NeuroImaging Training Program

mscohen@g.ucla.edu

2 TRUTHS AND 1 LIE

- Though I Perform Hypnosis, I Am Not Hypnotizable
- I Am A College Dropout
- My Lab Director Advised Me to Leave Science

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NIH RFA DA-06-011 and DA-11-006

Training in Neuroimaging: Integrating First Principles and Applications (T90)

Program Objective

This funding opportunity will enable the development of novel, interdisciplinary training programs that integrate comprehensive training in basic neuroscience, the physical and biological bases of neuroimaging, the technologies of *in vivo* neuroimaging, and the application of these technologies to understanding questions in neuroscience across the life span...

The goal of these training programs is to train the next generation of neuroimaging researchers who understand the underlying principles and the technologies of neuroimaging as well as their application to experimental questions in neuroscience. To realize this goal, it is imperative to recruit and expose students early in their careers to the ways in which their interests can be applied to questions in neuroscience through the mathematical, physical, and chemical principles of neuroimaging. Training programs are required to interface trainees from the quantitative, engineering, and physical/chemical sciences with trainees from biomedical/biological disciplines in the same integrated training program.

MULTIMODAL NEUROIMAGING TRAINING PROGRAM - U. Pittsburgh, Seong-Gi Kim
ADVANCED MULTIMODAL NEUROIMAGING TRAINING GRANT - Harvard, Bruce Rosen

NeuroImaging Training Program

- Funded since 2006 by the National Institutes of Health
- Two components:
  - Graduate Fellowship Program - eligible to UCLA students
  - $100,000/year for the Summer Program
- Approximately 350 students have been trained in our classes

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- 333 Total Summer Students
  - Australia, Belgium, Brazil, Canada, China, Egypt, Germany, India, Italy, France, Hungary, Japan, Mexico, Netherlands, Poland, Portugal, Spain, Switzerland, Turkey, United Kingdom, USA, and others
- 145 Academic Year Students
- 50 Fellowships

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- 93 Applicants
- 1,174 pages of application materials
- Your group: Belgium, Canada, China, Germany, Mexico, Netherlands, Portugal, United Kingdom, USA
- Average of:
  - 3.8 First author papers
  - 6.1 Co-author papers
  - 13.4 Abstracts

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WEBCAST

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SCHEDULE 2016

Week 1	Monday 7/11	Tuesday 7/12	Wednesday 7/13	Thursday 7/14	Friday 7/15
9:00	Welcoming Remarks Cohen <slides> <feedback> <video>	GLM 1 Monti <slides> <feedback> <video>	Functional Connectivity / PPI Lenartowicz <slides> <feedback> <video>	Diffusion MRI and the Fiber Architecture of the Brain Wedeen <slides> <feedback> <video>	Are Your Analyses Too Parametric? Monti <slides> <feedback> <video>
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11:00	Data Processing Monti <slides> <feedback> <video>		Q&A / Break		Q&A / Break
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12:30		LUNCH (provided!)			LUNCH (provided!)
1:00					
1:30	How Can fMRI Inform the Structure of the Mind? Poldrack Public Keynote <slides> <feedback> <video>		Introduction to Diffusion Weighted Imaging Wedeen <slides> <feedback> <video>	BrainSuite Shattuck <slides> <feedback> <video>	
		Group Analysis Monti <slides> <feedback> <video>			Student Data Blitz <slides> <feedback> <video>
2:30			Q&A / Break		
3:00	Experimental Design 1 Bookheimer <slides> <feedback> <video>	ROI and Brain-Behavior Correlations: *Avoiding Circularity* Rissman <slides> <feedback> <video>	TrackVis Wedeen <slides> <feedback> <video>	Q&A / Break	
3:30				BrainSuite Shattuck <slides> <feedback> <video>	Brain Stimulation TBA <slides> <feedback> <video>
4:00	Q&A / Break	Q&A / Break	MRI Tutorial *(Optional)* Cohen <slides> <feedback> <video>		
4:30	Experimental Design 2 Monti <slides> <feedback> <video>	Truths and Lies Class <slides> <feedback> <video>		Q&A / Break	Happy Hour
5:00			Student Data Blitz <slides> <feedback> <video>	Free	
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10:00	Q&A / Break	Q&A / Break	Q&A / Break	Q&A / Break	Career Panel Faculty <slides> <feedback> <video>
10:30	Break	Group ICA Calhoun <slides> <feedback> <video>	Multivariate Encoding Methods Gallant <slides> <feedback> <video>	Dynamic Causal Modeling Anderson <slides> <feedback> <video>	
11:00 / 11:30	NET-fMRI of Large -Scale Brain Networks Logothetis <slides> <feedback> <video>	Multi Modal Fusion Calhoun <slides> <feedback> <video>	Q&A PHOTO DAY! Break	Dynamic Causal Modeling: EEG Douglas <slides> <feedback> <video>	Debates in Neuroimaging Attendees <slides> <feedback> <video>
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SOME DEBATE IDEAS

- Is fMRI relevant to Cognitive Psychology?
- Interpreting shadows: how close is BOLD to actual neural activity? (what about negative BOLD?)
- Can we use EEG + fMRI to improve temporal accuracy?
- Is the future of fMRI in the assessment of the individual?
- Reverse Inference: What are the virtues and limitations?
- What is functional connectivity? Does it tell us how populations of neurons compute? Does it have a physiological/physical interpretations?

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SOME DEBATE IDEAS

- Resting state: Fad or Future? Is it just plumbing?
- Does the advantage of ultra-high field outweigh its costs?
- Is it worth running fMRI of small groups? What is the importance of big data?
- What can we learn from the connectome project?
- Should functional imaging be used in jurisprudence? How about brain reading?
- Can ML analyses be interpreted to understand brain mechanisms?

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Agatha Lenartowicz

Andrew Cho

Martin Monti Jesse Rissman

Malina Beatrice

Susan Bookheimer

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FACULTY 2015 (repeats)

Red Group

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Neuronal Signaling +The BOLD Experiment

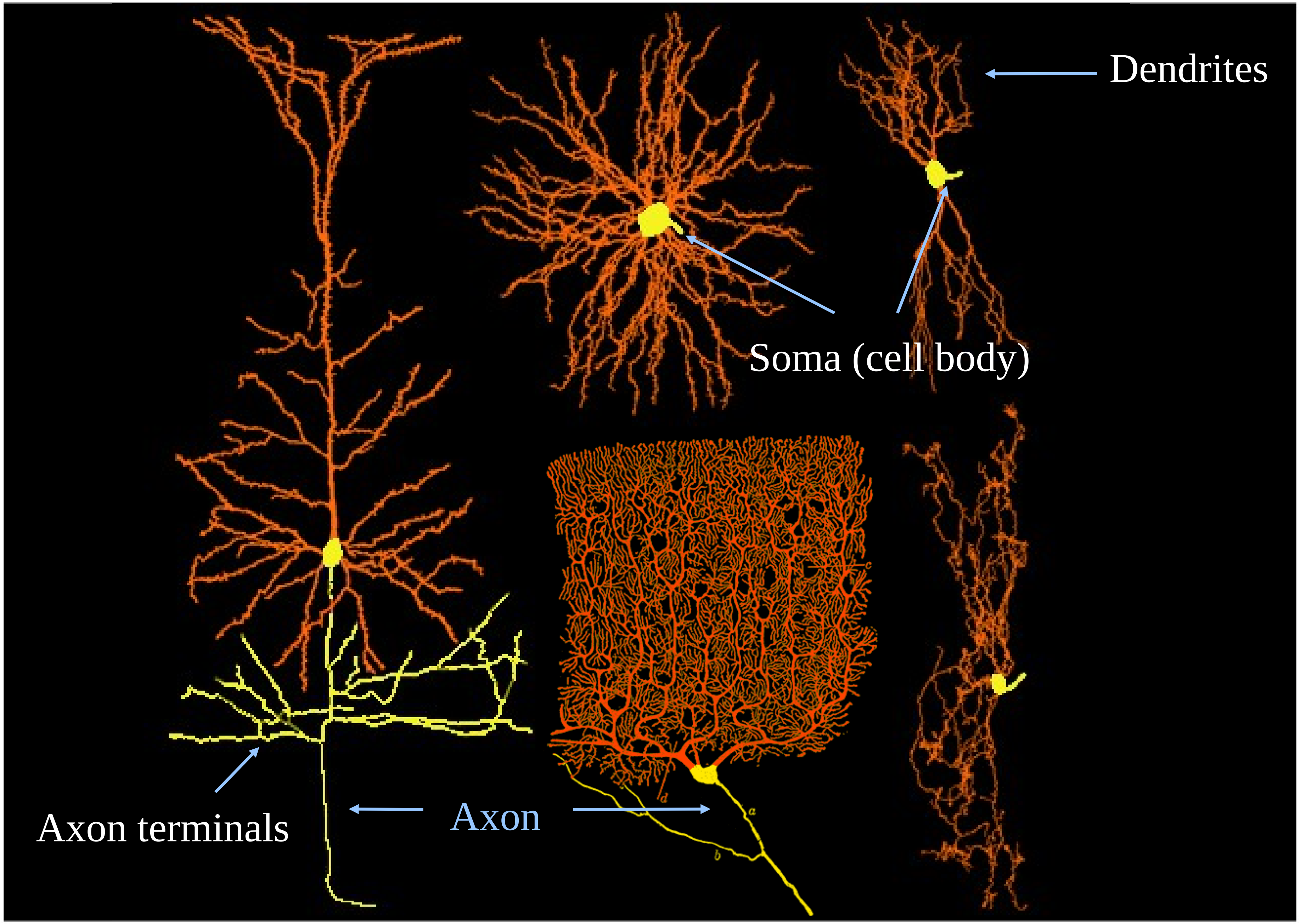
NeuroImaging Training Program

Mark Cohen, UCLA

TOPICS

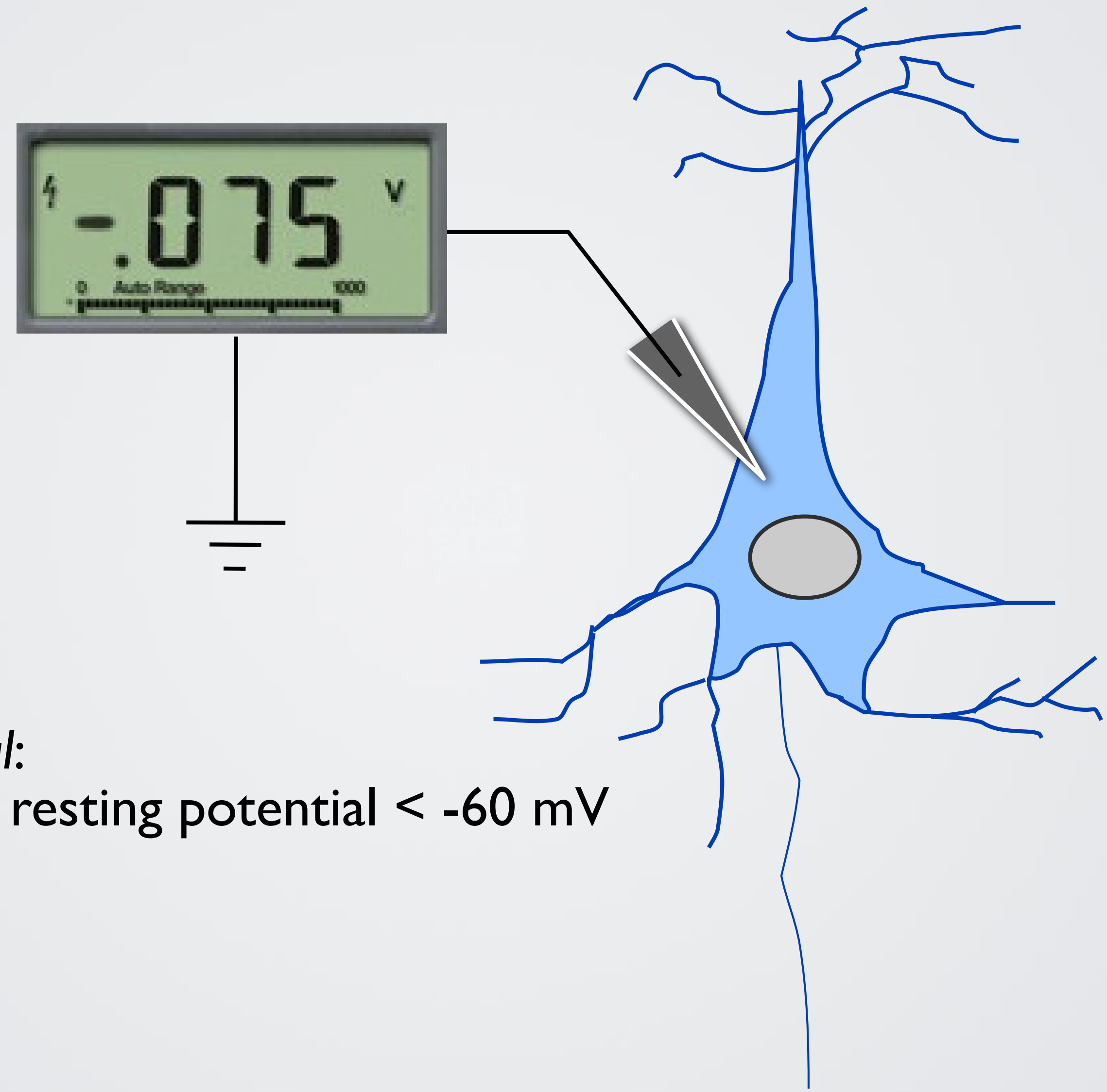
- anatomy of single neurons
- resting and action potentials
- transmission of signals
- chemical and electrical synapses
- information coding
- BOLD and unit activity
- EEG & SITE
- MR-visible effects

Types of Neurons



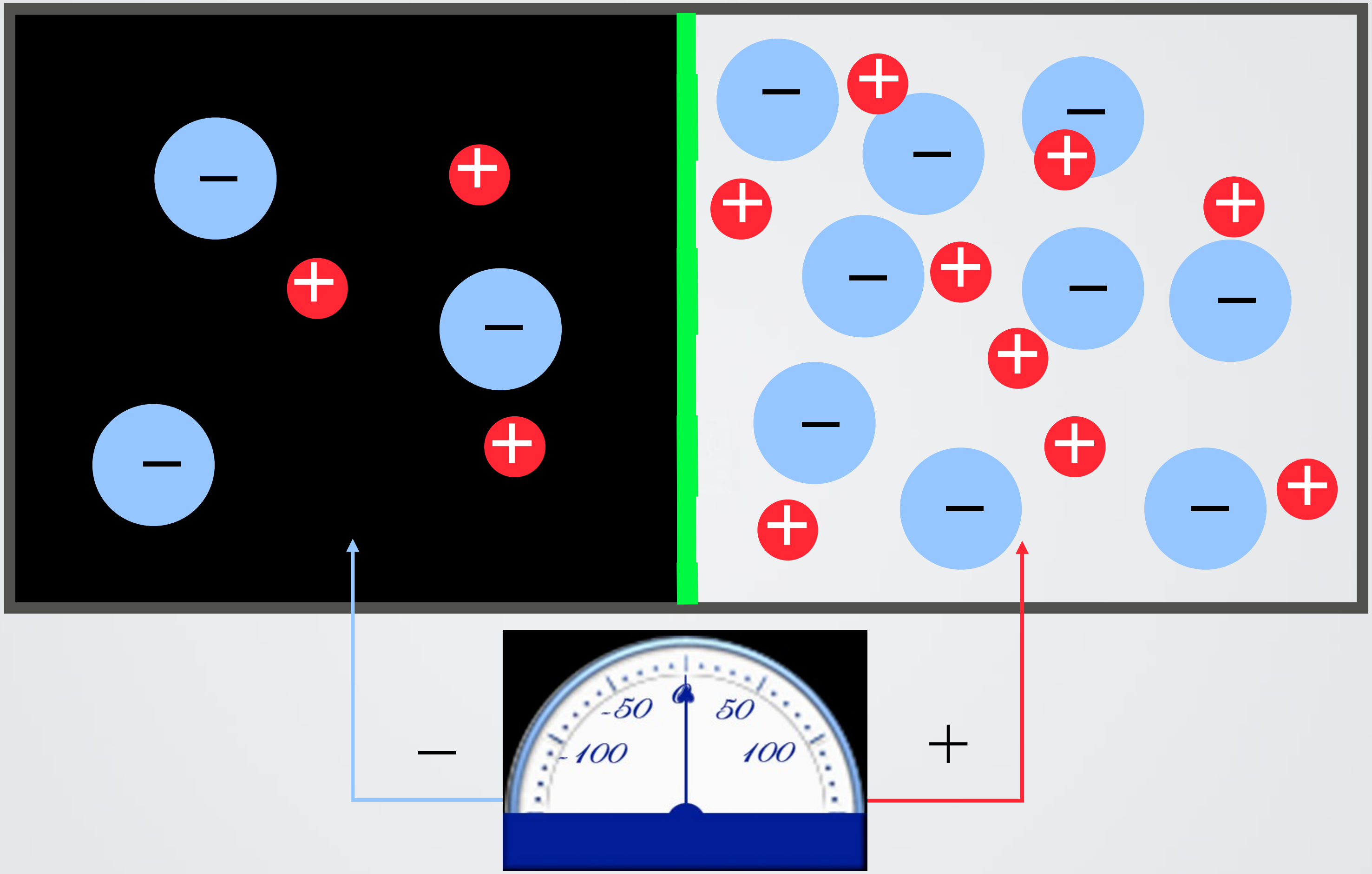
 www.brainmapping.org

RESTING POTENTIAL



Typical:
-90 < resting potential < -60 mV

Development of the Membrane Potential



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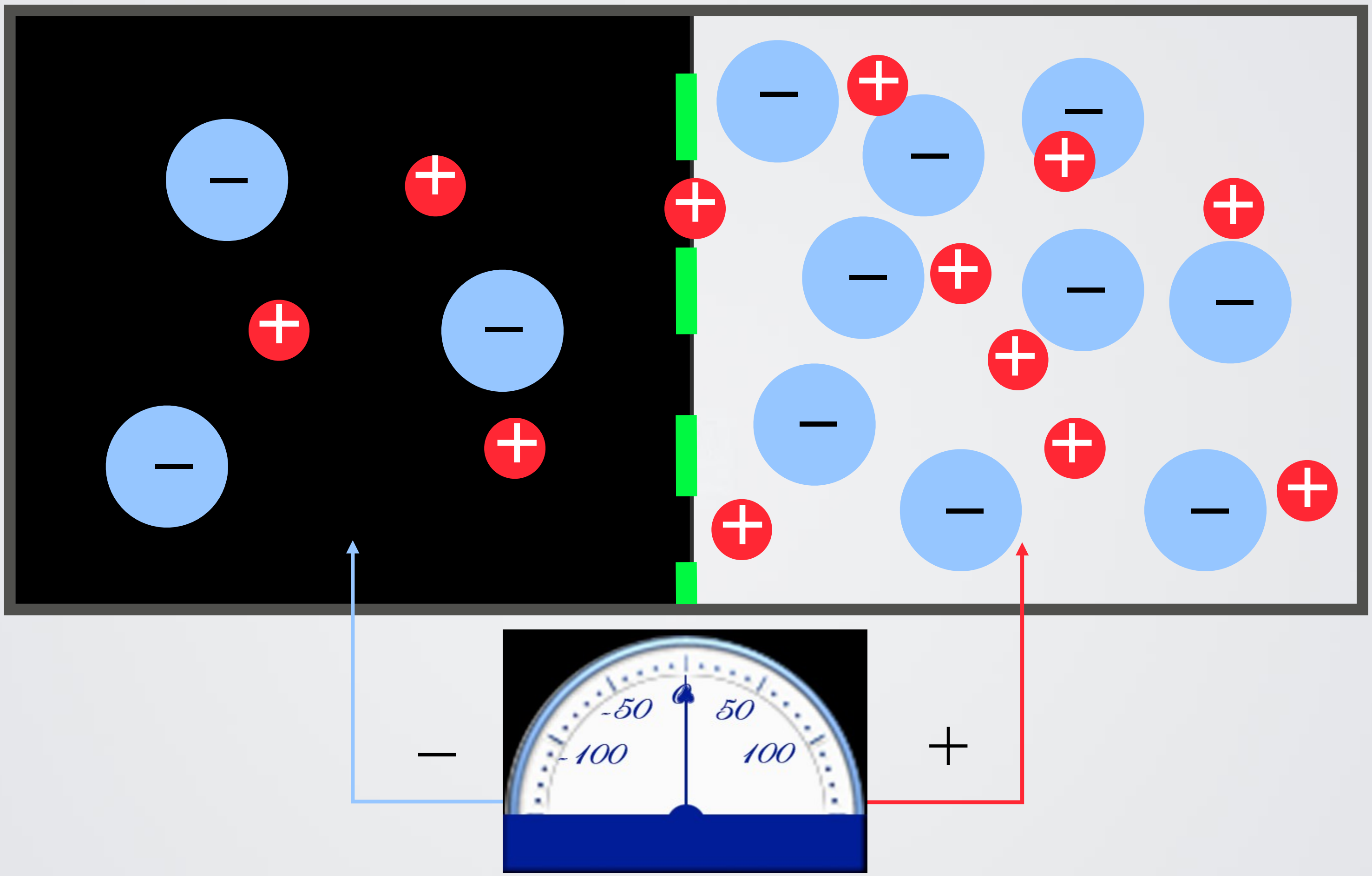

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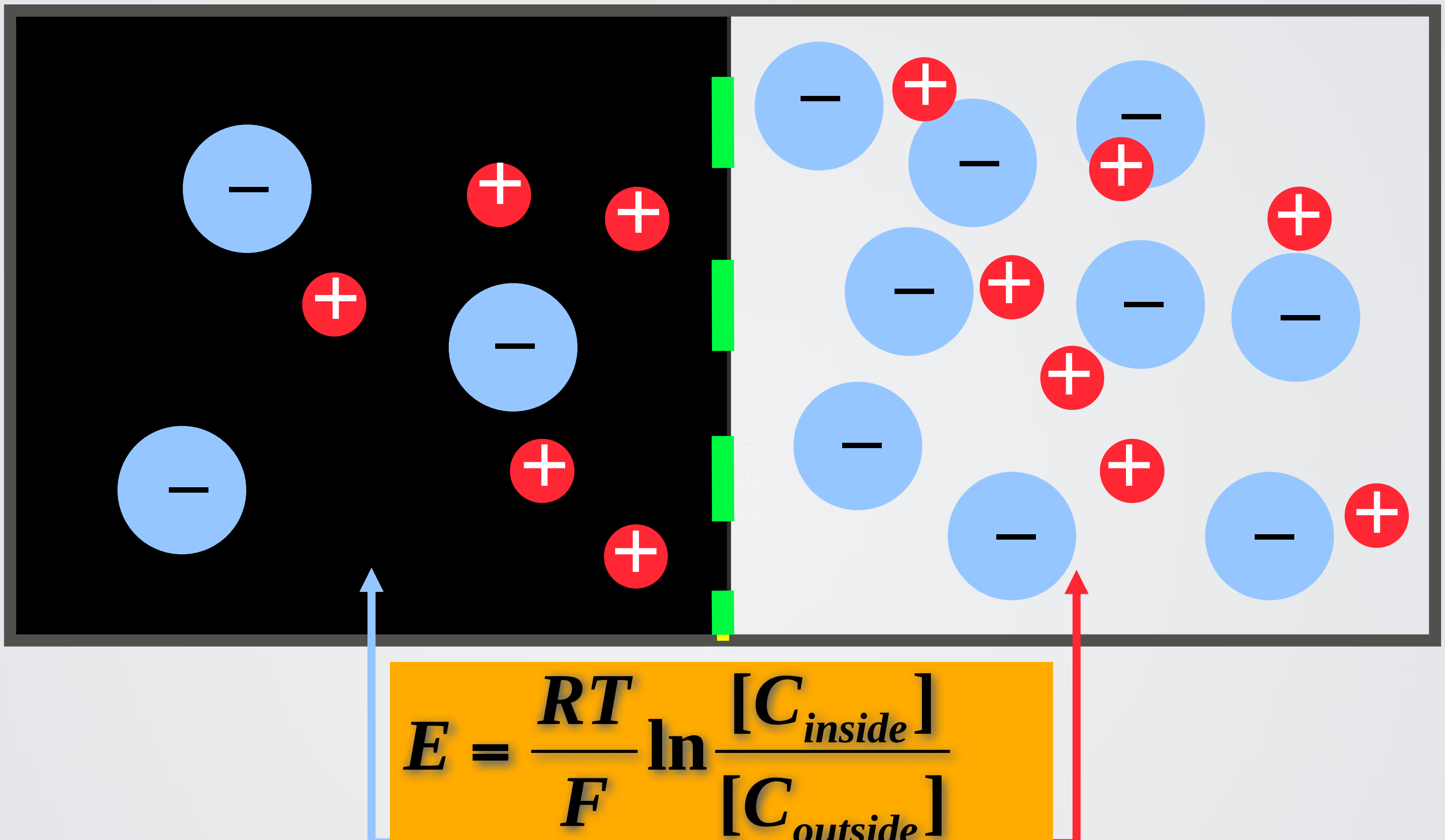


Nernst Potential:

$$E = \frac{RT}{F} \ln \frac{[C_{inside}]}{[C_{outside}]}$$

$$\approx 27\text{mV} \ \ln \frac{[C_{inside}]}{[C_{outside}]}$$

Observed Ion Concentrations

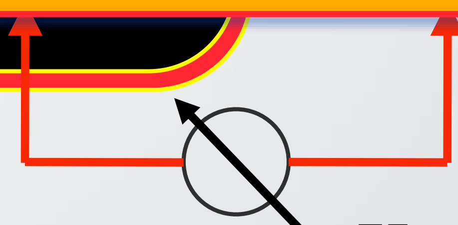
Nernst Potential @37°C

[Na+] 460 mM ······➝ [Na+] 50 mM +60 mV

$$E = \frac{RT}{F}\ln\left(\frac{p_A[A]_{out}\, p_B[B]_{out}\, p_y[x]_{in}\, p_y[y]_{in}}{p_A[A]_{in}\, p_B[B]_{in}\, p_x[x]_{out}\, p_y[y]_{out}}\right)$$

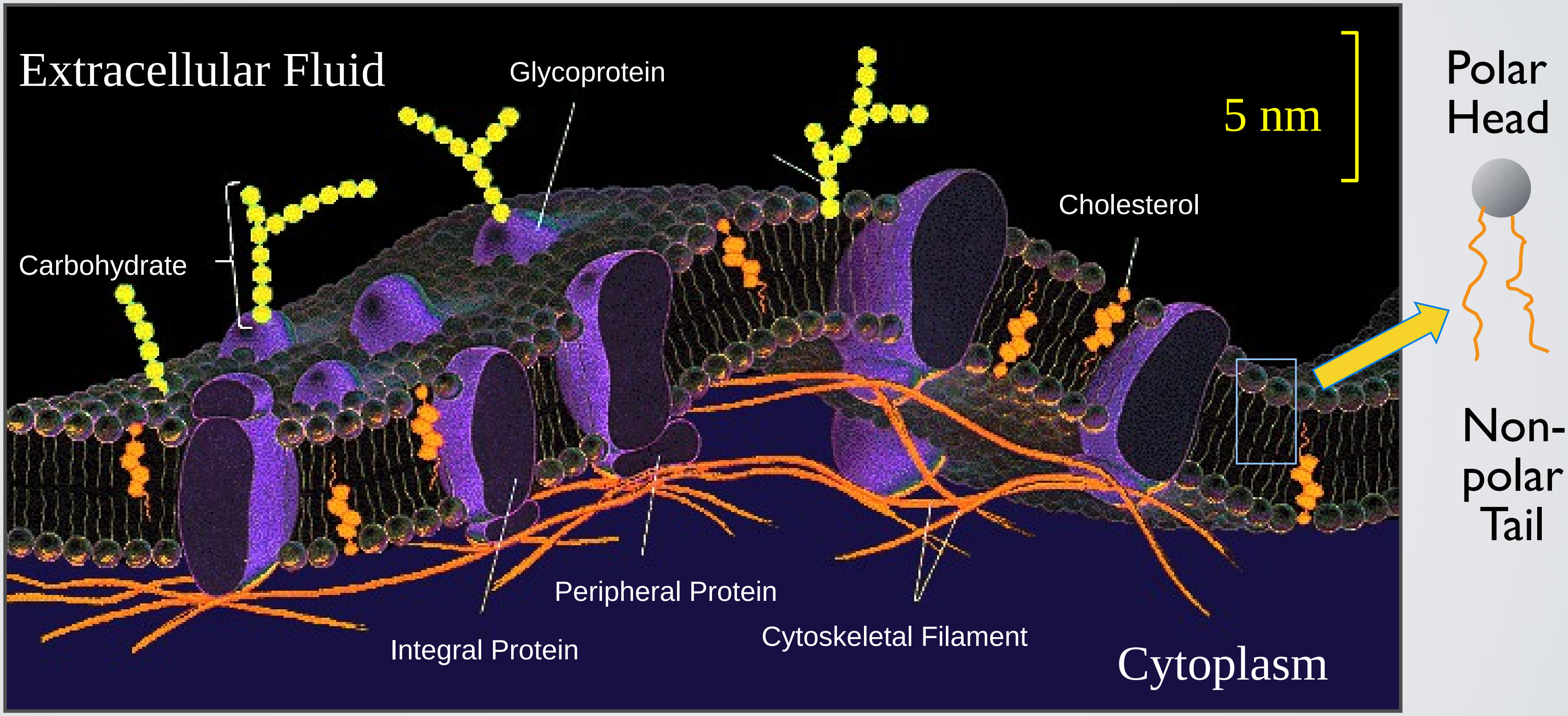
A,B are cations

x,y are anions



–75 mV

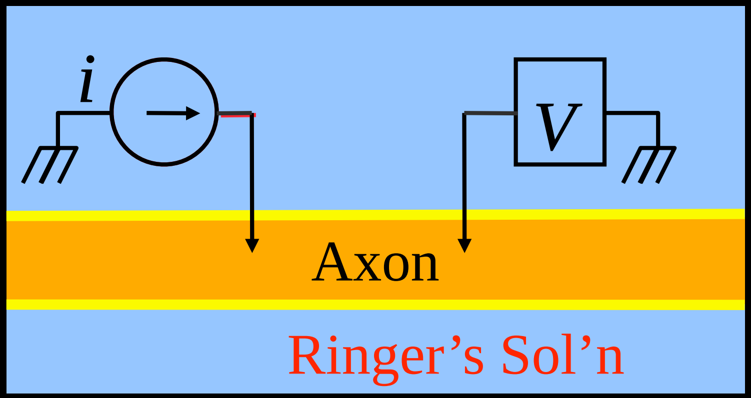
Structure of the Cell Membrane

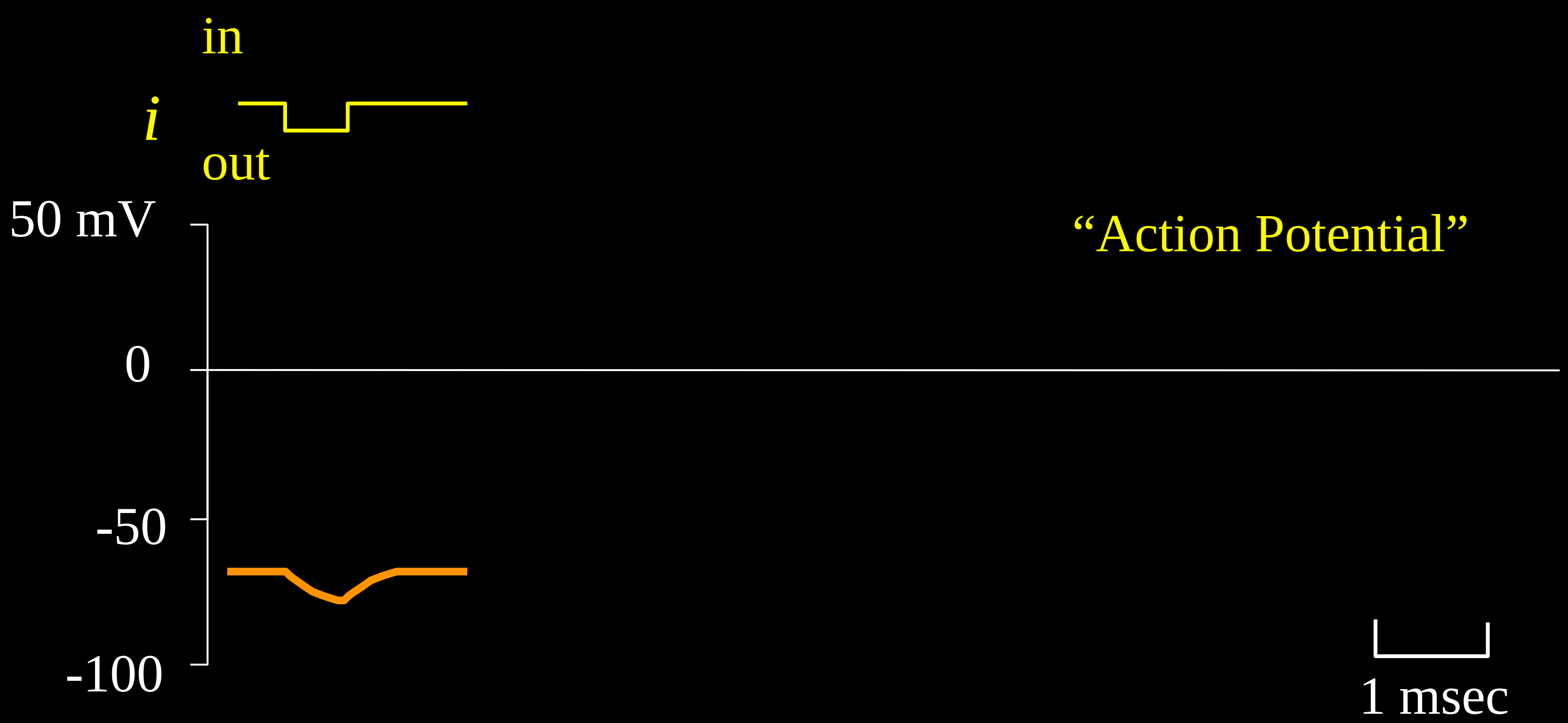


Note: E-field is >10 MV/m!

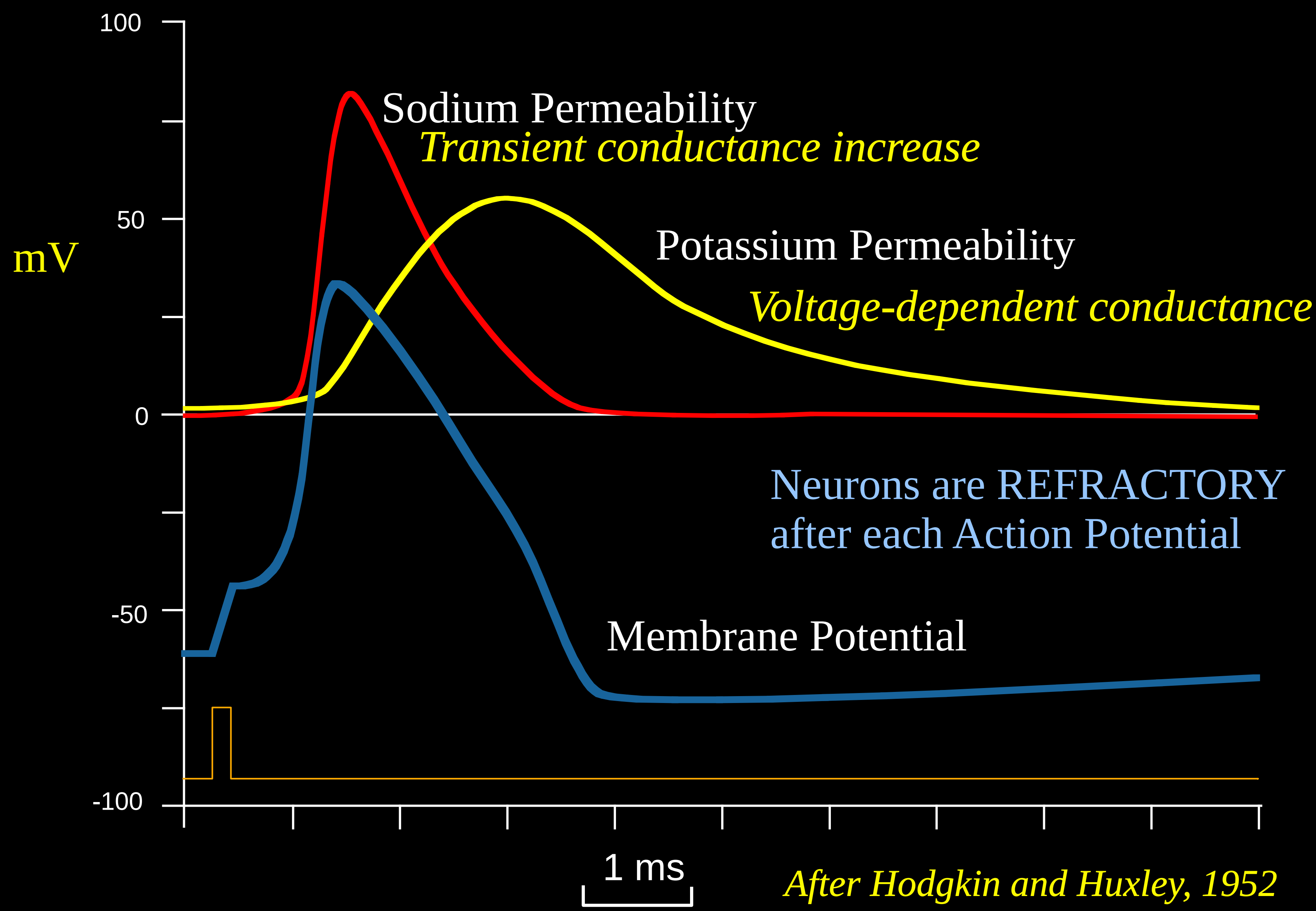
Taken from *Human Biology* by Daniel Chiras

Electrical Behavior of Neurons





Current and Voltage

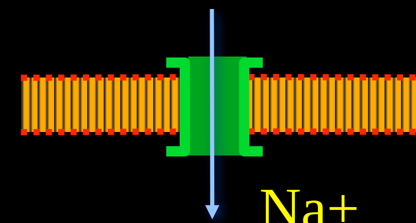


After Hodgkin and Huxley, 1952

Sodium Leakage with Action

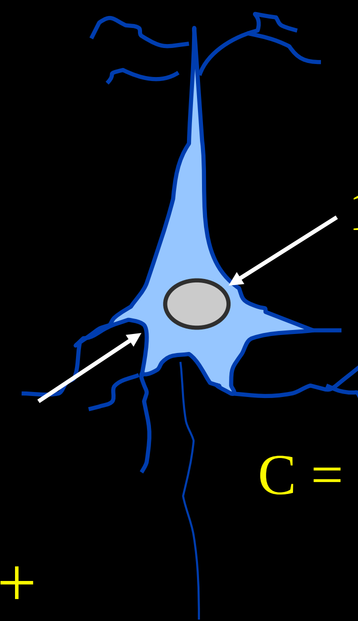
Cell Volume = 9 x 10 $^{-13}$ liters,
about half of which is liquid.

At 40 mM Sodium:
= 4.0 x 10^{-14} Moles Sodium/cell



With Each Action Potential:

ΔV = 0.13 Volt
Q = CV = 1.3 x 10^{-7} Coulombs /cm^2
= 1.4 x 10^{-12} Moles/cm^2



Surface Area = 2.8 x 10^{-5} cm^2

Each AP passes 3.7 x 10^{-17} Moles of Na+

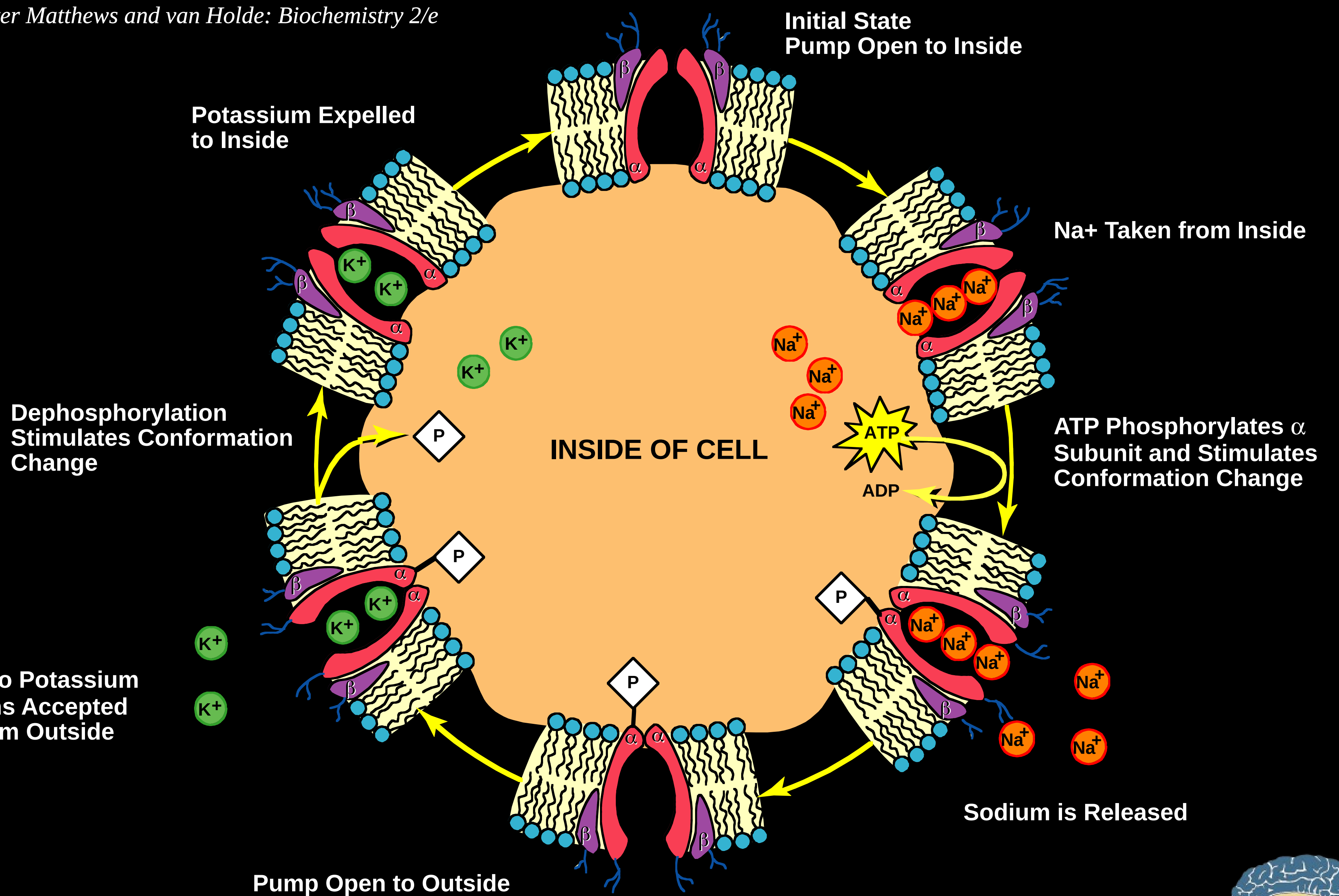
[Na+] is increased by 0.1% with each Action Potential!

Cohen. IEEE, 2009

Center for Cognitive Neuroscience

Sodium Potassium Pump

After Matthews and van Holde: Biochemistry 2/e



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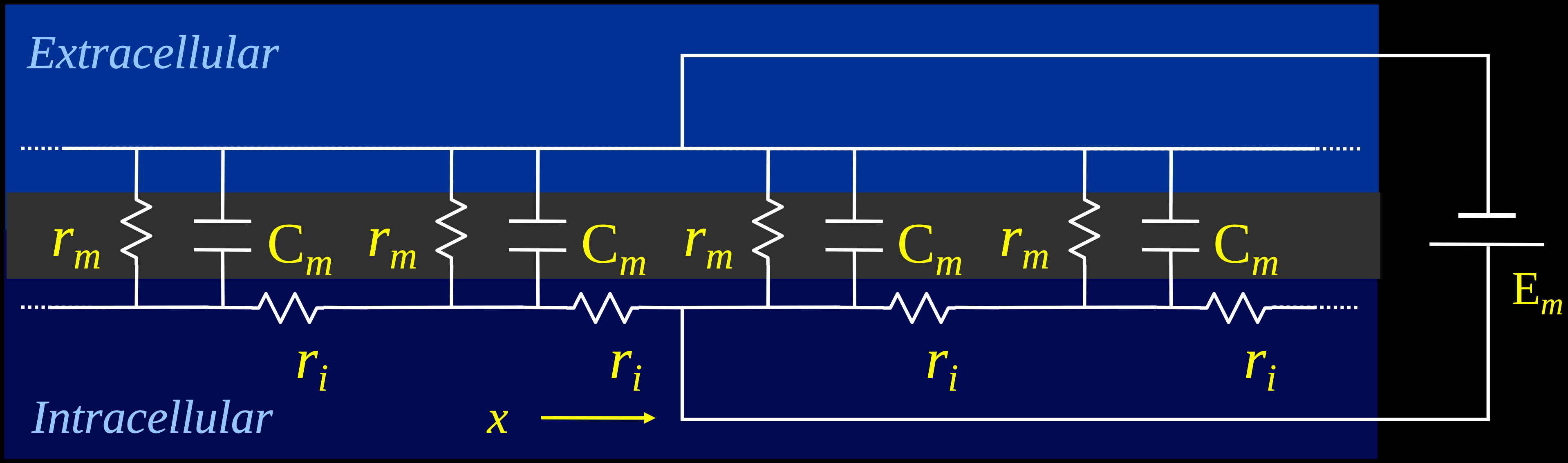
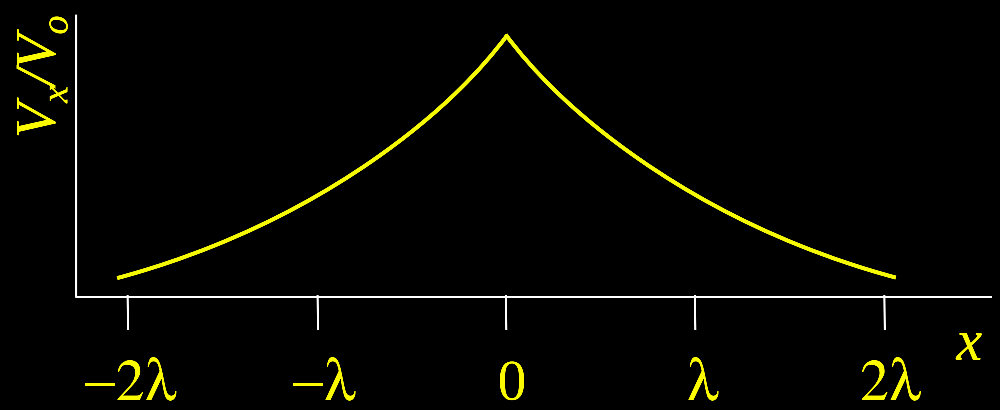
Cable Properties





$$\frac{V_x}{V_0} = e^{-x/\lambda}$$

$$\lambda = \sqrt{r_m / r_i}$$

For vertebrate neurons:
µm < λ < mm

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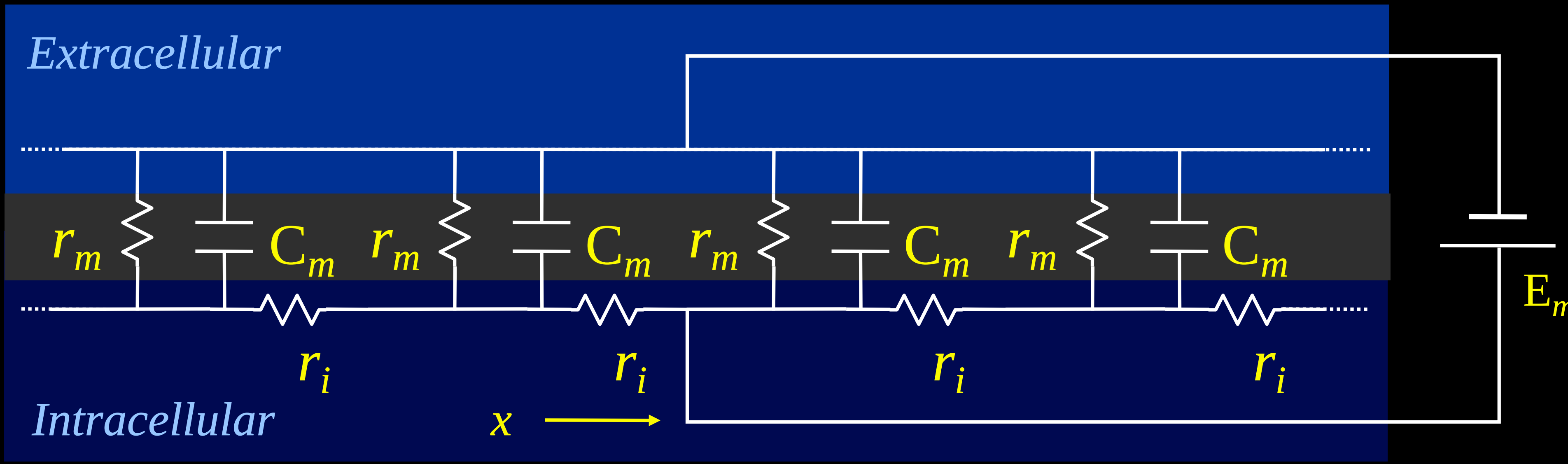
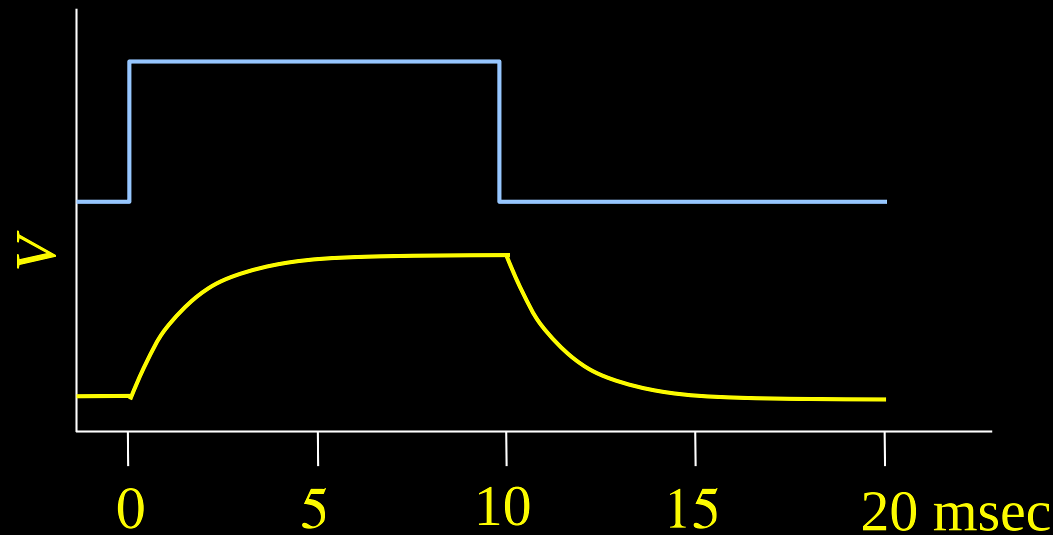
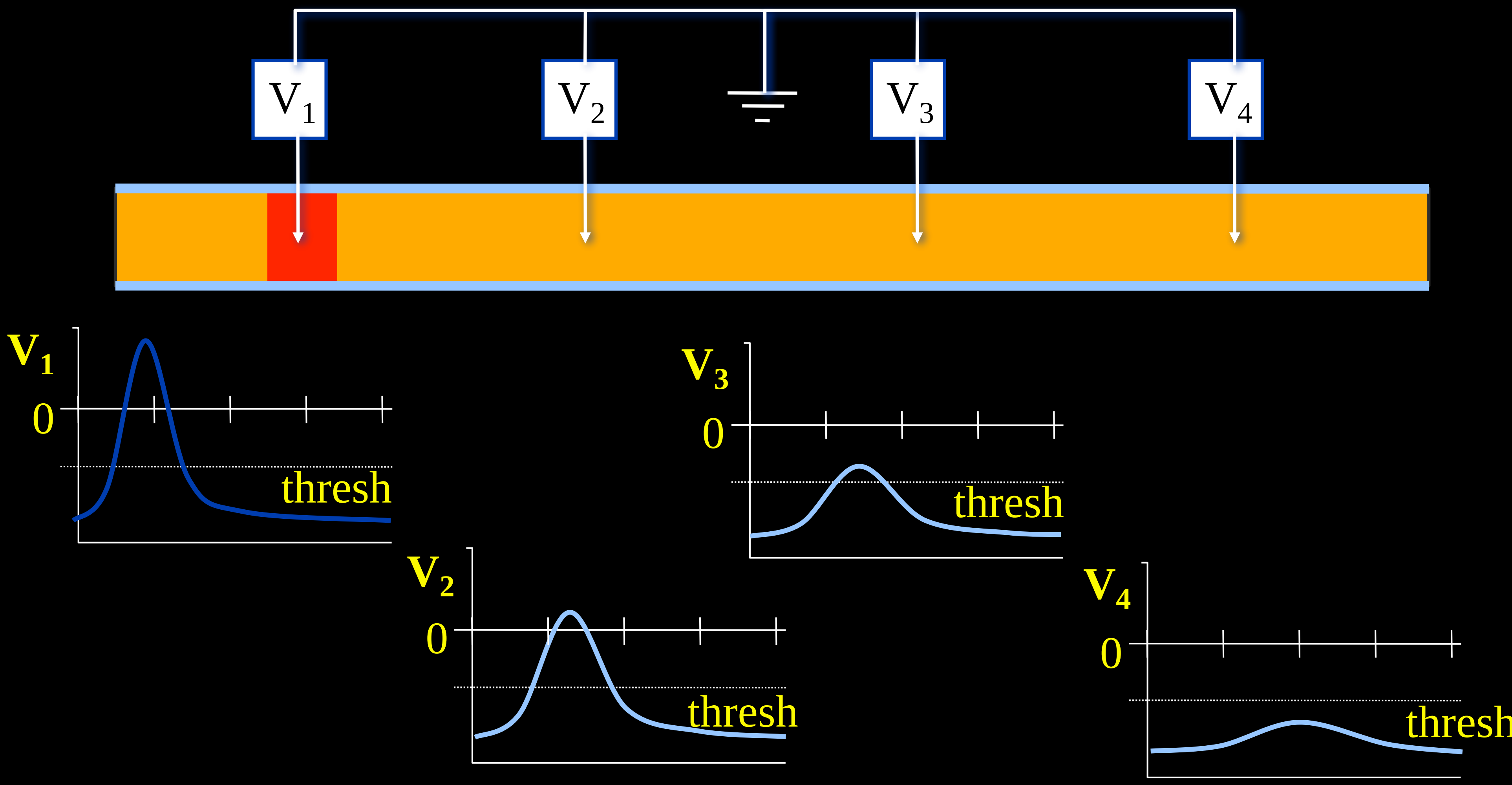
Cable Properties





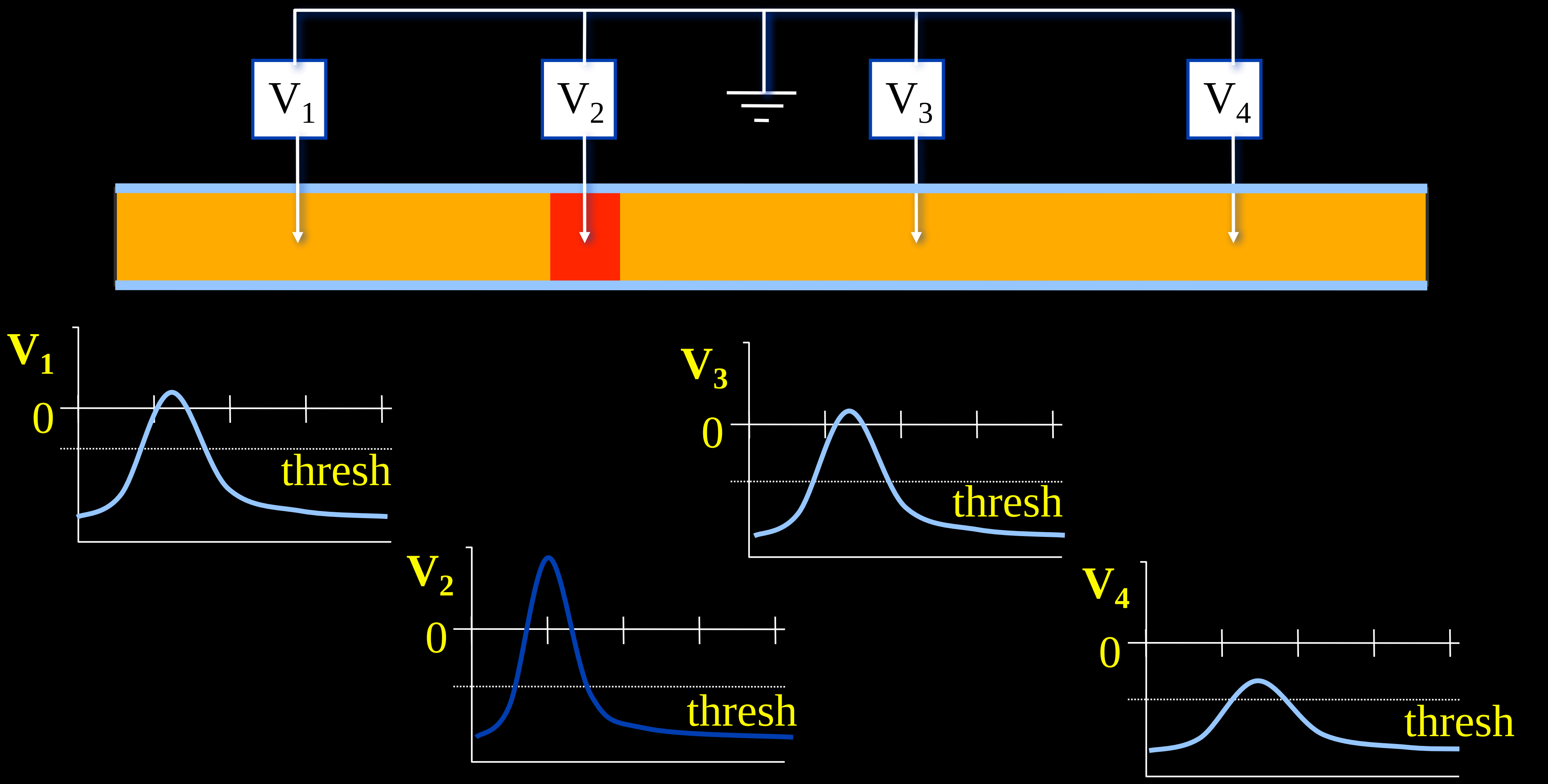
For vertebrate neurons:
0.5 msec < τ < 5 msec

Propagation of the Action Potential



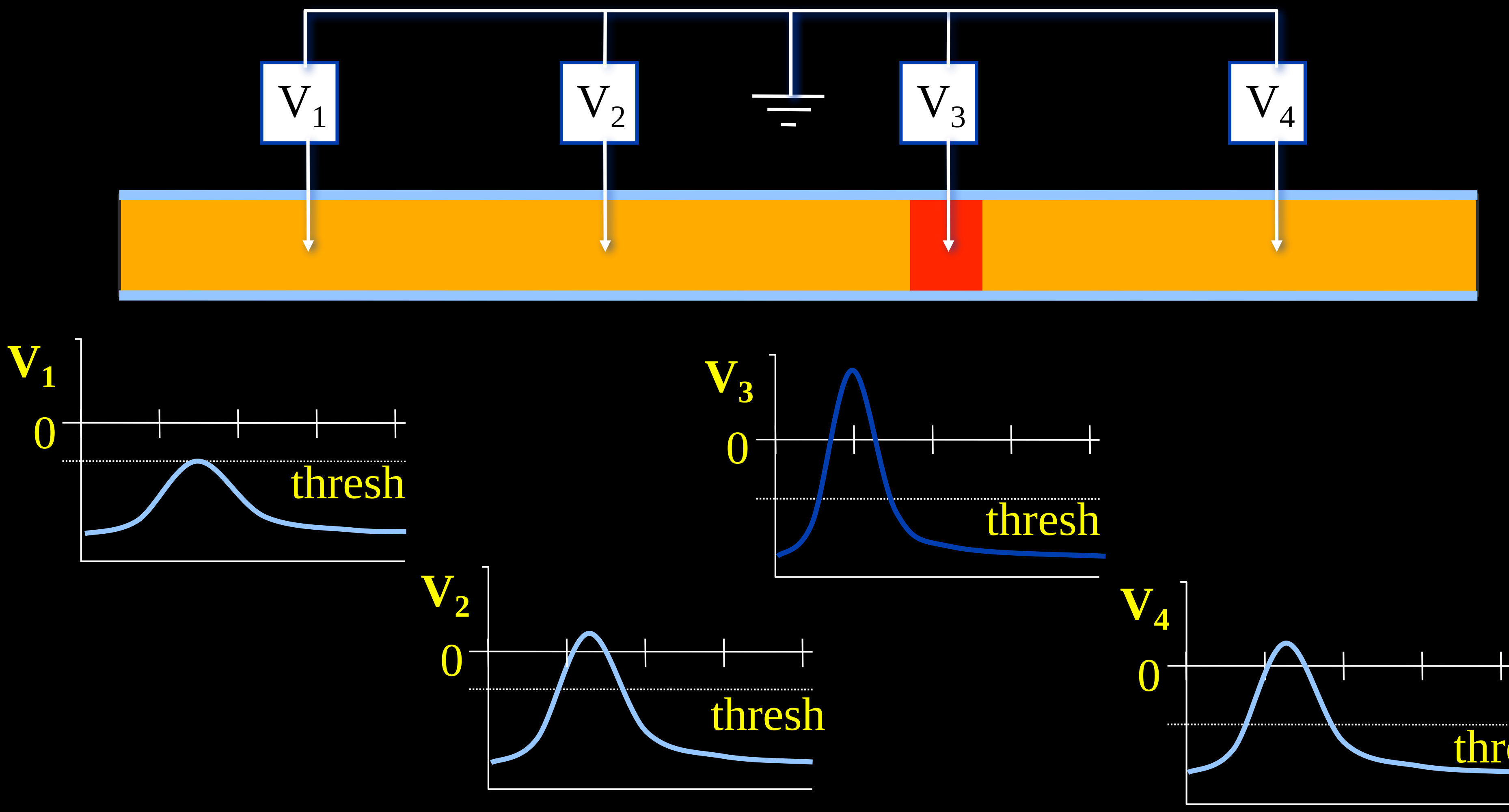
Resulting Velocity ~1-3m/sec

Propagation of the Action Potential



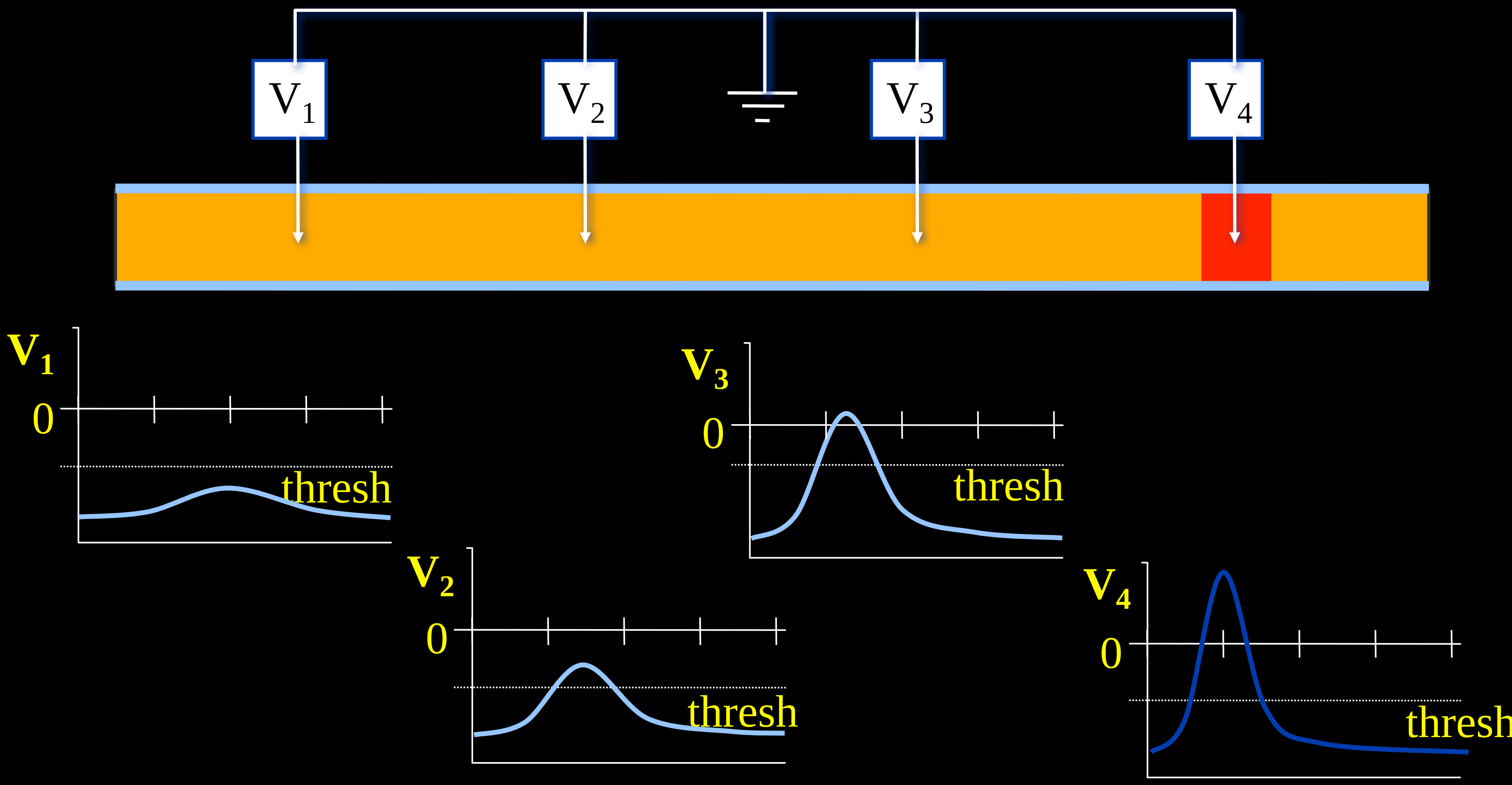
Resulting Velocity ~1-3m/sec

Propagation of the Action Potential



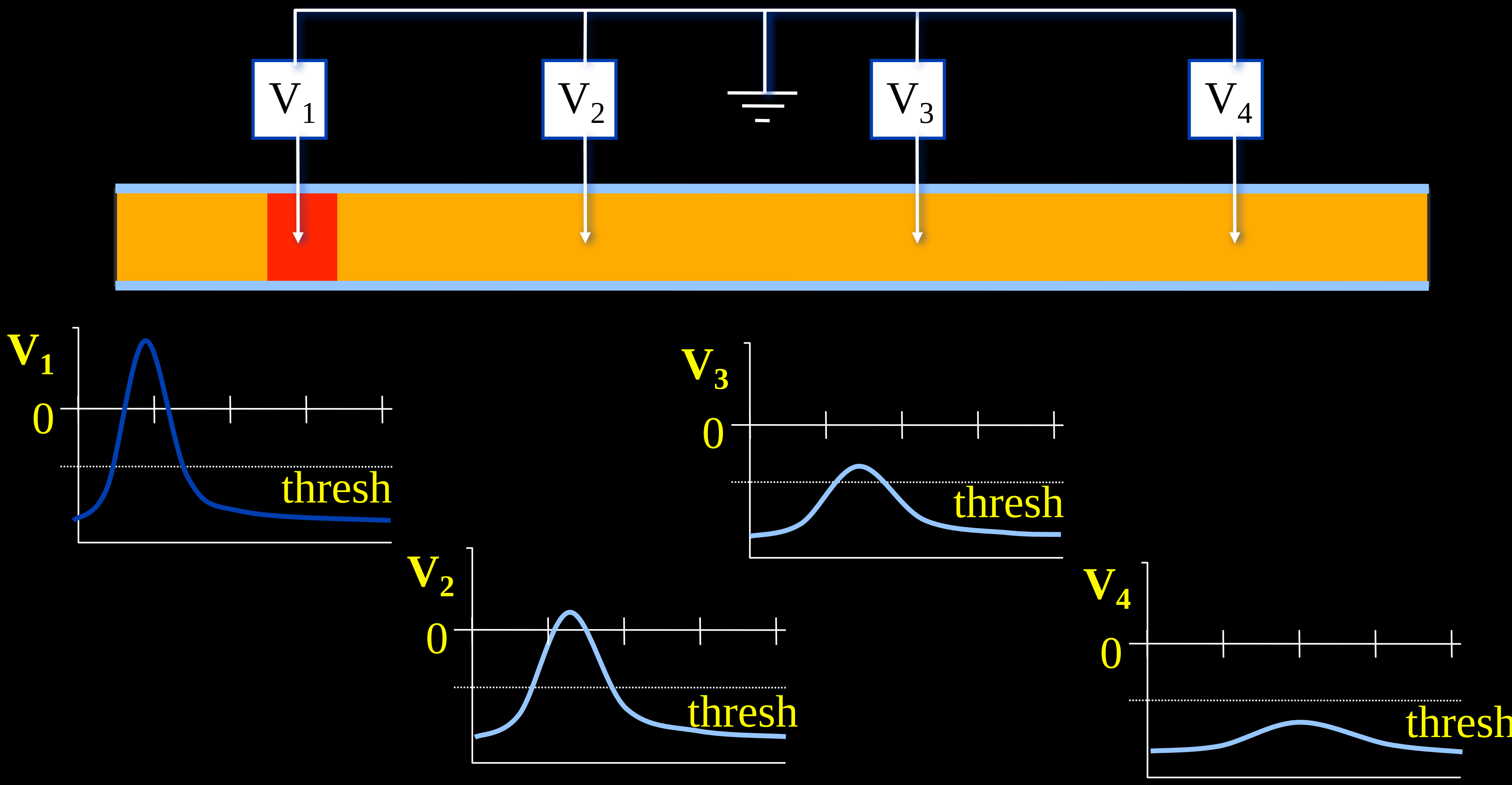
Resulting Velocity ~1-3m/sec

Propagation of the Action Potential



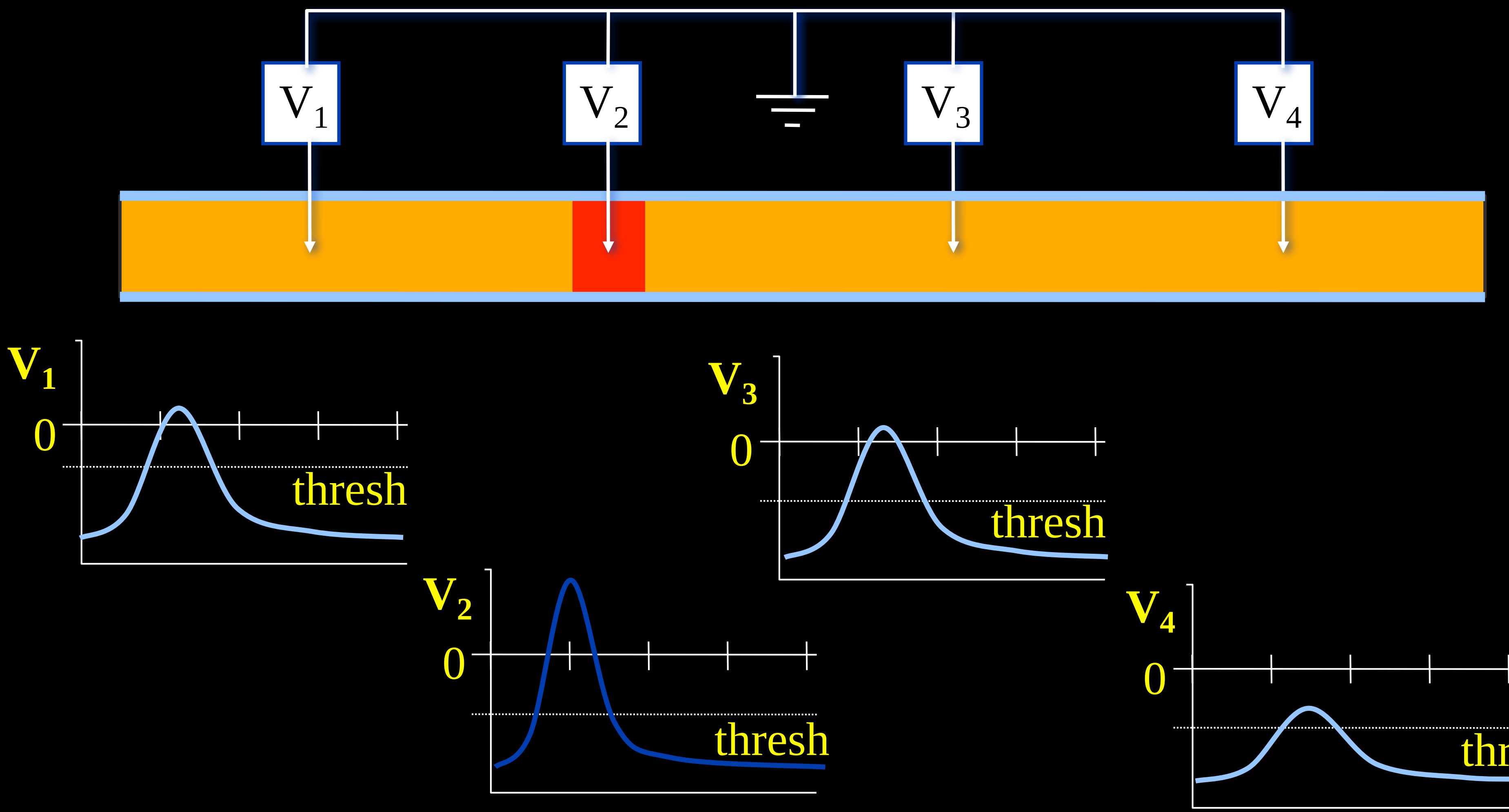
Resulting Velocity ~1-3m/sec

Propagation of the Action Potential



Resulting Velocity ~1-3m/sec

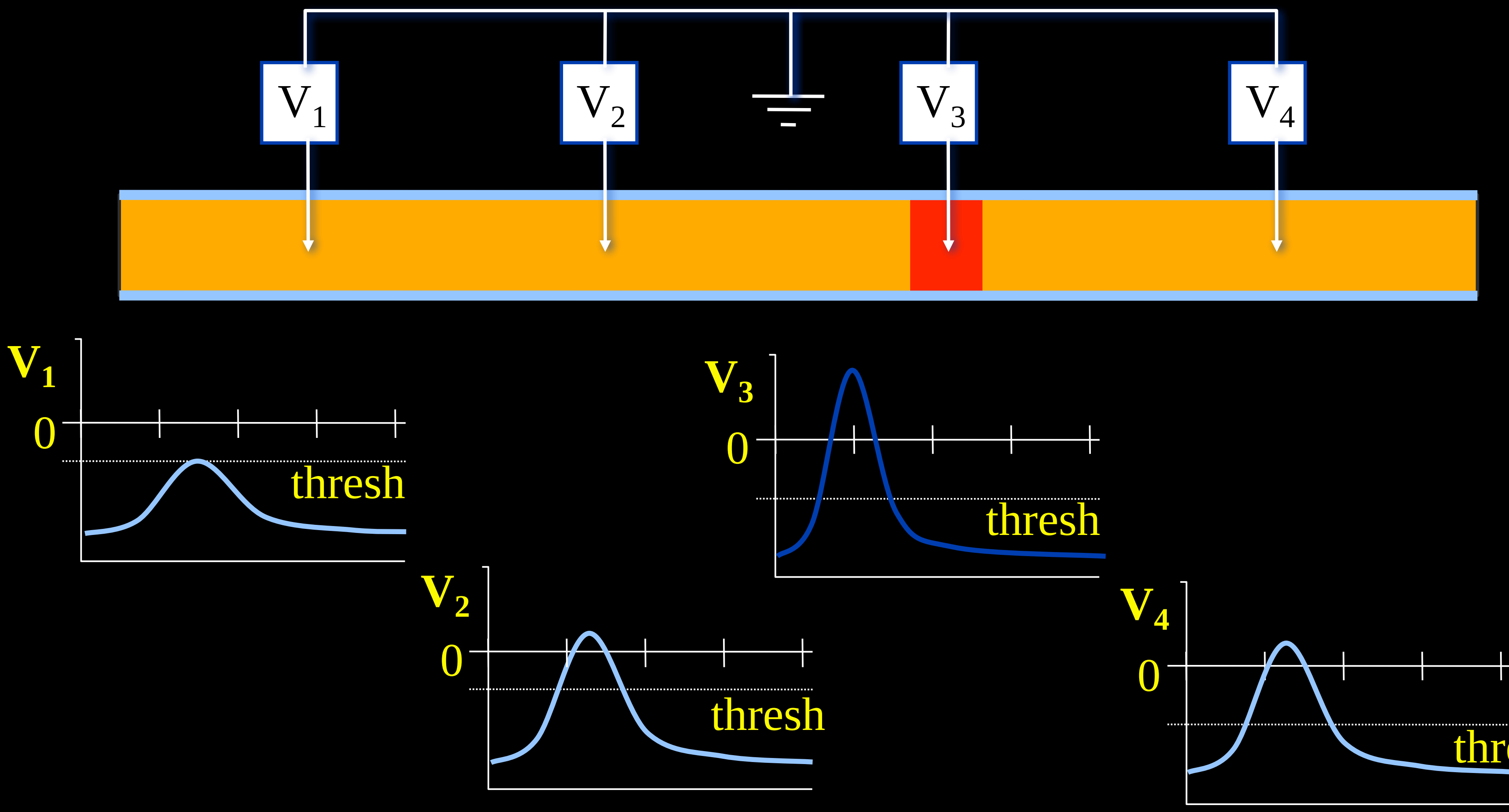
Propagation of the Action Potential



Resulting Velocity ~1-3m/sec

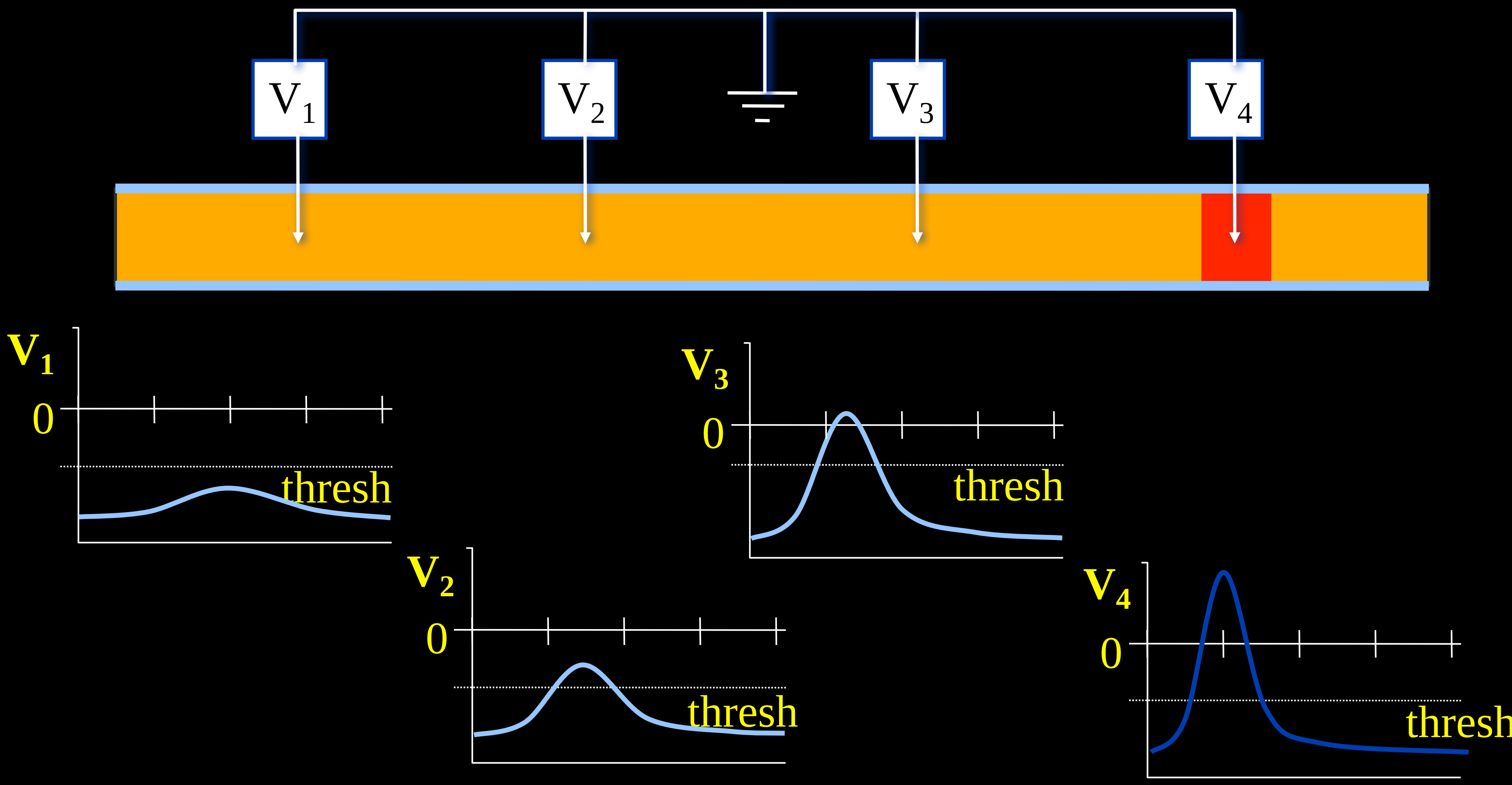
Center for Cognitive Neuroscience

Propagation of the Action Potential



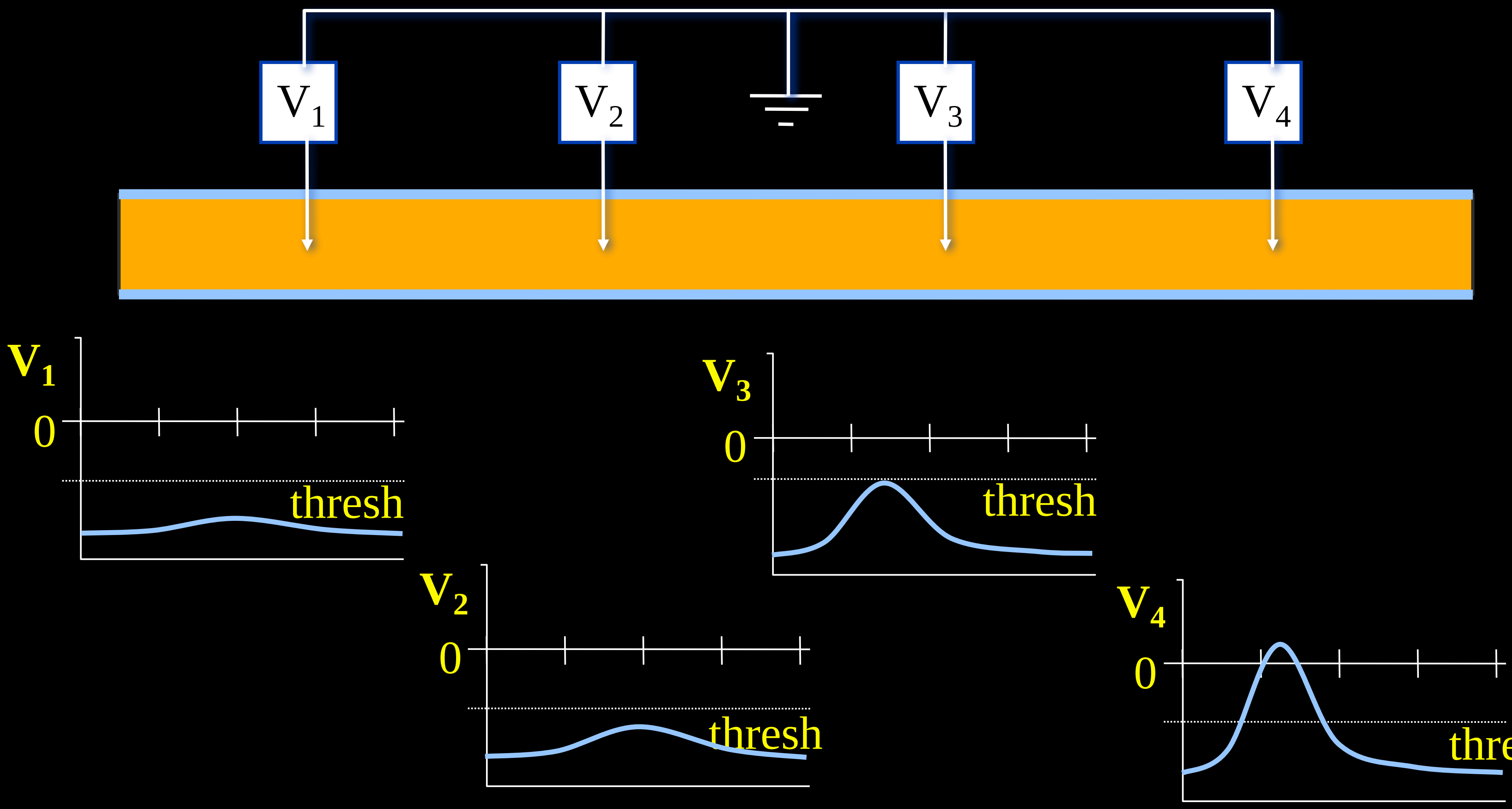
Resulting Velocity ~1-3m/sec

Propagation of the Action Potential



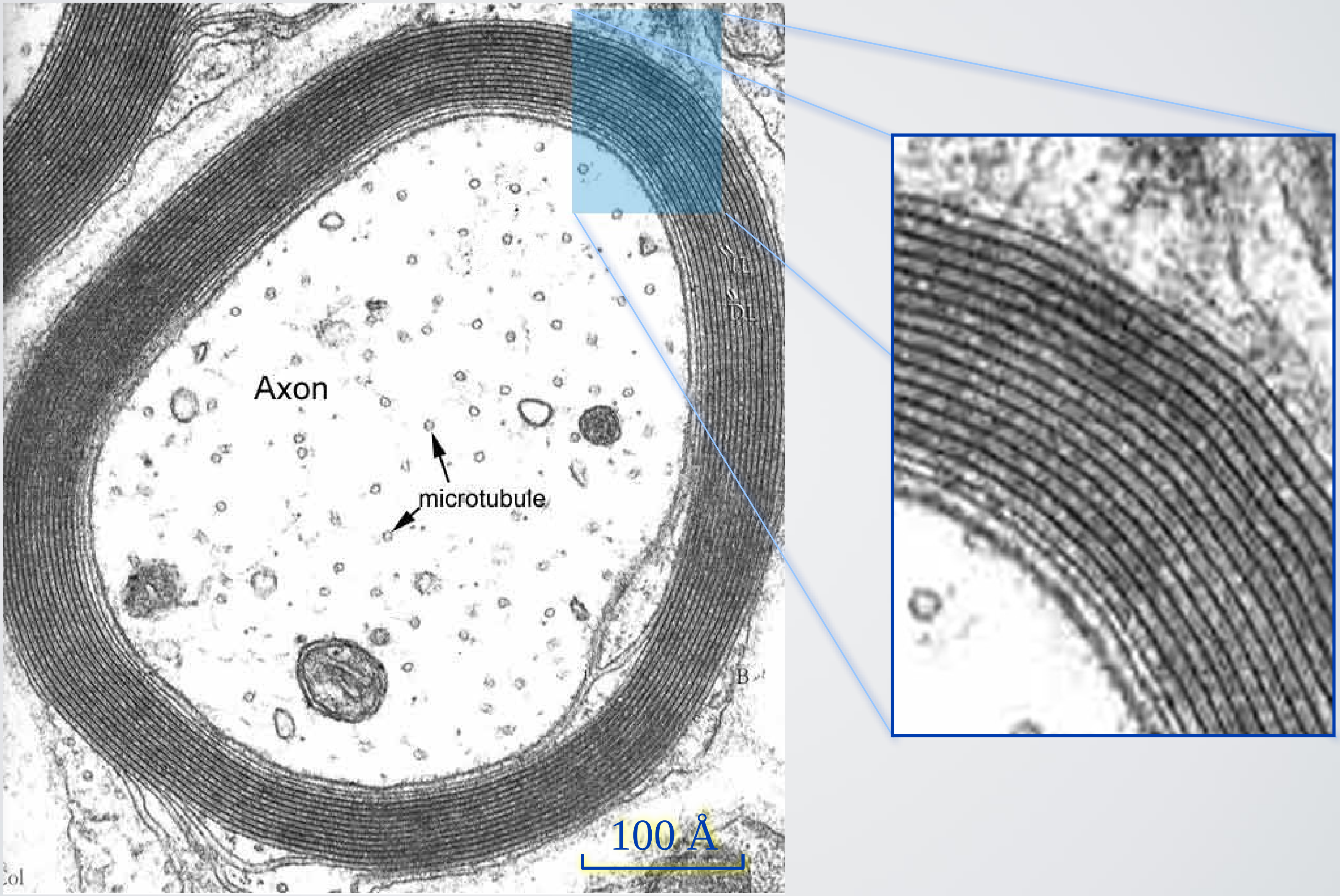
Resulting Velocity ~1-3m/sec

Propagation of the Action Potential

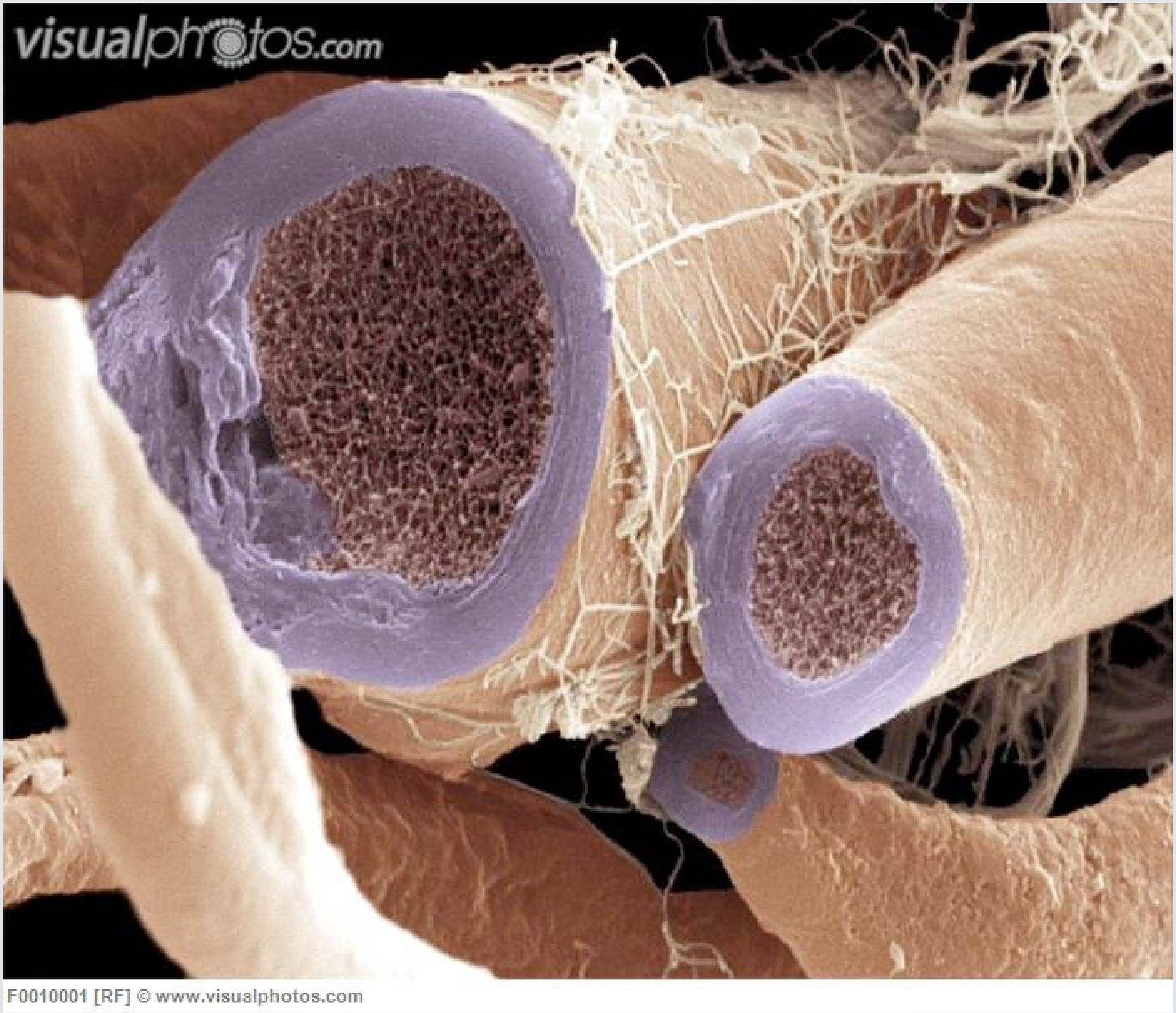


Resulting Velocity ~1-3m/sec

Myelin Sheath



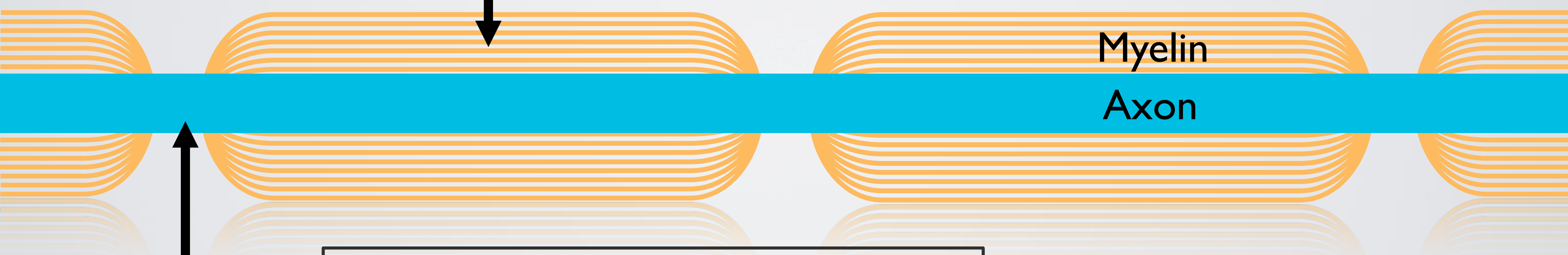
MYELIN SHEATH



NODES OF RANVIER

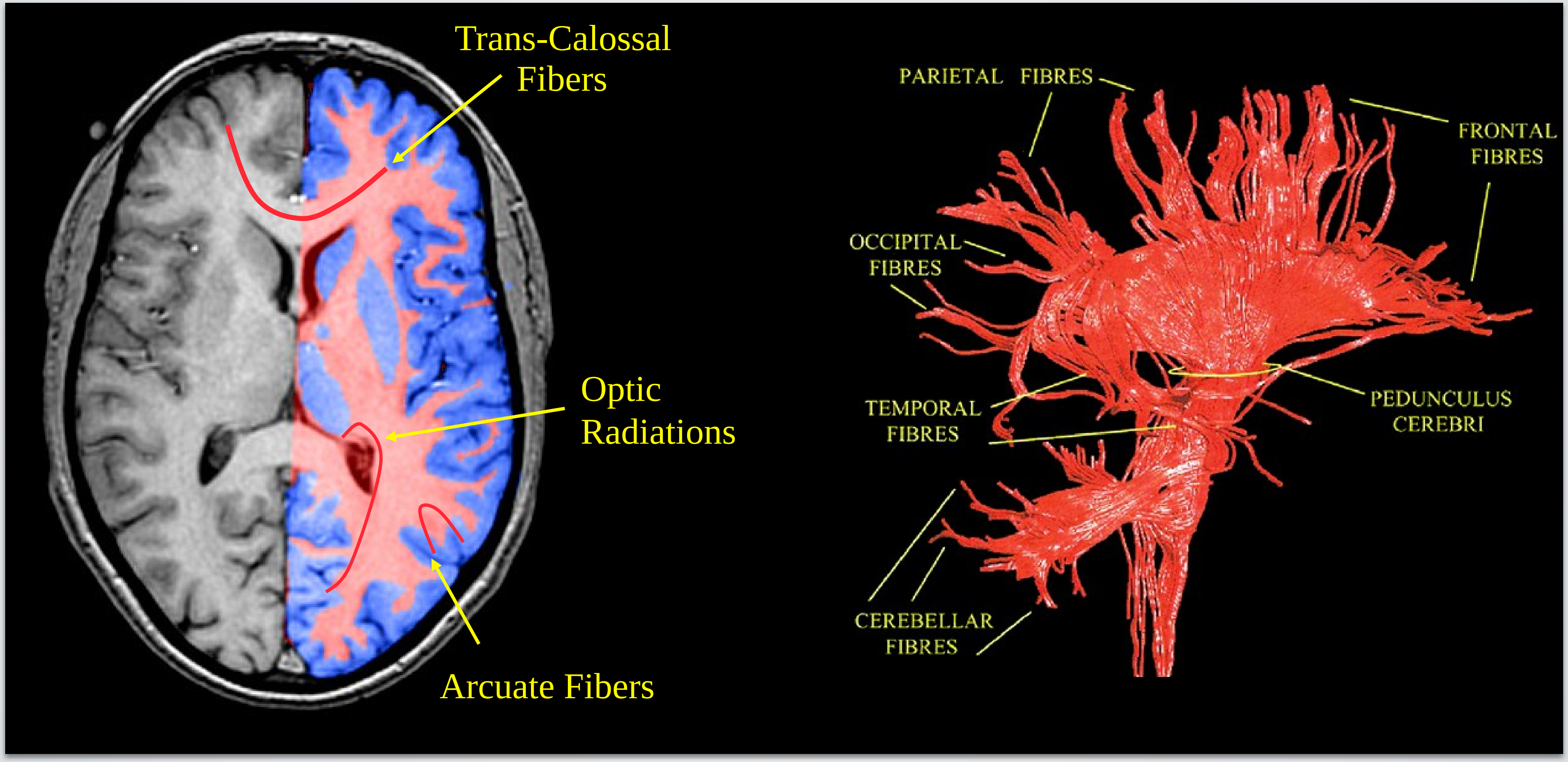
SALTATORY CONDUCTION

Internode:
High Membrane Resistance
Long Spatial Constant
Short Time Constant
Efficient Electrotonic Conduction



Node:
Low Membrane Resistance
High Membrane Current Flow
Fires Action Potential
Action Potential Regeneration

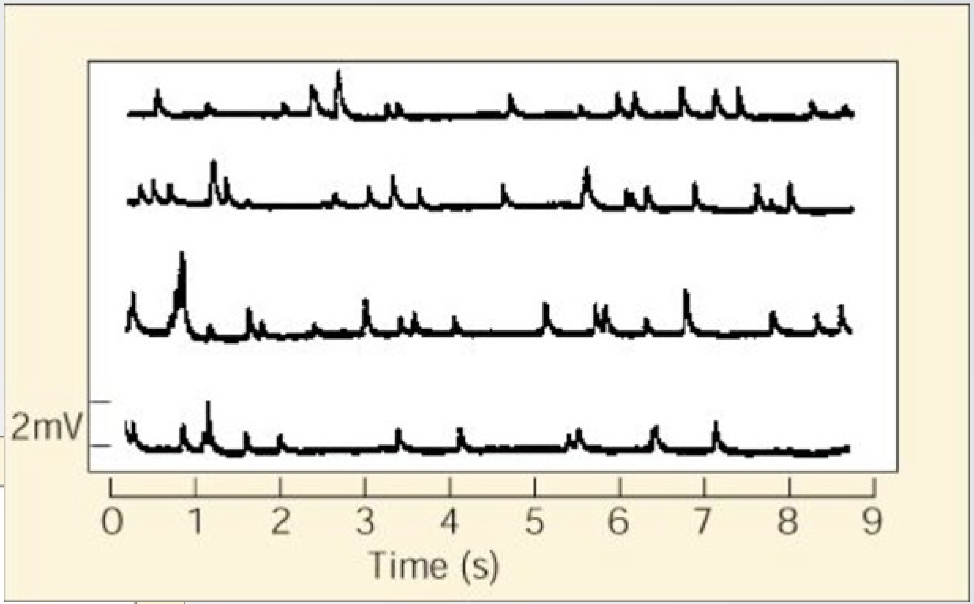
White and Gray Matter

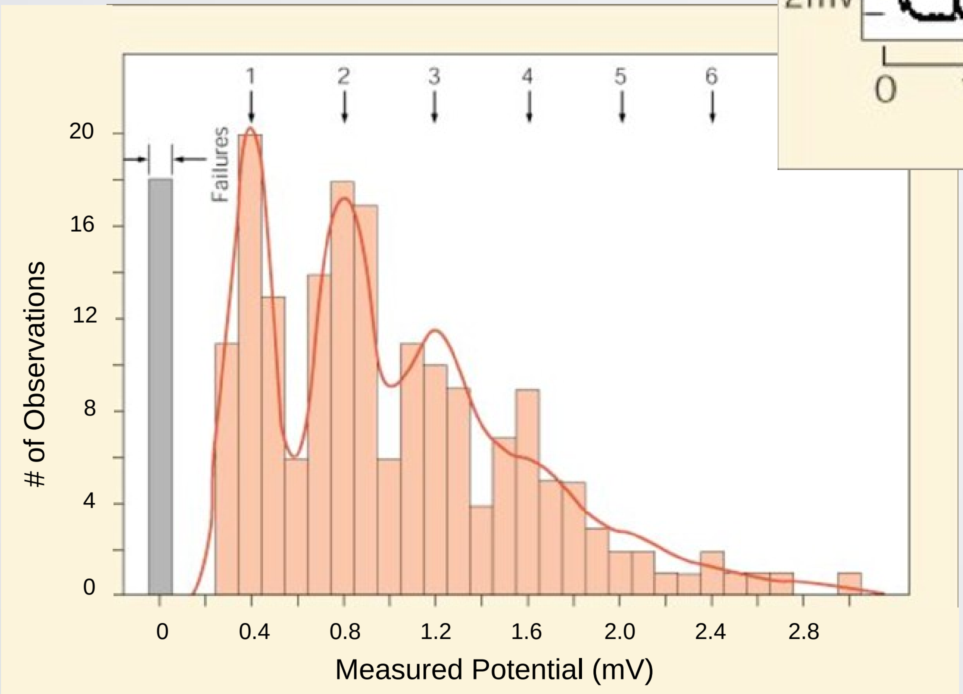


After: Catani, et al., NeuroImage **17**:77, 2002

EPSP'S: *EXCITATORY POST-SYNAPTIC POTENTIALS*

Muscle end plate potentials
Recorded in low Ca^{2+} / high Mg^{2+}



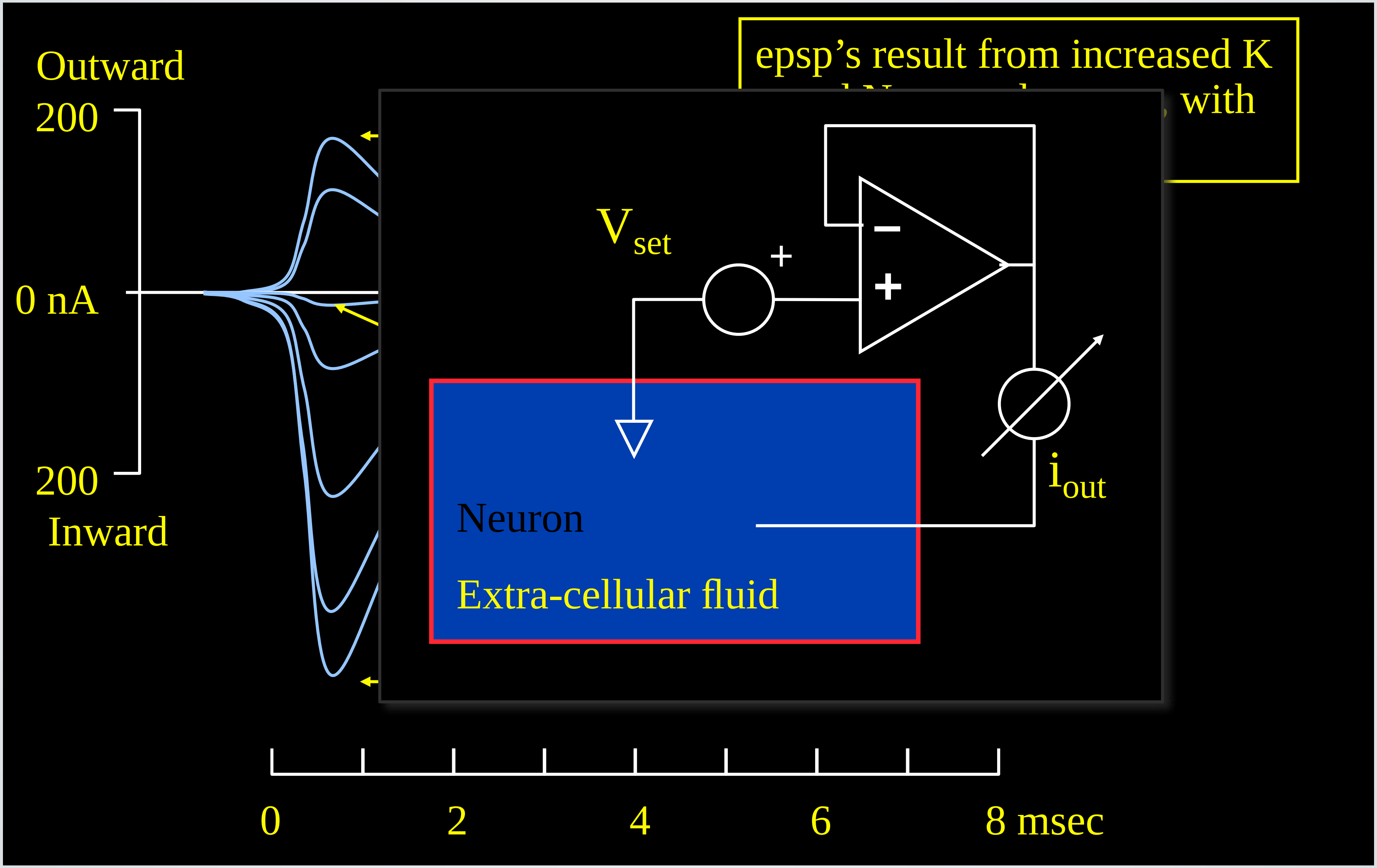


Amplitudes are *quantized* and display a Poisson distribution

Boyd and Martin. J Physiol, **132**. 1956

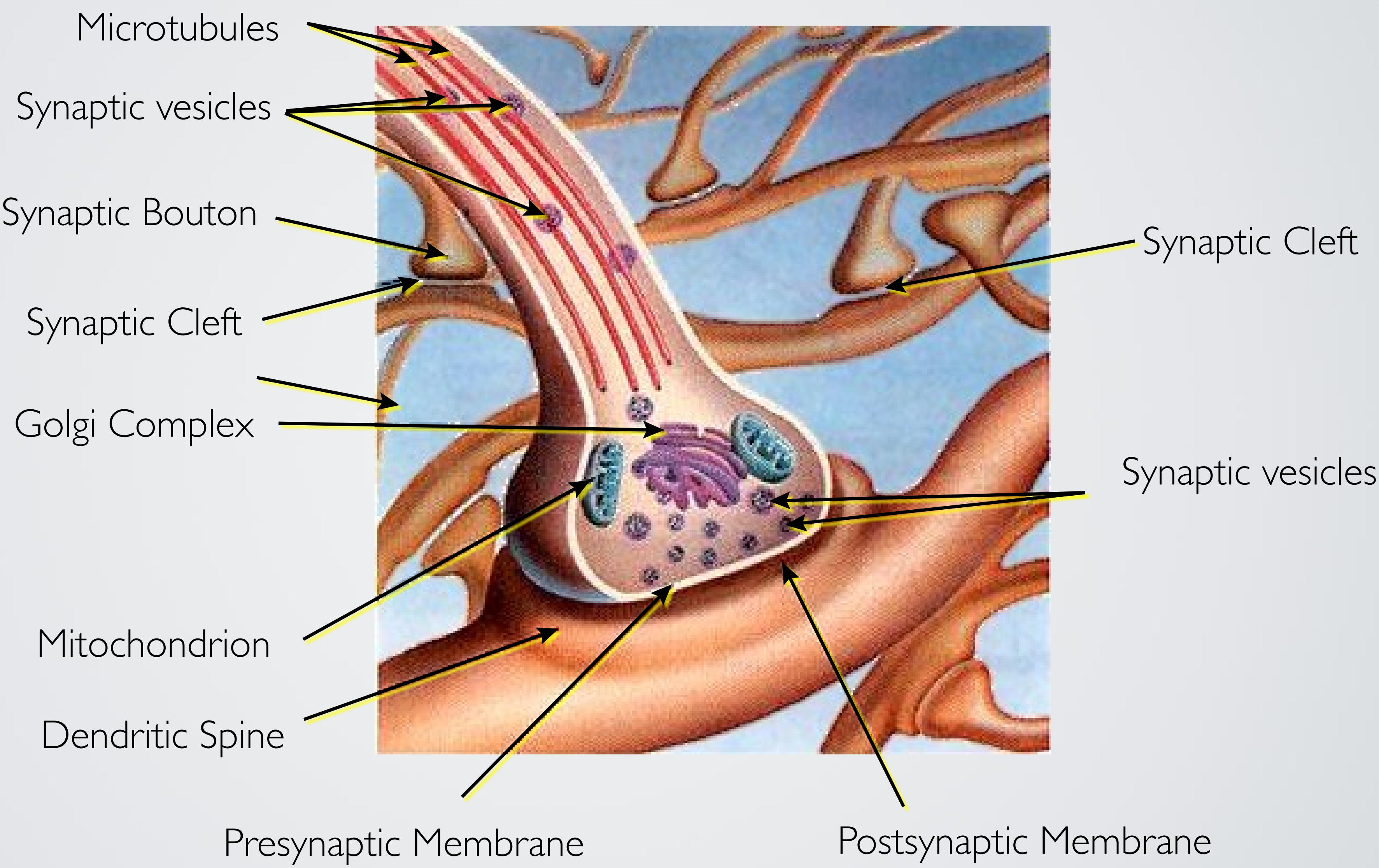
 www.brainmapping.org

Reversal Potential



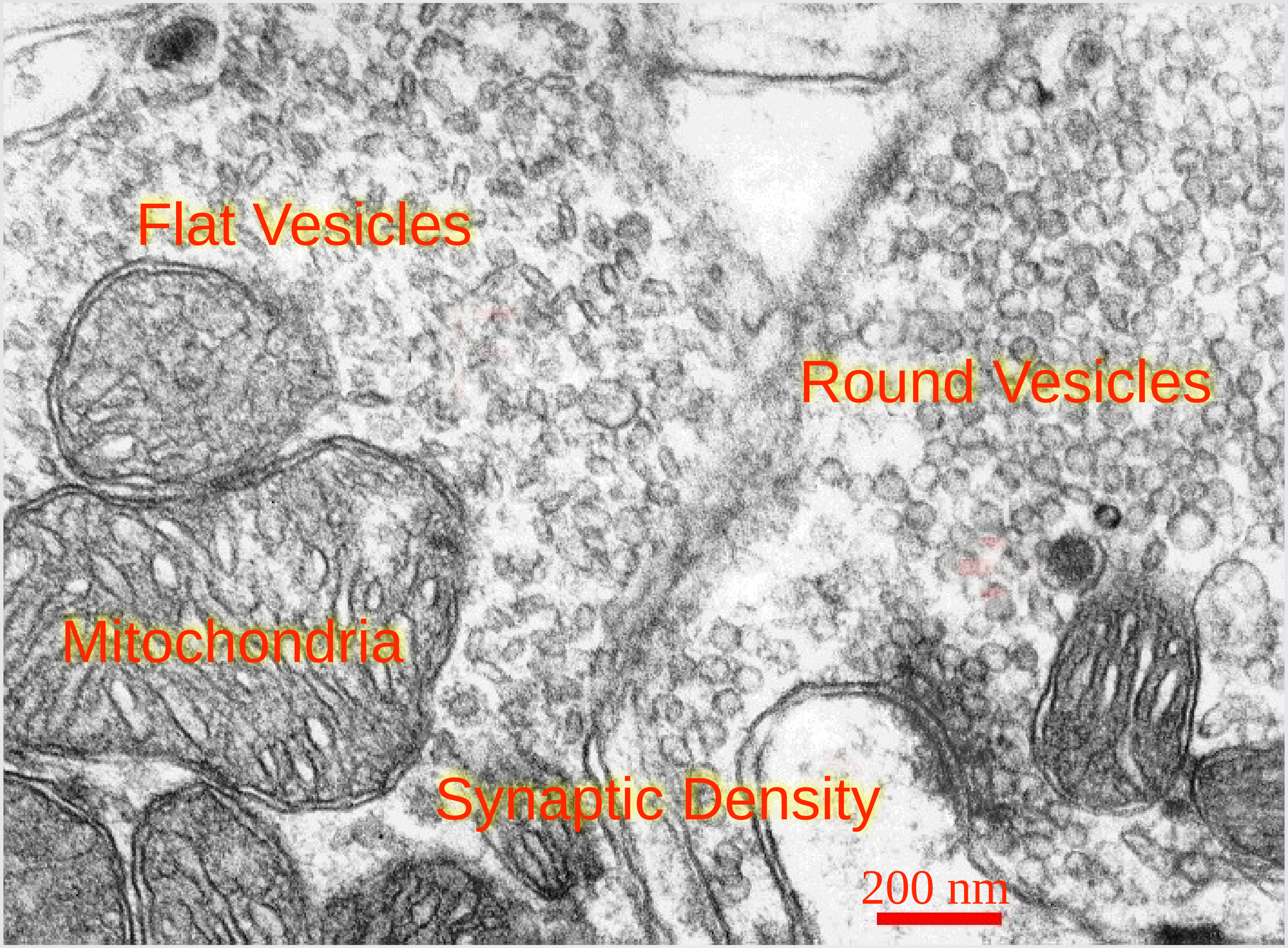
After Magleby and Stevens. J Physiol. **223**, 1972

Neural Synapse



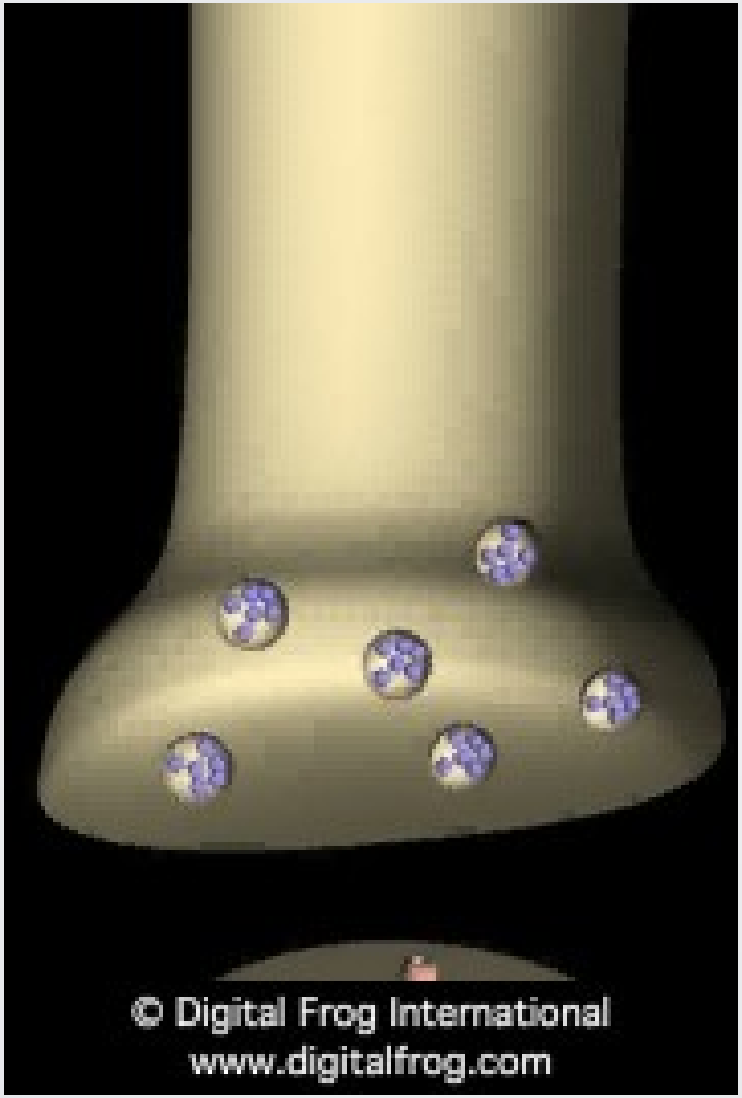
http://www.driesen.com/synapse.htm

SYNAPSES BY EM



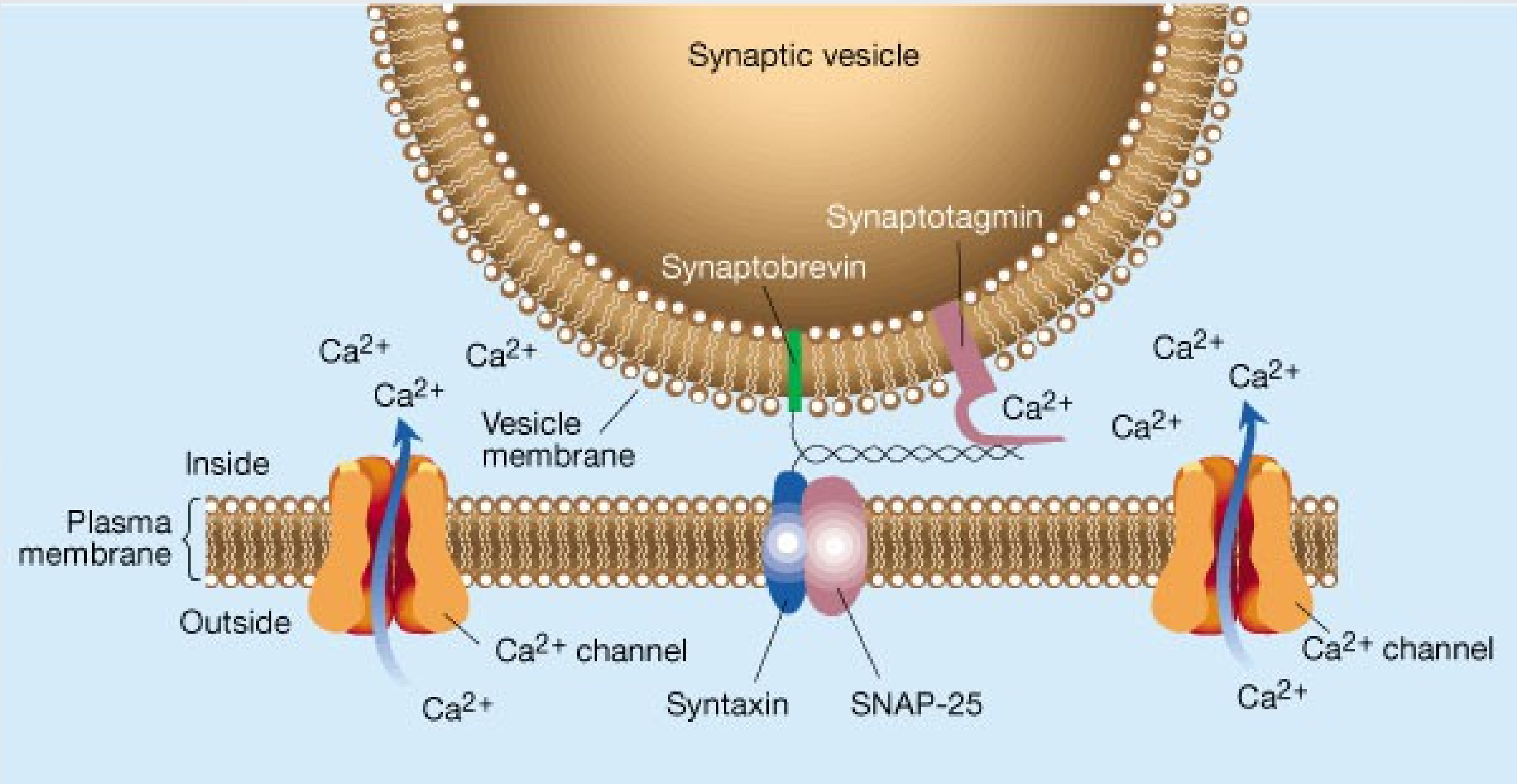
Atlas of Ultrastructural Neurocytology
http://synapses.mcg.edu/atlas/1_6_1.stm

SYNAPTIC MECHANISM (MOVIE)



Delay from Presynaptic Action Potential to Post-synaptic Voltage Change is ≈ 0.5 msec

SYNAPTIC VESICLES



Exocytosis of Transmitter requires Ca^{2+}

Matthews, G. Neurobiology: Molecules, Cells and Systems 2nd ed

Neurotransmitters

Small Molecules

- Acetylcholine
- Serotonin
- Histamine
- Epinephrine
- Norepinephrine
- Dopamine
- Adenosine
- ATP
- Nitric Oxide

Amino Acids

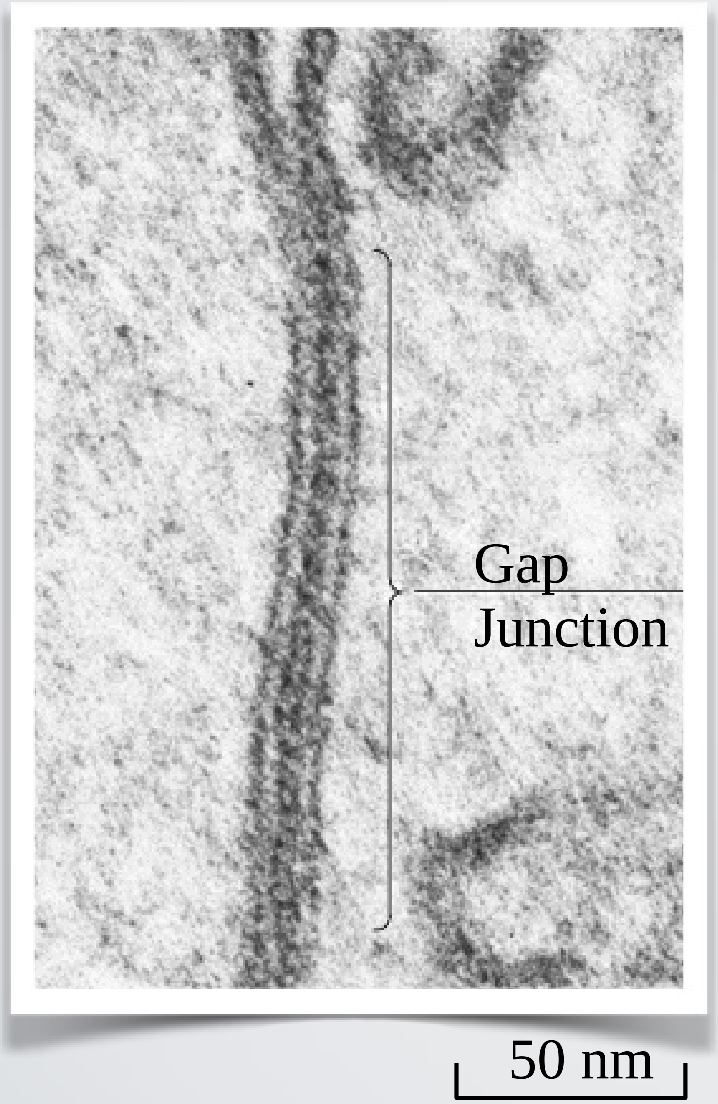
- Aspartate
- Gamma-aminobutyric Acid
- Glutamate
- Glycine

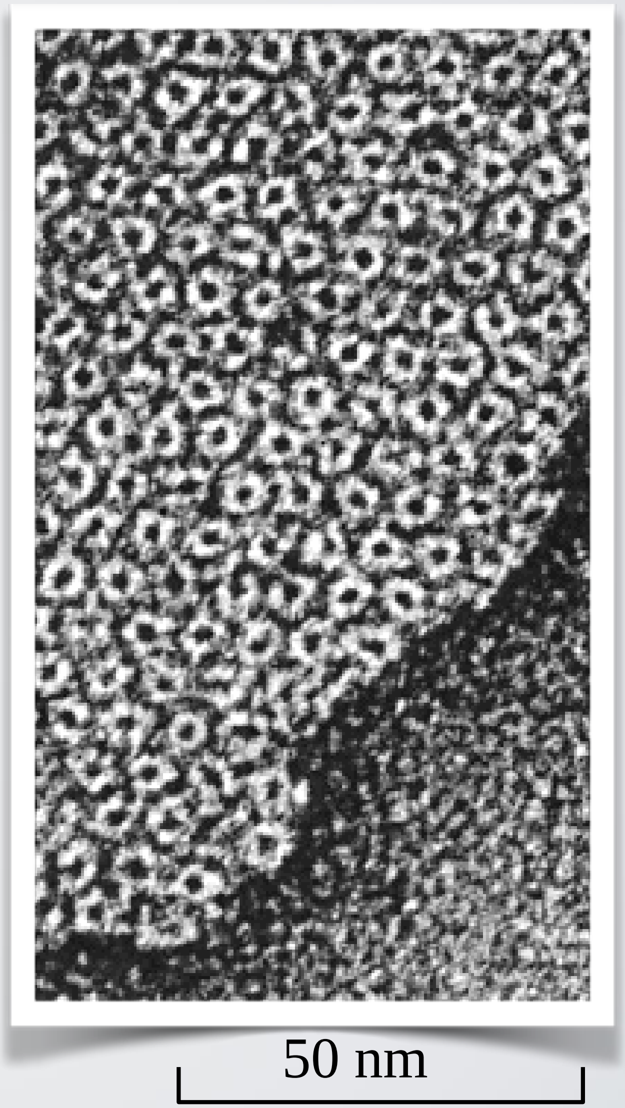
Peptides

- Angiotensin II
- Bradykinin
- Beta-endorphin
- Bombesin
- Calcitonin
- Cholecystokinin
- Enkephalin
- Dynorphin
- Insulin
- Galanin
- Gastrin
- Glucagon
- GRH
- GHRH
- Motilin
- Neurotensin
- Neuropeptide Y
- Substance P
- Secretin
- Somatostatin
- Vasopressin
- Oxytocin
- Prolactin
- Thyrotropin
- THRH
- Luteinizing Hormone
- Vasoactive Intestinal Peptide

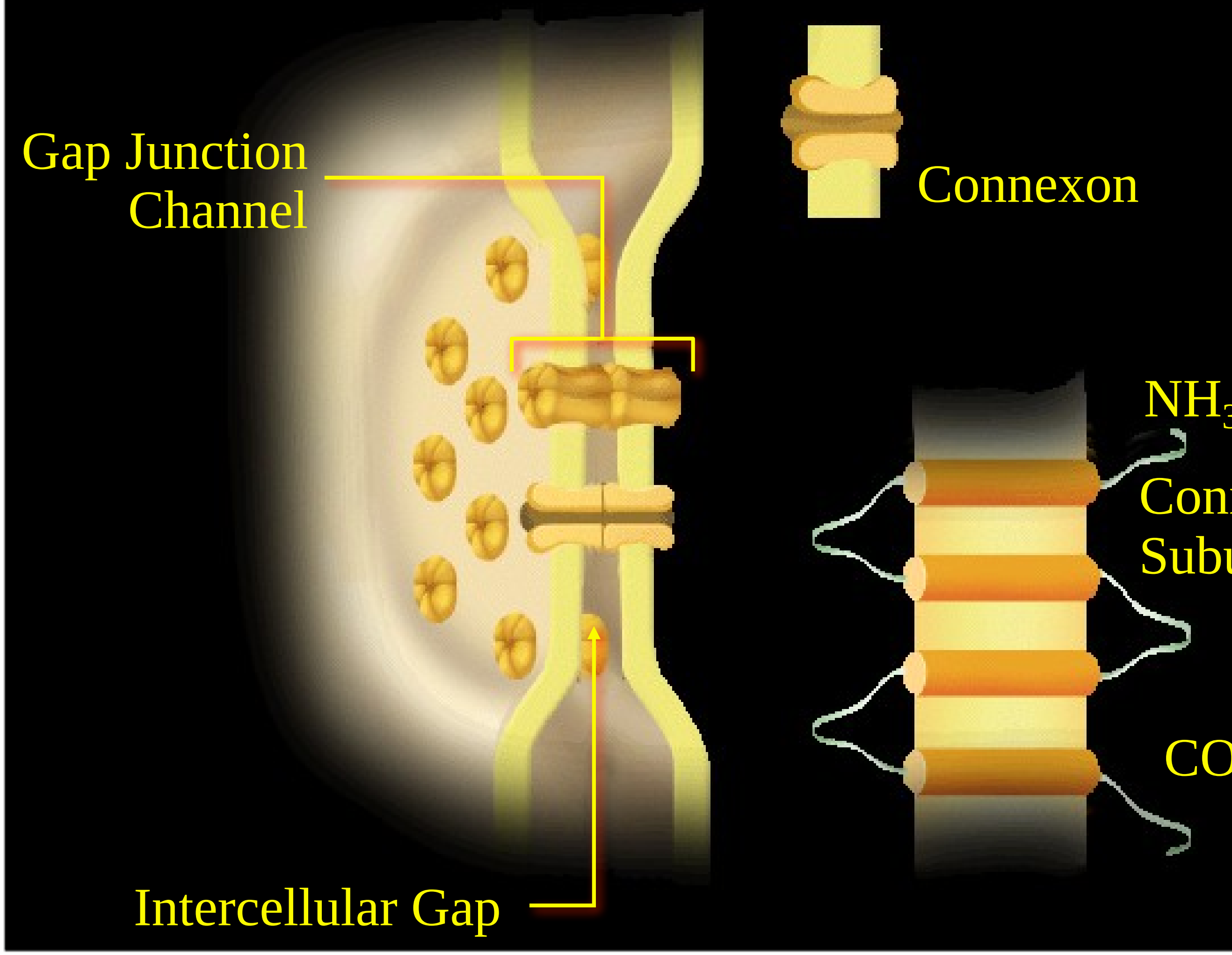
…and many others

ELECTRICAL SYNAPSES





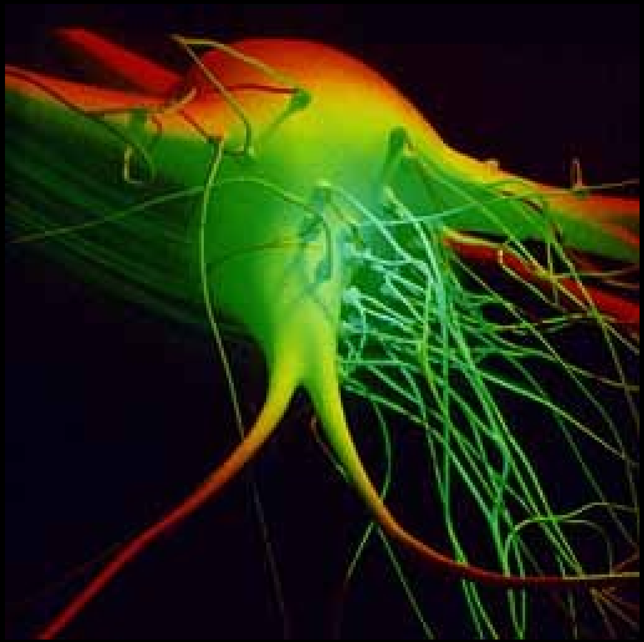
GAP JUNCTION MICROSTRUCTURE

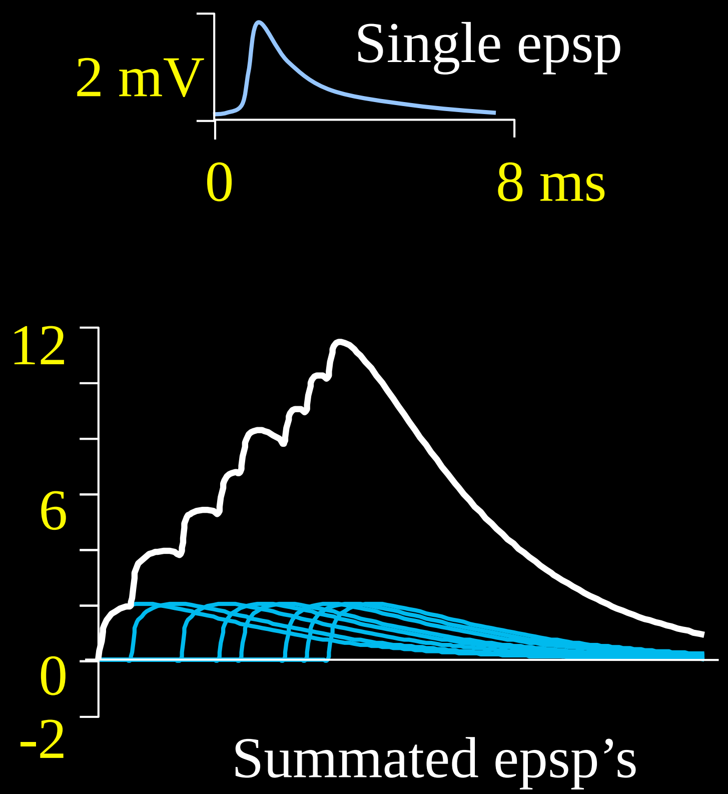


Gap Junctions have no synaptic delay, and may act as simple resistance or as electrical *rectifiers*

Modified from: http://aids.hallym.ac.kr

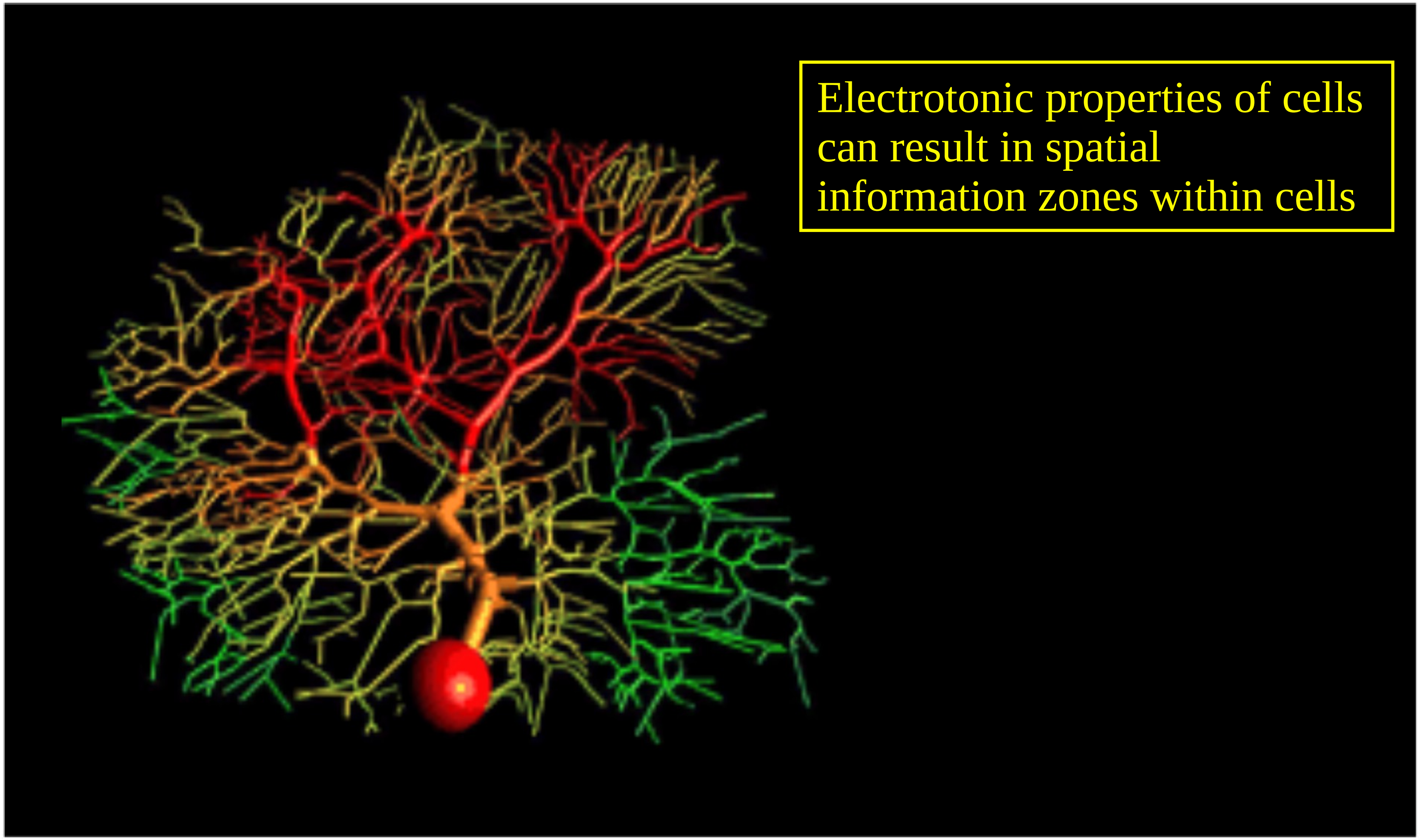
SpatioTemporal Summation of psp's



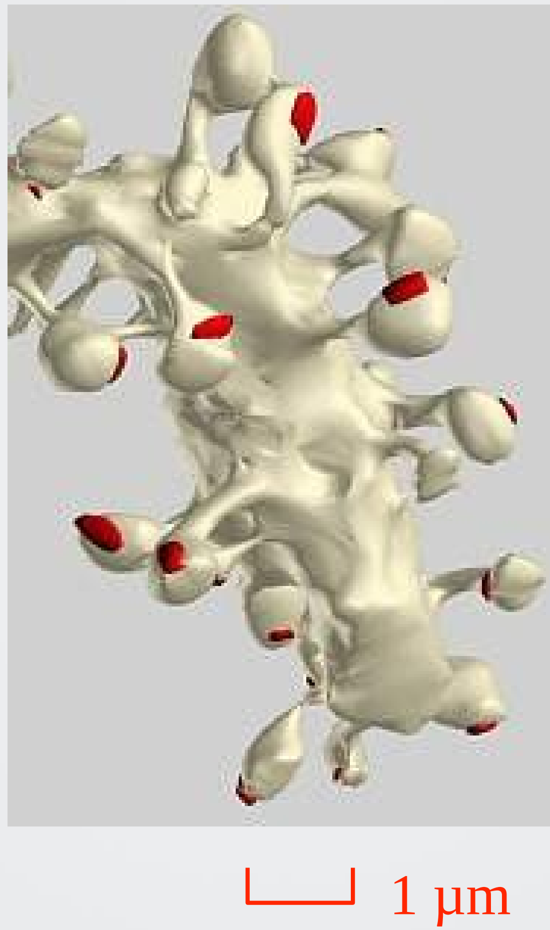


http://www.oseplus.de/Images/jpg/Synapse1.jpg

Integration of Inputs

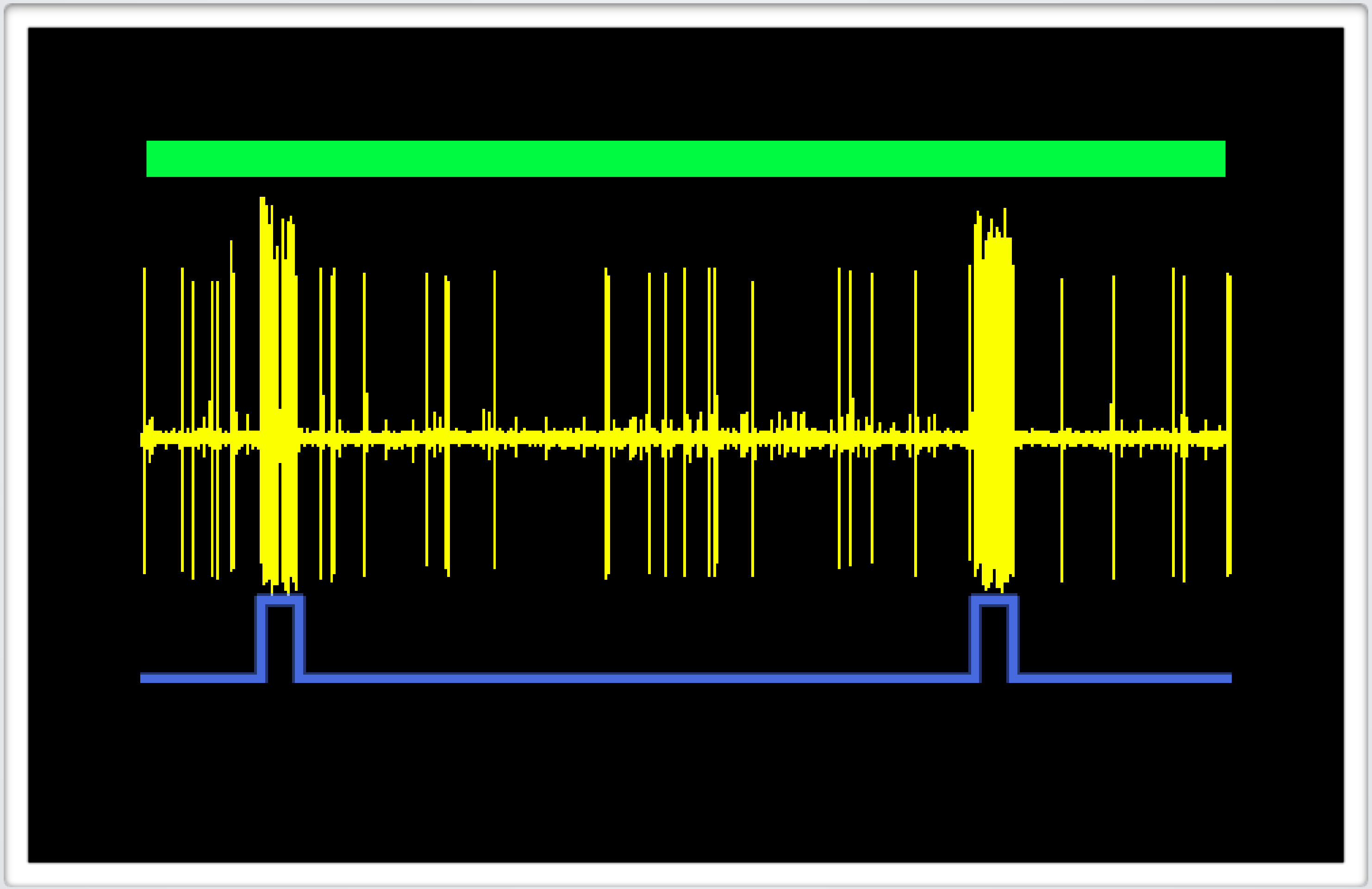


DENDRITIC SPINES



Atlas of Ultrastructural Neurocytology

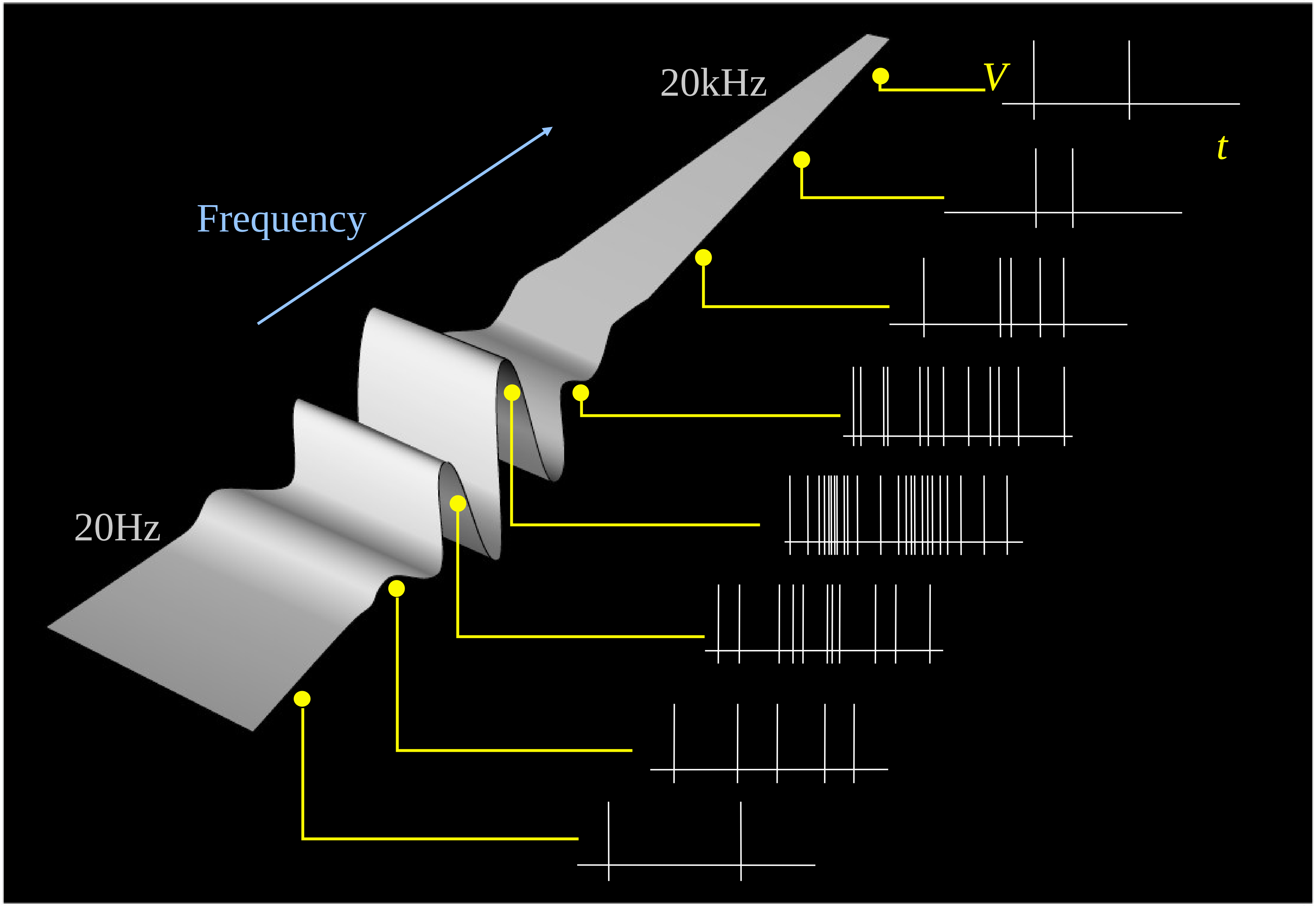
How Do Neurons Encode Information?



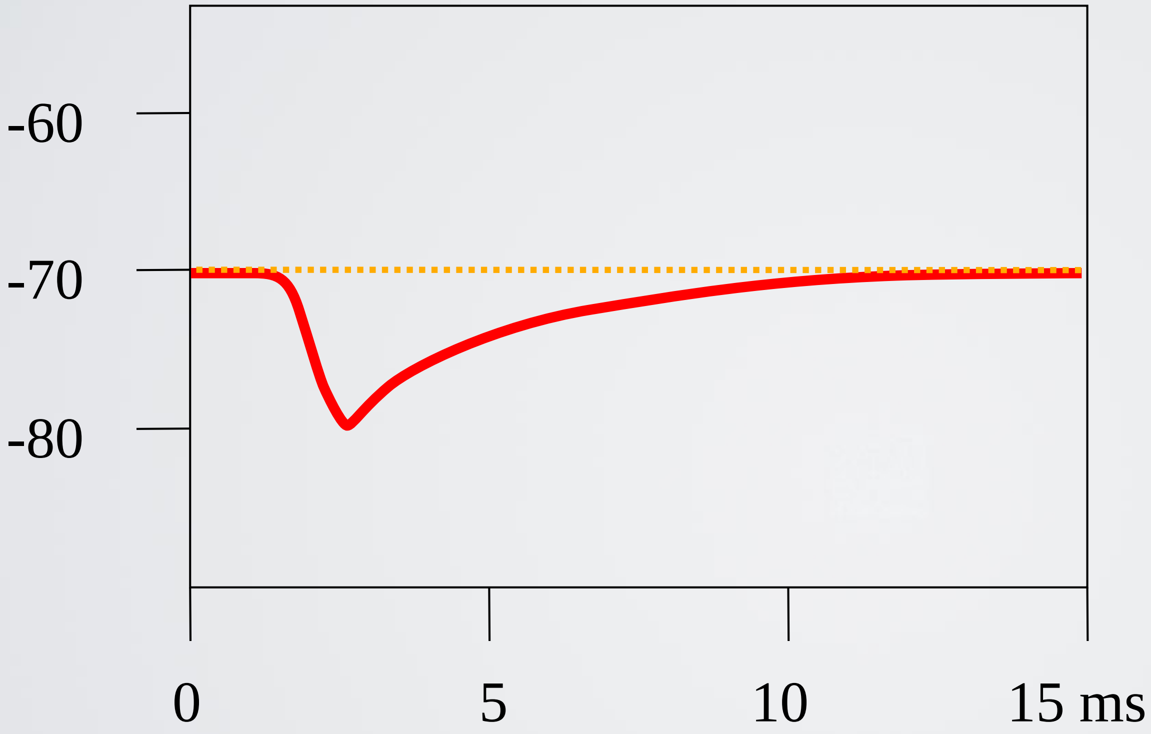
How Do Neurons Encode Information?

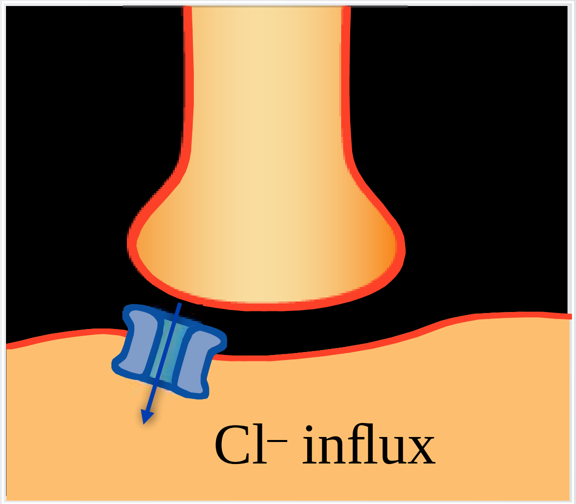
- Firing Rate: Ranges up to 1000 spikes/second
- Labeled Channels: Each neuron has different information content
- Modification of Synaptic Efficacy
- Firing Synchrony
- Transmitter Identity

Place Encoding - Basilar Membrane



Inhibition

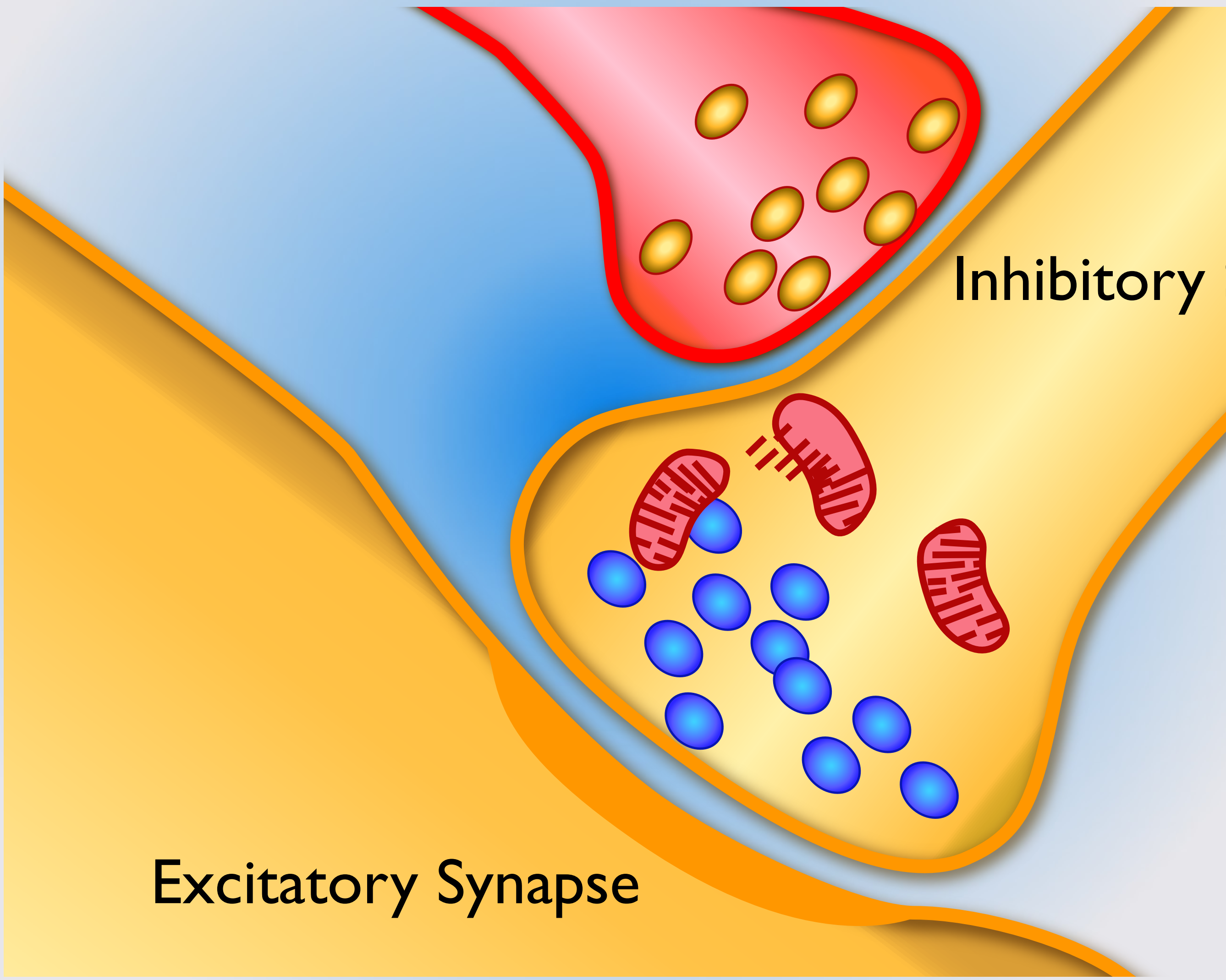




Reversal potential of Cl⁻ is near the resting potential. Therefore, its inhibition may be silent.

 www.brainmapping.org

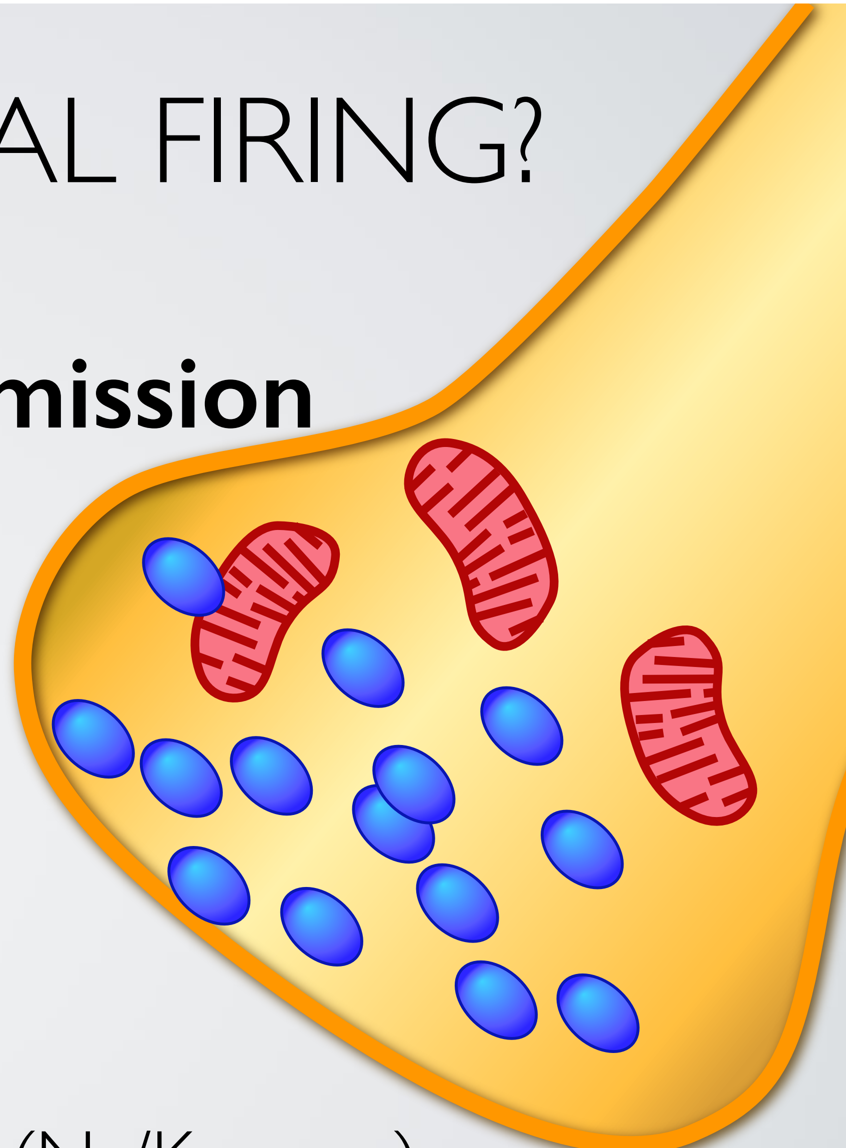
PRE-SYNAPTIC INHIBITION



What Might We Detect?

- Energy Demand
- Direct Electrical Signaling
- Morphological Differences
- Chemical Concentrations
- Tissue Density
- Fat/Water
- etc...

BOLD AND NEURAL FIRING?



Energy Demands in Transmission

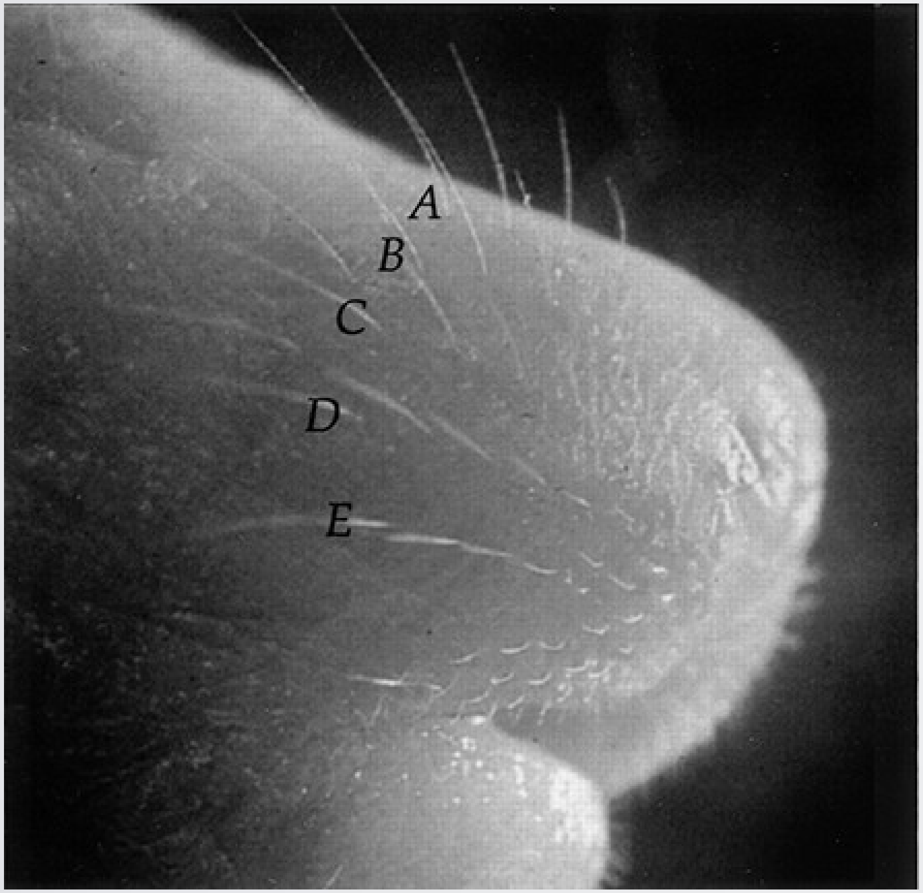
Pre-synaptic:

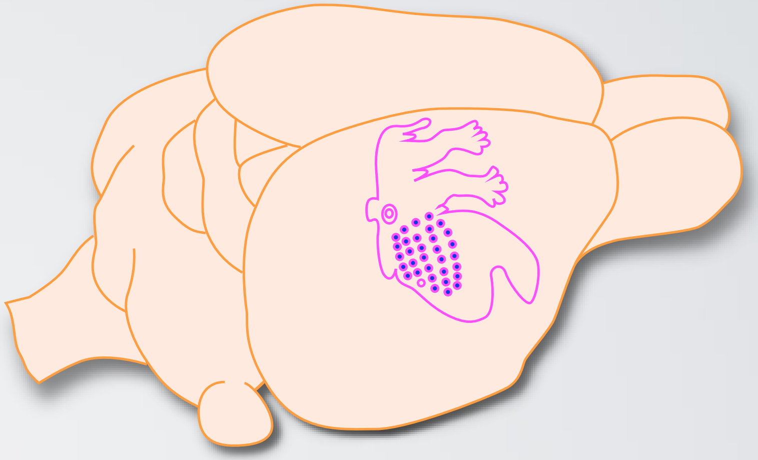
- Transmitter Synthesis
- Exocytosis
- Transmitter re-uptake

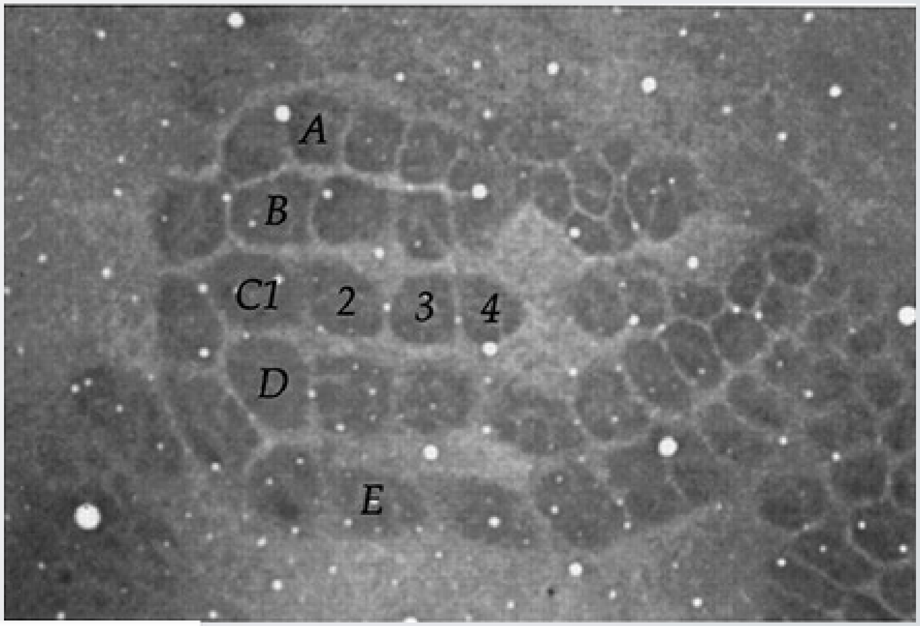
Post-Synaptic

- Excitatory: Removal of Sodium (Na/K pump)
- Maintenance of membrane potential after ion leakage
- Inhibitory: ???

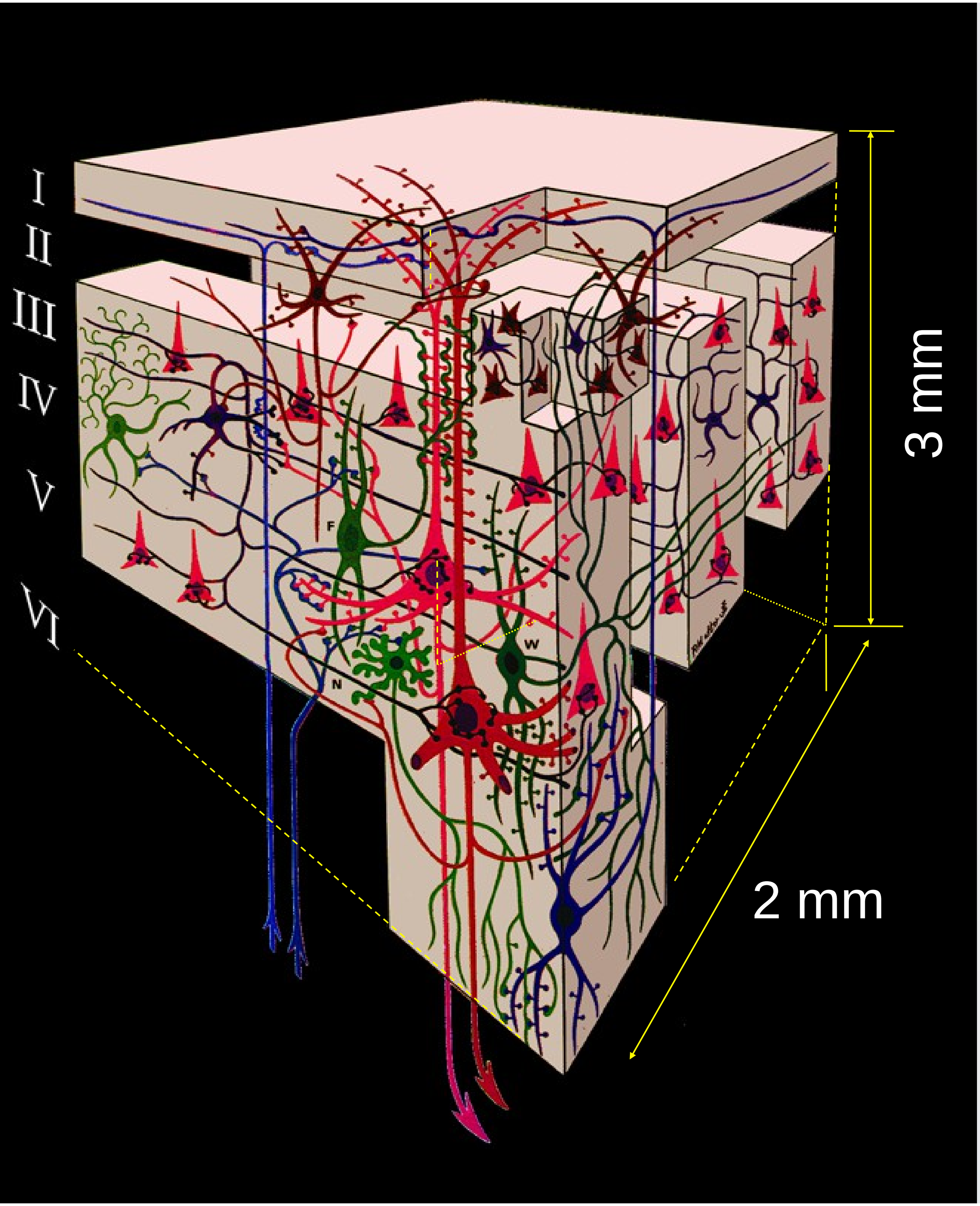
Cortical Column





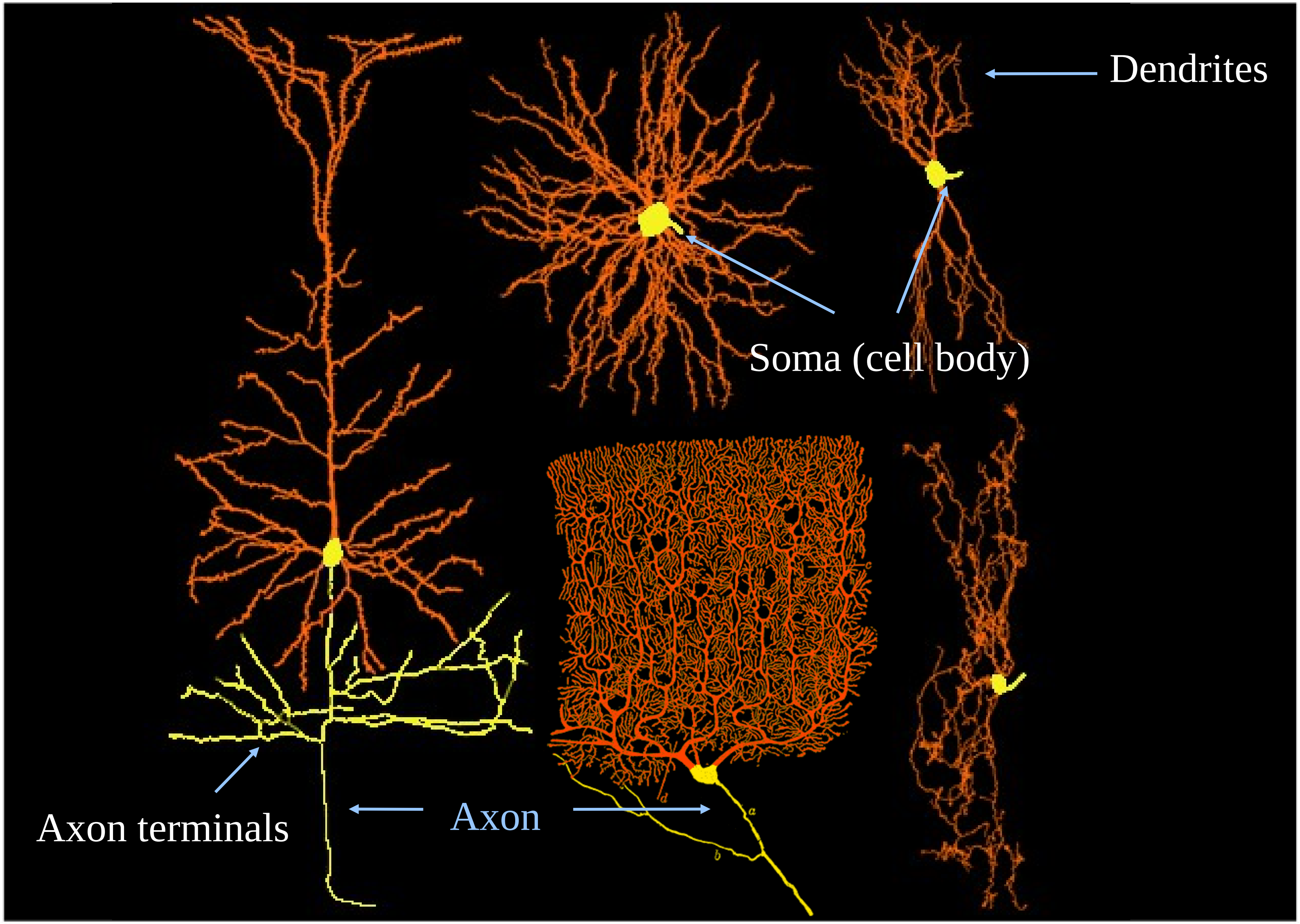


Wilson. PNAS **97**, 2000

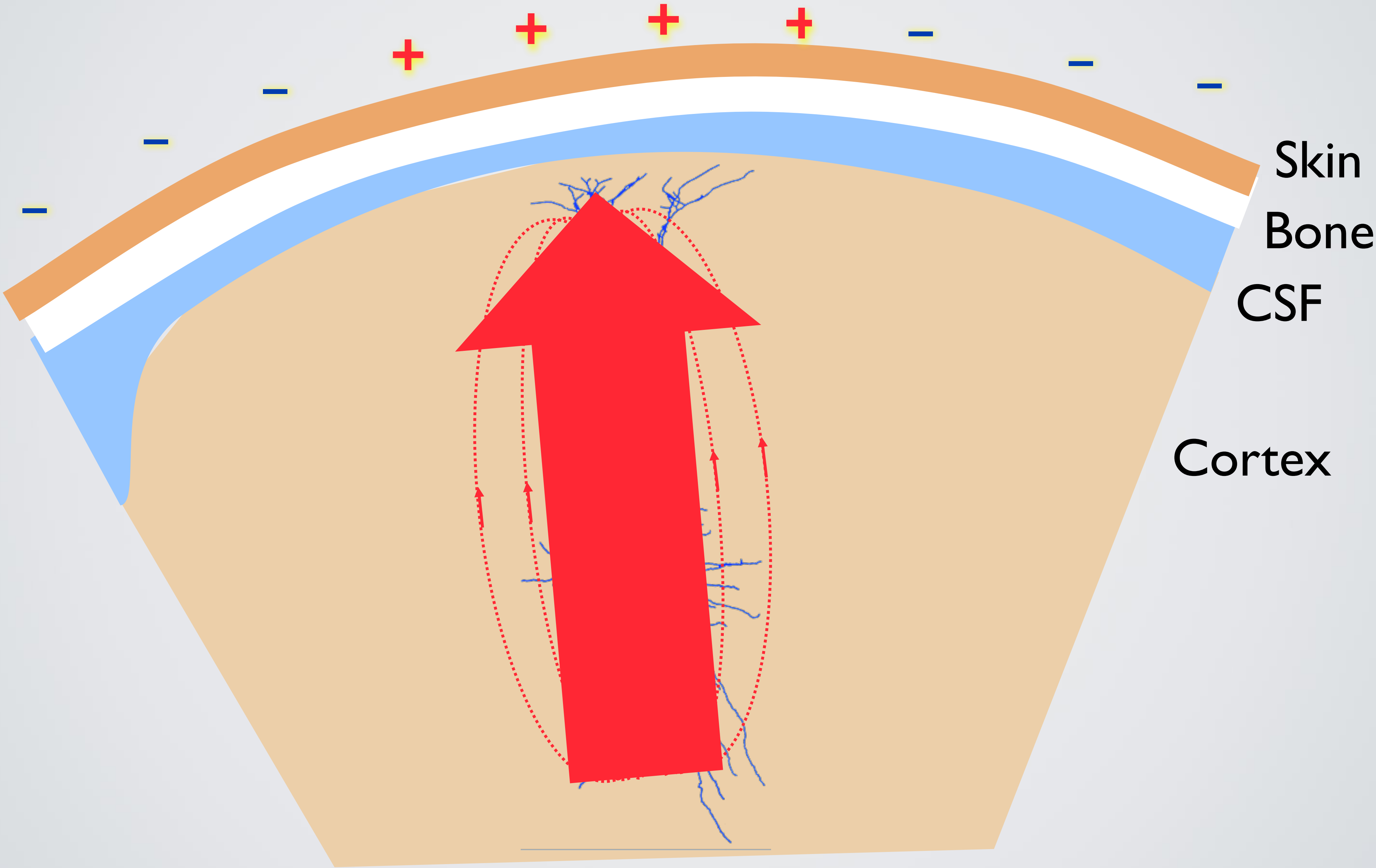


Imaging voxels and Neuropil

Types of Neurons



Presumed Origin of the EEG

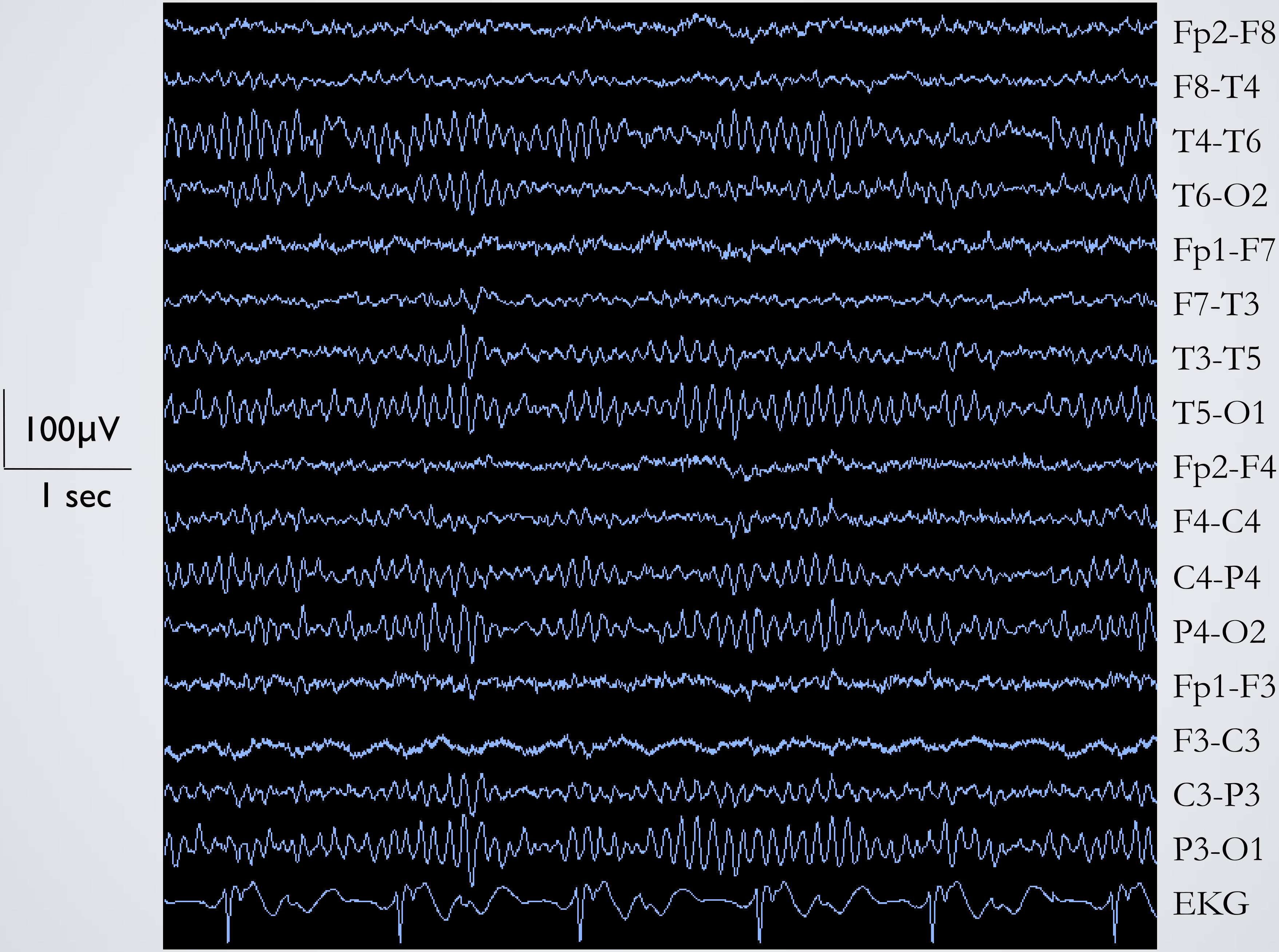


Many Neurons are Not "Seen" by EEG

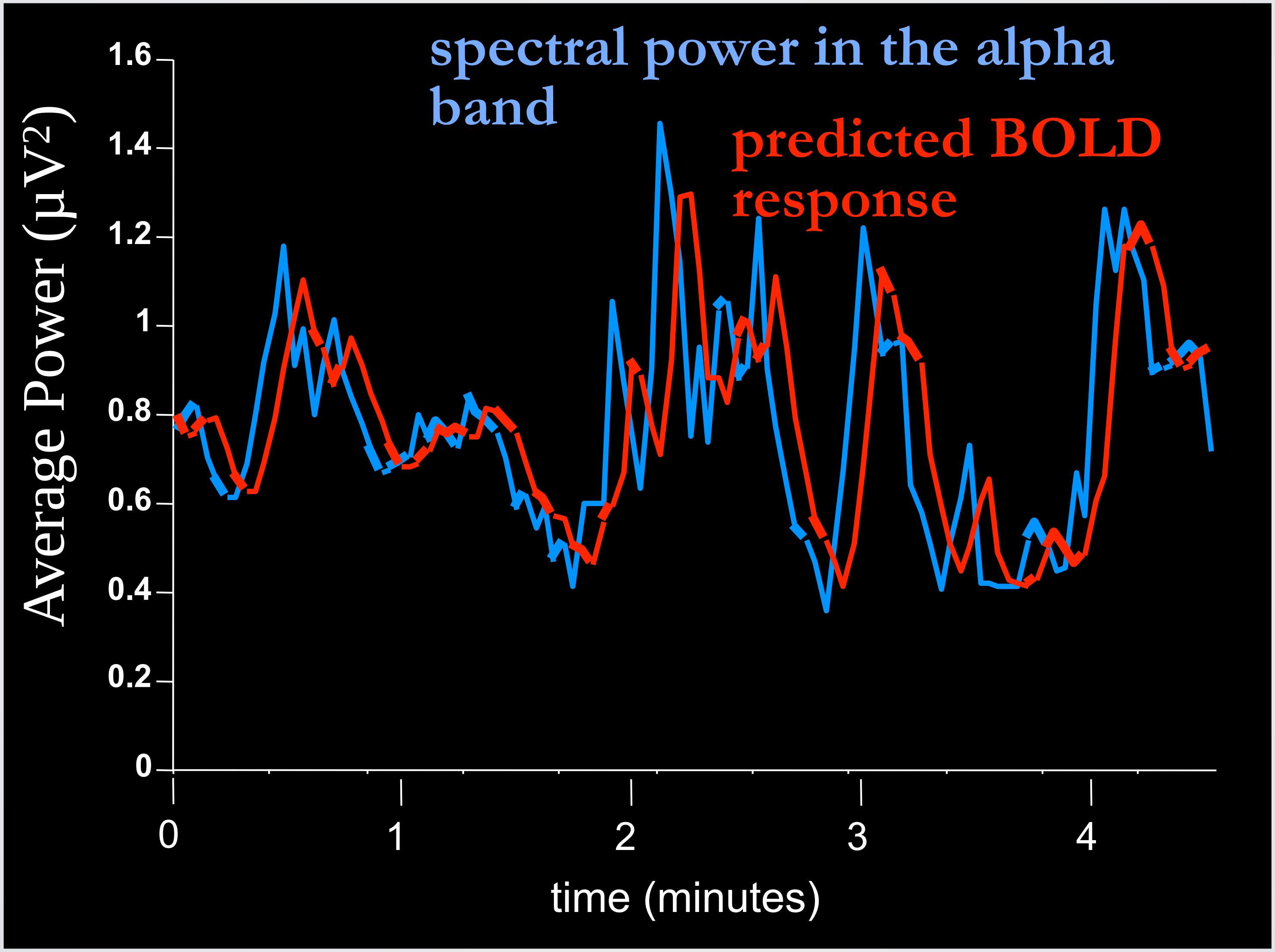
General Limitations in EEG Localization

- Deeper Sources Show Weaker Signals
- Magnitude Depends on Dipole Orientation
- Magnitude Depends on Temporal Synchrony
- Magnitude Depends on Spatial Coherence
- Conductivity of Body Tissues (CSF, scalp) Blur the Scalp Potentials

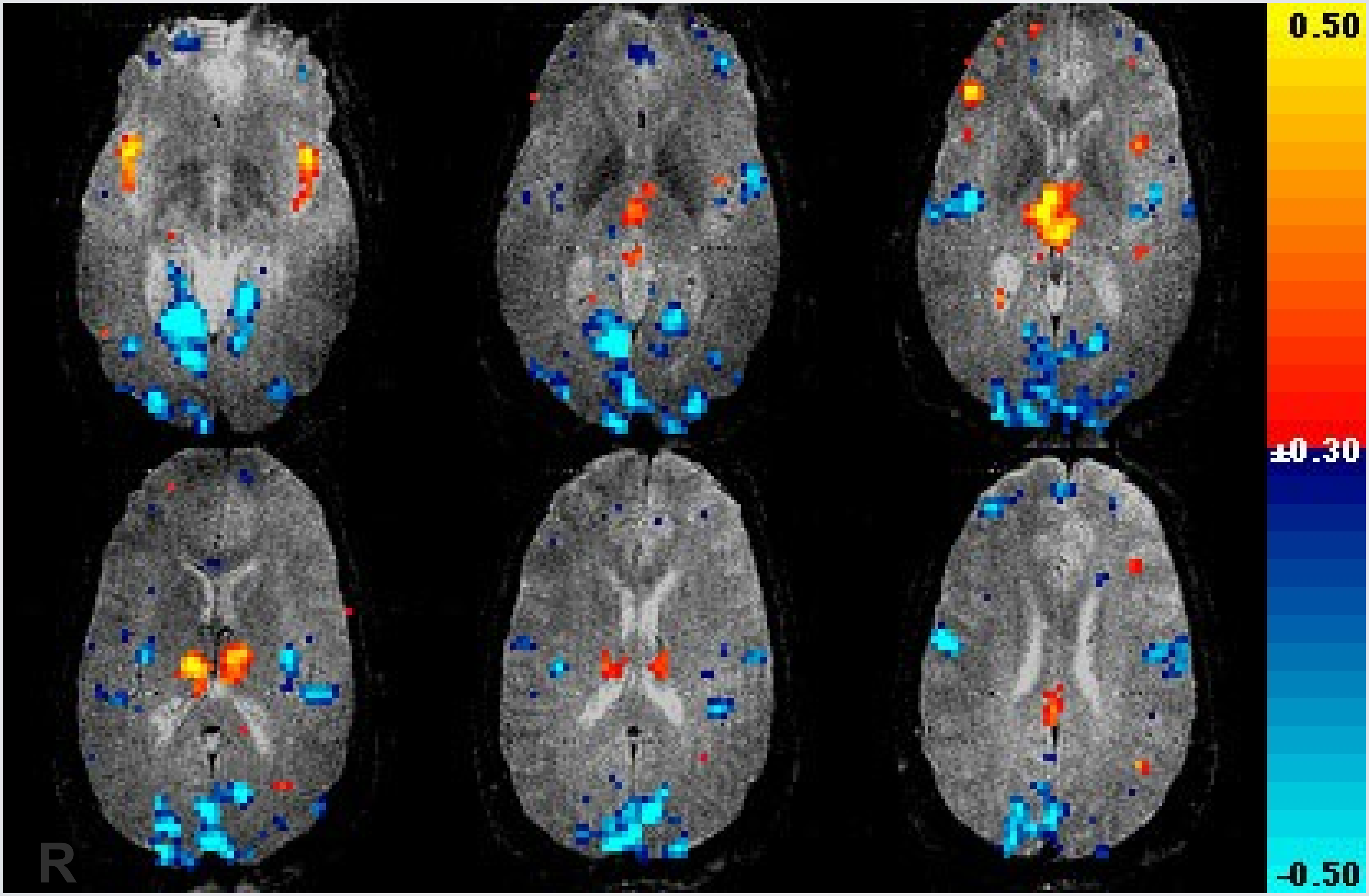
EEG at Rest


100µV
1 sec
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
EKG

ALPHA MAPPING



SITE OF RESTING ALPHA



Goldman (2002) Reference 13(18):2487

EEG-fMRI Issues

- Scalp Potentials are Proportional to the **Derivative** of the Voltage, whereas fMRI is Proportional to the **Integral** of the Firing
- The Action Potential, *per se*, Is Probably **Invisible** to BOLD
- The Rhythmic Structures in the EEG May Depend More on **Synchronous** Firing than on **High Firing Rate**
- The BOLD Signal is Likely Associated with the **Post**-Synaptic Neurons

Cohen, IEEE, 2009

MR-Lucent Neurophysiology

Energetic Demands .... *(BOLD, ASL)*

Transmitter Synthesis, Exocytosis, Metabolism

Na+/K+ Pump

[Na+] .... *Imaging*

Glucose Metabolism .... *Spectroscopy*

Extracellular Currents (?) .... *Phase Disturbance*

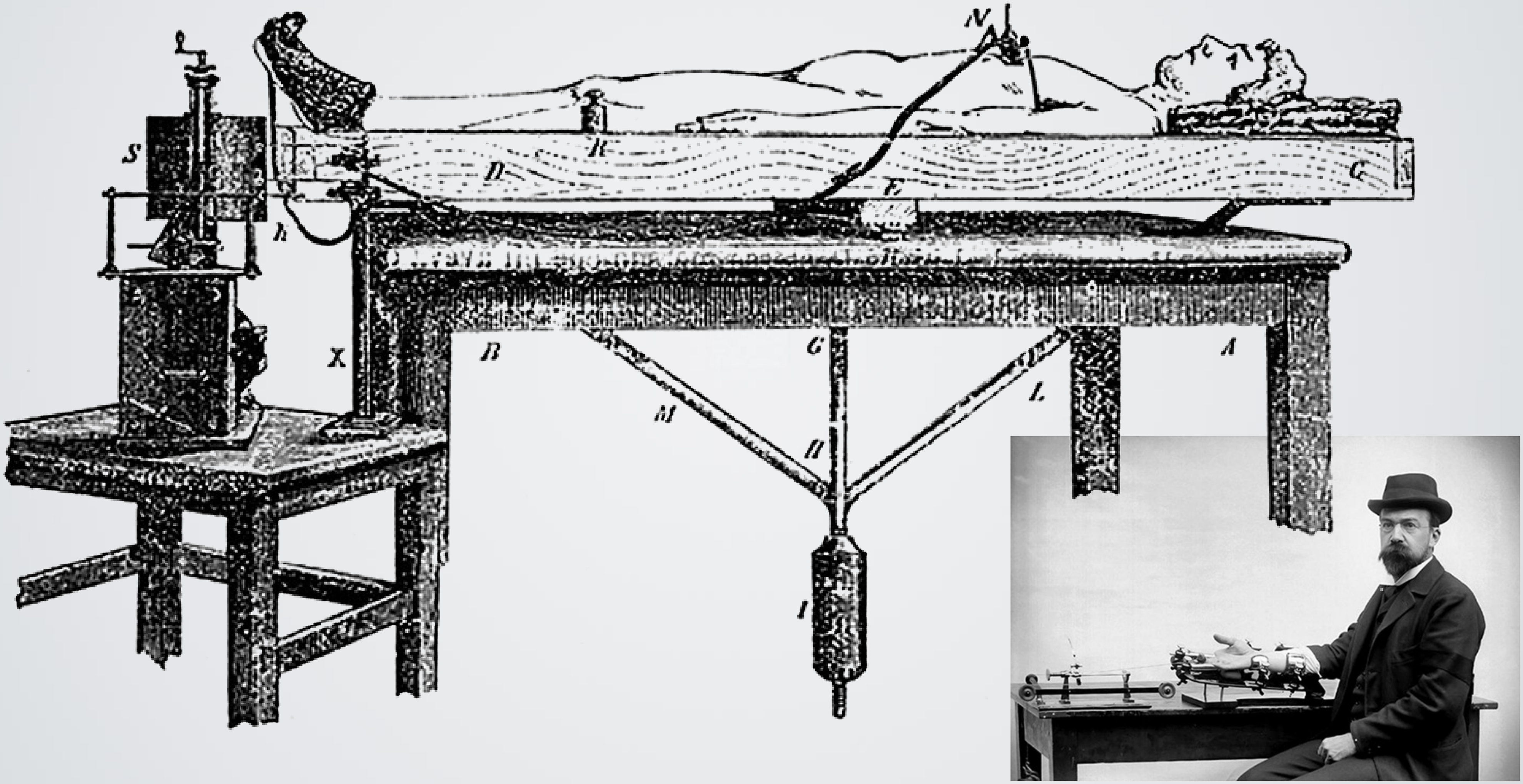
Anisotropic Diffusion .... *DTI, etc…*

Neural Constituents (NAA) .... *Spectroscopy*

BOLD

NeuroImaging Training Program

A Delicate Balance

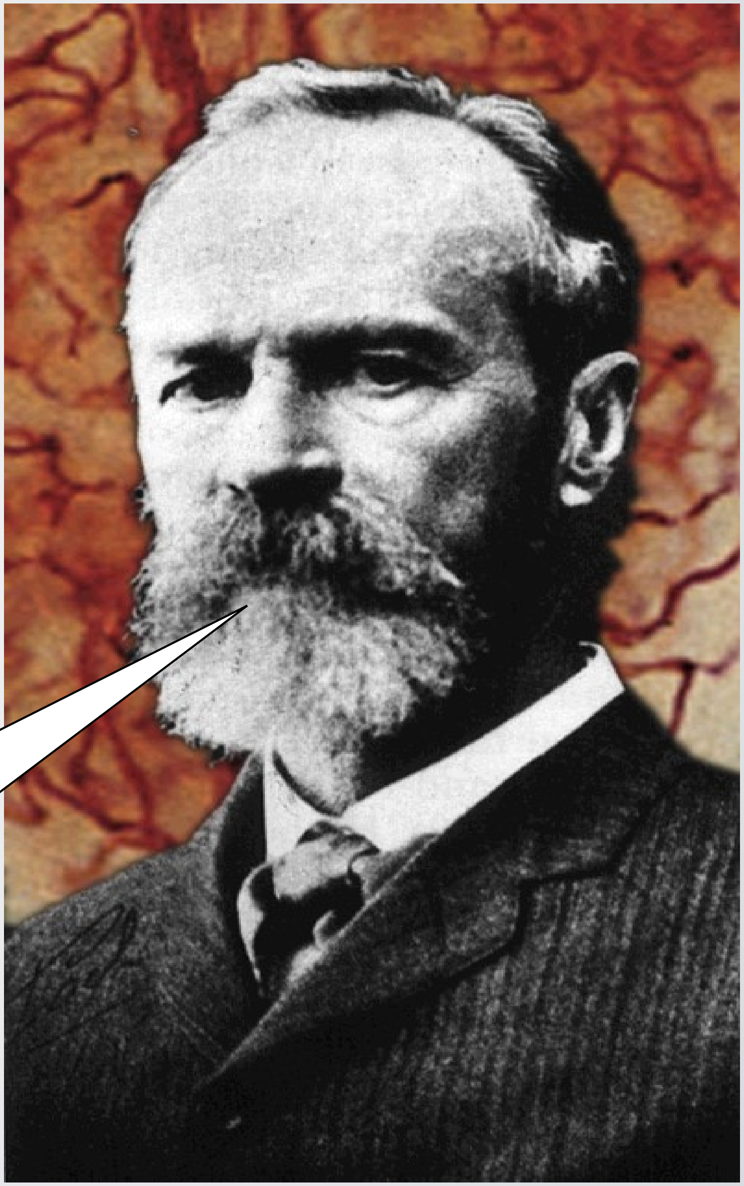


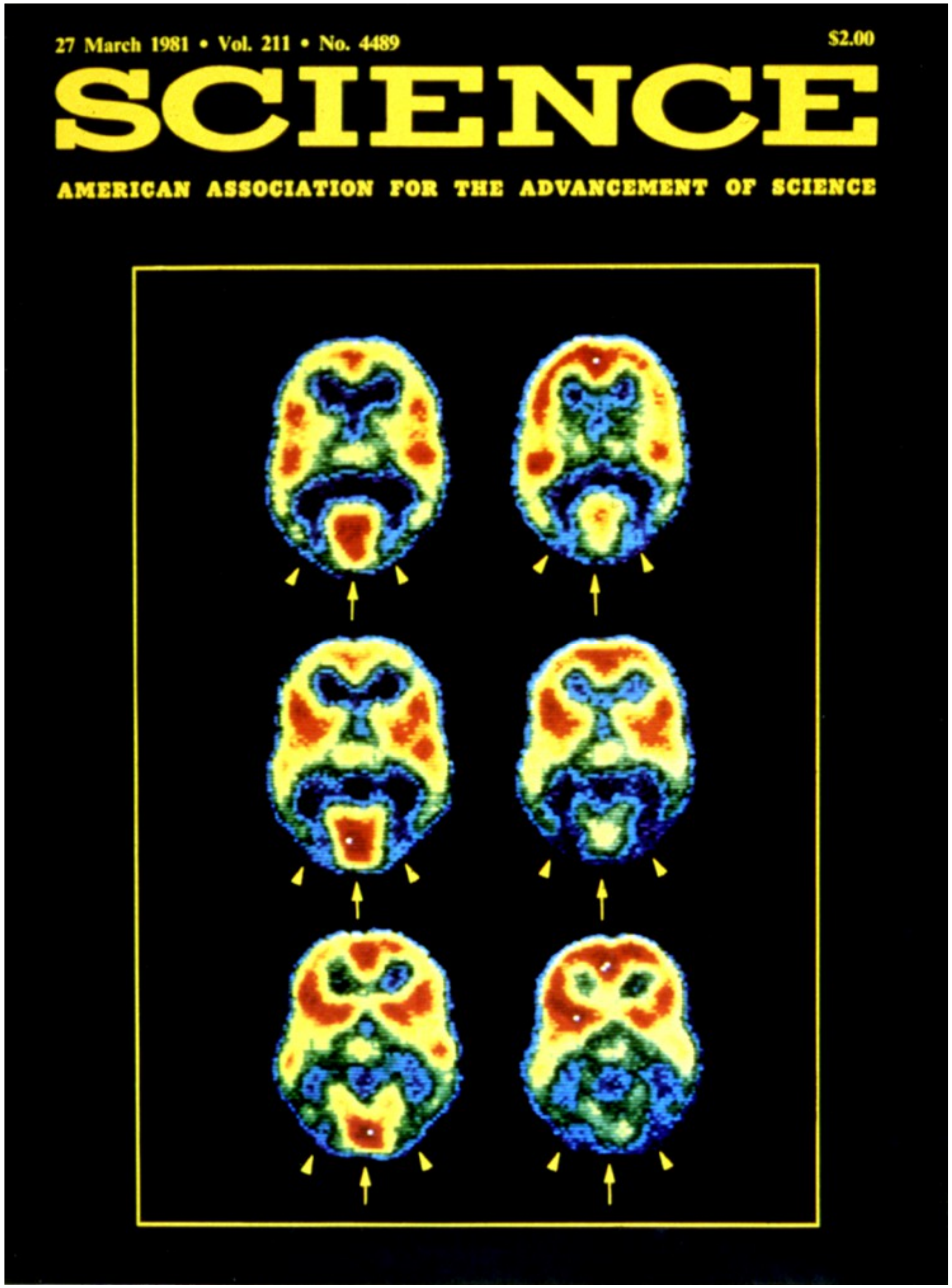
Angelo Mosso. *Atti R Accad Lincei Mem Cl Sci Fis Mat Nat*, **1884** ;XIX:531-43

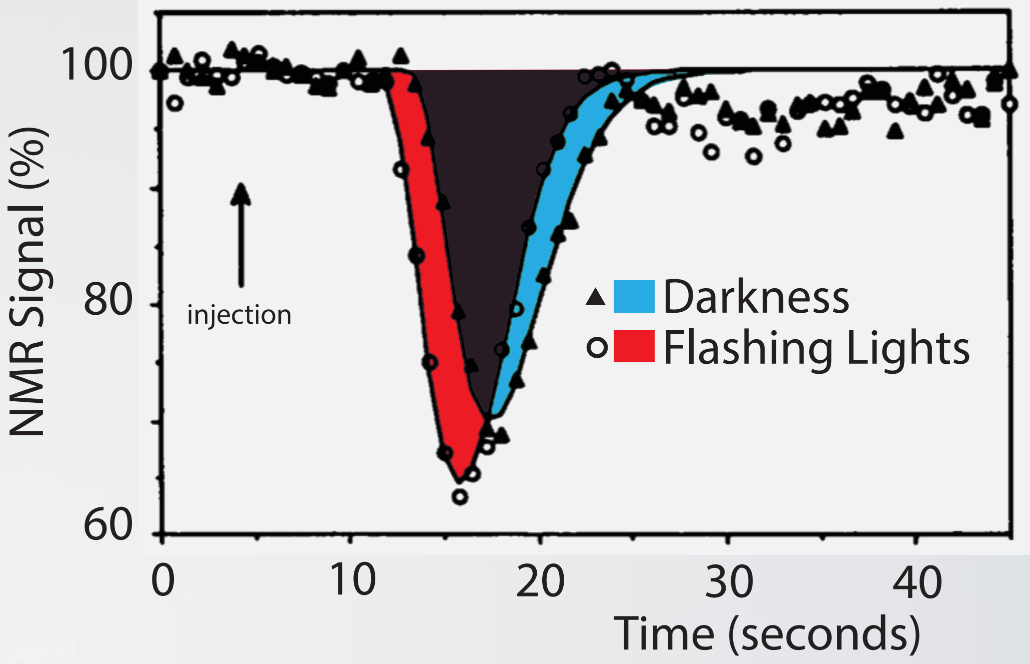
William James (1890)

"We must suppose a very delicate adjustment whereby the circulation follows the needs of the cerebral activity.

Blood very likely may rush to each region of the cortex according as it is most active, but of this we know nothing."




27 March 1981 • Vol. 211 • No. 4489
$2.00
SCIENCE
AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE



Jack Belliveau 1959-2014

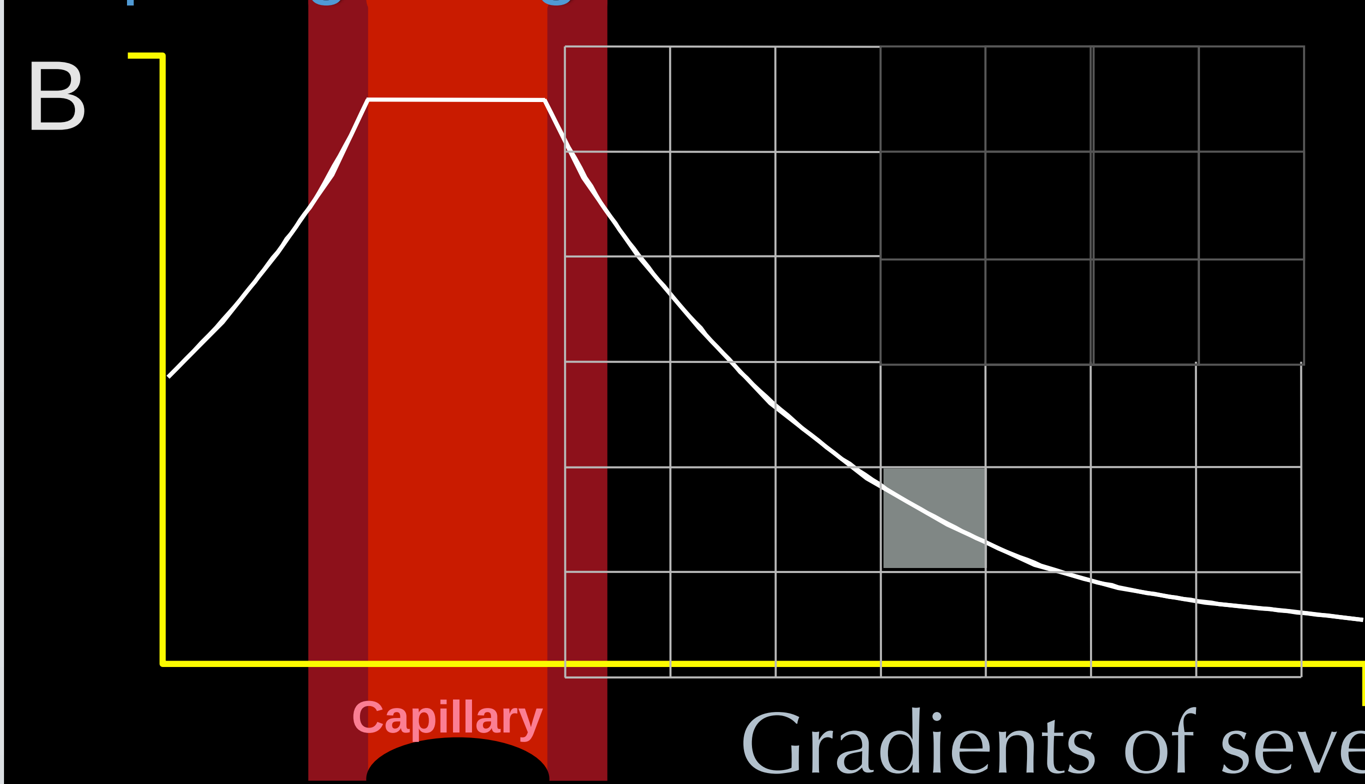
http://www.nmr.mgh.harvard.edu/in-memoriam-jack-belliveau

A DELICATE BALANCE: *REPRISE*

Pauling and Coryell. PNAS **22**, 1936

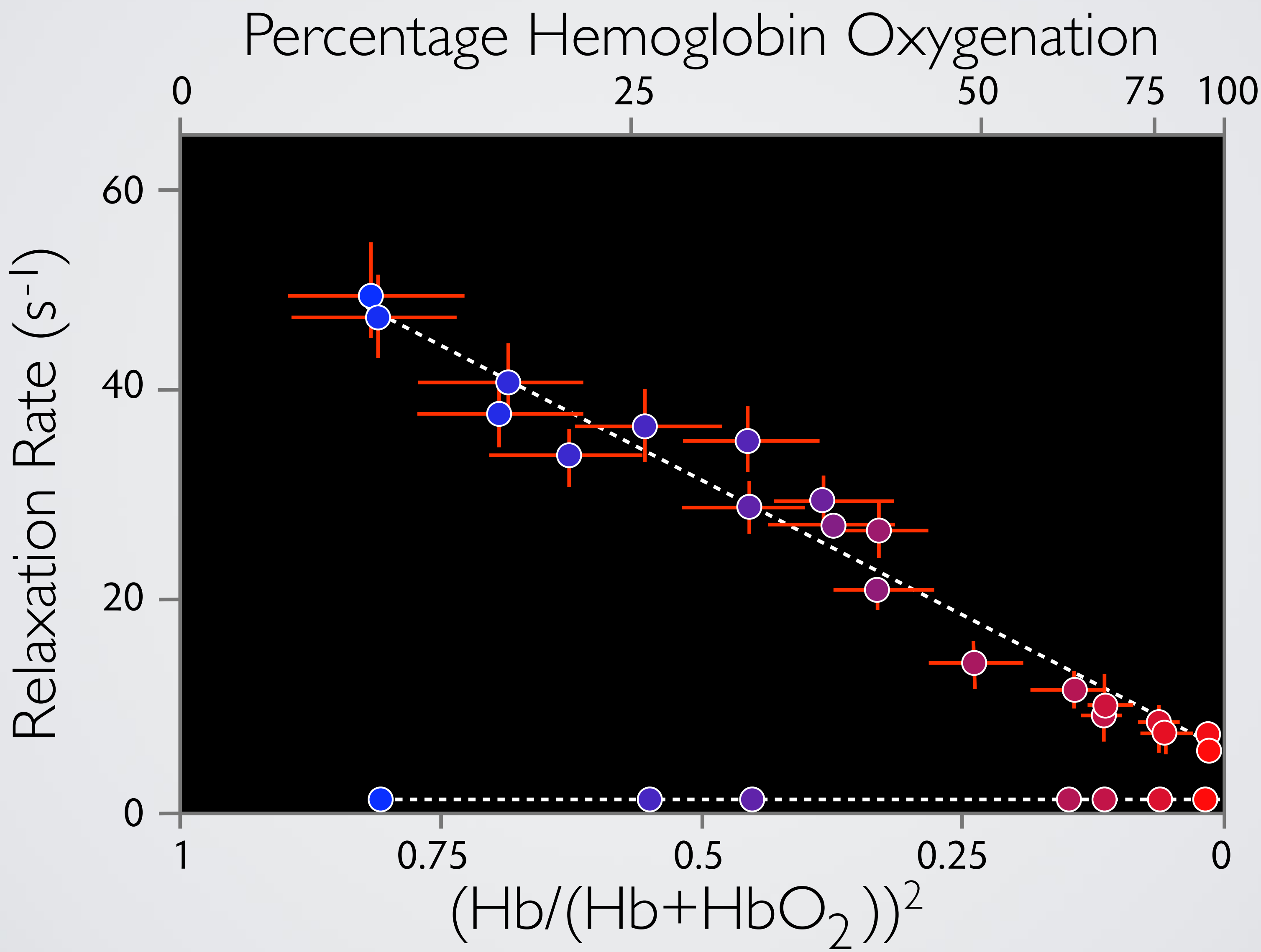
SIGNAL LOSSES FROM SPIN DEPHASING

Inhomogeneous Magnetic Fields Within Voxels Result in Spin Dephasing and Signal Loss in Gradient Echo Sequences



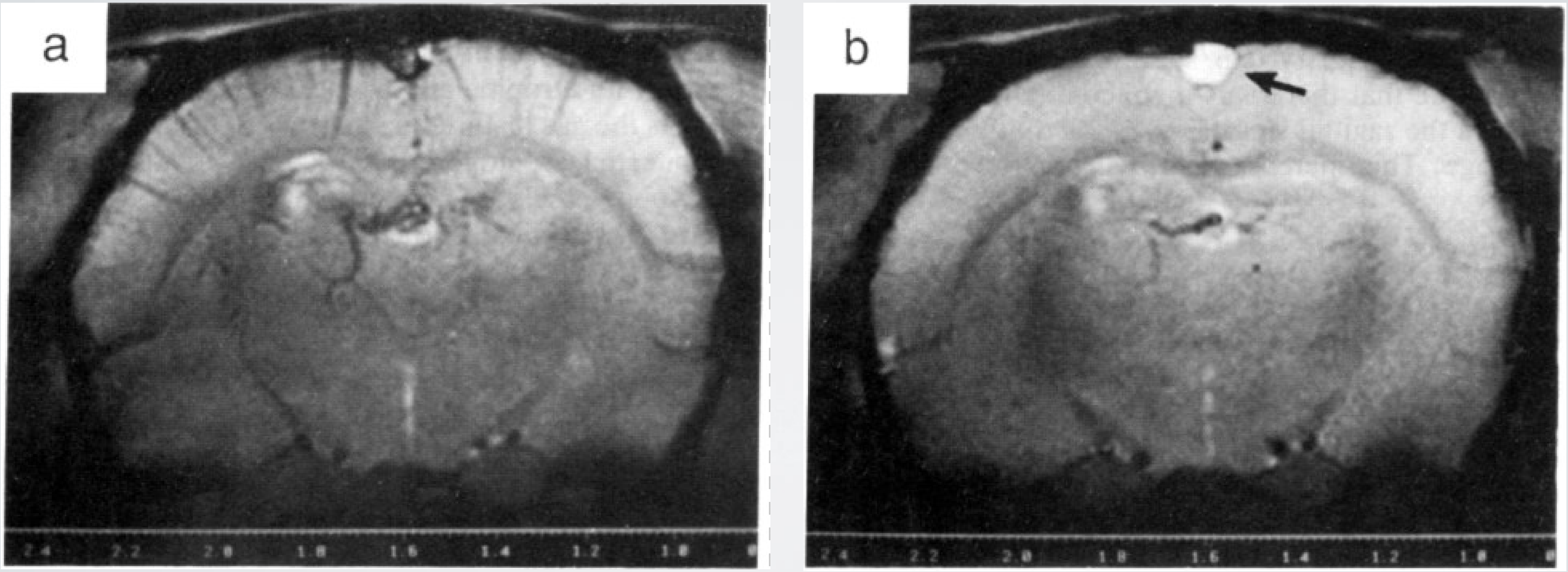
Gradients of several Gauss/cm may exist near deoxy-Hb-filled capillaries.

MRI Relaxation Rate and HbO2



Thulborn, et al., Biochimica et Biophysica Acta **714**, 1982

BOLD



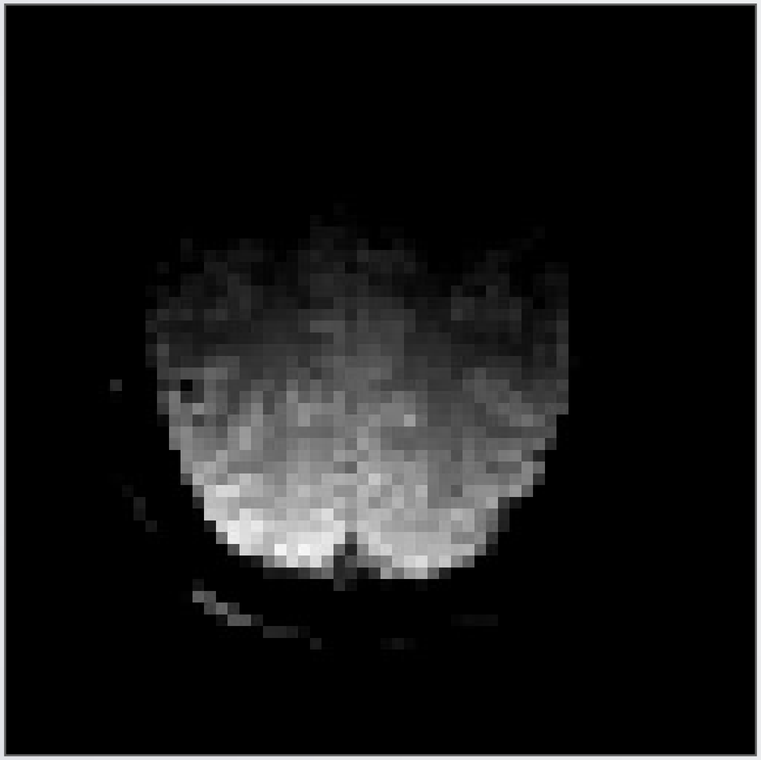
Effect of blood CO_2 level on BOLD contrast.
(*a*) Coronal slice brain image showing BOLD contrast from a rat anesthetized with urethane. The gas inspired was 100% O_2.

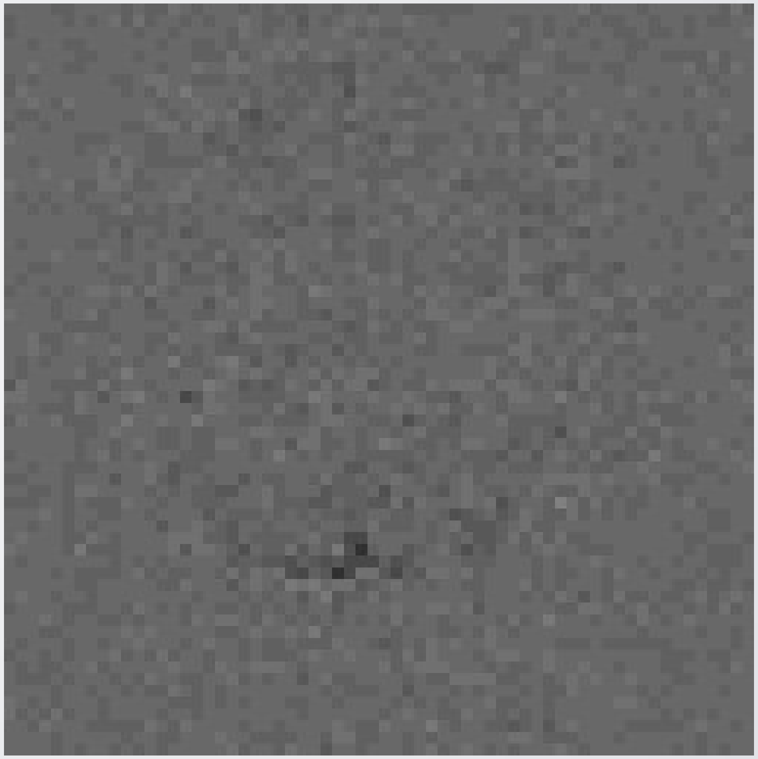
(*b*) The same brain but with 90% O_2/10%CO_2 as the gas inspired. BOLD contrast is greatly reduced.

S Ogawa, *et al.*,
PNAS, **87**(24):9868,1990

fMRI

explores intensity variations in MR signal

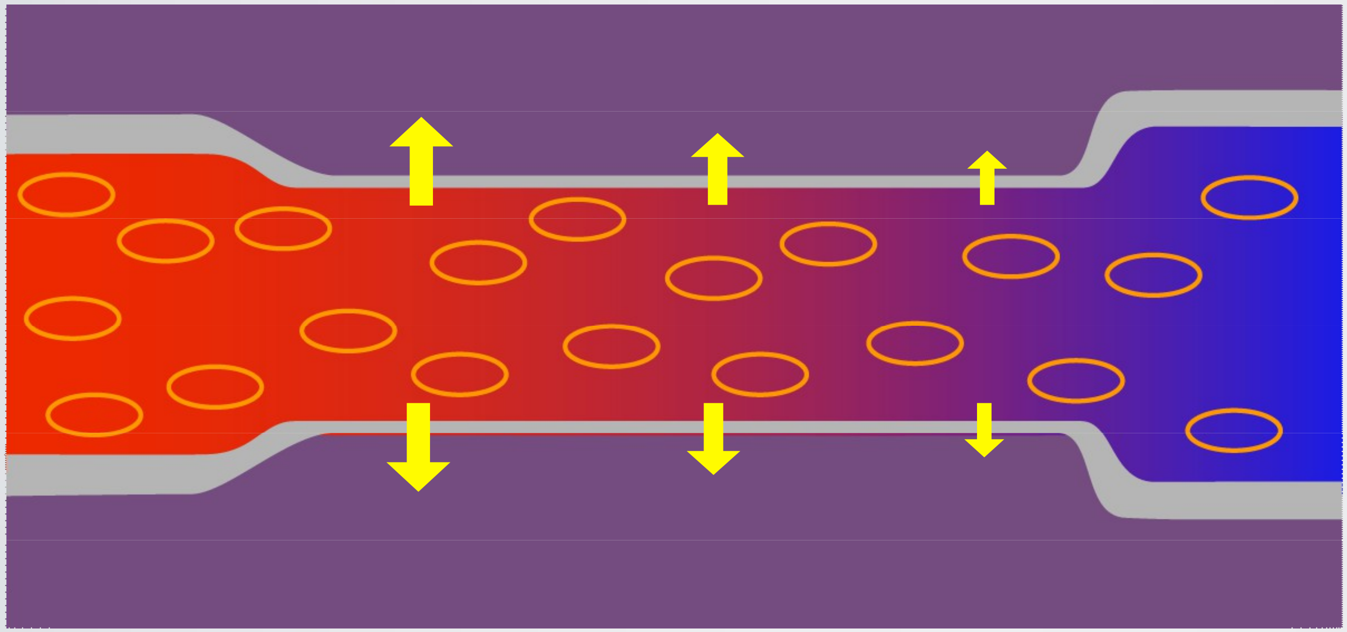


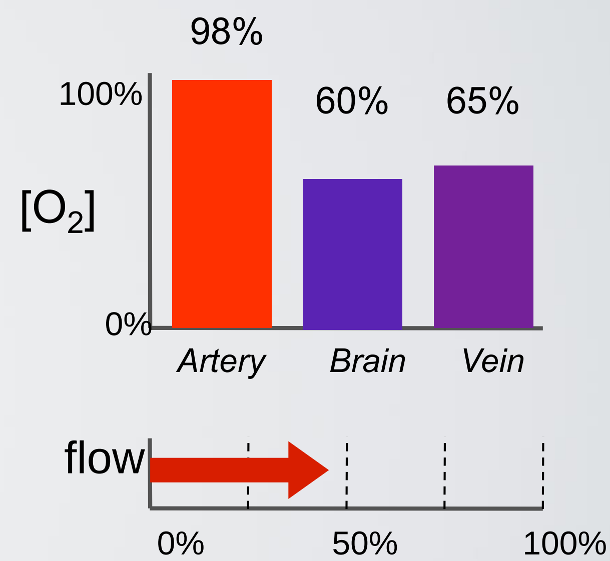


intensity variations reflect venous $[O_2]$

 www.brainmapping.org

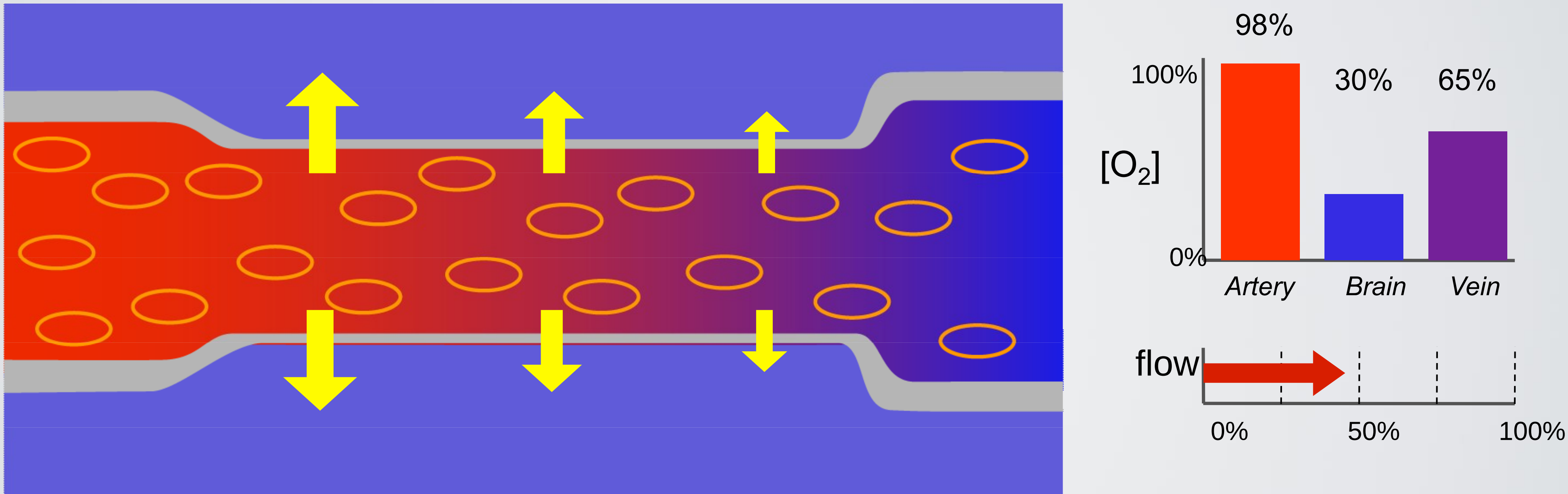
Why Does Venous O_2 Increase? (1)





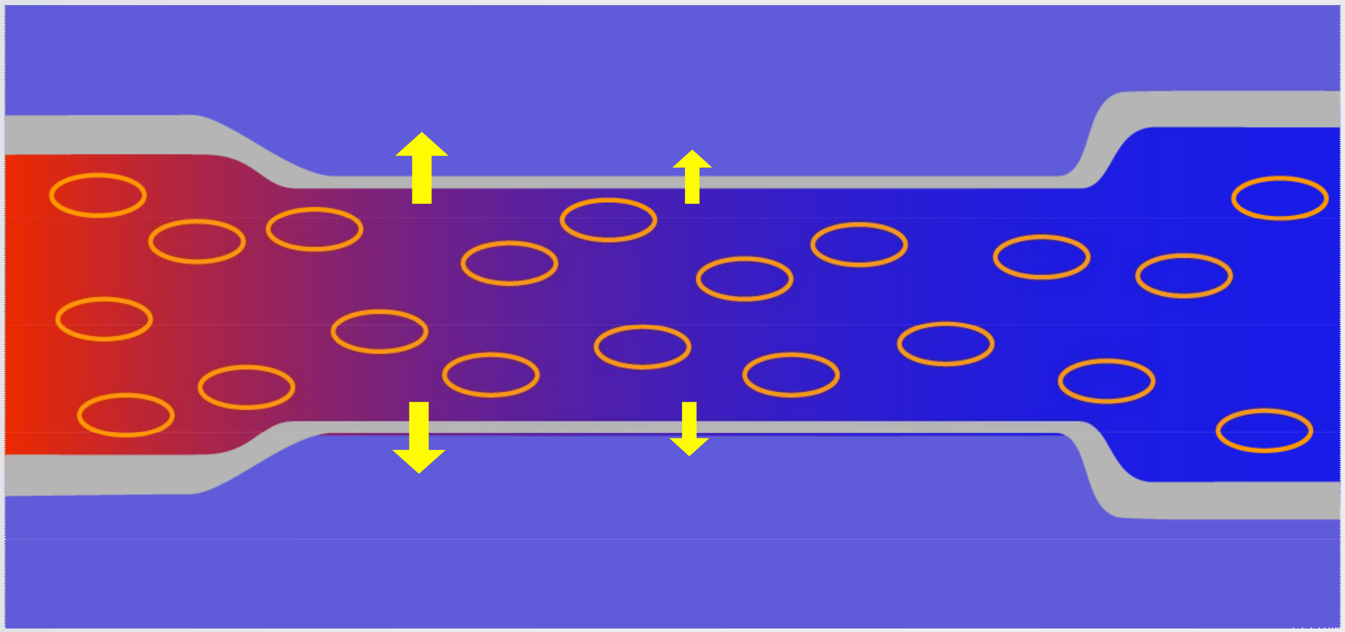
Under normal conditions oxygen diffuses down its concentration gradient from the capillary to the brain parenchyma

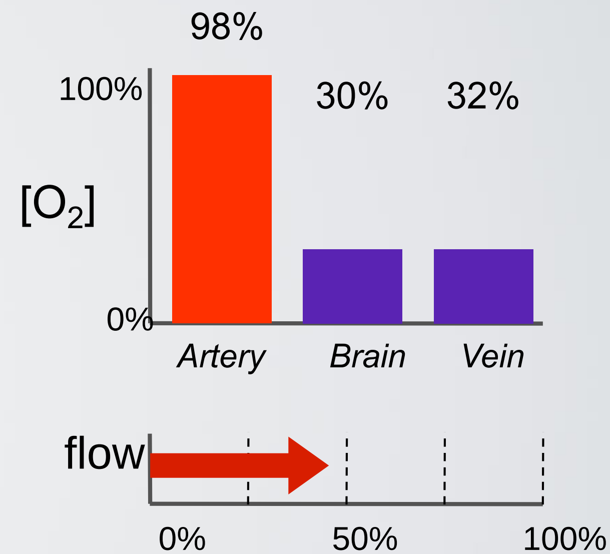
Why Does Venous O_2 Increase? (2)



As the brain becomes more active, the oxygen consumption increases, increasing the transluminal oxygen gradient.

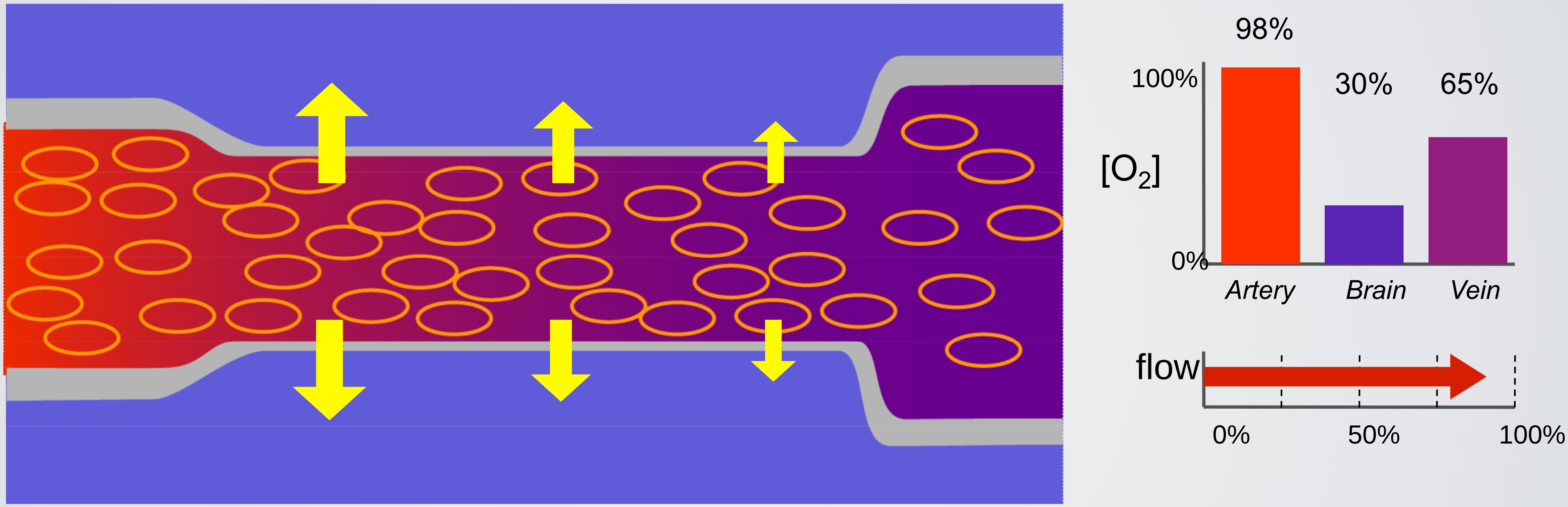
Why Does Venous O_2 Increase? (3)





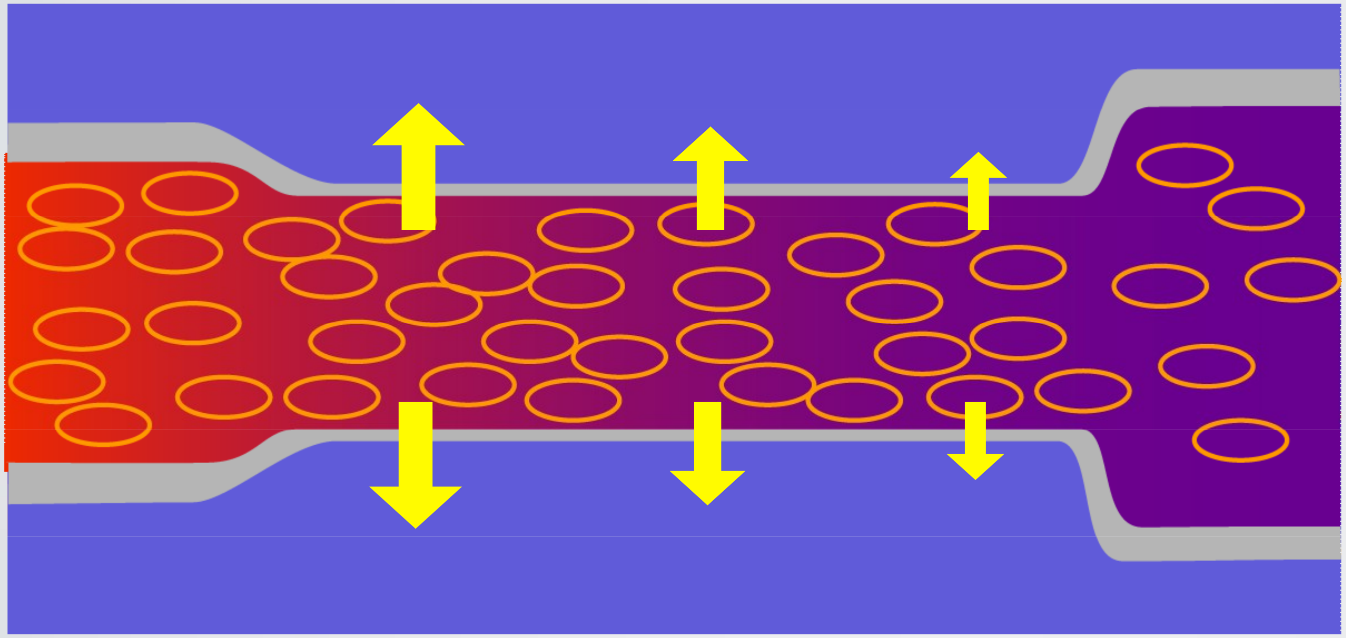
As oxygen flows across the capillary lumen it is depleted in the capillary and no further oxygen can be delivered

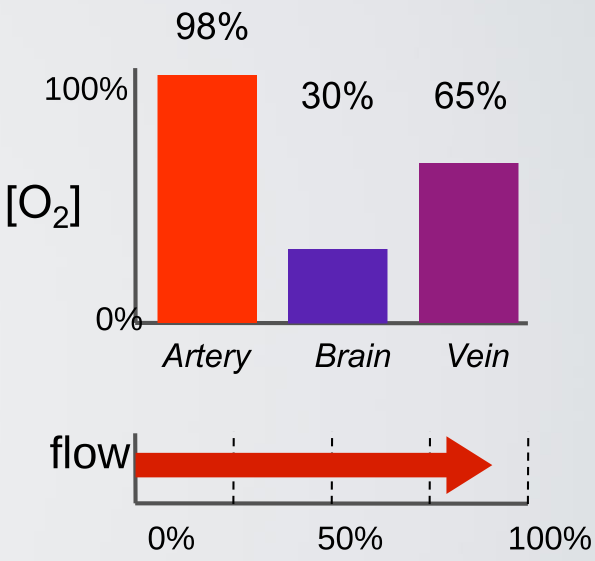
WHY DOES VENOUS O_2 INCREASE? (4)



The vascular system responds by increasing blood flow so that more oxygenated blood is available throughout the capillary

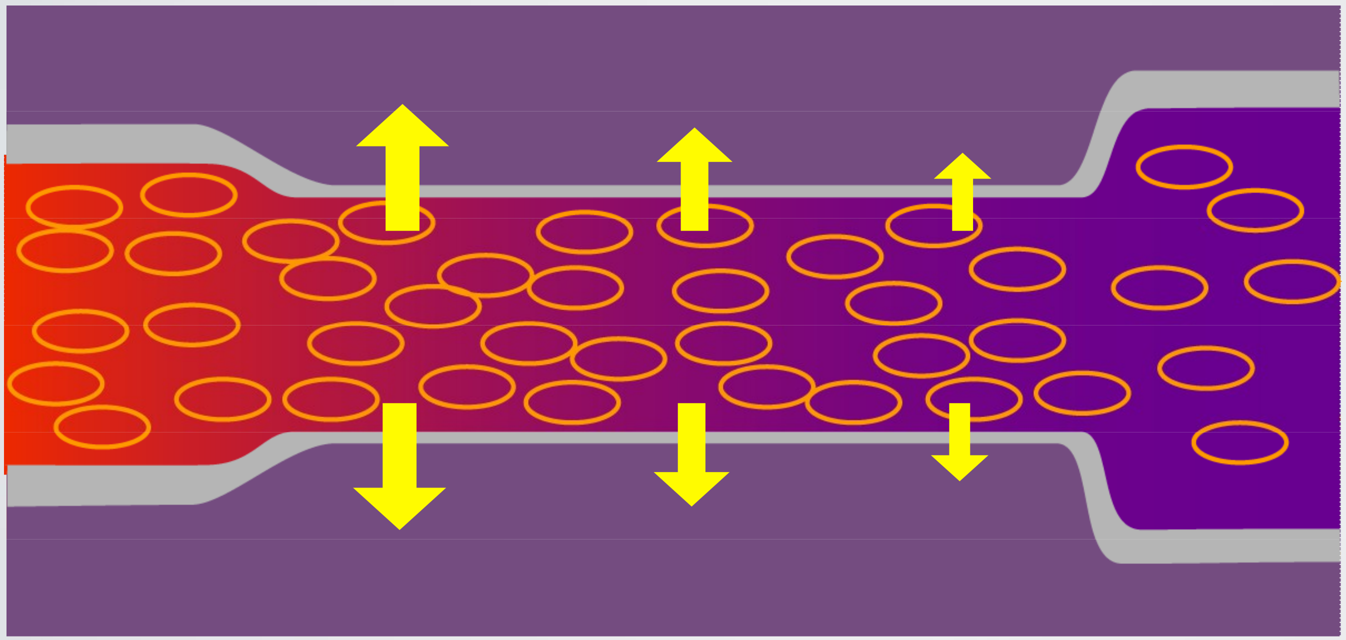
WHY DOES VENOUS O_2 INCREASE? (5)

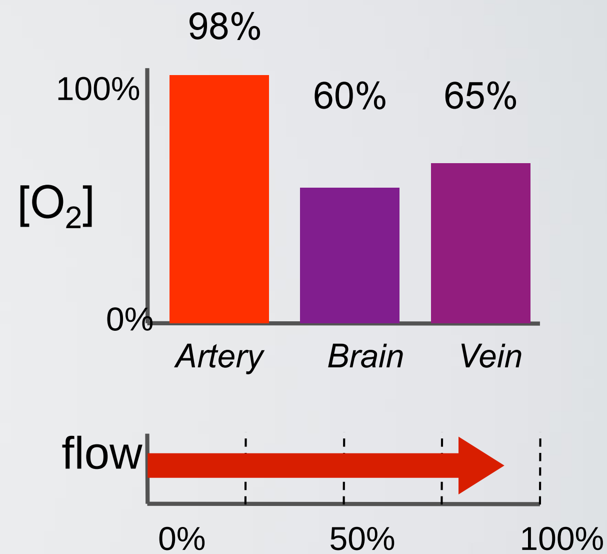




Because the blood flow is increased more oxygenated blood passes into the venous end of the capillary

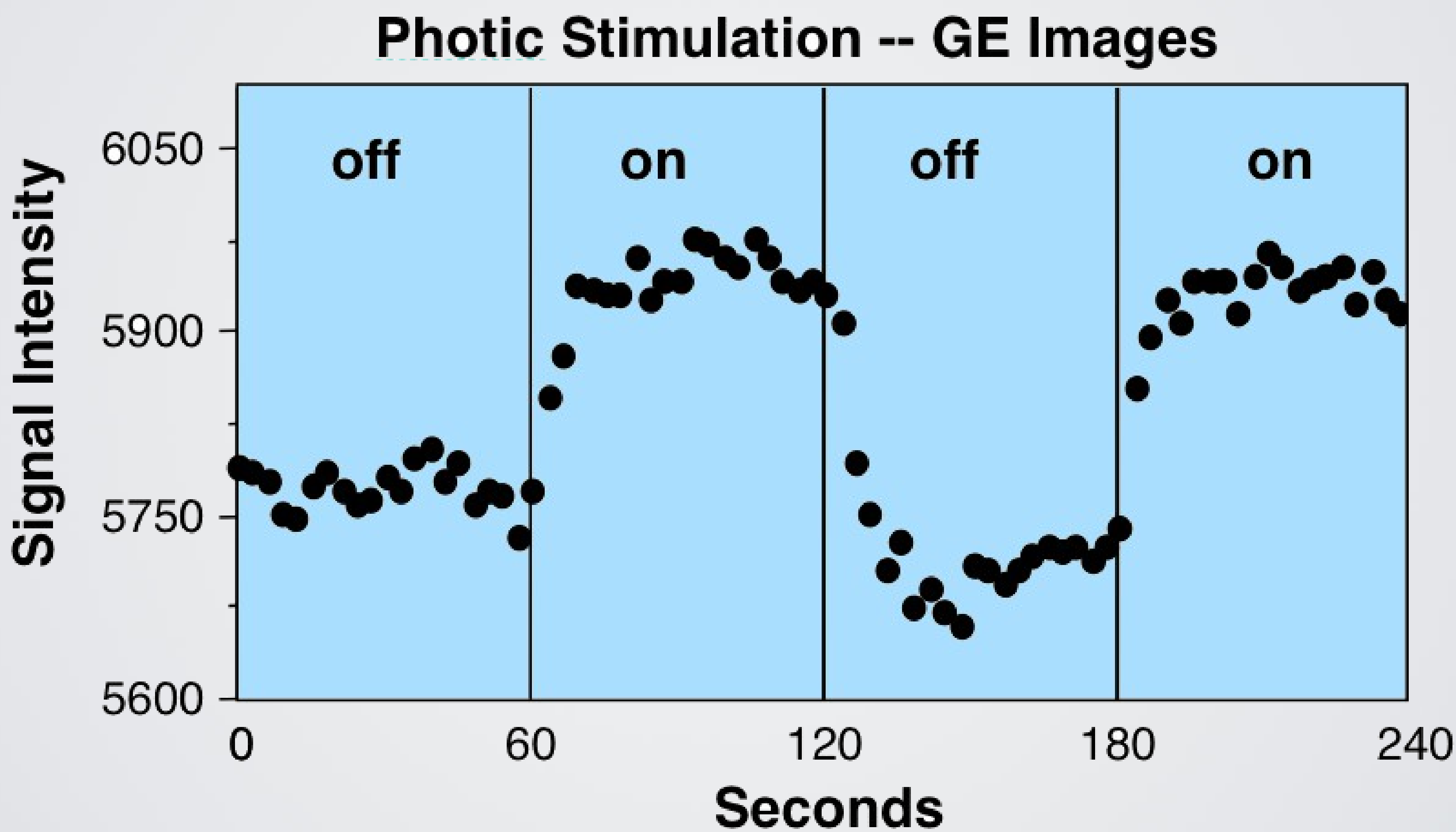
Why Does Venous O_2 Increase? (6)





With the Concentration Gradient Maintained Oxygen is Delivered to the Brain Parenchyma

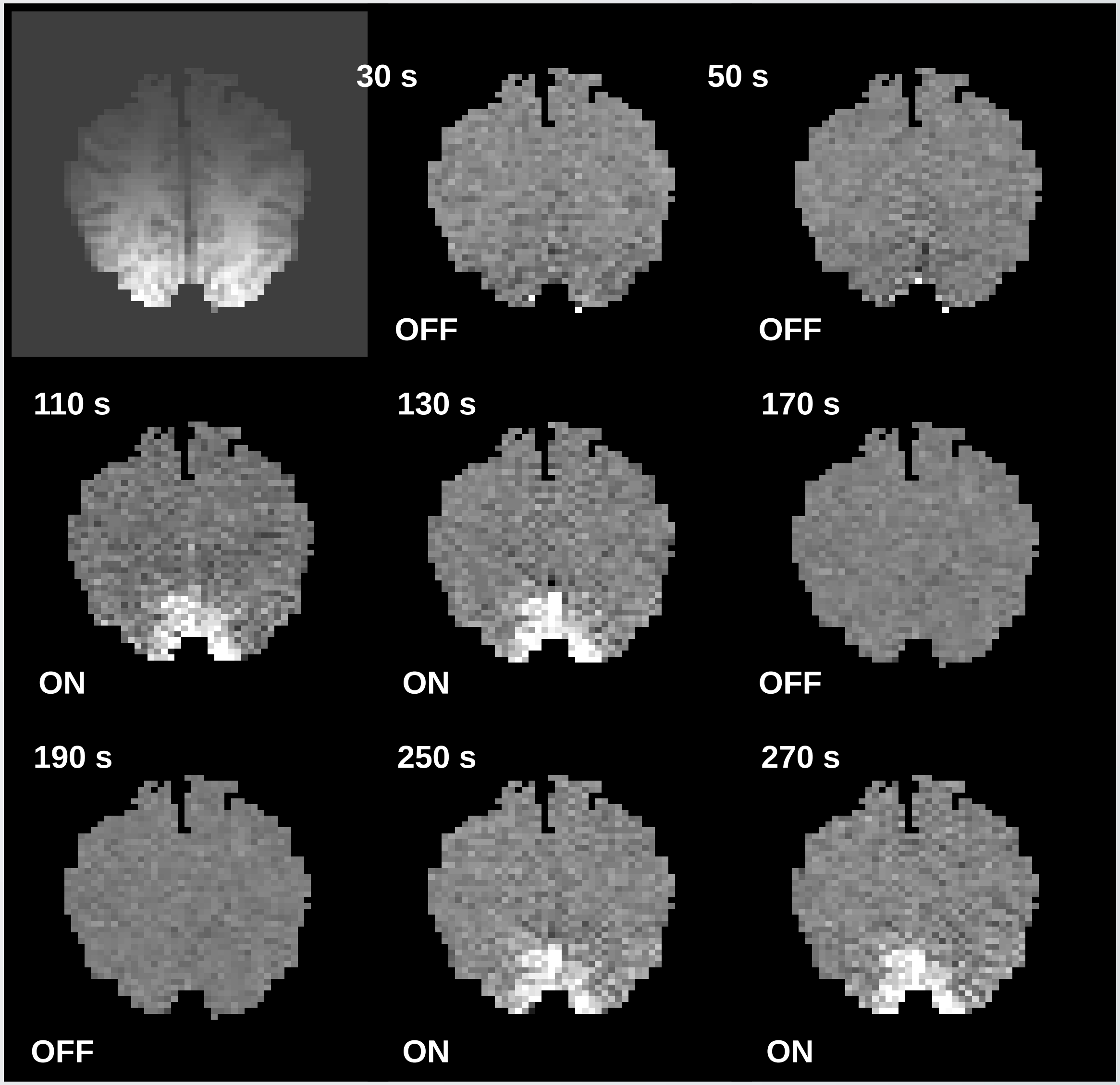
GRADIENT-RECALLED ECHO



Ken Kwong

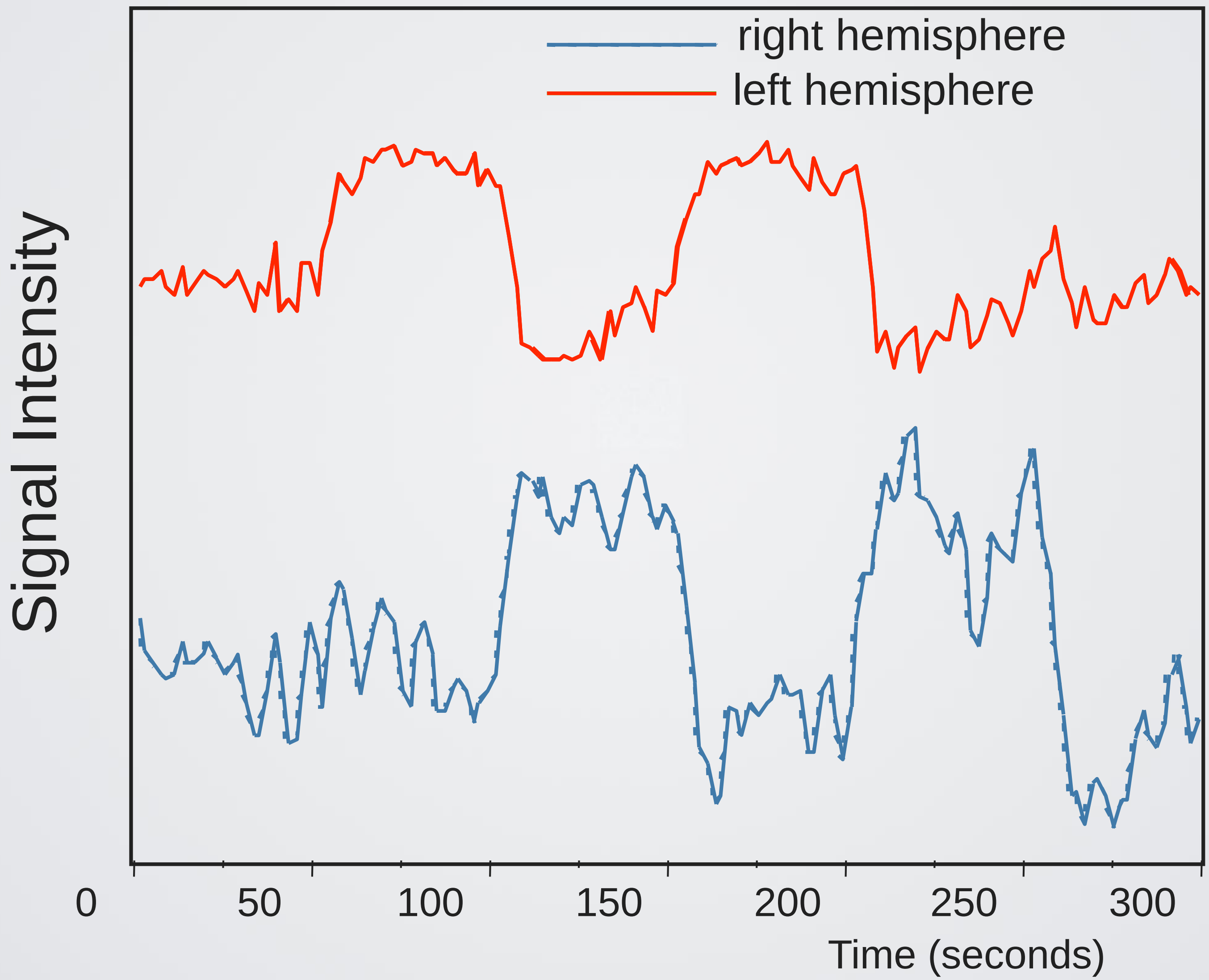
Ken Kwong

INVERSION RECOVERY
TE=42 TR=3000
TI = 1100
THICKNESS=10



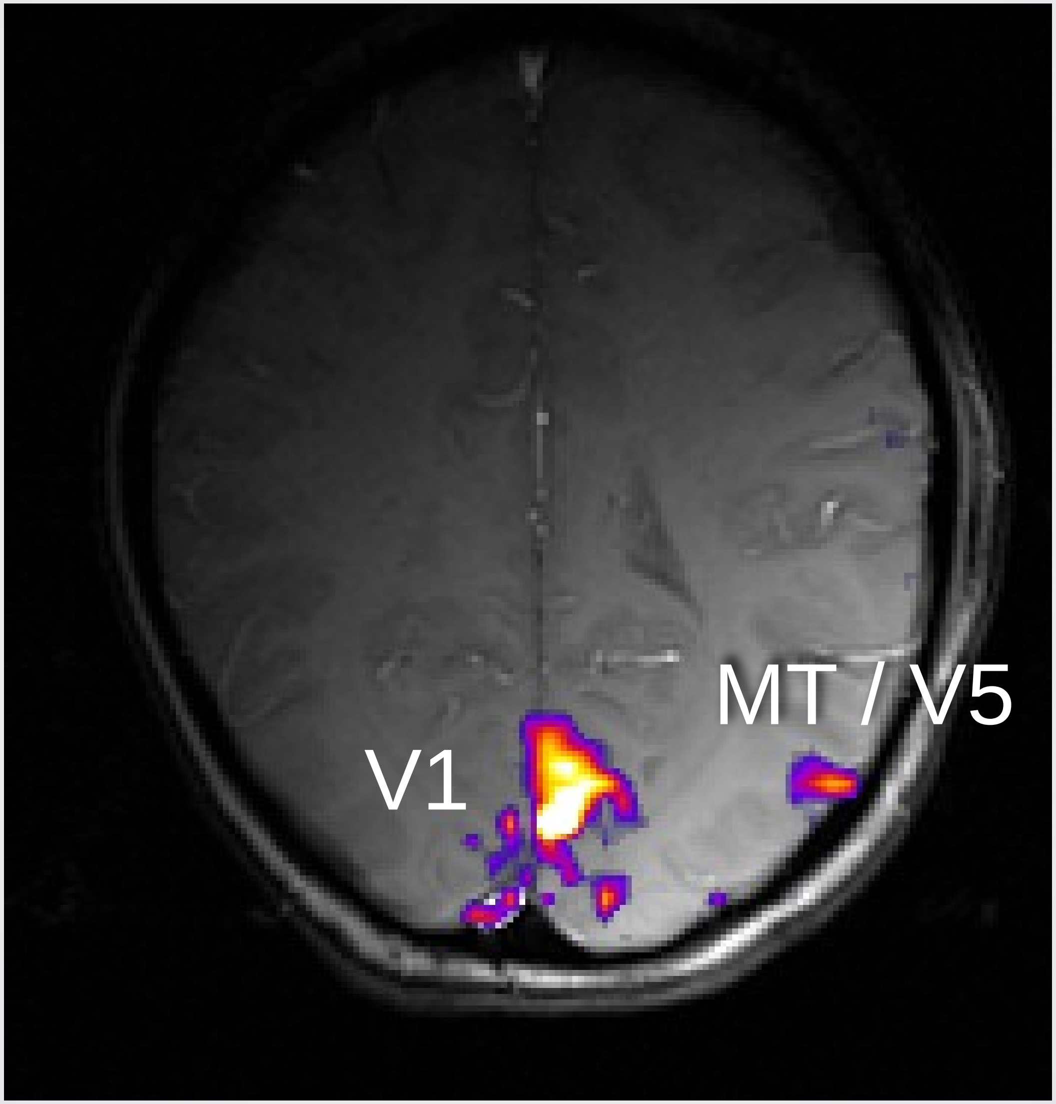
Seiji Ogawa   Ken Kwong

BRAIN MAPPING - HEMIFIELD ALTERNATION

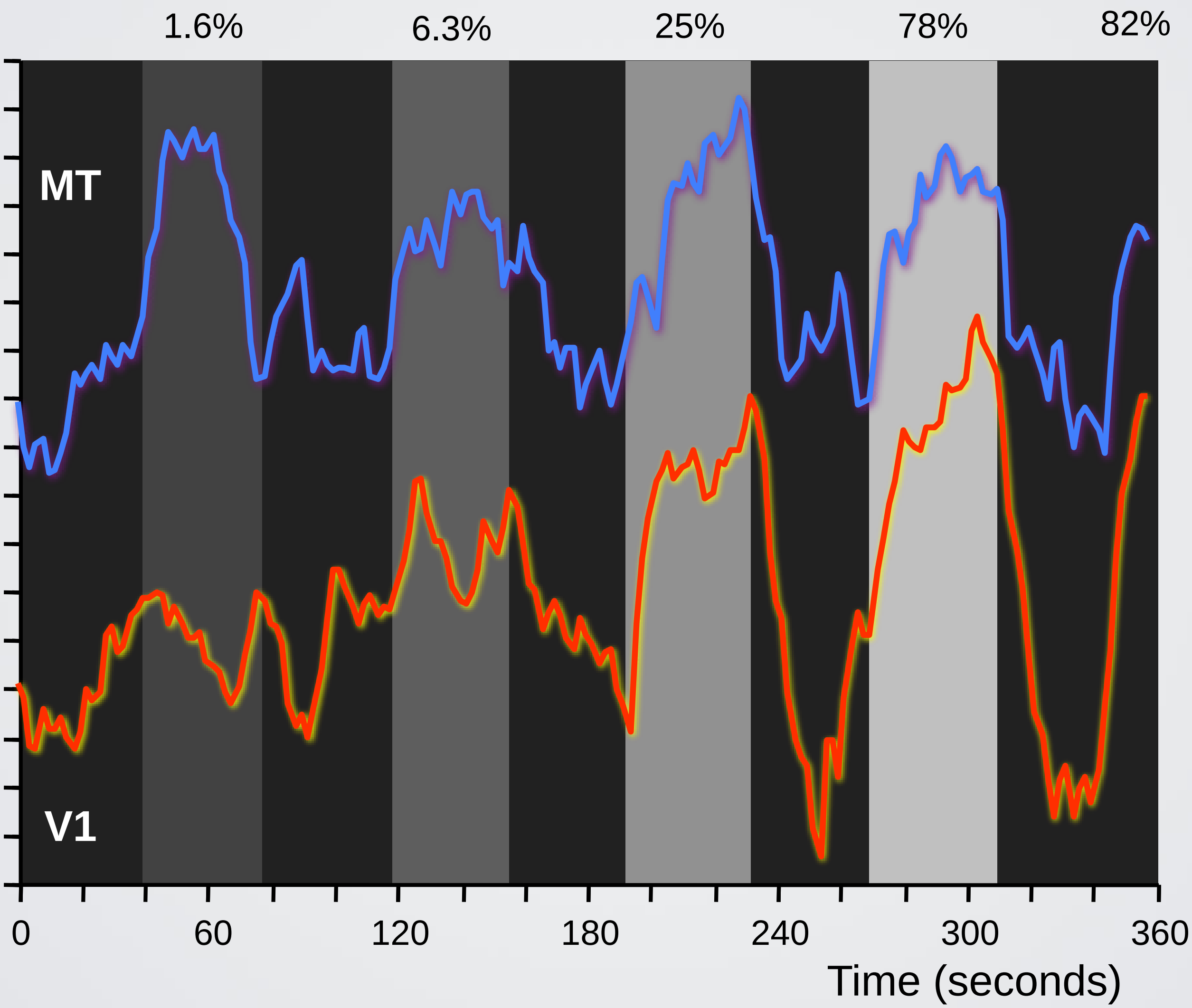


 www.brainmapping.org

Activation with Moving Visual Stimuli

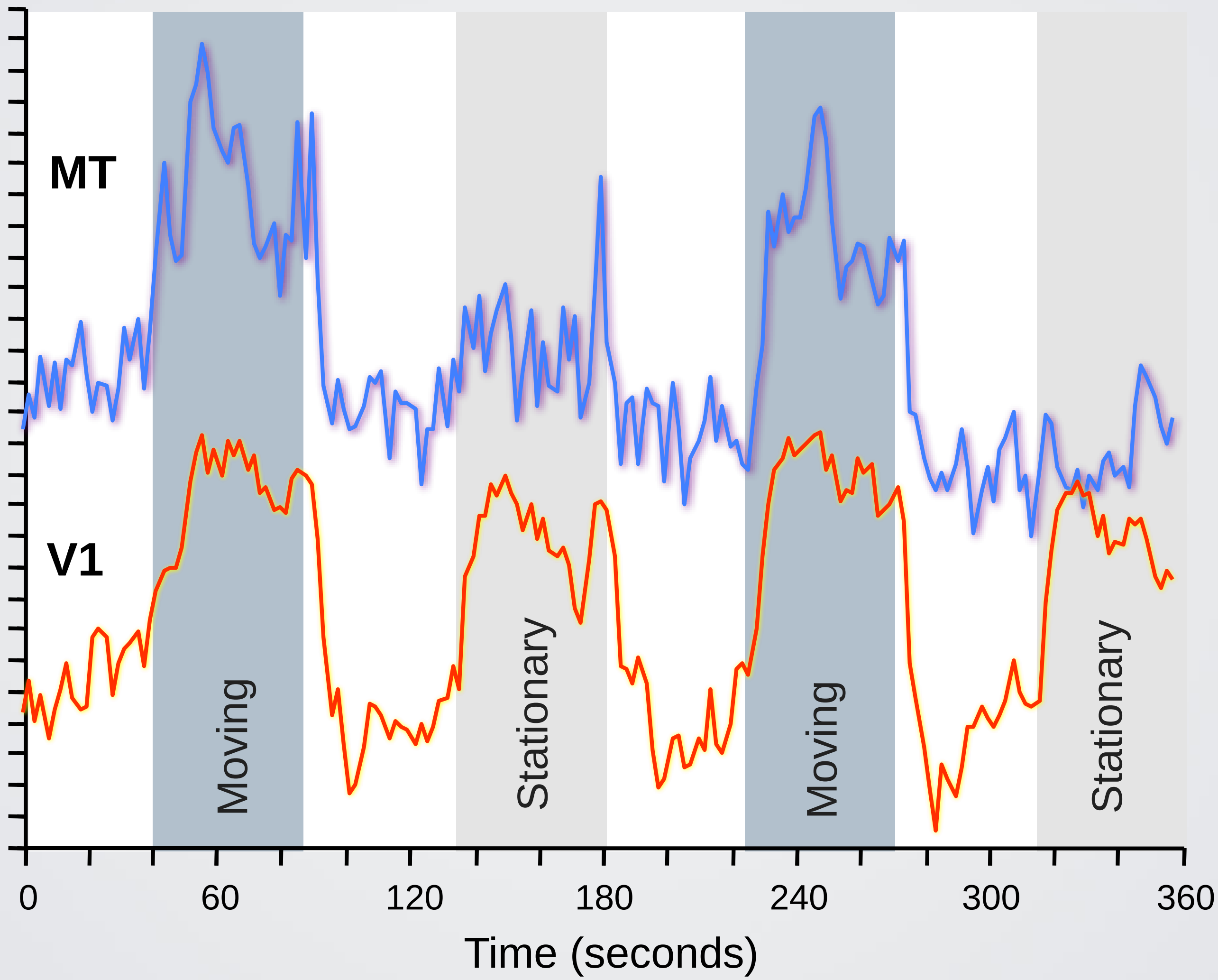


Contrast Response Test



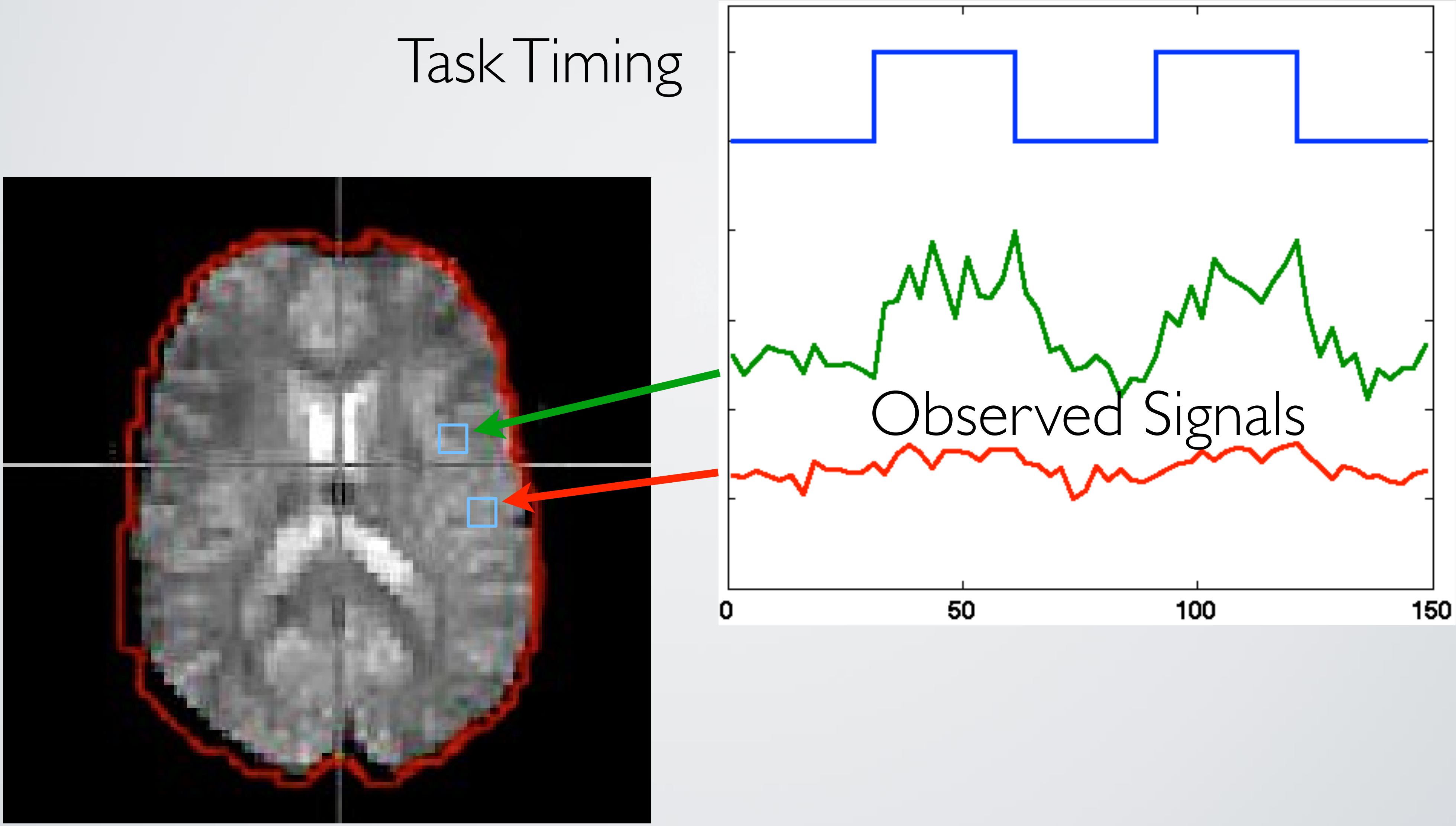
From R. Tootell

Motion Sensitivity Test

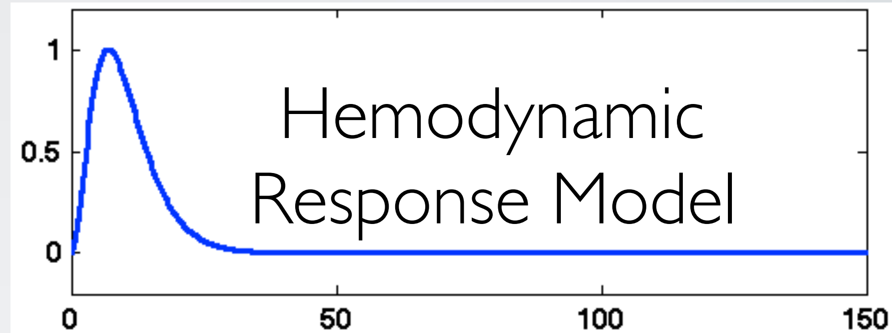


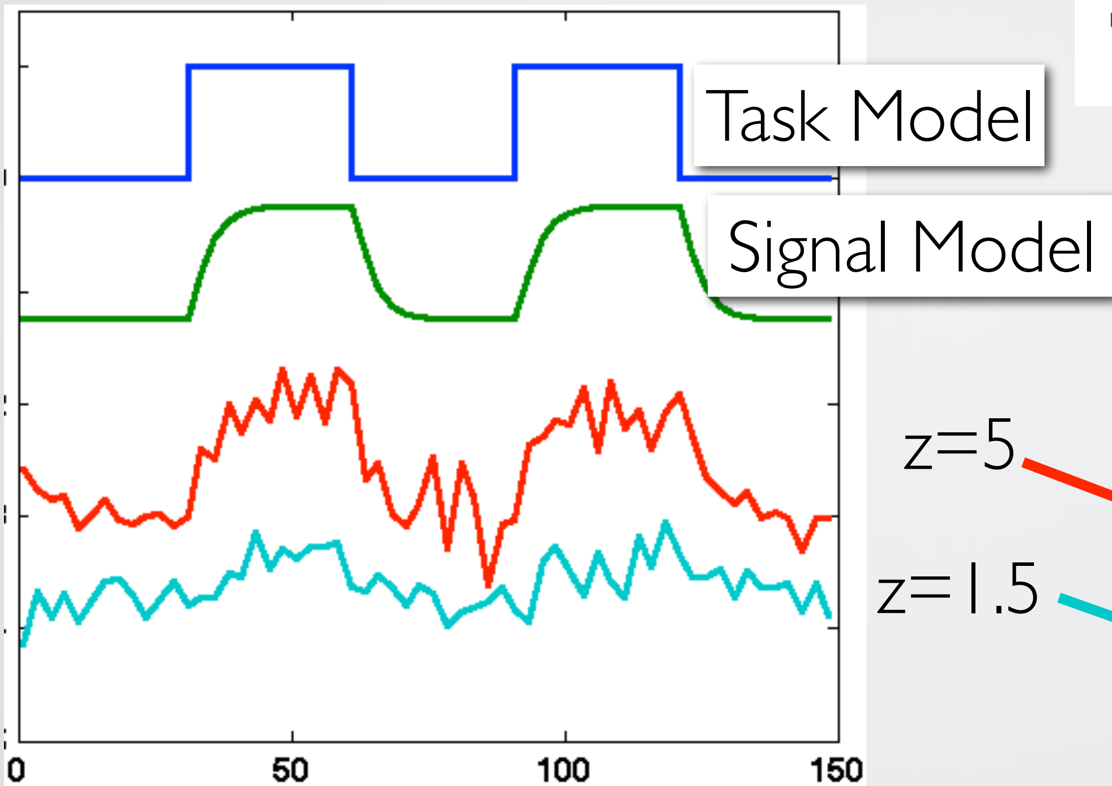
From R. Tootell

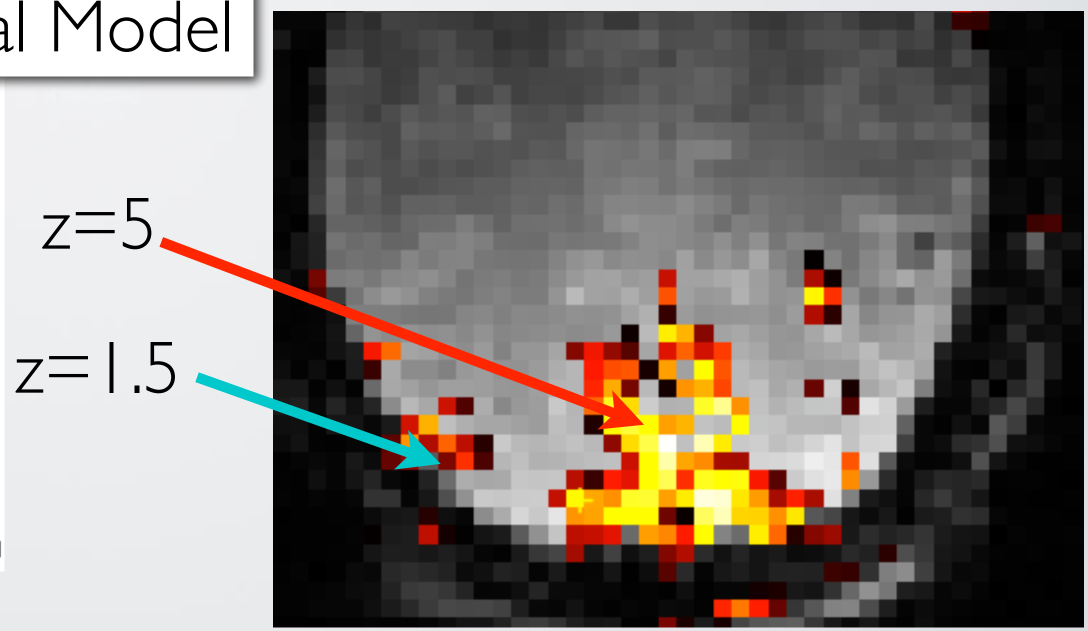
TRADITIONAL MRI ANALYSIS



PARAMETRIC MRI ANALYSIS - MODEL DRIVEN

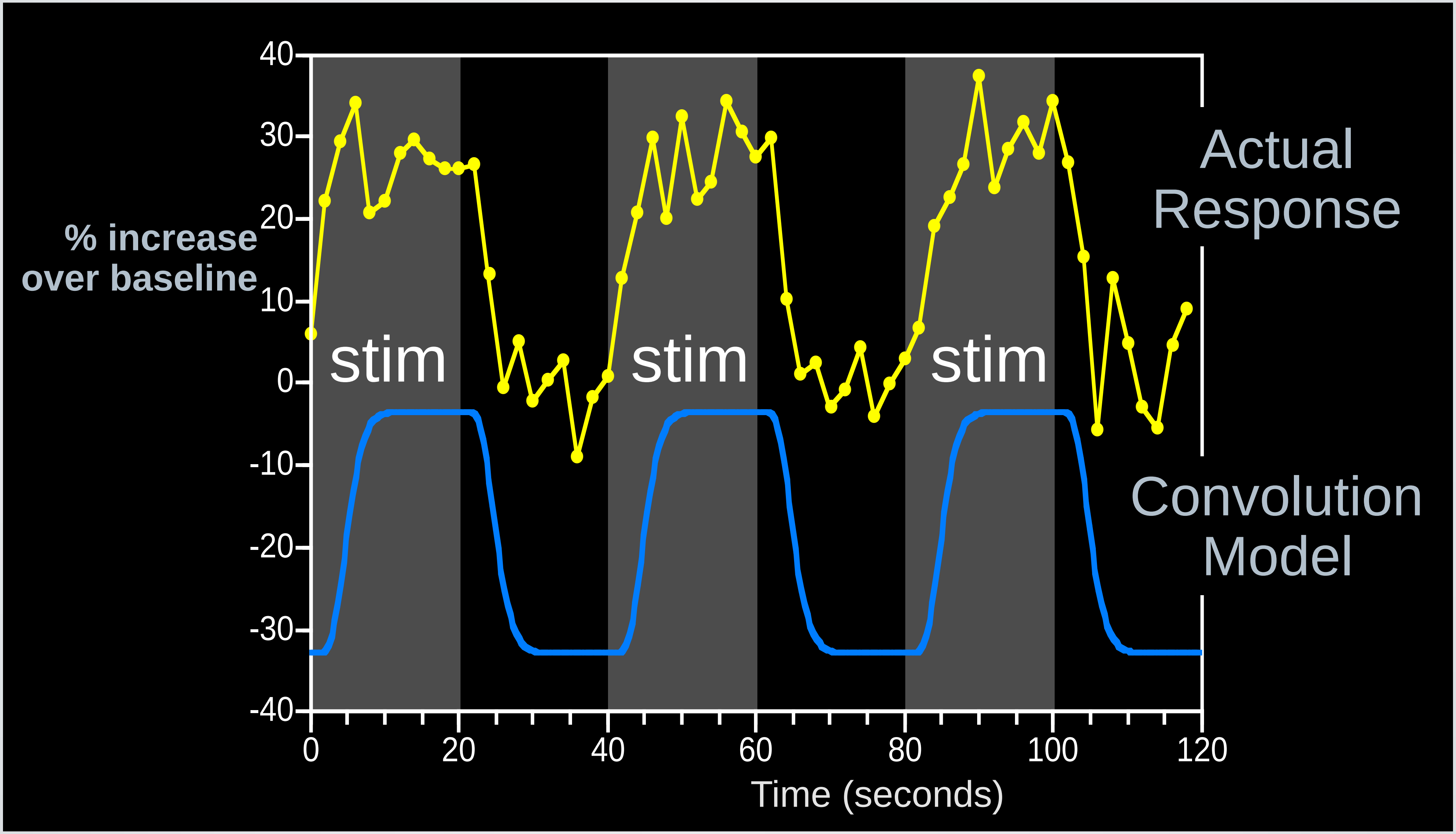






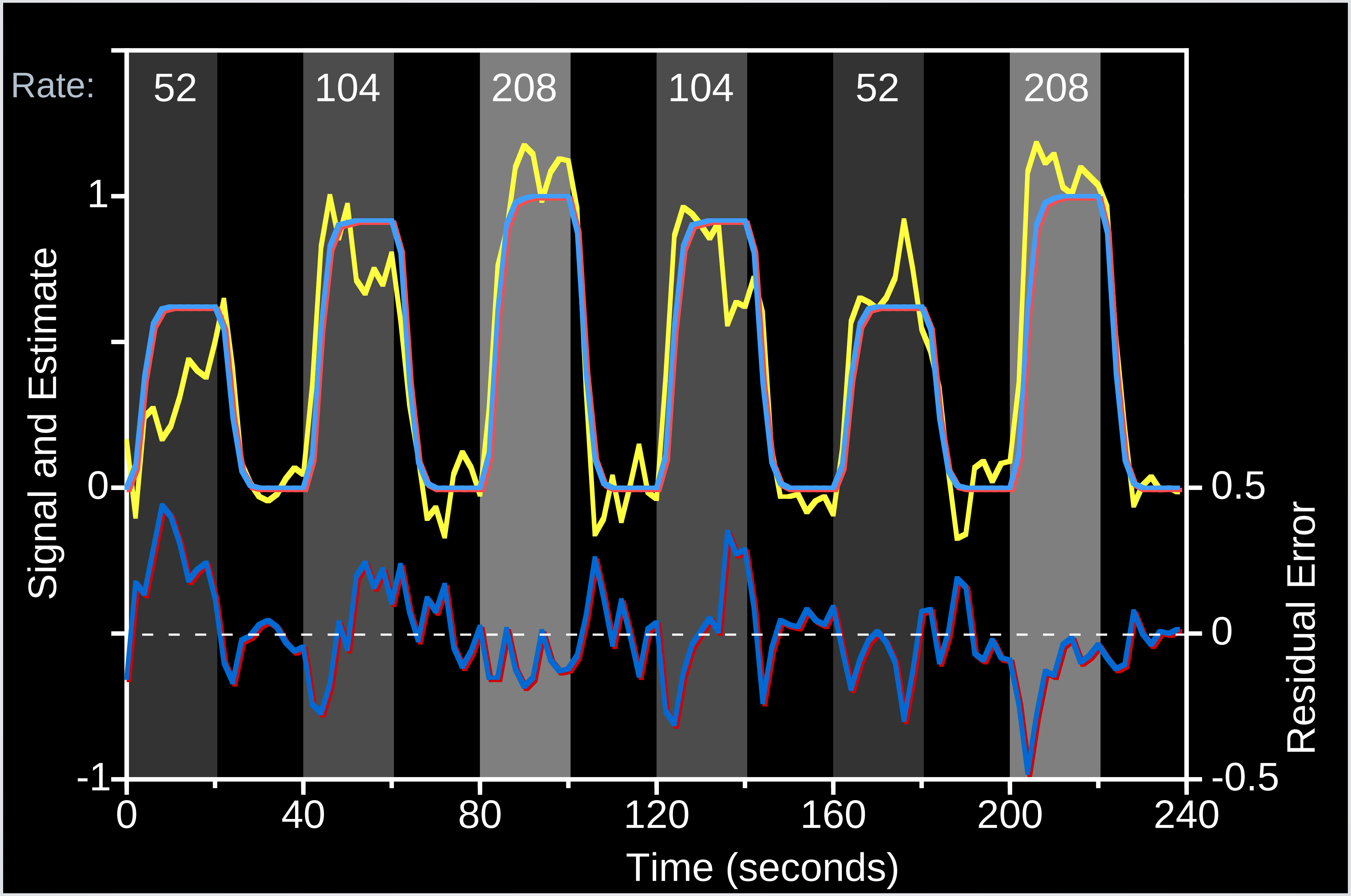
Cohen, NeuroImage **6**, 1997

STIMULUS - HRF CONVOLUTION



Cohen, NeuroImage **6**, 1997

AMPLITUDE-WEIGHTED LINEAR ESTIMATE



Cohen, NeuroImage **6**, 1997

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