Shock-induced termination of cardiac arrhythmias

Group members: Baltazar Chavez-Diaz, Chen Jiang, Sarah Schwenck, Weide Wang, and Jinglei Zhang

Cardiac arrhythmias, also known as irregular heartbeat, occur when the electrical activity of the heart is irregular, disrupting the flow of blood to the heart (1). Arrhythmias can result in either the heart beating too quickly as in ventricular tachycardia, or too slowly, as in bradycardia (2). While many arrhythmias are not life-threatening, they are still a leading cause of morbidity and mortality. In fact, over 300,000 individuals die suddenly yearly in the United States, and in most cases it is thought that arrhythmias are the cause (2). Furthermore, the Center for Disease Control estimated that 2.66 million people would have atrial fibrillation in 2010, indicating that they are a world-wide problem (2).

Now, the pumping of the heart is controlled through electrical impulses. Specialized cells within the right atrium known as the sinoatrial node fire spontaneously about 70 times per minute (2). These firings lead to the coordinated contraction of the atria and then, after a slight delay, the ventricles. As a result, in order to treat cardiac arrhythmias, the irregular electrical activity must be removed and the regular activity recovered.

Defibrillation is commonly used to terminate cardiac arrhythmias such as ventricular tachycardia (3). Defibrillation consists of delivering a controlled amount of electrical energy to the heart using a device called a defibrillator. This suppresses the chaotic cardiac action potentials caused by the arrhythmia and allows the normal rhythm to be reestablished (3). There are three main protocols commonly used in commercial defibrillators, which are based on monophasic and both symmetric and asymmetric biphasic shocks. The monophasic protocol consists of only one phase while the biphasic consists two phases, where the polarity of the electrodes is switched during the second phase. Biphasic shocks can be either symmetrical or asymmetrical, and the asymmetrical shocks can have either a shorter first or second phase. Biphasic shocks are thought to be more efficient than monophasic shocks based upon empirical evidence found by Ideker's group in the late 1980s (3). However, it is not yet fully understood why biphasic shocks are more efficient. As a result, in our project, we will quantitatively compare the efficiency of the three different protocols.

Our model uses the simplest geometry that can maintain a propagating action potential- a one-dimensional ring of cardiac tissue (see Figure 1) (3). Under normal circumstances, an action potential is initialized and travels around the ring. In our case, the shock will be modeled as the application of currents through electrodes on either side of the ring. These electrodes can either inject or subtract electrical charges during the shocks. A defibrillatory shock will be defined as successful if all wave propagation is removed within one second of the end of the shock (3). If any wave activity is still present, the shock will be characterized as unsuccessful.
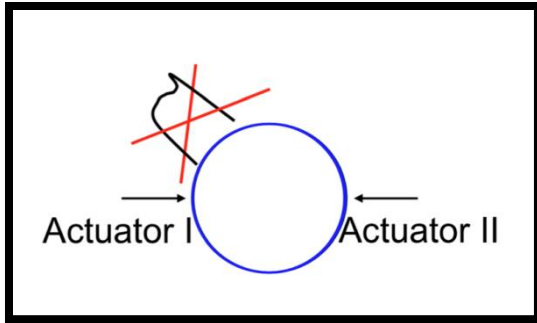
Figure 1. Schematic of the ring of cardiac tissue. The two areas represent the locations of the two electrodes.

In order to fully understand our model, we now need to switch from a more macroscopic standpoint to a microscopic view. By expanding upon the Beeler-Reuter equations, which describe the electrical activity of cardiac myocytes, the membrane potential can by calculated by solving :

$$\frac{\partial V_m}{\partial t} = -\frac{I_{BR} + I_{ep} + I_{fu}}{C_m} + \nabla \cdot \left(D_g \cdot \nabla V_m\right) + \nabla \cdot (D_g \cdot \nabla \varphi_e)$$

where V_m is the membrane potential (3,4).

This equation becomes important when considering how the membrane potential changes when the shock of defibrillation is applied, as this allows for an understanding of action potential waves which can determine the success or failure of defibrillation.

Now, membrane potential refers to the difference in electric potential between the inside and the outside of cells. In humans, there is a much higher proportion of sodium (Na^+) outside the cell than in and much more potassium (K^+) inside the cell than out (5). As a result, sodium moves into the cell and potassium out via ion channels according to their concentration gradients. In addition, membrane potentials are usually held stable at around -70 to -80 millivolts (5). However, when this potential rises past a certain threshold, an action potential can occur. Action potentials occur in several types of cells, including neurons, muscle cells and endocrine cells. During action potentials, the membrane potential of the cells changes as the cell is first depolarized by the opening of voltage-gated Na^+ channels and then repolarized by the opening of voltage-gated K^+ channels (see Figure 2) (5). Following an action potential, there is a refractory period where the potential falls below the resting potential. This prevents the action potential from travelling the opposite direction and continues the flow of information through the cells.
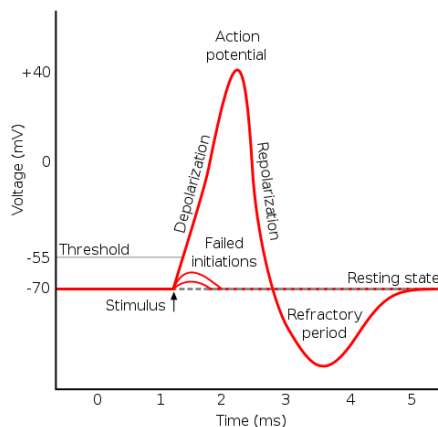

Figure 2. A typical action potential showing first the depolarization and then repolarization stages.

Referring back to our equation, this helps explain the first of the three terms. In this term, C_m represents the capacitance of the myocyte membrane, or its ability to store charge, I_{BR} is the membrane current, I_{ep} is the current associated with electroporation, and I_{fu} accounts for the possible stimulation of the tissue through an anode break. Looking first at I_{BR}, we can split this term into four parts:

$$I_{BR} = I_K + I_x + I_{Na} + I_s$$

In this case, I_K and I_X both represent potassium currents outward, I_{Na} represents the sodium current in, and I_S represents the calcium current inward. I_K and I_{Na} represent the currents generated during an action potential by the opening of voltage-gated sodium and potassium channels and I_X represents the current caused by the presence of leaky potassium channels in the cells which are consistently letting small amounts of potassium out of the cell.

Next, I_{ep} accounts for the electroporation phenomenon. This phenomenon occurs when a shock is applied and results in the creation of pores in the membrane of the cell. These pores allow for ion flow which prevents the membrane potential from reaching an unrealistic level.
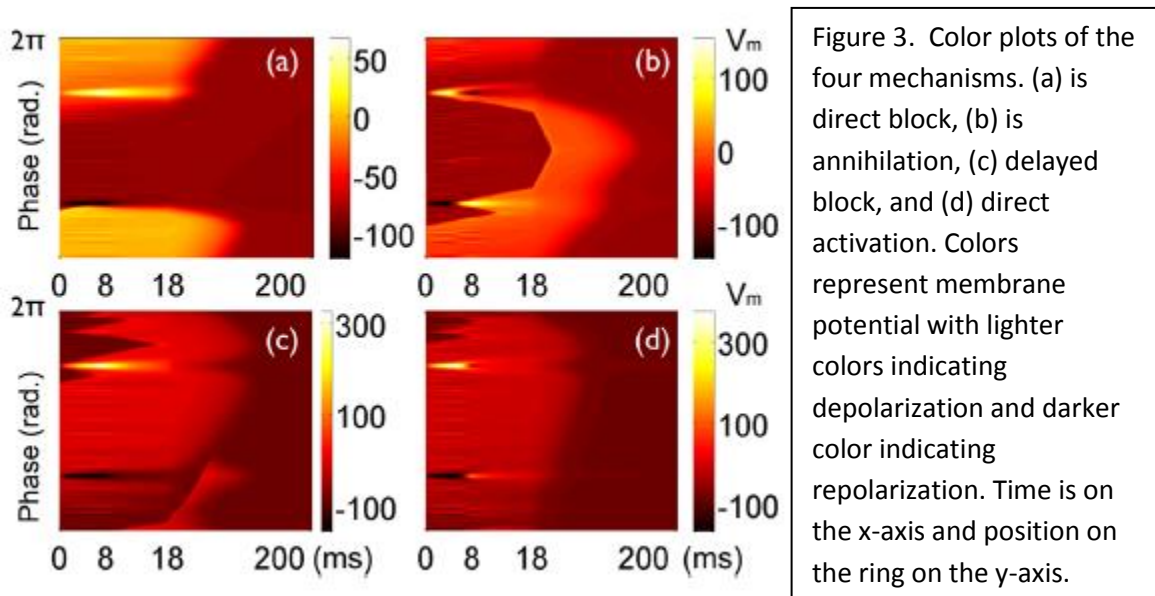
Moving on to the next two terms in the equation, φ_e represents the extra-cellular potential and D_g denotes intra-cellular diffusion of the electrical potential. The second term, $\nabla \cdot (D_g \cdot \nabla V_m)$, describes the diffusion of the potential from the inside of the cell out. By taking the divergence of this term, we can understand how the diffusion is changing with time. Similarly, the third term, $\nabla \cdot (D_g \cdot \nabla \varphi_e)$, describes the diffusion from the outside of the cell into the cell over time.

Now, within our model, we will be considering seven main parameters that can influence the success or failure of defibrillation. The first is the shock waveform, or the three basic protocols of defibrillation described above. The second, shock duration, refers to how long the shock is applied. In the simulations done by Bragard *et al.*, this was kept constant. Next, shock energy refers to how strong the shock is. The strength of the shock with be varied from E= 1 V/cm to E= 10V/cm. Next, shock timing refers to the location of the action potential wave front and back at the time of the shock. The size of the action potential is also important in determining defibrillation outcome as it is constantly varying as the dynamics are quasi-periodic. The heterogeneity of the cardiac tissue also plays a role as heterogeneities create more polarization sites within the tissue which makes excitation easier. Finally, the system size, or the size of the ring, plays a role. The system size in our model will be set to 6.7 cm, as was done by Bragard *et al.* In addition, our spatial discretization is 0.025cm. Also, during the first ten milliseconds of the shock, the time step with be set to 0.001 milliseconds. At every time following, it will be set to 0.01 milliseconds.

Simulations were done by Bragard *et al.* to determine which of the three protocols was most efficient. We plan to mimic the simulations to both replicate their results and then test how the data changes when either the shock duration is changed or when the asymmetric biphasic shock has a shorter first phase. The simulations conducted were split into three main parts.

First, the research team used an artificial neural network to classify four different types of successful defibrillations (see Figure 3). The first type, direct block, occurs when the front of the

action potential is near the anode when current is applied and is then directly blocked. This is shown by the dark block in the center of the color plot (a) followed by a vertical strip showing lower membrane potential, indicating a successful defibrillation. The second type, direct annihilation, occurs when two action potentials potentiate around the ring in opposite directions and annihilate each other. This is shown in figure 3(b) where the colors come to a peak and then die out. Delayed block occurs when the action potential generated propagates around the ring until it reaches a refractory region, or an area of lower membrane potential, and then dies out (see Figure 3(c)). This mechanism tends to last longer and the action potential can travel around the ring multiple times before dying out. The fourth and final mechanism is called direct activation. This is seen when the entire ring is excited to a higher membrane potential, as is shown in the bright red in the lower right graph of figure 3. Because the whole ring is activated, the action potential can no longer travel about the ring, rendering the defibrillation successful when the ring relaxes again once more.

Figure 3. Color plots of the four mechanisms. (a) is direct block, (b) is annihilation, (c) delayed block, and (d) direct activation. Colors represent membrane potential with lighter colors indicating depolarization and darker color indicating repolarization. Time is on the x-axis and position on the ring on the y-axis.

The proportions of the different mechanisms as well as the number of successes were determined for energy levels ranging from 1 to 10 V/cm. At lower energy levels (E= 1 V/cm), the monophasic protocol was most efficient with 27.50% of defibrillations being successful (3). In addition, the direct block mechanism was seen more at lower energy levels and only during monophasic runs. At higher energy levels (E= 7- 10 V/cm), greater than 90 % of all defibrillations were successful for each of the three protocols (3). In addition, direct activation was the most predominant mechanism seen at higher energies. Finally, at energies ranging from 2 to 5 V/cm, the asymmetric biphasic protocol was found to be most efficient.

Next, the efficiency of the shock was quantified using a Dose-Response curve: $\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 E$, where p is the probability of success, β_0 and β_1 are parameters fit to the curve, and E is the applied energy. Using this curve, it was determined that in order to have 90% of defibrillations be successful, the energy applied during the asymmetric biphasic shock should

range between 5.83 and 5.85 V/cm (3). This again indicated that the asymmetric biphasic protocol was more efficient than the other two, which required energy levels of 6.77-6.80 and 6.02-6.04 for monophasic and symmetric biphasic respectively (3).

Finally, two parameters, $\Delta\Phi$ (action potential duration) and Φ_b (action potential location on the ring), were varied and the probability of successful defibrillation mapped out on color histograms. The wave back of the action potential was used rather than the wave front to record the results as previous studies have shown that perturbations along the ring are more sensitive in the wave back. This was confirmed again by Bragard *et al.* as along the y-axis, constant Φ_b values yield similar results, indicating its relevance (3).

At low energy (E = 1V/cm), monophasic and asymmetric biphasic protocols have similar efficiencies (see Figure 4). In addition, the direct activation mechanism was not present at low energies and so was not included. Because direct activation works by exciting a large portion of tissue through multiple electrodes, or in the case of our model, by exciting the whole ring, it was not seen at low energies. Also, the direct block mechanism was only relevant in the monophasic protocol at low energies. Furthermore, because the regions of high probability of success are localized, if Φ_b and $\Delta\Phi$ are known when the shock is applied, the probability of defibrillation can be predicted with high accuracy at low energy.
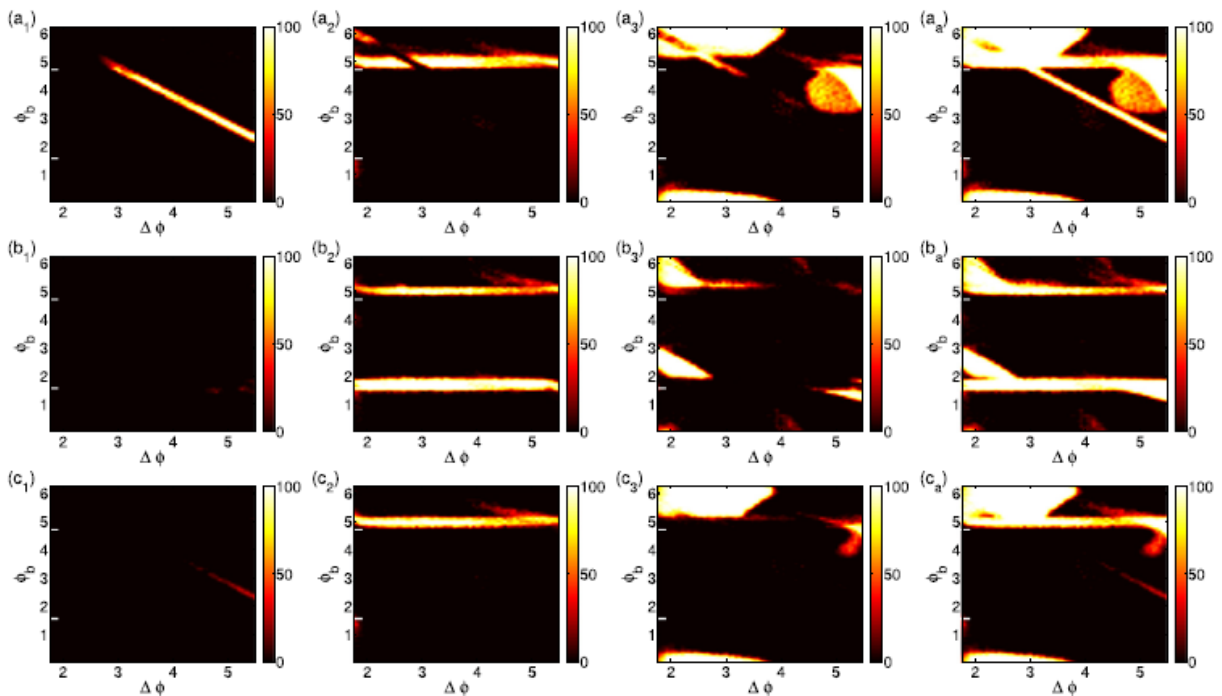

Figure 4. Color histograms showing the probability of successful defibrillation. The top row represents monophasic shock, the middle symmetric biphasic, and the bottom asymmetric biphasic. The first column shows the direct block mechanism, the second annihilation, the third delayed block, and the fourth is an overlay of the first three columns.

When the energy was slightly increased (E = 3V/cm), the monophasic protocol became less efficient than both biphasic protocols. In addition, the results were not as clear cut as they were for the lower energy. Rather than just yielding results of either 100% or 0% defibrillation, intermediate values such as 50% defibrillation as seen. This indicates that we cannot predict the probability of defibrillation by only knowing Φ_b and $\Delta\Phi$ for higher energies.

Next, when the energy was increased to 5V/cm, the direct block mechanism was no longer seen. However, the direct activation mechanism predominated and had the highest success rate of defibrillation throughout the three protocols. In addition, at lower $\Delta\Phi$ values, the success of defibrillation was increased. This is expected because at lower $\Delta\Phi$ values, there is more tissue to excite resulting in increased propagation which assists defibrillation, resulting in more successes.

Finally, when the energy was increased to 7 V/cm, direct activation was dominant for biphasic shocks, and the asymmetric biphasic protocol was the most efficient (see Figure 5). Also, successful defibrillations were uniformly spread throughout the variations of the two parameters in both biphasic protocols. This is expected as both asymmetric and symmetric biphasic protocols render both electrodes equivalent meaning that the probability of a successful defibrillation should be evenly dispersed. Also, for the monophasic protocol, there was less chance of a successful defibrillation for any of the mechanisms when Φ_b is located at the cathode. This results from the wave back at shock initiation being too close to the hyperpolarized region, which causes less refractory and thus shock failure.
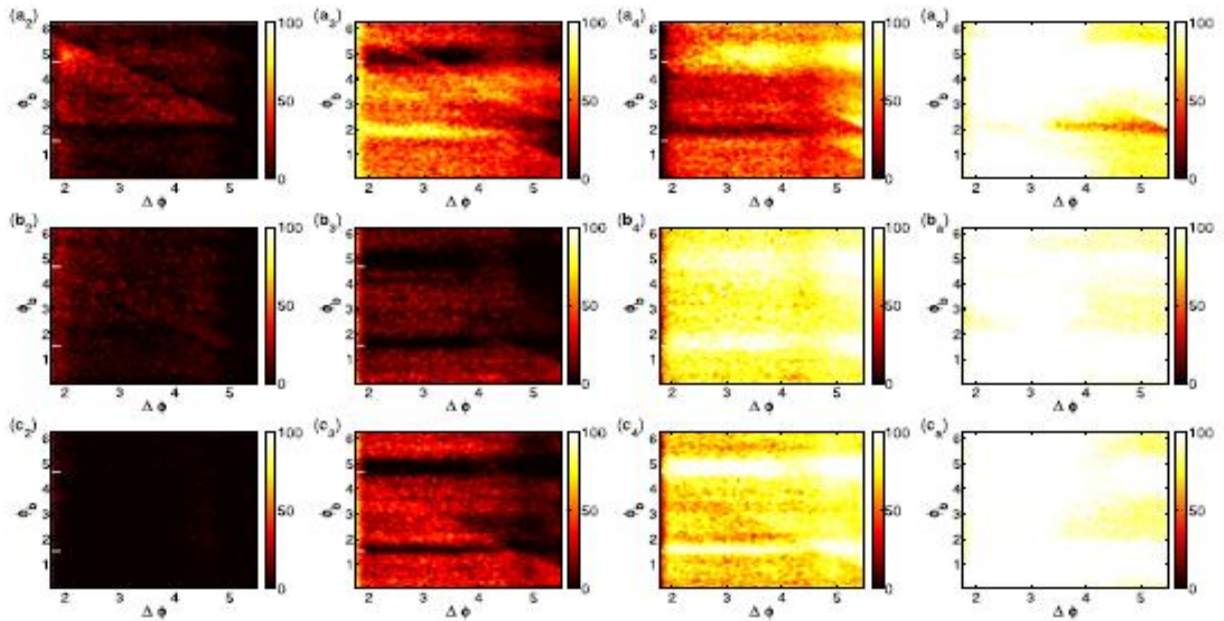

Figure 5. Color histograms showing the probability of successful defibrillation. The top row represents monophasic shock, the middle symmetric biphasic, and the bottom asymmetric biphasic. The first column shows the annihilation mechanism, the second delayed block, the third direct activation, and the fourth is an overlay of the first three columns.

In conclusion, the energy levels used throughout the experiment by Bragard *et al.* are values that could be used in a commercial defibrillator. Monophasic defibrillators, which are no longer commonly used, produce shocks vary around 5000 Volts. Biphasic defibrillators range from 200-2200 Volts with most common biphasic defibrillators using 1700 Volts. This corroborates the conclusion that biphasic shocks are more efficient than monophasic, as less energy is needed to successfully defibrillate. This is important to consider as lower energy shocks cause less damage to tissue (3).

In order to expand upon the work done by Bragard *et al.*, we plan to simulate how the rates of success of defibrillation change when the shock duration is shorten, as shorter shocks cause less damage to the tissue than longer shocks. In addition, we plan to test the differing efficiency of two asymmetric biphasic shocks. The first asymmetric shock will have a longer first phase and a shorter second phase as was tested in Bragard *et al.*. The second will have a shorter first phase and longer second phase. The simulations discussed above will be replicated and expanded on as we change these two other parameters.

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