

Visualization of spiral and scroll waves in simulated and experimental cardiac tissue

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Abstract. The heart is a nonlinear biological system that can exhibit complex electrical dynamics, complete with period-doubling bifurcations and spiral and scroll waves that can lead to fibrillatory states that compromise the heart's ability to contract and pump blood efficiently. Despite the importance of understanding the range of cardiac dynamics, studying how spiral and scroll waves can initiate, evolve, and be terminated is challenging because of the complicated electrophysiology and anatomy of the heart. Nevertheless, over the last two decades advances in experimental techniques have improved access to experimental data and have made it possible to visualize the electrical state of the heart in more detail than ever before. During the same time, progress in mathematical modeling and computational techniques has facilitated using simulations as a tool for investigating cardiac dynamics. In this paper, we present data from experimental and simulated cardiac tissue and discuss visualization techniques that facilitate understanding of the behavior of electrical spiral and scroll waves in the context of the heart. The paper contains many interactive media, including movies and interactive two- and three-dimensional Java applets¹.

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1. Introduction

The heart is a complex nonlinear system in which an electrical signal triggers a mechanical contraction. Dysfunction of electrical impulse propagation gives rise to cardiac arrhythmias, diseases that subsequently impair pumping and can have immediately life-threatening consequences. Despite the importance of understanding the heart's behavior, visualization of the electrical dynamics of the heart remains a significant challenge, and many aspects of arrhythmias remain poorly understood. Nevertheless, sophisticated visualization techniques can help to elucidate the dynamics of cardiac tissue and to lead to improved understanding of the mechanisms that give rise to arrhythmias as well as innovative approaches to terminating them.

On a global level, the heart functions as a spatially extended excitable medium and has many properties in common with other excitable systems [1], including neural [2] and pancreatic beta cells [3], the Belousov–Zhabotinsky chemical reaction [4, 5], and the aggregation of the social amoeba *Dictyostelium discoideum* [6, 7], among others. Upon electrical stimulation, individual cardiac cells exhibit a highly nonlinear response in which their membrane voltage depolarizes, producing an action potential (AP), during which a surge in intracellular calcium initiates the mechanical contraction (see figure 1 and the corresponding movie). Cells are interconnected via gap junctions, thereby allowing propagation of these electrical excitations from cell to cell in tissue. In two and three dimensions (2D and 3D), spiral and scroll waves can arise following stimulation during the vulnerable window [8], during which the tissue

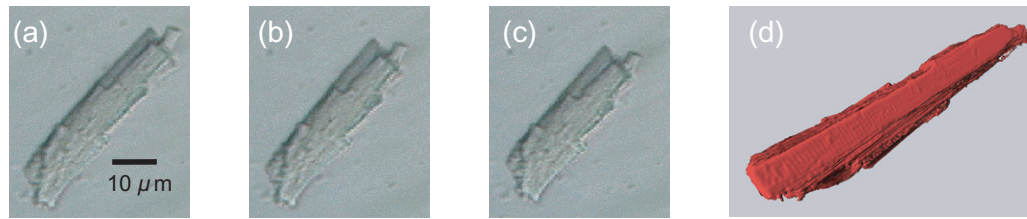


Figure 1. (a)–(c) Three snapshots showing a canine ventricular myocyte during contraction in response to an electric field pulse. 400 $\times$ magnification using a Nikon microscope. (d) 3D reconstructed canine ventricular myocyte obtained from a Z-stack using a Zeiss LSM-510 META confocal microscope. See [Figure_1ac_movie.gif](#) and [Figure_1d_movie.gif](#).

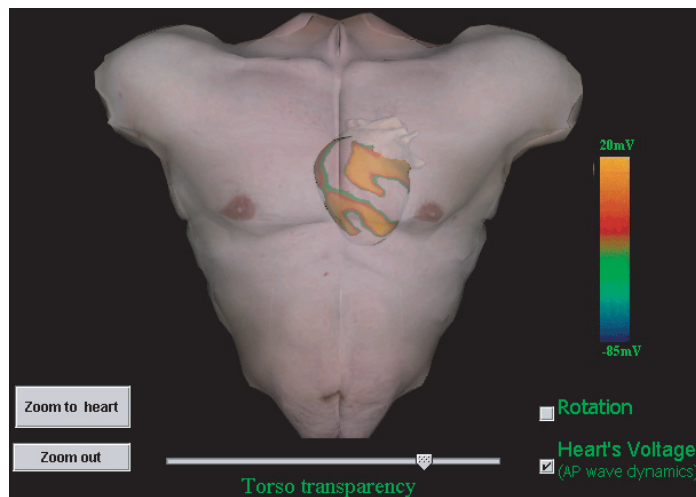


Figure 2. Visualization of human torso with heart in VF. The accompanying Java applet illustrates in 3D the complex electrical dynamics resulting from multiple reentrant waves (spiral waves) that render the heart unable to pump. In this and all following 3D applets, the structure depicted (here the heart and torso) can be rotated using the left mouse button, zoomed using the right mouse button, and panned using both the left and right mouse buttons. (For Macintosh users, the structure can be rotated using the mouse button, zoomed using the mouse button while pressing the control key, and panned using the mouse button while pressing the shift key.) See interactive Java applet [Figure2_applet.html](#).

is only partially refractory and the symmetry of propagation is broken. These spiral and scroll waves are life-threatening because they act as high-frequency sources and underlie complex cardiac electrical dynamics such as tachycardia and fibrillation (see figure 2 and the corresponding interactive 3D Java applet showing simulated ventricular fibrillation (VF)), which, when occurring in the ventricles, is responsible for the deaths of approximately 300 000 Americans each year [9].

Although the idea that electrical waves rotating around a functional region of block (spiral waves) are the primary sources of fibrillation emerged about three decades ago [10]–[14], the

exact mechanism or mechanisms responsible for the initiation and maintenance of fibrillation in the atria and ventricles [15]–[20] as well as for defibrillation efficacy [21]–[23] remain controversial. One of the main reasons for this is the difficulty in obtaining experimental data showing the behavior of these waves in whole hearts. The complicated structure of cardiac tissue together with the complexity of the cell dynamics have made it difficult to pinpoint the precise mechanisms of these life-threatening re-entrant arrhythmias.

Visualizing arrhythmias and cardiac electrical behavior experimentally poses a number of challenges. Although isolated cells and small tissue preparations can be studied using patch clamp or microelectrode techniques, investigating larger preparations or whole chambers involves different methods. Two primary methods of data acquisition are used: electrode arrays [24, 25] and optical mapping [26]–[29]. Electrode arrays use grids of electrodes to record from the tissue in multiple locations and thereby obtain electrical signals over a broad area. It is even possible to include multiple recording sites on a single electrode, so that information can be obtained not only from the surface of the tissue but also from the depth [30, 31]. However, the spatial resolution is often coarse, on the order of several millimeters, and the electrodes can damage the heart and potentially alter tissue responses [32]. In contrast, optical mapping uses voltage-sensitive dyes that fluoresce in proportion to the membrane potential and can provide data at much higher spatial resolutions, without the need for physical implantation of electrodes. Despite these advantages, optical mapping is still limited to surface recordings and is complicated by the fact that the response recorded represents multiple cells over some depth [33]–[35]. For both electrode arrays and optical mapping, interpretation of the data obtained can be difficult, and high-quality visualization techniques are crucial to gaining insights into tissue behavior.

Simulations of cardiac electrical behavior, on the other hand, are not associated with complications in data acquisition, because the values of all variables are known at all locations throughout the tissue. However, visualizing 3D data is still difficult. In 2D, a color can be used to represent voltage throughout the tissue, but in 3D this is no longer possible; the voltage can only be seen directly for cross-sections through the tissue. Nevertheless, other options become available. While in 2D a spiral wave can be characterized at a given time by the point at which the wave front meets the wave back (or phase singularity), in 3D scroll waves can be characterized similarly by the corresponding 1D vortex filament. Visualizing and characterizing the twist, torsion and curvature of these vortex filaments [36]–[38] provides a useful means of studying their global behavior within the tissue thickness.

In this paper, we bring together data from simulations of and experiments in cardiac tissue, survey the range of observed behaviors, and discuss methods of visualization of tissue-level phenomena. These visualization techniques not only provide access to the electrical dynamics of the heart, but also provide an opportunity to understand better the organizing structures and operative principles underlying cardiac arrhythmias.

2. Methods

2.1. Experimental methods

2.1.1. Cardiac preparations. All experimental procedures were approved by the Institutional Animal Care and Use Committee of the Center for Animal Research and Education at Cornell University. Experiments were performed using isolated arterially perfused sections of the

heart. Methods for obtaining the preparations have been described previously [39]. Briefly, after anesthesia with Fatal-Plus (390 mg mL^{-1} pentobarbital sodium; Vortex Pharmaceuticals; 86 mg kg^{-1} IV), hearts were excised rapidly via a left thoracotomy and placed in cold, aerated ($95\% \text{ O}_2$ – $5\% \text{ CO}_2$) Tyrode solution containing (in mmol L^{-1}): 124 NaCl , 4.0 KCl , 24 NaHCO_3 , $0.9 \text{ NaH}_2\text{PO}_4$, 2.0 CaCl_2 , 0.7 MgCl_2 and 5.5 glucose, adjusted to pH 7.4 with NaOH. The right or left coronary artery was cannulated using polyethylene tubing and the atrial and ventricular myocardium perfused by that artery was excised.

2.1.2. Optical mapping. As described in [40], electrical activity was assessed using voltage optical mapping using fluorescent imaging to map activation waves on the epicardial and endocardial surfaces. A transmural section of atrial and/or ventricular tissue typically measuring 3–5 cm wide, 3–9 cm long, and 1–3 cm deep was excised, perfused via the coronary artery, and placed in a heated transparent Plexiglas chamber superfused with normal Tyrode solution. Blebbistatin ($10 \mu\text{M}$) was added to the perfusate to prevent motion artifacts [41]. Perfusion pressure was 50–80 mm Hg, flow rate was 25 ml min^{-1} , and physiological temperature was maintained at 37.0 – 38.0°C . After equilibration, the preparation was stained with di-4-ANEPPS ($10 \mu\text{M}$), a voltage-sensitive dye.

For optical mapping, excitation light was produced by 18 high-performance light-emitting diodes (Luxeon III star, LXHL-FM3C, wavelength $530 \pm 20 \text{ nm}$), nine for the top view and nine for the bottom view, driven by a low-noise constant-current source. The illumination efficiency was enhanced significantly by collimator lenses (Luxeon, LXHL-NX05). The fluorescence emission light was collected by a Navitar lens (DO-2595, focal length 25 mm, F/No. 0.95), passed through a long-pass filter ($< 610 \text{ nm}$), and imaged by 128×128 back-illuminated EMCCD array (electron-multiplied charge coupled device, Photometrics Cascade 128+), a camera providing high quantum efficiency (peak QE $> 90\%$). The signal was digitized with a 16-bit A/D converter at a frame rate of 511 Hz (full frame, 128×128 pixels). The PCI interface provided high-bandwidth uninterrupted data transfer. An acquisition toolbox using C and Java was developed and used for experimental control, display, and data analysis, together with custom-made drivers for camera control and readout developed using C and OpenGL. The optical mapping system used here is described in more detail in [40].

2.1.3. Fibrillation initiation and defibrillation. Fibrillation was initiated using rapid pacing or a cross-field stimulation protocol. In atrial preparations, addition of acetylcholine (ACh) (1 – $6 \mu\text{M}$) generally was necessary to induce a sustained arrhythmia. Pacing stimuli were delivered using a WPI stimulator and stimulus isolator. Defibrillation was accomplished by applying an electric field from platinum plates ($60 \times 11 \text{ mm}^2$) on either side of the preparation 10 cm apart. Shocks were delivered from a custom-built power amplifier controlled by a function generator (Agilent 33220A).

2.1.4. Data analysis. Data were recorded in episodes lasting between 1 and 10 s. The data were subsequently processed to remove signal drift and normalized on a pixel-by-pixel basis.

2.1.5. Microelectrode recordings. As described in [39, 42], free-running Purkinje fibers as well as thin strips of epicardial or endocardial tissue were excised from either ventricle.

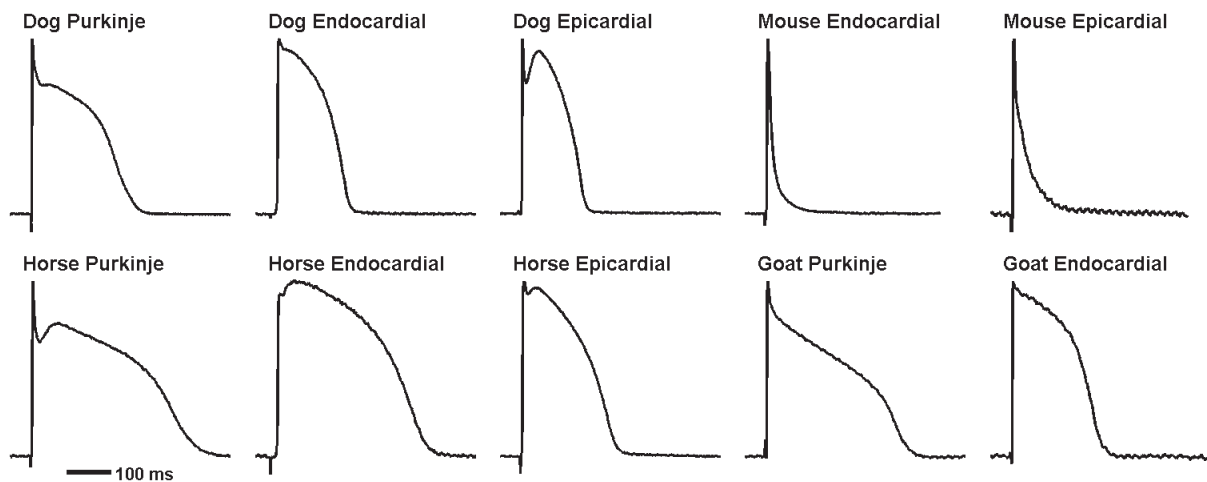


Figure 3. Experimental APs obtained using microelectrode recordings from different tissue preparations to illustrate the differences in shape and duration. All recordings were measured at 37 °C and were obtained after reaching steady state at a CL of 500 ms, except for the recordings in mouse endocardium and epicardium, which were obtained at a CL of 400 ms.

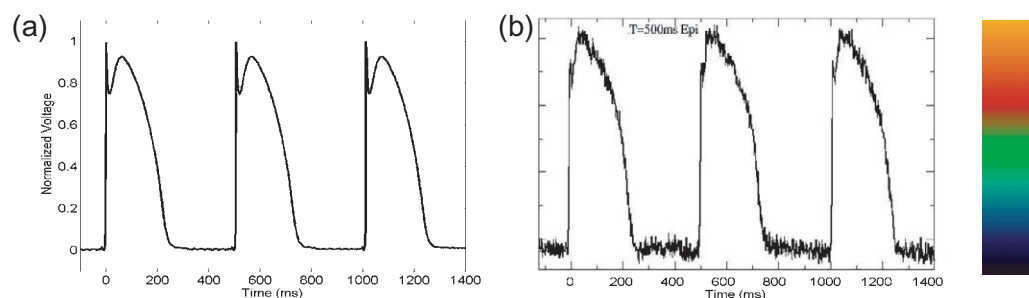


Figure 4. Canine epicardial APs obtained using microelectrodes and optical mapping. AP shapes and durations remain similar between the two techniques. The color-bar indicates the voltage mapping values related to color used throughout the rest of the paper.

The preparations were superfused with aerated (95% O₂–5% CO₂) Tyrode solution and were stimulated using rectangular pulses of 2 ms duration and 2–3 times the diastolic threshold current (0.1–0.3 mA) delivered through Teflon-coated bipolar silver electrodes. Transmembrane APs at different pacing cycle lengths (CLs) were recorded at 1 kHz using standard microelectrodes filled with 3 mM KCl. Examples of APs recorded at steady state in a variety of tissue preparations are shown in figure 3. Such APs exhibit much less noise and a more pronounced upstroke than those obtained using optical mapping, as shown in figure 4. Nonetheless, optical signals show similar AP shapes and durations.

2.1.6. Cell isolation. As described in [43, 44], a branch of the left anterior descending coronary artery was cannulated and part of the left ventricle excised and perfused with Tyrode

solution at 37 °C. After 10–15 min, the perfusate was switched to a Ca^{2+} -free solution containing (in mM) 118 NaCl, 4.8 KCl, 1.2 MgSO_4 , 1.2 KH_2PO_4 , 0.68 glutamine, 11 glucose, 25 NaHCO_3 , 5 pyruvate, 2 mannitol, and 10 taurine; pH 7.3. After another 3–5 min, collagenase (0.4 mg ml^{-1} ; type II, Worthington Biochemical) and BSA (0.5 mg ml^{-1} ; Sigma) were added to the perfusate. After 10–12 min, digested tissue was sliced away from the subepicardium, placed in 10 ml of enzyme solution, and swirled. The supernatant was collected, and 10 ml of fresh Ca^{2+} -free solution with 0.4 mg ml^{-1} collagenase and 0.5 mg ml^{-1} BSA was added and gently bubbled in a water bath maintained at 37 °C for a total of seven washes. After settling for 5 min, the final pellet was washed in 10 ml of incubation buffer containing (in mM) 118 NaCl, 4.8 KCl, 1.2 MgSO_4 , 1.2 KH_2PO_4 , 0.68 glutamine, 11 glucose, 20 NaHCO_3 , 5 HEPES, 5 pyruvate, 10 taurine and 0.5 CaCl_2 plus 2% BSA. After settling for another 30 min, the pellet was washed again with incubation buffer now containing 1 mM CaCl_2 and was allowed to equilibrate at room temperature for 60 min.

2.2. Computational methods

2.2.1. Monodomain and bidomain formulations of simulated cardiac tissue. Cardiac excitations propagate diffusively in tissue, so that the heart's electrical behavior is governed by reaction–diffusion equations. The tissue itself can be represented as either a monodomain or bidomain [45]. In the monodomain formulation, the extracellular potential is considered grounded and thus the intracellular potential is equal to the membrane potential, and the governing differential equation is

$$\partial_t V = \nabla(D\nabla V) - I_{\text{ion}}/C_m,$$

where V is the transmembrane potential, D is the conductivity tensor, C_m is the membrane capacitance, and I_{ion} is the ionic current specified by the model formulation used in each case. The bidomain formulation, in contrast, treats the intracellular and extracellular spaces separately, leading to the following coupled partial differential equations:

$$\nabla(D_i + D_e) \Phi_e = -\nabla \cdot (D_i \nabla V_m),$$

$$\nabla(D_i \nabla V_m) + \nabla \cdot (D_i \nabla \Phi_e) = -\beta(C_m \partial_t V_m + I_{\text{ion}}),$$

where Φ_i and Φ_e are the intracellular and extracellular potentials, D_i and D_e are the intracellular and extracellular conductivity tensors [46], β is the surface-to-volume ratio, and the membrane potential is given by $V_m = \Phi_i - \Phi_e$. In 1D, or when the intracellular and extracellular anisotropy ratios are equal in 2D or 3D, the bidomain representation reduces to the monodomain.

2.2.2. Ionic current models. The ionic current I_{ion} can be specified by any of the models of the electrophysiology of isolated cardiac cells. These models give equations for transmembrane currents, intracellular calcium handling, and other ionic concentrations; the currents are used to update the membrane potential. Over the past few decades, many models have been developed (see [47, 48] for reviews). The models range from relatively simple, such as generic models like the FitzHugh–Nagumo excitable media model [49], the Beeler–Reuter ventricular model [50], and the Noble Purkinje model [51], to more detailed models that are more specific to particular species and regions of the heart, such as guinea pig ventricular [52, 53], human ventricular [54]–[57], canine ventricular [58, 59], rabbit ventricular [60, 61], rat ventricular [62],

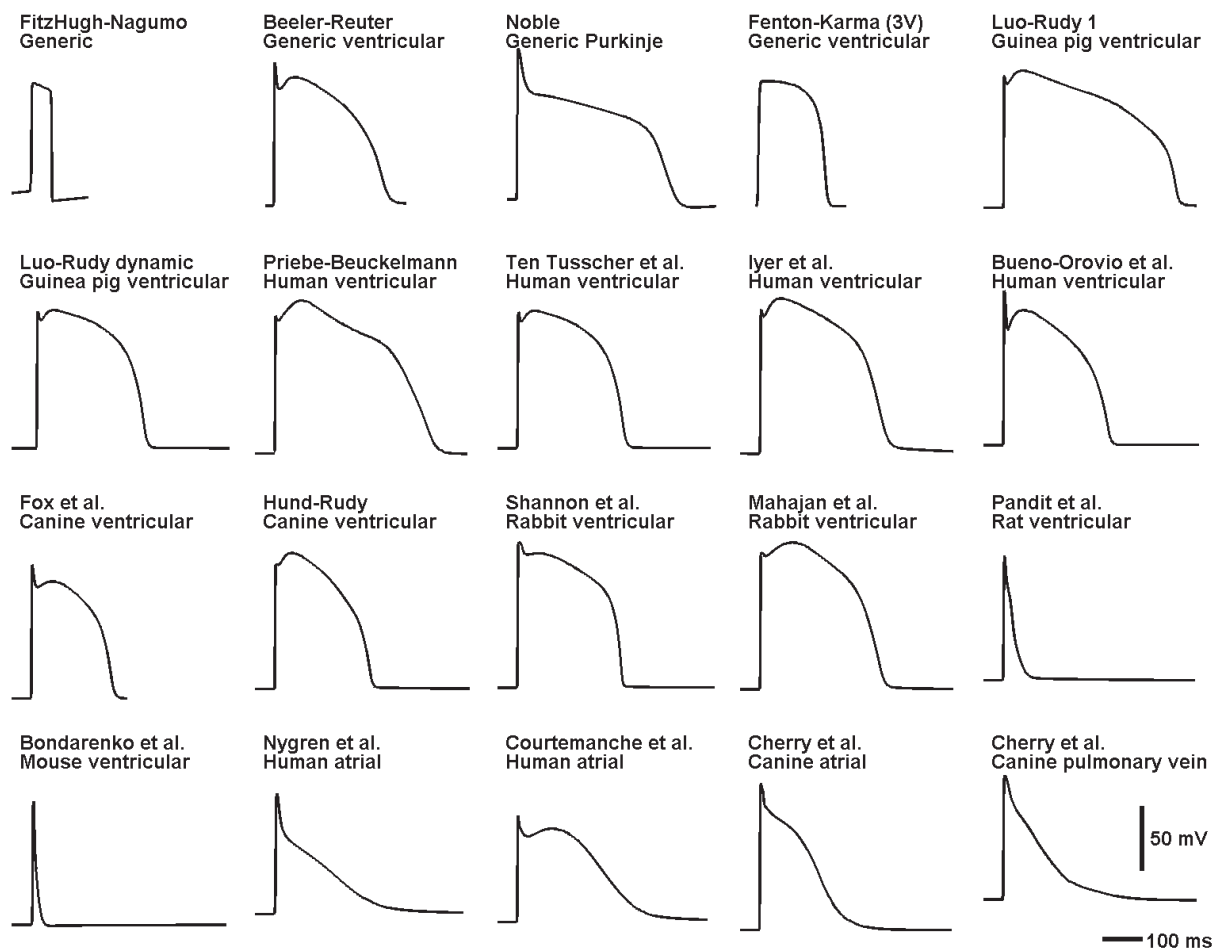


Figure 5. APs from a broad range of simple and complex mathematical models of cardiac cells (see [47], for a review of current cell models).

mouse ventricular [63], human atrial [64, 65], and canine atrial [66], as well as sinoatrial node cells [48]. For convenience, we focus on the three-variable model described in [38] and its four-variable extension [57] to analyze many of the phenomena presented here. Examples of a wide range of model action potentials are shown in figure 5. APs have different shapes because of the presence of different currents and variations in current densities in different species and regions of the heart. Figure 6 shows two examples of Java applets [67] that depict the APs and other variables of two different ionic models and also permit an interactive visualization of the transmembrane currents.

2.2.3. Numerical integration. Integrating the above equations numerically can be challenging because of the differences in time and space scales. As can be seen in figures 3–5, the timescale of the AP upstroke is much smaller (about two orders of magnitude) than the timescale of repolarization, and simulations may need to include tens of APs. Similarly, the size of a computational cell is about two orders of magnitude smaller than the necessary domain size. The difference in timescales has given rise to several advanced integration techniques [38], [68]–[70]. However, because it is important to reproduce conduction velocities

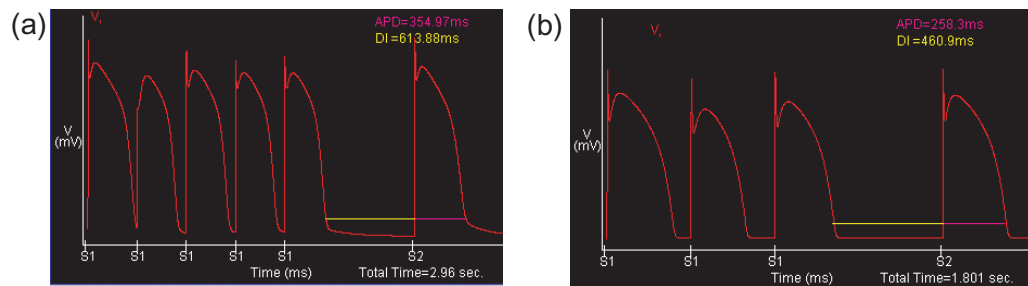


Figure 6. Examples of ionic models of cardiac electrophysiology: (a) the Iyer *et al* [56] canine ventricular model and (b) the Bueno-Orovio *et al* [57] human ventricular model. The applets [Figure_6\(a\)_applet.html](#) and [Figure_6b_applet.html](#) display the voltage, currents, and variables of the model for a user-defined number and frequency of pacing activations and time. Applet from [47].

as accurately as possible, it is often acceptable to use explicit integration methods because the larger time steps allowed by implicit or semi-implicit methods often can give rise to larger errors in velocity [71].

The monodomain models in most cases were simulated using a forward Euler method. However, some of the 2D and 3D monodomain simulations used the semi-implicit method described in [38]. The bidomain simulations were solved using forward Euler, with the extracellular field obtained using the GMRes algorithm. Irregular boundaries were implemented using the phase-field method [72]. Large-scale simulations were implemented in parallel using MPI and run on the Pittsburgh Supercomputing Center Cray XT3 MPP machine on up to 500 processors.

2.2.4. Initiation of spiral and scroll waves. Spiral waves were generated using a cross-field protocol. Transmural scroll waves were initiated using a stack of 2D spiral waves. Scroll rings were created from a rotation around a central axis of a 2D spiral wave obtained using polar coordinates.

2.2.5. Identification of spiral wave tips and scroll wave filaments. Spiral wave tips were identified as points having zero normal velocity, as described in [38]. Scroll wave filaments were determined similarly, by identifying spiral wave tips in all planes orthogonal to the three coordinate axes. Filaments were then reconstructed by ordering and connecting the filament points.

2.3. Heart structures

2.3.1. Obtaining geometric information using magnetic resonance imaging (MRI). The heart is a complex structure (see figure 7 and the corresponding 3D interactive Java applet), with right and left atria and right and left ventricles, along with valves, blood vessels and trabeculae. Quantitative characterization of the tissue structure is necessary to accurately account for the effects of anatomy and fiber orientation on the complex dynamics and stability of the electrical waves that propagate through it. Different data sets of ventricular anatomy and fiber structure

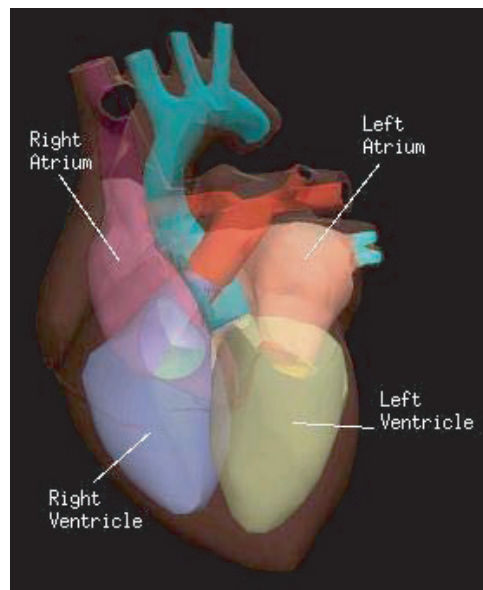


Figure 7. Interactive structure of the heart with heart components identified. The 3D Java applet [Figure_7_applet.html](#) illustrates interactively many of the heart's structures. Figure and applet from [1].



Figure 8. Images of 3D cardiac structures. (a) Human atria developed to match measured human atrial dimensions [76]. (b) Canine ventricles created from dissection [73]. (c) Porcine ventricles created from dissection [75]. (d) Canine whole heart developed from MRI at a resolution of $125\ \mu\text{m}$. See 3D interactive applets of the structures [Figure_8a_applet.html](#), [Figure_8b_applet.html](#), [Figure_8c_applet.html](#), and [Figure_8d_applet.html](#).

have been developed using dissection and subsequent reconstruction for canine [73], rabbit [74], and porcine ventricles [75], along with a human atrial structure created to match measured human atrial dimensions [76]. Several of these anatomical data sets are shown in figures 8(a)–(c) and the corresponding 3D interactive applets of the structures. More recently, MRI has been used as a non-destructive alternative [77]–[80] that allows high-resolution digitization of anatomy as well as fiber structure using diffusion tensor MRI (DT-MRI). It has been shown that the fastest direction of water diffusion coincides with the local tissue fiber orientation, and fibers measured using DT-MRI have been correlated successfully with histological measurements made on freshly excised [77], perfused [78], and fixed cardiac preparations [79]. In our MRI scans, the heart was filled with Silicone I to adequately expand the heart to a diastolic conformation, to preserve structural details while having negligible contrast in the MRI images, and to keep

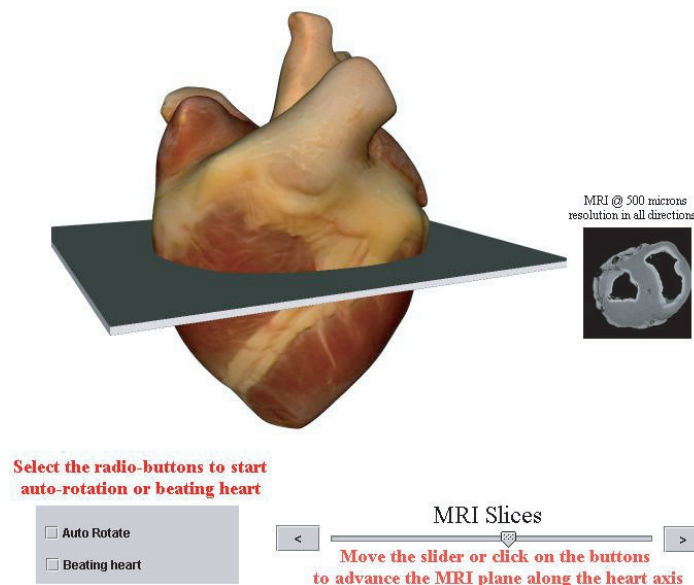


Figure 9. Reconstructed equine cardiac anatomy together with the MRI images from which it was developed. Resolution was $500\text{ }\mu\text{m}$ and height was 34 cm. The sliding plane corresponds to the MRI view. See interactive Java applet [Figure_9_applet.html](#).

the tissue moist during the full scan time (about 25 h per heart). Examples of reconstructed canine (resolution 0.125 mm) and equine (resolution 0.5 mm) heart structures developed from our MRI images are shown in figures 8(d) and 9, respectively. Many of these structures are used throughout the paper for simulation of electrical activity and to compare with optical mapping experiments.

2.3.2. Fractal structures in the heart. Different components of the heart form structures that are fractal in nature. Figure 10 shows the network of blood vessels throughout the heart visualized by two different methods. First, the blood vessels (see figure 10(a)) were recreated from MRI images at a resolution of $125\text{ }\mu\text{m}$ using a multidimensional graph search with cost functions [81]. By applying the cost function over the image in polar coordinates, a cost matrix was obtained. Then by graph searching along the columns of the matrix, the boundary points were segmented. The vessels also were imaged directly in a heart that was optically cleared [82] with Murray's solution and later injected with a blue resin (figure 10(b)). Vessels along with fatty tissue and intercellular clefts are part of the heterogeneous cardiac substrate that can act as secondary sources [83]–[85] of activation in response to electric shocks and that may explain how such shocks can terminate arrhythmias (see section 5.2).

Figure 11 shows another fractal structure, the specialized conduction system made up of Purkinje fibers that conduct at speeds of meters per second and rapidly excite the ventricles in a synchronized manner to produce an effective contraction. For direct visualization (figure 11(a)), canine ventricles were stained with Lugol's solution. Because the Purkinje system in canine hearts is generally confined to the endocardial surface [86], it is possible to digitize the photograph in figure 11(a) to create a representation of the Purkinje network, as shown in figure 11(b) and the corresponding movie. Both the blood vessels and Purkinje systems are

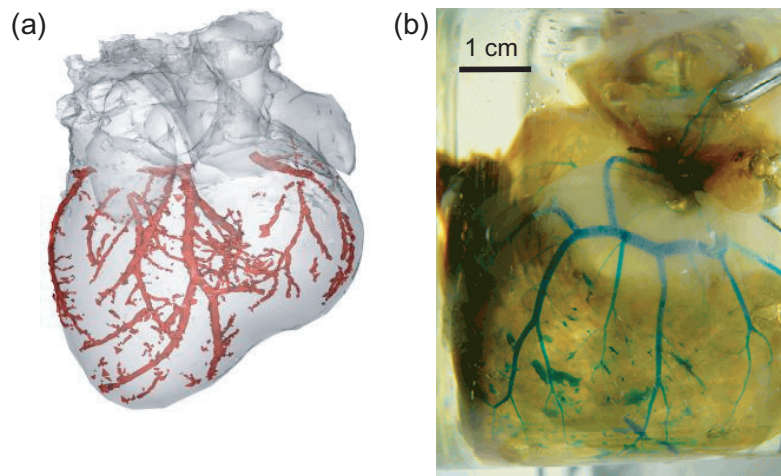


Figure 10. Blood vessels in the heart. (a) Reconstruction of vessels from MRI imaging. (b) Visualization of blood vessels using optical clearing [82] followed by injection of a resin to highlight the vessels. See 3D interactive Java applet [Figure_10_applet.html](#).

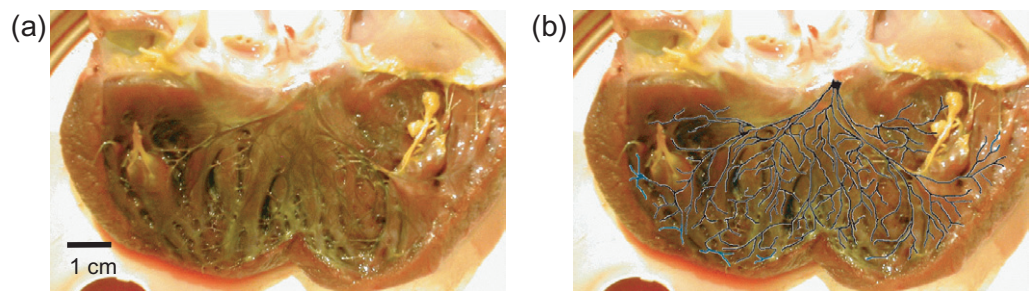


Figure 11. Purkinje system in right ventricular canine tissue (a) highlighted by Lugol's solution and (b) digitized to form a network. See movie [Figure_11_movie.gif](#), which shows simulated propagation along the network using the cell model from [57] fitted to reproduce canine Purkinje cell dynamics.

characterized by branching structures on increasingly fine scales, although, unlike a true mathematical fractal, both terminate at a finite size of the order of the size of a single cell. Although the Purkinje system normally functions to coordinate ventricular contraction, it also may be involved in ventricular arrhythmias [87] in various ways, including as a source of focal activations or other triggering activity [88]–[90], as a possible source for post-shock activations [91], or as part of a reentrant circuit [92, 93].

3. Reentrant waves in 2D

The concept of reentry as one of the mechanisms for the onset of cardiac arrhythmias was first suggested by McWilliam in 1887 [94], who suggested that differences in conduction in myocardial fibers could propagate an electrical impulse unevenly so that a wave circulating through a preparation could reenter and repeatedly re-excite previously excited tissue. It is now known that the most dangerous cardiac arrhythmias are due to reentrant waves, i.e. electrical

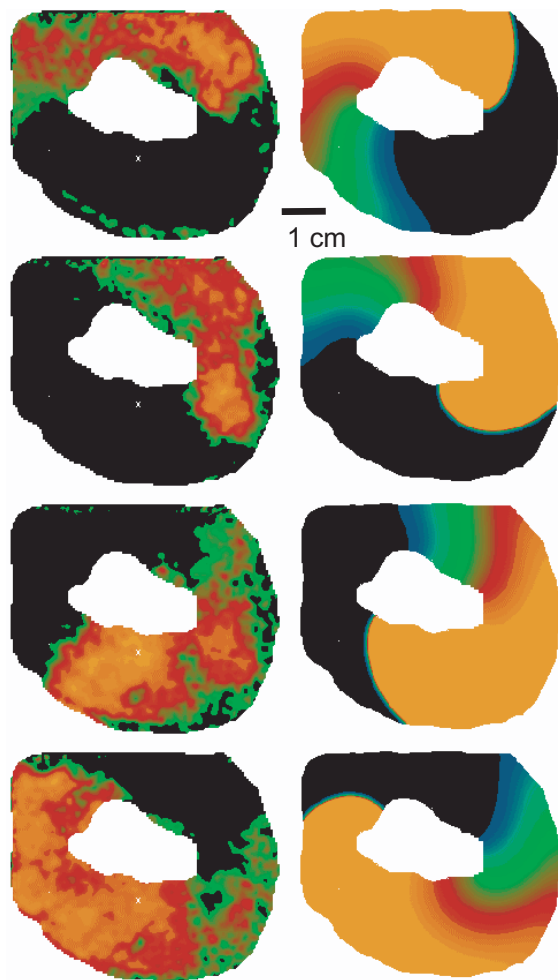


Figure 12. Experimental (left) and simulated (right) anatomical reentrant arrhythmia. The experimental preparation was goat ventricular tissue with a centrally located inexcitable obstacle created by cryoablation, and this geometry was digitized for use with the simulation in conjunction with the model of [38]. The propagating reentrant wave anchored to the inexcitable center and had a reentrant period of 350 ms. See movies [Figure_12ab_movie.gif](#) and [Figure_12a_movie.mov](#).

waves that recirculate repeatedly through the tissue with a higher frequency than that of the heart's natural pacemaker.

3.1. Anatomical and functional reentry

Cardiac tissue, like any other chemical or physical excitable media in 1D, 2D or 3D, can exhibit reentrant waves. For reentry to occur, it was believed initially that an obstacle around which the electrical wave would rotate was necessary. This kind of reentry is called *anatomical reentry* and it can occur whenever tissue contains an inexcitable obstacle, such as a scar produced by an infarct, around which electrical waves can rotate (or pin) provided that the perimeter of the geometric feature is longer than the wavelength. Figure 12 and corresponding movie show

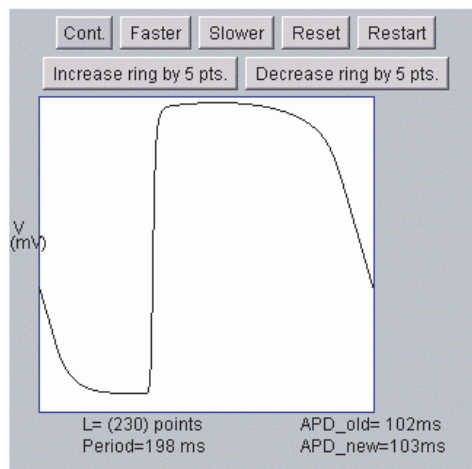


Figure 13. Example of reentry in a 1D ring. Periodic boundary conditions at the left and right edges allow continuous circulation of the propagating wave. The three-variable model [9] fitted to the Beeler–Reuter model [36] was used. See interactive Java applet [Figure_13_applet.html](#).

an example of anatomical reentry around an obstacle in an optically mapped preparation of goat right ventricle with a cryoablated central region serving as an obstacle and in simulated tissue using a digitized 2D representation of the experimental geometry. In some cases when the wavelength is comparable with the perimeter of the obstacle, transient detachment and re-attachment [95, 96] or more complex dynamics such as alternans [97] can occur. Anatomical reentry is of particular significance in the atria, which have an abundance of tissue boundaries, including large blood vessels and valve annuli of different sizes, around which waves can circulate. The importance of anatomical reentry in atrial arrhythmias, especially atrial flutter (Afl), has been known clinically since 1920 [98].

The simplest example of reentry is a 1D ring. In this case, periodic boundary conditions at the edges of a 1D cable create a tissue structure without edges. If the ring is longer than the wavelength, a wave can circulate around the ring repetitively, without the need for an obstacle. An example of a reentrant wave in a 1D ring is shown in figure 13 and the corresponding Java applet, where a wave propagates from right to left around the ring. More complex dynamics can occur when the ring length is close to the wavelength, which creates interactions between the wave front and wave back. This interaction can be seen directly in the Java applet by slowly decreasing the ring size to a size of $n = 200$ discretized points.

Functional reentry occurs in the absence of such anatomical anchors and rotates around a functional block dynamically produced by the reduced excitability at the spiral tip due to curvature and electrotonic effects [99]–[101]. The possibility of functional reentry or spiral waves in cardiac tissue was first demonstrated using cardiac cell models in 1991 by Courtemanche and Winfree [102] and by Holden and Panfilov [103]; a year later it was shown experimentally by Davidenko *et al* [104] in a sheep ventricular tissue using optical mapping.

Spiral waves can occur on their own, in pairs, or as multiple waves, depending on the electrophysiological properties of the medium, tissue size and initial conditions. Under normal conditions, spiral waves in atrial preparations do not occur spontaneously and self-terminate quickly if initiated. In the presence of cardiovascular disease or pharmacological

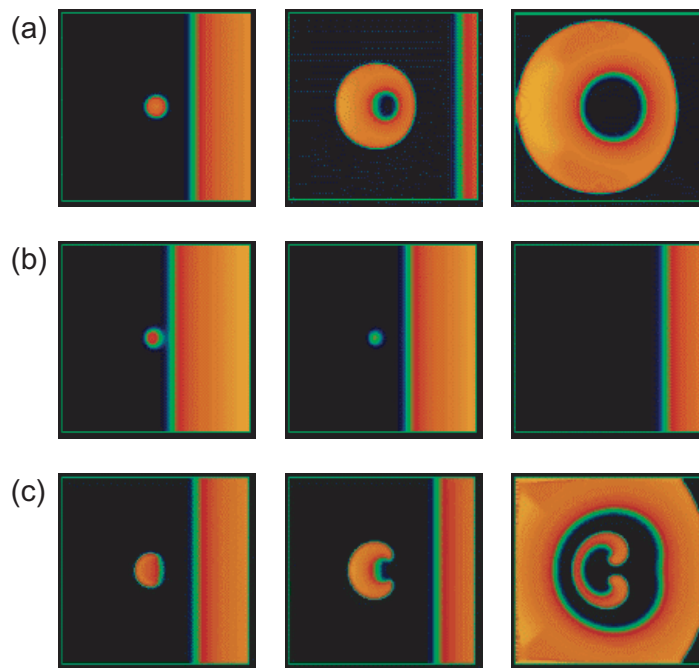


Figure 14. Initiation of reentry during the vulnerable window. A point stimulus was applied in the wake of a propagating plane wave. (a) The applied stimulus occurred too late, after the surrounding tissue was excitable again, and it propagated in all directions. (b) The applied stimulus occurred too early, while all the surrounding tissue was still refractory, thereby preventing propagation. (c) The stimulus was applied during the vulnerable window, with the tissue excitable on the left but initially refractory on the right, leading to the initiation of a pair of counter-rotating spiral waves. See movies [Figure_14a_movie.gif](#), [Figure_14b_movie.gif](#), and [Figure_14c_movie.gif](#).

agents, however, self-sustained atrial arrhythmias can be induced and maintained. In ventricular tissue, however, reentrant waves can be initiated and sustained readily in large hearts. The size requirement is related to the critical mass hypothesis, which was first described by Garrey in 1914 [105] and postulates a minimum mass necessary for fibrillation. For 3D scroll waves to exist, there is a minimum size and thickness required [87], [106]–[109], and this size is related to the wavelength [110].

3.2. Initiation of spiral waves

Spiral waves can be initiated in multiple ways. The central idea behind initiation, however, is activation of tissue during the vulnerable window [8]. During this time, the symmetry of propagation is broken and a wave front produced by the activation is blocked in some but not all directions. Figure 14 illustrates the importance of proper timing during the induction of a stimulus in the wake of a planar wave. In figure 14(a) and the corresponding movie, the induction stimulus was applied after the tissue was recovered from the previous passing plane wave that propagated from left to right. As a result, the initiated wave propagated in all directions, and no reentry occurred. In figure 14(b) and the corresponding movie, the induction

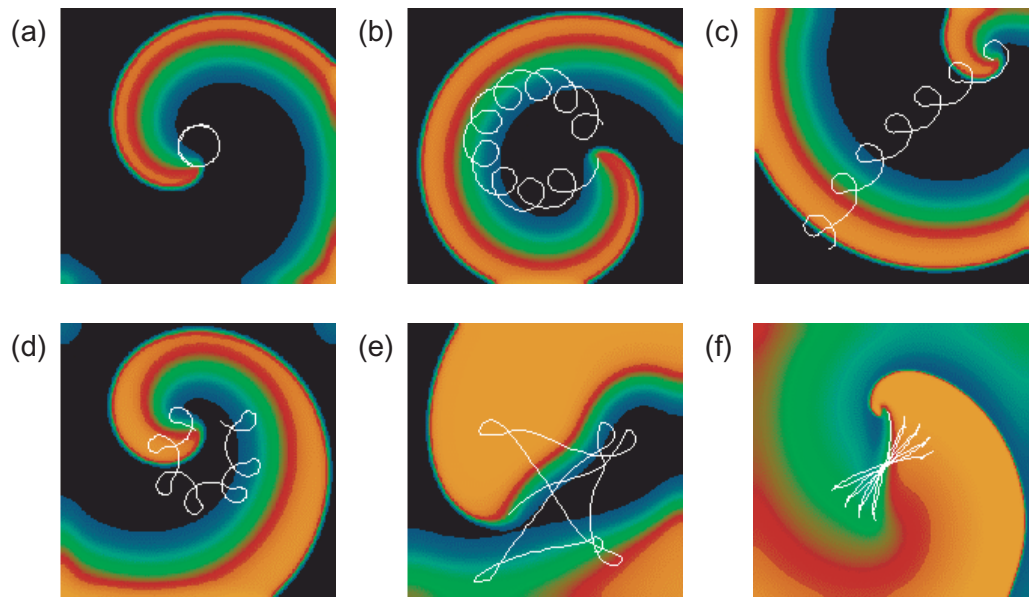


Figure 15. Six different types of spiral wave tip trajectories, including (a) circular, (b) epicycloidal, (c) cycloidal, (d) hypocycloidal, (e) hypermeandering, and (f) linear. The 3-variable model of Fenton and Karma [9] was used with the parameter settings given in [17]. See movies [Figure_15a_movie.gif](#), [Figure_15b_movie.gif](#), [Figure_15c_movie.gif](#), [Figure_15d_movie.gif](#), [Figure_15e_movie.gif](#), and [Figure_15f_movie.gif](#).

stimulus was applied too early, while the tissue was still refractory, and it was unable to propagate. However, in figure 14(c) and the corresponding movie, the stimulus was applied during the vulnerable window, when the tissue was refractory close to the previous wave back but excitable farther away. The stimulus thus propagated toward the left but initially was blocked toward the right. As the tissue on the right became excitable, the initiated wave front was able to propagate into that region, producing a pair of counter-rotating spiral waves.

Inhomogeneous media, with variations in electrophysiological properties or in cell-to-cell conduction, can provide more opportunities for spiral wave initiation or breakup from still other mechanisms. For instance, patchy intercellular connections can produce conduction blocks that can lead to the creation of new waves [66].

3.3. Spiral wave trajectories

Spiral waves in experiments and in mathematical models of cardiac tissue can follow different types of trajectories depending on the electrophysiological properties of the tissue and the substrate. These trajectories are obtained by tracking the location of the spiral wave's tip over time, which can be accomplished by a number of different methods (see [17] for a review). In isotropic media, the tip trajectory depends on the electrophysiology, particularly the wavelength and excitability [111]–[113]. Figure 15 and the corresponding movies show examples of six different trajectories obtained using a single cardiac cell model [17, 38]. The transition between tip trajectories (circular, epicycloidal, cycloidal, hypocycloidal, hypermeandering and linear) is obtained by varying parameters of the model to affect either the sodium dynamics (excitability)

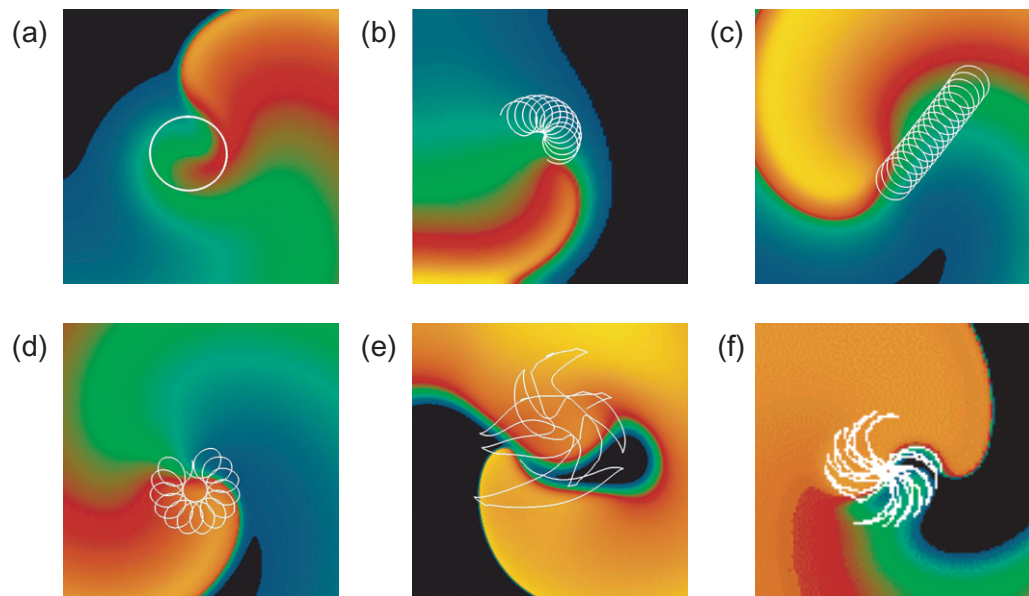


Figure 16. Six different types of spiral wave tip trajectories displayed by different models of cellular electrophysiology. (a) Circular trajectory of the Nygren *et al* model [64]. (b) Epicycloidal trajectory of the Bondarenko *et al* model [63]. (c) Cycloidal trajectory of the Nygren *et al* model [64] using the parameter fitting to the Courtemanche *et al* model [65] provided by Syed *et al* [174]. (d) Hypocycloidal trajectory of the Nygren *et al* model [64] with all ionic concentrations except intracellular calcium held constant. (e) Hypermeandering trajectory of the Hund–Rudy model [59]. (f) Linear trajectory of the ten Tusscher *et al* model [55].

or the calcium and/or potassium dynamics (wavelength). This range of tip trajectories also occurs in other more biophysically detailed models, as shown in figure 16.

Many of these trajectories have been observed experimentally in cardiac tissue [104, 108, 114, 115]. Figure 17 and the corresponding movies show two of trajectories observed most commonly in experiments, circular and linear.

3.4. Spiral wave breakup

3.4.1. Mechanisms of spiral wave breakup. Reentrant waves in cardiac tissue, even in a homogeneous simulated tissue, can exhibit wave break, in which induced spiral waves can break and produce multiple waves. Such breakup can be transient, which can occur during initiation as the medium adjusts to what is generally a faster period, or sustained over long periods of time. A number of different mechanisms have been shown to give rise to breakup (see [17] for a review). Several examples include steep APD restitution curves [17, 102, 103], discordant alternans [17, 116, 117], Doppler shift [17, 118], biphasic APD restitution curves [17, 119, 120], supernormal conduction velocity [17], and periodic boundary conditions [17], among others. Although new waves may be generated continuously through breakup, other waves may terminate through collisions or by leaving the domain before turning to reenter the tissue.

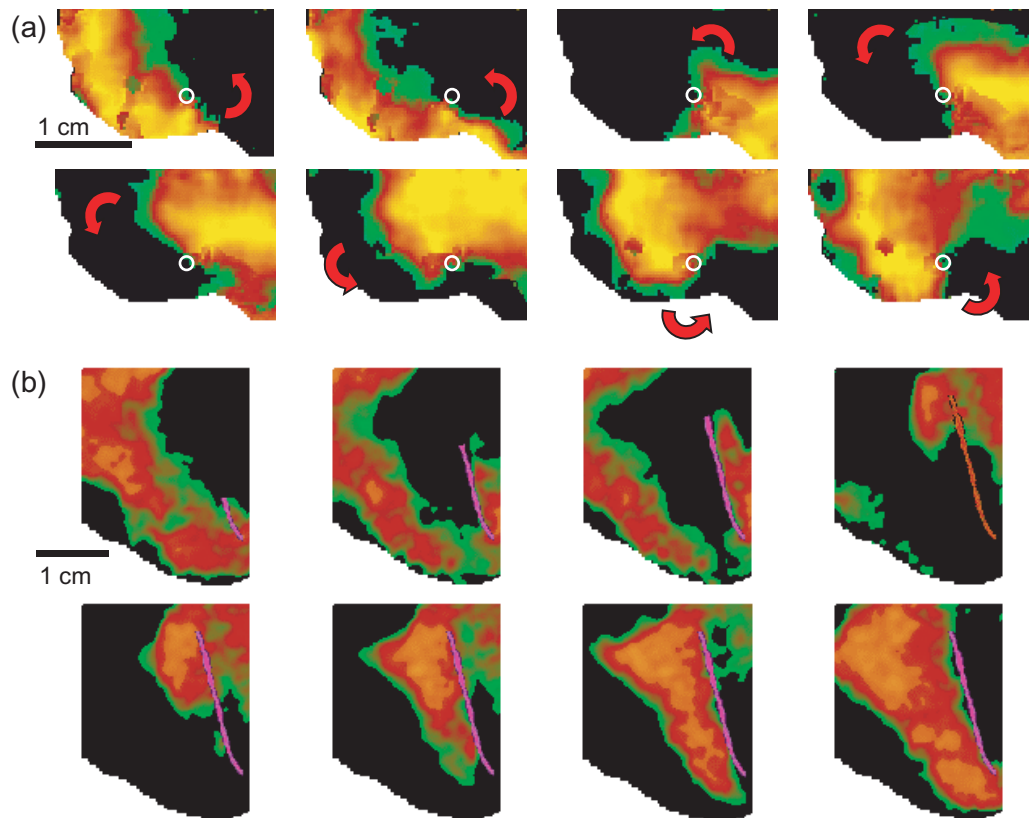


Figure 17. Reentrant wave trajectories in experimental preparations. (a) Circular trajectory in canine atrium with $3 \mu\text{M}$ ACh. (b) Linear trajectory in canine ventricle. See movies [Figure_17a_movie.gif](#) and [Figure_17b_movie.gif](#).

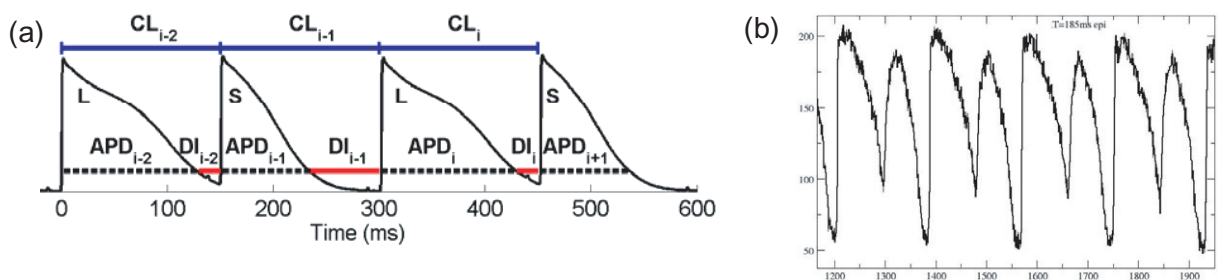


Figure 18. (a) Microelectrode recording of alternans in a canine Purkinje fiber at a constant CL of 150 ms. Note the alternating long (L)–short (S) response in APD. APD is measured at 90% of repolarization. (b) Optical signal from canine left ventricular epicardium showing alternans during pacing at a CL of 185 ms. See movie [Figure_18b_movie.mov](#).

To illustrate the phenomenon of spiral wave breakup, we focus on the mechanism of alternans. During fast pacing, excitable cardiac cells exhibit a shortening of APD. In some cases there is a critical period for which a bifurcation can occur such that the APD alternates between short and long values even while the period of stimulation (or CL) remains constant, a condition called alternans. Figure 18 shows examples of alternans in a microelectrode recording from a

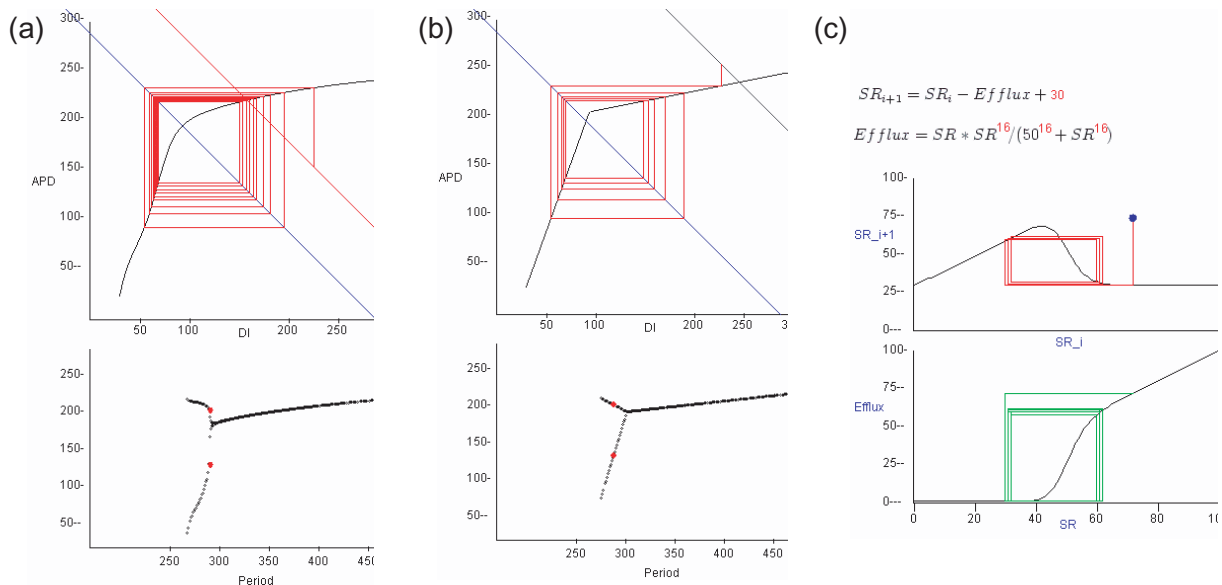


Figure 19. Maps of alternans in (a)–(b) voltage, and (c) calcium. (a)–(b) Iterative maps with (a) a continuous function leading to a pitchfork bifurcation and (b) a piecewise linear function leading to a border-collision bifurcation. Top: APD restitution curve with iterative cobweb showing alternans for a constant period (blue line). Bottom: APD as a function of pacing period or CL, with red dots denoting the alternating solutions in each case for the same period. (c) Alternans in calcium produced with the given map showing nonlinear calcium efflux from the sarcoplasmic reticulum (SR) internal calcium store. Figure and applet from [1]. See interactive Java applets [Figure_19a_applet.html](#), [Figure_19b_applet.html](#), and [Figure_19c_applet.html](#).

cardiac Purkinje fiber paced at a cycle length of 150 ms and in a single-pixel recording from optically mapped canine right ventricle paced at a CL of 185 ms.

The first explanation of the origin of alternans was based on the properties of the APD restitution curve [121, 122], which is a function constructed by measuring the APDs resulting from a series of decreasing CLs and plotting each steady-state APD as a function of the preceding diastolic interval (the time between APs) [39], as shown in figure 18(a) (further discussion on different types of APD restitution curves can be found in [17]). A simple linearization around the fixed point [1] shows that alternans develop when the slope of the APD restitution curve is greater than one (see the interactive applet corresponding to figure 19(a)). Although many cardiac models exhibit alternans similar to that shown in figure 19(a) [17, 55, 102] when the slope of the APD restitution curve is greater than one, some questions concerning the applicability of restitution curve slopes as a predictor of alternans have been raised recently. Some experiments have shown a much smaller alternans magnitude (compared to most models) of 10–30 ms [42, 123, 124], and the bifurcation type in some cases seems to be closer to a near-border collision bifurcation than a pitchfork bifurcation [125]–[127] (as shown in figure 19(b)). Moreover, alternans is not observed in some cases despite APD restitution curve slope greater than one [128, 129]. These apparent discrepancies may be due to the fact that restitution curves also depend on electrotonic and memory effects, both of which have been shown to suppress alternans [130]–[132]. Another possible explanation is that complex intracellular

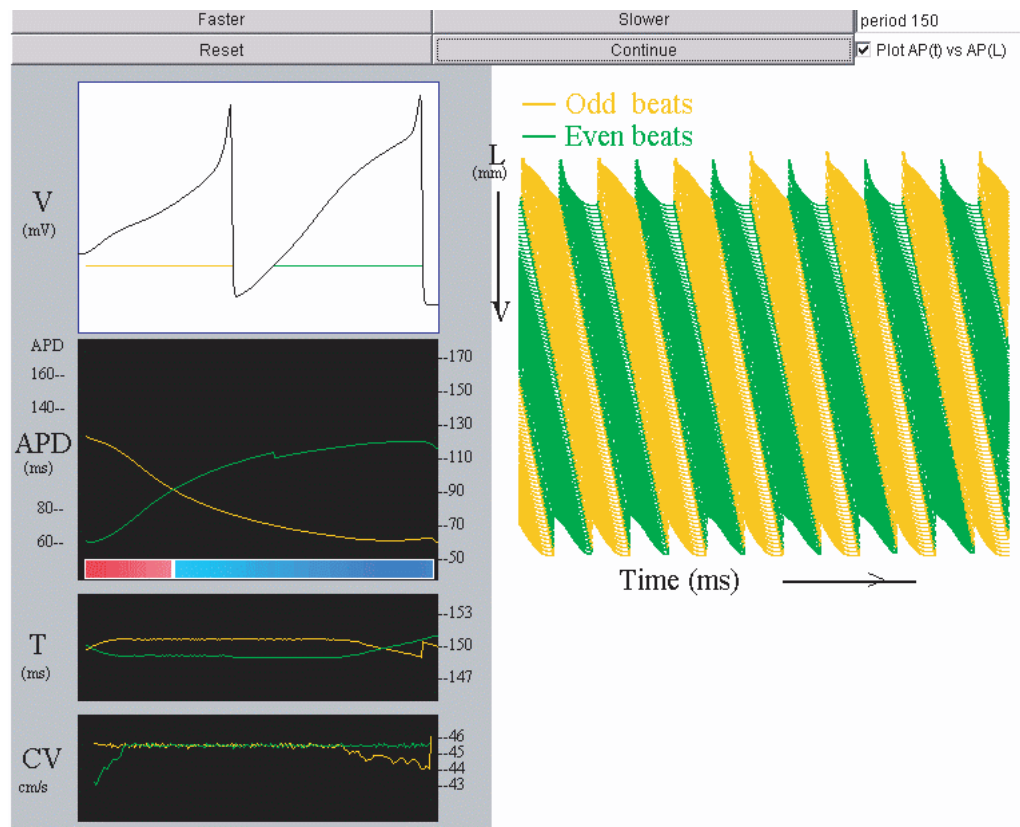


Figure 20. Spatially discordant alternans in a simulated 1D cable. Left shows instantaneous voltage (V), APD, period (T), and conduction velocity (CV) for all points along the cable. Right shows space–time plot of propagating APs. Odd beats are shown in orange and even beats in green. Alternans can be seen to be spatially discordant because odd (even) APs are long (short) at the top end of the cable but short (long) at the bottom end. See interactive Java applet Figure_20_applet.html.

calcium dynamics may underlie alternans [133]–[136]. Figure 19(c) shows how the nonlinear relation between the calcium fluxes across the sarcolemma and the sarcoplasmic reticulum (SR) content [134] can give rise to alternans. Regardless of the underlying mechanisms responsible for alternans, when it develops in tissue it can create large gradients of repolarization that can produce conduction blocks [137] and contribute to the initiation and maintenance of sustained reentrant waves.

In spatially extended systems, alternans can appear as spatially concordant, which is a trivial extension of alternans all along the tissue, as each AP remains either short or long as it propagates throughout the entire syncytium (see interactive Java applet corresponding to figure 20). However, a more complex dynamical state known as spatially discordant alternans, in which an AP transitions from short to long or from long to short as it propagates, also can arise (see figure 20 and the corresponding interactive Java applet). A number of factors are important in determining whether alternans are spatially concordant or discordant, including tissue length [17, 138], conduction velocity variations [17, 138, 139], initial conditions [138], pacing CL and electrophysiological heterogeneities [138, 140].

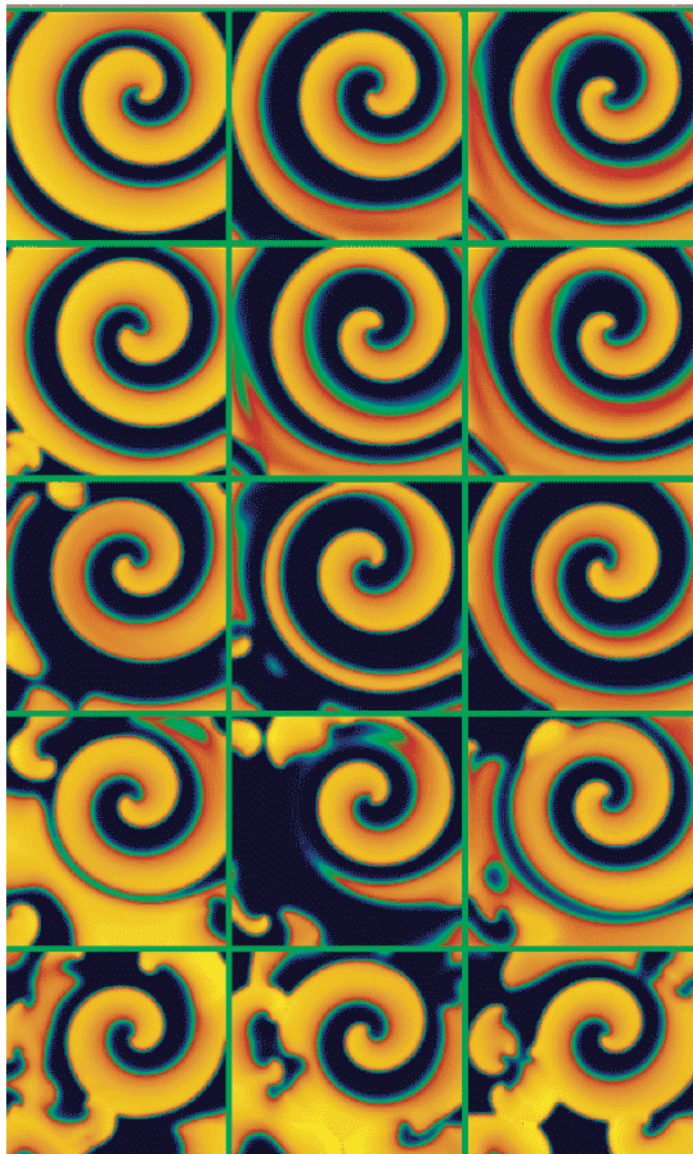


Figure 21. Spatially discordant alternans progressing to spiral wave breakup using the model of [38] with parameter values as in [17]. Top row shows the initiation of alternans. Second row depicts more pronounced spatially discordant alternans; regions with long APs and long wavelengths have shorter APs and shorter wavelengths during the next rotation. Breakup begins to occur away from the spiral wave tip (middle row) and over time invades a larger portion of the tissue (bottom two rows). See movie [Figure 21_movie.mov](#).

The spatial gradients produced by discordant alternans are conducive to arrhythmia development. When spiral waves are present, discordant alternans is manifest as variations in wavelength along the spiral arm. Figure 21 and the corresponding movie show an example of how spatially discordant alternans can progress to breakup in simulated tissue. The repolarization gradients over time lead to propagation block and an initial wave break, after

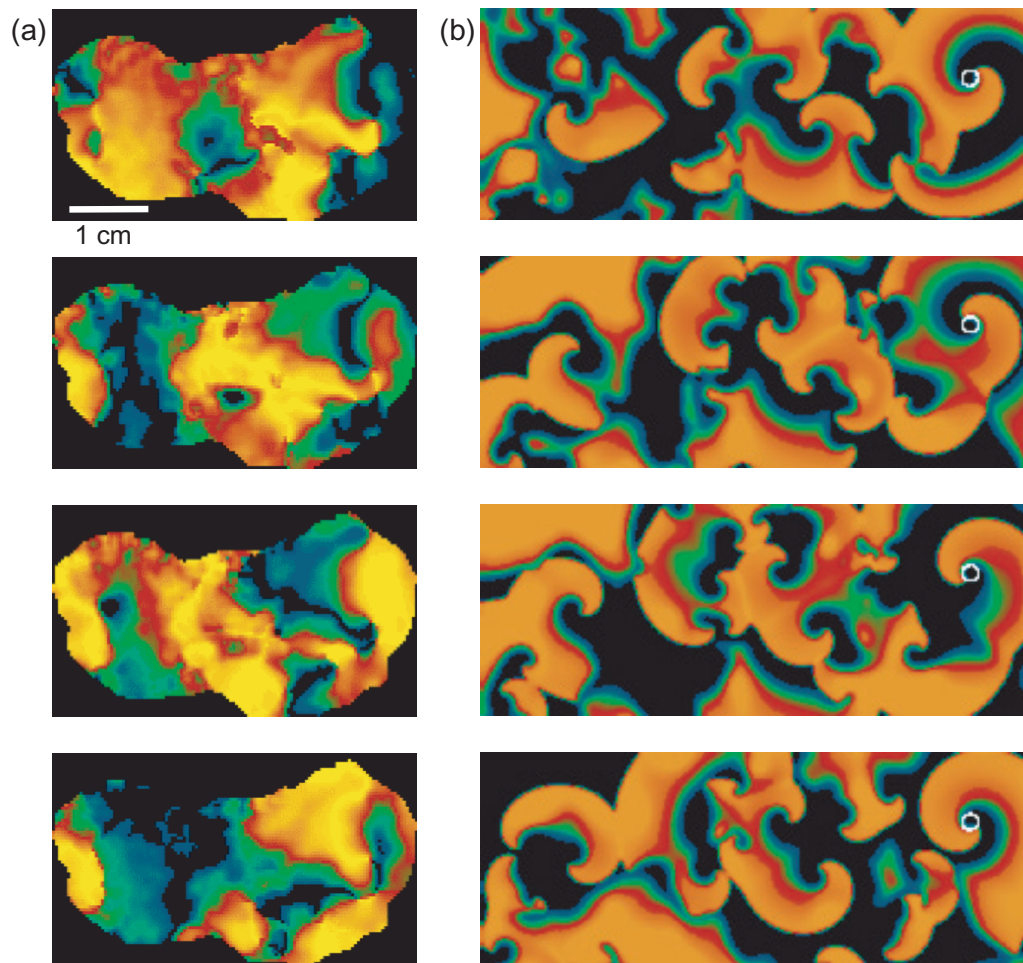


Figure 22. ‘Mother rotor’ with fibrillatory conduction and breakup. (a) Experimental example in canine atrium using $2\ \mu\text{M}$ ACh. A stable rotor remains on the right side of the domain despite irregular activity on the left. (b) Example in simulated cardiac tissue using the model of [38] with parameter values as in [17]. Breakup occurring on the left side of the domain does not affect the stable spiral wave on the right. See movie [Figure_22ab_movie.gif](#).

which the increased dynamic heterogeneity can lead to additional wave breaks and sustained complex fibrillatory dynamics.

Although many mechanisms have been postulated [17, 102, 103], [116]–[120], the precise mechanisms responsible for spiral wave breakup and fibrillation are not yet known and may vary in different regions of the heart, among different species, and under different conditions. Two competing hypotheses have been proposed to explain fibrillation. One, called the ‘mother rotor’ hypothesis, postulates the existence of stable, high-frequency reentrant sources (rotors) that induce repolarization gradients throughout the tissue that promote wave break [141]–[143]. The other hypothesis proposes that no such stable sources are needed, and that wave break occurs continuously [144]–[147]. While it is not known whether one or both of these hypotheses describe fibrillation, it is possible to obtain data under different conditions to support both claims. Figure 22(a) and the corresponding movie show an example of atrial fibrillation (AF)

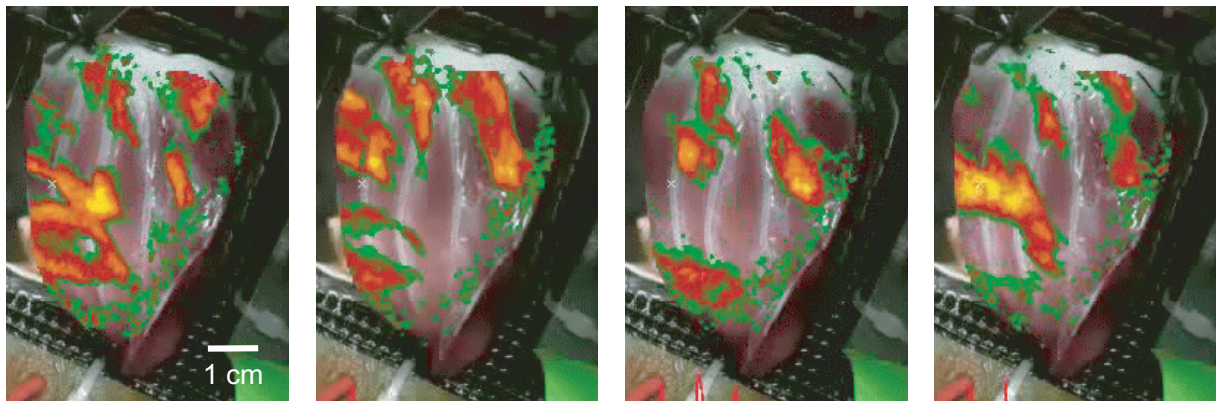


Figure 23. Breakup of reentrant waves in canine left ventricle. Data are superimposed on a digital photograph of the preparation. See movie [Figure_23_movie.gif](#).

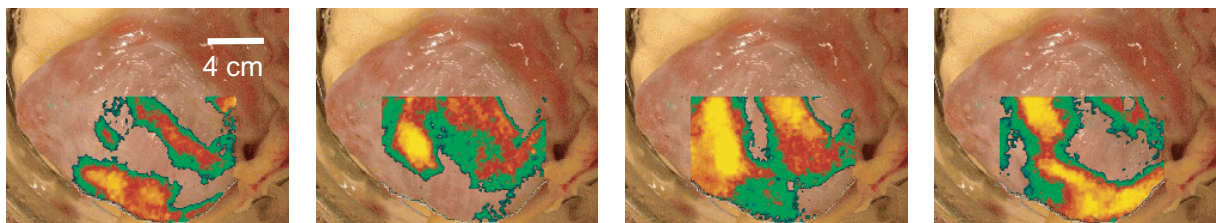


Figure 24. Fibrillation in equine right atrium using $1\ \mu\text{M}$ ACh. Data are superimposed on a digital photograph of the preparation. See movie [Figure_24_movie.mov](#).

in a canine preparation that appears to contain a stable reentrant source on the right side of the domain, with irregular activity on the left. Similar behavior can be obtained in simulated tissue, as shown in figure 22(b). However, no apparent stable source can be identified in other preparations that exhibit sustained wave break, such as canine left ventricle (figure 23 and the corresponding movie) and equine right atrium (figure 24 and the corresponding movie). Although it is possible that the stable source may be outside the mapped regions in these preparations, panoramic mapping of the entire epicardium has been unable to identify stable sources in swine ventricular preparations [29, 147, 148].

3.4.2. Importance of initial conditions in wave break dynamics. Breakup also can be related to the initial conditions of the medium. Figure 25 and the corresponding movie show a canine atrial preparation that exhibits arrhythmias consisting of (a) a single reentrant wave or (b) multiple reentrant waves. The different dynamics were induced within a short time frame and, although the dynamics could not be predicted, both types could be produced readily. Some models also can show stable reentrant waves or sustained breakup depending on the initial conditions, including the pacing history of the medium and the timing of spiral wave initiation [42, 57]. For example, in the Hund–Rudy model [59], different initial conditions can result in either a stable wave with a hypermeandering trajectory (figure 26(a) and the corresponding movie) or sustained breakup (figure 26(b) and the corresponding movie) [42]. In this case, the only difference was

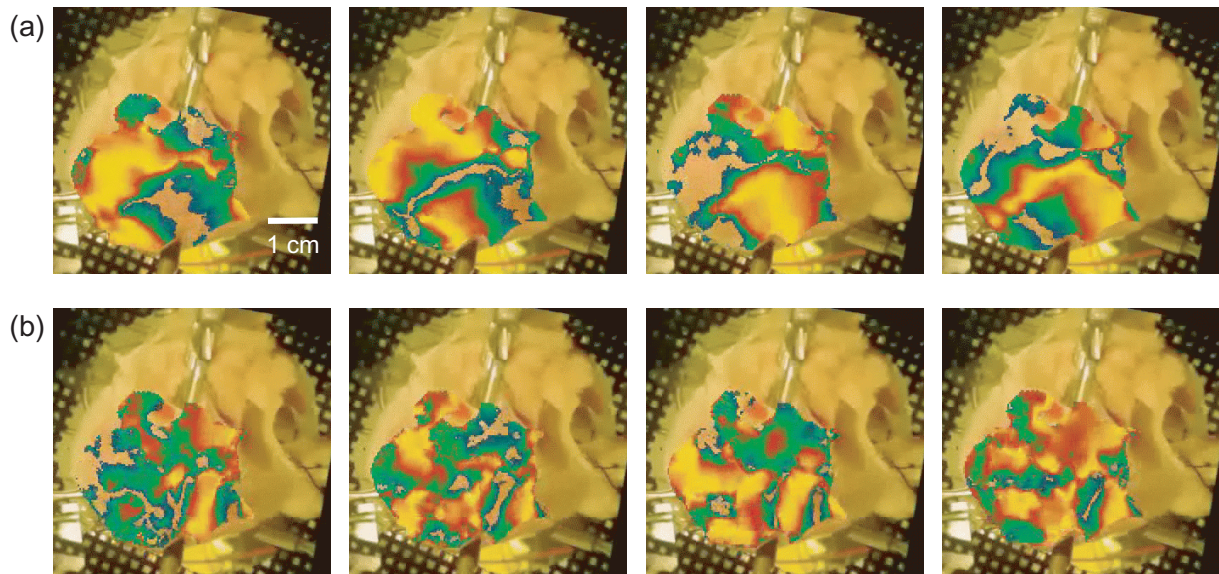


Figure 25. Canine atrial preparation with two different types of spiral wave dynamics. (a) Single stable reentrant wave. (b) Multiple reentrant waves with breakup. Data are superimposed on a digital photograph of the preparation. Arrhythmias were induced by application of an electric field. See movies [Figure_25a_movie.mov](#) and [Figure_25b_movie.mov](#).

the timing of the stimulus to induce the reentry. The ten Tusscher *et al* model [55] similarly can exhibit a stable spiral wave or sustained breakup but depending on the pacing history. Pacing at a longer CL before induction results in a stable spiral (figure 27(a)), whereas faster pacing before induction produces breakup (figure 27(b)) [57].

4. Reentrant waves in 3D

In 3D, reentrant spiral waves become scroll waves. Visualization of wave dynamics in 3D is more challenging because it is no longer possible to represent the membrane potential at each point by the use of a color. One possibility often used with experimental data is to visualize surface activity on the epicardium, endocardium, or both.

For simulations, a convenient alternative for scroll waves is to visualize instead the vortex filaments present in the domain. In 3D, the zero-dimensional tip (or phase singularity) of a spiral wave becomes a 1D vortex filament. The trivial case is a straight filament, which is simply a translation of a spiral wave through the depth of the medium. However, scroll waves have complex dynamics, and vortex filaments similarly can be complex, with nontrivial curvature, torsion and twist [36, 37]. Figure 28(a) and the corresponding movie show a vortex filament in 3D and the related 2D spiral waves for layers through the depth of the tissue. Filaments can have different primary orientations in 3D cardiac tissue depending on the scroll wave configuration. A filament extending between the epicardial and endocardial surfaces is called transmural or I-shaped. A U-shaped filament has both of its ends terminating on the same surface of the tissue. If the filament has no ends but loops back on itself, the wave is called a scroll ring or O-shaped filament and is entirely intramural, as shown in figure 28(b) and the corresponding movie.

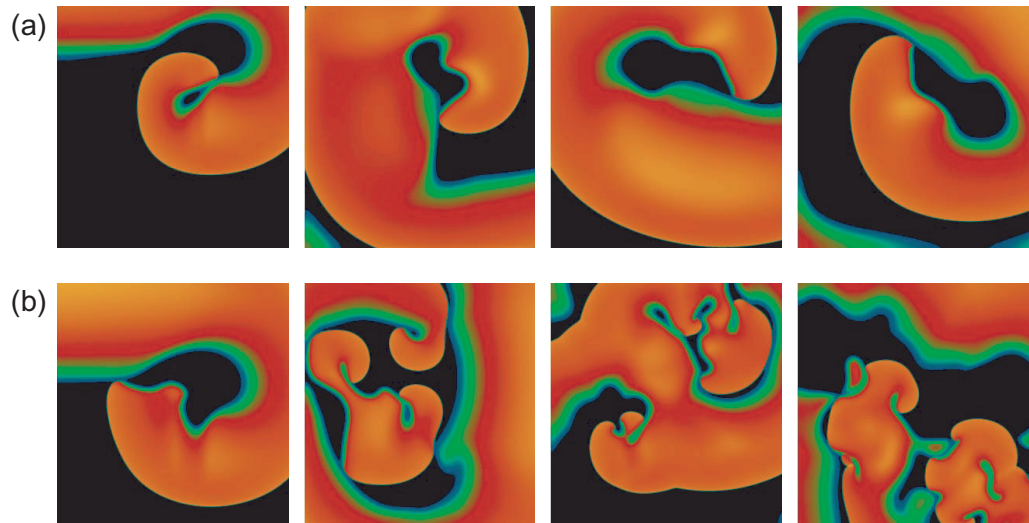


Figure 26. Spiral wave dynamics of the Hund–Rudy model [59] in an $18\text{ cm} \times 18\text{ cm}$ domain. A stable spiral wave (a) results when the reentry-inducing stimulus occurs farther behind the previous wave, while an earlier stimulus results in spiral wave breakup (b). In this case, the spiral waves were initiated (a) 480 ms and (b) 450 ms after a plane wave was launched from the left edge. Frame times are 0.7, 1.14, 2.26 and 3 s.

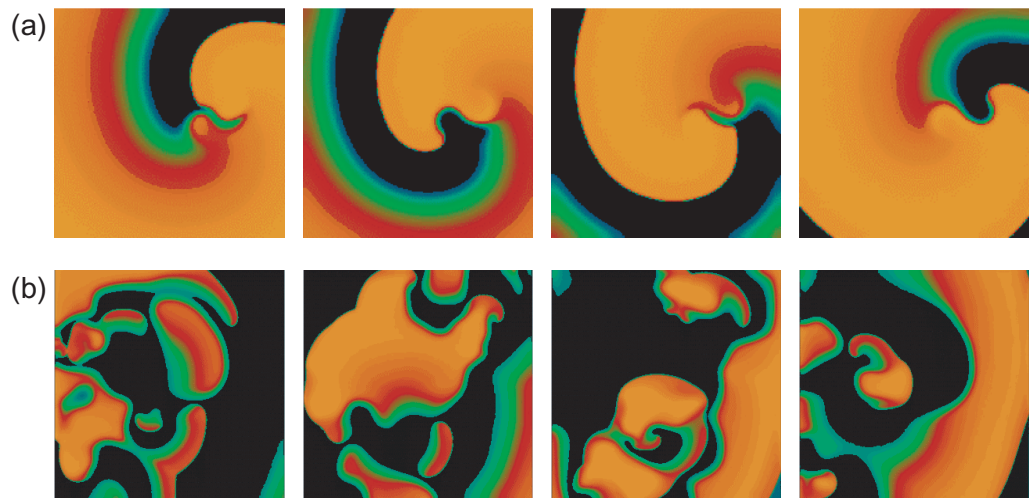


Figure 27. Spiral wave dynamics of the ten Tusscher *et al* model [55]. A stable spiral wave (a) occurs when the tissue is first paced at a CL of 1000 ms, but when the tissue is paced at a CL of 300 ms, sustained breakup arises (b). See movies [Figure_27a_movie.gif](#) and [Figure_27b_movie.gif](#).

4.1. Scroll wave breakup mechanisms

In addition to mechanisms that produce spiral wave breakup in 2D, new mechanisms can produce breakup in 3D due to purely topological effects [17, 37, 38], [149]–[151]. Figure 29 shows two examples of such mechanisms. Negative filament tension [17, 37, 152, 153],

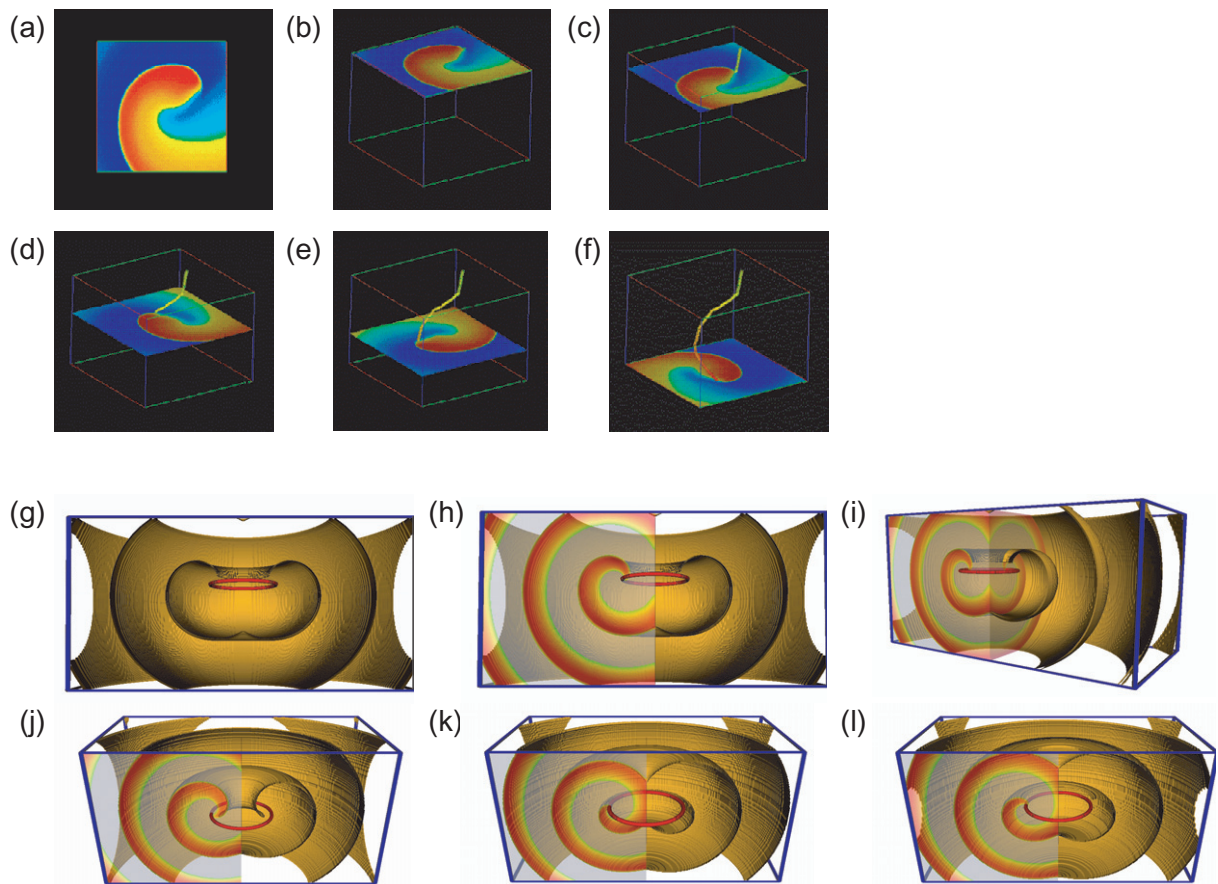


Figure 28. (a)–(f) Top view and view of the vortex filament together with the voltage in different planes. The vortex filament is revealed as the horizontal plane showing the voltage is lowered through the thickness of the simulated tissue. The scroll wave has curvature and twist as can be observed by the differences in spiral wave tip positions in the different planes. (g)–(l) Views during rotation of a scroll ring. See movies [Figure_28a_movie.mov](#) and [Figure_28b_movie.gif](#).

associated with low excitability (a condition that can occur during ischemia in cardiac tissue), causes filaments to be unstable to perturbations; as a result, filaments tend to elongate and produce additional filaments through collisions with boundaries or with other filaments (see figure 29(a) and the corresponding interactive 3D Java applet).

A property inherent to cardiac tissue called rotational anisotropy also can destabilize filaments. Ventricular cells, which are approximately cylindrical in shape (see figure 1), align end-to-end to form muscle fibers. The presence of these fibers results in propagation anisotropy, with conduction approximately three times faster along the fiber axis than across it. Although the details of the fiber geometry can be complex, fibers to first order can be considered to be arranged into planes roughly parallel to the endocardial and epicardial surfaces, with the primary fiber axis of each sheet slightly rotating through the thickness of the wall for a total fiber rotation of 120° – 180° [154, 155].

The inclusion of this rotational anisotropy representing the twisting of the orientation of fibers and hence, the direction of fastest propagation through the ventricular wall, also can result

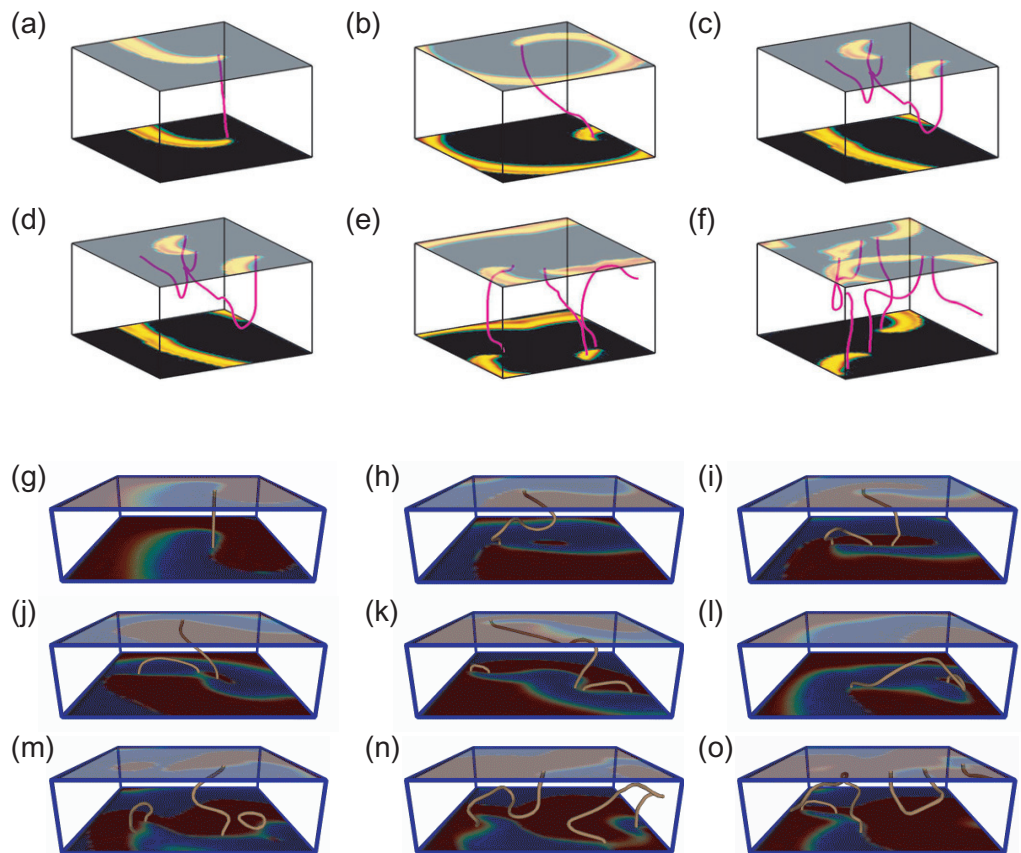


Figure 29. Breakup of scroll waves in a simulated 3D tissue slab. (a)–(f) Negative filament tension associated with low excitability results in an instability in 3D in which filaments continually elongate, leading to the production of new filaments through collisions with boundaries and other filaments. The model of [38] is used with parameter values as in [17]. (g)–(l) Filaments accumulate twist as a result of rotational anisotropy combined with an elongated tip trajectory, which together allow different layers of the tissue to experience the furthest reaches of the tip trajectory at different times. New filaments can form when twist produces elongation and buckling. The model of [38] is used with parameter values as in [17]. See interactive Java applets [Figure_29a_applet.html](#) and [Figure_29b_applet.html](#).

in breakup without the need for low excitability [17, 38, 149, 150]. In this case, if a 2D spiral wave exhibits an elongated trajectory, different portions of the 3D scroll wave analogue may reach the farthest point in the trajectory at different times, thereby inducing localized twist in the filament. The twist can build up and produce a localized buckling (called a twiston) [38] in the filament, and through elongation the buckle may reach the surface, resulting in a new U-shaped filament. If the twist is not located in this U-shaped filament, it will collapse quickly, but if the twist is in the new filament, it will continue to exist and will exhibit elongation, a process that can become self-sustaining, as shown in figure 29(b) and the corresponding interactive 3D Java applet.

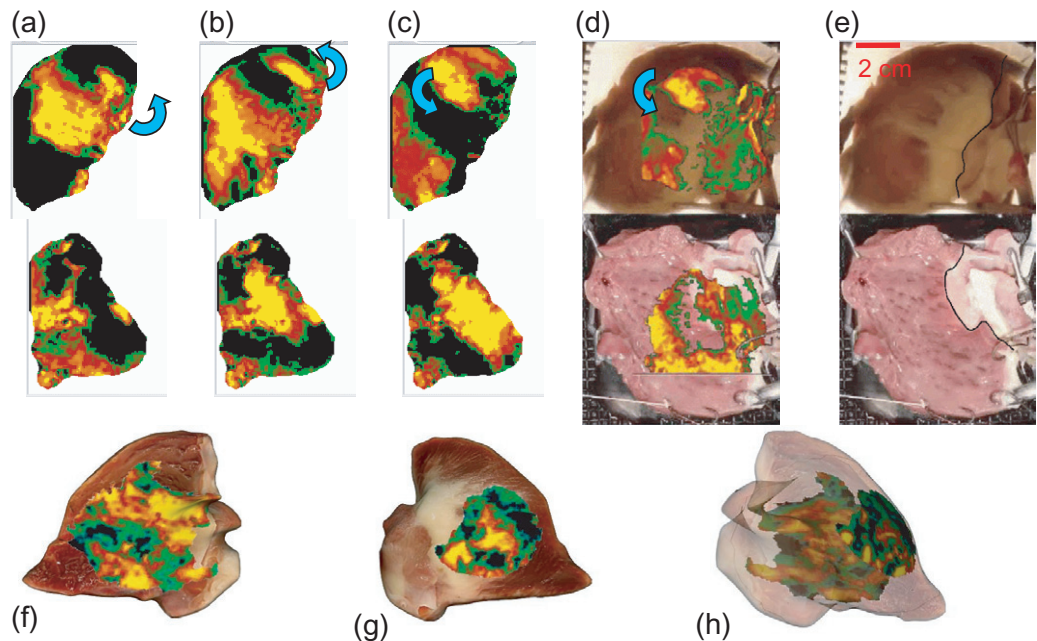


Figure 30. (a)–(c) Reentrant spiral wave on the epicardial (top) and endocardial (bottom) surfaces of a canine ventricular preparation. (d) Same reentrant waves on the epicardial (top) and endocardial (bottom) surfaces superimposed on a digital photograph of the preparation. (e) Digital photograph of the preparation with the ventricle (left) separated from the atrium (right) with a black line. (f)–(h) Reconstructed 3D anatomy with overlaid optical mapping images during fibrillation. (f) Epicardial view. (g) Endocardial view. (h) Transparent view to allow simultaneous viewing of both endocardial and epicardial surfaces. See movie [Figure_30ae_movie.mov](#) and interactive 3d java applet [Figure_30fg_applet.html](#).

4.2. Visualization of 3D experimental activity

Because depth information generally cannot be obtained at sufficient spatial resolution using experimental technologies like plunge electrodes, filament visualization usually is not possible for experimental data. Nonetheless, some basic characteristics of filaments can be inferred from surface data from optical mapping. Spiral waves visible on the surface correspond to endpoints of filaments. Repetitive activations in the absence of a visible spiral wave may be indicative of intramural filaments within the tissue depth. In some cases, the direction of propagation can be obtained from optical upstroke shapes [156], but it is not always possible to distinguish intramural scroll waves from ‘breakthrough’ excitations generated by focal (auto-oscillatory) activity. Because filaments can be complex in structure, the surface activity on the epicardium and endocardium can be quite different. Figures 30(a)–(e) show electrical activity recorded simultaneously from the epicardium (top) and endocardium (bottom). A clearly identifiable reentrant wave can be observed on the epicardial surface, whereas multiple reentrant waves can be seen on the endocardial surface (also see the corresponding movie), indicating complex intramural dynamics.

Reconstruction of cardiac anatomy from MRI can be a useful visualization tool for understanding optical mapping data in the context of 3D tissue. By performing MRI scans on the

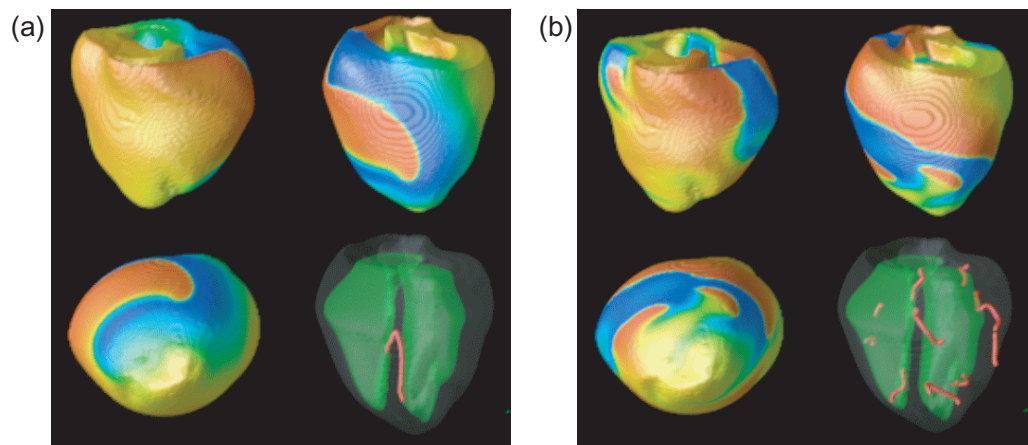


Figure 31. (a) Single spiral wave in the rabbit ventricular geometry of [74] simulating VT. (b) Multiple spiral waves in the same geometry simulating VF. In both cases, top views show surface wave activity; bottom views show filaments in red with transparent epicardium (gray) and endocardium (green). See movies [Figure_31a_movie.mov](#) and [Figure_31b_movie.mov](#).

experimental preparation after the experiment, the resulting images can be used to reconstruct the preparation anatomy in 3D. The experimental data then can be overlaid onto the structure, allowing the three-dimensionality of the preparation to be appreciated. Figures 30(f)–(h) show examples of epicardial and endocardial surface data overlaid on a reconstruction of the ventricular preparation on which it was observed. Using the corresponding 3D Java applet, the reconstructed preparation can be rotated and viewed from any angle and made transparent, and activations can then be correlated between epicardium and endocardium to assist in inferring the intramural dynamics.

Under certain conditions, it is possible to view the filament directly. Transmural illumination with optical mapping can give information about the location of the vortex filament, but only when it is stationary and follows a very small circular core and the tissue thickness is optimal [157]–[159]. Because fibrillation often is characterized by multiple non-stable reentrant waves, it is therefore still important to pursue other approaches to visualizing filament dynamics.

4.3. Simulated arrhythmias in anatomically realistic geometries

The complexity of anatomically realistic geometries allows more complicated patterns of reentry similar to what is observed during cardiac arrhythmias. Heterogeneous structures, including anisotropic fiber geometry, wall thickness variations, curvature, irregular boundaries such as blood vessels and valve annuli, and the periodicity of the structures can combine to produce complex dynamics.

4.3.1. Ventricular arrhythmias. Ventricular tachycardia (VT) is generally believed to correspond to a single scroll wave in the ventricles, whereas VF is believed to correspond to multiple waves. Figure 31 and the corresponding movies show examples of simulated VT and VF using a rabbit ventricular geometry [74] and the three-variable model from [38] with parameter values [160] to reproduce the dynamics observed experimentally [161] in rabbit

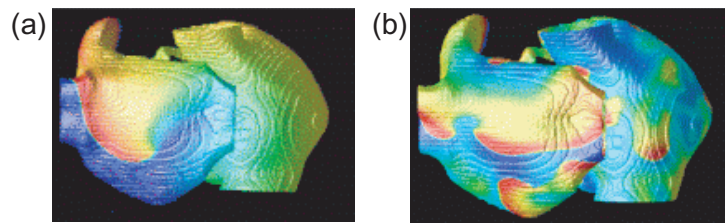


Figure 32. (a) Single spiral wave in the human atrial geometry of [76] simulating AFL. (b) Multiple spiral waves in the same geometry simulating AF. In both cases, surface wave activity is shown. See movies [Figure_32a_movie.gif](#) and [Figure_32b_movie.gif](#).

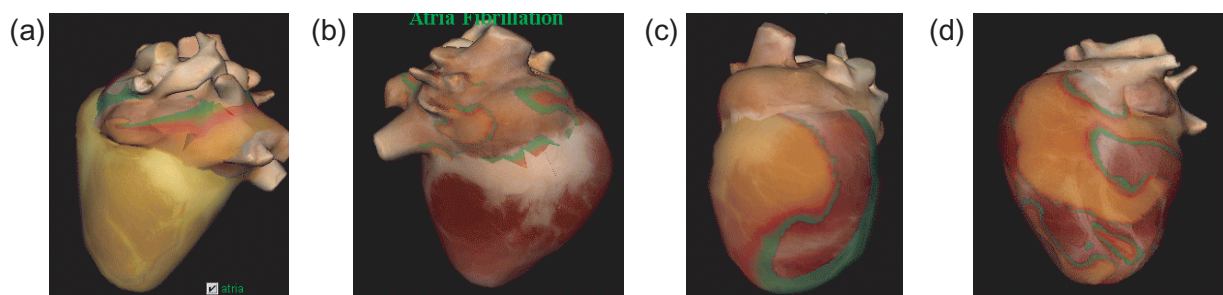


Figure 33. Arrhythmias in the context of the whole heart. (a) Atrial flutter. (b) AF. (c) VT. (d) VF. Applets from [1]. See interactive Java applets [Figure_33a_applet.html](#), [Figure_33b_applet.html](#), [Figure_33c_applet.html](#), and [Figure_33d_applet.html](#).

ventricles using two drugs, diacetyl monoxime (which results in VT) and cytochalasin-D (which results in VF). 2D spiral waves using both parameter sets are stable, but the set producing VF in the rabbit geometry has a longer wavelength and linear core trajectory leading to twist-induced breakup [17, 38, 149, 160].

4.3.2. Atrial arrhythmias. Atrial muscle is generally much thinner than ventricular muscle and in many cases can be considered quasi-2D. Nonetheless, the thin atria have a complex 3D anatomy that must be included in a realistic geometry, including complex irregular boundaries, curvature, and pectinate muscles and other regions with variations in conduction velocity [76]. Atrial arrhythmias can arise from multiple dynamical mechanisms, including ectopic foci and reentry [19]. When reentry is present, a single reentrant wave is thought to underlie AFL, whereas multiple reentrant waves are thought to underlie AF. Figure 32 and the corresponding movies show examples of simulated AFL and AF using the human atrial anatomy of [76] together with the human model of [64] for AFL and a model based on that of [65] for AF.

4.3.3. Arrhythmias in the context of the whole heart. Visualization of arrhythmias within the context of the whole heart allows a greater appreciation of organ-level phenomena. Figure 33 and the corresponding 3D interactive Java applets show simulations of AFL and AF as well as VT and VF using reconstructed canine hearts from MRI. Because the atria and ventricles are electrically isolated except for a single connection at the atrioventricular node,

arrhythmias generally remain confined to either the atrial or ventricular chambers (see the movie corresponding to figure 30(a)–(e), where atrial activation is independent of the VF). Because the ventricles are responsible for pumping blood, atrial arrhythmias therefore do not significantly compromise cardiac contraction, although they can elevate ventricular rate and increase the risk of blood clots that may lead to stroke. VT reduces the effectiveness of contraction but does not completely desynchronize it, as shown in the corresponding interactive 3D Java applet. However, VT is usually unstable and proceeds to VF, during which contraction becomes highly disorganized, with no coordinated pumping action, as shown in the simulation in the corresponding Java applet. VF therefore is considered the most dangerous arrhythmia and must be terminated as quickly as possible.

5. Arrhythmia termination

In most cases, arrhythmias become sustained upon induction and do not self-terminate. (Atrial arrhythmias in normal atria, which generally self-terminate, are an exception, but diseased atria can fibrillate readily.) Because the disorganized activity associated with VF prevents effective contraction and pumping of blood, VF is a life-threatening arrhythmia that must be terminated rapidly to prevent death and to minimize damage to cardiac tissue and other organs. Atrial arrhythmias, on the other hand, are less immediately dangerous but increase the risk of other cardiac problems, including stroke. Termination of ventricular arrhythmias is called defibrillation, whereas termination of atrial arrhythmias is called cardioversion. Arrhythmia termination generally is accomplished either through pharmacological therapy that modifies electrophysiological properties, thereby affecting arrhythmia dynamics, or through electrical interventions that act to reset electrical activity directly. Arrhythmias also can be terminated in some cases through the use of ablation, in which inexcitable lesions are created in a pattern to disrupt reentrant circuits.

5.1. Pharmacological defibrillation and cardioversion

A large number of anti-arrhythmia drugs are available either to terminate arrhythmias or to prevent their induction. Figure 34 and the corresponding movie show an example of equine AF induced in the presence of 4 μ M ACh that is terminated by administration of the antiarrhythmic agent quinidine (12 μ M). Although the precise mechanism by which the drug works is not completely understood, quinidine is believed to terminate atrial arrhythmias by increasing the effective refractory period [162] and decreasing the frequency of the arrhythmia until it can no longer be sustained. The increase in arrhythmia regularity and frequency decrease can be seen in the single-pixel optical recoding of figure 34.

5.2. Electrical defibrillation and cardioversion

Application of electrical shocks to terminate arrhythmias can be highly effective in a short period of time and is the best treatment available for VF. Achieving the optimal shock strength is important: shocks that are too weak can be ineffective or re-initiate the arrhythmia [22, 163, 164], but strong shocks can damage the heart [165]. Atrial arrhythmias also can be disrupted through electrical cardioversion, although prolonged AF can induce electrophysiological changes that allow AF to recur. Figure 35 and the corresponding movie show an example of cardioversion of an atrial arrhythmia in canine tissue and illustrate that upon application of the

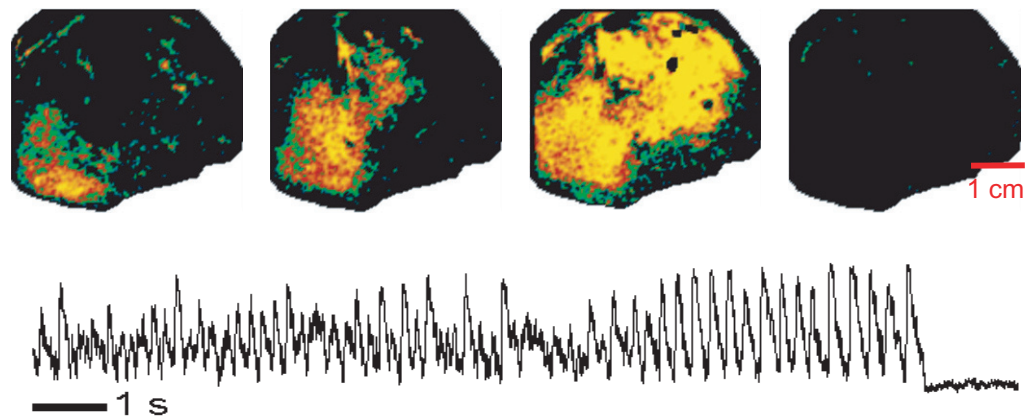


Figure 34. Termination of equine AF by quinidine. AF induced in the presence of $4 \mu\text{M}$ ACh is terminated by administration of $12 \mu\text{M}$ quinidine. Top: electrical activity during fibrillation. Times are 7.34, 9.11, 11.80 and 12.14 s. Bottom: optical signal from one pixel showing AF termination. See movie [Figure_34_movie.mov](#).

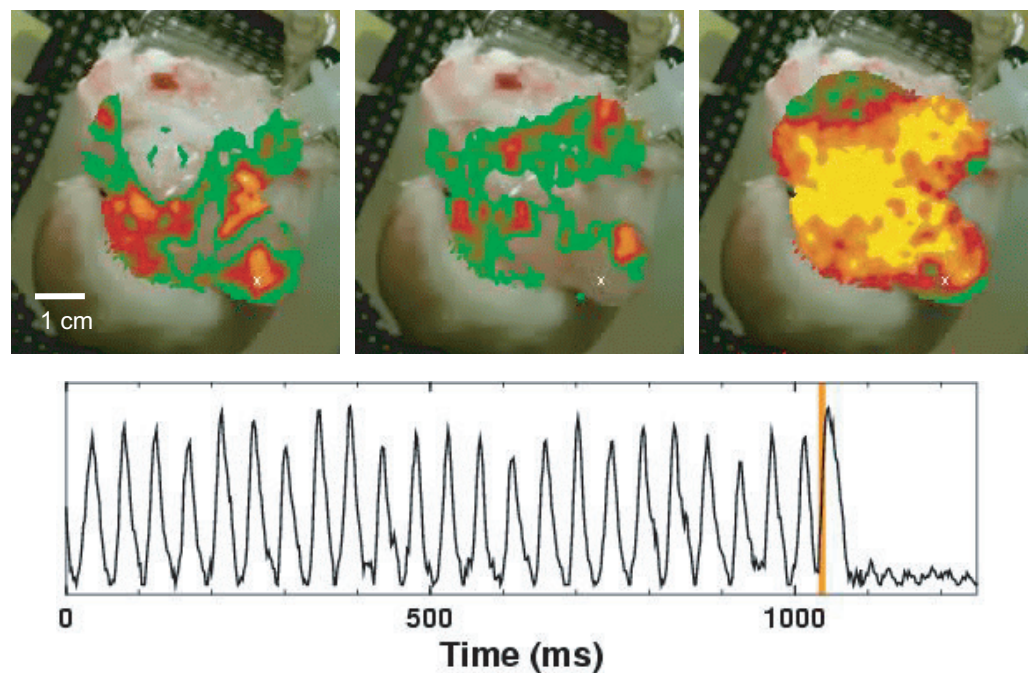


Figure 35. Example of defibrillation following application of a high-energy shock in canine atrium. Top: left and center frames show irregular activity characteristic of AF. Right frame shows near-simultaneous activation of almost the entire mapped region in response to the shock, after which quiescence ensues. Data are superimposed on a digital photograph of the preparation. $2 \mu\text{M}$ ACh was used. Bottom: optical signal from a single pixel showing termination of fibrillation following the shock. See movie [Figure_35_movie.mov](#).

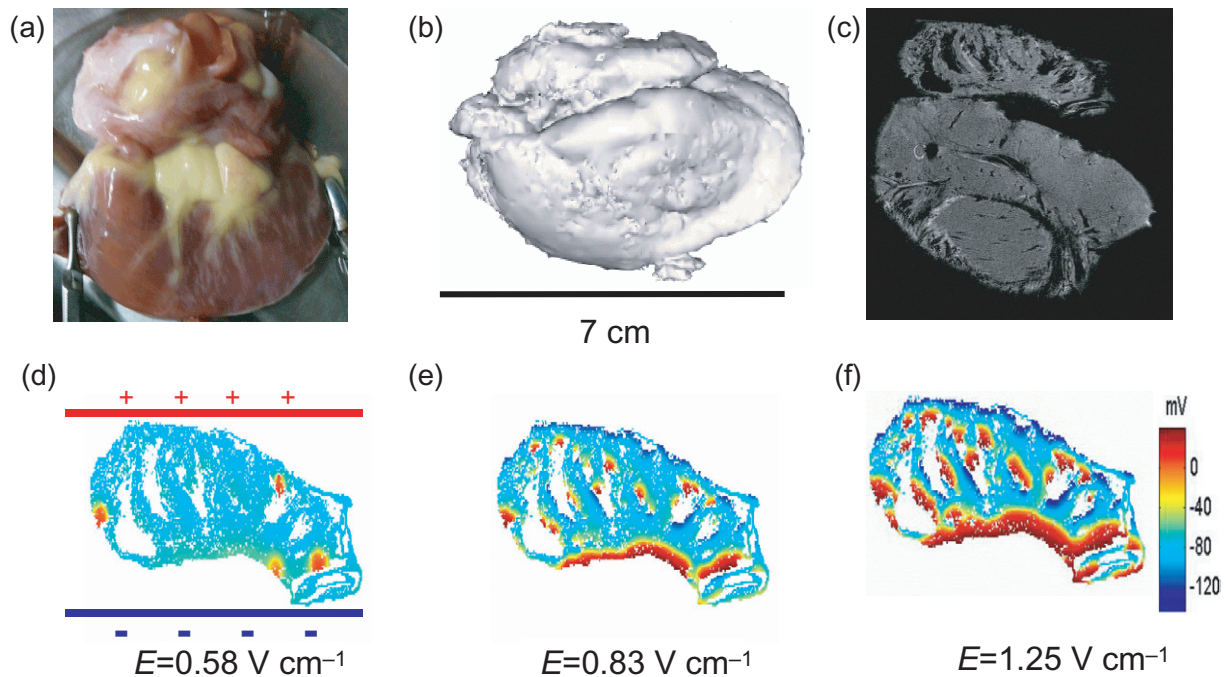


Figure 36. Formation of secondary sources in cardiac tissue. (a) Photograph of experimental tissue preparation. (b) 3D anatomy reconstructed from MRI images taken from tissue shown in (a) at a resolution of $120 \mu\text{m}$. (c) Sample MRI image. (d)–(f) Regions of depolarization and hyperpolarization formed from an applied electric field in a 2D slice of the atria shown in (c). As the electric field is increased, more secondary activations by internal virtual electrodes appear. Activations in (d) are shown 0.8 ms after application of the electric field, whereas (e) and (f) are shown 0.4 ms after. See applet [Figure_36b_applet.html](#) and movies [Figure_36d_movie.mov](#), [Figure_36e_movie.mov](#), and [Figure_36f_movie.mov](#).

shock, most of the tissue in the mapped region becomes excited, leading to termination of the arrhythmia.

Although defibrillation can be highly effective, the mechanism by which it works is still not well understood [21, 23]. The goal is to excite all remaining quiescent tissue, so that reentrant waves will be terminated. It is believed that defibrillation occurs in conjunction with the formation of ‘virtual electrodes’ [22]. Application of an electric field can give rise to the formation of secondary sources [83]–[85] at the interfaces between regions of different conductivity (heterogeneities such as blood vessels, collagen or other small-scale inexcitable regions). If the heterogeneities are widely distributed and the shock strength is high enough, the secondary sources can excite all remaining quiescent tissue, thereby terminating the activity. Figure 36 and the corresponding movies show an example of virtual electrode formation and secondary sources in simulated cardiac tissue using a realistic cardiac geometry reconstructed from an MRI scan of a canine ventricle at a resolution of $120 \mu\text{m}$. In this example, a lower electric field strength creates only a few virtual electrodes, whereas the higher strength field generates more. Thus, a sufficiently high field strength can defibrillate fibrillating tissue.

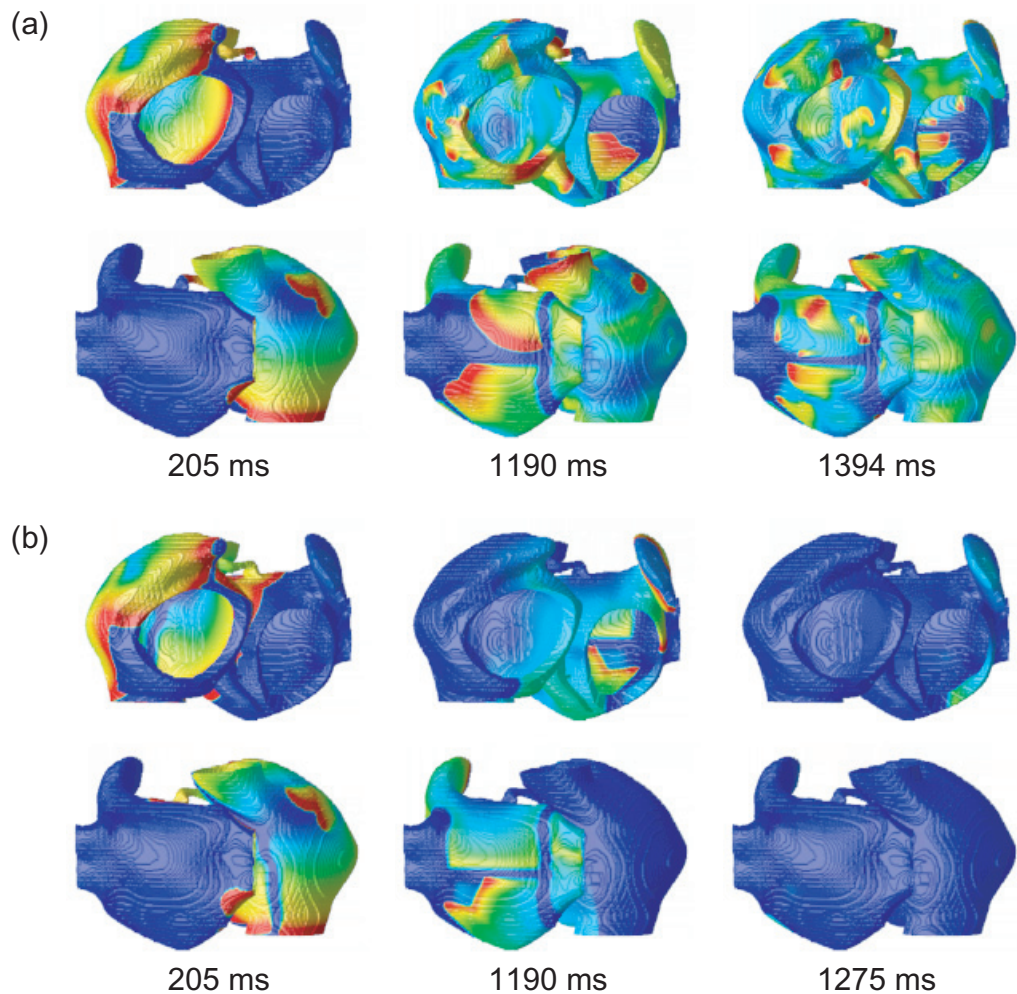


Figure 37. Simulated atrial fibrillation with inexcitable lesions simulating catheter ablation using the atrial structure from figure 8(a) [76]. (a) When lesions are included only in the left atrium, induced AF persists for the full 7 s simulated. (b) When lesions are included in both atria, induced AF terminates in just over 1 s. The model is the same as used in figure 32(b). Top views show right atrium on the left; bottom views show left atrium on the left. See movie [Figure_37a_movie.mov](#) and [Figure_37b_movie.mov](#).

5.3. Ablation

Ablation is an alternative technique that can be quite effective in terminating certain types of arrhythmias. In this treatment, highly localized lesions are created in the heart through the application of radiofrequency energy or cryoablation. Repetitive arrhythmias-like AFI [166] and some forms of VT [167], together with arrhythmias triggered from localized ectopic beats [168], are particularly well suited for ablation. However, ablation also can be effective for more complex arrhythmias, including AF that does not arise from ectopy [169, 170], when lesions are positioned appropriately. Figure 37 shows an example of simulated AF that can be terminated or not depending on the positioning of the ablation lesions. In figure 37(A), lesions

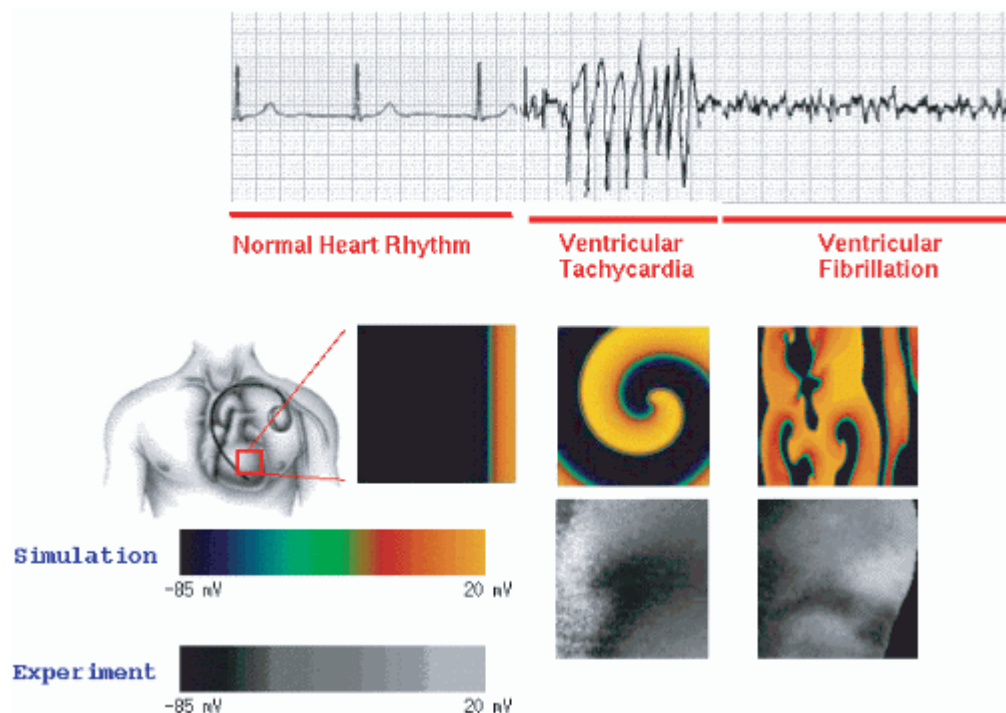


Figure 38. Visualization of ventricular arrhythmias including (top) ECG trace, (center) simulated tissue, and (bottom) experimental tissue preparation. A transition from normal sinus rhythm (corresponding to plane wave simulation) to VT (single spiral wave simulation and experiment) and ultimately to fibrillation (multiple spiral waves simulation and experiment) is depicted. See movie [Figure_38_movie.gif](#).

(simulated as inexcitable regions) are included only in the left atrium (isolating pulmonary veins and connecting to each other and to the mitral valve annulus), and the fibrillatory state persists for the entire 7 s simulated. However, the addition of lesions in the right atrium (lines connecting the superior and inferior venae cavae and connecting the inferior vena cava to the tricuspid valve annulus) terminated the same arrhythmia in just over 1 s.

6. Conclusions

Visualization techniques can allow a deeper appreciation of the propagation dynamics of electrical waves in cardiac tissue during normal rhythm and during its disturbances. Using such techniques can facilitate explanation of how arrhythmias develop. Increasingly realistic mathematical models and representations of the geometry of the heart are allowing more detailed studies of cardiac dynamics and will link more closely with experiments. Combining experimental and computational approaches therefore is becoming increasingly useful. For example, figure 38 shows a progression from normal sinus rhythm to VT and VF using a surface electrocardiogram together with simulated and experimental images of tachycardia and fibrillation featuring one spiral wave and multiple spirals, respectively. Such a visualization clearly depicts the difference in wave dynamics during these different states.

It will be important in the future to develop improved methods of obtaining experimental data. Recent advances in panoramic optical mapping have allowed the entire epicardial surface to be imaged [29, 147, 148], but a fuller understanding of scroll wave dynamics will require transmural information. Promising new techniques [31, 157], [171]–[173] are under development. However, increased experimental data will only be useful if it can be interpreted appropriately. Visualization methods will play an increasingly important role in understanding the complex dynamics of cardiac electrical waves.

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