

# Modeling Pharmacology in Cardiac Myocytes

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## Abstract

Cardiac myocytes are non-neural cells that possess the capacity to propagate regenerative depolarizing potentials. This allows them to coordinate the exquisite timing necessary to orchestrate millions of these individual muscle cells to generate a heartbeat. Abnormalities of cardiac conduction and cardiac electrophysiology are central to many disease processes and account for significant morbidity and mortality. Several of the various pharmacologic therapies used in clinical cardiology to treat those aberrations modulate the ionic conductances that generate the cardiac action potential. This project uses electrophysical models of cardiac myocytes in order to study the effects of pharmacologic intervention.

## 1 Introduction

According to the Centers for Disease Control 26% of deaths in the United States are caused by cardiac disease. This epidemic has led to the development of an army of cardiac drugs that are prescribed to help combat cardiac disease and alleviate patient symptoms. Many cardiac drugs exploit the complex electrophysiology which governs heart rate, contractility, and rhythm but many of these drugs have a narrow therapeutic index and come with a host of side effects. While the cost of running trials for drug design are becoming increasingly expensive computers and software are becoming more affordable. This project proposes using computational models of cardiac electrophysiology to affordably and accurately predict potential therapeutic applications and side effects of new drugs from their predetermined mechanisms of action.

## 2 Cardiac myocytes

Cardiac myocytes are heterogeneous populations of non-neural cells that propagate regenerative depolarizing potentials through gap junctions. This depolarization drives the influx of calcium ions as well as release of calcium from the sarcoplasmic reticulum. These processes raise the concentration of intracellular calcium which in turn is able to bind the troponin complex of cardiac sarcomeres disinhibiting the myosin and actin interactions which allows cardiac myocytes to contract in an ATP dependent manner.

### 2.1 Cardiac action potential

The generalized cardiac action potential (CAP) is composed of 5 phases. See figure 1. The first phase is phase 0 a rapid overshooting depolarization driven by voltage gated sodium channels. The next portion, phase 1, is a short transient inward Chloride current that brings the sharp peak to phase 2 where the potential plateaus as L type calcium channels open their inward current equals the outward current of the many potassium channels. Phase 3 is a slow inactivation of the calcium channels and an opening of the delayed rectifier ( $K_{ir}$ ) potassium channels that hyperpolarize the membrane potential. Finally phase 4 is the resting potential, determined largely by leak type potassium channels, before the next depolarization.

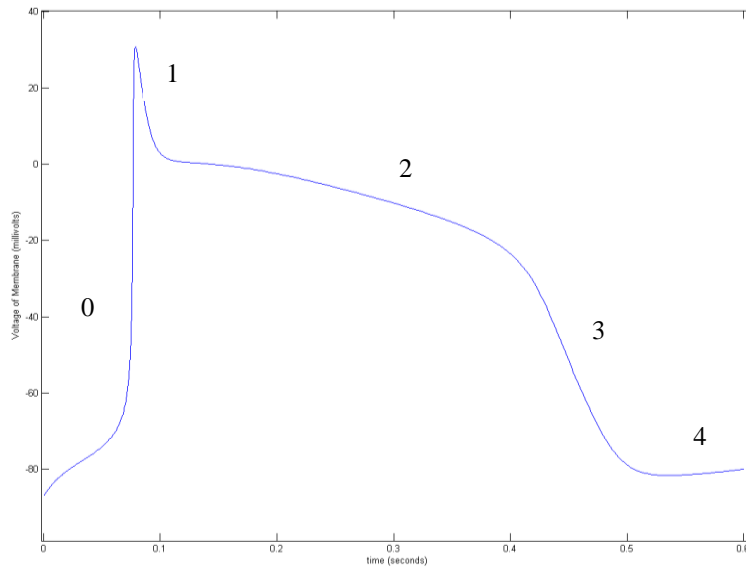


Figure 1: Phases of the cardiac action potential.

## 2.2 Conduction pathways

A specialized subset of cardiac cells makes up the conduction pathway. This pathway propagates a fast signal that coordinates both the atrial and ventricular contractions in order to precisely pump blood through the circulation. The conduction pathway consists of the sinoatrial node (SAN), the atrioventricular node (AVN), the bundle of His, and finally the Purkinje fibers. Of these components this work will focus primarily on the SAN, the pacemaker center of the heart.

## 2.3 Automaticity

Cells of the SAN, AVN, and Purkinje fibers demonstrate remarkable automaticity and periodicity in their firing rates to generate a regular heart rhythm. They are able to complete this timing task because of the different channels they express on their surface. One type channel is the funny channel which generates the funny current ( $I_f$ ). This current results in a steady sodium driven depolarization which gives rise to a phase 4 slope. Eventually as the membrane reaches threshold it fires a cardiac action potential with a phase 0 that is driven by voltage sensitive calcium channels. As these channels inactivate and potassium conductances increase the cell begins to hyperpolarize returning to a resting potential that activates and the funny channels again.

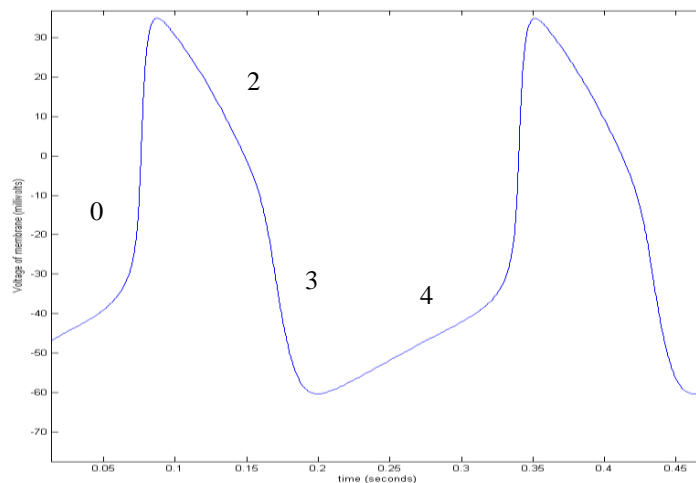


Figure 2: Phases of the SAN action potential showing its characteristic automaticity.

### 3 Models

Over 45 different models of cardiac myocytes have been described from 1962 to present. For this study, only two were used for proof of concept.

#### 3.1 Nobel 1962

This model is by far the simplest consisting of 4 variables. Because it was published shortly after Hodgkin and Huxley's mathematical characterization of the action potential in the squid giant axon, this model predates the discovery of calcium as an ion central to cardiac electrophysiology. This model relies only on sodium and potassium channels to generate a ventricular myocyte CAP.

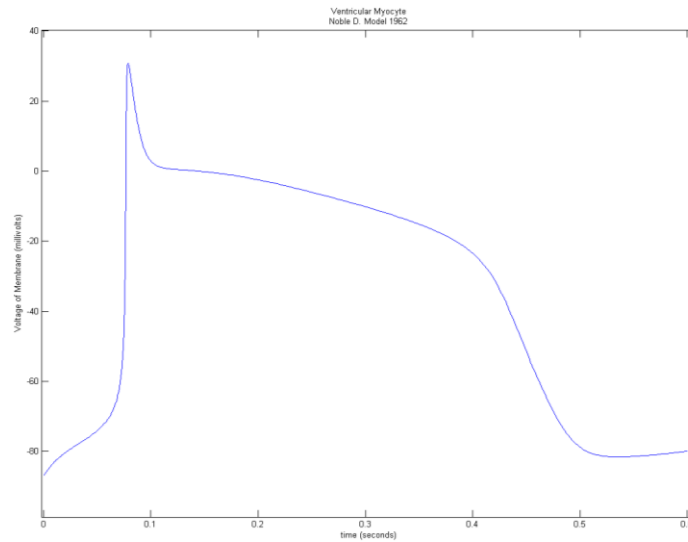


Figure 3: Membrane voltage of a ventricular myocytes cell using the Noble model.

#### 3.3 Sarai et al, 2003

The Sarai et al. (2003) model is also known as the Kyoto Model. It is a model composed of 50 variables that simulates the SAN cells in guinea pigs or rabbits. This model was selected to show the effect of drugs that modulate calcium currents because it accurately represents intracellular calcium handling.

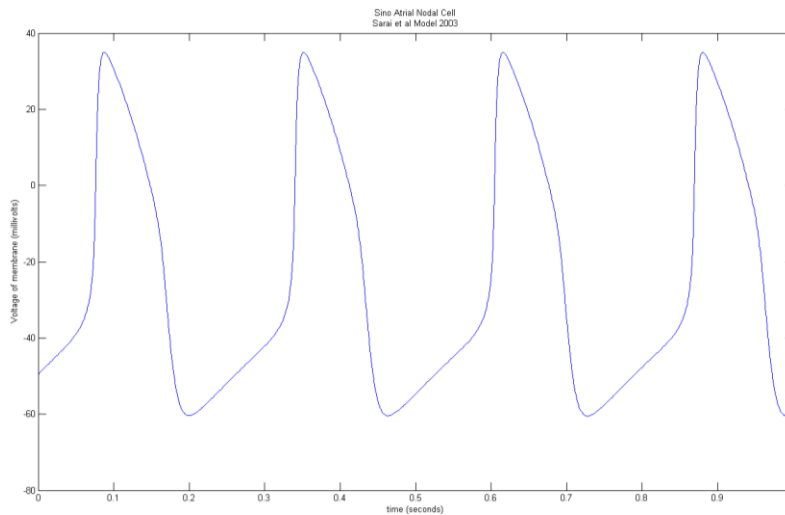


Figure 4: Membrane voltage of a SAN cell myocytes cell using the Sarai et al, 2003 model.

## 4 Results

### 4.1 Verapamil

Verapamil is an L-type calcium channel antagonist that is used as a class three antiarrhythmic medication (Naderamane et al, 1982). It has been determined pharmacologically to prolong the period of automaticity and decrease phase 4 slope. Verapamil was modeled by fractionally reducing the peak L-type calcium conductance. The side effects of verapamil include heart block, bradycardia, congestive heart failure, and edema. Phase 4 slope was decreased with fractional reduction of L-type calcium channels, and the period of automaticity was prolonged. This prolongation could lead to bradycardia, congestive heart failure, and edema because of backing up of pressures in the venous return. The model also showed that 30% and 40% reductions of L-type calcium channels could lead to abolishing the CAP altogether. The Noble model was not used in this analysis because it lacks calcium.

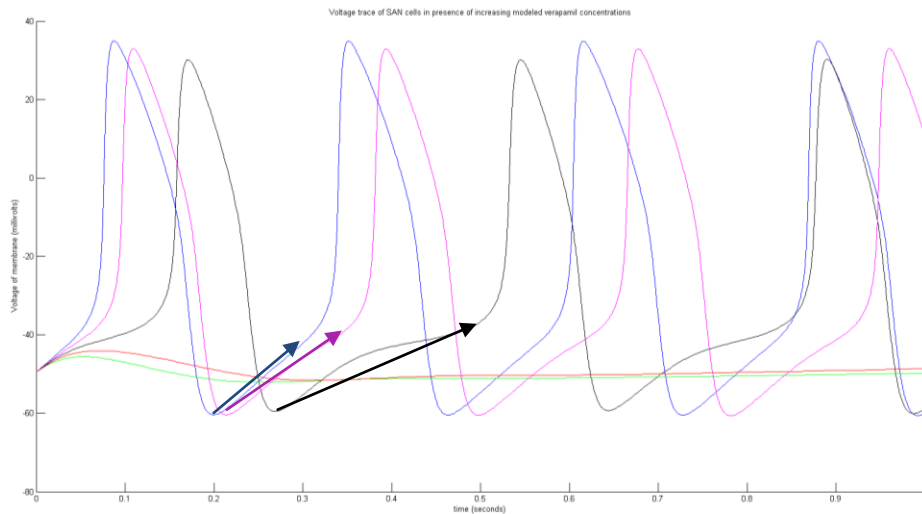


Figure 5: Membrane voltage of SAN cells in presence of increasing modeled Verapamil concentration. Note that the periodicity is changed as well as the phase 4 slope indicated by arrows. The red and green trials, corresponding to a 30% and 40% reduction in peak L-type calcium conductance, showed abolished cardiac action potentials. The blue trace is normal, magenta 10% reduction, black 20% reduction, red 30% reduction, green 40% reduction.

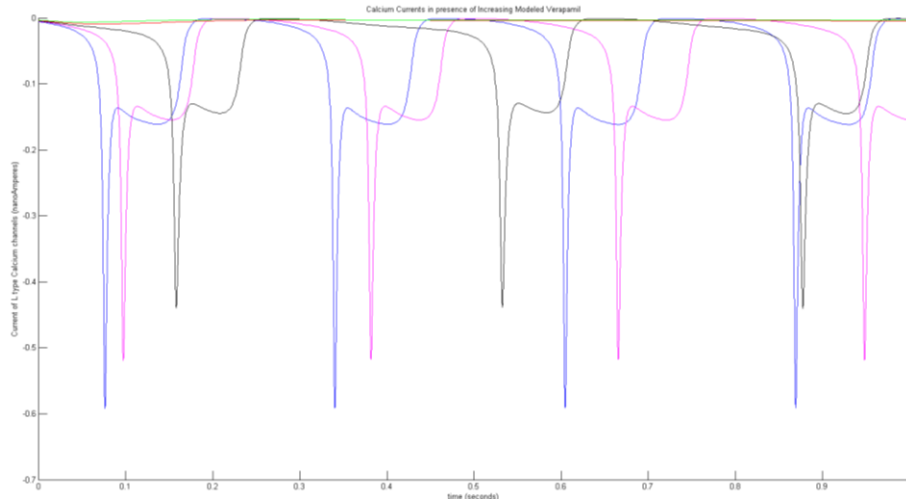


Figure 6: L-type channel calcium currents in presence of increasing modeled Verapamil concentration. Note that the periodicity and magnitude are changed. The blue trace is normal, magenta 10% reduction, black 20% reduction, red 30% reduction, green 40% reduction.

## 4.2 Ibutilide

Ibutilide is a  $K_{ir}$  potassium channel antagonists (Yang et al, 1995). It is commonly used to cardiovert patients with atrial fibrillation or atrial flutter. It is a class four antiarrhythmic whose side effects include arrhythmias and torsades de pointes, a type of ventricular tachycardia. The peak conductance of the  $K_{ir}$  potassium channel was fractionally reduced to model the presence of ibutilide. Modeling ibutilide showed the characteristic prolongation of repolarization which is associated with changes of electrocardiograms in the form of increased PR interval increased QRS complex length and prolonged QT interval. When modeling a system of ventricular myocytes it became clear how ibutilide may induce torsades de pointes. (Figure: 8) Cells that were linked by gap junctions had a smaller latency between their activation in the presence of ibutilide, and these cells were more likely to fire together. Such a phenomenon in vivo could cause the ventricle to contract in sync instead of in sequence causing a ventricular tachycardia.

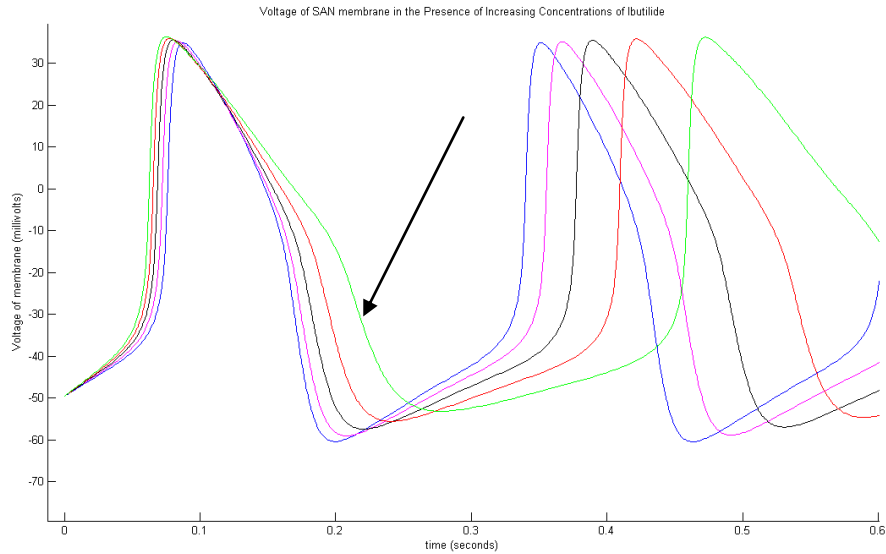


Figure 7: Voltage of SAN modeling Ibutilide administration. Note the prolongation of repolarization. The blue trace is normal, magenta 10% reduction in conductance, black 20% reduction, red 30% reduction, green 40% reduction.

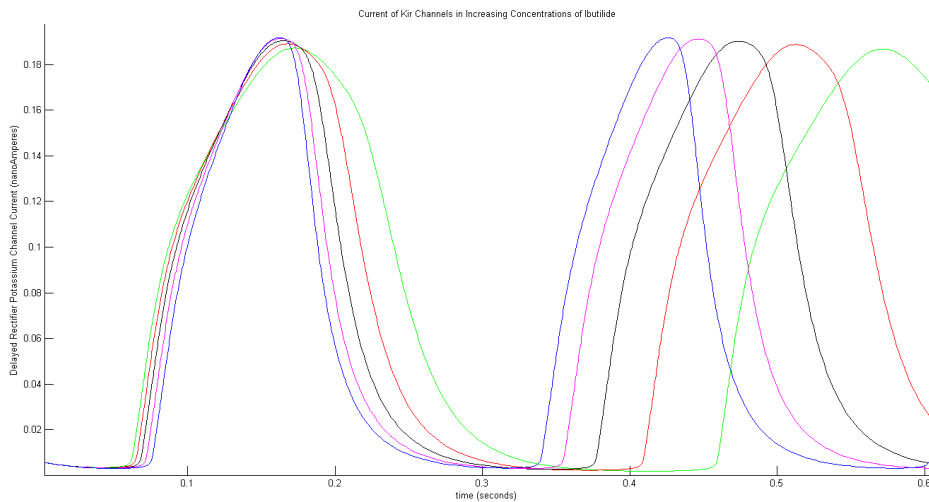


Figure 8: Plot of  $K_{ir}$  channels current. Note that the peak occurs at the beginning of phase 3. The blue trace is normal, magenta 10% reduction, black 20% reduction, red 30% reduction, green 40% reduction.

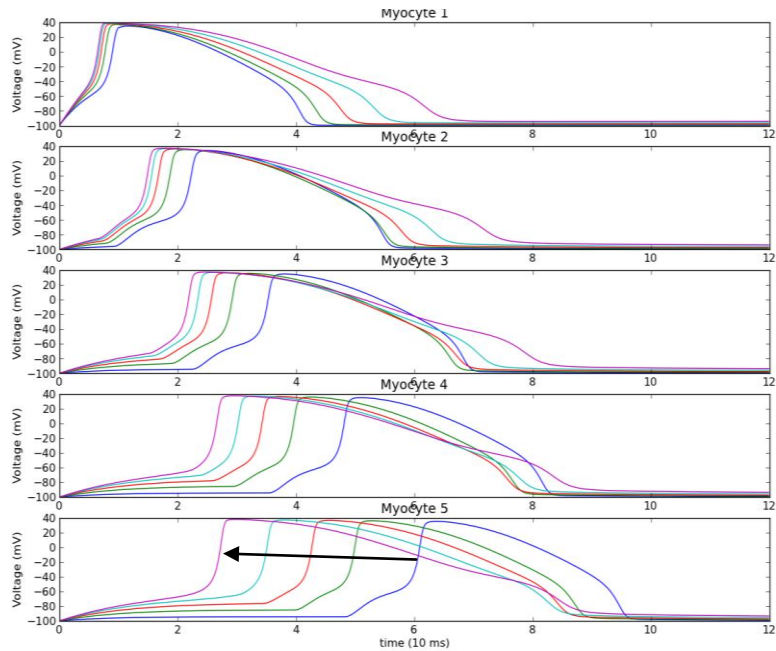


Figure 9: Plot of five Noble model ventricular myocytes sequentially connected by gap junctions. Note the leftward shift of myocytes phase 0 onsets in the presence of modeled ibutilide. The blue trace is normal, green 10% reduction of slow potassium conductance, red 20% reduction, Cyan 30% reduction, and magenta 40% reduction.

### 4.3 Digoxin

Digoxin is a cardiac glycoside that is an antagonist of the sodium potassium pump. It's mechanism of action indirectly causes an increase in the residual calcium therefore increasing cardiac contractility (Miura et al, 1985). It is used to treat patients with congestive heart failure by increasing their ejection fraction. It is known for its narrow therapeutic window, and can cause atrial tachycardia and AVN block. Digoxin was modeled by fractionally reducing the current of the sodium potassium pump.

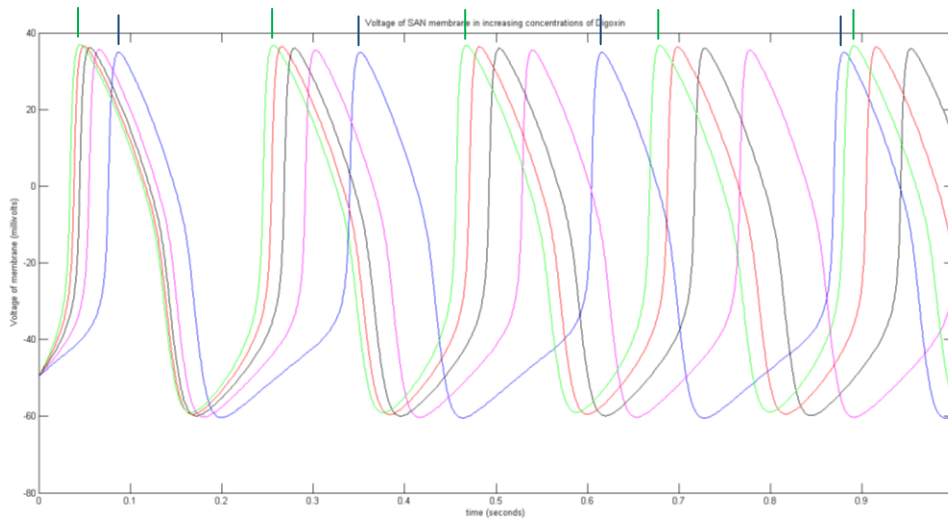


Figure 9: Trace of the SAN cell membrane voltage while modeling digoxin administration. Note that the threshold of firing is reduced and frequency of firing increased in the presence of digoxin. The blue trace is normal, magenta 10% reduction, black 20% reduction, red 30% reduction, green 40% reduction.

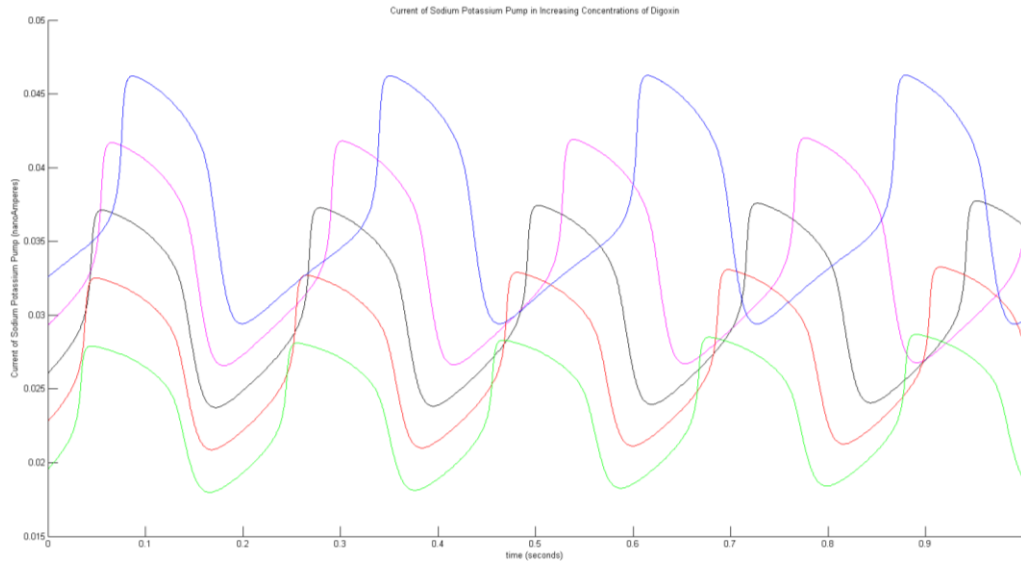


Figure 11: Plot of the sodium potassium pump current. The blue trace is normal, magenta 10% reduction, black 20% reduction, red 30% reduction, green 40% reduction.

Digoxin modeling showed an increase in firing rate which would be expected as a side effect (atrial tachycardia). Cells also had a lower threshold before reaching phase 0 depolarization with digoxin administration. Digoxin administration could not be modeled in the Noble myocytes because they lack sodium potassium pumps.

## 4 Discussion

### 4.1 Implications and Shortcomings

This project has implications for pharmacologic and pathology research and as well as education. Like was mentioned earlier computational models of cardiac myocytes could be used to predict potential drug interactions, side effects, and therapeutic ranges, without need for expensive phase 1 clinical trials. Also, these models could be as easily manipulated to look at the effects of disease mechanisms. They could also be used to help those learning in clinical curriculums the electrophysical and biophysical bases of the drugs prescribed to patients on a routine basis. These results serve as a proof of concept that side effects as well as therapeutic outcomes can be predicted from models of normal cardiac electrophysiology.

Unfortunately as was demonstrated with the Nobel ventricular myocyte, models do not need to be accurate to mimic experimental results. Careful scrutiny and analysis is required to ensure that results are valid.

### 4.2 Future Directions

In order to make this project more relevant to in vivo pharmacology experiments, modeling that is much larger in scale than single cells must be achieved. More work is needed in refining network or whole heart models that take into consideration the biophysical properties of cardiac myocytes including their shape and contractility. Hopefully these new models will help researchers design new therapies and unravel the origins of cardiac disease.

### Acknowledgments

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