Mathematical Modeling of the American Lobster Cardiac Muscle Cell: An Investigation of Calcium Ion Permeability and Force of Contractions

Lauren A. Skerritt
Bowdoin College, lskerrit@bowdoin.edu

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Mathematical Modeling of the American Lobster Cardiac Muscle Cell: An Investigation of Calcium Ion Permeability and Force of Contractions

An Honors Paper for the Department of Mathematics

By Lauren Alyson Skerritt

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1. Abstract

In the American lobster (*Homarus americanus*), neurogenic stimulation of the heart drives fluxes of calcium (Ca\(^{2+}\)) into the cytoplasm of a muscle cell resulting in heart muscle contraction. The heartbeat is completed by the active transport of calcium out of the cytoplasm into extracellular and intracellular spaces. An increase in the frequency of calcium release is expected to increase amplitude and duration of muscle contraction. This makes sense because an increase in cytoplasmic calcium should increase the activation of the muscle contractile elements (actin and myosin). Since calcium cycling is a reaction-diffusion process, the extent to which calcium mediates contraction amplitude and frequency will depend on the specific diffusion relationships of calcium in this system. Despite the importance of understanding this relationship, it is difficult to obtain experimental information on the dynamics of cytoplasmic calcium. Thus, we developed a mathematical diffusion model of the myofibril (muscle cell) to simulate calcium cycling in the lobster cardiac muscle cell. The amplitude and duration of the force curves produced by the model empirically mirrored that of the experimental data over a range of calcium diffusion coefficients (1-16), nerve stimulation durations (1/6-1/3 of a contraction period), and frequencies (40-80 Hz). The characteristics that alter the response of the lobster cardiac muscle system are stimulation duration (i.e., burst duration), burst frequency, and the rate of calcium diffusion into the cell’s cytoplasm. For this reason, we developed protocols that allow parameters representing these characteristics in the calcium-force model to be determined from isolated whole muscle experiments on lobster hearts (Phillips *et al.*, 2004). These parameters are used to predict variability in lobster heart muscle function consistent with data recorded in experiments.

Within the physiological range of nerve stimulation parameters (burst duration and cycle period), calcium increased the cell’s force output for increased burst duration. For example, increased duration of stimulation increased the muscle contraction period and *vice versa*. In terms of diffusion, a slower rate of calcium diffusion out of the sarcoplasmic reticulum decreased both the calcium level and the contraction duration of the cell. Finally, changes in stimulation frequency did not produce changes in contraction amplitude and duration. When considered in conjunction with experimental stimulations using lobster heart muscle cells, these data illustrate the prominent role for calcium diffusion in governing contraction-relaxation cycles in lobster hearts.
2. Introduction

2.1 Biological Background

The cardiac muscle system is an organization of biochemical processes and physical structures interworking to create forceful contractions that pump blood throughout the body. An essential component to this system is the cardiac muscle, which undergoes the rhythmic contractions of the heartbeat. Due to its relatively simple structure and function, modeling the cardiac muscle of the American lobster, *Homarus americanus*, is a good starting point for understanding heart function more generally.

A central feature of this system is the interaction of the muscle contractile microfilaments, myosin and actin, to produce a contraction (Rice *et al.*, 2000). When the muscle is relaxed, a protein called troponin blocks the myosin-binding site on actin and prevents myosin from binding. However, when calcium (Ca$^{2+}$) is present, calcium binds to troponin, altering its conformation with actin and allowing the myosin to bind to actin’s myosin-binding site.

Thus, it is important to understand mechanisms underlying the movement of calcium into the cytoplasm. Moving from a region of high concentration to a region of low concentration in the lobster muscle cell, calcium diffuses into the cytoplasm from an intracellular organelle that stores much of the cell’s calcium—the sarcoplasmic reticulum (SR)—and from the exterior of the cell (described in Shinozaki *et al.*, 2002). The presence of calcium in the cell is dependent upon a depolarization of the muscle cell membrane by nerve cells that functions to open calcium channels in the muscle cell membrane (the sarcolemma) and the SR.
There are many analogies between this diffusion process in lobster cardiac muscle cells and mammalian skeletal muscle cells (Shinozaki et al., 2004). Since *H. americanus* lobster cardiac muscle cells are organized much in the same way mammalian striated muscle cells are organized, and since calcium dynamics are better understood for mammalian striated muscle, a comparison can enable a more detailed understanding of calcium diffusion in the lobster heart. More specifically, muscle contractions are generated from an ordered series of cellular processes. When in a relaxed state, a heart muscle cell has a high concentration of calcium in the sarcoplasmic reticulum. Immediately following a depolarization event by a nerve cell, a small amount of calcium crosses the cell membrane via surface membrane calcium channel proteins (Keener and Sneyd, 2010). For example, the contribution of intracellular calcium from the extracellular space in rat heart muscle cells is on the order of 8% of the total calcium influx; however, it should be noted that in some mammals, such as rabbits, the contribution could be as high as 30% (Bers, 2000). Once open, these cell membrane proteins permit flow of extracellular calcium into the cell by diffusion. The influx of calcium from the exterior of the cell elicits an additional influx of calcium into the cytoplasm from the SR—a process termed calcium mediated-calcium release.

As discussed previously, calcium in the cytoplasm exposes the myosin-binding sites on actin. During this myosin and actin binding, one calcium ion binds causing one myosin to bind to one actin (Spudich & Watt, 1971). To return a contracted muscle cell (myofibril) to its relaxed state, calcium is extruded from the sarcoplasm by calcium pumps on the sarcoplasmic reticulum and the cell membrane. The muscle cell remains inactive until the following depolarization, in which this cycle repeats.
A stable heartbeat, with constant contraction amplitude, is produced by continuous repetition of this calcium release and extrusion cycle (Fig. 2A). Although there is a relatively clear understanding of calcium movement in the muscle cell, it is less clear how contraction force is modulated by calcium release from the sarcoplasmic reticulum (i.e., the excitation-contraction coupling relationship). For example, it is thought that a greater influx of Ca\(^{2+}\) in a contraction cycle increases the strength of the muscle contraction in the next cycle, but it remains unknown as to the scale of this effect on lobster heart contraction force. Rice et al. (1998) tracked the release and uptake of calcium in guinea pig hearts and found that a decrease in the fraction of calcium released from the sarcoplasmic reticulum during a muscle contraction also decreased the magnitude and the duration of the contraction. Conversely, an increase in the fraction of calcium released from the sarcoplasmic reticulum increased both the magnitude of the contraction and the duration of the heart muscle contraction. Most likely this is because the troponin had more calcium available to bind and elicit myosin-actin activity. Mathematical models of the calcium dynamics of the lobster heart muscle would enable a better understanding of the role of calcium diffusion heart contraction.

Flexibility in the diffusion of cellular calcium enables flexibility in the control of heartbeat in response to changing environmental conditions. The central feature of the lobster heart that controls this flexibility is the rhythm-producing network called the central pattern generator (CPG). The lobster CPG consists of nine neurons that together comprise the cardiac ganglion (Fig. 1). Thus, unlike the mammalian myogenic heart, the lobster heart is neurogenic such that a network of nerves in the cardiac muscle controls the heart’s rhythmic contractions. Experimental recordings of the natural lobster
heartbeat demonstrate the response of cardiac muscle to neurogenic stimulations (i.e., depolarization events). In these experiments, the ganglion was removed and the muscle was stimulated with an electrode. By mimicking neurogenic signals, researchers have been able to demonstrate how heartbeat variability results from variation in nerve stimulations (Williams et al., 2012). Parameters that control this variability allow us to observe the time difference between the muscle receiving a stimulus and the resulting contraction (Fig 2B). Such parameters include the duration of a stimulation (burst duration), the frequency of a stimulation, the duration of stimulation per period of a full stimulation cycle (duty cycle), and the rate of calcium diffusion into the cell (as mediated by the diffusion coefficient, which is a molecule and medium-specific proportionality constant). Thus, we may observe variation in the amount and timing of calcium release into the cytoplasm, providing us with pertinent insights into lobster heart muscle physiology.

In this study, the lobster cardiac muscle cell contraction was mathematically reproduced by creating a one-cell model of the lobster muscle cell, adapted from models of calcium diffusion (Sneyd, 2007; Farlow, 1993) and muscle contraction force (Phillips et al., 2004). Our model allowed us to make predictions about the effects of calcium variability on the qualitative features of the heartbeat, such as calcium diffusion, stimulation duration, and frequency of stimulations. This approach examines the effects of calcium permeability and fluxes of calcium across the sarcoplasmic reticulum during a lobster heart cell contraction. We found that altering the diffusion rate and the concentration of calcium moving across the sarcoplasmic reticulum qualitatively altered the pattern of lobster cardiac muscle contractions. Thus, our model results provide insight
into the dynamics of calcium and contraction force of muscle cells that may be
generalized to the larger, lobster muscle fibers.

2.2 Purpose

This study models the contraction of the lobster heart as it is driven by fluxes of
calcium between membrane-bound compartments in the cell. Our goal is to give insight
into the role of calcium in the excitation-contraction of the lobster heart (Shinozaki et al.,
2002). The model parameterizes the model’s force and calcium behavior using empirical
data on heart stimulation and contraction. The combination of a phenomenological force
differential equation with an initial boundary value problem (IBVP) representing the
outputs of calcium oscillations expands the understanding of how lobster heart cardiac
cells function.

Figure 1. (A) A schematic of the lobster heart. The lobster heart muscle, located between
its legs on the dorsal side of the lobster, is a highly organized contractile unit composed
of muscle cells, whose central function elicits a heartbeat. (B) Image of a lobster heart
preparation taken July 2013. (C) Three possible levels of modulation in the central
pattern generator of the H. americanus lobster heart exist. These include changes at the
level of the cardiac ganglion, the level of the cardiac muscle, and the stretch feedback
that acts directly on the cardiac ganglion and the myocardium. See Appendix C for more
experimental setup details.
Figure 2. (A) Force recording of a stably contracting lobster heart with similar burst durations and amplitudes of heartbeats, or contractions. The burst duration is the period of time it takes a lobster heart muscle to cycle through a contracted and relaxed state in a single contraction. The amplitude of a contraction is the magnitude of force output exerted by the muscle. Data were recorded using force recording software, Spike2 v7.3 (Cambridge Electronic Design, Cambridge, UK) on July 24, 2013 in the Dickinson Lab, Bowdoin College, Brunswick, ME. (B) Example trace of spike strains delivered to the motor nerve in the lobster heart (top) and the heart’s subsequent contraction response to the stimulation (bottom). These data were collected from a lobster-stimulated preparation performed by Andrew Calkins (2012). Calkins removed the nerves in the heart and stimulated the heart with a 60 Hz electrode.
3. Theory of Mathematical Modeling: Translating Biology into Math

In this section we create a calcium-force model that reflects the lobster cardiac cell contractions and better encompasses its muscle-chemical dynamics. The methods for modeling the diffusion of calcium are also described.

3.1 Isolated Muscle Cell Model

3.1.1 The Force Model

As discussed previously, the anatomical structures of *H. americanus* lobster cardiac muscle cells are organized much in the same way as human striated muscle. Thus, we developed our lobster heart model from a biomimetic-type model of skeletal muscle isometric contraction (constant length during force changes); however, we will alter the calcium diffusion dynamics of the model to better represent the movement of calcium in and out of the cell. Note that biomimetic models reproduce biological phenomena using differential equations. The Phillips *et al.* (2004) model for skeletal muscle contraction is an excellent model for understanding the chemical and force dynamics of the American lobster heart muscle model. Since another paper has detailed the strengths and limitations of the Phillips *et al.* (2004) model, we have used this model as the foundational starting point for the advancement of our isometric cardiac muscle cell model (Neidhard-Doll *et al*., 2004).

The mechanics of this tractable force model represent the rate of change of force with respect to time for a single muscle cell and is described for a striated skeletal muscle cell in the Phillips *et al.* (2004) isometric force model as

\[
\frac{dF}{dt} = \frac{1}{\tau_2} \frac{dF}{dc} C - \frac{1}{\tau_3} F \quad \text{(units } \frac{mg}{ms})\text{.}
\]
Note that all variables in this model are named by Phillips et al. (2004). The variables C and F represent the concentration of calcium in the muscle cell’s sarcoplasm (µM) at any point in time and the force of contraction in a muscle cell (mg), respectively. The time constant $\frac{1}{\tau_2}$ represents the absorption rate of calcium into the cytoplasm ($\frac{1}{ms}$) and is a fitted parameter of their model. The coefficient $\frac{dF}{dC}$ is a constant that models the rate of change of isometric force with respect to the calcium concentration in the cytoplasm of the muscle cell ($\frac{mg}{µM}$). Together $\frac{1}{\tau_2}$ and $\frac{dF}{dC}$ form the parameter by which the calcium concentration is chemo-mechanically coupled to the active force of contractions. Phillips et al. (2004) used a value of $0.0572 - \frac{mg}{µM*ms}$ in their model of a skeletal muscle cell. The time constant $\frac{1}{\tau_3}$ represents the exponential decay rate during the relaxation period following the cell’s contraction ($\frac{1}{ms}$) and is also a fitted parameter of the model. Units are those used by Phillips et al. (2004).

Phillips et al. (2004) have coupled the preceding force differential equation (ODE) with a system of differential equations representing the rate of change of calcium concentration cross the sarcoplasmic reticulum with respect to time ($\frac{dC}{dt}$) and the permeability of the sarcoplasmic reticulum membrane to ion fluxes ($\frac{dP}{dt}$). The Phillips et al.’s (2004) calcium differential equations can mathematically interpret calcium concentration within the muscle cell at any time as follows:

$$\frac{dC}{dt} = k_1^*P - k_2C \quad \text{(units } \frac{µM}{ms})$$

$$\frac{dP}{dt} = -k_1P \quad \text{(units } \frac{µm}{ms^2})$$
The variables P and C represent the permeability of the sarcoplasmic reticulum ($\frac{\mu m}{ms}$) and the concentration of calcium in the muscle cell’s sarcoplasm ($\mu M$) at any point in time, respectively. The constant $k_1^*$ represents the phenomenological coupling of the sarcoplasmic reticulum ion permeability to calcium concentration ($\frac{\mu M}{ms}$), where phenomenological coupling here means that a mathematical model is constructed such that the output fits the patterns shown in experimental recordings. The constant $k_2$, which is also a fitted parameter, represents the exponential decay rate of calcium concentration in the cytoplasm during the relaxation period following the cell’s contraction ($\frac{1}{ms}$), and the coefficient $k_1$ in the permeability differential equation imitates the exponential decay rate constant of the sarcoplasmic reticulum’s permeability. The solution curves for active force, calcium concentration, and permeability ODE’s during a single muscle cell contraction can be viewed using Wolfram Mathematica 9.0 (Fig. 3).

![Graph](image)

**Figure 3.** The simultaneous solution curve for active force, calcium concentration, and permeability during the time course of a single muscle cell contraction.
We are concentrating on the changing the Phillips et al. (2004) calcium concentration and permeability differential equations—the relationship of calcium is likely to be different in the lobster heart than the mammalian calcium model Phillips et al. (2004) created. So, despite the strengths of the Phillip et al.’s (2004) model in terms of modeling contraction force, we felt that the calcium and permeability differential equations could use further development (Neidhard-Doll et al., 2004). Thus, in this lobster muscle model, the calcium dynamical component, which defines the permeability of the muscle to calcium during an isometric contraction, is altered to qualitatively resemble the movement of calcium into the cytoplasm following a depolarization. Since calcium is a diffusion object, we use diffusion to model its behavior. Particularly, we must use a partial differential equation, to rely on both temporal and spatial variables when describing the diffusion of calcium from one compartment of the cell to the other. This calcium model is constructed to predict the calcium oscillations in the cytoplasm that generate physical contraction of the myosin and actin during the time course of a single cardiac cell contraction.

3.1.1 Modeling the Force of Contractions using Calcium Diffusion

Modeling calcium movement in the lobster heart muscle cell:

In this section, the methods developed to simulate calcium diffusion and re-uptake during the time course of a lobster heart muscle contraction were derived from the Sneyd (2007) diffusion model for calcium influx and outflow and were used in place of Phillips et al.’s (2004) calcium and permeability differential equation methods. The flux of calcium experimentally observed across the cell membrane and the sarcoplasmic reticulum membrane are dynamic and complex (Fig. 4), thus a more developed model is
necessary to better predict the oscillation of calcium in the sarcoplasm of the lobster heart muscle cell (Shinozaki et al., 2004).

![Figure 4. Schematic diagramming calcium's movement in a cell (from Sneyd, 2007).](image)

As Sneyd (2007) describes, a calcium concentration model in terms of a partial differential equation has much more descriptive power when modeling the oscillations of calcium in the sarcoplasmic reticulum as compared to Phillips et al.’s (2004) simple single temporal variable ODE (Keener and Sneyd, 1998). So, we will use both temporal and spatial variables when describing the diffusion of calcium from one compartment of the cell to the other. Using Sneyd’s (2007) model,

\[ \frac{\partial C}{\partial t} = D \nabla^2 C + J_{\text{release}} - J_{\text{serca}}, \]

as the starting point of the calcium concentration diffusion, the calcium PDE was developed to mathematically predict these calcium oscillations. The rate of change of calcium concentration with respect to time given an \((x,y)\) position in the muscle cell \(\frac{\partial C}{\partial t}\) is primarily driven by the Laplace two-dimensional diffusion variable \(\nabla^2 C\). Note,

\[ \nabla^2 C = C_{xx} + C_{yy} \]
represents the second-order PDE modeling the rapid movement of calcium into the
cytoplasm. The variable $J_{\text{release}}$ represents the diffusion rate of calcium from the
sarcoplasmic reticulum into the cytoplasm, and $J_{\text{serca}}$ represents the diffusion rate of
calcium uptake into the sarcoplasmic reticulum from the cytoplasm. The diffusion
coefficient D for calcium is an experimentally measurable quantity and is typically used
as a constant in modeling studies (Sneyd, 2007). For simplicity, to start we used a
diffusion coefficient of 1; later we show how changes in magnitude of the diffusion
coefficient alter the behavior of the model. Together, D and the Laplacian $\nabla^2 C$
determine the diffusion of calcium in the cell.

An important aspect of the model is the sarcoplasmic reticulum calcium
movement through the $J_{\text{release}}$ and $J_{\text{serca}}$ component. The channel receptors on the
surface of the sarcoplasmic reticulum open during a depolarization causing calcium to
diffuse down its concentration gradient. When the cell has completed its contraction,
calcium is actively pumped back into the sarcoplasmic reticulum and across the
sarcolemma, and the heart relaxes. Thus, the $J_{\text{release}} - J_{\text{serca}}$ term is representative of the
calcium injected inside the cell. Since this component is a time dependent parameter, and
thus it only changes over time, we can see the $J_{\text{release}} - J_{\text{serca}}$ can only be viewed as we
run the PDE with time increasing. We can think of the sarcoplasmic reticulum injecting
into this cell everywhere, because there is no spatial component (x,y) variable. This is
biologically reasonable, because the sarcoplasmic reticulum is dispersed across the entire
cell. As a starting point for building the model, a trigonometric function was used to
represent $J_{\text{release}} - J_{\text{serca}}$ because of the oscillatory nature of this function:

$$ J_{\text{release}} - J_{\text{serca}} = \pi \cos(t). $$
This function demonstrates a positive and negative influence in the flow of calcium within the system given an amplitude of \( \pi \) and a period of \( 2\pi \). Particularly, these values were experimentally determined to provide a stable mathematical representation of the influx and outflow of calcium from the sarcoplasmic reticulum.

The flow of calcium across the boundary of the cell couples the PDE to give the boundary conditions of the cell (Sneyd, 2007). The directional derivative in the normal direction, which determines the rate of change of the calcium concentration in the normal direction of a particular position \((x,y)\) in the cell cytoplasm (Fig. 5), describes the steepness of the calcium concentration gradient across the cell membrane \( C_n \). The boundary conditions are

\[
C_n = \frac{J_{\text{influx}} - J_{\text{pm}}}{D}
\]

such that \( J_{\text{influx}} \) represent the rate of calcium from the extracellular space into the cytoplasm and \( J_{\text{pm}} \) represents the rate of calcium expulsion from the cytoplasm to the outside of the cell. Again, \( D \) is the diffusion coefficient for calcium in a muscle cell, scaling the boundary conditions calcium concentration values appropriate for that for skeletal muscle cells.

**Figure 5.** Diagram demonstrating the flow of calcium at the boundary of the cell are represented by \( c_n \) is

\[
\begin{align*}
c_n(x,0,t) &= c_y(x,0,t) = 0, \\
c_n(x,1,t) &= c_y(x,1,t) = 0, \\
c_n(0,y,t) &= c_x(0,y,t) = 0, \\
c_n(1,y,t) &= c_x(1,y,t) = 0.
\end{align*}
\]
To build some intuition about the dynamics of the initial boundary value problem (IBVP), the boundary conditions are set to zero, meaning that no calcium is moving into or out of the cell.

\[ C_n = \frac{I_{influx} - I_{pm}}{D} = 0 \]

The final integral component of the calcium concentration IBVP is the initial condition, demonstrating the concentration of calcium at any position \((x,y)\) in the cell at time zero. The initial condition determines the start concentration of calcium within the cytoplasm at time \(t=0\). For all time greater than \(t=0\), the PDE is the component of this model that determines the concentration of calcium at position \((x,y)\) during a contraction (Fig. 6). Given this, an equation for the initial condition needed to satisfy the condition that there was a region of high concentration and a region of low concentration in the cell such that calcium would diffuse down its concentration gradient. For simplicity, we chose an equation

\[ C[x, y, 0] = \cos \left( \pi \left( x - \frac{1}{2} \right) \right) \times \cos \left( \pi \left( y - \frac{1}{2} \right) \right), \]

which describes a variation of concentrations across the cell cytoplasm at time 0 (Fig. 7). To develop a depiction of calcium concentrations in the cytoplasm, the next stage of this mathematical analysis must fit the initial condition with appropriate values found from fitting the data.
Figure 6. (modified from Sneyd, 2007) Diagram of the fluxes of calcium across the sarcoplasmic reticulum and the fluxes across the boundary of the muscle cell. The compartment labelled “c” is the cytoplasm.

Figure 7. Plot depicts the initial condition of calcium in the cytoplasm at time zero.

Although the calcium concentration IBVP is in its theoretical stages and lacks experimentally fit measurements of the lobster heart muscle cell, we may move forward to gain a theoretical understanding of the lobster heart’s chemical-muscle dynamics by analyzing the features of this theoretical equation. Later, we will discuss our methods for fitting the model to experimental data.

**Summary of equations:**

The force of contractions of a lobster heart muscle cell is modeled by

\[ \frac{df}{dt} = \frac{1}{\tau_2} \frac{df}{dc} C - \frac{1}{\tau_3} F. \]

The simultaneous calcium dynamics in a lobster heart muscle cell is modeled by

PDE: \[ \frac{\partial C}{\partial t} = D \nabla^2 C + \pi \cos(t) \]

Boundary condition: \[ C_n = \frac{j_{\text{influx}} - j_{pm}}{D} = 0 \]

Initial condition: \[ C[x, y, 0] = \cos\left(\pi \left(x - \frac{1}{2}\right)\right) \ast \cos\left(\pi \left(y - \frac{1}{2}\right)\right) \]
3.2 Analytical Solutions to the Calcium Diffusion Initial Boundary Value Problem

3.2.1 Separation of Variables

In this section, we will present the methods for solving the IBVP using a common procedure termed separation of variables (Tyn Myint, 1973). We begin by separating variables first into t versus (x,y), which lead to an ODE in t and a new PDE in (x,y). Then, the variable x and y in the new PDE are separate to turn it into a pair of ODEs. If this calcium PDE were to be solvable, this method of separation of variable should result in three ODEs which can each be solved separately using ODE techniques (Farlow, 2012). Let us, then, attempt to solve the calcium PDE using separation of variable methods as presented below.

Calcium IBVP (Cartesian):

<table>
<thead>
<tr>
<th>Equation</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \frac{\partial C}{\partial t} = D \nabla^2 C = D(C_{xx} + C_{yy}) )</td>
<td>( 0 \leq x \leq 1, 0 \leq t \leq \infty )</td>
</tr>
<tr>
<td>( \frac{J_{\text{influx}} - J_{\text{pm}}}{D} )</td>
<td>( 0 \leq t \leq \infty )</td>
</tr>
<tr>
<td>( C(x, y, 0) = \cos \left( \pi \left( x - \frac{1}{2} \right) \right) \cos \left( \pi \left( y - \frac{1}{2} \right) \right) )</td>
<td>( 0 \leq x \leq 1, 0 \leq y \leq 1 )</td>
</tr>
</tbody>
</table>

Step 1: Finding solutions to the calcium PDE

To begin, we look for solutions of the form \( C(x, y, t) = T(t)\phi(x, y) \) by substituting \( T(t)\phi(x, y) \) into the PDE and solving for \( T(t)\phi(x, y) \). Making this substitution gives

\[ \phi(x, y)T'(t) = D(\phi_{xx} + \phi_{yy})T(t). \]

We obtain the separated variables if we divide each side of the equation by \( D\phi(x, y)T(t) \) to arrive at
\[
\frac{T'(t)}{D T(t)} = \frac{\phi_{xx} + \phi_{yy}}{\phi(x,y)}
\]

In as much as \(x/y\) and \(t\) are independent of each other, each side must be a fixed constant \(k\) (non-negative); hence, we write
\[
\frac{T'}{D T} = \frac{\phi_{xx} + \phi_{yy}}{\phi} = k
\]
or
\[
T' - kD T = 0
\]
\[
\phi_{xx} + \phi_{yy} - k \phi = 0
\]
Now we solve the ODE in \(t\). Note, we are also left with a PDE in \(x, y\). Later, I will perform separation of variables to reduce the PDE into two standard-type ODEs of \(x\) and \(y\), respectively.

Renaming \(k = -\lambda^2\) where \(\lambda\) is nonzero, we can represent our separated variables as
\[
T' + \lambda^2 D T = 0
\]
\[
\phi_{xx} + \phi_{yy} + \lambda^2 \phi = 0
\]
Solving the standard-type ODE in \(t\), we get the solution
\[
T(t) = A e^{-\lambda^2 D t} \quad (A \text{ is an arbitrary constant})
\]
Next, we solve the \(x, y\) PDE. To begin, we look for the solutions of the form \(\phi(x, y) = f(x)g(y)\) by substituting \(f(x)g(y)\) into the PDE
\[
\phi_{xx} + \phi_{yy} + \lambda^2 \phi(x,y) = 0
\]
\[
\phi_{xx} + \phi_{yy} = -\lambda^2 \phi(x,y)
\]
Making this substitution gives
\[
f''(x)g(y) + f(x)g''(y) = -\lambda^2 f(x)g(y)
\]
So, we obtained the separated variables if we divide each side of the equation by \( f(x)g(y) \), we have

\[
\frac{f''(x)g(y) + f(x)g''(y)}{f(x)g(y)} = \frac{-\lambda^2 f(x)g(y)}{f(x)g(y)}
\]

implies

\[
\frac{f''(x)g(y) + f(x)g''(y)}{f(x)g(y)} = 1
\]

implies

\[
\frac{f''(x)}{f(x)} + \frac{g''(y)}{g(y)} = -\lambda^2.
\]

Thus, we arrive at the equation

\[
\frac{f''(x)}{f(x)} = -\lambda^2 - \frac{g''(y)}{g(y)}
\]

In as much as \( x \) and \( y \) are independent of each other, each side must be a fixed constant \( c \); hence, we write

\[
\frac{f''(x)}{f(x)} = -\lambda^2 - \frac{g''(y)}{g(y)} = c
\]

So

\[
\frac{f''(x)}{f(x)} = c \quad \text{and} \quad -\lambda^2 - \frac{g''(y)}{g(y)} = c
\]

Solving the standard-type ODE in \( x \) and \( y \) (using Wolfram Mathematica 9.0), we get the solutions

\[
\frac{f''(x)}{f(x)} = c \quad \text{and} \quad -\lambda^2 - \frac{g''(y)}{g(y)} = c
\]

implies
\[ f(x) = B \cos(\sqrt{c}x) + C \sin(\sqrt{c}x) \]

and implies
\[ g(y) = D \cos(\sqrt{(c - \lambda^2)}y) + E \sin(\sqrt{(c - \lambda^2)}y) \]

Summary of the PDE’s solutions:
\[ T(t) = A e^{-\lambda^2Dt} \quad \text{(A is an arbitrary constant)} \]
\[ f(x) = B \cos(\sqrt{c}x) + C \sin(\sqrt{c}x) \quad \text{(B, C are an arbitrary constants)} \]
\[ g(y) = D \cos(\sqrt{(c - \lambda^2)}y) + E \sin(\sqrt{(c - \lambda^2)}y) \quad \text{(D, E are an arbitrary constants)} \]

and hence all functions
\[ C(x, y, t) = A e^{-\lambda^2Dt} [B \cos(\sqrt{c}x) + C \sin(\sqrt{c}x)][D \cos(\sqrt{(c - \lambda^2)}y) + E \sin(\sqrt{(c - \lambda^2)}y)]. \]

Step 2: Finding solutions to the PDE and the Boundary Conditions

To choose a certain subset of our current crop of solutions
\[ C(x, y, t) = A e^{-\lambda^2Dt} [B \cos(\sqrt{c}x) + C \sin(\sqrt{c}x)] [D \cos(\sqrt{(c - \lambda^2)}y) + E \sin(\sqrt{(c - \lambda^2)}y)] \]

that satisfy the boundary conditions (BCs)
\[ C(0,0,t)=0 \]
\[ C(1,0,t)=0 \]
\[ C(0,1,t)=0 \]
\[ C(1,1,t)=0 \]

We must substitute our solutions into these BCs. This substitution gives
\[ C(0,0, t) = AB[D + E]e^{-\lambda^2Dt} = 0, \]
which implies

\[ AB[D + E] = 0, \]

and

\[ C(1,0,t) = A[D + E] e^{-\lambda^2 D t} \left[ B \cos(\sqrt{c}) + C \sin(\sqrt{c}) \right] = 0, \]

which implies

\[ B \cos(\sqrt{c}) + C \sin(\sqrt{c}) = 0. \]

When \( B = 0, \sqrt{c} = n\pi \) implies \( c = (n\pi)^2 \).

When \( C = 0, \sqrt{c} = \frac{(2n+1)\pi}{2} \) implies \( c = \left(\frac{(2n+1)\pi}{2}\right)^2 \).

\[ C(0,1,t) = AB e^{-\lambda^2 D t} \left[ D \cos\left(\sqrt{c - \lambda^2}\right) + E \sin\left(\sqrt{c - \lambda^2}\right) \right] = 0 \]

When \( D = 0, \sqrt{c - \lambda^2} = n\pi \) implies \( \lambda^2_n = c - (n\pi)^2 \).

When \( E = 0, \sqrt{c - \lambda^2} = \frac{(2n+1)\pi}{2} \) implies \( \lambda^2_n = c - \left(\frac{(2n+1)\pi}{2}\right)^2 \).

\[ C(1,1,t) = A e^{-\lambda^2 D t} \left[ B \cos(\sqrt{c}) + C \sin(\sqrt{c}) \right] \left[ D \cos\left(\sqrt{c - \lambda^2}\right) + E \sin\left(\sqrt{c - \lambda^2}\right) \right] = 0 \]

implies

\[ B \cos(\sqrt{c}) + C \sin(\sqrt{c}) = 0 \; ; \; D \cos\left(\sqrt{c - \lambda^2}\right) + E \sin\left(\sqrt{c - \lambda^2}\right) = 0 \]

In order that \( C(0,0,t)=0, C(1,0,t)=0, C(0,1,t)=0, C(1,1,t)=0 \), it is necessary to pick

\[ \sqrt{c} = \pm \pi, \pm 2\pi, \pm 3\pi \ldots \quad \text{or} \quad \sqrt{c}_n = \pm n\pi \quad n = 1,2,3, \ldots \quad \text{when} \; B = 0 \]

\[ \sqrt{c} = \pm \frac{\pi}{2}, \pm \frac{3\pi}{2}, \pm \frac{5\pi}{2} \ldots \quad \text{or} \quad \sqrt{c}_n = \pm \frac{2n-1}{2} \pi \quad n = 1,2,3, \ldots \quad \text{when} \; C = 0 \]

\[ \sqrt{c - \lambda^2} = \pm \pi, \pm 2\pi, \pm 3\pi \ldots \quad \text{or} \quad \sqrt{c - \lambda^2}_n = \pm n\pi \quad n = 1,2,3, \ldots \quad \text{when} \; D = 0 \]

\[ \sqrt{c - \lambda^2} = \pm \frac{\pi}{2}, \pm \frac{3\pi}{2}, \pm \frac{5\pi}{2} \ldots \quad \text{or} \quad \sqrt{c - \lambda^2}_n = \pm \frac{2n-1}{2} \pi \quad n = 1,2,3, \ldots \quad \text{when} \; E = 0 \]
Note the last BC could also imply A=0, but if we chose this, we could get the zero solutions in our answer. Now finishing the second step, we have found an infinite number of functions (index differently because the integers are different for each infinite series)

\[ C_n(x, y, t) = e^{-\lambda_n D t} \sin(n \pi x) \left[ D_n \cos \left( y \sqrt{- (n \pi)^2} \right) + E_n \sin \left( y \sqrt{- (n \pi)^2} \right) \right] \]

\[ C_m(x, y, t) = e^{-\lambda_m D t} \cos \left( \frac{(2m+1)\pi}{2} x \right) \left[ D_m \cos \left( y \sqrt{- \left( \frac{(2m+1)\pi}{2} \right)^2} \right) \right. \]

\[ \left. + E_m \sin \left( y \sqrt{- \left( \frac{(2m+1)\pi}{2} \right)^2} \right) \right] \]

\[ C_p(x, y, t) = e^{-\lambda_p D t} \left[ B_p \cos \left( x \frac{(2p+1)\pi}{2} \right) + C_p \sin \left( x \frac{(2p+1)\pi}{2} \right) \right] \sin \left( y \sqrt{- (p \pi)^2} \right) \]

\[ C_q(x, y, t) = e^{-\lambda_q D t} \left[ B_q \cos \left( x \frac{(2q+1)\pi}{2} \right) + C_q \sin \left( x \frac{(2q+1)\pi}{2} \right) \right] \cos \left( y \sqrt{- \left( \frac{(2q+1)\pi}{2} \right)^2} \right) \]

Lastly, we add the infinite series of \( C_n(x, y, t) \) to the infinite series of \( C_m(x, y, t) \), and so forth, to create the solution for the infinite number of functions that determine the concentration of calcium in the lobster heart muscle cell.

\[ C(x, y, t) = \sum_{n=1}^{\infty} C_n(x, y, t) + \sum_{m=1}^{\infty} C_m(x, y, t) + \sum_{p=1}^{\infty} C_p(x, y, t) + \sum_{q=1}^{\infty} C_q(x, y, t) \]
So

\[ C(x, y, t) = e^{-\lambda \Delta D t} \sin(n \pi x) \left[ D_n \cos \left( y \sqrt{-\left(\frac{n \pi}{2}\right)^2} \right) + E_n \sin \left( y \sqrt{-\left(\frac{n \pi}{2}\right)^2} \right) \right] + e^{-\lambda \Delta D t} \cos \left( \frac{(2m + 1) \pi}{2} \right) x \left[ D_m \cos \left( y \sqrt{-\left(\frac{(2m + 1) \pi}{2}\right)^2} \right) \right] + E_m \sin \left( y \sqrt{-\left(\frac{(2m + 1) \pi}{2}\right)^2} \right) \]

+ \left[ B_p \cos \left( \frac{(2p + 1) \pi}{2} \right) + C_p \sin \left( \frac{(2p + 1) \pi}{2} \right) \right] \sin \left( y \sqrt{-\left(\frac{p \pi}{2}\right)^2} \right)

\[ + e^{-\lambda \Delta D t} \cos \left( \frac{(2q + 1) \pi}{2} \right) \cos \left( x \sqrt{-\left(\frac{(2q + 1) \pi}{2}\right)^2} \right) \]

**Step 3: Finding solutions to the PDE, BCs, and the Initial Condition**

To add the fundamental solutions

\[ C(x, y, t) = \sum_{n=1}^{\infty} C_n(x, y, t) + \sum_{n=1}^{\infty} C_m(x, y, t) + \sum_{p=1}^{\infty} C_p(x, y, t) + \sum_{q=1}^{\infty} C_q(x, y, t) \]

in such a way that the initial condition (IC)

\[ C(x, y, 0) = \cos \left( \pi \left( x - \frac{1}{2} \right) \right) \ast \cos \left( \pi \left( y - \frac{1}{2} \right) \right) \]

is satisfied. By substituting the summations into the IC gives

\[ \cos \left( \pi \left( x - \frac{1}{2} \right) \right) \ast \cos \left( \pi \left( y - \frac{1}{2} \right) \right) = \sum_{n=1}^{\infty} C_n(x, y, t) + \sum_{m=1}^{\infty} C_m(x, y, t) + \sum_{p=1}^{\infty} C_p(x, y, t) + \sum_{q=1}^{\infty} C_q(x, y, t) \]
Since $C(x, y, 0)$ is a continuous function, it is possible to expand the initial calcium concentration $\cos \left( \pi \left( x - \frac{1}{2} \right) \right) \cdot \cos \left( \pi \left( y - \frac{1}{2} \right) \right)$ as the sum of the functions. The resulting series solution is the typical result of separating variables. To explore a different variation of this same process, we’ll now consider a version of the problem in polar coordinates instead.

3.3 Analytical Solution to the Polar Calcium Initial Boundary Value Problem

Since we would like to consider a model of the cell that has circular boundary, we develop a polar version of the IBVP. The development of the polar IBVP originated from the ideas described in “The Laplacian (an intuitive description)” in Farlow (2012, Lesson 31). The following section provides an analysis of the calcium IBVP in polar form using two cases: boundary conditions equal zero and otherwise, respectively.

<table>
<thead>
<tr>
<th>Separation of Variables: Polar Coordinate calcium PDE for Case I—BC equals zero</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PDE</strong> $\frac{\partial C}{\partial t} = D \nabla^2 C = D \left( C_{rr} + \frac{1}{r} C_r + \frac{1}{r^2} C_{\theta\theta} \right)$</td>
</tr>
<tr>
<td><strong>BC</strong> $C(0.5, \theta, t) = 0$</td>
</tr>
<tr>
<td>$C(1, \theta, t) = 0$</td>
</tr>
<tr>
<td><strong>IC</strong> $C(r, \theta, 0) = \cos \left( 2\pi \left( r - \frac{1}{2} \right) \right)$</td>
</tr>
</tbody>
</table>

Step 1: Finding solutions to the Polar PDE

To begin, we look for solutions of the form $C(r, \theta, t) = C(r, \theta)T(t)$. Carrying out the substitution of $C(r, \theta)T(t)$ into the PDE and solving for $C(r, \theta)T(t)$ gives

$$C(r, \theta)T'(t) = D \cdot \nabla^2 C \cdot T(t).$$
We obtain the separated variables if we divide each side of the equation by \( D * C(r, \theta)T(t) \) to arrive at

\[
\frac{T'(t)}{D T(t)} = \frac{\nabla^2 C}{C(r, \theta)}
\]

In as much as \( r \) or \( \theta \) and \( t \) are independent of each other, each side must be a fixed constant \( k \) (non-negative); hence, we write

\[
\frac{T'}{D T} = \frac{\nabla^2 C}{C(r, \theta)} = k
\]

or

\[
T' - kD T = 0
\]

\[
\nabla^2 C - kC(r, \theta) = 0
\]

Now we solve the ODE in \( t \). Note, we are also left with a PDE in \( r, \theta \). Later, I will perform separation of variables to reduce the PDE into two standard-type ODEs of \( r \) and \( \theta \), respectively.

Renaming \( k = -\lambda^2 \) where \( \lambda \) is nonzero, we can represent our separated variables as

\[
T' + \lambda^2 D T = 0
\]

\[
\nabla^2 C + \lambda^2 C(r, \theta) = 0
\]

This shape \( C(r, \theta) \) multiplied by the oscillatory factor \( T(t) \) allows us to arrive at the Helmholtz equation and the simple harmonic motion equation, respectively. Solving the standard-type ODE in \( t \), we get the solution

\[
T(t) = A e^{-\lambda^2 D t} \quad (A \text{ is an arbitrary constant})
\]

Next, we solve the \( r, \theta \) PDE. To begin, we look for the solutions of Helmholtz equation

\[
\nabla^2 C + \lambda^2 C(r, \theta) = 0 \quad \text{where} \quad \nabla^2 C = C_{rr} + \frac{1}{r} C_r + \frac{1}{r^2} C_{\theta\theta}
\]
Before solving, we must find the boundary condition. To find it, we substitute \( C(r, \theta, t) = C(r, \theta)T(t) \) into the boundary condition of the muscle cell to get

\[
C(1, \theta, t) = C(1, \theta)T(t) = 0 \quad 0 < t < \infty
\]

or

\[
C(1, \theta) = 0
\]

Thus, we can now solve the following problem to find the shapes \( C(r, \theta) \) of the fundamental calcium concentration:

\[
C''(r, \theta) + \lambda^2 C(r, \theta) = 0
\]

\[
C(1, \theta) = 0.
\]

To solve this Helmholtz eigenvalue problem as if it were a linear, homogeneous PDE with zero boundary conditions, we use separation of variables and let

\[
C(r, \theta, t) = R(r)\Theta(\theta)
\]

By substituting \( R(r)\Theta(\theta) \) into the PDE and solving for \( R(r)\Theta(\theta) \). Making this substitution gives Bessel’s equation:

\[
r^2 R'' + rR' + (\lambda^2 r^2 - n^2)R = 0
\]

\[
R(1) = 0
\]

\[
\Theta'' + \lambda^2 \Theta = C(r, \theta)
\]

How do we get to the Bessel’s equation? To begin, we look for solutions of the form \( C(r, \theta) = R(r)\Theta(\theta) \). Carrying out the substitution of \( R(r)\Theta(\theta) \) into the PDE and solving for \( R(r)\Theta(\theta) \) gives

\[
C_{rr} + \frac{1}{r} C_r + \frac{1}{r^2} C_{\theta\theta} + \lambda^2 C(r, \theta) = 0
\]

implies
\[ R''(r) \Theta(\theta) + \frac{1}{r} R'(r) \Theta(\theta) + \frac{1}{r^2} R(r) \Theta''(\theta) + \lambda^2 R(r) \Theta(\theta) = 0 \]

implies

\[ R'' \Theta + \frac{1}{r} R' \Theta + \frac{1}{r^2} R \Theta'' + \lambda^2 R \Theta = 0. \]

We obtain the separated variables if we divide each side of the equation by \( \frac{R \Theta}{r^2} \) to arrive at

\[ \frac{R'' \Theta + \frac{1}{r} R' \Theta + \frac{1}{r^2} R \Theta''}{R \Theta} + \frac{\lambda^2 \frac{R \Theta}{r^2}}{R \Theta} = 0 \]

implies

\[ \frac{r^2 R''}{R} + \frac{r R'}{R} + \Theta'' + \lambda^2 r^2 \]

implies

\[ \left( \frac{r^2 R''}{R} + \frac{r R'}{R} + \lambda^2 r^2 \right) + \Theta'' \frac{\Theta}{\Theta} = 0 \]

implies

\[ \left( \frac{r^2 R''}{R} + \frac{r R'}{R} + \lambda^2 r^2 \right) = -\Theta'' \frac{\Theta}{\Theta}. \]

In as much as \( r \) or \( \theta \) and \( t \) are independent of each other, each side must be a fixed separation constant \( n \) (assuming \( n \) is a positive real number); hence, we write

\[ \left( \frac{r^2 R''}{R} + \frac{r R'}{R} + \lambda^2 r^2 \right) = -\Theta'' \frac{\Theta}{\Theta} = n^2 \]

or

\[ \Theta'' + n^2 \Theta = 0 \]

\[ \frac{r^2 R''}{R} + \frac{r R'}{R} + \left( \lambda^2 r^2 - n^2 \right) = 0 \quad \text{implies} \quad r^2 R'' + r R' + \left( \lambda^2 r^2 - n^2 \right) R = 0 \]

Now we solve the ODE in \( \Theta \). Note, we are also left with a ODE in \( r \). Following this \( \Theta \) solution, I will then solve the standard-type ODE of \( R \) into its solution.
Solving $\theta'' + n^2 \theta = 0$ for $\theta$, we get the solution

$$\theta(\theta) = A_n \cos(n\theta) + B_n \sin(n\theta).$$

Solving $r^2 R'' + r R' + (\lambda^2 r^2 - n^2)R = 0$ for $R$, we get two kinds of $n$-th-order Bessel functions:

$$R_1(r) = A J_n(\lambda r) \quad \text{and} \quad R_2(r) = B Y_n(\lambda r)$$

We add the first kind and second kind to create the solution for the $n$-th-order of functions that determine the amount of calcium in the lobster heart muscle cell.

$$R(r) = A J_n(\lambda r) + B Y_n(\lambda r)$$

Often the zero and the negative case for $n^2$ reveal nonsensical parameters for physical systems.

Case $n^2 = 0$:
Here our equation reduces to

$$r^2 R'' + r R' + (\lambda^2 r^2 - n^2)R = -\frac{\theta''}{\theta} = 0$$

or

$$\theta'' = 0$$

$$r^2 R'' + r R' + (\lambda^2 r^2)R = 0$$

and it’s general solution is

$$\theta(\theta) = a \theta + b$$

$$R(r) = A J_0(\lambda r) + B Y_0(\lambda r)$$

Case $n^2 < 0$:
Here our equation reduces to

$$r^2 R'' + r R' + (\lambda^2 r^2 - n^2)R = -\frac{\theta''}{\theta} = -n^2$$
or

\[ \Theta'' - n^2 \Theta = 0 \]
\[ r^2 R'' + r R' + (\lambda^2 r^2 + n^2) R = 0 \]

and its general solution is

\[ \Theta(\theta) = a e^{\theta n} + b e^{-\theta n} \]
\[ R(r) = A J_n(\lambda r) + B Y_n(\lambda r) \]

Since \( \Theta(\theta) \) must be periodic with period \( 2\pi \), we must choose the case where \( n \) is greater than zero (i.e. case \( n^2 > 0 \)).

\[ n \geq 0 \quad \begin{cases} R(r) = A J_n(\lambda r) + B Y_n(\lambda r) \\ \Theta(\theta) = a_n \cos(n\theta) + b_n \sin(n\theta) \end{cases} \]

Note, \( B Y_n(\lambda r) \) are unbounded at \( r = 0 \) (Fig. 8), so we choose our solution to be

\[ n \geq 0 \quad \begin{cases} R(r) = A J_n(\lambda r) \\ \Theta(\theta) = a_n \cos(n\theta) + b_n \sin(n\theta) \end{cases} \]

**Figure 8.** (Courtesy of Farlow, 2012) Image of \( n \)-th order Bessel’s functions \( R_1(r) = A J_n(\lambda r) \) and \( R_2(r) = B Y_n(\lambda r) \) such that the concentration of calcium in the muscle cell’s cytoplasm for all radius \( r \) can be solved using these two equations.
Since any sum of these solutions is also a solution, we arrive at the general solution that determines the amount of calcium in the lobster heart muscle cell:

\[ C(r, \theta) = \sum_{n=0}^{\infty} J_n(\lambda r)(a_n \cos(n\theta) + b_n \sin(n\theta)) \]

Lastly, we combine the infinite series of \( C(r, \theta) \) with \( T(t) \) to arrive at the infinite series of the \( C(r, \theta, t) \), creating the solution for the infinite number of functions that determine the amount of calcium in the lobster heart muscle cell at any time \( t \).

\[ C(r, \theta, t) = \sum_{n=0}^{\infty} e^{-\lambda^2 D t} J_n(\lambda r)(a_n \cos(n\theta) + b_n \sin(n\theta)) \]

**Step 2: Finding solutions to the PDE and the Boundary Conditions**

The last step in finding \( R(r) \) is to use the boundary conditions \( R(0) = 0 \) and \( R(1) = 0 \) to find \( \lambda \). To choose a certain subset of our current crop of solutions

\[ R(r) = A J_n(\lambda r) + B Y_n(\lambda r) \]

that satisfy the boundary conditions where there is no flow of calcium across the sarcoplasmic reticulum (i.e. at \( R(0.5) \)) and the cell membrane (i.e. at \( R(1) \)).

\[ R(0.5) = 0 \text{ and } R(1) = 0. \]

However, note that \( B Y_n(\lambda r) \) are unbounded at \( r = 0 \), so we choose our solution to be

\[ R(r) = A J_n(\lambda r) \]

Substituting \( R(0.5) = 0 \) and \( R(1) = 0 \) into \( R(r) = A J_n(\lambda r) \), respectively, gives

\[ A J_n(0) = 0 \]

and

\[ J_n(\lambda) = 0 \quad \text{(A is an arbitrary constant).} \]
Thus, for $R(r)$ to be zero on the boundary of the circle, we must pick the separation constant $\lambda$ to be the $m$-th root of $J_n(\lambda) = 0$, which is

$$\lambda = k_{nm}.$$ 

Thus, the solution for the Helmholtz equation is

$$C(r, \theta) = J_n(k_{nm}r)[A_n \cos(n\theta) + B_n \sin(n\theta)]$$

such that $n = 0, 1, 2, ...; m = 1, 2, 3, ...$

Lastly, we combine the infinite series of $C(r, \theta)$ with $T(t)$ to arrive at the infinite series of the $C(r, \theta, t)$, creating the solution for the infinite number of functions that determine the level of calcium in the lobster heart muscle cell.

$$C(r, \theta, t) = \sum_{n=0}^{\infty} \sum_{m=1}^{\infty} e^{-\lambda^2 D t} J_n(k_{nm}r)[A_n \cos(n\theta) + B_n \sin(n\theta)]$$

**Step 3: Finding solutions to the PDE, BCs, and the Initial Condition**

To add the fundamental solutions

$$C(r, \theta, t) = \sum_{n=0}^{\infty} \sum_{m=1}^{\infty} e^{-\lambda^2 D t} J_n(k_{nm}r)[A_n \cos(n\theta) + B_n \sin(n\theta)]$$

in such a way that the initial condition (IC)

$$C(r, \theta, 0) = \cos\left(2\pi \left(r - \frac{1}{2}\right)\right)$$

is satisfied, we substitute the summations into the IC to get

$$\cos\left(2\pi \left(r - \frac{1}{2}\right)\right) = \sum_{n=0}^{\infty} \sum_{m=1}^{\infty} J_n(k_{nm}r)[A_n \cos(n\theta) + B_n \sin(n\theta)]$$

We find the solution for the very common situation where $C$ is independent of $\theta$ (the radial-only case), because we believe that models our problem well. Note, any input
\( n \neq 0 \) for \( \theta \) other than 0 shows the solutions dependence on \( \theta \), thus we may only use the \( n = 0 \) case.

With these assumptions, the solution now becomes

\[
C(r, t) = \sum_{m=1}^{\infty} A_m J_0(k_{0m} r) \quad (m, \text{ an arbitrary integer})
\]

and our goal is to find \( A_n \) such that

\[
\cos \left( 2\pi \left( r - \frac{1}{2} \right) \right) = \sum_{m=1}^{\infty} A_m J_0(k_{0m} r)
\]

So, we now may solve for the coefficients in the expression

\[
\cos \left( 2\pi \left( r - \frac{1}{2} \right) \right) = J_0(k_{01} r)[A_1] + J_0(k_{02} r)[A_2] + J_0(k_{03} r)[A_3] + \ldots
\]

Using the orthogonality condition of the Bessel functions \( \{J_0(k_{0m} r): m = 1, 2, \ldots \} \)
such that

\[
\int_0^1 r J_0(k_{0i} r) J_0(k_{0j} r) \, dr = \begin{cases} 
0 & \text{if } i \neq j \\
\frac{1}{2} f_1^2(k_{0i}) & \text{if } i = j
\end{cases}
\]

we multiply each side of the equation by \( r J_0(k_{0j} r) \) and integrate from zero to one; doing this, we get

\[
\int_0^1 r J_0(k_{0j} r) \cos \left( 2\pi \left( r - \frac{1}{2} \right) \right) \, dr = A_m \int_0^1 r J_0^2(k_{0j} r) \, dr \quad j = 1, 2, \ldots
\]

Solving for \( A_m \) gives

\[
A_m = 2 \int_0^1 \frac{r J_0(k_{0j} r) \cos \left( 2\pi \left( r - \frac{1}{2} \right) \right)}{J_1^2(k_{0j})} \, dr
\]

Thus, the solution determining the level of calcium in the lobster heart muscle cell is
\[
\sum_{n=0}^{\infty} \sum_{m=1}^{\infty} A_m e^{-\lambda^2 D t} J_n(k_{nm}r)[\cos(n\theta) + \sin(n\theta)]
\]

such that the coefficients \(A_m\) are given by

\[
A_m = 2 \int_0^1 r f_0(k_0 r) \cos \left( \frac{2\pi (r - \frac{1}{2})}{r} \right) \frac{dr}{J_0(k_0)}
\]

Although Case I polar IBVP produces the above solution, it fails to provide a biologically reasonable representation of the concentration of calcium in the cytoplasm of the muscle cell, because the concentration of calcium flowing across the sarcoplasmic reticulum boundary in a stably contracting heart can never continuously be zero. Alternatively, the boundary conditions are best modeled by a trigonometric function of fluctuating calcium concentrations. Thus, we proceed by solving this polar calcium \(\frac{\partial C}{\partial t} = C_{rr} + \frac{1}{r} C_r + \frac{1}{r^2} C_{\theta\theta}\) using a boundary condition for the sarcoplasmic reticulum that better resembles the qualitative features of the system:

\[
C(0.5, \theta, t) = \sin(t).
\]

**Polar Coordinate calcium PDE for case II—BC not equal to zero:**

<table>
<thead>
<tr>
<th>PDE</th>
<th>(\frac{\partial C}{\partial t} = D \nabla^2 C = D(C_{rr} + \frac{1}{r} C_r + \frac{1}{r^2} C_{\theta\theta}))</th>
<th>(0 \leq x \leq 1, 0 \leq t \leq \infty)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC</td>
<td>(C(0.5, \theta, t) = g(t) = \sin(t))</td>
<td>(0 \leq t \leq \infty, 0 \leq \theta \leq 2\pi)</td>
</tr>
</tbody>
</table>

**Step 1: Finding solutions to the Case II Polar IBVP**

To begin, we look for solutions of the form \(C(r, \theta, t) = C(r, \theta)T(t)\) (Farlow, 2012). Carrying out the substitution of \(C(r, \theta)T(t)\) into the PDE and solving for \(C(r, \theta)T(t)\) gives

\[
C(r, \theta)T'(t) = D \ast \nabla^2 \ast T(t).
\]
Similar to the methods drawn out in the section *PDE in Polar Coordinates*, solving the standard-type ODE in $t$, we get the solution

$$T(t) = A e^{-\lambda^2 t}$$

(A is an arbitrary constant)

Next, we solve the $r, \theta$ PDE. To begin, we look for the solutions of Helmholtz equation

$$\nabla^2 C + \lambda^2 C(r, \theta) = 0 \quad \text{where } \nabla^2 C = C_{rr} + \frac{1}{r} C_r + \frac{1}{r^2} C_{\theta\theta}$$

To solve this Helmholtz eigenvalue problem as if it were a linear, homogeneous PDE with zero boundary conditions, we use separation of variables and let

$$C(r, \theta) = R(r) \Theta(\theta)$$

By substituting $R(r) \Theta(\theta)$ into the PDE and solving for $R(r) \Theta(\theta)$, we arrive at the Bessel’s equation (see mathematical computation in the section *Step 1: Finding solutions to the Case I Polar PDE*):

Case $k = n^2 > 0$:

$$\left( \frac{r^2 R''}{R} + \frac{r R'}{R} + \lambda^2 r^2 \right) = - \frac{\Theta''}{\Theta} = n^2$$

or

$$\Theta'' + n^2 \Theta = 0$$

$$r^2 R'' + r R' + (\lambda^2 r^2 - n^2)R = 0$$

Now we solve the ODE in $\theta$. Note, we are also left with a standard-type ODE in $r$.

Solving $\Theta'' + n^2 \Theta = 0$ for $\Theta$, we get the solution

$$\Theta(\theta) = A_n \cos(n\theta) + B_n \sin(n\theta).$$

Solving $r^2 R'' + r R' + (\lambda^2 r^2 - n^2)R = 0$ for $R$, we get two kinds of $n^{th}$ order Bessel functions:

$$R_1(r) = A_j(r) \quad \text{and} \quad R_2(r) = B_j(r)$$
We add the first kind and second kind to create the solution for the n-th-order of functions that determine the amount of calcium in the lobster heart muscle cell when \( n^2 > 0 \).

\[
R(r) = A J_n(\lambda r) + B Y_n(\lambda r)
\]

Case \( k = n^2 = 0 \):

Here our equations reduces to

\[
\left( \frac{r^2 R''}{R} + \frac{r R'}{R} + \lambda^2 r^2 \right) = -\frac{\Theta''}{\Theta} = 0
\]

or

\[
\Theta'' = 0
\]

\[
r^2 R'' + r R' + (\lambda^2 r^2) R = 0
\]

and it’s general solution is

\[
\Theta(\theta) = a \theta + b
\]

\[
R(r) = A J_0(\lambda r) + B Y_0(\lambda r)
\]

Often the negative case for \( n^2 \) reveal nonsensical parameters for this biological system, so we can rule out this case:

Case \( k = -n^2 < 0 \):

Here our equation reduces to

\[
\left( \frac{r^2 R''}{R} + \frac{r R'}{R} + \lambda^2 r^2 \right) = -\frac{\Theta''}{\Theta} = -n^2
\]

or

\[
\Theta'' - n^2 \Theta = 0
\]

\[
r^2 R'' + r R' + (\lambda^2 r^2 + n^2) R = 0
\]

and its general solution is
\[ \Theta(\theta) = a e^{\theta n} + b e^{-\theta n} \]
\[ R(r) = A J_n(\lambda r) + B Y_n(\lambda r) \]

Since \( \Theta(\theta) \) must be periodic with period \( 2\pi \), we must choose the case where \( n \) is or equal to zero or greater than zero (i.e. case \( n^2 \geq 0 \)).

**Step 2: Finding solutions to the PDE and the Boundary Conditions**

Using separation of variables, our solution for the calcium concentration in the muscle cell depends on the product of separated dependent components, radius \( r \), the angle \( \theta \), and time

\[ C(r, \theta, t) = \sum_{n=0}^{\infty} e^{-\lambda^2 D t} J_n(\lambda r)(a_n \cos(n\theta) + b_n \sin(n\theta)). \]

The next step in finding \( C(r, \theta, t) \) is to use the boundary conditions \( C(0.5, \theta, t) = g(t) \) to find \( \lambda, a_n, \) and \( b_n \). To choose a certain subset of our current crop of solutions

\[ C(r, \theta, t) = \sum_{n=0}^{\infty} e^{-\lambda^2 D t} J_n(\lambda r)(a_n \cos(n\theta) + b_n \sin(n\theta)) \]

that satisfy the boundary conditions.

\[ C(0.5, \theta, t) = g(t) \quad \text{implies} \quad C(0.5, \theta, t) = \sin(t). \]

To further solve the equation for the coefficients using the given boundary conditions \( C(1, \theta, t) = g(t) \), we plug in \( r = 1 \) for all \( r \) in the solution, which locks in \( r \), but keep all \( \theta \) and \( t \) present, because this boundary has to work for all \( \theta \) and \( t \). The solution now becomes

\[ C(0.5, \theta, t) = R(0.5)\Theta(\theta)T(t) = \sum_{n=1}^{\infty} e^{-\lambda^2 D t} J_n(0.5\lambda)(a_n \cos(n\theta) + b_n \sin(n\theta)) \]

\[ = g(t) \]
However, we are analytically incapable of arriving at a family of solutions that satisfy the necessary trigonometric boundary conditions. Particularly, the inability to solve the boundary conditions with the solution lies in the exponential $T(t) = e^{-\lambda^2 t}$ portion of the separated solution $R(r)\Theta(\theta)T(t)$. Since the only boundary conditions we are capable of matching to this solution must be some multiple of an exponential function (because of the exponential term in the $T(t)$ component), we are not be able to use biologically relevant boundary conditions, such as $\sin(t)$, when solving for a family of solutions to the boundary condition and the PDE. The fundamentally different behavior of $\sin(t)$ from that of $e^{-\lambda^2 t}$ provides us with a general solution that is inseparable. The only case for a boundary condition that we are capable of solving, other than a multiple of $e^{-\lambda^2 t}$, would occur when

$$\mathcal{C}(0.5, \theta, t) = g(t) = 0,$$

which fails to provide our model with a qualitative representation of the concentration of calcium in the cytoplasm at the boundary of the cell. Thus, we do not show the family of solutions to the BC $g(t) = 0$ case. Since we cannot solve the PDE with analytical methods as those shown above, we are motivated to numerically solve it using Wolfram Mathematica 9.0 in our attempts to arrive a specific boundary conditions representative of trigonometric calcium flows that resemble qualitative features of the system.

**Homogenization of the Polar Boundary Conditions**

We are capable of pushing the analytical solution further by homogenizing the non-homogeneous boundary conditions. The non-homogeneity of the boundary conditions in our model prevents us from analytically solving using the homogeneous
methods above. If we were to evaluate the polar IBVP analytically, the boundary conditions would need converting to a homogeneous form. To do this conversion, changes made to the PDE equation would create a new term in the PDE. We could then use the Eigenfunction Expansion method to solve the resulting IBVP. So, following the analytic track for the polar IBVP would lead us to a solution in the form of an infinite series. To work with this series solution, we would need to create a numerical approximation that truncates the infinite number of terms in the series. Since a numerical solution of the polar IBVP is the end goal, we used Mathematica 9.0 to solve the model numerically, taking us more directly to the numerical solution.

### Summary of Polar Models:

The force of contractions of a lobster heart muscle cell is modeled by

\[
\frac{dF}{dt} = \frac{1}{\tau_2^2} \frac{dF}{dC} C - \frac{1}{\tau_3} F.
\]

The simultaneous calcium dynamics in a lobster heart muscle cell is modeled by polar version of the calcium PDE

PDE: \[ \frac{\partial C}{\partial t} = D \nabla^2 C = D(C_{rr} + \frac{1}{r} C_r + \frac{1}{r^2} C_{\theta\theta}) \quad 0 \leq x \leq 1, 0 \leq t \leq \infty \]

BC: \[ C(r, \theta, t) = \sin(t) \quad 0 \leq t \leq \infty, 0 \leq \theta \leq 2\pi, r = 0.5 \]

#### 3.4 Assumptions: Finding the Most Biologically Relevant Calcium Partial Differential Equation

Once we realized that a polar version makes it easy to create a segregated region of cytoplasm from the sarcoplasmic reticulum, we moved the polar calcium PDE in a more biologically reasonable direction by using an annulus (Fig. 9). An annulus allowed us to view the changes in the calcium concentration localized to the cytoplasm—the location in the muscle cell our model is targeting—while simultaneously allowing concentrations and fluxes of calcium across the inner edge and outer edge of the annulus. This inner edge, \( R_2 \), represents the location in the cell with a point source release and
uptake from the sarcoplasmic reticulum. Further, the outer edge of the annulus, $R_2$, represents location in the cell with a point source release and uptake across the cell membrane. Thus, the sarcoplasmic reticulum is center “white” circle on the annulus, the cytoplasm is the annulus itself, and cell membrane is the outer edge of the annulus (Fig. 10).

**Figure 9.** Polar plot of an annulus depicts the initial condition of calcium in the cytoplasm at time zero.

**Figure 10.** Diagram demonstrating the flow of calcium at the boundary of the cell are represented by an annulus, such that the sarcoplasmic reticulum membrane is located at radius $R_1=0.5$ and the plasma membrane is located at radius $R_2=1$.

Heart cell images have determined that the sarcoplasmic reticulum in most muscle cells have finger-like regions that reach the most distal edge of a muscle cell. Additionally, the cell is known to be more tubular in shape than circular. Despite these findings, we may move forward with this circular model of the cell, because we are only
using it to generate the effects of cytoplasmic calcium levels during a muscle cell contraction (Skinozaki et al., 2002). Putting diffusion into this model is valuable in that we gain insight into the flow of calcium in the cytoplasm during the time course of a muscle cell’s contraction; however, experimental data does not closely examine the spatial effects of cytoplasmic calcium during a contraction. So, despite the importance of relying on both temporal and spatial variables when describing the diffusion of calcium from one compartment of the cell to the other, the fundamental result of this model will be an understanding of the effects of changing cytoplasmic calcium concentrations on the amplitude of muscle contractions in only the temporal-dimension and not in the spatial dimension.

When fitting the parameters in this model to the polar IBVP we focus on total cytoplasmic calcium levels using a temporal scale rather than on a spatial scale. In our attempts to recreate the qualitative characteristics of the cellular compartments of a one-dimensional muscle cell, we chose to run experiments on this model to study the relationship between a time-dependent diffusion of calcium in the cytoplasm and a time-dependent force of the muscle cell contraction. Determining precisely how calcium diffuses between the compartments of the cell is not the focus of our analysis. Particular details describing the methods behind creating a temporally-dependent differential equation from the polar IBVP is presented later in Section 3.6.

Prior to fitting the model’s parameters, we analyzed the output of the annulus model using theoretical parameters that move the model in the direction of the system. For instance, the radius of the sarcoplasmic reticulum ($R_1$) and the radius of the cell membrane ($R_2$) were chosen to be 0.5 units and 1 unit, respectively. Other
parameterizations such as these exist throughout the polar IBVP, forming our motivation to determine a set of equations for the IBVP that will qualitatively recreate the mechanics of this lobster heart cell physiology.

3.5 Understanding the Model: Polar Coordinates Modeling of the Muscle Cell Contraction

By permuting the boundary conditions in the polar IBVP using three methods described in Farlow (2012), we are able to manipulate calcium levels to oscillate at the boundary of cytoplasm—the sarcoplasmic reticulum membrane and the cell membrane—to model the calcium injection into the cytoplasm. Particularly, there are three types of boundary conditions in our study: the first, Type 1, is a boundary conditions with calcium concentration specified. The next, Type 2, specifies the flow of calcium at the sarcoplasmic reticulum boundary in the normal direction with respect to \( r \). The final BC type, Type 3, blends both the flow and the concentration of calcium. Thus, the calcium dynamics in a lobster heart muscle cell can be specified using these three different types of boundary conditions. The following are the polar calcium PDEs created with permutations 1-3 that show the thought process in which we determined Type 3 BCs to present the type of boundary condition that most resembles the qualitative features of our lobster heart muscle cell’s calcium dynamics.

Recall the polar calcium value problem:

\[
\frac{\partial c}{\partial t} = D (C_{rr} + \frac{1}{r} C_r + \frac{1}{r^2} C_{\theta\theta}).
\]
The following calcium initial boundary value problems (IBVPs) use the polar PDE above; however, each exhibits a change to its boundary conditions and, occasionally, its initial condition.

**IBVP 1:**

- **Boundary condition (Type 1):**
  \[
  \begin{aligned}
  C[R_1, t] &= \sin^2(2\pi t) \\
  C[R_2, t] &= \sin^2(\alpha + 2\pi t)
  \end{aligned}
  \]
  where \( R_1 = 0.5 \) and \( R_2 = 1 \), \( \alpha = 0.1 \)

- **Initial condition:**
  \( C[r, 0] = 0 \)

The set of boundary conditions presented in Type 1 were chosen as such to theoretically gain an understanding of how calcium flows in the muscle cell. Since a heart cell exhibits symmetrical movement of calcium into and out of the cytoplasm from calcium injections and absorptions by the sarcoplasmic reticulum, it is appropriate to assign the concentration of calcium governing the cytoplasm-sarcoplasmic reticulum interface by the conductivity boundary condition

\[
C[R_1, t] = \sin^2(2\pi t).
\]

For simplicity in the model, we chose this squared sine term that gives a concentration of

Figure 11. The numerical solution curve for IBVP 1. The surface represents the concentration of calcium at any radius \( r \) between the inner boundary \( (R_1) \) and the outer boundary \( (R_2) \) of the cytoplasm at three snapshots in time: \( t=0 \), \( t=0.21 \), \( t=0.47 \), respectively.
calcium greater than or equal to zero and a periodicity of 1. The concentration of calcium at the cell membrane for any time $t$ is modeled by using the same oscillation rate as the sarcoplasmic reticulum BC with an added lag time component $\alpha$. For a theoretical understanding of the effects of this BC on the model, we assigned $\alpha$ as time 0.1, introducing a slight lag of calcium reaching the cell membrane from a sarcoplasmic reticulum calcium release $C[R_2, t] = \sin^2(\alpha + 2\pi t)$ (Fig. 11).

We have chosen the boundary conditions to model functions that can tell us the concentration of calcium at the boundary at any moment in time. Since these boundary conditions require that we know the exact amount of calcium being injected into the cytoplasm via the outer boundaries, we would like the parameters of this BC to fit with experimental data measuring the calcium concentrations at the sarcoplasmic reticulum and the cell membrane during a cardiac muscle cell contraction. Unfortunately, these exact concentrations are unknown. However, for context, the contributions of the calcium flux from the sarcoplasmic reticulum in mammalian heart muscle cells range from 92% to as low as 70% (Bers, 2000). As a starting point, we set the flux of calcium across the cell membrane to zero; however, changes can be made to the outer boundary to include the ranges of calcium fluxes across the sarcoplasmic reticulum. Thus, we model the flow of calcium at the cell membrane using $\frac{dc}{dr} [R_2, t] = 0$ as our outer boundary condition.

<table>
<thead>
<tr>
<th>IBVP 2:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boundary condition (Type 2):</strong></td>
</tr>
</tbody>
</table>
| $\begin{align*}
C[R_1, t] &= \sin^2(2\pi t) \\
\frac{dc}{dr} [R_2, t] &= 0
\end{align*}$ |
| where $R_1 = 0.5$ and $R_2 = 1$ |
| **Initial condition:** |
| $C[r, 0] = 0$ |
In IBVP 2, the same sine function as seen in IBVP 1 was used for the sarcoplasmic reticulum (inner) BC, \( C[R_1, t] = \sin^2(2\pi t) \); however, changes were made to the cell membrane (outer) BC to better capture the effects of diffusion near the outer boundary of the cytoplasm. It is important to understand that the flow of calcium across the cell membrane at any time \( t \) can be approximated to zero, representing a null calcium flow into or out of the cell. Given this understanding, we can model the flow of calcium across the cell membrane by

\[
\frac{dc}{dr}[R_2, t] = 0,
\]

such that \( \frac{dc}{dr} \) represents the slope of the calcium in the direction of increasing radius, and predicts the calcium concentration at any instant as \( r \) increases. It answers the question, how does the calcium concentration change across this boundary in the radial direction by increasing \( r \)? Given that the \( \frac{dc}{dr} \) term expresses the movement of calcium down its concentration gradient, a \( \frac{dc}{dr} \) of 0 at \( R_2 \) tells us that there is no flow of calcium across the outer boundary, so that any change in the amount of calcium will be governed by the diffusion of calcium from the inner boundary (Fig. 12). To summarize, IBVP 2 manipulates the inside boundary at the sarcoplasmic reticulum, such that no flow of calcium is allowed across the outside boundary. As a result we observe a pulse of calcium, beginning at the inner boundary, diffusing to the outer boundary, and returning to the inner boundary.
Since numerous studies verify that we can more reasonably fit the model to experimental results measuring the sarcoplasmic reticulum injection of calcium, rather than model the calcium concentration or calcium flow, we finally consider Type 3 boundary conditions. Modeling two different boundary condition setups, IBVP 3 presents the final model for the flow of calcium across the cytoplasm as the concentration of calcium in the sarcoplasmic reticulum changes. This model, IBVP 3, gives us an output that qualitatively resembles the relationship seen between calcium concentration and muscle contraction in living heart muscles. Type 3 boundary conditions allow us to dictate the outward normal flux of calcium. This outward normal flux is proportional to the difference between the amount of calcium there and an injected amount \( g(t) \).

Choosing a proportionality constant of 1, these boundary conditions take the form

\[
\frac{dC}{dr}[r, t] = c[r, t] - g(t)
\]

such that \( c[r, t] \) represents the calcium concentration at the boundary radius \( r \) for any time \( t \), and \( g(t) \) represents the amount of calcium injected there. For example,

\[
\frac{dC}{dr}[R_1, t] = c[R_1, t] - g(t)
\]

**Figure 12.** The numerical solution curve for IBVP 2. The surface represents the concentration of calcium at any radius \( r \) between the inner boundary \((R_1)\) and the outer boundary \((R_2)\) of the cytoplasm at three snapshots in time: \( t=0, t=0.21, t=0.45 \), respectively.
governs the flow of the calcium at the inner, sarcoplasmic reticulum boundary as radius increases based upon difference between the concentration of calcium inside the sarcoplasmic reticulum $g(t)$ and the concentration $c[R_1, t]$ of calcium in the cytoplasm with radius $r = R_1$. It models the calcium concentration gradient across the sarcoplasmic reticulum into the cytoplasm.

**IBVP 3A:**

Boundary condition (Type 3):

$$-C_n = \left\{ \begin{array}{ll}
\frac{dc}{dr}[R_1, t] &= c[R_1, t] - \sin^2(2\pi t) \\
\frac{dc}{dr}[R_2, t] &= 0
\end{array} \right.$$

where $R_1 = 0.5$ and $R_2 = 1$

Initial condition:

$$C[r, 0] = 0$$

**Figure 13.** The numerical solution curve for IBVP 3A. The surface represents the concentration of calcium at any radius $r$ between the inner boundary ($R_1$) and the outer boundary ($R_2$) of the cytoplasm at three snapshots in time: $t=0$, $t=0.23$, $t=0.5$, respectively.

IBVP 3A shows the calcium concentration surface in the cytoplasm increasing initially from zero and then fluctuating between 0 and 0.4 for the remainder of time $t$ (Fig. 13). Similarly, fluctuations in calcium have been observed experimentally in cytoplasmic calcium recordings that resulted in a summation of a muscle cell contraction (Shinozaki et al., 2001). Summation in muscle cells refers to the increase in force that occurs if the subsequent stimulation of the muscle cell occurs before the muscle relaxes back to a baseline force. Interestingly, this response is observed for any initial condition.
values, determining that the \( \sin^2(2\pi t) \) term will cause a boundary condition to retain its appearance for any choice of calcium concentration at time 0. As in the previous polar IBVPs, the initial condition \( C[r, 0] \) is zero, because, as a starting point for our model, we theoretically assume the concentration of calcium in the cytoplasm before a heart muscle cell contraction is close to zero.

The effect of the outer boundary condition

\[
\frac{dC}{dr} [R_2, t] = 0
\]

on the overall output of the polar IBVP can be described as a stabilizer of the calcium levels injected into the cytoplasm from the inner boundary and the calcium levels present in the cytoplasm by diffusion. To understand this property, we must begin with an understanding of the global calcium dynamics created by the IBVP. First, the inner boundary condition injects a pulse of calcium from the sarcoplasmic reticulum. Diffusion then pushes this pulse of calcium to the outer boundary of the cytoplasm. This cycle repeats with every consecutive calcium pulse from the sarcoplasmic reticulum. The outer boundary condition, which describes the flow of calcium at cell membrane, does not allow calcium to leak out of the cell. The cytoplasm does not continue to fill up with each consecutive sarcoplasmic reticulum release since calcium flows back into the sarcoplasmic reticulum when the level \( c[R_1, t] \) is higher than the injection \( g(t) \).

Since our research was interested in determining a boundary condition that depicted the calcium fluctuation in the cytoplasm of a stably contracting heart muscle cell, we removed the square on the sine function of the inner boundary condition and observe the dynamics of a IBVP with a BC of the following nature:
IBVP 3B:
Boundary condition (Type 3): \[ -C_n = \begin{cases} \frac{dc}{dr} [R_1, t] = c[R_1, t] - \sin(2\pi t) & \text{where } R_1 = 0.5, R_2 = 1 \\
\frac{dc}{dr} [R_2, t] = 0 & \end{cases} \]
Initial condition: \( C[r, 0] = 0.2 \)

Note that to prevent the calcium level from dropping below zero when \( \frac{dc}{dr} [R_1, t] = c[R_1, t] - \sin(2\pi t) \), the initial calcium concentration was required to rise from 0 to 0.2.
Additionally the flow at the outer boundary was kept at zero.

Similar to IBVP 3A’s boundary condition, the boundary condition in IBVP 3B presents a calcium curve using an analysis of calcium’s movement in the cell (Fig. 14). The \( \sin(2\pi t) \) term determines the release of calcium from the sarcoplasmic reticulum. Thus, the rate of change of calcium at the inner boundary begins downhill when time equals 0. This behavior means that the calcium concentration at the next radius in the cytoplasm should be lower than the previous radius, causing the calcium to flow across the boundary and into the cell. The outward normal flux of calcium will remain negative at the inner boundary provided that the calcium incoming from the sarcoplasmic reticulum is greater than the calcium level at \( R_1 \). On the other hand, a positive value for \( \frac{dc}{dr} [R_1, t] \) corresponds to a lower concentration of calcium inside the sarcoplasmic reticulum relative to that of the cytoplasm. Thus, a positive slope of calcium represents calcium flowing down its concentration gradient into the sarcoplasmic reticulum from the higher calcium levels in the cytoplasm.
Although both IBVP 3A’s and IBVP 3B’s model the fluxes of calcium present biologically explainable calcium mechanics for the heart muscle cells, we present only a discussion of IBVP 3A in the final parameterization section of this paper, Section 5.1. Particularly, IBVP 3A makes the most sense such that each term in the IBVP is justified biologically. The parameterization section will demonstrate why experimental data, fit to the parameters in the IBVP 3A, determines that this polar IBVP produces the most qualitatively appropriate calcium dynamics within the cell. In the meantime, the boundary conditions, the diffusion coefficient, and the initial condition for IBVP 3A will continue to have theoretical values.

3.6 Merging Phillips et al. (2004) Active Force ODE with the Calcium Concentration IBVP

Given that calcium IBVP 3A and IBVP 3B demonstrate a rate of calcium flow, or permeability, we may omit the permeability ODE from Phillips et al.’s (2004) system of ODEs when merging the calcium diffusion model with the Phillips et al. (2004) force model. In this case, the combination of a spatially-dependent calcium IBVP with the

![Figure 14. The numerical solution curve for IBVP 3B. The surface represents the concentration of calcium at any radius r between the inner boundary (R₁) and the outer boundary (R₂) of the cytoplasm at three snapshots in time: t=0, t=0.28, t=0.74, respectively.](image)
time-dependent force differential equation can be performed by integrating the solution of the calcium IBVP. Doing so causes the calcium IBVP to lose its two-dimensionality.

To properly arrive at a time-dependent calcium solution from the polar calcium IBVP, we divided the integrated solution by the area of the cytoplasm to obtain the average calcium concentration in the cytoplasm at any time t. The following arithmetic was used to calculate the area of the circular, heart muscle cell’s cytoplasm:

\[
\text{Area of the entire cell} - \text{Area of the sarcoplasmic reticulum} = \pi R_2^2 - \pi R_1^2
\]

Given we have arbitrary values set for R_1 and R_2, we plug in for these values and solve

\[
\pi (1)^2 - \pi (0.5)^2 = 0.75\pi.
\]

Note that the area of the cytoplasm in the Cartesian IBVP is the area of the entire cell such that

\[
\text{Length of the cell} \times \text{Width of the cell} = 1.
\]

Once the solution of the integrated IBVP was divided by the area of the cytoplasm, we labeled this calcium solution \( \zeta \). By performing this process of integration and division, respectively, the spatial dimension is integrated out of the calcium IBVP, resulting in a temporal, single dimensional calcium solution. Provided that the calcium solution is now one dimensional and varies only with respect to time, this solution of the calcium concentration \( \zeta \) in the cell is substituted for \( C \) in Phillips et al.’s (2004) active force differential equation:

\[
\frac{dF}{dt} = \frac{1}{\tau_2} \frac{dF}{dc} C - \frac{1}{\tau_3} F \quad \Rightarrow \quad \frac{dF}{dt} = \frac{1}{\tau_2} \frac{dF}{dc} \zeta - \frac{1}{\tau_3} F
\]
Note that *Mathematica* 9.0 code for this process is located in Appendix B and was also performed for IBVP 1 and IBVP 2 with the assumption that we know the exact calcium concentration or calcium flux at the boundaries, respectively. Since experimental data only exists for the injection of calcium from the sarcoplasmic reticulum into the cytoplasm, we must halt our analysis of IBVP 1’s and IBVP 2’s force-calcium models at a theoretical level, because fitting these models to non-existent empirical data is impossible.

This procedure of integrating out the spatial dimension from the calcium PDE is helpful because it moves the model closer to biologically relevant diffusion characteristics. Since the actin molecule is a long string, and along this molecule are calcium binding sites, we are interested in understanding the level of cellular calcium required for actin’s calcium binding sites to bind to calcium. In some probabilistic way, the varying locations of calcium-binding sites along the actin molecule should be dependent on calcium concentration. However, given the scientific community’s limited understanding of this process, it is biologically appropriate to analyze the effects of varying calcium flow in the cell on the force of the cell’s contraction by integrating out the spatial dimension from the calcium IBVP. To merge the spatial and time-dependent IBVP with the time-dependent force differential equation we must integrate out the IBVP’s spatial component. Performing this integration will retain a more realistic approach to modeling the contraction of the heart muscle cell.
Graphically Modeling calcium movement in the lobster heart muscle cell using polar coordinates:

The calcium-force models 1, 2, 3A, and 3B were graphically analyzed to demonstrate the chemo-mechanical behavior of the muscle cell during stable contractions. Thus, we concluded our model analysis with numerical solutions to both the Cartesian and polar calcium-force models. From these graphics we will be able to determine (1) how calcium is injected into the cytoplasm in a stably contracting heart, and (2) how this injected calcium affects the force amplitude of the contractions.

3.7 Numerical Solutions of the Muscle Model

3.7.1 Graphical Analysis of the Cartesian Model

Figure 15 shows a dotted solution curve representing the concentration of calcium at any point in time for a muscle cell exhibiting a stable oscillation of calcium in the cytoplasm. This plot was created using Wolfram Mathematica 9.0 from the integrated solution curve of the Cartesian calcium IBVP:

<table>
<thead>
<tr>
<th>PDE:</th>
<th>( \frac{\partial c}{\partial t} = D \ast \nabla^2 c + \pi \cos(t) ) where ( D = 10 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boundary condition:</td>
<td>( c_n = \frac{J_{influx} - J_{pm}}{D} = 0 )</td>
</tr>
<tr>
<td>Initial condition:</td>
<td>( c[x, y, 0] = \cos(\pi \left(x - \frac{1}{2}\right)) \ast \cos(\pi \left(y - \frac{1}{2}\right)) )</td>
</tr>
</tbody>
</table>

Note that the stable cycles of calcium level oscillations represent an equal movement of free calcium in and out of the cardiac cell’s cytoplasm. The dotted solution curve demonstrates the solution curve of \( \frac{dF}{dt} = \frac{1}{\tau_2} \frac{dF}{dc} \zeta - \frac{1}{\tau_3} F \), showing the force of contractions for a single lobster muscle cell over a time course, after plugging in the solution of the
Cartesian calcium IBVP in for $\zeta$. The observed initial shot of force is representative of the spike of calcium created by the initial condition.

**Figure 15.** Numerical outputs for the Cartesian model. Lines represent fluctuations of calcium concentration, $C$, in the cytoplasm of the cell during contractions (dotted lines) and the force of contraction of the myofibril from calcium and myosin-actin interactions (solid lines).

### 3.7.2 Graphical Analysis of the Polar Diffusion on a Symmetrical Annulus Models 1-3

Similar to Figure 15, Figures 16-19 (dashed) shows the concentration of calcium at any point in time for a muscle cell exhibiting an oscillation of calcium in the cytoplasm with known concentrations at the boundaries, the sarcoplasmic reticulum and the cell membrane. Each figure in this section corresponds to a given polar IBVP. Note that the asymptotic leveling of calcium and force observed as time increases for all plots represents the steady accumulation of free calcium in the cardiac cell’s cytoplasm following a contraction. In each model, the force curve lags the calcium curve for a given time $t$.

For example, this first plot, Figure 16, was created using Wolfram *Mathematica* 9.0 from the integrated solution curve of the polar calcium IBVP 1. Figure 16-19 also
each present a solid curve that demonstrates the solution of \( \frac{dF}{dt} = \frac{1}{\tau_2} \frac{dF}{dC} C - \frac{1}{\tau_3} F \), showing the force of contractions for a single lobster muscle cell over a time course, after plugging in the integrated solution of the polar IBVP. Note, \( \frac{1}{\tau_2} \frac{dF}{dC} = 1 \) and \( \frac{1}{\tau_3} = 1 \).

**Model 1:**

<table>
<thead>
<tr>
<th>PDE</th>
<th>( \frac{\partial C}{\partial t} = D(C_{rr} + \frac{1}{r} C_r + \frac{1}{r^2} C_{\theta\theta}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boundary condition (Type 1):</td>
<td>( \begin{cases} C[R_1, t] = \sin^2(2\pi t) \ C[R_2, t] = \sin^2(\alpha + 2\pi t) \end{cases} ) where ( R_1 = 0.5 ) and ( R_2 = 1, \alpha = 0.1 )</td>
</tr>
<tr>
<td>Initial condition:</td>
<td>( C[r, 0] = 0 )</td>
</tr>
</tbody>
</table>

**Figure 16.** Numerical outputs for Model 1. Lines represent fluctuations of calcium concentration, \( C \), in the cytoplasm of the cell during contractions (dotted lines) and the force of contraction of the myofibril from calcium and myosin-actin interactions (solid lines).
Model 2:

**IBVP 2**

PDE

\[ \frac{\partial C}{\partial t} = D(C_{rr} + \frac{1}{r} C_r + \frac{1}{r^2} C_{\theta \theta}) \]

Boundary condition (Type 2):

\[ \begin{cases} C[R_1, t] = \sin^2(2\pi t) \\ \frac{dC}{dr}(R_2, t) = 0 \end{cases} \text{ where } R_1 = 0.5 \text{ and } R_2 = 1 \]

Initial condition:

\[ C[r, 0] = 0 \]

**Figure 17.** Numerical outputs for Model 2. Lines represent fluctuations of calcium concentration, \( C \), in the cytoplasm of the cell during contractions (dotted lines) and the force of contraction of the myofibril from calcium and myosin-actin interactions (solid lines).
**Model 3A:**

**IBVP 3A**

PDE

\[
\frac{\partial C}{\partial t} = D\left(\frac{\partial^2 C}{\partial r^2} + \frac{1}{r} \frac{\partial C}{\partial r} + \frac{1}{r^2} \frac{\partial^2 C}{\partial \theta^2}\right)
\]

Boundary condition (Type 3):

\[
-C_n = \begin{cases} 
\frac{\partial C}{\partial r} [R_1, t] = c[R_1, t] - \sin^2(2\pi t) & \text{where } R_1 = 0.5 \text{ and } R_2 = 1 \\
\frac{\partial C}{\partial r} [R_2, t] = 0 
\end{cases}
\]

Initial condition:

\[
C[r, 0] = 0
\]

**Figure 18.** Numerical outputs for Model 3A. Lines represent fluctuations of calcium concentration, \( C \), in the cytoplasm of the cell during contractions (dotted lines) and the force of contraction of the myofibril from calcium and myosin-actin interactions (solid lines).
Model 3B:

**IBVP 3B**

\[
\frac{\partial C}{\partial t} = D(C_{rr} + \frac{1}{r} C_r + \frac{1}{r^2} C_{\theta\theta})
\]

Boundary condition (Type 3):

\[
-C_n = \left\{ \begin{array}{l}
\frac{\partial C}{\partial r}[R_1, t] = c[R_1, t] - \sin(2\pi t) \\
\frac{\partial C}{\partial r}[R_2, t] = 0
\end{array} \right. 
\]

where \(R_1 = 0.5\) and \(R_2 = 1\)

Initial condition:

\(C[r, 0] = 0.2\)

---

**Figure 19.** Numerical outputs for Model 3B. Lines represent fluctuations of calcium concentration, \(C\), in the cytoplasm of the cell during contractions (dotted lines) and the force of contraction of the myofibril from calcium and myosin-actin interactions (solid lines).

---

4. **Experiments and Results**

To better understand the qualitative features of these contractions, lobster heart experiments were performed in June-August of 2014. These experiments supply this model with stimulated heart muscle recordings that we compared to the model’s force graphics (Appendix B; Dickinson lab of Bowdoin College’s Program of Neuroscience).

It is known that calcium is released from the sarcoplasmic reticulum upon each depolarization. Thus, we wish to model how this release of calcium influences the cell’s contraction. Such factors that alter are the diffusion coefficient, the burst duration, and
the burst frequency. Experiments recorded 15, 60Hz depolarization trains reoccurring every 2 seconds to the heart. This number of bursts was found to produce heartbeats of similar timescale to that of a heart contracting in vivo. To predict the effects of changing the number and frequency of depolarization, we used the model to match these experimental burst values and then qualitatively predicted how the calcium levels in the heart alter the duration and strength of a contraction.

Recall that when enough calcium is released, myosin and actin bind to cause a buildup of muscle force. If enough calcium is released, this buildup of muscle force is presented as a heart muscle contraction. By altering the nerve stimulations from the 15 pulse events at 60Hz, the amount and timing of calcium release changes, providing crucial insights into lobster heartbeat physiology. More specifically, changing the duty cycle—the fraction of the heartbeat period that is undergoing stimulations of depolarization events—illuminates how calcium accumulates in the cytoplasm to cause the lagged muscle contraction. Thus, mimicking this heartbeat behavior in our model would allow us to make predictions of the force response to calcium release during depolarization events. Since fitting the data was beyond the timeframe of this project, we present the model’s predictions when one parameter of the model is adjusted at a time. Given that we do not yet have a model that directly connects the mathematical behavior to the biology, we do not yet know the values of each parameter in the model that would represent real timescales in the lobster heart. However, the following analysis section provides predictions of how adjustments made to the parameters affect a contraction. Thus, given the time limits of this research, the values for time constants presented in the
next section were our closest representation of the heart, providing insights as to the effect of each parameter on the heartbeat.

5. Qualitative Predictions of the Model

In this section, we analyze a heart cell muscle response as changes in the model’s time constants occur. Up to this point in our discussion of calcium levels and contraction amplitude, we have defined calcium and force in fairly loose terms, using some slightly vague lengths as a measure. We predicted the force-calcium relationship from the underlying physical rules of the mathematics. By using measurements from lobster hearts of different contraction forces to formulate descriptions of the calcium-dependence in the parameters of the model, we performed parameterization to understand how different parameters in the model may affect the heartbeat.

5.1 Comparing the Heartbeat Data to the Model: The Lobster Heart Muscle Cell

Comparing the various polar coordinate models to the experimental data, we determined that Model 3A is the most representative of a lobster heart muscle cell contraction, so we used this model to perform a qualitative analysis. Similar to the repeated pulses observed in Phillips et al.’s (2004) force model, Model 3A was expanded to include a pulse train of membrane permeability changes and their accompanying calcium pulses (see Mathematica 9.0 code in Appendix B). First, we added burst components to the IBVP 3A’s boundary condition to simulate a realistic depolarization delivered to the heart. These additions enhanced the burst duration and burst frequency
parameters. The pulses absorb into the inner boundary condition \( sin(2\pi t)^2 \) and are now labeled “innerboundary”:

\[
\begin{align*}
\text{ODE} & \quad \frac{dF}{dt} = \frac{1}{\tau^2_c} \frac{dF}{dc} \zeta - \frac{1}{\tau_3} F \\
\text{PDE} & \quad \frac{\partial C}{\partial t} = D(C_{rr} + \frac{1}{r} C_r + \frac{1}{r^2} C_{\theta\theta})
\end{align*}
\]

Boundary condition (Type 3):

\[
-C_n = \begin{cases} \\
\frac{dC}{dr} [R_1, t] = c[R_1, t] - \text{innerboundary} \\
\frac{dC}{dr} [R_2, t] = 0 \\
\end{cases}
\]

where \( R_1 = 0.5 \) and \( R_2 = 1 \)

Initial condition:

\[ C[r, 0] = 0 \]

The innerboundary term represents a burst duration, \( b_d(t) \), between 0 and 1 multiplied by the frequency of the calcium bursts, \( f_{\text{spikes}} \):

\[
\text{innerboundary} = b_d(t) \times \sin \left( 2\pi t \times \frac{f_{\text{spikes}}}{2} \right)^2.
\]

Note that \( b_d(t) \) turns the calcium pulsing on and off such that \( b_d(t) = 1 \) up to time \( d \) and is 0 afterwards. Changing the fraction of a constant cycle period (i.e., changing the duty cycle) at which a heart cell is undergoing stimulations of depolarization events determines how calcium accumulates in the cytoplasm to cause the lagged muscle contraction. Calcium diffusion has a delaying effect that transforms the muscle cell’s contraction such that the stimulations of the cell stop but the cell continues to contract (Fig. 2). Particularly, a depolarization spike frequency of 60 Hz allows bursts of calcium to be released from the sarcoplasmic reticulum in a way that produces a time-lagged, stable muscle contraction (i.e., a heartbeat). This lag in the force response could be due to the rate of calcium diffusion into the cytoplasm from the sarcoplasmic reticulum. For example, a high concentration of calcium could persist around the muscle contractile elements (myosin and actin) subsequent to a depolarization if there were a lag in the
response of the calcium pumps (that pump calcium out of the sarcoplasm). Thus, the goal of this section is to explore the time lag between calcium release and myosin-actin activation by changing the duration and frequency of the calcium pulses within the model. We hope that the patterns shown by the model may give insight into potential drivers of in vivo changes in contraction force relative to calcium dynamics.

**Calcium Diffusion Coefficient**

Before analyzing the burst parameters in further detail, we adjust the diffusion coefficient (D) to observe its effects on a heart with 15, 60 Hz calcium bursts. Rather than using the literature value for the diffusion coefficient for calcium (1.6 *10^-6 m²/s, junctional cleft to sarcolemmal compartment; Lo et al. (2013); where a sarcolemma is the outer membrane of a muscle cell) we start with a high diffusion coefficient of 8 m²/s to align the scales of our model with experimental force curves. We increase and decrease the diffusion coefficient to observe the effect of increasing or decreasing calcium’s ability to diffuse across the membrane, respectively. Decreasing the calcium diffusion coefficient to 1 gives both a smaller peak calcium level and peak contraction force as observed in the graphics for a diffusion coefficient of 8. Interestingly, both calcium and force decay to zero more slowly than those for diffusion coefficient 8 (Fig. 20). Lowering the diffusion coefficient should decrease the rate at which calcium leaves the cytoplasm, which should act to more gradually decrease the contraction force. Because the cycle period of the stimulation remains unchanged, the amount of calcium reaching the myosin and actin lessens. This effect decreases the amplitude of the contraction. Additionally, a diffusion coefficient of 16 gives an increase in the peak calcium level relative to that of
both diffusion coefficient 8 and 1. The peak contraction force is relatively equal to that of diffusion coefficient 8, indicating that the myosin and actin reach a peak saturation of calcium. Any additional calcium injected into the cytoplasm from the sarcoplasmic reticulum is not used by the contractile elements of the muscle cell. Furthermore, a physiological range of diffusion rates exists such that all other diffusion values produce calcium levels that are not qualitatively reasonable for a cell (data not shown). These results indicate that the model operated in a particular range of diffusion constants, above and below which the model produced nonsensical behavior.

Although the model illustrates the calcium and force dropping below zero in the graph for diffusion coefficient 1 of Figure 20, we presume the biology changes just prior to this point in a realistic contraction such that the contraction process restarts
before the levels are able to drop below zero. Although the presence of negative values for calcium level and muscle force in the model cannot be explained biologically, it is likely that this diffusion model is not capturing some specific aspects of the biology that trigger calcium channels to open and close in response to stimulus. If our intentions were to capture this behavior, the model would require a different set of equations—equations that model flow through a membrane calcium pump, rather than the total flow of calcium. Thus, we may accept that calcium and force dropping below zero as a biologically justified response for a model which omits membrane receptors modeling (Rice et al., 2000).

**Burst Duration**

The burst duration parameter, $b_d(t)$, produces intuitive calcium and force curves. Particularly, the results show that longer stimulation bursts cause a cell to increase the duration of contraction (Fig. 21). Conversely, as the duration of the bursts decrease, the muscle cell remains contracted for a shorter period of time. Note, however, that the amplitude of the contraction increases as the burst duration increases. Increasing the burst duration allows more calcium to flood into the cytoplasm per time. Peak calcium level in the cell is greater for longer burst durations. To explain this intuitive behavior, we must revisit the math in the boundary conditions.
The innerboundary setup of the boundary condition determines that all calcium curves have the same tail shape following the peak of calcium, regardless of the peak level calcium reached in the cell. For example, calcium levels may initially drop faster for curves with a higher peak, but we expect all curves to approach the same rate of removal.

To reason this behavior further, we test whether the diffusion of calcium is interacting with the sarcoplasmic reticulum’s ability to uptake calcium. To begin, we decrease the diffusion coefficient to 1 and run the model at the 3 burst durations, 1/6 s (10 bursts or

![Figure 21](image-url). The lobster heart muscle cell output given a diffusion coefficient of 8 and 60Hz bursts for a duration of 1/6 s (left), 1/4 s (top), 1/3 s (right). All other parameters remain unchanged. Period of the depolarization cycle is 1 s. Lines represent fluctuations of calcium concentration, $C$, in the cytoplasm of the cell during contractions (dotted lines) and the force of contraction of the myofibril from calcium and myosin-actin interactions (solid lines).
$b_{1/6}(t)$, $1/4$ s (15 bursts or $b_{1/4}(t)$), and $1/3$ s (20 bursts or $b_{1/3}(t)$), matching those in Figure 21 (Fig. 22). These results demonstrate that decreasing the diffusion coefficient when stimulating with 10 bursts gives a smaller contraction force as compared to this same graph for 10 bursts at diffusion coefficient 8. The reaction is analogous for 20 bursts at diffusion coefficient 1 such that this model with 20 bursts produces a smaller contraction force compared to a model with diffusion coefficient 8 at a duration of 20 bursts. Thus, the model with diffusion coefficient 1 produces force and calcium curves that are scaled-down versions of those produced in the model with diffusion coefficient 8, indicating stability in the model predictions. Thus, when adjusting both the duration of a stimulation and calcium’s ability to diffuse through the cell, the behavior of the model suggests that the sarcoplasmic reticulum retains its ability to stably inject and uptake calcium for a range of diffusion values and stimulation durations.

Suppose that diffusion spreads the calcium injected by the sarcoplasmic reticulum into the rest of the cell. Since the cell membrane boundary condition is set to zero such that no calcium flows out of the cell, calcium is sealed into the cell, which creates a prolonged dissipation of calcium levels from the initial calcium bursting in the cytoplasm. Slowing diffusion using a smaller diffusion coefficient prevents more calcium from releasing into the cell, and subsequently, less calcium returns back to the sarcoplasmic reticulum by the end of a burst cycle. Conversely, a larger diffusion coefficient spreads the calcium more rapidly. Therefore, we observe more calcium in the cytoplasm per time.

Although these investigations present calcium diffusion and the duration of the stimulations interplaying in an interesting way that suggests intuitive behavior, the model
parameters require deeper investigation. It is important that we do not rule out diffusion and burst duration values that could impact the output of the model in an interesting way. Thus, future efforts will seek to determine the range of values for diffusion and burst duration that best resemble the qualitative behavior of the system.

Returning to our single-parameter analysis, we conclude our qualitative predictions for calcium and force in the lobster muscle cell by presenting the following parameters: frequency of stimulations, size of the sarcoplasmic reticulum relative to the size of the entire cell, and the time constants in the Phillips et al. (2004) force model. Observing the model’s outputs provides preliminary insights into the effect of each parameter on the model’s behavior.

*Burst Frequency*

We begin by presenting three model outputs each representing a change to the frequency of the stimulation. When the lobster cardiac muscle cell is stimulated at a frequency smaller than the 60 Hz, the cell exhibits no change in its calcium and contraction force response (Fig. 23). Likewise, an increase in the frequency of the stimulation also does not change the calcium level and force. Since the amount of calcium entering into the cytoplasm is unaffected by changes in the stimulation frequency, the amount of myosin-actin activation in the cell remains unchanged. Experimental data supports these qualitative predictions such that changes in the frequency of nerve stimulations from 60 Hz did not change the duration and the amplitude of the lobster heart contractions (Williams et al., 2013).
Sarcoplasmic Reticulum Size relative to the Size of the Cell

Given that

\[ \frac{\text{Radius of Sarcoplasmic Reticulum}}{\text{Radius of the Cell Membrane}} = \frac{R_1}{R_2} = \frac{R_3}{1} = R_1, \]

we allow the size of the sarcoplasmic reticulum to have three values: 0.25, 0.50, and 0.75.

The calcium and force curves in Figure 24 reveal that a muscle cell increases in peak contraction force when the sarcoplasmic reticulum is small relative to the whole cell and decreases in peak contraction force when the sarcoplasmic reticulum is large relative to the whole cell. We propose that the cell with the shrunken sarcoplasmic reticulum and

66
expanded cytoplasm (i.e. $R_1=0.25$) has higher numbers of myosin and actin filaments present in the cytoplasm. With an increase in the myosin and actin, more myosin and actin interactions are possible. Conversely, a cell with a large sarcoplasmic reticulum (i.e. $R_1=0.75$) diffuses a smaller amount of calcium into the cytoplasm due to the smaller region of cytoplasm in the cell. Thus, fewer myosin and actin interactions are activated when a cell has an expanded sarcoplasmic reticulum. These results also suggest there is a physiologically viable size for the sarcoplasmic reticulum in which a muscle cell optimizes its cytoplasmic calcium levels and contraction force. The exact mechanistic explanation as to how a cell optimizes its sarcoplasmic reticulum size to ensure adequate

\[ R_1=0.5; \text{SR to Cell Membrane Ratio}=0.5 \]

\[ R_1=0.25; \text{SR to Cell Membrane Ratio}=0.25 \]

\[ R_1=0.75; \text{SR to Cell Membrane Ratio}=0.75 \]

**Figure 24.** The lobster heart muscle cell output when the cell’s sarcoplasmic reticulum is changed to a smaller size (left), larger size (right), and no size change (top). All burst parameters remain at 15 burst at 60Hz and $D_c=8$. Lines represent fluctuations of calcium concentration, $C$, in the cytoplasm of the cell during contractions (dotted lines) and the force of contraction of the myofibril from calcium and myosin-actin interactions (solid lines).
calcium diffusion following stimulation is unresolved.


The final parameter to adjust in the model is the Phillips et al. (2004) time constants. For simplicity, we initially chose the time constants $\frac{1}{\tau_2} \frac{dF}{dc}$ and $\frac{1}{\tau_3}$ to be 1 and 1, respectively. Recall that $\frac{1}{\tau_2} \frac{dF}{dc}$ is the parameter by which the calcium concentration is

$$\frac{1}{\tau_2} \frac{dF}{dc} = 1 \quad \text{and} \quad \frac{1}{\tau_3} = 1$$

Calcium concentration in a muscle cell/Isometric force of a muscle cell

$\frac{1}{\tau_2} \frac{dF}{dc} = 0.0572 \quad \text{and} \quad \frac{1}{\tau_3} = 0.0172$

**Figure 25.** The lobster heart muscle cell output when the cell’s sarcoplasmic reticulum is changed to fit the parameters given in Phillips et al. (2004) force differential equation $\frac{dF}{dt} = \frac{1}{\tau_2} \frac{dF}{dc} \zeta - \frac{1}{\tau_3} F$ (bottom), for comparison to the original model (top). The top graph represents our model’s output given the time constants equal 1. Lines represent fluctuations of calcium concentration, C, in the cytoplasm of the cell during contractions (dotted lines) and the force of contraction of the myofibril from calcium and myosin-actin interactions (solid lines).
chemo-mechanically coupled to the active force of contractions, and \( \frac{1}{\tau_3} \) represents exponential decay rate during the relaxation period following the cell’s contraction.

Assigning the values for these time constants as presented in Phillips et al. (2004), we present the effects of changing these constants to \( \frac{1}{\tau_2} \frac{dF}{dc} = 0.0572 \) and \( \frac{1}{\tau_3} = 0.0172 \) (Fig 25). By decreasing both the chemo-mechanical coupling and the rate at which the muscle cell relaxes, the cell does not contract because the myosin and actin cannot utilize calcium. Without the activation of myosin and actin, the cell fails to produce a contraction.

The preliminary qualitative analysis of the model’s calcium diffusion coefficient, duration of stimulations, frequency of stimulations, sarcoplasmic reticulum size relative to the whole cell, and time constants in the force differential equation will move us closer toward choosing the values for these parameters that best characterize living lobster hearts. Thus, as we begin to understand and explain the behavior of the model, we may be better able to determine the values that produce the calcium and force curves that are most representative of experimental recordings.

6 Future Work

This paper presents a set of differential equations that have not been previously attempted in the literature. Together, the set of equations represent the force output of a lobster heart. Interestingly, the equations also produce behavior that we do not yet understand and cannot explain given our model’s assumptions. A phenomenon occurs
when the following set of boundary conditions take the place of IBVP 2’s boundary conditions to predict the muscle output:

\[
\text{IBVP 4A}
\]

**PDE**

\[
\frac{\partial C}{\partial t} = D(C_{rr} + \frac{1}{r} C_{r} + \frac{1}{r^2} C_{\theta \theta})
\]

**Boundary condition (Type 2):**

\[
\begin{cases}
\frac{dC}{dr} [R_1, t] = -\sin(2\pi t) \\
\frac{dC}{dr} [R_2, t] = 0
\end{cases}
\]

where \( R_1 = 0.5 \) and \( R_2 = 1 \)

**Initial condition:**

\[ C[r, 0] = 0 \]

The boundary condition in IBVP 4A determines the rate of change in calcium concentration as changes in \( r \) occur. We searched for an inner boundary such that the calcium concentration always remained positive. The boundary condition we chose is negative as it causes calcium to start flowing into the cytoplasm away from the sarcoplasmic reticulum. So, the gradient along the inner boundary creates more calcium inside the sarcoplasmic reticulum than in the cytoplasm at time equals zero. The inner boundary condition \( \frac{dC}{dr} [R_1, t] = -\sin(2\pi t) \) will allow this gradient to oscillate, providing a calcium oscillation of equal calcium concentrations flowing between the sarcoplasmic reticulum membrane. To maintain a cell with calcium levels greater or equal to zero, we suspected that the boundary condition produces an output with the calcium level and force oscillating between zero and some positive real number for all time. Despite this expectation for the model graphics, these positive oscillations were not observed when we analyzed the model (Fig. 26). Although the amplitude of the contractions remains constant, the peak cytoplasmic calcium concentration decreases steadily with each consecutive oscillation.
This result prompted an investigation of other boundary condition equations that produces similarly strange graphs. Thus, when using an inner boundary condition of

\[
\frac{dc}{dr}[R_1, t] = \sin^2(2\pi t),
\]
we expected a similar flux of calcium in the positive region of the curve. However, the graphical output for a model using this inner boundary condition also produced puzzling results (Fig. 27).

**Figure 26.** Model 4A graphical output. Lines represent fluctuations of calcium concentration, \( C \), in the cytoplasm of the cell during contractions (dotted lines) and the force of contraction of the myofibril from calcium and myosin-actin interactions (solid lines).

\[
\begin{align*}
IBVP 4B \\
PDE & \\
& \frac{\partial c}{\partial t} = D\left(C_{rr} + \frac{1}{r} C_r + \frac{1}{r^2} C_{\theta\theta}\right) \\
\text{Boundary condition (Type 2):} & \begin{cases} \\
\frac{dc}{dr}[R_1, t] = \sin^2(2\pi t) \\
\frac{dc}{dr}[R_2, t] = 0
\end{cases} \text{ where } R_1 = 0.5 \text{ and } R_2 = 1 \\
\text{Initial condition:} & \quad C[r, 0] = 0
\end{align*}
\]
Figure 27. Model 4B graphical output. Lines represent fluctuations of calcium concentration, $C$, in the cytoplasm of the cell during contractions (dotted lines) and the force of contraction of the myofibril from calcium and myosin-actin interactions (solid lines).

In either case, we expected an obvious basement level of calcium based on the fact that the cell is starting with no calcium initially and calcium is pulsing into and out of the cytoplasm for a given amount of time. Unfortunately, we have not yet formulated a mathematical justification for the observed model behavior in either model. Particularly, we do not yet understand the steadily declining peak force as time increases. Given that the boundary conditions describe the flow of calcium across the sarcoplasmic reticulum, with no flow out of the cell, the calcium levels should remain the same peak amplitude following every oscillation.

The strange model output is a result of a number of possible processes. We suppose the outputs of Model 4A and 4B could have resulted from a numerical computation issue in *Mathematica 9.0*. Additionally, they could be due to an unintuitive behavior of the system of equations in the model. Since pulses may add up in strange ways, this odd behavior could have resulted from a reaction of the Laplacian term with
the boundary conditions, such that the sine function resonates at a frequency that interacts with the Laplacian. Thus, this particular set of trigonometric boundary conditions interact with the model to produce a behavior unique to these boundary conditions, such that all other boundary condition equations produce logical muscle outputs. To determine the cause of this behavior requires more time than this research project has permitted; however, future research efforts can explore the root of this behavior. Note that if the first explanation were the case, we would alter the inputs into *Mathematica* in such a way as to avoid numeric issues. To contrast, something more interesting might be occurring within the model such that we would need to adjust the IBVP to increase our understanding of the model. As to how we may adjust the model requires a much deeper investigation of the model dynamics—an investigation that is the next stage of this project. Along with this model investigation, there are additional adjustments to be performed on the model.

As described in Section 5’s *Qualitative Predictions of the Model*, further implementation of lobster heart calcium values will need to be added to the calcium model to phenomenologically represent the calcium dynamics within the lobster heart muscle cell. Furthermore, rather than setting \( \frac{1}{\tau_2} \frac{dF}{dc} = 1 \) and \( \frac{1}{\tau_3} = 1 \), values for \( \frac{1}{\tau_2} \frac{dF}{dc} \) and \( \frac{1}{\tau_3} \) will need to be taken from the Phillips *et al.* (2004) force model and inserted into

\[
\frac{dF}{dt} = \frac{1}{\tau_2} \frac{dF}{dc} \zeta - \frac{1}{\tau_3} F.
\]

Thus, a number of interesting problems warranting further development of this model are as follows:

(1) The parameters in the force differential equations need to be fit to experimental data to determine the correct amplitude and period of calcium
oscillation in the cytoplasm of a contracting lobster cardiac cell. Additionally, the parameters for the IC, BC, and PDE in Model 3A’s IBVP must be altered to more closely simulate the flow of calcium concentration in and out of the cytoplasm from calcium protein channels in the cytoplasm. For example, it would be interesting to move the model forward by looking at ranges of contributions of calcium fluxes from the sarcoplasmic reticulum versus the extracellular space (sensu Bers, 2000). To accomplish this task, changes must be made to the outer boundary condition to include the ranges of calcium fluxes across the sarcoplasmic reticulum.

(2) As stated in Section 2.3: Analytical Solution to the Polar Calcium Initial Boundary Value Problem, the full analytic solution of the polar IBVP should be determined to homogenize the model and produce an infinite series that can be tested numerically. This homogenization may expose time constants of the model, potentially enabling a better fit of the model parameters to lobster experimental data.

(3) A mathematical model of the cardiac ganglion, the source stimulating muscle cell depolarization, has recently been developed by other computational neuroscientists at Bowdoin College (Williams et al., 2010; Symonds et al., 2011). Together, our goal includes merging both the isolated muscle model with the isolated cardiac ganglion model to provide a model that predicts the function of the lobster cardiac heart system and illuminate particular lobster heart phenomena.
A nullcline analysis of the model should be run to better understand the stability of the solution curves and to better evaluate the bifurcation type.

5. Conclusion

In this paper, we have developed a general calcium diffusion-force model based on the flux of calcium ions across muscle cell membranes. The model is sensitive to value ranges for each parameter. For example, consistent with known activation of muscle contractile elements by calcium, increasing burst duration results in greater amplitudes and longer durations of muscle contraction. Furthermore, increasing the rate of calcium diffusion from the sarcoplasmic reticulum results in greater muscle forces. Similarly, a slower diffusion rate of calcium decreases the muscle contraction durations.

Future research efforts should focus on determining parameter values that most qualitatively resemble the lobster heart muscle system. With further investigation into the model’s behavior, this system of differential equations will provide an algebraic approach to examining the role of calcium diffusion in the contraction of the lobster heart.

5.1 Acknowledgements

This thesis is dedicated to my parents, who encouraged me to follow my interests, and to Professor Adam Levy of the Department of Mathematics, and Professor Amy Johnson, Professor Olaf Ellers, and Professor Patsy Dickinson of the Department of Biology, who were nothing but encouraging for the entirety of this project. I am forever grateful for these individuals’ invaluable guidance and insights.
References Cited


Appendix A. Model Parameters. Parameters used to define the calcium, force, and permeability components of the lobster heart muscle cell model are presented below with final values for these parameters determined via experimental data fitting.

### Ordinary Force Differential Equation (ODE)

*Units from Phillips et al. (2004)*

\[
\frac{dF}{dt} \quad \text{rate of change of force with respect to time for a single muscle cell}\left(\frac{mg}{ms}\right).*
\]

\[C\quad \text{concentration of calcium in the muscle cell’s sarcoplasm at any point in time in a muscle cell (}\mu M\).\]

\[F\quad \text{force of contraction in a muscle cell (}\, \, mg\).}\]

\[\frac{1}{\tau_1}\frac{dF}{dc} \quad \text{absorption rate of calcium into the cytoplasm}\left(\frac{1}{ms}\right).*\]

\[\frac{1}{\tau_2}\frac{dF}{dc} \quad \text{constant that models the rate of change of isometric force with respect to the calcium concentration in the cytoplasm of the cell}\left(\frac{mg}{\mu M}\right).*\]

\[\frac{1}{\tau_3} \quad \text{parameter by which the calcium concentration is chemo-mechanically coupled to the active force of contractions}\left(0.0572\frac{mg}{\mu M+ms}\right).\]

\[\frac{dc}{dt} \quad \text{rate of change of calcium concentration across the sarcoplasmic reticulum with respect to time}\left(\frac{\mu M}{ms}\right).\]

\[\frac{dp}{dt} \quad \text{rate of change of permeability of the sarcoplasmic reticulum membrane to ion fluxes with respect to time}\left(\frac{\mu M}{ms^2}\right).\]

\[P \quad \text{permeability of the sarcoplasmic reticulum}\left(\frac{\mu m}{ms}\right).\]

\[k_1 \quad \text{phenomenological coupling of the sarcoplasmic reticulum ion permeability to calcium concentration}\left(0.29\frac{\mu M}{\mu m}\right).\]

\[k_2 \quad \text{exponential decay rate of calcium concentration in the cytoplasm during the relaxation period following the cell’s contraction}\left(0.0628\frac{1}{ms}\right).\]

\[k_1 \quad \text{exponential decay rate constant of the sarcoplasmic reticulum’s permeability}\left(\frac{1}{ms}\right).\]

### Cartesian Initial Boundary Value Problem (IBVP)

\[\frac{dc}{dt} \quad \text{rate of change of calcium concentration with respect to time given an (x,y) position. muscle cell is primarily driven by the Laplace two-dimensional diffusion variable}\, \nabla^2 c.\]

\[f_{\text{release}} \quad \text{rate of calcium from the sarcoplasmic reticulum into the cytoplasm.}\]

\[f_{\text{serca}} \quad \text{represents the rate of calcium uptake into the sarcoplasmic reticulum from the cytoplasm.}\]
D  diffusion coefficient for calcium is an experimentally measurable quantity constant in most cells; the diffusion coefficient in lobster heart myofibrils has yet to be determined.

\( C_n \)  steepness of the calcium concentration gradient across the sarcolemma.

\( J_{intlux} \)  rate of calcium from the extracellular space into the cytoplasm.

\( J_{pm} \)  rate of calcium expulsion from the cytoplasm to the outside of the cell.

\( C[x,y,0] \)  variation of concentrations across the cell cytoplasm at time 0ms.

\( \zeta \)  calcium concentration for the calcium-force model.

<table>
<thead>
<tr>
<th>Polar Initial Boundary Value Problem (IBVP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R_1 )  radial location of the inner boundary of the cell (i.e. the sarcoplasmic reticulum membrane).</td>
</tr>
<tr>
<td>( R_2 )  radial location of the outer boundary of the cell (i.e. the cell membrane).</td>
</tr>
<tr>
<td>( C[R_1,t] )  concentration of calcium at the sarcoplasmic reticulum (i.e. at the inner boundary).</td>
</tr>
<tr>
<td>( C[R_2,t] )  concentration of calcium at the cell membrane (i.e. at the outer boundary).</td>
</tr>
<tr>
<td>( \frac{dc}{dr}[R_1,t] )  flow of calcium at the sarcoplasmic reticulum (i.e. at the inner boundary).</td>
</tr>
<tr>
<td>( \frac{dc}{dr}[R_2,t] )  flow of calcium at the cell membrane (i.e. at the outer boundary).</td>
</tr>
<tr>
<td>( c[r,t] )  calcium concentration at the boundary radius ( r ) for any time ( t ) and ( g(t) ) represents the amount of calcium at the boundary.</td>
</tr>
<tr>
<td>( g(t) )  amount of calcium at the boundary.</td>
</tr>
<tr>
<td>( -C_n )  outward normal flux of calcium.</td>
</tr>
</tbody>
</table>
Appendix B: Mathematica Notebook Templates

1. Mathematica 9.0 Template: Pre-fit Cartesian Diffusion Modeling of Calcium Permeability and Force of Muscle Cell Contraction

**Calcium & Force Model: Cartesian IBVP**

**Initial Condition**

\[ \text{in}[x,y] = \cos(\pi(x-1/2))\cos(\pi(y-1/2)); \]

\[ \text{Plot3D}[\text{in}[x,y],\{x,0,1\},\{y,0,1\},\text{PlotRange} \rightarrow \{0,1\}] \]

**Initial Boundary Value Problem**

LaPlacian Diffusion without Calcium Injections

\[ \text{release}[t] = 0; \]

(*the rate of calcium released in the cytoplasm from the sarcoplasmic reticulum*)

\[ dc = 10; \]

(*arbitrary diffusion coefficient for calcium Subscript[D, c]*)

\[ \text{dxc}[x,y,t] = D[c[x,y,t],x]; \]

\[ \text{dyc}[x,y,t] = D[c[x,y,t],y]; \]

\[ \text{dxin}[x,y] = D[\text{in}[x,y],x]; \]

\[ \text{dyin}[x,y] = D[\text{in}[x,y],y]; \]

\[ \text{sol1} = \text{NDSolve}\{ \]

\[ D[c[x,y,t],\{x,2\}] + D[c[x,y,t],\{y,2\}] + \text{release}[t] = \text{dc} D[c[x,y,t],t], \]

(*rate of change of calcium concentration with respect to time given an (x,y) position in the muscle cell is primarily driven by the Laplace two-dimensional diffusion variable describing the rapid movement of calcium in the cell*)

\[ -\text{dxc}[0,y,t] = 0, \text{dxc}[1,y,t] = 0, -\text{dyc}[x,0,t] = 0, \text{dyc}[x,1,t] = 0, \]

(*zero rate of change of the calcium concentration in the normal direction at the cell membrane means no flow of calcium across the boundary of the cell*)

\[ c[x,0] = \text{in}[x,y], c[x,0.1], y, 0.1, \{t,0,10\}, \text{Method} \rightarrow \{"MethodOfLines", "DifferentiateBoundaryConditions" -> \{True, "ScaleFactor" -> 100\}\}; \]

(*initial condition is as defined above*)

\[ \text{Manipulate}\{ \]

\[ \text{Plot3D}[\text{sol1}[1,1,2],\{x,0,1\},\{y,0,1\},\text{PlotRange} \rightarrow \{0,2\}],\{s,0,10\}\]

(*this command plots the numerical solution for the calcium PDE*)

**Integrated calcium over entire cytoplasm**

\[ \text{calcium}[t] = \]

\[ \text{Integrate[}\text{sol1}[1,1,2][x,y,t],\{x,0,1\},\{y,0,1\}]; \]

\[ \text{Plot[}\text{calcium}[t],\{t,0,10\},\text{PlotRange} \rightarrow \{0,0.7\}\]

*The above curve is essentially constant (as it should be since there’s no flow across boundaries, and there is no injection of calcium from the sarcoplasmic reticulum)*
LaPlacian Diffusion with Calcium Injections

\[ \text{release}[t_] = \pi \cos[t]; \]
(*the rate of calcium released in the cytoplasm from the sarcoplasmic reticulum*)

dc = 10;

dx[x_, y_, t_] = D[c[x, y, t], x];

dy[x_, y_, t_] = D[c[x, y, t], y];
dxin[x_, y_] = D[in[x, y], x];
dyin[x_, y_] = D[in[x, y], y];

sol2 = NDSolve[{D[c[x, y, t], {x, 2}] + D[c[x, y, t], {y, 2}] + release[t] == dc*D[c[x, y, t], t],
                 -dx[0, y, t] == 0, dx[1, y, t] == 0, -dy[x, 0, t] == 0, dy[x, 1, t] == 0,
                 \[c[x, y, 0] == in[x, y], \], Method -> {"MethodOfLines", "DifferentiateBoundaryConditions" -> True, "ScaleFactor" -> 100})];

Manipulate[
  Plot3D[sol2[[1, 1, 2]][x, y, s], {x, 0, 1}, {y, 0, 1}, PlotRange -> {0, 2}], {s, 0, 10}]

NDSolve::ibcinc: Warning: boundary and initial conditions are inconsistent. 

Integrated calcium over entire cytoplasm

calcium[t_] = Integrate[sol2[[1, 1, 2]][x, y, t], {x, 0, 1}, {y, 0, 1}];

Plot[calcium[t], {t, 0, 10}, PlotStyle -> {Blue, Thick, Dashed}]
(*This plots the calcium model*)

Phillips et al. (2004) force response to calcium

force[t_] = NDSolve[{D[f[t], t] == calcium[t] - f[t], f[0] == 0, f[t, 0, 10]};

Plot[force[t, 1, 1, 2][t], {t, 0, 10}, PlotStyle -> {Magenta, Thick}]
(*This plots the force model*)

Plot[{calcium[t], force[t, 1, 1, 2][t]}, {t, 0, 10}, PlotStyle -> {Dashing[Tiny], Blue, Thick}, {Magenta, Thick}]
(*This overlaps the force and the calcium curves*)

2. Mathematica 9.0 Template: Pre-fit Polar Diffusion Modeling of Calcium Permeability and Force of Muscle Cell Contraction

Annular region (assuming symmetric wrt r)
The goal of numerically solving the calcium diffusion initial boundary value problem using polar coordinates is to make a biologically relevant (and simple) initial condition and boundary condition of calcium in the cell's cytoplasm. To mimic the movement/diffusion of calcium from the sarcoplasmic reticulum into the cytoplasm and vice versa, we preferably want the calcium to start low in the cytoplasm and then increase before decreasing back to the initial condition calcium concentration.

IBVP 3A (the most biologically relevant BC)

\[ \text{in}[r_] = 0; \] (*initial condition*)

RevolutionPlot3D[in[r], {r, 5, 1}, AxesLabel -> {r, r, Calcium Concentration}]

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\[ \text{drc}[r,t] = D[c(r,t),r]; \]
\[ \text{d}c = 1; \]
\[ \text{sol} = \text{NDSolve}\{ (*\text{Phillip} \text{se} \text{t al.} (2004) \text{F}or\text{ce ODE}*). \]
\[ \{D[f[r,t],t] == c[r,t] - f[r,t], f[r,0] == 0, \}
\[ (*\text{PDE}*) \]
\[ D[c[r,t],r]/r + D[c[r,t],{r,2}] == d c D[c[r,t],t], \]
\[ (*\text{BC for the outer and inner circle}*) \]
\[ d[r,1,t] == 0; d[r,0.5,t] == 1(c[r,0.5,t] - (\text{Sin}[2 \pi t])^2), \]
\[ (*\text{IC}*) \]
\[ c[r,0] == \text{in}[r], \{c[f], c[r,0.5], t, 0, 10} \}

Note: When evaluating the IBVP 1–4, replace the highlighted boundary conditions with the IBVP 1, IBVP 2, IBVP 3B, IBVP 4A, or IBVP 4B boundary conditions using the following code:

**IBVP 1**
\[ \text{c}[t,1] == (\text{Sin}[2 \pi t - 0.1])^2, \]
\[ c[t,0.5] == (\text{Sin}[2 \pi t])^2, \]

**IBVP 2**
\[ \text{d}[t,1] == 0, \]
\[ c[t,0.5] == (\text{Sin}[2 \pi t])^2, \]

**IBVP 3B**
\[ \text{d}[t,1] == 0, \]
\[ \text{d}[t,0.5] == 1(c[t,0.5] - (\text{Sin}[2 \pi t])) \]

**IBVP 4A**
\[ \text{d}[t,1] == 0, \]
\[ \text{d}[t,0.5] == -\text{Sin}[2 \pi t] \]

**IBVP 4B**
\[ \text{d}[t,1] == 0, \]
\[ \text{d}[t,0.5] == (\text{Sin}[2 \pi t])^2 \]

**Calcium plot**

\[ \text{Manipulate[} \]
\[ \text{RevolutionPlot3D[sol[[1,1,2]][r,s],\{r,0.5,1\}, PlotRange->\{-1,1\},\{-1,1\},\{0,1\}\}],\{s,0,10\}\] \[\text{]} \]

**Integrated calcium over plate**

\[ \text{calcium}[t_] = \]
\[ (4/(3 \pi)) \text{Integrate[sol[[1,1,2]][r,t],\{r,0.5,1\}]]; \]
\[ \text{cp = Plot[calcium[t]],\{t,0,10\}, PlotStyle->\{Blue,Thick,Dashed\}} \]
\[ (*\text{This plots the calcium level in the cytoplasm}*) \]

**Phillips et al. (2004) force response to calcium**

\[ \text{force[t_] = NDSolve}[\{D[f[t],t] == \text{calcium}[t] - f[t], f[0] == 0, f[t,0,10\]; \]
\[ \text{fp = Plot[force[t]][[[1,1,2]][t,0,10], PlotStyle->\{Magenta,Thick\}]] \]
\[ (*\text{This plots the force model}*) \]
\[ \text{Plot[[calcium[t], force[t]][[[1,1,2]][t,0,10], PlotStyle->\{Dashing[Tiny],Blue, Thick\}] \]
\[ (*\text{This overlaps the force and the calcium curves}*) \]

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Incorporation of Heartbeat Data

Model 3A was expanded to include a pulse train of membrane permeability changes and their accompanying calcium pulses. These repeated pulses were absorbed into the sin\(^2\) term of Model 3A’s inner boundary condition.

\[
\text{sw[dur_] := If[0 < dur < 0.25, 1, 0]}
\]

(*This sets the burst duration*)

\[
f\text{spikes = 60;}
\]

(*the frequency of bursts*)

\[
\text{innerboundary} = \text{sw[t]} \left( \sin\left(\frac{2\pi}{2} \times \text{fspikes} \times t\right)\right)^2;
\]

(*Parameter determines the duty cycle of a train of stimulations*)

\[
\text{Plot[sw[t] innerboundary, \{t, 0, 2\}]} (*model spikes as Sin[t]^2 and assume time course of spikes is same as time course of calcium influx pulses at the SR membrane*)
\]

\[
dc = 9;
\]

(*arbitrary diffusion coefficient for calcium is dc*) (*cm\(^{2}\)s\(^{-}\) from Lo et al., 2013.*)


This section adds a version of Phillips et al. (2004) differential force equation for a single muscle cell to the diffusion of calcium IBVP. The following setup presents the parameters for IBVP 3, such that the rate of flow of calcium across the outer boundary is zero whereas the ambient level of calcium in the cytoplasm moving to/from the inner boundary is determined by sin squared.

\[
\text{in[r_] := 0 (*Initial concentration of calcium in the cell cytoplasm*)}
\]

\[
\text{drc[r_, t_] := D[c[r, t], r];}
\]

\[
\text{sol = NDSolve[}
\]


\[
\{D[f[r, t], t] == c[r, t] - f[r, t], f[r, 0] == 0,
\]

(*PDE*)

\[
D[c[r, t], r] + D[c[r, t], r, 2] == (1/dc) D[c[r, t], t],
\]

(*BC for the outer and inner circle *)

\[
drc[1.0, t] == 0, drc[0.5, t] == 1*c[0.5, t]-innerboundary,
\]

(*IC*)

\[
c[r, 0] == \text{in}[r], \{c[f], r, 0.5, 1\}, \{t, 0, 10\}
\]
Calcium plot
Manipulate[RevolutionPlot3D[sol[[1,1,2]][r,s],{r,0.5,1},PlotRange->{{-1,1},{-1,1},{-0.1,1}},{s,0,10}]

Integrated calcium over plate
calcium[t_]=
(4/(3\pi)) \text{Integrate}[sol[[1,1,2]][r,t],{r,0.5,1}];
cp=Plot[calcium[t],{t,0,10},PlotStyle->{Blue,Thick,Dashed}]
(*This is the experimentally fitted calcium curve at \text{dc}=1.6*)

force[t_]=
(4/(3\pi)) \text{Integrate}[sol[[1,2,2]][r,t],{r,0.5,1}];
fp=Plot[force[t],{t,0,10},PlotStyle->{Magenta,Thick}]
(*This is the experimentally fitted force curve at \text{dc}=1.6*)

Show[cp,fp]
(*This overlaps the force and the calcium curves*)
Appendix C: Summer Lobster Research Experimental Results

Interaction of crustacean myosuppressin (pQDLHVFLRFamide) and stretch in the Homarus americanus cardiac muscle

Lauren Skerrett, Patsy Dickinson, Amy Johnson, and Olaf Ellers
Department of Biology, Bowdoin College, Brunswick ME

INTRODUCTION

Central pattern generator (CPG): One characteristic of an effective control system is its ability to respond and adapt to change. This is seen in the heart of the lobster (Homarus americanus), which is controlled by a central pattern generator (CPG). The CPG is composed of clusters of neurons, the cardiac ganglion (CG), which generate rhythmic output without requiring sensory input. The neurons in these networks produce a periodic output that coordinates cardiac biological function.

Modulation: Controlling the output of the cardiac muscle can be achieved through neurotransmitters, which can act on smooth muscle properties of the lobster heart.

Neuropeptides: Homarus americanus is a neuropeptide that has been shown to affect CPGs. It is a member of a large family of peptides (Filshampeptide), which share a conserved five-amino-acid sequence (pQDLHVFLRFamide).

Stretch Feedbacks: The feedback of stretch variance appears to occur into the muscles and may cause inactivation of peripheral muscle stretch (as reviewed in Cooke 2001).

Goal: To understand the effect of myosuppressin on stretch feedback in the lobster cardiac muscle by recording contraction amplitudes and passive tension in intact (CPG intact) and eliminated (CPG removed) preparations.

EFFECTS OF PEPTIDE ON STIMULATED HEART

The effects of 10^(-6) M myosuppressin on contraction force and frequency stabilized after ~2 minutes.

1. Neuregic lobster heart includes several sites at which myosuppressin could theoretically modulate cardiac activity.

2. Cardiac muscle and/or neuregic muscle position

3. Feedback systems (stretches)

4. PDE-sensitive (pDE-sensitive) inactivation of the myosuppressin.

5. Estrogen (estrogen) increases active contraction force.

ACTIVE CONTRACTION FORCE

Contraction force increases linearly and non-linearly during extension.

Passive tension increases non-linearly during extension.

During stretch, 10^(-6) M myosuppressin increased active contraction force.

Passive tension increases non-linearly during extension.

During stretch, 10^(-6) M myosuppressin increases active contraction force.

PASSIVE TENSION

During stretch, the increase in passive tension with myosuppressin suggests that the peptide-induced increase in stretch does not act on the passive components of the muscle or NMR.

CONCLUSIONS

Both myosuppressin and stretch increased cardiac muscle active contraction force in normal hearts, but not in neuregic hearts.

There was no increase in passive tension with myosuppressin before or during stretch.

Mathematical models

PRELIMINARY MATHEMATICAL MODEL

PDE-sensitive (pDE-sensitive) inactivation of the myosuppressin.

Estrogen (estrogen) increases active contraction force.

During stretch, 10^(-6) M myosuppressin increases active contraction force.

Coefficients of C: Gasman = 0.5 (PDE-sensitive)

K = Gasman = 0.5 (PDE-sensitive)

dC/dt = kC - aP

F = 2.5 (PDE-sensitive)

EXPRESS

- Full Neuroscience Summer Research Fellowship
- Department of Biology, Bowdoin College