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Computational models of ventricular arrhythmia mechanisms: Recent developments and future prospects

R H Clayton[a], M J Bishop[b]

[a]Department of Computer Science and INSIGNEO institute for in-silico medicine,
University of Sheffield, Regent Court, 211 Portobello, Sheffield S1 4DP, United Kingdom.
email r.h.clayton@sheffield.ac.uk

[b]Division of Imaging Sciences and Biomedical Engineering,
King's College London, 4th Floor, Lambeth Wing, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH.
email martin.bishop@kcl.ac.uk

Corresponding author:
Richard Clayton,
Department of Computer Science, University of Sheffield, Regent Court, 211 Portobello, Sheffield S1 4DP, United Kingdom.

Telephone: +44 114 222 1845
Fax: +44 114 222 1810
email: r.h.clayton@sheffield.ac.uk

Abstract
Ventricular arrhythmias are an important cause of death, and can also be a serious side effect of drugs. Computational models are becoming established as important research tools, alongside experimental work, for understanding the mechanisms that initiate and sustain these dangerous events. Advances in computer power have enabled large-scale simulations of cell and tissue electrophysiology, and advances in imaging have generated detailed models of cardiac anatomy. Active research areas include action potential propagation around an infarct, detailed modeling of drug effects in multiscale models, low voltage defibrillation, and pipelines to establish patient specific models of structure and function. Although computational power remains a bottleneck for high throughput simulations, it is likely that electrophysiological models will continue to become increasingly important tools.

Introduction

Ventricular arrhythmias are an important cause of premature death, where the lethal event is often ventricular tachycardia (VT) or ventricular fibrillation (VF) [1]. Both VT and VF involve rapid and self-sustained electrical activity in the ventricles, resulting in pump failure. VT and VF can be sustained by re-entry, where a circulating wave of electrical activation continually propagates into electrically recovered tissue [2]. VT is sustained by a single re-entry circuit (or rotor), whilst VF is characterised by many interacting re-entrant circuits (see Figure 1).

From a clinical perspective, the most effective treatment for VF and pulseless VT is defibrillation, and many patients at risk will receive an implantable cardioverter-defibrillator (ICD). While ICDs are effective, precise risk stratification remains difficult, so many receive an ICD that never discharges [3], while others die suddenly in the community because their elevated risk was not identified. A preventative approach is to ablate re-entrant pathways with radiofrequency energy. This can be effective for incessant VT with a static re-entrant pathway [4], but procedure times can be lengthy, with high rates of complications and recurrence.

Effective risk stratification and prevention in individuals is difficult because the mechanisms that initiate and sustain re-entry in the human heart are not well understood. Recent experimental studies using in-situ electrical epicardial mapping [5] and ex-vivo optical mapping with voltage sensitive fluorescent dyes [6] have identified mechanisms sustaining VF in the human heart. However, an important limitation of these studies is that high-resolution mapping is restricted to the surface of the heart.

Computational models of 3D tissue electrophysiology therefore have an important role alongside experimental studies in establishing a mechanistic understanding of ventricular arrhythmias. This review aims to document recent developments, to explain the benefits and limitations of computational models, and to identify future trends.

Models and software

In physical sciences and engineering, models provide quantitative and mechanistic descriptions of real-world processes, such as flexing of an aircraft wing during flight, based on underlying physics. In the same way, models of cardiac cell and tissue electrophysiology aim to describe the generation and propagation of action potentials in terms of physiological mechanisms [7]. However, models always embed assumptions and simplifications, and to be used effectively models and simulations should be carefully calibrated against experimental data [8].

Care with both numerical solution of cardiac cell and tissue models, and their implementation in software, is also crucial. CellML (http://www.cellml.org) has become a standard repository for curating models at the cell scale, while several codes for implementing tissue scale simulations have been developed, and some of these are listed in Table 1. These codes differ widely in their implementation and performance, some are open source, and many have been evaluated against a benchmark problem [9].

Theoretical and simplified models

Figure 1 illustrates how re-entry propagates around a line of phase singularity (filament) in 3D tissue, and where a filament intersects the tissue surface there is a point of phase singularity (PS). The behaviour of PS and filaments provides a way to quantify complex activity in both experimental and simulated VF. Additional ideas from physics about the dynamical behaviour of nonlinear systems have contributed to our understanding of mechanisms that initiate and sustain re-entry [10–13]. Recent contributions include the dynamics of PS behaviour [14], the role of electrical coupling [15], and both diffuse [16] and focal [17] obstacles.

These approaches have often used a simplified model of cellular electrophysiology within a simplified tissue geometry that may be a 2D sheet or 3D cube. Despite the limitations, this abstract approach makes it possible to examine a specific hypothesis without the additional computational load resulting from biophysically detailed models, or the additional effects of anatomical complexity.

Biophysical detailed cell models

An important recent trend has been increasing use of models that represent cellular electrophysiology of human ventricular myocytes. The Ten Tusscher 2006 model [18] is widely used, but is not completely based on human data. Alternatives include both phenomenological models [19] and detailed mechanistic models based on experimental data from human myocytes [20, 21].

These models have enabled detailed comparison of how myocytes from different species respond to antiarrhythmic drugs [22], and an examination of how the response of cardiac cells and tissue to sex hormones influences vulnerability to re-entry [23]. However, an important consideration in using these models is computational load, which limits their use in large scale simulations.

Detailed models of normal anatomy

The ventricular wall is electrically anisotropic, and the orientation of myocytes rotates by ~120° anticlockwise from epicardium to endocardium. The resulting axially symmetric electrical anisotropy is usually included in models of ventricular tissue [7], although experimental evidence indicates that ventricular sheet structure may also be important [24], any corresponding effect on re-entry has not yet been investigated.

Recent advances in magnetic resonance (MR) imaging have enabled structural detail to be resolved to < 20 μm, so anatomical models that include blood vessels, trabeculations and papillary muscles can be constructed [25]. Whole ventricle simulations comparing re-entry in a structurally detailed model of the rabbit ventricles with an equivalent but anatomically simplified model have shown that the behaviour of a small number of re-entrant waves in the two models was similar, but for arrhythmias more closely resembling VF the presence of fine-scale anatomical features resulted in increased complexity, with filament clustering around endocardial structures [26]. A more recent study [27] showed, in an anatomically-simplified model of the rabbit heart, that transmural and base-apex heterogeneity in action potential shape

and duration had little impact on dynamics of sustained arrhythmias, due to attenuation of heterogeneities at the fast cycle lengths characteristic of re-entry. Despite having little effect on arrhythmia stability, it has also been recently shown in the same structurally-healthy rabbit model that reductions in sodium current during disease may interact with macroscopic structural heterogeneity such as regions of ventricular wall expansion to encourage arrhythmia induction [28].

The fast conduction system in the heart acts to synchronise electrical and mechanical activation during normal beats. In arrhythmias the conduction system may act as both a trigger for re-entry, and a source of stabilisation during VF [29]. Using a rabbit ventricular model incorporating an anatomically-based 3D branching Purkinje network, Deo et al [30] demonstrated how a single premature beat originating in the conduction system can produce re-entry, because electrotonic interactions at Purkinje-myocardial junctions lead to dispersion of repolarisation along the conduction system, resulting in unidirectional block. Accurate reconstruction of Purkinje network geometry remains a challenge. Cherry & Fenton [31] used photographs of stained endocardium to construct a 2D model, and showed that the conduction system can act to either terminate re-entry by providing long-range connections to excitable tissue, or sustain re-entry by increasing dispersion of recovery. More detailed models of structure and function will shed further light on the role of the conduction system in ventricular arrhythmias [32],

Detailed whole-organ models of abnormal anatomy

VT and VF are more prevalent in patients with existing structural heart disease or acute myocardial infarction, both of which provide the substrate of slowed conduction and dispersion of repolarisation necessary to initiate and sustain re-entry. Remodelling and fibrosis following myocardial infarction (MI) are thought to play a major role [33]. A combined histological imaging and modelling study has shown how structural fibrotic remodelling can affect conduction within the border-zone (BZ) of a healed MI [34]. Connected strands of surviving myocytes, surrounded by dense fibrosis, were identified within high resolution confocal microscopy images of LV tissue segments from rats 14 days after MI. Simulations using a 3D network model generated from the imaging data showed that stimulation within the BZ resulted in slow activation along tortuous, ‘zig-zag’ pathways through surviving myocytes, with direction- and rate-dependent conduction slowing and unidirectional block occurring due to source-sink mismatches at branching tissue strands. The authors demonstrated that these effects, due to structural remodelling alone, could combine to provide a sufficient substrate to support re-entry. The important role of structural heterogeneity was also shown previously in an earlier study in the case of a 2D histologically-derived model of patchy fibrosis [35].

The interaction of structural remodellng along with altered ionic membrane properties of surviving myocytes, reduced gap junction expression and electrotonic myocyte-fibroblast interactions within BZ regions might be expected to augment electrical instability in this region. McDowell et al [36] used an MR-derived whole ventricular model of a 7.5 week postinfarct rabbit heart to investigate how the presence of myofibroblasts influences vulnerability to re-entry. This study lacked the histological-detail of the studies described above, with a focus instead on electrophysiological remodelling in BZ regions identified from the MR data. Both BZ and scar

regions were modelled to include varying percentages of myofibroblasts by volume, represented by distributed clusters assigned specific myofibroblast membrane kinetics. Myofibroblast coupling shortened APD in the BZ region by acting as an electrotonic current sink. This effect combined with BZ electrophysiological remodelling resulted in APD dispersion, which increased vulnerability to re-entry. Although the extent of myofibroblast proliferation and coupling within the BZ and scar is not fully understood, this work highlights how the resulting structural and functional heterogeneity increases vulnerability to re-entry.

MR-derived whole ventricle models have also recently been used to dissect the contribution of the extent and composition of the BZ region in sustaining re-entrant VT. In a canine MR-derived ventricular model - including electrophysiological remodelling as above, although not representing myofibroblasts - Arevalo et al [37] showed that scroll-wave filaments driving the re-entrant activity were always contained entirely within the BZ. By varying the functional definition of the BZ region, they also showed that the specific location of the filaments was dependent on the size and morphology of the BZ, but not on structural composition. Models with insufficient BZ volume were unable to sustain re-entry.

These recent studies adopt differing approaches to scale and level of structural detail, which are constructed from different imaging modalities with huge differences in resolution. Despite this difference in approach, these studies show that both structural and electrical remodelling in the BZ regions of infarcted tissue are potent substrates for re-entry. Recent advances in numerical techniques for efficiently representing small scale conduction discontinuities, coupled with developments in imaging and processing algorithms, may soon enable histologically-based models of MI scar and BZ regions to be implemented within whole ventricular models, which will allow this hugely complex, yet clinically-relevant, structure-function interaction to be probed further.

Arrhythmia therapies

Driven by increasing availability of molecular and cell scale data and advances in computational techniques, cardiac modelling is being used to provide mechanistic links between drug-induced alterations in sub-cellular function and clinical arrhythmia risk, to aid drug development and screening [38]. Moreno et al [39] recently demonstrated the power of multi-scale electrophysiology modelling to assess drug toxicity by using single cell, tissue and whole organ simulations to predict potential arrhythmogenic side-effects of two antiarrhythmic drugs, lidocaine and flecainide. In accordance with observations in patients and in agreement with corresponding experimental rabbit measurements, the simulations demonstrated how flecainide causes both conduction slowing and dose- and frequency-dependent block, inducing re-entrant ventricular arrhythmias. This was not seen for lidocaine. This tissue-level phenomenon, due to increased electrotonic loading, was not observed at the single cell level, and thus could be missed by current drug-screening protocols. The exciting combination of detailed cell-level simulations, such as those representing drug actions on multiple channels simultaneously by Mirams et al [40], along with the multi-scale nature of the Moreno et al study, will no doubt have a significant impact in this area in coming years.

ICD device implantation is common, but the high shock strengths currently required to ensure successful defibrillation can cause significant physiological and psychological problems. Recent experimental and computational investigations have advanced the idea of low-voltage shocks [41]. Several rapid low-energy pulses, close to the VF cycle length, can successfully defibrillate in both atria [42, 43] and ventricles [43, 44]. The mechanism underlying these protocols still remains debated. Theoretical [43] and image-based [44] modelling has suggested their success is driven by far-field virtual-electrode excitations centred around either endocardial trabeculae invaginations [44] or blood vessels [43], which may only become relevant at higher field strengths [45]. Future application of these ideas to human models with realistic ICD electrode configurations, in combination with image-based active heart-torso modeling methodologies [46], as well as how low energy shocks interact with MI scar will prove important next steps prior to their testing during electrophysiology procedures.

Patient-specific models of structure and function

The use of patient-specific models to inform planning for catheter ablation of scar-related re-entrant VT has recently witnessed a significant step-forward [47, 48]. Although personalised ventricular geometry can be faithfully represented from late-gadolinium enhanced MR images, obtaining both patient-specific electrical properties and fibre architecture in-vivo is significantly harder. The different approaches taken by Ashikaga et al [48] and Relan et al [47] highlight the competing issues of the need to match patient-specific electrophysiological parameters from clinical measurements with the use of sufficiently realistic ionic models to allow simulation of clinically-relevant cellular-level arrhythmogenic mechanisms. Relan et al built upon an earlier electrophysiology model-personalisation pipeline [49] to optimise, in an inverse manner, model electrophysiological parameters from clinical non-contact endocardial mapping recordings, made possible due to the choice of a simplified phenomenologically-based ventricular ionic cell model. Conduction velocity, APD and even APD restitution properties, including scar and BZ specific properties, were captured and personalised by this approach. Ashikaga et al used a biophysically-detailed ionic model [18], with literature-based values to adjust membrane ionic conductances and tissue conductivities within the BZ, and default values used in the remainder of the myocardium. Despite the methodological differences, both approaches show promise for predicting patient-specific inducibility of VT and identifying optimal ablation targets. However, there is not yet a comprehensive comparison between the re-entrant VT circuits found in the model and those recorded in the clinic. Nevertheless, these studies show the type of patient-specific information needed for models to be clinically useful, indicating that personalised ventricular anatomy and scar/BZ geometry may be more important for predicting scar-related re-entrant circuits than identification of personalised electrophysiological properties and fibre orientation.

Conclusions

Computational models have made important contributions to our understanding of re-entrant ventricular arrhythmias. There is a trend towards models that include more anatomical and biophysical detail, and pipelines for generating patient-specific models for guiding intervention in the clinic. The interaction of structure and function, especially within the border zone of an

infarct, has been identified as an important substrate for re-entry. Emerging areas are detailed modelling of drug interactions, and low-voltage electrical therapy for terminating arrhythmias.

Several challenges remain. Simulation of a complete activation sequence in the human heart can currently be achieved in about 1 minute of computer time, but requires around 16,000 compute cores [50]. Developments in computer hardware and numerical implementation will result in some speedup, but simulation time is likely to remain a bottleneck. The interaction of the nervous system and the heart is known to influence the initiation of ventricular arrhythmias [51], yet remains an area that has not yet been explored using models. Finally, the importance of stochastic behaviour at the molecular scale has begun to be recognised [52], and early studies have begun to address parameter sensitivity [53], as well as how parameter uncertainties influence the range of behaviours simulated by a model [54].

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Conflict of interest
The authors have no conflict of interest to declare.

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Table 1. Example packages that can be used to simulate cardiac electrophysiology problems.

Package name	Website
BeatBox	http://empslocal.ex.ac.uk/people/staff/vnb262/software/BeatBox/
CARP	http://carp.meduni-graz.at
Chaste	http://www.cs.ox.ac.uk/chaste/
cHeart	http://cheart.co.uk
Continuity	http://www.continuity.ucsd.edu
openCMISS	http://physiomeproject.org/software/opencmiss/

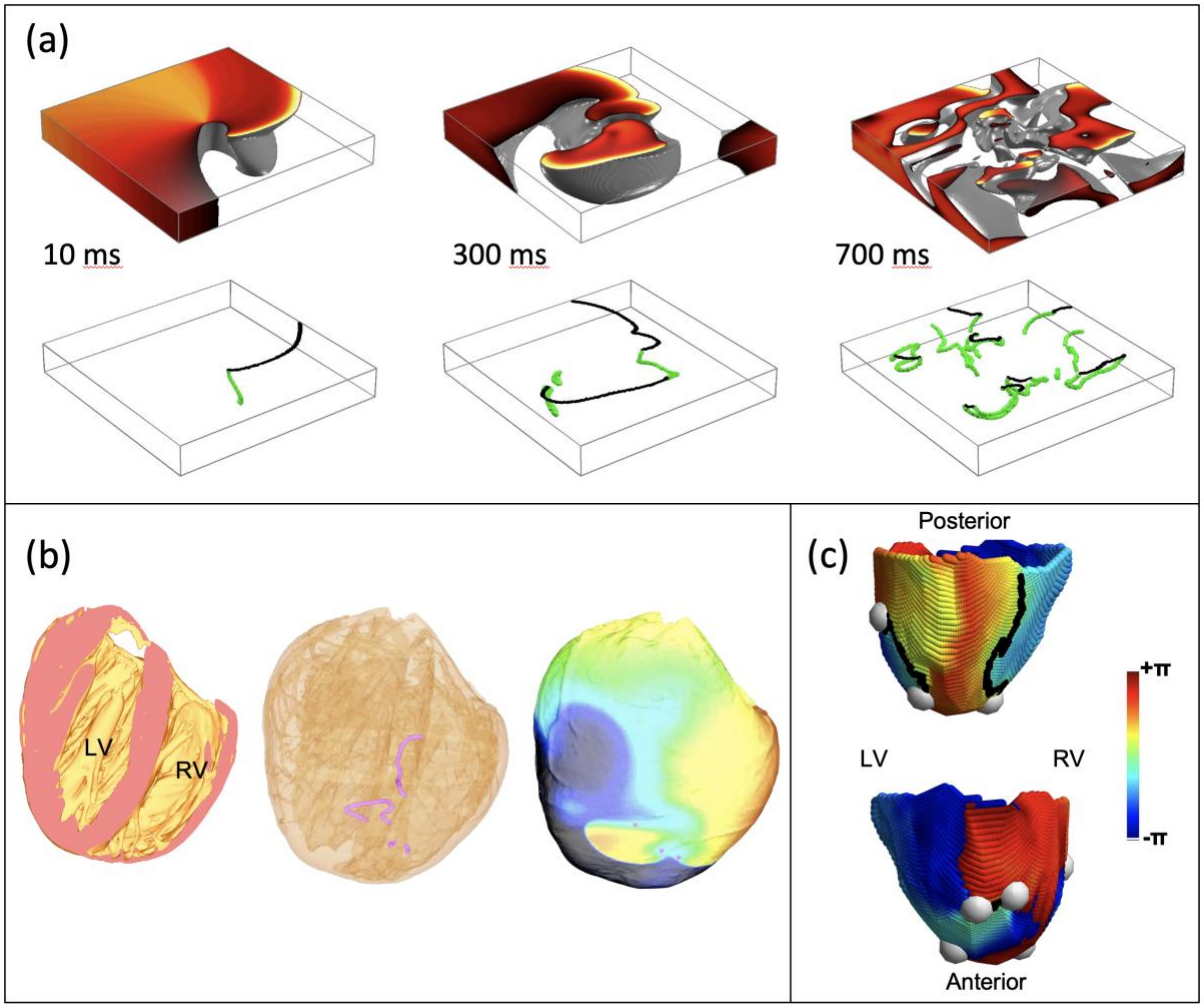

Figure 1. Ventricular arrhythmias and re-entry. (a) Snapshots of re-entry in a computational model of a tissue slab 10, 300, and 700 ms after initiation, showing the breakup of a single scroll wave into multiple re-entrant waves. The size of the tissue was 8.0 × 8.0 × 1.2 cm, with rotational anisotropy reflecting the orientation of fibres in the human ventricular wall. Cellular electrophysiology was described by a phenomenological model of the human action potential [19]. The top panels show regions of electrically active tissue, and brighter colours indicate more depolarized tissue. The bottom panels show wavefronts on the epicardial surface (black), and filaments round which the re-entrant waves rotate (green). The intersenction of filaments with the epicardial (top) surface are points of phase singularity. (PS) (b) Snapshot of re-entry in an anatomically detailed model of a rabbit heart [26], showing a section through the anatomical model (left) with right ventricle (RV) and left ventricule (LV) indicated, filaments shown in pink (middle), and epicardial membrane potential with PS shown as pink dots (right). These simulations were performed using the CARP package (Table 1). (c) Experimental data recorded during VF in the human heart [5], with similar (but not identical) arrangement of epicardial wavefronts and PS. Colours indicate the location in the activation-recovery cycle of each point on the epicardium. Black lines show wavefronts, and grey spheres show locations of PS.