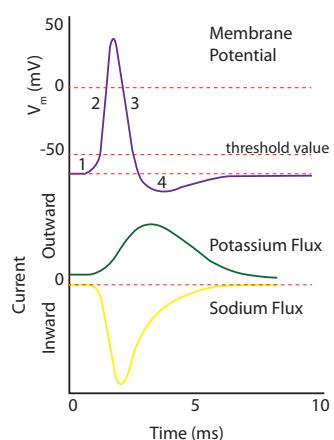


# NERVOUS SYSTEM PHYSIOLOGY 1

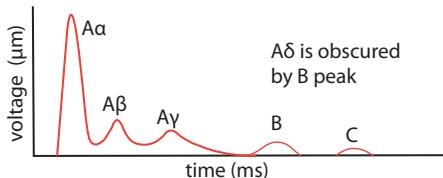
Neurons have two characteristic structural and functional features: an **excitable membrane**, and synapses. Excitability means the ability of neurons to generate and propagate stereotyped electrical impulses (action potentials). This is a feature which is also shared with muscle and some endocrine cells but it is most highly developed in neurons. The **action potential** is the primary means of communication in the nervous system. **Synapses are specialised points of communication** that allow neurons to communicate with each other. Neurons are organised such that dendrites collect input from other neurons, primarily through synapses, whereas axons transmit output from the cell body or soma to other neurons. The soma (body) contains the nucleus and the protein synthesis machinery for the cell.

**Resting membrane potential** is a fundamental and essential property of all cells. The membrane potential is an electrical gradient that results from the differences in concentrations of charged organic and inorganic ions across the cell membrane. For most mammalian cells the resting membrane potential is negative to the outside, usually  $-60$  to  $-70$  mV. The predominant ions involved are **organic anions and  $K^+$  inside the cell and  $Na^+$  and  $Cl^-$  on the outside**. These ions have two driving forces, the **concentration gradient** and the **electrical gradient**. The distribution of ions across the cell will equal equilibrium when these two forces are balanced. This relationship was first described by Nernst in 1888. It is represented by the **Nernst equation**,  $E = (RT/zF)\ln([ion_{outside}]/[ion_{inside}])$  where  $E$  is the Nernst potential,  $R$  is the gas constant,  $T$  is the temperature in Kelvins,  $z$  is the valence of the ion and  $F$  is faraday's constant. This can be simplified, if the ion is **single valence** ( $K$ ,  $Cl$ ,  $Na$ ) then the first part of the equation can be **simplified to 58**. Therefore it is possible to calculate the Nernst potential for these important ions.  $E_{potassium} = 58\log_{10}(4/140) = -90$ ,  $E_{chloride} = -58\log_{10}(116/4) = -85$ ,  $E_{sodium} = 58\log_{10}(145/12) = 65$ . This introduces a new concept which is **selective permeability**. The Nernst potential for potassium and chloride is similar to the resting membrane potential, and this is consistent with the fact that the cell membrane is highly permeable to these ions. The sodium potential is vastly different to the RMP and it follows that the cell membrane is not permeable to this ion (otherwise the RMP would become more positive). **Two key elements establish and maintain the membrane potential**; **cell membrane channels** which are **selectively permeable to ions** and **cell membrane pumps** which **actively transport charged particles against electrochemical gradients**. There is a slight permeability to sodium but the  $Na.K$ .ATPase pump ensures that the RMP does not become more +

**Action potentials**. All animal cells have a resting potential, ion pumps and a membrane which can act to conduct an electrical signal. What distinguishes neurons (and to a less extent muscles and endocrine cells) is their **excitability**. Excitability is the **ability of a cell to generate and propagate a large, rapid potential change** in response to a relatively **small trigger stimulus**. The central phenomenon of excitability is the action potential. The **actional potential** is a very **rapid, stereotyped** event, a coordinated **sequence** of several processes which leads to a **propagation** of signal along the axon **without decrement** which unlike passive conduction is **self regenerating**. The actional potential has **several characteristics** that are important for its information carrying behaviour. The first of these characteristics is **threshold behaviour**, which states that at a certain point (threshold) sodium channels initiate a positive feedback mechanism which is self sustaining and regenerative. The second characteristic is **all or none behaviour** and is closely related to the threshold characteristic. It states that a signal will continue undiminished as long as there are sodium channels to propagate it. The final characteristic is a **refractory period**. This is a short period of time following propagation where there cannot be an immediate repolarisation. A consequence is that if two signals are travelling towards each other they will be unable to pass and cancel each other out, terminating both signals. The action potential **depends on voltage gated ion channels** that respond to changes in membrane potential by opening or closing. Although there are many channels involved in the generation of the action potential there are only **two key participants**, the **sodium channels** and the **potassium channels**. **Phase one** is characterised by an **influx of sodium ions** until the neuron reaches the **threshold value** which is variable based on the RMP, the recent activity and the rate of depolarisation but **often** is assumed to be  $-55$  mV. Following threshold value being reached there is a **positive feedback mechanism** which leads to the all or nothing event where **sodium rushes into the cell (Phase 2)**. Shortly following the initiation of the action potential **potassium channels (delayed rectifier)** permit a potassium **efflux** (as there is now a large difference in the Nernst potential for potassium, this, coupled with the closing of the sodium channels leads to a **rapid repolarisation (Phase 3)**. **Phase 4** represents an **overshoot** before a **return to the RMP**.

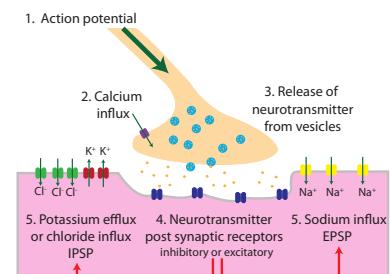


Fibre	Function	Diameter ( $\mu m$ )	Velocity ms $^{-1}$
A	Skeletal motor, joint position	10-20	60-120
	Touch, Pressure	5-10	40-70
	Muscle spindle, motor	3-6	15-30
	$\delta$ Pain, temp, touch	2-5	10-30
B	Preganglionic autonomic	1-3	3-15
C	Pain	0.5-1	0.5-2



**Axonal conduction** repeats the **same events as described above**. The inward sodium current depolarises the membrane, and this is propagated along the membrane. Unlike a **normal electrical signal** which decays, an **action potential maintains its size and shape** and will conduct unchanged along a neuron for a theoretically indefinite distance. Whilst the size of the action potential is constant, the **rate of transfer varies** greatly according to the characteristics of the axon. **Channel opening speed, ECF composition and temperature** all increase conduction speed. The **most important factors** however in terms of conduction velocities is **axon diameter** and the **presence of myelin**. Myelin is a tight spiral wrapping of glial cells around an axon, which is **usually evenly spaced** with **nodes of Ranvier**. These are characterised by a high concentration of sodium channels, action potentials will **skip along** the axon from node to node, increasing velocity. The relative conduction velocities are used to classify nerve axons. **Myelinated A fibres are the fastest** and these are further subclassified according to their width (and therefore conduction velocity) into four subcategories. B fibres are present in the autonomic nervous system. **Unmyelinated C fibres are the slowest fibres** and have the smallest diameters. Peripherical nerves contain a mixture of these fibres and nerve conduction studies will demonstrate this by recording a series of peaks in the **compound action potential** which is shown in the adjacent diagram.

**A synapse** is the **anatomical site** where **nerve cells communicate** with other nerves, muscle and glands. There are **two types** which have been identified, either a **chemical** or **electrical synapse**. In electrical synapses, the membranes of the presynaptic and postsynaptic neurons come close together, and gap junctions form between the cells. Like the intercellular junctions in other tissues, these junctions **form low-resistance bridges** through which ions can pass with relative ease. **Electrical synapses** may be found at the **dendritic sites of contact** that synchronise neuronal activity, but are **generally quite rare** in mammalian cells. Synaptic transmission **usually** occurs via **chemical neurotransmitters**. At chemical synapses, a **synaptic cleft** separates the terminal of the presynaptic cell from the postsynaptic cell. An impulse in the presynaptic axon causes secretion of a chemical that diffuses across the synaptic cleft and binds to receptors on the surface of the postsynaptic cell. This triggers events that open or close channels in the membrane of the postsynaptic cell.



**Neurotransmitters** are chemical mediators that are **released into the synaptic cleft** in response to the arrival of an **action potential at the nerve ending**. The release of all neurotransmitters is **voltage dependent** and **requires the influx of calcium ions** into the presynaptic terminals (see also full AI on neurotransmitters). Neurotransmitters may be **excitatory or inhibitory**, depending on the configurational change produced in the protein receptor by its interaction with the neurotransmitter. At the **inhibitory synapses**, a neurotransmitter **increases the permeability** of postsynaptic receptors to **potassium and chloride ions**. Receptors responding to inhibitory neurotransmitters are associated with protein channels that are too small to allow the passage of larger hydrated sodium ions. The predominant outward diffusion of potassium ions increases the negativity of the resting transmembrane potential, and the neuron is **hyperpolarized**. This is called a **inhibitory post synaptic potential or IPSP**. The permeability changes evoked by **excitatory neurotransmitters** allow **sodium influx** and thereby **decrease the negativity of the resting transmembrane potential**, bringing it **near threshold** potential. This is known as the **excitatory post synaptic potential or EPSP**. **Glutamate** (major **excitatory** amino acid neurotransmitter in the CNS; glutamate receptors [includes N-methyl-D-aspartate receptors] are ligand-gated ion channels.)  **$\gamma$ -Aminobutyric acid (GABA)** (major **inhibitory** neurotransmitter in the CNS; when two molecules of GABA bind to the receptor, the chloride ion channel opens and allows chloride ions to flow into the neuron causing it to become hyperpolarized.) **Acetylcholine** (**excitatory** neurotransmitter that interacts with muscarinic and nicotinic receptors in the CNS; contrasts with the **inhibitory** effects [increased potassium permeability] on the **peripheral parasympathetic nervous system**.) **Dopamine** (high concentrations are present, especially in the basal ganglia; most likely it is an **inhibitory** neurotransmitter.) **Noradrenaline** (neurons responding to noradrenaline send **predominantly inhibitory** impulses.) **Glycine** (principal **inhibitory** neurotransmitter in the **spinal cord**.) **Substance P** (**excitatory** neurotransmitter presumed to be released by terminals of pain fibers that synapse in the substantia gelatinosa of the spinal cord.) **Endorphins** (**excitatory** neurotransmitters for descending pathways that inhibit the transmission of pain.) **Serotonin** (**inhibitory** neurotransmitter exerting profound effects on mood and behavior.)