Ver Jul 13

- **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 fibrilation?**

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:

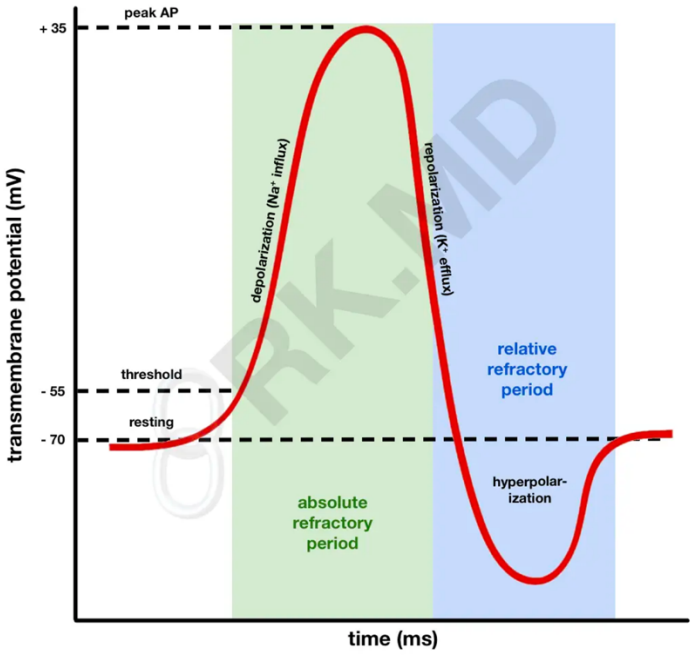
- Occurs immediately after an action potential.
- The cardiac cell can't respond to any new stimulus, regardless of its strength.
- This period is due to **inactivation of voltage-gated sodium channels**, which are essential for initiating and propagating action potentials.
- The heart's absolute refractory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

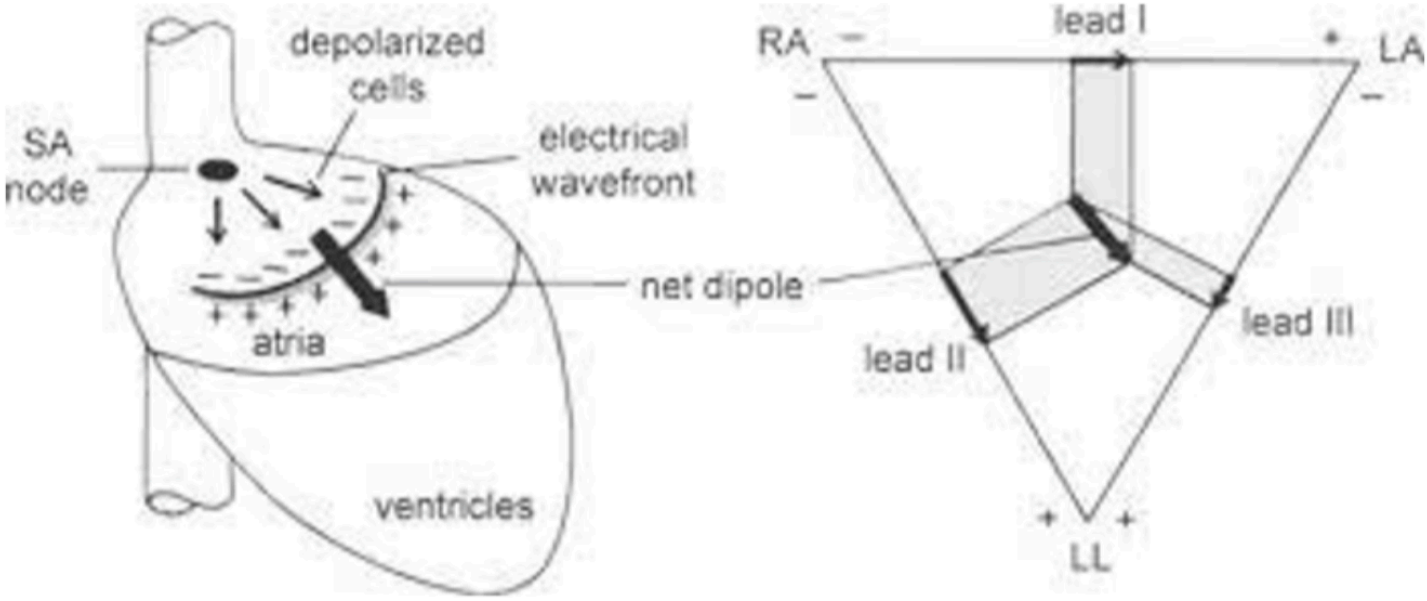
  1. Understanding Heart Dipole:
  - The heart's electrical activity creates a dipole - a pair of equal but oppositely charged electric charges or magnetic poles separated by a distance.
  - During each heartbeat, depolarization moves from the endocardium (inner layer of the heart wall) to the epicardium (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: $\nabla \cdot (\sigma \nabla \varphi) = I$, where:
      - σ is the conductivity tensor
      - $\nabla \varphi$ 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 Ca2+?

  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 Ca2+ 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.

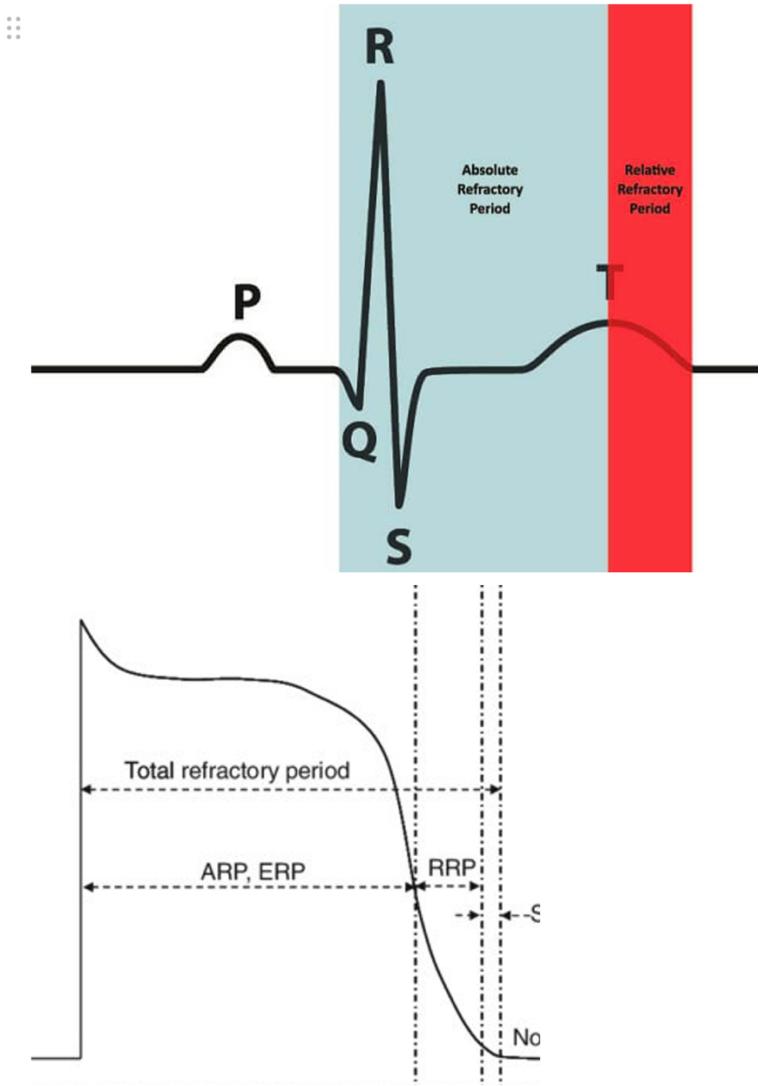
In a purely theoretical sense, if we were to propose an alternative ion to calcium for the generation of the plateau phase in a cardiac-like action potential, it would need to meet specific criteria. The ion would need to:

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 (Mg2+). 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 Mg2+ cannot replace Ca2+. For instance, Mg2+ ions are not generally known to pass through ion channels in the same way as Ca2+, and they do not trigger cellular processes such as muscle contraction in the way Ca2+ does. Furthermore, the body has not evolved mechanisms to rapidly transport Mg2+ across cell membranes in response to changes in membrane potential, unlike for Ca2+, Na+, and K+.

So while Mg2+ could theoretically play the role of Ca2+ in a highly simplified or artificial model, in biological reality, the role of Ca2+ in generating the cardiac action potential is unique and cannot be fulfilled by Mg2+ 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:

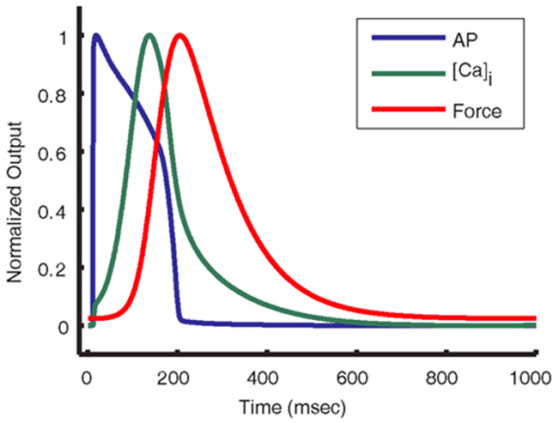
- Calcium Transient in Contraction: The calcium transient during contraction is responsible for initiating and regulating the process of myocardial contraction. It triggers the interaction between actin and myosin filaments, leading to the generation of force and subsequent cardiac muscle contraction.

- 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).

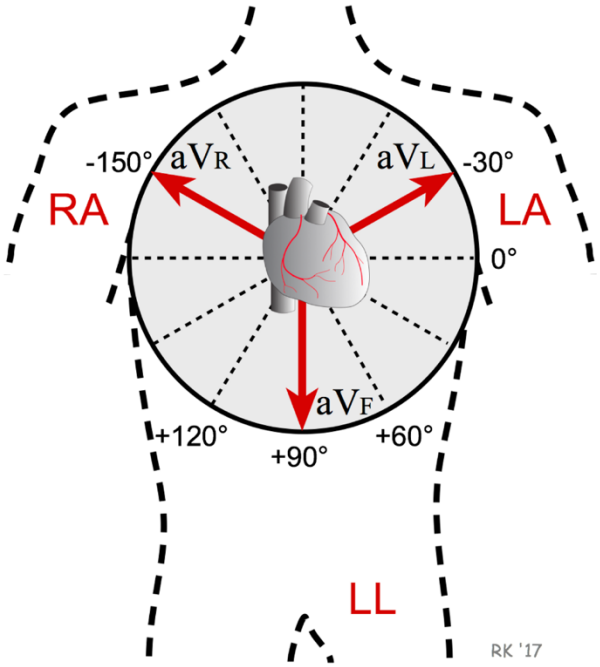
- **Is it possible to calculate Goldberger from Einthoven leads?**

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.

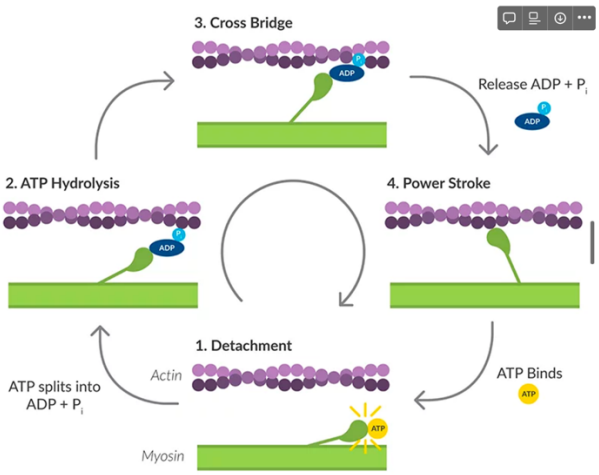
Indeed, it is possible to calculate the Goldberger leads from the Einthoven leads using the following formulas **(NOT SURE)**:

- 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.