School of Medical Sciences

Physiology 1A

Cell Physiology lecture #5

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Learning Aims – lecture 4

- To understand the forces that dictate how an ion moves across the cell membrane, including being able to describe electrochemical equilibrium and to predict how an ion moves across the membrane given the membrane potential and equilibrium potential.
- To know the Nernst equation and be able to use it (if given the values of the constants) to calculate equilibrium potentials
- To be able to describe how the resting membrane potential is generated and how changes in membrane potential occur (in terms of ion flows)
- Define depolarization, hyperpolarization, electrochemical equilibrium

Supporting activities

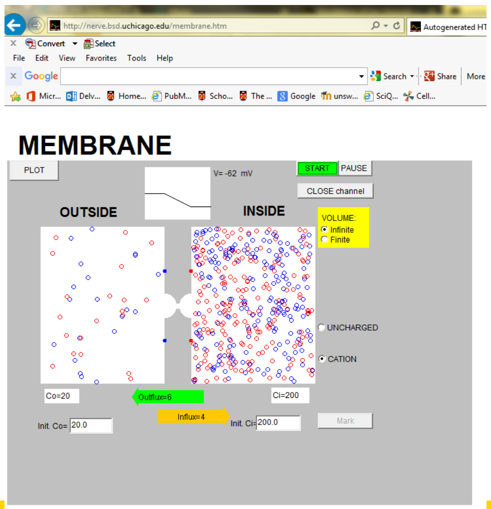
- Membrane Potentials Virtual Prac (via Moodle)
- Stanfield, Chapter 7.3, start of 7.4.

Recap: How membrane potentials are generated

A nice set of simulations to play with @ Francisco Bezanilla's home page :

http://nerve.bsd.uchicago.edu/

(use explorer not chrome & needs to allow JAVA to run)



Recap: How membrane potentials are generated

When ions move across membranes they change the membrane potential. To move across a membrane their must be 1) a force and 2) the membrane must be permeable. So the relevant physiology is about:

Electrochemical gradients

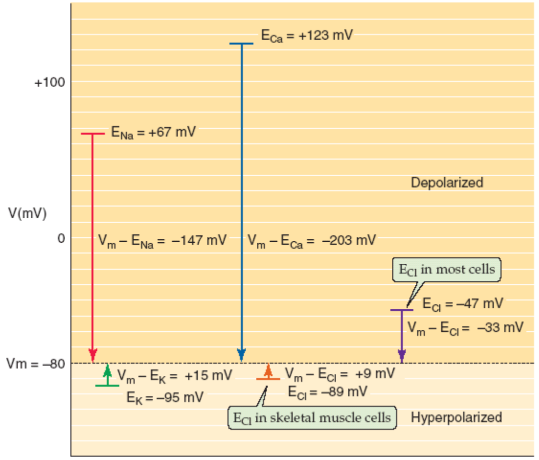
- **Chemical force (Diffusion)**
- **Electrical Force (Electrostatics)**

Membrane Permeability

- **What type of ion channels are open?**

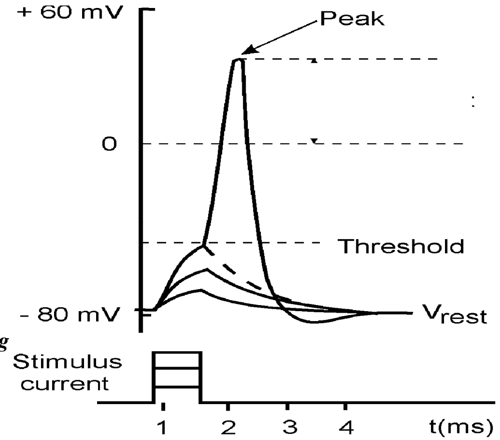
The electrochemical forces for ions in physiological conditions when a cell is at rest

- The difference between the equilibrium potential (E_x) and the membrane potential (V_m) is the driving force for movement of ion x



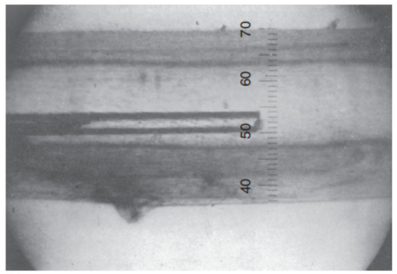
The nerve action potential….

1. *Concept of Threshold*
2. *Features / Phases*
3. *Ionic Currents involved*
4. *Ion Channels involved*
5. *Molecular Physiology*
6. *Voltage-dependent Gating*



The nerve action potential…. Underlying ionic Currents.

- *The 1st nerve action potential recording, from inside the giant axon of a squid*

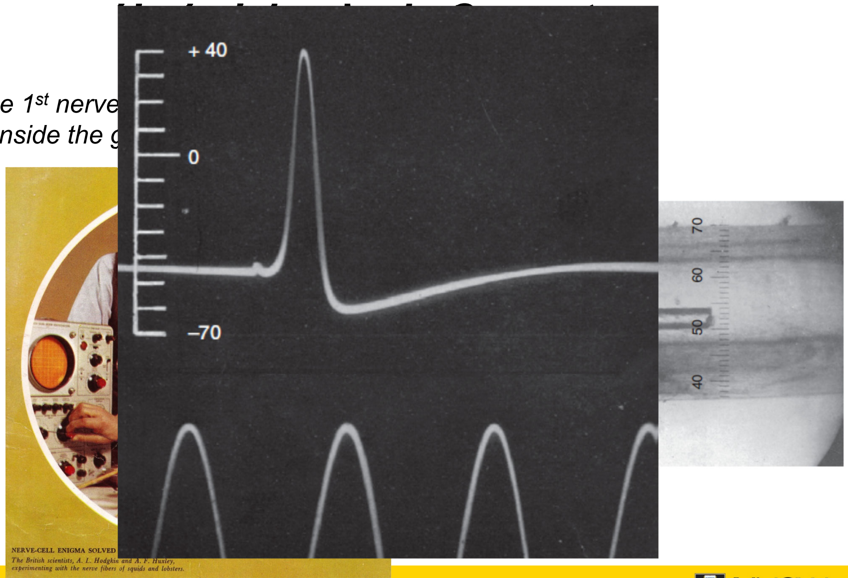


See also https://www.youtube.com/watch?v=k48jXzFGMc8 for video of this early experiment

Hodgkin & Huxley, Nature, 1939, J Physiol., 1945

The nerve action potential….

- *The 1st nerve*
from inside the g



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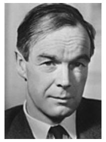
The nerve action potential…. Underlying ionic Currents.

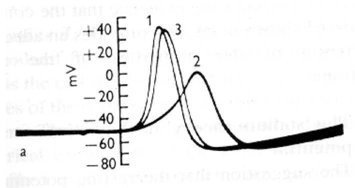


Sir Alan Hodgkin
Nobel Prize1963

Sir Bernard Katz
Nobel Prize1971

- *One of the 1st Action Potential experiments….*

J. Physiology, 1949



1 = control,
2 = low Na^+ in the sea water,
3 = wash / recovery response

Conclusion?:

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The nerve action potential…. Underlying ionic Currents.

1. Inward Na^+ current,
   - *Na^+ influx*

Rapid depolarization

2. Outward K^+ current
   - *K^+ efflux*

Slow repolarization

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The nerve action potential…. Underlying ionic Currents and the Channels involved.

1. Inward Na^+ current,
   - *Na^+ influx*
   - *Fast, voltage gated channels*

Rapid depolarization

2. Outward K^+ current
   - *K^+ efflux*
   - *Slow, voltage gated channels*

Slow repolarization

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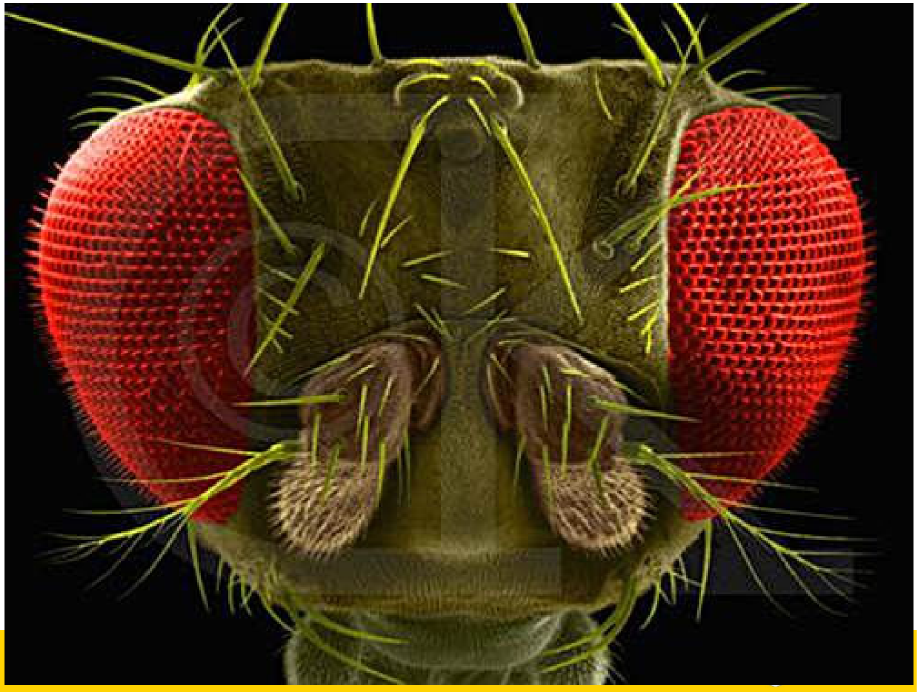
The molecular physiology of the nerve action potential

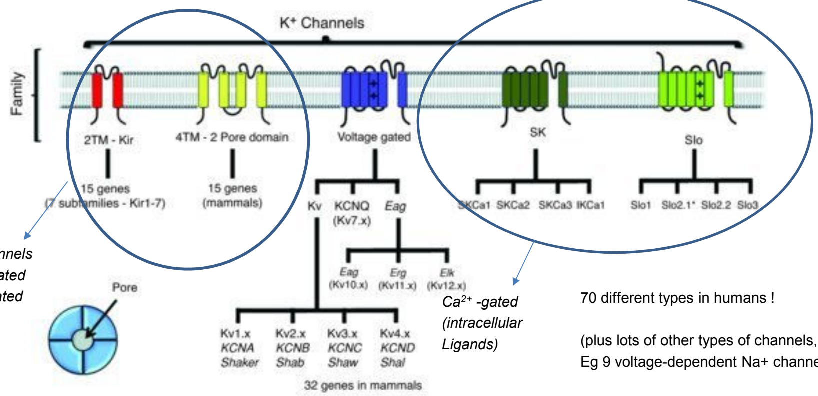
- *some more important contributors……*
  - *1) The giant squid*
  - *2) Hodgkin and Huxley*
  - *3) ….*
  - *4) ….*

(Biology provides some great insights into physiology and opportunities for discoveries)



The molecular physiology of the nerve action potential

- *From the 1st K+ channel gene from a fruit fly a family of different types of K+ ion channels genes were discovered (in mammals). The structures and properties have been extensively. Different families have similar functional properties but with subtle differences to give diversity.*



Leak channels
Strecth gated
Ligand gated
(H+, lipis)

Ca^{2+} -gated (intracellular Ligands)

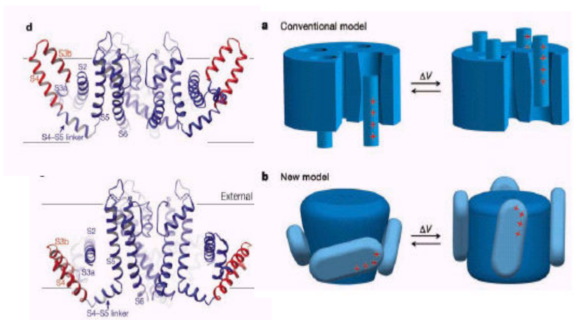
70 different types in humans !

(plus lots of other types of channels, Eg 9 voltage-dependent Na+ channels)

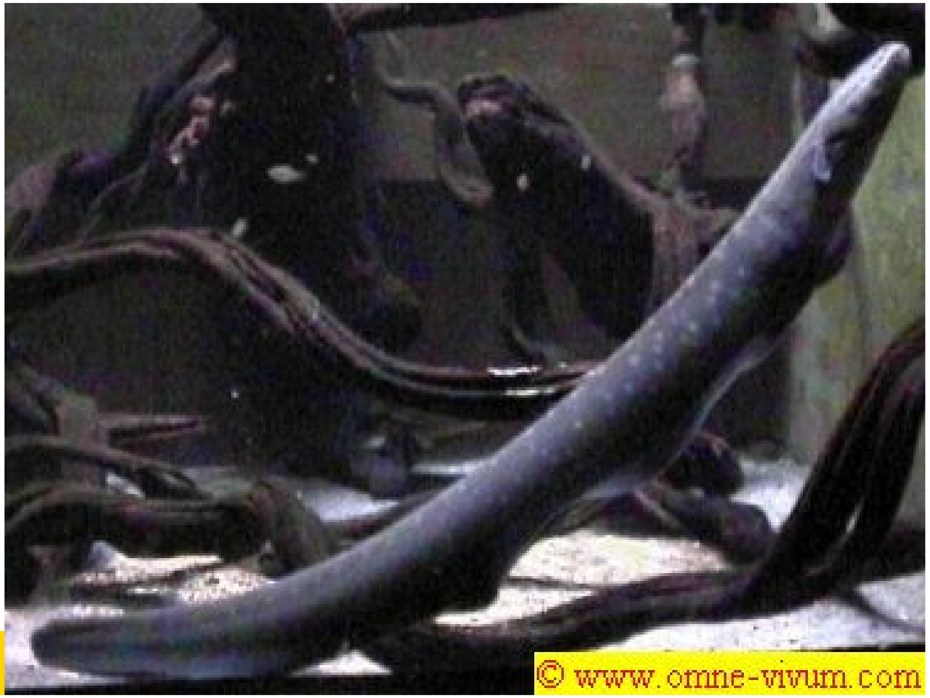
K+ Channels: Function-Structural Overview, July 2012
Comprehensive Physiology 2(3):2087-149

The molecular physiology of the nerve action potential

- *Voltage-dependent activation…*
- *All voltage-dependent channels have a voltage sensor that detects the membrane potential and acts as a molecular switch and opens (or activates) the channels at a specific voltage level or threshold*

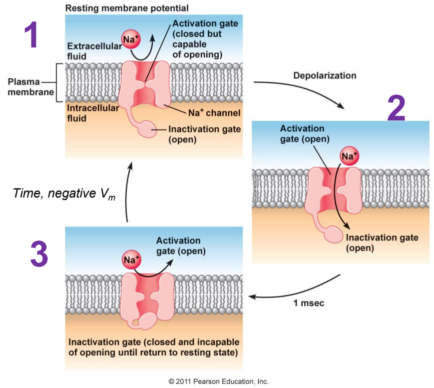


The voltage sensor is a region of the channel protein (containing charged amibno acids) that can detect and respond to changes in the membrane potential. The images suggest different models on how it may move in response to membrane potential changes. This movement initiates opening of the gate when the voltage threshold is reached.



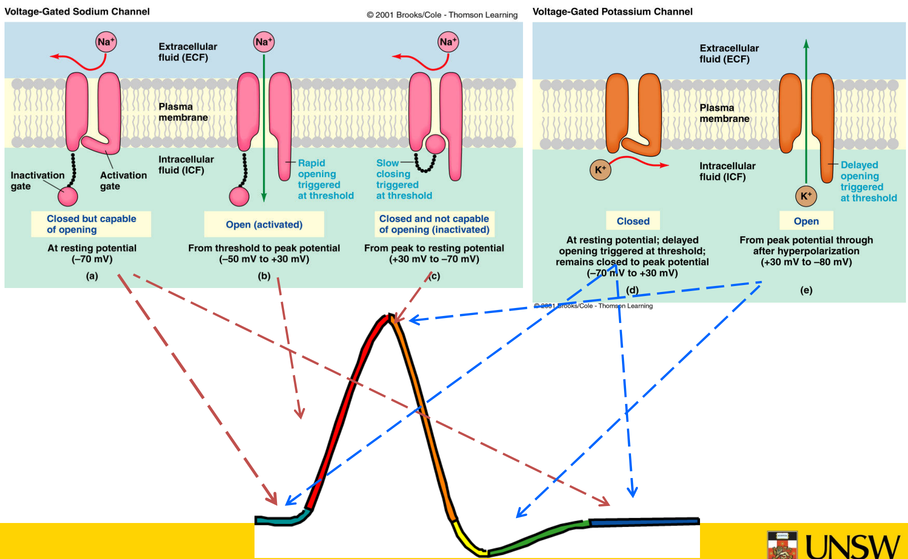
The molecular physiology of the nerve action potential

- *Voltage-dependent inactivation…The 3 conformational states of the voltage dependent Na^+ channel*



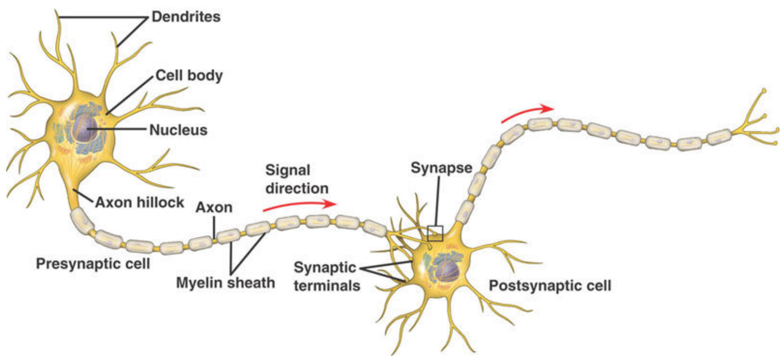
- 1. Closed state
  - Activation gate closed
  - Inactivation gate open
  - no ion movement
- 2. Activated state:
  - Activation gate open
  - inactivation gate open
  - ions pass through
- 3. Inactivated state:
  - activation gate open
  - inactivation gate closed
  - no ion movement

The nerve action potential….summary



The nerve action potential….

- *Generated in a specialised region of high Na+ channel density called the axon hillock. This signal must then be communicated to other nerves.*

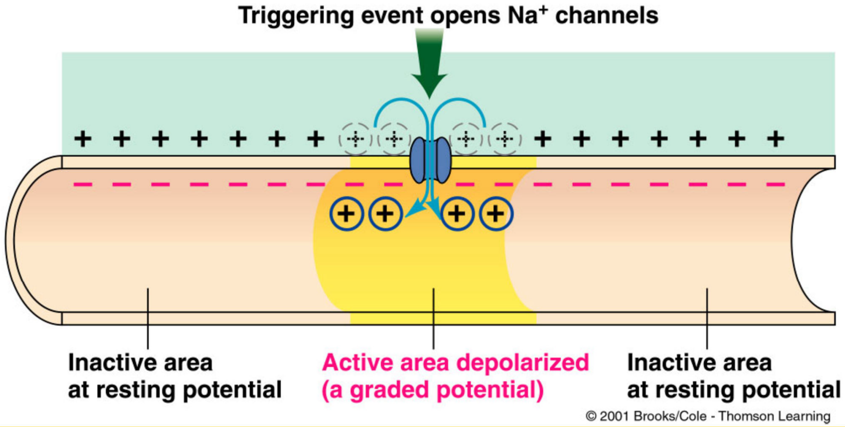


http://hplusmagazine.com/wp-content/uploads/neuron_structure2.jpg

- *How does this signal travel….*

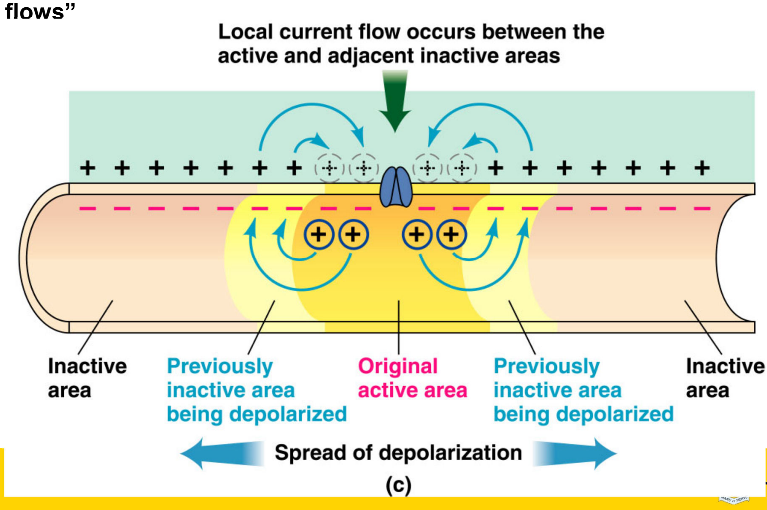
Propagation of Electrical Signals

1) Some ionic current enters the axon during the depolarization phase of the action potential. A single part of the axon (e.g., the axon hillock at the base of the axon) becomes depolarized while the axonal region ahead (or behind) is still hyperpolarized



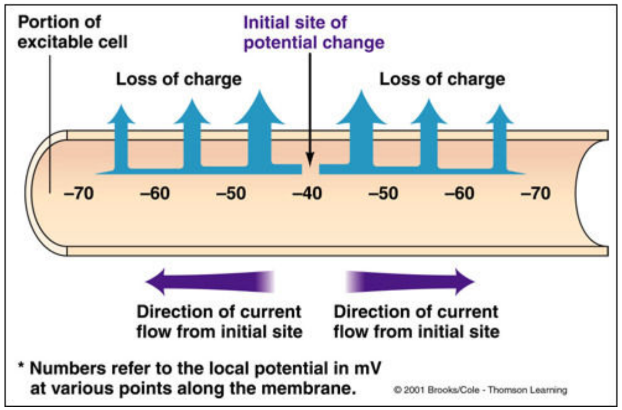
Propagation of Electrical Signals

2) The point depolarization initiates a spread of current along the length of the axon. This **passively** depolarizes adjacent sections of the axon. This passive spread of current along a fibre also called **"local current flows"**



Propagation of Electrical Signals

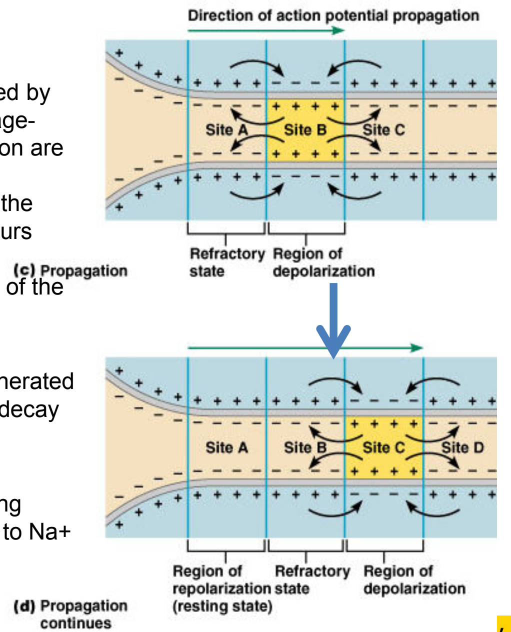
3) Some of this local current leaks out across the cell membrane (e.g., via "leak" channels) and hence the depolarization gets smaller and smaller as one moves along the axon. If too much current leaks out, the action potential would fail to propagate



Propagation

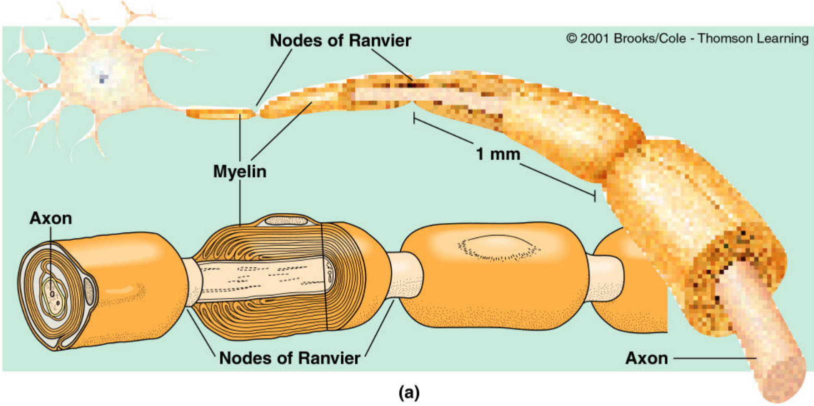
4) The adjacent region is depolarized by the passive spread of current. Voltage-gated channels in the adjacent region are activated if the membrane potential reaches the voltage threshold, and the action potential (Na+ influx etc) occurs once again. The action potential is regenerated along the entire length of the axon. This is **active propagation**.

- If the action potential is not regenerated the depolarization will passively decay and die out.
- The region behind the propagating action potential is refractory due to Na+ channel inactivation



Propagation of Electrical Signals

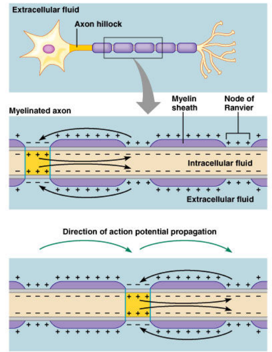
Some central and peripheral axons are **myelinated**. The wrappings of insulation decrease current leak out of the axon and thereby enable the passive voltage to spread further. This means the action potential propagation increases markedly, as the potential jumps ahead to the next Node of Ranvier. The need for ionic fluxes along the entire axon is reduced, so also increases efficiency.



(a)

Propagation of Electrical Signals

The jumping nature of the spread of depolarisation is called **saltatory conduction**. Voltage-dependent Na^+ channels and transmembrane ionic influx occurs only at the Nodes of Ranvier, located between the myelin sheaths.



The amount of myelin and hence the conduction velocity can be regulated and may be fine-tuned according to cell function.

Learning Aims – lecture 5

- To understand the physiological mechanisms of the Action Potential, including:
  - Being able to draw the nerve AP with correctly identified x and y axis, and with the major phases of the AP identified
  - To appreciate the voltage threshold concept and to describe briefly what happens here to elicit the action potential (ie voltage-dependent gating).
  - To describe the ionic currents that mediate the depolarisation and repolarisation phases of the AP
  - To be able to describe the ion channels that mediate the above ionic currents, and to link the different conformation states of these channels (i.e. their gates) to the different phases of the AP. To define what is meant by voltage-dependent gating, activation and inactivation (in terms of these ion channels)
- To describe what is meant by passive and active propagation and describe how these two processes contribute to AP propagation along an axon
- To appreciate what myelin is and how it affects AP propagation velocity

Supporting activities:

- Membrane Potentials Virtual Prac (via Moodle)
- Cell Physiology tutorial #2. Action Potentials
- Stanfield, Chapter 7.4

Next Concept (final one)
Communication of Signals from cell to cell

A nerve cell communicates with other nerve cells and with peripheral organs, and does this largely by converting the action potential into a chemical messengers at synapses