Lecture 6

Membrane Voltage of a neuron:

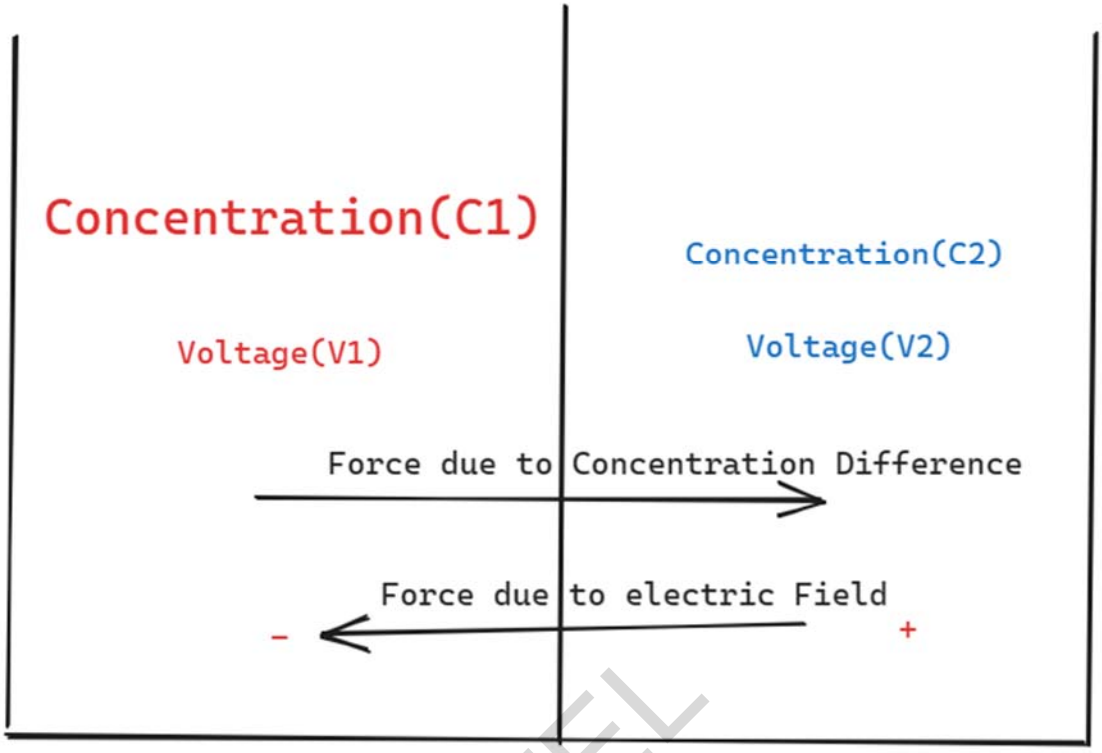
The membrane voltage, also known as the membrane potential, of a neuron refers to the electrical charge difference across the cell membrane of the neuron. It is a key component in the communication between and within neurons, allowing the transmission of signals across the nervous system.

Resting Potential: When a neuron is not transmitting a signal, it's at rest and maintains a resting potential. This is typically -70 millivolts (mV), meaning the inside of the neuron is 70 mV less than the outside. This voltage difference is maintained by ion channels and pumps, particularly those for sodium (Na+) and potassium (K+), in the neuron's membrane. The negative charge is largely due to negatively charged proteins and other molecules inside the cell.

Action Potential: When a neuron is stimulated and the stimulus is strong enough (reaches the threshold potential), an action potential is triggered. Voltage-gated Na+ channels open rapidly, allowing the influx of Na+ due to the concentration gradient, which causes a rapid depolarization (increase in membrane voltage) of the neuron. This causes the inside of the cell to become positively charged compared to the outside.

Signal Transmission: The changes in membrane potential allow the neuron to transmit signals. When an action potential occurs, it propagates down the neuron's axon in a wave-like manner, eventually leading to the release of neurotransmitters at the synaptic cleft, thereby transmitting the signal to the next neuron.

Ions separated by Semipermeable membrane:.



A beaker contains a solution containing ions. The beaker is divided into two parts by a semipermeable membrane. Let the concentrations and voltages be represented by C_i and V_i as shown in the figure.

Due to differences in concentration, ions move from higher concentration regions to lower concentration regions. As more positively charged ions leave the higher concentration side, it becomes negatively charged. While the other side becomes negatively charged. This creates an electric field that causes ions to move in direction opposite to the force due to difference in concentrations.

Mathematically:
Equation for the electrochemical potential on the left-hand side of the membrane (side 1):
$\mu_1 = \mu_1 + CRTlogC_1 + ZFV_1$

Equation for the electrochemical potential on the right-hand side of the membrane (side 2):
$\mu_2 = \mu_2 + CRTlogC_2 + ZFV_2$

Equating the left-hand side and right-hand side electrochemical potentials at equilibrium:
$\mu_1 = \mu_2$

Simplifying the equation at equilibrium:
$RT \log(C_2/C_1) + ZF(V_2 - V_1) = 0$

Rearranging the equation to determine the difference in potential (V□ - V□) at equilibrium:
V□ - V□ = (RT/ZF) log(C□/C□)

Definition of membrane potential (V_membrane or ΔV):
V_membrane = V_in - V_out

Calculation of the equilibrium potential (V_eq) or reversal potential (V_rev) for each ion:
V_eq = (RT/ZF) log(C_out/C_in)

Symbols:
μ (electrochemical potential), μ□ (molar free energy at standard conditions), C (ion concentration), R (ideal gas constant), T (temperature), Z (ion charge), F (Faraday constant), V (membrane potential), C_in (concentration inside the neuron), and C_out (concentration outside the neuron).

Ions in a typical neuron:
In neurons, as well as most other cells, there are different concentrations of ions inside and outside the cell. The concentration gradients of these ions across the cell membrane contribute to the resting membrane potential and also play a key role during the action potential. Here are some points regarding the concentration of various ions and their movements:

1. **Sodium (Na+)**: Sodium ions are more concentrated outside the neuron. Typical concentrations are approximately 10 mM inside and 140 mM outside. Sodium ions tend to flow into the neuron due to their electrochemical gradient when the sodium channels open, such as during an action potential.

2. **Potassium (K+)**: Potassium ions are more concentrated inside the neuron, with typical concentrations of about 140 mM inside and 5 mM outside. Potassium ions tend to move out of the cell when potassium channels open due to their electrochemical gradient. This outward movement of K+ ions is crucial in returning the neuron to its resting potential following an action potential.

3. **Calcium (Ca2+)**: Calcium ions are more concentrated outside the neuron, with a typical concentration of about 1-2 mM outside and 100 nM inside. Calcium ions tend to flow into the neuron when calcium channels open. The influx of calcium ions into the neuron, particularly into the axon terminal, plays a crucial role in the release of neurotransmitters into the synaptic cleft.

4. **Chloride (Cl-)**: Chloride ions are also more concentrated outside the neuron, with typical concentrations of about 110 mM outside and 10 mM inside. Chloride ions tend to move into the cell when chloride channels open. In many neurons, the inward movement of Cl- ions contributes to inhibitory postsynaptic potentials.

Lecture 7

Patch-Clamp Recordings:

1. A micropipette is pressed against a neuron's membrane, creating a seal.
2. The micropipette contains a solution that matches the ion concentration inside the cell.
3. This allows recording of the activity of a single or few ion channels.

Voltage-Clamp Recordings:

1. In a voltage-clamp recording, the voltage across the cell membrane is kept constant or 'clamped'.
2. The clamp is achieved using a feedback amplifier system.
3. Changes in current, or the amount of current needed to maintain the set voltage, are recorded. These changes represent the activity of the ion channels.

Current-Clamp Recordings:

1. In a current-clamp recording, the current injected into a cell is controlled or 'clamped'.
2. The clamp is maintained using an electronic feedback system.
3. Changes in the membrane voltage, or the amount of voltage change in response to the set current, are recorded. This allows for the study of action potentials and other changes in the membrane potential.

Two-photon Calcium Imaging:
Two-photon calcium imaging is a powerful technique used to record neuronal activity

1. Calcium Indicators: Neurons are filled with calcium indicator proteins that can bind to Ca2+. These indicators, such as GCaMP, have fluorescence properties.

2. Neuronal Activity: When a neuron fires an action potential, there's an influx of Ca2+ into the cell. The calcium ions bind to the calcium indicator proteins.

3. Fluorescence Increase: The binding of Ca2+ to the indicator proteins causes them to change shape, which increases their fluorescence.

4. Two-Photon Microscopy: A two-photon microscope is used to excite the fluorescent proteins and capture the emitted light. Two-photon excitation allows for deeper tissue penetration and less phototoxicity compared to one-photon excitation.

5. Measurement and Analysis: The change in fluorescence over time is measured, with increases in fluorescence indicating periods when the neuron was active. This fluorescent activity serves as a proxy for neuronal spiking activity.

Two-photon calcium imaging provides a valuable method for studying neuronal activity, particularly in living, behaving animals, giving insight into the complex workings of the brain.

Non-invasive methods - fMRI, EEG

EEG (Electroencephalography):

1. Non-invasive: EEG is a non-invasive method for recording electrical activity of the brain.
2. Measures Electrical Activity: It uses electrodes placed on the scalp to detect the summed electrical activity of large groups of neurons.
3. Temporal Resolution: EEG has high temporal resolution, meaning it can track changes in brain activity on a millisecond scale.

fMRI (Functional Magnetic Resonance Imaging):

1. Non-invasive: fMRI is also non-invasive and uses magnetic fields and radio waves, not radiation.
2. Measures Blood Flow: It measures brain activity by detecting changes in blood oxygenation and flow that occur in response to neural activity – a method known as Blood Oxygen Level Dependent (BOLD) imaging.
3. Spatial Resolution: fMRI has high spatial resolution, allowing it to pinpoint activity in specific regions of the brain, but its temporal resolution is lower than that of EEG.

In summary, both EEG and fMRI are non-invasive techniques used to measure brain activity. They complement each other as EEG provides high temporal resolution while fMRI offers high spatial resolution.

Lecture 8

Ion channels – Voltage gated and Ligand Gated

- The two main types of ion channels covered in the lecture are voltage-gated channels and ligand-gated channels.
- Voltage-gated channels open and close in response to changes in membrane potential, while ligand-gated channels open and close in response to the binding of specific molecules (ligands) such as neurotransmitters.
- Various examples of ion channels are presented, including voltage-gated sodium, calcium, potassium, and chloride channels, as well as ligand-gated channels such as AMPA receptors, NMDA receptors, GABA receptors, calcium-activated potassium channels, and cyclic nucleotide-gated channels.

Stochasticity and Selectivity of Ion channels

- Conductance of ion channels is stochastic in nature, meaning that the current flowing through them varies between different trials. However, by averaging multiple trials, the overall conductance can be determined.
- Ion channels are typically selective. For example, a sodium ion channel allows only passage of sodium ions, not any other type of ions.

Lecture 9

Types of Synapses:

1. Chemical Synapses: These are the most common type of synapse in the nervous system. At a chemical synapse, the signal (or action potential) arrives at the presynaptic terminal and triggers the release of neurotransmitters into the synaptic cleft. These neurotransmitters bind to receptors on the postsynaptic neuron, causing a change in the neuron's electrical state.

2. Electrical Synapses: In electrical synapses, the pre- and postsynaptic neurons are connected by gap junctions, which allow ions and other small molecules to pass directly from one neuron to the next. This results in near-instantaneous transmission and synchronization of electrical signals across multiple neurons.

Types of Receptors:

1. Ionotropic Receptors: These are also known as ligand-gated ion channels. When a neurotransmitter binds to an ionotropic receptor, it causes an immediate change in the receptor's shape, opening an ion channel and allowing specific ions to flow across the cell membrane. This can cause a rapid change in the neuron's membrane potential.

2. Metabotropic Receptors: Metabotropic receptors, also known as G-protein-coupled receptors, do not have an ion channel. Instead, when a neurotransmitter binds to a metabotropic receptor, it activates an intracellular G-protein. The G-protein can then activate various intracellular signaling pathways, leading to a wide range of effects, which can be slower but longer-lasting compared to ionotropic receptors.

In summary, synapses can be either chemical or electrical, with chemical synapses being more common. Receptors at these synapses can be either ionotropic, resulting in rapid but short-lived responses, or metabotropic, leading to slower but longer-lasting responses.

Post Synaptic Currents and Potentials:

EPSC (Excitatory Postsynaptic Current):

This is the current that flows into a postsynaptic neuron after the activation of excitatory synapses. This typically happens when neurotransmitters, like glutamate, bind to ionotropic receptors and cause an influx of positive ions, such as sodium or calcium. This inward current depolarizes the neuron, or makes it more positive, and thus more likely to fire an action potential. (Note here, that

the current that makes membrane potential positive is inward current, which is denoted by negative sign. It is confusing that negative current increases the voltage of the neuron, but its convention)

EPSP (Excitatory Postsynaptic Potential):
This is the change in membrane potential that results from an EPSC. It's a local depolarization of the postsynaptic membrane caused by the flow of positive ions into the neuron, making the neuron more likely to fire an action potential.

IPSC (Inhibitory Postsynaptic Current):
This is the current that flows into or out of a postsynaptic neuron after the activation of inhibitory synapses. This typically happens when neurotransmitters, like GABA, bind to ionotropic receptors and cause an influx of negative ions, such as chloride, or efflux of positive ions, such as potassium. This current hyperpolarizes the neuron, or makes it more negative, and thus less likely to fire an action potential.

IPSP (Inhibitory Postsynaptic Potential):
This is the change in membrane potential that results from an IPSC. It's a local hyperpolarization of the postsynaptic membrane caused by the flow of negative ions into the neuron or positive ions out of the neuron, making the neuron less likely to fire an action potential.

EPSCs and IPSCs are currents caused by the flow of ions into or out of the neuron following the binding of neurotransmitters to ionotropic receptors, and EPSPs and IPSPs are the resulting changes in the neuron's membrane potential. EPSPs/EPSCs are typically excitatory, meaning they increase the likelihood of an action potential, while IPSPs/IPSCs are typically inhibitory, meaning they decrease the likelihood of an action potential.

Process of Synaptic Transmission:

1. Voltage Generation at the Axon Hillock: The axon hillock is where the action potential is generated. This occurs when the membrane potential at the hillock reaches a certain threshold, primarily due to the influx of positive ions (like Na+) through ion channels.

2. Action Potential Traveling Down: Once the action potential is generated, it travels down the axon as a wave of depolarization. This happens due to the sequential opening of voltage-gated Na+ channels (during the depolarization phase) and K+ channels (during the repolarization phase).

3. Calcium Gates Opening: When the action potential reaches the axon terminal, it causes voltage-gated calcium channels to open. Calcium ions (Ca2+) then flow into the cell due to the concentration gradient.

4. Vesicles Fusing: The influx of Ca2+ triggers the fusion of synaptic vesicles (which contain neurotransmitters) with the cell membrane.

5. Neurotransmitter Release: The fusion of vesicles with the membrane causes the release of neurotransmitters into the synaptic cleft.

6. Attaching to Receptor in Postsynaptic Neuron: The released neurotransmitters diffuse across the synaptic cleft and bind to specific receptors on the membrane of the postsynaptic neuron. Depending on the type of receptor (ionotropic or metabotropic) and the type of ion channel it controls, this will either directly (in the case of ionotropic receptors) or indirectly (in the case of metabotropic receptors) lead to a change in the postsynaptic neuron's membrane potential.

This process of synaptic transmission is fundamental to all communication between neurons in the nervous system.

Lecture 10

Neuroscience Experiments:

Neuroscience experiments often involve the presentation of a specific stimulus such as light, sound, or touch to an experimental subject, which can be a human or an animal. The activity of neurons, usually in the form of action potentials or "spikes," is then recorded using techniques like electrophysiology or imaging. By examining the timing and patterns of these spikes in response to the presented stimulus, researchers can understand how neurons encode information about the external world.

Forward and Backward Problems:

In computational neuroscience, two essential problems are often considered - the forward and the backward problems. The forward problem involves starting with a known stimulus and predicting or modeling the resulting neuronal activity or spiking patterns. It's about understanding how a given input leads to specific responses in the neural system. On the other hand, the backward problem is about reverse engineering - starting with the observed neuronal activity and inferring or modeling the original stimulus or the behavior of the animal. This is usually more challenging due to the intricate dynamics of neuronal responses and the multitude of stimuli that can lead to similar neuronal activity patterns.

Decoding Applications and Forward Problem Significance:

Decoding, which deals primarily with the backward problem, has crucial applications in technologies like brain-computer interfaces (BCIs). In BCIs, decoding algorithms translate

neuronal activity into commands for external devices, which could range from moving a cursor on a computer screen to controlling a prosthetic limb. On the other hand, understanding the forward problem is essential for predicting the behavior of a neural system given new stimuli. It helps guide more efficient experimental designs, as researchers can anticipate system responses without needing to conduct numerous time-consuming experiments. These principles are fundamentally important in the progression of both theoretical and applied neuroscience.