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Computational cardiology: how computer simulations could be used to develop new therapies and advance existing ones

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This article reviews the latest developments in computational cardiology. It focuses on the contribution of cardiac modelling to the development of new therapies as well as the advancement of existing ones for cardiac arrhythmias and pump dysfunction. Reviewed are cardiac modelling efforts aimed at advancing and optimizing existent therapies for cardiac disease (defibrillation, ablation of ventricular tachycardia, and cardiac resynchronization therapy) and at suggesting novel treatments, including novel molecular targets, as well as efforts to use cardiac models in stratification of patients likely to benefit from a given therapy, and the use of models in diagnostic procedures.

Introduction

The iterative interaction between experimentation and simulation has long played a central role in the advancement of biological sciences. Among computational models of the various physiological systems, the heart is the most highly advanced example of a virtual organ, capable of integrating data at multiple scales, from genes to the whole organ.[1] State-of-the-art whole-heart models of electrophysiology and electromechanics are currently being used to study a wide range of mechanisms in the workings of the normal and the diseased heart.[2] The focus of this review is on the contribution of heart computational models to the treatment of the diseased heart, i.e. on the computational medicine aspect of cardiac modelling applications. Reviewed below are cardiac modelling efforts aimed at advancing and optimizing existing therapies for cardiac disease and at suggesting novel treatments, including novel molecular targets, as well as efforts to use cardiac models in stratification of patients likely to benefit from a given therapy, and the use of models in diagnostic procedures.

Subject-specific biophysically-detailed modelling of the heart for optimization and advancement of therapies for arrhythmias and pump dysfunction

Recent years have witnessed revolutionary advances in imaging, including *ex vivo* structural and diffusion tensor (DT) magnetic resonance imaging (MRI) that facilitate acquisition of the intact structure of explanted hearts with high resolution. Leveraging these advances, a new generation of whole-heart image-based models with unprecedented detail have emerged.[3,4] *Figure 1A* presents the development of one such model, of the normal canine heart, together with the activation map resulting from paced propagation in this heart. Such *ex vivo* heart models are currently being used, in combination with experimental electrophysiological data, to provide a better understanding of the role of the individual morphology of the infarct region in the generation and maintenance of infarct-related ventricular tachycardia (VT), the most frequent clinical ventricular arrhythmia, present in 64% of patients with ventricular rhythm disorder and in 89% of patients with sudden cardiac death.[5] Using a multi-scale model of the infarcted pig ventricles reconstructed from *ex vivo* MRI and DTMRI data, the study by Pop *et al.*[6] demonstrated a good correspondence between *in-silico* and experimental electroanatomical voltage maps, and was able to successfully predict infarct-related VT inducibility after programmed electrical stimulation. Arevalo *et al.*[7] examined the role of the extent of the infarct border zone in arrhythmogenesis, establishing that a minimum volume of remodelled tissue is needed for VT maintenance. Such simulation methodology could have a major clinical impact in predicting the optimal targets of catheter ablation of infarct-related VT in individual hearts, should the methodology be able to reconstruct patient hearts from clinical imaging data and evaluate the three-dimensional (3D) patterns of infarct-related VT[8] in the patient.

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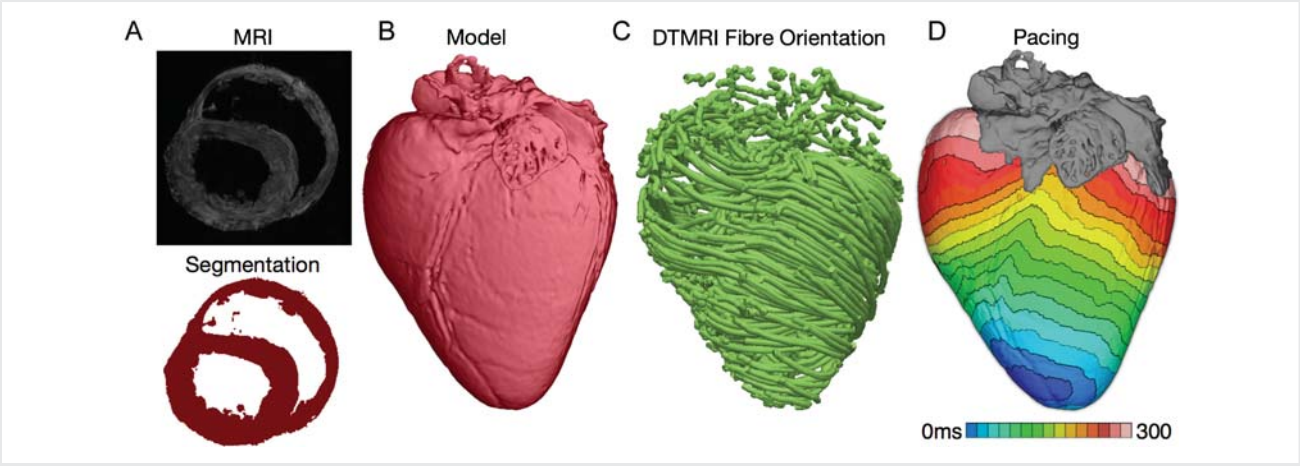

Figure 1 Magnetic resonance imaging-based high-resolution model of electrical activation in the normal canine heart. (*A*) Segmentation of the myocardium. (*B*) Reconstructed canine heart geometry. (*C*) Fibre orientation in the canine heart as determined from the diffusion-tensor magnetic resonance imaging data. (*D*) Paced activation in the heart.

The first attempts in this direction have already been made. Relan *et al.*[9] used a hybrid X-ray and MR environment to image a patient heart, which was further personalized with voltage measurements. The results demonstrated that the heart model could successfully be used to assess infarct-related VT inducibility from sites not accessible in the clinic.

Computational modelling of the electrophysiology of the human atria is also becoming an important component in the evaluation and advancement of therapeutic strategies, as recent state-of-the-art models can accurately simulate the complex spatio-temporal dynamics of atrial arrhythmias. Similar to ventricular modelling methodology, biophysically detailed atrial models are reconstructed from MRI[10] and computerized tomography (CT)[11] scans. Contemporary atrial models allow for realistic simulation of electro cardiograph (ECG) signals,[12] monophasic action potentials,[13] and electrograms,[14] serving as an important tool for analysing the aetiologies that underlie electrical signals obtained clinically. For example, simulation studies of bipolar electrograms in atrial tissue have found that fibroblast proliferation and microscale obstacles (such as collagenous septa) may be responsible for the fractionation of electrograms[15] during atrial fibrillation (AF), signals which guide catheter ablation of AF. Studies involving simulation of ECG signals in atrial models have helped optimize procedures such as haemodialysis therapy (which can cause AF)[16] and predicting the optimal position and direction of one-channel bipolar ECGs.[17] Full utilization of multi-scale atrial models in the clinic for preventative, diagnostic, or therapeutic purposes will require the generation of patient-specific atrial models; early efforts in this direction are already underway.[18] An example of a patient-specific model with the fibrosis regions delineated is shown in *Figure 2*.

Finally, biophysically detailed electromechanical models of the heart, which represent the most sophisticated models of the heart developed so far,[19] have also been harnessed in the development of therapies for pump dysfunction. Cardiac resynchronization therapy (CRT) employs bi-ventricular pacing to re-coordinate the contraction of the failing heart. Electromechanical modelling studies have provided insight into the mechanisms that govern CRT efficacy. Kerckhoffs *et al.*[20,21] have demonstrated that improvement of ventricular function following CRT in the failing heart with left bundle branch block (LBBB) is diminished with increasing infarct size and that infarct location also affects the response to CRT. Niederer *et al.*[22] revealed that the haemodynamic benefit from CRT is improved when length-dependent tension regulation is attenuated; the study suggested that a compromised Frank–Starling mechanism (the organ-level equivalent of length-dependent tension regulation) could be a clinical metric in identifying heart failure patients as potential responders to CRT. Electromechanical models of the heart have also been used as test beds to understand how different

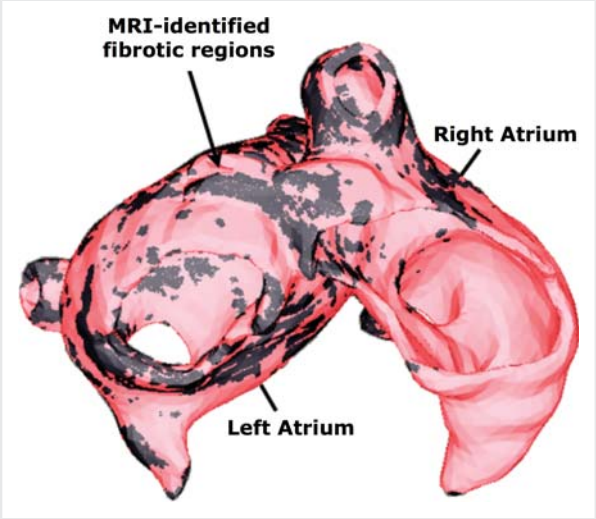

Figure 2 A reconstruction of patient atria with fibrotic remodelling from magnetic resonance imaging scans. MRI data courtesy of Dr R. Macleod, University of Utah.

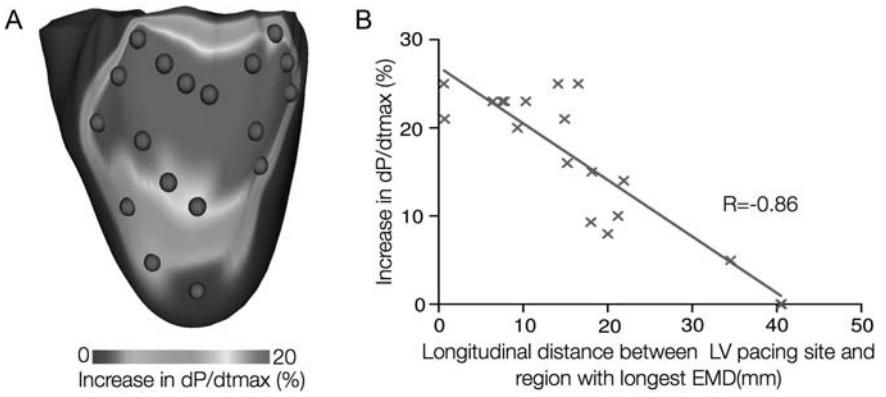

Figure 3 Optimizing the placement of the Left Ventricle (LV) pacing electrode for cardiac resynchronization therapy in the failing canine heart. (*A*) Map of the percentage increase in dP/dt_{max} as a function of the LV pacing site (P is pressure). Red dots denote LV pacing sites. (*B*) Correlation of longitudinal distance between LV pacing site and region with longest EMD, and percentage increase in dP/dt_{max}.

pacing parameters affect CRT efficacy.[23,24] Constantino *et al.*[25] recently proposed a strategy to optimize the response to CRT that involves placing the Left Ventricle (LV) pacing electrode at a location that targets the regions with the longest electromechanical delay; *Figure 3* presents simulation results demonstrating that maximal haemodynamic benefit occurred when the LV pacing site was located near the base and mid-ventricle, which was within the region of longest electromechanical delay. Finally, patient-specific models of hearts with contractile dyssnchrony have been recently developed,[26,27] holding high promise to become an important clinical tool in the treatment of dyssycnhronous heart failure.

Biophysically-detailed computational modelling of the heart as a testbed for new molecular therapies

A major avenue of scientific inquiry in computational cardiology relates the binding/unbinding of drugs to molecular target(s) to the instigation, termination or prevention of cardiac arrhythmias. In this section we focus on examples where emergent behaviour, resulting from integrations across the scales of biological hierarchy, has shed new light on existing or novel drug actions for treatment of arrhythmia.

At the level of the ion channel, Markov models with state specific drug binding/unbinding have been used to test hypotheses regarding the mechanisms of drug effects on macroscopic currents. Since the arrhythmogenic long QT syndrome (LQTS) type 2 is characterized by loss of repolarizing rapid delayed rectifier K^+ current, I_{Kr},[28] a straightforward approach for the prevention of LQT-2 arrhythmia, therefore, would be pharmacological enhancement of I_{Kr}. Perry *et al.*[29] explored the novel compound RPR260243, shown to enhance I_{Kr}, represented by the KCNH2 isoform 1a current expressed in *xenopus oocytes*. Rate constants in a proposed modal gating scheme were determined to best fit the experimental data. The model revealed that I_{Kr} enhancement could be explained by dose-dependent loss of deactivation; point mutation analysis provided the structural mechanism underlying this model prediction. Going a step further, Sale *et al.*[30] simulated the effects of the drug E4031, known to block I_{Kr} in its open state in a use-dependent manner[31] on the human ventricular action potential. Drug E4031 is known to block I_{Kr} in its open state, in a use-dependent manner.[31] Previously it was unclear as to why isoform 1a current, which is smaller than 1a/1b combination, was more sensitive to E4031. The Markov model for 1a-alone vs. 1a/1b mechanistically explained the discrepancy, and related action potential prolongation with E4031 as seen experimentally.

Type 3 LQTS is brought on by enhancement of the non-inactivating, or late Na^+ current (I_{Na}).[28] Using Markov models, Clancy *et al.*[32] compared the effect of two I_{Na} blocking drugs, lidocaine and mexiletine, revealing that mexiletine preferentially binds to the population of channels undergoing late burst opening; the latter events are dangerously common in LQT3, leading to arrhythmogenic early afterdepolarizations (EADs). In contrast, lidocaine preferentially binds to channels during the rapid activation/inactivation phase of I_{Na}. The model showed that there are mexiletine doses that selectively remove late current and EADs without detrimental effect to excitability.

Nesterenko *et al.*[33] also drew connections between drug binding kinetics and emergent effects on the action potential (AP) in the investigation of the novel anti-arrhythmic drug ranolazine. Among its many targets,[34] ranolazine reduces late I_{Na} in atrial-selective fashion.[35] Nesterenko *et al.* explained the mechanism behind this selectivity by introducing the concept of a 'pre-open' state to the I_{Na} Markov model. The effect of late I_{Na} block by ranolazine on tissue electrophysiology was examined by Morita *et al.*,[36] who demonstrated that late I_{Na} block suppresses EADs that lead to focal reentry after hydrogen peroxide application, as observed in experiments. Importantly, ranolazine is a mild I_{Kr} blocker at clinical doses, an effect of major significance for drug safety. Rodriguez *et al.*[37] proposed that computer modelling of multichannel affecting drugs, such as ranolazine, could be a testbed for determining the utility of new or previously rejected compounds or drug

combination approaches, with modelling as a force against rigid standards, and toward rational, more holistic drug candidate selection. Fundamentally, this is the modelling approach of Sarkar and Sobie[38] whose recent article explores basic mechanisms by which interrelated model parameters contribute to the consequence of I_{Kr} block, a phenomenon known as the 'repolarization reserve'.[39] The article makes the important discovery that subtle changes in ion channel substrate can have profound and indirect effects on the response to drugs. Simulating the subtle differences between species[40] and the effects of sex hormones[41,42] also demonstrated changes in drug block effects. Personalized medicine requires clear delineation of the subtle interspecies and inter-individual differences, which determine outcomes; this delineation is made possible in part by mechanistic simulation.

Relating effects of drugs on ion channels beyond the AP requires virtual tissue or whole heart organ simulation, to examine arrhythmia onset, termination and prevention. Recently, Benson *et al.*[43] related the effects of d-sotalol, an I_{Kr} blocker, and amiodarone, a complex multichannel effector, to arrhythmia formation in the heterogenous canine ventricular wedge. An emergent finding was the understanding of how the vulnerable window is enhanced by d-sotalol, but reduced by amiodarone due to different effects of the drugs on different cell types. Whereas the drug models used by Benson *et al.* were implemented by simple conduction scaling, a new study by Moreno *et al.*[44] has incorporated both state-dependent Markov modelling of drug effects and full integration to the human AP, human tissue, and finally realistic MRI-based human heart. This is the first instance of such massive integration across the space and time scales at play. Moreno *et al.* showed that the effects of flecainide and lidocaine on I_{Na} block are globally similar in response to dynamic protocols. However, clinical trials have shown previously that flecainide tended to be pro-arrhythmic at therapeutic doses, while lidocaine was not. Moreno *et al.* results make clear that neither simple reduction in sodium conductance, nor single cell simulation can resolve this paradox. At the macroscopic scale, the vulnerable window was greater for flecainide than for lidocaine (especially in heart failure simulations due to shortened diastole) and reentrant arrhythmia in the ventricle persisted (*Figure 4*). At the microscopic scale, Markov models explained that this was due to the relatively slow accumulation of and recovery from use-dependent block with flecainide.

Biophysically detailed computational modelling of novel defibrillation therapies

Controlling the complex spatio-temporal dynamics underlying life-threatening cardiac arrhythmias such as fibrillation is extremely difficult because of the non-linear interaction of excitation waves in a heterogeneous anatomical substrate. In the absence of a better strategy, strong electrical shocks have remained the only reliable treatment for ventricular fibrillation. Over the years, biophysically detailed multi-scale models of defibrillation have made major contributions to understanding how defibrillation shocks used in clinical practice interact with cardiac tissue.[45,46] Recently, however, defibrillation modelling has focused on the development of new methodologies for low-voltage termination of lethal arrhythmias or for applying defibrillation in novel, less damaging ways.

Based on simulations of the response of the myocardium to shocks,[47] the study by Luther *et al.*[48] offered a method for low-voltage control of atrial fibrillation using a sequence of low-energy electric field pulses. Mechanistically, following a series of low-voltage shocks, heterogeneities in the myocardium become sources of activation; the many pulses of the field recruit many such activation sites. The study demonstrated that the geometric structure of the coronary vasculature (one type of heterogeneity in the heart) allowed for the recruitment of a correspondingly dense and widespread series of wave sources inside the myocardium. These distributed wave sources acted as non-invasive, intramural multi-site pacing, which effectively terminated the wavefronts of fibrillation.

A recent novel approach to defibrillation also relied on biophysically detailed modelling of heart electrophysiology. The study by Tandri *et al.*,[49] was based on the premise that sustained kilohertz-range alternating current (AC) fields have been known to instantaneous and reversibly block electrical conduction in nerve tissue. The article provided proof of the concept that electric fields, such as those used for neural block, when applied to cardiac tissue, similarly produce reversible block of cardiac impulse propagation and lead to successful defibrillation, and that this methodology could potentially be a safer means for terminating life-threatening reentrant arrhythmias. The data revealed a previously unrecognized capacity for myocardial cells to be placed in an extended but immediately reversible state of refractoriness by an applied electric field. The imposed refractory state blocked all wave propagation and resulted in termination of reentrant arrhythmias, without impairment of subsequent cellular electrical function or initiation of post-shock fibrillatory activity. Since the same AC fields block neural and cardiac activity equally well, the proposed defibrillation methodology could possibly be utilized to achieve high-voltage yet painless defibrillation.

Biophysically detailed computational modelling of the heart in risk stratification for arrhythmias

Robust methods for stratifying the risk of lethal cardiac arrhythmias decrease morbidity and mortality in patients with cardiovascular disease and reduce health care costs.[50] The most widely used approaches currently used for stratifying risk of cardiac arrhythmias involve testing for abnormalities in the ECG, then using the results to identify patients who would benefit from Implantable Cardioverter-Defibrillator (ICD) therapy. Electrocardiogram-based risk stratification methods scan for abnormalities in ventricular depolarization (late potentials[51] and a fractionated QRS complex[52]) and repolarization (T-wave alternans,[53] QT variability or dispersion[54,55]). However, the mechanisms underlying these ECG indices, and their relationship to lethal cardiac arrhythmias, are not fully understood. This lack of knowledge likely explains why results of clinical trials to correlate surface EGG indices to lethal cardiac arrhythmias are often contradictory.[50] Computational models of the heart have made inroads in this clinical cardiology arena.[43,56–62]

Research has reported a strong correlation between increased arrhythmia risk and the presence of T-wave alternans.[63,64] In the

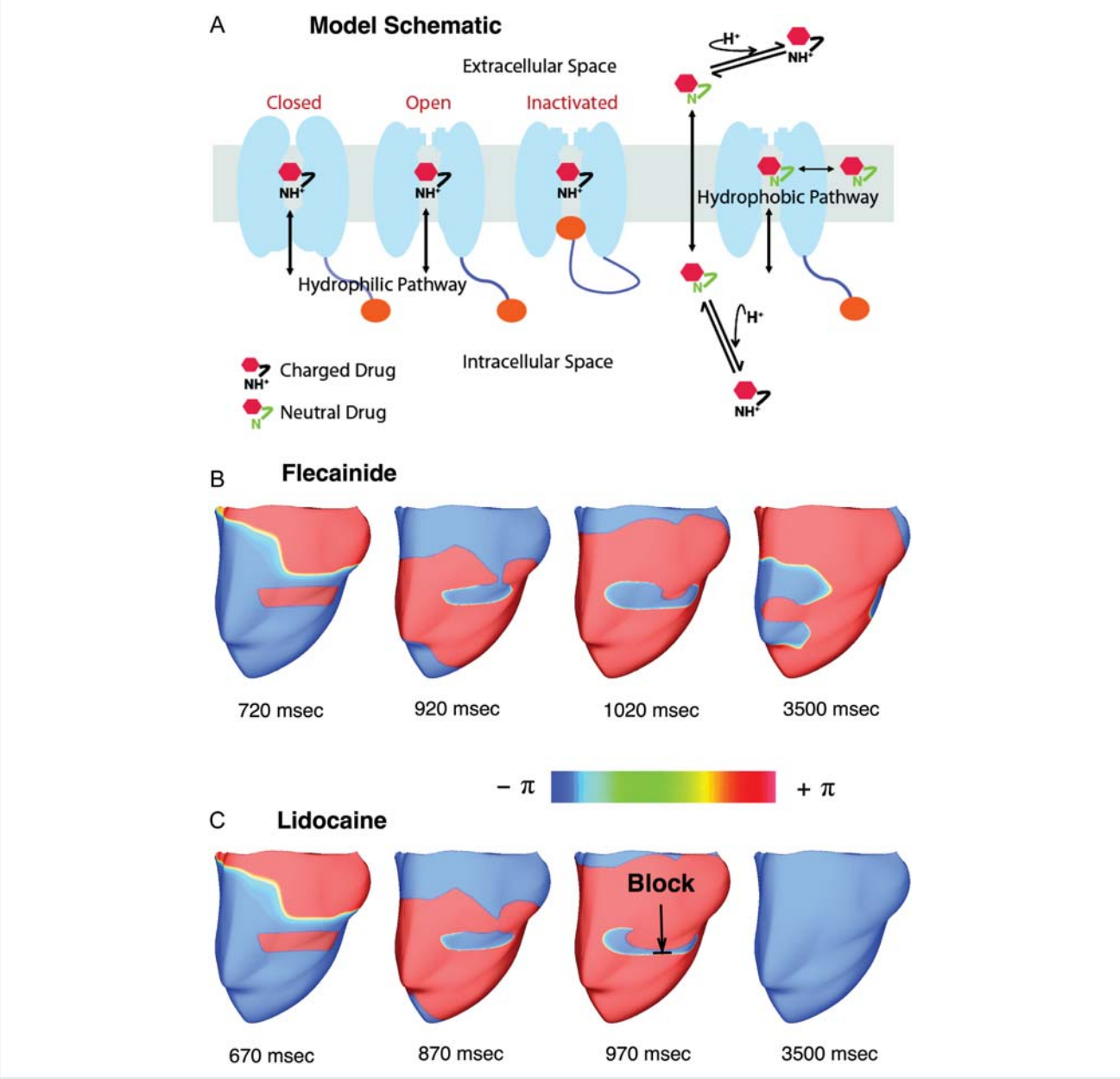

Figure 4 Drug-related arrhythmias. (*A*) Schematic for drug binding to sodium channels. Maps of the phase variable in (*B*) Sustained figure-of-eight reentry with 2 μM flecainide, and (*C*) Non-sustained reentry with 20 μM lidocaine, following premature stimuli (S2). Sustained reentry occurred when applying S2 within the vulnerable window (VW) of the model with 2 μM flecainide (VW = 660−735 ms), but not for the model with 20 μM lidocaine (VW = 630 −685 ms). Modified with permission from ref.[44]

clinical setting, testing for microvolt T-wave alternans (MTWA) has particularly shown promise for dichotomizing patients that would and would not benefit from ICD therapy.[65,66] However, the mechanistic basis of MTWA preceding lethal ventricular arrhythmias has been under debate. Until recently, it was believed that a steep action potential duration (APD) restitution (>1) at rapid heart rates[67] produces alternans in APD that underlie T-wave alternans and the genesis of fibrillation.[68] However, MTWA is most successful in stratifying risk in patients at heart rates <110 b.p.m., where APD restitution is flat.[69] Computational models of the LV wall in combination with clinical data revealed that abnormal handing of intracellular calcium underlies alternans in action potential voltage, which result in MTWA at heart rates <110 b.p.m;[56,57] abnormalities in intracellular calcium have long been linked to ventricular fibrillation.[70,71] Computational modelling studies have also shown that under the conditions of abnormal calcium dynamics, T-wave alternans magnitude is enhanced by structural heterogeneities in the myocardium.[58]

A recent study used an MRI-based computational model of the human ventricles to demonstrate that detecting instabilities in the

QT interval in clinical ECGs can predict VT onset, particularly in patients with acute myocardial infarction.[62] Thanks to the ease with which the frequency and degree of premature activations could be controlled in the model, the study found that increased frequency of premature activation can precede the onset of VT, with premature activations placing the system in a state where the QT interval is unstable. Therefore, screening the QT interval of the ECG for instabilities using the novel algorithm developed by Chen and Trayanova[72] could potentially be a robust risk stratification method for patients with acute myocardial infarction. These studies pave the way for executing computer simulations to determine patient-specific thresholds for arrhythmia stratification ECG indices, rather than relying on clinical guidelines based on large and diverse patient cohorts. Another approach for stratifying the risk of lethal cardiac arrhythmias that has recently gained traction is the use of computer models to predict arrhythmia outcome in patients that exhibit potentially lethal mutations in genes encoding cardiac proteins associated with long-QT syndrome.[43,59–61] These studies chart new directions for future genotype-based risk stratification and personalized gene therapy.

Inverse problem in electrocardiography: computational modelling of the heart as a diagnostic tool

Since the development of the ECG over a century ago, clinicians have sought to gain insight into the spatiotemporal patterns of electrical activation in the heart by interpreting non-invasively recorded signals. Inverse electrocardiography extends this inquiry, combining body surface electrograms and patient-specific anatomical data with state-of-the-art computational techniques. From a mathematical standpoint, the reconstruction of signals in the domain of the heart is ill-posed, in that it can easily be corrupted by low-amplitude electric noise or minute positional errors.

The application of inverse electrocardiography in humans has been led by the Rudy lab, whose electrocardiographic imaging (ECGI) method computes epicardial extracellular potential distributions. ECGI has been performed on Wolff–Parkinson–White (WPW) patients before and after accessory pathway ablation,[73] to characterize the size and extent of scar in post-myocardial infarction patients,[74] to identify responders to CRT therapy,[75] and to non-invasively map infarct-related ventricular arrhythmias.[76] Finally, the technique was used in a wide variety of AF patients to demonstrate that multiple AF mechanisms (isthmus propagation, macroscopic reentry, multiple coexisting wavelets, and wave break) often occur simultaneously in the same patient.[77]

Studies by the teams of He, Oosterom, Berger, and Kalinin[78–82] have advanced non-invasive electrocardiographic imaging beyond mapping of epicardial electrograms to intramural or endocardial electrical activity. The inverse methodology by the He team reconstructs an equivalent current density field throughout the ventricles, from which 3D maps of activation sequence are generated; while it has not been yet utilized in patient studies, the technique was able to accurately pinpoint sources of endocardial ectopy in pigs[83] and to image activation sequences during pacing and VT in both rabbits[84] and dogs.[85] Kalinin's approach[82] to map epicardial and endocardial electrograms has been applied in 200 patients in Russian hospitals.[86] Similarly, the methodology developed by Berger *et al.*[81] has been used to identify pre-excitation sites in WPW patients and to provide detail on simultaneous endocardial and epicardial activation sequences during CRT.[79]

Concluding remarks

Modern cardiac research has increasingly recognized that appropriate models and simulation can help interpret an array of experimental data and dissect important mechanisms and relationships. Advances in computer modelling have made major contributions to the understanding of cardiac function in health and disease. This review focuses on another aspect of computational modelling of the heart: its contribution towards improving the clinical practice of cardiology. The augmented role of cardiac modelling in the development of new therapies for cardiac dysfunction and diagnostic modalities arises from its function as the framework that unifies diverse cardiac electrophysiology and electromechanics insight. Multiscale, multiphysics models that incorporate electromechanical and structural remodelling in cardiac disease are well poised to become a first line of screening for new therapies and approaches, including pharmacological intervention. Furthermore, riding on the heels of diagnostic developments that stem from mathematical modelling and simulation will be new approaches to patient screening and diagnosis. The journey has begun.

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