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Review article

Lessons learned from multi-scale modeling of the failing heart

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ABSTRACT

Heart failure constitutes a major public health problem worldwide. Affected patients experience a number of changes in the electrical function of the heart that predispose to potentially lethal cardiac arrhythmias. Due to the multitude of electrophysiological changes that may occur during heart failure, the scientific literature is complex and sometimes ambiguous, perhaps because these findings are highly dependent on the etiology, the stage of heart failure, and the experimental model used to study these changes. Nevertheless, a number of common features of failing hearts have been documented. Prolongation of the action potential (AP) involving ion channel remodeling and alterations in calcium handling have been established as the hallmark characteristics of myocytes isolated from failing hearts. Intercellular uncoupling and fibrosis are identified as major arrhythmogenic factors.

Multi-scale computational simulations are a powerful tool that complements experimental and clinical research. The development of biophysically detailed computer models of single myocytes and cardiac tissues has contributed greatly to our understanding of processes underlying excitation and repolarization in the heart. The electrical, structural, and metabolic remodeling that arises in cardiac tissues during heart failure has been addressed from different computational perspectives to further understand the arrhythmogenic substrate.

This review summarizes the contributions from computational modeling and simulation to predict the underlying mechanisms of heart failure phenotypes and their implications for arrhythmogenesis, ranging from the cellular level to whole-heart simulations. The main aspects of heart failure are presented in several related sections. An overview of the main electrophysiological and structural changes that have been observed experimentally in failing hearts is followed by the description and discussion of the simulation work in this field at the cellular level, and then in 2D and 3D cardiac structures. The implications for arrhythmogenesis in heart failure are also discussed including therapeutic measures, such as drug effects and cardiac resynchronization therapy. Finally, the future challenges in heart failure modeling and simulation will be discussed.

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1. Introduction. Experimental heart failure

The definition of heart failure (HF) is still changing and evolving. Indeed, definitions of heart failure depend on the contexts in which this term is used, but it is generally considered a syndrome in which the pumping action of the heart fails to provide sufficient amount of blood and oxygen to the organs, including the heart itself [1]. HF is the final common pathway of various cardiac pathologies such as myocardial infarction, hypertrophy, congenital cardiac abnormalities, valve disease, hypertension, dilated cardiomyopathy, and tachycardia-dependent cardiomyopathy. The primary electrophysiological changes and the mechanisms of arrhythmogenesis associated with HF depend on the etiology [2]. However, there are some common features, which are described in this section.

At the cellular level, there is a prolongation of the action potential, resulting from the remodeling of some ion currents, such as the late sodium current (I_{NaL}) [4,5] which is significantly enhanced. Also, reductions of the inward rectifier K^+ current (I_{K1}), the transient outward K^+ current (I_{to}), and the Na^+/K^+ pump (I_{NaK}) [3] have been experimentally measured. The increased I_{NaL} and elevated cytosolic Na^+ ($[Na^+]_i$) in HF is linked to the cellular Ca^{2+} overload via the Na^+–Ca^{2+} exchanger (NCX) [6]. NCX activity is critically regulated by $[Na^+]_i$, and even a modest increase in $[Na^+]_i$ causes a decrease in the exchanger to extrude less Ca^{2+}, raising the cellular Ca^{2+} content [7,6]. Also upregulation of the NCX in HF may magnify the functional impact of altered $[Na^+]_i$, and thus Ca^{2+} overload. Alterations in calcium handling, i.e. an increase of diastolic $[Ca^{2+}]_i$, a decrease of systolic $[Ca^{2+}]_i$ peak, and a slow $[Ca^{2+}]_i$ decay, as well as intracellular sodium accumulation, have been established as the hallmark characteristics of myocytes and tissues isolated from failing hearts, especially in terminal HF [8–10]. Detubulation and changes in the beta adrenergic system have also been observed in failing hearts and have been related to the above mentioned alterations of Ca^{2+} transients [11,12].

Animal studies [13,14] have shown that the gap junctional protein connexin43 (Cx43) is redistributed from the intercalated disk to the lateral ventricular myocyte borders and that the amount of hypophosphorylated Cx43 is increased, leading to intercellular uncoupling and reduced conduction velocity in HF [15,16]. In addition, remodeling of the extracellular matrix including the presence of cardiac myofibroblasts [17–20] and their interactions with cardiomyocytes, alters electrical conduction, which is determinant in HF arrhythmogenesis.

During HF, electrophysiological remodeling and Ca^{2+}-handling alterations can lead to focal activity initiated by either early afterdepolarizations (EADs) or delayed afterdepolarizations (DADs), that may lead to a triggered premature beat [2]. If the altered myocardial structure represents a suitable substrate, characterized by repolarization heterogeneities, fibrosis and/or uncoupling, reentry may ensue. Reentrant rhythms have been observed in failing hearts and an improved understanding of the responsible mechanisms is much needed.

The complexity and variability of the experimental and clinical studies performed to characterize the HF pathology justify the need of further assistance to fully understand HF etiology and the underlying arrhythmogenic mechanisms. Computer models emerge as a complementary and very effective tool to fill this gap. Indeed, personalized multi-scale models are able to establish the link between the cellular or even genetic or molecular changes during disease and the consequent arrhythmogenic mechanisms. Simulation studies allow also component dissection, which is hardly feasible in experiments or in clinical environments, and enrich our understanding of these complex mechanisms.

2. Computational modeling of heart failure at the cellular level

2.1. Electrophysiological remodeling and altered Ca^{2+} handling

Multiple electrophysiological changes have been experimentally observed in isolated failing cardiac cells. Computational models have helped to analyze the cellular electrophysiological consequences of these changes. The first simulation study that focused on heart failure induced electrical alterations (at the cellular level) was carried out by Priebe and Beuckelmann in 1998 [21]. In this work, the AP of a human ventricular myocyte was modeled and modified to simulate HF. Selected ion currents (see Table 1), based on experimental data, were remodeled leading to HF phenotype, characterized by a longer action potential duration (APD) and a corresponding altered Ca^{2+} transient. Priebe and Beuckelmann [21] also showed that EADs could develop in HF conditions following the block of the rapid delayed K^+ current (I_{Kr}). They used the model results to propose how spontaneous calcium release triggered a premature AP in HF; the reduction of repolarization currents (I_{K1} and I_{NaK}) rather than an increase of the depolarizing current (I_{NaCa}) seemed to be responsible for the enhanced likelihood of triggered APs in failing myocytes. Because the effects of altered Ca^{2+} transients in HF are widely suggested to be critical for proarrhythmic phenomenon, a number of models have since been developed that describe in detail the behavior of intracellular calcium pathways.

Since the first study, a number of computational works have focused on describing HF phenotype on the basis of new emerging experimental data. Table 1 summarizes the HF computational models that have been developed to date. As shown in Fig. 1, several computational models reproduce not only APD prolongation, but also elevated diastolic $[Ca^{2+}]_i$ levels, the reduction of peak systolic $[Ca^{2+}]_i$ and the slow decay of Ca^{2+} transient observed experimentally in failing cells [22,23]. Specifically, Winslow et al. [24] defined the minimum model of 'end-stage heart failure' focusing on the protein levels of SR Ca^{+2} ATPase and NCX in canine cardiac ventricular failing myocytes. The model estimated a range for NCX upregulation and SERCA pump downregulation responsible for altered Ca^{2+} transients.

Using a similar approach, Puglisi et al. [25] developed a computational model to analyze the electrophysiological and Ca^{2+} transport properties of failing rabbit ventricular myocytes. They showed that combining enhanced Na^+/Ca^{2+} exchange with reduced I_{K1} (as occurs in HF) lowers the $[Ca^{2+}]_i$ threshold to trigger an AP.

A more detailed description of Ca^{2+} dynamics was developed by Shannon et al. [26], who predicted that increased Ca^{2+} affinity of the ryanodine receptors (RyR) increased the probability of delayed afterdepolarizations (DADs) when heart failure was simulated. Calcium calmodulin kinase II (CaMKII) pathway, another important factor for Ca^{2+} dynamics especially in HF, was recently introduced in AP models [27–29]. CaMKII is upregulated in HF and strongly affects Ca^{2+} handling. CaMKII shifts sodium current availability to more negative voltages, enhances intermediate inactivation, and slows recovery from inactivation, but also enhances the activity of the I_{NaL}. CaMKII also increases Ca^{2+} and K^+ currents (ICa and I_{to}). CaMKII-induced alterations of sodium current (I_{Na}), Ca^{2+} current (ICa), and transient outward K^+ current (I_{to}) were modeled by Grandi et al. [29] to analyze the complexity of CaMKII-dependent AP changes. Simulation results showed a

Table 1
Electrophysiological characteristics in computational models of heart failure. The percentage of increase (↑) or decrease (↓) of ion currents are indicated with respect to the original and physiological normal corresponding action potential model. In the case of Walmsley et al. study downregulation of a parameter is sampled in the range −60% to 0% change from the original parameter values (ORd model) and upregulation is sampled from 0 to +60% change from the original parameter values. The modified parameters are: the fast sodium current (I_{Na}), the late Na^+ current (I_{NaL}), the time constant of inactivation gate of the I_{NaL} ($τ_{hL}$), the L-type calcium channel current (I_{CaL}), the transient outward K^+ current (I_{to}), the rapid delayed rectifier potassium current (I_{Kr}), the slow delayed rectifier potassium current (I_{Ks}), the Na^+/Ca^{2+} exchanger (I_{NCX}), the inward rectifier K^+ current (I_{K1}), the Na^+/K^+ pump current (I_{NaK}), the sarcoplasmic reticulum (SR) Ca^{2+} pump (I_{up}/J_{SERCA}), the SR Ca^{2+} leak current (I_{Leak}), the background Na^+ current (I_{Nab}), and the background Ca^{2+} current (I_{Cab}).

HF simulation models	Species	I_{Na}	I_{NaL}	$τ_{(NaL)}$	I_{CaL}	I_{to}	I_{Kr}	I_{Ks}	I_{NCX}	I_{K1}	I_{NaK}	I_{up}/J_{serca}	I_{Leak}	I_{Nab}	I_{Cab}
Winslow et al. [24]	Dog								↑104%			↓28%			
Winslow et al. [38]	Dog					↓66%			↑75%	↓33%		↓68%			
Puglisi et al. [25]	Rabbit					↓36%			↑100%	↓49%		↓24%			
Shannon et al. [26]	Rabbit								↑100%			↓50%			
Morita et al. [39]	Rabbit				↑200%				↑200%			↓20%			
Priebe and Beuckelmann [21]	Human								↑65%	↓25%	↓42%	↓66%	↓65%		
Zhang et al. [34]	Human	↓57%	↑1200%		↑200%	↓36%		↓?	↑65%	↓25%	↓42%	↓?			
Narayan et al. [40]	Human		↓25–200%									↓25–200%			
Zlochiver [32]	Human		↓34%			↓36%		↓50%	↑36%	↓43%					
Moreno et al. [41]	Human				↑250%	↓36%			↑65%	↓25%		↓36%	↓31%		
Lu et al. [30]	Human	↓40%			↓64%			↓50%	↑65%	↓20%	↓42%	↓45%	=		↑53%
Trenor et al. [35]	Human		↑200%	↑200%	↓40%				↑75%	↓32%	↓10%	↓50%	↑500%	=0	↑53%
Moreno et al. [31]	Human		↑1000%			↓36%				↓25%	↓10–42%	↓36%	↑350%	↑1600%	
Walsmsley et al. [37]	Human				↓ (0–60%)	↓ (0–60%)	↓ (0–60%)	=	↑ (0–60%)	=		↓ (0–60%)			

prolongation of APD for CaMKII-induced ICa increase and APD shortening for CaMKII-induced I_{to} increase. Combining the effects of CaMKII-induced changes on different currents (I_{Na}, ICa and I_{to}) led to APD shortening. Furthermore, transmural heterogeneity in I_{to}, its downregulation in HF, and CaMKII-induced changes in this current may accentuate dispersion of repolarization. These simulation studies suggest potential pathways by which CaMKII may contribute to arrhythmogenesis.

Also, the development of an advanced coupled model integrating the spatiotemporal Ca^{2+} reaction–diffusion system into the cellular electrophysiological model by Lu et al. [30] revealed that the presence of rogue RyRs (non-clustered RyRs) destabilized Ca^{2+} dynamics, leading to the spontaneous initiation of Ca^{2+} waves. These pathological waves led to the generation of DADs or triggered action potentials in HF.

A further step in the simulation of HF was taken by Moreno et al. [31] by including the β-adrenergic signaling pathway in a computational work. The β-adrenergic pathway in the model includes CaMKII and PKA signaling, important regulatory pathways shown to be upregulated in human heart failure. They showed that overactive β-adrenergic activation resulted in increased I_{NaL} and elevated intracellular Na^+ that cause an increase in $[Ca]_i$ via NCX and ultimately electrical instabilities e.g. DADs, and beat-to-beat variability in APD.

Computer models of HF have also helped to understand how HF alters cellular excitability. Zlochiver et al. [32] employed the ten Tusscher et al. [33] model to demonstrate that higher stimulation current magnitudes were needed for excitation of the failing tissue, as well as larger stimulation areas. This reduction of excitability was attributed to I_{K1} remodeling in HF. This study also showed the non-linear effect of fibrosis on tissue excitability, highlighting the complexity of subthreshold excitation properties in the diseased myocardium, which strongly affects ectopic foci-originated arrhythmias and determines the efficient design of stimulating electrodes.

The experimentally reported ranges for electrophysiological (EP) changes at the cellular level, as well as the extent of changes in ion channels, transporters and overall remodeling, vary substantially for different experimental settings and HF stages. Therefore, taking into account the available literature, a sensitivity analysis aimed at assessing the impact of the main ionic parameters remodeled in HF was performed by Trenor et al. [35]. The ranges of remodeling considered in this study for the different ionic parameters in HF led to changes in AP and Ca^{2+}-handling biomarkers within experimental observations. Simulation results revealed the important role of I_{NaL} in the prolongation of

APD, in the triangulation of the shape of the AP, and in the changes of Ca^{2+} transient in failing conditions.

Although considerable research has been devoted to the effect of altered channel function in the failing heart, less attention has been paid to mRNA expression channel levels [36]. Functional ion channel activity is not always directly related with protein expression levels in the cell membrane, but it may be related. In this respect, the work of Walmsley et al. [37] focused on the role that mRNA expression levels may play in the electrophysiological changes in human HF. This work takes into account this variability by defining a population of models for HF using mRNA data obtained from failing and nonfailing human hearts. Simulations revealed that changes in AP biomarkers were driven mainly by I_{Kr}, while changes on calcium transient biomarkers were due to I_{CaL} and SERCA pump. Caution should be taken in the interpretation of these results, as the downregulation of I_{CaL} is controversial in the human failing heart.

2.2. Increased late sodium current (I_{NaL}) in heart failure

Experimental approaches and computational modeling are complementary methods for assessing how abnormalities in sodium behavior at the cellular level can lead to arrhythmias in the whole heart [42]. I_{NaL} has been recognized as one of the major factors contributing to abnormal repolarization in HF [43–46].

The enhancement of I_{NaL} in failing human hearts as compared to normal hearts has been measured by several experimental groups [4,5]. However, I_{NaL} was rarely included in the basic formulation of AP models developed for control conditions. In the last decade, substantial improvements in AP models have been made and this current has been modeled using both Markov models and Hodgkin Huxley formulations. I_{NaL} has been added to existing AP models for different animal species [29,31,35,47–50]. Hund et al. [50] included a formulation for the I_{NaL} in a canine cardiac ventricular AP model. Trenor et al. [35] adapted this formulation with the available experimental human data to reproduce the failing phenotype and included it in the Grandi et al., human AP model [51]. The most recent AP human model includes this formulation for control conditions [52].

The consideration of I_{NaL} in computational models of heart failure is crucial in simulating the activity of failing ventricular cells because of its important role in repolarization abnormalities, such as EAD generation [31,32,34,35,41,53]. Model predictions have suggested I_{NaL} as a novel

Winslow et al. 1999
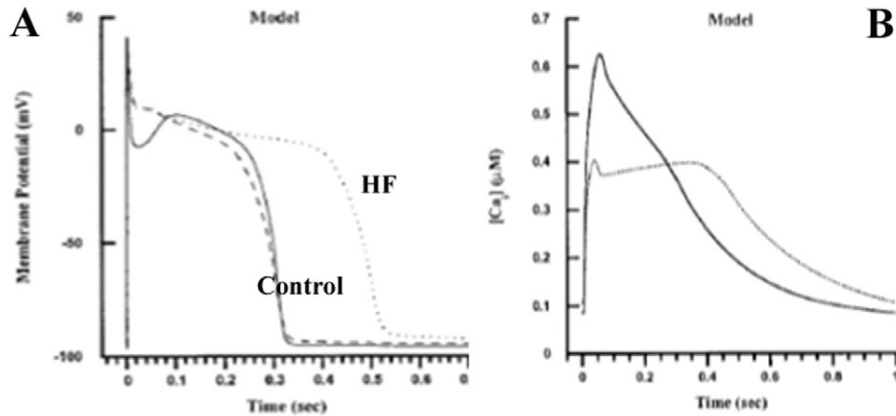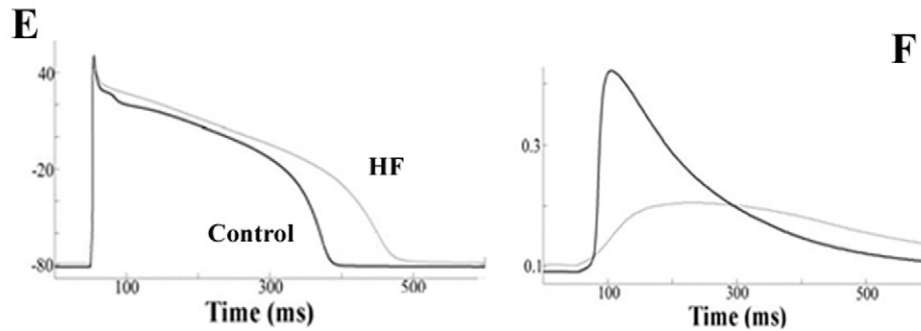

Zhang et al. 2005
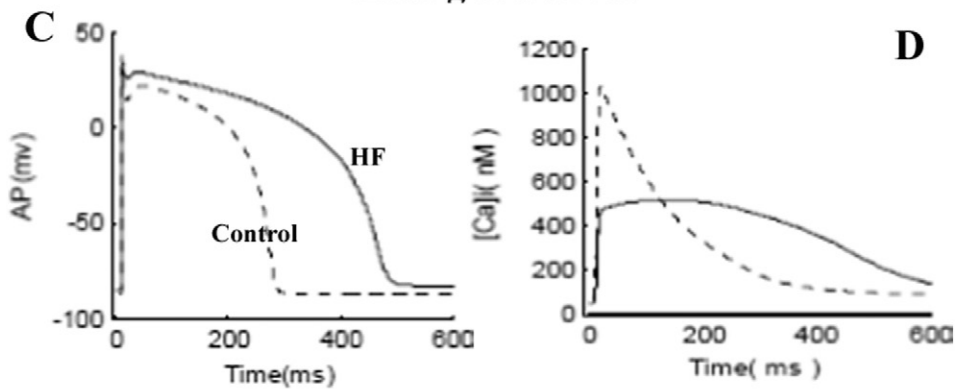
Trenor et al. 2012

Fig. 1. Electrophysiological changes in heart failure. Simulated action potentials (APs) (left panels) and Ca^{2+} transients (right panels) obtained in normal conditions and after heart failure electrophysiological remodeling. Panels A and B, C and D, and E and F illustrate the simulations carried out by Winslow et al. [24], Zhang et al. [34], and Trenor et al. [35], respectively. Reproduced with permission from [24].

therapeutical target in preventing arrhythmogenic situations in HF, such as DADs generation [54]. Indeed, computational studies have contributed to the understanding of the close relationship between Ca^{2+} dynamics and Na^+ fluxes, showing that increased intracellular Na^+ and increased I_{NaL} in the failing myocardium contribute to the alteration of Ca^{2+} load [42]. Although I_{NaL} increase contributes to the $[Na^+]_i$ accumulation reported in HF, computational studies have challenged the notion that I_{NaL} is the unique responsible. Indeed, I_{NaL} enhancement caused by CaMKII activation is not quantitatively sufficient to account for the $[Na^+]_i$ elevation observed in HF [54–56] (see Grandi and Herren 2014 for review [57]). Furthermore, the existence of a diastolic leak Na^+ influx in human failing myocytes has been suggested to significantly contribute to $[Na^+]_i$ elevation [54], as well as an increased activity of I_{NCX} and Na^+/H^+ exchanger promoted by acidosis [58,59].

2.3. Changes in T-tubules and cellular size in HF

It is now well-known that loss and/or disruption of T-tubules may occur in failing ventricular myocytes [12,60,61], contributing to dyssynchronous calcium release and impaired contraction. T-tubule disruption removes the L-type Ca^{2+} channels (LCC) from the associated Ca^{2+} release units and results in "orphaned" RyR clusters. In addition, loss of T-tubules leads to a redistribution of β2-adrenergic receptors (β2ARs) from T-tubules to detubulated membrane areas, especially affecting Ca^{2+} transients [62]. Indeed, it is well-known that the β1- and β2-adrenergic receptors (βARs) regulate the production of the second messenger cyclic adenosine monophosphate (cAMP). β2ARs are spatially confined in the T-tubules, and its stimulation is cardioprotective, whereas β1ARs are distributed across the entire cell surface and its

chronic stimulation promotes hypertrophy and apoptosis [62,63]. The redistribution of β2ARs from the T-tubules to the cell crest in HF is responsible for the loss of the normally cardioprotective properties of β2AR signaling, which may acquire the characteristics of the β1AR response [62]. The propagating β2AR-cAMP gradients observed in failing cardiomyocytes induces phospholamban and troponin I phosphorylation [62,64], which is associated with arrhythmogenic effects, by increasing the serca pump activity and Ca^{2+} SR load [64]. Thus, the redistribution of β2ARs in HF changes compartmentation of cAMP and might contribute to the failing myocardial phenotype.

It is also important to highlight the T-tubule localization of the inward rectifier K^+ channels [65]. Indeed, detubulation has been shown to decrease I_{K1} activity [66], which could have important consequences for membrane resting potential. The mechanisms by which detubulation disrupts the electrical activity in the failing heart are poorly understood and is an area in which computer simulations can definitely help.

In ventricular cardiomyocytes, calcium release occurs at distinct structures (dyads) along T-tubules. Only a few simulation studies have thus far modeled detubulation in the failing heart. Gaur et al. [67] developed a model of Ca^{2+} cycling which takes into account local dyadic Ca^{2+} release activities and interactions between dyads via Ca^{2+} diffusion. Under failing conditions, simulated as increased dyadic volume and reduced LCC/RyR relation, SR Ca^{2+} release becomes dyssynchronous and interdyad coupling serves as a compensatory mechanism that improves synchrony. These simulations provided insight into Ca^{2+} waves generation via calsequestrin interaction; the impaired function of this calcium sensor lead to diastolic Ca^{2+} accumulation and subsequent Ca^{2+} release events. Also in the combined experimental and simulation work of Louch et al. [68] the dyssynchronous Ca^{+2} release is attributed to T-tubule reorganization.

Alternans were also simulated in a computational HF cellular model promoted by detubulation [69]. Similarly, Wright et al. [70] simulated detubulation and highlighted the role of altered β2AR and cAMP signaling in failing cardiomyocytes. Including detubulation in cellular models of HF may be important in order to fully represent Ca^{2+} transient alterations.

Another important change observed in failing hearts is an increase of the cell size. The loss of contractile function is compensated by cardiac hypertrophy [2]. Patients with HF have an increased QRS duration, which cannot be attributed to decreased conduction velocity only, but also to an increase of myocyte size. Wiegerinck and coworkers carried out a set of simulations focused on the effect of hypertrophied myocytes [71] and found that although conduction velocity was increased, the larger cell size led to QRS prolongation. These simulations predicted a novel mechanism of conduction slowing in HF and also suggested the importance of considering cell size in HF models.

2.4. β-Adrenergic stimulation in HF

The β-adrenergic signaling pathway regulates cardiac myocyte contractility, which is impaired in the failing heart. Increased sympathetic activity is a hallmark of HF and β-blockers appear to reduce mortality in these patients [72], although the mechanisms responsible are not completely understood. Detailed electrophysiological models have become helpful in understanding complex β-adrenergic cell signaling pathway and its effects during HF.

β-adrenergic signaling and stimulation are included in several models of electrical activity of the cardiac cell (see table in pages 9 through 11 in the Supporting Material of Heijman et al. [73]). The modeling approaches include either parameter-shifts, i.e. selected conductances of ion channels or the voltage dependence of several ion channel gates are modified by β-adrenergic stimulation, or population-based, i.e. a portion of selected ion channel population is altered by β-adrenergic stimulation. Saucerman et al. [74] developed a detailed parameter-shift model of the β-adrenergic signaling pathway for rat ventricular myocytes considering that altered β-adrenergic signaling may also play an important role in

the progression of HF. Their simulation results suggested that phosphorylation of the L-type calcium channel and phospholamban are sufficient to predict the dominant changes in myocyte contractility. They improved this model by adding interactions of the protein Kinase A (PKA) with other ion channels, such as I_{Ks} to investigate how a gene mutation related with a long-QT syndrome may lead to ventricular arrhythmia during sympathetic stimulation [75].

The inclusion of CaMKII pathway combined with β-adrenergic activation of PKA to study excitation-contraction coupling under normal and failing conditions (CaMKII overexpression) was later studied by Soltis and Saucerman [76]. The model demonstrates how overall changes to calcium handling during CaMKII overexpression are explained by interactions between individual CaMKII substrates and identifies CaMKII-dependent ryanodine receptor hyperphosphorylation as a proarrhythmogenic trigger. Soltis and Saucerman framework was then adopted by several authors in a mouse AP model [56] and in rabbit AP models [77,78]. Morotti et al. showed that β-adrenergic stimulation enhanced CaMKII activation, potentiating the CaMKII–Na^+–Ca^{2+}–CaMKII feedback in CaMKII overexpressed mice myocytes, and thus increased the probability of DAD generation. Xie et al. [77,78] slightly modified Soltis and Saucerman formulation by establishing different dynamics of I_{CaL} and I_{Ks} increase induced by β-adrenergic stimulation. The faster increase of I_{CaL} vs I_{Ks} upon abrupt β-adrenergic stimulation could explain the generation of transient EADs [77] and the transient increase of APD restitution slope, which allows the degeneration of VT into VF [78].

Recently, the population-based model developed by Heijman et al. [73] incorporated the effect of CaMKII and β-adrenergic signaling systems in a multi-compartmental description of protein signaling networks for canine ventricular myocytes. The model predicted increased CaMKII activity during β-adrenergic stimulation due to rate-dependent accumulation and increased calcium cycling. The inhibition of CaMKII reduced compartmentation while selective blockade of β1-adrenergic receptors reduced the occurrence of DADs. O'Hara et al. [28] used this model and adapted it for human ventricular AP to analyze the effect of β-adrenergic stimulation in LQT syndrome. They concluded that with mutant I_{Ks}, β-adrenergic stimulation and I_{Ks} partial block favored EAD generation. Also Wright et al. [70] used Heijman et al., [73] model to simulate detubulation in HF and thus relocation of β2-adrenergic receptors, which alters the protective effect of β2-adrenergic stimulation. An important finding of their study is that caveolin-3 (Cav3) overexpression can partially restore the disrupted localization of these receptors. It is important to distinguish between β1AR and β2AR activity in simulating HF, because they could have different effects on arrhythmogenesis, as shown by clinical trials and a number of studies [79–81]. In this way, the model developed by Bondarenko for mouse myocytes [82] focused on the effects of β1-adrenergic receptor (β1AR) stimulation and represents an initial framework for future developments of cellular models for heart failure. The model elucidates the complex interactions of ionic currents which ultimately lead to a relative modest increase in APD and significant increase in calcium transients when β1AR are stimulated.

While much attention has been paid to β-adrenergic stimulation in HF progression and to the therapeutic benefits of β-blockers, less interest has been dedicated to the role of α-ARs in the failing heart. Controversial results about the positive inotropic effects of α-ARs stimulation in humans and detrimental outcome in clinical trials using α-ARs blockers have deviated the research interest, however, further research is needed in this respect. To our knowledge, no AP models integrate a mathematical formulation for the effects of α-ARs stimulation.

3. Structural remodeling in virtual failing cardiac tissues

In addition to electrophysiological remodeling, micro- and macro-anatomical changes, such as intercellular uncoupling and fibrosis, have been identified as major arrhythmogenic factors in HF etiology and

progression. This section describes the main findings derived from computational studies focused on structural remodeling during HF.

3.1. Consequences of fibrosis derived from computational studies

Fibroblasts are cells of mesenchymal origin that produce interstitial collagen and are responsible for the synthesis and maintenance of the extra-cellular matrix (ECM), which surrounds and supports cardiomyocytes. The amount of fibrosis has been measured in the human heart and reported in experimental studies. Reported values for normal tissue are 0–2% in tissue from patients with undiseased hearts. In the setting of documented ventricular fibrillation the amount of fibrosis increases to 5–20% [83]. In a different study, measurements taken from human explanted failing hearts yielded 7–43% fibrosis [84]. These densities are usually given as a percentage of fibrotic area from the total tissue analyzed. A detailed description of fibroblasts and the role they play in cardiac tissue is described in the work of Camelliti and coworkers [85]. The proliferation of fibroblasts in the failing heart substantially alters its electrical activity [2,44]. Despite the fact that fibroblasts form a majority cell population in the normal adult heart, they are electrically unexcitable, but the electrical interaction with myocytes through gap junction proteins was early observed by Kohl et al. [86] and corroborated later in several species [18,87,88] in vitro. However, the presence and extent of fibroblast–myocyte electrotonic coupling in native myocardium (in vivo) remain controversial [89]. Myocyte-fibroblast interaction is a key factor to a better understanding of electrical cardiac propagation in failing hearts.

Detailed findings concerning the electrophysiological behavior of fibroblast membranes are scarce. In this regard, only potassium ionic channels were found by Chilton et al. [90]. This study provided data on which an electrophysiological membrane model for mammalian ventricular fibroblasts was developed by MacCannell and coworkers [91]. This model includes four membrane currents describing the "active" fibroblast membrane potential behavior, and is able to simulate how myocyte APD is shortened when fibroblasts are coupled. This is the most widely used model. Another contemporary model developed by Sachse et al. [92] included a Markovian description of the outward potassium current. This study examined the impact of fibroblasts on conduction in one-dimensional strand of myocytes, obtaining a reduced conduction and upstroke velocity. Later, Maleckar et al. [93] adapted MacCannell's model to simulate the behavior of atrial fibroblasts, showing how myocyte resting potential and AP waveform were modulated by the properties and number of coupled fibroblast, the degree of coupling, and the pacing frequency. These models have enable the simulation of the electrical activity of 2D and 3D cardiac tissues with fibrosis and the analysis of the consequences of fibrosis in cardiac electrical activity.

The first computational study simulating electrical coupling between fibroblasts and myocytes (from sino-atrial node) was performed by Kohl et al. [86]. The model of the electrotonic interaction of these cells showed that stretch of the fibroblast during atrial diastole, simulating increased atrial wall tension during atrial filling, can raise the spontaneous depolarization rate of the pacemaker cell in a stretch-dependent manner by up to 24%. The fibroblast was modeled as an electrically passive cell, the most common description until MacCannell's model formulation was published [91]. Later, Turner and colleagues [94] simulated fibrotic content in the ventricle as lines of insulating, unexcitable elements in the longitudinal and transverse direction. They highlighted the role of fibrosis on electrogram fractionation. The results related the effects of fibrosis, AP abnormalities and dispersion of AP duration to the characteristic electrograms recorded in patients at risk of sudden death.

Computer simulations have also helped to interpret how location and distribution of fibrosis alters cardiac conduction and favors arrhythmias. Xie et al. [95] developed several configurations of two dimensional sheets with fibroblasts and myocytes, showing an increased vulnerability to reentry when fibroblasts were electrotonically coupled to myocytes

with respect to tissues where fibroblasts were uncoupled, acting as pure insulators. The same model was used later to study the formation of EADs during oxidative stress [39]. They concluded that in aged ventricles exposed to oxidative stress, fibrosis facilitates the ability of cellular EADs to emerge and generate trigger activity, ventricular tachycardia, and ventricular fibrillation at the tissue level. EADs generation was favored by intermediate degrees of fibrosis content. Along the same lines, Petrov et al. [96] showed the influence of fibrosis on restitution properties and spiral wave stability in a three-domain model approach. Their results predicted that depending on the value of the resting potential of the cardiac fibroblast, the stability of a spiral in tissue may change. Engelman et al. [97] used a computer model containing non-uniformly distributed barriers of excitation resembling patchy fibrosis to demonstrate that structural heterogeneity alone is sufficient to give rise to discordant alternans at rapid stimulus rates.

Cardiac fibroblasts may act as a "current sink" for connected myocytes changing cardiomyocyte excitability [98]. Zlochiver et al. [32] used a numerical model of human cardiac tissue to quantify the current threshold for atrial and ventricular tissues under diffuse fibrosis conditions. They concluded that subthreshold excitation properties of the myocardium, such as current threshold and stimulation area, are influenced in a non-linear manner by cardiac pathologies such as heart failure. Later, the same group showed how spiral wave dynamics is altered by the presence of fibroblasts [99]. This study showed that both fibroblast density and heterocellular coupling conductance exhibit a biphasic effect on the frequency of spiral waves and that both impact the wave stability. Similar results were obtained in the sinoatrial node by Oren et al. [100] and in ventricular tissue.

Very few simulation studies have focused on the effects of fibrosis in the setting of HF. Gomez et al. used computational models to describe various ways by which fibrotic content and structural remodeling modulates the arrhythmogenic substrate of the failing heart, increasing repolarization gradients and leading to abnormal impulse propagation [53]. The fibrotic content ranged from 4 to 40%, measured as a percentage of nodes assigned to the fibroblast ionic model, which would correspond to the experimental ranges in terms of fibrotic area. The vulnerability to reentry under HF conditions and several degrees of diffuse fibrosis was also assessed by considering active fibroblast interaction. The results showed that intermediate degrees of fibrosis (14% and 28%) increased the probability of reentrant arrhythmias [101]. Similarly, Nayak et al. [102] focused on the influence of fibroblast features on spiral-wave control in a 2D model. They found that the rotation speed and stability of a spiral wave can be controlled either by the coupling conductance between myocytes and fibroblasts or by the resting membrane potential of fibroblasts. They also showed that a spiral wave can get anchored to a local fibroblast inhomogeneity. In the same line, the work of Majumder et al. [103] classified a variety of spiral wave non-equilibrium states depending on the percentage of fibroblasts. None of these two last studies considered HF conditions in their simulations.

The effect of HF on fibroblast ion currents and its potential role in AF has been addressed recently in the experimental and computational study by Aguilar et al. [104]. They suggested that fibroblast K^+-current remodeling in HF is a novel component of AF-related remodeling that might contribute to arrhythmia dynamics.

Finally, other computational studies utilized 3D ventricular models to simulate the effects of fibrosis at the organ level [103,105]. Similarly to the results from Gomez et al., they found that intermediate fibrosis (within experimental ranges) increased vulnerability to arrhythmias [101]. These simulation results shed light into the mechanisms by which patients or animal models in moderate stages of HF are more prone to arrhythmias than patients in the end-stage of HF.

3.2. Simulation of intercellular uncoupling

As stated above, structural remodeling of the failing heart includes not only proliferation of fibroblasts but also cellular uncoupling. The

total amount of connexin 43 is reduced in the failing heart and is redistributed from an end-to-end to a lateral location in the myocyte [16,106,107]. This reduction and reorganization gives rise to decreased conduction velocities in the failing heart [108]. Gima and Rudy have addressed the effects of cellular uncoupling on AP propagation and conduction velocity in the normal cardiac tissue [109] using one dimensional fiber simulations. They showed how enhanced coupling increases electrotonic interactions between cells, decreasing transmural dispersion of repolarization (TDR) with respect to control and increasing conduction velocity (narrower QRS). On the other hand, slow conduction and increased APD dispersion results from reduced coupling. They concluded that slow conduction overrides the intrinsic repolarization differences in the 3 cell types (endocardial, midmiocardial and epicardial) leading to an inversion of the repolarization sequence and, consequently, inverts membrane potential gradient and the T wave.

Very few studies have simulated cellular uncoupling in the setting of heart failure. Moreno and coworkers [41] explored the effects of flecainide and lidocaine on failing myocardium. They calculated single-cell upstroke velocity and computed the minimum drug concentration that caused conduction block in one dimensional fiber. HF-induced cellular uncoupling exacerbated arrhythmia susceptibility by markedly reducing CV. This resulted in conduction block at slower frequencies and lower concentrations of both flecainide and lidocaine compared to normal tissue. In the work of Zlochiver and colleagues [32] an analysis of excitability under HF remodeling was performed. They observed a non-linear influence of increased fibroblast to myocyte coupling coefficient on current density thresholds, with an initial increase of current magnitude followed by a relaxation phase down to the current magnitude threshold for the control condition with no fibrosis. In our previous works, we showed that an intermediate degree of cellular uncoupling increased the vulnerability to reentry of the failing heart and how the degree of cellular coupling could ensure conduction [101,110].

4. In silico analysis of arrhythmias in the failing heart

It is well known that cardiac arrhythmias need a trigger and an electrophysiologically and structurally altered heterogeneous substrate to be initiated and maintained. These conditions are fulfilled in HF. Electrophysiological remodeling and altered Ca^{2+}-handling may facilitate DADs and EADs generation, which may trigger a reentrant arrhythmia if the myocardial substrate contains repolarization heterogeneities, fibrosis and/or uncoupling. This section describes how computational models have contributed to the understanding of arrhythmogenesis in the failing heart.

4.1. Triggered activity in HF

It is well known that APD prolongation favors the occurrence of EADs that are triggered during the plateau phase of an AP and caused mainly by reactivation of the L-type Ca channels. Ca^{2+} handling alterations also promote the occurrence of DADs, which are linked to upregulation of the NCX in combination with intracellular Ca^{2+} overload [2]. But what are the specific mechanisms underlying EAD and DAD formation in the failing heart? Computational models have been developed and utilized to elucidate mechanisms of triggered activity in the setting of HF.

Priebe and Beuckelmann [21] obtained EADs utilizing their HF cellular model but not the normal physiological model, showing that under HF remodeling conditions the block of I_{Kr} leads to EADs. The influence of RyR and L-type calcium channels CaMKII-induced phosphorylation occurring during HF on EAD generation has also been analyzed in a computational work by Hashambhoy et al. [27]. They predicted that reducing CaMKII phosphorylation of LCCs may be a more effective approach to decreasing diastolic SR Ca^{2+} leak, and thus the likelihood of EAD generation, than reducing CaMKII phosphorylation of RyRs. Indeed, the stronger sensitivity of RyR to $[Ca^{2+}]$ in the cytosol than to $[Ca^{2+}]$ in

the SR was responsible for the significant decrease of RyR Ca^{2+} leak when LCC activity was decreased, and thus $[Ca^{2+}]$ in the cytosol was diminished. Trenor et al. showed the important role of an enhanced I_{NaL} on EAD generation in simulated failing cells [35], as suggested experimentally by Maltsev et al. [111]. The results of the simulations showed that in failing myocytes, the enhancement of I_{NaL} significantly prolonged APD, increasing the probability of I_{CaL} reactivation and initiating EADs. Similarly, Morita and coworkers [39] simulated the electrical activity of aging hearts and showed that these hearts are prone to develop EAD-mediated arrhythmias due to oxidative stress, when I_{NaL} is enhanced. They concluded that in aged ventricles exposed to oxidative stress, intermediate levels of fibrosis facilitates the ability of cellular EADs to emerge and propagate.

Although DADs have been measured experimentally in the setting of HF [112], very little computational work has yet addressed this issue. The first HF computer modeling study by Priebe and Beuckelmann [21] showed how spontaneous Ca^{2+} release from the sarcoplasmic reticulum can trigger a premature action potential in single failing myocytes but not in normal myocytes, due to a greater I_{NCX}. However, DADs are not likely to trigger a premature beat in the intact heart because the strong electrotonic coupling between myocytes acts as a sink for local depolarizing currents. Mathematical models have shown that to overcome the source-sink mismatch, DADs must occur simultaneously in a large number of cells. These numbers are significantly decreased by reduced gap junction conductance, simulated fibrosis, reduced repolarization reserve, and heart failure electrical remodeling [113]. The beneficial effects of drugs, such as ranolazine, in reversing the formation of DADs have also been suggested in a computational study [31] of HF. Application of ranolazine blocks I_{NaL} and normalizes the increased $[Na^+]_i$ levels and the slowed inward NCX current. This allows a normalized Ca^{2+} extrusion through NCX abolishing the spontaneous Ca^{2+} transients that lead to DADs. Ranolazine also hyperpolarizes the resting membrane potential, thus elevating the threshold for triggered diastolic events. Computer simulations add value and provide insights into arrhythmogenic mechanisms testing different hypotheses that the experimental approach cannot assess or would imply an elevated time and resources demand. Computational approach complements experimental studies by showing how HF-induced alterations favor the occurrence of triggered activity and also provide the substrate for arrhythmia maintenance.

4.2. Altered substrate in HF

Arrhythmogenic processes develop in pathological cardiac tissues with altered biomarkers, such as repolarization gradients, restitution curves or conduction velocity. An important feature of diseased tissues is the presence of increased electrophysiological gradients, which favor the maintenance of reentrant rhythms. An increase of transmural dispersion of repolarization (TDR) has been identified in the failing canine heart [114], and was attributed to a pronounced APD prolongation in M cells. Enhanced gradients were directly responsible for development of functional conduction block, leading to polymorphic ventricular tachycardia. In the human right ventricle, Lou et al. [115] also observed an increase in APD gradients in HF using optical mapping technique and related it to the increased arrhythmogenesis they observed. In contrast, Coronel et al. [116] observed that in the pig ventricle it is not only the repolarization gradient but also the restitution characteristics in combination with the time of arrival of the premature wavefront, which determines the occurrence of conduction block and reentry. Furthermore, recent experiments have shown that TDR and APD gradients are reduced in human HF [117,118]. In these failing tissues no M cells were found. Thus, complex and sometimes controversial alterations of the electrophysiological properties have been observed in the failing tissue so that arrhythmogenic mechanisms remain poorly understood. This is where computational studies are of great help by performing mechanistic analyses using mathematical models of disease-specific APs in the human heart, and revealing mechanisms for arrhythmogenesis. In this

way, a simulation study by Gomez et al. revealed increased APD dispersion under HF conditions assuming transmural homogeneous ion channel remodeling with respect to control, regardless of the presence or absence of M cells, but decreased TDR values were found when transmural heterogeneous remodeling was considered [53] and only in the absence of M cells. This computational study explained the above mentioned experimental controversial findings for TDR in HF, showing that the absence of M cells in the human failing heart is important but not sufficient to bring TDR values below those of nonfailing hearts. Heterogeneous remodeling of ion channels through the ventricular wall has a crucial role in the decrease of repolarization gradients in HF. Also the presence or absence of fibrosis in experimentally analyzed cardiac tissues can significantly change TDR measurements, as shown by Gomez et al. who demonstrated computationally that the presence of fibrosis and cellular uncoupling increased repolarization gradients [53].

APD restitution gives information on APD adaptation to selected pacing rhythms. Glukhov et al. [117] obtained a smaller slope of the restitution curve in the failing human heart than in normal donor hearts. Different results were obtained by the computational study of Elshrif et al. [119], where restitution curves were steeper in virtual failing cells than in normal cells using the O'Hara et al. human AP model [52]. Further simulation studies would be very valuable to enrich our understanding of the relationship between this biomarker and arrhythmias in the setting of HF.

Computational simulation studies have also aimed to provide insights into ionic mechanisms underlying the occurrence of alternans [120–122]. Much emphasis has been placed on the restitution curve slope as a major factor in the onset of arrhythmias following the development of discordant alternans where flattening the APD restitution curve is predicted to inhibit alternans development and subsequent conduction block [123]. Walmsley et al. [37] suggested that alternans are due to different causes in the failing population versus non-failing population cellular models. Their results showed that alternans are primarily favored by low values of I_{Kr} conductance in failing human cardiomyocytes and by reduced SERCA pump and enhanced I_{CaL} conductance in non-failing human cardiomyocytes. This is a first step towards clinical translation from disease modeling.

A reduction in conduction velocity (CV) has been measured experimentally in the failing human heart [108]. Loss of gap junction proteins in the intercalated disk and interaction with fibroblasts give rise to alterations in conduction velocity. In this regard, several works studied how the percentage of fibrotic content alters normal wave propagation [53, 95,103,124,125]. Nayak and coworkers [102] calculated that the plane-wave conduction velocity CV decreases as a function of intercellular coupling between myocytes and fibroblast (Ggap), for zero-sided and one-sided couplings; however, for two-sided coupling, CV decreases initially and then increases as a function of Ggap. In other simulation study, Majumder and coworkers [103] showed in 2D domains with a random distribution of fibroblasts in a myocyte background that as the percentage of fibroblasts increases, the CV of a plane wave decreases, slowly at first and rapidly thereafter, until it reaches zero and there is conduction failure.

4.3. Reentrant arrhythmias in HF

Changes in myocardial structure, including microanatomy, in combination with the electrophysiological remodeling in the failing heart promote arrhythmias. Generation of triggered activity helps to initiate arrhythmias and an altered substrate contributes to arrhythmia maintenance. Reduced excitability at the cellular level emerges in coupled tissue as a slowing of conduction velocity of the propagating depolarizing wave. Furthermore, repolarization gradients and electrophysiological heterogeneity favor unidirectional block and reentry. To generate reentrant circuits, an excitable gap or a vulnerable window (VW) is required [2], and slow conduction and heterogeneities widen the VW.

Several simulation studies have modeled structural alterations observed in HF to reproduce reentrant activity. The importance of fibrosis in determining the dynamics and stability of reentry has been highlighted in several computational studies. Majumder and coworkers [103] characterized spiral wave dynamics depending on fibroblast content. As the percentage of fibroblasts increases, spiral wave dynamics was characterized in a variety of nonequilibrium states, (temporally periodic, quasiperiodic, chaotic and quiescent) and an intricate sequence of transitions between them. Indeed, the electrical coupling of cardiomyocytes with fibroblasts cells alters the anisotropic action potential propagation in the human failing heart in a fashion that significantly depends on the density of fibrotic content and on the degree of intercellular coupling. A range of intermediate levels of fibrosis and intercellular uncoupling can combine to favor reentrant activity [101].

In order to assess spiral wave dynamics phase maps analysis provides a powerful tool to explore abnormal conduction patterns in the setting of ventricular fibrosis. This method is a valuable tool which helps to identify and quantify spatiotemporal organization of reentry dynamics [126]. The phase tracks the progression of a defined region of the myocardium through the action potential. Points around which the phase progresses through a complete cycle from $-\pi$ to π are of special interest. At these points, the phase becomes indeterminate and the activation wave fronts hinge on these points and rotate around them in an organized fashion. These points in the phase map are called phase singularity points (PS). PS share location with anatomic heterogeneities, and their spatial meandering is modulated by these heterogeneities. Phase analysis was employed in Gomez et al. (see Fig. 2) [101] and other studies [127,128]. These studies showed that the presence of structural heterogeneities, such as fibrosis, increased the number of phase singularities, and thus the risk of wave break [101,129]. Furthermore, when intermediate levels of fibrosis are considered, the tip of the reentry meanders within a larger area and the vulnerable window is wider [101] as illustrated in Fig. 2. Finally, fibrosis seems to have an important role in the reduction of the rotation frequency of spiral waves. Simulation studies predicted that the rotation frequency of the spiral wave slightly decreased with increased fibrosis [99,101,129,130]. Further computational research combining structural and electrical remodeling [53,101] would be useful to improve our understanding of reentry mechanisms under failing conditions.

5. Heart failure treatment. Modeling of drug effects and CRT

5.1. Simulation of drug effects in heart failure

Integrative computational simulation has become a powerful tool to complement experimental and clinical research in multidisciplinary efforts that can elucidate the basic mechanisms of drug effects on ion channel-mediated phenomena. Pharmaceutical companies have already suggested the implementation of new testing protocols including the effects of drugs on multiple cardiac ion channels and integration of this information using computational modeling and simulation approaches [131]. Here we describe some insights given in this direction in the setting of HF. Moreno and coworkers developed a computational model to simulate the interaction of the anti-arrhythmic drugs flecainide and lidocaine with cardiac sodium channels [41] in the failing human heart. Their results suggested that lidocaine was less likely than flecainide to promote reentrant rhythms. The mechanism of this result was also revealed through a computation component dissection: the slow drug off rate, which dramatically slows Na channel recovery in the presence of flecainide was found to promote unidirectional conduction block and stable reentry. In a different study, Ranolazine was pointed out as an effective therapeutic strategy against HF due to I_{NaL} preferential targeting [31], as described previously. Further simulation works focusing the effects of other drugs, such as β-blockers, utilizing a detailed model of HF would be very useful. Indeed, β-adrenergic stimulation strongly influences ion channel activity, AP morphology and might contribute to
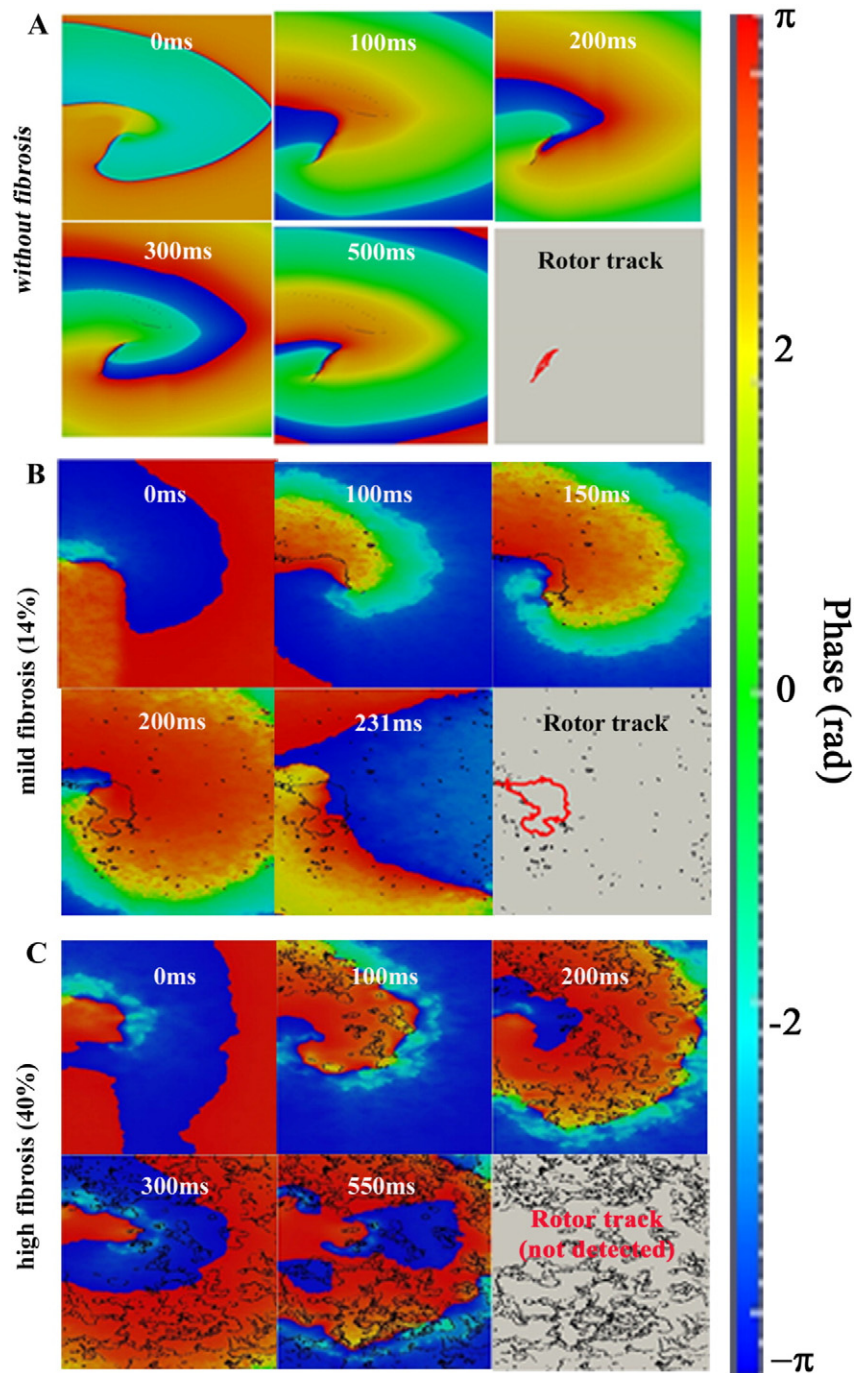
Fig. 2. Phase map analysis of evoked rhythm disturbances on the failing human ventricular tissue. Phase maps in electrically remodeled failing tissues assuming selected levels of fibrotic content. The rotor tip trajectory altered by structural heterogeneities. All transient phase singularities are indicated in black, and the tip of the trajectory is indicated in red in the last snapshot in each panel.
Reproduced with permission from [101].

arrhythmogenesis. Experimental studies with β-blockers are not able to dissect separate effects of the drug on the different cellular targets, while computer simulations can represent a hypothetic scenario with thousands of possible configurations.

5.2. Cardiac resynchronization therapy (CRT). Electromechanical approach

Cardiac resynchronization therapy (CRT) is an established therapy for selected heart failure patients. CRT typically employs bi-ventricular pacing, with an endocardial right ventricular (RV) pacing lead and an epicardial left ventricular (LV) pacing lead. It aims to capture RV and

LV and thus recoordinate contraction. Simulation approaches can be used to optimize CRT therapies. For example, seeking for the optimal pacing timing and location to induce the pacing stimulus helps to obtain most beneficial regional energy consumption [132]. These studies can also provide new tools to better discriminate CRT patients. Galeotti and coworkers [133] increased the specificity of left bundle branch block (LBBB) diagnosis in the presence of LV dilation and hypertrophy by defining new strict LBBB criteria. They developed five heart models based on a healthy male with increasing degrees of LV hypertroph and/or dilation. They simulated six conduction types with each model: normal conduction, four increments of delayed initiation of LV

activation (incomplete LBBB), and complete LBBB and evaluated the simulated ECGs.

Potse et al. [134] focused on the effects of uncoupling due to LBBB. A LBBB electrocardiogram type may be caused by either a block in the left branch of the ventricular conduction system or by uncoupling in the working myocardium. They used a realistic large-scale computer model to evaluate the effects of uncoupling with and without left-sided block. Their simulations showed that uncoupling in the working myocardium can mimic left-sided block in the ventricular conduction system and can explain an LBBB ECG pattern with low amplitude.

A three-dimensional computational model of ventricular electromechanics was developed by Usyk and McCulloch [135] to study the role of biventricular pacing on systolic mechanical performance and synchrony during the cardiac cycle of the dilated failing heart with LBBB. Their simulations showed that biventricular pacing improves mechanical synchrony and systolic function. However, experimental studies [136] suggest that electrical synchrony does not correlate directly with mechanical synchrony and systolic performance. Thus, sequential CRT can improve cardiac performance and mechanical synchrony better than simultaneous biventricular pacing [137].

Aiba et al. [138] showed that CRT reduces the frequency of EADs through I_{NaL} decrement, while others studied how geometry and anatomical structures, such as the conduction system, affects pacing in failing hearts. Rodriguez and coworkers [139] used an anatomically based rabbit ventricular model of electrical stimulation to provide mechanistic insight into the contribution of transmural electrical events in cardiac

vulnerability to externally applied shocks and the role of electrode polarity change in modulating the mechanisms of reentry induction. The information provided by the model was critical in understanding the etiology of shock-induced arrhythmogenesis. Romero and colleagues [140] used a human heart computer model which incorporated anatomical structures such as myofiber orientation and a Purkinje system (PS) to study how pacing affected failing hearts. Their results showed that retrograde conduction into the PS was a determining factor for achieving intraventricular synchrony. Omission of the PS led to an overestimate of the degree of electrical dyssynchrony while assessing CRT. These results should be carefully considered when determining lead placement and optimizing device parameters in clinical practice.

In this line, patient-specific models of hearts with contractile dyssynchrony have been recently developed providing a new clinical tool in the treatment of dyssynchronous heart failure [141–143].

An important step in computational modeling of the heart is the link between the electrical activity of the myocardium and mechanical contraction. Several simulation studies have been undertaken to evaluate the electromechanical behavior of the heart in selected animal species but literature is scarce in the setting of human HF [144,145]. The distribution of electromechanical delay (EMD), the time interval between local depolarization and myocyte shortening onset was analyzed by Gurev and coworkers [146] in 3D model of the rabbit ventricles during sinus rhythm and epicardial pacing. Simulations showed a nonuniform EMD distribution for both configurations that depends on activation sequence and on the pacing rate. Electromechanical simulations based on
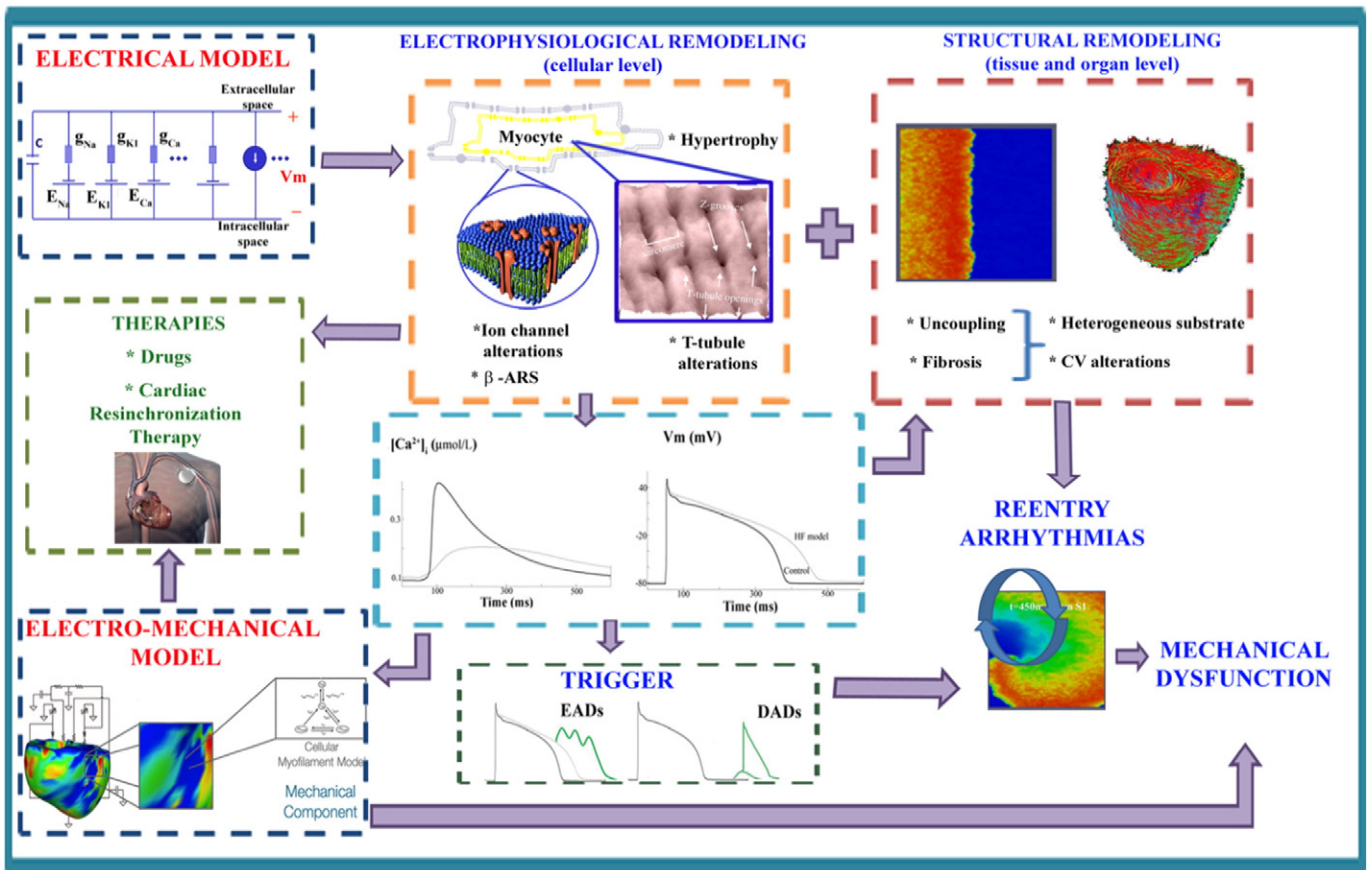

Fig. 3. What can be learnt from computer simulations in heart failure. Multi-scale electromechanical models of heart failure (HF) help to understand arrhythmogenic mechanisms. At the cellular level, electrophysiological remodeling can be modeled by alterations in ion channels, in β-adrenergic system, and in T-tubules (image taken from [148]) and is responsible for significant changes in action potential and Ca^{2+} transient waveforms, which might lead to EADs and DADs generation. At the tissue and organ level, structural remodeling (intercellular uncoupling and fibrosis) lead to discontinuous and decreased conduction velocity and electrophysiological heterogeneities. Triggered events and heterogeneous substrate set the stage for ventricular arrhythmias in the failing heart. Incorporating the mechanical response (electro–mechanical model reproduced with permission from [132]) in a HF model will improve the understanding of the mechanical dysfunction of the failing heart and the design of cardiac resynchronization therapy.

computational models could guide and improve CRT, as in Constantino et al., who suggested that an adequate pacing location would be the site of longest electromechanical delay [132].

6. Concluding remarks and future challenges

This article reviews the main computational studies on HF from cell to organ. These studies illustrate how modeling and computer simulations may reveal the mechanisms of arrhythmogenic processes and therapies in the setting of HF. In this last section, the main advances, as well as limitations and future challenges of the computational approach of HF are presented. In addition to the generic limitations of cardiac models [147], several improvements in the pathological models of HF should be highlighted to guide research towards future challenges.

As summarized in Fig. 3, simulations at the cellular level have contributed to elucidating the role of ion channel remodeling in AP and Ca^{2+} handling HF-induced changes. However, the effects of changes in the T-tubule system [148] and β-adrenergic pathways in the failing cell need further analysis. Simulations of AP prolongation and altered Ca^{2+} transient have also furthered our understanding of the mechanisms of triggered activity: EADs and DADs in failing cells. 1D, 2D, and 3D models of the failing tissue have made it possible to simulate the effects of structural remodeling in the failing heart. The increase of cellular uncoupling and fibrosis in heart failure may have a significant role in setting an arrhythmogenic substrate, leading to cardiac arrhythmias. Although fibroblast interaction with cardiomyocytes has been addressed in several multi-scale computational studies in normal physiological conditions, the literature is scarce in the setting of HF. In addition, only the work of Chilton and coworkers [90] provides experimental data to inform an electrical model of ventricular fibroblasts. Further experiments are needed to improve these models, such as the work of Chatelier et al. [149], who reported the expression of voltage gated sodium channels in human atrial fibroblasts. Recently a great effort has been made to improve electromechanical models of the heart, which identify the link between electrical activity and especially Ca^{2+} transient and cellular and organ contraction (see Fig. 3). In terms of HF, electromechanical simulation studies are scarce and further studies are needed. These computational models can help to evaluate mechanical heart dysfunction and improve CRT.

With regard to drug therapy in HF, apart from several studies focusing on sodium channel blockers, there is a lack of computational work. The analysis of the effects of β-blockers in the failing heart through computer simulations would help to understand why these drugs are effective in these patients. Recently, safety pharmacology assessments have highlighted the use of computer simulations in combination with in vitro experiments on human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) for drug safety screening. β-blockers have been proved to improve the function of iPSC-DC from dilated cardiomyopathy [150], and because this technology offers the possibility to obtain disease-specific cell lines, this could also be tested for other HF etiologies. Furthermore, mathematical models of hiPSC-CMs have been recently formulated [151], allowing in silico studies for drug safety and supporting the evaluation of this new in vitro technology [152].

It is important to mention that the efforts recently made in the development of patient-specific models, based on high-resolution images, will be of great help if they are extended to different stages of HF and different etiologies.

Finally, a crucial challenge is the integration of computer pathological models and simulations into clinical practice. This integration of computer models in the clinical routine requires the development of automatic tools to personalize models and validate them not only in the laboratory setting but also in a clinical environment, in which clinicians have to deal with patients with different characteristics. Research effort needs to be made to build the necessary user-friendly interfaces for clinicians and provide the clinically relevant answers to the specific questions of the physicians.

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