

- **Why is hypokalemia less threatening than hyperkalemia?**

90% of K⁺ is stored in the cells => compensate quickly

Hypokalemia can be treated with oral or intravenous potassium.

- **Brief about Frank-Starling law?**

Frank-Starling law represents the relationship between stroke volume of the heart (the blood volume pumped out of the left ventricle during each systolic cardiac contraction) and the end-diastolic volume.

It states that when there is an increase in the blood volume in the ventricles before contraction, the stroke volume increases to respond to that increase.

- **CaCl₂ increases what nerve? consequence of heart?**

the vagus nerve is the main component of the parasympathetic nervous system

CaCl₂ increases vagus nerve activity, leading to a slower heart rate

- **Alpha and Beta receptors (CG)**

- Alpha

Alpha receptors, also known as alpha-adrenergic receptors, are protein structures in the body that respond to the hormones norepinephrine (noradrenaline) and epinephrine (adrenaline). They are **part of the sympathetic nervous system** and are present in various types of tissues.

There are two main types of alpha receptors: Alpha-1 and Alpha-2 receptors.

1. Alpha-1 receptors: These receptors are found in many tissues throughout the body. In the vascular smooth muscle, their stimulation causes contraction, leading to vasoconstriction, which increases blood pressure. They're also found in the muscles of the iris, where their stimulation leads to pupil dilation. Other locations include the bladder and prostate.
2. Alpha-2 receptors: These receptors are both presynaptic and postsynaptic. When activated, they inhibit the release of norepinephrine, thereby reducing sympathetic activity. They're found in many areas, including the central nervous system, where they play roles in controlling the release of insulin, regulating the constriction and dilation of blood vessels, and managing pain.

Alpha blockers are a type of medication that inhibits the action of norepinephrine and epinephrine on alpha receptors. They're often used to treat conditions such as hypertension and benign prostatic hyperplasia.

It's important to note that the actions of these receptors can be complex and are influenced by a variety of factors, so this is a simplified explanation.

- Beta

Beta receptors, also known as beta-adrenergic receptors, are **part of the sympathetic nervous system** and respond to the hormones epinephrine (adrenaline) and norepinephrine (noradrenaline). These receptors are located in various tissues throughout the body, including the heart.

There are two main types of beta receptors in the heart, called Beta-1 and Beta-2 receptors.

1. Beta-1 receptors: These are the predominant beta receptors in the heart. When stimulated by adrenaline or noradrenaline, they increase the heart rate (positive chronotropic effect), increase the force of contraction of the heart muscle (positive inotropic effect), and speed up the rate of electrical conduction through the heart (positive dromotropic effect).
2. Beta-2 receptors: These are less abundant in the heart. Their stimulation also has positive inotropic and chronotropic effects but to a lesser degree than Beta-1 receptors. Beta-2 receptors are more abundantly found in the smooth muscle of blood vessels and in the bronchial tubes of the lungs. When stimulated, they cause dilation of these structures.

Beta blockers are a class of medications that block the effects of adrenaline and noradrenaline on beta receptors. They are often used to treat conditions like high blood pressure, angina, heart failure, and certain kinds of arrhythmias. By blocking the beta-1 receptors in the heart, they can reduce heart rate, decrease the force of contraction of the heart muscle, and slow the rate of conduction, thereby reducing the workload of the heart.

- **NE vs ACh? (CG)**

Norepinephrine (NE) and Acetylcholine (ACh) are two key neurotransmitters involved in the autonomic regulation of the heart and vasculature. They work in opposition to each other, with NE being the primary neurotransmitter of the sympathetic (fight-or-flight) nervous system and ACh being the primary neurotransmitter of the parasympathetic (rest-and-digest) nervous system.

1. **Effects of Norepinephrine (NE) on the heart and vasculature:**

- Heart: NE acts on beta-1 adrenergic receptors in the heart, increasing the heart rate (chronotropic effect), increasing the force of heart contraction (inotropic effect), and speeding up the electrical conduction through the heart (dromotropic effect).
- Vasculature: In the blood vessels, NE primarily acts on alpha-1 adrenergic receptors, causing vasoconstriction and therefore increasing blood pressure.

2. **Effects of Acetylcholine (ACh) on the heart and vasculature:**

- Heart: ACh acts on muscarinic receptors (mainly M2) in the heart, causing a decrease in heart rate and a reduction in the force of heart contraction.
- Vasculature: In the blood vessels, ACh causes vasodilation, thereby reducing blood pressure. This happens via the stimulation of muscarinic receptors on endothelial cells, leading to the production of nitric oxide (NO), a potent vasodilator.

Overall, the balance between these two systems (sympathetic and parasympathetic) helps to regulate cardiovascular function in response to changing body needs, such as during stress or rest.

Acetylcholine slows **the heart rate** by activating the M2 muscarinic receptor (M2R) that, in turn, opens the acetylcholine-activated potassium channel (IK,ACh) to slow the firing of the sinus node.

The acetylcholine-activated potassium current (IKACh) is **an inward rectifier that contributes to stabilization of the resting membrane potential and phase three repolarization**

It's important to note that the activation of the IKACh current by acetylcholine is indirect. Acetylcholine binds to muscarinic acetylcholine receptors (specifically M2), which are G protein-coupled receptors. This leads to activation of G proteins that can open the GIRK channels (G-protein activated inward rectifier potassium channels), which generate the IKACh current.

So while it may seem contradictory, the inward flow of potassium ions through these channels is a special case that doesn't violate the rules of electrochemical gradients; it's just that these channels have unique properties that allow them to preferentially conduct ions inwards under specific conditions

- **ACh and potassium?**

- Acetylcholine (ACh) released on vagal stimulation **reduces the heart rate by increasing K⁺ conductance of pacemaker cells** in the sinoatrial (S-A) node. (activation of inwardly rectifying *potassium current, which allow K⁺ to move more easily into rather than out of the cell*)
- ACh activates the muscarinic receptors, facilitating the opening of ACh-activated potassium channels to slow down (slow/fasten) the SA node

- **Atropine increase or decrease heart rate? how?**

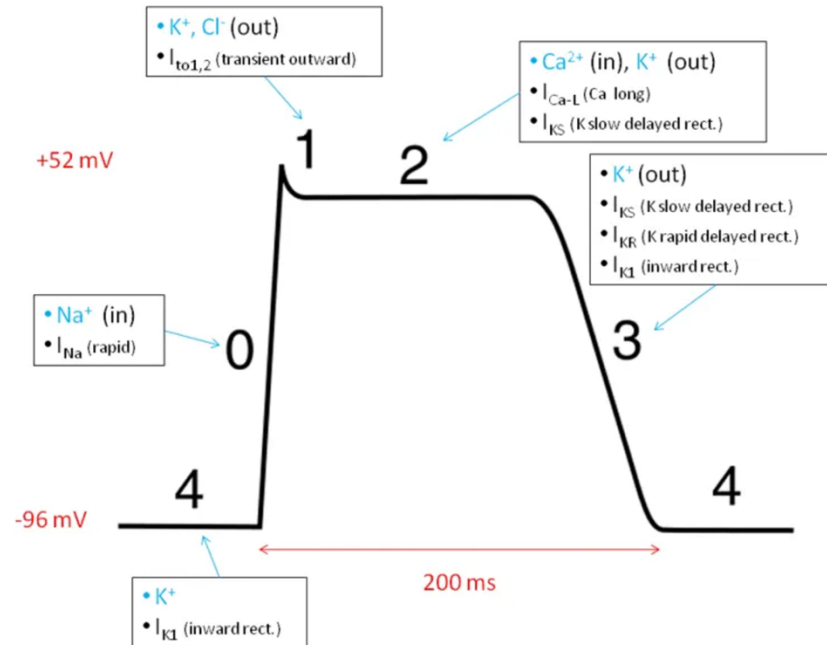
Atropine: block of the parasympathetic system, which improves the atrioventricular conduction (**conduction of the atrial impulses to the ventricles**).

Stimulation of the parasympathetic system serves to inhibit AV node conduction velocity

The use of atropine in cardiovascular disorders is mainly in the management of patients with bradycardia. Atropine increases the heart rate and improves the atrioventricular conduction by blocking the parasympathetic influences on the heart.

- **Phases of action potential? Why too much potassium $\Rightarrow$ heart stops?**

If too much extracellular K^+ , intracellular K^+ is stuck inside, 1 would not occur.



In cardiac muscle cells (myocytes), the action potential has a unique, longer shape compared to that in neurons or skeletal muscle cells. This is characterized by a prolonged depolarization phase known as the plateau phase, which is largely maintained by an influx of calcium ions (Ca^{2+}).

The phases of an action potential in a cardiac myocyte include:

1. **Rapid Depolarization (Phase 0):** Triggered by an electrical impulse from neighboring cells, voltage-gated sodium channels open, allowing a rapid influx of sodium ions (Na^+) into the cell, causing depolarization.
2. **Initial Repolarization (Phase 1):** The sodium channels close, and transient outward potassium channels open briefly, allowing potassium ions (K^+) to leave the cell, which causes a slight repolarization.
3. **Plateau (Phase 2):** Voltage-gated calcium channels (L-type) open, allowing calcium ions to enter the cell. This calcium influx balances the charge across the membrane against the ongoing efflux of potassium through slow potassium channels, creating a plateau phase in the action potential. The long plateau phase is crucial because it results in a prolonged contraction necessary for the pumping function of the heart.
4. **Repolarization (Phase 3):** Eventually, the calcium channels close, and more potassium channels open, which allows an increased outflow of potassium ions, causing the cell to repolarize and return to its resting membrane potential.
5. **Resting State (Phase 4):** The cell remains at its resting membrane potential until the next action potential is initiated.

The presence of the plateau phase helps to prevent summation and tetany by implementing a longer refractory period. This is critical in allowing the heart chambers to relax and refill with blood in preparation for the next beat. It is this unique characteristic of cardiac muscle that ensures the heart beats in a regular, coordinated manner.

- **EC coupling (CG)**

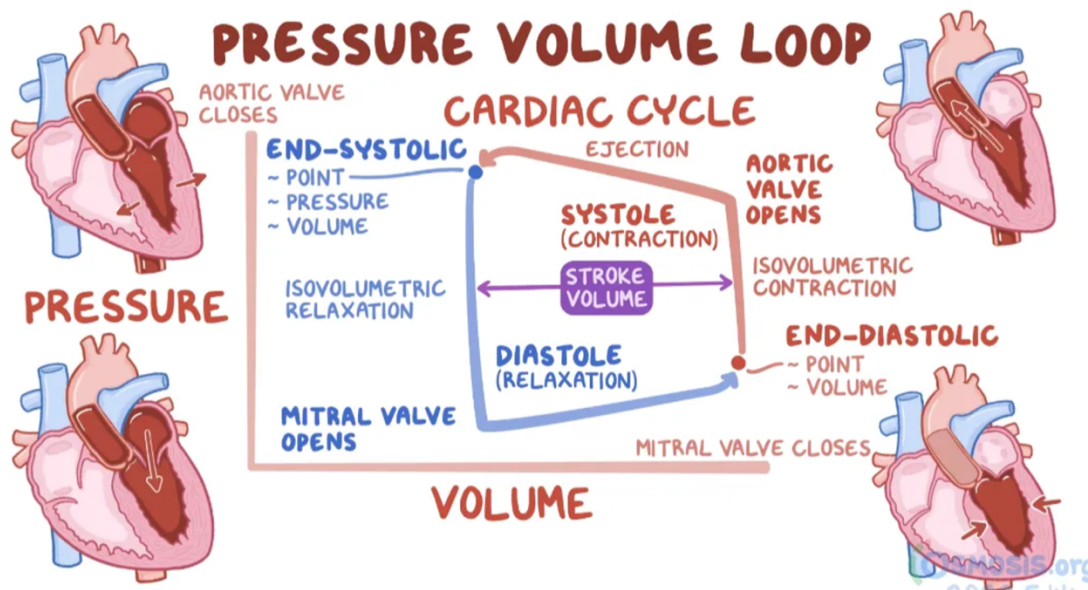
Excitation-contraction coupling (EC coupling) in cardiomyocytes, which are the muscle cells of the heart, follows a similar general process to skeletal muscle. However, there are some specific differences. Here are the steps involved in EC coupling in cardiomyocytes:

1. **Action Potential Initiation:** The action potential is generated at the sinoatrial (SA) node, which serves as the natural pacemaker of the heart. The action potential then propagates through the atria and reaches the atrioventricular (AV) node.
2. **Action Potential Propagation:** From the AV node, the action potential spreads through specialized conduction fibers called the bundle of His and the Purkinje fibers, which rapidly transmit the electrical signal to the ventricles.
3. **T-Tubule Depolarization:** Similar to skeletal muscle, the action potential spreads into the T-tubules of the cardiomyocytes.

4. **Calcium Influx:** The depolarization of the T-tubules leads to the opening of voltage-gated calcium channels, known as L-type calcium channels (LCCs), located on the sarcolemma. Calcium ions enter the cardiomyocyte cytoplasm from the extracellular space through these channels.
5. **Calcium-Induced Calcium Release:** The influx of calcium through the LCCs triggers a much larger release of calcium ions from the sarcoplasmic reticulum (SR) via the ryanodine receptors (RYRs). This process is known as calcium-induced calcium release (CICR). The released calcium further increases the cytoplasmic calcium concentration.
6. **Calcium Binding to Troponin:** The increased calcium concentration allows calcium ions to bind to troponin C, similar to skeletal muscle. This binding causes a conformational change in the troponin-tropomyosin complex, exposing the myosin-binding sites on the actin filaments.
7. **Cross-Bridge Formation and Muscle Contraction:** The myosin heads of the thick filaments bind to the actin filaments, forming cross-bridges, and initiate the sliding filament mechanism. This leads to muscle contraction and the generation of force.
8. **Calcium Removal and Relaxation:** Calcium is actively transported back into the SR by the sarcoplasmic reticulum calcium ATPase (SERCA) pumps, reducing the cytoplasmic calcium concentration. Additionally, some calcium is extruded from the cell by the sodium-calcium exchanger (NCX). As calcium levels decrease, troponin returns to its original conformation, blocking the myosin-binding sites on the actin filaments, and the muscle relaxes.

It's important to note that cardiomyocytes have a longer action potential duration compared to skeletal muscle cells, allowing for proper coordination of contraction and relaxation of the heart chambers during the cardiac cycle. Additionally, the regulation of calcium handling in cardiomyocytes involves various proteins and signaling pathways specific to the heart.

- **Pressure volume loop?**



CG

A pressure-volume loop is a graphical representation of the changes in pressure and volume that occur during one cardiac cycle. It provides insights into the mechanical function of the heart. Here's a summary of the pressure-volume loop:

1. **Diastole:** The cardiac cycle begins in diastole, the relaxation phase of the heart. The ventricles are filling with blood from the atria. The volume of blood in the ventricles increases, while the ventricular pressure remains low.
2. **Atrial Contraction:** Atrial contraction, also known as atrial systole, occurs near the end of diastole. It contributes to the final filling of the ventricles. The atria contract, further increasing ventricular volume.

3. **Isovolumetric Contraction:** Ventricular contraction begins, and the ventricular pressure rises rapidly. The AV valves (mitral and tricuspid valves) close, preventing blood from flowing back into the atria. This phase is called isovolumetric contraction because the ventricular volume remains constant.
4. **Ejection:** Once the ventricular pressure surpasses the pressure in the arterial system (aortic and pulmonary arteries), the semilunar valves (aortic and pulmonary valves) open. Blood is ejected from the ventricles into the arteries. Ventricular volume decreases, while ventricular pressure continues to rise during this phase.
5. **Isovolumetric Relaxation:** After ejection, the ventricles start to relax. The semilunar valves close, preventing blood from flowing back into the ventricles. The ventricular volume remains constant in this phase, hence the name isovolumetric relaxation.
6. **Ventricular Filling:** As the ventricular pressure decreases, it eventually falls below the atrial pressure. The AV valves open, allowing blood to flow from the atria to the ventricles. Ventricular volume increases again, completing one cardiac cycle.

The pressure-volume loop provides information about cardiac performance and can indicate abnormalities in heart function. The loop's shape, area, and position on the graph can vary depending on factors such as heart rate, contractility, and afterload. Analyzing pressure-volume loops helps in diagnosing and monitoring cardiac conditions.

- **Defect in calcium removal?**

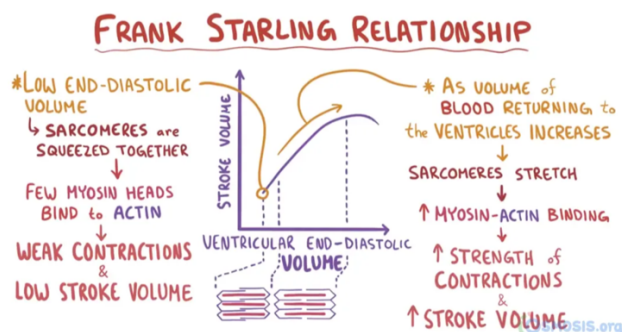
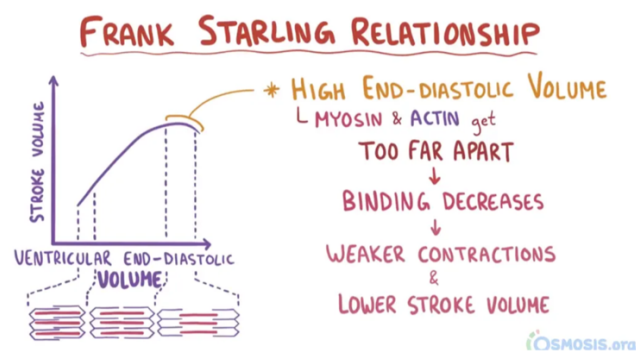
A **defect in the removal** of calcium from the cytosol during diastole would impair cardiac relaxation, which is critically important in that **it allows the heart chambers to refill with blood in preparation for the next beat.**

(calcium ions will remain bound to the contractile proteins (actin and myosin), maintaining their contracted state and preventing relaxation)

- **Beta blockers (CG)**

Mechanism of Action: Beta-blockers selectively block the beta-adrenergic receptors in the body. These receptors are located in various tissues, including the heart, blood vessels, and lungs. By blocking these receptors, beta-blockers reduce the effects of **adrenaline and noradrenaline**, leading to **decreased heart rate**, reduced force of heart contractions, and vasodilation (widening of blood vessels). These effects result in **decreased cardiac workload and reduced blood pressure.**

- **Frank-Starling, why too low and too high is not good? (Actin and myosin)**



- **Troponin?**

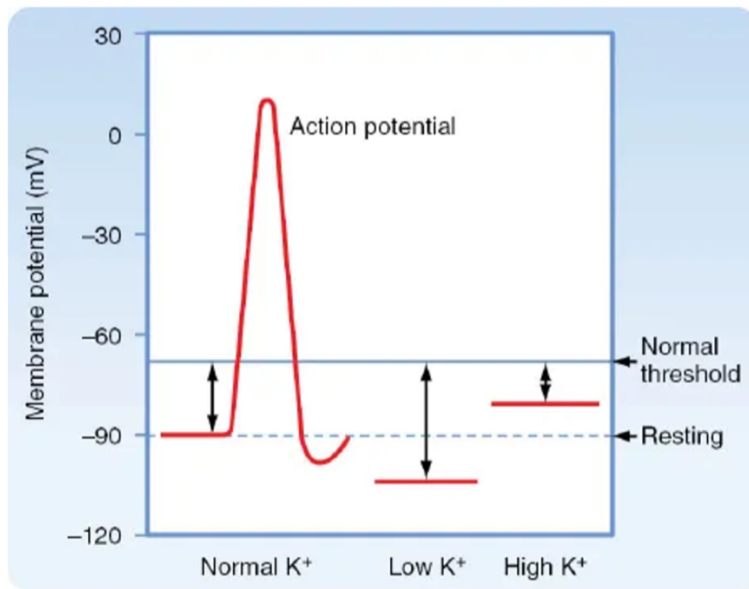
Troponin is bound within the filament of the contractile apparatus.

When cardiac myocytes are damaged, troponin is released into the circulation.

- At first the cytosolic pool is released, and then the structurally bound troponin enters the circulation

- **ECF potassium concentration and membrane potential? (CG)**

- **Excessive ECF potassium (hyperkalemia) decreases the membrane potential:** In hyperkalemia, the concentration of potassium ions in the extracellular fluid (ECF) is higher than normal. This reduces the electrical gradient across the cell membrane because there's less of a difference between the high concentration of potassium ions inside the cell and the now higher concentration of potassium ions outside the cell. This makes the membrane potential **less negative**, or closer to zero. In other words, the cell membrane is depolarized. This could potentially cause the cells to be more excitable, and in extreme cases, it can lead to life-threatening cardiac arrhythmias.
- **Too little potassium (hypokalemia) causes hyperpolarization and nonresponsiveness:** Conversely, in hypokalemia, the concentration of potassium ions in the ECF is lower than normal. This increases the electrical gradient across the cell membrane because there's a greater difference between the high concentration of potassium ions inside the cell and the now lower concentration of potassium ions outside the cell. This makes the membrane potential more negative. In other words, the cell membrane is hyperpolarized. This could make the cells less excitable, and in the case of muscle cells, it can lead to symptoms like muscle weakness or cramping.

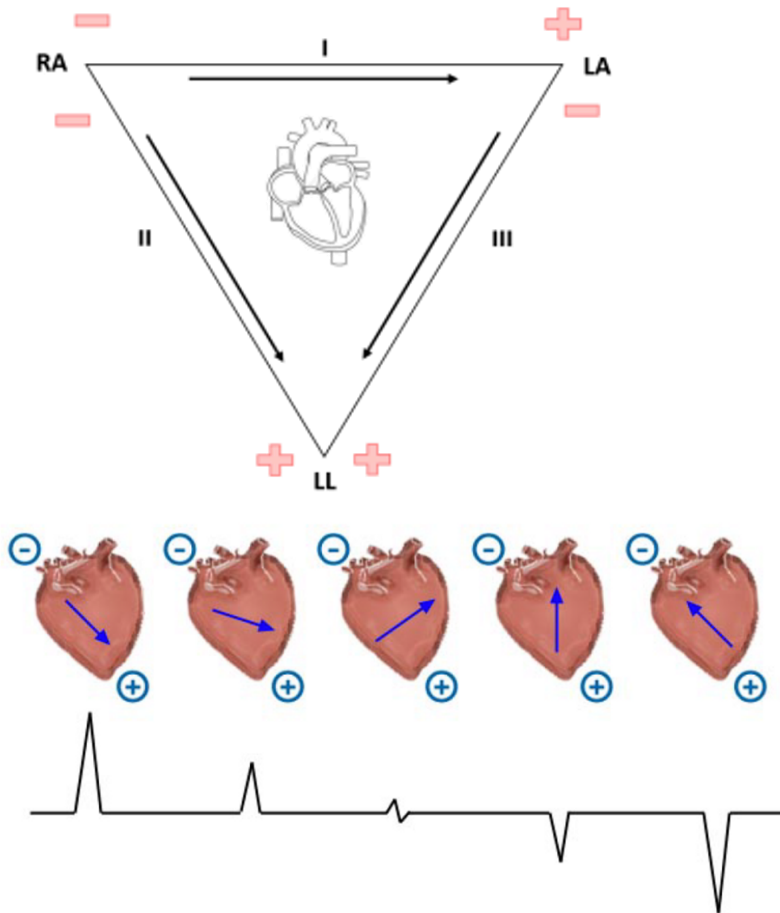


- **ECG**

ECG measures the electrical activity of the heart by placing electrodes on the skin. It records the summation of electrical signals generated by cardiac muscle cells and provides information about the heart's function.

- a surface ECG represents the electrical activity of the entire heart.
- It is the sum of all of the action potentials of all of the cardiac cells.
- Thus an ECG provides information about the sequence of cardiac depolarization and repolarization across the entire heart.

"The **Right Leg (RL)** electrode removes artefact from the ECG and is not a directly participating factor in the visible trace."



- Extracellular potentials (read from books) : how is it achieved?

achieved by intercellular transport of ions via the gap junctions. Additionally, extracellular potentials resulting from the electrical activity of cells or from an external current flow can modulate the propagation and initiate an excitation.

Extracellular potentials from a true point source

For a point source currents and potentials are uniform in all directions. Recall from (2.8) that

$$\Phi_e = \frac{1}{4\pi\sigma_e} \frac{I_0}{r} \quad (8.9)$$

where r is the distance from the point source to the field point, σ_e is the extracellular conductivity, and I_0 is the source's amplitude. The currents from a fiber obey related equations.

The challenge is in the interpretation of the extracellular measurement. Extracellular potential waveforms are weaker in magnitude and thus have features more easily obscured by measurement noise, and also are more variable in wave shape.

- Forward Problem (ECGSIM: an interactive....)
= computation of the resulting potentials based 2 model:

- Bioelectric generator: a source model
- Volume conductor model: a model for describing the effects on the observed signals of the body tissues that surround the active electric sources
- ECGSim focusing on the aspects of the **source parameters** that can be changed interactively
- **Problems/motivations that lead to the bidomain model? What are the ideas of bidomains?**
 - We need realistic cell-based modeling of tissue
 - complex geometry of cells
 - large number of cells
 - must account for extracellular and intracellular space, (not accounted for in the monodomain model)
 - Ideas
 - division of space into 2 domains
 - we can have separate calculations
- **In bidomain, with the inclusion of extracellular conduction → the extracellular conduction relevant for modeling of?**
 - **anisotropic propagation** of excitation
 - **stimulation** with extracellular current sources
 - **ECG** (electrocardiograms) and **BSPM** (body surface potential maps)
- **Schematic: the difference between monodomain and bidomain modeling of electrical conduction in 2D**
 - $\Phi_m = \Phi_i$ - ground
 - $\Phi_m = \Phi_i - \Phi_e$
 - whether or not existence of resistor of extracellular space

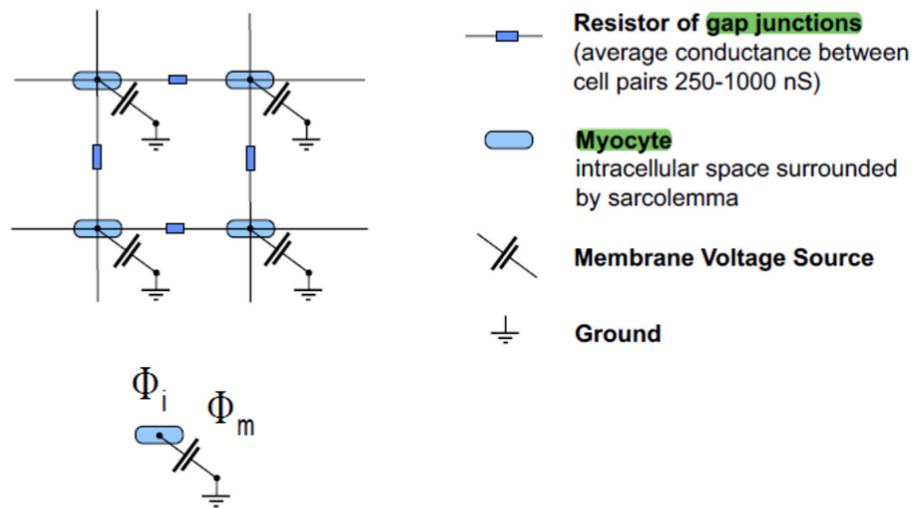
→ Mono: only myocytes and resistors of gap junctions

→ Bi: plus: Resistor of extra. and extracellular potential

are not considered. Simplified representation of the complex cardiac tissue, neglecting certain structural details and heterogeneities that may have significant physiological effects.

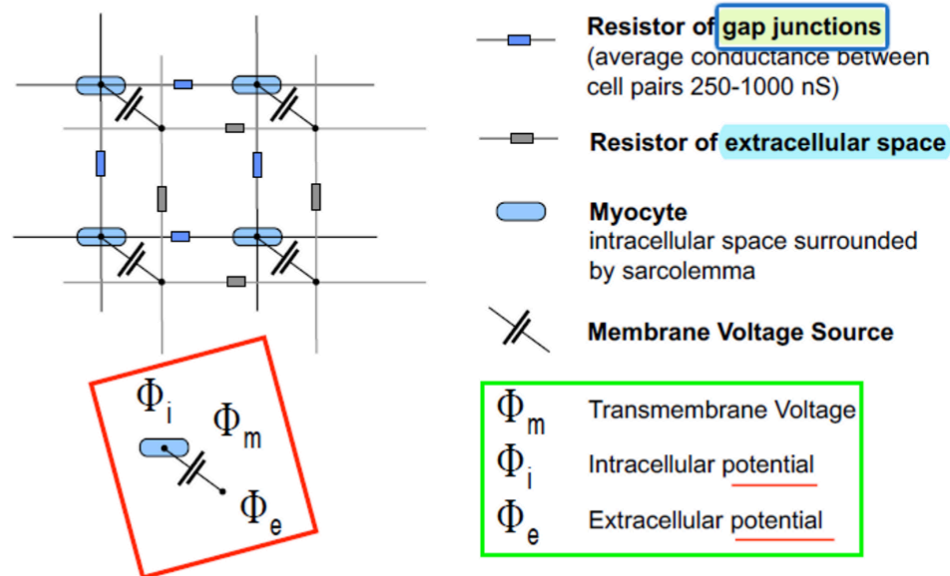
- Computing power
 - Bidomain models involve solving a system of partial differential equations, which can be computationally demanding and time-consuming, especially for large-scale simulations.
- Cardiac tissue is not static

Monodomain Modeling of Electrical Conduction in 2D



Bidomain Modeling of Electrical Conduction in 2D

for each point, have both Intra and extra



- Voltage: electromotive force / electric tension
- Potential difference: measure of stored energy of any form

- Compare discrete microscopic models with macroscopic bidomain models. List model parameters and types of simulation results.
 - Scale: Discrete microscopic models operate at the cellular level, while macroscopic bidomain models operate at the tissue level.
 - Complexity: Discrete microscopic models capture detailed cellular processes, while bidomain models simplify the tissue behavior by averaging over large numbers of cells.
 - Computational Demand: Discrete microscopic models are computationally intensive due to the large number of individual cells and complex interactions. Bidomain models are less computationally demanding since they operate at a macroscopic level.
 - Detail vs. Efficiency: Discrete microscopic models provide detailed information about cellular behavior but require substantial computational resources. Bidomain models sacrifice some cellular detail for more efficient simulations of tissue-scale phenomena.

Discrete Microscopic Models:

- Model Parameters: Parameters in discrete microscopic models typically include ion channel kinetics, membrane capacitance, conductances, intracellular and extracellular resistivities, cell geometry, and connectivity between cells.
- Simulation Results: Discrete microscopic models can provide detailed information about the electrical activity of individual cells, action potential shapes, propagation velocity, transmembrane currents, ionic concentrations, and cellular interactions. They can also simulate phenomena like calcium dynamics, calcium-induced calcium release, and cellular heterogeneities.

Macroscopic Bidomain Models:

- Model Parameters: Parameters in macroscopic bidomain models typically include intracellular and extracellular conductivities, membrane capacitance, diffusion coefficients, tissue geometry, and boundary conditions.
- Simulation Results: Bidomain models provide information about the macroscopic electrical behavior of cardiac tissue, including the propagation of electrical waves, activation patterns, recovery processes, conduction velocity, activation times, and voltage distributions. They can also simulate phenomena like wavefront collisions, reentry, and the effects of tissue heterogeneities.

• HH

- state variables and sum of currents
 - At rest, all currents are constant
 - State variables
 - evolution with time of $v, I_K, I_{Na} \dots$
 - at a time, knowing some values of state variables allows the other variables to be calculated for that same time
- mathematical model for dh/dt and dm/dt (K and Na)

$$g_{Na}(t, v_m) = \bar{g}_{Na} m^3(t, v_m) h(t, v_m) \quad (5.26)$$

In (5.26), $\bar{g}_{Na}$ is the maximum sodium conductance (*a constant*), m is an activation parameter ($0 < m < 1$), while h is an inactivation parameter ($0 < h < 1$).

We may interpret $m^3 h$ as the probability that a sodium channel is open. Hence, for a large population, $m^3 h$ is the fraction of the all-sodium channels that are open.

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m$$

$$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h$$

Pump included in steady-state model

The pump current can be included in a steady-state analysis. For example, it can be included in the parallel-conductance model. We continue to require that the total transmembrane current, I , under steady-state conditions be zero. However, the total current must now include the pump current, I_p , and hence,

$$I = I_K + I_{Na} + I_{Cl} + I_p = 0 \quad (5.73)$$

Consequently, in place of (3.30) we have

$$g_K(V_m - E_K) + g_{Na}(V_m - E_{Na}) + g_{Cl}(V_m - E_{Cl}) = -I_p \quad (5.74)$$

Solving for V_m in (5.74) yields

$$V_m = \frac{g_{Na}E_{Na} + g_KE_K + g_{Cl}E_{Cl}}{g_K + g_{Na} + g_{Cl}} - \frac{I_p}{g_K + g_{Na} + g_{Cl}} \quad (5.75)$$

It is seen in (5.75) that the pump current contributes to the resting potential. In fact, since I_p (representing a net efflux of cation) is positive, Eq. (5.75) demonstrates (not surprisingly) that the pump causes an additional hyperpolarization of the membrane.

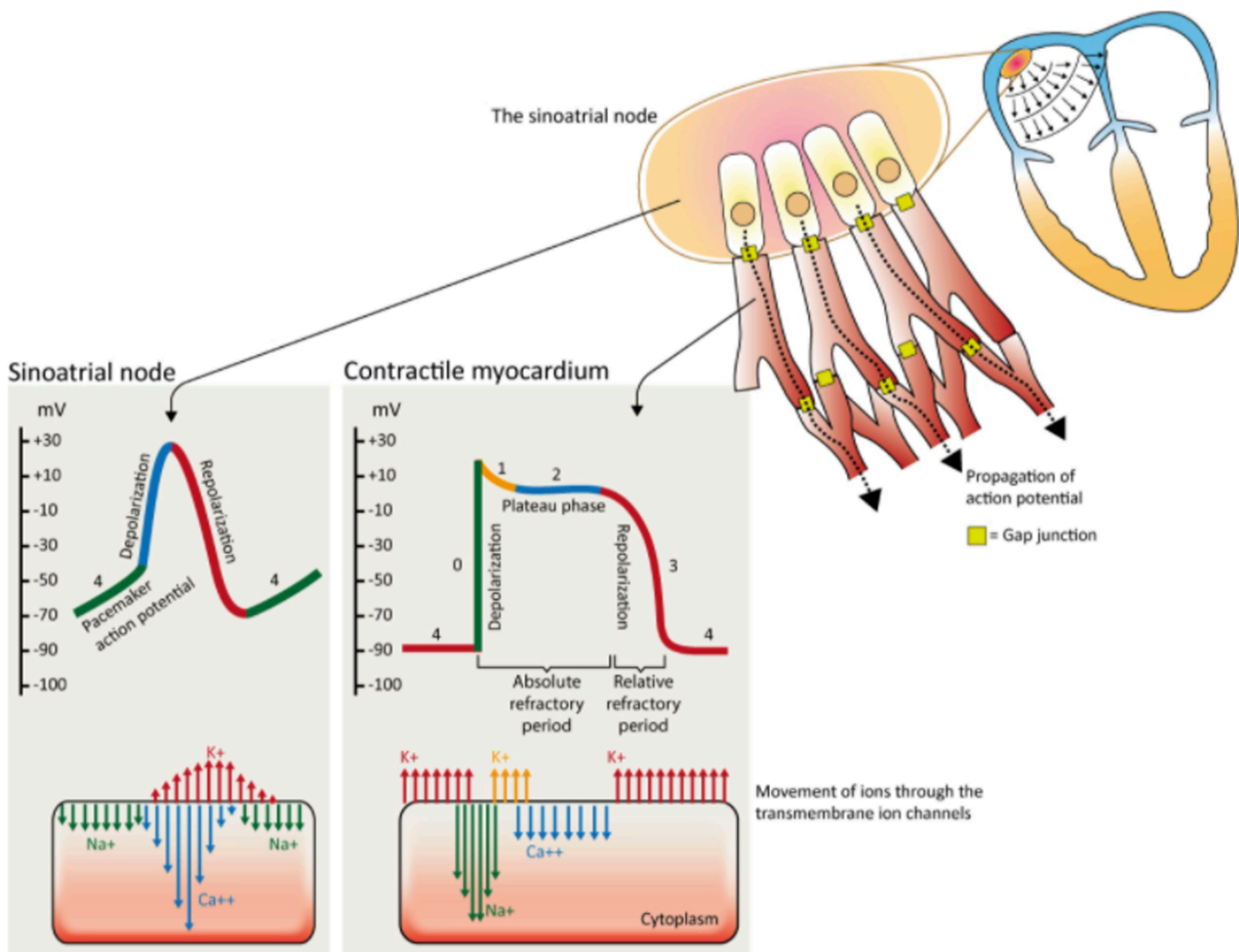


Figure 1. The action potential in the sinoatrial node and in contractile myocardial cells. Phase 4 of the action potential in the sinoatrial node is called 'pacemaker potential', because it is responsible for the spontaneous repetitive depolarization.

- **What occur during the resting phase? (CG)**

During the resting phase, or resting potential, of an action potential, the neuron (or other excitable cell, such as a muscle cell) is not actively transmitting signals. This period is characterized by the maintenance of a steady, negative electrical charge inside the cell relative to the outside. In other words, the cell is polarized.

1. **Ion Channels and Pumps:** The resting membrane potential is primarily maintained by ion channels and ion pumps in the cell's plasma membrane. There are more potassium ions (K^+) inside the cell and more sodium ions (Na^+) outside the cell. This difference in ion concentration is maintained by the sodium-potassium pump (Na^+/K^+ ATPase), which continuously pumps 3 Na^+ ions out of the cell and 2 K^+ ions into the cell against their concentration gradients, using energy from ATP.
2. **Resting Membrane Potential:** The combination of these ion movements and the selective permeability of the membrane to different ions (it's more permeable to K^+ than to Na^+) results in a net negative charge inside the cell, relative to the outside. This resting membrane potential is typically around -70 millivolts (mV).
3. **Ready for Stimulation:** Despite appearing "inactive," the neuron is actually ready to rapidly respond to a stimulus during this phase. When a sufficient stimulus is received, voltage-gated sodium channels will open, causing an influx of Na^+ into the cell, which is the start of the depolarization phase and the generation of an action potential.

After an action potential has been generated and propagated, the cell returns to the resting potential, a phase known as repolarization. This process is mediated by the closing of voltage-gated sodium channels and the opening of voltage-gated potassium channels, allowing K^+ to leave the cell. Once the resting potential is reestablished, the neuron is ready to fire another action potential if needed.

- **Funny channels (pacemaker cells) CG**

... slow influx of sodium → influx of calcium → depolarize → efflux of potassium → repolarize

Yes, that's a good basic understanding of how the pacemaker cells in the heart, such as those in the sinoatrial node (SA node), generate action potentials to set the heart rate.

1. **Funny Current (I_f):** At the end of the previous action potential, the membrane potential of the pacemaker cells is around -60 mV. From this point, the so-called "funny current" (also known as pacemaker current) begins, where certain ion channels (HCN channels) slowly allow an influx of positive ions, primarily sodium ions, into the cell. This current is "funny" because, unlike most voltage-gated channels, these open when the membrane potential is more negative (hyperpolarized). This slow depolarization is often referred to as the pacemaker potential.
2. **Calcium Influx:** As the membrane potential reaches about -50 mV, T-type (transient) calcium channels briefly open, allowing calcium ions to enter the cell and contributing to further depolarization.
3. **Rapid Depolarization:** At approximately -40 mV, L-type (long-lasting) calcium channels open. This leads to a more substantial calcium influx, causing the rapid depolarization phase and bringing the membrane potential to about +10 mV.
4. **Potassium Efflux:** At the peak of the action potential, potassium channels open, allowing an outflow of potassium ions (K^+) from the cell. This repolarizes the membrane, bringing the membrane potential back down. As the membrane potential approaches -60 mV, these potassium channels close, and the funny channels reopen to start the cycle again.

This sequence allows the pacemaker cells to generate rhythmic action potentials without any external input, effectively setting the pace of the heartbeat. The actual heart rate can be modified by nervous or hormonal influence, which can change the rate of these processes.

- **Differences between pacemaker cells (mostly found in SA node) and non-pacemaker cells**

- rest potential or not
- In the absence of stimulation, **non-pacemaker cells** (including the ventricular and atrial cells) have a relatively constant membrane potential; this is known as a resting potential. This resting phase (see cardiac action potential, phase 4) **ends when an action potential reaches the cell**. This produces a positive change in membrane potential, known as depolarization, which is propagated throughout the heart and initiates muscle contraction.

- Pacemaker cells, however, **do not have a resting potential**. Instead, immediately after repolarization, the membrane potential of these cells begins to depolarise again automatically, a phenomenon known as the pacemaker potential. Once the pacemaker potential reaches a set value, the threshold potential, it produces an action potential

- **How fibroblast affect conduction**

- acting as obstacles
- creating electronic loading (an electrical component or portion of a circuit that consumes electric power, such as electrical appliances and lights inside the home.)
- depolarizing myocytes
- An increase in myocyte resting V_m by coupling to the **more depolarized fibroblasts** can result in **increased conduction velocity** at low fibroblast densities
- passive electric insulators between myocytes
- act as current sinks, short-range conductors

- **Absolute and Relative refractory periods**

- ARP represents the time required for Na^+ ion channel gate to reset to their resting positions after an action potential has begun
- RRP: Na^+ channels reset to original position **while K^+ channels remain open** → only a larger-than-normal stimulus can initiate a new action potential

- **How action potential is transferred in the heart?**

- (SA) Sinus node → Atrial muscle → AV node → common bundle → bundle branches → Purkinje fibers → ventricular muscle

Yes, that's correct. The pathway you've outlined is the general route of electrical conduction in the heart, which ensures that the heart beats in a coordinated manner, with the atria contracting slightly before the ventricles to allow for efficient blood flow. Here's a bit more detail:

2. **Sinoatrial (SA) Node:** The action potential originates in the SA node, also known as the sinus node, located in the right atrium. The SA node is the natural pacemaker of the heart due to its high rate of automaticity—meaning it spontaneously generates action potentials at a faster rate than other cardiac cells.
3. **Atrial Muscle:** The electrical impulse from the SA node spreads through the walls of the atria, causing them to contract (atrial systole).
4. **Atrioventricular (AV) Node:** The action potential then reaches the AV node, located at the lower part of the interatrial septum. There is a slight delay here, allowing the atria to complete their contraction and the ventricles to fill with blood before they begin to contract.
5. **Bundle of His:** From the AV node, the impulse travels down the bundle of His (also known as the AV bundle or common bundle), a pathway located in the interventricular septum.
6. **Bundle Branches:** The bundle of His divides into the right and left bundle branches, which carry the impulse down either side of the interventricular septum.
7. **Purkinje Fibers:** The bundle branches further divide into Purkinje fibers, which rapidly spread the action potential throughout the ventricular myocardium (the muscle of the ventricles).
8. **Ventricular Muscle:** The electrical impulse triggers contraction of the ventricular muscle (ventricular systole), which pumps blood out of the heart—through the pulmonary artery from the right ventricle to the lungs for oxygenation, and through the aorta from the left ventricle to the rest of the body.

Following this, there is a brief period of electrical silence to allow the heart muscle to relax and refill with blood before the next cycle begins. This cycle of electrical conduction and corresponding contraction of heart muscle results in the rhythmic heartbeat.

Maintaining the Resting Membrane Potential Driving Force

(electrochemically)

- When an ion is not in equilibrium, a driving force acts on it, causing a net movement of the ion across the membrane down its electrochemical gradient.
- This driving force can be quantified as the difference between the membrane potential (E_m) and the Nernst potential for that ion (E_x) by the difference between the membrane potential and the ion equilibrium potential.

$$= E_m - E_x$$

(membrane - Nernst)
- The magnitude of the driving force is an indicator of how far an ion is from its electrochemical equilibrium.

...is the potential available to
drive ions across the membrane

- What is a syncytium?
 - (true def) is a **multinucleate** cell which can result from multiple cell fusions or uninuclear cells.
 - a network of cardiac muscle cells connected by gap junctions that allow **coordinate** contraction of the ventricle
 - cardiac muscle differs from a true syncytium (e.g. skeletal muscle) bc the cells are not long and multinucleated → is described as a **functional syncytium**

Strength–Duration Curve

- rheobase = minimum intensity of stimulus necessary no matter how long the applied time is

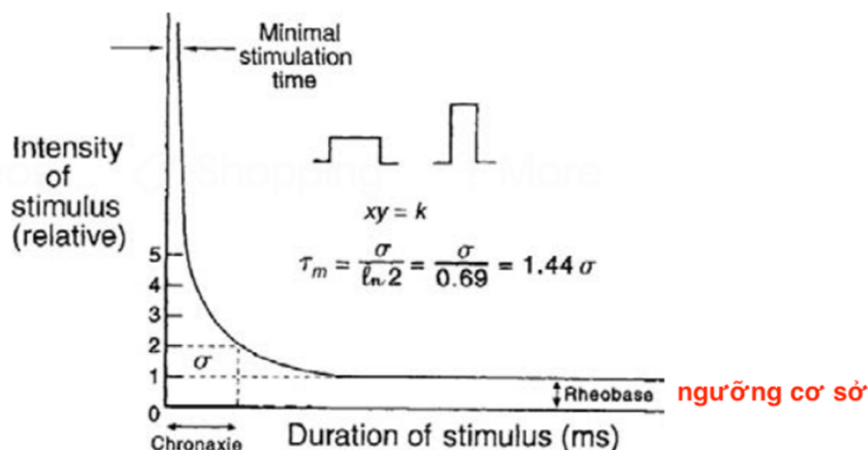


FIGURE 19.6 Strength–duration curve for AP initiation in excitable membranes. The intensity of rectangular stimulating pulses is plotted against their duration for stimuli that are just sufficient to elicit an AP. The rheobase current and chronaxie (σ) are indicated.

even for infinitesimal time, intensity never < rheobase

- $xy = k$ (or $Q = IT$): total charge transfer across the membrane required to produce excitation ~ nearly constant

- **Discuss the effects of remodeling in infarcted tissue on intercellular electrical coupling! Speculate about effects on anisotropy and velocity of electrical conduction! Note: Anisotropy of conduction is defined as the ratio of longitudinal to transverse conduction**

- more fibroblasts → CV decreases or even = 0 in extreme cases. bc
 - less coupling due to less volume fraction of myocytes

CG:

Remodeling in infarcted tissue can significantly impact intercellular electrical coupling, leading to alterations in anisotropy and velocity of electrical conduction.

2. Disruption of Gap Junctions: **loss or redistribution of gap junction** proteins responsible for electrical coupling between cells, leading to impaired intercellular electrical coupling.
 1. Decreased Cell-to-Cell Coupling: Reduced gap junction connectivity in infarcted tissue can result in decreased electrical coupling between neighboring cells, leading to conduction abnormalities, such as **slowed conduction and conduction blocks**.
3. Altered Anisotropy: Anisotropy refers to the **preferential conduction along specific directions** due to differences in tissue architecture.
 - In healthy cardiac tissue, anisotropy is **crucial for efficient propagation of electrical signals along the cardiac fibers**.
 - In infarcted tissue, the loss of structural integrity and remodeling can **disrupt the normal alignment of cardiac fibers, reducing anisotropy**, contribute to irregular or abnormal conduction patterns.
4. Formation of Conduction Pathways:
 - Infarcted tissue may develop **scar tissue**, consisting of **non-conductive fibrous tissue**, in the area of the infarct.
 - Scar tissue acts as a barrier to electrical conduction and can result in the **formation of conduction pathways around the infarcted region**.
 - These alternative conduction pathways can **create reentrant circuits and arrhythmogenic substrates**, leading to the development of abnormal cardiac rhythms.
5. Heterogeneous Conduction Velocity:
 - In infarcted tissue, **the presence of scar tissue and altered cellular coupling can result in spatial heterogeneity of conduction velocity**.
 - Areas of scar tissue typically **exhibit slower conduction due to the absence of viable cardiac cells**,
 - while adjacent regions with intact cells may show relatively normal conduction velocity. This heterogeneity in conduction velocity can **predispose the heart to arrhythmias, as it creates a substrate for conduction block, reentry, and wavefront collision**.

- **Scar - Reentrant circuit - Mismatch in conduction velocity - Wavefronts collisions?**

Scar tissue lacks viable cardiac cells and therefore exhibits slower conduction compared to adjacent regions with intact cells.

The slower conduction through scar tissue can lead to conduction block, where the electrical signal fails to propagate across the scarred area. This can create areas of unidirectional block, allowing for the formation of reentrant circuits. In a reentrant circuit, the electrical signal can continuously loop around the scar tissue, leading to abnormal, rapid, and potentially life-threatening arrhythmias.

Furthermore, the mismatch in conduction velocity between scar tissue and adjacent healthy tissue can result in wavefront collision. When an electrical **wave encounters an area of slower conduction, it can be partially blocked or delayed**. As a result, the wavefronts may collide, causing disturbances in the normal propagation of electrical signals. These collisions can further promote the formation of reentrant circuits and arrhythmias.

- a wavefront collision refers to the interaction or collision of two or more electrical wavefronts within the cardiac tissue. A wavefront represents the leading edge of an electrical activation or depolarization wave as it spreads across the heart.
- When a wavefront encounters an area of slower conduction, it may be partially blocked or delayed, causing it to slow down or **change direction**. As a result, the wavefronts may collide with each other, leading to disturbances in the normal propagation of electrical

signals. This collision of wavefronts can disrupt the coordinated contraction of the cardiac muscle and contribute to the formation of reentrant circuits.

- **Discuss the effects of the spatial arrangement of gap junction channels on cardiac conduction! Speculate** about effects of • side-to-side coupling • end-to-end coupling • down-regulation of connexins • up-regulation of connexins on anisotropy and velocity of conduction!

The **spatial arrangement of gap junction channels**, which are responsible for electrical coupling between cardiac cells, plays a crucial role in determining the conduction properties of the heart.

Side-to-Side Coupling:

- Anisotropy: Side-to-side coupling, refers to the **alignment of gap junction channels parallel to the direction of cardiac fibers**. This arrangement promotes **fast conduction along the longitudinal axis of the fibers**, leading to **high anisotropy**, facilitating efficient contraction and coordinated pumping.

End-to-End Coupling:

- Anisotropy: End-to-end coupling, involves the **alignment of gap junction channels perpendicular to the direction of cardiac fibers**. This arrangement promotes **conduction across the layers of the tissue**, providing electrical connectivity **between cells in different tissue depths**. It reduces anisotropy by facilitating conduction in multiple directions, rather than predominantly along the fibers.

- **Cellular Automaton**

CG

Cellular automaton models are computational models that **simulate complex systems through the interaction of discrete elements**, often referred to as "cells." Each cell **follows a set of predefined rules** based on its **current state and the states of its neighboring cells**. The cells are arranged in a regular grid or lattice structure, and the **system evolves in discrete time steps**.

In the context of cardiac conduction modeling, cellular automaton models can be used to simulate the propagation of excitation through discrete cells, representing the behavior of cardiac tissue. These models often involve rules that determine how excitation spreads and interacts with neighboring cells, allowing for the study of phenomena like arrhythmias, wave propagation, and the effects of tissue heterogeneities.

Cellular automaton models provide a **computationally efficient and conceptually straightforward** approach to simulate complex systems and have been valuable in understanding various phenomena in different scientific fields.

They have been particularly useful in understanding complex phenomena that exhibit **emergent behavior, such as pattern formation, self-organization, and phase transitions**.

▼ Atrial fibrillation

- No P waves
- irregularly irregular rhythm
- absence of an isoelectric baseline
- variable ventricular rate
- QRS usually < 120 ms (3 small blocks)
- Fibrillatory waves may mimic P waves leading to misdiagnosis



▼ Tachycardia

Two general types of arrhythmias that produce tachycardia:

- the supraventricular tachycardias, which arise in the atria of the heart
- the ventricular tachycardias, which arise in the ventricles

• Heart block

- Heart block occurs when the heart's **electrical impulses** are wholly or partially blocked as they travel **from the heart's atria to the ventricles**.
(There is delay without interruption in conduction from ATRIA TO VENTRICLES)
- Sign: prolonged PR interval
- When the heart's **ventricles can't get information from the sinus node about how fast to beat**, they use information **from another particular part of the heart between the atria and ventricles called the AV node**. This broken communication results in potentially dangerous bradycardia
- 3 degrees (may not necessary)
 - 1st: PR > 0.2 second (1 large box), no skipped beats
 - not symptomatic, ⇒ no treatment required
 - 2nd: some P waves are not followed by QRS → skipped beats occur
 - 3rd: no relationship between P waves and QRS (arbitrarily). P rate > QRS rate
 - No electrical communication between the Atria and the Ventricles
 - Cardiac function is maintained by an escape junctional or ventricular pacemaker⇒ Patients require a pacemaker

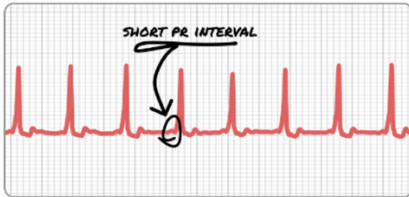
An ECG will help determine whether the slow heart rate is **due to sinus bradycardia or heart block**.

• Wolff-Parkinson-White (WPW) syndrome

Is a relatively common heart condition that causes the heart to beat abnormally **fast** for periods of time.

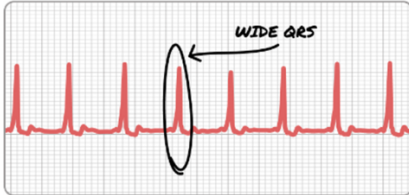
The extra electrical connection is caused by **a strand of heart muscle that grows** while the unborn baby is developing in the womb.

It's not clear exactly why this happens. It just seems to occur randomly in some babies, although rare cases have been found to run in families.



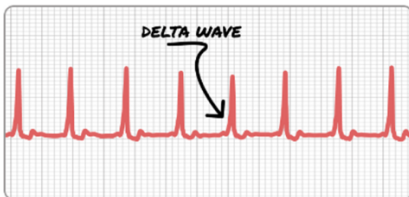
PR interval

- PR Interval is shorter than normal (less than 120 milliseconds)



QRS

- Wide QRS complex (greater than 120 milliseconds)



"Delta" wave

- Presence of a "delta" wave (slurred upstroke to the QRS complex)

STEMI

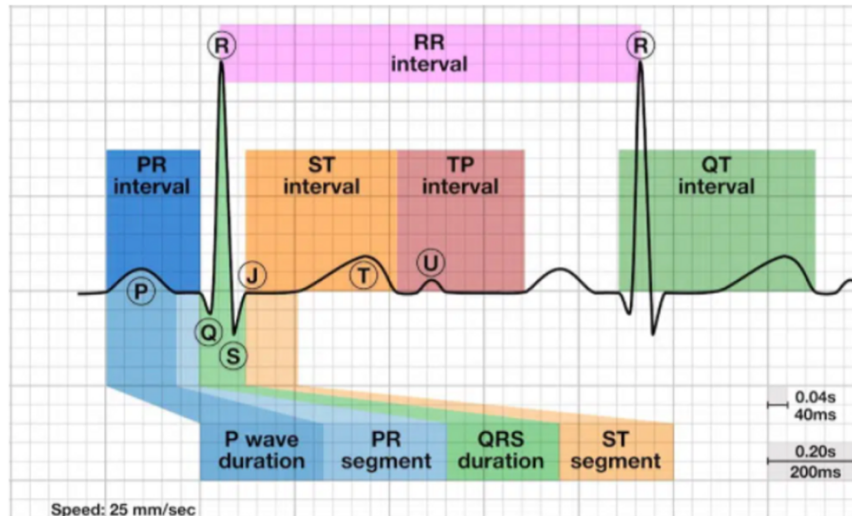
- A **STEMI** (ST-Segment Elevation Myocardial Infarction) is **the most severe type of heart attack**
- **STEMI**: Most commonly caused by an acute occlusion of a coronary blood vessel secondary to acute plaque rupture and thrombosis



S-T Segment

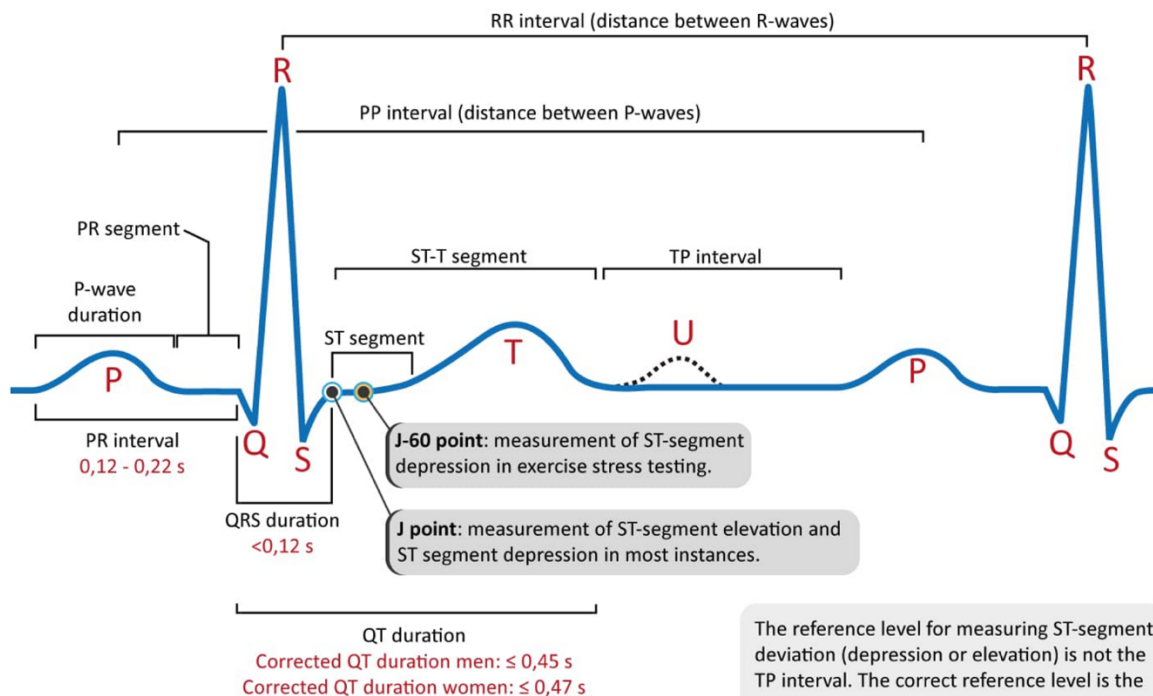
The **ST segment** is the flat, isoelectric section of the ECG between the end of the S wave (the J point) and the beginning of the T wave.

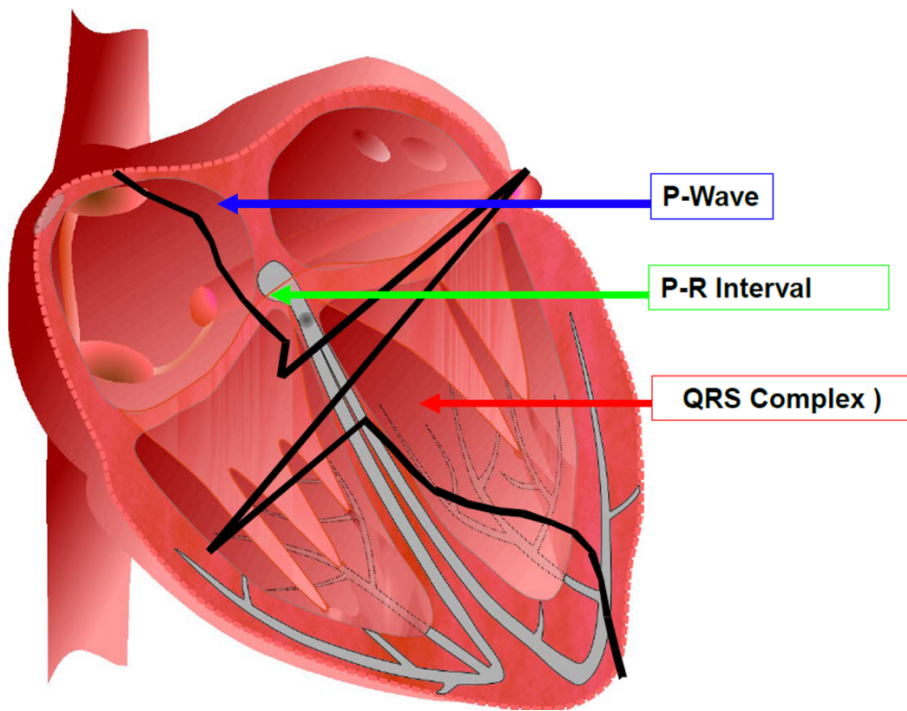
- The ST Segment represents the interval between ventricular depolarization and repolarization.
- The most important cause of ST segment abnormality (elevation or depression) is **myocardial ischaemia** or **infarction**.



P-wave, P-R interval, and QRS complex. PR interval? QRS duration?

- PR interval vs. PR segment
- PR segment = baseline level or isoelectric level





Atrial Flutter (flutter = Vẩy; vồ)

- Regular atrial activity at ~300bpm (1 big block)
- "saw-tooth" pattern of inverted flutter waves in leads II, III, aVF
- The ventricular rate is. fraction of the atrial rate

Fixed AV conduction ratio ("AV block")

Ventricular rate is a fraction of the atrial rate, e.g.

- 2:1 block = 150 bpm
- 3:1 block = 100 bpm
- 4:1 block = 75 bpm

Variable AV conduction ratio

- The ventricular response is irregular and may mimic AF
- On closer inspection, there may be a pattern of alternating 2:1, 3:1 and 4:1 conduction ratios

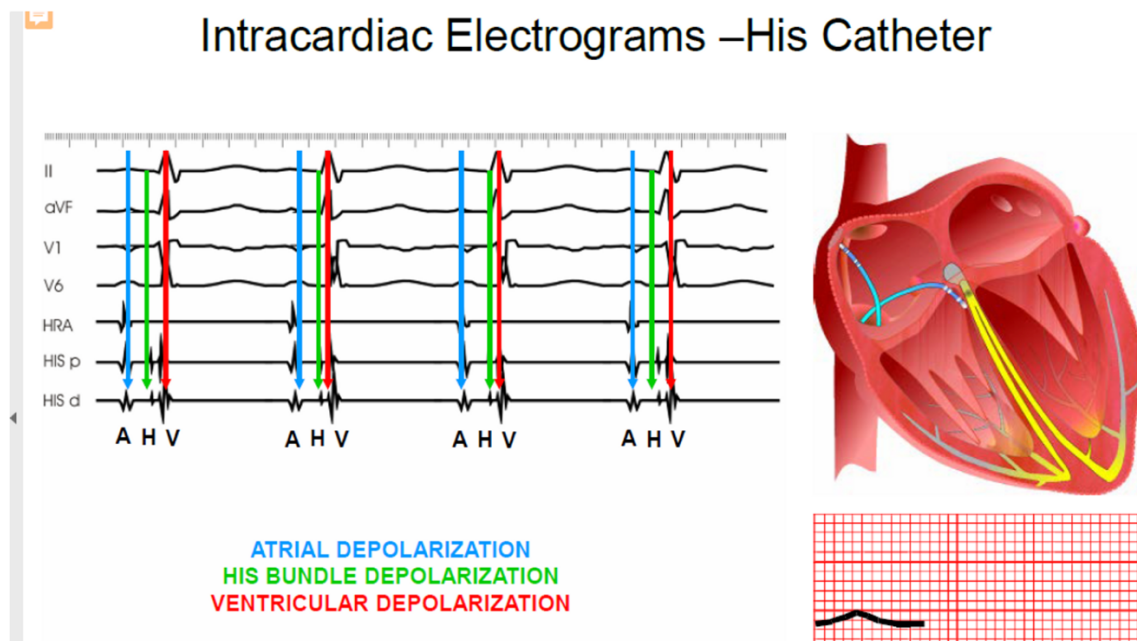


Atrial flutter with a 3:1 block

- P wave – the P wave represents the **atrial activation** as activation travels from the sinus node to just **before entering the AV node**.
- PR interval – the PR interval represents the **activation as it slowly travels through the AV node to just before the activation breaks out into the ventricles**.
- QRS complex – the QRS complex is the **activation of the right and left ventricles**.
- T wave?
 - Ventricular repolarization
 - (Atria repolarization happen during QRS)

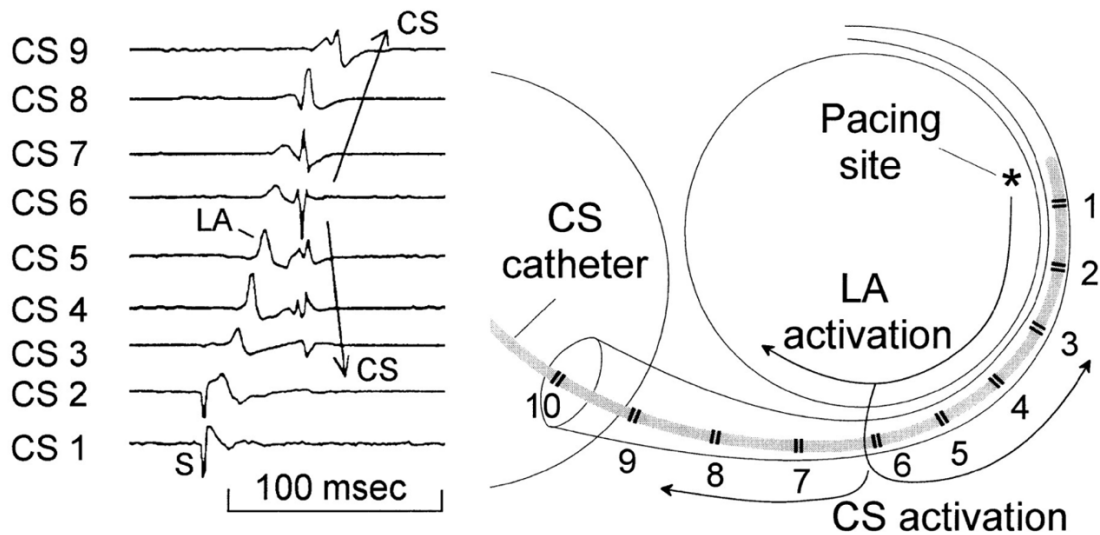
- **His Catheter: part in atrium and part in the ventricle**

- The AH interval represents **conduction from the lower atrium to the His**.
- Therefore, **the His catheter is excellent for evaluating AV node conduction**.
- If the **AH interval prolongs, that means conduction is slowing in the AV node**.



- **CS Catheter CS = Coronary Sinus. Accessory pathway criteria?**

- Since the CS catheter lies **between the left atrium and left ventricle**, it will record activity from the left atrium (A) and left ventricle (V).
- Thus, since conduction slows in the AV node, there should be **a delay between the A waves and V waves** as is seen in this diagram.
- If the patient had a **left sided accessory pathway** (abnormal connection between the atrium and ventricle which **allows direct conduction between them without a delay**) then there would be no or a very short delay noted at the **pair of electrodes close to the site of that accessory pathway**.



- **How EP study works**

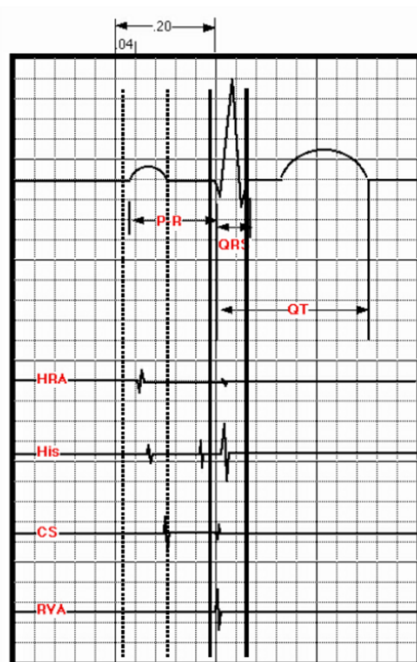
EP study involves

- the placement of multipolar electrode catheters in the heart, typically in the right side, which
- generates intracardiac electrograms (EGMs) followed by programmed electrical stimulation (PES) to trigger a focus arrhythmia.

- **AHV and 4 standard catheters in EP study**

- HRA: high right atrium
- His
- CS
- RVA: record the earliest ventricular activation

Electrogram Recordings - correlation with surface ECG



- Between dashed lines = A wave
- Between solid lines = V wave
- Between dashed & solid lines = H potential if from the His catheter

What if no P wave or QRS complex?

If a P wave is absent there is a lack of atrial depolarization. This is also known as atrial standstill. P waves that are combined in the QRS complexes are indicative of ventricular tachycardia or a junctional tachycardia. Present P waves that are without a QRS are indicative of an atrial depolarization that has not been conducted through the AV node. A QRS complex without a P wave demonstrate premature or escape beats.

- QRS: produced by the Atrioventricular Node (AV)
- P: atrial depolarization
- QRS: ventricular depolarization
- T: ventricular repolarization
- What is the forward problem? What is the inverse problem? (start with 3 factors). In a clinical situation?
 - Source; Conducting medium; Field
 - Forward: the problem in which the source and the conducting medium are known but the field is unknown and must be determined. $\Rightarrow$ the forward problem has a **unique solution**
 - always possible to calculate the field
 - accuracy is limited only by the accuracy with which we can describe the source and volume conductor
 - this problem does not arise in clinical (diagnostic) situations. In clinical situations, only the field can be measured (noninvasively) at the body surface
 - Inverse: the problem in which the field and the conductor are known but the source is unknown
 - In everyday clinical diagnosis, the cardiologist and the neurologist **seek to determine the source of the measured bioelectric or biomagnetic signals.**

What is the forward problem of ECG

Forward problem of ECG

- Forward problem involves computation of BSP (body surface potentials)
- from specified cardiac generators, that
- represent the electrical activity of the heart.

The problem can be formulated in different ways,

- depending on the assumptions regarding the EQUIVALENT SOURCES for the cardiac electrical activity and
- a representation of GEOMETRIC & ELECTRICAL properties of the VOLUME CONDUCTOR in which these sources are embedded.

▼ Current density $\mathbf{J}$ vs $\mathbf{E}$ and Φ

The current density $\mathbf{J}$ (current per unit of cross-sectional area) is related to the electric field, $\mathbf{E}$, by Ohm's law, namely,

$$\mathbf{J} = \sigma \mathbf{E} = -\sigma \nabla \Phi \quad \boxed{\mathbf{J} = \sigma \mathbf{E}} \quad (2.2)$$

▼ Thus, potential field is

The potential field may now be evaluated if we apply Eq. (2.2) to (2.17). The result is

$$\nabla \Phi = -\frac{I_0}{4\pi\sigma r^2} \bar{a}_r \quad (2.19)$$

so

$$\frac{d\Phi}{dr} = -\frac{I_0}{4\pi\sigma r^2} \quad (2.20)$$

Integration with respect to r gives an expression for the electric scalar potential, Φ_m , arising from a *monopole source* (a point source), namely,

$$\Phi_m = \frac{I_0}{4\pi\sigma r} \quad (2.21)$$

▼ Source density (current source density?) = divergence of current density $\mathbf{J}$

The conducting region, in general, may be considered to contain current sources described by a source density $I_v(x, y, z)$. Sources may occur naturally, as in a membrane, or artificially, as from a stimulus electrode.

From the divergence properties of the current density, $\mathbf{J}$, we require

$$\nabla \cdot \mathbf{J} = I_v$$

(scalar) (2.3) ✓
 $\boxed{\text{Div. of current density}} = \boxed{\text{Source density}}$

▼ Poisson's equation: For a region that contains a source density (with homogeneous conductivity)

$$\nabla \cdot \mathbf{J} = I_v = -\sigma \nabla^2 \Phi \quad (2.4)$$

$\nabla^2 \Phi$ scalar
 $-\sigma \nabla^2 \Phi = I_v$: current sources

Thus, for a region where the conductivity is homogeneous but which contains a source density I_v , Poisson's equation for Φ results, namely [from (2.4)],

$$\nabla^2 \Phi = -\frac{I_v}{\sigma} \quad \left(\begin{array}{l} = \nabla \cdot \mathbf{J} \\ (\mathbf{J} = \sigma \mathbf{E}) \end{array} \right) \quad (2.5)$$

- Rather than isolated monopoles, PAIRS of MONOPOLES of equal and opposite signs, close together, are the fundamental unit source in electrophysiology (CG)

In electrophysiology, the concept of pairs of monopoles, also known as dipoles, is used as the fundamental unit source rather than isolated monopoles. This is because dipole sources provide a more accurate representation of the electrical activity in biological systems, particularly in the context of measuring and analyzing bioelectric signals such as those generated by the brain or the heart.

Here are a few reasons why pairs of monopoles, or dipoles, are favored in electrophysiology:

1. Cancellation of far-field effects: When a pair of monopoles with equal and opposite charges are placed close together, the far-field effects produced by each monopole cancel each other out. This cancellation occurs because the electrical fields generated by the two monopoles have opposite polarities and tend to cancel each other when measured at a distance. By using dipoles, the focus is primarily on the near-field effects, which are of greater interest in studying bioelectric phenomena.
2. Localization of sources: Dipoles allow for better localization of the sources of electrical activity in biological systems. The spatial orientation and position of a dipole can provide information about the underlying electrical generators, such as the direction and magnitude of the current flow. By considering pairs of monopoles, the electrical activity can be characterized more accurately in terms of the specific locations and orientations of the dipole sources.
3. Dipole modeling of neurons and tissues: Neurons and tissues in biological systems are complex structures with distributed electrical activity. While individual neurons can be represented as point sources (monopoles), the collective behavior of neuronal populations is better approximated by dipole sources. By considering dipole models, it becomes possible to capture the net electrical activity of multiple neurons or tissue regions simultaneously, leading to a more comprehensive understanding of the underlying bioelectric processes.
4. Electrode configurations: In practical electrophysiological measurements, such as electroencephalography (EEG) or electrocardiography (ECG), electrode configurations are designed to capture the dipole-like patterns of electrical activity. The placement of multiple electrodes in specific arrangements allows for the detection and analysis of dipole sources and their orientation. This further supports the use of dipole models as the fundamental unit source in electrophysiology.

Overall, the use of pairs of monopoles, or dipoles, as the fundamental unit source in electrophysiology offers a more accurate representation and analysis of the electrical activity in biological systems. It allows for better localization, cancellation of far-field effects, and modeling of complex neuronal or tissue behavior, leading to improved understanding and interpretation of bioelectric signals.

current source density f

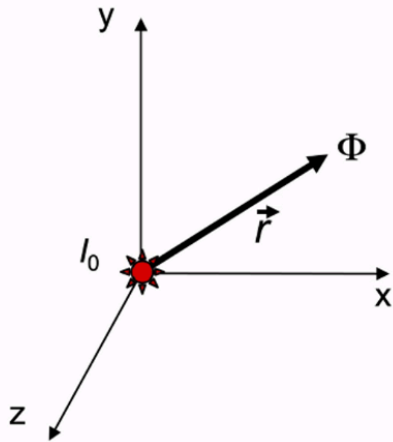
- charge/time/volume

$$\nabla \cdot (\sigma \nabla \phi) = f$$

f : Current source density [A / m³]

From Monopole to Dipole

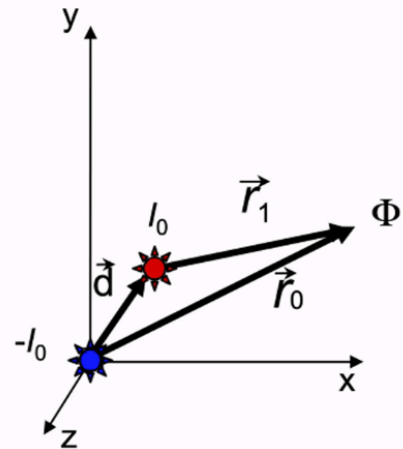
Monopole Source



$$r = |\vec{r}| \quad \vec{r} = r \hat{r}$$

$$\Phi = \frac{1}{4\pi\sigma_e} \frac{I_o}{r}$$

Dipole Source



$$\vec{p} = I_o \vec{d} \quad d \rightarrow 0, I_o \rightarrow \infty$$

$$\Phi = \frac{\vec{p}}{4\pi\sigma} \cdot \nabla\left(\frac{1}{r}\right) = \frac{\vec{p}}{4\pi\sigma} \cdot \frac{1}{r^2} \hat{r}$$

(see Plonsey&Barr, page 30-, for derivation)

▼ Electric current density [____] & Electric displacement field (電束密度) [____]

- Electric displacement: denoted by D , is the **charge per unit area** that would be displaced across a layer of conductor placed across an electric field

- J : A/m²

- D : C/m²

▼ $J = \text{_____}$ $D = \text{_____}$

- σE

- ϵE

▼ figure

Electrical Fields and Currents - Definitions

$$\mathbf{E} = -\nabla\phi$$

$\mathbf{E}$: Electric field [V/m]

ϕ : Electric potential [V]

∇ : Gradient operator

$$\mathbf{D} = \epsilon \mathbf{E}$$

D : Electric displacement field [C/m²]

ϵ : Electrical permittivity [F/m]

Electrostatics

F: Farad

C: Coulomb

[F] = [C] / [V]

$$\mathbf{J} = \sigma \mathbf{E}$$

$\mathbf{J}$: Electric current density [A/m²]

σ : Electrical conductivity [S/m]

Flux of charge

S: Siemens

[S] = 1 / [Ω]

- **How increasing K⁺ conductance of pacemaker cells lead to reduced heart rate?**

The pacemaker potential is determined by the balance of ions moving in and out of the pacemaker cells, including sodium (Na⁺), calcium (Ca²⁺), and potassium (K⁺). At the end of an action potential, potassium channels open, allowing K⁺ ions to flow out of the cell. This outward flow of positively charged ions causes the inside of the cell to become more negative, leading to repolarization.

When the conductance of K⁺ is increased, more K⁺ ions leave the pacemaker cells. This makes the inside of the cell more negative (hyperpolarizes the cell) and slows the rate of spontaneous depolarization. Since the pacemaker potential takes longer to reach the threshold potential for triggering an action potential, the result is a slower heart rate.

This mechanism is the basis for the action of certain drugs, like beta blockers, that work to slow the heart rate by increasing K⁺ conductance in the SA node.

- **How too low end-diastolic volume affect contraction according to frank starling?**

If the EDV is too low, this means that the ventricles are not filling with enough blood during diastole. As a result, the cardiac muscle fibers are not stretched as much, leading to a less forceful contraction and thus a lower stroke volume. This could result in a lower cardiac output (since cardiac output is the product of heart rate and stroke volume), which means that less blood and oxygen are being delivered to the tissues of the body. In severe cases, this could contribute to symptoms of heart failure.

- **Actin-myosin binding site**

Exposure of Actin Binding Sites: In a relaxed muscle fiber, the binding sites on actin are blocked by another protein called tropomyosin. However, when the muscle cell is stimulated to contract, calcium ions are released inside the muscle cell. These calcium ions bind to another protein called troponin, which then changes shape and moves tropomyosin out of the way, exposing the binding sites on actin.

Cross-Bridge Formation & Power Stroke: Once the binding sites on actin are exposed, the "cocked" myosin head binds to actin, forming a cross-bridge. Then, ADP and phosphate are released from the myosin head, which triggers the power stroke. During the power stroke, the myosin head pivots and pulls the actin filament towards the center of the sarcomere, the basic functional unit of the muscle fiber.

- **Examples of discrete microscopic models?**

Discrete microscopic models used in cardiac electrophysiology often involve the simulation of individual cells or networks of cells, with detailed representations of the ionic currents and other electrophysiological properties of these cells. Here are a few examples:

1. **Cellular Automata Models:** These are discrete models where the heart tissue is represented as a grid of cells, each of which can be in one of a finite number of states (e.g., resting, excited, refractory). The state of each cell at each time step is determined by the states of its neighboring cells according to a set of simple rules. Cellular automata models are particularly useful for studying the propagation of electrical waves through cardiac tissue and the formation of arrhythmias.
2. **Ionic Models:** These are detailed mathematical models that describe the behavior of individual ion channels and other subcellular structures within cardiac cells. These models can capture the complex dynamics of the various ionic currents that contribute to the cardiac action potential. One of the most famous ionic models is the Hodgkin-Huxley model, which was originally developed to describe the action potential in the squid giant axon but has been adapted for cardiac cells.
3. **Network Models:** These are models that represent the heart as a network of interconnected cells or groups of cells. Each node in the network represents a cell or group of cells, and the edges represent the connections between them. Network models can capture the complex interactions between different parts of the heart and can be used to study the propagation of electrical signals and the formation of arrhythmias.

Each of these models has its strengths and weaknesses, and the choice of model depends on the specific research question and the level of detail required.

- **Monodomain**

The **monodomain model** is a continuous, macroscopic model that represents the heart tissue as a single continuous domain. This model treats the intracellular and extracellular spaces as a single averaged domain. It simplifies the complex three-dimensional structure of the cardiac tissue into a single effective space and is widely used due to its computational efficiency.

The monodomain model is based on the assumption that the ratio of intracellular to extracellular conductivity is very large, meaning that the voltages inside and outside of the cells quickly equilibrate. This model uses partial differential equations to represent the spread of electrical signals through the cardiac tissue.

- **How can fibroblasts affect conduction in the heart? Give some mechanisms**

Fibroblasts are one of the major cell types in the heart, and their role has been traditionally associated with maintaining the structure of the cardiac tissue, producing extracellular matrix proteins, and contributing to wound healing and tissue repair. However, emerging evidence suggests that fibroblasts can significantly influence cardiac electrophysiology and contribute to abnormalities in heart rhythm, also known as arrhythmias. Here are a few mechanisms through which fibroblasts can affect cardiac conduction:

1. **Electrical Coupling:** Fibroblasts can electrically couple with cardiomyocytes (heart muscle cells) through structures known as gap junctions, which allow ions and small molecules to pass directly from one cell to another. This coupling can modulate the electrical activity of the heart. For example, it can reduce the conduction velocity and change the shape of the action potential, which can lead to abnormalities in heart rhythm.
2. **Fibrosis:** In response to cardiac injury or stress, fibroblasts can proliferate and differentiate into myofibroblasts, a cell type that produces excessive amounts of extracellular matrix proteins, leading to a condition known as fibrosis. The fibrotic tissue can disrupt the normal electrical pathways in the heart and create regions of slow conduction or conduction block, which can contribute to arrhythmias.
3. **Paracrine Signaling:** Fibroblasts can release a variety of signaling molecules that can influence the behavior of cardiomyocytes. For example, they can secrete growth factors, cytokines, and extracellular vesicles that can modulate the electrical properties of the cardiomyocytes, altering cardiac conduction.
4. **Modulation of Ion Channels:** Fibroblasts can influence the expression and function of ion channels in cardiomyocytes, which can alter the cardiac action potential and conduction velocity.

- **ECG signs of sinus bradycardia vs heart block?**

Sinus Bradycardia: Sinus bradycardia on an EKG will show a regular rhythm with a rate of less than 60 beats per minute. The P waves (which represent atrial depolarization) will be normal and precede each QRS complex (which represents ventricular depolarization), reflecting the normal conduction of electrical signals from the atria to the ventricles. The PR interval (the time from the onset of the P wave to the onset of the QRS complex) will be within the normal range (0.12 to 0.20 seconds).

Heart Block: The EKG findings for heart block depend on the type of heart block:

1. **First-degree heart block:** The EKG will show a regular rhythm with a prolonged PR interval of more than 0.20 seconds. Each P wave is followed by a QRS complex.
2. **Second-degree heart block (Mobitz type I or Wenckebach):** The EKG will show progressively lengthening PR intervals until a QRS complex is dropped (a P wave not followed by a QRS complex). The cycle then repeats.
3. **Second-degree heart block (Mobitz type II):** The EKG will show a regular or irregular rhythm, and some P waves are not followed by QRS complexes, but the PR intervals of the conducted beats remain constant.

4. **Third-degree heart block (complete heart block):** The EKG will show an atrial rate that is faster than the ventricular rate, and there is no relationship between the P waves and the QRS complexes (i.e., they are dissociated). The P waves and QRS complexes each follow a regular, but separate, rhythm.

- **Atrial flutter vs atrial fibrillation?**

Atrial Flutter:

- Regular, rapid contractions of the atria (250-350 beats per minute)
- On EKG, appears as regular, "sawtooth" flutter waves
- Ventricular response often fractionated (e.g., every second or third atrial impulse gets through to the ventricles)
- Typically due to a "re-entry circuit," often in the right atrium

Atrial Fibrillation (AFib):

- Irregular, chaotic electrical activity in the atria (rate can exceed 350-600 beats per minute)
- On EKG, characterized by irregular R-R intervals and absence of distinct P waves
- Ventricular response is irregularly irregular
- Occurs due to multiple re-entry circuits in the atria

- **Summarize 4 standard catheters in EP study**

An electrophysiology (EP) study uses catheters to record electrical signals from the heart and/or to stimulate different parts of the heart with electrical impulses. Typically, at least four catheter positions are used in a standard EP study:

- **High Right Atrium (HRA) Catheter:** This catheter is usually positioned in the high right atrium near the sinus node. It is often used for recording electrical signals from the atrium and for pacing the atrium.
- **His Bundle (HB) Catheter:** The HB catheter is positioned to record electrical signals from the bundle of His, which is the area of the conduction system that carries electrical signals from the atria to the ventricles. Recording from the His bundle allows the measurement of conduction times through the atria, the AV node, and into the ventricles.
- **Right Ventricular Apex (RVA) Catheter:** This catheter is positioned in the apex of the right ventricle. It can be used for pacing the ventricles and for recording ventricular electrical signals.
- **Coronary Sinus (CS) Catheter:** The CS catheter is positioned in the coronary sinus, a vein that collects blood from the myocardium. This catheter is typically used for recording electrical signals from the left atrium and/or left ventricle, as well as for pacing the left side of the heart.

These catheter positions offer the capability to measure the electrical activity across all chambers of the heart and to induce or pace different rhythms for diagnostic and treatment purposes. Each position helps provide a comprehensive view of the heart's electrical system and can contribute to diagnosing and treating various types of heart rhythm disorders.

- **Cardiac Muscle Contraction (preload, afterload)**

- **Preload**

- Defined as the volume of blood in the ventricles at the end of diastole, just before contraction.
- Essentially the stretch on the heart muscle prior to its contraction.
- According to the Frank-Starling law, a greater preload (more blood volume, more stretch) results in a stronger subsequent contraction, allowing the heart to adjust its pumping capacity.
- Factors increasing preload include venous return and overall blood volume.
- Health conditions like heart valve disorders, hypertensive heart disease, and congestive heart failure can alter preload.
- In cases of heart failure, the heart often can't pump out all the blood it receives, resulting in increased preload.

- **Afterload**
 - Defined as the pressure the heart must overcome to eject blood during systole.
 - Mainly determined by the resistance in the blood vessels.
 - If afterload is too high, as in conditions like hypertension, the heart must work harder, potentially leading to heart muscle weakness or failure.
- **GJ overview**
 - Specialized intercellular connections found between many types of animal cells.
 - Particularly important in the heart, enabling rapid transmission of electrical signals from cell to cell, which allows for coordinated and synchronized heart contractions.
 - **Structure**
 - Composed of two connexons or hemichannels, each from an adjacent cell, which join to form a direct pathway between the cells.
 - Each connexon consists of six proteins known as connexins.
 - Different types of connexins are expressed in various tissues, including the heart, and can create homomeric or heteromeric connexons, leading to homotypic or heterotypic gap junctions.
 - **Function in the Heart**
 - Gap junctions are located in the intercalated disks connecting cardiac muscle cells (myocytes).
 - Facilitate the fast transmission of the action potential (electrical signal) across the heart, enabling the heart to contract in a unified way.
 - The flow of ions, particularly sodium, potassium, and calcium, through these gap junctions swiftly depolarizes the cell membrane of the connected cells, inducing their contraction nearly simultaneously.
 - **Clinical Significance**
 - Alterations in the number, distribution, or function of gap junctions can significantly impact heart function.
 - In certain heart diseases, the typical pattern of gap junction distribution is disrupted (a process known as gap junction remodeling), which can lead to arrhythmias.
- **Intercalated Disks and Safety Factor and Redundancy**
 - **Intercalated Disks**
 - Located at the end-to-end connections between individual cardiac muscle cells (cardiomyocytes).
 - Allow for quick and coordinated transmission of electrical signals across the heart, essential for synchronized heart muscle contraction.
 - **Safety Factor in Cardiac Conduction**
 - Describes the redundancy built into the cardiac conduction system ensuring a coordinated heart beat, even under conditions potentially disrupting normal electrical conduction.
 - Redundancy refers to multiple structures and mechanisms ensuring reliable transmission of electrical signals across the heart, allowing coordinated contraction.
 - This redundancy provides a "safety factor" maintaining heart function, even if one or more components of the system are impaired.
 - **Elements of Redundancy**

- **Multiple Pacemakers:** Primary pacemaker is the sinoatrial (SA) node, but other cells in the atria, the atrioventricular (AV) node, and the ventricles can also initiate electrical impulses. These secondary pacemakers provide a backup mechanism if the SA node or its conduction pathway fails.
- **Bidirectional Conduction:** The bundle branches (part of the His-Purkinje system) in the ventricles allow activation of the ventricular myocardium from two directions, ensuring complete depolarization, even if there's a blockage in one of the bundle branches.
- **Cell-to-Cell Coupling:** Cardiac muscle cells are interconnected by intercalated disks containing numerous gap junctions, ensuring the electrical signal's propagation across the heart muscle, even if some gap junctions are malfunctioning.
- **The Source-Sink Relationship:** Each depolarizing cell ("source") connects to multiple adjacent cells ("sink"), ensuring signal propagation even if some connections are disrupted.
- **Long Refractory Period:** Cardiac cells have a relatively long refractory period, preventing backward propagation of electrical signals and maintaining one-way conduction, even if the conduction pathway is disrupted.
- **Summary:** Numerous redundant mechanisms contribute to the safety factor in cardiac conduction, maintaining a regular, coordinated heartbeat even amidst potential disruptions.
- **SA Node Regulation**
 - **Sinoatrial (SA) Node**
 - Often called the natural pacemaker of the heart.
 - A small, specialized region of cardiac tissue located in the right atrium, initiating each heartbeat.
 - Generates electrical impulses propagating through the heart muscle, leading to coordinated contractions.
 - The SA node's automaticity is regulated by the autonomic nervous system, hormones, and local conditions within the heart.
 - **Autonomic Nervous System Regulation**
 - **Parasympathetic Stimulation (via the Vagus Nerve):** Acetylcholine released from vagus nerve terminals binds to M2 receptors on SA node cells. This opens potassium channels, leading to hyperpolarization and a slower rate of spontaneous depolarization, thus slowing the heart rate. This is often referred to as "vagal tone."
 - **Sympathetic Stimulation:** Norepinephrine from sympathetic nerve terminals binds to beta-1 adrenergic receptors on the SA node cells, opening "funny" (If) channels and calcium channels. This leads to a faster rate of spontaneous depolarization and an increased heart rate. It also increases the strength of cardiac contraction.
 - **Hormonal Regulation**
 - **Epinephrine and Norepinephrine:** These hormones, released by the adrenal glands during stress ("fight or flight" response), bind to beta-1 adrenergic receptors on the SA node, increasing heart rate similarly to direct sympathetic stimulation.
 - **Thyroid Hormones:** Elevated levels of thyroid hormones (T3 and T4) increase heart rate, presumably by enhancing the number of beta-1 adrenergic receptors and thus the heart's sensitivity to sympathetic stimulation.
 - **Local Condition Regulation**
 - **Temperature:** An increase in body temperature increases heart rate, presumably by increasing the rate of spontaneous depolarization in SA node cells.
 - **pH and Ion Concentrations:** Changes in the concentrations of various ions (like potassium, calcium) or the blood pH can influence the SA node's activity.

- **Stretch:** The SA node can directly respond to atrial wall stretching, such as when blood volume in the atria is increased. This response, called the "Bainbridge reflex," can lead to an increased heart rate.
- **Chronotropes & Inotropes**
 - **Chronotropic Agents**
 - Influence the heart rate by affecting the heart's electrical conduction system, particularly the SA node's activity.
 - **Positive Chronotropes:** Increase heart rate by accelerating spontaneous depolarization in the SA node. Examples include sympathetic neurotransmitters (e.g., norepinephrine), hormones (e.g., epinephrine), and certain medications (e.g., atropine).
 - **Negative Chronotropes:** Decrease heart rate by slowing down the spontaneous depolarization in the SA node. Examples include parasympathetic neurotransmitters (e.g., acetylcholine) and certain medications (e.g., beta-blockers).
 - **Inotropic Agents**
 - Influence the contractility (strength) of the heart muscle.
 - **Positive Inotropes:** Increase the force of heart contractions, usually by increasing available calcium for contractile proteins in heart muscle cells. Examples include sympathetic neurotransmitters (e.g., norepinephrine), hormones (e.g., epinephrine), and certain medications (e.g., digoxin, dobutamine).
 - **Negative Inotropes:** Decrease the force of heart contractions, typically by reducing available calcium for contractile proteins in heart muscle cells. Examples include certain medications like beta-blockers and some calcium channel blockers.

In summary, chronotropic and inotropic agents play key roles in regulating heart function, under normal conditions and during stress, injury, or disease. They adjust heart rate (chronotropy) and contractility (inotropy) to ensure that the heart can effectively pump blood according to the body's changing needs.

- **Optical Mapping**
 - Optical mapping allows researchers to visualize and analyze the electrical activity across a large area of tissue in real-time.
 - Often, optical mapping studies are performed on isolated heart tissues or whole hearts for accurate measurements in a controlled environment.
 - Advancements in technology have made in vivo optical mapping possible, studying the heart in a more physiologically relevant context.
 - In vivo optical mapping, however, presents challenges such as difficulty in delivering dyes to the heart, potential for motion artifacts, and maintaining the animal's health and stability throughout the experiment.

Process:

- **Preparation:**
 - Isolation and perfusion (supplied with blood or balanced salt solution) of the heart tissue or whole heart.
 - The tissue is loaded with a fluorescent dye sensitive to changes in the membrane potential (voltage-sensitive dyes) or concentration of certain ions like calcium (calcium-sensitive dyes).
- **Stimulation and Recording:**
 - The heart is stimulated, often electrically, to cause a contraction.
 - Changes in the fluorescence of the dye are recorded over time, resulting in images where each pixel's brightness corresponds to the membrane potential or ion concentration at each point on the tissue.
- **Analysis:**

- Images are analyzed to generate a map of the electrical activity across the heart tissue.
- This can reveal the direction and speed of electrical wave propagation, the presence of any abnormal electrical pathways, and the heart's response to different drugs or conditions.

Applications:

- Optical mapping is a versatile technique used in cardiovascular research to:
 - Study the mechanisms underlying different types of arrhythmias.
 - Assess the effects of different drugs or conditions on the heart's electrical activity.
 - Investigate the electrical properties of engineered heart tissues.
 - Understand the roles of different ion channels and transporters in heart function.

Advantages and Limitations:

- Advantages include high-resolution, real-time, non-invasive data collection on a tissue-wide scale, and simultaneous measurement of multiple parameters.
- Limitations include the requirement of specialized equipment and expertise, sensitivity to factors like tissue motion and changes in light intensity, potential toxicity of used dyes, and complex data interpretation, especially when studying three-dimensional structures.
- Despite these challenges, optical mapping is a powerful tool that has significantly advanced our understanding of heart function and disease. Its utility in cardiac research and potential clinical applications is expected to grow with ongoing technological improvements.

• **Sarcomeres**

- Sarcomeres are the basic functional units of striated muscle tissue, including cardiac muscle.
- They are the smallest contractile units within a muscle fiber (myofibril), arranged end-to-end along the myofibril's length.
- Sarcomeres give the striated appearance to cardiac and skeletal muscle and generate the force for muscle contraction.
- Each sarcomere is bordered by two Z-discs (Z-lines), with overlapping thick (myosin) and thin (actin) filaments within these boundaries.
- The M-line, located in the center of the sarcomere, helps keep the thick filaments aligned.
- The H-zone surrounds the M-line and contains only myosin filaments; its width varies with muscle contraction or relaxation.
- The A-band spans the length of the myosin filaments and its length stays constant.
- The I-band, which contains only actin filaments, shrinks during muscle contraction.
- Muscle contraction is explained by the sliding filament theory, where actin and myosin filaments slide past each other, resulting in sarcomere shortening and thus muscle fiber contraction.

• **Fibroblasts and Myofibroblasts**

1. Introduction to Fibroblasts:

- Fibroblasts are cells found in connective tissues throughout the body, including the heart.
- They produce collagen and other extracellular matrix proteins, providing structural support to tissues.
- In the heart, fibroblasts maintain cardiac tissue structure, mediate repair after injury, and communicate with other heart cells.

2. Fibroblasts Transformation:

- Upon tissue injury, fibroblasts can transform into myofibroblasts.
- Myofibroblasts are more active in producing extracellular matrix components.

- Myofibroblasts exhibit contractile properties due to alpha-smooth muscle actin.

3. Myofibroblasts Role in Wound Healing:

- The main function of myofibroblasts is wound healing: they contract to close wounds and secrete extracellular matrix proteins to form scars.

4. Myofibroblasts and Heart Fibrosis:

- Persistent myofibroblasts in the heart post-injury can lead to fibrosis, an overgrowth of connective tissue that can interfere with normal heart function.
- Fibrosis is a common feature in various heart diseases, such as heart failure and myocardial infarction.

• Refractory Periods

- Refractory periods are divided into two distinct stages: Absolute Refractory Period and Relative Refractory Period.

Absolute Refractory Period:

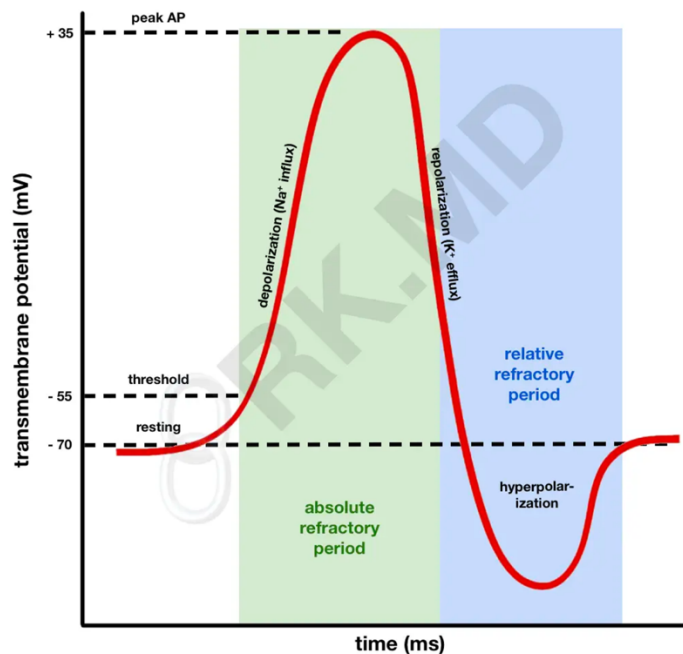
- Occurs immediately after an action potential.
- The cardiac cell can't respond to any new stimulus, regardless of its strength.
- This period is due to **inactivation of voltage-gated sodium channels**, which are essential for initiating and propagating action potentials.
- The heart's absolute refractory period is longer than in many other cell types, preventing tetanic contractions.

Relative Refractory Period:

- This period directly follows the absolute refractory period.
- During this time, a stronger than normal stimulus can initiate another action potential.
- This occurs as some sodium channels have transitioned from the inactivated state back to the resting state and can thus be opened again.

Importance of Refractory Periods:

- The sequence of these periods ensures unidirectional propagation of action potentials along nerves and muscle fibers, including those in the heart.
- It also prevents the occurrence of tetanus (a state of sustained contraction) in cardiac muscle, maintaining the heart's function as a pump.



- **Accommodation**

- 1. Definition:**

- Accommodation in electrophysiology refers to the adaptation of cells or tissues to sustained changes in their electrical environment.
 - The specific mechanisms of accommodation can differ based on cell type and the nature of the stimulus.

- 2. Accommodation in the Heart:**

- Accommodation can refer to the heart's ability to adapt to sustained changes in heart rate or blood pressure.

- 3. Example: Exercise**

- During exercise, the heart initially responds to increased demand with higher heart rate and contractility (due to sympathetic nervous system activation).
 - Over time, the heart "accommodates" this increased demand through cardiac remodeling, which involves increasing its size and strength.

- 4. Differentiation: Beneficial vs. Pathological Accommodation**

- Cardiac remodeling and accommodation is generally beneficial in response to exercise.
 - However, in the context of chronic heart disease, this process can become pathological.

- **The Heart Dipole and Projecting It onto Leads**

- 1. Understanding Heart Dipole:**

- The heart's electrical activity creates a dipole - a pair of equal but oppositely charged electric charges or magnetic poles separated by a distance.
 - During each heartbeat, depolarization moves from the endocardium (inner layer of the heart wall) to the epicardium (outer layer), establishing a temporary dipole. The direction points from the heart's base (near the atria) towards its apex.

- 2. Changing Dipole & Mean Electrical Axis:**

- The heart's dipole alters as different parts of the heart depolarize and then repolarize.
 - The 'average' of these varying dipoles forms the mean electrical axis of the heart, providing critical information about the heart's structure and function.
 - Deviation of the axis to the right or left may indicate the enlargement of the respective ventricles.

- 3. Projection onto ECG Leads:**

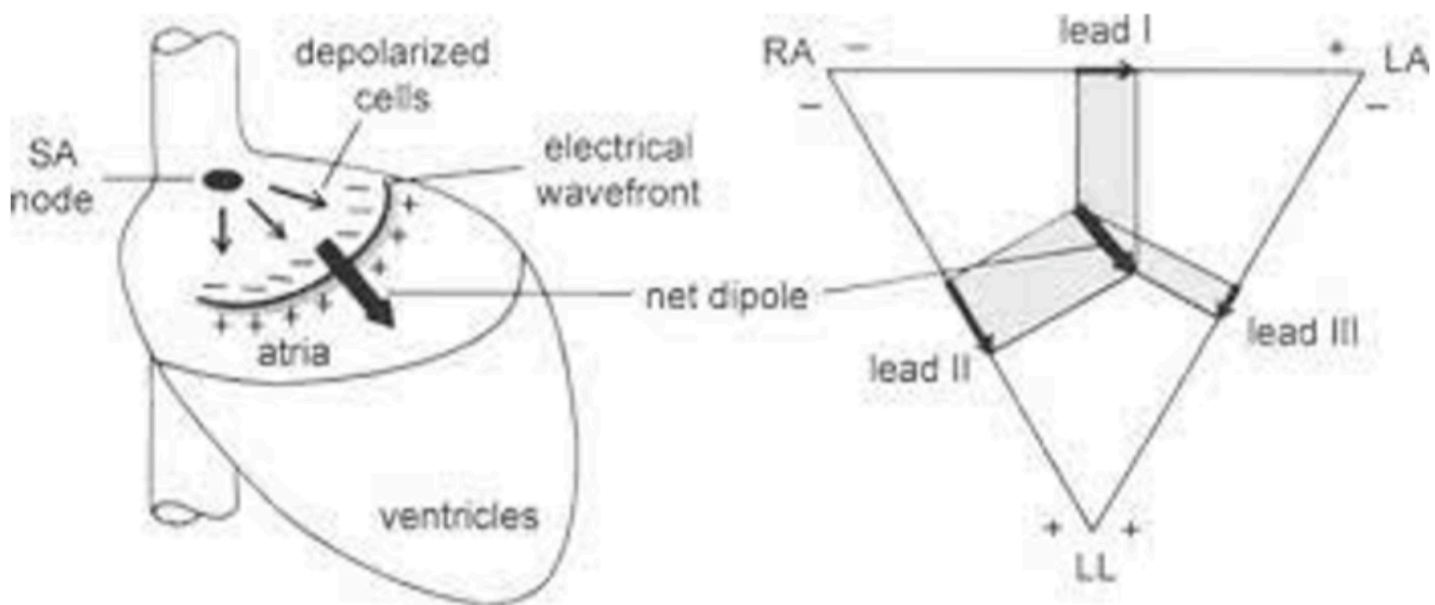
- ECG leads are 'viewpoints' for measuring the heart's electrical activity. Each lead gives a unique perspective on this activity.
 - 'Projecting' the heart dipole onto a lead means determining the dipole's activity visible from that lead's viewpoint.

- 4. Determining Projection:**

- The projection is the dot product of the lead's direction (represented as a unit vector) and the heart's dipole (also a vector). This gives the voltage measured by the lead.
 - If the lead's direction aligns perfectly with the heart's dipole, the projection will be large, resulting in a large wave on the ECG. If perpendicular, the projection will be zero, resulting in a flat ECG line.

- 5. Different Views from Different Leads:**

- Different ECG leads give different views of the heart's electrical activity. Limb leads (I, II, III, aVR, aVL, aVF) provide a frontal plane view, while precordial leads (V1 to V6) offer a horizontal plane view.
 - By examining ECG readings from all these leads, doctors can get a comprehensive picture of the heart's electrical function.



- **Mathematics of Volume Conductors (overview)**

- 1. Overview: Volume Conduction in Bioelectricity:**

- Volume conduction refers to the propagation of electric or magnetic fields through a three-dimensional conducting medium.
- In bioelectricity, volume conductors encompass tissues and body fluids like the heart, blood, and other body tissues, which the electrical signals generated by the heart or brain traverse.

- 2. Mathematics of Volume Conductors:**

- The mathematics of volume conduction involves solving Maxwell's equations (equations of electromagnetic theory) or their approximations in specific scenarios.
- This mathematics combines physics, differential equations, and numerical methods, which is key for understanding and interpreting bioelectrical measurements.

- 3. Principles of Volume Conductors:**

- **Ohm's Law:**
 - Ohm's law states that the current (I) between two points in a conductor directly relates to the voltage (V) across the two points and inversely relates to the resistance (R) between them.
 - In a three-dimensional volume conductor, Ohm's law becomes a differential equation known as the conduction equation: $\nabla \cdot (\sigma \nabla \phi) = I$, where:
 - σ is the conductivity tensor
 - $\nabla \phi$ is the electric field (gradient of the electric potential ϕ)
 - $\nabla \cdot$ is the divergence operator
 - I is the source current density.
- **Boundary Conditions:**
 - The solutions to the conduction equation depend on the boundary conditions, which outline the electrical properties at the interfaces between different tissues or between the body and the air.
- **Electrostatic Approximation:**

- In many bioelectricity cases, the electric fields change slowly relative to the speed of light, so the electromagnetic waves can be approximated as static fields. This simplification converts Maxwell's equations into Laplace's or Poisson's equation for electric fields.
- **The Forward Problem and the Inverse Problem:**
 - In bioelectricity, the forward problem involves calculating the electric potentials at the body's surface given the **source currents** inside the body. This problem can be solved numerically for complex geometries and inhomogeneous conductivities.
 - The inverse problem involves determining the **source currents** given the measured electric potentials. This problem is challenging because it's ill-posed: minor errors in measurements can lead to significant errors in estimated sources.

Group work 6460

1. How would you measure electrical fields in biological tissue?
2. Why is the conduction system crucially important for heart function?
3. What are the major microscopic components and features of cardiac tissues? Which properties of excitable tissues are important for electrophysiology?

1. Measuring Electrical Fields in Biological Tissue:

Electrical fields in biological tissues are primarily measured through electrophysiological techniques. The choice of technique depends on the scale of the measurement (cellular vs. tissue level), the type of measurement (intracellular vs. extracellular), and the specifics of the tissue under investigation.

- **Microelectrodes:** Intracellular recording using sharp microelectrodes can measure the electrical field within a single cell. The electrode penetrates the cell membrane and records the intracellular potential.
- **Patch Clamp Techniques:** This method allows for the measurement of currents through individual ion channels in cell membranes. It's a powerful tool in neuroscience and cardiac electrophysiology.
- **Multi-Electrode Arrays (MEAs):** MEAs can record the electrical activity from multiple sites in a tissue or a cell culture simultaneously. This method provides insight into the spatial distribution and propagation of electrical activity.
- **Electrocardiography (ECG) and Electroencephalography (EEG):** These are non-invasive methods used to measure the electrical activity of the heart and brain, respectively, from the body surface.

2. Importance of the Conduction System for Heart Function:

The cardiac conduction system is essential for the heart's function as it ensures the orderly and timely contraction of cardiac muscle cells. This system generates and propagates electrical signals (action potentials) that trigger the coordinated contraction of the heart chambers, thus enabling efficient blood pumping.

- The **Sinoatrial (SA) node**, often referred to as the heart's natural pacemaker, initiates the electrical signals. These signals spread through the atria, causing them to contract and push blood into the ventricles.
- The electrical signals then reach the **Atrioventricular (AV) node**, where they are delayed slightly to allow the ventricles to fill with blood from the atria.
- The signals then pass along the **Bundle of His**, which divides into left and right bundle branches running down the septum.
- Finally, they spread through the **Purkinje fibers** to the ventricles' apex, causing the ventricles to contract and eject blood into the pulmonary artery (from the right ventricle) and the aorta (from the left ventricle).

If this conduction system malfunctions, it could lead to arrhythmias—irregular heart rhythms—that can diminish the heart's pumping efficacy.

3. Major Microscopic Components and Features of Cardiac Tissues:

Cardiac tissue is made up of several types of cells and extracellular components.

- **Cardiomyocytes:** These are the primary cells responsible for contraction. They are unique in their ability to conduct electrical impulses due to a variety of ion channels in their membranes, allowing for the generation and propagation of action potentials. The cardiomyocytes are connected end-to-end at structures called intercalated discs, allowing for rapid conduction of electrical signals.
- **Fibroblasts:** These cells produce extracellular matrix components, contributing to the structural integrity of the heart.
- **Endothelial cells:** They line the heart's blood vessels and chambers, playing roles in controlling vascular tone, coagulation, and inflammation.

- **Pacemaker cells:** These are specialized cardiomyocytes found in the SA and AV nodes that can spontaneously generate electrical impulses.
- **Purkinje fibers:** Specialized conductive fibers that allow for rapid conduction of electrical impulses to the ventricles' apex.

Important properties of cardiac tissue for electrophysiology include:

- **Excitability:** Cardiac cells can respond to electrical stimuli by generating action potentials.
- **Conductivity:** Cardiac cells can propagate these action potentials from cell to cell, allowing for coordinated contraction of the heart.
- **Automaticity:** Certain cells, like the pacemaker cells in the SA and AV nodes, can spontaneously generate action potentials, enabling the heart to beat regularly in the absence of external neural stimuli.
- **Refractoriness:** After an action potential, cardiac cells undergo a refractory period during which they cannot be re-excited. This feature prevents the premature re-activation of cardiac cells, which would disrupt the coordinated contraction sequence of the heart.

You are familiar with intermyocyte coupling by gap junctions, which is the basis for electrical conduction in myocardium.

Assume now three different cases:

- Myofibroblasts are electrically coupled with myocytes and other myofibroblasts
- Myofibroblasts are coupled with other myofibroblasts, but not with myocytes
- Myofibroblasts are not coupled with other cells.

What are your predictions for electrical conduction in these three cases?

1. Myofibroblasts are electrically coupled with myocytes and other myofibroblasts

Myofibroblasts are non-excitable cells, but when coupled with myocytes, they can modulate the electrical properties of the cardiac tissue. They have a much lower resting membrane potential than cardiomyocytes, which can act as an "electrical sink," slowing the propagation of electrical signals and potentially disturbing the normal rhythm of the heart. Moreover, the presence of myofibroblasts can alter the extracellular matrix, potentially causing further changes in signal propagation.

2. Myofibroblasts are coupled with other myofibroblasts, but not with myocytes

When myofibroblasts are only coupled with each other, their impact on the electrical activity of the myocardium may be limited because the electrical signals generated by myocytes are not directly influenced by myofibroblasts. However, the altered extracellular matrix due to myofibroblast activity could still influence the propagation of electrical signals indirectly.

3. Myofibroblasts are not coupled with other cells

If myofibroblasts are not electrically coupled with other cells, they may have little direct impact on the propagation of electrical signals within the cardiac tissue. However, their influence on the extracellular matrix and their role in fibrosis can indirectly affect electrical conduction. Increased fibrosis can lead to structural barriers that slow down or block electrical conduction, leading to arrhythmias.

List methods for measuring of cardiac conduction! What types of analyses are commonly performed on these measurements?

1. Electrocardiography (ECG):

- **Description:** ECG is the most common non-invasive technique for measuring the electrical activity of the heart. It measures the summation of electrical potentials generated by the heart as it beats.

- **Analysis:** ECG gives information about the heart's rate, rhythm, and conduction pathways. The usual analyses performed on ECG measurements include rhythm analysis, rate calculation, axis determination, and analysis of waveforms and intervals for any abnormalities.

2. Electrophysiological Studies (EPS):

- **Description:** EPS is an invasive procedure where electrodes are introduced into the heart through a catheter.
- **Analysis:** The electrodes in EPS can precisely measure the electrical activity within different parts of the heart, identify abnormal electrical pathways, and test the heart's response to different electrical stimuli. Analyses include measurement of conduction times and refractory periods, identification of abnormal pathways or rhythms, and testing the effectiveness of antiarrhythmic drugs or devices.

3. Optical Mapping:

- **Description:** This technique involves the use of voltage-sensitive or calcium-sensitive dyes to visualize the electrical activity of the heart. This method is typically used in laboratory settings, often on isolated heart tissues or whole hearts.
- **Analysis:** The recorded data from optical mapping are analyzed to visualize the spread of electrical activity and the generation and propagation of arrhythmias.

4. Body Surface Potential Mapping (BSPM):

- **Description:** BSPM is an advanced form of ECG that uses many more electrodes distributed over the body surface to provide a detailed map of the electrical activity of the heart.
- **Analysis:** Analyses in BSPM may include localizing the origins of premature beats or arrhythmias, studying the spread of electrical activity, and non-invasive imaging of cardiac ischemia or infarction.

Summarize the major mechanisms of cardiac conduction! Suggest simple models for electrical conduction in

- normal tissue
- infarcted tissue
- co-culture of myocytes and myofibroblasts

Major Mechanisms of Cardiac Conduction

Cardiac conduction is the process by which the heart's electrical signals, which initiate contractions and thus heartbeats, are generated and propagated. The following are the major mechanisms of this process:

- **Automaticity:** Certain cells in the heart, especially those in the sinoatrial (SA) node, have the ability to spontaneously generate electrical impulses, or action potentials. This property is called automaticity, and it forms the basis of the heart's natural pacemaker.
- **Excitability:** Cardiac cells respond to electrical impulses by depolarizing and generating an action potential. This property is due to the presence of voltage-gated ion channels in the cell membrane that open or close in response to changes in the membrane potential.
- **Conductivity:** Once an action potential is generated, it needs to be conducted to the rest of the heart to cause a coordinated contraction. This conduction occurs through the specialized conduction system of the heart, which includes the SA node, atrioventricular (AV) node, bundle of His, and Purkinje fibers, as well as the cell-to-cell conduction facilitated by gap junctions in the myocardium.

- **Refractoriness:** After an action potential has been generated, cardiac cells enter a refractory period during which they cannot generate another action potential. This ensures that the action potentials propagate in one direction and that there is sufficient time for the heart chambers to refill with blood before the next contraction.

Models for Electrical Conduction

1. Normal Tissue: In normal cardiac tissue, the generation and propagation of action potentials can be modeled as a process involving many coupled differential equations, each representing a different ionic current or other processes in a cardiac cell. This is often referred to as a cellular automaton model or a reaction-diffusion model. One example is the Hodgkin-Huxley model, which describes the dynamics of the membrane potential and the underlying ionic currents.

2. Infarcted Tissue: In infarcted (or damaged) cardiac tissue, the electrical conduction is impaired due to cell death and the formation of non-conductive scar tissue. This can be modeled by modifying the parameters in the normal tissue model to represent reduced excitability or conductivity, or by introducing non-conductive barriers in the tissue geometry. Infarcted tissue can also have areas of surviving cells surrounded by scar tissue, which can form reentry circuits and cause arrhythmias. These areas can be modeled as islands of normal conductivity in a sea of non-conductive tissue.

3. Co-culture of Myocytes and Myofibroblasts: Myofibroblasts are non-conductive cells that can couple to myocytes and affect their electrical properties. The effects of myofibroblasts on cardiac conduction can be modeled by introducing additional terms in the cell model to represent the electrotonic loading by the myofibroblasts. Depending on the degree of coupling and the properties of the myofibroblasts, this can result in changes in the conduction velocity, the refractory period, and the susceptibility to arrhythmias. The exact effects will depend on the specific properties of the myofibroblasts and their spatial distribution in the tissue.

Compare cellular automata with mono-/bidomain models of cardiac conduction! Apply ~5 criteria for comparison.

• Biophysical Detail:

1. **Cellular Automaton:** The cellular automaton model is generally more abstract and simplistic. Each cell is considered to be in one of a finite number of states (e.g., resting, excited, refractory), and the transitions between states are governed by a set of rules. Ionic currents, membrane potentials, and other biophysical details are typically not represented explicitly.
2. **Monodomain/Bidomain:** These models provide a more detailed and accurate representation of cardiac electrophysiology. They model the distribution of the transmembrane potential and the ionic currents across the cardiac tissue, and they can capture the complex dynamics of cardiac action potentials.

• Computational Complexity:

1. **Cellular Automaton:** Due to their simplicity, cellular automaton models are computationally less intensive, making them suitable for large-scale simulations or when computational resources are limited.
2. **Monodomain/Bidomain:** These models are more computationally intensive due to the complexity of the equations and the need for numerical methods to solve them.

• Spatial Representation:

1. **Cellular Automaton:** In cellular automaton models, the cardiac tissue is typically represented as a regular grid of cells. Anisotropy (direction-dependent properties) and inhomogeneity (region-dependent properties) can be represented but may require more complex rules or modifications to the model.
2. **Monodomain/Bidomain:** These models are based on continuum mathematics and can represent the tissue as a continuous volume. They naturally incorporate anisotropy and inhomogeneity by varying the conductivity tensor.

• Applicability:

1. **Cellular Automaton:** Cellular automaton models are useful for studying the basic principles of wave propagation and the genesis of arrhythmias, especially at a large scale. They can be used to simulate the spread of excitation over the entire heart or to study the effects of simple interventions.
2. **Monodomain/Bidomain:** These models are more appropriate when detailed and accurate representation of the cardiac electrophysiology is required. They can be used to study the effects of changes in the ionic currents, the properties of the cardiac cells, or the tissue structure.

• **Modeling of Pathophysiological Conditions:**

1. **Cellular Automaton:** While they can model some forms of tissue heterogeneity and arrhythmias, cellular automata may not capture all the details of certain pathophysiological conditions, particularly those involving complex changes at the cellular or subcellular level.
2. **Monodomain/Bidomain:** These models can incorporate detailed representations of various pathophysiological conditions, including changes in the ionic channels, alterations in the cellular or tissue properties, and complex geometries such as infarct scars or fibrosis.

How the safety factor of conduction for a single cell is strongly affected by

- Na^+ influx during depolarization
- K^+ efflux during repolarization
- Capacitive current
- Gap junction conductance

The safety factor of conduction refers to the measure of the reliability of action potential propagation along an excitable tissue. It is influenced by several factors, including the ion currents involved in depolarization and repolarization processes.

During depolarization, Na^+ influx plays a crucial role in initiating and propagating the action potential. An adequate level of Na^+ influx is necessary to reach the threshold for action potential generation. Insufficient Na^+ influx can result in a reduced safety factor, making it more difficult for the action potential to propagate along the cell.

Similarly, during repolarization, K^+ efflux is responsible for restoring the cell's membrane potential to its resting state. Insufficient K^+ efflux can lead to a prolonged repolarization phase and a decrease in the safety factor.

Capacitive current refers to the current required to charge and discharge the cell membrane's capacitance during depolarization and repolarization. Alterations in the capacitive current can impact the time course of the action potential and, consequently, influence the safety factor of conduction.

Furthermore, gap junction conductance, which represents the degree of electrical coupling between adjacent cells through gap junctions, also affects the safety factor. Impaired gap junction conductance can lead to reduced cell-to-cell communication, compromising the efficient spread of the action potential and decreasing the safety factor.

Group Work – 6000

- **Compare electrode and fluorescence-based approaches to study cellular electrophysiology! Which approach is better?**

Advantages of Electrode-based Approaches:

- Direct measurement of electrical signals provides precise and real-time information.
- High temporal resolution allows for detailed characterization of rapid electrical events.
- Enables the study of individual ion channels and their properties.
- Well-established techniques with a long history of use and a wealth of available knowledge and protocols.

Limitations of Electrode-based Approaches:

- Invasive techniques may disrupt cellular integrity or introduce artifacts.
- Limited spatial information since measurements are typically made from a single point.
- Challenges in studying complex spatial dynamics or interactions within cell populations.
- Certain electrode-based techniques require specialized skills and equipment.

Advantages of Fluorescence-based Approaches:

- Non-invasive and compatible with live-cell imaging, allowing long-term observations.
- Provide spatial information and allow for imaging of large populations of cells simultaneously.
- Offer flexibility in monitoring various physiological parameters using different fluorescent indicators.
- Well-suited for studying dynamic cellular processes and phenomena like calcium signaling and synaptic activity.

Limitations of Fluorescence-based Approaches:

- Indicators may introduce perturbations to cellular function or require genetic modifications.
- Imaging depth and resolution may be limited in thicker or densely packed tissue samples.
- Some indicators have limited dynamic range or can be affected by photobleaching.
- Interpretation of fluorescence signals requires careful calibration and validation.

- **Which measurements would you perform to dissect action potentials in excitable cells? Specify experimental preparations, measurement setups, conditions and analyses!**

Experimental Methods for Dissecting Action Potentials in Excitable Cells:

- **Patch-Clamp Technique:**
 - Experimental Preparation: Glass micropipette sealed onto a small patch of cell membrane.
 - Measurement Setup: Ion currents are measured as changes in voltage.
 - Conditions: Voltage-clamp mode is used to control membrane voltage.
 - Analysis: Measure the amplitudes, kinetics, and voltage-dependence of the various ionic currents.
- **Intracellular Recording:**
 - Experimental Preparation: Sharp electrode inserted into the cell.
 - Measurement Setup: Direct measurement of the membrane potential.
 - Conditions: Natural resting potentials and action potentials.
 - Analysis: Determine the threshold, amplitude, duration, and frequency of action potentials.
- **Optical Imaging:**
 - Experimental Preparation: Use of voltage-sensitive dyes.
 - Measurement Setup: Visualization of action potentials as they propagate through tissue.
 - Conditions: Natural propagation of action potentials in tissue.
 - Analysis: Measure the speed, direction, and synchrony of action potential propagation.

- **Extracellular Recording:**

- Experimental Preparation: Electrodes placed outside of the cell or tissue.
- Measurement Setup: Recording of action potentials from many cells at once.
- Conditions: Natural firing of cells.
- Analysis: Spike sorting and averaging, assessing the firing rates and patterns of cells.

General Conditions for All Methods:

- Often performed at a constant temperature.
 - Solution used often mimics the physiological extracellular fluid.
 - Cells or tissues may be stimulated electrically or chemically to evoke action potentials.
 - Various drugs may be applied to block specific ion channels and dissect their contributions to the action potential.
- **Compare cardiac action potentials with action potentials in neurons. What are the major differences?** Would it be possible to generate a cardiac-like action potential, i.e. with plateau, without involvement of Ca^{2+} ?

Cardiac action potentials and neuronal action potentials differ in several key ways:

- **Duration:** Neuronal action potentials are typically brief, lasting only a few milliseconds. In contrast, cardiac action potentials have a much longer duration, often up to several hundred milliseconds. This difference is primarily due to the presence of a plateau phase in the cardiac action potential, which is absent in the neuronal action potential.
- **Refractory Period:** The long duration of the cardiac action potential results in a correspondingly long refractory period – the time during which a new action potential cannot be initiated. This is a key feature that helps prevent premature contractions and allows the heart chambers enough time to fill with blood before the next contraction. In contrast, neurons can fire action potentials much more rapidly.
- **Ion Channels Involved:** In neurons, the action potential is generated primarily by the rapid opening and closing of voltage-gated sodium and potassium channels. In cardiac cells, the action potential involves not only sodium and potassium channels, but also calcium channels. The influx of calcium ions through these channels during the plateau phase is vital for triggering the contraction of the heart muscle.
- **The Plateau Phase:** This is a characteristic feature of the cardiac action potential and is not seen in neurons. The plateau phase is primarily maintained by the balance between inward currents (mainly carried by Ca^{2+} ions) and outward currents (mainly carried by K^{+} ions). This phase is crucial for prolonging the action potential and thereby the refractory period, ensuring a delay between contractions to allow for ventricular filling.

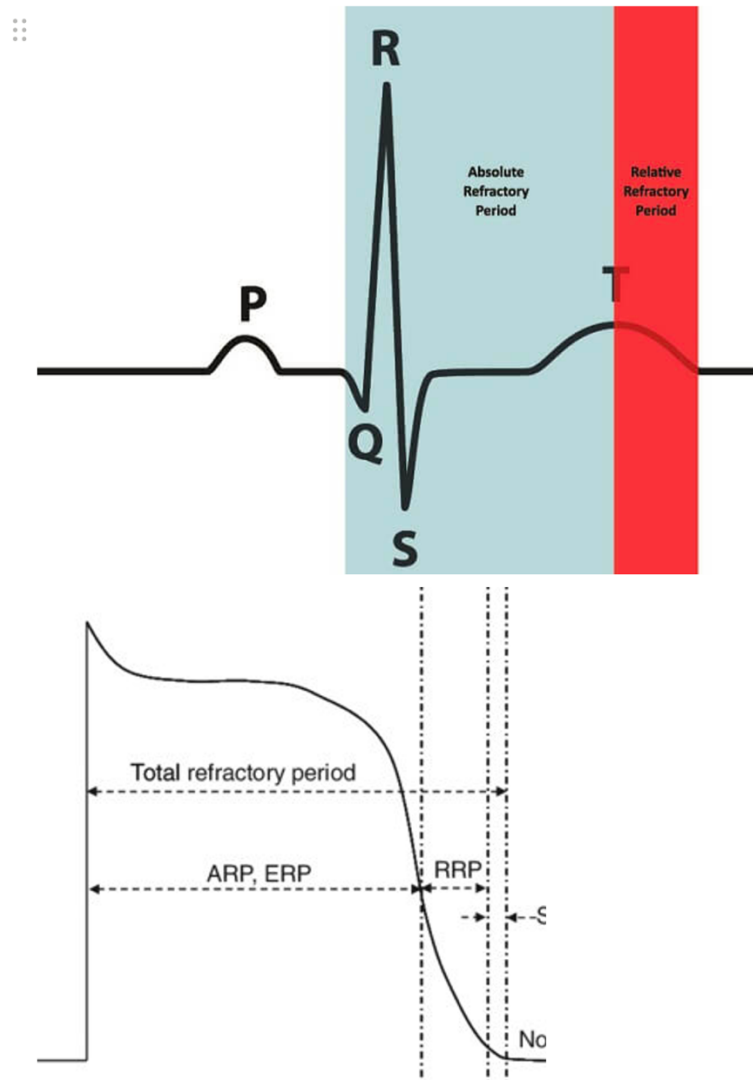
In a purely theoretical sense, if we were to propose an alternative ion to calcium for the generation of the plateau phase in a cardiac-like action potential, it would need to meet specific criteria. The ion would need to:

1. Be able to pass through the cell membrane via ion channels in a controlled way.
2. Exhibit a slow inward current to maintain the plateau phase.
3. Have a high enough concentration outside the cell so that there would be a strong driving force for its movement into the cell.

The most likely candidate that could theoretically fit this description might be magnesium ions (Mg^{2+}). They are divalent cations like calcium and present in significant quantities in the extracellular fluid.

However, in the context of living organisms, there are reasons why Mg^{2+} cannot replace Ca^{2+} . For instance, Mg^{2+} ions are not generally known to pass through ion channels in the same way as Ca^{2+} , and they do not trigger cellular processes such as muscle contraction in the way Ca^{2+} does. Furthermore, the body has not evolved mechanisms to rapidly transport Mg^{2+} across cell membranes in response to changes in membrane potential, unlike for Ca^{2+} , Na^{+} , and K^{+} .

So while Mg^{2+} could theoretically play the role of Ca^{2+} in a highly simplified or artificial model, in biological reality, the role of Ca^{2+} in generating the cardiac action potential is unique and cannot be fulfilled by Mg^{2+} or any other ion.



- **Why would someone be interested in mathematically describing (i.e. model) action potentials of cells?**

Mathematical modeling of action potentials serves several important purposes:

- Understanding: Mathematical models help us understand the underlying biophysical processes that generate action potentials, including the roles of different ion channels and transporters, the interactions between these elements, and the effects of cellular and subcellular structures.
- Prediction: Once we have a model that accurately describes action potentials under a range of conditions, we can use this model to predict how the cell will respond under new conditions, such as changes in ion concentrations, temperature, or the presence of drugs.
- Design of experiments: Models can also help design new experiments. For example, a model might predict that a certain modification should have a particular effect on the action potential. An experiment can then be designed to test this prediction.
- Drug development: Models can be used in the development of new drugs. For example, if a model predicts that blocking a certain type of ion channel should have a beneficial effect, this could lead to the development of new drugs that block this type of channel.

- **What is the mechanism underlying the autorhythmicity of pacemaker cells?**

Pacemaker cells, such as those found in the sinoatrial (SA) node of the heart, exhibit autorhythmicity, meaning they spontaneously depolarize and initiate action potentials without any external trigger. This is due to the unique ion channels they possess and the way these channels behave. The process is often divided into three phases:

- Phase 4 (Pacemaker Potential): This is a slow, spontaneous depolarization phase. It's driven by the opening of so-called "funny" (If) channels which allow sodium and potassium ions to flow in and out, respectively. There is also a decrease in potassium conductance, and T-type calcium channels begin to open.
- Phase 0 (Depolarization): Once the membrane potential reaches the threshold, there is a rapid depolarization due to the opening of L-type (long-lasting) calcium channels.
- Phase 3 (Repolarization): The L-type calcium channels close, and potassium channels open, leading to rapid repolarization.

- **Heart rate regulation in a nutshell!**

Heart rate is principally controlled by the autonomic nervous system through two branches: the sympathetic and parasympathetic nervous systems. The sympathetic system (through release of catecholamines like norepinephrine) increases heart rate and contractility, while the parasympathetic system (through release of acetylcholine) decreases heart rate. These neurotransmitters act on the pacemaker cells in the SA node, altering the rate of Phase 4 depolarization and thereby changing the heart rate.

Other factors can influence heart rate, including hormones (e.g., epinephrine), temperature, ions (e.g., potassium and calcium), and physical and emotional stress.

- **Propose extensions to the Luo-Rudy model that would allow us to simulate autorhythmicity and its modulation by the autonomous nerve system!**

The Luo-Rudy model is a well-established model of the cardiac action potential, specifically for ventricular myocytes. To extend this model to simulate autorhythmicity and its modulation by the autonomous nervous system, several modifications would be needed:

- Incorporate If (funny) currents, T-type calcium currents, and the respective channels, since these are crucial for pacemaker potential generation in autorhythmic cells.
- Implement mechanisms to simulate the effects of neurotransmitters (norepinephrine and acetylcholine) on these ion channels. This might involve creating parameters to represent the concentration of these neurotransmitters, and equations to represent how these concentrations affect the properties of the ion channels.
- Implement an automatic pacing mechanism to mimic the spontaneous generation of action potentials by pacemaker cells. This could involve setting the membrane potential to a certain value whenever it reaches a certain threshold.
- If the goal is to simulate the behavior of the whole heart, rather than individual cells, then the model would also need to be extended to include the different types of cells in the heart (e.g., atrial cells, ventricular cells, Purkinje fibers), and the connections between them. This would involve creating a network or lattice of cells, each governed by its own set of equations, but also influenced by the states of its neighboring cells.

- **Explanted/transplanted human hearts beat at higher rate than in situ hearts (95-115 BPM vs. 60-75 BPM) What might be the reason for this difference? Which medication would resolve this issue in a patient (with heart transplanted)?**

The heart's rate in situ (within the body) is controlled by both intrinsic factors (the pacemaker cells in the SA node) and extrinsic factors (the autonomic nervous system). The autonomic nervous system provides balance through the sympathetic (speeds heart rate) and parasympathetic (slows heart rate) systems. A heart that has been explanted and then transplanted no longer has these autonomic inputs, at least initially, and thus the rate is solely determined by the intrinsic pacemaker cells. This results in a faster rate, typically

around 100-110 BPM, also known as the inherent rate of the SA node. Over time, reinnervation of the heart can occur to some extent, and this can bring the rate down somewhat, though it may not fully reach the pre-transplant level.

To manage this, a patient might be prescribed beta-blockers, which work by blocking the effects of the hormone epinephrine, also known as adrenaline. This slows the heart rate, reduces blood pressure, and helps to prevent heart failure.

- **Predict changes of the calcium transient within a myocyte for:**

- **Increased L-type calcium channel inactivation:** This would reduce the influx of calcium during the plateau phase of the action potential. This, in turn, would decrease the triggering of calcium-induced calcium release (CICR) from the sarcoplasmic reticulum (SR), leading to a smaller amplitude of the calcium transient.
- **Delayed RyR activation:** RyR (Ryanodine receptors) are responsible for CICR from the SR. Delayed activation would cause a slower rise in the calcium transient and could potentially reduce the peak amplitude if the delay is long enough.
- **Wide distribution of RyR activation times:** This would also cause a slower rise in the calcium transient, but with more variation in the timing and possibly the amplitude of the peak. The shape of the transient might also be more irregular or "noisy".
- **Reduced SERCA uptake:** SERCA (sarcoplasmic/endoplasmic reticulum calcium ATPase) pumps are responsible for re-sequestering calcium into the SR after a contraction. Reduced SERCA function would slow the decay of the calcium transient and increase the baseline calcium level. Over time, this could lead to a reduced SR calcium load and smaller calcium transients.
- **Increased SR calcium load:** An increase in SR calcium load would likely increase the amplitude of the calcium transient, as more calcium is available for release. This assumes that the mechanisms for calcium release (RyR channels) and uptake (SERCA pumps) are functioning normally.
- **Reduced NCX activity:** The sodium-calcium exchanger (NCX) helps to extrude calcium from the cell during the relaxation phase. Reduced NCX activity would slow the decay of the calcium transient, resulting in higher baseline calcium levels. Over time, this could also affect the SR calcium load.

- **Differences between sketches of calcium transient in contraction and calcium in plateau phase of action potential**

Timing and Duration:

- **Calcium Transient in Contraction:** The calcium transient occurs during the contraction phase of the cardiac cycle. It typically has a shorter duration and corresponds to the rapid rise and fall of intracellular calcium concentration during systole.

Magnitude and Amplitude:

- **Calcium Transient in Contraction:** The calcium transient during contraction exhibits a sharp increase in intracellular calcium concentration, reaching peak levels that are significantly higher than baseline.
- **Calcium in Plateau Phase of Action Potential:** The calcium concentration in the plateau phase of the action potential is sustained at a moderate level throughout this phase, maintaining a plateau-shaped curve rather than exhibiting sharp rises or falls.

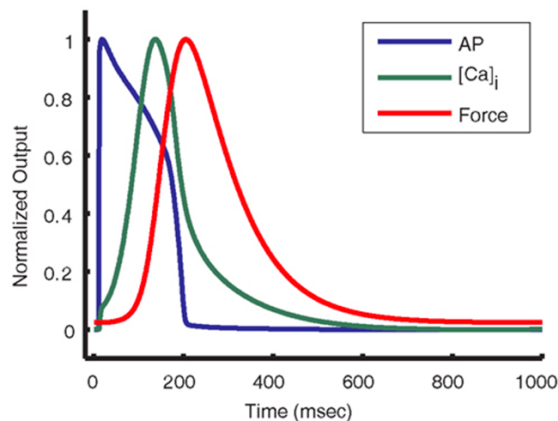
Functional Significance:

- **Calcium Transient in Contraction:** The calcium transient during contraction is responsible for initiating and regulating the process of myocardial contraction. It triggers the interaction between actin and myosin filaments, leading to the generation of force and subsequent cardiac muscle contraction.

- **Calcium in Plateau Phase of Action Potential:** The sustained elevation of calcium during the plateau phase of the action potential contributes to the maintenance of prolonged depolarization, which helps sustain myocardial contraction and promote efficient ejection of blood from the heart.

Triggering Mechanisms:

- **Calcium Transient in Contraction:** The calcium transient is triggered by the release of calcium ions from the sarcoplasmic reticulum (SR) in response to the influx of extracellular calcium through voltage-gated L-type calcium channels.
- **Calcium in Plateau Phase of Action Potential:** The sustained elevation of calcium in the plateau phase of the action potential is primarily due to the balance between calcium influx through L-type calcium channels and calcium efflux through various calcium-handling mechanisms, such as the sodium-calcium exchanger and the sarco-endoplasmic reticulum calcium ATPase (SERCA) pump.
- **Sketch a calcium transient, the associated force generation and cell shortening in a cardiac myocyte. Predict changes of the force generation within a myocyte with**
 - increased overlap of actin and myosin filaments
 - high diastolic cytosolic calcium concentration
 - increased SERCA uptake
 - increased NCX activity



In a typical cardiac myocyte, the calcium transient and the associated force generation and cell shortening would look like the following:

- The calcium transient would start with a rapid rise as calcium influx from L-type channels triggers calcium-induced calcium release (CICR) from the sarcoplasmic reticulum (SR). The peak of the transient corresponds to the maximum intracellular calcium concentration.
- The force generation (tension) would follow a slightly delayed and more prolonged curve as calcium binds to troponin, triggering the cross-bridge cycling of actin and myosin that leads to contraction. The peak tension would occur slightly after the peak of the calcium transient, and the decay of the tension would be slower as it depends on the detachment of cross-bridges and the re-sequestration of calcium into the SR.
- Cell shortening would follow a similar curve as the force generation, as it directly results from the contraction. The rate and extent of shortening can depend on the load against which the cell is contracting.

Predicted changes of the force generation within a myocyte for the given conditions:

- **Increased overlap of actin and myosin filaments:** An increase in filament overlap would likely increase the force of contraction, as more cross-bridges can form and contribute to force generation. However, there is an optimal range of

overlap for maximal force production (according to the length-tension relationship in muscle), and if the overlap becomes too large (the cell becomes too short), the force could actually decrease.

- **High diastolic cytosolic calcium concentration:** This would cause an increase in baseline tension (diastolic tension), as more calcium is available to bind to troponin and trigger cross-bridge cycling. If the calcium concentration is too high, it could lead to sustained tension and impaired relaxation (diastolic dysfunction).
- **Increased SERCA uptake:** Enhanced SERCA activity would speed up the re-sequestration of calcium into the SR during relaxation, thus reducing the time to relaxation and potentially allowing for faster cycling of contractions. However, it could also reduce the peak tension if the rate of uptake is so high that it reduces the peak cytosolic calcium concentration.
- **Increased NCX activity:** Enhanced NCX activity would help to extrude more calcium from the cell, potentially reducing the cytosolic calcium concentration and thus the force of contraction. However, the NCX also contributes to cell depolarization, so if its activity is too high, it could potentially affect the action potential and the triggering of calcium release.
- **Discuss differences between intercellular communication by gap junction channels in muscle cells and synapses in neurons.**
 - **Mechanism of Signal Transmission:** In muscle cells, the signal (an electrical current) is directly transmitted from one cell to the next through gap junction channels, which allow ions and small molecules to pass. In neurons, the signal is transmitted across a synapse by the release of neurotransmitters, which are chemicals that diffuse across the synaptic cleft and bind to receptors on the postsynaptic cell.
 - **Speed:** Communication through gap junctions is generally faster than synaptic transmission, as it does not involve the release and diffusion of neurotransmitters and the activation of postsynaptic receptors.
 - **Bi-Directionality:** Gap junctions allow for bidirectional communication, meaning that signals can pass in either direction between the connected cells. In contrast, communication across a synapse is typically unidirectional, with signals being transmitted from the presynaptic cell to the postsynaptic cell.
 - **Modulation:** Synaptic transmission is highly modulatable, with the strength and efficacy of the synapse being able to be altered by various factors (e.g., frequency of presynaptic firing, availability of neurotransmitter, receptor density or sensitivity on the postsynaptic cell). In contrast, while gap junction communication can also be modulated to some extent (e.g., by changes in phosphorylation or intracellular pH), it is generally less dynamic than synaptic transmission.
- **Unipolar/Bipolar- Which measurement approach is more sensitive to noise? Argue based on sources of noise!**
 - Bipolar recordings are generally more resistant to noise compared to unipolar recordings.
 - This is due to bipolar recordings capturing the differential measurements between two closely located points, reducing the impact of common-mode noise.
 - Primary sources of noise include environmental, physiological, and instrumentation noise.
 - Unipolar recordings, which measure the electrical potential at one point relative to a distant reference, are more susceptible to common-mode noise.
- **Compare electrical and optical measurements of conduction!**
 - Electrical measurements provide direct, high temporal resolution data but can lack spatial resolution, especially in non-invasive techniques like ECG.
 - Optical measurements offer high spatial resolution, allowing the visualization of the spread of electrical activity across the tissue.
 - Optical measurements, while potentially providing more detailed spatial information, can have lower temporal resolution and require more complex equipment.

- Optical techniques may also introduce noise or artifacts due to changes in light intensity or dye concentration.

- **What are the major inputs, parameters and outputs of models of conduction?**

Inputs:

- Initial conditions such as resting membrane potential, ion concentrations, and gating variables.
- Time-dependent input signals such as external stimuli or pacemaker activity.
- Spatial information such as tissue geometry and fiber orientation.

Parameters:

- Electrical properties of the tissues including intracellular and extracellular conductivities, and membrane capacitance.
- Parameters of the ion channels and transporters, including maximum conductances, reversal potentials, and rate constants.
- Parameters for the tissue structure, such as the space constant (which depends on the tissue's electrical properties and the cell dimensions).

Outputs:

- Membrane potentials as a function of time and space.
- Other state variables of the model, such as the ion concentrations and gating variables.
- Derived quantities of interest, such as the activation and recovery times, conduction velocity, and refractory period.

- **How would you program to determine ARI (Activation-recovery intervals) in an electrogram? Assume that the electrogram is artifact-free and only an electrogram is present. 3 commands!**

Assuming you have an array of voltage readings over time (electrogram), a simple way to determine ARIs might involve the following steps (expressed in pseudocode):

- **peaks = find_peaks(electrogram)** - Use a function to find the peaks in the electrogram, which represent the activations and recoveries.
 1. **activations = peaks[:,2]** - Assuming the first peak is an activation, every other peak is an activation.
 2. **recoveries = peaks[1::2]** - The peaks in between the activations are recoveries.
 3. **ARIs = recoveries - activations** - Subtract the activations from the recoveries to get the ARIs.

This is a simplified version and real implementations would need to take care of many additional details, such as dealing with noise, ectopic beats, and variable heart rates. The function **find_peaks** would be a routine that identifies local maxima and minima based on some criterion, which might be part of a scientific computing library or custom-written for the task.

- **When will reentrant waves circulating around obstacles detach?**

In the heart, reentrant waves or circuits can cause cardiac arrhythmias. These circuits can form when a wavefront of electrical activity, instead of moving linearly through the heart tissue, curves back on itself and continues to activate the heart in a circular or spiral pattern.

Reentry waves can occur around an obstacle, such as scar tissue from a previous heart attack, a region of tissue with different electrical properties, or a non-conductive anatomical boundary. The wave might keep circulating around the obstacle as long as the path length around the obstacle is longer than the wavelength of the electrical activity (which depends on the conduction velocity and the refractory period), and the conduction time around the path is longer than the refractory period.

Reentrant waves can "detach" from the obstacle and drift away in two main circumstances:

1. **Altered Excitability:** If the refractory period of the tissue changes, such as due to changes in autonomic tone or the action of drugs, the wavelength might become longer or shorter than the path length, preventing reentry.
2. **Anatomical or Functional Changes:** If the path length changes due to changes in the size or shape of the obstacle, or due to changes in the electrical properties of the tissue, the conditions for reentry might not be fulfilled anymore.

The detached waves can then propagate freely through the heart tissue, potentially causing or sustaining a fibrillatory state.

- **How would you model effects of ablation in simulations of tissue electrophysiology?**

In electrophysiology simulations, the effects of ablation can be modeled by changing the properties of the cells or tissue in the ablated area. Ablation typically creates a non-conductive scar, so in a simulation, this could be represented by reducing or eliminating the conductance or changing the cell's ionic properties in the affected area.

Ablated tissue would then no longer contribute to the propagation of electrical signals, which could be reflected in the simulation as a block or delay in signal transmission. This can change the pattern of electrical activation, which might be beneficial in cases where the original activation pattern was contributing to an arrhythmia. This would help simulate the intended therapeutic effects of the ablation.

Moreover, because the ablation changes not only the conductive but also the structural properties of the tissue, the model should also account for changes in tissue geometry, stiffness, and interactions with neighboring cells or tissue.

- **Why has the QRS complex (electrical activation of ventricles) a short duration and high amplitude in comparison to the t-wave (ventricular repolarization), which is prolonged and of low amplitude? Explain based on local action potential shape and associated extracellular currents!**

Comparison of QRS Complex and T-wave:

The QRS complex corresponds to the rapid depolarization of the ventricles, which occurs almost simultaneously throughout the heart, and involves a large amount of charge moving in a relatively homogeneous and synchronous manner. This synchronized and rapid movement of charge creates a large, sharp deflection on the ECG, resulting in a high amplitude and short duration of the QRS complex.

On the other hand, the T wave corresponds to ventricular repolarization. Unlike depolarization, repolarization is not a synchronous process, it starts from the epicardium and ends at the endocardium. This means that the electrical vectors at any given time during repolarization are smaller and have more varied directions, which can partially cancel each other out, leading to a smaller amplitude on the ECG. Moreover, because the repolarization process is more gradual and less synchronized, it lasts for a longer period, contributing to the prolonged duration of the T wave.

Additionally, the currents underlying the T wave are transmembrane currents (outward potassium currents), whereas the QRS complex primarily represents extracellular volume currents that are created by fast sodium inward currents, resulting in different ECG manifestations.

- **Is the dipole model a “good” model of the relationship of cardiac activity and ECG measurements?**

The dipole model simplifies the complex spatial distribution of cardiac electrical activity into a single vector (the cardiac vector or mean electrical axis). It is a basic model that provides a useful first approximation of the heart's electrical behavior.

However, the heart is not a perfect dipole. Its geometry is complex and the conductive properties of the tissues surrounding the heart (like the lungs and blood) can distort the electrical fields. Additionally, the dipole model assumes that the heart is located in an infinite, homogeneous, isotropic volume conductor, which is not true in reality.

The model's effectiveness can be evaluated by how well it predicts the features of the ECG.

While the dipole model is a good first approximation, more complex multipole models or detailed biophysical simulations may be required for accurate predictions in certain scenarios, such as when precise localization of cardiac events is necessary, or when the heart's structure is significantly altered (as in certain diseases or conditions).

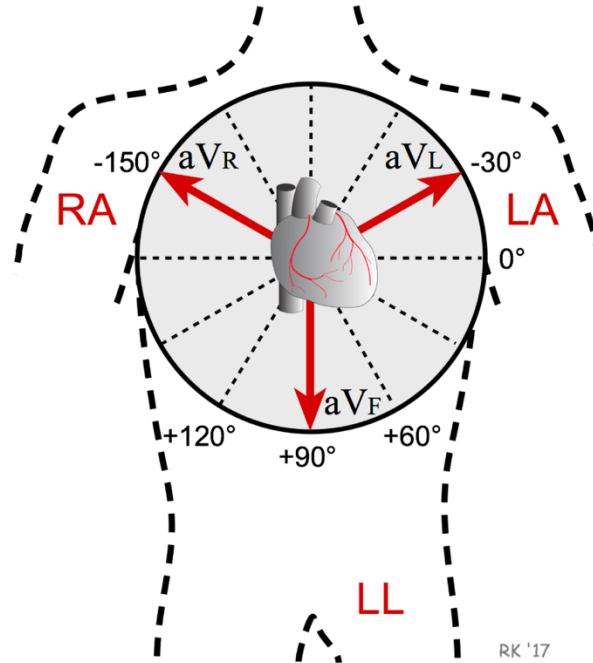
- **Is it possible to calculate Goldberger from Einthoven leads?**

Goldberger leads, also known as augmented limb leads (aVR, aVL, aVF), are unipolar leads that are derived from the same three electrodes used for the Einthoven leads (I, II, III), which are placed on the right arm, left arm, and left leg. The two systems of leads represent different views of the heart's electrical activity, but they are interrelated.

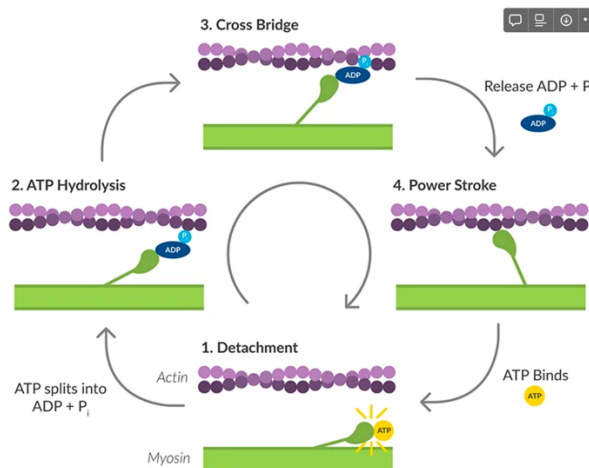
Indeed, it is possible to calculate the Goldberger leads from the Einthoven leads using the following formulas (**NOT SURE**):

- $aVR = -(I + II) / 2$
- $aVL = I - II / 2$
- $aVF = II - I / 2$

These formulas are derived from the concept that in a unipolar lead, the lead "looks" at the heart from the positive electrode's perspective with a reference point that is calculated as the average of the other two limb electrodes.



- **Roles of ATP in cardiac contraction**



Adenosine triphosphate (ATP) plays a critical role in cardiac contraction, serving as the energy source for several essential processes:

1. **Muscle Contraction:** ATP is required for the actin-myosin cross-bridge cycling that underlies muscle contraction. More specifically, ATP binds to the myosin head, causing it to release actin. ATP is then hydrolyzed to ADP and inorganic

phosphate, which results in the reorientation and energizing of the myosin head. The myosin head binds to actin, releasing the inorganic phosphate, and undergoes a power stroke that pulls the actin filament, leading to muscle contraction. The release of ADP then allows a new ATP molecule to bind to myosin, starting the cycle anew.

2. **Calcium Handling:** ATP is needed for the function of several proteins involved in calcium handling in cardiac cells, which is crucial for initiating cardiac contraction and allowing for relaxation. This includes:
 - **Sarcoplasmic Reticulum (SR) Calcium ATPase (SERCA):** This pump uses ATP to transport calcium ions from the cytosol back into the SR during relaxation, allowing the cell to be ready for the next contraction.
 - **Plasma Membrane Calcium ATPase (PMCA):** This pump also uses ATP to export calcium ions from the cell to the extracellular space, helping to maintain the low intracellular calcium concentration necessary for relaxation.
 - **Sodium-Calcium Exchanger (NCX):** While this doesn't directly use ATP, it relies on the sodium gradient across the plasma membrane that is maintained by the Na^+/K^+ ATPase pump, which does use ATP.
3. **Electrogenic Ion Pumps:** In addition to the Na^+/K^+ ATPase mentioned above, ATP powers other pumps like the H^+/K^+ ATPase and others, which maintain ionic gradients across the plasma membrane critical for the electrical activity of the heart.

- **Patch-clamp vs Voltage-clamp**

Patch-clamp and voltage-clamp are related electrophysiological techniques used to study the electrical properties of cells, particularly neurons.

Voltage-Clamp Technique: The voltage-clamp technique is used to control or 'clamp' the membrane potential of a cell and measure the current that flows across the cell membrane as a result. It allows researchers to study how ion channels open and close under different voltage conditions and thus understand the behavior of these ion channels.

1. An electrode is inserted into the cell, and a reference electrode is placed in the surrounding solution.
2. A device called a voltage-clamp amplifier is used. This device compares the actual membrane potential of the cell to the desired membrane potential (the 'clamp' voltage).
3. If the actual potential differs from the desired one, the amplifier injects current into the cell to bring the membrane potential back to the desired level.

This technique can be used to investigate how the flow of ions through channels depends on the voltage across the membrane. By observing the current flowing in response to different clamped voltages, researchers can deduce the properties of the ion channels.

Patch-Clamp Technique: The patch-clamp technique is a refinement of the voltage-clamp method that allows for the recording of current through individual ion channels, rather than the entire cell membrane.

4. In patch-clamp, a glass micropipette with a very fine tip is placed against the cell membrane to form a 'patch'. Suction is applied to form a high-resistance seal with the membrane (a 'gigaseal').
5. There are several variations of patch-clamp technique, differing in the specific membrane area they target. In 'cell-attached' mode, the patch of membrane under the micropipette remains part of the cell, and the currents through ion channels in that patch can be measured without disturbing the rest of the cell. In 'whole-cell' mode, more suction is applied to rupture the membrane patch, allowing for measurement of currents across the entire membrane.

In both patch-clamp and voltage-clamp techniques, the electrodes are usually connected to an amplifier that allows for the measurement of very small currents, and the data is usually recorded and analyzed using a computer.

- **Which predictions can we make if know the structure of an ion channel?**

If we know the structure of an ion channel, we can make several predictions:

- **Ion selectivity:** As mentioned, the structure of the channel pore can help us predict which ions will be able to pass through the channel.
- **Gating mechanism:** Many ion channels are 'gated', meaning they can open or close in response to specific signals. The nature of these signals (voltage, ligands, mechanical force, etc.) and how they affect the channel can often be predicted based on the channel's structure.
- **Conductance:** The size and shape of the pore can influence the rate at which ions can flow through the channel, known as its conductance.
- **Drug interactions:** If a drug acts by binding to an ion channel, the structure of the channel can help us predict how and where the drug will bind, and how this might affect the channel's function.

- **What are the major concepts of the Hodgkin and Huxley model? What are the modeled currents?**

The Hodgkin-Huxley model provides a mathematical description of how action potentials in neurons are **initiated and propagated**. The model was based on their experiments with the giant axon of the squid, which allowed them to measure **ionic currents under different voltage conditions**.

The major concepts of the Hodgkin-Huxley model are:

- **Ionic basis of the action potential:** The model proposes that action potentials are caused by the flow of sodium and potassium ions through voltage-gated channels in the neuron membrane.
- **Voltage-gated ion channels:** The model describes how the probability of these channels being open depends on the membrane voltage.
- **Differential equations:** The model uses a set of four coupled differential equations to describe how the membrane potential and the opening and closing of the ion channels change over time.

The primary currents modeled in the Hodgkin-Huxley framework are the sodium current (responsible for the depolarization phase of the action potential) and the potassium current (responsible for the repolarization phase).

- **What causes gating currents of ion channels?**

Gating currents of ion channels are caused by the **movement of the voltage-sensing domains** within voltage-gated ion channels. These voltage-sensing domains are rich in **positively-charged amino acids**, and they move in response to changes in the electric field across the membrane (i.e., changes in membrane potential).

When the membrane potential changes, these charged amino acids move, causing a tiny displacement of charge across the membrane. Even though no ions cross the membrane during this process, this charge displacement can still be measured as a current, known as the gating current. The movement of these voltage-sensing domains triggers the opening or closing of the ion channel, allowing ions to pass through the channel, creating the ionic current.

- **Develop ideas to model drug effects on ion channels. How would you modify models to reflect drug effects?**

To model drug effects on ion channels, several modifications could be made to existing models like the Hodgkin-Huxley model, which primarily models the behavior of ion channels in response to changes in membrane potential. Here are some general ideas for modifications:

- **Modify rate constants:** If a drug affects the opening or closing rates of the channel (as is often the case), the rate constants in the model could be modified accordingly. For example, if a drug slows down channel activation, the rate constant for the transition from the closed to the open state could be reduced.
- **Add additional states:** If a drug binds to the channel and causes it to enter a new state (e.g., a blocked state), this state could be added to the model, along with transitions to and from this state. For example, if a drug binds to the open state of the channel and blocks it, a 'blocked' state could be added with transitions from the open state to the blocked state (described by the drug binding rate) and from the blocked state to the open state (described by the drug unbinding rate).

- **Include drug concentration:** The effects of a drug are often concentration-dependent, so the concentration of the drug could be included as a variable in the model. For example, the rate of drug binding could be made proportional to the drug concentration.
- **Develop a topology for a model of hERG to be used in studies of drug effects. Assume that (1) The drug slows activation only (2) Drug binding is only in closed states. Sketch the topology!**

To develop a model of hERG (a potassium channel important in cardiac repolarization) with drug effects, let's assume the following states: Closed (C), Open (O), and Drug-Bound Closed (D).

- The transition from the Closed to Open state represents the activation of the channel, which we'll say is slowed down by the drug.
- The transition from Closed to Drug-Bound Closed represents the binding of the drug, which we're assuming only happens when the channel is in the closed state.

Given these assumptions, a possible topology for this model could be represented like this:

mathematicaCopy code

```

      k_co
C <-----> O
|           ^
| k_on      |
v           |
D <-----> X
      k_off

```

Where:

- C is the closed state
- O is the open state
- D is the drug-bound closed state
- X represents other states not relevant to this model (e.g., inactivated state)
- k_{co} and k_{oc} are the rate constants for the transition from closed to open and open to closed, respectively
- k_{on} and k_{off} are the rate constants for drug binding and unbinding, respectively

In this model, a drug binding to the channel would slow down the transition from closed to open (lower k_{co}), as specified in the problem statement. This diagram is a simplification and in a more detailed model, the open and closed states could be subdivided into several different states to better capture the kinetics of the channel

- **Which experiments would you have proposed (in 1962) to identify the mechanisms underlying the plateau of an action potential?**
 - **Voltage Clamp Experiments:** The use of the voltage clamp technique (as developed by Hodgkin and Huxley) would have allowed researchers to control the membrane potential and measure the resulting ion currents. By doing so, they could observe the changes in ionic currents during the plateau phase and infer the mechanisms at play. For example, they might have noted

that a prolonged inward current coincides with the plateau phase, suggesting the involvement of certain ion channels (such as L-type calcium channels).

- **Pharmacological Blockade:** By applying drugs that block specific types of ion channels and then observing the effect on the action potential, researchers could have identified which channels are necessary for the plateau phase. For example, if the application of a calcium channel blocker abolishes the plateau phase, this would suggest that calcium influx is necessary for the plateau.
- **Ion Substitution Experiments:** By replacing the ions in the extracellular fluid with impermeant ions, researchers could determine which ions are involved in the plateau phase. For example, if replacing extracellular calcium with another cation abolishes the plateau, this would suggest that calcium influx is necessary for the plateau.

- **What do you expect remodels in cardiac cells from diseased hearts? What are the effects on function? How do you describe these effects in a cell model?**

In cardiac cells from diseased hearts, we can expect to see significant remodeling at multiple levels:

- **Electrical Remodeling:** Changes in the expression and function of ion channels can alter the action potential shape and duration. For instance, downregulation of potassium channels or upregulation of calcium channels could prolong the action potential and contribute to arrhythmogenesis.
- **Structural Remodeling:** Changes in the size and shape of the heart cells, as well as changes in the extracellular matrix, can affect the conduction of electrical signals. This can lead to conduction abnormalities and increased risk of arrhythmias.
- **Calcium Handling Remodeling:** Alterations in the proteins that regulate calcium handling (like SERCA, RyR, etc.) can affect the contractile function of the heart cells and contribute to heart failure.
- **Metabolic Remodeling:** Changes in the metabolism of the heart cells can affect their function and viability. This can lead to heart failure or increase the risk of arrhythmias.

In a cell model, these effects could be represented by altering the parameters that describe the behavior of the ion channels, calcium handling proteins, and other elements of the model. For example, if downregulation of a certain type of potassium channel is observed in diseased hearts, the conductance of this channel could be reduced in the model. Similarly, if alterations in calcium handling are observed, the parameters that describe the uptake and release of calcium by the sarcoplasmic reticulum could be modified accordingly. The effects of structural and metabolic remodeling might be harder to incorporate directly into a cell model, but they could be represented indirectly through their effects on the electrical and calcium handling properties of the cell.

- **Assume that you have models for all ion channels in a cardiac cell. What additional information is necessary to model an action potential of this cell? List at least 5 different parameters!**

1. **Resting Membrane Potential:** This is the baseline electrical potential across the cell membrane in the resting state, when the cell is not undergoing an action potential. This parameter is important for initializing the model and determines the starting point for the depolarization that triggers the action potential.

2. **Cellular Capacitance:** This reflects the ability of the cell membrane to store electrical charge. It influences the rate at which the membrane potential changes in response to ion currents and is determined by the surface area and thickness of the cell membrane.
3. **Intracellular and Extracellular Ion Concentrations:** The concentrations of key ions (such as sodium, potassium, and calcium) on both sides of the cell membrane are crucial for determining the driving forces for ion movement through the channels. They can also affect the behavior of certain ion channels and transporters.
4. **Reversal Potentials/Equilibrium Potentials:** These are the membrane potentials at which there is no net flow of a particular ion across the membrane. They are determined by the intra- and extracellular ion concentrations and are critical for determining the direction and magnitude of ion flows.
5. **Parameters Related to Calcium Handling:** In cardiac cells, the handling of intracellular calcium is crucial for both the electrical activity of the cell (since calcium ions carry part of the depolarizing current) and for the contraction of the cell (since calcium triggers the interaction of actin and myosin that leads to contraction). Important parameters include the buffering capacity for calcium, the rate of calcium uptake and release by the sarcoplasmic reticulum, and the permeability of the cell membrane to calcium.

Other important parameters could include the properties of the gap junctions that connect cardiac cells (which affect the spread of the action potential from cell to cell), the temperature (which can affect the rates of many of the processes involved), and the presence of any hormones or drugs that could affect the behavior of the ion channels or other components of the cell.

- **How would you model electrophysiological coupling of fibroblasts and myocytes? In a myocyte-fibroblast pair, which cell is the major determinant of the membrane voltage?**

Cardiac fibroblasts and myocytes are electrotonically coupled via gap junctions. When these two types of cells interact, the more hyperpolarized fibroblasts can affect the resting membrane potential and the action potential of myocytes. A potential approach could be a multi-compartment model where:

- Each cell type is represented as a separate compartment with its own set of ion channels, pumps, and exchangers.
- The myocyte compartment includes the major ion currents that contribute to the cardiac action potential, including sodium, calcium, and various types of potassium currents. The fibroblast compartment includes the currents that are known to be present in these cells, which are fewer and different in nature.
- A conductance term could be added to represent the electrical coupling between the two compartments through gap junctions.

In this model, the overall membrane voltage would be determined by the interplay between the currents in both compartments. However, since myocytes have a much larger repertoire of voltage-gated ion channels and generate action potentials, they are often considered to be the primary determinants of the membrane voltage in the myocyte-fibroblast pair. Yet, the fibroblasts can modulate this membrane voltage significantly, especially under pathological conditions where the fibroblast-myocyte coupling is enhanced.

- **Imagine you are responsible for treatment of a Timothy Syndrome patient. Suggest a therapy! How would you apply modeling to support your decision?**

Timothy Syndrome Treatment and Modeling: Timothy Syndrome is a rare genetic disorder characterized by a mutation in the CACNA1C gene, leading to abnormal function of the L-type calcium channel. This causes calcium to flow into the cells longer than normal, leading to prolonged action potentials, and various symptoms including cardiac abnormalities.

Treatment options could include calcium channel blockers like verapamil or diltiazem to decrease the excessive calcium influx. In severe cases, a pacemaker or implantable cardioverter-defibrillator (ICD) might be needed to control cardiac arrhythmias.

To support treatment decisions using modeling, you could simulate the effect of the CACNA1C mutation on cardiac electrophysiology. This would involve modifying the parameters of an existing cardiac cell model to reflect the prolonged calcium influx seen in Timothy Syndrome. Then, you could simulate the effects of different doses of calcium channel blockers, or the action of a pacemaker or ICD, to predict their impact on cardiac rhythm. This might help you choose the most effective treatment option and optimize the dosage or device settings.

- **Imagine you are responsible for treatment of a Short QT patient. What type of drug and/or implant could be helpful? How would you apply modeling to support your decision?**

Short QT Syndrome Treatment and Modeling: Short QT Syndrome is a rare genetic disorder characterized by abnormally short QT intervals on an EKG, leading to an increased risk of sudden cardiac death due to ventricular fibrillation.

Treatment options could include antiarrhythmic drugs like quinidine, which can prolong the QT interval by blocking certain types of potassium channels. In high-risk patients, an ICD might be necessary to automatically detect and treat life-threatening arrhythmias.

To support treatment decisions using modeling, you could simulate the effects of the genetic mutations known to cause Short QT Syndrome on cardiac electrophysiology. This would involve modifying the parameters of an existing cardiac cell model to reflect the faster repolarization seen in Short QT Syndrome. Then, you could simulate the effects of different doses of quinidine or the action of an ICD to predict their impact on the QT interval and the risk of arrhythmias. This might help you choose the most effective treatment option and optimize the dosage or device settings.

- **What differences of action potentials do you expect for electrically coupled cells in tissue versus an isolated cell?**

In tissue where cells are electrically coupled (like in cardiac or neural tissue), the action potentials can display some distinct characteristics compared to those of isolated cells:

- **Propagation:** In a network of coupled cells, an action potential in one cell can trigger action potentials in neighboring cells, leading to the propagation of the signal across the tissue. In an isolated cell, the action potential does not propagate beyond the cell itself.
- **Synchronization:** In a network of coupled cells, cells can synchronize their electrical activity, leading to coordinated firing of action potentials. This is especially important in the heart, where synchronization ensures effective pumping of blood. An isolated cell fires action potentials independently.

- **Altered Characteristics:** The properties of the action potential (such as duration, amplitude, and shape) can be affected by the coupled cells due to electrical influences from neighboring cells. In contrast, the properties of the action potential in an isolated cell are determined solely by the cell's own ion channels and membrane properties.

- **Normal vs Infarct border cardiac tissue**

Structural Differences:

- **Fibrosis:** In the infarct border zone, there's typically an increase in fibrosis as the body attempts to repair the damage. This means that this region will contain more fibroblasts and extracellular matrix proteins compared to normal tissue. Normal cardiac tissue is mostly composed of cardiac muscle cells (cardiomyocytes) with few fibroblasts.
- **Cellular Changes:** Cardiomyocytes in the border zone may undergo changes such as hypertrophy (enlargement) or apoptosis (programmed cell death) as a stress response to the infarction. Normal cardiomyocytes do not undergo such changes under physiological conditions.
- **Remodeling:** The border zone may undergo structural remodeling, including changes in the arrangement and shape of cells and extracellular matrix, as it adapts to the changes in load and strain following the loss of contractile tissue in the infarct zone. Normal cardiac tissue maintains a well-organized, aligned structure optimal for its contractile function.

Functional Differences:

- **Contractility:** The contractility in the border zone may be compromised due to changes in the cellular structure, increased fibrosis, and alterations in the cellular signaling. Normal cardiac tissue has regular, coordinated contractions.
- **Electrical Conductivity:** The infarct border zone can have altered electrical properties due to changes in the expression and function of ion channels, leading to electrical instability and arrhythmias. Normal cardiac tissue has consistent, reliable electrical activity that is necessary for synchronous contractions.
- **Cellular Communication:** The border zone may exhibit a reduction or remodeling of gap junctions, structures that allow electrical signals to pass from cell to cell, leading to abnormal cellular communication. In normal cardiac tissue, gap junctions ensure efficient and coordinated electrical signaling.
- **Metabolic Changes:** Cells in the border zone may experience alterations in metabolism due to changes in oxygen and nutrient supply, inflammation, and stress responses. Normal cardiac cells have a stable metabolic state, primarily relying on fatty acid oxidation for energy production.

- **Short descriptions for principles of western blot, electron microscopy, light microscope, fluorescence microscopy (standard and confocal), plasmid DNA, Antibody markers**

- **Western Blot:** This is a widely used analytical technique in cell and molecular biology to detect specific proteins in a sample. It involves separating proteins by size using gel electrophoresis, transferring them onto a membrane, and then using specific antibodies to detect the protein of interest.
- **Electron Microscopy:** Electron microscopy uses a beam of accelerated electrons to create an image of a sample. It offers much higher resolution than light microscopy, allowing visualization

of structures down to the level of individual atoms in some cases. There are two main types: transmission electron microscopy (TEM), which can provide detailed cross-sectional images of cells and tissues, and scanning electron microscopy (SEM), which can provide detailed surface images.

- **Light Microscope:** A light microscope uses visible light and a system of lenses to magnify images of small samples. It's a foundational tool in biology, allowing for the visualization of cells and tissues. It offers lower resolution than electron microscopy but is simpler to use and more accessible.
- **Fluorescence Microscopy:** This technique uses fluorescence to generate an image. The specimen is usually labeled with fluorophores (fluorescent molecules) and when illuminated with light of a specific wavelength, they emit light of a longer wavelength. This provides high-contrast images and allows for the visualization of specific components within cells.
- **Confocal Microscopy:** A subtype of fluorescence microscopy, confocal microscopy uses a laser to excite a single point in the specimen. An aperture (pinhole) is placed in front of the detector that excludes out-of-focus light, providing optical sectioning capability and allowing for the reconstruction of three-dimensional structures from the obtained images.
- **Plasmid DNA:** Plasmids are small, circular pieces of DNA that are separate from the chromosomal DNA in a cell. They are found in many bacteria and can replicate independently. Plasmids are frequently used in genetic engineering as vectors to introduce new genes into cells.
- **Antibody Markers:** Antibodies are proteins that can bind specifically to certain other molecules, called antigens. In research, they are often used as markers because they can be designed to bind specifically to a protein of interest, allowing for that protein to be detected and located within a sample. The antibodies themselves can be labeled with enzymes, fluorescent tags, or other markers to make them visible under appropriate conditions.

- **Injected current in voltage-clamps**

In the context of voltage-clamp experiments, the injected current is designed to be the opposite of the total ionic current flowing through the membrane.

In a voltage-clamp experiment, the objective is to hold the membrane potential of a cell at a desired or "command" level. To achieve this, the system injects a current to counterbalance the ionic currents flowing through the membrane. If the ion channels open and cause positive charge to flow into the cell (an inward current), the system will inject an equal but opposite (outward) current to prevent the membrane potential from changing.

- **About HH**

Alan Hodgkin and Andrew Huxley are renowned for their groundbreaking experiments on the giant axon of the squid, which led to the formulation of the Hodgkin-Huxley model of the action potential. These experiments were performed in the early 1950s and earned them the Nobel Prize in Physiology or Medicine in 1963.

Here is a summary of their key experiments and findings:

1. **Voltage Clamping:** Hodgkin and Huxley used the voltage-clamp technique to fix the membrane potential of the squid giant axon at various levels. They then measured the ionic currents that

flowed in response to these voltages. This was made possible by the size of the squid giant axon, which is large enough to insert two electrodes: one for measuring voltage and the other for injecting current. The use of the voltage-clamp technique was one of the significant innovations in their work.

2. **Ionic Basis of the Action Potential:** Hodgkin and Huxley found that the action potential is caused by two types of currents: an inward sodium current and an outward potassium current. They showed that during an action potential, the sodium current activates first, causing depolarization of the membrane. This is followed by the activation of the potassium current, which repolarizes the membrane.
3. **Time and Voltage Dependence:** Hodgkin and Huxley discovered that the sodium and potassium currents are not only voltage-dependent but also time-dependent. The sodium current quickly activates and then inactivates, while the potassium current activates more slowly and does not inactivate. This explained the shape of the action potential and the refractory period following it.
4. **Hodgkin-Huxley Equations:** Based on their experimental data, Hodgkin and Huxley developed a set of differential equations that describe how the sodium and potassium currents depend on the membrane potential and time. These equations, known as the Hodgkin-Huxley equations, are a mathematical model of the action potential.

$$I = C_m \frac{dV_m}{dt} + \bar{g}_K n^4 (V_m - V_K) + \bar{g}_{Na} m^3 h (V_m - V_{Na}) + \bar{g}_l (V_m - V_l),$$

$$\frac{dn}{dt} = \alpha_n(V_m)(1 - n) - \beta_n(V_m)n$$

$$\frac{dm}{dt} = \alpha_m(V_m)(1 - m) - \beta_m(V_m)m$$

$$\frac{dh}{dt} = \alpha_h(V_m)(1 - h) - \beta_h(V_m)h$$

5. **Prediction of Channel Behavior:** While Hodgkin and Huxley did not know about the existence of ion channels (they were discovered much later), their model indirectly predicts their behavior. The model suggests the existence of voltage-gated sodium and potassium channels, which open and close in response to changes in the membrane potential, and the concept of gating variables, which represent the probability of a channel being open.

- **Nernst Equation for EQUILIBRIUM potential**

Resting Potential

- All ions contribute weighted by the membrane permeability
- Goldman-Hodgkin-Katz equation for sodium, potassium and chloride

$$E_{m,K/Na/Cl} = \frac{RT}{F} \ln \left(\frac{P_{Na^+} [Na^+]_{out} + \boxed{P_{K^+} [K^+]_{out}} + P_{Cl^-} [Cl^-]_{in}}{P_{Na^+} [Na^+]_{in} + \boxed{P_{K^+} [K^+]_{in}} + P_{Cl^-} [Cl^-]_{out}} \right)$$

- **Ion movement at rest**

At rest, a cell's membrane potential is not equal to the equilibrium potential of any single ion. Instead, it's a balance determined by the equilibrium potentials of all ions that the membrane is permeable to, weighted by their relative permeabilities. This is described by the Goldman-Hodgkin-Katz (GHK) equation.

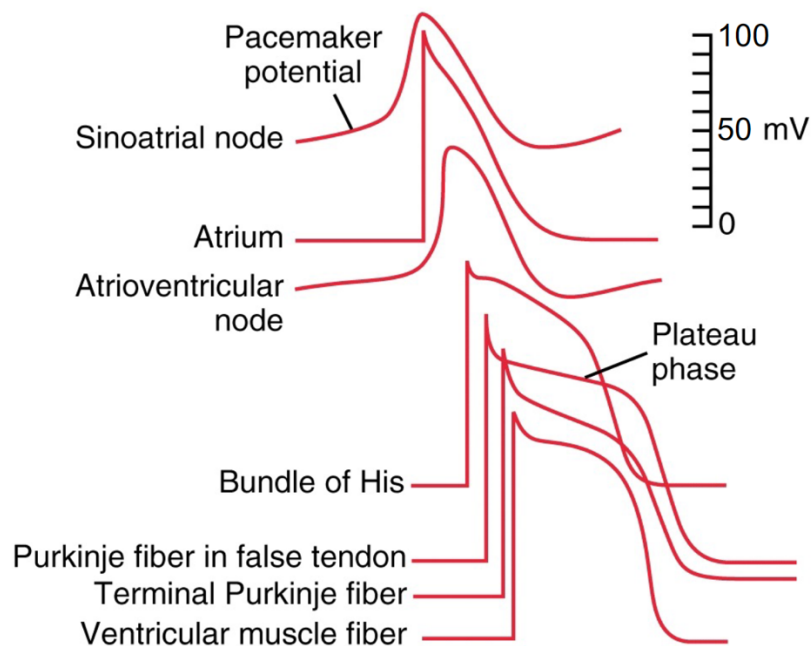
At rest, the membrane is most permeable to potassium ions, so the resting membrane potential is close to the potassium equilibrium potential.

The term "resting" refers to a stable state where the overall inward and outward currents balance each other out, so there's no net change in the membrane potential. In other words, the ion fluxes are in a steady state, even though individual ions are still moving across the membrane.

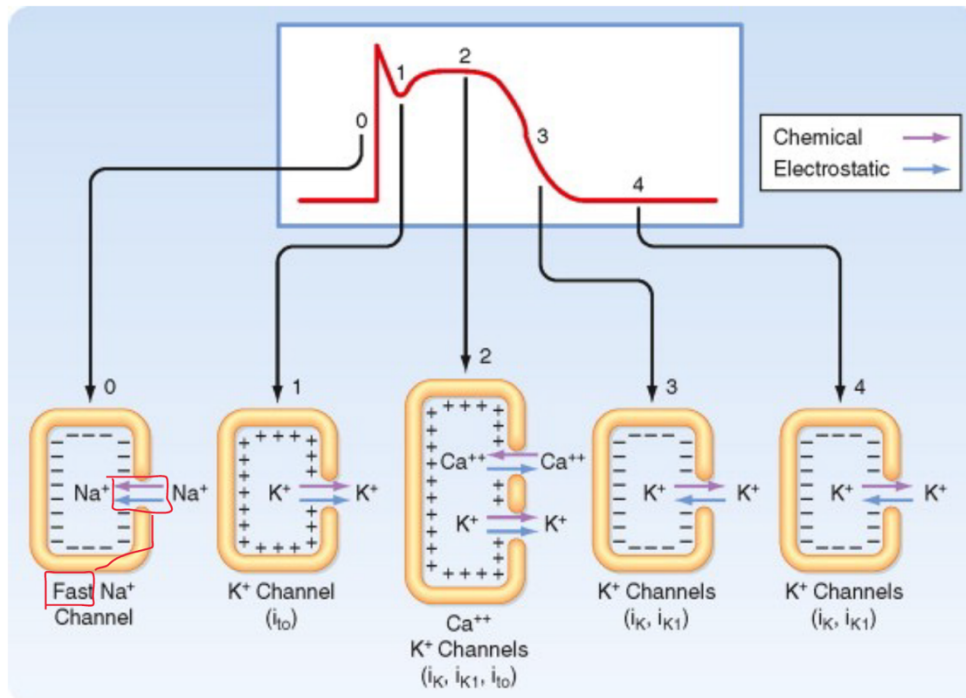
This balance is actively maintained by the cell through several mechanisms:

1. **Leak Channels:** These are ion channels that are open at rest, allowing ions to move down their concentration gradients. For instance, potassium leak channels allow potassium ions to move out of the cell, which is a major determinant of the resting membrane potential.
2. **Ion Pumps:** These are active transporters that use energy to move ions against their concentration gradients, maintaining the differences in ion concentrations inside and outside the cell. The sodium-potassium pump, which pumps 3 sodium ions out of the cell for every 2 potassium ions it pumps in, is particularly important in maintaining the resting membrane potential.

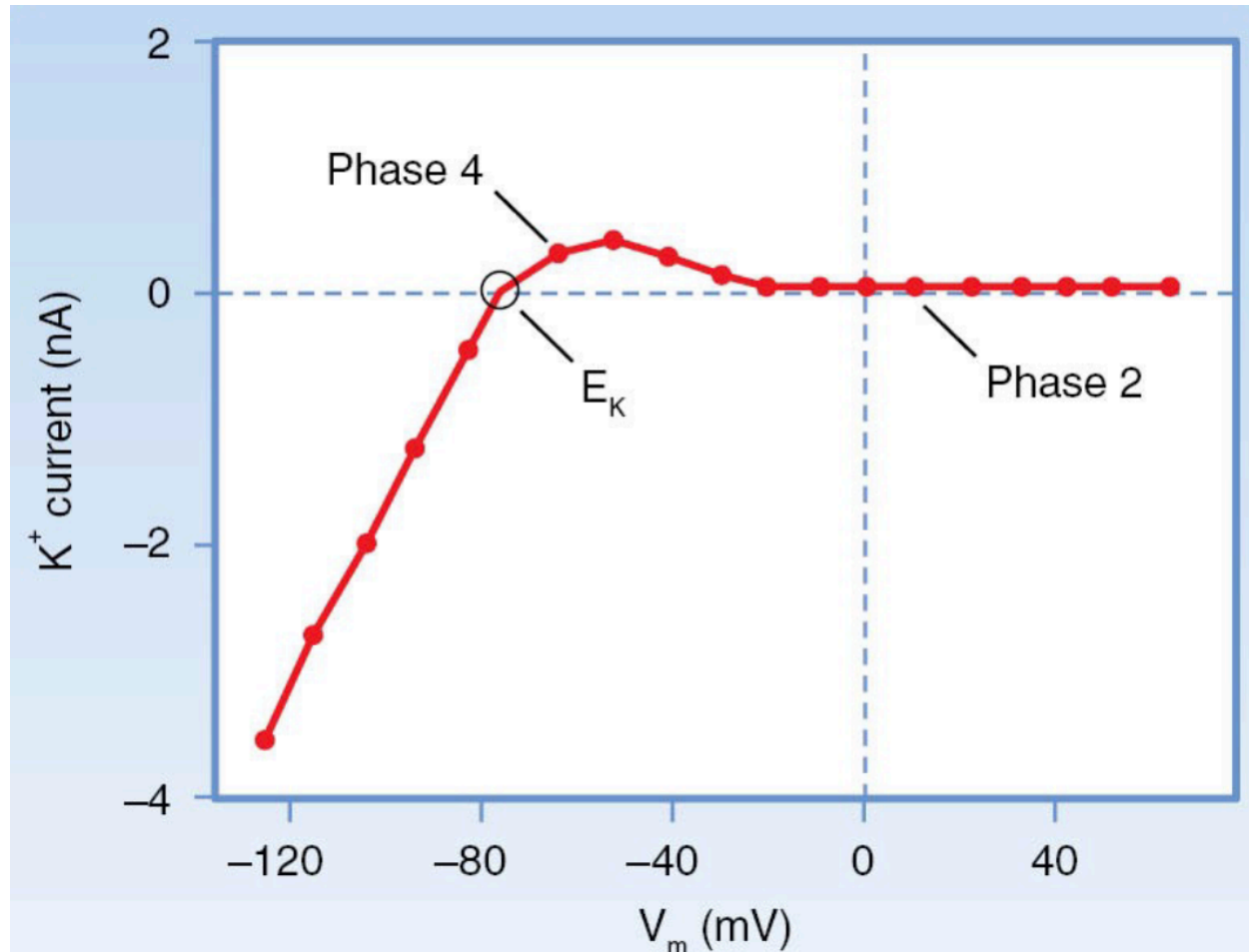
Cardiac Action Potentials



Currents and Phases of the Cardiac Action Potential



Inwardly rectifying K^+ channels support the flow of positively charged K^+ ions into the cell, pushing the membrane potential back to the resting potential



Tetrodotoxin is a sodium channel blocker. It inhibits the firing of action potentials in neurons by binding to the voltage-gated sodium channels in nerve cell membranes and blocking the passage of sodium ions (responsible for the rising phase of an action potential) into the neuron. This prevents the nervous system from carrying messages and thus muscles from contracting in response to nervous stimulation

- **If TTX completely abolish upstroke of sodium, would we still see phase 1, 2, 3, 4 for those purkinjer fiber action potential?**

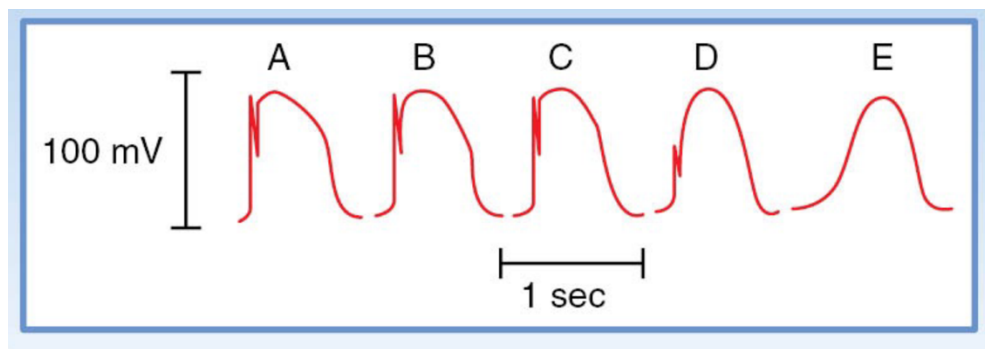
The typical action potential in a Purkinje fiber (or a ventricular myocyte) has five phases, numbered 0 through 4.

1. **Phase 0** is the rapid upstroke of the action potential, caused by the opening of voltage-gated sodium channels and the consequent rapid influx of sodium ions into the cell. This phase represents depolarization.
2. **Phase 1** is a brief initial repolarization, caused by the closure of the sodium channels and the opening of transient outward potassium channels.
3. **Phase 2** is the plateau phase, characterized by a balance between inward movement of calcium ions (through voltage-gated calcium channels) and outward movement of potassium ions.
4. **Phase 3** is the rapid repolarization phase, due to the closure of the calcium channels and continued outflow of potassium ions.
5. **Phase 4** is the resting phase, where the membrane potential is maintained near the potassium equilibrium potential until the next action potential is initiated.

Now, if a sodium channel blocker like TTX is present, it will block the voltage-gated sodium channels, eliminating the rapid influx of sodium ions during Phase 0. This would result in the elimination or severe attenuation of Phase 0 depolarization.

However, TTX does not directly affect the other ion channels involved in the later phases of the action potential. So, theoretically, if another depolarizing event (e.g., opening of voltage-gated calcium channels) could bring the membrane to the threshold potential, the other phases might still occur.

But in practical terms, without the strong depolarizing current provided by sodium influx, it is unlikely that the membrane potential would reach the threshold needed to open voltage-gated calcium channels and proceed to Phases 1, 2, and 3. Therefore, the presence of TTX would likely prevent a normal action potential from occurring in the Purkinje fiber.



(Redrawn from Carmeliet E, Vereecke J: Pflügers Arch 313:300, 1969.)

[Tetrodotoxin]	0 μ M	0.03 μ M	0.3 μ M	3 μ M (early)	3 μ M (later)
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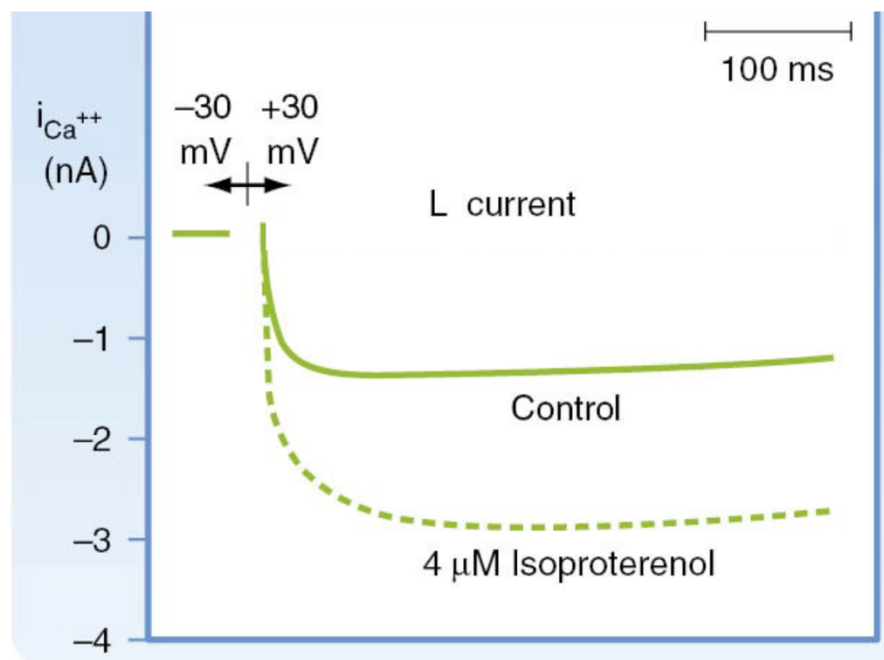
(Complete block but still has AP due to Autorhythmic: some cardiac cells depolarize spontaneously)

- **Effect of Isoproterenol on L-type Ca^{2+} Currents?**

Isoproterenol is a non-selective beta-adrenergic agonist, meaning it stimulates the beta-adrenergic receptors in the body. These receptors are linked to a G-protein signaling pathway, and their activation initiates a cascade of intracellular events that ultimately influence the activity of various ion channels. When it comes to L-type calcium channels in the heart, isoproterenol has a notable effect. Upon binding to beta-adrenergic receptors, it triggers the production of cyclic AMP (cAMP) via the enzyme adenylyl cyclase. This increase in cAMP activates protein kinase A (PKA), an enzyme that phosphorylates various proteins, including L-type calcium channels.

Phosphorylation of these channels increases their open probability, which means they are more likely to be open at any given membrane potential. This results in an increase in the inward calcium current ($I_{\text{Ca,L}}$) during an action potential, effectively enhancing the calcium influx into the cell.

This increase in calcium influx has several important effects on cardiac physiology. It not only contributes to the plateau phase of the cardiac action potential, prolonging the depolarization phase, but also triggers the release of more calcium from the sarcoplasmic reticulum into the cytosol (a process known as calcium-induced calcium release, or CICR). The increased cytosolic calcium, in turn, enhances the contractility of the cardiac muscle cell, a response known as the positive inotropic effect. Thus, isoproterenol can lead to an increase in the strength and rate of heart contractions by increasing the L-type calcium current. However, if the signaling pathway is overly stimulated (as might occur during prolonged stress), it can lead to abnormal heart rhythms and other cardiac pathologies.

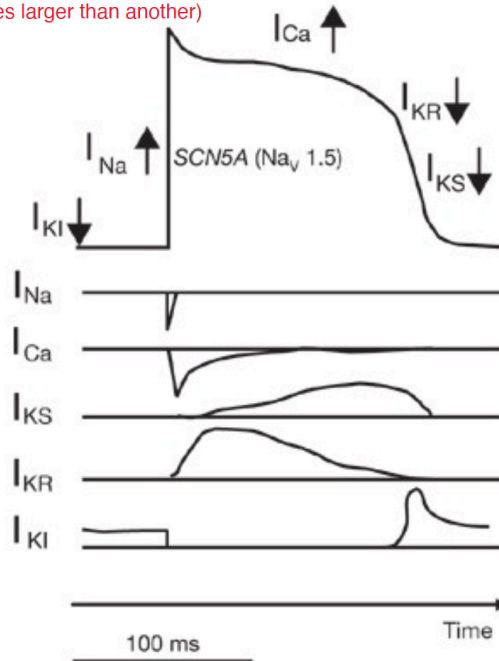


(Redrawn from Bean BP: J Gen Physiol 86:1, 1985.)

Summary: Cardiac Action Potential

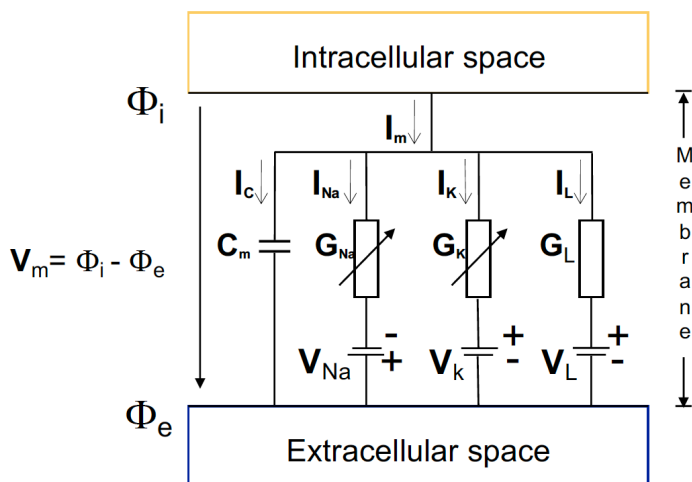
Magnitudes here are not represented (some currents are hundred times larger than another)

- Resting potential depends almost entirely on K^+ gradient
- Some cardiac cells depolarize spontaneously (autorhythmic)
- Most do not and those cells exhibit:
 - Depolarization after activation of Na^+ channels at -65 mV
 - Na^+ channels inactivate at more positive V_m
 - Ca^{2+} channels activate at -35 mV and inactivate at more positive V_m
 - Plateau represents balance between Ca^{2+} and K^+ currents
 - Repolarization caused by K^+ currents



Nature Cell Biology 6, 1039 - 1047 (2004)
Thomas J. Jentsch, Christian A. Hubner & Jens C. Fuhrmann

Hodgkin-Huxley Model: Equivalent Circuit Diagram



G_{Na}, G_K, G_L
Membrane conductivity of Na, K and other ions [S/cm²]

I_{Na}, I_K, I_L
Currents of Na, K and other ions [mA/cm²]

V_{Na}, V_K, V_L
Nernst voltages of Na, K and other ions [mV]

C_m, I_m, V_m
Membrane capacitor [F/cm²], current [mA/cm²] and voltage [mV]

$$I_m = C_m \frac{dV_m}{dt} + (V_m - V_{Na})G_{Na} + (V_m - V_K)G_K + (V_m - V_L)G_L$$

Hodgkin-Huxley Model: Principles

Ohm's law:

~~$$G_{Na} = \frac{I_{Na}}{V_{Na}} \quad G_K = \frac{I_K}{V_K} \quad G_{Na} = \frac{I_L}{V_L}$$~~

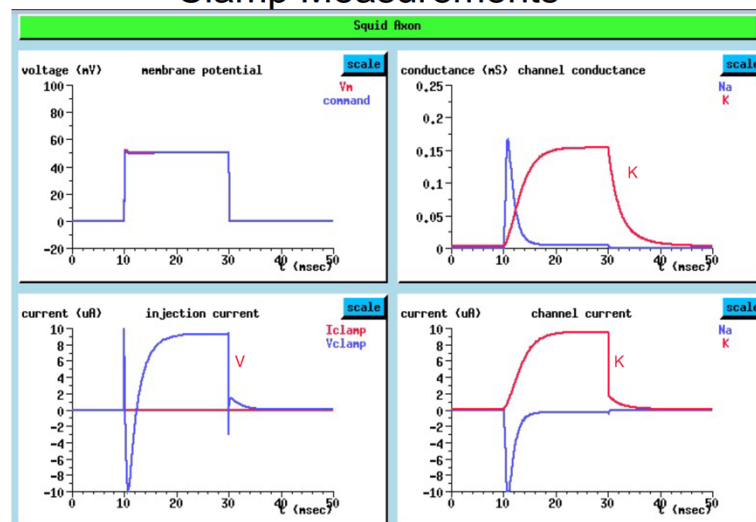
Nernst voltages for calculation of conductance and current

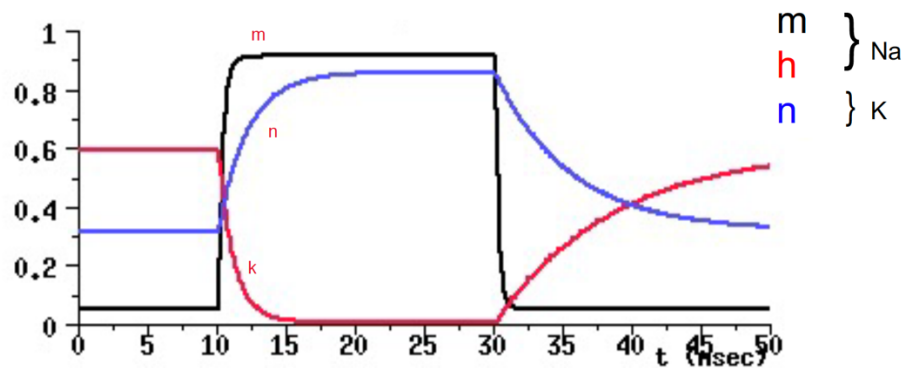
$$G_{Na} = \frac{I_{Na}}{V_m - V_{Na}} \quad G_K = \frac{I_K}{V_m - V_K} \quad G_{Na} = \frac{I_L}{V_m - V_L}$$

driving force

- K and Na conductance overtime in an AP?

Hodgkin-Huxley Model: Simulation of Voltage Clamp Measurements

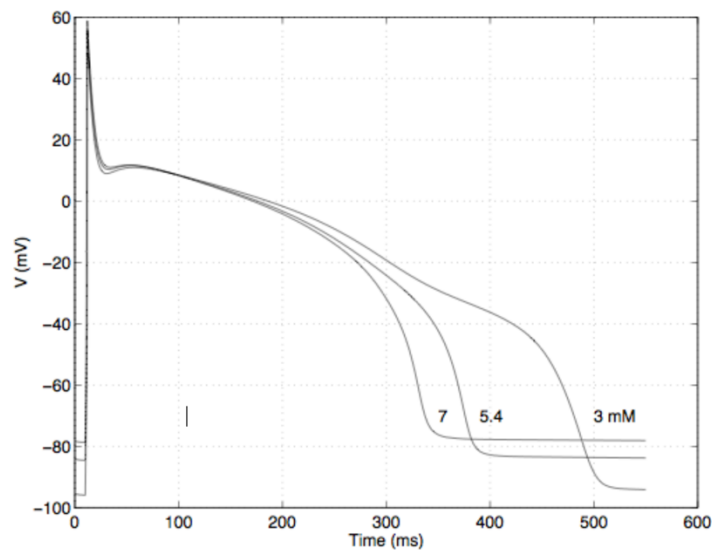




- **How would repolarization phase of cardiac action potential look like as extracellular potassium concentration increases?**

During the repolarization phase of the action potential (Phase 3), voltage-gated potassium channels open, allowing potassium ions to flow out of the cell, moving down their concentration gradient. This outward movement of positive charges causes the cell to repolarize, returning the membrane potential back towards the resting level. However, if $[K^+]_o$ is high, the concentration gradient for potassium is reduced, slowing down the repolarization process. This means that the action potential duration would increase, lengthening the QT interval on an EKG.

Varying Parameters – Extracellular K^+



- **Pacemaker Cells**

UNIQUENESS

- Their resting membrane potential (-60mV) is UNSTABLE
- As it never actually rests, it is called "pacemaker potential" instead of "resting membrane potential"

Why Pacemaker potential exists?

- They have unusual channels that are permeable to both Na^+ and K^+ ; they have Na^+ channels with unusually/funny properties => they are called I_f channel (f = funny)

4:

When I_f opens, Na influx exceeds K outflux => net influx of positive charges slowly depolarizes cell. As V_m becomes more positive, I_f closes and Ca (L and T) open transiently, further depolarizing cell.

to 0:

When threshold is reached, a burst of Ca L type opens, more Ca rushes in, steep phase of depolarization occurs.

to 3:

At peak, K open, K rushes out of the cell, repolarizing

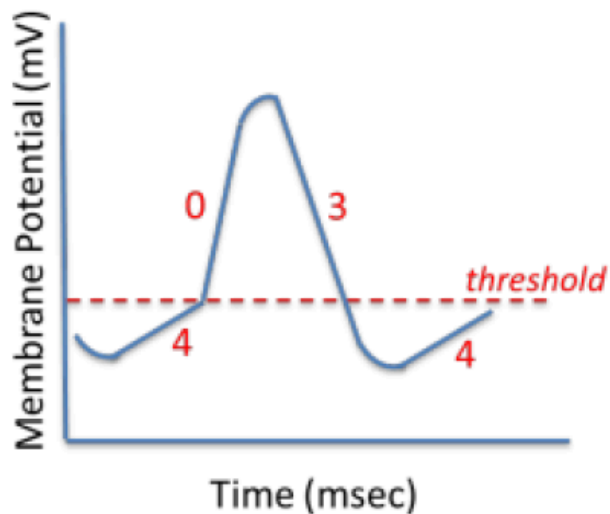


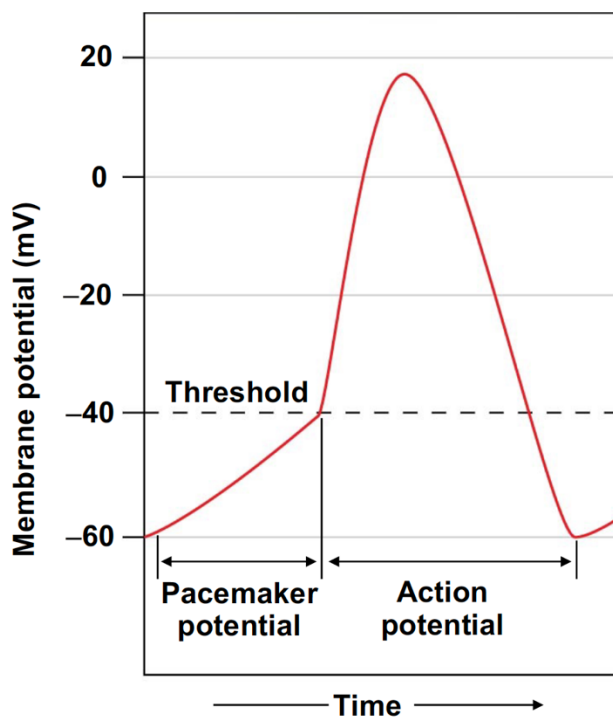
Figure 2. Slow action potential has 3 phases (0, 3 and 4).

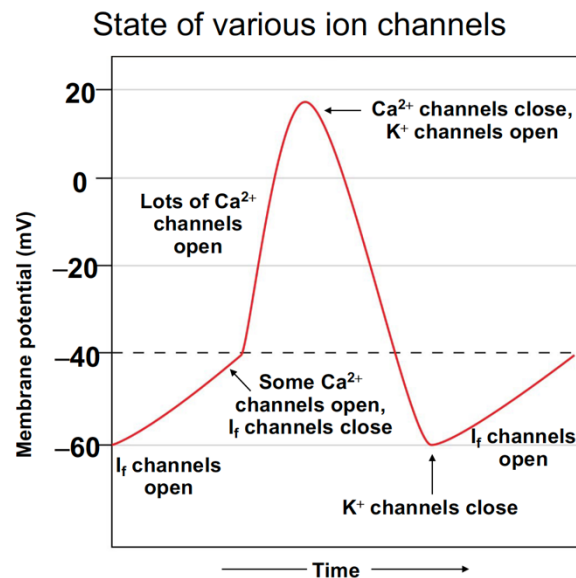
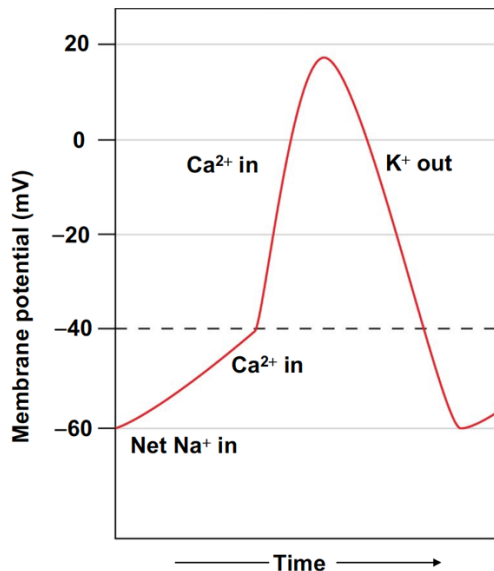
Membrane voltage of pacemaker cell gradually becomes less negative until it reaches threshold, triggering an action potential.

Underlying current: I_f

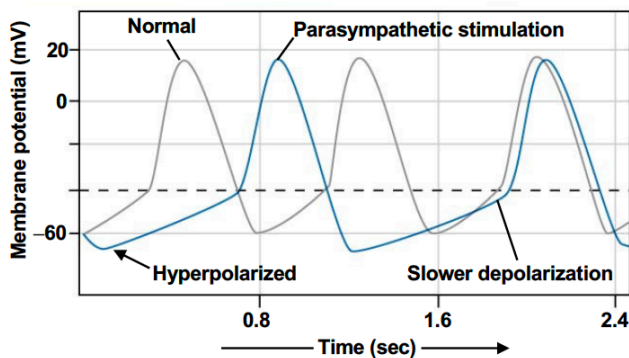
“Funny current”

Carries Na^+ and (less) K^+

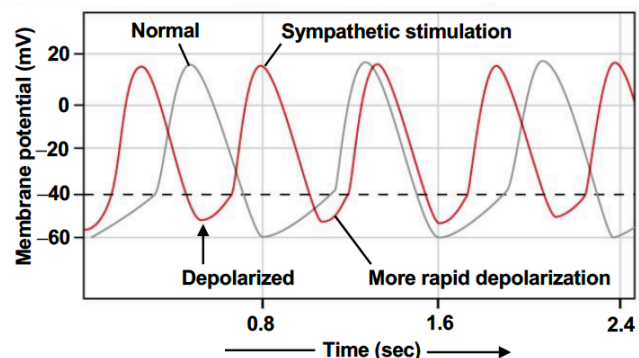




(d) Parasympathetic stimulation hyperpolarizes the membrane potential of the autorhythmic cell and slows depolarization, slowing down the heart rate.



(e) Sympathetic stimulation and epinephrine depolarize the autorhythmic cell and speed up the pacemaker potential, increasing the heart rate.



- **Positive chronotropes of pacemaker cells are achieved by Increased current through voltage-gated Ca^{2+} channels, correct? how about a negative chronotrope?**

Yes, positive chronotropic effects, which are associated with an increase in heart rate, are often achieved through an increase in the current through voltage-gated calcium channels, specifically the L-type calcium channels. The mechanism behind this involves the activation of the sympathetic nervous system, which leads to the release of neurotransmitters such as norepinephrine. Norepinephrine binds to beta-1 adrenergic receptors on the heart's pacemaker cells, leading to an increase in cyclic AMP (cAMP) levels. This in turn activates protein kinase A (PKA), which phosphorylates and thus opens L-type calcium channels. The increase in calcium influx through these channels enhances the depolarizing current during the action potential, leading to faster rates of spontaneous action potential generation and thus increasing the heart rate.

Negative chronotropic effects, which are associated with a decrease in heart rate, can be achieved by several mechanisms. One important mechanism involves the activation of the parasympathetic nervous system, which releases the neurotransmitter acetylcholine (ACh). ACh binds to muscarinic receptors (specifically M2) on the heart's pacemaker cells. This leads to the activation of G-protein gated inwardly

rectifying potassium channels (GIRKs), causing an increase in potassium efflux, which hyperpolarizes the cell and slows the rate of spontaneous depolarization.

At the same time, the activation of the **M2 receptor inhibits adenylyl cyclase**, leading to a decrease in cAMP and thus less PKA activation. This leads to less phosphorylation and opening of L-type calcium channels, further slowing the rate of spontaneous action potential generation and thus decreasing the heart rate.

Additionally, ACh decreases the activity of the funny current (I_f), a mixed Na^+/K^+ current that is responsible for the slow depolarization phase of the action potential in pacemaker cells. The net effect of these actions is a decrease in heart rate.

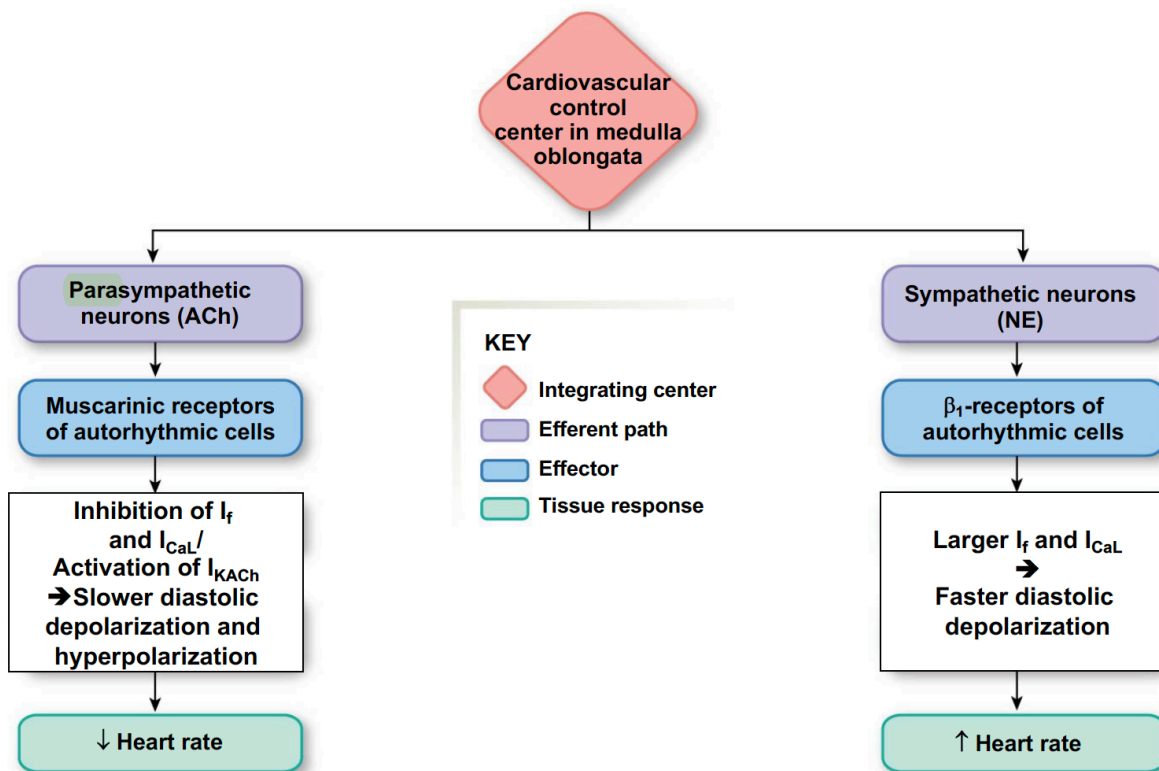
So while

- positive chronotropic agents typically work by increasing the activity of calcium channels
- negative chronotropic agents work by increasing potassium current and decreasing both calcium current and the funny current.

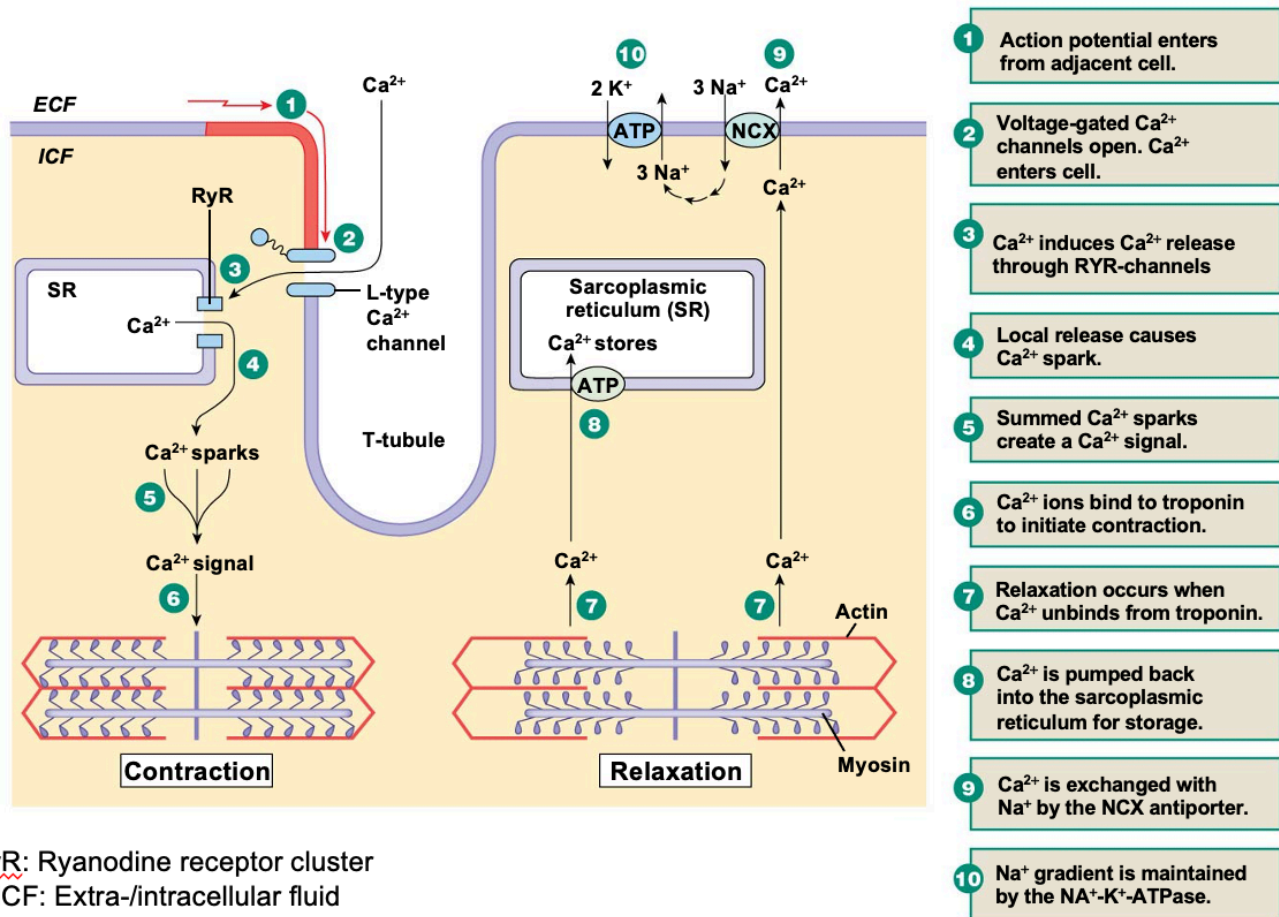
Low ACh (0-100 nM): Decreased rate is primarily caused by decreased slope of diastolic depolarization due to inhibition of I_f .

Higher ACh (≥ 100 nM): Increased I_{KACH} contributes to slowing of activation rate by membrane hyperpolarizing and counterbalancing I_f . This may lead to termination of cell activation.

Parasympathetic and sympathetic neurons alter heart rate through antagonistic control



EC COUPLING IN CARDIAC MYOCYTES

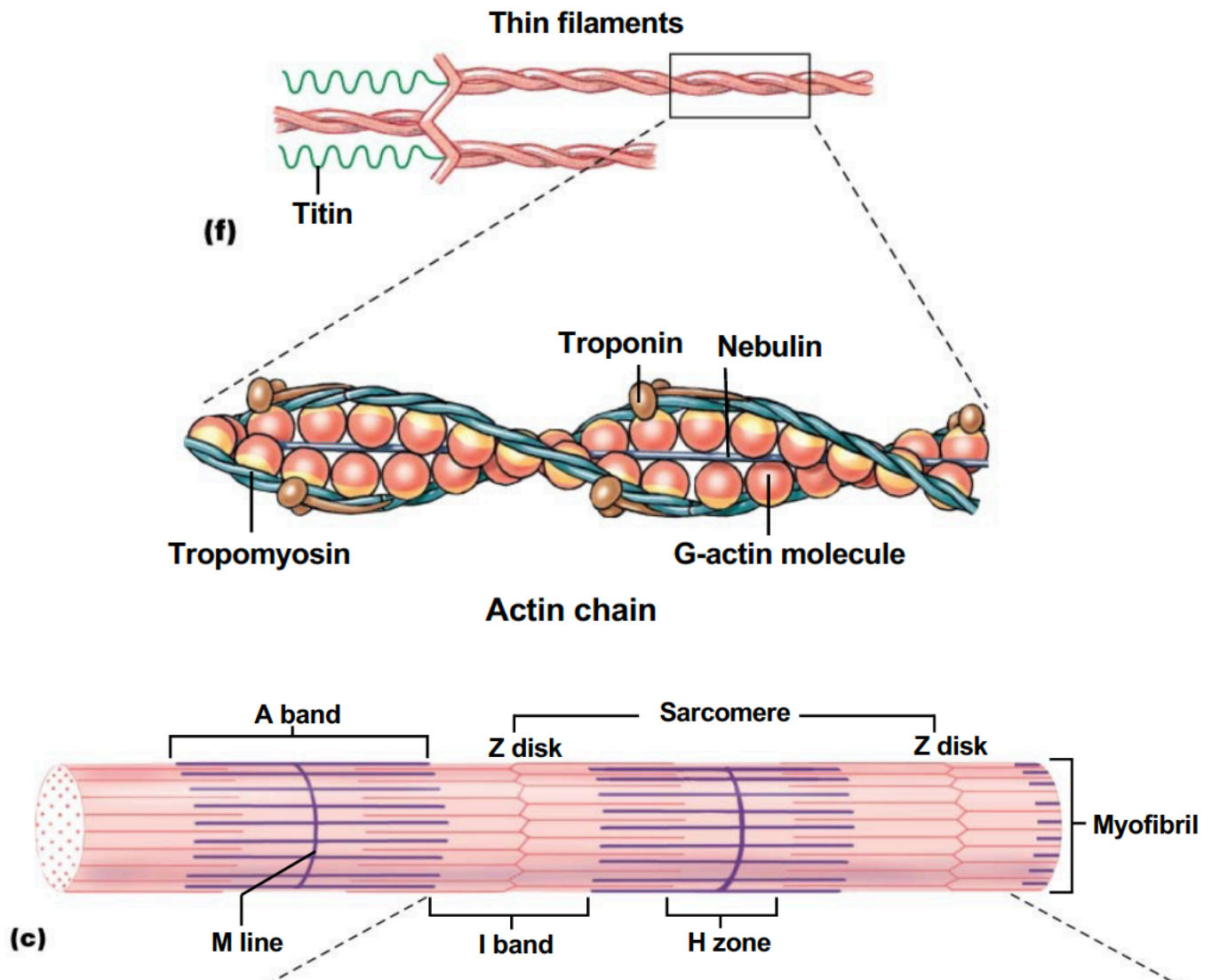


RyR: Ryanodine receptor cluster
E/ICF: Extra-/intracellular fluid

- Troponin and tropomyosin**

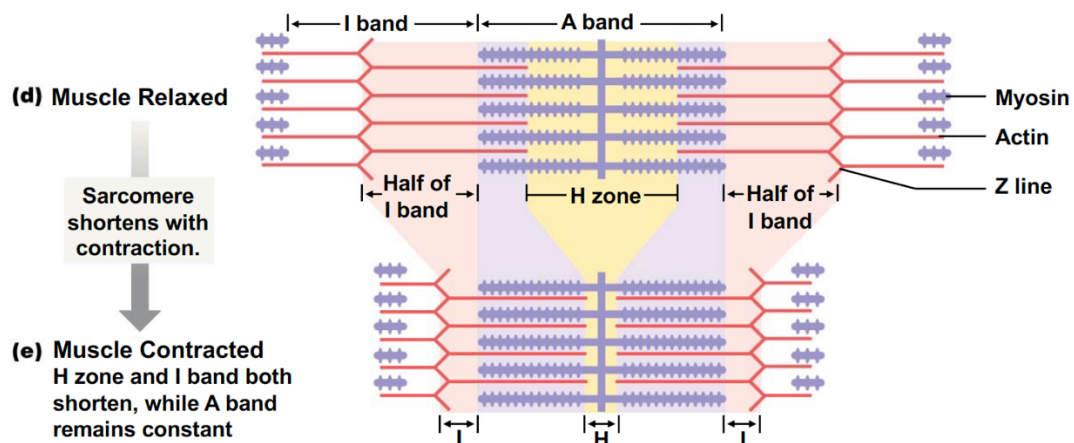
The troponin (Tn) is bound to tropomyosin in striated (skeletal and cardiac) muscle cells.

When calcium ions bind to Tn, it causes a conformational change in the entire troponin complex, which then moves tropomyosin out of the way of the myosin-binding sites on the actin filament. This allows the myosin heads to bind to actin and the muscle to contract.

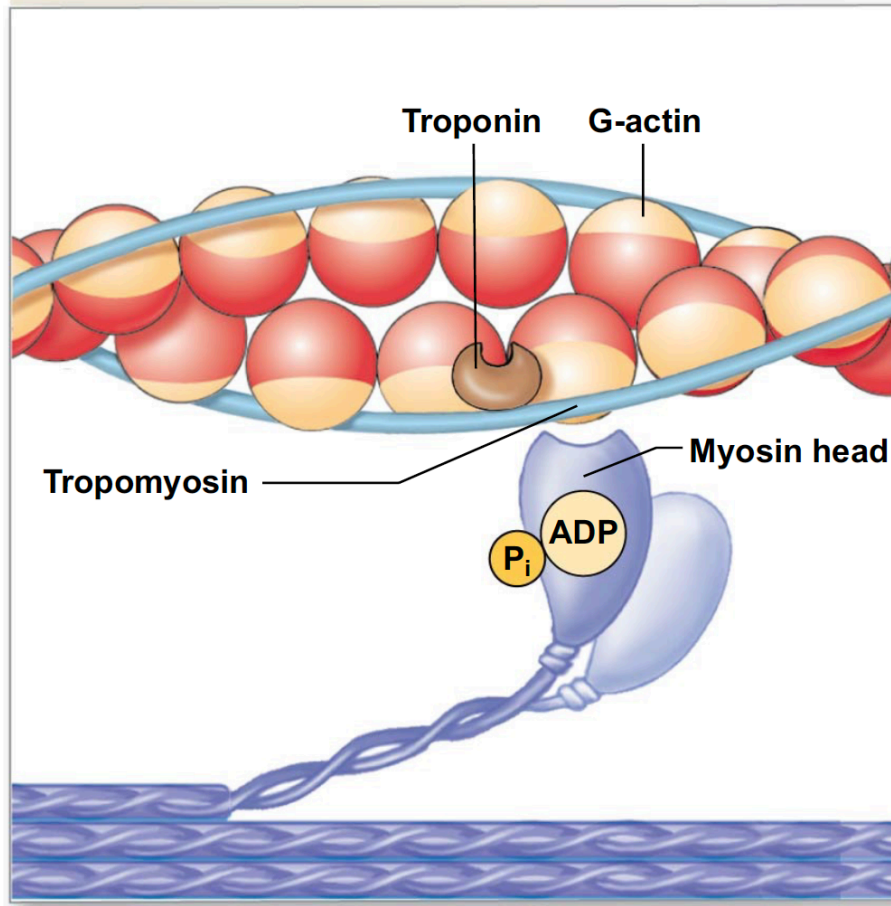


Sarcomere Shortening Leads to Myocyte Contraction “Sliding Filament Theory”

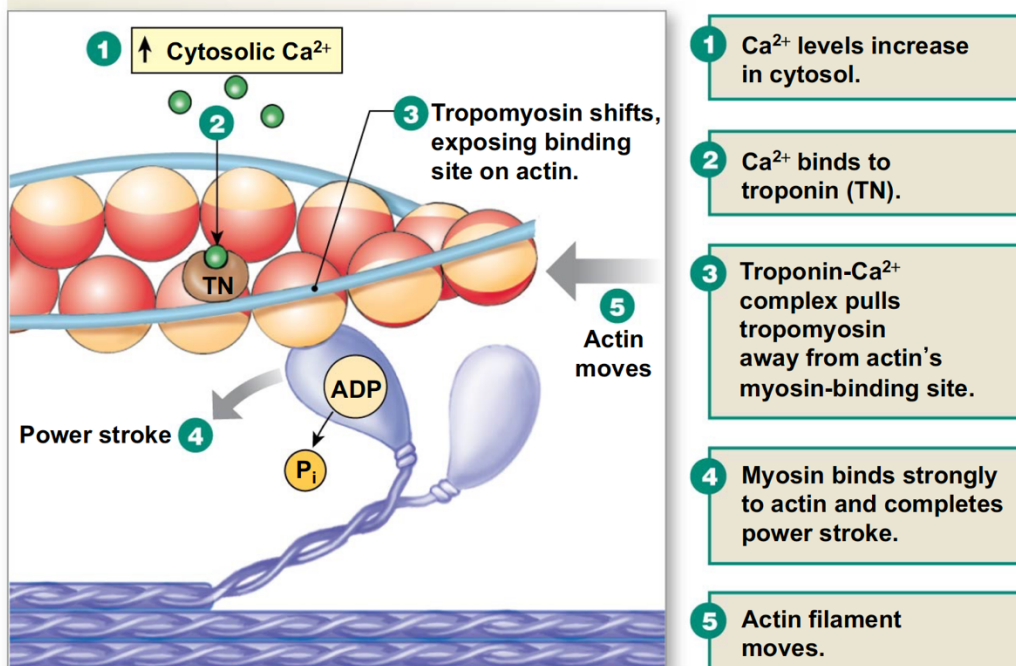
As contraction takes place, actin and myosin filaments do not change length, but instead slide past one another.



(a) Relaxed state. Myosin head cocked. Tropomyosin partially blocks binding site on actin. Myosin is weakly bound to actin.



(b) Initiation of contraction. A calcium signal initiates contraction.



- **Crossbridge Cycling and ATP Hydrolysis of Myosin?**

The crossbridge cycle is the process by which myosin and actin interact to cause muscle contraction. It's driven by ATP hydrolysis and involves several steps:

1. **Attachment:** The myosin head binds to an actin filament, forming a crossbridge. In the relaxed state, myosin is bound to an ATP molecule. The hydrolysis of ATP into ADP and inorganic phosphate by the ATPase activity of the myosin head energizes the myosin, which changes its conformation and binds to the actin filament.
2. **Power Stroke:** The release of the inorganic phosphate initiates the power stroke, a change in the conformation of the myosin head that pulls the actin filament towards the center of the sarcomere. This is the actual contractile step in the cycle.
3. **Detachment:** Following the power stroke, ADP is released from the myosin head. The binding of a new ATP molecule to myosin causes the myosin head to detach from the actin filament.
4. **Recovery Stroke:** Hydrolysis of the newly-bound ATP re-energizes the myosin head, returning it to its original conformation and position. The myosin head is now ready to form a new crossbridge with actin and repeat the cycle.
5. If calcium is present (as in when a muscle is being stimulated to contract), the cycle repeats. If calcium is absent (as in a relaxed muscle), the cycle stops, and the muscle relaxes.

The process of ATP hydrolysis provides the energy for the crossbridge cycle. It's the "fuel" that powers muscle contraction. Without ATP, the myosin heads would not be able to detach from actin and reset to their high-energy conformation, and muscle contraction would not be possible.

the "cocked" myosin head is essentially a primed, ready-to-go molecular motor that's prepared to do the work of muscle contraction.

The opposite to the "cocked" state in the context of myosin and muscle contraction would be the "relaxed" or "uncocked" state.

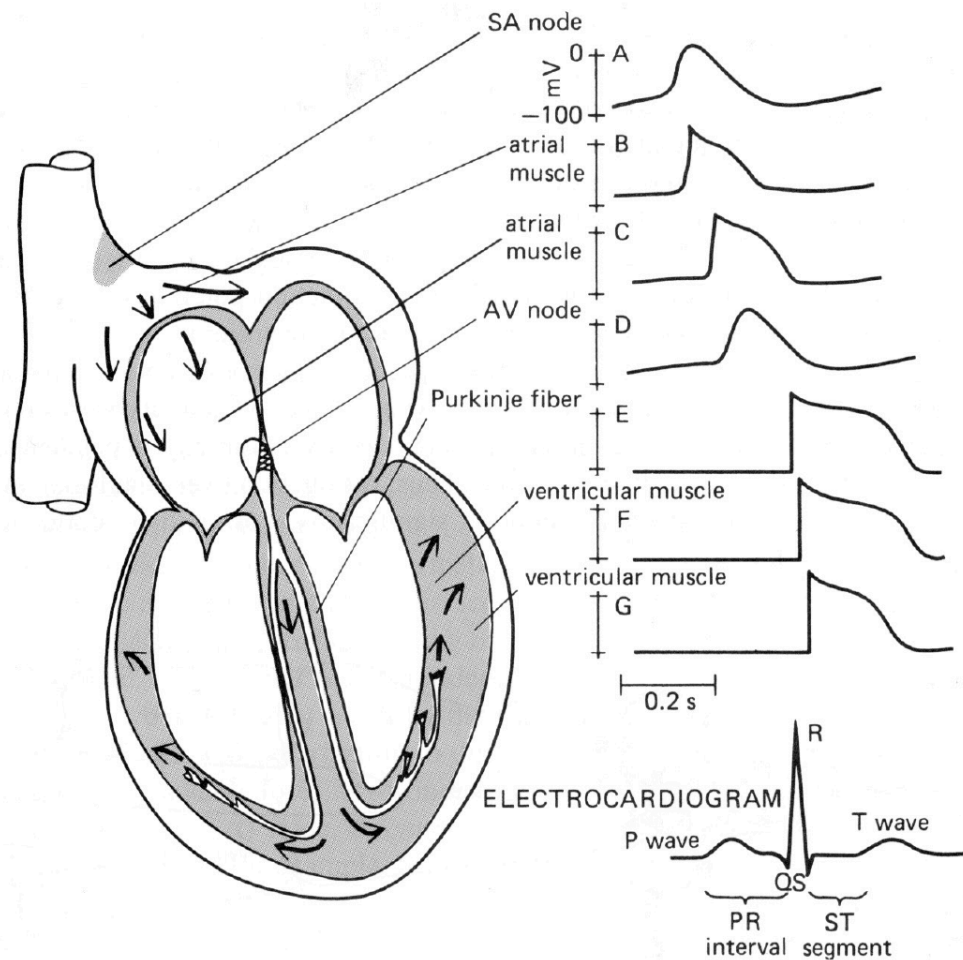
Upon the binding of ATP, the myosin head returns to a lower-energy conformation - this is the "uncocked" or "relaxed" state.

Once the ATP bound to the myosin head is hydrolyzed to ADP and inorganic phosphate, the myosin head becomes "cocked" again and ready for the next round of interaction with the actin filament, starting a new cycle of muscle contraction.

Cardiac Conduction: Summary

- Requires a network of connected, excitable cells
- All-or-nothing phenomenon
 - no superposition (unlike other waves)
 - collisions result in annihilation
 - amplitude does not diminish with distance
- Anisotropy due to preferential connections between cells and cell shape
 - wavefronts are elliptical and not spherical
 - propagation depends on muscle microstructure (fiber orientation)
- Insensitivity to further immediate stimulation, i.e. refractoriness

Cardiac Activation Sequence



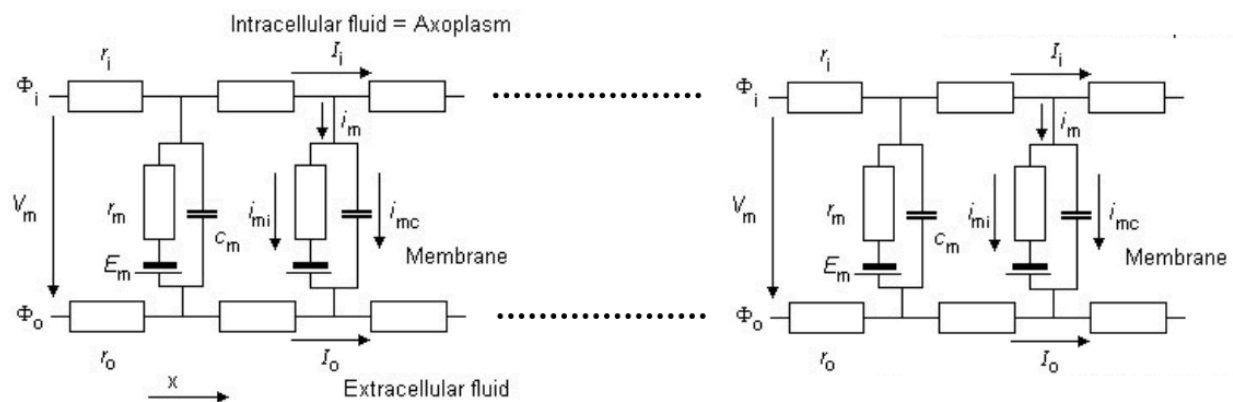
- **Reaction Diffusion System-Cable Theory in cardiac conduction?**

The cable theory is a mathematical model used in neuroscience and cardiac electrophysiology to estimate how electrical signals propagate through space in neurons or cardiac cells, which can be likened to cables. The "cable" here refers to the cylindrical, long shape of these cells. This theory combines aspects of both reaction-diffusion systems and electrical circuit analysis.

Here's a basic overview of how cable theory applies to cardiac conduction:

1. **Passive Cable Properties:** The cells are treated as electrical cables with certain properties like resistance and capacitance. The cell membrane resistance is determined by ion channels, while capacitance relates to the ability of the membrane to store charge. The cytoplasmic resistance (longitudinal resistance) is determined by the conductivity of the cytoplasm.
2. **Voltage Change Over Distance:** The cable theory provides the equations that allow us to calculate how much voltage change would occur over a certain distance along the cable (cell). This is crucial in understanding how the action potential propagates.
3. **Time Constant and Length Constant:** Two important parameters in cable theory are the time constant (how rapidly the voltage changes over time) and the length constant (how rapidly voltage changes over distance). These two parameters are influenced by the resistive and capacitive properties of the cell, and they determine how far and how quickly electrical signals can travel within the cell.
4. **Propagation of Action Potentials:** In cardiac tissue, an action potential in one cell can stimulate the neighboring cell to depolarize, creating a domino effect that allows the signal to propagate through the heart tissue. This is crucial for the synchronized contraction of the heart.

Cable theory, thus, provides the mathematical underpinnings that help us understand how electrical signals (action potentials) propagate through cardiac cells and tissue. It is a simplified model but provides valuable insights into the basic principles governing electrical conduction in the heart.



Cable Model: Steady State Response to Non-Excitatory Current

Length constant λ describes spatial distance between two points:

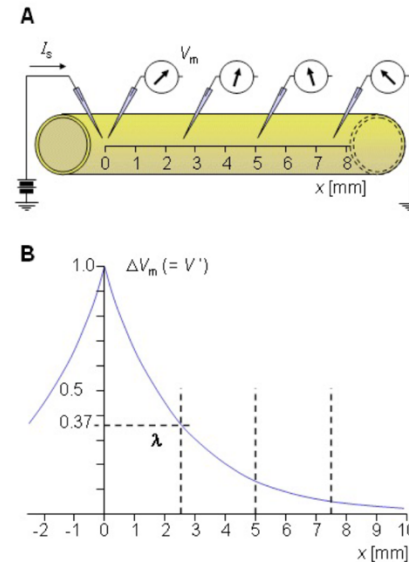
1. Position of electrode for injection of current causing membrane voltage ΔV_m
2. Position at which the membrane voltage equals $\Delta V_m/e$ (commonly interpolated from measurements)

$$\Delta V_m(\lambda) = 0.368 \Delta V_m(0)$$

Length constant λ is determined by intra-, extracellular and membrane resistances, r_i , r_o , and r_m :

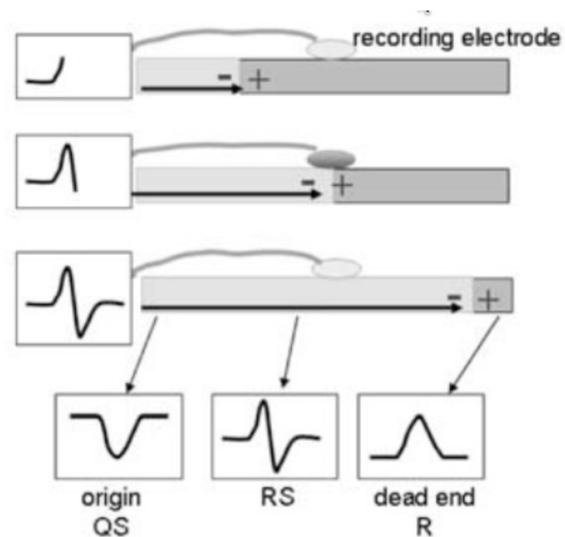
$$\lambda = \sqrt{\frac{r_m}{r_i + r_o}} \approx \sqrt{\frac{r_m}{r_i}}$$

Challenge: r_m is function of time, space, voltage, ...



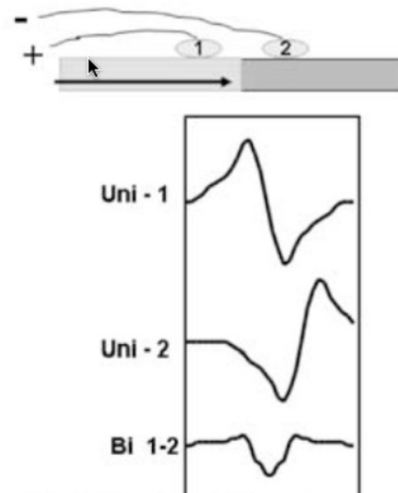
Unipolar Measurement

- Differences of electrical potentials between a single electrode site and a remote reference
- Features
 - Recording field is infinite and uniform in all directions, hence no directional sensitivity
 - Signals contain far field components and are sensitive to distant electrical activity.
 - Signal morphology indicates wavefront direction
 - Morphology depends on choice of reference

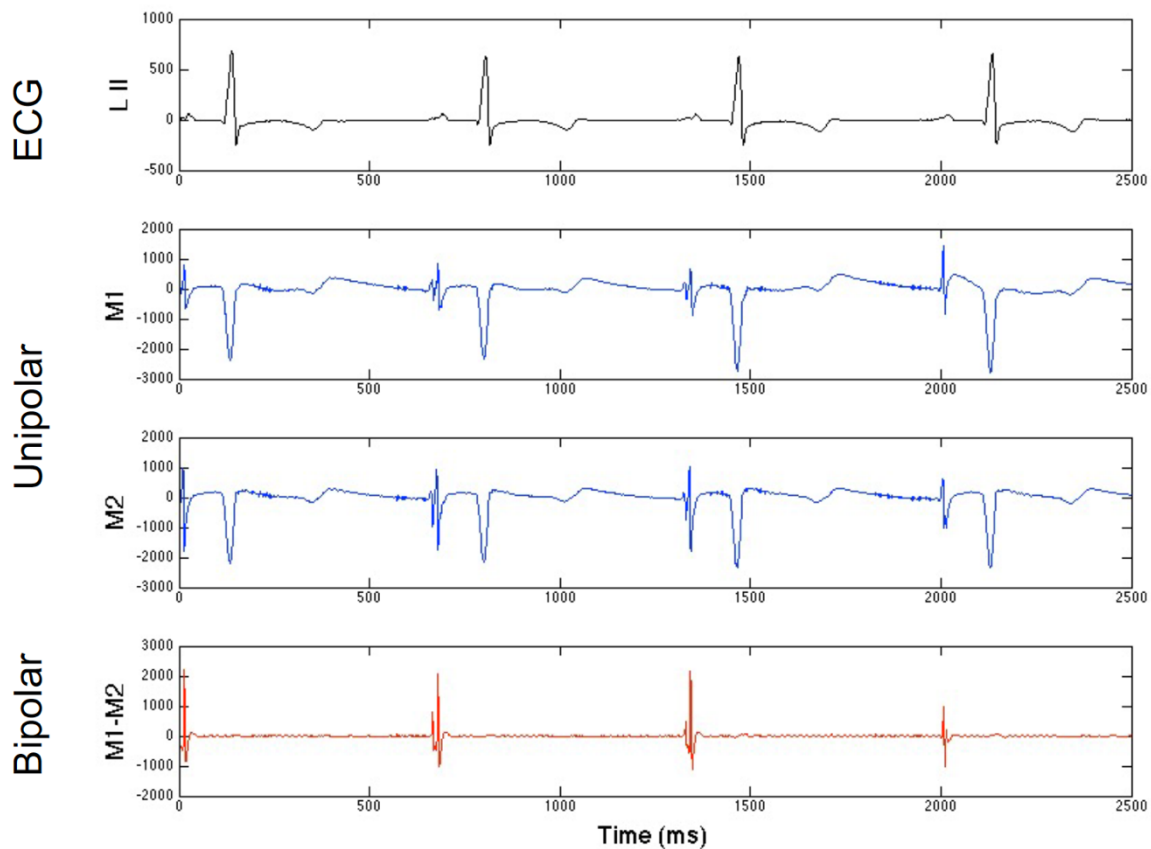


Bipolar Measurement

- Differences of electrical potentials between two closely spaced electrodes
- Features
 - Recording field falls off quickly, much less sensitive to distance activation fronts, hence recording of local events.
 - Method is sensitive to directional differences of the wavefront with respect to the axis of the bipole.
 - Morphology does not indicate wavefront direction



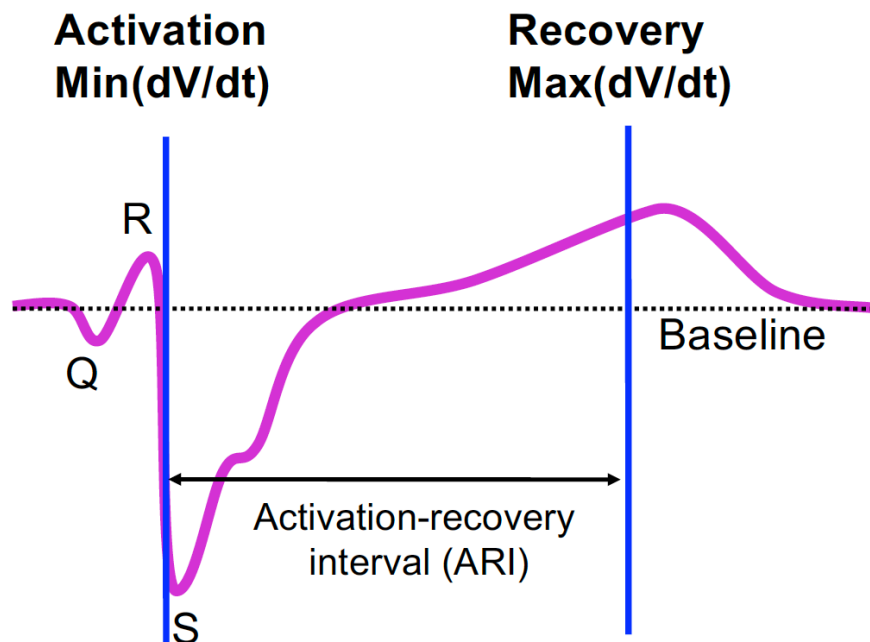
Electrogram Examples



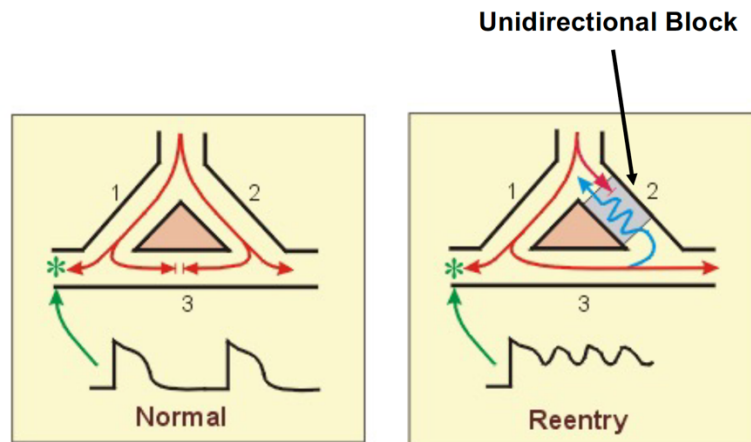
Optical Mapping

- Fluorescent Dyes
 - voltage sensitive
 - calcium sensitive
- Setup similar to fluorescence microscope
- Multiple sensors
 - photodiodes
 - CCD cameras
- Advantages
 - no impalement or contact
 - direct measure membrane potential
- Disadvantages
 - commonly, measures relative change so calibration a challenge
 - motion artifacts; need for excitation-contraction uncouplers

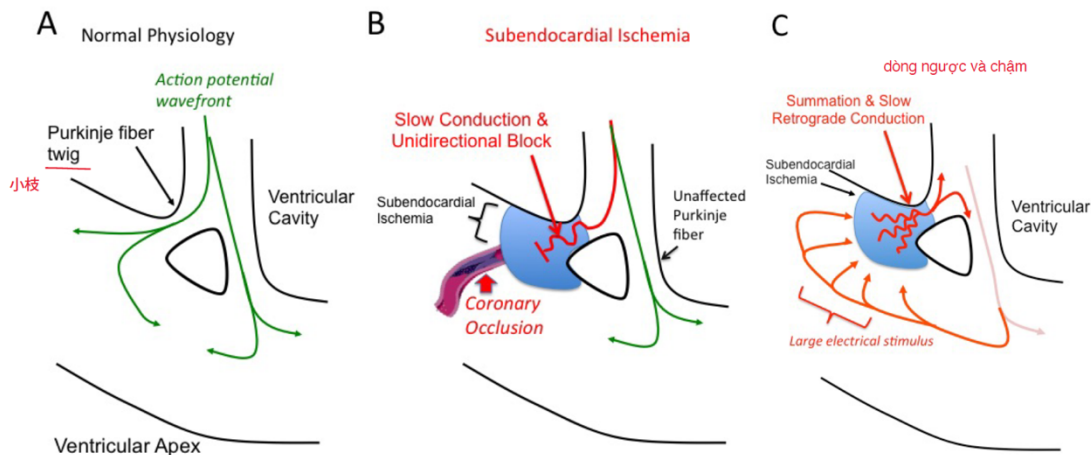
Signal Processing of Unipolar Cardiac Electrograms: Example



Cardiac Conduction - Reentry



Reentry Onset – Myocard/Purkinje Junction

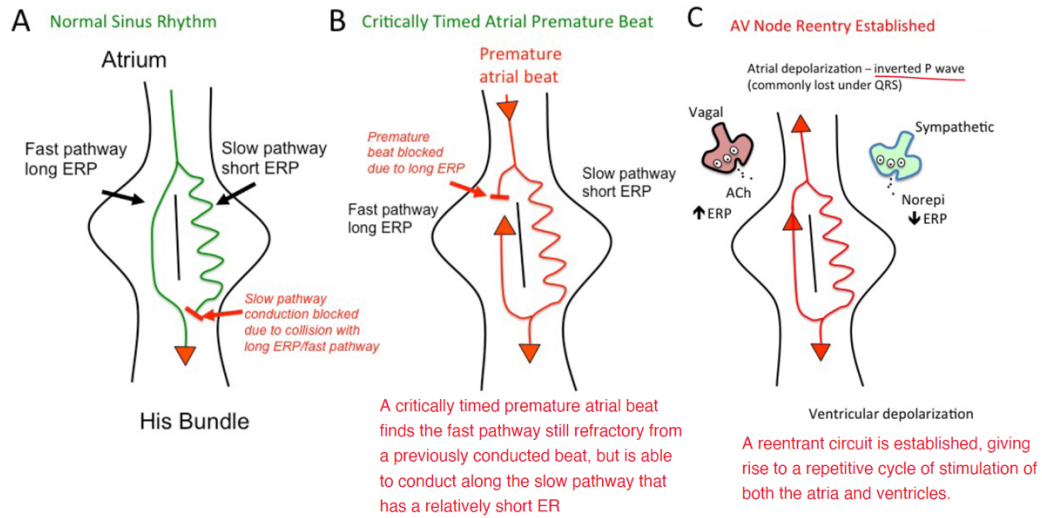


- Why does the system commonly fail in VF but not AF?**

The system commonly fails in VF due to the role of the ventricles as the main pumping chambers of the heart. When the ventricles fibrillate, they are unable to pump blood out to the body, leading to a cessation of circulation and causing immediate life-threatening symptoms.

On the other hand, while the atria contribute to filling the ventricles with blood, a significant portion of this filling occurs passively from blood flow into the relaxed ventricle. Thus, even with the atria fibrillating in AF, some blood still fills the ventricles and gets pumped out into the body, allowing for the maintenance of circulatory function. That being said, AF can still lead to a reduced cardiac output and pose a risk for the development of serious complications, as mentioned earlier.

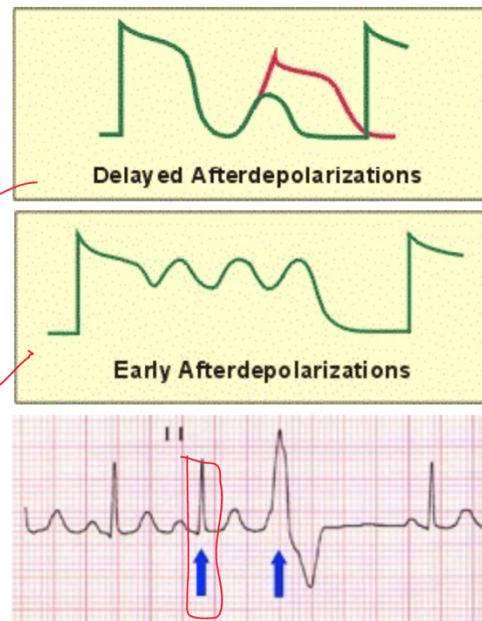
AV Node Reentry



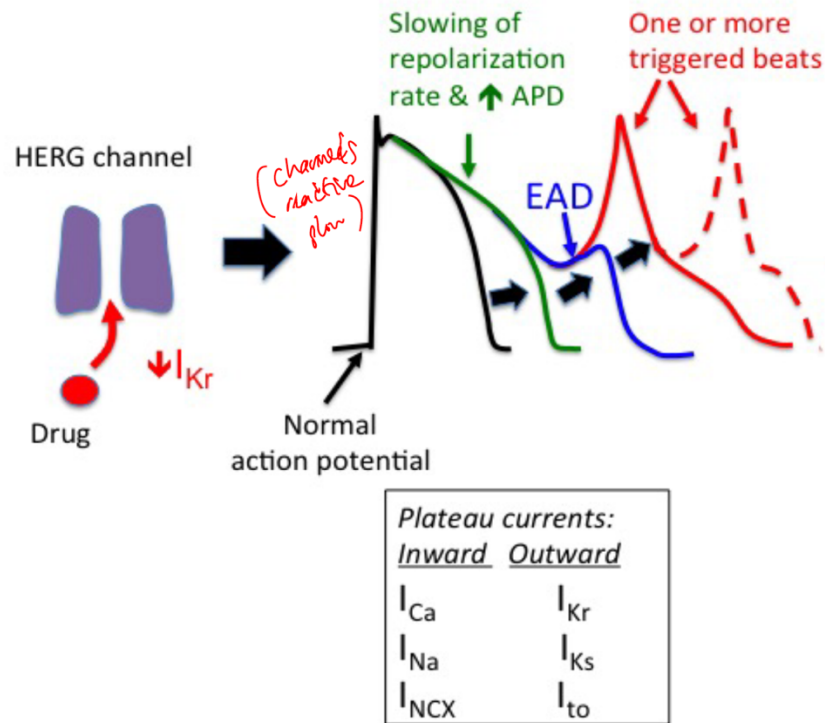
ERP: Effective Refractory Period

Extrasystole (Premature Beat)

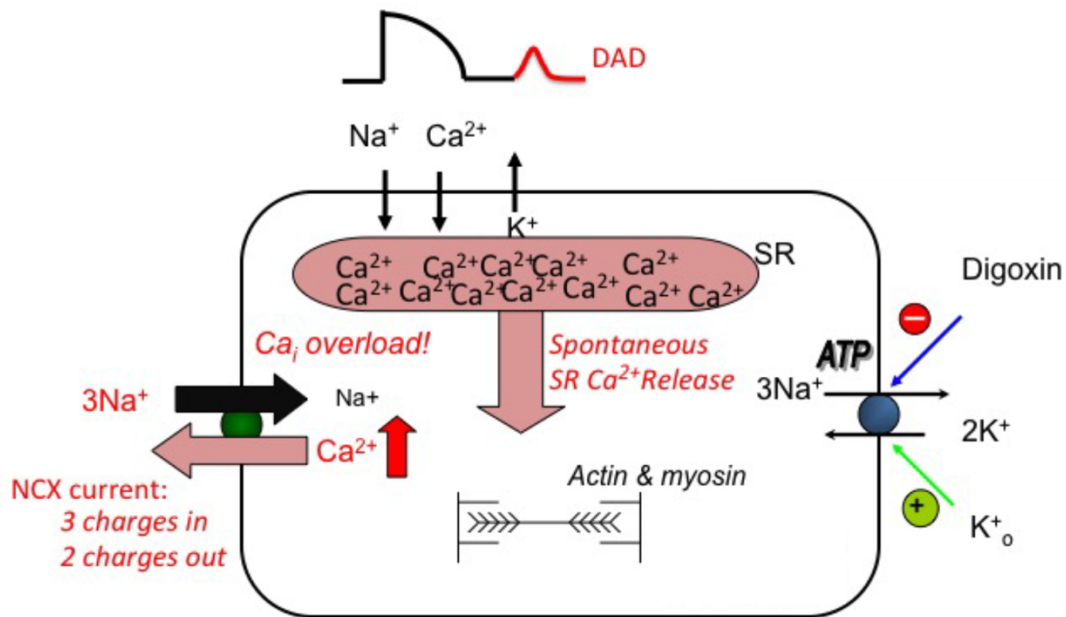
- Cellular origins
 - Abnormal Ca^{2+} handling
 - Ion concentrations
 - Drugs
 - Genetic mutations
 - ...
- Mechanisms
 - Delayed afterdepolarization (DAD)
 - Spontaneous sarcoplasmic Ca^{2+} release
 - Na^+ - Ca^{2+} exchanger
 - Early afterdepolarization (EAD)
 - Reopening of L-type Ca^{2+} channels
- Whole heart consequences
 - Extra beat
 - Compensatory pause



EAD Mechanisms: Reopening of L-type Ca Channel



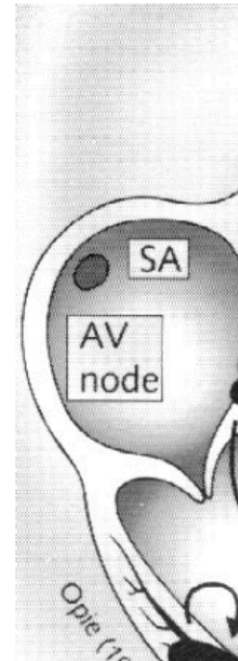
DAD Mechanisms: Spontaneous Ca Release



$$I_{NaK} \downarrow \rightarrow Na_i \uparrow \rightarrow Ca_i \uparrow \rightarrow Ca_{SR} \uparrow \rightarrow SR \text{ Ca release} \rightarrow I_{NCX} \uparrow \rightarrow V_m \uparrow$$

Clinical Arrhythmias

- **Mechanisms**
 - automaticity
 - reentry
- **Substrate**
 - necrotic or fibrotic tissue
 - unidirectional block
 - accessory pathway
- **Stimulus**
 - extrasystoles
 - afterdepolarizations

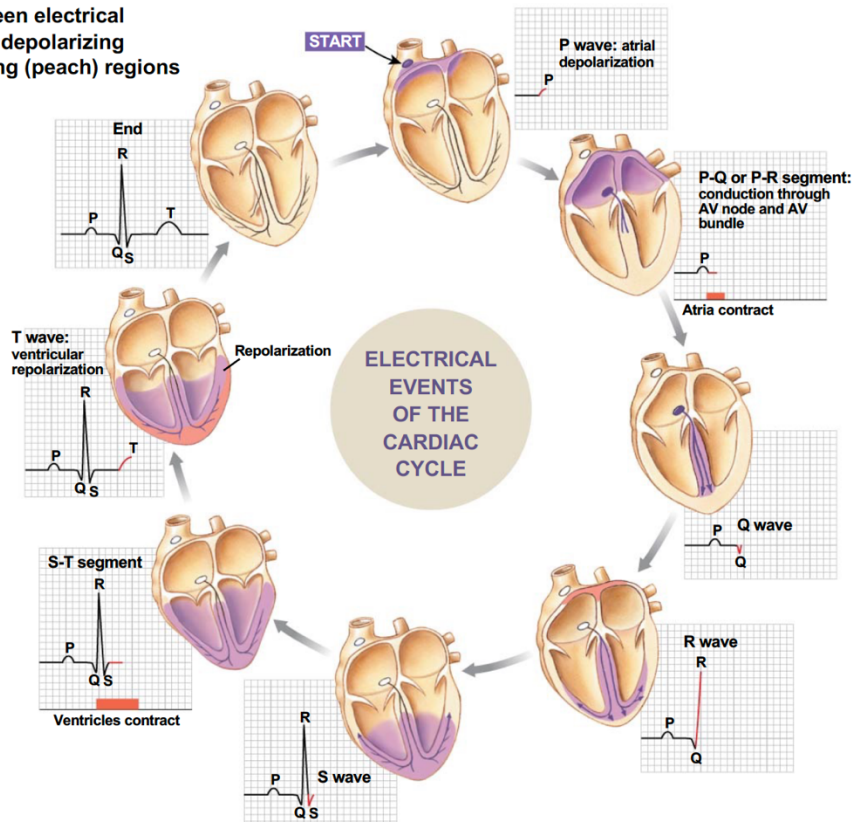


Treatment of Cardiac Arrhythmias: Drugs

- **Class I:** Reduce excitability - reduce dV/dt of AP upstroke
Na⁺ channel blockers
- **Class II:** Reduce sensitivity to sympathetic stimulation
Beta blockers
- **Class III:** Prolong repolarization
K⁺ channel blockers
- **Class IV:** Reduce excitability of nodal cells
(mostly in SA and AV node)
Ca²⁺ channel blockers
- **Class V:** Other or unknown mechanism

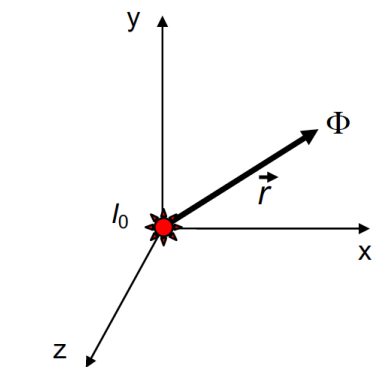
CORRELATION BETWEEN AN ECG AND ELECTRICAL EVENTS IN THE HEART

Correspondence between electrical events in the ECG and depolarizing (purple) and repolarizing (peach) regions of the heart.



Monopole and Dipole

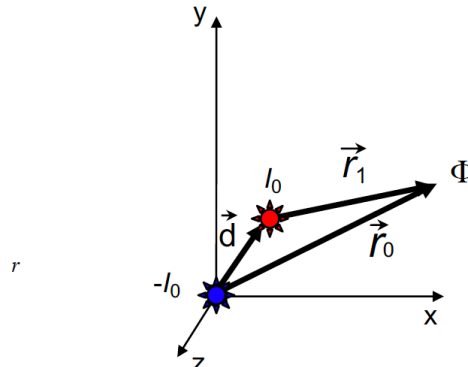
Monopole Source



$$r = |\vec{r}| \quad \vec{r} = r \hat{r}$$

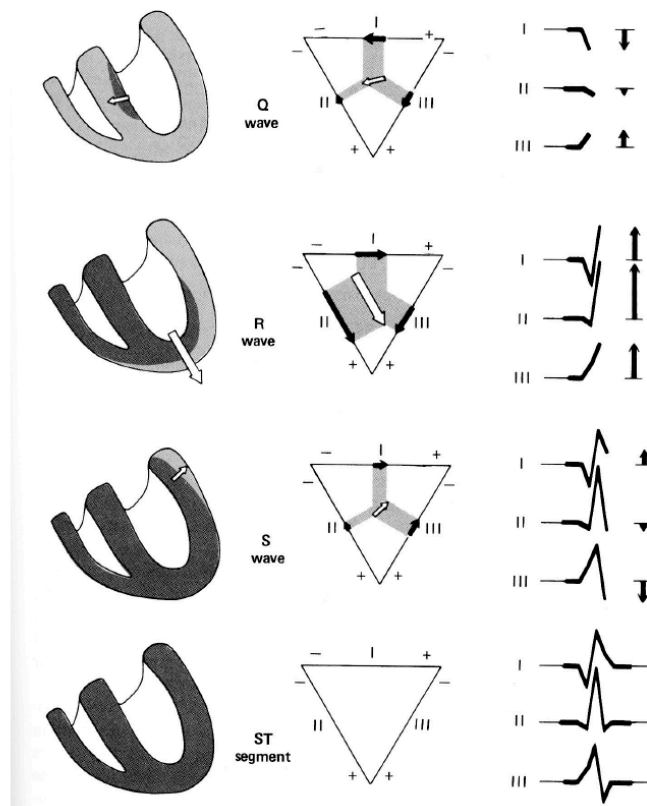
$$\Phi = \frac{1}{4\pi\sigma_e} \frac{I_o}{r}$$

Dipole Source

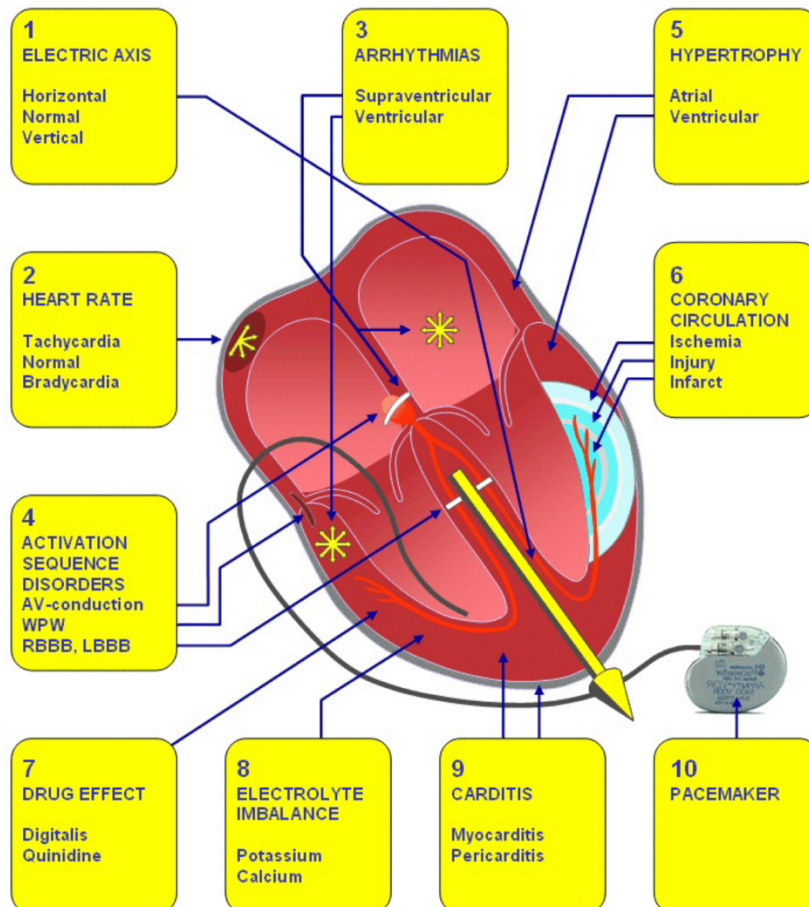


$$\vec{p} = I_o \vec{d} \quad d \rightarrow 0, I_o \rightarrow \infty$$

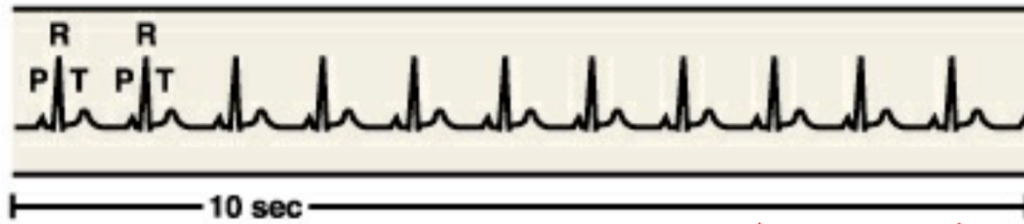
$$\Phi = \frac{\vec{p}}{4\pi\sigma} \cdot \nabla\left(\frac{1}{r}\right) = \frac{\vec{p}}{4\pi\sigma} \cdot \frac{1}{r^2} \hat{r}$$



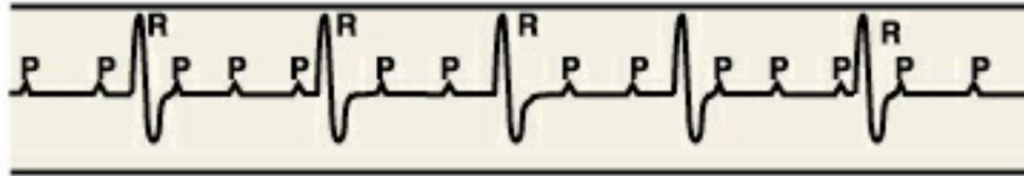
AV blocks
 1st - delay
 2nd - transient
 3rd - complete



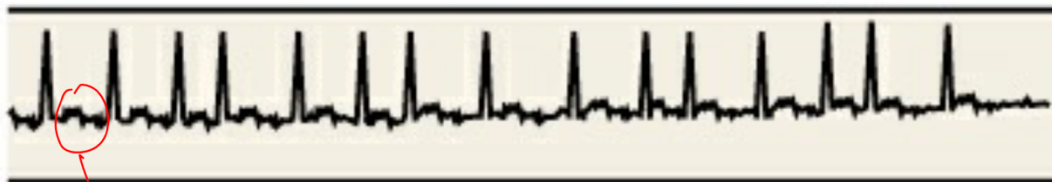
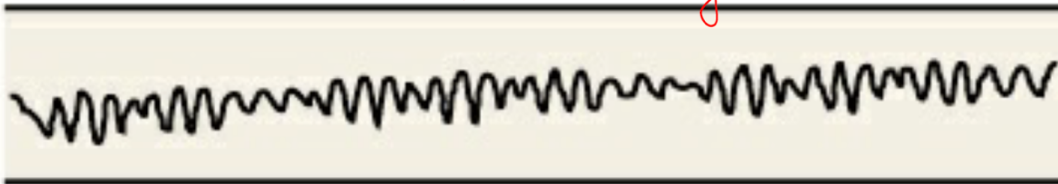
Normal ECG



Atrium & Ventricle go by their own pace
 → issue between A & V → (AV blocks 3rd)



Ventricular fibrillation



atrial fibrillation
 no clear P wave
 fluttering
 random waves of Atrium

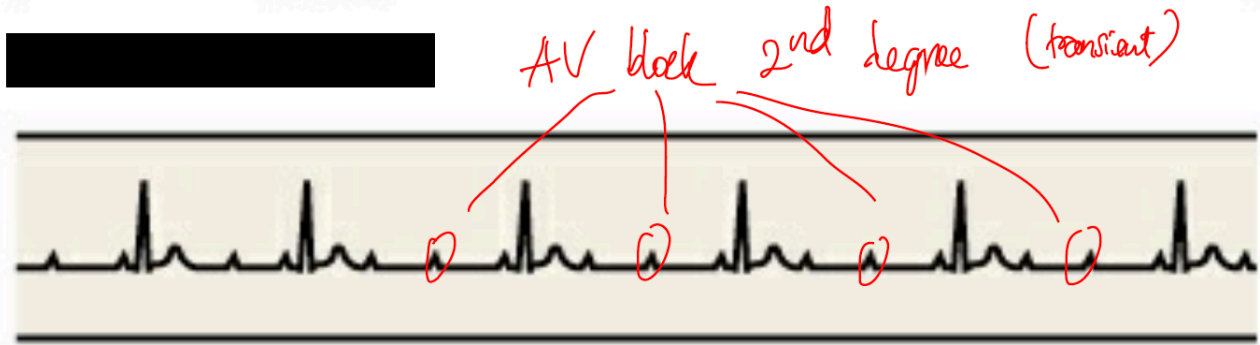
- What cellular mechanism might underlie success of Ca blocker application in the patient with ventricular tachycardia?

The cellular mechanism by which CCBs could treat VT includes:

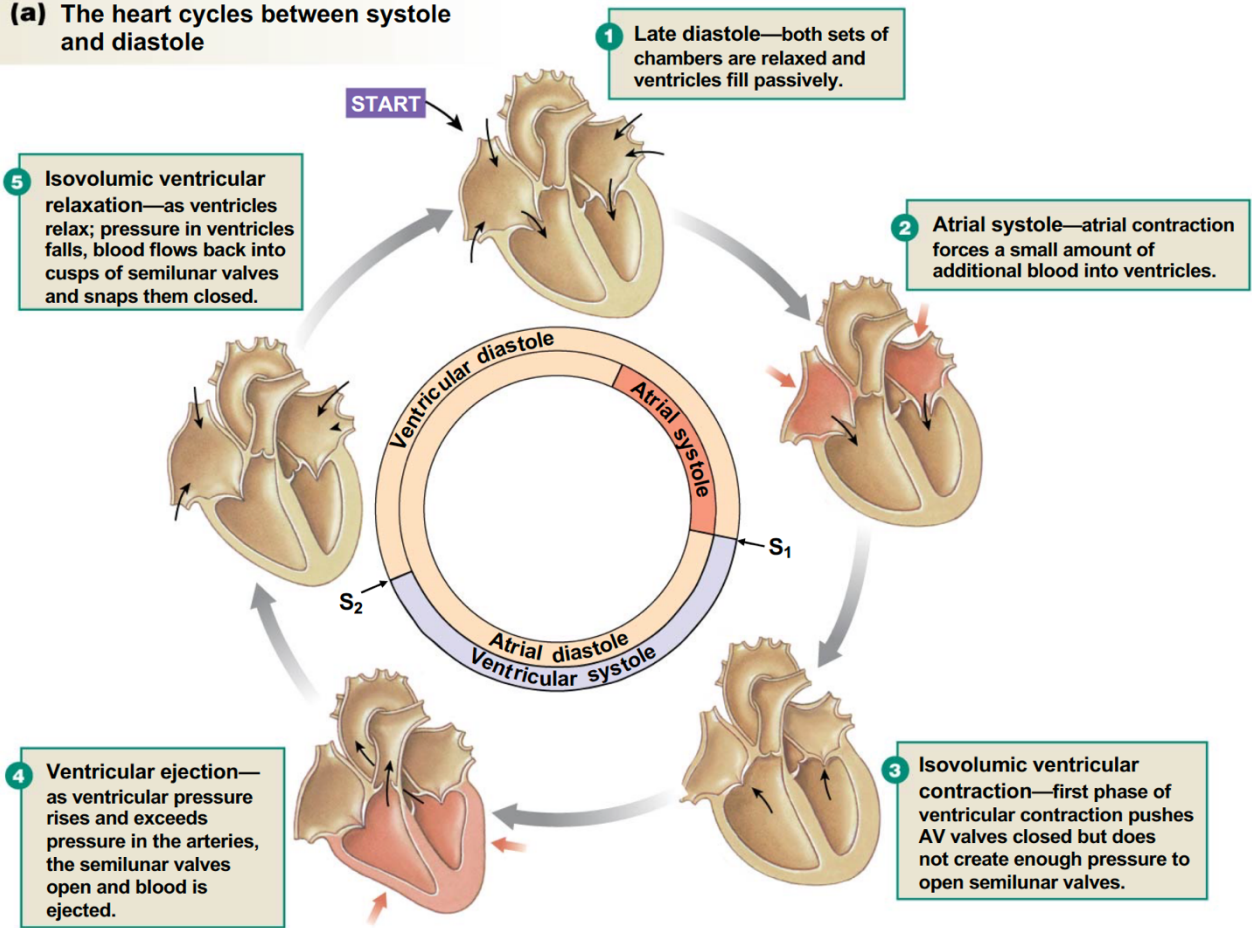
1. **Slowing Down the Heart Rate:** Calcium channel blockers can slow down the conduction of electrical signals through the heart. Specifically, they decrease the rate of spontaneous phase 4 depolarization in cells with automaticity, such as those in the sinoatrial (SA) and atrioventricular (AV) nodes. This results in a slower heart rate, which can help manage VT.
2. **Decreasing Contractility:** CCBs also decrease myocardial contractility by blocking the influx of calcium ions during phase 2 of the cardiac action potential. This decreases the force of

contraction of the heart muscle, which can relieve the demand on the heart and help manage conditions like VT.

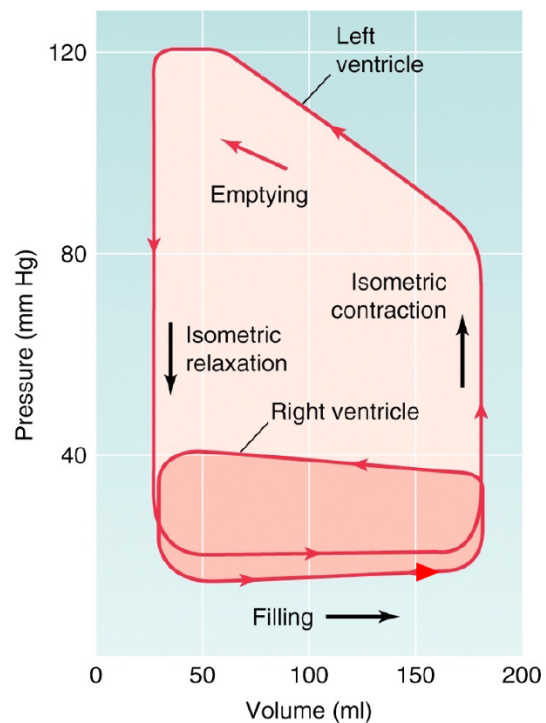
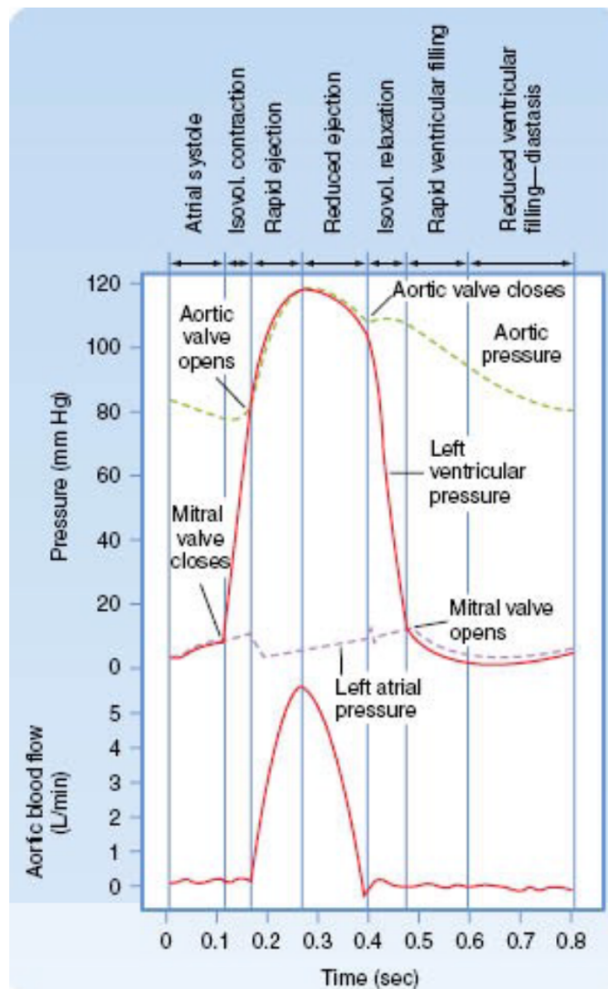
3. **Prolonging the Refractory Period:** CCBs may prolong the refractory period of the AV node. This can prevent the re-entry of electrical signals, which is one of the mechanisms that can contribute to tachycardia.
4. **Suppressing Abnormal Foci:** By decreasing the excitability and automaticity of the heart cells, CCBs can help suppress the abnormal pacemaker activity that often underlies VT.



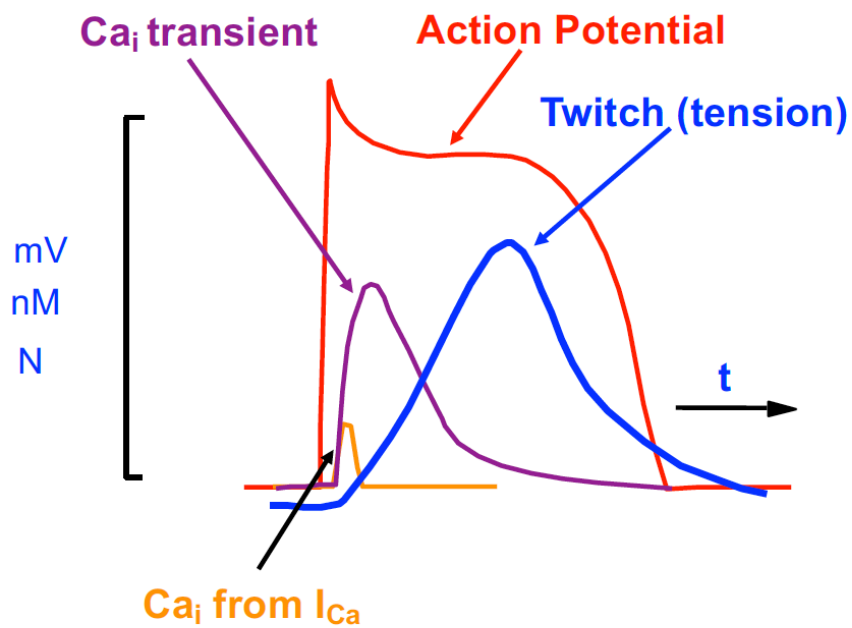
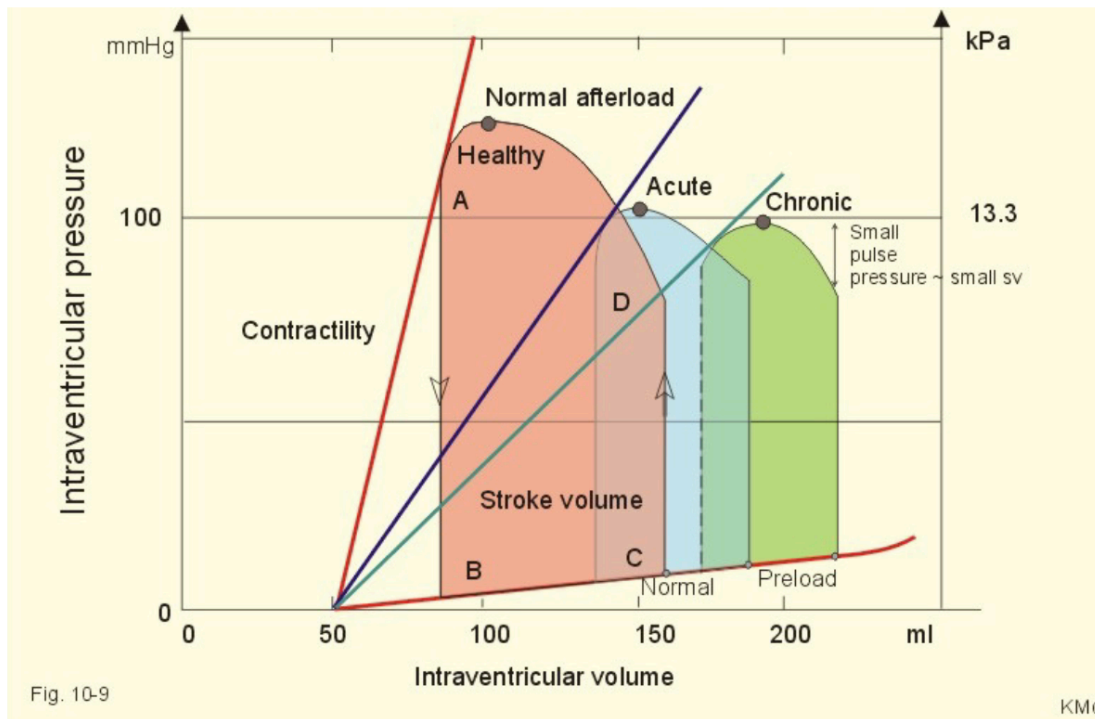
(a) The heart cycles between systole and diastole



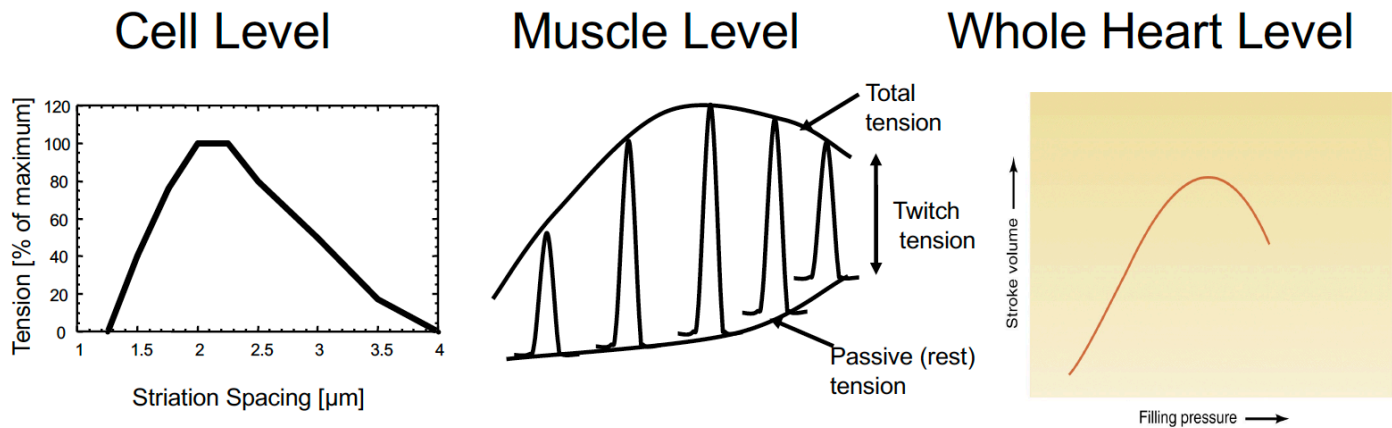
Left Ventricular Pressure and Blood Flow



PV Diagram for Control and Heart Failure

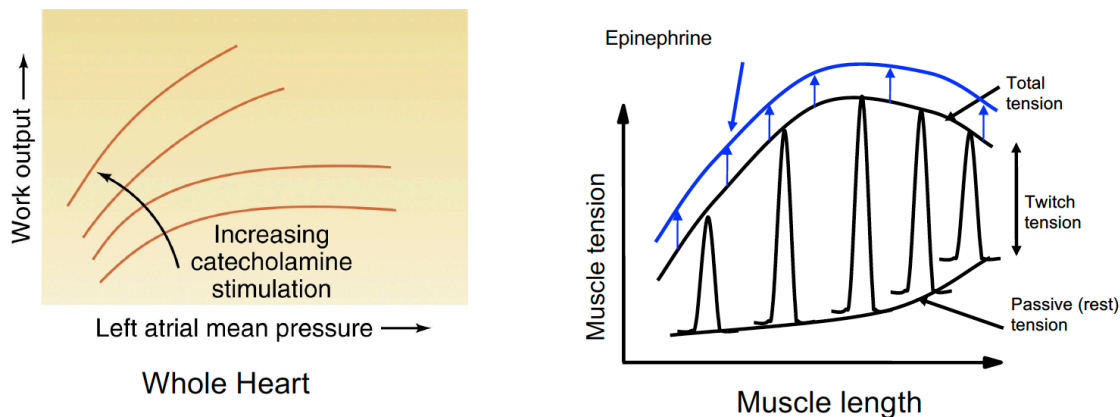


Frank Starling Mechanism



- Under physiological conditions, increased pretension increases tension
- Cell: striation spacing
- Muscle: pretension
- Heart: Increased filling produces increased output
- Does not require neural input

Extrinsic Regulation of Contractility



- Positive inotropes
 - Epinephrine: stimulate β receptors, increase Ca influx and sarcoplasmic uptake
- Negative inotropes
 - Acetylcholine: acts mostly on atria to shorten AP and reduce $[\text{Ca}]_i$
 - Beta-blockers
 - Ca channel blockers

- ****Positive inotropes****: These are substances that increase the force of contraction of the heart muscle (myocardium). An example is Epinephrine, a hormone and neurotransmitter, which binds to beta-adrenergic

receptors, leading to increased influx of calcium ions into the cells, and increased uptake of calcium by the sarcoplasmic reticulum. Both of these effects increase the contractile force of the heart.

- **Negative inotropes**: These are substances that decrease the force of contraction of the heart muscle.

Examples include:

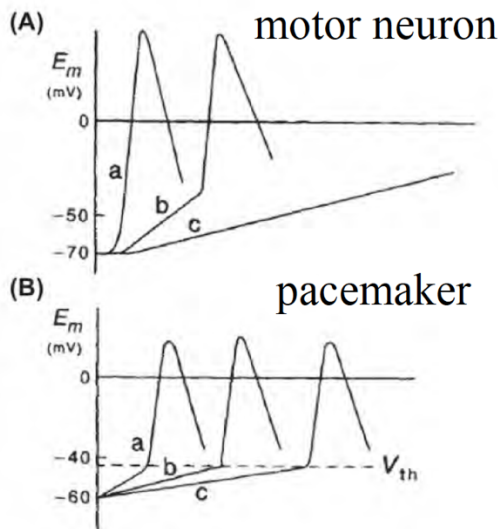
- **Acetylcholine**: A neurotransmitter, mainly influences the atria. It shortens the action potential duration and reduces the intracellular calcium concentration, thus reducing the contractility of the heart muscle.

- **Beta-blockers**: These are drugs that inhibit the effects of the sympathetic nervous system by blocking the action of catecholamines like adrenaline at the beta-adrenergic receptors. This reduces the heart rate, decreases the force of contraction, and lowers blood pressure.

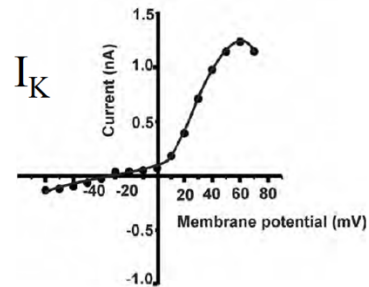
- **Calcium channel blockers**: These are drugs that inhibit the entry of calcium ions into cells by blocking voltage-dependent calcium channels. This reduces the force of contraction of the heart muscle, and can also slow the heart rate.

SA node generally dictates the pace under normal conditions because it has the fastest intrinsic rate of spontaneous depolarization. However, if the SA node fails or the signal it generates is blocked, the AV node or the His-Purkinje system can take over the role of the pacemaker, albeit at a slower rate.

Action potential Characteristics - Accommodation



Sperelakis, Cell Physiology, 4th edition



Accommodation occurs for two reasons:

- spontaneous **inactivation** of Na^+ channels
- increase g_K

Accommodation refers to the phenomenon where a slowly rising depolarization fails to elicit an action potential or requires a greater depolarization to trigger one. This can occur due to two primary mechanisms:

1. **Spontaneous Inactivation of Sodium (Na^+) Channels:** Voltage-gated sodium channels are responsible for the rapid depolarization phase of the action potential. These channels have three states: resting, open, and inactivated. When a slow or prolonged depolarization occurs, more sodium channels may transition to the inactivated state before the membrane potential reaches the threshold to trigger an action potential. In the inactivated state, the channels are unresponsive to further depolarization, making it harder to generate an action potential.
2. **Increase in Potassium Conductance (g_K):** Potassium channels are primarily responsible for the repolarization phase of the action potential, helping to restore the negative membrane potential after the spike of the action potential. If potassium conductance increases, it means more potassium ions can leave the cell, which tends to make the interior of the cell more negative (hyperpolarization). This would counteract the depolarizing influence and make it more difficult to reach the threshold to trigger an action potential.

Passive and active Roles of (Myo-)Fibroblasts in Electrophysiology?

Fibroblasts and myofibroblasts, two types of cells involved in wound healing and fibrosis, play both passive and active roles in cardiac electrophysiology.

****Passive Roles:****

1. ****Structural remodeling****: After an event like a myocardial infarction, fibroblasts proliferate and differentiate into myofibroblasts, leading to the production of extracellular matrix proteins that replace necrotic tissue. This results in scar formation which physically disrupts the continuity of the cardiac muscle and hinders the normal propagation of electrical signals.
2. ****Electrical insulation****: The scar tissue formed is non-conductive, creating areas of electrical insulation in the heart. This can disrupt the normal sequence of electrical activation in the heart, leading to a reentrant circuit and arrhythmia.

****Active Roles:****

1. ****Electrical coupling****: Fibroblasts can electrically couple to myocytes via gap junctions, potentially modulating the electrical properties of the myocardium. They can cause a decrease in the speed of electrical conduction and change the resting membrane potential, both of which can contribute to arrhythmogenesis.
2. ****Ion channel expression****: Fibroblasts express various ion channels and can secrete factors that may alter the expression and function of ion channels in cardiomyocytes. This could further influence the electrical activity of the heart.
3. ****Paracrine signaling****: Fibroblasts secrete various cytokines and growth factors that can influence cardiomyocyte function and survival. For example, transforming growth factor-beta (TGF- β), secreted by myofibroblasts, can affect the electrical properties of cardiomyocytes and is involved in the fibrotic process.

Cable Theory

Cable theory is a mathematical model used to describe how electrical signals propagate along thin, cylindrical structures like neuronal axons. It treats the axon as an electrical cable, with resistances and capacitances representing the properties of the cell membrane and the intracellular and extracellular fluids.

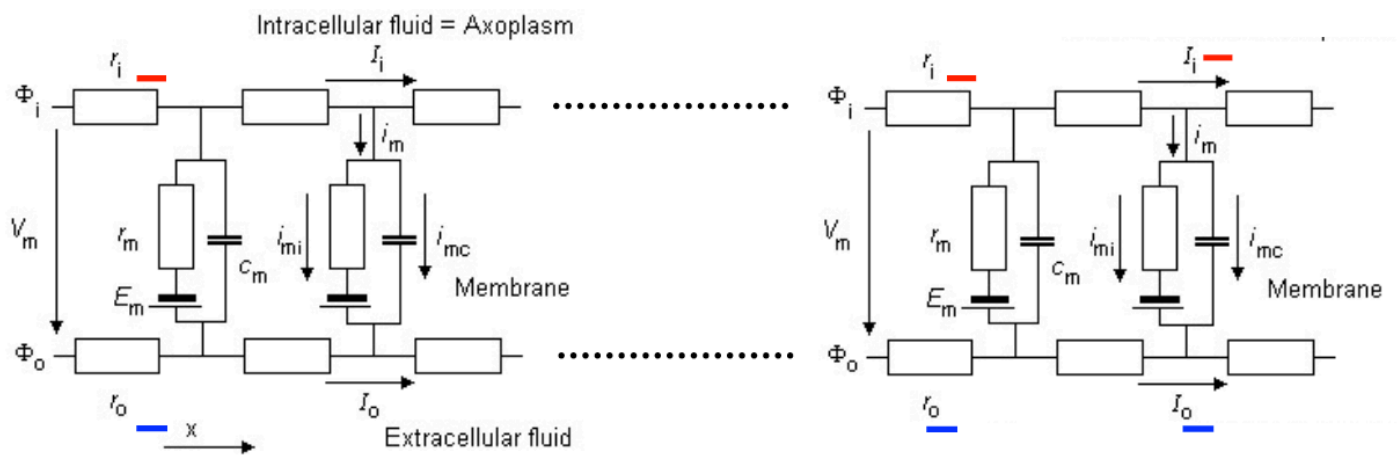
The cable equation, which is a type of partial differential equation, can be discretized for numerical solution. This is often done using the finite difference method, similar to the spatial discretization in reaction-diffusion systems.

Reaction-Diffusion System in cardiac electrophysiology?

Reaction: The reaction term typically represents the changes in voltage across the cell membrane as ions move through ion channels. This process is often modeled by the Hodgkin-Huxley equations or other similar systems of ordinary differential equations. These equations capture the dynamics of various ion channels and pumps that contribute to the action potential, such as sodium channels, potassium channels, and calcium channels.

Diffusion: The diffusion term typically represents the passive spread of electrical signals from cell to cell. In the heart, this occurs primarily through gap junctions that electrically couple neighboring cells. The diffusion term can be modeled by a partial differential equation that describes how the electrical signal (often represented by the membrane potential) changes in space and time.

The resulting reaction-diffusion system is a partial differential equation that describes how the membrane potential of the cells in the heart tissue changes over time and space. By solving this system, researchers can simulate the spread of electrical signals through the heart and study phenomena like normal heart rhythms, arrhythmias, and the effects of drugs or other interventions.



Monodomain Modeling of Electrical Conduction in 1D, 2D, and 3D?

Monodomain modeling is a common approach used to simulate the propagation of electrical signals in cardiac tissue. In this model, the heart is treated as a single continuous domain, or "monodomain".

The monodomain model is based on a reaction-diffusion equation. The "reaction" part represents the biophysical processes occurring within individual cardiac cells (like the opening and closing of ion channels), and the "diffusion" part represents the spatial propagation of electrical signals between cells.

Here's how it's applied in 1D, 2D, and 3D:

1D Monodomain Model: This is the simplest case, where the heart tissue is represented as a one-dimensional cable. It's useful for studying the basic properties of action potential propagation, such as the speed and shape of the action potential wave. However, it's a simplification and doesn't capture the full complexity of real heart tissue.

2D Monodomain Model: This extends the 1D model to two dimensions, allowing for the study of wave propagation in a plane of cardiac tissue. This can be useful for investigating phenomena like wavefront curvature and spiral wave reentry, which can contribute to the development of cardiac arrhythmias.

3D Monodomain Model: This is the most complex and realistic case, where the heart tissue is represented as a three-dimensional volume. This allows for the study of electrical propagation in a whole heart or a large piece of heart tissue. It can capture the effects of complex geometries and anisotropies (differences in properties in different directions) on wave propagation.

In each case, the monodomain model must be solved numerically using methods like finite difference or finite element methods. This requires discretizing the domain into a grid of points (or elements in 2D and 3D), and approximating the solution at each point.

Keep in mind that the monodomain model is a simplification that assumes the intracellular and extracellular spaces are electrically connected and have the same electrical potential. In reality, this is not the case, and the more complex bidomain model may be used when this distinction is important.

Bidomain Model: Motivation

Problem: Realistic cell-based modeling of tissue

- complex geometry of cells
- large number of cells
- account for extracellular and intracellular space

Idea „Bidomain Model“

- division of space in two domains
- separated calculation

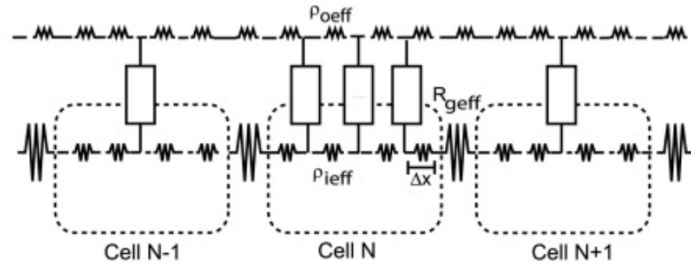
Inclusion of extracellular conduction relevant for modeling of:

- anisotropic propagation of excitation
- stimulation with extracellular current sources
- body surface potential maps (BSPM) and electrocardiograms (ECG)

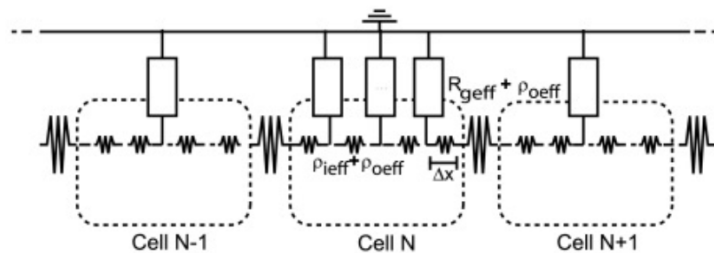


Microscopic Modeling Using Diffusion-Excitation Equation

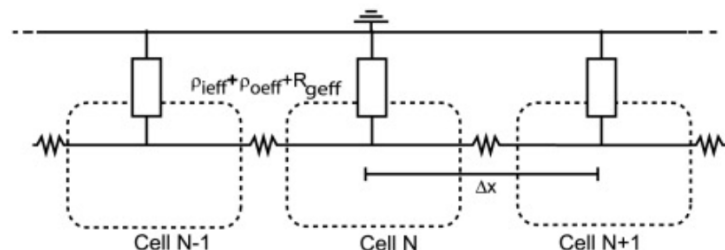
Discrete microscopic bidomain



Discrete microscopic monodomain



Cable model discretized with $\Delta x ==$ cell length



Ratio of Myocyte Surface to Volume?

This parameter, β , appears in the bidomain equations because the currents across the cell membrane, which depend on the surface area, and the currents within the intracellular and extracellular spaces, which depend on the volume, must be appropriately balanced.

Bidomain Model: Intracellular Space

$$-\nabla \cdot \mathbf{J}_i = \nabla \cdot (\sigma_i \nabla \Phi_i) = \beta I_m - I_{si}$$

σ_i : Intracellular conductivity $\left[\frac{S}{m}\right]$

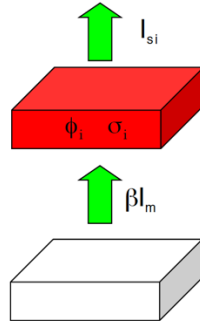
J_i : Intracellular current density $\left[\frac{A}{m^2}\right]$

Φ_i : Intracellular potential $[V]$

I_{si} : Intracellular current source density $\left[\frac{A}{m^3}\right]$

I_m : Membrane source density $\left[\frac{A}{m^2}\right]$

β : Ratio of myocyte surface to volume $[m^{-1}]$



Bidomain Model: Extracellular Space

$$-\nabla \cdot \mathbf{J}_e = \nabla \cdot (\sigma_e \nabla \Phi_e) = -\beta I_m - I_{se}$$

σ_e : Extracellular conductivity $\left[\frac{S}{m}\right]$

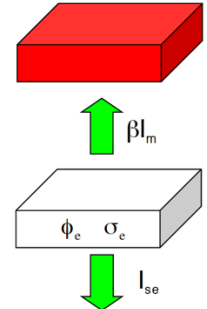
J_e : Extracellular current density $\left[\frac{A}{m^2}\right]$

Φ_e : Extracellular potential $[V]$

I_{se} : Extracellular current source density $\left[\frac{A}{m^3}\right]$

I_m : Membrane source density $\left[\frac{A}{m^2}\right]$

β : Ratio of myocyte surface to volume $[m^{-1}]$



Bidomain Model: Relationships Extra- and Intra-

$$\mathbf{J} = \mathbf{J}_i + \mathbf{J}_e = -\sigma_i \nabla \Phi_i - \sigma_e \nabla \Phi_e$$

with $\Phi_m = \Phi_i - \Phi_e$:

$$\mathbf{J} = -\sigma_i \nabla \Phi_m - \sigma_e \nabla \Phi_e - \sigma_e \nabla \Phi_e$$

with $\sigma_H = \sigma_i + \sigma_e$:

$$\mathbf{J} = -\sigma_i \nabla \Phi_m - \sigma_H \nabla \Phi_e$$

with $\nabla \cdot \mathbf{J} = 0$:

$$\nabla \cdot (\sigma_H \nabla \Phi_e) = -\nabla \cdot (\sigma_i \nabla \Phi_m)$$

Generalized Poisson's Equation

Bidomain Model: Numerical Solution

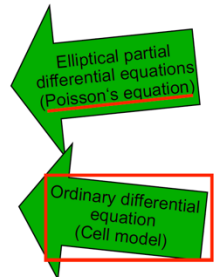
$\Phi_m(\mathbf{x}, t)$ and $\Phi_e(\mathbf{x}, t)$ are unknown

We need to calculate
- membrane potential and
- extracellular potential

$$\nabla \cdot (\sigma_i \nabla \Phi_m) = -\nabla \cdot (\sigma_H \nabla \Phi_e)$$

$$I_{stim} = \nabla \cdot (\sigma_i \nabla \Phi_m) + \nabla \cdot (\sigma_i \nabla \Phi_e)$$

$$\frac{\partial \Phi_m}{\partial t} = \frac{1}{C_m} \left(\frac{I_{stim}}{\beta} - I_{ion} \right)$$



Problem: Spatio-temporal discretization!

The bidomain model can be represented mathematically by the following equations:

- $C_m \partial V / \partial t = I_{ion}(V, w) + I_{stim} - \beta (\nabla \cdot (\sigma_i \nabla V_i) - \nabla \cdot (\sigma_i \nabla V_e))$
- $\nabla \cdot (\sigma_i \partial V_i / \partial t + \sigma_e \partial V_e / \partial t) = 0$

where:

- V is the transmembrane voltage
- I_{ion} is the total ionic current
- I_{stim} is the stimulus current
- V_i and V_e are the intracellular and extracellular potentials
- σ_i and σ_e are the intracellular and extracellular conductivities
- β is the surface-to-volume ratio

The bidomain model consists of two partial differential equations (PDEs), one for the intracellular domain and one for the extracellular domain:

1. **Intracellular Domain:**

$$C_m \frac{\partial V}{\partial t} = -I_{ion}(V, w) + \nabla \cdot (\sigma_i \nabla V_i) - \nabla \cdot (\sigma_i \nabla V_e)$$

Here, C_m is the membrane capacitance, V is the transmembrane potential (difference between intracellular and extracellular potentials V_i and V_e), t is time, $I_{ion}(V, w)$ is the total ionic current (which depends on V and other variables w), σ_i is the intracellular conductivity tensor, and ∇ is the gradient operator. The term $\nabla \cdot (\sigma_i \nabla V_i) - \nabla \cdot (\sigma_i \nabla V_e)$ represents the difference in current flow in the intracellular domain compared to the extracellular domain.

2. **Extracellular Domain:**

$$\nabla \cdot (\sigma_i \nabla V_i + \sigma_e \nabla V_e) = 0$$

Here, σ_e is the extracellular conductivity tensor. The equation represents conservation of current: the total current (both intracellular and extracellular) at any point must be zero, because any current that flows into that point must also flow out.

The ionic current $I_{ion}(V, w)$ is often described by the Hodgkin-Huxley equations or modifications thereof, which describe how the opening and closing of ion channels generate the action potential. These equations have the general form:

$$C_m \frac{\partial V}{\partial t} = -I_{ion}(V, w) + I_{stim}$$

$$\frac{dw}{dt} = f(V, w)$$

Here, I_{stim} is a stimulus current, and $f(V, w)$ is a function that describes the dynamics of the variables w (such as the opening probabilities of ion channels).

To solve these equations numerically in 3D, we would discretize the spatial domain into a grid of nodes, replacing the gradient ∇ and divergence $\nabla \cdot$ operators with finite difference approximations. We would also discretize the time domain into time steps, replacing the derivatives $\partial / \partial t$ with finite difference approximations. This turns the PDEs into a system of algebraic equations, which can be solved using a numerical solver.

Simulation of Arrhythmia: Protocol Design and Models Choice

Abnormal impulse initiation: In the context of cardiac arrhythmias, abnormal impulse initiation refers to conditions that lead to the abnormal generation of electrical signals in the heart. This can be due to various factors such as:

- **Stimuli:** The abnormal signals can be initiated by inappropriate stimuli, which could be either extracellular (from outside the cell) or intracellular (from within the cell).

- **Timing:** The timing of the stimuli is crucial as well. For instance, a normal stimulus arriving too early or too late can trigger an arrhythmia.
- **Cellular electrophysiology:** This refers to the properties and behaviors of the cardiac cells, which can influence how they respond to stimuli. Changes in the electrophysiology of the cells, such as alterations in the action potential, can contribute to abnormal impulse initiation.
- **Density and gating of ion channels:** Ion channels play a critical role in generating and propagating the electrical signals in heart cells. Changes in the number (density) or function (gating) of these channels can disrupt the normal electrical activity and potentially lead to arrhythmias.
- **Ion concentrations:** The concentrations of various ions (like sodium, potassium, and calcium) inside and outside the cells are fundamental to the generation of electrical signals. Disruptions in these ion concentrations can lead to abnormal impulse initiation.

Abnormal conduction: Abnormal conduction refers to problems with how the electrical signals travel through the heart tissue.

This could be due to:

- **Tissue geometry:** The physical structure of the heart tissue can affect how signals are conducted. For example, areas of scar tissue can disrupt the normal pathways of electrical conduction.
- **Substrate properties:** This refers to the inherent characteristics of the cardiac tissue which can influence electrical conduction, such as the presence of fibrosis or fatty deposits.
- **Conductivities:** The ability of the tissue to conduct electrical signals can also influence conduction. Changes in the conductivities of the intracellular and extracellular spaces can disrupt normal conduction.
- **Cellular composition and electrophysiological properties:** The types of cells in the tissue and their electrical properties can also affect how signals are conducted. For instance, changes in the ratio of different types of cells or in their electrophysiological properties can disrupt normal conduction.

Challenges: Simulating arrhythmias accurately can be very challenging due to:

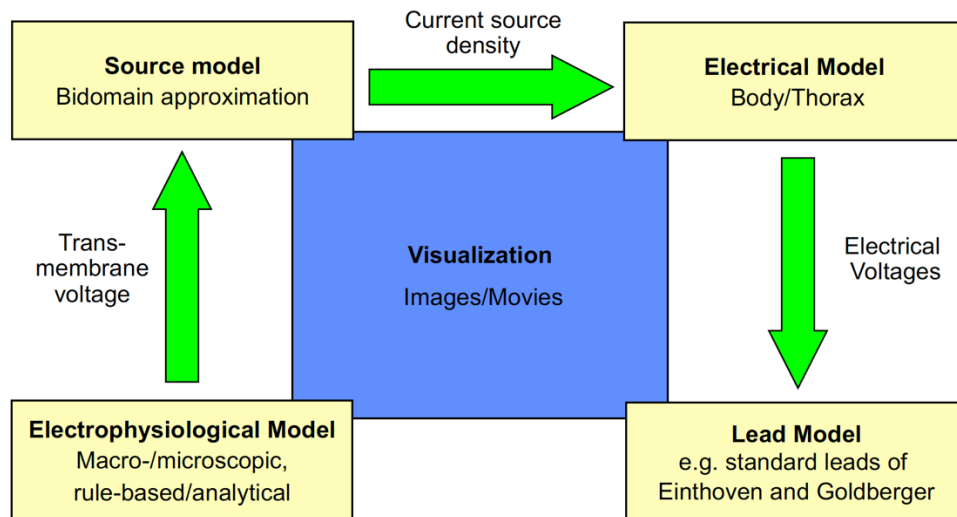
- **Realism:** The heart is a complex, dynamic organ that changes over time (remodeling), and its function involves processes on many different scales (from cells to the whole organ) and of many different types (electrical, mechanical, etc.). Capturing all of this accurately in a model is difficult.
- **Computational demands:** Even with today's powerful computers, simulating arrhythmias in a realistic, detailed way can require significant computational resources. This includes both processing power and memory, especially for 3D simulations or those that involve complex geometries or intricate electrophysiological models.

In both the monodomain and bidomain models, unidirectional blocks can occur under conditions such as:

1. **Heterogeneity in tissue properties:** Differences in the conductive properties, refractory periods, or other electrophysiological characteristics of different regions of the heart tissue can lead to unidirectional blocks. For instance, an area of scar tissue (due to a previous heart attack) or an area with altered cellular properties (due to disease or drug effects) can block the propagation of electrical impulses.
2. **Premature stimuli:** If an impulse arrives at a location where the cells are still in their refractory period (due to a previous impulse), it can be blocked. This is the basis for the phenomenon of "reentry," where an impulse circles around a non-conductive area or a line of blockage, continually reactivating itself. If the timing and location of the stimuli are such that the impulse can travel in one direction (where the cells have recovered from their refractory period) but not the reverse direction (where the cells are still refractory), this can create a unidirectional block.

3. **Anisotropic conduction:** The heart tissue is anisotropic, meaning that the speed of electrical conduction varies in different directions due to the alignment of cardiac fibers. This can also contribute to unidirectional blocks, especially in the bidomain model which explicitly models the separate intracellular and extracellular spaces and can therefore capture the effects of anisotropic conduction more accurately.

Simulation System: Overview



This slide appears to be outlining the different stages involved in simulating the electrical activity of the heart and its measurement via electrocardiograms (ECGs).

1. **Electrophysiological Model (Macro-/microscopic, rule-based/analytical):** This stage involves modeling the electrical behavior of the heart at the cellular or tissue level. Macroscopic models capture the overall behavior of large populations of cells, while microscopic models capture the detailed behavior of individual cells. Rule-based models use heuristic rules to represent the behavior, while analytical models use mathematical equations derived from the underlying biophysics.
2. **Transmembrane voltage:** This is the voltage difference across the cell membrane, which is the key variable that the electrophysiological model is simulating. The transmembrane voltage changes in response to electrical currents flowing through ion channels in the cell membrane, and it drives the contraction of the heart muscle cells.
3. **Source model (Bidomain approximation):** This stage involves modeling the propagation of the electrical activity through the heart tissue, taking into account both the intracellular and extracellular spaces (the "bi-domain"). The source model translates the transmembrane voltages from the electrophysiological model into electrical current sources that drive the propagation of the electrical activity.
4. **Current Source density:** This represents the density of the electrical current sources in the heart tissue, which is the output of the source model.
5. **Electrical Model (Body/Thorax):** This stage involves modeling how the electrical activity of the heart propagates through the rest of the body to the skin surface, where it can be measured by ECG electrodes. This requires a model of the electrical properties of the body tissues, particularly the thorax.
6. **Electrical voltages:** These are the voltages on the skin surface resulting from the heart's electrical activity, which are the output of the electrical model.

7. **Lead Model (e.g., standard leads of Einthoven and Goldberger):** This final stage involves modeling how the ECG electrodes (the "leads") measure the electrical voltages on the skin surface. The lead model takes into account the locations of the electrodes and the way they are connected to form the different ECG leads (for example, the standard leads of Einthoven and Goldberger). The output of the lead model is the simulated ECG signals.

Current source density (CSD) is a measure of the net amount of current entering or leaving a small volume of tissue. In the context of cardiac electrophysiology, the transmembrane currents (i.e., currents crossing the cell membrane) generated by the ionic flow due to action potentials, serve as sources or sinks of current, and are represented as a source density within the tissue volume.

In the bidomain model, the intracellular and extracellular spaces are treated as two interconnected domains, and the movement of ionic currents through these domains is described by partial differential equations. The model takes into account both the propagation of action potentials along and across the fibers (longitudinal and transverse directions), and the transfer of current between the intra- and extracellular spaces through the cell membrane.

The transmembrane current per unit volume, which results from the difference between the intracellular and extracellular potentials, is the source term in the bidomain equations. The distribution of these transmembrane currents across the tissue volume is referred to as the "current source density".

In this way, the bidomain model can describe the propagation of electrical activity in the heart tissue, taking into account both the active properties of the cardiac cells (generation of action potentials, represented by the transmembrane voltages) and the passive properties of the tissue (conduction of electrical currents, represented by the source densities). The output of the bidomain model, the source densities, serve as the input to the next stage in the simulation process, which is the modeling of how this electrical activity propagates through the rest of the body to the skin surface.

The current source density (CSD) is generally considered as a scalar quantity, as it measures the amount (density) of current entering or leaving a small volume of tissue. In the context of the bidomain model, the current source density (often denoted as I_{ion} or I_m) is given by the difference in current across the cell membrane per unit volume.

However, current flow itself has a direction and can be represented as a vector. In the bidomain model, the intracellular and extracellular currents are represented as vectors, which are given by the product of the conductivity tensor and the gradient of the voltage in each domain.

The bidomain equations, which include the current source density, can be written as follows:

$$\nabla \cdot (\sigma_i \nabla V_i) - \nabla \cdot (\sigma_e \nabla V_e) = \beta I_m$$

$$\nabla \cdot (\sigma_i \nabla V_i + \sigma_e \nabla V_e) = I_{stim}$$

where:

- σ_i and σ_e are the intracellular and extracellular conductivity tensors,
- V_i and V_e are the intracellular and extracellular potentials,
- β is the surface-to-volume ratio of the cells,
- I_m is the transmembrane current per unit volume (the current source density),
- I_{stim} is any externally applied current.

Here, I_m is usually given by an ionic model that describes the ionic flows across the cell membrane.

In the bidomain model, the term $\nabla \cdot (\sigma_i \nabla V_i) - \nabla \cdot (\sigma_e \nabla V_e)$ represents the net current flow through the cell membrane per unit volume, which is equal to the current source density multiplied by the surface-to-volume ratio of the cells.

The term $\nabla \cdot (\sigma_i \nabla V_i + \sigma_e \nabla V_e)$ represents the total current flow in both the intracellular and extracellular domains, which is equal to any externally applied current.

Therefore, while the current source density itself is a scalar quantity, it is derived from the vector quantities representing current flow in the bidomain model.

In some literature, the term " f " is used instead of " I_m " to represent the current source density or the transmembrane current per unit volume

Generalized Poisson Equation for Electrical Current

$$\nabla \cdot (\sigma \nabla \Phi) + f = 0$$

Φ : Electrical potential [V]

σ : Conductivity tensor [S/m]

f : Current source density [A/m³]

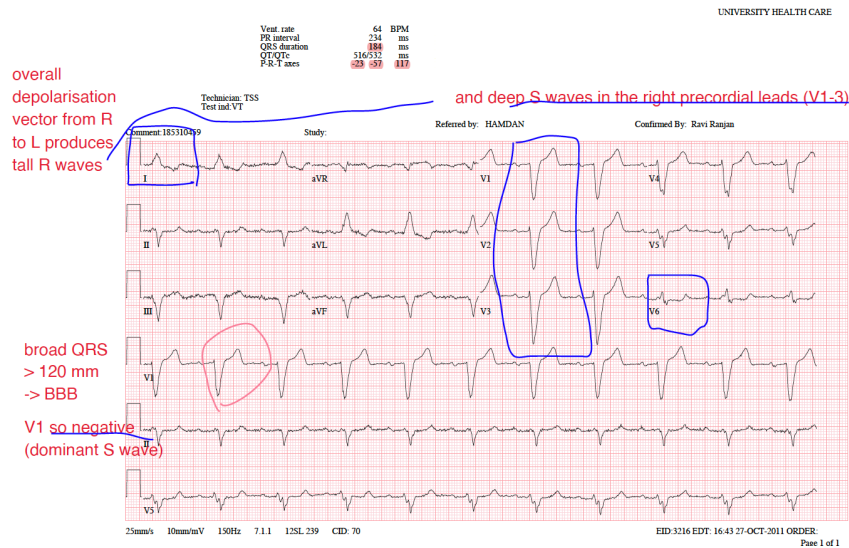
Scalar/ complex quantities

In Left Bundle Branch Block (LBBB), the electrical signal going to the left ventricle is blocked. Instead of travelling down the left bundle branch, the signal must travel to the right ventricle first, then cross the wall of the heart to reach the left ventricle. This causes the left ventricle to contract a bit later than it normally would. Despite this, the heart can still pump and function. However, the coordination between the ventricles might not be as efficient, and the overall functioning of the heart may be reduced.

In addition, the LBBB can also cause the heart's electrical activity to appear altered on an electrocardiogram (ECG). For instance, the QRS complex, which represents the depolarization of the ventricles, may be wider than usual due to the delay in conduction.

1. **Left Bundle Branch Block (LBBB)**: In an LBBB, the electrical signal is delayed or blocked along the pathway that sends electrical signals to the left ventricle. On an ECG, LBBB can be recognized by:
 - A widened QRS complex (> 120 ms)
 - The absence of a Q wave in leads I, V5, and V6
 - Broad, slurred R wave in I, V5, and V6
 - Deep S wave in V1
 - An ST segment and T wave in a direction opposite the QRS complex.

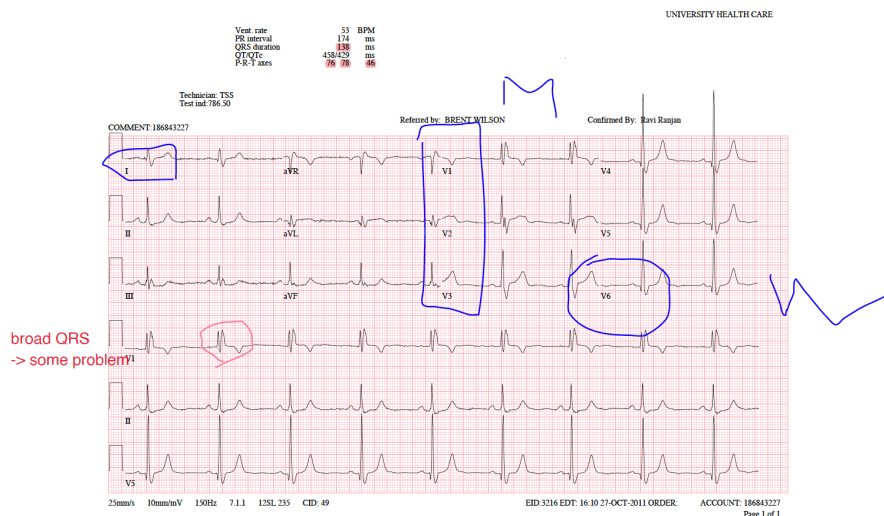
LBBB



2. **Right Bundle Branch Block (RBBB):** In an RBBB, the electrical signal is delayed or blocked along the pathway that sends electrical signals to the right ventricle. On an ECG, RBBB can be recognized by:

- A widened QRS complex (> 120 ms)
- An RSR' pattern in leads V1 and V2 (known as a 'bunny ear' pattern)
- Wide, slurred S wave in the lateral leads (I, aVL, V5-V6)
- The terminal QRS deflection is positive in V1.

RBBB



Sinus Bradycardia and Sinus Tachycardia are heart rhythms originating from the sinus node, the natural pacemaker of the heart. The primary difference between them is the heart rate, i.e., the number of times the heart beats per minute. In both cases, the rhythm is regular, and each QRS complex is preceded by a normal P wave, indicating that the impulse is starting in the sinus node.

Sinus Bradycardia: Sinus Bradycardia is a rhythm in which the rate of impulses coming from the sinus node is slower than normal. The normal resting heart rate for adults ranges from 60 to 100 beats per minute (bpm). Sinus bradycardia is usually defined as a sinus rhythm with a rate **less than 60 bpm**. This can be seen on an ECG as regular but infrequent QRS complexes. Sinus bradycardia can be normal in some people, particularly in well-trained athletes or during sleep. However, it can also be a sign of heart disease or other medical conditions.

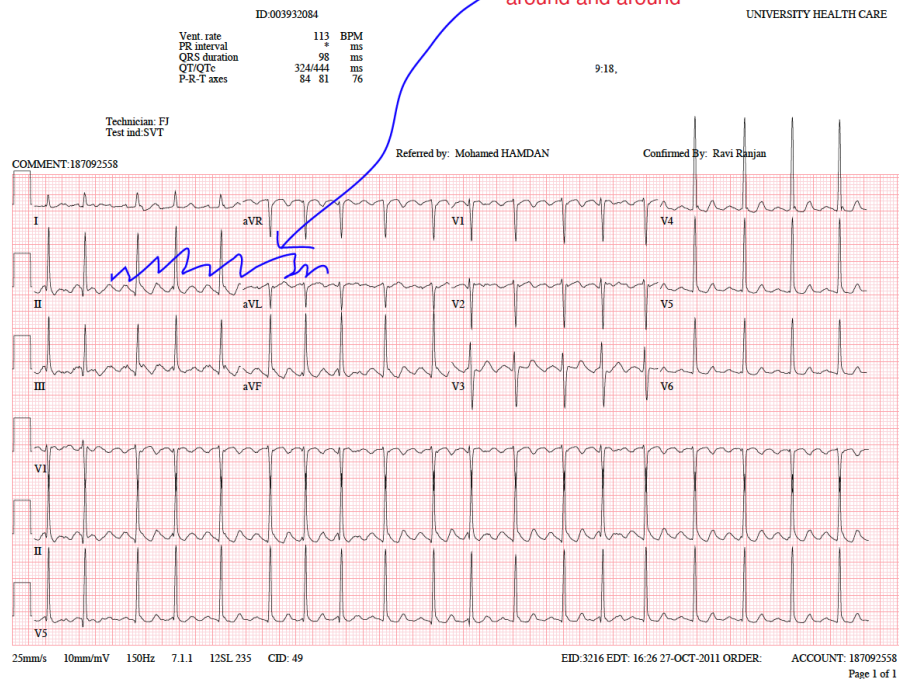
Sinus Tachycardia: Sinus Tachycardia is a rhythm in which the rate of impulses coming from the sinus node is faster than normal. Typically, sinus tachycardia is defined as a heart rate **greater than 100 bpm**. This rhythm can be seen on an ECG as regular but more frequent QRS complexes. Sinus tachycardia can be a normal response to strenuous exercise, strong emotions, fever, or some medications. However, if sinus tachycardia is occurring at rest, it can indicate a medical condition or a problem with the heart.

Atrial flutter is a form of supraventricular tachycardia
- caused by a re-entry circuit within the right atrium

Atrial Flutter

regular atrial activity at ~300 bpm

almost no resting between p waves -> keep atrial signal fire around and around



"Heart block" or "AV block" refers to a delay or disruption in the electrical signals that control the timing of the heart's pumping action. There are several types of heart block, each of which can appear differently on an electrocardiogram (ECG):

1. **First-degree heart block:** In this condition, the electrical signals are still able to pass from the atria to the ventricles, but they are delayed. On an ECG, this is characterized by a prolonged PR interval (greater than 0.20 seconds). Despite the delay, each electrical impulse still manages to reach the ventricles, so there is no dropped beat.
2. **Second-degree heart block, Type I (Mobitz I or Wenckebach):** In this condition, the electrical signals become increasingly delayed with each heartbeat until one signal fails to reach the ventricles entirely. On an ECG, this presents as a progressively lengthening PR interval until a beat is dropped (a QRS complex is missing).
3. **Second-degree heart block, Type II (Mobitz II):** In this condition, some electrical signals fail to reach the ventricles. Unlike Mobitz I, there is no progressive delay; some signals simply don't get through. On an ECG, this is seen as a

dropped beat without a progressive lengthening of the PR interval. This type is more serious than Mobitz I and may require a pacemaker.

4. **Third-degree heart block (complete heart block):** In this condition, no electrical signals are able to reach the ventricles from the atria. The atria and ventricles beat independently of each other, often at different rates. On an ECG, there is no apparent relationship between the P waves and the QRS complexes. This is the most serious type of heart block and usually requires a pacemaker.

1. **How does the Frank-Starling law of the heart explain the relationship between end-diastolic volume and cardiac output?**
2. **How does the actin-myosin interaction contribute to muscle contraction?**
3. **How can fibroblasts affect electrical conduction in the heart?**

1. **Frank-Starling law of the heart:**

- Describes the relationship between end-diastolic volume (EDV) and stroke volume (SV).
- An increase in EDV leads to more stretched cardiac fibers at end of diastole.
- The increased stretch optimizes the overlap of actin and myosin filaments in the cardiac muscle cells, thereby enhancing the force of contraction (length-tension relationship).
- There's an upper limit: if the heart is overly stretched (beyond optimal length-tension point), the force of contraction may decrease, leading to lower SV and cardiac output.

2. **Actin-myosin interaction in muscle contraction:**

- Upon muscle cell stimulation, calcium ions are released into the cytosol.
- Calcium ions bind to the protein troponin on the actin filament, which triggers a conformational change, moving tropomyosin away from myosin-binding sites on actin.
- This enables myosin heads to bind to actin (cross-bridge formation).
- The myosin head undergoes a change in its position or orientation, a process that effectively drags the actin filament towards the sarcomere's center - a stage commonly referred to as the power stroke.
- ATP binds to the myosin head, causing it to release the actin and re-cock, preparing for the next power stroke if calcium is still present.

3. **Effects of fibroblasts on cardiac conduction:**

- Fibroblasts are non-excitable cells and can act as an electrical sink, slowing down conduction.
- They can disrupt the uniform structure of the cardiac syncytium, potentially creating non-conductive barriers that can lead to reentrant circuits and arrhythmias.
- Fibroblasts can couple electrically with cardiomyocytes via gap junctions, altering the electrophysiological properties of the cardiomyocytes (e.g., lowering their resting membrane potential).
- Fibroblasts can play a significant role in cardiac remodeling, proliferating and differentiating into myofibroblasts, and secreting extracellular matrix proteins that can further disrupt electrical conduction and contribute to arrhythmogenesis.

1. **What are the key differences between sinus bradycardia and heart block?**
2. **Can you differentiate between atrial flutter and atrial fibrillation?**

3. What is the difference between the PR interval and the PR segment, and between the ST interval and the ST segment on an ECG?

- 1. Sinus Bradycardia vs Heart Block:** Sinus bradycardia is characterized by a slower than normal heart rate, typically under 60 beats per minute, due to decreased firing of the sinoatrial (SA) node. However, the rhythm remains regular with a normal P wave preceding each QRS complex. Heart block, or atrioventricular (AV) block, on the other hand, involves an interruption or delay in the electrical conduction from the atria to the ventricles. There are three types: First-degree AV block is marked by a consistently prolonged PR interval but no missed beats. In second-degree AV block (Mobitz type I and II), some P waves are not followed by QRS complexes. In third-degree, or complete heart block, the atria and ventricles beat independently of each other, often resulting in a slow ventricular rate and no clear relationship between P waves and QRS complexes.
- 2. Atrial Flutter vs Atrial Fibrillation:** Atrial flutter is characterized by regular, rapid contractions or fluttering of the atria, often seen on the ECG as a series of 'sawtooth' flutter waves before each QRS complex. In contrast, atrial fibrillation is characterized by an irregular, often rapid, heart rate that results from chaotic electrical activity in the atria. On ECG, there are no clear P waves. Instead, you'll see a variable and disorganized baseline representing fibrillatory waves.
- 3. PR interval vs PR segment, ST interval vs ST segment:** The PR interval on an ECG represents the time it takes for an electrical impulse to travel from the sinoatrial (SA) node, through the atria, AV node, bundle of His, to the ventricles, marking the onset of ventricular depolarization. It includes both the P wave and the PR segment, and normally ranges from 0.12 to 0.20 seconds. The PR segment is the isoelectric line following the P wave and ending at the start of the QRS complex. The ST segment is the isoelectric line between the end of the QRS complex (J point) and the start of the T wave and represents the period when the ventricles are depolarized. The ST interval extends from the end of the QRS complex to the end of the T wave and represents the total time during which ventricular depolarization and repolarization occur.

- 1. What are the key advantages of an electrophysiological study using catheters over an ECG?**
- 2. Can you explain the concept of monopoles and dipoles in the context of cardiac electrophysiology? Are they concepts used to model conduction in the heart, or are they intrinsic characteristics of the heart?**
- 3. What is a His catheter and why is it advantageous for evaluating AV node conduction?**

1. Advantages of an Electrophysiological Study over ECG

- More detailed and direct information: An EP study can provide a more comprehensive view of the heart's electrical system.
- Ability to stimulate and observe responses: Specific parts of the heart can be directly stimulated, and the response can be observed and measured.
- Real-time diagnostics and treatment: An EP study allows for real-time detection and treatment of abnormalities.

2. Monopoles and Dipoles in Cardiac Electrophysiology

- Conceptual tools: Monopoles and dipoles are mathematical concepts used to model electrical conduction in the heart, not intrinsic characteristics of the heart.

- Definitions: A monopole refers to a single electric charge or a region of the heart where current appears to emanate from a single point. A dipole refers to a pair of equal and opposite charges or a pair of points in the heart where current flows from one to the other.

3. His Catheter and AV Node Evaluation

- Specific location: A His catheter is placed at the bundle of His, part of the AV node conduction system.
- Direct measurement: It allows for the direct measurement of electrical activity at this specific point in the heart's conduction system.
- Detection of abnormalities: The use of a His catheter enables the detection of conduction abnormalities specifically at the AV node, which is critical in diagnosing different types of heart block.

1. Describe the four standard catheters used in an electrophysiological study.

- Hint: Consider the placement and specific function of each catheter.

2. What is the concept of the inverse problem in cardiac electrophysiology and what does it involve?

- Hint: Think about the process of trying to infer the sources of electrical activity from measurements taken at the body's surface.

3. How do fibroblasts affect conduction in the heart?

- Hint: Consider both the electrical and structural roles of fibroblasts.

1. Four Standard Catheters in an Electrophysiological Study

- High Right Atrium (HRA): Records SA node and right atrial activities.
- His Bundle: Measures AV node and His-Purkinje system activities.
- Coronary Sinus (CS): Collects signals from the left atrium and ventricle.
- Right Ventricular Apex (RVA): Records right ventricular depolarization and repolarization.

2. The Inverse Problem in Cardiac Electrophysiology

- It's the challenge of deducing heart's electrical source distribution from body surface potentials.

3. Effects of Fibroblasts on Cardiac Conduction

- Fibroblasts act as electrical sinks, can couple with myocytes altering their electrical properties, and secrete extracellular matrix proteins during injury, leading to tissue fibrosis and affecting electrical propagation.

Power Stroke in Muscle Contraction

- The power stroke starts when the myosin head, which is in a high-energy configuration after ATP hydrolysis, binds to the actin filament.
- This binding triggers the release of the stored energy, driving the myosin head to pivot and pull the actin filament toward the sarcomere center (this is the actual power stroke).
- After the power stroke, the myosin head remains attached to actin until a new ATP binds, which leads to detachment.
- Upon detachment, the myosin head can again hydrolyze ATP and return to its high-energy configuration, ready for the next power stroke.

Epi and NE In pathological conditions: like heart failure, excessive release of these catecholamines can lead to detrimental effects, such as cardiac remodeling and arrhythmias.

The 'inverse problem' in cardiac electrophysiology:

- The inverse problem involves determining the electrical sources within the heart from body surface potential measurements.
- Current techniques like ECG imaging (ECGI) can **provide noninvasive solutions**.
- Major challenges include the need for **accurate personalization of the thorax model and the non-uniqueness of the solutions**.

Explore the potential mechanisms by which fibroblasts could influence cardiac conduction. How might this understanding be applied in the context of heart disease and its treatment?

- Fibroblasts can form heterocellular gap junctions with cardiomyocytes, altering electrical conduction.
- Fibroblast proliferation and collagen deposition in the setting of heart disease can disrupt the normal electrical pathways, leading to arrhythmias.
- Fibroblasts can also influence cardiac conduction by releasing factors that modulate ion channel expression and function in cardiomyocytes.

6. Utility and limitations of discrete microscopic models in cardiac electrical conduction:

Microscopic models simulate the behavior of individual cells or small clusters of cells. They excel in investigating phenomena at the cellular level, such as the response of a cell to various stimuli or the effects of pharmaceuticals on ion channel function. They can also be used to simulate the process of cardiac excitation at a microscopic level, offering insights into how an action potential is initiated and propagated.

- An example of a discrete microscopic model application would be the development of anti-arrhythmic drugs. Scientists can model how a new pharmaceutical compound would interact with ion channels, thus predicting its potential effects on cardiac action potential and conductivity.
- However, these models have limitations in that they may not accurately represent the complex anisotropic structure of the whole heart, which includes interactions between millions of cells, fibrotic tissues, and blood vessels.

Macroscopic models are more suitable for studying these large-scale phenomena.

8. Advantages of electrophysiological study using catheters over traditional ECG:

Catheter-based electrophysiological (EP) studies provide detailed and direct information about the electrical activity within the heart. They offer advantages over traditional ECG in that they can directly stimulate and record from different regions of the heart, allowing clinicians to precisely pinpoint the location of electrical abnormalities.

- For instance, in a patient with a ventricular tachycardia, an EP study can help determine the exact location of the abnormal pathway or focus that is causing the tachycardia. This information can then guide a catheter ablation procedure, during which the abnormal pathway is destroyed to restore normal heart rhythm.
- EP studies can also be used to test the effectiveness of certain medications in controlling heart rhythms and to predict the risk of future heart events, especially sudden cardiac death.

10. Concepts of monopoles and dipoles in cardiac electrophysiology:

The concepts of monopoles and dipoles are fundamental to understanding how electrical activity is generated and conducted within the heart. A monopole represents a single point source of electrical activity, while a dipole represents a pair of electrical charges – one positive and one negative.

- In cardiac electrophysiology, these concepts are important for understanding the propagation of action potentials across the heart and the generation of ECG signals. For example, during the depolarization phase of an action potential, a dipole is created with the inside of the cell becoming positively charged and the outside negatively charged. This creates a current that propagates to neighboring cells.
- These principles are also important in interpreting and designing technologies used in cardiology. For example, multi-electrode mapping catheters used in EP studies to locate arrhythmia origins use the principles of monopoles and dipoles to pick up electrical signals from the heart. By understanding these concepts, clinicians can better interpret the data obtained from these catheters, leading to more accurate diagnoses and targeted treatments.

Afterload represents the resistance the heart must overcome to eject blood during systole.

- Afterload is influenced by factors like systemic vascular resistance and aortic pressure. An increase in afterload reduces stroke volume because the heart must work harder to pump blood, and vice versa.
- Clinically, the concepts of preload and afterload are used to guide therapy for heart failure. Diuretics and vasodilators can reduce preload and afterload, respectively, to help improve cardiac function.

What specific role do gap junctions play in synchronizing the contraction of cardiomyocytes, and how might this be disrupted in disease states?

- Gap junctions are specialized intercellular connections that allow for **direct electrical coupling** between neighboring cardiomyocytes.
- They permit the rapid propagation of action potentials across the heart, ensuring **coordinated and synchronous contraction**.
- Disruptions in gap junctions, either through changes in their **quantity, distribution, or conductance**, can lead to dyssynchronous contraction and arrhythmias.
- For example, during ischemic conditions, there's a reduction in gap junctional communication, leading to the slowing of electrical conduction which can precipitate re-entrant arrhythmias.

Discuss the role of intercalated disks in cardiac muscle contraction. How might their structural and functional changes contribute to the pathophysiology of cardiac diseases?

- Intercalated disks are specialized structures in cardiac muscle that contain gap junctions, **adherens junctions, and desmosomes**.
- Gap junctions, as mentioned above, are crucial for electrical coupling and synchronous contraction. Adherens junctions and desmosomes provide **mechanical strength and alignment**, enabling the heart to function as a syncytium.
- Any structural or functional changes in intercalated disks can disrupt the electrical and **mechanical functions** of the heart.

What is the concept of the "safety factor" in cardiac conduction? How might this concept be relevant to the prevention of arrhythmias?

- The "safety factor" is a fundamental principle in cardiac electrophysiology, ensuring robust and reliable propagation of action potentials from one cardiomyocyte to the next.
- The concept is based on the source-sink relationship. The upstream cardiomyocyte that is undergoing action potential acts as the current "source". The downstream cardiomyocyte, which is ready to receive the action potential, acts as the current "sink".
- The safety factor is maintained when the source current supplied by the depolarizing upstream cell is larger than the sink current needed to depolarize the downstream cell. This helps ensure that the downstream cell successfully reaches the threshold potential and triggers its own action potential.
- Factors contributing to the safety factor include:
 - Gap junction conductance, which mediates the flow of current between cells.
 - Membrane excitability, which determines the ease with which the downstream cell can be brought to threshold.
 - Action potential morphology, where the plateau phase can enhance the safety factor by providing a sustained source current.
- Diminished safety factor can occur due to factors like ischemia, hypoxia, or acidosis, which may reduce gap junction conductance or alter membrane excitability. Certain pharmacological agents can also influence the safety factor.
- If the safety factor decreases significantly, the current provided by the upstream cell may fail to depolarize the downstream cell, leading to conduction block. This discontinuous propagation can cause reentry, a major mechanism of cardiac arrhythmias.
- Therefore, understanding and preserving the safety factor is key in maintaining normal cardiac rhythm and preventing arrhythmias. Therapeutic strategies aiming to increase the safety factor, for example, by enhancing gap junction conductance or membrane excitability, could potentially be beneficial in preventing arrhythmias.

Redundancy in conduction pathways provides an added layer of protection. For instance, the atrioventricular node (AV node) can take over the role of pacing the heart if the SA node fails. Similarly, the His-Purkinje system ensures that the ventricles can still be activated if there's a block at the AV node.

Reentry is a common mechanism underlying many types of cardiac arrhythmias. The basic concept is that instead of the action potential moving through the heart's conduction pathway and ending, the electrical impulse instead gets 'trapped' in a self-perpetuating loop. This leads to a rapid and repetitive firing of the action potential, which can cause the heart to beat in a disorganized or unusually fast manner.

Here's a more detailed breakdown:

1. **Formation of a Conduction Block:** For reentry to occur, there typically needs to be an area of unidirectional conduction block. This can happen when the safety factor for conduction is decreased, for example, due to ischemia, structural heart disease, or certain medications, causing an electrical impulse to fail to propagate in one direction.
2. **Establishment of a Reentry Circuit:** The unidirectional block creates a situation where an electrical impulse can travel down one pathway (the pathway without block), and then loop back around via another pathway to re-stimulate the same area of tissue. This forms a self-sustaining loop or 'reentry circuit'.

3. **Rapid and Repetitive Firing:** Once established, this reentry circuit can lead to rapid and repetitive firing of action potentials, causing the heart to beat faster than normal. This can result in tachycardia (fast heart rate) or fibrillation (irregular and fast heart rhythm).
4. **Disruption of Normal Heart Rhythm:** This reentry can interfere with the normal coordinated contraction of the heart, leading to decreased cardiac output and symptoms such as palpitations, dizziness, or even loss of consciousness.

Reentry can occur in various regions of the heart, leading to different types of arrhythmias. For example, reentry circuits in the ventricles can lead to ventricular tachycardia or ventricular fibrillation, which are life-threatening conditions. Similarly, reentry in the atria can cause atrial fibrillation or atrial flutter, which can increase the risk of stroke.

5. Describe the Patch Clamp technique. How has it revolutionized our understanding of ion channel behavior?

- The patch clamp technique is a high-resolution method that allows for the measurement of currents through individual ion channels in a cell's membrane.
- It involves using a glass micropipette to "clamp" onto a small patch of a cell's membrane and record ion currents passing through the channels.
- The technique allows for precise control of the membrane potential, enabling researchers to investigate how ion channels respond to changes in voltage.
- Patch clamp has revolutionized our understanding of ion channel behavior by providing direct evidence of ion channel's selectivity, gating mechanisms, and conduction properties.
- It has further allowed us to better understand the role of ion channels in a wide range of physiological processes, such as neuronal signaling, muscle contraction, and hormone secretion.

6. Discuss the regulatory mechanisms of the Sinoatrial (SA) Node. How do these mechanisms contribute to the node's role as the heart's natural pacemaker?

- The SA node, located in the right atrium of the heart, is a group of cells that generates spontaneous action potentials, controlling the heart rate under normal conditions.
- This automaticity is due to the unique properties of SA node cells, including the presence of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels which allow for the "funny current" (I_f) that initiates the spontaneous depolarization during diastole.
- The rate of these spontaneous depolarizations, and hence the heart rate, is regulated by the autonomic nervous system. The parasympathetic neurotransmitter acetylcholine slows down the heart rate by increasing potassium permeability and decreasing the funny current. Conversely, the sympathetic neurotransmitter norepinephrine speeds up the heart rate by increasing the funny current and the calcium current.
- Disorders affecting the SA node, such as sick sinus syndrome, can cause irregular heart rhythms and may require the implantation of an artificial pacemaker.

8. Describe the Markov Model in the context of ion channel gating. How can it be utilized to predict the behavior of ion channels under various physiological and pathological conditions?

- Markov models provide a statistical method for representing ion channel gating behavior, specifically the transitions between different channel states (e.g., open, closed, inactivated).
- Each state in the model is assigned a certain probability, and the transitions between states are governed by rate constants.

- By adjusting these probabilities and rate constants based on experimental data, Markov models can simulate the dynamic behavior of ion channels under different conditions.
- These models can be used to predict how changes in voltage, temperature, or the presence of drugs might affect ion channel function.
- In a pathological context, Markov models can help us understand how mutations affecting ion channels alter their function and contribute to diseases, such as channelopathies, which include certain types of epilepsy, cystic fibrosis, and long QT syndrome.

9. What is the Goldman-Hodgkin-Katz (GHK) equation and how is it used in studying ion channel dynamics?

- The Goldman-Hodgkin-Katz equation is a fundamental equation in biophysics that describes the ionic equilibrium potential across a cell membrane as a function of the concentrations and permeabilities of different ions.
- This equation allows us to predict the membrane potential given the concentration gradients and permeabilities of different ions. This is critical in understanding resting potentials, action potentials, and the function of ion channels.
- It also forms the theoretical basis for understanding the effects of ion concentration changes and ion channel mutations on cell excitability, which can be important in disease states like epilepsy or heart disease.

Define optical mapping in cardiac electrophysiology. What is its significance and what sort of information can it provide?

- Optical mapping is a technique used to record the electrical activity of the heart in real-time. It uses voltage-sensitive or calcium-sensitive dyes that fluoresce in response to changes in membrane potential or calcium concentration.
- This allows for the visualization of the propagation of action potentials across the heart tissue, enabling the study of wave dynamics and the identification of complex arrhythmias.
- It provides high spatial and temporal resolution data, allowing researchers to study the spread of electrical signals, action potential durations, and other aspects of electrical conduction and refractoriness.
- It's also instrumental in studying the mechanisms of arrhythmias, testing the effects of pharmacological agents, and assessing the impacts of therapeutic interventions such as ablation.

Elucidate the principles of volume conductor theory as it applies to the heart. How does this theory help us understand the electrical activity of the heart as recorded by techniques like EKG?

- Volume conductor theory describes how electrical fields propagate through a medium, like the body tissues in the case of the heart. This theory is fundamental to understanding electrocardiography (EKG).
- In the heart, an electrical dipole is created during the cardiac cycle due to the difference in charge between the **depolarized and repolarized regions of the heart**. This dipole generates an electrical field that spreads throughout the body.
- Volume conductor theory helps explain how the electrical activity of the heart can be detected at the body surface, as in EKG. The EKG represents a summation of the electrical activity of many cardiac cells as the **wave of depolarization and repolarization passes through the heart**.
- The size and direction of the EKG waveform depend on the orientation of the heart's electrical dipole **relative to the recording electrodes**, which can be understood in the context of volume conductor theory.

Discuss the cardiac refractory periods. How do the absolute and relative refractory periods regulate the rhythm of the heart and prevent arrhythmias?

- The absolute refractory period (ARP) is the interval during which a second action potential cannot be initiated, no matter how large a stimulus is applied. This is because the majority of **sodium channels are inactivated immediately after their opening**.
- The relative refractory period (RRP) follows the ARP. During this period, a stronger-than-normal stimulus can trigger a new action potential because some sodium channels have **transitioned from the inactivated state back to the resting state**.
- These refractory periods ensure **orderly** propagation of action potentials, which is crucial for coordinated contraction of the heart. By preventing **immediate re-excitation**, they help maintain a regular heart rhythm and protect against arrhythmias.
- For instance, the refractory periods prevent the formation of **reentry circuits**, which can lead to tachyarrhythmias. If a premature stimulus arrives when a part of the circuit is still refractory, it won't be able to sustain a reentrant loop.

Illustrate the dipole of the heart and how it's projected onto EKG leads. What insights does this provide about the heart's electrical activity?

- The cardiac dipole is a vector that represents the **direction and magnitude** of the heart's electrical activity at any given point in the cardiac cycle.
- The projection of the heart's dipole onto the EKG leads determines the **amplitude and direction of the EKG waveforms**. For example, if the dipole is aligned with a lead, it will record a positive deflection.
- The 12-lead EKG system provides different views of the heart's electrical activity by measuring the potential difference between different sets of electrodes. This allows for a **three-dimensional representation** of the heart's dipole.
- By analyzing the dipole's projection onto different leads, clinicians can identify the location and extent of **myocardial infarction**, detect **electrical axis deviation**, and diagnose various **arrhythmias**.

Comparison of Cardiac Action Potentials with Neuronal Action Potentials

- Cardiac Action Potentials (APs):
 - Cardiac APs have a plateau phase due to the balance of inward Ca^{2+} and outward K^{+} currents. This prolongs the AP, aiding in the contraction and relaxation of the heart muscle.
 - Cardiac APs also exhibit automaticity (autorhythmicity) due to the special cells in the heart (SA and AV nodes).
 - Unlike neurons, cardiac cells have a refractory period that almost equals the contraction duration to prevent tetanic contractions, which would be lethal in the heart.
- Neuronal Action Potentials:
 - Neuronal APs are much shorter, typically 1-2 ms, with no plateau phase.
 - They are initiated by a strong enough external stimulus that depolarizes the neuron's membrane potential.
 - They also have a relatively short refractory period which allows high-frequency firing.

Why Model Action Potentials?

- Modeling action potentials aids in the **understanding** of the physiological processes at the cellular level.
- It helps **predict** the behavior of cells or tissues under normal and pathological conditions.

- They can guide the **development of treatments** for diseases involving electrical signaling, such as arrhythmias and epilepsy.
- It allows **simulation of drug effects** on ion channel function, aiding in drug discovery and testing.

Luo-Rudy Model and Its Extensions for Autorhythmicity and Nervous System Modulation

- The Luo-Rudy model is a computational model of the action potential in ventricular myocytes, which does not intrinsically include automaticity.
- To simulate autorhythmicity, one could integrate the HCN channel (funny current, I_f) that is found in pacemaker cells of the SA and AV nodes, and which contributes to automaticity.
- Modulation by the autonomous nervous system could be implemented by adjusting the rates of specific ion channels. For instance, sympathetic stimulation could be modeled by increasing the **conductance of calcium and sodium** channels, while parasympathetic stimulation could be modeled by increasing the **conductance of potassium channels and the HCN channel**.

Effects of Myofibroblasts on Cardiac Electrical Conduction

- Scenario 1 (Myofibroblasts coupled with myocytes and other myofibroblasts): Can lead to **slow conduction and potential arrhythmias** due to the less efficient conduction properties of myofibroblasts.
- Scenario 2 (Myofibroblasts coupled with other myofibroblasts, but not myocytes): Conduction might be less affected **as long as there's a continuous network of myocytes**.
- Scenario 3 (Myofibroblasts not coupled with other cells): This would isolate these cells and probably have less impact on overall conduction, **unless they cause significant structural disruption**.

Role of ATP in Cardiac Contraction:

- ATP provides the energy for muscle contraction by fueling the cross-bridge cycle of actin and myosin filaments.
- ATP is generated primarily through oxidative phosphorylation in mitochondria, using energy derived from the oxidation of nutrients. Lesser amounts are produced by glycolysis and the creatine phosphate shuttle.
- ATP also powers ion pumps (including the Na^+/K^+ ATPase and Ca^{2+} ATPase) which help restore and maintain the ionic gradients that are crucial for electrical excitability and contractility.

Sick Sinus Syndrome and its Effect on the Order of Electrical Activation:

- Sick sinus syndrome is characterized by dysfunction of the sinus node, the heart's primary pacemaker.
- This can lead to various arrhythmias, including bradycardia, tachycardia, or a combination of both (tachy-brady syndrome).
- When the sinus node is dysfunctional, other parts of the heart (such as the atrioventricular node or ventricular tissue) may take over as the pacemaker, leading to an altered order of electrical activation and potentially reduced cardiac performance.

Structure and Properties of Cardiac Tissue and their Contribution to QRS Complex and T-wave:

- The QRS complex represents the rapid, synchronized activation of ventricles, while the T-wave represents the slower, more dispersed repolarization.

- The high amplitude of the QRS complex is due to the nearly simultaneous activation of a large mass of ventricular tissue, while the lower amplitude and longer duration of the T-wave reflect the more gradual and less synchronized repolarization process.
- The dipole model provides a simplified representation of these processes, but may not fully capture the complex spatial patterns of activation and repolarization, especially under pathological conditions.

1. Major Changes in Action Potentials and Calcium Transients Under Various Conditions:

- **Altered Ion Channel Function:** Changes in ion channel function can dramatically alter the shape, duration, and frequency of action potentials. For instance, a mutation or drug that increases the conductance of a particular type of potassium channel could shorten the action potential, as potassium ions would exit the cell more rapidly, hastening the return to the resting potential. This could, in turn, decrease the duration of the associated calcium transient and thus shorten the contraction. Conversely, if a mutation or drug decreased the conductance of a potassium channel, the action potential and calcium transient could be prolonged, potentially leading to a longer and stronger contraction.
- **Changes in Calcium Handling Proteins:** Calcium handling proteins play a crucial role in regulating the intracellular calcium concentration, which directly influences the force and duration of contraction. For example, an increase in the activity of the sarcoplasmic reticulum Ca^{2+} -ATPase (SERCA), which pumps calcium from the cytosol back into the SR, could enhance the rate of calcium removal during diastole, leading to a more rapid relaxation. On the other hand, a decrease in SERCA activity could prolong the calcium transient and thus the contraction. Similarly, alterations in the function of the ryanodine receptors (RyRs), which release calcium from the SR, or the L-type calcium channels, which allow calcium entry from the extracellular space, could have significant effects on the calcium transient and contractility.

2. Cellular Automata vs. Mono-/Bidomain Models in Cardiac Conduction:

- **Cellular Automata:** In a cellular automaton model, the heart tissue is represented as a grid of discrete cells, each of which can be in one of a finite number of states (e.g., resting, excited, refractory). The state of each cell at a given time step is determined by its own state and the states of its neighbors at the previous time step, according to a set of predefined rules. Cellular automata are simple to implement and computationally efficient. They can be useful for studying phenomena such as wave propagation and reentry in a qualitative manner. However, they are highly simplified and do not take into account the continuous, anisotropic nature of cardiac tissue or the detailed biophysics of membrane ion channels and transporters.
- **Mono-/Bidomain Models:** In mono- and bidomain models, the heart tissue is represented as a continuous medium, and the propagation of action potentials is described by partial differential equations. The monodomain model assumes that the intracellular and extracellular spaces are electrically connected, whereas the bidomain model treats them as two separate domains. These models take into account the anisotropic conduction properties of the cardiac tissue (due to the alignment of the cardiac fibers) and can incorporate detailed models of the ion channels and transporters. As such, they provide a more realistic and quantitative description of cardiac electrophysiology. However, they are more complex and computationally demanding. The choice between these models depends on the specific research question and the required level of detail and realism. For example, the bidomain model may be needed to accurately simulate the effects of electrical stimulation or to study the interaction between the intracellular and extracellular spaces.

Explain the structure-function relationship of ion channels and the influence of their molecular structure on their function.

How can this knowledge be applied to predict the behavior of an ion channel?

Ion channels are integral membrane proteins that allow ions to pass through the membrane in response to a specific stimulus, which could be a change in the membrane potential (voltage-gated ion channels) or binding of a specific molecule (ligand-gated ion channels). The structure of an ion channel, including its size, shape, and the properties of the amino acids lining its pore, dictates its ion selectivity and gating mechanism. For example, potassium channels have a selectivity filter lined with carbonyl oxygen atoms that replace the hydration shell of a K⁺ ion, facilitating its passage through the pore, while preventing the passage of smaller Na⁺ ions. The voltage-gated sodium channels have specific voltage-sensing domains that respond to changes in membrane potential, which leads to conformational changes in the channel and opening of the pore.

Understanding the structure-function relationship of ion channels can help predict their behavior under different conditions, which is crucial in the development of drugs targeting these channels.

Elucidate the main concepts of the Hodgkin and Huxley model. What are the modeled currents and how do they contribute to the action potential?

The Hodgkin-Huxley model, proposed by Alan Hodgkin and Andrew Huxley in the 1950s, describes how action potentials in neurons are initiated and propagated. According to this model, the action potential results from the coordinated opening and closing of voltage-gated sodium and potassium channels.

At rest, a small number of potassium channels are open, leading to a negative resting potential (around -70 mV). When a stimulus depolarizes the membrane, voltage-gated sodium channels open, causing an influx of sodium ions and further depolarization, a positive feedback that results in the rapid upstroke of the action potential. Once the membrane potential reaches a peak, sodium channels close, while voltage-gated potassium channels open, causing an efflux of potassium ions and repolarization of the membrane, forming the downstroke of the action potential. The excess efflux of K⁺ causes a brief hyperpolarization after which the membrane returns to its resting potential. The distinct opening and closing of these ion channels create the characteristic phases of the action potential.

Explain how the two-state model is used to represent ion channels. How do ion channels transition between states and what factors influence these transitions?

The two-state model is a simplified conceptual framework used to represent the behavior of ion channels. In this model, an ion channel is considered to have two states: open (O) and closed (C). Transition between these states is a stochastic process, usually depicted as $C \rightleftharpoons O$. The transition rates between the two states are represented as rate constants: the rate of channel opening (k_{co}) and the rate of channel closing (k_{oc}).

Various factors can influence these transitions. For voltage-gated ion channels, the membrane potential is a crucial determinant of the transition rates. For ligand-gated ion channels, the concentration of the specific ligand dictates the transition between states. Physical factors such as temperature and pressure can also affect these transitions. Understanding these transitions and the factors that influence them is critical for understanding the functioning of ion channels and for the development of drugs that can modulate their activity.

Describe how the cardiac action potential is generated and propagated. What are the different phases of the action potential and what ion movements contribute to these phases?

The cardiac action potential is a sequence of ion movements across the cardiac cell membrane that leads to a contraction of the heart muscle. It consists of five phases (0-4):

Phase 0 - Rapid depolarization: Triggered by a stimulus that brings the membrane potential to a threshold level, causing the voltage-gated sodium channels to open rapidly, allowing Na^+ ions to rush into the cell, which results in rapid depolarization.

Phase 1 - Initial repolarization: The sodium channels start to inactivate and close, reducing the inward Na^+ current. Transient outward potassium channels open, allowing a small outward flux of K^+ , causing a small initial repolarization.

Phase 2 - Plateau phase: The membrane potential remains relatively constant during this phase due to a balance between inward Ca^{2+} current (via L-type calcium channels) and outward K^+ current (via slow delayed rectifier potassium channels). The influx of Ca^{2+} triggers the release of more Ca^{2+} from the sarcoplasmic reticulum, initiating the process of contraction.

Phase 3 - Rapid repolarization: L-type Ca^{2+} channels close and **delayed rectifier** K^+ channels open **more fully**, resulting in a net outward current that repolarizes the cell.

Phase 4 - Resting membrane potential: The membrane potential is maintained by the **inward-rectifier** K^+ channels that **resist changes** in membrane potential until the next action potential.

Describe the mechanism of ion transport across the cell membrane. What are the different types of transporters and channels involved in this process?

Ion transport across the cell membrane is an essential process for maintaining cellular homeostasis. It involves two main types of proteins: ion channels and transporters.

Ion channels form pores in the cell membrane that allow ions to pass through by diffusion, down their **electrochemical gradient**. These channels can be selectively permeable to certain types of ions, and their opening and closing can be regulated by various factors, such as changes in membrane potential (voltage-gated channels), binding of a ligand (ligand-gated channels), or mechanical forces (mechanically-gated channels).

Transporters, on the other hand, bind to specific ions (or molecules) and undergo conformational changes to transport these substances across the membrane. This process can occur down the electrochemical gradient (facilitated diffusion via uniporters) **or against the gradient** (active transport via pumps or secondary active transport via symporters and antiporters).

What are the key steps involved in excitation-contraction coupling in cardiac myocytes?

Excitation-contraction (EC) coupling in cardiac myocytes is the process that **links the electrical excitation of the cell (action potential) to contraction of the myocyte**. The process begins with the initiation of an action potential, which propagates along the cell membrane and into the T-tubules. This depolarization triggers the opening of voltage-gated L-type calcium channels, leading to a small influx of calcium into the cell. This influx of calcium triggers the ryanodine receptors in the sarcoplasmic reticulum (SR) to release a larger quantity of calcium into the cytoplasm in a process known as calcium-induced calcium release (CICR). The increase in intracellular calcium causes the myofilaments to slide over each other, leading to contraction of the myocyte. The calcium is then pumped back into the SR by the **SR calcium ATPase (SERCA)** and **out of the cell by the sodium-calcium exchanger (NCX) and plasma membrane calcium ATPase (PMCA)**, allowing the cell to relax and prepare for the next cycle of contraction.

Describe the principles and limitations of the cable theory in the context of cardiac conduction. How does the source-sink relationship influence the conduction velocity?

The cable theory is a model that describes the propagation of electrical signals in biological tissues such as nerve fibers and cardiac muscle. According to this theory, a cell or fiber can be represented as a cylindrical cable with resistance and capacitance. The cable theory can **accurately describe the passive spread of electrical signals, but it fails to consider the active processes**, such as the opening and closing of voltage-gated ion channels, which are crucial in the regeneration of the action potential along the fiber.

The source-sink relationship plays a critical role in cardiac conduction. The 'source' refers to the active region of the cell membrane that is generating the current (through the movement of ions across the membrane), and the 'sink' refers to the adjacent, unexcited region that absorbs the current. The balance between the source and sink determines the conduction velocity. If the sink is larger (i.e., the downstream tissue has a larger capacitance or a lower resistance), more current is needed from the source to depolarize the downstream tissue to threshold, potentially slowing down the conduction velocity.

Explain the concept of refractoriness in the context of cardiac electrophysiology. How does it contribute to unidirectional block and reentry?

Refractoriness refers to the period following an action potential during which the cardiac cell is unable to respond to a new stimulus. This refractory period is subdivided into the absolute refractory period, during which it is impossible to initiate a second action potential, and the relative refractory period, during which initiation of a second action potential is possible but requires a stronger stimulus. Refractoriness is **crucial in the unidirectional propagation of cardiac impulses**, preventing backward propagation of action potentials. In terms of unidirectional block and **reentry**, if a premature stimulus encounters a region that is still refractory (unable to respond), it will be blocked in that direction. However, if there is a pathway that has **recovered from refractoriness**, the stimulus can propagate in that direction, potentially leading to reentry if it encounters a region that has now recovered from refractoriness.

Explain the role of gap junctions in the propagation of electrical signals in cardiac tissue. How does their distribution and density influence conduction velocity and anisotropy?

Gap junctions are specialized intercellular connections that allow direct electrical and metabolic coupling between adjacent cells. In cardiac tissue, they enable the rapid spread of action potentials from cell to cell, ensuring a synchronized contraction of the heart. The distribution and density of gap junctions in cardiac tissue play a crucial role in determining conduction velocity and anisotropy (direction-dependent conduction). Specifically, a higher density of gap junctions can enhance conduction velocity **by reducing the resistance** to the flow of current between cells. Anisotropy, on the other hand, arises from the uneven distribution of gap junctions in the cardiac tissue. For instance, in ventricular myocardium, gap junctions are more densely located at the ends of cells (longitudinal direction) compared to the sides (transverse direction), leading to faster conduction in the longitudinal direction compared to the transverse direction.

The 12-lead electrocardiogram (ECG) is a critical tool for **diagnosing** a wide range of cardiac disorders. It works by **detecting and recording** the electrical activity of the heart through electrodes placed on the body surface. In terms of leads, six of them provide information from the **frontal plane** (I, II, III, aVL, aVR, and aVF) and the other six provide information from the **horizontal plane** (V1 to V6). Each lead offers a **specific view** of the heart's electrical activity.

Discuss the cellular mechanisms underlying the therapeutic effect of calcium blockers in ventricular tachycardia.

Calcium blockers, such as verapamil and diltiazem, exert their therapeutic effect in ventricular tachycardia by inhibiting the L-type calcium channels. These channels are critical for the inward calcium current (I_{Ca}) that triggers the plateau phase (Phase 2) of the cardiac action potential and contributes to the depolarization of pacemaker cells in the SA and AV nodes. By blocking these channels, calcium blockers reduce the inward calcium current, **which can slow down the heart rate, decrease conduction velocity through the AV node, and reduce myocardial contractility.** In the context of ventricular tachycardia, these effects can **interrupt the reentry circuit**, stabilize the membrane potential, and **suppress abnormal automaticity**, thereby helping to restore normal rhythm.

Briefly discuss the following therapeutic agents, including their mechanism of action and therapeutic effects: positive inotropes (e.g., epinephrine), negative inotropes (e.g., acetylcholine, beta-blockers, calcium channel blockers).

- Positive inotropes like epinephrine increase cardiac contractility by stimulating β_1 -adrenergic receptors, which leads to an increase in cyclic AMP (cAMP) levels, activation of protein kinase A, and enhanced calcium influx and uptake into the sarcoplasmic reticulum. The end result is an increased contractile force.
- Negative inotropes decrease cardiac contractility. **Acetylcholine** primarily acts on the atria to shorten the action potential and reduce the intracellular calcium concentration ($[Ca^{2+}]_i$), thereby reducing contractility. **Beta-blockers**, such as propranolol, inhibit the effects of catecholamines (like epinephrine) on beta-adrenergic receptors, thus reducing heart rate and contractility. **Calcium channel blockers**, such as verapamil and diltiazem, inhibit L-type calcium channels, reducing the influx of calcium into the cell, and thereby decreasing contractility.

Discuss the role of ion gradients and ion channels in establishing the resting membrane potential and action potentials.

Ion gradients are maintained across the cell membrane mainly by the activity of the sodium-potassium pump. This results in a higher concentration of sodium ions outside the cell and a higher concentration of potassium ions inside the cell. The difference in concentration of these ions on either side of the membrane, together with their permeability due to ion channels, establishes the resting membrane potential. **The action potential** is initiated when voltage-gated sodium channels open, leading to an influx of sodium ions, causing depolarization. Repolarization occurs when voltage-gated potassium channels open and sodium channels close, allowing an efflux of potassium ions.

What are the fundamental principles of the Reaction-Diffusion system as it pertains to cardiac conduction?

The reaction-diffusion system is a mathematical model that describes how the action potential (reaction) propagates through the cardiac tissue (diffusion). The reaction term refers to the **biophysical properties** of the cardiac cells, including the opening and closing of ion channels, which produce changes in the transmembrane potential. The diffusion term relates to the spatial propagation of these changes in potential, which depends on **cell-to-cell connectivity and the properties of the cardiac tissue**. Together, these principles govern how an action potential generated in one part of the heart spreads to other regions, orchestrating the coordinated contraction of the heart.

Describe the mechanisms underlying the establishment of a unidirectional block in a 1D homogeneous model of cardiac tissue.

A unidirectional block in a 1D homogeneous model of cardiac tissue can occur when one region of the tissue is in a refractory state, while adjacent regions are excitable. This can be due to **heterogeneity in the refractory periods** of the cells, or it can be due to a **conduction velocity that is too slow** to overcome the refractoriness of the downstream tissue. When an action

potential approaches the refractory tissue from one direction, it will be blocked and will not propagate through. However, if an action potential approaches the same tissue from the opposite direction, once the tissue has recovered from its refractory state, the action potential will be able to propagate through. This creates a unidirectional block. Such mechanisms are critical to the development of **reentrant circuits and can lead to arrhythmias**.

Discuss the role of myocardial heterogeneity, excitability, conduction, and repolarization in the context of classic arrhythmia mechanisms.

Myocardial heterogeneity refers to the differences in **electrophysiological properties** among different regions of the heart. This heterogeneity can be a factor in arrhythmogenesis, as it can lead to non-uniform conduction and the formation of reentrant circuits.

Excitability, which refers to the ability of cardiac cells to generate an action potential in response to a stimulus, can be altered in various pathological conditions, leading to a higher susceptibility to arrhythmias.

Changes in **conduction velocity** can also contribute to arrhythmia; for example, slow conduction can increase the likelihood of reentry.

Lastly, **abnormal repolarization** can lead to afterdepolarizations, which can trigger arrhythmias. Understanding these factors is essential for developing strategies to prevent and treat arrhythmias.

Compare atrial fibrillation and ventricular fibrillation in terms of their mechanisms, clinical presentations, and consequences.

Atrial fibrillation (AFib) and ventricular fibrillation (VFib) are both types of cardiac arrhythmias, but they occur in different chambers of the heart and have distinct mechanisms, presentations, and consequences.

AFib typically arises from rapid, irregular firing of electrical impulses usually originating from the **pulmonary veins**. This results in a **quivering** or irregular heartbeat. Clinically, patients with AFib may experience **palpitations, fatigue, and shortness of breath, but some individuals may be asymptomatic**. **Chronic AFib** can increase the risk of stroke and heart failure.

VFib, on the other hand, is due to **disorganized electrical activity** in the ventricles. The ventricles quiver and are unable to contract effectively to pump blood. This is a medical emergency, causing a sudden collapse in the affected individual and leading to **cardiac arrest** and sudden death if not treated immediately with defibrillation.

The main reason why the system commonly fails in VFib but not in AFib is due to the role each chamber plays in the circulation. Ventricles are the main pumping chambers of the heart, pumping blood to the entire body. Disruption of ventricular function by VFib, therefore, has immediate, life-threatening consequences. The atria, in contrast, play a more supportive role in cardiac function, aiding ventricular filling. Therefore, while AFib can be chronic and debilitating, it is not immediately life-threatening like VFib.

What is the role of the pulmonary veins in the initiation and maintenance of atrial fibrillation?

The pulmonary veins play a significant role in the **initiation and maintenance** of atrial fibrillation. Studies have shown that ectopic foci, or "triggers" for the irregular electrical activity characteristic of AFib, often reside **in or around the pulmonary veins**. These foci generate rapid and irregular electrical impulses that can overwhelm the normal electrical pathways of the atria, leading to the chaotic electrical activity characteristic of AFib.

Moreover, the **tissue around the pulmonary veins can facilitate the maintenance** of AFib due to its unique electrical properties, which can facilitate reentrant circuits - the perpetuating loops of electrical activity that maintain the fibrillation.

CCBs

Increasing the refractory period: The refractory period is the time during which a new action potential cannot be initiated in a cell. CCBs can prolong this period, which allows more time for the heart to fill with blood before the next contraction. This can help prevent the rapid, uncoordinated contractions characteristic of ventricular tachycardia.

Decreasing automaticity: Automaticity refers to the ability of certain cardiac cells to spontaneously depolarize and trigger an action potential. In normal physiology, this property is crucial for the function of pacemaker cells in the SA and AV nodes. However, in the context of disease, abnormal automaticity in ventricular cells can lead to ventricular tachycardia. Calcium plays a crucial role in the phase 4 depolarization of these pacemaker cells. By blocking the L-type calcium channels, CCBs can decrease the slope of phase 4, thereby decreasing the automaticity of these cells.

The term "afterdepolarization" refers to depolarizations that occur after an action potential has already started. They are called "after" depolarizations because they occur "after" or during the normal repolarization phase of the action potential. Afterdepolarizations can either be "early" (EADs) or "delayed" (DADs):

1. **Early Afterdepolarizations (EADs):** These occur during phases 2 and 3 of the action potential, which are the plateau and repolarization phases, respectively. They can occur when the action potential duration (APD) is prolonged (such as in long QT syndrome) and can trigger additional action potentials, potentially leading to arrhythmias.
2. **Delayed Afterdepolarizations (DADs):** These occur after completion of the action potential, during phase 4, which is the resting phase. They can occur when there is an overload of intracellular calcium, leading to additional calcium release from the sarcoplasmic reticulum, which can trigger an additional depolarization and potentially an additional action potential, leading to arrhythmias.

Both types of afterdepolarizations are associated with various types of cardiac arrhythmias, including ventricular tachycardia and fibrillation. **A Delayed Afterdepolarization (DAD)** is considered abnormal **because it's an additional or extra** depolarization that occurs after the completion of a normal action potential cycle. This extra depolarization can disrupt the regular rhythm of the heart.

This spontaneous depolarization, or DAD, arises after the cell has repolarized following a regular action potential and usually during phase 4 (resting potential phase) of the cardiac action potential. It happens due to a variety of conditions but most commonly **as a result of elevated intracellular calcium levels**, which can lead to **spontaneous calcium release** from the sarcoplasmic reticulum and cause the cell membrane to depolarize via the sodium-calcium exchanger (3Na^+ in, 1Ca^{2+} out). If the magnitude of this spontaneous depolarization is large enough to reach the threshold potential, it can trigger **a new, abnormal action potential, leading to an early or extra heartbeat**, or in certain circumstances, can even trigger a cardiac arrhythmia. That's why the timing and existence of DADs are abnormal and potentially harmful.

Mindfulness

- 1. Have daily off-time and weekly off-time**
- 2. Write down what I am thinking**
- 3. Take a deep breath**
- 4. Go out, have a walk**
- 5. Read a book**
- 6. Practice focusing, such as playing the piano**
- 7. Meditation, Yoga, Exercise**
- 8. Listen to music**
- 9. Sleep**
- 10. Deep, not shallow, in everything (bottom neck book)**

Ca²⁺ Sparks: Each spark represents the opening of a small cluster of RyRs, leading to a rapid, localized increase in calcium concentration.

A **Ca²⁺ transient** is a temporary increase in the global intracellular calcium concentration, typically following an action potential

Ca²⁺ sparks can be considered the fundamental building blocks of a Ca²⁺ transient. A synchronized activation of multiple clusters of RyRs across the cell leads to a coordinated release of calcium, producing the global increase in calcium concentration that characterizes the Ca²⁺ transient.

The calcium-sensitive dye (e.g., Fluo-4) is typically supplied as a non-fluorescent, cell-permeant acetoxymethyl (AM) ester form. This form of the dye is lipophilic and can pass through the cell membrane.

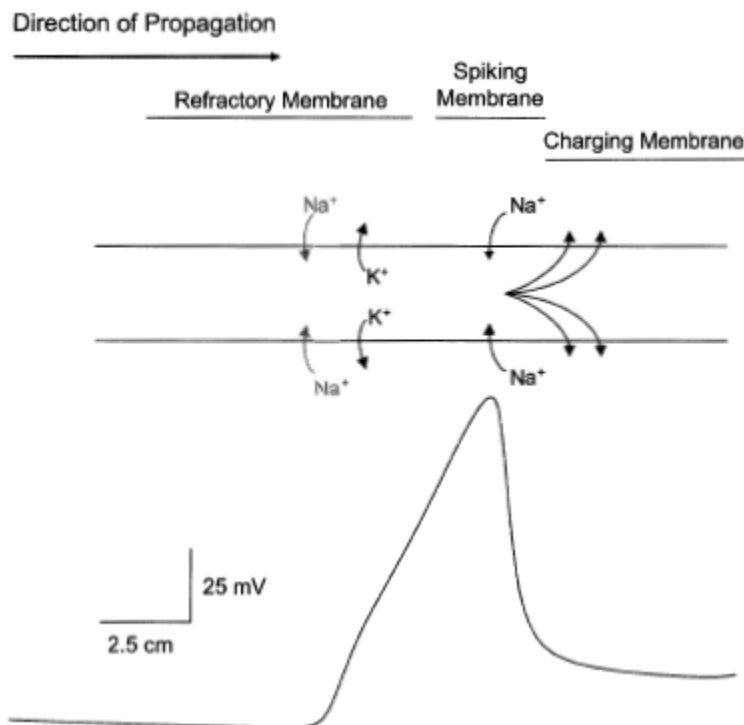
T-Tubules: Cardiac myocytes contain deep invaginations of the cell membrane called transverse tubules (T-tubules). These structures penetrate into the interior of the cell, bringing the cell membrane close to the SR.

Part of the SR forms junctions with the T-tubules, creating the dyadic junctions or clefts. This junctional SR contains the ryanodine receptors (RyRs).

Clustered RyRs: RyRs are typically arranged in clusters within the SR. The close proximity allows them to act in concert, so that the opening of one RyR can influence the neighboring RyRs. This coordinated opening leads to a localized release of calcium known as a "Ca²⁺ spark."

Spark-to-Wave Transition: The localized Ca²⁺ sparks can then sum together to create a global Ca²⁺ wave, leading to muscle contraction. If RyRs were spaced too far apart, this coordinated opening and summation might not occur efficiently.

Refractory Period of RyR: After the release of calcium from the SR, there is a refractory period during which the RyRs are less likely to be reactivated. This period ensures that the Ca²⁺ sparks are discrete events tied to individual action potentials rather than continuous or chaotic releases.



The sodium-calcium exchanger (NCX) is a critical membrane protein that helps regulate intracellular calcium (Ca^{2+}) levels in various cell types, including cardiac myocytes. NCX achieves this by utilizing the electrochemical gradient of sodium (Na^+) to transport Ca^{2+} across the cell membrane. It can operate in two main modes, depending on the cellular conditions:

1. **Forward Mode (Ca^{2+} Efflux):**

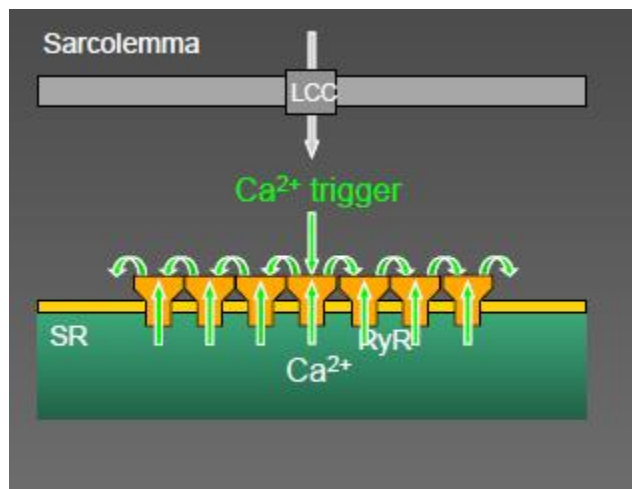
- **Direction:** 3 Na^+ ions move into the cell, and 1 Ca^{2+} ion moves out of the cell.
- **Conditions:** This mode is typically active during cellular excitation when there is a high intracellular Ca^{2+} concentration, such as after an action potential in a cardiac cell.
- **Result:** Helps in removing Ca^{2+} from the cell, contributing to relaxation.

2. **Reverse Mode (Ca^{2+} Influx):**

- **Direction:** 3 Na^+ ions move out of the cell, and 1 Ca^{2+} ion moves into the cell.
- **Conditions:** This mode can occur under certain pathological or experimental conditions, such as ischemia, where the Na^+ gradient is altered.
- **Result:** Leads to an increase in intracellular Ca^{2+} , which may contribute to altered cell function or damage.

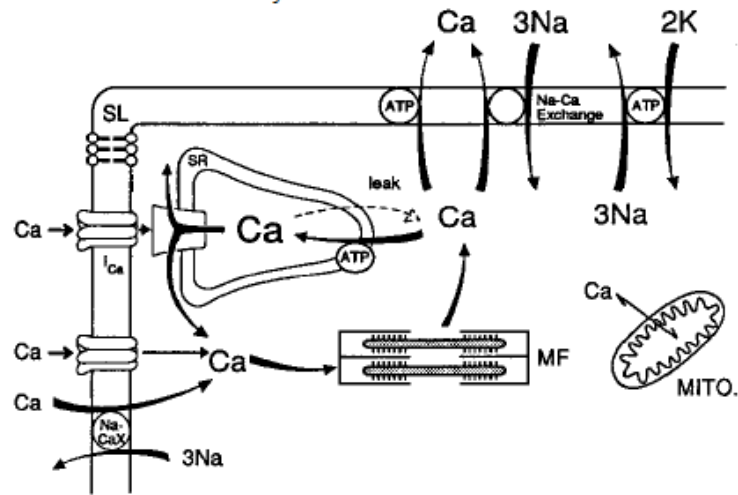
The NCX is crucial for maintaining cellular Ca^{2+} homeostasis, especially in excitable cells like neurons and cardiac myocytes. Its direction of ion movement is tightly regulated by factors such as membrane potential, and the concentrations of Na^+ and Ca^{2+} on both sides of the membrane.

In the heart, the NCX plays a vital role in the relaxation phase of the cardiac cycle by facilitating Ca^{2+} removal from the cytosol. Dysfunction in NCX can lead to impaired Ca^{2+} handling and may contribute to cardiac diseases such as heart failure and arrhythmias.

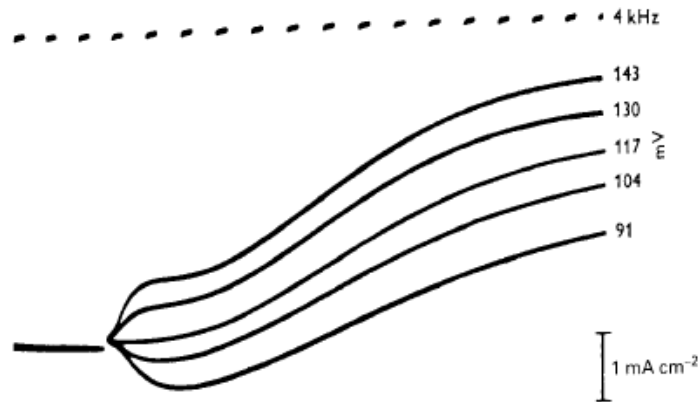


Reverse mode of NCX: In some cardiac tissues, the reverse mode of NCX might contribute to the Ca^{2+} influx during the early phase of the action potential. This can be part of the complex interplay between different ion channels and transporters that shape the cardiac action potential.

Calcium Cycle in Cardiac Muscle

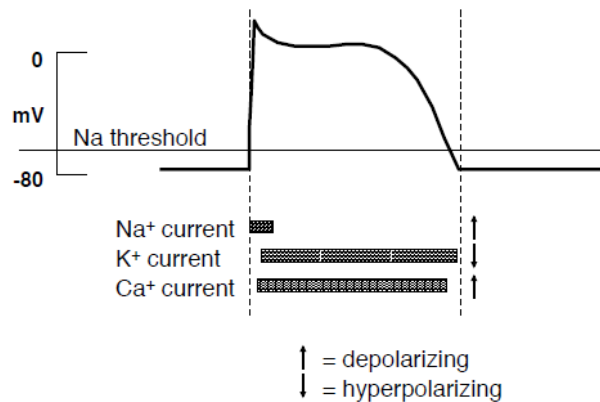


Membrane currents at large depolarizations. Values of V are shown at the right of each record. (From Hodgkin, 1958, after Hodgkin, Huxley and Katz, 1952.)



The potential at which the initial (Na current) is neither inward nor outward is the reversal potential E_{Na} for the Na current i.e about 117 mV.

Cardiac Action Potential



If we knew the time and voltage dependence of g_{Na} and g_K we could obtain the form the the action potential by numerical integration of the following equation.

$$I_m = C_m dV/dt + g_K(E - E_K) + g_{Na}(E - E_{Na}) + g_l(E - E_l)$$

$$g_K = \bar{g}_K n^4 \quad n = \text{probability of 4 charged particles being in the correct configuration for conduction.}$$

$$g_{Na} = \bar{g}_{Na} m^3 h \quad n = \text{probability of 3 charged particles being in the correct configuration. } 1-h = \text{probability of inactivation.}$$

n is the potassium activation parameter, m and h are the Na activation and inactivation parameters.

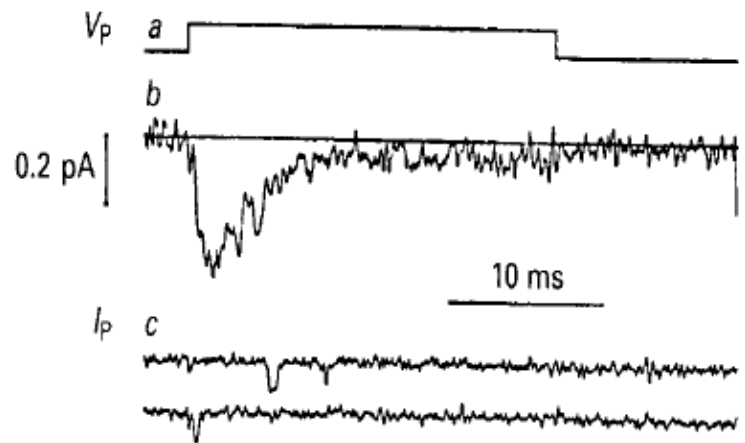
$$\begin{aligned} I_m &= C_m dE/dt + I_K + I_{Na} + I_l \\ &= C_m dV/dt + g_K(E - E_K) + g_{Na}(E - E_{Na}) + g_l(E - E_l) \\ &= C_m dV/dt + \bar{g}_{Na} n^4(E - E_K) + \bar{g}_{Na} m^3 h(E - E_{Na}) + g_l(E - E_l) \end{aligned}$$

With the voltage and time dependence of m , n and h the Above equation can be solved for V by numerical integration

1. Voltage-Clamp Experiment

1. **Preparation of the Neuron or Muscle Fiber:** For example, you could use the giant axon of the squid, as Hodgkin and Huxley did. The large size of this axon makes it ideal for experimental manipulation.
2. **Insertion of Electrodes:** Insert one microelectrode into the axon to measure the membrane potential and another to inject current, thereby "clamping" the membrane potential at a desired level.
3. **Application of the Voltage Clamp:** Apply a step change in voltage to activate the sodium channels, e.g., from a holding potential of -70 mV to 0 mV.
4. **Measurement of the Sodium Current:** Measure the total current required to hold the membrane potential at the clamped value. This represents the sum of the sodium and potassium currents.
5. **Blockade of Sodium Channels:** Apply a sodium channel blocker like tetrodotoxin (TTX) to isolate the potassium current.
6. **Subtraction to Isolate the Sodium Current:** By subtracting the potassium current from the total current, you can obtain the sodium current.

Single sodium channel currents from cultured rat muscle cells, recorded with the cell-attached patch-clamp technique. Trace *a* shows the imposed membrane potential, held at $V = -30$ mV (where $V = 0$ is the resting potential) and depolarized by 40 mV to $V = +10$ mV for about 23 ms at 1 s intervals. Trace *b* shows the average of a set of 300 of current records elicited by these pulses. *c* shows nine successive individual records from this set.



2. Phase 1 (Early Repolarization):

- **Transient Outward Potassium Current (I_{to}):** Contributes to the notch in the action potential waveform.

3. Phase 2 (Plateau Phase):

- No specific potassium currents play a prominent role here, but the balance between inward (e.g., Ca^{2+}) and outward (e.g., K^+) currents maintains the plateau.

4. Phase 3 (Rapid Repolarization):

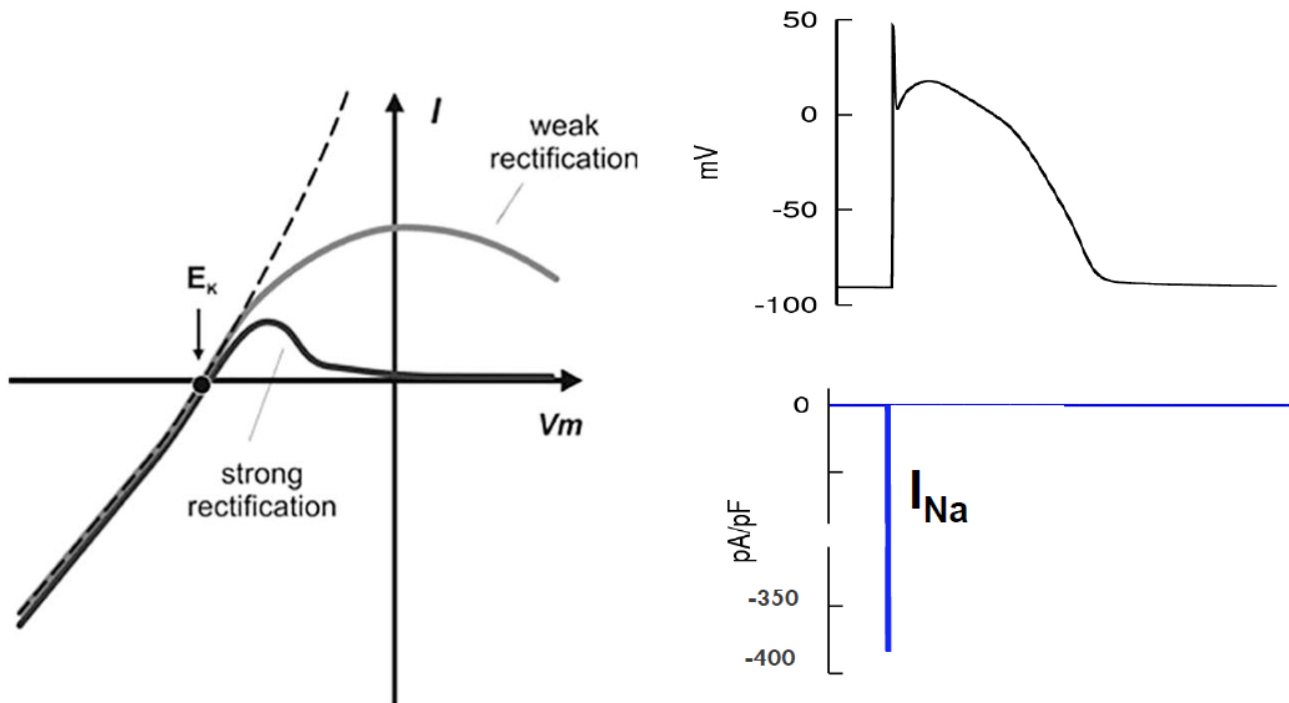
- **Rapid Delayed Rectifier Potassium Current (I_{Kr}):** Contributes to the beginning of this phase.
- **Slow Delayed Rectifier Potassium Current (I_{Ks}):** Contributes later in this phase.
- **Inward Rectifier Potassium Current (I_{K1}):** Helps to complete repolarization near the end of this phase.

5. Phase 4 (Resting Membrane Potential):

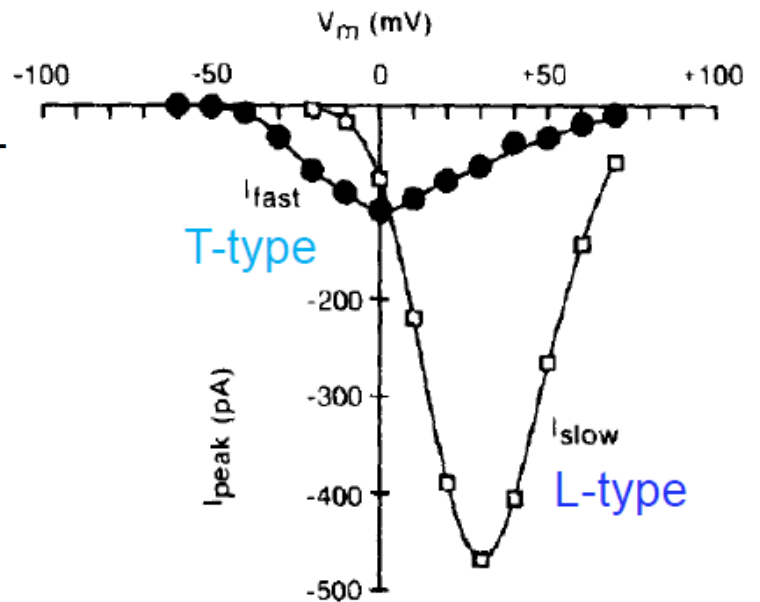
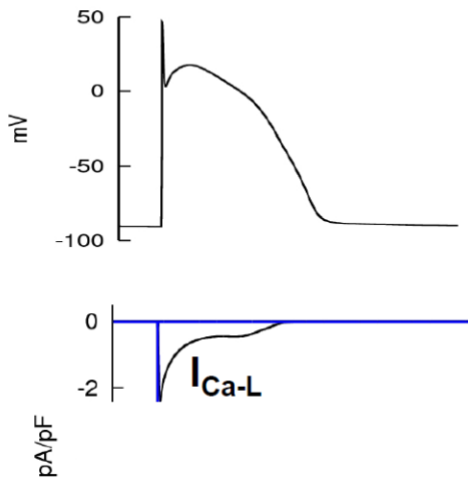
- **Inward Rectifier Potassium Current (I_{K1}):** Helps maintain the resting membrane potential.

pA/pF: this unit used in the context of whole-cell patch-clamp recordings, where the measured current is divided by the cell's capacitance to obtain a current density

Inward sodium current: I_{Na}



Inward L-type calcium current: I_{Ca-L}

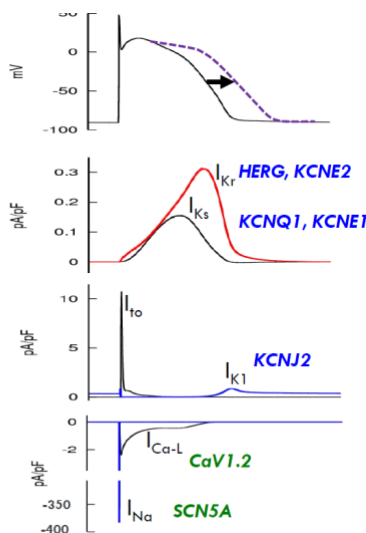


canine atrial myocytes

Long QT syndrome

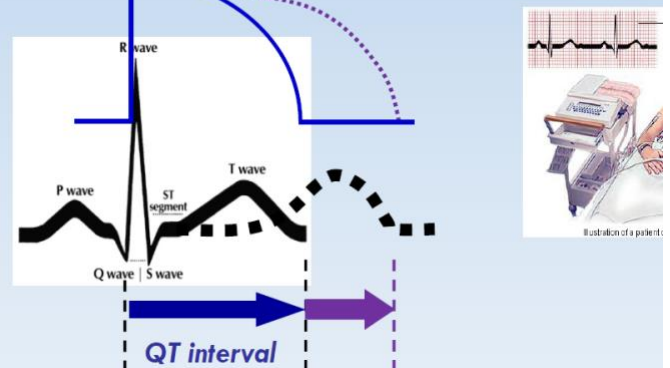
Loss of function mutations in 5 different K channel genes

Gain of function mutations in Na or Ca channel genes



Long QT syndrome: prolonged ventricular repolarization

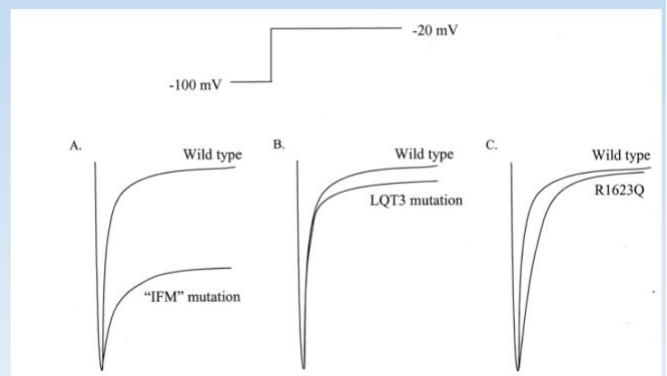
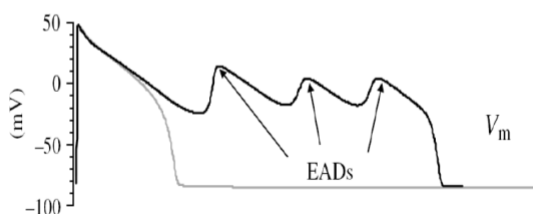
"long": $QT_c > 440 - 460$ ms



Mutations can alter Na channel inactivation

Long QT syndrome:

early afterdepolarizations (EADs) trigger arrhythmia

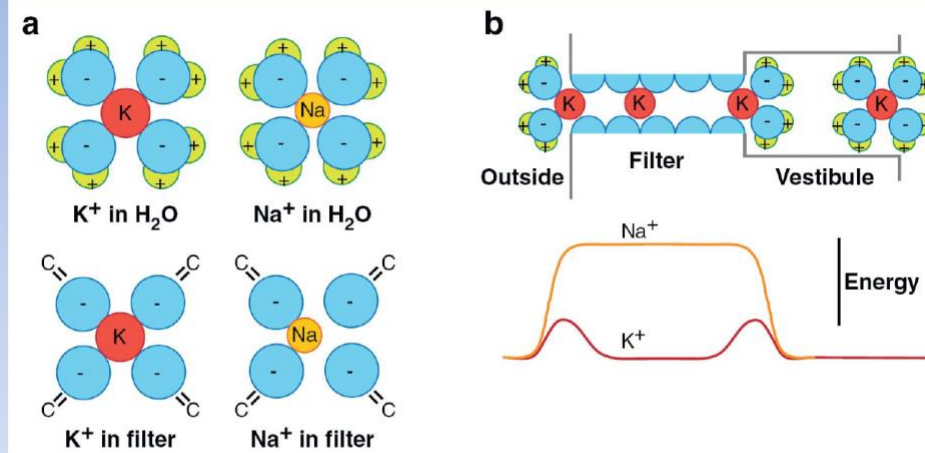


Early afterdepolarizations (EADs) are abnormal depolarizations that occur during the repolarization phase of the cardiac action potential. In the context of Long QT Syndrome (LQTS), EADs can be a critical factor in the initiation of arrhythmias. Here's how they can lead to arrhythmogenic events:

1. **Prolonged Repolarization Phase:** In LQTS, the repolarization phase (Phase 2 and Phase 3) of the action potential is prolonged due to defects in ion channels, such as a decrease in potassium current or an increase in sodium or calcium current. This leads to a longer QT interval on the ECG.
2. **Formation of EADs:** The prolonged repolarization phase provides a window of opportunity for certain inward currents to reactivate (e.g., L-type calcium current or sodium current). This can lead to EADs, which are essentially premature depolarizations occurring before the completion of repolarization.
3. **Triggered Activity:** EADs can cause "triggered activity," where these premature depolarizations are sufficient to cross the threshold for an action potential, leading to an additional beat. This is distinct from the normal, rhythmically triggered activity by the sinoatrial node.
4. **Reentry Circuits:** If EADs occur in some regions of the heart but not others, they can create a situation where different regions of the heart are out of sync. This can set up reentry circuits where the electrical impulse circulates in a small region of the heart, repeatedly reactivating that region and leading to a tachyarrhythmia like Torsades de Pointes, which is often seen in LQTS.
5. **Increased Susceptibility to Arrhythmias:** The heart in LQTS is more susceptible to arrhythmias, and EADs can act as a trigger, especially if other factors are present, such as an increased sympathetic tone or electrolyte imbalances.
6. **Potential Progression to Fatal Arrhythmias:** In the worst-case scenario, the arrhythmias triggered by EADs can degenerate into more serious and potentially fatal arrhythmias, such as ventricular fibrillation.
7. **Treatment Challenges:** The nature of EADs and the underlying ion channel defects in LQTS make treatment challenging. Beta-blockers are often used to reduce the risk of arrhythmias, but they may not be effective in all cases. Sometimes, more invasive strategies such as an implantable cardioverter-defibrillator (ICD) or left cardiac sympathetic denervation may be required.

🔄 Regenerate

Why is K^+ favored over Na^+ ?



Armstrong (2007) *Ann Rev Physiol* 69:1-18

The energy for K^+ in water and the selectivity filter is similar (~ 79 kcal/M)

Coordination of Na^+ in selectivity filter is energetically unfavorable (lower binding affinity than K^+)

Delayed afterdepolarizations (DADs) are abnormal depolarizations that occur during the phase 4 (resting phase) of the cardiac action potential. They arise after full repolarization of the membrane potential and can be a precursor to arrhythmogenic events, especially when they reach the threshold potential and trigger a subsequent action potential.

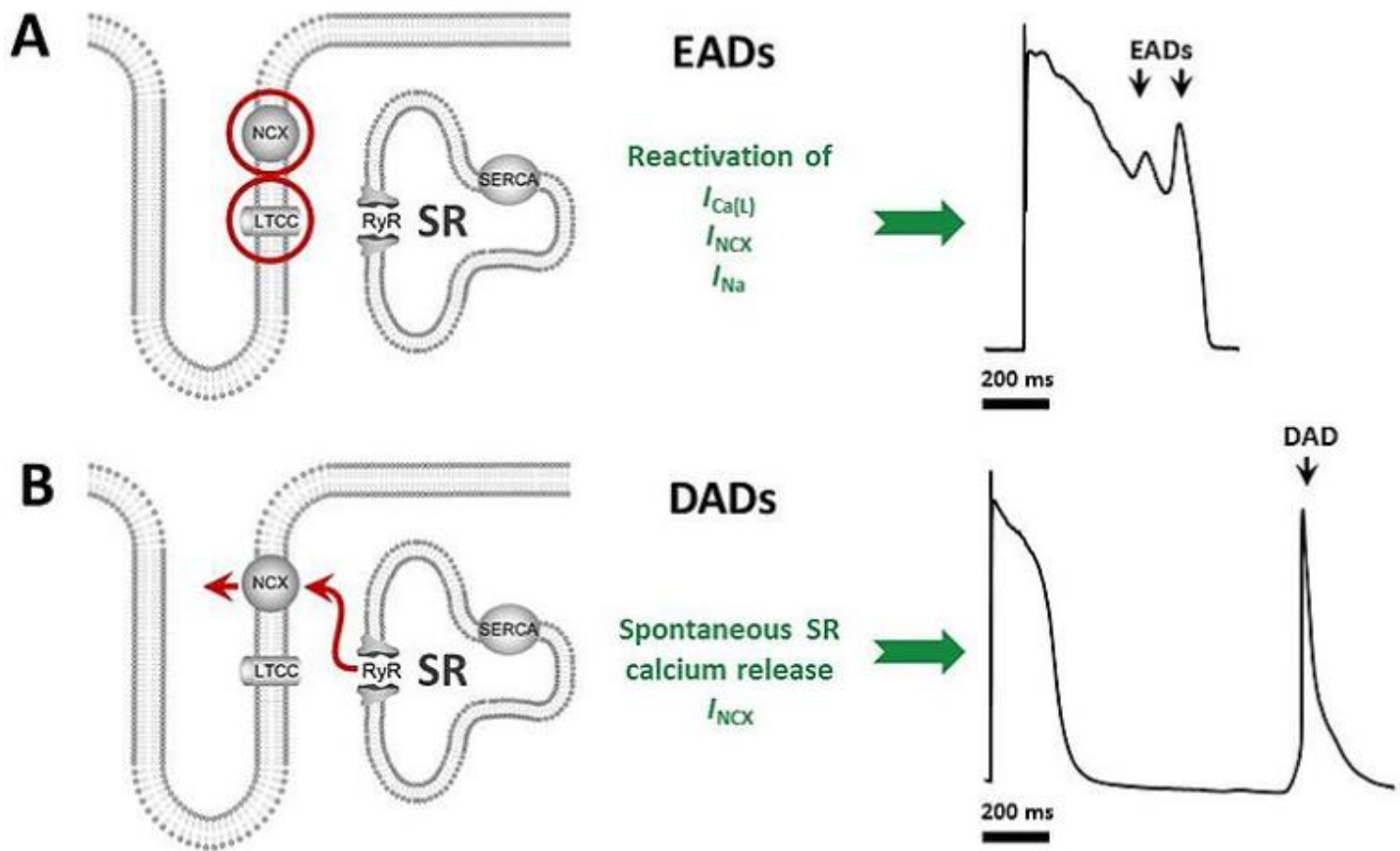
Mechanism of DADs:

Calcium Handling: The primary mechanism responsible for DADs involves disturbances in intracellular calcium homeostasis. In certain conditions, excessive calcium accumulates within the cardiac myocyte's sarcoplasmic reticulum (SR).

Calcium Release: The overloaded SR can spontaneously release this calcium into the cytosol. This spontaneous calcium release activates the sodium-calcium exchanger (NCX) on the cell membrane.

Sodium-Calcium Exchanger (NCX): To extrude this excess calcium from the cell, the NCX operates in "reverse mode", where it imports three sodium ions into the cell for every one calcium ion it pumps out. This net inward current (due to the three sodium ions) can depolarize the cell membrane.

Potential for Action Potential: If this depolarization (DAD) is significant enough to reach the threshold potential, it can trigger a full action potential, potentially leading to arrhythmias.



Let's succinctly contrast the primary differences between Delayed Afterdepolarizations (DADs) and Early Afterdepolarizations (EADs):

1. Timing:

- **DADs:** Occur **after** the completion of the action potential and during diastole.
- **EADs:** Occur **during** the action potential, specifically during phases 2 (plateau phase) or 3 (rapid repolarization phase).

2. Primary Mechanism:

- **DADs:** Caused by **spontaneous calcium release** from the sarcoplasmic reticulum leading to activation of the sodium-calcium exchanger, generating a net inward current.
- **EADs:** Result from **prolongation of the action potential duration**, leading to reactivation of certain inward currents like the L-type calcium current.

3. Triggering Conditions:

- **DADs:** Conditions that lead to **calcium overload**, such as digitalis toxicity or excessive beta-adrenergic stimulation.
- **EADs:** Conditions that **prolong the action potential duration**, including potassium channel blocking drugs, bradycardia, or electrolyte imbalances.

Calcium Overload During Ischemia:

- During ischemia, the depletion of ATP affects the function of ATP-dependent ion pumps, particularly the sodium-potassium ATPase and the calcium ATPase. This leads to an accumulation of intracellular sodium.
- The increase in intracellular sodium can drive the sodium-calcium exchanger (NCX) to operate in reverse mode, leading to an influx of calcium into the cell.

- As a result, intracellular calcium levels rise during ischemia, which can activate various detrimental pathways, including those that lead to cell death.

1. Digoxin:

- **Mechanism:** By inhibiting the Na⁺/K⁺ ATPase pump, digoxin increases intracellular sodium levels. This affects the sodium-calcium exchanger (NCX), leading to an increase in intracellular calcium. Elevated calcium enhances cardiac contractility (positive inotropy).
- **Therapeutic Use:**
 - **Heart Failure:** In heart failure, the heart's pumping ability is compromised. Digoxin improves the force of heart contraction, helping the heart pump more efficiently.
 - **Atrial Fibrillation and Atrial Flutter:** Digoxin can **slow down the heart rate** by increasing vagal (parasympathetic) activity and decreasing the conduction velocity through the atrioventricular (AV) node. This makes it useful in controlling the rapid heart rate associated with these arrhythmias.

2. Tetrodotoxin (TTX):

- **Mechanism:** TTX is a potent blocker of many voltage-gated sodium channels (Nav), preventing sodium influx and **inhibiting action potential generation**.
- **Therapeutic Use:**
 - **Pain Management:** While TTX itself is highly toxic and not used therapeutically, understanding its mechanism has led to the development of Nav channel blockers for pain management. By blocking sodium channels in pain-sensing neurons, these drugs can reduce pain signals.

3. Tetraethylammonium (TEA):

- **Mechanism:** TEA blocks certain voltage-gated potassium channels (Kv), affecting the repolarization phase of the action potential.
- **Therapeutic Use:**
 - **Research Tool:** TEA is primarily used as a research tool to study Kv channels and their role in various physiological processes. Its direct therapeutic applications are limited.

4. Verapamil:

- **Mechanism:** Verapamil **blocks L-type calcium channels**, reducing calcium influx in cardiac and smooth muscle cells. This leads to **relaxation of vascular smooth muscle (vasodilation) and a decrease in heart contractility**.
- **Therapeutic Use:**
 - **Hypertension:** By causing vasodilation, verapamil reduces blood pressure.
 - **Angina:** Verapamil reduces the heart's oxygen demand by decreasing heart contractility and causing coronary artery vasodilation, alleviating angina symptoms.
 - **Supraventricular Tachycardia (SVT):** Verapamil **slows down AV node conduction**, making it effective in terminating certain types of SVT.

Digoxin's ability to slow the heart rate is primarily due to its effects on the atrioventricular (AV) node of the heart. Here's a detailed breakdown of the mechanism:

1. Inhibition of Na⁺/K⁺ ATPase Pump:

- Digoxin's primary action is the inhibition of the sodium-potassium ATPase pump. This leads to an accumulation of intracellular sodium, which subsequently affects the sodium-calcium exchanger (NCX). As a result, there's an increase in intracellular calcium.

2. Stimulation of Vagal (Parasympathetic) Activity:

- The increased intracellular calcium, particularly in cells of the sinoatrial (SA) and AV nodes, stimulates the vagal nerve activity. The vagus nerve is a component of the parasympathetic nervous system.
- Enhanced vagal activity leads to the release of acetylcholine, a neurotransmitter that slows down the heart rate by decreasing the automaticity of the SA node (the heart's natural pacemaker) and slowing conduction through the AV node.

FORWARD PROBLEM

1. Modeling the Bioelectric Source (the Heart):

- **Computational Methods:** Use methods like the Finite Element Method (FEM) to create a computational model of the heart. This involves generating a 3D geometric model, discretizing it into a mesh, and defining the governing equations (e.g., the bidomain or monodomain equations for cardiac electrophysiology).
- **Incorporating Measured Data:** Integrate the measured epicardial potentials into the model. This data serves multiple purposes:
 - Setting boundary conditions to ensure the model's behavior aligns with actual observations at the heart's surface.
 - Providing insights into regional variations in electrophysiological properties, allowing for adjustments in parameters like ion channel conductances or tissue conductivity.
 - Serving as a basis for model calibration, where parameters are systematically adjusted to minimize the difference between model predictions and measured data.

2. Performing the Forward Problem:

- **Simulation:** Given the cardiac source model (with incorporated measurements and adjusted parameters), simulate the propagation of electrical activity from the heart to the body's surface. This involves solving the forward problem to predict body surface potentials based on the cardiac sources.
- **Comparison with Measured Data:** Compare the predicted body surface potentials with actual measurements (e.g., from body surface potential mapping or ECG recordings).
- **Fine-Tuning the Model:** If discrepancies exist between the predicted and measured body surface potentials, further refine the model. This might involve adjusting parameters like tissue conductivities in the torso or refining the cardiac source model. The goal is to enhance the model's accuracy and predictive capability.

Experimental and Computational Methodology Employing the Forward Problem to Investigate Ventricular Tachycardia

Ventricular tachycardia (VT) is a life-threatening arrhythmia originating from the ventricles of the heart. Understanding its mechanisms is crucial for developing effective treatments. In this context, the forward problem in electrophysiology refers to predicting the body surface potential given the cardiac sources. By combining experimental and computational approaches, we can gain deeper insights into VT's underlying mechanisms.

1. Experimental Approach:

Setup: Begin with an animal model, preferably a large mammal like a pig or sheep, due to their heart's anatomical and physiological similarities to humans. The chosen animal should be anesthetized, and its heart exposed.

Electrode Placement: Place a dense array of electrodes on the epicardial surface of the heart. These electrodes will record the electrical activity during normal rhythms and induced VT episodes.

VT Induction: VT can be induced using programmed electrical stimulation, where a series of rapid stimuli are delivered to the ventricles. This can create reentrant circuits, leading to VT.

Data Collection: Record the electrical activity during normal rhythms and VT episodes. This data will serve as the ground truth for validating our computational models.

2. Computational Approach:

Geometry and Mesh Generation: Using medical imaging techniques like MRI or CT, obtain high-resolution images of the heart. These images will be used to create a 3D geometric model of the heart, which is then discretized into a finite element mesh.

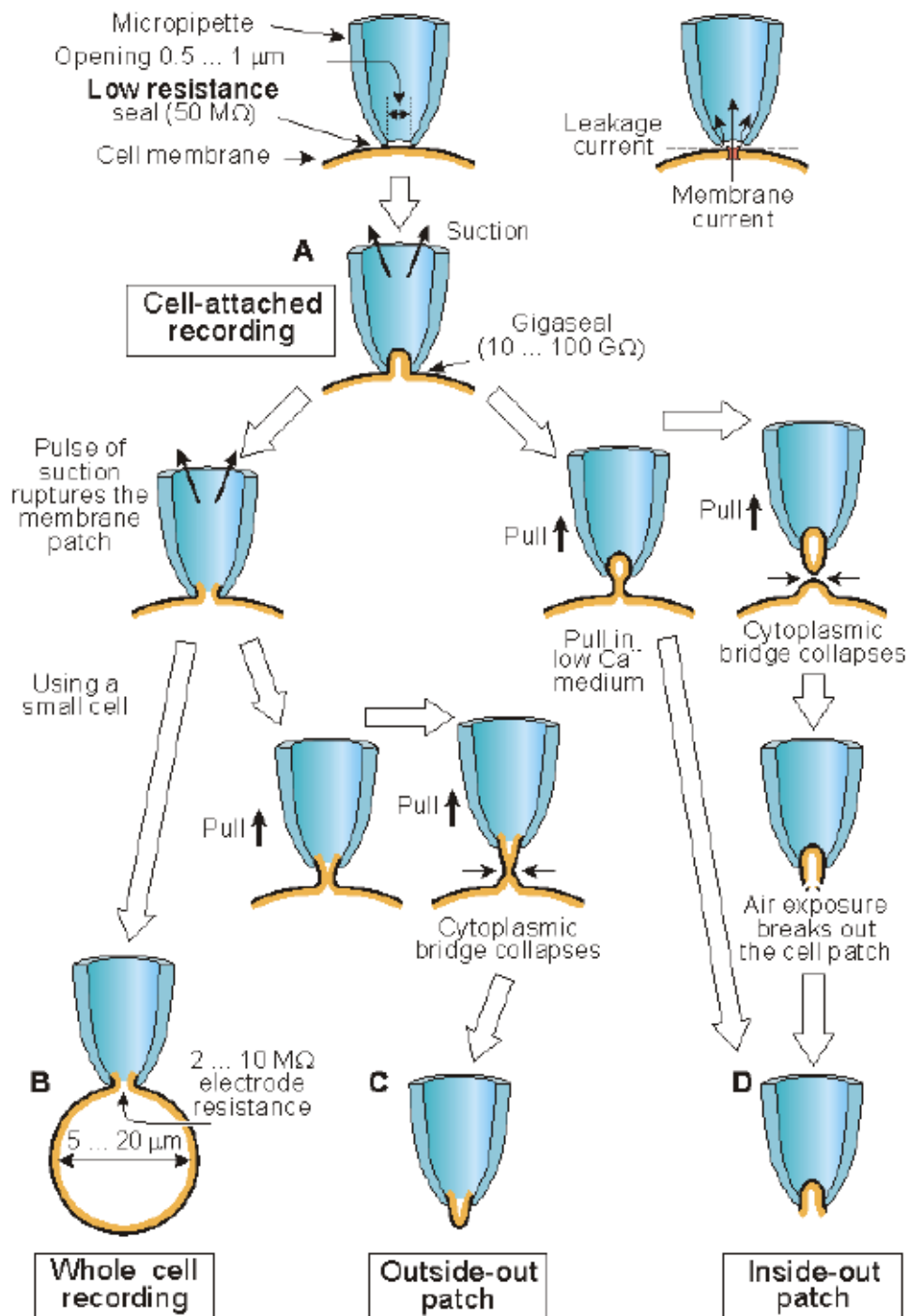
Tissue Properties: Assign electrical properties to the heart tissue based on experimental measurements. This includes the myocardium's conductivity values and the membrane properties of cardiac cells.

Electrophysiological Modeling: Implement the bidomain model, which describes the electrical activity in the heart tissue. This model considers both the intracellular and extracellular spaces and their interactions. For the cell membrane dynamics, use ion channel models like the Hodgkin-Huxley model, modified to represent ventricular myocytes.

Simulation of VT: Using the experimental data, set the initial conditions for the computational model. Simulate the electrical activity during VT, capturing the formation and propagation of reentrant circuits.

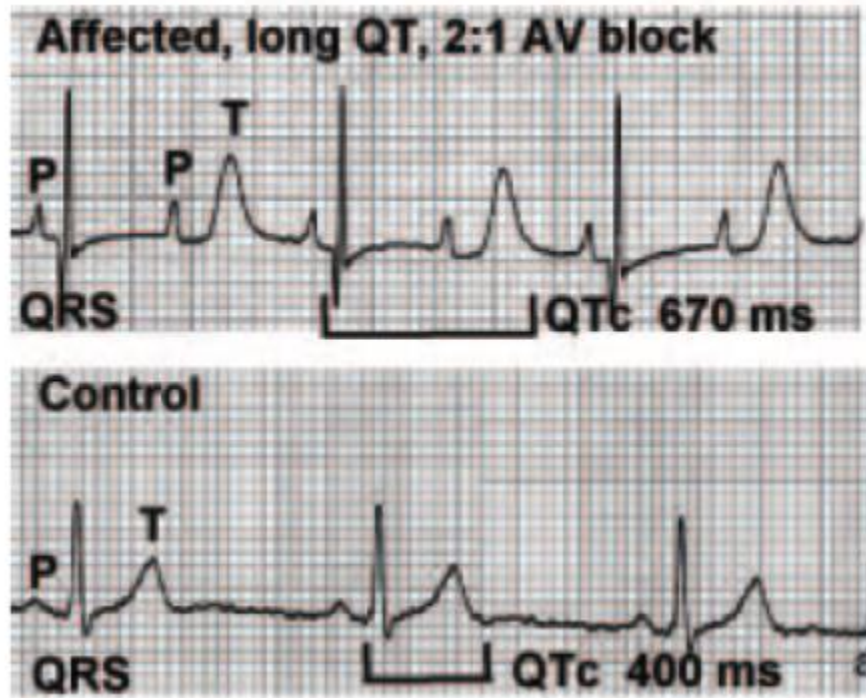
Forward Problem Solution: Given the cardiac sources (currents) from the VT simulation, solve the forward problem to predict the body surface potentials. This involves considering the conductive properties of various tissues (like the lungs, bones, and skin) and solving the bidomain equations throughout the torso.

Validation: Compare the predicted body surface potentials with actual measurements (from body surface potential mapping) to validate the computational model.



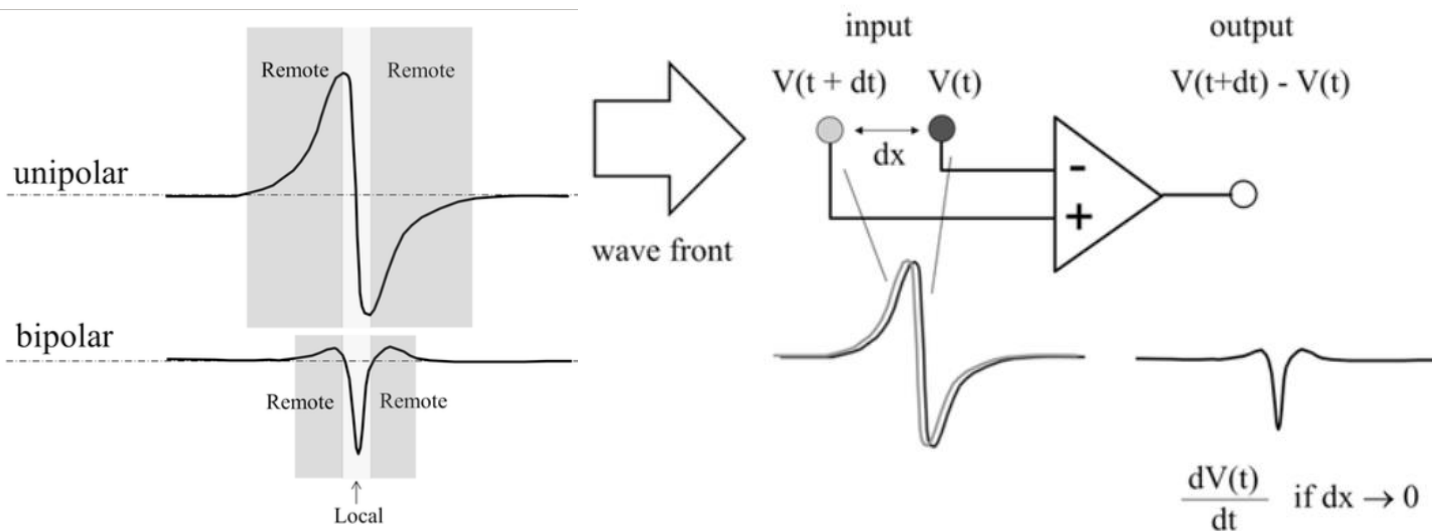
A normal QTc interval for:

- **Men:** Less than 430 milliseconds (ms)
- **Women:** Less than 450 ms



In this scenario, the T wave from the previous cardiac cycle might be closely followed by the P wave of the subsequent cycle, making them appear close together. However, it's crucial to recognize that the T wave is still associated with the preceding QRS complex and represents its ventricular repolarization.

So, in the context of certain AV blocks, you might observe patterns that look like P - T - P - QRS, but it's essential to interpret them correctly within the context of the block and the overall rhythm.



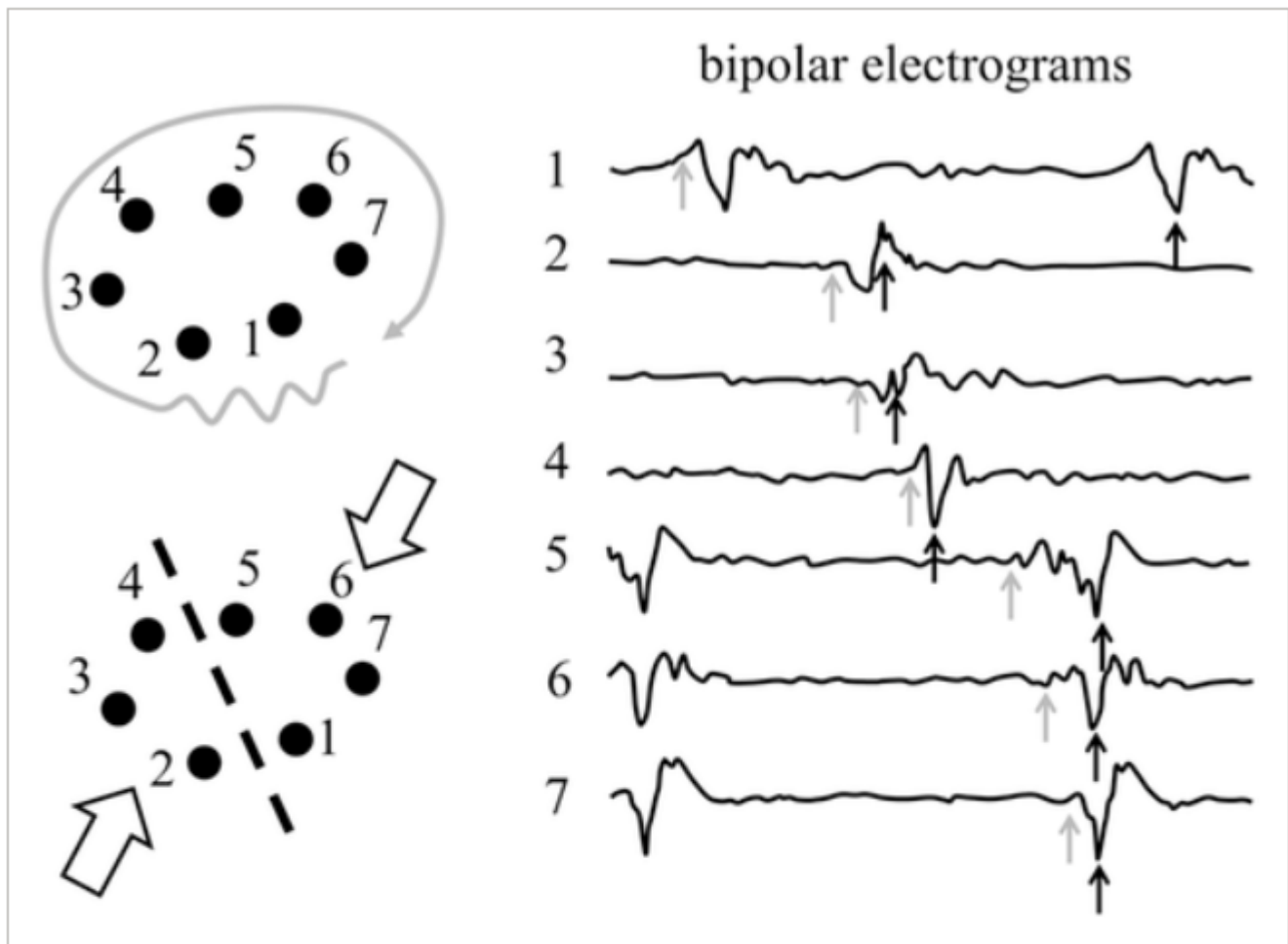


Figure 8

[Open in figure viewer](#)

[↓ PowerPoint](#)

Right panel: Bipolar electrograms recorded at seven sites during an atrial arrhythmia. The position of the electrodes is indicated by the black dots in the left panels. Gray arrows indicate “activation times” if the onset of the bipolar deflections is (erroneously) chosen as activation time. The corresponding activation pattern at the left suggests re-entrant activation (left upper panel). Black arrows indicate activation times if the largest positive or negative deflection is chosen as activation time. Now the activation map shows that recordings are made at a site where two activation fronts collide (left lower panel). Electrode size: 1 mm; inter-electrode distance: 4 mm; reference electrode: WCT; filter setting: 30-500 Hz

Macro-reentry: Seen in conditions like atrial flutter or ventricular tachycardia associated with scar tissue. The circuit can be several centimeters in diameter.

Steps in remodeling following MI

- **Necrosis of Myocytes:** The immediate result of an MI is the death of cardiac muscle cells in the affected area. As these cells die, they lose their structural integrity.
- **Inflammatory Response:** Following MI, there's an inflammatory response where immune cells infiltrate the damaged area. This inflammation can further disrupt the local architecture.
- **Fibrosis:** Over time, the necrotic tissue is replaced by fibrous scar tissue. This scar tissue does not have the same organized alignment of fibers as the original myocardium. Instead, it's non-contractile and can disrupt the normal orientation and continuity of adjacent, surviving cardiac fibers.
- **Ventricular Remodeling:** In the weeks to months following an MI, the entire heart, especially the left ventricle, can undergo structural changes, a process known as remodeling. This can involve dilation of the ventricle, thinning of the walls, and further disruption of the normal fiber architecture.

Formulation to Calculate Heart Functioning Properties:

- **Cardiac Output (CO):** It is the volume of blood pumped by the heart in one minute.

$$CO = HeartRate(HR) \times StrokeVolume(SV)$$

- **Stroke Volume (SV):** It is the volume of blood pumped by the heart with each beat.

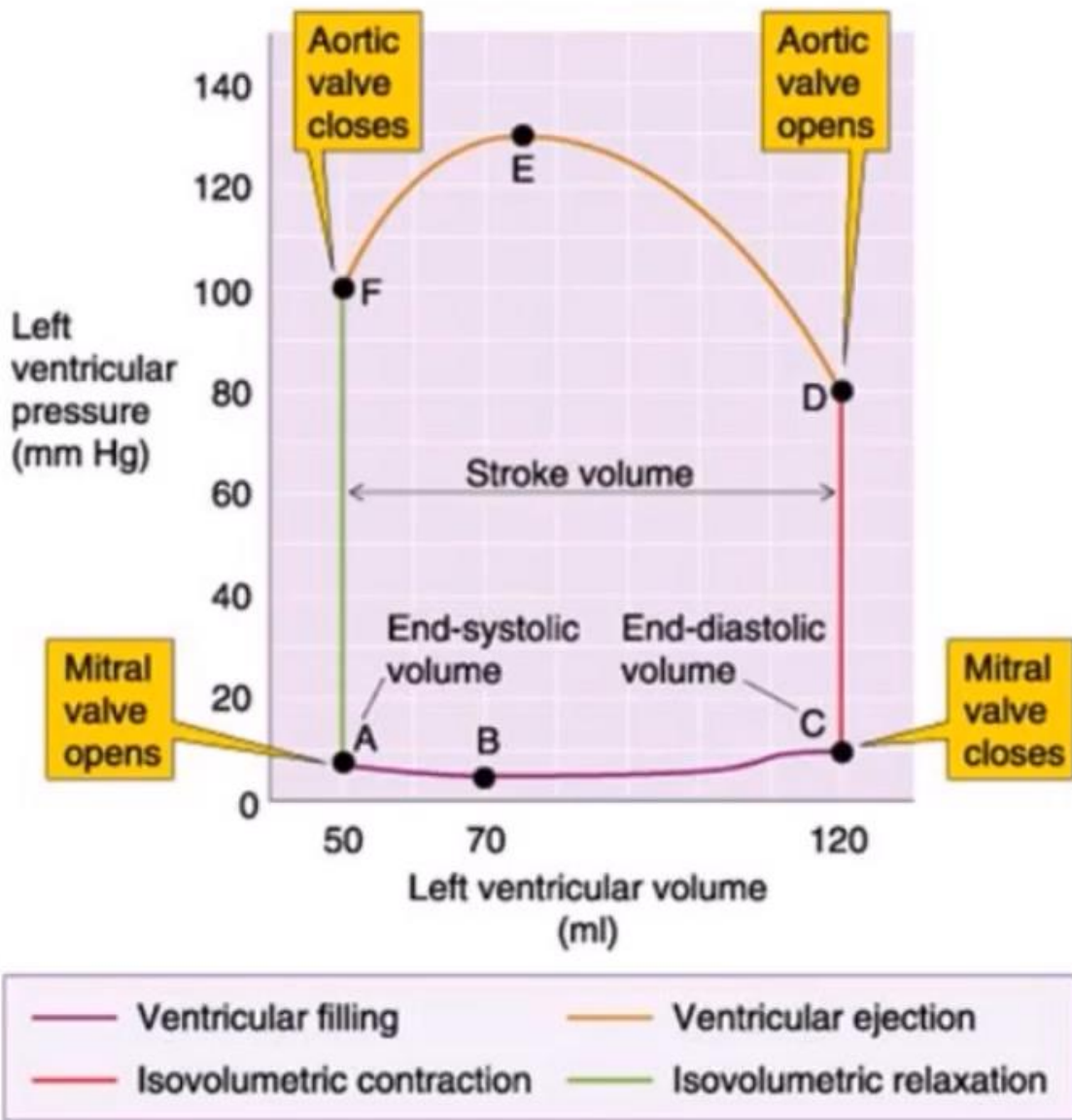
$$SV = EndDiastolicVolume(EDV) - EndSystolicVolume(ESV)$$

- **Ejection Fraction (EF):** It is the percentage of blood that's pumped out of a filled ventricle with each heartbeat.

$$EF = \left(\frac{SV}{EDV} \right) \times 100\%$$

or

$$EF = \left(\frac{EDV - ESV}{EDV} \right) \times 100\%$$



Boron, Walter & Boulpaep, Emile. *Medical Physiology 2nd Edition*

Effect of Positive Inotropes (e.g., Digoxin) on ESPVR and EDPVR:

- **Digoxin's Mechanism:** Digoxin inhibits the sodium-potassium ATPase pump. This leads to an increase in intracellular sodium, which in turn promotes calcium influx via the sodium-calcium exchanger. The increased intracellular calcium enhances myocardial contractility.
- **Effect on ESPVR:** Positive inotropes like digoxin increase the contractility of the heart. This is reflected in the PV loop as a steeper ESPVR (End-Systolic Pressure-Volume Relationship). A steeper ESPVR indicates a more forceful contraction for a given volume of blood in the ventricle.
- **Effect on EDPVR:** Digoxin doesn't have a direct effect on the passive filling properties of the ventricle, so it doesn't significantly alter the EDPVR (End-Diastolic Pressure-Volume Relationship). However, by improving contractility and potentially enhancing cardiac output, digoxin might indirectly influence diastolic function and ventricular filling in some patients.

3. Ryanodine Receptors on the SR:

Ryanodine receptors (RyRs) on the sarcoplasmic reticulum (SR) are primarily calcium-activated calcium release channels. This means that their primary mode of activation is through the binding of calcium, leading to a process called calcium-induced calcium release (CICR). However, phosphorylation of RyRs by protein kinases, such as PKA (which can be activated by beta-adrenergic stimulation), can modulate their sensitivity to calcium. When phosphorylated, RyRs become more sensitive to calcium, meaning they can open more readily in response to lower calcium concentrations. While phosphorylation enhances their sensitivity, the presence of calcium is still generally required for their activation.

1. Muscarinic Acetylcholine Receptors (M2 subtype):

- These receptors are activated by acetylcholine released from parasympathetic nerve endings.
- Activation of M2 receptors leads to the opening of potassium channels, causing an outward potassium current that hyperpolarizes the cell. This slows down the heart rate by decreasing the rate of spontaneous depolarization in pacemaker cells.
- M2 receptor activation also inhibits adenylate cyclase, reducing cAMP levels and opposing the effects of beta-adrenergic stimulation.

- **Physical Basis Lacking in CA:** Cellular automata are discrete, both in time and space, and they operate based on predefined rules. They lack continuous variables and differential equations that describe the detailed kinetics of molecular interactions or the biophysical properties of membranes and channels. As such, they might not capture the full complexity and continuous nature of biological systems.

3. Parameters in Cellular Automaton:

The specific parameters in a cellular automaton model depend on the system being modeled and the details of the model. For cardiac electrophysiology, parameters might include:

- **States:** Such as resting, excited, refractory.
- **Neighborhood:** Defines which adjacent cells influence a given cell's state. This could be immediate neighbors (von Neumann neighborhood) or include diagonally adjacent cells (Moore neighborhood).
- **Transition Rules:** Define how a cell's state will change based on its current state and the states of its neighbors.
- **Duration:** How long a cell remains in a particular state, such as the refractory period after excitation.
- **Excitability:** A parameter that might determine how easily a cell can be excited.
- **Conduction Velocity:** In models simulating wave propagation, this might define how quickly the excitation spreads.

Examples:

- In a cardiac CA model, a cell might transition from a resting to an excited state if one or more of its neighbors are excited.
- A cell might remain in the refractory state for a certain number of time steps after being excited before it can be excited again.

Req

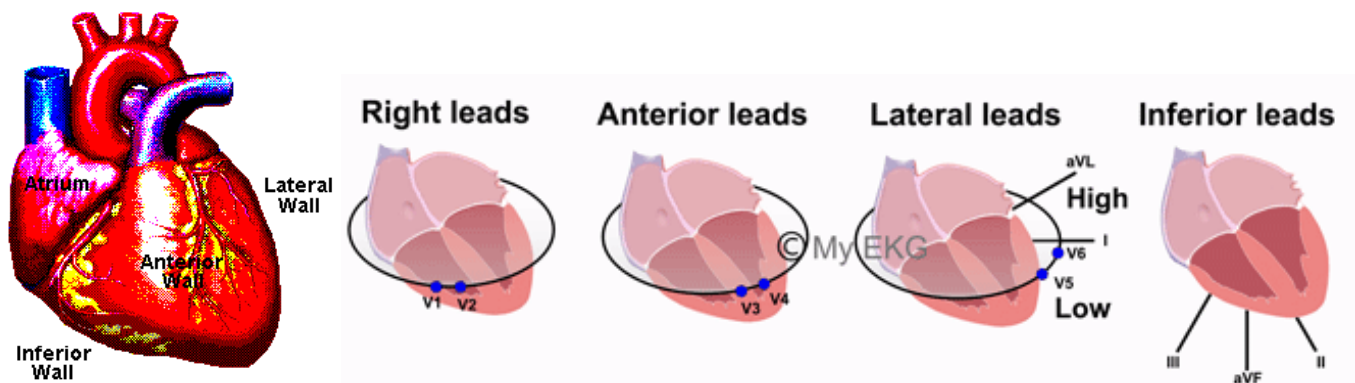
Further Detail on Activation of M2 Receptors Leading to Opening of Potassium Channels:

The M2 muscarinic receptor, when activated by acetylcholine, couples primarily to the inhibitory G-protein, G_i . The subsequent cascade is as follows:

- **Activation of G_i :** When acetylcholine binds to the M2 receptor, it causes a conformational change that activates the associated G_i protein.
- **Inhibition of Adenylate Cyclase:** The activated G_i protein has an alpha subunit ($G_{\alpha i}$) that inhibits adenylate cyclase, an enzyme responsible for converting ATP to cAMP.
- **Decrease in cAMP Levels:** With adenylate cyclase inhibited, the intracellular levels of cAMP decrease.
- **Activation of Muscarinic K^+ Channels:** The beta-gamma subunits ($G_{\beta\gamma}$) of the activated G_i protein directly activate certain potassium channels, known as muscarinic K^+ channels or $I_{K,ACh}$.
- **Outward K^+ Current:** The opening of these channels allows potassium ions to flow out of the cell, leading to hyperpolarization. This hyperpolarization slows the rate of spontaneous depolarization in pacemaker cells, thereby decreasing the heart rate.

3. **Using Monodomain/Bidomain Alone:** If you use the monodomain or bidomain model without a cellular model, you would need some other way to represent the generation and propagation of action potentials. This could be a very simplified representation, like a threshold-based mechanism. However, this would not capture the detailed ionic mechanisms underlying the cardiac action potential, and the results would be more phenomenological rather than biophysically accurate.
4. **Applications:** There might be scenarios where a detailed representation of the cellular action potential is not necessary, and a simplified approach is sufficient. For instance, if the primary interest is in the large-scale spatial patterns of excitation and not the underlying ionic mechanisms, a simplified approach might be used. However, for studies that require understanding arrhythmia mechanisms, drug effects, or other phenomena that depend on the intricate details of cellular electrophysiology, coupling with a detailed cellular model is crucial.

ACh to reduced I_f : Additionally, the beta-gamma subunits ($G\beta\gamma$) of the activated G_i protein can directly inhibit the HCN channels responsible for the funny current (I_f).



2. Transition Rates vs. Probabilities in Markov Models:

- **Transition Rates:** These are constants that describe the likelihood of transitioning from one state to another per unit time. They are not probabilities but rather define the rates at which transitions occur.
- **Probabilities:** These describe the likelihood of the system being in a particular state at a given time.
- **Effect on Rates:** Changing the opening rate (e.g., k_{ij}) does not necessarily affect the closing rate (e.g., k_{ji}). They are independent parameters, typically determined by experimental data.

3. Specificity in ECG Leads V6 and I:

Leads V6 and I both provide views of the lateral aspect of the heart, but their perspectives and sensitivities can differ:

- **Lead I:** Measures the electrical activity between the right and left arms, capturing the lateral wall but also influenced by other regions.
- **Lead V6:** Positioned closer to the left lateral wall, providing a more direct view of this region.

Examples of Specificity:

- **Ischemia or Infarction in the Lateral Wall:** Lead V6 might show **more pronounced ST-segment** changes compared to Lead I due to its closer proximity to the affected area.
- **Left Ventricular Hypertrophy (LVH):** Lead V6 might provide clearer evidence of LVH, such as increased R-wave amplitude, due to its orientation towards the left ventricle.

Detailed Mechanisms of Norepinephrine Increasing Heart Rate (HR) and Contractility:

Norepinephrine exerts its effects on cardiac cells primarily through the activation of β_1 -adrenergic receptors, which are G-protein coupled receptors. Here's how norepinephrine influences HR and contractility:

- **Heart Rate:**
 - Norepinephrine binds to β_1 -adrenergic receptors on pacemaker cells in the sinoatrial (SA) node.
 - This activates the stimulatory G-protein (Gs).
 - Gs activates adenylate cyclase, which increases the conversion of ATP to cyclic AMP (cAMP).
 - Elevated cAMP activates protein kinase A (PKA).
 - PKA phosphorylates and enhances the activity of Hyperpolarization-activated Cyclic Nucleotide-gated (HCN) channels, responsible for the funny current (I_f). This leads to a faster rate of spontaneous depolarization, increasing the heart rate.
- **Contractility:**
 - In ventricular cardiomyocytes, norepinephrine also binds to β_1 -adrenergic receptors.
 - The subsequent increase in cAMP and PKA activation leads to the phosphorylation of several targets:
 - **L-type Calcium Channels:** Their activity is enhanced, leading to increased calcium influx during the action potential's plateau phase.
 - **Ryanodine Receptors:** Phosphorylation of these receptors on the sarcoplasmic reticulum (SR) enhances calcium release from the SR.
 - **Troponin and Myosin Light Chain:** Phosphorylation of these proteins increases their sensitivity to calcium, enhancing contractility.
 - **Phospholamban:** PKA-mediated phosphorylation of phospholamban relieves its inhibition on the SR calcium ATPase (SERCA), leading to faster calcium reuptake into the SR and enhancing relaxation (lusitropy).

3. IC50 in Drug Testing:

IC50 stands for "Inhibitory Concentration 50%." It is a key parameter in pharmacology and represents the concentration of a drug or compound required to inhibit a biological process or biological response by 50%. In the context of drug testing:

- **Measurement:** IC50 is determined experimentally by measuring the effect of different concentrations of a drug on a specific biological response (e.g., enzyme activity, receptor binding, cell proliferation).
- **Interpretation:** A lower IC50 value indicates a higher potency of the drug, as a smaller concentration is needed to achieve 50% inhibition.
- **Applications:** IC50 values are widely used in drug development to compare the potencies of different compounds and to guide dose selection in therapeutic applications.

1. Initiators of Ventricular Tachycardia (VT) vs. Ventricular Fibrillation (Vfib):

• Ventricular Tachycardia (VT):

- **Locations:** VT can originate from any part of the ventricles but is commonly associated with the scar tissue from a previous myocardial infarction.
- **Causes:**
 - Myocardial infarction (heart attack) and its resulting scar tissue.
 - Cardiomyopathies (diseases of the heart muscle).
 - Electrolyte imbalances, especially potassium and magnesium.
 - Certain medications and drugs.
 - Genetic conditions like Long QT syndrome.
 - Structural heart diseases.

• Ventricular Fibrillation (Vfib):

- **Locations:** Vfib doesn't have a single point of origin. Instead, multiple wavefronts of electrical activity chaotically move throughout the ventricles.
- **Causes:**
 - Acute myocardial infarction.
 - Untreated VT can degenerate into Vfib.
 - Electrolyte imbalances.
 - Severe hypoxia (lack of oxygen).
 - Electric shock or trauma.
 - Certain medications and drugs.
 - Underlying heart diseases.

1. **Power Stroke, Inorganic Phosphate (Pi), and ADP:**

The power stroke is a critical phase in the cross-bridge cycle, where the myosin head pivots and pulls the actin filament toward the center of the sarcomere, resulting in muscle contraction.

- **Role of Inorganic Phosphate (Pi) Release:** After the myosin head binds to actin, the release of inorganic phosphate (Pi) from the myosin head triggers the power stroke. This release causes a conformational change in the myosin head, making it pivot and pull the actin filament.
- **Role of ADP Release:** Following the release of Pi and the power stroke, ADP is then released from the myosin head. The release of ADP prepares the myosin head to bind with a new ATP molecule, which will lead to the detachment of myosin from actin, resetting the myosin head for another cycle.

In summary, the release of Pi initiates the power stroke, and the subsequent release of ADP sets the stage for the detachment of the myosin head from actin upon ATP binding.

ATP Hydrolysis in the Absence of Calcium:

In the absence of calcium, the myosin head can still bind ATP and hydrolyze it to ADP and inorganic phosphate (Pi), transitioning to the high-energy or "cocked" state. However, without calcium, the actin-binding sites remain blocked by tropomyosin. This means the myosin head cannot bind to actin and execute the power stroke. As a result, ADP and Pi remain bound to the myosin head for a longer duration than they would if the power stroke occurred. Over time, these molecules might still dissociate from the myosin head, allowing another ATP molecule to bind. But without the actin-myosin interaction, this cycle would be less efficient and not coupled to muscle contraction.

3. Molecular Mechanisms of Sinus Bradycardia:

Sinus bradycardia refers to a slower-than-normal firing rate of the SA node. Several molecular and cellular mechanisms can underlie this condition:

- **Altered Ion Channel Function:** Changes in the function or expression of ion channels involved in the pacemaker potential, especially the HCN channels responsible for the "funny current" (I_f), can slow down the rate of spontaneous depolarization.
- **Autonomic Influence:** Increased vagal tone (parasympathetic stimulation) can slow the firing rate of the SA node. This is mediated by the release of acetylcholine, which activates muscarinic receptors, leading to increased potassium efflux and decreased calcium influx.
- **Metabolic or Structural Changes:** Conditions like hypoxia, ischemia, or degenerative changes in the SA node can affect its pacing ability.
- **Medications:** Some drugs, like beta-blockers or calcium channel blockers, can slow down the SA node firing rate.
- **Electrolyte Imbalances:** Abnormal levels of key electrolytes, like potassium or calcium, can impact the SA node's electrical activity.

2. Deducing Single Channel Properties Based on Current Steps:

The basic principle behind deducing single channel properties using patch-clamp techniques is observing the discrete current steps that represent the opening and closing of individual channels.

- **Current Steps:** When a channel opens, it allows ions to flow across the membrane, producing a measurable current. If you have a patch with a single channel and it opens, you'll observe a step in the current. If the channel closes, the current returns to baseline.

The size of the step corresponds to the conductance of the channel and the driving force (difference between the membrane potential and the ion's reversal potential).

- **Multiple Channels:** If there are multiple channels in a patch, you might observe multiple discrete current steps. For instance, if two identical channels open simultaneously, the current step will be twice the size of a single channel opening. If they open and close independently, you'll observe a variety of step sizes corresponding to different numbers of open channels.

4. Significance of PMCA in EC Coupling:

The plasma membrane calcium ATPase (PMCA) is responsible for pumping calcium out of the cell, helping to maintain low intracellular calcium concentrations. While PMCA plays a crucial role in overall calcium homeostasis, its contribution to rapid calcium removal during EC coupling in cardiac and skeletal muscle cells is less significant compared to the NCX and the sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA). SERCA pumps calcium back into the SR, and NCX expels calcium from the cell, both of which are vital for muscle relaxation. PMCA's role is more pronounced in other cell types and in fine-tuning intracellular calcium levels over longer periods.

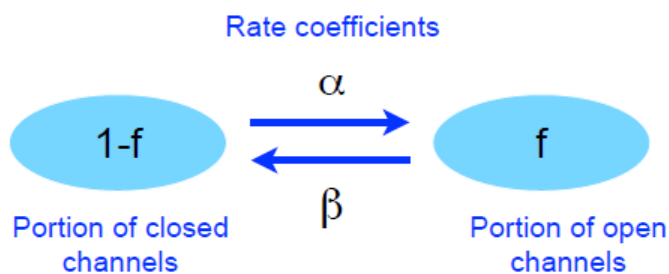
However, there are conditions and mechanisms other than calcium overload that can lead to muscle contraction in the absence of an arriving action potential:

Stretch-Activated Channels: Mechanical stretch can activate certain ion channels in the muscle membrane, leading to an influx of calcium and subsequent muscle contraction. This is particularly relevant in some types of smooth muscle.

Spontaneous Calcium Release: In certain pathological conditions, the ryanodine receptors (RyRs) on the SR can become leaky, leading to spontaneous calcium release and muscle contraction.

Pharmacological Agents: Some drugs can induce muscle contraction by directly increasing intracellular calcium levels or sensitizing the contractile proteins to calcium. For example, drugs like digoxin can increase intracellular calcium by inhibiting the sodium-potassium ATPase pump.

Store-Operated Calcium Entry (SOCE): In some cells, depletion of calcium stores in the SR can activate calcium channels in the plasma membrane, leading to calcium influx and muscle contraction.

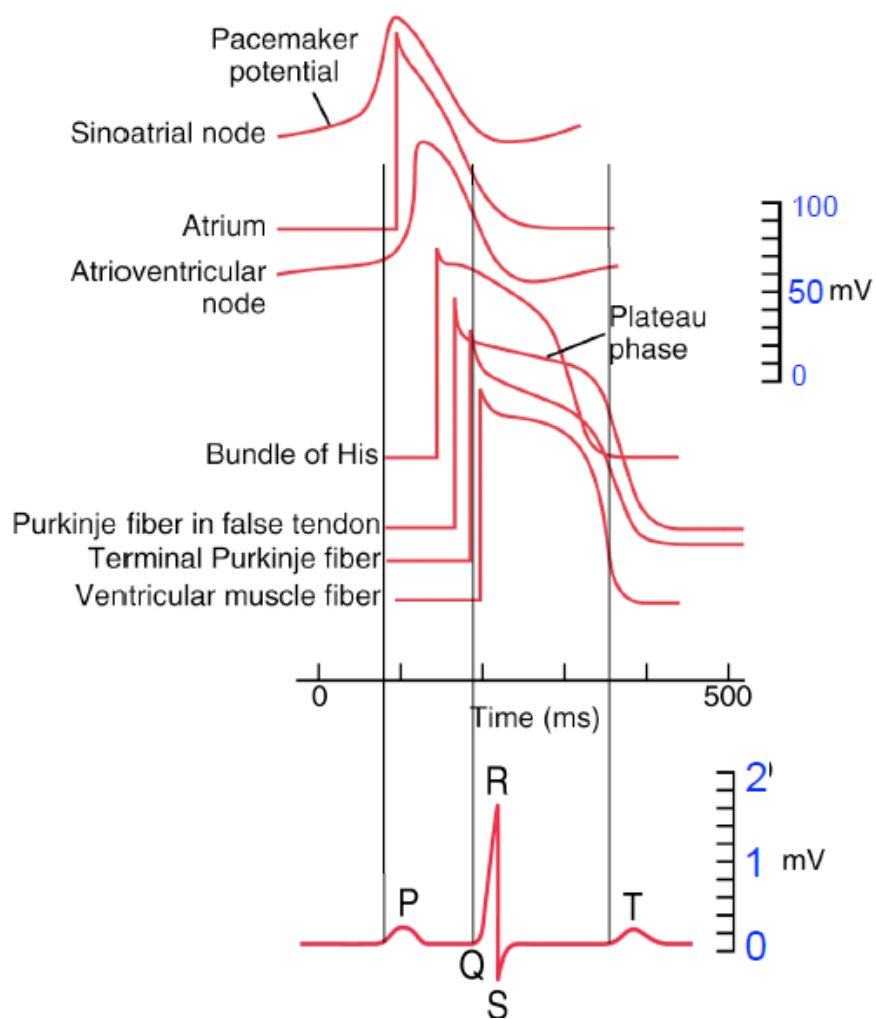


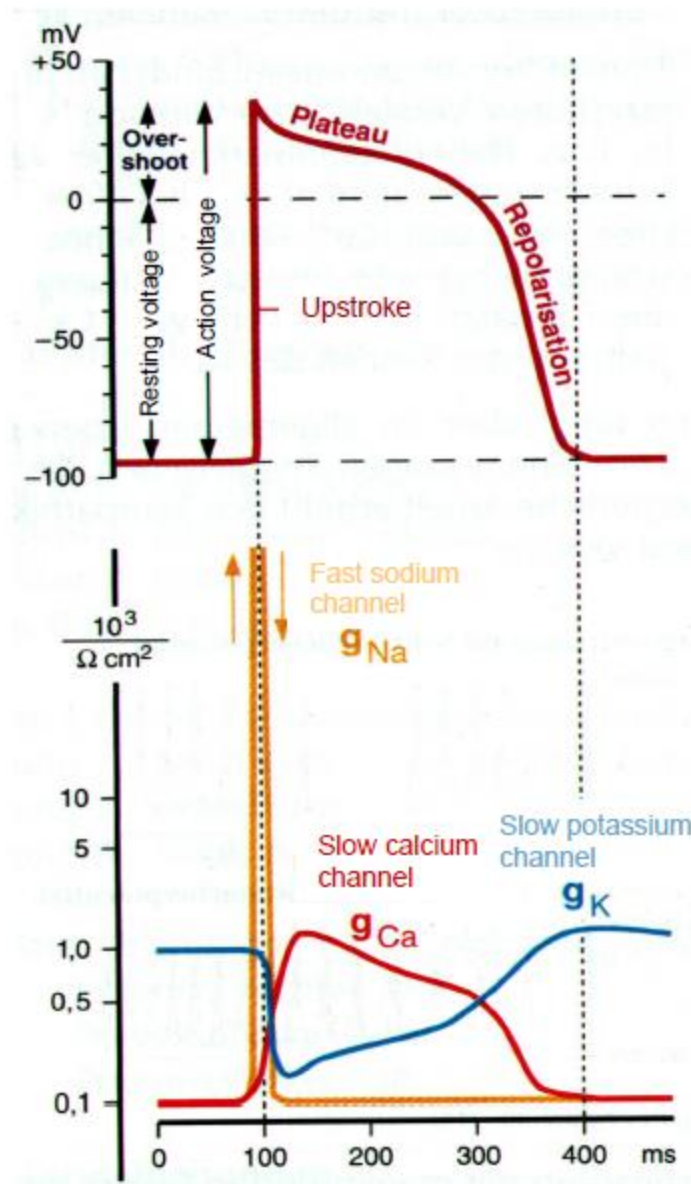
$$\frac{df}{dt} = \alpha_f(1 - f) - \beta_f f$$

f = Gating variable

$$\tau_m = \frac{1}{\alpha_m(V) + \beta_m(V)}$$

Multiscale: ECG





If I were responsible for the treatment of a patient with Short QT Syndrome (SQTS), a rare genetic disorder characterized by a shortened QT interval on the electrocardiogram (ECG) and an increased risk of sudden cardiac death, I would consider the following therapeutic strategies:

1. Drugs:

- **Quinidine:** This is an antiarrhythmic drug that has been shown to prolong the QT interval in some patients with SQTS. Quinidine blocks the rapid component of the **delayed rectifier potassium current (I_{Kr})** and can help in prolonging the action potential duration.

- **Pacemaker:** Continuously monitors the heart's rhythm and sends electrical pulses when needed to correct a slow rhythm.
- **Defibrillator:** Continuously monitors the heart's rhythm and only intervenes by delivering a shock or rapid pacing when it detects a dangerous arrhythmia.

1. KCNQ1 Mutations and I_{Ks} :

- Gain-of-function mutations in KCNQ1 can lead to an increased I_{Ks} current, which can shorten the action potential duration. A shortened APD can increase the risk of reentrant circuits, a primary mechanism underlying AFib.
- Loss-of-function mutations can lead to a decreased I_{Ks} current, prolonging the action potential duration. This can also predispose to arrhythmias, though the mechanisms might differ from those of a shortened APD.

2. **KCNH2 Mutations and I_{Kr} :**

- Gain-of-function mutations in KCNH2 can lead to an increased I_{Kr} current, which, like an increased I_{Ks} , can shorten the action potential duration and increase the risk of reentrant circuits.
- Loss-of-function mutations can decrease the I_{Kr} current, leading to a prolonged action potential duration. This can increase the risk of early afterdepolarizations (EADs), which can trigger arrhythmic events.

3. **Reentrant Circuits:**

- The atria are particularly susceptible to reentrant circuits due to their thin-walled structure and complex electrical properties. If the action potential duration is altered (either shortened or prolonged), it can create regions of the heart where electrical waves can reenter and circulate, leading to AFib.

4. **Triggered Activity:**

- Prolonged action potentials, especially due to reduced I_{Kr} , can lead to EADs. These are abnormal depolarizations during the action potential's plateau or repolarization phases. EADs can act as triggers for arrhythmic events, including AFib.

gap junction channels allow only very small molecules to pass through. Amino acids, water, simple sugars, and most intracellular signal molecules freely move through gap junction channels but larger molecules, such as proteins and fats, cannot.

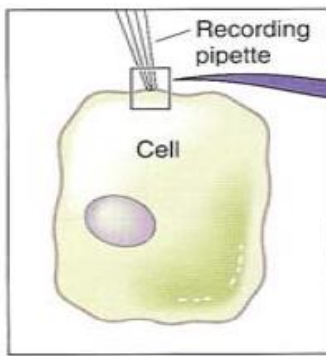
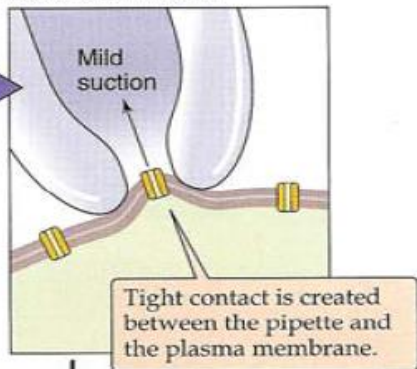
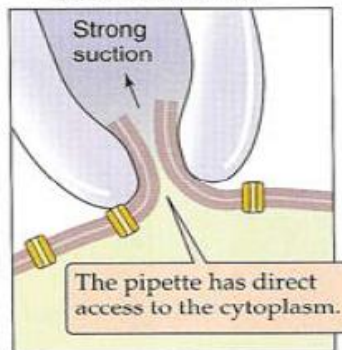
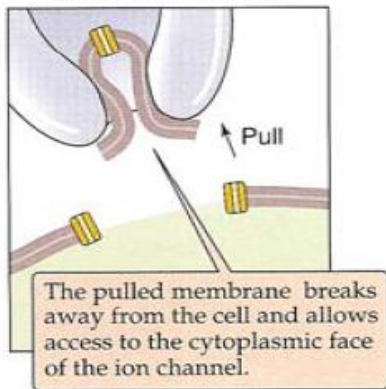
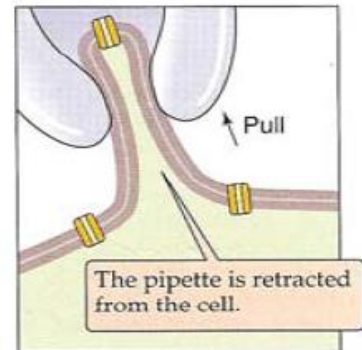
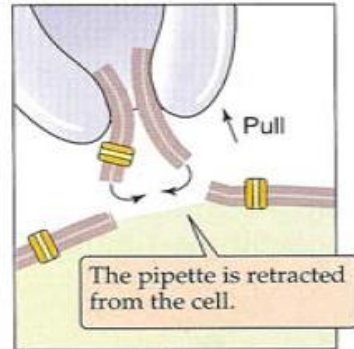
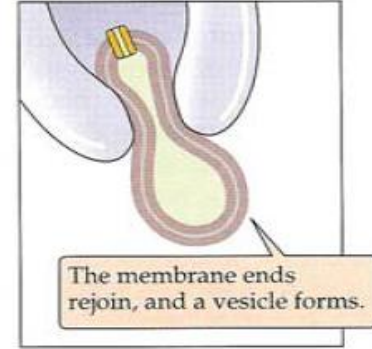
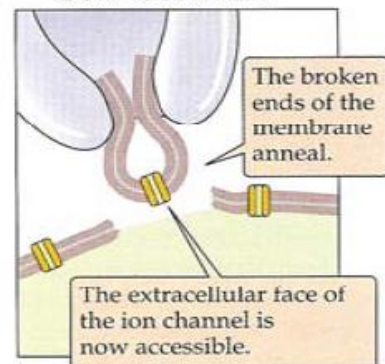
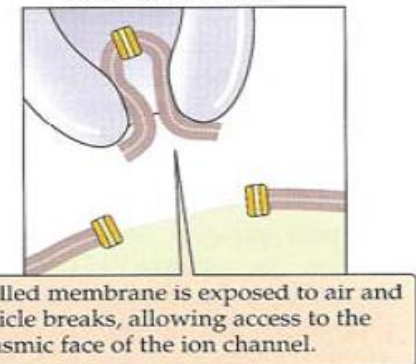
Electrically we evaluate gj or junction conductance

$$g_j = n * \gamma_j * P_o$$

n = number of channels (Insertion-removal)

γ_j = unitary conductance (Phosphorylation)

P_o = open probability (gating e.g. pH, PO_4)

A**CELL-ATTACHED CONFIGURATION****B WHOLE-CELL CONFIGURATION****E INSIDE-OUT CONFIGURATION****F****C****G****D OUTSIDE-OUT CONFIGURATION****H INSIDE-OUT CONFIGURATION**

1. Gating by Voltage:

- **Transjunctional Voltage (V_j):** This refers to the voltage difference across the gap junction channel, i.e., the difference in membrane potential between the two connected cells. Gap junction channels can be sensitive to V_j , and depending on the type of connexin, channels might close in response to either positive or negative V_j .
- **Transmembrane Voltage:** This refers to the voltage difference across an individual cell's plasma membrane. Some gap junction channels can respond to changes in the transmembrane voltage of one or both of the connected cells.

2. Gating by Intracellular pH:

- A decrease in intracellular pH (acidification) often leads to the closure of gap junction channels. This is thought to be a protective mechanism, preventing the spread of harmful conditions from one cell to its neighbors. For instance, during ischemic conditions, cells might experience acidification, and closing gap junctions can help contain the damage.

3. Gating by Protein Phosphorylation:

- The connexin proteins that make up gap junction channels can be phosphorylated by various kinases. Phosphorylation can influence the assembly, function, and degradation of gap junctions.
- Depending on the specific connexin and the site of phosphorylation, this post-translational modification can either enhance or inhibit channel function. For instance, phosphorylation of certain connexins can lead to channel closure, while dephosphorylation (by phosphatases) can lead to channel opening.
- Various signaling pathways and cellular conditions can regulate the phosphorylation state of connexins, thereby influencing gap junction communication.

Voltage-gated sodium (Na^+) and potassium (K^+) channels have distinct structural characteristics:

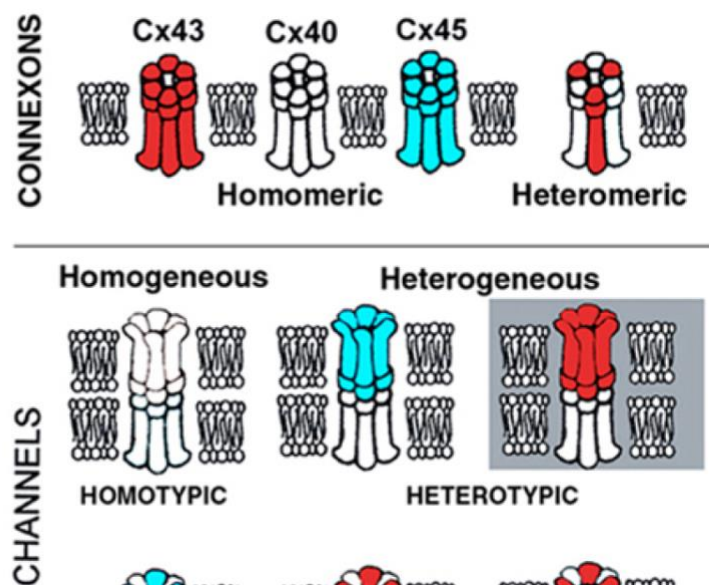
1. Voltage-Gated Potassium (K^+) Channels:

- **Tetrameric:** Yes, voltage-gated K^+ channels are **tetrameric**. They are composed of **four identical or similar subunits** that come together to form a functional channel.
- **Transmembrane Domains:** Each subunit of a voltage-gated K^+ channel has **six transmembrane domains (S1-S6)**. The S4 segment acts as the voltage sensor, while the region between S5 and S6 forms the pore of the channel.

2. Voltage-Gated Sodium (Na^+) Channels:

- **Tetrameric:** No, voltage-gated Na^+ channels are **not tetrameric**. Instead, they are composed of **a single polypeptide chain**.
- **Transmembrane Domains:** The single polypeptide chain of a voltage-gated Na^+ channel is organized into **four homologous domains (DI-DIV)**, each of which resembles a K^+ channel subunit. **Each of these domains has six transmembrane segments (S1-S6)**, making a total of **24 transmembrane domains** for the entire channel. As with K^+ channels, the S4 segment in each domain acts as the voltage sensor, and the regions between S5 and S6 form the pore.

Gap Junction Channels Multiple Configurations



The Nernst potential (or Nernst equation) describes the membrane potential at which the net flow of a specific ion (due to its concentration gradient) is exactly counterbalanced by the net flow of that ion due to the electrical gradient. At this potential, the ion is in electrochemical equilibrium, meaning there's no net movement of the ion across the membrane.

Let's break down your questions:

1. **Electrical Gradient:** The electrical gradient refers to the difference in electric potential across the cell membrane. This gradient drives the movement of charged ions across the membrane. If the inside of a cell is negatively charged relative to the outside, positively charged ions will tend to move into the cell, and negatively charged ions will tend to move out.
2. **Multiple Ions and the Electrical Gradient:** While the Nernst potential is specific to one ion, the actual membrane potential (or resting potential) of a cell is influenced by multiple ions, primarily sodium (Na^+), potassium (K^+), chloride (Cl^-), and calcium (Ca^{2+}). The Goldman-Hodgkin-Katz (GHK) equation takes into account the contributions of multiple permeable ions to determine the overall membrane potential.

3. **Nernst Equation and Electrical Properties:** The Nernst equation is:

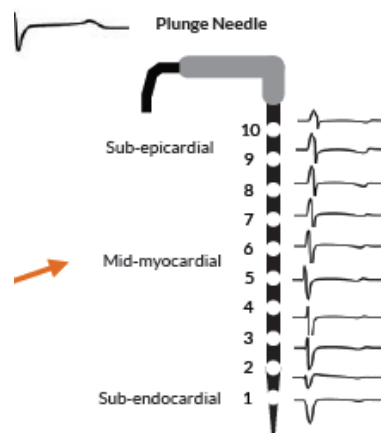
$$E_{ion} = \frac{RT}{zF} \ln \left(\frac{[ion]_{outside}}{[ion]_{inside}} \right)$$

Where:

- E_{ion} is the Nernst potential for the ion.
- R is the universal gas constant.
- T is the absolute temperature.
- z is the valence of the ion.
- F is Faraday's constant.
- $[ion]_{outside}$ and $[ion]_{inside}$ are the concentrations of the ion outside and inside the cell, respectively.

The electrical properties are inherently present in the equation. The term $\frac{RT}{zF}$ represents the voltage required to counterbalance the concentration gradient for an ion with a valence of z . The logarithmic term represents the concentration gradient of the ion. When you combine these, you get the potential at which the electrical and chemical forces on the ion balance out.

In summary, while the Nernst potential is specific to one ion, the overall membrane potential is influenced by multiple ions. The Nernst equation inherently includes both the chemical (concentration) and electrical (voltage) gradients for a specific ion, describing the potential at which they balance for that ion.



Finite element forward modeling

To represent the relationship between brain sources and bioelectric fields, we made use of the standard approaches to simulation based on the quasistatic Maxwell equations. These lead to an expression of Poisson's equation (Sarvas, 1987)

$$\nabla \cdot (\sigma \nabla \Phi) = -\nabla \cdot \mathbf{j}^p \text{ in } \Omega, \quad (4)$$

in which $\mathbf{j}^p$ is the primary or impressed current, Φ is the scalar potential and Ω is the head domain. Homogeneous Neumann conditions apply on the head surface $\Gamma = \partial\Omega$,

$$(\sigma \nabla \Phi \cdot \mathbf{n})|_{\Gamma} = 0, \quad (5)$$

Cardiac mapping consideration: sampling density (number of data points/electrodes used within a given area/volume), surface/volume coverage, temporal resolution (frequency at which data is sampled over time)

1. Voltage Mapping:

- **What it Maps:** Voltage mapping captures the amplitude of electrical signals in the heart. It provides a snapshot of the electrical activity at a specific point in time, often during a specific phase of the cardiac cycle (e.g., during atrial or ventricular diastole).
- **Type of Potential Measured:** Voltage mapping measures **extracellular potentials**. These potentials represent the summed activity of many cells and can give insights into tissue health. For instance, areas of low voltage might indicate scarred or non-viable tissue, which is especially relevant in conditions like post-myocardial infarction or in the context of arrhythmias like atrial fibrillation.

2. Activation Mapping:

- **What it Maps:** Activation mapping visualizes the sequence of cardiac activation. It shows how the electrical impulse propagates through the heart tissue, allowing clinicians to determine the origin and pathway of an arrhythmia.
- **Type of Potential Measured:** Activation mapping also measures **extracellular potentials**. The timing of the steepest negative slope of these potentials (often referred to as the $dV/dt \text{ min}$) is used to determine the local activation time. By mapping these activation times across the heart, clinicians can visualize the sequence of activation and identify abnormal pathways or origins of arrhythmias.

The timing of the steepest negative slope of the extracellular potentials (often referred to as the $dV/dt \text{ min}$) is used to determine the local activation time in cardiac tissue for several reasons:

1. **Representation of Depolarization:** The steepest negative slope of the extracellular potential corresponds to the rapid depolarization phase of the underlying cardiac cells. When a cell depolarizes, the inside of the cell becomes more positive. This rapid change in the intracellular potential causes a corresponding rapid negative deflection in the extracellular potential. Thus, the $dV/dt \text{ min}$ in the extracellular potential reflects the moment when the majority of cells in the vicinity of the recording electrode are undergoing depolarization.

The distinction between using the minimum voltage (min V) and the steepest negative slope (dV/dt min) in cardiac mapping is rooted in the nature of what each parameter represents and the information it provides about cardiac activation:

Dynamic vs. Static Information:

- **dV/dt min** provides dynamic information about the rate of change of the voltage. It represents the moment of the fastest depolarization of the cardiac tissue, which is directly related to the influx of sodium ions during the action potential's upstroke. This rapid change in voltage is a clear indicator of the tissue's activation time.
- **min V** is a static value, representing the lowest voltage reached during the cardiac cycle. While it does provide information about the tissue's electrical state, it doesn't directly convey the speed or timing of activation.

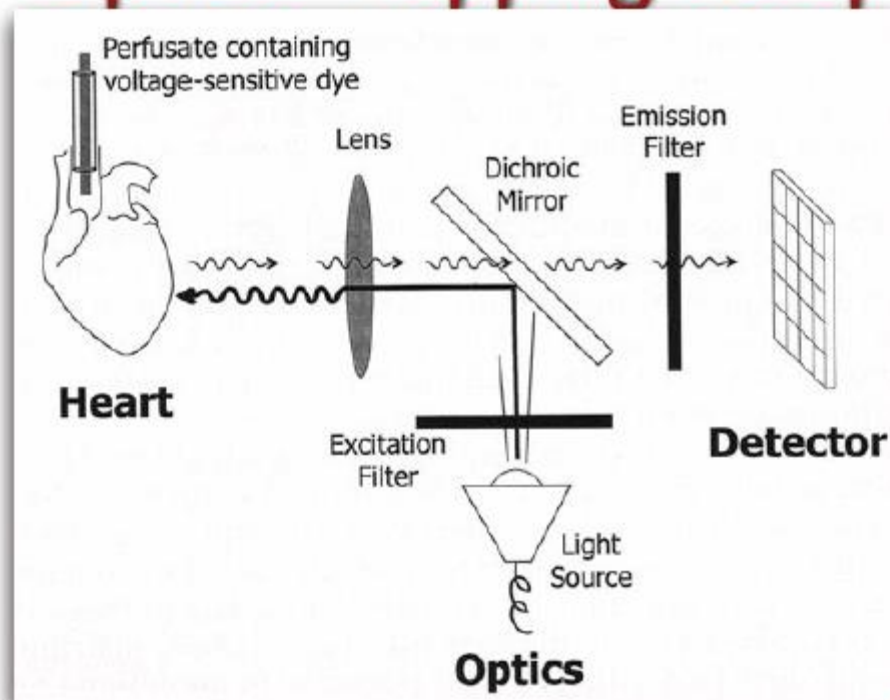
Clarity and Consistency:

- The steepest negative slope (dV/dt min) is a distinct and sharp feature in the extracellular electrogram, making it easier to identify consistently across different regions of the heart.
- The minimum voltage (min V) might vary more significantly based on factors like tissue health, scar presence, or electrode-tissue contact. This variability can make it less reliable as a universal marker for activation timing.

Temporal Precision:

- Using dV/dt min provides a precise temporal marker for the onset of tissue activation. It captures the exact moment when the tissue is undergoing rapid depolarization.
- Relying on min V might not provide the same level of temporal precision, as the voltage could remain at or near its minimum value for a more extended period.

Optical Mapping Setup



The recovery phase of a cardiac action potential is associated with repolarization, during which the cell returns to its resting membrane potential after depolarization. The maximum rate of change of voltage with respect to time ($\max dV/dt$) during this phase is indicative of the rapid repolarization process. Here's why:

1. **Ionic Currents:** During the repolarization phase, potassium ions (K^+) flow out of the cell, leading to a rapid decrease in the intracellular positive charge. This outward flow of positive ions results in the cell's return to its resting membrane potential. The $\max dV/dt$ during this phase represents the peak rate of this repolarization process.
2. **ECG Representation:** On an ECG, the repolarization of the ventricles is represented by the T wave. The peak of the T wave, which is the most prominent point of the wave, corresponds to the maximum rate of repolarization (or $\max dV/dt$) of the ventricular myocardium. Similarly, the repolarization of the atria is represented by the less prominent U wave, which follows the T wave, but it's often not visible on a standard ECG due to its smaller amplitude and its temporal overlap with ventricular depolarization.
3. **Clinical Relevance:** Changes in the T wave, such as its inversion, flattening, or changes in its symmetry, can be indicative of various cardiac conditions, including ischemia, electrolyte imbalances, or specific syndromes like the long QT syndrome. The morphology and timing of the T wave, and by extension the $\max dV/dt$ of repolarization, provide valuable information about the repolarization process and the overall electrical health of the heart.

In summary, the $\max dV/dt$ during the recovery phase is associated with the rapid repolarization process of the cardiac cells, and this is typically represented by the peak of the T wave on an ECG.

Delayed afterdepolarizations (DADs) are abnormal depolarizations that occur after the completion of the action potential and during the phase of diastolic repolarization. They can lead to triggered activity and arrhythmias, especially in conditions of intracellular calcium overload. Here's the molecular mechanism underlying DADs:

- 1. **Calcium Overload:** The primary mechanism responsible for DADs is intracellular calcium overload. This can occur due to various reasons, such as sympathetic stimulation, digitalis toxicity, or other conditions that increase intracellular calcium.
- 2. **Calcium Release from the Sarcoplasmic Reticulum (SR):** In a cell with calcium overload, spontaneous and uncontrolled release of calcium ions can occur from the SR, the primary intracellular calcium storage site. This release is mediated by the ryanodine receptor (RyR).
- 3. **Activation of the Sodium-Calcium Exchanger (NCX):** To restore calcium homeostasis, the cell tries to extrude the excess intracellular calcium. One of the primary mechanisms to achieve this is through the NCX, which operates in the "reverse mode" during this situation. For every calcium ion it extrudes out of the cell, the NCX allows three sodium ions to enter. This net inward current (due to more positive charges entering than leaving) can depolarize the cell membrane.
- 4. **Threshold Potential:** If this depolarizing current is sufficient to bring the membrane potential to the threshold level, it can trigger a new action potential, leading to a premature ventricular contraction (PVC) or other arrhythmias.
- 5. **Role of Other Channels:** While the NCX plays a central role in the genesis of DADs, other ion channels, like the L-type calcium channel or various potassium channels, can modulate the propensity for DADs to occur.
- 6. **Conditions Favoring DADs:** Several conditions can predispose to DADs by promoting calcium overload. These include:
 - Sympathetic stimulation, which increases the activity of the L-type calcium channel.
 - Digitalis toxicity, which inhibits the sodium-potassium ATPase, leading to intracellular calcium accumulation.
 - Heart failure, where altered calcium handling and increased sympathetic activity can promote DADs.
 - Certain genetic mutations affecting calcium handling proteins.



Reentry is a mechanism of arrhythmia where an electrical impulse continuously travels in a circular pathway, reactivating a region of the heart after a premature beat or other initiating event. This can lead to tachycardias. Let's break down how each of the mentioned factors can contribute to reentry:

1. Arrhythmogenic Factors:

- **Slow Conduction Velocity:** Slow conduction can create a situation where one part of the heart is still refractory (i.e., it cannot be reactivated by a new impulse) while an adjacent part has recovered and can be reactivated. This disparity can set the stage for a reentrant circuit, especially if a premature beat occurs.
- **Short Refractory Period:** A short refractory period means that cardiac cells can be reactivated sooner after an action potential. If one pathway has a shorter refractory period than an adjacent pathway, it can facilitate the establishment of a reentrant circuit.
- **Long, Looping Pathway:** A long, looping pathway provides the physical substrate for a reentrant circuit. The impulse can travel down one path and loop back to its origin, continuously reactivating the tissue.

2. Initiation:

- **Premature Beat (Extrasystole):** A premature beat can "test" the conditions set by the arrhythmogenic factors. If, for example, one pathway is still refractory due to slow conduction, but an adjacent pathway has recovered due to a short refractory period, **the premature beat can travel down** the recovered pathway and loop back to reenter the initially refractory pathway once it has recovered. This can establish a reentrant circuit.
- **Unidirectional Block:** This is a situation where an impulse can travel down one pathway but is blocked from traveling back up an adjacent pathway. If a premature beat or another impulse comes down the unblocked pathway, it can loop back up the initially blocked pathway if it has since recovered. This can establish a reentrant circuit.

Early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs) are specific types of abnormal electrical events that can lead to extrasystoles:

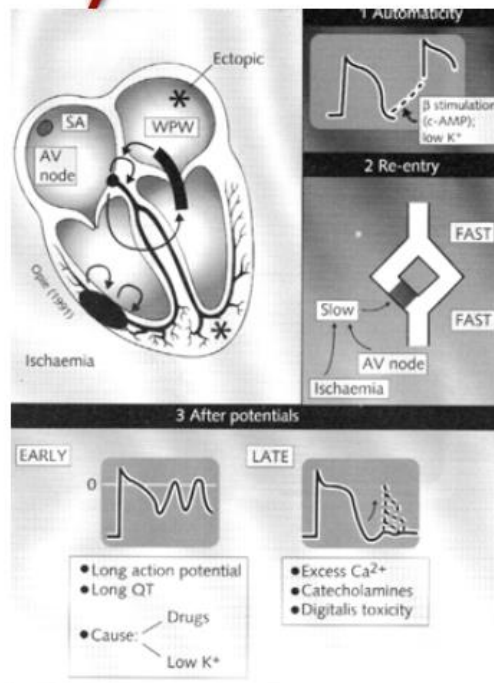
1. **Early Afterdepolarizations (EADs):** These are abnormal depolarizations that occur during phase 2 or phase 3 of the action potential, before the cell has fully repolarized. EADs can lead to premature ventricular contractions (PVCs) or premature atrial contractions (PACs), depending on where they occur. EADs are often associated with long QT syndromes and can be provoked by drugs that prolong the QT interval.
2. **Delayed Afterdepolarizations (DADs):** These are abnormal depolarizations that occur after the completion of the action potential, during phase 4 (the resting phase). DADs are often associated with conditions that increase intracellular calcium, such as digitalis toxicity or catecholaminergic polymorphic ventricular tachycardia (CPVT). DADs can also lead to extrasystoles like PVCs or PACs.

In summary, both EADs and DADs can lead to extrasystoles, but they occur at different times relative to the cardiac action potential and have different underlying mechanisms.

- 1, Automaticity
- 2, Reentry
- 3, After potential

Clinical Arrhythmias

- Mechanisms
 - automaticity
 - reentry
- Substrate
 - necrotic tissue
 - unidirectional block
 - accessory pathway
- Stimulus
 - extrasystoles
 - afterdepolarizations



Class III antiarrhythmic drugs primarily act by prolonging the duration of the action potential, specifically by blocking the rapid component of the delayed rectifier potassium current (I_{Kr}) during phase 3 of the cardiac action potential. By doing so, they extend the repolarization phase, leading to a prolonged QT interval on the ECG.

Regarding heart rate:

Class III antiarrhythmic drugs do not primarily affect heart rate (i.e., they don't have a direct chronotropic effect). Their main action is on the duration of the action potential and the refractory period. However, by prolonging the action potential duration and the refractory period, they can indirectly influence the heart rate, especially in the setting of reentrant arrhythmias. By prolonging the refractory period, these drugs can prevent reentrant circuits from sustaining tachyarrhythmias, effectively reducing the heart rate in the context of those arrhythmias.

It's important to note that while Class III agents prolong the action potential duration, they don't significantly affect phases 0 (rapid depolarization) or phase 4 (resting potential) of the action potential, which are more directly related to heart rate. Drugs that affect phase 4, like Class II (beta-blockers) or Class IV (calcium channel blockers), have a more direct effect on heart rate.

2. **Pacemaker Current (I_f or "funny" current) Unaffected:** The primary mechanism responsible for the spontaneous depolarization in phase 4 of pacemaker cells is the "funny" current (I_f). Class III drugs do not directly target this current, so the primary pacemaking activity remains largely unaffected.

4. **Potential for AV Block:** By prolonging the refractory period in the AV node, Class III drugs can slow conduction through the node. This can lead to a first-degree AV block (prolonged PR interval on ECG) or even higher degrees of block in susceptible individuals or when used in combination with other drugs that affect AV nodal conduction.

Antiarrhythmic Drugs: Na-channel Blockers

Sodium channel blockers

[Disopyramide](#)
[Flecainide](#)
[Lidocaine](#)
[Mexiletine](#)
[Procainamide](#)
[Propafenone](#)
[Quinidine](#)

Arrhythmias (which can be fatal, particularly in people who have a heart disorder)
For some drugs:
Digestive upset
Dizziness
Dry mouth
Light-headedness
Retention of urine
Tremor
In people with glaucoma, increased pressure in the eyes

These drugs slow the conduction of electrical impulses through the heart. These drugs are used to treat ventricular premature beats, ventricular tachycardia, and ventricular fibrillation and to convert atrial fibrillation or atrial flutter to normal rhythm (cardioversion). Except for lidocaine and mexiletine, these drugs may also be used to prevent episodes of atrial fibrillation or atrial flutter and, less commonly, paroxysmal supraventricular tachycardia.

Antiarrhythmic Drugs: Categories

- **Class I, sodium channel blockers:** These drugs prevent sodium from getting through cell membranes. This can slow electrical impulses in the heart muscle. Examples include disopyramide, flecainide, mexiletine, propafenone and quinidine.
- **Class II, beta blockers:** These drugs slow down the heart rate, often by blocking hormones such as adrenaline. Examples include acebutolol, atenolol, bisoprolol, metoprolol, nadolol and propranolol.
- **Class III, potassium channel blockers:** These drugs prevent potassium from getting through cell membranes. This can slow down electrical impulses in all of the heart's cells. Examples include amiodarone, bretylium, dofetilide, dronedarone, ibutilide and sotalol.
- **Class IV, nondihydropyridine calcium channel blockers:** These drugs block calcium channels in heart muscle. This can decrease heart rate and contractions. Examples include diltiazem and verapamil.

Other antiarrhythmic drugs not included in the VW classification system include:

- **Adenosine:** This medication can block or slow down electrical impulses at the atrioventricular node, between the upper and lower chambers of the heart.
- **Digoxin:** This drug can slow the heart rate and increase contractility of the heart.

Antiarrhythmic Drugs: Beta Blockers

Examples	Some Side Effects	Comments
Beta-blockers		
Acebutolol Atenolol Betaxolol Bisoprolol Carvedilol Esmolol Metoprolol Nadolol Propranolol	An abnormally slow heart rate (bradycardia) Fatigue Depression Possible masking of low blood sugar levels Impaired circulation in the trunk, arms, and legs Insomnia Raynaud syndrome Sexual dysfunction Shortness of breath Swelling of the lower extremities	These drugs are used to treat ventricular premature beats , ventricular tachycardia , ventricular fibrillation , and paroxysmal supraventricular tachycardia . They are also used to slow the ventricular rate (how fast the heart's lower chambers—the ventricles—beat) in people with atrial fibrillation or atrial flutter . People who have asthma should ask their doctor before taking these drugs.

- **Adenosine:** This medication can block or slow down electrical impulses at the atrioventricular node, between the upper and lower chambers of the heart.
- **Digoxin:** This drug can slow the heart rate and increase contractility of the heart.

Digoxin is a cardiac glycoside derived from the foxglove plant (*Digitalis purpurea*). It has been used for centuries to treat heart conditions, particularly heart failure and atrial arrhythmias. One of its notable effects is the ability to slow the heart rate. Here's how digoxin achieves this:

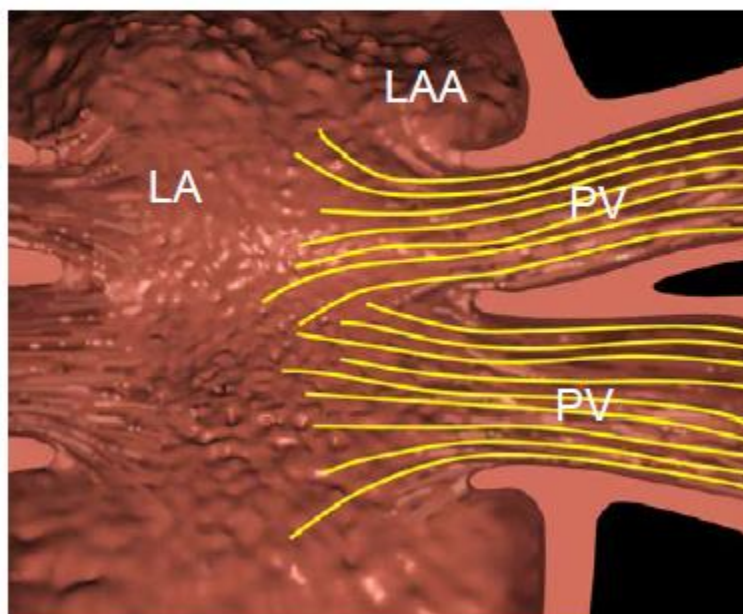
1. **Inhibition of the Sodium-Potassium ATPase Pump:** The primary mechanism of action of digoxin is the inhibition of the sodium-potassium ATPase pump located on the cell membrane of cardiac myocytes. By inhibiting this pump, digoxin increases the intracellular concentration of sodium.
2. **Secondary Increase in Intracellular Calcium:** The increased intracellular sodium concentration indirectly leads to an increase in intracellular calcium. This is because the sodium-calcium exchanger, which usually exports one calcium ion in exchange for three sodium ions, becomes less efficient when intracellular sodium is high. As a result, more calcium remains inside the cell.
3. **Enhanced Contractility:** The increased intracellular calcium concentration enhances the contractility of the cardiac muscle, a phenomenon known as a positive inotropic effect. This is beneficial in heart failure, where the pumping function of the heart is compromised.
4. **Effects on the AV Node:** Digoxin has a direct effect on the atrioventricular (AV) node. It increases the vagal (parasympathetic) tone and decreases sympathetic activity on the AV node. This leads to a reduction in the conduction velocity through the AV node and an increase in the refractory period of the AV node.
5. **Slowing of the Heart Rate:** Due to its effects on the AV node, digoxin slows down the heart rate, especially in conditions like atrial fibrillation or atrial flutter, where rapid conduction through the AV node can lead to a fast ventricular response. By slowing down AV nodal conduction, digoxin can help control the ventricular rate in these arrhythmias.

The phrase "AF begets AF" is a commonly used axiom in cardiology to describe the phenomenon where the presence and persistence of atrial fibrillation (AF) can lead to structural and electrical changes in the atria that make the heart more susceptible to further episodes of AF. In other words, the longer a person has AF, the more likely they are to have recurrent and longer-lasting episodes of AF. This concept underscores the importance of early detection and treatment of AF to prevent its progression.

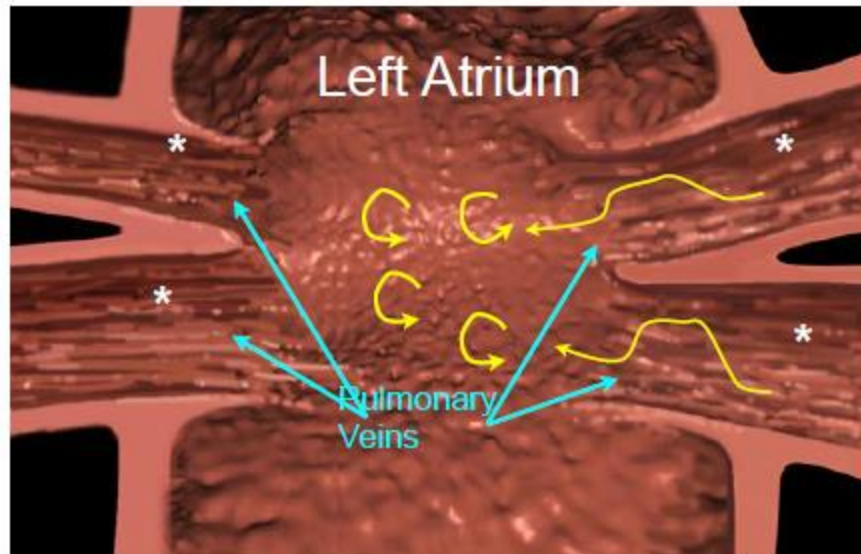
Here's a breakdown of how "AF begets AF" works:

1. **Electrical Remodeling:** Soon after the onset of AF, rapid and irregular electrical impulses in the atria lead to changes in the atrial tissue's electrical properties. This can result in shorter and more variable refractory periods (the time during which cardiac cells cannot be re-excited after an initial impulse). These changes can make it easier for AF to persist.
2. **Structural Remodeling:** Over time, persistent AF can lead to structural changes in the atria. This includes atrial enlargement, fibrosis (scarring), and changes in the atrial architecture. These structural changes can create an environment that is more conducive to the maintenance and recurrence of AF.
3. **Loss of Atrial Contractile Function:** Over time, the atria may lose their ability to contract effectively, leading to "atrial stunning." This can result in reduced atrial function even after sinus rhythm is restored.
4. **Increased Risk of Stroke:** The irregular and often rapid contractions in AF can lead to blood stasis in the atria, particularly in the left atrial appendage. This can result in clot formation, which can travel to the brain and cause a stroke.
5. **Progression of AF:** Initially, AF episodes might be **paroxysmal (self-terminating)** and last for a short duration. However, over time, as remodeling occurs, AF can become persistent (lasting more than seven days) or even permanent (lasting more than a year, with attempts to restore sinus rhythm either not undertaken or unsuccessful).

Substrate: Extension of PV muscle sleeves



Mechanisms of Afib



The muscle sleeves in the pulmonary veins (PVs) are significant in the context of atrial fibrillation (AF) because they can act as sources of ectopic (abnormal) electrical activity, which can trigger and perpetuate AF. Here's how these muscle sleeves can become a substrate for AF:

1. **Ectopic Foci:** The muscle sleeves within the pulmonary veins can generate ectopic beats. An ectopic beat is an early heartbeat originating outside the heart's normal rhythm pathway. When these ectopic beats are frequent and rapid, they can trigger AF.
2. **Electrical Heterogeneity:** The junction between the pulmonary vein muscle sleeves and the atrial myocardium can have electrical heterogeneity, meaning there are differences in the electrical properties between these two regions. This can create a substrate for reentry, a mechanism where electrical impulses circle back on themselves and continue to activate the heart tissue.
3. **Structural Remodeling:** Over time, especially with repeated episodes of AF, there can be structural changes in the heart, including fibrosis (scarring) and dilation. These changes can further promote the conditions for AF to occur and persist. The muscle sleeves in the PVs can undergo such remodeling, making them more prone to generate erratic electrical impulses.
4. **Autonomic Innervation:** The region around the pulmonary veins is rich in autonomic nerve endings, both from the sympathetic and parasympathetic nervous systems. These nerve endings can modulate the electrical activity of the heart. Stimulation of these nerves can lead to conditions that favor the initiation of AF, especially when combined with the ectopic activity from the PV muscle sleeves.
5. **Reentry Circuits:** The unique anatomy and the presence of muscle sleeves can create conditions for reentry circuits to form, especially if there's a combination of slow conduction and short refractory periods. Reentry is a primary mechanism by which AF is sustained once it starts.

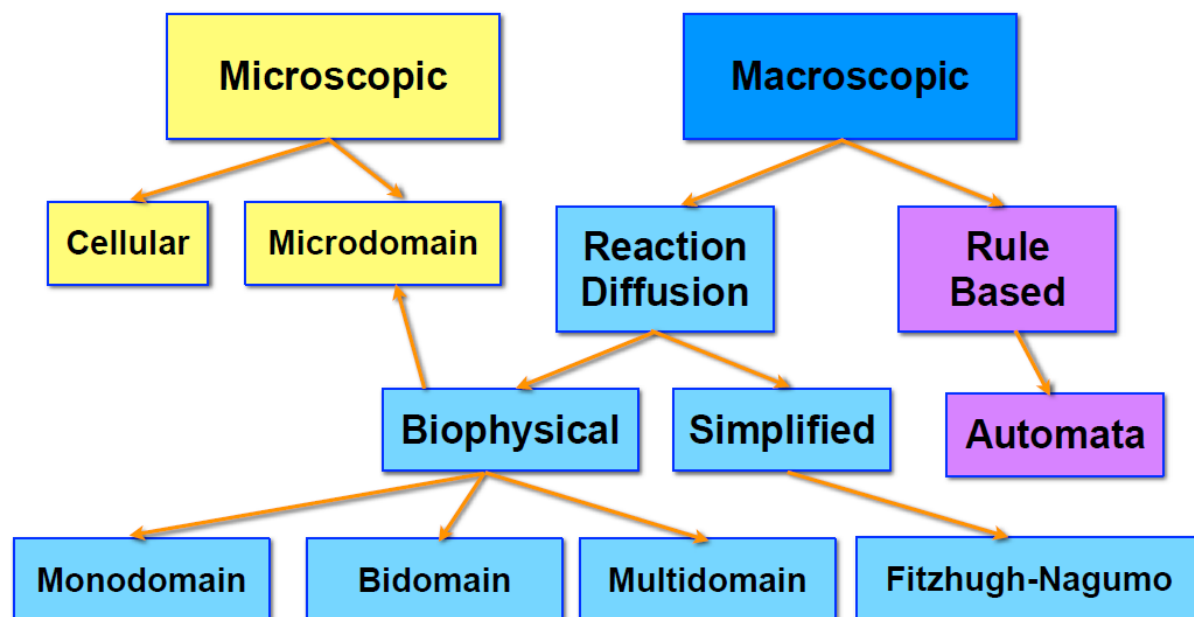
Categories of AF

TABLE 3

Management strategy for recurrent Atrial Fibrillation based on episode duration.

AF classification	Paroxysmal	Persistent ^a	Permanent ^a
AF episode duration	≤7 days	>7 days and ≤1 year	Typically >1 year
Structural remodeling	Atrial fibrosis	Atrial fibrosis	Atrial and ventricular fibrosis
Severity	Minimal to mild	Mild to moderate	Moderate to severe
Electrical remodeling	Pulmonary veins	Atria	Atria
Severity	Focal	Diffuse	Diffuse
Pathology	Minimal	Atriomyopathy	Cardiomyopathy
Main strategy	Rhythm control	Rhythm or rate control ^b	Rate control only
First-line therapy ^b	Catheter ablation	Antiarrhythmic drugs ^c	Antiarrhythmic drugs ^d
Second-line therapy	Antiarrhythmic drugs ^c	Catheter ablation	N/A

Simulation of Propagation



Cable Assumptions

Linear intracellular resistance

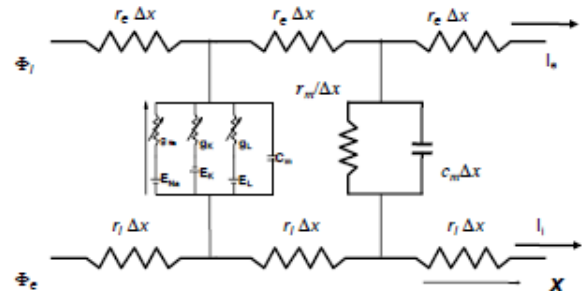
$$r_i = \frac{R_i}{\pi a^2} \quad \Omega/\text{cm}$$

Linear transmembrane resistance

$$r_m = \frac{R_m}{2\pi a} \quad \Omega\text{cm}$$

And capacitance

$$c_m = C_m 2\pi a \quad \mu\text{F}/\text{cm}$$



From which we can write

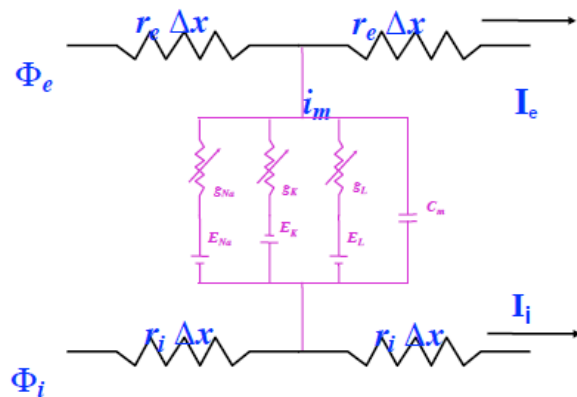
$$\frac{\partial \Phi_e}{\partial x} = -I_e r_e$$

$$\frac{\partial \Phi_i}{\partial x} = -I_i r_i$$

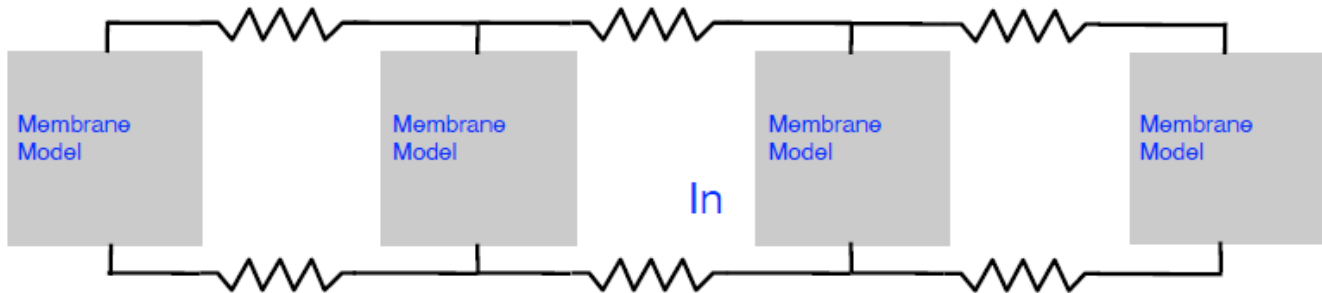
Propagation with HH membranes

Setting the previous equation equal to the HH formulation for membrane current

$$I_m = I_o + \bar{g}_K n^4 (V_m - E_K) + \bar{g}_{Na} m^3 h (V_m - E_{Na}) + \bar{g}_L (V_m - E_L) + C_m \frac{dV_m}{dt}$$



Cable Model



Starting from the Hodgkin-Huxley formalism, we had

$$\frac{dV}{dt} = \frac{1}{C} \left[I_{\text{app}} - \bar{g}_{Na} m^3 h (V - V_{Na}) - \bar{g}_K n^4 (V - V_K) - g_L (V - V_L) \right]$$

with the secondary equations

$$\begin{aligned} \frac{dn}{dt} &= \alpha_n(V)(1 - n) - \beta_n(V)n \\ \frac{dm}{dt} &= \alpha_m(V)(1 - m) - \beta_m(V)m \\ \frac{dh}{dt} &= \alpha_h(V)(1 - h) - \beta_h(V)h \end{aligned}$$

Reduction of Variables

Fitzhugh observed that the time constant for m , τ_m , was much smaller than the other equivalent variables so that starting from

$$m(t, V) = m_{\infty}(V)(1 - e^{-t/\tau_m(V)})$$

he could write

$$m(t, V) \approx m(V) = m_{\infty}(V)$$

He also observed empirically, that

from which he could eliminate h with $n(t) + h(t) \approx 0.8$

$$h(t) = 0.8 - n(t)$$

Reduced form of the Equations

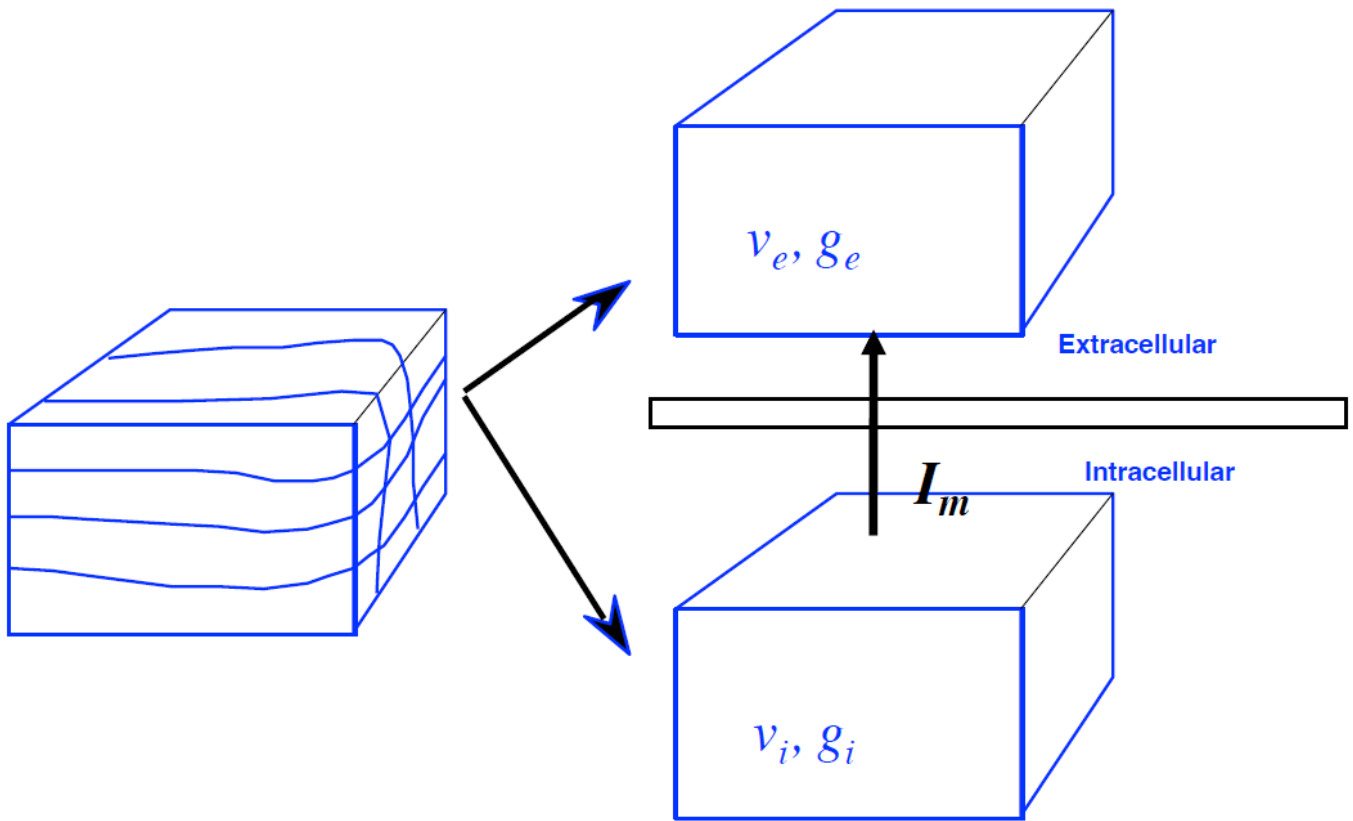
With these simplifications, we can reduce the 4 original equations with these two

$$\frac{dV}{dt} = \frac{1}{C} \left[I - \bar{g}_{Na} m_{\infty}(V)^3 (0.8 - n)(V - V_{Na}) - \bar{g}_K n^4 (V - V_K) - g_L (V - V_L) \right]$$

and

$$\frac{dn}{dt} = \alpha_n(V)(1 - n) - \beta_n(V)n$$

Bidomain Model



2 domains share the same space.

Membrane separates the domains

All properties (v , g , i) are macroscopic averages

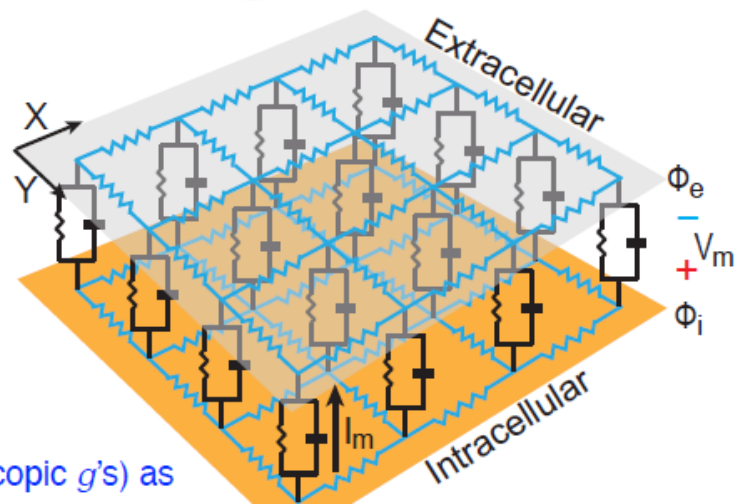
Basic Bidomain Equations

Starting with Ohms Law

applied to both domains, we get

$$\begin{aligned}\bar{J}_i &= \bar{\sigma}_i \nabla \Phi_i \\ \bar{J}_e &= \bar{\sigma}_e \nabla \Phi_e\end{aligned}$$

Which we can write out (assuming macroscopic g 's) as



Conductivity Tensor

We can always write conductivity tensors in diagonalized form as

$$\mathbf{G} = \begin{bmatrix} g_x & & \\ & g_y & \\ & & g_z \end{bmatrix}$$

And then transform them to align with local coordinate systems with $\mathbf{A}$.

$$\mathbf{G}' = \mathbf{A} \mathbf{G} \mathbf{A}^T$$

Generalized Bidomain Equations

Taking the divergence of both sides of the basic bidomain equation, we get

$$\begin{aligned}\nabla \cdot \bar{J}_i &= \nabla \cdot \mathbf{G}_i \nabla \Phi_i = -I_{mv} + I_{av}^i \\ \nabla \cdot \bar{J}_e &= \nabla \cdot \mathbf{G}_e \nabla \Phi_e = I_{mv} + I_{av}^e\end{aligned}$$

Where I_{mv} is the membrane voltage per unit volume and I_{av} are applied volume currents. We have the with continuity condition

$$-\nabla \cdot \bar{J}_i = \nabla \cdot \bar{J}_e = I_{mv}$$

and the definition of membrane voltage as

$$V_m = \Phi_i - \Phi_e$$

Membrane Equations

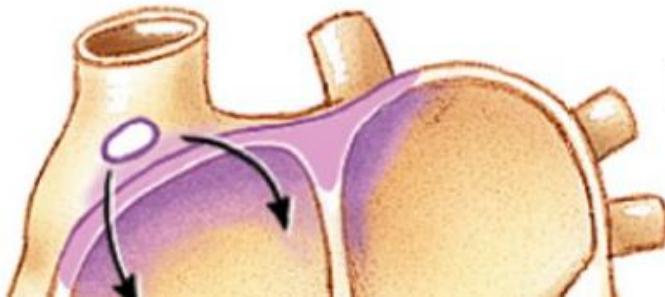
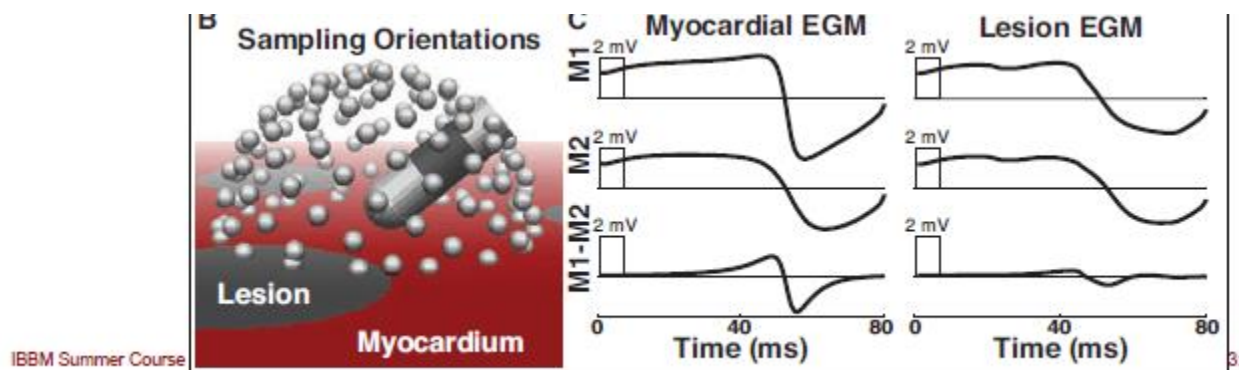
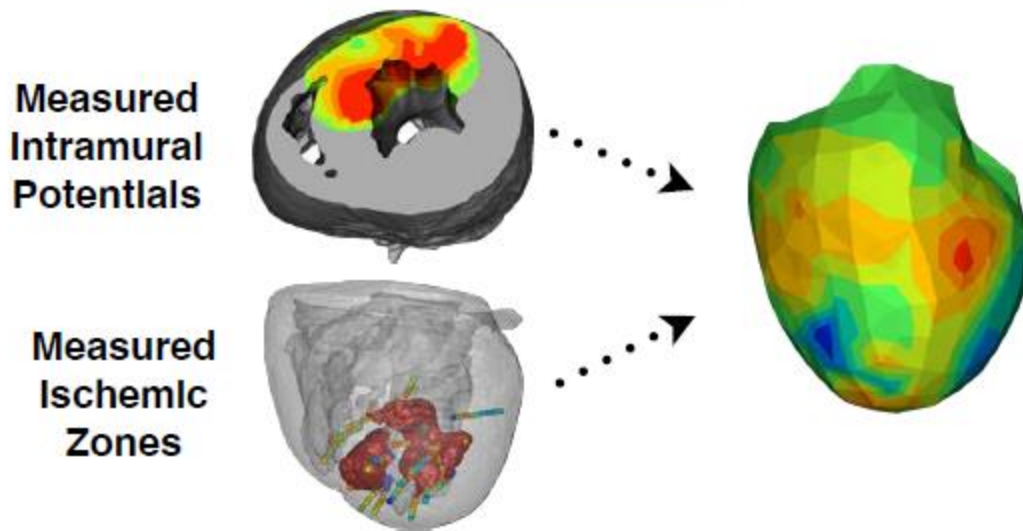
We will wish to couple the bidomain equations with a set of membrane current sources, e.g., HH models

For this, we convert from volume to surface based currents using the surface-to-volume ratio and can write

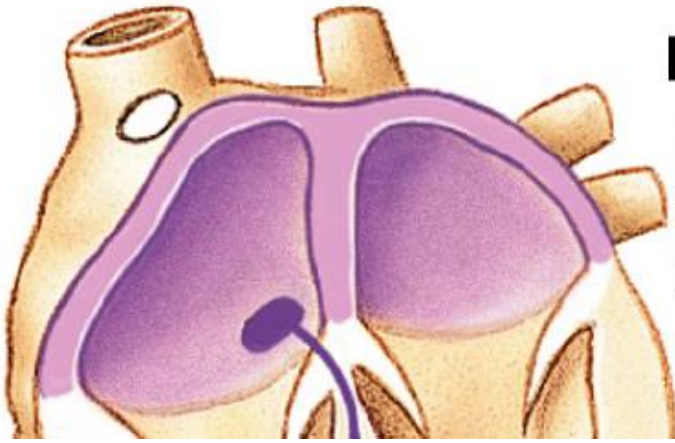
$$I_{mv} = \boxed{S_V I_m} = S_V \left(C_m \frac{\partial V_m}{\partial t} + I_{ion} \right)$$

This we now have a way to apply both stimulus and describe membrane current characteristics

Simulating Epicardial Potentials from Tissue Measurements



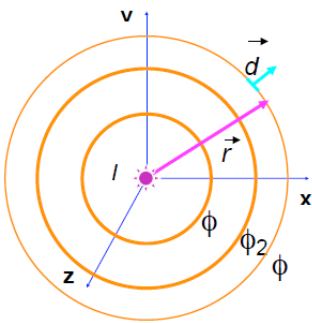
Electrical activity goes rapidly to AV node via internodal pathways.



Depolarization spreads more slowly across atria. Conduction slows through AV node.

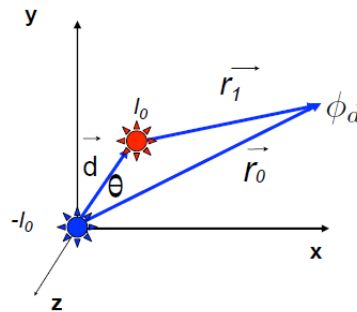
Dipole Source Description

Monopolar Source



$$\phi_m = \frac{I_v}{4\pi\sigma r} + C$$

Dipolar Source



$$\phi_d = \frac{1}{4\pi\sigma} \nabla \left(\frac{1}{r} \right) \cdot \vec{p}$$

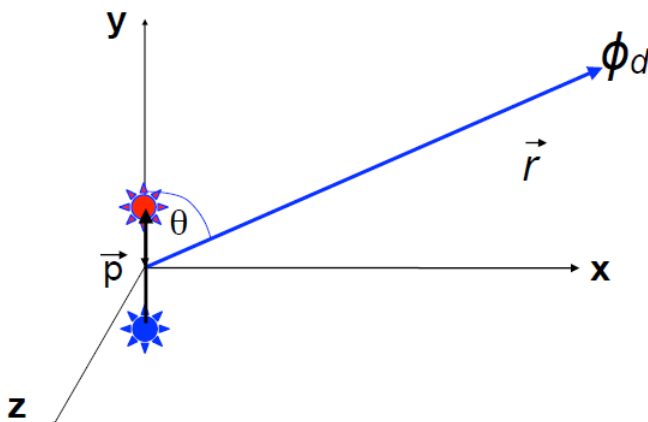
$$\nabla \left(\frac{1}{r} \right) = \frac{1}{r^2} \vec{a}_r$$

$$\vec{a}_r \cdot \vec{p} = p \cos \theta$$

$$\phi_d = \frac{p \cos \theta}{4\pi\sigma r^2}$$

.....

$$\phi_d = \frac{I_0}{4\pi\sigma} \nabla \left(\frac{1}{r} \right) \cdot \vec{p}$$

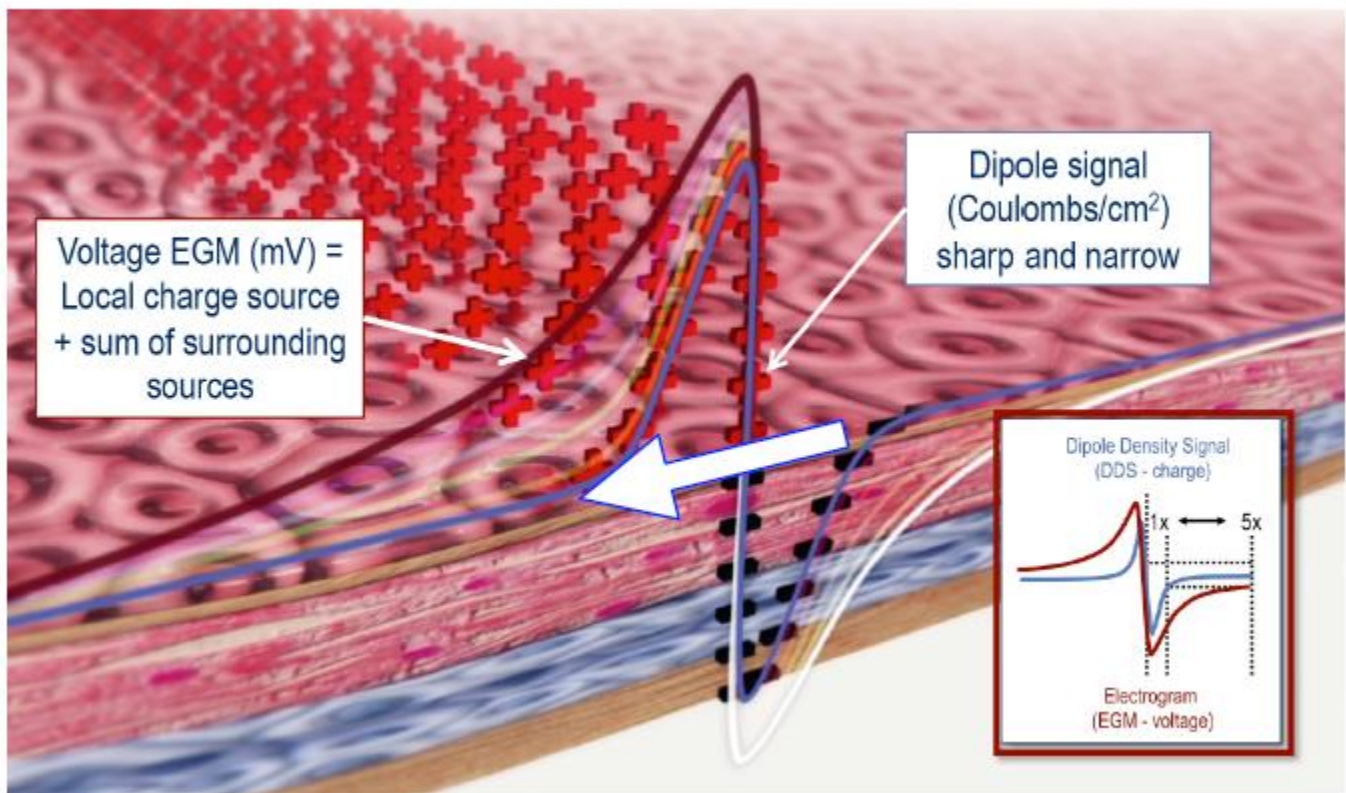
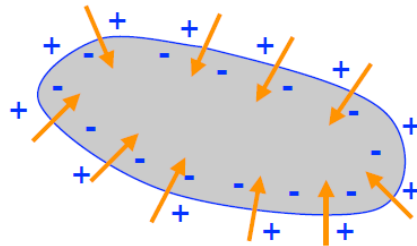
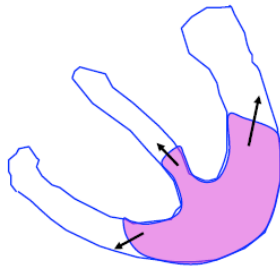
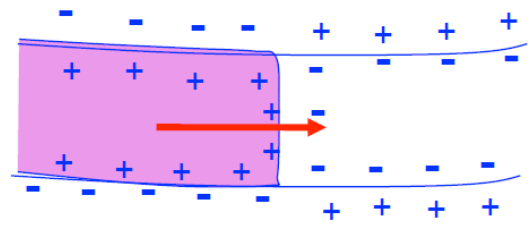


$$\phi_d = \frac{p \cos \theta}{4\pi\sigma r^2}$$

Potential from a dipole in an infinite homogeneous medium

Why Dipole Sources?

- Represent bioelectric sources
 - Membrane currents
 - Coupled cells
 - Activation wavefront
 - Whole heart



The concept of the "solid angle" in the context of cardiac electrophysiology and ischemia refers to the geometric relationship between the source of electrical activity (e.g., a region of the heart) and the location where it's being measured (e.g., an electrode on the body surface). The solid angle theory helps explain the changes observed in electrocardiographic recordings during myocardial ischemia.

Here's a basic overview:

1. Solid Angle:

- In geometry, a solid angle is a measure of the amount of the field of view from some particular point that a given object covers. It's a three-dimensional equivalent of the two-dimensional angle we're familiar with.
- In the context of the heart and ECG, the solid angle describes the orientation and area of myocardium (heart muscle) relative to a recording electrode.

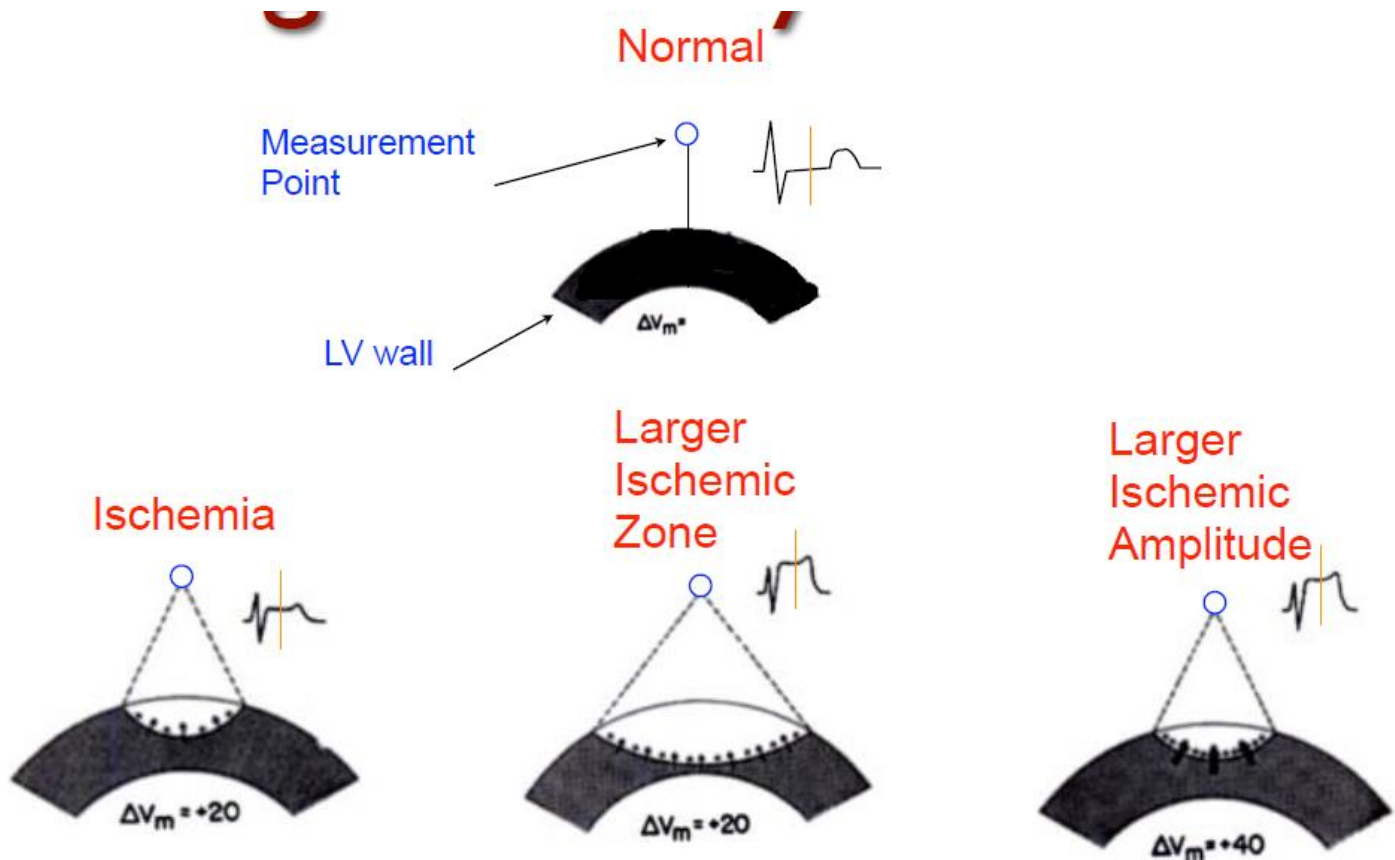
3. Solid Angle Theory and Ischemia:

- When a region of the heart becomes ischemic, the electrical activity of that region changes. The solid angle theory posits that the magnitude of the change observed on the ECG depends not only on the size of the ischemic region but also on its orientation relative to the recording electrode.
- For instance, if a large portion of the heart facing an electrode becomes ischemic, the change in the ECG might be significant. Conversely, if a similarly sized region becomes ischemic but is oriented perpendicular to the electrode, the change might be less pronounced.
- This theory helps explain why certain ischemic events might produce strong ECG changes in some leads but not in others.

4. Clinical Implications:

- Understanding the relationship between the solid angle and ischemia can help clinicians interpret ECG changes more accurately. For instance, certain patterns of ST-segment elevation or depression might suggest ischemia in specific regions of the heart, which can guide diagnosis and treatment.

In summary, the solid angle theory provides a geometric framework for understanding how the orientation and size of an ischemic region in the heart can influence the changes observed on an ECG. This understanding can be crucial for diagnosing and managing heart conditions like myocardial infarction.

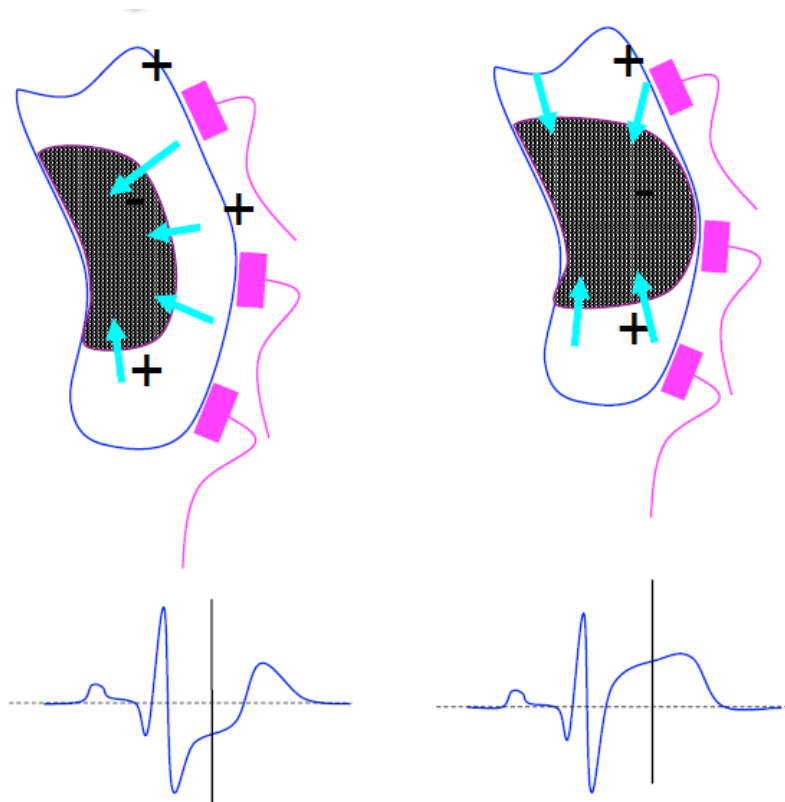


When a region of the myocardium becomes ischemic, the cells in that region become depolarized due to a lack of oxygen and nutrients. This means that the resting membrane potential of the ischemic cells becomes **less negative (or more positive)** than that of the surrounding healthy cells.

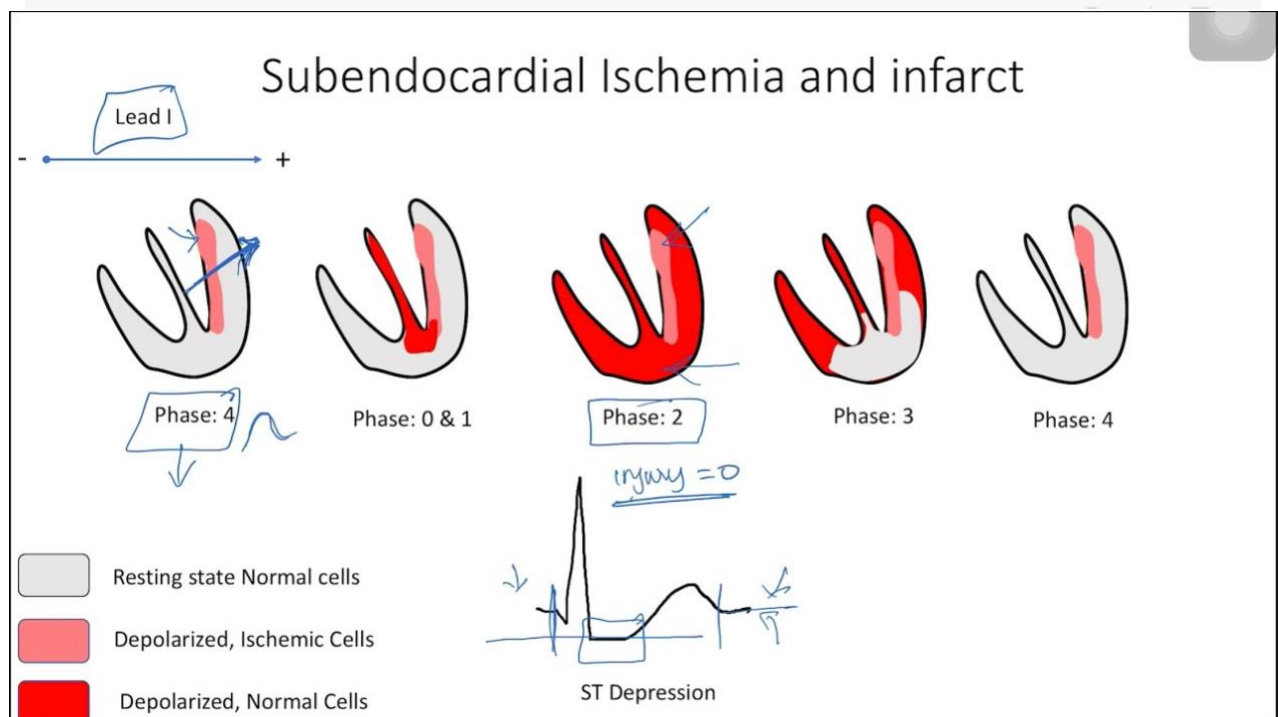
However, the relationship between the endocardial and epicardial surfaces in the context of ischemia is more nuanced:

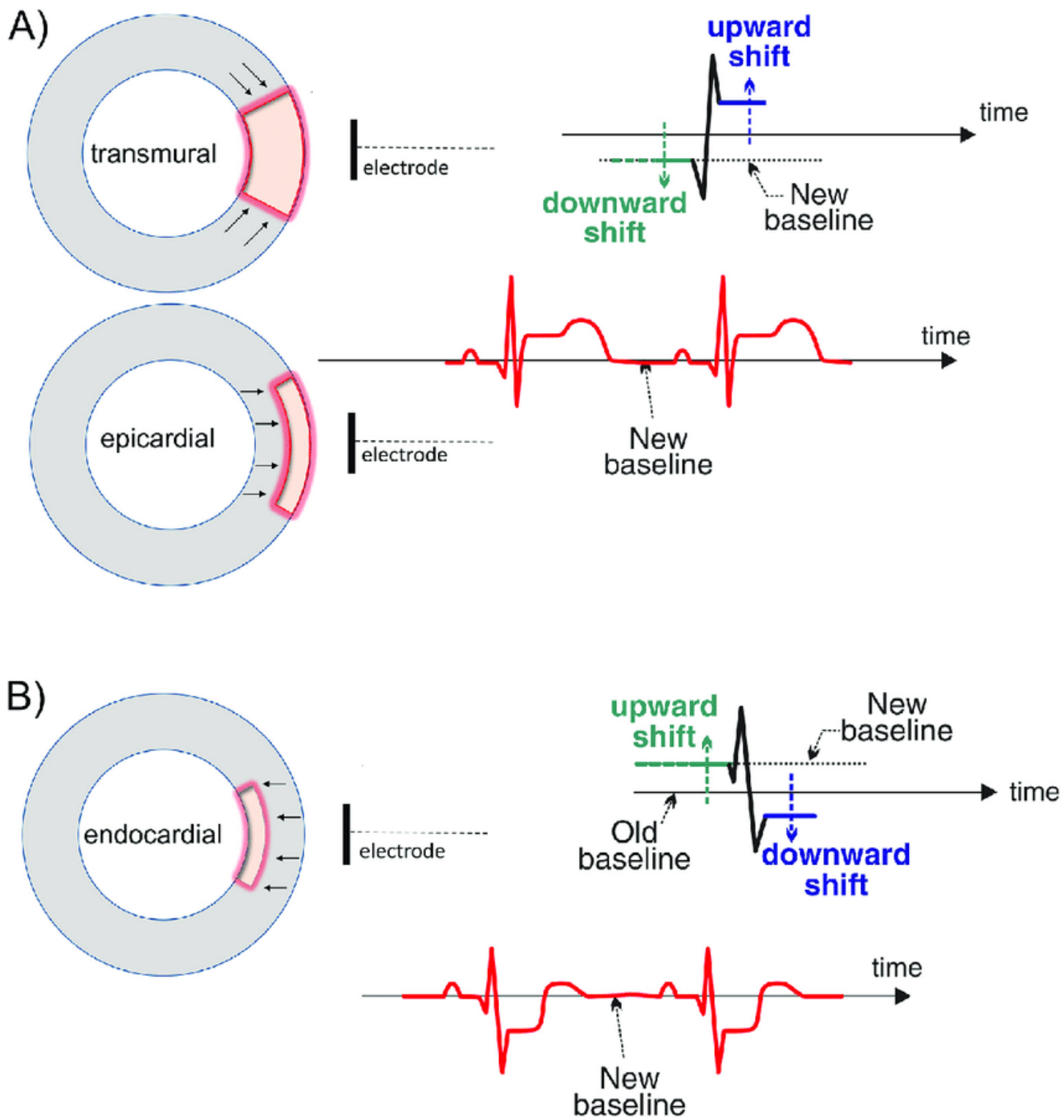
1. **Transmural Ischemia:** In cases of transmural ischemia, the entire thickness of the myocardial wall is affected. This can lead to ST elevation on the ECG.
2. **Subendocardial Ischemia:** If only the subendocardial region is ischemic, the innermost layer of the heart is affected. This type of ischemia can lead to ST depression on the ECG. The reason is that the subendocardium, being the innermost layer, is the first to be affected in conditions of reduced blood flow, as it's the last to receive oxygenated blood.

The voltage gradient between the ischemic and non-ischemic regions is due to the difference in resting membrane potentials. The ischemic cells, being depolarized, have a more positive resting membrane potential than the surrounding healthy cells. This difference creates a "current of injury" that can be detected on the ECG as ST-segment changes.

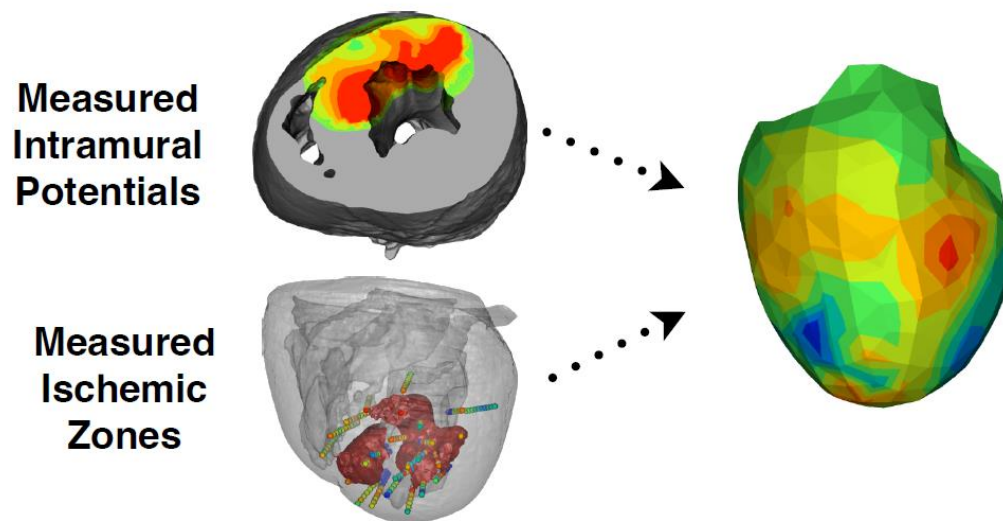


In summary, ST-segment elevation in the setting of myocardial ischemia is the result of electrical differences between ischemic and non-ischemic myocardium. The solid angle theory helps explain how the orientation and size of the ischemic region influence the ECG findings. The structural characteristics of the ischemic zone, including its transmural extent, size, and location, further modulate the ST-segment changes observed on the ECG.





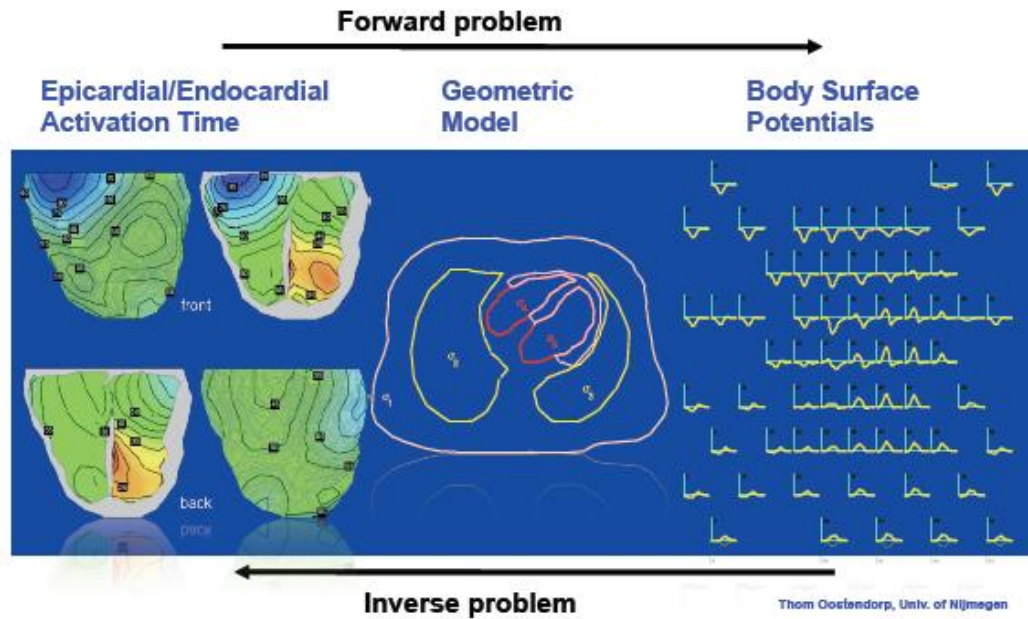
Simulating Epicardial Potentials from Tissue Measurements



The term "current of injury" refers to the electrical current generated by the difference in voltage between ischemic myocardial tissue and the surrounding normal tissue. This current is most evident during the resting phase (diastole) of the cardiac cycle, and it's this difference in resting membrane potential that leads to the ST-segment changes seen on the ECG.

1. **During Resting Phase (Diastole):** The ischemic tissue has a less negative resting membrane potential compared to the surrounding healthy tissue. This difference in potential creates the current of injury. During diastole, when the majority of the myocardium is at rest, this current is most evident and is responsible for the ST-segment deviation seen on the ECG.
2. **During Action Potential Generation (Systole):** During systole, when the myocardium is actively depolarizing and repolarizing, the current of injury is still present, but its effects are somewhat masked by the larger currents associated with normal cardiac electrical activity. Thus, the ST-segment deviation is not as evident during the active phases of the cardiac cycle.

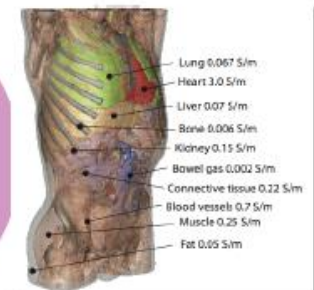
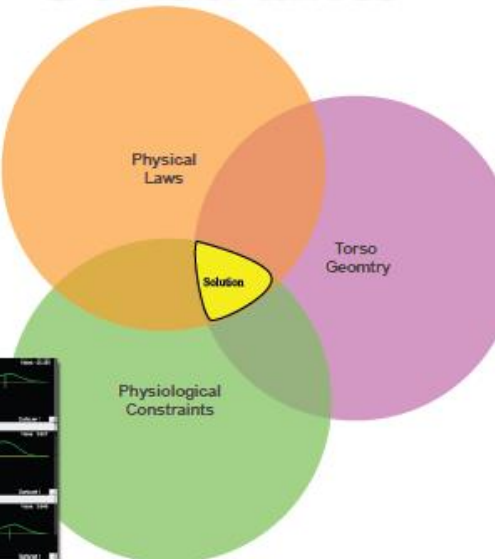
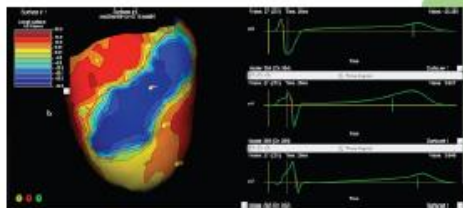
What are Inverse Problems?



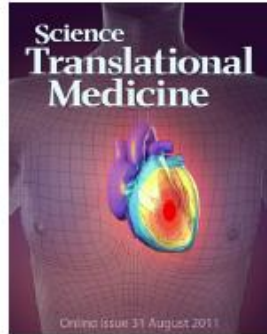
Constraints

$$\nabla^2 \phi = -\frac{I_v}{\sigma}$$

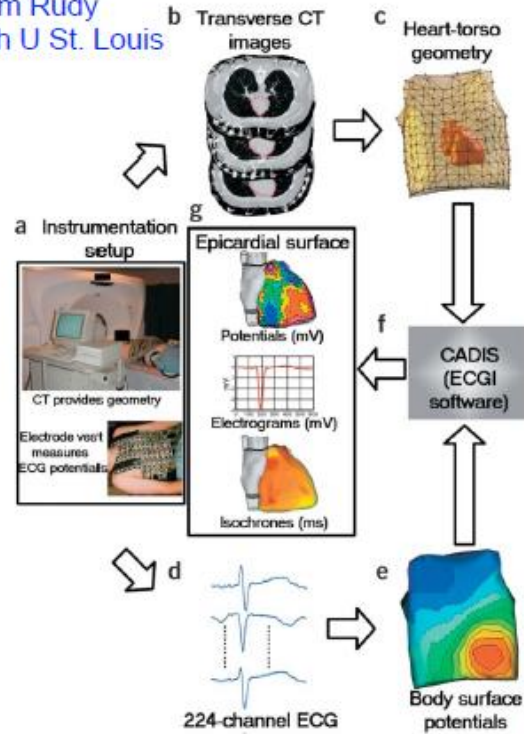
$$\nabla^2 \phi = 0$$



Yoram Rudy
Wash U St. Louis



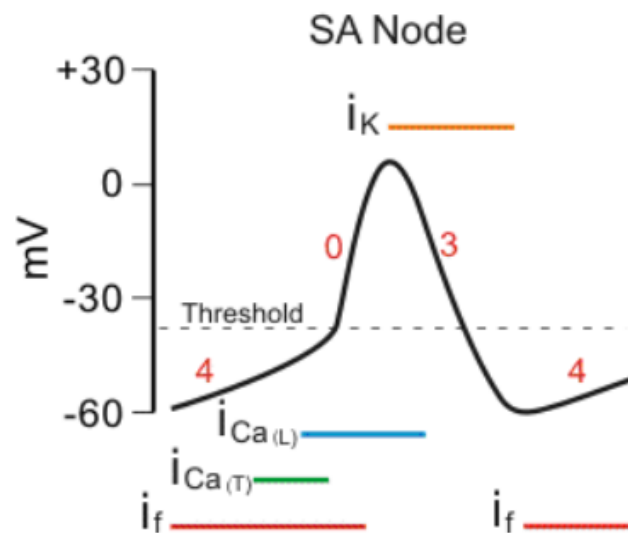
IBBM Summer Course



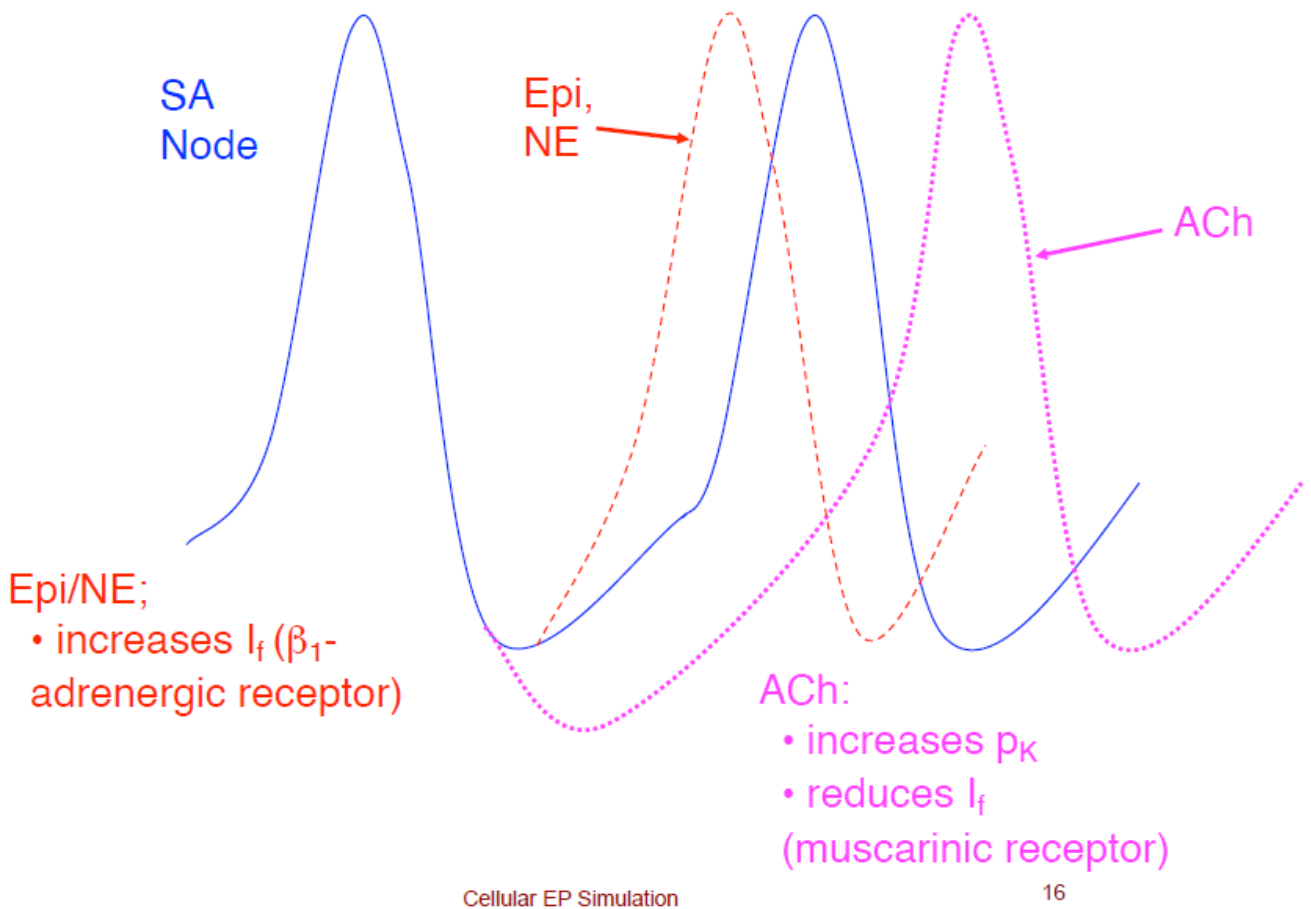
t 6: Inverse Problems

30

Pacemaker Cells in the Heart



Regulation of Heart Rate



To clarify:

- The QRS complex represents the volume currents generated by the rapid influx of sodium ions during ventricular depolarization.
- The T wave represents the volume currents generated by the outward movement of potassium ions during ventricular repolarization.