Excitable Tissues, Resting Membrane Potential & Action Potential

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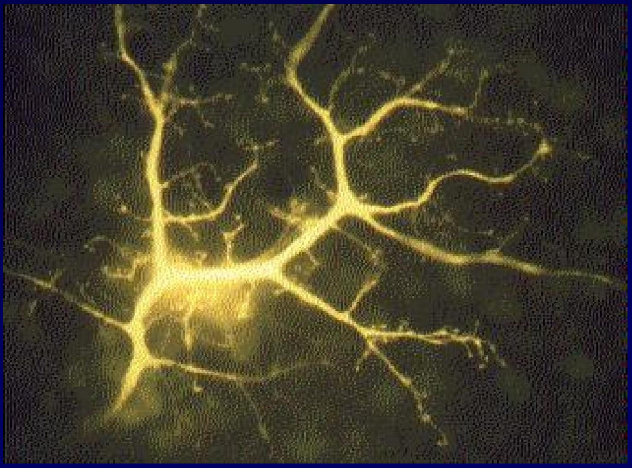
Objectives

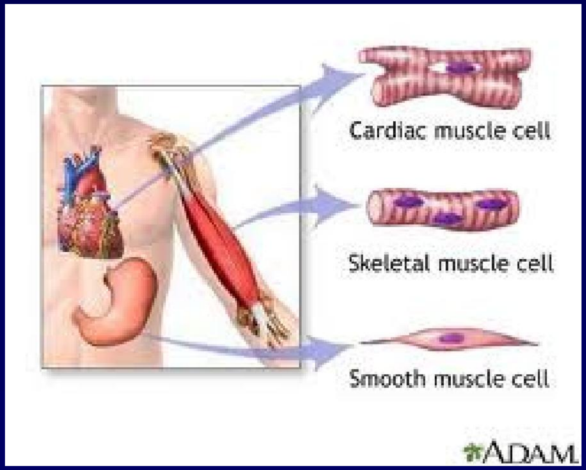
1. Explain why some membranes are excitable
2. Describe the electrochemical basis of RMP

Excitable Tissues

- Tissues which are capable of generation and transmission of electrochemical impulses along the membrane

Nerve

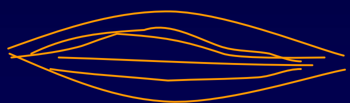




Excitable tissues

excitable

neuron

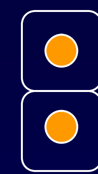


muscle

- Nerve
- Muscle
  - Skeletal
  - Cardiac
  - Smooth

Non-excitable

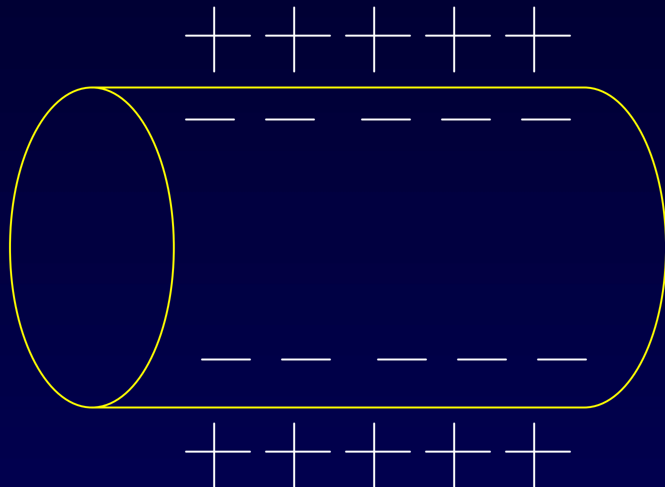
Red cell



GIT

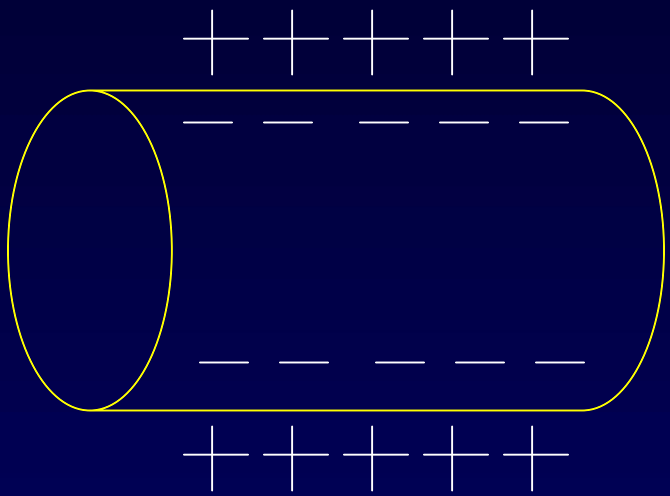
- RBC
- Intestinal cells
- Fibroblasts
- Adipocytes

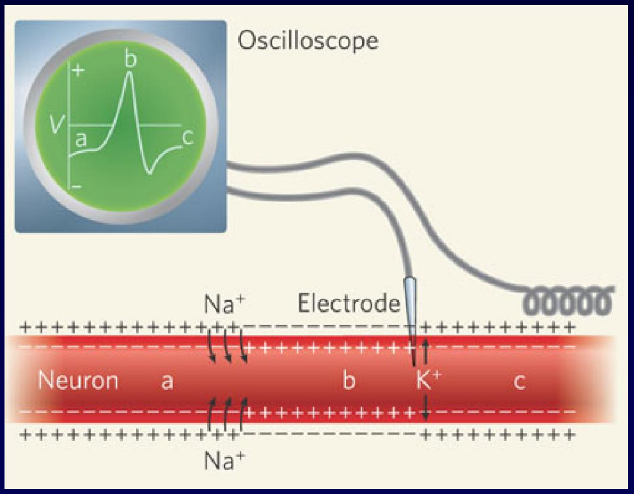
Membrane potential



- A potential difference exists across all cell membranes
- This is called
  - – Resting Membrane Potential (RMP)

Membrane potential



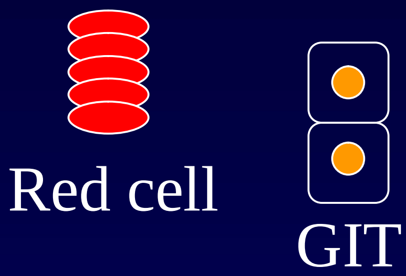


- – Inside is negative with respect to the outside
- – This is measured using microelectrodes and oscilloscope
- – This is about -70 to -90 mV

Excitable tissues

excitable

Non-excitable



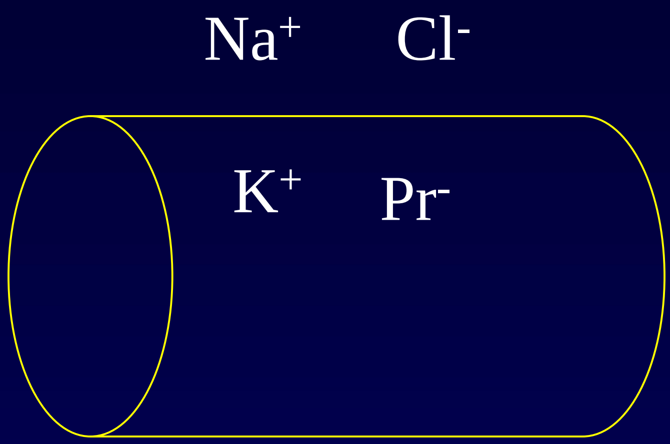
- Excitable tissues have more negative RMP
  (- 70 mV to - 90 mV)

- Non-excitable tissues have less negative RMP
  -53 mV epithelial cells
  -8.4 mV RBC
  -20 to -30 mV fibroblasts
  -58 mV adipocytes

Resting Membrane Potential

- This depends on following factors
  - Ionic distribution across the membrane
  - Membrane permeability
  - Other factors
    - Na^+/K^+ pump

Ionic distribution



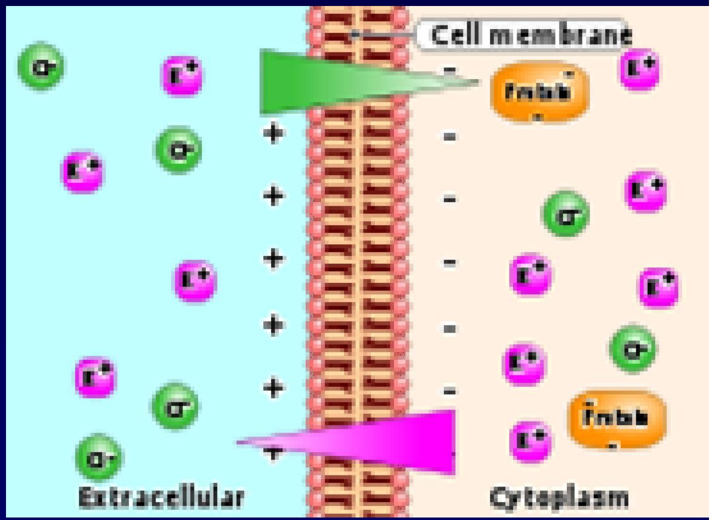
- Major ions
  - Extracellular ions
    - Sodium, Chloride
  - Intracellular ions
    - Potassium, Proteinate

Ionic distribution

Ion	Intracellular	Extracellular
Na^+	10	142
K^+	140	4
Cl^-	4	103
Ca^{2+}	0	2.4
HCO_3^-	10	28

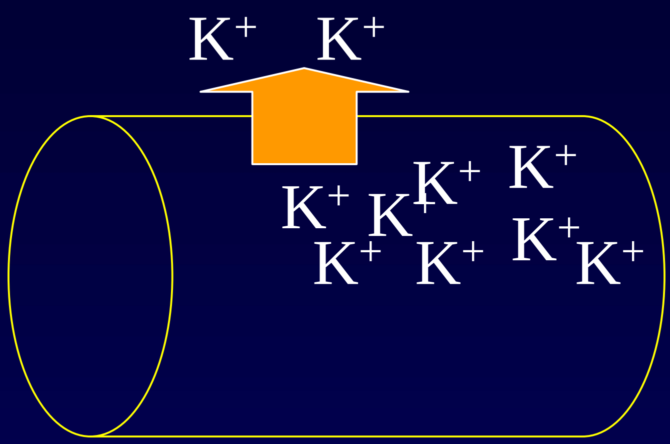
Gibbs Donnan Equilibrium

- When two solutions containing ions are separated by membrane that is permeable to some of the ions and not to others an electrochemical equilibrium is established



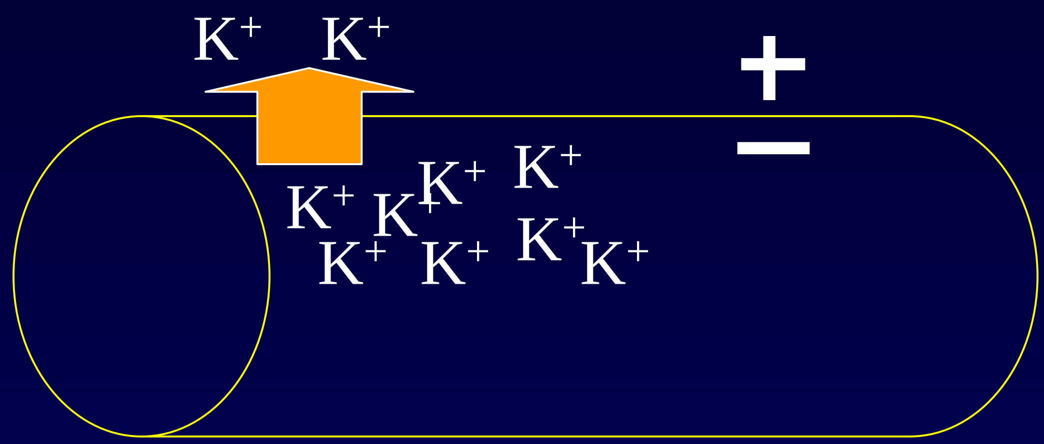
- Electrical and chemical energies on either side of the membrane are equal and opposite to each other

Flow of Potassium



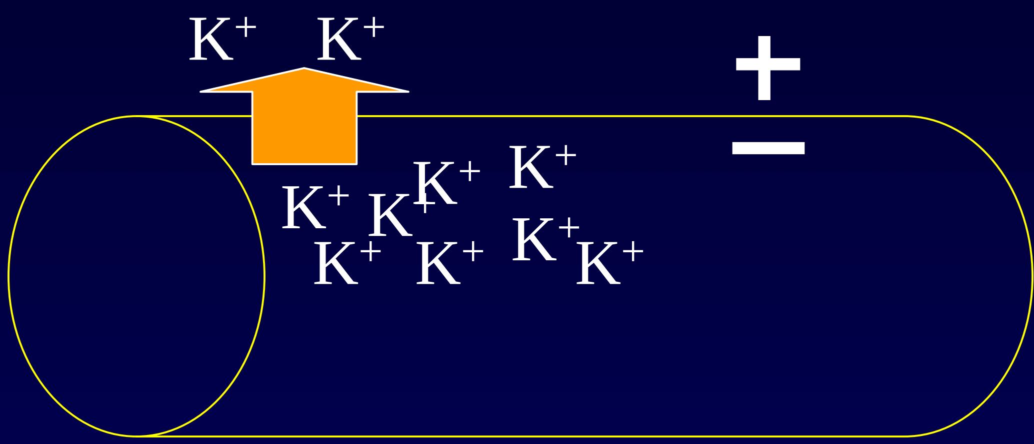
- Potassium concentration intracellular is more
- Membrane is freely permeable to K^+
- There is an efflux of K^+

Flow of Potassium



- Entry of positive ions in to the extracellular fluid creates positivity outside and negativity inside

Flow of Potassium



- Outside positivity resists efflux of K^+
- (since K^+ is a positive ion)
- At a certain voltage an equilibrium is reached and K^+ efflux stops

Nernst potential (Equilibrium potential)

- The potential level across the membrane that will exactly prevent net diffusion of an ion

- Nernst equation determines this potential

$$E = \frac{RT}{zF} \ln \frac{[\text{ion outside cell}]}{[\text{ion inside cell}]}.$$

Nernst potential (Equilibrium potential)

- The potential level across the membrane that will exactly prevent net diffusion of an ion

Ion	Intracellular	Extracellular	Nernst potential
Na^+	10	142	+58
K^+	140	4	-92
Cl^-	4	103	-89
Ca^{2+}	0	2.4	+129
HCO_3^-	10	28	-23

(mmol/l)

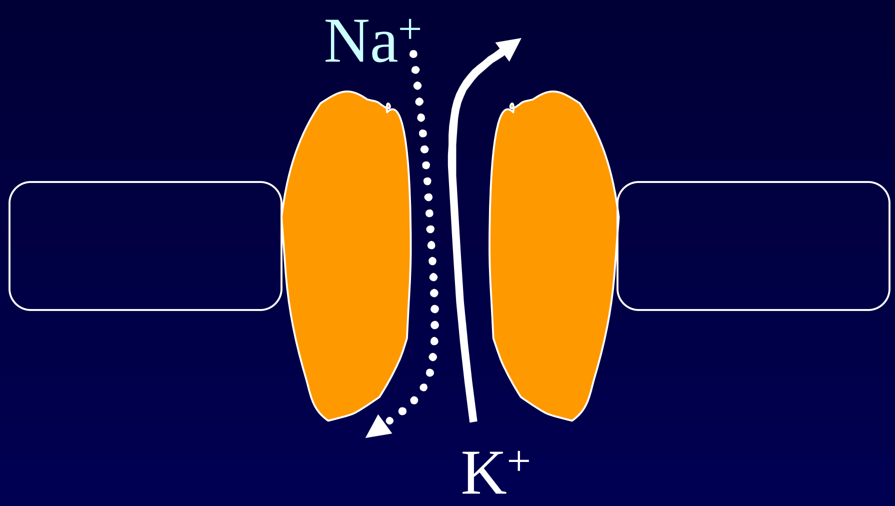
Goldman Equation

- When the membrane is permeable to several ions the equilibrium potential that develops depends on
  - Polarity of each ion
  - Membrane permeability
  - Ionic conc
- This is calculated using Goldman Equation (or GHK Equation)

$$V_m = \frac{RT}{F} \ln\left(\frac{p_K[K]_o + p_{Na}[Na]_o + p_{Cl}[Cl]_i}{p_K[K]_i + p_{Na}[Na]_i + p_{Cl}[Cl]_o} \right)$$

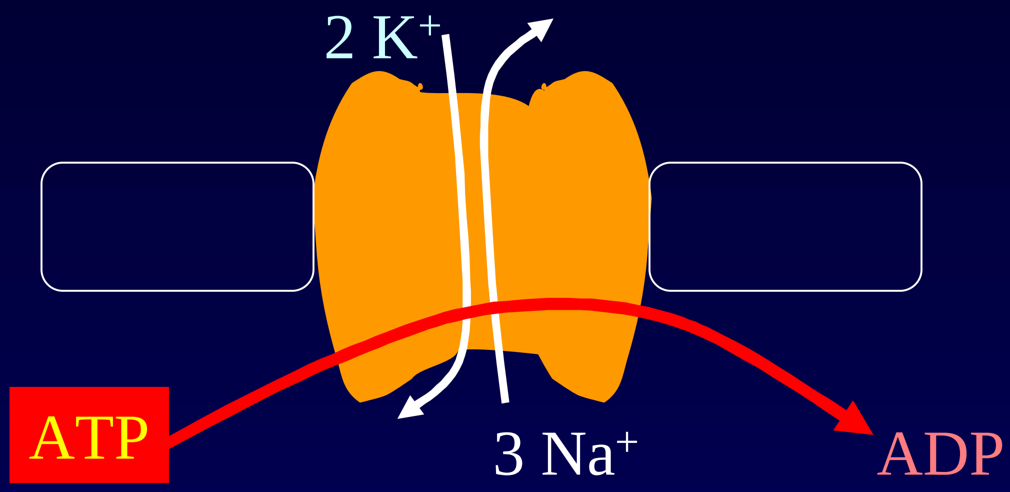
- In the resting state
  - K+ permeability is 20 times more than that of Na+

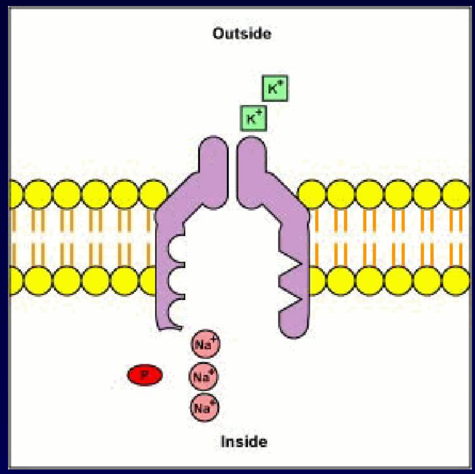
Ionic channels



- Leaky channels (K-Na leak channel)
  - More permeable to K
  - Allows free flow of ions

Na/K pump





- Active transport system for Na+-K+ exchange using energy
- It is an electrogenic pump since 3 Na+ efflux coupled with 2 K+ influx
- Net effect of causing negative charge inside the membrane

Factors contributing to RMP

- One of the main factors is K+ efflux (Nernst Potential: -94mV)
- Contribution of Na influx is little (Nernst Potential: +61mV)
- Na/K pump causes more negativity inside the membrane
- Negatively charged protein ions remaining inside the membrane contributes to the negativity
- Net result: -70 to -90 mV inside

Electrochemical gradient

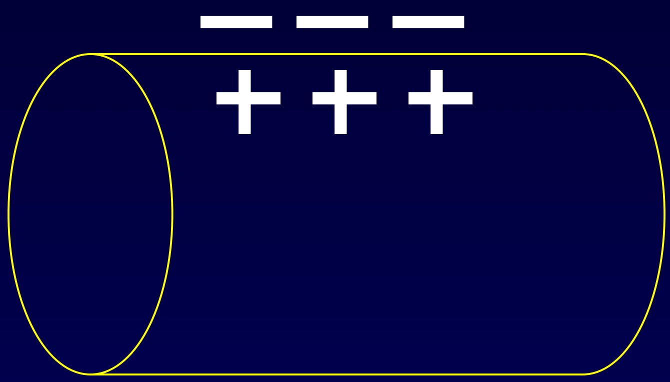
- At this electrochemical equilibrium, there is an exact balance between two opposing forces:
- Chemical driving force = ratio of concentrations on 2 sides of membrane (concentration gradient)
  - The concentration gradient that causes K+ to move from inside to outside taking along positive charge and
- Electrical driving force = potential difference across membrane
  - opposing electrical gradient that increasingly tends to stop K+ from moving across the membrane
- Equilibrium: when chemical driving force is balanced by electrical driving force

Action potential

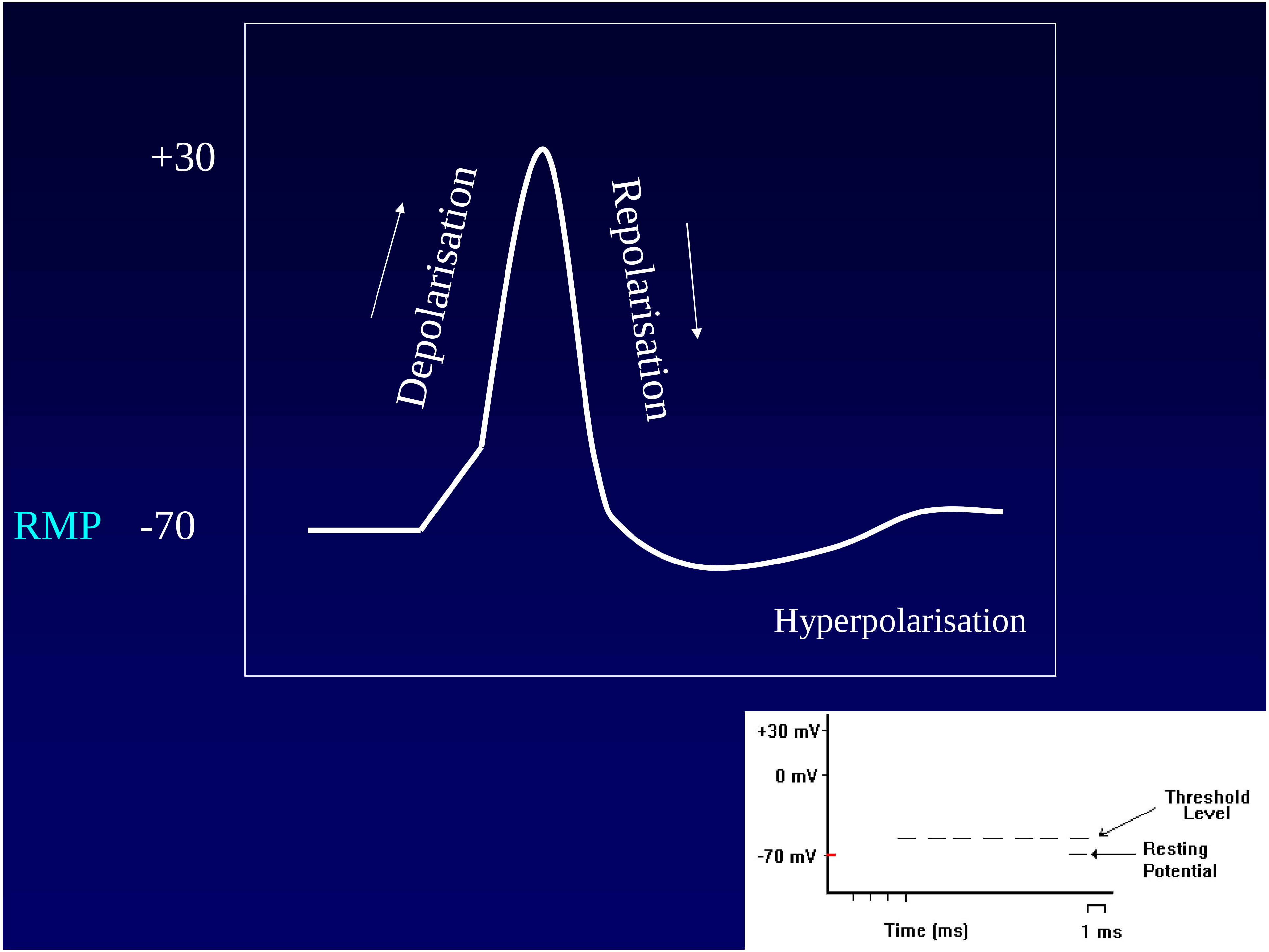
Objectives

- Describe the mechanism of generation and propagation of AP
- Explain the differences in AP of skeletal, cardiac and smooth muscles

Action Potential (A.P.)

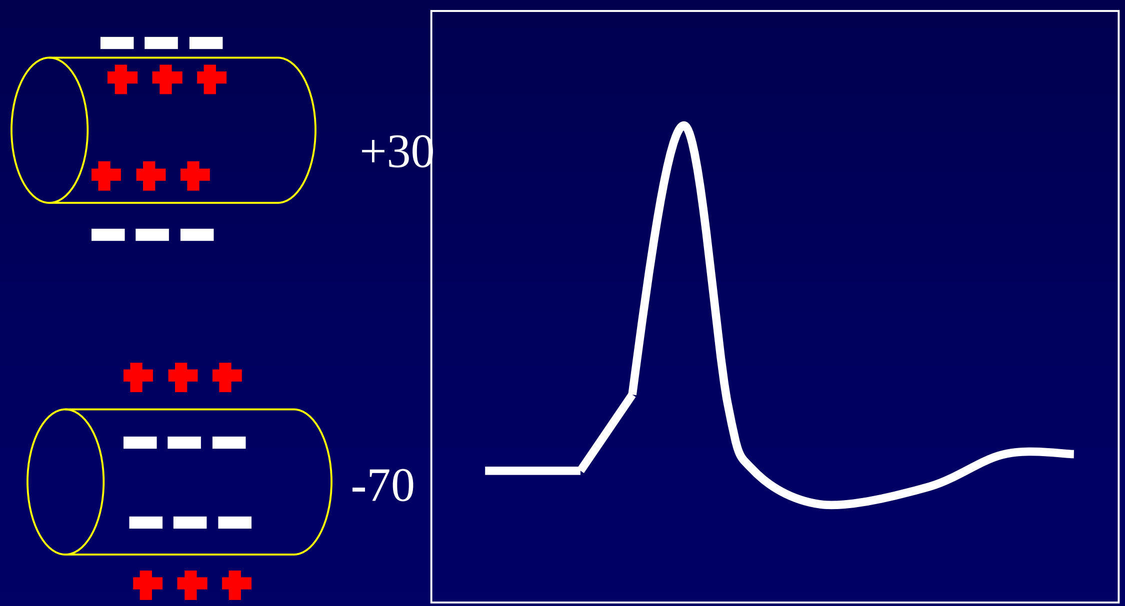


- When an impulse is generated
  - – Inside becomes positive
  - – Causes depolarisation
  - – Nerve impulses are transmitted as AP

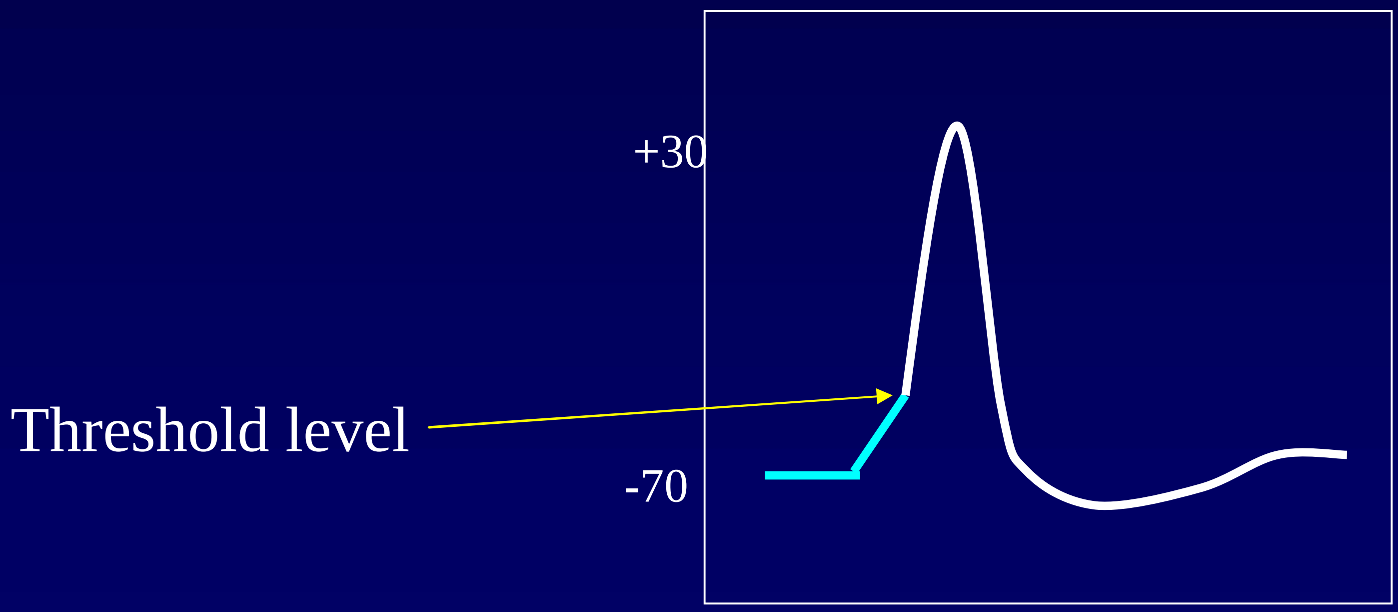

+30
RMP
-70
Depolarisation
Repolarisation
Hyperpolarisation
+30 mV
0 mV
-70 mV
Threshold Level
Resting Potential
Time (ms)
1 ms

Inside of the membrane is

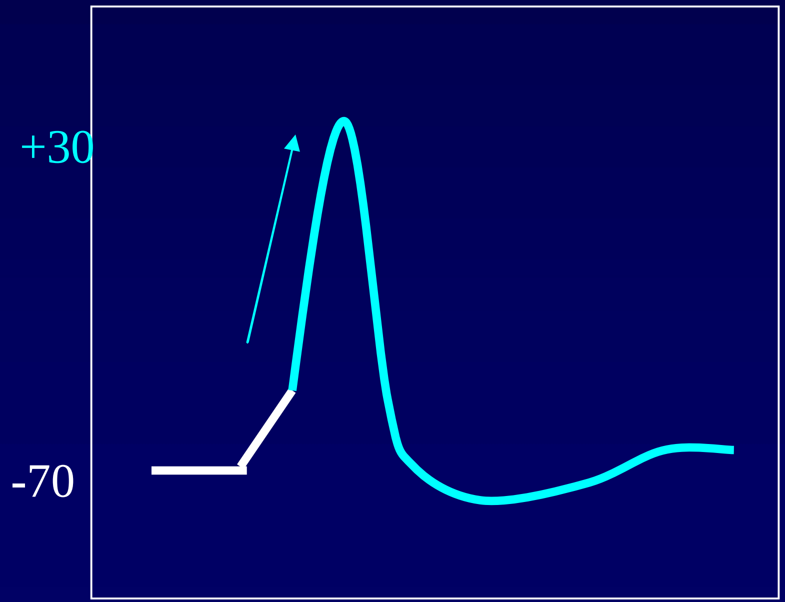
- Negative
  - During RMP
- Positive
  - When an AP is generated



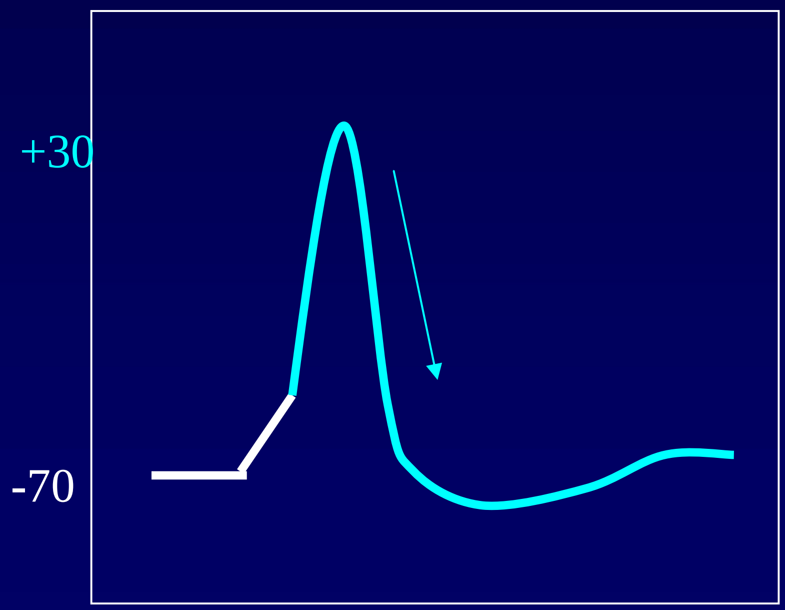
- Initially membrane is slowly depolarised
- Until the threshold level is reached
  - (This may be caused by the stimulus)



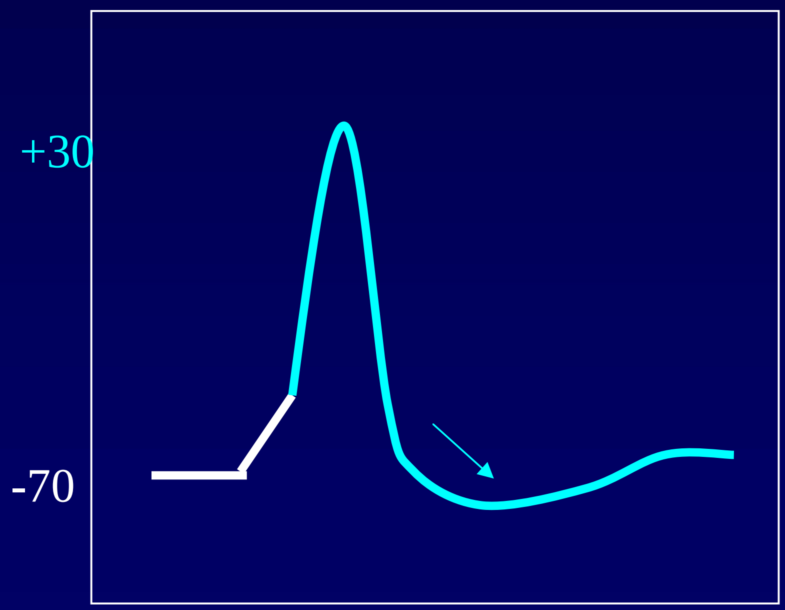
- Then a sudden change in polarisation causes sharp upstroke (depolarisation) which goes beyond the zero level up to +35 mV



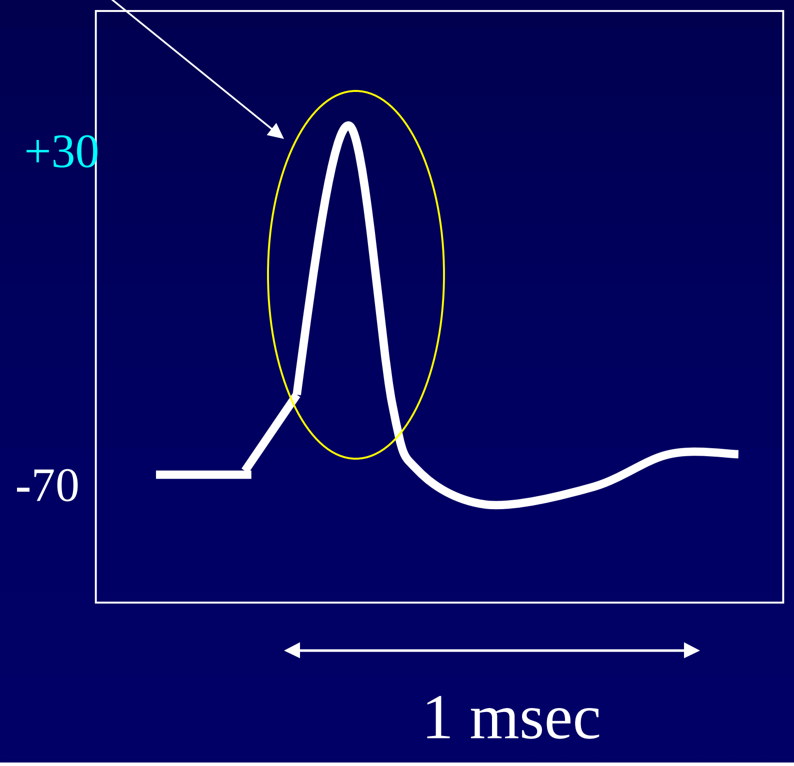
- Then a sudden decrease in polarisation causes initial sharp down stroke (repolarisation)



- When reaching the Resting level rate slows down
- Can go beyond the resting level
  - hyperpolarisation

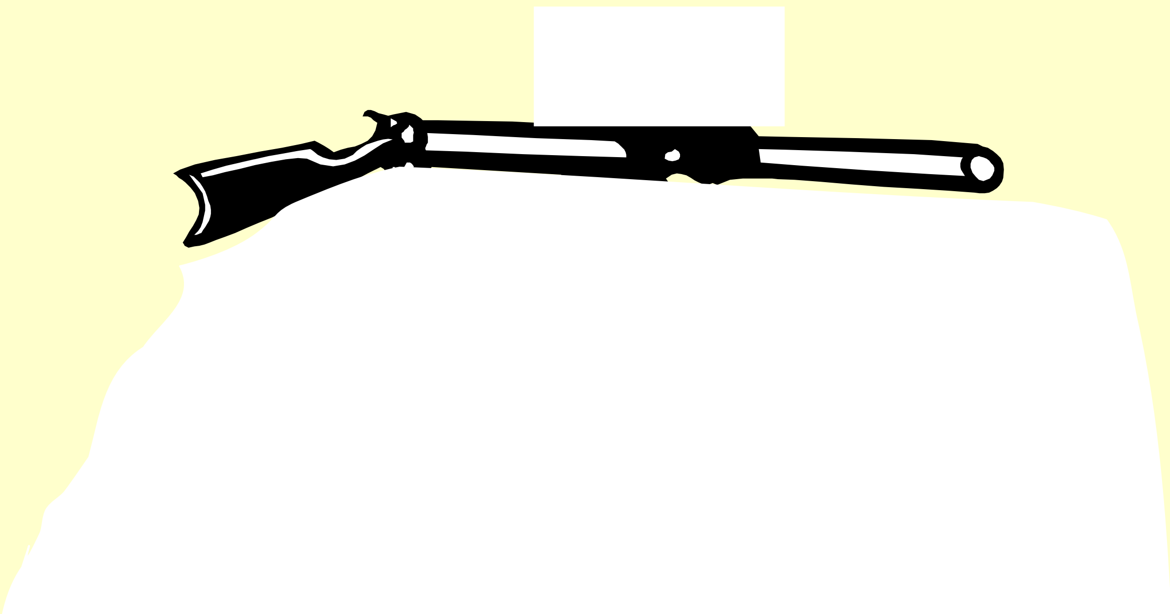


- Spike potential
  - Sharp upstroke and downstroke
- Time duration of AP
  - 1 msec



All or none law

- Until the threshold level the potential is graded
- Once the threshold level is reached
  - AP is set off and *no one can stop it !*
  - *Like a gun*



All or none law

- The principle that the strength by which a nerve or muscle fiber responds to a stimulus is not dependent on the strength of the stimulus

- If the stimulus is any strength above threshold, the nerve or muscle fiber will give a complete response or otherwise no response at all

Physiological basis of AP

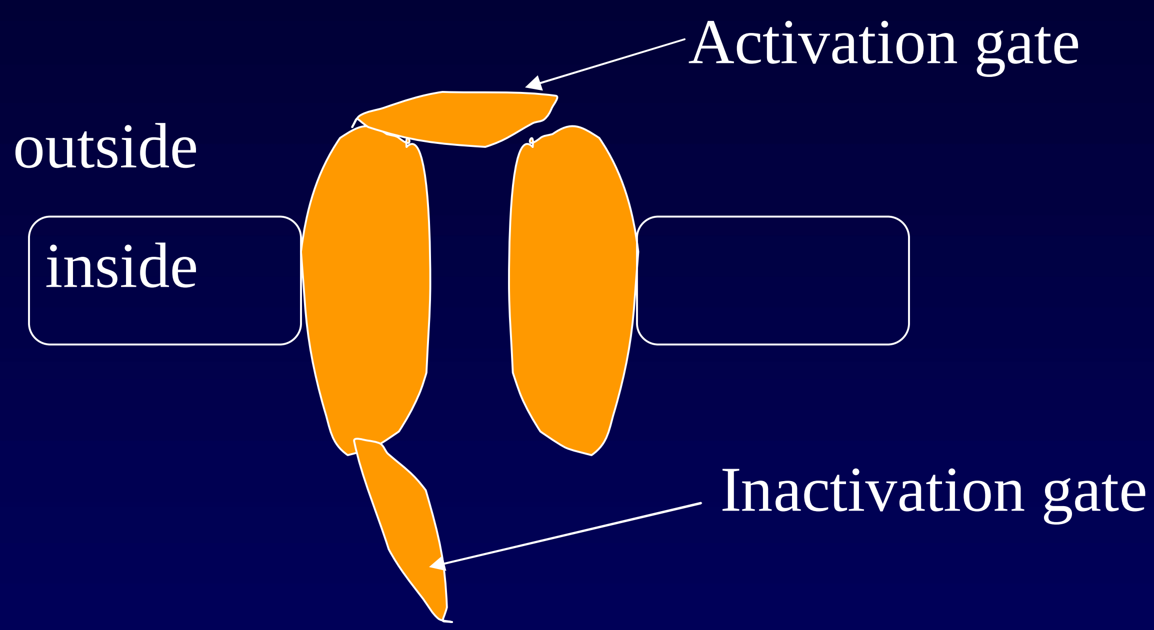
- When the threshold level is reached
  - Voltage-gated Na+ channels open up
  - Since Na conc outside is more than the inside
  - Na influx will occur
  - Positive ion coming inside increases the positivity of the membrane potential and causes depolarisation
  - When it reaches +30, Na+ channels closes
  - Then Voltage-gated K+ channels open up
  - K+ efflux occurs
  - Positive ion leaving the inside causes more negativity inside the membrane
  - Repolarisation occurs

Physiological basis of AP

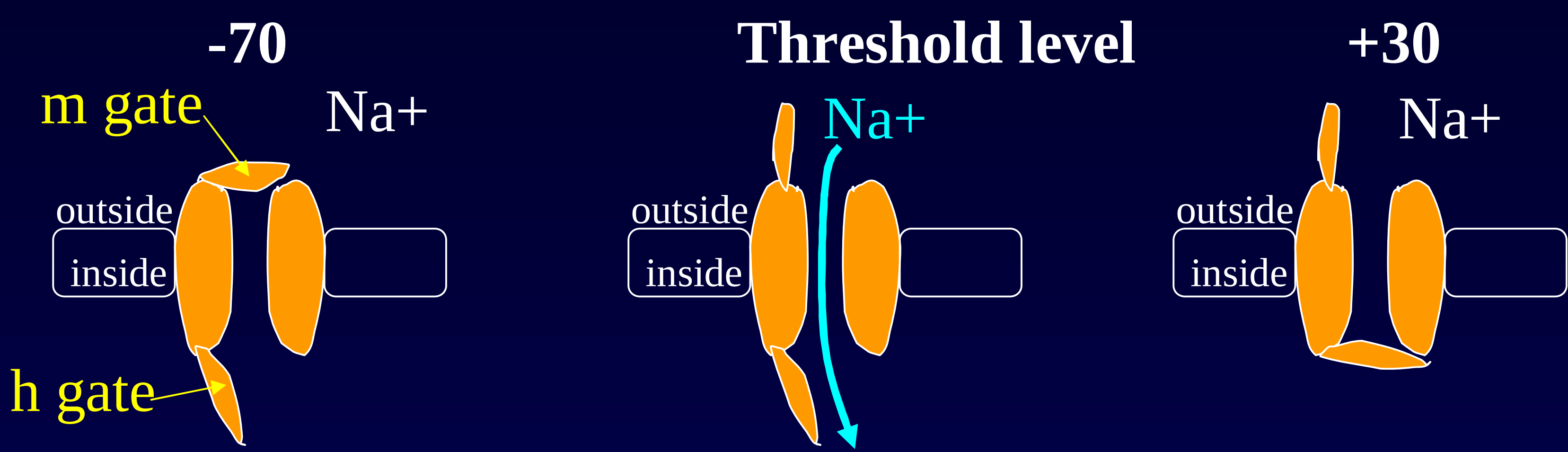
- Since Na+ has come in and K+ has gone out
- Membrane has become negative
- But ionic distribution has become unequal

- Na+/K+ pump restores Na+ and K+ conc slowly
  - By pumping 3 Na+ ions outward and 2+ K ions inward

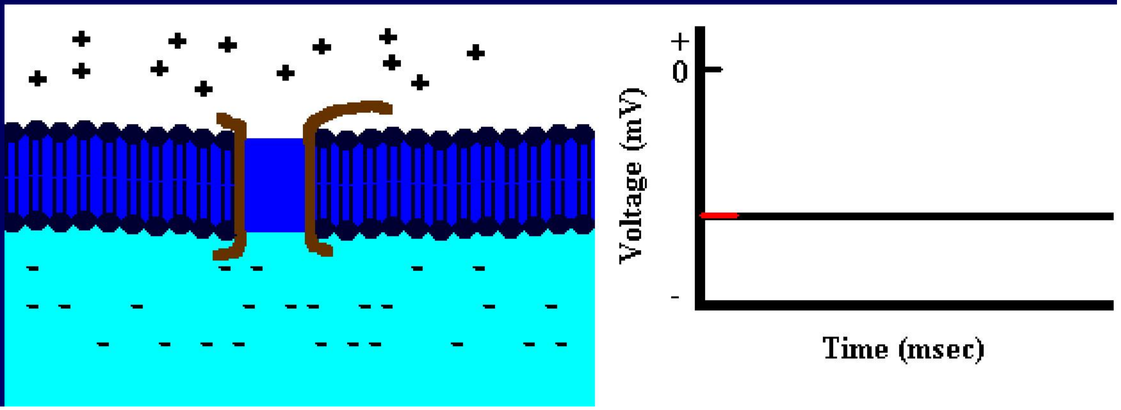
VOLTAGE-GATED ION CHANNELS



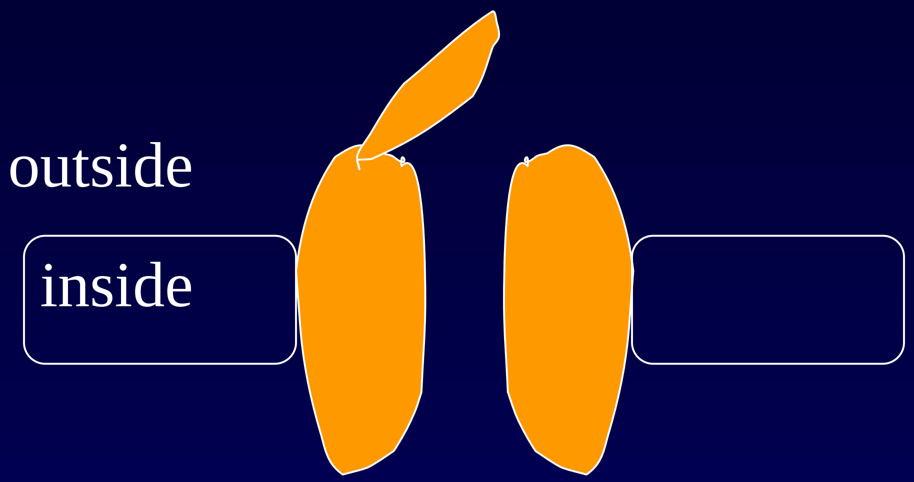
- Na+ channel
  - This has two gates
    - Activation and inactivation gates



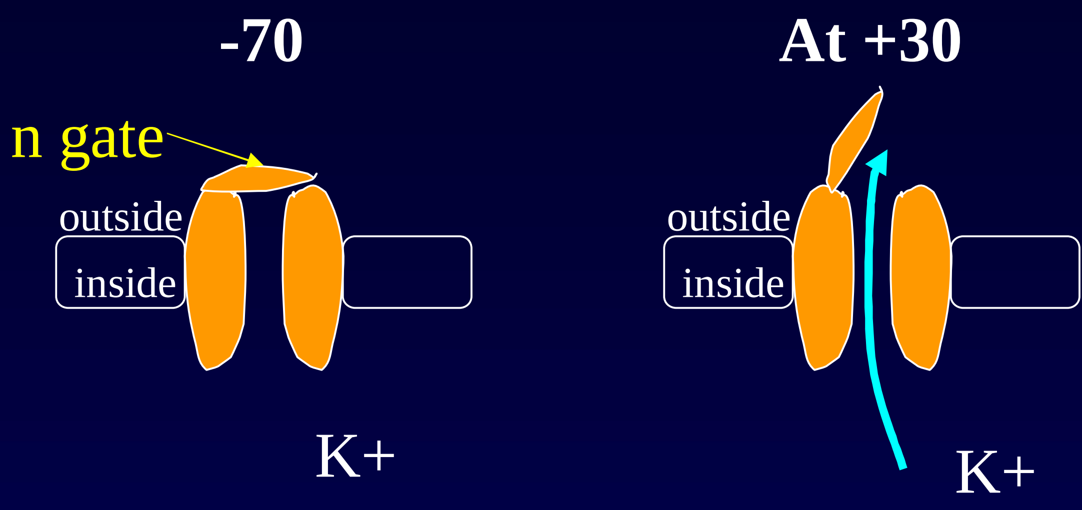
- At rest: the activation gate is closed
- At threshold level: activation gate opens
  - Na+ influx will occur
  - Na+ permeability increases to 500 fold
- when reaching +30, inactivation gate closes
  - Na influx stops
- Inactivation gate will not reopen until resting membrane potential is reached
- Na+ channel opens fast



VOLTAGE-GATED K+ Channel



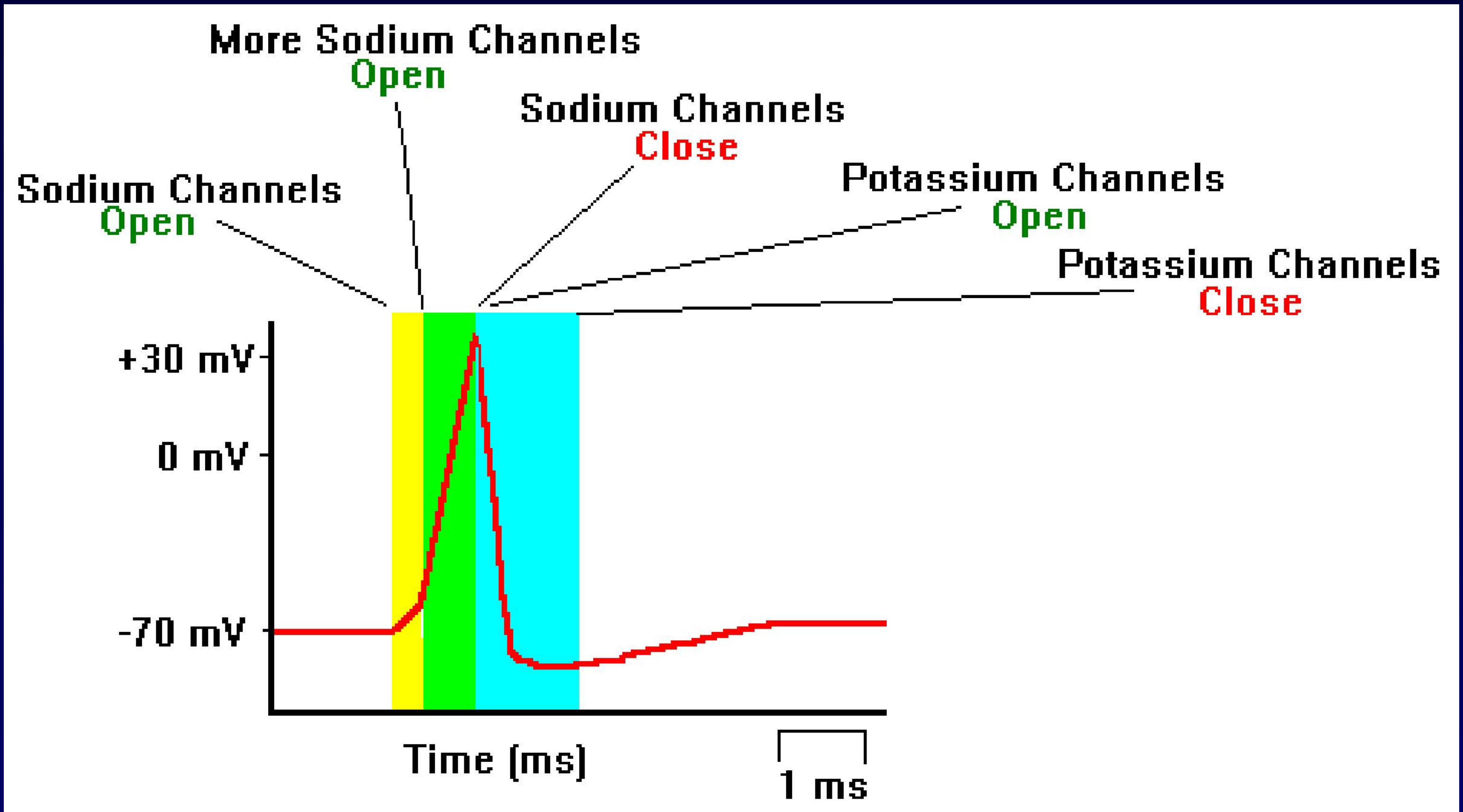
- K+ channel
  - This has only one gate



- At rest: K+ channel is closed
- At +30
  - K+ channel open up slowly
  - This slow activation causes K efflux

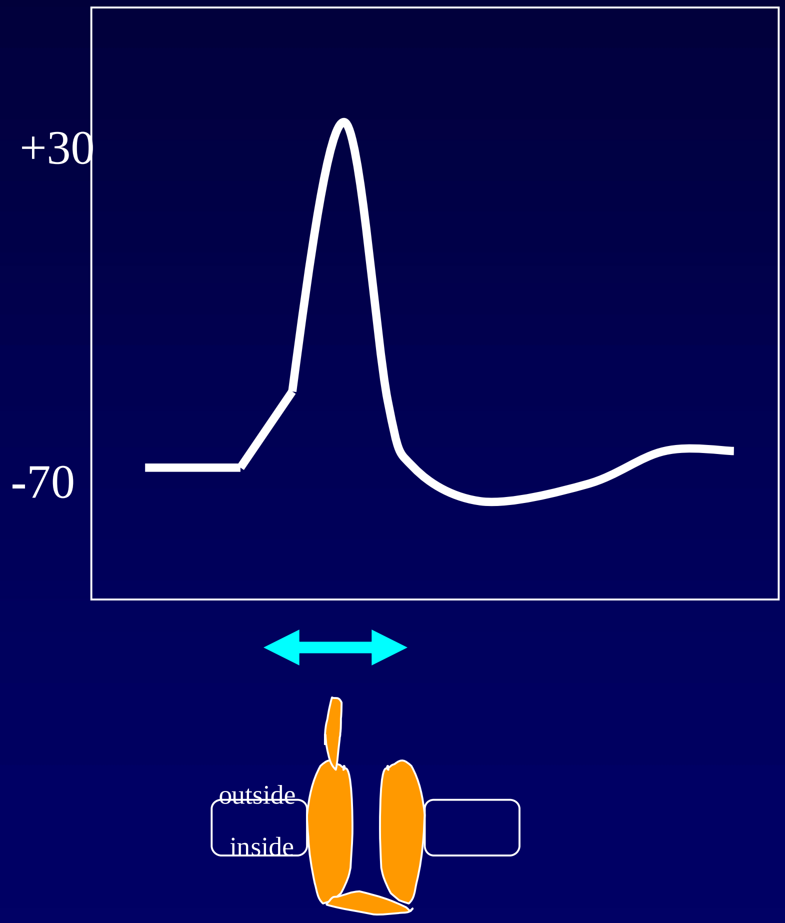
- After reaching the resting still slow K+ channels may remain open: causing further hyperpolarisation

Summary


More Sodium Channels
Open
Sodium Channels
Close
Sodium Channels
Open
Potassium Channels
Open
Potassium Channels
Close
+30 mV
0 mV
-70 mV
Time (ms)
1 ms

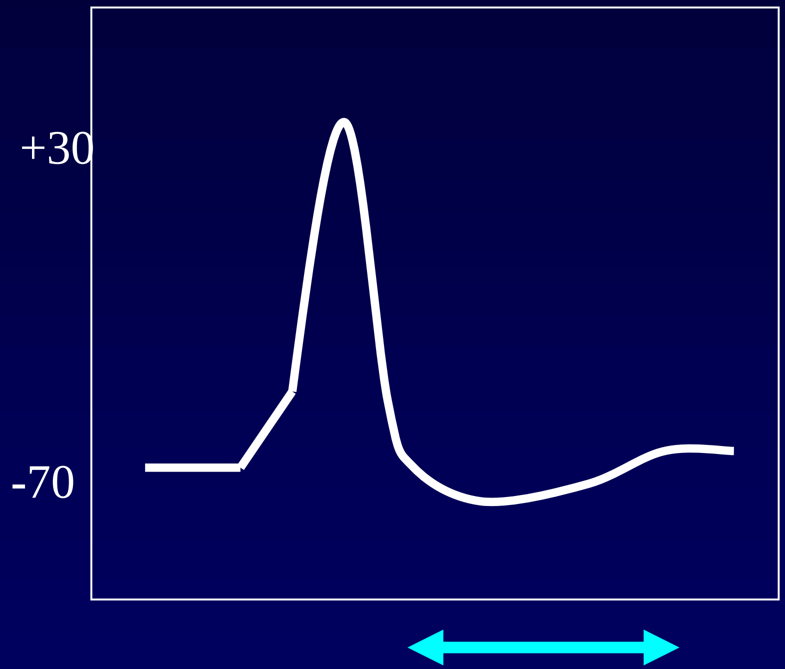
Refractory Period

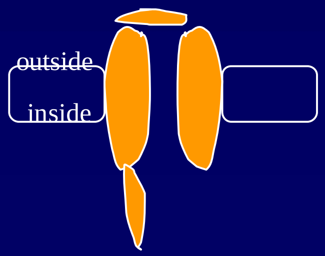
- Absolute refractory period
  - During this period nerve membrane cannot be excited again
  - Because of the closure of inactivation gate



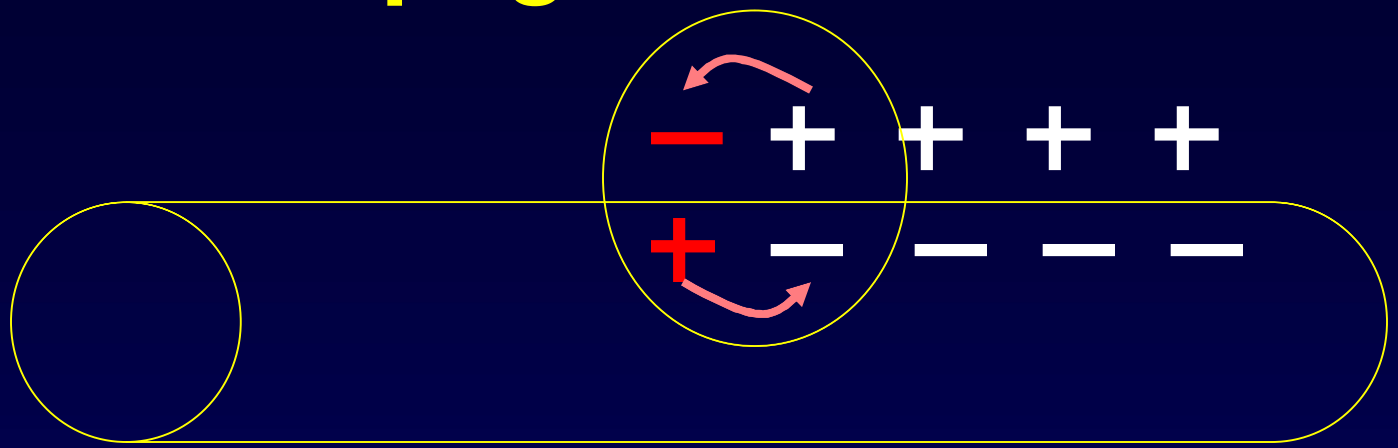
Refractory Period

- Relative refractory period
  - During this period nerve membrane can be excited by supra threshold stimuli
  - At the end of repolarisation phase inactivation gate opens and activation gate closes
  - This can be opened by greater stimuli strength



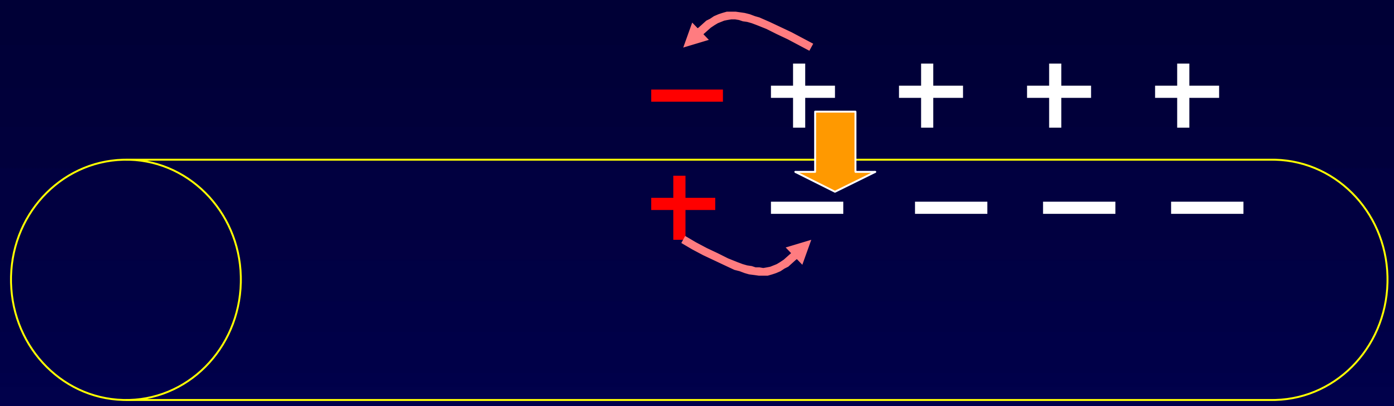


Propagation of AP



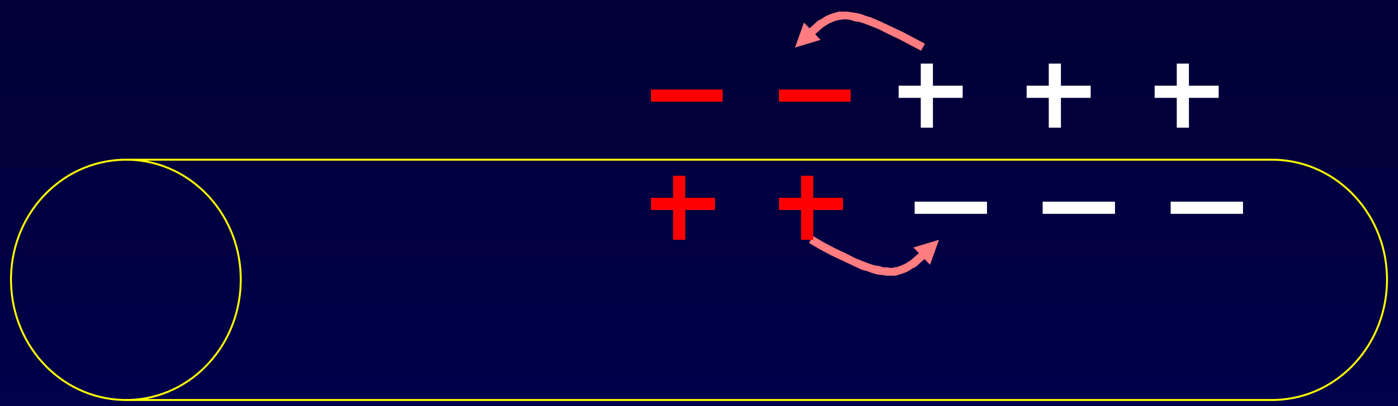
- When one area is depolarised
- A potential difference exists between that site and the adjacent membrane
- A local current flow is initiated
- Local circuit is completed by extra cellular fluid

Propagation of AP



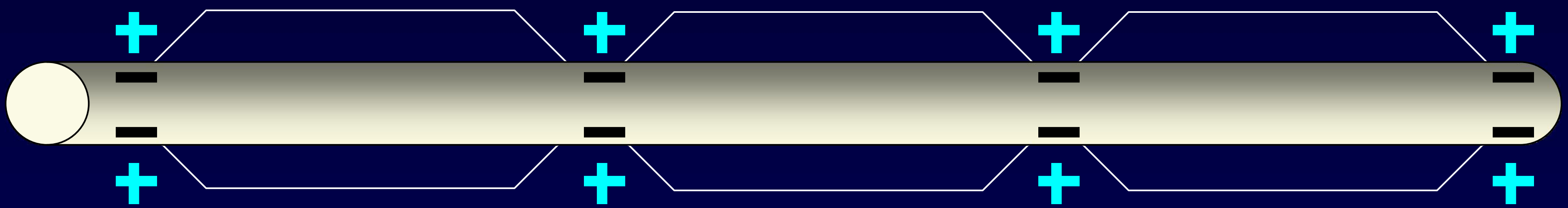
- This local current flow will cause opening of voltage-gated Na channel in the adjacent membrane
- Na influx will occur
- Membrane is deloparised

Propagation of AP

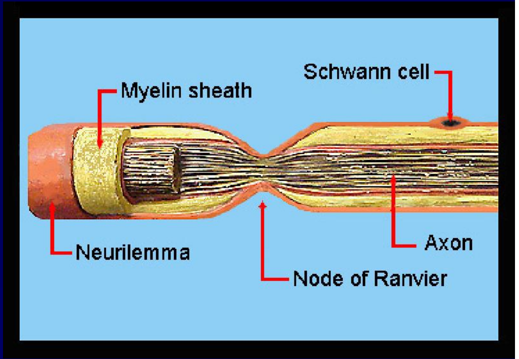


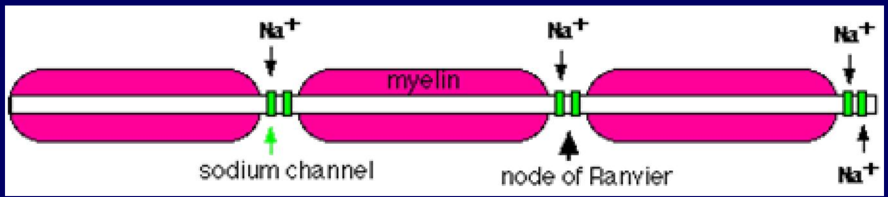
- Then the previous area become repolarised
- This process continue to work
- Resulting in propagation of AP

AP propagation along myelinated nerves

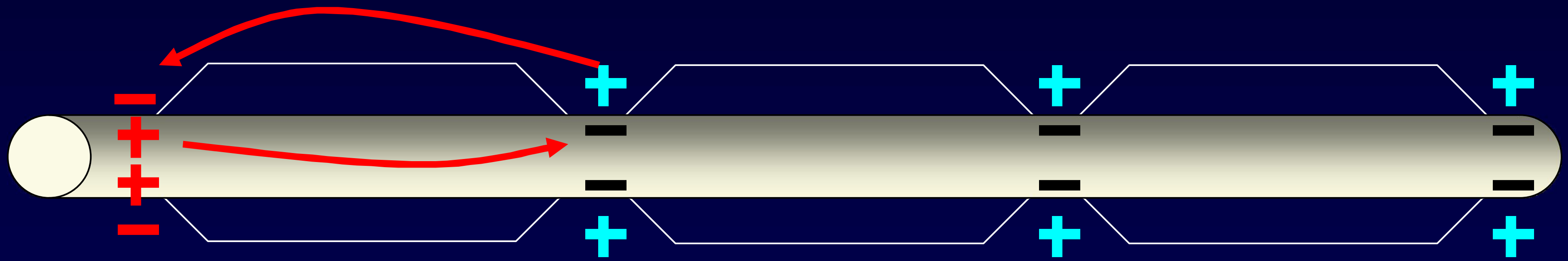


- Na channels are conc around nodes
- Therefore depolarisation mainly occurs at nodes



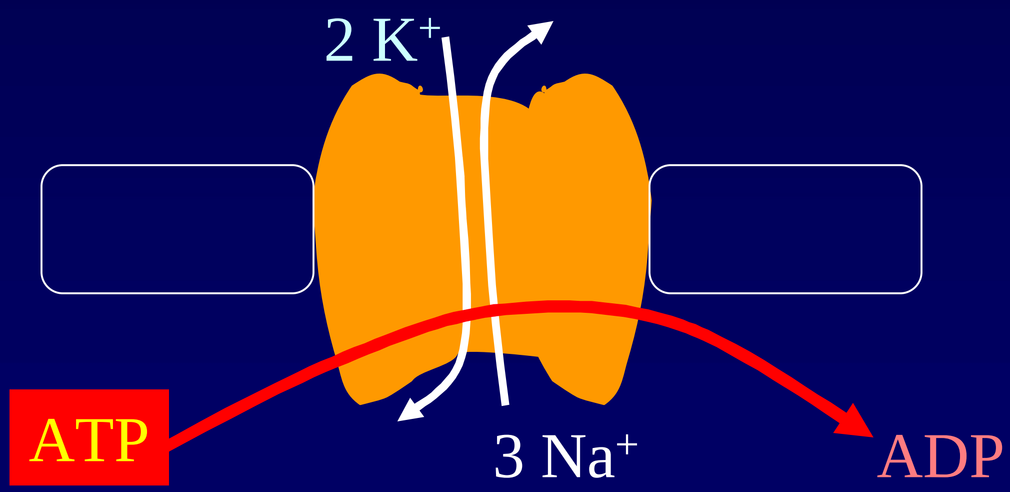


AP propagation along myelinated nerves



- Local current will flow one node to another
- Thus propagation of A.P. is faster. Conduction through myelinated fibres also faster.
- Known as Saltatory Conduction

- Re-establishment of Na & K conc after A.P.
  - Na-K Pump is responsible for this.
  - Energy is consumed



Membrane stabilisers

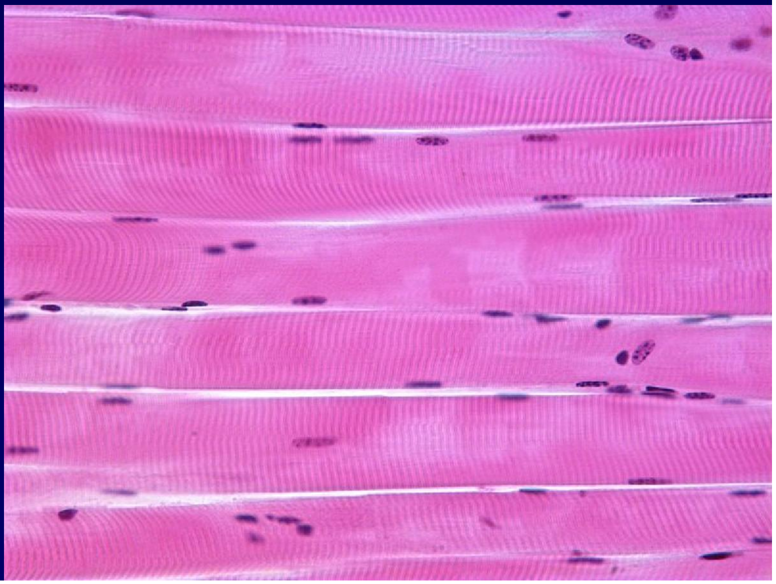
- Membrane stabilisers (these decrease excitability)
  - Increased serum Ca++
    - Hypocalcaemia causes membrane instability and spontaneous activation of nerve membrane
    - Reduced Ca level facilitates Na entry
    - Spontaneous activation
  - Decreased serum K+
  - Local anaesthetics
  - Acidosis
  - Hypoxia
- Membrane destabilisers (these increase excitability)
  - Decreased serum Ca++
  - Increased serum K+
  - Alkalosis

Muscle action potentials

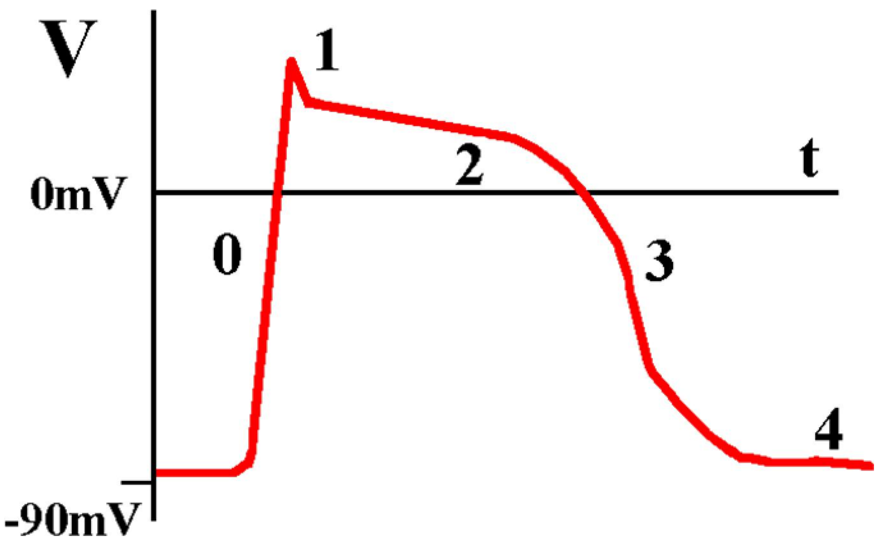
- Skeletal muscle
- Smooth muscle
- Cardiac muscle

Skeletal muscle

- Similar to nerve action potential



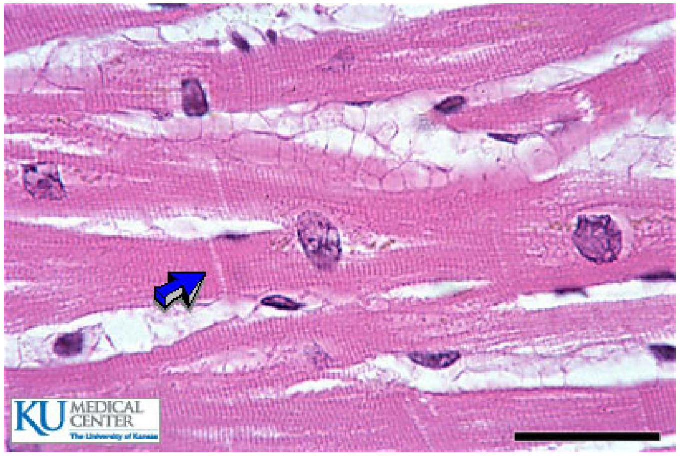
Cardiac muscle action potential



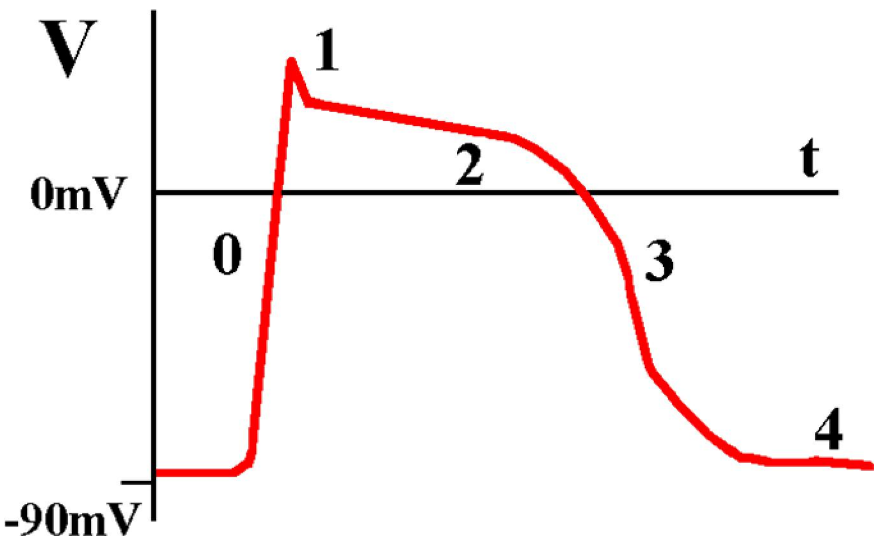
Phases

- 0: depolarisation
- 1: short repolarisation
- 2: plateau phase
- 3: repolarisation
- 4: resting

Duration is about 250 msec



Cardiac muscle action potential

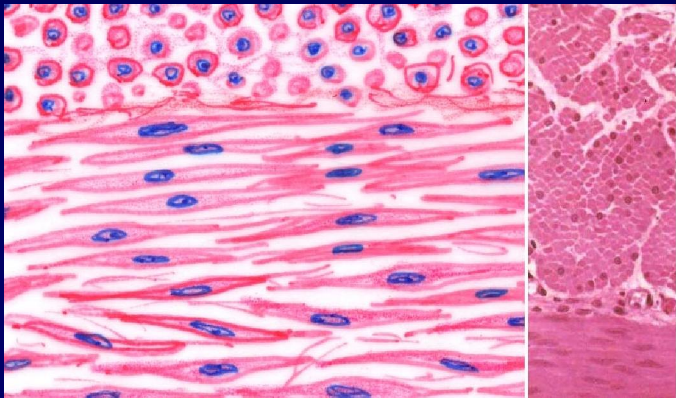


Phases

- 0: depolarisation (Na+ influx through fast Na+ channels)
- 1: short repolarisation (K+ efflux through K+ channels, Cl- influx as well)
- 2: plateau phase (Ca++ influx through slow Ca++ channels)
- 3: repolarisation (K+ efflux through K+ channels)
- 4: resting

Smooth muscle

- Resting membrane potential may be about -55mV
- Action potential is similar to nerve AP
- But AP is not necessary for its contraction
- Smooth muscle contraction can occur by hormones



Depolarisation

- Activation of nerve membrane
- Membrane potential becomes positive
- Due to influx of Na^+ or Ca^{++}

Hyperpolarisation

- Inhibition of nerve membrane
- Membrane potential becomes more negative
- Due to efflux of K+ or influx of Cl^-