# The action potential and nervous conduction

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**The nature of an action potential.**

An excitable cell is one that is able to generate an action potential, a transient depolarisation of the membrane potential from the resting state, where the inside of the cell is negative with respect to the outside, to one when it is transiently positive. The duration of this change of state may be about a millisecond in nerves or skeletal muscle cells to several hundred milliseconds, as occurs in myocardium for example. From the beginning of the $20^{th}$ century action potentials were investigated in a wide variety of animal, and even plant, cells. Figure 1 shows examples recorded from different mammalian nerve and skeletal muscle fibres: they show a variety of morphologies, especially in the terminal phase. The figure also contains useful terminology. In these tissues several consistent features of the action potential were observed, these include:

- a rapid upstroke (or depolarising) phase with an 'overshoot', where the membrane potential actually exceeds the zero value for a transient period.
- in a given cell the amplitude of the action potential is always same – the all-or-none law.
- when the action potential propagated along the cell, its amplitude always remained the same.
- $Na^+$ were crucial in the generation of an action potential

**Functions of action potentials.**

Action potentials support two important functions in different cells:

- they convey (propagate) information between and along excitable cells – a process known as conduction
- they initiate cellular events

Conduction is important to co-ordinate the activity of different cells, or to convey information between the different ends of the same cell. An example is conduction of an action potential along an afferent nerve from its origin by a sensory cell to the central nervous system where the information is processed. Information is coded by altering the frequency of action potentials, a greater frequency generally indicates a more intense stimulus in this example. Another example is

the rapid transmission of action potentials between different myocardial cells during the excitatory phase of the cardiac cycle, the co-ordinated excitation of all cells in the ventricle, say, ensures that it contracts as a single entity.

Numerous examples exist of how action potential initiate cellular events. At the neuromuscular junction (see article in this issue) the generation of an action potential in the skeletal muscle fibre initiates muscle contraction through a process known as excitation-contraction coupling.

**The ionic basis of membrane and action potentials.**

**The use of the Nernst equation.** Biological membranes exhibit a property of semi-permeability towards ions; that is some ions readily cross the membrane whereas others less so. For the purpose of this discussion, and without too great a loss of generality, we need only to consider the important monovalent cations, $Na^+$ and $K^+$. In the resting state, excitable cells such as nerves are permeable to $K^+$ but much less so to $Na^+$. One consequence of this property is that there is an asymmetric distribution of ions between the inside and outside of the cell, with the intracellular compartment having a much greater $[K^+]$ than the extracellular space, with the opposite distribution for $Na^+$ (see figure 2A). The reasons for this asymmetric distribution of $K^+$ and $Na^+$ are due to physical chemistry principles (the Donnan equilibrium) and the presence of an ATP-consuming $Na^+$-$K^+$ ATPase (Na pump) in the membrane. The details need not concern us at present but the interested reader is referred to reliable textbooks of physiology.

Biological membrane potentials result from the asymmetric distribution of permeable ions; in the resting state of a nerve membrane the relevant ion is $K^+$. The value of $E_m$ depends only on the $K^+$ concentration gradient across the cell membrane and is embodied in the Nernst equation (figure 2A).

The important point is that the equation predicts a negative value for $E_m$ because the extracellular $[K^+]$ is smaller than the intracellular $[K^+]$. This predicted value is called the equilibrium potential for $K^+$, $E_K$, the calculation is shown in the box at the lower left of figure 2A

In fact we can turn the argument on its head: by experiment we can measure the value of $E_m$ and find that it has a negative value. Therefore we can deduce that the membrane is permeable more to $K^+$ than $Na^+$.

Appreciation of the Nernst equation is also useful to understand how changing the extracellular $K^+$ affects excitable cells. If the $[K^+]$ is raised (hyperkalaemia) the value of $E_m$ becomes less negative (depolarises) with consequences as we shall see later for cellular excitability.

**The ionic basis of the action potential.** The observation that the action potential 'overshoots' the zero level is now of interest, coupled with a second property that the value of the overshoot potential is a fairly constant – the all-or-none law. If we return to the Nernst equation and insert he values of the intracellular and extracellular $[Na^+]$ to calculate the value for $E_{Na}$, we find it has a positive value (figure 2A). Thus, the calculated value of $E_{Na}$ and the measured value of the overshoot potential are both positive. In biophysical terms we can say that at the peak of the action potential the value of $E_m$ approaches $E_{Na}$. Because the Nernst equation is relevant only to permeable ions we can again deduce that at the overshoot the membrane transiently becomes permeable to $Na^+$.

This deductive approach allows us to understand the nature of an action potential. During the resting phase the membrane is more permeable to $K^+$ than $Na^+$, the value of $E_m$ is negative, near to the value of $E_K$. The depolarising phase of the action potential is due to the fact that the membrane now becomes more permeable to $Na^+$ and $E_m$ approaches the value of $E_{Na}$. This however, is only transient as membrane repolarisation refers to the return of the membrane to a predominantly $K^+$-permeable state.

This explanation of the ionic basis of the action potential was demonstrated by Hodgkin, Huxley and Katz with experiments using the giant nerve axon from a squid and published in the early 1950s. They showed that depolarisation is indeed accompanied by a rapid but transient influx of $Na^+$, as would be expected if the membrane became suddenly permeable to the ion. Repolarisation was accompanied by an efflux of $K^+$, as the increase of $Na^+$ permeability was transient and the cell then reverted to the $K^+$-permeable state. Note that they, and subsequent researchers, refer more precisely to changes of membrane conductance, $g$, to different ions rather than changes to membrane permeability, thus we speak about an increase of $Na^+$ conductance, $g_{Na}$, and $K^+$ conductance, $g_K$, during the depolarising and repolarising phases of the action potential. If an ion has a greater membrane conductance, it means it can flow more readily across the membrane. The ionic basis of the action potential is summarised in figure 2B. Note that very small amounts of $Na^+$ and $K^+$ cross the membrane during an action potential. At its termination the $Na^+$ that flowed into the cell is ejected by the Na-pump, expelling $Na^+$ against an energy gradient and thus consuming ATP, the $K^+$ can passively diffuse back into the cell.

**Ion channels**

We understand a great deal more now about the membrane properties that allow ion movements across the lipid membrane. Ions traverse the membrane through ion channels. In principle most ion channels can be opened by two mechanisms:

- a change of membrane potential (voltage-gated ion channels)
- binding of a ligand to the ion channel or associated protein.

In nerves and skeletal muscle most ion channels are voltage-gated (but see *Synaptic Transmission* below). When the membrane is depolarised from the normal resting potential by a stimulus, towards a threshold value $Na^+$ channels open, and the consequent $Na^+$ influx continues the depolarisation. At the peak of depolarisation the $Na^+$ current inactivates (the ion channels tend to close more readily)

and certain $K^+$ channels open so terminating the action potential. The process is therefore self-limiting and so the change of membrane potential is transient.

Although voltage-gated ion channels form a super-family of related structures, their differences may be exploited. In particular specific modulators of different ion channels are known, including the ability of local anaesthetics, such as procaine and lignocaine, as well as neurotoxins, such as tetrodotoxin, to block $Na^+$ channel function, and hence initiation of the action potential.

**Factors affecting action potential initiation**

**Threshold:** The generation of an action potential requires that the resting membrane is depolarised towards a threshold value. Then voltage-gated $Na^+$ channels open and initiate the self-regenerative phase of the upstroke through influx of $Na^+$ further depolarisation. Factors that facilitate this process will render the system more excitable and *vice versa*.

Modest hyperkalaemia (<8-10 mM) will depolarise the cell and so tend to make it more excitable, as smaller external stimuli are required to further depolarise the cell to the threshold value. Hypokalaemia will have the opposite effect.

Hypercalcaemia tends to move the threshold for $Na^+$ channel opening to a more depolarised level, thus decreasing excitability, whilst hypocalcaemia renders cells more excitable. The latter is manifest as tetany, due to an increased excitability of the neuromuscular system. Similar directional changes to the extracellular [Mg] exert equivalent effects on membrane excitability. It is believed that these divalent cations hinder the opening of $Na^+$ channels and a larger depolarisation is required when their concentrations are raised.

**Refractoriness**: while the cell membrane is undergoing an action potential, it is impossible to generate a second no matter the strength of the stimulus – the absolute refractory period. This is because it is necessary to return the membrane to the resting state before $Na^+$ channel opening is

again possible. Immediately after repolarisation a second action may be elicited, but a larger-than-normal stimulus is required - the relative refractory period. The absolute refractory period puts an upper limit to the frequency of action potential generation. The relative refractory period is however a very important feature of information transfer. If a large stimulus during the relative refractory period a second action potential may be elicited, whilst a smaller stimulus may be unsuccessful. In this way stimulus strength has been decoded to a frequency-dependent signal. This has several implications: in synaptic transmission this is the principle of summation (see below), in the sensory system the magnitude of a sensory cell response is decoded into a frequency dependent signal in the afferent nerve. These periods are illustrated in figure 3.

**From the resting state to threshold:** there are in principle a number of ways in which the membrane potential may be depolarised from the resting state to the threshold potential

- Pacemaker cells spontaneously depolarise the membrane to the threshold value, e.g in the sino-atrial node of the heart.
- Depolarisation can occur from excitatory transmitters binding to the postsynaptic membrane (see below and the following article on neuromuscular transmission)
- An artificial stimulus may be applied, as may occur in the laboratory or the emergency room
- A depolarising stimulus can arise from another part of the same cell (a local circuit current).

The final situation leads to a consideration of how action potentials can propagate along an axon or skeletal muscle fibre without decrement; at its basis is the local circuit hypothesis.

**Conduction of the action potential**

Figure 4A shows a schematic diagram of a nerve axon, represented as a tube filled with an aqueous ionic solution, the cytoplasm. The cytoplasm is separated from a second ionic solution, the extracellular space, by an electrically insulating cell membrane. The process of conduction ca be considered in a series of steps associated with the accompanying diagrams.

i). The inside of the unstimulated cell is at a negative potential with respect to the extracellular space, the resting potential.

ii). An action potential is generated in a section of this axon (at left depicted here) – through stimulating processes described above. The action potential may be represented by a change of membrane polarity, from the normal inside-negative to an inside-positive condition. The small circle in the diagram represents the membrane potential immediately in front of the action potential, and is still at the resting level (see action potential trace on the right also).

Because the cytoplasm is an ionic solution, and so conducts electricity, a small electrical current will flow between the regions of different polarity – we can think of it as positive current passing from the active (action potential) to the resting region – this is called local circuit current.

iii). This current will depolarise the resting region of the cell membrane, especially the region immediately adjacent to the action potential where the current density is greatest. Note that the electrical circuit has to completed by a corresponding current in the extracellular fluid.

iv). If this local circuit current is great enough it will depolarise the resting region of the membrane to threshold and initiate an action potential in this region – the action potential has propagated along the axon.

v). The action potential in the new region then acts as a new source of local current and thus it propagates along the fibre.

Apart from the small local circuits nothing actually flows along the axon – it is an example of a standing wave propagating along the axon, much as a wave will propagate along a piece of string if oscillated at one end.

What stops the action potential from then activating the region just behind the conducting wavefront and so propagating backwards? Refractoriness saves the situation, as this region will be at least relatively refractory and so forward conduction is easier.

In certain cell types intracellular local circuit current can even cross from one cell to another through low resistance connections that link the cytoplasm of two adjacent cells - gap junctions. This is best exemplified in myocardium where the gap junctions are concentrated at intercalated disks. This tissue behaves as a functional synctium of cells, an action potential generated in one region will spread throughout the tissue mass.

**Factors affecting conduction velocity**

Action potentials propagate along excitable cells with a wide variation of speeds. For example type IA afferent nerve fibres from muscle spindles propagate up to 120 $m.s^{-1}$, whilst in C-fibres from somatosensory receptors the speed may be as low as 0.5 $m.s^{-1}$. In tissue such as the atrio-ventricular the cardiac impulse propagates even more slowly – about 0.05 $cm.s^{-1}$.

**Fibre diameter:** One factor that determines propagation velocity is fibre diameter, the larger the diameter the greater the velocity: IA afferents are up to 20 µm in diameter, whereas C-fibres are <1 µm. The reason is that the internal electrical resistance of a large axon is less than that of a smaller axon thus facilitating the spread of local circuits in the former.

**Myeination**: This is a In vertebrates a key evolutionary development in vertebrates to increase conduction speed. A 10 µm myelinated fibre conducts an action potential at about 50 $m.s^{-1}$; about twice as fast as in an invertebrate unmyelinated axon of about 500 µm (0.5 mm) diameter. Figure 4B illustrates the difference in local circuit spread in a myelinated axon. The myelin sheath around the nerve axon forms an effective electrical insulator, broken at 1-2 mm intervals at nodes of Ranvier. Local circuits do not depolarise the internodal region of the axon because of this insulation, and are therefore concentrated at the nodes where the membrane has direct access to the extracellular space. In consequence an action potential is only generated at these nodes, and thus appears to propagate by jumping from node to node: called saltatory conduction (Lat: *saltere=to*

*jump*). Because only small regions of the axon are depolarised to threshold the process is very efficient and conduction velocity greatly enhanced.

**Temperature, pressure, hypoxia**: An increase of temperature will quicken conduction velocity as ion channel kinetics are faster, and conversely a lower then normal body temperatures slow conduction. This must be considered for example in carrying out nerve conduction velocity tests to diagnose neuropathies, that themselves tend to slow nerve conduction. However, at temperatures <40°C conduction block may also occur as $K^+$ opening is enhanced more than that for $Na^+$ channels and so action potentials may fail to be generated. Physical pressure applied to nerves and hypoxia also slow conduction speed and may be significant in a clinical setting when these conditions occur.

**Ion channel number**: the number of ion channels contributing to the depolarising phase of the action potential influence conduction velocity. A decreased number reduces the magnitude of local circuits and so reduces conduction velocity. Local anaesthetics, by blocking $Na^+$ channels, achieve this before total block occurs, and in some tissue such as the atrio-ventricular node the number of ion channels is less than in other regions of the heart, thus contributing to slow conduction of the cardiac impulse in this region of the heart.

**Synaptic transmission**

Transmission of information between two nerve cells is generally achieved at a chemical synapse, whereby arrival of the action potential at the presynaptic terminal releases a transmitter. The transmitter is stored in vesicles and is released in quantal packets. The transmitter diffuses across the synaptic cleft, activates receptors on the postsynaptic membrane that in turn mediate changes to membrane potential at this site. Release of transmitter is preceded by an influx of $Ca^{2+}$ across the presynaptic membrane that initiates a series of events to facilitate movement of the vesicles to the

surface membrane and release of their contents into the synaptic cleft. Agents, such as botulinum toxin, inhibit this process and so block transmitter release.

Neurotransmitter receptors regulate or constitute ligand-gated ion channels, that generally lack the ionic specificity of voltage-gated channels. Some neurotransmitters depolarise the postsynaptic membrane, usually on a nerve dendrite, by increasing the cation conductance of the membrane, generating an excitatory postsynaptic potential (EPSP). An EPSP is a transient change of membrane potential only a few millivolts in amplitude. Such neurotransmitters include glutamate and aspartate in the central nervous system and acetylcholine in the autonomic nervous system. The synaptic region itself is not particularly electrically excitable but the depolarisation spreads to a region called the axon hillock-initial segment. If large enough the depolarisation initiates an action potential here, which subsequently conducts along the axon. The arrangement is summarised in figure 5A). Other neurotransmitters (glycine, γ-amino butyric acid - GABA) hyperpolarise the postsynaptic membrane, usually by increasing the anion conductance of the membrane, generating an inhibitory postsynaptic potential (IPSP).

**Integration of synaptic activity**

An important feature of the nervous system is that information carried by different nerves can be manipulated to form more complex outputs, and this is a function of synapses. A single postsynaptic neuron may receive many inputs and the resultant depolarisation that reaches the initial segment will be a function of their net effect. Figure 5B illustrates two phenomena related to integrated activity at the synapse.

**Temporal summation:** a process when two action potentials in the same nerve generate a large net EPSP, as the second is generated before the first has fully declined.

**Spatial summation**: this occurs when EPSPs are generated by action potentials arriving at the same time from two separate nerves, each EPSP may be insufficient to initiate an action potential, but

their sum may be. In addition, inhibitory nerves, generating IPSPs, offset the effect of an EPSP so the net result depends on the number of excitatory and inhibitory nerves impinging on the post-synaptic membrane.

**Summary**

Action potentials are generated in excitable cells, and are the agents whereby the body can rapidly transmit information in a frequency-coded system, as well as initiate crucial cellular functions. Voltage- and ligand-gated ion channels underlie such activity, and their particular types vary greatly in different excitable cells. The variety of different channels in various tissues allows them to be differentially regulated, and also permits some tissue-specificity of therapeutic agents. An understanding of the physiological processes that determine the ease with which action potentials are generated (excitability) and the velocity at which they are conducted is essential to appreciate how tissues respond to external stimuli and how this information is conveyed within the sensory system, integrated and conveyed to the motor system.

**Further reading**

Several monographs have been written by the most important contributors to this field. They all give valuable first-hand and historical insights. Several textbooks also give reasonable summaries of the subject matter in this article.

*Physiology* RM Bern and MN Levy. Mosby Press, 4th edition, 1998.

*Nerve and Muscle* RD Keynes & DJ Aidley, Cambridge University Press, 3rd edition 2001

*Nerve, Muscle and Synapse* B Katz, McGraw Hill, NY, 1966

*The Physiology of Nerve Cells* JC Eccles. The Johns Hopkins University Press 1968.

**Figure legends**

Figure 1. Examples of action potentials: top, cat motoneurone; middle, squid giant axon; bottom, frog sartorius muscle fibre. The solid horizontal lines mark the zero mV level and the dotted lines show the resting membrane potential, $E_m$. Against the uppermost race are shown useful definitions: a depolarisation is a change of $E_m$ from the resting value to a more positive inside value; a hyperpolarisation is a change of $E_m$ to a more negative value compared to the resting level; repolarisation refers to restoration of the resting value of $E_m$ from any previous change to its value.

Figure 2. Ionic movements and action potentials. *A.* The cell membrane separates an intracellular and extracellular space of different ionic composition, the values of $[Na^+]$ and $[K^+]$ are shown. The Nernst equation describes the relationship between membrane potential, $E_m$, and the transmembrane ion gradient for a permeant ion at 37°C. The bottom panels calculate theoretical equilibrium potentials for $K^+$, $E_K$, and $Na^+$, $E_{Na}$, assuming they are respectively solely permeable. *B.* Diagram of the action potential and the associated changes to $Na^+$ conductance, $g_{Na}$, and $K^+$ conductance, $g_K$. The units of conductance are on the right of the plot as $mS.cm^{-2}$ – *S* (Siemen) is the S.I. unit of conductance; the inverse of resistance. The values of $E_K$ and $E_{Na}$ are also shown.

Figure 3. Definition of refractory periods. The darker and lighter shaded boxes superimposed on the action potentials show the absolute and relative refractory periods. The bottom trace represents the relative stimulus strengths required to elicit a second action potential during the relative refractory period.

Figure 4. Action potential conduction in nerves *A.* The local circuit hypothesis underlying action potential conduction in an unmyelinated axon. The state at the initial resting potential and four successive intervals in an action potential propagating from left to right - i) to v). The action potential is represented as a change in the polarity of the membrane potential in the light box. The red circles represent the membrane potential at different points on the axon and superimposed on the action potentials shown right.

*B.* Representation of a myelinated axon showing the axon, surrounded by a myelin sheath, broken at intervals at nodes of Ranvier. The lower panel shows the equivalent local circuit pathway where intracellular currents generate membrane depolarisation only at the node of Ranvier.

Figure 5. Synaptic events at a neuron. *A.* The cell body and associated myelinated axon is shown. The axon hillock/initial segment portion is shown. On the left one incoming neurone makes a synapse with a dendrite. A single action potential in the incoming neurone (thick bar) generates an EPSP which conducts to the initial segment region. If the depolarisation is great enough here an action potential is generated, if not the transient depolarisation remains subthreshold. *B.* Diagram of temporal and spatial summation. On the left a single incoming neuron fires two action potentials in rapid succession. The second EPSP is superimposed on the first to generate a larger net depolarisation. At the bottom two incoming neurones generate near-simultaneous EPSPs – the summated depolarisation is larger than a single EPSP. In each case the summated EPSP has a greater chance of generating an action potential at the initial segment.

**Summary**

An action potential is a transient depolarisation of the membrane potential of excitable cells. They serve two main functions: to transmit and encode information, and to initiate cellular events such as muscular contraction. In this article action potential generated in nerves will be the focus of attention. An action potential results from a transient change to the properties of the cell membrane, from a state where it is much more permeable to $K^+$ than $Na^+$, to a reversal of these permeability properties. Thus during the action potential an influx of $Na^+$ is responsible for the rapid depolarisation and an efflux of $K^+$ causes repolarisation. This ionic basis of the action potential can be predicted from Nernst equation and is illustrated in the text. Changes to membrane ionic permeability are due to the opening and closing of voltage-gated ion channels, and the properties of such channels explain additional phenomena such as refractoriness, threshold and cellular excitability. Action potentials conduct with a finite velocity along nerve axons, and the actual velocity depends on a number of factors that include: fibre radius, temperature, functional ion channel number and the presence of a myelin sheath. The physical basis of conduction is explained by the local circuit hypothesis. Synaptic transmission of an action potential is explained in terms of excitatory post-synaptic potential (EPSP) generation at the post-synaptic membrane. The facility by which post-synaptic action potential may be developed is explained in terms of temporal and spatial summation as well as the influence of inhibitory transmitters.