Signal integration and propagation, nerve conduction, glial cells

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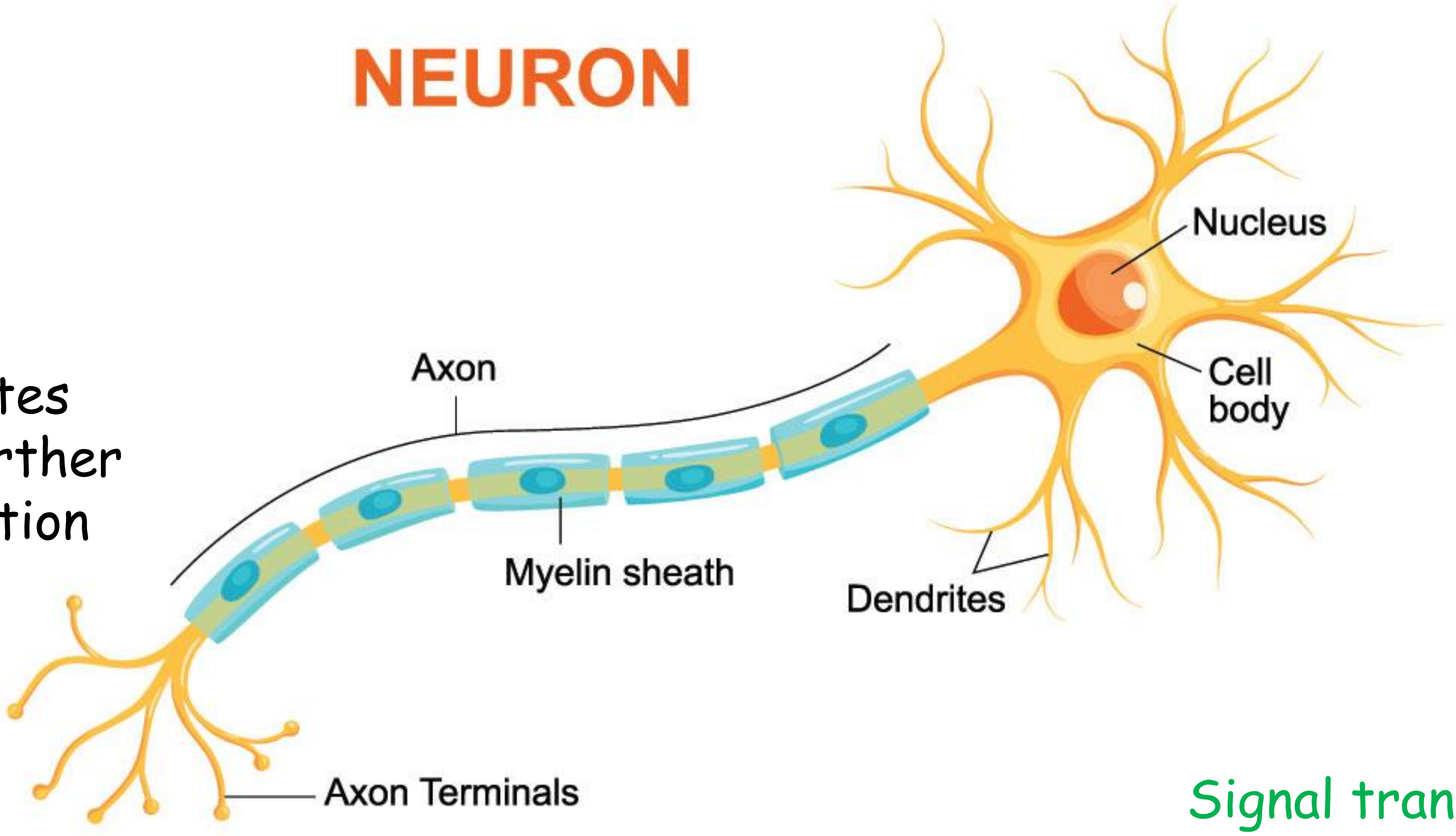
Structure of a neuron and electrical activity



Dendrites receive and integrate information from other neurons

Axons propagates information further in a form of action potential

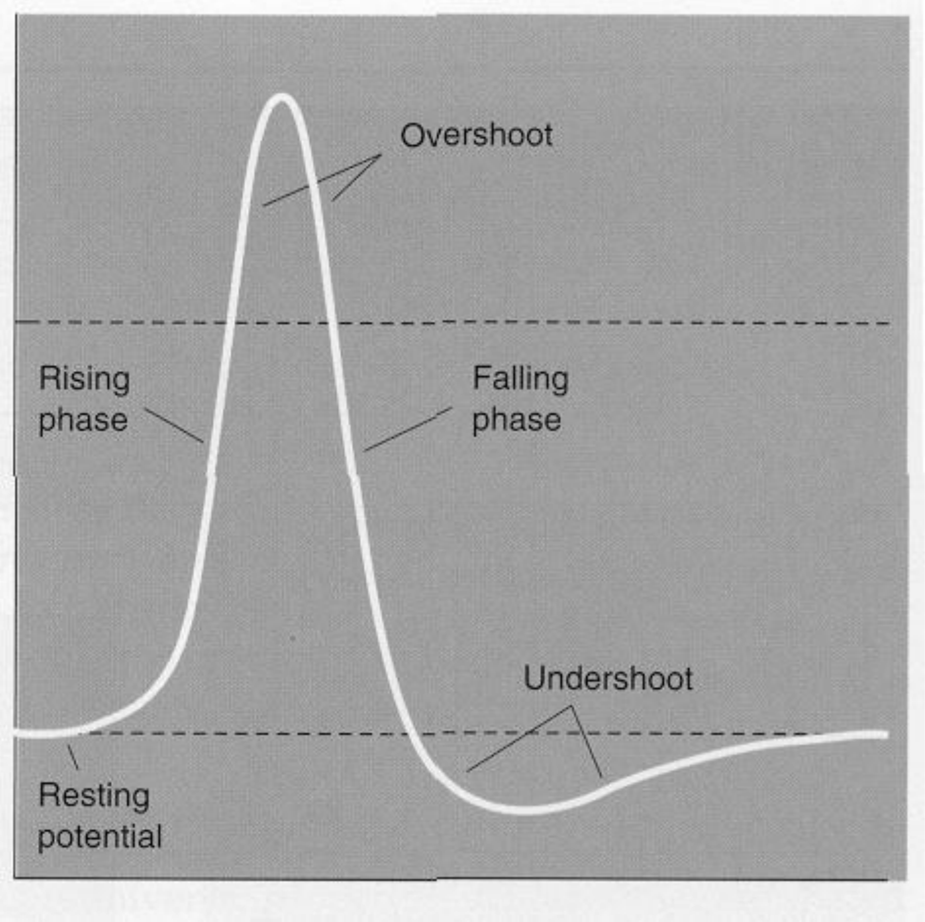
Signal transmission regulation - Glial cells

Axonal endings - synapse – transfer of the information

How do neurons use electrical signals to transfer information?

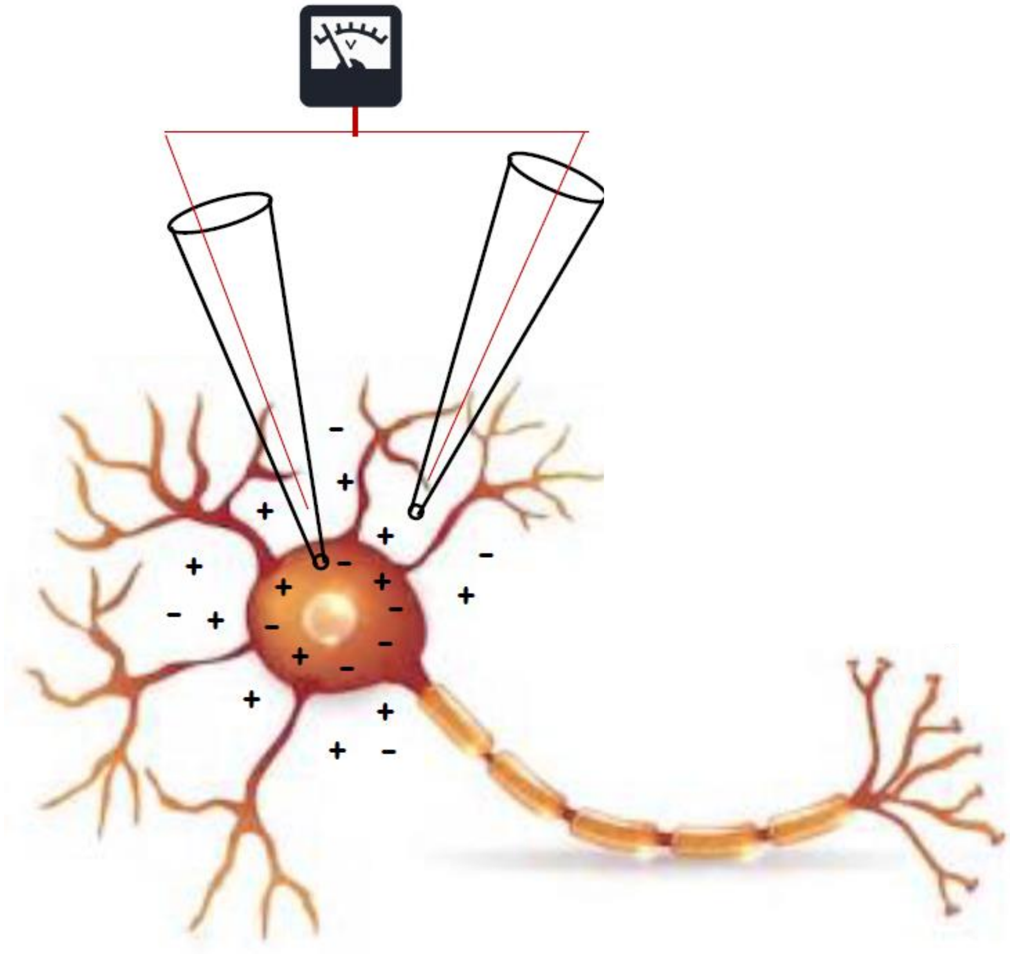
1. Recapitulation: Resting membrane potential, Ion channels, Action potential
2. Dendritic integration, synaptic potentials, signal propagation
3. Action potential propagation in the nerve – axon, myelin
4. Glial cells

Neurons are in a state of electrical activity all the time. What does it mean?



Neurons generate electrical activity even in a resting state.

Potential difference on a membrane

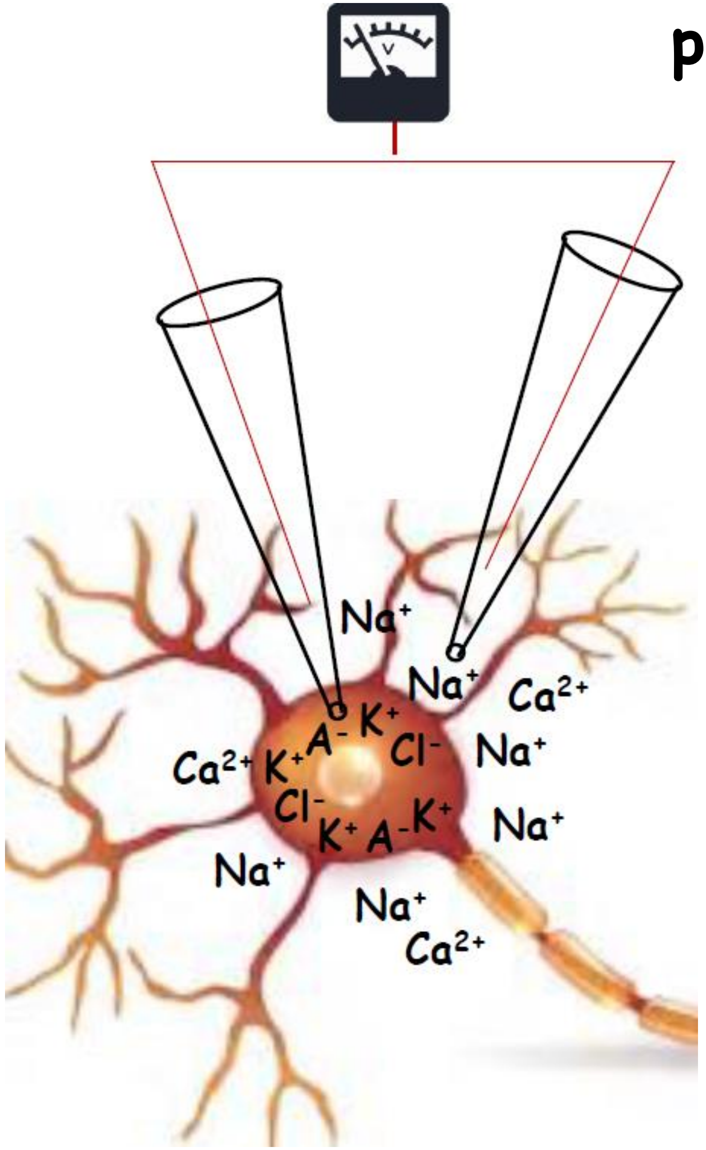


- Potential recorded in volts by a voltmeter

- It arises from a different amount of positive and negative particles on each side of the membrane

- The bigger the difference in the amount of the particles, the bigger the potential (= membrane is <u>polarized</u>)

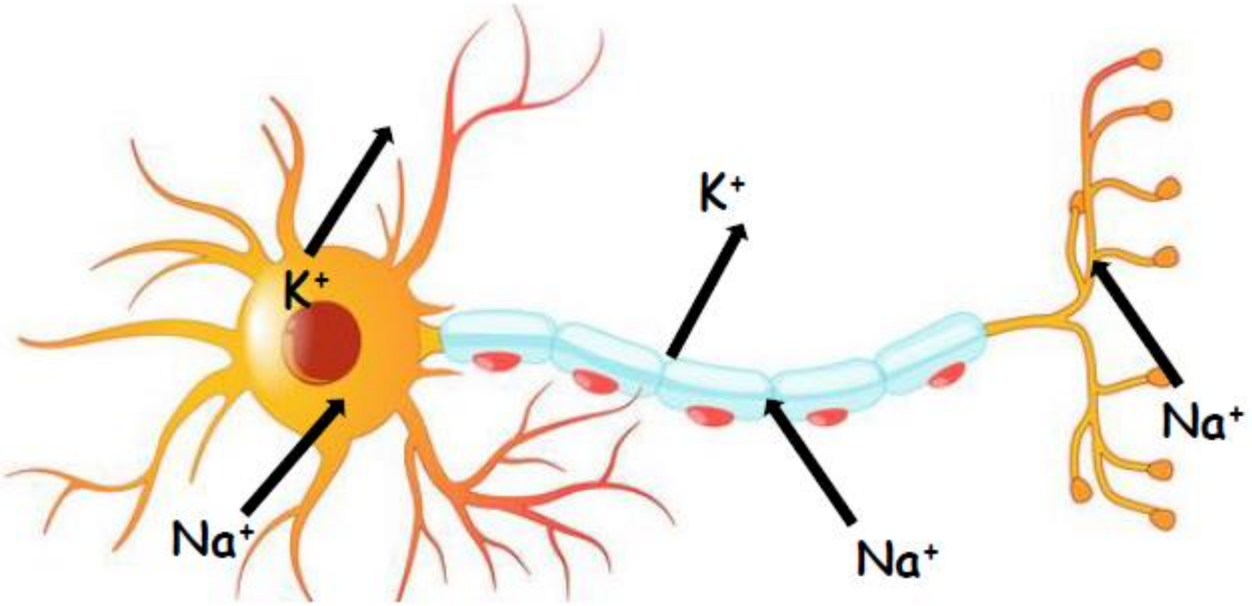
Water solutions – ion particles carry the potential and current



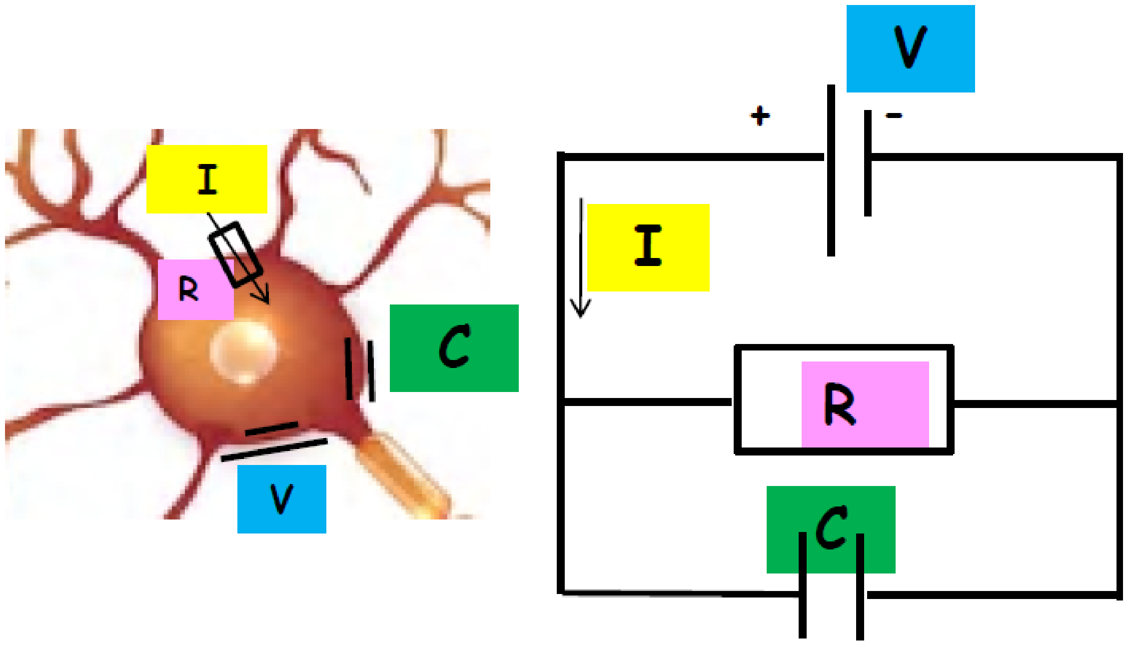
- Charged ions are atoms or molecules in a solution which gained or lost an electron (or more electrons)
- *The main ions are: Na^+, K^+, Ca^{2+}, Cl^-*
- *Cations and anions move through the membrane and carry thus electric signal*
- The charge might be stored in proteins (A^-)

Movement of charged ions causes electrical current

In a neuron the current of ions is responsible for the transmission of signals in dendrites and axon.



Neuron works as an electrical circuit and cell membrane as a capacitor



I = current
V = voltage = potential
R = resistance
G = conductance = 1/R
C = capacitance

Phospholipid membrane – non-conductor
Separates conducting solutions in and outside the cell

Before voltage on the membrane changes, the membrane first needs to be charged or discharged

Capacitance limits signal transmission on the membrane

Ohm's law

$$V = IR$$

Time constant

$$t_m = R_m C_m$$

Higher capacitance

-> longer the time constant
-> the longer it takes for the membrane to charge or decharge
-> the longer it takes for the transmembrane potential to change
-> the longer it takes for the signal to propagate

-> we want to keep the capacitance low

How to achieve that? (myelin)

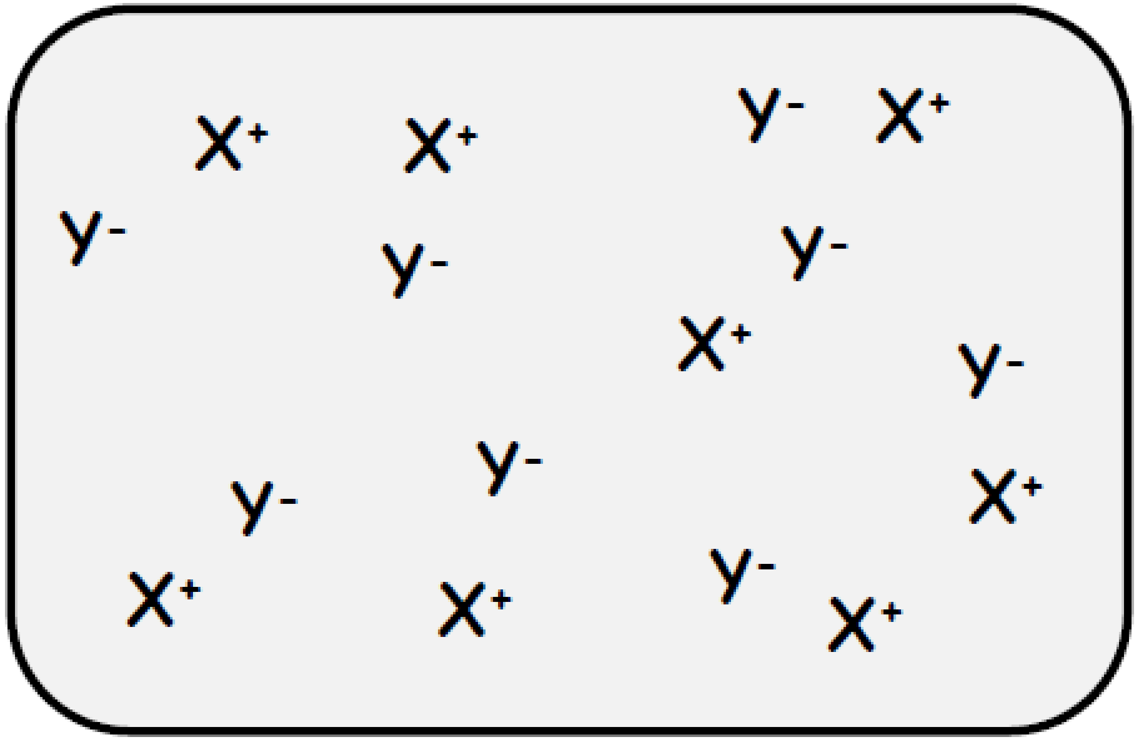
What determines ion movement through a semipermeable membrane?

In a solution there are two forces which determine the movement of ions:

1. **Charge**

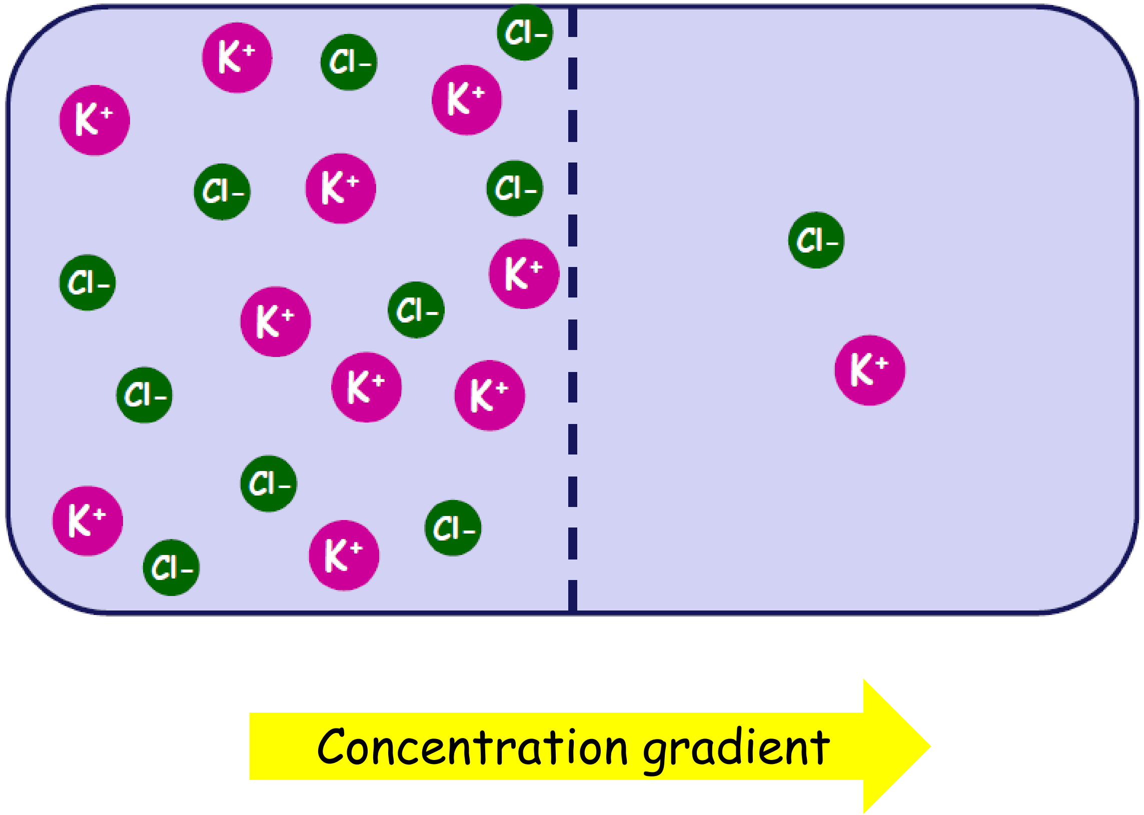
- Ions with the same charge repel each other
- Ions with different charge attract each other

2. **Concentration**



Two solutions with a different concentration separated by a semipermeable membrane

The membrane is selectively permeable for K^+

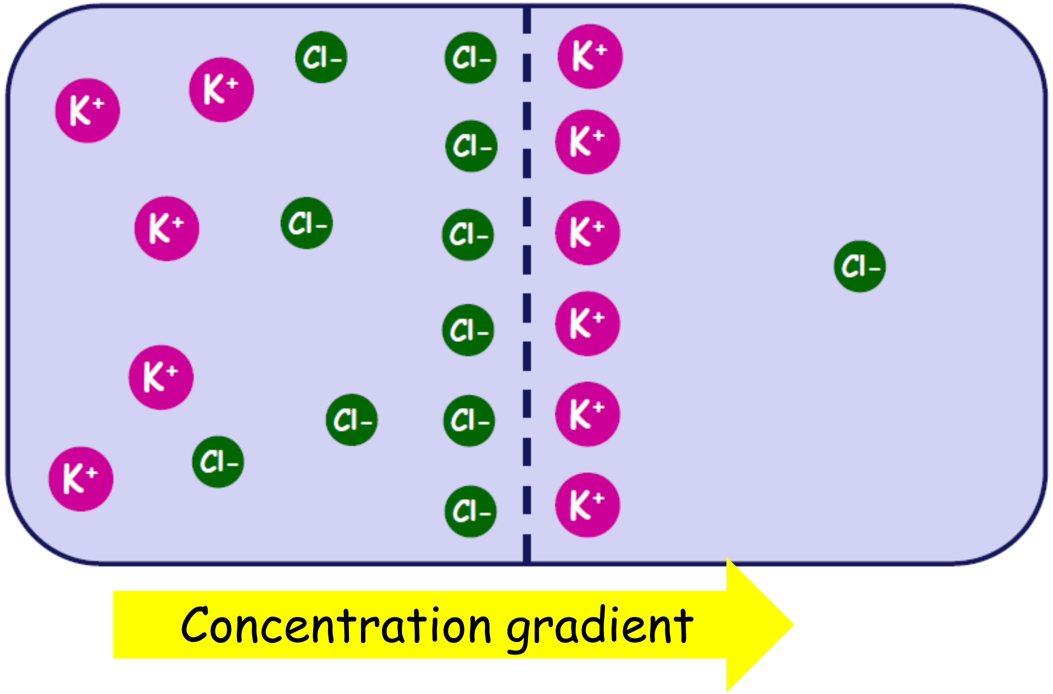


Concentration gradient

Concentration gradient pro both ions, but only K^+ ions can move through the membrane

K$^+$ ions move along their concentration gradient

=> This changes the charge on both sides of the membrane and charge gradient thus develops

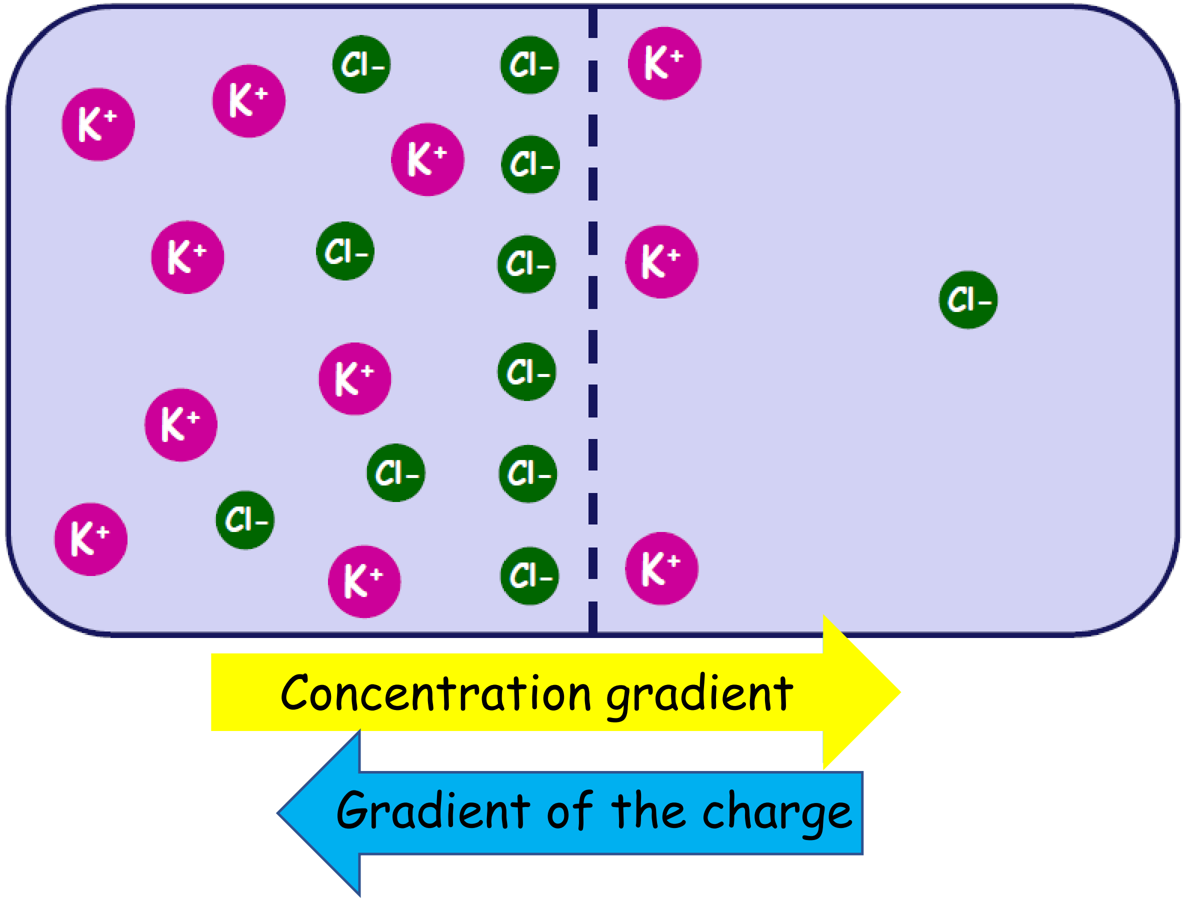


Negative charge

proteins$^-$

Positive charge

K^+ ions move along the charge gradient towards negative charge



At some point the movement stops and the amount of ions on both sides stabilizes (the two forces stabilize) – the ion is in equilibrium potential

- Equilibrium potential for a given ion – the gradients are in equilibrium (no net movement of the ion)

- Factors which affect the equilibrium potential for a given ion are described by Nernst equation

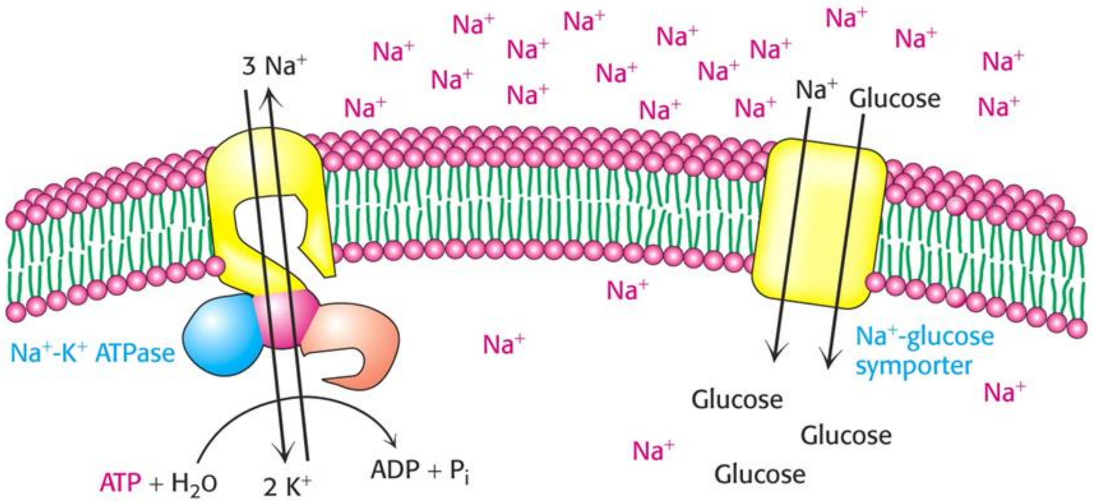
$$E_{ion}= RT/(+1)xF \ln \{ [ION_{out}] / [ION_{in}] \}$$

$$\downarrow$$

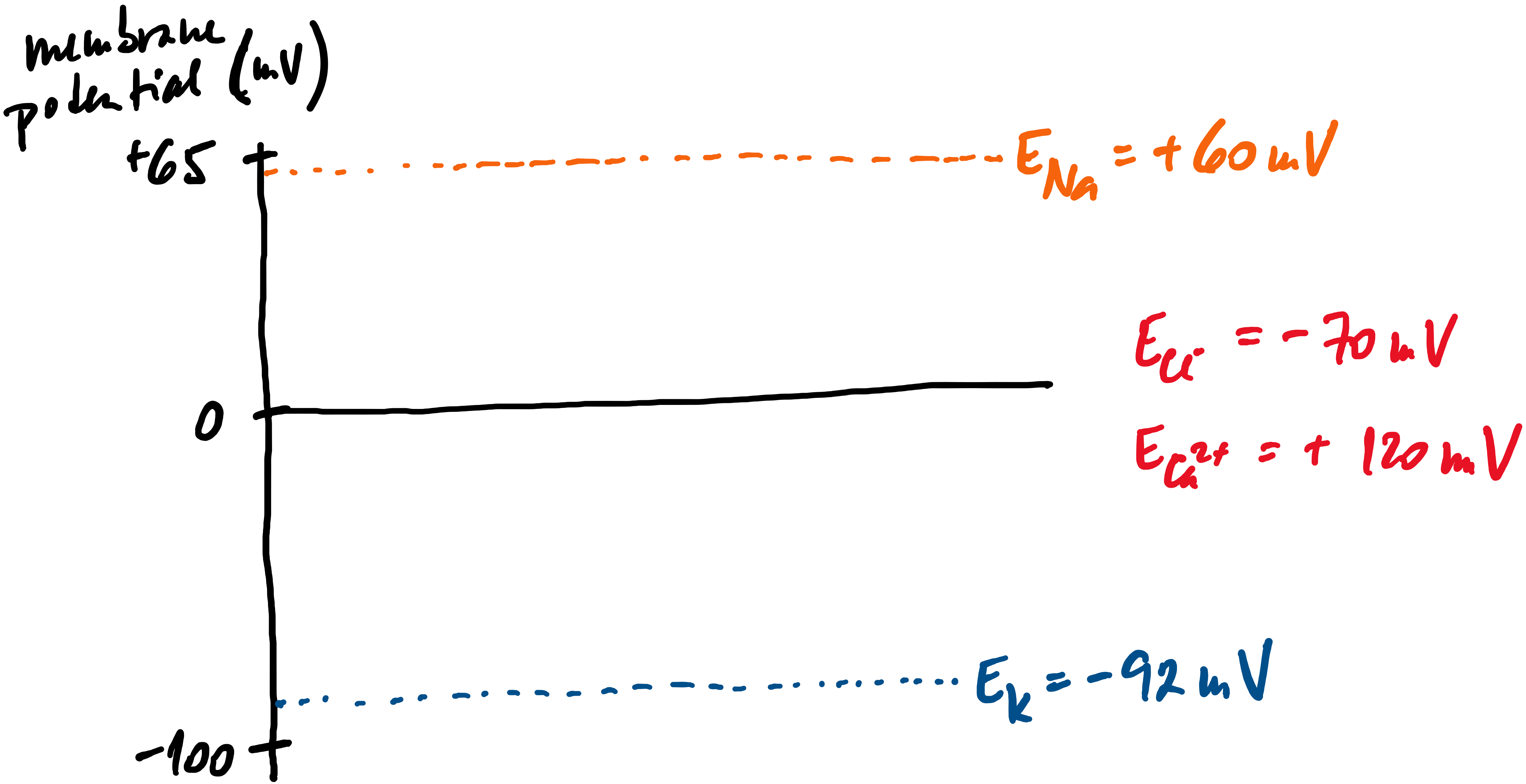
$$E_{ion}= 60 \log \{ [ION_{out}] / [ION_{in}] \}$$

Ion concentrations on a neuronal cell membrane

Ion	[Out] mM	[In] mM
K^+	5	140
Na^+	150	15
Ca^{2+}	2	0.0002
Cl^-	110	10

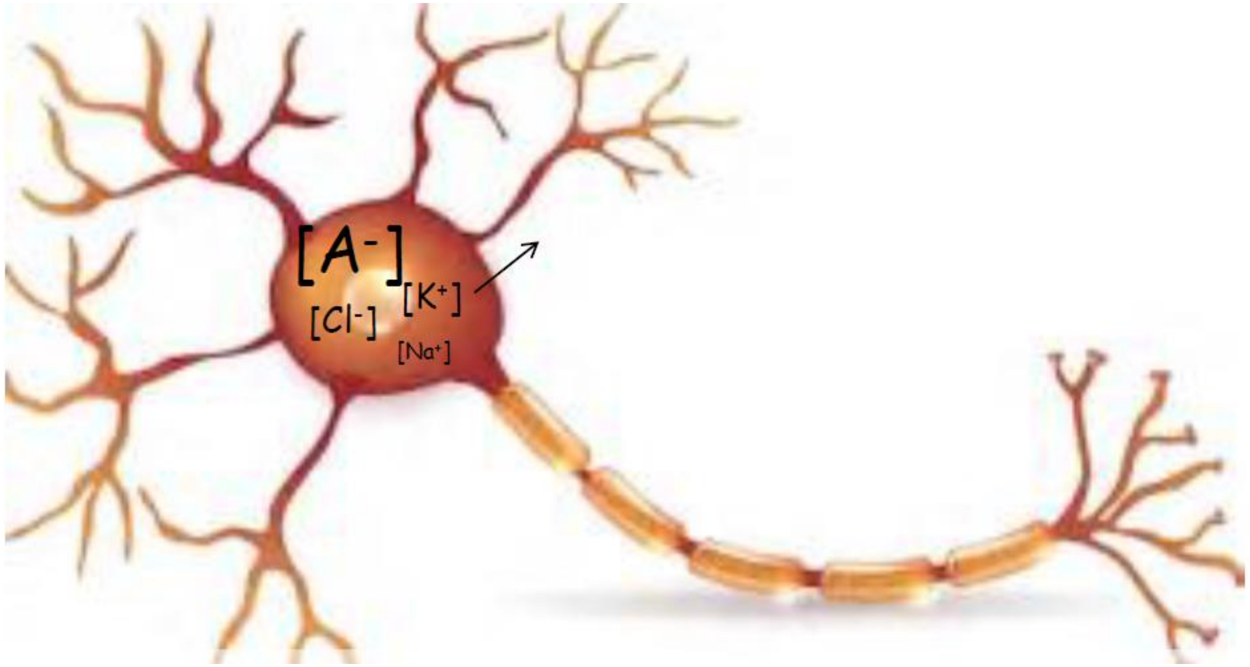


Na^+/K^+ ATPase – maintain K^+ and Na^+ concentrations on a membrane


membrane potential (mV)
+65
0
-100
$E_{Na} = +60$ mV
$E_{Cl^-} = -70$ mV
$E_{Ca^{2+}} = +120$ mV
$E_K = -92$ mV

Resting membrane potential (RMP)

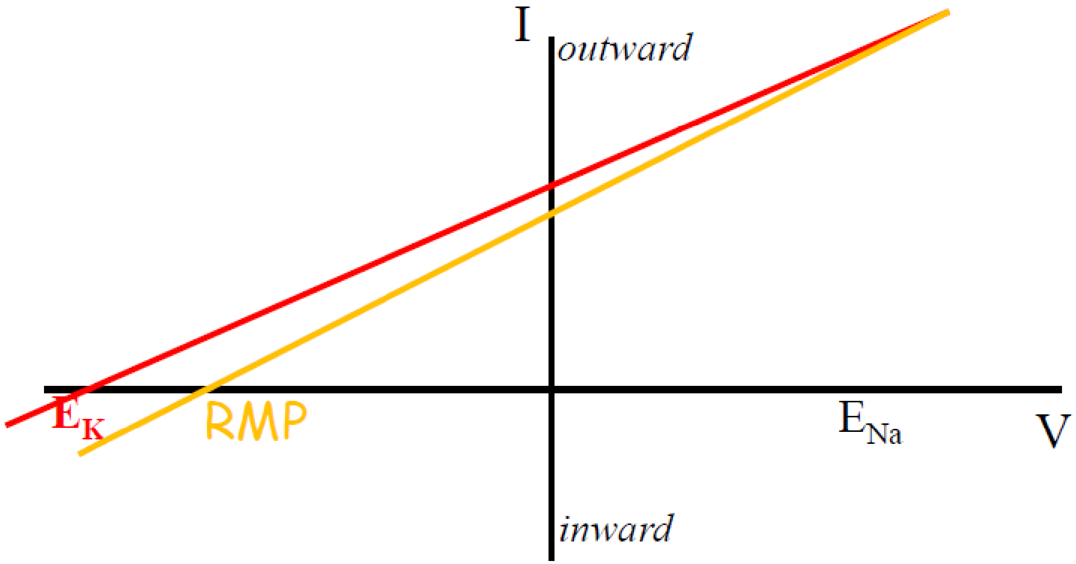
- Resting membrane potential is a potential on the membrane at rest when no signal is transmitted (no AP, no depolarization…)
- All cells have RMP
- Most of the cells are negative inside
- Most neurons are at rest only temporarily



If the membrane would be permeable only for K+, the RMP would equal E_K

RMP does not equal E_K, thus other conductancies are involved

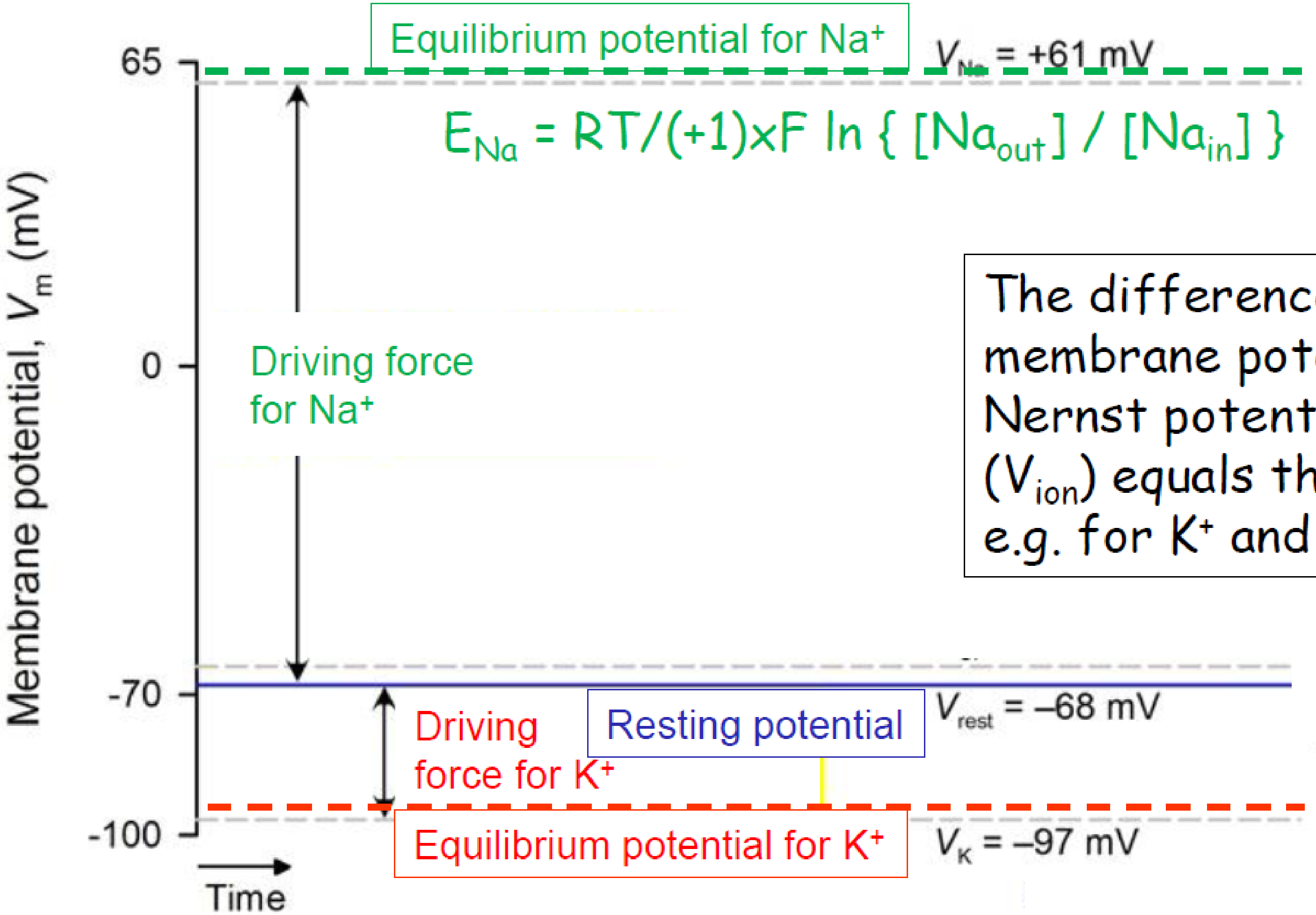
Goldman-Hodgkin-Katz equation describes relative conductance (permeability, P) of the membrane for different ions and its contribution to the RMP



Leak channels/currents

$$E_{mem} = RT/F \ln \frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o}$$

Driving force enables ion movement through the membrane + open ion channels



$$E_{Na} = RT/(+1)xF \ln \{ [Na_{out}] / [Na_{in}] \}$$

The difference between the membrane potential (V_M) and the Nernst potential for a given ion (V_{ion}) equals the driving force e.g. for K^+ and Na^+....

$$E_K = RT/(+1)xF \ln \{ [K_{out}] / [K_{in}] \}$$

This works when ion channels open

Summary #1: electric properties of the membrane and RMP

Electrical signals in neurons are changes in membrane voltage caused by movement of charged particles - ions.

The size of the ion current depends on the "driving force" - this is determined by the concentration gradient and the charge gradient together with the conductivity of the membrane.

Ions move across the non-conductive membrane thanks to specialized proteins - ion channels.

RMP is primarily determined by the permeability for K^+ ions, and other permeabilities are also involved (Cl^-, Na^+)

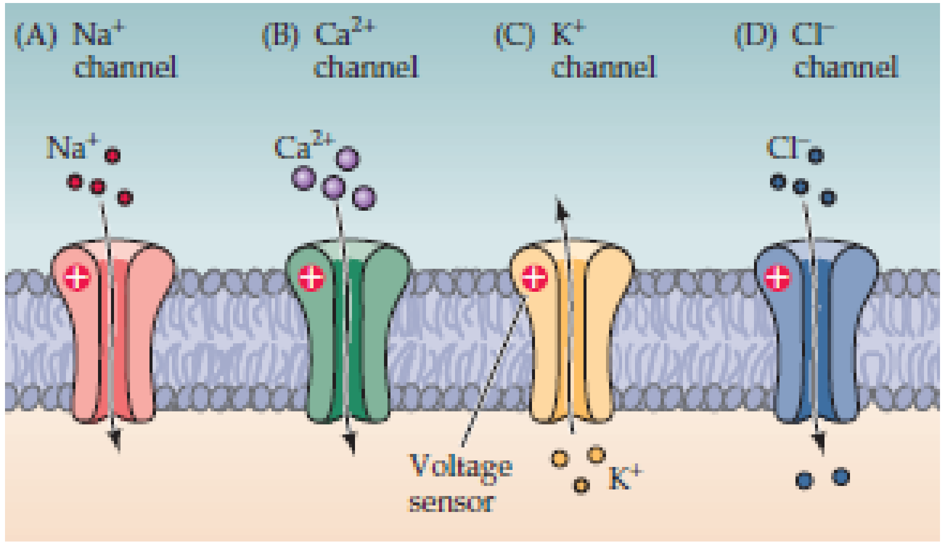
=> These properties determine how dendrites, axons, and neuron terminals generate electrical signals to communicate with each other.

Ion channels

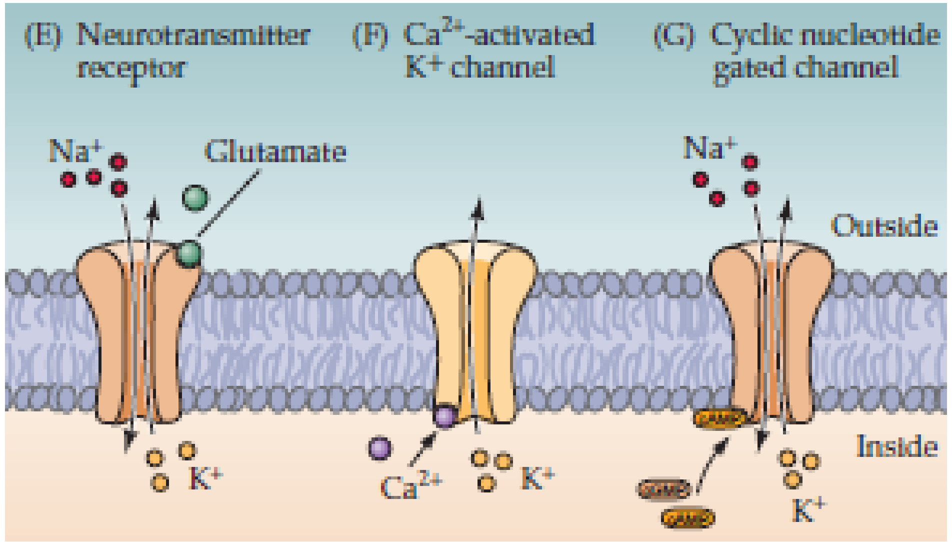
Ions move across the non-conductive membrane thanks to specialized proteins - ion channels.

Voltage-gated ion channels **Ligand-gated ion channels**

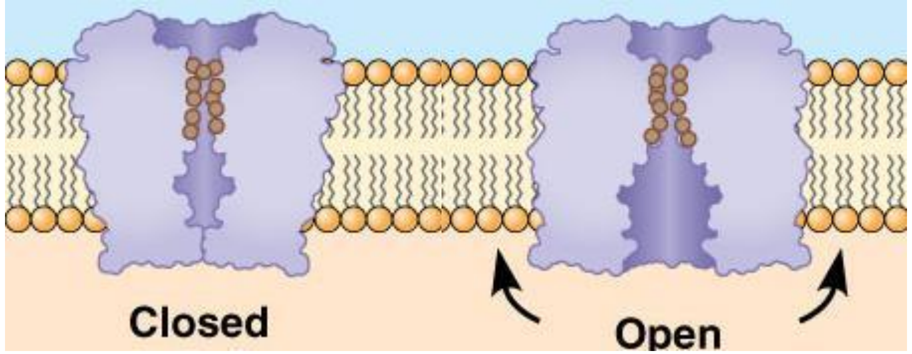
VOLTAGE-GATED CHANNELS



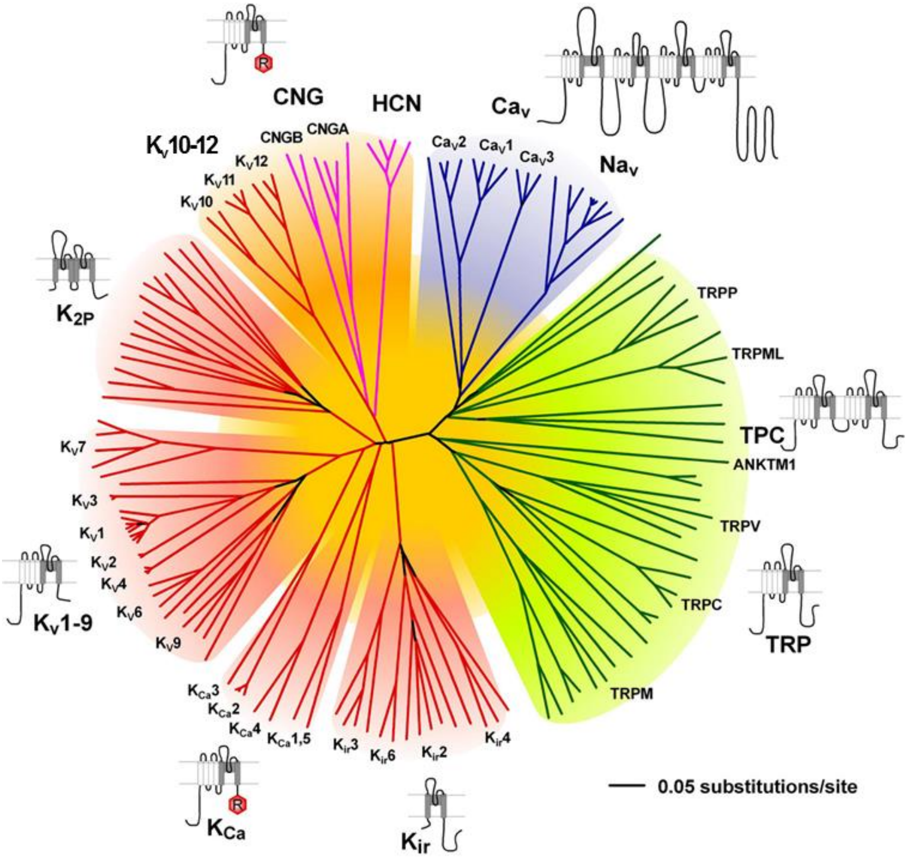
LIGAND-GATED CHANNELS



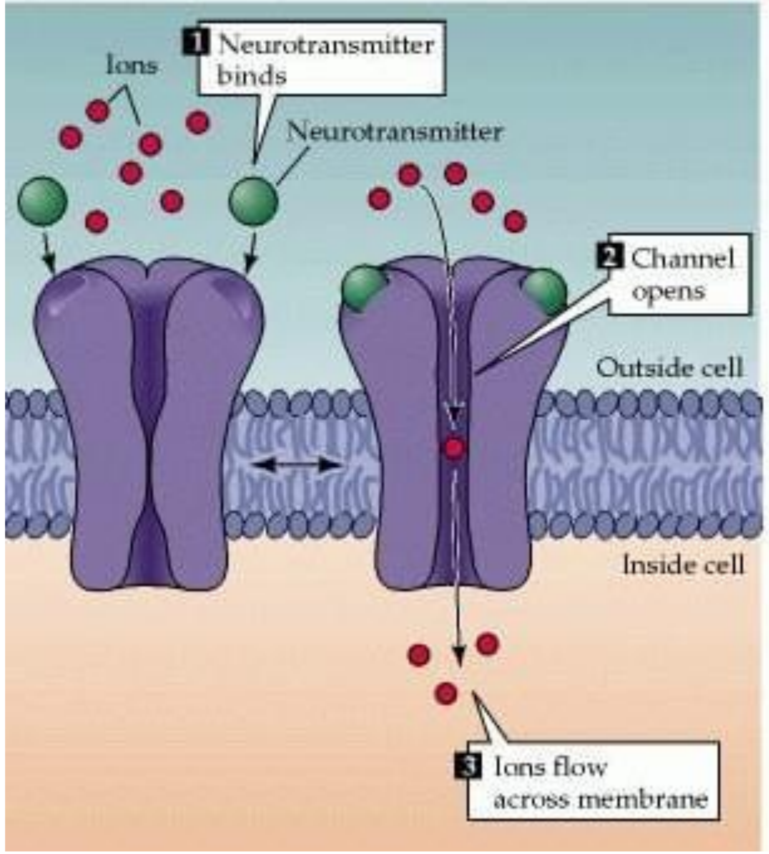
Voltage-gated ion channels



- Their opening is triggered by a potential change on the membrane
- They are selectively permeable for one ion type
- Their reversal potential correlates with the Nernst (equilibrium) potential for a given ion

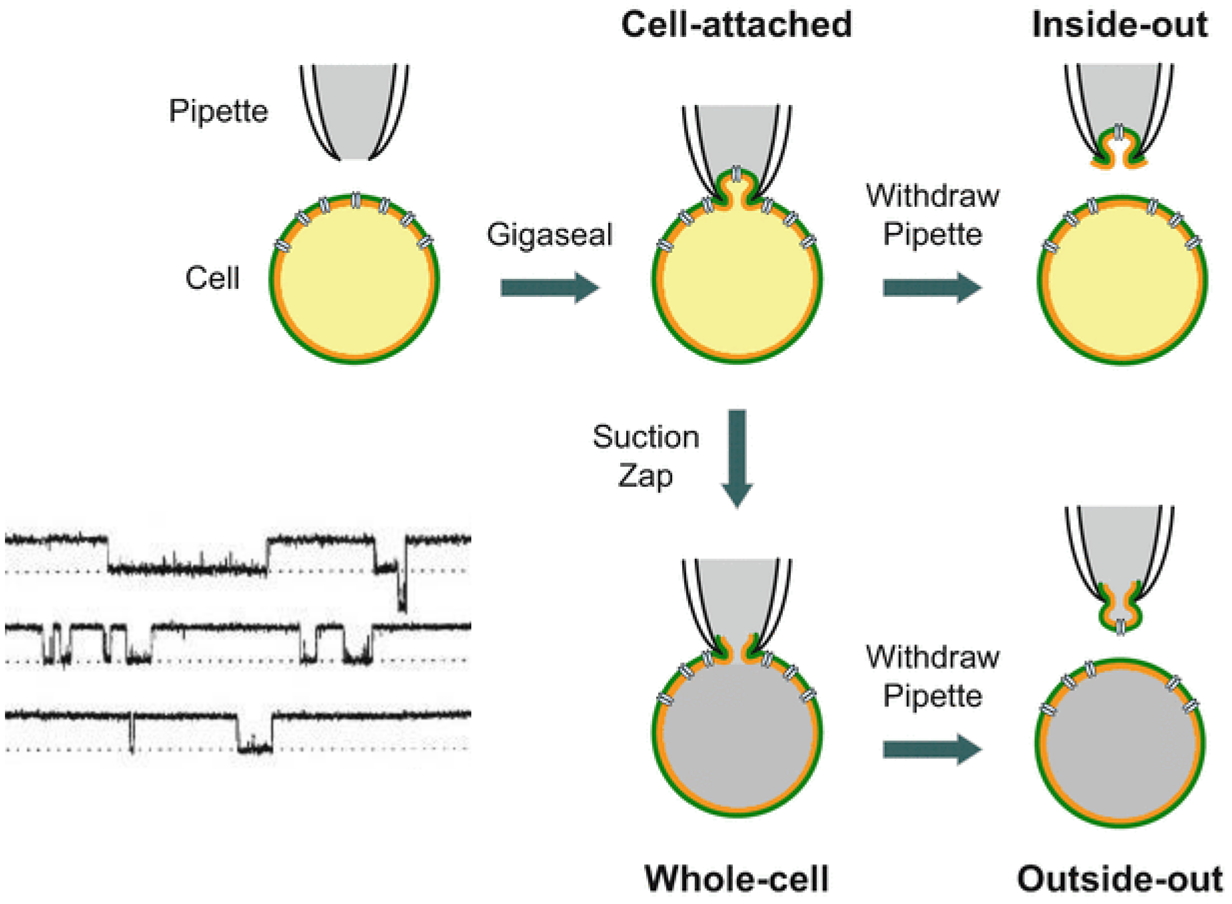


Ligand-gated ion channels



- They open after interaction with a ligand inside or outside the cell
- They don't have to be selective for one ion (cation channels)
- Their reversal potential is not close to Nernst potential for one ion

Patch-clamp

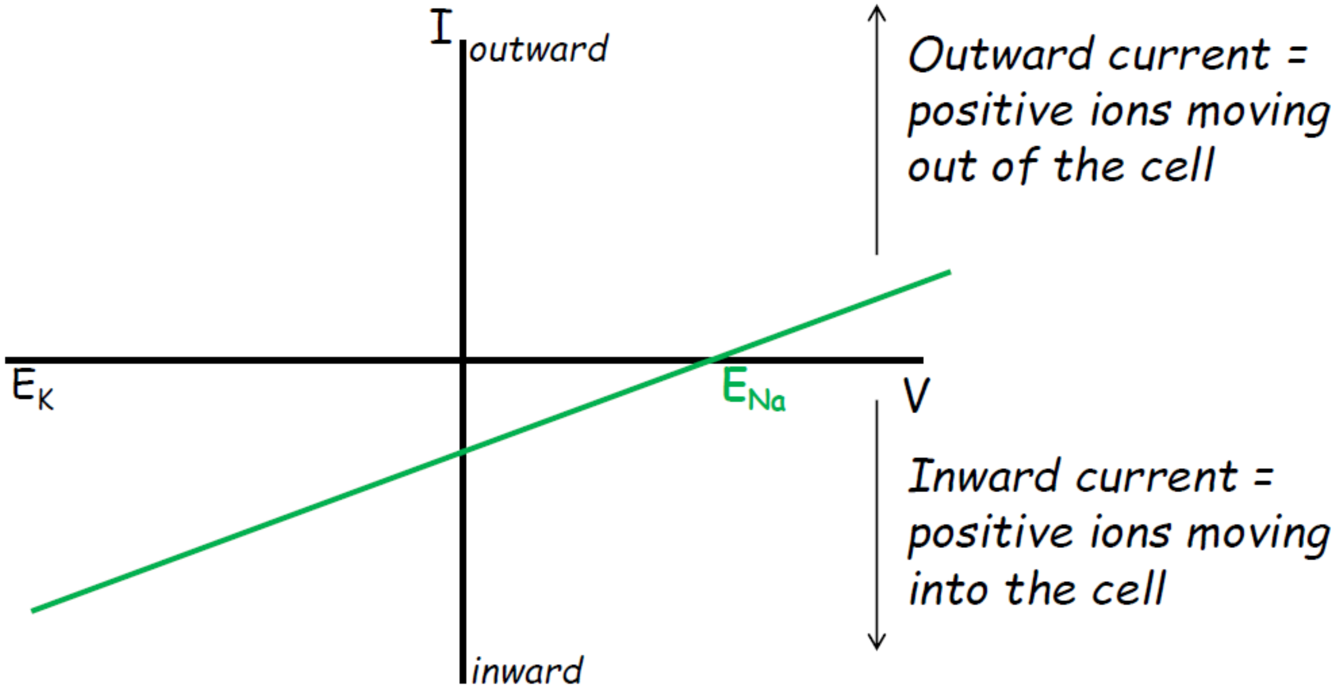


Sakman
Neher
Nobel prize 1991

voltage-clamp
current-clamp

Passive Na^+ current

If the membrane were permeable only to Na+, then the current at a given voltage could be read from the Nernst equation for Na+.



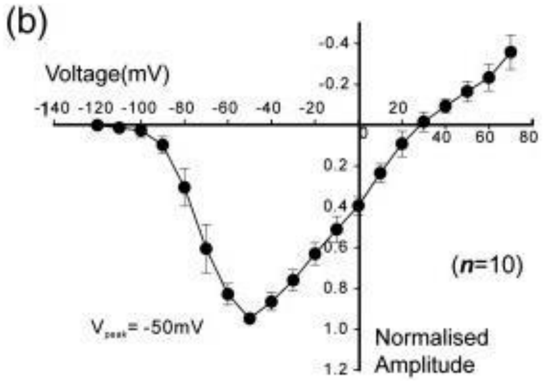
Outward current = positive ions moving out of the cell

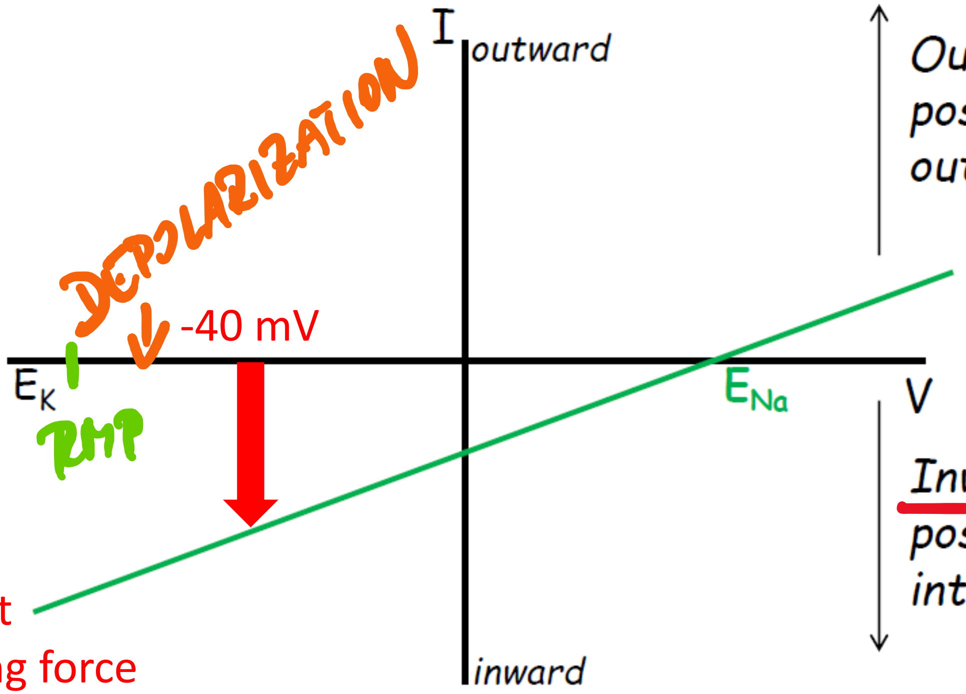
Inward current = positive ions moving into the cell

Passive Na$^+$ current

If the membrane were permeable only to Na+, then the current at a given voltage could be read from the Nernst equation for Na+.

Neuron at different voltages





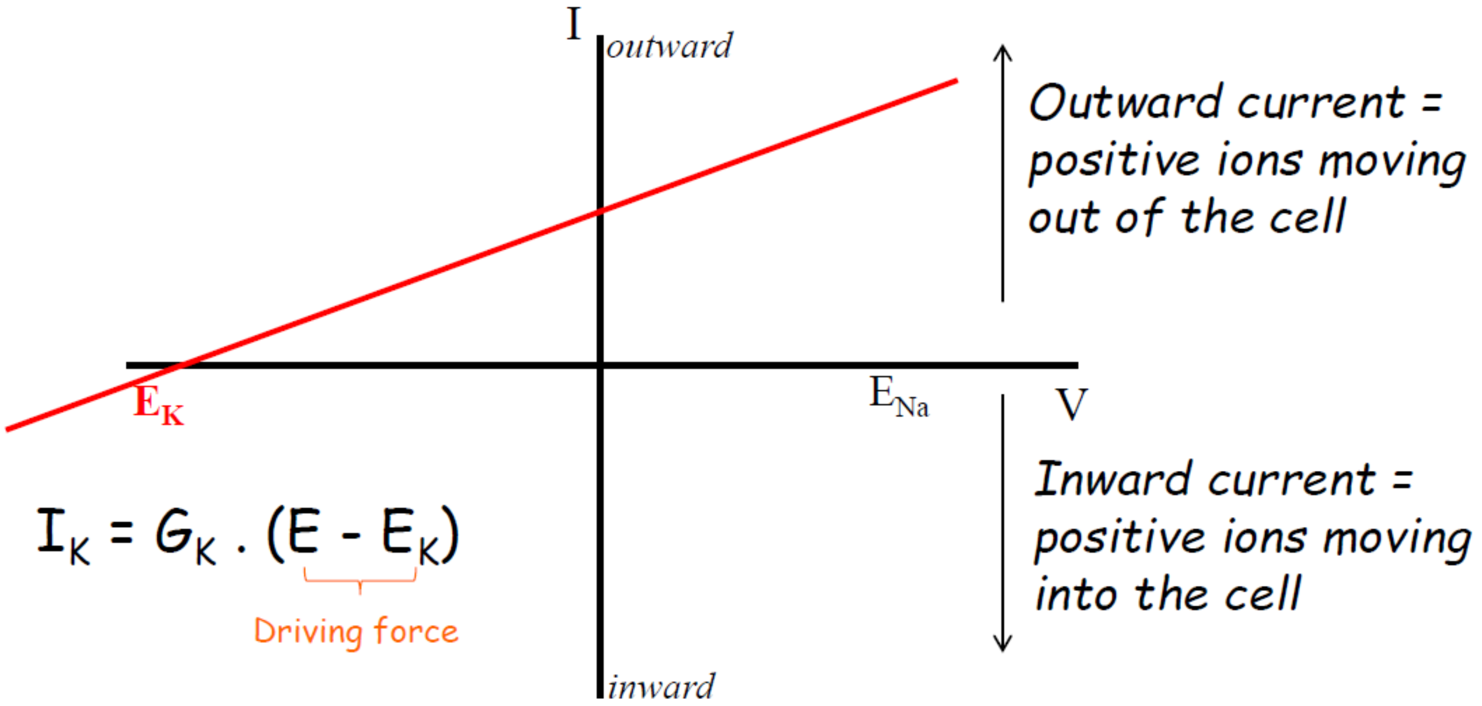
Outward current = positive ions moving out of the cell

Inward current = positive ions moving into the cell

Threshold for opening
Driving force – inward current
Amplitude given by the driving force

Passive K^+ current

If the membrane were permeable only to K+, then the current at a given voltage would be given by the Nernst equation for K+.



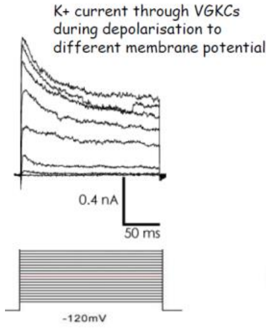
Outward current = positive ions moving out of the cell

Inward current = positive ions moving into the cell

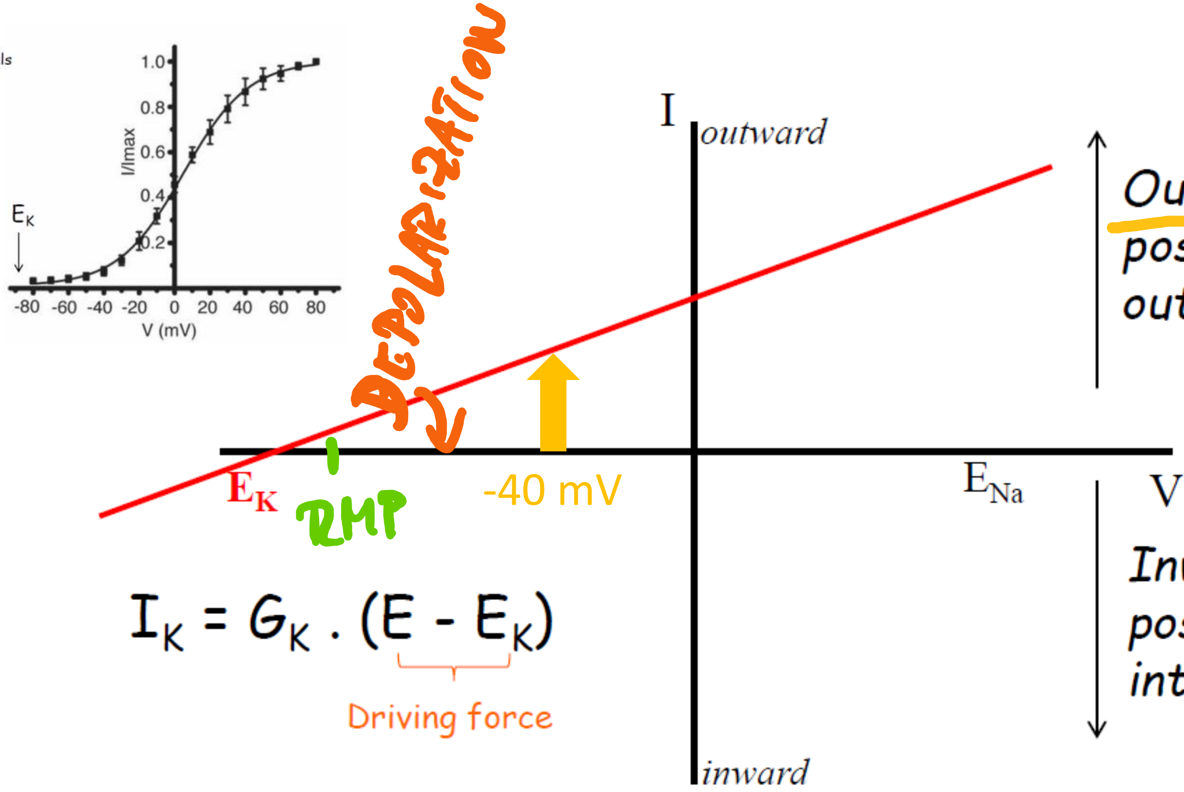
$$I_K = G_K \,.\, (\underbrace{E - E_K}_{\text{Driving force}})$$

Passive K^+ current

If the membrane were permeable only to K+, then the current at a given voltage would be given by the Nernst equation for K+.



K+ current through VGKCs during depolarisation to different membrane potentials



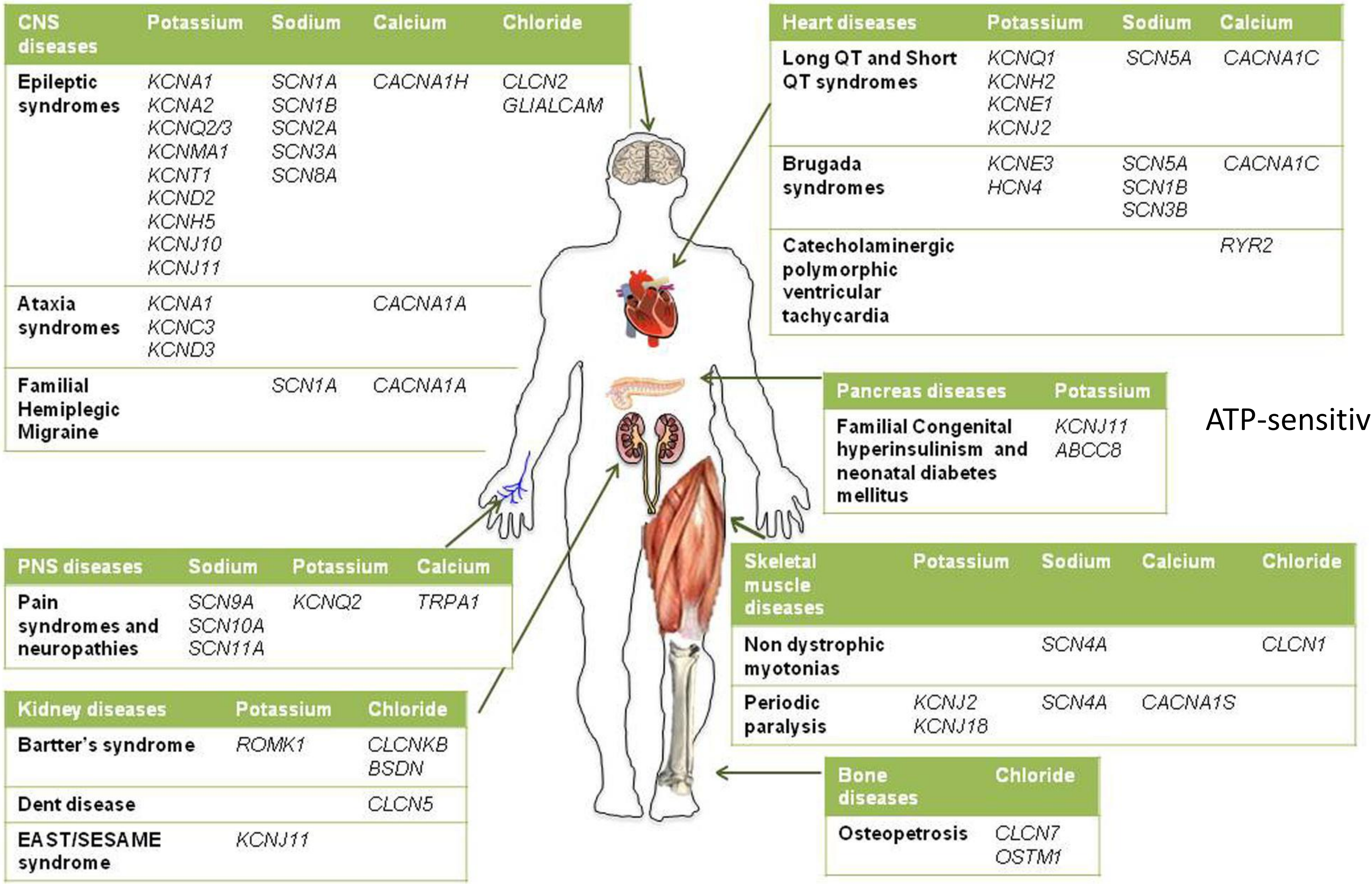
Outward current = positive ions moving out of the cell

Inward current = positive ions moving into the cell

$$I_K = G_K \,.\, (\underbrace{E - E_K}_{\text{Driving force}})$$

Current amplitude given by the driving dorce

Channelopathies



CNS diseases	Potassium	Sodium	Calcium	Chloride
Epileptic syndromes	*KCNA1* *KCNA2* *KCNQ2/3* *KCNMA1* *KCNT1* *KCND2* *KCNH5* *KCNJ10* *KCNJ11*	*SCN1A* *SCN1B* *SCN2A* *SCN3A* *SCN8A*	*CACNA1H*	*CLCN2* *GLIALCAM*
Ataxia syndromes	*KCNA1* *KCNC3* *KCND3*		*CACNA1A*	
Familial Hemiplegic Migraine		*SCN1A*	*CACNA1A*	

PNS diseases	Sodium	Potassium	Calcium
Pain syndromes and neuropathies	*SCN9A* *SCN10A* *SCN11A*	*KCNQ2*	*TRPA1*

Kidney diseases	Potassium	Chloride
Bartter's syndrome	*ROMK1*	*CLCNKB* *BSDN*
Dent disease		*CLCN5*
EAST/SESAME syndrome	*KCNJ11*	

Heart diseases	Potassium	Sodium	Calcium
Long QT and Short QT syndromes	*KCNQ1* *KCNH2* *KCNE1* *KCNJ2*	*SCN5A*	*CACNA1C*
Brugada syndromes	*KCNE3* *HCN4*	*SCN5A* *SCN1B* *SCN3B*	*CACNA1C*
Catecholaminergic polymorphic ventricular tachycardia			*RYR2*

Pancreas diseases	Potassium
Familial Congenital hyperinsulinism and neonatal diabetes mellitus	*KCNJ11* *ABCC8*

ATP-sensitive K+ channel

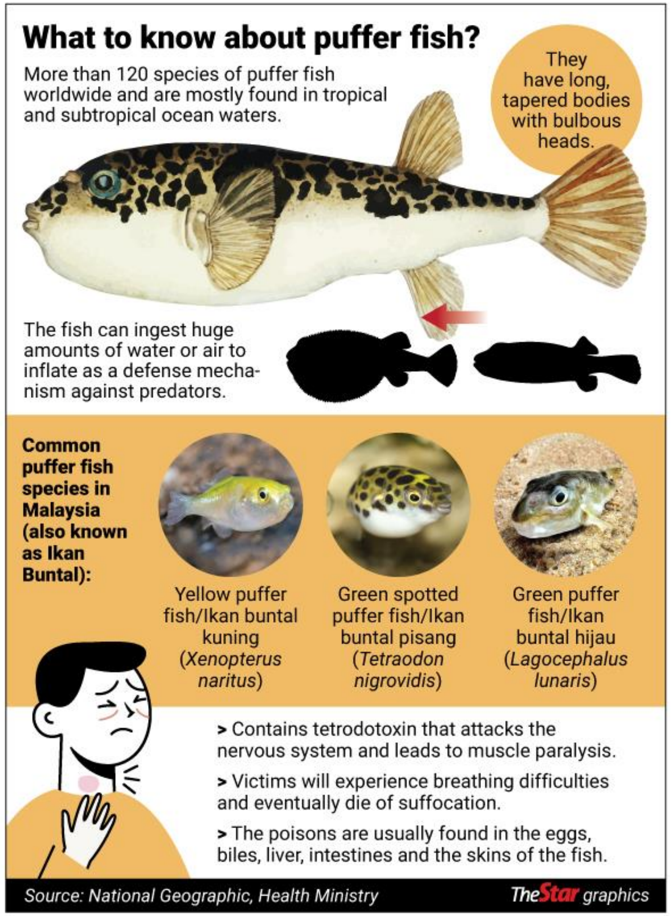
Skeletal muscle diseases	Potassium	Sodium	Calcium	Chloride
Non dystrophic myotonias		*SCN4A*		*CLCN1*
Periodic paralysis	*KCNJ2* *KCNJ18*	*SCN4A*	*CACNA1S*	

Bone diseases	Chloride
Osteopetrosis	*CLCN7* *OSTM1*

Toxins and drugs

Tetrodotoxin – a voltage-gated sodium channel blocker
fish fugu

Dendrotoxin - a voltage-gated potassium channel blocker
mamba snake



What to know about puffer fish?

More than 120 species of puffer fish worldwide and are mostly found in tropical and subtropical ocean waters.

They have long, tapered bodies with bulbous heads.

The fish can ingest huge amounts of water or air to inflate as a defense mechanism against predators.

Common puffer fish species in Malaysia (also known as Ikan Buntal):

Yellow puffer fish/Ikan buntal kuning (*Xenopterus naritus*)	Green spotted puffer fish/Ikan buntal pisang (*Tetraodon nigrovidis*)	Green puffer fish/Ikan buntal hijau (*Lagocephalus lunaris*)

- > Contains tetrodotoxin that attacks the nervous system and leads to muscle paralysis.
- > Victims will experience breathing difficulties and eventually die of suffocation.
- > The poisons are usually found in the eggs, biles, liver, intestines and the skins of the fish.

Source: National Geographic, Health Ministry

TheStar *graphics*

Summary #2: Ion channels

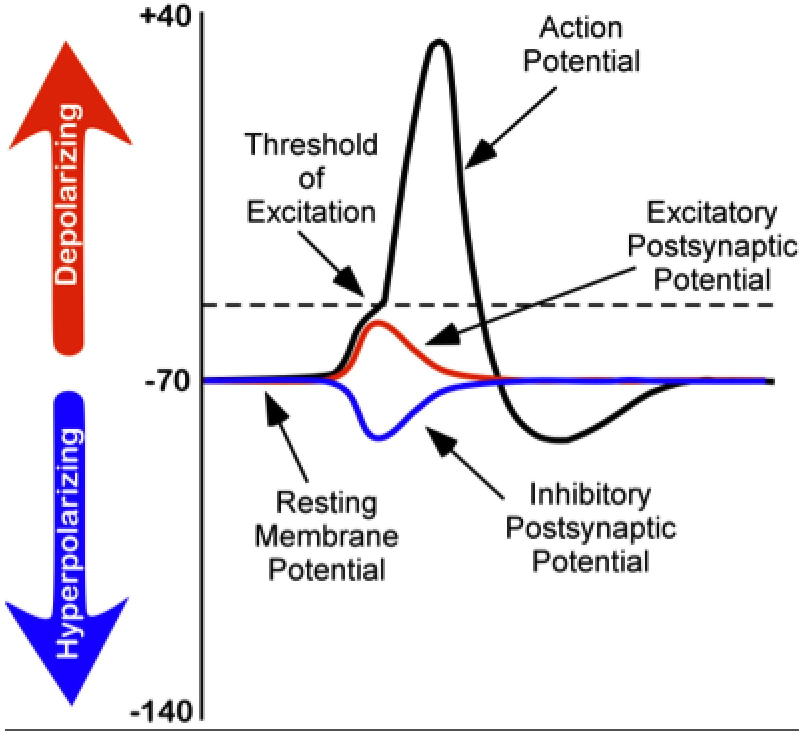
- Charged ions move across the membrane through ion channels and transporters

- Voltage-gated ion channels
- Ligand-gated ion channels

- The sequence, structure and membrane organization of most ion channels is known

- The structure of ion channels reflects their function in generating neuronal signals

Electrical signals in dendrites

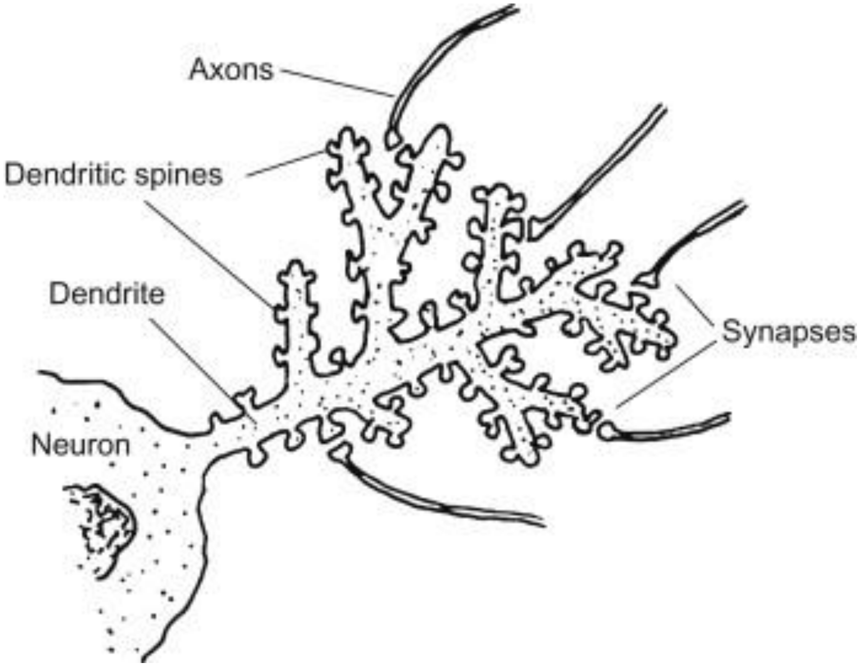


Dendritic potentials and dendritic integration

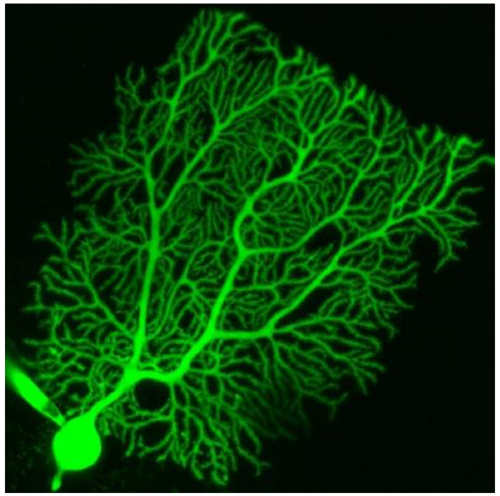
- Electrical signals in dendrites – excitatory and inhibitory postsynaptic potentials
- Passive linear dendritic integration
- Active non-linear dendritic integration

Depolarization x action potential

The initiation of action potential in a neuron depends on the processing of incoming synaptic signals in dendrites - dendritic integration



Purkinje cells



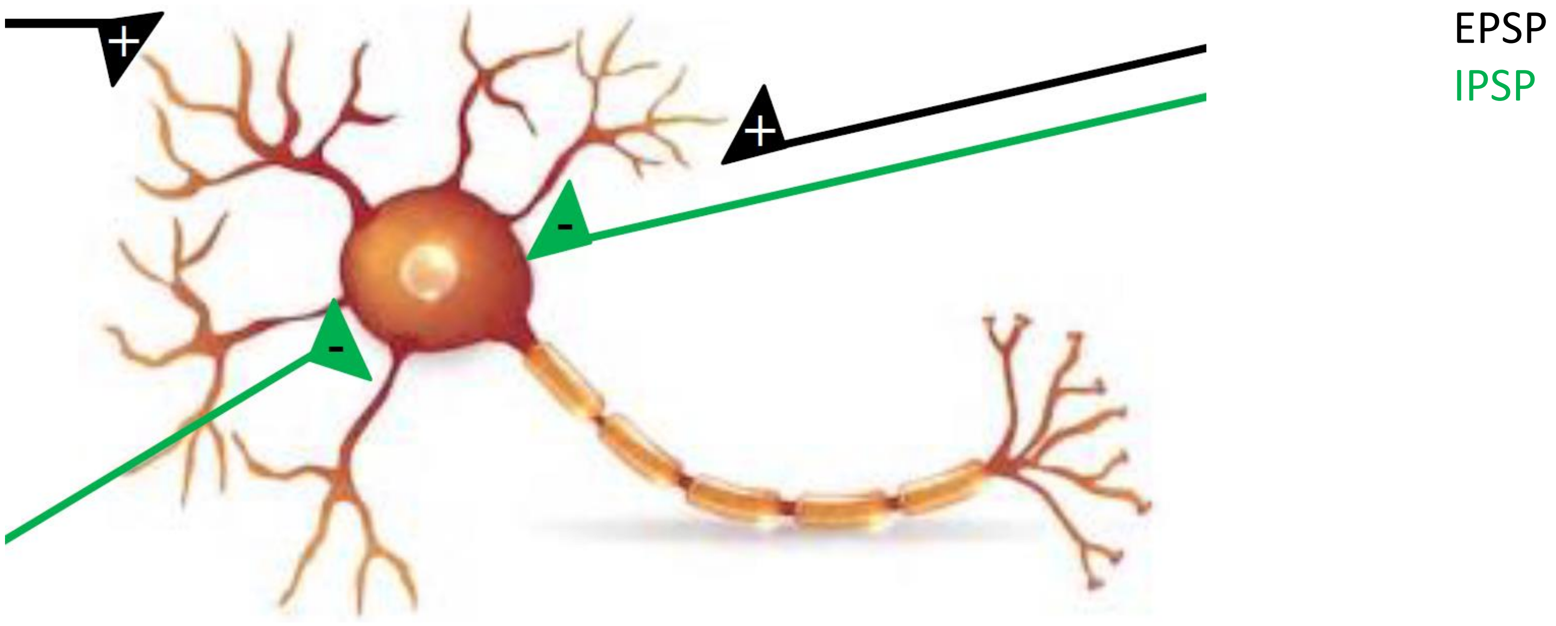
Dendrite morphology
Electrical properties (length, branching, synapses localization)

Dendron - tree

Electric signals in dendrites: excitatory and inhibitory postsynaptic potentials

Graded postsynaptic potentials (analogue signal)

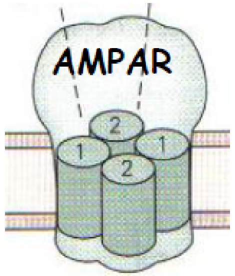
Excitatory are initiated in distal dendrites
Inhibitory are initiated in proximal dendrites and on neuronal somata

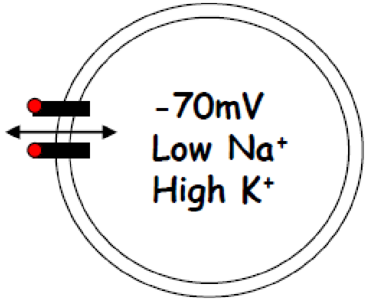


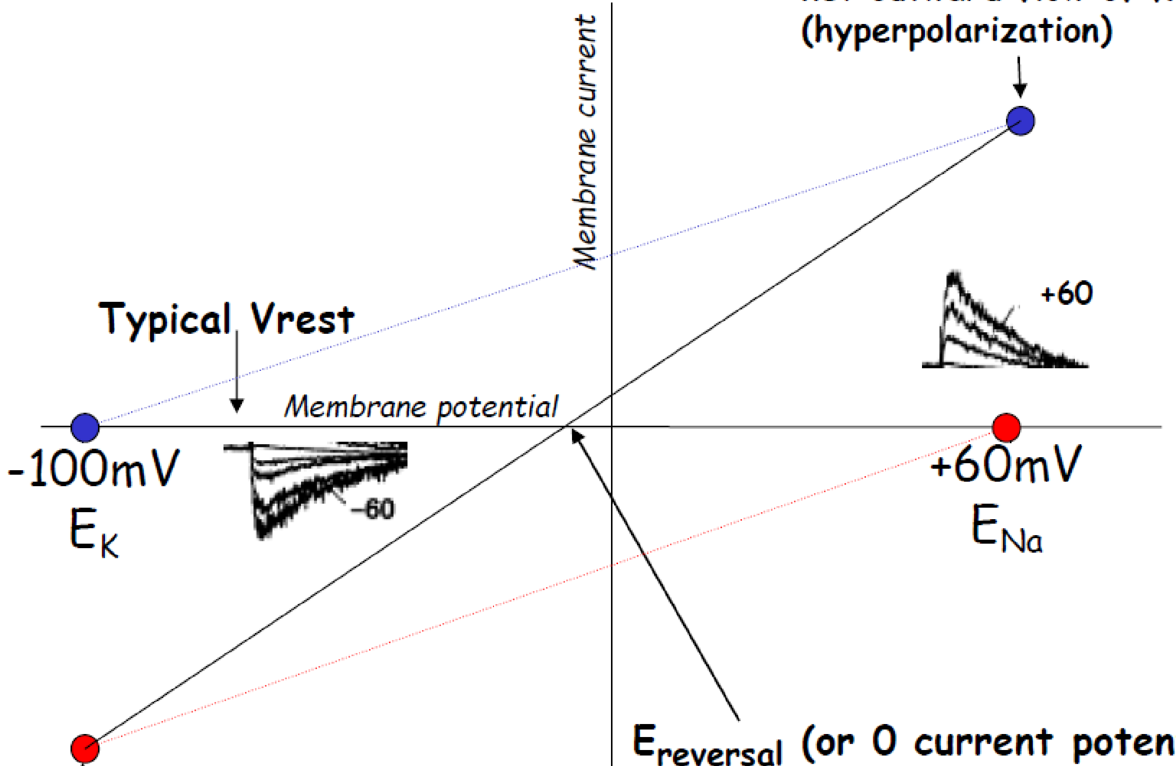
excitatory and inhibitory postsynaptic potentials are initiated by activation of ligand-gated ion channels at the synapses – glutamate, GABA

excitatory postsynaptic potentials – glutamate receptors

NMDA
AMPA/kainate




-70mV
Low Na$^+$
High K$^+$



Typical Vrest

-100mV
E_K

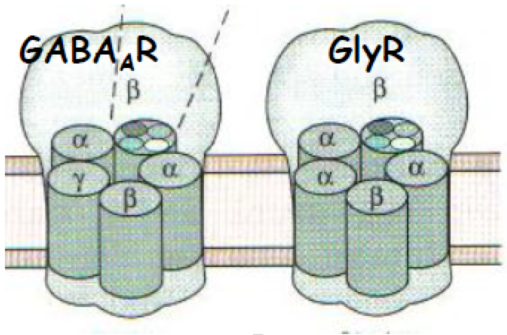
+60mV
E_{Na}

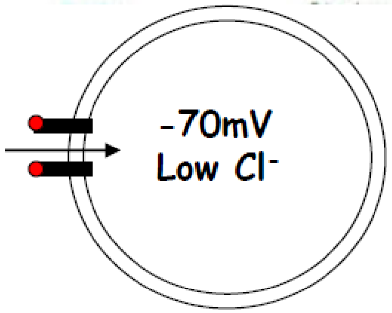
No net flow of Na$^+$ ions:
net outward flow of K$^+$ ions
(hyperpolarization)

$E_{reversal}$ (or 0 current potential):
no net flow of inward Na$^+$ or
outward K$^+$ current

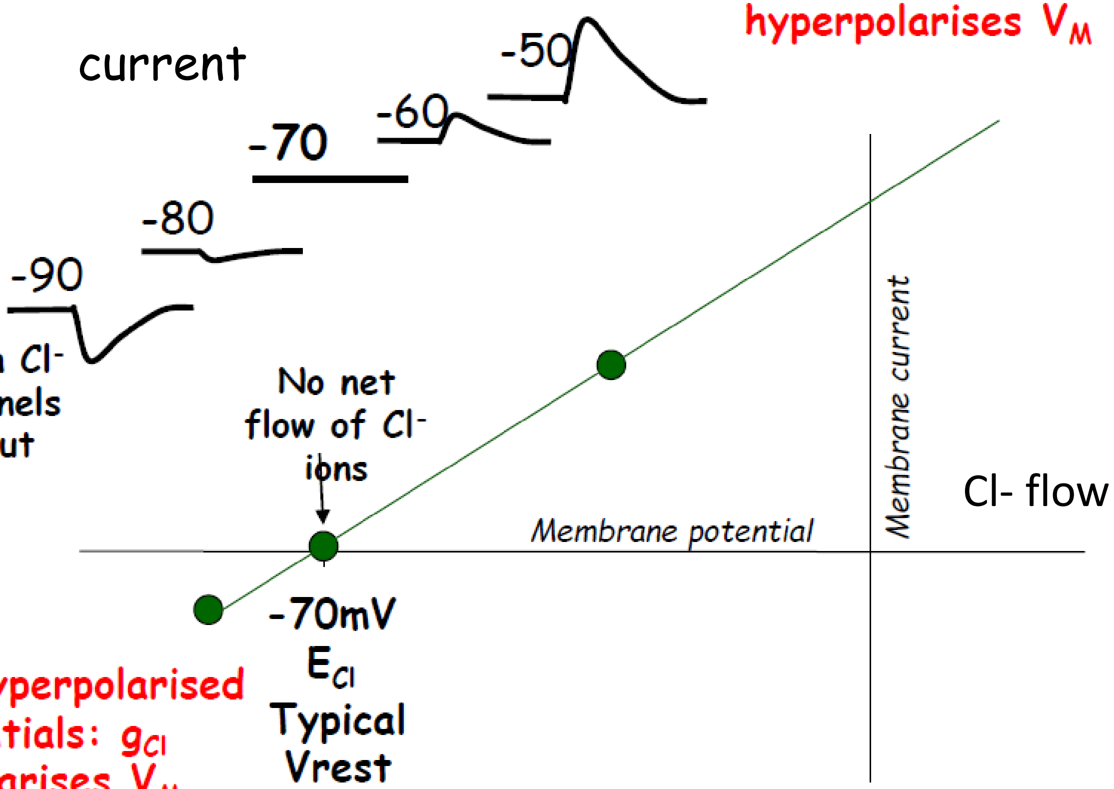
No net flow of K$^+$ ions:
net inward flow of Na$^+$
ions (depolarization)

inhibitory postsynaptic potentials – GABA a glycin receptors





$$\boxed{I = g(V-E_{Cl})}$$



Open Cl- channels Cl- out

No net flow of Cl- ions

Open Cl- channels Cl- in

At depolarised potenitals: g_{Cl} hyperpolarises V_M

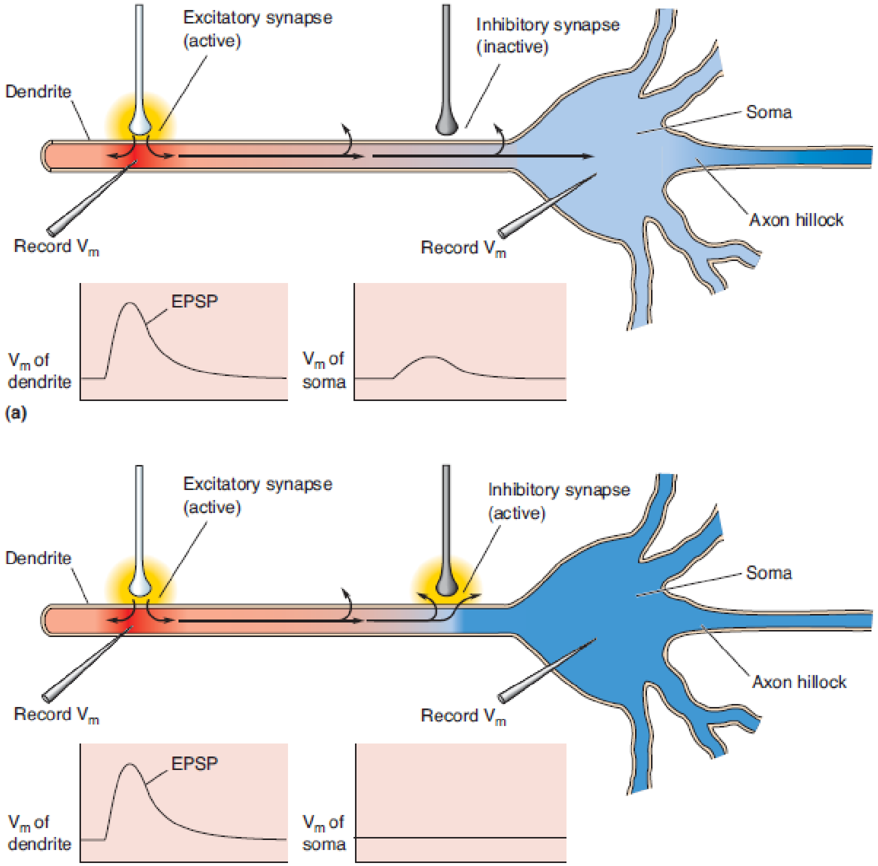
Cl- flow into the cell

-70mV E_{Cl} Typical Vrest

At hyperpolarised potentials: g_{Cl} depolarises V_M

Passive integration of excitatory and inhibitory postsynaptic potentials
Postsynaptic inhibition

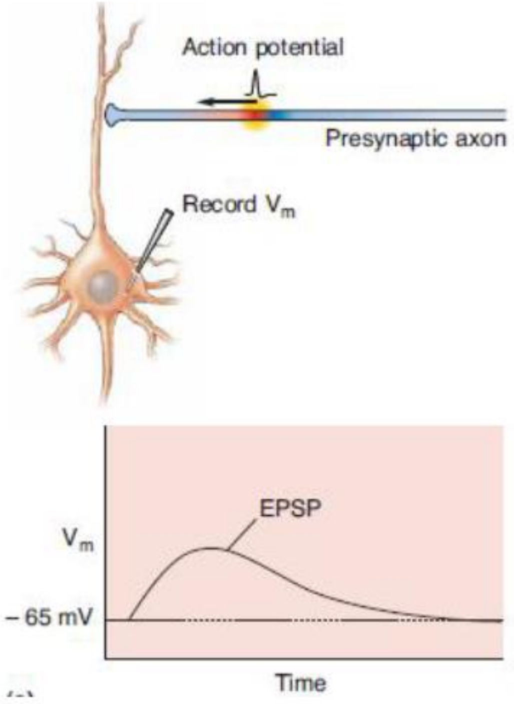
'Shunting inhibition': inhibitory synapse – block of excitatory signal



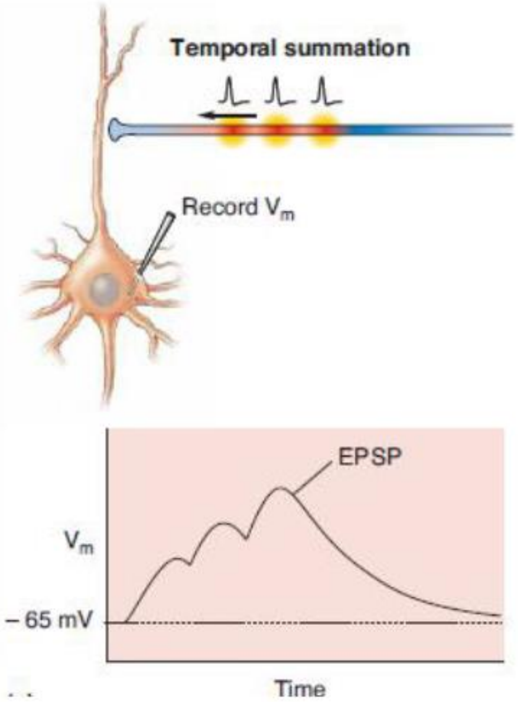
Activation of Cl- conductance at around RMP will keep RMP close to E_{Cl} => inhibitory action

Passive (linear) integration of excitatory postsynaptic potentials

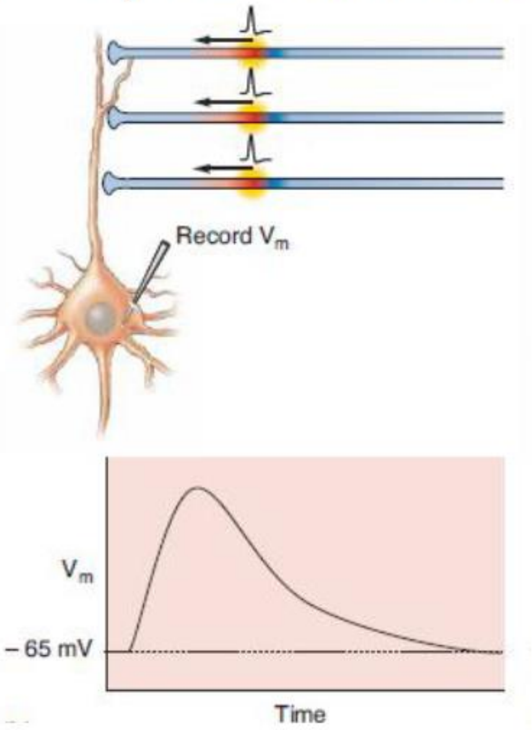
Signals of the same type are added



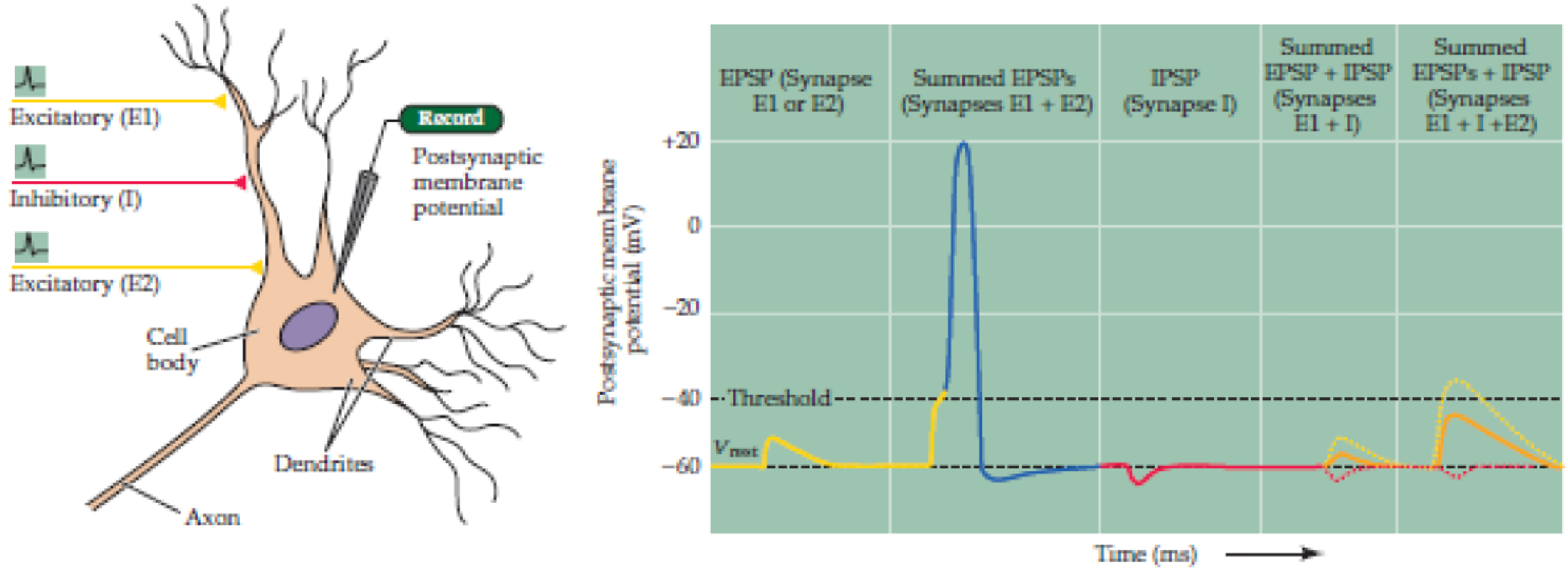
Temporal summation



Spatial summation



Passive linear integration of excitatory and inhibitory postsynaptic potentials



Linear integration occurs in dendrites which act passively
Response to a stimulation = addition of individual responses

Active non-linear dendritic integration

Axons and dendrites can passively carry signals only for several mm

Axons have voltage-gated ion channels which enable active signal propagation, together with myelin

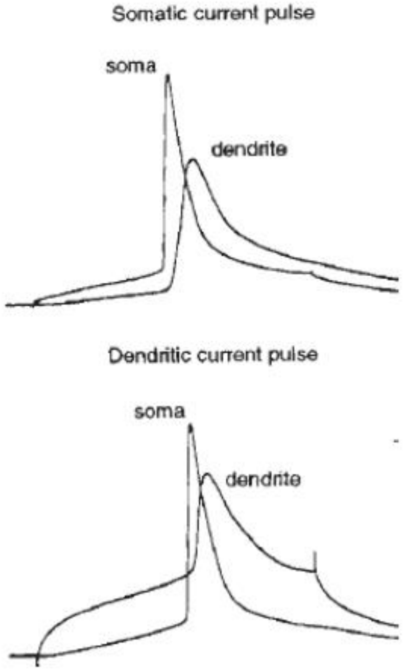
Are dendrites passive or active conductors?

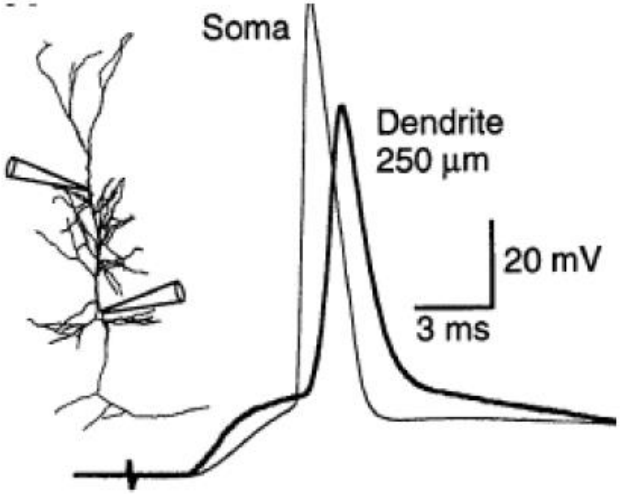
- They were regarded passive until 1970s
- Some can be passive and some active
- Active – expression of voltage-gated ion channels
- =>Then the integration is not linear

Action potentials in dendrites

Voltage-gated Na^+ and Ca^{2+} channels enable propagation of APs

Stuart & Sakmann
1994 Nature

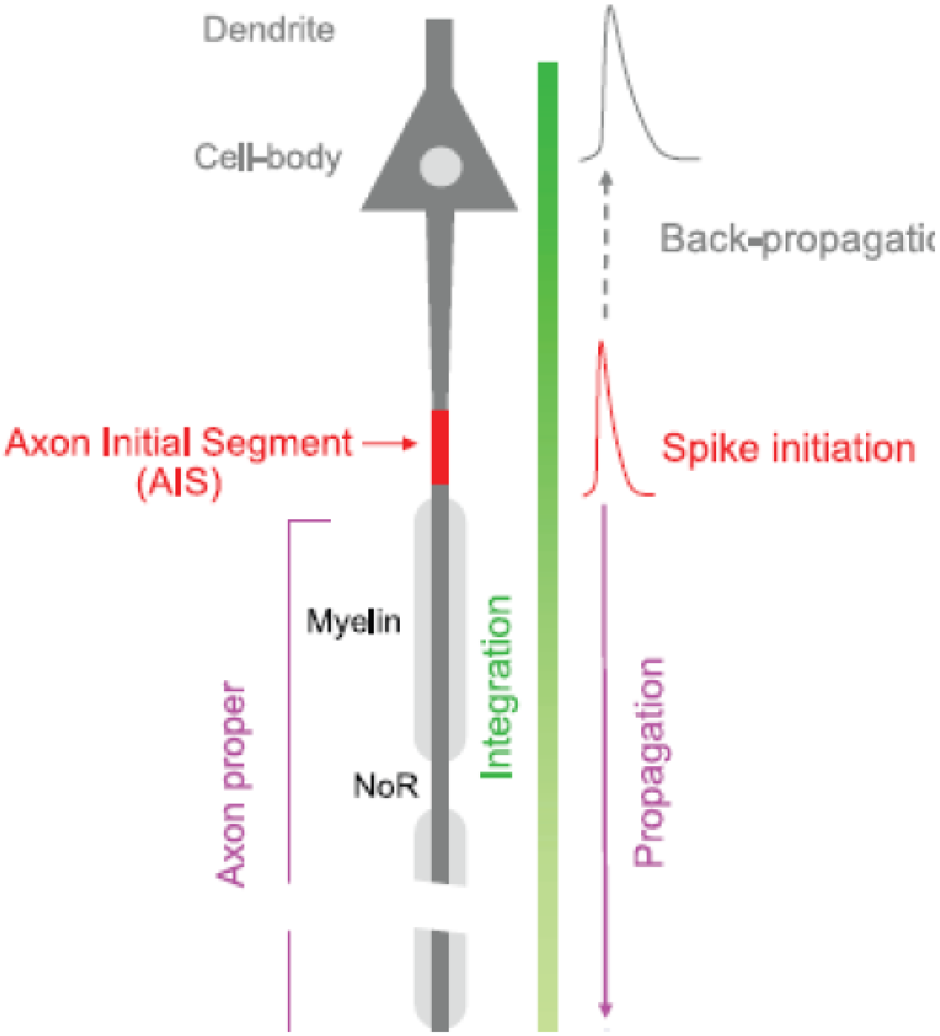




Spruston et al, 1995 Science

Where can an AP be initiated in a dendrite?

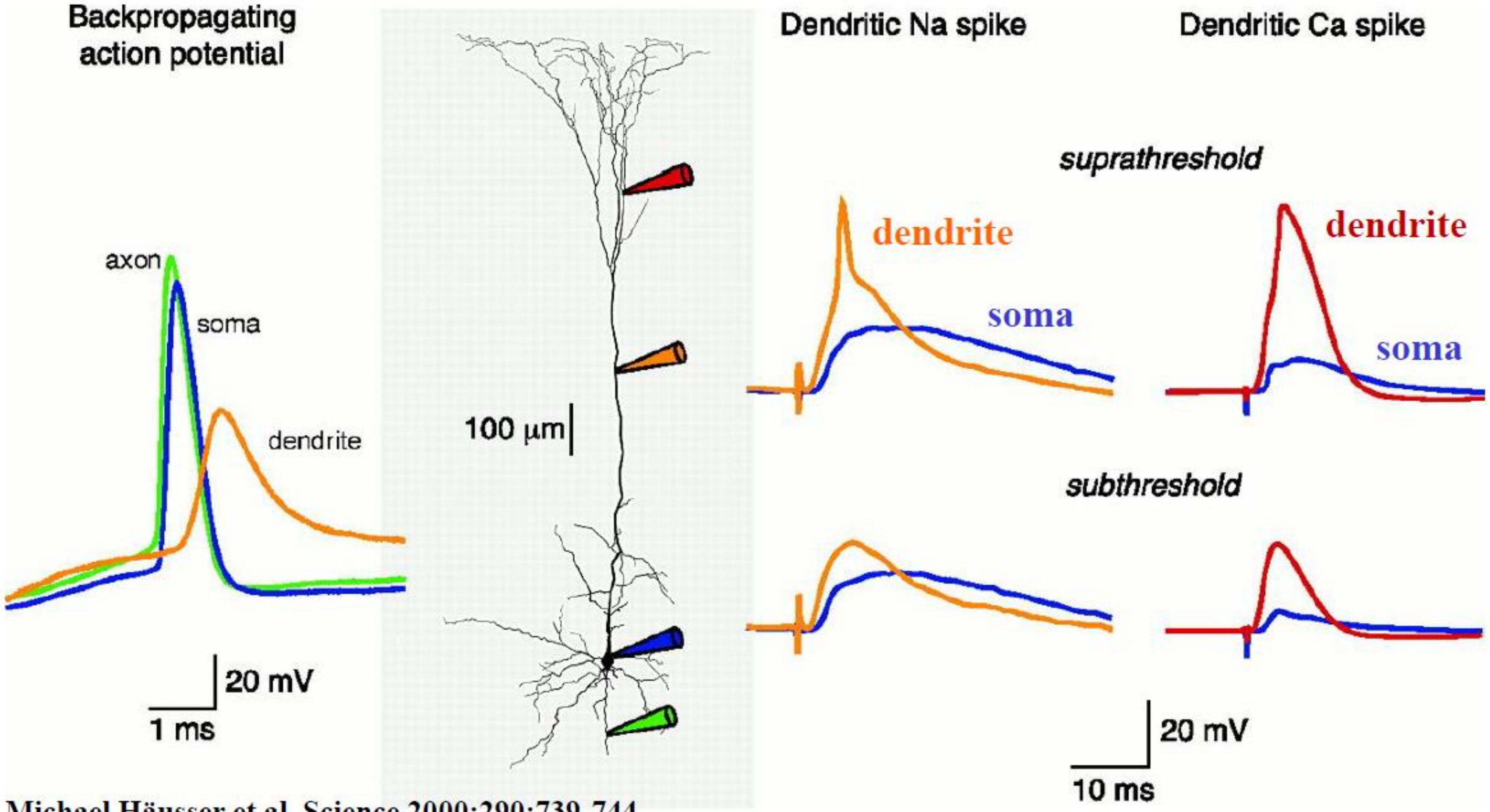
Back propagation of APs in dendrites



APs are iniciated in axonal initial segment but they can back propagate to dendites

Mechanism – expression of voltage-gated ion channels in dendrites, which can be specific for different types of neurons

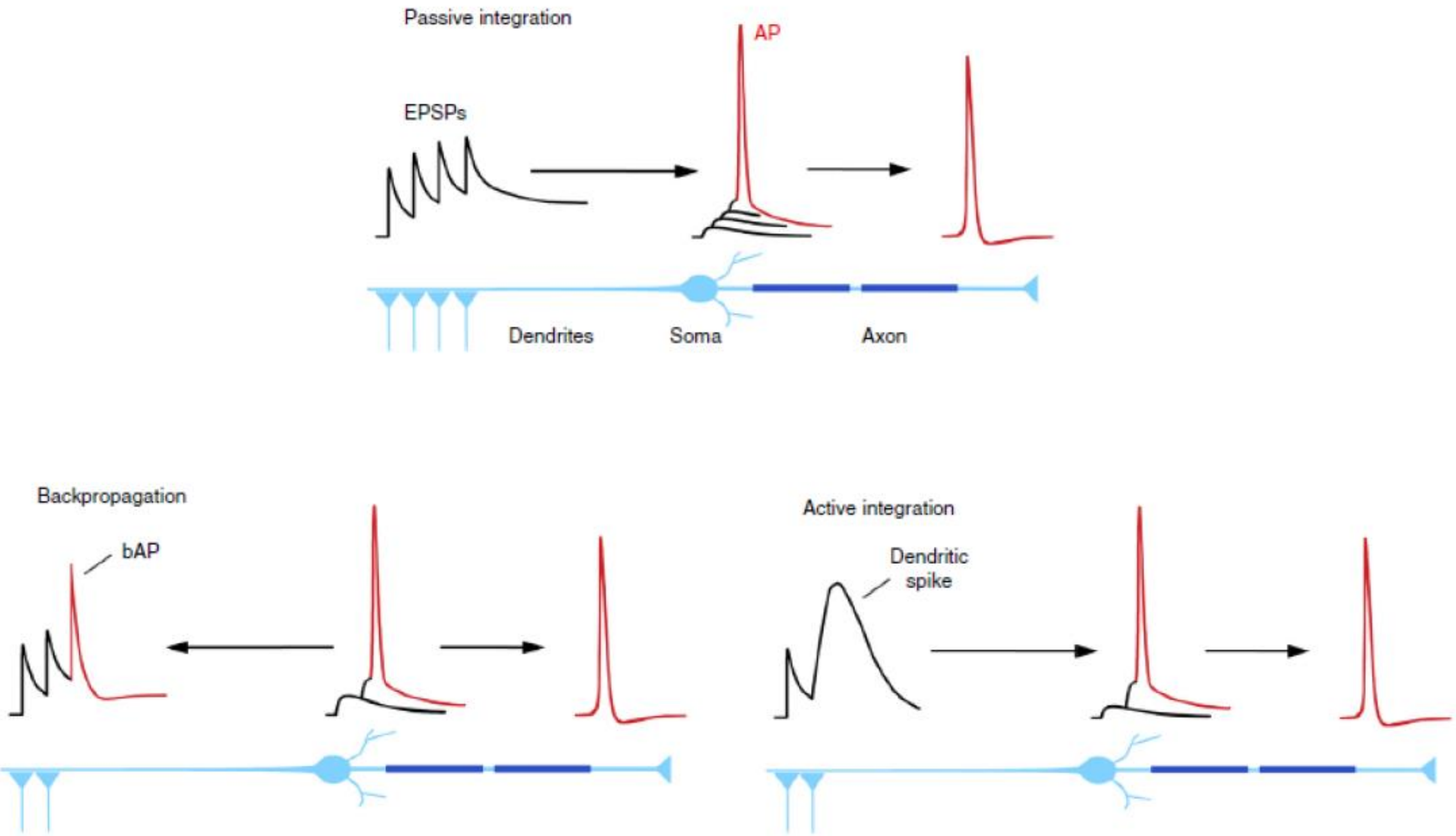
Generation of action potentials in dendrites



Michael Häusser et al. Science 2000;290:739-744

Synaptic potentials can initiate APs in dendrites – dendritic spikes

Types of dendritic integration



These processes are a foundation for synaptic plasticity (the ability to change the response to a signal)

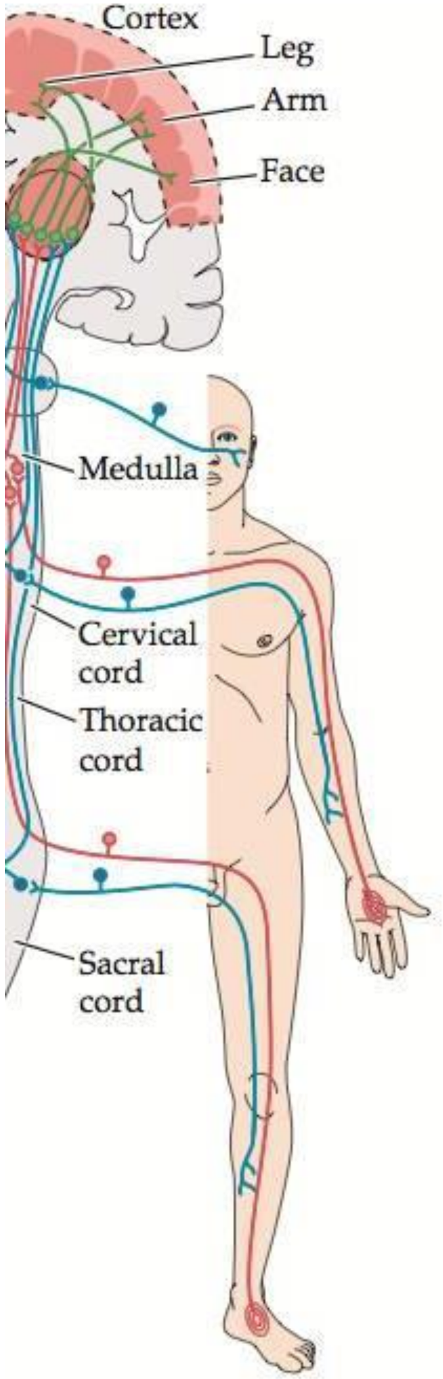
Stuart & Nelson 2015 Nature Neuroscience 18:1713

Summary #3: generation of an AP depends on the integration of incoming signals in dendrites

Integration of the signals in dendrites is impacted by:

- Synaptic currents (excitation and inhibition)
- Dendrite morphology – length, branching, spines, synapse location
- Passive properties of dendrites (Ri, Rm, Cm)
- Summation of subthreshold signals
- Active properties of dendrites (expression of ion channels)
- The ability to propagate or even initiate signals

Decision process – AP yes/no???



Transport of the signal – action potential and its conduction along axon

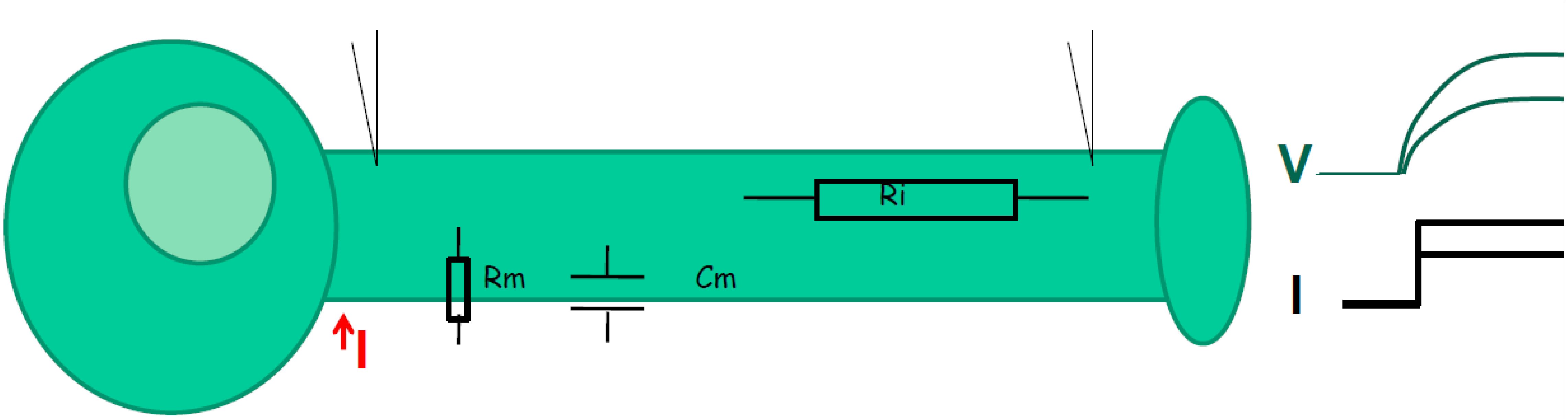
Axons connect neurons on long distances

- The longest axons in a human body carry tactile information from hands and feet to the spinal cord and to the brain stem
- Up to 1.5 m long
- Velocity up to 70 m/s

>250 km/h!

Spread of action potential along axons

Passive electrical properties of an axon



No ion channels present – what happens after current I injection?:
Voltage = potential change - **Ohm's Law**
Velocity of voltage change - t_m= $\mathbf{R_m C_m}$

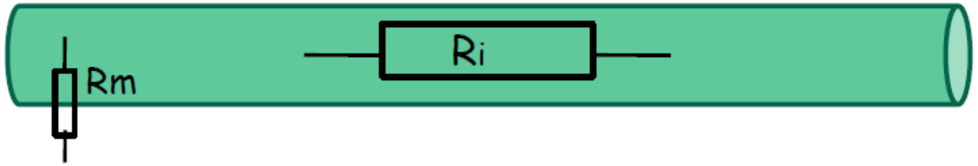
How far would change in potential spread?
Length constant $ʌ = \sqrt{}(R_m/(R_i + R_o))$
ʌ = distance to potential lowering to 37% of the starting amount

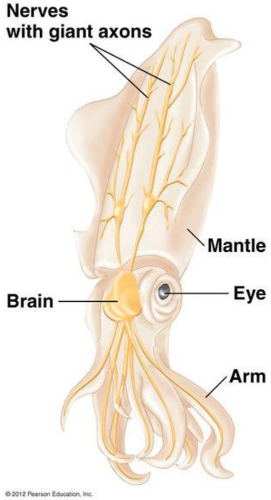
Passive electrical properties of an axon – voltage signals diminish gradually

$\lambda = \sqrt{(R_m/R_i)}$

You want λ to be high
To increase λ:
- Increase Rm – myelin (vertebrates)
- Decrease Ri – thicker axon

Biological cable (axon nebo dendrit)
~1 µm diameter: Λ ~ 0.25mm
~10 µm diameter : Λ ~ 0.75mm
~1000 µm diameter : Λ ~ 10mm
(giant squid axon)



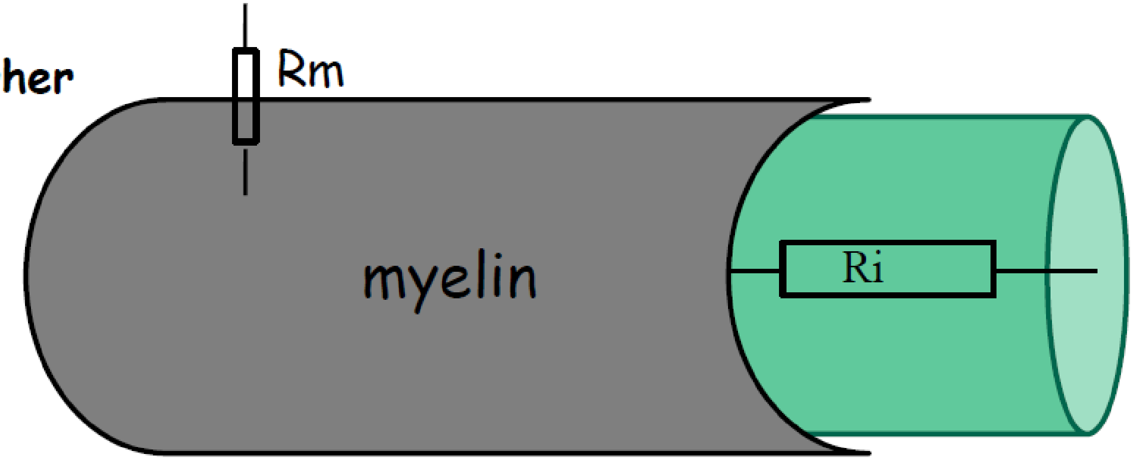


Biological cables passively transmit electrical signals max for a few mm

However, some axons are as long as 1 m!

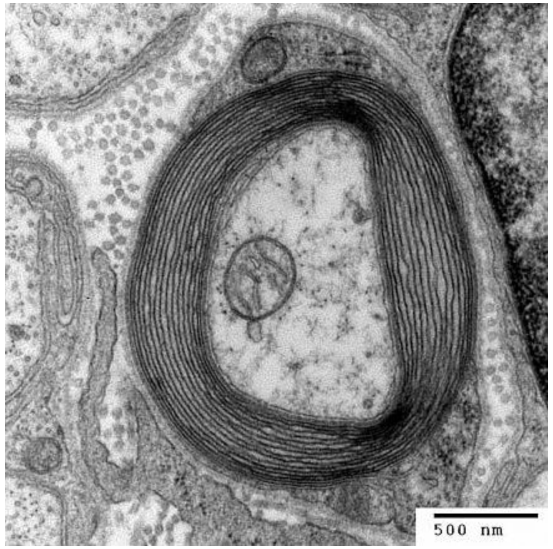
How does the transmission work on long distances?

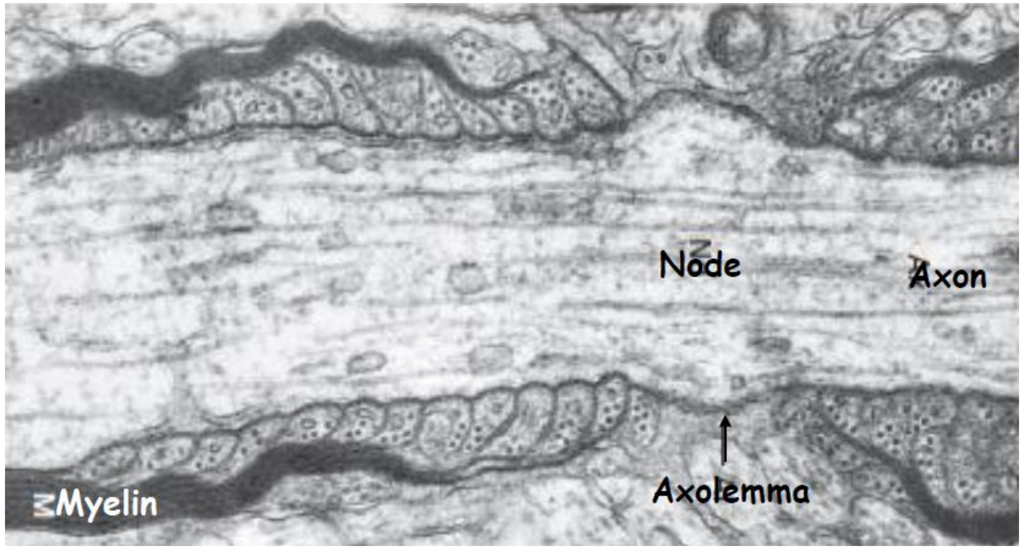
Passive electrical properties of an axon - **isolation**



Rm is higher

Ri is the same



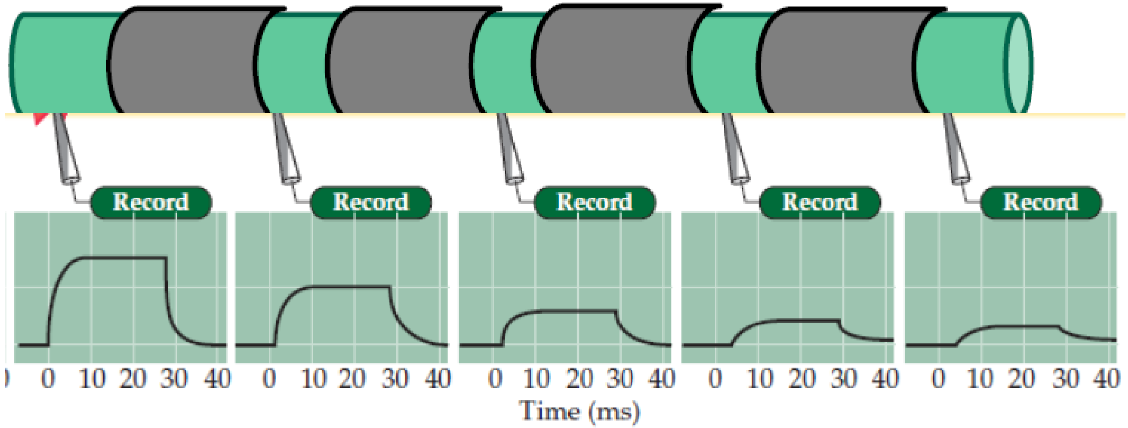


Action potential transmission in a myelinated fiber

Myelin insulation can improve passive electrical signal transmission over shorter distances (mm)

Passive myelinated axon:

Voltage responses:

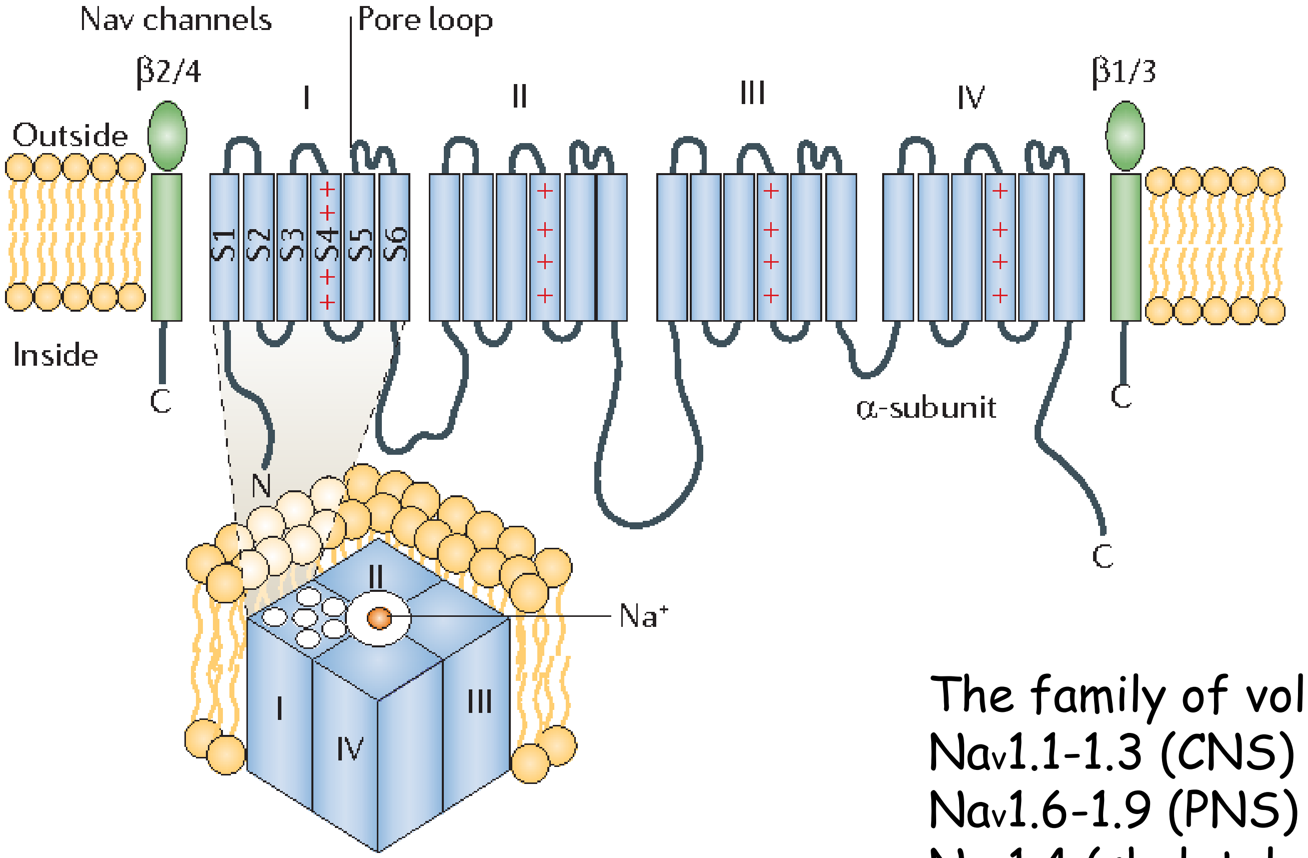


Only axons with diameter bigger than 10 µm are myelinated

So how do unmyelinated axons or myelinated axons transmit a signal over longer distances?

The signal is amplified by voltage-dependent ion channels

Voltage-gated Na^+ channels, Na_v



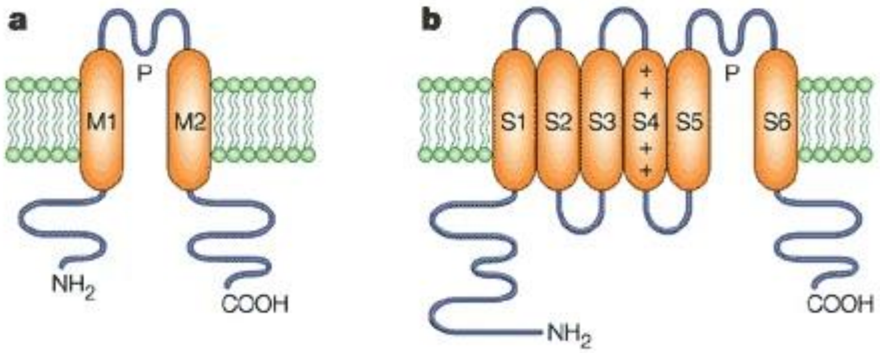
4 parts
4x6 TM segments
voltage senzor
pore – selectivity
activation-inactivation

The family of voltage-gated Na channels:
Na_v1.1-1.3 (CNS)
Na_v1.6-1.9 (PNS)
Na_v1.4 (skeletal muscle)
Na_v1.5 (cardiac muscle)

K^+ channels

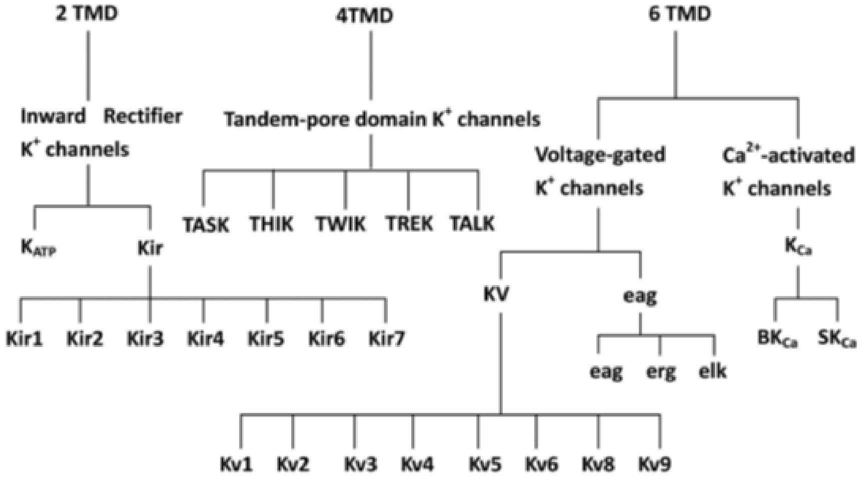
Large heterogeneous family

Kir
2TM/P
tetramers



Voltage-gated K^+ channels

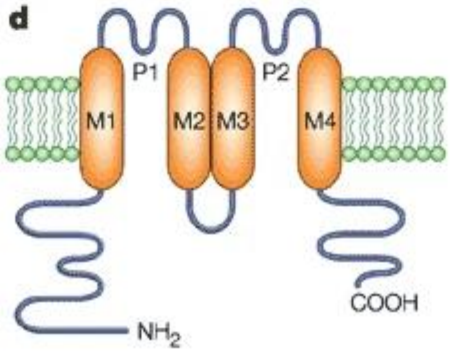
Kv
6TM/P



2 TMD
Inward Rectifier K^+ channels
K_{ATP}
Kir
Kir1 Kir2 Kir3 Kir4 Kir5 Kir6 Kir7

4TMD
Tandem-pore domain K^+ channels
TASK THIK TWIK TREK TALK

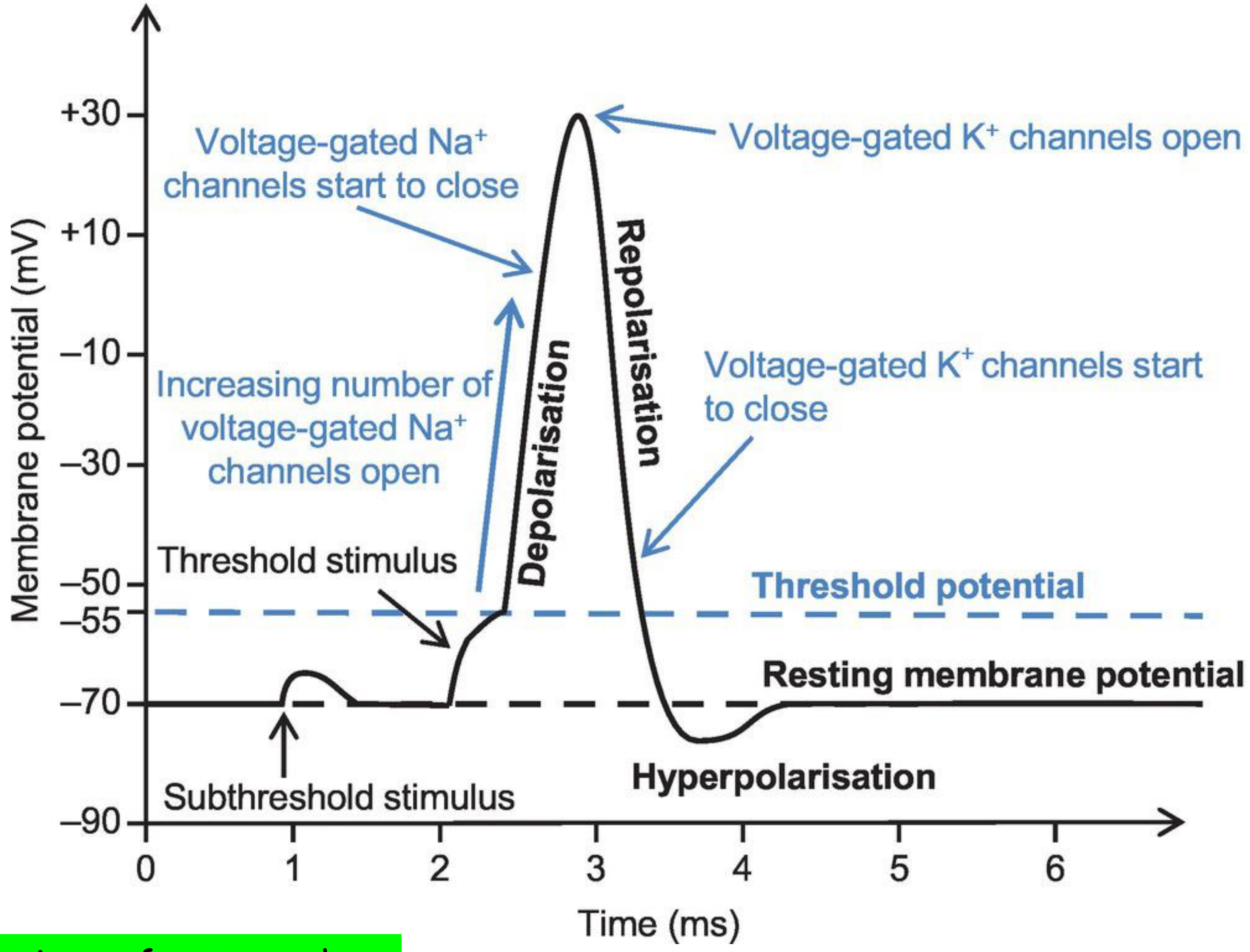
6 TMD
Voltage-gated K^+ channels
KV
Kv1 Kv2 Kv3 Kv4 Kv5 Kv6 Kv8 Kv9
eag
eag erg elk
Ca^{2+}-activated K^+ channels
K_{Ca}
BK_{Ca} SK_{Ca}



4TM/2P
dimers

Nature Reviews | Neuroscience

Mechanism of development and transmission of the action potential

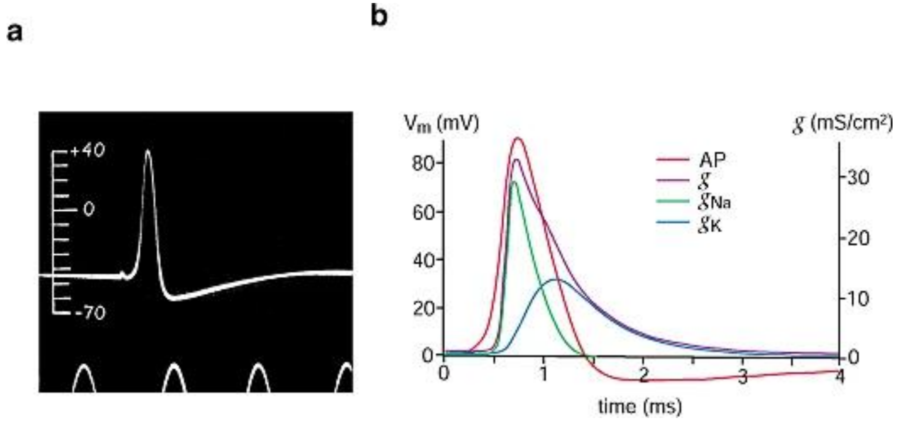


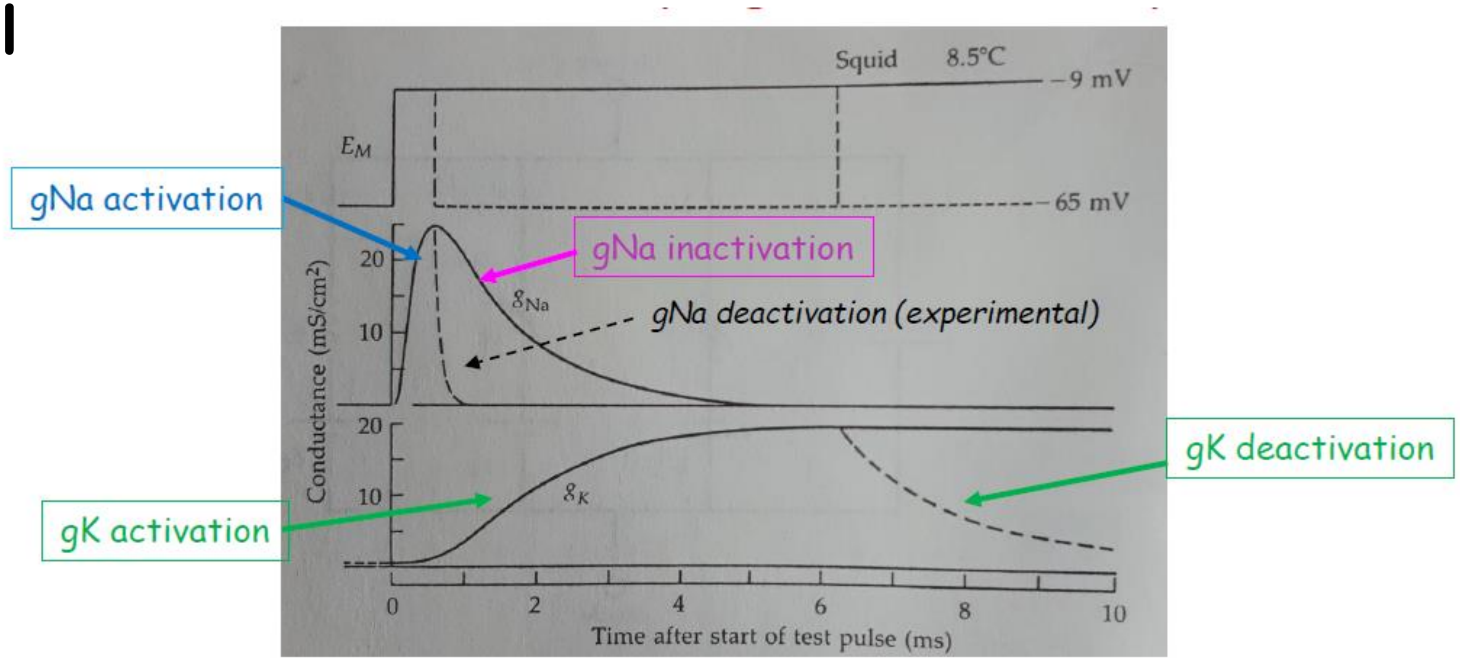
Transpolarization (overshoot)

Absolute and relative refractory phase

Model of the action potential

Hodghin a Huxley (NP 1963)
Giant squid axon
Voltage-clamp
microelectrodes




gNa activation

gNa inactivation

gNa deactivation (experimental)

gK activation

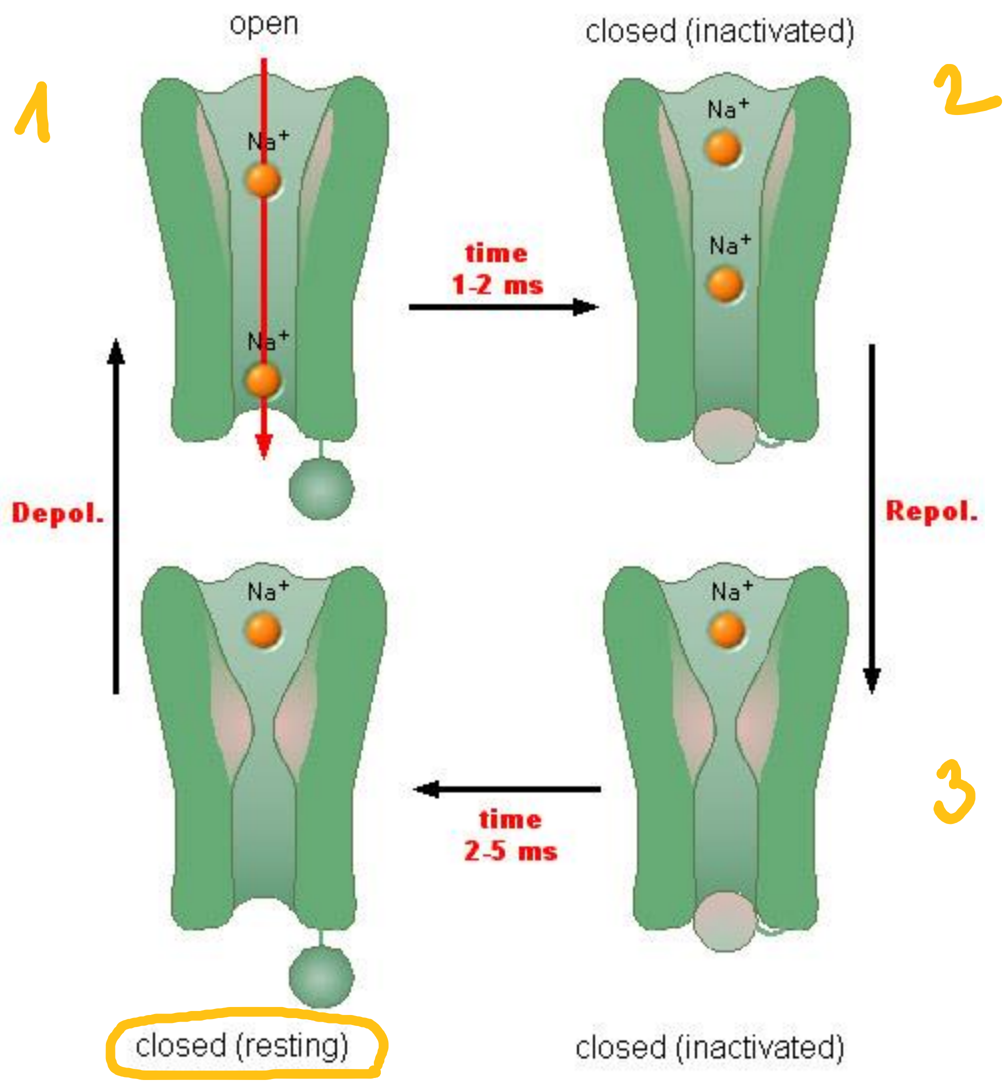
gK deactivation

1. The conductance of the axon membrane for Na+ ions increases rapidly and then slowly decreases during the voltage pulse – Na+ channels are activated and then inactivated

2. The conductance of the axon membrane for K+ ions slowly increases and decreases only after the end of the voltage pulse – K+ channels are activated and then deactivated

Conformation changes of Na$^+$ channels during action potential

Activation gate



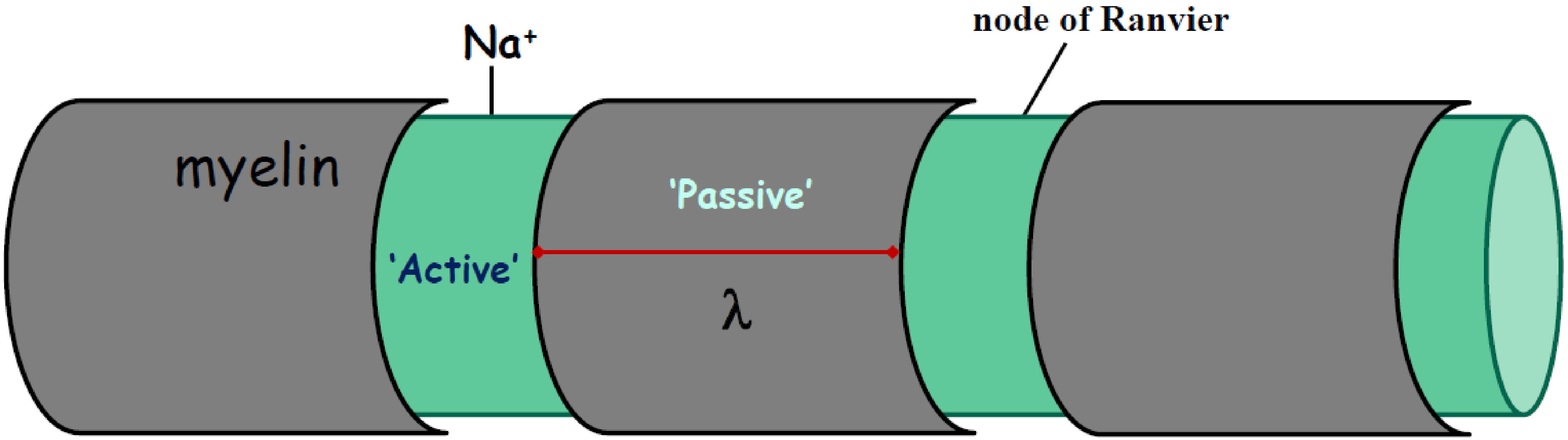
m-gate

Inactivation gate

h-gate

Active electrical properties of the axon

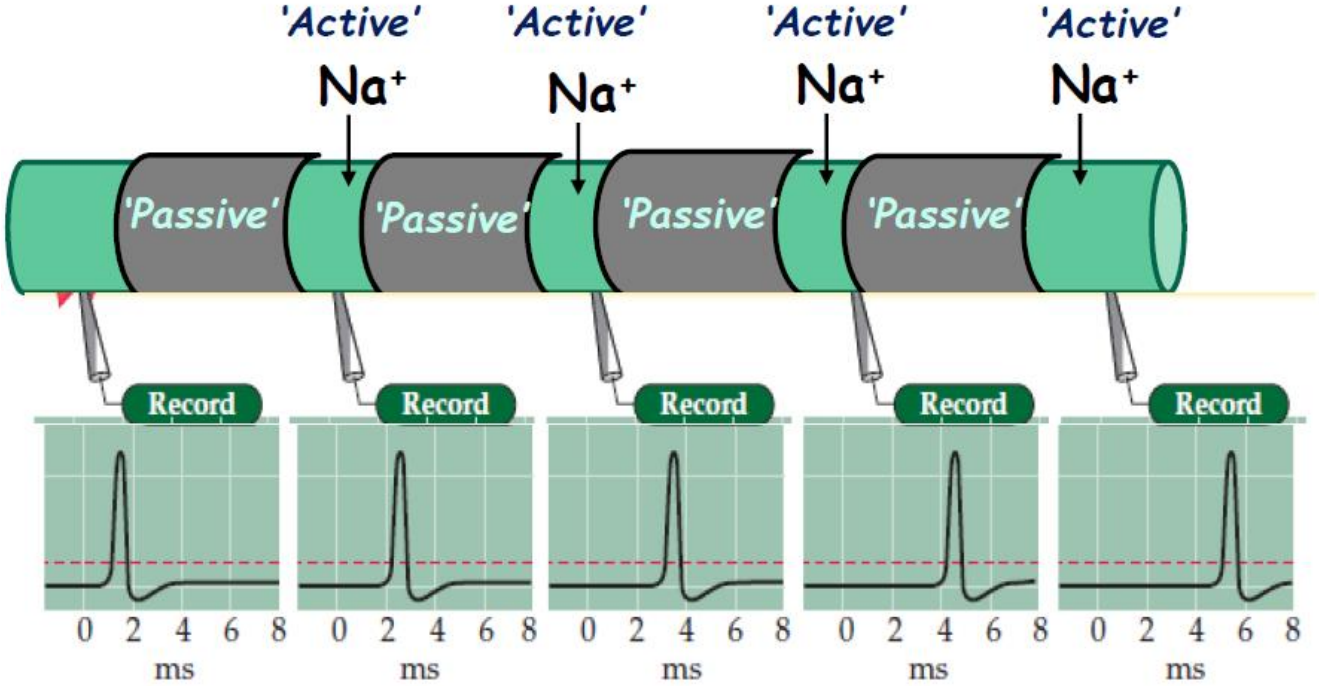
- Voltage-gated Na^+ and K^+ channels are clustered at the nodes of Ranvier
- They actively regenerate the voltage signal



Action potential:
-Nav channels open quickly and then inactivate
-Kv channels activate slowly and repolarize the node of Ranvier
-Nav channels can only reopen after the end of the refractory phase - the direction of signal propagation

AP propagation in myelinated fibers with voltage-gated channels – saltatory conduction

Myelinated axon with voltage-gated channels

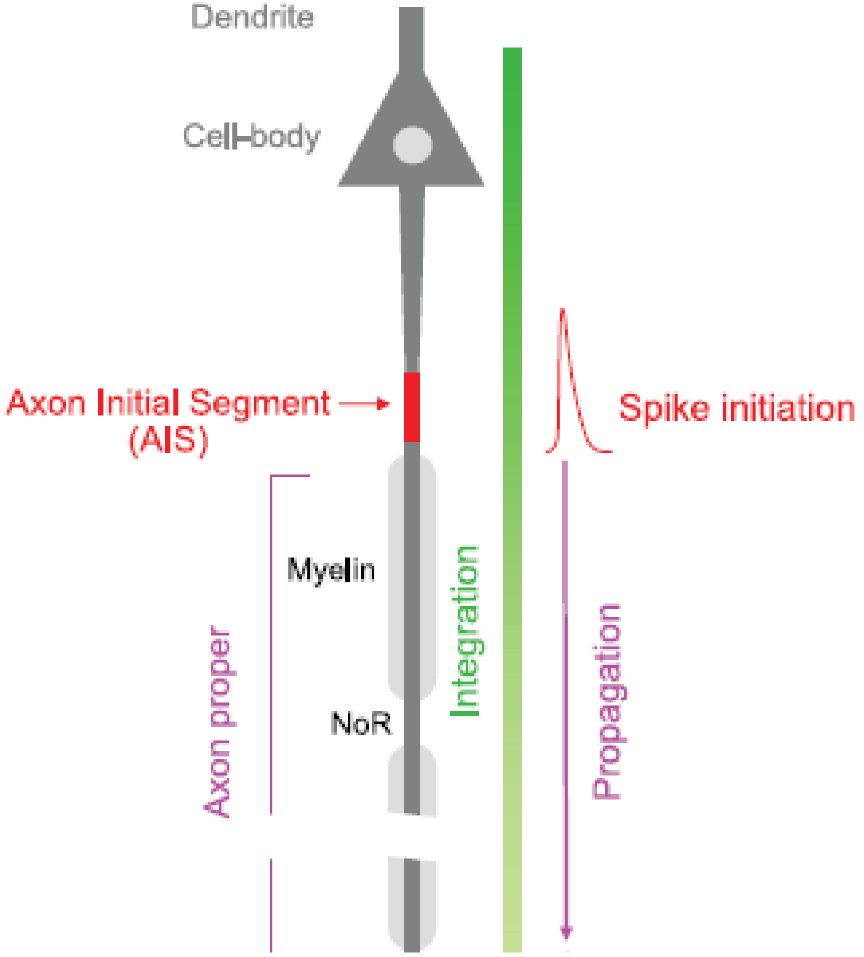


Myelin and voltage-gated ion channels:
- A combination of passive and active conduction
- speed of signal propagation up to 100 m/s
- Saltatory conduction consumes less energy

Nerve fiber classification	Diameter (μm)	Myelination	Conduction velocity (m/s)	Afferent or Efferent	Type
Aα	13–20	Thick	80–120	Both	Sensory and Motor
Aβ	6–12	Medium	33–75	Both	Sensory and Motor
Aγ	5–8	Medium	4–24	Efferent	Motor
Aδ	1–5	Thin	3–30	Afferent	Sensory
B	< 3	Thin	3–14	Afferent	Autonomic
C	0.2–1.5	None	0.5–2	Afferent	Sensory and Motor

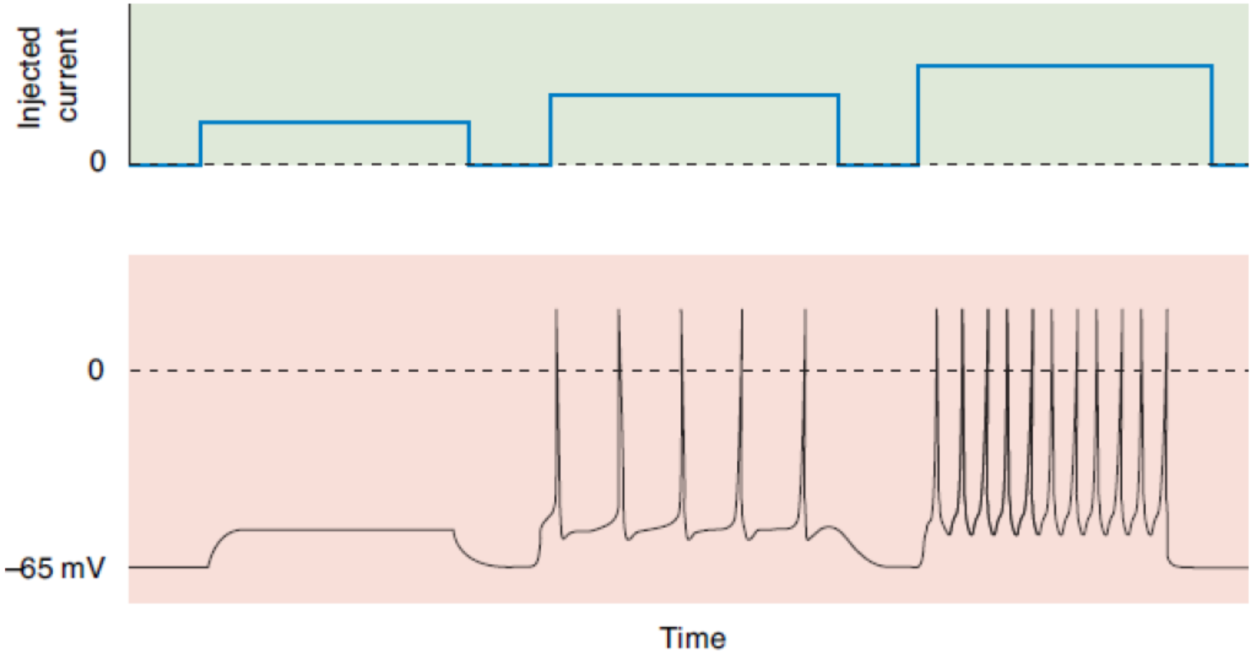
Adapted from Fix and Brueckner (2009).

How do axons initialize voltage signals?



- In most neurons, the AP develops in the initiation segment of the axon (Axon Initial Segment)
- It is located between the beginning of the axon and the first myelinated segment
- It is highly excitable – high density of Nav channels
- Nav channels with lower threshold for opening

Signal coding using the action potential



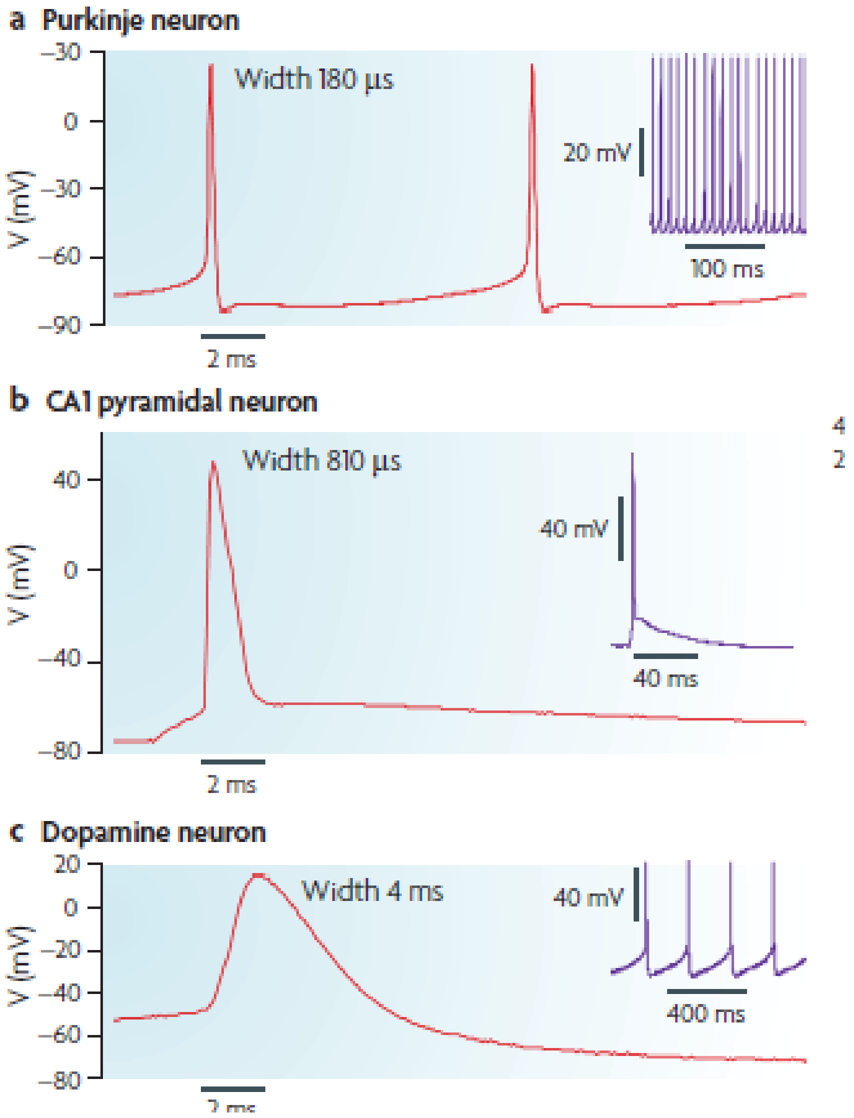
If injected current does not depolarize the membrane to threshold, no action potentials will be generated.

If injected current depolarizes the membrane beyond threshold, action potentials will be generated.

The action potential firing rate increases as the depolarizing current increases.

Digital signal – all or none (0-1)
The information here is not encoded using the amplitude of the signal

Signal coding using the action potential

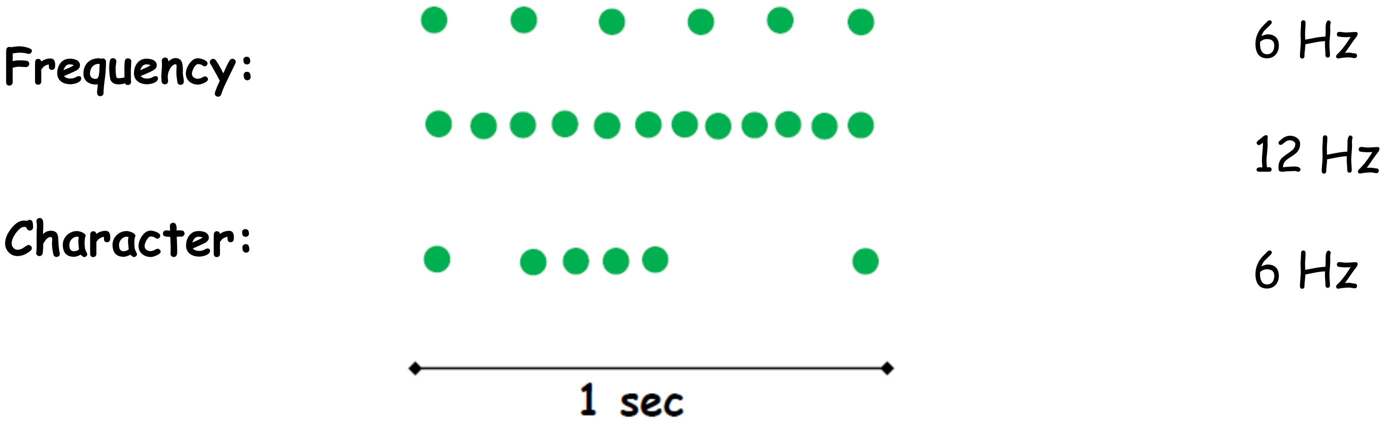


Shape of AP
-width
-repolarization
-afterhyperpolarization

Frequency of AP
(spikes/sec)
-Low versus
-High frequency

Character of the firing
-regular
-irregular
-discharges

Signal coding using the action potential



Frequency:

6 Hz

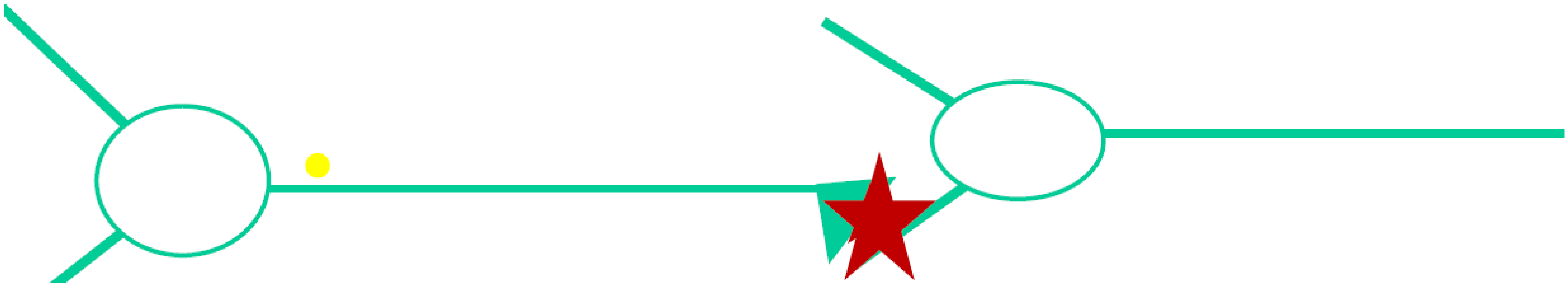
12 Hz

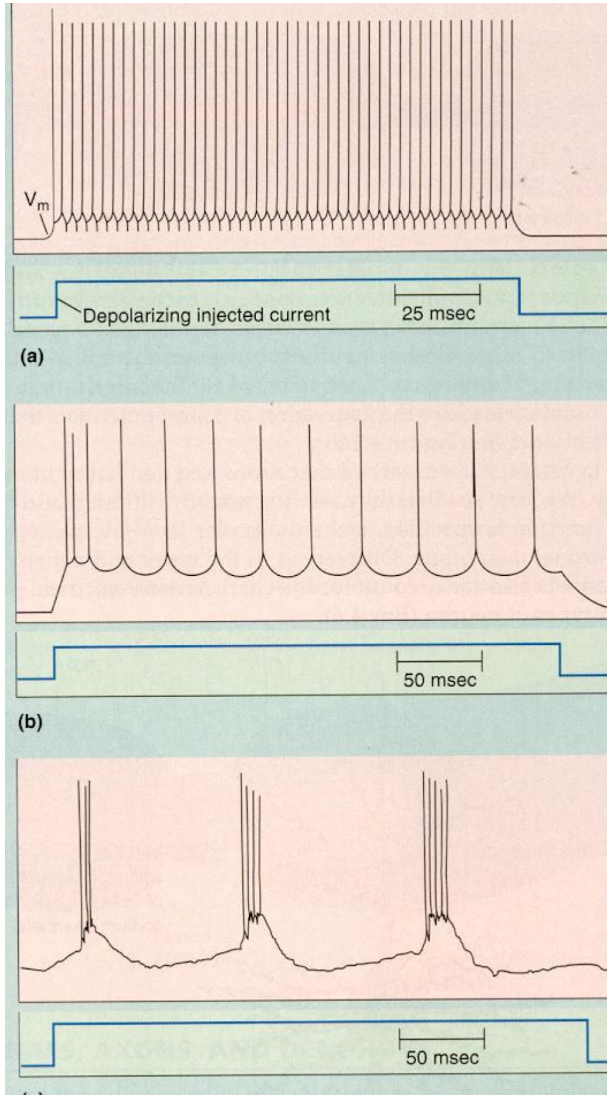
Character:

6 Hz

1 sec

The frequency and nature of APs affect the amount of neurotransmitter released at the axon terminal





Cortical neurons

Fast spiking neurons (inhibitory)
Fast activating and deactivating Kv channels (Kv3) quickly repolarize the membrane after AP

Regularly slowly firing neurons (excitatory)
A-type K current
Stabilize low-frequency firing

Neurons firing in bursts
Protracted depolarization

Voltage-gated ion channels help signal encoding

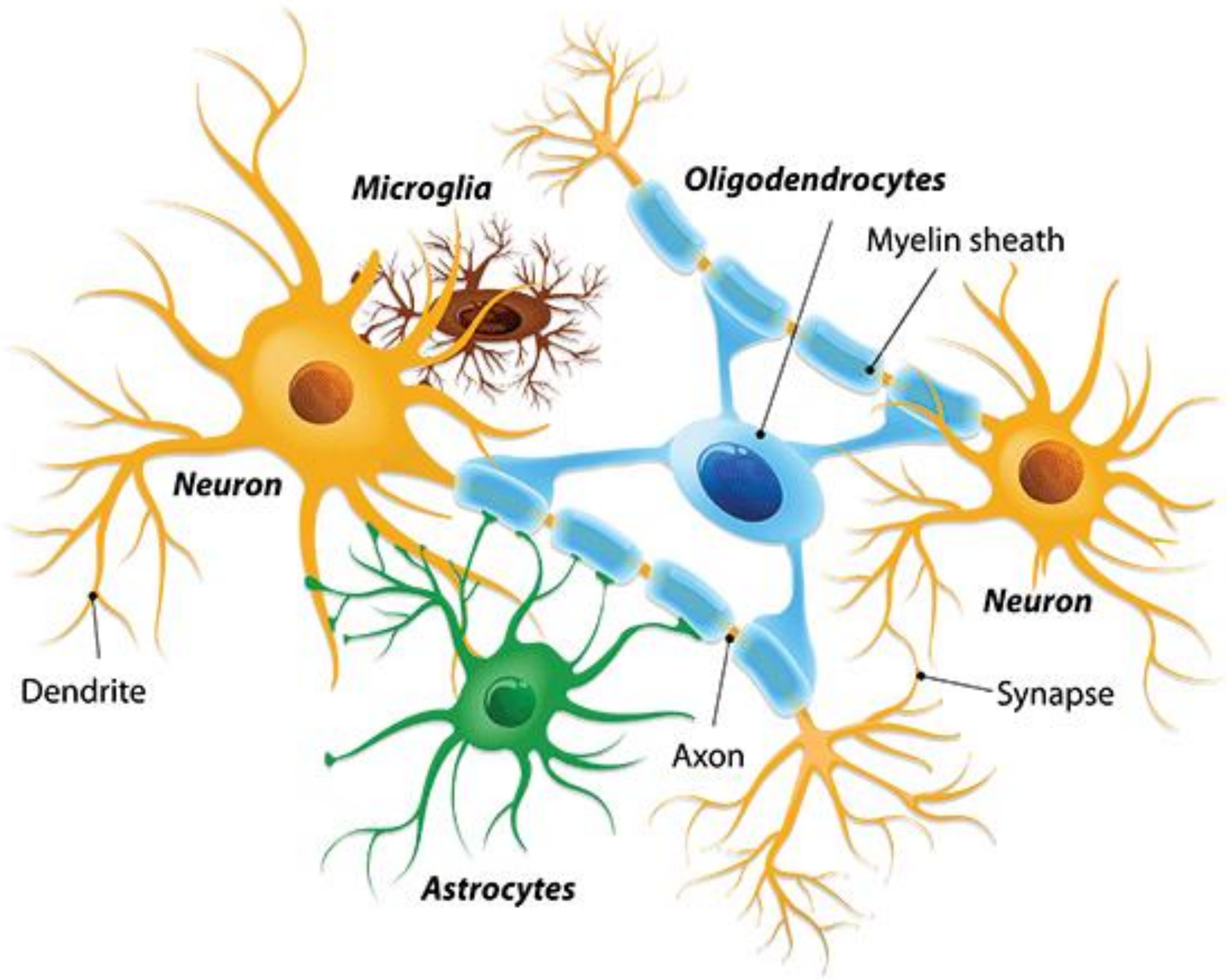
Summary #4: Action potential, axon, myelin and signal conduction

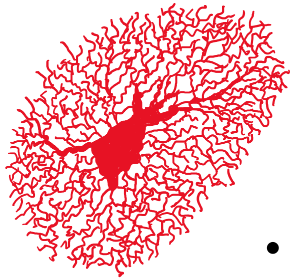
- Axons serve to quickly transmit signals to other cells
- Biological cables are very poor conductors of electricity - high internal resistance and low membrane resistance
- Myelin and voltage-gated ion channels help overcome these deficiencies and thus make signal transmission more efficient
- Model of the AP – conductance during AP
- Action potentials arise in the initiation segment of the axon
- Action potentials encode information in the CNS

Glial cells

CNS
Astrocytes
Oligodendrocytes
Microglia

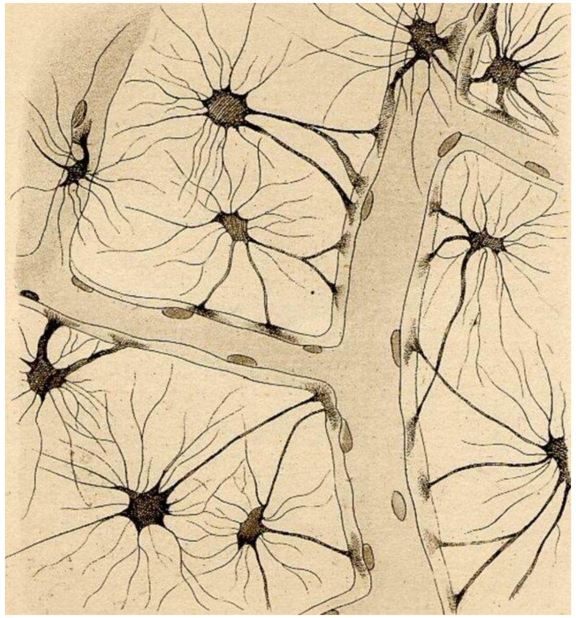
PNS
Schwann cells
Satellite cells



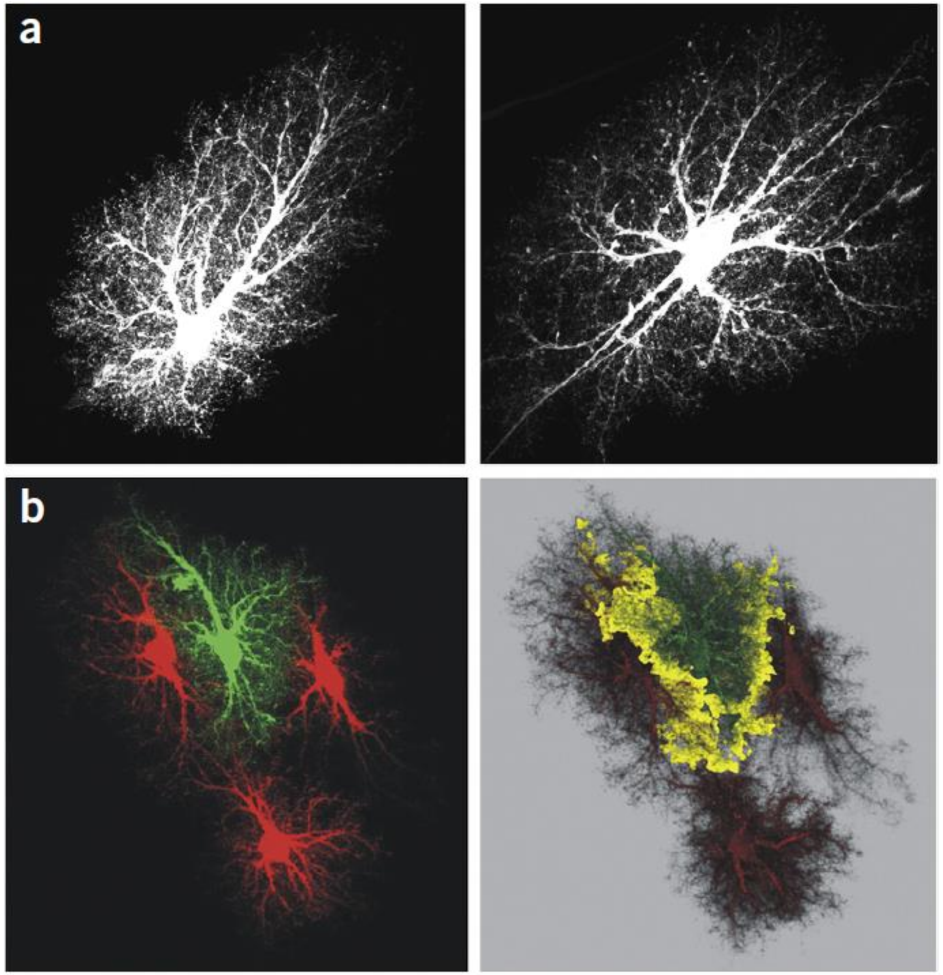


Astrocytes

- Known since 19th century
- Camillo Golgi – silver chromate staining



Non-overlapping domains

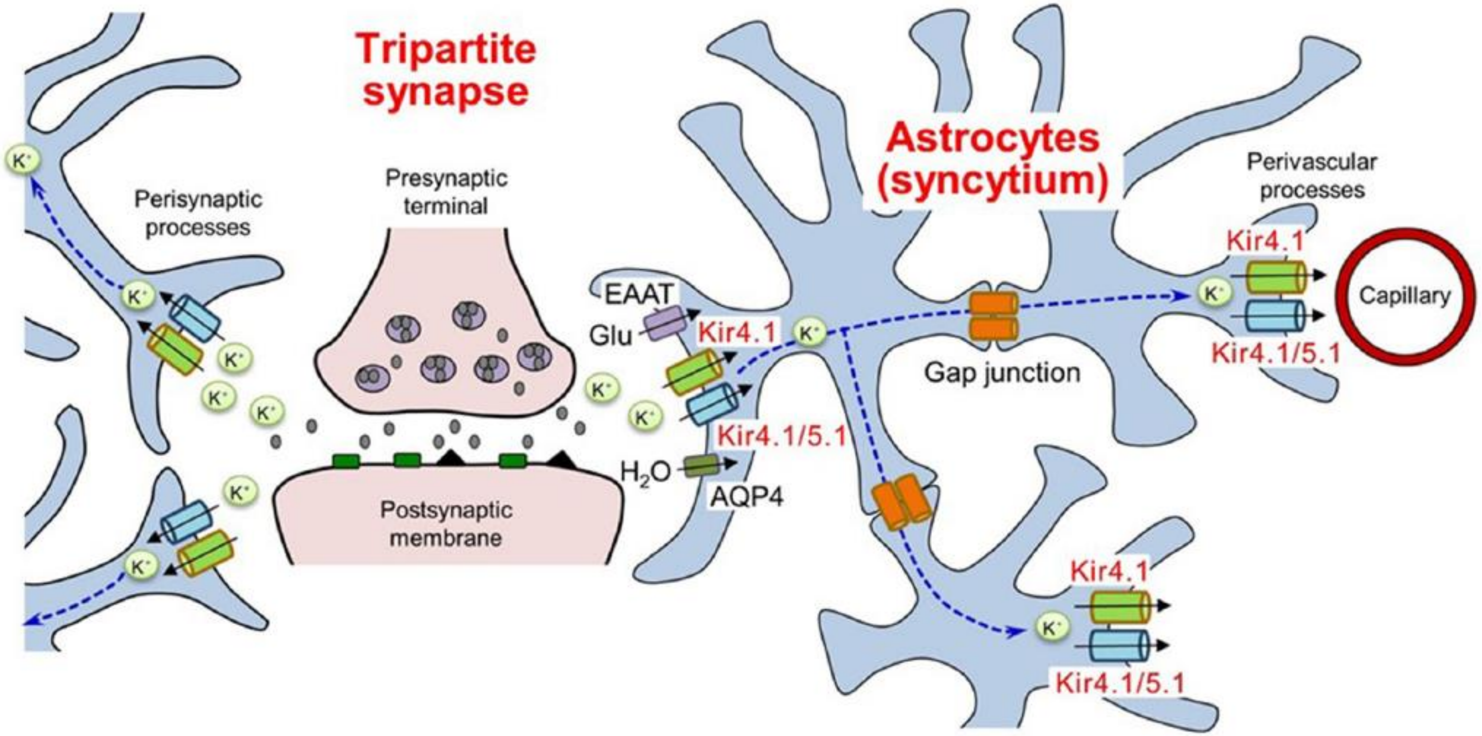


Khakh and Sofroniew, Nat Neurosci, 2015

- 1 astrocyte can contact thousands of synapses

Astrocytes

- 1960th – large K^+ conductance
- -> K^+ uptake = K^+ buffering = K^+ siphoning = K+ redistribution from sites with high neuronal activity to low activity sites or to blood vessels
- Syncytium – gap junctions
- **Ion homeostasis** in the CNS

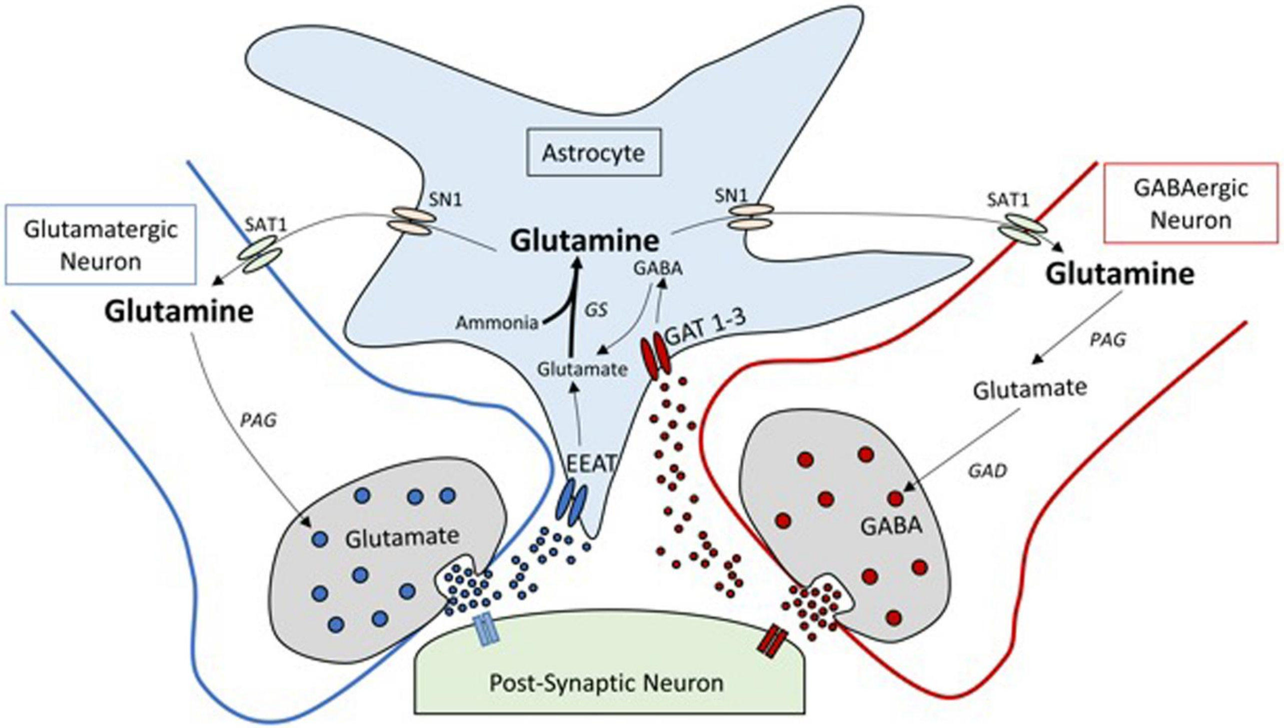


Kinboshi 2020

Astrocytes

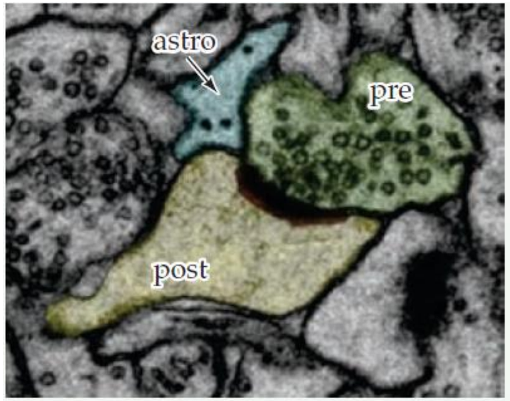
- **Neurotransmitter uptake**

- Glutamate uptake – EAAT1,2 transporters
- Glutamate-glutamine cycle
- GABA and glutamate recycling
- (GS = glutaminesynthetase)

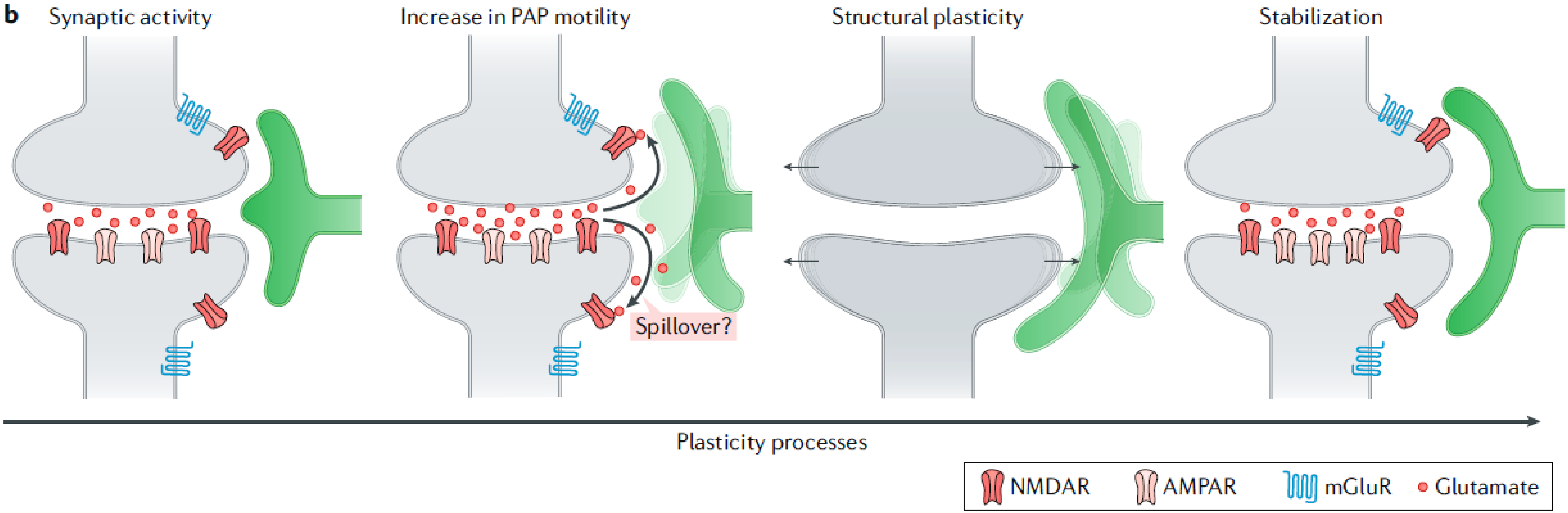


Newsholme 2023

Astrocytes – synaptic plasticity



- Modulation of synaptic transmission
- Tripartite synapse

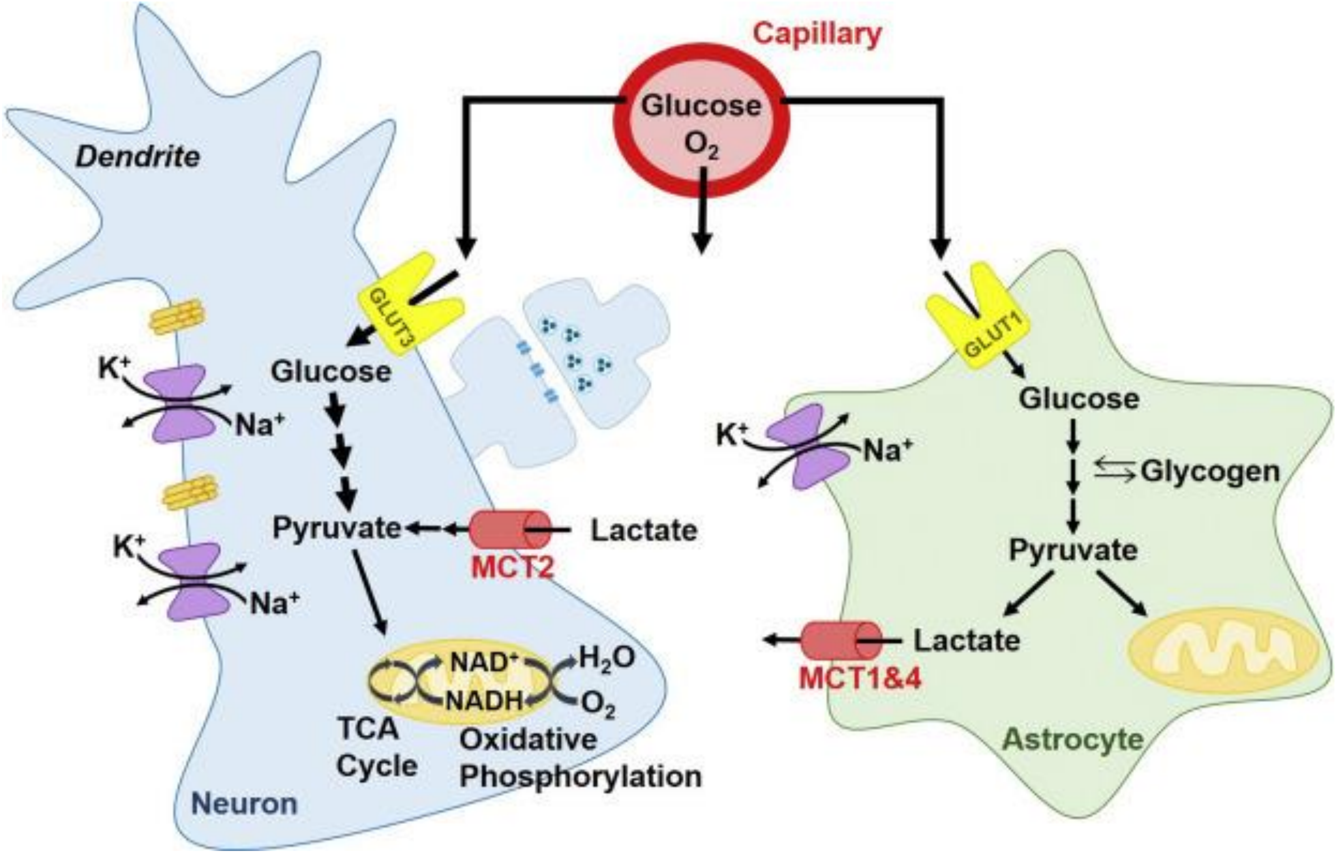


Perisynaptic astroglial processes

Dallerac et al., 2019

Astrocytes

- Provide **metabolic substrates** to neurons (glucose, lactate)
- Glycogen storage, gluconeogenesis
- Astrocyte–Neuron Lactate Shuttle
- Stimulated by glutamate

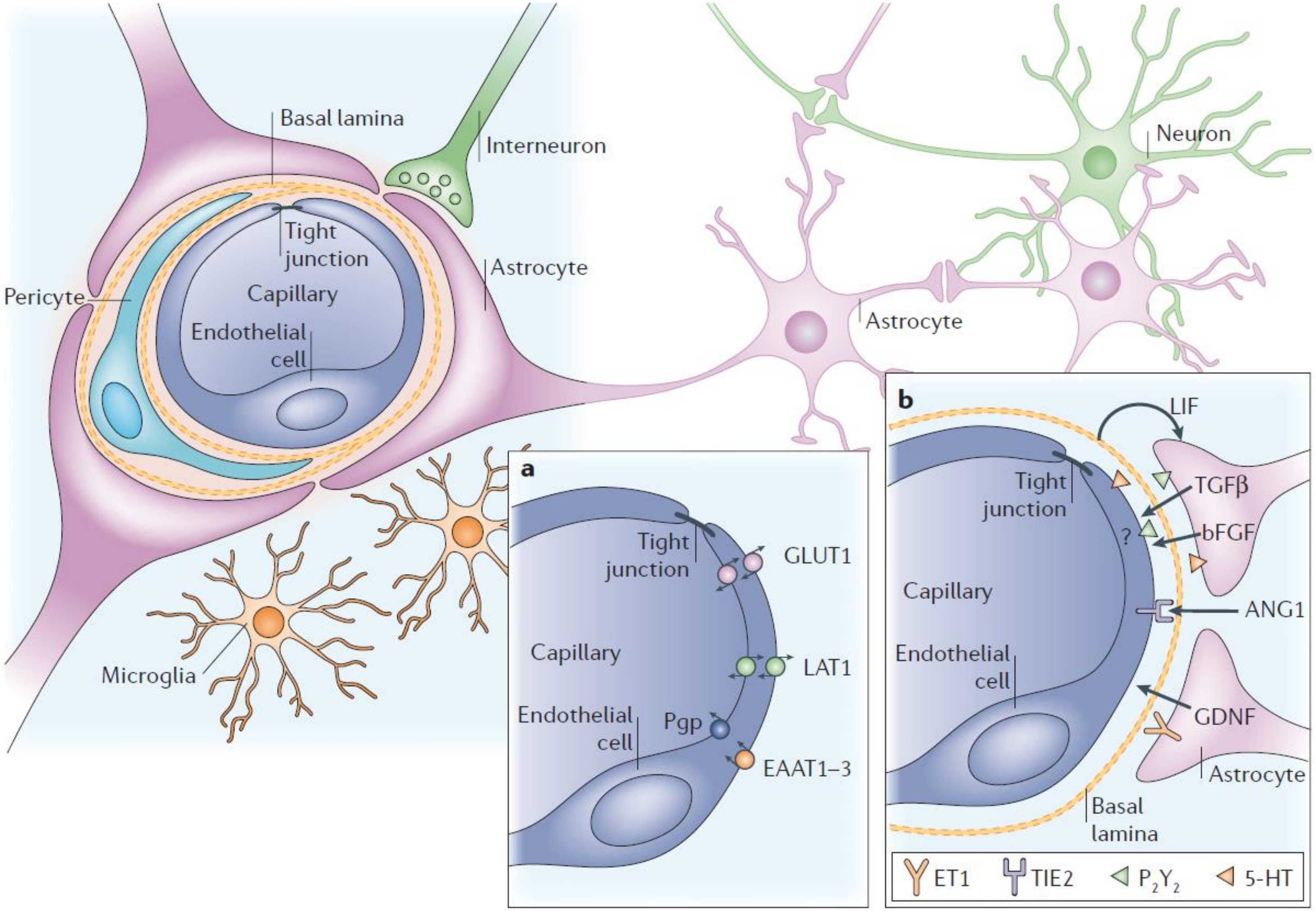


Pellerin 2007

Astrocytes – blood brain barrier

BBB:

- Astrocyte endfeet
- Endothelial cells
- Basal lamina

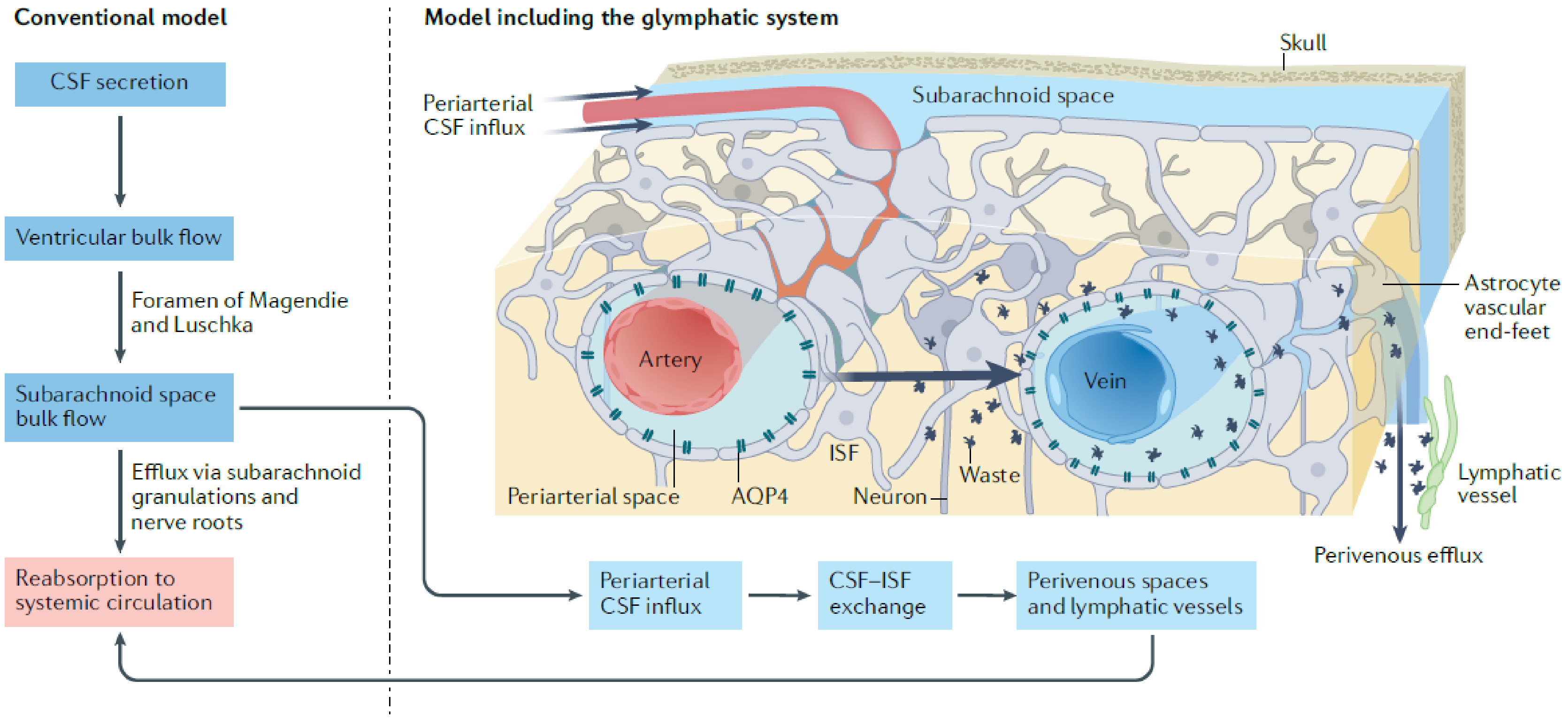


- Development – induction of BBB formation by astrocytes

Abbott et al., 2006

Astrocytes – glymphatic system

- glymphatic fluid transport is facilitated by astrocytic endfeet and their expression of aquaporin-4 water channels
- Removal of toxic metabolic waste products (proteins) x dementia, Alzheimer disease



Conventional model

CSF secretion

Ventricular bulk flow

Foramen of Magendie and Luschka

Subarachnoid space bulk flow

Efflux via subarachnoid granulations and nerve roots

Reabsorption to systemic circulation

Model including the glymphatic system

Periarterial CSF influx

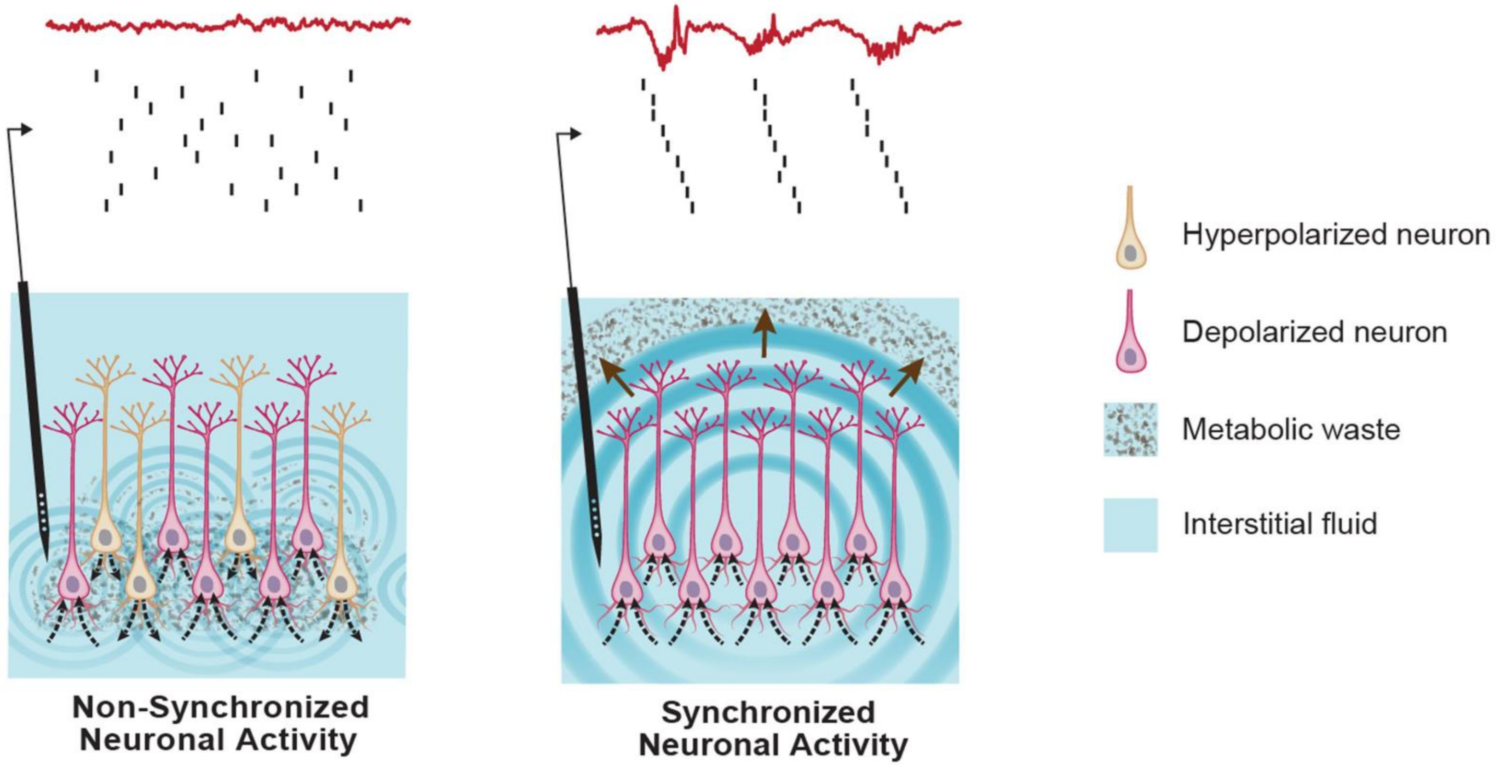
CSF–ISF exchange

Perivenous spaces and lymphatic vessels

Lohela et al., 2022

Astrocytes – glymphatic system

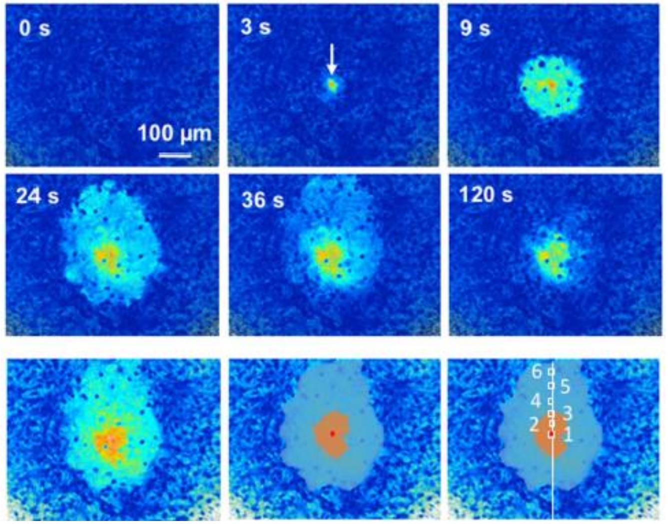
- Sleep – slow waves of neuronal activity promote waste flush during sleep



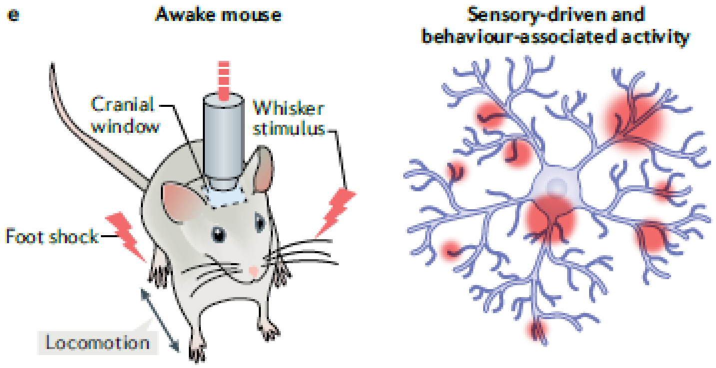
Jiang-Xie et al., Nature, 2024

Astrocytes – active signaling

- Gliotransmitters – glutamate, serotonin, ATP
- Intracellular Ca^{2+} waves – communication throughout the syncytium
    - Modulation of neurotransmission



Cell cultures (*Fujii, 2017*)



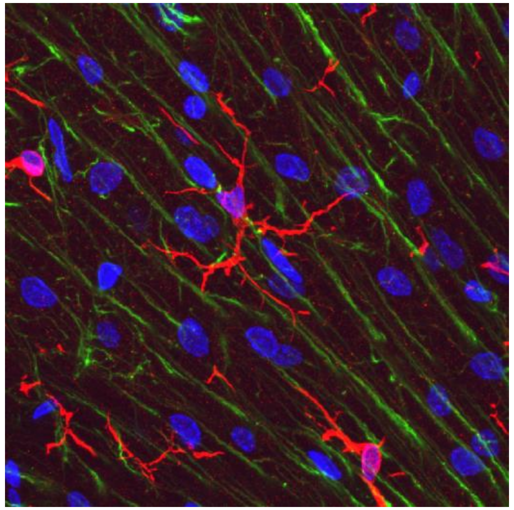
Semyanov 2020

Astrocytes - pathology

- Kir4.1 channels mutation (AR) – EAST (Epilepsy, Ataxia, Sensorineural deafness, Tubulopathy) or SeSAME (Seizures, Sensorineural deafness, Ataxia, Mental retardation, and Electrolyte imbalance) syndrome

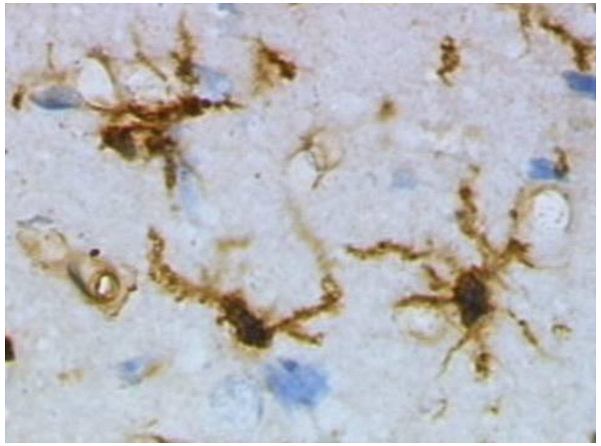
- **Reactive astrogliosis** – *general response to pathological insult – glial scar formation*
  - Hypertrophy + hyperplasia + increased expression of intermediate filaments – GFAP (glial fibrillary acidic protein), vimentin
  - Impaired homeostatic functions
  - Secretion of inflammatory cytokines (TNFα,...)
  - Nervous system repair

Microglia



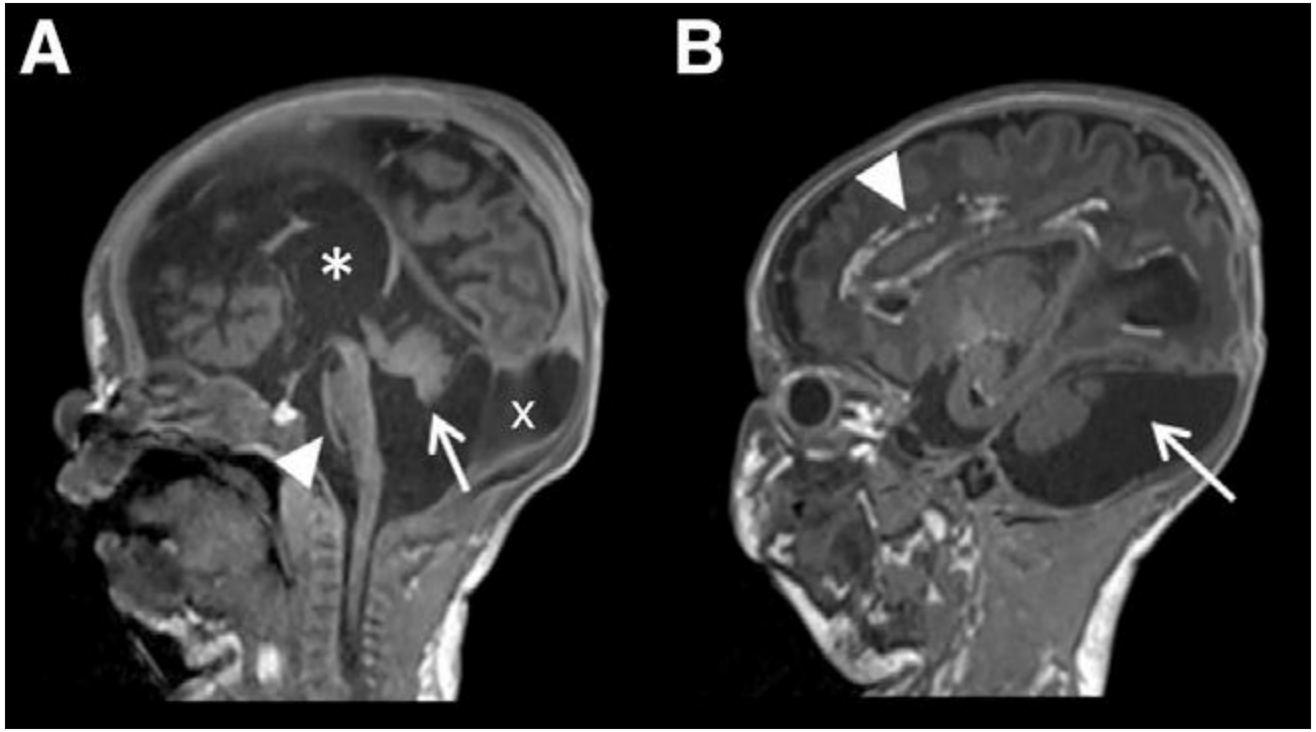
- Originate in the yolk sack (mesenchymal cells)
- Resident macrophage cells
- Immune cells in the brain, antigen presenting
- Activated after injury, release of inflammatory cytokines
- Promote tissue regeneration x detrimental after strong insult
- Promote synapse development (early development) and pruning (during adolescence)

- **=> interaction with other brain cells for proper functioning of the brain**



Microglia

- Csf1r mutation (colony-stimulating factor – 1 receptor)
- Congenital microglia depletion – disruption of brain development

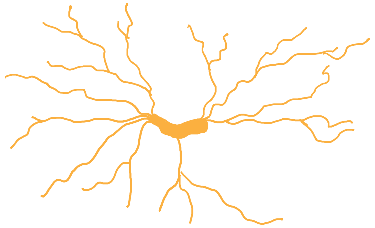


Oosterhof 2019

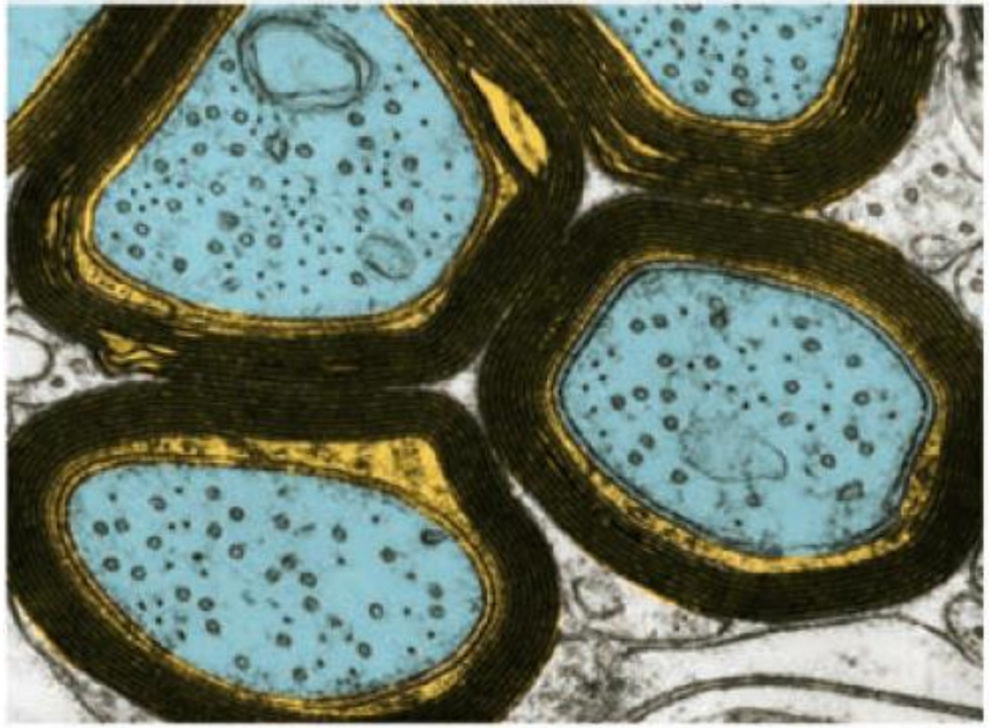
Oligodendrocyte lineage cells and myelin in CNS

White matter

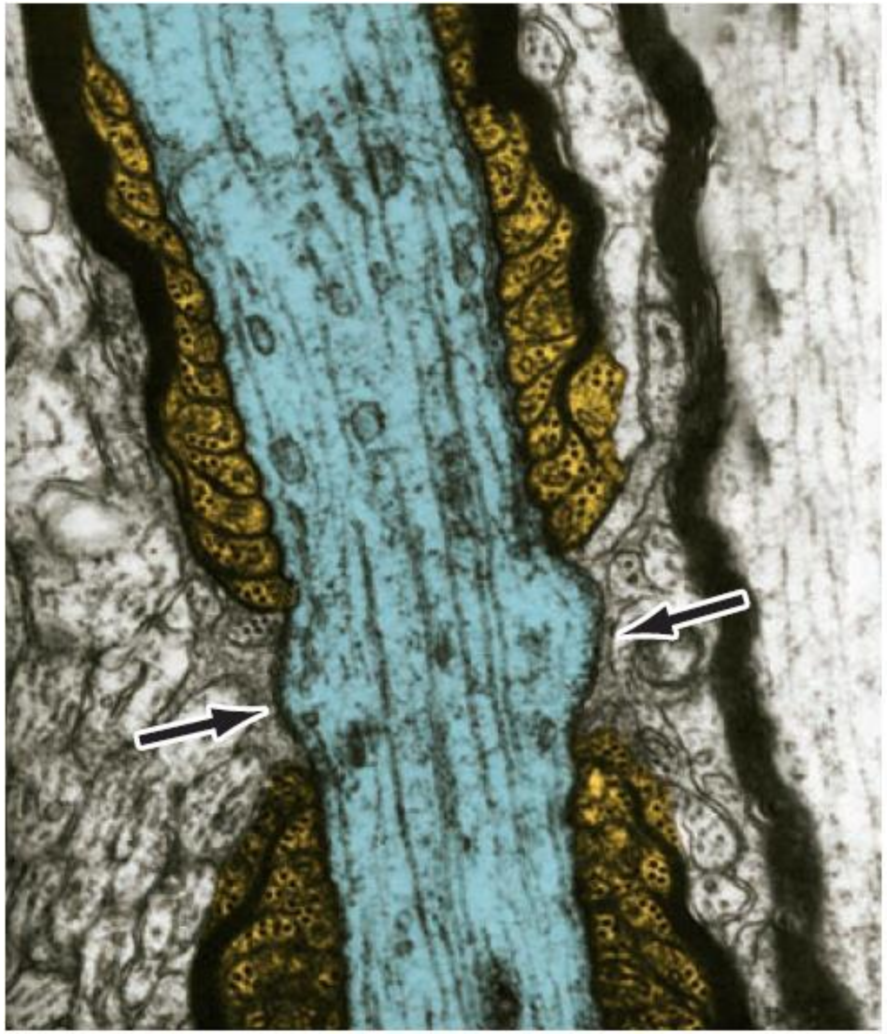
Diffusion MRI (diffusion tensor imaging)



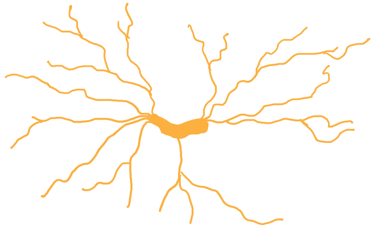
Oligodendrocytes and myelin



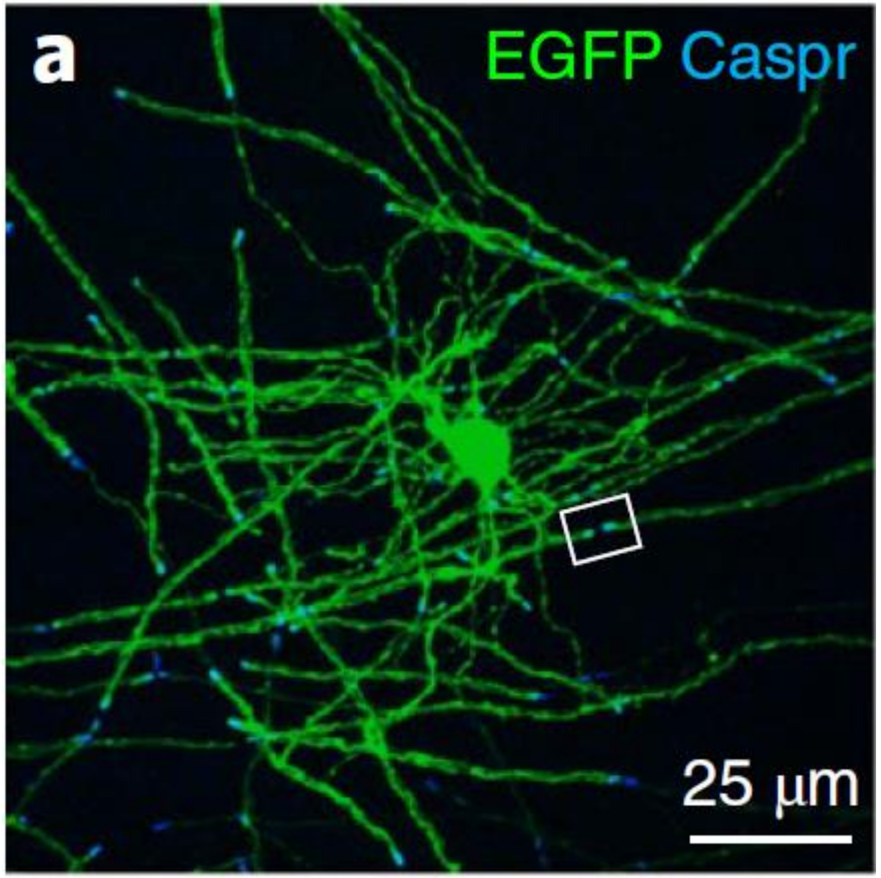
Axon
Myelin
Oligodendrocyte



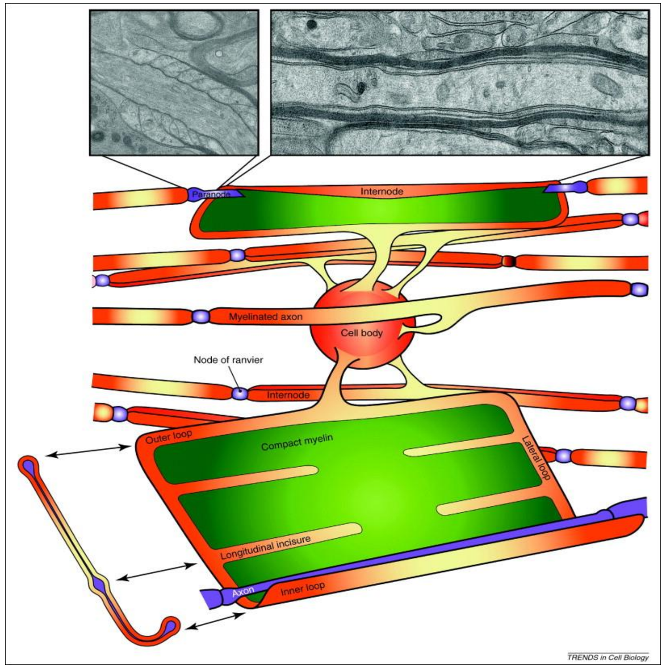
Nodes of Ranvier



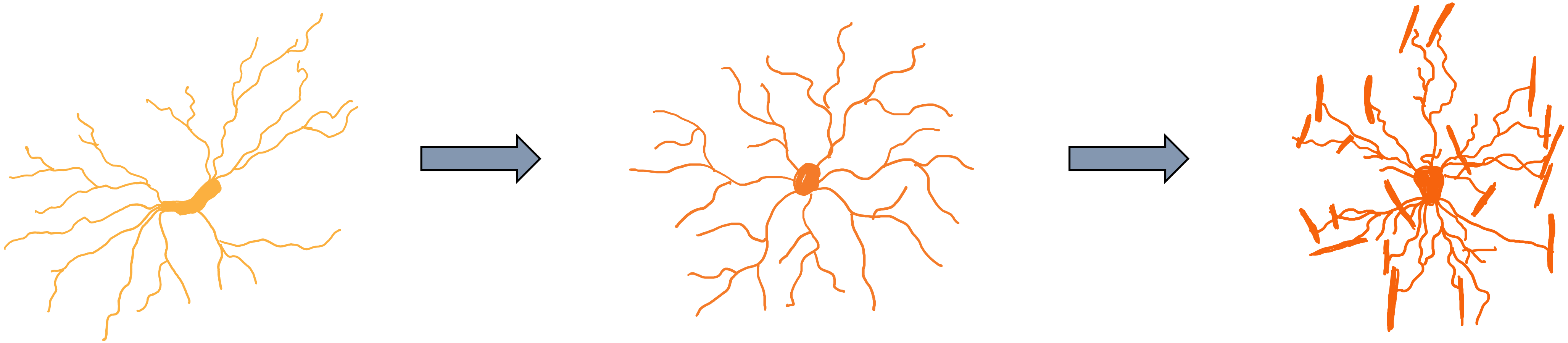
Oligodendrocytes and myelin



Hughes et al., 2018



Oligodendrocyte lineage cells



Oligodendrocyte precursor cells (OPCs)

Olig2
NG2
PDGFRa

Immature oligodendrocytes

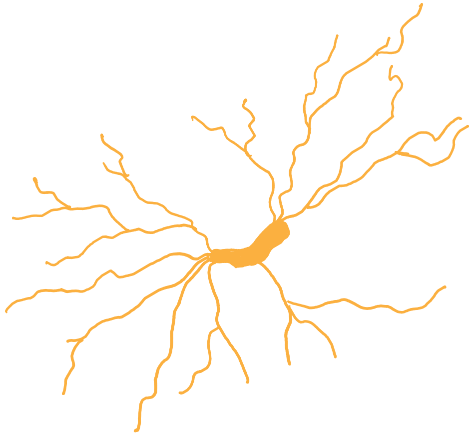
Olig2
O4
GalC
CNPase

Myelinating oligodendrocytes

Olig2
CNPase
MBP
MOG

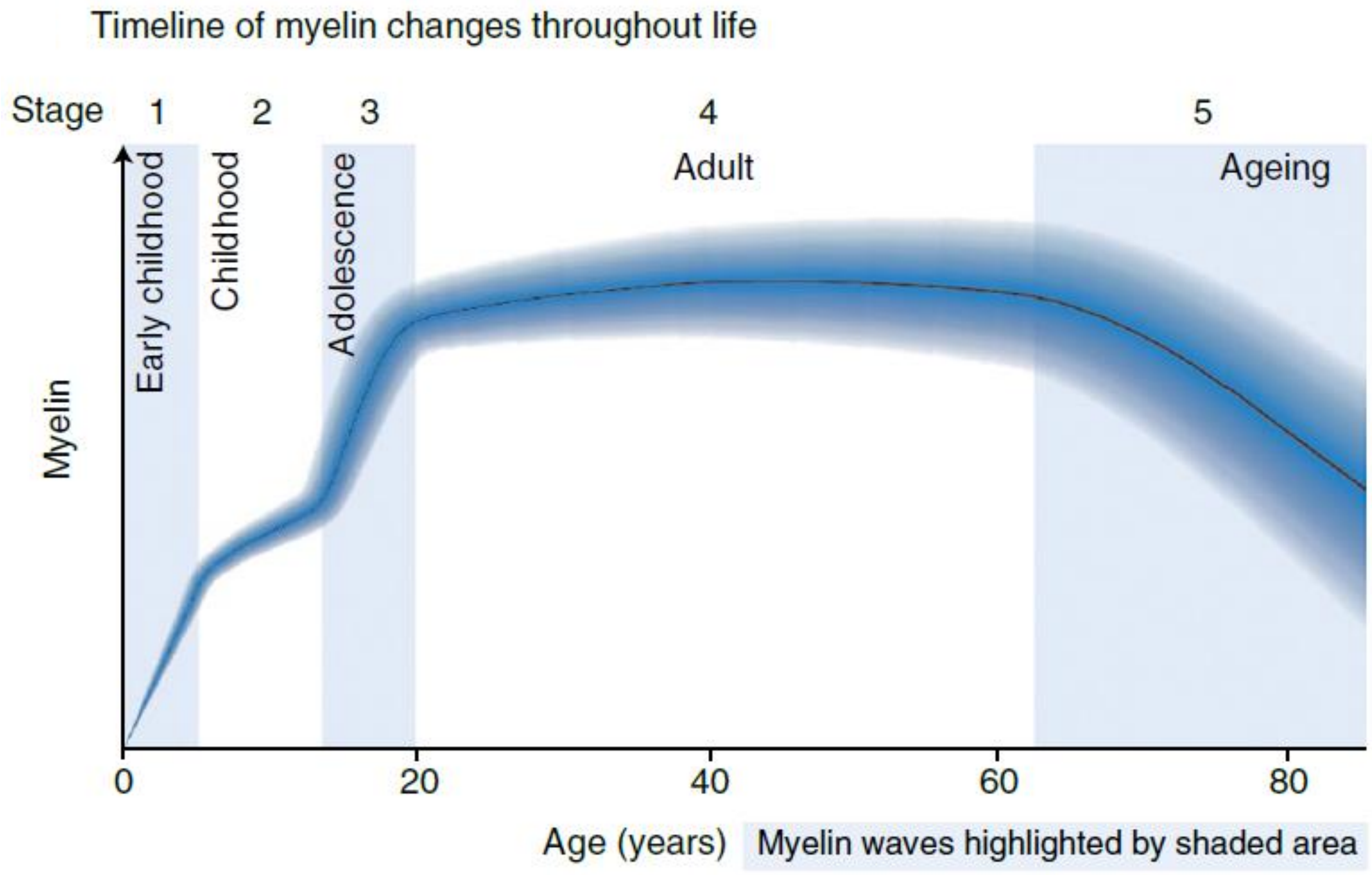
Oligodendrocyte precursor cells (OPCs)

- Found only 25 years ago
- About 3-5% of all cells in the adult brain
- Everywhere throughout the brain
- !! Receive synaptic inputs from neurons
- Main function – a pool to produce new oligodendrocytes
- -> activity-dependent myelination
- Development – synapse formation

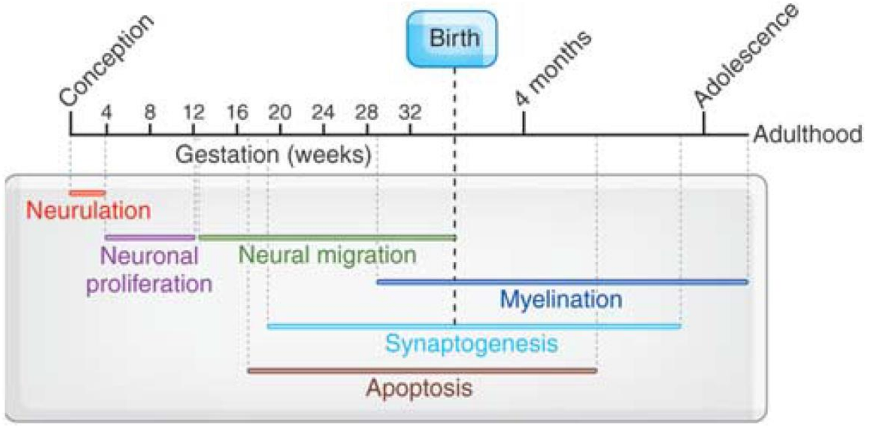


Olig2
NG2
PDGFRα

Myelination during brain development

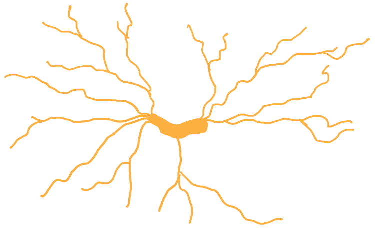


de Faria Jr, Pivonkova,… Nat Neurosci 2021



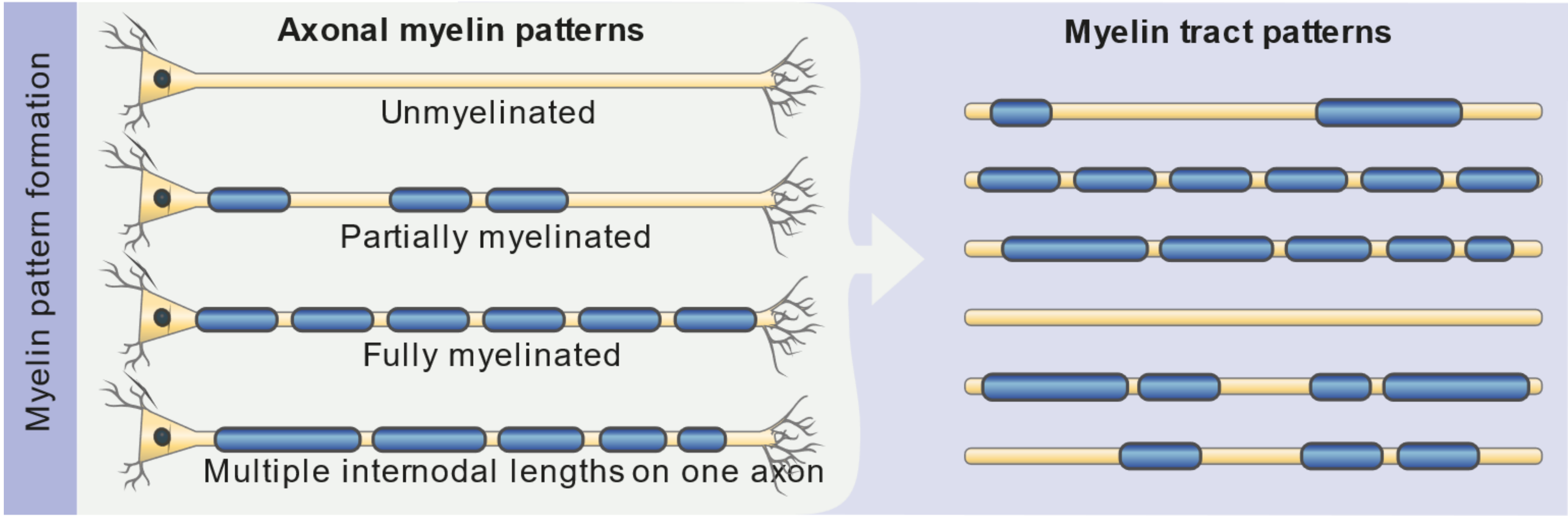
Tau and Peterson, Neupsypharm 2010

Senzorimotor tracts myelinate first
Association tracts myelinate last



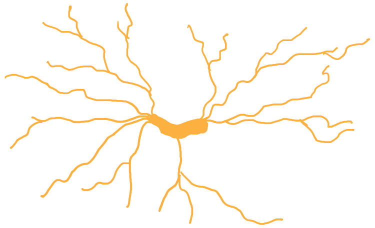
Myelin patterns along axons

Corpus callosum – 30% myelinated axons
Cerebellar peduncles – 100% myelination



de Faria Jr, Pivonkova,… Nat Neurosci 2021

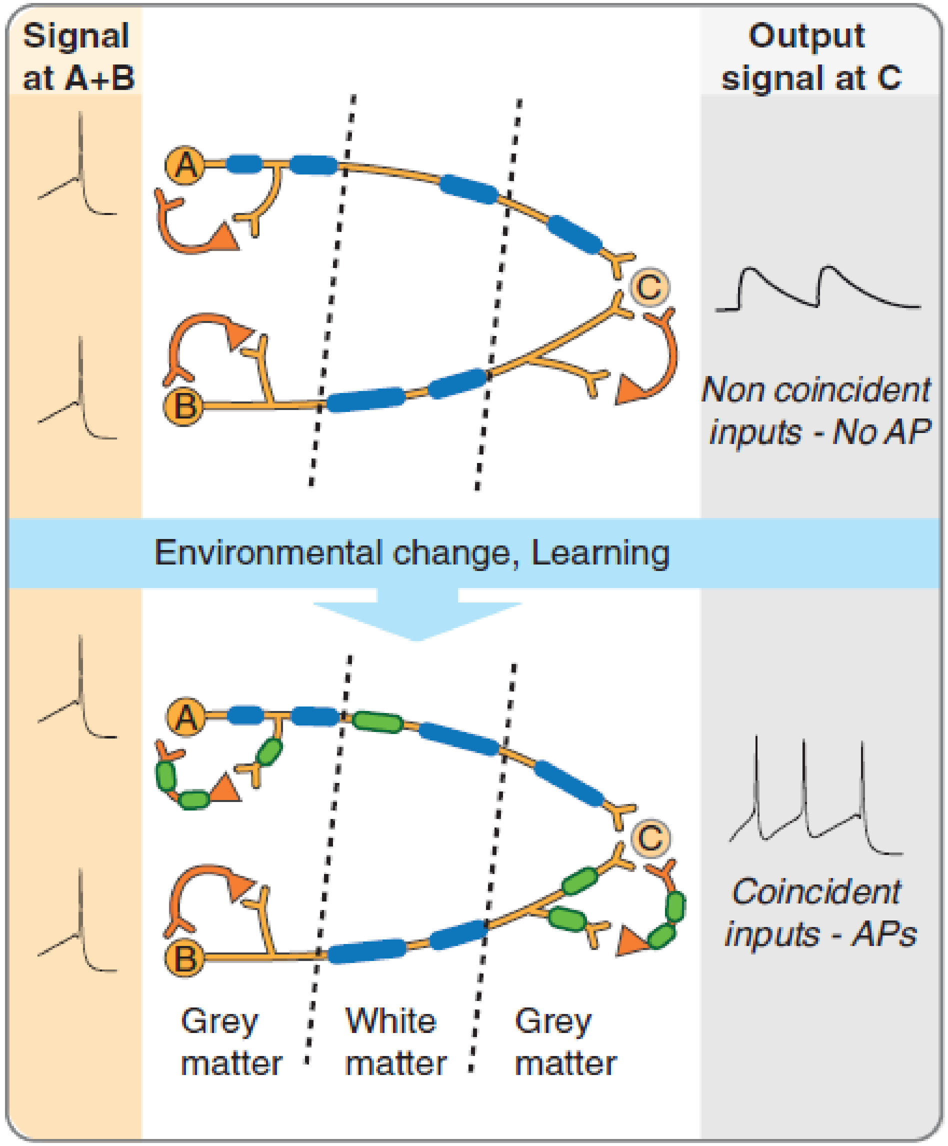
Space for plasticity



Myelin plasticity in neuronal circuits

- AP failure rate
- AP arrival time
- Coincidence detection
- Synchronization

Remodeling of neuronal circuits



Bonetto et al., Science 2021

Oligodendrocyte lineage cells – main functions

- Myelination
- Insulation of axons
- Metabolic support for axons
- Homeostasis

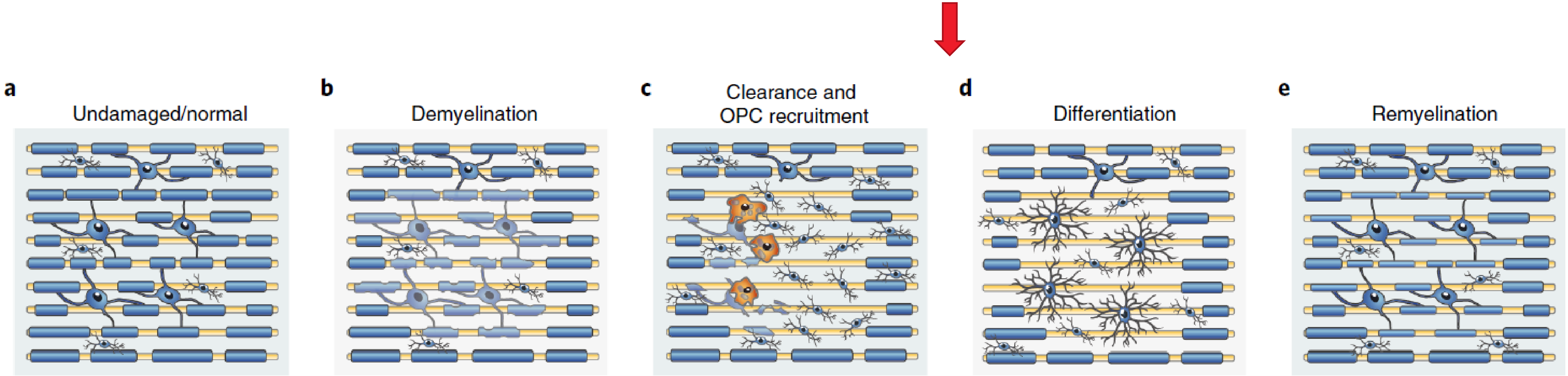
- **=> modulation of signal transmission**

- High level of flexibility
- Activity-dependent myelination

OLCs and myelin in CNS - pathology

- *Multiple sclerosis*
- *Alzheimer disease – WM hypoxia*

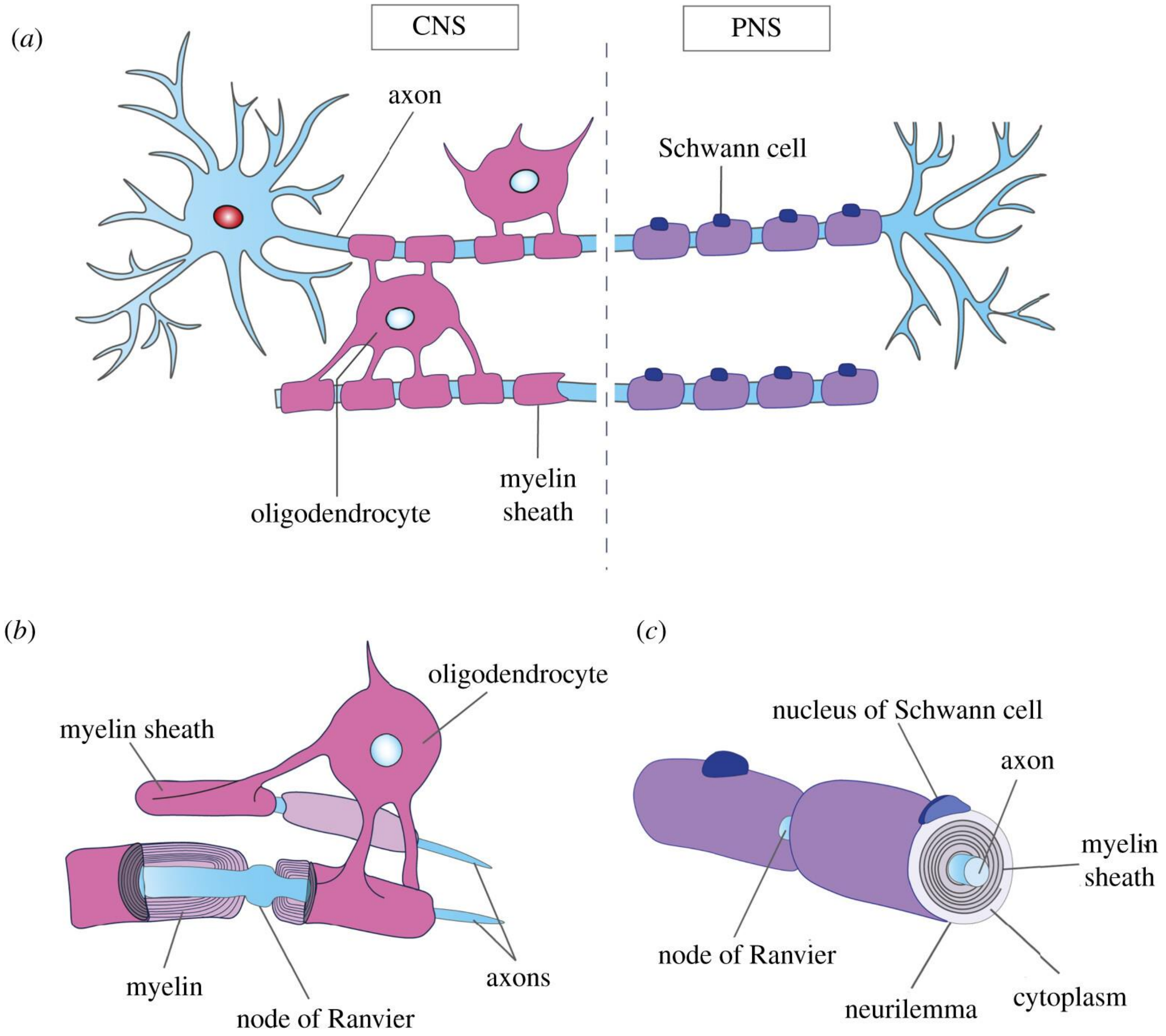
Failure of OPCs differentiation in MS



de Faria Jr, Pivonkova,… Nat Neurosci 2021

Current research focused on finding drugs to stimulate OPCs differentiation

Oligodendrocytes and Schwann cells



Other glial cell types

Ependymal cells

Specialized astrocytes – Muller glia in retina
Bergmann glia – cerebellum
radial glia – development

Stem cells in the brain – subventricular zone, dentate gyrus (radial glia)

Tanycytes – median eminence

PNS – satellite glia in dorsal root ganglia

Summary #6 – basic glial cell functions

CNS
Astrocytes
Oligodendrocytes
Microglia

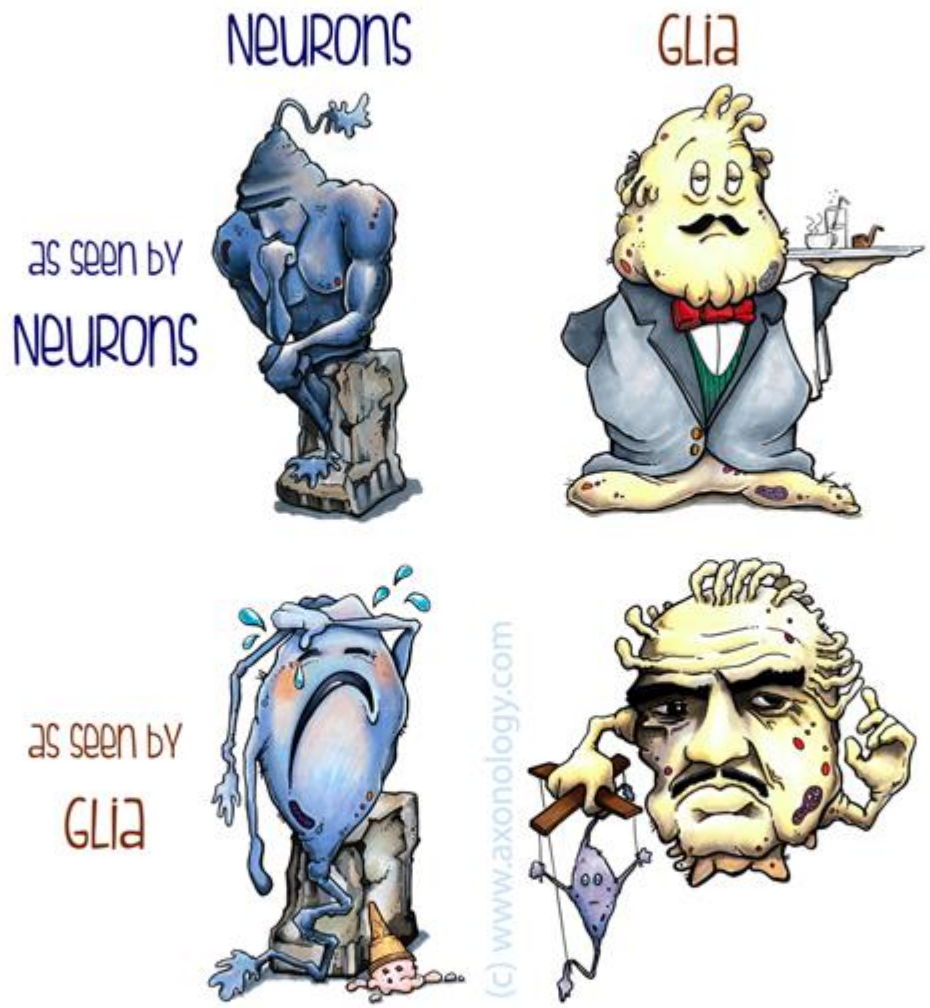
PNS
Schwann cells
Satellite cells

Glial cells support neurons on many levels:

Homeostasis
Energy
Signal transmission - myelin
Modulation of synaptic signaling
Brain development
Immune protection

=> modulation of neuronal functions

Thank you!


Neurons
Glia
as seen by
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