interactions?)
Is this also a theory for noise in intracellular signals?

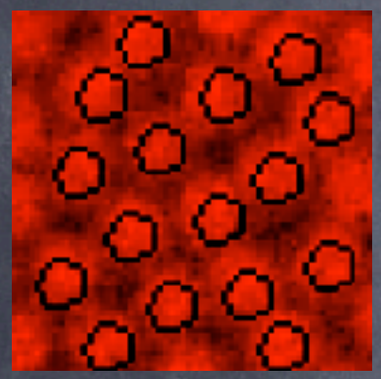
Physical limits to biochemical signaling
W Bialek & S Setayeshgar
Proc Nat'l Acad Sci (USA) 102, 10040-10045 (2005)

Cooperativity, sensitivity and noise in biochemical signaling
W Bialek & S Setayeshgar, q-bio.MN/0601001

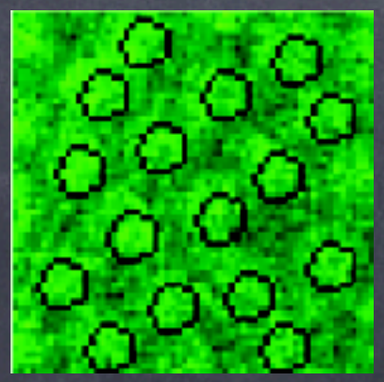
stain the DNA so we can find every nucleus ...







and then in each nucleus we can measure the bicoid (bcd) and hunchback (hb) concentrations



The hb level in each nucleus gives a "readout" of the bcd concentration with a precision of better than 10%

enough to draw boundaries with an accuracy of one nucleus (!)

BUT: at the "decision" point,
c ~ binding constant ~ 1 nM
= 0.6 molecules/$\mu\mathrm{m}^3$

"receptor site" = promoter sequence
a ~ nanometers

diffusion constants $\sim \mu\mathrm{m}^2/\mathrm{s}$

with these numbers 10% accuracy requires hours!

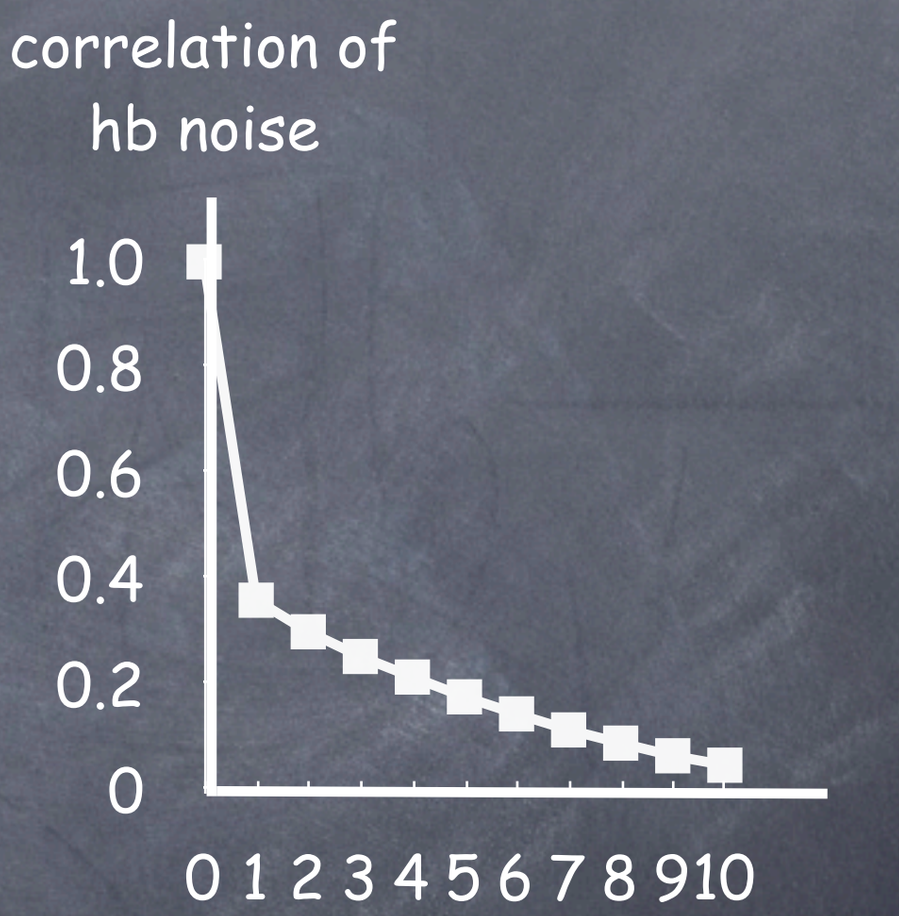
Biophysics problems in early embryonic development:
Precision and dynamics in the bicoid morphogen gradient.
T Gregor (PhD thesis, 2005)
advisors: W Bialek, DW Tank & EF Wieschaus

Not enough time? Average over space ...

If nuclei communicate to "agree" on bcd concentration, can reduce hours to minutes (~ one cell cycle)

but if spatial averaging is important, there must be correlations

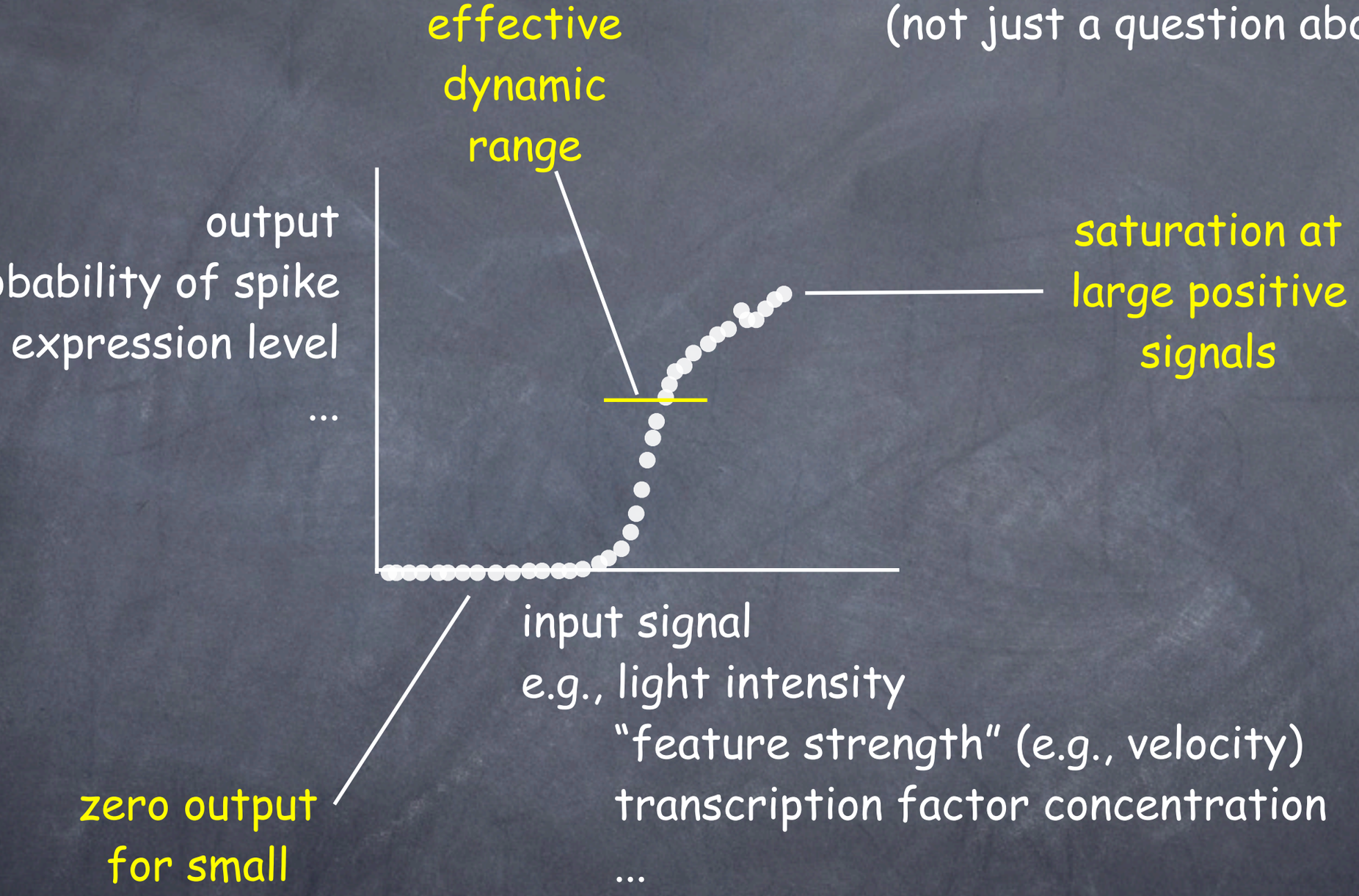
having measured mean hb vs bcd, we can subtract this mean for each nucleus to get a "field of noise" for hb



although plenty of rough edges, spatial correlations are on just the scale needed to make noise levels consistent with available integration times

What determines the structure of input/output relations?

(not just a question about neurons!)



In particular, what sets the scale along the input axis?

Efficient representation:

Choose the input/output relation to maximize the information I(input; output) ...

$$I(X;Y) = \int dx \int dy\, P(x,y) \log_2 \left[\frac{P(x,y)}{P(x)P(y)} \right] \text{ bits}$$

Because mutual information is context dependent, the optimal input/output relation is matched to P(input)

if P(input) is mostly in this range, then there is no built in scale ...

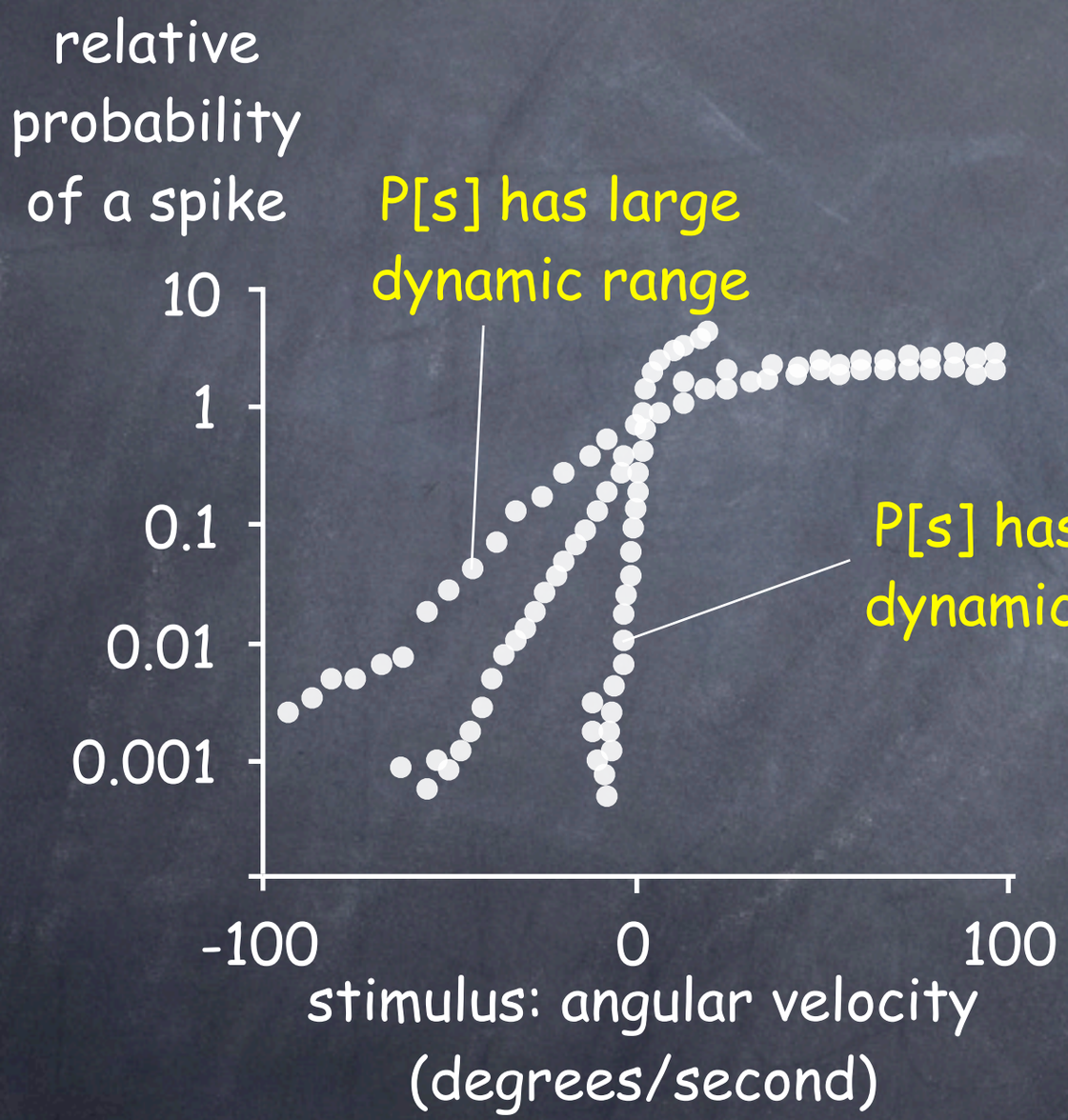
$\Rightarrow$ the only way to get a scale on the input axis is from P(input) itself!

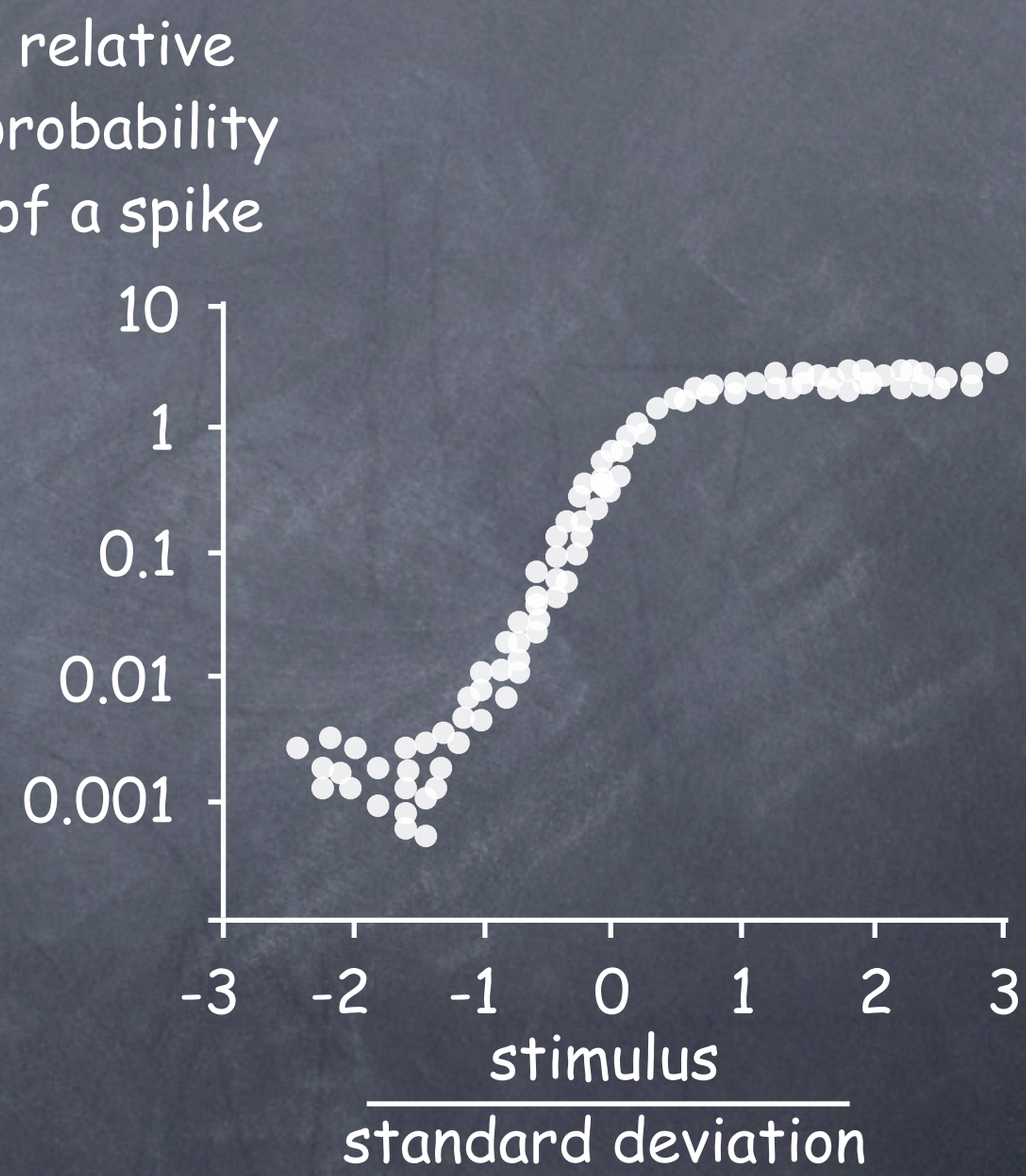
these are scales "built in" to the system itself

(somewhat embarrassingly, equations don't add much to this picture)

Measure input/output relations when inputs are drawn from different distributions P[s]

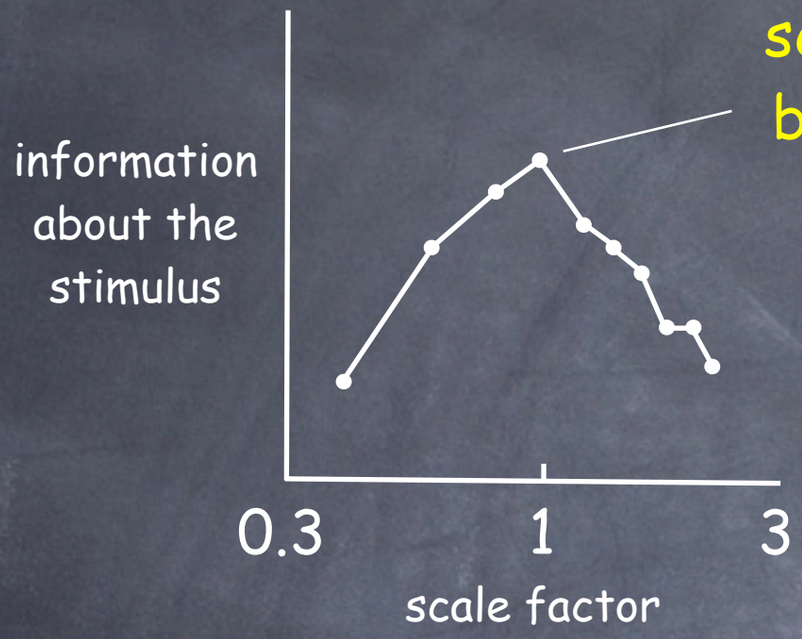
(important technical question of how to do this!)





Adaptive rescaling optimizes information transmission.
N Brenner, W Bialek & RR de Ruyter van Steveninck,
Neuron 26, 695-702 (2000).

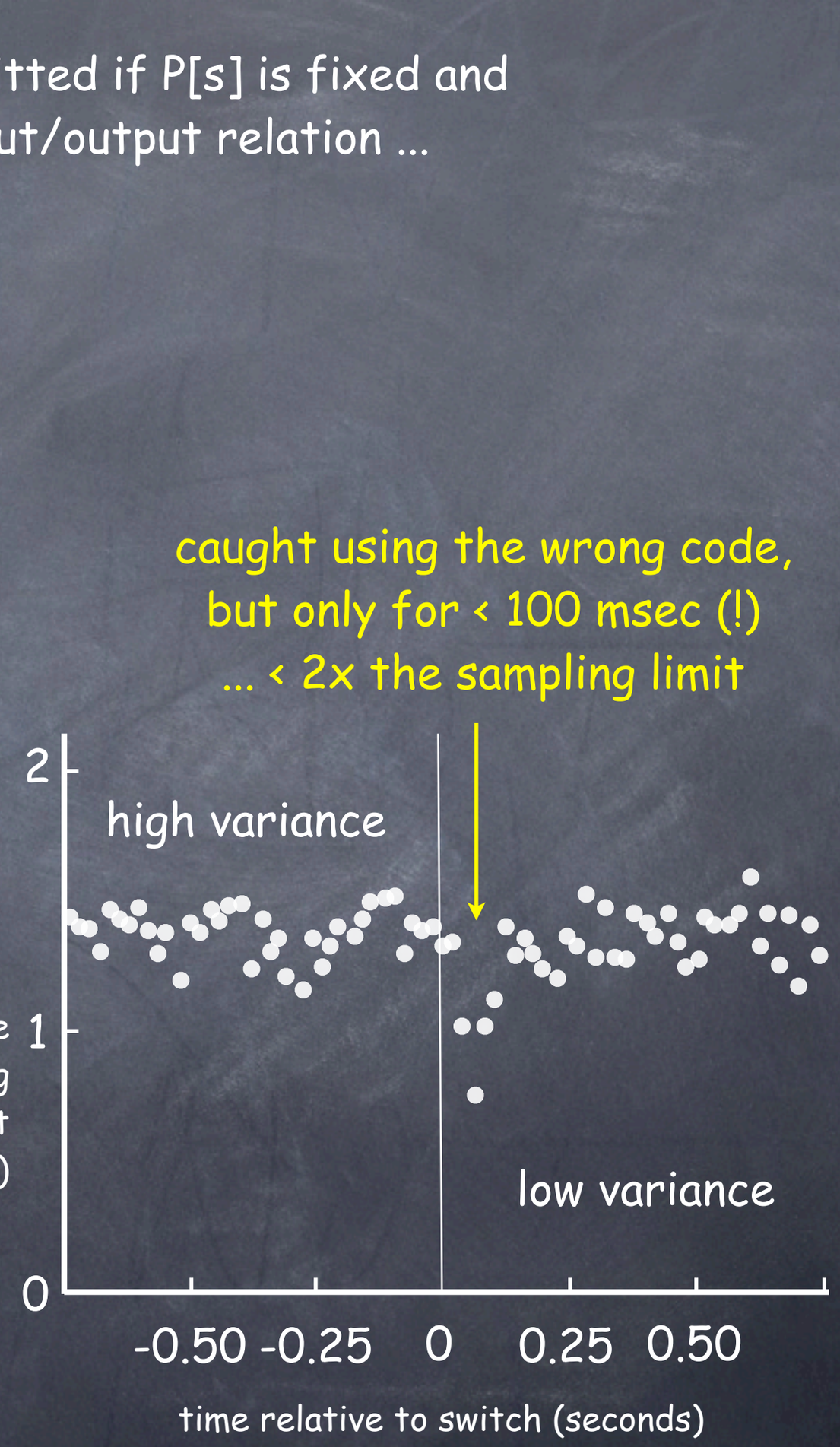
calculate the information that would be transmitted if P[s] is fixed and the cell chooses different rescalings of the input/output relation ...



scaling chosen by adaptation maximizes information

caught using the wrong code, but only for < 100 msec (!) ... < 2x the sampling limit

how long does it take to be sure that we are seeing a new distributions vs. outliers in the old distribution?



Efficiency and ambiguity in an adaptive neural code.
AL Fairhall, GD Lewen, W Bialek & RR de Ruyter van Steveninck,
Nature 412, 787-792 (2001).

Some possible principles ...

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