A Simple 2-D Model of Cardiac Tissue Conduction

by

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Abstract:
This paper utilizes computational modeling techniques to simulate cardiac tissue conduction. The heart is a complex system designed to convert electric signals into mechanical forces that pump blood throughout the body. The myriad of interactions among the myocytes are difficult to study in vivo and are ideally suited to examination using computational techniques. Cellular automata (CA) is the computational tool utilized by the authors to model cardiac ventricular conduction. The electric activity of the heart is modeled using a set of rules that defines the changes in electric potential of individual myocytes. The myocytes are represented by “cells” that interact with other myocytes in their local neighborhood. The model is implemented using a publicly available software package, NetLogo, produced by Northwestern University. This CA model of electric activity of the heart successfully reproduces the normal spread of electric impulse in the heart as well as tachyarrhythmias generated by a prolonged QTc.

Introduction:
The heart is a finely tuned organ that requires coordinated activity amongst tens of millions of individual myocytes to generate adequate pumping pressure; that this coordination is achieved entirely via local intercellular interactions is phenomenal. The spread of electric activity through cardiac tissue is the main mechanism by which the coordination occurs. The cardiac conduction system is composed of pacemaker cells, specialized conduction cells, and myocytes. Under normal conditions, the signal to contract is generated by the sinus node in the right atrium. This signal is conducted to the cells of both the right and left atrium and enters the atrioventricular (AV) node. The AV node slows conduction to allow the atrium time to finish contraction, thereby maximizing the filling of the ventricles. The AV node then initiates conduction of signals to both ventricles via the right and left “bundle branches”. This signal initiates contraction of both ventricles, starting from the bottom, anatomically maximizing the ejection of blood into the pulmonary and systemic circulation by pushing the blood from the blind end of the ventricles towards the pulmonary arteries and aorta¹.

Figure 1: The 4 phases of a ventricular myocyte action potential

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At the cellular level, voltage gated channels and gap junctions are responsible, respectively, for the generation and propagation of action potentials in cardiac tissue (Figure 1).\(^1\,^2\) In a typical ventricular myocyte, the “phase 0 upstroke” depolarization results from the activation of voltage-gated Na\(^+\) channels at -55 millivolts (mV) and resultant influx of Na\(^+\) ions due to a depolarizing current spread from adjacent cells through gap junctions. Phase 1 results from the opening of voltage gated K channels allowing an efflux of K\(^+\) ion. The action potential plateau (phase 2) is due to the influx of Ca\(^{++}\) ions through a voltage gated Ca\(^{++}\) channel as well as the efflux of K\(^+\) ions through K\(^+\) voltage gated channels. The repolarization of the myocyte (phase 3), is driven by the efflux of K\(^+\) ions through K\(^+\) voltage gated channels once Ca channels become inactivated\(^3\). Phase 4 is the resting stage of the myocyte, which is driven by the K\(^+\) transmembrane gradient generated by the Na\(^+\)-K\(^+\) pump, at negative resting potential (between -80 to -95 mV).

Computational systems biology is an emerging field that provides tools to model and analyze complex dynamic systems such as the heart. The goal of modeling cardiac tissue is to provide a platform to study and understand the features underlying the spread of electric activity through the cardiac tissue\(^4\,^5\). These simulations may offer novel approaches to design and test therapeutic strategies. In addition, these approaches may allow us to predict and prevent adverse events before they happen; for example, pre-release detection of the arrhythmogenic properties of the allergy drug terfenadine when combined with the antibiotic erythromycin during drug development (terfenadine, of course, was infamously pulled from the market after these arrhythmogenic events were noted).

A computational approach germane to the modeling of cardiac tissue is to build a cellular automata (CA) model\(^6\,^7\). CA are dynamic systems that are discretized in time, space, and internal state. CA modeling provides an alternative to analytic differential equation approaches typically used in chemistry. Their behavior is defined by rules that are a function of their local environment and their state. Specifically, CA models are built on a grid of usually square spaces called ‘cells’ that are capable of entering a finite number of states. Each cell is assigned a state with a discrete probability of interacting with cells around it. Every cell has the same set of

![Figure 2: State diagram of the virtual myocytes](image-url)
rules for updating its internal state, based on the values of its neighboring cells as well as its own current state. At each time step, the rules are applied to the whole grid a new generation of cells is created. Repeated iteration of the rules create a time series which can then be analyzed for behavioral characteristics. We approached the modeling of cardiac tissue by developing a 2-D CA model that used, for its ruleset, a simplified state description at several points in the action potential of an individual cell. Our goal was to provide a platform to study and understand the complex dynamics underlying cardiac conduction.

The advantages to using CA include the ease of implementing rule based system, the inherent spatial information encoded in the model, and the lack of biological parameters needed for the system. Furthermore, the model is able to extrapolate the behavior of a system beyond the known behavior of a system. CA models avoid the often intractably large number of differential equations needed to describe the parametric space of a large number of independently behaving agents. In addition, state descriptions allow us to ignore gaps in our knowledge about the underlying physical mechanisms behind the behavior of certain biological systems; such gaps will often make equation writing problematic at best. Differential equations rely on homogenous actors and only with great difficulty capture spatial aspects of complex biologic processes, whereas CA models are naturally suited to modeling such processes. CA models also have some disadvantages. For example, the time it takes to update the individual cells is time consuming and results in lengthy simulations.

CA allow a real time analysis of the conduction system that is impossible to obtain in vivo experiments. Additionally, CA provide an opportunity to understand the mechanism of arrhythmogenesis due to the complex interplay among the various myocytes. Reductionist in vitro experimental techniques have allowed a detailed understanding of the individual changes in electric potential associated with the various types of voltage gated ion channels. The information obtained by studying individual channels and various electrolyte concentrations can utilized to develop the stepwise rules used to the update the CA in such a model.

The successful creation of an accurate model of in vivo cardiac conduction will allow in silico simulations that provide the opportunity to run vast numbers of virtual experiments in order to understand the underlying physiology and diseases related to alterations in cardiac conduction. Ventricular dysrhythmias are a significant source of morbidity and mortality in the United States, accounting for approximately 300,000 deaths annually. Such diseases that are difficult to study in the lab may be extensively studied over thousands of virtual simulations.
Materials and Methods:
The CA model in this paper uses a two dimensional excitable media model. The excitable media model is one in which for each cell there is a unique rest state which may be perturbed into a transient excited state that subsequently relaxes back into the rest state. Furthermore, the cell is unable to be re-excited during a defined refractory period. The state diagram for the individual is myocyte is illustrated in Figure 2. In this case, the grid of cells is in the shape of a torus allowing cells across the opposite face of the grid to interact. As a result, there is no need to create rules to define the boundary conditions. The software platform used to implement the CA model was NetLogo 4.01 Beta 10. NetLogo is a free program originally written by Uri Wilensky, available for download at http://ccl.northwestern.edu/netlogo/, which provides a cross-platform multi-agent programmable modeling environment. The cells of the system (patches) represent ventricular myocytes. The grid is 16 cells by 16 cells. The neighborhood of each cell is a von Neumann neighborhood composed of four directly adjoining cells. The grid is designed to simulate a single ventricle in which, given the lack of boundary conditions, waves of electrical activity are sustainable. The specialized conduction cells are not included as they are not needed for signal propagation given the size of the system we are modeling. The AV nodal pacemaker is simulated by a depolarizing signal sent by a row of cells that occurs at a user defined rate. Each tick of the simulation clock is equivalent to one millisecond (ms).

The ventricular myocytes are capable of intrinsic pacemaker activity at a rate of 40 beats per minute. The Na⁺ channel opening time is a user defined variable in the range of 1 ms to 10 ms. The Ca²⁺ channel opening time is a user defined variable in the range of 200 ms to 400 ms. The QTc is a user defined variable in the range of 300 ms to 1000 ms. This variable therefore controls the K⁺ channel opening time and the repolarization time. The myocyte goes from a state of rest (at an electric potential of -90 mV) to a depolarized state (an electric potential of +30 mV) upon exposure to a depolarizing current of -55 mV. The myocyte enters an absolute refractory period in which the myocyte is not capable of being depolarized. A relative refractory period follows once the electrical potential reaches -65 mV. The cell then enters the rest state at a rate that is determined by the user defined QTc. The user is also able to input the
depolarizing potential and the calcium channel potential. Figure 3 demonstrates the user display.

**Results:**

![Figure 3: Depolarizing potential and calcium channel potential](image)

Given normal physiologic parameters of heart rate, length of Na+/Ca++ channel opening times, and QTc, the CA model simulates the normal conduction of the heart. The waves of depolarization and repolarization spread through the cardiac tissue without formation of pathologic dysrhythmias over hundreds of thousands of heart beats. The virtual rhythm strip created by a virtual electrocardiogram lead shows a narrow complex rhythm at the rate set by the user defined pacemaker parameter (Figure 4). Given the 2-D nature of the model, the T wave is in the opposite direction to the QRS as there is no epicardium or endocardium. The plot of the electric potential at a time t+1 vs. time t shows a stable system that occupies a stable orbit (Figure 5).

![Figure 5: State plot of the electric potential during normal sinus rhythm](image)

Once the system is perturbed by increasing the QTc, the CA model enters into an unstable tachycardia. The rate of ventricle depolarization ranges from 120 beats per minute (bpm) to 180 bpm depending on the exact setting of the QTc. The resultant rhythm strip (Figure 6) shows the tachyarrhythmia with a pacemaker spike occurring at regular intervals that is independent of the ventricular rhythm (i.e. AV dissociation). The tachycardia is narrow complex due to the small number of cells in the virtual cardiac tissue. The state diagram shows the system trapped in a tachyarrhythmia from which it is unable to escape (Figure 7).

![Figure 6: State plot of the electric potential. The arrow demonstrates the creation of a ventricular tachycardia and the inability to escape after its generation](image)

![Figure 7: Abnormal EKG with AV dissociation](image)
Discussion:
Although multiple computational approaches exist, we have employed CA modeling in our current approach due to its ability to analyze the electric activity of the cardiac tissue as a function of time and space. Cellular automata (CA) are dynamic modeling and simulation tools that allow the study of dynamic non-linear network systems. They provide a non-reductionist approach to studying the biologic system as a whole, while retaining the information at an individual level by specifically modeling the behavior of individual agents and their interaction with their local environment.

The initial results of this paper indicate that the cardiac conduction system can be readily simulated using cellular automata. CA simulations offer a major advantage in their ability to monitor the electric potential of each myocyte as depolarization and repolarization proceeds. This implies that the effect of a large number of factors that influence conduction, e.g., electrolyte concentrations, congenital and acquired alterations in voltage gated channels, and ischemia induced changes in conduction, can be readily simulated. These CA simulations are expected to provide information on the overall progress of both normal and abnormal electric activity as well as on individual myocyte function over time. Thus, CA modeling of cardiac tissue affords the novel possibility of creating simulations of the effect of anti-arrhythmic medications and ischemia at the cardiac myocyte and tissue level.

Only by creating models which account for the various electrolyte concentrations and the functioning of electrolyte channels can one hope to improve our overall understanding of cardiac conduction. An accurate model of cardiac conduction will provide a wealth of clinical information and interventions including more powerful diagnostic and therapeutic targets, predictive tools for determination of individual outcomes, and bedside adjustments of patients with simple and complex conduction abnormalities. Furthermore, it will result in the development of new software and algorithms for simulation. We have successfully developed a von Neumann-based modeling approach, using cellular automata to simulate these highly networked conduction systems in a comprehensive manner to understand and predict the pathophysiological responses arising from variations in molecular and cellular components of the cardiac conduction system. In summary, CA modeling of the cardiac conduction system may readily provide for further elucidation of the pathophysiology of diseases related to the formation of dysrhythmias. These include but are not limited to genetic and acquired disorders.

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