Cardiac Action Potential - Luo-Rudy Model

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Introduction

In this project, we study cardiac action potential using the Luo-Rudy model. Action potential is a quick change in voltage across the cell membrane, which cells use to signal other cells, and in the case of the heart, trigger contraction. It is mediated by the movement of ions across the cell membrane. The Luo-Rudy model and cable equations are mathematical models that use a set of nonlinear differential equations to describe how action potentials in cardiac myocytes behave and propagate. There is no analytical solution, so we use numerical methods to solve and simulate results. Finally, we use the computational results to gain insight into the model and the biological phenomenon it represents.

Biological background

We model both a single cell and a chain of cells. The first model describes an action potential in an isolated cell in response to a stimulus current. The second describes how neighboring cells stimulate each other along a continuous cardiac fiber.

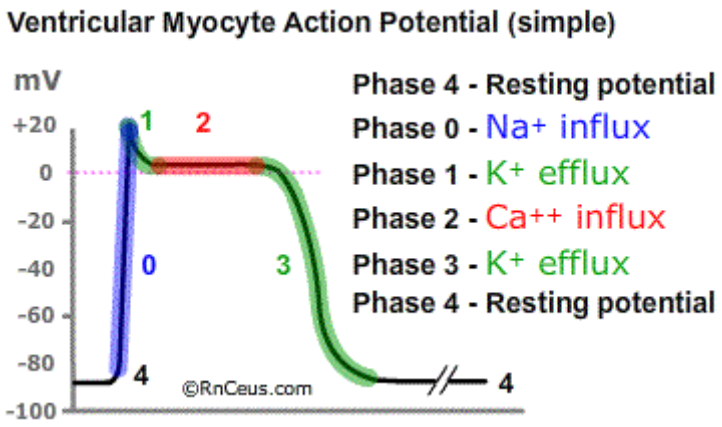
Single cell

An action potential is a rapid rise and fall in voltage across a cellular membrane. Cardiac cells use these electrical pulses to signal each other and trigger contraction. An action potential requires sufficient stimulus current to start a full response. If the stimulus current is below a specific threshold, the action potential will not start. In the absence of stimulus, the cell membrane is said to be at resting potential.

To regulate their membrane potential, myocytes use concentration gradients of charged ions, specifically sodium, potassium, and calcium. Special channels called *voltage gated ion channels* let specific ions naturally diffuse across the membrane from high concentration to low concentration. These channels open and close in response to the membrane potential, which determines whether an ion can diffuse. Closed channels prevent the flow for a specific ion, while open channels allow that ion to flow, causing a further change in voltage. *Ion pumps* then expend energy to maintain the concentration gradient.

During the resting potential phase, the channels are mainly closed. There are more potassium ions inside the cell than outside, and more sodium ions and calcium ions outside the cell than inside. Throughout the process, we consider these concentrations to be effectively

constant, since a single ion moving across the membrane changes the voltage gradient substantially more than the concentration gradient.



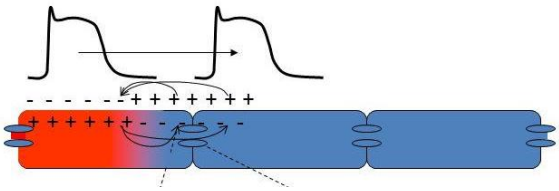
The action potential of a cardiac myocyte can be broken down into stages:

- Phase 0 (depolarization): If the stimulus reaches the threshold voltage, it will cause the rapid opening of voltage gated sodium channels on the cell membrane. The resulting rapid influx of sodium ions leads to depolarization.
- Phase 1 (fast-repolarization): Once the membrane voltage reaches 30 mV, the sodium channels will close. Now the potassium voltage gated channels open in response to the higher voltage. The movement of the positively charged ions out of the cell causes the inside to become less positive.
- Phase 2 (plateau): Once the cell reaches a voltage difference of about 0 mV, the rate of influx of calcium balances the effects of potassium efflux, extending the repolarization period.
- Phase 3 (repolarization): As the calcium voltage gated channels begin to close, the efflux of potassium exceeds the influx of calcium. This causes even more potassium voltage-gated channels to open, causing a rapid decrease in the membrane potential until it returns back to normal.
- Phase 4 (resting potential): The membrane potential returns to approximately -90 mV, and stays there until the next stimulus triggers another action potential. There is a brief refractory period before the cell will respond again.

Propagation of action potential

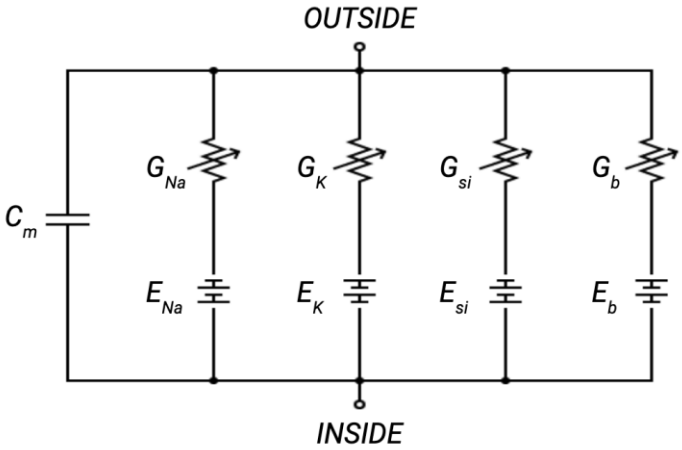
We also studied the propagation of the action potential along a cardiac fiber. There are two levels to consider: the intracellular level and the intercellular level.

Within a cell, before applying any stimulus, the membrane is negatively charged inside. Applying a stimulus will cause the sodium channels to open. As the sodium ions rush in, they will reverse the polarity of the membrane in the area where the stimulus occurred, making the inside more positive. The increase in positive charge inside will cause the increase of the positive charge in adjacent regions along the membrane. This will simulate the sodium channels to open up in adjacent areas. This domino effect continues as each consecutive region is depolarized. In this manner, the action potential moves.



Once the action potential reaches the end of the cell, the voltage change triggers the cell to send a chemical signal to its neighbor. That signal stimulates receptors that allow positive ions to flow into the next cell, triggering an action potential in that cell as well. At a large enough scale, this cell-to-cell interaction is the dominant effect in the propagation of the electrical signal, and it begins to resemble a diffusion process.

The Luo-Rudy Model



The Luo-Rudy model uses a circuit to represent the behavior at the cell membrane. The circuit consists of a capacitor representing the cell's ability to store charge at the membrane in parallel with components representing the behavior for each ion channel. Each ion channel has a variable resistor (which represents the ability of a channel to open and close in response to voltage) and a battery (which has a voltage equivalent to the equilibrium potential for that ion, and represents the forces in the cell that maintain a concentration gradient.

The circuit diagram depicted here is slightly simplified, since there should be three different potassium channels (I_K, I_{K1}, and I_{Kp}). Note that the calcium channel is indexed with "si", which stands for "slow inward". Also note the inclusion of a background current, indexed by "b", which represents ions naturally leaking across the barrier.

From this diagram, we can derive the set of differential equations that make up the model. By Kirchoff's junction law, the current through the capacitor and each ion channel must sum to the total current through the circuit, I_{stim}. Using the fact that capacitance is the ratio between the current through the capacitor and the derivative of the voltage across the capacitor with respect to time, we have our first equation:

$$C\frac{dV}{dt} + I_{ion} = I_{stim}$$

I_{ion} is the sum of the ion currents. Each channel has a voltage variable resistor, so these depend explicitly on V. In order to understand the form of the ion currents, we will need to discuss gating variables.

Each channel has some number of voltage gates. Taking all the channels of a particular type together, at any moment some proportion of these gates are open and some are closed. The Luo-Rudy model represents the proportion of gates that are open with a gating variable. The gating variables range between 0 and 1. Each instant, some of the open gates will close and some that are closed will open. The rates of these transitions depend on the voltage, and each gating variable has associated functions alpha and beta to represent those rates. This description yields the following differential equation for each gating variable y:

$$\frac{dy}{dt} = \alpha_y(V)(1-y) \; - \; \beta_y(V)\, y$$

Another way that the Luo-Rudy model represents gates is directly through functions of V that output a value between 0 and 1. If a gate responds very quickly to changes in voltage, we can assume that the open proportion of gates immediately jumps to their equilibrium proportion, with no need to introduce an additional variable into the system. Only six gates have their own gating variable; the rest are gating functions.

The voltage gates have a direct impact on the ion currents. Each ion current has a maximum conductance G, representing the highest flow of ions when all the gates are fully open. Closed voltage gates reduce the conductance. For instance, the sodium channel has three voltage gates, represented by variables m, j, and h. There are three m gates in a channel. Following standard circuit rules, the current through the ion channel is given then by this equation:

$$I_{Na} = G_{Na} \cdot m^3 \cdot h \cdot j \cdot (V - E_{Na})$$

Every ion channel takes on this form, though with its own gating variables or gating functions, and using its own maximum conductance and equilibrium potential. For the potassium channels, the conductance and equilibrium potential also depend on a parameter $[K]_o$, which represents the concentration of potassium outside the cell. This parameter is constant throughout the process, but can be set to different values at the beginning of a simulation.

There is one more variable in this system, in addition to V and the six gating variables. The concentration of calcium inside the cell $[Ca]_i$ is a variable that changes with time, unlike every other concentration. The other concentrations are taken as constant throughout the action potential, because the voltage changes so much faster than the concentration as ions move across the membrane. However, the concentration of calcium inside the cell is so small that the action potential does make a big difference. The differential equation used to model the change in concentration is as follows:

$$\frac{d[Ca]_i}{dt} = -10^{-4} \cdot I_{si} - 0.07(10^{-4} - [Ca]_i)$$

Note the dependence on the inward calcium current I_{si}. Also keep in mind that the equilibrium potentials for each ion are a function of the concentrations inside and outside the cell, so the equilibrium potential for calcium is not constant and depends explicitly on $[Ca]_i$.

All together, here is the model (with some function definitions omitted for brevity):

$$C\frac{dV}{dt} + I_{ion} = I_{stim}$$

$$\frac{d[Ca]_i}{dt} = -10^{-4} \cdot I_{si} - 0.07(10^{-4} - [Ca]_i)$$

$$\frac{dy}{dt} = \alpha_y(V)(1-y) - \beta_y(V)\,y$$

where y is a gating variable m, h, j, d, f, X

$$E_{si} = 7.7 - 13.0287\,ln\,([Ca]_i)$$

Note the other equilibrium potentials also depend on the relative concentrations of their ions, which are set as parameters.

$$I_{ion} = I_{Na} + \left(I_K + I_{K1} + I_{Kp}\right) + I_{si} + I_b$$

$$I_{Na} = G_{Na} \cdot m^3 \cdot j \cdot h \cdot (V - E_{Na})$$

$$I_K = G_K \cdot X \cdot X_i \cdot (V - E_K)$$

$$I_{K1} = G_{K1} \cdot K1_\infty \cdot (V - E_{K1})$$

$$I_{Kp} = G_{Kp} \cdot Kp \cdot \left(V - E_{Kp}\right)$$

$$I_{si} = G_{si} \cdot d \cdot f \cdot (V - E_{si})$$

$$I_b = G_b \cdot (V - E_b)$$

where X_i, $K1_\infty$, and Kp are functions of V

Numerical Methods

For our single cell simulations, we used the forward difference method, a standard numerical technique with a simple implementation. After discretizing the time axis into evenly spaced steps, one can calculate the value of the next point in time based on the previous point by essentially treating the function as locally linear and projecting forward to the next point. Accuracy naturally increases as step-size decreases, since the evaluation takes place at a finer resolution. The drawback is increased computation to simulate the same span of time. However, if the step size is too large, the resulting behavior can be chaotic and have no bearing on the actual solution. In the context of the Luo-Rudy model, we used the following equations to update for each new point in time:

$$V_{i+1} = V_i + \Delta t\left(\frac{1}{C_m}\right)(I_{stim} - I_{ion})$$

$$y_{i+1} = y_i + \Delta t\left(\alpha_y(V)(1-y_i) - \beta_y(V)y_i\right)$$

$$Cai_{i+1} = Cai_i + \Delta t\left(-10^{-4} \cdot I_{si} - 0.07(10^{-4} - Cai_i)\right)$$

For the PDE version, we must also incorporate the spatial dimension into the simulation. We used the central difference method to approximate the second spatial derivative, another standard technique. In the context of the Luo-Rudy model, we used the following update rule for the voltage:

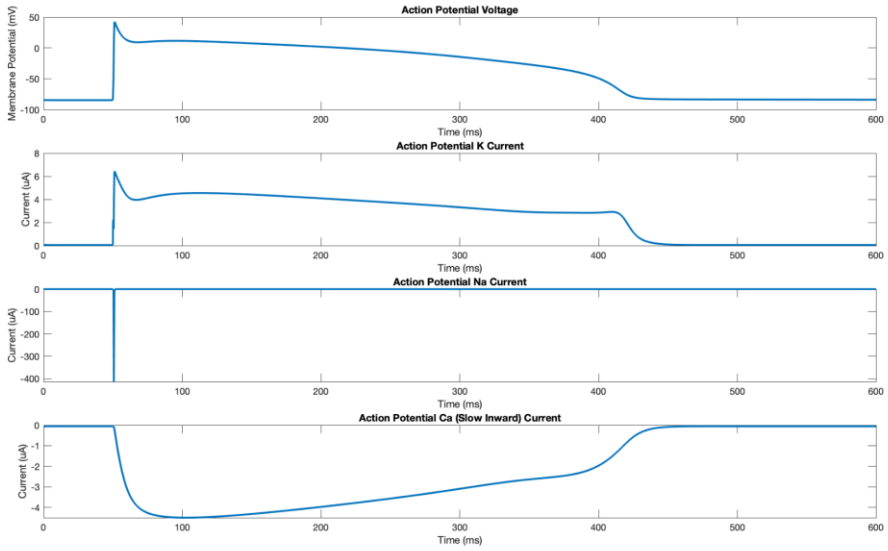
$$V^{j}{}_{i+1} = V^{j}{}_{i} + \Delta t \left(\frac{1}{C_m}\right)\left(I_{stim} - I_{ion} + \frac{V_i{}^{j-1} - 2V_i{}^{j} + V_i{}^{j+1}}{R_a \Delta x^2}\right)$$

While only the voltage equation changes substantially, the move to higher dimensions has an impact on the other variables as well. They are now defined at each point in space, and so they must be updated for the entire domain. Neighboring points are like neighboring cells in that they have their own independent gating variables. The only correlation comes from the diffusion of the signal, which we model with a diffusion of voltage.

In addition to the usual consideration of larger step size, this method requires that the ratio between the time step and the square of the space step is bounded by a constant determined by the coefficients of the diffusion term. This constraint is known as the CFL condition, and if violated, the results explode and have no meaning.

Results

We ran several numerical simulations to investigate different aspects of the model. In our first simulation in the single cell application, we used a 0.01ms time-step for a total time window of 600ms. We injected a stimulus current of 80μA at the 50ms mark, which lasted for 0.5ms. We used the default value 5.4mM for $[K]_o$. The goal was to analyze a single action potential under standard conditions. We plotted the standard voltage response of the action potential along with the currents associated with each ion:



The phenomenon we see in the graph reflects the high level overview of ion movement in the biological background. A fast and intense influx of sodium begins the process, before the sodium gates slam shut at the higher voltage the influx caused. The potassium gates rapidly open in response to the voltage spike, and the cell begins to repolarize as potassium leaves the cell, causing an initial dip in the voltage. By this time, the slowly opening calcium gates have finally begun to let calcium into the cell, and we see the characteristic long plateau of the

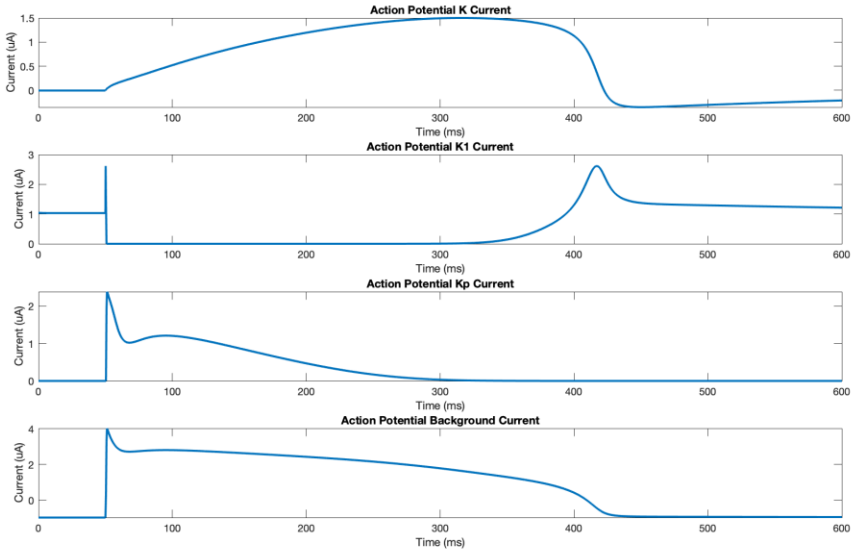
cardiac action potential. However, the potassium outflux outpaces the calcium influx, and the voltage continues to fall. The calcium gates begin to close in response, and in a final spike from the potassium current, the cell fully repolarizes.

The graph demonstrates a fuller picture than the original qualitative description. We begin to see why the original Luo-Rudy paper refers to the contributions of Na and Ca as the “fast sodium current” and the “slow-inward current” respectively. We can also see the limits of the notion of gates as either fully open or fully closed. The phenomenon of slow-inward calcium is only possible because the gates take time to open.

The graph also raises some questions. For instance, why are the sodium and calcium currents negative and the potassium current is positive? If a positive sodium ion enters the cell and makes the membrane potential more positive, it would make sense for the current to be positive too. However, the sign convention for Hodgkin-Huxley type models is typically inward negative for the ions and inward positive for the stimulus. The reason may be due to the historical usage of voltage clamps. Instead of measuring ion currents directly, experiments measure the current required to keep a voltage clamp constant. That current must oppose the ion current, hence the negative current convention.

Another question is why the calcium current is never the reverse sign. The calcium concentration must reach its original levels at some point, and so if calcium enters the cell, it should leave eventually. A closer look at the differential equation modeling $[Ca]_i$ shows that the model incorporates calcium concentration differently. The first term represents the increase in calcium due to the inward current. The second represents the concentration’s tendency to fall to 10^{-4}mM at a rate of decay of 0.07. It is worth remembering that this model is not about the movement of the ions, but rather the effect that moving ions have on the membrane potential.

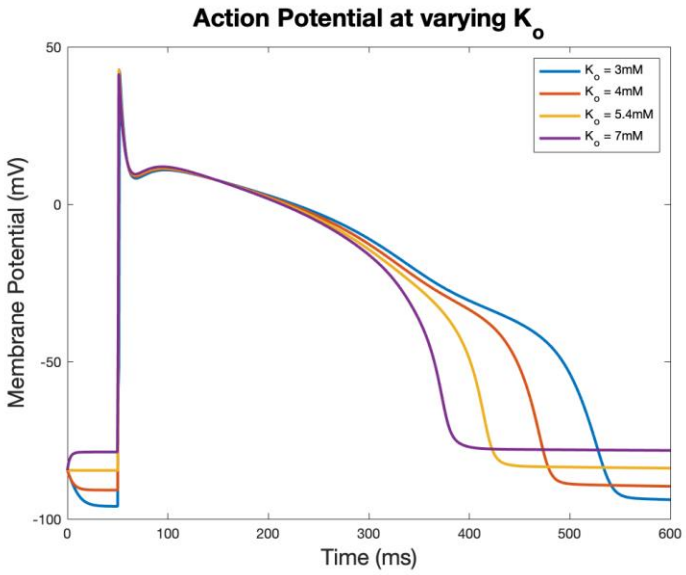
We also examined the role of the three different potassium channels. Prior to the Luo-Rudy model, cardiac action potential models typically had two potassium current terms. The contribution of the second channel is actually due to two separate channels (K1 and K_p) and a background current, collectively called the time-independent sodium current K1(T).



The time-dependent potassium current I_K takes a relatively long time to ramp up. The K_p channel is responsible for the initial response to the rapid sodium influx. The K1 channel is responsible for the final spike in potassium that repolarizes the cell. The Luo-Rudy model represents both time-independent currents with voltage gate functions rather than variables, which represent the gates' fast response to voltage change relative to the gates represented by time-dependent variables.

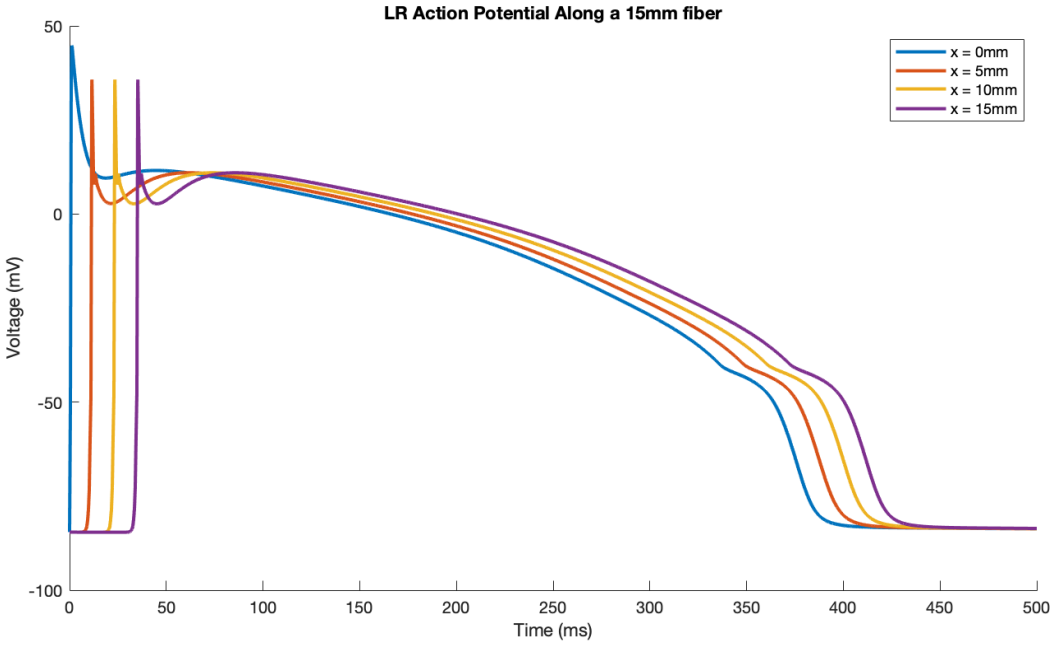
Note also that the K1 current is not 0 at equilibrium. Instead, the background current cancels out the K1 current, which is "leaky" at resting potential. The gate is firmly closed at higher potentials and fully open just above resting potential (which is what causes the last potassium spike at the end of the action potential). The initial spike of the K1 current is somewhat anomalous, since it is really a reaction to the first spike in voltage moving through the range where the gate is open.

Another main contribution of the Luo-Rudy model is its parameterization of potassium concentration outside the cell. One of the body's methods of regulating heart rate involves modulating the concentration of potassium. Both the equilibrium potential for potassium and the maximum conductance respond to changes in $[K]_o$. We can see the effects in the graph *Action Potential at varying* K_o:



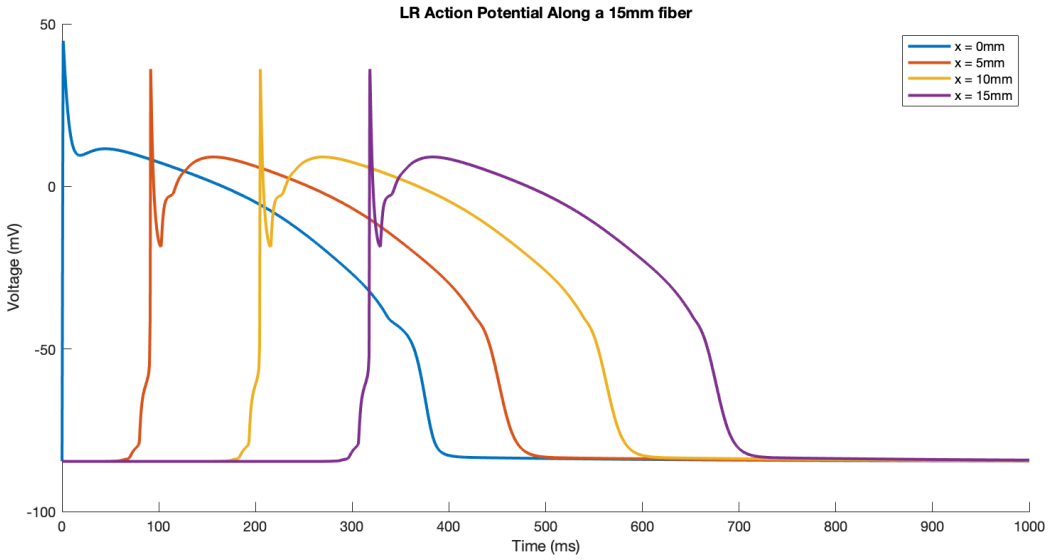
A higher concentration of potassium outside translates to a shorter duration for the action potential. A shorter duration would allow for more beats per minute. Also notice the higher resting potential at higher concentrations. All the simulations began at the resting potential for $[K]_o$=5.4mM, but they quickly converge to the equilibrium for the given concentration, and return to that point after the action potential has ended.

After thoroughly studying the single cell model, we moved on to the fiber model. We used a 15mm cardiac fiber, with a spatial step size of 0.5mm and a temporal step size of 0.01. We used a stimulus with the same size and duration as in the single cell experiments, localized to the cell at the 0mm point. We experimented with the value of the resistance. For the first trial, we used a resistance of 50kOhms.



We can see from the graph that the signal takes some time to propagate along the fiber, and it takes approximately equal intervals to reach equidistant points. At each point, the voltage reaches a certain threshold, an action potential fires, and the voltage takes on the shape of an ordinary action potential in the single cell model.

In the next experiment, we used a resistance of 150kOhms. The results make intuitive sense: a higher resistance translates to a lower diffusion constant, and it takes longer for the action potential to travel down the fiber.



Conclusion

In our project, we simulated the membrane potential of a cardiac cell and a cardiac fiber during action potential using the Luo-Rudy model. We used numerical methods (finite difference) implemented in Matlab to approximate solutions to the model's eight variable system of ordinary differential equations. We also studied an extension of the model that includes a spatial component, and solved the system of one partial differential equation and seven ordinary differential equations. We used these simulations to explore the effects of potassium concentration of the duration of the action potential, and the effect of resistance on the rate of propagation. Our project is an example of how biology, mathematics, and computation can converge to refine and quantify our descriptions of vital phenomena.

References

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