In silico evaluation of arrhythmia

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Abstract

Iteration between computational and experimental physiology has largely contributed to expanding scientific knowledge in cardiovascular research over the last decades. In this article, we briefly review key progress in cardiac modeling for the understanding of arrhythmia, from subcellular dynamics to whole heart electrophysiology. *In silico* modeling has demonstrated its ability to capture the required physiological complexity, covering stochastic subcellular processes, neural and hormonal regulatory effects, and physiological variability as widely observed *in vitro*, *ex vivo* and *in vivo*. As a result of this unique integration of scales, arrhythmias in both congenital and acquired conditions are currently being investigated *in silico*, caused by channelopathies, ischemia, and drug cardiotoxicity. This witnesses a close future where *in silico* methods, deeply integrated with clinical data, are called to play a central role towards the development of personalized medicine.

Introduction

Since the publication of the first model of cardiac electrophysiology over five decades ago, mathematical modeling has provided increasingly more important insights into cardiac arrhythmia mechanisms. To date, mathematical models for various cell types, different species, including human, have been developed and validated using experimental recordings [1]. The field is currently pushing technological boundaries for bringing these technologies closer to their full translation to the biomedical and clinical settings. This is supported by solid scientific grounds, especially in our present understanding of modeling human physiology at multi-scales as illustrated in Figure 1 [2]. In this review, we recapitulate some of the most recent progress in the field, with an emphasis in the *in silico* evaluation of arrhythmia, and the assessment of potential therapeutic methods.

Calcium cycling and mitochondrial impairment on arrhythmias

Due to the fundamental role of Ca^{2+} signaling in the maintenance of both normal rhythm and the initiation of pro-arrhythmic conditions, refined understanding of subcellular Ca^{2+} homeostasis has become a priority in experimental physiology, deeply complemented by cardiac modeling. To date, modeling studies have provided crucial mechanistic interpretations for Ca^{2+}-mediated pro-arrhythmic events such as cardiac alternans [3], early afterdepolarizations, and delayed afterdepolarizations [4][5]. Recent modeling advances are also contributing to understanding stochastic gating in Ca^{2+} release units (CRUs) of the sarcoplasmic reticulum [6], enabling investigations of spatially distributed CRUs and the role of subcellular Ca^{2+} sparks in arrhythmogenesis [7]. These studies have demonstrated a tight coupling between Ca^{2+} loading, CRU firing stochasticity, cell-to-cell variability, and pacing rate in the

generation of pro-arrhythmic events [3-7]. The simulations have provided complementary evidence to wet lab experiments on the intricate interactions between subcellular Ca^{2+} signaling and sarcolemmal currents.

In silico modeling has also shown how regional mitochondrial impairment [8] may contribute to increased arrhythmic risk. Such research revealed how oxidative stress under ischaemic conditions can lead to non-uniform collapse of mitochondrial inner membrane potential. This then triggers the activation of sarcolemmal ATP-sensitive K^+ channels, leading to action potential (AP) shortening and increased propensity for re-entry due to the metabolic sink.

β-adrenergic stimulation on subcellular signaling

Pro-arrhythmic events and abnormality of calcium cycling are often triggered by external factors such as neural stimulation. As shown by Pueyo *et al*., phasic β-adrenergic stimulation (βAS) can induce oscillations in AP repolarization, which can be further amplified by mechanoelectric feedback [9]. In the recent work by Tomek *et al*., the effect of βAS was modelled in postmyocardial infarction border zone, showing that βAS can inhibit alternans generation, providing evidence on the controversial anti-arrhythmic effects of postmyocardial infarction hyperinnervation [10]. These and additional *in silico* studies have also greatly contributed to the current understanding of βAS.

Growing attention is also being placed into the compartmentation and signaling of downstream ubiquitous secondary messengers, such as cAMP/PKA. Experiments in cardiac myocytes have shown that βAS can produce compartmentalized cAMP responses [11]. Computational simulations of cAMP/PKA compartmentation have qualitatively reproduced such experimental phenomena, revealing that heterogeneity of cAMP signaling can regulate cardiac contractility upon βAS [12]. In addition to the degradation by phosphodiesterases, simulations suggested that additional mechanisms are likely to contribute to cAMP gradients occurring in submicroscopic domains [11].

Pro-arrhythmogenic genetic conditions

Genetic mutations have been associated with many cardiac inherited conditions associated with arrhythmic risk, such as long-QT, short-QT or Brugada syndromes. Over the past decades, mathematical modeling has been increasingly used as a powerful tool to investigate the role of ion channel mutations in arrhythmia [13] (Figure 2). In the study by Hoefen *et al.* [14], 633 multinational subjects with 34 long-QT syndrome type 1 mutations were studied. Associations were found between transmural repolarization prolongation and the risk for cardiac events. The study provides evidence that simulated repolarization can be used to predict clinical outcomes and to improve risk stratification [14]. Efforts have also been put into the simulation of channelopathies under βAS, which can unravel the arrhythmic phenotype of ion channel mutations, resulting in repolarization abnormalities [15].

Recently, there is growing attention into the effect of somatic mosaicism, in which the genetic variation of an individual arises from DNA replication errors in early development. As an example of progress in this area, by incorporating early somatic mosaicism of long-QT syndrome into simulations of Purkinje fibers, Priest *et al.* showed that the heterogeneous expression of mutant channels can lead to 2:1 atrio-ventricular block and arrhythmia [16].

Gender related risk in arrhythmia

In the genome-scale high-throughput human study by Gaborit *et al.* [17], male vs female differences were revealed in the expression of key genes encoding cardiac ion channels and transporters subunits in human epicardial and endocardial tissues. Female hearts exhibit reduced expression of the K^+ channel subunits hERG, minK, Kir2.3, Kv1.4, KChIP2, SUR2, and Kir6.2, and lower expression of connexin43 and phospholamban compared to males. These data explained the longer female cardiac AP, and the fact that females are more prone to develop Torsades de Pointes arrhythmias under inherited and acquired long-QT comparing to males. Yang *et al.* [18] investigated both the role of gender-based differences in ion channel expression and the acute regulatory effects of sex hormones in human ventricular cell and tissue electrophysiology. The simulation results further evidenced mechanisms of female susceptibility to repolarization abnormalities, consistent with clinical phenotypes. In a recent study by the same group, a protein structure-based molecular docking approach was developed to explore the interaction between sex hormones, blocking drugs and hERG channels [19]. Females were predicted to have increased susceptibility to reentrant arrhythmia following acute sympathetic stimulation in the settings of long-QT syndrome.

Understanding human variability in arrhythmic risk

In cardiac electrophysiology, there are significant inter-subject differences in the electrical activity of human hearts, and even within a same region of a heart, there are cell-to-cell differences [20]. Physiological variability is difficult to investigate with experimental platforms alone, where the raw data are normally averaged [20]. Attempts of reproducing the electrophysiological variability have been made in recent years by multiple approaches, such as cell-specific dynamic parameterization [21] combined with parameter sensitivity analysis [22], and populations of models [23] [24]. The common assumption underlying the modeling of cardiac variability is that the expression level of ion channels can be regulated by many environmental factors, so the maximal conductances of ionic currents can vary to produce variable electrophysiological phenotypes [20][22].

Novel insights have been gained by using population-based modeling approaches to include physiological variability as observed experimentally or clinically. For instance, experimentally-calibrated human myocyte models have shown to reproduce the electrophysiological features of different pro-arrhythmic phenotypes in hypertrophic cardiomyopathy [25] and the role of microRNAs and nitric oxide synthases in atrial

fibrillation [26]. Through the combination of human *in vivo* variability and population-based modeling, cellular mechanisms to explain different types of human cardiac alternans have been revealed [3]. Potential therapeutic treatments can also be explored for pathological conditions such as hypertrophic cardiomyopathy [25] or atrial fibrillation [27], to provide not only insights for future drug developments but to identify the molecular mechanisms underlying responders versus non-responders to therapy. This is expected to yield refined strategies towards personalized medical care, especially in high-risk groups of patients with cardiovascular disorders.

In silico assessment of cardiotoxicity

Investigations on the electrophysiological effects of drug action have always been one of the key topics of cardiac modeling. With the announcement of the Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative by the USA Food and Drug Administration, academia, industry, and regulatory bodies are working to replace current testing for drug-induced proarrhythmia with *in vitro* and *in silico* assays [28]. While simple block pore models are widely used in the *in silico* assessment of drug safety [23][29][30], more detailed kinetic models of drug-channel interaction for sodium channels [31][32] and hERG [33][34] have been developed recently.

To achieve a more accurate evaluation of drug safety and translation to human, it is crucial to account for inter-species differences. As shown in the quantitative model comparison by O'Hara *et al.* [29], due to the different contribution of individual channels across species, the extrapolation from animal to human electrophysiology and drug response requires caution. In addition to the species, the aforementioned inter-subject variability within the wide population should also be considered in *in silico* drug safety assessments. Using a population of human ventricular models approach, Passini *et al.* showed that *in silico* models exhibited consistent and more accurate clinical risk prediction compared to animal experiments and human induced pluripotent stem cell-derived cardiomyocytes (Figure 3) [35]. An innovative study by Lancaster *et al*. also showed that applying machine-learning techniques on the metrics of baseline models can also predict accurate drug risk as in a small synthetic population of models [36].

From arrhythmia mechanisms to personalized treatment

Since the birth of mathematical models of cardiac electrophysiology, reproducing the arrhythmic conditions observed at tissue level has always been a focus of the field. Many pathological phenomena such as conduction block and re-entry cannot be investigated without tissue coupling effects. Recently, tissue level simulations have been conducted to predict phenotypes of short-QT syndrome [13], Brugada syndrome [37], atrial fibrillation [27] [38] [39], acute ischaemia [40][41] (Figure 4A), myocardial infarction [42], and electromechanical dynamics [43], to cite some. Potential effects of channel blockers and the effect of variability were also explored in some of these studies [37][38][40]. In addition, novel quantitative metrics have been proposed and validated through tissue modeling, to aid the identification of

scar-related reentrant pathways in clinic [44]. Meanwhile, new approaches are being developed to improve the mathematical description of tissue structural heterogeneity [45] and to establish the link between whole-organ physiology and body surface ECGs using detailed heart-torso human anatomical models [46][47][48] (Figure 4B).

With the development of medical image processing techniques, personalized modeling based on magnetic resonance imaging (MRI) can be developed to include into consideration more detailed and specific variability of individuals, such as fiber orientation, conduction anisotropy, and spatial heterogeneities [38]. For example, in the study by Arevalo *et al*. [42], personalized MRI models were developed including patient-specific ventricular anatomy and the location of post-infarction scar and gray zones. After *in silico* reconstruction, arrhythmia inducibility in the virtual models was shown as more predictive of sudden death risk than standard clinical metrics. The results highlight the potential of cardiac modeling to assist in the clinical prevention of sudden cardiac death [42]. Similar approaches are being evaluated in other cardiac diseases, such as atrial fibrillation with the existence of atrial fibrosis [39], and to test the effects of *in silico* ablation [49]. Another new noninvasive approach to assist clinical diagnosis and treatment of arrhythmia is electrocardiographic imaging. After combining body surface potentials and computer tomography or MRI scans, epicardial activation and repolarization maps can be reconstructed to help identifying the arrhythmic substrate of human hearts [50][51]. Recent studies have shown that electrocardiographic imaging can identify electrical and structural substrates of arrhythmia in human hearts. These include slow discontinuous conduction and steep dispersion of repolarization in Brugada syndrome [50], as well as prolonged repolarization, non-uniform conduction and sites of premature ventricular contractions in arrhythmogenic right ventricular cardiomyopathy patients [52]. Integration of these data and computer models is expected to increase the potential of both technologies for personalized diagnosis [51].

Future prospects and conclusions

After more than half a century of history, the iteration between computational and experimental physiology has built new scientific knowledge with concomitant benefits for human health, with some recent examples shown in Table I. Mathematical modeling is now widely present at all levels of cardiac physiological research: from subcellular to whole heart levels, and from basic mechanistic research to clinical risk stratification. Together with a continuous refinement in the description of cardiac function and structure, the field is now ready to further realize its impact, including:

1) *In silico* screening of drug cardiotoxicity beyond acute ion channel inhibition, and in particular contractility and long-term drug exposure as urgent needs.

2) Integration of molecular dynamics into cellular models, enabling direct mechanistic insights of genetic defects from channel to cellular function, and structural-molecular interactions of drug action.

3) Extended representation of signaling pathways and ion channel trafficking, and their modulation by disease, drug action and environmental factors.

4) Integration of the transcriptome, proteome and metabolome, as additional sources of biological data.
5) Tighter integration of medical data into the construction and validation of *in silico* approaches, aiming at their realization into clinical support systems.

In summary, modeling approaches can provide unique contributions to the understanding of cardiac function, promoting the development of *in silico* medicine in the era of big data.

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This work evidenced, using electrocardiographic imaging, that patients with arrhythmogenic right ventricular cardiomyopathy can have premature ventricular contractions in both of their ventricles, suggesting potential applications for the techniques in noninvasive diagnosis and follow-up of patients.

Figure captions

Figure 1: Experimental data from multiple scales are integrated in computational models of human cardiac electrophysiology. Reproduced from [2].

Figure 2: Effect of a KCNQ1 mutation leading to short-QT on the pseudo-ECG (A) action potentials and IKs profiles of epicardial (B), mid-myocardial (C), and endocardial (D) cells. Color-code represents wild type (WT; blue), and WT-V307L (green) and V307L (red) conditions. Reproduced from [13].

Figure 3: Simulated effect of Moxifloxacin (A), Dofetilide (B), and Flecainide (C) on a population of human ventricular cardiomyocytes leading to depolarization (green) and repolarization abnormalities (pink), from Passini *et al* [35].

Figure 4: Linking human whole ventricle electrophysiology to body surface ECGs. A: Simulation of a reentrant arrhythmia in the human ventricles around the acute ischemic zone with similar pattern in control (top) and for 30% (middle) and 50% (bottom) IKr reduction following premature excitation, from Dutta *et al* [40]. The limits of the border zone are marked with green lines and the direction of propagation with white arrows. B: Hemiblock of the left ventricular (LV) human posterior wall conduction system, resulted in delayed LV basal paraseptal activation, affecting the time course and position of the negative pole in the front of the torso, with the associated clinical manifestations of left posterior fascicular block (LPFB), from Cardone-Noott *et al* [46].

Table I: Combining experimental and clinical knowledge generates new insights with benefits for human health

Experimental or clinical observations	**In silico modeling approach**	**New insights from the combined approach**	**Ref**
Two types of repolarization alternans with distinct rate-dependence identified in patients.	Population of human ventricular cell models calibrated based on the *in vivo* human variability.	Differences in L-type Ca^{2+} current density are responsible for the different types of alternans. Na^{+}/Ca^{2+} exchanger blockers identified as therapeutic target.	3
Low frequency oscillations in ventricular repolarization identified in heart failure patients.	Human ventricular model of electrophysiology, β-adrenergic signaling and electromechanical feedback.	β-adrenergic signaling and phasic mechanical loading can induce low-frequency oscillations of repolarization. Heart failure increases these oscillations, leading to arrhythmogenic events.	9
Female sex is a risk factor for acquired long-QT and arousal arrhythmias. Sex hormones regulate cardiac ion channel activity.	Human ventricular model for male and female, combining acute sex hormone effects, ion channel mutation, and molecular docking.	Acute sympathetic nervous activity discharge, and structural-molecular interactions of oestrogens with hERG mutations and blockers, increase torsadogenic effects in females.	19
Hypertrophic cardiomyopathy ionic remodeling includes both increased inward and reduced outward currents.	Population of human ventricular cell models calibrated with experimental data.	Ionic mechanisms underlying different phenotypes of repolarization abnormalities in the disease. Multichannel block strategies to increase efficacy without compromising contractility.	25
Multiple drugs were tested in HEK293 cell line, stably expressing the human hERG1a subunit.	Dynamic hERG-binding model.	hERG channel-drug binding kinetics incorporated into *in silico* assessment of proarrhythmia risk, relevant for both clinical management and drug development.	34
Post-infarction patients are at high risk of lethal arrhythmias due to myocardial heterogeneity.	3D patient-specific ventricular model based on contrast-enhanced clinical MRI.	Inducibility of arrhythmias in the personalized models shown as more predictive of sudden death risk than standard clinical metrics.	42

Exit sites in scar-related reentry are important targets for catheter ablation, but their accurate location is difficult.	2D, 3D and anatomically-detailed rabbit whole ventricular model.	A new algorithm is developed to identify sites susceptible to reentry in order to facilitate clinical catheter ablation.	44
Diagnosis and risk stratification challenging in arrhythmogenic right ventricular cardiomyopathy.	Non-invasive electrocardiographic imaging to reconstruct patient-specific epicardial potentials.	Ventricular ectopy can be detected non-invasively, which can contribute to the early diagnosis and follow-up of patients.	52