Circuits and Signals: Biological Applications, Bio-potentials, ECG and Instrumentation Requirements

Based on materials from Prof. Mark Niedre and Prof Dana Brooks

References

- *“Medical Instrumentation: Application and Design” John G. Webster 4th Edition*
- *“Biomedical Transducers and Instruments” Togawa, Tamura and Oberg*
- *“Molecular Biology of the Cell, 5th Edition”*
- *Alberts, Johnson, Lewis, Raff, Roberts*

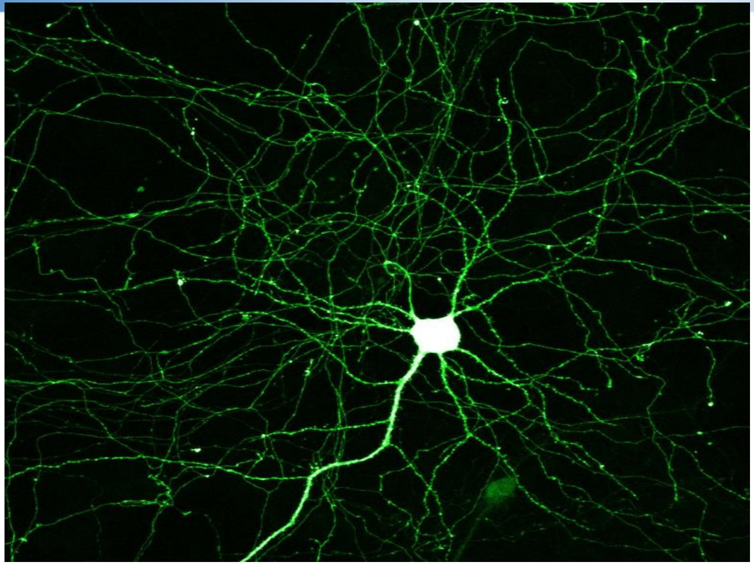
The Nervous System

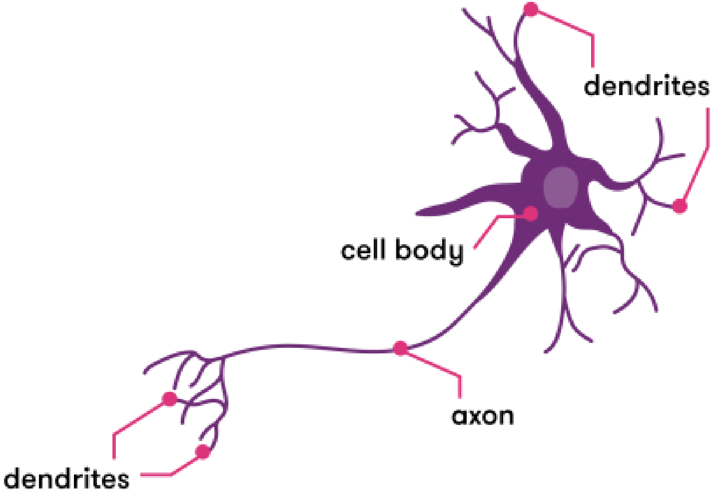
- "The task of controlling the various functions of the body and coordinating them into an integrating living organism is not simple. Consequently, the nervous system, which is responsible for this task, is the most complex of all systems in the body… Composed of the brain, numerous sensing devices, and a high speed communication network that links all parts of the body, the nervous system not only influences all the other systems but is also responsible for the behavior of the organism… Behavior includes the ability to learn, remember, acquire a personality, and interact with its society and the environment. It is through the nervous system that the organism achieves autonomy and acquires the various traits that characterize it as an individual"

  - Biomedical Instrumentation and Measurements

  L. Cromwell, F. Weibell, E. Pfeiffer

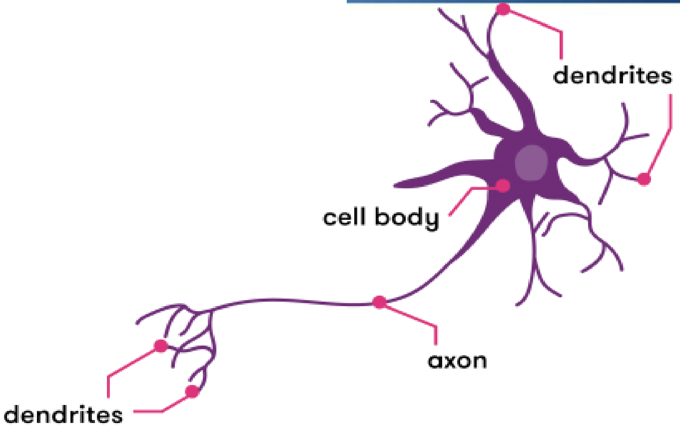
Neurons are the basic unit of the nervous system:





- Neurons are highly specialized nerve cells are responsible for communicating information throughout the body in both chemical and electrical forms.
- Different types of neurons are responsible for different tasks in the human body.
- Sensory neurons carry information from the sensory receptor cells throughout the body to the brain. Motor neurons transmit information from the brain to the muscles of the body.

Useful Terminology



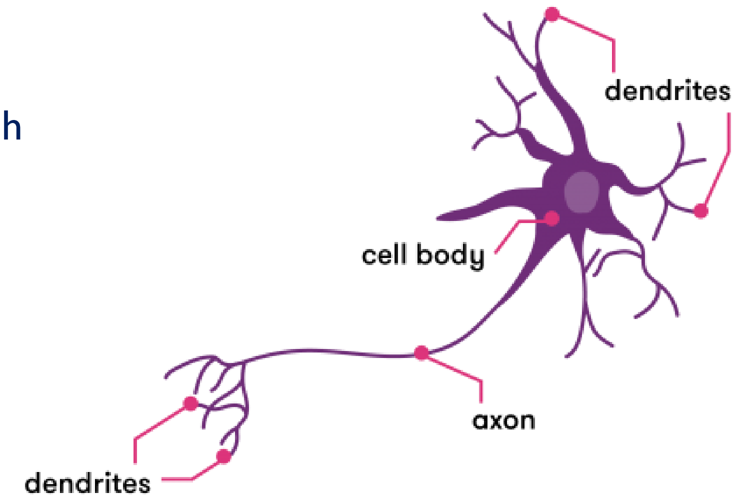
- Dendrites are "inputs"
- Axons are "outputs"
- Axons and dendrites are both nerve fibers
- A bundle of nerve fibers is called a nerve
- Axons connect to dendrites at **synapses**, uni-directional excitation
- A synapse is a complex membrane junction or gap
- Generally several axons are connected to a dendrite

Neurons are the basic unit of the nervous system:

- Every neuron maintains a voltage gradient across its membrane, due to concentration differences in ions of sodium, potassium, chloride and calcium within the cell, each of which has a different charge. If the voltage changes significantly, an electrochemical pulse called an action potential (or nerve impulse) is generated.

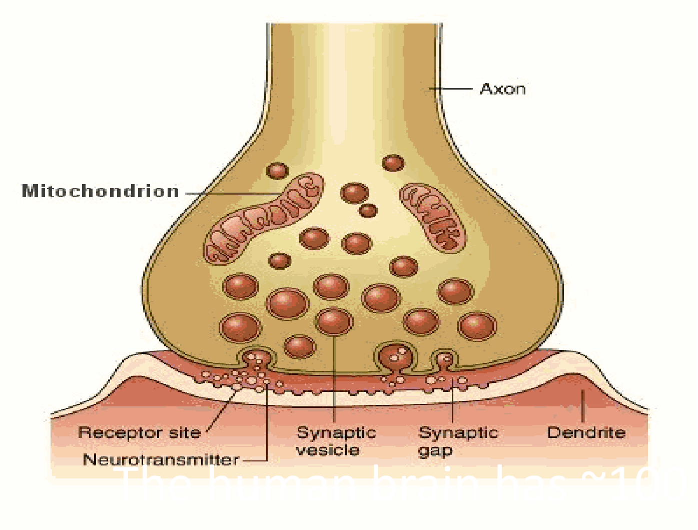
- The action potential pulse travels along the cell's axon, and is transferred across a specialized connection known as a **synapse** to a neighboring neuron, which receives it through its dendrites.

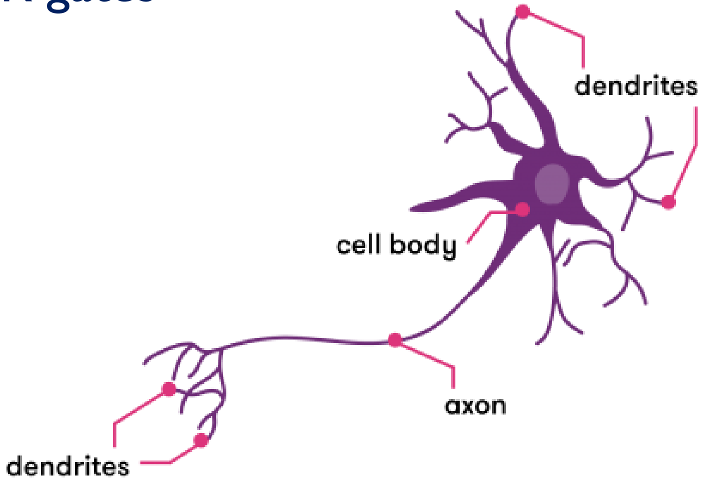
- Dendrites receive chemical signals from other neurons, which are then converted into electrical impulses that are transmitted toward the cell body.



Synapse: Neural-neural junction

- Chemical junction between axon and dendrite
- Electrochemical transmission occurs via neurotransmitters (inhibitory and excitory). Causes ~0.5-1ms delay
- Can behave like multi-input AND, OR, NOR gates

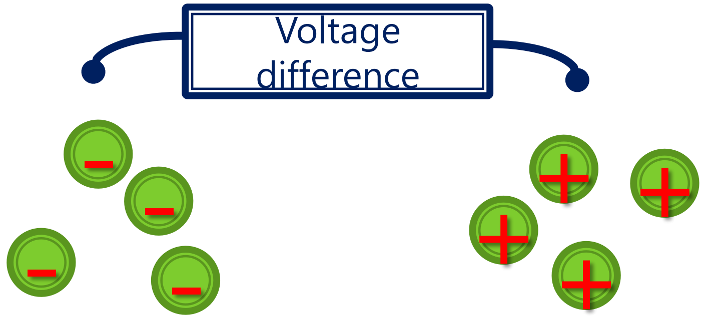




Basis of cellular potentials

- The electrical potential difference between the inside of a cell and the surrounding extracellular fluid is termed membrane potential and is used to code and transmit information
- An electric potential difference exists between two locations is there is a separation of charges
- A nerve or a muscle at rest has a resting

Membrane potential of -70 mV, the inside of the cell has a negative voltage relative to the extracellular fluid

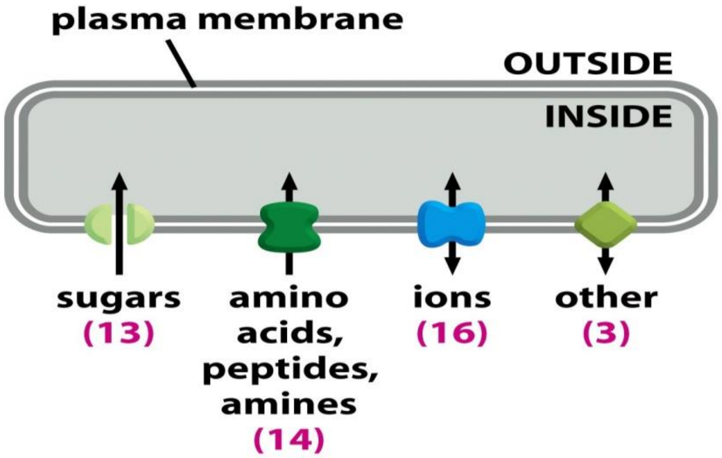


The basis of cellular potentials

- Neurons do not use electrons to carry current, but carry ***ionic*** current
- Cell membrane is a thin lipoprotein (lipid bi-layer) complex surrounding the cell that tightly controls movement of ions and nutrients in and out of the cell
- The important ions responsible for

  establishing membrane potential

  are **K^+**, **Na^+** and **Cl^-**.



An excitable cell (neuron) is in either resting or active state:

- **Resting Potential:** Steady electrical potential difference across the cell membrane. In a resting cell, the concentration of N_a^+ is much higher outside the cell than inside, K^+ is much higher inside, but the presence of –vely charged protein ions keeps a negative potential of the inside of the cell relative to the outside Typically between -50 to -100 mV relative to the external medium. Because of the potential difference across the membrane, the membrane is said to be polarized.

- If the membrane potential becomes more positive than the resting potential, the membrane is said to be depolarized, when it become more negative, it's said to be hyperpolarized.

What changes ion concentration across the cell membrane

- Baseline ion (Na^+, K^+, Cl^-) concentration differentials inside and outside of the cell are maintained through a combination of:
  - Diffusion due ionic concentration gradients
  - Electric field gradients
  - Membrane pores / permeability
  - Active transport of ions through cell membrane channels
- Note that the transport of ions across the membrane by diffusion or by an electric field gradient can be in opposite directions. Controlled changes of the cell membrane permeability to a particular ion (such as Na^+ or K^+) will also change ion concentration across the cell membrane and consequently the membrane potential

Calculation of the membrane potential

- The membrane potential can be calculated by using the **Goldman-Hodgkin-Katz equation (GHK equation)**.
- The relative contribution of any given ion is determined not only by its concentration gradient across the plasma membrane, but also by its relative membrane permeability.
- Permeability is a measure of the ease with which ions cross the membrane, and is directly proportional to the total number of open channels for a given ion in the membrane. Permeabilities can be reported as relative permeabilities with p_K (permeability for Potassium)having the reference value of one

Goldman-Hodgkin-Katz equation

- $E = \frac{RT}{F} \ln \left[\frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o} \right]$
  - ***R*** is the universal gas constant (8.314 $J.K^{-1}.mol^{-1}$).
  - ***T*** is the temperature in Kelvin (K = °C + 273.15).
  - ***F*** is the Faraday's constant (96485 $C.mol^{-1}$).
  - ***p*** is the membrane permeability in (m/s). Permeability of the ion can also be given as relative permeability with P_K having the reference value of one
  - $[\boldsymbol{ion}]_o$ is the concentration of ion in the extracellular fluid
  - $[\boldsymbol{ion}]_i$ is the concentration of ion in the intracellular fluid
  - concentration units for all the ions must match.

Frog muscle neuron

- Using the "Goldman-Hodgkin-Katz equation", we can calculate the membrane potential (the equilibrium potential) based on the K, Na and Cl concentrations inside and outside the cell.

e.g. frog muscle neuron

Species:	Intracellular Conc (mmol/L)	Extracellular Conc. (mmol/L)	Permeability (P, cm/s)
Na^+	12	145	2e-8
K^+	155	4	2e-6
Cl^-	4	120	4e-6

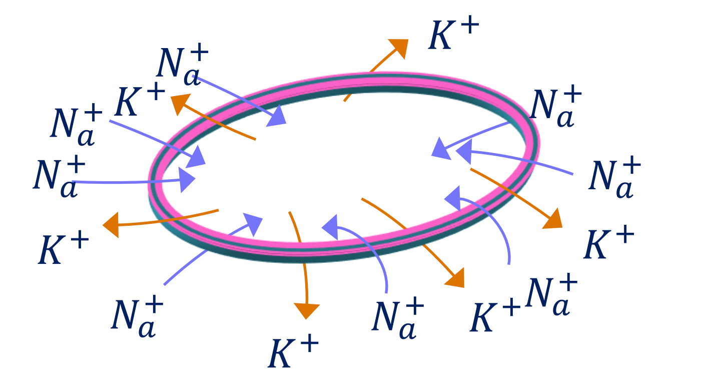
$$\boxed{\approx -85mV}$$

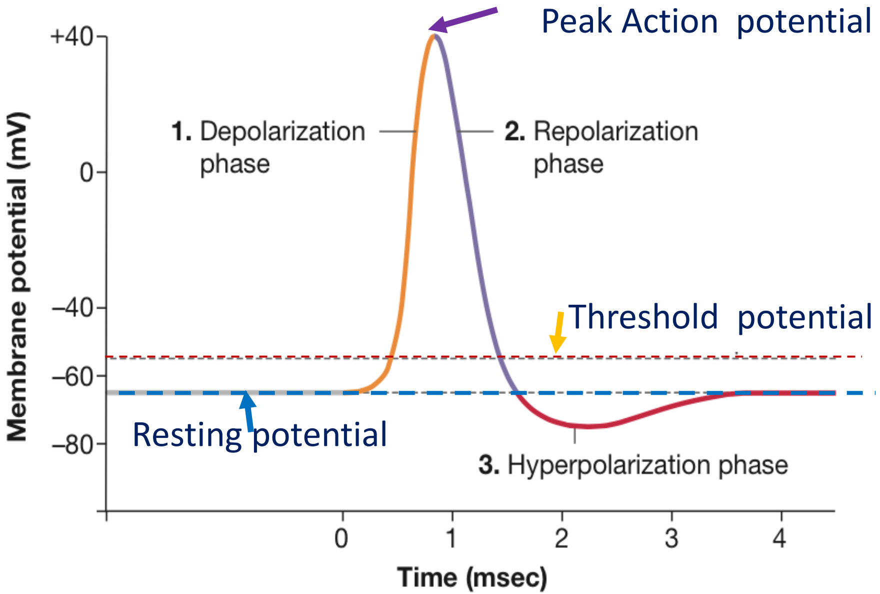
Action Potentials

- Excitable cells (nerve cells and muscle cells) have the ability to generate an action potential.
- An action potential, is a transient (short lasting) reversal in the membrane potential that is conducted down the length of the fiber
- An action potential can be triggered chemically, electrically or mechanically. The most common(natural) is chemically with chemicals called neurotransmitters.

Action Potentials ("De-polarization"; "Spikes")

- Electrical response to adequate stimulation. consists of "all-or-none" action potential after the cell threshold potential has been reached
- Requires activating potential (100mv for 1ms)
- Transient changes in membrane permeability to
  1. Na^+ ions, allowing sodium ions in and increasing membrane potential(depolarization)
  2. K^+ ions rush out of the cell reducing membrane potential to its resting potential, notice also the under shoot

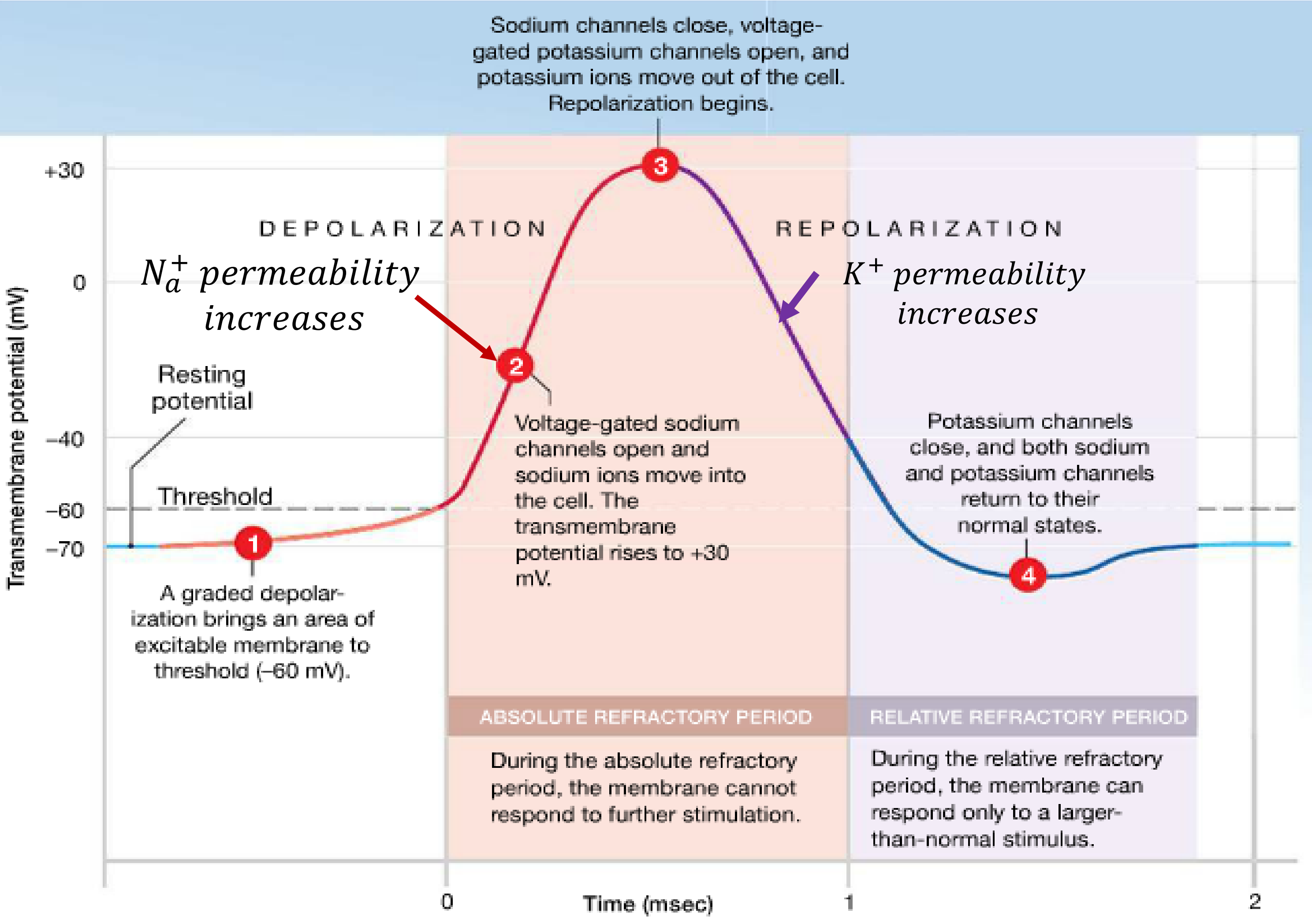




Action Potentials ("De-polarization"; "Spikes")

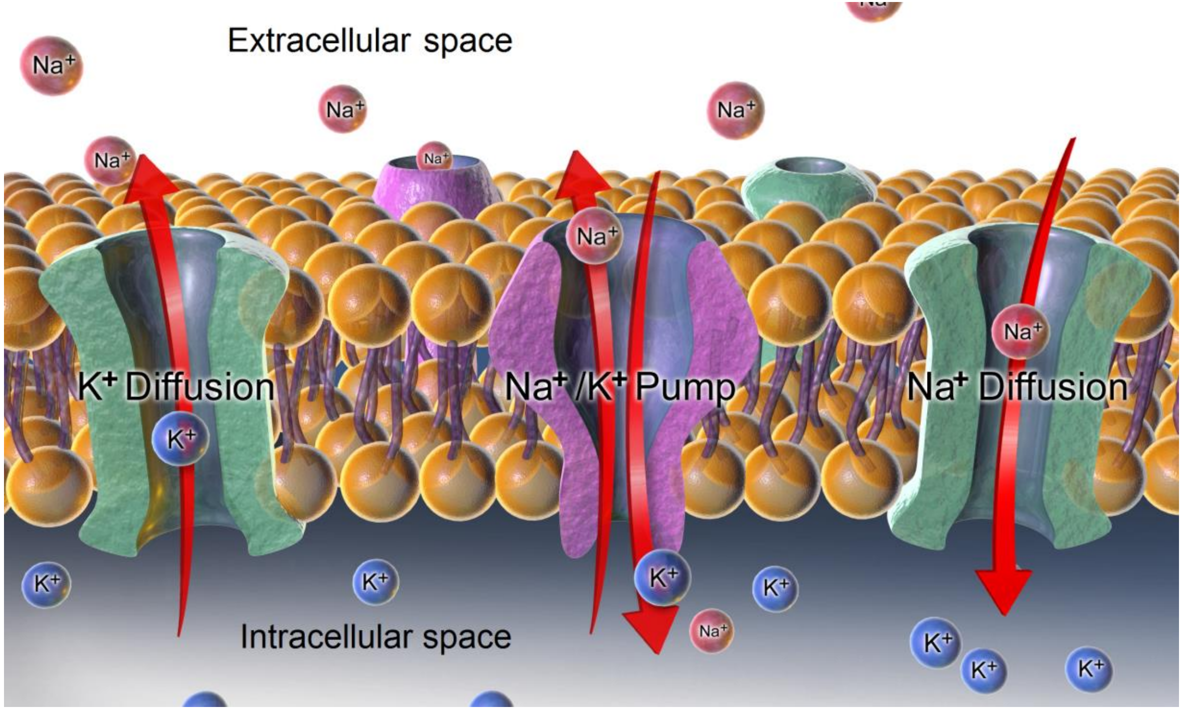
- The stimulation of the cell by neurotransmitters partially opens channel-shaped protein molecules in the membrane. Sodium diffuses into the cell, due to the concentration. The diffuse of Na^+ causes the membrane potential to become less negative. When the potential reaches the threshold potential (measuring about −60 mV), then sodium channels open completely. Depolarization activates sodium channels in adjacent parts of the membrane, so that the impulse moves along the fiber
- When the membrane potential reaches up to +30mV, the Na^+ ion channels close and become unresponsive to the voltage
- So how does the cell repolarize back? With the inside of the cell at a positive potential relative to the outside, a set of voltage-gated potassium channels open, allowing potassium to rush out of the cell due to the concentration gradient and electric field gradient. This will rapidly decrease the membrane potential, bringing it back towards its normal resting state.

In response to stimulus (initial depolarization), the membrane becomes transiently more permeable to Na+ and K+



Restoring the Membrane potential

- **During repolarization, as** potassium ions exit the cell, lowering the potential of the inside of the cell, the membrane potential is lowered to the resting level but with different chemicals than when the stimulus occurred. Originally there was high concentration of N_a^+ outside and high concentration of K^+ inside.
- Na+/K+ ATP(Adenosine triphosphate) pump, is used to recover the cell resting concentration of N_a^+ and K^+
- In order to move the ions (Na+ and K+) against their concentration gradients, energy is required. This energy is supplied by ATP molecule (adenosine triphosphate). ATP loses one phosphorous atom and is converted into ADP (adenosine diphosphate). Energy stored in the chemical bond is released and used to move sodium out of cells while pumping potassium into cells.
- Transport that uses ATP for energy is referred to as **active transport**

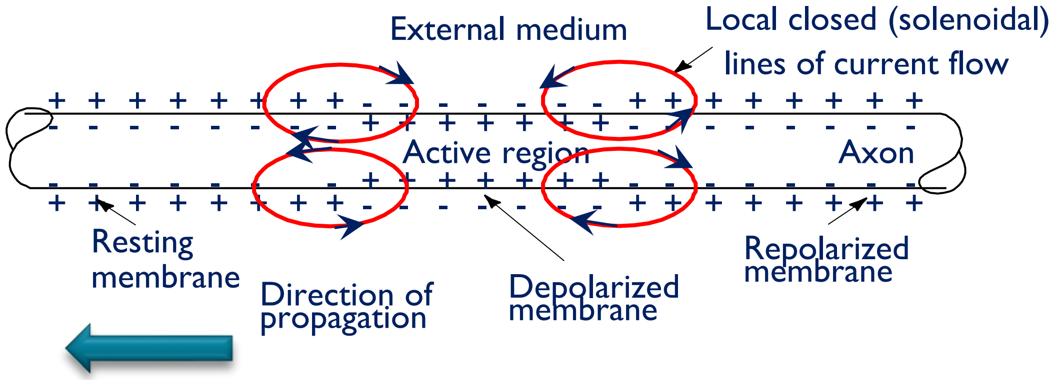

Extracellular space
Na+
K+ Diffusion
Na+ /K+ Pump
Na+ Diffusion
K+
Intracellular space

Myelinated versus non myelinated Neurons

- Myelinated neuron: The neuron whose axon is covered by myelin sheath . The myelin sheath insulates the axon and inhibits current leakage through the plasma membrane. This allows the current to travel the long distances between nodes without decaying below threshold level. For this reason, conduction of nerve impulse is faster in this neuron than non-myelinated neuron.
- Non-myelinated,: The neuron whose axon is not covered by myelin sheath. The conduction of nerve impulse in this neuron is slower than myelinated neuron

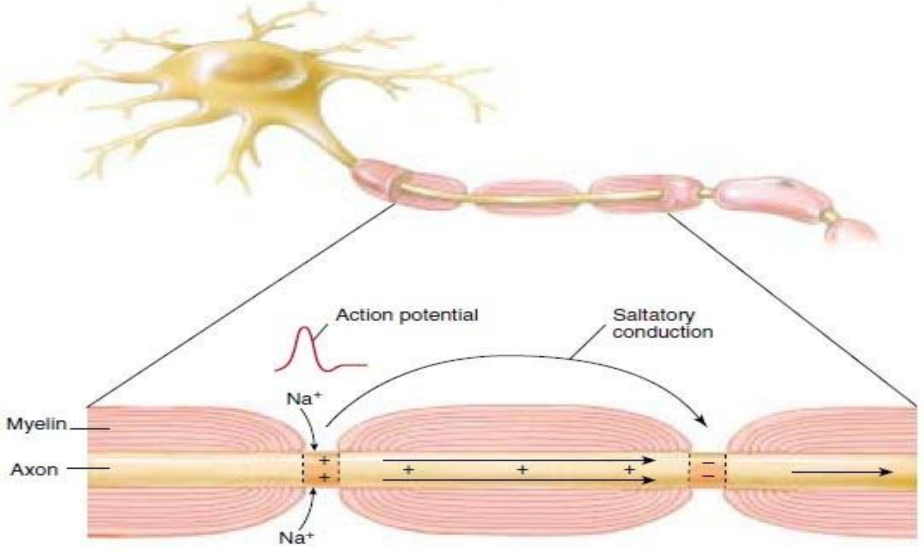
Conduction of an impulse in un-myelinated nerve

- **un-myelinated nerve: (most invertebrates)*
- Nerve cells conduct an action potential along the membrane of a cell
- Area undergoing depolarization is small relative to the axon (“active region”)
- Because of refractory period, potential can only propagate in one direction



Conduction of an impulse in myelinated nerve (most vertebrates)

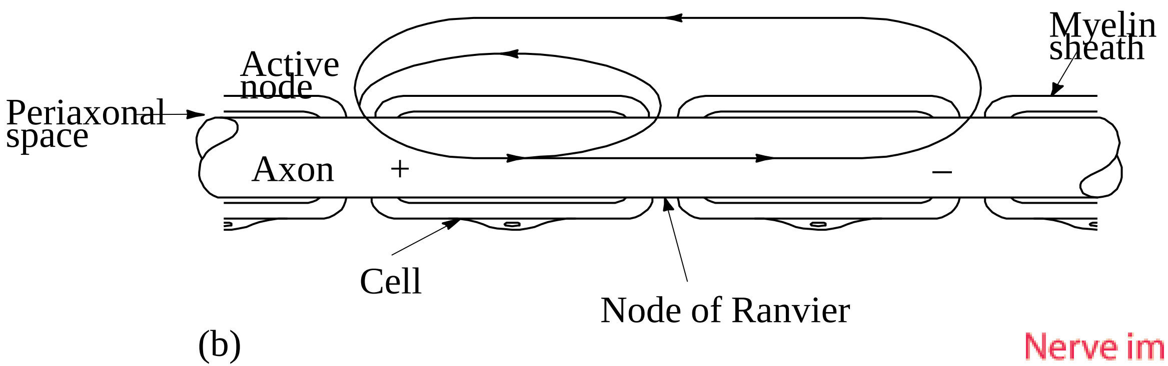
- The myelin sheath prevents the local current from flowing across the membrane. This forces the current to travel down the nerve fiber to the unmyelinated nodes of Ranvier, which have a high concentration of ion channels.
- Passive current develops due to attractions between oppositely charged ions in the adjacent nodes which triggers an action potential in the next node while the previous node repolarizes



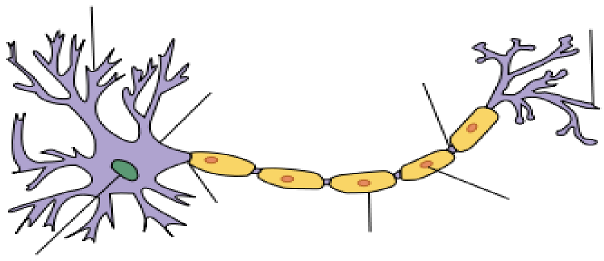
Saltatory conduction allows an action potential to propagate along the axon of a neuron at rates significantly higher than without the myelination of the axon

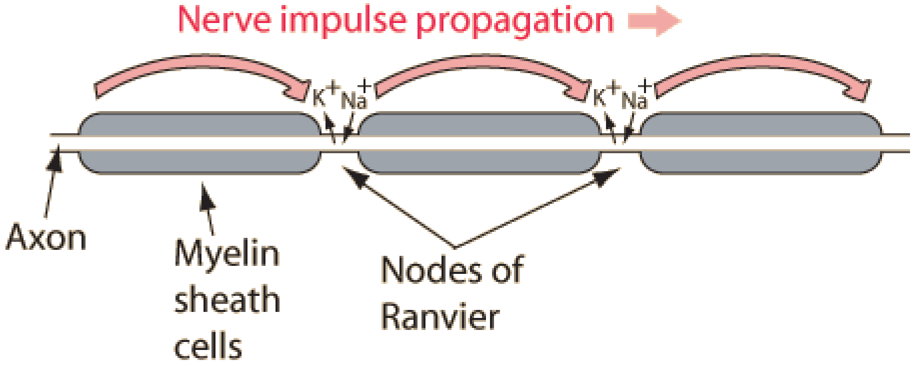
Conduction of an impulse in myelinated nerve (most vertebrates)

myelinated nerve: (most vertebrates)

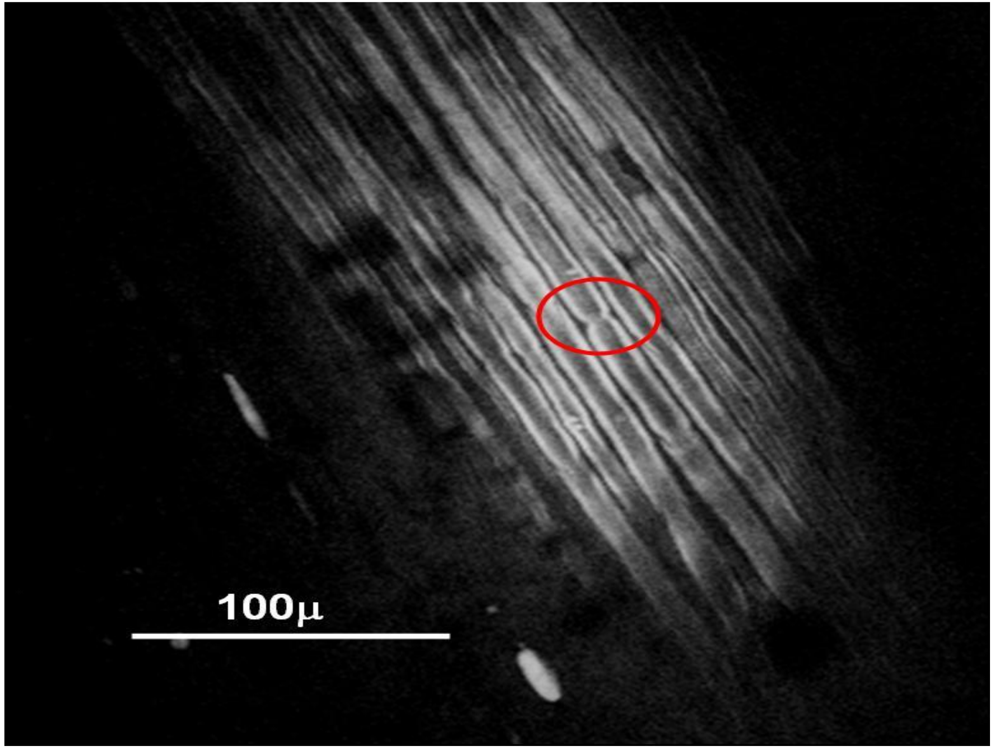


- Thus, the action potential jumps along the fiber as it is regenerated at each node. This type of conduction is called c conduction





Myelination – Rat Spinal Cord



Source: Prof. Daniel Cote Laval University
CARS Microscopy Image

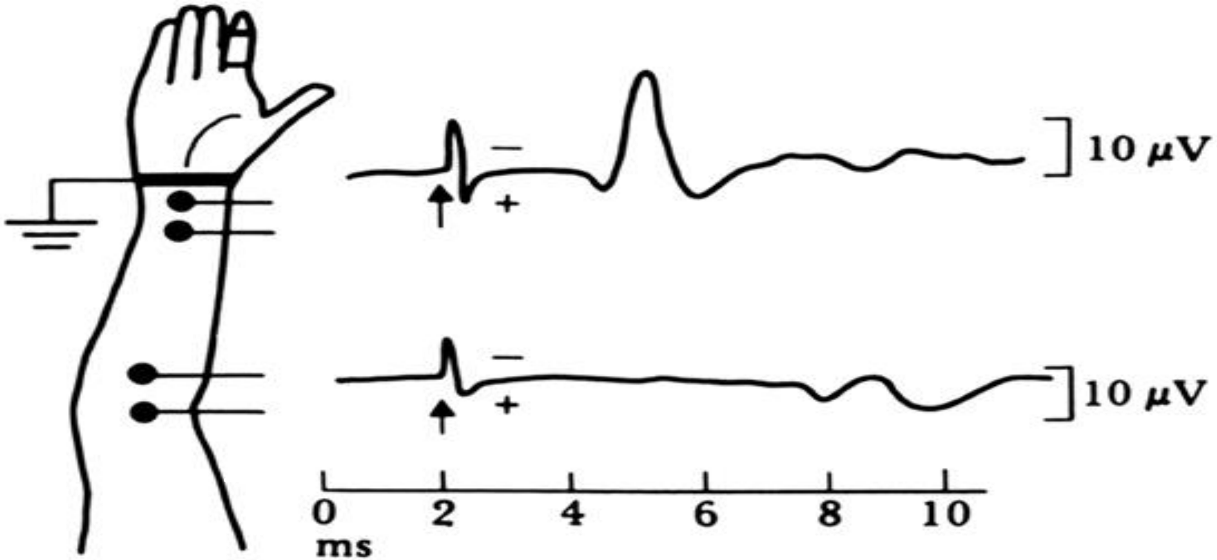
Measuring bio-potentials from the surface of the body ("zooming out")

What is an Electrocardiogram

- The electrocardiogram or ECG (sometimes called EKG) is a relatively simple way of diagnosing heart conditions.
- An electrocardiogram is a recording of the small electric signals being generated during heart activity.
- In the heart there are cells specialized in producing electric signals. These are called pacemaker cells.
- If the whole heart muscle contracted at the same time, there would be no pumping effect. Therefore the electric activity starts at the top of the heart and spreads down, and then up again, causing the heart muscle to contract in an optimal way for pumping blood.

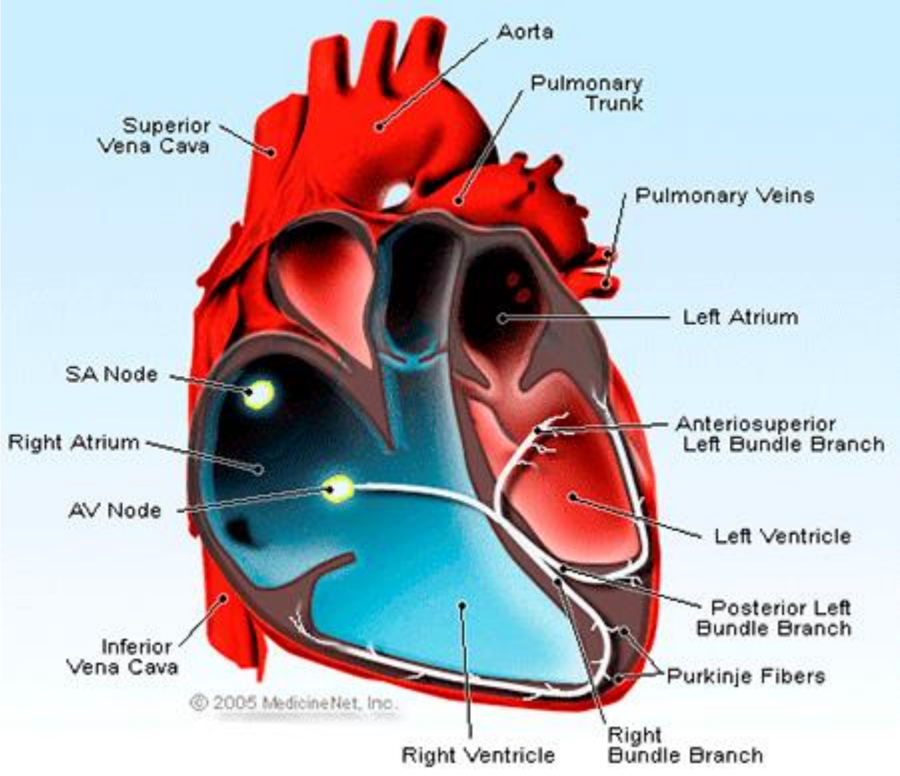
The simplest example: Electro Neurogram (ENG)

- Stimulation of median nerve
- detection of potential at wrist and elbow positions



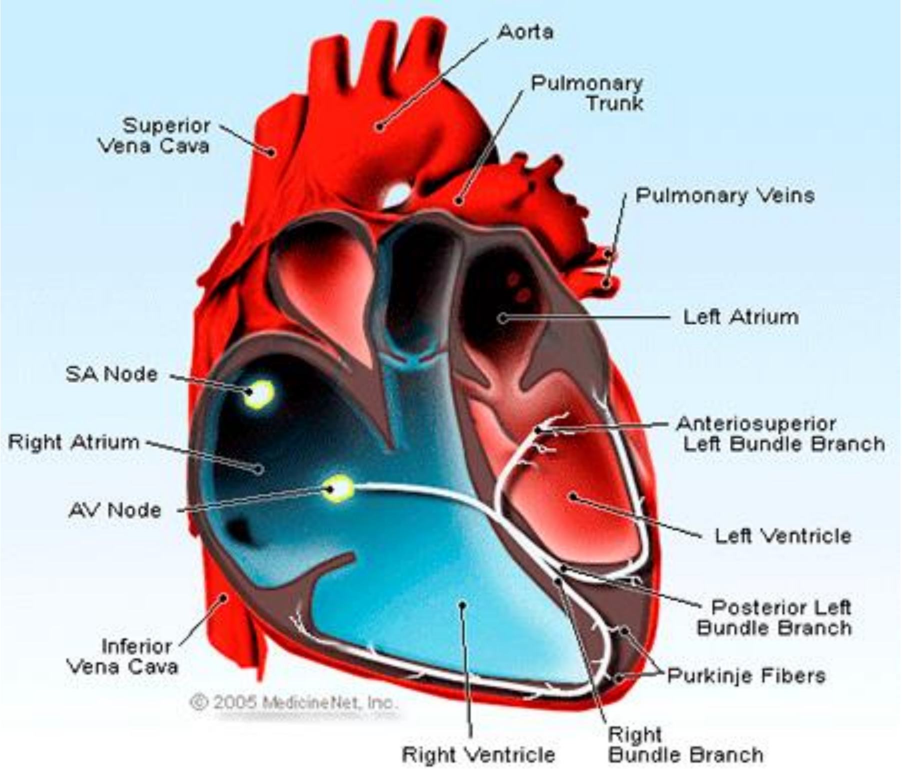
Normal function of the heart

- The heart has four chambers. The upper two are the atria, and the lower two chambers are the ventricles.
- The atria deliver blood to the ventricles, and the ventricles deliver blood to the lungs and to the rest of the body.
- The heartbeat (pulse) that we feel is caused by the contraction of the ventricles.
- The heartbeat is normally controlled by the electrical system of the heart. Formed by the sinoatrial node (SA) atrioventricular (AV) node and special tissues in the ventricles that conduct electricity.

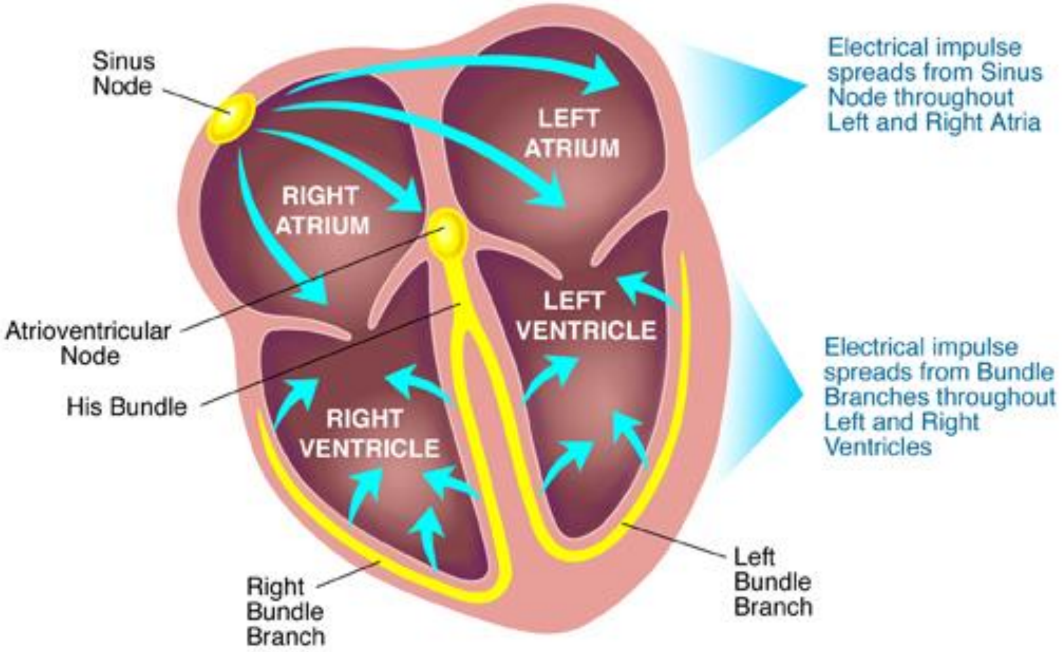


Electric Impulses in the heart

- The sinoatrial (SA) node initiates the electrical signal responsible for the heart beat
- The SA node is the heart's electrical pacemaker.
- It is a small patch of cells located in the wall of the right atrium;. The SA node keeps the heart beating in a regular manner. At rest, the frequency of the electric impulses originating from the SA node is low, and the heart beats at the lower range of normal (60 to 80 beats/minute).

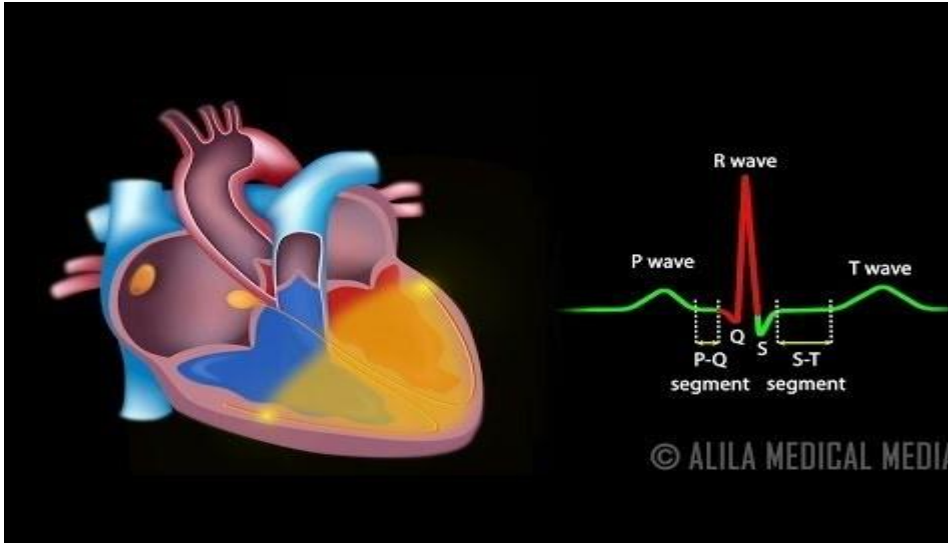


Specialized Conductive Tissues in the Heart

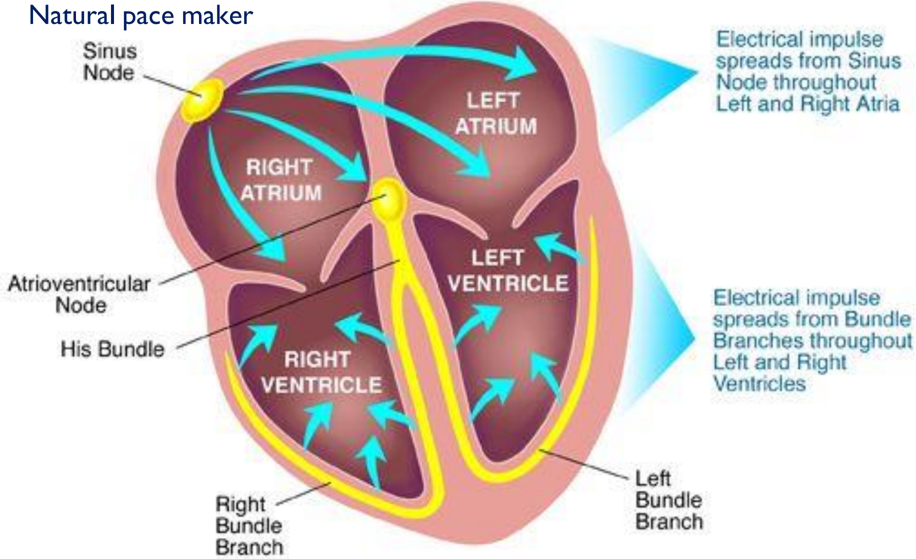


- Cardiac impulse starts at sinoatrial node (atrial depolarization)
- Travels via anterior, middle, and posterior internodal tract to atrioventricular (AV) node(delay line)
- Through the Bundle of His, through ventricle tissue (ventricular depolarization)

Cardiac Conduction System and Understanding ECG, Animation



Natural pace maker



Measuring Electrical activity of the Heart (EKG)

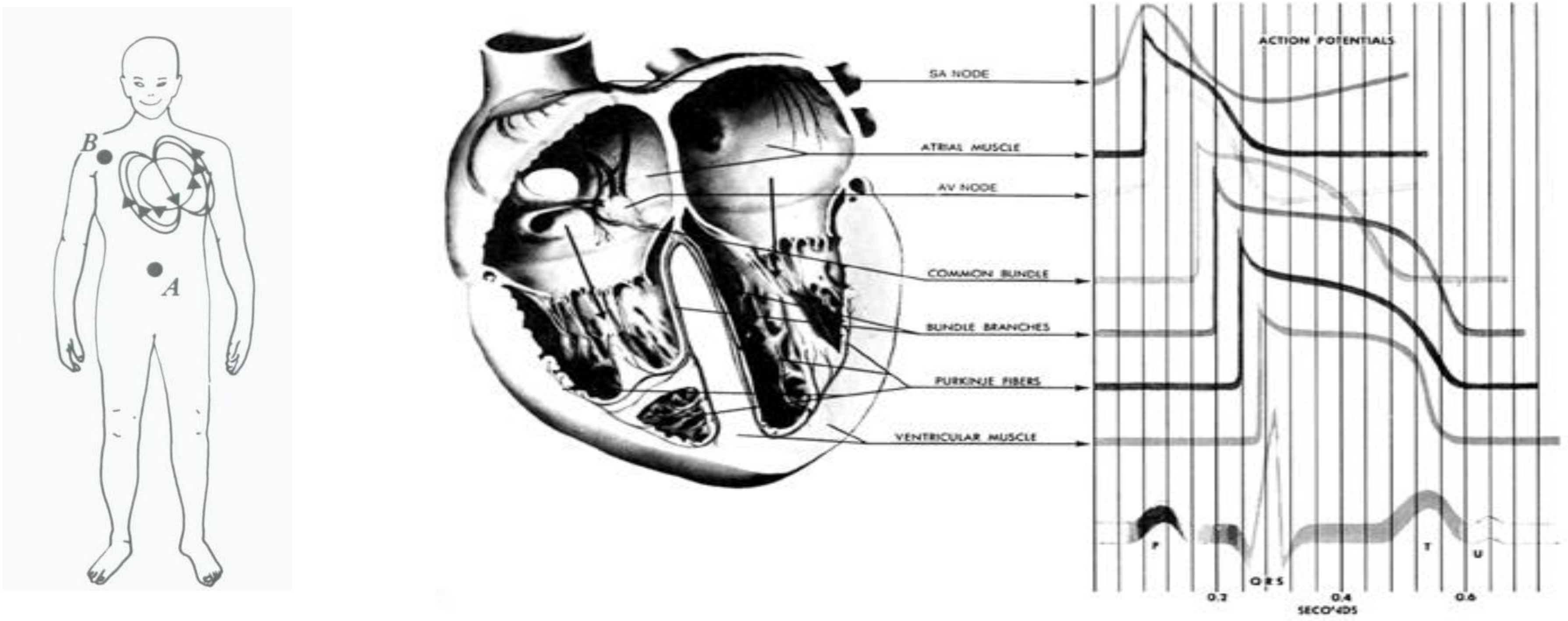
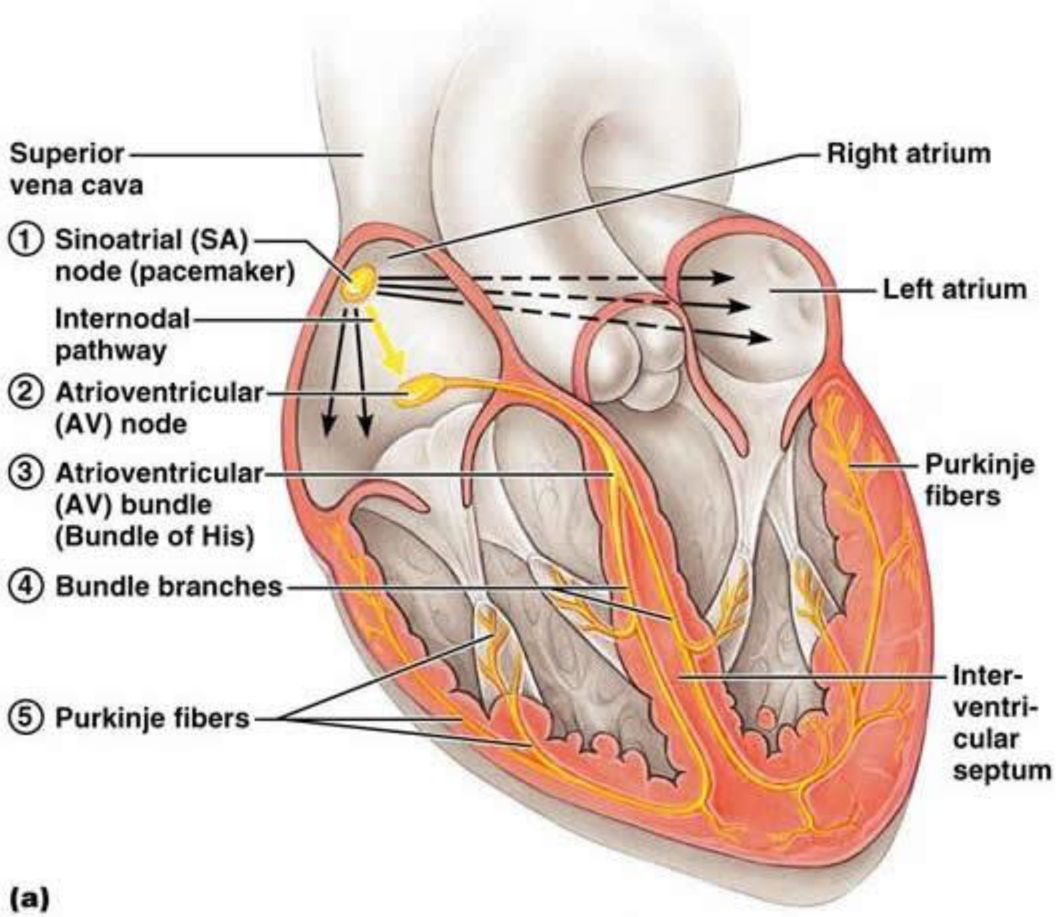
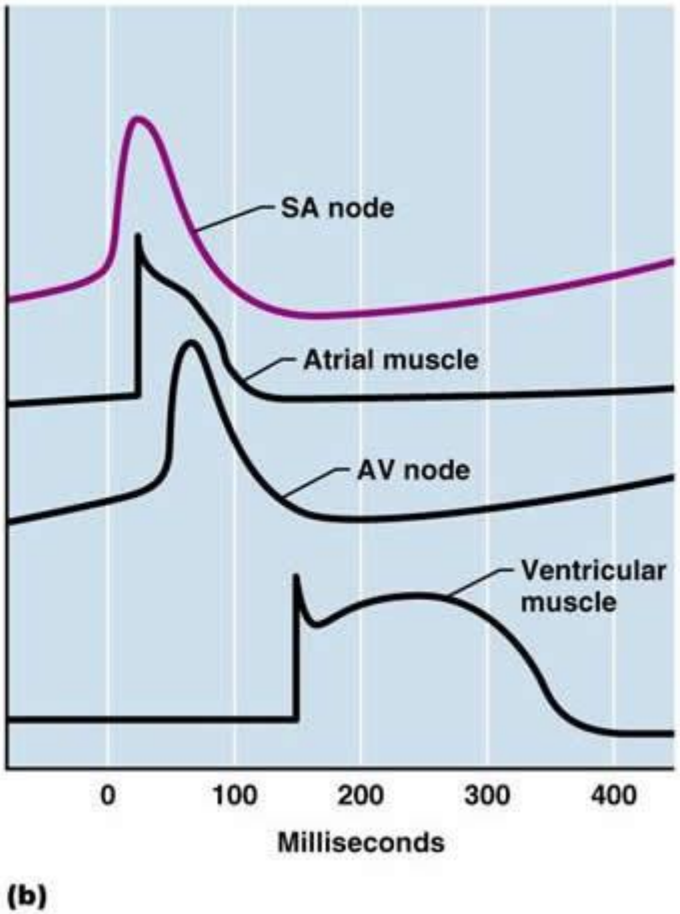


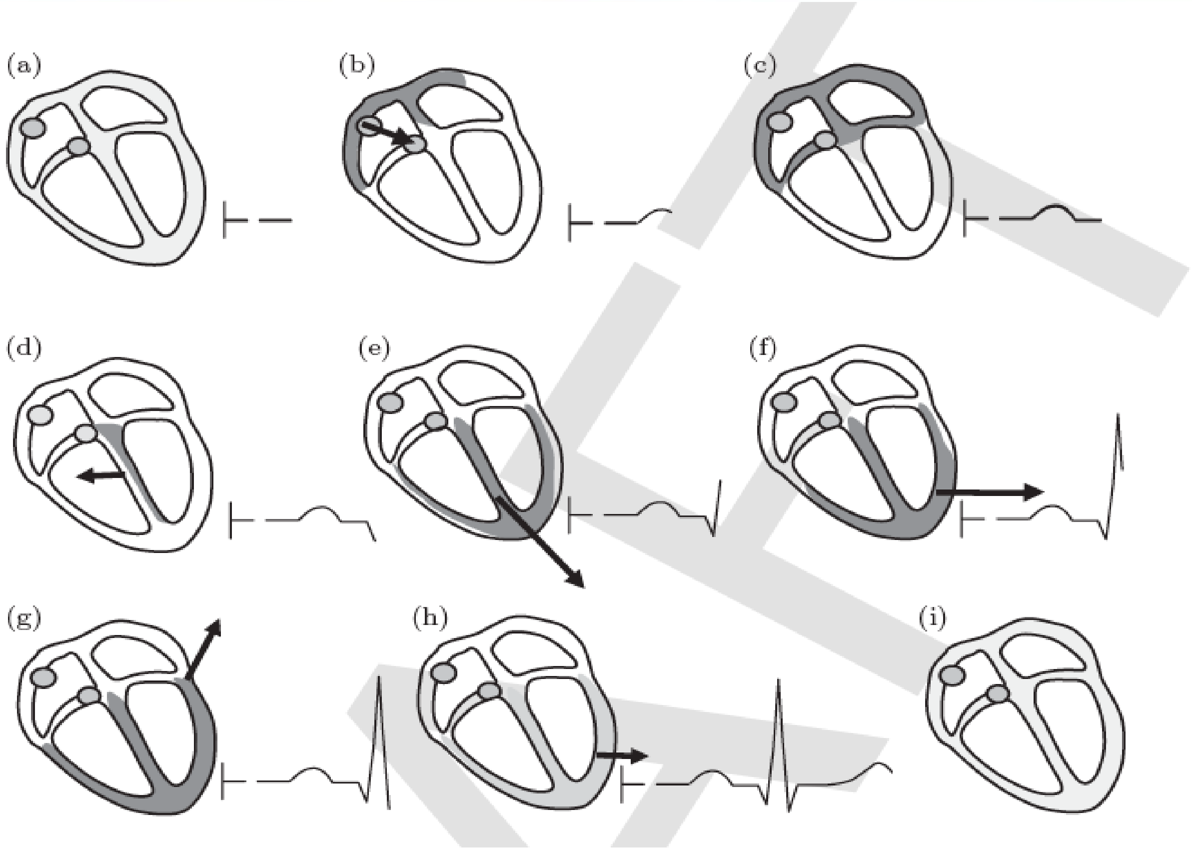
Figure 4.13 Representative electric activity from various regions of the heart. The bottom trace is a scalar ECG, which has a typical QRS amplitude of 1-3 mV. (© Copyright 1969 CIBA Pharmaceutical Company, Division of CIBAGEIGY Corp. Reproduced, with permission, from The Ciba Collection of *Medical Illustrations*, by Frank H. Netter, M. D. All rights reserved.)



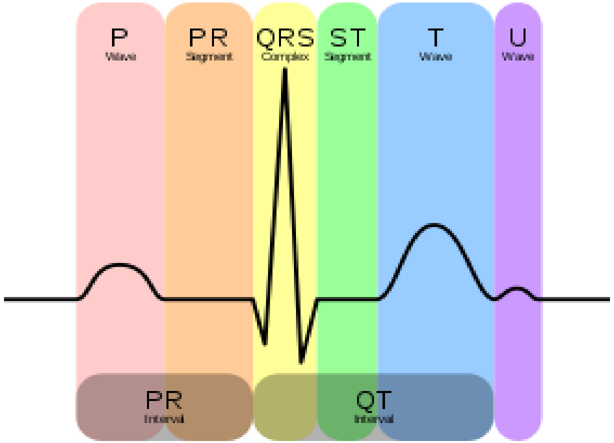
Superior vena cava
① Sinoatrial (SA) node (pacemaker)
Internodal pathway
② Atrioventricular (AV) node
③ Atrioventricular (AV) bundle (Bundle of His)
④ Bundle branches
⑤ Purkinje fibers
Right atrium
Left atrium
Purkinje fibers
Inter-ventri-cular septum
(a)



SA node
Atrial muscle
AV node
Ventricular muscle
0
100
200
300
400
Milliseconds
(b)


(a)
(b)
(c)
(d)
(e)
(f)
(g)
(h)
(i)

"QRS" Complex in EKG



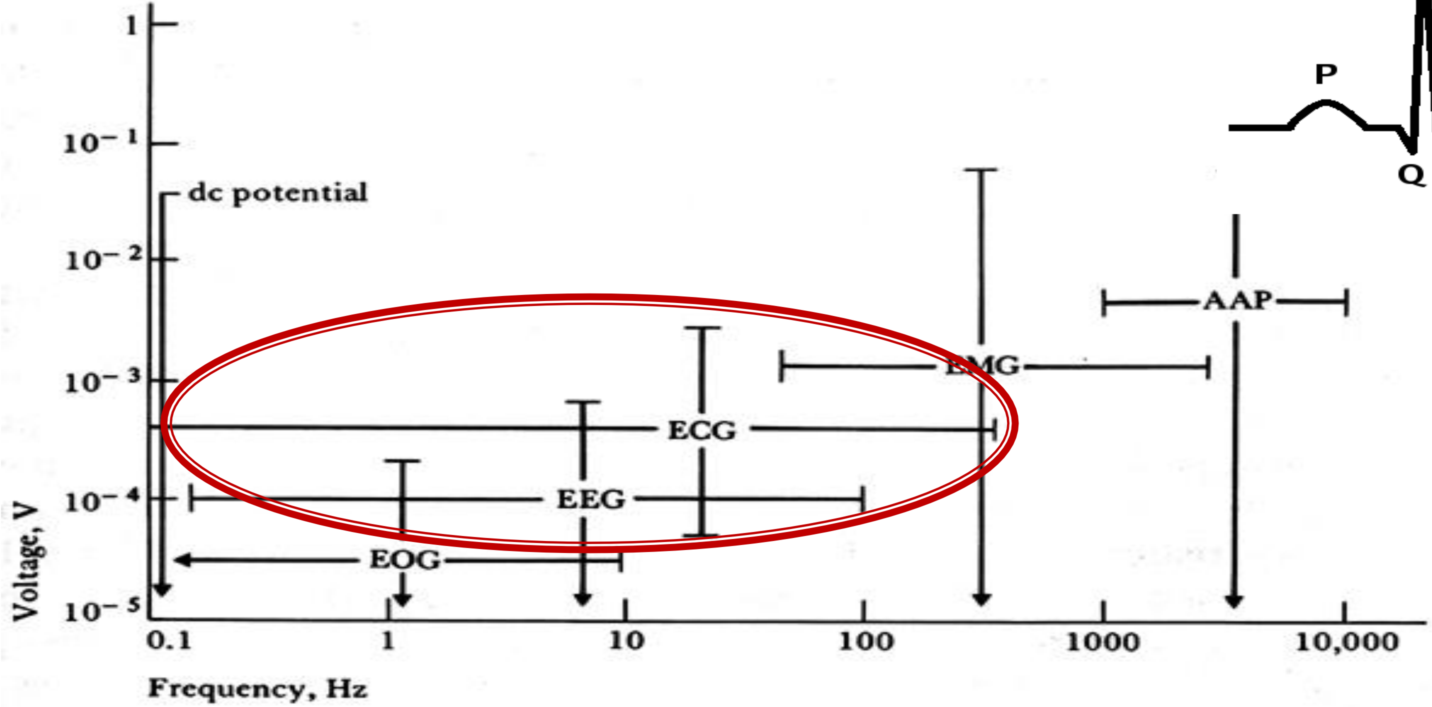
- Typical values:
- P-R interval 0.12 to 0.2s
- QT interval 0.25 to 0.44 s
- S-T segment 0.05 to 0.15s
- P wave interval 0.11 s
- QRS interval 0.09s

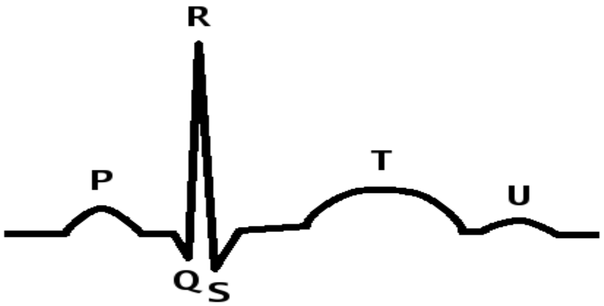
- A scalar quantity which is a summation of the electrical activity in the heart for a given lead (electrode pair)
- P – Atrial depolarization
- QRS - Ventricular depolarization, atrial repolarization
- The T wave represents ventricular repolarization.
- The U wave represents papillary muscle repolarization.
- Magnitude of R-wave is ~100 μV*

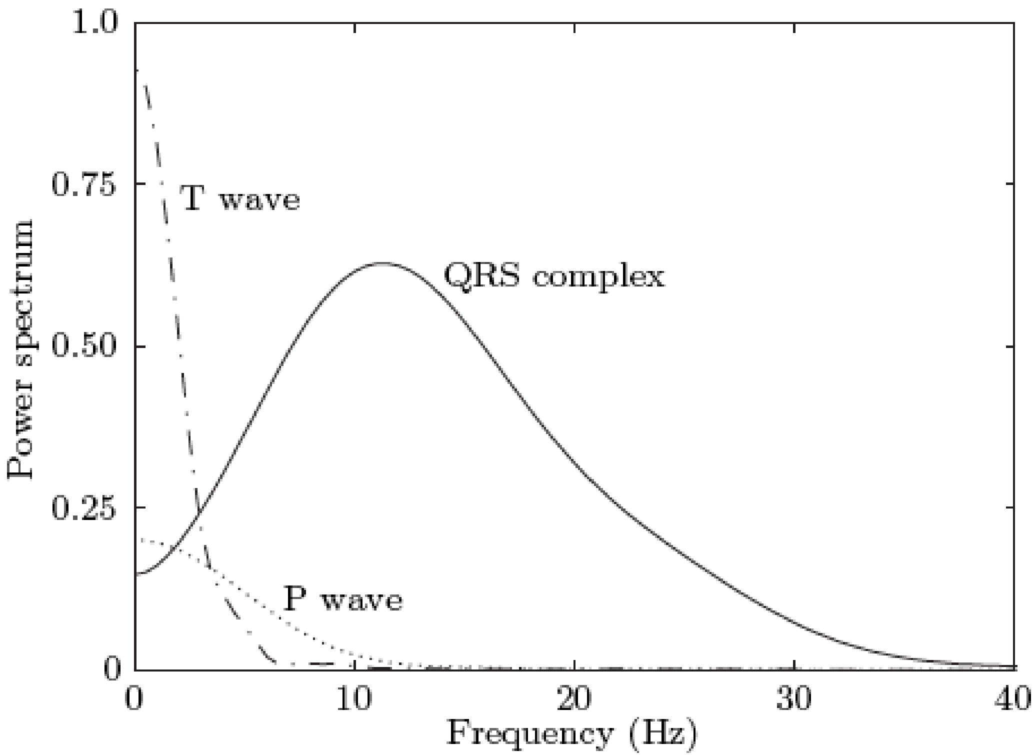
depolarization represent the contraction phase of a heart muscle and repolarization is the relaxation phase.

Frequency / Amplitude of EKG Signal

Frequency Range of Human EKG is 0.1-400Hz



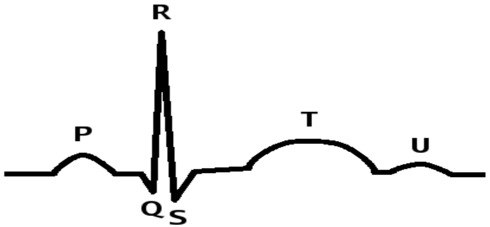




1.0
0.75
0.50
0.25
0
Power spectrum
T wave
QRS complex
P wave
0
10
20
30
40
Frequency (Hz)

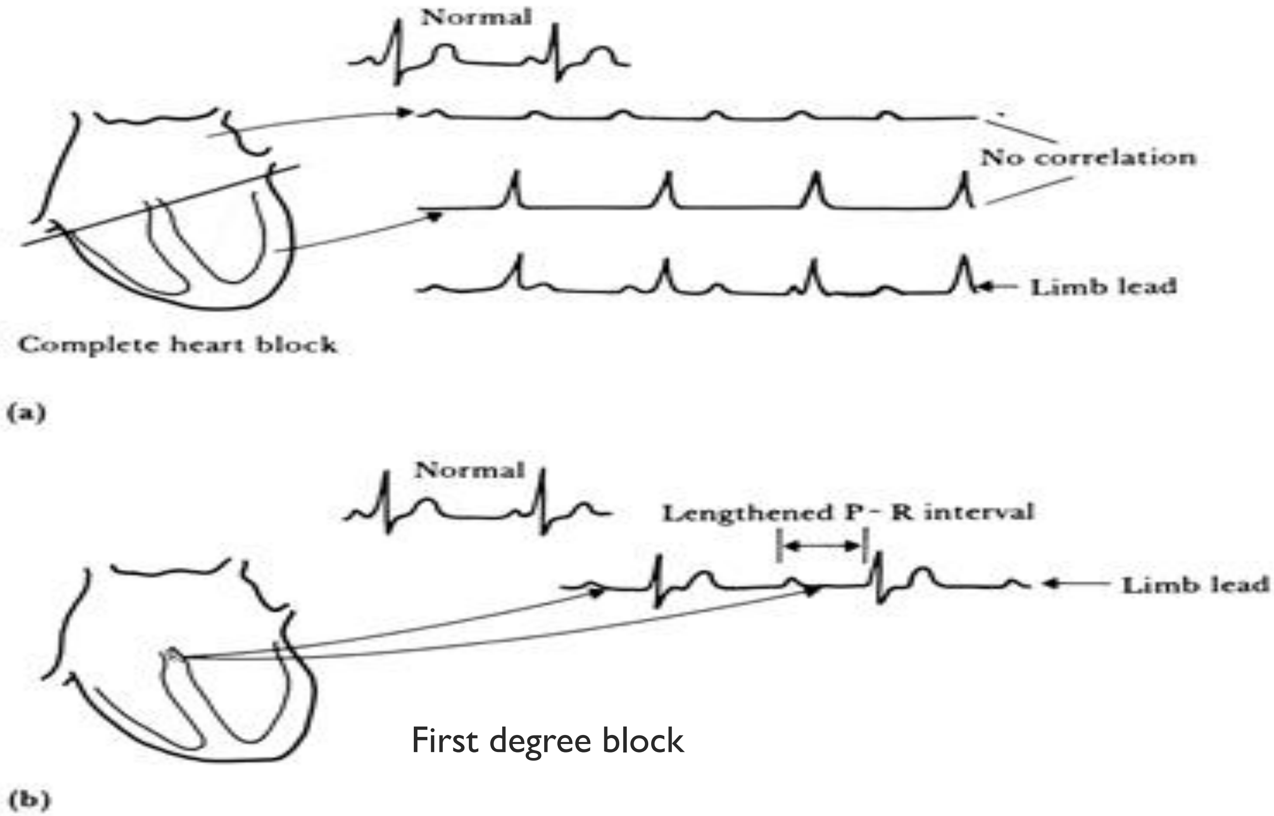
Some examples of abnormalities and how they appear on the ECG

Atrioventricular Block



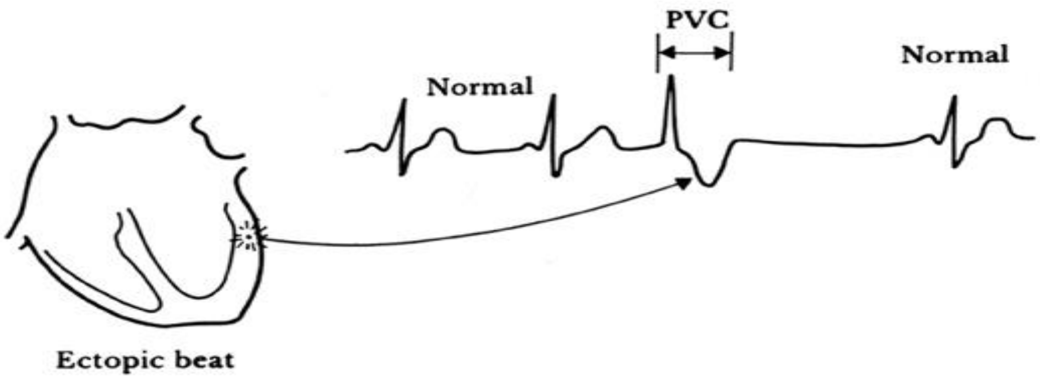
- Atrioventricular (AV) block is partial or complete interruption of impulse transmission from the atria to the ventricles.
- For 1st-degree block, conduction is slowed without skipped beats. All normal P waves are followed by QRS complexes, but the PR interval is longer than normal (> 0.2 sec).
- For second degree, complete but intermittent blocking of pacing impulse Some normal P waves are followed by QRS complexes, but some are not.
- For 3rd-degree block, total and continuous blocking of the impulse there is no relationship between P waves and QRS complexes, and the P wave rate is greater than the QRS rate.

Atrioventricular Block



First degree block

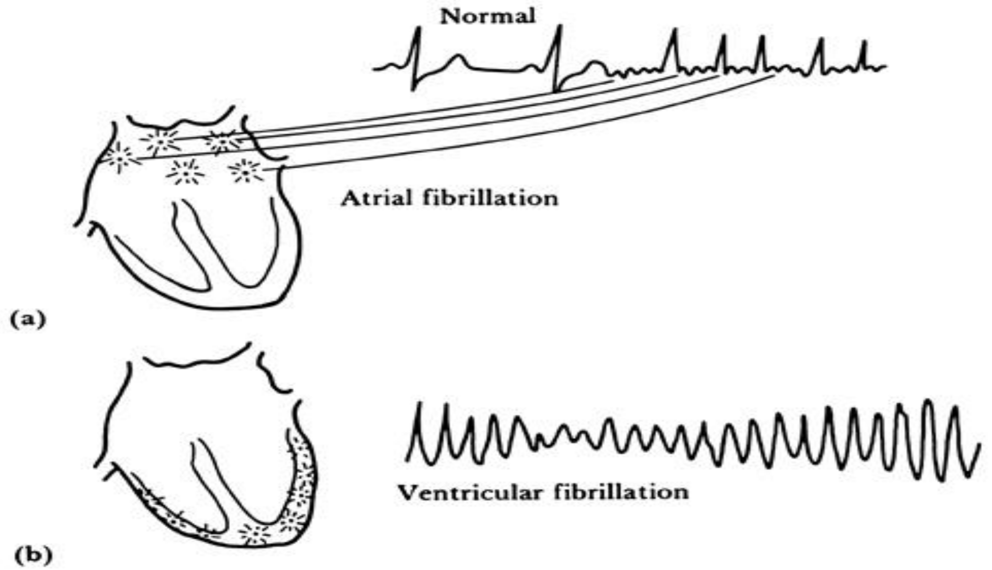
Ectopic Beat (premature ventricular contraction) PVC



Premature ventricular contractions are abnormal contractions that begin in the ventricles. The extra contractions beat sooner than the next expected regular heartbeat. And they often interrupt the normal order of pumping, which begins with the atria, then ventricles. As a result, the extra, out-of-sync beats are usually less effective in pumping blood throughout the body.

Atrial / Ventricular Fibrillation

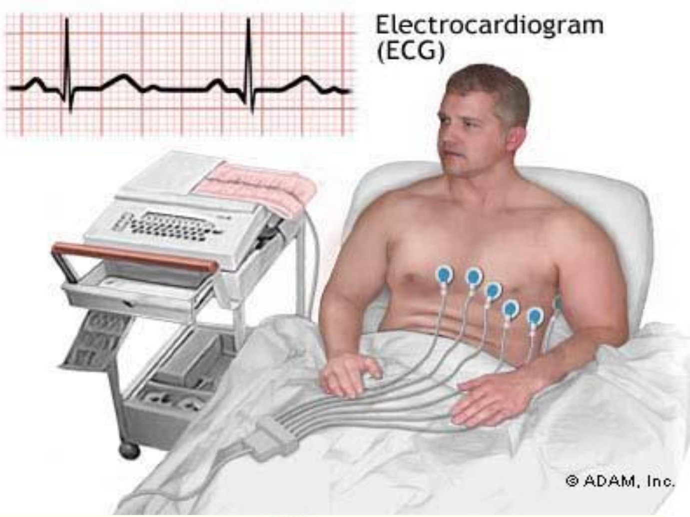
- Fibrillation – random, uncoordinated twitching, the heart's electrical activity becomes disordered
- Atrial fibrillation – not necessarily life threatening

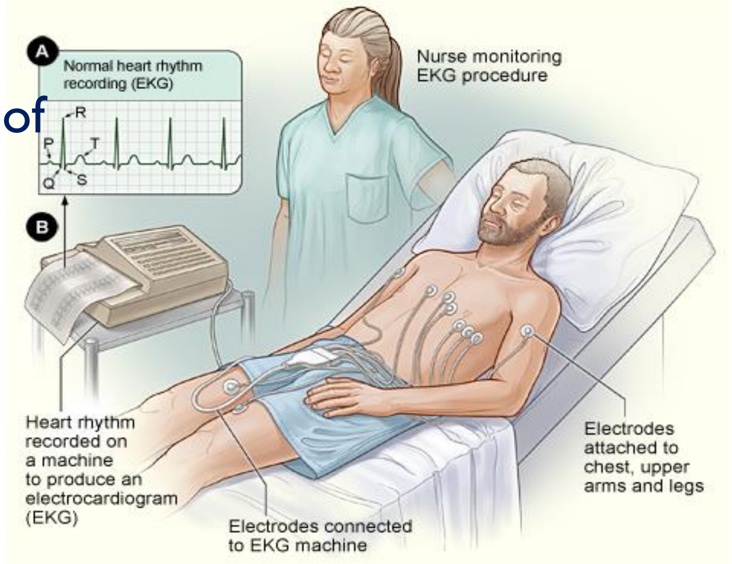


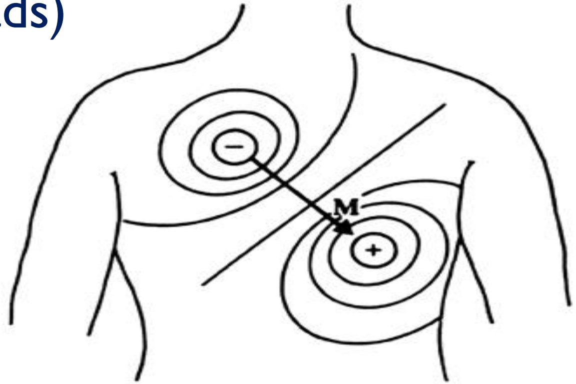
- Ventricular fibrillation – very serious (life threatening), must be treated immediately
- When this happens, the heart's lower (pumping) chambers contract in a rapid, unsynchronized way. (The ventricles "fibrillate" rather than beat.) The heart pumps little or no blood. Collapse and sudden cardiac arrest follows -- this is a medical emergency!

Measurement of ECG Signal

- EKG is always measured between pairs of electrodes called "leads"
- Clinically, a set of 10 electrodes, 12 electrode pairs or leads are usually used to measure the cardiac vector M
- The QRS complex is the mean scalar (amplitude) of multiple leads)

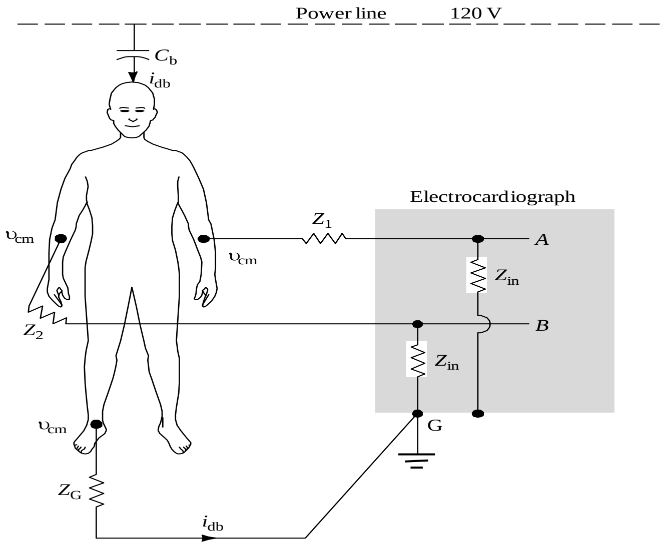


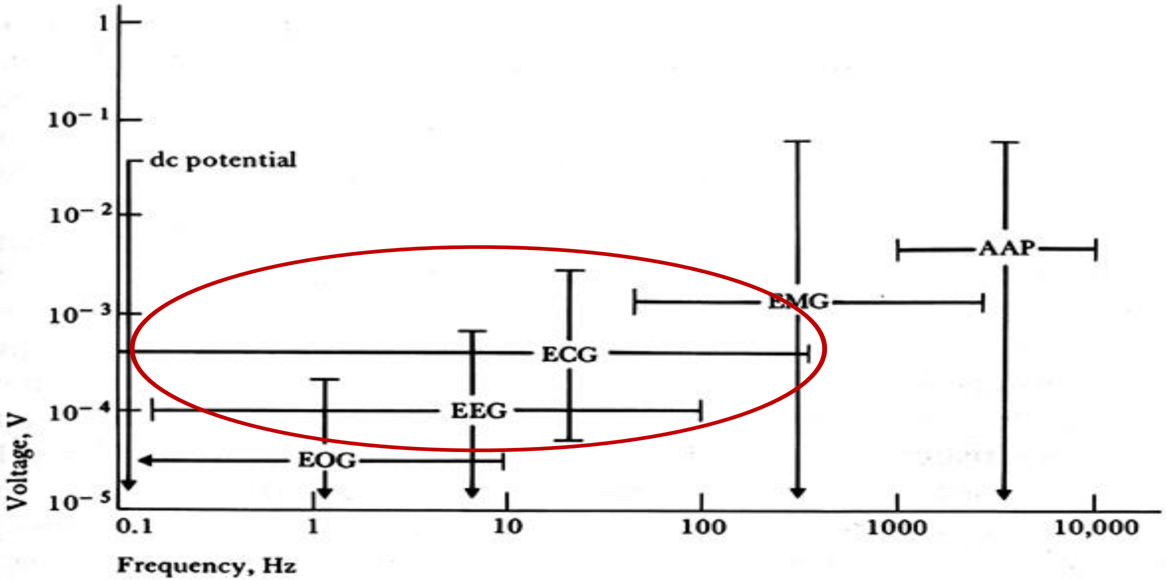




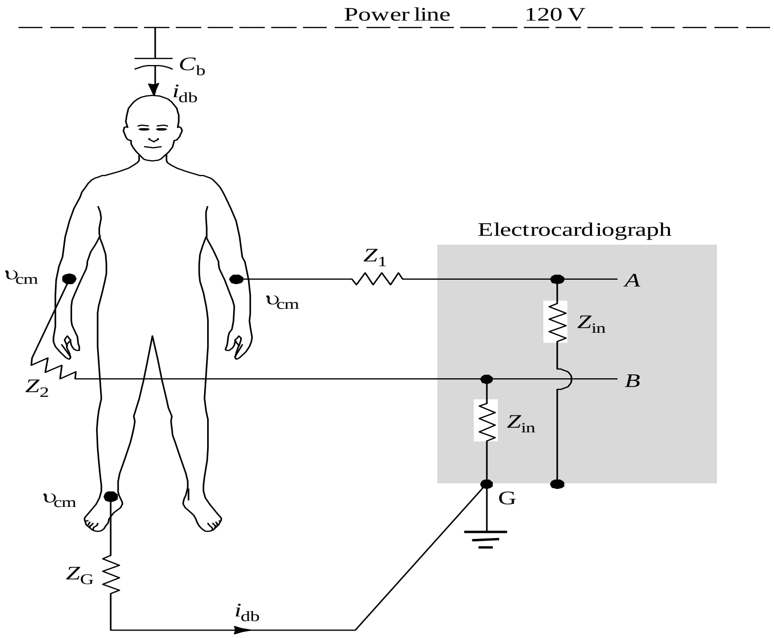
**Why do we always measure bio-potentials between pairs?

- In practice interference is significant! e.g. from capacitive coupling through person from room power supply
- Can easily produce ~mV of interference at (60 Hz) at each input
- Cannot ignore or easily filter out!



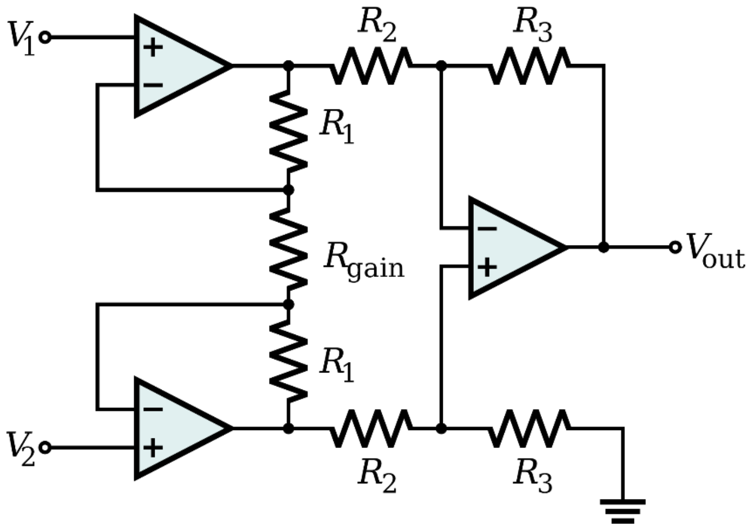


- Happily, as it turns out much of the interfering signal is similar on both inputs
- Therefore, we can **reject** signals that appear at both inputs and amplify (measure) the **difference**



This is why common mode rejection ratio is so critical in bio-potential amplifiers:

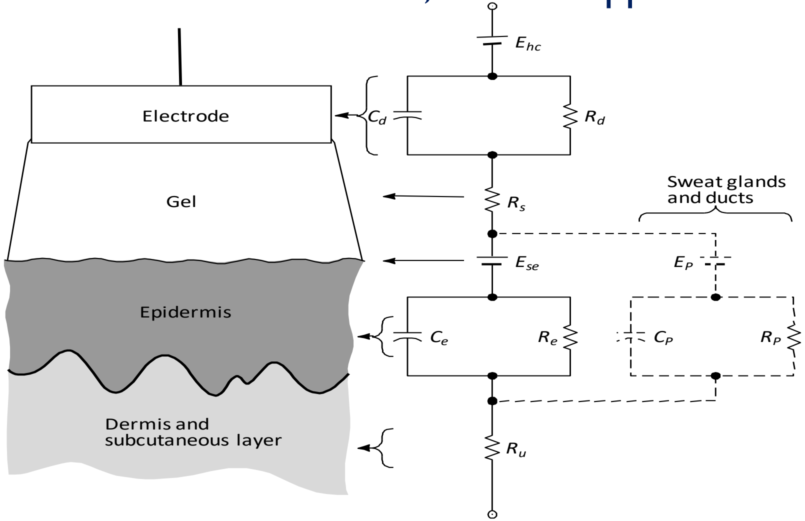
CMRR = common mode rejection ration = Gd/Gc



3-stage Instrumentation Amplifier, to be discussed.

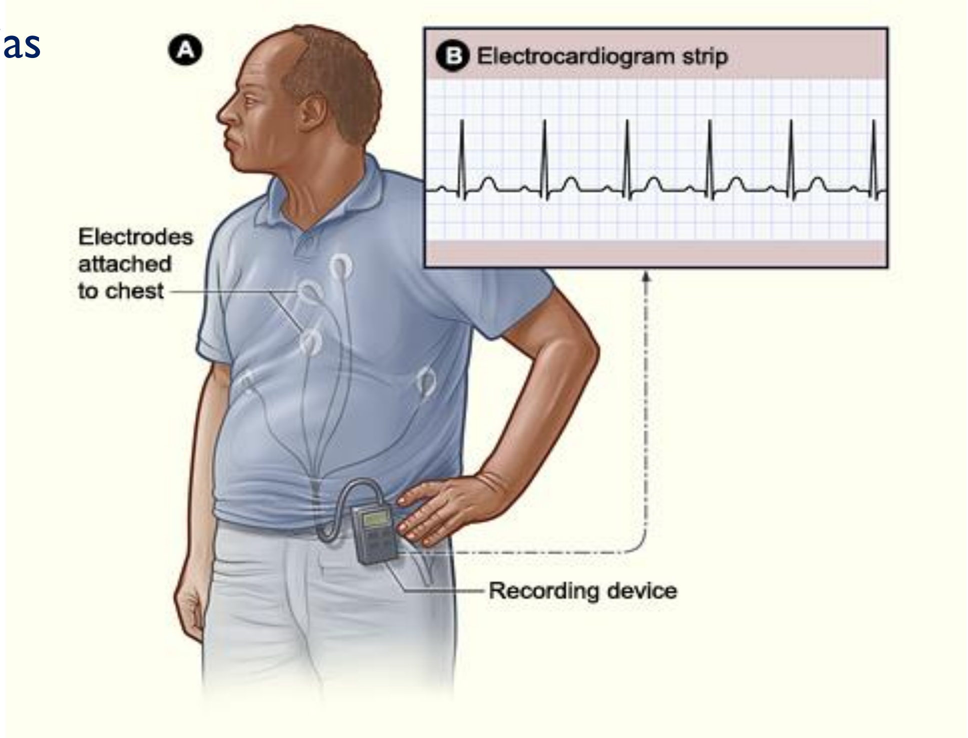
Finally, On Electrodes…

- As we just learned, current is carried by ions (K+, Na+, Cl-) in the body.
- But, current is carried into an amplifier by electrons
- Therefore, we need a <u>*transducer*</u> that converts ionic current into electrical current, *i.e. an electrode*
- The ionic currents generate an **electric field**. If an electrode is placed close enough to the electric field, it cab sense the changes in the potential around the electrode, and this appears as a varying voltage.



Holter EKGs

Portable, continuous acquisition of EKG signal for detection of transient arrhythmias



12 Lead ECG measurement

- In total, 10 electrodes are used to obtain 12 EKG pairs (leads):

  6 frontal plane

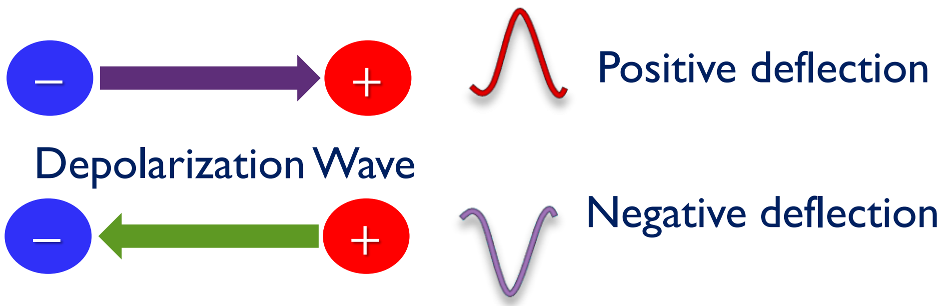
  6 transverse plane

  ….for measuring the cardiac vector.

- A lead provides a view of the heart's electrical activity between two points, or poles
- This can give more accurate diagnostic information for cardiac disorders and arrhythmias.

ECG Measurements Basics

- When a signal of depolarization travels towards the + electrode and away from the electrode attached to the -ve terminal, a positive-going deflection will result.

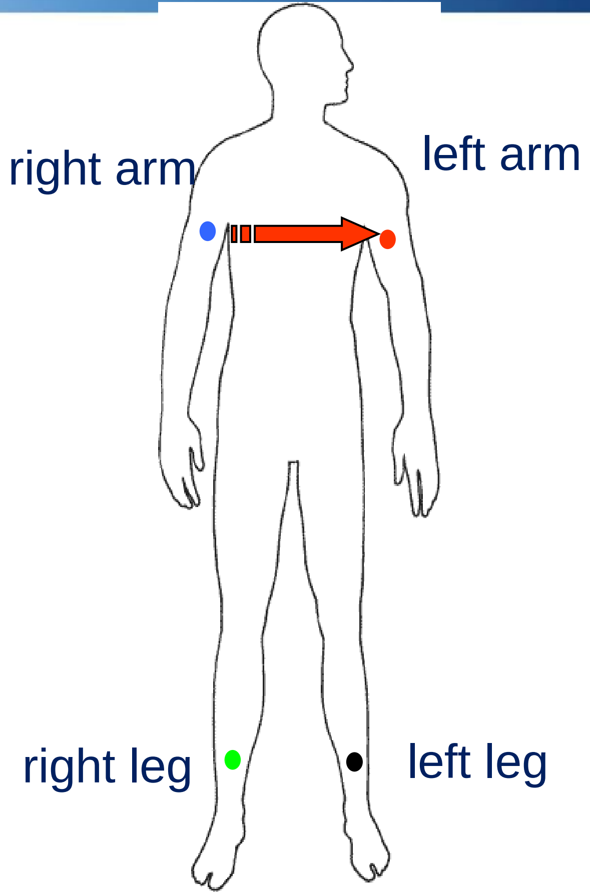


- The voltage recorded along a particular lead axis at a given time represents the projection onto that axis of the vector representing the magnitude and direction of depolarization signal at that time.
- If the depolarization signal is travelling in a direction perpendicular the lead axis where the two electrodes are placed, no deflection will be produced.

Frontal Planes leads: Lead I (toward left)

electrical polarity:

- neutral or mutual reference (green)
- negative (blue)
- positive (red)

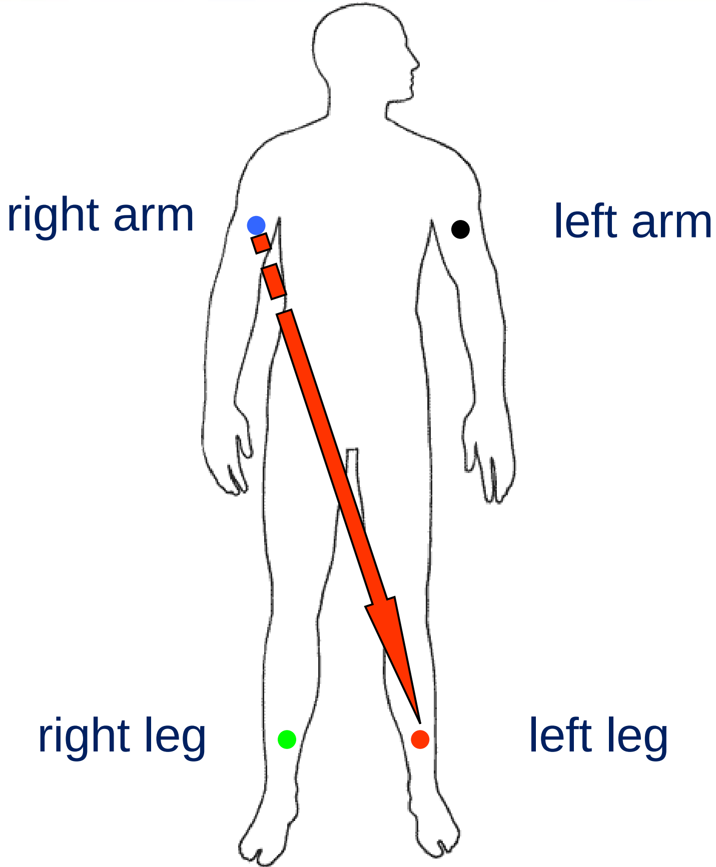


Note: the normal average direction for the heart's electrical activity is from the upper right, in the right atrium, to the lower left.

Frontal plane leads: Lead II (toward left foot)

electrical polarity

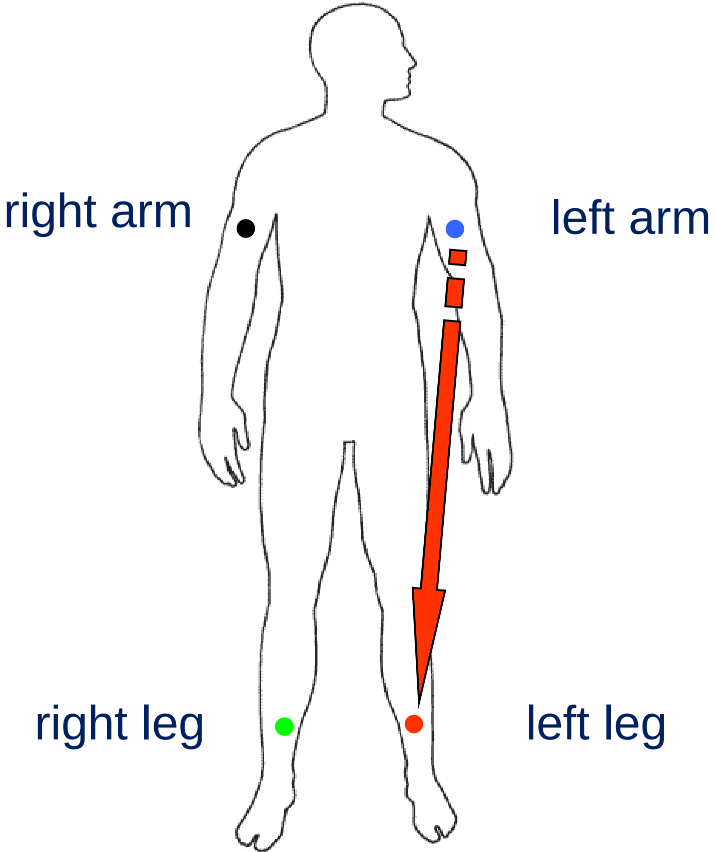
- neutral or mutual reference
- negative
- positive



Frontal plane leads: Lead III (down & rightward)

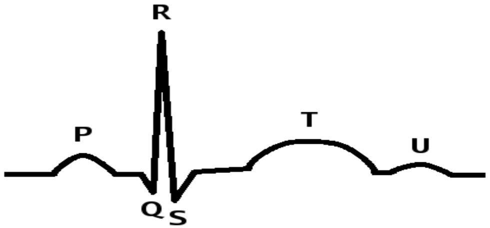
electrical polarity:

- neutral or mutual reference
- negative
- positive

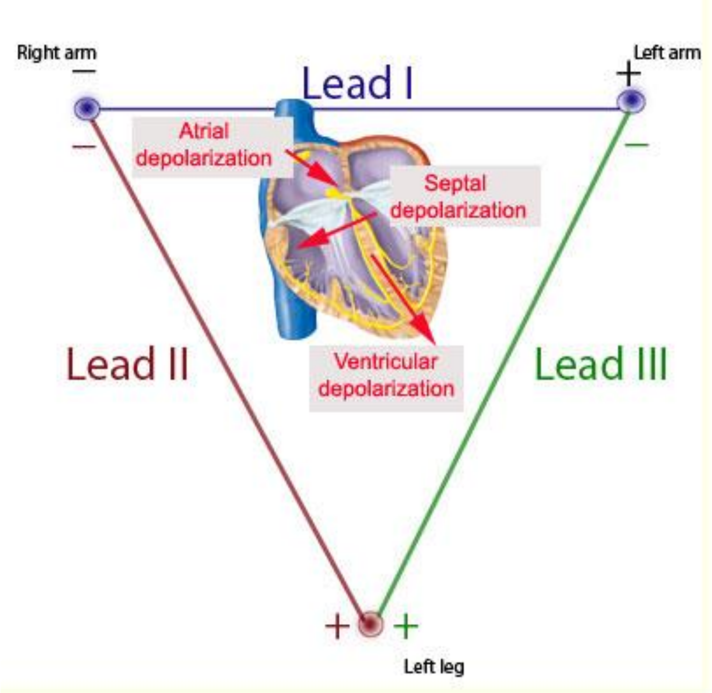


Leads I, II, and III require a pair of electrodes for monitoring, which makes these leads bipolar.

ECG Measurements Basics

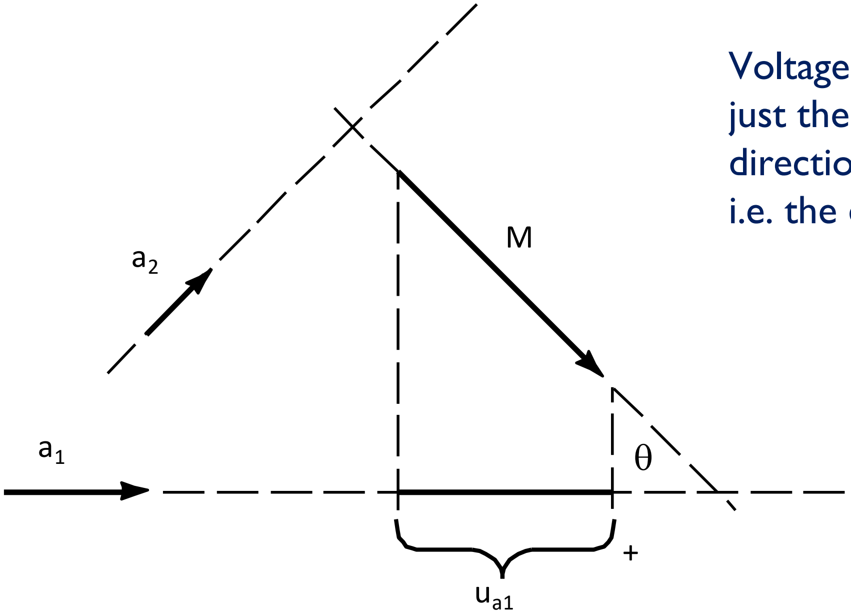


- The direction of atrial depolarization is parallel to the axis of lead II ,therefore a positive-going deflection (P wave) would result in that lead.
- The depolarization of the two ventricles is downwards and toward the left leg: this produces again a positive-going deflection (R-wave) in lead II,
- As septal depolarization moves from left to right, the depolarization vector is directed towards the - electrode of lead II (therefore a negative-going deflection (Q-wave) is produced.



https://www.medicine.mcgill.ca/physio/vlab/cardio/ECGbasics.htm

Electrode pairs represent a lead vector for measuring the cardiac vector



Voltage induced in a lead (vector $\mathbf{a}_1$) is just the component of $\boldsymbol{M}$ in the direction of $\boldsymbol{a}_1$,
i.e. the dot product:

$$V_{a1} = \boldsymbol{M} \cdot \boldsymbol{a}_1$$

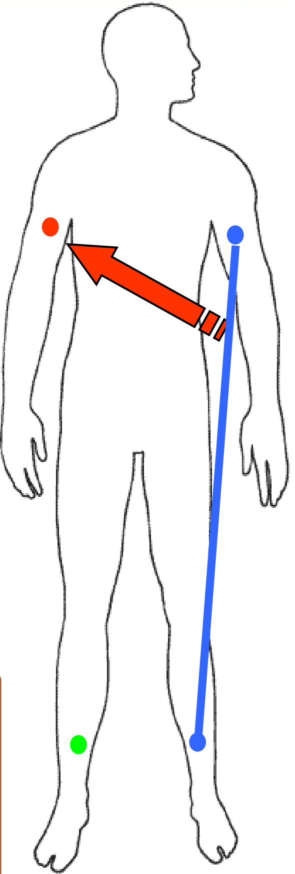
$$Va1 = |\boldsymbol{M}|\cos\theta$$

Figure 6.2 Relationships between the two lead vectors $\mathbf{a}_1$ and $\mathbf{a}_2$ and the cardiac vector **M**. The component of **M** in the direction of $\mathbf{a}_1$ is given by the dot product of these two vectors and denoted on the figure by v_{a1}. Lead vector $\mathbf{a}_2$ is perpendicular to the cardiac vector, so no voltage component is seen in this lead.

Plus 3 frontal "augmented" leads, e.g., augmented Vector leads

electrical polarity:

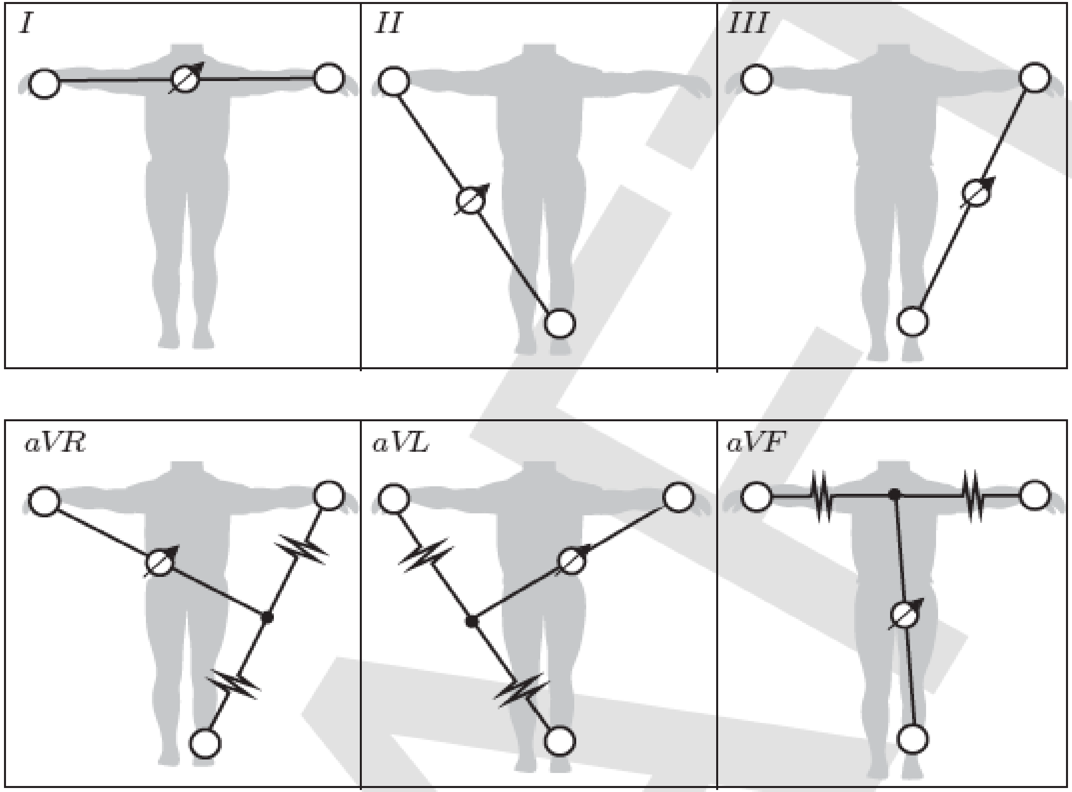
- neutral or mutual reference
- negative
- positive



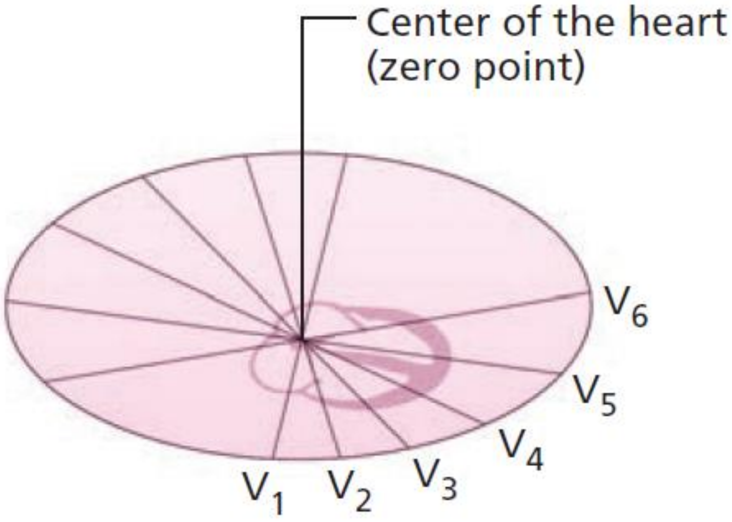
With augmented vector leads, the electric impulses are measured at one point relative to the mutual reference yielding unipolar vectors. The vectors are modified to yield augmented leads aVR, aVL, and aVF . The lead measurement for aVR is synthesized as the actual measurement of the right arm electrode minus the average of the two electrode measurements on the left side

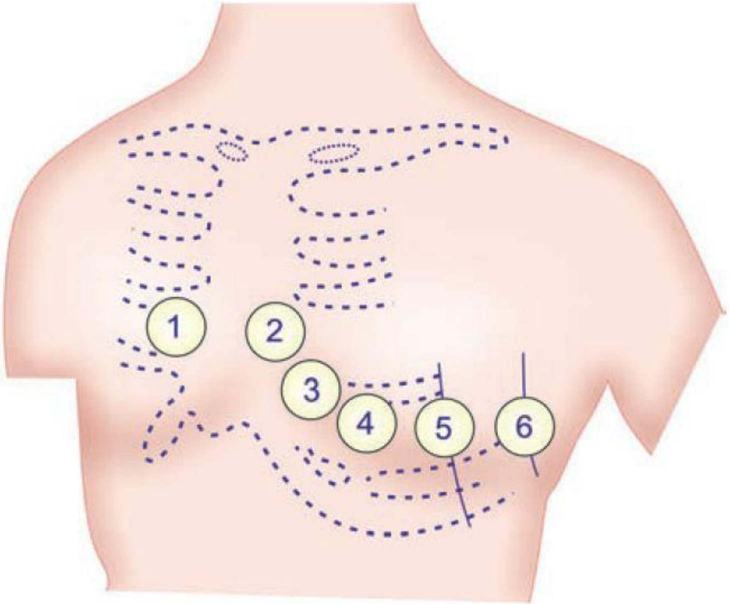
Lead aVR Augmented Vector Right, positive electrode right shoulder.
Lead aVL Augmented Vector Left, positive electrode left shoulder.
Lead aVF Augmented Vector foot, positive electrode on left foot

6 Frontal plane Leads



Plus 6 chest Lead electrode placement, transverse plane

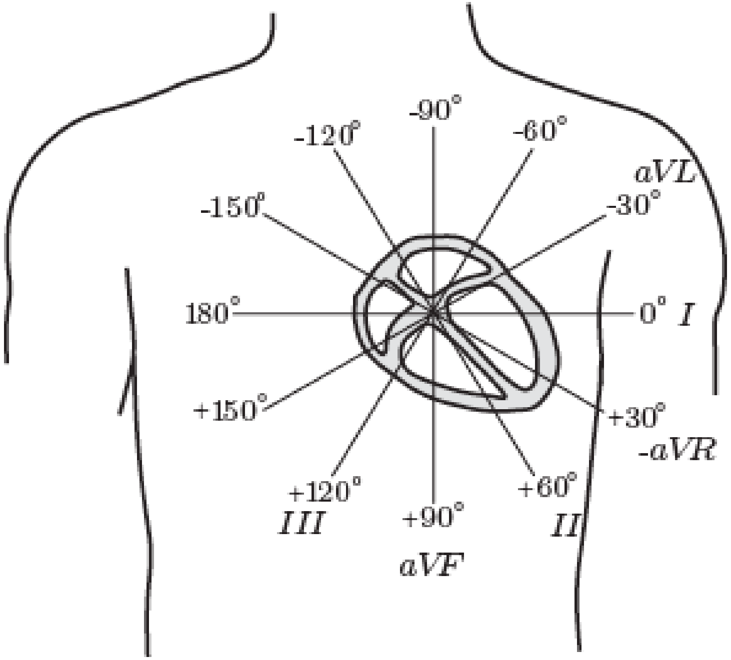




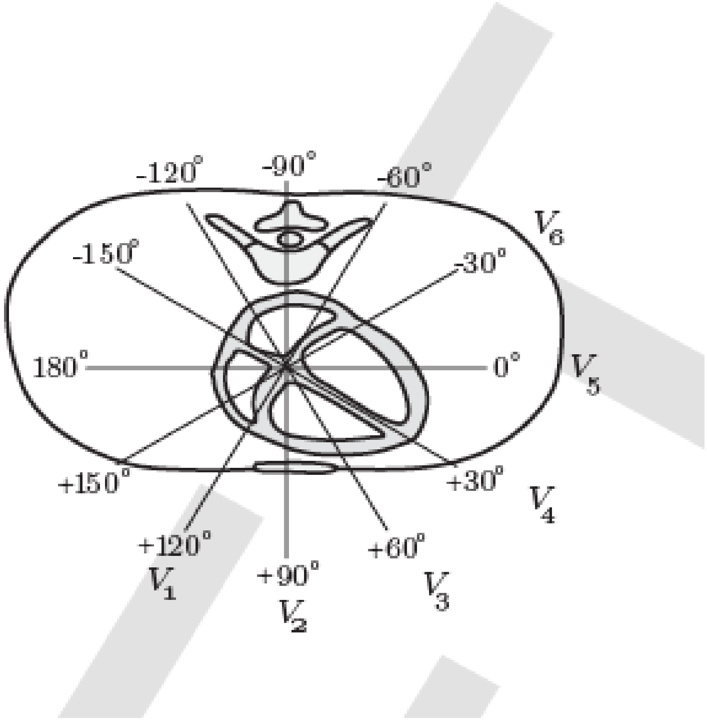
Summary of all 12 leads

- I, from the right arm (-) toward the left arm (+)
- II, from the right arm toward the left leg
- III, from the left arm toward the left leg
- aVR, augmented lead toward the right (arm)
- aVL, augmented lead toward the left (arm)
- aVF, augmented lead toward the foot
- Chest leads (transverse plane) V1 through V6, a positive electrode strategically placed on the chest of the patient. starting over the right atrium with V1, and placed in a semi-circle of positions leftwards, to the left side of the left ventricle

12 Lead Measurement



Frontal Plane



Transverse Plane

Example Left ventricular hypertrophy (LVH)

- Left ventricular hypertrophy (LVH) is a condition in which the muscle wall of heart's left pumping chamber (ventricle) becomes thickened (hypertrophy)
- The cardiac vector extends further to the left than normal
- A larger than normal positive lead I frontal plane vector measurement will be observed during the QRS wave (as well as a larger R wave)