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EFFECT OF HETEROGENEITY ON SPIRAL WAVE DYNAMICS IN SIMULATED CARDIAC TISSUE

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There is considerable spatial heterogeneity in the electrical properties of the heart muscle and there are indications that anisotropic conduction may play an important role in the pathogenesis of clinical cardiac arrhythmias. Spiral waves of electrical activity are related to reentrant cardiac arrhythmias as ventricular tachycardia and ventricular fibrillation, and the generation of a wave breakup is hypothesized to underlie the transition from ventricular tachycardia to ventricular fibrillation — the leading cause of sudden cardiac death. Here we investigate the effect of heterogeneity on spiral wave reentry in a two-dimensional modified FitzHugh–Nagumo membrane model. Spiral wave breakup induced by the heterogeneity is found. The spiral wave dynamics is invariant under translational and rotational transformations in homogeneous tissue, but for heterogeneous tissue, this symmetry is broken due to the heterogeneity. The reentry dynamics depends on the degree of heterogeneity and the point where the reentry is initiated within the simulated tissue. This study may open potentially exciting new diagnostic and therapeutic possibilities in a clinical context.

Keywords: Cardiac membrane properties; heterogeneity simulation; nonlinear dynamics; pattern formation modeling; reentrant arrhythmia; spiral wave.

1. Introduction

The bright red human heart ordinarily beats with a regular rhythm and the spontaneously beating heart fascinated early scientists. The earliest attempts to understand this pump performance are probably lost in antiquity and by now, our knowledge concerning the normal and abnormal changes that occur in the heart has increased considerably. A question that comes to mind is whether this knowledge has improved our methods of treatment in actual practice. There are now patients suffering from certain heart affections who are treated effectively. On the other hand, ventricular fibrillation (VF) and reentrant ventricular tachycardia (VT) continue being the leading cause of sudden cardiac death. Yet, in spite of the efforts in understanding their behavior, their spontaneous initiation has not been mapped, neither the manner in which VT converts into VF, or vice versa. Understanding the

arrhythmia mechanisms is essential, as a better knowledge of these mechanisms will allow offering targeted curative treatments to a greater number of patients.

At present, from combined theoretical and computer studies as well as experimental evidence, it is firmly established [Garfinkel *et al.*, 2000; Gray & Jalife, 1996] that spiral waves of electrical activity are related to reentrant cardiac arrhythmias as VT and VF. Nowadays reentry is believed to be the major mechanism underlying most lethal cardiac arrhythmias [Samie & Jalife, 2001] even though, focal and nonreentrant mechanisms do play a role in arrhythmogenesis. It is considered that the transition from VT (high — up to 10 Hz — frequency activity, believed to be due to simple reentry in the ventricle) to VF (irregular, high-frequency activity due to multiple reentrant sources) may be caused by the breakdown of reentrant propagating waves of excitation into multiple reentrant sources [Biktashev *et al.*, 2002; Qu *et al.*, 1999; Xie *et al.*, 2001a]. VF is not random, but rather a complicated sequence of ventricular excitation that is organized in space and time [Gray *et al.*, 1998]. It is believed to be produced by one or many reentrant propagating waves of excitation in the ventricular wall, which may be modeled as spiral waves in two-dimensional excitable media, and scroll waves in three dimensions [Biktashev *et al.*, 2002]. There are two major classes of reentry — anatomical and functional. The functional reentry depends on heterogeneity of the electrophysiological properties of the cardiac fibers caused by local differences in the transmembrane currents, action potentials, resting potentials, time course of repolarization and recovery of excitability [Allessie *et al.*, 1977; Wit *et al.*, 1990].

The anatomy of the cardiac muscle may participate in determining its functional properties. The structural characteristics of the heart muscle, which include the orientation of the myocardial fibers and the way the fibers or bundles of fibers are connected to each other, can influence both conduction and refractoriness. Variations in velocity and in patterns of conduction of myocardial electrical activity can affect cardiac rhythm as well as the coordination of contraction; abnormal electrical coupling between cardiomyocytes through gap junctions is, therefore, considered an important factor in various pathophysiologic conditions [van der Velden & Jongsma, 2002; Clerc, 1976; Osaka *et al.*, 1987]. In auricles and ventricular muscle, fibers are arranged parallel to each other while the cells comprising the fiber bundles have a relatively high density of cell junctions arranged longitudinally, connecting the end of one cell to the end of another; the cells in the transverse direction may also be tightly coupled, but they are sparsely connected since the fibers are subdivided into groups [Sommer & Dolber, 1982]. An increase in connective tissue can result from fibrosis associated with a number of pathological states; after myocardial infarction the degree of anisotropy is enhanced by collagenous septa dividing the myocardial fibers. The effects of the presence of uniform or nonuniform anisotropy on the characteristics of reentry have been the topic of intense research. Anisotropic tissue structure of cardiac muscle on conduction may confer the heterogeneity of functional properties necessary to cause reentry as an arrhythmogenic mechanism. Experimental studies indicate [Allessie *et al.*, 1990] that anisotropic conduction may play an important role in the occurrence of spiral waves in auricles and ventricular muscle, and in the pathogenesis of clinical cardiac arrhythmias.

In spite of the fact that the human heart is a complex organ, both anatomically and electrically, it may seem surprising that simplified mathematical models may show a qualitative correspondence with experimental and clinical data in the intact heart. By utilizing a mathematical model of cardiac electrical activity to study the transition from regular to irregular dynamics, new insights may be gained into the origin of the erratic, sometimes fatal arrhythmias observed in the clinical context. Very extensive work has been dedicated to the development of models in an effort to achieve the ionic mechanism responsible for the cardiac cell excitation and rhythmic activity, such as the Luo and Rudy (LR) action potential model of ventricular muscle [Luo & Rudy, 1991] and sinoatrial node model [Yanagihara *et al.*, 1980]. In this work we simulate the cardiac tissue by a two-dimensional modified FitzHugh–Nagumo membrane model (a more detailed discussion can be found in [FitzHugh, 1961, 1969; Guttman *et al.*, 1980]. We focus our studies on the effect of heterogeneity on the stability of an initiated spiral wave within the cardiac tissue.

In Sec. 2 we present a rather detailed discussion of the physiology of the cardiac tissue, which will lead to the presentation of the model in Sec. 3. Results and discussion are developed in Sec. 4, while in Sec. 5 we present our conclusions.

2. Physiological Heterogeneity in the Cardiac Tissue

2.1. *Spatial heterogeneity in action potential duration (APD)*

Cardiac muscle has local nonlinear properties due to the membrane's electrical properties. It also has a diffusive interaction owed to electrical current flow in and between cells that form an electrical syncytium. Its response to a localized subthreshold perturbation is localized and decremental, whereas the response to a localized suprathreshold perturbation is the so called action potential (i.e. the sequence of depolarization and repolarization of the plasma membrane, which separates the cell from its surroundings). The action potential of an excitable cell is generated by several ionic membrane currents associated with the ion channels and pumps. Knowledge of the intrinsic membrane properties is required for a complete understanding of how the heart works, given that heart rhythm is controlled by the ion channel activity in the constituent cells as well as the global nature of a network system. In healthy hearts, the heterogeneous distribution of ion channels produces spatial variations in APD [Baker *et al.*, 2000]. Recently, several studies addressed VF-to-VT transitions by studying the role of APD on fibrillatory dynamics. Some of them suggest [Dorian & Newman, 1997; Qi *et al.*, 1999] that it is possible to alter the arrhythmia dynamics by altering the APD.

The cardiac muscle is unique among the excitable tissues of the human body: the muscle cells in the heart must coordinate their contraction. This mechanism of coordination includes the electrical interaction between cells by the spatiotemporal behavior of the action potential. Conduction in the heart muscle occurs by local circuits that are controlled by the inward current, the transmembrane voltage and the geometry of the muscle to be excited. Propagation of the cardiac action potential from one point to the remainder of the cell and to the heart as a whole depends additionally on the characteristics of the entire cell and its neighbors. Excitation of one fiber results in a propagating wave of excitation that spreads to all fibers and to the entire heart, activating an effective contraction in an all-or-none fashion.

Several studies have suggested [Garfinkel *et al.*, 2000; Riccio *et al.*, 1999] that the manifestation of the VF and VT is determined by the property of restitution of the cardiac APD. Restitution refers to the fact that APD and the conduction velocity both depend on the previous diastolic interval, which is the rest period between repolarization and the next depolarization of the plasma membrane [Garfinkel *et al.*, 2000]. Meanwhile, in the LR model, APD restitution is the major determinant of spiral wave behavior and instabilities arising from APD restitution are the main determinants of spiral wave breakup [Qu *et al.*, 2000]. The major effect of fiber rotation is to maintain twist in a spiral wave, producing filament bending and spiral breakup; fiber rotation also induces curvature changes in the spiral wave, which weakens conduction and further facilitates wave break [Qu *et al.*, 2000]. Combined experimental and theoretical work has shown [Weiss *et al.*, 2002] that the APD restitution and conduction velocity contribute to breakup of reentrant wave fronts during cardiac fibrillation independent of preexisting electrophysiological heterogeneity in the tissue.

Recently Xie *et al.* [2001a] investigated how dynamic factors and fixed electrophysiological heterogeneity interact to promote wave break in simulated two-dimensional cardiac tissue, using the LR model. The degree of dynamic instability was controlled by varying the maximal amplitude of the slow inward calcium current to produce spiral waves in homogeneous tissue that were either nearly stable, meandering, hypermeandering or in breakup regimes; fixed electrophysiological heterogeneity was modeled by randomly varying APD over different spatial scales to create dispersion of refractoriness. They found that the degree of dispersion of refractoriness required for inducing wave break decreased markedly as dynamic instability of the cardiac model increased. These findings suggest [Xie *et al.*, 2001a] that reducing the dynamic instability of cardiac cells by interventions, such as decreasing the steepness of APD restitution, may still have some merit as an antifibrillatory strategy. Ten Tusscher and Panfilov [2003] emphasized recently the importance to study the heterogeneity of cardiac tissue as a factor determining the initiation and dynamics of cardiac arrhythmias. They showed that a gradient of APD resulted in spiral wave drift, which consisted of the following two components: the longitudinal (along the gradient) component was always directed toward regions of longer spiral wave period; the transverse (perpendicular to the gradient) component had a direction dependence on the direction of rotation of the spiral wave.

2.2. *Structural sites for heterogeneity in the heart*

Recently, using spectral analysis of optical epicardial and endocardial signals from sheep ventricular slabs, Zaitsev *et al.* [2000] concluded that ventricular fibrillation may be the result of a sustained high frequency three-dimensional intramural spiral wave, which creates a highly complex pattern of activation when wave fronts emanating from it fragment, as a result of interaction with the heterogeneity present in the cardiac tissue.

The peculiar electrical properties of the heart determine most of its special mechanical properties, whose primary function is to pump blood to all parts of the body. The main function of the blood circulation is the distribution of essential constituents to the tissues throughout the body and the elimination of noxious products, mainly through the lungs and kidneys; the heart propels unoxygenated blood to the lungs and delivers oxygenated blood to the peripheral tissues. The heart beat rate under different circumstances and in different persons varies a lot, even so under normal conditions the heart action is automatic, which means that it does not depend upon external impulses to initiate its contraction at the rate of about 70–80 times per minute. Although each cardiac cell is surrounded by high-resistance membrane, the cardiac muscle, because of the low-resistance pathways allowing for current flow between cells, behaves electrically as a continuous medium on a macroscopic-size scale. The pattern of spread of excitation in the heart determines the complex sequence of mechanical events that contribute to the proper functioning of this muscle as an effective pump for producing a unidirectional flow of blood. For pumping, the heart must both contract and relax synchronously, and normally the electrical impulse that initiates the heart beat arises at the plasma membrane of the sinoatrial (SA) node — the natural pacemaker of the heart, located in the upper region of the right auricle.

The SA node responds to a variety of external stimuli, including activity of the vagus nerve, whose brief bursts of activity cause the release of acetylcholine (ACh) in the vicinity of SA cells. The Ach then interacts with membrane receptors, resulting in an increase in conductance of the plasma membrane to potassium ions, leading to hyperpolarization of the membrane of the SA cells. In tissue preparations and in mathematical models, this membrane effect can either prolong or shorten the cycle length of the sinus pacemaker, depending upon the phase of the cycle at which it occurs and the magnitude of the intrinsic cycle length [Jalife *et al.*, 1983; Michaels *et al.*, 1984]. Under conditions where the heart rate is normal and higher (and the intrinsic cycle length is short), vagal pulses can produce a delay in the next spontaneous discharge, and the delay increases in magnitude as the pulse occurs later in the cycle; when the cycle length is long (i.e. at a slow heart rate), vagal pulses accelerate the next spontaneous discharge. It was shown by Winfree [1980] that the most important factor underlying the dynamics of the response of a pacemaker to external perturbations is the phase dependence of the effect, which should include that of the Ach. Such phase dependence means that the degree to which the pacemaker will be speeded up or slowed down depends upon the time during the pacemaker cycle at which the perturbation occurs.

The heart is a multicellular muscle. The SA node is a system of oscillators comprised of thousands of electrically coupled cells, each of which is a biological pacemaker capable of generating spontaneous action potentials, but they communicate with each other and synchronize their activity to generate a propagated impulse. The rate of the heart beat is regulated by the firing rate of this spontaneous electrical activity, and it is thus clear that the cell membrane exerts tight control over the contractile machinery. From the SA node the impulse spreads rapidly over the auricles and causes both auricles to contract simultaneously. Normally the atrioventricular (AV) node, which is located in the lower region of the right auricle, is the sole egress for the propagation of auricles impulse to ventricles. The AV node delays the impulse and the AV nodal activation is followed by rapid depolarization of the specialized conduction fibers that make up the ramifying His–Purkinje network. Purkinje fibers distribute the impulse from the ends of the bundles to the ventricular muscle. There are many anatomical and electrophysiological differences between the Purkinje cells of the conducting system and the ventricular muscle cells of the ventricular wall, since the junctional process between Purkinje and ventricular muscle tissue is spatially discontinuous; the transmission process occurs only at some discrete sites of the endocardial wall, but the arrangement is such that both ventricles are stimulated to contract simultaneously.

2.3. *Anisotropic electrical conduction*

Cardiac impulse propagation is heterogeneous by nature. In addition, the anatomical and biophysical properties of the normal auricle and ventricular muscle fibers depend on the direction in the cardiac syncytium in which they are measured, thus these properties are anisotropic [Wit *et al.*, 1990]. Simulations of heterogeneity along one-dimensional cable due to geometrical change or to altered cell coupling have shown conduction delays with the possibility of block or reflection; such irregularities in conduction have been considered relevant to cardiac reentry phenomena [Rinzel, 1990]. The velocity of propagation of electrical impulses is an anisotropic property of cardiac tissue, since it is faster in the direction along the long axis of the myocardial fibers than in the direction perpendicular to this axis; the impulse propagates about three to five times faster in the direction parallel to the long axis of the myocardial fibers than in the transverse direction [Clerc, 1976]. The shape of the upstroke of the action potential across the plasma membrane depends on the direction of the impulse: fast action potential upstrokes are associated with slow propagation velocities transverse to the longitudinal fiber axis, and slower upstrokes are associated with higher velocities in the longitudinal direction [Spach *et al.*, 1981; Spach, 1983].

An important feature of the geometry of the ventricles is that the cardiac fibers are oriented parallel to each other and conduction of the cardiac impulse is strongly influenced by the microarchitecture of the myocardium [Allessie *et al.*, 1990]. The impulse propagation by the main branches and Purkinje fibers is very fast; the conduction rate of the AV node is slow, which allows the auricles sufficient time to finish their contraction before the contraction of the ventricles, which is necessary for a properly coordinated heart action. Thus, the AV node is a key element of the specialized conduction system of the heart. Normally the various muscle fibers of each ventricle contract in an orderly, coordinated manner, so that by their united action the pressure in the cavity is increased and the blood expelled.

The normal heart beats normally at a fairly regular rate, but under abnormal condition, it may beat irregularly, at fast rates, leading quickly to death [Gray & Jalife, 1996]. The perturbations in blood gases, electrolytes, drugs and heart structural integrity can change the cardiac rhythms. When the fibers no longer act in coordination, some contracting before others and relaxing while the latter are in contraction, the cardiac muscle contracts asynchronously, and this is known as fibrillation. Atrial fibrillation is the commonest clinical arrhythmia and is associated with substantial morbidity and mortality; VF is the main mechanism of sudden cardiac death [Hassaguerre *et al.*, 2002; Peters *et al.*, 2002]. Because of the lack of harmonious action, electrical impulses traverse the ventricles so rapidly that a disordered and ineffective contraction occurs, with the result that the heart actually stops beating and fails to eject blood into the circulation system. In human beings, VF is usually irreversible, and since it causes the coronary circulation through the heart muscle to fail, it is fatal. An interruption in coronary circulation results in an insufficient supply of oxygen to the heart muscle, because the cardiac tissue is supplied with blood by the coronary arteries.

VF has been shown to be induced repeatedly in normal ventricles by a single, critically-timed electrical stimulus of appropriate strength [Chen *et al.*, 1988; Karagueuzian & Chen, 2001]. Three-dimensional studies in intact canine ventricles have shown that shock-induced VF in the normal ventricles is initiated by the immediate formation of a single functional reentrant wave front of excitation, which breaks down into multiple reentrant sources that signal the onset of VF [Chen *et al.*, 1988; Karagueuzian & Chen, 2001]. The timing of the electrical shock plays a crucial role in restoring normal rhythmicity [Krinsky *et al.*, 1990]; successful defibrillation results when an electrical stimulus fails to induce reentry and, conversely, failed defibrillation is analogous to successful formation of reentry [Efimov *et al.*, 1998; Karagueuzian & Chen, 2001]. It has been shown by Karagueuzian and Chen [2001] that a relationship exists between a shock that fails to defibrillate a fibrillating ventricle and a shock that induces reentry and VF during a regular rhythm.

By using potentiometric dye and video imaging to record the dynamics of transmembrane potentials from a large region of the heart, Gray *et al.* [1998] showed that there is a spatiotemporal organization underlying cardiac fibrillation in the whole heart. Analysis of optically recorded irregular electrical wave activity on the surface of the heart during experimentally induced fibrillation revealed local temporal periodicity [Biktashev *et al.*, 2002].

There is some determinism during fibrillation and stroboscopic phase maps reveal the sources of fibrillation to be topological defects around which spiral waves rotate; transmembrane signals at each site exhibit a strong periodic component centred near 8 Hz [Gray *et al.*, 1998]. The size and dynamics of the core around which reentrant waves rotate is an important factor that determine whether the arrhythmia is VF or VT [Samie *et al.*, 2000]. A mechanism for wave break developed by Fenton and Karma [1998] focuses on the fact that propagation within the three-dimensional myocardium is highly anisotropic, owing to the intramural rotation of the fibers, producing instability of the organizing centre, which results in its multiplication after repeated collisions with the heart boundaries.

Some forms of fibrillation depend on the uninterrupted periodic activity of discrete reentrant circuits. It has been suggested by several authors that VF is the result of a high frequency stable source [Gray *et al.*, 1998; Jalife *et al.*, 1998; Samie *et al.*, 2000; Zaitsev *et al.*, 2000]; the complex patterns of activation are the result of the fragmentation of emanating electrical activity from that source within the ventricular wall, which has a laminar structure. During the course of fibrillation, the number of reentrant sources increases with time, to fluctuate about some mean [Biktashev *et al.*, 2002]. The connections between neighboring sheets of ventricular tissue might form the anatomical sites for the heterogeneity that produces the n-furcations of the initial source impulse [Biktashev *et al.*, 2002]. VF usually begins with a more orderly state, consisting of just one or a pair of spiral waves, which then breakdown into the multispiral disordered state that is VF [Chen *et al.*, 1988]. Individual waves in VF have short lifetimes, such as less than half a second [Cha *et al.*, 1994]. Thus, the breakdown into VF and the continued maintenance of VF require a continual formation of new waves, through the process of wave break, in which a single wave splits into two [Garfinkel *et al.*, 2000].

As said before, there has been substantial experimental evidence suggesting that the electrophysiological and anatomical heterogeneity is the cause of wave break. On the other hand, the dynamic heterogeneity resulting from the property of restitution of the cardiac APD may be more critical for the production of VF than the fixed electrophysiological and anatomical heterogeneity, even if it is not always true [Garfinkel *et al.*, 2000; Qu *et al.*, 1999; Weiss *et al.*, 1999].

2.4. *Effect of ischaemia on the spatial cardiac heterogeneity*

The factors that increase the initial spatial heterogeneity in the electrical properties of heart muscle all make it easier to induce certain cardiac arrhythmias. For instance, myocardial ischaemia greatly increases the electrical heterogeneity of ventricular tissue and often triggers life-threatening cardiac arrhythmias such as VT and VF [Xu & Guevara, 1998]. Regional ischaemia can be simulated by raising the external potassium concentration (hyperkalemia) from its nominal value of 5.4 mM in ventricular muscle, thus creating a localized heterogeneity [Xie *et al.*, 2001b; Xu & Guevara, 1998]. The cardiac signs of plasma hyperkalemia are bradycardia, followed by peripheral vascular collapse, and heart arrest.

When the hyperkalemia is sufficiently high (e.g. 20 mM) in the abnormal region, there is a complete block of propagation of the action potential into that region, resulting in a free end or wave break as the activation wave front encounters the abnormal region; with lower hyperkalemia (e.g. 10.5 mM) in the abnormal region, there is partial propagation in and out of the abnormal region [Xu & Guevara, 1998]. In this case, a different kind of spiral wave can be evoked, implying backward propagation of the action potential through the abnormal region, where the number of turns made by the wave depends on the level of external potassium concentration within the abnormal region and its physical size [Xu & Guevara, 1998].

In two-dimensional simulations with a central ischaemic region, reentry, once initiated, was destabilized by the heterogeneity; in general the possibility to reentry increased as the heterogeneity of the fiber increased, although under some conditions it decreased below the level for uniform tissue [Clayton *et al.*, 2002]. The hyperkalemic ischaemic region produces wave break in the surrounding normal tissue by accelerating the rate of spiral wave reentry, even after the depolarized ischaemic tissue itself had become unexcitable and regional hyperkalemia during acute myocardial ischaemia is a major cause of electrophysiological abnormalities leading to VF [Xie *et al.*, 2001b].

3. The Model

It is clear from Sec. 2 that it is very important to model the effect of heterogeneity on the complex

dynamics of the heart. Thus, we simulate the effect of heterogeneity on the stability of an initiated spiral wave within the cardiac tissue, by using the two-dimensional modified FitzHugh–Nagumo membrane model, which describes the interaction of an activator field $u\ (t, x, y)$ with an inhibitor field $v\ (t, x, y)$ via the following partial differential equations:

$$\begin{aligned} \frac{\partial u}{\partial t} &= D \bigtriangledown^2 u + \frac{1}{\varepsilon} u(1-u)\left(u - \frac{v+b}{a}\right), \\ \frac{\partial v}{\partial t} &= f(u) - v\,, \end{aligned} \tag{1}$$

where $D = 0.5$, $a = 0.84$, $b = 0.07$ and the function $f(u)$ has the form

$$f(u) = \begin{cases} 0\,, & 0 \le u < 1/3\,, \\ 1 - 6.75u(u-1)^2\,, & 1/3 \le u \le 1\,, \\ 1\,, & 1 < u\,. \end{cases} \tag{2}$$

In order to reflect the heterogeneity of the tissue, we set the parameter ε as a function of the tissue as follows:

$$\varepsilon(x, y) = \begin{cases} \varepsilon_1\,, & r \le r_1\,, \\ \varepsilon_1 + \Delta\varepsilon(r - r_1)\,, & r_1 < r \le r_2\,, \\ \varepsilon_2\,, & r > r_2\,, \end{cases} \tag{3}$$

where $r = \sqrt{(x - L_x/2)^2 + y^2}$, $\varepsilon_2 = \varepsilon_1 + \Delta\varepsilon(r_2 - r_1)$ and r_1, r_2, ε_1 and $\Delta\varepsilon$ are fixed parameters. L_x is the tissue size in the x-direction. Equation (1) is integrated by an explicit scheme with time step $\Delta t = 0.01$ and spatial grid size $\Delta x = \Delta y = 0.25$. The tissue size ($L_x \times L_y$) is fixed at 50×62.5 (200×250). No-flux boundary conditions are used in all simulations. We apply this procedure to study the reentry dynamics in the homogeneous tissue and in the heterogeneous one. The surface patterns of this "numerical fibrillation" demonstrate the same qualitative features as the patterns observed in optical mapping experiments [Biktashev *et al.*, 2002].

4. Results and Discussion

Here, we show that the reentry dynamics in heterogeneous tissue is very complex and this makes it more interesting. The reentry activity depends on the strength as well as the position of the heterogeneity and on the place where the reentry is initiated. When the heterogeneity is strong enough and the spiral reentry is initiated in the short cycle length region, spiral wave breakup induced by the heterogeneity occurs even if the parameters in the whole heterogeneous tissue are in a nonbreakup regime of a homogeneous tissue. Although this type of spiral wave breakup is found based on a two-dimensional modified FitzHugh–Nagumo membrane model and a heterogeneity function, it is independent of the specific model and the heterogeneity function. Thus, our results are generic in heterogeneous media and can be applied to excitable media such as autocatalytic chemical reactions such as the Belousov–Zhabotinsky reaction [Winfree, 1972] and aggregates of slime-mold [Siegert & Weijer, 1991]. Cardiac fibrillation is obviously a more complex process than the numerical mechanisms considered above. On the other hand, some qualitative results can be obtained for simpler models, which caricature the electrophysiological and anatomical heterogeneity in the cardiac tissue. Our investigation focuses on a model that we believe provides a useful way to understand the cause of abnormal cardiac rhythms in spite of its simplicity.

4.1. *Reentry dynamics in homogeneous tissue*

Several interesting features of spiral waves such as stable spiral waves, meandering spiral waves and spiral wave breakup, and their transition mechanisms have been extensively studied in homogeneous media, based on various simple and complex models [Bar & Eiswirth, 1993; Strain & Greenside, 1998; Winfree, 1994]. The spiral wave reentry dynamics in homogeneous systems present a complicated and interesting problem [Bar & Eiswirth, 1993; Strain & Greenside, 1998]. When $\Delta\varepsilon = 0$ or $r_1 = r_2$, Eq. (1) represents the homogeneous tissue. As ε is continuously varied from zero, several transitions of the reentry activities occur. For $\varepsilon \le 0.054$, the reentry is a stable spiral wave; for $0.054 < \varepsilon \le 0.069$, the reentry behavior displays meandering spiral waves; and for $\varepsilon > 0.069$, the spiral wave is broken into multiple wavelets producing complicated spatiotemporal disorder reentry activities. Spiral wave activities for $\varepsilon = 0.035$, 0.047, 0.065, 0.080 are shown in Figs. 1(a)–1(d), respectively. The corresponding trajectories of the tip of the wave or tip (wavelet) number are shown in Figs. 1(e)–1(h), while the Poincáre plots of cycle length (or period of the reentry) are presented in Figs. 1(i)–1(l). It is clearly observed that these reentry activities are essentially different. The motion of the tip of the spiral wave in Figs. 1(e) and 1(f)

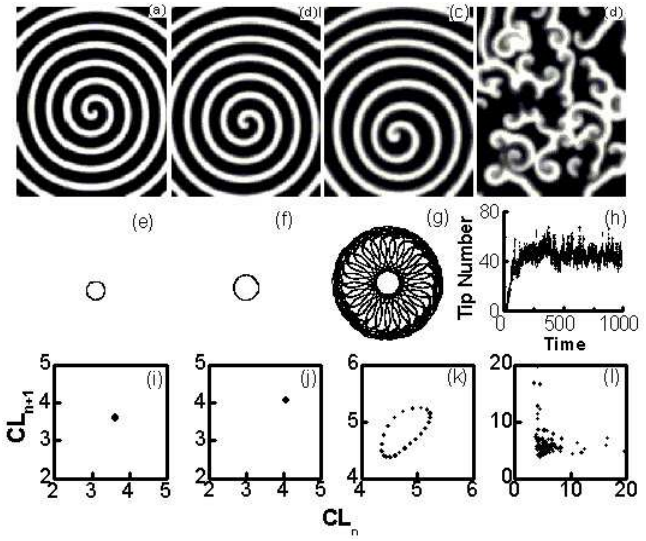

Fig. 1. Reentry dynamics in homogeneous tissue: (a)–(d) Snapshots of the reentry activities with density, $u(x, y)$, values (1–0) (values decreasing from white to black) for $\varepsilon = 0.035$, 0.047, 0.065, 0.080, respectively. (e)–(h) The tip trajectory or tip number versus time corresponding to (a)–(d), respectively. (i)–(l) Cycle length return maps corresponding to (a)–(d), respectively.

is a complete circle, and their corresponding circle length Poincáre plots in Figs. 1(i) and 1(j) are fixed points, which characterize the reentry as a stable spiral wave. The tip trajectory in Fig. 1(g) traces an epicycloidal-shaped flower petal, and the corresponding cycle length Poincáre plot in Fig. 1(k) displays a perfect ring-like structure. This reentry is known as a meandering spiral wave. For $\varepsilon = 0.080$, the initial spiral wave was quickly broken up into very complicated multiple wavelets, which are shown in Fig. 1(d) after several rotations. The tip number first increases linearly, and then it fluctuates around 45 in a complicated fashion. This averaged tip number depends on the simulated tissue size. The corresponding Poincáre plot in Fig. 1(l) is completely disordered. These characteristics show that the reentry activity is fully spatiotemporally chaotic.

4.2. *Reentry dynamics in heterogeneous tissue*

As $\Delta\varepsilon \neq 0$ and $r_1 \neq r_2$, Eq. (1) represents the heterogeneous tissue. Some studies [Lee, 1997; Vinson, 1998] have shown that this heterogeneity significantly influences the behavior of spiral wave reentry. We fixed $\varepsilon_1 = 0.02$, $\Delta\varepsilon = 0.0006$, and $r_1 = 60$ throughout this paper. Thus, the strength of the heterogeneity depends on the parameter r_2, and so does ε_2. When r_2 increases continuously starting from r_1, the spiral wave reentry dynamics displays a more complex structure and becomes more interesting than that in homogeneous tissue. In the latter, the spiral wave dynamics is invariant under translational and rotational transformations. But for heterogeneous tissue, this symmetry is broken owing to the heterogeneity. In fact, the reentry dynamics strongly depends on the actual location where the spiral wave initiates. Figures 2(a)–2(d) show four sets of snapshots of the reentry activities initiating at the lower part of the tissue (region with $\varepsilon = \varepsilon_1$) and the corresponding cycle lengths for $r_2 = 20$, 45, 75, 100, i.e. $\varepsilon_2 = 0.032$, 0.047, 0.065, 0.080, respectively. The cycle lengths represented by the square, solid circle, and solid triangle in the corresponding right-hand graphs, are measured from the lower ($\varepsilon = \varepsilon_1$), middle ($\varepsilon$ linear increasing region), and upper ($\varepsilon = \varepsilon_2$) regions, respectively.

The following characteristics are worth commenting on. First, the spiral wave reentry in Fig. 2(a) always keeps a single stable spiral wave. The corresponding cycle lengths in the three different regions are quickly asymptotic to the unique cycle length 2.84 in the lower region, where the tip of the spiral wave is located. But it is very surprising that, although all values of ε of the tissue are within the values of ε where the spiral waves do not breakup for a homogeneous tissue, the wave front of the spiral wave initiated in the middle region in Figs. 2(b)–2(c) was broken up into multiple spiral waves, which creates complicated spatiotemporal reentry activities. The part of the spiral wave in the lower region is still stable, which produced the small constant cycle length 2.84 after a short transient time, as shown in the cycle length plots in Figs. 2(b) and 2(c). However, in the middle region, the cycle length of the electric wave is irregular owing to the irregular multiple wavelet interactions [the solid circles in Figs. 2(b) and 2(c)].

The most striking new result is that the wavefronts in the upper region finally arrive at a stable propagation with large constant cycle lengths 4.06, 4.26, for Figs. 2(b) and 2(c), respectively, showing self-organization after the transient period. Thus, after the spiral wave was broken up, the system displayed a nonuniform cycle length distribution. As r_2 increases, and ε_2 also becomes large enough, the wavefront of spiral wave in the upper region is also broken up and produces complete disordered

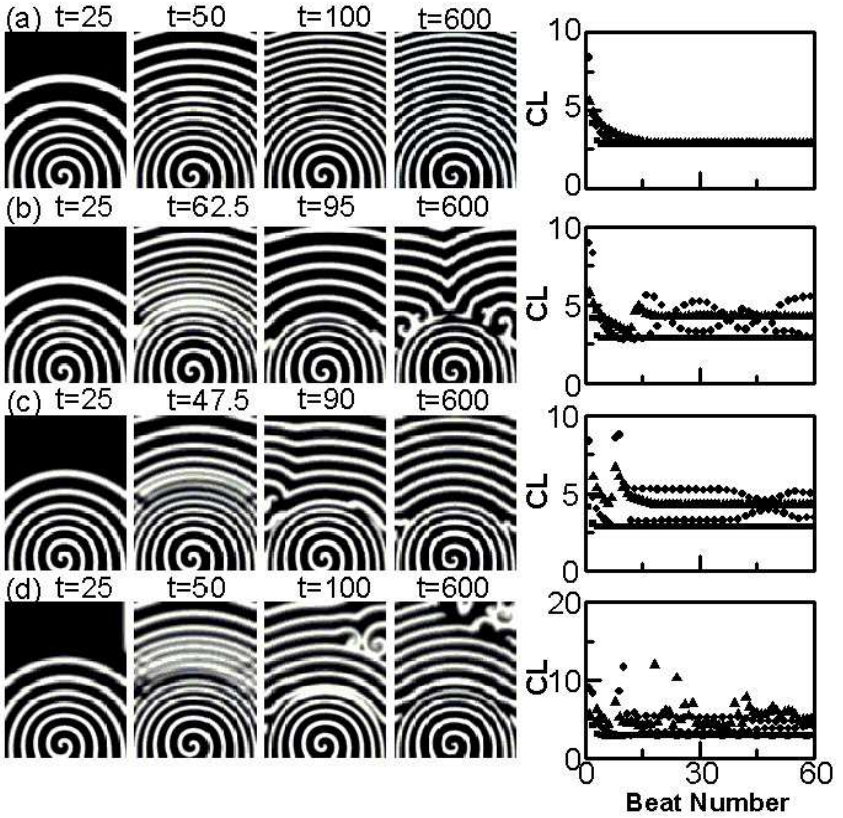

Fig. 2. Reentry dynamics in heterogeneous tissue. Different time snapshots of reentry activities with density, $u(x, y)$, and the corresponding cycle length plots versus beat number for various ε_2. (a) $\varepsilon_2 = 0.032$; (b) $\varepsilon_2 = 0.047$; (c) $\varepsilon_2 = 0.065$; (d) $\varepsilon_2 = 0.080$. The spiral wave is initiated at the lower region of the heterogeneous tissue. The square, dot, triangle represent the cycle length measured from the lower, middle and upper areas of the heterogeneous tissue, respectively.

reentry activity in both middle and upper regions. However, the reentry dynamics in the lower region still remains that of a stable spiral wave. The snapshots of this disorder reentry activity are shown in Fig. 1(d) for $r_2 = 100$, $\varepsilon_2 = 0.080$. It is very clear that the reentry behaviors and cycle lengths in the upper and middle regions are complicated and irregular, but the cycle length in the lower region stays at the same constant value 2.84 as in Figs. 2(a)–2(c).

When the spiral wave starts at the upper border of the tissue, we find a startling result: the reentry dynamics is essentially different from that shown in Fig. 2. These reentry activities with the initiated location at the upper region are shown in Fig. 3, where all the respective parameters are exactly the same as those of Fig. 2. In Fig. 3(a), although the reentry is also a single stable spiral wave, the unique cycle length 3.59 of the spiral wave is selected by the core of spiral wave in the upper region (ε_2), and is larger than the value 2.84 in Fig. 2(a). Instead of the breakup of the waves in the middle region, as shown in Figs. 2(b) and 2(c), the reentry dynamics in Figs. 3(b) and 3(c) always keeps a single spiral wave. The cycle length of the spiral wave in Fig. 3(b) is also constant 4.06, and different from that in Fig. 2(b). Thus, the spiral wave is still stable. On the other hand, in Fig. 3(c), since the value of ε_2 is in the meandering region of a homogeneous tissue and the cycle lengths in the three regions are the same, it oscillates as a function of the beat number. Thus the spiral wave is still meandering. Figure 3(d) corresponds to the breakup region of a homogeneous tissue since $\varepsilon_2 = 0.080$ and the initiated spiral wave is quickly broken into very complicated state of multiple spiral waves. It is interesting to note that two spiral waves are stabilized near the left and right boundaries of the lower region after a long time. The regular motion in the lower region is also clear in the cycle length plots (square) on the right of Fig. 3(d), where it has arrived at a constant value after the transient time. Therefore, when the spiral wave is initiated in the upper region of the tissue, the heterogeneity cannot

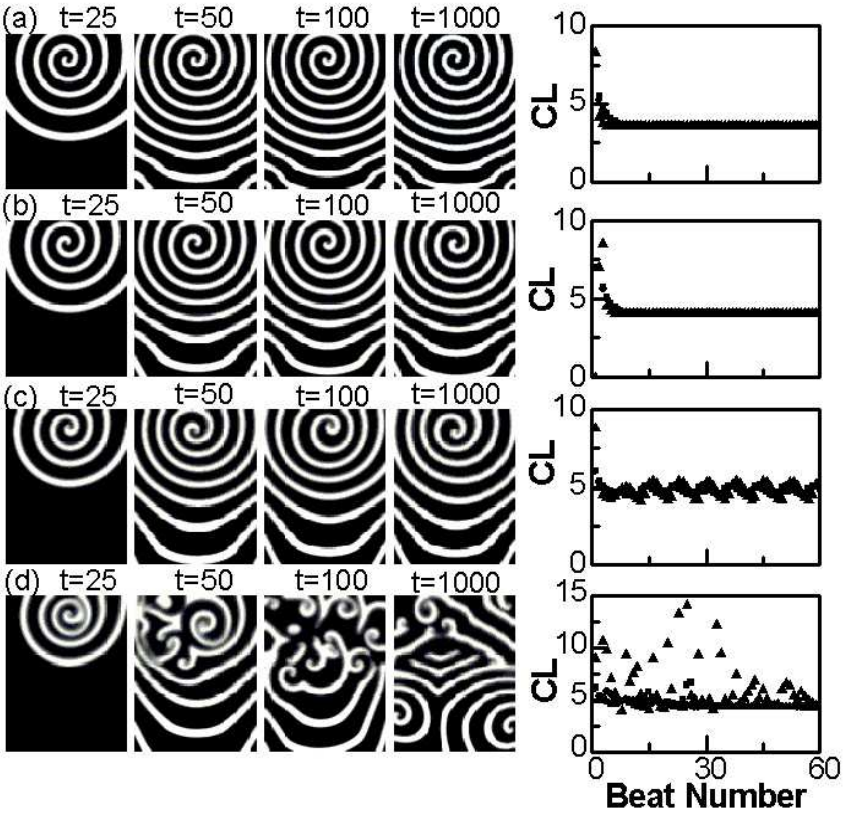

Fig. 3. The same as Fig. 2 except that the spiral wave is initiated in the upper region of the heterogeneous tissue. It is clear that the reentry activities are essentially different from those in Fig. 2.

cause its breakdown in spite of the strength of the heterogeneity.

4.3. *Lyapunov exponent*

The Lyapunov exponent can be used to distinguish periodicity, quasiperiodicity and chaos [Wolf *et al.*, 1985]. The maximum Lyapunov exponents versus ε_2 are shown in Fig. 4. The solid circles represent the exponents for homogeneous tissue ($\varepsilon = \varepsilon_1 = \varepsilon_2$), open circles those of a heterogeneous tissue with spiral waves initiated at the lower region, while triangles correspond to heterogeneous tissue with spiral waves starting in the upper region. Two important characteristics are clearly observed in Fig. 4. First, the transition of the Lyapunov exponent from zero to a positive value, i.e. from a single spiral wave to spiral wave breakup, for a homogeneous tissue is equal to that of a heterogeneous tissue with a spiral wave initiated in the upper region, and it occurs at $\varepsilon_2 \approx 0.069$. Second, as the spiral wave is initiated in the lower region in a heterogeneous tissue, the transition is near $\varepsilon_2 \approx 0.0422$, earlier than that in the other two cases. The first transition is originated by the core instability of the spiral wave. For the latter, the transition to a spiral wave breakup is completely induced by the heterogeneity.

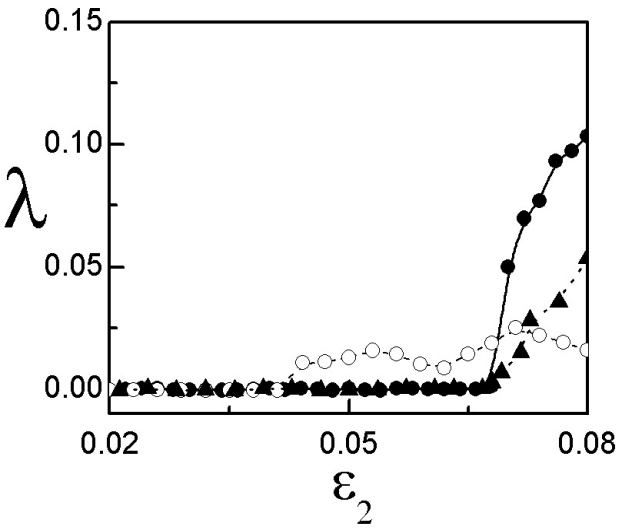

Fig. 4. The Lyapunov exponents versus ε_2 for homogeneous tissue (solid circle), heterogeneous tissue with spiral wave initiated in the lower region of the tissue (open circle) and in the upper region of the tissue (triangle).

The mechanism of the spiral wave breakup as the one above can be explained as follows. In a

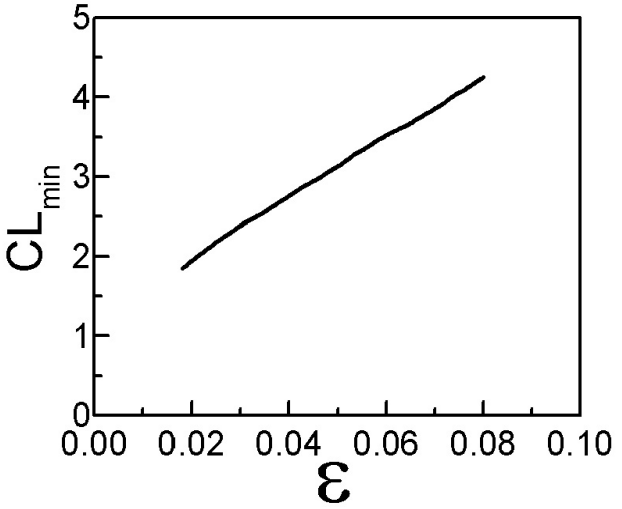

Fig. 5. The minimum cycle length of the propagated wave in one-dimensional ring tissue versus ε.

homogeneous tissue, for each fixed parameter ε, each wave has a minimum cycle length ($CL_{\min}$). The wave can successfully propagate in the excitable tissue only up to $CL_{\min}$, otherwise it will fail. The $CL_{\min}$ versus ε measured from one-dimensional ring simulation is shown in Fig. 5. It increases linearly with ε. In a heterogeneous tissue, the wave propagation in different regions has different $CL_{\min}$. In Figs. 2 and 3, the parameter ε in the lower region is equal to 0.02, and smaller than those in the other regions. As the spiral wave starts in the lower region, the cycle length of the spiral wave is 2.84. Under this cycle length, the maximum value of ε in the tissue where the wave can propagate is near 0.0422 or $r_2 = 37$, as shown in Fig. 5. As ε_2 is beyond 0.0422, the wave in that region cannot propagate, so it must be broken up into multiple wavelets after the transient propagation time. This critical value for ε_2 for this transition is exactly the same as that in Fig. 4. When the spiral wave initiates at a high ε region [upper region in Figs. 3(a)–3(d)], the cycle length selected by the initiated spiral wave is greater than all $CL_{\min}$ of the low ε region. Thus, the wave can always propagate through the whole tissue. In this situation, the heterogeneity cannot induce spiral wave breakup. The spiral wave breakup also originates from the core instability. The transition point is therefore exactly the same as that in a homogeneous tissue.

5. Concluding Remarks

We studied the effect of heterogeneity on spiral wave propagation based on a two-dimensional modified FitzHugh–Nagumo membrane model in an attempt to model the complex dynamics of the heart. The heart is a three-dimensional anisotropic medium, whose electrical activity changes with time and cardiac impulse propagation is heterogeneous by nature. There has been substantial experimental evidence favoring theoretical predictions of the propagation of spiral waves in cardiac muscle and the generation of wave breakup may play an important role in cardiac arrhythmias. We show that the reentry activity depends on the strength as well as the position of the heterogeneity and on the place where the reentry is initiated. When the heterogeneity is strong enough and the spiral reentry is initiated in the short cycle length region, spiral wave breakup induced by the heterogeneity occurs even if the parameters in the whole heterogeneous tissue are in a nonbreakup regime of a homogeneous tissue. Owing to the complexity of the cardiac muscle, our result is an oversimplification of the real situation; even the model seems to reproduce some important features that are associated with the initiation of the VF. In practice, however, life is more complicated and an understanding of detailed mechanisms underlying complex dynamics in experimental and clinical situations requires an analysis of more realistic theoretical models. Our results are generic in heterogeneous media.

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