The Effect of Calcium Channel Blockers on Ventricular Fibrillation

Submitted by

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Abstract

The most frequent cause of sudden cardiac death is unstable ventricular tachycardia or fibrillation. Fibrillation is characterized by the propagation and breakup of rotary electrical waves, which leads to a chaotic distribution of electrical activation of the tissue. This leads to uncoordinated contraction of the chambers of the heart, inhibiting the heart from pumping blood to the rest of the body. Successful electrical defibrillation has been limited to delivering high-energy shocks to the entire heart, causing rotary electrical activity to cease and normal sinus rhythm to resume. This has several adverse effects on the heart, including tissue damage and post-shock dysrhythmias. The high-energy shock also causes significant pain and anxiety to the patient. Thus, a combination of low-energy electrical stimulations with antiarrhythmic, ion channel-blocking drugs is of interest. This combination is examined *in silica* using the Fenton-Karma model. Calcium channel block was found to sustain fibrillation when compared to defibrillation rates without drug or electrical intervention. The number of phase singularities on the tissue was also found to decrease initially but increase at higher concentrations of calcium channel block. These findings provide some insight into possible mechanisms of the proarrhythmic effects of calcium channel blocking drugs, and will ultimately aid in progress toward a lower-energy defibrillator.

The Effect of Calcium Channel Blockers on Ventricular Fibrillation

Sudden cardiac death is among the leading causes of death in the United States. Most often, this phenomenon occurs due to either rapid heart rate of the ventricles or ventricular fibrillation. Numerous drugs have been developed that aim to suppress arrhythmias such as fibrillation. Increased mortality during the Cardiac Arrhythmia Suppression Trial (The CAST Investigators, 1989), a drug trial conducted in 1989, has led to investigation into the causes of ventricular fibrillation to better explain the mortality rate seen in these trials. In addition to antiarrhythmic drugs, cardiac arrhythmias can be suppressed by electrical stimulation; this method is currently limited to delivering strong shocks to large regions of tissue, which can lead to tissue damage as well as pain and anxiety for the patient receiving the shock (Navab, Nikoo, Pasyar, Rakhshan, & Sharif, 2015). This investigation will examine the effectiveness of defibrillation strategies involving calcium-channel blocking drugs. The aim is to obtain an ideal combination of electrical stimulation and drug concentration to achieve a greater rate of successful defibrillation. These findings will aid in the understanding of antiarrhythmic drug mechanisms as well as the mechanism of fibrillation in the heart. Furthermore, this will aid in development of a lower energy electrical defibrillator, in contrast to those currently in use.

Fibrillation involves a complex distribution of electrical activation of the tissue in the heart. This electrical activation involves the formation of rotary waves in the tissue which, through propagation, break up to form additional waves. This mechanism has been modeled *in silica* by numerous researchers including the Fenton-Karma model (Bueno-Orovio, Cherry, & Fenton, 2008; Cherry, Evans, Fenton, & Hastings, 2002) which will be employed to numerically simulate ventricular fibrillation and incorporate various levels of calcium channel block. The use of a model will avoid any harmful physiological effects and ethical considerations, and help

direct future research to eventually benefit patients, especially those with easily suppressed arrhythmias following a myocardial infarction (Bigger et al., 1994).

Until recently, the primary method used to suppress cardiac arrhythmias was electrical stimulation. Defibrillators first began to be used on patients in the mid-20th century. This method originally involved delivering a shock externally to the chest with paddles (Deyell, Tung, & Ignaszewski, 2010). In 1980, the implantable cardioverter-defibrillator (ICD) was invented. The device is implanted inside the chest cavity to internally stimulate the cardiac tissue (Deyell, Tung, & Ignaszewski, 2010). This allows for the use of a weaker current, since the current delivered by the ICD no longer must pass through tissues such as skin or hair. However, because the devices were not programmable, a major downside to the first ICD was the delivery of occasional shocks which were not necessary: "An occasional inappropriate shock was the price one paid to make certain patients always received an appropriate shock when needed" (Winkle, 2012). Today, many advancements have been made in ICD technology including programmability, which allows for the device to detect an arrhythmia developing and deliver premature stimulation before fibrillation can develop.

Drug therapy is the primary method used to suppress the formation of cardiac arrhythmias. There are four classes of antiarrhythmic drugs, each targeting a specific ion channel such as calcium. In the heart, calcium channel blockers target a type of calcium channel present in the membrane of heart tissue (Camm & Grace, 2000). These blockers have various mechanisms, such as prolonging the resting phase of the cardiac action potential. Though they are in use, calcium channel blockers have been shown to decrease the symptoms of arrhythmia rather than mortality (Camm & Grace, 2000). In fact, some cardiac drugs have been shown to increase mortality rather than decrease it, notably in patients with heart failure: "Clinical

observation suggest[s] serious questions regarding the safety of most calcium-channel blockers in patients with heart failure"(Camm & Grace, 2000). This question of safety is seen in several drug trials including the Multicenter Diltiazem Post-Infarction Trial (Packer, 1990), which evaluated the effect of a calcium-channel blocker, diltiazem, on cardiac death in 2,466 patients who had suffered a recent myocardial infarction. Patients who showed evidence of heart failure upon entering this trial "experienced a significant increase in mortality when treated with diltiazem"(Packer, 1990). A similar trend was observed during the CAST, conducted between 1986 and 1989. This trial blindly tested two drugs, encainide and flecainide, to examine if they improve survival after a heart attack or myocardial infarction (MI). The drugs were administered to participants who experienced arrhythmias following the occurrence of a MI. Prior to the beginning of the clinical trial, encainide and flecainide were shown in preliminary tests to reduce the incidence of premature ventricular contractions (PVC's), or uncoordinated contractions of the heart that can develop into fibrillation. For the clinical trial, 730 patients were recruited who had previously suffered a MI. These subjects were given one of the two drugs over a ten-month period. Of these patients, 33 died due to myocardial infarction and the trial was ended prematurely (Moyé & Pratt, 1994). Despite the prior evidence that they successfully stopped PVC's, these drugs were evidently pro-arrhythmic in patients with a history of heart attack.

The cause of the increase in mortality of the CAST is not well established. There is great need for continued investigation into the mechanism of fibrillation, particularly for patients with heart disease. In fact, patients who have PVC's with a history of myocardial infarction are of particular concern as they have a "twofold to threefold risk of dying" compared to patients who do not have arrhythmia (The CAST Investigators, 1989). Aside from drug therapy alone, there may be combined therapies that reduce arrhythmias, such as the use of implantable cardiac

defibrillators (ICD) and drugs together. In some studies, ICD's have been shown to be more effective than drug therapy. However, in one such study, treatment was not randomized and patients receiving an implanted defibrillator had already failed drug therapy (Buxton et al., 2002). Therefore, I was motivated to investigate here the effects of drug and electrical therapies.

Methods

In this investigation, I will examine different levels of calcium channel blockage and different rates of electrical pacing. The relationship between calcium channel blockage and the number of phase singularities on the tissue will also be examined. The mathematical model of tissue that will be used is the Fenton-Karma model (Cherry, Evans, Fenton, & Hastings, 2002; Bueno-Orovio, Cherry, & Fenton, 2008). Fenton-Karma model represents the cardiac action potential in the ventricular myocardium, or ventricular muscle, and electrical impulses moving through the intracellular space. In heart tissue, the action potential involves the flow of sodium, calcium, and potassium ions across the cell membrane and through the intracellular and extracellular spaces. The relationship between this charge flow and corresponding potentials was first established by Hodgkin & Huxley in the Cable Equation (1952).

To derive the Cable Equation, an Ohm's law approximation must first be made, where the electrical current in the intracellular space is proportional to the intracellular potential gradient. Because extracellular gradients are small values, the gradient of the intracellular potential is approximated as the gradient of the transmembrane potential. The transmembrane potential V is:

$$V = U_i - U_e, \tag{1}$$

where U_i and U_e represent the intracellular and extracellular currents, respectively. Using the Ohm's law approximation, the intracellular current density J can be written as:

$$\boldsymbol{J} = -\sigma \nabla U_i \approx -\sigma \nabla \mathrm{V}, \tag{2}$$

where σ is the electrical conductivity of the membrane.

According to the continuity equation, a source of current in a region must be from adding or removing charges:

$$\nabla \cdot \boldsymbol{J} = -\frac{\partial Q}{\partial t} / Vol, \tag{3}$$

where Q is the net electric charge, t is time, Vol represents the membrane volume, and $\frac{\partial Q}{\partial t}$ represents the change in charge over time. Due to the cell membrane's poor conductivity, and inherent capacitance of approximately 1 microFarad per square centimeter, charges may accumulate as surface charges along the surface of the cell membrane. Charges may also accumulate within the cell volume due to the flow of ions through membrane channels. Combining these two possibilities yields the following:

$$\frac{\partial Q}{\partial t} = Surface\ Area \times \left(C_m \frac{\partial V}{\partial t} + I_{Ion,\,Membrane} \right), \tag{4}$$

where surface area represents the surface area of the membrane, C_m represents membrane capacitance per unit area, $\frac{\partial V}{\partial t}$ represents change in membrane potential over time, and $I_{ion\ membrane}$ represents ion current passing through the membrane. Substituting $\frac{\partial Q}{\partial t}$ in the equation of the intracellular current density J yields the Cable Equation

$$\beta \left(C_M \frac{\partial V}{\partial t} + I_{Ion,Membrane} \right) = \nabla \cdot (\sigma \nabla V), \tag{5}$$

where β represents the surface area to volume ratio of the cell.

In a normal cardiac rhythm, electrical activity begins at the sinoatrial node, a specialized region of cells in the right atrium or top right chamber of the heart. When an arrhythmia develops, abnormal electrical activity is sustained within the tissue and disrupts the normal wave of current that originates from the sinoatrial node (Cherry, Fenton, Hastings, & Evans, 2002).

This abnormal activity can take the form of a spiral or scroll shaped wave of electrical activation. Through spiral wave breakup, this can develop into disorganized or "chaotic" activity termed fibrillation, which can lead to cardiac arrest if it is not controlled

The two variables being evaluated in these simulations are frequency of electrical pacing and level of calcium channel block. For the first 100 milliseconds of each simulation, fibrillation is initialized. At 100 milliseconds, pacing and calcium channel blockage begins. Depending on the rate of pacing, 3-millisecond shocks will be delivered at certain intervals rather than continuously. For simulations not defibrillated by 3100 milliseconds, pacing is stopped and the electrical activity is observed for a further 1000 milliseconds to see whether induced instability terminates. The maximum duration of these simulations is 4100 milliseconds. Therefore, a simulation will be considered successfully defibrillated if a resting state is achieved before 4100 milliseconds.

Each trial of calcium channel block will include 75 simulations pacing by the delivery of a 3-millisecond stimulus at 5x the threshold to initiate an electrical activation, with the stimulus delivered every 242 milliseconds, 299 milliseconds or 499 milliseconds. Additionally, there will be a control trial in which no electrical stimulation is delivered. Each trial will also include one of two levels of calcium inhibition (either 2 percent or 10 percent). Because the Fenton-Karma model contains a computationally optimized current, these levels of block do not reflect a physiological concentration; instead, 2 percent or 10 percent of the total slow, inward portion of the ion current will be blocked. A control involving no calcium inhibition and a control involving neither electrical stimulation nor calcium inhibition will be conducted. I sought to determine if there is a combination of these variables which will result in the greatest amount of successful trials.

In trials 1 through 3, the program will be modified so that there is a 2% calcium channel block. The tissue is stimulated every 241 milliseconds in trial one, every 299 milliseconds in trial two, and every 499 milliseconds in trial three. Cycle Length (CL) is the average rate of electrical activity of the tissue without stimulus; these rates of pacing were arbitrarily chosen as 80% of CL, CL, and 70% longer than CL, respectively. In trials 4 and 5, the program will be modified so that there is a 10% calcium channel block. The tissue is stimulated every 241 milliseconds in trial four, and every 499 milliseconds in trial five. In trials 6 and 7, calcium channel block will be delivered at 2% or 10% with no electrical stimulation. Trial 8 through 10 will consist of electrical stimulation every 241 milliseconds, 299 milliseconds, or 499 milliseconds without calcium channel block. Trial 11 will consist of neither calcium channel block or electrical stimulation.

In trials 12 through 14, the number of phase singularities will be monitored over time at three levels of calcium channel block with no electrical stimulation. A phase singularity is the center of the spiral of a rotary wave; therefore, the number of phase singularities will be considered the number of rotary waves over time. Trial 15 will also be conducted in which phase singularities are monitored with no calcium channel block. The maximum simulation duration of these trials is 10,000 milliseconds. The goal of these trials will be to examine the effects of calcium channel blocker alone on spiral wave activity. The mean phase singularity counts of trials 12 through 14 will be compared to evaluate any relationship between the level of block and the number of phase singularities. A difference in mean phase singularity and overall positive trend between the count and block will indicate that calcium channel block is correlated to spiral wave breakup. This positive trend indicates that an increase in calcium channel block corresponds to a greater number of phase singularities.

A simulation which terminated fibrillation within 4100 milliseconds will be considered a successful defibrillation. The proportions of successful defibrillations will be compared between the nine different trials. A statistically significant difference between two proportions will determine that the greater proportion was a more successful combination of defibrillation and calcium channel blocker. The code used for the simulations can be found in Appendix A; the subroutine which monitors phase singularities can be found in Appendix B.

Results

Snapshots taken from the calcium channel block trials are shown in Figures 1-4, beginning at 100 milliseconds in the simulation and taken at intervals of 200 milliseconds. The initial state of fibrillation is visible in the first snapshot of each figure. The subsequent spiral wave breakup can be seen over time as the number and distribution of spiral waves appears to increase in each image. In Figure 1, the final image shows the tissue reaching sinus rhythm, after which the tissue reached resting state and the simulation ended. However, in Figures 2-4 there is sustained spiral wave activity visible throughout the images; therefore, the tissue did not come to rest in these simulations. As shown in Table 1, the success rate of termination without calcium channel blockage or electrical intervention was 21.9%. With 2% and 10% level of calcium channel blockage respectively, the success rate decreased to 12.0%. Without calcium channel blockage, the percent of successful trials at each rate of pacing was 4%. The highest success rate of 20.0% occurred in two trials, once at 2% calcium channel blockage with pacing of 248.988 and once at 2% blockage with pacing of 499.166. Overall, the success rates decreased as the level of blockage increased.

In the phase singularity trials (Table 2), the average number of phase singularities without calcium channel blockage was 30.532. With 10% calcium channel blockage, the average phase

count was 21.597. With 15% blockage, this average increased to 22.006. The average count further increased to 24.473 with 20% blockage. As Figure 5 shows, the simulation without calcium channel blockage came to rest before 3,000 milliseconds. The simulation with 20% blockage was in a continued state of fibrillation at the end of the simulation (Figure 6).

Conclusions

From the results of the simulations, there is evidence of a negative trend between calcium channel blocker concentration and success rate of defibrillation. The most optimal combination of blocker and electrical stimulation, having a success rate of 20.0%, appears to be of 2% blockage with pacing of 248.988 and pacing of 499.166, respectively. However, this success rate is less than the success rate obtained without blocker or electrical intervention.

In the phase singularity trials, the average phase singularity count decreases from 30.532 with no calcium channel blockage to 21.597 with 10% blockage. This suggests there is some antiarrhythmic activity since the number of rotary waves decreased with blocker present. However, with 15% blockage this average increased to 22.006; the average count increased further to 24.473 with 20% blockage. This suggests proarrhythmic activity as the concentration of blockage increases past 10%.

Thus, a mechanism is proposed by which calcium channel blockers may sustain fibrillation in the heart. It has been demonstrated that in high concentrations or overdose, ion channel blockers are proarrhythmic: “the risk of proarrhythmia has been demonstrated in class I and class III drugs, but significant variability has been observed between agents of the same class” (Barman, 2015). Therefore, the initial decrease and subsequent increase in phase singularity count with calcium channel block may be a result of the proarrhythmic effect of the drug. For example, the increase in phase singularities without altering tissue size suggests that the rotary wave size is decreased by the presence of the drug, allowing for greater breakup of

rotary waves. According to the critical mass hypothesis (Chen, Ideker, & Wolf, 1991), tissue must be of a certain size to sustain spiral waves and permit fibrillation. When this was proposed, it was believed that small hearts such as that of a rat could not sustain fibrillation due to their size. However, the results indicate that fibrillation is sustained with calcium channel blocker present. It is proposed that calcium channel blockers reduce the size of rotary waves which allows them to be sustained on a smaller region of tissue.

There are possible limitations to the Fenton-Karma model. While it can be implemented as 3-dimensional, a 2-dimensional tissue was chosen as it is easier to examine. Therefore, the findings may not fully translate to true three-dimensional cardiac tissue. It has also been suggested that the Fenton-Karma model may not accurately simulate "action potential morphology", a variable which can affect how the rotary waves travel throughout the tissue (Bragard, Cantalapiedra, Echebarria, & Peñaranda, 2012). Therefore, the effects of the calcium channel block may be a result of mathematical artifacts. The current approximated by the model is also computationally optimized, and the model does not completely distinguish between the currents of different ions. Therefore, the calcium channel blocker may be influencing the current of potassium or sodium ions rather than reflecting the true physiological effects of a calcium channel antiarrhythmic drug. Furthermore, true cardiac tissue is not homogeneous nor is it isotropic (Christini & Krogh-Madsen, 2006), and there are cases *in vivo* in which this lack of homogeneity causes the duration of the action potential to change in different regions of tissue; this was not considered in the implementation of the model here.

Hence, further study using other models is also warranted. The conditions of the investigation could be repeated using a more complex model which allows for the alteration of individual ion currents. Also, this could enable lesser and more physiologically accurate

concentrations of calcium channel block to be explored. There are other conditions which should be considered in the future, including delivery of drug at varying concentrations over time as well as at different points in the simulation. Additionally, the model could be further explored using multiple electrodes, rather than the single electrode used in this investigation. These electrodes could be distributed throughout the tissue and more accurately reflect the electrode placement of an implantable cardiac defibrillator.

In conclusion, these findings still provide insight into possible mechanisms of the proarrhythmic effects of calcium channel blocking drugs. The decrease in the success of defibrillation and the increase in phase singularity count both suggest that calcium channel block sustains fibrillation. Further investigation could improve the understanding of the effects of antiarrhythmic drug therapy. This will ultimately aid in the discovery of an optimal combination of electrical and drug therapy in the treatment of arrhythmias.

Acknowledgements

I would like to thank Dr. Steffan Puwal for his mentorship and thoughtful advice, and for our many helpful discussions throughout this project. The original code used in this project was also co-authored and provided by Dr. Puwal and his research assistant, Natalia Melkus, B.S.

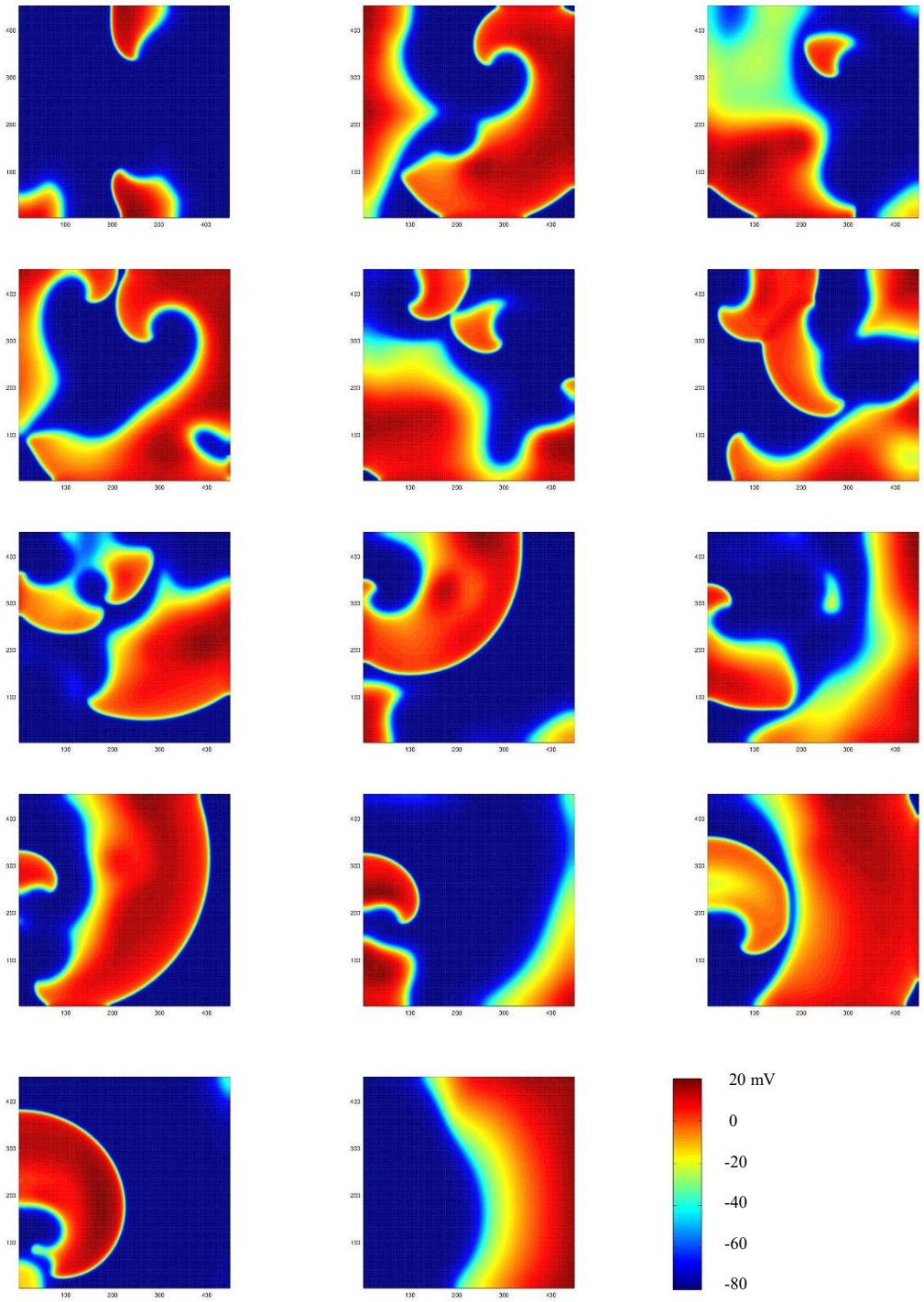

Figure 1: Snapshots during a simulation with neither calcium channel blocker nor electrical intervention are shown above. The first snapshot was taken at 100 milliseconds, followed by a snapshot taken every 200 milliseconds. As shown, the initial state of fibrillation is visible in the first snapshot. The subsequent spiral wave breakup can be seen over time as the number and distribution of spiral waves appears to increase in each image. The final image shows the tissue reaching sinus rhythm, after which the tissue reached resting state and the simulation ended.

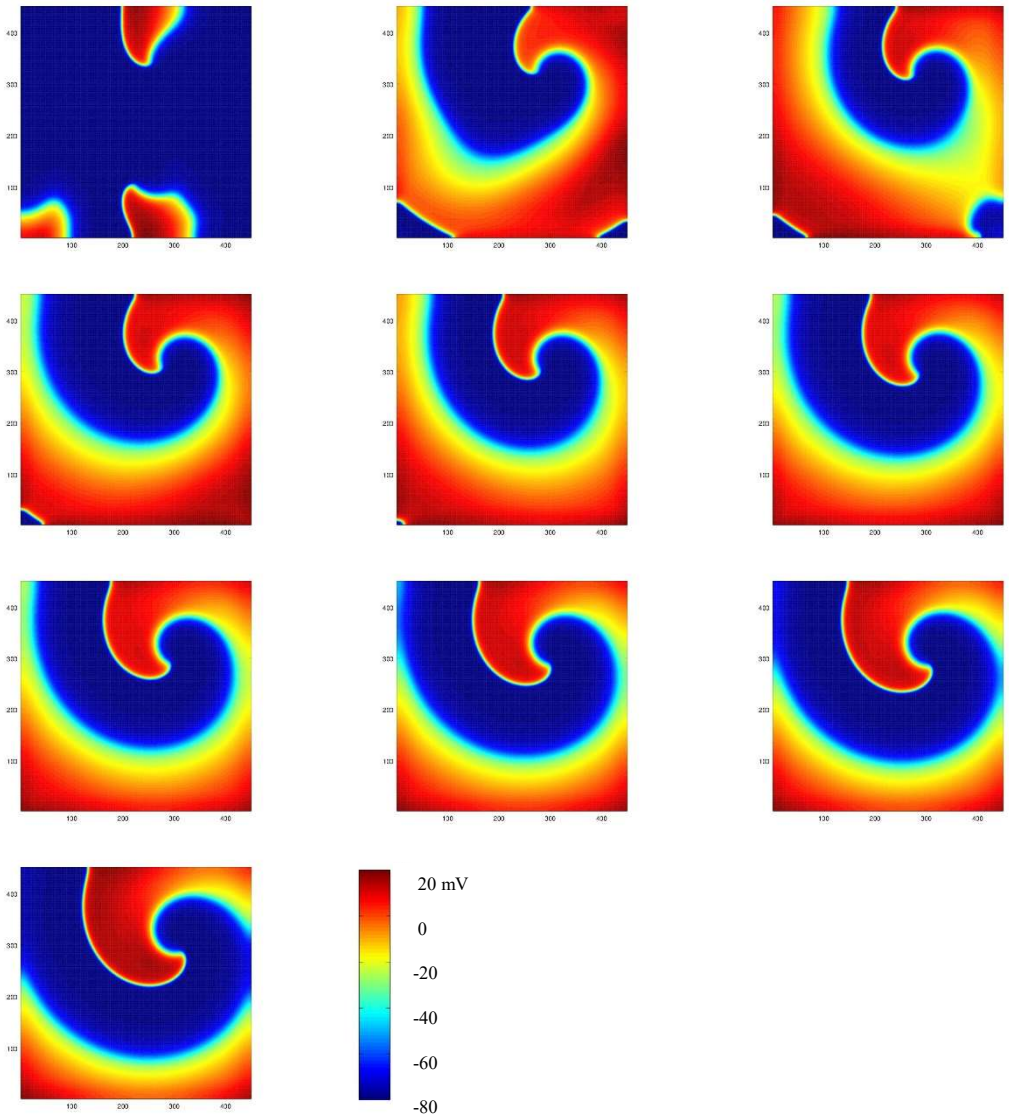

Figure 2: Snapshots of a simulation with 2% calcium channel blocker and no electrical intervention are shown above. The first image was taken at 100 milliseconds. The remaining images are shown at 1000 millisecond intervals. There is sustained spiral wave activity visible throughout the images; therefore, the tissue did not come to rest.

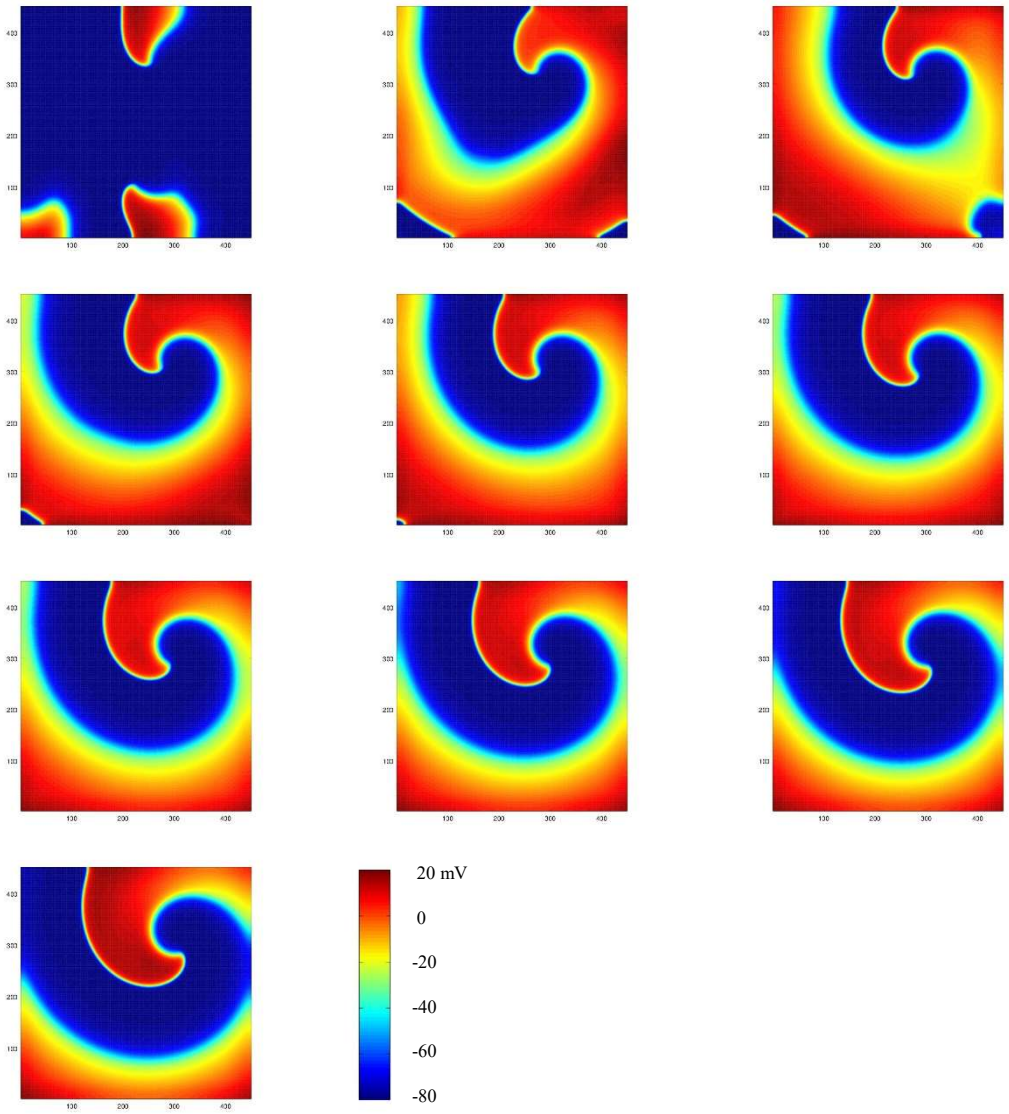

Figure 3: Snapshots of a simulation with 2% calcium channel blocker and pacing of 241.988 milliseconds are shown above. The first image was taken at 100 milliseconds. The remaining images are shown at 1000 millisecond intervals. There is sustained spiral wave activity visible throughout the images; therefore, calcium channel block failed to suppress fibrillation.

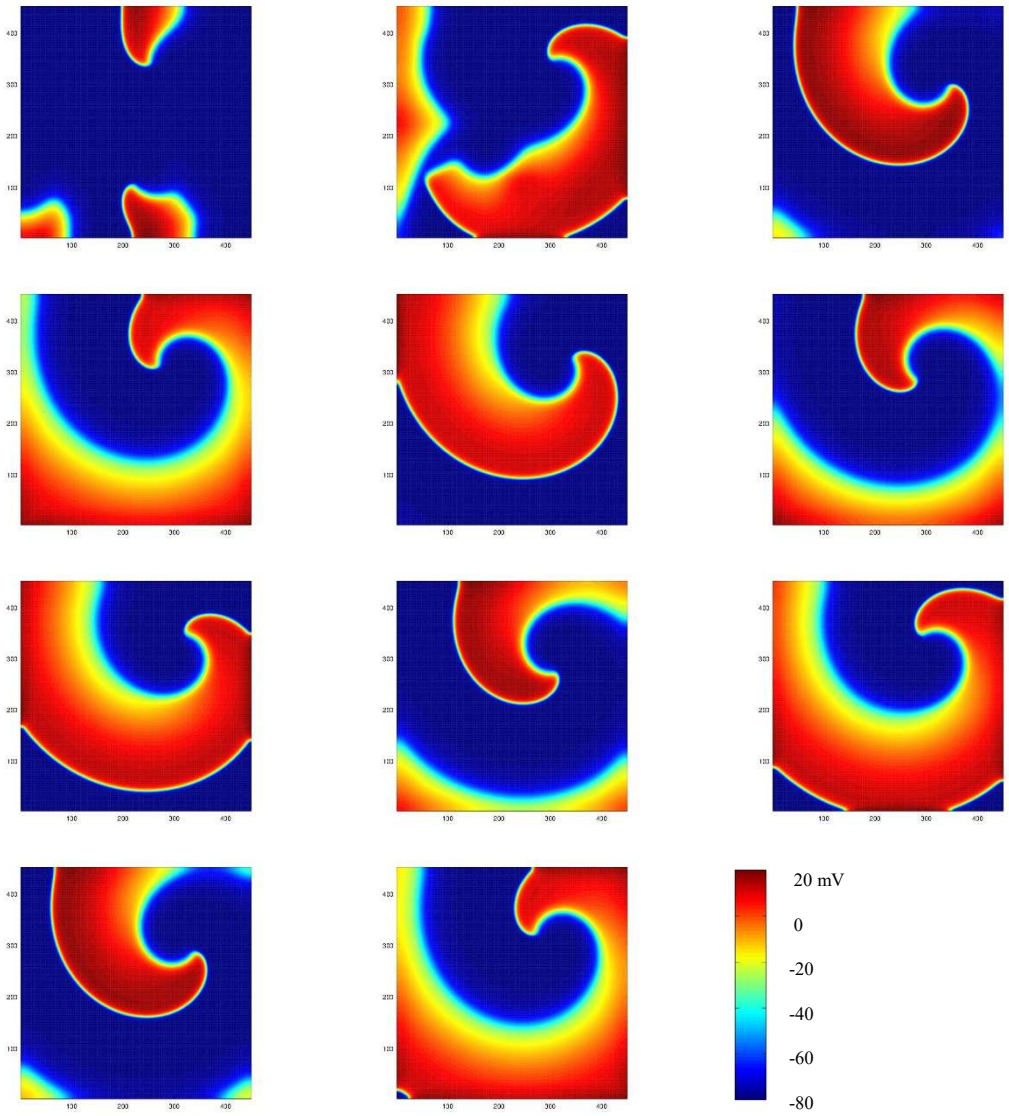

Figure 4: Snapshots of simulation with 10% calcium channel blocker and no electrical intervention are shown. The first image was taken at 100 milliseconds. The remaining images are shown at 1000 millisecond intervals. After fibrillation was initialized in the first image, the subsequent spiral wave breakup can be seen in the second image. There is sustained spiral wave activity visible throughout the images; therefore, 10% calcium channel block failed to suppress arrhythmia.

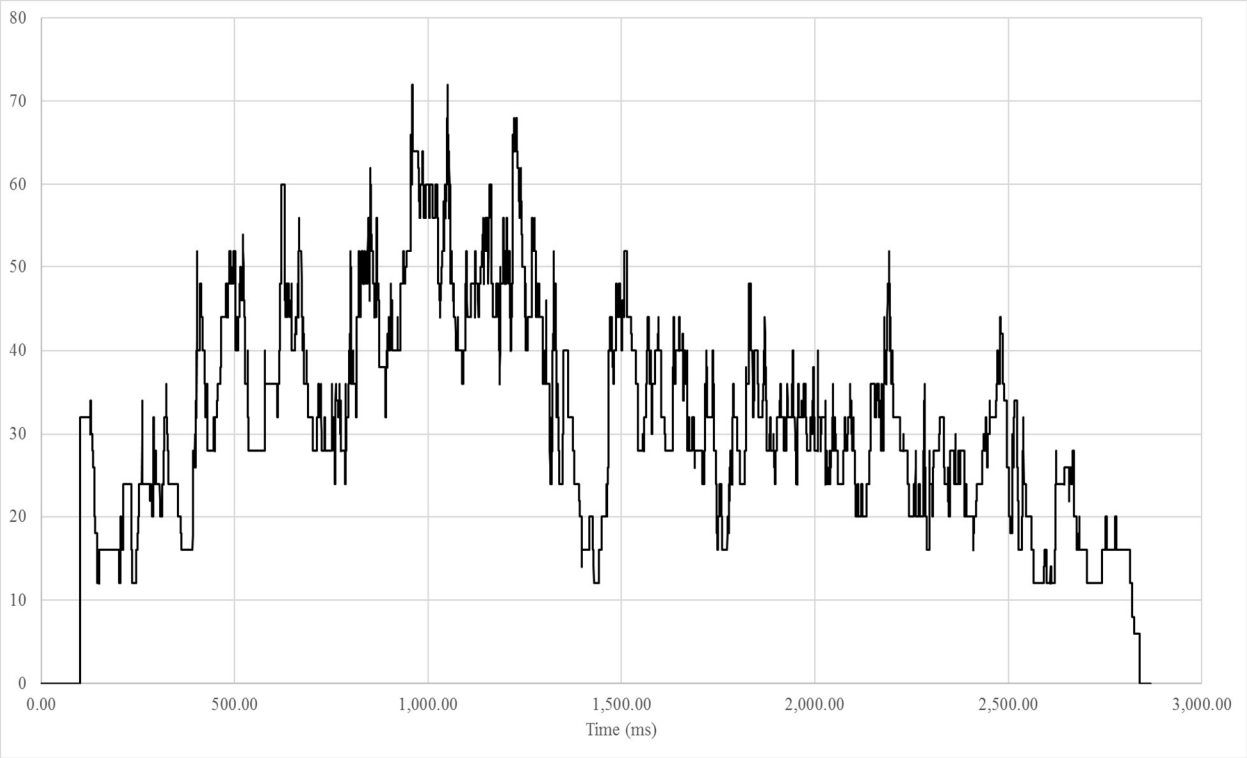

Figure 5: This graph shows phase singularity count versus time without calcium channel block or electrical intervention. For the first 1,000 milliseconds, there appears to be a positive trend in phase singularity count, suggesting that spiral wave breakup occurred during this interval. Near 1000 milliseconds there is a peak phase singularity count of approximately 70. Following this, there is a negative trend in phase singularity count. The count reached zero at approximately 2800 milliseconds, indicating that the tissue came to rest at that time.

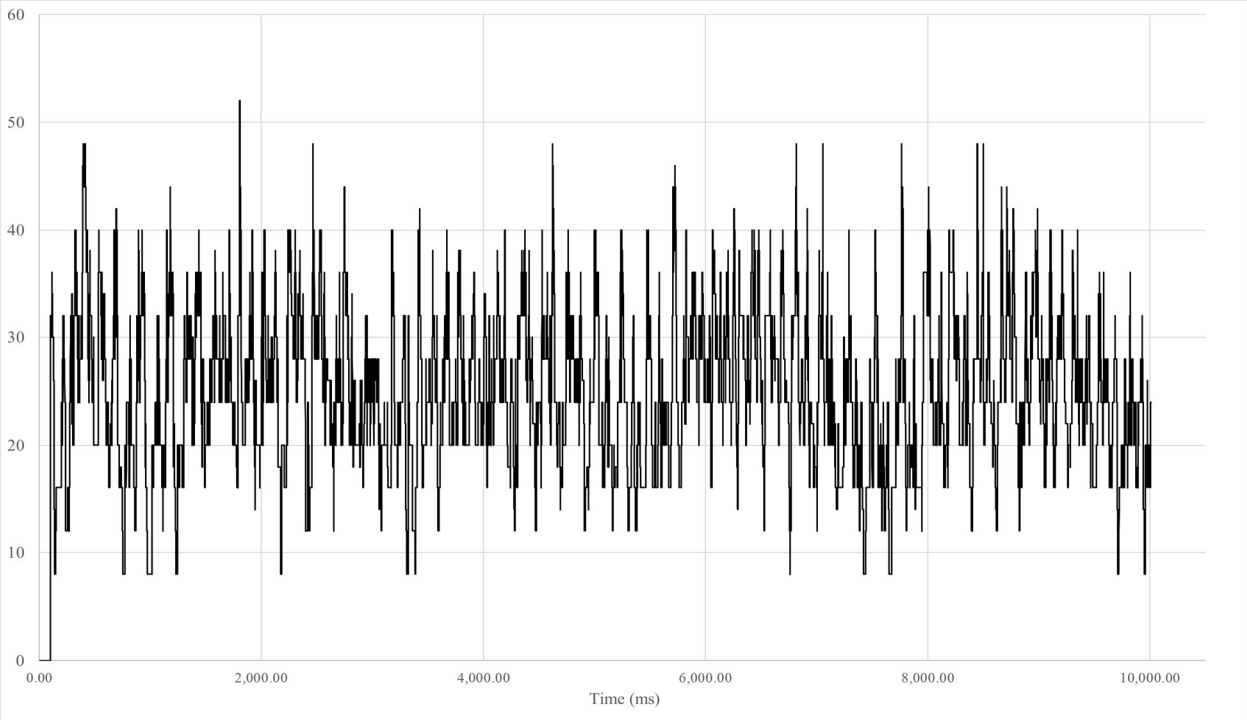

Figure 6: This graph shows phase singularity count versus time with 20% calcium channel block and no electrical intervention. There appears to be no overall trend in phase singularity count throughout the simulation. The phase singularity count is nonzero at 10,000 milliseconds, the maximum duration of the simulation. Therefore, 20% calcium channel block sustained fibrillation in this simulation.

Trial	Calcium channel block level	Pace (ms)	Successes
1	2%	241.988	15/75 (20.0%)
2	2%	299.026	12/75 (16.0%)
3	2%	499.166	15/75 (20.0%)
4	10%	241.988	11/75 (14.7%)
5	10%	499.166	11/75 (14.7%)
6	2%	0	9/75 (12.0%)
7	10%	0	9/75 (12.0%)
8	0%	241.988	2/50 (4%)
9	0%	299.026	2/50 (4%)
10	0%	499.166	2/50 (4%)
11	0%	0	16/93 (21.9%)

Table 1: This table shows the percent of successes for each of trials 1-11. The success rates for trials 8-11 are shown from Melkus & Puwal (2012). As noted in trials 1-5, calcium channel block combined with electrical intervention yielded a greater termination rate than trials 8-10, which involved pacing without calcium channel block. Similarly, the termination rates of trials 1-5 were greater than those of trials 6-7 which involved calcium channel block without electrical intervention. However, the success rates of trials 1-5 were still less than that of trial 11, which involved neither calcium channel block nor electrical intervention.

Trial	Calcium channel block level	Average number of phase singularities
12	20%	24.473
13	10%	21.597
14	15%	22.006
15	0%	30.532

Table 2: This table shows the average phase singularity counts of trials 12-15. With 10% calcium channel block, there was an initial decrease in average phase singularity count compared to trial 15 which involved no calcium channel block. This suggests some antiarrhythmic activity since the number of spiral waves decreased with 10% block. However, as the level of calcium channel block was increased in trials 13-14, the average phase singularity count increased. This suggests that calcium channel block sustains fibrillation at these concentrations.

Appendix A

```
c     Department of Physics, Oakland University, Rochester, MI
c     This program simulates a 2-D isotropic membrane using the Fenton-Karma
c     model as presented in "Multiple mechanisms of spiral wave breakup in a
c     model of cardiac electrical activity" by Fenton, Cherry, Hastings, and
c     Evans in Chaos Vol 12 No 3, 2002 and uses a Forward Euler integration.
c     It, further, uses the Iso correction for stimulus proposed by Puwal and
c     Roth in the Journal of Biological Systems Vol 14 No 1, 2006.

c     Compatible with FORTRAN 77, 90, and 95 Compilers
c     Written for explicitness with the model, not speed

c     I have explicitly type defined, rather than using some of the implicit
c     type definitions allowed by FORTRAN.  Therefore, all variables are defined
c     below and only these names are forbidden for additional variables.

      REAL V(450,450),Vnew(450,450),nu(450,450),w(450,450)
      REAL Ifi,Iso,Isi,Istim(450,450),snapshot,snapint
      REAL P(10,13),D,Cm,tau,time,dt,dt2,dx,diffusion
      REAL stimon, stimoff, pace, tn, block
      INTEGER pulse,psnum
      INTEGER i,j,size,simnum,name,set,snapcount


c     Define Which parameter set are we using
      set=4
      call params(dt,dt2,dx,P,D,Cm,diffusion)


c     SNAPSHOTS and TIMING OF SIMULATION
c     snapshot is the first time to take a snapshot (in msec)
c     snapint is the interval between successive snapshots (in msec)
c     duration is the duration of the simulation (in msec)
      snapshot = 100.0
      snapint  = 200.0
      duration = 10001.0
      pace=241.988

c     Open the file that will contain the data
      OPEN(UNIT=15, FILE='block2and241.dat')
      OPEN(UNIT=16, FILE='block2and241ps.dat')

c     Begin the set of simulations
      DO simnum=23,23
```

```
c       Initialize the tissue in a state of fibrillation
        size=450
        CALL initial2fib(V,nu,w,size,simnum)

        block=0.02

c       Begin the time loop
        snapcount=1
        DO time=0.0,duration,dt

        DO j=1,size
                DO i=1,size
                        Istim(i,j)=0.0
                END DO
        END DO

c       IF(time.le.3100) THEN
c       DO pulse=0,25
c               stimon=100+pulse*pace
c               stimoff=stimon+3
c               IF((time.ge.stimon).AND.(time.le.stimoff)) THEN
c       DO i=173,177
c               DO j=173,177
c                       Istim(i,j)=4*(-.12)
c               END DO
c       END DO
c               END IF
c       END DO
c       END IF

         psnum=0
        IF(time.gt.100) THEN
                CALL pscount(nu,V,psnum)
        END IF
        write(16,*) time,psnum

c       Depending on how you write code, here is where you can put in the
c       stimulus

c       DO tn=1.0,30.0
c               IF((time.gt.(tn*1000.0)).AND.(time.le.((tn+1.0)*1000.0))) THEN
c                       block=0.02*tn
c               END IF
c       END DO

c       Begin the space loops
```

```
      DO j=2,(size-1)
            DO i=2,(size-1)

c     I have eliminated the step functions p and q from the paper by simply
c     using their value (1 or 0) over the specified range of potentials

      IF(V(i,j).ge.P(set,13)) THEN
            tau=P(set,3)
      ELSE
            tau=P(set,2)
      END IF

      IF(V(i,j).ge.P(set,12)) THEN
            Ifi=-nu(i,j)*(V(i,j)-P(set,12))*(1-V(i,j))/P(set,6)
            Iso=1/P(set,8)
            Isi=-w(i,j)*(1+tanh(P(set,10)*(V(i,j)
     &                  -P(set,11))))/(2*P(set,9))
            nu(i,j)=nu(i,j)*(1-dt/P(set,1))
            w(i,j)=w(i,j)*(1-dt/P(set,4))
      ELSE
            Ifi=0
            Iso=V(i,j)/P(set,7)
            Isi=-w(i,j)*(1+tanh(P(set,10)*(V(i,j)
     &                  -P(set,11))))/(2*P(set,9))
            nu(i,j)=nu(i,j)+dt*(1-nu(i,j))/tau
            w(i,j)=w(i,j)+dt*(1-w(i,j))/P(set,5)
      END IF

c     Here is the correction to Iso for the stimulus
      IF(V(i,j).ge.1.25) THEN
            Iso=Iso+(V(i,j)-1.25)/(1.25*P(set,8))
      END IF
      IF(time.gt.100) THEN
            Isi=Isi*(1.00-block)
      END IF

c     Now find the new potential
      Vnew(i,j)=V(i,j)+dt*(diffusion*(V(i+1,j)+V(i-1,j)+V(i,j+1)
     &      +V(i,j-1)-4*V(i,j))-(Ifi+Iso+Isi+Istim(i,j))/Cm)

c     Now end the space loops
            END DO
      END DO

c     Now I have to do the edges (boundary conditions)
      DO i=2,(size-1)
```

```
            Vnew(1,i)=Vnew(2,i)
            Vnew(size,i)=Vnew(size-1,i)
            Vnew(i,1)=Vnew(i,2)
            Vnew(i,size)=Vnew(i,size-1)
        END DO
        Vnew(1,1)=Vnew(2,2)
        Vnew(1,size)=Vnew(2,size-1)
        Vnew(size,size)=Vnew(size-1,size-1)
        Vnew(size,1)=Vnew(size-1,2)

c       Now I need to say V=Vnew to complete the update and see
c       if the tissue is at rest
        rest=0
        DO j=1,size
            DO i=1,size
                V(i,j)=Vnew(i,j)
                IF(Vnew(i,j).gt.0.01) THEN
                    rest=1
                END IF
            END DO
        END DO

c       Now break the time loop if we're at rest
        If(rest.eq.0.and.time.gt.100.0) THEN
            GO TO 1000
        END IF

c       Now write the snapshots of what the potential looks like.  A lot of this block
c       of code is just naming the file I will write to.  Do not exceed 999 simulations
c       with this code.
        IF((time.ge.(snapshot-dt2)).AND.(time.le.(snapshot+dt2))) THEN
c           name = simnum*10000 + snapcount
            name =10600 + snapcount
            CALL writesnapshots(V,size,name)
            snapshot=snapshot+snapint
            snapcount=snapcount+1
        END IF

c       Now end the time loop
        END DO

1000    CONTINUE
c       Here is where you can write the time a simulation came to rest
        WRITE(15,*) simnum, ' 5x threshold ', ' 3ms pulse ', pace, time

c       Now end the simnum loop
```

```
      END DO

c     Now close the data file
      CLOSE(UNIT=15)
      CLOSE(UNIT=16)

c     Now end the program
      STOP
      END



c     The following are subroutines used in the program.  Be careful
c     and probably do not edit these.


c     ------------------------------------------------
c     The function for the random number generator.
      FUNCTION ran0(idum)
      INTEGER idum,ia,im,iq,ir,mask
      REAL ran0,am
      PARAMETER (ia=16807, im=2147483647, am=1./im,
     &           iq=127773, ir=2836, mask=123459876)
      INTEGER k
      idum=ieor(idum,mask)
      k=idum/iq
      idum=ia*(idum-k*iq)-ir*k
      IF(idum.lt.0) idum=idum+im
      ran0=am*idum
      idum=ieor(idum,mask)
      RETURN
      END
c     ------------------------------------------------


c     ------------------------------------------------
c     The subroutine that assigns the parameter values for the mechanism
c     of breakup we will be using.
      SUBROUTINE params(dt,dt2,dx,P,D,Cm,diffusion)
      REAL dt,dt2,dx,P(10,13),D,Cm,diffusion
      dt          =     0.04
      dt2         =     dt/2
      dx          =     0.015
      D           =     0.001
      Cm          =     1.0
      diffusion   =     D/(dx**2)
```

```
c       P is an array that contains all the (P)arameter Values from the paper.
c       The first index references the parameter set, the second index
c       references the parameter.
c       tau_nu+             =       P(set,1)
c       tau_nu1-    =       P(set,2)
c       tau_nu2-    =       P(set,3)
c       tau_w+              =       P(set,4)
c       tau_w-      =       P(set,5)
c       tau_d       =       P(set,6)
c       tau_0       =       P(set,7)
c       tau_r       =       P(set,8)
c       tau_si      =       P(set,9)
c       k           =       P(set,10)
c       V_c_si      =       P(set,11)
c       V_c         =       P(set,12)
c       V_nu        =       P(set,13)

c       Set 1 - stable spiral
        P(1,1)=3.33
        P(1,2)=19.6
        P(1,3)=1000.0
        P(1,4)=667.0
        P(1,5)=11.0
        P(1,6)=0.25
        P(1,7)=8.3
        P(1,8)=50.0
        P(1,9)=45.0
        P(1,10)=10.0
        P(1,11)=0.85
        P(1,12)=0.13
        P(1,13)=0.055

c       Set 3 - breakup close to tip
        P(3,1)=3.33
        P(3,2)=19.6
        P(3,3)=1250.0
        P(3,4)=870.0
        P(3,5)=41.0
        P(3,6)=0.25
        P(3,7)=12.5
        P(3,8)=33.33
        P(3,9)=29.0
        P(3,10)=10.0
        P(3,11)=0.85
        P(3,12)=0.13
```

P(3,13)=0.04

c Set 4 - breakup far from tip
P(4,1)=3.33
P(4,2)=15.6
P(4,3)=5.0
P(4,4)=350.0
P(4,5)=80.0
P(4,6)=0.407
P(4,7)=9.0
P(4,8)=34.0
P(4,9)=26.5
P(4,10)=15.0
P(4,11)=0.45
P(4,12)=0.15
P(4,13)=0.04

c Set 5 - 2 regions of slope less than 1
P(5,1)=3.33
P(5,2)=12.0
P(5,3)=2.0
P(5,4)=1000.0
P(5,5)=100.0
P(5,6)=0.362
P(5,7)=5.0
P(5,8)=33.33
P(5,9)=29.0
P(5,10)=15.0
P(5,11)=0.70
P(5,12)=0.13
P(5,13)=0.04

c Set 6 - bistability and Doppler shift
P(6,1)=3.33
P(6,2)=9.0
P(6,3)=8.0
P(6,4)=250.0
P(6,5)=60.0
P(6,6)=0.395
P(6,7)=9.0
P(6,8)=33.33
P(6,9)=29.0
P(6,10)=15.0
P(6,11)=0.50
P(6,12)=0.13
P(6,13)=0.04

```
      RETURN
      END
c     ------------------------------------------------


c     ------------------------------------------------
c     The subroutine that initializes the tissue in a state
c     of fibrillation
      SUBROUTINE initial2fib(V,nu,w,size,simnum)
      REAL V(450,450), nu(450,450), w(450,450),pi,c(36)
      INTEGER iseed,simnum,seedloop,i,j,size
      pi=3.141592653589
      size=450
      iseed=simnum
      DO seedloop=1,36
            c(seedloop)=ran0(iseed)
      END DO
      DO j=1,size
            DO i=1,size
      V(i,j)=( c(1)*0.5 + c(2)*sin(2*pi*(float(i)/size+c(3)))
     &            +c(4)*sin(2*pi*(float(j)/size+c(5)))
     &            +c(6)*sin(4*pi*(float(i)/size+c(7)))
     &            +c(8)*sin(4*pi*(float(j)/size+c(9)))
     &            +c(10)*sin(2*pi*(float(i)/size+c(11)))
     &                  *sin(2*pi*(float(j)/size+c(12)))
     &            +c(13)*sin(4*pi*(float(i)/size+c(14)))
     &                  *sin(2*pi*(float(j)/size+c(15)))
     &            +c(16)*sin(2*pi*(float(i)/size+c(17)))
     &                  *sin(4*pi*(float(j)/size+c(18))) )
      IF(V(i,j).le.0) THEN
            V(i,j)=0.0
      ELSE
            V(i,j)=1.0
      END IF
      nu(i,j)=( c(19)*0.5 + c(20)*sin(2*pi*(float(i)/size+c(21)))
     &            +c(22)*sin(2*pi*(float(j)/size+c(23)))
     &            +c(24)*sin(4*pi*(float(i)/size+c(25)))
     &            +c(26)*sin(4*pi*(float(j)/size+c(27)))
     &            +c(28)*sin(2*pi*(float(i)/size+c(29)))
     &                  *sin(2*pi*(float(j)/size+c(30)))
     &            +c(31)*sin(4*pi*(float(i)/size+c(32)))
     &                  *sin(2*pi*(float(j)/size+c(33)))
     &            +c(34)*sin(2*pi*(float(i)/size+c(35)))
     &                  *sin(4*pi*(float(j)/size+c(36))) )
      IF(nu(i,j).le.0) THEN
```

```
                nu(i,j)=0.0
        ELSE
                nu(i,j)=1.0
        END IF
        w(i,j)=0.5
                END DO
        END DO
        RETURN
        END
c       ------------------------------------------------


c       ------------------------------------------------
c       The subroutine that outputs the snapshots
        SUBROUTINE writesnapshots(V,size,name)
        INTEGER name,size,i,j
        REAL V(450,450)
        CHARACTER*20 filename

        IF(name.gt.9999.AND.same.lt.100000) THEN
                WRITE(filename,996) name
996             FORMAT('fort.',i5)
        ELSE IF(name.gt.99999.AND.same.lt.1000000) THEN
                WRITE(filename,997) name
997             FORMAT('fort.',i6)
        ELSE
                WRITE(filename,998) name
998             FORMAT('fort.',i7)
        END IF
        OPEN(UNIT=16,FILE=filename)

        DO i=1,size
                WRITE(16,999) (V(i,j), j=1,size)
        END DO
999     FORMAT(4096(e8.3,' '))
        CLOSE(UNIT=16)
        RETURN
        END
c       ------------------------------------------------
```

Appendix B

```
SUBROUTINE pscount(nu,v,psnum)
REAL nu0,v0,phi(450,450),nu(450,450),v(450,450),gradphix(450,450)
REAL gradphiy(450,450),dkydx(450,450),dkxdy(450,450)
REAL curlkz(450,450),pi
INTEGER i,j,pa,pb,pc,pd,size,psnum
pi=3.1415926535
size=450
v0=0.3581
nu0=0.4505
DO j=1,size
        DO i=1,size
                phi(i,j)=atan2(nu(i,j)-nu0,v(i,j)-v0)
        END DO
END DO

DO j=1,size
        DO i=1,size
                pa=i-1
                pb=i+1
                pc=j-1
                pd=j+1

                IF(pa.lt.1) THEN
                        pa=size
                END IF
                IF(pb.gt.size) THEN
                        pb=1
                END IF
                IF(pc.lt.1) THEN
                        pc=size
                END IF
                IF(pd.gt.size) THEN
                        pd=1
                END IF
        gradphix(i,j)=(phi(pb,j)-phi(pa,j))
        gradphiy(i,j)=(phi(i,pd)-phi(i,pc))
        DO WHILE(gradphix(i,j).gt.pi)
                gradphix(i,j)=gradphix(i,j)-pi;
        END DO
        DO WHILE(gradphix(i,j).lt.-pi)
                gradphix(i,j)=gradphix(i,j)+pi
        END DO
        DO WHILE(gradphiy(i,j).gt.pi)
                gradphiy(i,j)=gradphiy(i,j)-pi
```

```
        END DO
        DO WHILE(gradphiy(i,j).lt.-pi)
                gradphiy(i,j)=gradphiy(i,j)+pi
        END DO
END DO
END DO

DO j=1,size
        DO i=1,size
                pa=i-1
                pb=i+1
                pc=j-1
                pd=j+1

                IF(pa.lt.1) THEN
                        pa=size
                END IF
                IF(pb.gt.size) THEN
                        pb=1
                END IF
                IF(pc.lt.1) THEN
                        pc=size
                END IF
                IF(pd.gt.size) THEN
                        pd=1
                END IF
                dkydx(i,j)=gradphiy(pb,j)-gradphiy(pa,j)
                dkxdy(i,j)=gradphix(i,pd)-gradphix(i,pc)
        END DO
END DO

DO j=1,size
        DO i=1,size
                curlkz(i,j)=dkydx(i,j)-dkxdy(i,j)
        END DO
END DO

psnum=0
DO i=1,size
        DO j=1,size
                IF((curlkz(i,j).gt.1).or.(curlkz(i,j).lt.-1)) THEN
                        psnum=psnum+1
                END IF
        END DO
END DO
```

```
RETURN
END
```

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