Chapter 6.2. Resonance and feedback strategies for low-voltage defibrillation.

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1 Introduction

Early experiments on defibrillation revealed that it is sometimes possible to achieve defibrillation by lower voltage pulses, if they are applied several times and are properly timed [1]. In this chapter we review some ideas about detailed mechanisms how this method may work. Most of these ideas are theoretical and tested only in numerical simulations, or in "chemical model" of the cardiac tissue, the Belousov-Zhabotinsky (BZ) reaction medium; only in some cases experimentalists have attempted a direct verification in cardiac preparations. The literature on the subject is vast; as the space allocated for this review is limited, we shall focus on a few "cornerstone" ideas and somewhat arbitrarily selected examples.

2 Localized stimulation: induced drift of spiral waves

Multiple wave sources in an excitable medium compete with each other. During such competition, the fastest source entrains more and more of the tissue. If the faster source is the stimulating electrode, and it entrains the whole of the cardiac tissue, it would have expelled the re-entrant circuits and perhaps stopped the fibrillation. However the success of that depends on what happens to the re-entry source when the high-frequency waves reach it.

This has been first investigated in the chemical model of excitable tissues, the BZ reaction medium [3], and then subsequently in more details in numerical simulations of a variant of the FitzHugh-Nagumo model [2]. Figure 1 illustrates the main concept. The first panels show the process of entrainment of the medium by the faster source, which in this particular case is the

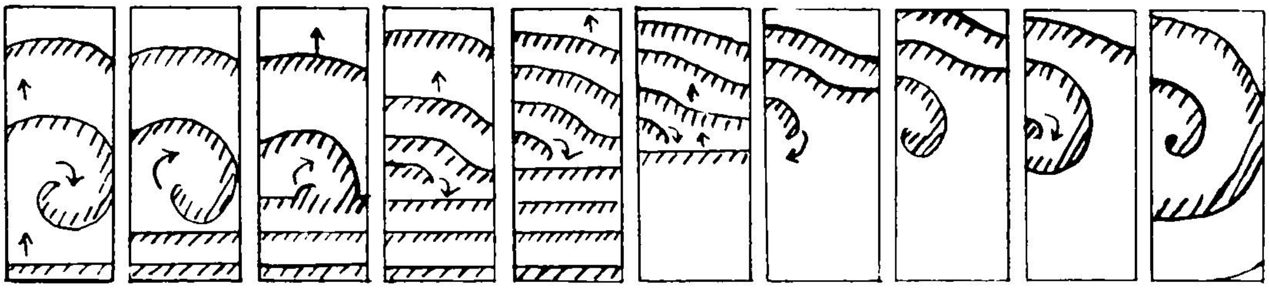


Figure 1: Enslaving (panels 1-4), drift (panels 4-6) and recovery (panels 6-10) of a spiral wave in the field of externally induced plane waves, in numerical experiments (schematic, similar to [2]). For comparison, the original position of the spiral rotation center is shown by a cross on panels 6-9.

electrode located at the lower boundary of the model medium. When the entrained region reaches the spiral wave, the latter changes its nature: it is no longer a rotating source of waves, but is a dislocation in the otherwise regular field of waves emitted by the fast source. Notice that it cannot disappear completely for topological reasons, as it carries a "topological charge". When the approximately periodic waves are passing through a certain point in the medium, one observes oscillations of the dynamic variables at that point, and can assign a phase to those oscillations. The increment of change of the phase of oscillations around a contour encircling the spiral or is the dislocation is the same for both of them, as it cannot change as long as the oscillations persist which they do unless the contour is crossed by the dislocation. Hence the dislocation carries this topological charge of the spiral wave. Typically it does not stay but drifts (this is sometimes called (high-frequency) induced drift of spirals, to distinguish from drift caused by other mechanisms). The direction of drift depends on the parameters of the problem, in particular on the frequency of the entraining source. When the entraining source stops, the dislocation immediately turns back into a spiral wave, which locates in a new place. If the duration and direction of the induced drift are such that the dislocation reaches the place where the regular oscillations are not observed, e.g. the inexcitable border or a Wenckebach block zone, then the topological restriction is lifted and the dislocation may be eliminated, so when the high-frequency source stops, the spiral wave does not resume, and the re-entry is stopped.

So the success of this method depends on the time factor: if the inexcitable border is far from the initial location of the spiral core and the induced drift speed is low, it could take a long time to expel the spiral, and if the stimulation stops earlier it fails. Notably, the amplitude of the stimulation plays a secondary role here: it should only be enough to initiate the entraining wavetrain; further increase of that amplitude does not enhance (at least within this particular mechanism) the chances of success. One can, however, control other parameters, such as the speed of the drift (through stimulation frequency) and its direction (through location of the stimulating electrode(s)). If one uses not a point electrode but a "grid" of synchronously working electrodes, then the distance required for the induced drift is limited by the size of the cell of this grid [4, 5].

3 Delocalized stimulation: resonant drift of spiral waves

Another approach is based on an alternative idealization of the action of the electric current on cardiac tissue. Suppose, for simplicity and in the first approximation, that a reasonably spatially uniform electric field (say as produced by a transtoracic defibrillator) acts simultaneously and similarly on all cells in the tissue. Mathematically, that is equivalent to introduction into the model of a parameter which explicitly depends on time. Davydov *et al.* [7] considered a simplified "kinematic" description of spiral waves and predicted that if the parameters of the model are changed periodically with a period close to the rotation period of the spiral wave, then the spiral exhibits large-scale wandering, which in the case of a precise resonance degenerates into a drift along a straight line, see fig. 2. This theoretical prediction was supported by numerical simulations of a piecewise linear FitzHugh-Nagumo model, and then immediately confirmed by experiments in BZ reaction [6]. Subsequent studies have demonstrated that this "resonant drift" phenomenon is not restricted to the two particular cases but can be reproduced in a wide variety of spiral wave models, including cardiac models (see *e.g.* [9]).

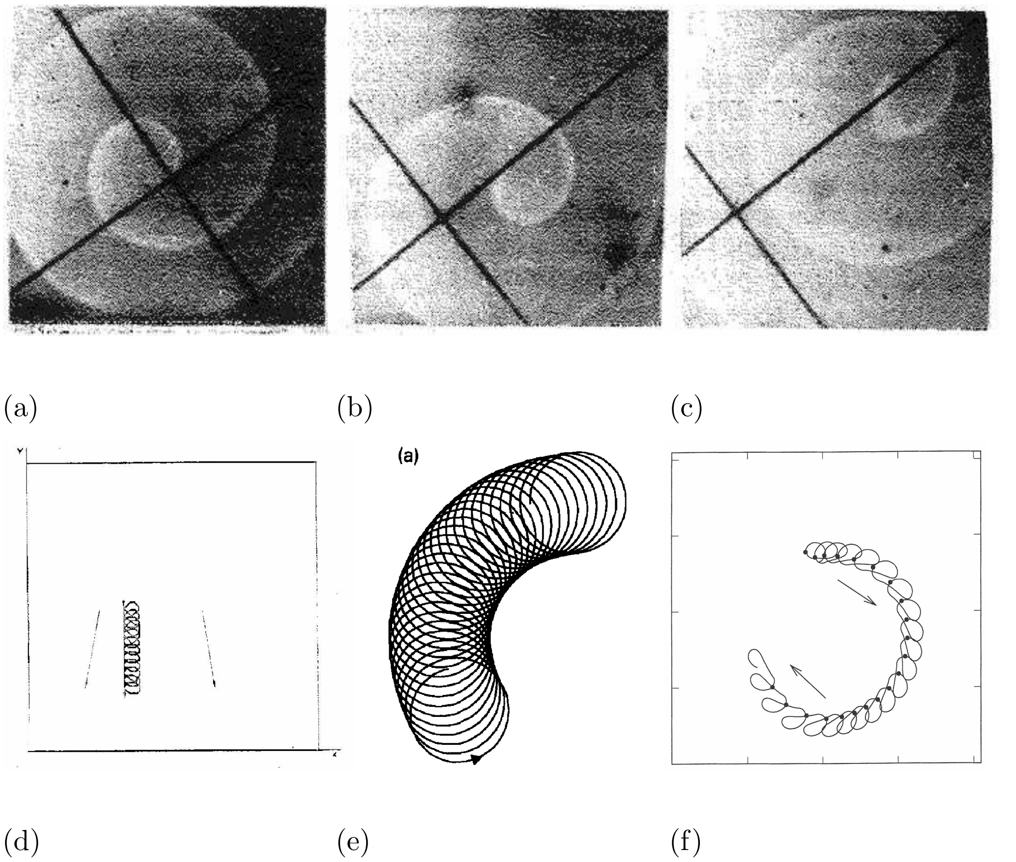


Figure 2: Resonant drift of spiral waves. (a–c) Snapshots of a spiral wave in a BZ experiment at a precise resonance; black cross is reference (reprinted with permission from [6], ©1987, IEEE). (d) In a pieceswise variant of FitzHugh-Nagumo system at a precise resonance (reprinted from [7] with kind permission of Springer Science and Business Media). (e) In a "kinematic model" of a generic excitable medium without refractorinesss, away from a precise resonance (reprinted with permission from [8], ©1994, Elsevier). (f) In the reaction-diffusion model with OXSOFT rabbit atrium kinetics, away from a precise resonance (reprinted with permission from [9], ©1995, Royal Society).

Following the same logic as with the high-frequency induced drift, if the excursion of the resonantly drifting vortex is large enough to bring it into an inexcitable boundary, this can lead to extermination of the spiral wave, and thus can be thought of as another low-voltage defibrillation strategy. Some difficulties in practical application of this idea are immediately obvious. As with the case of the high-frequency induced drift, one needs to know the appropriate frequency of the stimulation: the further it is from the resonance, the more compact is the trajectory of the drift. The theory proposed in [7] gives the following expression (up to choice of notations):

$$R_d = \left| \frac{c_d}{\omega_s - \omega_f} \right| \tag{1}$$

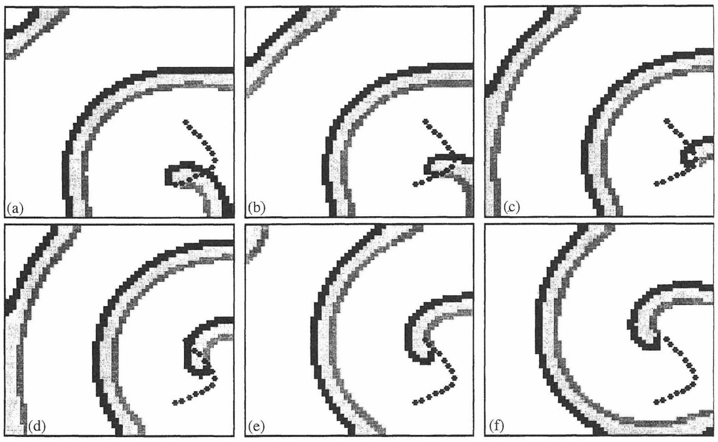


Figure 3: Mechanism of repulsion of resonantly drifting vortex from an inexcitable boundary (reprinted with permission from [10], ©1993, Elsevier). Shown are successive positions of the vortex in exactly 3 periods of stimulation. Black dots at each picture denote the positions of the vortex tip at the instants of stimulation. (a–c) The stimuli occur in the same rotation phase, and the trajectory is straight. (c), (d) The natural frequency of the vortex increases near the boundary, each successive stimulus occurring at a later phase, and the direction of the drift turns. (d–f) The vortex goes away from the boundary, it resumes its original natural frequency, and the trajectory is again straight.

for the radius of the drift trajectory R_d, where c_d is the resonant drift speed depending on the forcing mode and magnitude, ω_f is the angular frequency of the forcing and ω_s is the angular frequency of the spiral. So the lower is the stimulation amplitude, the lower is the drift speed c_d and the more precise should be the resonance to achieve needed R_d.

However, even if the resonant frequency is found, it is still not enough to eliminate the spiral. Figure 3 illustrates a simulation in a variant FitzHugh-Nagumo model in which a spiral wave drifting in a straight line reaches the vicinity of an inexcitable boundary. However the spiral does not annihilate there, but instead turns around and drifts away from the boundary. The mechanism of such “resonant repulsion” has been considered in [10, 11], where it was shown that the resonant drift can be approximately described by a system of ordinary differential equations of the form

$$\begin{aligned} \frac{\mathrm{d}\Phi}{\mathrm{d}t} &= \omega_s(R) - \omega_f, \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= c_d(R)e^{i\Phi} + (C_x(R) + iC_y(R)), \end{aligned} \tag{2}$$

where $R = R(t) = X(r) + iY(t)$ is the complex coordinate of the instant centre of rotation of the spiral, $\Phi = \Phi(t)$ is the phase difference between the spiral rotation and the periodic forcing, ω_s and c_d are, as before, the spiral's frequency and the speed of the resonant drift, and (C_x, C_y) is the vector of the spontaneous drift of the spiral which would happen without external perturbation, say due to spatial gradients of tissue properties or to proximity to inexcitable obstacles. If $C_x = C_y = 0$ and $\omega_s, c_d = \text{const}$ then system (2) is easily solved leading to (1). In terms of system (2), the explanation of the resonant repulsion is in the dependence of its key parameters on the spatial position of the spiral, particularly $\omega_s = \omega_s(R)$. In fig. 3, the closer is the spiral to the boundary, the higher is its frequency. That destroys the resonance $\omega_s = \omega_f$, which by the first equation leads to increase in Φ which means a change of the direction of the resonant drift given by $c_d e^{i\Phi}$. Such change continues until the spiral is sufficiently far from the boundary. Then $\omega_s = \omega_f$ again and the spiral drifts along a different straight line, now away from the boundary.

4 Feedback controlled resonant drift

The phenomenon of resonant repulsion makes it clear that it may not be the best strategy to keep stimulation frequency constant or to change it according to a prescribed program, but this change should be determined by actual events, via a feed-back. The feedback may be realized by monitoring activity at a point in the medium with a recording electrode. Since the frequency of real rotation of a drifting vortex is close to, and changes together with the resonant frequency, the simplest control strategy is to stimulate synchronously with the monitoring of an action potential spike by recording electrode, or after a fixed delay. The recorded frequency differs from the vortex frequency in the frame of reference of its core, due to its motion (a Doppler effect), and therefore the induced motion of the vortex will not be strictly along a straight line.

The mechanism of feedback driven resonant drift is illustrated in fig. 4. In contrast to the case of constant frequency stimulation, the trajectory of the vortex core far from boundaries is a

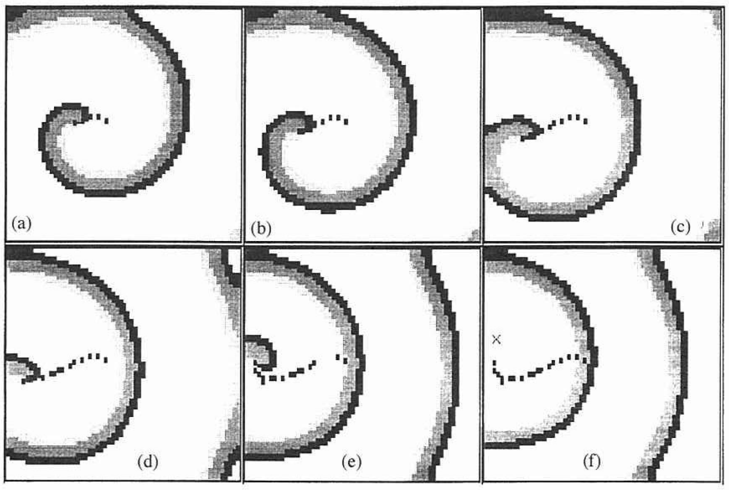
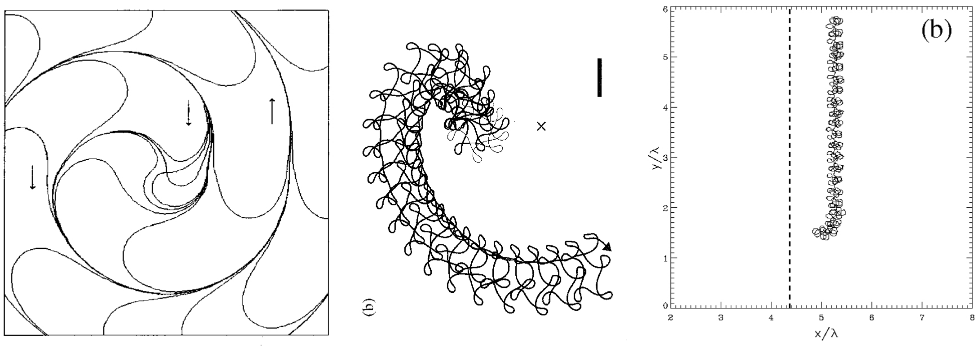


Figure 4: Mechanism of feed-back driven resonant drift, numerical experiment (reprinted with permission from [11], ©1995, Elsevier). Excitation patterns are shown synchronously with stimuli beginnings, which are issued synchronously with arriving wavefront to the left top corner of the preparation. Due to the feed-back, each stimulus occurs at the same rotation phase, up to the phase distance from the registration point to the vortex core. Therefore, the trajectory is affected only by the usual attraction/repulsion from boundary, without resonant repulsion taking place. As a result, the vortex annihilates at the boundary.

curve, not a straight line, since with motion of the vortex, the phase distance from its core to the recording point changes. Close to the boundary, there is no resonant repulsion. The trajectory deviates from what it would be in the absence of boundary, seemingly due to the terms C_x, C_y in the phenomenological model (2). As a result, the vortex reaches the boundary and annihilates, at a stimulation amplitude at which constant frequency stimulation fails. Numerical simulation show that the stimulation amplitude necessary for extinguishing the vortex by feedback driven resonant drift can be by an order of magnitude less than that required for single-pulse defibrillation [12].

The feed-back driven motion of the spiral can be described by an appropriate modification of the phenomenological model (2). The phase difference Φ between the spiral wave and the stimulation depends on the phase delay, required for the excitation wave emitted by the spiral rotating around a point R to reach the registration electrode location. If we denote this dependence as $\Phi = \Phi_{fb}(R)$, the third-order system (2) reduces to a second-order system

$$\frac{\mathrm{d}X}{\mathrm{d}t} = C_x(X,Y) + c_d(X,Y)\cos\left(\Phi_{fb}(X,Y)\right),$$



(a) (b) (c)

Figure 5: Resonant attractors. (a) Phase portrait for resonantly drifting spirals as predicted by the theory (reprinted with permission from [11], ©1995, Elseviert). (b) Tip trajectory computed in light-sensitive variant of the Oregonator model, with the point registering electrode (the cross) (reprinted with permission from [13], ©1995, American Physical Society). (c) Tip trajectory measured in an experiment with light-sensitive variant of the BZ reaction with the registered electrode in the form of a straight line (vertical dashed line) (reprinted with permission from [14], ©2007, World Scientific).

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = C_y(X,Y) + c_d(X,Y)\sin\left(\Phi_{fb}(X,Y)\right). \tag{3}$$

An analytical expression for the function Φ_{fb} can be obtained by approximating the shape of the spiral wave by an Archimedean spiral, which gives a system (3) very well describing the behavior of the feed-back driven spirals [12, 11]. Moreover, this approach can be extended to the cases when the electrode used for detection of the feed-back signal is not point-like, but is spatially extended over a certain domain; variation of this domain shape and location can be a very effective tool in controlling the trajectories of the resonant drift [15, 14]. System (3) is an autonomous second-order system of equations, and it is convenient to study its behavior using phase-plane analysis, see fig. 5. As it would be expected in a generic ODE system, there are attracting trajectories, which could be compact, i.e. attracting stationary points or limit cycles ("resonant attractors"), or noncompact and run away from the medium. Naturally, from the practical viewpoint a resonant attractor within the tissue boundaries signifies a failure of the the low-voltage defibrillation attempt, so one would like to avoid it.

Fibrillation, at least in some cases, is associated with multiple re-entrant sources, hence the

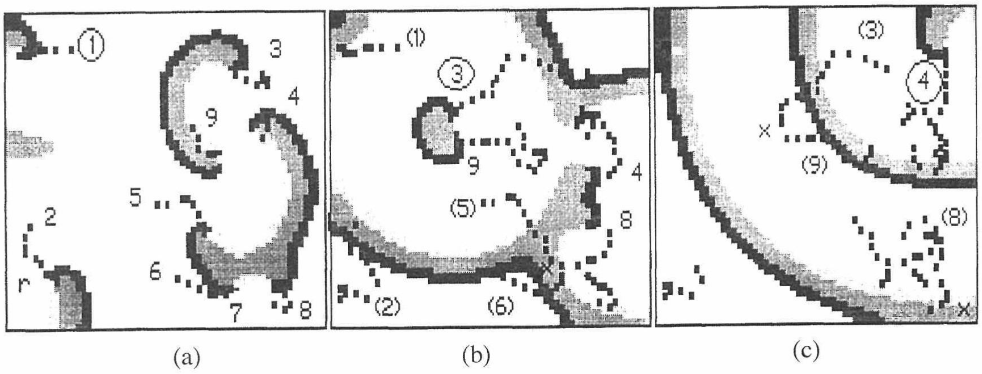
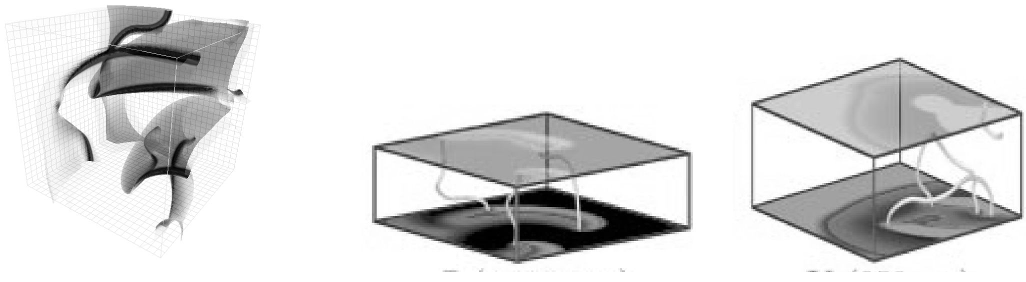


Figure 6: Evolution of multiple vortices under feedback driven stimulation (reprinted with permission from [11], ©1995, Elsevier). The "leading" vortex is circled on each panel, traces of annihilated vortices are marked by digits in parentheses. (a) Vortex 1 leads, vortex 2 repulses from boundary.(b) Vortices 1, 2, 5, 6 have annihilated, vortex 3 leads. (c) Vortices 3, 8, 9 have annihilated, the only alive vortex 4 leads. Further evolution results in annihilation of vortex 4.

question, whether the above described feedback control strategy can cope with that. Simple simulations demonstrate that multiplicity of re-entrant sources in itself is not a significant impediment to their elimination [11]. Say, for the case of point registering electrode, the feedback signal will come from the one spiral whose waves reach the electrode site, which ensures a directed drift of at that spiral. Cores of such "leading" spirals are circled on the figure. Other spirals may or may not annihilate during this stage. Upon reaching the boundary, the leading spiral is extinguished and the electrode monitors the wavefront from another one, which in turn is extinguished and so on. As a result, all the spiral waves are progressively extinguished in a time not much longer than that needed for extinguishing one (see fig. 6).

In reality, the number of spiral waves may not be fixed and they may "multiply" via wave break-ups while the resonant drift forces them out. The chances of success in that case seem to heavily depend on concrete parameters, such as size of the medium, the rate of multiplication of spirals and the rate of their elimination [16].



(a) (b) (c)

Figure 7: Three-dimensional scroll wave turbulence, (a,b) due to negative filament tension, (c) due to twisted anisotropy. (a) FitzHugh-Nagumo model, wavefronts are grey semi-transparent, their edges, representing the filaments, are dark and non-transparent (same data as in [17]). (b,c) Fenton-Karma model, shown are surface voltage distribution (top surface semitransparent), and the scroll filament between them (reprinted with permission from [18], ©2002, American Institute of Physics).

5 Three-dimensional aspects

Another important feature of fibrillation is its three-dimensionality. Although available experimental evidence is not conclusive, there are theoretical concepts about possible specifically three-dimensional mechanisms which can contribute. Here we focus on "scroll wave turbulence", an essentially three-dimensional mechanism of multiplication of vortices, observed even in cases when a two-dimensional medium with the same properties has stable spiral waves.

Early numerical simulations of scroll waves have revealed that the scroll rings are not stationary but can contract as well as expand [19]. It has been soon realized that if this behavior is extrapolated for an arbitrary shape of scroll filament, it would mean that the straight shape is unstable in favor of some more complicated behavior [20]. The earliest asymptotic theory of evolution of scroll waves with arbitrary shapes did not cover expanding rings [21], and the first that did [22] was too complicated to clarify this question unequivocally, as the filament motion equations were linked the evolution of scroll twist and depended on many parameters. However, it has been subsequently noted that with account of the symmetry of the problem some of the terms in fact vanish and the dynamics of the filament shapes decouple in the main order from the dynamics of the twist. These dynamics designate a property of an excitable medium, the "filament tension", which is positive if scroll rings collapse and negative rings expand [23]. This happens to be the most important parameter for the behaviour of scrolls. Straight filaments with negative tension are indeed unstable which could lead to self-supporting complicated behavior, where the filaments curve and extend, and multiply when their segments annihilate on medium boundaries or with each other. It has been speculated that such complicated behavior could be relevant to fibrillation [23, 24]. The first definitive observation of "scroll wave turbulence" as persistent self-supporting activity mediated by negative filament tension was in FitzHugh-Nagumo model [17] (fig. 7(a)) and then in other models, including Barkley variant of the FitzHugh-Nagumo model [18] (fig. 7(b)), the Oregonator model of the BZ reaction [25] and Luo-Rudy model of ventricular tissue [26].

An alternative mechanism with similar phenomenology has been discovered by Fenton and Karma [27, 28]. It is also related to curving and multiplication of scroll filaments, but it is only observed in simulations with spatially non-uniform anisotropy of the diffusion tensor, mimicking the twisted fibre structure of ventricular walls. This has been observed in FitzHugh-Nagumo model as well as in a simplified cardiac excitation model developed by the authors for this particular purpose, since then known as the Fenton-Karma model. At the moment of writing this review, its author is unaware of detailed theoretical explanation of this phenomenon, although there are theoretical developments promising that such explanation could be obtained soon [29].

Although these particular mechanisms are difficult to identify in real experiments with cardiac tissue, the essentially three dimensional nature of fibrillation, particularly ventricular fibrillation, is well known. So the question whether these or other complications caused by three-dimensionality can be overcome by low-voltage defibrillation techniques, is very important. Theoretical progress here is limited but nonzero:

- Three-dimensional aspects of the high-frequency induced drift have been numerically investi-

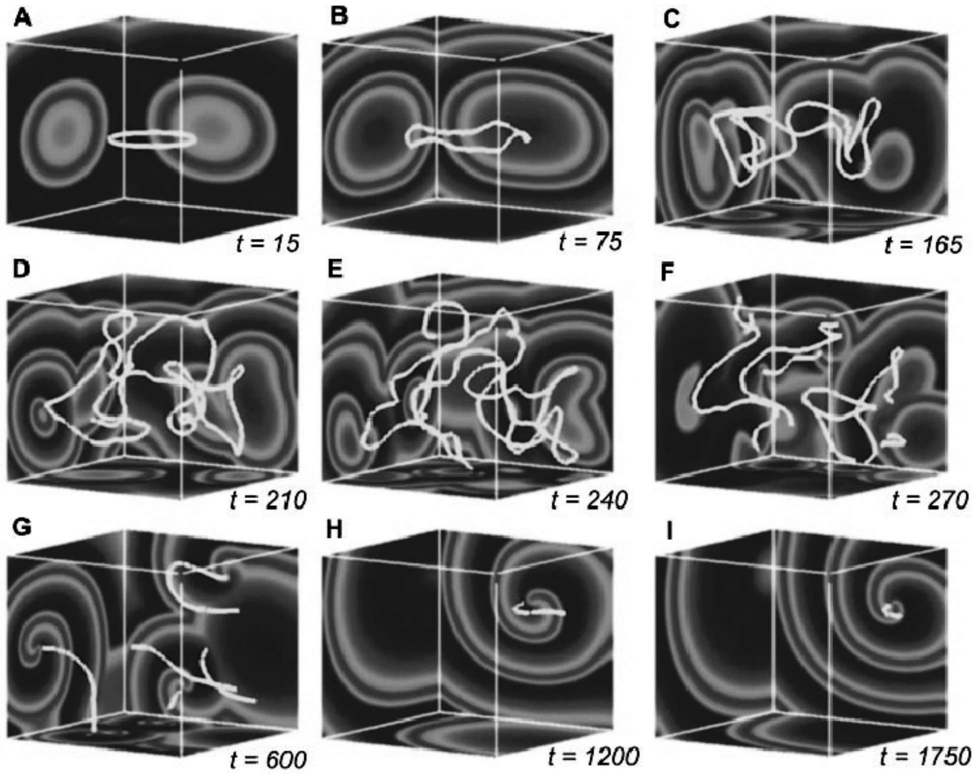
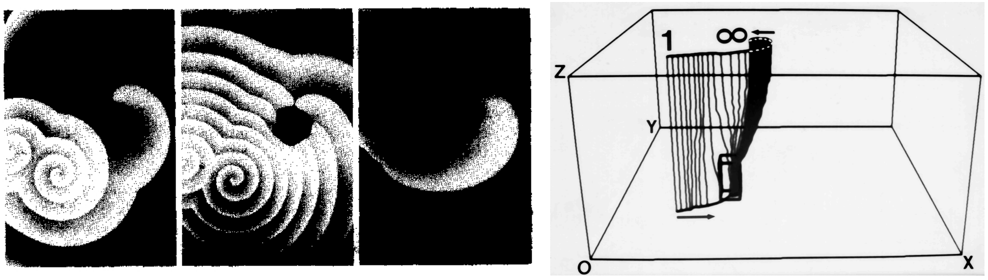


Figure 8: (A–C) Development of a scroll wave turbulence and (F–I) its suppression by delocalized periodic external forcing. Numerical simulations with Barkley model with parameters giving negative scroll filament tension ($a = 1.1$, $b = 0.10$, $\epsilon = 0.02$), the external forcing is implemented by time-dependent modulations of parameter b with amplitude $b_f = 0.03$ and frequency $\omega_f = 1.20$ close to the fequency of free spiral waves ($\omega_s = 1.19$) (reprinted with permission from [30], ©2003, AAAS).

gated for grid-like stimulating electrodes in the already mentioned work [4]. The advantage of a grid-like stimulation extends to three dimensions even though the grid of the electrodes stays on the surface, as long as the tissue is not too thick. In that case the third dimension adds little to the distance the forced vortices must travel before expulsion.

- Resonant stimulation has been studied for the negative-tension mediated scroll wave turbulence in Barkley model [30, 31]. It has been demonstrated that small oscillations of one of the parameters with a near-resonant frequency can successfully exterminate all scroll wave activity. The optimal frequency for achieving this is shifted from the solitary spiral frequency, and the decisive mechanism involved may be not resonant drift as such but inversion of the filament tension from negative to positive.

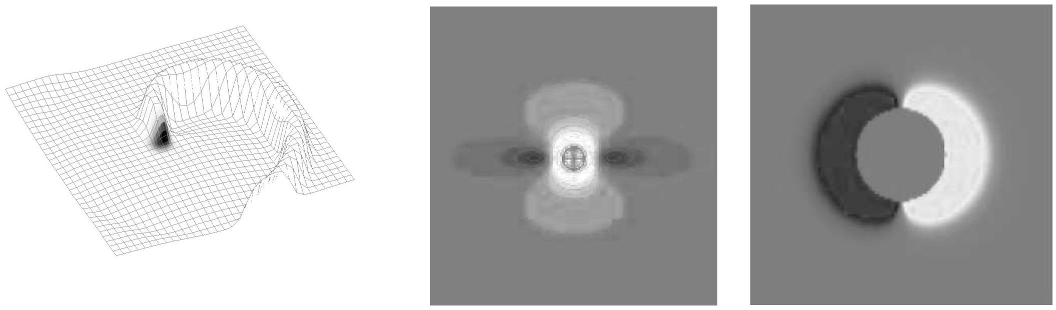


(a) (b) (c) (d)

Figure 9: Pinning to an obstacle. (a–c) Pinning of high-frequency induced drift in 2 dimensions. Spiral wave in BZ reaction rotating around an inexcitable hole (seen as a black spot in the middle frame) is entrained by a higher frequency wavetrain, but resumes the rotation as soon as the wavetrain is over (reprinted with permission from [3], ©1983, Elsevier). (d) Pinning of gradient induced drift in 3 dimensions. Scroll wave in FitzHugh-Nagumo model drifting due to spatial gradient of medium parameters is "anchored" to a localized inhomogeneity near the bottom and stops drifting. "1" is the initial position of the scroll, "∞" is the anchored stationary position in which the filament stops drifting (reprinted with permission from [32], ©1994, Elsevier).

6 Pinning and unpinning

The theoretical mechanisms considered above all ignored an important property of cardiac tissue, its heterogeneity. One important effects this can have on spiral and scroll waves is their "pinning" to localized inhomogeneities. This has been observed both for high-frequency induced drift [3] and for "soft" such as drift caused by gradient of tissue properties [32] or resonant drift with or without feedback [33], in two as well as in three spatial dimensions (see fig. 9). The mechanism of the pinning to small and/or week local inhomogeneities can be understood in terms of attracting, "centripetal" force by means of perturbation theory [34], including, in 3 dimensions, the filament tension [32]. When the inhomogeneity is strong, *e.g.* an "inexcitable hole", the pinning is evident from topological reasons, see fig. 9(b). Obviously, if the drift was induced with the aim of expelling the vortex from the tissue, its pinning inside the tissue indicates a failure. Hence a question, whether it is possible to "unpin" such a pinned vortex by a low-energy intervention. If that is achieved, then it will be possible to eliminate this vortex by either of the induced drifts, or it may even self-terminate via spontaneous drift.



(a) (b) (c)

Figure 10: Localization of spiral sensitivity and of electric field action. (a) Response functions of a spiral wave. Elevation represents the activator variable, and the surface shade of grey represents the sum of absolute values of rotational and translational response functions. FitzHugh-Nagumo model, same data as in [35] (b) "Dog-bone" shape "virtual electrode" near a point electrode. Shade of grey represents instant distribution of transmembrane voltage, white for positive and black for negative. Bidomain Luo-Rudy model (reprinted with permission from [36], ©2003, American Physiological Society). (c) "Weidmann zones" near an anatomical obstacle. Voltage distribution around a circular inexcitable hole caused by homogeneous external electric field. Bidomain passive membrane model (reprinted with permission from [37], ©2004, American Physical Society).

Figure 10 gives three hints as to how unpinning could be achieved. Panel (a) illustrates that as far as small perturbations are concerned, a spiral wave is only sensitive to perturbations near its core. This is well known phenomenologically and is mathematically formalized as localization of "response functions" of the spiral wave [23, 39, 35]. Panel (b) illustrates one of the effects a bidomain structure of cardiac tissue has on the interaction of the external electric field and the spatial distribution of the transmembrane potential. Despite the fact that the electrode is a "point", the "virtual electrode" it produces is spread in space, has a nontrivial shape, and in some places the sign of the induced potential is opposite to the sign of the potential at the electrode. Panel (c) shows how the bidomain structure of the tissue manifests itself around an obstacle in a uniform external field. The disturbance in the Ohmic properties of the intracellular and extracellular domains distorts the electric field around the obstacle and create a depolarized zone to one side of it and a hyperpolarized zone to the other side.

So if a spiral wave rotates around such an obstacle, we observe that

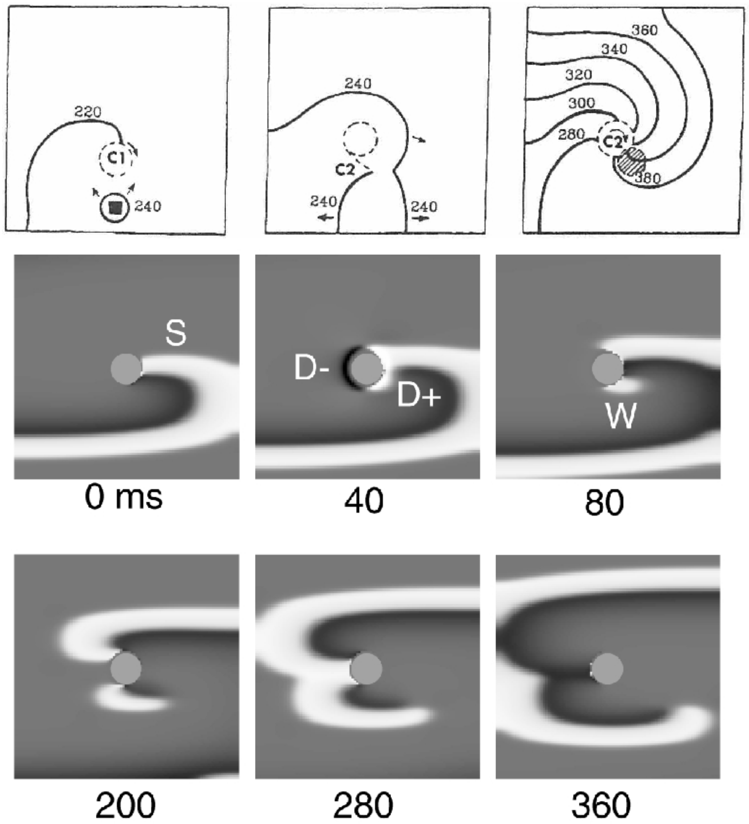


Figure 11: Top row: a localized stimulus issued in an appropriate phase of the spiral, can shift the spiral core. If the original location was around an inexcitable hole, the new location can be away from it, i.e. spiral gets unpinned. Piecewise-linear FitzHugh-Nagumo model, (reprinted with permission from [40], ©1990, Wiley-Blackwell Publishing Ltd). Second and third row: unpinning of a spiral from an inexcitable hole, bidomain FitzHugh-Nagumo model (reprinted with permission from [37], ©2004, American Physical Society).

- To move this spiral wave, we need to apply a stimulus in a properly chosen zone near its core = the obstacle,
- A delocalized, nearly homogeneous external electric field, by virtue of its interaction with the heterogeneity itself, produces a localized stimulus to the tissue just where it is needed, near the obstacle.

That is, the stimulus is automatically delivered near to where it is needed, and one only needs to choose the timing, for the Weidmann zone to superimpose with the maximum of the translational response function, to achieve a displacement of the spiral. If the displacement is large enough to get away from the zone of attraction of the inhomogeneity, this is unpinning.

The reasoning referring to response functions is valid in the case when the heterogeneity is weak so a perturbation theory applies. When the heterogeneity is strong, *e.g.* an inexcitable hole, the reasoning is different but the result is qualitatively the same. Figure 11 (top row) illustrates the idea qualitatively. A localized stimulus near to the core of the spiral, issued in the excitable gap, can initiate a circular wave (left panel). This circular breaks around the refractory zone, one of the new wavebreaks joins and annihilates with the spiral (middle panel). The other newly generated wavebreak curls into spiral in another place, away from the hole (right panel). The net result is that the spiral is unpinned. To achieve that, the stimulus should be in the correct place, sufficiently close to the hole, and at the right time, in the excitable gap.

The second and third rows of fig. 11 show numerical simulation of unpinning of a spiral by a properly timed homogeneous external electric field in a bidomain model. One can see the Weidmann zones $D+$ and $D-$ on the panel $t = 40$. The $D-$ zone serves as the localized stimulus initiating a new circular wave W (panel $t = 80$). The circular wave breaks about the refractory tail ($t = 200$). One of the new wavebreaks annihilates with the original spiral ($t = 280$). The other wavebreak creates a new spiral which is unpinned from the obstacle ($t = 360$).

The possibility of unpinning a spiral wave from an obstacle using a localized stimulus close to it was recognized early [40]. It was relatively straightforward to verify it in an experiment with BZ reaction [41]. The crucial step was the idea of using a Weidmann zone as such localized stimulus [42]. It was first investigated in simulations with relatively simple models [42] and then extended to more detailed and realistic models [37, 38] and verified in experiments with rabbit heart preparations [43].

7 “Black-box” approaches

For the sake of completeness, we should mention attempts to approach the problem of control of cardiac arrhythmia using generic methods of control of dynamical systems regardless of detailed mechanisms how the control actually works. We consider two such lines of enquiries.

Alekseev and Loskutov [44] observed that a weak parametric periodic perturbation can stabilize the chaotic behaviour of a nonlinear system and turn chaos into periodic oscillations. That was done for a mathematical model of phytoplankton-zooplankton community, a system of four ordinary differential equations. This idea has been applied to a number of other model systems. In particular, its application to a two-dimensional spiral wave turbulence in a piecewise-linear FitzHugh-Nagumo model [45, 46] allowed elimination of all spiral wave activity. This application involved point stimulation with a frequency small enough so waves can propagate, but larger than the frequency of the spirals. Note this is precisely the conditions that are required for high frequency induced drift of spirals. Alas data available in the paper do not allow to conclude whether the detailed mechanism was indeed the high-frequency resonant drift or something different.

Ott, Grebogi and Yorke [47] have proposed that a small modification of a chaotic dynamical system can change chaos to stable periodic motion. Unlike Alekseev and Loskutov method, their approach required that changes do not depend on time explicitly, but rather on the current state of the system, *i.e.* feedback. This idea was hugely popular and applied to a great variety of dynamical systems. Cardiac arrhythmias were not an exception: *e.g.* application of this technique to oubaine-induced ventricular arrhythmia in rabbit ventricle allowed conversion of chaotic to period behavior [48]. Again, data available in the paper do not allow identification of detailed mechanism; however, the ”proportional perturbation feedback” protocol used there, though quite complicated, could have produced a nearly-resonant perturbation that could cause a resonant drift.

8 Conclusion

A striking picture emerges from the above review. Although a wide variety of theoretical mechanisms is considered, the resulting experimental protocols required to exploit these mechanisms are not so varied. So implementation of the idea of unpinning involves a correct choice of the phase of the stimuli with respect to the spiral rotation around the hole, say to ensure that the depolarizing Weidmann zone falls within the excitable gap. A practical way to achieve that is using some kind of feedback, and the protocol of that feedback may be close or indistinguishable from the one required for resonant drift. Moreover, "scanning through the phases" may leed to series of stimuli of the sort that would be needed to arrange a high-frequency resonant drift. The stimulation protocol to implement Alekseev-Loskutov chaos control strategy seems to be indistinguishable from the one needed for high-frequency resonant drift, and the protocol for Ott-Grebogy-Yorke strategy could produce feedback-driven resonant drift. Application of the sufficiently homogeneous external electric field, which is important for classical single-shock fibrillation, is crucial for the success of resonant-drift approach, and is also required for unpinning. Even successful experiments with low-voltage defibrillation may be interpreted in different ways; *e.g.* results of [49] are, in principle, consistent with such scenaria as high-frequency induced drift, feedback-driven resonant drift and unpinning. So, while experimental testing of theoretical ideas as always remains a priority, there are still theoretical challenges, such as formulation of unequivocal experimental protocols and criteria that would allow to distinguish between different mechanisms. Such distinction hopefully should allow to to suggest possible ways to improve the efficiency of the low-voltage defibrillation.

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