# Neural Communication

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# Neural Communication

## Structure of the Neuron

### Overview

The neuron (nerve cell) is the basic information-processing and transmission unit of the nervous system. There are various forms and types of neurons, defined according to their functions. Most neurons contain several**several** basic components, including the soma, dendrites, axon, and terminal boutons. These components enable the reception, processing, and transmission of neural information.

**Soma**

The soma contains the cell *nucleus* and structures responsible for the life processes of the cell. The shape of the soma varies in different types of neurons. Most molecules essential for the cell's functions are formed within the soma (see also “Internal Structure: The Cell Body”).

**Dendrites**

Dendrites usually appear as branch-like processes extending from the cell soma. The dendrites receive information from terminal boutons of adjacent neurons or from sensory receptors (such as receptors for light, sound, or tactile stimuli). The neural information is transmitted passively through the dendrites until it reaches the soma.

**Nucleus**

The nucleus is a round or oval structure encased in its own membrane. The nucleus contains the nucleolus and the chromosomes, which include the cell's DNA. The DNA carries the organism’s genetic information.

**Axon Hillock**

The *axon* originates out of the soma from a cone-shaped region called the axon hillock. This area, which is rich in sodium channels, is where the action potential develops. From here, the action potential is transmitted along the axon to the terminal boutons.

**Axon**

The axon is a long, thin cytoplasmic branch extending from a cone-shaped region on the *soma* called the axon hillock. The axon usually ends with many branches, and in this way can communicate with many other nerve cells. Axons can be very long relative to their diameter and the size of the soma. For example, the longest axons in the human body are those that connect the toes to the *brain stem*. The action potential develops in the axon hillock and is transmitted along the axon to the terminal boutons at a speed of 1 to 100 meters per second. Once the action potential reaches the terminal boutons, it triggers the release a chemical substance (transmitter), which in turn influences the electrical charge within the neurons adjacent to the boutons.

**Myelin Sheath**

Axons are insulated from each other and from their environment by a myelin sheath. This insulation is vital for rapid and efficient conduction of the *action potential* along the axon. Myelin (80 percent lipids, 20 percent proteins) is formed by certain glia cells (oligodentrites or Schwann cells) and wraps around the axon. Between the segments of myelin are 1–2 micrometer (one-thousandth of a millimeter) of uncoated gaps, known as *nodes of Ranvier*.

**Terminal Boutons**
Terminal boutons are ball-like structures located at the ends of axon branches. These boutons form synapses (junctions) with other neurons. When an action potential reaches the terminal bouton, the bouton secretes a chemical substance (*neurotransmitter*) that excites or inhibits the receiving neuron.

**Synapse**
The synapse is a junction at which the terminal bouton of the sending neuron—the presynaptic *membrane*—passes information to the *soma* or dendrites of a receiving neuron—the postsynaptic membrane. A narrow gap called the synaptic cleft separates the pre- and postsynaptic membranes, through which the neural information is transmitted.

## Internal Structure

### Cell Body

The cell body, or soma, contains the *nucleus* and other structures important for the life processes of the cell. Among these structures are the *Golgi apparatuses* (which prepare substances for secretion out of the cell and pack *transmitters* in synaptic vesicles), mitochondria (which generate energy-rich molecules from nutrients), ribosomes (which serve as the site of cell protein production), and microtubules (which compose part of the cytoskeleton and involved in the intracellular transportation of cell substances).

**Cell Membrane**
The membrane is the envelope that separates the cell and its surroundings. It is made of a double layer of phospholipids, which are molecules with a polarized head and a lipid tail, and protein molecules that have various functions. Some of these proteins are capable of identifying extracellular substances (e.g., *hormones*) and informing the cell interior about their presence. Other proteins transport substances across the cell membrane, into and out of the cell, allowing the entry of certain substances and barring others. There are also proteins that function as *enzymes*.

**Cytoplasm**
Cytoplasm is a semi-liquid gel-like substance that fills the cell space within the membrane. It contains all of the soluble proteins and enzymes, nutrients, *ions*, and cytoskeleton proteins, as well as the nucleus and several other structures with specific functions.

**Nucleus**
The nucleus is a round or oval structure encased in its own *membrane*. The nucleus contains the nucleolus and the chromosomes. The chromosomes consist of DNA

strands and proteins and carry the organism's genetic information.

**Nucleolus**
The nucleolus is located within the nucleus and is the site where ribosomes are produced.

**Ribosomes**
Ribosomes are tiny structures formed within the nucleolus and released into the cytoplasm. Ribosomes function as the site where proteins are synthesized from amino acids according to genetic information carried by messenger RNA (mRNA).

**Mitochondria**
Mitochondria are elliptical bead-like structures surrounded by a double *membrane*. The inner membrane forms a system of folds called cristae, which fill the inside of the mitochondria. The cristae provide surface for the biochemical processes associated with energy production resulting from the breakdown of nutrients (glucose and lipids). The mitochondria produce the energy-rich molecules of adenosine triphosphate (ATP), which are the cell's immediate energy source. Biologists have speculated that ages ago the mitochondria were independent single-cell organisms, which originally invaded larger cells as parasites and lived with them symbiotically. Over the years, the mitochondria have become an integral part of the cell.

**Rough Endoplasmic Reticulum**
The rough endoplasmic reticulum consists of parallel layers of membrane. It forms a network of channels which are involved in protein production and enable the transport of molecules through the cytoplasm. Attached to the outer surface of the rough endoplasmic reticulum are protein-building ribosomes, which give it the rough appearance.

**Smooth Endoplasmic Reticulum**
The smooth endoplasmic reticulum consists of parallel layers of *membrane*. It forms a network of channels that enable the transport and storage of molecules through the cytoplasm and serve as the site of lipid synthesis.

**Microtubules**
Microtubules are cylindrical structures made of long, thin protein fibers found in the cell body and along the *axon*. The microtubules are part of the cytoskeleton that give the neuron its shape. They also serve an important role in the transport of molecules along the neuron. Since the axon does not include *ribosomes*, proteins are mainly synthesized in the soma and transported along the axon to the Terminal Boutons. This *axoplasmic transport* is an active process (requiring energy) performed through the microtubules.

**Golgi Apparatus**
The Golgi apparatus is a structure made of stacked membranes. It serves as a site of assembly, packaging and modifying materials. Molecules produced within the cell (e.g., transmitters) pass through the Golgi apparatus, where they are packed in small *synaptic vesicles* before they are released from the cell. The Golgi apparatus also produces *lysosomes*.

**Synaptic Vesicles**
Synaptic vesicles are tiny storage ”bladders” that contain chemical substances (neurotransmitters). The neurotransmitter is wrapped into vesicles by the Golgi apparatuses either in the cell soma or in the Terminal Boutons. Vesicles produced in the cell body migrate to the Terminal Boutons via the microtubules. When an *action potential* reaches the end of an axon (the terminal bouton), some of the vesicles fuse with the postsynaptic membrane, and their content (the neurotransmitter) is released into the synaptic cleft. This process is called exocytosis.

**Lysosomes**
Lysosomes are membrane-encased structures that look like tiny sacs. They are formed within the *Golgi apparatus* and contain *enzymes* that break down waste or foreign substances that enter the cell. These products are then recycled or excreted from the cell.

**Axon**
The axon is a long, thin cytoplasmic branch extending from a cone-shaped region on the soma called the axon hillock. The axon usually ends with many branches, and in this way can communicate with many other nerve cells. Axons can be very long relative to their diameter and the size of the soma. For example, the longest axons in the human body are those that connect the toes to the *brain stem*. The action potential develops in the axon hillock and is transmitted along the axon to the Terminal Boutons at a speed of 1 to 100 meters per second. Once the action potential reaches the terminal boutons, it triggers the release a chemical substance (transmitter), which in turn influences the electrical charge within the neurons adjacent to the boutons.

**The Axon**

The axon is a long, narrow tube that transmits action potentials from the cell *soma* to the terminal boutons. It is often covered by a myelin sheath. The axon contains various organelles that serve vital cellular functions, including *mitochondria* (which provide the cell with usable chemical energy) and microtubules (which transport molecules along the axon).

**Myelin Sheath**
The myelin sheath is a multi-layer lipid substance. It is wrapped around the axon in segments separated by 1–2 micrometer gaps called nodes of Ranvier. The myelin sheath isolates axons from one another and from their environment, and plays a vital role in the fast and efficient conduction of the action potential along the axon.

**Nodes of Ranvier**
Nodes of Ranvier are the tiny gaps (1–2 micrometers) that separate segments of the myelin sheath. At the nodes of Ranvier, the axon is exposed to the extra-cellular fluid. It is in these ion-channel rich-nodes that the action potential is retriggered.

**Schwann Cells**
Schwann cells are supporting cells found in the peripheral nervous system, where they produce the *myelin sheath* along the axon. Each Schwann cell wraps around a single axon, providing a single myelin segment. Schwann cells also play an important role in the rehabilitation of damaged axons in the peripheral nervous system, by digesting

damaged or dead tissue and guiding the regrowth of axons.

Oligodendrocytes perform the same function in the central nervous system as Schwann cells perform in the periphery. Unlike Schwann cells, however, a single oligodendrocyte sends out a number of myelin branches, which make up several myelin segments on different axons. In this way, a single oligodendrocyte is connected to a number of adjacent axons, thus creating a supportive infrastructure.

**Microtubules**
Microtubules are cylindrical structures made of long, thin protein fibers found in the cell body and along the axon. The microtubules are part of the cytoskeleton that give the neuron its shape. They also serve an important role in the transport of molecules along the neuron. Since the axon does not include ribosomes, proteins are mainly synthesized in the soma and transported along the axon to the terminal boutons. This *axoplasmic transport* is an active process (requiring energy) performed through the microtubules.

**Mitochondria**
Mitochondria are the cell structures that convert nutrients into immediately available energy-rich ATP molecules. Mitochondria can be found along the entire axon. As the transport of molecules along the axon (axoplasmic transport) is an active process requiring energy, the existence of energy-supplying mitochondria along the axon is highly important. Moreover, the mitochondria provide the chemical energy required for maintaining the *resting potential* of the neuron.

**Synaptic Vesicles**
Synaptic vesicles are tiny storage ”bladders” that contain chemical substances (neurotransmitters). The neurotransmitter is wrapped into vesicles by the Golgi apparatuses either in the cell soma or in the terminal boutons. Vesicles produced in the cell body migrate to the terminal boutons via the microtubules. When an *action potential* reaches the end of an axon (the terminal bouton), some of the vesicles fuse with the postsynaptic membrane, and their content (the neurotransmitter) is released into the synaptic cleft. This process is called exocytosis

## The Synapse

The synapse is a junction between the terminal boutons of one neural *axon* (the presynaptic membrane) and the soma or *dendrites* of an adjacent neuron (postsynaptic membrane). Between the pre- and postsynaptic membranes there is a narrow gap called the synaptic cleft. *Neurotransmitter* molecules are released by the presynaptic neuron, cross the synaptic cleft, and bind to *receptors* on the postsynaptic membrane.

**Synaptic Cleft**
The synaptic cleft is the space between the presynaptic and postsynaptic membranes. This gap measures about 20–40 nanometers (one nanometer is a millionth of a millimeter or $10^{-9}$ meters). A *neurotransmitter* is released from the presynaptic membrane into the extracellular fluid of the synaptic cleft, crosses the gap, and binds to receptors on the postsynaptic membrane. This binding causes changes in the ion permeability of the postsynaptic membrane and consequently leads to other changes in the receiving cell.

**Presynaptic Membrane**
The presynaptic membrane is the membrane of the terminal bouton that faces the postsynaptic membrane. It is from this membrane that the *neurotransmitter* is released.

**Postsynaptic Membrane**
The postsynaptic membrane is the membrane of the receiving neuron located on the other end of the *synaptic cleft* (facing the terminal bouton). Most *synapses* are located on the dendrites or *soma* of the receiving neuron.

**Neurotransmitter**
A neurotransmitter (sometimes just called a transmitter) is a chemical substance released from the terminal bouton of the presynaptic neuron into the synaptic cleft. Transmitter molecules bind to receptors on the postsynaptic membrane. There are many types of neurotransmitters within the nervous system.

**Synaptic Vesicles**
Synaptic vesicles are tiny storage ”bladders” that contain chemical substances (neurotransmitters). The neurotransmitter is wrapped into vesicles by the *Golgi apparatuses* either in the cell soma or in the terminal boutons. Vesicles produced in the cell body migrate to the terminal boutons via the microtubules. When an *action potential* reaches the end of an axon (the terminal bouton), some of the vesicles fuse with the postsynaptic membrane, and their content (the neurotransmitter) is released into the synaptic cleft. This process is called exocytosis.

**Golgi Apparatus**
The Golgi apparatus is a stacked-membrane structure found in the cell soma and in terminal boutons, where it serves to package neurotransmitter substance into synaptic vesicles. The Golgi apparatuses in the terminal boutons are particularly efficient in recycling the membrane residue of emptied vesicles to produce new synaptic vesicles.

**Mitochondria**
Mitochondria are the cell organelles that convert nutrients into immediately available energy-rich ATP molecules. Mitochondria are found at the terminal boutons and provide energy for the processes involved in the release of neurotransmitters.

**Microtubules**
Microtubules are cylindrical structures made of long and thin protein fibers found in the cell body and along the *axon*. They serve an important role in the transportation of molecules along the axon. Since the axon does not include ribosomes, proteins are mainly synthesized in the soma and transported along the axon to the terminal boutons. This *axoplasmic transport* is an active process (requiring energy) performed through the microtubules.

**Postsynaptic Receptors**
Receptors are specialized protein molecules in the postsynaptic membrane that bind the *neurotransmitter* released by the presynaptic cell. Receptors for chemical transmitters have a specific recognition site for the transmitter they bind, and they induce changes within the cell either by gating (opening or closing) *ion channels* or

by activating second-messenger cascades (See also animation: Synaptic Transmission: Inhibitory Metabotropic Synapse).

**Transmitter-Dependent Ion Channels**
Transmitter-dependent ion channels are protein molecules in the membrane that permit the flow of ions into and out of the cell. These channels either open or close in response to the binding of neurotransmitter molecules to receptors. In this way they induce changes in the ion permeability of the postsynaptic membrane and consequently lead to a change in the electrical potential of the receiving cell. There are a number of transmitter-dependent ion channels, such as sodium, potassium, chloride, and calcium channels.

**Calcium ($Ca^{2+}$) Channels**
Calcium channels are voltage-dependent channels on the surface of the presynaptic membrane. When these channels open, they allow the rapid flow of calcium ions into the terminal boutons. This flow is necessary for the process of exocytosis, in which a transmitter is released from the synaptic vesicles into the synaptic cleft.

**Vesicle Fusion—The Reuptake Mechanism**
The reuptake mechanism operates in the presynaptic membrane via specific carriers to transport a transmitter from the synaptic cleft into the terminal bouton from which it was released. The reuptake terminates the effect of the released neurotransmitter on the postsynaptic receptors.

# The Membrane Potential

## The Resting Potential

One of the characteristics of cells is their ability to maintain an electrical potential across the cell *membrane*, with the inside of the cell negative relative to the outside. This is called the membrane resting potential. Neurons typically have a resting potential of about -65 mV.
The resting potential is established as a result of the uneven distribution of ions across the cell membrane and the membrane selective permeability to ions. Ionic movement across the membrane is influenced by two forces: the electrical force (determined by the voltage difference across the membrane) and the diffusion force (determined by the concentration difference of ions across the membrane). In the following animation a segment of the membrane is shown, including *ion channels* and a *sodium-potassium pump*. Also shown are two electrodes on the outside and inside of the cell, connected to an oscilloscope, which displays the electric charge across the membrane. The animation consists of five segments.

**Segment 1: Forces Acting on Ions Across the Membrane**
A membrane segment is displayed on the screen, including *ion channels*, a sodium-potassium pump, and dispersed ions on the inside and outside of the cell. The sodium ions, which are positively charged, are attracted by the electrical force into the cell, which is negatively charged. In the resting state, the concentration of sodium ions on the outside of the cell is higher than inside, so sodium ions are also pushed into the cell by the diffusion force. The concentration of potassium ions, by comparison, is higher within the cell than outside, so these ions are pushed toward the outside of the

cell by the diffusion force, while the electrical force attracts them inward. As for organic anions (negatively charged ions), both electrical force and diffusion force act to push them outward; but the membrane is impermeable to these anions, and they cannot leave the cell. Chloride ions carry a negative charge, so the electrical force repels them outward, but their concentration outside the cell is higher than inside, so the diffusion force pushes them inward.

**Segment 2: Measuring the Resting Potential**
When one *electrode* is inserted across the membrane during the resting state, the oscilloscope displays a voltage drop from 0mV to -65mV. This drop represents the voltage difference between the outside and inside of the cell. This is the cell's resting potential.

**Segment 3: Sodium and Potassium Channels**
Two opposing forces act on potassium ions—the diffusion force and the electrical force—both of which are equal when the membrane potential is at -70mV. This is the equilibrium potential of potassium. Because ions can only pass across the membrane through ion channels, and because most of these channels are closed, the membrane permeability to ions during the resting state is low. However, a small number of positive sodium ions gradually leak into the cell through a few open sodium channels and cause the cell to depolarize. This depolarization reduces the electrical force that attracts the potassium ions into the cell, and as a result, potassium ions move out of the cell through potassium channels. Eventually, the membrane potential reaches a new *resting potential*. Because the number of open potassium channels during the resting state is much larger relative to the number of open sodium channels (at a ratio of 40:1), the resting potential of the cell is close to the equilibrium potential of potassium, at around -65mV.

**Segment 4: Sodium-Potassium Pump**
The constant leakage of sodium ions into the cell and of potassium ions out of the cell, if left unopposed, would ultimately reduce the concentration gradients of potassium and sodium ions, reducing the cell's resting potential. The sodium-potassium pump, a protein located in the cell's membrane, maintains the ion concentration gradients, thus preserving the resting potential. The pump operates in two stages:

A. Three sodium ions from within the cell bind to the pump protein. A high-energy phosphate (P) of ATP (adenosine triphosphate) attaches to the pump, triggering ATP breakdown into ADP (adenosine diphosphate) and the release of energy. This leads to a change in the molecular structure of the pump and to the release of sodium ions out of the cell.

B. Two potassium ions from the extracellular fluid bind to the pump protein, triggering the detachment of the phosphate group from the pump. This leads to another change in the structure of the pump and to the release of potassium ions inside the cell.

The process repeats itself.

**Segment 5: Maintaining the Cell's Resting Potential**
The membrane resting potential is a negative value close to the equilibrium potential

of potassium. The electrical and diffusion forces lead to a constant leakage of sodium ions and potassium ions through the few open channels. This leakage is balanced by the dynamic action of the sodium-potassium pump. The pump extrudes sodium from the cell at an average rate equal to the leaking rate of sodium into the cell, and brings in potassium at an average rate equal to the leaking rate of potassium outward. The pump operates against the electrical and diffusion forces and thus requires energy for its operation. The sodium-potassium pump continuously maintains the concentration gradients across the membrane and thus keeps the resting potential at a steady state.

## The Action Potential

The action potential is a brief electrical impulse initiated at the *axon hillock* and propagated to the terminal boutons. It provides the basis for conduction of information along the *axon*. The generation of an action potential depends on the opening and closing of voltage-dependent sodium and potassium *ion channels.* A sodium channel may be in one of three states: closed (rest), open (active), or refractory (nonactive). A potassium channel can be in either one of two states: open or closed.

The animation presents part of an axon hillock membrane with a number of voltage-dependent sodium and potassium channels. An oscilloscope monitor, presented in the upper part of the animation, displays changes in voltage across the axon membrane as a function of time. Changes in membrane potential are presented as varying shades of red at the inside of the membrane. The animation comprises six segments.

**Segment 1: Threshold of Excitation**
When most of the potassium and sodium channels are closed, the membrane of the cell is at a resting potential. When a stimulus excites the cell soma or the dendrites, the inside of the cell becomes depolarized (positively charged), and this depolarization spreads within the cell soma. The greater the excitatory stimulus, the greater the depolarization that develops along the membrane, as represented by a deeper red color inside the membrane. The oscilloscope displays changes in voltage across the axon membrane as a function of time. When the membrane potential reaches the threshold of excitation, voltage-dependent sodium channels in the axon hillock open up in a positive feedback process.

**Segment 2: Opening of Voltage-Dependent Sodium Channels**
Many sodium channels open up and sodium ions rush into the cell. Two strong forces push the sodium ions into the cell: the electrical force (determined by the voltage difference across the membrane) and the diffusion force (determined by the concentration difference across the membrane). The influx of sodium ions leads to a rapid *depolarization* of the membrane. The increased depolarization is represented by an even deeper red color.

**Segment 3: Opening of Voltage-Dependent Potassium Channels**
With the increased depolarization, potassium channels also begin to open, and potassium ions flow out of the cell. When most sodium channels are open and only a few potassium channels are open, the rapid depolarization halts and the membrane potential reaches its peak.. This is represented by the deepest red color.

**Segment 4: Repolarization**

At the peak of the action potential, sodium channels become refractory (nonactivable), and the influx of sodium ions is blocked. At the same time, more potassium channels open up. The electrical force acting on potassium ions is great, as is the diffusion force, thus many potassium ions leave the cell. This leads to a decline in membrane potential (repolarization), as represented by the fading of the red color.

**Segment 5: Hyperpolarization**
As the membrane potential declines, potassium channels slowly begin to close. Since many potassium channels are still open, potassium ions continue to flow out of the cell and the membrane potential declines below its resting value *(*hyperpolarization), as represented by a bluish color.

**Segment 6: Return to the Resting Potential**
Potassium channels continue to close during *hyperpolarization*. When most of the sodium channels have closed through inactivation and most of the potassium channels have also closed, the cell returns to the resting potential. At this stage, the sodium channels shift from a refractory state to a "regular" closed state. This process is termed "recuperation," as represented by disappearance of the bluish color. From their "regular" closed state, sodium channels can once more be activated by depolarization.

## Conduction of the Action Potential

The following animation describes the conduction of an action potential in two types of *axons*: myelinated axons (those covered by a sheath of myelin) and unmyelinated axons (those without a myelin sheath). The animation first presents the conduction of action potentials in an unmyelinated axon, then in a myelinated axon, and finally, in both types of axons simultaneously.

**Segment 1: Conduction in an Unmyelinated Axon**
An action potential, represented by a red strip, spreads from the *axon hillock* (not shown) along the axon. The action potential depolarizes an adjacent axon segment, bringing it above the threshold of excitation. This depolarization leads to the opening of voltage-dependent sodium channels and to regeneration of the action potential in that segment. Since there are sodium channels along the entire length of the axon membrane, the action potential is actively regenerated at every point along the axon. The action potential thus advances toward the terminal boutons at a constant rate.

**Segment 2: Conduction in a Myelinated Axon**
An action potential, represented by a red strip, spreads from the axon hillock (not shown) along the axon. When the depolarization reaches a node of Ranvier, where the axon is exposed to the extracellular fluid and is rich with voltage-gated sodium channels, the action potential is regenerated. It then continues along the myelin-covered segments via passive conduction, as the myelin insulates the axon and prevents the generation of action potentials. The depolarization moves along the myelinated segments in a fast but decaying fashion. Thus, action potentials advance via saltatory conduction, actively regenerated at each node of Ranvier, while conduction between the nodes is passive.

**Segment 3: Comparison Between Conduction in Myelinated and Unmyelinated Axons**

When conduction in the two types of axons is compared, saltatory conduction in myelinated axons is up to 15 times faster than in unmyelinated axons, as a result of the passive conduction along the myelinated segments. Saltatory conduction is also more efficient; since less sodium enters the axon in its myelinated segments, less energy is required to maintain the sodium balance (by the *sodium-potassium pumps*). The depolarization in both types of conduction proceeds in one direction—from the *soma* to the terminal boutons. As the sodium channels in the segments where the action potential has just passed are in a refractory state, no action potential can be generated in those segments.

# Synaptic Transmission

## Excitatory Ionotropic Synapse

The animation presents a synapse with presynaptic *terminal bouton*, postsynaptic membrane, and the *synaptic cleft* in between. Synaptic vesicles are "docked" to the presynaptic membrane. The animation shows how an action potential moves along the axon, reaches the terminal bouton, and induces the release of *neurotransmitter* molecules into the synaptic cleft. The neurotransmitter molecules bind to ionotropic *receptors* (receptors that gate *ion channels* directly), and excite the postsynaptic membrane. The animation is comprised of four segments.

**Segment 1: Presynaptic Processes**

The action potential reaches the end of the axon and *depolarizes* the presynaptic membrane. This process is represented by red dots spreading in the terminal bouton. This depolarization of the terminal bouton causes voltage-dependent calcium channels to open. Calcium ions flow into the cell and diffuse to the presynaptic membrane, where the synaptic vesicles are docked.

**Segment 2: Neurotransmitter Release**

Calcium causes synaptic vesicles (in this case, vesicles filled with the neurotransmitter *acetylcholine*) to fuse with the presynaptic membrane. Following this fusion, the vesicles release the neurotransmitter into the synaptic cleft through a process termed *exocytosis*.

**Segment 3: Excitatory Postsynaptic Potential (EPSP)**

The acetylcholine molecules diffuse across the synaptic cleft and bind to a specific type of ionotropic receptor, *nicotinic receptors*, in the postsynaptic membrane, leading to the opening of transmitter-dependent sodium channels. Positively charged sodium ions flow into the cell and induce an *excitatory postsynaptic potential (EPSP)*, represented by the red color in the postsynaptic membrane. Acetylcholine detaches from the receptors and is split into its constituents, acetate and choline, by the enzyme *acetylcholinesterase (AChE)*. This inactivation terminates the postsynaptic potential. The choline is then carried into the presynaptic membranes by special transporters and recycled into acetylcholine molecules in the cell soma.

**Segment 4: Docking of Synaptic Vesicles**

Synaptic vesicle docking sites become available inside the presynaptic membrane. At the same time, calcium continues to diffuse within the terminal bouton, leading to the

release of vesicles from the *microtubules*. The vesicles migrate in the direction of the presynaptic membrane and bind to the docking sites.

## Inhibitory Ionotropic Synapse

The animation presents a synapse with presynaptic *terminal bouton*, postsynaptic membrane, and the synaptic cleft in between. Synaptic vesicles are "docked" to the presynaptic membrane. The animation shows how an action potential moves along the axon, reaches the terminal bouton, and induces the release of *neurotransmitter* molecules into the synaptic cleft. The neurotransmitter molecules bind to ionotropic receptors (receptors that gate ion channels directly), and inhibit the postsynaptic membrane. The animation is comprised of four segments.

### Segment 1: Presynaptic Processes

The *action potential* reaches the end of the axon and depolarizes the presynaptic membrane. This process is represented by red dots spreading in the terminal bouton. This depolarization of the terminal bouton causes voltage-dependent calcium channels to open. Calcium ions flow into the cell and diffuse to the presynaptic membrane, where the synaptic vesicles are docked.

### Segment 2: Neurotransmitter Release

Calcium causes synaptic vesicles (in this case, vesicles filled with the *neurotransmitter* GABA) to fuse with the presynaptic membrane. Following this fusion, the vesicles release the neurotransmitter into the synaptic cleft through a process termed exocytosis.

### Segment 3: Inhibitory Postsynaptic Potential (IPSP)

The GABA molecules diffuse across the synaptic cleft and bind to to a specific type of ionotropic receptor, $GABA_A$ receptors, in the postsynaptic membrane, leading to the opening of transmitter-dependent chloride channels. Negatively charged chloride ions flow into the cell and induce an *inhibitory postsynaptic potential* (IPSP), represented by the blue color in the postsynaptic membrane. The transmitter detaches from the receptors and is removed from the synaptic cleft by the *reuptake* process, carried into the presynaptic membrane by special transporters. This reuptake process closes the chloride channels.

### Segment 4: Docking of Synaptic Vesicles

Synaptic vesicle docking sites become available inside the presynaptic membrane. At the same time, calcium continues to diffuse within the terminal bouton, leading to the release of vesicles from the *microtubules*. The vesicles migrate in the direction of the presynaptic membrane and bind to the docking sites.

## Inhibitory Metabotropic Synapse

The animation presents a synapse with presynaptic terminal bouton, postsynaptic membrane, and the *synaptic cleft* in between. *Synaptic vesicles* are "docked" to the presynaptic membrane. Shown on the postsynaptic membrane are a receptor, a G protein, the enzyme adenylate cyclase, and a transmitter-dependent potassium channel. Within the postsynaptic membrane the enzyme protein kinase and an ATP molecule are shown. The animation describes an inhibitory synapse, wherein the binding of the transmitter to the postsynaptic metabotropic receptor leads to the opening of potassium channels indirectly via a second messenger. This animation is

comprised of three segments.

**Segment 1: Presynaptic Processes**
The *action potential* reaches the end of the axon and depolarizes the presynaptic membrane. This process is represented by red dots spreading in the terminal bouton. This depolarization of the terminal bouton causes voltage-dependent calcium channels to open. Calcium ions flow into the cell and diffuse to the presynaptic membrane, where the synaptic vesicles are docked.

**Segment 2: Neurotransmitter Release**
Calcium causes synaptic vesicles (in this case, vesicles filled with the *neurotransmitter* GABA) to fuse with the presynaptic membrane. Following this fusion, the vesicles release the neurotransmitter into the synaptic cleft through a process termed *exocytosis*.

**Segment 3: IPSP in a Metabotropic Synapse**
A.The GABA molecules diffuse across the synaptic cleft and bind to a specific type of metabotropic receptor, $GABA_B$ receptors, in the postsynaptic membrane. This binding alters the structural confirmation of the receptor, exposing a binding site for a G protein.

B.G protein attaches to the receptor, leading to the replacement of a GDP by a GTP molecule. A subunit of the G protein dissociates from it, binds to the adenylate cyclase enzyme, and activates it.

C.The activation of adenylate cyclase produces many molecules of cyclic-AMP (cAMP) from ATP. Cyclic-AMP binds to the *enzyme* protein kinase, liberating the catalytic subunits. These subunits bind to a transmitter-dependent potassium channel, causing it to open.

D.Positively charged potassium ions flow out of the cell, leading to the development of an IPSP, as represented by the blue color.

E.The transmitter detaches from the receptors terminating this series of events. The proteins return to their original conformation, and the potassium channels close.

## Neural Integration

The animation presents a simple neural network made up of three neurons (marked 1, 2, and 3) that form synapses with a single target neuron. An additional axon (marked 4) forms a synapse with the terminal bouton of neuron 3. Depolarization (action potential or EPSP) is represented by red dots, whereas hyperpolarization (IPSP) is represented by blue dots. This simple network is used to demonstrate the process of neural integration.

**Segment 1: Excitatory Synapse**
An *action potential* (red dots) moves from the soma of the activated cell (2), via the axon, to the *terminal bouton*. The depolarization reaches the terminal bouton, leading to transmitter release and to an *excitatory postsynaptic potential* (EPSP) in the soma of the target cell. The depolarization spreads passively, in a decreasing fashion, within

the target cell until it reaches the *axon hillock*. When the depolarization at the axon hillock is lower than the excitation threshold, an action potential is not generated, and resting potential is resumed.

**Segment 2: Temporal Summation**
Successive activation of neuron 2 at short intervals brings to summation the excitation (EPSPs) in the target cell, a process known as temporal summation. If at a given moment the depolarization at the axon hillock exceeds the excitation threshold, an action potential is generated and travels along the axon to the terminal boutons of the target cell.

**Segment 3: Spatial Summation**
Action potentials arrive from neurons 1 and 2 at lengthy intervals. The EPSP induced by neuron 1 diminishes before the excitation induced by neuron 2 arrives, and no action potential is generated. When both neurons simultaneously excite the target cell, the excitation builds up, a process known as spatial summation. If at a given moment the depolarization at the axon hillock exceeds the excitation threshold, an action potential is generated and travels along the axon to the terminal boutons of the target cell.

Note that the animation describes the basic process of neural integration, whereas in reality the process of temporal and spatial summation is far more complex. Hundreds of excitatory and inhibitory synapses converge on a single cell, and it is neural integration that determines the firing rate of the target neuron.

**Segment 4: Inhibitory Synapse**
An action potential arrives from neuron 3, reaches the terminal bouton, and releases a neurotransmitter, which in turn leads to inhibitory postsynaptic potential (IPSP) in the target cell. The hyperpolarization (blue dots) spreads passively along the target cell until it reaches the axon hillock. As the negative charge causes the cell to hyperpolarize, the cell membrane potential declines further from the excitation threshold.

**Segment 5: Temporal and Spatial Summation**
Action potentials simultaneously arrive from an excitatory neuron 1 and an inhibitory neuron 3. The excitatory potential (red dots) merges with the inhibitory potential (blue dots), so that the membrane potential remains unchanged.

An *action potential* arrives from neuron 3 and causes the target cell to hyperpolarize. When the membrane voltage begins to return to its resting potential, excitation stimuli are simultaneously triggered by cells 1 and 2. The temporal and spatial summation of these sub-threshold potentials initiate an action potential in the axon hillock of the target cell.

**Segment 6: Presynaptic Inhibition**
In addition to excitatory and inhibitory *synapses* along the cell *soma* and dendrites, there are also axo-axonic synapses. In this type of synapse, the terminal bouton of one axon (4) synapses on the terminal bouton of another cell (3), which synapses on the target cell. The potential arriving at terminal bouton 4 leads to an inhibitory postsynaptic potential (IPSP) in axon 3. An action potential moving down axon 3

reaches the hyperpolarized area and dissipates. This prevents the release of the *transmitter* from the terminal bouton of cell 3 to the target cell.