Announcement:

- TA/IA office hours are posted on TritonEd.

Worksheet #1: DUE TODAY

Worksheet # 2: DUE WEDNESDAY

Midterm1: WEDNESDAY before lecture – CH2/WS1

...ask questions  ...discuss  ...listen  ...learn.
Before we go on

Let’s recap important points from CH2 – Neurons and Glia
<table>
<thead>
<tr>
<th>Neurons</th>
<th>Glia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can communicate precisely and rapidly</td>
<td>Less excitable</td>
</tr>
<tr>
<td>Can communicate over long distances</td>
<td>Membranes contain transported proteins to facilitate the uptake of ions and proteins</td>
</tr>
<tr>
<td>Morphological functional asymmetry:</td>
<td></td>
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<tr>
<td>- Receptive dendrites</td>
<td>Can remove neurotransmitter from extracellular area to regulate neuronal function</td>
</tr>
<tr>
<td>- Transmitting axon</td>
<td></td>
</tr>
<tr>
<td>Structural basis for unidirectional signaling</td>
<td></td>
</tr>
<tr>
<td>Neurons are excitable – chemically or electrically</td>
<td>Neurons and Glia develop from common neuroepithelial cells of the embryonic nervous system..</td>
</tr>
<tr>
<td>Ion channels and receptors facilitate the flow of ions to redistribute the voltage across the membrane</td>
<td>Neurons and glia share many structural and molecular characteristics.</td>
</tr>
<tr>
<td>Propagating action potential along axon</td>
<td></td>
</tr>
</tbody>
</table>
Neuronal classifications

dendrites

soma

axon

cortical pyramidal neuron

projection neuron → can communicate over long distances.
Example of a projection neuron

Cortical pyramidal neuron

- Pyramidal cell
- Local axon collateral (local circuitry)
- Stellate cell
- Dendrites
- Descending axon (output)
The cytoskeleton determines cell shape!

- Microtubules: \( \approx 20 \text{ nm} \)
- Neurofilaments: \( \approx 10 \text{ nm} \)
- Microfilaments: \( \approx 5 \text{ nm} \)
Microtubules
1. Long scaffolds that extend over the length of the neuron
2. Responsible for shape of cell
3. Made up of α and β-tubulin subunits
Microtubules

1. Long scaffolds that extend over the length of the neuron
2. Responsible for shape of cell
3. Made up of α & β-tubulin subunits

**Microtubule-associated proteins (MAPs)**
- Stabilize tubulin

α-tubulin
β-tubulin
ALZ. DISEASE $\rightarrow$ CYTOSKELETAL ABNORMALITIES

- ACCUMULATION OF NEURONFIBRILLARY TANGLES

TANGLES ARE HYPERPHOSPHORYLATED TAU PROTEIN.
Tau protein associates with normal microtubules and contributes to the structural integrity of the neuron. In AD, tau protein becomes hyperphosphorylated and begins to disassemble. That causes it to associate with paired helical filaments and become NFTs.
Fast transport and trafficking:

Proteins and lipids of secretory organelles are synthesized in the endoplasmic reticulum and transported to the Golgi complex, where large dense-core vesicles (peptide-containing secretory granules) and synaptic vesicle precursors are assembled.

Large dense-core vesicles and transport vesicles that carry synaptic vesicle proteins travel down the axon via axonal transport.

At the nerve terminals the synaptic vesicles are assembled and loaded with nonpeptide neurotransmitters. Synaptic vesicles and large dense-core vesicles release their contents by exocytosis.

Following exocytosis, large dense-core vesicle membranes are returned to the cell body.

Retrograde transport for degradation or reuse.
• A Specialist among glia
• found in white matter – because it is the white matter!
• Peripheral nervous system myelin: Schwann cells
• Myelin aids in the propagation of neural signals along myelinated axons
• Pro: Present antigens that influence the outgrowth of axons in developing and recovering brain to regenerate lost connections
• Con: present antigens that can attack CNS – Multiple sclerosis.
Glia

- Myelin insulates the axons of both central and peripheral neurons.
  - Oligodendroglia (in CNS)
  - Schwann cells (in PNS)
Axons in the CNS are wrapped in several layers of myelin produced by oligodendrocytes.

Each oligodendrocyte can myelinate many axons.
Peripheral nerve fibers are myelinated by Schwann cells.
• Insulate axons by generating layers of membrane that wrap around axon segments
• Myelin makes the passive flow of current along the axon more efficient.
• Having gaps between myelin segments enables the neuron to conserve its resources by having ion channels and pumps concentrated in and around the myelin gap.
– Oligodendrocyte
– Node of Ranvier
  • Region where the axonal membrane is exposed
The Neuronal Membrane at Rest

MARY ET BOYLE, PH.D.
DEPARTMENT OF COGNITIVE SCIENCE
UCSD
Hippocrates (450 BC)  Disease could be related to body fluids and humors

Galen (150 AD) Proposed that “humors” flowed from the brain to the muscles along hollow nerves.
“Galvani and assistant touching rods of different metals to the amputated frogs legs to produce a convulsion.”

https://www.tcd.ie/Physics/research/groups/magnetism/facts/guide/animagus.php
Expériences de Galvani sur les grenouilles. (Extrait des Œuvres de Galvani.)
(Collection de M. E. Sartiaux.)
"In January 1803, the body of the murderer George Forster was pulled from the gallows of Newgate Prison in London and taken to the Royal College of Surgeons. There, before an audience of doctors and curiosity-seekers, Giovanni Aldini, nephew of the late Luigi Galvani, prepared to return the corpse to life.”
Brain to muscle command mediated by flow of electricity along nerve fibers.
Julius Bernstein (1839-1917)

"Membrane Theory" of 1902

• earliest biophysical explanation of propagating action potential

• the first quantitative theory in electrophysiology

http://www.bfnt-goettingen.de/AboutBFNT/JuliusBernstein
Bernstein proposed that the impulse is related to changes in the ion permeability of the membrane.

Julius Bernstein (1839-1917)

“Membrane Theory” of 1902
- earliest biophysical explanation of propagating action potential
- the first quantitative theory in electrophysiology
Transient Electrical Signals

- carry information quickly over long distances
- action potential
- receptor potential
- synaptic potential
 transient electrical signals

- carry information quickly over long distances
- action potential
- receptor potential
- synaptic potential

Q. How are they produced?

A. By changes in the electric current into & out of the cell.

Flow of + or - ions across the membrane.
Transient Electrical Signals
- Carry information quickly over long distances
- Action potential
- Receptor potential
- Synaptic potential

Q. How are they produced?

A. By changes in the electric current into & out of the cell.

Flow of + or - ions across the membrane

Q. What is "potential"?
Q. How are they produced?

A. What is "potential"?

- By changes in the electric current into & out of the cell.
- Flow of $\text{\textbf{+}}$ or $\text{\textbf{-}}$ ions across the membrane.

Q. What is the separation of electrical charge across the membrane?
ACTION POTENTIAL RECORDED BETWEEN INSIDE AND OUTSIDE OF AXON. TIME MARKER, 500 CYCLES/SEC. THE VERTICAL SCALE INDICATES THE POTENTIAL OF THE INTERNAL ELECTRODE IN MILLIVOLTS, THE SEA WATER OUTSIDE BEING TAKEN AT ZERO POTENTIAL.
transient electrical signal!
What is the nature of the action potential?

The conduction of information along the axon is mediated by the active generation of an electrical potential.
Loligo pealii
Electrode in giant axon

Axon approximately 0.5 mm in diameter
Action potential in the nervous system

Collect
distribute
integrate
Learning objectives:

1. Describe the concept of \textit{electrochemical equilibrium} and relate this concept to the resting membrane potential of neurons.
2. K+ permeability accounts for the resting membrane potential of neurons.
You can *derive* the membrane potential using the NERNST EQUATION,

You will need to know the concentration gradient of a single permeant ion.
Overview - Neurons generate electrical signals

Problem: neurons are poor at conducting electricity.

Solution: evolved mechanism to overcome limitations.

How: electrical signals are based on the flow of ions across the plasma membrane.
Q: How are electrical potentials generated across the membrane of a neuron?

- Electrical potentials are generated across the membranes of neurons—
- Because:
  - there are differences in the concentrations of specific ions across nerve cell membranes, and
  - the membranes are selectively permeable to some of these ions.

Know this! ✌️
Consider the following experimental setup:

- Stimulate neuron with a microelectrode to inject current.
- Record membrane potential with a microelectrode.
The experiment:

- **record**
- **stimulate**
Receptor Potential –
(e.g. Pacinian corpuscle)

Receptor potentials are due to the activation of sensory neurons by external stimuli.
Communication between neurons at synaptic contacts -- Activation of these synapses generates synaptic potentials, which allow transmission of information from one neuron to another.
Neurons generate a special type of electrical signal that travels along their long axons. Such signals are called action potentials – spikes or impulses. Action potentials are responsible for long-range transmission of information within the nervous system and allow the nervous system to transmit information to its target organs, such as muscle.
Signaling in the brain depends on the ability of nerve cells to respond to **very small stimuli** with rapid and large changes in the electrical potential difference across the cell membrane. = sensitive.
### Graded vs Action Potentials

<table>
<thead>
<tr>
<th>Receptor Potentials are a type of Graded Potential</th>
<th>Action Potentials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depending on the stimulus, graded potentials can be depolarizing or hyperpolarizing</td>
<td>Action potentials always lead to depolarization of membrane and reversal of the membrane potential.</td>
</tr>
<tr>
<td>Amplitude is proportional to the strength of the stimulus.</td>
<td>Amplitude is all-or-none; strength of the stimulus is coded in the frequency of all-or-none action potentials generated.</td>
</tr>
<tr>
<td>Amplitude is generally small (a few mV to tens of mV).</td>
<td>Large amplitude of ~100 mV.</td>
</tr>
<tr>
<td>Duration of graded potentials may be a few milliseconds to seconds.</td>
<td>Action potential duration is relatively short; 3-5 ms.</td>
</tr>
<tr>
<td>Ion channels responsible for graded potentials may be ligand-gated (extracellular ligands such as neurotransmitters), mechanosensitive, or temperature sensitive channels, or may be channels that are gated by cytoplasmic signaling molecules.</td>
<td>Voltage-gated Na⁺ and voltage-gated K⁺ channels are responsible for the neuronal action potential.</td>
</tr>
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</table>
Graded Action Potential

<table>
<thead>
<tr>
<th>The ions involved are usually Na(^+), K(^+), or Cl(^-).</th>
<th>The ions involved are Na(^+) and K(^+) (for neuronal action potentials).</th>
</tr>
</thead>
<tbody>
<tr>
<td>No refractory period is associated with graded potentials.</td>
<td>Absolute and relative refractory periods are important aspects of action potentials.</td>
</tr>
<tr>
<td>Graded potentials can be summed over time (temporal summation) and across space (spatial summation).</td>
<td>Summation is not possible with action potentials (due to the all-or-none nature, and the presence of refractory periods).</td>
</tr>
<tr>
<td>Graded potentials travel by passive spread (electrotonic spread) to neighboring membrane regions.</td>
<td>Action potential propagation to neighboring membrane regions is characterized by regeneration of a new action potential at every point along the way.</td>
</tr>
<tr>
<td>Amplitude diminishes as graded potentials travel away from the initial site (decremental).</td>
<td>Amplitude does not diminish as action potentials propagate along neuronal projections (non-decremental).</td>
</tr>
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</table>
Graded potentials are brought about by external stimuli (in sensory neurons) or by neurotransmitters released in synapses, where they cause graded potentials in the post-synaptic cell. 

In principle, graded potentials can occur in any region of the cell plasma membrane, however, in neurons, graded potentials occur in specialized regions of synaptic contact with other cells (post-synaptic plasma membrane in dendrites or soma), or membrane regions involved in receiving sensory stimuli.

<table>
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<th>Action Potentials</th>
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<td>Graded potentials are brought about by external stimuli (in sensory neurons) or by neurotransmitters released in synapses, where they cause graded potentials in the post-synaptic cell.</td>
<td>Action potentials are triggered by membrane depolarization to threshold.</td>
</tr>
<tr>
<td>In principle, graded potentials can occur in any region of the cell plasma membrane, however, in neurons, graded potentials occur in specialized regions of synaptic contact with other cells (post-synaptic plasma membrane in dendrites or soma), or membrane regions involved in receiving sensory stimuli.</td>
<td>Occur in plasma membrane regions where voltage-gated Na^+ and K^+ channels are highly concentrated.</td>
</tr>
</tbody>
</table>

http://www.physiologyweb.com/lecture_notes/neuronal_action_potential/neuronal_action_potential_graded_potentials-versus-action_potentials.html
Comparison of electrical problems...

**Copper wire**
- Electrical charge is carried by free electrons
- Well insulated-plastic coating; air
- Great conductor

**Cytosol in Axon**
- Electrical charge is carried by ions.
- Not perfectly insulated; salty extracellular fluid will conduct electricity
- Less than perfect conductive medium!

Squid giant axon
Two **basic concepts** critical to understanding neuronal signaling...

**Charge**
- Ions are needed to carry the electrical charge
- Concentration gradient is a means to store energy

**Flow**
- Permeability mechanism to redistribute ions across the membrane
- Ion flow regulation and management
Essential Resting Membrane Potential Properties:

- Salty fluids on either side of the membrane
- The membrane
- Proteins that span the membrane
Water

- Key ingredient in intracellular and extracellular fluid
- Key feature – water is a polar solvent – which means that other polar molecules tend to dissolve in water.

The most important property of the water molecule is its uneven distribution of electrical charge.
NaCl *dissolves* in water because the polar water molecules have a *stronger attraction* for the electrically charged sodium and chloride ions than the ions do for one another.
Ions: Atoms or molecules with a net electrical charge

Cations: ions with a net positive charge
Anions: ions with a net negative charge

Major charge carriers in the neuron:

cations \{ \cdot \text{Na}^+, \text{K}^+, \text{Ca}^{++} \}
anions \{ \cdot \text{Cl}^- \}

The electrical charge of an atom depends on the difference between the number of protons and electrons. When this difference is 1, the ion is said to be monovalent; when the difference is 2 the ion is divalent.
Hydrophilic v. Hydrophobic

-philic
- Dissolve in water
- Uneven electrical charge
- NaCl

-phobic
- Do NOT dissolve in water
- Shared electrons are distributed evenly
- lipids
• Neuronal membrane is a sheet of phospholipids two molecules thick.

• Hydrophilic heads face the outside and inner watery environments

• *Hydrophobic tails face each other.*

Polar “head” containing phosphate

Non-polar “tail” containing hydrocarbon
Phospholipid bilayer: the cell membrane
The membrane lab
The membrane lab
Recall, the basic structure of an amino acid. The properties of the R group determine the chemical relationships in which each amino acid can participate.
Other amino acids:

- **Glycine** (Gly or G)
- **Alanine** (Ala or A)
- **Cysteine** (Cys or C)
- **Serine** (Ser or S)
- **Threonine** (Thr or T)
- **Tyrosine** (Tyr or Y)
- **Proline** (Pro or P)
- **Tryptophan** (Trp or W)

Amino acids with strongly hydrophobic R groups:

- Valine (Val or V)
- Leucine (Leu or L)
- Isoleucine (Ile or I)
- Phenylalanine (Phe or F)
- Methionine (Met or M)

Amino acids with strongly hydrophilic R groups:

- Aspartic acid (Asp or D)
- Glutamic acid (Glu or E)
- Asparagine (Asn or N)
- Glutamine (Gln or Q)
- Lysine (Lys or K)
- Arginine (Arg or R)
- Histidine (His or H)
Peptide bonds and polypeptides

Four levels of protein structure

1° - a chain of linked amino acids linked by peptide bonds

2° - chain coils into a spiral – alpha helix

3° - interaction with R-groups defines 3-D structure

4° - chains bond together to form a larger molecule – i.e. subunit
Thinking about channels

Regions where nonpolar R groups are exposed will be hydrophobic and will tend to associate readily with lipid.

Regions with exposed polar R groups will be hydrophilic and will tend to avoid a lipid environment.
The differences between amino acids result from the differences in the size and nature of the R groups.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>True</td>
</tr>
<tr>
<td>b</td>
<td>False</td>
</tr>
</tbody>
</table>
Ion specificity is determined by:

- Diameter of pore
- R-Groups lining the pore
- Gating
- Ion pumps

Ion channels can be opened and closed by changes in the local microenvironment of the membrane.

A channel across a membrane is like a bridge across a river.

A gated channel is a like a drawbridge.
How do ion movements produce an electrical signal?

1. Difference of ionic concentration across the membrane
2. Membranes are selectively permeable to some of these ions.

active transporters
ion channels
membrane

Container

barrier

Inside

Outside

4000
Molecules in one chamber cannot cross to the other side. Why?

Barrier is impermeable!
it is so crowded on this side

Yeah, I wish we could leave.

Look, no "reds" are on the other side.

It would be so nice, we could spread out...
Then magically, the “reds” dream came true – a channel “just for reds” appeared in the barrier and it became semi-permeable.

Me too! Yippeee!

Hey --- it is crowed over here now – we have to spread out – it is the law!

Look --- we can do it! Bye!

Flux goes from regions of **high** concentration to regions of **low** concentration, with a magnitude that is proportional to the concentration gradient.
Initially, there are solute molecules on the left side of a barrier and none on the right. The barrier is removed, and the solute diffuses to fill the whole container.

A single molecule moves around randomly.

This smooth flow is described by Fick’s laws.

With more molecules, there is a clear trend where the solute fills the container more and more uniformly.

With an enormous number of solute molecules, randomness becomes undetectable. The solute appears to move smoothly and systematically from high-concentration areas to low-concentration areas.
The Movement of Ions- Factor #1: Diffusion

- Impermeable membrane
- Na\(^+\) and Cl\(^-\) channels
- Equal distribution of ions
The Movements of Ions- Factor #2: Electricity

Movement of ions are influenced by electrical fields.

Place wires from two terminals of a battery in a solution containing dissolved NaCl.

Recall: opposite charges attract and like charges repel.
The movement of electrical charge is called electrical current ($I$) and measured in units called amperes (amps).

By convention, current flows from + to –

Two important factors determine how much current will flow:

- Electrical potential
- Electrical conductance
Voltage
From Wikipedia, the free encyclopedia

Voltage, otherwise known as electrical potential difference or electric tension (denoted ΔV and measured in volts, or joules per coulomb) is the potential difference between two points — or the difference in electric potential energy per unit charge between two points.[1] Voltage is equal to the work which would have to be done, per unit charge, against a static electric field to move the charge between two points. A voltage may represent either a source of energy (electromotive force), or it may represent lost or stored energy (potential drop). A voltmeter can be used to measure the voltage (or potential difference) between two points in a system; usually a common reference potential such as the ground of the system is used as one of the points. Voltage can be caused by static electric fields, by electric current through a magnetic field, by time-varying magnetic fields, or a combination of all three.[2][3]
Electrical potential - voltage

Electrical potential is the force exerted on a charged particle.

It reflects the difference in electric potential per unit charge between the anode and the cathode.

More current will flow as this difference is increased.

Voltage is represented by the symbol V and is measured in volts.

The difference in electrical potential between the terminals of a car battery is 12V.

Car Battery
12V
Lipid Bilayer enables the separation of charge

The neuron’s cell membrane has thin clouds of positive and negative ions spread over its inner and outer surfaces.

* AT REST
The membrane potential is the result of the separation of the net positive & net negative charges on either side of the membrane.

Recall: The charge separation gives rise to a difference of electrical potential.
The membrane potential is the result of the separation of the net positive and net negative charges on either side of the membrane.

Recall: The charge separation gives rise to a difference of electrical potential.

\[ \text{VOLTAGE} = \text{the difference of electrical potential} \]
the membrane potential is the result of the separation of the net positive and negative charges on either side of the membrane.

\[ \text{Voltage} = \text{difference of electrical potential} \]

This is the membrane potential, \( V_m \).
The membrane potential is defined as:

\[ V_m = V_{in} - V_{out} \]

- **potential on the inside**
- **potential on the outside**

This is the membrane potential, \( V_m \).

\( V_{in} \) is the voltage on the inside and \( V_{out} \) is the voltage on the outside.
The resting potential is equal to \( V_{in} \approx -60 \text{ to } -70 \text{ mV} \).

By convention, the potential outside the cell is defined as \( 0 \).
Remember:

1. The electric current is carried by ions.

2. In an ionic solution, cations $\text{\texttt{\textbullet}}$ move in the direction of the electric current.
Electrical conductance (g)

Is the relative ability of an electrical charge to migrate from one point to another.

It is represented by the symbol g and measured in units called Siemens (S).

Conductance depends on the number of particles available to carry electrical charge-

and the ease with which these particles can travel through space

What is the Na+ conductance?

What is the Cl- conductance?

Conductance for Na+ & Cl- is _____.

What is the Na+ conductance? Type of question

What is the Cl- conductance? Type of question

Conductance for Na+ & Cl- is _____.
Electrical resistance (R) is the relative inability of the charge to migrate. Resistance is the inverse of conductance. Resistance is represented by the symbol $R$ and is measured in units called ohms ($\Omega$).

Mathematically, resistance $R$ is given by:

$$R = \frac{1}{g}$$

where $g$ is the conductance.
Ohm’s Law: \( V = IR \)

How would you express Ohm’s law using conductance (\( g \)) instead of resistance?

Express Ohm’s law as:

\[ I = \underline{\text{_______}} \]
Current (I) = conductance (g) * potential difference (V)

How much current (I) will flow if:

1. g = 0 and V=100?

Recall: Ohm’s law

2. V = 0 and g=30?
Example 1:

What would happen if \( \text{NaCl} \) were dissolved in equal concentrations on either side of a phospholipid bilayer?
Example 1:

What would happen if \( \text{NaCl} \) were dissolved in equal concentrations on either side of a phospholipid bilayer?
Example 1:

What would happen if NaCl were dissolved in equal concentrations on either side of a phospholipid bilayer?

There will be a large potential difference across the membrane.

No current will flow – because there are no channels to allow the migration of Na\(^+\) and Cl\(^-\) across the membrane.
Example 2:

The direction of an electric current is by convention the direction in which a positive charge would move.

Thus, the current in the external circuit is directed away from the positive terminal and toward the negative terminal of the battery.

Electrons would actually move through the wires in the opposite direction.
To drive ions across the membrane electrically:

1. The membrane possesses channels permeable to that ion.
2. There is an electrical potential difference across the membrane.
A voltmeter measures the difference in electrical potential between the tip of a microelectrode inside the cell and a wire placed in the extracellular fluid.
glass microelectrode

Extracellular bath

intracellular

wire

amplifier

$V_{out}$

ground
Selective permeability $\rightarrow$ K$^+$ can move between the inside and outside but A$^-$ cannot

ADD K$^+$ channels

Initially, K$^+$ ions would get out of the cell along the steep concentration gradient.

$V_m = ???$ mV

Eventually diffusion and electrostatic pressures are perfectly balanced and ....

A$^-$ Any negative charged ion.
Selective permeability $\rightarrow$ $K^+$ can move between the inside and outside but $A^-$ cannot.

Diffusional and electrical forces are equal and opposite.

Net movement across the membrane ceases.

$$E_{\text{ion}} = V_m \text{ mV}$$

EQUILIBRIUM POTENTIAL $E_{\text{ion}}$ represents the ionic equilibrium potential.

$A^-$ Any negative charged ion.
Equilibrium Potential ($E_{ion}$)

- No net movement of ions when separated by a phospholipid membrane.
- Equilibrium reached when $K^+$ channels inserted into the phospholipid bilayer.
- Electrical potential difference that exactly balances ionic concentration gradient.
4 points of Equilibrium Potentials

- Large changes in $V_m$
  - Minuscule changes in ionic concentrations
- Net difference in electrical charge
  - Inside and outside membrane surface
- Rate of movement of ions across membrane – ionic driving force
  - Proportional $V_m - E_{ion}$
- Concentration difference known for an ion: Equilibrium potential can be calculated
The uneven charges inside and outside the neuron line up along the membrane because of electrostatic attraction across the very thin barrier.

Notice that the bulk of the cytosol and extracellular fluid is electrically neutral.
Steps to establishing the equilibrium potential of Na⁺
The Nernst Equation

- Calculates the *exact* value of the equilibrium potential for any permeant ion (mV)
- Takes into consideration:
  - $R$ Gas constant
  - $z$ Valence of the permeant ion (electrical charge)
  - $T$ Temperature (absolute – degrees Kelvin)
  - $F$ Faraday constant (amount of electrical charge in a mole of a univalent ion)
  - $[\text{ion}]_o$ concentration of ion outside of the cell
  - $[\text{ion}]_i$ concentration of ion inside of the cell

$$E_{ion} = 2.303 \frac{RT}{zF} \log \frac{[\text{ion}]_o}{[\text{ion}]_i}$$
$E_{ion} = 2.303 \frac{RT}{zF} \log \frac{[ion]_o}{[ion]_i}$

- $E_{ion}$ = Ionic equilibrium potential
- $R$ = Gas constant
- $T$ = Absolute temperature
- $z$ = Charge of the ion
- $F$ = Faraday’s constant
- $\log$ = Base 10 logarithm
- $[ion]_o$ = Ionic concentration outside the cell
- $[ion]_i$ = Ionic concentration inside the cell
At body temperature (37°C), the Nernst equation for the important ions, K⁺, Na⁺, Cl⁻ and Ca²⁺ simplify to:

<table>
<thead>
<tr>
<th>Ion</th>
<th>Equation</th>
</tr>
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<tbody>
<tr>
<td>K⁺</td>
<td>( E_K = 61.54 \text{ mV} \log \left( \frac{[K^+]_o}{[K^+]_i} \right) )</td>
</tr>
<tr>
<td>Na⁺</td>
<td>( E_{Na} = 61.54 \text{ mV} \log \left( \frac{[Na^+]_o}{[Na^+]_i} \right) )</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>( E_{Cl} = -61.54 \text{ mV} \log \left( \frac{[Cl^-]_o}{[Cl^-]_i} \right) )</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>( E_{Ca} = 30.77 \text{ mV} \log \left( \frac{[Ca^{++}]_o}{[Ca^{++}]_i} \right) )</td>
</tr>
</tbody>
</table>
If \[ \frac{[K^+]_o}{[K^+]_i} = \frac{1}{20} \]

and

then

\[ \log \frac{1}{20} = -1.3 \]

\[ E_K = 61.54 \text{ mV} \times -1.3 \]

\[ = -80 \text{ mV} \]
The logarithm of a number is the exponent to which another fixed value, the base, must be raised to produce that number.

\[ \log_{10}(1000) = ? \]

The logarithm of 1000 to base 10 is 3.

1000 is 10 to the power 3.

1000 = 10 \times 10 \times 10 = 10^3

More generally, if \( x = b^y \), then \( y \) is the logarithm of \( x \) to base \( b \), and is written \( y = \log_b(x) \).
If extracellular sodium is 10x greater than the intracellular sodium: 

\[
\frac{[Na^+]_o}{[Na^+]_i} = \frac{10}{1}
\]

\[
\log \frac{10}{1} = \Box
\]

\[
E_{Na} = 61.54 \text{ mV} \times \Box
\]

\[
= \Box \text{ mV}
\]

and the neuronal membrane is selectively permeable only to sodium -

What will the resting membrane potential be?
The Distribution of Ions Across The Membrane

- K\(^+\) more concentrated on inside,
- Na\(^+\) and Ca\(^{2+}\) more concentrated outside

<table>
<thead>
<tr>
<th>Ion</th>
<th>Concentration outside (in mM)</th>
<th>Concentration inside (in mM)</th>
<th>Ratio Out : In</th>
<th>(E_{ion}) (at 37°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K(^+)</td>
<td>5</td>
<td>100</td>
<td>1 : 20</td>
<td>-80 mV</td>
</tr>
<tr>
<td>Na(^+)</td>
<td>150</td>
<td>15</td>
<td>10 : 1</td>
<td>62 mV</td>
</tr>
<tr>
<td>Ca(^{2+})</td>
<td>2</td>
<td>0.0002</td>
<td>10,000 : 1</td>
<td>123 mV</td>
</tr>
<tr>
<td>Cl(^-)</td>
<td>150</td>
<td>13</td>
<td>11.5 : 1</td>
<td>-65 mV</td>
</tr>
</tbody>
</table>
What is the Equilibrium Potential for an Ion?

An equilibrium potential for an ion is the membrane potential that results if a membrane is selectively permeable to that ion alone.
The sodium-potassium pump

- **Enzyme** - breaks down ATP in the presence of internal Na\(^+\)
- **Pump** exchanges internal Na\(^+\) for external K\(^+\)
Calcium Pump

An enzyme that actively transports Ca\(^{++}\) out of the cytosol.

Additional mechanisms decrease intracellular Ca\(^{++}\) to a very low level (0.0002mM)

Intracellular calcium-binding proteins and organelles – mitochondria and ER that sequester Ca\(^{++}\)

Ion pumps work in the background to ensure that the ionic concentration gradients are established and maintained.
• Recall – The NERNST equation calculates the equilibrium potential of a given ion –

• Note: it is the membrane potential that results if the membrane is selectively permeable to that ion alone!!
What would happen to $V_m$ if the membrane were EQUALLY permeable to $K^+$ and $Na^+$?

$V_m$ would equal some average of $E_K$ and $E_{Na}$
What would happen to $V_m$ if the membrane were 40x more permeable to $K^+$ than to $Na^+$?

$V_m$ would be between $E_K$ and $E_{Na}$ but much closer to $E_K$ than $E_{na}$ this approximates what happens in real neurons.

The resting membrane potential of -65mV approaches, but does not achieve, the potassium equilibrium potential of -80mV.

This difference arises because, although the membrane at rest is highly permeable to $K$, there is also a steady leak of $Na$ into the cell.
Relative Ion Permeabilities of the Membrane at Rest

- Recall, the Nernst equation is about $V_m$ if a membrane is selectively permeable to that ion alone.
- However, neurons are permeable to more than one type of ion.
- Membrane permeability determines membrane potential.
- Goldman equation
  - Takes into account permeability of membrane to different ions.
Calculating the $V_m$ using the Goldman Equation

### Assumptions:

- **$K^+$**
  - $[K]_o = 5$ mM
  - $[K]_i = 100$ mM

- **$Na^+$**
  - $[Na]_o = 150$ mM
  - $[Na]_i = 15$ mM

**Permeability @ rest**

- $K^+$ is 40 x $> Na^+$
The Goldman Equation

\[ V_m = 61.54 \text{ mV} \log \frac{P_k[K]_o + P_{Na}[Na]_o}{P_k[K]_i + P_{Na}[Na]_i} \]

\( V_m \) is the membrane potential.
\( P_k \) and \( P_{Na} \) are the relative permeabilities to K and Na ions.
Constants are the same as in the Nernst equation.

If the resting membrane ion permeability is to \( K^+ \) is 40 times greater than it is to \( Na^+ \), then solving:

\[ V_m = 61.54 \text{ mV} \log \frac{40(5) + 1(150)}{40(100) + 1(15)} \]

\[ V_m = 61.54 \text{ mV} \log \frac{350}{4015} \]

\[ V_m = -65 \text{ mV} \]

\[ \log_{10} \left( \frac{350}{4015} \right) = -1.05 \]
Topology of the *Shaker* Potassium Channel Probed with Hydrophilic Epitope Insertions

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Images of purified Shaker potassium channels

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Fig. 2. The purified Shaker protein negatively stained with uranyl acetate. The Shaker protein was oriented predominantly with the four-fold symmetry axis perpendicular to the support film, resulting in a square-shaped appearance. (Bar = 150 Å.)

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Potassium channel

From Wikipedia, the free encyclopedia

In the field of cell biology, potassium channels are the most widely distributed type of ion channel and are found in virtually all living organisms.[1] They form potassium-selective pores that span cell membranes. Furthermore, potassium channels are found in most cell types and control a wide variety of cell functions.[2][3]

Contents

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POTASSIUM CHANNEL STRUCTURES

Senyon Choe

The molecular basis of K⁺ channel function is universally conserved. K⁺ channels allow K⁺ flux and are essential for the generation of electric current across excitable membranes. K⁺ channels are also the targets of various intracellular control mechanisms, such that the suboptimal regulation of channel function might be related to pathological conditions. Because of the fundamental role of K⁺ channels in controlling membrane excitability, a structural understanding of their function and regulation will provide a useful framework for understanding neuronal physiology. Many recent physiological and crystallographic studies have led to new insights into the workings of K⁺ channels.
The four main classes of potassium channels.

a | 2TM/P channels (which consist of two transmembrane (TM) helices with a P loop between them), exemplified by inwardly rectifying K+ channels and by bacterial K+ channels such as KcsA.

b | 6TM/P channels, which are the predominant class among ligand-gated and voltage-gated K+ channels.

c | 8TM/2P channels, which are hybrids of 6TM/P and 2TM/P, and were first found in yeast.

d | 4TM/2P channels, which consist of two repeats of 2TM/P channels. 8TM/2P and 4TM/2P probably assemble as dimers to form a channel. 4TM/2P channels are far more common than was originally thought. These so called ‘leakage’ channels are targets of numerous anesthetics. S4 is marked with plus signs to indicate its role in voltage sensing in the voltage-gated K+ channels.
P LOOP
In an ion channel, the P loop is a short amino-acid segment between two transmembrane helices that dips into the membrane without fully crossing it. The primary sequence of the P loop of K⁺ channels has the signature sequence Thr–Val–Gly–Tyr–Gly.

INWARDLY RECTIFYING K⁺ CHANNELS
Potassium channels that allow long depolarizing responses, as they close during depolarizing pulses and open with steep voltage dependence on hyperpolarization. They are called inward rectifiers because current flows through them more easily into than out of the cell.
There are four major classes of potassium channels:

- **Calcium-activated potassium channel** - open in response to the presence of calcium ions or other signalling molecules.
- **Inwardly rectifying potassium channel** - passes current (positive charge) more easily in the inward direction (into the cell).
- **Tandem pore domain potassium channel** - are constitutively open or possess high basal activation, such as the “resting potassium channels” or “leak channels” that set the negative membrane potential of neurons. When open, they allow potassium ions to cross the membrane at a rate that is nearly as fast as their diffusion through bulk water.
- **Voltage-gated potassium channel** - are voltage-gated ion channels that open or close in response to changes in the transmembrane voltage.

**Crystallographic structure of the bacterial KcsA potassium channel (PDB 1K4C).**

In this figure, only two of the four subunits of the tetramer are displayed for the sake of clarity. The protein is displayed as a green cartoon diagram. In addition backbone carbonyl groups and threonine side chain protein atoms (oxygen = red, carbon = green) are displayed. Finally potassium ions (occupying the S2 and S4 sites) and the oxygen atoms of water molecules (S1 and S3) are depicted as purple and red spheres respectively.
Resting Membrane Potential is Close to $E_k$

- Resting membrane potential is close to $E_k$ because it is mostly permeable to $K^+$
- Membrane potential sensitive to extracellular $K^+$
- Increased extracellular $K^+$ depolarizes membrane potential
- A tenfold change in $[K^+]_o$ from 5 to 50mM, causes a 48mV depolarization of the membrane.
Increasing extracellular $K^+$ from 5mM to 50mM causes a 48mV depolarization.
Regulating the External K Concentration

- **Blood-Brain barrier**
  - Limits the movement of potassium into the extracellular fluid.

- **Potassium spatial buffering**
  - Astrocytes have membrane potassium pumps and channels that concentrate K+ in their cytosol.
Dr. Jack Kevorkian Dies at 83; A Doctor Who Helped End Lives

By KEITH SCHMIDT

Dr. Jack Kevorkian, the medical pathologist who willfully helped dozens of terminally ill people end their lives, becoming the central figure in a national drama surrounding assisted suicide, died on Friday in Royal Oak, Mich. He was 83.

He died at Willow Beaumont Hospital, where he had been admitted recently with kidney and respiratory problems, said Geoffrey N. Davis, the lawyer who represented Dr. Kevorkian in several of his trials in the 1990s.

Mayer Morganthau, a friend and lawyer, told The Associated Press that the official cause of death would most likely be pulmonary thrombosis, a blood clot.

In appealing for the right of the terminally ill to choose how they die, Dr. Kevorkian challenged social taboos about disease and dying while defying prosecutors and the courts. He spent eight years in prison after being convicted of second-degree murder in the death of a woman in his care and the deaths of about 130 other patients whose lives he had helped end, beginning in 1990.

Originally sentenced in 1996 to 15 to 25 years in a maximum security prison, he was released after asserting the authorities that he would never conduct another assisted suicide.

His critics were as impressed as his supporters, but all generally agreed that his stubborn and often interoperative advocacy of assisted suicide helped spur the growth of hospice care in the United States and made many doctors more sympathetic to those in severe pain and more willing to prescribe medication to relieve it.

In Oregon, where a schoolteacher had become Dr. Kevorkian's first assisted suicide patient, state lawmakers in 1997 approved a statute making it legal for doctors to prescribe lethal medications to help terminally ill patients end their lives. In 2008 the United States Supreme Court upheld a lower court ruling that found that Oregon's Death With Dignity Act protected assisted suicide as a legitimate medical practice.

During the period that Oregon was considering its law, Dr. Kevorkian's confrontational strategy gained wide publicity, which he actively sought, national magazines put his picture on their covers, and he drew the attention of television programs like "60 Minutes." His nickname, Dr. Death, and his own-made suicide machine, which he variously called the "Marlboro" or the "Therasaur," became fodder for late-night television comedians.

In 2010 his story was dramatized in the HBO movie "You Don't Know Jack," starring Jack Palance as Dr. Kevorkian. Mr. Palance received Emmy and Golden Globe awards for his performance, in his funny acceptance speech, he said he had been grateful to "try to portray someone so brilliant and interesting and unique" as Dr. Kevorkian.

Dr. Kevorkian, who was in the audience, smiled in appreciation.

Concepts to Remember

- Activity of the sodium-potassium pump
- Large $K^+$ concentration gradient
- Electrical potential difference across the membrane
  - Similar to a battery
- Potassium channels
  - Contribute to resting potential
- Roles of ion pumps
Watch Review Animation-the resting membrane