V.N. Biktashev, I.V. Biktasheva. Final Report: FEEDBACK CONTROL OF RESONANT DRIFT AS A TOOL FOR LOW VOLTAGE DEFIBRILLATION

Background and context

Low-voltage defibrillation There are more than 100 thousand premature cardiac deaths every year in the UK alone. Most of these are associated with re-entrant cardiac arrhythmias. Milder forms of arrhythmias, such as paroxysmal tachycardia or atrial flutter, seriously decrease quality of life. The extreme form is the ventricle fibrillation, which is related to persistent re-entrant waves in the the larger chambers of the heart, and is usually lethal.

The last line of defense against re-entrant arrhythmias and fibrillation is electrical defibrillation, which is a powerful electric shock, delivered transthoracically or by implanted devices, aiming at "resetting" all the excitable cells in the heart to the same state.

Unfortunately, the defibrillation is not always effective, and causes collateral damage to the heart itself and surrounding tissues. Defibrillating shock is extremely painful, even with the implantable devices (transthoracic defibrillators usually are applied to unconscious patients as ventricular fibrillation causes loss of consciousness very quickly). Thus there is a high clinical demand on alternative methods of defibrillation which would work with smaller voltages. Such methods exist, e.g. overdrive pacing, and are sometimes attempted by the implantable devices or on the operating table, and the high-voltage shocks are delivered if the milder methods fail. Such milder methods, however, fail too often, so search for more efficient low-voltage defibrillation algorithms continues.

Resonant drift In 1987, Davydov, Mikhailov and others [9, 10] have discovered a phenomenon of "resonant drift" of a spiral wave when one of the parameters of a simplified "kinematic" model of an excitable medium was changed with time with the period equal to that of the spiral wave. Subsequently, this phenomenon was shown to be fairly universal, i.e. observed in excitable media models satisfying rather general assumptions [11, 12]. The resonant drift could be used to eliminate spiral waves from the excitable medium by driving them to inexcitable boundaries or towards each other, and thus annihilating them. However, it has been observed that finding the resonance frequency may not be easy in practical circumstances, and the resonance can be easily destroyed by all sorts of system inhomogeneities, thus resulting in failure to eliminate spirals.

Feedback control of resonant drift As the main reason for the unruly behaviour of the spiral wave is the untuning of the resonance due to the variation of the spiral's own frequency, this can be rectified by adjusting the frequency of the external forcing accodingly, based on some kind of feedback obtained from the spiral wave itself [13–15]. The feedback control of the resonant drift has been shown to overcome the repulsion of the boundaries and deviation caused by tissue inhomogeneities, interaction of spiral waves with each other, and also can be used to extinguish multiple spiral waves [11], and it can be observed in models with detailed ionic kinetics of modern cardiac models [16–18]. Variants of resonant drift and elimination of re-entrant sources by small repetitive stimulation have been demonstrated in various geometries of the excitable medium [14, 15] and in two- and three-dimensional models where the vortices tend to spontaneously multiply [19, 20].

The challenge: more realistic models of cardiac muscle However, the models in which the feedback controlled resonant drift was observed were too simplified and experimentalists were unwilling to test the method in experiments. We have identified a number of features of realistic models, which were not present in modelling simulations so far and which made the experimentalists skeptical. The purpose of the present project was to test whether these features may render the resonant drift unworkable as a tool of low voltage defibrillation.

Key Advances and Supporting Methodology

The work proceeded in accordance with the "Features", "Aims" and "Objectives" laid out in the original grant proposal. Briefly, we identified **features** that presented a challenge for the theory of resonant drift pacing:

- inhomogeneity and anisotropy of cardiac tissue,
- bidomain nature of cardiac tissue,

- three-dimensionality of cardiac tissue,
- complicated geometry of heart chambers,
- the excitable kinetics,

identified **aims**:

(i) to assess the resonant drift pacing as a tool of low-voltage defibrillation,
(ii) to identify and suggest ways to overcome possible difficulties in its implementation,
(iii) thus to stimulate work on experimental testing of the method,

and set **objectives** for the study:

1. to test responant pacing by numerical simulations of the most up-to-date models of cardiac tissue,

2. to extend the existing asymptotic theory of resonant drift,

3. to infer possible reasons resonant drift pacing may not work, and formulate practical recipes to overcome those that could be tested in experiments.

The work done can be summarized in the form of four inter-related studies:

Study 1: two-dimensional bidomain human atrial tissue. This was a numericaly study with the numerical setting similar to that of the single-shock defibrillation simulation study by Plank *et al.* [21]. The particular features of the numerical setting were:
- detailed "human atrial cell" excitable kinetics due to Courtemanche *et al.* [22], in two variants (with steadily rotating and with meandering spirals), supplemented by
- "electroporation current" added to the kinetics to prevent transmembrane voltage raising to unphysiological values during electric shocks.
- bidomain description,
- anisotropy,
- microscopic inhomogeneities of intracellular conductivity tensor,

This choice was made with the view of making comparison with the previous study [21].

Re-entry was initiated and low energy shocks were applied through two point electrodes with the same period as the re-entry, using feedback to maintain resonance. We demonstrated that such stimulation can move the core of re-entrant patterns, in the direction depending on location of electrodes and a time delay in the feedback. Termination of re-entry was achieved with shock strength one order of magnitude weaker than in conventional single-shock defibrillation.

We concluded that resonant drift pacing can terminate re-entry at a fraction of the shock strength currently used for defibrillation and can potentially work where antitachycardia pacing fails, due to the feedback mechanisms. Success depends on a number of details which these numerical simulations have uncovered. The principal potential difficulty identified was the generation of new wavebreaks due to macroscopic inhomogeneity of the electric field generated by the point electrodes, which led to "infinite loops". The suggested ways to overcome that difficulty were making more homogeneous field (say plate rather than point electrodes) and adjustment of the feedback delay which was demonstrated to be capable of disrupting the inifinte loops via change of direction of the drift and thus successfully terminating the simulated arrhythmia.

Study 2: three-dimensional simplified excitable medium. This was a numericaly study with the numerical setting similar to the study by [20]. The similarity was again deliberate for the sake of comparison. The features of this model were
- monodomain isotropic homogenous description of the tissue structure,
- three-dimensionality with a simple cubic geometry,
- one of the simplest possible excitable kinetics (Barkley model [23]),
- parameters of the model chosen so as to ensure negative tension of scroll filaments.

Due to the negative tension, the scroll waves in this model at the chosen parameters tended to self-multiply leading to a "scroll wave turbulence", a sort of spatio-temporal chaos resembling well-developed fibrillation.

In this study we investigated suppression of the turbulence using stimulation of two different types, "modulation of excitability" asin [20] and "extra transmembrane current" which is a simplistic description of what happens in response to electric shocks. With cardiac defibrillation in mind, we used a single pulse as well as repetitive extra current with both constant and feedback controlled frequency. We showed that turbulence can be terminated using either a resonant modulation of excitability or a resonant extra current. The turbulence was terminated with much higher probability using a resonant frequency perturbation than a non-resonant one as used by Alonso *et al.* [20]. Suppression of the turbulence using a resonant frequency is up to fifty times faster than using a non-resonant frequency, in both the modulation of excitability and the extra current modes. In this study, the main difficulty was that the amplitude of the shocks should exceed a certain threshold, to ensure that scroll waves are eliminated quicker on average than they self-replicate. However, this threshold have been found at least one order of magnitude lower than that of a single pulse. A lesser difficulty was a relatively long time that was required by feedback-driven compared to resonant fixed-frequeny stimulations. The reason for this paradox was found to be related to large distances between the scrolls and the feedback electrodes, in such a way that makes this issue not relevant for real cardiac fibrillation.

Study 3: asymptotic theory of resonant drift of scroll waves. Technically, the asymptotic theory was based on two previous studies, the Keener [24] and Biktashev *et al.* [25] theory of the spontaneous evolution of scroll waves, and Biktashev and Holden [11] perturbation-driven drift of spiral waves, by combining the two. The result is a 1+1-dimensional partial differential equation describing period-averaged motion of the filament of a scroll wave subject to a near-resonant perturbation of a generic nature. We have demonstrated that this equation describes both the phenomenon of resonant drift, and the filament tension. We have also demonstrated a new feature emerging in the theory: stationary helical filaments, in which the effects of resonant drift and filament tension equilibrate each other. The value of this result for the project is that it demonstrates a new, essentially three-dimensional type of difficulty in eliminating re-entrant waves by resonant pacing: theoretically, the helical scroll can persist forever despite the perturbation being in resonance with it.

Study 4: whole-ventricle model. This was a numericaly study with the numerical setting remotely similar to the studies by Trayanova, Rodriguez *et al.* [26–28]; however a closer similarity was proved to be impractical for insufficiency of published data about those studies. The essential features of this our study were:

- excitable kinetics defined by a variant of Beeler-Reuter model of mammalian ventricular cells [29], which is intermediate between the simplified and modern detailed models, both in terms of complexity and realism;
- modification of the model, in particular to include the electroporation current,
- bidomain description,
- the “UCSD” finite element mesh of a rabbit ventricle [30], including anisotropic defined by fiber directions,
- microscopic heterogeneities of the intracellular conductivity tensor.

The computational cost of this model by far exceeded those in Studies 1 and 2, thus the number of numerical experiments here was limited. Nevertheless, we have been able to demonstrate that the feedback-driven resonant pacing can indeed successfully eliminate re-entrant activity, at an amplitude of stimulation by an order of magnitude smaller than that required by the standard single-shock defibrillation. The success depended on the position of the feedback electrodes and on the delay in the feedback loop. We have demonstrated that in cases where the resonant drift pacing is unsuccessful, a change in the feedback loop can overturn the course of events and lead to elimination of re-entry. In cases when the re-entry was not eliminated for a long time, we have been able to identify stationary helical-shaped filaments, thus confirming the theoretical prediction. We also have established that the microscopic heterogeneities are not essential for the work of resonant drift pacing, and it works even in the model where the heterogeneities are completely absent. Our interpretation of that is that the far-field action of electric field is due to macroscopic inhomogeneities of inhomogeneous anisotropic of cardiac muscle, which was not present in Studies 1 and 2.

To summarise:

1. We have demonstrated, using a variety of computational models of varying complexity and realism, that resonant drift pacing can eliminate re-entrant activity by using pacing amplitude an order of magnitude smaller than those required by the single-shock defibrillation in the same models.

2. In particular, we have demonstrated that resonant drift pacing can successfully overcome such peceived problems as three-dimensionality and complicated geometry of the heart muscle, local

application of electric current, macroscopic and microscopic inhomogeneities of heart properties, meandering, and spontaneous, as well as stimulation-driven multiplication of re-entrant circuits.

3. We have identified typical obstacles that can occur: multiplication of re-entries due to inhomogeneity of the electric field, and wrong direction of resonant drift, which does not drive the re-entries towards inexcitable obstacles but engages them in stationary or repetitive configurations.

4. In all cases of resonant drift pacing being unsuccessful despite sufficient amplitude of stimulus, we have found that change of the feedback-delay was able to generate success.

One particular perceived difficulty was not addressed in any of our studies: the possibility of re-entry being "pinned" to a localized macroscopic inhomogeneity. However, as we have argued in [A1], this issue has been studied both in numerical and in real experiments, and the suggested protocol of "unpinning" is in fact indistinguishable from resonant drift pacing with adjustable feedback delay, so the difference between "unpinning" and "resonant drift" mechanisms of low-voltage defibrillation may be a matter of different interpretation or idealizations of the same phenomena.

So, all the objectives set out in the original plan have been achieved, and we have a very strong case for testing the resonant drift pacing in experiments.

Project Plan Review

The main deviation from the original reseach plan were as follows:

- Originally we planned to implement ourselves the needed numerical methods based on what is published in literature. However, soon after the project started, we have established a working contact with G. Plank of Medical University Graz, Austria, who, in coauthorship with E.J. Wigmont, University of Calgary, Canada, have developed Cardiac Arrhytmia Research Package [31] which appeared a rather sophisticated and possibly the most advanced computational tool for precisely the kind of problems we needed. With the support of an ad hoc visiting grant from the Royal Society, Dr Plank has installed the software in Liverpool and instructed us in using it. Subsequently he continued to give advice about using CARP and effected modifications to it that were needed for our simulations.
- When we proceeded to the final stage of the problem (Study 4), it has become apparent that even with such sophisticated tool as CARP, it would be very challenging and not cost effective to try and do realistic geometry calculations on any locally installed computers within the budget of the grant, which made a case for considering using a national facility HPCx. An extra argument in favor of such solution was that CARP was already tested and running on CARP. We have requested if we could spend the research consumables funds of the grant to purchase computation time at HPCx; the response was that now we could not, but we could request allocation of computation time via EPSRC. We have submitted such request and it was granted. We note here that in Autumn 2008, there has been a long period of unlimited access to computing resource, so actual time used was much longer than the 198,000 units applied for; however the exact figure has not been recorded. So the funds allocated for equipment were spend on local computers after all, but their main use was for visualization rather than computations; however it should be noted that 3D visualization needed in Study 4 has proved to be just as challenging.
- In the theoretical studies, it was envisaged that extention of the asymptotic dynamics of scrolls would be done for the case of anisotropic medium. However, soon after beginning of the project, we have become aware of the the study by Verschelde *et al.* [32] which addressed precisely that problem, so further efforts in this direction appeared unnecessary and we could concentrate on other directions.

Other deviations were minor and amounted to practical choice of concrete model features required for each particular study.

Research Impact and Benefits to Society

We believe that we have presented a solid case for testing resonant drift pacing for low-voltage defibrillation in experiments. In fact, as we have argued in [A1], there is at least one published study in which the feasibility of this approach has been demonstrated experimentally, without authors realizing it. Subsequent experiments made with full awareness of their value by the experimentalists can pave the way towards clinical implementation of this method. The precise areas of clinical applicability of the method can become clear after further experimental studies, but possibilities include a more efficient treatment of atrial flutter and atrial fibrillation, as well as a low-voltage alternative to the single-shock defibrillation of ventricles, particularly by implantable devices. This would have implications in biomedical industry and clinical practices and ultimately lead to saving lives and serious improvement of the quality of life of cardiac patients.

Explanation of Expenditure

The most significant variation against the original plan, affecting expenditure, was that travel and subsistence expenses were in fact less than anticipated, particularly for overseas travel, but research consumables, which mainly involved computers and related expenses, were bigger by about the same amount. The explanation of this deviation is that the main results which are most interesting for cardiological conferences were obtained (as anticipated) in the last year of the project, 2008, and there were high-profile relevant conferences in Europe (Cardiostim, Nice, France; Computers in Cardiology, Bologna, Italy), so expensive visits to USA conferences were not necessary. On the other hand, as already mentioned above, visualization challenges revealed during the last stage of the project motivated use of high-spec Apple computers which, in addition to the publication charges in Biophysical Journal [A1] have increased the Consumables part of the budget. In either case the difference was within £2k, which should be compared to the overall budget of the grant of £78k.

Further Research or Dissemination Activities

Publications This three-year studentship has so far produced two papers in very good journals, Biophysical Journal [A1] (Study 1) and Physical Review E [A2] (Study 2), each of them is a very authoritative journal in its field. The results obtained in Studies 3 and 4, are not yet published other than in S.W. Morgan's thesis [A6], so two journal papers are in preparation [A7, A8]. Two of the conferences at which the results were presented produced printed outputs [A3, A4].

Separately, we mention publication [A5], which is an invited contribution to a collective monograph, and presents a review of approaches to low-voltage defibrillation in various ways similar to the approach studied in this project. We understood that acknowledgement of the source of funding was not appropriate for the style of the monograph as envisaged by the editors and the publisher, so in that sense does not follow EPSRC rules. On the other hand, this publication is within the scope of the grant, was done during the project, was useful for training of the research student (it was written during the student's initil training stage) and contributes to the dissemination of our results, so we thought it necessary to mention it, together with the above comment on the EPSRC rules.

Presentations

- "Feedback control of resonant drift: a bidomain study", International Workshop on Non-Linear Dynamics in Excitable Media, Ghent, Belgium, 17th April 2007.
- "Termination of scroll wave turbulence in excitable media by resonant drift", British Applied Mathematics Colloquium, Manchester, 1st April 2008.
- "Low voltage defibrillation using resonant drift pacing", Northern Cardiovascular Research Group meeting, Liverpool, 29th April 2008.
- "Feedback control of resonant drift as a tool for low-voltage defibrillation", CARDIOSTIM (16th world congress in cardiac electrophysiology and cardiac techniques), Nice, France, 20th June 2008.
- "Feedback control of resonant drift as a tool for low voltage defibrillation", Computers in Cardiology, Bologna, Italy, 16th September, 2008.
- (title TBA) The Cardiac Physiome, Newton Institute, Cambridge, 20-24 July 2009.

Further dissemination activity The Cardiostim and Computers in Cardiology presentations has been met with genuine interest from audience, and several possible new research contacts regarding the topic of this project become feasible, including interest from industry (Sorin group). The planned presentation at a Newton Institute workshop in July 2009 will re-emphasize our achievements within the keynote cardiac modelling community, with the view to involving more modellers into further investigation of resonant drift low-voltage defibrillation. It is anticipated that further publications, particularly [A8] should have a significant resonance in experimental community, which hopefully should result in directed testing of the method in experiments.

References

Publications resulted from the project (peer reviewed marked★)

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