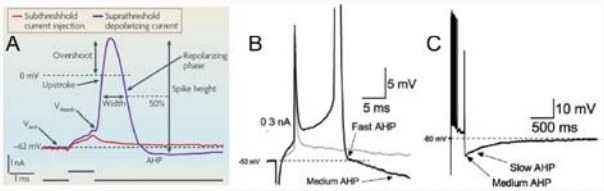
Active Properties of Neurons

From Passive to Active Properties

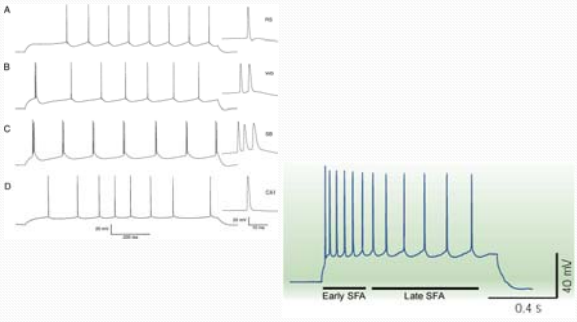
- Passive properties influence the timecourse of the neuron's response to inputs
- Passive properties have minimal effect on Action Potentials – these are dominated by active properties
- Active properties include
  - Separating charge across the membrane (resting potential)
  - Allowing charge to move across the membrane (action potentials & graded potentials)

Significance of the Action Potential

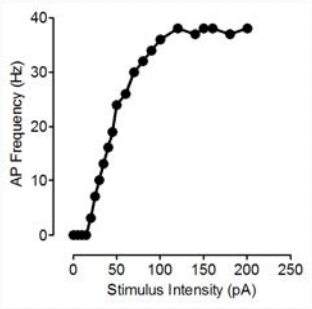
- The "vocabulary" of the nervous system
- Information is encoded in AP waveform, frequency, and pattern

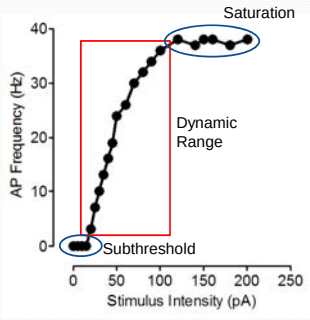


Spike frequency and patterning



The F-I plot (frequency – current)





Three key concepts:

- Driving force
- Conductance
- Current

Ohm's law returns

- V= IR V = I/G I = GV

- Driving force (V)
- Conductance (G)
- Current (I)

Driving force: Separation of Charge Across the Membrane

- Equilibrium Potentials
  - Two forces at work: Diffusion and Electromotive
    - Particles of same identity diffuse to areas of lower concentration
    - Different charges attract, similar charges repel
  - Whiteboard example: calculating E_K
- Equilibrium potentials can be predicted if we know the relative concentrations of ions inside and outside of the cell

Nernst Equation for Equilibrium Potentials

$$E_x = \frac{RT}{z_x F} ln \frac{[X]_o}{[X]_i}$$

Example: Calculating E_K

Internal (Pipette) solution, in mM		ACSF (external saline), in mM:	
Potassium gluconate	130	NaCl	130
Sodium phosphocreatine	20	Glucose	20
EGTA	0.5	KCl	3
HEPES	10	$NaHCO_3$ (pH buffer)	10
$MgCl_2$	2	NaH_2PO_4	2
MgATP	2	$MgCl_2$	1
NaGTP	2	$CaCl_2$	2

$$E_K = \frac{RT}{F} \ln \frac{[K]_o}{[K]_i}$$

TABLE 1.2 Values of *RT/F*

Temperature (°C)	*RT/F* (mV)
0	23.54
5	23.97
10	24.40
15	24.83
20	25.26
25	25.69
30	26.12
35	26.55
37	26.73

Significance of equilibrium potentials

If the membrane is exclusively permeable to one type of ion, the membrane potential will move to E_{ion}

Resting Potential: Separation of Charge Across the Membrane

- Equilibrium Potentials
- Sodium/Potassium Pump
  - Active transporter
  - Requires energy (ATP hydrolysis)
  - Ejects 3 Na+ / Inserts 2 K+
- Net result: High Na+ outside cell / High K+ inside cell
- At rest, membrane is much more permeable to K+ than to Na+, therefore closer to E_K
- How do we predict membrane potential from these parameters?

The Goldman Hodgkin Katz (GHK) Equation

Membrane potential is determined by the relative membrane permeability of each ion species and its Equilibrium potential.

$$V_m = \frac{RT}{F} \ln \frac{P_K[\mathrm{K^+}]_o + P_{Na}[\mathrm{Na^+}]_o + P_{Cl}[\mathrm{Cl^-}]_i}{P_K[\mathrm{K^+}]_i + P_{Na}[\mathrm{Na^+}]_i + P_{Cl}[\mathrm{Cl^-}]_o}$$

The Goldman Hodgkin Katz (GHK) Equation

Simplified by ignoring chloride

$$V_m = \frac{RT}{F} \ln \frac{P_K[\mathrm{K^+}]_o + P_{Na}[\mathrm{Na^+}]_o}{P_K[\mathrm{K^+}]_i + P_{Na}[\mathrm{Na^+}]_i}$$

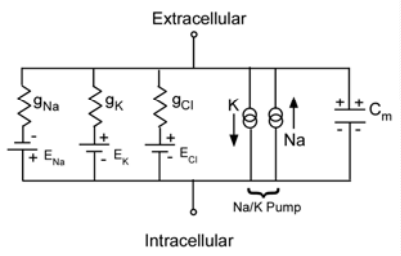
Action Potentials: The building blocks of neural signaling

- Determined primarily by the flux of Na+, K+, and Ca^{2+} through *ion channels*
- We will focus on Na+ and K+ conductances in our experiments because these are primarily responsible for the action potential in neurons
- *Membrane potential is an epic never-ending battle between sodium and potassium conductances*

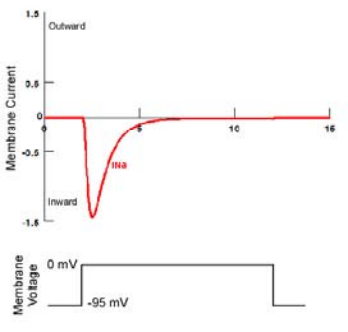
Conductance: Voltage-gated Ion Channels

- Voltage gated channels open (activate) in response to changes in membrane potential
- Ion channels are selectively permeable to particular ion species (they increase *conductance* for that ion when open)
- The equilibrium potential for that ion provides the driving force
- Open ion channels provide conductances
- Force x Conductance = Current

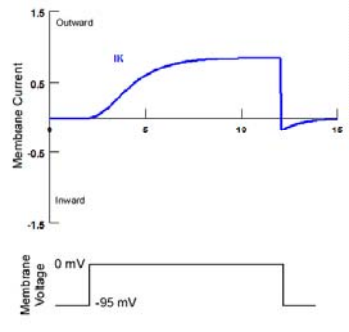
Equivalent Circuit of the Neural Membrane



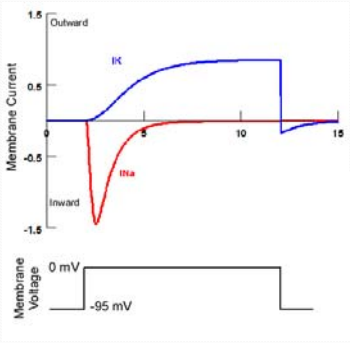
Sodium currents under voltage clamp



Potassium currents



Time courses compared



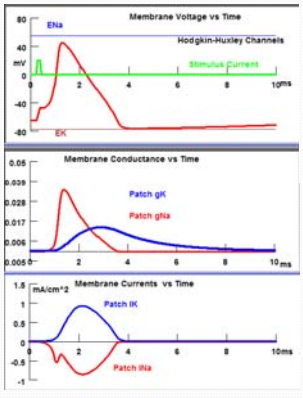
Action Potentials: Simple version

- Action potentials are initiated by the activation of voltage gated sodium channels
  - Result is inward sodium current
  - Threshold occurs when inward INa > outward IK
- Terminated by inactivation of sodium channels and/or activation of potassium channels
  - Result is outward potassium current
- The particular combination of ion channels present determines the AP threshold, waveform, and spiking pattern

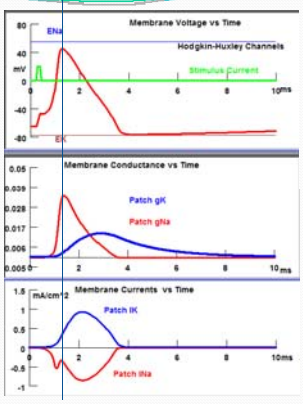
Action Potentials: Complex version

- As the membrane voltage changes:
  - Ionic conductances change (ion channels open and close in accordance with their *Voltage Dependence*)
  - Currents change independently of conductances because the membrane voltage is shifting relative to the equilibrium potentials for each ion
- We must model what we cannot measure

Dissecting the Action Potential
- Conductances
- Currents



Dissecting the Action Potential
- Conductances
- Currents



What does this mean?

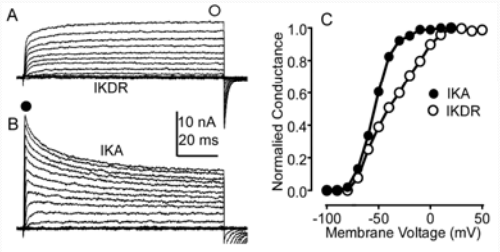
- The *driving force* on an ion is a function of the difference between membrane potential and E_{ion}
- $I_{ion} = (V_m - E_{ion}) * G_{ion}$

Potassium Channels add Diversity

- Most CNS neurons have multiple Potassium channels with different characteristics:
  - Voltage dependence of activation (Low-voltage activation vs. High voltage activation)
  - Rate of activation (how fast the population reaches maximum conductance)
  - Inactivation properties
    - Some inactivate quickly
    - Some inactivate slowly
    - Some don't inactivate
- This allows diversity of spike waveforms and spike patterns for different cells

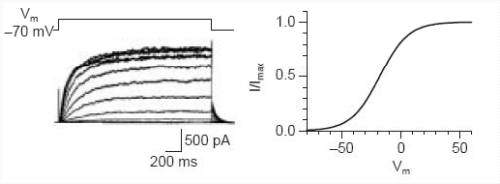
IK_{DR} and IK_A

- Common K+ conductances in CNS neurons



IK_M (M-Current)

- Slowly-activating, noninactivating K+ conductance



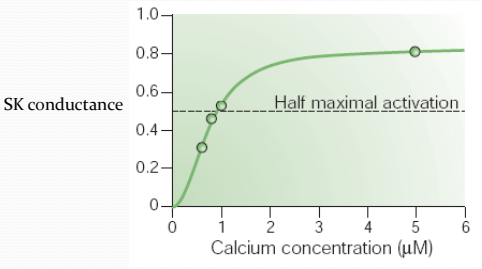
Rogawski (2000) Trends Neurosci.

Calcium entry during the AP activates K+ channels

- Voltage-gated Ca++ channels open during the AP
- Calcium entry through multiple channel types
  - Small effect on membrane potential
  - Large effect on intracellular signalling
  - Activates calcium-gated K+ channels

SK Channels

- Activated by intracellular Calcium

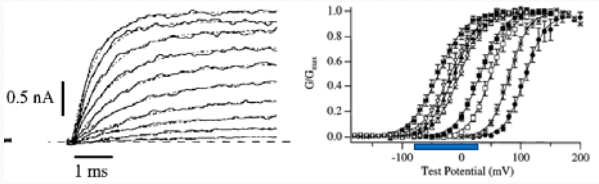


Stocker (2004) Nat. Rev. Neurosci.

The mystery current: sI_{AHP}

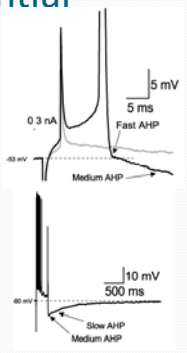
- Activated by intracellular Calcium
- Slow activation (100's of ms)
- Very slow deactivation (1000 – 3000 ms)
- Molecular identity of the responsible channel remains unknown

BK channels are activated by Ca++ *and* voltage



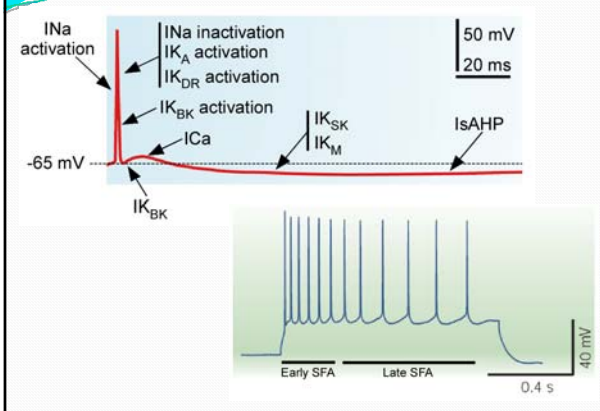
After the Action Potential

- Active processes continue after the action potential ends
- Afterhyperpolarization (AHP) occurs on at least three timescales
  - Fast AHP (2-5 ms)
    - mediated by BK channels
  - Medium AHP (10-100 ms)
    - mediated by SK and M-type channels
  - Slow AHP (100-3000 ms)
    - mediated by an unknown Calcium activated K+ channel



Functional Roles of the AHP

- Fast AHP (2-5 ms)
  - Shortens the AP by quickly repolarizing the membrane
  - Only affects early spike frequency at very high frequencies
- Medium AHP (10-100 ms)
  - Controls early interspike interval
  - contributes to early spike-frequency adaptation
- Slow AHP (100 ms – 3000 ms)
  - Limits firing frequency
  - Controls late spike-frequency adaptation



Information coding by neurons