Three dimensional aspects of re-entry in experimental and numerical models of ventricular fibrillation

V.N. Biktashev[1,2], A.V. Holden [1],
S.F. Mironov[3], A.M. Pertsov[3] and A.V. Zaitsev[3]

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[1]School of Biomedical Sciences, University of Leeds, Leeds LS2 9JT, UK
[2]On leave from: Institute for Mathematical Problems in Biology, Pushchino, 142292, Russia
[3]Department of Pharmacology, SUNY Health Science Center, 750 East Adams St., Syracuse, NY 13210, USA

Abstract

Ventricular fibrillation is believed to be produced by the breakdown of re-entrant propagation waves of excitation into multiple re-entrant sources. These re-entrant waves may be idealised as spiral waves in two dimensional, and scroll waves in three dimensional excitable media. Optically monitored, simultaneously recorded endocardial and epicardial patterns of activation on the ventricular wall not always show spiral waves. We show that numerical simulations, even with a simple homogeneous excitable medium, can reproduce the key features of the simultaneous endo- and epicardial visualisations of propagating activity, and so these recordings may be interpreted in terms of scroll waves within the ventricular wall.

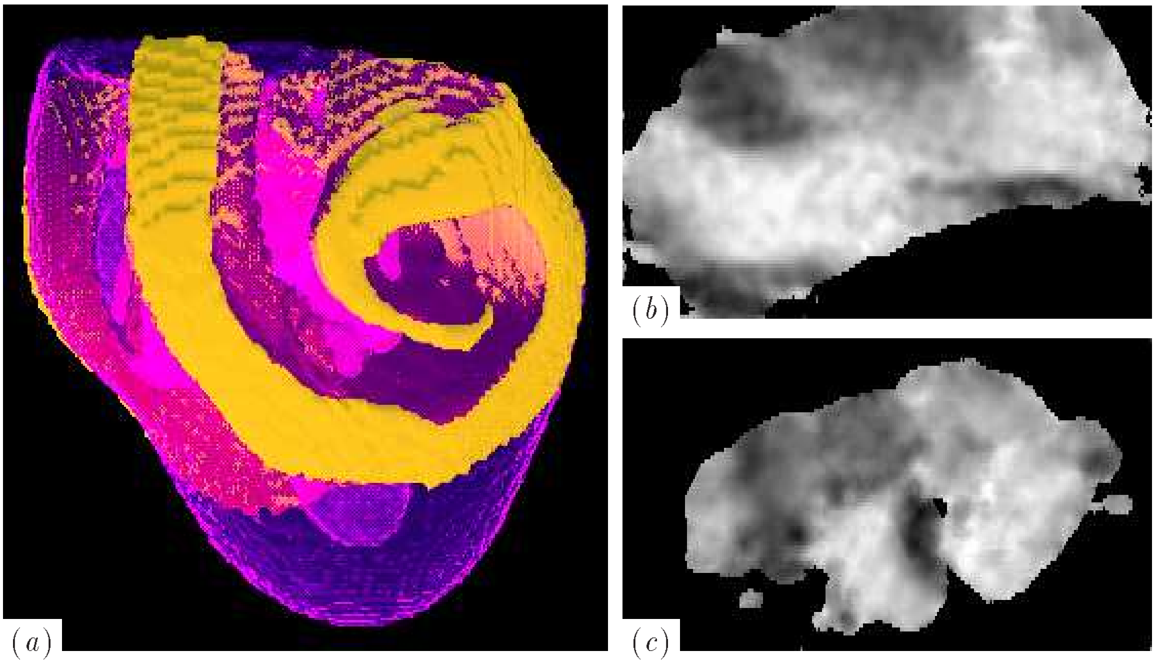

Figure 1: Theoretical understanding and experimental observations of ventricular fibrillation. (a) Scroll wave in an anatomically detailed model of canine ventricles. The ventricular wall is shown dark-blue and semi-transparent, the excited region is yellow and seen as magenta through the wall. (b,c) Snapshots of surface activity in an optical mapping experiment with electrically induced fibrillation in coronary perfused sheep ventricle preparation, synchronous (b) epicardial and (c) endocardial views of the same preparation.

1 Introduction

Ventricular fibrillation almost invariably occurs during the process of dying, and its onset underlies sudden cardiac death. It is widely believed that the mechanism of ventricular fibrillation is that it is produced by one or many re-entrant (spiral in 2D or scroll in 3D) propagating waves of excitation in the ventricular wall. This theoretical understanding is illustrated schematically on Fig. 1(a), showing a coupled-map-lattice excitable medium model [Holden, Poole & Tucker 1996] within the geometry of the Auckland anatomically accurate model of the canine heart [Hunter, Nielsen, Smaill, Legrice & Hunter 1992] (see also [Panfilov & Keener 1995a], [Gray & Jalife 1996], [Panfilov 1997] and [Berenfeld & Jalife 1998] for numerical experiments with scroll waves in anatomically accurate models with excitability described by partial differential equations). In this illustration, the scroll wave manifests itself as a spiral on the surface. However, even such a simple scroll wave need not appear as a spiral wave on the surface of the heart; a side view would show an almost planar wave train, a rear view a "V"-shape resulting from the collision of the propagating wavefronts.

Recently, detailed mapping of the surface electrical activity of the heart has become possible [Gray, Pertsov & Jalife 1998, Witkowski, Leon, Penkoske, Giles, Spano, Ditto &

Winfree 1998]. The patterns of excitation during experimental fibrillation may show no spiral waves on either surface of the heart muscle (see Fig. 1(b,c)). This difference between theory and experiment may mean either that the fibrillation is not due to re-entry, or that the re-entry waves are masked by the inhomogeneity, anisotropy and three-dimensional nature of the ventricular wall. In this Letter we show that the three-dimensional nature of the wall alone is enough to qualitatively explain the experimental observations, as these observations can be reproduced in numerical experiments with a simple mathematical model.

Mathematical models of cardiac excitability based on voltage clamp experiments with single cardiac cells and single channels use many variables to describe each cell, and can take into account the bidomain and anisotropic nature of the cell-to-cell conductivity and tissue inhomogeneity:

$$\begin{aligned} \partial_t E &= F(E, g_j, \vec{r}) + \hat{\mathcal{D}} \cdot E, \\ \partial_t g_i &= G_i(E, g_j, \vec{r}), \\ i, j &= 1, \ldots, N, \end{aligned}$$

where $\vec{r}$ is a vector of spatial coordinates; E is the transmembrane voltage; $\hat{\mathcal{D}}$ is the conductivity operator, which may explicitly depend on $\vec{r}$ and is integro-differential to take into account the bidomain structure of the tissue or degenerates into a Laplacian if it does not; and $g = (g_1, g_2 \ldots)^{\mathrm{T}}$ is a column-vector of local variables, including gating variables and ionic concentrations. In the case of the OXSOFT model of guinea-pig ventricular cell [Noble 1990, Biktashev & Holden 1996], $N = 16$. An illustration of re-entrant activity obtained in such a model is shown on Fig. 2(a), where we have used a second-order differential operator for conductivity suggested by Panfilov & Keener [1995b] and Fenton & Karma [1998]:

$$\hat{\mathcal{D}} \cdot E = \sum_{i,j=1}^{3} \frac{\partial}{\partial r_i} D_{i,j}(\vec{r}) \frac{\partial E}{\partial r_j}. \tag{1}$$

This form takes into account the rotational anisotropy of the real ventricular tissue: the direction of the fibres which is the direction of the largest eigenvector of the conductivity tensor $D_{i,j}$. This is a scroll wave in a small ($5 \times 5 \times 1.5\,\mathrm{mm}$) slab of tissue with specially chosen boundary conditions, to permit the existence of a re-entrant wave (with zero-flux boundary conditions, a persistent re-entry wave in this model requires a larger piece of ventricular wall). As shown by Fenton & Karma [1998], for simplified FitzHugh-Nagumo local kinetics, with parameters that have stable scroll waves in a homogeneous, isotropic medium, such inhomogeneity and anisotropy of tissue can be sufficient to make a simple re-entrant, transmural scroll wave unstable and lead to spatiotemporal irregularity.

Complicated local kinetics and complicated description of conductivity make modelling computationally expensive. Some qualitative results can be obtained for simpler models, which caricature the excitation and propagation properties of cardiac tissue. Neither complicated and stiff local kinetics, nor inhomogeneity or anisotropy are required to produce

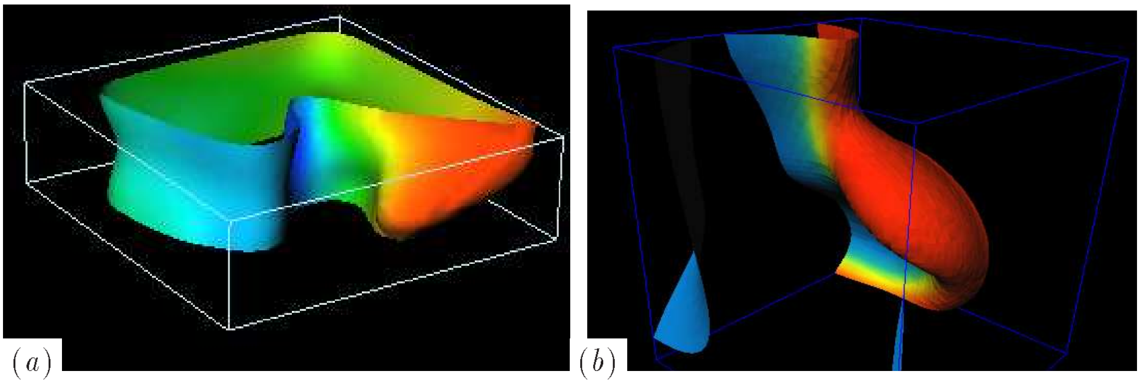

Figure 2: Scroll waves in mathematical models of excitable tissues. (a) Kinetics of OXSOFT guinea-pig ventricular cell, with rotational anisotropy of conductivity tensor. (b) FitzHugh-Nagumo model with homogeneous isotropic conductivity, but with negative tension of scroll filaments. Shown are the isosurfaces of the excitation variable, painted depending on the recovery status, so that red corresponds to the front of the excitation wave, blue to its back and yellow to the edge between the front and the back, *i.e.* the scroll filament.

complicated spatio-temporal behaviour of the excitable medium. We used for simulations the simple homogeneous FitzHugh-Nagumo ($N = 1$) excitable medium model with simple diffusion-like conductivity. At some parameter values, the scroll wave filaments in this model have negative tension, which leads to their breakup and development of a three-dimensional "turbulence" of excitation waves, resembling fibrillation [Biktashev, Holden & Zhang 1994, Biktashev 1998]. Figure 2(b) shows a scroll wave in this model before the breakup into two pieces. In this Letter we show, that the surface patterns of this "numerical fibrillation" demonstrate the same qualitative features as the patterns observed in optical mapping experiments.

2 Methods

Numerical We used for simulations FitzHugh-Nagumo system of equations:

$$\begin{aligned} \partial_t E &= \epsilon^{-1}(E - E^3/3 - g) + \nabla^2 E, \\ \partial_t g &= \epsilon(E + \gamma - \beta g), \end{aligned} \tag{2}$$

where $\epsilon = 0.3$, $\beta = 0.75$ and $\gamma = 0.5$, with forward-time Euler differencing with time step 0.03 t.u. and simplest seven-point approximation of the Laplacian on a rectangular grid with space step 0.5 s.u., in media of different size with non-flux boundary conditions. The period of spiral wave in this model is about 20 t.u., This choice of parameters provides negative tension of the filaments, *i.e.* scroll waves in sufficiently large media are unstable, their filaments tend to lengthen, curve, touch the boundaries and each other and break onto pieces, each of which then grows again etc. At the same time, the same set of

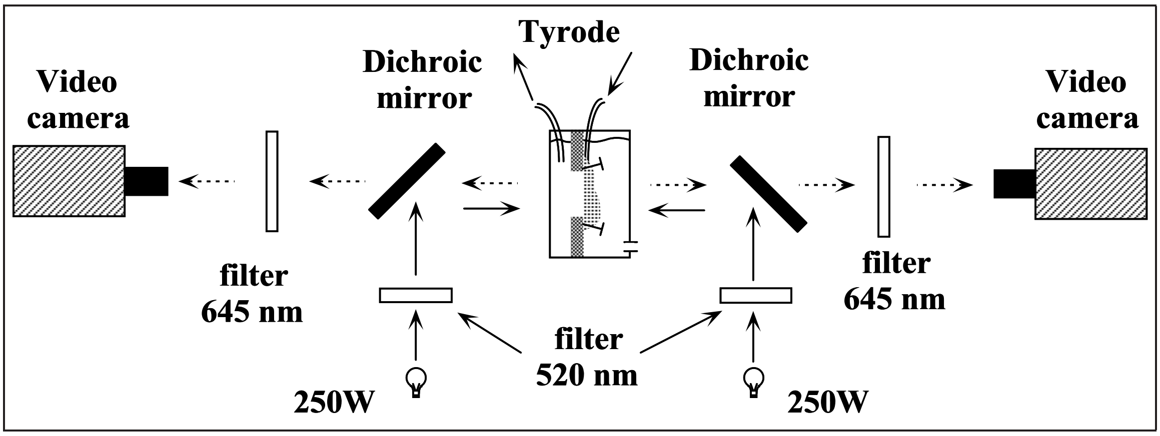

Figure 3: Schematic of the experimental setup.

equations in two spatial dimensions shows quite stable spiral waves. This is in qualitative correspondence with the fact that real fibrillation is only observed in sufficiently thick hearts or heart preparations. The activation patterns at the opposite (upper and lower) surfaces of the medium were recorded and visualised in the same way as experimental patterns (see below).

Experimental Experimental visualisations of electrical activity were from the endo- and epicardial surfaces of pieces of sheep ventricular wall (5-11 mm thick) that had been excised and perfused via the coronary arteries, and superfused with oxygenated physiological saline containing a drug (diacetyl monoxime), that blocked contraction, and a potential-sensitive dye (di-4-ANEPPS). The video images were obtained at 120 frames/s with a spatial resolution of approximately 0.5 mm (see Fig. 3). The optical signals at different points were normalised to allow for the variations of the dye concentration etc. The points where the signal was too low were excluded from consideration, so the shape of the patterns represents not the excitable ventricular preparation, but merely the stained part of it, typically of the size of about $3 \times 3\,\mathrm{cm}^2$. More technical details can be found in [Pertsov, Davidenko, Salomonsz, Baxter & Jalife 1993].

Irregular, self-sustained re-entrant propagation can be induced in a resting tissue preparation by rapid electric pacing; this provides an experimental model for the electrical activity during ventricular tachycardia (high — up to about 10 Hz— frequency activity, believed to be due to simple re-entry in the ventricle) and fibrillation (irregular, high frequency activity due to multiple re-entrant sources). Figure 1(b,c) shows typical simultaneous images of endocardial and epicardial activity.

Periods of excitation in our experiments were up to about 200 ms in “monomorphic tachycardia” and in the range of 100–150 ms in “fibrillation”. So we may scale the time unit of (2) roughly as 5–10 ms.

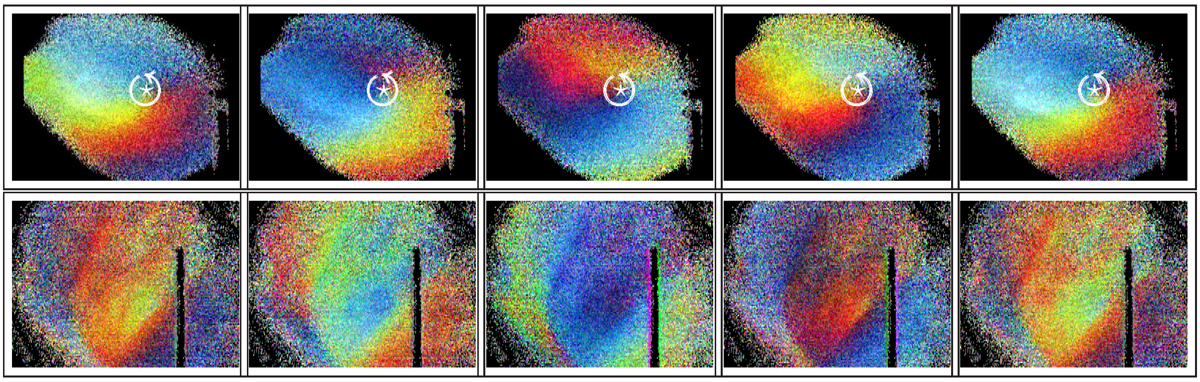

Figure 4: Time-delay coloured snapshot of a simple propagation pattern. Counter-clockwise rotating spiral wave is seen on epicardial surface (upper row), while focal source is seen on the endocardial surface (lower row). Interval between snapshots 33 ms.

Visualisation Raw images like Fig. 1(*b,c*) are not easy to interpret. For visualisation purposes, in all further experimental pictures we use a time-delay colouring method (see *e.g.* Fig. 4). The method was as follows: three copies of the same experimental series are made, the second with delay of 25 ms and third with delay of 50 ms with respect to the first one, and assigned three different colours (red, green and blue) and superimposed. Each frame now shows not only the instantaneous activation pattern, but also its direction of propagation: *e.g.* red is the front of the excitation wave.

This method of colouring is essentially similar to that described in [Gray et al. 1998], as here the colour represents the oscillation phase. The cores of the spiral waves are seen as the site around which the whole loop of colours is seen (the sequence red-yellow-green-cyan-blue-magenta-red). Not always the whole sequence would be seen on one frame, as both the visual propagation velocity and the shape of the optical signal at different points vary significantly. Still, this method proved to be convenient for finding cores of the spiral waves where the spiral shapes are not pronounced. Figure 4 shows an "ideal" example of the spiral wave seen on the epicardial surface.

The delay for colouring of numerical patterns was 1.8 t.u. which is only slightly shorter than the duration of the excitation pulse in the model and so could not be made longer. As a result, in numerical pictures there is large amount of black colour.

The volume patterns (Fig. 6(*c*) and Fig. 7(*c*)) were visualised analogously to Fig. 2, using isosurfaces of E, namely $E = 0$. To reveal more details of the complicated spatial structures, we showed only wavefronts (lower values of g, red and semi-transparent), and their edges (intermediate values of g, greenish and non-transparent), and made the wavebacks (higher values of g) invisible.

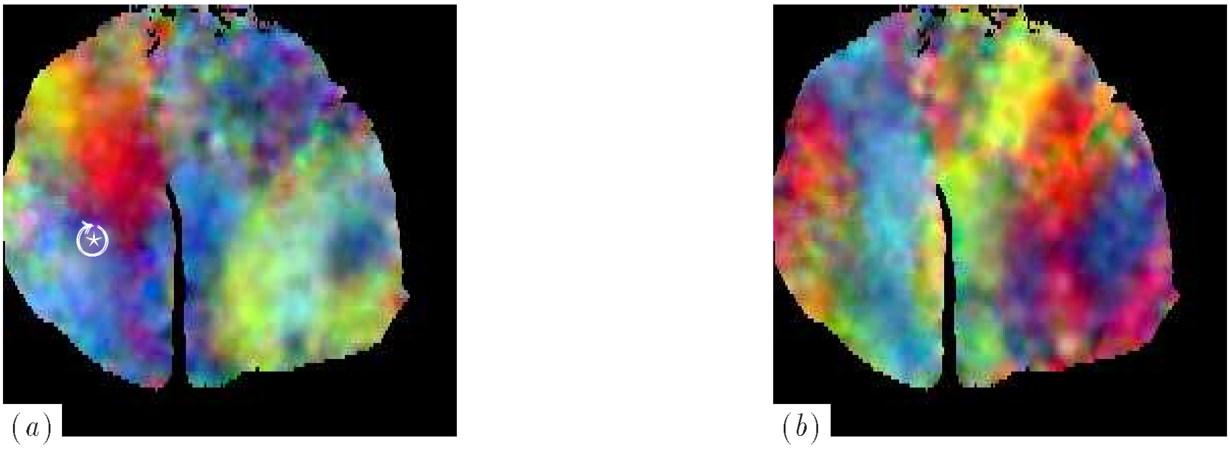

Figure 5: Transient spiral wave on the epicardial surface. (a) Spiral wave rotates clockwise, symbol shows the rotation center. (b) The same preparation, 2.5 s later. No spiral wave is seen; the activation pattern is nearly plane waves propagating from left to right. The dark line is the "shadow" of an electrode.

3 Results

Experimentally observed patterns of surface activity, shown on Figures 1(b,c) are more complicated than the caricature of Fig. 1(a). In exceptional cases, clear spiral waves can be observed, as seen on the epicardial surface in the example shown on Fig. 4. This figure also illustrates that if a spiral wave is visible on one surface, it may not be seen on the other surface. Indeed, the activity on the endocardial surface on Fig. 4 is qualitatively different, and resembles that of a focal source. Note that spiral waves and focal sources have been considered to underlie alternative mechanisms of tachycardia. This example illustrates that activity in ventricular muscle is essentially three-dimensional, and this allows the two different patterns to be different surface manifestations of the same events happening in the bulk of the tissue.

Most often, no spiral waves are apparent and the activity appears to be irregular in space, while at any point it is repetitive (roughly periodic) in time. The apparent complexity of the patterns of activity on the heart surface does not remain the same during an episode of experimental ventricular fibrillation, and this does not appear to be by spiral waves breaking down into irregularity. Cores of spiral waves are shown in the pictures by symbols and . The locations of these cores were done manually by visiual analysis of the movies rather than still pictures. Though the automatic detection of phase singularities is possible [Gray et al. 1998], manual detection is more reliable. Figure 5 shows two snapshots from the same experiment. In less than three seconds, the propagation pattern has changed completely, and where a spiral wave was at one moment, plane waves are seen later.

The typical qualitative properties of experimentally observed excitation patterns can be summarised as follows.

- Synchronous endo- and epicardial views of the same preparation can, and most often do, show different dynamics. In case of simple excitation pattern, corresponding to monomorphic tachycardia, the patterns are different but synchronous; in more complex cases, corresponding to polymorphic tachycardia/fibrillation, they seem virtually independent.

- At every particular point, most of the time the electrical activity is approximately periodic. The spatio-temporal pattern as a whole can be approximately periodic, in the examples that correspond to monomorphic tachycardia, but not in the examples that correspond to polymorphic tachycardia/fibrillation.

- During fibrillation, spiral waves are sometimes seen on the surfaces, but quite often they are not. If they are seen, they appear only transiently, for a few rotations, and then disappear.

- The (visual) complexity of the patterns changes with time; at large times, it appears to increase.

All these observations are consistent with scroll waves of excitation within the bulk of the ventricular wall. We illustrate this by numerical simulations. Mathematical models can be used to reconstruct the excitation patterns on the surface and within the bulk of the tissue, while with current experimental techniques only the surface patterns can be directly visualised. Simulating this model in different medium sizes, we were able to reproduce the qualitative features of the experimental surface patterns. Two typical examples are shown on Fig. 6 and Fig. 7.

Figure 6(a) shows activity in which the epicardial surface is being depolarised by an almost spatially uniform, time periodic depolarisation, while activity on the endocardial surface is a wave train propagating from left to right. In both cases the temporal period is approximately 190 ms. A simple three dimensional mechanism for this would be a single scroll wave, with its filament roughly parallel to the surfaces of the heart, and its position closer to the endocardial surface, as illustrated by Fig. 6(b,c). If the filament were far from the epicardial surface, the excitation wavefront would meet the epicardial surface almost simultaneously, giving a spatially uniform depolarisation. If the filament were closer to the epicardial surface, the curved excitation wavefront would first meet the epicardial surface as a narrow band, and excitation would propagate perpendicular to the band, in both directions, at a velocity faster than the propagation velocity for a plane wave. This is seen in Fig. 6(c), where the apparent velocity of the simulated epicardial wave front is considerably higher than that of the endocardial wave, that has the same period. Krinsky, Pertsov, Fast & Biktashev [1991] have suggested such a scroll wave, or scroll ring, as an explanatory mechanism for a narrow band of surface excitation that spreads away in both directions from its midline. For the model (2), with the parameters used, a single scroll wave is unstable in a large medium[Biktashev 1998], and so a double scroll is used to reproduce this behaviour in Fig. 6(b,c). On the nearest and on the most distant surfaces of the medium, two-armed spiral waves would be seen; but the activation patterns on the

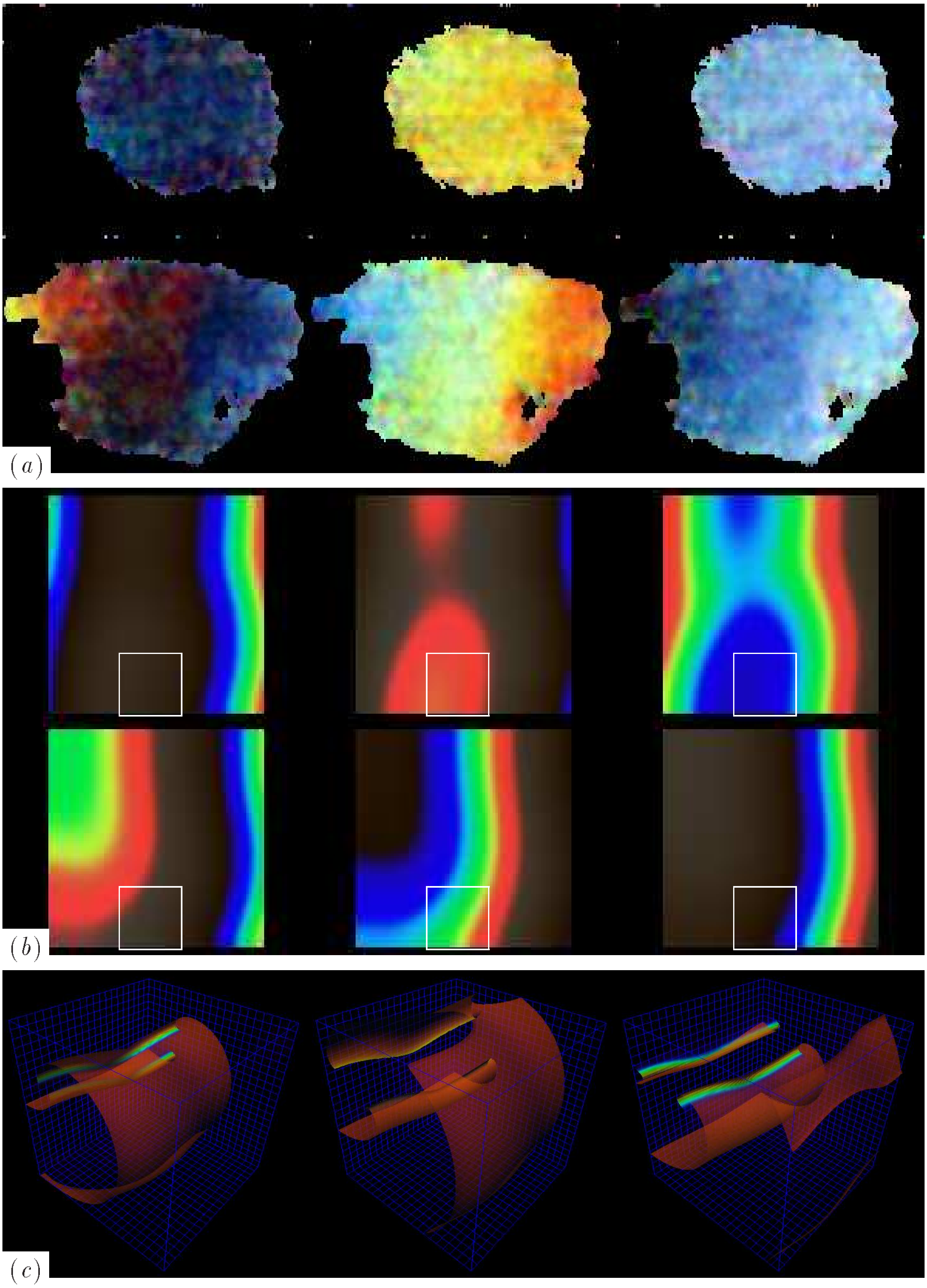

Figure 6: Comparison of experimental surface views of simple excitation pattern ("monomorphic tachycardia") with numerical simulations of metastable double scroll in FHN (medium size $43 \times 43 \times 43$ s.u.). (a) experimental patterns, the upper three pictures are epicardial views and the lower three pictures are endocardial views with interval 50 ms. (b): numerical simulations, surface patterns. White frames show the region where the behaviour in the experiment. (c): numerical simulations, corresponding volume view.

upper and lower surfaces do not show spiral waves. The filaments of the double scroll are curved and far enough from the upper surface. Therefore, the front is convex when approaching this surface, and a focal source of waves is observed at the point where the wavefront first touches it. And the lower surface shows just waves propagating from left to right, as it is close to the double scroll filaments, and the emanated wave is not convex enough to form a focal source.

White frames on Fig. 6b indicate an area where the experimental excitation patterns of Fig. 6a are reproduced almost literally. Namely, synchronous oscillations on the epicardial surface, and waves from the top-left corner to the right-hand side, not the endocardial surface. That is, if only the region within this white frame was "stained" with the voltage-sensitive dye, we would see exactly the same activation pattern as in the real experiment.

The more complicated, irregular surface views are characteristic of the later, "fibrillation" stages. Such views can be qualitatively reproduced by a small number of interacting scrolls that are continually breaking down and being born from broken wavefronts. This is illustrated in Fig. 7, where the model parameters are such that simple (single or double) scroll waves are unstable and breakdown occurs. The endo- and epicardial images show coherence at the scale of the action potential wavelength, so can be described as propagating, curved wavefronts, that sometimes have ends (corresponding to a phase singularity), and occasionally spiral forms can be identified. The feature of these surface images can be simulated by a few interacting scroll waves. The "literal" reproduction of experimental patterns in the mathematical model seem to have little sense. The reason is that the dynamics of the scroll waves in this model is inherently unstable, analogously to the Kuramoto-Sivashinsky wavefronts, and arbitrarily small difference in initial conditions leads to significant difference in the solution [Biktashev 1998]. This feature is essential for the imitation of the fibrillation, if the latter to be considered as a chaotic process. Figure 7 shows a typical experimental pattern and its rough qualitative analogue found in a numerical experiment. On the epicardial surface of the experiment and on the top surface in the model, there are two spiral waves, one rotating clockwise and the other counterclockwise. On the endocardial and bottom surfaces, the pattern is more complicated: one counterclockwise rotating spiral (close to the right edge of visible area of the experimental preparation, and close to the upper edge of the numerical picture), and two-armed clockwise spiral in the middle. The positions of single spiral waves in all cases were relatively stable, *i.e.* they remained on the same place for a few rotations or slowly drifted, both in experiment and in the model. The two-armed spirals showed significant meander, again, both in the experiment and in the model, so the double $\circledast$ symbols only very approximately show their location. Double spiral wave could be produced by an appropriately oriented double scroll analogous to that shown on Fig. 6(b). However, we can see from Fig. 7(c) that it was not the case here, and the two filament are close to each other only near the surface and are independent in the bulk; perhaps, this could be related to their strongly nonstationary behaviour. This suggests that the appearance of the double spiral *i.e.* of the two spirals of the same sign together, might be a transient and, in a sense, an accidental event, same as an appearance of a single spiral. This is different from the appearance of pairs of spirals of opposite signs as described in [Gray et al. 1998] which appear or annihilate on a regular basis as a result

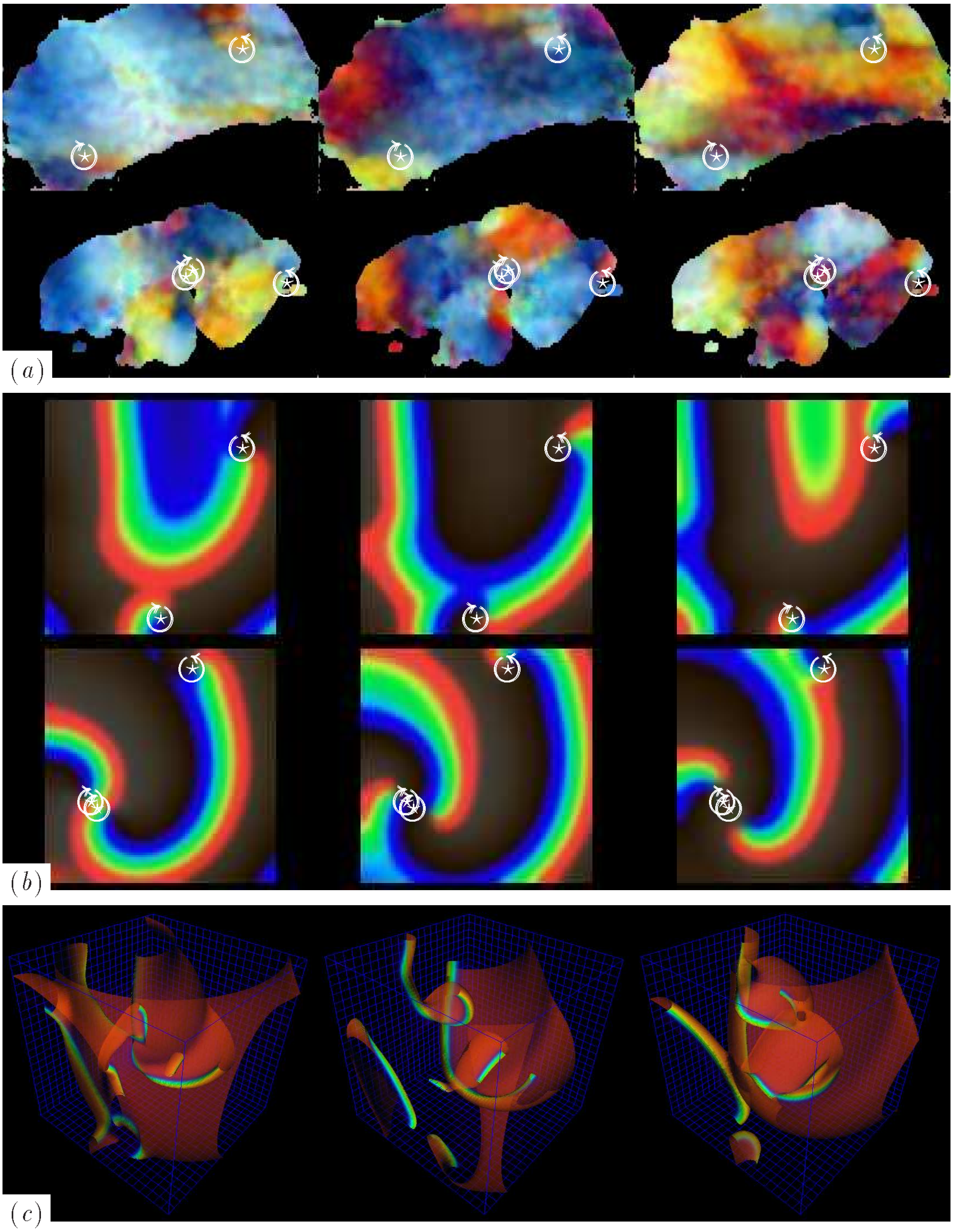

Figure 7: Comparison of experimental surface views of polymorphic tachycardia with numerical simulations of scroll turbulence in FHN (medium size $50 \times 50 \times 50$ s.u.). Layout is the same as on Fig. 6. The spiral waves are shown by white ⟳ and ⟲ symbols. Interval between experimental patterns 50 ms; between numerical patterns 4.2 t.u.

of a scroll filament touching the surface or detaching from from it.

All qualitative features summarised above, are reproduced in the numerical model. Namely,

- The patterns on opposite surfaces are indeed different, which is an obvious consequence of the three dimensional nature of the model. Moreover, if multiple scrolls are present, the pictures are not only different, but look uncorrelated.
- The dynamics of scroll waves is approximately periodic rotation around the filaments which can slowly move. This provides local approximate periodicity almost everywhere. Filaments of multiple scroll waves do not remain in rest, which provides the absence of global periodicity. Only simple (single or double) scrolls contained in a small volume, or attached to medium boundary, showed no drift in this model, and in this case the surface patterns were approximately periodic as a whole.
- The mobility of the multiple scrolls makes it quite likely for the filaments to appear on a surface for a short time and then disappear again; this is seen on the surface as a transient spiral wave.
- The complexity of the volume behaviour and of the surface patterns increases with the size of the medium, and requires lowered excitability of the local kinetics. Both these factors are in correspondence with changes in electrophysiology of the cardiac tissue during fibrillation.

4 Conclusion

Optical monitoring of surface activity is providing high-resolution images of the irregular spatio-temporal activity in different experimental models of ventricular fibrillation [Holden 1998, Gray et al. 1998, Witkowski et al. 1998]. The differences in spatial activity reported here demonstrate the essentially three-dimensional nature of the electrical activity that generates fibrillation in this animal tissue model. The computations show that the patterns of activity can, in principle, be accounted for by scroll waves within the ventricular wall. The scroll waves used to reproduce the surface patterns are roughly parallel to the ventricular surfaces, in contrast to the transmural filament illustrated in Fig. 1(a). In an intact heart, these waves would be around filaments which are closed (*i.e.* scroll rings) or that terminate an inexcitable boundary. A deeper understanding of the nonlinear wave processes that underlie fibrillation requires their direct three-dimensional visualisation, say via transillumination [Pertsov, Vinson & Muller 1993, Pertsov, Baxter, Cabo, Gray, Davidenko & Jalife 1994], perhaps using optical tomographic techniques [Winfree, Caudle, Chen, McGuire & Szilagyi 1996], or by a combination of multisite surface and intramural electrophysiological recordings from the ventricle [Akar, Yan, Antzelevitch & Rosenbaum 1997]. However, until three-dimensional visualisation of propagating activity in the heart wall is available, appropriately chosen mathematical models may be used to construct three-dimensional patterns consistent with visualised surface activity.

Acknowledgements

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