Neuronal Signaling
+ The BOLD Experiment

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

- Axon terminals
- Axon
- Dendrites
- Soma (cell body)
**Typical:**

-90 < resting potential < -60 mV
DEVELOPMENT OF THE MEMBRANE POTENTIAL
DEVELOPMENT OF THE MEMBRANE POTENTIAL
Development of the Membrane Potential

Nernst Potential:

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

\[ \approx 27 \text{mV} \ln \frac{[C_{\text{inside}}]}{[C_{\text{outside}}]} \]
OBSERVED ION CONCENTRATIONS

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

\( A, B \) are cations
\( x, y \) are anions

Nernst Potential
@ 37°C

[Na+] 460 mM → [Na+] 50 mM +60 mV
-75 mV
STRUCTURE OF THE CELL MEMBRANE

Extracellular Fluid

Cytoplasm

Glycoprotein

Carbohydrate

Integral Protein

Peripheral Protein

Cytoskeletal Filament

Cholesterol

Polar Head

Non-polar Tail

Note: E-field is >10 MV/m!
Electrical Behavior of Neurons

![Diagram: Electrical Behavior of Neurons]

- **Axon**
- **Ringer’s Sol’n**

**Graph:**
- **V**: Voltage
- **i**: Current
- **50 mV**
- **0 mV**
- **-50 mV**
- **-100 mV**
- **-100 mV spike**

**Timeline:**
- **1 msec**

**Action Potential**
Current and Voltage

- Sodium Permeability
  - *Transient conductance increase*
- Potassium Permeability
  - *Voltage-dependent conductance*
- Membrane Potential

Neurons are REFRACTORY after each Action Potential

*After Hodgkin and Huxley, 1952*
SODIUM LEAKAGE WITH ACTION POTENTIALS

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:
\[ \Delta V = 0.13 \text{ Volt} \]
\[ Q = CV = 1.3 \times 10^{-7} \text{ Coulombs /cm}^2 \]
\[ = 1.4 \times 10^{-12} \text{ Moles/cm}^2 \]

Surface Area = 2.8 x 10^{-5} cm²
Each AP passes 3.7 x 10^{-17} Moles of Na+

\([\text{Na}^+] \text{ is increased by 0.1% with each Action Potential!}\)
PASSIVE FIRING OF ACTION POTENTIALS


With 5 plates and 12 text-figures
Printed in Great Britain

REPLACEMENT OF THE AXOPLASM OF GIANT NERVE FIBRES WITH ARTIFICIAL SOLUTIONS

By P. F. BAKER, A. L. HODGKIN AND T. I. SHAW

<table>
<thead>
<tr>
<th>Row</th>
<th>Axon (μ)</th>
<th>Diameter (μ)</th>
<th>Temperature (°C)</th>
<th>Condition</th>
<th>Internal solution</th>
<th>Period of stimulation (min)</th>
<th>Main stimulation frequency (shocks/sec)</th>
<th>Number of impulses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>770</td>
<td>15</td>
<td>Fully inflated</td>
<td>K- isethionate</td>
<td>120</td>
<td>50</td>
<td>3.6 × 10⁵</td>
</tr>
<tr>
<td>2</td>
<td>101</td>
<td>720</td>
<td>21</td>
<td>40% inflated</td>
<td>K₂SO₄</td>
<td>80</td>
<td>50</td>
<td>2.3 × 10⁵</td>
</tr>
<tr>
<td>3</td>
<td>114</td>
<td>880</td>
<td>18</td>
<td>60% inflated</td>
<td>K₂SO₄</td>
<td>120</td>
<td>50</td>
<td>4.1 × 10⁵</td>
</tr>
<tr>
<td>4</td>
<td>115</td>
<td>810</td>
<td>18</td>
<td>Intact</td>
<td>Axoplasm</td>
<td>107</td>
<td>50</td>
<td>3.9 × 10⁵</td>
</tr>
<tr>
<td>5</td>
<td>118</td>
<td>750</td>
<td>19.5</td>
<td>Intact</td>
<td>Axoplasm</td>
<td>186</td>
<td>125</td>
<td>1.1 × 10⁶</td>
</tr>
</tbody>
</table>
Sodium Potassium Pump

After Matthews and van Holde: Biochemistry 2/e

Initial State
Pump Open to Inside

Na⁺ Taken from Inside
ATP Phosphorylates α Subunit and Stimulates Conformation Change

Pump Open to Outside

Two Potassium Ions Accepted from Outside
Dephosphorylation Stimulates Conformation Change

INSIDE OF CELL

K⁺

P

Sodium is Released

ATP
ADP

INSIDE OF CELL

K⁺

P

INSIDE OF CELL

K⁺

P

INSIDE OF CELL

K⁺

P

INSIDE OF CELL

K⁺

P

INSIDE OF CELL

K⁺

P

INSIDE OF CELL
Cable Properties

For vertebrate neurons: $\mu m < \lambda < mm$

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

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

For vertebrate neurons: $0.5 \text{ msec} < \tau < 5 \text{ msec}$
Propagation of the Action Potential

Resulting Velocity ~1-3m/sec
Propagation of the Action Potential

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**MYELIN SHEATH**
MYELIN SHEATH
NODES OF RANVIER
**Saltatory Conduction**

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

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

Myelin
Axon
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
**Reversal Potential**

epsp’s result from increased K+ and Na+ conductance, with ΔNa+ > ΔK+

Neuron

Extra-cellular fluid

After Magleby and Stevens. J Physiol. 223, 1972
Neural Synapse

- Microtubules
- Synaptic vesicles
- Synaptic Bouton
- Synaptic Cleft
- Golgi Complex
- Mitochondrion
- Dendritic Spine
- Presynaptic Membrane
- Postsynaptic Membrane

http://www.driesen.com/synapse.htm
SYNAPSES BY EM

Flat Vesicles
Round Vesicles
Mitochondria
Synaptic Density

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 $\approx 0.5$ msec
**SYNAPTIC VESICLES**

Exocytosis of Transmitter requires $\text{Ca}^{2+}$

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

**Small Molecules**
- Acetylcholine
- Serotonin
- Histamine
- Epinephrine
- Norepinephrine
- Dopamine
- Adenosine
- ATP
- Nitric Oxide

**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

**Amino Acids**
- Aspartate
- Gamma-aminobutyric Acid
- Glutamate
- Glycine
ELECTRICAL SYNAPSES

Gap Junction

50 nm

50 nm
Gap Junctions have no synaptic delay, and may act as simple resistance or as electrical rectifiers.
SpatioTemporal Summation of PSP’s

http://www.oseplus.de/Images/jpg/Synapse1.jpg
INTEGRATION OF INPUTS

Electrotonic properties of cells can result in spatial information zones within cells.
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

20kHz

20Hz

Frequency

$V$

$t$

Frequency $20kHz$

$20Hz$
Reversal potential of Cl\textsuperscript{-} is near the resting potential. Therefore, its inhibition may be silent.
Pre-Synaptic Inhibition

Excitatory Synapse

Inhibitory Synapse
WHAT MIGHT WE DETECT?

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

- Axon
- Dendrites
- Soma (cell body)
- Axon terminals
PRESUMED ORIGIN OF THE EEG

Skin
Bone
CSF
Cortex
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
**Alpha Mapping**

- **Spectral power in the alpha band**
- **Predicted BOLD response**

The graph shows the average power (µV²) over time (minutes) with two lines representing the spectral power in the alpha band and the predicted BOLD response.
SITE OF RESTING ALPHA

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
MR-Lucent Neurophysiology

Energetic Demands  \( \text{(BOLD, ASL)} \)

Transmitter Synthesis, Exocytosis, Metabolism

\( Na+/K+ \) Pump

\([Na+]\)  \( \text{Imaging} \)

Glucose Metabolism  \( \text{Spectroscopy} \)

Extracellular Currents (?)  \( \text{Phase Disturbance} \)

Anisotropic Diffusion  \( \text{DTI, etc…} \)

Neural Constituents (NAA)  \( \text{Spectroscopy} \)
BOLD
A DELICATE BALANCE

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

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
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.
FMRI

explores intensity variations in MR signal

intensity variations reflect venous [O2]
Why Does Venous O$_2$ Increase? (1)

Under normal conditions oxygen diffuses down its concentration gradient from the capillary to the brain parenchyma.
As the brain becomes more active, the oxygen consumption increases, increasing the transluminal oxygen gradient.
As oxygen flows across the capillary lumen it is depleted in the capillary and no further oxygen can be delivered.
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 \( \text{O}_2 \) Increase?**

With the Concentration Gradient Maintained Oxygen is Delivered to the Brain Parenchyma
GRADIENT-RECALLED ECHO

Photic Stimulation -- GE Images

Signal Intensity

Seconds

off

on

off

on

Ken Kwong
INVERSION RECOVERY
TE = 42, TR = 3000
TI = 1100
THICKNESS = 10
Brain Mapping - Hemifield Alternation

![Graph showing signal intensity over time for the right and left hemispheres.](image-url)
ACTIVATION WITH MOVING VISUAL STIMULI
Contrast Response Test

From R. Tootell
MOTION SENSITIVITY TEST

From R. Tootell
TRADITIONAL MRI ANALYSIS

Task Timing

Observed Signals
Parametric MRI Analysis - Model Driven

Hemodynamic Response Model

Task Model

Signal Model

z=5

z=1.5

Cohen, NeuroImage 6, 1997
STIMULUS - HRF Convolution

% increase over baseline

stim
stim
stim

Actual Response

Convolution Model

Cohen, NeuroImage 6, 1997
Amplitude-weighted Linear Estimate

Rate: 52 104 208 104 52 208

Cohen, NeuroImage 6, 1997