

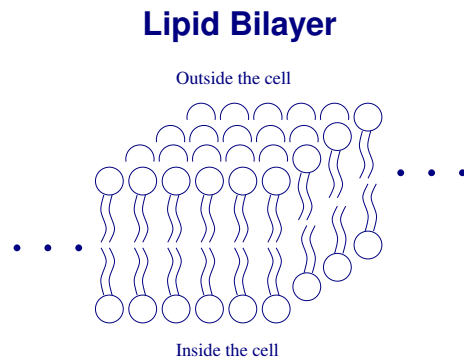
Membrane Properties and Neurotransmitter Actions

Shepherd (2004) Chapter 2 by David A. McCormick

- Cell membrane.
- Ionic concentration.
- Ion channels and currents.
- Action potential.
- Neurotransmitter actions.

Instructor: Yoonsuck Choe; CPSC 644 Cortical Networks

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- Cell membrane is made up of lipid (i.e., fat) bilayer.
- Each lipid molecule consists of the polar head (round, hydrophilic) and non-polar tails (wiggly, hydrophobic).
- A very effective barrier of non-fatty stuff: ions, fluids, etc.

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Introduction

- Neurons with very similar morphology may act differently depending on the cell's **intrinsic properties**.
- Electrochemical and pharmacological properties become important.
- Electrochemical behavior may change due to ionic currents into and out of the cell and neurotransmitters that modulate such currents.

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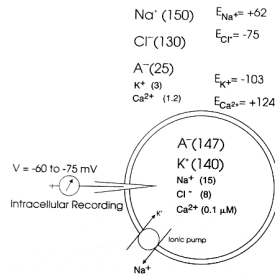
Ion Channels

Ion channels are large proteins embedded in the cell membrane, and they allow passage of specific ions.

- Pores: allows ions to pass through.
- Specificity: only a certain ion species can pass.
- Voltage- or neurotransmitter sensitive (or both).
- Can be modified by intracellular mechanisms.

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Ionic Concentration Difference



- Ions are differentially concentrated inside vs. outside the cellular membrane.
- For example, Na^+ ions are 10 times more abundant in the extracellular space than inside the cell.
- So, if an opening (ion channel) is made on the membrane, the Na^+ ions outside will flow inside to reach balance in the concentration.

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Calculating the Equilibrium Potential

- The Nernst equation for ion X :

$$E_X = \frac{RT}{zF} \ln \frac{[X]_o}{[X]_i},$$

where: R = gas const., T = abs. temp. z = valence, F = Faraday const., and $[X]_n$ = concentration of X in compartment n (o: outside, i: inside).

- It is more conveniently written as:

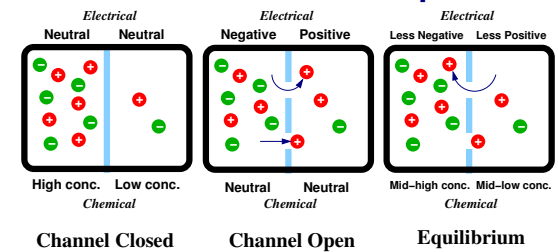
$$E_X = \frac{58.2}{z} \log \frac{[X]_o}{[X]_i},$$

assuming $T = 20^\circ\text{C}$ (room temperature).

- Note: compartment o is the reference point. Voltage is determined as voltage of compartment i relative to compartment o.

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Chemical and Electrical Equilibrium



- Ions will move from compartments of higher concentration to lower concentration.
- However, the ions are not electrically neutral, so the two compartments will become positively/negatively charged.
- Such charge will hinder the movement of ions that are trying to achieve chemical balance.
- This will lead to a potential difference across the membrane.

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Equilibrium Potential: Squid Giant Axon

- In compartment 1, 10 mM of Na^+ .
- In compartment 2 (reference), 1 mM of Na^+ .
- Na^+ has valence 1 ($z = 1$).

$$E_X = \frac{58.2}{z} \log \frac{[X]_2}{[X]_1}.$$

$$E_{\text{Na}^+} = \frac{58.2}{1} \log \frac{1}{10} = -58.2\text{mV}$$

- At the equilibrium potential, ions will not flow.
- If current is applied to move the membrane potential away from the equilibrium potential, ions will start to flow: i.e., conductance will increase (conductance = 1/resistance).

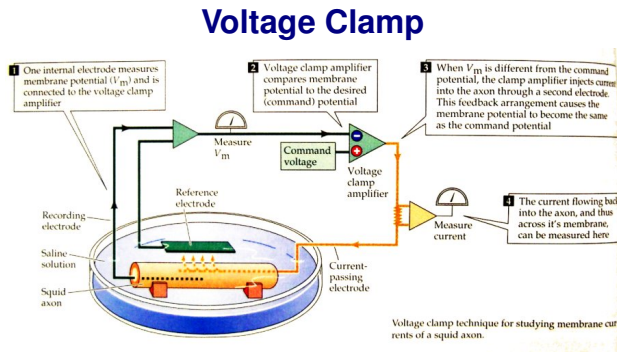
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Permeability

Permeability: The ease with which an ion diffuses across the membrane.

- Increased permeability lead to increased electrical conductance, and will bring the membrane potential closer to that ion's equilibrium potential.
- Higher permeability tends to keep the membrane potential near that ion's equilibrium potential.
- Lower permeability allows other kinds of ions to change the membrane potential away from that ion's equilibrium potential.

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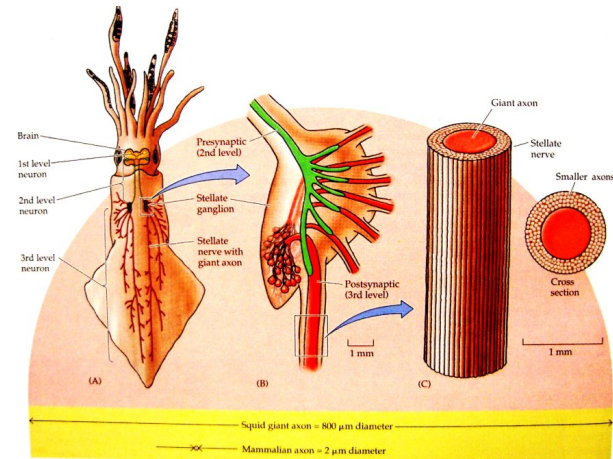


Adapted from Purves et al. (1997)

- Dynamic controller kept the membrane potential at a fixed voltage, by adjusting the current injection level.
- Hodgkin and Huxley used this on the squid giant axon to study membrane properties.

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The Squid Giant Axon



Adapted from Purves et al. (1997)

- Squid giant axons are very thick, so it was easy to experiment with it to study membrane properties.

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Goldman-Hodgkin-Katz Equation: Resting Membrane Potential

For the squid giant axon:

- Weighted mixture of all ionic currents considered:

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

where P_X is the weight (relative permeability), which is

$$P_K : P_{Na} : P_{Cl} = 1 : 0.04 : 0.45.$$

- Plugging in the actual values:

$$V_m = 58.2 \log \left[\frac{1 \cdot 20 + 0.04 \cdot 440 + 0.45 \cdot 40}{1 \cdot 400 + 0.04 \cdot 50 + 0.45 \cdot 560} \right] = -62mV.$$

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Depolarization and Hyperpolarization

- The resting membrane potential is negative (e.g., -62 mV), thus it is “polar”.
- Increasing membrane potential is called “depolarization”.
- Decreasing membrane potential is called “hyperpolarization”.

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Various Ionic Currents

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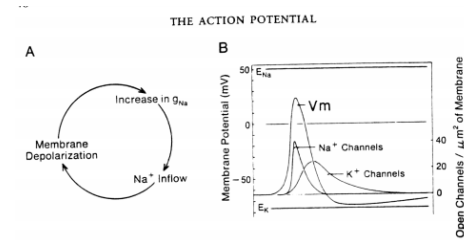
Table 2.1. Neuronal Ionic Currents

Current	Description	Function
Na^+		
$I_{\text{Na,t}}$	Transient; rapidly activating and inactivating	Action potentials
$I_{\text{Na,p}}$	Persistent; noninactivating	Enhances depolarization; contributes to steady state firing
Ca^{2+}		
I_T , low threshold	“Transient”; rapidly inactivating; threshold negative to -65 mV	Underlies rhythmic burst firing
I_L , high threshold	“Long-lasting”; slowly inactivating; threshold around -20 mV	Underlies Ca^{2+} spikes that are prominent in dendrites; involved in synaptic transmission
I_N	“Neither”; rapidly inactivating; threshold around -20 mV	Underlies Ca^{2+} spikes that are prominent in dendrites; involved in synaptic transmission
I_P	“Purkinje”; threshold around -50 mV	
K^+		
I_K	Activated by strong depolarization	Repolarization of action potential
I_C	Activated by increases in $[\text{Ca}^{2+}]_i$	Action potential repolarization and interspike interval
I_{AHP}	Slow afterhyperpolarization; sensitive to increases in $[\text{Ca}^{2+}]_i$	Slow adaptation of action potential discharge; the block of this current by neuromodulators enhances neuronal excitability
I_A	Transient; inactivating	Delayed onset of firing; lengthens interspike interval; action potential repolarization
I_M	“Muscarinic” sensitive; activated by depolarization; noninactivating	Contributes to spike frequency adaptation; the block of this current by neuromodulators enhances neuronal excitability
I_h	Depolarizing (mixed cation) current that is activated by hyperpolarization	Contributes to rhythmic burst firing and other rhythmic activities
$I_{\text{K,ns}}$	Contributes to neuronal resting membrane potential	The block of this current by neuromodulators can result in a sustained change in membrane potential

Lesson: There are many currents related to diverse functions.

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Action Potential (or Spike)



- Na^+ channels open, triggered by depolarization.
- The increase in membrane voltage due to depolarization triggers a more Na^+ channels to open, thus further depolarizing the membrane (transient sodium current $I_{\text{Na,t}}$).
- Such depolarization will trigger depolarization in neighboring membranes.
- Since $I_{\text{Na,t}}$ is transient, it will quickly inactivate, and further more, voltage-gated K^+ channels will open, thus “repolarizing” (potassium current I_K). I_K is slower.

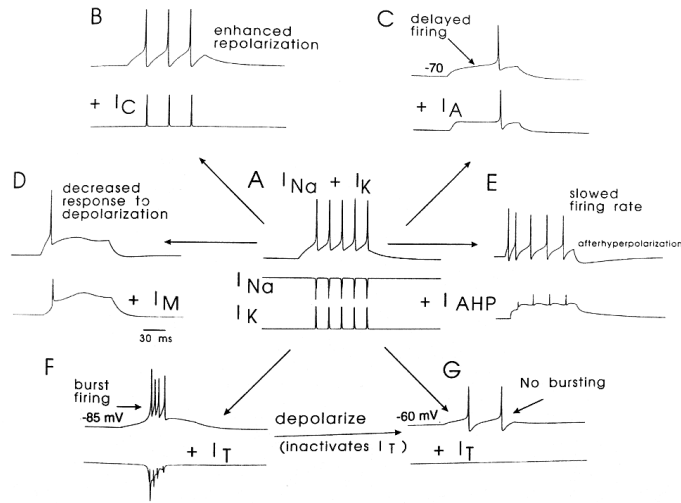
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Some Notable Ionic Currents

- $I_{\text{Na,t}}$: Transient Na^+ current – action potential.
- I_K : activated by strong depolarization – repolarization.
- I_T : Transient Ca^{2+} current – low threshold burst firing.
- I_h : activated by hyperpolarization – depolarizing current related to burst firing.
- Ca^{2+} currents in general: Involved in diverse functions such as neurotransmitter release, synaptic plasticity, neurite outgrowth during development, and even gene expression.

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Firing Pattern Dependent on Ionic Currents



- The presence or absence of different ionic currents drastically alter the spike behavior of neurons.

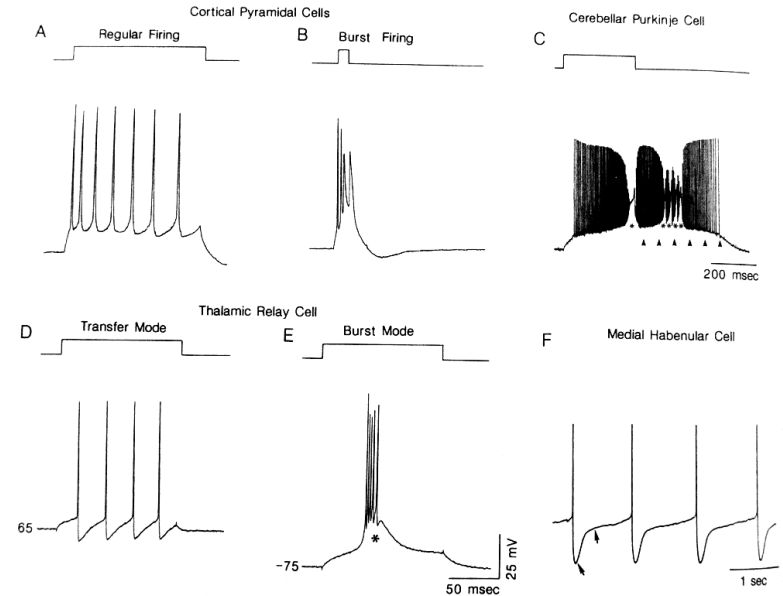
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Neuronal Communication

- Gap junctions: Direct flow of current across cells.
- Ephaptic interactions: Electrical field effect.
- Chemical synapses: Neurotransmitter action.

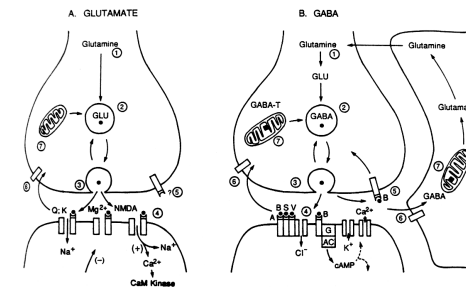
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Firing Modes of Typical Neurons



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Chemical Synapses



- Neurotransmitter release and binding.
- Channel opening or secondary effects (G-protein).
- Re-uptake of neurotransmitter by presynaptic terminal (GLU) or glia (GABA).
- GLU induces excitatory post synaptic potential (EPSP).
- GABA induces inhibitory post synaptic potential (IPSP).

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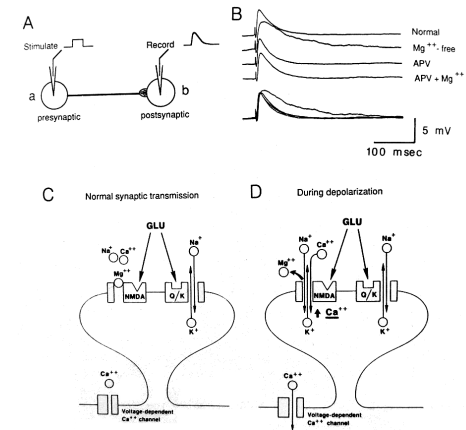
Neurotransmitter and Ionic Currents

Table 2.2. Common Neurotransmitter Responses in the Central Nervous System

Response	Neurotransmitter	Receptor
$\uparrow I_{Na}$, $\uparrow I_K$	Glutamate	Quisqualate/kainate
	Glutamate	<i>N</i> -Methyl-D-aspartate (NMDA)
	Acetylcholine	Nicotinic
$\uparrow I_{Na}$, $\uparrow I_K$, $\uparrow I_{Ca}$		GABA _A
$\uparrow I_{Cl}$	γ -Aminobutyric acid	
$\uparrow I_{K,IR}$	Glycine	
	Acetylcholine	M ₂
	Norepinephrine	α_2
	Serotonin (5-hydroxytryptamine [5-HT])	5-HT ₁
	GABA	GABA _B
	Dopamine	D ₂
	Adenosine	A ₁
$\downarrow I_{AHP}$	Somatostatin	SST ₅
	Enkephalins	μ , δ
	Acetylcholine	Muscarinic
	Norepinephrine	β_1
	Serotonin	5-HT ₇
	Histamine	H ₂
	Glutamate	Glutamate metabotropic
$\downarrow I_{K,leak}$	Acetylcholine	Muscarinic
	Norepinephrine	α_1
	Serotonin	5-HT ₂
	Glutamate	Glutamate metabotropic
$\downarrow I_{Ca}$	Multiple transmitters	

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Action of NMDA



- At high-frequency activation, Mg⁺ will be unblocked, leading to long term potentiation (LTP), which is believed to play an important role in memory.

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Neurotoxins and Drugs

- Agonist: Binds and turns on ion channel; Antagonist: Binds and blocks ion channel; Allosteric modulator: Binds and up- or down-modulate channel activity.
- Tetrodotoxin (TTX): Binds to the pores of voltage-gated Na⁺ channels, thus blocking action potentials (found in puffer fish, toads, etc.).
- Benzodiazepine, Barbiturate: Binds to GABA-A receptors to up-modulate GABA binding.
- Bicuculine: Occupies GABA-A receptors, preventing GABA from activating the receptor. Overdose can lead to epilepsy.

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