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Studies on the dynamics of chaotic multi-wavelet reentrant propagation using a hybrid cellular automaton model of excitable tissue

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Dissertation

STUDIES ON THE DYNAMICS OF CHAOTIC MULTI-WAVELET
REENTRANT PROPAGATION USING A HYBRID CELLULAR
AUTOMATON MODEL OF EXCITABLE TISSUE

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STUDIES ON THE DYNAMICS OF CHAOTIC MULTI-WAVELET REENTRANT PROPAGATION USING A HYBRID CELLULAR AUTOMATON MODEL OF EXCITABLE TISSUE

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ABSTRACT

There is a compelling body of evidence implicating continuous propagation (reentry) sustained by multiple meandering wavelets in the pathology of advanced human atrial fibrillation (AF). This forms the basis for many current therapies such as the Cox MAZE procedure and its derivatives, which aim to create non-conducting lesions in order to “transect” these circuits before they form. Nevertheless, our ability to successfully treat persistent and permanent AF using catheter ablation remains inadequate due to current limitations of clinical mapping technology as well as an incomplete understanding of how to place lesions in order to maximize circuit transection and, more importantly, minimize AF burden. Here, we used a hybrid cellular automaton model to study the dynamics of chaotic, multi-wavelet reentry (MWR) in excitable tissue. First, we used reentry as an exemplar to investigate a hysteretic disease mechanism in a multistable nonlinear system. We found that certain interactions with the environment can cause persistent changes to system behavior without altering its structure or properties, thus leading to a disconnect between clinical symptoms and the underlying state of disease. Second, we developed a novel analytical method to characterize the spatiotemporal dynamics of MWR. We
identified a heterogeneous spatial distribution of reentrant pathways that correlated with the spatial distribution of cell activation frequencies. Third, we investigated the impact of topological and geometrical substrate alterations on the dynamics of MWR. We demonstrated a multi-phasic relationship between obstacle size and the fate of individual episodes. Notably, for a narrow range of sizes, obstacles appeared to play an active role in rapidly converting MWR to stable structural reentry. Our studies indicate that reentrant-pathway distributions are non-uniform in heterogeneous media (such as the atrial myocardium) and suggest a clinically measurable correlate for identifying regions of high circuit density, supporting the feasibility of patient-specific targeted ablation. Moreover, we have elucidated the key mechanisms of interaction between focal obstacles and MWR, which has implications for the use of spot ablation to treat AF as some recent studies have suggested.
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1 INTRODUCTION

1.1 Atrial Fibrillation

Atrial fibrillation (AF) is an abnormal heart rhythm (arrhythmia) in which the atria contract rapidly and irregularly, leading to inadequate pumping of the blood from the atria to the ventricles. It is the most commonly encountered arrhythmia in clinical practice, accounting for approximately one third of hospitalizations related to cardiac rhythm disturbance\(^1\). While it affects predominantly the elderly\(^2,3\), the prevalence is estimated between 0.4% and 1% in the general population, with approximately 6.7 million cases in the United States and Europe (as of 2006)\(^1\). In 2005, the healthcare cost associated with AF was estimated at $6.65 billion per year, including hospital visits, in- and outpatient care, and medication\(^4\).

Multiple factors increase the risk of AF, such as high blood pressure, heart failure, diabetes, advanced age, hyperthyroidism, and heart disease\(^1\). Symptoms can include heart palpitations, chest pain or pressure, lightheadedness and fatigue, often resulting in poor quality of life. The severity of disease is classified based on duration of episodes: paroxysmal AF is defined as episodes that come and go, lasting less than seven days; persistent AF is defined as episodes that come and go, lasting longer than seven days; and permanent AF is defined as an on-going long-term episode\(^1\).

While generally not life-threatening itself, AF increases the risk of stroke, heart failure, and all-cause mortality\(^5-7\). It is also a severe complicating factor in other heart
disease. Several studies have shown the mortality rate of patients in AF, while linked to the severity of the underlying heart disease, to be approximately twice that of patients in sinus rhythm\textsuperscript{8–10}.

1.1.1 Mechanisms of Atrial Fibrillation

AF is distinct from other atrial arrhythmias in that it is irregular, or chaotic, in nature. It results from rapid, disorganized electrical signals spreading through the atria. It is identified on the electrocardiogram (ECG/EKG) by the replacement of consistent P waves with rapid oscillations, or fibrillatory waves\textsuperscript{1}. These oscillations vary in amplitude, shape, and timing and are associated with an irregular and frequently rapid ventricular response.

The mechanisms underlying AF are believed to involve two separate processes. The first is enhanced automaticity, where aberrant foci rapidly depolarize leading to fibrillatory conduction elsewhere in the atria\textsuperscript{11,12}. The second is self-sustaining reentrant propagation (reentry) in which waves of excitation continuously circulate around stationary of spatiotemporally varying circuits\textsuperscript{13,14}. There has long been a debate over which mechanism underlies AF in humans and the leading school of thought has alternated between the two over the past 100 years\textsuperscript{15}.

The role of enhanced automaticity was proven in 1998 when Haissaguerre et al. showed that the pulmonary veins are a common source of ectopic beats capable of initiating paroxysms of AF\textsuperscript{12}. They demonstrated that these cases could be successfully treated by encircling the pulmonary veins using radio-frequency ablation (RFA) and
isolating these focal drivers from the rest of the atrial myocardium\textsuperscript{11}.

The role of reentry in sustaining (advanced) AF is difficult to prove but is supported by a compelling body of evidence\textsuperscript{16–19}. Reentry, however, is not a singular phenomenon. It is a type of behavior which may take one of several forms. The fundamental requirement for reentrant propagation is at least one closed circuit whose path length exceeds the wavelength (WL) of excitation of the tissue\textsuperscript{20}. In the simplest case, this can manifest as a single wavefront of excitation traveling continuously around a fixed circuit defined by anatomical obstacles, similar to a car driving around a race track. This is the form of reentry that underlies most supraventricular tachycardias and is also how Lewis first envisioned AF\textsuperscript{21,22}. (In Lewis’ theory, the WL of excitation during AF was similar to the path length to the circuit, causing the wavefront to advance through irregular channels as they opened up in the wake of the of the wave itself, leading to the irregular activation seen on the EKG.) However, reentrant propagation may also occur in the absence of structurally defined circuits – this type of reentry is often termed \textit{functional reentry}. Self-sustaining rotors, also called spiral waves or vortices, were first demonstrated in a numerical model by Selfridge\textsuperscript{13}. To continue the driving metaphor, one may envision a car doing doughnuts in a parking lot. This phenomenon was studied experimentally in chemical mixtures\textsuperscript{23,24} before being reproduced in isolated animal myocardium\textsuperscript{25,26}. In a parallel vein, Moe demonstrated a disorganized form of functional reentry using a computer model in which multiple wavelets would meander chaotically throughout the myocardium; they would collide, break, and spawn new daughter wavelets\textsuperscript{14,27}. As the metaphor breaks down, one may imagine multiple cars driving
around chaotically in the same parking lot. He advanced the notion of multi-wavelet reentry (MWR) as a potential mechanism for AF, which also gained traction when it was observed experimentally in canine atrial tissue$^{28}$.

In the 1990’s the first in vivo human mapping studies were performed to elucidate the specific dynamics of propagation underlying human AF. The first of these studies was performed in patients undergoing open heart surgery for Wolff-Parkinson-White syndrome$^{17}$. AF was induced by rapid pacing while multi-site electrical recordings were used to reconstruct the flow of electrical activity. The results suggested sustained propagation in the absence of localized sources, such as stable rotors or ectopic foci, offering support to the multiple-wavelet hypothesis. However, recent studies performed on natural human AF revealed conflicting results; some cases offering further evidence of MWR$^{29}$ and others demonstrating stable rotors$^{30,31}$. These studies suggest that AF is likely driven by multiple forms of reentry ranging in complexity from stable rotors to chaotic MWR.

1.1.2 The Cox MAZE Procedure

Mild cases of AF are typically treated with anti-arrhythmic or rate controlling drugs$^{32}$. These can reduce symptoms to improve quality of life as well as slow disease progression$^{33}$. Advanced AF which is ineffectively treated pharmacologically requires interventional therapy. Before the discovery of ectopic foci in and around the pulmonary veins$^{12}$, the gold standard in interventional treatment of AF was the Cox MAZE procedure$^{16}$. The objective is to create non-conducting lines of scar tissue in the
myocardium spaced such that macro-reentrant circuits cannot form between them\textsuperscript{16}. It aims to interrupt circuits by physically obstructing where they \textit{would} be. (Its success, in fact, is arguably the most compelling clinical evidence of MWR underlying human AF.) In its original form, lesions were created by placing incisions in the myocardium during open-heart surgery. This yielded what is still the highest success rate in treating advanced AF, however the procedure suffered from a high complication rate due to its invasive nature\textsuperscript{34}. Today, the lesions are created by RFA delivered via intracardiac catheters\textsuperscript{35}. While the less invasive nature of the procedure reduces the risk of complication, the full MAZE lesion set is seldom performed as it is extensive, therefore still presenting a non-trivial risk to the patient, and unnecessary in many cases\textsuperscript{36–39}.

\textbf{1.1.3 Pulmonary Vein Isolation}

In the past 15 years, catheter ablation has grown into favor as an alternative to pharmacologic therapy. Multiple studies have established that it is safe and more effective than anti-arrhythmic drugs alone\textsuperscript{32,40}. Since the discovery of Haissaguerre et al., the standard for managing AF in clinical labs is to perform pulmonary vein isolation (PVI)\textsuperscript{1}. The long-term success of PVI alone is reported in the 70-80\% range after repeat procedures against paroxysmal AF\textsuperscript{36–39}, but drops significantly to as low as 20-30\% when used to treat persistent or permanent AF\textsuperscript{41–43}. In these latter cases, it is common to create additional linear lesions in the left atrium, inspired by the MAZE procedure. PVI plus left atrial ablation has increased long-term success rates to nearly 70\% against persistent AF (after repeat procedures)\textsuperscript{41,43} and improved outcome for paroxysmal AF to near 90\%\textsuperscript{36–38}.
In patients with paroxysmal AF, limited ablation is often sufficient to achieve acceptable outcomes (typically PVI alone), in contrast to patients with persistent and permanent AF where extensive ablation is required to achieve the same end (PVI plus multiple lines).\textsuperscript{37,39,44} Catheter ablation is a challenging technique and widespread application to a specific heart has several risks, including procedural complications and pro-arrhythmic effects due to incomplete lines.\textsuperscript{45–47} For this reason, optimizing the total lesion load is critical in maximizing likelihood of positive outcome without exposing the patient to unnecessary risk. While there is no clear consensus on how to achieve this, one group in particular has developed and used a biophysical model to investigate the effectiveness of various lesion sets in reducing AF burden without inducing secondary atrial tachycardia.\textsuperscript{48–50} They demonstrated a graded effect on AF burden as a function of the lesion set, starting from right atrial lines alone (least effective), through PVI, and extending to the full MAZE set (most effective).\textsuperscript{49,50} Their results suggest a graded incremental approach to ablation to achieve the optimal benefit/risk ratio in each patient.\textsuperscript{48}

1.1.4 Substrate-Guided Ablation

The current approach to AF ablation is in fact an anatomical one. The objective is to modify the substrate using a one-size-fits-all procedure in order to isolate common trigger sites (i.e. the pulmonary veins) and neutralize pro-fibrillatory regions (e.g. the left atrium). In the last decade, the notion of substrate- or electrogram-guided ablation has emerged as a way to reduce the total ablation burden and increase procedural outcome by targeting patient-specific AF drivers. This was previously thought to be infeasible due to
the random, non-stationary nature of the micro-circuits driving reentry. However, multiple recent studies have suggested that these drivers can in fact be relatively stable spatially\textsuperscript{19,51–53}.

Fractionated or fragmented electrograms have long been recorded during atrial and ventricular arrhythmias in humans\textsuperscript{54–60}. Studies in animal models have investigated the effects of multiple factors such as slowed conduction\textsuperscript{55–57,61–63}, tissue anisotropy\textsuperscript{57,59,64,65}, conduction block\textsuperscript{59,60,62,65,66}, reentry\textsuperscript{57,59,65}, and wavefront collision\textsuperscript{67}. The relationship of the electrode recording resolution to the spatiotemporal variability of tissue excitation induced by these multiple factors also plays a critical role in determining the morphology of unipolar and bipolar electrograms\textsuperscript{68}. Konings et al. attempted to elucidate which of these factors contribute to fractionation during human AF by comparing electrical recordings to atrial activation mapped during pacing-induced AF in a group of patients undergoing surgery for Wolff-Parkinson-White syndrome\textsuperscript{69}. They found that reentry played an important role in the genesis of fractionated potential recordings and demonstrated multiple activation patterns associated with specific characteristics of electrogram morphology. In 2004, Nademanee et al. demonstrated that AF could be terminated by targeting sites of so-called complex fractionated atrial electrograms (CFAE) with focal ablation, based on the premise that these signals correlated with sites of AF drivers\textsuperscript{51}. Despite their success, follow-up studies have yielded mixed results when using CFAE ablation alone\textsuperscript{52,70–72}. One of the difficulties in evaluating the effectiveness of CFAE ablation stems from a lack of concise definition. They are generally defined as low-amplitude, high-frequency signals but the numerical values vary among
Despite this ambiguity, CFAE ablation appears to play an incremental role against PVI-refractory AF, however comparison with additional linear ablation has demonstrated similar success.

1.1.5 Mechanisms of Termination Using Catheter Ablation

Even with our deep understanding of the factors that lead to fractionated electrograms, it remains unclear to which extent each component contributes to electrogram fractionation in the atria during human AF. It is thus difficult to understand the anti-arrhythmic mechanism of lesions delivered to these sites. The primary hypotheses are that CFAEs correlate with focal triggers away from the pulmonary veins, ganglionated plexi, or sites of relatively stable rotor cores. The anti-arrhythmic effect of the former two is well understood. Ablation of ectopic foci neutralizes AF triggers. Ganglionated plexi are input sites from the autonomic nervous system and their ablation has been shown to reduce AF burden by, for example, increasing the WL of excitation in the tissue. On the other hand, the anti-arrhythmic effect of focal lesions delivered to rotors cores remains unclear. It has been well established that anatomical obstacles create a substrate for arrhythmia, and that these can anchor spiral wave tips. Logic would dictate that focal lesions are thus pro-arrhythmic. Yet, computational and clinical studies have demonstrated an anti-arrhythmic effect, the mechanism of which awaits proper elucidation.

In contrast to focal ablation, the anti-arrhythmic mechanism of linear lesions is well established: transecting reentrant circuits. This is a trivial concept in the case of
anatomically defined circuits. For functional reentry sustained by stable rotors or multiple wavelets the notion of a circuit is not spatially well-defined. It has been known for some time that rotors terminate when the spiral wave tip collides with a boundary\textsuperscript{86}. This implies that the circuit for a stable rotor extends from an outer tissue boundary to the very tip of the spiral wave\textsuperscript{87}. In the case of MWR, however, the notion of a circuit is nebulous. Wave tips appear and disappear as wavelets collide and break chaotically throughout the medium. The anti-arrhythmic mechanism of linear ablation is likely still circuit interruption, yet a concise definition is required in order to understand how to optimally place these lesions in order to maximize the probability of circuit annihilation.

Ultimately, improved therapies for treating AF will come in the form of new pharmaceuticals or improved interventional strategies. The pharmaceutical route is generally hampered by development costs and (typically unavoidable) adverse side-effects. Ablation holds the most promise for further improving our ability to treat AF in the clinic. However, a number of questions remain open about the anti-arrhythmic mechanisms of ablation in the context of advanced human AF driven by various manifestations of reentry. Answering these questions is a critical step towards devising patient-specific and optimized lesion sets that maximize likelihood of freedom from AF while minimizing risk to the patient.

1.1.6 Computer Modeling in Cardiac Electrophysiology

Animal models have been extensively used to study AF under a number of different pathologic conditions\textsuperscript{88–91}. In contrast to human studies, they allow for specific control of
multiple variables such as age, underlying pathology, and the use of anti-arrhythmic drugs. They allow invasive measurements to be performed and consequently have lead to most of what we currently understand about the possible mechanisms of AF as well as the structural, electrophysiological, and molecular remolding processes that take place in patients. Such models, however, are expensive and time consuming. As such, recently-developed sophisticated computational models have been used in their stead to study specific questions surrounding arrhythmogenesis\textsuperscript{92}. In fact, much of the insight we have acquired into the mechanisms underlying the onset and maintenance of cardiac fibrillation over the past couple of decades has stemmed from computational modeling of cardiac cells\textsuperscript{93}. The mathematics behind these models originates with the pioneering work of Hodgkin and Huxley who studied the giant squid axon\textsuperscript{94}. They used a set of nonlinear differential equations to explain the ionic mechanisms underlying the propagation of action potentials in excitable cells. The first adaptation to cardiac cells was the Noble model of a generic Purkinje fiber\textsuperscript{95}, which uses four variables to account for membrane potential, sodium current, potassium current, and a third background current. Following the Noble model, numerous updates were published which took into account new currents as they were discovered experimentally\textsuperscript{96-98}. There is currently a plethora of cell-type-specific models fitted to experimental data obtained by voltage clamping ventricular cells\textsuperscript{99,100}, atrial cells\textsuperscript{101-103}, and pacemaker cells\textsuperscript{104,105}. The most sophisticated of these models employ tens of variables to account for detailed gating kinetics and a large number of ion currents.

While the increasing sophistication of these computational models yields great
insight into cellular mechanisms underlying certain function (or dysfunction), this increased complexity comes at the cost of greater computation time. This poses a significant challenge for simulating large numbers of cells (i.e. whole tissues) over clinical timescales (minutes to hours). Several “minimum-variable” models have been described which reproduce complex cellular & tissue-level phenomena\textsuperscript{98,100,106}. Unfortunately, these are still bound by small spatial and temporal discretization in order to converge on a numerical solution. Investigation of large solutions spaces remains impractical. For example, several studies have investigated the impact of various components of the MAZE lesion set using a biophysical model\textsuperscript{48–50}. This type of model is well suited to investigating the detailed effects of a small subset of possible solutions, as they did in these studies, yet are incapable of exploring unknown solutions in a practical timeframe.

Spector proposed a physics-based cellular automaton which exhibits emergent phenomena relevant to studies at the tissue scale\textsuperscript{107}. Unlike previous cellular automata\textsuperscript{14,108,109}, Spector’s model is designed to recapitulate specific phenomena that are fundamental to cardiac excitation and propagation. The model implements action-potentials, rather than the ion channels which give rise to them. In addition, action-potentials are programmed as piece-wise linear functions, which may be evaluated using primarily addition in a numerical context. This greatly reduces the computational complexity of the model and provides for the possibility of exploring a much larger solution space when searching for ablation patterns.

The Spector model falls into a void in the modeling of excitable cardiac cells,
which extends between the toy models of Kaplan\textsuperscript{108} and Wilby\textsuperscript{109} and the minimum-variable differential equations models\textsuperscript{106}. It encapsulates realistic physiology (like the latter), yet remains conceptually and computationally simple (like the former). It is well suited to studying phenomena which emerge from interacting cells, rather than from interacting ion kinetics. In particular, it is the ideal tool to studying the impact of tissue level alterations on the dynamics of stable-rotor and multi-wavelet propagation in a statistical framework. Spector’s model, however, has remained limited to two-dimensional substrata and has yet to be validated on realistic atrial geometries. Extending this model to support three-dimensional structures will provide an invaluable tool in the future study of ablation for advanced human AF.

1.2 Research Aims

1.2.1 Aim 1: Build a computational model capable of exhibiting multi-wavelet reentry at a minimal computational cost

We desire a model capable of simulating a large number of tissues (spanning a large space of structural and electrical properties) over clinically relevant timescales in a reasonable timeframe in order to investigate many potential solutions with statistical confidence. To this end, we devised a hybrid cellular-automaton-diffusion model which encapsulates the specific details of single-cell electrophysiology in order to provide a tremendous benefit in computation time. The model presented herein is an extension of an earlier iteration\textsuperscript{107} and is designed to recapitulate specific propagation phenomena at the tissue level. In chapter 2, we present the mathematical formulation of the model in
terms of physically meaningful parameters as well as computationally optimized parameters.

1.2.2 **Aim 2: Investigate the substrate conditions favorable to the spontaneous initiation of reentrant propagation**

The substrate requirement for reentrant propagation is well known: the presence of at least one circuit whose path length exceeds the WL of the tissue\(^{20}\), be this circuit structurally defined or functionally emergent. However, reentrant propagation also requires a triggering mechanism. This mechanism is unidirectional block in structural circuits\(^{110}\) and wave break in functional ones\(^{111}\). It has remained unclear how substrate properties and structure interact to cause chronic arrhythmia in some patients and not in others. We investigate the susceptibility to reentry of a single structural circuit over a wide range of temporally varying electrical properties. This work leads to a natural understanding of electrical heart disease as a phenomenon we term *dynamic entrapment* in a complex nonlinear system. In chapter 4, we demonstrate this phenomenon in the context of structurally defined reentrant propagation and discuss its impact on diagnosis and treatment strategies as well as its relevance to complex MWR.

1.2.3 **Aim 3: Elucidate the impact of focal lesions or obstacles on the dynamics of multi-wavelet reentry**

There is a clinical relationship between atrial tachycardia (AT), in which the atria contract periodically, and AF, in which they do so aperiodically. However, the mechanistic relationship is unclear. Inter-conversion between the two has been mapped in
dogs\textsuperscript{112} and observed in humans\textsuperscript{113}. Moreover, AF often organizes into AT during RFA\textsuperscript{114}, after which AT is a common recurrence\textsuperscript{115}. In chapter 5, we investigate the relationship between focal obstacles, which create a substrate for AT, and MWR.
2 A DIFFUSION-BASED CELLULAR AUTOMATON MODEL OF CARDIAC PROPAGATION

2.1 Abstract

Objective: We require a model capable of performing a large number of simulations in a reasonable timeframe such that it may be employed to evaluate the efficacy of ablation patterns throughout a vast space of potentials solutions.

Methods: The model elements are electrically excitable “cells” (each representing a large number of myocytes) which exchange charge via ohmic resistors. The electric potential of a model cell is determined by an active internal process and by passive diffusion with elements in its neighborhood. The active component encompasses the total activity of ion channels in the cell membrane. For computational efficiency, it is implemented by a series of rules rather than differential equations. Diffusion is calculated by a simple difference equation.

Results: The model parameters were tuned to produce action potential durations (APD) and conduction velocities in the ranges reported in the literature for both healthy and diseased atrial tissue. The behavior of the model was validated by demonstrating selected emergent phenomena critical to the maintenance of reentrant propagation, namely, curvature-dependent conduction velocity (CV)\textsuperscript{116}, unidirectional block caused by source-sink mismatch \textsuperscript{110}, stable or meandering spiral waves \textsuperscript{117}, and chaotic MWR \textsuperscript{18}. A mesh segmentation method was developed to minimize computational artifacts. Finally, model elements were fit to human X-ray computed tomography data and used to
demonstrate whole heart sinus rhythm simulations on a standard desktop computer in realistic time.

The model is published as the experimental basis in two journal papers\textsuperscript{118,119}.

2.2 Introduction

Theoretical and computational modeling has proven invaluable in the study of electrical excitation in cardiac tissue, from understanding the generation and propagation of action potentials\textsuperscript{94} to elucidating the role of reentrant propagation in cardiac arrhythmia\textsuperscript{13,120}. Numerous models have been developed, posed usually as nonlinear partial differential equations (PDE) or cellular automata. These are validated against experimental data – typically voltage clamping or, more recently, optical mapping studies – and are used to explain experimental observations or probe the space of possible behaviors relevant to cardiac propagation.

The complex mathematical descriptions of these models render analytic studies near impossible and thus numeric simulation is used instead. The convergence and stability of nonlinear PDEs typically requires small integration steps due to the rapid dynamics of cardiac propagation and the steep spatial gradients in membrane potential. The result is a high computation time thus making these models impractical for simulating large tissue structures over clinical timescales. Multiple numerical methods have been employed to improve the computation time of these models, including multi-level finite element modeling\textsuperscript{121}, adaptive integration schemes\textsuperscript{122}, and multi-resolution mesh refinement techniques\textsuperscript{123}. Even the most sophisticated of these methods, however,
still require hours of computation time to simulate only seconds of clinical data\textsuperscript{123}. In contrast, cellular automata sacrifice insight into the detailed physical mechanisms in favor of decreasing computational cost\textsuperscript{27,108,124}.

Recently, the use of catheter ablation in treating cardiac arrhythmia has spawned a new line of questioning in which computational modeling provides a powerful platform of study. In particular, the relative ineffectiveness of current ablation strategies in treating chronic AF has launched an investigation into the anti-arrhythmic mechanisms of ablation\textsuperscript{82,87} and a search for improved lesion patterns\textsuperscript{48–50}. Most studies thus far have employed detailed ionic models of the human atria. While these provide high fidelity to propagation in a real heart, they suffer from a high computational cost. They have been limited to comparing known ablation sets\textsuperscript{48} instead of searching for unknown solutions. Moreover, their results have limited statistical power as each case can only be simulated a small number of times in a practical timeframe.

Here we develop a diffusion-based cellular automaton model of propagation in excitable tissue. Similar to ion-based models, it encapsulates propagation phenomena characteristic of cardiac tissue and is amenable to ablation studies. Yet its computational simplicity, similar to other cellular automata, enables for the exploration of a vast space of potential ablation sets, and in many tissue configurations spanning the spectrum of possible AF substrates. This tool provides a unique capability in simulating cardiac disease, and may therefore play a critical role in improving our understanding of and ability to treat AF and other severe electrical dysfunction.
2.3 Methods

The elements are electrically excitable “cells” which are interconnected to model a tissue. Each model cell represents a large group of myocytes and generates an action potential once it has accumulated sufficient charge from its neighbors. The state of a given cell $i$ at time $t$ is thus specified by a voltage $V_i[t]$ and a phase $P_i[t]$. The evolution of $V_i[t]$ over time is driven by cell $i$’s coupling to its neighbors, and by its active response to potential changes caused by internal machinery, as expressed in equation 2.1

$$V_i[t] = V_i[t - 1] + \Delta V_i^D[t] + \Delta V_i^R[t]$$

(2.1)

where $\Delta V_i^D[t]$ is the change caused by diffusion and $\Delta V_i^R[t]$ is the change caused by internal reactions.

2.3.1 Diffusion

The change in $V_i[t]$ caused by the connection between cell $i$ and its neighbor cell $j$ can be expressed as $(V_j[t] - V_i[t]) \Gamma_{ij}$, where $\Gamma_{ij}$ is the coupling strength between those two cells (figure 2.1(a)). ($\Gamma_{ij}$ may be considered zero for non-connected cell pairs.) $\Delta V_i^D[t]$ is then given by equation 2.2.

$$\Delta V_i^D[t] = \sum_j (V_j[t] - V_i[t]) \Gamma_{ij}$$

(2.2)

While the simplicity of equation 2.2 is attractive, it is limiting because $\Gamma_{ij}$ has no direct physical meaning. We thus consider the model cells to be capacitors, each with a capacitance $C_i$, interconnected by ohmic resistors $R_{ij}$ (figure 2.1(b)). $\Delta V_i^D[t]$ is then
expressed in terms of the charge exchanged between the two capacitors $C_i$ and $C_j$, as in equation 2.3

\[
\Delta V_i^D[t] = \sum_j \frac{\Delta Q_{i\leftarrow j}[t]}{C_i}
\]

\[
= \sum_j \frac{I_{i\leftarrow j}[t] \Delta t}{C_i}
\]

\[
= \sum_j \frac{V_j[t] - V_i[t]}{R_{ij}C_i} \Delta t
\]

where $\Delta Q_{i\leftarrow j}$ is the charge transferred from cell $j$ to cell $i$ through the resistor $R_{ij}$, which is equal to the current $I_{i\leftarrow j}$ times an interval of time $\Delta t$, and where the current equals the voltage drop across the resistor divided by the resistance.

Finally, $R_{ij}$ and $C_i$ can be written in terms of constant material properties. The resistance between two cells scales inversely with the size of the boundary separating them. In two dimensions, for example, the boundary is a line and a longer line is equivalent to more unit resistors in parallel. If we let $\Delta x$ equal the edge length of a square element, such as depicted in figure 2.1, then in two dimensions $R_{ij} = \rho_{ij} / \Delta x$ where $\rho_{ij}$ is the resistivity of the tissue at the interface of elements $i$ and $j$. In three dimensions, the resistance scales inversely with the area of the boundary yielding $R_{ij} = \rho_{ij} / \Delta x^2$ for cubic elements. Thus for square or cubic elements, the resistance between two elements can be expressed as $R_{ij} = \rho_{ij} / \Delta x^{D-1}$ in terms of the dimensionality $D$. In general, the relationship is
\[ R_{ij} = \frac{\rho_{ij}}{B_{ij}} \]  

(2.4)

where \( B_{ij} \) is the size of the boundary between elements \( i \) and \( j \), which is in units of length in two dimensions and area in three dimensions. Equation 2.4 can be applied to arbitrary tissue segmentation geometries including triangles, hexagons, and tetrahedra. Similarly, \( C_i \) is expressed in terms of a position-dependent unit capacitance \( \gamma_i \) and scales with the size of an element – area in two dimensions and volume in three dimensions. Thus,

\[ C_i = \gamma_i \Delta x^D \] for square and cubic elements, or more generally

\[ C_i = \gamma_i S_i \]  

(2.5)

where \( S_i \) is the size of element \( i \), which is in units of area in two dimensions and volume in three dimensions. Combining equations 2.3, 2.4, and 2.5 produces the diffusion equations below written in terms of physically meaningful quantities for (2.6 a) square or cubic elements and (2.6 b) arbitrary element geometries.

\[ \Delta V^D_i[t] = \sum_j \left( V_j[t] - V_i[t] \right) \frac{1}{\rho_{ij} \gamma_i \Delta x^D} \Delta t \]  

(2.6 a)

\[ = \sum_j \left( V_j[t] - V_i[t] \right) \frac{B_{ij}}{\rho_{ij} \gamma_i S_i} \Delta t \]  

(2.6 b)
Figure 2.1 – Schematic representation of the model elements. (a) A simple representation where elements are connected by coupling parameters $\Gamma_{ij}$. (b) A physically meaningful representation where elements are capacitors interconnected by ohmic resistors.

2.3.2 Reaction

The change in $V_i[t]$ caused by the active internal machinery, $\Delta V_i^R[t]$, is best understood by considering how $V_i[t]$ itself should change as a function of cell $i$’s phase $P_i[t]$ (figure 2.2). $P_i[t]$ is a descriptive function which assumes the values Rest, Upstroke, Plateau, Repolarization, and Relative Refractory (table 2.1); and typically begins at Rest.

For the duration of the Rest phase, $V_i[t]$ fluctuations are caused primarily by
diffusion with neighboring elements or by artificial current injections. $\Delta V_i^R[t]$ equals a small leak potential, $\pm V_i^{LEAK}$, which slowly returns $V_i[t]$ towards its resting value $V_i^{REST}$. Therefore the sign of $\Delta V_i^R[t]$ during this phase is $\text{sgn}(V_i^{REST} - V_i[t])$.

If $V_i[t]$ meets or exceeds a threshold value $V_i^{TH}$, then $P_i[t]$ advances to Upstroke during which time $\Delta V_i^R[t]$ is a large positive constant value $\Delta V_i^{UP}$. Upstroke lasts for $N_i^{UP}$ time steps, or $T_i^{UP} = N_i^{UP} \Delta t$ time, and therefore $\Delta V_i^{UP} = (V_i^{PEAK} - V_i^{REST})/N_i^{UP}$, where $V_i^{PEAK}$ is the peak voltage reached by $V_i[t]$ during activation.

Following Upstroke, $P_i[t]$ advances to Plateau during which time $\Delta V_i^R[t] = -\Delta V_i^D[t]$, such that $V_i[t]$ maintains a constant value of $V_i^{PEAK}$. Plateau phase lasts for $N_i^{PLAT}$ time steps, or $T_i^{PLAT} = N_i^{PLAT} \Delta t$ time.

Next, $P_i[t]$ advances to Repolarization during which time $\Delta V_i^R[t]$ assumes a small negative value $\Delta V_i^{REPOL}$. Repolarization lasts until $V_i[t]$ drops below the activation threshold $V_i^{TH}$ and can therefore be shortened or lengthened by diffusion.

Following Repolarization, $P_i[t]$ advances to Relative Refractory and $\Delta V_i^R[t]$ continues to assume the value $\Delta V_i^{REPOL}$. The duration of this phase is determined by one of three events. If $V_i[t]$ reaches the resting voltage $V_i^{REST}$ or if $N_i^{RELREF}$ time steps have elapsed, $P_i[t]$ returns to Rest. If, however, $V_i[t]$ returns above the activation threshold $V_i^{TH}$, for example as a result of strong inward diffusion from neighboring elements, then $P_i[t]$ returns to Upstroke. In other words, a cell becomes excitable again once it enters the Relative Refractory phase.
Figure 2.2 – The phases, $P_i[t]$, of a cell and the evolution of $V_i[t]$ over time in response to an electrical stimulus. The internal reaction function $\Delta V_i^R[t]$ is a piece-wise constant function of $P_i[t]$.

$\Delta V_i^R[t]$ can be expressed as a piece-wise constant function as in equation 2.7. Note that during Rest phase, $\Delta V_i^R[t]$ can be set to $V_i^{REST} - V_i[t]$ when $|V_i^{REST} - V_i[t]| < |V_i^{LEAK}|$ to avoid oscillations around $V_i^{REST}$.

$$\Delta V_i^R[t] = \begin{cases} 
\text{sgn}(V_i^{REST} - V_i[t])V_i^{LEAK}, & \text{if } P_i[t] = \text{Rest} \\
\Delta V_i^{UP}, & \text{if } P_i[t] = \text{Upstroke} \\
-\Delta V_i^{DP}[t], & \text{if } P_i[t] = \text{Plateau} \\
\Delta V_i^{REPOL}, & \text{if } P_i[t] = \text{Repolarization} \\
\Delta V_i^{REPOL}, & \text{if } P_i[t] = \text{Relative Refractory}
\end{cases} \quad (2.7)$$
<table>
<thead>
<tr>
<th>Phase, $P_i[t]$</th>
<th>Duration</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>Persists until a cell’s potential exceeds the threshold for excitation: $V_i[t] \geq V_i^{TH}$</td>
<td>The cell is quiescent. It injects no energy into the system.</td>
</tr>
<tr>
<td>Upstroke</td>
<td>Lasts for $N_{iUP}^{UP}$ time steps</td>
<td>The cell has become excited. It depolarizes, raising its potential to an elevated level.</td>
</tr>
<tr>
<td>Plateau</td>
<td>Lasts for $N_{iPLAT}^{PLAT}$ time steps</td>
<td>The cell has finished depolarizing and maintains a constant level of excitation.</td>
</tr>
<tr>
<td>Repolarization</td>
<td>Lasts until the cell’s potential drops below the threshold for excitation: $V_i[t] &lt; V_i^{TH}$</td>
<td>The cell is repolarizing gradually back towards its resting potential. It cannot be re-excited.</td>
</tr>
<tr>
<td>Relative Refractory</td>
<td>Last until the cell gets re-excited, $V_i[t] \geq V_i^{TH}$ (goes to Upstroke phase), or it returns to resting potential, $V_i[t] \leq V_i^{REST}$ (goes to Rest phase), or until $N_{iRELREF}^{RELREF}$ time steps have passed (goes to Rest phase).</td>
<td>The cell continues to repolarize but is now excitable again. If its potential increases back up past activation threshold, restitution rules are applied (described later) and the cell becomes activated again. Otherwise, it returns to quiescence.</td>
</tr>
</tbody>
</table>

Table 2.1 – The phases of activation of an excitable model cell. These are traversed in order from Rest to Relative Refractory, and then back to either Rest or Upstroke depending on the end condition of the Relative Refractory phase.

Finally, $\Delta V_i^R[t]$ is written in terms of physically meaningful parameters, as was done with $\Delta V_i^D[t]$.

$$\Delta V_i^R[t] = \frac{\Delta Q_i^R[t]}{C_i}$$

$$= \frac{i_i^R[t] \Delta t}{\gamma_i S_i}$$

$$= \frac{i_i^R[t] \Delta t}{\gamma_i}$$  \hspace{1cm} (2.8)
where $\Delta Q_i^R$ is the change in charge in cell $i$ caused by internal reactions, $I_i^R$ is the total reactive current into the cell, and $j_i^R$ is the density of reactive currents. $I_i^R$ scales with the size of a cell (area in 2D and volume in 3D) because it represents the sum of all surface currents of the biological cells within the model cell. $I_i^R$ therefore scales with the number of biological cells represented by a model cell, which scales with mass rather than boundary size.

### 2.3.3 Hybrid Model Equations

Combining equation 2.2 into 2.1 we obtain the final hybrid model equation 2.9, where $\Delta V_i^R[t]$ is a constant value specified by equation 2.7. Combining equations 2.6a and 2.8 into equation 2.1 we obtain the physically meaningful equation 2.10, where $j_i^R[t]$ is now a piece-wise constant function whose value is obtained by scaling equation 2.7 by $\gamma_i/\Delta t$. Note that equation 2.10 is a difference equation resulting from the discretization of a partial differential equation, where the spatial differential is encompassed in the tessellation terms $B_{ij}$ and $S_i$. This reveals the true nature of our hybrid cellular automaton model. It is in fact a discretized partial differential equation (a reaction-diffusion system) where physical constants are grouped into a reduced set of computational constants and where the reaction function is chosen to be piece-wise constant for the computational benefit.

$$V_i[t] = V_i[t-1] + \sum_j (V_j[t] - V_i[t]) \Gamma_{ij} + \Delta V_i^R[t]$$

\[(2.9)\]
\[ V_i[t] = V_i[t-1] + \sum_j (V_j[t] - V_i[t]) \frac{B_{ij}}{\rho_{ij} \gamma_i S_i} \Delta t + \frac{j_i^R [t] \Delta t}{\gamma_i} \]  

(2.10)

2.3.4 Action Potential Restitution

In response to rapid activation, cells exhibit action potential restitution where the CV and APD decrease\textsuperscript{125,126}. Restitution is a critical component in cardiac rhythm maintenance and is an important factor in the genesis of certain abnormal rhythms through, for example, the generation of action potential alternans\textsuperscript{100,127} and wave-break\textsuperscript{98}. CV restitution is determined primarily by the kinetics of the inward sodium current responsible for rapid depolarization at the beginning of an action potential. Premature excitation during the relative refractory phase of the previous action potential results in a number of these sodium channels being inactivated. This lack of available ion channels decreases the magnitude of the depolarizing current and thus slows activation time. This leads to slowed CV as each cell requires additional time to reach peak voltage and thus takes longer to excite neighboring cells. The model parameter responsible for activation time is \( N_{i,UP} \). We implement CV restitution by dynamically varying this value as a function of the potential trough reached by a cell in the prior diastolic interval (DI) - the time from when the cell last became excitable until it was most recently excited (duration of Relative Refractory and Rest phases). We let \( N_{i,UP} \) increase linearly from \( N_{i,min}^{UP} \) to \( N_{i,max}^{UP} \) as the trough potential increases from the resting value to the threshold for excitation:
\[ N_i^{UP}(V_i^{\text{TROUGH}}[t]) = \begin{cases} 
N_{i,\text{min}}^{UP} & \text{if } V_i^{\text{TROUGH}}[t] \leq V_i^{\text{TH}} \\
N_{i,\text{max}}^{UP} - N_{i,\text{min}}^{UP} \left( \frac{V_i^{\text{TH}} - V_i^{\text{REST}}}{V_i^{\text{TROUGH}}[t] - V_i^{\text{REST}}} \right) & \text{otherwise} 
\end{cases} \tag{2.11} \]

APD restitution occurs in response to rapid activation and therefore a short DI. The result is a shorter action potential due to a shortening of the repolarization phase. The relevant model parameter is \( N_i^{\text{REPOL}} \) which we allow to vary dynamically with the value of the preceding DI. We let \( N_i^{\text{REPOL}} \) decrease linearly from \( N_{i,\text{max}}^{\text{REPOL}} \) to \( N_{i,\text{min}}^{\text{REPOL}} \) as DI decreases from \( DI_{\text{max}} \) to 0:

\[ N_i^{\text{REPOL}}(DI) = \begin{cases} 
N_{i,\text{min}}^{\text{REPOL}} + \frac{N_{i,\text{max}}^{\text{REPOL}} - N_{i,\text{min}}^{\text{REPOL}}}{DI_{\text{max}}} \times DI, & \text{if } DI < DI_{\text{max}} \\
N_{i,\text{max}}^{\text{REPOL}}, & \text{otherwise} 
\end{cases} \tag{2.12} \]

The full state of a cell \( i \) is therefore a combination of its potential \( V_i[t] \), phase \( P_i[t] \), and restituted parameters \( N_i^{UP}[k] \) and \( N_i^{\text{REPOL}}[k] \) which change each time cell \( i \) enters Upstroke phase, and thus may be indexed as a function of action potential index \( k \), rather than time step \( t \). The full set of model parameters and variables is listed in table 2.2.

2.3.5 Numerical Stability

Numerical stability while integrating the model over time is primarily limited by the diffusion term and the values of \( \Gamma_{ij} \). The changes in potentials of cells \( i \) and \( j \) at time \( t \) due to diffusion, \( \Delta V_i^D[t-1] \) and \( \Delta V_j^D[t-1] \), will contribute to their potential gradient at time \( t \) and thus contribute to the diffusion terms \( \Delta V_i^D[t] \) and \( \Delta V_j^D[t] \). If the contributions of \( \Delta V_i^D[t-1] \) and \( \Delta V_j^D[t-1] \) to \( \Delta V_i^D[t] \) and \( \Delta V_j^D[t] \) exceed the values of \( \Delta V_i^D[t-1] \)
and $\Delta V^D [t - 1]$ themselves, then the system is unstable and the magnitudes of $V_i[t]$ and $V_j[t]$ will grow to infinity. Consider two coupled cells $i$ and $j$ with no reactive term.

Using $V_i[t] = V_{i,t}$ to simplify notation, their potentials at time $t$ may be written as

$$V_{i,t} = V_{i,t-1} + (V_{j,t-1} - V_{i,t-1}) \Gamma_{ij}$$

$$V_{j,t} = V_{j,t-1} + (V_{i,t-1} - V_{j,t-1}) \Gamma_{ji}$$

The change in potential of cell $i$ due to diffusion at time $t$ can then be written as

$$\Delta V^D_i [t] = (V_{j,t-1} + (V_{i,t-1} - V_{j,t-1}) \Gamma_{ji} - V_{i,t-1} - (V_{j,t-1} - V_{i,t-1}) \Gamma_{ij}) \Gamma_{ij}$$

$$= (V_{j,t-1}(1 - \Gamma_{ij} - \Gamma_{ji}) - V_{i,t-1}(1 - \Gamma_{ij} - \Gamma_{ji})) \Gamma_{ij}$$

$$= (1 - \Gamma_{ij} - \Gamma_{ji})(V_{j,t-1} - V_{i,t-1}) \Gamma_{ij}$$

$$= (1 - \Gamma_{ij} - \Gamma_{ji}) \Delta V^D_{i,t-1}$$

For the purpose of simplification, consider a homogeneous tissue where $\Gamma_{ij} = \Gamma_{ji}$.

We obtain the following condition for convergence:

$$\frac{\Delta V^D_i [t]}{\Delta V^D_i [t - 1]} = 1 - 2\Gamma_{ij} \in (0, 1)$$

The range $(-1, 0]$ is also numerically stable but represents oscillating solutions so we ignore it. The first condition for convergence states that the time step of integration must be less than half the value of the largest charging time-constant:

$$0 < 1 - 2\Gamma_{ij}$$

$$\rightarrow 2 \frac{B_{ij} \Delta t}{\rho_{ij} Y_i S_i} < 1$$
The second condition for convergence states that $\Gamma_{ij}$ must be positive:

$$1 - 2\Gamma_{ij} < 1$$

$$\Rightarrow -2\Gamma_{ij} < 0$$

$$\Rightarrow \Gamma_{ij} > 0$$

Note that this condition is already imposed by the definition of $\Gamma_{ij}$ (equations 2.9 and 2.10). It is the product of physical quantities that have no physical meaning when negative.

The choice of time step $\Delta t$ should also be informed by the kinetics of the reactive term which are determined by $N_{iUP}[k]$ and $N_{iREPOL}[k]$. In physiologic cells, the former is much shorter than the latter and is thus responsible for the steepest gradient in $V_i[t]$. If $N_{iUP}[k] = 1$ (i.e. $\Delta t = T_{iUP}[k]$), then the Upstroke phase will last exactly one time step during which the potential $V_i[t]$ rises from $V_{iTH}$ to $V_{iPEAK}$. Using $\Delta V_{iUP}$ larger than $V_{iPEAK} - V_{iTH}$ will not lead to instability, but it will skew the shape of the action potential by overshoting $V_{iPEAK}$ at the beginning of Plateau phase. This is generally avoided by calculating $\Delta V_{iUP}$ as $(V_{iPEAK} - V_{iTH})/N_{iUP}$, rather than using physical parameters $T_{iUP}$ and $\Delta t$. 

\[
\frac{2\Delta t}{R_{ij}C_i} < 1
\]
2.3.6 Mesh Segmentation

In an appropriate parameter regime, propagation in our model behaves like propagation in a cellular automaton. Consider the case where it takes one time step for a cell to activate \( N_i^{UP} = 1 \) or \( \Delta t = T_i^{UP} \), and one time step for a fully activated cell to supply enough potential to its neighbor so as to bring it above threshold as well

\[
\left( (V_i^{\text{PEAK}} - V_i^{\text{REST}}) \Gamma_{ij} \geq V_i^{TH} - V_i^{\text{REST}} \right).
\]

In this case, propagation follows a simple rule: for each cell, if any neighbor is activated, become activated at the next time step. Like other cellular automata used to study cardiac propagation, this can lead to marked anisotropy, where the structure of the computational elements (more precisely, the connectivity of the network) translates into macroscopic artifacts such as square or hexagonal wavefronts\textsuperscript{108,128}. The problem is most easily understood in the context of taxicab geometry, where the distance between two points is different from the Euclidean distance except for points aligned in one of the cardinal directions. Propagation velocity in cellular automata is directly linked to the connectivity distance (i.e. the Manhattan distance), and therefore is skewed by the network structure. An example of propagation from a point source in a regular square mesh is shown in figure 2.3a.

Markus and Hess offered a clever solution to the problem of anisotropy in cellular automata by randomly displacing the elements of a regular square mesh and using circular neighborhoods of connectivity with radii larger than the spacing in the original mesh\textsuperscript{124}. A similar result can be achieved using Delaunay triangulation and Voronoi neighborhoods\textsuperscript{129}, which offers the advantage of (typically) much smaller neighborhoods,
and therefore fewer computations per element. In addition, it applies naturally to unstructured triangular meshes which are needed to represent curved three-dimensional surfaces. Tissue thickness can also be accounted for using tetrahedral elements obtained by the three-dimensional Delaunay triangulation. The critical point is to ensure a segmentation which is unstructured and yields a narrow distribution of element areas (or volumes). An example of propagation in an unstructured mesh is shown in figure 2.3b. The mesh is generated by starting from a regular square grid of vertices, randomly displacing each vertex by a distance chosen from a uniform distribution over [0, 1) and at an angle chosen from a uniform distribution over [0, 2π), and finally performing a Delaunay triangulation to obtain the elements (cells).

![Figure 2.3](image)

**Figure 2.3** – Cellular automaton-like propagation in (a) a regular square mesh and (b) an unstructured triangular mesh. \[ N_i^{UP} = 1, \Gamma_{ij} = 5, V_i^{TH} = 0.2 \times \frac{V_i^{PEAK}}{V_i^{REST}} \]
From visual inspection it appears that the unstructured mesh in figure 2.3b exhibits less directional bias than the structured square mesh in figure 2.3a. We can better visualize the difference by comparing the average propagation velocity from the point of initiation to each cell as a function of that cell’s angular position relative to the site of initiation; figure 2.4. For the square mesh, we find a periodic curve with peaks in the cardinal directions and troughs at 45 degree angles to these directions. In the unstructured mesh, we find a higher degree of variability for any given direction; however, there is no correlation with the angle. Moreover, we find the outliers occur at very small distances near the point of initiation where the heterogeneous cell sizes cause larger variations. These average out after only a few steps and ultimately lead to smaller variation in velocity as a function of distance relative to the square mesh.

Diffusion-based models typically avoid this problem with sufficiently small integration steps. However, even in these models structured microscopic asymmetry manifests at the macroscopic level. For example, a regular mesh composed of rectangular elements will conduct more rapidly in the long direction, unless anisotropic conduction velocities are programmed to compensate for the segmentation bias. Note that in models such as the one described here, CV is an emergent property determined by element shapes and network connectivity. As it was derived from physical quantities including both spatial and temporal integration step sizes, our choices of computational parameters thus reflect an implicit choice for these step sizes. We can then ask the question: if we are to use a regular square mesh, how should we choose our parameters such that we minimize the directional bias induced by cellular automaton-like propagation? By
comparing equations 2.9 and 2.10, we see that the computational term $\Gamma_{ij}$ scales with $\Delta t / \Delta x$. $\Delta V_i^R[t]$ scales only with $\Delta t$. If we decide to decrease $\Delta t$ without changing the physical quantities that determine $\Delta V_i^R[t]$, then $\Delta V_i^R[t]$ will decrease. If we decide to keep $\Delta x$ fixed, then $\Gamma_{ij}$ will decrease as well. On the other hand, if we decide to decrease $\Delta x$ in proportion to $\Delta t$, then $\Gamma_{ij}$ will remain constant. This is a convenient result: in order to decrease both integration steps, we simply need to scale the reactive potential changes. It is important to remember, however, that decreasing $\Delta x$ implies that each cell now represents a smaller portion of tissue and therefore more elements are required to represent the original size – this will cost computation time! Ultimately, the answer to our question is in fact to achieve a balance between decreasing the integration constants enough that we are not inducing directional propagation bias, such as demonstrated in figure 2.3a, without adding unnecessary computation time.
**Figure 2.4** – Comparison of regular and unstructured mesh segmentations. Top-left: The average propagation velocity from the point of initiation in the center of a tissue to each element exhibits strong directional dependence. Top-right: The average propagation velocity in an unstructured triangular mesh does not exhibit directional dependence; however, it does exhibit slightly more variation for a particular direction of propagation. Bottom-left: The average propagation velocity to each cell is independent of the distance from the point of initiation. Bottom-right: The randomness in the layout of the mesh elements creates a larger fluctuation in average propagation velocities for cells close to the point of initiation; however, these fluctuations cancel out over medium distances. The standard deviation of propagation velocities is ultimately lower in unstructured meshes than regular meshes after a distance of approximately 5 units (cell “lengths”).
### Model Parameters

<table>
<thead>
<tr>
<th>Parameters &amp; Variables</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_i[t] ) ((V))</td>
<td>Potential of cell ( i ) at time ( t ).</td>
</tr>
<tr>
<td>( P_i[t] ) (--)</td>
<td>Phase of cell ( i ) at time ( t ).</td>
</tr>
<tr>
<td>( N_i^{UP}[k], N_i^{PLAT}[k], N_i^{REPOL}[k] ) ((s))</td>
<td>Duration of cell ( i )'s ( k )-th action potential split into upstroke duration, plateau duration, and repolarization duration.</td>
</tr>
<tr>
<td>( V_i^{TROUGH}[k] ) ((V))</td>
<td>Minimum value of ( V_i[t] ) reached in the diastolic interval preceding the ( k )-th action potential of cell ( i ).</td>
</tr>
</tbody>
</table>

### (Physical Parameters)

<table>
<thead>
<tr>
<th>Parameters &amp; Variables</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_i^{REST}, V_i^{TH}, V_i^{PEAK} ) ((V))</td>
<td>Resting cell potential, threshold potential to trigger activation, and peak potential reached during excitation for cell ( i ).</td>
</tr>
<tr>
<td>( I_i^{LEAK} ) ((A))</td>
<td>Leak current of cell ( i ) while in Rest phase. This is a determinant of cell excitability and returns cell potential to ( V_i^{REST} ) following sub-threshold stimulation. Note that if ( I_i^{LEAK} ) is negative, then it acts as a pacemaker current.</td>
</tr>
<tr>
<td>( C_i ) ((F))</td>
<td>Capacitances of each cell ( i ). These values can be obtained by integrating the capacitance density function ( \gamma(x) ) over the area (or volume) of each element.</td>
</tr>
<tr>
<td>( R_{ij} ) ((\Omega))</td>
<td>Resistances between connected element pairs ( i ) and ( j ). These values can be obtained by integrating the resistivity ( \rho(x) ) over the interface between each pair of connected elements. (For disconnected pairs this value is infinite, in which case the diffusion current is always zero.)</td>
</tr>
<tr>
<td>( T_i^{UP}<em>{\min}, T_i^{UP}</em>{\max}, T_i^{REPOL}<em>{\min}, T_i^{REPOL}</em>{\max} ) ((s))</td>
<td>Baseline action potential duration for cell ( i ) split into Upstroke duration, Plateau duration, and Repolarization duration. Notice that the baseline Upstroke duration is shorter than restituted Upstroke durations, while the inverse is true for Plateau and Repolarization durations. See equations 2.10 and 2.11.</td>
</tr>
<tr>
<td>( T_i^{UP}<em>{\min}, T_i^{UP}</em>{\max}, T_i^{PLAT}<em>{\min}, T_i^{PLAT}</em>{\max} ) ((s))</td>
<td>Fully restituted values of Upstroke duration, Plateau duration and Repolarization duration for cell ( i ). See equations 2.10 and 2.11.</td>
</tr>
<tr>
<td>( Dl_{\max} ) ((s))</td>
<td>Maximum length of diastolic interval for which restitution of Plateau and Repolarization phases occur. See equation 2.11.</td>
</tr>
</tbody>
</table>

### (Computational Variables)

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<tr>
<td>( P_i[t] ) (--)</td>
<td>Phase of cell ( i ) at time ( t ).</td>
</tr>
<tr>
<td>( \Delta V_i^{UP}[k] ) ((V))</td>
<td>Change in cell ( i )'s potential during a single time step of computation while in Upstroke, and Repolarization or Relative Refractory phases, respectively, of its ( k )-th action potential.</td>
</tr>
<tr>
<td>( \Delta V_i^{REPOL}[k] ) ((V))</td>
<td>Change in cell ( i )'s potential during a single time step of computation while in Upstroke, and Repolarization or Relative Refractory phases, respectively, of its ( k )-th action potential.</td>
</tr>
<tr>
<td>( V_i^{TROUGH}[k] ) ((V))</td>
<td>Minimum value of ( V_i[t] ) reached in the diastolic interval preceding the ( k )-th action potential of cell ( i ).</td>
</tr>
</tbody>
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</tr>
<tr>
<td>( \Delta V_i^{LEAK} ) ((V))</td>
<td>Change in potential of cell ( i ) during a single time step of computation due to leak currents while in Rest phase.</td>
</tr>
<tr>
<td>( I_{ij} ) (--)</td>
<td>Change in cell ( i )'s potential via diffusion with cell ( j ) relative to the difference in their potentials, ( V_j[t] - V_i[t] ). See equation 2.8.</td>
</tr>
</tbody>
</table>

Table 2.2 – Model parameters and variables.
Table 2.2 cont’d –

*T$_l^{REPOL}$ is the duration of the Repolarization phase for a single, un-coupled cell. Repolarization lasts until a cell repolarizes (i.e. when its potential decreases back to $V_{th}$) which is affected by electrotonic interactions with coupled cells. Thus the durations of this phase and of the actual action potential duration are emergent properties.

**$\Delta V_{l^{UP}}$ and $\Delta V_{l^{REPOL}}$ are in fact variables that change for each cell when the cell in question enters Upstroke phase, but it is easier to consider them as constants which simply need recomputing when the specified condition occurs.

2.4 Results

2.4.1 Action Potentials

Physiologic measurements of cell properties such as APD, CV, and effective refractory period (ERP) have been performed in numerous animal studies$^{33,130–133}$. In contrast, physiologic data from human tissues and cells are relatively scarce due to the invasive nature of the techniques. Nevertheless, APD ranges for human atrial cells have been collected by voltage clamping cells collected from excised human tissue$^{134}$ or using monophasic action potential recordings in vivo$^{135,136}$. The reported values of APDs for healthy human atrial cells range from 150ms to 350ms when activated at increasingly long cycle lengths$^{134,135}$. The same measurements performed in humans with
longstanding AF revealed greatly reduced values in the 100-200ms range\textsuperscript{134,135}, consistent with the electrical remodeling processes observed in animals\textsuperscript{33,130,137}. APD rate adaptation (restitution) curves were also estimated using monophasic action potential recordings for humans with no history of arrhythmia, atrial flutter, and AF\textsuperscript{135}. In the former case, APD increased from 175ms at a cycle length of 250ms to 350ms at a cycle length of 800ms. In the latter two cases, APD started at 150ms at a cycle length of 250ms and increased 200ms at a cycle length of 400ms, after which it remained in the 200-250ms range as cycle length increased to 800ms.

In our model, the specific profile of a given cell’s action potential is determined by baseline parameter values (e.g. upstroke velocity and repolarization slope), as well as by electrotonic currents resulting from non-uniform potential distributions in the tissue. APD is affected by the coupling of a cell with its neighbors in a tissue. The repolarization phase lasts until a cell’s potential has returned to a threshold value. The time it takes to achieve this is determined by the rate at which its potential changes during this phase. This in turn is a function of both its internal repolarization current and the current it receives from or loses to its neighbors. Electrotonic interactions can thus increase or decrease the rate of repolarization by acting as an extra sink or source of current. We measured the emergent APD as a function of various Plateau and Repolarization phase parameters. APDs were measured in the center of 3,000 cell tissues during planar wavefront propagation (figure 2.5). There is a linear relationship between the programmed APD and the emergent APD, where the emergent APD is always less than the theoretical APD. This is the result of the activated wavefront being surrounded by
inactivated tissue which acts as a sink of current and thus increases the rate of repolarization. This effect is lessened in tissues where APDs have longer Plateau phase relative to Repolarization phase, likely as a result of the fact that cells in the Plateau phase act as a source for those in Repolarization and offset the effect of the surrounding inactivated tissue.

**Figure 2.5** – Real (emergent) action potential durations versus programmed theoretical (or single-cell) action potential durations. $T_{i_{\text{UP}}} = 10\, ms$ & $\Gamma_{ij} = 10$ in all cases. $T_{i_{\text{PLAT}}} = 5\, ms$ values are hidden under the $T_{i_{\text{PLAT}}} = 25\, ms$ values.
Action potential morphology also varies across regions of the myocardium. For example, pacemaker cells in the sinoatrial node typically exhibit triangular action potentials, while those of the atrial and ventricular tissue have sharper upstrokes and more pronounced plateaus. In figure 2.6 we plot the activation time course of two cells with different programmed parameters, each in the center of homogeneous tissue with the same properties. On the left, we plot the time course of a cell with a triangular action potential similar to those seen in the sinoatrial node. On the right, we demonstrate a cell with a rapid upstroke, a significant plateau phase, and a prolonged repolarization similar to cells found in the ventricles. Action potential morphology plays an important role in tissue excitability and CV and may therefore impact the dynamics of emergent patterns of propagation.
Figure 2.6 – Different action potential morphologies. Top: Cell potential. Middle: Inter- and intracellular changes in potential. Bottom: Cell phase. (3x1000 tissues initiated at one end using 20 ms pulse.)

2.4.2 Conduction Velocity

Measuring CV is more challenging than APD because it is a property of a tissue and cannot be obtained from single cell experiments. Typically, a large electrode array must be placed in contact with the myocardium in order to record sufficient electrical signals so as to reconstruct the flow of electrical activity. Konings et al. measured conduction velocities in humans with varying degrees of AF while undergoing elective surgery.
They reported conduction velocities of 70-75 cm/s during sinus rhythm regardless of disease. During pacing-induced AF in patients with no history of natural AF, conduction velocities decreased to 60 cm/s, while in patients with a history of long-standing AF, they reported average conduction velocities as low as 38 cm/s. Measurements of CV restitution curves have only recently been obtained for healthy human atrial cells\textsuperscript{138}. This is due to difficulties in obtaining values without whole heart mapping and specific control over activation frequencies. At the time of this writing, no reliable sources of atrial CV restitution could be obtained for patients with chronic AF. However, the importance of restitution in driving wave-break and reentry has been demonstrated\textsuperscript{111}, thus is it possible that restitution curve remodeling is an important part of pathology.

In our model, the CV of a wavefront is a product primarily of tissue activation time (duration of Upstroke phase) as well as the strength of the coupling between cells. Shorter $T_{i}^{UP}$ and lower $R_{ij}$ both contribute to increasing CV. Fitting parameters to physiologic data therefore requires selecting activation times and cell coupling strengths that give rise to appropriate CV values. This can be achieved by calculating the CV of planar wavefronts as a function of both of these parameters to produce calibration curves. Sample curves are shown in figure 2.7.

The dependence of CV on wavefront shape has been well described\textsuperscript{116,139,140}. The curvature of a wavefront alters the ratio of excited cells to unexcited cells and thus affects the source-sink balance. This causes convex wavefronts to conduct more slowly\textsuperscript{116} and in extreme cases can cause conduction block altogether\textsuperscript{140}. Concave wavefronts, on the other hand, will conduct more rapidly as a larger group of cells is providing charge to a
small sink. This has interesting implications for example in accelerating the rate of rotating spiral waves as the collision sites create very concave wavefronts. We measured CV of a circular wavefront initiated from a point site in the center of a square tissue (figure 2.8). The radius of curvature is measured as $1/r$, where $r$ is the distance of the wavefront from the point of initiation (the radius of the circular wavefront). Instantaneous CV increased as the wavefront traveled away from the center point, but reached a plateau after a certain distance when the curvature was too small to affect the source-sink balance in a noticeable way.

**Figure 2.7** – Conduction velocities vary with cell coupling and upstroke time.

$T_{i_{PLAT}}^{PLAT} = 1\text{ms and } T_{i_{REPOL}}^{REPOL} = 200\text{ms}$ in all cases.
2.4.3 Unidirectional Block

Multiple mechanisms of wavefront block exist. Interestingly, these mechanisms may be asymmetric, causing wavefronts propagating in one direction to travel uninhibited while those traveling in the opposite direction are blocked (i.e. unidirectional block\(^\text{110}\)). Generally, this occurs as the result of asymmetric source-sink relationships. These can emerge from propagation patterns such as curved wavefronts, or they result from tissue structure, for example at the interface of heterogeneous regions of tissue or by asymmetric pathways. In fact, this is the mechanism behind concealed accessory pathways seen clinically\(^\text{141}\). Consider the tissue construct in figure 2.9, left. The pathway narrows gradually from right-to-left, then abruptly widens. From left-to-right, on the other hand, the pathway abruptly narrows and then gradually widens. This creates an

Figure 2.8 – Curved wavefronts exhibit decreased conduction velocity. \(T_i^{UP} = 25\, ms, T_i^{PLAT} = 0.25\, ms, T_i^{REPOL} = 250\, ms, \Gamma_{ij} = 10\).
asymmetry in the source-sink relationships of wavefronts traveling in opposite directions. Wavefronts traveling from the left will easily enter the pathway at the abrupt narrowing, and then face only a gradual widening and hence slight decrease in source-sink balance. Wavefronts traveling from the right, however, will also enter with ease through the gradual narrowing but will face a sharp decrease in source-sink balance as they exit through the abrupt widening. We assessed the conductivity of the tissue configuration in figure 2.9 (left) as a function of tissue excitability controlled by R and $\Delta V_{repO}$ (figure 2.9, right). Tissue excitability decreases as R increases and APD decreases. Therefore, the wedge conducts in both directions when the tissue is highly excitable, and blocks in both directions when it is not very excitable. In the transition region, however, conduction from right-to-left fails before (at higher tissue excitability) it does from left-to-right due to the source-sink asymmetry caused by the geometry of the structure.

2.4.4 Whole Heart Propagation

We obtained four sets of point clouds each representing the endocardial surface of one of the four chambers of a human heart imaged by X-ray computed tomography (CT). Model elements were mapped to each chamber individually using a Poisson surface reconstruction method\textsuperscript{142} implemented in the open source MeshLab software package (http://meshlab.sourceforge.net/). The reconstruction parameters were chosen to yield approximately 8,000 faces (cells) per surface; figure 2.10. The resulting meshes (composed of triangular elements) can be refined by decimating vertices or subdividing elements. Vertex displacement can also be used to homogenize element sizes; however, we found this to be generally unnecessary. The importance of element size homogeneity
stems from the size-dependence of each element’s capacitance. This acts to homogenize CV across elements of various sizes; however it also creates asymmetric source-sink relationships and can lead to propagation artifacts. It is therefore important to ensure that the mesh is unstructured and composed of elements which are similar in area (or volume in 3D).

Figure 2.9 - Variable behavior of a wedge-shaped pathway narrowing. Left: Tissue with a wedge-shaped narrowing. The pathway narrows gradually and widens abruptly when traveled from right to left, and vice versa when traveling left to right. Right: Conductivity of the wedge as a function of parameter values. Tissue excitability decreases as R increases and APD decreases. As a result, conduction fails first in the right to left direction since the abrupt widening causes a strong source-sink imbalance.
In the right atrium, holes were manually created for the inferior and superior vena cava as well as the tricuspid valve by effectively removing cell elements. The process was repeated in the left atrium for the four pulmonary vein ostia and the mitral valve, in the right ventricle for the pulmonary valve and the tricuspid valve, and in the left ventricle for the aortic valve and the mitral valve. Purkinje fibers were manually added by duplicating a tree-like pattern of cells and disconnecting them from the rest of the ventricular tissue, except at the terminal branch cells (figure 2.11). The atrial surfaces were connected at three sites corresponding to Bachmann’s bundle, the atrial septum, and the coronary sinus. The ventricular surfaces were connected at the septum. Finally, the Purkinje fibers were electrically connected to the bottom of the right atrium at the exit site of the atroventricular node.

Excitation initiated at the sinoatrial node spreads across the right atrium and to the left atrium. It enters the His-Purkinje system at the atroventricular node, propagates through the Purkinje fibers, and finally excites the bottom of each ventricle at multiple sites. Excitation then spreads through the ventricles and terminates near the valve annuli. A simulation of sinus rhythm is depicted in figure 2.12. Atrial cells were assigned $T_i^{UP} = 0.3ms$, $T_i^{PLAT} = 0.7ms$, and $T_i^{REPOL} = 150ms$ and were coupled by $\Gamma_{ij} = 22$. Ventricular cells were assigned $T_i^{UP} = 0.3ms$, $T_i^{PLAT} = 3.3ms$, and $T_i^{REPOL} = 280ms$ and were coupled by $\Gamma_{ij} = 25$. 
Figure 2.10 – Poisson surface reconstruction (right) from CT point cloud data (left) of the right atrium using MeshLab.
Figure 2.11 – Purkinje fibers are manually added by duplicating a tree-like network of cells in each ventricle. SVC: Superior vena cava; RA/LA: right/left atrium; RV/LV: right/left ventricle.
Figure 2.12 – Sinus rhythm propagation in a whole heart using ~33,000 model cells. This simulation ran for ~5s on an Intel Core i7-2860 CPU (2.5GHz) with 8GB of system RAM.
2.4.5 Reentrant Mechanisms of Atrial Fibrillation

The two mechanisms believed to underlie AF are single rotors with fibrillatory conduction and MWR. The difference between these two cases is that in the former, a single relatively stable spiral core is driving continuous excitation while in the latter there is no apparent driver of reentry. Multiple cores co-exist and meander in the tissue, appearing and disappearing as wavefronts collide and break. We simulate the first case in a square tissue of 100x100 elements (figure 2.13). The tissue properties are homogeneously assigned to $T_{i,UP} = 45 ms$, $T_{i,PLAT} = 1 ms$, $T_{i,REPOL} = 225 ms$. Restitution is a critical component in yielding fibrillatory conduction from a stable rotor. We used $T_{i,UP}^{max} = 65 ms$, $T_{i,REPOL}^{max} = 175 ms$, $DI_{max} = 32 ms$. To obtain sustained MWR, we required faster conduction velocities and longer WLs of activation (figure 2.14). Here, we used $T_{i,UP} = 35 ms$, $T_{i,PLAT} = 1 ms$, $T_{i,REPOL} = 205 ms$ with no restitution. While restitution plays an important role in wave-break, it is not critical in yielding MWR as demonstrated here.
Figure 2.13 – Mother rotor with fibrillatory conduction. Time advances from left to right, then top to bottom. Fibrillatory conduction is most apparent in the first two and last two panels.

Figure 2.14 – Multi-wavelet reentrant propagation in homogeneous tissue. Time advances from left to right, top to bottom.
2.5 Discussion

2.5.1 Summary

We demonstrated the implementation of a hybrid diffusion-based cellular automaton model which exhibits physiologic propagation phenomena at the tissue scale by implementing coarse action-potential like behavior at the cell-group level. It can be programmed to produce arbitrary APDs, conduction velocities, and WLs and thus can be fit to all cell types. It exhibits curvature-dependent CV and geometry-dependent source-sink relationships thus permitting unidirectional block. Finally, it manifests stable rotation as well as complex MWR – the two reentrant propagation phenomena thought to underlie advanced human AF. Unlike conventional differential equations models currently used to investigate the impact of ablation lesions, our model implements action potentials rather than the ion channels that give rise to them. This confers a tremendous benefit in computation time and therefore enables simulations over much larger solution spaces and with larger statistical confidence.

2.5.2 Physiologic Validation

Validation of our model with respect to physiologic data is achieved by observing the emergence of the same behavior which is critical to real cardiac propagation, such as variable source-sink relationships, as well as the occurrence of stable rotors, fibrillatory conduction, and multi-wavelet reentrant propagation. Reported values of APD, ERP, and CV vary substantially among studies\textsuperscript{134,135,138}. The choice of values becomes somewhat arbitrary once within the physiologic range. Importantly, the possible behaviors
supported by a tissue are determined by the choice of parameters. For example, a stable rotor requires a shorter WL of excitation than a meandering rotor with fibrillatory conduction. In yet another regime, such rotors are unstable and will degenerate into MWR. Part of the fitting process is therefore to select values which yield the desired behavior of study.

While the role of reentry in driving AF is supported by a compelling body of evidence, the nature of this reentry remains unclear. There is still a debate over the role of stable rotation with fibrillatory conduction versus MWR. These in fact are simply two manifestations at different ends of a spectrum. They are both forms of functional reentrant propagation, but with different levels of complexity. It is important that we be able to model the full spectrum of reentry in order to test hypotheses on a variety of possible underlying mechanisms. The model presented here provides a unique capability in spanning a large parameter (or behavior) space in a reasonable computational timeframe.

2.5.3 Multi-Scale Modeling

Cellular automata sacrifice insight into the details of cellular and subcellular mechanisms in exchange for computational performance. As a result they are often labeled as “simplistic”, with the implication that their results do not necessarily translate to the clinical world. This is in fact true of every model. The cellular automaton described here is designed with rules that emulate the summed effects of known cellular and subcellular physiology. For example, action potential restitution results from nonlinear
ion channel kinetics. The overall effect, however, is that action potentials shorten and conduction velocities decrease in response to rapid activation according to some nonlinear curves. When represented in terms of simple rules, the result is the same: nonlinear restitution can cause the development of action potential alternans and contribute to wave-break, effects which are seen in both detailed ionic models as well as our cellular automaton.

The intended use of this model is to study the impact of various ablation patterns on the dynamics of MWR. Performing such studies using detailed ionic models, or even minimalistic differential equations models, is overkill for the task. They can obscure the important details which are critical to understanding the question at hand. Certainly there is value to validating the results produced by a simpler model on a more detailed model, but the first course of action should be using a model which abstracts the details in order to gain a general understanding of the important factors.

The model described here is capable of reproducing realistic whole-heart propagation, including sinus rhythm and most, if not all, known arrhythmias. The low computational burden enables for near real-time simulation of these rhythms, opening the door for user-interaction. This may enable, for example, virtual training of clinical staff by not only providing a visual understanding of cardiac propagation, but by enabling simulation of clinical procedures, such as entrainment mapping and ablation.
2.5.4 Limitations

The model accounts for many nonlinear phenomena that result from cellular physiology, such as APD and CV restitution. In its current formulation, however, the model is effectively a mono-domain model and therefore does not account for effects such as local extracellular calcium depletion in response to persistent rapid firing. Nevertheless, these effects could be accounted for by appropriate modifications to the cellular update rules in a later iteration. In the context for which the model was developed – studying MWR – ignoring these effects is an acceptable first approximation.

In general, two-dimensional substrata are sufficient for studying the impact of geometry on the dynamics of MWR. While real tissue is indeed three-dimensional with some thickness, the manifestation of functional reentrant propagation has been shown to occur in the form of scroll waves, rather than complex surfaces. One of the reasons for this is that the thickness of the tissue in fact too thin to support rotation in the plane of the tissue. Therefore, results derived from two dimensional studies – in particular those on the impact of ablation lesions – imply that in three dimensional tissues, lesions penetrate through the full thickness.

2.5.5 Conclusions

A hybrid cellular-automaton model of propagation in cardiac tissue is capable of replicating emergent phenomena such as stable rotors and MWR by aggregating and representing the summed effects of cellular physiology into simple rules. Such a model is an ideal tool for studying the effects of macroscopic changes such as geometric and/or
topologic alterations caused by ablation lesions. In contrast to differential equations based models which are currently employed to address these questions, the model presented here permits exploration of a vast solution space in a reasonable timeframe.
3 MULTISTABILITY AND HYSTERESIS IN THE ONSET OF REENTRANT PROPAGATION

3.1 Abstract

Objective: We seek to demonstrate how multistability arises in cardiac tissue as a function of structural and electrophysiologically properties, and therefore allows for the possibility of dynamic entrapment in the clutches of a pathological attractor.

Methods and Results: We simulated a cylindrical tissue containing an asymmetric narrowing at one location over a wide range of electrical parameter values and initial conditions. We found four regions of parameter space, each supporting a different combination of stable behaviors. A single multistable region existed that supported both “healthy” and “pathologic” behavior. We demonstrated that transient incursions into neighboring regions of parameter space (caused by oscillating physiologic parameters) were capable of driving the system between these attractors and thus is a hysteretic mechanism of disease onset (and termination). Finally, we found that the system’s predisposition to switching between attractors, in the face of oscillating parameters or ectopic depolarizations, depended on its location within the multistable region suggesting a mechanism of disease progression.

This work was presented in a talk at the annual Biomedical Engineering Society conference in fall 2013. It has been prepared into a manuscript and was accepted by Plos One in January 2015.
3.2 Introduction

Nonlinear dynamic systems have the property of potentially supporting multiple attractors, each with some basin of attraction in which every state ultimately leads back to the attractor itself $^{144}$. Many systems in biology are well characterized by nonlinear dynamic models and thus are believed to share this property. In certain instances, the ability to support multiple stable attractors is in fact crucial to the proper functioning of the system. The well-known Hopfield network for instance, a model for human memory, relies on multiple stable attractor states to store different patterns or “memories” $^{145}$. Another example lies at the heart of cell biology; Kauffman postulated that gene regulatory networks must also possess multiple basins of attraction and that these could correspond to the various cell phenotypes $^{146}$.

From another perspective, however, the ability to support multiple attractors may be a liability. If one or more of the attractors of a biological system represents a state of dysfunction, then the system may potentially be driven there by some external perturbation, and subsequently remain stuck. Kauffman, in fact, proposed that this may be true of gene regulatory networks by advancing the notion of cancer attractors, which posits that certain gene network attractors correspond to cancerous cell phenotypes $^{147}$. Bates recently coined the term dynamic entrapment in reference to a general mechanism in which disease corresponds to an undesired behavior of a system $^{148}$, one that can be entered into in response to factors which when removed do not result in return of the system to its initial status. An entrapped system could appear structurally normal, yet behave pathologically. The instigating agent responsible for pushing the system into its
abnormal attractor could be absent at the time of diagnostic evaluation.

Several characteristics of electrical heart disease strongly suggest that they are instances of dynamic entrapment. Kaplan, for example, described various forms of arrhythmia as corresponding to multiple attractors in the vast state space of excitable cardiac tissue. He described AF as being a chaotic attractor in the phase space of the healthy heart. He further suggested that appropriate electrical stimulation could push the heart between this attractor and the attractor corresponding to normal conduction.

Nevertheless, exactly how dynamic entrapment arises as the result of the details of cardiac anatomy and physiology has remained unclear. Kaplan even acknowledged that his description is purely heuristic due to the intractably large size of the heart’s state space. In the present study, we show a plausible example of dynamic entrapment in cardiac electrophysiology using a computational model of electrical wave propagation in the heart. We show how manipulations of system parameters or external perturbations can lead to reentrant arrhythmia in a system capable of normal rhythm.

3.3 Methods

3.3.1 Computational Model

In order to study the interplay between model parameters and system behavior we required a model detailed enough to exhibit the multiple phenomena relevant to cardiac propagation while being computationally inexpensive enough to enable us to investigate behavior throughout a large parameter space in a reasonable timeframe. To this end, we
used the hybrid diffusion-based cellular automaton model described herein. The model elements are electrically excitable cells which are interconnected by ohmic resistors, through which they can exchange charge. Each model cell (representing a large group of myocytes) generates an action potential once it has accumulated sufficient charge from its neighbors. The specific profile of a given cell’s AP is determined by baseline upstroke velocity and repolarization slope, as well as by electrotonic currents resulting from non-uniform potential distributions in the tissue.

In the present study, all parameters were spatially homogeneous; over time we varied the intercellular resistance, \( R \), and the baseline repolarization slope, \( \Delta V_{\text{repol}} \). The value of \( R \) affects primarily the CV of waves of excitation in the model. The value of \( \Delta V_{\text{repol}} \) affects primarily the APD. The resistance between two cells determines how rapidly an excitable cell can deliver charge to an unexcited neighbor. Increasing \( R \) makes it more difficult for a given cell to excite his neighbors, until at a critical threshold conduction fails altogether. A similar effect is seen when altering \( \Delta V_{\text{repol}} \), although in this case, an increase in \( \Delta V_{\text{repol}} \) (shorter APD) causes a given cell to spend less time with an elevated potential relative to its unexcited neighbors, which decreases its capacity to bring these neighbors up to threshold, and vice-versa. Together, \( R \) and \( \Delta V_{\text{repol}} \) influence the WL (the product of CV and APD) and the ability of the tissue to support continuous propagation (“reentry”). Reentry is a form of propagation in which a wave of excitation continuously travels around a circuit. In the simplest case, the circuit is determined by fixed anatomic structures and is host to a single wave. This form of propagation underlies most known arrhythmias.
3.3.2 **Tissue Structure**

It is well known that reentrant propagation involves a circuit with a path length that exceeds $WL^{20}$. We achieve this in the present study with a two-dimensional disc having a circumference of 50mm and a width of 9mm (figure 3.1). Spontaneously depolarizing pacemaker cells are located at $-30$ degrees (colored in dark grey in figure 3.1). An asymmetric narrowing of the tissue is located at $-90$ degrees. Propagation of a wave of excitation is governed by the relationship between the excited cells at the head of the wave and the unexcitable cells immediately in front of it. The cells in the wavefront comprise a source of excitability (charge) which can fill the sink of unexcited cells, until these in turn reach their threshold and become part of the source. The relationship between source and sink thus determines how a wavefront will propagate or, in the case of source-sink mismatch, fail to do so. Many tissue properties affect this relationship. APD, for example, determines how long cells in the source maintain an elevated potential, and thus how much charge they can transfer to the sink. Tissue geometry also plays a crucial role in source sink balance. At the site of the tissue narrowing, a wavefront traveling from the wide end becomes a small source at the narrow end where it encounters a large sink (as the tissue abruptly widens). A wave front traveling in the opposite direction encounters a much more gradual transition in source sink balance. Thus, a “wedge”-shaped narrowing alters local conduction properties asymmetrically.
Figure 3.1 – Model setup for simulating anatomically defined reentry. The tissue contains a pacemaker site (dark grey cells) and a narrowing “wedge” which allows for the possibility of unidirectional block due to asymmetric source-sink relationships.

3.3.3 Estimating Phase Diagrams

We represent system states in terms of wavefront locations and directions, using arrows overlaid on the tissue. Similar states are grouped together into macro-states (e.g. all states in which a single counter-clockwise propagating wave front is located between 0 and 90 degrees on the tissue (figure 3.2). We construct a coarse-grain representation of the phase diagram by running the model (with a fixed parameter set) from various initial states, binning the explored states into macro-states, and drawing the paths between these macro-states (e.g. figure 3.5).
Figure 3.2 – Sample grouping criterion of specific system states into macro-states. The two states depicted on the top-left are considered similar since they both correspond to a single wavefront (albeit with variable wavelength) traveling counter-clockwise and located in the upper-right quadrant of the circuit (i.e. 0 to 90 degrees). The states depicted on the bottom-left are considered similar since they both correspond to wavefronts traveling counter-clockwise and located in the 90-180 degrees quadrant.

3.3.4 Computational Simulations

First, to investigate the role of parameter oscillations in causing stable shifts in system behavior, we set $\Delta V_{repol} = 1.5 \text{ mV/ms}$ and $R = 38 \Omega$, initialized the system to rest, and then varied $\Delta V_{repol}$ sinusoidally with an amplitude of 0.7 mV/ms as the simulation evolved.

Second, to investigate the role of external stimuli, we again set $\Delta V_{repol} = 1.5 \text{ mV/ms}$
and \( R = 38 \, \Omega \), initialized the system to rest, and then applied ectopic activation at various locations and timings relative to pacemaker activation. We repeated this procedure with multiple pairs of \( \{ \Delta V_{\text{repol}}, R \} \) values (see results table 3.1) and quantified the susceptibility of the tissue to ectopic activation as the percent of activations which resulted in reentry.

3.4 Results

3.4.1 Multiple Stable Behaviors

We identified four stable behaviors in the system while varying \( R \) and \( \Delta V_{\text{repol}} \) (figure 3.3). The first behavior, which we label *Sinus Rhythm with Clockwise Conduction* (SR\text{cond}), corresponds to the system being driven by the spontaneous depolarization of the pacemaker cells (figure 3.3a). Each depolarization gives rise to two wavefronts originating in the pacemaker cells and traveling in opposite directions around the circuit – one in the counter-clockwise direction (over the top of the circuit) and the other in the clockwise direction (through the wedge located on the bottom). These waves collide opposite the pacemaker site and annihilate, after which the system returns to rest and waits to be re-excited by the pacemaker cells. In analogy to a real heart, this sequence of electrical activity corresponds to one normal beat. The second behavior, which we label *Sinus Rhythm with Bi-directional Block* (SR\text{block}), is similar to SR\text{cond} in that ongoing activity is still driven by the pacemaker cells (figure 3.3b). However, in this rhythm, the wedge is non-conducting in both directions. Each depolarization gives rise to two oppositely directed wavefronts as in SR\text{cond}. The clockwise wave blocks at the exit of the
narrow segment of tissue (-90 degrees) and the counter-clockwise wave propagates around the circuit (past the point where collision occurred in SR\textsubscript{cond}) and terminates at the tissue narrowing. Once again, the system returns to rest and waits to be re-excited by the pacemaker cells. The third and fourth behaviors correspond to counter-clockwise reentry (CCWR) (figure 3.3c) and clockwise reentry (CWR) (figure 3.3d), in which a single wavefront continuously propagates in the counter-clockwise or clockwise direction, respectively. In these behaviors, tissue excitation is no longer driven by the spontaneous activity of the pacemaker cells, but rather is driven continuously by a circularly propagating wavefront, provided that the time required to perform a full rotation around the circuit is less than the cycle length of the pacemaker cells.

Each of these stable behaviors is the manifestation of the system operating within the domain of a particular stable attractor. These attractors, however, do not coexist because not all behaviors are possible with a given set of parameters. For example, SR\textsubscript{cond} requires a wavefront to propagate clockwise through the wedge while SR\textsubscript{block} requires the wedge to block wavefronts traveling in both directions. The existence of these basins of attraction is determined by the system parameters. Here, we are specifically interested in how $\Delta V_{\text{repol}}$ and $R$ affect the stability of each behavior. Thus, we explored the regions of $R$-$\Delta V_{\text{repol}}$ space in which each of the attractors exist.
Figure 3.3 – Stable system behaviors: (a) Sinus Rhythm with Clockwise Conduction, SR_{cond}, requires that the wedge conducts in the clockwise direction; (b) Sinus Rhythm with Clockwise Block, SR_{block}, requires that the wedge be non-conducting; (c) Counter-Clockwise Reentry, CCWR, requires that the wedge conducts in the counter-clockwise direction; (d) Clockwise Reentry, CWR, requires that the wedge conducts in the clockwise direction.

By running the model repeatedly from different initial states and with a range of values of $R$ (30-50 $\Omega$) and $\Delta V_{repol}$ (0.9-2.5 mV/ms), we identified four distinct regions of $R-\Delta V_{repol}$ space (figure 3.4). For each region, we constructed a coarse-grained representation of the phase diagram (representing system states in terms of wavefront locations and directions using arrows (figure 3.5)). Potential behaviors correspond to specific paths through states (dotted arrows in figure 3.5) and stable behaviors correspond to those paths which form a closed loop (black dotted arrows in figure 3.5). In region 1, WL exceeds the path length of the circuit and the wedge supports propagation in both directions. The first condition ensures that no reentry is supported, and the second condition supports SR_{cond} as opposed to SR_{block}. In region 2, WL is less than the path length of the circuit, while the wedge still supports bi-directional propagation. Therefore,
CWR and CCWR are possible here in addition to $SR_{\text{cond}}$. In region 3, WL is less than the path length and the wedge exhibits unidirectional block – it supports propagation of counter-clockwise traveling waves, but blocks those traveling in the clockwise direction (due to source sink mismatch). The latter condition prevents CWR, and unidirectional block implies that $SR_{\text{cond}}$ is not supported because the clockwise traveling wave generated by the pacemaker cells will always terminate at the wedge, leaving the system in CCWR. In region 4, WL is less than path length but the wedge does not support propagation in either direction. Reentry is impossible, only $SR_{\text{block}}$ is supported.

**Figure 3.4** – Regions of parameter space and their supported stable behaviors
Figure 3.5 – Coarse-grain representation of system phase diagrams in four parameter regimes identified: Black dotted arrows represent paths which are part of a stable (repetitive) behavior, while grey dotted arrows represent transitional pathways that lead into stable behaviors; (a) Region 1 contains only the $\text{SR}_{\text{cond}}$ attractor since $WL \geq CL$ in this region;
Figure 3.5 cont’d – (b) Region 2 contains the SR\text{cond} attractor and both clockwise and counter-clockwise reentry attractors since WL < CL and the wedge conducts in both directions; (c) region 3 contains only the counter-clockwise reentry attractor (regardless of where the system starts it ends in CCWR) since the wedge now only allows propagation in one direction (left-to-right); (d) region 4 contains only the modified sinus attractor SR\text{block} since the wedge does not conduct in either direction (the tissue no longer contains a circuit for reentry).

3.4.2 Mechanisms of Dynamic Entrapment

Three stable attractors exist in region 2 of $R$-$AV_{repol}$ space (figure 3.4). When the system is operating in this region, it can exhibit one of three behaviors, depending on the initial conditions. If the initial state is within the basin of attraction of SR\text{cond}, the system will exhibit sinus rhythm as demonstrated in figure 3.3a. If, on the other hand, the system is initiated with a single wave traveling in either the clockwise or counter-clockwise direction, it will exhibit CWR or CCWR, respectively, and remain within the corresponding basin of attraction. In this system, dynamic entrapment as a disease process occurs when the system starts in the basin of attraction of SR\text{cond}, and then is pushed by some perturbation into the attractor basin of either CCWR or CWR\textsuperscript{1}. We explore two mechanisms by which this may occur.

\footnote{In fact SR\text{cond} is “entrapped” as well but we reserve the term for behaviors that are deemed pathologic.}
Parameter variation:

We first investigated the role of parameter oscillations in causing stable shifts in system behavior. We initialized the system in $SR_{\text{cond}}$ using a $\Delta V_{\text{repol}}$ value of 1.5 mV/ms and an $R$ value of 38 Ω, in region 2 of $R$-$\Delta V_{\text{repol}}$ space, and varied $\Delta V_{\text{repol}}$ sinusoidally with an amplitude of 0.7 mV/ms such that the system alternately exited region 2 into regions 1 and 3 (figure 3.6). We observed two critical transitions. First, when the system exhibited $SR_{\text{cond}}$ and crossed from region 2 to region 3, it shifted its behavior to CCWR because moving from region 2 to region 3 caused the $SR_{\text{cond}}$ attractor to disappear (wedge no longer conducts in the clockwise direction, counter-clockwise conduction immediately results in CCWR), leaving CCWR as the sole stable attractor. Upon returning to region 2, the system remained trapped in the basin of the CCWR attractor as it exists in both regions and nothing pushed the system out of it. Thus, this transient change in the $\Delta V_{\text{repol}}$ parameter caused dynamic entrapment of the system by temporarily eliminating the $SR_{\text{cond}}$ attractor. The second transition occurred when the system (exhibiting CCWR) in region 2 crossed into region 1. It shifted back to $SR_{\text{cond}}$ because here the CCWR attractor disappeared (wedge no longer supports conduction in either direction) leaving $SR_{\text{cond}}$ as the only stable attractor. When the system returned to region 2, it remained in the basin of $SR_{\text{cond}}$.
Figure 3.6 – Mechanism of dynamic entrapment: parameter oscillation. A shift in behavior (SR\textsubscript{cond} to CCWR) occurs when $\Delta V\textsubscript{repol}$ rises above a critical value and the system enters region 3 of $R-\Delta V\textsubscript{repol}$ space (at 2,000ms & 17,000ms); CCWR does not revert back to SR\textsubscript{cond} despite reversal of $\Delta V\textsubscript{repol}$ back into region 2 (at 5,000ms & 20,000ms). The inverse occurs when $\Delta V\textsubscript{repol}$ falls below another critical value and the system enters region 1 of parameter space (at 9,000ms & 24,000ms); the system returns to SR\textsubscript{cond} and remains there even when the system returns to region 2 (at 13,000ms & 28,000ms).

External stimulus:

We next investigated the ability of external perturbations, in the form of ectopic depolarizations, to push the system from sinus rhythm into reentry. Again, we initialized
the system in region 2, with $\Delta V_{repol}$ at 1.5 mV/ms and $R$ at 38 $\Omega$, and established $SR_{cond}$.

We then applied ectopic activation at various locations and timings (relative to pacemaker activation), and observed the resulting behavior (figure 3.7). Ectopic depolarizations occurring within approximately 100 ms from when local cells became re-excitable were capable of pushing the system into reentry. The precise size of this window varied with location on the disc. Ectopic depolarizations which lead to reentry satisfied two criteria. First, they captured local tissue and initiated propagation. Second, one of the spawned wavefronts was blocked, allowing its counterpart to propagate continuously. Unidirectional block was achieved by two different mechanisms. In cases where wavefronts were initiated in the wake of an existing wave and sufficiently close to its refractory tail, CV was increased by the higher excitability of local cells which had not fully returned to resting potential. The spawned wavefront traveling in the same direction as the original wave rapidly propagated into its refractory tail and terminated. In cases where two wavefronts traveling in the same direction were separated by a sufficiently small excitable gap, the follower would collide with the leader’s refractory tail once it entered the wedge, where CV slowed and the excitable gap decreased to zero.

The susceptibility of the system to dynamic entrapment in the presence of ectopic activation may be quantified as the percent of the area of the location-timing offset plane which results in reentry (i.e. the gray and black area divided by the total area in figure 3.7). We investigated the impact of system parameters on its susceptibility by repeating this simulation using additional pairs of $\{\Delta V_{repol}, R\}$ values within region 2. These are listed in table A along with the corresponding computed susceptibility values. As the
system (in region 2) moves away from the boundary with region 1, the susceptibility increases.

**Figure 3.7** – Inducibility of reentry by premature depolarization: grey and black areas represent ectopic activations that successfully induced reentry (CCWR and CWR respectively), while white area represents those which failed to induce reentry and left the system in SR\textsubscript{cond}. Y-axis: coupling interval of external stimulus (ms) relative to pacemaker firing; x-axis: location of premature activation on disc (degrees).

### 3.5 Discussion

Disease can be thought of as a possible behavior of a biological system (albeit one deemed undesirable); i.e. pathology is what a structure *does*, not what it *is*. Nonlinear dynamic systems, which abound in biology, are capable of supporting multiple behaviors.
In this case, structure and function (behavior) do not share a one-to-one relationship. While structure determines the possible behaviors of a system, the specific behavior exhibited depends on past history as well. This raises the possibility for a particular biological system to exhibit both healthy and diseased behaviors without any structural modifications. In such a system, sufficient external perturbations may drive it between its various behaviors (attractors in its phase diagram) in which it remains until further change or perturbation to the system – a phenomenon we term dynamic entrapment.

In the present study, we have shown that reentry in a structurally defined circuit is a plausible example of dynamic entrapment. We demonstrated, using a computational model, that an excitable tissue can support multiple stable behaviors, that transient changes in excitability or ectopic depolarizations can cause the system to shift between these behaviors, and that these shifts do not reverse spontaneously when the perturbing influence is removed.

<table>
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<th>36.5</th>
<th>37</th>
<th>37.5</th>
<th>38</th>
<th>38.5</th>
<th>39</th>
</tr>
</thead>
<tbody>
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<td>1.30</td>
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<td>1.5</td>
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<td>5.54</td>
<td>6.3</td>
<td>6.58</td>
<td>6.64</td>
</tr>
</tbody>
</table>

**Table 3.1** – Susceptibility of the system to dynamic entrapment in the presence of ectopic activation as a function of parameters (in region 2): susceptibility increases as the system moves away from region 1.
In the system shown in figure 3.1, we demonstrated four distinct behaviors (figure 3.3), two of which are healthy behaviors (sinus rhythm) and two of which are unhealthy behaviors/disease (reentry). These stable behaviors each correspond to an underlying attractor basin in the phase diagram of the system, which is determined by the structure of the tissue and the specific parameter values of its excitable components. As parameters are varied, the landscape of the phase diagram changes. Even in the simplified system studied here, which contains only two possible pathways compared to the numerous ones present in the human heart, multiple attractors can co-exist for a given parameter range (e.g. region 2 in figure 3.4 and figure 3.5b), and therefore the system is capable of many behaviors without any structural alterations. Transient shifts in tissue parameters, which may result from nervous inputs for example, are capable of driving the system from sinus rhythm to reentry by inducing temporary block in a susceptible region of the circuit (figure 3.6). Alternatively, an appropriately timed ectopic depolarization can convert sinus rhythm to reentry by blocking in only one limb of the circuit (figure 3.7). The latter mechanism in particular correlates strongly with clinical observation; premature atrial complexes are a common trigger for initiating reentry in humans, e.g. 12,149.

Dynamic entrapment does not imply that there are no differences between a healthy or diseased system, which is a separate distinction from a system exhibiting healthy or diseased behavior. A healthy system, in this context, may be thought of as one which is less prone to dynamic entrapment and/or more easily escapes a disease attractor once entrapped. For example, the system considered in the present study becomes more susceptible to dynamic entrapment (when in region 2) the farther it gets from the
boundary with region 1 (table 3.1). One might consider this as a simple model of disease progression, where symptoms worsen as a result of increased susceptibility to entrapment. In real electrophysiology, it is known that sustained tachycardia triggers electrical remodeling processes that, among other things, shorten WL and decrease CV\textsuperscript{137}. Such remodeling is analogous to our system migrating away from the boundary with region 1 (while in region 2), which corresponds to an increase in susceptibility to dynamic entrapment.

Two ways of treating dynamic entrapment are 1) to alter the system parameters or structure such that the aberrant attractors have a reduced (or eliminated) basin of attraction, and 2) to persistently push the system back into the healthy attractor when it gets stuck elsewhere. In the latter case, the specific mechanism by which the system is pushed back into the desired basin of attraction is not necessarily the same as the one that pushed it away to begin with. Interestingly, both approaches are used clinically to treat cardiac arrhythmias. Many anti-arrhythmic drugs, for example, prolong WL\textsuperscript{150, 151}; in our model, this can push the system into region 1 and thus eliminate the CCWR attractor. Alternatively, (non-conducting) scar tissue can be created with catheter ablation, to, for example, physically eliminate conduction through the wedge in our model. This results in a system where only sinus rhythm is supported. These two therapies thus entail altering the structure of the system reversibly (anti-arrhythmic drugs) or permanently (catheter ablation). Another approach to therapy is the use of defibrillators or anti-tachycardia pacing to convert reentry to sinus rhythm. This simply shifts between attractors but does
not eliminate the potential for recurrence of disease because the pathologic attractors remain in existence.

3.5.1 Conclusions

The topic of disease in nonlinear dynamic systems has previously been discussed. Mackey developed the notion of dynamical disease, with reference to Leukemia, and showed how stable physiologic behavior can suddenly change at critical points in parameter space \(^{152,153}\). In this case, however, reversal of the parameters is sufficient to reestablish healthy behavior, and thus it is not an example of dynamic entrapment. Interestingly, we observe a similar phenomenon in our system when it moves (through \(R-\Delta V_{repol}\) space) from region 4 to region 3 and back (figure 3.4). Entering region 3 initiates reentry, while returning to region 4 reestablishes sinus rhythm. The critical distinction between the transition into region 4 and the transitions into region 2 discussed in section 3.2 is that system behavior in region 4 is independent of what the system was doing previously, or where it was in parameter space. Conversely, system behavior in region 2 depends entirely on how it entered that region, or more specifically, which behavior it was exhibiting. The key element is thus system memory. In fact, dynamic entrapment is a particular disease mechanism belonging to a broader class of pathologies that might be termed hysteretic diseases. A hysteretic disease can only manifest in a system with memory.
4 WAVE-TREE ANALYSIS OF CHAOTIC MULTI-WAVELET REENTRY

4.1 Abstract

Objective: It is unclear how to take something as complex as MWR and decompose it into manageable pieces. We propose to study MWR in terms of individual wavelets and seek, therefore, an analytical method to quantify the wave population dynamics under various substrate conditions.

Methods: We developed a wave-tracking algorithm in which individual wavefronts are identified at each time step of simulation and then correlated to one another across sequential time frames. The resulting tree-like structure (the “wave-tree”) contains information about wave breaks (nodes with multiple children), fusions (nodes with multiple parents), terminations (childless nodes), and spontaneous wave formations (parentless nodes). Moreover, it enables for the identification of continuous pathways of excitation, as well as those which are passively excited.

Results: We validated the wave-tree on a case of single-circuit structural reentry. We then applied it to MWR in a heterogeneous medium and were able to locate regions of high reentrant-pathway density as well as high wave-break density, both of which correlated with the region of shortened WL and increased local heterogeneity. Moreover, this region exhibited higher overall activation frequency and therefore offers a potential clinically accessible metric for localizing regions of high circuit-density.
4.2 Introduction

Understanding the dynamics of complex MWR remains a challenge. The lack of organization makes it difficult to compare the levels of complexity of various episodes, which makes, for example, assessment of severity quite difficult. In previous work, investigators have tracked the paths of individual wave-ends, or phase singularities\textsuperscript{154,155}. This provides some measure of complexity but does little to yield insight into the pathways of reentrant propagation. Here, we develop a technique to track waves and assign relationships between waves in sequential time frames such that key events (wave-break, wave-fusion, termination, and spontaneous formation) can be identified both temporally and spatially. The basic algorithm is described in the Methods section of this chapter, but many of the practical uses of the wave-tree are best described using examples. These are presented in the Results section.

4.3 Methods

Constructing a wave-tree involves three steps, described below:

1. Identify activated cells, i.e. those which belong to wavefronts.
2. Group these cells into clusters – i.e. identify distinct wavefronts.
3. Build the wave-tree, i.e. establish causal relationships between wavefronts in sequential time steps.
Figure 4.1 – Wavefront identification using “most recently activated” criterion: (left) isopotential map, and (right) colored wavefronts. Wavefront cells are identified as cells which became activated within a short period of time from the current time step. Contiguous groups of wavefront cells are grouped into distinct wavefronts (colored uniquely in the right panel).

4.3.1 Identifying Wavefront Cells

The first step is to identify wave front points in each time frame of a particular episode of MWR. This can be done in a number of ways. The process can be treated like an edge-detection problem, where a common approach is to apply the Sobel operator to a two-dimensional voltage map. This identifies local maxima in the voltage gradients as edges, or in this case wavefronts. This is usually accompanied by a thresholding step where only maxima exceeding a certain value are considered edges. A downside to this
approach is that it is only well defined on flat two-dimensional sheets and is not trivially applied to curved surfaces using arbitrary element shapes and sizes. An alternative approach, which we consider here, is to select cells which have been activated within a certain time of the current time frame. Activation may be defined as the moment their voltage exceeds a threshold (ideally, the one for activation if it is known). For example, if cell $i$’s potential exceeds the prescribed threshold value of, say, -40mV at time $t_0$, then cell $i$ is considered as wavefront point until time $t_0+T$; e.g. figure 4.1.

4.3.2 Grouping Wavefront Cells

Once the wavefront cells have been identified, they must be grouped to form distinct waves. This is a trivial process of grouping connected cells. From an algorithmic perspective, one may perform the following:

A. Begin with the first wavefront cell and add it to a new list (these lists define wavefronts).

B. Pick the next wavefront cell;
   a. If any of its neighbors are already in a list, add it to that list.
   b. If several of its neighbors belong to different lists, merge those lists.
   c. If none of its neighbors are assigned to a list, create a new list for that cell.

C. Repeat B for each wavefront cell (defined in step 1; see section 4.3.1).

An example of steps 1 and 2 is shown in figure 4.1. Wavefront cells are highlighted with thick borders and the border colors are uniquely assigned to each list (distinct wavefront).
4.3.3 Building the Wave-Tree

Given a wavefront A at a time $t_1$ and a wavefront B at a later time $t_2$ (figure 4.2), we seek a function to characterize the spatial similarity of these two wavefronts in order to decide whether wavefront A evolved into wavefront B or not. We do so by first assigning the following relationships: for each cell $a_i$ which comprises wavefront A, find the nearest cell $b_k$ which is part of wavefront B as illustrated by the red arrows in figure 4.2 (note that $k$ is therefore a function of $i$). The average length of these arrows is $D_{AB}$, as defined in equation 4.1, where $\|a_i - b_k\|$ is the distance from cell $a_i$ to cell $b_k$, and $N_A$ is the number of cells comprising wavefront A. With that, we define the correlation function of wave A to wave B using equation 4.2.

$$D_{AB} = \frac{\sum_i \|a_i - b_k\|}{N_A}$$  \hspace{1cm} (4.1)

$$corr(A, B) = \frac{1}{1 + D_{AB}}$$  \hspace{1cm} (4.2)

Equation 4.2 evaluates to 1 when $D_{AB} = 0$, meaning each cell in A is also in B so A fits perfectly within B, and it approaches 0 as $D_{AB}$ increases, implying that waves A and B are spatially quite distant. Moreover, equation 4.2 is asymmetric: $corr(A, B) \neq corr(B, A)$ since $D_{AB} \neq D_{BA}$. This asymmetry is important. Consider as scenario in which wave A splits into two waves B1 and B2 as it evolves (figure 4.3). In this case, the correlation of A to either B1 or B2 will yield a small value. On the other hand, both B1 and B2 will produce strong correlation values to wave A. This informs us that wave A caused both waves B1 and B2. The inverse situation may also be accounted for; where two parent wavefronts A1 and A2 fuse to form a single daughter wavefront B.
The goal, ultimately, is to establish the causal relationships between the set of wavefronts \( \{A_k\} \) at a time \( t_1 \) and the wavefronts \( \{B_k\} \) at a later time \( t_2 \). This is accomplished as follows: for each pair of waves \( \{A_i, B_j\} \) in sequential time frames, calculate the two correlation values \( \text{corr}(A_i, b_j) \) and \( \text{corr}(B_j, A_i) \). This yields two matrices (per time step pair) of correlation values \( M_{AB} \) and \( M_{BA} \) where the entries of the former are \( m_{AB,ij} = \text{corr}(A_i, B_j) \) and the entries of the latter are \( m_{BA,ij} = \text{corr}(B_i, A_j) \).

For each wave \( A_i \), a connection is added to the wave \( B_j \) yielding the highest value in the \( i \)-th row of \( M_{AB} \), provided this value meets some threshold correlation value. Similarly, for each wave \( B_i \), a connection is added to the wave \( A_j \) yielding the highest value in the \( i \)-th row of \( M_{BA} \). The result is a tree-like structure where each node is a wave, each row of
the tree is a generation (or a time step), and the connections between nodes of sequential generations are established using the method above (figure 4.4). The resulting tree-like structure can be used to identify critical events. Specifically, nodes with multiple children correspond to waves that break; nodes with multiple parents correspond to waves that resulted from wave-wave collisions; nodes with no parents correspond to spontaneous newly formed waves; and nodes with no children correspond to waves that terminated. The applications of the wave-tree are more easily understood in the context of specific experiments, and therefore are described in further detail in the results section.

**Figure 4.3** – In the occurrence of wave break, the asymmetry of the correlation function enables us to establish the parent wavefront, A, is neither daughter wavefront B1 or B2. However, both B1 and B2 resulted from the existence of A at a prior time.
Figure 4.4 – The wave-tree is constructed by identifying the highest correlation values between each wave in time step 1 and each wave in time step 2 and vice-versa. The resulting relationships are represented graphically in the form of a tree structure.

4.4 Results

4.4.1 Structural Reentry with a Blind Alley

We constructed a wave-tree for a simple flat tissue with a single circuit and an additional conducting branch – a “blind alley” (figure 4.5). An asymmetric narrowing is present in the circuit permitting the induction of reentry from point stimulation via unidirectional block. The tissue properties were homogeneously assigned to $\Gamma_{ij} = 15 \& N^{UP}, N^{PLAT}, N^{REPOL} = [1,1,50]$. Cells activated within 8 time steps of the current time step were considered wave-front cells for the analysis. The resulting wave-tree structure becomes periodic once reentry is established as a single driving wave continues.
to circulate around the circuit and passively excites the blind alley. The wave in the blind
alley is identifiable in the wave-tree as a long line of singly-connected nodes which
eventually terminates (time steps 104 to 149). The reentrant wave (the other branch of the
tree at time step 149) continues to exist until it once more splits in two as it reaches the
top portion of the circuit and spawns a new wave in the alley (time steps 90 and 251).
Notice that the bottom-left portion of the circuit also acts as a very short passively excited
branch (time step 160).

4.4.2 Multi-Wavelet Reentry in Heterogeneous Tissue

Next, we constructed a wave-tree for a 15,000 time step episode of MWR (figure
4.6). We used a flat tissue of 80 x 80 cells. All tissue properties were homogeneously
assigned ($\Gamma_{ij} = 15, N^{UP}, N^{PLAT} = [5,1]$) other than $N^{REPOL}$. In cells in the upper-left
quadrant, values were randomly chosen from a uniform distribution over [65, 115]. In the
rest of the tissue it was uniformly set to 125 (figure 4.6(c)). The wave-tree appears
structure-less (figure 4.6(b)). However, we create density maps of where key events
occur: spontaneous new wave formation, wave termination, and waves breaking apart
(figure 4.6(d-f)). Spontaneous wave births are few in number, supporting the notion that
continued activity is indeed caused by continuous propagation rather than spontaneous
triggered firing (caused by re-excitation). Wave termination occurs predominantly in the
corners of the tissue, and otherwise mostly on the edges of the tissue. Finally, wave-
breaks occur very favorably in the region of heterogeneity and shortened wavelength.
Figure 4.5 – Example wave-tree constructed on a reentrant circuit with a “blind alley”. The numbers indicate the computational time step. The wave-tree exhibits a periodic structure described by the bottom two rows, since the final frame (bottom-right) corresponds to the 5th frame (middle-left). Activity is initiated from a point source identifiable in the first frame (top-left).
Figure 4.5 cont’d – The narrow pathway on the bottom of the circuit conducts unidirectionally such that reentrant propagation results from the point stimulus (4th frame). The wave in the blind alley is identifiable in the wave-tree by the long terminal branch spanning time steps 104 to 149 (middle row).
Figure 4.6 – Wave-tree computed for a 15,000 time step episode of multi-wavelet reentry. (a) A series of snapshots of activation. (b) A sample of the wave-tree structure.
Figure 4.6 cont’d – (c) The tissue properties are homogeneously assigned except for the programmed repolarization rate. (d) Very few spontaneous wave births occur. (e) Almost all wave terminations occur in the corners or the boundaries. (f) The distribution of wave-breaks is heavily biased towards the heterogeneous region with shorter action potential duration.

4.4.3 Trimmed Wave-Tree

In the context of continuous propagation, waves which terminate are of little interest in identifying the pathways contributing to reentrant excitation. Using the wave-tree, we can identify the pathways that participated in perpetuating continuous propagation by starting with all the nodes (or waves) in the last computed generation and working our way up through their parents. This way, all pathways which terminated before the end of the simulation will be ignored and only those which were continuous throughout will be highlighted, e.g. figure 4.7(a). A density map can be generated each time a particular cell appears in a node of the pruned wave-tree (the highlighted nodes). We performed this exercise on the wave-tree generated earlier for 15,000 time steps of MWR in the square tissue with a heterogeneous patch in the upper-left quadrant (figure 4.7(b)). We found that most of the reentrant pathways involved cells from the upper-left quadrant. Interestingly, we compared this result with the total activation count of each cell during the simulation time. Unsurprisingly, the shorter WL region has a higher activation frequency than the rest of the tissue. However, approximately 80% of the
activations in this quadrant were part of reentrant pathways, whereas only ~50% were in the remainder of the tissue. (These numbers drop dramatically near the boundaries.)

**Figure 4.7** – Wave-tree pruning. (a) Example of a pruned wave-tree (highlighted in green) starting from time step 2975. (b) Maps of cell activation counts over a 15,000 time step window of multi-wavelet reentry: (top) activation count of pruned wave-tree; (bottom) total activation count. The pruned wave-tree highlights activations which are part of continuous propagation pathways that persist until the last computed generation of the wave-tree.
Figure 4.7 cont’d – The heterogeneous patch is therefore host to most pathways of reentrant propagation. This appears to correlate with the total activation count which is potentially measurable clinically.

4.5 Discussion

4.5.1 Summary

Studies on the mechanisms of sustained chaotic propagation have typically focused on phase singularity mapping and tracking, as it can be argued that these are the drivers of continuous propagation\(^{100,143,154}\). Indeed, it is well known that phase singularity annihilation, either by collisions with boundaries or collision between counter-rotating vortices, terminates continuous propagation. In the context of chaotic propagation, however, single phase singularities, or wave-ends, do not persist for extended periods of time. They form and disappear as waves collide, break, spawn, and terminate. We have proposed to study chaotic propagation from the perspective of the wavelet itself by characterizing the dynamics of the population and identifying the pathways of continuous propagation. To that end, we have developed and demonstrated a novel algorithm for wave tracking in the context of MWR.

4.5.2 Wave Population Dynamics

In the pioneering computer modeling studies of Moe, MWR required somewhere from 15-40 wavelets to be self-sustaining\(^{27}\). The first experimental validation, performed
by Allessie’s group, demonstrated that it can be sustained by 4 to 6 in excised canine atrial tissue\textsuperscript{28}. Most recently, \textit{in vivo} mapping studies of acute and persistent human AF demonstrated fibrillatory waves ranging in numbers from 2.3/cm\textsuperscript{2} to 4.5/cm\textsuperscript{2} \textsuperscript{29}. In these studies, however, the idea of robustly defining the pathways of continuous propagation taken by these waves has remained an afterthought, though it is generally accepted that circuits do exist somewhere. The MAZE procedure in fact is based on this notion \textsuperscript{16}. These circuits are even ascribed a size; an idea dating back to the start of the century \textsuperscript{156}. In an effort to improve current ablation therapy, Spector proposed that the inherent heterogeneity of the atrial myocardium must result in a disproportionate distribution of circuits throughout the medium \textsuperscript{87}. Targeting the high-density regions preferentially might then result in equal or better treatment outcome with fewer overall lesions.

Identifying these regions, however, has remained a challenge. Here we’ve demonstrated a method by which they may be detected. In the tissue studied in figure 4.6, the high density of reentrant pathways in the upper-left quadrant (figure 4.7) suggests this to be an ideal site to target with anti-fibrillogenic treatment such as linear ablation. In support of this hypothesis, a related study showed that linear ablation delivered to regions of shortened WL and increased heterogeneity had a more beneficial impact than the same lesions delivered elsewhere \textsuperscript{118}. One might then ask: by what mechanism do these lesions have an effect? The results of figure 4.7 suggest the intuitive answer: increased circuit transection. In the cited study, the authors used closed-loop circuit tracking as a way of identifying circuit \textit{cores} and showed these to be in higher number in the shorter-WL regions as well. They proposed that linear lesions delivered to this region connected
circuit cores to the tissue boundaries and therefore transected the circuits that evolved around them.

4.5.3 **Physiologic Validation and Application**

The application of the wave-tree to clinical data is hampered by the lack of appropriate mapping tools. It is currently impossible to obtain complete high-density maps of atrial activation in humans. Multi-lead EKG vests, e.g. 157, are being developed to solve this problem, however, they currently lack appropriate spatial resolution to be of any use here. On the other hand, the wave-tree may be used to identify and validate clinically measurable targets for ablation. For example, here we’ve demonstrated that a high density of reentrant pathways and wave breaks correlates spatially with a high overall activation rate. The frequency of activation can in fact be measured *in vivo* currently. The primary limitation is in the spatial resolution of single electrodes which often appear fractionated during human AF and therefore cannot provide appropriate activation frequency. This limitation will likely be resolved more rapidly than those of the EKG vests. One of the perks to frequency mapping is that it can be done sequentially, since it likely reflects a stable tissue property more than a transient behavior pattern. This idea, in fact, has recently been proposed and demonstrated *in silico* 119.

4.5.4 **Limitations**

The wave-tree is designed to characterize the dynamics of MWR. AF, however, can be caused by other mechanisms, such as rapid ectopic activity or stable spiral waves with fibrillatory conduction. While we have not validated its use on these scenarios, the
algorithm is in theory capable of detecting spontaneous activity and distinguishing continuous propagation of a stable spiral wave from the fibrillatory waves which are destined to terminate.

4.5.5 Conclusions

We have demonstrated an automated algorithm for analyzing the spatiotemporal dynamics of continuous propagation sustained by multiple wavelets. With it, we have demonstrated the co-localization of wave-breaking events and diseased myocardium with shortened WL and increased heterogeneity. Finally, we have also demonstrated a spatial correlation between tissue activation frequency and the pathways of reentrant propagation in a particular case suggesting a potential clinical target for catheter ablation therapy and an avenue for future investigation.
5 CONVERSION OF MULTI-WAVELET REENTRY IN THE PRESENCE OF ISLAND OBSTACLES

5.1 Abstract

Objective: We seek to elucidate the impact of various topologic interruptions on the dynamics of chaotic multi-wavelet propagation in order to study focal ablation in the treatment of AF.

Methods: We used four square tissues with APDs and conduction velocities spanning the physiologic range and chosen to produce chaotic continuous propagation with varying degrees of complexity. We initiated chaotic propagation by rapid pacing. Immediately following the pacing protocol, we applied a circular lesion to the center of each tissue. This was repeated many times for each tissue and using many different obstacle sizes. Each simulation progressed until the tissue either returned to quiescence or the MWR organized into structural reentry around the center obstacle.

Results: There existed three regimes of lesion size. In the smallest regime, the obstacles were too small to interact with the chaotic propagation. They had no impact on episode duration, nor were they able to sustain stable anchored rotation. In the next size regime, lesions had a strong affinity for anchoring waves. Moreover, sharp decreases in the fraction of quiescent outcomes and the average lifetime suggest an active mechanism converting the chaotic propagation into organized structural reentry. In the largest regime, obstacles only had a passive impact on the dynamics of chaotic propagation by altering the geometry and topology of the tissue. In the middle regime, we found multiple
mechanisms by which anchored waves can become detached from the center obstacle in the midst of chaotic propagation and observed interplay between structural reentry and chaotic propagation. These observations are consistent with alternations between periods of relative organization and periods of complete disorganization seen on electrogram recordings during AF\textsuperscript{112,113,115}.

This work was prepared into a manuscript but has yet to be published at the time of this writing.

5.2 Introduction

Radio-frequency ablation delivered via intracardiac catheters has become the most effective curative therapy for many atrial arrhythmias\textsuperscript{40}. Unfortunately, it continues to exhibit only moderate success against AF\textsuperscript{38,41,43} – the most commonly encountered arrhythmia\textsuperscript{1}. This lack of success stems in large part from incomplete knowledge of what is driving AF in each patient\textsuperscript{1,15,158} leading to an inadequate understanding of the anti-arrhythmic effects of various lesion distributions.

Recent clinical studies have shifted focus from anatomically-motivated lesion sets in favor of substrate-specific, electrogram-guided procedures. The objective of such procedures is to identify supposed AF drivers like stable rotors using CFAE\textsuperscript{51,71} or rotor mapping algorithms\textsuperscript{30}, which are then treated with focal ablation. While the results of these methods are mixed and the topic of some debate\textsuperscript{31,52,75}, it remains unclear how focal lesions promote AF termination from a mechanistic perspective. It is known that anatomical obstacles can create a substrate for arrhythmia by allowing meandering spiral
wave tips to anchor and thus convert fibrillation to tachycardia\textsuperscript{86}. It has been shown clinically that incomplete lines\textsuperscript{45,46} and myocardial infarct\textsuperscript{54,55} can be pro-arrhythmic by the same mechanism. However, recent in silico studies have yielded conflicting results, in one case showing that focal ablation of rotor cores causes immediate anchoring\textsuperscript{87} and in other case showing that focal lesions can drive untethered wave ends away from a region of diseased tissue and towards external tissue boundaries where they terminate\textsuperscript{82}.

As we continue to validate novel guided-ablation strategies, the interaction between focal lesions and the dynamics of reentrant propagation remain unclear, particularly in the context of multiple meandering wavelets. Understanding the impact of ablation from a mechanistic perspective is an important step towards developing patient-optimized lesion sets that trade off likelihood of successful outcome with patient risk. Therefore, in the present study we sought to elucidate the mechanisms by which focal lesions impact the fate of complex MWR – either conversion to stable tachycardia or termination – using a computational model for propagation in excitable media.

### 5.3 Methods

#### 5.3.1 Computational Model

In order to investigate the impact of a large variety of lesion configurations with statistical confidence, we required a model capable of performing a large number of simulations in a reasonable timeframe. To this end, we used the diffusion-based cellular automaton model described in chapter 2. The model elements are excitable “cells” coupled by ohmic resistors and each model cell represents a large group of coherently
activated myocytes. In contrast with the myriad of commonly employed ionic models\textsuperscript{92} (in which action potentials emerge from differential equations describing ion current kinetics), these elements implement action potentials explicitly using piece-wise linear functions. As we are interested in investigating the dynamics of emergent phenomena at the tissue scale – i.e. the relationship between tissue topology and properties, and MWR – implementing action potentials directly provides a tremendous benefit in computation time with no loss of insight.

5.3.2 Tissue Configurations

Four tissue configurations were used. Each tissue was a flat sheet of 120x120 equally-sized square cells. (The unit of length used in this manuscript is the edge length of these cells.) The intercellular resistance was homogeneously set in each tissue to either 10\(\Omega\) or 14\(\Omega\). The APD was heterogeneously assigned in each tissue. A circular center region of 40 units in radius (thus containing 80 cells along the diameter) contained the shortest APD, homogeneously set to either 127.5ms or 137.5ms. An annulus of 5 units in width surrounded this center region and contained a gradient of APDs that smoothly transitioned from the value in the center region the value beyond the annulus, which was homogeneously set to 150ms in all tissues.

5.3.3 Pacing Protocol

Initiation of MWR was achieved by rapid burst pacing using pulses 7.5ms in width. One hundred stimuli were applied to the center of a given tissue, each randomly located within a circular region with a 10 unit radius. Each inter-beat interval was randomly
selected from a uniform distribution over the range [75ms, 100ms]. The total pacing time thus varied across simulations with a mean time of 8.75s.

### 5.3.4 Lesion Configurations

We investigated the impact of two lesion types: first, focal circular lesions centered in the tissue with a radius ranging from 0 (no lesion) to 20 units; second, the same circular lesions but with an additional linear lesion connecting them to the outer boundary of the tissue, including the case where the line is applied alone, extending from the outer boundary to the center of the tissue.

### 5.3.5 Simulation Protocol

Each simulation began with pacing to initiate MWR. One thousand time steps following the final paced beat, the selected lesion was applied to the tissue. Initiation was considered successful if excitation persisted for at least another 1000 time steps. The simulations were allowed to run until one of two conditions was met: MWR converted to structural reentry; or MWR terminated and the tissue became quiescent. The first condition was identified when every cell in a tissue became activated periodically and at the same rate, and the second condition was identified when every cell’s potential fell below the threshold for activation. For detecting periodicity, we imposed the condition that ten sequential cycle lengths of activation had to fall within a range of 3 time steps from one another. The time at which conversion occurred was marked as the time of the first of those ten activations. We also allowed for the detection of double- and triple-cycle length periodicity, since large obstacles can support multiple co-anchored waves. In these
cases, the condition for detection was twenty or thirty activations, respectively, alternating between each cycle length; similarly, the ten samples per cycle length had to fall in a range of 3 time steps. To distinguish single wave anchoring from symmetrically opposed co-anchored waves, which manifest as a single cycle length of activation, we compared the detected cycle length to the known cycle length of a single anchored wave. If the detected value was less than 90% of the known value, the simulation was categorized as conversion with double-wave anchoring (as opposed to single-wave anchoring). Similarly, when two cycle lengths were detected, we compared the sum of these cycle lengths to the known cycle length of a single anchored wave. If the sum was less than 90% of the known value, the simulation was categorized as conversion with triple-wave anchoring (as opposed to double-wave anchoring).

5.3.6 Statistical Model

We analyzed the results of these simulations using a generalized Bernoulli process – one where each Bernoulli trial has three possible outcomes: perpetuation of MWR (M), conversion to structural reentry (C), or termination of propagation (T). The stationarity criterion of the Bernoulli process is satisfied by allowing trials to occur every \( N \) time steps, where \( N \) is some interval number of time steps after which the autocorrelation function has decayed to zero. The three possible trial outcomes have probabilities \( p_M \), \( p_C \) and \( p_T \) (in units of probability per s, or 1/s), respectively, and where

\[
p_M + p_C + p_T = 1 \quad (5.1)
\]
The process begins with trial number \( t = 1 \) and continues until a trial returns \( C \) or \( T \). In other words, the process can only end in conversion or termination. The probabilities that a single process ends in conversion at exactly trial number \( t_C \), or termination at exactly trial number \( t_T \) are therefore given by

\[
P[C, t = t_C] = p_M^{t_C-1} p_C
\]

\[
P[T, t = t_T] = p_M^{t_T-1} p_T
\]

The probabilities that a single process ends in conversion or termination at any trial are given by

\[
P[C] = \sum_{t_C=0}^{\infty} P[C, t = t_C]
\]

\[
= \sum_{t_C=0}^{\infty} p_M^{t_C-1} p_C
\]

\[
= \frac{p_C}{1 - p_M}
\]

\[
= \frac{p_C}{p_C + p_T}
\]

\[
P[T] = \frac{p_T}{p_C + p_T}, \quad \text{by symmetry}
\]

Lastly, the expected values of \( t_C \) and \( t_T \) are given by
\[ E[t_C] = \frac{\sum_{t=0}^{\infty} P[C, t]t}{P[C]} \]
\[ = \frac{\sum_{t=0}^{\infty} P_M^t p_{t_0}}{p_C / (p_C + p_T)} \]
\[ = \frac{p_C / (1 - p_M)^2}{p_C / (p_C + p_T)} \]
\[ = \frac{1}{p_T + p_C} \]

\[ E[t_T] = \frac{1}{p_T + p_C} = E[t_C], \quad \text{by symmetry} \] \hspace{1cm} (5.4)

These correspond to the average durations (number of trials) for all processes which end in conversion or termination, respectively. This result says that the average time before episodes convert is equal to the average time before episodes terminate and that this average time is dependent on both the probability of conversion and the probability of termination at any given trial.

By combining equations 5.2 and 5.4, the trial probabilities \( p_C \) and \( p_T \) can be solved for in terms of measurable parameters:

\[ p_C = \frac{P[C]}{E[t_C]} \] \hspace{1cm} (5.5)

\[ p_T = \frac{1 - P[C]}{E[t_C]} \] \hspace{1cm} (5.6)

The value of \( E[t_C] \) is estimated by averaging the durations of episodes ending in conversion for a given tissue and lesion configuration. Because this is equal to \( E[t_T] \), we used the average episode duration regardless of end condition to improve our estimates in
equations 5.5 and 5.6. \( P[C] \) is estimated by the fraction of episodes (for a given tissue and lesion configuration) which end in conversion rather than termination. However, there is a caveat. We have no robust way of measuring the autocorrelation decay interval \( N \). Thus, our estimates of \( E[t_c] \) are in units of time-steps rather than trials, and are therefore scaled by a factor of \( N \). This possibly prohibits comparison of \( p_C \) and \( p_T \) values across different tissues since the dynamics of MWR (and therefore \( N \)) are dependent on tissue properties. However, for a given tissue with a varying lesion configuration, we assumed the value of \( N \) to remain constant.

5.4 Results

5.4.1 Conversion to Structural Reentry

We investigated the impact of focal lesion size on the fraction of simulations that converted to structural reentry rather than terminated. For each combination of tissue configuration and lesion size, we performed 1000 simulations. Approximately 91% of these simulations successfully initiated with no apparent correlation to tissue properties. The fraction of the initiated simulations which eventually converted to structural reentry exhibited a multi-phasic trend as lesion radius increased from 0 to 20 units (figure 5.1). For each tissue, there was a critical lesion radius below which no conversion occurred (2-3 units, depending on the tissue). As the lesion radius increased beyond this threshold, the conversion fraction first rose to a sharp peak (50-95% for 3-4 unit radii) then rapidly decayed to a moderate range (40-60% for 3-6 unit radii). The location of the peak varied across tissues; it moved towards increasing lesion radius as intercellular resistance
decreased. The prominence of the peak also decreased with increasing resistance and decreasing APD, suggesting that the mechanism for its appearance is dependent on WL and/or excitability. The conversion fraction exhibited a secondary deflection at lesion radii of 7-8 units. These were most prominent in the high resistance cases and corresponded to peaks in the fraction of conversion with two or three anchored waves (figure 5.1, right). Finally, as lesion size continued to increase (beyond radii of 8-10 units in the high resistance cases and 6 units in the low resistance cases), the conversion fraction increased along a shallow linear curve (up to 50-70% for 20 unit radius). The slope of this curve appeared similar across tissues while the intercept differed. This indicated that the rate of conversion of MWR in the presence of large lesions is dependent on both lesion size and tissue properties, likely in relation to one another.

To investigate the mechanism underlying the sharp peak in conversion fraction, we calculated the average cycle length of activation in the center region of each tissue (where APD is shortest) during MWR with no lesion and compared this value to the cycle lengths of single waves anchored to small lesions (figure 5.2). In each tissue, the highest conversion rate occurred when the cycle length of the anchored wave was closest to the average cycle length of MWR. We note that these cycle lengths in fact do not represent the shortest ones supported by each tissue. Cells excited by MWR are activated chaotically, many times at faster or slower rates than the average. By visual inspection, we confirmed that anchored waves going at the same rate exhibited (relatively small) excitable gaps. Our sampling of lesion sizes did not include smaller lesions capable of anchoring at faster cycle lengths. This notion is confirmed by the occurrence of the
secondary conversion-fraction deflections at cycle lengths less than twice the average cycle length of MWR (figure 5.2, right).

**Figure 5.1** – Conversion rate of multi-wavelet reentry (MWR) to structural reentry. Left: Fraction of simulations that end in conversion (rather than termination) with any number of anchored waves. Right: Fraction of simulations that end in conversion with two or three anchored waves.
Figure 5.2 – Cycle lengths of anchored waves compared to those of multi-wavelet reentry (MWR). Left: (solid) Cycle lengths of single anchored waves as a function of lesion radius compared to (dashed) the average cycle length of cells in the center region of each tissue activated by MWR in the absence of any lesion. Right: (solid) Fraction of simulations that end in conversion with any number of anchored waves relative to the difference between the cycle length of a single anchored wave and the average cycle length of MWR. The conversion fraction is maximized when this difference is closest to zero. The dashed lines represent the harmonic values of the MWR cycle lengths for each tissue – the points at which the cycle lengths of single waves is twice that of MWR.

5.4.2 Mechanisms of Detachment

We visually inspected sample simulations to establish if wave-anchoring was a definitive event or if detachment and re-attachment occurred regularly before episodes
ended. We found two mechanisms by which waves become detached from an obstacle once anchored (figures 5.3 and 5.4). In both cases, the mechanism of detachment involves anchoring of a new wave traveling opposite in direction to the original wave. When two such waves collide, they fuse and travel off the obstacle. In one scenario (figure 5.3), an extraneous wave is guided to the lesion by colliding with the refractory tail of the anchored wave. It travels toward the lesion along the line of refractory tissue (conduction block) created by the latter. The new wave then anchors to the lesion, fuses with the previously anchored (and opposing) wave-front, and detaches. In the other scenario (figure 5.4), an extraneous wave becomes anchored by direct collision with the lesion itself in the excitable gap of the anchored wave. Upon collision, two newly anchored waves are formed: one traveling opposite the original anchored wave, and one traveling in the same direction. The first of these waves (traveling opposite the anchored wave) fuses with the original wave and drives it off the lesion. Due to the proximity of the wave-lesion collision to the refractory tail of the originally anchored wave, the second wave propagates into a wall of refractory tissue and is driven off the obstacle as well. We noted many similar wave-lesion collisions occurring in the simulations but farther away from the refractory tail. In these cases, the second wave remained anchored and no net detachment event occurred.
**Figure 5.3** – Mechanism of anchored wave detachment: external wave collision with anchored wave tail. Top: snapshots of tissue activation over time (left to right). Middle & Bottom: snapshots of tissue phase distribution; (grey) rest, (yellow) upstroke, (green) refractory, (blue) relative refractory. Bottom: Arrows indicate moving wavefronts. The dotted line is the refractory tail of the anchored wave. The extraneous wave is guided to the lesion along the line of block created by the anchored wave.
**Figure 5.4** – Mechanism of anchored wave detachment: external wave collision with lesion. Top: snapshots of tissue activation over time (left to right). Middle & Bottom: snapshots of tissue phase distribution; (yellow) upstroke, (green) refractory, (blue) relative refractory, (grey) rest. Bottom: White arrows represent moving wavefronts. The dotted white line is the tail of the anchored wave. An extraneous wave breaks on the lesion creating two newly anchored waves. One fuses with the original and oncoming wavefront, while the other collides with the anchored wave tail.

### 5.4.3 Episode Duration

For each tissue and lesion configuration, the average duration of episodes which ended in conversion was equal to the average duration of episodes which ended in
termination (figure 5.5), consistent with the generalized Bernoulli model (equation 5.4).

These averages appeared to correlate inversely with the fraction of episodes that ended in conversion. There were pronounced negative deflections at small lesion sizes followed by secondary negative deflections, each corresponding in location to the peaks in conversion fraction (figure 5.1). In general, increasing lesion size decreased the average episode duration. This occurred linearly after a radius of 10 units in the shortest WL tissue, or 6 units in the other tissues; the same ranges where the conversion fraction increased linearly. As expected from the mass hypothesis, the average time to termination was greatest in the shortest WL tissue (relative to the same area), and vice versa. However, the relative impact of focal lesions on episode duration was greatest in the shortest WL case (figure 5.5, right).

5.4.4 Lesion Impact on Multi-Wavelet Reentry

To understand the mechanisms underlying the changes in conversion fraction and mean episode duration, we modeled each episode as a generalized Bernoulli process and calculated the trial probabilities $p_C$ and $p_T$ as a function of the lesion radius (figure 5.6). These values correspond to the probabilities that an episode either converts to structural reentry or terminates at any given time step. The changes in $p_C$ and $p_T$ were distinct from one another as lesion radius was varied; however these changes were similar across tissues. We observed three regions of behavior. For small lesions with radii less than 2-3 units (including no lesion), $p_C$ remained at zero while $p_T$ maintained a constant value. For lesions with radii of 2-6 units, $p_T$ remained at the same constant value while $p_C$ exhibited a biphasic variation. It rose from zero to a sharp peak (aligned with the
maximum conversion fraction; figure 5.1) and then quickly decayed to a lower value. These observations indicate that small lesions have no impact on the probability of terminating MWR. They only modulate the probability of converting it to structural reentry. Thus, the variation in mean episode duration (including those that terminated) caused by small lesions results from changes in $p_C$ alone. Finally, for lesions exceeding 6 units in radius, both $p_C$ and $p_T$ increased along steady curves; however $p_C$ grew faster, as manifested by the steady increase in conversion fraction in this range (figure 5.1). The changes in mean episode duration caused by large lesions is thus a result of changing both $p_C$ and $p_T$.

5.4.5 Additional Linear Lesions

Finally, we looked at the effect of an additional linear lesion on the trial probability $p_T$ and the average time to termination. For each focal lesion, we added a linear lesion extending from its outer boundary to the outer boundary of the tissue. The topology was reverted to that of an uninterrupted plane. As a result, no conversion was possible and the conversion fraction and trial probability $p_C$ were uniformly zero. The average time to termination with the combined lesion set decreased linearly as the focal lesion radius increased (figure 5.7, left). When compared to the mean episode duration with no applied lesion, the initial decrease caused by the linear lesion alone (focal radius of zero) was approximately 50% in each tissue. The greatest effect was seen in the shortest WL case.
Figure 5.5 – Mean episode durations. Left: Average episode durations in each tissue showing mean time to conversion is similar to mean time to termination in all tissues and for all lesion sizes. Right: Mean episode durations normalized to the no-lesion (radius = 0 units) case showing the relative impact of focal lesions increases with decreasing wavelength of excitation.

The relative impact of the additional line was measured by comparing the mean episode durations with and without its application (figure 5.7, right). For focal lesions less than 2-3 units in radius, the additional line decreased episode duration by 50%. For lesion sizes corresponding to the maximum conversion fractions, the addition of a line increased mean episode duration in three out of four tissues. For radii larger than 4 units, the impact of the line was approximately constant, decreasing mean episode duration by 20-25%.
Figure 5.6 – Bernoulli trial probabilities that an episode will convert or terminate at each time step.
Figure 5.7 – Mean episode duration with an additional linear lesion. Left:
Average time to termination normalized to the no-lesion (radius = 0 units) case showing a linear decrease in duration with increasing focal lesion radius. Right:
Average time to termination of the combined focal-linear lesion set relative to the respective focal lesion alone showing a constant decrease of 20-25% with the additional line except in the high conversion range (of focal lesions).

The relative change in the trial probability $p_T$ was similarly measured (figure 5.8). In each tissue, the presence of the line alone caused a twofold to fourfold increase in the probability of termination at each time step. When applied in addition to a focal lesion, the relative change in $p_T$ appeared to increase with its radius. By comparing $p_T$ of the combined lesion set to the sum $p_C + p_T$ of the focal lesion alone, we could establish if the impact of the line was simply to “convert” the probability of conversion into a probability of termination. The value of this ratio was much higher than one for small (or no) lesions
where the value of $p_C$ was already zero. It dipped below one for focal lesions with very high conversion rates, indicating that the additional line could not convert all of $p_C$ into $p_T$. Beyond lesion radii of 4 units, the ratio settled in the 1.2-1.5 range, indicating that the additional line increases $p_T$ by more than the value of $p_C$ and by an amount which is independent of lesion size.

**Figure 5.8** – Relative Bernoulli trial probabilities of termination with the additional linear lesion. Solid: Trial probability of termination with the additional line relative to the trial probability of termination without the line showing a two-to fourfold increase. Dashed: Trial probability of termination with the additional line relative to the trial probability of termination-or-conversion without the line showing a consistent increase of 25-50% except in the maximum conversion range of focal lesions.
5.5 Discussion

5.5.1 Summary

In the present study, we investigated the impact of focal lesions on the dynamics of MWR in a computational model for propagation in cardiac tissue. Our results demonstrated that focal lesions can both promote the conversion of MWR to stable structural reentry and promote the termination of reentry altogether. We showed that MWR protects itself against conversion by detaching anchored waves from anatomic obstacles, indicating that focal lesions do not necessarily lead to tachycardia as was previously suggested. Finally, we demonstrated the importance of linear lesions in the presence of existing focal lesions (or obstacles). Our study suggests that recurrence of tachycardia cannot be prevented with certainty using isolated focal ablation alone.

5.5.2 Regimes of Focal Lesion Size

The fraction of episodes of MWR that ended in structural reentry indicates three regimes of lesion size, where the range of each regime is a function of the tissue parameters (figure 5.1). The first regime is the trivial case where focal lesions are too small to interact with the dynamics of propagation in any way. This regime is characterized by no conversion to structural reentry and a constant average time to termination similar to the no-lesion case (figure 5.5). The ability of a wave to attach and remain anchored to a circular obstacle is dependent on two conditions: the path length of the lesion must be longer than the WL of the anchored wave, where this WL is shortened by the curvature of the path around the obstacle; and the curvature of the wavefront at
the point where it is anchored to the obstacle must be equal to or greater than the minimum wavefront curvature required for conduction. These two factors determine the upper bound of the first regime in terms of lesion radius (2 or 3 units in the present study).

In the second regime, lesions are large enough to allow wave anchoring, yet small enough to allow anchored waves to interact with the dynamics of MWR. This regime is characterized by the maximum peak in conversion fraction for small lesions (with radii in the [2, 5] unit range, depending on the tissue; figure 5.1). Firstly, these lesions are too small to affect the probability of termination by tissue mass reduction nor do they alter wave dynamics in a way which is favorable or unfavorable to such a fate; $p_T$ is constant this range (figure 5.6). Secondly, their circumferences are only slightly larger than the WLs of anchored waves, leading to cycle lengths close to the theoretical limit of each cell, and thus similar to the average cycle length of MWR (figure 5.2). This implies that an anchored wave is capable of capturing local tissue and disrupting the dynamics of nearby MWR. (Conversion to tachycardia, however, requires global capture and therefore that the cycle length of the anchored wave be comparable to that of MWR elsewhere in the tissue. Left-to-right frequency gradients mapped during human AF suggest that conversion to tachycardia by such a mechanism could only take place in the left atrium.) The variability in cycle length of cells activated by MWR provides opportunities for the anchored wave to increase its zone of capture. It also provides opportunities for the MWR to disrupt the activity of the anchored wave and possibly detach it from the obstacle (figures 5.3 and 5.4). The vulnerability to detachment increases with the size of
the excitable gap, demonstrated by the decrease in conversion fraction as the cycle length of anchored waves increased (figure 5.2, right). This implies that the peak in conversion fraction should occur at larger lesion radii as the WL of excitation increases. The coarseness of our sampling of lesion radius (and hence circumference) only showed a difference between high and low resistance tissues. However, we confirmed this hypothesis by calculating the conversion fraction with finer-grain sampling of lesion circumference using elliptical lesions (not shown).

In the third regime, lesions become comparable in scale to the size of the tissue and are too large to interact with the dynamics of individual wavelets. This regime is characterized by the linear increase in conversion fraction (figure 5.1) and linear decrease in average time to termination and conversion (figure 5.5) for lesion radii greater than 5 units. Note that this regime contains a sub-region where double-wave anchoring occurs with cycle lengths slightly faster than those of MWR, favoring conversion and producing the secondary hump most prominently seen in the shortest WL tissue. In general, however, lesions in this regime affect propagation dynamics in two ways. First, they increase the time step probability of termination ($p_T$ increases; figure 5.6). In accordance with the critical mass hypothesis, this is likely caused by the significant decrease in tissue area. Second, they increase the time step probability of conversion ($p_C$ also increases; figure 5.6). The mechanism by which this occurs is less well understood. One plausible explanation is that the decreasing distance between the two anatomic boundaries favors the anchoring of a wave to both of them. We further validated these mechanisms by investigating the impact of decreasing tissue area (to 110x110 cells and
100x100 cells) on the values of $p_C$ and $p_T$. For a fixed lesion size, both values increased as tissue area (and therefore distance between boundaries) decreased.

5.5.3 Impact of Small Lesions on Time to Termination

The impact of small lesions in the second regime, where conversion rate is maximized and average episode duration minimized, on the average time to conversion is intuitive. One would expect that lesions optimized for anchoring and conversion would do so in a short period of time (as they do; figure 5.1). It is counterintuitive, however, that these lesions provide the same benefit to the average time to termination. We wondered if there was a pro-termination mechanism incurred from such lesions, yet were unable to identify one. We tracked the number of phase singularities over time and found that both the mean number and the mean frequency with which the number changed were identical both before and after lesions were applied. The absence of mechanism is actually pointed to by the constant probability of terminating at each time step in this regime ($p_T$ is unchanged by lesions with 0-5 unit radii; figure 5.6).

The sharp decrease in time to termination is in fact a statistical phenomenon. The average duration of MWR, regardless of end condition, is determined by the total probability of either converting or terminating at each interval (equation 5.4). The expected lifetime of MWR is therefore a function of $p_M$ and is independent of the relative values of $p_C$ and $p_T$ (equation 5.1). The sharp increase in $p_C$ caused by pro-anchoring lesions thus causes all episodes to decreases drastically in lifetime. The fact that $p_C$ has increased rather than $p_T$ simply manifests as a higher overall conversion rate. In concrete
terms, the average time to termination decreases because more episodes convert (rather than perpetuate) at earlier time steps, leaving fewer episodes to terminate at later time steps. The net effect is that the increase in $p_c$ brings episodes from the termination pool to the conversion pool, but does so preferentially for longer lasting episodes.

5.5.4 Clinical Implications

The rates of conversion to tachycardia measured here are surprisingly high; >40% in all four tissues with lesions larger than 2 or 3 units in radius (figure 5.1). These suggest that AF driven by MWR should seldom be encountered in clinical practice and that atrial tachycardia can be preceded by a period of fibrillation. Interestingly, the latter has been observed clinically in the onset of atrial flutter. However, the occurrence of AF still exceeds that of any other atrial arrhythmia. But, AF is not a singular phenomenon. There is compelling evidence supporting the implication of focal sources, stable rotors, and MWR. The results of this study only apply to the latter. Furthermore, human atria differ in geometry and topology from the tissues studied here: they are globular and punctuated by multiple obstacles of various sizes. Nevertheless, for those cases driven by true MWR the principles elucidated here still apply; anatomic obstacles with a path length longer than the local WL of excitation will promote conversion. However, the persistent activity of ectopic beats believed to trigger most AF may also contribute to the destabilization of established tachycardia. This would suggest some occurrence of alternations between tachycardia and fibrillation, as have also been observed clinically on Holter monitor recordings.
The results of this study further support the importance of converting the topology of the atria to that of an uninterrupted plane in order to prevent conversion of MWR to stable tachycardia. Interestingly, our results demonstrate that the anti-arrhythmic benefit of this topological alteration exceeds the pro-tachycardic effect of large obstacles (figure 5.8). In other words, the additional line promotes termination in a shorter timeframe than large obstacles can convert chaotic reentry to structural reentry (figure 5.7). The exception to this observation is the case where lesions are similar in scale to the WL of excitation. However, in such cases the importance of linear ablation for preventing tachycardia is maximized (figure 5.1). In agreement with these results, studies have demonstrated a higher recurrence of atrial tachycardia after focal ablation relative to linear ablation. It is surprising that the differences reported in these studies are not larger. However, CFAE ablation is likely affecting other arrhythmogenic factors as well such as ganglionated plexi, focal triggers, or regions of highly diseased tissue.

5.5.5 Conclusions

Focal lesions or obstacles are capable of promoting both the conversion of MWR to structural reentrant tachycardia as well as its termination. The ability of smaller lesions to promote conversion through anchoring is sensitively dependent on the relationship between the lesion’s size and the WL of excitation in the tissue. MWR protects itself against conversion by detaching anchored waves with slower cycle lengths. Larger obstacles can promote termination by removing mass from the tissue, yet they can also promote conversion to tachycardia likely by creating narrower circuits. Finally, while the presence of floating structural obstacles does not guarantee it, preventing conversion of
MWR to tachycardia cannot be guaranteed unless the topology of the tissue is that of an uninterrupted plane.
AF is distinct from other atrial tachycardias because it is chaotic in nature. It is characterized by disorganized activation of the atrial myocardium coupled with an irregular and frequently rapid heartbeat. In many cases AF is paroxysmal, caused by ectopic activations arising in and around the pulmonary veins. These can be successfully treated by electrical isolation of the pulmonary veins (via catheter ablation). Thus paroxysmal AF is a disease initiated intermittently by an instigator, which if removed could restore “health”.

In more advanced cases AF episodes last indefinitely (in the absence of external intervention). In such cases AF is rarely eliminated by pulmonary vein isolation alone; removal of initiators is insufficient for cure, the ability of the atria to maintain ongoing AF must be altered as well. There is compelling evidence that in many patients advanced AF is sustained by complex reentry, in which multiple waves of excitation continuously propagate in dynamic functionally defined circuits. It is plausible that functional reentry occurs as a result of dynamic entrainment, in which case there are two possible courses of treatment. The first, cardioversion, entails delivery of high current to the heart to push it out of the AF attractor. In this case the system remains capable of AF and can become entrapped again. The second is to alter the substrate such that reentry is no longer a supported behavior (i.e. with antiarrhythmic medications or catheter ablation).

Targeted ablation holds great promise for drastically improving the way we treat chronic AF in the near future. Recent improvements in catheter technology and ablation
techniques have already made great strides towards reducing overall AF burden. It remains unclear, however, exactly how to treat chronic AF. There is still a debate over the anti-arrhythmic mechanisms proposed to underlie some of the emerging methodologies\textsuperscript{31,51}. As a case in point, clinical evidence thus far shows a beneficial impact of focal lesions delivered by RFA, especially in addition to conventional box lesion sets\textsuperscript{70,76}. Yet, focal lesions caused by fibrosis or myocardial infarct create pro-arrhythmic substrates for tachycardia as these can act as anchor points for meandering spiral wave cores\textsuperscript{167}. We demonstrated here that focal obstacles, such as those created by small lesions, can have a variable impact on complex, MWR, in some cases inducing the conversion to AT and in other cases merely acting as passive anchoring sites. We also showed that sufficiently small lesions have no interaction with MWR. It is thus plausible that sufficiently small lesions, such as those created by spot ablation, may be able to de-enervate the myocardium without creating a suitable obstacle to sustain stable rotation and thus leading to AT. This offers support to the beneficial impact of CFAE ablation, provided CFAEs do in fact correlate with nervous endings. On the other hand, the premise of focal impulse rotor modulation (FIRM)\textsuperscript{168} ablation is to treat stable (spatially fixed) rotors with spot ablation delivered to their centers. The efficacy of this method remains confusing as stable rotors have been shown to become anchored to fixed obstacles; and in the absence of MWR, they are likely to remain anchored to these obstacles. One possible explanation for the reported success of FIRM is that these rotors cores become anchored in regions of low APD which can occur at input sites of the autonomic nervous system where acetylcholine has been shown to decrease WL\textsuperscript{169}. In
this case, spot ablation at their core is in fact de-enervating the tissue and decreasing its overall capacity to sustain fibrillation. In such a case, the identification of rotors cores is then a surrogate for identifying driver regions of the substrate, similar to CFAE targeting. This, however, is merely speculation.

The notion that MWR underlies at least a subset of advanced AF is well supported\textsuperscript{16,18,170}. In this manuscript, we chose to model MWR in a computational environment in order to study features which cannot be addressed in animals or tissue preparations. One caveat to this approach is that validating a model of MWR is extremely challenging. The primary difficulty arises from the fact that MWR is a somewhat nebulous description. It is simply defined as multiple meandering wavelets. One can be more specific in providing an average number of wavelets, for example Moe reported more than 15 in his computer model\textsuperscript{27} while Allessie reported only a handful in his human mapping studies\textsuperscript{18}. Yet these numbers still make no specification about the dynamics of the process. MWR is a subset of behavior in the category of functionally defined reentry. It is part of a continuum starting from many spatially-fixed spiral waves, which result in multiple wavelets, and extending to many meandering spiral wave tips, which appear and disappear as waves collide and break. Part of the modeling process is thus identifying regions of parameter space in which a suitable (and visually validated) behavior emerges, but validating the model against physiologic behavior is currently infeasible.

Many models have been used to study reentry in the context of AF, e.g.\textsuperscript{48,82,171}. Most of these models use differential equations to model ion currents. These give rise to action potentials, and which are therefore an \textit{emergent phenomenon} in these cases. MWR
is also an emergent feature; one that is dependent on the behavior of individual cells and their ability to perform action potentials. In the context of studying drag actions on the capacity of a tissue to sustain fibrillation, this approach makes complete sense since drugs typically interact with specific ion channels\textsuperscript{93}. However, in the context of studying the role of structural features such as tissue topology or geometry (as affected by ablation lesions), this approach seems overpowered. A simplified model which implements action potentials directly (including restitution and source-sink influences) can also give rise to MWR as demonstrated by the model described herein. This (small) sacrifice of insight into microscopic factors not only yields a tremendous benefit in computation time but also sheds light onto the general properties responsible for the perpetuation of MWR, such as WL and CV in relation to tissue size and topology.
7 CONTRIBUTIONS

- A computational model for simulating realistic cardiac propagation in near real-time, permitting statistical studies of the relationship between tissue parameters and behavior.
- Insight into the regimes of behavior of a hybrid diffusion-cellular automaton model for propagation.
- A mesh segmentation technique that minimizes propagation artifacts at the macroscopic level (directional conduction-velocity bias) resulting from microscopic mesh structure in a cellular automaton model.
- A novel wave-front tracking and analysis method to automatically identify critical events and reentrant pathways during chaotic MWR.
- Insight into the relationship between tissue pathology and the manifestation of multistability and hence the possibility for dynamic entrapment in a nonlinear dynamic biologic network.
- Elucidation of the impact of focal obstacles on the dynamics of MWR; more specifically, of the interaction between anchored wavefronts (similar to atrial tachycardia) and chaotic reentry (potentially underlying AF).
8 FUTURE WORK

8.1 Model Improvements

In the current model formulation, the refractory period is intimately linked to the APD. It is only once the cell potential decreases below the threshold for excitation that the cell may be activated again. While this is generally true in cardiac cells, it is possible for the refractory period to become significantly shorter than the APD and give rise to early after depolarization which can be pro-arrhythmic. This is, for example, a common side-effect of certain chemicals that were classically used to initiate AF in animal studies, e.g. \textsuperscript{131}. This can be incorporated into the model in a number of ways. One possibility is to use two voltage thresholds; one for activation and the other for refractoriness. Another possibility is to have a refractoriness time which is distinct entirely from the APD and the voltage profile.

8.2 Characterizing Multi-Wavelet Reentry with the Wave Tree

The wave tree algorithm described herein is presented in a proof-of-concept manner. It has the capacity to not only automate the process of identifying key events in the dynamic process of MWR, but to quantify their frequencies and distributions. This allows the wave tree to calculate metrics which may serve to describe, for instance, the “complexity” or severity of an episode of MWR, which presumably bears a strong relationship with the substrate. It would be an interesting development to link the frequency of, for example, wave-break with the average lifetime of MWR. One could
also test the effectiveness of lesion sets against the spatial distribution of wave-breaks or spontaneous wave formation.

8.3 Investigating the Impact of Tissue Heterogeneity on the Relationship between Multi-Wavelet Reentry and Isolated Obstacles

While the relationship between focal obstacles and MWR has been elucidated here, a number of interesting questions remain. These series of studies may be extended to include multiple obstacles of various sizes to see how wave anchoring is either inhibited or promoted based on their relative or absolute sizes. Another interesting avenue for development is to investigate how regional heterogeneity affects the ability of MWR to interact with an anchored wave. For example, one might ask whether a wave anchored to an obstacle in a region of higher WL is protected from detachment by MWR (by one of the mechanisms demonstrated here) if the MWR is sustained in a region of shorter WL.

8.4 Experimental Validation

Assessing the impact of island obstacles on the dynamics of MWR is difficult to assess in vitro as the time required to perform sufficient experiments to be statistically confident is unrealistic. However, a wealth of data is readily available regarding the cycle lengths of intermittent organized activity during chronic AF. A prospective clinical study can be performed to calculate the mean duration of these episodes as a function of their cycle lengths (as a surrogate for obstacle size) to see if the same multi-phasic trend appears.
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Teaching Experience

Graduate Teaching Fellow, Boston University, Boston, MA

Introduction to Probability
Fall 2011

Introduction to Solid Biomechanics
Spring 2013

Professional Work Experience

Visible Electrophysiology LLC
Feb 2013 – Feb 2015

Chief Technology Officer

Raymark Xpert Business Systems Inc.
May 2009 – Nov 2009

Software Developer

Genizon Biosciences Inc.
May 2008 – Nov 2008

Data Analyst and Programmer

Publications


Presentations


Honors and Awards

Doctoral Postgraduate Scholarship, National Sciences and Engineering Research Council of Canada (2012)

Distinguished Fellowship in Biomedical Engineering, Boston University (2010)

Master’s Postgraduate Scholarship, National Sciences and Engineering Research Council of Canada (2010)

Electronics Inc. Scholarship, McGill University (2009)

Erim Kubmaracibasi Award, McGill University (2008)

Faculty of Engineering Award, McGill University (2007)

Undergraduate Student Research Award, NSERC (2007)

Certificate of Merit, McGill University (2006)