Journal of Statistical Physics, Vol. 128, Nos. 1/2, July 2007 (© 2007)
DOI: 10.1007/s10955-006-9191-y

Stochastic Aspects of Cardiac Arrhythmias

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Received February 23, 2006; accepted July 26, 2006
Published Online August 26, 2006

Abnormal cardiac rhythms (cardiac arrhythmias) often display complex changes over time that can have a random or haphazard appearance. Mathematically, these changes can on occasion be identified with bifurcations in difference or differential equation models of the arrhythmias. One source for the variability of these rhythms is the fluctuating environment. However, in the neighborhood of bifurcation points, the fluctuations induced by the stochastic opening and closing of individual ion channels in the cell membrane, which results in membrane noise, may lead to randomness in the observed dynamics. To illustrate this, we consider the effects of stochastic properties of ion channels on the resetting of pacemaker oscillations and on the generation of early afterdepolarizations. The comparison of the statistical properties of long records showing arrhythmias with the predictions from theoretical models should help in the identification of different mechanisms underlying cardiac arrhythmias.

KEY WORDS: stochastic differential equations, early afterdepolarizations, ionic models, premature ventricular complexes, phase resetting.

1. INTRODUCTION

The heart is an amazing organ. In human beings, the heart beats over two billion times over a 70-year lifetime. An interruption of this beating pattern for a time as brief as a few minutes often leads to serious neurological damage. Thus, the heart rhythm must be incredibly robust, able to sustain itself despite a variety of changes in the body that arise over the short term as a consequence of one's

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daily activities, as well as over the long term as a consequence of normal aging and disease. Viewed from a theoretical perspective, one can think of the heart rhythm as a stable limit-cycle oscillation, some of whose properties, such as the period, may be modified to suit bodily demands that are conveyed to the heart by neural activity and circulating hormones that regulate cardiac activity. In this article we argue that in some experimental and clinical situations, deterministic differential equations may give results that are qualitatively incorrect and that it is essential to consider stochastic mathematical models.

In Sec. 2 we give a brief introduction to the key concepts of cardiac electrophysiology that we use in this article. In Sec. 3, we give some phenomenological observations about abnormal heart rhythms as recorded from the electrocardiogram, focusing especially on the patterns of a type of abnormal heartbeat called a premature ventricular complex. In Sec. 4 we introduce a few of the stochastic sources that influence the cardiac rhythm. In Sec. 5, we give two examples of how the stochastic opening and closing of ion channels in the cell membrane can lead to important qualitative changes in the dynamics in mathematical models of cardiac systems when compared with the dynamics in deterministic models.

2. A PRIMER ON CARDIAC ELECTROPHYSIOLOGY[36]

In the normal heart, electrical activity originates on each heartbeat in a specialized pacemaker region called the sinus node. The activity then spreads through the upper chambers of the heart (the atria), then through the atrioventricular node and the His-Purkinje system to the lower chambers of the heart (the ventricles). At the cellular level, the heartbeat is associated with cyclic changes in the electrical potential difference across the cell membrane, which separates the intracellular and extracellular milieu. This potential difference arises as a consequence of concentration differences of several ions, chiefly Na^+, K^+, and Ca^{2+}, across the cell membrane. These concentration differences are maintained by specialized molecular complexes called ion pumps that use energy to transport ions across the cell membrane. Further, there are individual channels in the cell membrane which stochastically open or close. Ions flow through these channels and thus change the voltage across the cell membrane. The rate at which ionic channels open and close is different for each type of channel and is based largely on the potential difference across the membrane in which they are embedded. The activity of channels can also be modulated by neurotransmitters and circulating hormones. On each heartbeat, there is an action potential, in which there is an increase in the transmembrane voltage (depolarization), associated with a transient increased permeability of the cell membrane to Na^+ and Ca^{2+}, followed by a repolarization to the resting membrane potential, associated with an increasing permeability of the cell membrane to K^+. The changes in membrane potential lead to a sequence

of events that result in the contraction of the heart muscle and the consequent pumping of blood through the body.

A central goal of research over the past 50 years has been to understand and mathematically model the ionic processes underlying activity in the heart. The foundation was set in landmark work by Hodgkin and Huxley who developed nonlinear ordinary differential and partial differential equations for the ionic processes underlying the generation and conduction of nerve impulses.[29] Subsequently Noble[55] and others extended this approach to the heart. Current mathematical models of a single cardiac cell are formulated as systems of tens of coupled equations with hundreds of parameters (e.g., Refs. 50, 75).

Abnormal cardiac rhythms (i.e., cardiac arrhythmias) can be viewed as arising as a consequence of one of two different mechanisms. There is either abnormal generation of action potentials or abnormal conduction of the action potential within the heart. Abnormalities in heartbeat generation occur if the sinus node beats too quickly or too slowly, or if other regions of the heart develop an intrinsic rhythm that is not entrained to the normal sinus rhythm, leading to ectopic beats. Abnormal patterns of conduction can arise as a consequence of blocked conduction. For example, in some people not all the action potentials originating in the sinus node are conducted to the ventricles. In other people, conduction abnormalities produce reentrant rhythms, in which the period of the cardiac rhythm is set by the time it takes for an excitation to travel in a reentrant path, rather than by the period of the sinus rhythm.[36, 84]

The recognition of the presence of cardiac arrhythmias must have arisen in antiquity when people felt abnormalities in the rhythm of the pulse. However, the analysis of arrhythmias has been enormously aided by the electrocardiogram, which measures the potential difference arising between points on the surface of the body as a consequence of the propagation of the action potential through the entire heart. The electrocardiographic signal, which is of the order of 0.1–5 millivolts in amplitude, has been recorded and analyzed for about the past 100 years. Examples of electrocardiograms, which we will discuss in more detail as the paper progresses, are given in Fig. 1. Abnormalities in the qualitative features of the electrocardiogram are used to classify cardiac arrhythmias into a number of different types, based on the nature of the abnormality and the portion of the heart affected. For example, ventricular tachycardia refers to an abnormally fast heartbeat originating in the ventricles. But there are several types of ventricular tachycardia: some of these result in the heart pumping an adequate blood flow to the body and so can be consistent with the continued existence of life, while others do not generate enough blood flow and will lead to death. In most people, the terminal rhythm is ventricular fibrillation, a rhythm in which there are believed to be multiple co-existing reentrant spiral waves of excitation in the ventricles.[84] In Fig. 1, the end of each record shows ventricular tachycardia, which can degenerate

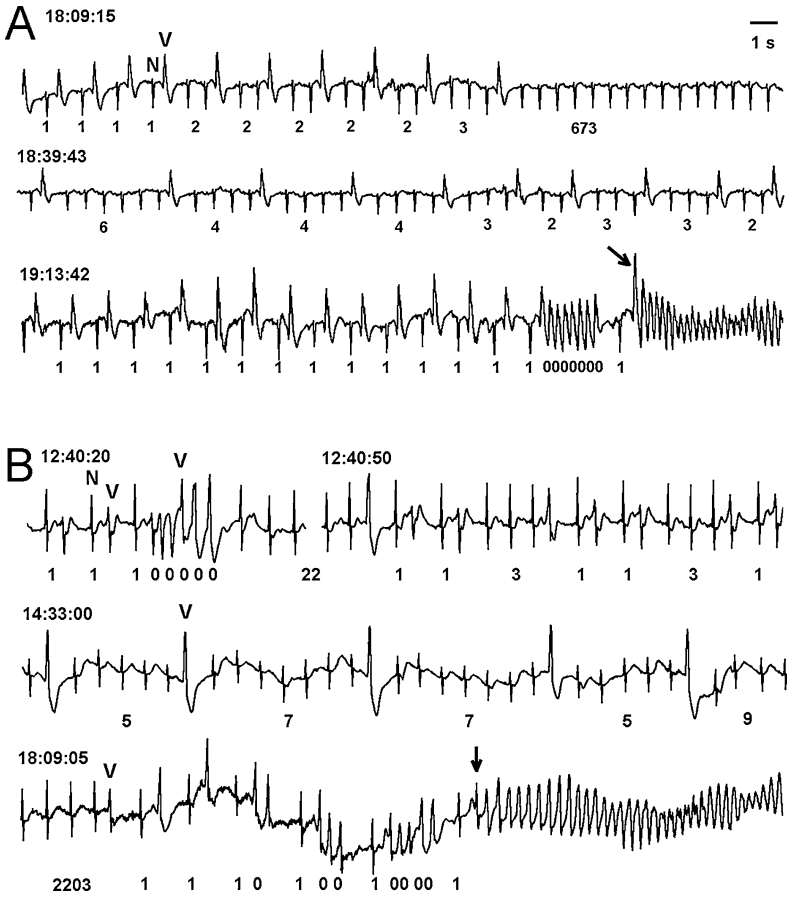


Fig. 1. Electrocardiographic Holter-recording traces from two patients who suffered sustained ventricular tachycardia (arrows indicate onset), obtained from the Sudden Cardiac Death Holter Database.[72] (A) An 82-year-old woman with heart failure (patient 52). (B) A 68-year-old man with a history of ventricular arrhythmias who was taking quinidine and digoxin (patient 45). The electrocardiographic complexes are labeled as being of normal (N) or ventricular (V) origin. The number of normal intervening beats between two ventricular beats (NIB) is indicated below each trace.

into ventricular fibrillation, resulting in death. In fact, this is exactly what happened subsequent to the end of the last record shown in Fig. 1A.

We now try to place the initiation of arrhythmias into a nonlinear dynamics context. Clearly, the normal pacemaker oscillation and propagation in the intact heart are extraordinarily robust. By this we mean that under a wide range of circumstances, the rhythm is qualitatively identical. The sinus node is the pacemaker and sets the rate, initiating an orderly spread of excitation over the entire heart.

However, in some circumstances, parameters describing part or all of the heart may change from normal values so that qualitatively different dynamics occur. Mathematically, such qualitative changes in dynamics are called bifurcations. In some cases changes in parameter values are abrupt, taking place over a time scale of seconds or minutes (a heart attack, changes in the activity of the nervous system or in the circulation of hormones, administration of drugs that change cardiac properties). In other cases the changes are gradual: e.g., slow changes over the years as a consequence of a faulty heart valve leading to increased atrial pressure, consequent development of fibrotic tissue, and remodelling of the mix of ion channels in the atria, resulting in atrial fibrillation.[54] *The bifurcation boundary in parameter space between normal and abnormal dynamics might be traversed slowly with respect to the time between heartbeats. In such a situation, stochastic effects will become prominent since a minute change in some parameter would lead to one behavior or another*. This concept is central to the following discussion.

3. ELECTROCARDIOGRAM ANALYSIS

The electrocardiogram provides a visualization of the electrical activity of the heart. In Fig. 1, we show examples of electrocardiograms of two patients taken from the Physionet Sudden Cardiac Death Holter database.[72] A Holter recording is an ambulatory recording of the electrocardiogram, usually over a period of $\sim$24 h. These two patients had ventricular tachycardia (onset indicated by arrows in Fig. 1) and the subject in Fig. 1A died while her electrocardiogram was being recorded. Based on the morphology of the deflections on the electrocardiogram, we distinguish normal sinus beats (labelled N) and premature ventricular complexes (labelled V). The premature ventricular complexes arise from a site within the ventricles. In the patient in Fig. 1A there is one morphology for the premature ventricular complex, whereas, in Fig. 1B, there is more than one morphology. There are two possible mechanisms for different morphologies in the same patient. Either the premature ventricular complexes arise from different sites in the ventricles, or the premature ventricular complexes arise from a single site, but are conducted through the ventricles differently on different heartbeats. Although there are several different physiological mechanisms that have been hypothesized to generate premature ventricular complexes, in most cases it is not known how to identify a mechanism for the premature ventricular complex based on inspection of the electrocardiogram.[36, 65] One of the main points of this article is to make statistical physicists aware of the fascinating problems encountered in trying to decode the patterns of premature ventricular complexes.

One way to obtain an impression of the pattern of premature ventricular complexes in the electrocardiogram is to count the number of normal sinus beats between two premature ventricular complexes. In the records in Fig. 1, we display these numbers under each trace for several different segments of the recording.

Most readers of this will be aware that medical exams often evaluate the electrocardiogram only for short time intervals of the order of several seconds. Such short segments do not always give a clear impression of the record over more extended times. One way to characterize electrocardiograms with premature ventricular complexes over longer times is to simply write out the integer sequence of the number of such complexes between consecutive normal beats over long times. In Fig. 2, we show these sequences for the records from which Fig. 1 was derived.

The data in Fig. 2A shows a preponderance of low integers. These are not randomly distributed. There are long sequences of consecutive 1s, but also an apparent gradual increase of the integer values followed by a decrease. There are also long sequences in which there are no premature ventricular complexes, so that the integers in the table are then on the order of several hundred. The data in Fig. 2B are quite different. Although there are again long sequences of consecutive 1s, there are many more long stretches in which there are no premature ventricular complexes. Moreover, there is also a strong preponderance of odd numbers in the sequence. The middle trace in Fig. 1B comes from a stretch of 45 numbers of which 6 are even.

A likely hypothesis about these records is that over the long time intervals of these recordings, there are some sort of changes in the parameters describing the state of the heart. Unfortunately, unlike the situation in laboratory experiments, data collected while wearing portable monitors is not well controlled, and it is not routine to simultaneously document some of the changes that might underly the changes in rhythm in these subjects (e.g., change in posture, respiration, mental state, drugs). Worse still, there are almost certainly physiological changes of which we are not aware and do not therefore currently monitor.

Consequently, as a means of displaying this information over long times, we have developed a visualization technique called a "heartprint."[64-66] We designate the number of intervening N beats between two consecutive V beats as the NIB value. A pair of two consecutive V beats is termed a couplet, while a sequence of 3 or more successive V beats that spontaneously terminates is termed non-sustained ventricular tachycardia. Premature ventricular complexes that are not part of a couplet or non-sustained ventricular tachycardia are called isolated. The NN interval is the time between two consecutive N beats, while the coupling interval (CI) is the time from an N beat to an immediately following V beat.

A heartprint (Fig. 3) is a way to represent dependencies between the NN interval and (i) the ectopic beat interval (between two V beats, or VV intervals), (ii) NIB values, and (iii) the CI. The ordinate of the 3 colored plots in the heartprint is the NN interval. The incidence of the VV intervals, NIB values, and the CI are indicated in the three colored plots, respectively, where the relative frequency of occurrence is indicated by the color (e.g., red is associated with the highest incidence, and dark blue with the lowest). The histograms above the colored plots

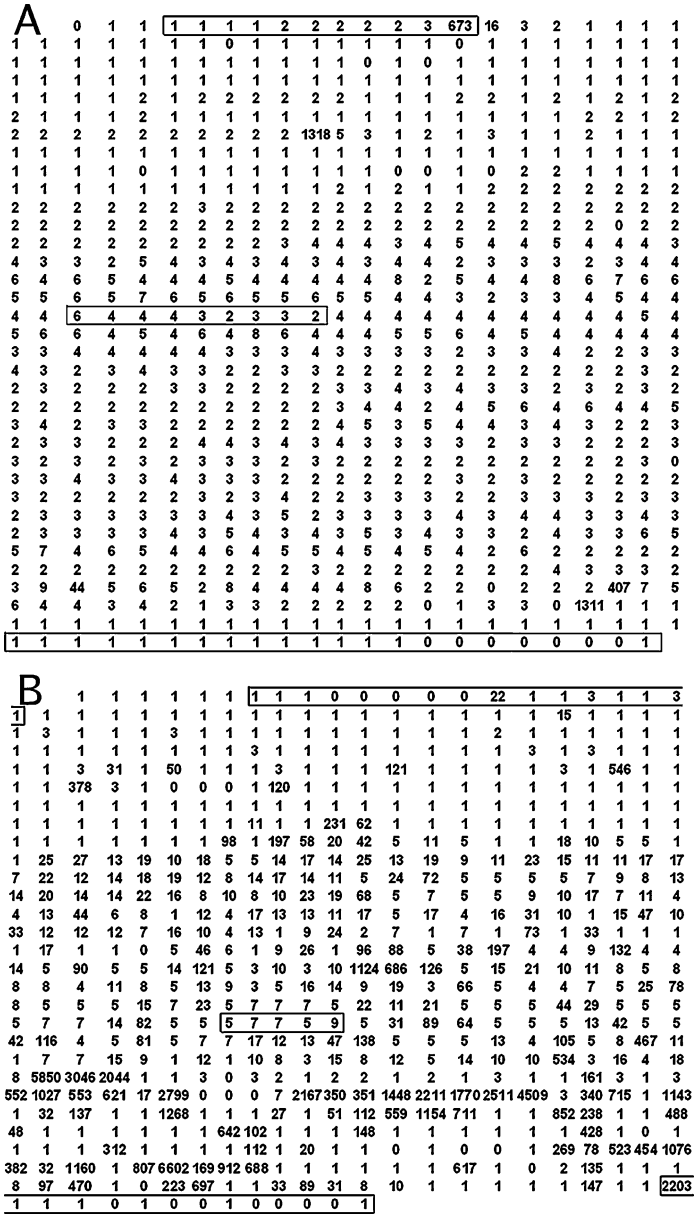


Fig. 2. Excerpts of consecutive number of intervening normal (N) beats between two ventricular (V) beats (NIB) measured from same two patients as in Fig. 1. The boxed sequences indicate the NIB values associated with the ECG segments shown in Fig. 1.

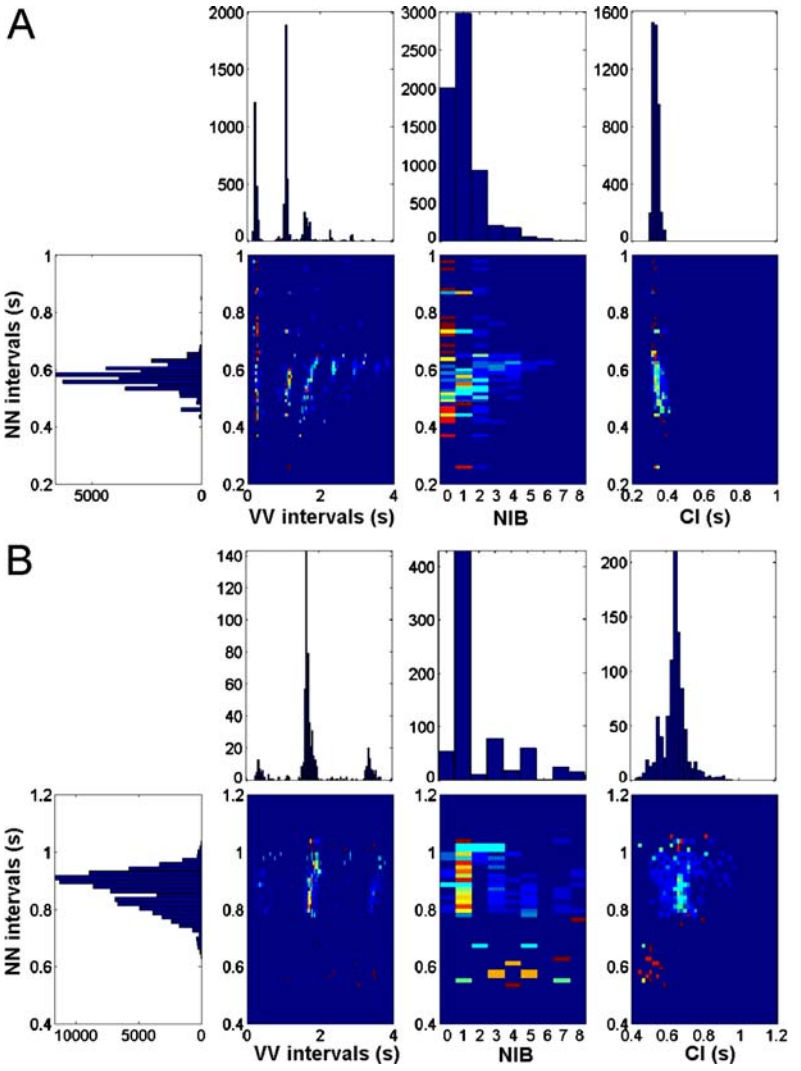


Fig. 3. (Color online) Heartprints from the same two patients presented in Fig. 1. The heartprint represents the dependency between the intervals between two normal beats (NN) and three other intervals: time between two ventricular beats (VV), number of intervening normal beats (NIB), and the coupling interval (CI), i.e. the time from an N beat to a V beat. The ordinate of the three colored plots is the NN interval. The incidence of the VV intervals, NIB values, and the CI is indicated in the three colored plots respectively, where the relative frequency of occurrence is indicated by the color (e.g., red is associated with higher incidence). The histograms above the colored plots are those of the VV intervals, the NIB values, and the CI, respectively, while the histograms to the left give that of the NN values.

give the histograms of the VV intervals, the NIB values, and the CI, respectively. The histogram to the left of the colored plots gives the histogram of NN values.

Figure 3 shows the heartprints for the subjects from whom the electrocardiograms in Fig. 1 were taken. There are striking differences, especially with respect to the distribution of the numbers of sinus beats between ectopic beats, the sinus rates, and the coupling intervals. In Fig. 3B, there is evidence that the distribution of the NIB values depends on the sinus rate, with a larger range of NIB values occurring at lower NN intervals.

An underlying goal of our work is to decode the mechanisms of ventricular arrhythmia by analyzing data such as that in Figs. 1–3. Further, since some mechanisms may be associated with a high risk, whereas other mechanisms are associated with benign rhythms, the analysis of arrhythmia may help guide therapy.

For one class of arrhythmias, called parasystole, there are striking qualitative features of the heartprint that are reproduced in theoretical models. In parasystole, there is an independent pacemaker in the ventricle that beats with its own frequency and competes with the sinus rhythm for control of the ventricles. In some circumstances, the parasystolic rhythm is only marginally affected by the sinus rhythm. In an earlier paper we have analyzed and modeled a record of this sort (Case 3 in Ref. 65) by using a stochastic difference equation, obtaining excellent agreement between the model and the clinical record. However, the two records in Fig. 1 are qualitatively different from this case that we have analyzed and we do not have a good theoretical understanding of the dynamics in these records.

There are several possible mechanisms for the dynamics in these records.[64, 65] It is possible that there is a parasystolic focus that is strongly reset by the sinus rhythm - a situation that is termed modulated parasystole.[35] It is also possible that there are abnormal regions in the heart that initiate an extra action potential. On the cellular level, one mechanism that can lead to this is called an early afterdepolarization. An early afterdepolarization is a transient increase in the membrane potential following an action potential. Although afterdepolarizations have been recognized for a long time based on experimental studies,[12] their importance in a clinical context is becoming increasingly clear. For example, several drugs that have been associated with premature death also lead to early afterdepolarizations.[15, 36] Further, some genetic defects in Na^+ and K^+ channels have been identified which lead to an increased rate of early afterdepolarizations and increased risk of sudden death.[53] Evidence for a mechanism implicating early afterdepolarizations is particularly strong for the record in Fig. 1B, since there are several electrocardiographic characteristics that are consistent with early afterdepolarizations (abnormally long QT-interval, presence of U-waves) and the patient was taking a drug, quinidine, that can produce early afterdepolarizations and ventricular tachyarrhythmias in experimental settings.[1, 46, 49]

To date, there has not been a thorough theoretical analysis of the expected dynamics that would result if an ectopic focus or an early afterdepolarization focus

were embedded in the ventricle. In our view, a model would have to include both propagation into and out of the focus. Further, in order to understand statistical aspects of records such as those in Fig. 1, we believe it would be essential to treat stochastic aspects including the fluctuation of the sinus rhythm. Carrying out such a computation is a future goal. As a partial step in that direction, in Sec. 5 we will use two ionic models to demonstrate that stochastic effects on the level of the ion channel can lead to gross macroscopic changes in dynamics. First we review earlier experimental and theoretical work on stochastic dynamics in cardiac systems.

4. SOURCES OF STOCHASTICITY OF CARDIAC DYNAMICS

4.1. External Stochastic Influences on the Heartbeat

There are numerous influences that control the heart rhythm. Some of these are external to the heart (or even the body) whereas others are in the heart itself.

People exist in a fluctuating environment. During the course of the day, as activity changes, the heart reacts to the changing demands. For example, everyone is familiar with the notion that physical activity leads to a more rapid heartbeat. But the heart rate also typically increases somewhat during inspiration and decreases during expiration. These changes are under the control of a large number of feedback control systems and are mediated by the nervous system and circulating hormones. Activity of a class of neurons called sympathetic neurons tends to increase the heart rate and the force of contraction of the heart, whereas activity of another class of neurons, called parasympathetic neurons, tends to decrease the heart rate. There are stochastic aspects of this influence. The firing (action potential) of a nerve cell leads to the release of neurotransmitters in the vicinity of heart cells, which in turn influence the heart. The neurotransmitters are released in discrete quantal packets called vesicles. In experimental systems, the number of vesicles released due to a single action potential is not constant, but is generally thought to reflect an underlying stochastic process, being often described using binomial or Poisson distributions.[51] There has been some modelling of the control systems regulating heart rate that includes a stochastic component.[38, 41, 60, 69]

The result of these influences leads to fluctuations in the heart rate. Analysis of the fluctuations of the heart rate in normal people has been intensively studied by analysis of 24-hour Holter recordings. The fluctuations are variously described as being chaotic or displaying $1/f$ noise, multifractality, or long-range scaling.[34] Although there is no strong evidence for deterministic chaos in normal heart rate variability, complex fluctuations are observed even if environmental fluctuations are held constant, perhaps reflecting the dynamics of multiple feedback control circuits. In the normal heart the variability is greatly reduced when drugs are given that block the effects of sympathetic and parasympathetic nerve activity,[86] or in

patients who have had heart transplants that end up largely eliminating functional nerve fiber endings on the heart.[32] The significant reduction in the variability is associated with an increased risk for sudden cardiac death in patients who have suffered a heart attack.[37, 57]

External environmental circumstances not only lead to variations in the normal heart rate, but are also implicated in the genesis of certain cardiac arrhythmias. This is captured by the common expression, "My heart skipped a beat [i.e. generated a premature beat] when I saw . . .." A more dramatic example is given in Fig. 1 in Ref. 81, in which the ringing of an alarm-clock induced ventricular fibrillation.

4.2. Intrinsic Stochastic Influences on the Heartbeat

In addition to external factors, there are also stochastic influences on the heartbeat from the heart itself. One way to consider such influences is to consider factors involved in the generation and propagation of the action potential, and to analyze those factors using both experimental and theoretical approaches.

4.2.1. Noisy Pacemakers

The heart rate is normally set by the sinus node. The sinus node is highly heterogeneous in terms of various properties including cell morphology, density of ionic currents and cell coupling through the gap junctions.[2] Therefore, each of the many thousands of pacemaker cells within this structure beats spontaneously, but each has its own intrinsic rate.[58] The beat rate of a single pacemaker cell is not perfectly regular, with the coefficient of variation of the time between action potentials being on the order of 2%.[83] One source of this irregularity is the stochastic opening and closing of the several thousand single ionic channels that lie within the membrane of each cell.[24, 83] The cells within the sinus node are coupled together by gap junctions, which allow electrical currents to flow from cell to cell. When individual pacemaker cells are coupled together electrically in an experimental system, the cells mutually synchronize to a common rate, and the coefficient of variation of the interbeat interval of the population oscillator falls as $\sqrt{1/N}$, where N is the number of cells, $2 < N < 50$.[9] The same result is found in an ionic model of coupled cells.[82] These experimental and modelling results are nicely accounted for by a simple phenomenological model in which the slow diastolic depolarization of the membrane potential between action potentials is regarded as a random walk superimposed on a linear drift to threshold, resulting in an Ornstein-Uhlenbeck process.[9] When many model sinus node cells of widely differing random intrinsic rates are coupled together, they can mutually synchronize so that all the cells in the population oscillate at the same common rate.[3]

4.2.2. Noisy Excitability and Refractoriness

A cell in the heart that does not beat spontaneously (i.e., a non-pacemaker cell) is excited by a current flowing into that cell from adjacent cells that have become excited as a result of the normal activation sequence in the heart. This process of excitation can be studied in a single neural or cardiac cell by injecting a pulse of current into that cell through a microelectrode at a given time after an action potential. Provided that the stimulus strength is sufficiently large, when the stimulus is given a sufficiently long time after an action potential it elicits a new action potential. The time interval during which a stimulus does not elicit a new action potential is called the refractory period. In general the duration of the refractory period depends on the stimulus amplitude. For a fixed timing of the stimulus, when the stimulus amplitude is too low (at a fixed pulse duration), a small subthreshold voltage deflection is recorded. Injection of a pulse with a sufficiently large current amplitude results in an action potential, which is a regenerative voltage response much larger in both amplitude and duration than the subthreshold response. There is generally a very narrow range of stimulus current within which a tiny increase in stimulus current amplitude results in the conversion of a subthreshold response into an action potential. The response can be probabilistic: as the stimulus amplitude is raised within this threshold range of potential, the fraction of trials at a fixed pulse amplitude yielding an action potential gradually increases from zero to one.[73] The amplitude at which half the stimuli result in an action potential, with the other half producing a subthreshold response, is termed the threshold current. It is generally accepted that the reason for the stochastic response at a fixed stimulus amplitude and coupling interval (with some stimuli yielding action potentials, others not) is that on different trials the membrane is not in exactly the same state, and, following delivery of the stimulus, does not respond in exactly the same way. This is because the action potential is generated by the aggregate activity of many single ionic channels in the membrane, with the numbers of different channels in the open and closed states at the start of the stimulus pulse, as well as the numbers of channels that open and close during the course of the response to the stimulus, fluctuating stochastically from trial to trial.

The two concepts of refractory period and threshold are also relevant to the study of spontaneously oscillating cells. In Sec. 5.1, we discuss a situation in which there is threshold behavior in a mathematical model of a cardiac pacemaker cell.

The easiest way to obtain a true threshold in a noise-free system is to have a saddle-point in the N-dimensional phase space of the system, and for that saddle point to have an (N-1)-dimensional stable manifold that serves to divide the phase space.[17] The effect of noise on such a threshold phenomenon has been studied and compared with experiment.[44, 45] In noise-free situations in which there is no such

saddle-point present, there is not a true threshold: the size of the response simply grows in a continuous way as the stimulus amplitude is increased, producing graded action potentials of all intermediate sizes.[17] But in electrophysiologically-based deterministic models, the continuous transition from subthreshold response to full-sized action potential is so sharp as to be effectively discontinuous.[7, 39] Models constructed as populations of individual channels have been used to investigate excitability.[8, 39, 67, 68]

In cardiac tissue, the refractory properties will not be identical in neighboring cells. Experimental studies have demonstrated that there is a good deal of cell-to-cell variability in the electrophysiological properties of single cells isolated from ventricular muscle.[79, 80, 87] This is presumably due to a different mix of currents in different cells. Some of this variation is due to intrinsic large-scale spatial gradients in electrical properties of cells in the ventricles.[43, 48] In both experimental and theoretical work, when cells are coupled together, the dispersion of action potential parameters is much reduced.[47, 62, 87] However, one of the important concepts in cardiac electrophysiology is that situations that lead to enhanced spatial dispersion of refractoriness also tend to lead to a higher incidence of cardiac arrhythmias.[27, 59]

5. STOCHASTIC MODELS OF CARDIAC ACTIVITY

5.1. Phase Resetting

In some individuals, the pattern of premature ventricular complexes is compatible with the existence of an ectopic pacemaker within the ventricles.[11, 35, 36, 64, 65] In that case, the ectopic pacemaker is subjected to input from the sinus node. It is thus important to consider the effect of stimuli on the rhythm of a pacemaker.

In a phase-resetting experiment one perturbs the rhythm of a spontaneously oscillating system by applying a brief stimulus at a given phase of the cycle. In general, the intrinsic rhythm of the system is re-established after a while, but its timing is typically shifted in time compared to the unperturbed rhythm. This reestablishment of the oscillation in biological experiments provides the basis for the usual assumption that biological oscillators are best described mathematically by stable limit-cycle oscillations.[85] Mathematically, the phase is a point on the unit circle and a phase resetting curve is the map $f_\mu : S^1 \to S^1$. The map f_μ describes the new phase as a function of the phase of the stimulus of magnitude μ. If a stimulus of magnitude μ always leaves one in the basin of attraction of the cycle, then f_μ must be a continuous function. We call this the Continuity Theorem; it is a robust result for resetting of stable limit-cycle oscillators.[18, 23]

Earlier experiments from our group studied the phase-resetting response of spontaneously beating aggregates of cells from the embryonic chick ventricles

produced by injection of a brief current pulse.[22, 25, 26] The time within the periodic oscillation at which the stimulus is injected is the coupling time, t_c. Typically, a depolarizing stimulus given early enough during the cycle (usually the cycle is defined to start on the upstroke of the action potential), e.g., during the action potential, never evokes another action potential, while a stimulus given late enough in the cycle, outside of the refractory period, always evokes an immediate action potential. However, when the stimulus amplitude is chosen appropriately, there is an intermediate range of t_c during which repeated trials at a fixed phase resulted in a response that was either one or the other of two very different outcomes: an immediate action potential or an action potential after some delay.[26] Moreover, even after several beats had elapsed, the envelopes of the action potentials did not overlap as they must have if the resetting curve was continuous. Since no stimuli were observed which led to the annihilation of the oscillation, this experiment apparently contradicts the Continuity Theorem.

We have proposed that the resolution of this apparent contradiction lies in the fact that the membrane noise produced by the gating of single-channels must be incorporated into ionic models, thus converting them from deterministic models to stochastic models.[26] In a previous study we simulated phase-resetting experiments using an ionic model of the sinus node that takes into account the stochastic gating of the channels.[39] Figure 4A shows ten repeated phase-resetting trials at a fixed stimulus amplitude (150 pA) and coupling time ($t_c = 117$ ms), each made using a different seed for the random number generator. The response was either an immediate action potential (the "all" response), or a delay until the next action potential (the "none" response). This classic "all-or-none" response leads to discontinuous phase resetting.

In contrast, phase-resetting using the deterministic noise-free form of the ionic model with the same stimulus amplitude and the same t_c results in a "none" response (solid black trace in Fig. 4B). An "all" response can be evoked by increasing t_c to 118 ms (dashed black trace in Fig. 4B). One would therefore think that varying t_c between 117 and 118 ms will ultimately give responses intermediate to the all and the none responses, since the model does not possess a saddle-point.[17] The blue and the red traces (purple where they virtually superimpose) in Fig. 4B are the results of varying t_c down to a difference of 10^{-12} ms (which brings us to the limits of the precision of our numerical integration routine). While a stimulus injected at $t_c = 117.158751189269$ ms (red trace) does not elicit an immediate action potential, at an infinitesimally later time ($t_c = 117.158751189270$ ms; blue trace) there is an action potential after a much shorter delay.

Thus, while the noisy single-channel model (Fig. 4A) replicates the experimentally observed behavior, the noise-free ionic model (Fig. 4B) gives very different dynamics. We turned next to a simpler version of the ionic model, obtained by reducing the original 7-dimensional model down to a 3-dimensional model.[39]

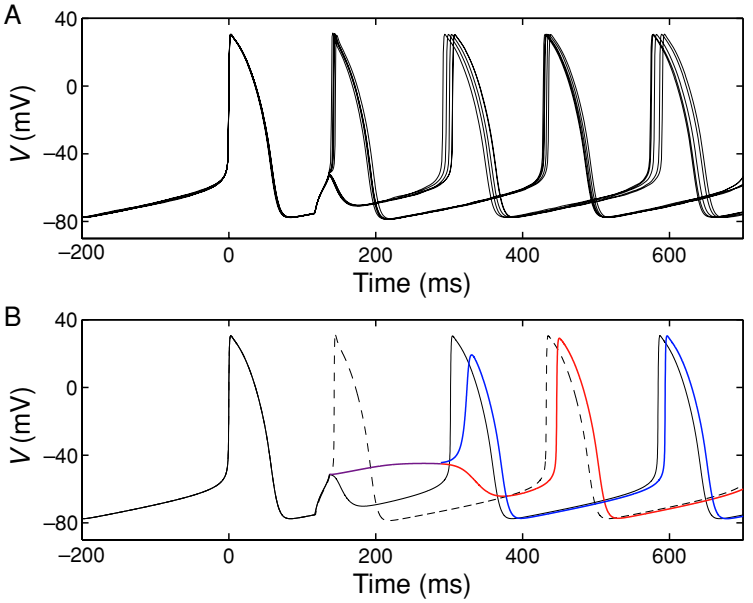


Fig. 4. (Color online) Differences in phase-resetting dynamics between noisy (A) and noise-free (B) sinus node models. (A) Repeated phase-resetting simulations using a stochastic single-channel model at a fixed coupling time (t_c) of 117 ms results in an immediate action potential or an action potential after a delay. The failure of the two sets of traces to superimpose a long time after the delivery of the stimulus indicates that the resetting response is discontinuous. (B) In the corresponding deterministic Hodgkin–Huxley-type model, phase-resetting simulations at $t_c = 117$ ms give a "none" response (solid black trace), while at $t_c = 118$ ms there is an "all" response (dashed black trace). Fine-tuning t_c at intermediate values results in delayed action potentials, but the response is quite different at two very close values of t_c ($t_c = 117.158751189269$ ms (red trace); $t_c = 117.158751189270$ ms (blue trace)). Panel A is reprinted from Ref. 39, with permission from the publisher.

The purpose of this simplification was to obtain a model for which we could plot and visualize trajectories and manifolds in phase space.

The 3-dimensional model displays the same type of behavior shown for the 7-dimensional model in Fig. 4B, albeit at smaller values of t_c (85.336376727283 ms and 85.336376727284 ms). The two corresponding trajectories are shown in phase space in Fig. 5A. The limit cycle is given by the black curve, and the stimulus is injected when the state point is at location A, bringing the state point to location B (again, purple indicates that the two trajectories are superimposed on the scale of the figure). At this time the stimulus is turned off. The state point then travels from location B to location C, from which point on the two trajectories sharply diverge (red and blue traces). The gray surface shows the slow manifold of the system (obtained by setting $dV/dt = 0$). The stimuli that give these two delayed responses

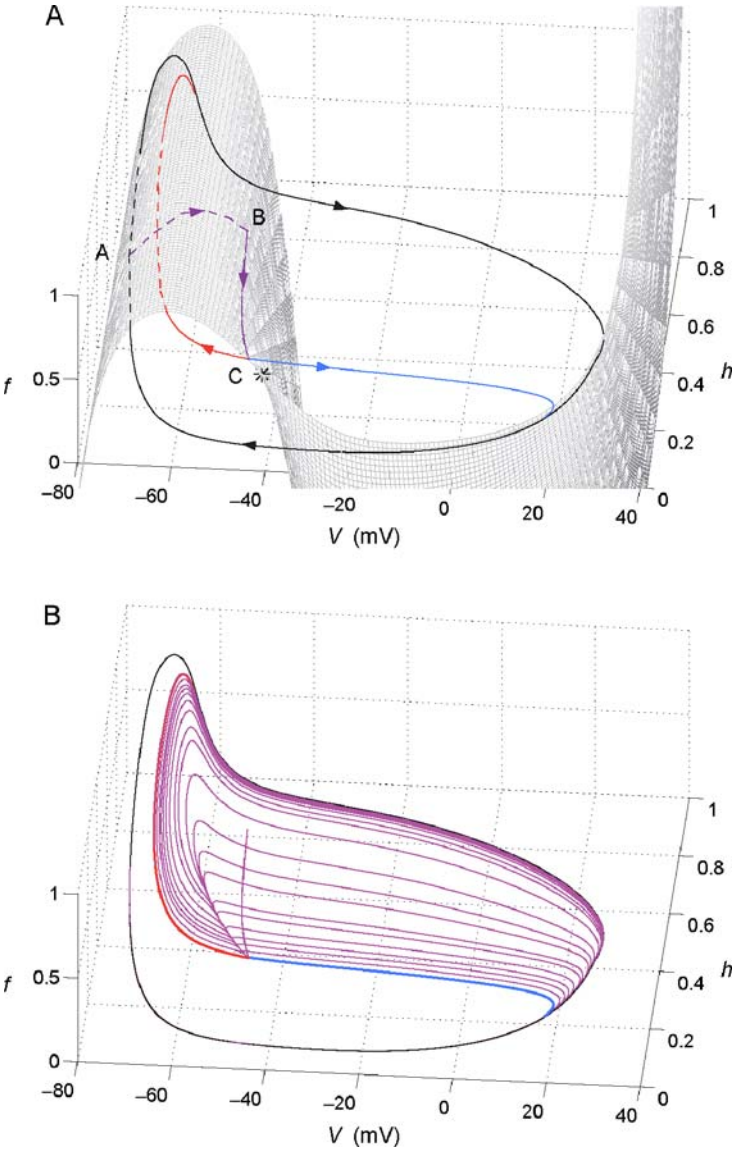


Fig. 5. (Color online) Separation of "all" and "none" responses in a reduced 3-dimensional noise-free Hodgkin–Huxley-type ionic model of a sinus node cell. (A) When $t_c = 85.336376727283$ ms (red trace) or $t_c = 85.336376727284$ ms (blue trace) the trajectories are initially almost superimposed (purple trace) while the state-point travels very close to the slow manifold (gray surface; obtained by setting $dV/dt = 0$). The black curve gives the unperturbed limit cycle, while the fixed point is marked by an asterisk. (B) Continuation method reveals a family of trajectories that are intermediate to the two responses above (magenta traces). Reprinted with modifications from Ref. 39, with permission from the publisher.

are well-timed in the sense that they deliver the state point to the neighborhood of the middle (unstable) branch of the slow manifold. The state-point then generates a trajectory lying very close to the unstable branch of the slow manifold. Such a trajectory is called a canard, and is notoriously sensitive to small perturbations.

Because of this sensitivity, we turned to continuation methods[13] to probe the phase-resetting response even more finely over the critical range of t_c. Using continuation to compute responses intermediate to the red and the blue responses in Fig. 5A, we obtained the magenta trajectories shown in Fig. 5B. There is a continuous family of intermediate trajectories between the two illustrated in Fig. 5A so that the Continuity Theorem is not violated. However, this behavior is so delicate, that one can compute that the opening or closing of a single channel would be sufficient to convert the all to the none response, or vice versa, leading to the observation of effectively discontinuous resetting.[39]

The application of the principles engendered in this analysis to arrhythmias in the intact heart is necessarily speculative. However, it is generally accepted that in normal hearts there can be several regions where there are (ectopic) pacemakers that are normally synchronized or entrained by the sinus rhythm and so are concealed. That is, should the trace in Fig. 4B represent activity in such an ectopic pacemaker, each sufficiently strong stimulus stemming from the sinus node will elicit an action potential if it comes after the end of the refractory period (dashed black trace in Fig. 4B). Thus, the activity of this ectopic pacemaker would not lead to activity competing with the sinus rhythm, since it would be entrained or phase-locked in a 1:1 fashion to the sinus rhythm. However, any one of a variety of different changes might lead to either a longer period for the ectopic pacemaker or a weaker input originating from the sinus node, resulting in a loss of 1:1 entrainment. This might lead to a delayed firing of the ectopic pacemaker after the refractory period of the surrounding ventricular tissue was over, producing a premature ventricular complex. We imagine that in general the parameter boundary for 1:1 synchronization would be transgressed in a gradual fashion so that stochastic properties at the cellular level might lead to stochastic ectopy on the electrocardiogram.

An alternative scenario occurs when there is a pacemaker in some region of the heart that might be stimulated only after an abnormal delay. For example, there could be an ectopic pacemaker in a viable strand of tissue in a scar formed after a heart attack.[70] Entrainment of this pacemaker might lead to a premature ventricular complex, provided the delay was sufficiently long that the resulting propagated beat originating in the entrained pacemaker occurred after the remainder of the ventricular muscle was out of its refractory period. For example, if there is a 2:1 phase-locked rhythm with two sinus beats for each ectopic beat, then if every beat from the ectopic pacemaker led to a premature ventricular complex there would be a long sequence in which there was one sinus beat between successive premature ventricular complexes. If noise causes some of the entrained beats to fall within

the refractory period of the ventricle and others to fall within the period when the ventricles are excitable, then the resulting rhythm would display an odd number of sinus beats between ectopic beats, generating a rhythm similar to that observed in Fig. 1B — note the NIB histogram in Fig. 3B (see Refs. 11, 21, 64, 65).

5.2. Early Afterdepolarizations

Yet another mechanism that can produce a premature ventricular complex is an early afterdepolarization occurring in an abnormal area of the ventricles. In an early afterdepolarization, following the upstroke of the action potential — but before repolarization is complete — there is an additional depolarization (indicated by arrow in Fig. 6A (right)). Early afterdepolarizations typically occur in circumstances in which there is a prolonged action potential duration, and as such they occur following administration of a variety of drugs that decrease potassium currents or increase sodium or calcium currents, or with genetic disorders that have a similar effect (the long-QT syndrome). As previously mentioned, it is likely that the premature ventricular complexes in Fig. 1B are due to early afterdepolarizations.

Early afterdepolarizations have been seen previously in noise-free ionic models of Purkinje fibre[4, 10, 16, 52] and ventricular muscle.[5, 6, 19, 28, 31, 50, 56, 74–76, 78, 88] In several of these studies, early afterdepolarizations are produced by blocking a potassium current. Randomly occurring early afterdepolarizations have also been found recently in an ionic model of paced quiescent ventricular muscle, in which the noise is associated with a calcium current.[71]

We use a Hodgkin–Huxley-type ionic model of a small three-cell cluster of spontaneously beating 7-day embryonic chick ventricular cells.[40] Briefly, the model contains a Ca^{2+} current (I_{Ca}), three K^+ currents (I_{Ks}, I_{Kr}, I_{K1}), a background current, and a seal-leak current. I_{Ca} generates a slow upstroke, whereas I_{Ks}, I_{Kr}, and I_{K1} contribute to repolarization. All the currents are involved in spontaneous diastolic depolarization. We simulated the stochastic fluctuations of the ionic currents by adding a Gaussian white noise current (I_{noise}; mean = 0, standard deviation = σ) to the total sum of the deterministic ionic currents (see Appendix). The maximal conductance g_{Ks} of I_{Ks} was reduced from its standard value of 7.8 nS in order to generate a prolonged repolarization time, a condition that is commonly observed in the presence of certain drugs or congenital diseases that reduce I_{Ks}[15] (e.g., the patient in Fig. 1B has a long QT interval, which is indicative of a prolonged repolarization time, and was taking quinidine, a drug known to block potassium channels and to lead to early afterdepolarizations[36]).

Figure 6A shows the transmembrane potential obtained with $g_{Ks} = 1.7$ nS in the absence of noise (left). The prolongation in the repolarization time causes the interbeat interval (IBI) to be prolonged to 0.54 s (normal value is 0.39 s). The histogram of the interbeat interval (the time between successive crossings of -50 mV

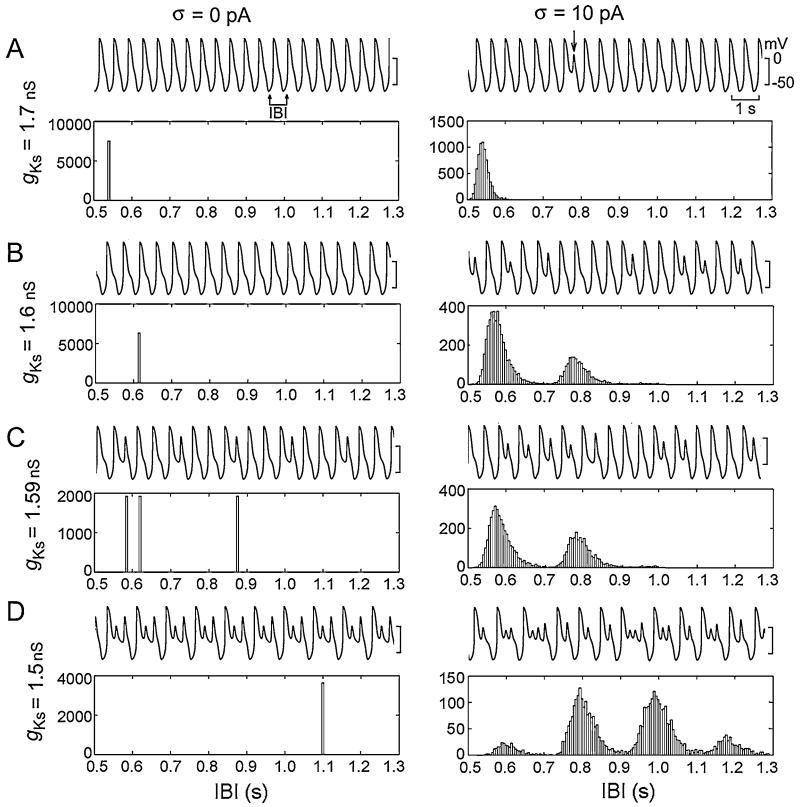


Fig. 6. Transmembrane potential or voltage from model of a small cluster of three embryonic chick ventricular cells during spontaneous activity, and the corresponding histograms of the interbeat intervals (IBI) obtained from 4000 s simulations without noise (left, $\sigma = 0$ pA), and with noise (right, $\sigma = 10$ pA). The conductance (g_{Ks}) of I_{Ks} is 1.7 nS (A), 1.6 nS (B), 1.59 nS (C) and 1.5 nS (D).

on the action potential upstroke) yields a single narrow peak (Fig. 6A (left)). When a noise current with $\sigma = 10$ pA is added (right), the dispersion in the interbeat interval increases, and early afterdepolarizations (arrow) are induced in only 0.2% of the action potentials. Figure 6B shows that when g_{Ks} decreases to 1.6 nS in the absence of noise (left), the repolarization time and IBI increases even further, but no early afterdepolarizations are observed. When a noise current with $\sigma = 10$ pA is added (Fig. 6B (right)), about a third of the action potentials are followed by an early afterdepolarization, leading to a bimodal histogram of interbeat intervals. The average interbeat interval between two consecutive action potentials (without an intervening early afterdepolarization) is shorter than the noise-free value (contrast histograms in Fig. 6B, left and right). Also, action potentials occurring

immediately after an early afterdepolarization tend to be shorter than those that follow a regular action potential. Recordings showing similar mixtures of action potentials with and without isolated early afterdepolarizations have been made in experiments on quiescent ventricular cells.[77]

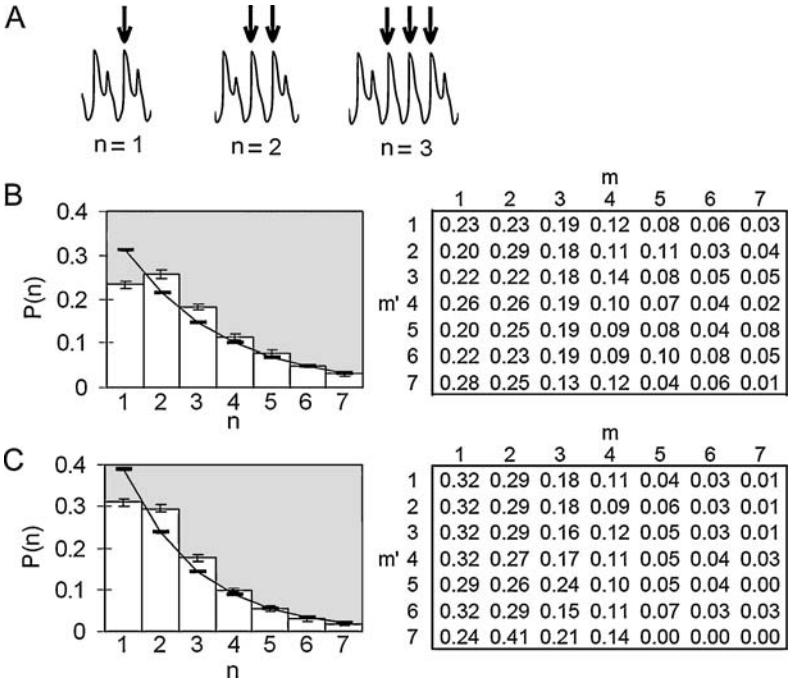
Figure 6C (left) shows the effect of a further decrease of g_{Ks} to 1.59 nS in the absence of noise. The rhythm is periodic, with every third action potential being followed by an early afterdepolarization. Each early afterdepolarization is followed by a single action potential with a relatively short repolarization time, then by another single action potential with a more prolonged repolarization time, and then by an action potential accompanied by an early afterdepolarization. As a result, three different peaks are observed in the corresponding interbeat interval histogram. With a noise current of 10 pA, early afterdepolarizations are observed following 39% of the action potentials (Fig. 6C, right), which is higher than the value (33%) in the noise-free case (Fig. 6C, left). The periodic pattern in the sequences of early afterdepolarizations in the noise-free model is abolished by the noise. Also the interbeat intervals are shorter than in the noise-free case, and the amplitude of the early afterdepolarizations becomes heterogeneous.

Further decrease of g_{Ks} to 1.5 nS in the absence of noise (Fig. 6D, left) leads to two successive early afterdepolarization following every action potential, in a repetitive pattern. Adding noise (Fig. 6D, right) abolishes the repetitive pattern and induces variability in the number of consecutive early afterdepolarizations after each action potential (from cases with no early afterdepolarizations, to cases with 3 consecutive early afterdepolarizations).

In order to analyze the noisy sequences of early afterdepolarizations, we counted the number n of single action potentials between each pair of consecutive early afterdepolarizations (Fig. 7A) in 10 simulations of 4000 seconds, each containing about 6000 action potentials. The bar plots of Fig. 7B (left) and C (left) show the averaged normalized histograms for n computed from the simulations with $g_{Ks} = 1.6$ nS and 1.59 nS respectively at $\sigma = 10$ pA. If we assume that there is a probability p that an early afterdepolarization occurs randomly during each action potential, then the expected probability for n action potentials between successive early afterdepolarizations is

$$P(n) = p(1 - p)^{n-1}, \tag{1}$$

where p is the fraction of action potentials that have early afterdepolarizations and $n \geq 1$. For each simulation run, p was computed, and the histogram and error bars in Fig. 7B and C give the mean and standard deviation of p for the 10 runs. For each run, the value of p was used to calculate $P(n)$, and the horizontal bars give the mean value of $P(n)$ (the standard deviation is within the width of these bars). The difference between the observed values and the predicted values was statistically significant for $n = 1$ to $n = 4$ ($p \leq 0.01$, unpaired t-test).



m' \ m	1	2	3	4	5	6	7
1	0.23	0.23	0.19	0.12	0.08	0.06	0.03
2	0.20	0.29	0.18	0.11	0.11	0.03	0.04
3	0.22	0.22	0.18	0.14	0.08	0.05	0.05
4	0.26	0.26	0.19	0.10	0.07	0.04	0.02
5	0.20	0.25	0.19	0.09	0.08	0.04	0.08
6	0.22	0.23	0.19	0.09	0.10	0.08	0.05
7	0.28	0.25	0.13	0.12	0.04	0.06	0.01

m' \ m	1	2	3	4	5	6	7
1	0.32	0.29	0.18	0.11	0.04	0.03	0.01
2	0.32	0.29	0.18	0.09	0.06	0.03	0.01
3	0.32	0.29	0.16	0.12	0.05	0.03	0.01
4	0.32	0.27	0.17	0.11	0.05	0.04	0.03
5	0.29	0.26	0.24	0.10	0.05	0.04	0.00
6	0.32	0.29	0.15	0.11	0.07	0.03	0.03
7	0.24	0.41	0.21	0.14	0.00	0.00	0.00

Fig. 7. Analysis of the distribution of the early afterdepolarizations. (A) The number of single action potentials (arrows), n, between two successive early afterdepolarizations. (B) Simulations with $g_{Ks} = 1.6$ nS and $\sigma = 10$ pA, and (C) simulations with $g_{Ks} = 1.59$ nS and $\sigma = 10$ pA. Left: normalized histogram of n obtained from 10 simulations runs (bar plots indicate the mean values, error bars indicate the standard deviations), and averaged values of 10 random distributions of n, as predicted by a geometric distribution (curve). The difference between the observed values and the predicted values was statistically significant for $n = 1$ to $n = 4$ ($p \leq 0.01$, unpaired t-test). Right: the conditional probability matrix $P(m|m')$ was obtained from one of the simulations.

We also examined the conditional probability $P(m|m')$ that the value m follows the value m' in the sequence giving the numbers of normal action potentials between two consecutive early afterdepolarizations (Fig. 7A). Figure 7B and C (right) show the conditional probability matrices for one of the simulations. This analysis shows that the $n = 1$ probability is decreased from what would be expected if early afterdepolarizations occurred randomly (i.e., $P(1)$). Further, the conditional probabilities also show a tendency for temporal ordering different from what would be expected by chance. For example, in Fig. 7B a value of $m' = 2$ is preferentially followed by a value $m = 2$, rather than $m = 1$ as would be expected by chance.

These computations demonstrate that a decrease of g_{Ks} in a theoretical model for a cardiac pacemaker produces prolonged repolarization times and longer

interbeat intervals. If the decrease is sufficiently great, the model shows early afterdepolarizations, as in several of the references cited earlier. In the absence of noise, the early afterdepolarizations occur in a regular rhythm for both values of g_{Ks} used in Fig. 6, with $g_{Ks} = 1.6$ nS being the boundary below which the early afterdepolarizations occur. However, in the presence of stochastic fluctuation caused by the opening and closing of ion channels (and perhaps other effects), the early afterdepolarizations occur irregularly. The patterning of the early afterdepolarizations as a function of the noise is sensitive to the details of the mathematical model and the magnitude of the noise, and this requires more investigation. We have also observed that slight changes in the value of g_{Ks} in the absence of noise lead to systematic changes in the patterns of early afterdepolarizations similar to those observed in earlier work on a model of cardiac Purkinje fibre as a bias current was systematically changed.[4] Consequently if early afterdepolarizations are the source of some premature ventricular complexes as is now believed, then a possible source for stochasticity in the observed phenomenology may be the fluctuations intrinsic in the opening and closing of ion channels.

It is generally believed that the local generation of an early depolarization by a group of cells is one mechanism that can lead to the generation of premature ventricular complexes in the electrocardiogram. Presumably, as with a normal pacemaker complex, it is the flow of the current through gap junctions that synchronizes the activity within the focus. Should the early afterdepolarization propagate out of the focus where it is generated and into the bulk of the ventricular muscle, this would induce a premature ventricular complex. There is both experimental and modelling evidence that the surrounding tissue can either facilitate or suppress the ability of the early afterdepolarization to escape from the focus where it is generated and to subsequently initiate reentry.[28, 30, 31, 52, 61, 63, 78, 87] Different ventricular arrhythmias, including a type of ventricular tachycardia known as torsade de pointes (the terminal rhythm in the bottom trace of Fig. 1B) are thought to be initiated by a premature ventricular complex stemming from such an early afterdepolarization. Since one of the cases shown above (Fig. 1B) is in a patient who was taking a drug, quinidine, that is known to increase the incidence of early afterdepolarizations in model experimental systems, there is a strong possibility that early afterdepolarizations represent an arrhythmogenic mechanism in that subject. The current computations offer a possible mechanism for the intermittent occurrence of the premature ventricular complexes evident in Figs. 1 and 2, since at the critical values at which the early afterdepolarizations appear, extremely small changes in parameters or noise lead to markedly different appearances for the early afterdepolarizations. Thus, comparatively small changes in the concentration of a circulating drug might potentially be a factor inducing bifurcations in the dynamics.

6. DISCUSSION

Electrocardiograms in people often show complex rhythms containing premature ventricular complexes and runs of non-sustained ventricular tachycardia prior to sudden death.[72] Although there have been a large number of clinical studies characterizing complex ventricular arrhythmias, e.g. see Refs. 15, 36, 42, at the current time there has been a diminution of interest in the analysis of these sorts of rhythms. We believe that one important reason for the relative disinterest was the Cardiac Arrhythmia Suppression Trial (CAST).[14] This clinical trial was based on the hypothesis that drugs that reduced the incidence of premature ventricular complexes in patients who had recently experienced a heart attack would also reduce the incidence of sudden cardiac death in the same patients. In this study, involving about 1500 patients, half of whom were given placebo and the other half drugs, there was a significantly greater death rate amongst those who were administered drugs. To date, only one class of drugs, β-blockers, which inhibit the effects of sympathetic activity, has been demonstrated to be effective in reducing the incidence of sudden cardiac death in clinical trials.[33]

The analysis of these arrhythmias from a perspective of basic science will be a difficult task. Short segments of data do not contain adequate information about the rhythms, and long segments reveal distinct differences between records that might seem superficially alike. Consequently, it will be essential to collect data over long times and to subject this data to a variety of data processing algorithms. It would also be extremely useful to gather reliable clinical data about the subjects during the course of their daily activities during the acquisition of the Holter recordings. However, the relative rarity of Holter recordings of individuals who experience sudden death makes research in this area an extremely challenging task. Further, arrhythmias in which there are frequent isolated premature ventricular complexes are extremely common and are generally considered to be benign, and the prognostic significance of analyzing such records remains to be demonstrated.

Our major goal in this article has been to make statistical physicists aware of these challenging problems. We hope others will think that they are worthy of study.

APPENDIX: COMPUTATIONAL METHODS FOR MODELS WITH NOISE

A commonly used method for adding noise to an ionic model is to add Gaussian white noise current to the deterministic ionic membrane currents. We use this method in Sec. 5.2. Thus, the equation for the rate of change of transmembrane potential is

$$\frac{dV}{dt} = -(I_{\mathrm{Ca}} + I_{\mathrm{Ks}} + I_{\mathrm{Kr}} + I_{\mathrm{K1}} + I_b + I_{\mathrm{seal}} + I_{\mathrm{noise}})/C_m, \qquad \text{(A.1)}$$

where I_{Ca} is the calcium current, I_{Ks} and I_{Kr} are the slow and rapid delayed rectifier potassium currents, I_{K1} is the inward rectifier potassium current, I_b is the background current, I_{seal} is the seal-leak current, I_{noise} is the added Gaussian white noise current, and C_m is the capacitance of the membrane of a three-cell cluster of embryonic chick ventricular cells. The equations governing the dynamics of the ionic membrane currents and the initial conditions are taken unchanged from Ref. 40. The noise current is given by I_{noise} with standard deviation σ. Uniformly distributed pseudorandom numbers generated using the *rand* function in gcc version 3.4.2 were transformed into Gaussian distributed numbers using the Box-Muller transformation. Numerical integration was carried out using a forward Euler scheme with a time step of 0.1 ms (see Ref. 40 for details).

The current noise mentioned immediately above is in fact generated by the apparently stochastic opening and closing of the gates within a finite number of channels, each having a finite single-channel conductance. Hence, a lower-level approach to simulating membrane noise is to model a population of randomly gating single channels. This can be done quite efficiently without keeping track of the state of each of the gates within each channel (i.e. whether gate open or closed)[8, 68] by determining the state and lifetime of an ensemble of gates.[20, 68] We use this method in Sec. 5.1 (for more details, see Ref. 39).

ACKNOWLEDGMENTS

This research has been supported by grants from NSERC, CIHR, the Canadian Heart and Stroke Foundation, MITACS, and the National Research Resource for Complex Physiologic Signals.

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