

Arrhythmias by Dimension

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ABSTRACT. The mathematical study of cardiac arrhythmias can be organized by classifying arrhythmias by their spatial dimension. This paper gives an overview of cardiac arrhythmias from this organizational viewpoint, emphasizing the insights that are gained and the problems that result from identifying the arrhythmias in these terms.

1. Introduction

Abnormalities of function of the cardiac conduction system are the cause of death of thousands of people every day. For that reason, the study of cardiac arrhythmias is of great interest from a medical and scientific perspective. However, cardiac arrhythmias are also interesting for mathematical reasons because they can be studied from the viewpoint of dynamical systems theory.

Strictly speaking, a cardiac arrhythmia is any departure of the heartbeat from strict periodicity. In that sense, all living persons have arrhythmias all the time, since the normal heartbeat is never exactly periodic. However, the arrhythmias of interest here are those which are considered abnormal, and which have nontrivial physiological consequences.

There are (at least) three challenges presented by cardiac arrhythmias. The first is simply to identify the different arrhythmias and their underlying mechanisms. The second is to understand the cause or origin of each arrhythmia, and the third is to determine how to control the arrhythmia so that its harmful effects can be avoided. To the mathematician, there is also the challenge and fascination with the mathematics that underlies the description and understanding of arrhythmias.

The purpose of this paper is to provide a brief introduction to each of these, organized on the basis of their spatial dimension.

2. The Normal Cardiac Rhythm

Before we can discuss cardiac arrhythmias, we must have a description of the normal course of events.

1991 *Mathematics Subject Classification.* **change these**Primary 92C30, 92C50; Secondary 35K57.

Key words and phrases. cardiac arrhythmias, reentry, spiral waves, scroll waves.

This work was supported in part by NSF Grant DMS-99700876.

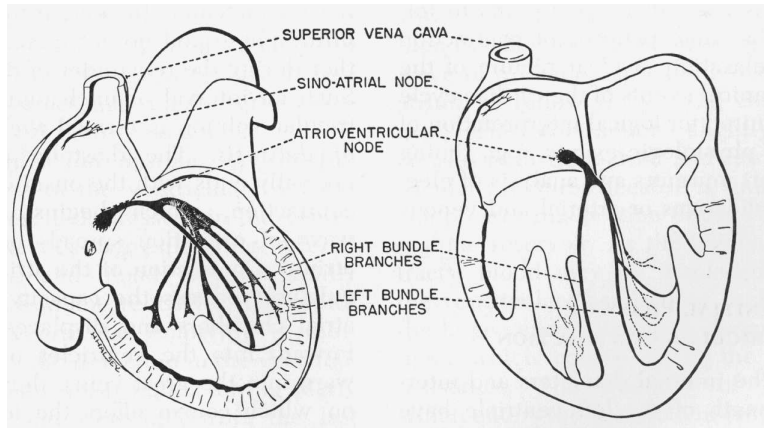


FIGURE 1. Schematic diagram of the cardiac conduction system.

The human heartbeat is a contraction of cardiac muscle that is stimulated by an electrical event, occurring about once per second, during which every cell in the heart experiences a rapid excursion of transmembrane potential, lasting about 300 ms, before returning to rest. This excursion from rest, called an action potential, is coordinated by a wave of electrical activity. This wave of electrical activity (see Fig. 1) is initiated by a small collection of cells in the right atrium, near the superior vena cava, called the sinoatrial node (SA) node. These cells are all autonomous oscillators, and are synchronized by local electrical coupling. Once initiated, a wave of electrical activity propagates across the atria, terminating at the atrial-ventricular (AV) septum, a non-conducting septum between atria and ventricles. This wave of activity enters another small clump of cells in the AV septum, the AV node, through which it propagates slowly. Leaving the AV node, the wave enters a bundle of specialized fibers called the His-Purkinje system, consisting of the bundle of His, bundle branches and Purkinje fibers, which branch out in tree-like fashion to reach the interior (endocardial) wall of the ventricles. The excitation emerges from the Purkinje fibers to activate the ventricular tissue, propagating from inside to outside, terminating at the epicardium.

The standard diagnostic tool for the clinical evaluation of the heartbeat is the electrocardiogram (ECG), which measures the body surface potential generated by the traveling heartbeat (see Fig. 2). The normal ECG has three characteristic signals, the P wave, corresponding to activation of the atria, the QRS complex, corresponding to the activation of the ventricles, and the T wave, corresponding to recovery (return to rest) of the ventricles. Other electrical events involve too little tissue mass to be recorded at the body surface.

3. Zero Dimensional Arrhythmias

Zero dimensional arrhythmias are those involving single cells or small collections of cells, and do not rely on the spatial arrangement of the cells to exist. These can be classified roughly into three categories. The first are single cells that change their behavior from normal behavior to a different type of rhythmic or arrhythmic behavior. For example, SA nodal cells are normally autonomous oscillators while

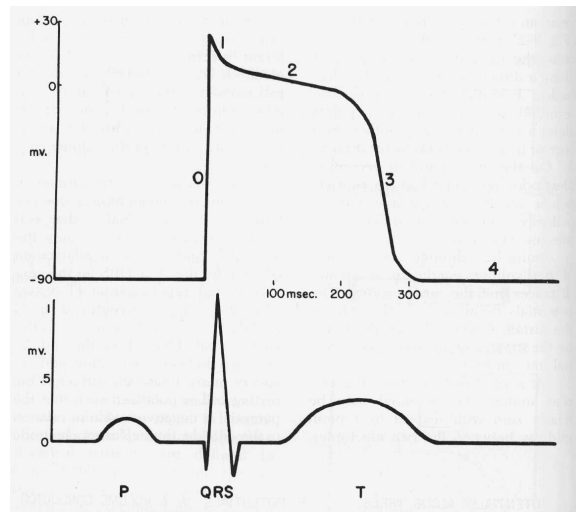


FIGURE 2. Cellular transmembrane potential and electrocardiogram. The upper tracing represents the transmembrane potential of a single ventricular myocyte and the lower tracing shows the body surface potential during the same electrical event. The numbers on the upper tracing designate phases in the action potential cycle: 0: the upstroke, 1: the brief spike, 2: the plateau, 3: the rapid recovery, 4: resting potential.

most other myocardial cells do not spontaneously fire without external stimulus. An ectopic focus is a collection of cells that spontaneously oscillates although it should not. Similarly, some cells may experience a change from their normal action potential trajectory. For example, early after depolarizations (EAD's) occur when cells do not return directly to rest after having been stimulated, but spontaneously fire before returning to rest [LR94b].

The second class of zero dimensional arrhythmias are those associated with coupled oscillators. For example, parasystole is a condition in which there are (purportedly) two autonomous oscillators vying for control of the heartbeat.

The third class of zero dimensional arrhythmias are those associated with failure of a group of cells to be entrained to an external signal. AV nodal block is usually viewed in this way.

The mathematical study of these arrhythmias makes use of dynamical systems theory to characterize the possible behaviors and bifurcations. There are two primary approaches. In the first, detailed (quantitative) ionic models of single cells are studied to determine how physical parameters affect the behavior of a cell in a variety of conditions. There is a long history of modeling studies of this type. The first detailed model of cardiac cell activity was proposed by Noble [Nob62], and was a modification of the Hodgkin-Huxley model [HH52]. This style of modeling was continued by many authors, including [DN85] for Purkinje fiber, [BR77] for ventricular cells, and [YNI80] for SA nodal cells. As more information has

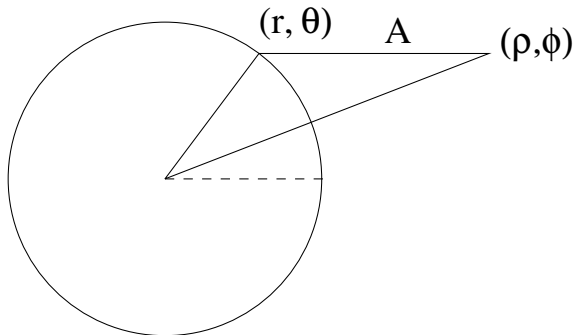


FIGURE 3. Diagram of phase resetting for the Poincaré oscillator.

become available concerning the complexities of cardiac cells, the models have become correspondingly more complex, as represented by [LR94a] and [JRW98] for ventricular cells, [WKVN93] for SA nodal cells, [CRN98] for atrial cells.

Much of the current research activity using detailed models is aimed at understanding cellular behavior in a pathological environment, such as ischemia, which occurs immediately following a heart attack. There are a large number of changes that take place [Car99], and we are a long way from having a clear mathematical description of these events. Detailed models have been used to study a variety of related abnormalities. For example, [LR94b] examines EAD's, [WKV⁺93] examines ectopic rhythms, [CVJCN98] examines pH regulation in ischemic cells, [FSFT96] examines the role of K-ATP channels during ischemia, and [RJV99] examines irregularities in the dynamics of calcium handling.

The second approach, and the one that is described here, seeks an understanding of arrhythmias using qualitative models. This approach has been quite successful by exposing general properties of arrhythmias.

3.1. The Poincaré Oscillator. There are numerous challenges associated with the qualitative behavior of a zero dimensional arrhythmia. The most obvious is simply to describe the different possible behaviors of an oscillator and the bifurcations between these behaviors.

The study of cellular arrhythmias from a qualitative perspective has a long history, initiated by the famous van der Pol equation, initially proposed as a model of the heartbeat [vdPvdM28]. In more recent times there have been many studies of coupled oscillators and forced oscillators that take into account a range of features relevant to cardiac cell activity.

A simple model of forced periodic oscillations, called the Poincaré oscillator (also called a radial isochron clock or snap back oscillator) manages to portray many of the important ideas. We suppose that a point is moving counterclockwise around a circle of radius 1 at fixed velocity $\frac{d\theta}{dt} = 1$. At some point in its rotation, the point is moved horizontally by an amount A and then allowed to instantly “snap back” to radius 1, moving along a radial line toward the origin, without additional change of phase. (See Fig. 3)

It is fairly easy to determine that the relationship between the phase ϕ immediately after reset as a function of phase θ immediately before reset is given

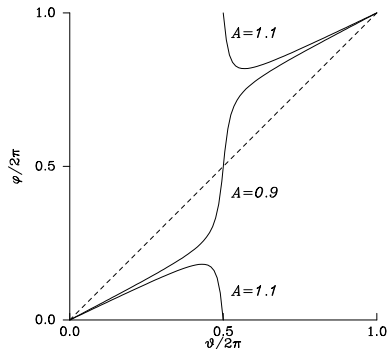


FIGURE 4. The phase resetting curve for the Poincaré map, shown modulo 2π . With $A < 1$ this is a type 1 map, while with $A > 1$ it is a type zero map.

by

$$(3.1) \quad \cos \phi = \frac{A + \cos \theta}{(1 + 2A \cos \phi + A^2)^{1/2}}.$$

This relationship is called the phase resetting curve for this process, and depending on the amplitude of A can be of two distinct topological types. If $A < 1$, then $\phi(\theta + 2\pi) = \phi(\theta) + 2\pi$, and is called a type 1 map, since ϕ goes through a full rotation of 2π as θ goes through 2π . If $A > 1$, then $\phi(\theta + 2\pi) = \phi(\theta)$, and is called a type 0 map, since ϕ goes through no rotation as θ goes through 2π . (see Fig. 4)

Having determined the phase resetting curve, one can now study the long term behavior of this oscillator by examining the map

$$(3.2) \quad \theta_{n+1} = (\phi(\theta_n) + T) \bmod 2\pi = f(\theta_n).$$

Here we have a simple example of a continuous circle map, that is, a map of the circle to itself, $f : S^1 \rightarrow S^1$.

It is a straightforward matter to find the parameter values for which there is one-to-one phase locking (defined as a stable fixed point of the map (3.2)), but there are many more complicated response patterns that are much more difficult to unravel. In fact, sorting out the details of this apparently simple map has been the focus of numerous papers, including [GM79] [GP82] [GG82] [GGSP83] [KG84] [GGBS84] [MFV88] [GS94].

One very important idea that has emerged from these studies is the idea of phase resetting and phase resetting curves, allowing cardiac rhythms to be studied as iterates of maps [GG99]. This idea was important, because phase resetting curves can be measured experimentally and their consequences examined without reference to a detailed ionic model [JA79]. In this way, situations that are far more complicated than the simple Poincaré map can be studied and analyzed.

3.2. AV node. As an example of how dynamical systems theory (specifically 1-D maps) can be used to understand specific cardiac arrhythmias, we consider AV nodal block. In the normal heart, the only pathway for an action potential to travel

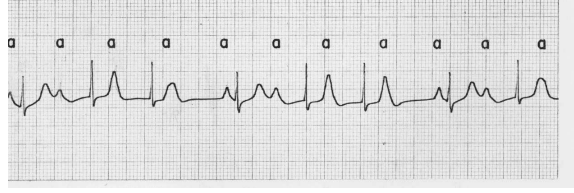


FIGURE 5. ECG recording of a Wenckebach pattern in which every fourth or fifth atrial beat is not conducted. The symbol “a” denotes an atrial excitation (P-wave).

to the ventricles is through the AV node. As noted above, propagation through the AV node is slow compared to propagation in other cardiac cells, and as a result is somewhat more likely to fail.

Propagation failure in the AV node leads to skipped QRS complexes on the ECG, or, more prosaically, skipped heartbeats. A skipped heartbeat once in a while is not particularly dangerous, but it is certainly noticeable. During diastole (the period of ventricular relaxation during the heartbeat cycle), the ventricles fill with blood. Following an abnormally long diastolic period, the heart becomes enlarged and when the next compression (systole) occurs, Starling’s law (i.e., that compression is stronger when the heart is more distended initially) takes control and compression is noticeably more vigorous, giving the subject a solid thump in the chest.

AV nodal conduction abnormalities are classified into three classes that are all readily visible from ECG recordings by looking at the time interval between the P wave and the QRS complex, i.e., the P-R interval. Type I AV nodal block shows itself as an increase in the P-R interval as the SA pacing rate increases. Type III AV nodal block corresponds to no AV nodal conduction whatever, and total lack of synchronization between P and QRS complexes.

Type II AV nodal block is phenomenologically the most interesting. In the simplest type, there is one QRS complex for every two P waves, a 2:1 pattern. A more complicated pattern is as follows: On the ECG (Fig. 5) P waves remain periodic, although the P-R interval is observed to increase gradually until one QRS complex is skipped. Following the skipped beat, the next P-R interval is quite short, but then the P-R lengthening begins again leading to another skipped beat, and so on. A pattern with n P waves to $n - 1$ QRS complexes is called an n to $n - 1$ Wenckebach rhythm, after the German cardiologist Wenckebach [Wen04].

A simple mathematical description of AV nodal signal processing can be given as follows: we view the AV node as a collection of cells that fire when they are excited, which happens if their potential reaches a threshold, $\theta(t)$. (Notice that here θ refers to the firing threshold, whereas in the previous section, θ referred to the phase of the Poincaré oscillator.) Immediately after firing, the cells become refractory, but then gradually recover. Effectively, at firing, the threshold increases dramatically, but then decreases back to its steady state value as recovery proceeds. This model ignores the fact that the AV node is self-oscillatory, and will fire without stimulus with a low frequency of 30-40 per minute. The self-oscillatory nature of the AV node becomes evident only in cases of SA nodal failure, at very low SA nodal firing rates or in third degree (type III) block. Thus, the model discussed

here is valid at high stimulus rates (appropriate for AV nodal block), but not at low stimulus rates.

Input to the AV node comes from the action potential propagating through the atria from the SA node. The AV node experiences a periodic (period T), time varying potential, say $v(t)$. Firing occurs if the input signal reaches the threshold. Therefore at the n^{th} firing time, denoted t_n ,

$$(3.3) \quad v(t_n) = \theta(t_n).$$

Subsequent to firing, the threshold evolves according to

$$(3.4) \quad \theta(t) = \theta_0 + [\theta(t_n^+) - \theta_0]e^{-\gamma(t-t_n)}, \quad t > t_n.$$

Note that $\theta \rightarrow \theta_0$ as $t \rightarrow \infty$, and thus θ_0 denotes the base value of the threshold. Further, $\theta = \theta(t_n^+)$ at $t = t_n$, and thus $\theta(t_n^+) - \theta(t_n^-)$ denotes the jump in the threshold caused by the firing of an action potential. To complete the model we must specify $\theta(t_n^+)$. The important feature of $\theta(t_n^+)$ is that it must have some memory, that is, depend in some way on $\theta(t_n^-)$. Therefore, we take

$$(3.5) \quad \theta(t_n^+) = \theta(t_n^-) + \Delta\theta.$$

The simplest choice is to take $\Delta\theta$ a constant.

Now we can find the next firing time as the smallest solution of the transcendental equation

$$(3.6) \quad v(t_{n+1}) = \theta_0 + [\theta(t_n^+) - \theta_0]e^{-\gamma(t_{n+1}-t_n)}.$$

Equation (3.6) can be rearranged into an equation of the form

$$(3.7) \quad F(t_{n+1}) = F(t_n) + \Delta\theta e^{\gamma t_n} = G(t_n),$$

where

$$(3.8) \quad F(t) = (v(t) - \theta_0)e^{\gamma t}.$$

Plots of typical functions $F(t)$ and $G(t)$ are shown in Fig. 6. Here we have taken $v(t) - \theta_0 = \sin^4(\pi t)$. The dashed lines in this figure follow a few iterates of the map.

The key observation is that the map $t_n \mapsto t_{n+1}$ as defined by (3.7) is the lift of a circle map. If $F : S^1 \rightarrow S^1$ is a circle map, then the lift of a circle map is defined as the monotone increasing function $F : R \rightarrow R$ with

$$(3.9) \quad f(x) = F(x \bmod 1) \bmod 1.$$

and $F(x+1) = F(x) + 1$. (For convenience we normalize the circumference of the circle to be of length 1, rather than 2π .)

Notice that the map defined by (3.7) is indeed the lift of a circle map, since, if t_n and t_{n+1} satisfy (3.7), then so do $t_n + T$ and $t_{n+1} + T$. To find a circle map, we let k_n be the largest integer less than t_n/T and define $\psi_n = (t_n - k_n T)/T$. In these variables the map (3.7) can be written as

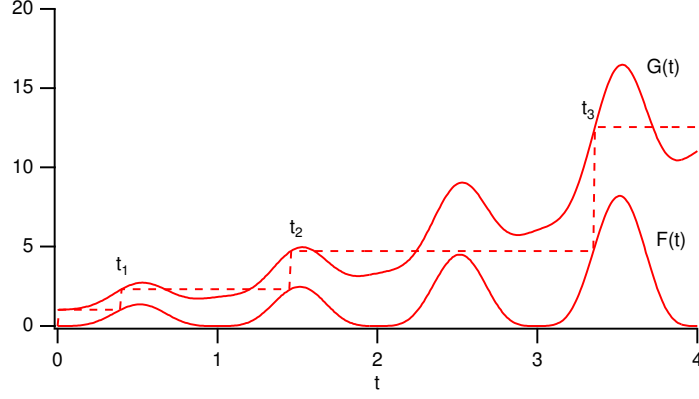
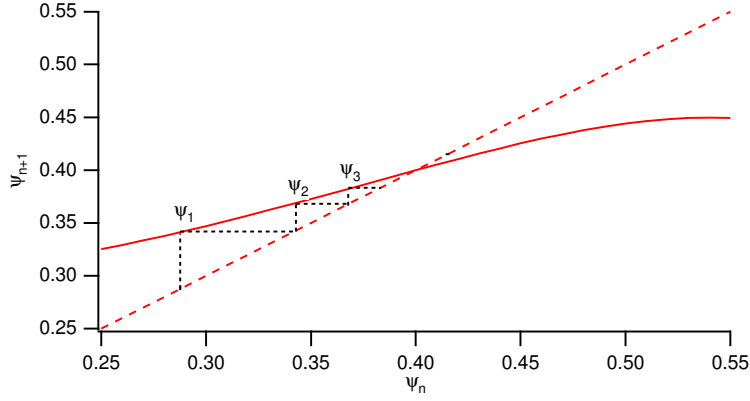
$$(3.10) \quad f(\psi_{n+1}) = (f(\psi_n) + \Delta\theta e^{\gamma T \psi_n})e^{\gamma T \Delta k_n},$$

where

$$(3.11) \quad f(\psi) = (\Phi(\psi) - \theta_0)e^{\gamma T \psi}, \quad \Phi(\psi) = v(T\psi),$$

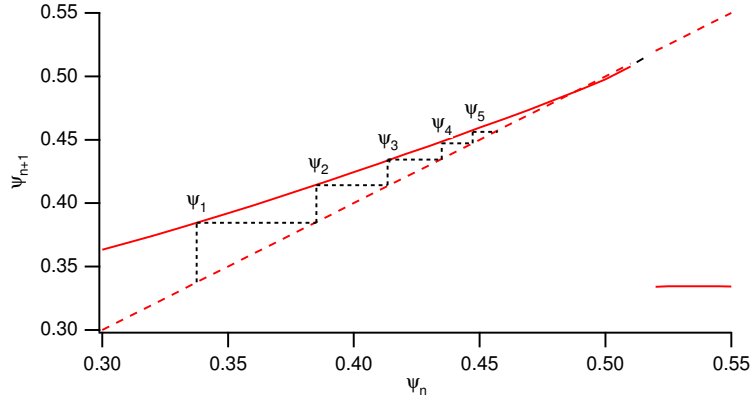
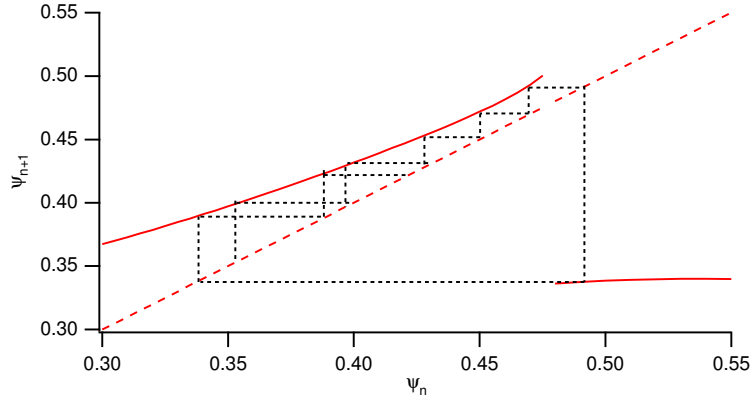
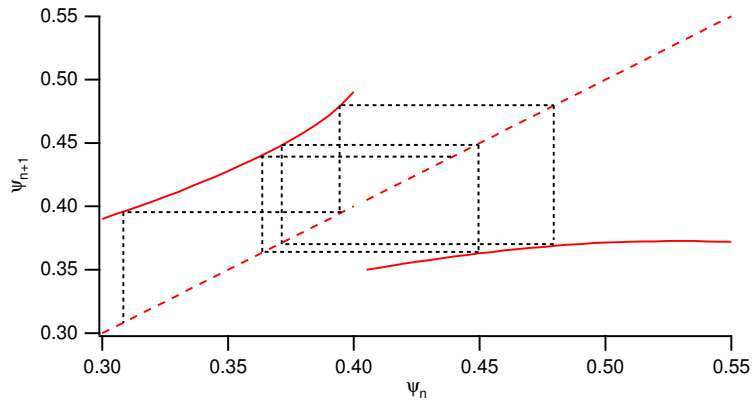
and $\Delta k_n = k_{n+1} - k_n$.

We can make a few observations about the map $\psi_n \mapsto \psi_{n+1}$. First, and most disconcerting, the map is not continuous. In fact, it is apparent that there are

FIGURE 6. Plot of the functions $F(t)$ and $G(t)$ with $\Delta\theta = 1.0, \gamma = 0.6$.FIGURE 7. Plot of the map $\psi_n \mapsto \psi_{n+1}$ with $\Delta\theta = 1.0$, with $\gamma T = 0.8$.

values of t on the unit interval that can never be firing times. For t to be permitted as a firing time it must be the first point at which $F(t)$ reaches the level $G(t_n)$, i.e., the first time that the threshold is reached. At such a point, $F'(t) > 0$. Since there are regions for which $F'(t) < 0$ which can therefore never be firing times, this is a map of the unit interval *into*, but not *onto*, itself. However, the map $t_n \mapsto t_{n+1}$ is order preserving since $G(t)$ is increasing whenever $F(t)$ is increasing.

Since the entire unit interval is not covered by the map, it is only necessary to examine the map on its range. Examples of the map $\psi_n \mapsto \psi_{n+1}$ are shown in Figs. 7–10. Here we have plotted the map only on the attracting range of the unit interval. These show important and typical features, namely that the map consists of either one or two (but not more) continuous, monotone increasing branches. The first branch, with values above the one-to-one curve, corresponds to firing in response to the subsequent input (with $k_{n+1} = k_n + 1$), and the second, with values below the one-to-one curve, corresponds to firing after skipping one beat (with $k_{n+1} = k_n + 2$). The skipped beat occurs because when the stimulating pulse arrives, it is subthreshold and so does not evoke a response.

FIGURE 8. Plot of the map $\psi_n \mapsto \psi_{n+1}$ with $\Delta\theta = 1.0$, with $\gamma T = 0.695$.FIGURE 9. Plot of the map $\psi_n \mapsto \psi_{n+1}$ with $\Delta\theta = 1.0$, with $\gamma T = 0.67$.FIGURE 10. Plot of the map $\psi_n \mapsto \psi_{n+1}$ with $\Delta\theta = 1.0$, with $\gamma T = 0.55$.

The sequence of figures in Figs. 7–10 is arranged in order of decreasing values of γT . Note that as γ decreases, the rate of recovery from refractoriness decreases. For γT sufficiently large, there is a unique fixed point, corresponding to firing in 1:1 response to the input signal. This makes intuitive sense, for when γ is large the recovery from inhibition is fast, and thus the AV node can be driven at the frequency of the SA node. For large γT the map is relatively insensitive to changes in parameters. As γT decreases the first branch of the map increases and the value of the fixed point increases, corresponding to a somewhat delayed firing. Furthermore, because the slope of the map in the vicinity of the fixed point is close to 1, the fixed point is sensitive to changes in parameter values (depicted in Fig. 8), corresponding to type I AV block.

As the parameter γT is decreased further, the fixed point is lost and a second branch to the map appears (as in Fig. 9). Iterations show that subsequent firings become later and later in the input cycle until one beat is skipped, followed by a firing which is relatively early in the input cycle. For this region of parameter space, the map replicates the Wenckebach phenomenon.

Finally, as γT decreases further the second branch “slides over” to the left and eventually intersects the one-to-one line (the identity line), yielding a fixed point. This fixed point corresponds to a periodic pattern of one skipped beat for each successful firing, a two-to-one pattern, and replicates type II AV block.

The behavior of the map in the region with no fixed point can be described by the rotation number. For maps of the type (3.7) the rotation number can be defined by

$$(3.12) \quad \rho = \lim_{n \rightarrow \infty} \frac{t_n}{nT}.$$

A detailed exposition of the rotation number for continuous, monotone, circle maps can be found in chapter 17 of [CL84]. For circle maps that are monotone, but not continuous, the following features of the rotation number ρ can be verified [Kee81] [Kee80].

- (1) ρ exists and is independent of initial data.
- (2) ρ is a monotone decreasing function of γT .
- (3) ρ attains *every* rational level between 0 and 1 on an open interval of parameter space.

For continuous circle maps, it is generically true, and therefore not certain, that every rational level is attained on an open interval of parameter space.

The main consequence of this result is that between 1:1 phase locking and 2:1 AV block, for every rational number there is an open interval of γT on which the rotation with that rational number is attained. The last two features of ρ make the behavior of the orbits so unusual, being a function that is monotone non-decreasing, yet locally constant at all the rational levels. Such a function is called the Devil’s Staircase. Notice that if ρ is rational on an open interval of parameter space, then phase locking is robust.

This model of AV nodal conduction block is quite simple. However, these maps can be, and have been, measured experimentally and used to compute the effects of periodic stimuli [SDR⁺87]. Furthermore, generalizations of this map, again using clinical data, have been found that are nonmonotonic circle maps having correspondingly more complicated phenomena [SAGB95] [BAZS94]. Other examples

of how circle maps can be applied to biological rhythms include [Kni72], [GM79] [KHR81].

3.3. Pacing and Alternans. The ideas of iterates of maps can also be used to study the response of single atrial or ventricular cells to periodic stimuli. We suppose that a cell is stimulated by a brief pulse at a fixed period, called the basic cycle length (BCL). This basic cycle length is divided between two types of cellular activity, its action potential and its recovery. Clearly the action potential duration (APD) during the n^{th} cycle, APD_n , and following recovery time, RT_n , must sum to the basic cycle length

$$(3.13) \quad APD_n + RT_n = BCL.$$

The fundamental assumption (an approximation, at best) is that APD_n is a function of the *previous* recovery time RT_{n-1} , $APD_n = a(RT_{n-1})$, called the restitution curve. It follows that

$$(3.14) \quad RT_n = BCL - a(RT_{n-1}),$$

provided there are no skipped beats. This equation was first applied in a dynamic context in [GWSG84]. The restitution curve is typically monotone increasing [FSS⁺83] [WOG95] [YJAG99] and the bifurcations of this map can be studied using standard methods. Two simple observations are, first, that if a is monotone increasing, then, if it exists, a fixed point (a 1:1 response) is unique, and second, the fixed point is stable if and only if $a' < 1$ at the fixed point. Since $a' \rightarrow 0$ for large RT , the response to a periodic stimulus fails to be 1:1 only if the BCL is small, i.e., the stimulus is rapid. Notice also that if the 1:1 solution is unstable, then iterates alternate above and below the fixed point, a 2:2 periodic solution. These oscillations of APD are called alternans in the cardiology literature.

The simple map discussed here fails to take into account that the success of a stimulus at evoking an action potential depends not only on the recovery time, but also on the stimulus strength, and if either are too small, beats can be skipped. Recently, [YJAG99][HBG99][Cyt01][CK01a] have described maps that depend on both BCL and stimulus strength and exhibit both APD alternans and Wenckebach patterns of skipped beats, giving results that compare nicely (both qualitatively and quantitatively) with experimental data and results from detailed ionic models. This success of one dimensional maps to capture important features of complicated dynamics points out that in large regions of physically relevant parameter space, cellular dynamics collapse to a one dimensional invariant manifold [Cyt01][CK01a].

These methods have also been applied to models of other arrhythmias, specifically parasystole, as in [MJMM77], [AM80], [GGB86], [JML86], [GGCS87], [CGRG89], [CGJ90]. Additional discussions of maps and chaos and the like with application to a wide array of biological oscillators can be found in [GM88], [GK95], [Str94].

4. One-Dimensional Arrhythmias

One-dimensional arrhythmias are characterized as such because their existence relies in a crucial way on a one-dimensional path of propagation.

The classic example of a one-dimensional arrhythmia is associated with Wolff-Parkinson-White (WPW) Syndrome. With this syndrome, it is observed that the

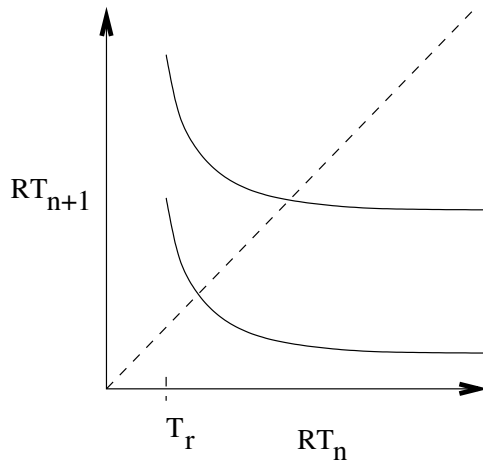


FIGURE 11. Schematic diagram of the map (3.14) for two different values of basic cycle length. For the larger BCL, the fixed point is stable, while for the smaller BCL, the fixed point is unstable, since $a' > 1$ at the fixed point.

action potential enters the ventricles through two conducting pathways, the normal AV nodal pathway, and a second pathway through the AV septum, called an accessory pathway. If this is the case, the AV node could fail to conduct a pulse, while the activation could enter the ventricles through the accessory pathway, propagate retrogradely along the Purkinje fibers to the AV node thence into the atria to complete a circuit. A permanently circulating wavefront results in a very rapid heartbeat with inefficient pumping activity, and would likely lead to fainting or dizziness.

One-dimensional reentrant arrhythmias were first studied in the early 1900's by Mines [Min14] when he intentionally cut a ring of tissue from around the superior vena cava and managed to initiate waves that traveled in only one direction.

One-dimensional arrhythmias are the easiest of all arrhythmias to treat clinically. If they can be identified as such, one-dimensional reentrant arrhythmias are treated by permanently burning a point on the pathway through which the circulating wave must go, thereby breaking the circuit. Thus, the important issues concerning one dimensional arrhythmias are to determine how they are formed, if they are stable once formed, and how to eliminate them. More important from a clinical point of view is to ascertain when an arrhythmia is truly one-dimensional, how to locate a narrow pathway through which the circuit passes, and how to destroy the circuit without damaging other important parts of the cardiac conduction system (such as the AV node).

We can get an idea of how a one-dimensional reentrant arrhythmia is initiated using a simple model. Suppose that there are cells located next to the exit from a one-dimensional path with one-way-block (Fig. 12). A path with one-way block means that propagation can go through the cells in one direction but not in the opposite direction. While this is not typical, it is certainly possible if there is some sort of arborization or branching of a pathway [Pau82] [Kee84] [Kee87] [LG91]. Indeed, conditions for one-way block are promoted and therefore arise more often

in certain pathological situations. Suppose further that these cells are normally stimulated by some external pacemaker, with period T . We define the instantaneous period of stimulus as $\Delta T_{n+1} = t_{n+1} - t_n$, where t_n is the n^{th} firing. Now we take a simple kinematic description of propagation in the one-way-path, and suppose that the speed of propagation in the path is a function of the instantaneous period, $c = c(\Delta T)$, called the dispersion curve. (Like the restitution curve, c is typically an increasing function of ΔT [MR81].) Then, the travel time around the one-way loop is $\frac{L}{c(\Delta T)}$. In well recovered ventricular tissue, the speed of an action potential is on the order of 0.5 m/s, so that travel time around the loop is much shorter than the period of external stimulus. Thus, the wave on the loop (typically) returns to the stimulus site long before the next external stimulus arrives (i.e. we assume that $L/c < T$). If this travel time is larger than the absolute refractory period T_r of the cells but smaller than T , the period of the external stimulus, then it stimulates the cells and initiates another wave around the loop. Thus,

$$(4.1) \quad \Delta T_{n+1} = t_{n+1} - t_n = \frac{L}{c(\Delta T_n)},$$

provided $T > \frac{L}{c(\Delta T_n)} > T_r$.

On the other hand, if this travel time is smaller than T_r , the reentering stimulus is not successful, and the cells must await the next external stimulus before they fire, so that

$$(4.2) \quad \Delta T_{n+1} = t_{n+1} - t_n = T$$

if $\frac{L}{c(\Delta T_n)} < T_r$.

With this information, we can construct the map $\Delta T_n \rightarrow \Delta T_{n+1}$, (shown in Fig. 13). There are obviously two branches for this map (shown as solid curves). Of interest are the fixed points of this map, corresponding to a periodic pattern of stimulus. The fixed point on the upper branch corresponds to the normal stimulus pattern from the external source, whereas the fixed point on the lower branch corresponds to a high frequency, reentrant, pattern. The key feature of this map is that there is hysteresis between the two fixed points. In a “normal” situation (Fig. 13a), with L small and T large, the period of stimulus is fixed at T . However, as L increases or as T decreases, rendering $L > T_r c(\delta T_n)$, there is a “snap” onto the smaller period fixed point, corresponding to initiation of a reentrant pattern (Fig. 13b). The pernicious nature of the reentrant pattern is demonstrated by the fact that increasing the period of the external pacemaker back to previous levels does not restore the low frequency pattern - the iterates of the map stay fixed at the lower fixed point, even though there are two possible fixed points. This is because the circulating pattern acts as a retrograde source of high frequency stimulus on the original stimulus site, thereby masking its periodic activity. The reentrant oscillator obstructs the activity of the external pacemaker (much as in parasystole).

Note that there are a number of ways that this reentrant pattern might be initiated. First, following a heart attack, a growing infarcted region may lead to a gradual increase in L , initiating the reentrant pattern while keeping T fixed. On the other hand, an infarcted region may exist but remain static (L fixed), and the reentrant pattern is initiated following a decrease in T , for example, during strenuous exercise. Thus, a static one-way-loop acts like a “frequency bomb” (rather than a time bomb), ready to go off whenever the frequency of stimulus is sufficiently high.

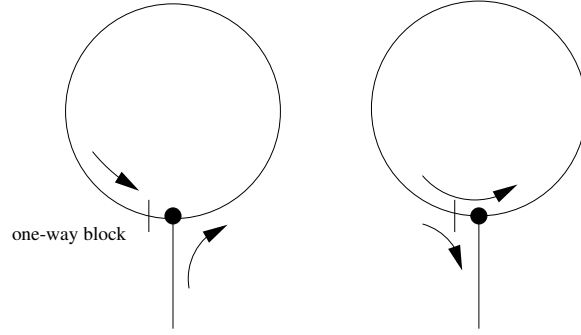


FIGURE 12. Diagram of a conducting path with one way block, preventing conduction from right to left. left) Conduction of a stimulus around the loop until it encounters refractoriness and fails to propagate further. right) Conduction of a reentrant pattern circulating continuously around the loop, and exiting via the entry pathway on every circuit.

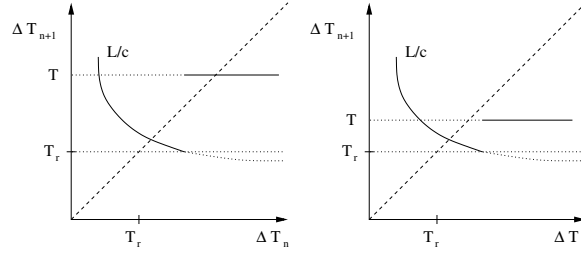


FIGURE 13. Next interval map for a one way conducting loop in two cases, a (left) with T large so that two stable steady solutions exist, and b (right) with T small so that the only steady solution corresponds to reentry.

The analysis of waves on a one-dimensional ring is substantially easier and more convenient than of reentrant waves in higher dimensional domains. For that reason waves on a ring have served well as a model for the study of arrhythmias. In that context, the stability of reentrant waves on a ring was studied in [IG92] [CKG93] [CKG96].

The above model for initiation of reentry does not take into account that the speed of propagation varies at different points of the ring. A simple model for reentrant waves on a ring that takes this into account is derived as follows. We assume that the time of arrival of an action potential at position x on the ring is $t(x)$ so that at each position x

$$(4.3) \quad APD(x) + RT(x) = t(x) - t(x - L),$$

for a ring of length L (an extension of (3.13)). As for a single cell, we assume that the action potential duration is a function of the previous recovery time, $APD(x) = a(RT(x - L))$. (Note that on a ring of length L , $t(x - L)$ is the previous time of firing at position x .) We also assume that the local speed of travel is a function of

the local recovery time,

$$(4.4) \quad C(x) = c(RT(x)).$$

Now we use that

$$(4.5) \quad t(x) - t(x - L) = \int_{x-L}^x \frac{dt}{dx} dx = \int_{x-L}^x \frac{1}{c(RT(x))} dx$$

to find the integral delay equation for $RT(x)$,

$$(4.6) \quad RT(x) = \int_{x-L}^x \frac{1}{c(RT(x))} dx - a(RT(x - L)).$$

In [CKG93][CKG96] it was shown that solutions of this equation are unstable if $a' > 1$. That this is the same as the condition for alternans in (3.14) is intriguing and has led to similar conjectures for higher dimensional arrhythmias, as discussed below. Also intriguing is the clinical observation that alternans often precede ventricular tachycardia and fibrillation, suggesting a link between instability and these more complicated arrhythmias. It is important to note, however, that the function a is an idealization and there is no true restitution curve for detailed ionic models. Thus, characterizations of stability based on properties of the restitution curve must be recognized as approximate.

In fact, it has recently been shown that the condition $a' > 1$ is neither necessary nor sufficient for stability of waves on a ring. With more realistic assumptions about action potentials and recovery, it has been found that there are stable waves for which a' is arbitrarily large, and also that there are unstable waves for which a' is arbitrarily small [Cyt01][CK01b].

It is important for clinical reasons to be able to ascertain if a reentrant pattern follows a one-dimensional path. This is usually done clinically using point stimuli from catheters inserted into the right atrium and examining the resulting entrainment patterns. A theoretical study of the response of a reentrant excitation on a ring to single stimuli is given in [GJ95] [NG96], emphasizing the effect of pacing using point stimuli, entrainment patterns and annihilation (see also [FR88]).

5. Two-Dimensional Arrhythmias

The two most noticeable common reentrant arrhythmias are tachycardia and fibrillation. Both of these can occur on the atria (atrial tachycardia or flutter and atrial fibrillation) or on the ventricles (ventricular tachycardia and ventricular fibrillation). When they occur on the atria, they are not immediately life threatening because there is little disruption of blood flow. However, when they occur on the ventricles, they are life threatening. Ventricular fibrillation is fatal if it is not terminated quickly.

Tachycardia is often classified as being either monomorphic or polymorphic, depending on the assumed morphology of the activation pattern. Monomorphic tachycardia is identified as having a simple periodic ECG, while polymorphic tachycardia is usually quasiperiodic, apparently the superposition of more than one periodic oscillation. A typical example of a polymorphic tachycardia is called *Torsade de Pointe*, and appears on the ECG as a rapid oscillation with slowly varying amplitude (Fig. 14).

Two-dimensional arrhythmias are associated with two-dimensional self-sustained waves of activity, spiral waves, such as occur on the atria during atrial flutter or

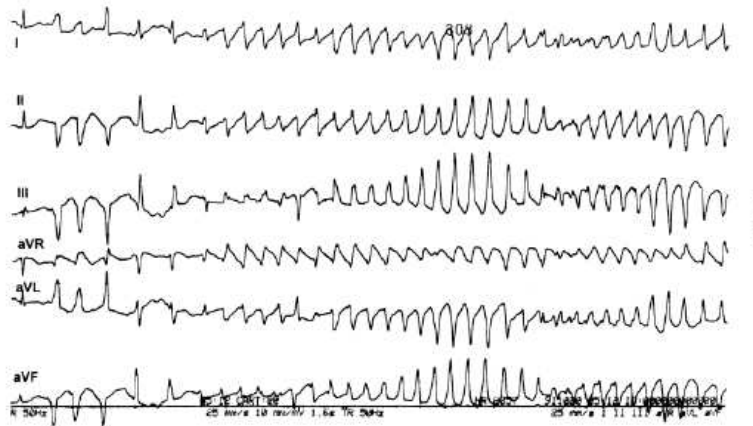


FIGURE 14. A six-lead ECG recording of Torsade de Pointe. From [ZJ95] Fig. 79-1, pg. 886.

fibrillation. The reason these arrhythmias are thought of as two rather than three-dimensional is because the atrial wall is quite thin.

The first suggestion that spiral activity could be associated with arrhythmias came from the work of Wiener and Rosenbluth [WR46], although in their view a spiral had to circulate around a nonfunctional hole, similar to the preparation of Mines with circulation around the superior vena cava.

A simple model for such a spiral is to assume, as above, that the normal velocity of waves is determined by their period. It is an easy matter to show that a wave with constant normal velocity is the involute of a circle, and is asymptotic to an Archimedean spiral [KS98], pg. 306. Thus, the period of rotation is related to the circumference of the hole around which the involute is rotating.

We now know that a nonfunctional hole at the center is not necessary for spiral activity. A less simple model for the evolution of a spiral with no hole is provided by the eikonal-curvature equation,

$$(5.1) \quad R_t \cdot \mathbf{n} = c - D\kappa$$

where $R_t \cdot \mathbf{n}$ is the normal velocity of the wave, c is the local plane wave velocity, a function of period, κ is the curvature of the wave, and D is a coupling (diffusion) coefficient. According to this equation, the normal velocity of a wavefront is the plane wave velocity, which is determined by local properties of the medium, decremented by a term proportional to the wavefront curvature. Notice that the term $D\kappa$ has units of velocity. That the decrement is $D\kappa$ (with no additional scalar factor) has been verified experimentally [FMH89], but is correct only for reaction-diffusion equations of a specific type [SA93], and only when wavefront curvature is small [Kee86]. With this assumption on wave motion, it is found that spirals are uniquely determined by a nonlinear eigenvalue problem, and they do not require a hole at their center [TK88]. Following this understanding, the mathematical study of spiral activity in models of two-dimensional excitable tissues has burgeoned [Kee88b] [PS91] [Ber91][Kee92][Kar92] [KK96].

Early numerical understandings of spiral activity were provided by finite state automata [MRA64] [Kri66] [Kri78] (see also [SC84]). The paradigm for initiation and maintenance of spiral waves suggested by [MRA64] was that they resulted from a high degree of random dispersion of refractoriness. This idea held sway for many years, but is gradually being recognized as inadequate.

The first experimental confirmation that reentrant waves could have a truly two-dimensional structure came from the mapping studies of Allesie et al. [ABS73] [ABS76], showing a wave of electrical activity rotating around a fixed point. It took much longer for cardiologists than mathematicians to recognize that reentrant activity was not necessarily one-dimensional, but could be truly two-dimensional [JD93] [PDS⁺93]. For a long time in the cardiology literature, a reentrant arrhythmia was described as following a fixed reentrant conduction pathway, implicitly assumed to be one-dimensional. That this is incorrect is important to understand. An important difference between one-dimensional and two- or three-dimensional arrhythmias is that one-dimensional arrhythmias can *always* be eliminated by proper application of a point stimulus or ablation, while two- or three-dimensional arrhythmias cannot.

In the meantime, early numerical simulations of spiral activity using realistic ionic models showed that spirals could be unstable [CW91], and this led to the study of spiral stability [Win90] [Bar94] [QWG00]. That instabilities may lead to spiral breakup is the subject of numerous recent investigations [IG91] [BE93] [Kar93] [PH93] [Kar94] [Pan98], and remains the focus of ongoing research. In particular, it is of interest to determine the relationship between the restitution curve, alternans, spiral stability and breakup. In [Kar93] [Kar94], Karma found that by varying certain parameters in a simple two-variable model, the period of spiral rotation could be reduced until alternans occurred. With further parameter variation, the amplitude of alternans increased until spiral breakup was observed. Similar observations have been made using a more detailed ionic model [QWG99] (see also [RKG99] [GKV⁺00]), although there is as yet no mathematical analysis showing a relationship between a steep restitution curve and spiral stability and breakup. In fact, in view of the result for one dimensional waves [CK01b], there may be no such relationship.

Atrial arrhythmias are not immediately life threatening and so they can be allowed to continue in a patient for a long time. Of course, this is not particularly pleasant for a patient as it may require a decrease from normal activity. Long lasting atrial arrhythmias lead to the formation of clots in the atria, which if they get into the blood stream, can lead to strokes. Furthermore, atrial arrhythmias lead to atrial remodeling, a consequence of which is that the longer an arrhythmia is allowed to proceed, the easier it becomes for a new arrhythmia to be initiated [WKDA95] [LT97]. The mechanism of remodeling and the resultant propensity for reoccurrence is not understood.

The standard clinical method to eliminate two-dimensional atrial reentry is by application of a large (3-15 Joules) electrical shock. If this is done while the patient is conscious, it is quite painful. Thus, the search for efficient but less painful ways to eliminate reentrant atrial arrhythmias is of major current interest.

There are several ideas that are currently being pursued. It is known that some reentrant arrhythmias drift [RP83] [DPS⁺91] because of tissue inhomogeneities. Spirals have also been observed to drift when they are periodically stimulated.

Thus, the response of spirals to periodic forcing has become a topic of interest, with the hope that they can be forced to drift off of their finite spatial domain and thereby disappear [SZM93] [BH94] [GZM95] [ZMM97] [NBH98] [PMZK00]. To date, the clinical application of this idea has not found much success.

6. Three-Dimensional Arrhythmias

Three-dimensional arrhythmias are self-sustained waves of electrical activity that occur in the ventricles, and are called scroll waves. They are three dimensional, and not two-dimensional, because the ventricular wall is quite thick. The observation that reentrant waves in the ventricles had to be scroll-like came rather early from the work of Winfree [Win73], however, the experimental verification of this did not come until much later [FKC⁺88].

The simplest example of a reentrant ventricular arrhythmia, monomorphic tachycardia, is probably a scroll wave [Win87], however, ventricular fibrillation certainly has a more complicated three-dimensional structure and behavior [WP90] [WLP⁺98].

Our current understanding of scroll waves comes from two sources, mathematical analysis of greatly idealized models, and numerical simulation of less idealized models.

The mathematical analysis of scroll waves has focused on the behavior of the organizing center of the scroll, the scroll wave filament. In a series of papers [WS84a] [WS83a] [WS83b] [WS83c] [WS84b], Winfree and Strogatz explored the topology of scroll wave filaments. General equations of motion for scroll wave filaments were derived in [Kee88a], and the consequences of these equations explored in [Bik89] [KT90] [KT92] [BHZ94].

The study of the two- and three- dimensional arrhythmias is complicated by the fact that cardiac tissue is an anisotropic, inhomogeneous, irregularly shaped, bidomain [KS98]. At this point in time, our understanding of these waves for realistic tissue models comes almost entirely from numerical simulations. A three-dimensional view of a (numerically computed) monomorphic ventricular tachycardia is shown in Fig. 15.

Stable monomorphic ventricular tachycardia is (apparently) rare, as most reentrant tachycardias are unstable and degenerate into fibrillation (although they are often observed in patients who survive a heart attack). It is possible that a stable monomorphic tachycardia on the ventricles is actually a one-dimensional arrhythmia in that it passes through a small pathway in imperfectly infarcted tissue and this may suggest a strategy by which to eliminate them.

Fibrillation is believed to correspond to the presence of many reentrant patterns moving throughout the ventricles in continuous, perhaps erratic, fashion, leading to an uncoordinated pattern of ventricular contraction and relaxation. A surface view of a (numerically computed) fibrillatory pattern is shown in Fig. 16.

The likely reason that monomorphic ventricular tachycardia is rare is because there are a number potential sources of instability, although the mechanisms of the instability have not been decisively determined. A popular contender for the cause of instability is the steep slope of the restitution curve. Until recently, however, there was no experimental evidence in support of this hypothesis, as data on restitution properties showed slopes that were consistently less than one [ES83]. This situation changed when steep restitution curves were found in dog myocardium

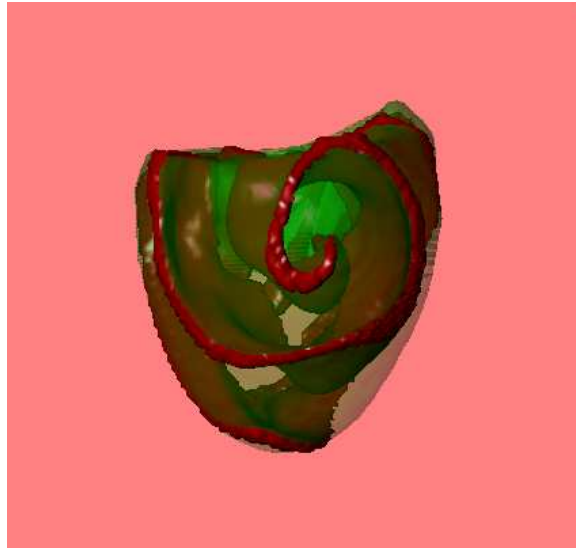


FIGURE 15. Numerically computed scroll wave in ventricular muscle. From [PK95b].

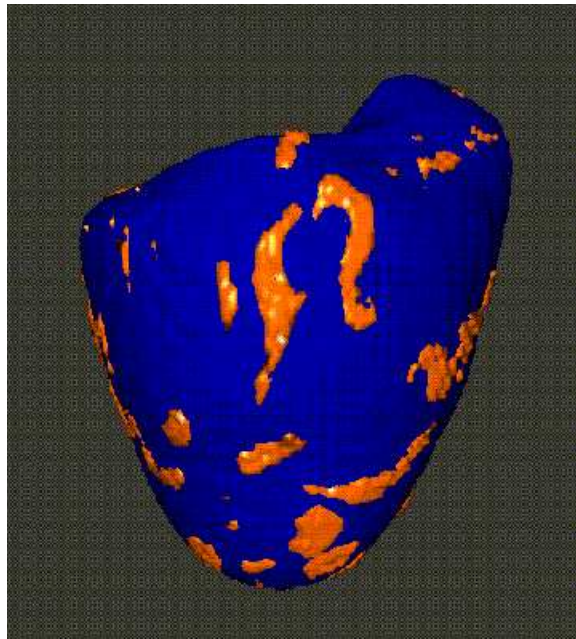


FIGURE 16. Surface view of fibrillatory reentrant activity in the ventricles (computed by A. V. Panfilov)

[KRGJ98]. According to these authors, the previous findings were because restitution properties were measured at a relatively long periods of stimulation, where restitution curves can be expected to be quite flat. With their improved technique,

they were able to measure restitution properties at much shorter cycle lengths, finding slopes as large as 1.7.

Additional evidence favoring the importance of the restitution curve comes from studies showing that certain drugs (diacetyl monoxin and verapamil in [RKG99] and bretylium in [GKV⁺00]) can flatten the restitution curve and actually prevent the occurrence of ventricular fibrillation. In [RKG99] it was also found that another anti-arrhythmic drug, procainamide, did not reduce the slope of the restitution curve, and neither did it prevent induction of ventricular fibrillation. These experiments also provided a plausible explanation for why a breakup instability was not seen in earlier studies. The earlier studies used fluorescent dye techniques which required electrical-mechanical uncouplers to prevent motion artifacts in the optical recordings. The decouplers used were diacetyl monoxime and verapamil, which, as mentioned above, are known to flatten restitution curves and thereby (perhaps) make spiral breakup less likely. These results must be tempered, however, by the finding of [Cyt01][CK01a] in which stability of one dimensional waves and restitution properties are found to be disconnected.

A steep restitution curve is not likely to be the only cause of instability, as there are probably several other, mostly geometrical, factors. It is curious that breakup of spirals or scrolls occurs more readily in three-dimensions than in two [PH95] [PH96]. Some other possibilities of instability mechanisms include vortex shedding in the vicinity of spatial inhomogeneity [PK93b] [AKMP91] [CPD⁺96], scroll wave filament instability [BHZ94], rotational anisotropy of myocardial tissue [PK95a] [PK93a] [PK95b] [FK98] [QXG99] [QKGW00] and gradual tissue heterogeneities [PJ95].

The observation that reentrant arrhythmias on the ventricles are three-dimensional has important clinical consequences. As we have seen, if an arrhythmia is one-dimensional, then there must be a point somewhere on the circuit that can be destroyed that will eliminate the arrhythmia. Similarly, if a two-dimensional arrhythmia is the result of rapid periodic pacing from an ectopic focus (i.e., not reentry), then destroying the oscillator will eliminate the arrhythmia [JHS⁺97]. However, if a point on the surface of the ventricles appears to be a point of first activation, there is no guarantee that this point is an ectopic focus or a point on a one-dimensional circuit. In fact, a reentrant arrhythmia that is circulating deep within the tissue may have a point on the surface at which it first emerges, but because the arrhythmia is sustained by a three-dimensional reentrant cycle, destruction of the surface cells will have no effect whatever on the arrhythmia. This fact is unfortunately not completely appreciated by all cardiac electrophysiologists, and this misunderstanding has resulted in some disappointing surgical procedures.

7. Conclusion

Our understanding of cardiac arrhythmias is enhanced by viewing them from the vantage point of their spatial dimension. From this perspective, we not only learn some interesting mathematics, but we also gain important practical insights. In fact, with mathematical reasoning and models we are able to visualize behavior (for example, the three dimensional structure of ventricular tachycardia and fibrillation) that is far beyond the current capabilities of experimental techniques.

While many difficulties remain unresolved, there is reasonable hope that these mathematical ideas will continue to be fruitful.

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