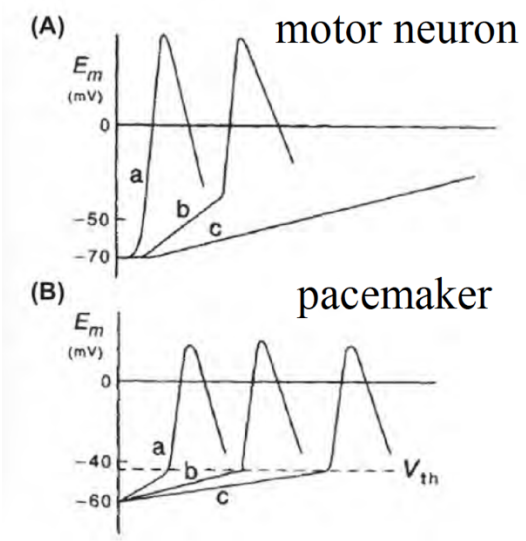
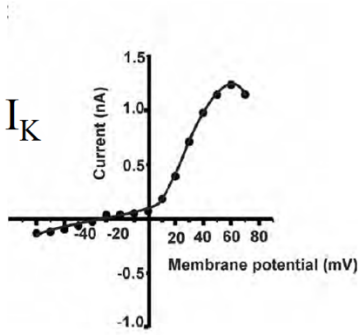
QE ver 4

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 (gK)**: 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 adn actives 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.

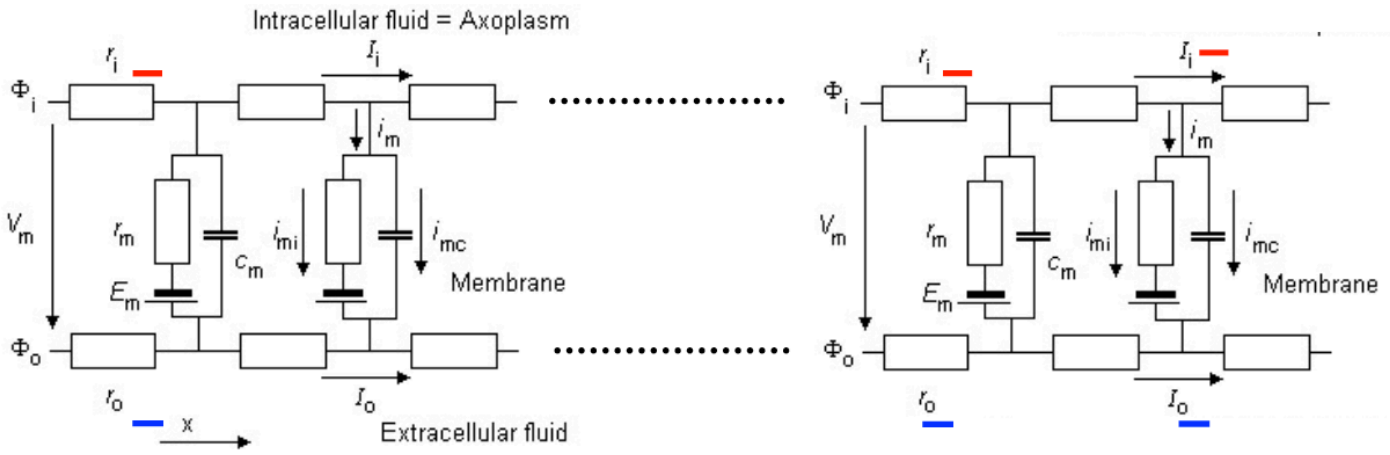
The cable equation, which is a type of partial differential equation, can be discretized for numerical solution. This is often done using the finite difference method, similar to the spatial discretization in reaction-diffusion systems.

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

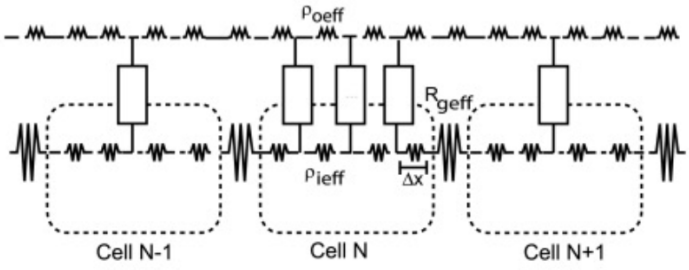
Problem: Realistic cell-based modeling of tissue
- complex geometry of cells
- large number of cells
- account for extracellular and intracellular space

Idea „Bidomain Model“
- division of space in two domains
- separated calculation

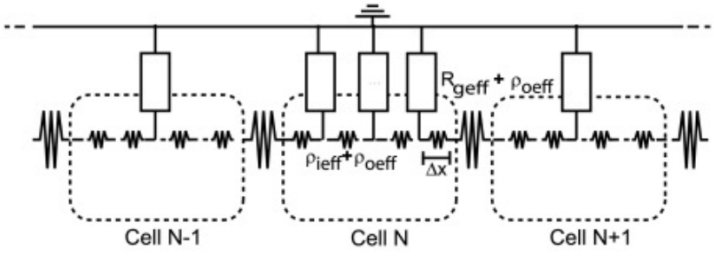
Inclusion of extracellular conduction relevant for modeling of:
- anisotropic propagation of excitation
- stimulation with extracellular current sources
- body surface potential maps (BSPM) and electrocardiograms (ECG)

Microscopic Modeling Using Diffusion-Excitation Equation

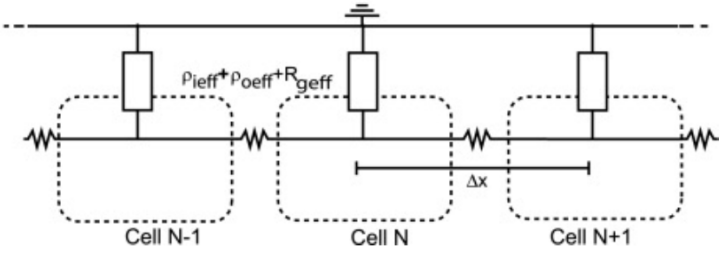
Discrete microscopic bidomain



Discrete microscopic monodomain



Cable model discretized with Δx == 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

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

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

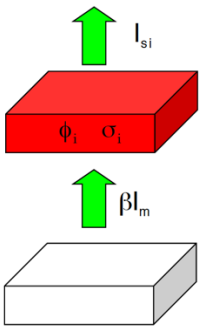
J_i : *Intracellular current density* $\left[\frac{A}{m^2}\right]$

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* $\left[m^{-1}\right]$



Bidomain Model: Extracellular Space

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

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

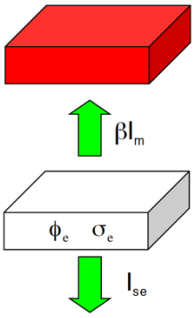
J_e : *Extracellular current density* $\left[\frac{A}{m^2}\right]$

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* $\left[m^{-1}\right]$



Bidomain Model: Relationships

Extra- and Intra-

$$J = J_i + J_e = -\sigma_i \nabla \phi_i - \sigma_e \nabla \phi_e$$

with $\phi_m = \phi_i - \phi_e$:

$$J = -\sigma_i \nabla \phi_m - \sigma_i \nabla \phi_e - \sigma_e \nabla \phi_e$$

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

$$J = -\sigma_i \nabla \phi_m - \sigma_H \nabla \phi_e$$

with $\nabla \cdot J = 0$:

$$\nabla \cdot (\sigma_H \nabla \phi_e) = -\nabla \cdot (\sigma_i \nabla \phi_m)$$

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

unknown

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

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

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

unknown

Elliptical partial differential equations (Poisson's equation)

Ordinary differential equation (Cell model)

Problem: Spatio-temporal discretization!

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

1. Cm ∂V/∂t = Iion(V, w) + Istim - β (∇ · (σi ∇Vi) - ∇ · (σi ∇Ve))
2. ∇ · (σi ∂Vi/∂t + σe ∂Ve/∂t) = 0

where:

- V is the transmembrane voltage
- Iion is the total ionic current
- Istim is the stimulus current
- Vi and Ve are the intracellular and extracellular potentials
- σi and σe 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:**

`Cm ∂V/∂t = -Iion(V, w) + ∇ · (σi ∇Vi) - ∇ · (σi ∇Ve)`

Here, Cm is the membrane capacitance, V is the transmembrane potential (difference between intracellular and extracellular potentials Vi and Ve), t is time, Iion(V, w) is the total ionic current (which depends on V and other variables w), σi is the intracellular conductivity tensor, and ∇ is the gradient operator. The term ∇ · (σi ∇Vi) - ∇ · (σi ∇Ve) represents the difference in current flow in the intracellular domain compared to the extracellular domain.

2. **Extracellular Domain:**

`∇ · (σi ∇Vi + σe ∇Ve) = 0`

Here, σe 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 Iion(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:

`Cm ∂V/∂t = -Iion(V, w) + Istim`

`dw/dt = f(V, w)`

Here, Istim 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 ∇ · operators with finite difference approximations. We would also discretize the time domain into time steps, replacing the derivatives ∂/∂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.

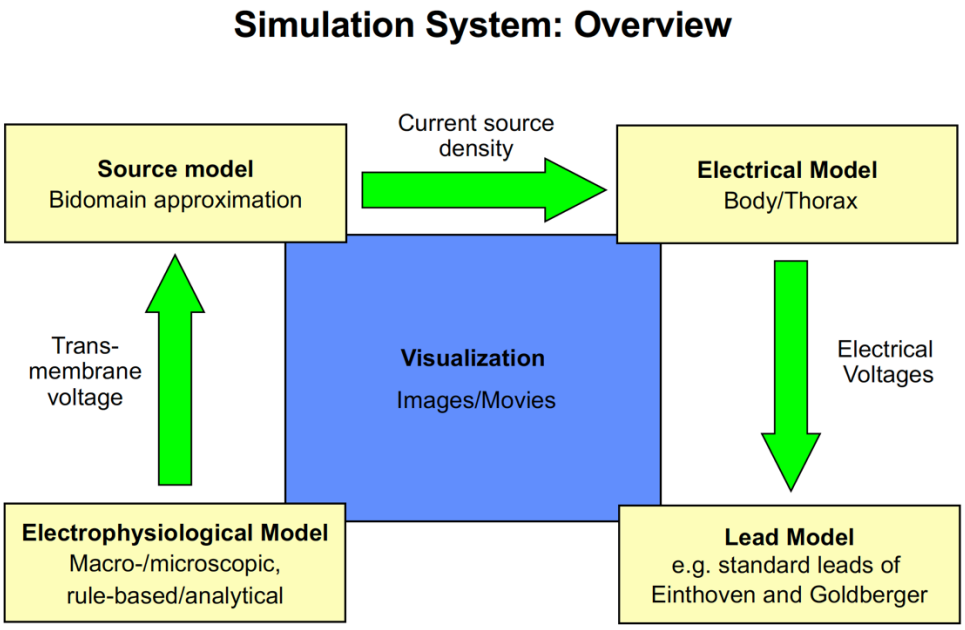
Challenges: Simulating arrhythmias accurately can be very challenging due to:

- **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.



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:

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

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

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 $\nabla \cdot (\sigma_i \nabla V_i) - \nabla \cdot (\sigma_i \nabla V_e)$ 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 ∇ · (σ_i ∇V_i + σ_e ∇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

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

Φ: Electrical potential [V]

σ: Conductivity tensor [S/m]

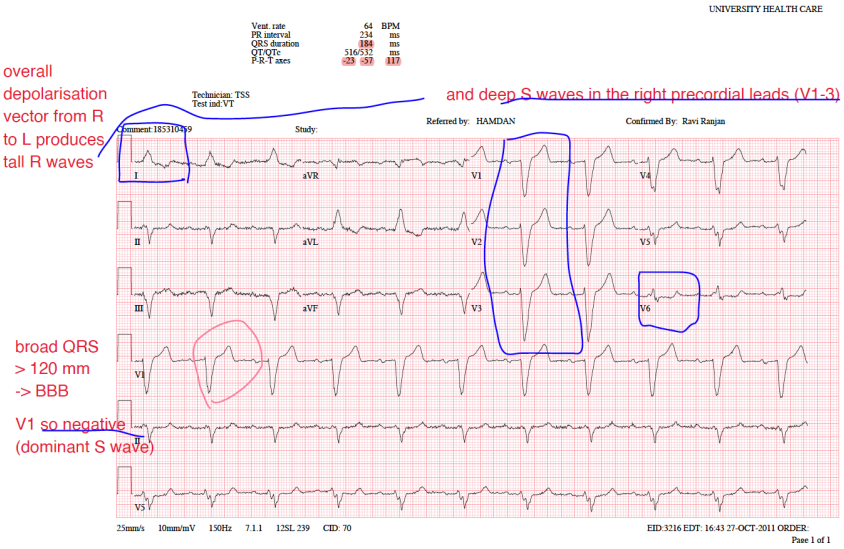
f: Current source density [A/m^3]

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.

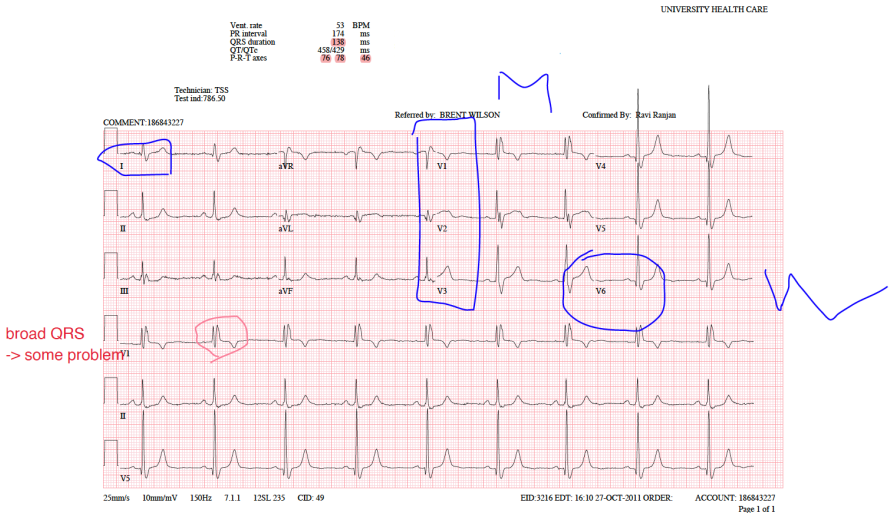
1. **Left Bundle Branch Block (LBBB)**: In an LBBB, the electrical signal is delayed or blocked along the pathway that sends electrical signals to the left ventricle. On an ECG, LBBB can be recognized by:
    - A widened QRS complex (> 120 ms)
    - The absence of a Q wave in leads I, V5, and V6
   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

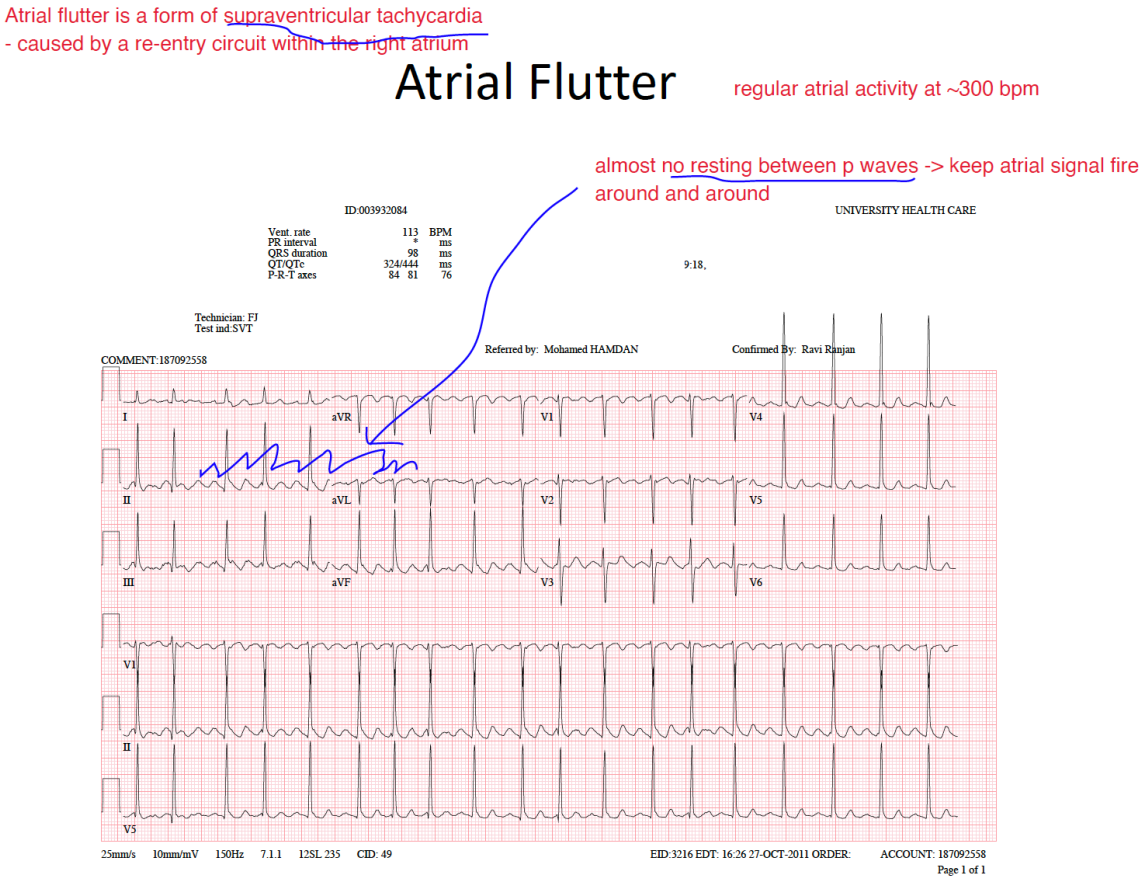
RBBB



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.



"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 Ca2+ 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, If) 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 Ca2+ 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 Ca2+-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 Ca2+ current (via L-type calcium channels) and outward K+ current (via slow delayed rectifier potassium channels). The influx of Ca2+ triggers the release of more Ca2+ from the sarcoplasmic reticulum, initiating the process of contraction.
Phase 3 - Rapid repolarization: L-type Ca2+ 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 (ICa) 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 β1-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 ([Ca2+]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, 1Ca2+ 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. **Meditatation, Yoga, Exercise**
8. **Listen to music**
9. **Sleep**
10. **Deep, not shallow, in everything (bottom neck book)**