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Development of Complex Curricula for Molecular Bionics and Infobionics Programs within a consortial* framework**

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ELECTROPHYSIOLOGICAL METHODS FOR THE STUDY OF THE NERVOUS- AND MUSCULAR-SYSTEMS

(Az ideg- és izom-rendszer elektrofiziológiai vizsgálómódszerei)

LECTURE 4

ACTION POTENTIAL

(Akciós potenciál)

RICHÁRD CSERCSA, ISTVÁN ULBERT
and GYÖRGY KARMOS

AIMS:

In this lecture, the student will become familiar with the generation and propagation of the action potential, the basic element of information processing in the brain.

DEFINITION:

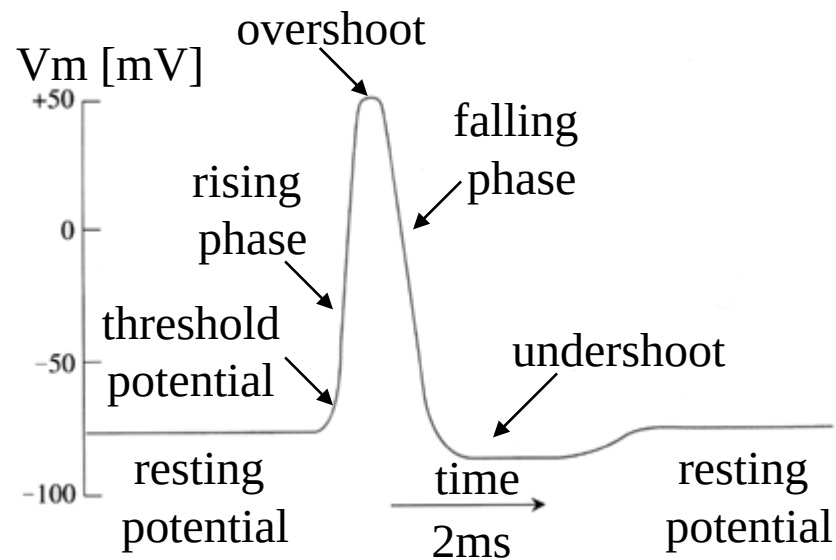
When the membrane potential of a neuron depolarizes and reaches a threshold, the neuron will generate an action potential, in other words, it will ‘fire’.

The action potential, also known as a ‘spike’ is a short-lasting event in which the membrane potential of the cell rapidly rises and falls, following a stereotyped trajectory. In neurons, they play a central role in cell-to-cell communication.

The amplitude of an action potential is independent of the amount of current that produced it. In other words, larger currents do not create larger action potentials. Therefore action potentials are said to be all-or-none, since they either occur fully or they do not occur at all. (wikipedia)

An action potential is typically generated in the initial segment of the axon (hillock) of the neuron and propagates along the axon, and at the axon terminals it is transmitted to other neurons through synapses.

SCHEMATIC ACTION POTENTIAL



SCHEMATIC ACTION POTENTIAL

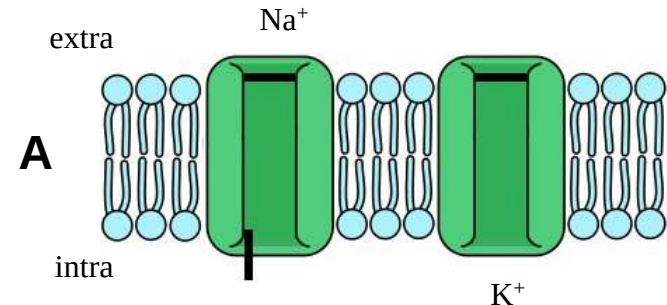
When the depolarizing membrane potential reaches a threshold, a stereotypic process is initiated. The depolarization opens Na^+ channels and Na^+ ions flow into the cell. This further depolarizes the cell (rising phase). Na^+ channels are inactivated after a small delay, and K^+ channels open. Thus, Na^+ flow into the cell stops, and K^+ flow out of the cell starts. This hyperpolarizes the membrane (falling phase). The membrane potential goes below resting potential (undershoot), then finally returns to rest.

After initiated, the action potential always takes place the same way, its amplitude is independent from the amount of current that produced it (all-or-nothing). It propagates along the axon and launches synaptic events at the axon terminals. Hence, it is the basis of neuronal communication and information processing.

ION CHANNEL ACTIVITY

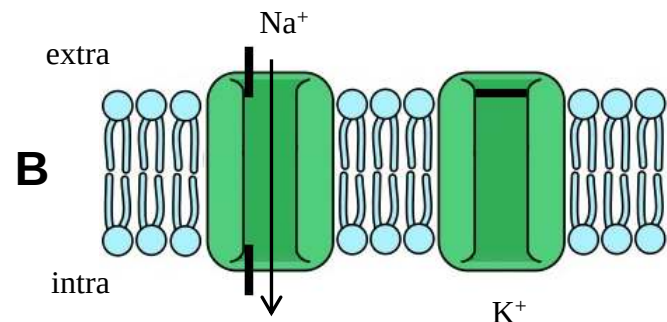
A: Resting phase

- Channels and membrane are at rest
- $V_m = V_r$



B: Depolarizing phase

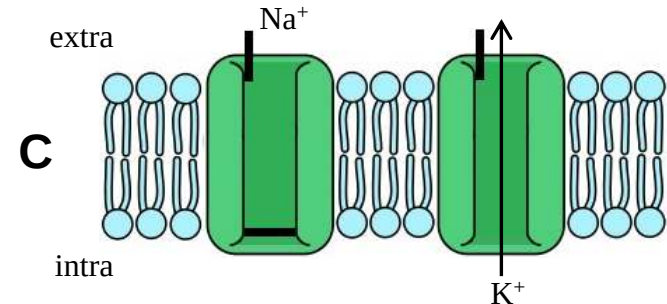
- V_m exceeds opening threshold of Na^+ channel
- Na^+ channel opens, Na^+ flows into the cell
- V_m depolarizes
- K^+ channel still closed, no K^+ current flow



ION CHANNEL ACTIVITY

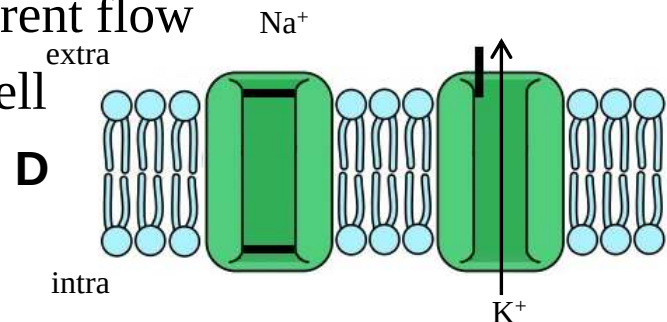
C: Repolarizing phase

- Na^+ channel inactivates, Na^+ current stops
- K^+ channel opens, K^+ flows out of the cell
- V_m repolarizes

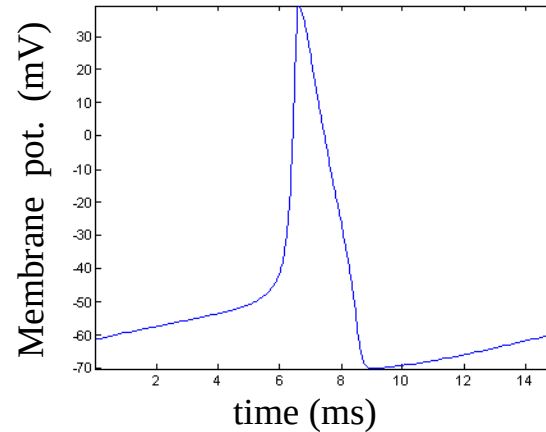


D: Afterhyperpolarizing phase (AHP)

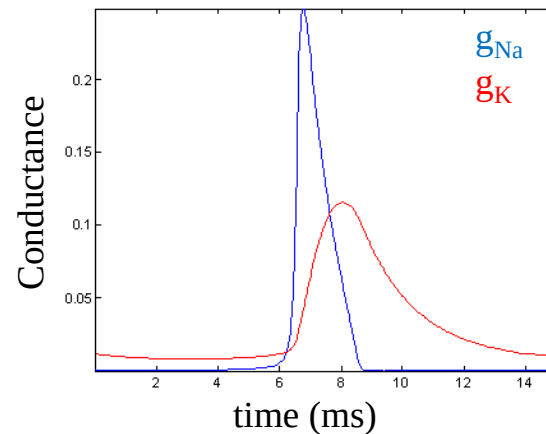
- Na^+ channel closed, close to rest, no Na^+ current flow
- K^+ channel still active, K^+ flows out of the cell
- V_m hyperpolarizes



CHANGES IN CHANNEL CONDUCTANCES



Membrane potential



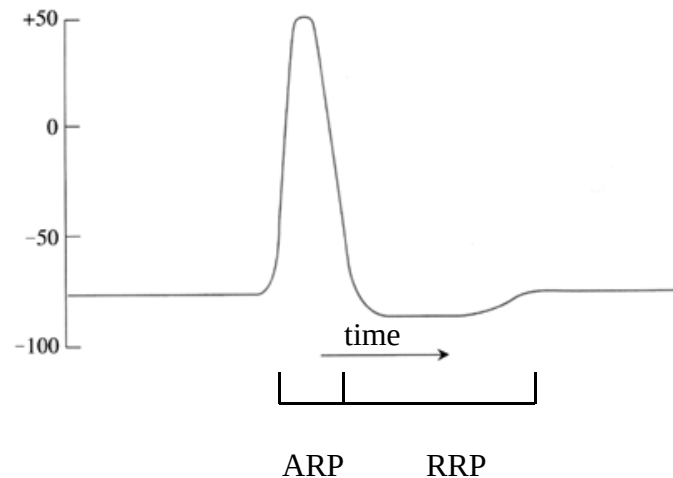
Ion channel conductances

REFRACTORY PERIOD

Refractory period starts at the rising phase of an action potential, during this period the cell cannot be stimulated, no action potential can be generated.

Absolute refractory period (ARP): no stimulus can evoke a response

Relative refractory period (RRP): only strong stimulus can generate an action potential



REFRACTORY PERIOD

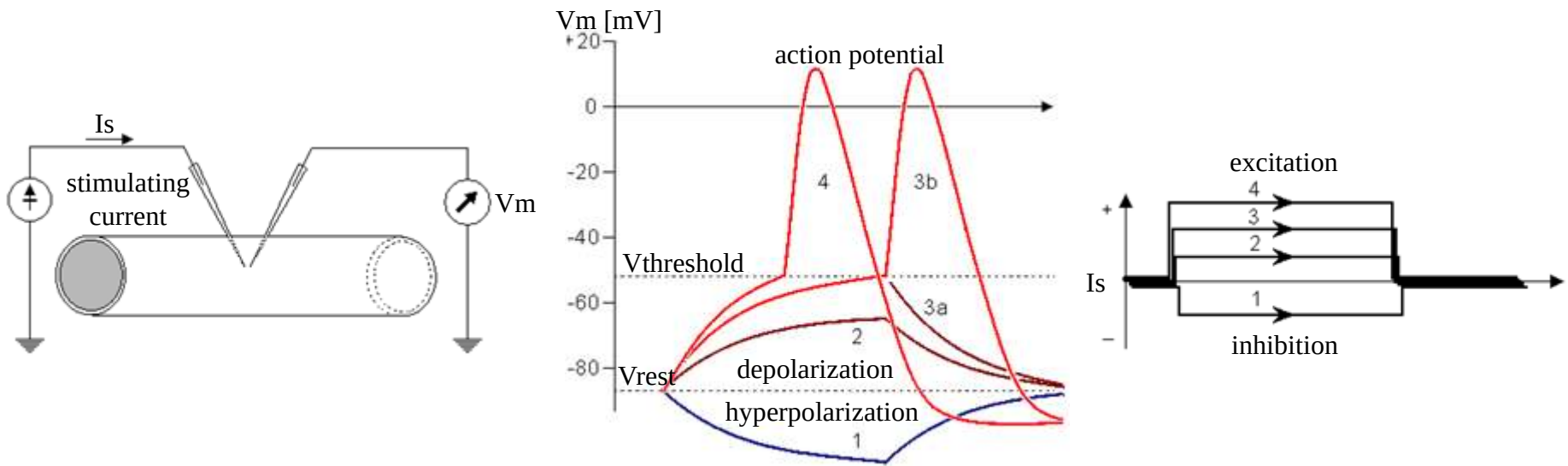
Causes of ARP:

1. During the depolarizing phase no more Na^+ channels can activate.
2. During repolarization, Na^+ channels become inactive, time is needed for reaching resting state, the channel won't open during this time.

Causes of RRP:

1. Na^+ channels do not return from inactivity in the same time, stronger stimulus is necessary to activate enough Na^+ channels to generate an action potential.
2. K^+ channels are still open, hence the cell is hyperpolarized, stronger stimulus is necessary for reaching the opening threshold of Na^+ channels.

EVOKING AND MEASURING ACTION POTENTIALS



MEMBRANE CONSTANTS

Time constant:

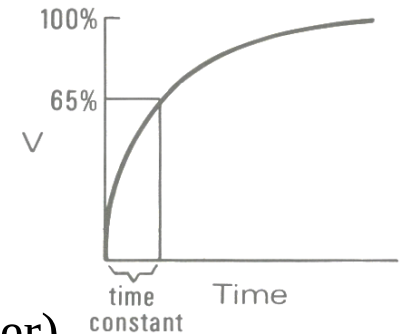
$$\tau = r_m c_m$$

r_m : membrane resistance (depends on the number of open ion channels)

c_m : membrane capacitance (depends on properties of lipid bilayer)

The time when the 63% ($1-1/e$) of the maximal action potential amplitude is reached.

The bigger the time constant, the slower the rising phase of AP.



Length constant:

$$\lambda = \sqrt{\frac{r_m}{r_i}}$$

r_i : intrinsic resistance (depends on the diameter of axon)

The distance where the amplitude of the electrotonically spread depolarization decreases to 37% of its initial value.

The greater the length constant, the farther the AP has effect.

SUMMATION

Summation:

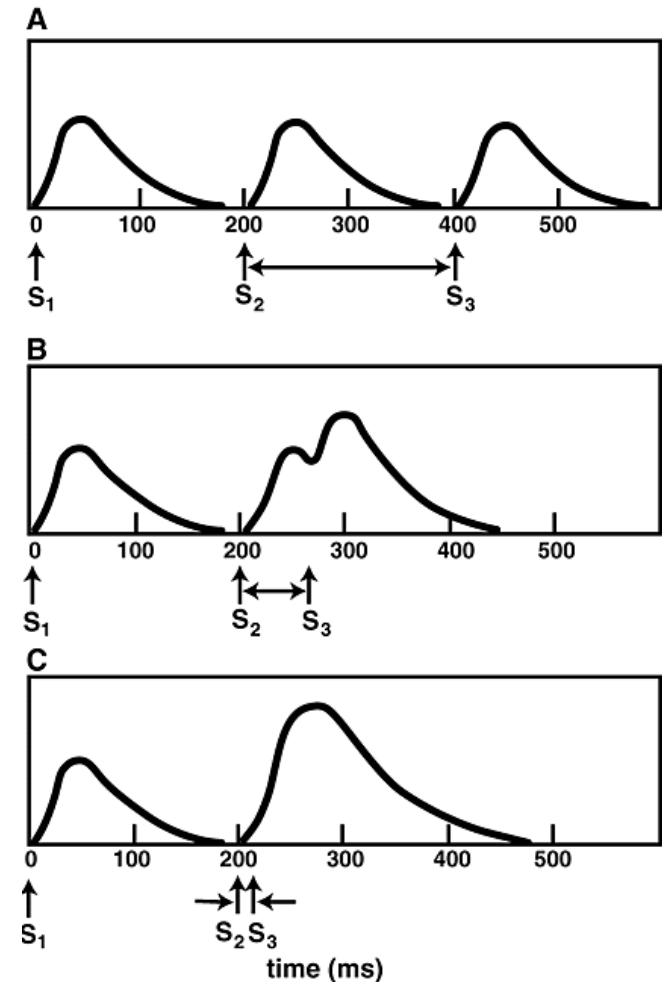
Linear summation of postsynaptic potentials that can pull the membrane potential closer or farther from the AP threshold.

Summation in time:

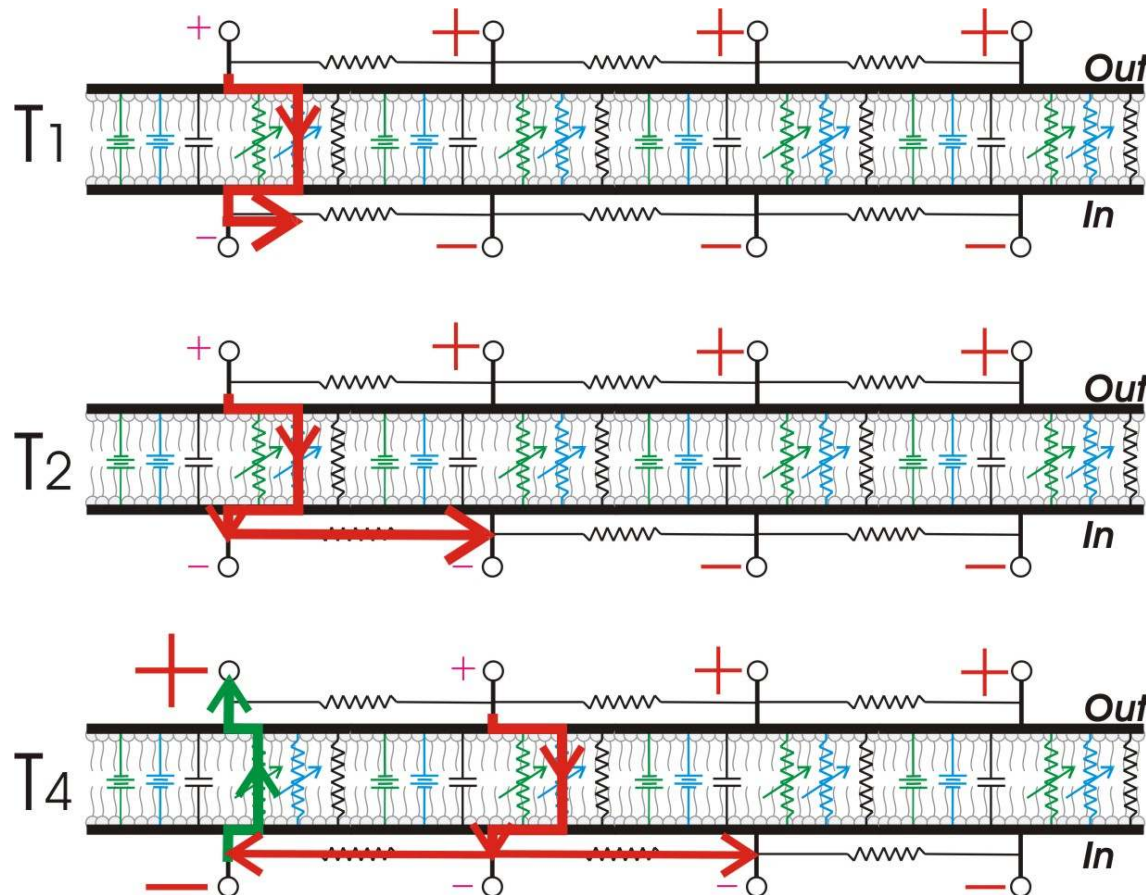
If the time constant is big enough, consecutive postsynaptic potentials are summed.

Summation in space:

If the length constant is big enough, postsynaptic potentials from different locations are summed.



MODEL OF PROPAGATION



(commons.wikimedia.org)

MODEL OF PROPAGATION

A local depolarization opens local sodium channels. Sodium current causes membrane depolarization (T1) which spreads to adjacent membrane, depolarizing it as well (T2). Sodium channels then open in this adjacent membrane, and the depolarization spreads further down the membrane (T4). Meanwhile, delayed rectifier potassium current flows in the original membrane patch, causing the falling phase of the AP.

Note that in T4, depolarization spreads in both directions down the membrane (i.e. also toward the place where the AP originated. A second action potential is not fired in that membrane because it is refractory, thus allowing for one-way AP conduction.

(commons.wikimedia.org)

PROPAGATION OF ACTION POTENTIALS

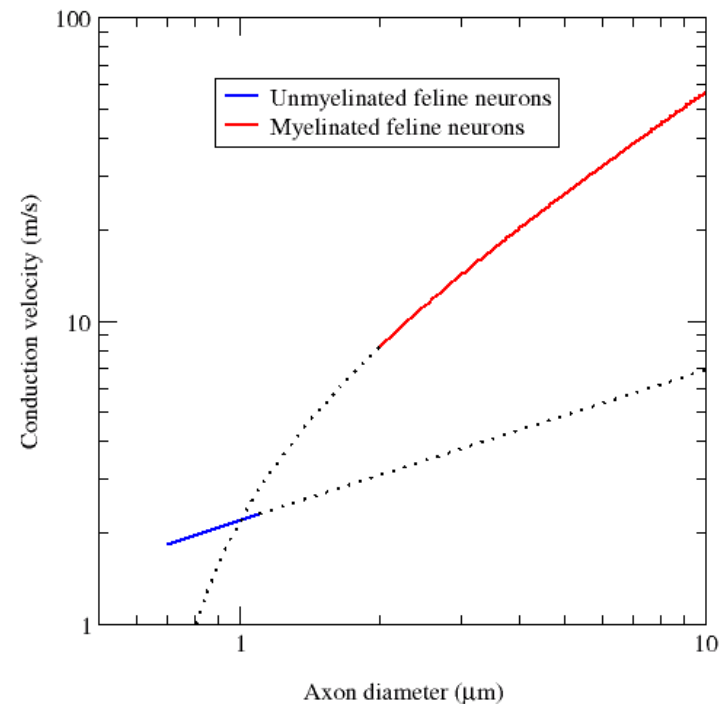
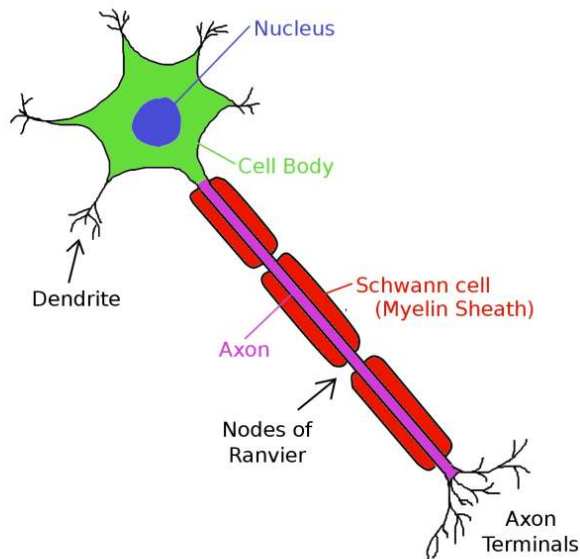
Axons of neurons are protected by a myelin sheath that are formed by glial cells: Schwann cells in the peripheric nervous system, and oligodendroglia cells in the central nervous system. They help the action potential (and the information) spread faster.

Action potential propagation on myelinated axons can be 10 times faster than on unmyelinated axons. The reason is that the myelin sheath does not allow current flow, so it can take place only on nodes of Ranvier, where no myelin sheath protects the cell (called saltatory propagation).

Thus the presence of myelin sheat increases the propagation velocity, which is, in general, proportional with the thickness of the axon.

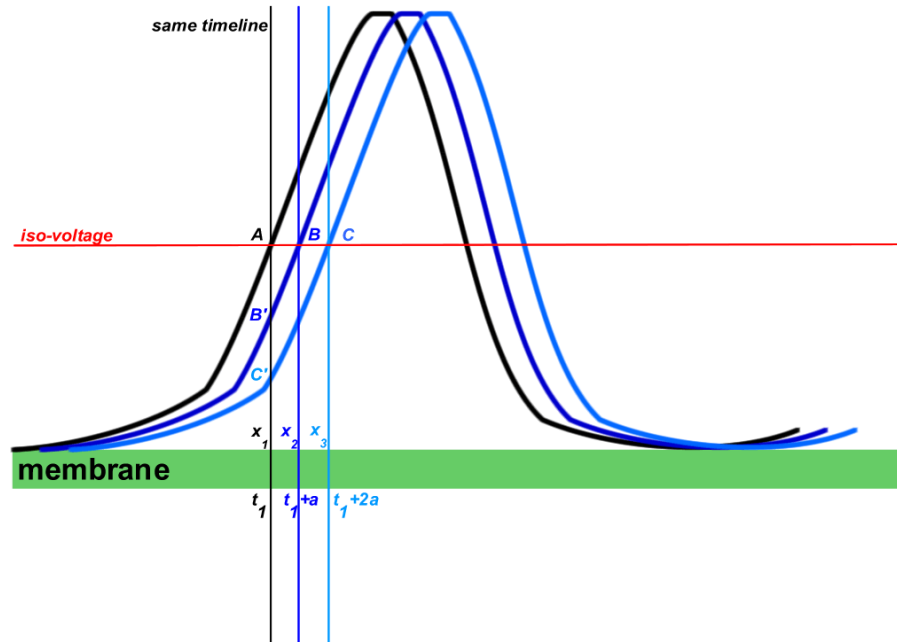
Losing the myelin sheath can cause serious dysfunction in the nervous system, like multiple sclerosis.

PROPAGATION OF ACTION POTENTIALS



(commons.wikimedia.org)

PROPAGATION OF ACTION POTENTIALS



Action potentials generated on the axon hillock propagate through the axon in a wave. The inward current at one node of the axon depolarizes the surroundings of the node, activating the neighbouring voltage-gated ion channels. This results in an inward current at the neighbouring node, causing the spread of depolarization on the axon.

(commons.wikimedia.org)

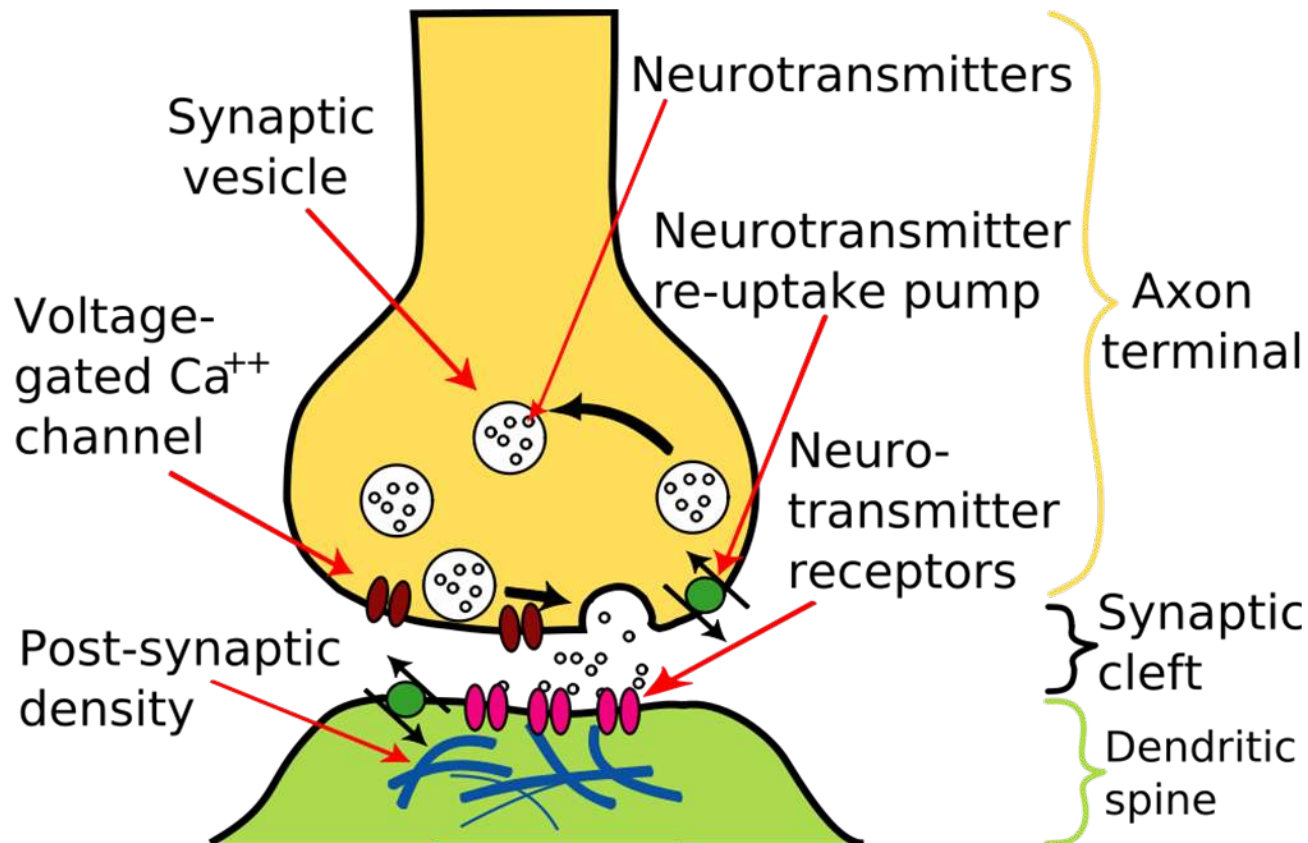
SUMMARY

- Electrochemical basis of action potentials is the ion concentration difference between the two sides of the membrane
- Molecular basis is the voltage-gated ion channel (Na, K)
- Action potential is triggered by membrane depolarization
- Phases: depolarization, repolarization, afterhyperpolarization (AHP)
- Depolarizing phase: membrane depolarization opens Na channel > Na flows in > depolarization > Na channel inactivation
- Repolarizing phase: K channel opens > K flows out > repolarization
- AHP phase: K channel still open > K flows out > afterhyperpolarization

SUMMARY

- All-or-nothing (digital)
- Propagates without amplitude loss
- No summation
- Absolute and relative refractory period
- Can be evoked on axon hillock and along the axon, because voltage-gated channels are located there
- Can not be evoked on the soma and dendrites

SYNAPTIC COMMUNICATION



(commons.wikimedia.org)

FUNCTIONING OF SYNAPSES

- Synaptic vesicles in the presynaptic terminal
- Action potential arrives to the terminal
- Ca flows in through the presynaptic membrane
- Initiates exocytosis
- Synaptic vesicle dump neurotransmitters into the synaptic cleft
- Neurotransmitters diffuse to the receptors on the postsynaptic cell
- Ion channel opens
- Postsynaptic potential is generated on the postsynaptic membrane
- Neurotransmitter is broken down or re-uptaken

TYPES OF POSTSYNAPTIC POTENTIALS

EXCITATORY PSP (EPSP):

V_m depolarizes

AP chance increases

INHIBITORY PSP (IPSP):

V_m hyperpolarizes

AP chance decreases

EXCITATORY

NEUROTRANSMITTERS:

Depolarizes

Opens Na, Ca (K) channel

Glutamate, Ach, etc...

INHIBITORY

NEUROTRANSMITTERS:

Hyperpolarizes

Opens Cl or K channel

GABA (gamma-amino butyric acid)

POSTSYNAPTIC

RECEPTORS:

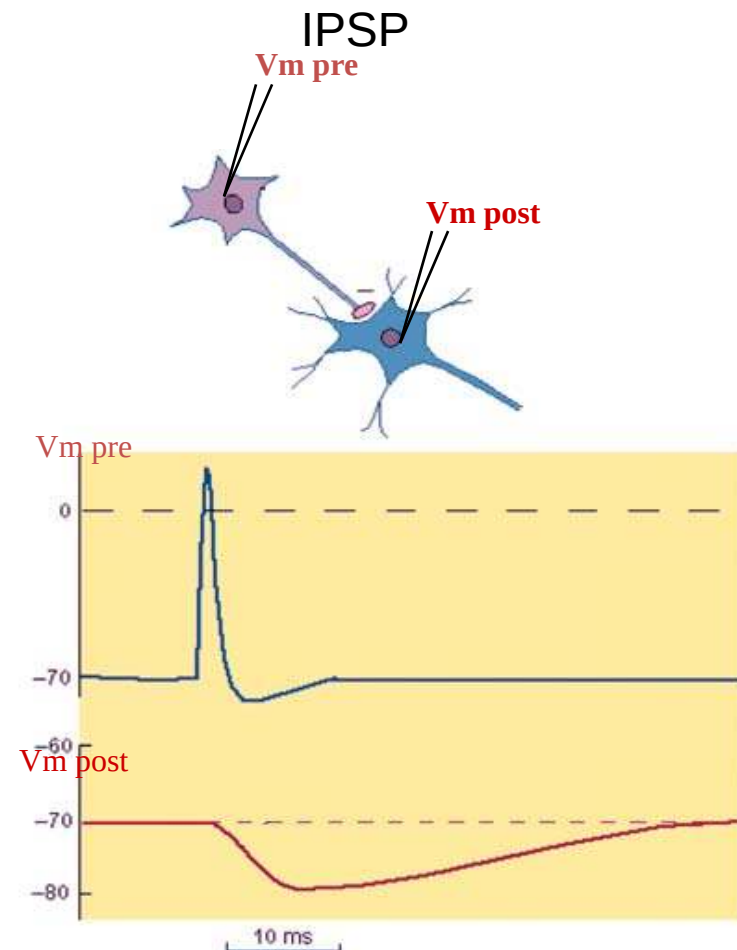
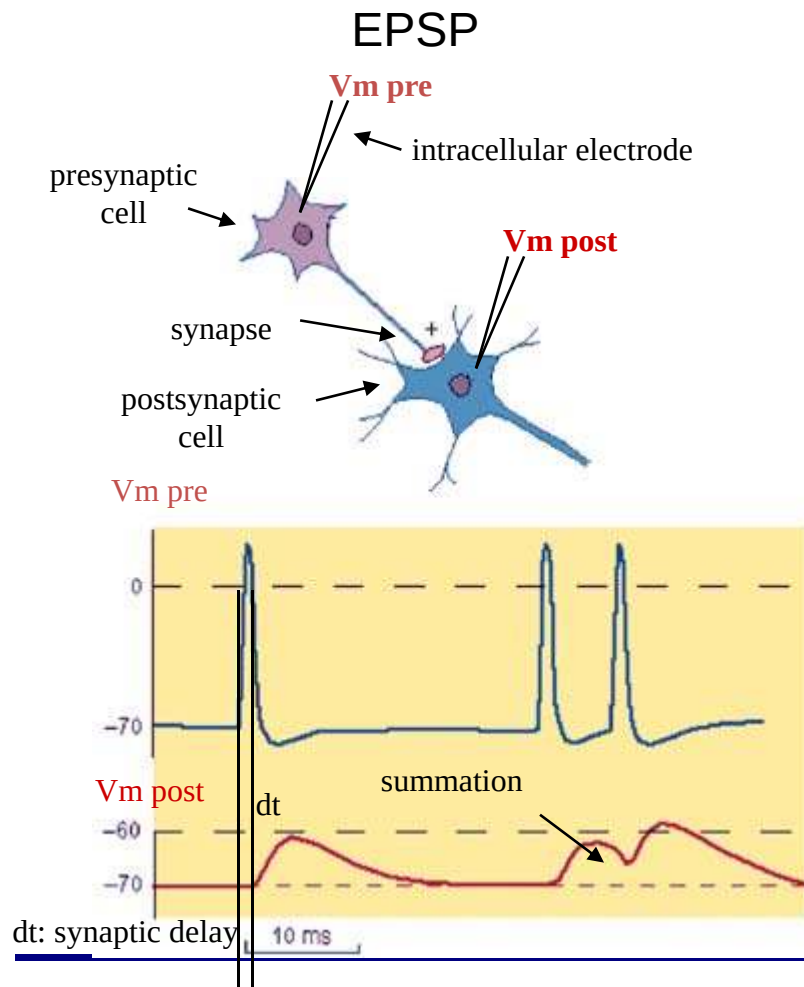
AMPA, kainate

POSTSYNAPTIC

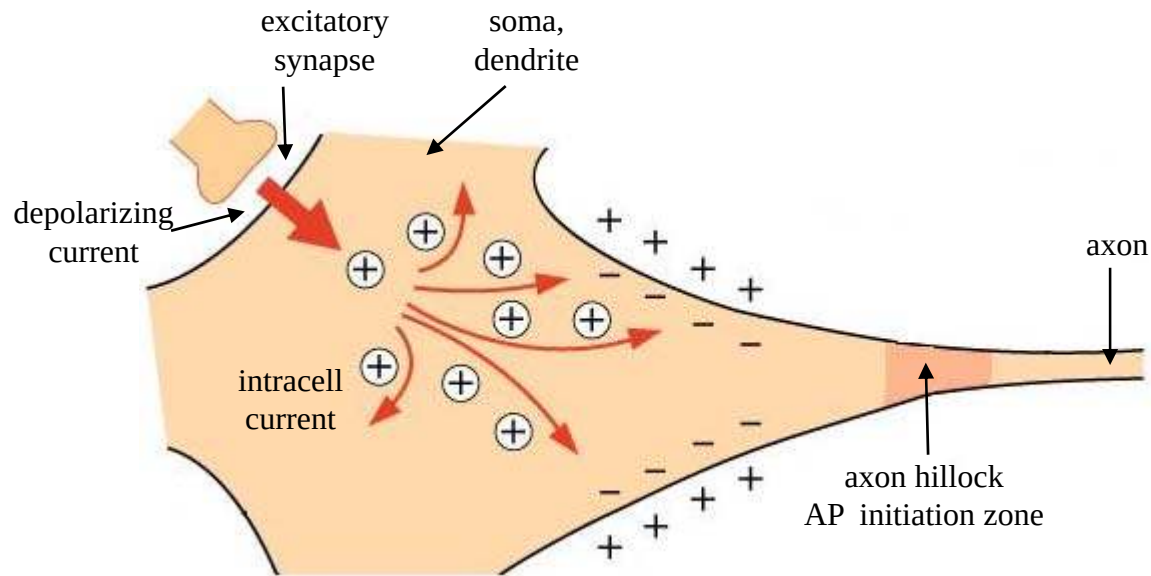
RECEPTORS:

GABA_A, GABA_B

MEASURING POSTSYNAPTIC POTENTIALS



POSTSYNAPTIC POTENTIALS AND ACTION POTENTIALS



POSTSYNAPTIC POTENTIALS AND ACTION POTENTIALS

- Synapses are usually located on dendrites or on the soma
- They do not have voltage-gated ion channels, can not initiate AP
- AP is initiated on axon hillock or on the axon
- Depolarizing or hyperpolarizing current flows in intracellular space
- One synapse has small effect in initiation zone
- AP generation usually requires several EPSPs
- IPSP sums in time and space with EPSP
- IPSP decreases chance of AP generation

POSTSYNAPTIC POTENTIALS AND ACTION POTENTIALS

Postsynaptic pot.	Action potential
Generated on soma and dendrites	Generated on axon hillock
Propagates with loss	Propagates without loss
Summation	No summation
Analog	Digital (all-or-nothing)
Propagation speed: 50000 m/s	Propagation speed: 0.1 – 100 m/s

SUMMARY

- Chemical synapses
- Presynaptic device (axon terminal): AP > Ca flows in > neurotransmitter release
- Postsynaptic membrane: neurotransmitter > receptor > PSP
- Excitatory PSP (EPSP) depolarizes
- Inhibitory PSP (IPSP) hyperpolarizes
- EPSP > Na/Ca channel (glutamate) > Na/Ca flows in > depolarization > increases chance of AP
- IPSP > Cl channel (GABA) > Cl flows in > hyperpolarization > decreases chance of AP

SUMMARY

- Most synapses on soma and dendrites
- AP initiation on axon hillock
- PSPs propagate electrotonically (analog, fast, with loss)
- Summation in time and space
- The potential on the axon hillock (created by summed EPSPs and IPSPs) decides AP generation
- Creates basis of neuronal information processing

LINKS

AP propagation & Synapse:

<http://www.youtube.com/watch?v=90cj4NX87Yk>

Action potential:

http://mcb.berkeley.edu/courses/mcb64/action_potential.html

Resting potential:

<http://bcs.whfreeman.com/thelifewire/content/chp44/4402001.html>

Action potential:

<http://bcs.whfreeman.com/thelifewire/content/chp44/4402002.html>

<http://trc.ucdavis.edu/biosci10v/bis10v/week10/06potential.html>

<http://www.blackwellpublishing.com/matthews/channel.html>

<http://www.ywpw.com/cai/software/hhsimu/>

Synaptic transmission:

<http://bcs.whfreeman.com/thelifewire/content/chp44/4402003.html>

<http://trc.ucdavis.edu/biosci10v/bis10v/week10/06synapse.html>

REFERENCES

Don L. Jewett, Martin D. Rayner: *Basic Concepts of Neuronal Function*, Little, Brown, and Company, Boston, 1984.

Michael J. Zigmond, Floyd E. Bloom, Story C. Landis, James L. Roberts, Larry R. Squire: *Fundamental Neuroscience*, Academic Press, 1999.

REVIEW QUESTIONS

- What phases does an action potential have?
- What is the ion channel activity in each phase?
- What is the change of conductance of channels during the action potential?
- What is the refractory period?
- How do action potentials propagate?
- How do chemical synapses function?
- What are the types of postsynaptic potentials?
- What are the membrane constants?
- What are the differences between action potentials and postsynaptic potentials?