Nerve Structure and Function

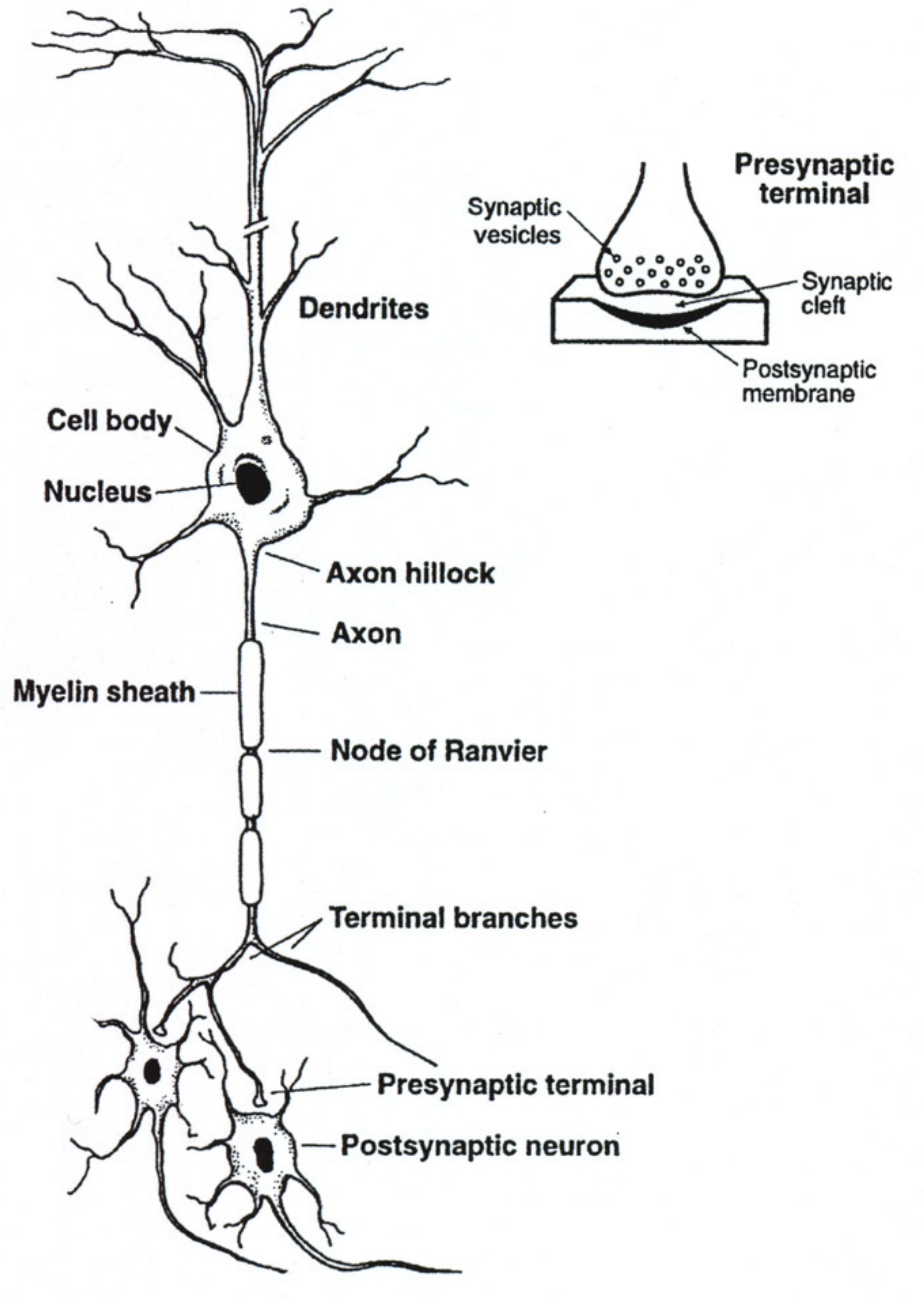
The Physiology of Transduction, Conduction and Transmission

Jim Borowczyk 2011

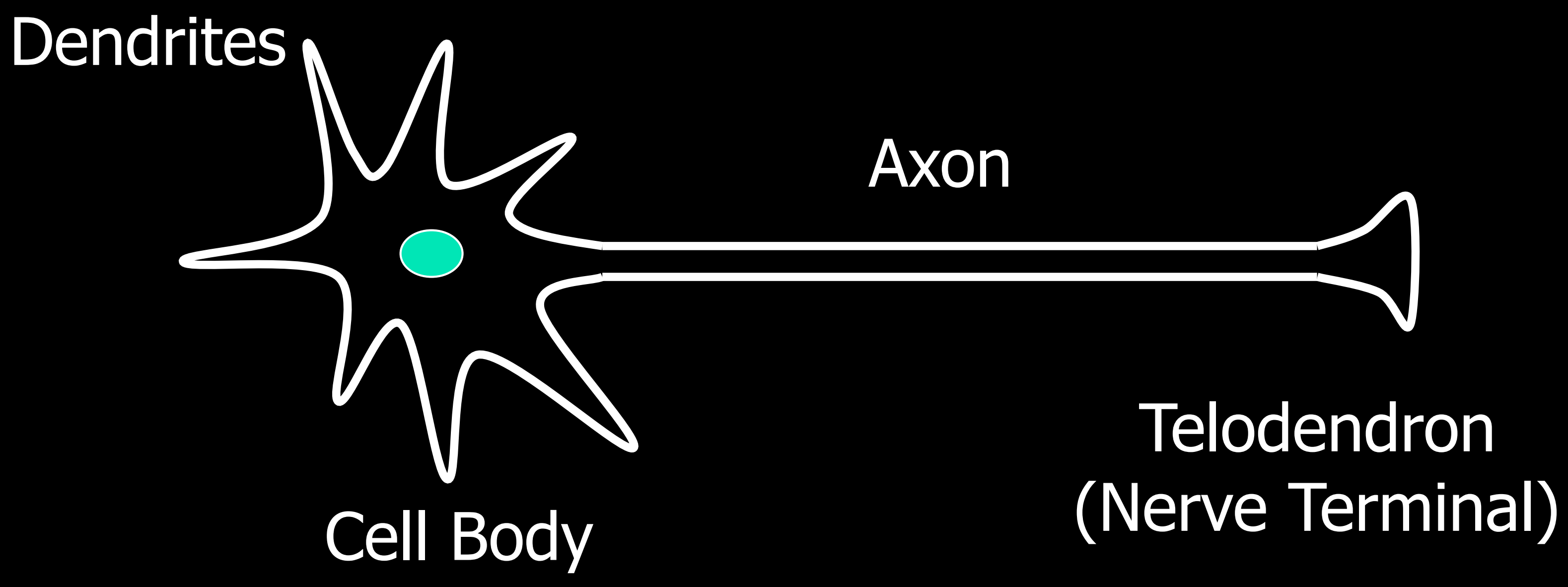
MSMX 702, 704 and 708 and PAIX 701

Neuron

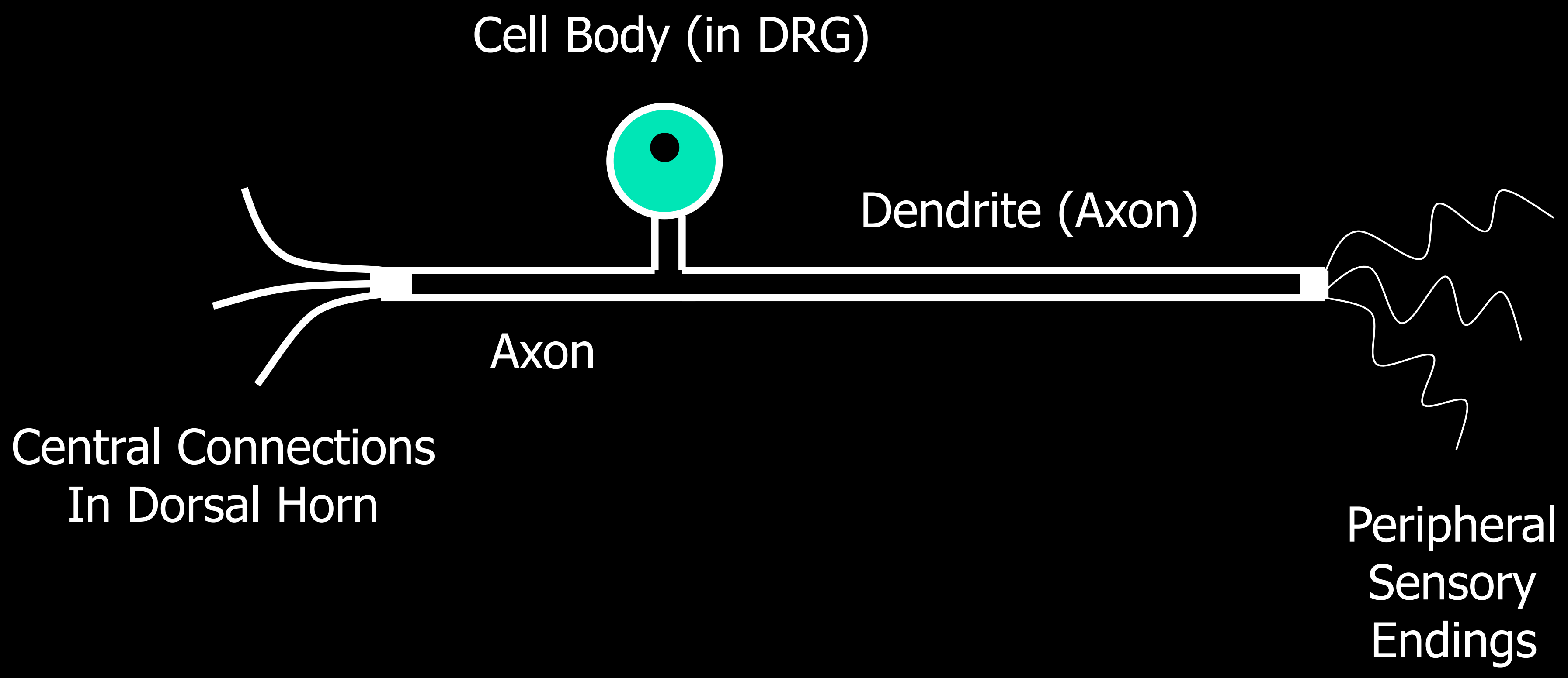
- Composed of cell body, dendrites, axon and presynaptic terminal
- Cell body holds nucleus, protein formation and metabolic centre
- It gives rise to only I axon
- Axon is specialised for propagating electrical signals
- To maintain structural integrity proteins are synthesised in the cell body and tranported in the axon


Presynaptic terminal
Synaptic vesicles
Synaptic cleft
Postsynaptic membrane
Dendrites
Cell body
Nucleus
Axon hillock
Axon
Myelin sheath
Node of Ranvier
Terminal branches
Presynaptic terminal
Postsynaptic neuron

Motor Neuron



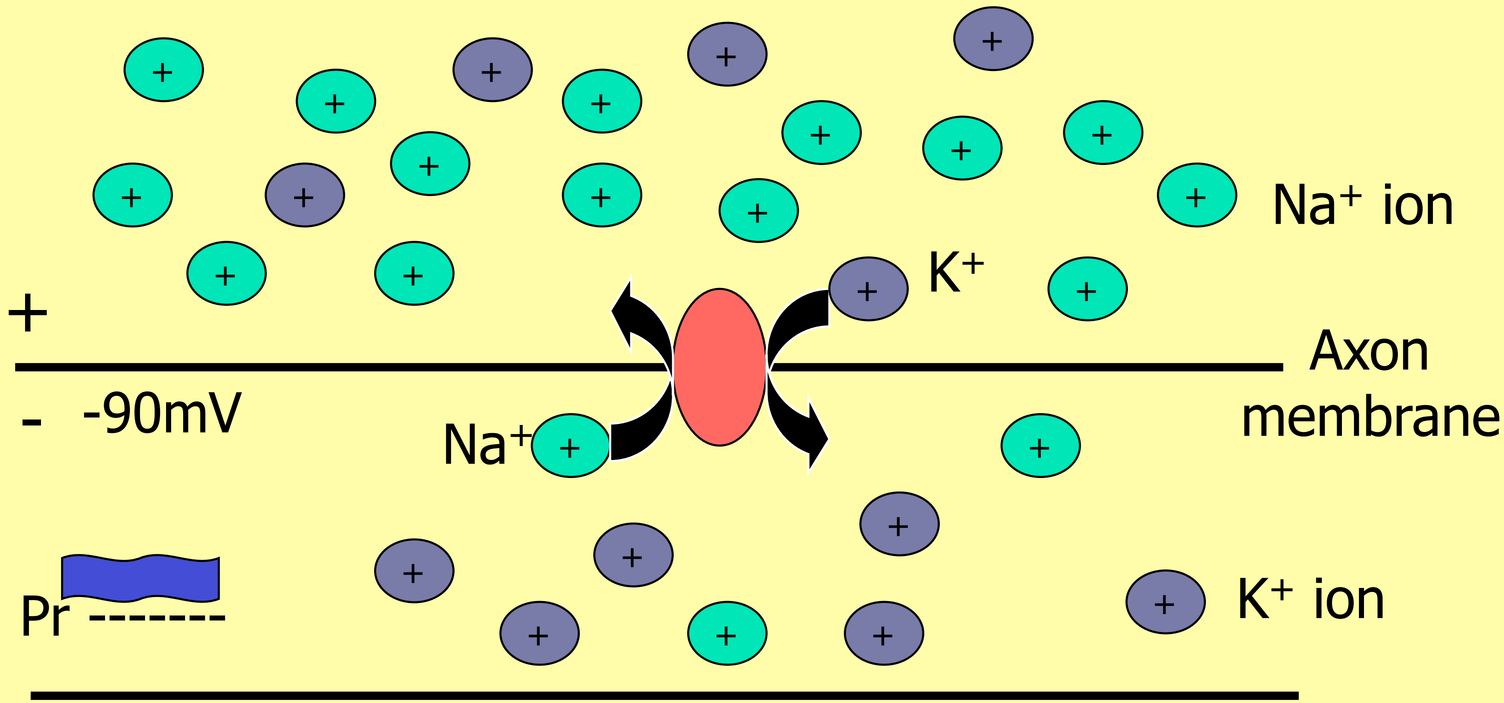
Peripheral Neuron



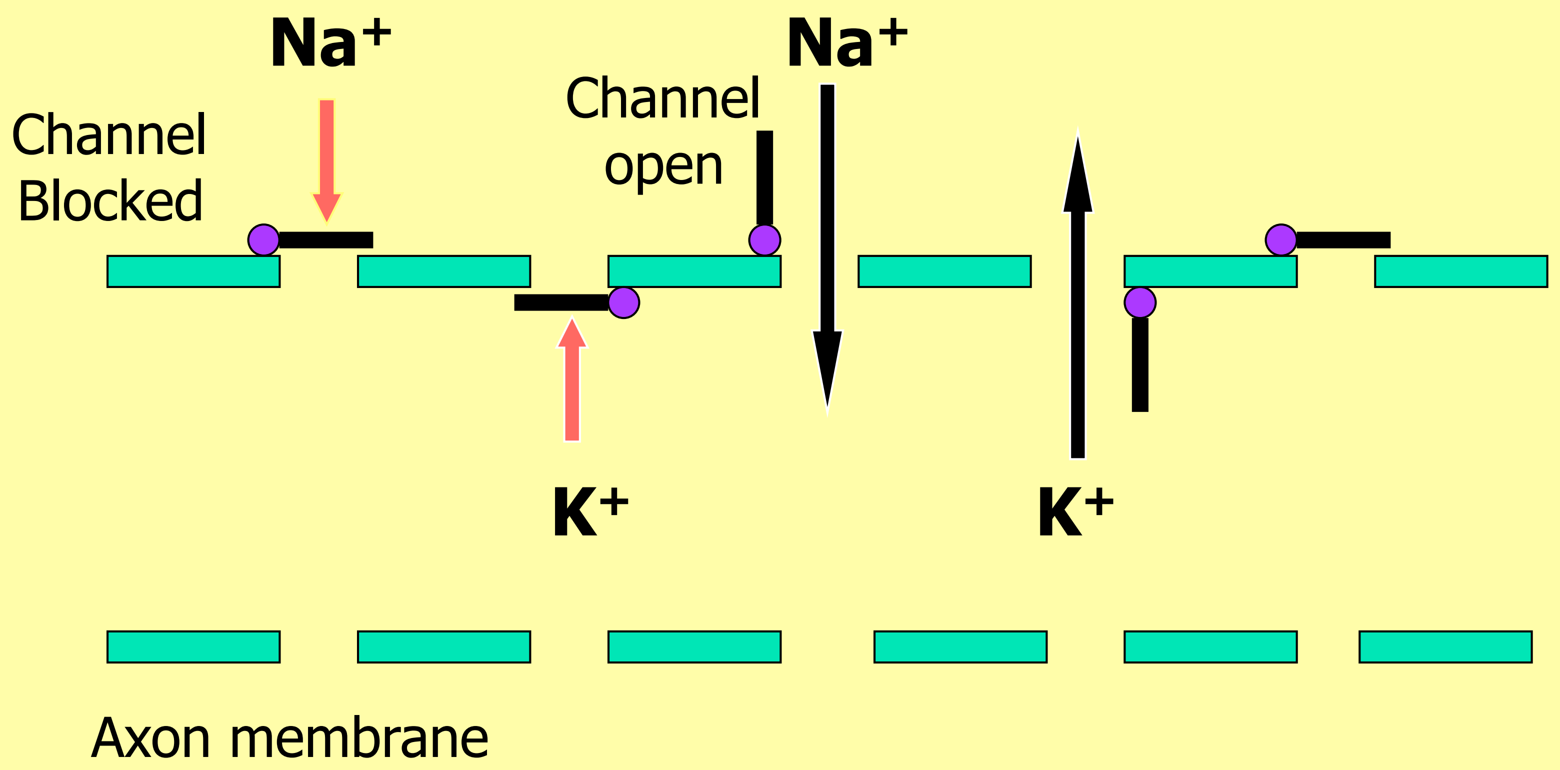
Axonal membrane

- Bilayer of phospholipid molecules
- Fatty acyl chains face each other
- Surfaces facing cytoplasm and ECF formed by charged polarised hydrophilic groups
- Globular proteins penetrate entire thickness
  - *Act as ionic channels*
  - *Pump ions and transport metabolites*
  - *Act as enzymes*
  - *Receptors for hormones and transmitters*
  - *Structural*

Section of Axon



Sodium and potassium channels



Sodium and Potassium Channels

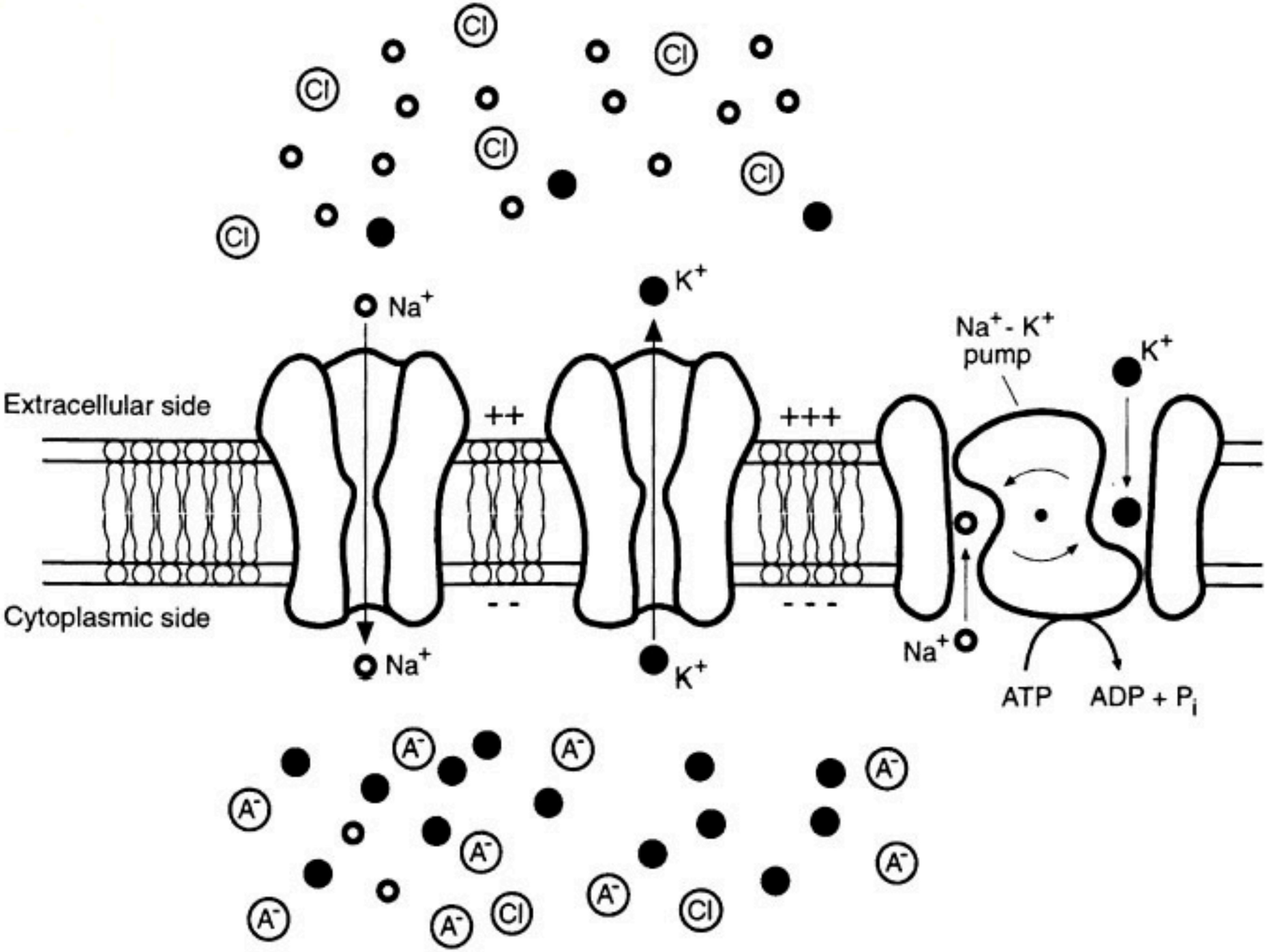
The Physiology of the Action Potential

Voltage gated sodium channels

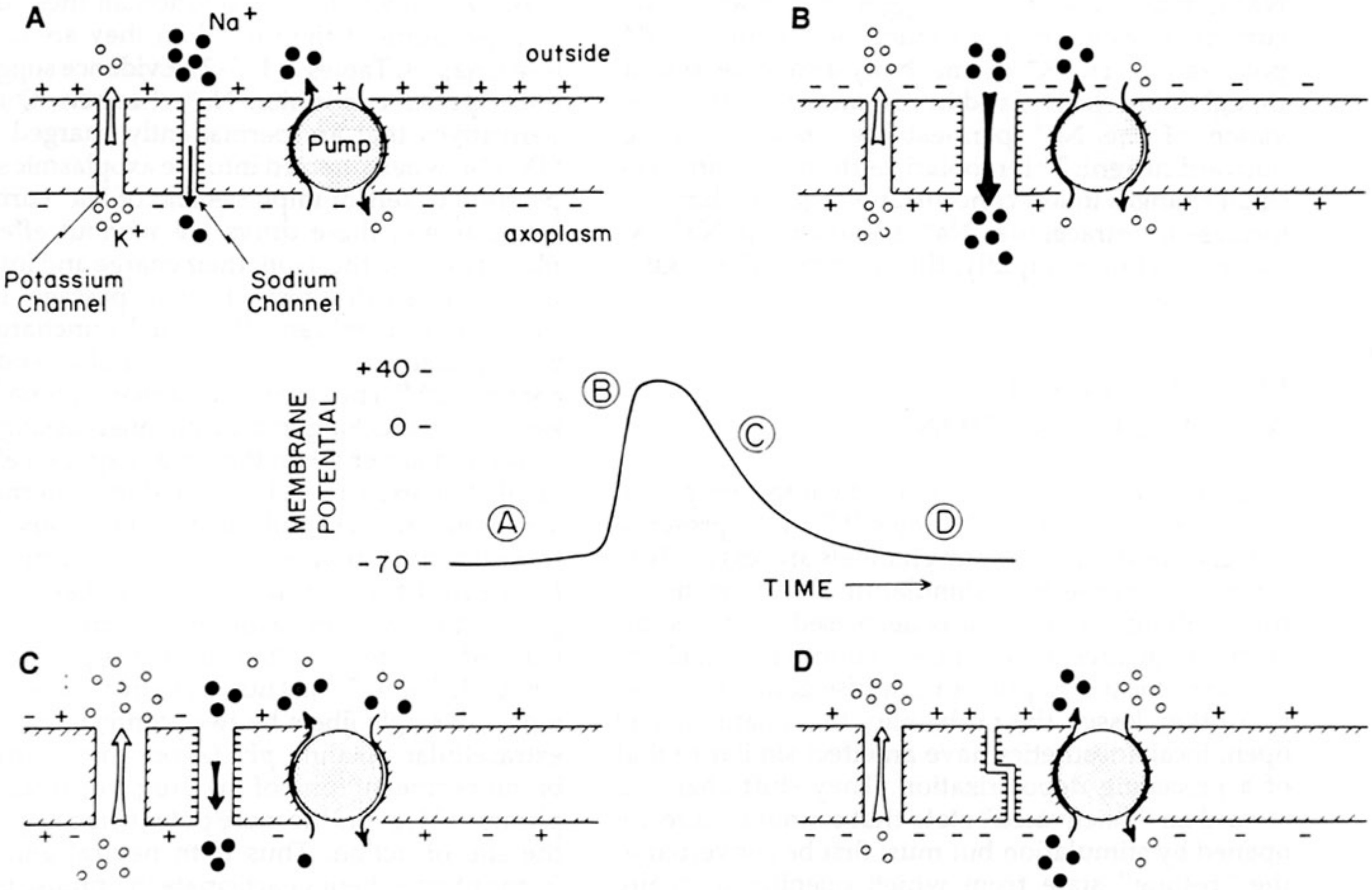
- At least 9 different types of sodium channel are now recognised
- Different types of nerves have different types of sodium channels and this may affect the shape and length of the action potential
- It is thought that that in some pain states there may be an increased genetic expression of certain types of channel inside the neuron

Classification

- These are sub-classified according to their sensitivity to tetrodotoxin (TTX), a sodium channel blocker
- As a general rule TTXs are found in the periphery, and TTXr in the cardiac neuronal pathways
- Nociceptive nerves have a predominance of Tetrodotoxin resistant channels
- TTX sensitive channels are widespread and found predominantly in A delta fibres
- TTX resistant channels are found in a subset of primary C afferents involved in nociception (Akopian 1996)



Cl
Na^+
K^+
Na^+- K^+ pump
Extracellular side
++
+++
Cytoplasmic side
- -
- - -
ATP
ADP + P_i
A^-


A
Na+
outside
Pump
K+
axoplasm
Potassium Channel
Sodium Channel
B
+40
0
-70
MEMBRANE POTENTIAL
TIME
C
D

Nerve Injury

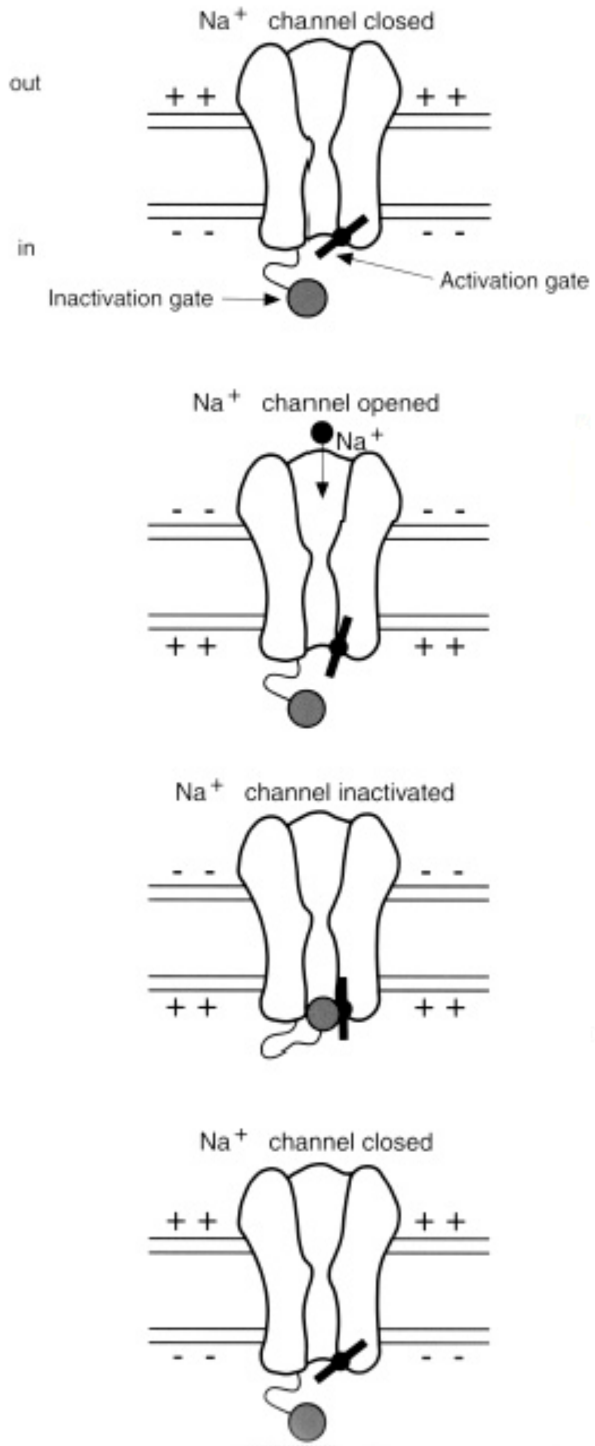
- In the presence of nerve injury there is an altered expression of these channels
- This increase in sodium channels is found in both the cell body and at the terminal neuroma (Devor, 1989)
- The genetic expression of these ion channels in the DRG cell body changes in response to nerve injury (Waxman 1994)

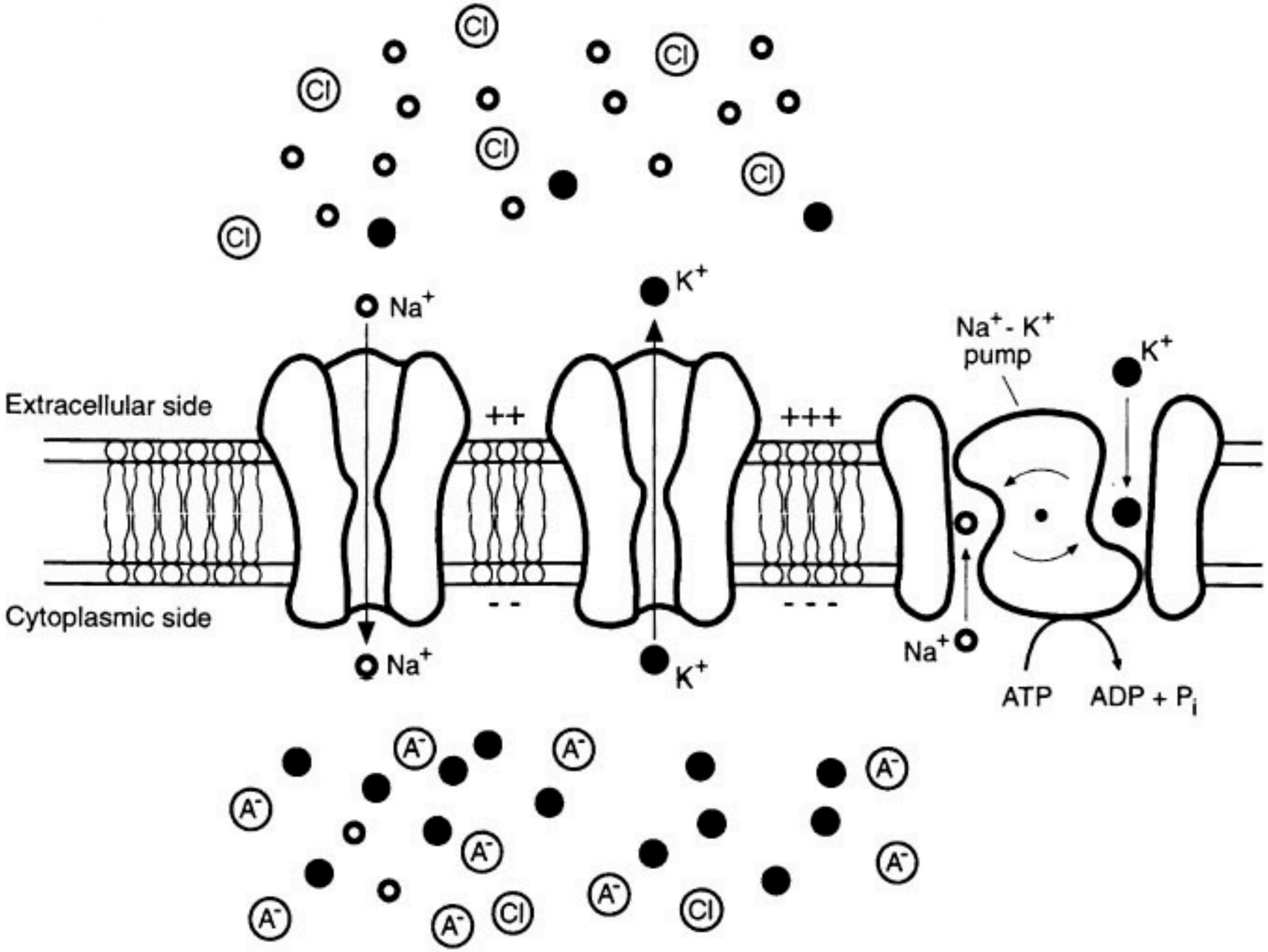
- There is an increase in of Type III TTX sensitive channels
- There is a decrease in SNS/PN3 and SNS2/NaN channels (Dib Hajj, 1996)
- These latter channels also tend to translocate to the neuroma and may partially explain the increased hyperexcitability

Voltage gated potassium channels

- There are many types of K channels
- They are not essential in themselves for an action potential to occur
- Different types decide the actual shape of the action potential
- They underlie much of the subtle changes in the AP
- When open they steer the membrane towards K equilibration and so reduce the excitability of the membrane

Sodium and potassium channels





Glial Cells

Myelination

- All nerve cells are surrounded by glial tissue
- Microglia are derived from macrophages, and have a phagocytic function
- Macroglia include:
  - *Schwann cells*
  - *Oligodendrocytes*
  - *Astrocytes*

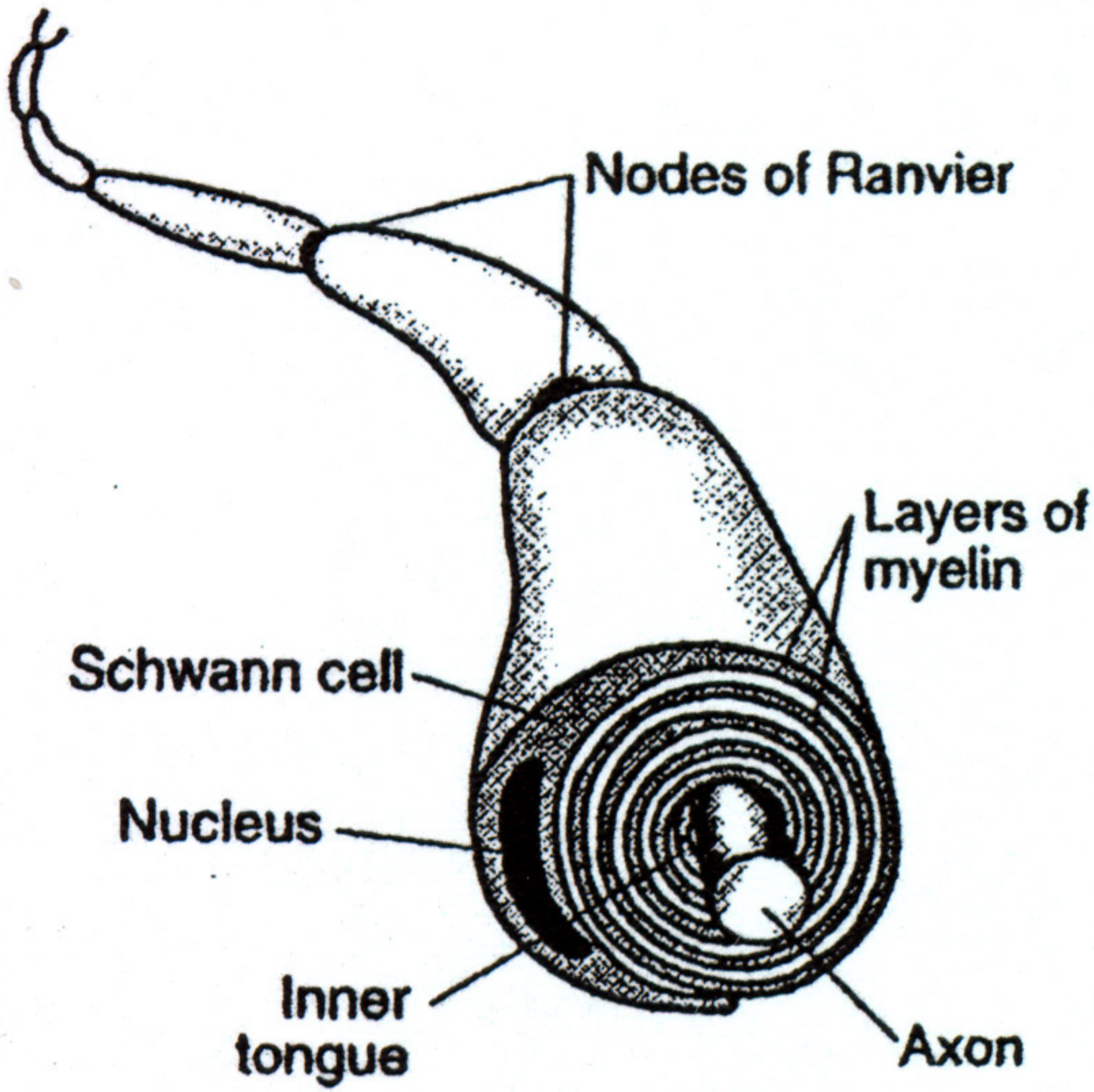
Myelin

- 70% lipid and 30% protein
- High cholesterol and phospholipid concentration
- Produced by Schwann cells and oligodendrocytes
- Myelinated axons conduct electrical impulses faster and with greater frequency
- Myelin sheath formed by the cells wrapping their cytoplasmic processes round the axon

Schwann cells

- Occur in the peripheral CNS
- There may be as many as 500 Schwann cells for 1 axon
- They line up at intervals of 0.1 to 1 mm
- The intervals are known as the nodes of Ranvier
- The double cell membrane is wrapped round in concentric spirals
- So called unmyelinated cells normally have at least one layer of myelin

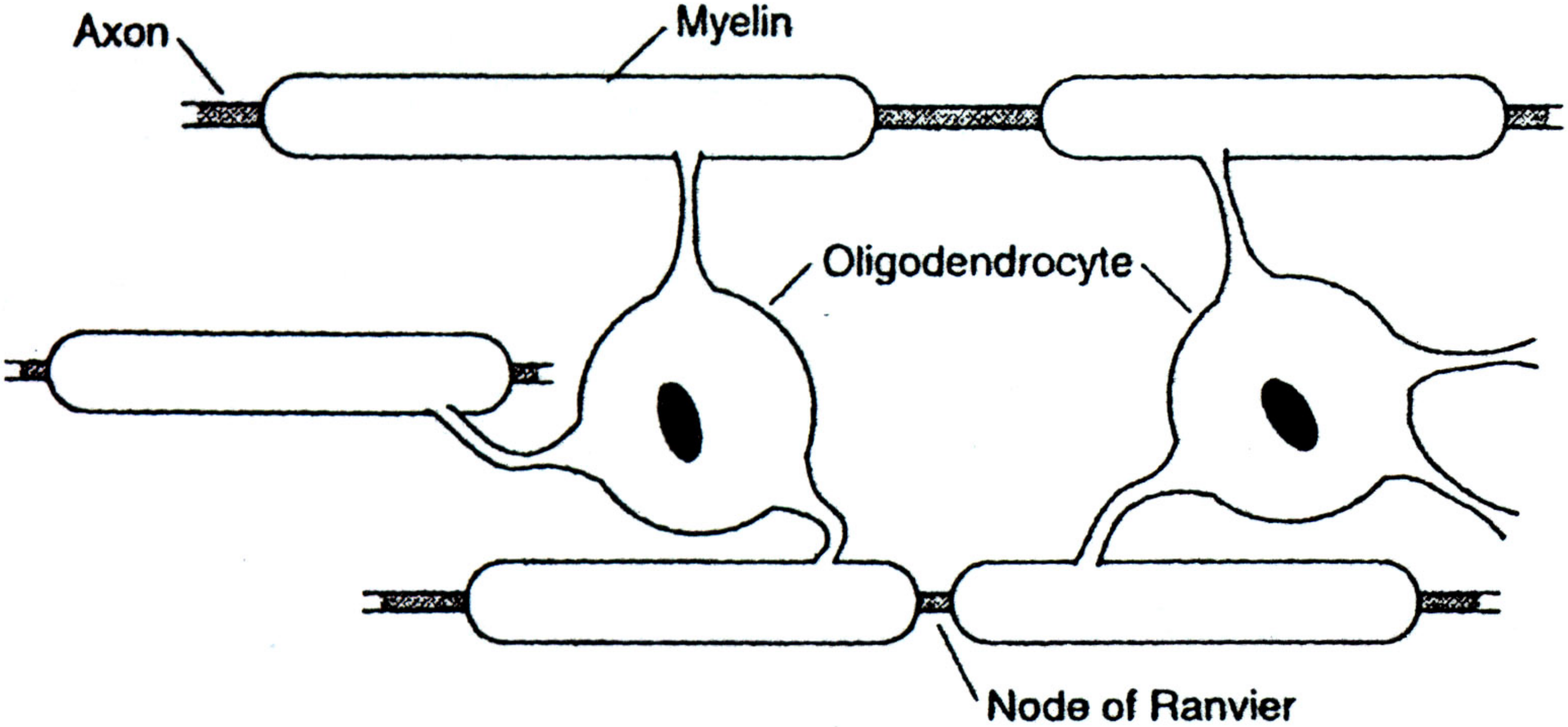
Schwann cell



Oligodendrocytes

- Found only in the CNS
- A single cell may myelinate several different cells
- Average 15

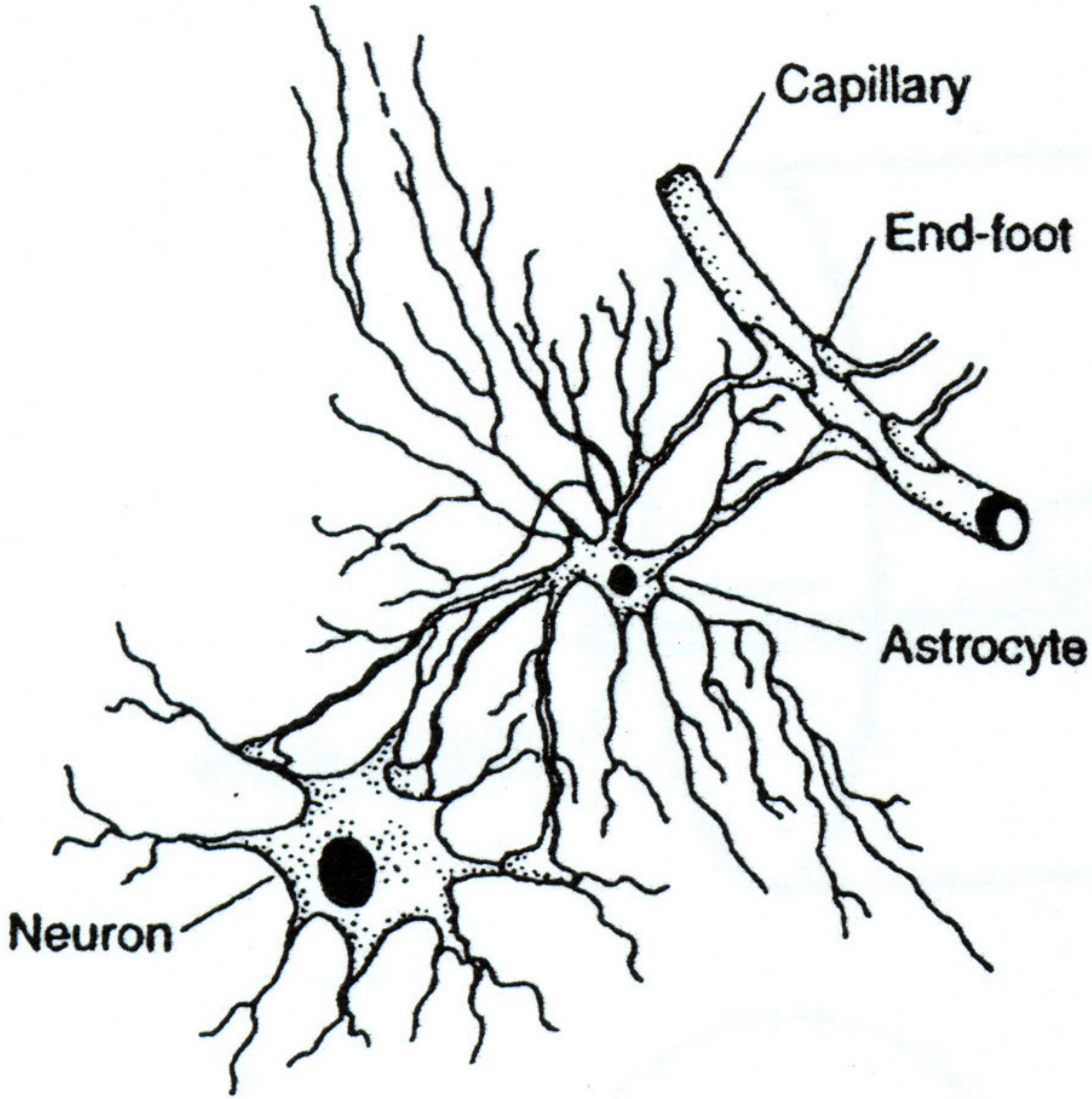
Oligodendrocyte



Astrocytes

- Only found in CNS
- Most abundant glial cells
- Functions include:
  - *Supporting structures*
  - *Provide firmness to brain*
  - *Contact capillaries for ? Nutrients*
  - *Scavenger and debris clearing role*
  - *Remove cations and neurotransmitters from the synaptic cleft*
  - *Turn on myelin expression in oligodendrocytes*

Astrocyte



Axoplasmic Transport

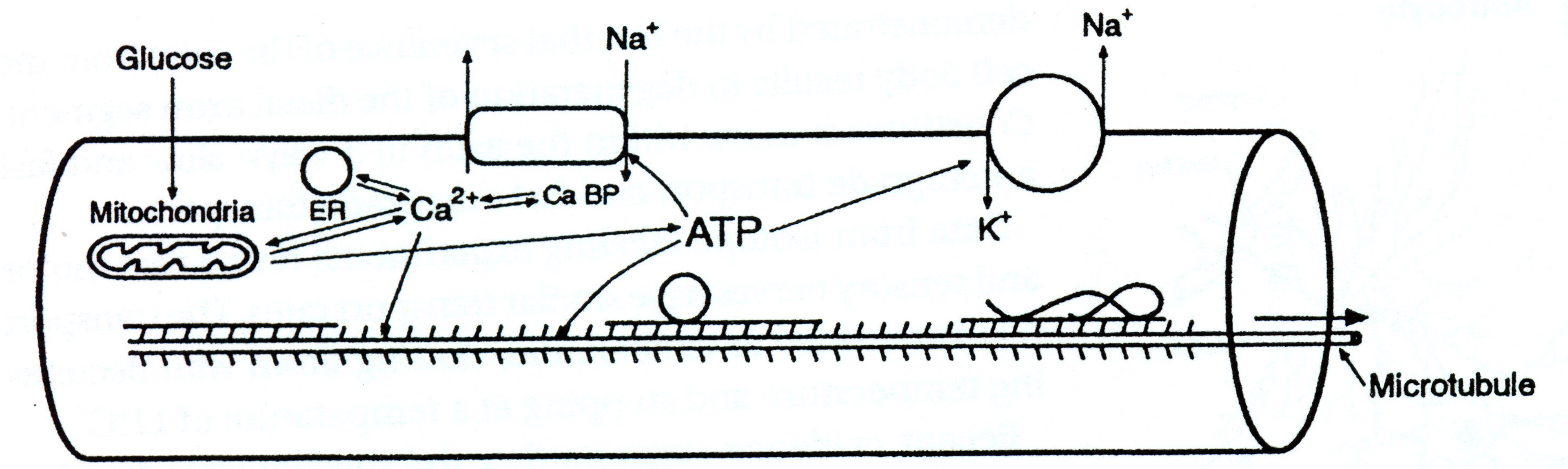
- Cell body and presynaptic terminal may be at some distance from each other
- Proteins only made in cell body and must be transported
- Transport system delivers molecules to the periphery and returns degradation products to the cell body for reprocessing
- Three transport systems
  - *Slow and fast antegrade*
  - *Fast retrograde*

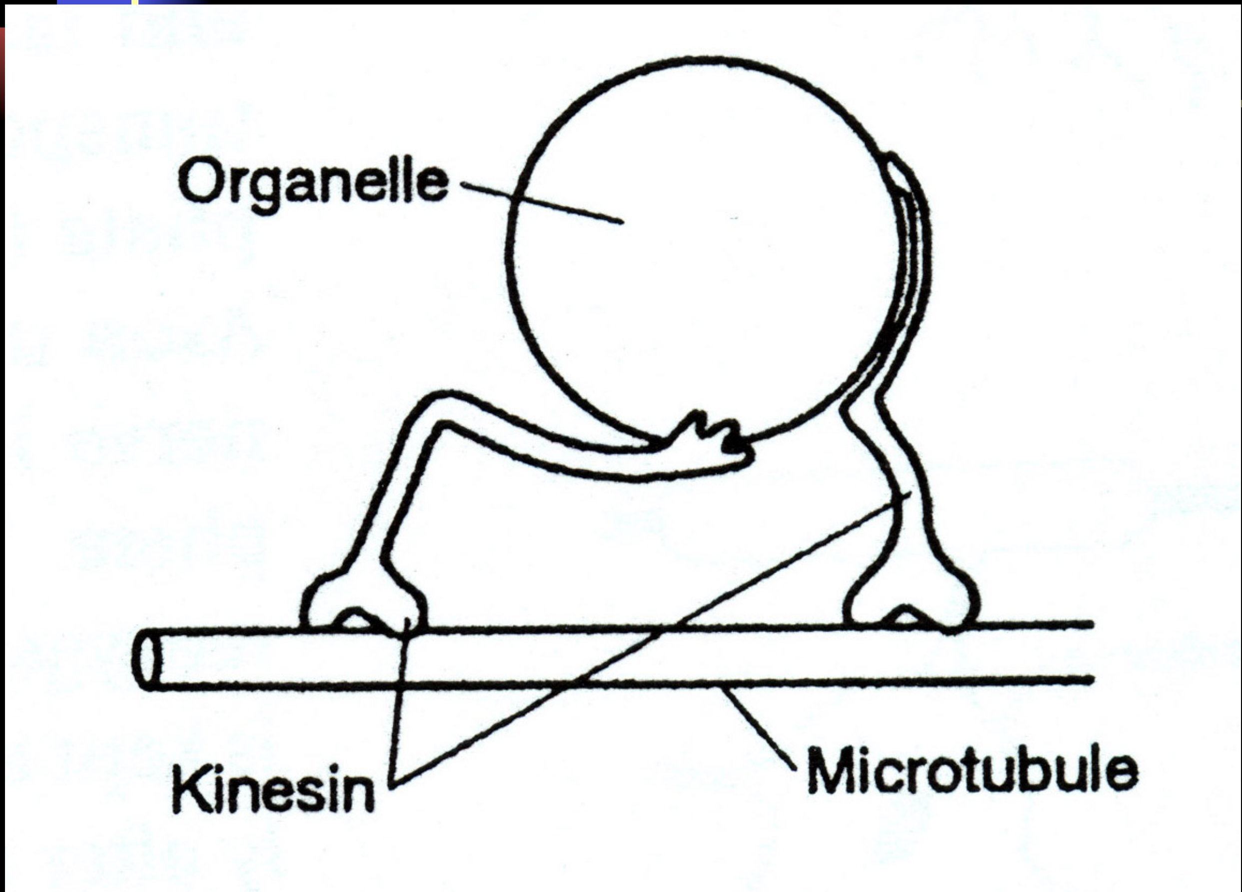
- Motor and sensory fibres have similar systems and rates of transport
- Depends on ATP derived from oxidative metabolism
- Also depends on Ca++ concentration
- This is sequestered in mitochondria and smooth ER
- Is bound to calmodulin

Microtubules

- Require ATP, ATPase, calcium, carrier proteins
- Organelle or protein binds to carrier protein
- Carrier protein binds to microtubule
- Microtubule side arms use ATP
- This enables microtubule to move the carrier protein
- Different carrier proteins are used for different transport rates
- Different speeds are due to different drop off rates

Axonal Microtubule system

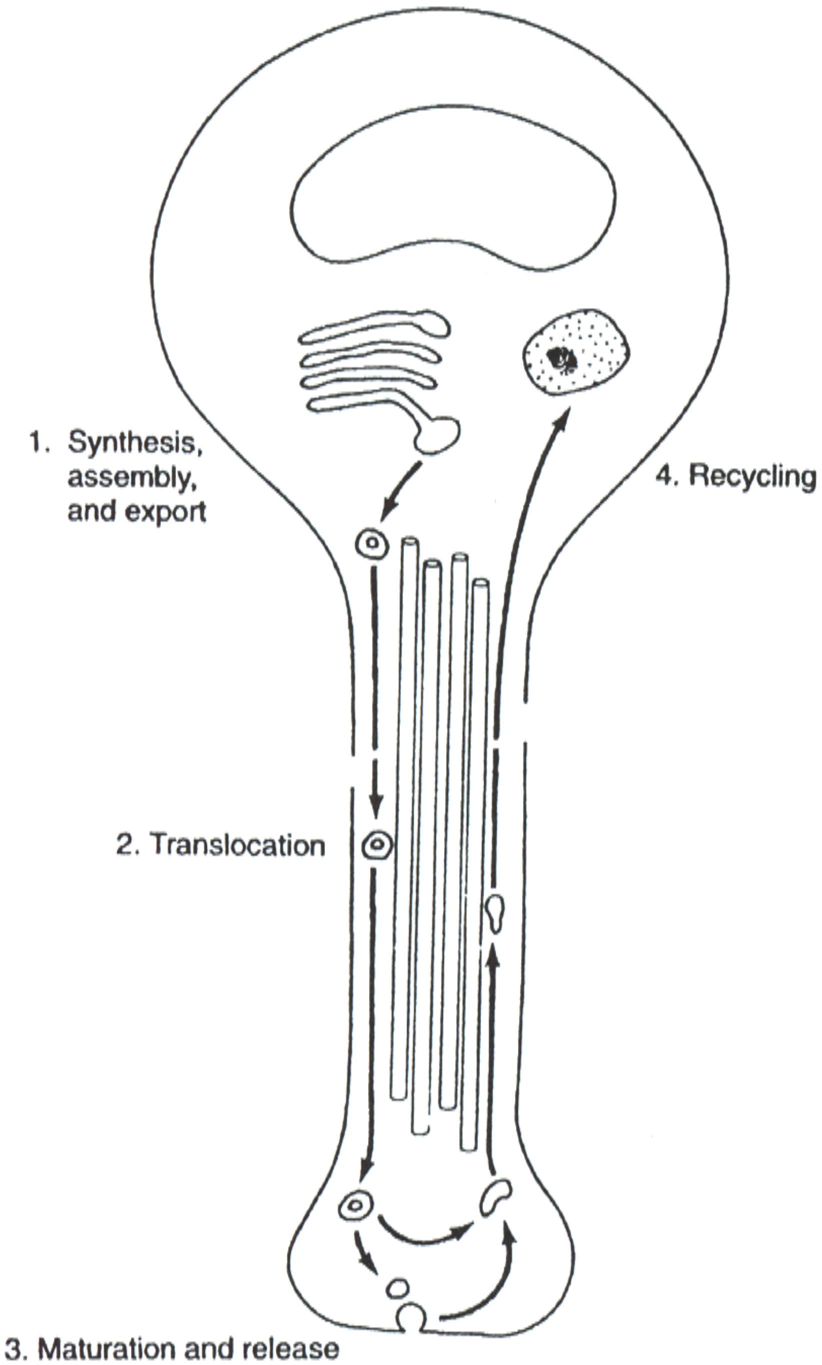




Side arms move The organelle or protein using energy derived from ATP

Retrograde Transport

- Returns material such as empty neurotransmitter vesicles to cell body
- Materials are packed in large membrane bound organelles
- Retrograde transport also delivers extracellular factors such as NGF to the cell body
- This also includes viruses (polio, herpes zoster, rabies) and tetanus toxin
- Dyes can be carried and allow axonal tracking

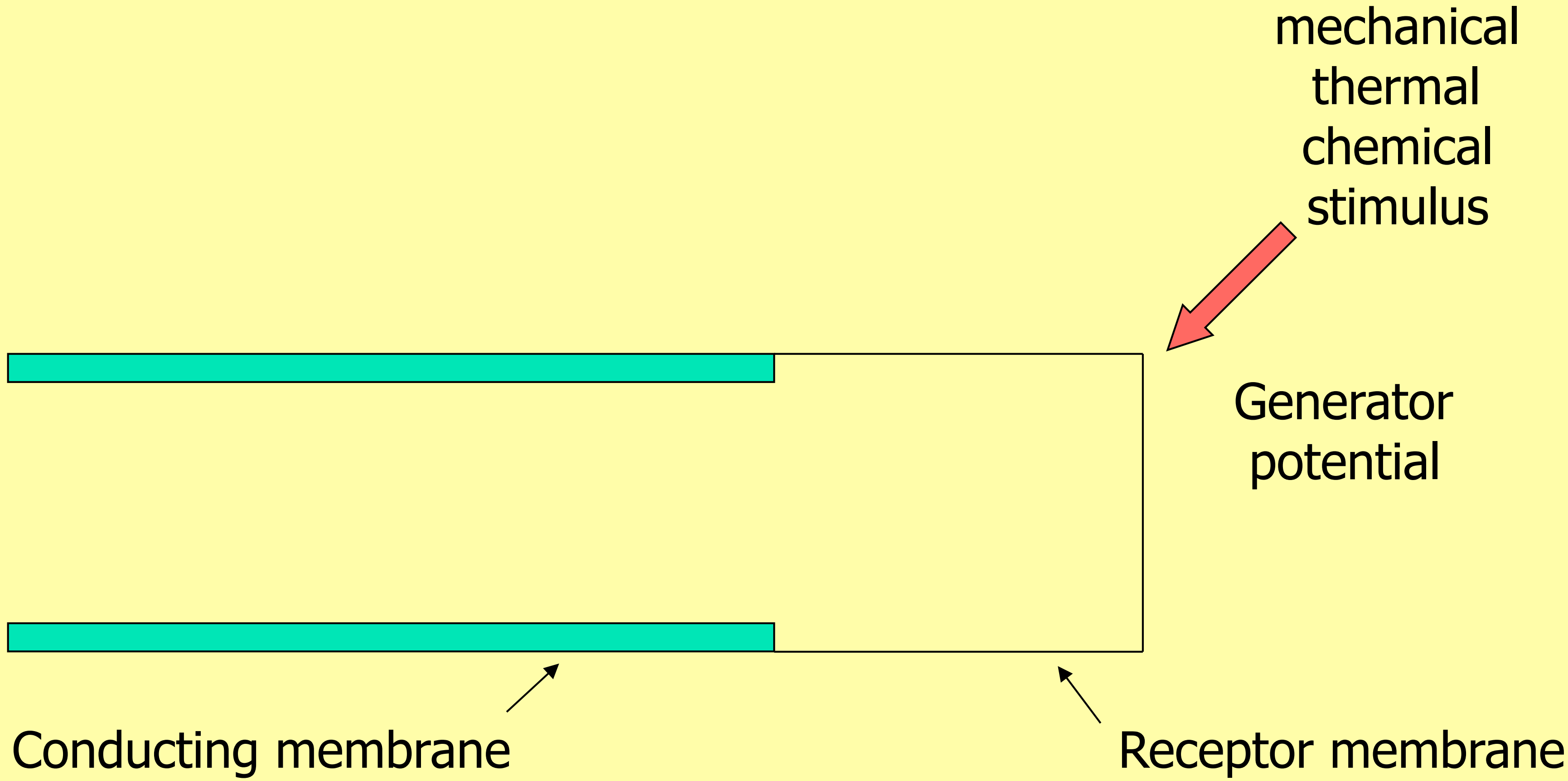


1. Synthesis, assembly, and export
4. Recycling
2. Translocation
3. Maturation and release

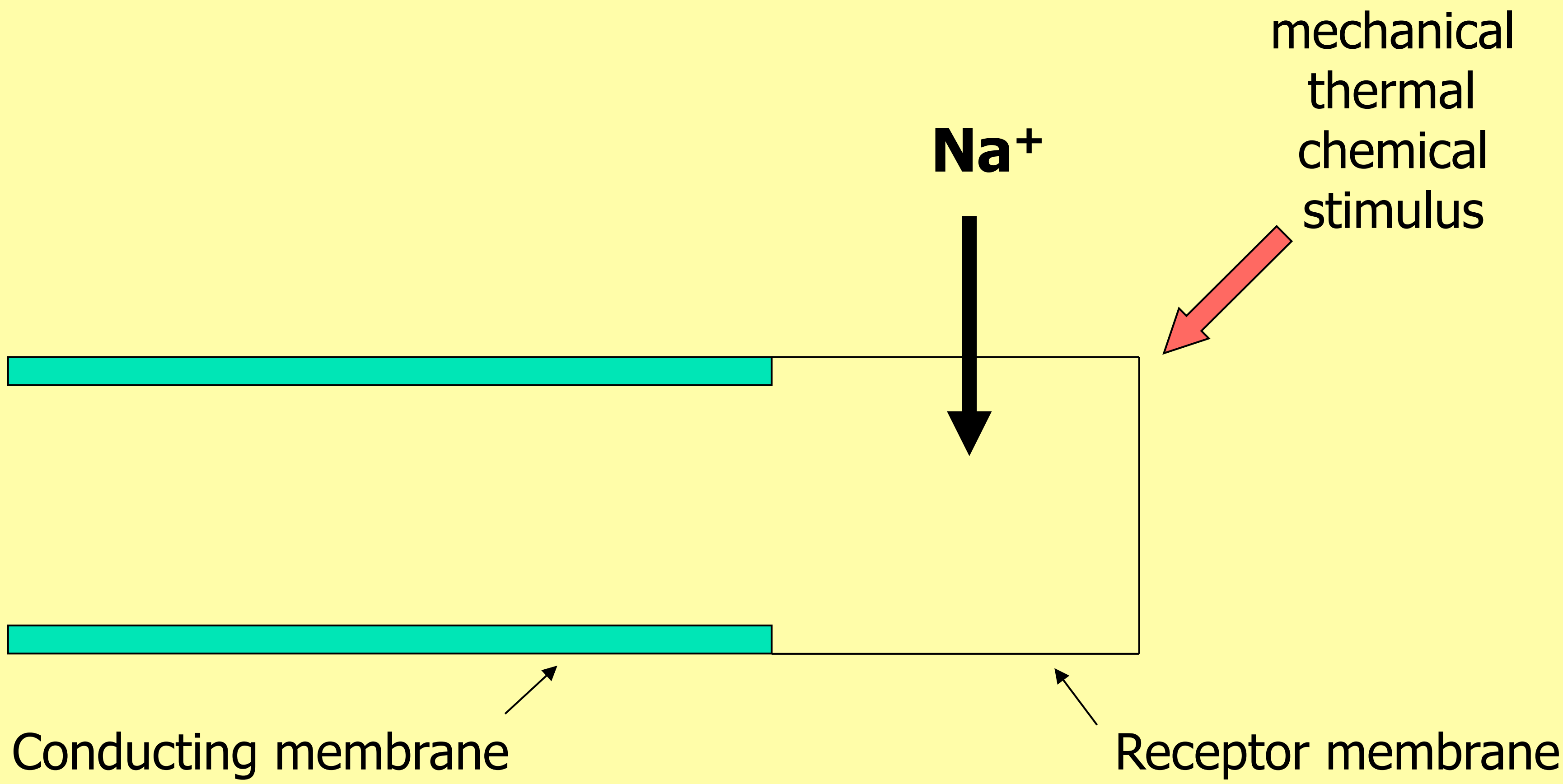
Peripheral Nerve Transduction

Detecting the Stimulus

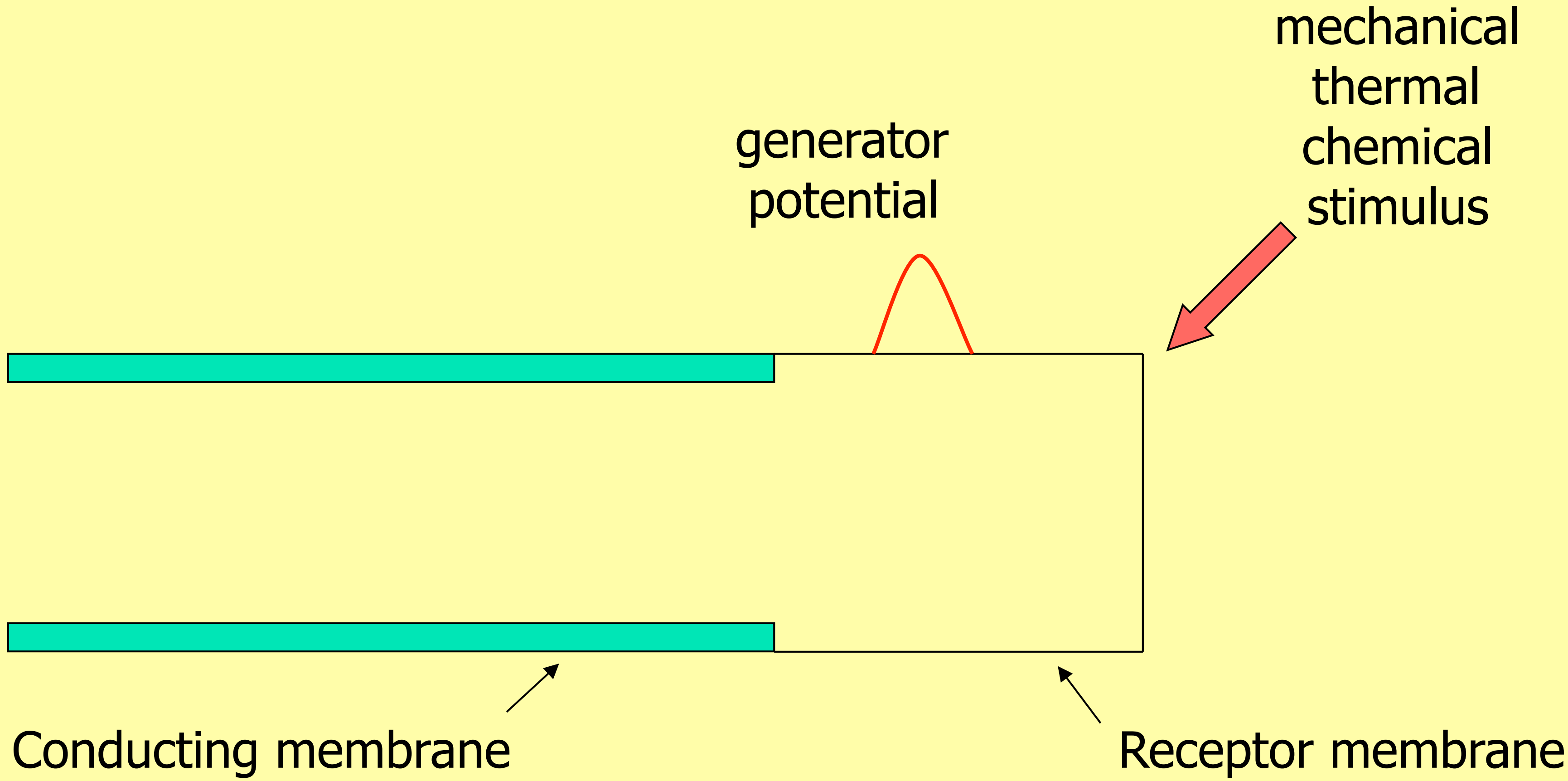
Transduction



Receptor membrane Na channels open

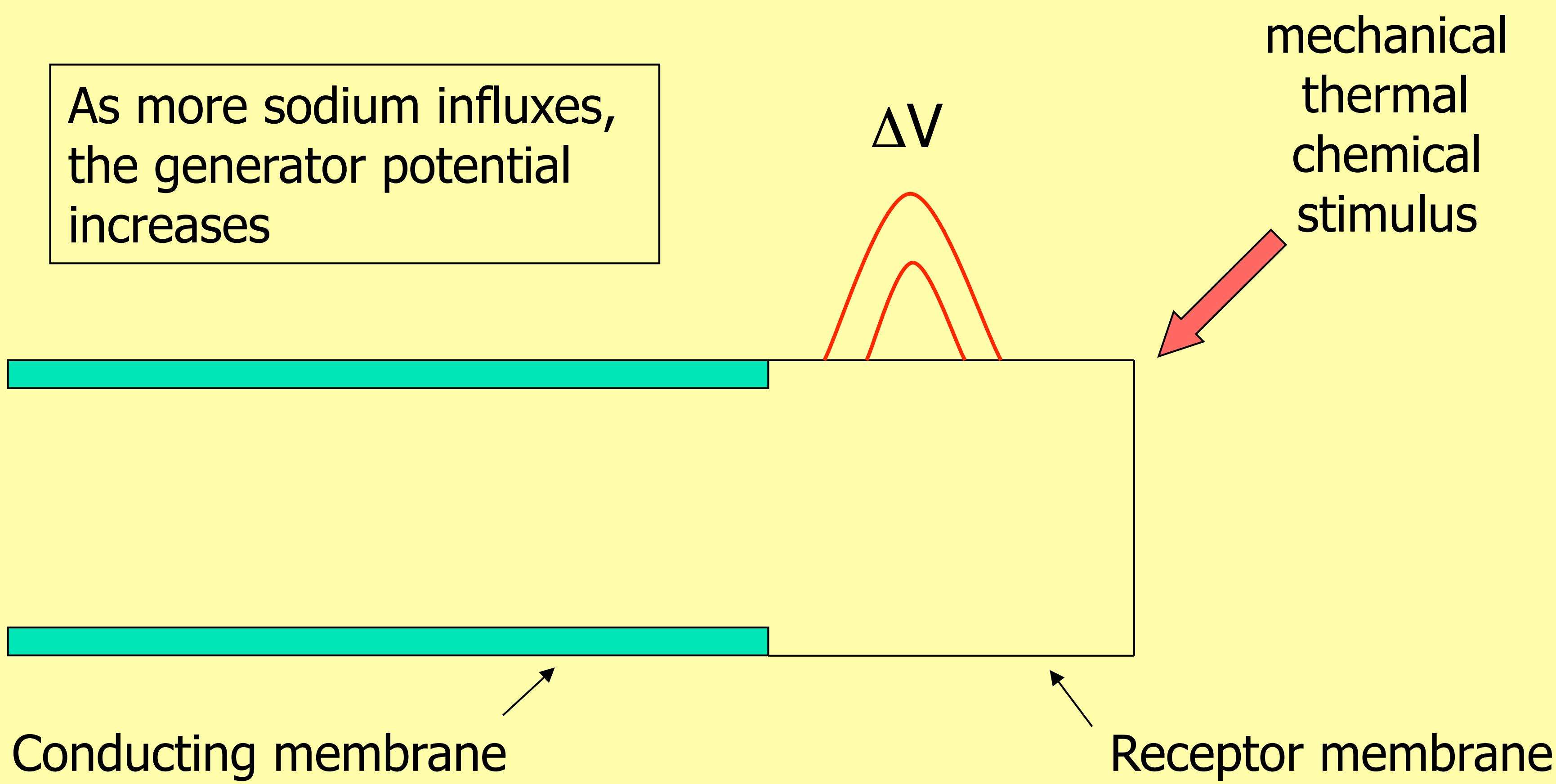


Generator potential



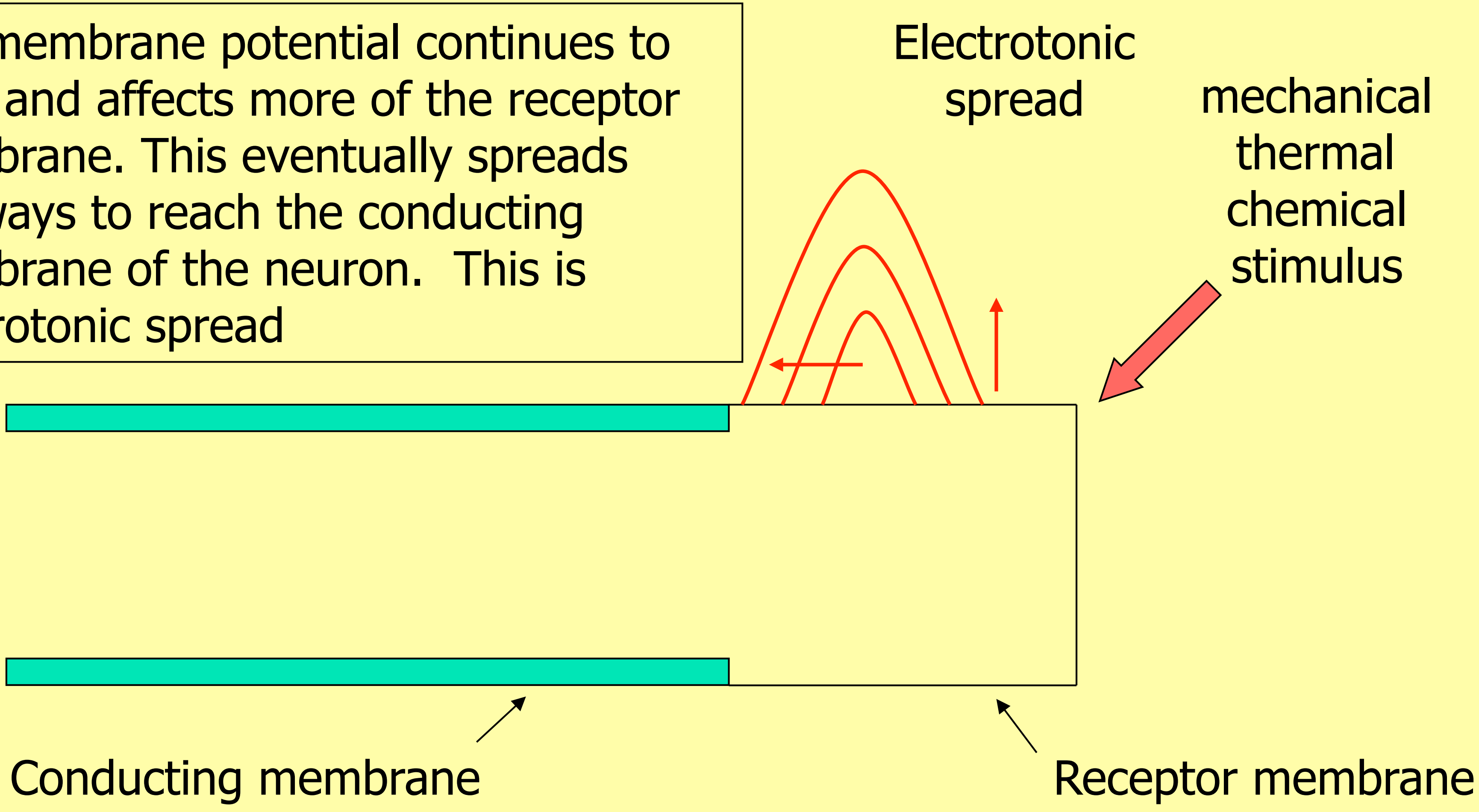
Generator potential

As more sodium influxes, the generator potential increases



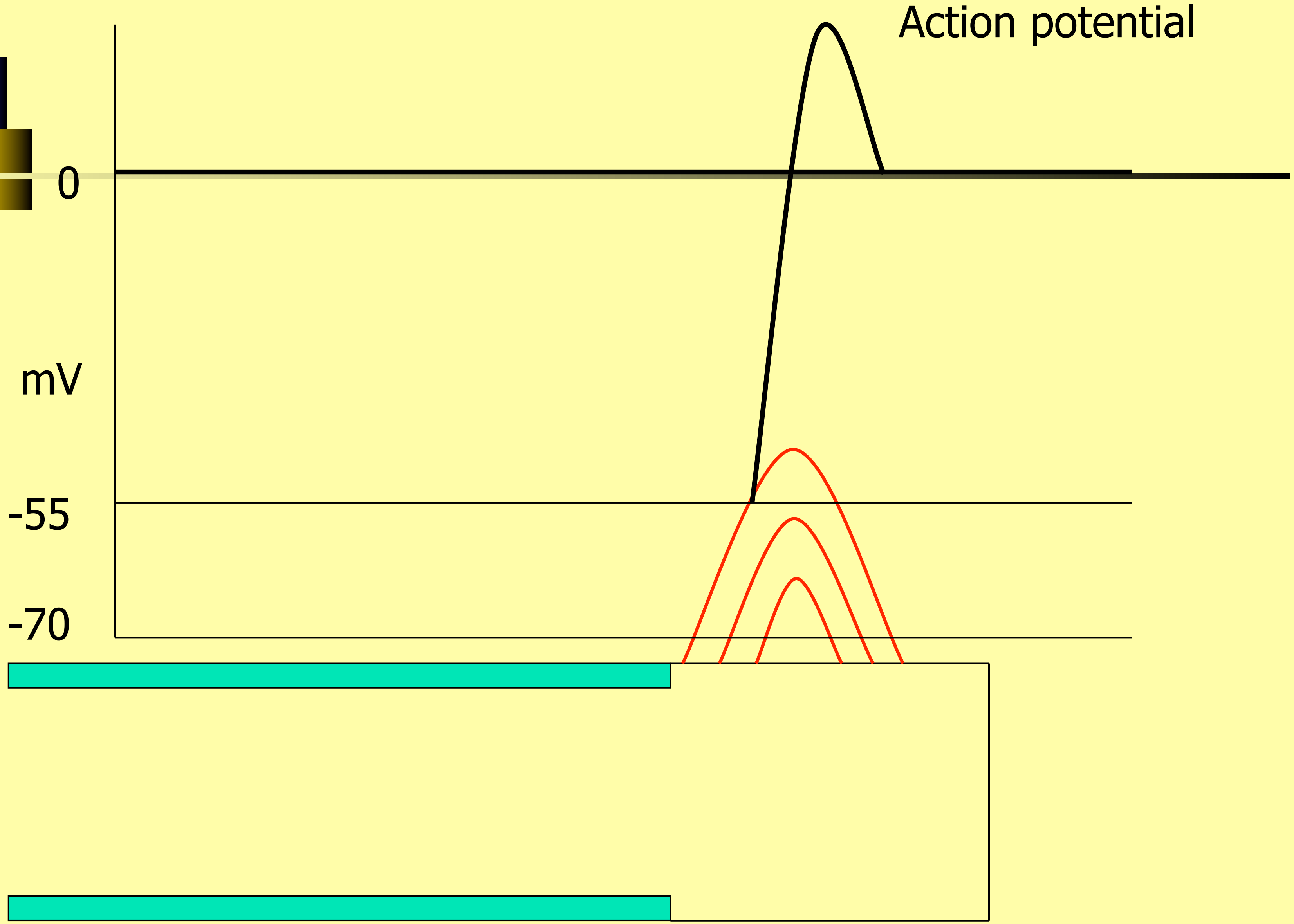
Electrotonic spread - sideways

The membrane potential continues to build and affects more of the receptor membrane. This eventually spreads sideways to reach the conducting membrane of the neuron. This is electrotonic spread



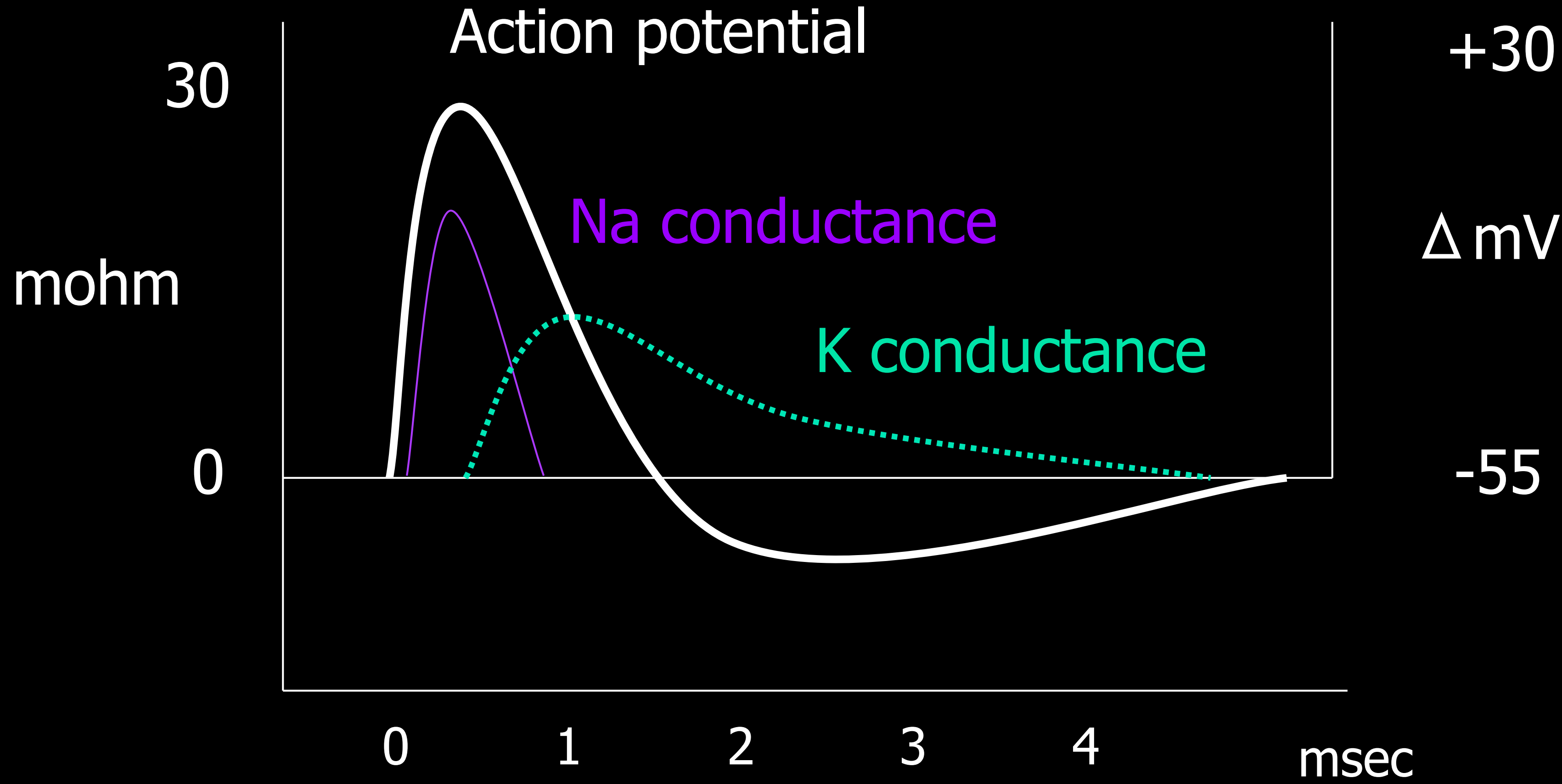
Generation of the Action potential

- When the generator potential approaches the conducting membrane of the axon and reaches approx -55mv, an action potential is generated
- The action potential is generated firstly because of the rapid flux of sodium into the cell and then the slightly slower efflux of potassium ions out of the cell


Action potential
0
mV
-55
-70

- Whereas the action potential is first caused by the rapid influx of sodium ions, this is reversed by the slightly slower efflux of potassium
- The cell then repolarises back towards its normal resting potential of -70 to -90 on the inside

Action Potential



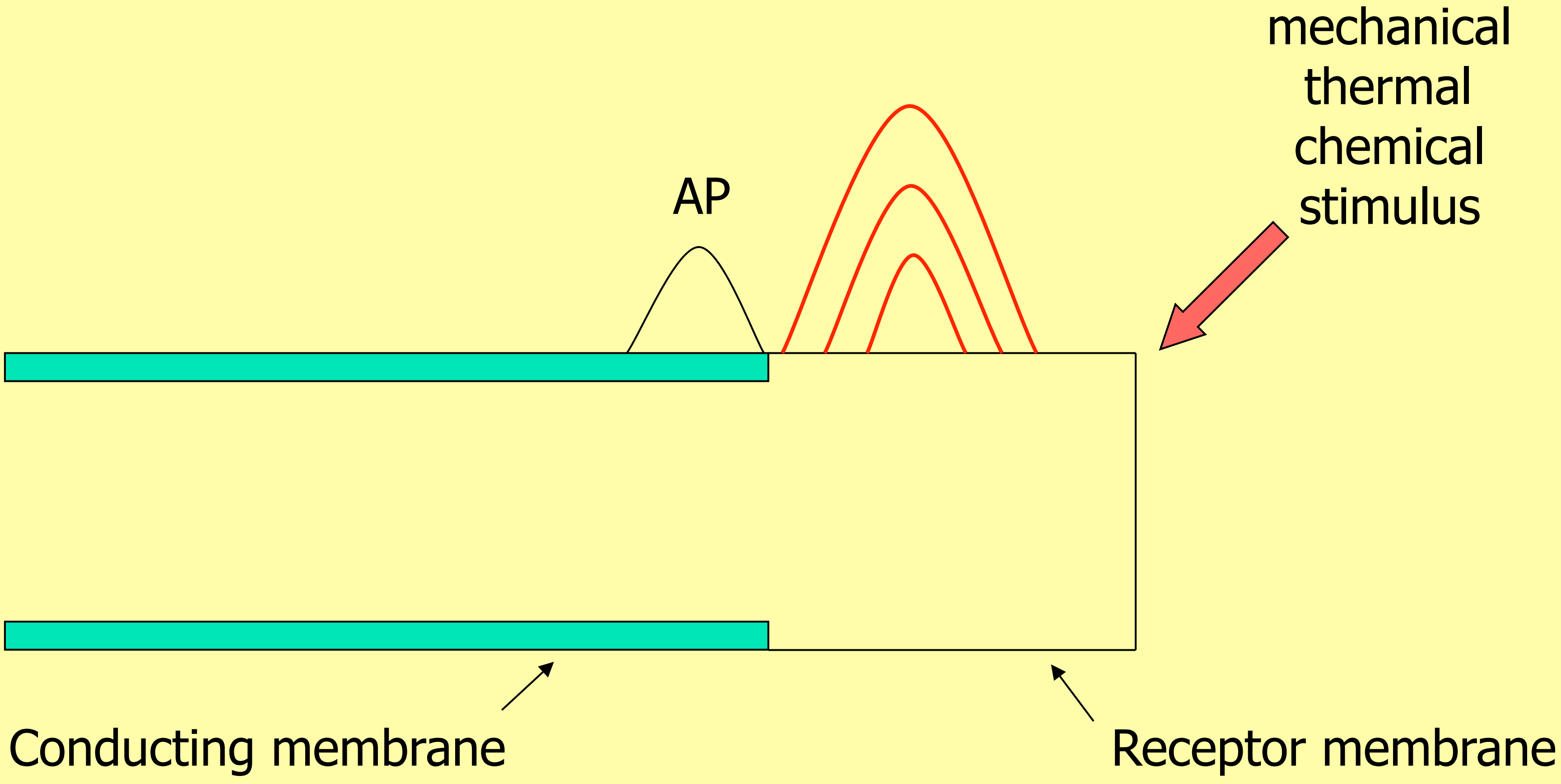
Circumduction

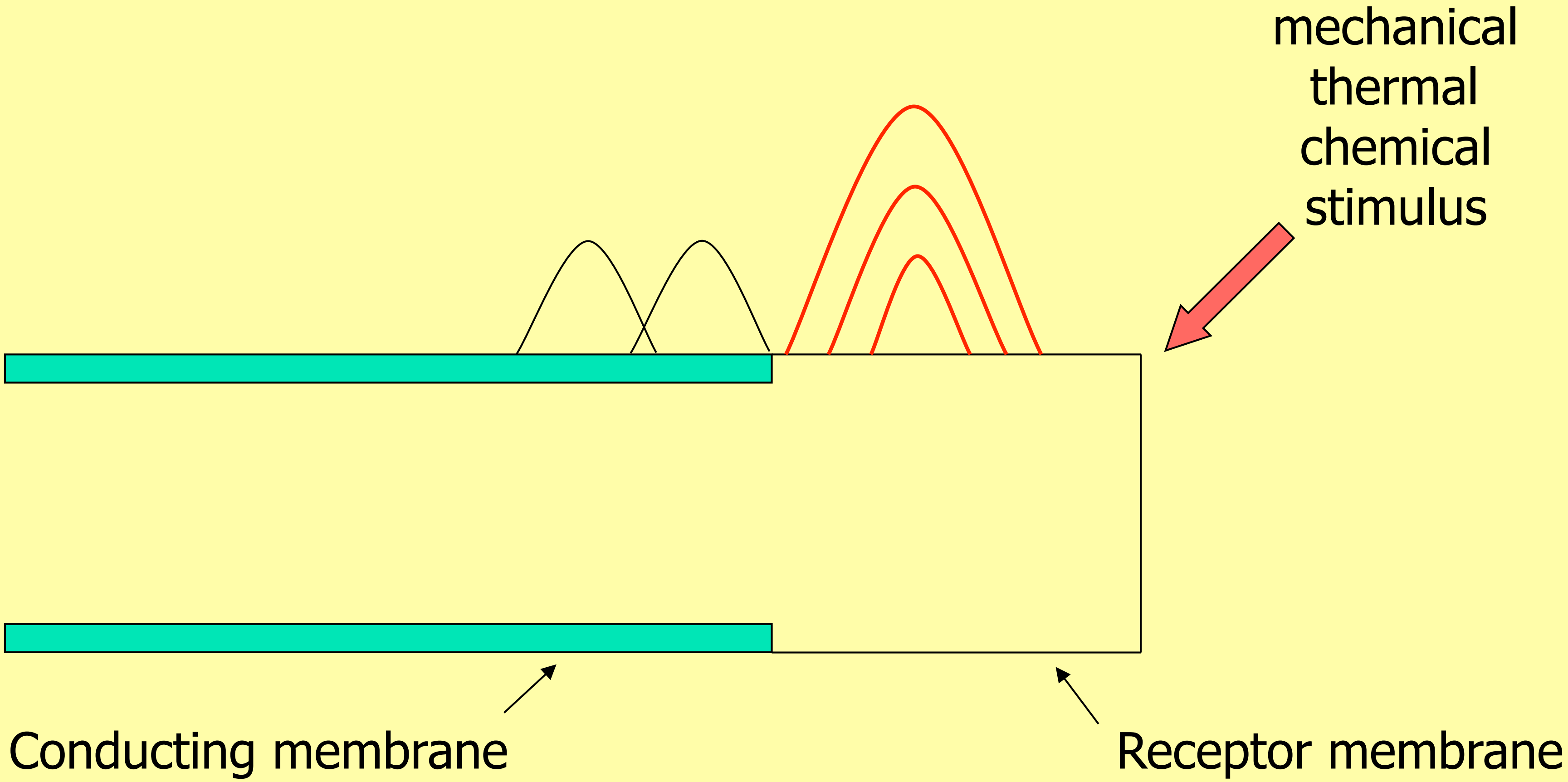
Transmission in Non-myelinated Nerves

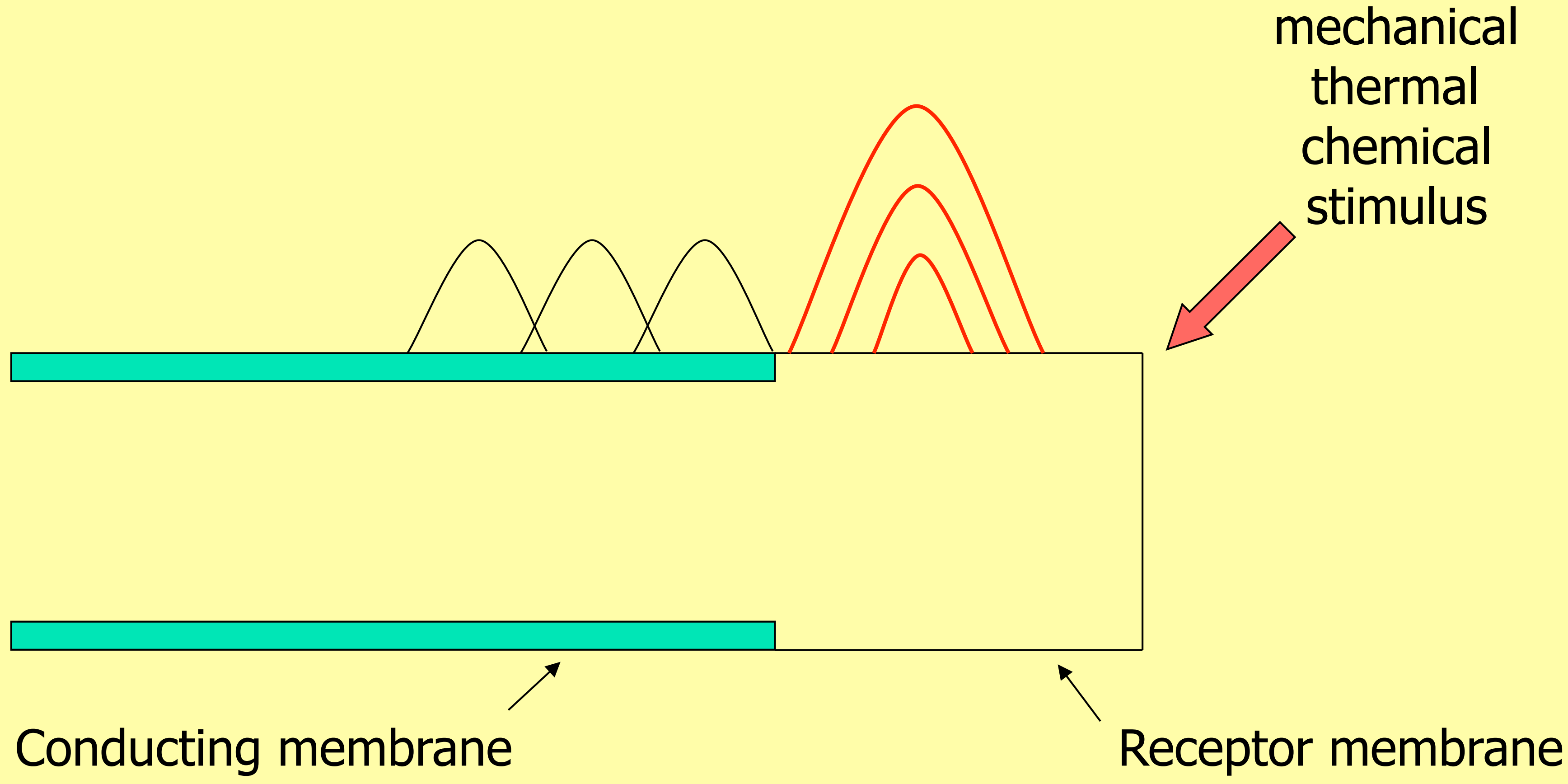
Circumduction – transmitting the AP

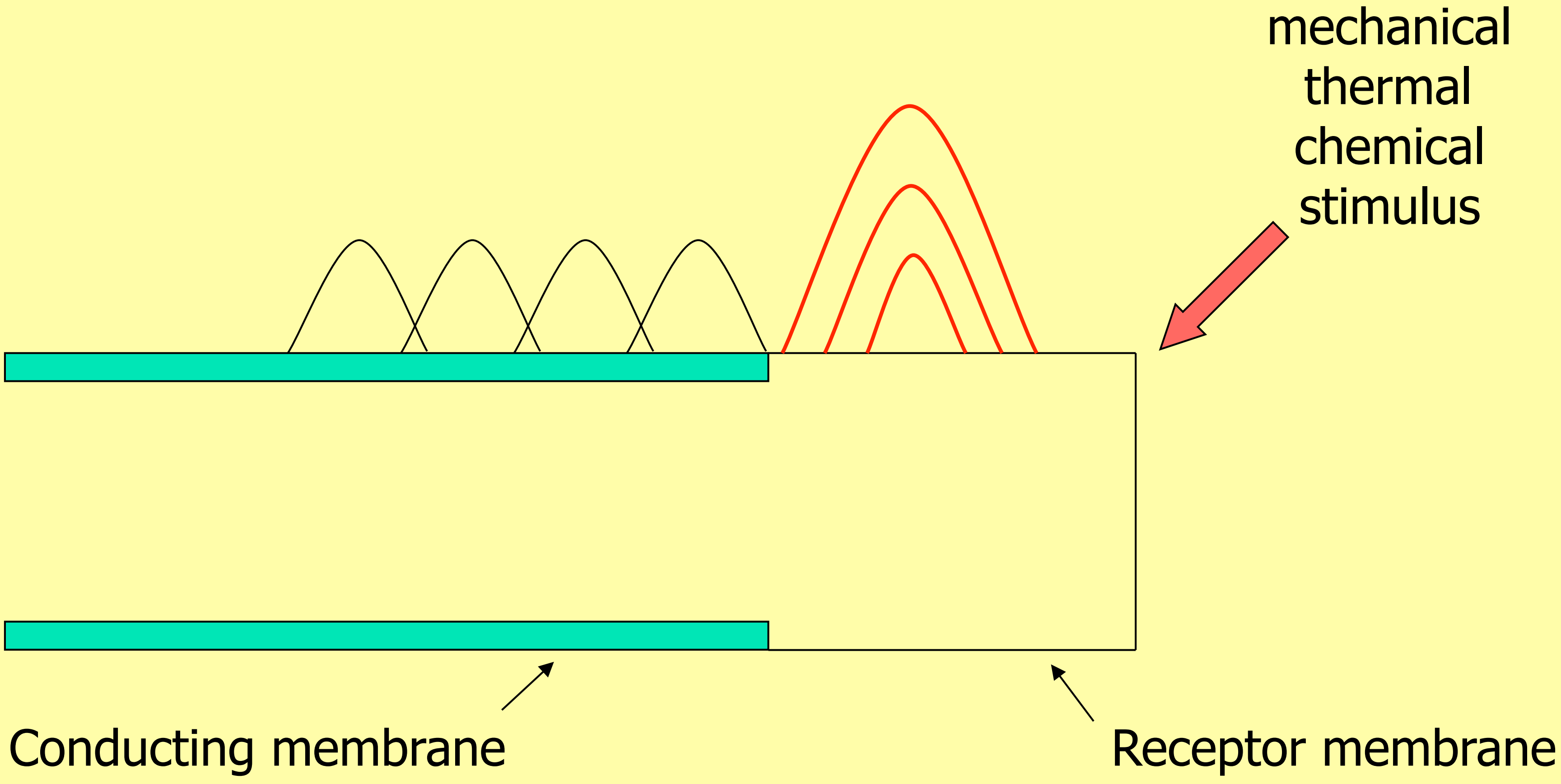
- The first action potential itself creates its own electrical field
- At its edges it depolarises the next section of the conducting membrane
- This opens the next set of sodium channels resulting in a further action potential
- Thus the action potentials propagate along the nerve

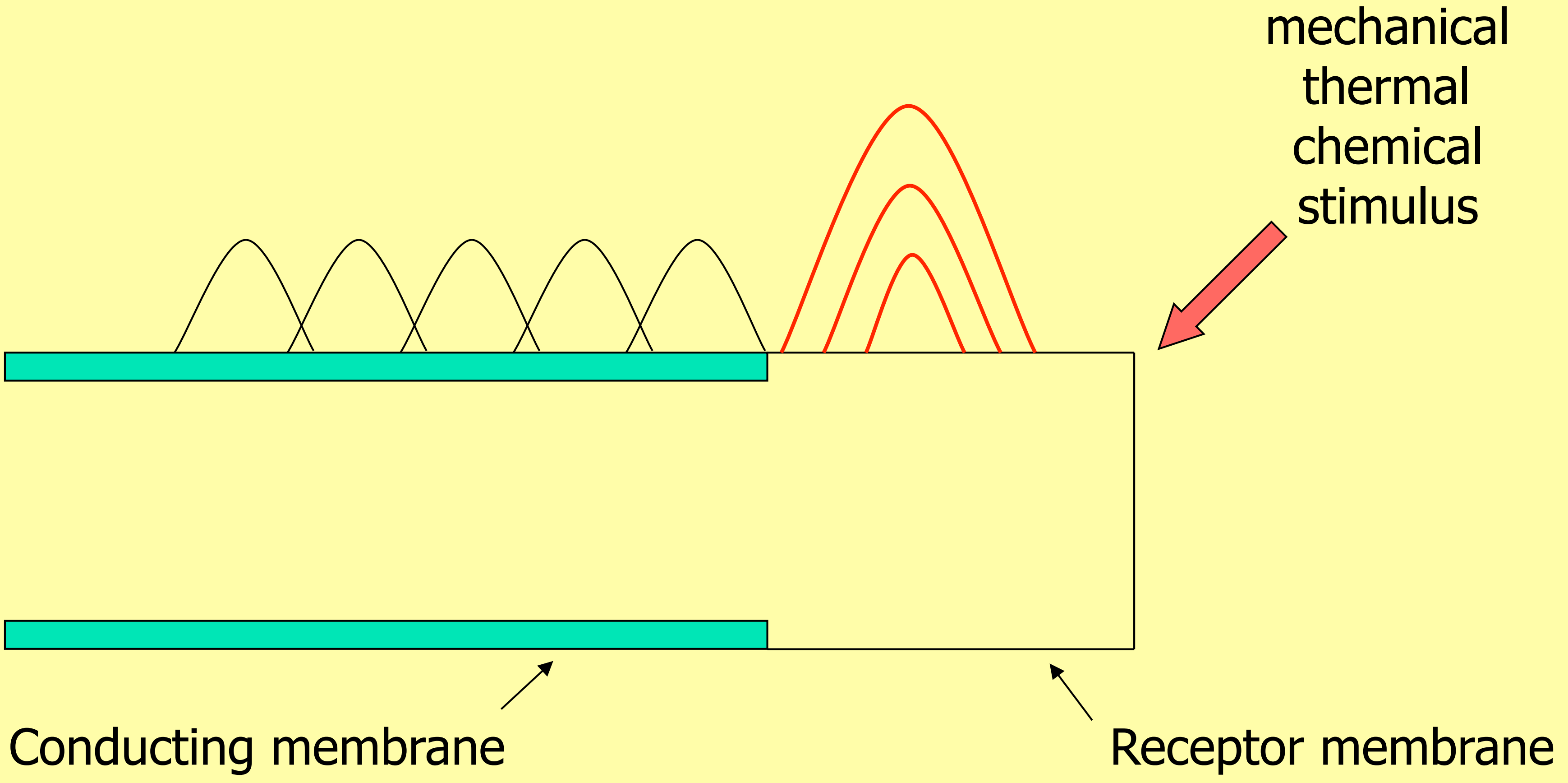
Circumduction – transmitting the AP



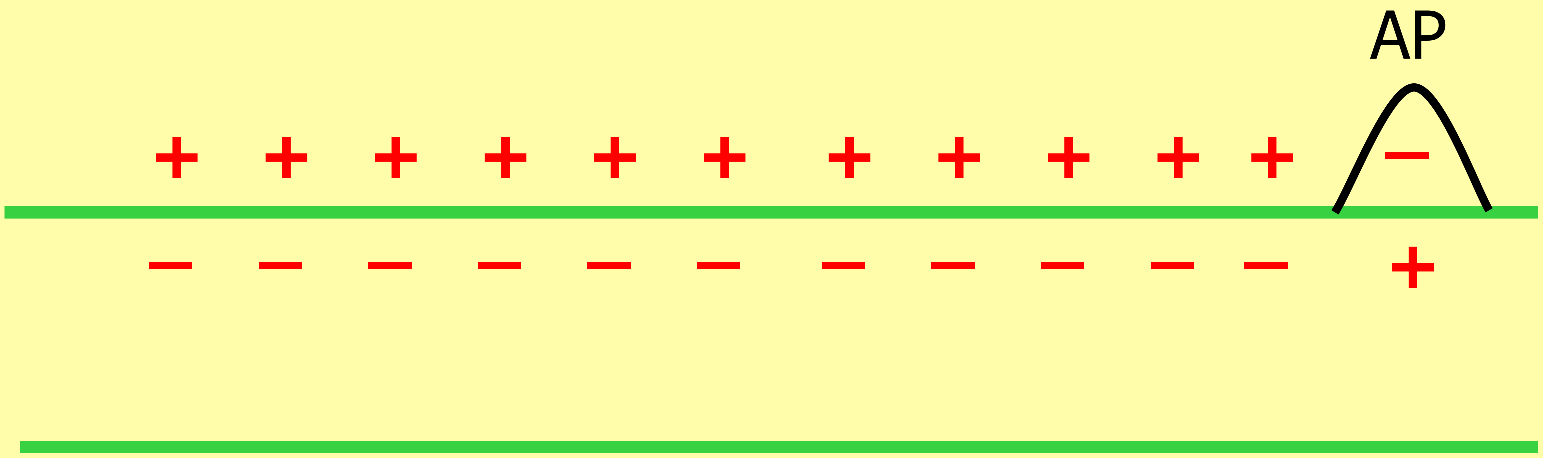

mechanical
thermal
chemical
stimulus
Conducting membrane
Receptor membrane

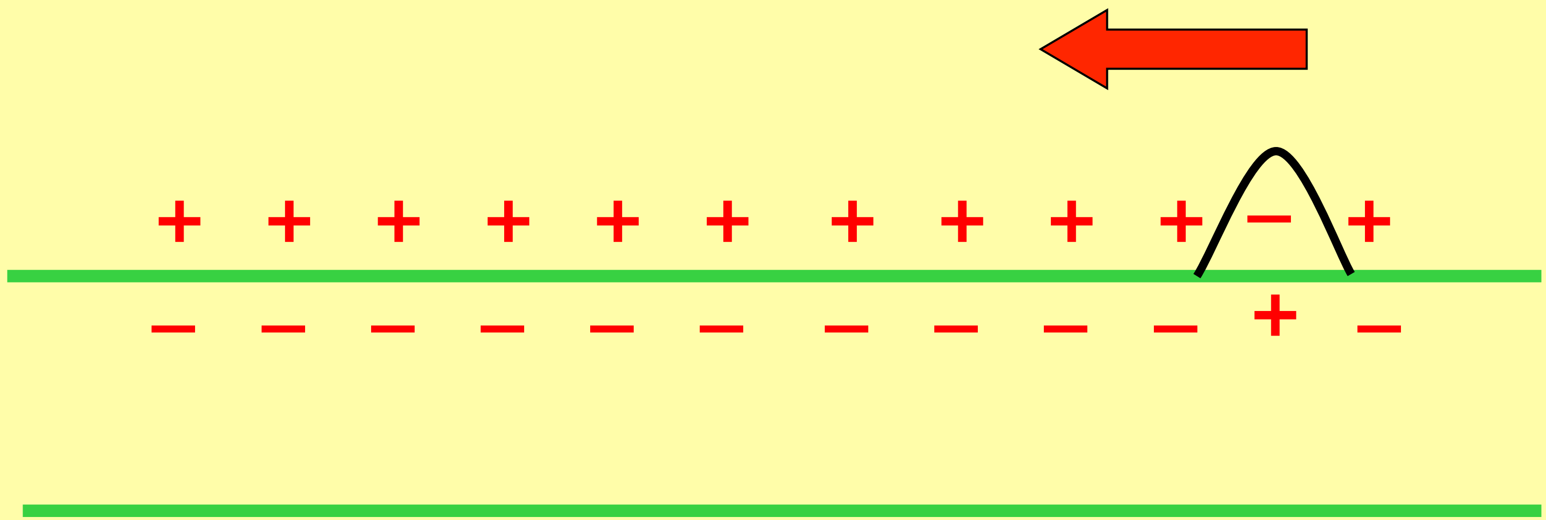

mechanical
thermal
chemical
stimulus
Conducting membrane
Receptor membrane

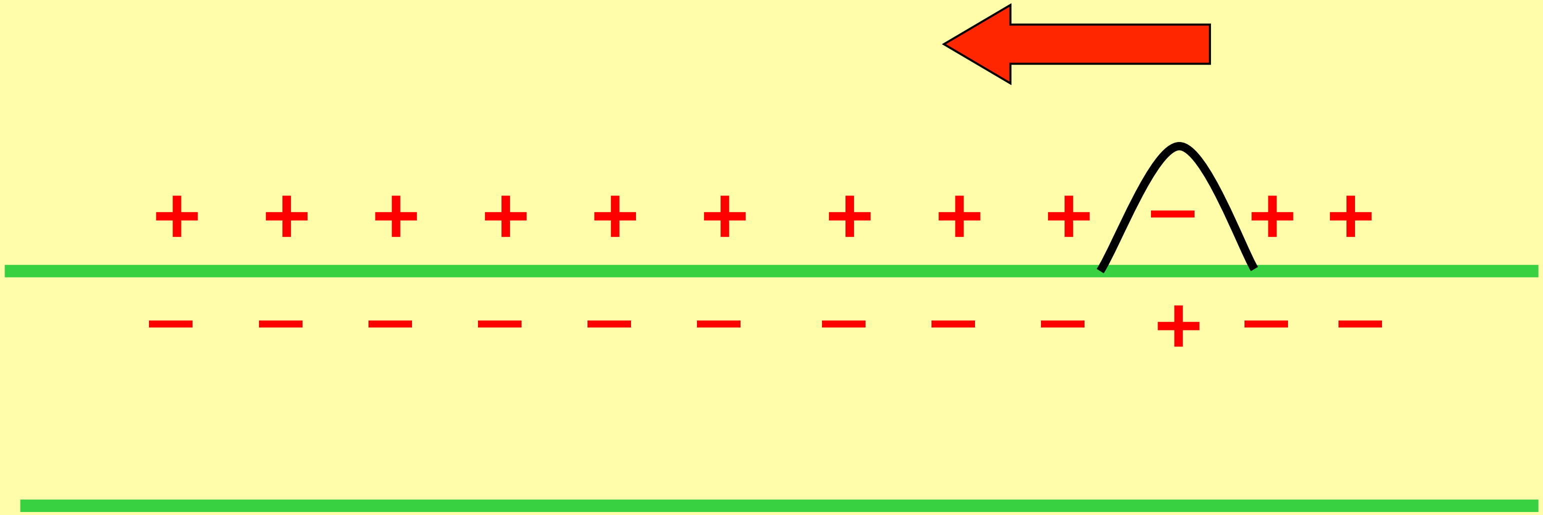

mechanical
thermal
chemical
stimulus
Conducting membrane
Receptor membrane

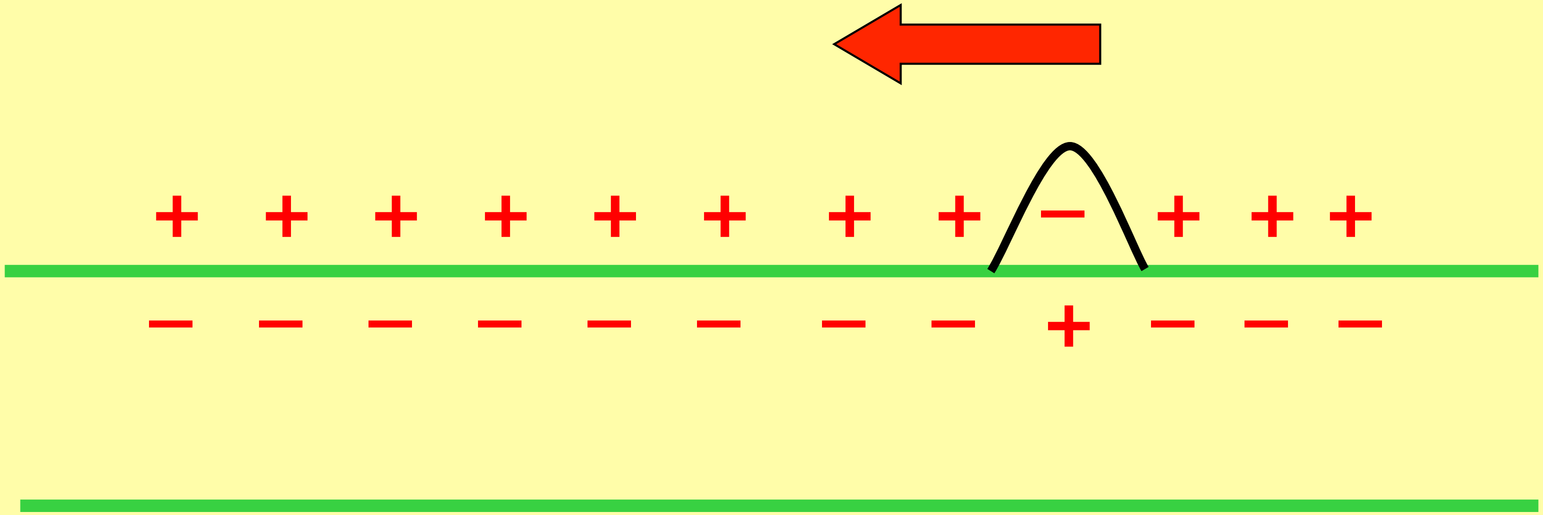

mechanical
thermal
chemical
stimulus
Conducting membrane
Receptor membrane

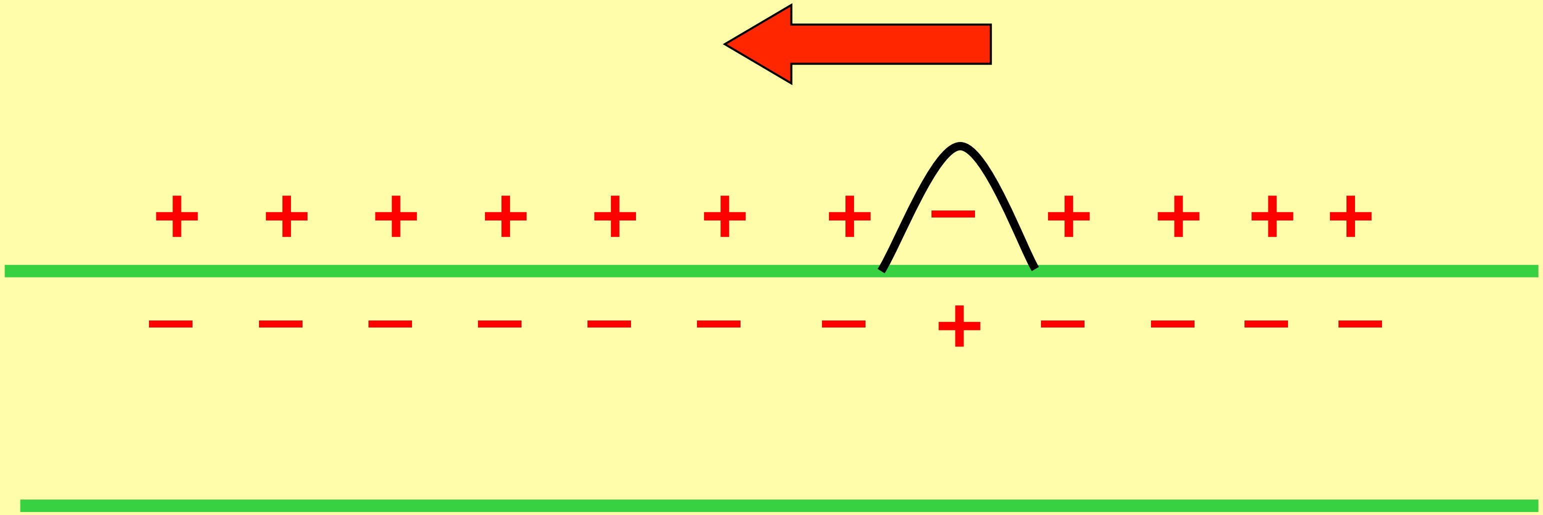
- There is no physical movement along the membrane, merely a series of ionic movements across the membrane

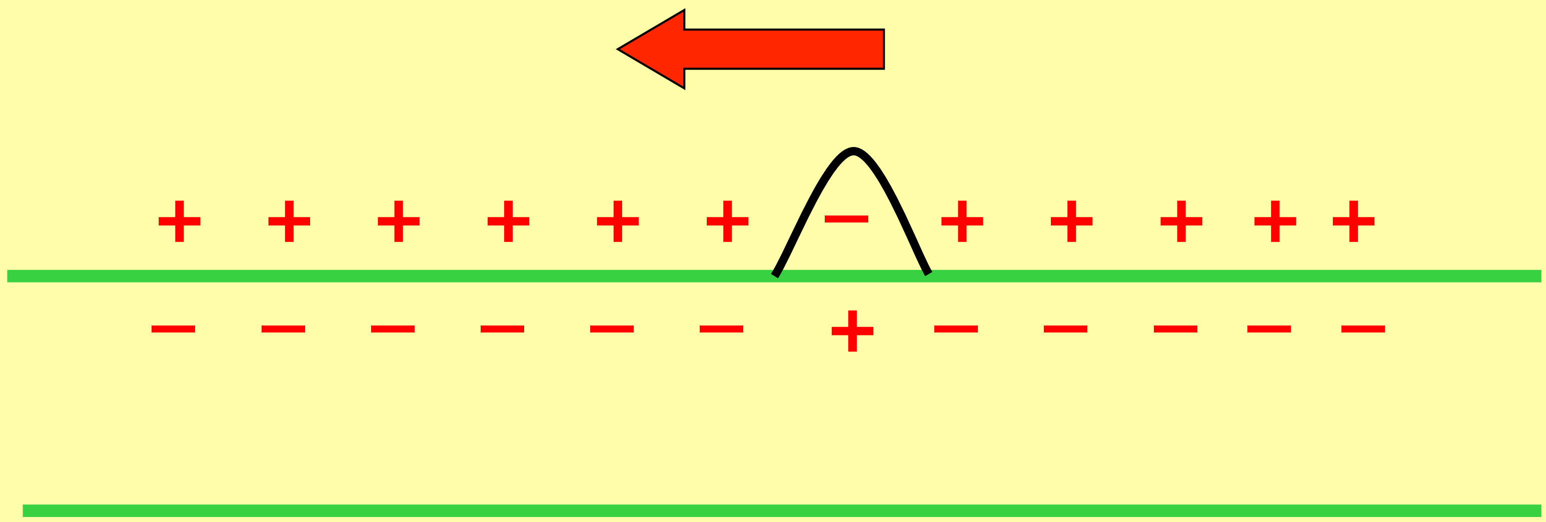












Transduction

Nerve Conduction in Myelinated Nerves

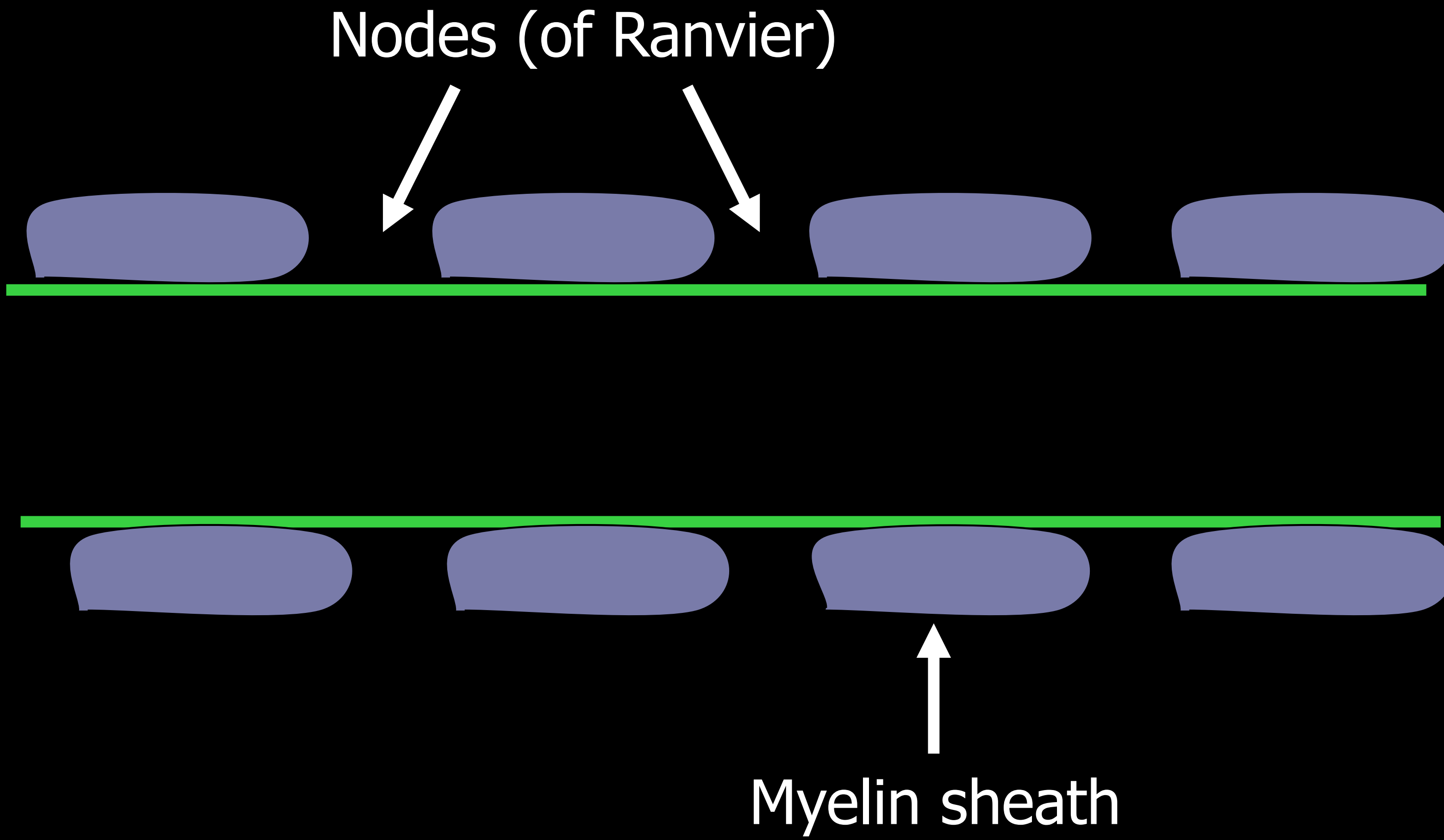
Myelination

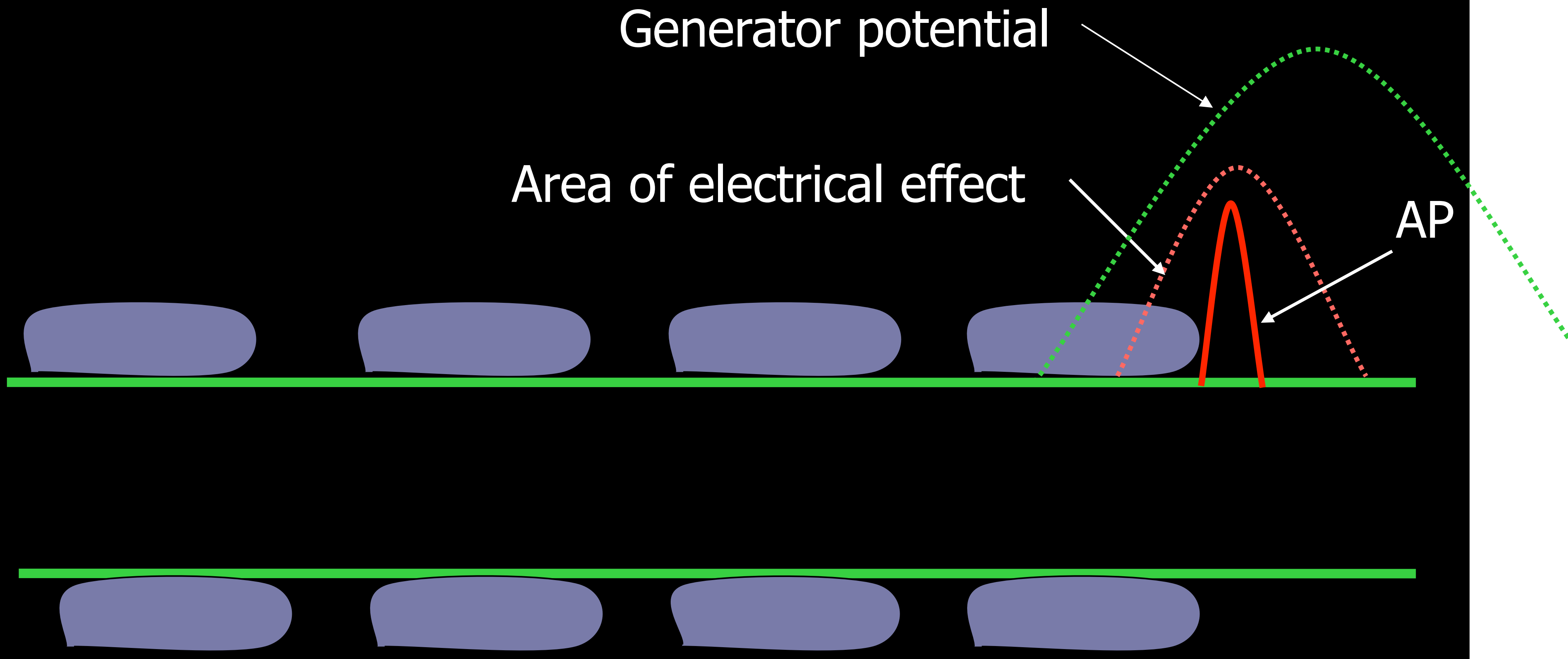
- The cylinders of axoplasm are encased in the axonal membrane
- They are always enveloped by a Schwann cell
- Many unmyelinated axons lie within invaginations of a single Schwann cell
- Myelinated axons have a single Schwann cell wrapped round them many times
- Myelin is a fat and therefore acts as an insulator
- The myelin sheath is interrupted at the Node of Ranvier

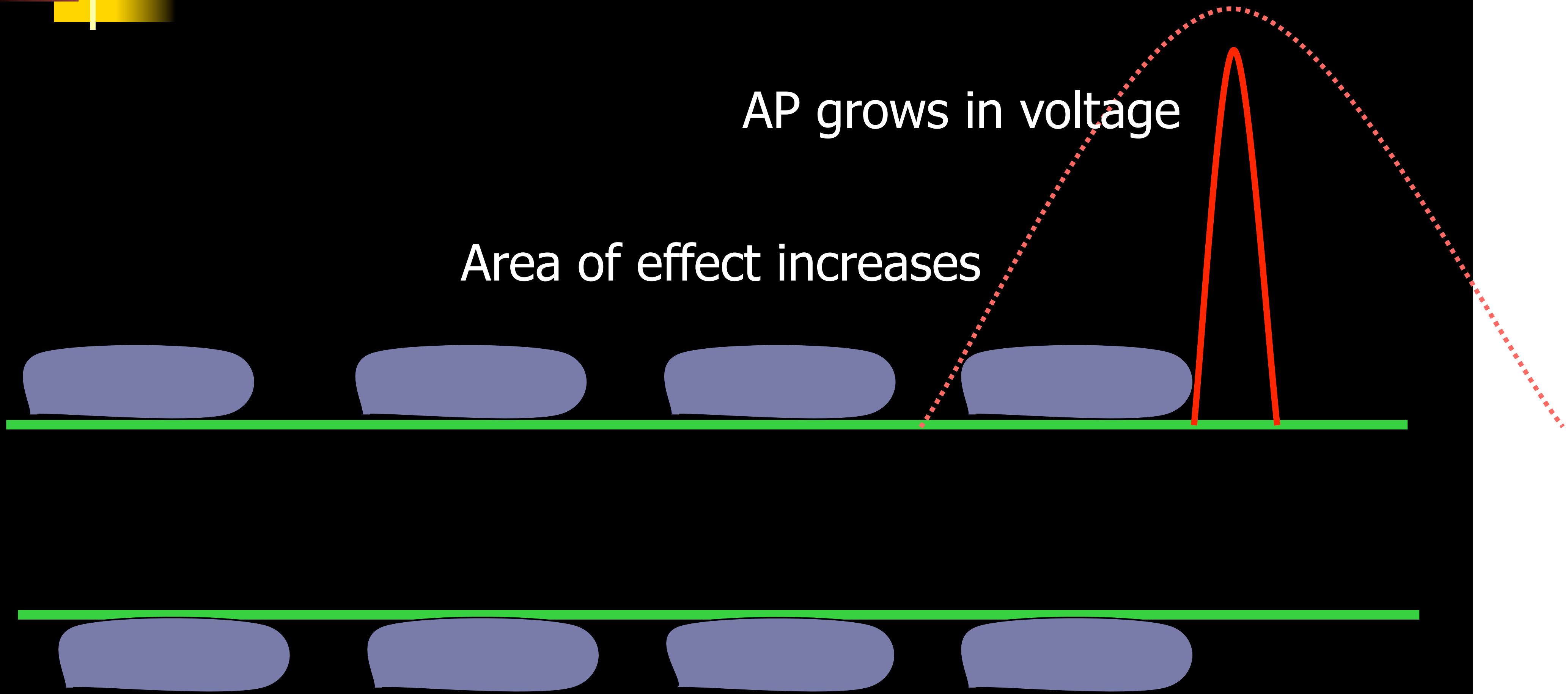
Myelination

- Nodes allow for saltatory (jumping) conduction
- The action potential jumps from node to node
- This occurs in 3 dimensions
- Under normal conditions this is directionally specific due to the refractory period
- This requires the Na/K pump to restore the membrane to normal
- If stimulated mid-way both orthodromic and antidromic conduction may occur

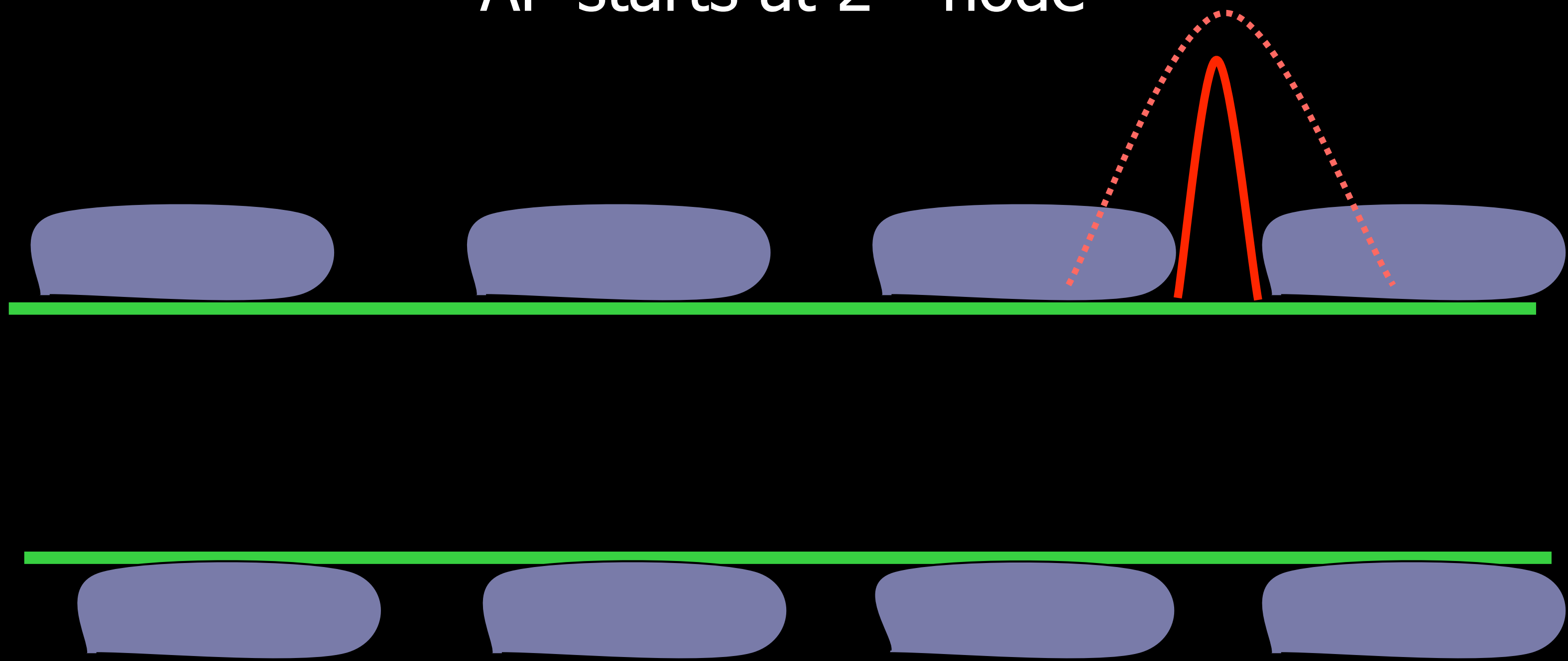
Nodes

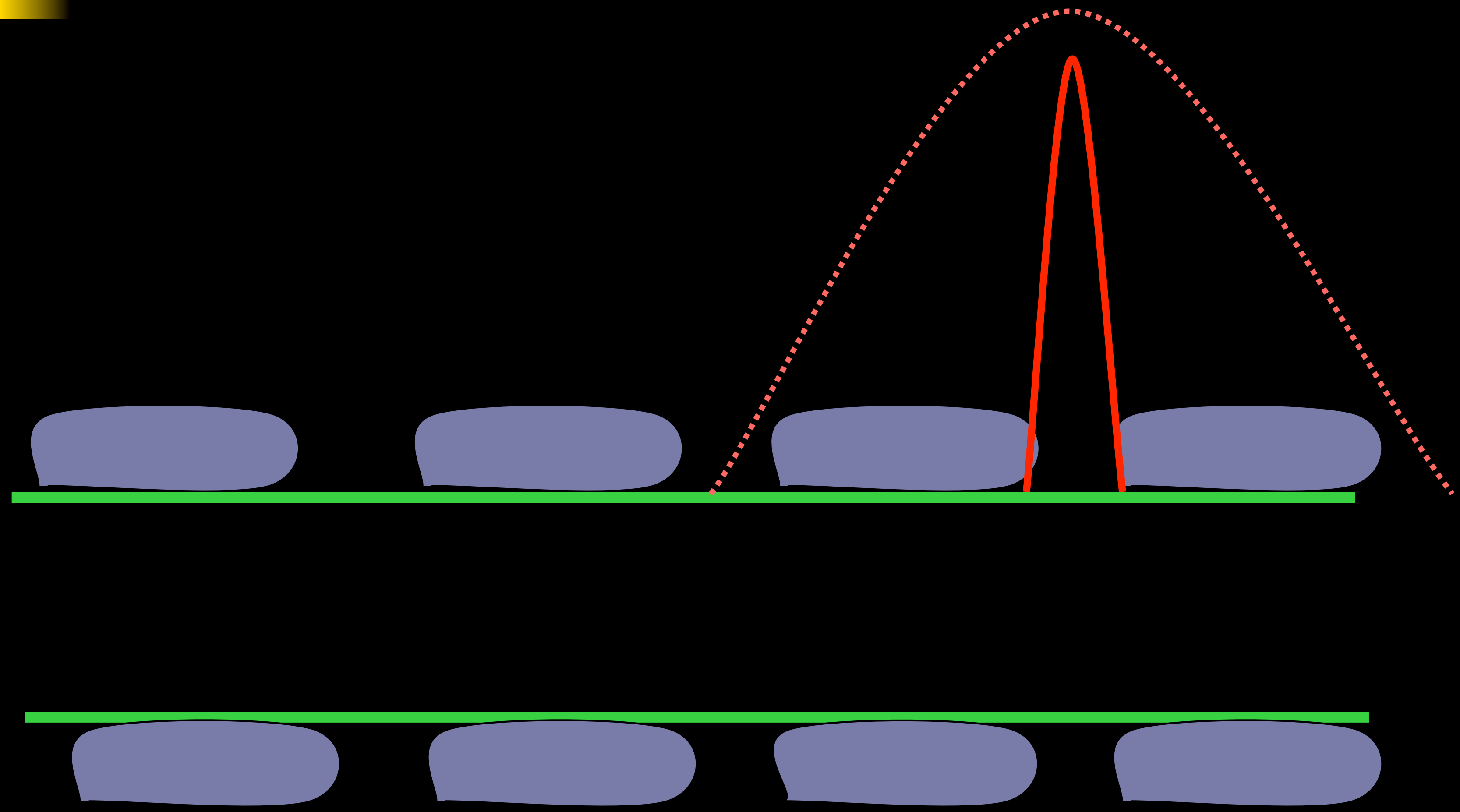


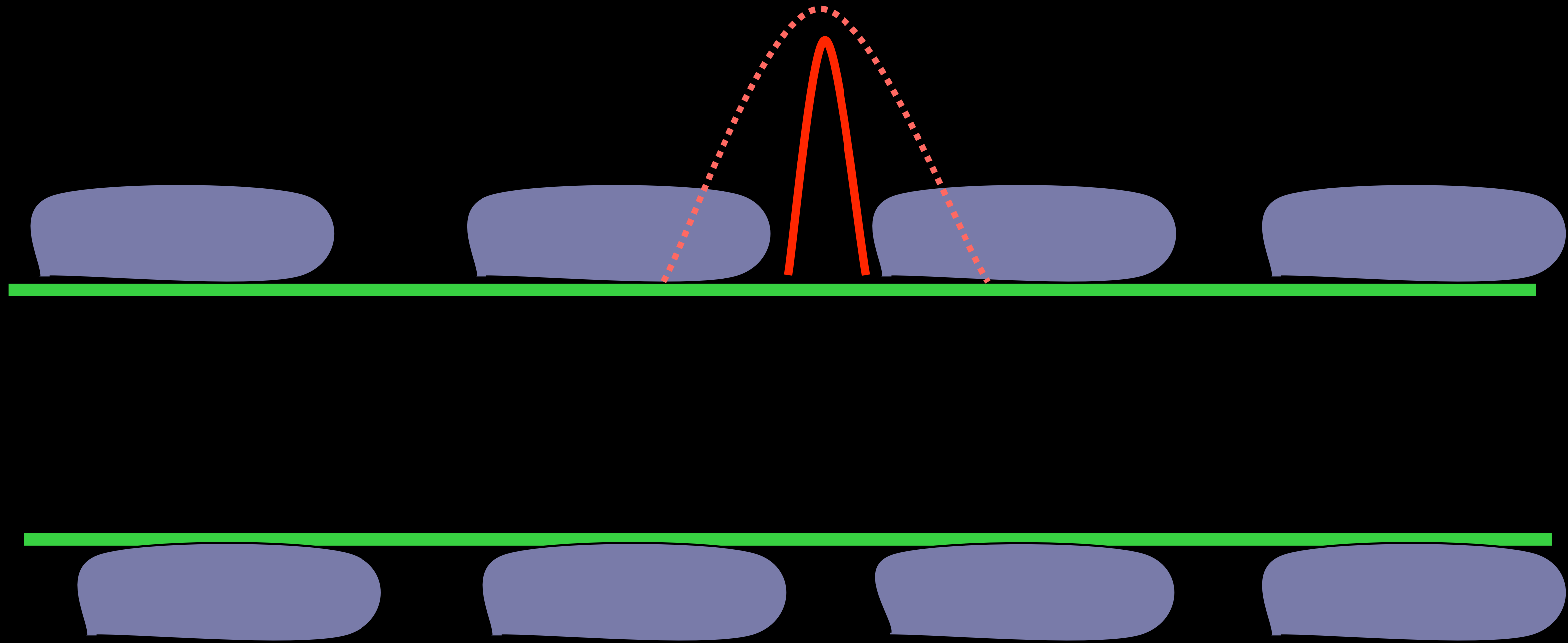

Generator potential
Area of electrical effect
AP

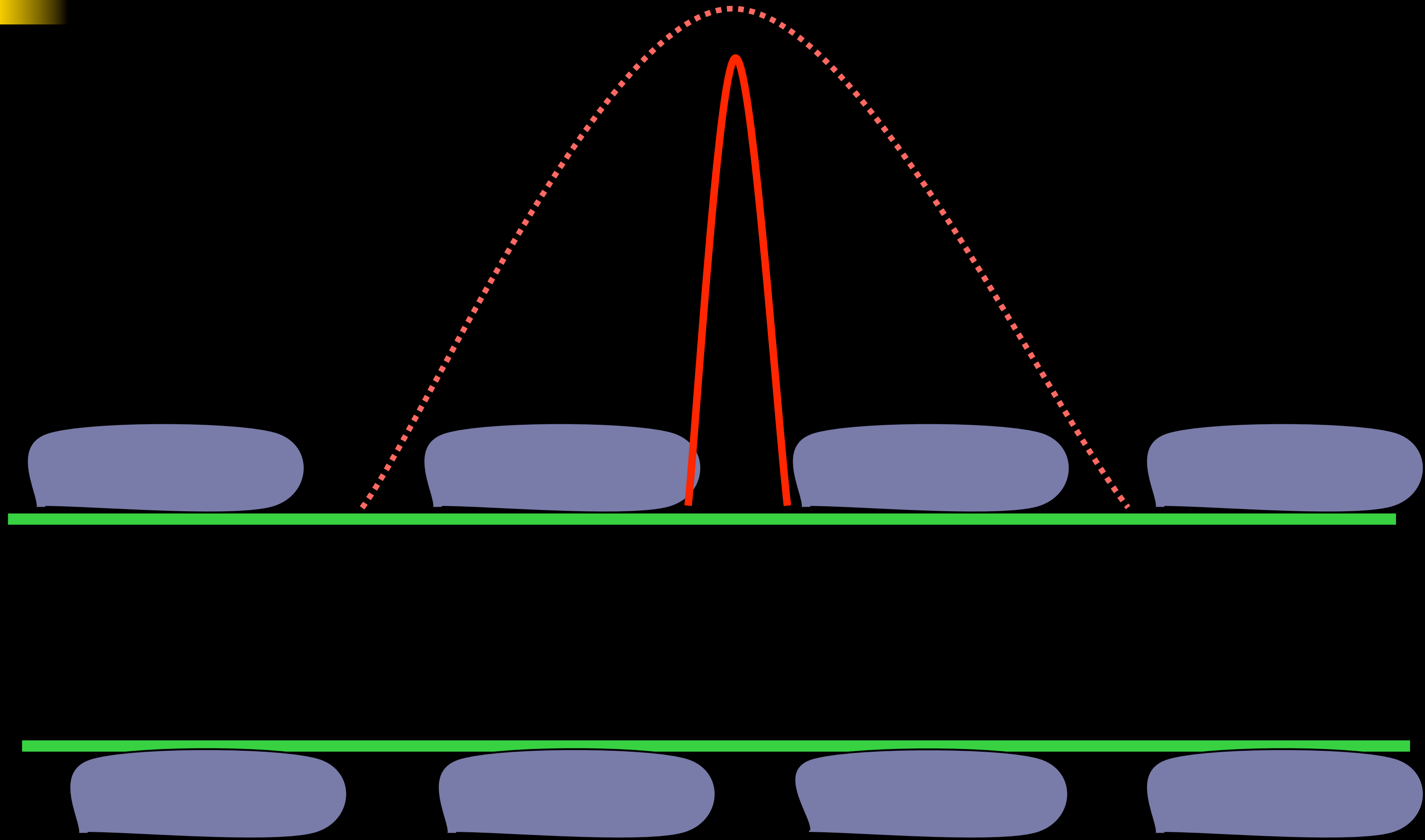

AP grows in voltage
Area of effect increases

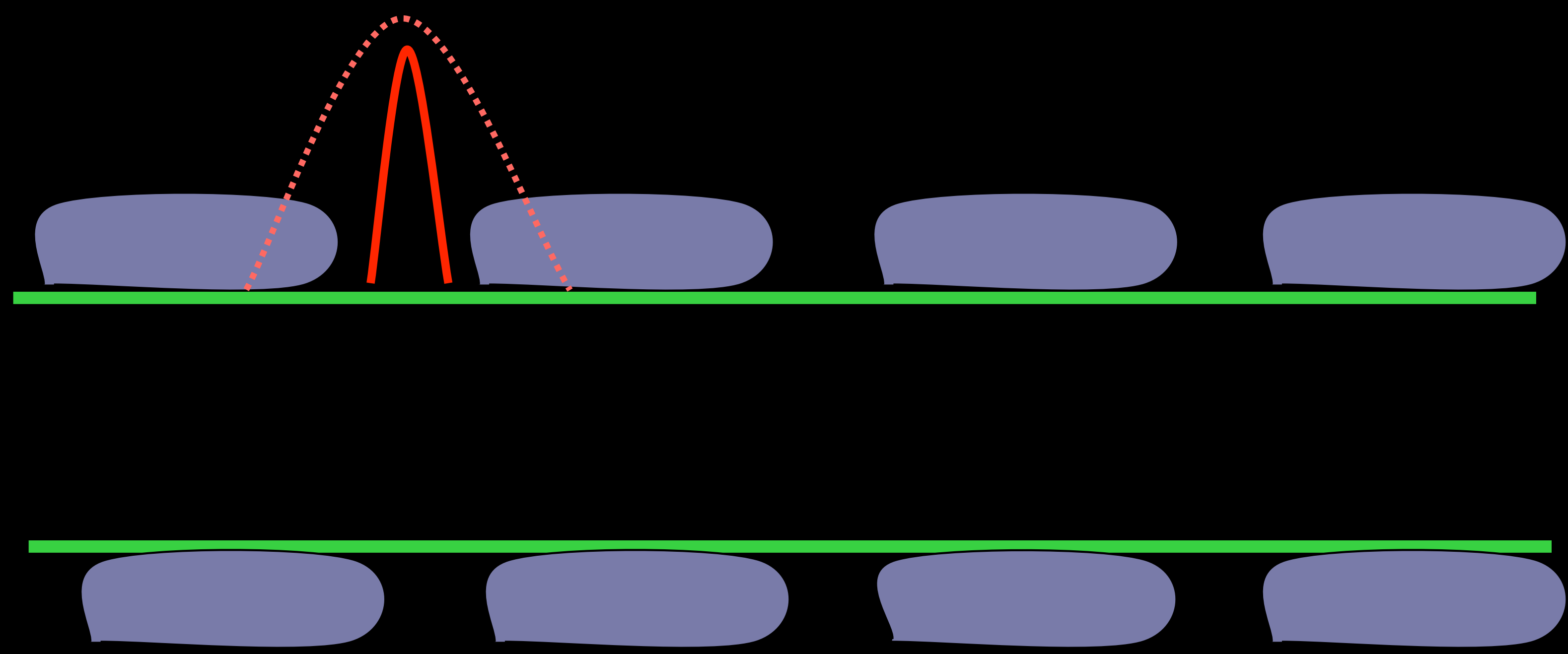
AP starts at 2nd node

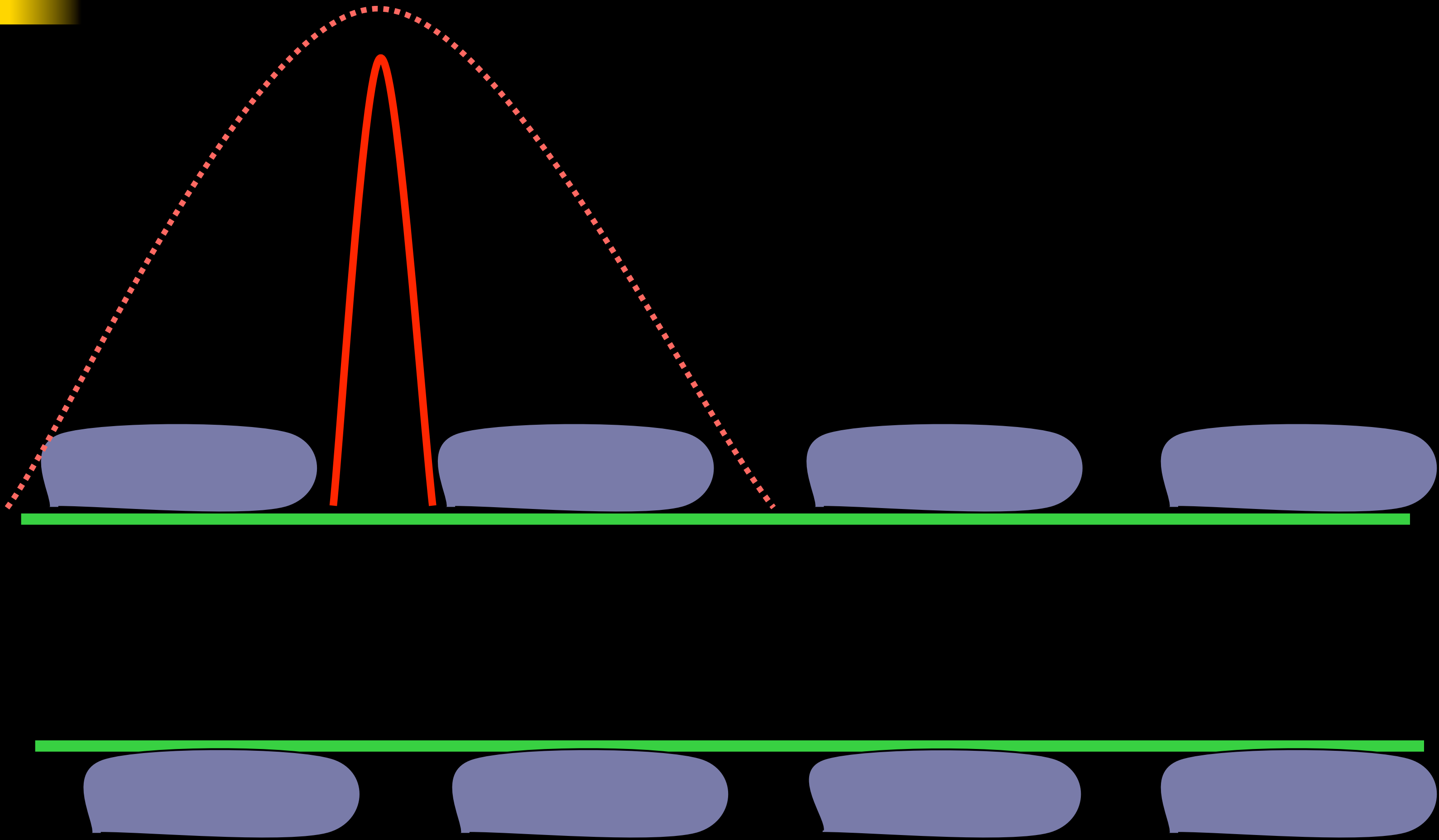




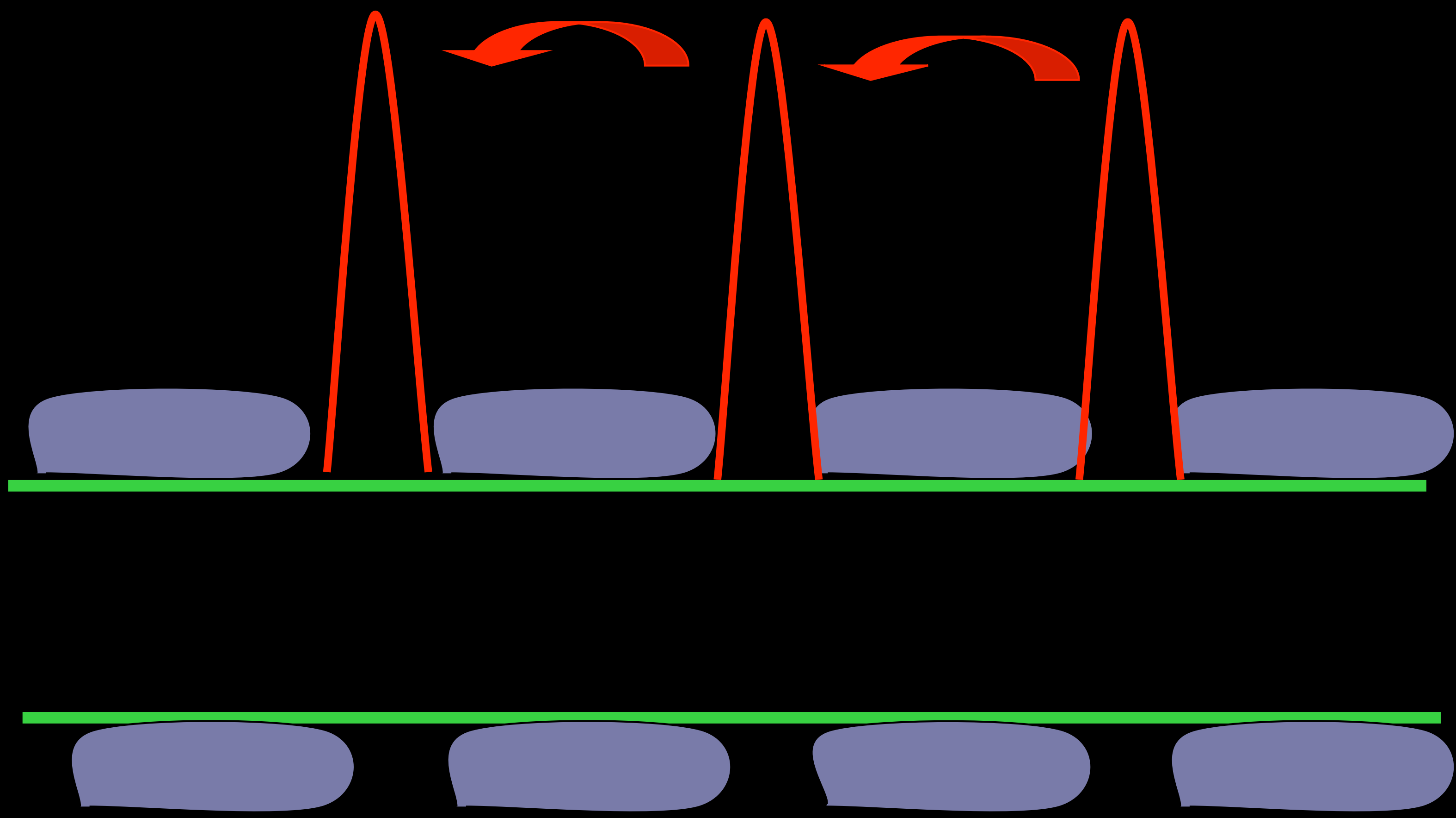








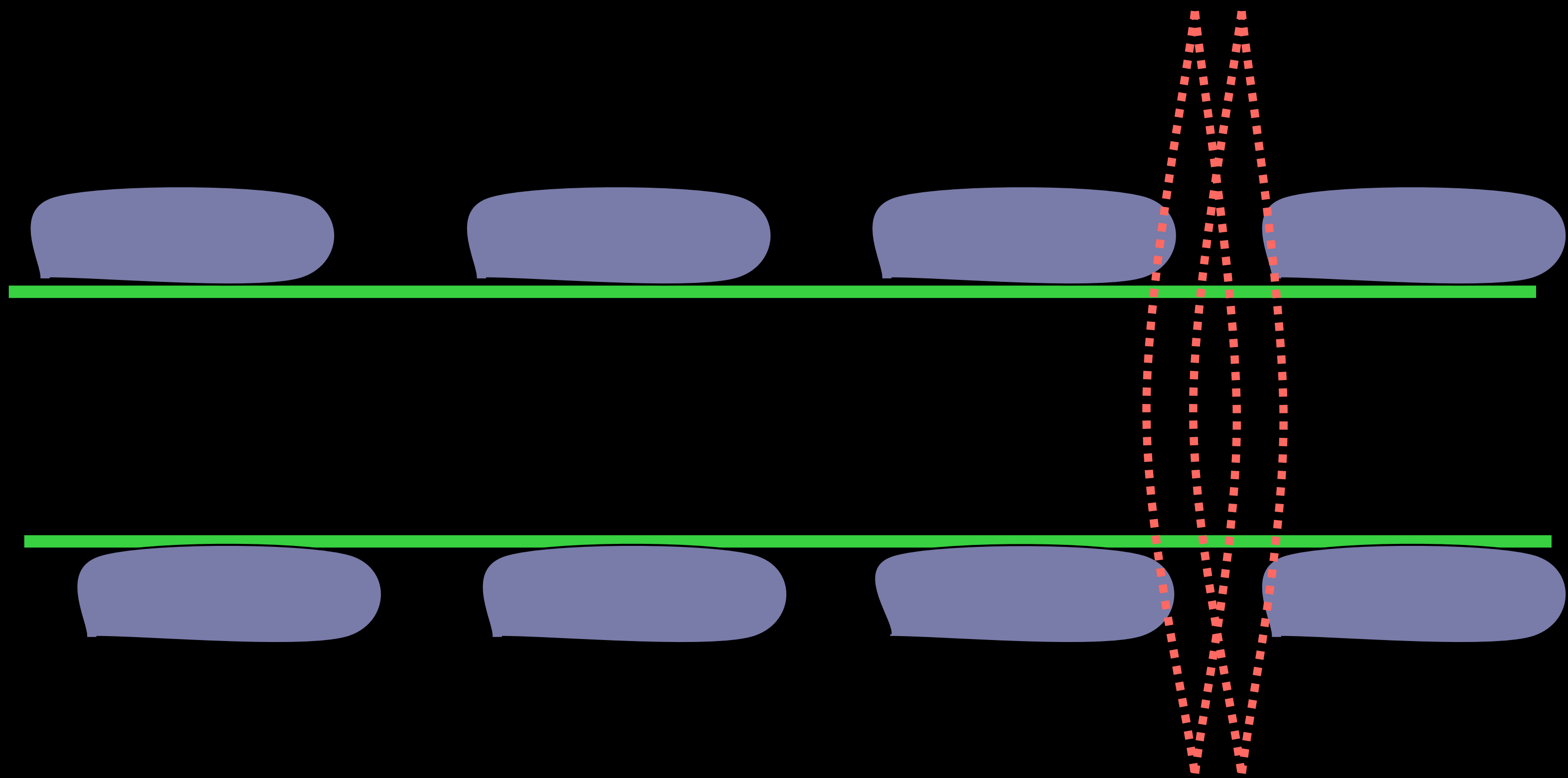
Saltatory conduction

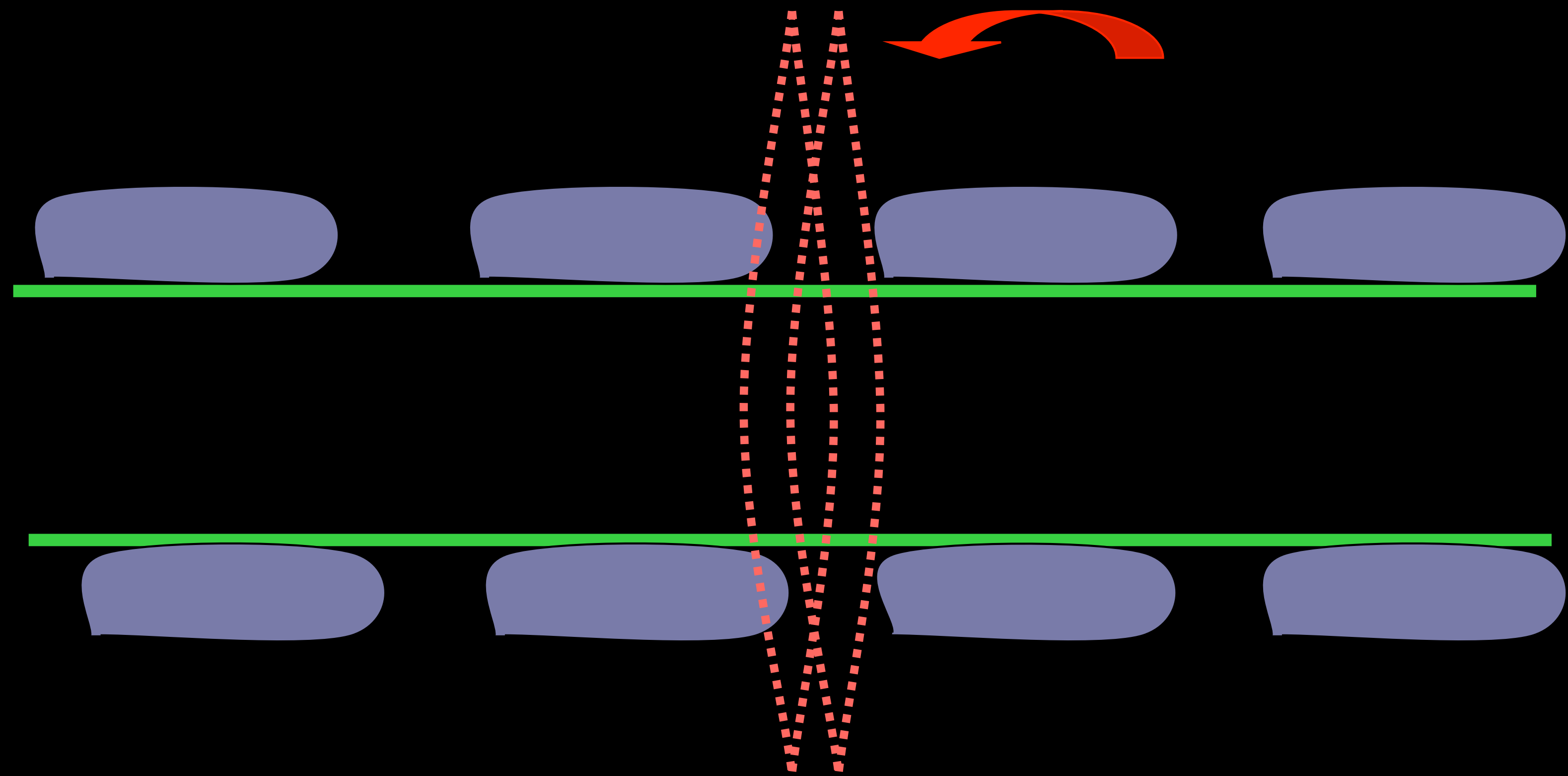


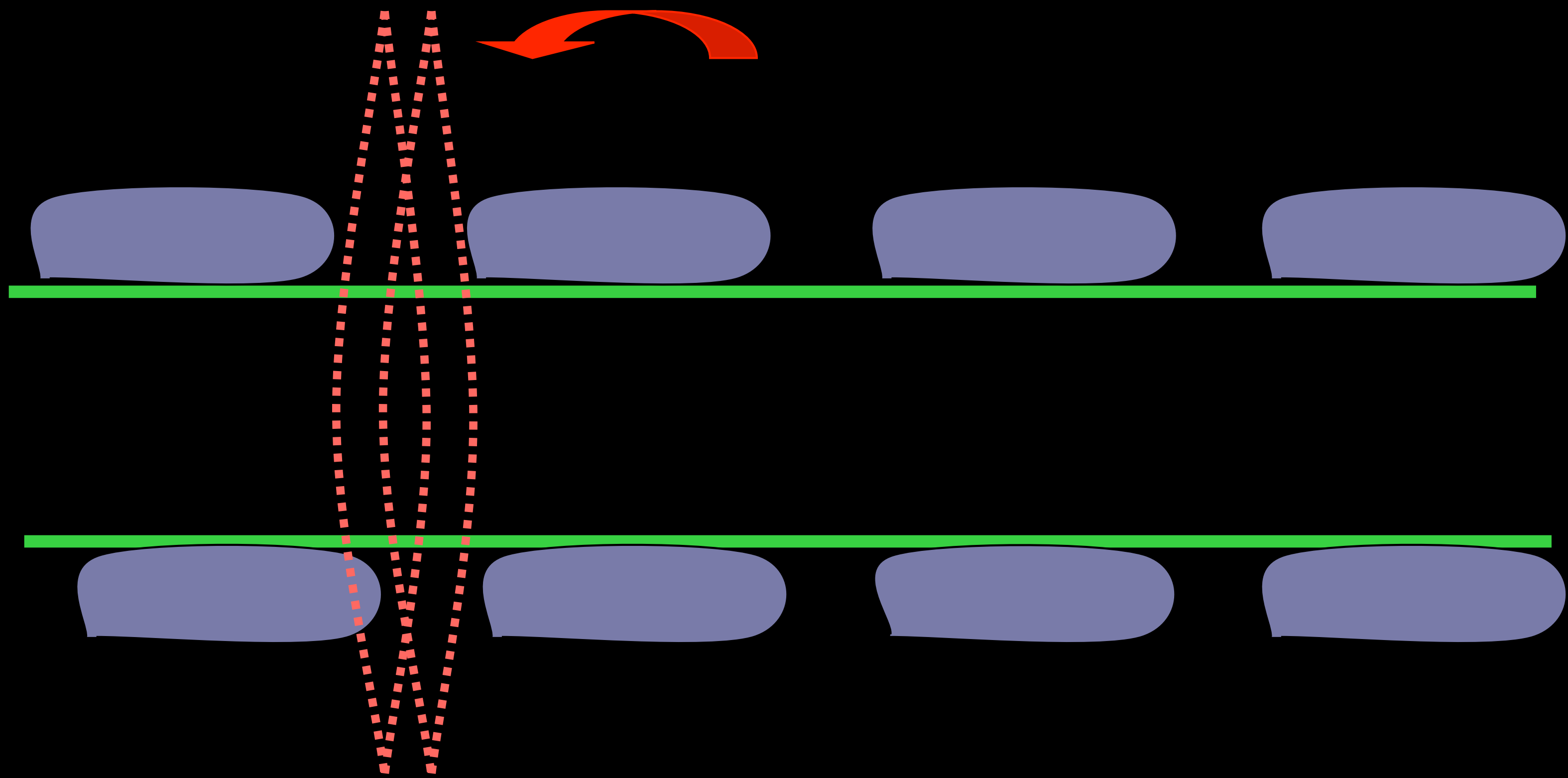
Speed of transmission

- The action potential jumps from node to node rapidly
- This because the nerve does not have to depolarise at each set of sodium channels
- This depolarisation is three dimensional

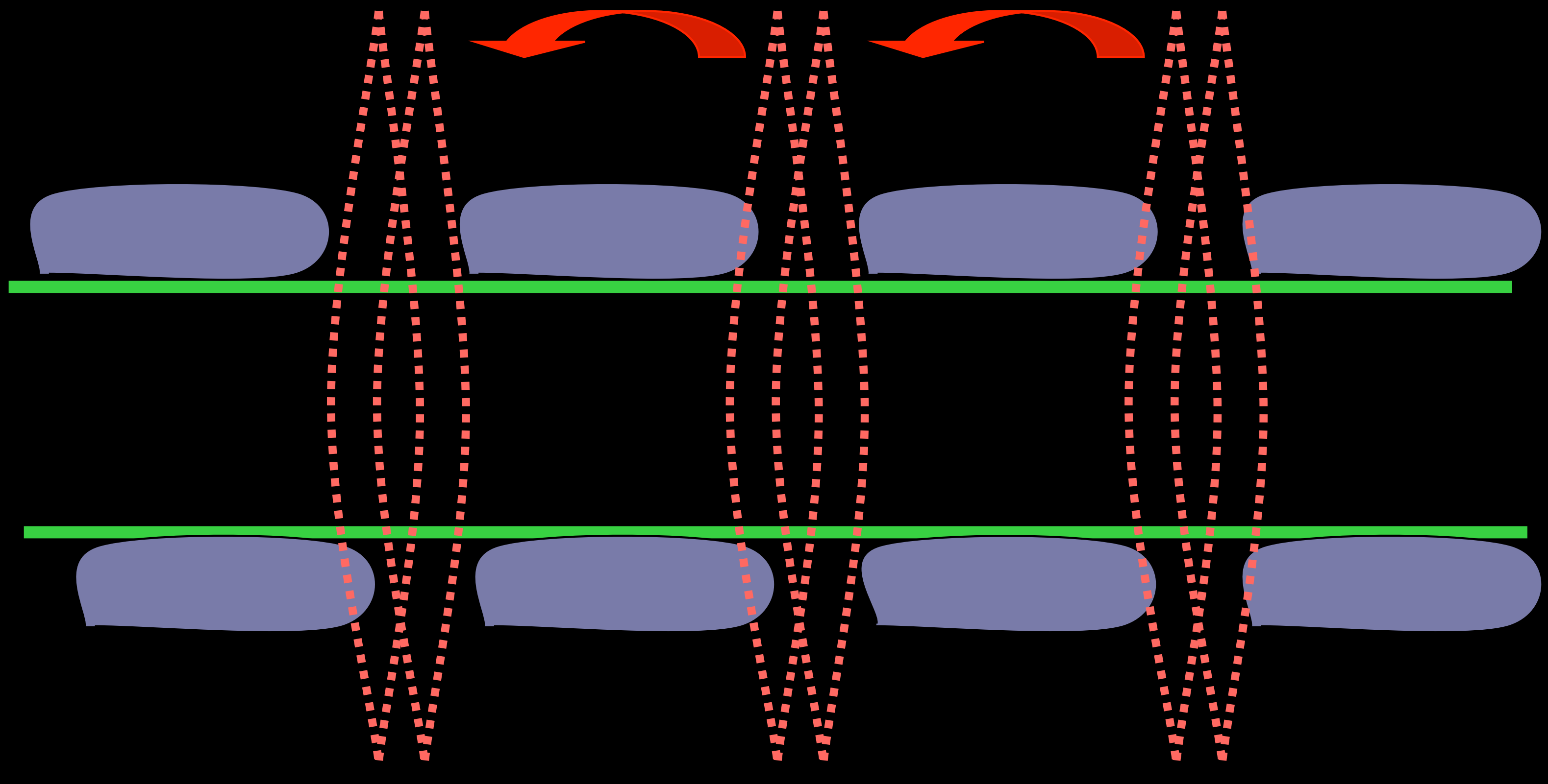
Three dimensional conduction





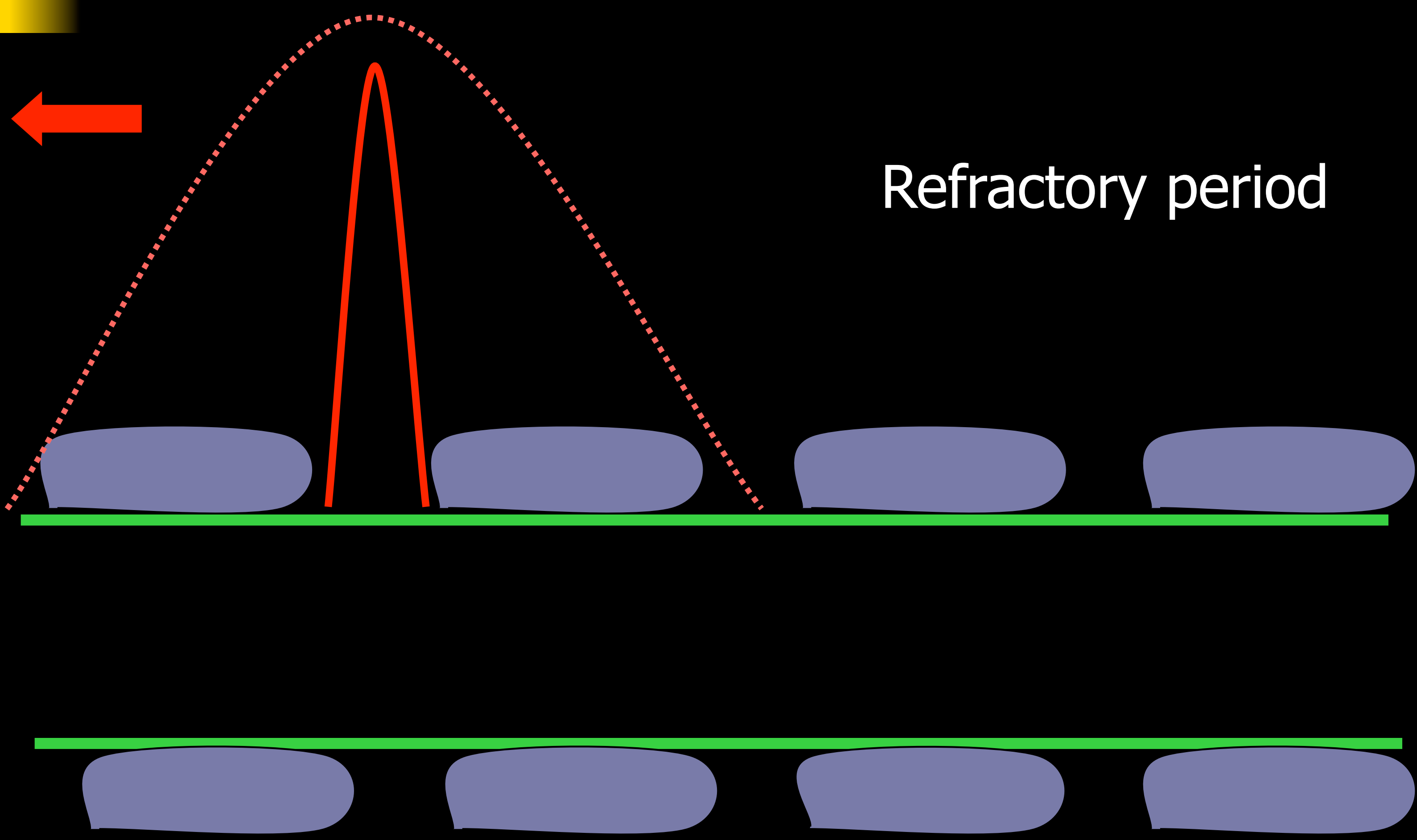


3D depolarisation



Refractory period

- Under ordinary circumstances the movement of the AP along the axon is directionally specific
- For a short period after the AP has depolarised a particular section of axon the membrane is unable to be further stimulated – this is the refractory period
- This lasts for the period it takes the sodium pump to restore the membrane to its normal resting potential
- This ensures that under normal circumstances, action potentials move only in one direction

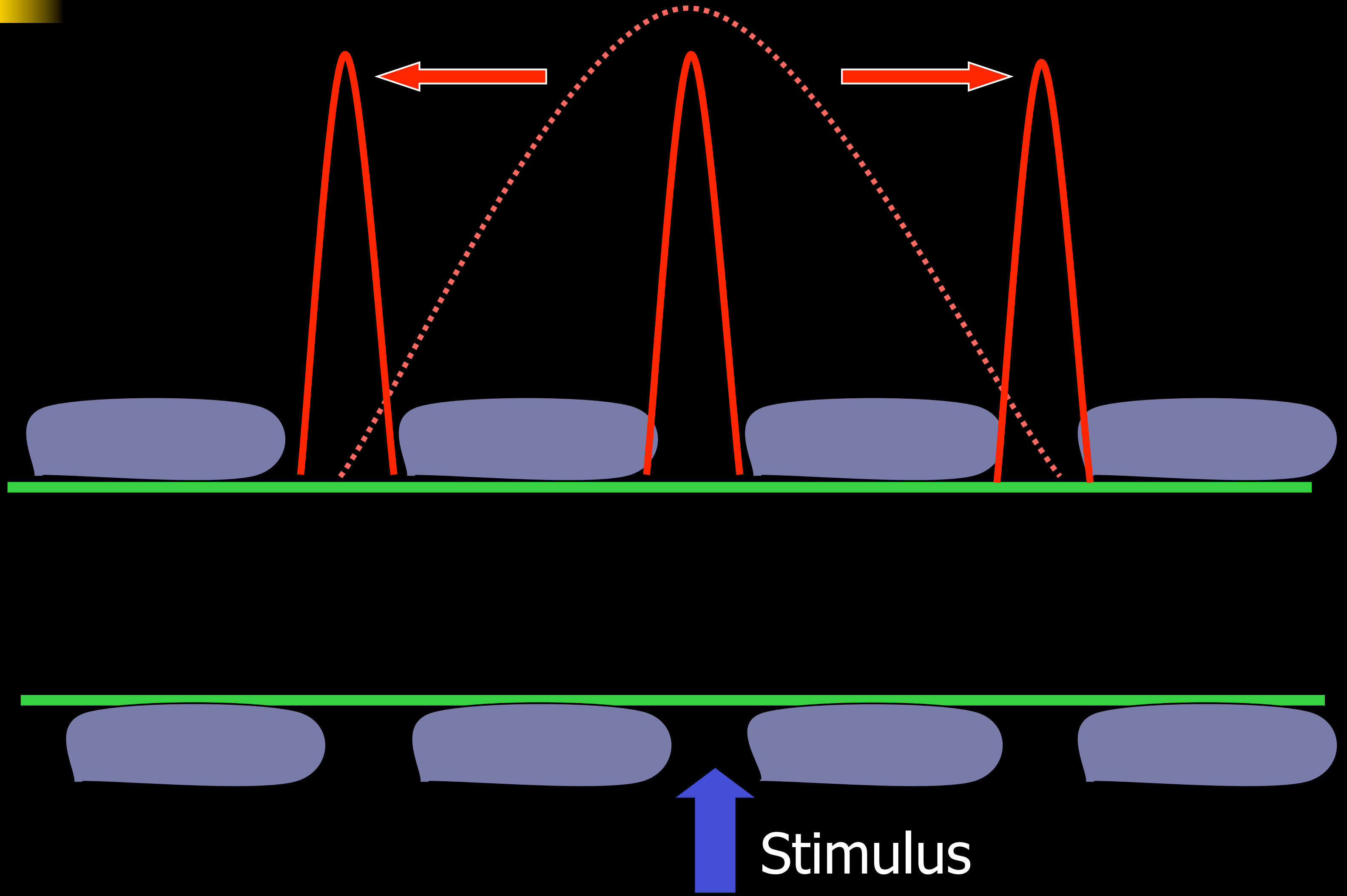


Refractory period

Antidromic conduction

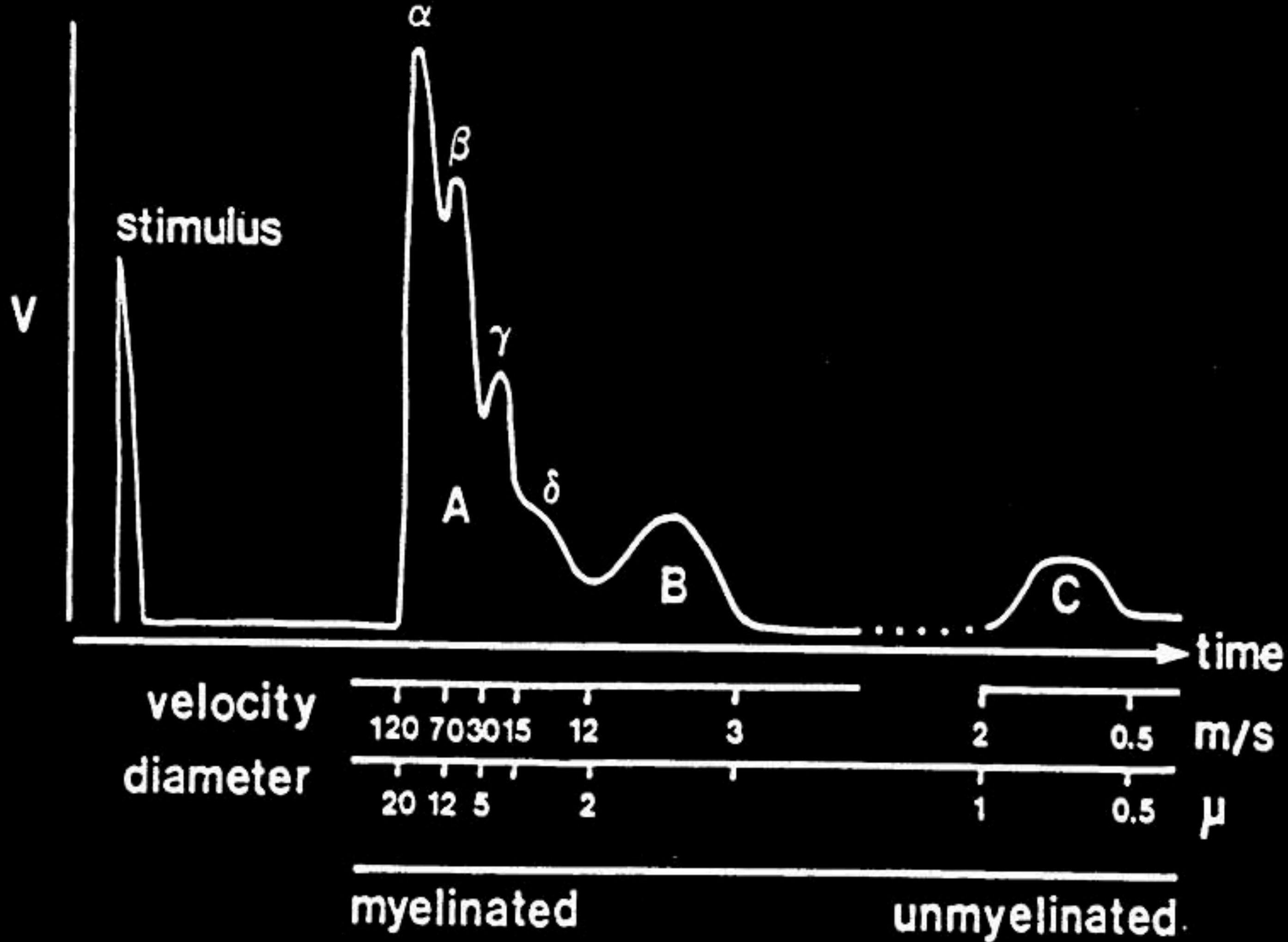
- If a nerve is stimulated somewhere along the length of its axon by electrical stimulation or mechanical pressure or pathology an axon potential may be generated that will travel in two directions, both centrally and towards the periphery

- These leave refractory periods behind the AP which will recover and be able to conduct again


Stimulus

Conduction speed

- Different nerve fibres conduct action potentials at different speeds according to their size and diameter
- The following slide depicts a neurogram recorded from a mixed nerve when it is electrically stimulated
- There are 3 main peaks of activity – an A wave, a B wave and a C wave
- The A wave is further subdivided into Aα, Aβ, Aχ and Aδ peaks – all conducting at slightly different velocities



V
stimulus
α
β
γ
δ
A
B
C
time
velocity
120 70 30 15 12 3 2 0.5 m/s
diameter
20 12 5 2 1 0.5 μ
myelinated
unmyelinated

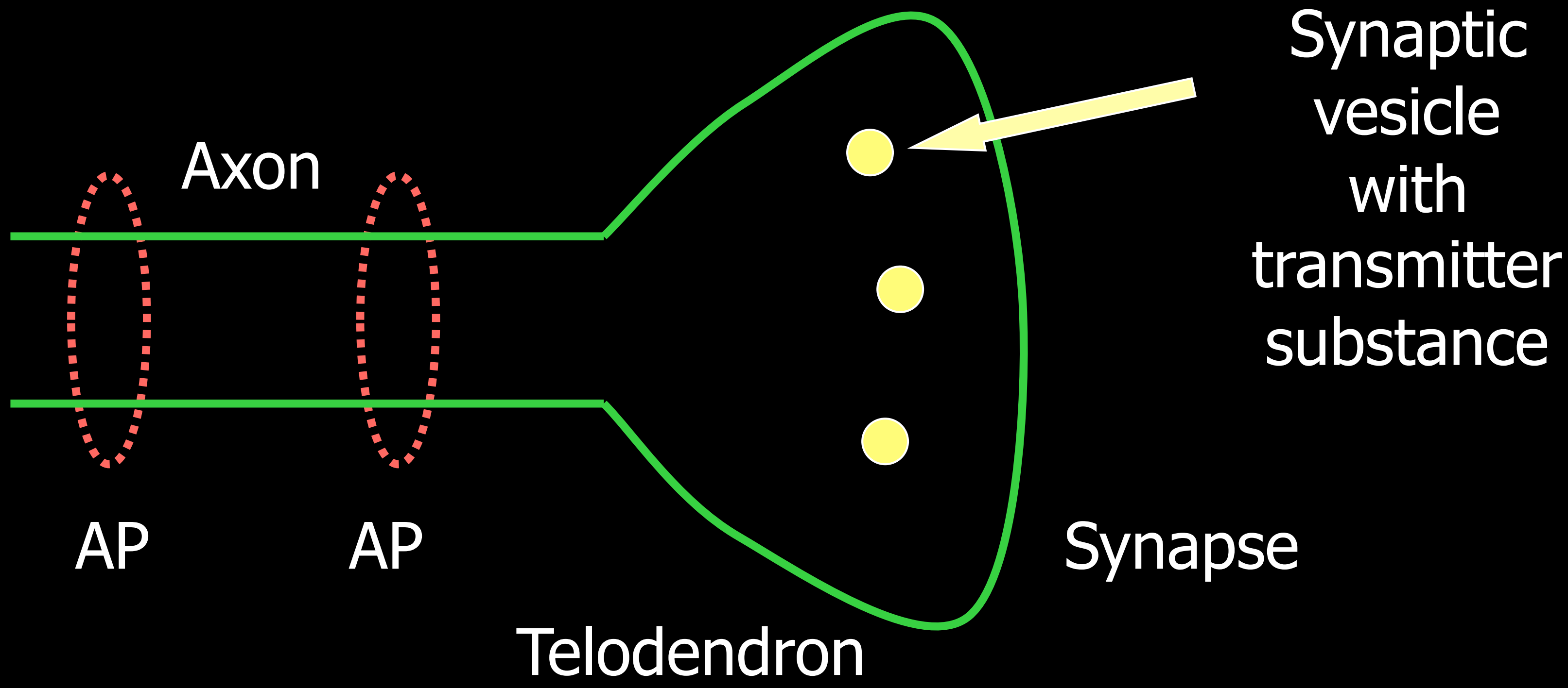
- In the A wave the Aα wave is conducting at up to 120m/sec, whilst the Aδ wave is conducting at rates of between 12 and 30m/sec
- These fibres are myelinated
- The C wave is produced by waves that conduct between 0.5 and 2m/sec
- These fibres are unmyelinated
- These conduction velocities are also proportional to the diameter of the fibres (diameter x6 = conduction velocity)

Fibre	*Innervation*	*Diameter*	*Conduction Velocity*
Aα Aβ Aχ Aδ	Primary motor to muscle Cutaneous prop/touch/press Motor and Proprioception Nociceptors and Mechanoreceptors	15 μm 8 μm 6 μm 3 μm	120m/sec 60 m/sec 30 m/sec 15 m/sec
B	Sympathetic preganglionic	3 μm	7 m/sec
C	Nociceptors, including Thermal and Mechanoreceptors	1 μm	0.5 - 1 m/sec

Synaptic Transmission

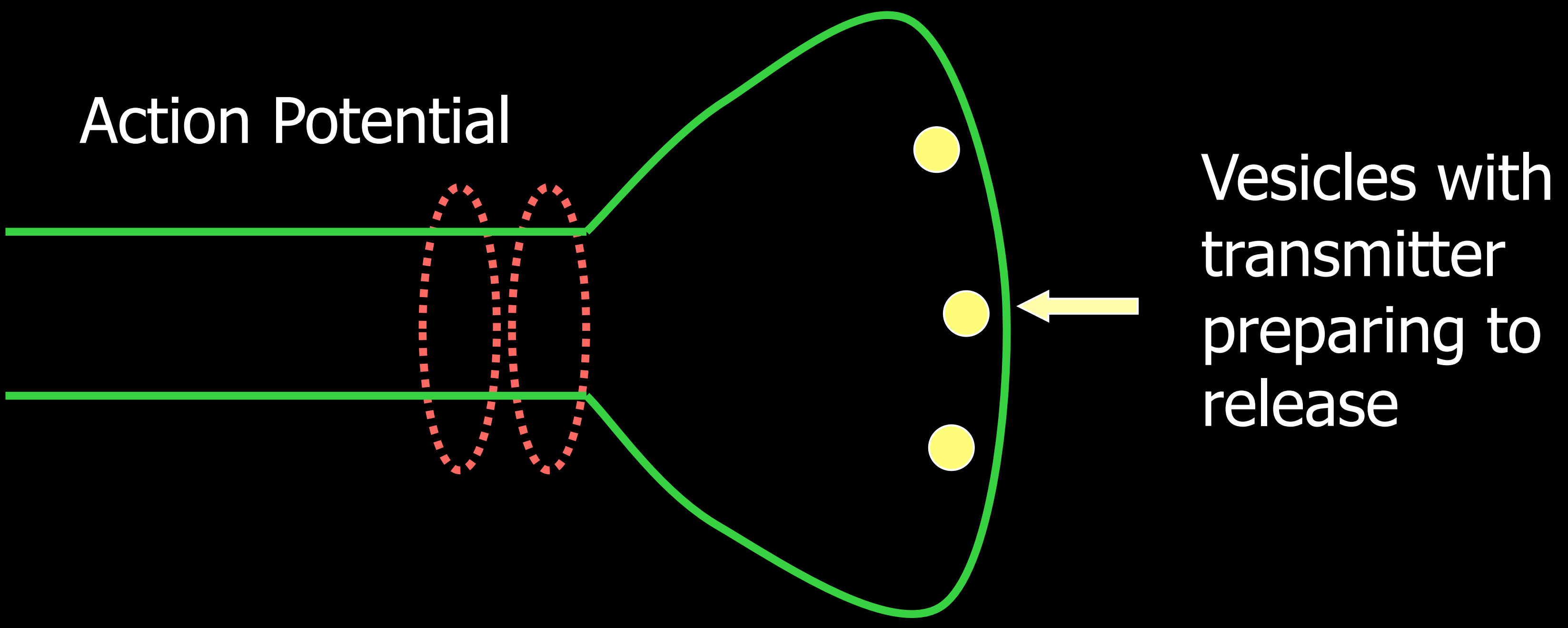
What happens at the Other End

Synaptic transmission

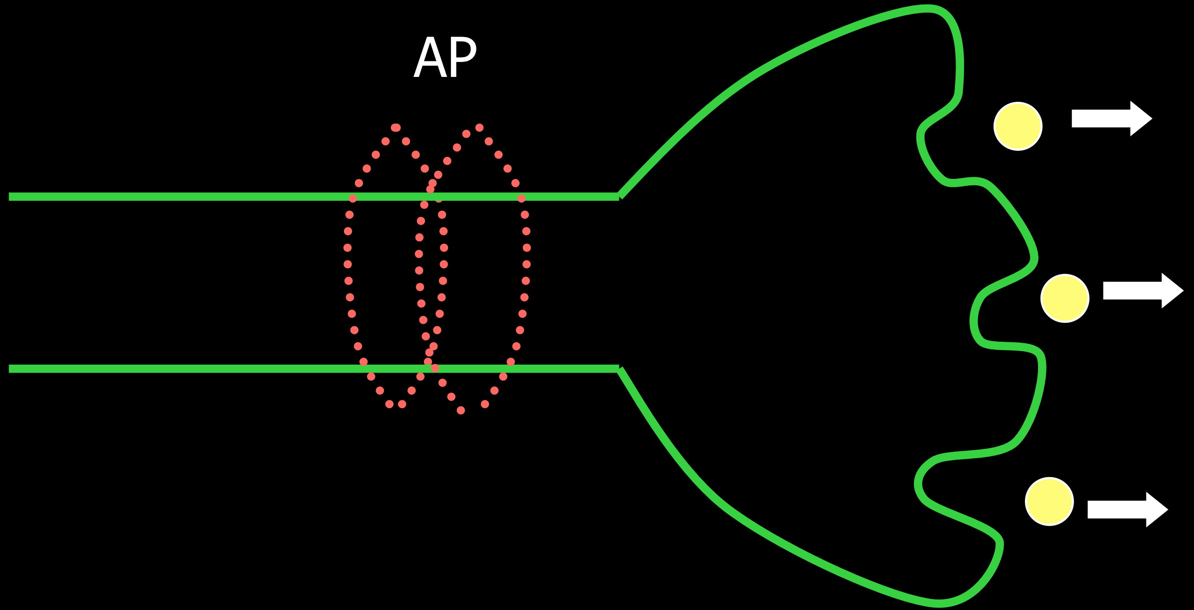


Synaptic transmission

- When the AP reaches the central terminal of a peripheral nerve it influences events there
- The terminal end of the axon contains vesicles full of neurotransmitter substances
- The AP pushes the vesicles to the surface of the membrane and subsequently causes them to rupture, releasing the transmitter substances into the synaptic cleft


Action Potential
Vesicles with transmitter preparing to release

Common Transmitter Substances

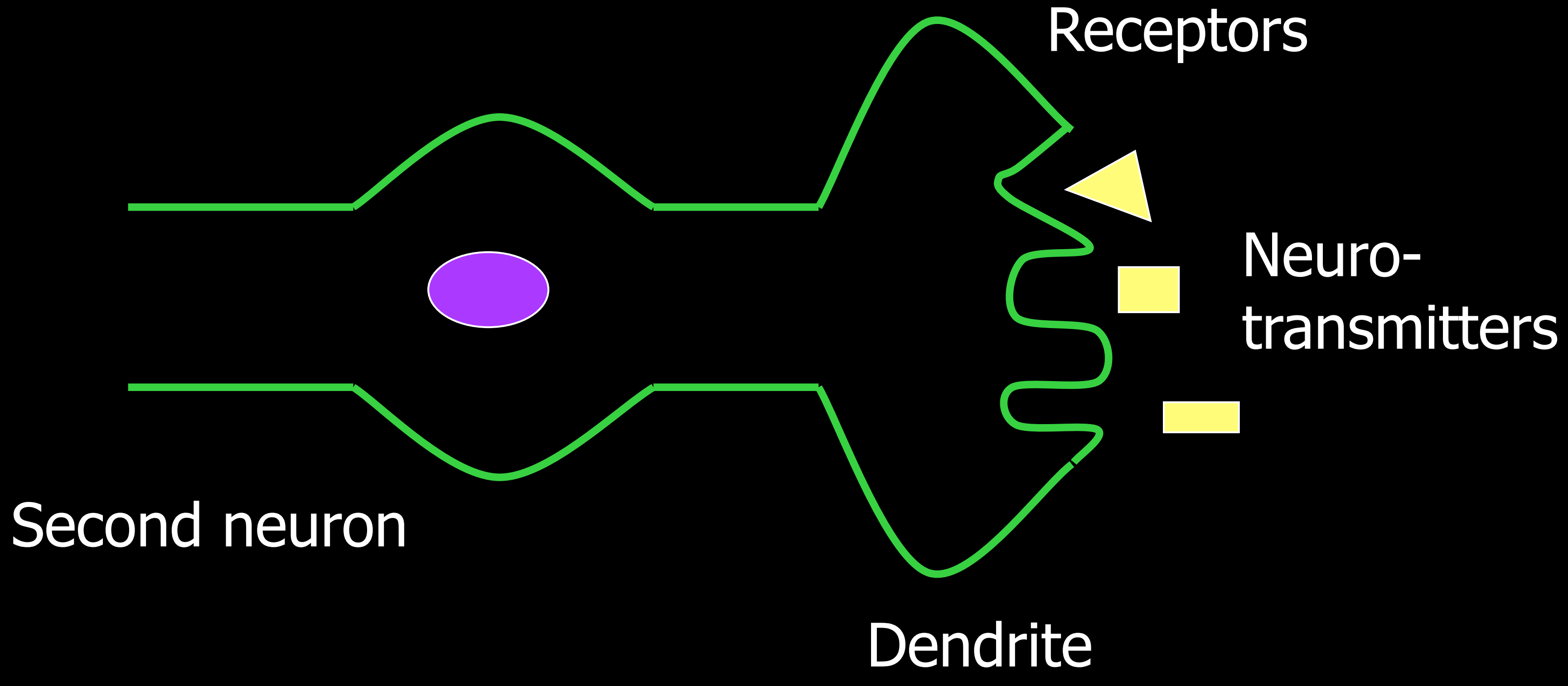


Acetylcholine
Noradrenalin
5HT (Serotonin)
Glycine
Substance P
Glutamate
Aspartate
Enkephalin

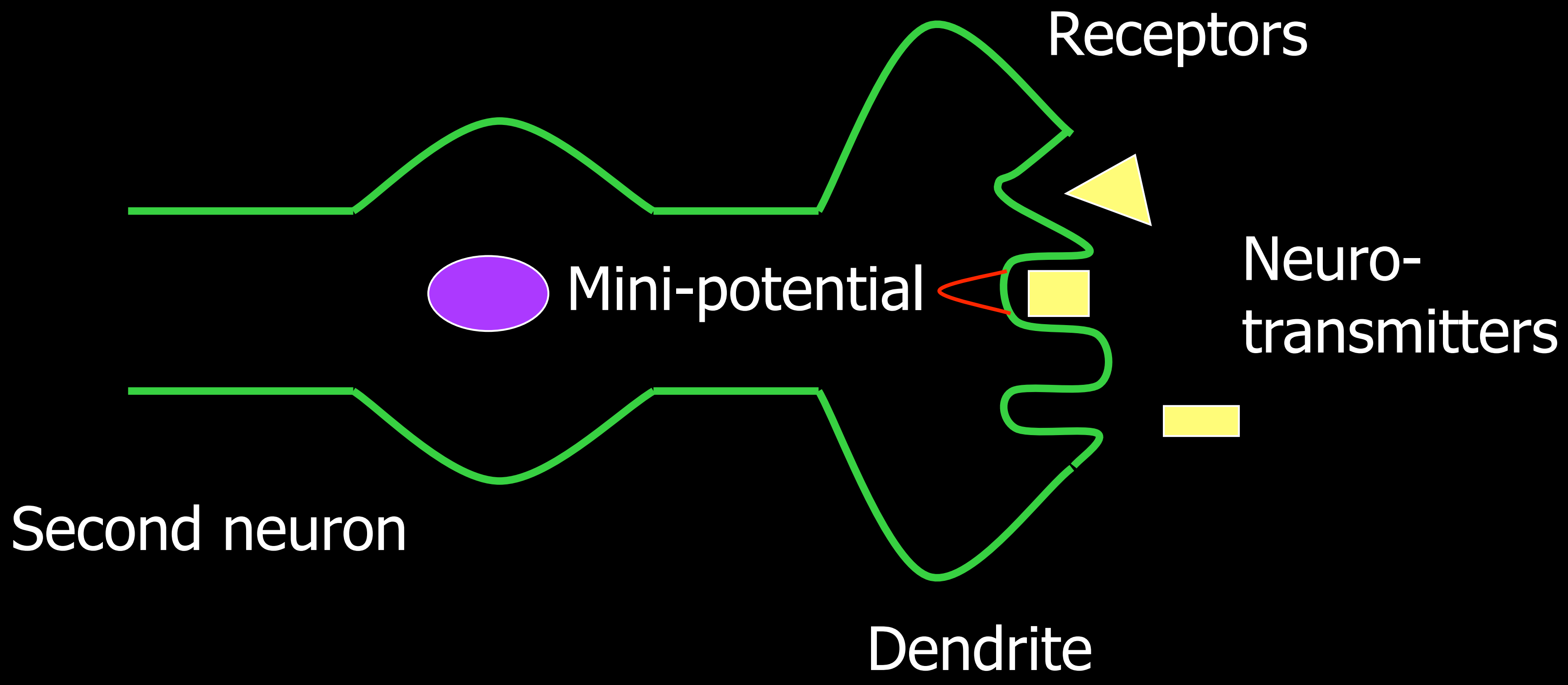
Second order receptors

- Any of these substances may be released uniquely, or several or all may be released together
- They are designed to act on the second order or receiving neuron
- The dendrites of the receiving neuron carry receptors for the transmitter substances
- Upon reaching the receptor the transmitter produces a miniature AP – it depolarises the membrane
- As more transmitter arrives more mini-AP are produced resulting in a depolarisation of the dendrite

Receptors



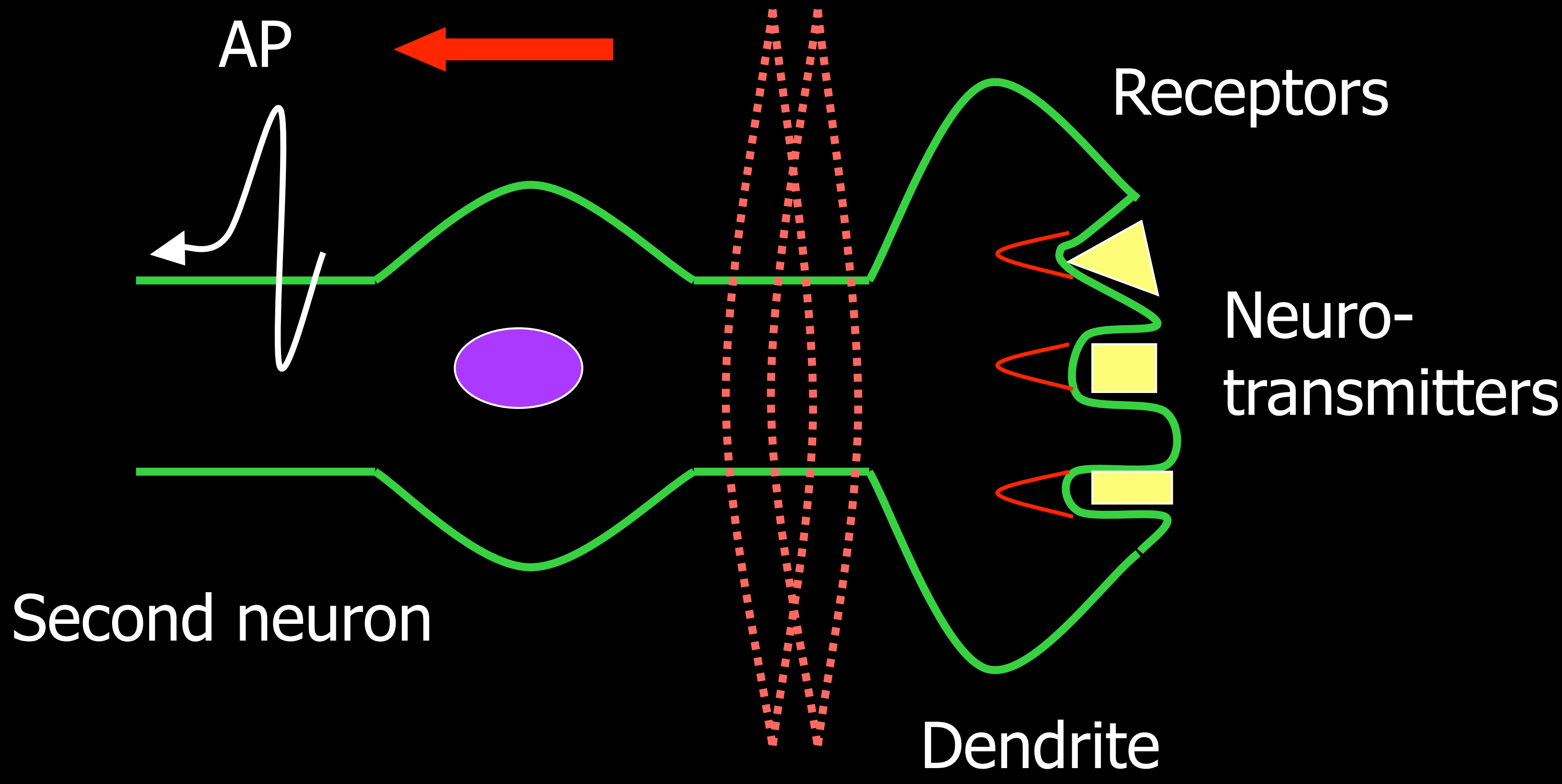
Mini potentials



New Action potential

- As the miniature potentials summate, eventually an action potential is produced in the second neuron, and onward transmission proceeds

Summation of minipotentials

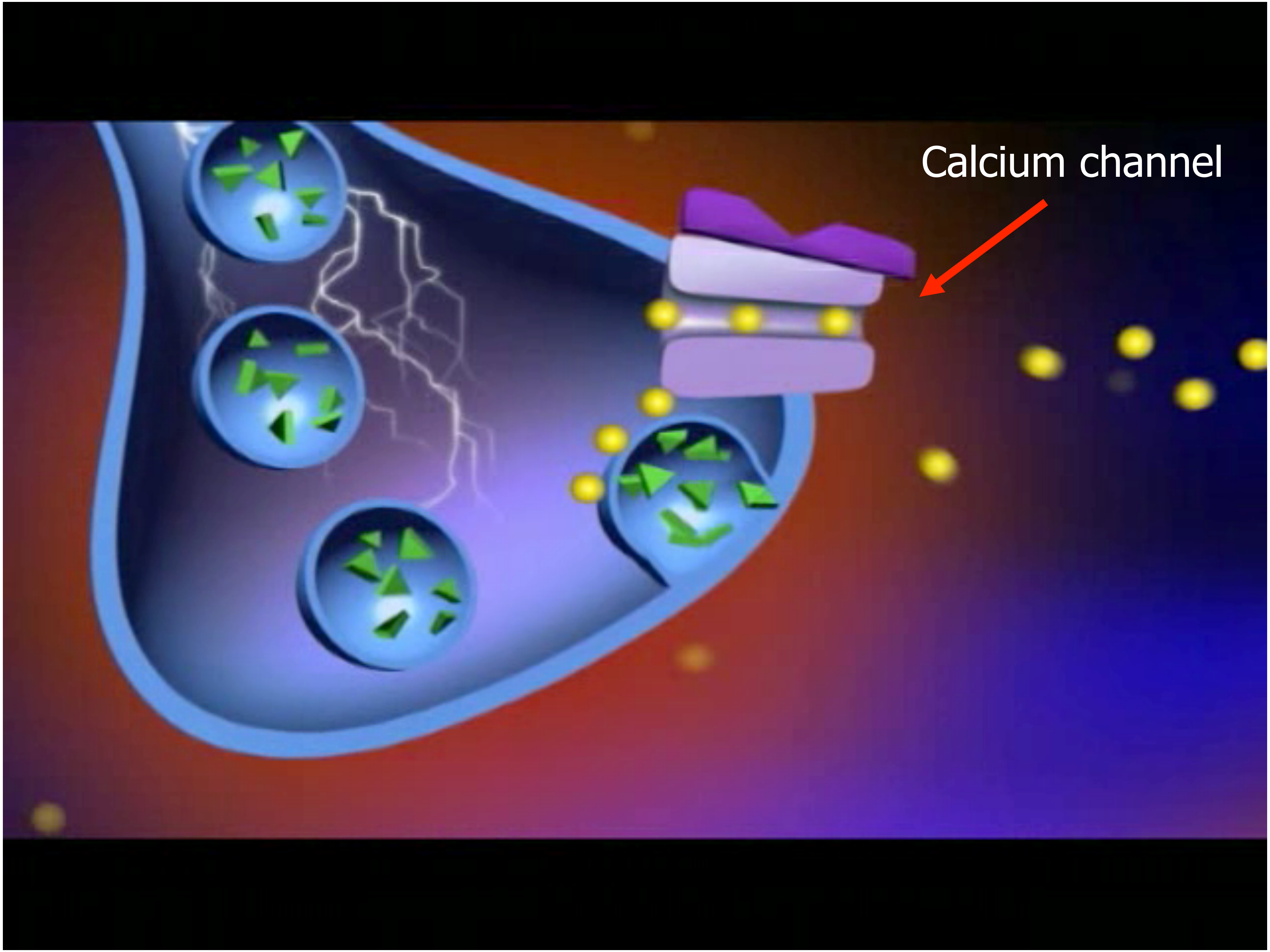


Receptors and transmitters

- Note that any given transmitter will only act on its own given receptor
- This is done by a ‘lock and key’ mechanism at a molecular level
- The control of which type of transmitter is released, and which type of receptor is present is the property of genetic expression within the respective cells

Calcium channels

- The rate of release of neurotransmitters is also dependant on the activity of calcium channels in the terminal axon
- A greater increase in calcium channel activity (influx into the neuron) results in a greater release of transmitter from a given AP
- This sensitivity may be important in situations of ‘wind-up’ and in central sensitisation


Calcium channel

Terminating transmission

- Terminating transmission is brought about by
  - *Reuptake of transmitters into the primary neuron*
  - *Diffusion of transmitters away from receptors*
  - *Deactivation of transmitters by enzymes in the synaptic cleft*

Why synapses?

- The purpose of having a synapse is to control the transfer of information, otherwise they would not exist
- Many nerves can relay to a second order nerve
- Some may be excitatory, while others are inhibitory
- This allows the peripheral nervous system to regulate the passage of information to higher levels

Hyperpolarisation Inhibition

- An inhibitory transmitter can affect the membrane by hyperpolarisation of the membrane of the second order neurone
- This is brought about by causing K to leak out of the receiving neurone
- This causes the resting membrane potential to drop (less than –70 to say -90mv)
- This now requires a greater stimulus to reach the the –55mv threshold for depolarisation of the cell

Summary

- Nerve cells and their axons are structurally highly specialised in order to allow for the transmission of electrical impulses
- This is primarily achieved through the flux of sodium and potassium ions across the conducting membrane
- The conduction of impulses varies according to the diameter of the axon, and whether or not it is myelinated
- Onward transmission of this electrical message to the second order neuron is by chemical signaling

END