Taking Math to Heart: Mathematical Challenges in Cardiac Electrophysiology

John W. Cain

On his website, University of Utah mathematics professor James Keener poses the question, "Did you know that heart attacks can give you mathematics!?" Indeed, there are a host of important research problems in cardiology that appear ideal for unified attack by mathematicians, clinicians, and biomedical engineers. What follows is a survey of six ongoing Challenge Problems that (i) seem tractable and (ii) draw from a variety of mathematical subdisciplines. We hope that this article will serve as a "call to arms" for mathematicians so that we, as a community, can contribute to an improved understanding of cardiac abnormalities.

The emphasis of this article will be on cardiac *electrophysiology*, because some of the most exciting research problems in mathematical cardiology involve electrical wave propagation in heart tissue. The quantitative study of electrophysiology has a fascinating history, with its notable milestones touched by tragedy and triumph. Nearly a century has passed since the tragically premature death of George Ralph Mines (1886–1914), a brilliant physiologist who apparently died from self-experimentation in his laboratory. Perhaps Mines would be comforted to know that his pioneering research continues to influence the mathematical study of reentrant arrhythmia (see *Temporal Pattern Challenge* below). Nearly half a century after Mines's death, in a stunningly elegant blend of mathematics and experimentation, British physiologists Alan Hodgkin and Andrew Huxley introduced a model of electrical propagation in the squid giant axon [11]. Their mathematical model was so far ahead of its time that it is mind-boggling to think that it was constructed without the luxury of modern computing. Soon after Hodgkin and Huxley shared the 1963 Nobel Prize in Medicine or Physiology for their efforts, the first of many adaptations of their model to cardiac tissue was proposed. Such models are the subject of our first two challenge problems.

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Electrophysiology

Examining the electrical activity in a person's body can reveal a great deal of physiological information. At some point in our lives, many of us will undergo an electroencephalogram (EEG), a recording of electrical activity in the brain, or an electrocardiogram (ECG), a recording of electrical activity in the heart. To understand where these tiny electrical currents originate, we must "zoom in" to the molecular level. Bodily fluids such as blood contain dissolved salts and, consequently, contain positively charged sodium, potassium, and calcium ions. As these ions traverse cell membranes, the resulting electrical currents elicit changes in the voltage v across the membrane. In the absence of electrical stimulation, v rests at approximately -85 millivolts, the negative sign indicating that a cell's interior contains less positive charge than its exterior. Electrical stimuli can cause a resting cardiac cell to respond in a rather dramatic fashion. Namely, if a sufficiently strong stimulus current is applied to a sufficiently well-rested cell, then the cell experiences an *action potential*: v suddenly spikes and remains elevated for a prolonged interval (Figure 1). The existence of threshold stimulus strengths provides a mechanism by which a cell can distinguish

between "background noise" and real electrical stimuli [16].

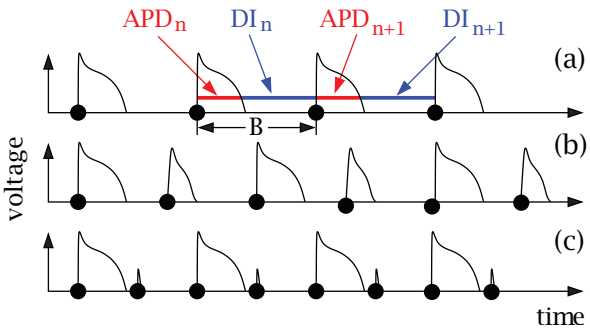


Figure 1. Action potentials in a paced cardiac cell. Bold circles correspond to periodically applied stimuli (period *B*). (a) Slow pacing (large *B*) yields a normal response in which every stimulus elicits an action potential. (b) Faster pacing (smaller *B*) can cause *alternans*, an abnormal alternation of APD. (c) Under extremely rapid pacing (very small *B*), every second stimulus fails to produce an action potential.

Modeling the Action Potential

Mathematically modeling the cardiac action potential is an attractive research topic, in part because such models tend to be rooted in the Nobel Prize-winning work of Hodgkin and Huxley. For a well-written, modern mathematical treatment of how that model was constructed, see the text of Keener and Sneyd [16]. The key idea is to model the cardiac cell membrane as an electrical circuit. The membrane acts both as a capacitor because it supports a charge differential and as a variable resistor because it can open and close ion channels to regulate the inward and outward flow of current. Letting C_m denote the capacitance of a cardiac cell membrane, then the capacitive current $C_m dv/dt$ must balance the total ionic current I_{ionic}. In other words, $C_m dv/dt + I_{\text{ionic}} = 0$. In building a realistic model, the tricky part is to determine the specific form of I_{ionic}. Herein lies a challenge for mathematicians, amounting to a balancing problem.

Modeling Challenge: *Simultaneously keep the model minimally complicated so that it is amenable to mathematical analysis, but make the model sufficiently detailed that it can reproduce as much clinically relevant data as possible.*

Reference [23] provides the address of a large Internet repository of ionic models. Although the models span a wide range of complexity, virtually all of them are based upon the original Hodgkin-Huxley formalism and are presented as systems of ordinary differential equations. Lower dimensional systems are easier to analyze, allowing us to characterize how certain physiological parameters affect the dynamics. For example, FitzHugh-Nagumo [7] reduction of the Hodgkin-Huxley model can, under suitable rescaling, be written as

$$\begin{aligned} \epsilon \frac{dv}{dt} &= f(v,w) = Av(v-\alpha)(1-v) - w \\ \frac{dw}{dt} &= g(v,w) = v - \beta w, \end{aligned}$$

where ϵ, A, α, and β are positive parameters, and $0 < \alpha < 1$. This two-variable system can be analyzed using standard phase-plane techniques and, in the case that $\epsilon \ll 1$, one may extract asymptotic solutions via singular perturbation techniques. Adapting this single-cell model to the tissue level, the resulting system of partial differential equations has been well studied, revealing (i) existence of traveling pulse solutions (solitary action potentials); (ii) existence of periodic wave-train solutions; (iii) stability of these solutions and how they evolve from initial data; (iv) asymptotic estimates of action potential duration and velocity in terms of the parameters; (v) existence of spiral (2-D tissue) and scroll (3-D tissue) wave solutions; and (vi) asymptotic estimates of the rotation frequencies of spiral and scroll waves. We remark that spiral waves are important in the genesis of certain arrhythmias (see the last two Challenge Problems below). For one of the earliest detailed mathematical analyses of the FitzHugh-Nagumo system, see Keener [15].

Although low-dimensional models allow us to characterize how certain physiological parameters affect the dynamics, such models may lack important details known about cardiac electrophysiology, thereby limiting their clinical use. By contrast, higher-dimensional systems may successfully mimic many features of the action potential, but their resistance to mathematical analysis makes it difficult to understand how solutions depend upon parameters and initial conditions.

Simulating Whole-Heart Dynamics

Action potentials can propagate through cardiac tissue because the individual cells are electrically coupled. In the domain Ω formed by heart tissue, transmembrane voltage has both spatial and temporal dependence: $v = v(x,y,z,t)$ where $(x,y,z) \in \Omega$. The usual way to model electrical wave propagation in cardiac tissue is via the equation

$$\frac{s_m}{v}\left(C_m \frac{\partial v}{\partial t} + I_{\text{ionic}}\right) = \nabla \cdot (\sigma \nabla v), \tag{1}$$

where s_m/v is the cell surface area per unit volume, σ is a matrix of conductivities, I_{ionic} is the total

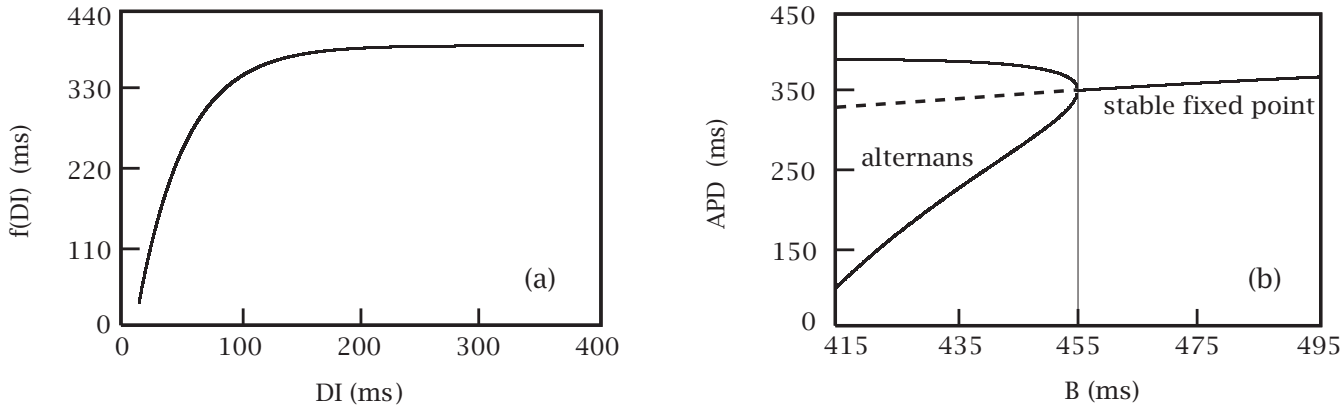


Figure 2. (a) Example of a restitution function f. (b) The corresponding bifurcation diagram for the mapping (2). The period-doubling bifurcation leads to *alternans*, an abnormal period-2 alternation of APD.

ionic current that flows across the cell membrane, and the gradient ∇v is taken with respect to the spatial variables. Neumann boundary conditions are enforced on the boundary $\partial\Omega$. For a derivation of equation (1), see Chapter 11 of [16].

Equation (1) presents a nice challenge for numerical analysts. Modeling groups around the world, including those led by Peter Hunter (Auckland Bioengineering Institute, University of Auckland) and Rob MacLeod (Scientific Computing and Imaging Institute, University of Utah), have made considerable progress in tackling the following.

Simulation Challenge: *Numerically solve* (1) *with (i) a physiologically realistic choice of* I_{ionic}*; (ii) a domain* Ω *that mimics the geometry of the whole heart; and (iii) enough computational efficiency to simulate many heartbeats, in order to better understand how arrhythmias may suddenly develop.*

Of course, operating within all of these constraints is difficult. As a rule, the more physiologically detailed the model, the larger the number of differential equations and parameters that govern I_{ionic}. The domain Ω is quite complicated because the heart has four distinct chambers (left and right atria and ventricles) and is connected to various large veins and arteries (e.g., pulmonary veins and arteries, superior and inferior vena cava, and the aorta). To further complicate matters, different types of cardiac tissue (atrial, ventricular, Purkinje fiber) have different conduction properties, implying that the conductivity tensor σ, as well as I_{ionic}, have spatial dependence.

For animations of action potential propagation in a simulated heart, please see the websites [24] and [25]. In particular, the latter website contains some lovely movies showing action-potential propagation around anatomical obstacles (e.g., dead tissue), as well as the formation of abnormal spiral waves.

Restitution

Constructing an ionic model (1) of the action potential requires careful description of I_{ionic}. However, to be clinically useful, a model should be able to do more than just reproduce traces of v and/or the various transmembrane currents that affect v. One of the ultimate goals of cardiac modeling is to understand mechanisms for the onset of arrhythmias that, by definition, are all about *timing*. The ability to accurately predict the duration and propagation speed of an action potential is an important benchmark for an ionic model.

Electrical *restitution* is a special feature of cardiac tissue that can be loosely defined as follows: the more well-rested the tissue is, the longer the duration of each action potential, and the faster they propagate. More quantitatively, suppose that a cell is repeatedly stimulated (paced) with period B, eliciting a sequence of action potentials. Define APD_n, the action potential duration (APD) of the nth action potential, as the amount of time during which v remains elevated above some specified threshold between the nth and $(n+1)$st stimuli (Figure 1). By *restitution* of APD, we mean the dependence of APD on the pacing period B—typically APD decreases as B decreases.

The amount of rest that the cell receives between consecutive action potentials is known as the *diastolic interval (DI)*. As illustrated in Figure 1a, the DI preceding the nth action potential is simply $\text{DI}_{n-1} = B - \text{APD}_{n-1}$. Numerous authors have modeled restitution using a one-dimensional mapping

$$\text{APD}_n = f(\text{DI}_{n-1}) = f(B - \text{APD}_{n-1}). \tag{2}$$

The graph of the APD restitution function f can be measured experimentally by recording the steady-state APD values for a range of different pacing periods B. Depending upon the shape of f, the mapping (2) may suffer from physiologically

undesirable period-doubling bifurcations as the pacing period B is varied (Figure 2). The resulting abnormal alternation of APD is called *alternans*, and its onset can be understood by straightforward analysis [9] of equation (2). Assuming that f has the qualitative appearance indicated in Figure 2a, then the mapping (2) has a unique fixed point satisfying $\mathrm{APD}^* = f(B - \mathrm{APD}^*)$. The fixed point is a stable attractor if $|f'(B - \mathrm{APD}^*)| < 1$, and this condition implicitly determines the critical pacing interval B at which the bifurcation to alternans occurs. In the literature, the conjecture that alternans would occur if the slope of f exceeds 1 was known as the *restitution hypothesis*. Given the complexity of the heart, it should not be surprising that the restitution hypothesis is false—alternans may occur if restitution functions have shallow slope or may fail to appear even when restitution functions are steep. Over the past two decades, groups of mathematicians, physicists, biomedical engineers, and physiologists have attempted to modify the restitution hypothesis, a collective effort that I will refer to as the:

Alternans Challenge: *Derive a mathematical criterion that accurately predicts the onset of alternans.*

Although it may serve as a reasonable model in certain dynamical regimes, equation (2) is too simplistic to capture all of the relevant behavior of cardiac rhythm. First, in order to reproduce experimentally obtained restitution data, the one-dimensional mapping (2) should be replaced with a higher dimensional mapping [19]. Second, a cardiac cell needs a certain threshold amount of recovery time θ before it is able to produce another action potential, and any stimuli that are applied before the cell recovers its excitability are simply ignored (Figure 1c). Thus, in order to account for abnormally rapid rhythms (small B), the mapping (2) should be replaced by $\mathrm{APD}_n = f(kB - \mathrm{APD}_{n-1})$, where k is the least positive integer for which $kB - \mathrm{APD}_n > \theta$.

We remark that, as action potentials propagate through tissue, their propagation speed exhibits the same sort of dependence upon how well rested the tissue is (i.e., speed depends upon DI). Letting $c(\mathrm{DI})$ denote the restitution function for action potential speed, the graph of c is qualitatively similar to that of f.

Rhythm

Coordinated, rhythmic contraction of the cardiac muscle is vital for the heart to perform its primary function: pumping oxygenated blood throughout the body. Improving our ability to diagnose and treat abnormal rhythms (arrhythmias) is critical in our fight against heart disease, the leading cause of death in the United States. In this section, we discuss three important problems involving cardiac rhythm: (i) analysis of heart rate variability, (ii) predicting spontaneous initiation and termination of arrhythmias, and (iii) techniques for controlling arrhythmias. The first two of these have been past themes of the annual Computers in Cardiology Challenge [26].

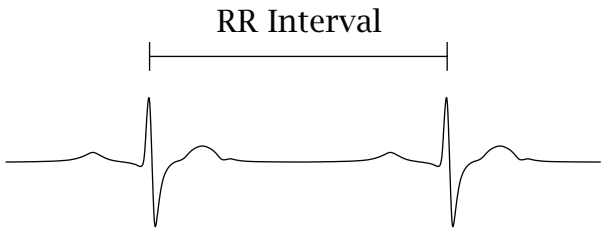


Figure 3. Schematic diagram of one lead of an electrocardiogram (ECG). The RR interval is the time between consecutive peaks.

Heart Rate Variability

A perfectly regular heart rhythm is actually a sign of potentially serious pathologies. The heart rate is regulated by the autonomic nervous system (ANS), baroreceptors, and other factors. The ANS uses the neurotransmitters norepinephrine and acetylcholine to speed up or slow down the heart, respectively, and tiny fluctuations in the levels of these neurotransmitters induce some degree of variability in the intervals between consecutive beats. The interbeat interval can be identified with the RR interval in an ECG (see Figure 3), and attempts to quantify heart rate variability (HRV) usually involve analyzing time series of RR intervals. Mathematicians and statisticians can be of assistance by rising to the following:

HRV-Time Series Challenge: *Devise quantitative methods for distinguishing between the RR time series of normal subjects and those with cardiac pathologies. Can some pathologies be diagnosed solely by analysis of RR time series, and, if so, which ones?*

Analysis of RR time series was the theme of the 2002 Computers in Cardiology Challenge and continues to be one of the most active research initiatives in mathematical cardiology. Before briefly surveying three past attempts to quantify HRV, let us consider two natural questions related to this Challenge. First, could the variance of a sequence $u_1, u_2, \ldots, u_n$ of RR intervals be a useful diagnostic? Although an extremely low variance is a sign of serious trouble, many patients with potentially fatal cardiac abnormalities can exhibit perfectly normal variance. For example, infants who suffer an aborted sudden infant death syndrome (SIDS) episode may have almost identical RR-interval variance as normal infants [17]. To spot more subtle

pathologies, we need methods for quantifying the "regularity" of a cardiac rhythm (see also Figure 4).

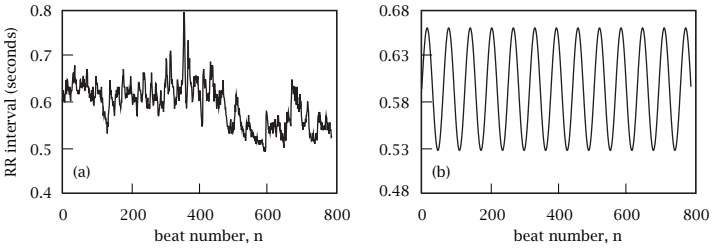


Figure 4. Two signals with identical mean and variance but much different approximate entropies. (a) RR intervals u_n versus beat number n from a healthy patient. Data were obtained from the MIT-BIH Normal Sinus Rhythm database at PhysioNet [26]. (b) A sine wave with the same mean (0.594 s) and variance (0.00224 s^2) as the data in panel (a).

Second, given the existing array of diagnostic tests that clinicians have at their disposal, what advantages might "automated" mathematical/statistical methods convey? Techniques such as multiscale entropy (MSE) analysis (see below) could likely be useful in diagnoses, risk stratification, or detecting drug toxicity [5]. Consider, for example, that the diagnosis of congestive heart failure often involves a battery of tests such as an echocardiogram, chest X-ray, and ECG. In an encouraging finding [4], MSE analysis of routine twenty-four-hour Holter monitor recordings demonstrates that patients with congestive heart failure are statistically well separated from normal subjects.

Approximate Entropy, ApEn. Pincus and Goldberger [17] noted that, for the purposes of distinguishing between normal infants and those with aborted SIDS episodes, a statistic known as the *approximate entropy (ApEn)* appears to provide a useful diagnostic. In their data, ApEn is roughly twice as large in a normal infant relative to an infant with an aborted SIDS episode. The definition of ApEn = ApEn(m, r) incorporates the conditional probability that data patterns that remain close (i.e., within some tolerance r) over a window of m observations will also remain close if the window size is increased to $m+1$. More specifically, ApEn is calculated as follows: (1) Given a sequence $u_1, u_2, \ldots, u_n$ of RR intervals and a window size $m \in \mathbb{N}$, for each $i = 1, 2, \ldots, n-m+1$ define vectors $\mathbf{x}_i = (u_i, u_{i+1}, \ldots, u_{i+m-1})$ consisting of m consecutive data points. (2) For each pair of vectors $\mathbf{x}_i$ and $\mathbf{x}_j$, compute their distance (e.g., maximum difference between corresponding components). (3) Given a tolerance $r \in \mathbb{R}^+$, for each $i = 1, 2, \ldots, n-m+1$, compute the (estimated) probability that a vector will be within distance r of the vector $\mathbf{x}_i$. (4) Let $\Phi(m, r)$ denote the average of the logarithms of these probabilities. Repeat the above steps with a larger window size $m+1$ and calculate $\Phi(m+1, r)$. (5) Approximate entropy is defined as

$$\mathrm{ApEn}(m, r) = \lim_{n \to \infty} [\Phi(m+1, r) - \Phi(m, r)].$$

Note that the limit is taken as the number of data points grows without bound.

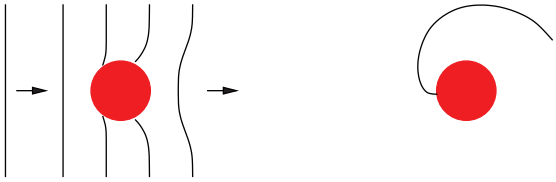
Although ApEn may be clinically useful in predicting aborted SIDS episodes, as explained below, detecting other pathologies may require a finer approach.

Multiscale Entropy Analysis. Subsequent work, much of it by the same research group, points out that ApEn has several drawbacks. Whereas ApEn performs well in distinguishing between normal and abnormally *regular* rhythms, ApEn can be misleading when it comes to recognizing abnormally *irregular* rhythms (which are likely to produce higher ApEn values). The ApEn statistic fails to account for the multiple scales involved in regulating cardiac rhythm—the physiological control mechanisms for heart rate span a wide range of spatial scales (subcellular to systemic) and temporal scales. These issues are addressed in [4], which illustrates how a multiscale entropy (MSE) method can be used to analyze cardiac rhythm. The MSE method can successfully distinguish between normal rhythms and two different routes to heart disease: increased regularity due to heart failure versus increased randomness due to arrhythmias such as atrial fibrillation.

Fast Fourier Transforms and Power Spectra. Another way to seek regular patterns within sequences of data points is to take the fast Fourier transform (FFT) and create a power spectral density plot [1]. Any tall, narrow spikes in such plots correspond to dominant frequencies and are a signature of regularity. Power spectral density plots for normal infants and aborted-SIDS infants both have been shown to exhibit broadband noise. However, the plots for normal infants tend to be more broadbanded, with power distributed over a wider range of frequencies [17]. Although this does indicate that normal infants have less regularity in their heart rhythms, it remains to be seen whether the FFT can give a clinically useful diagnostic.

Spontaneous Initiation and Termination of Arrhythmias

Anatomical obstacles such as regions of dead (nonconducting) cardiac tissue can interfere with the normal propagation of electrical signals. Normally, the heart relies upon its own native pacemaker cells to supply electrical stimuli that generate propagating action potentials. Both the timing of the stimuli and the positioning of the pacemaker



(a) (b)

Figure 5. Wavefront of an action potential propagating around a circular, nonconducting obstacle in homogeneous tissue. (a) Snapshots of a single wave front propagating left to right. The wavefront breaks at the obstacle but reemerges on the other side. (b) A spiral wave propagates unidirectionally (counterclockwise in this case) while anchored to the obstacle.

relative to the obstacle are critical in determining whether an arrhythmia will result. For example, Figure 5a shows five snapshots of a solitary action potential wavefront colliding with a circular, nonconducting obstacle in a square sheet of otherwise homogeneous tissue. In this case, the wavefront breaks at the obstacle but reemerges (with a slight deflection) on the far side of the obstacle. The deflection of this wavefront causes spatial heterogeneity in the amount of local recovery time that the cells experience. One specific pathology that can be induced by such heterogeneity is the formation of spiral waves (Figure 5b) that become anchored to the obstacle [12]. The figure shows a counterclockwise rotating spiral wave whose tip is pinned to the nonconducting obstacle. Spiral waves in cardiac tissue can be quite dangerous, because the period of the rotation is often significantly faster than the period of the heart's native pacemaker cells. As the rotating spiral arm collides with advancing wavefronts emanating from the pacemaker, the higher frequency spiral arm may seize control of more territory, ultimately taking over the pacing of the heart and resulting in tachycardia (faster-than-normal rhythm). Competition between the heart's pacemaker and these abnormal reentrant spiral waves can lead to sporadic episodes of tachycardia, which is the subject of the following.

Temporal Pattern Challenge: *Create a mathematical model that reproduces temporal patterns of spontaneous initiation and termination of tachycardia.*

This problem is a variant of the 2004 Computers in Cardiology Challenge.

There is a significant ongoing effort devoted to this Challenge and related problems, and, in particular, it is known that there are many mechanisms and tissue geometries that can support the creation and destruction of spiral waves. However, few modeling studies focus specifically on temporal patterns of intermittent bursts of rapid activity. One interesting exception was provided by Bub et al. [2], who blended mathematics with experiment to investigate bursting dynamics of rotors. Their experiments with cultures of embryonic chick heart cells revealed intermittent bursts of rotor waves, each lasting on the order of half a minute and with consecutive bursts separated by approximately forty seconds. Using a cellular automaton model of an idealized two-dimensional sheet of cardiac cells, they qualitatively reproduced the same bursting dynamics.

Because cellular automata models are difficult to analyze, other mathematical studies tend to incorporate another type of discrete-time model. As a first step toward understanding whether tissue can support a sustained spiral wave, numerous authors (e.g., [13, 20, 21]) have used partial difference equations (PΔEs) to model propagation of action potentials in idealized, one-dimensional circular domains, such as the one formed by the boundary of the obstacle in Figure 5b. For example, Ito and Glass [13] introduced the following discrete, restitution-based model of a reentrant action potential in a ring composed of m cells, each of length ΔL:

(3)

$$\mathrm{DI}_{i,n} = -f(\mathrm{DI}_{i,n-1}) + \sum_{j=1}^{i-1} \frac{\Delta L}{c(\mathrm{DI}_{n,j})} + \sum_{j=1}^{m} \frac{\Delta L}{c(\mathrm{DI}_{n-1,j})}, \quad i = 1, 2, \ldots, m.$$

Here, $f(DI)$ and $c(DI)$ are the restitution functions for action potential duration and speed, respectively, and are defined only for $DI > \theta$, the threshold amount of rest required to sustain propagation. Although this PΔE incorporates less physiological detail than the one-dimensional version of the PDE in equation (1), solution of PΔE (3) is far less computationally intensive. This allows for simulation over long time scales, which is important in studying intermittent reentrant tachycardia.

Equation (3) does not account for the competition between the action potentials supplied by the heart's native pacemaker and those that are recirculated around the obstacle. Recently, Sedaghat and collaborators [20] modified (3) to allow for spontaneous transitions between normal pacing, in which the rhythm is driven by the heart's native pacemaker, and (abnormal) reentry, in which the rhythm is driven by a recirculating action potential in a ring-shaped pathway. It remains to be seen whether such models can reproduce the erratic patterns of intermittent arrhythmias, patterns that involve time scales ranging from seconds to months.

Controlling the Rhythm

Upon detecting an arrhythmia, the natural next step is to (try to) stop it. Virtually every hospital-themed television program includes scenes in which a manual external defibrillator is used to violently shock a patient during cardiac arrest. Although wonderful for dramatic effect, this sort of defibrillation has adverse physiological side effects. Certain patients with heart disease receive a more humane alternative: battery-operated implantable cardioverter defibrillators (ICDs) that intervene when onset of an arrhythmia is detected. Although newer ICDs are better at distinguishing between non-life-threatening tachycardia and life-threatening fibrillation, when an ICD elects to defibrillate, it can cause excruciating pain. Rather than having an ICD deliver a high-frequency train of strong stimuli, is it possible (via careful timing) to deliver a train of *tiny* stimuli that accomplish the same goal? Below is a brief discussion of two attempts to tackle our final challenge.

Control Challenge: *Devise a robust feedback control algorithm that can suppress abnormal rhythms in the whole heart.*

In both experiments and numerical simulations, Isomura et al. [12] were able to terminate an abnormal spiral wave by applying a brief, high-frequency train of tiny electrical stimuli. This is precisely what an ICD does during antitachycardia pacing, and this technique is often effective in restoring a normal rhythm. Prior explanations of why antitachycardia pacing works tend to be heuristic as opposed to mathematical. It would be of great physiological interest if mathematical analysis could show either (i) why existing antitachycardia pacing techniques often work or (ii) that there is a better way.

Another abnormal rhythm that has been successfully controlled both experimentally and in simulations is known as *T-wave alternans*. Mathematically, the onset of alternans can be understood by examining the bifurcation diagram in Figure 2b. In the one-dimensional mapping (2), a period-doubling bifurcation may occur as the pacing period B is decreased. The bifurcation causes APD alternans, a pattern in which APD values exhibit beat-to-beat alternation.

Both experiments [10] and theory [14] indicate that simple feedback control can terminate alternans in small patches of cardiac tissue. The idea is to make small perturbations to the period B in order to prevent the period-doubling bifurcation from occurring in the restitution mapping (2). As an illustration, consider the famous discrete logistic mapping $x_{n+1} = \mu x_n(1 - x_n)$, where $x_0 \in [0, 1]$ and $0 \le \mu \le 4$. As the parameter μ is increased, a cascade of period-doubling bifurcations ultimately leads to chaos when $\mu \approx 3.5699$. This cascade can be prevented if small adjustments are made to μ at each iteration. If μ is replaced by $\mu + \epsilon \cdot (x_n - x_{n-1})$ where $\epsilon > 0$ is a *feedback gain* parameter, then, depending upon the choice of ϵ, we can (i) stabilize previously unstable fixed points; (ii) prevent period-doubling cascades from occurring; and (iii) control chaos.

Although the aforementioned feedback control algorithms succeed in small patches of tissue, both experimental [3] and theoretical [6] studies suggest that applying such schemes locally (via an implantable electrode) cannot control the rhythm over large enough spatial domains to be useful in the whole heart. This issue lies at the core of the above Challenge problem—controlling whole-heart dynamics is difficult!

Discussion and Further Reading

This article is intended to serve as an open invitation to the mathematics community to join the fight for an improved understanding of cardiac electrophysiology and arrhythmias. The featured Challenges were chosen, in part, because each problem has aspects that will appeal to various mathematical subdisciplines (e.g., numerical analysis, discrete dynamical systems, topology, differential equations, and mathematical statistics). The reader is urged to consider how his or her own areas of mathematical expertise might aid in these exciting research efforts.

The above presentation should be accompanied by several disclaimers. First, much of this article represents a mathematician's interpretation of various cardiac phenomena. For example, Figure 5 is a mathematical idealization of the substrate for a pinned spiral wave and is quite different from the anatomical circuits that a cardiologist would associate with tachycardia. Readers interested in a more accurate portrayal of reality are encouraged to consult with cardiologists and electrophysiologists. Second, it must be emphasized that there is already a vast literature dedicated to these six Challenges. Rather than vainly attempting to compile a comprehensive bibliography, the references are merely intended to provide a few leads for those who might be interested in this fascinating field.

For more information on mathematical cardiology (or mathematical physiology in general), there are several books that serve as good starting points. Keener and Sneyd's text [16], *Mathematical Physiology*, provides an excellent mathematical treatment of electrophysiology and heart rhythm. Some older books, such as Glass and Mackey [8], Plonsey and Barr [18], and Winfree [22], include well-written introductions to mathematical cardiology. Finally, most of the websites that are referenced in this article contain extensive bibliographies.

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