FOCUS ISSUE: Mapping and Control of Complex Cardiac Arrhythmias

Introduction: Mapping and control of complex cardiac arrhythmias

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This paper serves as an introduction to the Focus Issue on mapping and control of complex cardiac arrhythmias. We first introduce basic concepts of cardiac electrophysiology and describe the main clinical methods being used to treat arrhythmia. We then provide a brief summary of the main themes contained in the articles in this Focus Issue. In recent years there have been important advances in the ability to map the spread of excitation in intact hearts and in laboratory settings. This work has been combined with simulations that use increasingly realistic geometry and physiology. Waves of excitation and contraction in the heart do not always propagate with constant velocity but are often subject to instabilities that may lead to fluctuations in velocity and cycle time. Such instabilities are often treated best in the context of simple one- or two-dimensional geometries. An understanding of the mechanisms of propagation and wave stability is leading to the implementation of different stimulation protocols in an effort to modify or eliminate abnormal rhythms. © *2002 American Institute of Physics.* [DOI: 10.1063/1.1504061]

Sudden cardiac death, primarily caused by ventricular arrhythmias, is a major public health problem—it is one of the leading causes of mortality in the United States, resulting in more than 450 000 deaths each year. In recent years, the study of the heart's electrical activity (called cardiac electrophysiology) has evolved from a discipline of interest primarily to physicians and physiologists to one that has caught the attention of physicists, mathematicians, and engineers. Such scientists have come to realize that cardiac dynamics are characterized by many of the same principles that underlie the physical systems with which they are intimately familiar. The corresponding influx of new (to cardiology) analyses and techniques has led to many important contributions. This paper summarizes the basic electrophysiological properties of the heart, the nature of cardiac arrhythmias, and the ways in which dynamicists are investigating the analysis and control of arrhythmias, with special attention on the articles in this Focus Issue.

I. INTRODUCTION

A. A cardiac electrophysiology primer

Although the primary function of the heart (pumping blood throughout the body) is mechanical, the muscular pumping contractions are the product of electrical activity. Each heartbeat is the result of a wave of electrical activity that originates near the top of the right atrium in a small region of tissue called the sinoatrial node. The electrical wave propagates through the atria causing them to contract, and then enters a specialized structure called the atrioventricular node. Conduction through the atrioventricular node is relatively slow, producing a delay that is necessary for blood to flow from the atria into the ventricles. The electrical impulse then passes through a specialized conduction system (the bundle of His and Purkinje fibers) that rapidly distributes the impulse throughout the ventricles. Resultant contraction of the ventricles pumps the blood throughout the body.

Arrhythmias (abnormal heart rhythms) can be more rapid (tachycardia) or slower (bradychardia) than normal activity. Although there are many types of arrhythmias, the most prominent and deadly is *reentry*. Normally each cardiac impulse propagates as a wave that leaves behind a wake of refractory tissue that cannot be reexcited immediately. During reentry, the impulse will propagate back into a previously depolarized area that has recovered excitability.[1,2] Depending on the conduction properties of the tissue, the impulse may propagate indefinitely around a reentrant circuit—a situation that can be life-threatening if the rate is so fast that the heart's pumping efficiency is impaired. *Anatomical reentry* often occurs following a myocardial infarction (a ''heart attack''), a mechanical event in which one of the coronary arteries (the arteries that supply oxygenated blood to the myocardial tissue itself) becomes blocked such that downstream cardiac cells die from oxygen deprivation (ischemia) and form a scar of nonconducting tissue. Such scar tissue might form an anatomical obstacle about which a reentrant impulse can propagate. Alternatively, reentry can occur with-

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out a specific anatomical circuit or abnormal myocardium. Such *functional reentry* occurs in regions with steep excitability gradients (i.e., where refractory tissue is adjacent to excitable tissue) that provide the substrate for unidirectional functional block and conduction back into repolarized tissue.

The stability of reentry is highly dependent on conduction velocity and circuit length—the rhythm can sustain itself as long as the ''head'' of the reentrant impulse does not catch up to the ''tail.'' Destabilization of reentry is occasionally preceded by an oscillation[3–5] in the period of the rhythm. Sometimes when reentry destabilizes, the arrhythmia will terminate, thereby allowing the normal heartbeat to resume. Alternatively, a reentrant wave may break into multiple wavelets of excitation, with each wave traveling into a distinct nonrefractory tissue region. This seemingly random excitation pattern is known as *fibrillation*.[6] Fibrillation, which can occur either in the atria or the ventricles, causes the myocardium tissue to lose all synchronicity and rhythmicity—the muscle twitches spastically as if it were a bag of writhing worms. Atrial fibrillation will generally lead to an abnormally fast and irregular ventricular rate, but is typically not life-threatening. In contrast, ventricular fibrillation effectively eliminates the heart's ability to pump blood, a situation that leads to death within minutes if not corrected.

B. Clinical arrhythmia therapy

Because of the life-threatening nature of arrhythmias (it is estimated that more than 450 000 individuals die of sudden cardiac death, most from arrhythmias, each year in the United States of America[7]), the primary focus of clinical electrophysiology is arrhythmia elimination, termination, or suppression. Clinical cardiac electrophysiology is an evolving discipline characterized by rapidly improving arrhythmia identification and control techniques. Prior to the 1980s, the main method of arrhythmia control was antiarrhythmic drugs. However, recent decades have seen major advancements in other methods of arrhythmia management, most notably in the areas of radio-frequency ablation and implantable cardiac devices. Here we discuss the advantages and disadvantages of each of these approaches to give dynamicists a better appreciation of the current state of the art in arrhythmia management.

1. Antiarrhythmic drugs

For many years, the only method of controlling cardiac arrhythmias was pharmacologic therapy. While newer methods have overtaken medication as the preferred method of control for many types of arrhythmias, drugs are still important tools. Antiarrhythmic drugs function in a variety of different ways—some slow impulse initiation while others prolong refractoriness. Thus, with proper drug selection, a wide variety of arrhythmias can be managed with at least moderate success.[1,2] One disadvantage of pharmacologic therapy is that drugs can be proarrhythmic, meaning that they can actually induce life-threatening arrhythmias (usually a different arrhythmia than that for which they were prescribed).[8] A drug that is therapeutic for one arrhythmia may be proarrhythmic for another, hence the importance of accurate diagnosis of arrhythmia mechanism prior to pharmacologic therapy. Furthermore, accumulating clinical evidence indicates that ablation and implantable devices, discussed in the following two sections, are often more effective than antiarrhythmic drugs.[9]

2. Radio-frequency ablation

Radio-frequency ablation, which uses catheter-delivered energy to kill cardiac cells and make them nonconductive, is used if there exists a spatially identifiable area of cardiac tissue that is a vital component of the substrate underlying a cardiac arrhythmia (for example, one of the pathways of a reentrant arrhythmia), but is not necessary for normal conduction. During ablation, catheters are moved into the appropriate (depending on the nature of the arrhythmia) chambers of the heart and positioned against the heart wall to monitor or stimulate the tissue. A variety of monitoring techniques, including electroanatomical mapping techniques discussed in this issue by Stein and colleagues,[10] are used to determine the precise location of the arrhythmogenic substrate to be ablated. At that point, alternating radio-frequency energy is passed through the appropriate electrode, resulting in thermal tissue damage. The ablation is continued until the arrhythmogenic tissue has been destroyed and the arrhythmia can no longer be induced by the appropriate stimulation pattern. Unlike other therapies, when ablation is effective, it is a cure, i.e., the arrhythmia cannot recur because the arrhythmogenic substrate has been eliminated. For this reason, ablation is often the therapy of choice for eliminating certain arrhythmias.

In spite of the frequent success of ablation therapy, this procedure is often infeasible for the treatment of ventricular arrhythmias. One obstacle is the considerable thickness of the ventricular wall. Ablation lesions, which are applied to the endocardial tissue, extend only a finite distance beyond the tissue surface. Thus, if the arrhythmia substrate is deep in the heart muscle, ablation may not be successful. Additionally, for ventricular tachycardia resulting from ischemia, ablation is often hindered by the spatially extended and discontinuous nature of the scar tissue. Because of this, there are often multiple large regions of arrhythmogenic substrate—making ablation impractical. In short, while ablation is a powerful technique, it is practical for only a subset of arrhythmias.

3. Implantable cardioverter defibrillators

For life-threatening ventricular arrhythmias, recent advancements in implantable cardiac devices offer promising therapeutic options. Stimulation and detection electrode wires (leads) run from the device, which is implanted above the pectoral muscle in the chest, into the subclavian vein and pass into the heart, where they are secured to the myocardial wall via a remotely operated screw anchor or a passive anchor similar to a grappling hook. Devices for the control of tachycardia and/or fibrillation are known as implantable cardioverter defibrillators (ICDs). ICDs monitor the heart's rhythm and typically use some form of rate analysis to detect arrhythmias. If tachycardia is detected, a relatively simple pacing algorithm is activated to eliminate the arrhythmia.

One common algorithm paces the heart at a fixed percentage of the tachycardia rate for a preset number of stimuli. If the tachycardia persists, the pacing is repeated at a slightly faster rate. If the tachycardia continues to persist, the device shifts into defibrillation therapy. Defibrillation therapy (for the above-mentioned scenario or for detected fibrillation) uses a large voltage shock to reset the electrical activity of the entire heart. If the shock fails, a higher-energy shock is delivered. Such shocks are extremely painful. Fortunately, this is often irrelevant because the arrhythmia usually causes fainting prior to the shock delivery. Even if the person is still conscious at the time of the shock, the pain from the shock is better than the usual alternative (death).

Implantable cardioverter defibrillators are revolutionary medical inventions which have saved thousands of lives. That being said, there is clearly room for enhancement of their control algorithms. For example, defibrillation requires powerful battery-draining shocks that can cause pain if inappropriately applied and antitachycardia pacing efficacy decreases as tachycardia rate increases.[11] Furthermore, current algorithms are dynamically simplistic (brute force for defibrillation; simple ramp or burst patterns for antitachycardia) and utilize little, if any, feedback information regarding their beat-to-beat effects on the arrhythmia. These shortcomings suggest that dynamics might be exploited to produce more elegant arrhythmia therapies.

C. Contributions of dynamicists

In parallel with the advances in clinical cardiology, electrophysiology has caught the attention of physicists, mathematicians, and engineers.[12] Such scientists have come to realize that cardiac dynamics are characterized by many of the same principles that underlie the physical systems with which they are intimately familiar. The corresponding influx of new (to cardiology) analyses and techniques has led to many important contributions—theoretical, computational, and experimental—to the understanding of cardiac arrhythmias. Theoretical analyses of mechanisms of arrhythmias have been facilitated by the exponential increases in computational power that have enabled the simulation of models that incorporate increasingly realistic ionic mechanisms and three-dimensional geometry. Such work has often been combined with experimental studies that enable observation of cardiac dynamics *in vivo* and *in vitro*. In addition, techniques from nonlinear dynamics have enabled researchers to move beyond simulation to analyze the stability and geometrical organization of normal and abnormal rhythms with a view toward understanding the bifurcations underlying the onset of complex arrhythmia.

Despite the parallel interests and objectives between physicians and scientists, most clinical practice today is based on empirical methods combined with large clinical studies that statistically estimate the efficacy of different treatment modalities. The significant advances provided by medical device manufacturers to map and control cardiac arrhythmias have largely depended on engineering approaches combined with clinical input. To our dismay, years of experimental and theoretical investigation into the dynamical aspects of arrhythmias have not yet had a significant impact on clinical practice. Hopefully this Focus Issue will help to change that.

This Focus Issue had its origin in the ''Workshop on Mapping and Control of Complex Arrhythmia'' held at the Center de Recherches Mathématiques at the Université de Montréal in the fall of 2000. The participants at that meeting felt that the striking theoretical and experimental advances in mapping and controlling cardiac arrhythmias subsequent to the publication of the *Chaos* Focus Issue ''Fibrillation in normal ventricular myocardium'' (Vol. 8, Issue 1; edited by A. T. Winfree) warranted the publication of a *Chaos* Focus Issue in this area. Importantly, there is significant room for application of theoretical methods to a wide variety of different arrhythmias, not just fibrillation. Further, since arrhythmias usually arise in hearts that have abnormal physiology and/or anatomy, theory must also focus on the ways in which arrhythmias arise in abnormal hearts. Although nonlinear dynamics promises to offer novel perspectives for the understanding and control of cardiac arrhythmias, at the moment there is a need for development of links between the theoretical and experimental approaches, clinical practice, and medical device manufacturers. This Focus Issue is meant to illuminate the current advances in the study of complex cardiac arrhythmias and, in so doing, to facilitate new approaches and collaborations that will lead to the translation of the understandings developed in basic research to improve clinical practice.

In the following sections we attempt to provide context for the Focus Issue contributions. In Sec. II, we discuss techniques to map data from the intact heart and discuss the development of anatomically realistic models of cardiac propagation. In Sec. III we describe the theoretical work that focuses on the mechanisms underlying instabilities that arise during cardiac propagation. Section IV describes the use of electrical stimulation to modify and control the rhythms in the intact heart and experimental and theoretical models.

II. MAPPING CARDIAC ARRHYTHMIAS: ANATOMICAL AND GEOMETRIC ASPECTS

Quantification of the spatiotemporal dynamics of propagating waves of a cardiac arrhythmia is of fundamental importance to understanding arrhythmias. Such quantification is accomplished via a range of continually evolving techniques of cardiac-excitation mapping. Original mapping methods involved recording electrical activity in the whole heart, or in tissue preparations, from a limited number of sites during spontaneous rhythms or in the response to stimulation. Such electrode recording typically involves off-line data analysis to determine local activation times at a limited number of points and interpolation methods to generate propagation maps. At the current time, electrical recording in the intact human heart can be accomplished by extension of these methods. Catheters with embedded electrodes can be threaded via the systemic vascular tree directly into the chambers of the heart. The position and timing of electrical activation of the catheter electrodes are monitored, and in this fashion it is possible to compile an image of the propagation pattern inside the human heart. Although immensely

useful clinically, the ''images'' from this procedure are limited to numerous voltage electrograms which the highly skilled cardiac electrophysiologist mentally interpolates into an accurate spatiotemporal understanding of the involved electrophysiology. The introduction of spatially extended arrays of electrodes greatly expanded the ability to study complex propagation patterns. For example, in animals, Allessie and colleagues[13] demonstrated circulating excitation in atrial tissue using simultaneous recordings from multiple electrodes and Ideker and colleagues mapped the excitation from ventricular tissue using plunge electrodes.[14] More recently, as described in this issue by Stein and colleagues,[10] similar three-dimensional mapping approaches, using techniques that include an endocardial analog of the Global Positioning System and an inflatable ellipsoid covered by dozens of electrodes, have improved the ability of clinicians to image the heart's electroanatomy and electrophysiology.

Optical mapping methods, used *in vitro* or in *in vivo* animal experiments, are complementary to electrode recording techniques. In optical mapping, a chemical dye that is either sensitive to membrane voltage or local calcium concentration is added to cardiac tissue. Thus, by monitoring the fluorescence from cardiac tissue treated with the appropriate dyes, striking images of propagation can be achieved.[15–17] In recent years, mapping of myocyte monolayers has provided a well-controlled environment for investigating basic electrophysiological dynamics.[18–21] In this issue, Bub and Shrier investigate the effects of cell density on propagation in such monolayers.[22] Changes in density generate spatial patterns of propagation that are similar to arrhythmias observed in whole hearts. The manipulation of such properties in tissue culture could offer great promise for the systematic analysis of the impact of myocardial density (which can be altered by disease) on arrhythmogenesis.

The ability to visualize the spread of excitation in intact hearts enables careful comparisons between recorded dynamics and numerical simulations using realistic cellular kinetics and heart geometries.[23,24] The mammalian heart has extraordinarily complex geometry and the extent to which the heart functions well as a consequence of that geometry, or despite that geometry, is still poorly understood. For example, the inside of the atrium is highly variable from species to species and even within a given species. In this issue, Virag and colleagues study electrophysiological dynamics in anatomically accurate models of the atria with a goal of understanding the factors that lead to the establishment of reentrant rhythms in the atrium.[25] These studies may also offer new ideas on how electrical stimulation or surgical modification can help control such rhythms. Atrial reentry is also examined here in computational models by Zou and colleagues.[26] Additionally, Rogers uses an anatomically realistic ventricular model to illuminate how geometry affects the stability of propagating waves.[27] Such analysis is vital to our understanding of how reentrant tachycardia may break down into ventricular fibrillation, a problem that is the focus of other articles in this issue (described later).

III. INSTABILITIES IN CARDIAC PROPAGATION

During reentry, excitation travels in a circuitous path, leading to the frequent reexcitation of tissue at a rapid rate. Such reentrant arrhythmias can be imagined in an idealized fashion by different geometric configurations ranging from a pulse circulating in a one-dimensional pathway,[28–32] to spiral waves circulating in two-dimensional sheets,[15,33–36] to scroll waves circulating in three dimensions.[37,38] From a purely theoretical perspective, there is great interest in understanding the factors that might lead to the establishment of reentrant excitation, the factors that lead to the destabilization of such reentrant rhythms, and the ways to modify or control these rhythms. In Sec. IV we consider methods to control these rhythms using electrical stimulation. Here we consider the factors that affect the stability of propagating waves.

During periodic pacing, homogeneous myocyte aggregates can show complex bifurcations and instability as a function of the pacing frequency and amplitude that is well described theoretically by a one-dimensional difference equation.[39] One striking type of instability is *alternans* rhythms, in which there is a beat-to-beat variation of an important physiological characteristic such as duration of the action potential or the conduction time. The presence of alternans suggests the occurrence of a period-doubling bifurcation in an appropriate mathematical model. As one example, we consider the restitution curve, which gives the duration of the action potential as a function of diastolic interval (the time that has elapsed since the end of the previous excitation). If the restitution function is sufficiently steep (slope>1) there can be a period-doubling bifurcation such that periodically timed stimuli will lead to an alternation of action-potential duration.[40–42] These results have been extended to help understand propagation in spatially extended systems. If a cardiac excitation is circulating on a one-dimensional ring, then a related instability can lead to the development of complex quasiperiodic fluctuations of action-potential duration and propagation velocity.[5] In the current issue Cytrynbaum and Keener[43] extend this analysis by considering the rules governing the propagation of the pulse front and the pulse back, and show that the earlier formulations are incomplete. If there are nonmonotonic restitution functions, then this will lead to complex dynamical patterns.[45,44] Such dynamics are examined in the current issue by Panfilov and Zemlin for restitution curves with negatively sloped segments.[46]

Excitation waves traveling in space can be susceptible to related instability effects, but as shown in experiments[47,48] and models,[49,50] the details get much more complicated as a consequence of the spatial structure. (As mentioned earlier, Rogers examines wave stability in this issue.[27]) In this issue Arce and colleagues study a model of a system in which there is a localized region of poor conductivity.[51] In this system, at certain pacing rates, there is again a period-doubling bifurcation leading to a local alternation of action-potential duration. The model also shows bistability, in which the observed dynamics depend on the stimulation history. The extension of this result to more complex and realistic ionic and anatomical models will not be straightforward. In a modeling

study in this issue Sampson and Henriquez extend an elegant experimental study[52] and consider the contributions of one such complicating factor, localized heterogeneities, on action-potential duration in two dimensions.[53] They demonstrate that such heterogeneities provide an enhanced substrate for reentry. Such analysis is of central importance to the understanding of the contributions of post-myocardial-infarction scar tissue to arrhythmogenesis.

Although it has long been appreciated that spiral waves can circulate in two-dimensional excitable media, such propagation is not always stable. The tip of the spiral wave can circulate in a regular or irregular pattern called meander.[54–57] Here, Otani provides a rigorous analysis of the factors that govern spiral-wave meandering.[58] This work has possible therapeutic implications, given that several control techniques proposed in recent years attempt to exploit meander as a means of terminating reentry.[59–62] To that end, Aslanidi and colleagues propose novel ways to modify cardiac tissue to increase such meandering, hypothesizing that increased meandering will lead to movement of the reentrant wave into a nonconducting region of the heart, thereby leading to its termination.[63]

Circulating waves in two or three dimensions are subject to additional instabilities that can lead to the breakup of the wave itself. Spiral-wave breakup has been hypothesized to underly the transition from ventricular tachycardia to ventricular fibrillation.[64–68] A current debate is whether such breakup occurs by a single mechanism, or whether there are multiple mechanisms. The restitution hypothesis holds that the restitution properties of the cardiac tissue underlie this transition. Data supporting this hypothesis have demonstrated that pharmacological agents that make the restitution curve less steep may prevent the breakup of spiral waves into spirals.[69,70] In the current issue, Fenton and colleagues examine the many different mechanisms that have been proposed to underlie spiral wave breakup. This comprehensive article makes clear that there are many possible mechanisms for the breakup of spiral propagating waves, and suggests directions for future theoretical and experimental studies.[71]

IV. ELECTRICAL STIMULATION AND CONTROL OF CARDIAC ARRHYTHMIAS

As described earlier, implantable cardioverter defibrillators offer therapy by delivering electrical stimulation directly to the heart using relatively simple algorithms. In contrast, a preferred therapy for a reentrant arrhythmia would exploit the dynamics of the arrhythmia and use appropriately timed low-voltage pulses (or perhaps even a single pulse) to collide with and annihilate the reentrant wave. While employing a single stimulus sounds like a ''magic bullet,'' in theory there should exist a critical stimulus that could annihilate any reentrant excitation—at least one circulating on a one-dimensional ring.[28] In the current issue, Sinha and Christini examine such stimulus-induced termination for the two-dimensional case in the presence of a conduction inhomogeneity.[72] This work shows that the presence of inhomogeneities (as might be expected following a myocardial infarction) increases the size of the stimulation parameter regime that leads to annihilation. Further, the work suggests that the criteria for annihilation of reentry in a one-dimensional ring may not easily extend to the termination of reentry in two dimensions. In a complementary article in this issue, Comtois and Vinet examine the effects of multiple pulses on resetting and annihilating impulses circulating on a one-dimensional ring.[73]

In addition to such investigations of anatomical reentry, several papers in this issue examine control of functional reentry. One intriguing therapy approach attempts to prevent the very onset of functional reentry. To this end, Echebarria and Karma have examined terminating repolarization alternans, which is a potential mechanistic precursor to functional reentry.[47–49,74] In previous work, Hall and Gauthier demonstrated the ability to terminate such alternans in *in vitro* frog sections.[75] In a one-dimensional modeling study, Echebarria and Karma demonstrate that such control may be practically limited by an inability to alter electrophysiological dynamics of tissue that is distant from the stimulating electrode (as would be required to prevent reentry in the whole heart).[76]

Given such potential limitations, termination, rather than prevention, of functional reentry may be necessary. To this end, several methods for controlling functional reentry have been proposed.[77] These techniques include: (i) the application of an external forcing signal to the excitable medium[59–62] in an attempt to move the spiral wave in a desired direction, (ii) global feedback via electric-field modulation,[78,79] (iii) introduction of localized spatial inhomogeneities between the boundary and the core of the spiral wave,[77] and (iv) stimulation via multiple electrodes in an electrode array.[80,81] In this issue, Stamp and colleagues investigate an approach in which, for a narrow range of stimulation parameters, rapid stimulation forces a spiral wave to the boundary of the domain, thereby leading to its annihilation.[82] Also in this issue, Gray uses computational modeling to analyze control approaches to prevent spiral-wave breakup, which (as mentioned earlier) is a prime suspect for the initiation of ventricular fibrillation.[83] If such control is possible, the deadly breakdown of ventricular tachycardia to ventricular fibrillation might be preventable in some cases.

Given that mathematical models from nonlinear dynamics have been useful in describing many of the instabilities observed in cardiac tissue, it is possible that control methods suggested by nonlinear dynamics will be useful for the control of cardiac arrhythmias.[12,84] The first implementation of this notion regularized aperiodic behavior in *in vitro* sections of rabbit heart tissue.[85] Similar techniques were later used to control abnormal electrophysiological dynamics of the atrioventricular node in rabbits[86] and, more recently, in humans.[87] Ditto and colleagues demonstrated limited ability to control atrial fibrillation in humans using similar methods.[88] In the current issue, these matters are examined further by Gauthier and colleagues, who investigated nonlinear-dynamical control of atrial fibrillation in sheep heart.[89] In contrast to the earlier Ditto *et al.* study, Gauthier and colleagues found that it was not possible to control atrial fibrillation. This careful study highlights the need for additional analysis of such techniques before clinical implementation can be considered.

In addition to the use of electrical stimulation to control

arrhythmia, it is also well known that strong electrical stimulation can induce fibrillation (this is what occurs during electrocution). Here, Trayanova and Eason examine the induction of reentrant excitation by defibrillation shocks (the very therapy meant to terminate arrhythmias!) in computer models of the heart.[90] Better understanding of this phenomenon (which brings to mind the earlier-discussed phenomenon of arrhythmias induced by antiarrhythmic drugs) may help physicians obey the fundamental rule to ''First, do no harm.'' In complementary work, Roth critically examines the ability of theoretical models to reproduce accurately the events that occur following a large shock to the heart, pointing out the many subtleties that may mislead the investigator.[91] Such considerations are certainly essential if theory is ever to migrate into clinical application like we hope.

V. CONCLUSIONS

Arrhythmia therapy has undergone remarkable advances in recent decades. As described in this paper, notable areas of progress include implantable devices, mapping techniques, and ablations. That being said, there remains significant room for improvement and dynamicists are well-suited to help advance the field.

Although dynamicists have had little therapeutic impact to date, there are a number of ways in which that could change. For example, perhaps the greatest hindrance to improved therapy is the huge variety of arrhythmias (both underlying mechanistic differences and intra-patient physical variations), many of which exhibit extremely rich, poorly understood dynamics. To deal with such variety, clinicians adapt their hospital procedures on a case-by-case basis in ways that are sure to impress any dynamicist observer. Yet, the devices and drugs that they use for long-term care are not nearly so nimble because they are based on massive clinical studies that are directed toward finding a therapy that works best in a large cohort of ''similar'' patients. At first it may not seem that the work of dynamicists, which has focused almost exclusively on general arrhythmia properties rather than real-world variability, would be of much help in improving the ability of devices to deal with individuality. Yet, as the area of nonlinear-dynamical control has demonstrated, once the general dynamical rules are understood, algorithms might be developed that exploit those rules while adapting to the specifics of a particular heart.

The articles in this Focus Issue suggest many other ways in which dynamicists might impact cardiac electrophysiology in the future. In our opinion, a common link between all of these approaches is that the likelihood of success is sure to increase as dynamicists engage in closer collaborations with clinical electrophysiologists. In addition to helping dynamicists ensure that their models do not drift toward irrelevance, clinicians have invaluable knowledge (and data!) about real-world dynamics. On the flip side, dynamicists offer a unique perspective, along with numerical and analytical skills, that could open new therapeutic avenues.

To date, dynamicists have not had a major impact in generating clinically relevant therapies. However, the obvious nonlinear dynamical aspects of the heart and their parallels with the dynamics of well-defined physical systems, the innovative research being carried out on many fronts, and the importance of heart disease to the human condition, should lead to exciting developments in coming years.

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