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Preface

Nonlinear waves in excitable media: Approaches to cardiac arrhythmias

Olivier Bernus [a], Arun V. Holden [a], Alexander V. Panfilov [b]

[a] University of Leeds, Faculty of Biological Sciences, Multidisciplinary Cardiovascular Research Centre, Institute of Membrane and Systems Biology, Leeds, LS2 9JT, United Kingdom
[b] University of Utrecht, Theoretical Biology, Padualaan 8, 3584 CH, Utrecht, The Netherlands

1. Introduction

Biological systems have triggered the development of nonlinear science; the Van der Pol oscillator was first published as a model for the electro-mechanical oscillations of the beating heart [1]. Spiral re-entrant waves were initially characterised in a cellular automaton for cardiac arrhythmias [2], but later also in the reaction-diffusion equation that was introduced to applied mathematics as the KPP equation for spread of a gene in a population [3], and the Belousov–Zhabotinsky reaction [4] that was proposed as an analogue for metabolic biochemical oscillations. The continuing growth of quantitative biology and the development of computing resources have led to computational modelling forming an essential part of the interpretation of experimental results, and the formulation of quantitative hypotheses. The baroque complexity of biological systems – the periodic rhythm of the heart is produced by a set of currently several dozen membrane proteins (ion channels, exchangers and pumps) [5] that is modulated by intracellular ionic and biochemical dynamics — means that the computational modelling needs to be firmly guided by mathematical insights, based on simple nonlinear systems, or on rationally reduced systems. Studies of the heart using methods of non-linear science resulted in the development of the concept of an excitable medium, which is currently one of the most developed and important branches of modern computational biology.

This special issue has grown from a meeting "International Workshop on Non-Linear Dynamics in Excitable Media" held at the University of Ghent in April 2007. This workshop was organised by Prof. Henri Verschelde (Ghent University), Dr. Olivier Bernus (University of Leeds), Dr. Thomas Desaive and Prof. Pierre Dauby (University of Liège), Prof. Albert Goldbeter (Université Libre de Bruxelles), and Dr. Alexander Panfilov (University of Utrecht), and was funded by the Research Foundation - Flanders (FWO) and the Faculty of Sciences of the University of Ghent. The aim of this conference was to bring together researchers who study dynamics of excitable media, using various approaches from pure theoretical analytical methods to computational and experimental techniques, and to promote an active interaction between these groups who normally do not attend the same meetings. This issue contains papers which are being published as a result of the meeting. Below we put them within the context of non-linear dynamics in the heart after short introductory statements.

2. Excitable systems in biology

Excitable systems are, in general, spatially distributed systems which as a result of application of a super-threshold stimulus are able to generate and conduct non-linear waves of excitation. These regenerative waves propagate without decrement as a solitary travelling wave, or wave train. The medium requires some time to recover its excitability after wave propagation and thus during this time, the refractory period, the medium cannot be excited again. Chemical examples of excitable media are the Belousov–Zhabotinsky reaction [4] and reaction of oxidation of CO on platinum catalysts, the study of which contributed to the award of the Nobel prize in Chemistry in 2007 to Gerhard Ertl [6]. Biological examples of excitable media include electrical membrane excitation in nerve and muscular tissue, intracellular waves of calcium induced calcium release and some simple morphogenetic systems.

The major area of application of the theory of excitable media in biomedical sciences is propagation and arrhythmic behaviour in the heart. It is important in medicine — heart disease is a major and growing cause of morbidity and mortality in the developed world, and accounts for approximately one adult premature death per thousand populations per year.

There are both experimental and theoretic approaches to study wave propagation in the heart. Experimentally, the spatiotemporal cardiac electrical activity can be recorded from the heart's outer (epicardial) or inner (endocardial) surfaces. In experimental perfused tissue preparations, optical methods can be applied to map epi- and endocardial activity, [7–9] whereas in clinical practise, the electrical activity can be recorded via catheter electrodes from the endocardium [10,11], but also from the outside surface of the heart during open chest surgery [12,13]. Finally, detailed structural information can be obtained using high-resolution ($\sim$100 μm cuboid voxels) diffusion tensor magnetic resonance imaging of cardiac tissue anisotropic and orthotropic architecture [14,15]. It is challenging — propagation in cardiac muscle is intrinsically three-dimensional, involves multiple time and space scales, and heterogeneities in cell properties, anisotropy and orthotropy over different spatial scales.

Theoretically, non-linear dynamics in excitable media have been studied in various spatial dimensions, ranging from zero (single cell) to three (whole organ).

In an ordinary differential system representing the electrophysiology of a single excitable cell, application of bifurcation theory

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allows the determination of the stability of equilibria, how they change at bifurcations (Hopf, homoclinic), and how periodic solutions can arise from bifurcation (period doubling into alternans, or into chaos). Bifurcation analysis is important in evaluating the normal pacemaker mechanisms, and how pacemaking can be induced, or arise pathologically, in excitable tissue.

In a one-dimensional excitable medium, a solitary wave propagates rapidly, at a velocity of up to 80 cm/s in ventricular tissue, and annihilates on collision with another wave. The propagation velocity for a wave train shows rate dependence (nonlinear dispersion). Wave front instabilities can lead to conduction block. One-dimensional models can be used to quantitatively predict the effects of heterogeneities, pharmacological agents and pathologies on propagation [16], alternating and intermittent [17] conduction, and the vulnerability to re-entry following unidirectional block, and are widely used in biomedically motivated studies.

In two-dimensional excitable media, there is also the effect of wave front curvature that allow re-entrant spiral waves that can meander [18], drift, and break down [19] into spatiotemporal irregularity [20]. In three dimensional media the re-entrant waves are scrolls that rotate in an anisotropic and orthotropic medium around meandering and drifting filaments. Within the heart these re-entrant arrhythmias are occurring within a complicated and moving geometry, and are believed to underlie ventricular fibrillation, which, if not defibrillated, can prove lethal.

3. Cardiac arrhythmias and their dynamics

3.1. Spiral and scroll waves

Spiral waves have been studied extensively in simple numerical models: e.g. Winfree mapped the "flower garden" of the spiral tip meandering patterns for the FitzHugh-Nagumo system seen in the "recovery-excitation" parameter space [21]. Spiral waves have also been observed in biophysically detailed models of cardiac tissue [22], and in thin experimental preparations of cardiac tissue. In homogeneous systems they can rotate rigidly, or meander, and gradients in parameters cause a directed drift, and localised heterogeneities can cause pinning of a spiral [23]. At a qualitative level, the spiral is rotating as fast as it can, as its wave front approaches the wave back of the preceding spiral. Even for rigidly rotating spiral wave solutions of the FitzHugh–Nagumo model there is no unified quantitative theory that can lead to the prediction of the wavelength and rotation frequency of the spiral, and how it changes with excitability; different approaches are needed for highly or weakly excitable media. In this issue, Zykov [24] uses a free-boundary approach to explore both the highly and weakly excitable limits that link the asymptotics for the highly and weakly excitable media, and is consistent with numerical solutions. Cardiac tissue is three-dimensional, and so re-entry is around scroll wave filaments, rather than a spiral core. Dierckx et al. [25] develop fully covariant equations of motion for thin (i.e in highly excitable media) scroll wave filaments in anisotropic media, where the metric tensor is the inverse diffusion (conductivity) tensor. Stationary filaments obey the geodesic equation, as found numerically and formulated in Wellner et al.'s minimal principle [26]. In the heart during ventricular fibrillation, there are multiple re-entrant waves, and so the evolution of scroll waves also depends on interactions between them. The number of filaments follows a birth and death process, with filaments being born (created *de novo*, or by filament splitting), having an apparently stochastic lifetime, and being lost at boundaries or by amalgamation. Clayton [27] presents computational results on filament dynamics, using a simplified excitation model within a cuboid slab. The number of filaments varies with the anisotropy ratio.

3.2. Atrial arrhythmias

The atrial chambers of the heart are thin ($\sim$2 mm) walled, and so two-, rather than three- dimensional phenomena are expected to predominate. Re-entrant atrial arrhythmias produce morbidity rather than death, and so can persist long enough to produce re-modelling of the tissue. The atria have a complicated geometry, with the venous entry to the atrial chambers, and the atrio-ventricular valves, acting as holes, giving each atrium the geometry of a cylinder. van Oosterom et al. [28] show that the action potential duration in homogenous tissue in such a geometry is influenced by boundaries and smoothed by the curvature-dependence of propagation velocity, and is longer at the initiation site and smaller at the termination site. Atrial fibrillation begins as short-lived, paroxysmal episodes initiated at the junctions with the pulmonary veins. Zemlin et al. [29] uses a computational model to show how a drop in heart rate can allow transient re-entry to develop in the pulmonary vein region, triggering an episode of atrial fibrillation. However, one episode of atrial fibrillation makes another more likely [30], and so the intervals between episodes decreases, until there is persistent fibrillation. These changes are remodelling, produced by changes in the expression of proteins involved in excitation and in coupling between cells. Zhang et al. [31] uses cell, tissue and whole atrial model to separate the effects of remodelling on excitability, propagation velocity and heterogeneity in the development of persistent atrial fibrillation

3.3. Mechanisms for defibrillation

Electrical defibrillation, by a single, large amplitude, and appropriately shaped pulse, is the most effective means of eliminating persistent atrial fibrillation, and in terminating potentially lethal episodes of ventricular fibrillation. An alternative possible approach is to use a periodic, low voltage perturbation: Aslandi et al. [32] use 1-, 2- and 3-dimensional tissue models to reproduce the standing waves seen when an isolated *in vitro* heart is defibrillated by periodic pulses applied to the bathing medium.

3.4. Multiscale and mechano-electrical aspects of cardiac physiology

Although action potentials in the heart extend throughout the tissue – the wavelength (product of duration and propagation velocity) is of the order of 1–10 cm with a steep wavefront of over a few mm thickness – cardiac electrophysiology is multiscale, with molecular, membrane or cell level changes influencing whole heart behaviour. Li et al. [33] model nonlinear wave behaviours – travelling waves and re-entrant waves – that occur inside cardiac cells, as waves produced by calcium-induced calcium release. A different illustration of the multiscale nature of cardiac nonlinear wave behaviour is Keldermann et al.'s [34] review on the modeling of mechano-electrical feedback, using reaction-diffusion-mechanics systems. In excitable media models of cardiac tissue, the emphasis is on the spatiotemporal pattern of excitation, which, via intracellular calcium dynamics, triggers contraction. However, mechanical perturbation of the heart, say by a sudden impact, alters the electrical activity. This mechano-electric feedback is mediated by stretch activated ion channels in the cell membranes, and is believed to be important in the initiation of arrhythmias in the pathological heart, where abnormal spatial patterns of mechanical stress at the whole organ level may produce changes in cellular electrophysiology that trigger arrhythmias.

3.5. Optical approaches to experimental recordings of cardiac electrical activity

Our current understanding of cardiac arrhythmias is based on the theory of nonlinear waves in dissipative systems, and on computational investigations. These quantitative predictions need validation, by experimental recordings of the spatiotemporal patterns of excitation. Optical methods of recording, using voltage sensitive dyes, provide such data, at a spatial resolution finer than the upstroke of the propagating wavefront and a temporal resolution of about 1 ms. However, optical recordings of electrical activity are sensitive to the optical properties of the tissue. This can be simulated by coupling an optical model representing photon scattering and absorption in tissue, with the nonlinear diffusion systems representing the spread of excitation. The optical signal in a surface pixel is a spatially weighted average of excitation from a tissue volume below the pixel. This produces distortions, that need to be taken into account in the interpretation of optically recorded signals, but also opens up the possibility for extracting information with depth, and so probing into the heart wall to visualise the excitation in 3-dimensions. Bishop et al. [35] combine Monte-Carlo simulation of photon transport within the ventricular wall with a model of the recording optics, and provide a guide towards the interpretation of optically recorded excitation signals, and towards the design of recording optics for optimizing mapping performance. Roth et al. [36] review computational modelling of the optical action potential and how it has provided quantitative explanations for specific details of the shape of optical action potentials, and their interpretation, and review theoretical approaches towards extending optical mapping of surface activity into the ventricular wall by the development of transillumination imaging of filaments and optical tomographic methods.

4. Conclusions and outlook

Many of the central ideas about nonlinear wave behaviours in cardiac arrhythmias were current in the late 1980's [37,38], the major advances follow from developments of techniques, that allow the visualisation of the electrical activity in experimental ventricular fibrillation and the construction, from diffusion-tensor magnetic resonance imaging, of detailed models of individual heart geometry and anisotropic and orthotropic architecture, and from the growth of computational power, that allows large scale (whole ventricles, and towards isolated whole heart) computational simulations. As in the other biological sciences, the move towards high throughput methods has resulted in an explosive growth of data that threatens to overwhelm the underlying simplicity of the physics. Many of the biomedically relevant applications are specific examples – such as patient specific modelling – rather than exemplars. However, this quantitative explosion in data and models has led to qualitatively new problems in physics. In metrology, there are developments towards three-dimensional imaging of the electrochemical activity of the heart – optical tomography, magnetic resonance spectroscopy, and the binding of molecular markers to magnetic contract agents. All the models discussed above are deterministic, and although they provide insight into the evolution of arrhythmias, they do not address the apparently stochastic initiation of arrhythmias. The use of families of models and populations of data sets is setting the framework for a more statistical approach that will account for stochasticity of initiation and persistence of re-entrant arrhythmias. The multiple scale aspects, where molecular, cellular and tissue level effects have separate but interacting length and time scales is providing enough information for the development of evidence based, mechanistic multiscale models, rather than descriptive multiscale models.

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