

Systems Bioengineering II

Midterm # 1

TA Review Session

Disclaimer

These notes are for review purposes only.

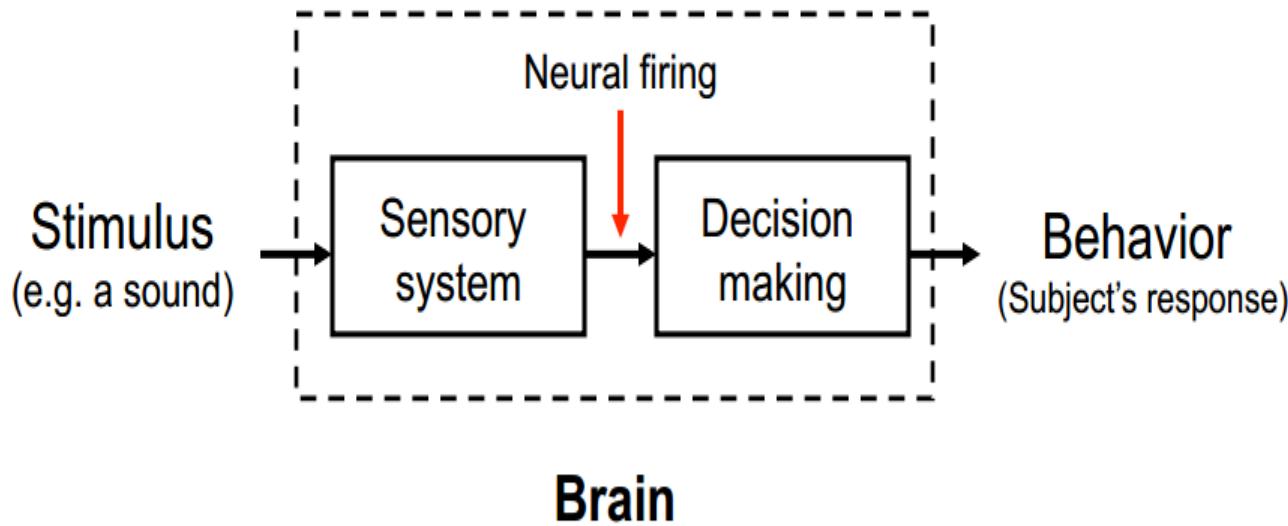
There is no guarantee that any of this material will be on the exam.

The exams will be developed from the lecture material.

Credit will not be given for any arguments derived from these notes.

Dr. Wang's lectures

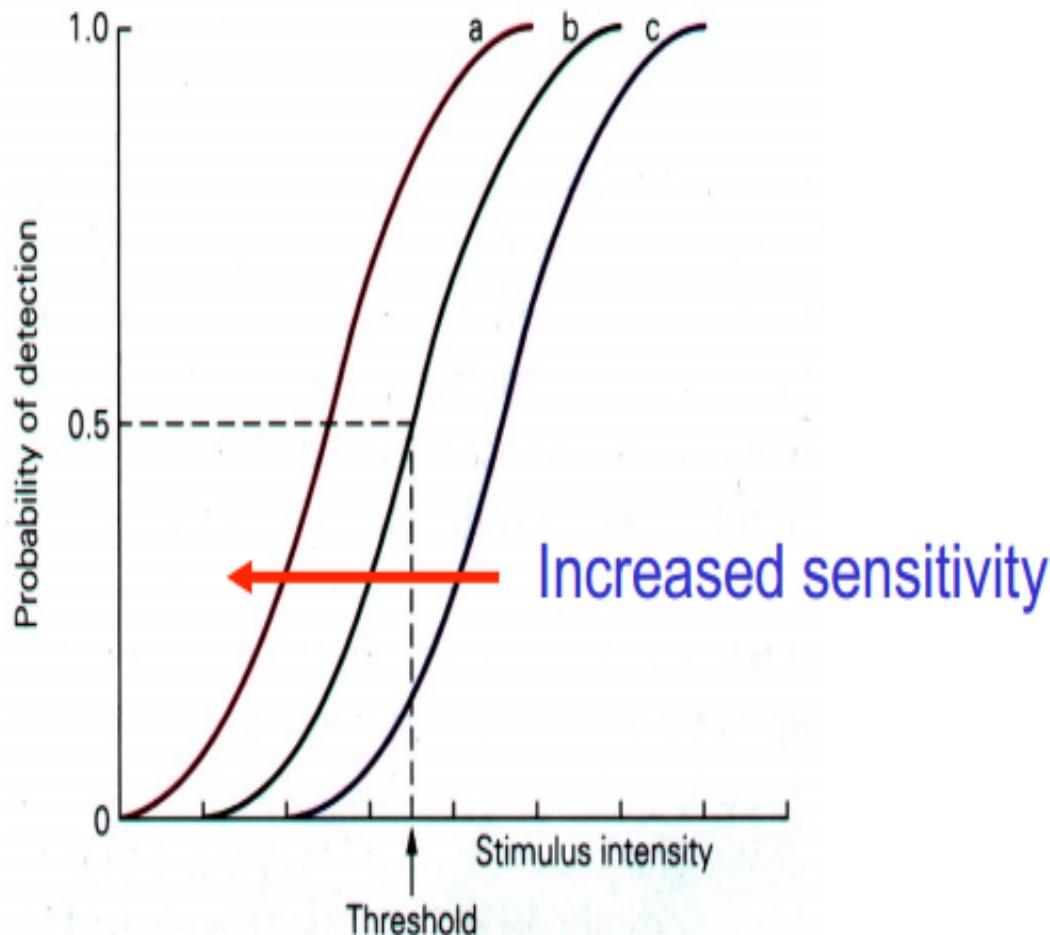
How does the brain quantify information?



What is a psychometric function?

- Psychophysics is the scientific discipline that explores the connection between physical stimuli and subjective responses.
- “Psychometric function” provides the fundamental data for psychophysics. It relates the subject’s response to the physical stimulus and is used to quantitatively measure behaviors.
Its abscissa (x-axis) plots the physical parameter of a stimulus and the ordinate (y-axis) plots the observer’s response.

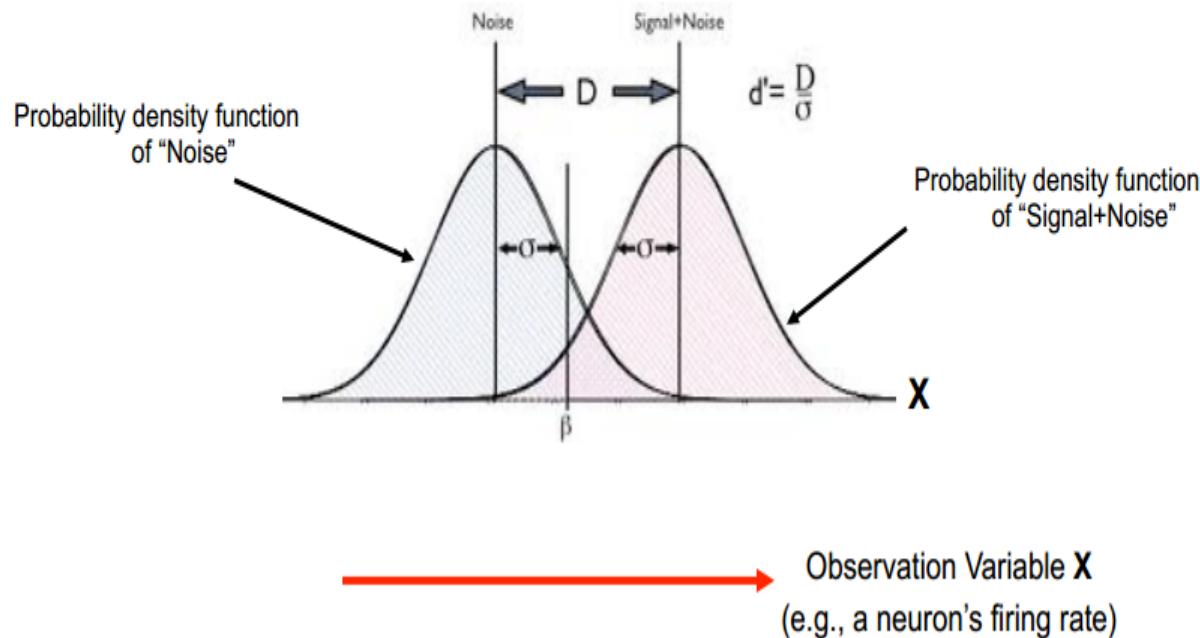
How does stimulus sensitivity affect the psychometric function?



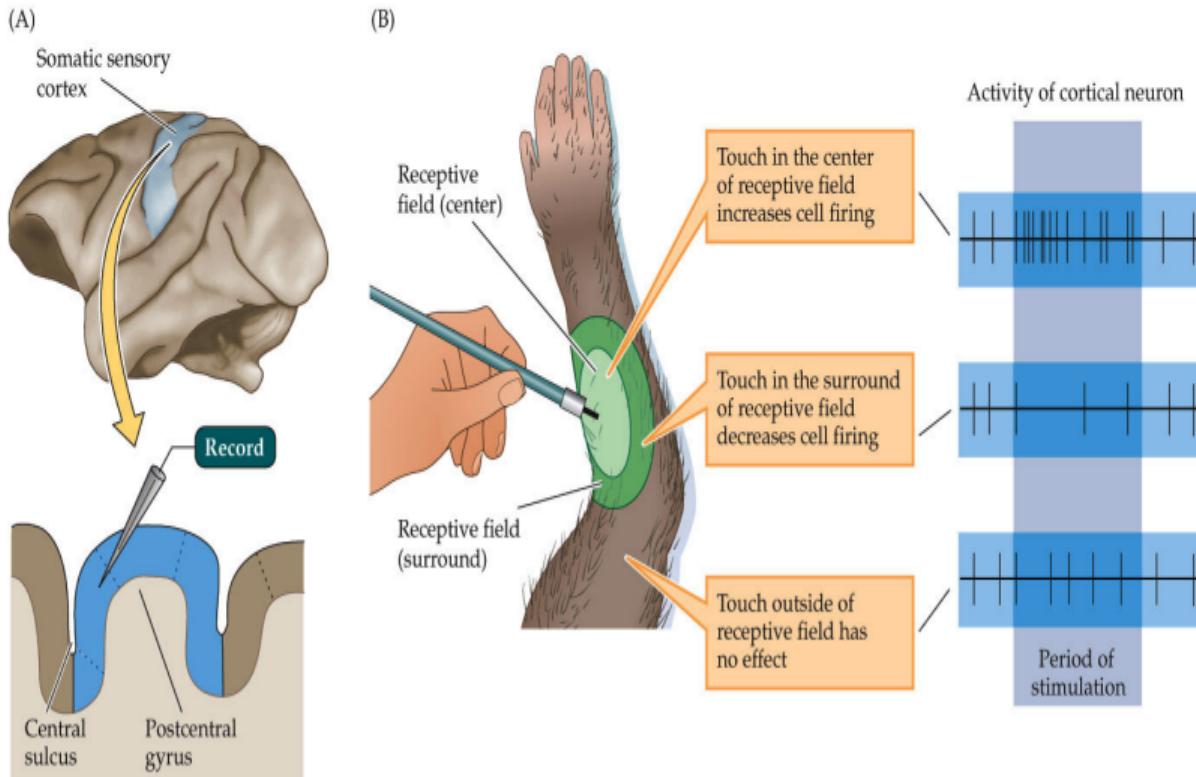
What is Discriminability index?

Discriminability Index (d')

A measure to quantify the discriminability of a stimulus
independent of the criterion an observer adopts



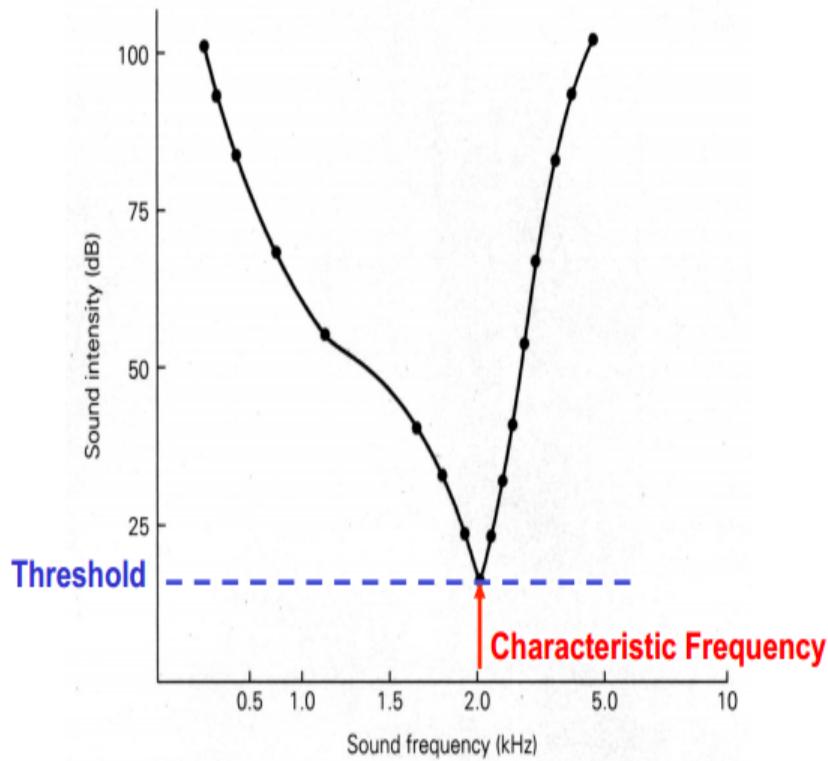
What is a receptive field?



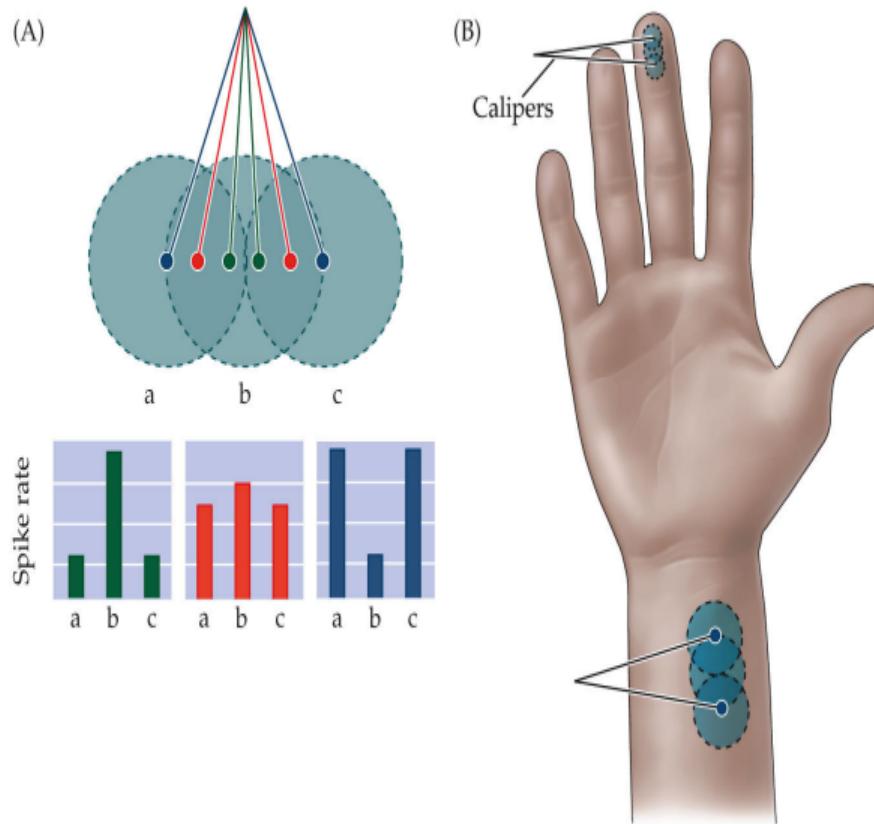
“Receptive field”

How does a tuning curve for an auditory neuron look like?

Tuning curve (receptive field) of an auditory neuron



RF fields and the two-point discrimination task



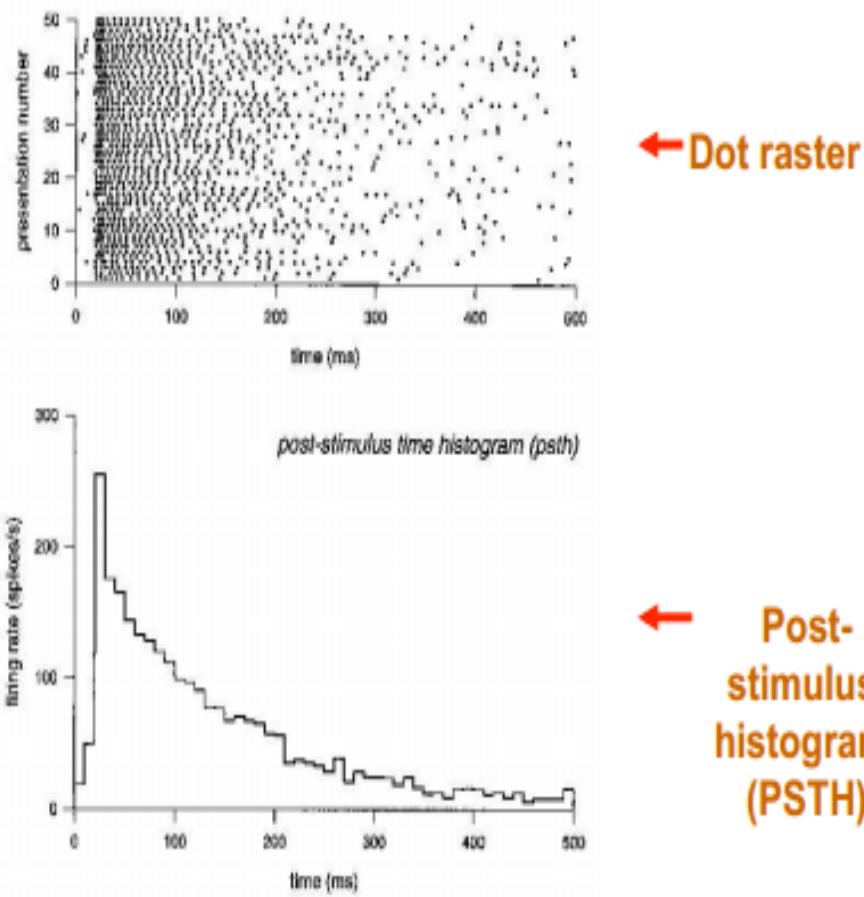
NEUROSCIENCE, Fourth Edition, Figure 9.3 (Part 1)

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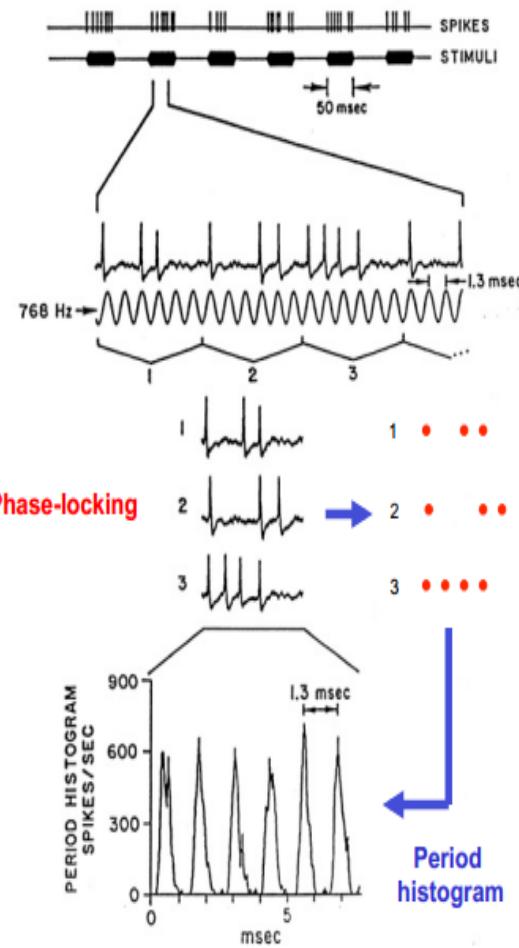
Response measures of spike trains

- Mean firing rate
- Post Stimulus Histogram
- Period Histogram
- Inter-Spike Interval Histogram

PSTH



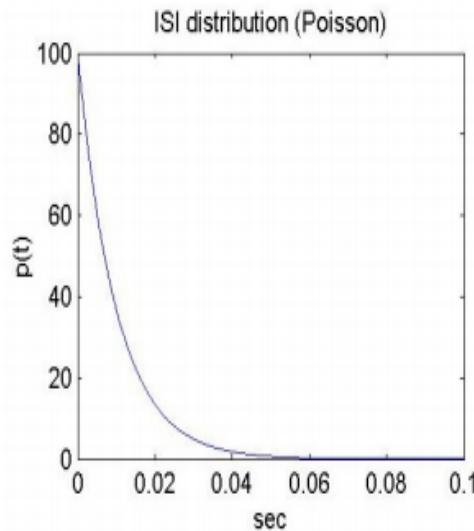
Period Histogram and phase locking



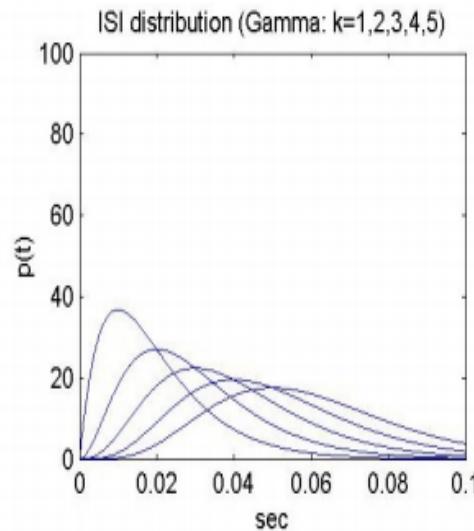
ISI with refractory period

Refractory periods modify the Poisson process model

$$p(\tau) = \lambda \exp(-\lambda\tau)$$



$$p(\tau) = \lambda(\lambda\tau)^k \exp(-\lambda\tau)/k!$$

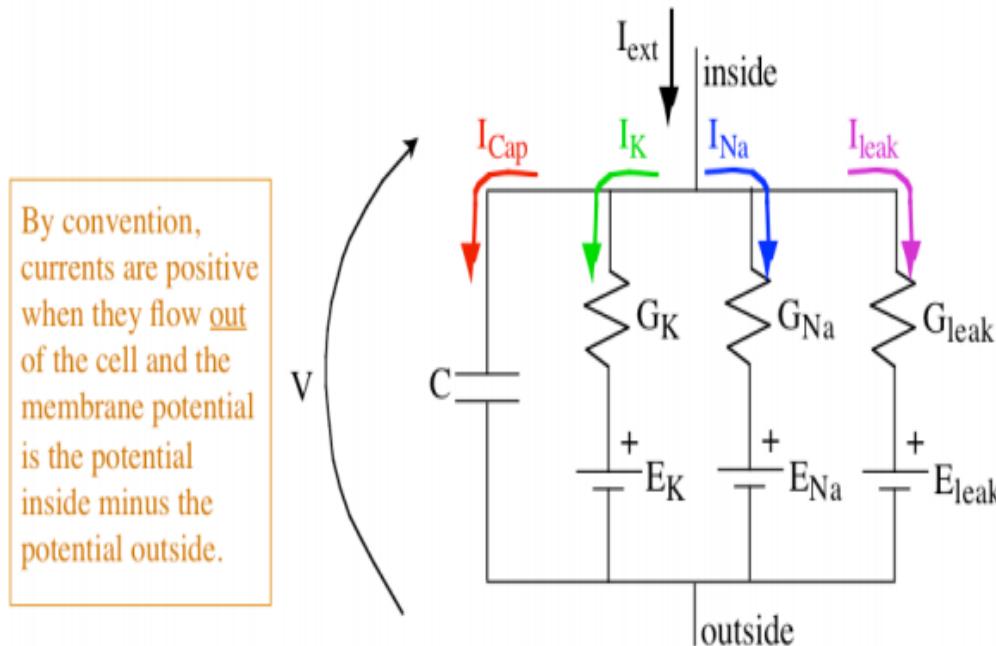


Dr. Young's lectures

Battery-resistor model for a neuron

$$I_{cap} + I_K + I_{Na} + I_{leak} = I_{ext}$$

$$C \frac{dV}{dt} = I_{ext} - G_K(V - E_K) - G_{Na}(V - E_{Na}) - G_{leak}(V - E_{leak})$$



Model the ion channel currents in above using HH variables

$I_K = G_K(V - E_K)$ and so on for I_{Na} and I_{leak}

where the conductances are given by

Later, we will see that this model is inadequate for Ca⁺⁺ currents.

$$G_K = \bar{G}_K n^4 \quad G_{Na} = \bar{G}_{Na} m^3 h$$

$$\frac{dn}{dt} = \frac{n_\infty(V) - n}{\tau_n(V)} \quad \frac{dm}{dt} = \frac{m_\infty(V) - m}{\tau_m(V)} \quad \text{and} \quad \frac{dh}{dt} = \frac{h_\infty(V) - h}{\tau_h(V)}$$

The variables n , m , and h are called *activation* (n , m) and *inactivation* (h) variables. They represent the probability of a channel's gate being open.

What are the different types of ion channels and what do they do?

Na⁺ channels

Purely voltage gated. Brings in Na⁺.

K⁺ channels

Purely voltage gated K⁺ channels.

Ca dependent voltage gated K⁺ channels: KCa channels. BK and SK.

Na/K channels

H-type channels. Provide leakage.

Ca channels:

Normal voltage gated Ca channels.

T- type voltage gated Ca channels.

L-type voltage gated Ca channels.

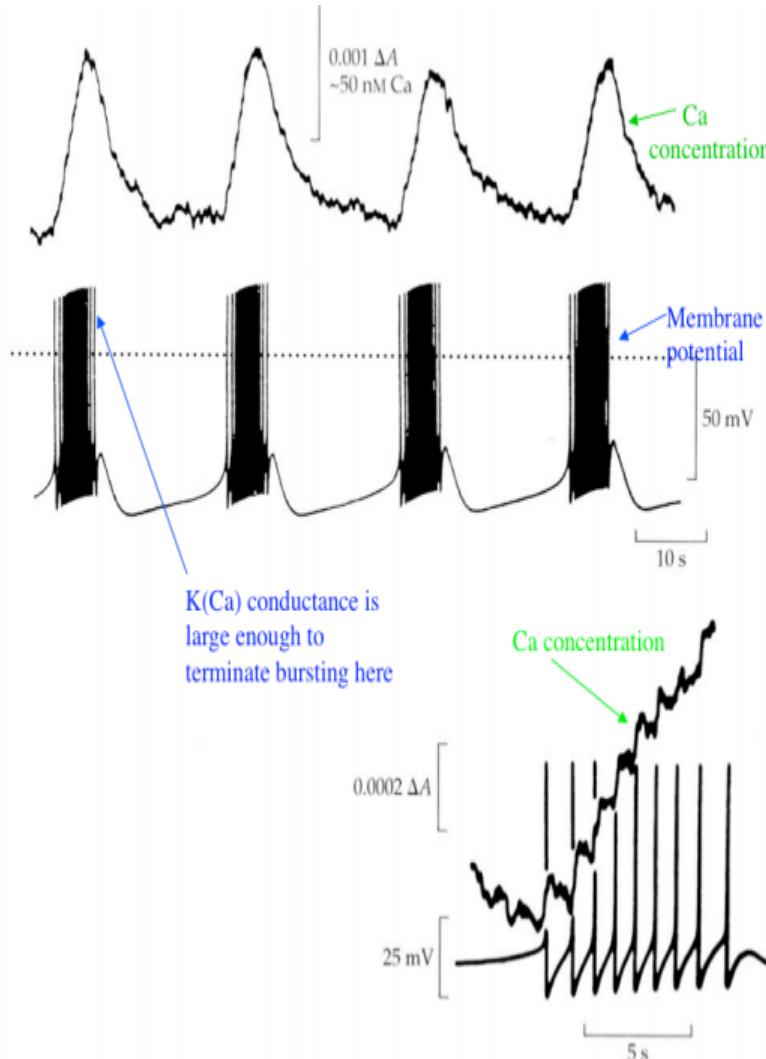
Bursting

Some neurons show **bursting** activity, meaning a short period of high-rate firing with intervals of no spiking.

Often this is accompanied by Ca^{++} accumulation in the cytoplasm.

The burst is terminated by a *calcium-dependent potassium conductance* $K(\text{Ca})$ whose conductance increases as the $[\text{Ca}^{++}]$ increases, until it is large enough to stop the burst.

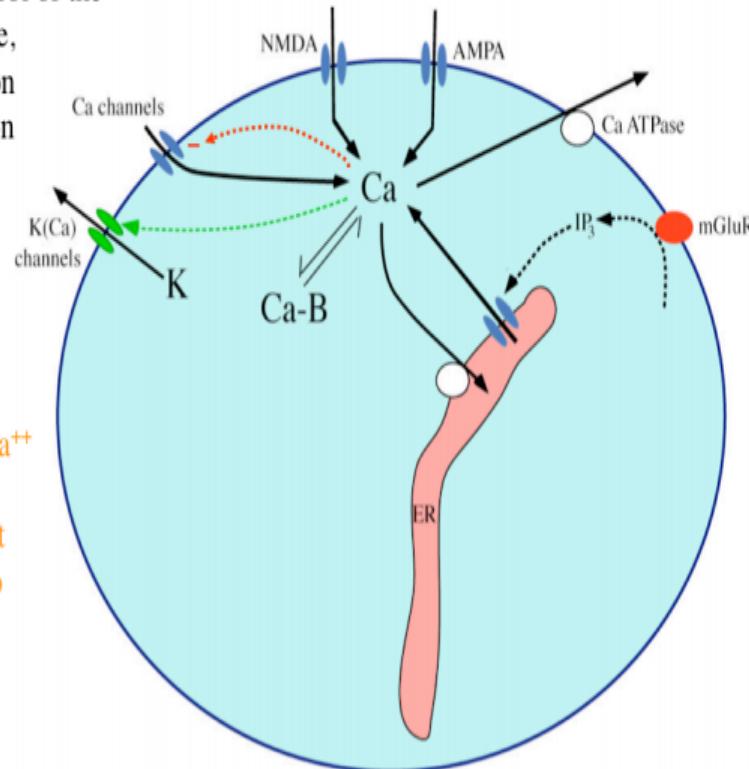
Sometimes Ca^{+} -inactivation of Ca^{+} channels also contributes.



How is Ca important to membrane voltage regulation?

The K(Ca) channel is one of many cellular processes that depend on the **calcium concentration** in some part of the cell. Calcium has three kinds of effects:

1. Immediate control of channel gating, as for the K(Ca) channel, or inactivation as for some Ca channels.
2. Short-term control of such processes as neurotransmitter release (later)
3. Longer-term control of the cellular steady state, protein modification and gene expression (also later).



Of course, the ubiquitous role of Ca^{++} in control of cell functions means that models have to keep track of $[\text{Ca}^{++}]$.

A minimal set of equations for a bursting neuron

A *minimal model for bursting* can be obtained by adding a calcium pool and a K(Ca) channel to the MLE discussed previously.

$$C \frac{dV}{dt} = I_{ext} - G_K(V - E_K) - \underline{G_{KCa}(V - E_{KCa})} - \bar{G}_{Ca} m_\infty(V)(V - E_{Ca}) - G_L(V - E_L)$$

$$\frac{dw}{dt} = \frac{w_\infty(V) - w}{\tau_w(V)}$$

$$G_K = \bar{G}_K w$$

$$\frac{dCa}{dt} = A \left(-\frac{I_{Ca}}{2F} - B Ca \right)$$

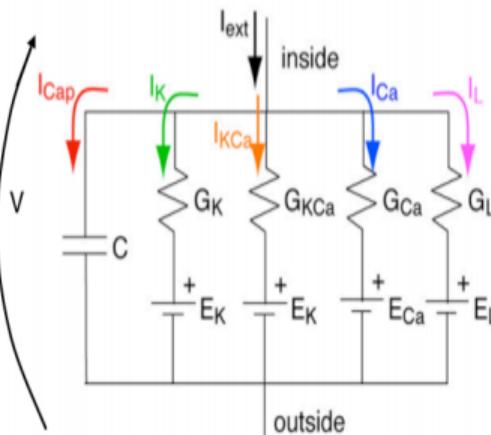
$$G_{KCa} = \bar{G}_{KCa} \frac{Ca}{Ca+1}$$

The basic MLE model.
New equations for the
KCa channel dependent
on Ca concentration.

There are three differential equations,
for V , w , and the calcium
concentration Ca .

G_{KCa} is a function of Ca only.

G_{Ca} is governed only by the m_∞
function.



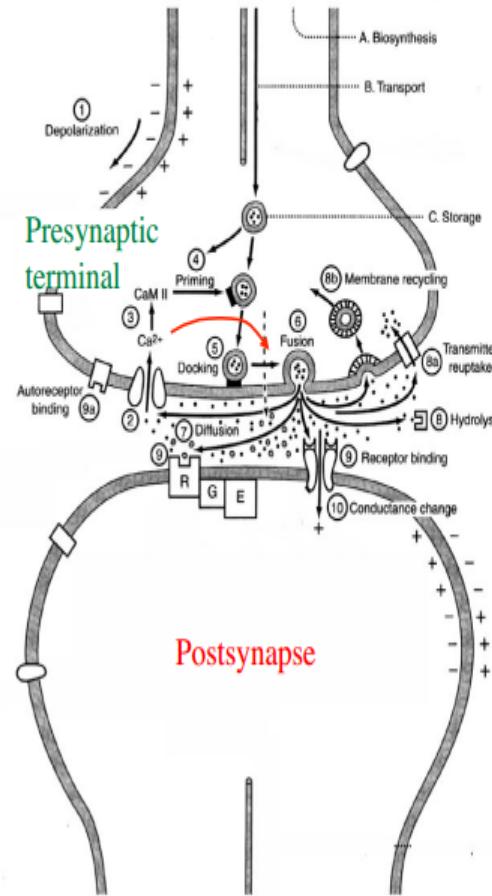
What are the steps happening in the presynaptic side leading to a synaptic transmission?

The sequence of steps in synaptic transmission:

1. Depolarization of the presynapse
2. Calcium entry through V-gated calcium channels opened by depolarization
- 3-5. Transfer of synaptic vesicles to the membrane.
6. Fusion of the vesicle with the membrane, releasing neurotransmitter.
7. Diffusion of the neurotransmitter across the synaptic cleft
9. Binding of transmitter to the postsynaptic receptor.
10. Change in the postsynaptic cell (later)

11. To terminate the synaptic action, the transmitter is metabolized (8) or removed from the cleft by reuptake (8a, 8b) in the neuron itself or in adjacent glia.

Some synaptic vesicles are synthesized in the cell body (A) and transported to the terminal (B), where they are filled with transmitter, primed (4) and docked (5) in preparation for release. Others are synthesized in the terminal; after release (6) the vesicle membrane is recycled by uptake (8b) and refilled with transmitter.

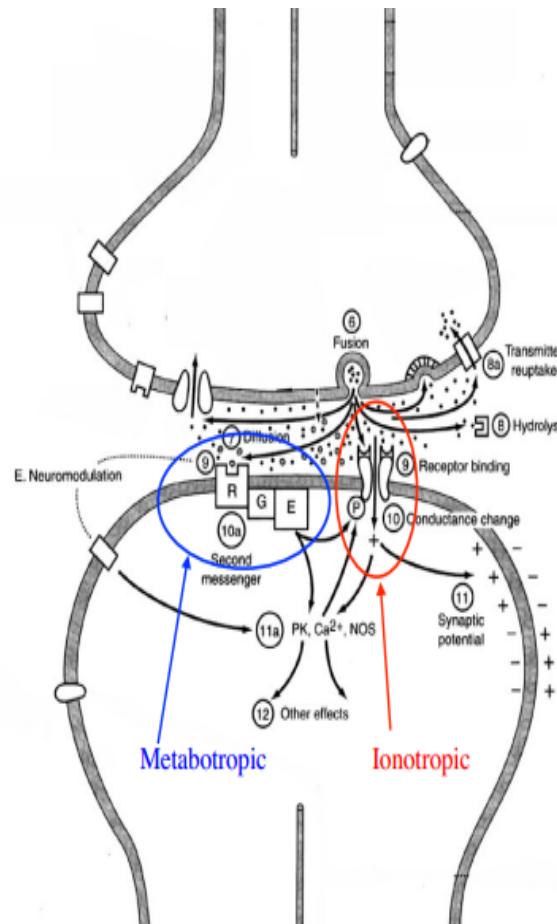


What are the steps happening in the postsynaptic side after a synaptic transmission?

On the postsynaptic side, neurotransmitter binds to a receptor (9).

Ionotropic receptors open an ion channel (10) for some ion or mixture of ions, allowing a current to flow. The effect of the synapse depends on which ion the channel conducts.

Metabotropic receptors are coupled to G-proteins and/or kinases which produce second messengers (10a, 11a) in the cell. Their effects often include changing the membrane potential, but they also have other effects, ranging from modulating ion channels to causing the production of new channels or receptors in the cell (12).

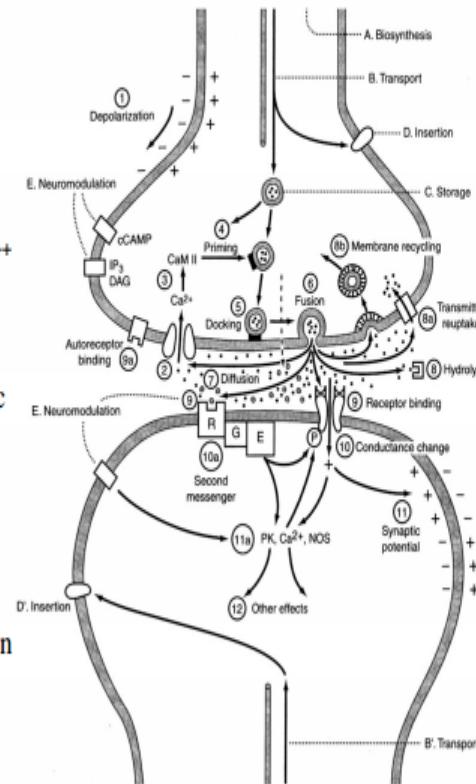


Factors for determining synaptic strength

What is the strength of a synapse? This question will be central to the lectures on network theory later in the course.

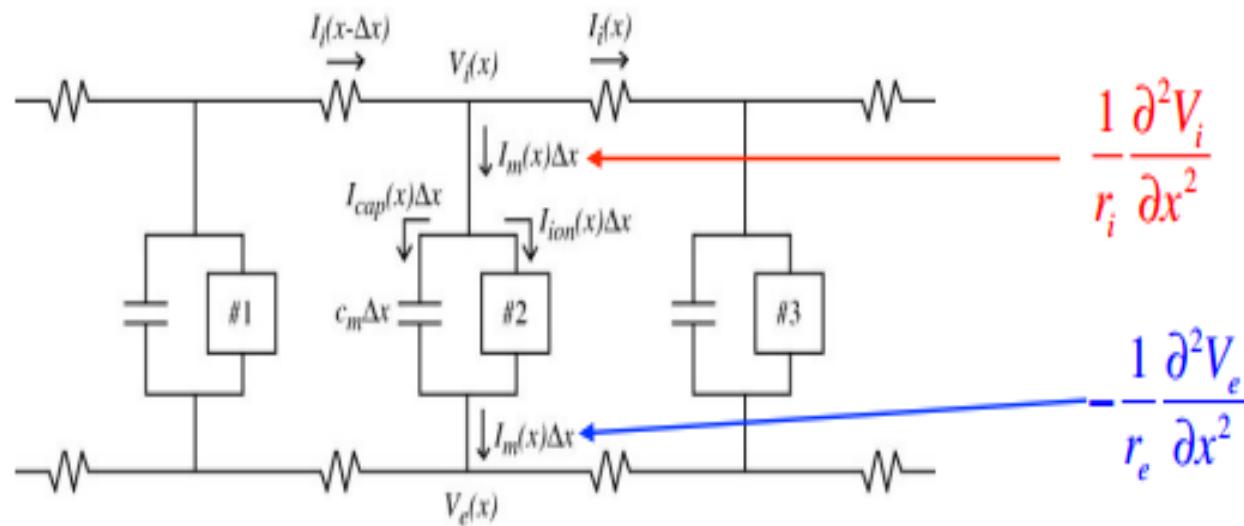
Synaptic strength is determined by a number of factors:

1. The size of the neurotransmitter release can be varied by **presynaptic inhibition**, often through metabotropic mechanisms (e.g. decreasing Ca currents in the presynaptic terminal).
2. **Synaptic facilitation**, due to accumulation of Ca⁺⁺ in the presynaptic terminal, can increase transmitter release.
3. **Synaptic depression**, due to depletion of synaptic vesicles, can decrease release.
4. **Synaptic depression** due to desensitization of receptors (similar to inactivation, see slide 11).
5. **Number of receptors**. The postsynaptic effect of NT release depends on the number of receptors in the postsynaptic membrane, especially AMPA receptors. Important for long-term plasticity.
6. **Postsynaptic electrical processing**. Changes in potassium currents through modulation of K⁺ channels can change the EPSP or IPSP produced by the synapse.



Cable equation

$$\frac{1}{r_i + r_e} \frac{\partial^2 V}{\partial x^2} = c_m \frac{\partial V}{\partial t} + I_{ion}$$



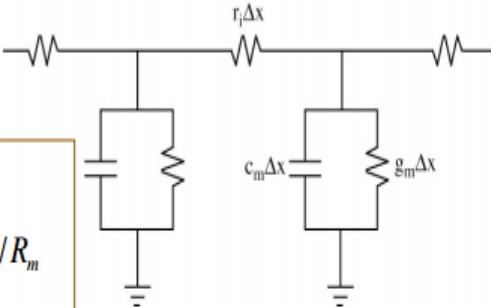
Linear Cable Theory Equations

Parameters: it is useful to relate the parameters of the ladder model to properties of the cylinder membrane.

$$c_m = \text{cap. per unit length of cylinder} = 2\pi a C$$

$$g_m = \text{conductance of unit length of cyl.} = 2\pi a / R_m$$

$$r_i = \text{resistance of unit length of cytoplasm} = R_i / \pi a^2$$



where C is the capacitance of a unit area of membrane, $\approx 1 \mu\text{Fd}/\text{cm}^2$

R_m is the resistance of a unit area of membrane, $\approx 10^3\text{-}10^5 \Omega\text{-cm}^2$

R_i is the resistance of a unit cube of cytoplasm, $\approx 200 \Omega\text{-cm}$

and a is the radius of the cylinder.

THEN the two parameters of the cable equation are given by

$$\lambda = \sqrt{\frac{1}{g_m(r_i + r_e)}} \approx \sqrt{\frac{1}{g_m r_i}} = \sqrt{\frac{a R_m}{2 R_i}} \quad \text{and} \quad \tau = \frac{c_m}{g_m} = R_m C$$

$$\text{velocity} \approx \frac{\lambda}{\tau} = \frac{\sqrt{a}}{\sqrt{2 R_m R_i C}}$$

The different types of neuron length measures?

Two measures:

1. **Electrotonic length** (as defined previously)

$$L_{PQ} = \frac{l_{PQ}}{\lambda}$$

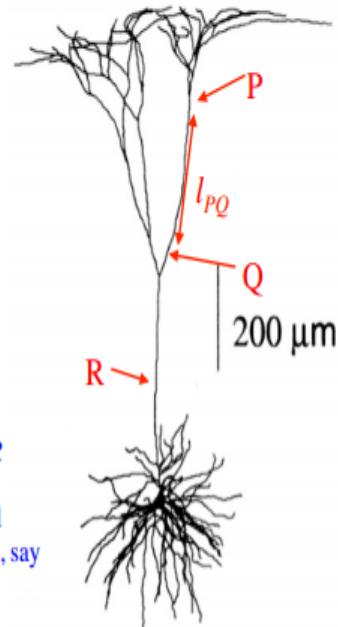
2. The **morphoelectrotomic transform (MET)**, in which distance is defined in terms of **voltage attenuation** A as follows:

$$A_{PR} = \frac{V_R}{V_P}$$

resulting potential observed at point R
membrane potential produced at point P, say by a synapse

then the MET is

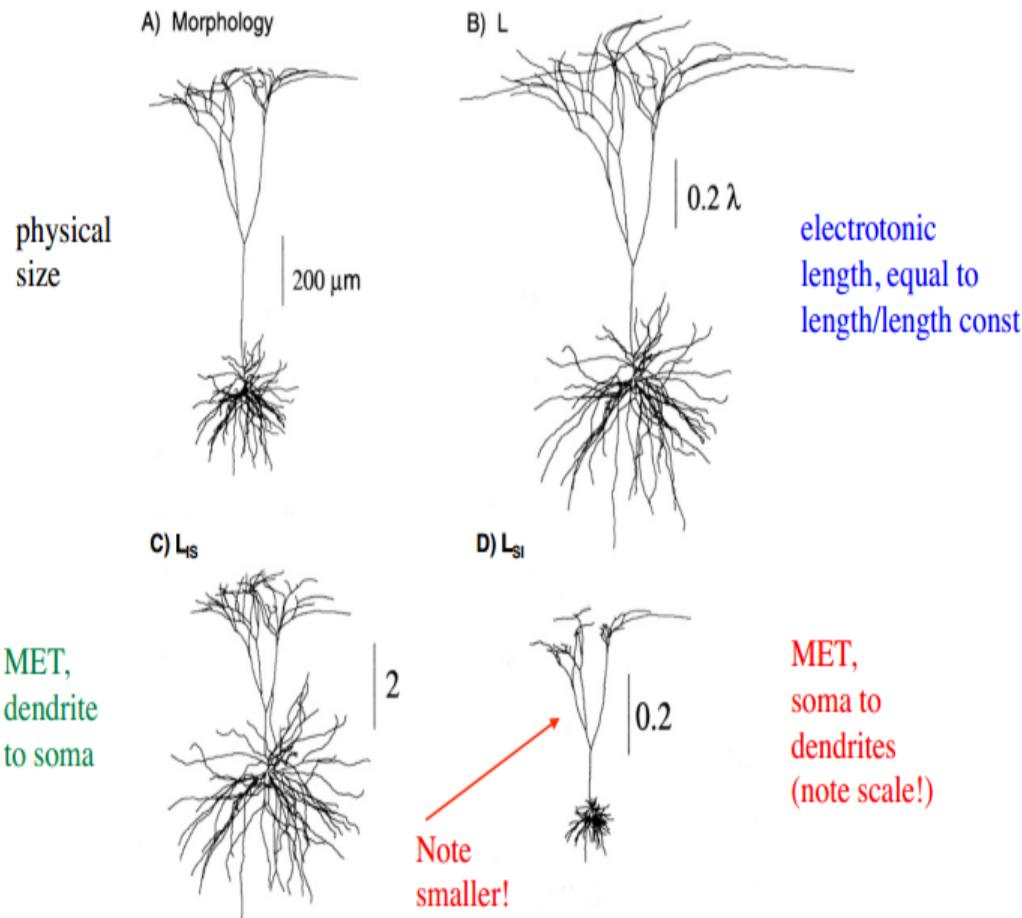
$$\Lambda_{PR} = -\ln A_{PR}$$



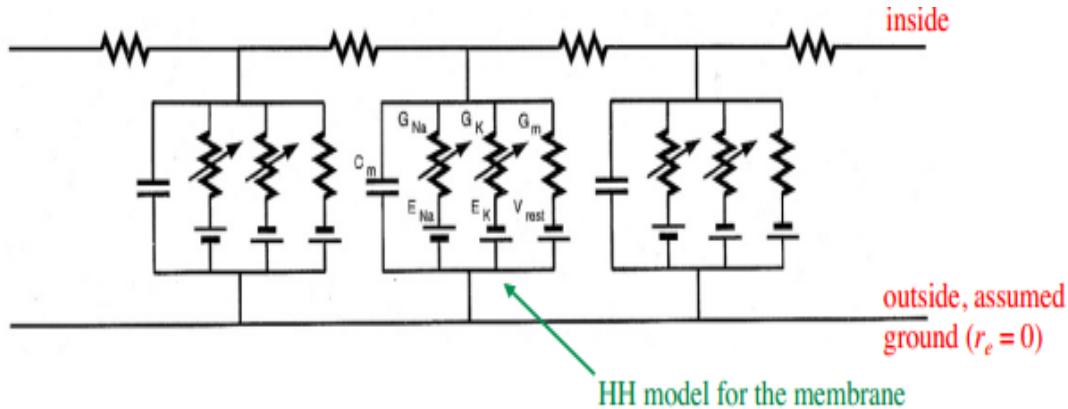
Note that Λ_{PR} incorporates both the exponential decay of potential with distance and the effects of branching (which the cumulative electrotonic length $L_{PQ} + L_{QR}$ would not).

More on different length types

How large is the dendritic tree? Note that the MET is different depending on the direction in which it is defined.



Non-linear cable theory



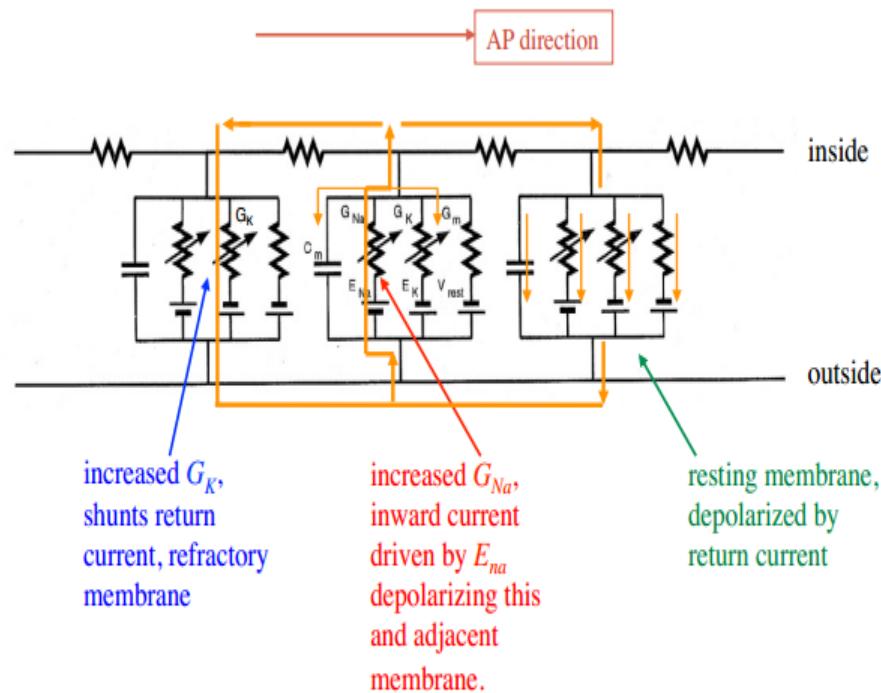
The cable equation must include the **non-linearities** in the transmembrane ion current term:

$$\frac{1}{r_i} \frac{\partial^2 V}{\partial x^2} = c_m \frac{\partial V}{\partial t} + I_{ionic} = c_m \frac{\partial V}{\partial t} + G_{Na} m^3 h (V - E_{Na}) + G_K n^4 (V - E_K) + G_m (V - E_{rest})$$

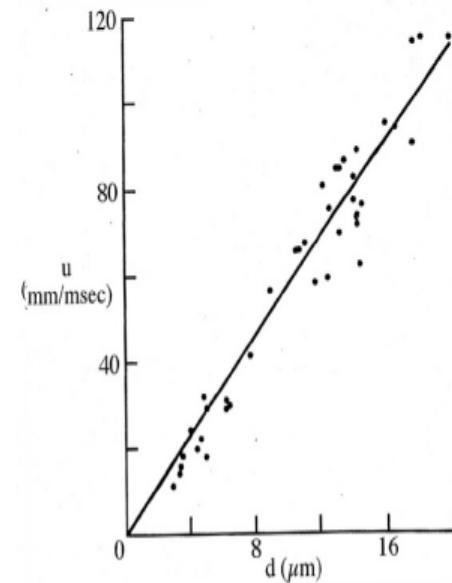
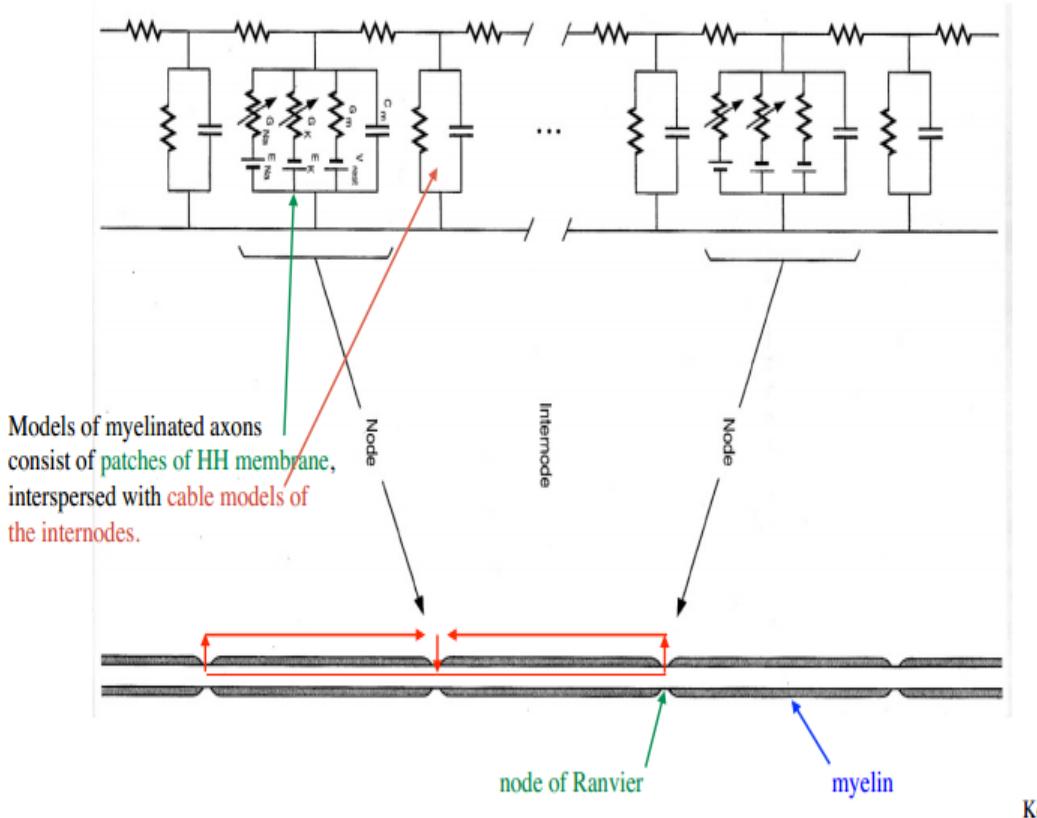
plus additional differential equations to describe the evolution of m , h , and n .
An important test of the HH formulation is whether it can predict the propagation of the AP along an axon.

$$= I_{Na} + I_K + I_m$$

Why do APs go only in one direction?

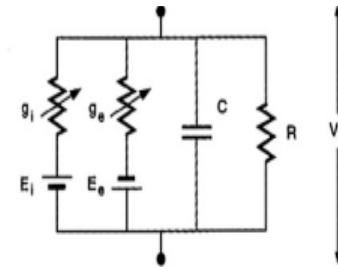


What is myelination and why is it important?



What is synaptic shunting?

Synaptic interactions are inherently non-linear, because synapses change the conductance of the membrane, instead of performing some linear operation like injecting current.



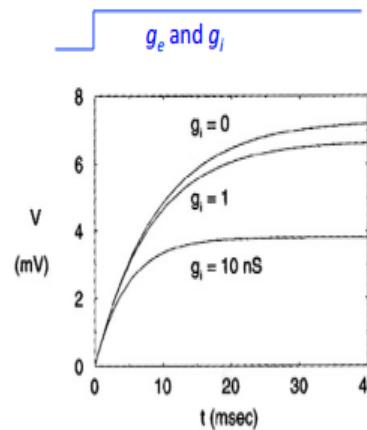
The steady-state ($dV_m/dt=0$) value of V_m is

$$V_m(t \rightarrow \infty) = V_{\max} = \frac{g_e E_e + g_i E_i}{g_e + g_i + 1/R}$$

Note the nonlinear dependence of V_m on synaptic conductance g_e and g_i .

The excitatory response is saturating, so as g_e gets large compared to $1/R$, V saturates at E_e .

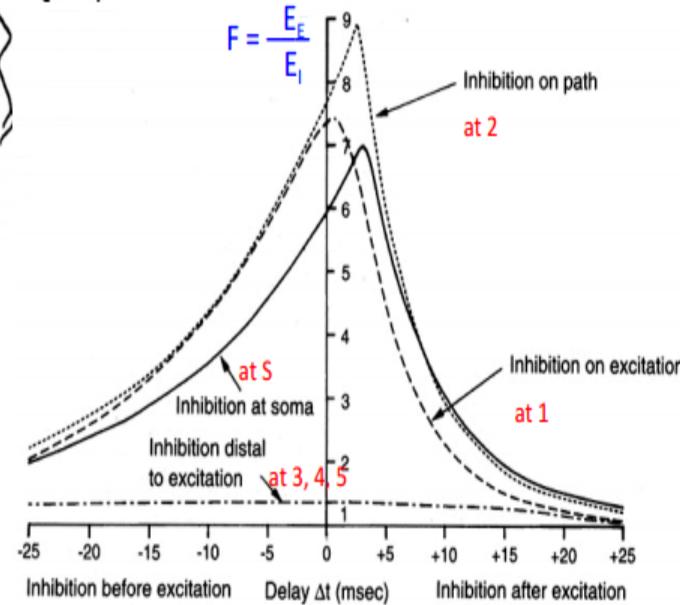
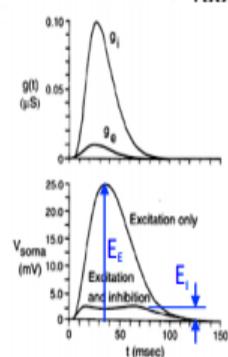
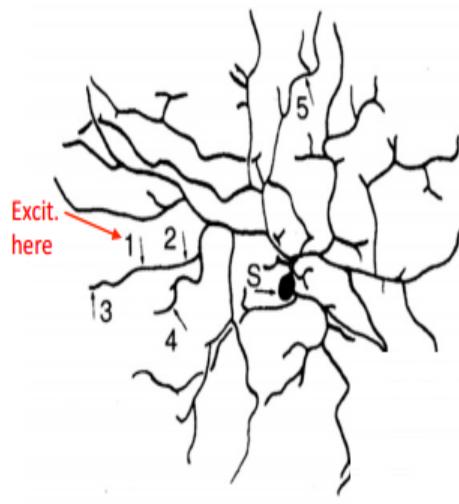
Note also that the synaptic inhibition can be effective even if $E_i = 0$ (the resting potential), called shunting inhibition.



1/R=10 nS, $g_e=1$ nS
 $E_e=80$ mV, $E_i=0$ mV

Where do inhibitory synapses need to be to optimally cutoff EPSPs?

What is the effect of relative placement of synapses on the dendrites? Because cells are not electrically compact, the relative placement of synapses on dendrites matters.



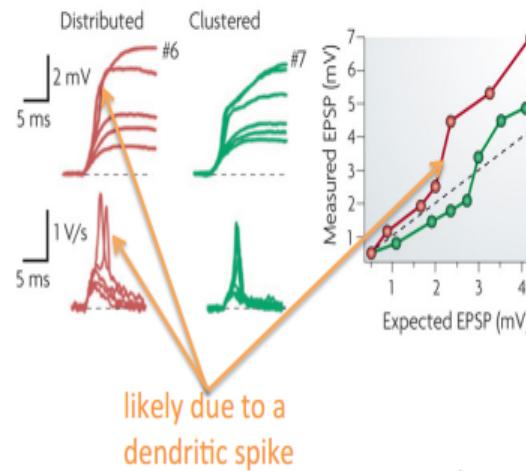
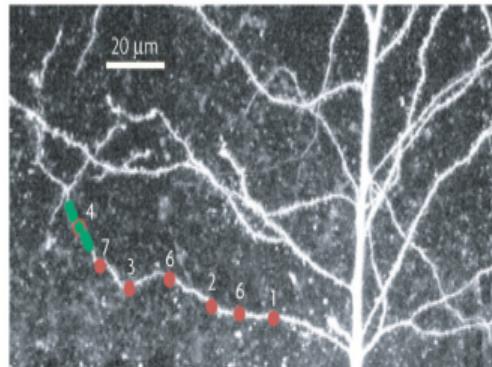
How do synapses interact?

Because of the nonlinearity of the synaptic effect, clustering of inputs reduces the net synaptic effect. The red data show the response in the soma to (near) simultaneous glutamate uncaging at 7 sites spread out along a dendrite.

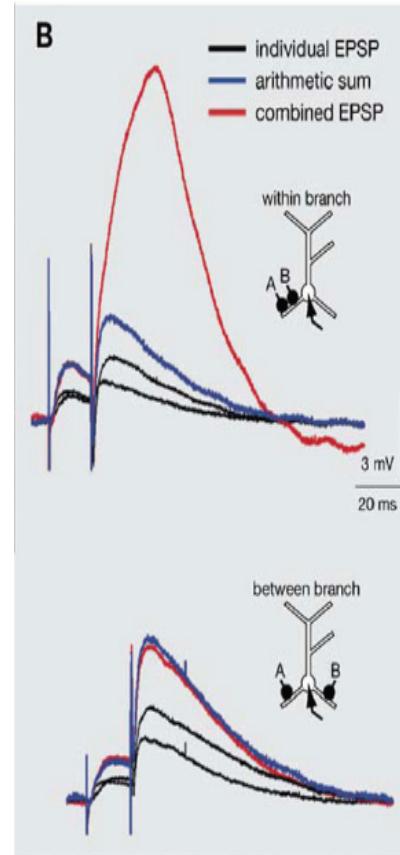
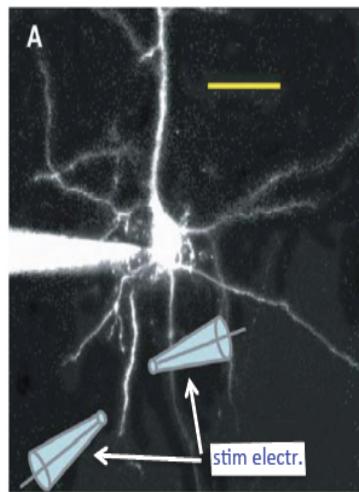
The green data show responses when the sites are clustered together.

Note that the response is smaller when clustered for small EPSPs.

Larger EPSPs (>3 mV in this case) show an increase in relative size, probably due to dendritic active channels.



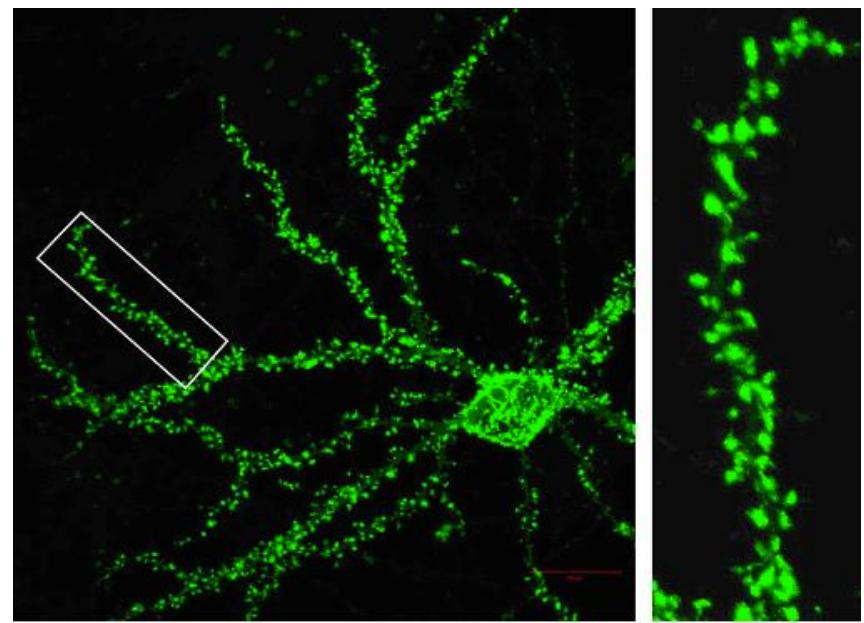
How do synapses interact?



Summation of dendritic inputs (electrical stimulation of small numbers of synapses): linear between branches and nonlinear (supralinear) within a branch.

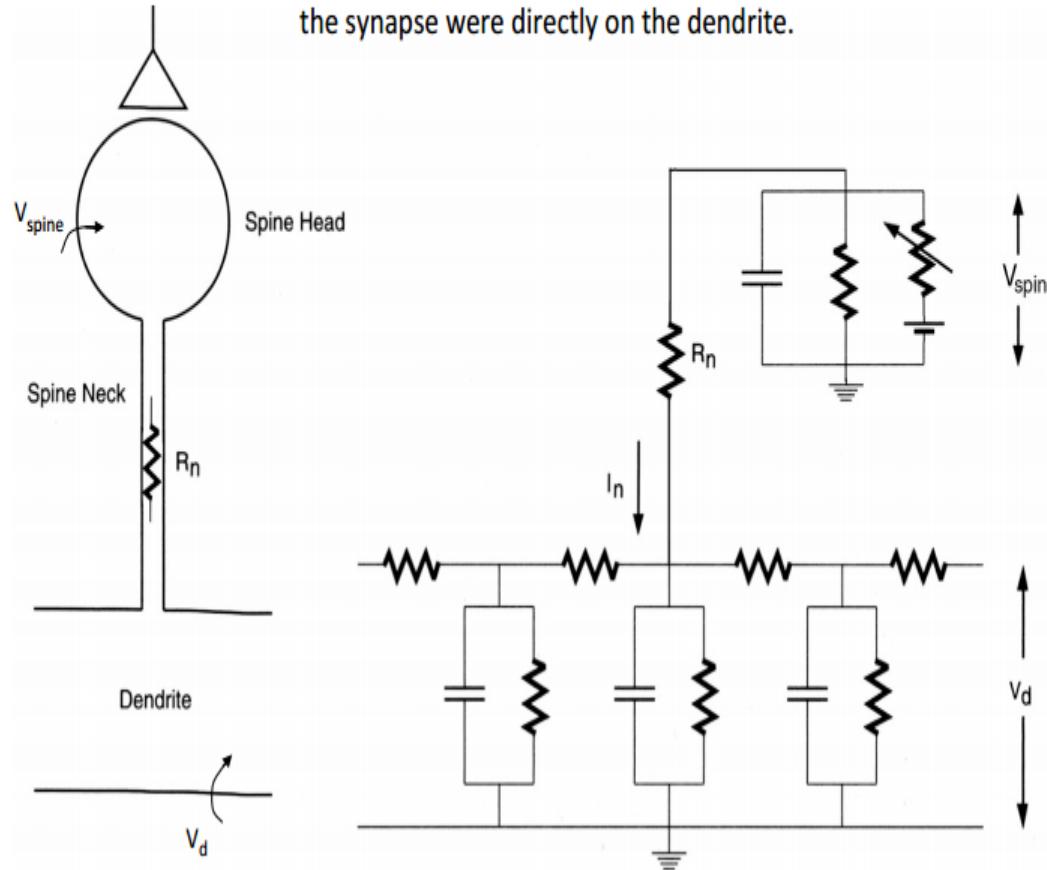
Dendritic Spines

- Protrusions from the dendrite
- Excitatory synapses



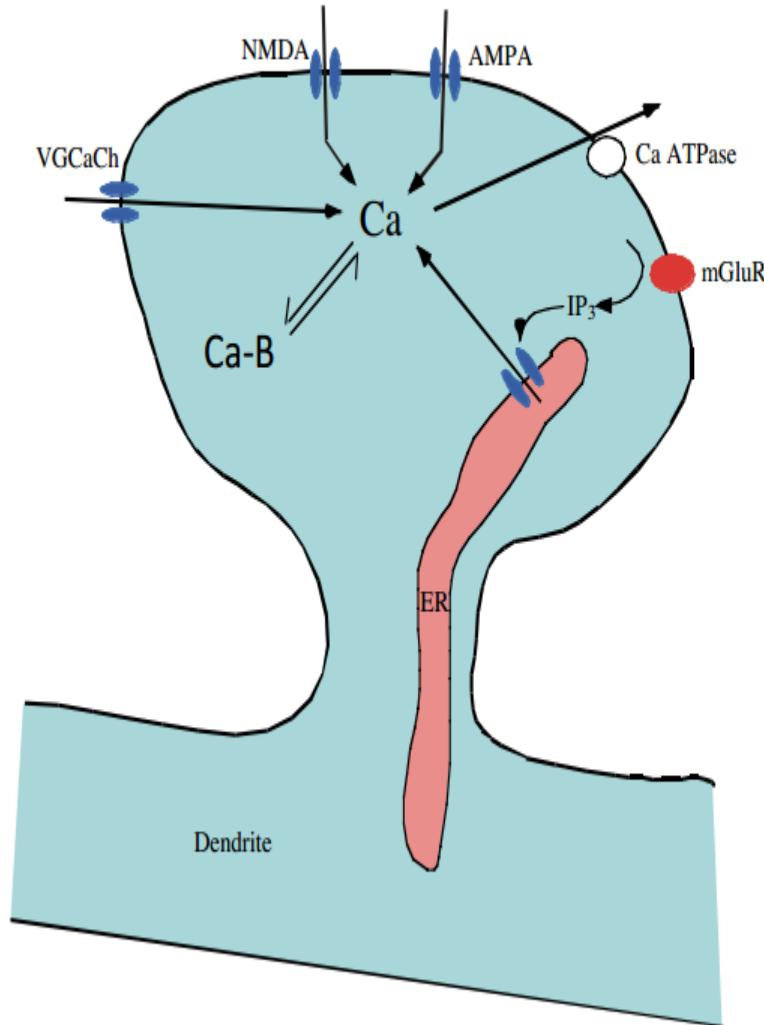
What are spines and why are they there?

What is the effect of spines on input/output processing in a neuron? **Spines do not have a significant electrical effect:** the worst-case electrotonic length (L) of the spine neck is about 0.02, so there is negligible cable effect. Calculations show that the current injected into a dendrite by a synapse on a spine head is about the same as if the synapse were directly on the dendrite.



More on spines

The calcium signal in spines is an essential message for postsynaptic plasticity, discussed in a subsequent lecture. Confining Ca to a single spine makes the changes produced by that Ca specific to the synapse on the same spine.



Dr. Kirkwood's lectures

How do we think are memories formed?

- *By redistributing the synaptic weights in the brain neuron network.*
- Look up experimental examples from slides

What are the two rules according to which these happen?

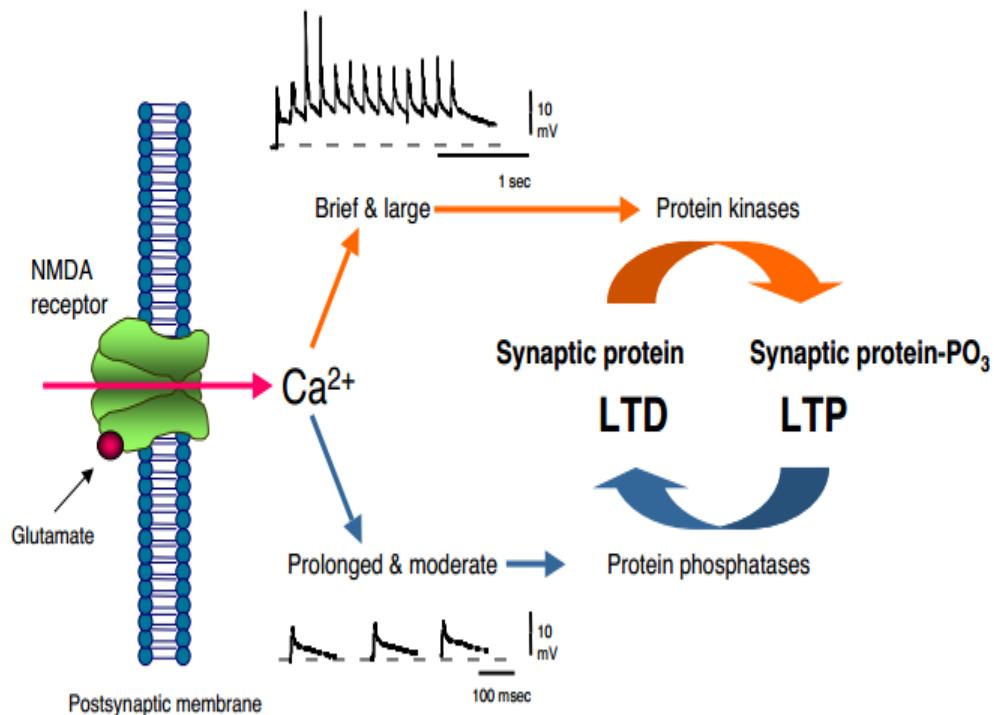
Hebb's rule (Neurons that fire together are wired together) and

Stent's rule (Neurons that fire out of sync lose their link)

What are the two main types of synaptic strength changes?

- *LTP and LTD*

What is the overall mechanism in which LTP/ LTD happen?



Long-Term Potentiation Induction and Blocking

1. Synaptic tetanus
2. Pairing a low frequency stimulation with postsynaptic depolarization
 - Postsynaptic hyperpolarization
 - NMDAR antagonists
 - Pairing with depolarization to E_{Ca}

Long-Term Depression Induction and Blocking

May be produced by:

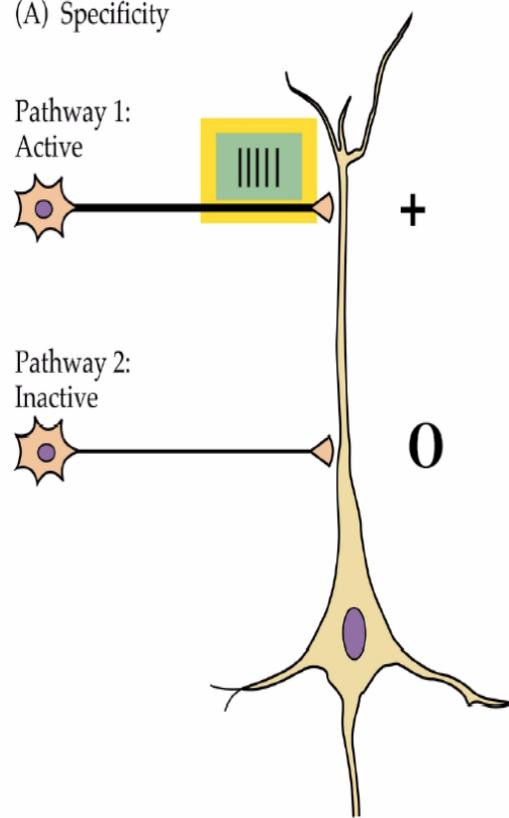
prolonged low-frequency stimulation
bath-applied glutamate
pairing with depolarization to -40 mV

Is blocked by:

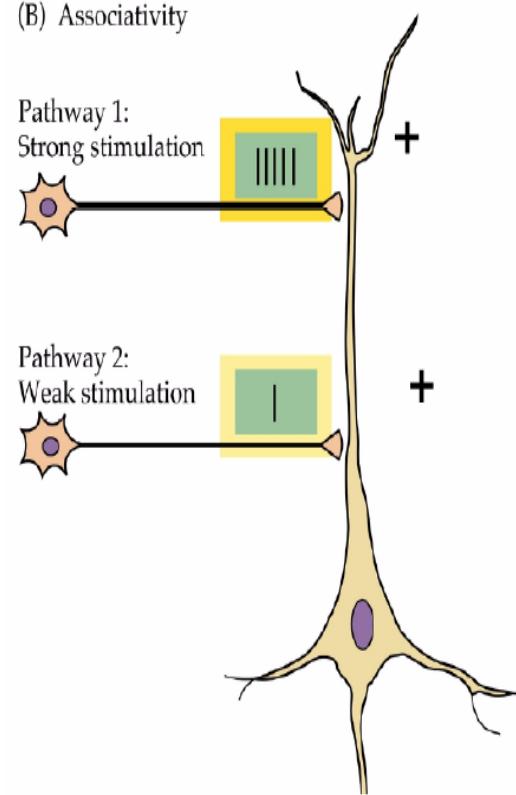
NMDA-R antagonists
postsynaptic Ca chelators
postsynaptic calcineurin/PP-1 inhibitors
mutants which lack calcineurin activity

2 main LTP characteristics

(A) Specificity



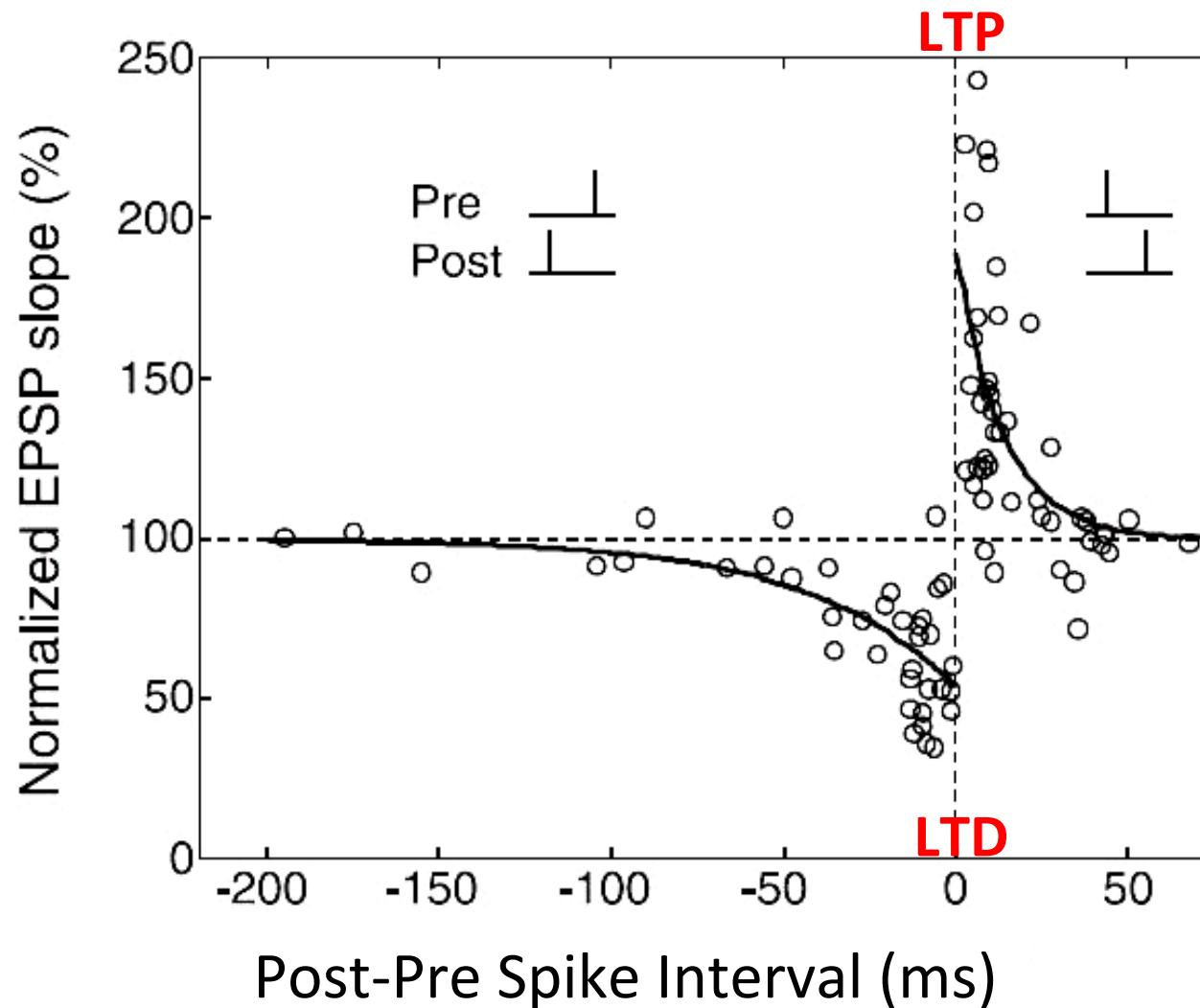
(B) Associativity



How plasticity might be happening in the brain?

*Not through tetanus or slow
stimulations, but through spike timing
dependent plasticity.*

Spike timing dependent plasticity



What is meta-plasticity and why is it required?

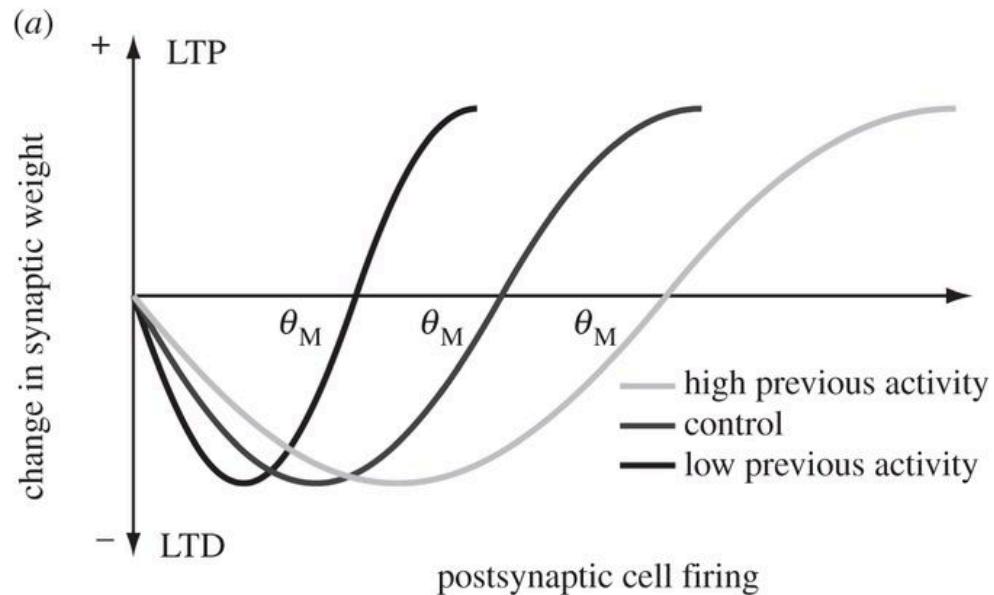
Regulation (or plasticity) of synaptic plasticity.

Prevents oversaturation due to positive feedback

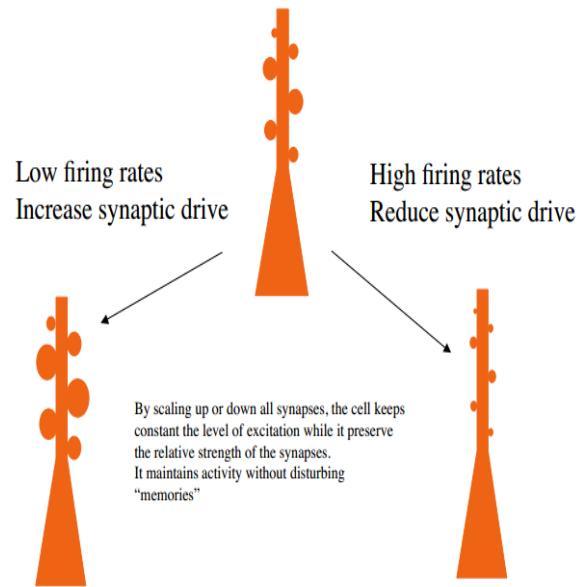
Synapse's previous history of activity determines its current plasticity.

Two Theories as to How Meta-Plasticity Occurs

Sliding Threshold



Synaptic Scaling



Properties of Both Theories

Sliding threshold

Global: affects all synapses

Dark rearing reduces
threshold for LTP in visual
cortex

Does not affect stored
memories

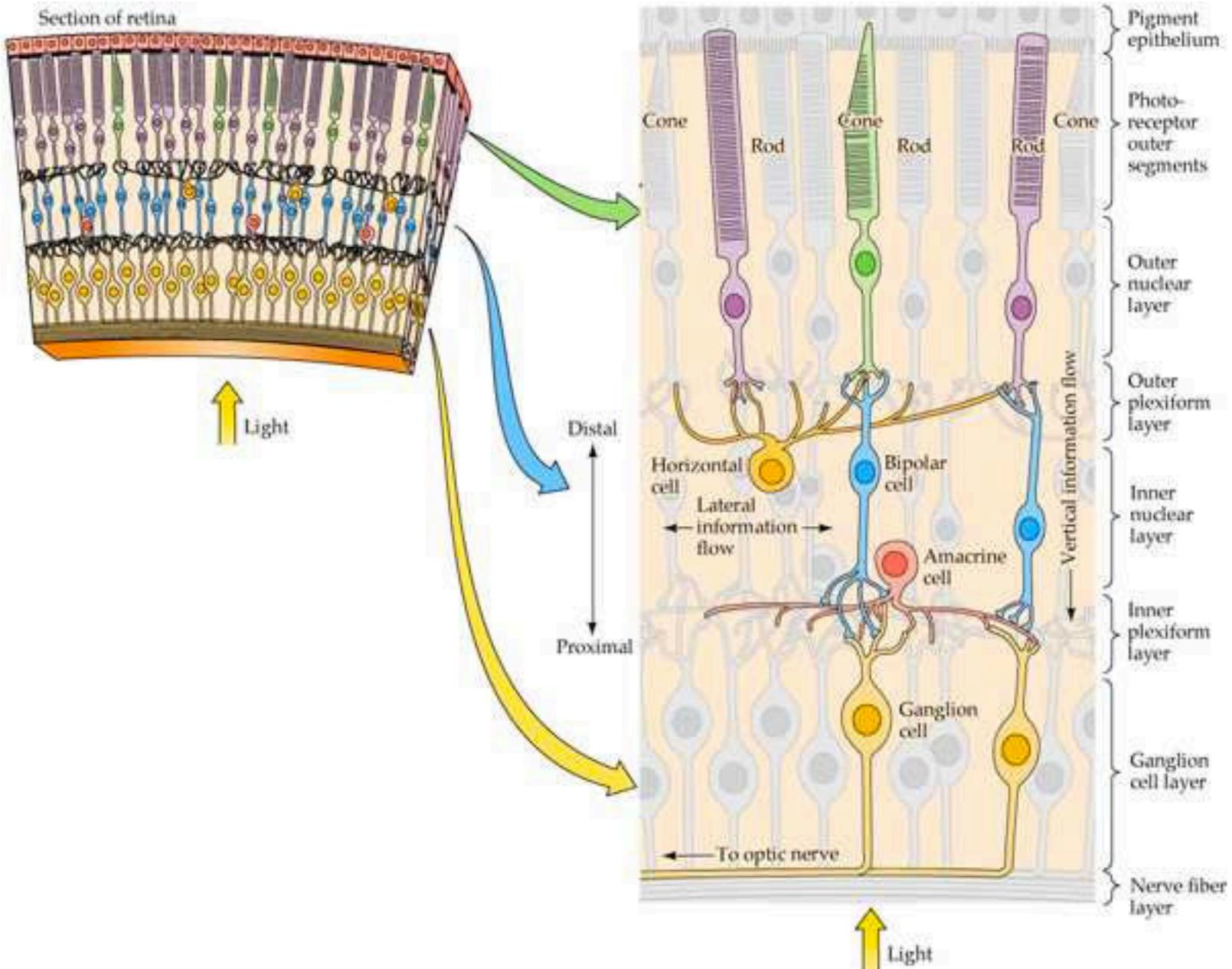
Synaptic scaling

Global: affects all synapses

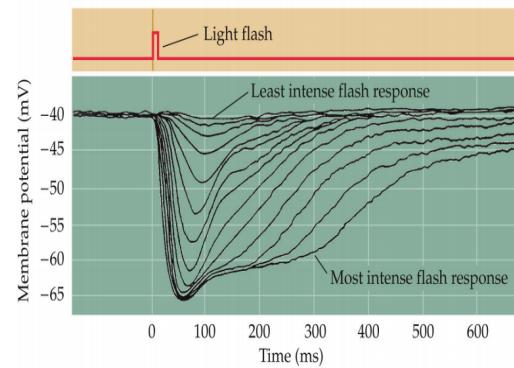
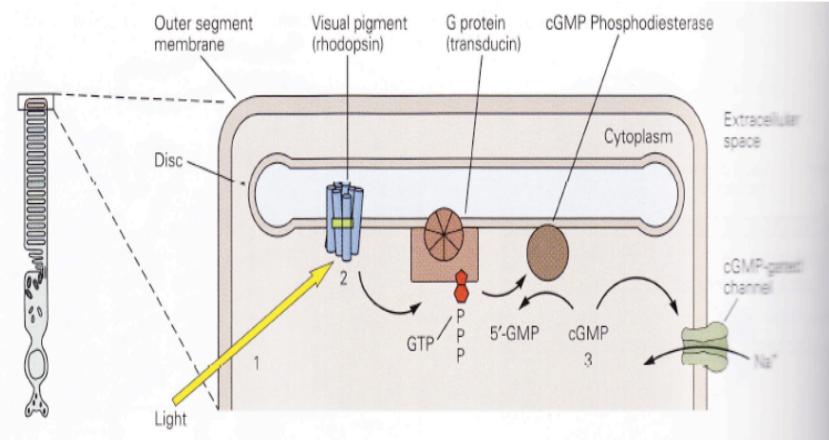
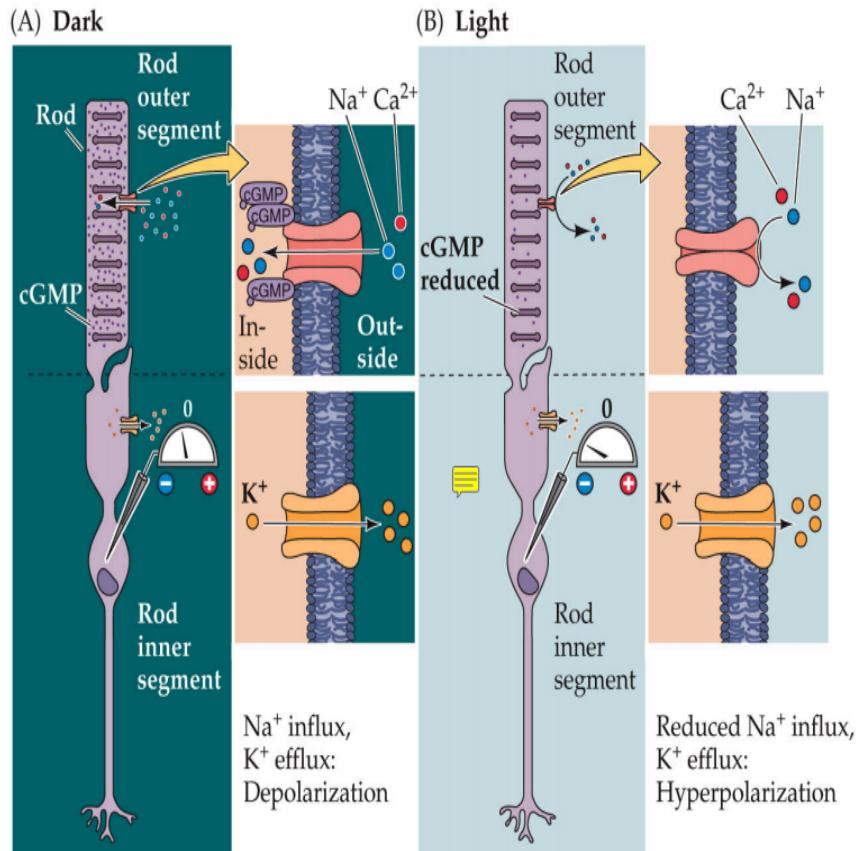
Dark rearing increases the
size of the unitary responses
in visual cortex

Does not affect stored
memories

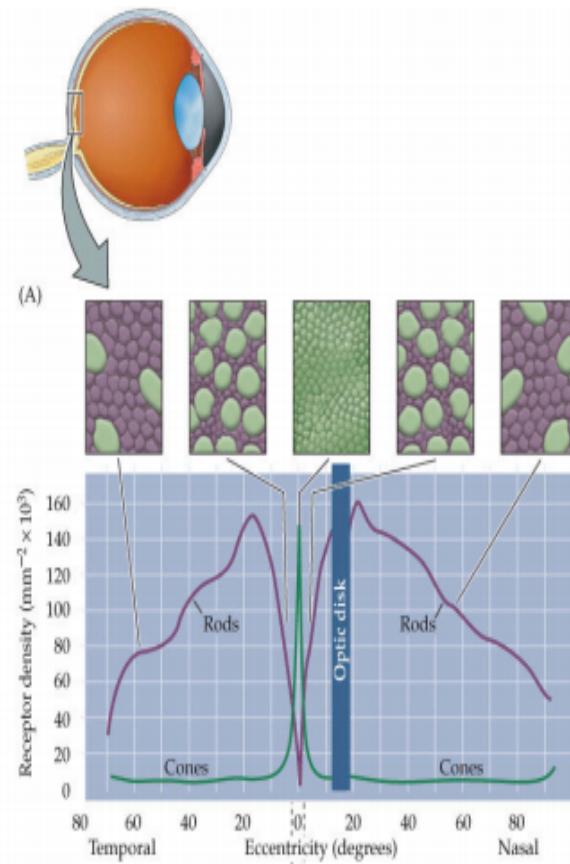
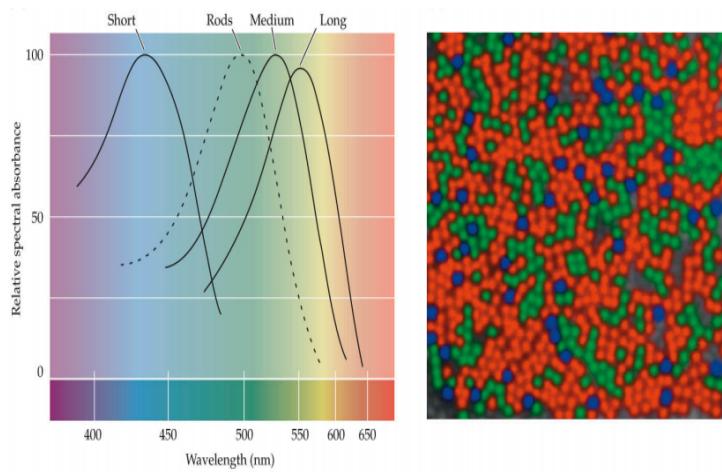
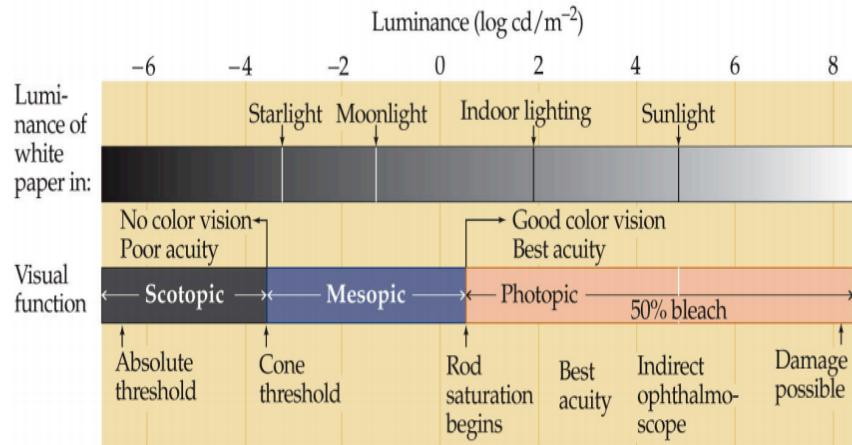
Dr. Connor's Lectures



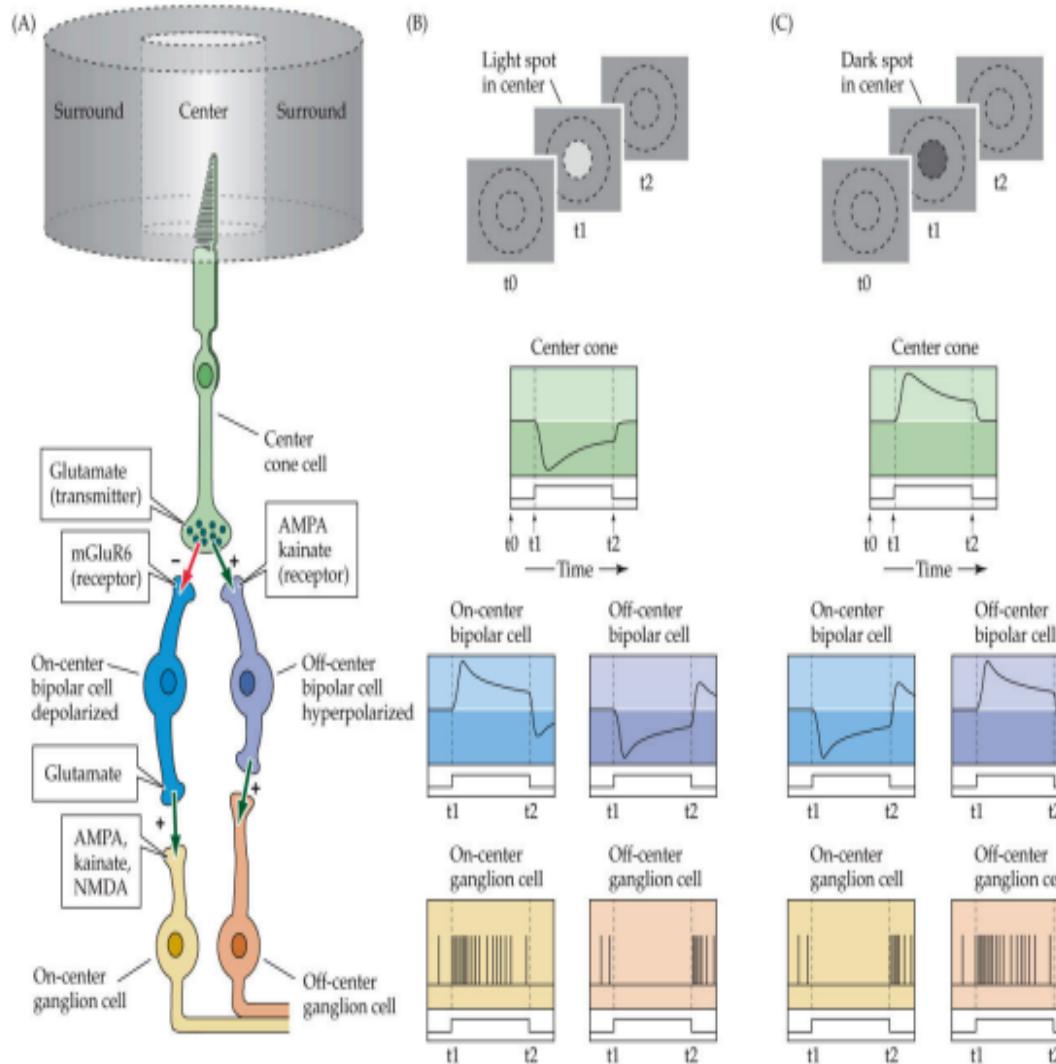
Photoreceptors Response to Light



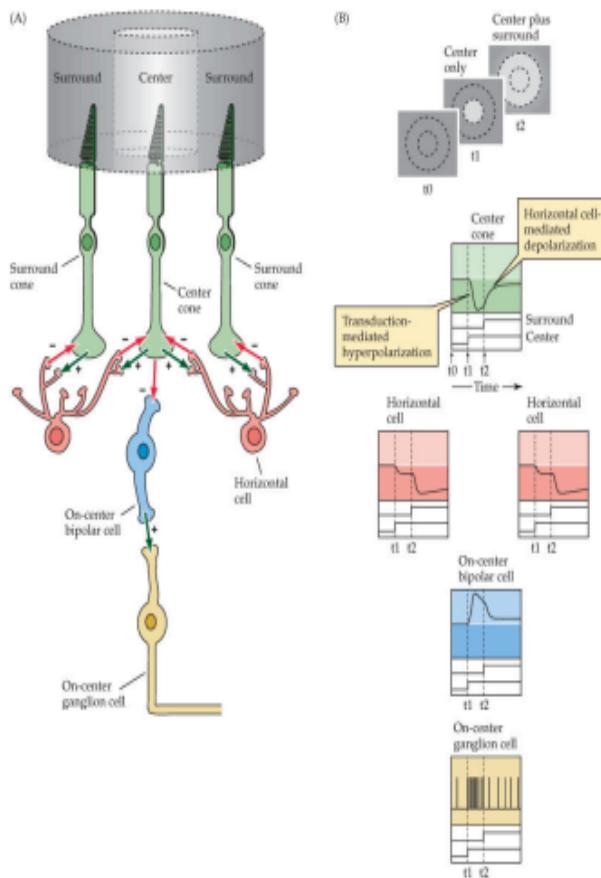
More Info on Rods and Cones



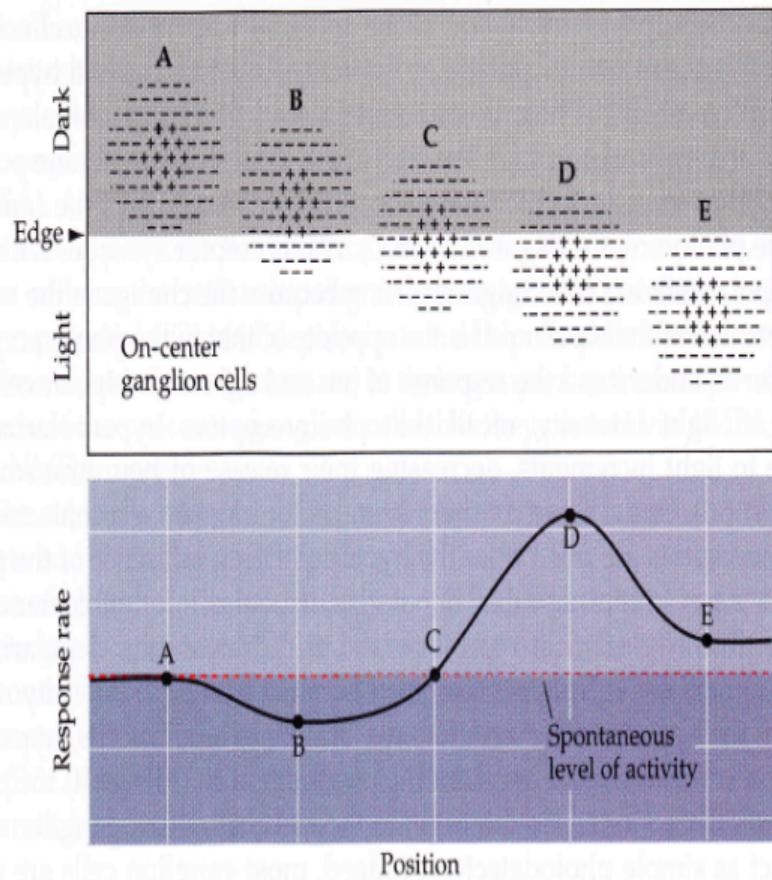
ON VS. OFF DEPENDS ON BIPOLAR CELL RECEPTORS



CENTER-SURROUND RECEPTIVE FIELD CIRCUITRY



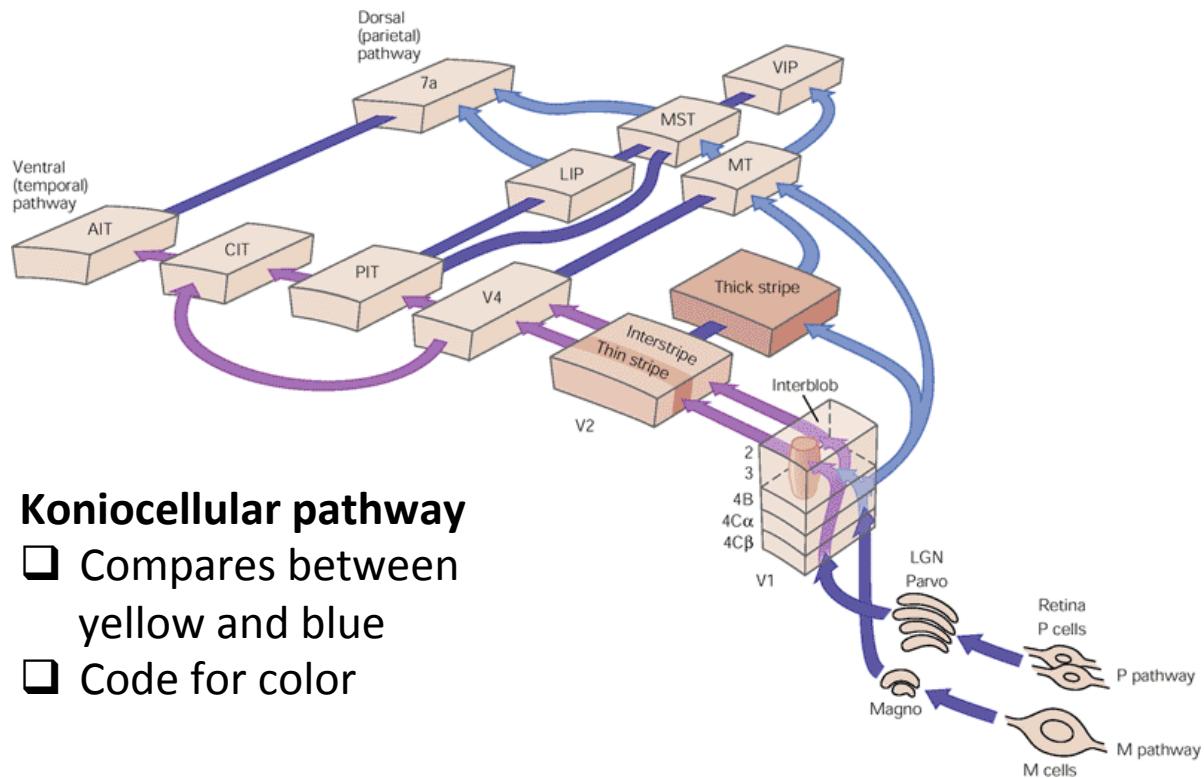
CENTER-SURROUND CELLS RESPOND TO EDGES



P, K and M pathways

Parvocellular pathway

- Thin 4 strips in LGN
- High spatial acuity (red/green cones)
- Code for color



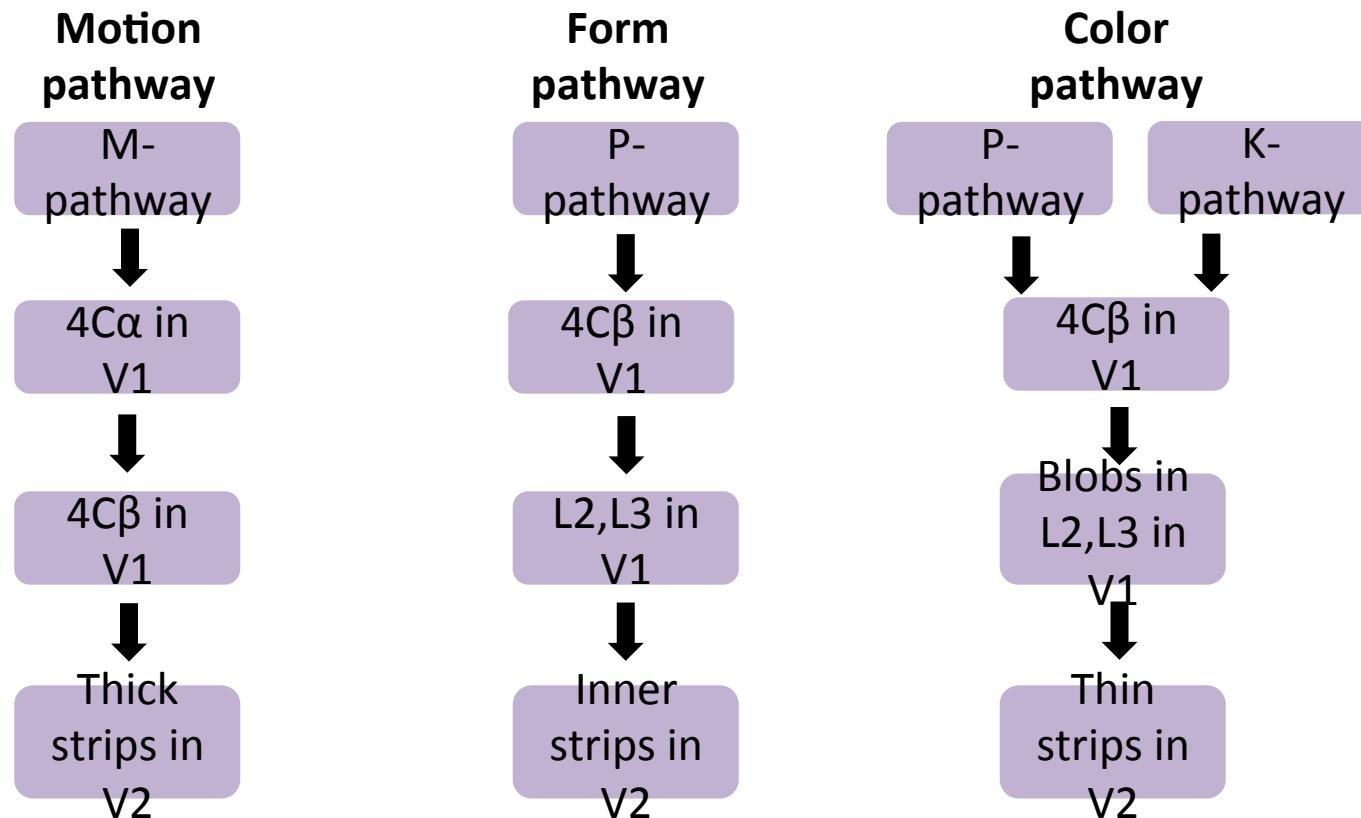
Magnocellular pathway

- Thick first 2 strips in LGN
- Low spatial acuity (Mainly rods)
- Code for motion

Koniocellular pathway

- Compares between yellow and blue
- Code for color

Three separate information pathways in V1 and V2



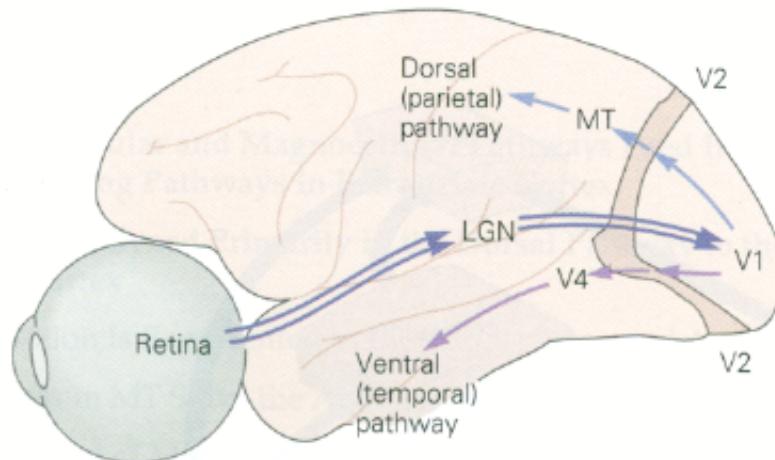
Beyond V1 and V2

Ventral Pathway

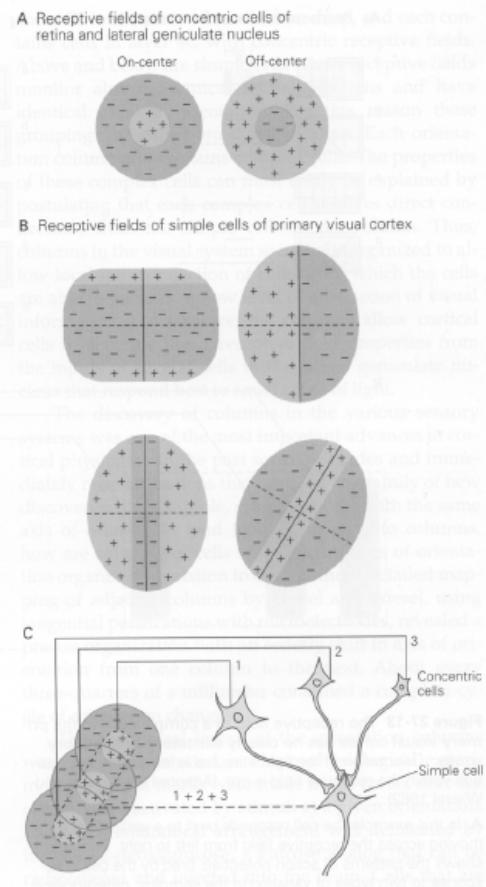
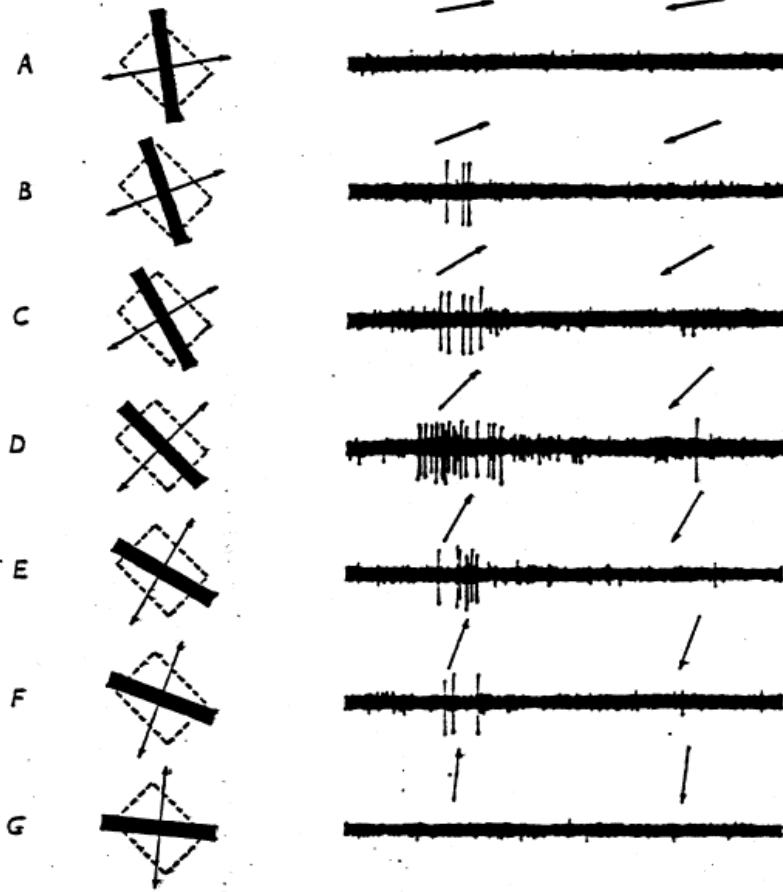
- Goes to temporal lobe
- “What” pathway

Dorsal Pathway

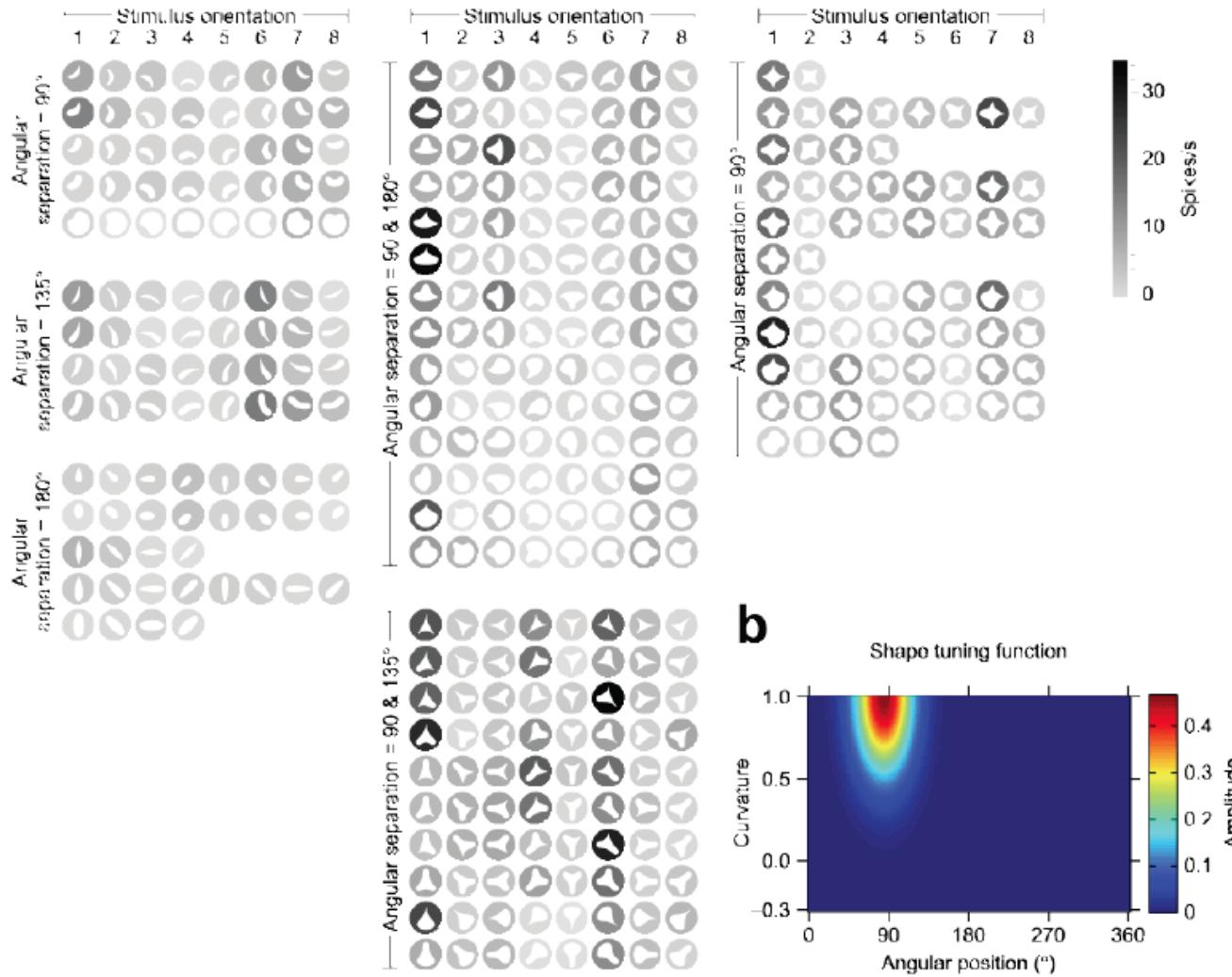
- Goes to parietal lobe
- “Where” (in space and time) pathway



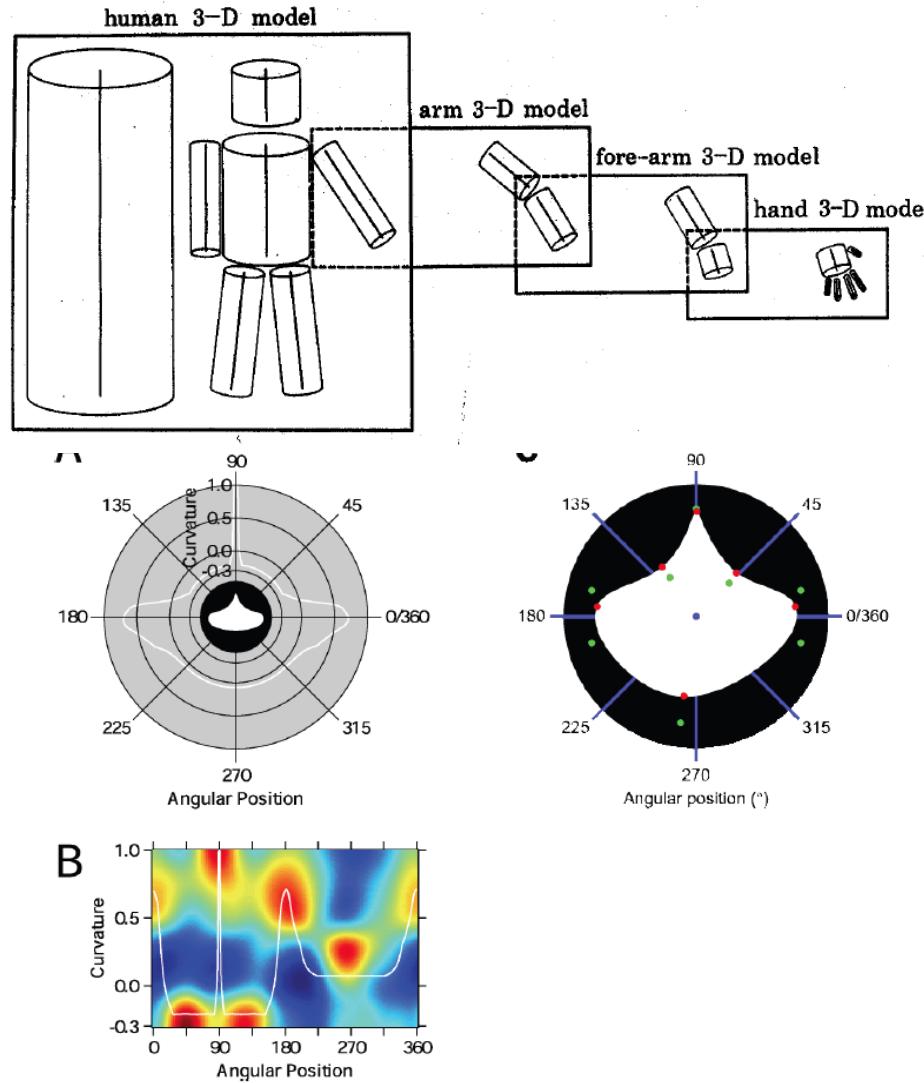
Orientation and Motion-Direction Tuning in V1



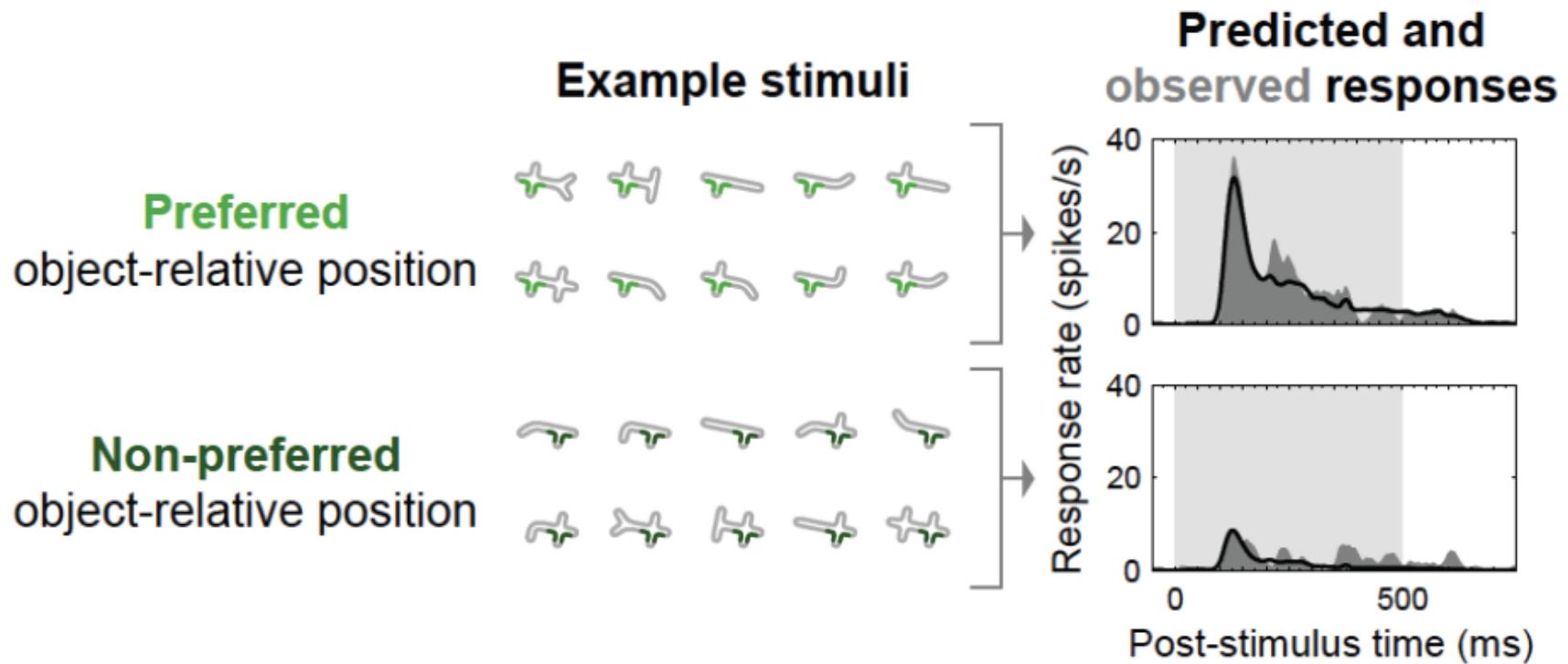
Curvature Tuning in V4



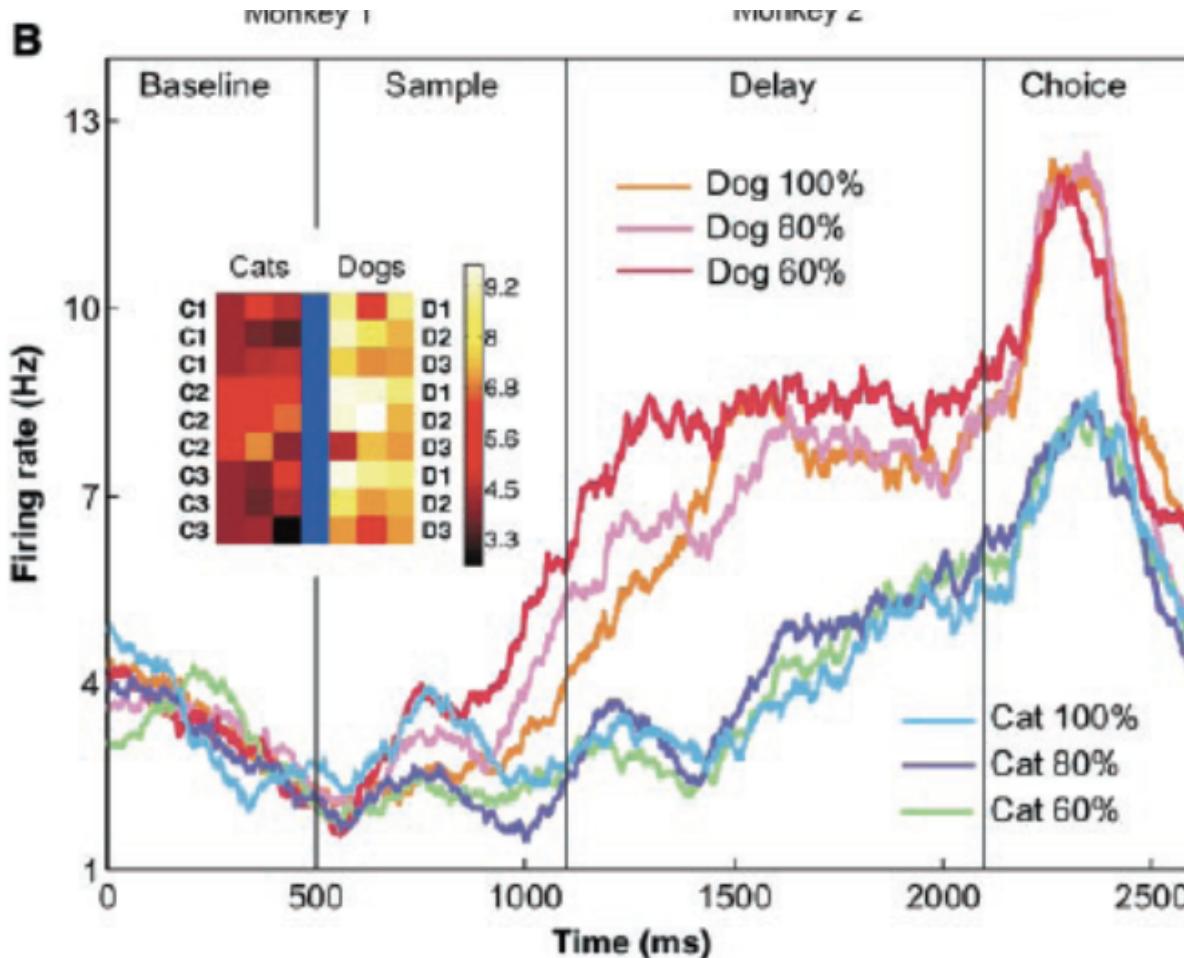
Configural Coding in V4



Object-Centered Position Coding



Prefrontal Encoding of “Dog”



Hand-Centered Position Coding

