

A Model of the *Drosophila* Heart

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Abstract

The heart of *Drosophila melanogaster* is a tubular organ that contains two types of excitable cells which work together to pump hemolymph through the body. At the cellular level, specific ion channels involved in the heartbeat of *Drosophila* have been identified and studied using genetic mutations and pharmacological agents. In this work the *Drosophila* heart is modeled as a network of excitable cells in order to explore the biophysical mechanisms underlying the generation of the heartbeat. The model cells are arranged in a tubular shape to form a network connected by gap junctions. Pacemaker cells with an intrinsic rhythm are added at one end of the network model and generate a wave of contraction down the heart. Using the model, channel kinetics are manipulated to explore the effects of different channels on *Drosophila* heartbeat. Model results are compared to experimental data.

1 Introduction

The heart of *Drosophila melanogaster* is a tubular muscle that pumps hemolymph, the invertebrate analogue to blood, throughout the insect. The heart uses waves of contraction that originate in the muscle tissue at the caudal end of the heart [4]. Muscle cells are excitable, which means that the electrical potential of the cell will change in response to a stimulus. This change in potential, called an action potential, is caused by the opening and closing of ion channels in the cell membrane, allowing specific ions to pass through. When the potential is high enough, the tissue will contract. The cells where the contraction originates provide the necessary stimulus to cause the rest of the cells in the heart to fire action potentials. These cells, called the pacemaker cells, are responsible for setting the frequency and rhythmicity of the heart beat. The pacemaker cells contract on their own with no outside stimulus and are influenced by a variety of neurotransmitters which serve to modulate the heartbeat [9, 11].

Studies involving pharmacological blockers of ion channels have determined that the ions responsible for the change in action potential in the *Drosophila* heart are calcium and potassium [10]. When the cell fires, calcium, a highly positively charged ion, enters the cell thus raising the membrane potential. Potassium, an ion with a lower positive charge, then moves out of the cell to bring the potential back down to rest. The specific channels that are found in the *Drosophila* pacemaker cells have been identified by observing the effects of genetic mutations on the heartbeat [10, 16]. These studies have shown that there are at least two different types of calcium channels in the pacemaker cells, both triggered to open by small changes in the electrical potential of the cell [16]. There is also a potassium channel which opens due to the presence of calcium in the cell. Voltage gated potassium channels seem to play a less significant regulatory role in the pacemaker cells [10].

Although the ion channels that are essential to the cardiac pacemaker can be identified experimentally, the effects of these channels on the dynamics of the system are much harder to study. The cells in the *Drosophila* heart are too small to collect data for each individual cell, so the only observable results of ion channel mutations come from whole heart optical recordings [10]. Lack of experimental data on the dynamics of individual cells is the main motivation for using mathematical modeling to study the heart.

The movement of ions through ion channels changes the electrical potential of the cells in the heart, suggesting that the cells can be modeled as electrical circuits. Many such models have been developed to describe the activity of neurons and other excitable cells, one example being the two state variable Morris-Lecar model.

The Morris-Lecar model was originally used to study barnacle muscle fibers [15]. This model uses calcium and potassium ion channels that are gated by voltage, which makes it good system to use as we begin a mathematical investigation of the *Drosophila* heart. Starting with a model for a single cell, one can create a network model by coupling each cell to its neighbors [14]. A network model of the *Drosophila* heart can provide insight into the effects of specific ion channels on the network dynamics.

In this paper we study two models of the *Drosophila* heart. We discuss some of the general background that is necessary to understand models of excitable cells and explain the derivation of the Morris-Lecar system of equations. We then introduce and discuss the first model of the heart, which uses Morris-Lecar excitable cells and a variation of the Morris-Lecar model cell, which functions as a pacemaker. We then develop another model that incorporates calcium gated potassium channels into the Morris-Lecar model. We compare the two models, discuss how our results can be used to aid in *Drosophila* heart research and explore future work.

2 Model Background

Many excitable cell models are based on the same general principles. This section outlines the general background and motivation for this type of model and states some of the basic assumptions on which these models are built.

Ions move in and out of excitable cells through channels in the cell membrane. Since the ions flowing through these channels are charged, there is a resulting change in the electrical potential of the cell. Both the interior and exterior of the cell are primarily composed of water. The charged particles can move throughout the water, and the membrane separates the inside of the cell from the outside. Considering the ions as an electrical charge, the water as a conductive material, and the membrane as an insulator, the resulting situation is similar to a capacitor, where two plates of conductive material are separated by an insulator [1]. Since the membrane also allows ions to pass through channels in it, it can be considered as a resistor and capacitor in parallel and therefore modeled as an electrical circuit.

We can begin formulating the model using Ohm's law, $I = \frac{V}{R}$, where V is the difference in potential (voltage), I is the current and R is resistance. Since resistance and conductance are inversely related, we replace $\frac{1}{R}$ with the conductance g , and rewrite Ohm's law as $I = gV$. In a cellular context, the "conductance" of a cell is the permeability of the cell membrane to ions. The potential difference in a cell is the difference between the voltage inside the cell, V_i and the voltage outside the cell, V_e . We call

$V = V_i - V_e$ the membrane potential. The relationship $I = gV$, then, tells us that the current due to the movement of ions through the membrane depends both on the permeability of the membrane to the ions and on the membrane potential [8].

When particles diffuse, they move from areas of high concentration to areas of low concentration. The conductance g is always positive. When V is positive, the potential inside the cell is larger than the potential outside the cell. Since current moves against the voltage gradient, it will flow out, and by convention current flowing out of the cell is negative, so we write the current as $I = -gV$.

Looking at the capacitive properties of the membrane, we have $q = cV$ from the capacitive law, which states that charge is equal to capacitance times voltage. Taking the derivative of this equation, while assuming that capacitance remains constant, gives us $\frac{dq}{dt} = c\frac{dV}{dt}$. In this equation, $\frac{dq}{dt}$ is the change in charge over time, which is a current. This gives $I = c\frac{dV}{dt}$, the capacitive current [1].

By Kirchoff's law of conservation of charge, the capacitive current must be balanced with the ionic current [8], so we have

$$c\frac{dV}{dt} = -gV. \quad (1)$$

The solution to Equation 1 exponentially decays to zero. A cell at rest, however, has a membrane potential of approximately $-60mV$. The leakage of ions should cause the membrane potential to return to this value, which we will call V_L . Thus we rescale the equation to be

$$c\frac{dV}{dt} = -g(V - V_L), \quad (2)$$

a basic model for a leaking membrane.

In addition to non-specific channels which allow ions to leak across the membrane, excitable cells also have ion specific channels that can be open or closed depending on the state of the cell and its environment. If we let the number of channels for a specific ion be N and the number of open channels be N_o , then the number of closed channels is $N_c = N - N_o$. Normalizing, we obtain $f = \frac{N_o}{N}$, the fraction of open channels. The fraction of closed channels is then $1 - f$.

The channels in many excitable cells open due to changes in the membrane potential. In this case, we can consider the rate at which open channels close to be $k^-e^{-\beta V}$ and the rate at which closed channels open to be $k^+e^{-\alpha V}$ [8]. We can use the law of mass action to look at how the channels change between

the “open” and “closed” states. This gives the equation

$$\frac{df}{dt} = k^+ e^{-\alpha V} (1 - f) - k^- e^{-\beta V} f.$$

We rewrite this as

$$\frac{df}{dt} = -(k^+ e^{-\alpha V} + k^- e^{-\beta V}) \left(f - \frac{k^+ e^{-\alpha V}}{k^+ e^{-\alpha V} + k^- e^{-\beta V}} \right),$$

so the equilibrium $f = \frac{k^+ e^{-\alpha V}}{k^+ e^{-\alpha V} + k^- e^{-\beta V}}$ is easier to see. Now we let

$$\begin{aligned} f_\infty(V) &= \frac{k^+ e^{-\alpha V}}{k^+ e^{-\alpha V} + k^- e^{-\beta V}} = \frac{1}{1 + \frac{k^-}{k^+} e^{(\alpha-\beta)V}} \\ \tau(V) &= \frac{1}{k^+ e^{-\alpha V} + k^- e^{-\beta V}} = \frac{1}{k^+ e^{-\alpha V}} \frac{1}{1 + \frac{k^-}{k^+} e^{(\alpha-\beta)V}}, \end{aligned}$$

so the equation for the change in the fraction of open channels over time becomes

$$\frac{df}{dt} = \frac{-1}{\tau} (f - f_\infty).$$

Simplifying, we make the substitution $S = \frac{1}{\beta-\alpha}$ and $V_0 = \frac{\ln \frac{k^-}{k^+}}{\beta-\alpha}$. This gives

$$\begin{aligned} f_\infty(V) &= \frac{1}{1 + e^{-\frac{V-V_0}{S}}} \\ \tau(V) &= \frac{e^{\alpha V}}{k^+} \frac{1}{1 + e^{-\frac{V-V_0}{S}}}. \end{aligned}$$

For large τ we see a slow change in the fraction of open channels, and vice versa since τ is a time constant. The function $f_\infty(V)$ has an inflection point at V_0 , and S controls the steepness of the curve near V_0 . Figure 1 demonstrates how changes in V_0 and S affect the function.

In summary, the actual conductance for a specific ion channel, which is gated in this manner is the product of the maximum conductance for that ion, \bar{g}_{ion} , and the fraction of open ion channels, f . The current that passes through these channels is then $I_{\text{ion}} = \bar{g}_{\text{ion}} f(V - V_{\text{ion}})$, where V_{ion} is the equilibrium potential for that ion, which is often called the reversal potential. Thus, the model of an excitable membrane must include gated ion currents as well as a passive leak current, and from Equation 2 we now have

$$c \frac{dV}{dt} = - \sum_j \bar{g}_{\text{ion}} f(V - V_{\text{ion}}) - g(V - V_L), \quad (3)$$

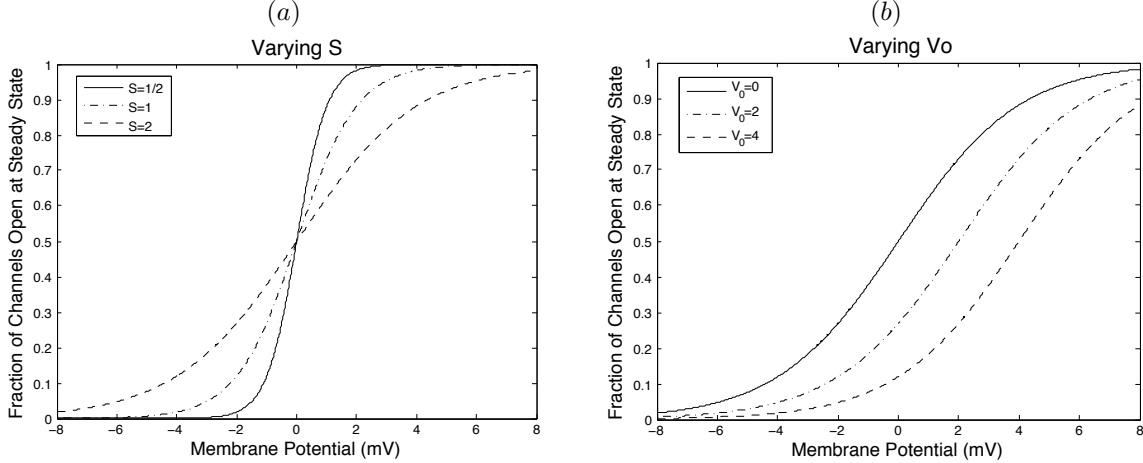


Figure 1: (a) Holding V_0 constant, we vary S . Smaller values of S give a steeper curve for f_∞ , while larger values make the slope less steep. (b) Holding S constant we vary V_0 to shift the inflection point.

where j denotes the different types of ion channels found in the membrane. For a more in depth discussion of how these models are formulated, see [8, 18].

3 Formulation of the Morris-Lecar model

In Section 2 we looked at how to describe the activity of a general voltage gated ion channel. Here we want to discuss how specific ion channels are accounted for in the Morris-Lecar model, since it is the model that we use to build the heart.

Morris-Lecar is a two-dimensional system that describes the change in potential due to voltage gated channels for calcium and potassium. Let w be the fraction of open potassium channels. Then one can derive an equation to describe the rate at which the fraction of open potassium channels changes, similar to the general case presented in Section 2. The change in the fraction of open potassium channels is described by $\frac{dw}{dt} = \phi \frac{1}{\tau_w(V)} (w_\infty(V) - w)$, where ϕ is a parameter that scales the rate at which these channels open due to changes in temperature. Similarly, let m be the fraction of open calcium channels, then $\frac{dm}{dt} = \frac{1}{\tau_m(V)} (m_\infty(V) - m)$ describes the rate at which the calcium channels open. In the general case, the equations for the steady states and the time constants are in the exponential form shown in Section 2. The Morris-Lecar model expresses $w_\infty(V)$, $m_\infty(V)$ and $\tau_w(V)$ as hyperbolic functions, which have a similar form.

Now that we have equations for the gating of each ion, we can consider the current due to each of these

ion channels. The maximal conductance of potassium is \bar{g}_K . The current generated is proportional to the difference between the equilibrium potential for potassium, V_K , and the voltage of the cell. Therefore, if all the channels were open the current would be $\bar{g}_K(V - V_K)$. Since w is the fraction of open potassium channels, the actual current due to potassium is $I_K = \bar{g}_K w(V)(V - V_K)$. In light of the experimental observation that the calcium channels open much quicker than the potassium channels, it is assumed that the fraction of open calcium channels instantaneously reaches its steady state, so m is approximated by m_∞ [15]. Thus the current due to calcium is $I_{Ca} = \bar{g}_{Ca} m_\infty(V)(V - V_{Ca})$.

Putting all of this together gives the Morris-Lecar model of excitable cells:

$$\begin{aligned}
C_m \frac{dV}{dt} &= - \sum_j I_{\text{ion}} - I_L + I \\
&= -I_{Ca} - I_K - I_L + I \\
&= -\bar{g}_{Ca} m_\infty(V)(V - V_{Ca}) - \bar{g}_K w(V)(V - V_K) - \bar{g}_L(V - V_L) + I \\
\frac{dw}{dt} &= \phi \frac{w_\infty(V) - w}{\tau_w(V)},
\end{aligned}$$

where

$$\begin{aligned}
m_\infty(V) &= \frac{1 + \tanh\left(\frac{V - V_1}{V_2}\right)}{2} \\
w_\infty(V) &= \frac{1 + \tanh\left(\frac{V - V_3}{V_4}\right)}{2} \\
\tau_w(V) &= \frac{1}{\cosh\left(\frac{V - V_3}{2V_4}\right)},
\end{aligned}$$

I is the injected current (in units of $\frac{\mu A}{cm^2}$) [15].

We use two different parameter sets to investigate the possible dynamics of Morris-Lecar cells. These parameters are taken from [18] and shown in Table 1, along with their units and meaning. Note that V has units of mV and t has units of ms .

Table 1: Parameter sets used in Morris-Lecar

Parameters	Set 1	Set 2	Units	Meaning of parameter
C_m	20	20	pF/cm^2	Capacitance of the membrane
V_k	-84	-84	mV/cm^2	Reversal potential of potassium
V_{Ca}	120	120	mV/cm^2	Reversal potential of calcium
V_L	-60	-60	mV/cm^2	Resting membrane potential
\bar{g}_k	8	8	mS/cm^2	Maximal conductance of potassium channels
\bar{g}_{Ca}	4.4	4	mS/cm^2	Maximal conductance of calcium channels
\bar{g}_L	2	2	mS/cm^2	Conductance of channels allowing ions to leak across the membrane
ϕ	0.04	$\frac{1}{15}$	$1/ms$	Scales for temperature
V_1	-1.2	-1.2	mV	Adjusts threshold of $m_\infty(V)$
V_2	18	18	mV	Adjusts steepness of $m_\infty(V)$
V_3	2	12	mV	Adjusts threshold of $w_\infty(V)$
V_4	30	17.4	mV	Adjusts steepness of $w_\infty(V)$

4 Analysis of the Morris-Lecar model

Before we put the Morris-Lecar cells into a network, we first look at the dynamics of a single cell and two coupled cells.

4.1 Phase Plane Analysis

Firstly, we look at the phase plane analysis for each set of parameters given in Table 1. The equations of the nullclines for V and w are

$$w = \frac{I - g_{Ca}m_\infty(V)(V - V_{Ca}) - g_L(V - V_L)}{g_K(V - V_K)},$$

and

$$w = w_\infty(V),$$

respectively. For a more in depth discussion of how to use phase planes to analyze the Morris Lecar model see [18].

Threshold Behavior

Consider a Morris-Lecar cell which uses parameter set 1 from Table 1. When $I = 0$ the nullclines intersect only once, as is shown in Figure 2. The point at which the nullclines intersect is a stable equilibrium point, the resting potential of the cell. The V nullcline acts like a graded threshold for the

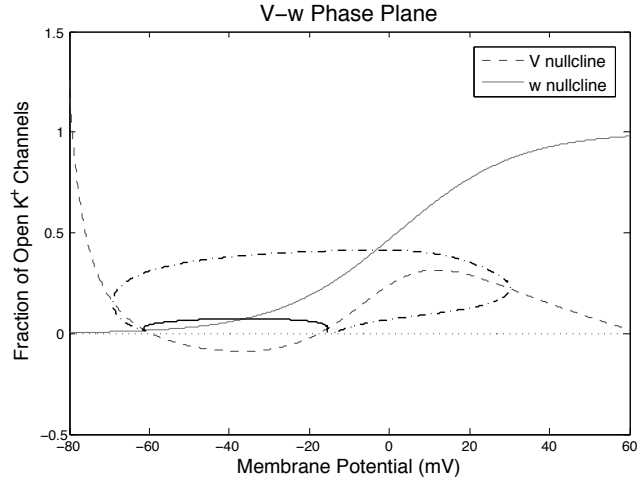


Figure 2: Phase plane with a single stable node. Trajectories with initial conditions of $V=-14$ (dashed line) and $V=-16$ (solid line) demonstrate the threshold when $I = 0$.

activation of calcium channels. This threshold becomes much sharper if we decrease C_m , creating the effect of an “all-or-none” response to stimuli [18].

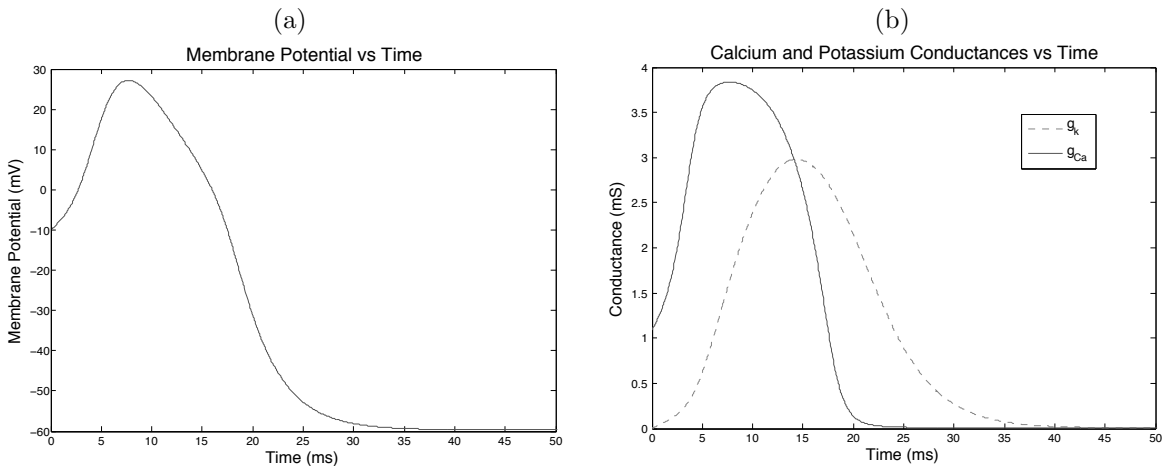


Figure 3: $I = 0$ and initial conditions are $V = -10$, $w = 0$. (a) The cell fires one action potential and then returns to rest. (b) The conductances of potassium and calcium channels as the cell fires

If we start above threshold, the opening of calcium channels increases the voltage in the cell, causing it to depolarize. In response to the voltage increase, potassium channels begin to open and potassium starts to leave the cell, causing the the voltage inside the cell to go down (repolarize). As the cell repolarizes, the voltage gated potassium channels begin to close, and the cell returns to its resting state. The relationship

between the conductance of the ion channels and the action potential can be seen in Figure 3. The peak of the conductance of the calcium channels occurs just before the peak of the action potential, while the peak of the potassium channel conductance is just after the peak of the action potential.

Hopf Bifurcation

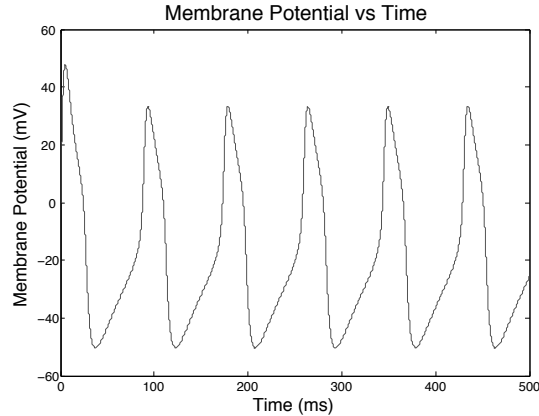


Figure 4: Sustained oscillations emerging from the Hopf Bifurcation.

Now consider what happens when current is applied to this cell. If enough current is applied (the value of I is increased), instead of firing a single action potential the cell fires continuously, as shown in Figure 4. These sustained oscillations emerge due to a Hopf bifurcation [18]. In the phase plane, this occurs when the intersection of the nullclines moves from the left branch of the V nullcline to the middle branch. Figure 5 shows the new nullclines when the applied current is just high enough to produce these oscillations. There is a small region just after the bifurcation occurs where an unstable limit cycle divides the domain of attraction of the stable equilibrium point and the stable limit cycle [18]. Trajectories which illustrate both the stable limit cycle and the unstable limit cycle are shown on the phase plane. It is worthy of notice that the oscillations due to a Hopf bifurcation emerge at a non-zero frequency.

Saddle-Node Bifurcation

The second set of parameter values gives a phase plane in which the nullclines intersect three times at $I = 0$. The first intersection is a stable equilibrium, the middle one is a saddle, and the final one is an unstable spiral. As we increase the value of I , the V nullcline moves up, causing the saddle point and the stable node to move closer together and eventually coalesce, which causes a saddle-node bifurcation on an invariant circle (SNIC) to occur (see Figure 6 (a)). Unlike the previous case, the oscillations that appear due to the SNIC emerge at a zero frequency. Practically, this means that these types of cells can

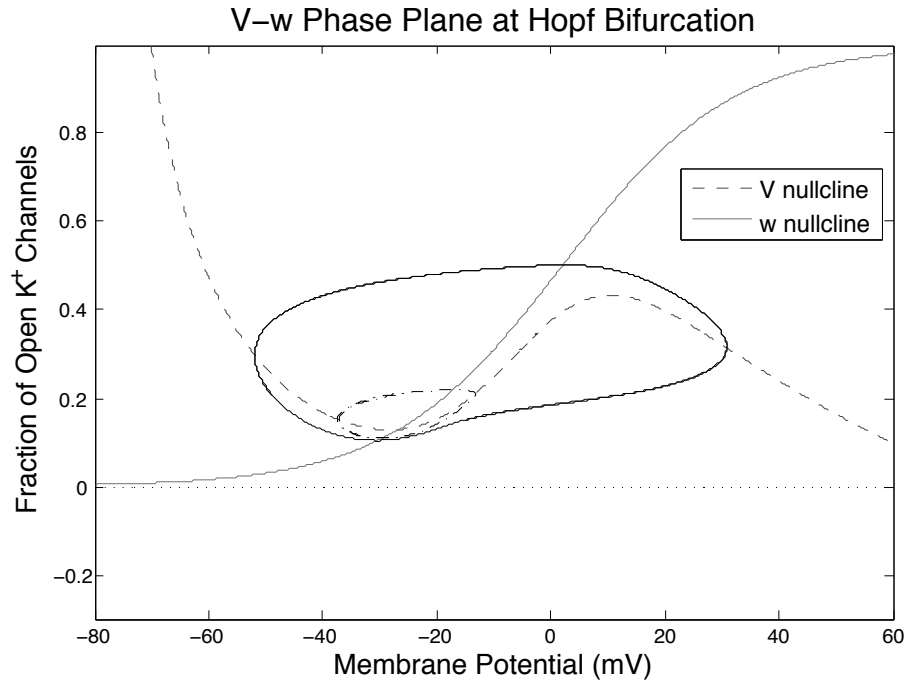


Figure 5: After the Hopf bifurcation, an unstable limit cycle separates the stable node from the stable limit cycle. Unstable limit cycle is dashed and the stable limit cycle is solid.

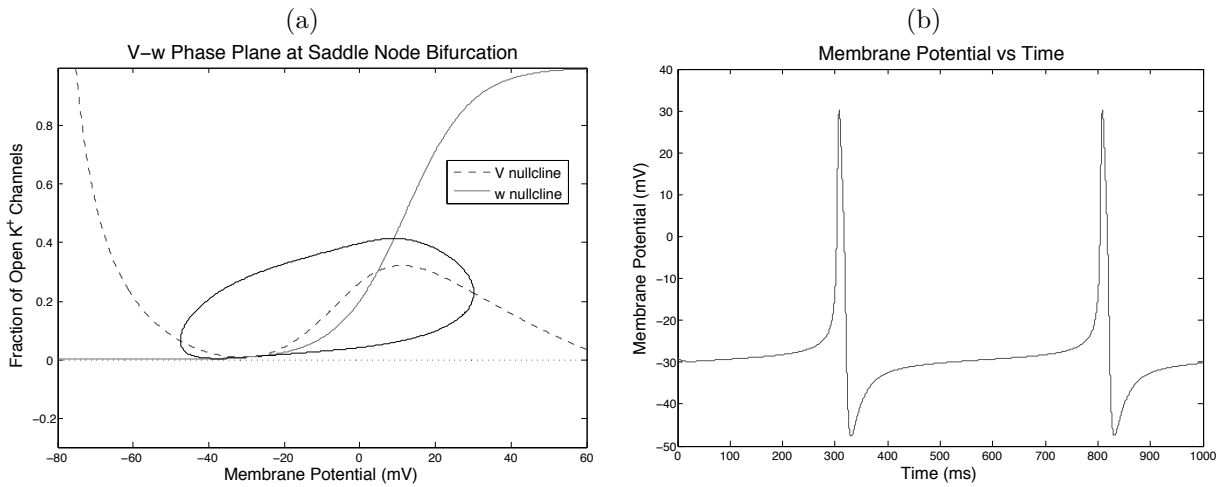


Figure 6: (a) Phase plane demonstrating the coalescence of the stable node and the saddle node into a single equilibrium at the bifurcation. (b) Oscillations emerging from saddle node bifurcation with a very low frequency.

fire at very low frequencies, as shown in Figure 6 (b) [18].

4.2 Developing a Pacemaker Cell

The Morris-Lecar model for an excitable cell gives a good framework for studying the dynamics of the cardiac cells of *Drosophila*. However, the dynamics of the Morris-Lecar cells do not entirely agree with what is known about some of the cells in the *Drosophila* heart. In particular, *Drosophila* has a myogenic heartbeat [4]. This means that the heart can beat on its own with no stimulation. In contrast, the cells that we have considered so far do not fire repetitively unless an outside stimulus is applied to the cell.

We create a pacemaker cell from the Morris-Lecar model by lowering the threshold for the activation of calcium so that the cell fires repeatedly with no applied current. To do this, we change the parameters that govern $m_\infty(V)$ and $w_\infty(V)$ until the nullclines cross on the middle branch of the V nullcline (see Figure 7). For these parameter values the system produces sustained oscillations with no applied current. Thus, these parameters give us an appropriate model for a pacemaker cell.

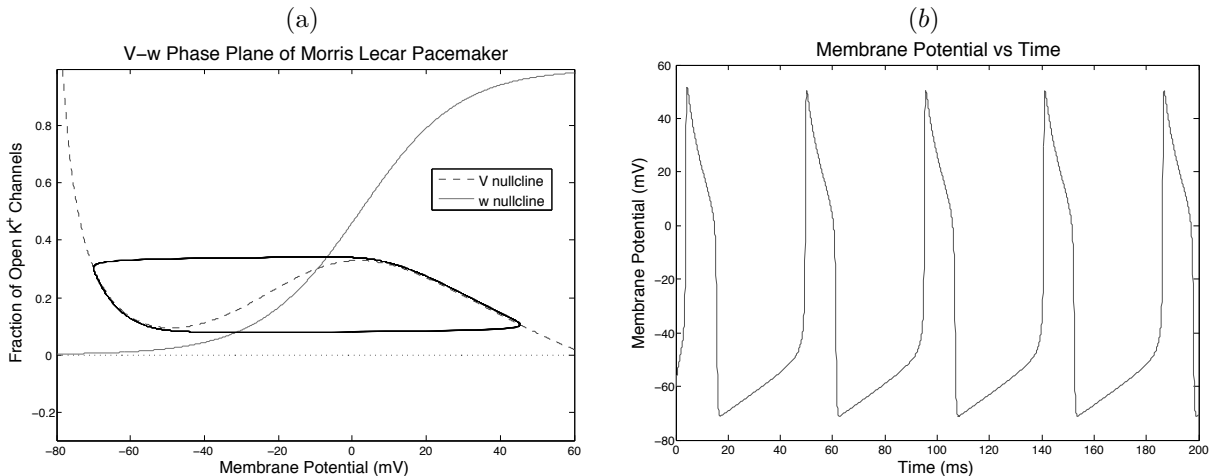


Figure 7: Dynamics of a pacemaker cell with parameters taken from parameter set 1 in Table 1 with the following changes: $V_1 = -9$, $V_2 = 30$, $V_4 = 27$, $C_m = 1$ and $I = 0$. (a) V and w nullclines on the phase plane, along with a trajectory which shows the stable limit cycle. (b) Repetitive firing of the pacemaker cell with no applied current.

4.3 Phase reduction approach for coupled Morris-Lecar cells

We investigate the dynamics of just two coupled cells so that we can predict how they should behave in a network. The limit cycle solution of the Morris-Lecar system, when explored in terms of change

in voltage over time, is a periodic function. Thus, we can begin by looking at how small perturbations to the membrane potential affect the phase of a cell. We then look at how weak coupling of two cells through gap junctions can cause phases of the two cells to either synchronize or to become asynchronous.

A gap junction is a direct electrical connection between two cells, which allows ions to pass between the cells. When we create the network model, the cells are connected to their neighbors by gap junctions. The current that flows into each cell through the gap junctions is called I_{gap} and is expressed as $\sum_i g_g (V_i - V)$, where g_g is the conductance of the gap junction and V_i is the potential of a neighboring cell.

Consider a pacemaker cell, as defined in Section 4.2, with the voltage oscillation $V(t)$. Let $t = 0$ be the time of the first voltage peak, and let the period of the oscillation be T . Suppose there is a small perturbation to the voltage oscillation of the firing cell. This perturbation will cause a change in the timing of the oscillator, which depends on the point during the oscillation that it occurs. A function $z(t)$, which gives the phase shift, depends on the time of the perturbation. This is called the phase response function. If the next peak of the oscillation occurs sooner due to the perturbation, $z(t)$ is positive, while if the peak occurs later then $z(t)$ is negative. The graph of $z(t)$ allows us to easily visualize how perturbations to the membrane potential affect the dynamics of the cell [5, 18]. Figure 8 shows $z(t)$ for a pacemaker cell.

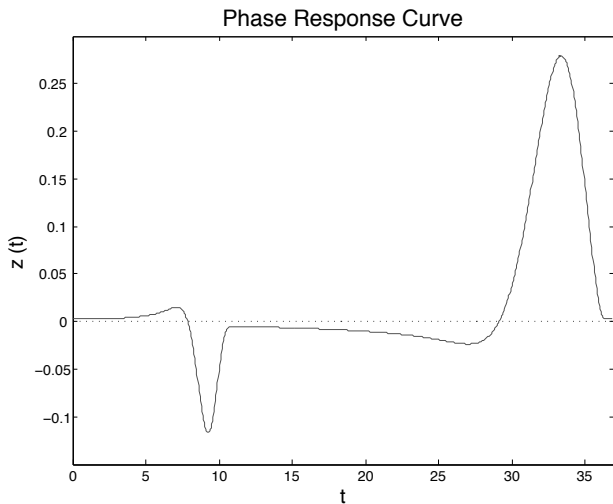


Figure 8: Infinitesimal phase response curve for a single pacemaker cell. Parameters are taken from parameter set 1 in Table 1 with the following changes: $V_1 = -9$, $V_2 = 30$, $V_4 = 27$, $C_m = 1$, and $I = 0$.

Now consider what happens when we have two pacemaker cells that are weakly coupled by gap junctions. Using a phase-reduction approach, we let $\theta_1(t)$ and $\theta_2(t)$ be the phases of these two oscillators.

The phase variable $\theta_i(t)$ lies on the interval $[0, T]$. Then the phase shift of cell 1 at any moment in time due to the current of the gap junction with cell 2, is given by

$$\Delta\theta_1 = -z(t)I_{\text{gap}}(\theta_1(t), \theta_2(t)), [18]$$

where

$$I_{\text{gap}}(\theta_i, \theta_j) = g_g(V(\theta_i) - V(\theta_j)).$$

We want to study how the coupling of these two cells affects their dynamics. The change of the phase of each cell is dependent on its intrinsic frequency, as well as on its interactions with the other cell, so

$$\begin{aligned} \frac{d\theta_1}{dt} &= \frac{1}{T} + g_g H(\theta_2 - \theta_1) \\ \frac{d\theta_2}{dt} &= \frac{1}{T} + g_g H(\theta_1 - \theta_2). \end{aligned}$$

The interaction function H depends only on the phase difference between the two oscillators and is determined by the form of the synaptic coupling [7]. We let $\phi = \theta_2 - \theta_1$ and compute $H(\phi)$ by averaging the influence of one cell on the cycle of the other. For two cells connected by gap junctions, the interaction function is

$$H(\phi) = \frac{1}{T} \int_0^T z(t)(V(t + \phi) - V(t))dt.$$

We integrate over the region from 0 to T to describe the convolution due to averaging (for a more detailed explanation of the interaction function, see [2, 6, 7, 18]).

From the equations for the change in θ_1 and θ_2 , we have

$$\frac{d\phi(t)}{dt} = g_g(H(-\phi) - H(\phi)) = -2g_g G(\phi),$$

where $G(\phi)$ is the odd part of $H(\phi)$. Solutions to the equation $\frac{d\phi(t)}{dt} = 0$ are the phase-locked solutions of the system, since the difference between the phases of the two cells is not changing.

To determine the stability of these solutions, we linearize $\frac{d\phi(t)}{dt}$ near a phase locked solution, $\bar{\phi}$ and obtain

$$\frac{d\phi(t)}{dt} \approx -2g_g G'(\bar{\phi})\phi(t).$$

Thus when the slope of $G(\phi)$ is positive, the phase-locked solution is stable and when the slope is negative,

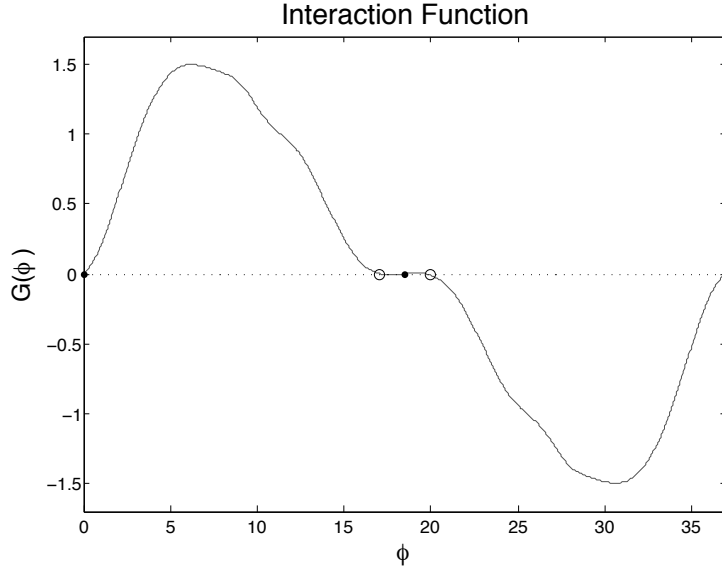


Figure 9: The odd part of the interaction function for coupled pacemaker cells. Closed circles mark stable phase-locked solutions and open circles mark stable ones. Parameters are taken from parameter set 1 in Table 1 with the following changes: $V_1 = -9$, $V_2 = 30$, $V_4 = 27$, $C_m = 1$, and $I = 0$.

the solution is unstable [2]. Figure 9 shows the function $G(\phi)$ for two pacemaker cells. The points where the curve intersects the x-axis are the phase-locked solutions, since $\frac{d\phi(t)}{dt} = 0$. In this particular case, there are two stable solutions: synchrony and the anti-phase solution. Because the unstable solutions are very close to the stable asynchronous solution, we can expect the pacemaker cells in the network model of the heart to synchronize under most initial conditions.

Now we consider how two regular excitable cells with injected current affect each other when they are connected through gap junctions. We look at the interaction functions for coupled Morris-Lecar cells using both parameter sets, and find that the dynamics are very similar. The odd part of the interaction function, $G(\phi)$, is shown for $I = 40$ and $I = 120$ in Figure 10. We can see that for low injected current, there are two stable phase-locked solutions, a synchronous solution and an asynchronous one. We can also observe that the lower the injected current, the further apart the unstable solutions are from the anti-phase solution. This suggests that at lower values of I , it is more likely for the oscillations of the coupled cells to be asynchronous. As we increase the value of I , the two unstable solutions move closer together until they merge and leave us with only one asynchronous solution, which is unstable. This indicates that if the cells are firing fast enough, they are bound to synchronize. The results are the same for both parameter sets.

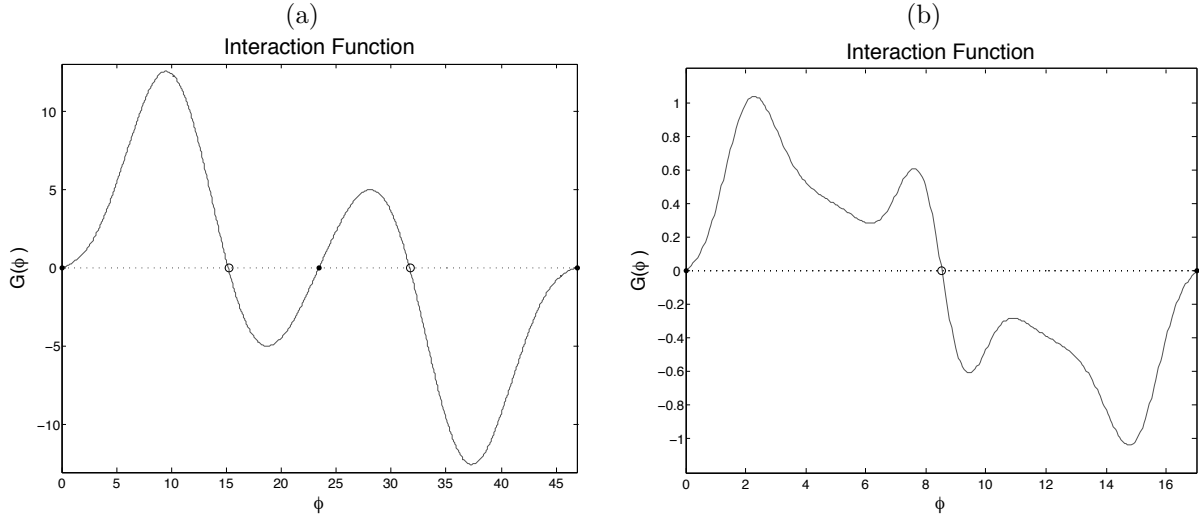


Figure 10: The odd part of the interaction function for regular excitable cells that use parameter set 2 from Table 1. Closed circles mark stable phase-locked solutions and open circles mark stable ones. (a) Shows that synchronous and anti-phase solutions are both stable when $I = 40$, while (b) shows that synchrony is the only stable solution when $I = 120$.

In the network model, the regular excitable cells will not be receiving injected current. Instead, their stimulation will come from the pacemaker cells. However, since this technique only works when the coupled oscillators are identical, we cannot analyze what happens when we couple a pacemaker cell with an excitable cell. Thus we consider the injected current into the excitable cells to be an approximation for the input from the pacemaker cells. Our results predict that when the excitable cells are firing at a high enough frequency, the cells will synchronize.

5 Model of the *Drosophila* Heart with Morris-Lecar Cells

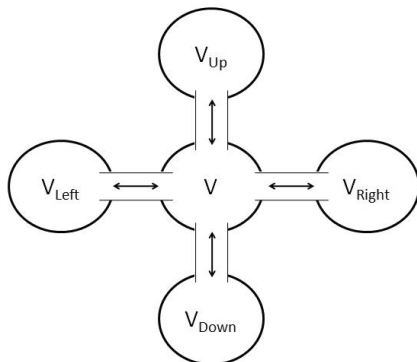


Figure 11: The cells in the network are connected by gap junctions.

We create a network model of the heart in which single excitable cells are connected to their neighbors by gap junctions as shown in Figure 11. The differential equation for the membrane potential of a cell becomes

$$C_m \frac{dV}{dt} = - \sum_{\text{ion}} I_{\text{ion}} + I_{\text{leak}} + I_{\text{gap}} + I,$$

where $I_{\text{gap}} = \sum_i g_g (V_i - V)$. The network is constructed from 50 rings of cells, each 10 cells in circumference, arranged into a cylinder as shown in Figure 12. For further details on how this model is coded into Matlab, see Appendix A.



Figure 12: Layout of cells in the network model of the heart. There are three rings of pacemaker cells at one end. The rest of the cells are simply excitable. The heart is 50 cells long and 10 cells in circumference.

We model the pacemaker cells in two different ways when we numerically solve the model. In one case, all of the cells in the heart use parameter set 1 from Table 1 and $C_m = 1$. To create pacemaker cells, we inject current into the first three rings of cells only, while the rest of the cells remain simply excitable. In the other case, we make the first three rows of cells into pacemakers by changing the parameters

as described in Section 4.2. We observe that the results from these two different methods of creating pacemaker cells are nearly the same. Thus, we consider both together in this discussion.

Starting all the cells at random initial conditions of $-70 < V < 30$, we observe that each ring of cells quickly starts firing in synchrony (see Figure 13). This is consistent with our conclusion from Section 4.3 that the phase-locked solution is stable.

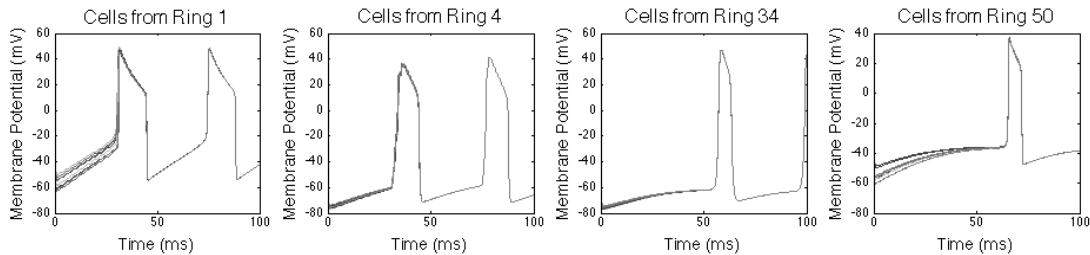


Figure 13: All of the cells in each ring down the heart fire in synchrony with each other. Here we use $g = 3$ and applied current of $I = 120$ to the cells in rings 1-3 only.

Although we see synchrony in each ring of cells as predicted in Section 4.3, we do not want the entire heart to synchronize, since the contraction of the heart muscle starts at one end of the heart and moves to the other. We achieve this effect by putting only three rings of pacemaker cells at one end. Figure 14 shows that the pacemaker cells fire first, triggering action potentials in each successive ring of cells. This delay in firing can be attributed to the strength of the gap junctions, which affects the change in membrane potential of neighboring cells and thus the rate at which the membrane potential reaches threshold.

The heart of *Drosophila* beats approximately two to four times per second, depending on the temperature [4]. The parameter values that are typically used in the Morris-Lecar model make the cells in our model fire much faster than this. Thus, we look at which parameters can be changed in order to make the cells in our model fire at a more realistic rate. The parameter ϕ is a good candidate, since it was added to the Morris-Lecar model to make it fit data, which demonstrated that the cells being studied fire faster at higher temperatures [15]. Thus we change ϕ to make the model fit the *Drosophila* heart rate better (see Figure 15).

We can already see the dynamics that we hope to see in a heart. The Morris-Lecar pacemaker cells cause all of the cells in the heart to fire repetitively without any injected current. Also, the model of the heart shows that due to the coupling, the cells in each ring synchronize, causing the whole ring to contract at the same time. We see a wave of contraction starting with the pacemaker cells and moving

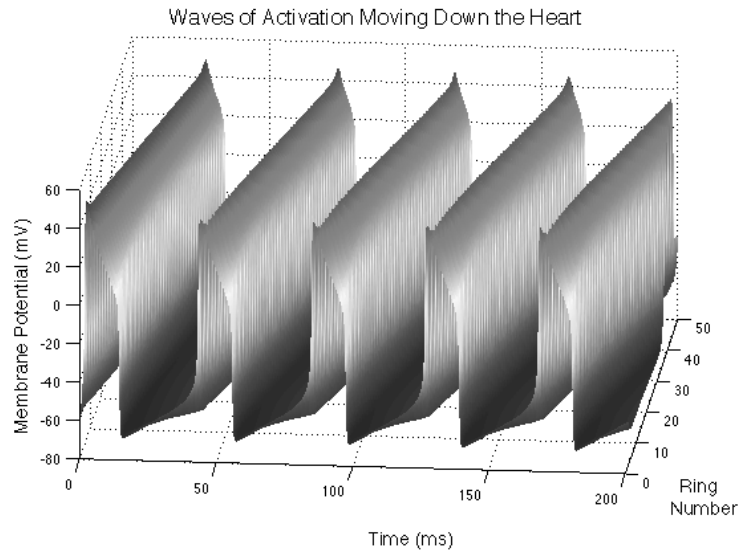


Figure 14: The activity of one cell from each ring in the heart is shown. Three rings of Morris-Lecar pacemaker cells are used and $g = 3$. (a) The 2-D figure of membrane potential vs time. Waves of activation move down the length of the heart.

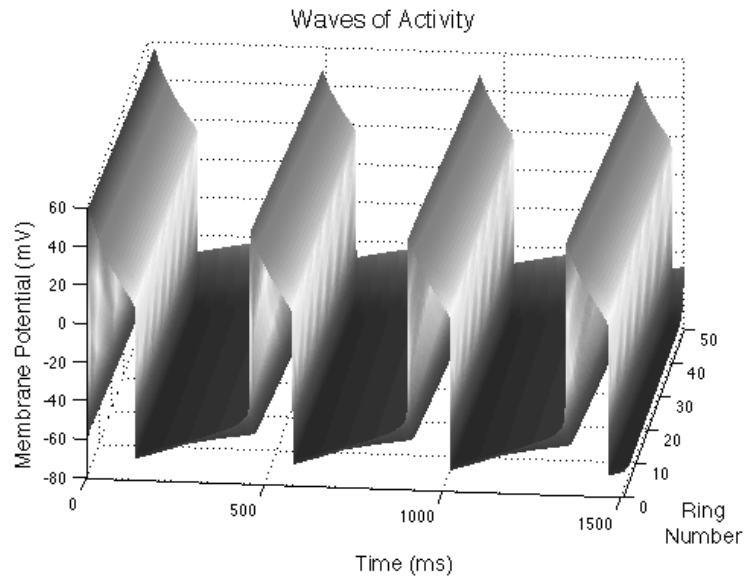


Figure 15: Lowering the temperature parameter in both the pacemaker cells and the regular excitable cells slows the heartbeat. $\phi = 0.003$ and $g = 3$.

down the length of the heart. This model also reflects the sensitivity of heart rate to temperature that has been observed in the *Drosophila* heart [4]. The next step in creating a more realistic model of the *Drosophila* heart is to incorporate potassium channels that are gated by calcium.

6 Model of the *Drosophila* heart with calcium gated potassium channels

The network model consisting of Morris-Lecar excitable cells can mimic the dynamics of the *Drosophila* heart quite well. However, the pacemaker cells in the heart of *Drosophila* rely mainly on *potassium* channels that are gated by calcium instead of voltage [10]. When calcium binds to a receptor on the calcium gated potassium (*K-Ca*) channel, it causes the ion channel to open. To make our network model of the heart more biologically accurate we introduce *K-Ca* channels to the Morris-Lecar equations. Before we look at how these new cells affect the whole heart model, we first describe the model for a single cell with *K-Ca* channels and look at some of the dynamics. Then we use coupled oscillators to predict how these cells should behave in a network. Finally, we confirm these predictions with our model of the heart and discuss the model dynamics.

6.1 Single Cell Model

In this model, the fraction of open *K-Ca* channels, $q(Ca)$, must depend on the concentration of free calcium in the cell, given in units of μM . We write $q(Ca)$ as a saturation function, $\frac{Ca}{Ca+1}$ where Ca is the cell's calcium concentration. In order to keep track of the concentration of calcium in the cell we introduce an equation that describes the rate of change of Ca . The amount of calcium entering the cell is directly proportional to $-I_{Ca}$, and it is written as $-\mu I_{Ca}$, where μ is a parameter that converts calcium current to calcium concentration. Also, calcium concentration inside the cell decays exponentially as pumps remove calcium from the cell, so we write the amount of calcium that leaves the cell as εCa . Thus the equation for the rate of change of calcium in the cell is $\frac{dCa}{dt} = -\mu I_{Ca} - \varepsilon Ca$. Hence, we obtain the following system of three ordinary differential equations:

$$\begin{aligned}
C_m \frac{dV}{dt} &= -I_{Ca} - I_K - I_{K-Ca} - I_L + I_{app} \\
&= -\bar{g}_{Ca} m_\infty(V)(V - V_{Ca}) - \bar{g}_K w(V - V_K) - (\bar{g}_{K-Ca})q(Ca)(V - V_K) - \bar{g}_L(V - V_L) + I_{app} \\
\frac{dw}{dt} &= \phi \frac{w_\infty(V) - w}{\tau_w(V)} \\
\frac{dCa}{dt} &= -\mu I_{Ca} - \varepsilon Ca.
\end{aligned}$$

The parameters used for the model in this section are the same as those in parameter set 2 from Table 1 with the addition of $\bar{g}_{K-Ca} = 1$ (in units of $\frac{mS}{cm^2}$), $\mu = 1.25 \times 10^{-5}$ (in units of $\frac{\mu M}{pA \cdot ms}$), and $\varepsilon = .0005$ (in units of $\frac{1}{ms}$).

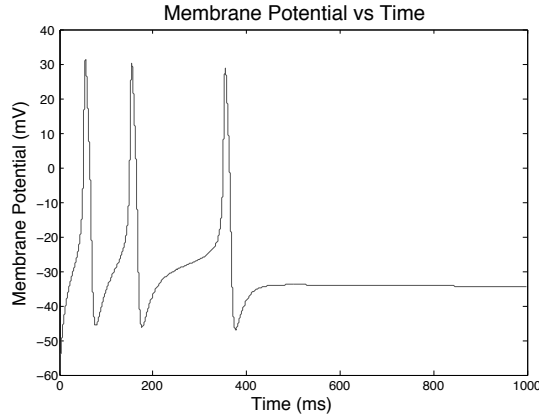


Figure 16: Decreased spiking frequency caused by $K-Ca$ channels opening when $I = 50$

We take $Ca = 0.02$ as the initial condition for calcium so the initial number of open $K-Ca$ channels is very small. Hence, the modified model behaves just like the regular Morris Lecar model when $I = 0$: the cell fires just once and then returns to its resting state. The concentration of calcium in the cell increases due to the opening of the calcium channels as the cells fires, and slowly decays when the cell returns to rest.

As we add injected current to the cell by raising I , the cell fires a few times, but these oscillations are not sustained and eventually the system returns to rest (Figure 16) due to calcium entering the cell each time it fires. The increased concentration of calcium inside the cell causes the fraction of open $K-Ca$ channels to increase. These channels lower the resting membrane potential of the cell, so more applied current is necessary for the membrane potential to reach threshold.

As we continue to increase I , the cell starts firing repetitively as shown in Figure 17 (a). However, the frequency of firing is not constant because K - Ca channels open as calcium concentration rises in the cell, and it takes longer for the cell to reach its threshold. In Figure 17 (b) one can see that eventually the delay is long enough for the decay of Ca between each action potential to balance the amount of calcium that comes in each time the cell fires. The system reaches a state where the frequency of firing is constant, and the cell is said to have adapted. Since a heartbeat should be rhythmically stable, we want the cells in the heart model to show this pattern of sustained membrane potential oscillations and level calcium concentration so that the heart is always in an adapted state.

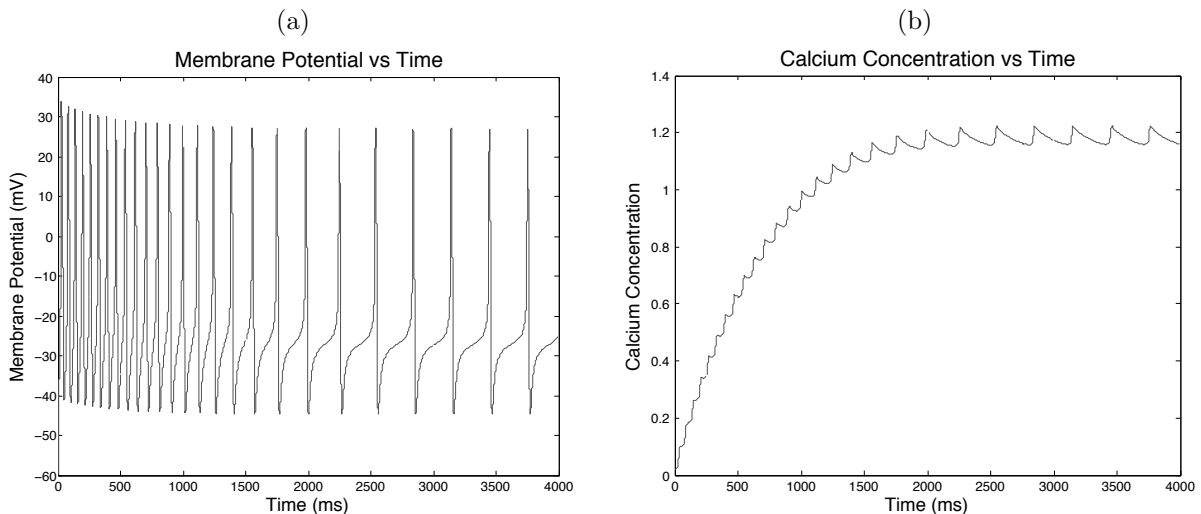


Figure 17: These graphs show that eventually the calcium moving in balances the calcium moving out when $I = 70$ (a) The sustained oscillations slow down as the concentration of calcium in the cell increases. (b) Ca jumps up each time the cell fires and slowly decays between action potentials.

We also find parameters values in this model that cause the cell to fire repetitively with no applied current. We use these cells as pacemakers in the network model of the heart. The parameters for these pacemaker cells in this model are given in Figure 22.

6.2 Phase-shifting and Phase-locking in the Modified Morris Lecar Model

Using the method described in Section 4.3, we investigate how external stimuli applied to an excitable cell during a single oscillatory period affect the dynamics of a cell with calcium gated potassium channels. Just as for the original Morris-Lecar model, we look at the phase-response curves for a single cell with K - Ca channels (see Figure 18) and at the function $G(\phi)$ to determine the phase locked solutions for

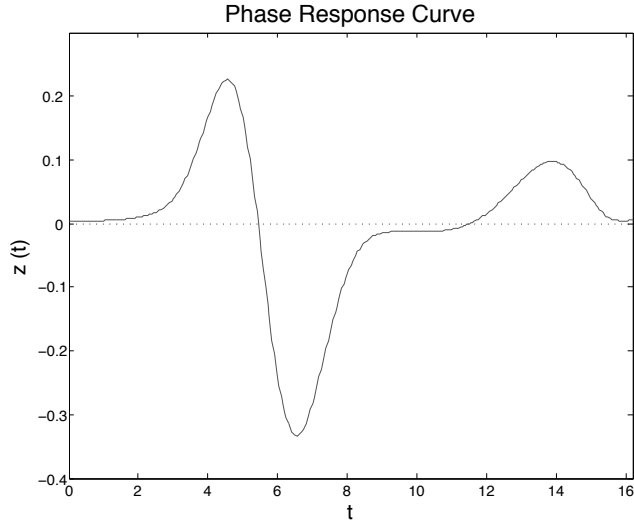


Figure 18: Phase response curve for a pacemaker cell with K - Ca channels.

coupled cells. Consistent with our observations in the previous model, the pacemaker cells and regular excitable cells have very similar dynamics in this model as well (see Figure 19). We once again see that the likelihood of synchrony in the regular excitable cells increases with I . For the pacemaker cells, the synchronous phase-locked solution is the only stable solution. Thus we predict that the pacemakers with calcium-dependent potassium channels will synchronize in the network model.

6.3 Whole Heart Model

We now put the cells with K - Ca channels into the network model of the *Drosophila* heart. The cells are connected by gap junctions and arranged in the same way as the cells in the Morris-Lecar network model. We assume that the contribution of calcium in each cell is affected only by the calcium current that enters the cell when it fires and that the current flowing through the gap junctions does not add any calcium to the cell. As in the model which used Morris-Lecar cells, this model has three rings of “pacemaker” cells; the rest of the cells are simply excitable. Similarly to the first model, we use two ways of creating “pacemaker” cells: using injected current of $I = 80$ and changing the parameters. In the first case, the regular cells and the pacemaker cells use the same parameters, except that there is no current injected into the regular cells. In the second case, the parameters are changed to make the pacemaker cells fire on their own, and to make the excitable cells a little more excitable.

We assume that the cells of the heart are always in an adapted state. In other words, there is no

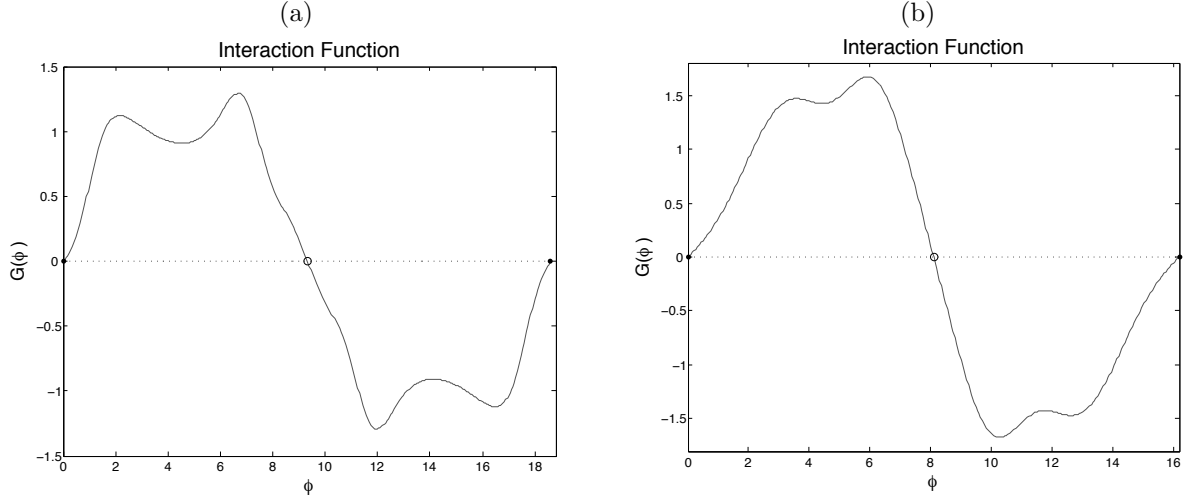


Figure 19: The odd part of the interaction function for cells with $K-Ca$ channels. Closed circles mark stable phase-locked solutions and open circles mark stable ones. In (a) we use regular excitable cells with $I = 80$ and in (b) we use pacemaker cells.

net change in the calcium concentration in the heart over time. We find that in order to get sustained oscillations from the model, we must lower ϕ , because if the cells in the model are firing too fast there is not enough time for calcium to leak out of the cell between action potentials. As a result, the $K-Ca$ channels would eventually hyperpolarize the cell enough for it to stop firing. In order to correct for this effect we set $\phi = 0.01$. Doing so gives sustained oscillations.

We first discuss the results from the model when we inject current into the first three rows of cells. Figures 20 and 21 show calcium levels and membrane potential of one cell from each ring. The amount of calcium that comes in each time the cell fires is approximately the same as the amount that leaks out between each action potential. Noticeably, the calcium concentration in each ring of cells is different, and it decreases with distance from the pacemakers. We do not have data on the actual calcium concentration in the heart, so it is unclear whether or not this decrease in calcium concentration down the length of the heart is accurate.

Similar to the first model, the activity moves down the heart like a wave (see Figure 21), and when started at random initial values of $-70 < V < 30$, the cells in each ring synchronize. However, starting Ca at random initial conditions affects the smoothness of the wave of action moving down the heart and significantly delays the time that it takes for the cells to synchronize. This observation further suggests that the $K-Ca$ channels significantly impact the dynamics of the cells. When we use pacemaker cells that

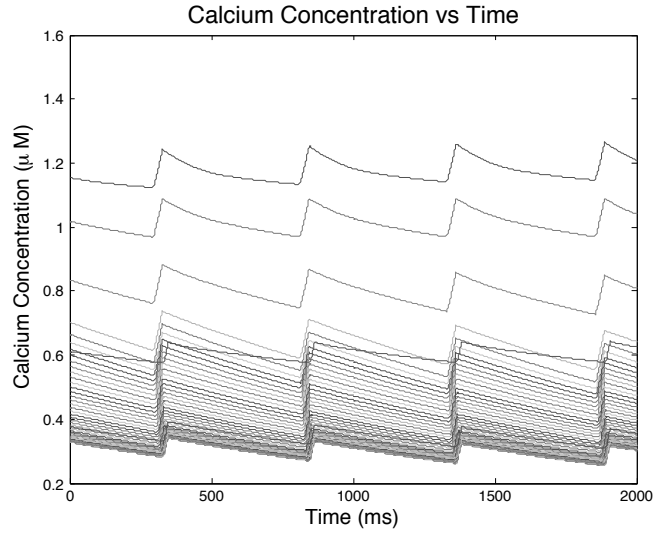


Figure 20: Each time a cell fires, the calcium concentration in that cell spikes and then decays until the next time it fires. One cell from each ring is shown. Current is injected in the first three rings of cells at $I = 80$.

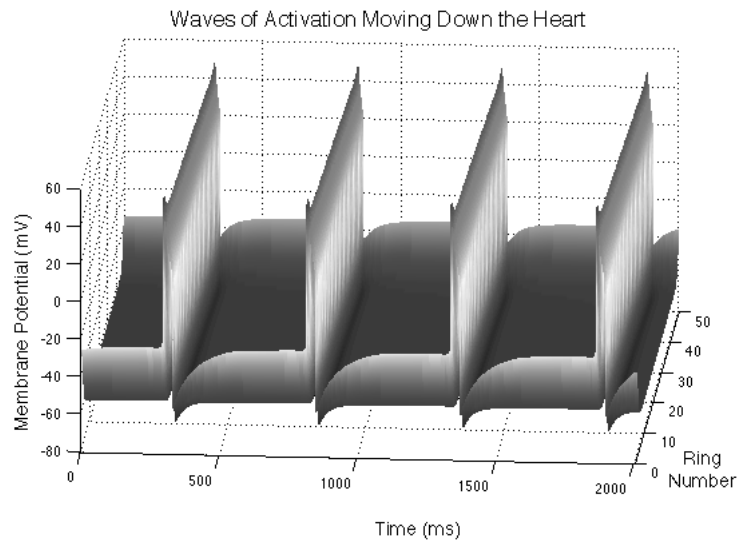


Figure 21: Three dimensional visualization of the heartbeat. Current is injected in the first three rings of cells at $I = 80$

are created by changing the parameters we get similar results (see Figures 22 and 23)

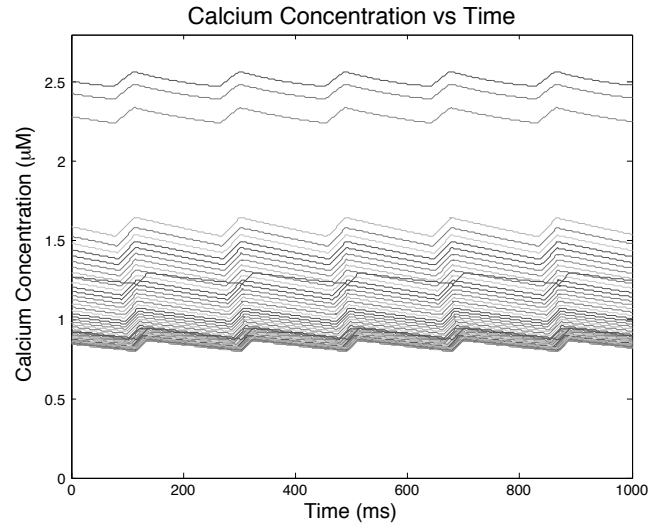


Figure 22: The first three rings of cells are pacemaker cells. Parameters are the same as those used in Section 6.1 except $V_1 = -5$ in the regular excitable cells and in the pacemaker cells we use $V_1 = -7$, $V_2 = 35$, $V_3 = 12$, $V_4 = 20$. Calcium concentration spikes each time the cells fire and then decays until the next time they fire.

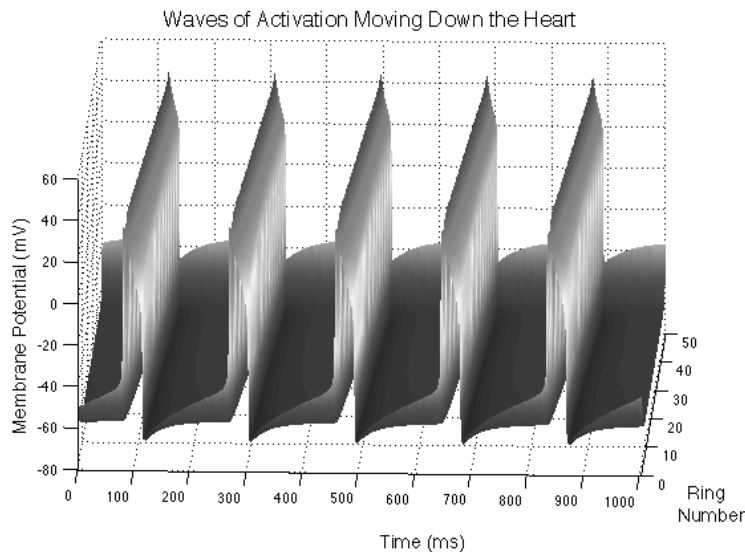


Figure 23: The first three rings of cells are pacemaker cells. Parameters are the same as those used in Section 6.1 except $V_1 = -5$ in the regular excitable cells and in the pacemaker cells we use $V_1 = -7$, $V_2 = 35$, $V_3 = 12$, $V_4 = 20$. The heartbeat is stable.

7 Discussion

In this work we model the dynamics of the heart of *Drosophila melanogaster* using excitable cell models. The heart beat of *Drosophila* is driven by pacemaker cells [4]. Regular excitable cells require external stimulation to raise the membrane potential above the threshold, which causes the cell to fire. Pacemaker cells have a lower firing threshold and are therefore capable of firing by themselves. We model the heart as a network of regular and pacemaker cells, connected by gap junctions.

We start from the Morris-Lecar single cell model. It models change in membrane potential caused by the activity of voltage gated calcium and potassium channels. By increasing the injected current we can observe the appearance of sustained oscillations through a Hopf bifurcation or a saddle-node bifurcation on an invariant circle. We change the parameters to make pacemaker cells. Using the phase-reduction approach we find that two coupled Morris-Lecar cells are more likely to synchronize as the amount of injected current is raised.

We put the cells into a network that models the *Drosophila* heart by setting three rings of cells at one end as pacemakers and the remaining cells as regular excitable cells. Our model produces a wave of activity, generated at the pacemaker end, which moves down the length of the heart to mimic the heart beat of the fly. The cells in each ring synchronize with each other, supported by the prediction made using

the phase-reduction approach. We also observe that the frequency of the heart beat is greatly influenced by the temperature parameter, which is consistent with experimental observations of *Drosophila* [4].

The initial model does not take into consideration the calcium-gated potassium channels that have been experimentally shown to play an important role in the heart of *Drosophila* [10]. In order to make the model more biologically accurate we add potassium channels that are directly dependent on the concentration of calcium. To do this, we add another equation to account for the rate of change of calcium concentration in the cell.

Through phase-plane analysis of the single cell system we can observe that the amount of current that needs to be injected to cause repetitive firing in the cell is very high. This effect is due to opening of the calcium gated potassium channels as the calcium concentration in the cell increases, making the cell less excitable. Results from the phase-reduction approach indicate that just as in the Morris Lecar model, the cells are highly likely to synchronize when coupled by gap junctions.

When we put these cells into the whole-heart model we observe a wave of activity originating at the pacemaker end and moving down the length of the heart. The heartbeat is slowed due to the calcium gated potassium channels, and the heart beats in an adapted state. This means that the amount of calcium entering the cell each time it fires is the same as the amount of calcium leaking out.

The modified model of the heart is more biologically accurate than the original model that used Morris-Lecar cells. However, there are still a number of changes that would need to be made in order to explain the data that is available about the heart of *Drosophila*. For instance, it is hypothesized that there are two types of calcium channels in the heart of *Drosophila* which are analogous to the T type and L type channels in the vertebrate heart. If a mutation hinders the activity of the L type channels, the heart is forced to rely solely on T type channels. Since the voltage threshold for channel opening is lower for T type channels, this results in increased heart rate [16]. Taking different types of calcium channels could make the model more biologically relevant.

Also, many experiments have explored the effects of different ion channels on the heart rate frequency and rhythmicity [10, 12]. In future work we plan to create a more biologically accurate model of the heart that will mimic the effects of ion channel mutations in order to explain available data and make predictions about biophysical mechanisms underlying the heart beat and its variations.

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A Coding Method

Each cell is modeled as a single system of equations. The heart is a cylinder. Cells in the heart have a von Neumann neighborhood, and are connected to the cells in their neighborhood by gap junctions. We have zero boundary conditions.

To code this, we construct a sheet of cells, contained in a matrix with dimensions [circumference] by [length]. We seam this rectangle together on the [length] edge in order to create our cylinder. We have one matrix per state variable. We use a single vector of length [circumference] [length] [number of state variables].

First, we must define the neighborhood for each of the cells. For most cells, the neighborhood is simple to define. The only places we need to be careful is on the edges of the sheet of cells. Since we have zero boundary conditions, the cells on the top (and bottom) of the sheet of cells have only three neighbors. In our equations, the gap junctions are modeled as $g_g(V - \text{up}) + g_g(V - \text{down}) + g_g(V - \text{left}) + g_g(V - \text{right}) = g_g(4V - \text{up} - \text{down} - \text{left} - \text{right})$. In the case of the cells at the top, there is no up neighbor, and thus no leak into the cell, so that neighborhood is modeled as $g_g(V - \text{down}) + g_g(V - \text{left}) + g_g(V - \text{right}) = g_g(3V - \text{down} - \text{left} - \text{right})$. For convenience, we let the “up” neighbor of the cells in the top round be themselves. The result is we have $g_g(V - \text{up}) + g_g(V - \text{down}) + g_g(V - \text{left}) + g_g(V - \text{right}) = g_g(V - V) + g_g(V - \text{down}) + g_g(V - \text{left}) - g_g(V - \text{right}) = g_g(3V - \text{down} - \text{left} - \text{right})$, which is what we wanted, in the same form as the standard. Alternatively, we can think of this as the cell leaking into itself, which results in no leakage to an “up” neighbor.

The case for the last round is analogous. We code this as follows:

```
round = floor((i-1)/radius);

if round==0                                % If the cells is in the initial round
    up   = y(i);                            % the "up" neighbor is itself
    down = y(i + radius);                   % the "down" neighbor is the cell in the same
                                           % position in the next round
elseif round==length                       % If the cell is in the last round
    up   = y(i-radius);
    down = y(i);                            % the down neighbor is itself
else
    up   = y(i-radius);
```

```

    down = y(i+radius);
end

```

The next thing to consider is left and right neighbors. In each round, the left and right neighbors are the cells before and after it, respectively. We need to be sure, however, to seam the edges of the tube together so that the cell in the first position is in the neighborhood of the cell in the last position. We code this as following:

```

    position = mod(i,radius);
if position==1                % If the cell is at the beginning of the round
    left = y(i+radius-1);      % left is the last cell--
                                % go forward a round and subtract 1
    right= y(i+1);
elseif position==0           % If the cell is at the end of the round
    left = y(i-1);
    right= y(i-radius+1);     % go back a round and add one to get the right neighbor
else                          % Everywhere else, it is as you would expect
    left = y(i-1);
    right= y(i+1);
end

```

Several rounds at the beginning of the heart are pacemaker cells. These are cells will continually fire, triggering the firing of the cells in the rest of the heart. Pacemaker cells and regular cells differ only in their parameters. We make sure to define the parameters used for each round:

```

round = floor((i-1)/radius);
if round<PMLength           % If the cell is in the pacemaker, use the pacemaker parameters
    parameter = pacemaker;
else                         % Otherwise use the cell parameters
    parameter = cell;
end

```