THE STOCHASTIC NATURE OF CARDIAC ELECTRICAL INSTABILITY: THEORY AND EXPERIMENT

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Abstract

Non-uniformity of cellular excitability is hypothesized to be the substrate underlying many cardiac
rhythm disturbances. We present herein a qualitative review of this concept and provide a
quantitative, stochastic model for testing its implications. Drawing on results from computer
simulations on finite-element models and semi-analytic approaches based on percolation theory, we
demonstrate that many disparate clinical observations regarding re-entrant dysrhythmias
(ventricular tachycardia and ventricular fibrillation), intra-cardiac conduction delays, fixed ratio
blocks, as well as the Wenkebach phenomenon may be linked under this one unifying conceptual
framework. We further show that a wide variety of experimental observations regarding tissue-level
cardiac electrophysiology also follow from this same stochastic model of cardiac conduction. We go
on to demonstrate that, in addition to providing a parsimonious conceptual framework for
contemplating cardiac conduction abnormalities, the model makes an important prediction of a
subtle alternation in electrocardiographic (ECG) morphology which would serve as an indicator of
decreased cardiac electrical stability (increased tendency to develop malignant re-entrant rhythm
disturbances). Due to the enormous potential value of a non-invasive marker for decreased cardiac
electrical stability, and in an attempt to test a novel model prediction, we conducted a series of
animal experiments to determine whether such alternation occurs in vivo, and whether its occurrence
signals episodes of decreased electrical stability. Canine preparations of coronary artery occlusion,
hypothermia, and rapid atrial pacing were examined for alternating ECG morphology, with cardiac
electrical stability being measured via an objective, invasive technique (ventricular fibrillation
threshold determination). The results of these studies demonstrate that alternation in ECG
morphology does occur in vivo and that regardless of intervention, the degree of alternating activity
present in the electrocardiogram is correlated with objective measures of cardiac electrical stability.
Lastly, we undertook a clinical trial to determine whether patients thought to be at increased risk of
Sudden Cardiac Death from ventricular fibrillation could be identified on the basis of this
electrocardiographic measure. Preliminary results suggest that the presence of alternating ECG
morphology may provide a useful discriminant for isolating the population at increased risk.

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Chapter 1

Introduction

Sudden Cardiac Death (SCD), defined as death resulting from cardiac cause within 24 hours of onset of symptoms, has been referred to as the most challenging problem facing contemporary cardiology (Lown, 1979). Most sudden deaths are unexpected, unheralded by symptoms of any duration or by overt coronary artery disease (Kannel and Thomas, 1982). In this country alone SCD typically claims between 400,000 and 500,000 lives each year, and represents the major cause of death for men between the ages of 20 and 64 (Lown and Graboys, 1977; Horowitz and Morganroth, 1982).

It is thought that the mechanism responsible for the great majority of sudden cardiac deaths is ventricular fibrillation, a state in which the normally organized electrical activity of the heart becomes disorganized and apparently chaotic. This disorganized electrical activity initiates similarly disorganized and ineffectual mechanical contraction of the pumping chambers of the heart resulting in circulatory collapse and death.

Treatment is usually a viable option only for in-hospital episodes, perhaps with the exception of rapid response teams trained in emergency medical procedures. In the overwhelming majority of out-of-hospital episodes, death ensues before effective therapy can be begun. By far the more desirable and potentially the more effective response to this problem is prevention, in which the first step would necessarily be the identification of those individuals at increased risk.
Contemporary Identification Techniques

In that SCD is often the first presenting symptom of severe cardiac disease, identification of those at risk is understandably a difficult problem. In those individuals with some prior cardiac symptomatology, the problem is only marginally less difficult in that a great percentage of the adult population suffers from some cardiac ailment, yet relatively few of these individuals die suddenly. Despite these obvious difficulties, contemporary medical practice has made some inroads.

By appealing to epidemiology, it has been possible to determine statistical correlations between incidence and severity of atherosclerotic coronary heart disease (ASCHD) and various environmental and behavioral factors. Via multivariate analysis, these correlations can be reduced to a list of risk factors, and by comparing an individual’s behavioral traits, diet, level of activity, past medical history, family medical history, etc., to a global set of risk factors, an assessment can be made as to the relative likelihood of an individual having significant ASCHD. Unfortunately, the risk factors for enhanced susceptibility to ASCHD do not singly or in combination identify a subset of patients prone to SCD (Lown, 1979; Kannel. et. al., 1975; Doyle, et. al., 1976). Those individuals who are eventually to die from SCD do not appear to be neatly separated from the rest of the population with ASCHD in terms of obvious demographic characteristics.

In the hope of gaining specificity and sensitivity, attempts have been made to directly or indirectly assess the “cardiac status” of a given individual. Electrocardiographic, echocardiographic, hemodynamic factors, and infrequently radiographic information are combined to arrive at a determination of an individual’s cardiac health. The most recent and potentially most accurate procedure for assessing an individual’s risk for SCD is electrophysiologic (EP) testing. In this procedure, a patient is subjected to provocative testing to determine
whether or not his or her heart can be made to lapse into life threatening rhythm disturbances. This testing modality can then quantitatively determine the ease with which an individual can be made to evidence malignant cardiac dysrhythmias. The non-invasive or minimally-invasive techniques (hemodynamic studies, X-ray, electrocardiography, and echocardiography), while questionably feasible as screening techniques, are ineffective in accurately distinguishing the population at increased risk. Advanced-grade ectopy on 24-hour holter monitoring, left-ventricular ejection fraction less than 40%, left-ventricular end-diastolic pressures greater than 19 mm Hg, and other similar factors have been shown to correlate with increased susceptibility to SCD, but as yet no set of criteria has been shown to isolate the at-risk group with enough accuracy to allow for effective screening (Lown, 1979; Ruberman, et. al., 1976; Schulze, et. al., 1977). Electrophysiologic testing, while potentially more effective, will remain unacceptable as a general screening procedure due to the associated high cost and potential morbidity/mortality.

**Prophylaxis**

Once those at increased risk are identified, they can be medicated with any of a host of anti-arrhythmic drugs. While it has yet to be confirmed that SCD can be totally averted via anti-arrhythmic therapy, preliminary studies have shown that in certain patient populations, anti-arrhythmic therapy significantly reduces the incidence of SCD (McGovern et. al., 1983; DiMarco, et. al., 1980). As mechanisms of dysrhythmogenesis become better understood, and as more powerful and specific anti-arrhythmic drugs become available, the likelihood of finding an effective schema for prevention of SCD increases.

**Medical engineering - A different viewpoint**

Medical engineering has offered a different vantage point from which to view the problem of SCD. By modeling the salient features of cardiac conduction
processes, we have been able to study the mechanisms of dysrhythmogenesis which are thought to be responsible for SCD. The results of computer simulations and analytical treatments based on percolation theoretic concepts have suggested that one underlying feature of diseased myocardium may be responsible for an extremely wide variety of observations regarding tissue-level and organ-level cardiac electrophysiology including SCD, and that this pathology would display tell-tale signs of its presence even before frank rhythm disturbances are in evidence. Predictions made by this parsimonious model have been tested in animal preparations and in an initial clinical trial wherein quantitative determination of cardiac electrical stability was possible using provocative, invasive measures. The results of these studies have demonstrated the existence of an electrocardiographic marker of decreased stability.
Chapter 2

Background

2.1 Anatomy and Electrophysiology

Microscopically, the heart is composed of a complicated network of striated muscle fibers (see Figure 2-1). The fiber network is not a true syncytium as once thought, but is instead made up of millions of separate cellular subunits joined at surface specializations known as intercalated discs. The average fiber is 100 - 150 microns long with a diameter of approximately 15 microns. These cells are not simple cylinders, but often bifurcate to connect with adjacent fibers. The intercalated discs do provide a low resistance electrical connection between cells, and therefore cardiac muscle fibers have been traditionally viewed as constituting an \textit{electrical syncytium}. Recent evidence suggests, however, that this may represent an oversimplification (Spach and Kootsey, 1983; Spach, et. al., 1981). It is now recognized that conduction may be discontinuous or \textit{saltatory} in nature, with active regions jumping from one intercalated disc to the next (Spach in de Carvalho et. al., 1982).

Each cell has four properties of special interest to this discussion, features which are shared by almost all excitable tissue: (1) a resting transmembrane potential, (2) an action potential, (3) an intrinsic velocity for the spread of activation along the length of the cell, and (4) a refractory period.
2.1.1 Resting Potential

The typical myocardial cell has a resting transmembrane potential of approximately -90 millivolts (inside negative). This transmembrane potential results from differences in the membrane permeabilities to the various ionic species and the differences in the concentrations of the charged species on either side of the membrane. A quantitative description of the resting transmembrane potential can be had by considering a one-dimensional development, wherein the cellular membrane is assumed to be uniform, homogeneous, semipermeable, and uncharged. The details of this development are provided in Smith, J. M. (1982).

2.1.2 Action Potentials

The cardiac action potential represents the highly reproducible time course of the transmembrane potential of the typical myocardial cell once it has been
depolarized to threshold (see Figure 2-2). The mechanisms responsible for
generating the precise form of the cardiac action potential remain incompletely
known, however, the basic mechanisms are thought to be similar to those of nerve
action potentials. That is, the major determinants are thought to be time and
voltage dependent changes of the membrane permeabilities to the various ionic
species. One major difference is that for cardiac cells, in addition to the sodium,
potassium, and chloride ions which play a role in nerve action potentials, the
calcium ion also plays an important role. It is the action of calcium which is
believed largely responsible for the unique long plateau of the cardiac action
potential. The duration of the cardiac action potential is typically 200 msecs as
opposed to 2 msecs for nerve action potentials.

Figure 2-2: Representation of typical action potential
of ventricular myocardial cell. FRP = functional refractory
period, ARP = absolute refractory period, RRP = relative
refractory period.
It is important to distinguish at least two different types of cardiac action potentials: "sodium dependent" action potentials and "calcium dependent" action potentials. It has been established that the initial rapid upstroke of the prototypical cardiac action potential results from the opening of the membrane sodium channels, while the subsequent plateau phase is largely a result of calcium ion flux. Action potentials which have the sodium-dependent rapid initial upstroke are said to be sodium-dependent action potentials. Those action potentials which lack this rapid initial upstroke are referred to as calcium-dependent in that their initial upstroke (as well as the plateau) is caused by calcium ion flux.

2.1.3 Conduction of the Action Potential

The cardiac action potential is propagated along the length of a cardiac cell at a velocity related to cell dimension, cytoplasmic resistance, membrane capacitance, action potential upstroke velocity, etc. Conduction velocities range from 0.02 m/sec in A-V nodal tissue to 0.5 - 1 m/sec in ventricular muscle to 2 - 4 m/sec in the specialized His-Purkinje ventricular cardiac conduction system (Katz, 1977). A theoretical treatment relating conduction velocity to cellular parameters is given in Smith, J. M. (1982).

It is important to note here that the velocity with which an action potential is propagated is a function of the type of action potential. The calcium dependent action potential is conducted more slowly than its sodium dependent counterpart. This slower conduction velocity has been attributed to the decreased upstroke velocity of the calcium dependent action potential.
2.1.4 Refractory Period

Myocardial cells experience a refractory period, i.e., a period of time immediately following electrical activation during which the cells are refractory to re-excitation. In particular, once a cell has been excited, a requisite time must elapse before that cell will again be able to respond to normal amplitude stimulation. This period of time is referred to as the functional refractory period (FRP). This FRP can be divided into an absolute refractory period (ARP) during which no stimulus, regardless of amplitude, can excite the cell, and a relative refractory period (RRP) during which the cell can be re-excited, but only by a stimulus greater than that which it would normally experience (see Figure 2-2). Action potentials elicited during the RRP are often calcium dependent action potentials.

2.2 Normal Spread of Depolarization

The precise timing of the contraction of the chambers of the heart is mediated by the time course of the spread of the depolarization wave throughout the cardiac structures (see Figures 2-3 and 2-4). Normally, cardiac activation is initiated in the sino-atrial node which contains “automatic” cells which spontaneously depolarize to reach threshold and initiate an action potential. This action potential spreads to depolarize the atria with the question of some preferential conduction along the paths of the internodal tracts toward the atrioventricular (A-V) node. The atria are electrically isolated from the ventricles except for the connection at the A-V node. Conduction velocities in the A-V node are relatively slow, on the order of 0.02 m/sec. The 0.1 sec delay caused by transmission through the A-V node provides for adequate delay between contraction of the atria and that of the ventricles. This delay allows the atria to serve as physiologic “booster pumps” by augmenting the
Figure 2-3: The four chambered mammalian heart. The normal spread of electrical activation begins in the sino-atrial node, spreads across the atra to the atrioventricular node, then through the His-Purkinje system to the terminal ramifications in the left and right ventricles.

passive filling of the ventricles. On emerging from the A-V junction, the wave of excitation continues its spread through the ventricular myocardium. While the bulk of the ventricular myocardium does itself conduct the depolarization wavefront, there exists a specialized cardiac conduction system (His-Purkinje) which serves to rapidly conduct and distribute the wavefront of depolarization throughout both ventricles. This scheme for rapidly transmitting the depolarization wavefront serves to spatially synchronize the activation of the ventricles so that mechanical contraction will be coordinated for the effective ejection of blood.
2.3 The Electrocardiogram

The series of electrical events outlined above can be tracked at the body surface by monitoring the surface potentials which are caused by the flow of ionic currents within the cardiac structures. The recording of such body surface potentials is known as electrocardiography, with a single recording of the potential difference between two points on the body surface being referred to as an electrocardiogram. A theoretical basis for the relationship between body surface potentials and myocardial transmembrane potentials is given in Smith, J. M. (1982).
The Normal Electrocardiogram

The normal electrocardiogram consists of a P wave, a QRS complex, a T wave, and an infrequent U wave (see Figure 2-5). The P wave, temporally the first component of the ECG, is a result of

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**Figure 2-5:** Schematized ECG tracing. The P-wave is the result of atrial depolarization, the QRS complex is the result of ventricular depolarization, and the T-wave is the result of ventricular repolarization. The infrequently seen U-wave is thought to result from repolarization of the His-Purkinje system.
atrial depolarization. The QRS complex, which follows the P wave after a delay of approximately 150 msecs (A-V nodal delay) is the result of ventricular depolarization. The T wave which follows the QRS complex by a variable period of time is the result of ventricular repolarization. The repolarization of the atria are not in evidence in the surface ECG partly because the mass of the atria is relatively small, and as such the potentials generated at the body surface would be small, but more because the time course of atrial repolarization coincides with ventricular depolarization. The infrequently seen U wave is thought to be the result of the repolarization of the His-Purkinje system, and it follows the T wave by roughly 25 msecs because the action potential duration of the Purkinje cells is approximately 25 msecs longer than that of ordinary myocardial cells (Katz, 1977).

The greatest value of the ECG rests in its ability to convey information about the electrical abnormalities which accompany many cardiac pathologies. While the discussion of the interpretation of the ECG is best left to more thorough treatments (Phillips, 1980), a few rhythm disturbances will be reviewed to aid in further discussion.

2.4 Dysrhythmias

We now briefly discuss a few of the most commonly observed cardiac rhythm disturbances and conduction abnormalities. We will first describe the conduction abnormalities associated with A-V nodal conduction and then we will describe the most common ventricular rhythm disturbances.

2.4.1 Atrioventricular Nodal Conduction Abnormalities

As discussed above, the atrioventricular (A-V) node is normally the sole conductive pathway between the atria and the ventricles. The physiologic delay in
impulse propagation experienced in the node allows for atrial contraction to precede ventricular contraction; a necessity if atrial contraction is to augment ventricular filling. Because the A-V node plays such an important role in the propagation of the cardiac impulse, abnormalities in nodal conduction are of significant clinical importance. We will briefly discuss the major types of conduction abnormalities associated with conduction through the A-V node.

**Figure 2-6:** ECG tracing showing normal sinus rhythm.

2.4.1.1 Conduction Delay (First Degree Block)

As mentioned above, the conduction delay normally associated with transmission through the A-V node is approximately 0.1 sec. In some pathologic states, conduction through the node can be significantly slower. In the surface electrocardiogram, this prolonged delay in the A-V node is evidenced by a longer than normal P-R interval (normal being between 0.1 and 0.2 sec). An example of slowed conduction, or first degree block as it is sometimes called, is given in Figure 2-7. Compare to Figure 2-6, where the A-V conduction time is normal (∼0.1 sec).
Figure 2-7: ECG tracing during first degree heart block. Note the prolonged P-Q interval as compared to Figure 2-6.

2.4.1.2 Wenckebach Phenomenon (Mobitz type I)

Conduction through the A-V node is not always the same for each beat. In Wenckebach conduction, the time it takes for an impulse to propagate through the node is variable, depending on recent past history. One example of Wenckebach conduction is illustrated in Figure 2-8. On the first beat, conduction through the node is grossly normal, with the associated P-R interval being approximately 200 msecs. The second atrial impulse is propagated much slower through the node, resulting in a P-P interval of approximately 300 msecs. The third and fourth atrial impulses meet with increasing delay, until finally the fifth atrial impulse fails to successfully traverse the node. With the next atrial impulse, the process starts again. The strip as shown represents 5:4 Wenckebach block (5 atrial impulses to 4 ventricular impulses), but a variety of ratios are possible.
Figure 2-8: The Wenckebach phenomenon. P-R intervals gradually lengthen until finally conduction is blocked through the A-V node.

2.4.1.3 Fixed Ratio Conduction Block (Mobitz type II)

Perhaps closely related to the Wenckebach conduction just discussed is another conduction abnormality in which not every atrial impulse leads to a ventricular impulse. In fixed ratio conduction block (Mobitz type II), a fixed fraction of atrial impulses propagate through the node. The major difference between Mobitz II and Mobitz I block is that in Mobitz II, the block is thought to occur below the A-V node, in the initial segments of the specialized cardiac conduction system. In Mobitz II, impulses that successfully propagate through to the ventricles do so without abnormal conduction delay. An example of 2:1 block is given in Figure 2-9.

2.4.1.4 Complete Heart Block

Heart block is said to occur when no transmission occurs through the A-V node. Atrial impulses are initiated at a normal rate, but none are successful in traversing the node. Ventricular activation is accomplished by pacemakers within
Figure 2-9: **2:1 fixed-ratio heart block.** Every other atrial depolarization is blocked in its attempt to traverse the A-V node.

The A-V node or the ventricles, and as such, the timing of atrial and ventricular contractions are dissociated (see Figure 2-10). The net effect is a decreased rate of ventricular contractions, (due to the lower intrinsic rate of nodal or ventricular pacemakers) with a decreased or normal cardiac output.

Figure 2-10: **Complete heart block.** Atrial activation is blocked in its attempt to traverse the A-V node.
2.4.1.5 Bypass Tract Conduction

While not vital for future discussion, it would be remiss not to mention the existence of bypass tract conduction as an abnormality of A-V nodal conduction. Bypass tracts are anatomical structures which provide a second conductive pathway between the atria and the ventricles. The bypass tracts most often have conduction velocities which are much greater than that of the A-V node, and hence "short-circuit" the node. Bypass tracts allow for "pre-excitation" of the ventricles. The clinical significance of bypass tracts rests not with their ability to defeat the physiologic delay normally required for the atria to empty their contents into the ventricles, but instead with their propensity to serve as one arm of a re-entrant loop. Re-entry will be discussed in detail in section 2.5.2.

2.4.2 Ventricular Dysrhythmias

A-V nodal conduction abnormalities are important because the A-V node serves to both conduct and delay the atrial impulse. By and large, however, these abnormalities are associated with relatively minor morbidity. Ventricular dysrhythmias, on the other hand, have far more malignant potential, with ventricular fibrillation and some rapid ventricular tachycardias resulting in circulatory collapse and death.

2.4.2.1 Premature Ventricular Depolarizations

A premature ventricular depolarization (PVD) occurs when ventricular activation is initiated at a site within the ventricles and not as a result of the normal chain of cardiac activation initiated in the SA node. Since the activation is not distributed via the rapidly conducting His-Purkinje system, but rather more slowly through the bulk of the ventricular myocardium itself, the PVD appears as a broader than normal ventricular complex in the electrocardiogram (see Figure 2-11).
Figure 2-11: Premature ventricular depolarizations (PVD's). Note that the complexes of ventricular origin are wider than sinus-conducted complexes.

Isolated PVD's are relatively common, and are thought to be of little diagnostic importance. PVD's which occur closely coupled to the preceding depolarization (early PVD's or "R-on-T" phenomenon) have been thought to have malignant potential in terms of the likelihood of initiating more severe rhythm disturbances (although this idea has been recently questioned) (El-Sherif, et. al., 1976; Engel, et. al., 1978; Swerdlow, et. al., 1983). Frequent successive PVD's, and PVD's originating from multiple sites are also believed to be harbingers of more severe rhythm disturbances (Lown and Grayboys, 1977; Lown, 1979).

2.4.2.2 Ventricular Tachycardia

Ventricular tachycardia consists of repetitive spontaneous ventricular depolarizations at a rate between 100 and 300 beats per minute (see Figure 2-12). Rates above 250 beats per minute usually result in diminished cardiac output, and in some patients, failure to generate sufficient cardiac output to maintain life. As such, ventricular tachycardia is associated with increased morbidity and mortality. Ventricular tachycardia also frequently degenerates to ventricular fibrillation (Josephson, 1982).
2.4.2.3 Ventricular Fibrillation

Ventricular fibrillation is the ventricular dysrhythmia thought to be responsible for the great majority of sudden cardiac deaths. In ventricular fibrillation, while the individual cardiac cells may be undergoing nearly periodic activation and recovery, the activity is not correlated over large segments of the myocardium. As such, fibrillation is characterized by asynchronous, apparently chaotic, electrical activity resulting in disorganized and ineffectual contractions leading to negligible cardiac output, circulatory collapse, and death. The ECG during ventricular fibrillation reflects the complicated, self-sustained electrical activity within the heart (see Figure 2-13).

2.5 Mechanisms of Dysrhythmias

Mechanisms of dysrhythmogenesis are presently thought to fall into two categories: (1) abnormalities in impulse formation, and (2) abnormalities of impulse conduction (Wit and Rosen, 1983; Zipes, et. al., 1983; Josephson, 1982; Hoffman and Rosen, 1981; Gadsby and Wit, 1981). The major abnormality of impulse
Figure 2-13: Ventricular fibrillation. Note the highly irregular electrical activity with loss of distinction of individual QRS complexes.

formation associated with the malignant ventricular arrhythmias is ectopic (from the Greek ektopos, meaning “out of place”) impulse formation. In this event, a wavefront of activation is initiated from a site other than the normal pacemaker locations. Ectopic impulse formation is believed responsible for the great majority of PVD's. We will digress briefly to consider the different varieties of ectopic impulse formation.

2.5.1 Disorders of Impulse Formation

2.5.1.1 Abnormal Automaticity

Normally functioning atrial and ventricular myocardial cells do not characteristically show spontaneous diastolic depolarization. If, however, the resting transmembrane potential of these cells is reduced to less than approximately -60 mV, spontaneous diastolic depolarization may occur, and may result in repetitive impulse initiation. This type of abnormal automaticity has been observed in the Purkinje fibers that survive on the subendocardial surface of canine infarcts and it has been suggested that abnormal automaticity may underlie some forms of ventricular tachycardia (Friedman, et. al., 1973; Lazzara, et. al., 1973).
Preparations of diseased human atrial and ventricular myocardium have shown similar abnormal automaticity (Hordof, et. al., 1976; Singer, et. al., 1981).

The depolarized level of transmembrane potential at which abnormal automaticity may occur has been suggested to also cause a block of impulse conduction into the abnormal focus. This would lead to parasytsole, a condition where an ectopic pacemaker discharges at its own intrinsic rate, not being reset or entrained by other pacemakers (Wit and Rosen, 1983).

2.5.1.2 Triggered Activity

Triggered activity is impulse generation caused by afterdepolarizations. An afterdepolarization is a second subthreshold depolarization that occurs either during repolarization (early afterdepolarization) or after repolarization is complete or nearly complete (delayed afterdepolarization). Under certain conditions, the afterdepolarizations can lead to a second triggered upstroke, resulting in a second action potential prior to complete repolarization of the first. The term “triggered” refers to the notion that the second action potential is initiated or triggered by the first. In the absence of the initial action potential, there would be no subsequent depolarization and hence no subsequent action potential.

Early afterdepolarizations have been observed in isolated tissue preparations subjected to hypoxia, hypercapnia, and high concentrations of catecholamines (Trautwein, et. al., 1954; Coraboeuf, et. al., 1953; Brooks, et. al., 1955). It has been conjectured that because these same conditions are known to result from myocardial ischemia and infarction, triggered activity resultant from early afterdepolarizations may cause some of the in vivo dysrhythmias that occur soon after myocardial ischemia (Wit and Rosen, 1983).

Delayed depolarizations are transient or oscillatory depolarizations that occur
after repolarization. As with early afterdepolarizations, delayed depolarizations can be subthreshold, or they can be large enough to bring the transmembrane potential to threshold, giving rise to a triggered action potential. Delayed afterdepolarizations have been shown to occur in a variety of isolated tissue preparations with elevated intracellular calcium ion concentrations (Kass, et. al., 1978). Toxic amount of cardiac glycosides is one of the most widely recognized causes of delayed afterdepolarizations. By inhibiting the "sodium-potassium pump", cardiac glycosides serve to increase intracellular sodium which is then exchanged with extracellular calcium, resulting in increased intracellular calcium.

In fibers showing delayed subthreshold afterdepolarization, triggered activity may result if the rate at which the fiber is driven is increased; the amplitude of the afterdepolarization increasing as the drive rate increases. Self-perpetuation of triggered activity above a certain drive rate has been observed in in vitro preparations (Wit and Cranefield, 1977).

2.5.2 Disorders of Impulse Conduction

Abnormalities of impulse conduction can take many forms. Conduction of the wave of depolarization can be blocked or delayed as it traverses a particular region of myocardium, giving rise to various macroscopic dysrhythmias. The major mechanism thought to be responsible for conduction delay across a region of myocardium is a decrease in the intrinsic conduction velocity of the cells, either as a result of metabolically induced changes in the passive electrical properties of the cells, or as a result of derangement of the availability or function of the membrane ionophores (sodium channels being most often implicated). Total conduction block is most often explained by decreased excitability of a region of tissue as a result of a severe insult (ischemia, poisoning, electrical ablation, etc).
2.5.2.1 Re-entry

One of the most interesting types of conduction disturbances, and the one believed by many to be responsible for the maintenance of the malignant tachyarrhythmias (ventricular tachycardia and ventricular fibrillation) is re-entry. During re-entry, a wavefront remains active after many of the cells in its wake have recovered. This abnormal persistence permits the impulse to re-excite, or re-enter, cells which it had excited previously. Re-entrant wavefronts are often thought of as forming loops within the tissue. Such re-entrant loops can either be self-extinguishing or self-sustaining. Unsustained re-entry is thought to be the underlying mechanism responsible for some PVD's, especially those which occur at fixed delays after a normal depolarization sequence (fixed coupling), although recent work suggests that some fixed-coupling PVD's may be the result of a parasystolic focus whose timing is electrotonically modulated by surrounding electrical activity (Anzelovitch and Moe, 1983). Sustained re-entry is the mechanism believed responsible for the tachyarrhythmias such as ventricular tachycardia and ventricular fibrillation. In the case of ventricular tachycardia, the re-entrant wavefront is thought either to traverse a loop which circulates around the bulk of the ventricular tissue (circus movement, first proposed by Mines in 1914) or, to complete itself within a small portion of the myocardium (micro-reentry) and send off confluent waves of depolarization throughout the remainder of the myocardium. In ventricular fibrillation, it is thought that there are many small re-entrant loops which migrate over the surface of the myocardium (Zipes, et. al., 1983; Hoffman and Rosen, 1981).

While it is easy to imagine how re-entry could give rise to the rhythm disturbances such as circus movement tachycardia and fibrillation, the underlying substrate required for the evolution of re-entry is far less obvious.
2.5.2.2 Dispersion of Refractoriness

The traditional explanation of re-entrant loop formation requires directional specific, or "one-way," block to conduction in some region of the myocardium (Josephson, 1982). In this model (see Figure 2-14), a wavefront of activation is blocked in its attempt to go from A to C, while successful in its passage from A to B. The wavefront then spreads from B to C. From C, the wavefront travels retrograde to A (which has recovered in the intervening time). From this point, the circuit can be retraced indefinitely by the wavefront provided no region of the path is refractory when the wavefront arrives. Should this occur, the re-entrant loop experiences a conduction block and is extinguished.

Figure 2-14: Traditional representation of re-entry
The dispersion of refractoriness hypothesis provides an alternate explanation for the generation of re-entrant dysrhythmias (Han, et. al., 1964a, 1966; Han, 1969). According to this hypothesis, a spatial dispersion in cellular refractory times leads to the appearance of evanescent islands of refractory tissue (see Figure 2-15).

Figure 2-15: Islands of refractory tissue serve to fractionate the impinging wavefronts of excitation, allowing for re-entrant wavefronts to be established.

The dispersion of refractoriness not only allows these islands to form, but insures that they will recover their excitability at varying times (see Figure 2-16). An incoming wave of depolarization which impinges upon these islands of refractory tissue will fractionate. This fractionated wavefront may then develop into re-entrant eddies circulating about the continuously shifting islands of refractoriness. The dispersion of refractoriness hypothesis provides a unifying framework from which to view a number of seemingly disparate interventions which all promote the
development of re-entrant dysrhythmias. For example, coronary artery disease, increased sympathetic nervous system activity, hypothermia, tachycardia, and ventricular ectopic activity itself - all are well known promoters of re-entrant ventricular dysrhythmias (Han, et. al., 1969; Han, et. al., 1964b,c). Coronary atherosclerosis, even in the absence of infarction, increases the spatial dispersion of refractoriness because of the spatially inhomogeneous blood supply to the
myocardium (Han, et. al., 1969). Increased sympathetic tone increases the inhomogeneity in cardiac electrical activities because of the spatially inhomogeneous density of the $\beta$-receptors (Han, et. al., 1964b). Hypothermia has been shown to increase the measured dispersion of refractory times (Han, et. al., 1964c). Tachycardia, even in the absence of increased $\beta$-sympathetic tone, predisposes to re-entry because the shorter the interval between depolarizations, the greater the fraction of cells that will be refractory when the depolarization wavefront is initiated, and therefore, the greater the number of refractory islands of tissue contributing to wavefront fractionation and re-entry (see Figure 2-17).

![Figure 2-17: Distribution of cellular refractory periods. With interstimulus interval T, those regions with refractory periods greater in excess of T will be unable to respond to every wavefront.](image)

Thus, tachycardia promotes wavefront fractionation. Ventricular ectopic activity leads to increased spatial dispersion of refractoriness because the depolarization
process is itself less well synchronized (not being conducted through the His-Purkinje system). Also, since PVD's are premature, they initiate depolarization when a greater fraction of the myocardium is refractory, thus promoting wavefront fractionation and re-entry.

The dispersion of refractoriness hypothesis also predicts the presence of a ventricular vulnerable period roughly coinciding in time with the occurrence of the T wave in the ECG (see Figure 2-18). Recovery does not occur synchronously throughout the myocardium. Thus, during the time course of ventricular recovery (coinciding in time to the evolution of the T wave) there is a dispersion of refractoriness across the ventricular myocardium. During this time of disparate excitability, the dispersion hypothesis would suggest that the ventricles would be susceptible to re-entrant rhythm disturbances.

Figure 2-18: The vulnerable period, the time during which exogeneous stimuli may initiate ventricular fibrillation.

Experimentally, it has been noted that during the vulnerable period, a current pulse of sufficient amplitude delivered to the ventricular myocardium will initiate ventricular fibrillation even in a normal heart. The amplitude of the minimum current pulse required to initiate fibrillation is taken as a measure of electrical
stability of the heart - the ventricular fibrillation threshold (Wiggers and Wegria, 1940; Han, et. al., 1969).

While the dispersion of refractoriness hypothesis provides a parsimonious explanation for re-entrant dysrhythmogenesis, a quantitative test of the hypothesis was needed. In an attempt to provide such a quantitative evaluation and gather further insight into the pathologic substrate required for re-entry to occur, a simple finite element model of ventricular myocardium, explicitly incorporating the notion of a dispersion of refractoriness, was constructed and studied (Smith and Cohen, 1984; Smith et. al., 1983).
Chapter 3

Computer Simulation Studies

The goal of the simulation studies presented here was not to closely approximate the intricate detail of cardiac electrophysiology. Rather, the goal was to test whether a dispersion of refractoriness is sufficient to account for a wide variety of re-entrant rhythm disturbances. In an attempt to isolate the effect of a dispersion of refractoriness, much of the known complexity of cardiac conduction was not included. Specifically, the modeling did not include any degree of automaticity, neither was relative refractoriness nor slow conduction analogously represented. While the methods for the simulations have been described in detail elsewhere (Smith and Cohen, 1984; Smith, et. al., 1983), they will be reviewed here for completeness.

3.1 Methods

A simple computer model of the ventricular myocardium, qualitatively similar to that of Moe, et. al. (1964), was implemented (see Figure 3-1). In these studies of ventricular dysrhythmias, a cylindrical shell model was taken to be a first order approximation to ventricular geometry. The cylinder, with a length to diameter ratio of 2, was constructed from an array of square elements of linear dimension $\xi$. Each element was randomly assigned a refractory period from a Gaussian probability density function with mean $\tilde{r}$ and standard deviation $\sigma$. Each element was taken to be conductively linked to its eight nearest neighbors, and the spread of depolarization was controlled by a simple conduction scheme wherein an element was depolarized if and only if two conditions were met; the time since its last
depolarization exceeded the element's refractory period, and one or more of its neighbors was depolarized during the previous time step. Conduction velocity was controlled by appropriate scaling of the iteration time, with one iteration per \( t \) seconds corresponding to a conduction velocity of \( \xi / t \) (mm/sec). Typical element size was on the order of a few square millimeters, and thus each element was representative of a rather macroscopic region of myocardium.

For the ventricular simulations, simulated ECG's were obtained in the following manner. First, the total electric dipole of the model array was computed by regarding each interface between depolarized and repolarized elements as a unit dipole. These individual dipoles were then summed vectorially to constitute the total electric dipole. The single lead ECG's were then obtained by projecting the total dipole onto a given lead axis. This approach is completely analogous to a simple solution of the "forward problem" of electrocardiography (Plonsey, 1969).

In simulation studies of A-V nodal dysrhythmias, the A-V node was modeled as a rectangular array of elements, with all other aspects of the simulation studies being analogous to that presented for the ventricular model. Conduction across the
array was begun by stimulation of three equidistant sites on one edge of the rectangular array. Conduction was said to have traversed the array when the wavefront of activation first contacted the opposite edge. Typical array size was $32 \times 64$ elements, and thus the linear dimension of a model element corresponded to much less than 1 mm. of actual nodal dimension.

3.2 Results

Results of simulation studies on the model of ventricular myocardium described above have shown that such a model successfully simulates a variety of rhythm disturbances which are similar to those rhythm disturbances seen clinically (see Figure 3-2).

![ECG tracings](image)

**Figure 3-2:** Simulated ECG's constructed from dipole projection of cylindrical finite element model.

A detailed analysis has shown that the occurrence and type of such rhythm disturbances is dependent on the values of model parameters (conduction velocity,
mean refractory period, and standard deviation of refractory period or dispersion of refractoriness) (Smith, 1982).

Simulation studies on the model of the A-V node evidenced behavior which is analogous to commonly seen A-V nodal conduction abnormalities including first degree block (conduction delay), alternating delay, and Wenckebach block (see Figure 3-3). The different types of conduction abnormalities were found to be localized to particular regions of the parameter space \((\sigma, \bar{r}, T)\) (see Figure 3-4).

3.3 Discussion of Simulation Results

Several points should be noted. First, the model behavior as depicted in the simulated ECG's gives evidence that a wide variety of clinically observed rhythm disturbances can be analogously represented by re-entrant activity. Second, the major tenet of the dispersion of refractoriness hypothesis, namely that a dispersion of refractoriness is sufficient to cause rhythm disturbances of re-entrant origin, has been verified in terms of model performance. We have also demonstrated that A-V nodal dysrhythmias can be analogously represented by a model including no more than a dispersion of refractoriness. This finding suggests that one mechanism may underlie a great many of the different cardiac rhythm disturbances, and that one need not invoke non-linear coupled oscillator theory to give an explanation for such behavior, such as is often done in attempts to model Wenckebach behavior (van der Pol and van der Mark, 1928; Honerkamp, 1983; Geuvara and Glass, 1982). Because Wenkebach conduction has been so often treated as a feature of non-linear coupled oscillators, we will discuss in detail how a dispersion of refractoriness in a conducting media gives rise to such a pattern of conduction. We will also discuss the model's prediction of alternating conduction times, and examine the literature to see if reports of such exist.
Figure 3-3: Ladder diagrams depicting transmission through the model A-V node: a) normal 1:1 conduction, b) alternating (and delayed) conduction times, c) markedly prolonged conduction times, d) Wenckebach periodicity, and e) fixed-ratio (2:1) conduction block.
3.3.1 The Wenckebach Phenomenon

To illustrate Wenckebach type conduction, consider an array of actively conducting tissue which incorporates the notion of dispersion of refractoriness. If we represent A-V nodal conduction as conduction from one edge of the array to the other, we can note particular modes of conduction behavior (Figure 3-4). Specifically, for interstimulus rates sufficiently long, conduction sweeps directly across the array in a reproducible fashion. As interstimulus interval decreases or
mean refractory period increases, wavefront fractionation begins to occur, and conduction times across the array are lengthened, corresponding to first degree heart block. Simulation studies revealed that in many regimes, the conduction times were not simply prolonged, but that the values of the conduction times alternated, as one might expect from previous discussions. For sufficiently short interstimulus intervals, 2:1 conduction block occurs. But, for a region of interstimulus intervals approximately equal to mean refractory period duration, Wenckebach behavior is evidenced in the conduction times. Specifically, conduction times are seen to gradually lengthen until finally a block to conduction occurs; the process repeats itself with the next stimulation. A study of model behavior yields the following explanation.

Dynamically, within the array some regions cannot respond to the second in the series of stimulations, and as such they serve as conduction blocks around which the wavefront of excitation must circulate. As these wavelets circulate around these barriers, they find that some of the previously refractory neighboring regions are now recovered, and the wavelets enter these regions only to be extinguished as they impact recently excited (and now refractory) regions. On the next stimulation, the wavefront of excitation encounters more refractory regions to block its course because those regions re-stimulated by the wavelets are now refractory. These islands of refractoriness cause greater wavefront fractionation, resulting in more tortuous circulation of the wavefront and resultant wavelets, with the result of even more decreased effective conduction velocity. This process continues until finally the wavelets leave enough refractory regions in their wake that a wavefront of excitation can no longer complete a path through the array (see Figure 3-5). With this block to conduction, most of the array will then have two interstimulus intervals in which to recover, and thus the process can start anew with the next
Figure 3-5: Illustration and explanation of Wenckebach block. The first wavefront to pass through the node leaves an inhomogeneous refractory wake. On subsequent stimulation, the wavefront is initially delayed in the proximal region of the node (due to the presence of refractory islands) and then traverses through the distal part of the node unimpeded (distal segment allowed greater time to recover). The next stimulation results in a wavefront which finds increased refractoriness in the proximal node by virtue of those elements being activated with some delay following the previous stimulation. Increased refractoriness results in increased delay which in turn results in increased refractoriness until finally a conductive path between the refractory islands cannot be found, resulting in conduction block. The process then starts anew with the next conducted wavefront.
stimulation. [In simulation studies, we observed conduction ratios from 3:2 to 6:5.]

This mechanism of Wenckebach conduction would predict that each successive conduction would leave a successively greater fraction of refractory sites in its wake. This gradually increasing refractoriness would be expected to slow conduction, not only of the appropriately timed stimulus, but of any stimulus which was timed to fall before the refractory sites could recover. In this way, one would expect different conduction-time vs. interval curves following each cycle. In particular, one would expect that the conduction delays for premature stimuli would be longer for each successive beat in the cycle. In a classic paper by Simson, et. al. (1979) measurements of the conduction times of stimuli introduced after each beat in a Wenckebach sequence of the A-V node of dogs during Wenckebach conduction revealed this pattern in a set of conduction-time vs. interval curves (See Figure 3-6).

![Graph](image)

**A:** The refractory curve for each beat of a 4:3 Wenckebach cycle. The basic cycle length was 237 msec. The control conduction times for beats 1, 2, and 3 were 98, 126, and 144 msec respectively. **B:** The H-H' vs. the A-A' curves during the same 4:3 Wenckebach cycle. The functional refractory period is numbered after the preceding beat.

**Figure 3-6:** Data from Simson, et. al., 1979, illustrating that the refractoriness of the A-V node, as measured by successive conduction time vs. interval curves, increases for each cycle during Wenckebach periodicity.
3.3.2 Alternating Conduction Times

From this discussion and others presented in this paper, one might guess that alternating conduction times might be seen across a conductive array with a dispersion of refractoriness. Our model of A-V nodal conduction showed this anticipated behavior (see Figure 3-4). As before, the reason for this alternating effect in conduction times is that some sub-populations of the array are only responsive every other beat. Thus, while a short path might be available across the array at one time, the next beat will have to traverse the refractory islands left behind by the preceding beat, resulting in a longer conduction time.

Having said that the model demonstrates such behavior, we are left to see if such behavior occurs in vivo. Brat, et. al. (1983) reported observing P-R interval alternation, and explained their results in terms of two distinct A-V nodal pathways (longitudinal dissociation within the A-V node, a proposal put forth by Moe et. al. (1968)). Our model would predict this alternation in conduction times, but would not necessarily require two morphologically distinct paths. Kinoshita, et. al., (1983) reported alternating coupling intervals for PVD's in ventricular bigeminy. They concluded that they have presented evidence in support of longitudinal dissociation in the re-entrant pathway of the extrasystoles, but their observations of alternating conducting times for a segment of a re-entrant loop are also consistent with our model of alternating conduction times. Hope, et. al., (1980) demonstrated that fixed rate pacing of an ischemic area of ventricular myocardium resulted in alternating conduction times from their pacing electrodes to various locations within the ischemic zone (see Figure 3-7). Their observations in ischemic myocardium (which has been shown to have an enhanced dispersion of refractoriness) may also follow from our simple model.

It is important to point out that the dispersion of refractoriness in our model
which gives rise to alternating conduction need not be considered as an alternate hypothesis to that of longitudinal dissociation. Longitudinal dissociation can be viewed as a specific case of the more general dispersion of refractoriness; specific in that longitudinal dissociation may represent a dispersion of refractoriness with large spatial correlation lengths so that distinct macroscopic pathways with different refractory properties may form.

3.3.3 Precursors to Tachyarrhythmias

By adjusting the parameters of the model (mean refractory period, standard deviation of refractory period, conduction velocity) it was possible to study the behavior of this model as it approached states of re-entrant behavior. We noted that when "unstable" states were approached by stepwise variation of model parameters, a distinct pattern of regular oscillations occurred in simulated ECG-complex morphology. The most robust oscillation was an alternation in

Figure 3-7: Data from Hope, et. al., 1980. The authors reported alternation in conduction times through an ischemic region of ventricular myocardium.
morphology, a situation analogous to electrical alternans (see Figure 3-2). On close inspection of the model, the source of the alternation in morphology of the simulated ECG was a sub-population of model elements whose refractory periods exceeded the interstimulus interval. These elements could not "follow" every stimulation as a results of their relatively long refractory periods. Instead, these elements were left to respond to every other stimulation, thus giving rise to an alternation in gross model behavior as evidenced by the simulated ECG. We will return to a discussion of electrical alternans as a possible marker of increased likelihood of re-entrant dysrhythmogenesis in section 6.2. For now, it is only important to note that this alternating behavior ALWAYS preceded any frank rhythm disturbance.
Chapter 4

Percolation Theory - A Semi-quantitative Treatment for Dysrhythmogenesis

4.1 Introduction to Percolation Theory

Percolation theory is an area of statistical physics which has been successfully used to describe fluid flow through densely packed powders, conductivity in doped semi-conductors, sol-gel transitions in polymers, etc. While the applications of percolation theory are diverse, the underlying principles are quite simple.

An intuitive grasp of percolation theory can be had by considering a very large chessboard. If every square in this chessboard is black with probability $p$ and white with probability $q = 1 - p$, and the "state" or color of any particular square (or lattice site) is independent of that of its neighbors, then the description of the features of the chessboard is a problem of percolation theory. If $p$ is very small, then there will be relatively few black squares on the chessboard, and what black squares there are will most likely occur as isolated entities. As $p$ increases, the number of black squares increases, and the black squares will begin to occur as clusters, with clusters being defined as a group of black squares connected by nearest-neighbor distances (in the case of our chessboard, squares connected on their sides to other squares of the same color). In this discussion we will concentrate on the relationship between probability $p$ and the distribution of cluster sizes.
4.2 Critical Probability

At \( p \) near zero, the black squares are few and far between. At \( p \) near one, the black squares form a huge cluster which dominates the chessboard. Given these extremes, it is reasonable to postulate that there is some intermediate value of \( p \), referred to as \( p_c \), where one contiguous cluster of black squares forms which extends from one end of the chessboard to the other. In the limit of an infinitely large chessboard, this cluster will also be infinite, and when such an infinite cluster forms, the lattice is said to percolate. Thus, if one looks at the chessboard for a value of \( p < p_c \), the black squares will occur in clusters of various sizes, much as the distribution of hole sizes in a slice of swiss cheese. For \( p > p_c \) the chessboard would show an infinite cluster of black squares, as well as a number of smaller clusters distinct from the infinite cluster. The infinite cluster would then resemble the cheese in our slice of swiss cheese. At \( p = p_c \) the infinite cluster would appear as the coalescence of many smaller clusters, and thus its shape would be highly ramified and its perimeter would be very tortuous.

Under the above assumptions, percolation is a phase transition (generally defined as the phenomenon that a system exhibits a qualitative change at a sharply defined parameter value). By analogy to thermodynamic phase transitions, we can define a percolation probability, \( P_\infty \), as the fraction of occupied squares (sites) which belong to the infinite percolating cluster. Below \( p_c \), \( P_\infty \) vanishes, and in the neighborhood of \( p_c \) (with \( p > p_c \)), we will postulate \( P_\infty \) is proportional to \( (p - p_c)^\beta \) (Stauffer, 1979). We will write this as

\[
P_\infty \sim (p - p_c)^\beta
\]

This is the probability that an occupied site is a member of the infinite cluster. For
an arbitrary site, this probability becomes $\sim p(p-p_c)^2$.

4.3 Distribution of Cluster Sizes

While the infinite cluster dominates the behavior of the lattice for $p$ large, the distribution of cluster sizes is also of interest. If we define a function $n_s(p)$ to be the number (normalized per total number of lattice sites) of clusters of size $s$, we can begin to study the relationship between cluster size distribution and probability $p$.

For small values of $s$, one can directly calculate $n_s(p)$ (Sykes, et. al., 1976a,b). For example, an $s$-cluster with $s = 2$ consists of two black squares surrounded by six white squares. The probability of this event can be explicitly written as $2p^2(1-p)^6$. Such calculations have been carried out for $s < 15$, but generalizable solutions for arbitrary $s$ have not been found.

Another approach for arriving at a functional form for $n_s(p)$ is Monte Carlo simulation, wherein computer simulations with large lattices are conducted and the number of clusters of size $s$ are counted (Binder, 1979). This “brute force” approach has been the mainstay in this area until recently. The major limitations of this approach are computation speed and edge-effects resulting from the use of finite size arrays.

Renormalization group technique has been used since 1975 to study cluster size distributions (Harris, et. al., 1975; Reynolds, et. al., 1977). The concept underlying renormalization group theory is that one can describe a given lattice by observations at different length scales. By constructing renormalized lattices which are derived by “averaging” over several lattice sites of the initial lattice, and equating relationships for the original and the renormalized lattices, it has been possible to calculate some of the exponents which describe lattice behavior near $p_c$. 
The use of exact inequalities is the latest method employed for the study of cluster size distributions (Schwartz, 1978; Reich and Leath, 1978). By assuming functional forms for $n_s(p)$, and making inferences based on Monte Carlo simulation data, it has been possible to bound the parameters in the assumed functional forms.

By combining results from all these techniques, it has been possible to arrive at a reasonable approximate relationship for $n_s(p)$, for $p$ in the neighborhood of $p_c$ and $s$ large. For all the results to be presented, the underlying assumption is the scaling assumption, i.e.,

$$\frac{n_s(p)}{n_s(p_c)} = f(z), \text{ or } n_s(p) \sim f(z) \cdot s^{-r}$$

with $z \equiv (p - p_c) \cdot s^\sigma$ and $f(0) = 1$.

While there are several forms of the scaling function, $f(z)$, postulated in the literature, for the sake of further discussion we will limit ourselves to a functional form which gives good results on either side of $p_c$ for the three-dimensional lattice (when compared to results from Monte Carlo simulations). One such relation is the Gaussian approximation suggested by Leath (1976a,b). With a further modification as suggested by Klein, et. al., (1978) we have that

$$n_s(p) \sim s^{-r} \cdot e^{-K_1 |(z/p_c) + K_2|^2}$$

with $K_1 = 0.6$, and $K_2 = 0.8$. With this relation in hand, we will leave percolation theory per se and turn to a three dimensional representation of ventricular myocardium in an attempt to motivate the application of these results to the study of cardiac conduction.
4.4 Finite Element Model of Cardiac Tissue

4.4.1 Motivation

Cardiac tissue has long been viewed as an *electrical syncytium*, with the gap junctions occurring between cells being viewed as low-impedence pathways for the spread of ionic currents. Only recently has this view been brought into question (Spach, et.al., 1981), with some suggestions being made as to the importance of discontinuous conduction. For the purpose of this development, we will assume that at some macroscopic level, spread of electrical activation can be viewed as propagation of wavefronts from place to place in a spatially and temporally discontinuous fashion. If we assume a constant set of electrical properties over a region of our model myocardium, a wavefront of activation would spread in a totally homogeneous fashion. If, however, we assumed a distribution of electrical properties, i.e., a distribution as to whether or not sub-regions of our region of interest were excitable, an inhomogeneous spread of the wavefront of activation would be expected.

To recap for a moment, this notion of a distribution or *dispersion* of excitability is the central theme behind the dispersion of refractoriness hypothesis of re-entrant dysrhythmogenesis (Han, et. al., 1964). This hypothesis states that a distribution of cellular recovery periods results in a dispersion of cellular excitability which gives rise to fractionation of the wavefronts of excitation, ultimately predisposing to re-entrant excitation. Re-entry is said to occur when a wavefront traverses a closed path within the tissue such that it is self-perpetuating.

One can model the effect of a dispersion of recovery times in a region of myocardium by representing such a region as a three dimensional lattice wherein activation spreads in a nearest neighbor fashion. Thus, if we assume a lattice of
cubes, excitation can be modeled as spreading from a given cube to each of its six near neighbors which are eligible to be excited. Eligibility for excitation can be determined in a fashion analogous to recovery times of myocardial cells. Each lattice site or cube can be randomly assigned a recovery time from a fixed probability density function. A lattice site would then be eligible for excitation only if the time since its previous excitation exceeded its recovery period, otherwise, that site would be refractory to stimulation.

If we assume a particular form for the probability density function of the refractory periods, and assume that the wavefront of activation spreads through the region very rapidly with respect to the time course of recovery, then we can calculate the fraction of lattice sites that are refractory at time \( t \) after the region has been stimulated. This fraction of refractory sites can be thought of as the probability of a given site being refractory at time \( t \):

\[
p(t) = 1 - \int_{0}^{t} \text{pdf} (\tau) \, d\tau
\]

where \( \text{pdf}(\tau) \) is the probability density function for the refractory times. If we assume that the refractory periods of adjacent sites are uncorrelated (or viewed another way, if we confine the characteristic dimension of the lattice element to be equal to or greater than the correlation length of refractory properties within the tissue), then we can begin to view the problem of conduction in this model of myocardium as a percolation problem.

4.4.2 Susceptibility to Re-entry

Re-entrant loop formation is thought by many to be the process responsible for sustained tachyarrhythmias and ventricular fibrillation. It has been noted that
even in apparently normal hearts, exogenous current stimuli applied to the myocardium during the time course of ventricular repolarization can initiate ventricular fibrillation, presumably through the formation of re-entrant loops. Percolation theory may provide a pseudo-analytical treatment for susceptibility of myocardial tissue to re-entrant loop formation. To examine this problem, we will examine the probability of forming a closed self-avoiding loop of length \( L \) of non-refractory tissue around a refractory obstacle. The probability of forming a loop in three dimensions rapidly becomes mathematically intractable, so we will recast the problem as one of finding the probability of there being a three dimensional cluster of refractory elements with characteristic radius \( R \). Results from percolation theory (Stauffer, 1978) suggest a relationship between finite cluster size \( s \) and characteristic radius \( R \) for \( p \) in the neighborhood of \( p_c \):

\[
R \sim s^{2/(d+2)}
\]

or,

\[
R \sim s^{3/(d+2)}
\]

where \( d \) represents spatial dimension (for our case \( d = 3 \)). We will take an intermediate stand and approximate the relationship between \( R \) and \( s \) to be

\[
R \sim s^{1/2}
\]

To simplify further analysis, we will take the constant of proportionality to be unity. This assumption does not affect the qualitative nature of subsequent results, and in the spirit of the rest of this discussion, we will maintain it as a first approximation. Drawing on results discussed in section 4.3, we can now construct an expression for the probability of finding a cluster of refractory elements with
radius $R$ as a function of $p$ and $R$:

$$n(R) \sim (R/\xi)^{-4}e^{-0.6[(p(t)-p_c)/p_c](R/\xi)+0.8}^2$$

For re-entrant behavior to be self-sustained, it must be the case that the length of the re-entrant loop, $L$, exceed the product of conduction velocity and maximum refractory period within the loop. This condition guarantees that the wavefront of excitation traversing the loop never encounter its own refractory wake. An additional constraint must be that the re-entrant loop be traversed in the time remaining until the next stimulation; otherwise, the wavefront would be interrupted in its path around the loop by the subsequent wavefront of excitation, and no self-sustaining activity would result. If we take the interstimulus interval to be $T$ then:

$$L_{max} = 2\pi R_{max} = v(T-t) > R > v_{min} = 2\pi R_{min} = L_{min}$$

where $v$ is the conduction velocity and $t$ is time elapsed since the previous depolarization. If we assume that the maximum refractory period within the loop is approximately equal to the mean refractory period of the entire population, then we can factor in the dependency of mean refractory period and conduction velocity in our estimate of the probability of forming the substrate for a sustained re-entrant loop, $p_s(t)$.

$$p_s(t) \sim \sum_{R=R_{min}}^{R_{max}} (R/\xi)^{-4}e^{-0.6[(p(t)-p_c)/p_c](R/\xi)+0.8}^2$$

where $p(t)$ is given by
\[ p(t) = 1 - \int_0^t \text{pdf} (\tau) \, d\tau \]

While the absolute probability for forming a re-entrant loop will depend on \( N \) (the total number of elements or lattice sites), for fixed \( N \) we can examine the dependence of this probability on each of the parameters of interest. For ease of discussion, we will assume a Gaussian distribution for refractory period duration, with mean \( \bar{\tau} \) and standard deviation \( \sigma \).

Figure 4-1 depicts the predicted general relationship between the \( p_\delta(t) \) and \( t \), time elapsed since previous depolarization. The characteristic feature is that this probability has a well-defined maximum which occurs at a value of \( t \) slightly greater than \( \bar{\tau} \). [The approximate value of \( t \) at which this maximum occurs is when \( p(t) \) is equal to \( p_c \). This occurs when \( \text{erf} \left( (t-\bar{\tau})/\sigma \right) = p_c \) or when \( t = \bar{\tau} + (0.49)\sigma \).]

### 4.4.2.1 Mean Refractory Period (\( \bar{\tau} \))

Figure 4-2 depicts the predicted relationship between \( p_\delta(t) \) and \( \bar{\tau} \). As \( \bar{\tau} \) increases, the maximum \( p_\delta(t) \) rapidly decreases, and the time corresponding to maximum \( p_\delta(t) \) increases.

### 4.4.2.2 Conduction Velocity (\( v \))

Figure 4-3 depicts the predicted relationship between \( p_\delta(t) \) and \( v \). As \( v \) increases, the maximum \( p_\delta(t) \) rapidly decreases, with no change in the time corresponding to maximum \( p_\delta(t) \).

### 4.4.2.3 Dispersion of Refractoriness (\( \sigma \))

Figure 4-4 depicts the predicted relationship between \( p_\delta(t) \) and \( \sigma \), the standard deviation of the refractory period. For increasing \( \sigma \), the maximum \( p_\delta(t) \) remains
constant; only the time course of the relationship changes. For increasing $\sigma$, the effective range over which $p_\delta(t)$ is elevated is lengthened, with the peak $p_\delta(t)$ occurring at a later time.

4.4.2.4 Interstimulus Interval ($T$)

Figure 4-5 depicts the relationship between $p_\delta(t)$ and the interstimulus interval. Note that the maximum probability decreases as the interstimulus interval decreases, illustrating that only those loops that can be traversed before the subsequent depolarization arrives contribute to the substrate for sustained re-entry.
Figure 4-2: Predicted relationship between $p_\delta(t)$ and $\bar{\tau}$.
As the mean refractory period increases, the time of the peak probability occurs later (time measured from previous stimulation), and the peak probability decreases.

4.4.2.5 Correlation Length ($\xi$)

The effect of $\xi$, the spatial correlation length on the likelihood for formation of the substrate requisite for re-entry is shown in Figure 4-6. As $\xi$ is increased, two competing influences alter the shape of $p_\delta(t)$. With $\xi$ increasing, fewer lattice elements are required to form a loop of a given length, tending to increase $p_\delta(t)$. However, under the assumption of a finite volume array, the total number of lattice sites, $N$ is proportional to $\xi^{-3}$. Thus, as $\xi$ increases, the number of lattice sites decreases, decreasing $p_\delta(t)$. The net effect is that the peak $p_\delta(t)$ increases moderately while the shape broadens for increasing $\xi$. 


4.4.3 Excitability

If one considers the problem of initiating a wavefront of activation at a time $t$ after a previous activation, one can approximate the likelihood of such a stimulation being successful in causing a propagated wavefront throughout the lattice by once again appealing to percolation theory. To do this, we will shift our emphasis from dealing with the refractory population to dealing with the excitable population. If we examine the entire lattice at time $t$ after an activation wavefront has swept through, we can describe the state of the lattice by the probability $p(t)$ of finding a given lattice site excitable, i.e., non-refractory. If $p(t)$ is near zero, corresponding to $t \ll \bar{\tau}$, (where $\bar{\tau}$ is the mean refractory period) the probability of initiating a conducted wavefront is small. If $p(t)$ is near unity, corresponding to $t \gg \bar{\tau}$, the probability of evoking a propagated response is very high. We can view the

Figure 4-3: Effect of conduction velocity on $p_s(t)$. As conduction velocity increases, the peak probability decreases.
Figure 4-4: Effect of standard deviation, $\sigma$, on $p_s(t)$. As $\sigma$ increases, the probability remains elevated for a longer time course, while the peak probability remains unchanged.

probability of initiating a propagated response from a given site as the probability that that site of stimulation is a member of the infinite cluster of non-refractory sites. With the probability of a given site being non-refractory equal to $p(t)$, we can again utilize the results from section 4.3, and conclude that the probability of initiating a propagated wavefront from a single point of stimulation is

$$P_\infty \sim p(t)(p(t) - p_c)^\beta \text{ for } p(t) > p_c, \text{ and 0 otherwise}$$

where $\beta = 0.4$ in three dimensions (Stauffer, 1979).

As we will see later, comparison of this result with the literature is initially difficult in that the analogous in vitro or in vivo experiment does not provide a measure of the probability of a conducted response, but instead provides a measure
of the intensity (in milliams) of the current pulse needed to result in a conducted wavefront. To provide the opportunity for comparison, let us examine the relationship between current intensity and the volume of tissue which experiences sufficient current density to be excited. If we assume a dipole as the source of the current, the current density at a distance $r$ from the dipole origin is proportional to $r^{-3}$. In that volume is proportional to $r^3$, the volume of tissue which experiences a current density greater than or equal to some threshold value will be proportional to $(I - I_0)$ where $I$ is the current through the dipole and $I_0$ is the minimum current required to cause a single site to be excited.

We are now prepared to determine the relationship between current applied through the dipole and the probability of exciting some site within the infinite cluster. To calculate the probability of exciting an element within the infinite
Cluster, all we need do is calculate the probability that at least one member of the volume of excitability is a member of that cluster. Thus, the probability of a conducted response is $1 - P_p(t)$, the probability that none of the elements in the volume is a member of the infinite cluster. If $n$ is the number of sites in the volume of excitability, then we might initially estimate the probability of a conducted response as

$$1 - [1 - p(t)P_\infty(t)]^n$$

Implicit in this approximation is the assumption that adjacent elements are independent with respect to $P_\infty(t)$. This is clearly not the case. The probability of a given element being a member of the infinite cluster is very dependent on whether its neighbors are members of that cluster. To improve our estimate, we will
consider \( n' \), the number of independent sites in the volume of excitability. We will estimate \( n' \) to be \( n/\xi^3 \), where \( \xi \) is the correlation length in the lattice, i.e., the number of lattice sites over which statistical properties are correlated.

\[
n \sim (I - I_0)
\]

Thus,

\[
n' \sim \frac{I - I_0}{\xi^3}
\]

and

\[
p( \text{conducted beat at time } t ) = 1 - [1 - p(t) \cdot P_\infty(t)]^{K \cdot (I - I_0)/\xi^3}
\]

From Stauffer, 1979, we have

\[
\xi \sim |p - p_c|^{-v}
\]

Combining the above relations, we can derive the relationship between \( I \) and \( p(t) \) along lines of isoprobability for the initiation of a propagated beat.

\[
I(t) - I_0 \sim \frac{\xi^3}{\log [1 - p(t) \cdot P_\infty(t)]}
\]

or, substituting for \( \xi \) and \( P_\infty(t) \),

\[
I(t) - I_0 \sim \frac{|p(t) - p_c|^{-3 \cdot v}}{\log [1 - p(t) \cdot K \cdot (p(t) - p_c)^{\beta}]}\]
substituting an expansion around \( p_c \) for the log term allows us to incorporate the constant \( K \) into the total proportionality

\[
I(t) - I_0 \sim \frac{|p(t) - p_c|^{-3\nu}}{p(t) \cdot (p(t) - p_c)^\beta}
\]

Under the assumption of a Gaussian probability density function for the recovery periods, we finally arrive at the predicted strength-interval curve for myocardial excitability (See Figure 4-7). \( T_c \), the coupling interval at which it is impossible to stimulate a conducted response, occurs when the infinite cluster can no longer form. This occurs when \( p(t) = p_c = 0.311 \), or, in terms of the parameters of the refractory period distribution, \( T_c = \bar{r} - 0.49\sigma \). The width of the transition region of the strength-interval curve, i.e., the range of coupling intervals for which the threshold for conduction is elevated by some fixed percentage above its minimal value, is directly proportional to \( \sigma \). These simulated curves compare to those in Figure 5-3.

### 4.4.4 Protective Zone

In our discussion of \( p_g(t) \), we argued that only those refractory clusters which gave rise to barriers with radii between certain limits were figured into our calculation. Those clusters with radii too small to fulfill the re-entry condition were excluded, as were those with radii so large that a circulating wavefront would take too long to completely traverse them, where "too long" was set to be the time until the next stimulation. The argument for excluding these large clusters from the calculation was that a wavefront would not successfully circulate around the
Figure 4-7: Family of simulated strength-interval curves. \( T_c \), the time at which no stimulation intensity can initiate a propagated response occurs when \( p(t) = p_c = 0.311 \), or when \( T_c = \bar{t} - 0.49\sigma \). The width of the transition band, i.e., the range of coupling intervals over which the threshold is elevated by some fixed percentage over its minimum value, is directly proportional to \( \sigma \), the standard deviation of the refractory period distribution. Compare with Figure 5-3.
barrier, but would be interrupted in its path, and re-entry would not be sustained.

One implication of this argument is that there would exist a period of time, immediately after the vulnerable period, wherein exogenous stimuli would decrease the likelihood of forming the requisite substrate for re-entry. The effect of an exogenous stimulation during this protective zone would be to interrupt wavefronts in their paths around refractory regions, thereby diminishing the likelihood of sustained re-entry being established.

For the sake of later comparison with experimental observations, we can combine our predictions regarding ventricular excitability, ventricular vulnerability, and the protective zone into one graph (See Figure 4-8). This will be seen to compare favorably with experimental observations (Figure 5-4).

We have seen that a semi-quantitative analysis based in large part on results from percolation theory makes a host of predictions regarding the determinants of myocardial electrical stability. Before moving on to examine the literature in an attempt to evaluate these predictions, we will discuss some additional predictions which can be made using similar reasoning.

4.4.5 Effective Conduction Velocity and Coupling Interval

If we view the spread of the wavefront of activation as the wavefront percolating through the partially refractory lattice, we would contend that the pattern of the spread of the wavefront would be strongly dependent on the fraction of the sites which are non-conducting or refractory. In particular, in that we have modeled the probability of a given lattice site being refractory as a monotonically decreasing function of the time after the previous stimulation, we would expect the pattern of activation to vary with the time between successive stimulations. If the time between successive stimulations is long with respect to the mean refractory
Figure 4-8: Temporal relationships between the strength-interval curve, the vulnerable period and the protective zone as predicted from percolation arguments.

period, relatively few of the sites would be refractory, and the wavefronts would be reasoned to spread relatively homogeneously from the point of stimulation. As the time between successive stimulations is decreased, the fraction of sites which are refractory at the time of stimulation increases, and the resultant wavefront would be forced to navigate around the refractory islands.

If the description above is relevant to cardiac conduction processes, one might expect to see that conduction patterns in myocardial tissue change as a function of coupling interval. One might also expect that as coupling intervals decrease, the time it takes for a propagated wavefront to travel from one point to another would increase, owing to the increasing tortuosity of the conductive pathway linking these two sites. Discussions of specific conduction patterns does not readily lend
itself to percolation theoretic arguments, but a good deal more can be said
regarding the relationship between conduction times and interstimulus intervals.
Ritzenberg (1984) offered a development for the relationship between conduction
velocity and interstimulus interval in a two-dimensional array.

The minimal conductive path between two points on a three-dimensional
percolation lattice is a quantity whose dependence on \( p \) has been calculated
(Stanley, et. al, 1981, 1983). The form of the dependence is similar to that of other
quantities, i.e., \( L \sim D \cdot (p - p_c)^\gamma \), where \( L \) is the minimal path length, \( D \) is the
direct distance separating the two points, and \( \gamma \) has been found to be \(-1.18 \pm 0.02\). If
we argue that the wavefront must traverse this path, and that the intrinsic
conduction velocity is unchanged, then the conduction time for the wavefront to
travel from one point to another should be proportional to \((p(t) - p_c)^{-1.18}\). Figure
4-9 depicts the predicted relationship between conduction time and \( T \) (coupling
interval) for several values of \( \sigma \), the standard deviation of refractory times. Note
that as \( \sigma \) increases, 1.) the range of coupling intervals over which prolonged
conduction times are seen increases, and 2.) the minimum coupling interval for
which a conducted response is seen shortens. The minimum coupling interval which
could possibly result in a conducted response is the minimum coupling interval
which allows for the repolarization of an infinite cluster. This occurs when \( p = p_c \),
or when \( T = \tau - 0.49\sigma \).

4.4.6 Prolonged Residence of Activation Wavefront in Inhomogeneous
Lattice - Delayed Depolarizations

Our immediately previous argument can be interpreted as stating that the
conduction time between two points in a lattice increases as the number of non-
conductive sites in the lattice increases. In a lattice with fixed barriers to
Figure 4-9: Predicted family of curves of conduction time vs. coupling interval. $T_o$, the coupling interval for which conduction no longer occurs, is equal to $\bar{r} - 0.49\sigma$, where $\bar{r}$ is the mean refractory period and $\sigma$ is the standard deviation of the refractory period distribution. The width of the transition band, i.e., the time period over which conduction still occurs but is delayed by more than a fixed percentage of its minimum value, is directly proportional to $\sigma$. 
conduction, one would expect that a wavefront of activation spreading throughout the lattice would require a greater time to spread to all receptive sites. The presence of non-conductive sites within the lattice would therefore increase the residence time of the activation wavefront. An appropriate analogy of non-conductive lattice sites in myocardial tissue would be areas of infarction. Prolonged residence times for the wavefront of activation would be reflected in prolonged QRS durations, and thus, one would predict from this argument that myocardial infarcts would be accompanied by prolonged QRS durations. We will examine this prediction in Chapter 5, however it should be noted that the predominant cause of prolonged QRS duration is an intraventricular defect in the specialized cardiac conduction system. Because of the special role of the conduction system in quickly spreading the activation front throughout the myocardium, a defect in conduction here could result in significant prolongation of the QRS duration. A defect in conduction in the bulk of the ventricular myocardium would be expected to cause a less significant prolongation of QRS duration.

This concludes the discussion of what quantitative and qualitative predictions can be made regarding aspects of cardiac conduction with a synthesis of the dispersion of refractoriness hypothesis and results from percolation theory. We will now turn to an examination of the literature to evaluate these predictions, where possible.
Chapter 5

Observations Regarding Model Predictions

5.1 Ventricular Vulnerability

We have discussed how the model we have developed suggests the existence of a vulnerable period during ventricular recovery, during which time ectopic stimuli could initiate self-sustained re-entrant activity. We have also suggested how the "severity" and time course of the ventricular vulnerability might depend on electrophysiologic parameters. We will now examine the clinical and experimental literature for evidence which impacts on the model's predictions.

5.1.1 Clinical Observations

5.1.1.1 Coupling Interval

Numerous reports suggest that spontaneous ventricular fibrillation is often immediately preceded by "R-on-T" activity, with the salient feature being that one wavefront of activation follows a previous one so closely as to fall during that time when the myocardium is only partially recovered (El-Sherif, et., al., 1976; Engel, et. al., 1978). Our model would predict that such a situation would be a destabilizing influence, a prediction which seems borne out by these observations. Similarly, the common observation of fast ventricular tachycardias rapidly degenerating into ventricular fibrillation would be predicted by our simple model.

What might seem at odds with the above discussion is the observation that many episodes of spontaneous ventricular fibrillation are not preceded by "R-on-T" activity, but instead are preceded by PVD's with relatively long coupling intervals
(Swerdlow, et.al., 1984). This observation is potentially reconcilable with the bulk of our foregoing discussion by recalling that the T wave corresponds to the time course of repolarization of the majority of ventricular tissue. It is well documented (as in the case of the Purkinje system) that some regions of the myocardium may repolarize well after the T wave has been enscribed. Furthermore, in the ischemic state, there can exist highly regional delays in conduction such that activation of some regions of tissue occurs after the inscription of the T wave (El-Sherif, et. al., 1975). With this in mind, we might understand that a PVD may impact on refractory regions of myocardium even though it falls (temporally) after the inscription of the T wave. Of course, the possibility exists that other mechanisms might underlie the observation of late-cycle PVD giving rise to ventricular tachyarrhythmias. The point to be made here is that even this observation regarding late-cycle PVD’s might be easily explained in light of this present discussion.

5.1.1.2 Nonuniform Recovery Properties

Myocardial ischemia and myocardial infarction are two disease states known to alter cellular refractory properties in an inhomogeneous fashion across the myocardium. From our previous discussions, we would conclude that these two conditions would represent destabilizing influences on cardiac conduction. Numerous studies have shown that both of these conditions are accompanied by increases in both incidence and malignant potential of cardiac rhythm disturbances.

5.1.1.3 Mean Refractory Period

A number of anti-arrhythmic drugs serve to prolong mean refractory period, with quinidine being the prototypical drug in this category (Goodman and Gilman, 1983). The effectiveness of these drugs in preventing dysrhythmogenesis is consistent with the arguments presented here which suggest that increasing mean
refractory period would be a stabilizing influence by making it more difficult to form re-entrant loops (increasing the minimum loop length).

5.1.1.4 Conduction Velocity

Myocardial ischemia and infarction are also known to result in regions of myocardial tissue with decreased conduction velocities. The increased incidence of malignant dysrhythmias in patients with myocardial ischemia and infarction is then consistent with our predictions that diminished conduction velocity is a destabilizing influence.

5.1.2 Experimental Observations

While clinical observations are left to be predominantly qualitative, experimental studies afford the opportunity to measure those parameters which our simple model would predict to be important in determining the stability of a given preparation. A review of the experimental literature, however, reveals that simple conclusions will not be forthcoming. The myocardium is a sufficiently complex system as to frustrate attempts to design experiments which measure the effect of changes in only one of the variables of interest. Nonetheless, it is important to review the nature and results of experimental studies.

The experimental literature has been dominated by myriad reports claiming to substantiate the empirical relationship between measured dispersion of refractoriness and electrical stability, with the benchmark study being the comprehensive report by Han and Moe (1964c). They were able to conclusively demonstrate that the degree of temporal dispersion of refractoriness increased with: (1) premature stimulation; (2) increased activity from the cardiac sympathetic nerves; (3) chloroform administration; (4) ouabain intoxication; (5) quinidine intoxication; (6) myocardial ischemia, and (7) hypothermia -- all interventions known to decrease
myocardial electrical stability. This study, and those to follow, firmly established a relationship between measured dispersion of refractoriness and diminished electrical stability. Unfortunately for our purposes, however, none of the interventions were selective in altering only the measured dispersion of refractoriness. Premature stimulation, myocardial ischemia, hypothermia, and ouabain toxicity all result in decreased effective conduction velocity. Hypothermia, chloroform and quinidine in high doses all tend to increase mean refractory periods. Premature stimulation, myocardial ischemia, and ouabain toxicity have also been shown to decrease mean refractory periods. Because these interventions affect several of the electrophysiologic parameters which (our model suggests) determine stability, it is impossible to ascertain how much of the observed decrease in myocardial electrical stability was directly attributable to any particular parameter. In particular, it is impossible to determine how much of the measured change in electrical stability was the result of the increase in the dispersion of refractoriness.

Studies specifically designed to test the effects of rate, and those studies which reported the effects of changes in mean refractory period and conduction velocity (Han and Moe, 1964b; Han et. al. 1966a,d; Kent et. al., 1973) suffer from the same lack of specificity. Overall, the interventions commonly employed to alter particular electrophysiologic properties have confounding effects on other such properties, complicating the interpretation of experimental results.

One major prediction of the model does, however, lend itself to experimental testing, that being the characteristic time course of the likelihood of re-entrant loop formation as a function of coupling interval. The critical experiment would be to examine the relationship between re-entrant dysrhythmogenesis and excitatory stimuli introduced at varying intervals after the onset of depolarization. This experiment has been carried out numerous times by various investigators, and is
referred to as the *ventricular fibrillation threshold* (*VFT*) measurement. Reports confirm that the propensity toward re-entrant loop formation is a singly peaked function of coupling interval, with the maximum occurring near the peak of the T wave, corresponding to a coupling interval approximately equal to the mean refractory period (Wiggers and Wegria, 1940; Verrier et. al., 1978). This observation corresponds exactly to predictions made from our simple model of re-entrant loop formation.

\[ P_s(t) \]

\begin{align*}
\bar{r} &= 250 \text{ msecs} \\
\nu &= 50 \text{ cm/sec} \\
T &= 1000 \text{ msecs} \\
\xi &= 0.1 \text{ cm}
\end{align*}

**Figure 5-1:** \( p_s(t) \) vs. \( t \).

One robust feature of our prediction of the ventricular vulnerable period is that the width of the vulnerable period would increase as the dispersion of refractoriness increased (see Figure 5-1). We entertained an experimental test of this prediction, but in the course of the literature review we were pleasantly surprised to find that the experiment had already been done. Axelrod, et. al., (1975) studied the effect of coronary artery occlusion on the time course of the
vulnerable period. With coronary artery occlusion serving as the vehicle for decreasing electrical stability (presumably by increasing the dispersion of refractoriness), the authors were able to demonstrate that instability was marked by a broadening of the ventricular vulnerable period (See Figure 5-2). Thus, the model prediction of a widening in the ventricular vulnerable period in situations with increased dispersion of refractoriness is borne out by experimental data. Under the assumption that coronary artery ligation only increases the dispersion of refractoriness, there is slight discrepancy between the model prediction and the experimental results shown in Figure 5-2. The model would predict that the window of vulnerability would be broader, and also that the window would be moved later into diastole (Figure 5-1). While the measured window of vulnerability does move later in diastole, the movement is greater in the trailing edge than in the leading edge, with the leading edge movement being minimal. One possible explanation for this discrepancy is that ligation and the resultant ischemia doubtlessly alters other electrophysiologic properties. If the ligation-induced ischemia could be modeled as slightly decreasing the mean refractory period duration as well as increasing the dispersion of refractoriness, then one could easily account for slight discrepancy in experimental results vs. model predictions.

5.2 Ventricular Excitability Curves

In section 4.4.3, we discussed the implications of dispersion of refractoriness on ventricular excitability, specifically with respect to the measurement of such via strength-interval curves. An example of the experimental counterpart (Michelson, et. al., 1980) of our derived relationship is shown in Figure 5-3 for three different regions of tissue. For normal myocardium, the transitional region of the curve appears relatively narrow, whereas for the two curves made from infarcted
Figure 5-2: Plot of the duration of the vulnerable period as a function of time during coronary artery occlusion. A marked prolongation of the vulnerable period started within one minute after occlusion and persisted for approximately five minutes. Upon release of the occlusion, a slight prolongation again occurred. Within 3 minutes after reperfusion, the vulnerable period duration had returned to its pre-occlusion value.

myocardium show wide transition regions. This broadening of the transition region is in agreement with our derived strength-interval relationships for the case of increasing dispersion of refractoriness.

5.3 Protective Zone

In section 4.4.4. we discussed our model's prediction of a period of time, directly following the vulnerable period, which would serve as a protective zone. Exogenous stimuli timed to stimulate the myocardium during this time would be expected to diminish the vulnerability of the myocardium to re-entrant loop formation. The existence of just such a protective zone has been established in vivo.
Figure 5-3: Strength-interval curves from normal and infarcted myocardium, taken from Michelson, et. al., 1980. The filled circles represent measurements in non-infarcted tissue; the squares and triangles represent measurements made in two different infarcted regions.

by Verrier, et. al., (1978) (See Figure 5-4). While our analysis would predict that the amount of protection afforded by stimuli timed to fall in this zone would be dependent on their precise timing, the experiments of Verrier, et. al. did not investigate the effect to this level. The experimental verification of the existence of this protective zone, while not logically lending support to our model, adds to the parsimony and utility of the model in accounting for a seemingly disparate set of
Figure 5-4: a) The location of the vulnerable period and the protective zone, as described by Verrier, et. al., 1978. b) The effect of activating the protective zone (i.e., providing exogeneous stimulation during the protective zone) on the measured ventricular fibrillation threshold, VFT. Note that the VFT is higher when the protective zone (PZ) is activated.
observations.

5.4 Conduction Velocity and Coupling Interval

Several investigators have reported relationships between interstimulus intervals and the measured conduction times between electrode locations on or within the heart, showing a decrease in effective conduction velocity with increasing stimulation rate (Wyse, 1982; Simpson et. al., 1982). While Simpson et. al. (1982) conclude that these findings suggest a slowing in conduction velocity within the myocardial fibers themselves, this data can easily be interpreted in light of this present discussion. Greater stimulation rates would result in more and larger regions of alternating conduction block, resulting in more wavefront fractionation and increased conduction times. It remains to be determined to what extent the observations reflect true slowing of intrinsic cellular conduction velocities vs. effective conduction velocity slowing secondary to wavefront fractionation (a population effect). Cosio, et. al., (1983) studied slow conduction in response to premature atrial stimulation and found that in those patients prone to atrial fibrillation (AF), the conduction delay zones (i.e., range of coupling intervals over which delayed conduction was seen) were longer than in control patients, and that the effective refractory period of the AF-prone patients was shorter than that of the controls, with effective refractory period being defined as the minimal coupling interval for which a conducted response was elicited. If we assume that the patients prone to AF have a larger dispersion of refractoriness, (an assumption which is reasonable in light of measurements of refractory period durations in diseased atria by Engel and Luck, 1983) then both of these observations follow our predictions based on percolation theory (See section 4.4.5).
5.4.1 The Ashman Phenomenon

When two ventricular responses to atrial fibrillation occur with close coupling intervals, the second response is often noted to be aberrantly conducted. This is clinically referred to as the Ashman phenomenon. The understanding of this event is that the second wave of depolarization is coupled so closely to the preceding one that its conduction through the myocardium is obstructed by the partially refractory myocardium (Gouaux and Ashman, 1947). This is obviously in line with our discussion of the consequences of a dispersion of refractoriness.

5.4.2 Conduction of PVD’s

Premature ventricular depolarizations suffer the same fate as the closely coupled ventricular responses. The coupling interval to the preceding excitation is short, perhaps short enough so that the wavefront cannot spread normally across the myocardium, but instead must impact regions of relative or totally refractory tissue, resulting in aberrant conduction and decreased effective conduction velocities.

5.5 Delayed Depolarization

5.5.1 Fractionated Atrial Activity

A recent report suggests that fractionated atrial activity, taken to be electrical activity within the atrium that exceeds (in time) 150% of the normal duration of atrial activity, is a function of interstimulus interval and a valuable index of a tendency to develop atrial fibrillation (Ohe, et. al., 1983). The authors conclude that “The mechanism of the atrial fragmented activity is not known,” however, the data they present is totally consistent with our discussion of wavefront fractionation. They conclude that the width of the range of interstimulus intervals
which produces fragmented activity is a marker of likelihood of developing atrial fibrillation, with increased width being demonstrative of increased likelihood. This too is totally consistent with our foregoing discussion. The greater the range of interstimulus interval that produces wavefront fractionation, the greater must be the width of the distribution, and hence, the greater the dispersion of refractoriness.

5.5.2 Delayed Depolarization in Post-MI Patients

There has recently been a great deal of effort to isolate the group of post-myocardial infarct patients at increased risk of Sudden Cardiac Death. It has been repeatedly noted that those individuals who have recurrent episodes of symptomatic ventricular tachycardia after a myocardial infarction also have prolonged QRS durations, and low-level high-frequency content in the terminal portions of their QRS complexes (Simson, 1981).

In the context of our model, we may view a myocardial infarct as providing fixed obstacles to conduction. Electrophysiologic and anatomic evidence suggests that these obstacles may not be homogeneously inactive tissue, but instead may be surrounded by or even traversed by tortuous paths of surviving tissue (Richards, et. al., 1984; Michelson, et. al., 1980). We have previously given the result that, in three dimensions,

\[ L \sim D(p - p_c)^{-1.18} \]

where \( L \) is the conductive path length and \( D \) is the straight-line distance between the two points of interest. Under the assumption of a constant intrinsic conduction velocity, we would predict

\[ CT \sim D(p - p_c)^{-1.18} \]
where CT is conduction time.

One can easily see that the time it takes for a wavefront to traverse a given physical distance can be, depending on the tortuosity of the available path, many times the minimum possible conduction time. Thus, we would expect the existence of a tortuous path of viable tissue through an inexcitable region (aneurysm) to result in a wavefront of excitation being present in the tissue later than would normally be the case. The macroscopic measure of this long-lived wavefront would be a prolonged QRS duration. We would expect that this wavefront would have a relatively small active interfacial area, (due in part to the constraints implied by the tortuosity) and as such we would expect the energy in the later aspect of the QRS to be small.

If the argument we have presented is correct, why would we expect the finding of a prolonged QRS duration to go hand-in-hand with susceptibility to re-entrant dysrhythmias (VT and VF)? The answer is to be found in our previous analysis of the vulnerable period. In that discussion we maintained that the substrate required for re-entrant loop formation was a conductive path of length $L$ around a refractory barrier. While our previous analysis was for refractory barriers which evolved and disappeared in time, the same requirements would hold for static barriers. The loop of excitable tissue must exceed the wavelength of the excitation wave ($L > \nu - \tau$). Clearly, the existence of a fixed tortuous path through an inexcitable aneurysm would facilitate the formation of a loop of the critical length.

Thus, the finding of a prolonged QRS duration in the setting of an old myocardial infarct is consistent with the argument of the wavefront of activation percolating along some viable path through inexcitable tissue. Because of the implications which this lengthened pathway would have on re-entrant loop
formation, prolonged QRS duration would be expected to be indicative of an increased propensity toward re-entrant dysrhythmogenesis.
Chapter 6
Markers of Decreased Electrical Stability

6.1 Delayed Depolarization

Our immediately previous discussion would suggest that delayed depolarization (characterized by prolonged QRS duration) would signal an increased likelihood of developing re-entrant dysrhythmias. Delayed depolarizations, we have argued, may have either of two related but different etiologies. As in the post-myocardial infarct patients discussed above, delayed depolarizations may be the result of a wavefront of depolarization traversing a protracted path, a path made tortuous by the existence of fixed obstacles of non-excitable tissue (infarcted tissue). Or, delayed depolarizations may result from dynamic obstructions, evanescent islands of refractory tissue which force the depolarization wavefront to navigate a complex circuitous route. In either case, the delayed depolarizations can be seen to signal the presence of the requisite substrate for re-entrant dysrhythmogenesis.

6.2 Electrical Alternans as a Signal of Decreased Stability

We have held that for dispersion of refractoriness to be responsible for conduction abnormalities, some wavefront fractionation must occur, and the sites of this fractionation are those cells or regions of cells whose refractory periods exceed the interstimulus interval. As often discussed, during fixed-rate pacing these regions of cells could at best respond to every other wavefront of excitation. In the case of a spontaneously varying heart rate, where the variation in inter-beat intervals is small, we might still expect alternation of excitation of some sub-populations of
cells. With significant variation in inter-beat interval, one would expect a rather diffuse distribution of excitation activity, as slightly different (inter-beat interval dependent) populations fractionate the impinging wavefronts.

If the model we have presented so far is representative of the underlying mechanisms for cardiac rhythm disturbances, evidence of alternating behavior during fixed-rate pacing would be expected in terms of alternation of appropriate indices of wavefront propagation. The electrocardiogram provides a non-invasive measure of wavefront propagation and repolarization, and as such, if there exists within the myocardium a dispersion of refractoriness sufficient to induce dysrhythmogenesis, its presence may be reflected in alternation of ECG morphology.

It is important to realize that the links between dispersion of refractoriness, alternation of activation patterns, dysrhythmogenesis, and alternation of ECG morphology are not simplistic one-to-one relationships. First, a dispersion of refractoriness only gives rise to alternating activation patterns if the stimulation rate is fixed and sufficiently rapid so as to initiate an excitation wavefront prior to total recovery of the myocardium from the preceding excitation. The resultant alternation in activation wavefronts leads to dysrhythmogenesis in a geometry-specific fashion. The likelihood of re-entrant loop formation is strongly dependent on the time-dependent geometry of the refractory barriers and the relationship between these barriers and the activation wavefronts surrounding them. Thus, one would not expect a simple, monotonically increasing relationship between likelihood of dysrhythmogenesis and degree of alternation of activation patterns. The final link in the chain, that between fluctuations in activation wavefront morphologies and fluctuations in body-surface potential recordings (ECG's) is both complex and apparently degenerate (many-to-one). An exact link between body-surface
potentials and myocardial activation wavefront patterns would involve a solution of the "inverse problem" of electrocardiography, and it is currently believed that an exact solution is theoretically impossible. Thus, one might expect that alternation in myocardial activation patterns might not be directly in evidence in body surface potential recordings. To summarize then, the nature of the link between dispersion of refractoriness in myocardial tissue and alternation of ECG morphology would suggest that alternation in ECG morphology would be an insensitive indicator of the presence and severity of a dispersion of refractoriness present in the myocardium. As to the specificity of alternation of ECG morphology as an indicator of underlying dispersion of refractoriness, there is at least one other pathophysiologic state which may cause alternation of ECG morphology; alternation which is apparently unrelated to the distribution of cellular properties. In the setting of a pericardial effusion (fluid surrounding the heart within the pericardial sac), one can see alternation in ECG morphology caused by beat-to-beat "flip-flopping" of the heart within the pericardial sac. Aside from this situation, however, alternation of ECG complex morphology is ascribed to alternation of electrical properties of whole regions of myocardium or disjoint populations of myocardial cells.

6.2.1 Electrical Alternation - A Historical Perspective

Electrical alternation of electrocardiographic complexes is hardly a new finding. Sir Thomas Lewis wrote of "alternation of the heart" in the Quarterly Journal of Medicine as early as 1910. He concluded that such alternation occurs under two circumstances:
"It is seen when the cardiac muscle is not of necessity altered structurally, as an accompaniment of great acceleration of rate of rhythm. It is also found when the pulse is of normal rate, and under such circumstances the muscle is either markedly degenerate or the heart shows evidence of embarrassment as a result of poisoning or some other factor."

George Mines, another of the pioneers in the study of mechanisms of cardiac rhythm disturbances (who died as a result of self-induced ventricular fibrillation during one of his experiments), wrote in 1912 on his observation of alternation in the electrical activity recorded from the excised heart of Spanish terrapin.

"It may suffice to say that the condition of alternation depends essentially on local differences in the condition of the ventricular musculature."

The concepts embodied in these very early statements reflect the core of the current understanding of electrical alternation of ECG complexes. This is not to say, however, that there has not been further elucidation of the mechanisms by which some "embarrassment" of the cardiac musculature mediates the macroscopically observable alternation. By 1950, case reports of electrical alternation were relatively common, with several excellent reviews being available (Katz and Feil, 1937; Hellerstein and Liebow, 1950). By this time, electrical alternation had been linked to intoxications, paroxysmal tachycardias, cauterization of the myocardium, and coronary occlusions. In 1950, Hellerstein and Liebow reported a study of a canine preparation in which the effects of coronary artery occlusion were studied in terms of the frequency of producing electrical alternation. They demonstrated that 8 of 9 dogs surviving coronary artery occlusion developed electrical alternation of the ST segment of the surface electrocardiogram, and they stated that:
"Fundamentally, the factor underlying all forms of alternation is a marked prolongation of the refractory phase of some part of the heart leading to alternating localized blocks."

A recent study has substantiated this claim of S-T segment alternans accompanying myocardial ischemia (Russell, et. al, 1979).

With this information in hand, a general hypothesis begins to evolve. Any agent which adversely affects the myocardium and, as a result, causes some region of the myocardium to have lengthened refractory periods will initiate an alternating form of electrical activity. These depressed regions with long refractory periods will only be able to respond to alternate stimulations (provided that the interstimulus interval is shorter that the lengthened refractory times).

The first experimental evidence that this explanation might be an oversimplification was provided by Kleinfeld, Stein and Magin in 1956. By recording electrical activity from single ventricular fibers in frog heart, they were able to document four distinct types of alternating behavior; alternation of (1) the rate of depolarization, (2) the rate of repolarization, (3) the magnitude of the action potential, and (4) hyperpolarization. The authors were initially unable to provide an explanation for their observations. Nonetheless, the simple explanation of macroscopic alternation based on discrete regions of the myocardium which responded only to alternate stimulations was brought into serious question. Here was experimental evidence that the source of alternation need not be alternate firings of specific cells, but may instead be alternations in the morphology of cellular responses. Thus, the basis of the alternation could be a cellular effect, not a population effect.

These new findings can be reconciled with our previous arguments by
extending the concept of refractoriness to cover not only total cellular response (all-or-none), but also to cover the behavior of the various constituents of the overall cellular response. By viewing the overall cellular response as being made up of a number of independent cellular processes (for instance, the different time and voltage dependent membrane ion channels) each with their own characteristic refractory times, one can easily extend our original arguments of alternating response in an all-or-none fashion to include alternating *types* of responses, with the alternation being the result of a dispersion of refractoriness of the constituent cellular processes. While the exact mechanisms responsible for cellular refractoriness remain incompletely known, it is now appreciated that the different ion channels of the cardiac cell membrane recover their excitability with different time dependencies, a proposal which Kleinfeld and Stein were instrumental in elucidating in their subsequent paper in 1968.

A totally different explanation, but one that we have previously alluded to, was put forth by McGregor and Baskind (1955) to account for electrical and mechanical alternation as a clinical entity in the setting of pericardial effusion. Their proposal, simply stated, was that the cardiac structures were "flip-flopping" within the pericardial sac, and thus, surface measures of electrical activity were left to reflect this "flip-flopping" as an alternation. This proposal has been experimentally verified by simultaneously recording surface ECG's and visualizing the cardiac structures via 2-dimensional echocardiography. It is important to note, however, that this explanation is not in competition with the notion of electrical alternation on the basis of variations in refractoriness across the myocardium. The two proposals merely explain different entities which have one clinical presentation in common: electrical alternation.

Thus, three different mechanisms have been hypothesized as causing
macroscopically observed electrical alternans; localized blocks in various regions of the myocardium, alternation of the cellular response (by alternation of any of four different aspects of the cellular action potential), and gross "flip-flopping" of the cardiac structures within the chest. In the course of future discussion, we will concentrate on the first two hypothesized mechanisms, with the realization that these two different concepts can be viewed as stemming from some aspect of cellular refractoriness; either the cell is totally refractory to stimulation (i.e., a conduction block) or it is partially refractory so that its response lacks one or more of the constituent ionic responses.

This last point is extremely important because it broadens our discussion to include not only alternation resultant from highly localized 2:1 conduction blocks, but also alternation resultant from subtle alternation in the morphology of cellular responses. These two different phenomena can be appreciated as end-points of a continuum of refractoriness-induced responses. On the one hand, total refractoriness would lead to total lack of a cellular response, whereas partial refractoriness (only a small fraction of ionic channels remaining refractory) could give rise to an altered response. While the computer models presented previously incorporated only an all-or-none response, it is clear that the electrophysiology of cardiac cells allows for a richer variety of responses, with a range of refractoriness associated with even a single cell.

While we may argue that subtle alternation in type of response and total alternation (presence-absence) of response are two points on a continuum, we have argued that it is the fractionation of activation wavefronts as they encounter totally refractory regions that leads to dysrhythmogenesis. Partially refractory responses, even if they alternate with respect to morphology, would only be argued to lead to dysrhythmogenesis if these responses were aberrantly conducted, and thus served to
fractionate the wavefront. In light of this, it is good to remember that responses from partially refractory myocardial cells are typically of the "calcium-dependent" type, with diminished upstroke velocity. These responses are indeed aberrantly conducted, and thus would serve to fractionate an impinging wavefront of excitation, but admittedly to a lesser degree than would total lack of response. But perhaps more central to our model of dispersion of refractoriness giving rise to wavefront fractionation and re-entry is the concept that alternation in response, whether subtle or all-or-none, is taken here to be indicative of regions of myocardium being excited prior to complete recovery. It is a dispersion of refractoriness that potentiates the likelihood of such an event, thus establishing a link between dispersion of refractoriness and alternation of cellular responses, and thus a link between dispersion of refractoriness and alternation in ECG morphology. From this point it should be clear that because alternation of cellular response is not limited to the upstroke or depolarization phase, our later attempts to determine the role of alternation of ECG morphology should not be restricted to the QRS complex, but should include the ST segment and T wave as well.

6.2.2 Clinical Literature

A comprehensive review of the clinical case reports of electrical alternation would be out of place in this particular discussion. It is nonetheless important to note that while electrical alternans is a rare clinical finding, there have been well over 100 published case reports, with the overwhelming majority being in individuals with demonstrable organic heart disease. What is of significant interest is the finding that electrical alternans is a relatively common clinical finding in a number of disease states: specifically prolonged Q-T interval syndromes and Prinzmetal's angina (Schwartz, et. al., 1975; Schwartz and Malliani, 1975; Puletti, et. al., 1980; Rozanski, et al., 1978; Rozanski and Kleinfeld, 1982; Kleinfeld and
Rozanski, 1977).

Two clinical entities are recognized as prolonged Q-T interval syndromes; Jervell and Lange-Nielsen syndrome, characterized by prolonged Q-T interval, congenital deafness, and syncopal attacks due to ventricular fibrillation, and Romano-Ward syndrome, similar to Jervell and Lange-Nielsen with the absence of congenital deafness. Both conditions have a very high mortality rate and are recognized to contribute to sudden death in children.

These two clinical entities are of significant interest in this discussion because a prolonged Q-T interval is indicative of prolonged recovery times within the myocardium. The observation that individuals suffering from these syndromes frequently evidence electrical alternation is supportive of the general hypothesis that electrical alternation is resultant from regions of myocardium which have refractory times too long to allow for 1:1 conduction. These regions of prolonged recovery times thus experience 2:1 conduction (either absolute conduction block on alternate beats or simply alternation in response), thus giving rise to the macroscopic appearance of electrical alternation. The very high incidence of ventricular fibrillation in these individuals is to be expected in light of our previous discussions.

Prinzmetal's angina describes a particular disease state which is believed to be characterized by vaso-spasm of the coronary arteries. Of 21 individuals suffering from this condition, 8 or 38% were found to have electrical alternation of the S-T segment during episodes of presumed vaso-spasm (Rozanski, et. al, 1978; Rozanski and Kleinfeld, 1982; Kleinfeld and Rozanski, 1977). This is again supportive of the notion of electrical alternans being caused by a variation in cellular refractoriness, in that transient vaso-constriction of a coronary artery is accompanied by ischemic changes in downstream myocardial tissue. Ischemia has been shown to elicit many responses from myocardial cells, including a lengthening of cellular recovery times.
Thus, the finding of electrical alternation of the S-T segment in individuals with Prinzmetal's angina is consistent with the notion of a temporary vaso-constriction which leads to ischemia-induced prolongation of recovery times which in turn creates regions of tissue which show 2:1 conduction patterns. It is of interest to note that individuals with Prinzmetal's angina are at high risk of developing ventricular fibrillation and sudden death. In a recent study by Rozanski and Kleinfeld, it was demonstrated that the occurrence of S-T and T wave alternans heralded the onset of serious ventricular dysrhythmias, including ventricular fibrillation (Rozanski and Kleinfeld, 1982).

Before leaving the discussion of electrical alternans as a recognized entity, it is important to mention one other experimental correlation that has been noted in the literature, namely the relationship between electrical alternans and sympathetic nervous system activity. It has been experimentally shown that either pharmacologic blockade of the right stellate ganglion or direct stimulation of the left stellate ganglion leads to prolongation of the Q-T interval and subsequent electrical alternation of the S-T segment and/or the T wave (Schwartz and Malliani, 1975). The mechanism responsible for these findings is still under debate, but the current wisdom is that an increase in left stellate ganglion outflow (either by direct stimulation or via reflexogenic increase subsequent to right stellate ganglion suppression) causes a spatially inhomogeneous effect on cellular recovery times, causing some subset of myocardial cells to have refractory times longer than the interstimulus interval. The spatial inhomogeneity in effect stems from the spatially inhomogeneous sympathetic innervation of the cardiac structures.

In summary thusfar, we have demonstrated that the dispersion of refractoriness hypothesis argues for the existence of electrical alternans (EA) as a predictor of decreased myocardial stability and that this prediction seems to be
borne out by a few experimental and clinical observations. The question arises, however, as to why EA is not commonly seen as a precursor to re-entrant rhythm disturbances. If our model of dispersion of refractoriness as presented herein is correct, one would expect that EA would serve as a non-invasive “flag” that the substrate for re-entrant dysrhythmogenesis is present. There are many different possible reasons as to why EA is not observed as a pre-dysrhythmic indicator, not the least of which is that the model of dispersion of refractoriness as presented here may be invalid or at least incomplete. If this simple model is basically correct, however, EA may not be globally appreciated because the effect may be subtle, and may therefore escape observation by all but sensitized observers. In any event, an experimental and clinical evaluation of the utility of using EA as a measure of electrical stability is thought to provide valuable insight into mechanisms of dysrhythmogenesis, in that such a study will afford a quantitative test of one major and heretofore apparently overlooked prediction of the model of dispersion of refractoriness. To this end, a series of animal experiments have been undertaken. The animal model used is a canine preparation wherein coronary artery ligation, hypothermia, and rapid atrial pacing are the interventions used for inducing electrical instability.

Before going on to a discussion of experimental protocols used to quantitatively evaluate this prediction, it would be remiss to fail to discuss a possible link between EA and newly evolving theories of chaos in deterministic systems.
Chapter 7

Is Electrical Alternans to Fibrillation
What Period Doubling is to Chaos?

(N.B.: Segments of the discussion of dynamical systems theory presented here are modeled after Rapp, P., 1982; 1983; and personal discussions.)

Up to this point, we have framed our discussions in terms of specific properties of individual myocardial cells and the way in which these specific properties might determine the composite behavior of connected populations of such cells. In this way, we have hoped to deduce certain predictions about overall performance from elemental properties. This functional modeling has allowed us to put forth explanations of a rich variety of tissue-level behavior in terms of simple, readily observable properties of individual cells.

One can take a distinctly different approach to viewing certain features of the propagation of electrical impulses across a region of myocardium; one can ignore the many particulars of the system, and simply view this problem as a specific case of a very general problem. By "stepping back" in this fashion, one might diminish the requirement for precise detail about the specific system under study while concentrating on the most fundamental or universal aspects of system behavior.

One particularly interesting and potentially relevant area of research along the lines of universal system behavior has been that of the study of chaos in dynamical systems. The apparent similarity between the transition of normal sinus rhythm to ventricular fibrillation and the transition of a deterministic system from a normal stable regime to a chaotic regime encourages at least an introductory discussion of the methodology and results of this emerging area of research. We will attempt to
present, without mathematical rigor, the few central ideas in this area, and discuss what implications may be drawn about the specific problem of dysrhythmogenesis in myocardial tissue.

One can describe many systems by a series of coupled differential equations (difference equations in the case of discrete systems) relating the instantaneous change of any state variable in terms of a function of all system variables, system parameters, and time, viz:

\[
\begin{align*}
\frac{dx_1}{dt} &= f_1(x_1, x_2, \ldots, x_n, t, p_1, p_2, \ldots, p_m) \\
\frac{dx_2}{dt} &= f_1(x_1, x_2, \ldots, x_n, t, p_1, p_2, \ldots, p_m) \\
&\quad \vdots \\
\frac{dx_n}{dt} &= f_1(x_1, x_2, \ldots, x_n, t, p_1, p_2, \ldots, p_m)
\end{align*}
\] (7.1)

where \(x_1\) through \(x_n\) are dynamic state variables, \(t\) is time, and \(p_1\) through \(p_m\) are system parameters which determine the system (i.e., they do not vary in time, but instead vary from system to system or case to case).

From this formulation, one can either set out to characterize \(f_1\) through \(f_n\) and \(p_1\) through \(p_m\) and thereby arrive at an exact solution to the dynamic evolution of the state variables from a known set of initial conditions, or one can discuss, in general terms, the type of behavior which the solutions may have. The former approach is perhaps exemplified by the work of Hodgkin and Huxley (Hodgkin and Huxley, 1952). The Hodgkin-Huxley equations have been improved or altered to account for more accurate measurements, and there is hope that such an approach will eventually allow for a complete characterization of the dynamics of the spread of ionic current and activation wavefronts in myocardial tissue. Until a complete
and accurate characterization of the system exists, the latter approach, that of examining the different types of possible solutions, may offer some insight into system behavior.

In general, the system of equations represented by equation (7.1) may demonstrate only three different classes of solutions. The simplest and most intuitive form of the solution is the fixed-point solution. A fixed-point solution is a solution to equation (7.1) where the functions $f_1$ through $f_n$ simultaneously pass through zero. In general, two different types of fixed-point attractors exist, stable or attracting fixed-points and unstable or non-attracting fixed-points. For a fixed-point solution to be a stable or attracting solution, it must be the case that if the system is displaced from this fixed point, it will return to it in finite time. Obviously, if the solution does not return to the fixed-point once displaced from it, the fixed point is said to be non-attracting or unstable.

Systems may have any number of fixed points, but only one such fixed point can be said to be globally attracting, i.e., the system will converge to that solution regardless of its initial conditions. If we imagine an $n$-dimensional space where each axis corresponds to one of the system state variables, then we can frame the above discussion in terms of system trajectories in the $n$-dimensional space. The initial conditions describe a point in the $n$-dimensional space, and the dynamic evolution of the system to a fixed point corresponds to a trajectory or path in the $n$-dimensional space to a stable point. Clearly, if there is one globally attracting fixed-point attractor, the path of system trajectory from any point (other than other non-globally attracting fixed-points) in the space will terminate on that single point.

A simple example should illustrate the concepts we have just described (see Figure 7-1). Consider the system of a ball bearing in a concave-up semi-circular track in a uniform gravitational field.
Figure 7-1: The concept of fixed point attractors. a) Following any initial placement, the bearing will follow a trajectory to the stable fixed-point attractor located at the bottom of the semi-circular track. b) Two stable fixed-point attractors now exist at the two basins of the track, and three non-stable fixed-point attractors also exist at the three flat peaks in the track.
Regardless of the initial placement of the ball bearing, the position of the ball bearing will converge (due to frictional losses) to the lowest point on the track. Thus, the bottom of the track is a globally attracting fixed point attractor. Now, consider deforming the track so that it forms two periods of a cosine wave. This track configuration will have two "lowest" points which will each be locally attracting (at $\pi$ and $3\pi$) and three non-attracting fixed-points (at 0, $2\pi$, and $4\pi$).

Moving on from fixed-point solutions, we may consider periodic solutions to equation (7.1). Periodic trajectories in complex systems are commonplace. The all too familiar acoustic ringing which occurs in improperly adjusted public address systems and the periodic trajectories of planets and satellites are examples of periodic solutions. [Note: Planet orbits are only truly periodic in the case of zero frictional losses. Otherwise, the orbits degenerate to a fixed-point. In the case of the Earth, the Sun may be thought of as the fixed-point attractor.] In terms of our $n$-dimensional state variable space, periodic trajectories are closed paths, i.e., trajectories which close on themselves. The path of a periodic solution can be either attracting or non-attracting, just as was the case with fixed point attractors.

The last type of solution to equation (7.1) is the aperiodic or chaotic solution. This is potentially the least intuitive, but most interesting of the types of possible solutions, and as such we will discuss this type of solution in detail. At the outset, it is important to note that the chaotic nature of the solution is not the result of stochastic variability of the system -- equation (7.1) is a deterministic system. Thus, the solution is deterministically chaotic.

As the convergent fixed-point solution was characterized in our $n$-dimensional space by a fixed-point attractor, and the convergent periodic solution was described by a periodic attractor, aperiodic or chaotic solutions are said to be governed by strange attractors. Apart from the statement that strange attractors are attractors
“of the third kind,” i.e., neither fixed-point nor periodic, one can further restrict the
definition of a strange attractor to include only those attractors which result in the
system trajectory being exquisitely sensitive to initial conditions. The nature of the
sensitivity to initial conditions is such that for initial conditions in the neighborhood
of the strange attractor, infinitesimally small changes in initial conditions result (for
short time intervals) in exponentially divergent trajectories. The exponent
associated with the divergence in system trajectories is referred to as the Lyapounov
exponent, and it is used as an experimental measure of a system’s chaotic nature.

What is meant by deterministic chaos? Chaos, as a word, has nearly lost its
meaning. In this context, we say that a particular solution is chaotic if its trajectory
is governed by a strange attractor. In terms of our $n$-dimensional state space, the
trajectory of the system “wanders” about the space, choosing to travel in a path
which may recur near itself, but never re-tracing its same steps. Typically, systems
governed by strange attractors exhibit quasi-periodic behavior, i.e., the solutions
have large periodic components, but there is always a degree of pseudo-randomness
which serves to perturb the system from following a periodic trajectory. This quasi-
periodicity in system trajectory displays itself when frequency analysis is done on
the time-trajectories of state variables - the resulting spectra show prominent peaks
amidst a background of broad-spectrum “noise”. Thus, deterministic chaos is
usually not a state of total randomness akin to a white noise process, but is instead
usually characterized by a non-repeating, quasi-periodic system trajectory.

Until now, we have only succeeded in describing nomenclature, hopefully
taking some of the mystery out of phrases like “strange attractors” and
“deterministic chaos.” To regain a perspective of the “trajectory” of this
discussion, we will recall that the analogy between the transition of normal sinus
rhythm to ventricular fibrillation and the transition of a stable solution to a chaotic
one is what drew us down this line of discussion. Having said this, we will now investigate what is known about the transition from a stable state (governed by either a fixed-point or periodic attractor) to a chaotic state (governed by a strange attractor).

To examine the transition from a stable solution to a chaotic solution we will investigate the behavior of the solution as a function of the system parameters. In terms of equation (7.1), this corresponds to smoothly changing the system parameters, $p_1$ through $p_m$. If we smoothly alter the system parameters from one case where the system trajectory is governed by a stable attractor (either fixed-point or periodic) to a regime where the trajectory is described by a strange attractor, can we expect any "universal" behavior? In particular, may we expect to see precursors to the transition to chaos? If the transition to chaos for the general system described in equation (7.1) is marked by a universal type of system behavior, then perhaps it is this behavior which we should search for as a precursor of ventricular fibrillation. On the other hand, if the chaotic regime is arrived at by "falling off a cliff" in the parameter space, i.e., there is no transition region, only a discontinuity in qualitative system behavior occurring at some border, then we might just as well have avoided this discussion entirely. Having said this, it should now be clear to the reader that there are specific system behaviors which, for whole classes of systems, are characteristic of the transition to a chaotic regime.

Of special interest in this thesis in the observation that some experimental systems have been shown to have a common path to chaos through a series of "period-doubling bifurcations" (Feigenbaum, 1980). A period-doubling bifurcation is said to occur when, for a infinitesimal change in a system parameter there is a qualitative change in system behavior, such that the system moves from following a periodic trajectory of period $T$ to one of with period $2T$. Thus, period-doubling
simply describes the change in the period of the system trajectory, and *bifurcation*
alludes to the abruptness of the change. We will discuss a mathematical example of
a simple system which illustrates such behavior (taken from Sparrow, 1980).

Consider the system governed by:

\[
\begin{align*}
\frac{dx_1}{dt} &= n \cdot (f(x_n) - x_1) \\
\frac{dx_2}{dt} &= n \cdot (x_1 - x_2) \\
\frac{dx_3}{dt} &= n \cdot (x_2 - x_3) \\
&\quad \vdots \\
\frac{dx_n}{dt} &= n \cdot (x_{n-1} - x_n)
\end{align*}
\]  

(7.2)

where \( n = 50 \), and \( f(x) = r \cdot x \cdot e^{-x} \). This system of equations contains only one non-
linear element, one loop, and only one system parameter \( r \), yet it demonstrates the
transition to chaos which we have just discussed.

For \( 0 < r < 1 \), there is a fixed-point attractor for all positive initial conditions
at \( x_j = 0, \forall j \). For \( 1 < r < r_0 \), \( r_0 \) being dependent on \( n \), for \( n = 50 \), \( r_0 \) is
approximately 8.2] there are two non-negative fixed-point solutions, \( x_j = 0, \forall j \)
(non-attracting) and \( x_j = \ln (r), \forall j \). The second solution is an attracting fixed-
point solution for all positive initial conditions. At \( r = r_0 \), the attracting fixed-
point solution undergoes a Hopf bifurcation, i.e., the fixed-point attractor gives rise
to a periodic attractor with a period \( T \) approximately equal to 2. As \( r \) is smoothly
increased, the attracting periodic solutions go through a series of bifurcations where
solutions of approximate period \( 2^i \) give way to solutions of period \( 2^{i+1} \). At some
value of \( r \), in this case where \( n = 50 \), for \( r > 21 \), solutions appear no longer
periodic, and the system appears to be in a chaotic regime. As \( r \) is increased further, the system behavior retracts its steps, going through a series of “reverse bifurcations” to a stable periodic attractor of period approximately equal to 2.

The scenario depicted above, that of a system making a transition to chaos through a series of period-doubling bifurcations, (the Feigenbaum scenario of a period-doubling route to chaos), might be a behavior peculiar to a very special set of systems which have little or nothing to do with physical reality. This does not appear to be the case, however, as many different types of systems which evidence chaotic regimes demonstrate approximate Feigenbaum scenarios (May, 1981; Rapp, 1982). In particular, a large class of discrete systems defined by difference equations can be analytically shown to yield this “universal” behavior, and much has been done to characterize the exact nature of the bifurcations, and predict where such bifurcations occur (May and Oster, 1976; Feigenbaum, 1980). Of the continuous systems, hydrodynamic systems are perhaps the best studied “chaotic” systems, and these systems often show period-doubling bifurcations en route to chaos (Ahlers, 1974; Ahlers and Behringer, 1978a,b; Gollub, 1981; Libchaber and Maurer, 1981). However, not all systems (discrete or continuous) which experience chaotic behavior make an orderly transition through period-doubling bifurcations (Eckmann, 1981), and thus the “universality” of the Feigenbaum scenario is not to be taken literally. Indeed, without (and often with) an exact expression for the system functions in equation (7.1) it is impossible to predict whether the system will possess chaotic regimes, and if so, whether the passage to chaos will be through a series of period-doubling bifurcations.

Having introduced the topic of deterministic chaos and the potential of period-doubling bifurcations serving as a common marker for the transition to chaos, what inferences may we make about precursors to ventricular fibrillation? If we assume
that the system of cardiac conduction may be described by a set of equations similar to equation (7.1), we might look for period-doubling bifurcations in system state variables as an indicator that the system is headed toward a chaotic regime. One such bifurcation would be in the form of an alternation of ECG morphology on a beat-to-beat basis (electrical alternans), where the ECG had previously been identical from beat to beat. Several points should be stressed here. First, the analogy of ventricular fibrillation to chaos, while attractive, may not be accurate; experimental verification that an observed process is truly chaotic is impossible. Secondly, the processes of cardiac conduction may have stochastic elements which may play a role in determining system behavior. As such, we may not be able to rigorously apply the results from studies of dynamical systems and deterministic chaos. Even given these reservations, the path to chaos (here questionably compared to ventricular fibrillation) need not be through a series of period-doubling bifurcations. The chaotic regime may be approached in an entirely unrelated fashion (Eckmann, 1981). If we assume that the system of cardiac conduction is a system which moves from stable to chaotic regimes through a series of period-doubling bifurcations, we are still not guaranteed that the period-doubling would be observable. Indeed, of the many state variables which are involved in the description of cardiac conduction, relatively few are observable. Even the time course of the transmembrane potential experienced by the population of cardiac cells is unobservable due to the degenerate nature of the mapping of myocardial electrical activity to body surface potentials. Finally, if we do observe period-doubling (the first period-doubling bifurcation corresponding to electrical alternans), this does not necessarily indicate that the system is moving toward chaos. Period doubling can be demonstrated in systems which do not show chaotic behavior.

What have we learned from this discourse on the emerging theory of
dynamical systems analysis and deterministic chaos? We have learned that many systems which evidence chaotic behavior make the transition from a stable regime to a chaotic one by moving through a series of period-doubling bifurcations. We have suggested, with many reservations, that the appearance of electrical alternans might be viewed as a first step from stable cardiac conduction toward the evolution of ventricular fibrillation ("cardiac chaos").

7.1 Limit-cycles in the Model - Re-examined

The immediately preceding discussion focussed on the possibility of viewing electrical alternans as a period-doubling bifurcation, a potential indicator that the system of myocardial conduction is headed toward a chaotic regime. We have already provided a discussion of the nature of the alternation in the simple finite-element or discrete-element model (see Chapters 3 and 6), demonstrating that such alternation is to be expected as the system acquires the substrate required for re-entrant loop formation. Attempts to combine the "universal" theory of a period-doubling bifurcation route to chaos with our simple model which demonstrates period-doubling (and, in some cases, higher order limit-cycles) have been largely unsuccessful (Ritzenberg, 1984), with conclusions limited to conjecture. In this discussion, we will show that limit-cycle oscillations of period greater than 2 need not be indicative that the system is progressing toward chaos, but may instead be a direct result of the particulars of the model. Such a conclusion is most damning to attempts to view these higher order cycles as analogous to "universal" behavior as described by Feigenbaum, in that such "universal" behavior is believed to be independent of system particulars.

Consider the initial state of the array at the time that an activation sequence is initiated. What is meant by initial state here is the sum total of all information
required to uniquely specify the refractory properties of the complete array. In our model, this information is provided by the refractory period duration of each element within the array, and the refractory-time remaining for each element. When put in this framework, it is clear that three types of responses (trajectories, or qualitative behaviors) are possible: the system can relax back to its zero-state (all elements excitable), the system can cycle, periodically re-exciting itself (analogous to circus-movement tachycardia), or the system can aperiodically re-excite itself (ventricular fibrillation). From this very simple presentation, we might conclude that the problem of assessing system behavior reduces to a problem of initial conditions, and in the simple case of only one excitation, that is indeed the case. The more interesting case, however, is when the system is externally driven (periodically or quasi-periodically). How does one extrapolate the system response from initial conditions to the case of repetitious excitation?

The problem as stated is theoretically solved by noting that the if the system trajectory is exactly determined by its state at the time of a stimulation, then its behavior in response to a series of stimulations is also determined. The system trajectory from the initial conditions can be evaluated at the time of the second impulse to ascertain the "initial conditions" for the second impulse. From this point, the situation is iterative. For any arbitrary time of stimulation, the system trajectory is totally determined by the state of the system at that time. It is this single feature, that the system trajectory depends only on the current state, that is called the Markov property.

The fact that the role of system's history in determining its future is totally determined by the present state of the system allows us to rephrase our questions about system behavior. To determine whether the system may evolve to show chaotic behavior, we need only ask if the system can generate a state which is in the
subset of initial states which results in chaotic behavior. The question in essentially the same for periodic solutions (circus-movement tachycardia). These may seem to be trivial statements, but they have real implications. For instance, given an array with zero-state initial conditions, and no dispersion of refractory periods, it is impossible to yield a sequence of identical stimulations which give rise to either self-sustained periodic or aperiodic behavior. This is obvious because under these conditions, the system has no opportunity to break symmetry -- the trailing edge of the activation front (the front of recovery) is exactly similar to the leading edge, thus, each wavefront must follow exactly the same path as the previous, with the system returning after a fixed time to the zero-state. In order for either of the self-sustaining modes to evolve, the system must first be able to break symmetry. Somewhere in the system's trajectory must be a state which, if used as an initial condition, would result in a trajectory which differs from the preceding one. This opportunity to break the symmetry of the trajectories is a requirement if the system is to show anything other than stereotypical return to the zero-state.

There are countless ways in which the symmetry can be broken. A very simple example would be that all elements share a common refractory period, \(r\), with the exception of one which has a refractory period somewhat longer than the rest, say \(r^*\). If we start in the zero-state initial state, we will see that the trajectory (the time course of the state of the array) will experience a number of symmetry breaking states. These symmetry-breaking states are those in which the trailing edge of the activation front (the border between excitable and refractory elements) at time \(t\) differs from the leading edge of the activation wavefront (advancing border of active sites) at time \(t - T\). See Figure 7-2. For the case described here, symmetry is broken for a period of time equal to \(r - r^*\).

What happens next? There are three possibilities. The system may not have
Figure 7-2: Illustration of how the symmetry between the leading and trailing edge of a travelling wave is broken as a result of elements with refractory prolonged periods.
been stimulated during these times of broken symmetry and as such, it relaxes back
to the symmetrical part of the trajectory and subsequent stimulation results in an
identical trajectory. If the system is stimulated during the times of broken
symmetry, the new system trajectory will differ from its immediate predecessor. At
this point there are two possibilities. The new trajectory may experience some
times of broken symmetry or it may not. If it does not, the system reverts back to
it initial trajectory. In this case, a series of activation sequences would give rise to
alternating trajectories. In the case where this new trajectory experiences some
degree of broken symmetry, a new distinct trajectory may be created. This pattern
of forming new trajectories may continue for some fixed number of cycles (thereby
giving rise to the appearance of limit-cycle behavior in a sequence of successive
activations) or new trajectories may be formed indefinitely (giving rise to a state of
apparent chaos). We should note here that in a system such as ours with a fixed
number of elements, there are not an indefinite number of possible trajectories.
Chaos in discrete systems such as this usually is taken to mean periodicity on the
order of $2^N$ (Ritzenberg, 1984).

To illustrate the notion of broken symmetry, and how it may give rise to new
trajectories, consider the case of a single element having a refractory period which is
$\tau_d$ time units longer than that shared by the the rest of the population. The first
activation wavefront leaves a refractory wake which is not symmetrical to the
activation front which gave rise to it. Depending on the specific rule for conduction
(see Figure 7-3) a properly-timed second activation front may result in several
different trajectories (different activation wavefronts). Again, depending on the
conduction scheme and also on the particular new trajectory, different refractory
wakes are left behind. These wakes may in turn give rise to new and distinct
activation patterns (see Figure 7-4).
**Figure 7-3:** Two different possible conduction rules for a two-dimensional lattice. In a), only those neighbors that share a "face" are stimulated on the next game turn. In b), even those neighbors that only share a vertex are stimulated on the following game turn.

For the case of the simple conduction scheme shown in Figure 7-3a, four different activation sequences are possible when there is a singular outlier encountered (one element whose refractory period exceeds the rest) with $r_d = 1$ (see Figure 7-4). In the case of a zero-rest state, with all elements recovered, the activation wavefront proceeds uniformly through the region containing the irregular element. Following such an activation sequence, this irregular element will be refractory for a one-unit longer than its neighbors. If the next activation sequence arrives at the one time unit when there is this differential excitability (corresponding to an interstimulus interval equal to the refractory period of the bulk
Figure 7-4: Different limit-cycles that result from a single element having a dissimilar and prolonged refractory period.
of the population), the conduction scheme allows the wavefront of activation to circle around this one element and excite it from the side one time unit later. This sequence will result in this one element being refractory for two time units longer than its neighbors (one unit because of the activation delay and one because of the intrinsic difference in refractory period duration). If another stimulus arrives at the time of maximum differential excitability, then the activation wavefront circles around the initially refractory element, this time exciting it from behind, with a delay of three time units (one unit up, one unit over, and one unit down). Since this delay is the maximum that the conduction rule can support for the activation of an isolated element, if the next activation sequence arrives at the time of maximum differential excitability, the element will not be activated. As such, the element will no longer provide an obstruction, and a perfectly homogeneous spread will again occur. Provided the stimulation sequence is periodic, this behavior will correspond to a limit-cycle of four in the activation sequence. In the case where $3 \geq \tau_d > 1$, only a three-cycle would evolve, in that the conductive path with delay of one unit would not have resulted in the element being activated, while the path with a delay of three would still be successful. In the case where $\tau_d \geq 4$ only a two cycle would be possible.

We can generalize the above result to describe the effect of any conduction scheme. If the scheme allows for $N$ different activation possibilities (each with an associated unique time delay) then, there is an orderly sequence of bifurcations associated with the limit-cycle of activation sequences for an isolated unit with a refractory longer than its neighbors. For $\tau_d = 0$, each activation sequence is the same, corresponding to an limit-cycle of period 1. For $\tau_d = 1$, an $N$-cycle in the activation sequence evolves. As $\tau_d$ increases, as many as $N-1$ bifurcations occur, each successive bifurcation resulting in a longer period limit-cycle. For $\tau_d$ greater
than the maximum delay which the conduction rule can support, the limit-cycle stabilizes at a period of 2.

The relationship between these conduction-rule-induced limit-cycle bifurcations and self-sustaining activity is neither obvious nor simple. We will now discuss the link between these two types of behavior, and at the same time make an important distinction between deterministic chaos in a model such as ours when periodically driven vs. aperiodic self-sustained behavior.

7.2 Closing the Loop

It is obvious that a single element with a refractory period different from that of the rest of the population cannot give rise to complex, self-sustained activity. As best, a single element can be responsible for the evolution of limit-cycles in the activation sequence, with the period of the longest limit-cycle limited by the nature of the conduction scheme. For the simple case of four nearest neighbors on a square lattice, 2-, 3-, and 4-cycles could evolve from such a singularity. Self-sustained activity can only result when there is "cooperation" of a number of such elements, i.e., when a number of elements combine to form a conductive path of sufficient length to allow for re-entrant excitation. The important questions become how does such cooperation evolve and what are the touchstones along this route toward self-sustaining behavior.

The evolution of such cooperation is easy to describe in a simplistic sense in the context of our conceptual model of the role of a dispersion of refractoriness. As the dispersion of refractoriness (standard deviation of the refractory period distribution) increases from zero, more and more isolated elements appear with refractory periods which differ from their neighbors. These outlying elements are not all characterized by the same $r_d$; there is instead a distribution of values of $r_d$. 

According to our foregoing discussion, many of these different $\tau_d$ may be associated with different limit-cycles in their activation sequences. Taken as a whole, the activation sequence describing the entire array would then have an overall limit-cycle equal to the least common multiple of the individual limit-cycles. For the simple case of a four-neighbor conduction scheme, one would expect to see not only 2-, 3-, and 4-cycles, but as the dispersion of refractoriness increased, one would expect to see 6- and 12-cycles. These cycles have been observed in exactly this context (Ritzenberg, 1984); however, they were incorrectly conjectured to be analogous to the period-doubling bifurcations en route to chaos.

As the dispersion of refractoriness is increased further, the outlying elements begin to occur in clusters (as was pointed out in the section on percolation theory). This clustering allows for cooperation between elements to the point that a conductive path is eventually formed which allows for re-entrant excitation. Re-entrant excitation can be here defined as excitation which travels from the organized wavefront of activation to the following wavefront of recovery In this context, what behavior can we expect as the process of cooperative clustering evolves?

We discussed how single isolated elements with refractory periods different from their neighboring environment could give rise to a series of limit-cycle bifurcations, and that a disjoint population of such elements could give rise to even more bifurcations, with the derivative limit-cycles having periods which are multiples of the fundamental limit-cycles determined by the conduction scheme. Evidence of cooperation between elements would be the evolution of limit-cycles with periods different from the small set of periods explained by linear superposition of the fundamental periods. In our simple example with 2-, 3-, 4-cycles being the fundamental cycles, 6- and 12-cycles could be arrived at via linear superposition,
but, for example, a 24-cycle could only result from some interaction between elements. Similarly, other non-fundamental cycles would also indicate that some level of cooperation was taking place. It is important to note, however, that the cooperation of neighboring elements need not force the evolution of such higher or lower period limit-cycles.

To demonstrate that cooperation between elements can give rise to limit-cycles with periods not simple multiples of the fundamental periods, consider the array pictured in Figure 7-5.

\[
\begin{array}{ccc}
\tau & \tau + 2 & \tau \\
\tau + 1 & \tau & \tau \\
\tau & \tau + 1 & \tau \\
\end{array}
\]

**Figure 7-5:** Array of refractory times which gives rise to “cooperativity” and a resultant limit-cycle for overall activation with a period of 20 (stimulation periods).

The combination of the three elements with prolonged refractory periods in close proximity causes an interaction which leads to the formation of a limit-cycle of period five for the activation of one of the elements, and a limit cycle of period twenty (20) for the activation sequence for the overall array.

It is clear that in a large array, periodicities in local areas may take on a wide variety of values as the local cooperativity increases. The result is that the period of the limit-cycle for the activation sequence of the entire array (equal to the least
common multiple of these regional periods) may approach a "relative infinity" compared to the time scale of our observations. So, it would seem that while there appears no simple period-doubling route to chaos, there may be a period-lengthening route to a nearly-chaotic regime. Even this, however, is an oversimplification. The periods of the limit-cycle need not grow monotonically. One can easily imagine scenarios wherein greater cooperation between elements results in the cancellation of higher order effects, giving rise to lower period limit-cycles, and because adjacent refractory periods are modeled as independent realizations of a random process, cooperativity need not evolve in any particular fashion. Thus, all that one can safely say is that with greater cooperation between elements, longer period limit-cycles are possible.

It is very important to point out that the very long period limit-cycle for the activation of the entire array which we have just discussed is not analogous to ventricular fibrillation. This very long cycle is the result of variations in local response to periodic stimulation. If the system were not periodically driven, it would return to its rest state. The analogy to ventricular fibrillation applies instead to the case of a self-sustained, aperiodic activation sequence. The onset of this self-sustained activity occurs when some threshold level of cooperativity between elements in some region of the array is surpassed. Rather than this form of periodic activity being the end result of a very large number of period-lengthening bifurcations, this self-sustained behavior may be triggered long before the majority of the potential limit-cycles are seen. In this way, the transition to self-sustained, aperiodic, re-entrant activation may be seen to interrupt the period-lengthening bifurcation sequence, and at this point, it seems impossible to predict exactly where in the bifurcation sequence such a transition to self-sustained behavior is likely to occur.
We will conclude this section by summarizing our observations. First, there is a great deal of interest and activity in the field of non-linear dynamical systems, particularly those which demonstrate deterministically chaotic behavior. One major result from recent investigation suggests that a wide variety of systems which evidence chaotic behavior may have a common route to the chaotic regime - a path marked by sequential period-doubling bifurcations. It has been suggested that electrical alternans may represent one such period-doubling bifurcation on the route to "cardiac chaos" or ventricular fibrillation. While this suggestion for actual myocardial conduction processes is left to the level of conjecture, investigation of our simple model reveals the potential for many different limit-cycles, alternation being only one such cycle. The model fails to display a period-doubling route to chaos, and instead suggests that the transition to self-sustained aperiodic behavior need not be directly preceded by any particular progression of period-altering bifurcations. What limit-cycles that are observed in model behavior are explained in terms of the specific deterministic conduction rule and interactions between cooperating regions (an "artifact" of the conduction scheme?).

Where does this leave us in our search for a precursor to the transition from normal sinus rhythm to ventricular fibrillation? We have demonstrated that a dispersion of refractoriness may combine with the different conduction rules to yield a variety of limit-cycles in the activation pattern. While the existence of limit cycles other than period 2 depend on the particulars of the conduction rule, period 2 limit-cycles can evolve from any plausible conduction rule. That this is true, one need only consider that a given element only has $N$ chances in time to be activated as an activation front passes by, where $N$ is set by the conduction scheme. If the elements refractory period is greater than $N$ time units longer than the interstimulus interval (but less than twice the interstimulus interval) a 2-cycle for
activation will develop. This is true for any \( N \), and as such, the 2-cycle, or alternation, is the most robust cycle which one could expect to precede the onset of self-sustained aperiodic activity. Higher order periodicities which are independent of the particular conduction scheme may occur, and future work (perhaps that by B. Saxberg) will hopefully provide additional insight into this very important area. For now, however, the potential role of these higher order periodicities in predicting the vulnerability to ventricular fibrillation \textit{in vivo} is brought into serious question, both because such periodicities in the studied models are apparently conduction-rule dependent and because the particular sequence of period-altering bifurcations is determined by stochastically influenced cooperativity between adjacent model elements. The particular sequence of bifurcations seen in model studies, with the exception of the first period-doubling bifurcation (that of electrical alternans) varies both as a function of the particular conduction scheme employed and as a function of the spatial arrangement of refractory times, which is under stochastic influence. For these reasons, the animal studies which we next describe will focus on detection of alternation in ECG morphology (the 2-cycle) and the correlation of such alternation with decreased electrical stability.
Chapter 8

Animal Studies -- Phase I

8.1 Experimental Method

The experiments were performed on 20 mongrel dogs, 15-25 kilograms in weight, anesthetized with 1 mg/kg of morphine intramuscularly and 20 mg/kg of sodium pentobarbital (Nembutal) intravenously. Additional Nembutal was given as needed to maintain the dogs deeply anesthetized. Respiration was maintained by means of an air-cuffed endotracheal tube and a mechanical ventilator. Saline filled Tygon tube catheters were advanced into the right femoral artery and vein for the recording of arterial and central venous pressures via Statham P23a transducers. Two transcutaneous needle electrodes were applied on either side of the chest at the level of the 4th or 5th intercostal space, just lateral to the mid-clavicular line for recording of a modified lead I surface electrocardiogram (Electronics for Medicine ECG amplifier bandpassed 0.04 - 500 Hz). Three different interventions were used to decrease myocardial electrical stability: hypothermia, coronary artery ligation, and rapid atrial pacing. All physiologic waveforms were recorded on a Hewlett-Packard 3968A 8 track FM instrumentation tape recorder, with tape speed of 3-3/4 inches per second. The 3dB bandwidth at this setting is 0 - 1250 Hz.

The hypothermia experiments were carried out in closed chest preparations. Transvenous bipolar electrodes were introduced through a femoral incision. One was advanced to the right atrium for atrial pacing, the other was advanced to the right ventricle for VFT (Ventricular Fibrillation Threshold) determination. A carotid artery - jugular vein bypass heat exchanger was used for cooling and
maintaining the animals at a rectal temperature of 28 - 30 °C.

For the myocardial ischemia experiments, the heart was exposed via a split sternum preparation. The left anterior descending coronary artery was prepared for reversible ligation at the level of the third diagonal, by passing a nylon ligature around it. The sinus node was crushed to slow the intrinsic sinus rate, with the heart being paced via the transvenous atrial catheter electrodes. Two sets of ventricular electrodes were attached to the left ventricle for recording epicardial electrograms. The electrodes were positioned so that they would be in the border zone between ischemic and non-ischemic tissue. Three to five transient (10 minute) coronary artery occlusions were carried out in each experiment.

The tachycardia experiments were performed on either closed chest or open chest preparations where the animals were maintained as a rectal temperature of 37 - 38 °C. Atrial pacing was accomplished either via transvenous atrial pacing or via bipolar epicardial electrodes.

**VFT Determinations**

Ventricular Fibrillation Threshold determinants (VFT's) were determined via the pulse train technique (see Figure 8-1) wherein a train of current pulses is applied through a set of electrodes on the surface of the myocardium during the vulnerable period (Han et. al., 1966). [The vulnerable period is the period of time during each cardiac cycle wherein minimal electrical stimulation of the myocardium can result in ventricular fibrillation. Temporally, the vulnerable period extends from roughly the midpoint of the QT interval to, or slightly beyond, the peak of the T-wave in the scalar ECG (see Section 4.4.2).] The pulse train consisted of a series of equally spaced current pulses, 2 msecs wide and presented at a rate of 100/sec. The pulse train was initiated 60 msecs following the R wave and was terminated 200 msecs later. The minimum amplitude current pulse train necessary to fibrillate
Figure 8-1: Determination of the Ventricular Fibrillation Threshold was accomplished by determining the minimum amplitude current pulse train which, when applied to the ventricular myocardium during the time course of electrical recovery (i.e., during the T wave), initiated ventricular fibrillation. The pulse train was set to extend through the vulnerable period and the protective zone.
the preparation was taken to be the VFT.

The experimental procedure was initiated with a set of control measurements carried out at each of several pacing frequencies. At each state, physiological data were recorded over a period of at least 10 minutes to obtain stable data suitable for analysis. Following this recording, the VFT was determined for each state. After allowing at least 15 minutes for recovery, the experimental intervention (either hypothermia or coronary artery ligation) was initiated. During the hypothermia studies, a decrease in temperature was attained and a sequence of measurements made at different atrial pacing rates. As before, for each rate, a 10-minute recorded date segment was followed by a VFT determination. In the coronary artery ligation studies, the LAD was ligated multiple times for 10 minute periods, with successive ligations being separated by at least 20 minutes so as to allow for recovery. At each heart rate, the physiologic data were recorded during the period two to eight minutes following the ligation. The VFT was determined at subsequent ligations during the same period of two to eight minutes following the initiating of occlusion.

For the hypothermia and coronary artery ligation experiments, each pair of control and post-intervention electrogram recordings and VFT’s were obtained at either the identical pacing rates, or the nearest possible rates. The atrial pacing rate used was 200 beats per minute, or, if this was not possible, the highest atrial rate which resulted in 1:1 atrioventricular conduction in both control and post-intervention states. The tachycardia experiments were conducted with baseline recordings of 140 beats per minute, with the intervention being atrial pacing at 200 beats per minute. In the ligation and tachycardia interventions, surface and/or epicardial electrograms were recorded. In the hypothermia experiments (n=7), only surface electrograms were recorded. In the ligation (n=11) and tachycardia experiments (n=10), the reported epicardial TWAIs (T-Wave Alternans Index)
represent the root-mean-squared average of the TWAI's obtained from analysis of simultaneously recorded epicardial electrograms. Within each analysis group (hypothermia-surface, ligation-surface, ligation-epicardial, tachycardia-surface, tachycardia-epicardial), each experiment corresponds to a different animal.

8.2 Analysis Methods

The analog signals recorded on magnetic tape during the animal experiments were analyzed off-line. Following a selection of the appropriate data segments to be analyzed, the ECG output channels from the Hewlett-Packard 3968a FM tape recorder were connected through \( \times 10 \) gain and filtering amplifiers (0.125 Hz to 68 Hz bandpass) to a dedicated 8085 microprocessor system. The ECG channels were sampled at a rate of 360 samples per second, and QRS complexes were identified and classified using a feature extraction - clustering program (Schluter, 1981). Once a QRS complex was detected, two time delimiters were imposed, one set to occur either at the J-point (point of inflection of the ST segment) or at the first deflection of the T-wave, and the other following the end of the T-wave. In the case of rapid pacing rates were pacing stimuli fell within these delimiters, the second delimiter was moved to just before the pacing spike. The T-wave energy (defined as the square of the ECG voltage minus its baseline, integrated over the interval defined by the delimiters), was calculated.

The T-wave energy, \( E_i \), was calculated for each of 1024 consecutive ECG epochs, i.e.,

\[
E_i \equiv \sum_{T-wave} [v(i, nT) - v_{PR}(i)]^2
\]

where \( v_{PR} \) represents the average voltage in the ECG lead during the PR interval of
the \( i \)th beat and \( v(i, nT) \) represents the ECG voltage samples during the T-wave of the \( i \)th beat. From these \( E_i \)'s, a 1024 point number series was then constructed:

\[
X_i = \frac{E_i - \bar{E}}{\bar{E}}
\]

where \( \bar{E} \) represents the mean T-wave energy. This number sequence was then analyzed for periodic fluctuations via power spectral estimation. The discrete power spectrum was estimated as the discrete Fourier transform (here using the FFT, or Fast Fourier Transform) of the sample autocorrelation function.

Sample Autocorrelation Function  =

\[
R_n = \frac{1}{N-n-1} \sum_{k=0}^{N-1} X_{n+k} \cdot X_k \quad \text{for} \quad (N-1 \geq n \geq 0)
\]

Discrete Power Spectrum  =

\[
|Y(k)| = |\sum_{n=0}^{N-1} R_n \cdot e^{-jn\omega_0}| \quad \text{where} \quad \omega_0 = \frac{2\pi}{N}
\]

The \textit{T-Wave Alternans Index} (TWAI) was computed as the square-root of the noise-corrected amplitude of the point in the spectrum corresponding to alternation in the original sequence of T-wave energies. As defined here, the point in the spectrum corresponding to alternation is the point in the spectrum at \( k = N/2 \).

Spectral Noise Estimate  = \( |Y_{\text{noise}}| = \frac{1}{10} \sum_{k=N/2 - 10}^{N/2 - 1} |Y(k)| \)
The estimate of the noise in the spectrum was made by averaging the values of the 10 immediately preceding points in the spectrum. Noise-correction here refers to a subtraction of the noise estimate. Thus, the TWAI was the square-root of the difference between the last point in the spectrum and the average of the preceding 10 points in the spectrum.

$$TWAI = (|Y[N/2]| - |Y_{noise}|)^{1/2}$$

In the event that the last point of the spectrum had an amplitude less than the average amplitude of the preceding 10 frequency samples, the TWAI was taken to be zero.

8.3 Results

In these preliminary studies, we investigated the alternation in ECG T wave energy (as measured by the TWAI) which accompanied a decrease in myocardial electrical stability. Ventricular fibrillation threshold determinations were taken as objective measurements of cardiac electrical stability. Figure 8-2 illustrates several examples of segments of surface ECG tracings with their associated TWAI's and VFT's.

Hypothermia, in 6 of 7 experiments, caused a decrease in VFT (mean decrease 13 mA -- $p < 0.03$). Similarly, in 6 of 7 experiments hypothermia resulted in a marked increase in TWAI (overall mean TWAI increased from 0.26 to 1.85 -- $p < 0.03$).

Ligation of the left anterior descending coronary artery in all experiments caused a reduction of VFT. In 11 of 11 experiments, the TWAI computed from
Figure 8-2: ECG tracings and their associated VFT's and TWAI's.

epicardial recordings increased (overall mean TWAI increased from 0.06 to 0.33 - \( p < 0.001 \)). The corresponding decrease in VFT was 13 mA \( (p < 0.001) \). In 7 of 10 experiments the TWAI computed from body surface recording increased (overall mean TWAI increased from 0.06 to 0.20 -- \( p < 0.08 \)). The corresponding decrease in mean VFT was 12.5 mA -- \( (p < 0.001) \). [In one experiment, equipment failure distorted surface lead recordings.]

Increase of the atrial pacing rate from 140 to 200 beats per minute resulted in an increase of TWAI in epicardial ECG in 6 of 6 experiments (mean TWAI increased from 0.02 to 0.15 -- \( p < 0.02 \)). VFT measurements showed a decreased VFT in 5 of these 6 experiments (overall mean decrease of 12 mA -- \( p < 0.08 \)). In the 10 experiments with surface ECG recordings, tachycardia caused VFT to decrease in all 10 experiments (mean VFT decreased by 15 mA -- \( p < 0.001 \)).
TWAI computed from the surface ECG increased in 7 of 10 experiments (mean TWAI increased from 0.09 to 0.37 – $p < 0.09$).

Pooling all experiments, (see Figure 8-3) we find that VFT decreased as a result of the intervention in 26 of 27 experiments ($p < 0.001$).

Figure 8-3: Summary of the results from all experiments. On average, each intervention was associated with a decrease in myocardial electrical stability (as measured by the VFT), and an increase in alternating activity (as measured by the TWAI).

In 20 of 27 experiments, the TWAI measured from the surface ECG increased (decreased) when VFT decreased (increased) ($p < 0.01$). In these experiments, the correlation coefficient between changes in TWAI and changes in VFT was -0.352 ($p < 0.04$). In 16 of 17 experiments TWAI measured from the epicardial electrograms increased (decreased) when VFT decreased (increased) ($p < 0.04$).
these experiments, the correlation coefficient between changes in TWAI and changes in VFT was $-0.652 (p < 0.005)$.

8.4 Discussion

In the animal experiments presented herein, we sought to test the prediction of alternation in ECG morphology serving as a non-invasive marker of decreased myocardial electrical stability. We used hypothermia, coronary artery ligation, and rapid atrial pacing as interventions to decrease the electrical stability. Ventricular fibrillation threshold (VFT) measurements were used as an independent measure of electrical stability. ECG morphology was represented by ST-T wave energy. By constructing an event series corresponding to the normalized ST-T wave energies for a contiguous sequence of ECG epochs, equally spaced in time, we were then able to use the Discrete Fourier Transform to isolate the component of this event sequence which corresponded to alternation in our morphological measure. By comparing our measure of alternation (TWAI) to electrical stability, as measured by the VFT, we were able to determine whether alternation in morphology did serve as an indicator of decreased stability.

We have demonstrated that a decrease in electrical stability (as documented via VFT measurement) is accompanied by an increase in the alternation of ECG ST-T wave morphology; an observation independent of whether the destabilizing influence is hypothermia, coronary artery ligation, or rapid atrial pacing. The alternation, as captured by the ST-T wave energy, was often so subtle as to avoid visual detection. In these experiments, there was no clear relationship between absolute level of electrical stability and absolute level of alternation.

The results of these experiments suggest that electrical alternans is not an episodic, all-or-none phenomenon as it is currently viewed in the medical literature,
but rather that a degree of electrical alternation may be present even when it is not appreciated via visual inspection of the ECG. The results further suggest that alternation in ECG morphology might be used to assess the efficacy of anti-arrhythmic drug therapy, in that a decrease in alternation in morphology would suggest an increase in myocardial stability. These results raise the question of the use of the degree of morphological alternation as a screening procedure to isolate those individuals with decreased electrical stability and increased susceptibility to sudden cardiac death. A lack of a relationship between absolute level of alternation (as assessed by ST-T wave energy) and electrical stability (as measured by VFT) suggests, however, that simple application of the techniques presented here would not be useful as a screening technique; more sensitive techniques need be developed to assess the full implications of morphological alternation. We believe that several modifications of the present method may significantly enhance the sensitivity and specificity of the approach.

First, the present study utilized only single lead recordings for the TWAI determination. The three-dimensional vector characterizing the alternating component of the ECG vector need not have been parallel to the particular lead employed. Our observations of alternation in only one of two epicardial electrograms would seem to suggest that alternation may be a local event, and as such its projection onto the body surface leads might be specific to the lead vector employed. It may be that more significant results would be obtained by studying fluctuations in the vectorcardiographic representation of the instantaneous cardiac dipole.

Second, in the present study we used ST-T wave energy as the sole metric for ECG epoch morphology. This single metric is not only restricted to describing only repolarization processes, but also results in a many-to-one map of ST-T wave
morphology to the real number line. More significant results might be expected by studying morphological fluctuations throughout both depolarization (QRS) and repolarization (ST-T), and by representing morphology in a less degenerate fashion.

Apart from the problems of sensitivity in measuring alternating cardiac electrical activity, there is the problem of specificity. We have previously noted that electrical alternans is well known to result from a "flip-flopping" of the cardiac structures within the pericardial sac. The surface ECG reflects this motion as alternation in ECG morphology, yet this alternating morphology is not the result of alternating electrical activity within the myocardium. One possible solution to this difficulty would be the construction of a rotationally invariant metric of ECG activity. The magnitude of the three-dimensional cardiac dipole is theoretically one such metric.

In summary, even considering the above limitations, the model's prediction of the existence of subtle morphological alternation in the ECG has been tested with positive results. It is important to emphasize, however, that the nature of the electrocardiogram is such that it represents a non-invertible, degenerate map of microscopic electrical events occurring within the myocardium to body-surface potential recordings. As such, the model prediction of greater sub-populations of regions of the myocardium serving to (alternately) delay the wavefront of excitation, and greater sub-populations only responding to every other beat would not have a direct projection to increased alternation in the ECG morphology. Nonetheless, these preliminary studies demonstrated that a decrease in stability was accompanied by an increase in ST-T wave alternation as measured by the TWAI. The enormous utility of a non-invasive technique for the measurement of cardiac electrical stability coupled with these modestly successful results (despite obvious methodological limitations) mandated that this work be extended.
Chapter 9

Animal Studies -- Phase II

9.1 Experimental Methods

This second set of experiments were performed on a second set of 20 mongrel dogs, 15-25 kilograms in weight, anesthetized with 1 mg/kg of acepromazine subcutaneously and 30 mg/kg of sodium pentobarbital (Nembutal) intravenously. Additional Nembutal was given as needed to maintain the dogs deeply anesthetized. Respiration was maintained by means of an air-cuffed endotracheal tube and a mechanical ventilator. Three pairs of transcutaneous needle electrodes were applied along the three cardinal orthogonal directions (lateral limb lead - X; rostral-caudal lead - Y; dorsal-ventral lead - Z) for the recording of the three orthogonal lead electrocardiogram (Electronics for Medicine ECG amplifier bandpassed 0.04 - 500 Hz). Systemic arterial blood pressure was monitored via intra-arterial catheters connected through Statham P23a transducers. All physiologic waveforms were recorded on a Hewlett-Packard 3968A 8-track FM instrumentation tape recorder with tape speed of 3-3/4 inches per second. The 3dB bandwidth at this setting is 0 - 1250 Hz.

As before, three different interventions were employed to decrease the cardiac electrical stability; hypothermia, coronary artery occlusion, and rapid atrial pacing. Also as before, objective measurement of the cardiac electrical stability was made via Ventricular Fibrillation Threshold (VFT) determinations.

The surgical preparation for each of the experiments was begun with a left lateral thoracotomy. The pericardium was incised and the heart was suspended in a
pericardial cradle. One pair of barb-type pacing electrodes was applied to the left atrial appendage (for pacing), and a pair of screw-type electrodes (for VFT determinations) was applied to the left-ventricular free-wall between the first and second diagonal branch of the Left Anterior Descending (LAD) coronary artery. The inter-electrode distance was set to be approximately 2 cm.

For the coronary artery occlusion experiments, a 1 cm. segment of the LAD just distal to the first diagonal branch was dissected free of surrounding fascia, and an inflatable, saline filled vascular occlusion cuff (In Vivo Metric, Healdsburg, CA, 95448) was fastened in place around the artery. The pericardium was than loosely approximated, the muscle and skin layers were closed separately, and the chest was evacuated of air via a suction drainage tube. Following a recovery period of 30 - 45 minutes, recordings were made at various atrial pacing rates under control conditions, with VFT measurements being made at the extremes of the ranges of pacing rates. Fifteen minutes was allowed to elapse between successive VFT determinations. Transient (10 minute) coronary artery occlusions were then conducted at each of the same atrial pacing rates. VFT measurements were made between the third and fifth minute of occlusion. In the event of spontaneous ventricular fibrillation, the VFT was taken to be zero (0) and the data segment associated with this zero value was taken to be the last stable (without PVC's or ventricular tachycardia) record suitable for analysis.

In the hypothermia experiments, a thermocouple was sutured in place within the pericardium, and the pericardium and chest were closed as described above. In addition, a counter-current heat exchanger was put in place between the right femoral artery and the left femoral vein. Following a recovery period of 30-45 minutes, recordings were made at various atrial pacing rates with VFT measurements again being made at the extremes of the range of pacing rates. The
dogs were then heparinized (100 ug/kg), and the femoral artery - femoral vein bypass heat exchanger was opened. The blood flow through the heat exchanger was determined by the driving pressure (here, the femoral artery pressure), while the temperature drop was controlled by the flow rate and temperature of the countercurrent coolant flow (here tap water). The target temperature of 29°C was reached in 90-120 minutes. At this temperature, the experimental protocol established under normothermic conditions was repeated (as tolerated). [It was often the case that the higher pacing rates could not be reproduced at the lower temperature. In this case, the highest tolerated pacing rates were substituted.] Once data collection at hypothermic temperatures had been completed, the temperature of the counter-current flow was raised to approximately 40—45°C, and the animal was rewarmed to normothermic conditions. This rewarthing was accomplished in approximately 60-90 minutes. Data recording and VFT measurements were repeated.

Experiments were terminated and the animal euthanized by not electroconverting (defibrillating) the terminal episode of ventricular fibrillation induced by the last VFT determination.

**VFT Determinations**

VFT's were again determined via the pulse train technique. In contrast to the initial study, the electrodes used for VFT determination were, in these experiments, directly attached to the myocardium. In the initial experiments, the electrode pair was situated on an intracavitary catheter which could potentially shift position as a result of cardiac motion. By affixing the electrodes directly to the myocardium, the complicating factor of relative electrode motion was removed. Also in contrast to the initial studies, the appropriate offset and width for the pulse train were individually determined prior to each VFT determination so that the train of
current pulses scanned from the middle of the Q-T interval to just beyond the T wave in the scalar ECG. The current pulses themselves were also changed with respect to their duty cycle. Initial studies used a 20% duty cycle at 100 Hz, and this study used a 50% duty cycle at 100 Hz. As before, the minimum amplitude current pulse train necessary to fibrillate the preparation was taken to be the VFT.

9.2 Analysis Methods

The data analysis scheme is depicted in Figure 9-1. The analog signals recorded during the animal experiments were analyzed off-line. Following selection of the appropriate data segments to be analyzed, the ECG output channels from the Hewlett-Packard 3868a FM tape recorder were connected through 6-pole Butterworth low-pass filtering amplifiers (cutoff frequency set to 360 Hz) to a Masscomp MC500 computer outfitted with a 16 channel multiplexor - analog-to-digital convertor, 166 Mbyte disk, and 2Mbyte core memory. The ECG channels were sampled at a rate of 1000 samples per second and placed on disk in contiguous files. QRS complexes were identified and fiducial points (timing markers corresponding to the location of each QRS) determined by a template matching scheme (Moody, 1983). Following this initial phase of QRS complex detection, a second refinement phase was initiated, wherein an iterative, adaptive template-matching (matched filter) scheme was employed to refine initial fiducial point estimates. The waveform chosen for this fine alignment scheme was the vector magnitude (square root of the sum of the squares of the three orthogonal leads) of the QRS complex. Viz.,

\[
\text{Vector Magnitude of the } i^{th} \text{ QRS Complex } =
\]

\[
m_{QRS}(i, nT) = \left[ x_{QRS}^2(i, nT) + y_{QRS}^2(i, nT) + z_{QRS}^2(i, nT) \right]^{1/2}
\]
where \( i \) is the index for beat number, \( n \) is the index for sample number within a beat, and \( T \) is the time between adjacent samples.

\[
\text{Average QRS Vector Magnitude} =
\]

\[
\bar{m}_{QRS}(nT) = \frac{1}{N} \sum_{i=0}^{N-1} m_{QRS}(i, nT)
\]

With this average as a template, the fiducial points corresponding to each QRS complex were then shifted to maximize the cross-correlation between \( \bar{m}_{QRS}(nT) \) and \( m_{QRS}(i, nT) \). \( \bar{m}_{QRS}(nT) \) was then recalcualted based on the shifted fiducial points, and the process was repeated until all fiducial point locations are stable. In practice, one pass through the alignment scheme was sufficient.

At this point, the inter-epoch intervals were examined graphically for user-assisted detection and correction of missed epochs. [This was a rare problem encountered early on in the analysis procedure which was almost completely avoided by minor adjustment of the initial detection template.] Next, waveform segments (defined as the array of sampled value in a time window relative to the refined fiducial point) of sequential vector magnitude waveforms were examined for alternating morphology.

The analysis procedure used to detect and quantify alternation in waveform morphology consisted of examining each sample point within the waveform segment of interest for alternation, and then integrating over the entire waveform segment. An example should illustrate the salient features of this technique. Up to this point we have described an epoch detection / alignment procedure which would allow for the construction of a two dimensional matrix of sampled values; the columns being
Figure 9-1: Data analysis scheme.
indexed in terms of \( nT \), samples into the waveform segment (corresponding to time) and the rows being indexed in terms of \( i \), beat number. Looking across in one row we would see the sampled values corresponding to (for example) a single QRS complex, \( m_{QRS}(i, n_{fixed}T) \). Looking down a single column (down the ensemble at the same temporal offset from the fiducial marker), we would see the different values that the waveform took one at one particular time in its evolution, \( m_{QRS}(i, n_{fixed}T) \). If (for example) QRS peak amplitude were alternating on a beat-to-beat basis, we could identify this by locating the column corresponding to the time at which the QRS reached its peak, \( n_{peak}T \), and then looking down that particular column (at the series corresponding to \( m_{QRS}(i, n_{peak}T) \)), for the alternation.

If we were to model the waveform under study, \( m(i, nT) \), as consisting of a static part, \( s(i, nT) \), which is independent of \( i \), and an alternating part, \( a(i, nT) \), which can be viewed as a fixed waveform which alternates polarity on a beat-to-beat basis, then we can construct a method for quantify the amount of energy associated with \( a(i, nT) \), or simply \( \sum_n a^2(nT) \). This is a marked improvement from our previous studies. In our initial studies, we studied the alternation present in waveform energy (forgetting for the moment that the initial studies used only single lead data), i.e., alternation in the series

\[
E_i = \sum_{i^{th \, waveform}} m^2(i, nT)
\]

or, expanding \( m(i, nT) \),

\[
E_i = \sum_{i^{th \, waveform}} [s^2(i, nT) + 2s(i, nT)a(i, nT) + a^2(i, nT)]
\]
The only alternating component in this constructed series in the cross term, \(2s(i, nT)a(i, nT)\), since \(s(i, nT)\) is static with respect to \(i\) and \(a^2(i, nT)\) is static because \(a(i, nT)\) only alternates in sign with \(i\). Thus the measured alternation in this series in very dependent on the form of \(s(i, nT)\), not just on \(a(i, nT)\). The effect of \(s(i, nT)\) could be to enhance, diminish, or even completely obscure the presence of alternation in the original waveform morphologies.

Here, we will describe a methodology for measuring the energy of the alternating component present in a waveform. The difference, which may initially seem subtle, is extremely important. In our initial studies we measured alternation of waveform energies and therefore failed to detect alternation in waveform morphology which resulted in alternating wave-shapes of equal energy. Additionally, the amount of alternation detected was dependent on the specific static wave-shape. The same amount of alternation superimposed on a different amplitude signals resulted in different values for the TWAI. If we measure the energy of the alternating component of the waveform, both these issues are addressed. Energy is a positive-definite metric, and as such, if alternation is present in the series of waveforms, its energy will always be a positive term. There is no opportunity for alternation present in the series of waveforms to be masked or enhanced by the particular form of the alternating component. Secondly, a measurement of the energy of the alternating component is independent of the specific wave-shape of the static component. We may wish to later scale our results by the energy of the static component to construct a proportional metric, but our initial metric of energy of the alternating component is independent of the underlying static wave-shape.

Having espoused the benefits of measuring the energy of the alternating
component of the series of waveforms, we are now left to describe the method for doing so. To this point we have described a technique for constructing a matrix of data, the columns corresponding to \( m(i, n_{\text{fixed}} T) \) and the rows corresponding to \( m(i_{\text{fixed}}, n T) \). If we estimate the alternating energy in the sequence \( m(i, n_{\text{fixed}} T) \) via spectral techniques (i.e., calculate the discrete energy spectrum of the series), and repeat this for each sample point, \( n \), and sum the alternating energy at each sample point over all sample points within the waveform, we will have succeeded in measuring the energy of the alternating component of \( m(i, n T) \). Viz.,

\[
m(i, n T) = s(i, n T) + a(i, n T)
\]

Sample Autocorrelation Function =

\[
R_{m(i, n = n_0 T), m(i+l, n = n_0 T)} = \frac{1}{N-l-1} \sum_{i=0}^{N-l} m(i, n_0 T) \cdot m(i+l, n_0 T)
\]

expanding \( m(i, n_0 T) \) and \( m(i+l, n_0 T) \),

\[
R_{m(i, n_0 T), m(i+l, n_0 T)} =
\]

\[
\frac{1}{N-l-1} \sum_{i=0}^{N-l} [s(i, n_0 T) + a(i, n_0 T)] \cdot [s(i+l, n_0 T) + a(i+l, n_0 T)]
\]

but, \( s(i, n_0 T) = s(i+l, n_0 T) \), and \( a(i, n_0 T) = (-1)^l a(i+1, n_0 T) \), and therefore
\[ R_{m(i, n_0T), m(i+l, n_0T)} = \]
\[ \frac{1}{N-l-1} \sum_{i=0}^{N-l} [s(i, n_0T) + a(i, n_0T) \cdot s(i+l, n_0T) + (-1)^l \cdot a(i, n_0T)] \]

Now, for \( l \) odd we have

\[ R_{m(i, n_0T), m(i+l, n_0T)} = \frac{1}{N-l-1} \sum_{i=0}^{N-l} s^2(i, n_0T) - a^2(i, n_0T) \]

and for \( l \) even we have

\[ R_{m(i, n_0T), m(i+l, n_0T)} = \]
\[ \frac{1}{N-l-1} \sum_{i=0}^{N-l} s^2(i, n_0T) + 2s(i, n_0T) \cdot a(i, n_0T) + a^2(i, n_0T) \]

but, the cross term \( 2s(i, n_0T) \cdot a(i, n_0T) \) alternates its sign with \( i \) because \( a(i, n_0T) \) alternates its sign with \( i \); and because we are summing up an even number of these cross terms, their sum is zero. Thus, for \( l \) even we have

\[ R_{m(i, n_0T), m(i+l, n_0T)} = \frac{1}{N-l-1} \sum_{i=0}^{N-l} s^2(i, n_0T) + a^2(i, n_0T) \]

Regrouping terms, we have (for all \( l \)
\[ R_{m(i, n_0T), m(i+l, n_0T)} = \frac{1}{N-l-1} \sum_{i=0}^{N-l} s^2(i, n_0T) + (-1)^l a^2(i, n_0T) \]

If we now construct the discrete Fourier transform of this autocorrelation function, estimating the discrete power spectrum, we have that

**Power Spectrum Estimate:**

\[ |Y_{n_0}(k)| = | \sum_{l=0}^{N-1} R_{m(i, n_0T), m(i+l, n_0T)} e^{-jkw_0} | \quad \text{where} \quad w_0 = \frac{2\pi}{N} \]

substituting in for \( R_{m(i, n_0T), m(i+l, n_0T)} \), and evaluating \(|Y_{n_0}(k)|\) at \( k = N/2 \), we have

\[ |Y_{n_0}(k = N/2)| = | \sum_{i=0}^{N-1} [s^2(i, n_0T) + (-1)^l a^2(i, n_0T)] e^{-j\pi l} | \]

Recognizing that \( e^{-j\pi} = (-1)^l \), we have

\[ |Y_{n_0}(k = N/2)| = | \sum_{l=0}^{N-1} s^2(i, n_0T)(-1)^l + a^2(i, n_0T)(-1)^{2l} = N \cdot a^2(i, n_0T) | \]

Thus, by constructing the estimate of the discrete power spectrum of the series \( m(i, n_0T) \) with \( i \) indexed through the series of sequential beats from 0 to \( N \), and evaluating this power spectrum at \( N/2 \) (corresponding to the frequency of alternation), we arrive at \( N \) times the energy of the alternating component at that value of \( n_0 \). It is clear that by carrying out this process for each value of \( n \) along the time-course of the waveform of interest, summing the results, and dividing by
\[ \frac{1}{N} \sum_n |Y_n(k = N/2)| = \]

\[ \frac{1}{N} \sum_n N \cdot a^2(nT) = \sum_n a^2(nT) = \text{energy of the alternating component} \]

With this explanation in hand, we can go on to give additional specific details of the method. For each aligned ECG epoch (QRS complex, ST segment and T wave) \((N=128)\), the vector magnitude function was created. Two data matrices were then constructed, one corresponding to depolarization (QRS complex), here defined as a 100 millisecond window centered about the middle of the average QRS vector magnitude waveform, and one corresponding to repolarization (ST segment and T wave), here defined as the 200 millisecond window immediately following the end of the QRS window. The QRS data matrix thus consisted of 128 rows (each corresponding to a successive QRS complex) and 100 columns (each column corresponding to a one sample point during the QRS). The ST-T wave data matrix similarly had 128 rows, each corresponding to a different, but sequential ST-T wave, and 100 columns, here representing every other sample of the original ST-T waves. For each column in each of the data matrices, the power spectral estimate was calculated by constructing the discrete Fourier transform of the Hanning-windowed sample autocorrelation function. These estimates were then algebraically summed over all of the columns, thus generating one power spectrum for each of the two data matrices. The point in the aggregate power spectrum corresponding to alternation was compared to an estimate of the noise in an adjacent spectral band by constructing the sample mean and sample standard deviation of 8
frequency samples in that band. (Noise estimate made in frequency band extending to $15/16$ths of the alternating frequency). Alternation in morphology was judged significant if the power at the frequency of alternation exceeded the estimate of the noise mean by 3 standard deviations. [Note: Because the variance of the power spectrum estimate is twice its nominal value at both DC and at the frequency of alternation, the measure for significance was actually whether the power at the frequency of alternation exceeded the noise mean by $3 \times \sqrt{2}$ or 4.24 standard deviations]. The value reported for the amount of alternation present was the noise corrected estimate of the energy of the alternating component divided by the energy of the average waveform. So, for the QRS complex, the noise corrected estimate of the energy associated with the alternating waveform component was scaled by the energy in the average vector QRS complex and reported as the Alternating ECG Morphology Index (AEMI) for the QRS, denoted AEMI(QRS). For the ST-T wave, this was denoted AEMI(ST-T)

A Note on Statistics:

Due to the obviously non-normal distribution of both the VFT and the AEMI data, non-parametric statistics were employed to test for significance of results. In particular, the sign test was used to test for significance of changes in VFT and AEMI within a matched pair of data points, and correlation between the AEMI values and the VFT values was tested via the rank correlation test. To determine whether changes in AEMI were correlated with changes in VFT within paired data sets, the rank differences for each metric were correlated.
9.3 Results

In this second set of animal studies, we again studied alternation in ECG complex morphology under a variety of conditions, but with many methodological improvements over our initial studies. In these studies, alternation in ECG vector magnitude morphology was studied using a multidimensional spectral estimation technique. The amount of alternation present in the ECG was compared to myocardial electrical stability where such was measured by Ventricular Fibrillation Threshold (VFT) determination.

Ten (10) dogs were subjected to hypothermia (lowering of their core temperature to 29° C from the control state of 35 – 37° C). The typical time course of temperature, VFT, and ECG alternation (here measured by AEMI(ST-T)) are shown in Figure 9-2. Figure 9-3 illustrates the ECG waveforms during normothermic and hypothermic condition, providing a blatant example of alternation in ECG morphology which accompanies hypothermia.

In 7 of these experiments, two set of measurements were made (at pacing rates different by at least 25 bpm from each other), while in the remaining 3 experiments, only 1 set of measurements could be made. In the 17 sets of measurements, hypothermia reduced VFT in all experiments, from a normothermic value of 23.8 ± 2.5 mA (Mean ± SEM) to a hypothermic value of 8.5 ± 1.0 mA (p < .0001). On average, hypothermia reduced the measured VFT by 61%. AEMI(QRS) was found to increase in 16 of the 17 measurement sets as a result of hypothermia, and remain unchanged (undetectable) in the remaining measurement set (p < .0001). The average AEMI(QRS) under normothermic conditions was 3.7 ± 3.0 ppm (Mean ± SEM), and under hypothermia was 1488 ± 548 ppm. AEMI(ST-T) was found to increase in all 17 of the measurement sets as a result of hypothermia, from a
Figure 9-2: Time course of changes in temperature, VFT, and AEMI(ST-T) during hypothermia experiments.
Figure 9-3: Three orthogonal lead electrocardiograms under normothermic and hypothermic conditions. At $37^\circ C$, with a VFT of 14 mA, no alternation is appreciated, either visually or via spectral analysis. At $29^\circ C$, 1 minute prior to spontaneous ventricular fibrillation, frank alternation is observable in QRS peak amplitude and ST-T waves morphology (middle trace).
normothermic value of $43.9 \pm 18.4$ ppm (Mean $\pm$ SEM) to a hypothermic value of $19178 \pm 5579$ ppm ($p < .0001$). Figure 9-4 illustrates the relationship between VFT and AEMI(ST-T) for all measurement sets.

Ten (10) dogs were subjected to Left Anterior Descending (LAD) coronary artery occlusion. Figure 9-5 depicts the time course of coronary ligation in one experiment with it effect on AEMI(QRS) and AEMI(ST-T). Figure 9-6 illustrates the combined effect of pacing rate and coronary artery ligation on AEMI(QRS) and AEMI(ST-T) and VFT in another experiment.

Over the series of ten experiments, 24 different measurement sets were obtained. Coronary artery occlusion was accompanied by a decrease in VFT in all of the 24 measurement sets, from a pre-occlusion value of $23.0 \pm 2.4$ mA (Mean $\pm$ SEM) to a value of $7.8 \pm 1.6$ mA in the occluded state ($p < .0001$). On average, coronary artery occlusion reduced the measured VFT by 61%. Occlusion was accompanied by an increase in AEMI(QRS) in 10 of the 24 measurement sets, no change (i.e., alternation was undetectable) in 11 of the 24 sets, and a decrease in AEMI(QRS) in 3 of the 20 sets ($p < .05$). The average pre-occlusion value for AEMI(QRS) was $76.3 \pm 46.5$ ppm (Mean $\pm$ SEM) with the occluded state having an average value of $245 \pm 111$ ppm. AEMI(ST-T) was found to increase in 17 of the 24 measurement sets, remain unchanged (and undetectable) in 4 of the sets, and was found to decrease in the remaining 3 sets ($p < .002$). The pre-occlusion average value for AEMI(ST-T) was $842 \pm 505$ ppm (Mean $\pm$ SEM), with the occluded state having a mean value of $1365 \pm 392$ ppm.

In fourteen (14) experiments, the effect of an increase in pacing rate (of at least 15 beats per minute) on VFT and AEMI was studied, yielding a total of 41 sets of measurements. An increase in pacing rate was accompanied by a decrease in VFT in 28 of the 41 data sets; VFT was unchanged in 7 sets and increased in the 6
The Effect of Hypothermia on ECG Morphology Alternation and Ventricular Fibrillation Threshold.

Figure 9-4: The relationship between VFT and AEMI(ST-T) as a result of systemic hypothermia. The open circles represent the normothermic control state and closed circles represent the hypothermic state. With hypothermia, electrical stability decreases and alternation increases.
Figure 9-5: Time course of the development of alternation with coronary artery occlusion. Alternation accompanies coronary artery ligation and disappears upon reperfusion.
Figure 9-6: Relationship between AEMI(QRS) and AEMI(ST-T), VFT, and pacing rate during coronary artery occlusion. The amount of alternation detected during coronary artery occlusion increases with increasing rate, as the VFT decreases with increasing rate.
remaining data sets (p < .0002). On average, increasing the pacing rate reduced the measured VFT by 25%. AEMI(QRS) increased in 21 of the 41 sets, was unchanged (undetectable) in 13 experiments, and decreased in the remaining 7 experiments (p < .0002). AEMI(ST) increased in 20 of the 41 experiments, remained unchanged (undetectable) in 8 of the experiments, and decreased in the remaining 13 experiments (NS).

In total, 119 pairs of measurements (VFT and AEMI) were made in this set of animal experiments (see Figure 9-7a and 9-7b). The rank correlation coefficient between VFT and AEMI(QRS) was -0.30 (p < .001). The rank correlation coefficient between VFT and AEMI(ST-T) was -0.55 (p < .0001). These results are perhaps best displayed in the form of a histogram (see Figure 9-8).

9.4 Discussion

In this second set of animal experiments, we set out to address the question as to whether alternation of ECG morphology might serve as a non-invasive indicator of myocardial stability, using hypothermia, coronary artery occlusion, and rapid atrial pacing as interventions. By examining the magnitude of the vector ECG instead of just a single ECG surface lead, and by quantifying morphology in a multidimensional non-degenerative fashion instead of just by a single waveform metric, shortcomings of the initial study have been corrected.

We have demonstrated the hypothermia is accompanied by a decrease in electrical stability (as documented via VFT measurement) and that the ECG vector magnitude during hypothermia evidences alternating morphology, both in the QRS complex and in the ST-T wave. We have also demonstrated that coronary artery occlusion is accompanied by a decrease in electrical stability (as measured by the VFT) and that occlusion is accompanied by an increase in the observed alternation
Figure 9-7: Summary of all paired data sets (VFT and AEMI). In total, there were 119 data sets in 17 different preparations.
Figure 9-8: Histogram of the 119 data sets. The amount of measured alternation is negatively correlated with the VFT, demonstrating that diminished electrical stability is accompanied by alternation in ECG morphology.
in ECG vector morphology. In the case of coronary artery occlusion, alternation was more frequently detected in the ST-T wave than in the QRS complex. Rapid atrial pacing was also accompanied by a decreased cardiac electrical stability (again as measured by the VFT), and also by an increase in the observed alternation in ECG vector magnitude morphology.

We have therefore shown that a decrease in cardiac electrical stability is accompanied by an increase in the alternation of ECG ST-T wave morphology; an observation independent of whether the destabilizing influence is hypothermia, coronary artery occlusion, or increase in atrial pacing rate. The results from the hypothermia experiments show the most consistent relationship between VFT and AEMI. Across these experiments, the VFT was reproducibly diminished by 61% as a result of hypothermia, and all hypothermic states evidenced much greater ECG waveform alternation than their normothermic controls.

The coronary occlusion experiments were slightly less consistent, but remained highly significant. Occlusion also reduced VFT by an average of 61%, but was not as consistent in this regard, demonstrating nearly one and one-half times the standard deviation in fractional reduction of VFT. The relationship between ECG waveform alternation and VFT was also not as consistent as in the hypothermia experiments, with each measure of alternation, AEMI(QRS) and AEMI(ST-T), showing less alternation with ligation in 3 of the 24 measurement sets.

The study of the effect of increasing atrial pacing rate was the least consistent. As an intervention, an increase of atrial pacing rate reduced VFT by only 25% ± 38%. As such, increasing atrial pacing rate was neither an effective, reliable, nor consistent way of decreasing cardiac stability as measured by the VFT. Not surprisingly, the relationship between decreased stability and alternating ECG morphology was least consistent, although still significant for AEMI(QRS).
9.4.1 Confounding Influences / Sources of Error

While we have shown that the decrease in cardiac electrical stability which accompanies hypothermia, coronary artery occlusion, and increased rate of atrial pacing is also frequently (and statistically significantly) accompanied by an increase in ECG waveform alternation, we see that the technique for detecting alternation in morphology often fails to detect such alternation (even in states of decreased electrical stability) and that occasionally, the measured alternation decreases as electrical stability decreases. There are many potential sources of error and confounding influences which could account for these observations, and we shall briefly discuss them and their implications for future work.

9.4.1.1 Degeneracy of the Mapping from Cardiac Electrical Activity to the Vectorcardiogram

As briefly discussed in the discussion of the initial animal results, the surface ECG constitutes a degenerate mapping of electrical events within the myocardium to body surface potentials. As such, electrical activity taking place within the myocardium may be unobservable in the body surface potentials. Specifically, alternation of excitation patterns may be unobservable, only partially observable, or totally observable in the surface vectorcardiogram depending on the location and the geometry of the regions of alternating behavior. With this in mind, one could easily imagine scenarios in which the fraction of the myocardium undergoing alternating activation patterns could increase while the observed alternation in the surface vectorcardiogram could increase, remain unchanged, or even decrease. The distortion of cardiac electrical events which occurs in the degenerate map from myocardial events to surface potentials could, by itself, account for the variability in our observations.
9.4.1.2 Rotational Invariance at What Cost?

As treated in the discussion of the initial animal studies, "flip-flopping" of the cardiac structures within the thorax would result in false positive detection of alternation of cardiac electrical activity unless measures are taken to counter this influence of cardiac rotation. In this study, the magnitude of the net cardiac vector was taken as the metric of cardiac electrical activity, hoping to answer just this problem. To the extent that the heart can be modeled as an equivalent dipole in a homogeneous isotropic spherical thorax, the vector magnitude is rotationally invariant. Unfortunately, the magnitude operation is such that it does not neatly cancel only the alternation attributed to rotation of the cardiac structures. A simple analysis will show that true alternation of cardiac electrical activity could be suppressed by the magnitude operation.

Consider that the measured cardiac dipole vector, \( \vec{m}(n, t) \), can be viewed as having a static component, \( \vec{s}(n, t) \), and an alternating component, \( \vec{a}(n, t) \), where \( n \) represents beat number and \( t \) represents time, i.e.,

\[
\vec{m}(n, t) = \vec{s}(n, t) + \vec{a}(n, t)
\]

\[
|\vec{m}(n, t)| \approx |\vec{s}(n, t)| + |\vec{a}(n, t)| \cdot \cos(\theta)
\]

The "alternating" energy in \( |\vec{m}(t)| = |\vec{a}(t)|^2 \cdot \cos^2(\theta) \) If we assume that

\[
\frac{|\vec{a}(t)|^2}{|\vec{s}(t)|^2} = \alpha
\]

is directly proportional to stability (as measured by the VFT), then

\[
r_{\alpha, \text{VFT}} = 1
\]
However, we measure $\alpha' = \alpha \cdot \cos (\theta)$.

$$r_{\alpha', \text{VFT}} = \frac{E[\cos^2(\theta)] \cdot \sigma_{\text{VFT}}}{(E[\text{VFT}^2] \cdot E[\cos^4(\theta)] - E[\text{VFT}^2] \cdot E[\cos^2(\theta)]^2)^{1/2}}$$

If we provide the data dependent terms in this expression, then we have $r_{\alpha', \text{VFT}} = -0.55$ Thus, it would seem that even if the energy of the alternating component of the vectorcardiogram was perfectly linked to stability, our measurement technique would be expected to show a correlation coefficient of only -0.55. [It is interesting that this is exactly the value we calculated for the rank correlation coefficient between VFT and AEMI(ST-T)].

This “problem” was addressed by re-examining all of the collected data, and calculating the the metric of alternation in a different way. Rather than calculate the alternating energy in the vector magnitude waveform, as we have done, we calculated the alternating energy in each of the three orthogonal leads and summed the results, normalizing by the energy in the vector magnitude waveform. This technique, while allowing for false-positive detection of mechanical alternation causing a perceived electrical alternation, does succeed in calculating the energy associated with the alternating component of the vectorcardiogram. Figures 9-9 through 9-12 illustrate the results of this modified analysis on the 119 paired sets of data. No significant improvement was made in the overall rank correlation between measured alternation in ECG morphology and VFT.
Figure 9-9: 119 paired data sets with alternation in QRS and ST-T morphology measured by summing up "alternating energy" in each of the three orthogonal leads.
Figure 9-10: Total alternating energy in the ECG waveform vs. VFT for all data sets.
**Figure 9-11:** Histogram of QRS and ST-T alternation (as measured by summing "alternating" energy in each of the three orthogonal leads) vs. VFT, illustrating that as interventions decrease electrical stability, alternation in ECG morphology is increased.
Figure 9-12: Histogram of alternation in total ECG waveform (QRS-T) vs. VFT across all experiments, again illustrating the negative correlation between alternation and electrical stability.
9.4.1.3 Adverse Effects of Iterative Cross-correlative Alignment

Prior to any measurement of alternation in waveform morphology, waveform epochs were aligned via an iterative technique which forced maximum overlap between all realizations and the average realization. While this alignment procedure was crucial to avoid the spurious contributions from variable intra-atrial and A-V nodal conduction times to subsequent analysis, it also served to minimize the mean-squared differences between all the epochs. It is easy to see, however, that this type of alignment scheme could serve to shift fiducial points in such a way as to reduce the measured degree of alternation in waveform morphology.

9.4.1.4 The Effects of Respiratory Modulation of the Body-surface Potentials

There are phasic changes in the conductivity of the lungs which occur with respiration, and as a direct result, the body surface potentials resultant from cardiac sources experience an obvious modulation with respiration. In these animal experiments, respiration was maintained through the action of a periodic, fixed-volume, single piston pump. The strictly periodic nature of the artificial respirator combined with the non-sinusoidal air-flow to induce non-sinusoidal periodic oscillations in ECG waveform morphology. The spectrum of waveform morphology fluctuations characteristically contained very significant contributions at the frequency of respiration, and the first few harmonics thereof. The presence of these frequency-specific fluctuations in waveform morphology could provide either false positive or false negative detection of waveform alternation, depending on the relative magnitude of the respiratory modulation and on whether the harmonic of respiration coincided with the frequency of alternation, or fell in the frequency band where spectral noise was estimated. In reality, the harmonics of respiration were often seen in the spectrum, and on occasion, significant energy was found to be
present even in the 7th and 8th harmonics.

9.4.1.5 Ambient Noise / Induced Noise Considerations

The surface ECG is subject to muscle noise, power-line (60 Hz) pick-up, electrode motion artifact, and the ubiquitous sources of electronic noise. Apart from this, the data used in these studies was recorded on FM tape recorders which introduced non-negligible wide-band noise in addition to distorting the time base with wow and flutter. With the exception of the time-base distortion, the remainder of the noise could be viewed as additive broad-band noise and thus thought of as contributing to a loss in sensitivity (causing false negative detection of waveform alternation). The time base distortion induced by the periodic fluctuations in the capstan motor speed in the tape recorders could create frequency specific fluctuations in recorded waveform morphology. Spectral analysis was conducted on these tape-recorder induced fluctuations, and they were found to have the bulk of their energy above the spectral region of interest, with fundamental frequencies in excess of 3 Hz. [In these studies, spectra were only examined out to a maximum of one-half of 200 bpm, or 1.667 Hz.]

The combination of these confounding influences could obviously combine to yield false positive or false negative detection of waveform alternation, as well as enhance or diminish the observed amount of alternation. Taken together, these factors could well account for the lack of a totally consistent relationship between decreasing electrical stability and increasing amounts of waveform alternation.

9.4.2 ECG Waveform Alternation as an Absolute Metric of Cardiac Electrical Stability

In the initial study, using single lead ECG data and a single metric for waveform morphology, we found that alternation in ECG morphology served as a
relative metric for cardiac electrical stability, i.e., as stability decreased, observed alternation increased. Due to shortcomings of that study, however, the question as to whether alternation in ECG morphology might serve as an absolute measure of stability was unanswered. This second set of animal studies was conducted to extend that initial study and determine whether a more careful analysis might yield a non-invasive method for measuring absolute cardiac electrical stability. It is important to note that even if our underlying model is essentially correct, such an absolute relationship between electrical stability and the amount of waveform alternation was not to be expected (for reasons discussed in section 9.4.1.1). The finding of a highly significant statistical correlation between our measures of ECG waveform alternation AEMI(QRS) and AEMI(ST-T) suggest that alternation in waveform morphology may have a direct relationship to cardiac electrical stability, and may, with further refinements, serve as a non-invasive metric for cardiac electrical stability.
Chapter 10
Clinical Trial

10.1 Electrophysiologic (EP) Testing - An Introduction

The general concepts underlying electrophysiologic testing are quite simple. Patients thought to be susceptible to malignant cardiac rhythm disturbances are evaluated by their response to exogenous cardiac electrical stimulation. In an attempt to allow for comparison across patient populations and different testing laboratories, some standardization of stimulation protocol has been achieved. A typical EP study commences with the passage of three quadripolar transvenous catheters through the femoral veins. These catheters are then positioned (with the aid of flouroscopy) in the high lateral right atrium, the right ventricular apex, and across the triscupid valve in a position that allows for recording of a His electrogram. Electrograms from these catheter positions, together with selected surface electrograms are monitored and recorded.

10.1.1 Patient Preparation

Patients to be evaluated by EP testing are initially drug-free i.e, at least 5 half-lives away from their last dose of cardiac medication. Small doses of valium (diazepam) may be administered intravenously if a patient is particularly anxious. Subsequent studies to assess anti-arrhythmic drug therapy are conducted with patients on prescribed medication with blood drug levels in the recommended therapeutic range.
10.1.2 Stimulation Protocol

Exogenous electrical stimulation (1 - 2 msec current pulses at amplitudes equal to 2 - 5 times diastolic threshold) is provided via the transvenous catheters. The protocol describing the order and type of stimulation is given below. The general approach is one of providing an "electrical challenge" to the myocardium, and gradually increasing the level of the challenge until a malignant rhythm disturbance (ventricular tachycardia and/or ventricular fibrillation) occurs.

- Step 1. Single and double premature ventricular stimulations during sinus rhythm.

- Step 2. Single and double premature ventricular stimulations during ventricular pacing at basic drive cycle lengths.

- Step 3. Triple premature ventricular stimulations during sinus rhythm.

- Step 4. Triple premature ventricular stimulations during ventricular pacing.

- Optional:
  - Step 5. Left ventricular stimulation.

10.2 Experimental Methods

Electrocardiographic data in the form of three orthogonal lead projections (either the Frank lead system or leads I, aVF, and V1-2) were recorded from each of a series of 25 randomly selected patients immediately prior to EP testing. The recorded data included 5 minutes of sinus rhythm and 2-1/2 minutes of ventricular pacing at each of 3 different rates (100, 120, 150 bpm). The three channels of data were initially recorded on a Teac 14-channel FM tape recorder and later re-recorded on an HP 3968A 8 channel tape recorder (tape speed = 3-3/4 inches per
second, corresponding to a 3dB bandwidth of 0 - 1250 Hz) for subsequent analysis.

Results of off-line analysis were compared to the results of the EP stimulation protocol. While a true quantitative metric for myocardial electrical stability was obviously not to be had from the results of EP study, patients could be grouped first in terms of whether or not they were inducible into a malignant rhythm disturbance, and second in terms of where in the protocol they were made to evidence a particular dysrhythmia.

10.3 Analysis Methods

The method of analysis of this data differed only in the particulars of the data windows corresponding to the QRS and ST-T wave segments. In the animal studies, the window corresponding to depolarization was taken to be 100 msecs centered about the middle of the vector magnitude QRS complex. In the human studies, this window was extended to be 150 msecs wide, a necessary consequence of the fact that the patients were paced from ventricular sites, and as a result, the QRS complexes were much wider than in the animal experiments where atrial pacing sites were used. Similarly, the window corresponding to repolarization (ST-T) was taken to be 225 msecs wide as compared to 200 msecs in the animal data. All remaining data analysis was the same as in the second set of animal studies.

10.4 Results

Of the test series of 25 patients, 2 were subsequently removed from the study by virtue of discrepancies from the standard EP testing protocol. Alternation was said to be detected if significant (compared to a spectral noise estimate) alternation was detected at any of the 3 pacing rates. Of the 23 patients, 17 were found to
have significant alternation of ECG morphology (either in the QRS complex or in the ST-T wave), with 13 demonstrating QRS alternation, and 14 demonstrating ST-T wave alternation. Of the 23 patients, 13 were found to be inducible into ventricular tachycardia, and the remaining 10 were not inducible. AEMI(QRS) for the inducible group was 426 ± 288 (ppm) (Mean ± SEM) and for the non-inducible group was 32 ± 17 (ppm) (NS). AEMI(ST-T) for the inducible group was 1571 ± 1091 (ppm) (Mean ± SEM) and for the non-inducible group was 362 ± 192 (ppm) (NS).

Standard 2 × 2 contingency tables were constructed to determine whether alternation of ECG morphology was a significant discriminant in identifying the inducible patients. (See Figures 10-1a, b, and c.)

\begin{figure}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Alternation Detected} & \textbf{Inducible to VT/VF} & \textbf{Inducible to VT/VF} & \textbf{Inducible to VT/VF} \\
\hline
+ & 9 & 4 & + \\
\hline
- & 4 & 6 & - \\
\hline
\end{tabular}
\caption{A) The 2 × 2 contingency table using alternation in QRS complex as a discriminant. B) The same using ST-T alternation as the discriminant. C) The 2×2 contingency table using alternation in either QRS complex or ST-T wave.}
\end{figure}

As one can see from the above tables, neither QRS alternation (Figure 10-1a)
nor ST-T wave alternation (Figure 10-1b) alone proved to be a statistically significant discriminant in stratifying the patient population into inducible / non-inducible categories. With QRS and ST-T wave alternation taken together, however, (Figure 10-1c) the results suggest that alternation in ECG morphology may serve as a significant discriminant for this purpose.

10.5 Discussion

Motivated by the discovery of a relationship between alternating ECG morphology and cardiac electrical stability in two series of canine experiments, this clinical trial was undertaken to determine whether such a relationship might also exist in the clinical setting. Alternation in ECG morphology was measured at each of three ventricular pacing rates using the vector magnitude as the ECG waveform and multidimensional spectral analysis as the detection technique.

While the mean values for AEMI(QRS) and AEMI(ST-T) were greater for the inducible population than the non-inducible group, the scatter in the measurements precluded a neat separation of the two populations based on these metrics. The $2 \times 2$ contingency tables suggested that using the presence of alternation in either the QRS complex or in the ST-T wave was both more sensitive and more specific than using alternation in either waveform segment separately. Using alternation in either waveform segment as a discriminant for identifying the inducible patient population was found to have sensitivity of 92%, and specificity of 70% ($p < 0.05$), with only 1 of the 13 inducible patients “missed” by our metric.

10.5.1 Confounding Influences / Sources of Error

Before going on to discuss the implications of the results, it is important to touch on the differences between this clinical trial and the preceding animal
experiments. The sources of error and confounding influences discussed with respect to the animal experiments also apply to this study, with some minor modifications. The inherent degeneracy of the ECG is obviously still an issue, but the degree to which the human ECG does not reflect all cardiac events may differ from that in the canine case. The ambient and induced noise sources are somewhat more significant in this clinical trial in that:

1. paste-on skin-surface electrodes were used as opposed to the transcutaneous needle electrodes used in the canine studies;

2. the patients were conscious and moving about (although cautioned to remain still) as opposed to the unconscious, partially paralyzed state of the animals in the canine experiments;

3. the ECG data was recorded and played back one additional time (to re-record the data from the hospital-bound Teac recorder to the laboratory HP tape recorder).

The effect of respiration was potentially less of an issue in these clinical trials in that the patients were free-breathing, and as a result, did not induce a perfectly periodic respiratory influence on ECG morphology.

Ventricular pacing vs. atrial pacing:

In the canine studies, atrial pacing was used to fix the inter-beat interval. In this clinical trial, ventricular pacing was used to fix the inter-beat interval. Atrial pacing was not an option due to the specifics of the EP study protocol. The differences between atrial pacing and ventricular pacing are many, and merit some brief discussion. In an atrially paced beat, excitation presumably follows the normal excitation pathway from the paced atrium through the atrioventricular node, down the limbs of the His-Purkinje system, to the terminal ramifications of the specialized cardiac conduction system, and finally to the bulk of the ventricular myocardium. Ventricular pacing, in contrast, results in an abnormal spread of excitation, starting instead at the pacing site within the ventricle, and spreading, without the aid of the
synchronizing specialized cardiac conduction system, throughout the bulk of the ventricular myocardium. Retrograde conduction through the A-V node does not always take place. When there is a failure of the excitation wavefront to move retrograde into the atria, the sinus node pacemakers are not reset, and as a result, the atria continue to beat at their own intrinsic rate. The net effect of this failure to entrain the sinus node pacemakers is a decoupling of atrial and ventricular excitation. As a result, the electrocardiogram will show equally spaced ventricular complexes, with superimposed atrial activity which appears to "march through" the ventricular complexes, having no temporal relationship to the occurrence of ventricular complexes. This superposition of unsynchronized atrial activity results in highly variable electrocardiographic complexes, which in turn makes detection of subtle waveform alternation all the more difficult. So it must be concluded that ventricular pacing, especially in the absence of retrograde conduction, offers additional hurdles to the detection of potentially meaningful fluctuations in waveform morphology.

Having provided ample justification for increased experimental error in this clinical trial, we may nonetheless conclude our discussion on a positive note. *This brief clinical trial provides the very first evidence that subtle alternation of ECG morphology does indeed exist under conditions of fixed-rate ventricular pacing, and this, in itself, is a novel discovery which was successfully predicted by our simple model. This study goes on to suggest that the presence of statistically significant alternation of ECG morphology may provide a useful discriminant for identifying the patient population which is inducible into ventricular tachycardia with programmed stimulation. Under the assumption that such inducibility reflects an underlying cardiac electrical instability, alternation of ECG morphology may provide a marker for decreased electrical stability.*
Chapter 11

Final Discussion

Before providing a closing summary, we should examine the major statements and findings enclosed herein, and provide sufficient overall discussion to give direction to future efforts in these areas.

11.1 Computer Studies

The modest computer studies discussed in Chapter 3, while simple and easily understood (perhaps even elegant), made no attempt to include the enormous wealth of morphological and electrophysiological detail presently available about the human heart and electrical conduction therein. As this work is extended, these details must doubtlessly be taken into consideration. The specialized cardiac conduction system, complete to the level of the geometry of its terminal ramifications, must be appropriately modeled if the details of re-entrant loop formation in vivo are to be understood. The effects of overall cardiac geometry, perhaps even to the level of specific fiber orientation information, may make very important contributions to the current concepts regarding the specifics of cardiac conduction and abnormalities therein.

If, as was done in this thesis, attempts are made to predict ECG activity based on a forward solution of the model’s electrical activity, the nature of the degenerate map from cardiac electrical activity to body-surface potentials must be further investigated. It may be the case that information gleaned from the study of anatomically correct cardiac models may serve as sufficient constraints to make a unique solution of the inverse problem of electrocardiography possible.
[The author is aware that these issues and others are currently being addressed by B. Saxberg, and wishes to express his gratitude for the many enlightening discussions regarding these and other topics.]

11.2 Statistical Approximations / Percolation Theory

The journey into the land of statistical physics in search of a useful approach for dealing with the description of the dynamics of re-entrant loop formation (as described in Chapter 5) should be examined further. The author claims little expertise in that area, and as such, the successes described in that chapter are potentially only the first of many. The problem of re-entrant loop formation is essentially one of dynamical percolation theory, and this relatively new area is attracting significant interest. As such, there is great potential for the development of new techniques for dealing with this and similar problems, perhaps eventually allowing for a closed form quantitative description of the dynamics of self-sustained rhythm disturbances.

11.3 Universal Non-linear Systems Theory

Here too is an area of intense recent interest. The analogy between chaos in deterministic systems and ventricular fibrillation would seem to justify a more detailed study of the "universal" behavior of systems near their chaotic regimes. While there is no evidence to support that cardiac conduction traverses through the period doubling cascade described by Feigenbaum, further study may reveal modifications of such "universal" notions which directly impact our understanding of abnormal cardiac conduction and the genesis of ventricular fibrillation (cardiac chaos?).
11.4 Fluctuations in ECG Morphology as an Indicator of Decreased Cardiac Electrical Stability

In Chapters 8, 9, and 10, we established that decreased cardiac electrical stability is accompanied by an increased level of alternation in surface ECG morphology in a variety of situations. Successes aside however, this work constitutes the beginning of the search for a non-invasive technique for measuring cardiac electrical stability, not the conclusion. The limitations of the present methodology are several, and merit being treated separately to guide future efforts.

11.4.1 ECG Metrics

From our initial study of ECG morphological variation where we used relatively unsophisticated metrics of morphology (Chapter 8) we progressed to a multidimensional approach (Chapters 9 and 10). We similarly progressed from examining single lead data to examining the three-dimensional representation of the cardiac vector dipole. We discussed how examining the magnitude of the three-dimensional vector help to cancel the effects of cardiac motion, but that it had a detrimental effect on our ability to accurately detect and quantify true electrical alternation (Sections 8.4. and 9.4.1.2.). In future work, efforts might be made to independently assess cardiac motion and counter for its effects. In particular, if the attempt is to provide a screening test, one might just as well detect alternation in surface ECG from any cause (motion of the heart or alternating electrical patterns) and then exclude false positives on the basis of independent measures (perhaps echocardiography). In this way, one might avoid the deleterious “smearing” effects of the filtering operation which cancels such motion effects.

In moving from single lead data to three-dimensional vectorcardiographic data, we made an initial effort to capture more information about the cardiac
sources. While the vectorcardiogram does represent an improvement, even greater improvement is to be expected from body surface potential mapping. By examining body surface potential maps, one might be able to provide an estimate of the fraction of the myocardium involved in alternating electrical behavior, and thus provide a better test of the notions presented herein, and perhaps provide a more refined screening procedure for the identification of those at risk.

11.4.2 Fixed Inter-beat Interval Requirement

The model of cardiac conduction underlying the efforts described herein is one of a continuous-time discrete-space Markov system. That is to say, any one element of the heart yields one of a finite set of responses when stimulated, where the determining factor for the specific response is the refractory period of the element and the time since last stimulation. The aggregate response of the entire heart can then be modeled as the aggregate of a finite number of finite-state Markov elements, which is also a finite-state Markov system. Early on, the complex influence of continuously variable time was removed by requiring a fixed inter-beat interval. By forcing the time between successive stimulations to be constant, the number of possible aggregate states was reduced to either 1 or 2, depending on the relationship between the interstimulus interval and the distribution of refractory times. If the interstimulus interval was longer than the shortest refractory period within the model heart, each response was the same. If elements had refractory periods in excess of the interstimulus interval, they were forced to alternate in their responses, giving rise to an alternating aggregate response. [This is a simplification for the purpose of making a point - the cooperativity of nearby elements can of course give rise to periods different than 2 - see Chapter 7.]

Once interstimulus intervals are allowed to vary, as is the case during sinus
rhythm, the model of alternating behavior no longer applies. Instead, a wide variety of aggregate behaviors are to be expected, and the problem reverts back to the analysis of a continuous-time, discrete-space Markov system. With this model, one is left with a very difficult problem in trying to detect these different states based on observable metrics. Leaving model space and examining the problem of detecting and quantifying such behavior in an animal preparation, one is confronted with an extremely difficult problem. The finite number of potential aggregate responses may be extremely large (approximately the product of number of independent sites within the heart and the number of unique responses each site is capable of producing). In a setting of broad-band noise, the distinction between the overwhelming majority of these states may be impossible. One possible approach might be to compare and contrast the morphologies of ECG epochs following different length RR intervals. Interpretation of the morphologic differences linked to different preceding RR intervals will be complicated because longer RR intervals will allow for longer periods of cardiac filling, and thus the shape of the cardiac sources will vary with RR interval.

11.4.3 Spectral Techniques vs. Time Series Approaches

In this thesis, spectral techniques were employed to detect and quantify the alternation in ECG waveform morphology. Spectral techniques offer the ability to easily detect periodic oscillations in the data being examined, even when such periodic fluctuations are not easily observed in the time-domain representation. As alternation is periodic, spectral techniques were useful in this present study. As discussed above, however, alternation in morphology was believed to be directly linked to the fact that the inter-beat intervals were held constant. If attempts are made to extend this work to the case of non-paced (sinus rhythm) data, spectral techniques may no longer be appropriate. In this case, it is likely that
autoregressive techniques may provide potential detection and quantification schemes, owing to our model of the process as being autoregressive in nature.
Chapter 12

Conclusion

This thesis has concerned itself with the discussion of a theory of cardiac rhythm disturbances based on the evolution of self-sustained activation (re-entrant loop formation) in non-uniformly excitable media (cardiac tissue). We first described the rich variety of clinically observable cardiac rhythm disturbances and the qualitative theories believed responsible (Chapter 2). In Chapter 3, we went on to provide a quantitative interpretation of one popular qualitative theory of cardiac rhythm disturbances (the Dispersion of Refractoriness Hypothesis), and subsequently tested (via simple finite-element models) the ability of this theory to account for the rich variety of rhythm disturbances previously described. In that Chapter, we also discussed the discovery (in the space of the model) of an electrocardiographically observable precursor of the re-entrant rhythm disturbances, i.e., a subtle alternation in ECG waveform morphology which heralded the presence of the requisite substrate for re-entrant loop formation. In Chapter 4, we developed a more detailed quantitative description of the implications of a stochastic distribution of refractory period duration in actively propagating media such as myocardium (based in part on percolation theory). In this Chapter, we developed the first quantitative theory to successfully predict the existence of the vulnerable period (the window of time during ventricular repolarization when exogenous stimulation of the ventricles results in ventricular fibrillation) and the protective zone (a temporal window immediately following the vulnerable period during which exogenous stimuli to the ventricles would deter the formation of ventricular fibrillation). We discussed an extension of the same theory which explained the shape of the ventricular
excitability curves, the relationship between conduction velocity and prematurity, and the presence of delayed depolarizations / late potentials. In Chapter 5, we compared the predictions made in Chapter 4 with experimental and clinical evidence. In Chapter 6, we focussed on the model prediction of alternating ECG morphology serving as an indicator of decreased electrical stability, and reviewed the relevant experimental and clinical literature regarding electrical alternans. The tempting link between electrical alternans and universal bifurcation theory as applied to non-linear systems required some discourse, and such was provided in Chapter 7. In Chapter 8, we discussed the first set of animal experiments designed to test the model prediction of alternating ECG morphology serving as a marker for decreased electrical stability. These animal experiments, despite their many limitations, provided the first evidence to suggest that alternating ECG activity may provide information regarding relative cardiac electrical stability. A second set of animal experiments, including many improvements in experimental and analytical techniques, was discussed in Chapter 9. This second study demonstrated a definite correlation between the measured degree of alternation in ECG morphology and objective measures of cardiac electrical stability, lending further support to the early model prediction. A detailed discussion of the limitations of that second study suggested improvements for subsequent studies. In Chapter 10, we described a first clinical trial testing whether alternating ECG morphology might serve to identify the population at risk to Sudden Cardiac Death. By comparing our results to those of invasive Electrophysiologic Testing, we found that the presence of alternating ECG morphology was a significant discriminant in identifying the patient population susceptible to induction to re-entrant rhythm disturbances.
References


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Biographical Sketch

Joseph Martin Smith was born of Margaret Jane and Leo Arthur Smith on May 31, 1957, in Baltimore, Maryland. He is the youngest of four children, with two sisters (Rita and Stephanie) and one brother (Leo Jr.). He attended St. Ambrose Catholic School (graduated in 1971), the Baltimore Polytechnic Institute (graduated in 1975) and the Johns Hopkins University (graduated with Bachelor of Engineering Science in Electrical Engineering in 1979). In 1979, he enrolled in the Harvard-MIT Division of Health Sciences and Technology - Medical Engineering / Medical Physics doctoral program, and the MIT Department of Electrical Engineering. In 1982, he was awarded the Master of Science degree in Electrical Engineering from MIT. This dissertation marks the completion of his doctoral work in Medical Engineering in the Harvard-MIT Division of Health Sciences and Technology in 1985.

Joe found graduate school in Medical Engineering an infinitely preferable alternative to either building better bombs for a brighter tomorrow, or racking wrists and retinas with raster-scan video games. He hopes to continue his research in biomedical signal processing and biomedical physics in the cardiovascular system, and most enjoys being in a community of people who can all get a joke.