



HHS Public Access

Author manuscript

Nat Rev Cardiol. Author manuscript; available in PMC 2019 June 08.

Published in final edited form as:

Nat Rev Cardiol. 2019 February ; 16(2): 100–111. doi:10.1038/s41569-018-0104-y.

Computational models in cardiology

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Abstract

The treatment of individual patients in cardiology practice increasingly relies on advanced imaging, genetic screening and devices. As the amount of imaging and other diagnostic data increases, paralleled by the greater capacity to personalize treatment, the difficulty of using the full array of measurements of a patient to determine an optimal treatment seems also to be paradoxically increasing. Computational models are progressively addressing this issue by providing a common framework for integrating multiple data sets from individual patients. These models, which are based on physiology and physics rather than on population statistics, enable computational simulations to reveal diagnostic information that would have otherwise remained concealed and to predict treatment outcomes for individual patients. The inherent need for patient-specific models in cardiology is clear and is driving the rapid development of tools and techniques for creating personalized methods to guide pharmaceutical therapy, deployment of devices and surgical interventions.

With precision medicine emerging as the future for cardiology, the diagnostic and therapeutic assessment of patients with cardiac disease increasingly relies on advanced imaging technology, genetic profiling, pharmaceuticals and medical devices¹. However, at present, the choice of treatment still depends largely on the outcome of empirical clinical studies in which the effects of different therapeutic options are compared statistically between large groups of patients with similar cardiac pathologies. The increasing level of

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Author contributions

All the authors researched data for the article, contributed substantially to the discussion of the content, and wrote, reviewed and edited the manuscript before submission.

Competing interests

N.A.T. declares no competing interests.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Reviewer information

Nature Reviews Cardiology thanks B. Rodriguez and the other anonymous reviewer(s) for their contribution to the peer review of this work.

detail in the diagnostic data has uncovered more and more interindividual variability in pathophysiology². The growing realization that patient groups are less uniform has led clinical researchers to stratify patients into smaller and more numerous subgroups^{3,4}. In addition, the choice and possible gradation of therapeutic interventions have increased alongside the exponential advances in medical technology. Consequently, reaching the level of significance to identify better treatments for cardiac disease would be difficult in the conventional empirical setup of clinical trials⁵.

An alternative to the empirical route is to integrate the patient's diagnostic data using physiological and physical principles important for cardiac function and to use analytical approaches to characterize most accurately the underlying disease and tailor the treatment for an individual's pathology. Computational models of the heart are increasingly used to address this issue by providing a common framework to integrate multiple data sets from individual patients (FIG. 1). Often, these mechanistic models are complemented with population-based computational techniques, such as atlas-based estimations of global cardiac geometry or regional myocardial fibre orientations, and with principles of control theory, such as the rules of tissue adaptation that control global cardiac geometry through mechano-feedback⁶⁻⁹. These techniques are instrumental in providing reasonable parameter estimates when insufficient patient-specific clinical data are available to constrain the model and in ensuring that these parameters stay within physiological ranges. This integrative and mechanistic power enables computational simulations to reveal novel pathophysiological insights that would otherwise have remained concealed and eventually to predict the optimal treatment option for an individual patient. In contrast to the epidemiological approach, the integrative biophysical approach is primarily based on cause-consequence relationships. A patient-specific simulation is obtained by adjusting a well-chosen set of relevant parameters in the computational model, so that model simulation and clinical measurements agree. The capacity of the model to replicate validation data sets provides confidence that the model can be used to make reliable predictions and simulate the most likely status of a patient given the available measurements. The resulting 'virtual patient' can be used for further improvement of diagnosis and for in silico optimization and planning of a treatment.

As the field of cardiology is entering a new era of individualized precision care, patient-specific cardiac modelling might be an important technology to pave the way for personalized medicine^{10,11}. The inherent need for patient-specific models in cardiology is clear. Patients routinely have distinct pathologies, which limits the efficacy of a 'one-size-fits-all approach'. Patient-specific computational models provide a framework that addresses the challenges of representing the pathophysiology of the individual patient and provides a platform to test multiple therapies and determine the optimal therapy for a specific patient at a specific time. The need for patient-specific modelling is driving the rapid development of tools and techniques for creating personalized models to guide pharmaceutical therapy, deployment of devices and surgical interventions. This Review demonstrates the potential of cardiac models to represent a paradigm shift from population-based clinical decision-making to a true personalization of care that is based on an individual's specific physiology and pathophysiology. We focus on multi-scale physiology-driven simulations of cardiac mechanics and electrophysiology. The parallel and important field of fluid simulations in the ventricles, coronary arteries and across the valves has been reviewed previously^{12,13}.

Clinical cardiac simulation studies are built on a substantial investment in imaging and modelling methods that are described in more technical reviews^{14,15}. In addition, this Review summarizes how personalized cardiac models can increase cost savings and time efficiency of preclinical and clinical trials in cardiology and thereby shorten the path of novel diagnostic and therapeutic strategies to clinical application.

Modelling human cardiac cells

Using biophysical models to link protein function to emergent cellular physiology.

The first computational models of cardiac physiology were cellular models that provided a physiologically and physically constrained framework for quantitatively combining measurements and models of protein function into emergent cellular phenotypes. In the past 3 decades, the modelling of ventricular myocytes has moved from modelling generic mammalian cardiac myocytes by combining data from multiple species to species-specific modelling^{16,17}. Cellular models that include K^+ , Na^+ and Ca^{2+} channels (FIG. 2a), as well as physiological processes, such as pH regulation, β -adrenergic stimulation and Ca^{2+} homeostasis have been developed^{18,19}. The functional properties of ion channels, buffers, pumps and transporters are represented in mathematical models that can be used in preclinical and human studies to link, for example, changes in channel function caused by mutations, drugs or physiological regulation to cellular and organ function. As an example, Fernandez-Chas and colleagues used detailed models of cellular membrane electrophysiology and Ca^{2+} handling in rabbit and human cardiac myocytes to predict the effect of doxorubicin and its metabolite doxorubicinol on the action potential and Ca^{2+} transient²⁰.

Biophysical models of human cardiac cells are now available to simulate the electrophysiology and Ca^{2+} dynamics in the sinoatrial node and in atrial and ventricular myocytes, as well as tension generation in the ventricles^{21–31}. These models have facilitated the development of studies with four different aims: modelling the effect of channel mutations on cellular and organ function, linking molecular drug effects to emergent cellular and organ function, simulating acute ischaemia, and translating molecular and preclinical physiological studies into clinical readouts.

Effects of protein mutations on cellular and organ function.

Since the identification of the first channelopathy-associated genes, the list of specific mutations associated with the risk of arrhythmia has grown substantially^{32,33}. However, moving from a correlation between a mutation and the disease to a causative relationship as a precursor to identifying new therapeutic targets first requires finding a mechanistic explanation of the link between the mutation, the change in protein function and the increased risk of arrhythmia. In the case of channel mutations, the characterization of the mutated protein in an expression system often allows a specific mutation to be linked to the protein function³⁴. However, this experimental characterization of the protein does not show whether a specific mutation causes a clinical phenotype. Consequently, linking a change in protein function to an increased risk of arrhythmia and to clinical electrocardiogram (ECG) morphologies remains challenging.

Simulations provide an increasingly important link between the characterization of a protein function in expression systems and clinical indices. Biophysical models of the wild-type channels can be adapted to represent the change that a specific mutation introduces in channel kinetics (FIG. 2b). The model of the mutated channel can be introduced into a whole-cell model to predict the effects of this mutation on emergent cellular function and to link the effects to the ECG. Four years after the identification of the first channelopathy-associated gene, models of the cardiac myocyte were used to link changes in Na⁺ channel function caused by a K⁺ mutation to cellular electrophysiology³⁵. This work was primarily used to study patients with a long QT (LQT) interval associated with mutations in the Na⁺ channel, referred to as type 3 LQT syndrome (LQT3) but has since been extended to other LQT mutations with simulations to study LQT1 (REFS^{36,37}), LQT2 (REFS^{38,39}), LQT3 (REFS^{35,40–45}) and LQT8 (REFS^{46–51}) as well as the related inherited cardiomyopathies Brugada syndrome^{44,52,53} and short QT syndrome^{54,55}. As an example, Moreno and colleagues used biophysical models to link a *KCNQ1* missense mutation that had been associated with functional changes in channels expressed in HEK293 cells to the clinically observed shortened QT interval⁵⁴.

Biophysical models capturing the complex cellular electrophysiology, combined with models representing measured changes in channel kinetics, can be used to demonstrate that a specific channel mutation is sufficient to explain the observed cellular and clinical phenotypes. This approach has been extended to provide mechanistic explanations for the clinical presentation of channel mutations in the context of altered heart rate or sympathetic stimulation^{36,56,57}. In these cases, biophysical models explicitly represent the effects of altered heart rate or sympathetic stimulation and isolate these effects from the effects of the channel mutation, which allows the characterization of the interdependence of these effects. Additionally, models have been used to explain specific clinical manifestations of channelopathies caused by multiple channel mutations or genetic mosaicism^{58,59}. The development of models that characterize the effect of a specific mutation at the scale of a channel, cell and organ has also provided a platform for predicting how drugs mitigate potential pathologies associated with a mutation⁶⁰.

In the past 10 years, models of cardiac myocyte contraction have also been developed to simulate the biochemical reactions between the sarcomeric proteins^{61,62}. These models are used to predict the effects of mutations on sarcomeric proteins and the emergent changes in tension development^{63,64}.

Effects of drugs on cellular and organ function.

Models are now created to predict how drugs act on specific channels or on combinations of channels to affect cardiac cellular and tissue electrophysiology⁶⁵. Drug effects on ion channels can be characterized in expression systems that provide a dose–response curve for a given compound on a given channel. The resulting dose–response curve can be used to scale the number of functioning channels (FIG. 2c). The effects of drugs on the channel can then be introduced into the whole-cell model to predict emergent therapeutic or toxic effects of drugs on cellular physiology. In this way, models provide a framework for combining preclinical data from binding assays, stem cell models, expression systems or animal studies

within the context of known human physiology. The identification of novel therapies through computational models is still speculative and has yet to translate into novel therapies. The FDA Comprehensive In vitro Proarrhythmia Assay (CiPA) initiative is, however, currently leading the way for the translation of computer models into screening tools for cardiac toxicity^{52,66}.

Building on the successful adoption in drug development and guidelines of physiology-based pharmacokinetic models that simulate drug distribution in the blood for a given dosing regimen⁵², biophysical cardiac model simulations are increasingly applied to predict the functional response of the heart to novel compounds. Simulations have demonstrated that they can be used to combine drug effects across multiple channels for arrhythmogenic risk prediction, account for biological variation in model predictions, test hypothesized adverse pathways, and predict how a compound and its metabolite influence preclinical and human electrophysiology^{20,67–70}. These models are aiming to predict measures of drug efficacy or drug-related risk by using data that are available early in the drug-development process. As an example, in a 2014 study linking data from binding assays to results from a clinical study on QT interval, the models could correctly classify proarrhythmic drugs with a sensitivity and specificity of up to 79% and 100%, respectively⁷¹.

Effects of acute ischaemia on cellular and organ function.

Ischaemia has a prominent role in sudden cardiac death (SCD)⁷². The capacity to monitor the development of local acute ischaemia in patients is limited. Experimentally, transient ischaemia can be readily induced and monitored at the cellular and organ scales. In this context, modelling and simulation provide a framework for linking the effects of ischaemia on cellular function observed in animal studies with whole-organ function in human hearts⁷³. Acute ischaemia is characterized by hyperkalaemia, hypoxia, and acidosis⁷⁴. The effects of these changes on individual proteins have been recorded and characterized in biophysical protein models. In turn, these protein-scale models have been integrated into models of human ventricular myocytes to predict how changes in single proteins alter phenotypes at the cellular scale^{75–77}. In human tissue models, ischaemia is recapitulated by a combination of increased extracellular K^+ concentrations, introduction of an ATP-sensitive K^+ current, and a decrease in the conductivity of the L-type Ca^{2+} and fast Na^+ channels. These models have been used to investigate drug effects and the effect of non-transmural ischaemic regions on ECG morphology^{78,79}. The work by Kazbanov and colleagues is noteworthy for providing a plausible mechanistic explanation for the decreasing dominant activation frequency during ischaemia from whole-heart epicardial activation patterns recorded during open-heart surgery⁸⁰. The use of models to analyse complex activation sequences is likely to increase with the growing use of inverse-ECG methods and the large and complex data sets collected from whole-heart activation recordings.

Translating molecular and preclinical physiological studies into clinical readouts.

The fourth application of human cardiac cell models is linking the changes in protein or cellular physiology observed or hypothesized from animal models to cellular changes in human cells and predicting whole-organ human clinical phenotypes. This application has particular relevance for cardiac myocyte Ca^{2+} handling, given that in vivo measurements are

not available and that few studies have characterized Ca^{2+} regulation in human myocytes. Models can be used to extrapolate changes observed in preclinical studies in Ca^{2+} dynamics and Ca^{2+} regulation into human contexts. Models have been successfully used to predict the effect of L-type Ca^{2+} channel relocation in patients with heart failure with increased arrhythmogenic risk and to explain the role of a decrease in the function of sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase on action potential alternans in patients with atrial fibrillation (AF) or the role of Ca^{2+} dysregulation in the increase in arrhythmia complexity and substrate^{81–83}. Analogously to genetic and drug studies, the characterization of physiological and pathological regulation of channels can be done in expression systems and interpreted within the context of human physiology⁷⁵. In the past 5 years, the advances and availability of pluripotent stem cell-derived cardiac myocytes have also led to the development of models tailored to recapitulate these cells. Paci and colleagues have developed models that describe atrial-like and ventricular-like stem cell phenotypes⁸⁴. These models have been used to interpret toxicology screens and to facilitate the translation of findings from stem cells into mature cardiac myocytes and are likely to have a role in accelerating the analysis and design of stem-cell patches for regenerative medicine^{85–88}.

Modelling the heart of patients

Model generation.

The advent of personalized and precision medicine in cardiology has generated a growing need to mechanistically link molecular treatments with functional outcomes at the cellular and organ scales. The use of biophysical models provides an efficient means to evaluate preclinical observations within the context of human physiology, thereby accelerating the translation of benchtop findings to the bedside. The development of patient-specific electrophysiological heart models became possible through the availability of cardiac images from patients, usually MRI or CT, and was substantially propelled by the movement towards personalized medicine. Clinical MRI scans with a contrast agent (late gadolinium enhancement) are used to visualize the structural remodelling in atria and ventricles and, therefore, have been used in computational modelling^{89,90}. Atlases of ventricular geometry and shape have been assembled by averaging 3D cardiac image data sets from individuals and generating a mean 3D cardiac image or shape representative of cardiac anatomy^{91,92}.

Given that patient-specific myocardial fibre orientations cannot currently be acquired in routine clinical practice, these data need to be estimated for inclusion in the individualized heart models. To date, two methodologies have been developed for estimating fibre orientations on the basis of the individual geometry of the ventricles. The first methodology is an atlas-based approach, in which the patient's fibre orientation is estimated by morphing an atlas of heart anatomy generated from ex vivo MRI and diffusion tensor magnetic resonance imaging (DT-MRI) onto the patient's heart anatomy^{7,93}. The second approach uses a rule-based fibre orientation estimation derived from histological and DT-MRI data⁹⁴. Utilization of patient-specific models for clinical applications emphasizing the use of noninvasive approaches, as described below, often necessitates the use of averaged human electrophysiology, for both normal and remodelled tissue, given that electrophysiological properties cannot be acquired noninvasively^{95–97}. By contrast, some studies have aimed at

the personalization of electrophysiological properties through invasive electro-anatomical mapping measurements^{98–100}.

The success of modelling the ventricles as well as their pathologies and treatments has been mirrored in models of the atria. 3D models of human atria have been created to represent the atrial anatomy by using surface or volumetric models and have mainly been used to simulate AF^{101–111}. Most models incorporate atrial geometries created from multimodality imaging^{102,103,110,111}. Fibre structure has also been incorporated in these models, most often by using a rule-based approach; DT-MRI has also become available to estimate fibre orientations in the human atria^{112–114}. Models of atrial electrophysiology can be generated by fitting clinical measurements from individual patients or using averaged human values^{115,116}.

FIGURE 3, which presents cardiac model generation from clinical images or imaging information, illustrates the variety of imaging modalities that can be used as model inputs and highlights the different degrees of model complexity that can be reached depending on the problems addressed by the simulations.

Ventricular arrhythmias.

The vision to use computational ventricular electrophysiological models in the clinic stems from a number of studies using a single model of the human ventricle to understand the mechanisms by which arrhythmias arise and are sustained in the human heart. The aim of these studies included understanding the mechanisms underlying ventricular arrhythmias, such as the characteristics of ventricular fibrillation under a variety of conditions including heart failure, the effect of afterdepolarizations on propagation and the maintenance of torsades de pointes^{78,80,117–121}. Furthermore, the model has been successfully used to reveal the origin of specific characteristics of the ECG such as the notched T waves, the effects of ionic current changes, and the propagation pattern such as left bundle branch block, as well as to detect instabilities in the QT interval, a predictor of the onset of ventricular tachycardia in patients with acute myocardial infarction^{122–125}. Combined with an image-based torso representation, the human heart model has been used to evaluate the effect of heart position on ECG morphology in patients with heart failure and the signatures of left ventricular (LV) hypertrophy in the ECG^{126,127}. Although these simulation studies do not involve patient populations, their insight has been pivotal in advancing human cardiac electrophysiology modelling and the field of cardiac arrhythmogenesis.

Applying patient-specific heart or ventricular modelling to populations of patients has become the new frontier of computational cardiology. Arevalo and colleagues conducted a retrospective study of 41 patients after myocardial infarction and with left ventricular ejection fraction (LVEF) < 35% to determine the patient's propensity to develop infarct-related ventricular arrhythmias and, therefore, to assess the risk of SCD⁹⁵. This noninvasive approach to SCD risk stratification was termed the virtual-heart arrhythmia risk predictor (VARP). The comparison of the predictive capabilities of VARP with those of other clinical risk assessment metrics, including LVEF — the current clinical stratifier for SCD — revealed that only VARP outcome was significantly associated with arrhythmic risk in this cohort. Of note, the noninvasive nature of VARP is an additional advantage over clinical

testing that entails risks of vascular access, sedation and induction of ventricular arrhythmias requiring defibrillation in already-weakened patients with cardiomyopathy. VARP has also been successfully applied in the past 2 years for the analysis of data from patients after myocardial infarction and with LVEF >35%⁹⁶.

Patient-specific electrophysiology models have also been employed to predict noninvasively the target for catheter ablation, a procedure based on the delivery of heat or cold to destroy the ability of cardiac tissue to generate and conduct electrical signals locally. Zhu and colleagues demonstrated that heart models could be used to localize noninvasively accessory pathways in patients with Wolff–Parkinson–White syndrome¹²⁸. In a retrospective analysis of 13 patients, Ashikaga and colleagues demonstrated that the prediction of ablation targets for infarct-related ventricular tachycardia could also result in lesions that are much smaller than those executed in the clinic¹²⁹. Finally, a biophysically detailed heart–torso modelling approach has been used to predict the optimal location of the implantable cardioverter–defibrillator leads in a patient with congenital heart disease¹³⁰. The study demonstrated that defibrillation shock energy could be reduced if computational simulations were used as part of the device implantation planning.

Atrial arrhythmias.

The growing burden of AF and the difficulties associated with the personalized treatment of the disease has led the field of cardiac computational modelling to focus on understanding how functional and structural remodelling result in the turbulent propagation associated with AF^{116,131}. Atrial computational models have made major contributions in understanding how intrinsic atrial structural and electrophysiological heterogeneities predispose to atrial arrhythmias^{132–135}. Examples of such contributions include investigating the role of pulmonary vein triggers in initiating paroxysmal AF, determining the mechanisms of lone paroxysmal AF that arise from inherited ion channel dysfunction, establishing the mechanisms for atrial alternans, elucidating the role of the ganglionic plexi in initiating AF and revealing the contribution of the electrical uncoupling between the endocardial and epicardial layers^{83,136–140}. In the past couple of years, the understanding of the role of fibrosis in maintaining persistent AF has led to a number of new computational studies aimed at determining how the remodelled atrial structure alters AF dynamics. These studies include the assessment of the different representations of fibrosis and the spatial resolution of clinical measurement needed to detect re-entrant drivers that sustain AF^{141–143}.

Predictive approaches that combine clinical imaging and computational modelling and can be applied for the treatment of AF have also been developed. The first attempt at a clinical application of human 3D atrial modelling was in the context of pacing for AF termination^{144,145}. In the past decade, catheter-based AF ablation has become one of the next big frontiers in the use of 3D computational modelling to guide patient therapy. For example, human atrial models have been used to suggest how to optimize AF ablation, explore strategies to minimize the size of ablation lesions and study the effect of gaps in ablation lines^{103,146}. Atrial models that incorporate the ganglionic plexi and the resulting AF have also been developed and have already been used successfully in a patient cohort to guide ablation for paroxysmal AF¹⁴⁷. Although pulmonary vein isolation is currently the

recommended treatment for patients with persistent AF and fibrosis, no reliable ablation option is available. Therefore, simulation approaches can make a great difference for this specific application by providing guidance for ablation in addition to the standard pulmonary vein isolation. A number of human atrial models have been developed for the sole purpose of guiding ablation in the fibrotic substrate, primarily through the detection of regions of high-dominant frequency or locations of the re-entrant drivers perpetuating AF^{110,111,142,147,148}. Models of atrial fibrosis have already shown early preliminary success in providing guidance in substrate ablation; these results have raised expectations that atrial models could be used to predict optimal AF ablation strategies in a patient-specific manner^{149,150}.

Of note, atrial and ventricular models for clinical applications that aim at noninvasive assessment of risk of arrhythmias or noninvasive computational prediction of ablation targets cannot include patient-specific electrophysiology, given that acquisition of these parameters is currently invasive. Using averaged human electrophysiology associated with the given atrial or ventricular disease in the models will entail a certain level of model uncertainty. Further model uncertainty could result from the low resolution of clinical scans. In the past 7 years, studies have started to assess the level of uncertainty in the models and to take steps to out-line the potential clinical applicability of the different modelling approaches^{151–158}.

Heart failure therapy.

Cardiac resynchronization therapy (CRT), a clinically important device therapy for patients with dyssynchronous heart failure, has been the subject of many computational modelling studies. These studies addressed the absence of a response to CRT, which is often a multifactorial problem related to the large interindividual variability in underlying disease patterns and therapy delivery¹⁵⁹. Computer models covering this complexity in an integrative way and at different scales have been frequently used to investigate ways to optimize patient selection and therapy delivery¹⁶⁰. Simulations of the cardiovascular system have been used to provide representative models for specific patient groups, giving insight into disease-specific mechanisms. By contrast, personalized 3D models have aimed at capturing an individual's anatomy and pathophysiology to provide insight into disease mechanisms and therapy outcomes for individual patients. In regard to patient selection for CRT, computational studies have demonstrated that several electromechanical aspects of the patient's baseline physiology and pathophysiology can determine the response to CRT. Most consistently, the presence of a marked right-to-left ventricular-activation delay has been shown to be an absolute pre-requisite for response to CRT, which is well-represented by the criteria of QRS widening and left bundle branch block morphology of the QRS complex in current clinical guidelines for CRT^{161–166}. Other modelling studies have found that a prolonged intrinsic atrioventricular conduction time increases the likelihood of acute haemodynamic improvement with CRT because biventricular pacing at a shorter atrioventricular delay increases LV filling time and thereby preload¹⁶⁷. The presence of a myocardial infarct modulates, but does not necessarily preclude, an improvement in ventricular function after CRT^{164,168,169}. Simulations also revealed that the size and location of the infarct are important baseline characteristics, with the observation that the acute haemodynamic response to CRT decreases with increasing infarct size and with a more

lateral location^{168,169}. Another electromechanical modelling study showed that CRT response is decreased when the length-dependence of tension generation — the innate myocardial-tissue property responsible for the Frank–Starling mechanism at the organ level — is compromised^{170,171}.

Studies combining model simulations with experimental and clinical measurements of pacing-induced changes in cardiac electromechanics were the first to show quantitatively the importance of right ventricular myocardial function for CRT response, which was explained by the increase in right ventricular workload during pacing through interventricular interaction^{172,173}. In the past 5 years, simulations of CRT in virtual patients have been used to devise a myocardial strain-based diagnostic index that quantifies a combination of electrical and mechanical substrates amenable to CRT¹⁶⁴. Interestingly, the same study illustrated the added clinical value of a simulation-based design of the diagnostic index by showing that it accurately identified patients with a more favourable outcome after CRT, including those with intermediate electrocardiographic criteria for whom CRT response was less certain according to the current guideline criteria only.

In silico studies on CRT have also contributed to the optimization of therapy delivery. Many computational studies investigated the effect of LV-pacing location on acute haemodynamic response to CRT^{174–178}. Despite the use of different modelling approaches, these studies consistently reported that the lateral LV free wall was the optimal LV pacing location in noninfarcted failing hearts. In the presence of a myocardial infarction, simulation studies have demonstrated that pacing remotely from the infarct zone and multisite pacing using a quadripolar lead were more efficient than conventional CRT^{168,169,179}. Furthermore, the beneficial effect of endocardial LV pacing over epicardial LV pacing was attributed to its relatively faster and, therefore, more synchronous ventricular activation¹⁸⁰. In addition to the number and location of pacing sites, the timing of lead stimulation, configurable through atrioventricular and ventriculo-ventricular pacing delay settings, has also been the subject of in silico optimization studies^{167,175,176,181–183}. Optimal atrioventricular and ventriculo-ventricular delay settings were shown to be highly patient-specific and even to change over time for the same patient¹⁷⁶. The application of virtual-patient simulations for prediction of the response to CRT is less mature. Several personalized modelling studies have shown the feasibility of patient-specific prediction of acute haemodynamic CRT response in small numbers of patients^{175–177,179,184–187}. These successful proof-of-principle studies have demonstrated the translational potential of this emergent technology and brought it an important step closer to being adopted as an actual support tool for clinical decision-making in the field of pacing therapy.

The future of computational models

The advances in cardiac research reviewed above demonstrate the enormous progress made to date in using computational approaches to address both the mechanisms of cardiac dysfunction and the issues related to the clinical application of therapies for cardiac disease. Computational models of the heart now cover most of the biophysical complexity of the individual patient's cardiac pathology. As a result, models linking cellular electrophysiology, myocardial tissue mechanics, and system haemodynamics have become promising platforms

for virtual-patient simulations and for in silico evaluation of novel diagnostic and therapeutic strategies¹⁸⁸. These biophysically detailed models of the heart are having an increasingly important role in the road to personalized medicine in cardiology clinics^{189,190}. In this time of growing regulatory and administrative burdens that restrict the ability to develop new drugs, medical devices and diagnostic technologies, simulations of virtual patients and therapy provide the means for the pharmaceutical and biomedical device industries to reduce the developmental costs of innovation and the time to market¹⁸⁹. Models allow fast evaluation of medical device settings, modes of therapy delivery and patient-selection criteria through relatively low-cost simulation and are thereby poised to complement, augment and even fully replace conventional preclinical and clinical device development and evaluation steps.

Although simulations have made inroads in the clinic, a number of barriers to their widespread adoption remain. Simulation applications in cardiology are currently targeted at a narrow range of heart diseases for which the effect of treatment is well-characterized, imaging and invasive measurements are routinely made and treatment can be evaluated with a short-term measure of success. To broaden the application beyond these conditions and extend the use of simulations in cardiology will require specific challenges spanning model creation, speed and physiological detail of simulations and the communication of model predictions to cardiologists to be addressed. Currently, the customization of cardiac models to represent a specific patient or make a representative model of a specific pathology focuses on how parameters can be inferred directly from clinical data. Although this matter is important to ensure that models are informed by the clinical data available, the desired data will not be available in many potential clinical applications or simply cannot be measured in a clinical context or with sufficient accuracy. Whereas preclinical measurements can be used to inform on unknown or patient model parameters, the uncertainty introduced by these parameters is poorly characterized¹⁹¹. Improved methods for translating preclinical measurements into patient-specific models would substantially improve our ability to create models of a broader range of complex pathologies and robustly and reliably use this information to inform clinical decisions. In turn, this framework for linking animal research to the clinic would shorten development times and improve experimental design of pre-clinical studies. Another approach to this problem of model parameterization is to tailor model complexity, for example the number of model parameters, to the clinical application¹⁹². This approach has been particularly well-developed in cardiac cell models, so that it is large enough to describe the cardiac pathology of interest and small enough to estimate the model parameters reliably from the scarce clinical data^{193–195}.

Personalizing models to patient-specific data requires large numbers of simulations to be performed. The speeds of current simulations limit the ability to create models reliably on clinical timelines and to perform simulation studies on > 40–50 patients¹⁸⁵. This limitation makes the advancement of algorithms and approaches for high-speed simulations of critical importance to enable cardiac modelling to become a routine clinical tool.

Although new developments in algorithms and implementation have improved simulation speed, new modelling tools and techniques still need to be developed to incorporate fine-grained cardiac structural and functional data in the models and enable models to run in a

period of time appropriate for clinical applications^{196,197}. Research efforts need to be invested in dramatically improving the scalability of heart models and simulation standards, in modularizing and interfacing multiple model levels, as well as in preserving and curating models and data in easy-to-access repositories^{198–202}.

All the applications of simulations in cardiology described in this Review focused on predicting short-term responses to treatment such as prolongation in action potential, termination of arrhythmia or pacing-induced improvement of cardiac pump function. However, the primary interest of cardiologists is not in the patient's immediate response after a procedure, but how the heart of the patient will respond in the long term. This limitation of the models poses a physiological and simulation challenge. Simulations of cardiac tissue remodelling and growth are still in their early stages because they are driven by rule-based phenomenological models and require further development of theory and implementation^{8,9,203}. At the same time, the physiology and drivers of remodelling and growth are often characterized by pathway topology and not quantitative dynamics, which limits their utility in quantitative predictive cardiac modelling. The ability to predict how the heart will remodel in response to disease progression or to a treatment is an essential element in making long-term predictions related to clinical outcome and intervention success and will substantially increase the applications of simulations in cardiology.

Finally, communicating model results to cardiologists and caregivers in a simple format and under the right conditions will be critical for the adoption of model predictions in clinical decision-making. The development of electrophysiological and electromechanical models of the heart currently requires a great amount of expertise in several different fields including numerical analysis, computer science, cardiac electrophysiology, mechanics and image processing. Translating the models to the clinic has necessitated the development of interfaces that allow model utilization by clinical non-experts. Even though displaying results of simulations in an office environment presents simple requirements for interface development — a cardiologist should be able to manipulate and examine the results of simulations — the utilization of model predictions in an environment in which procedures are performed, such as in the surgical theatre or catheter laboratory, poses a particular challenge^{204,205}. The generation of model predictions for procedure guidance requires the integration of results from different clinical devices, such as electroanatomical mapping systems (including CARTO (Biosense Webster) and EnSite NavX (St. Jude Medical/ Abbott)), x-ray fluoroscopy or MRI^{206,207}. This application will require working with the technical support staff of the devices to integrate the results of the model with imaging data sets and to dynamically guide the clinical procedure.

Conclusions

Computer models in cardiology have an enormous potential to become the new quantitative approach for detecting and treating cardiac disease given the capacity of these models to provide low-cost, low-risk, rapid and integrative analysis of a patient's physiology and pathology with predictions that are free from subjective assessments. The discipline of computational cardiology will continue to grow and develop, driving new clinical developments and personalization of cardiac care.

Acknowledgements

S.A.N. acknowledges support from the UK Engineering and Physical Sciences Research Council (EP/M012492/1, NS/ A000049/1 and EP/P01268X/1), the British Heart Foundation (PG/15/91/31812 and PG/13/37/30280) and King's Health Partners London National Institute for Health Research (NIHR) Biomedical Research Centre. J.L. acknowledges support from the Dr. Dekker Program of the Dutch Heart Foundation (grant 2015T082) and the Netherlands Organisation for Scientific Research (NWO-ZonMw, VIDI grant 016.176.340). N.A.T. acknowledges support from Leducq Foundation and from the NIH (grants DP1-HL123271 and R01HL116280). M. Strocchi (King's College London, UK) provided assistance with creating the four-chamber heart images in figure 3.

S.A.N. has received support from Abbott, Boston Scientific, Edwards Lifesciences, Pfizer, Roche and Siemens. J.L. has received support from Medtronic.

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Key points

- Computational models of the heart have an important and growing role in cardiology, enabling patients to be diagnosed and treated on the basis of their specific pathophysiology.
- Simulations provide the link between the effects of genetic mutations, physiological regulations or drugs on protein function and emergent cellular and tissue function or clinical phenotypes.
- Models representing an individual patient or a specific pathology are now used to identify the mechanisms underpinning a disease, improve patient selection and predict clinical outcomes.
- Predictive modelling also contributes to the development of new diagnostics and devices and to the tailoring of therapies for individual patients.
- Translational barriers remain regarding model personalization, speed and detail of the simulations and how to communicate model predictions to cardiologists within a clinical environment.

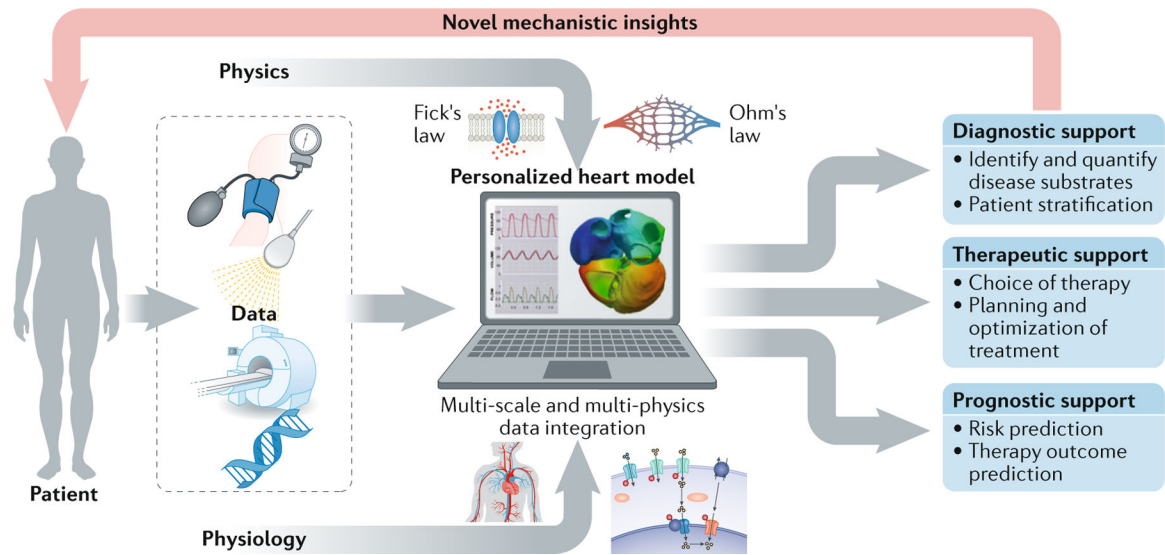


Fig. 1. How can computational models improve current cardiology care?

A computational model of the human heart and circulation enables synergistic integration of multiple diagnostic data obtained with the use of different clinical modalities (such as echocardiography, MRI, electrocardiography, genetics and blood-pressure measurements) in one personalized heart simulation on the basis of widely accepted physical and physiological principles. The personalized integrative nature of such a virtual-patient simulation adds value to the existing clinical workflow by offering more quantitative and objective insight in the underlying disease substrates of a patient. In addition, the model provides a platform for virtual evaluation and optimization of a therapy.

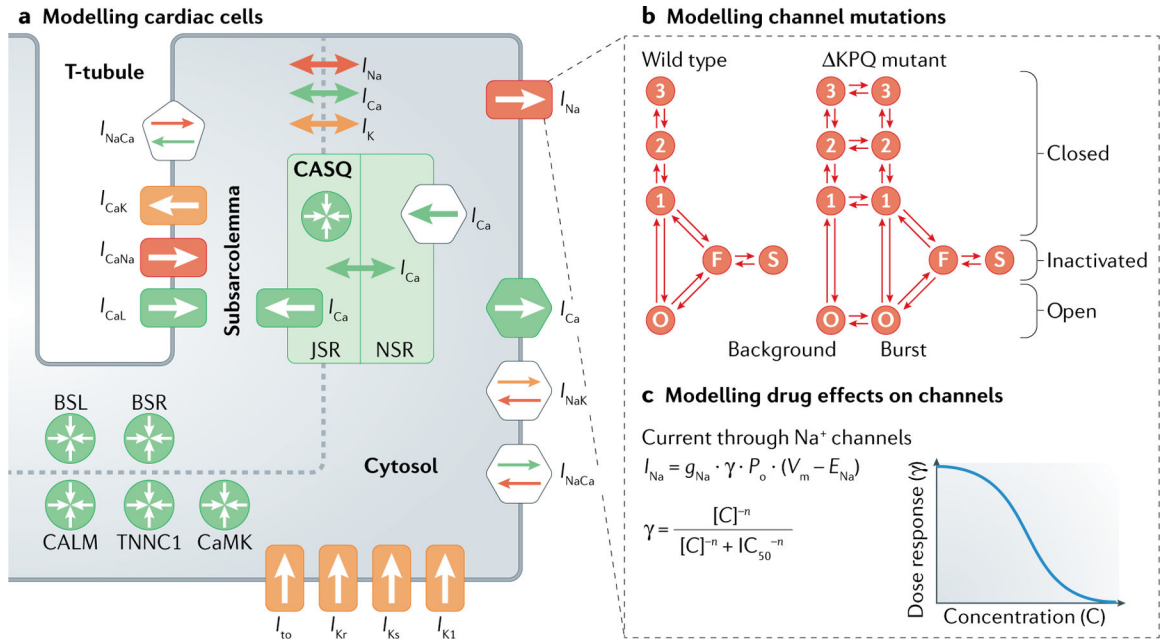


Fig. 2. Modelling cardiac cells, channel mutations and drug response.
a | Schematic showing the level of detail in a cardiac cell model. The model is separated into the transverse (T)-tubule, subsarcolemma, cytosol, junctional sarcoplasmic reticulum (JSR) and network sarcoplasmic reticulum (NSR). The model shows the different ionic currents: Na⁺ current (I_{Na}), K⁺ currents (transient outward K⁺ current (I_{to}), rapid component of the delayed rectifier K⁺ current (I_{Kr}), slow component of the delayed rectifier K⁺ current (I_{Ks}) and inward rectifier K⁺ current (I_{K1})), Na⁺-K⁺ exchange current (I_{NaK}), Ca²⁺ currents from L-type Ca²⁺ channels (I_{CaL} , I_{CaNa} and I_{CaK}), current from the membrane-bound Ca²⁺ pump (I_{Ca}), cytosol and subsarcolemmal Na⁺-Ca²⁺ exchanger currents (I_{NaCa}) and Ca²⁺ currents (I_{Ca}) from the ryanodine receptor and sarcoplasmic reticulum Ca²⁺ pump. The model includes intracellular Ca²⁺ fluxes within the sarcoplasmic reticulum, fluxes of Na⁺, K⁺ (I_K) and Ca²⁺ between the subsarcolemmal space and the cytosol, and Ca²⁺ buffers (calsequestrin (CASQ), calmodulin (CALM), troponin C1 (TNNC1), Ca²⁺/calmodulin-dependent protein kinase (CaMK), anionic sarcoplasmic reticulum binding site for Ca²⁺ (BSR) and anionic sarcolemmal binding site for Ca²⁺ (BSL)). **b** | Schematic of the model of the structure of a wild-type Na⁺ channel in its three possible states: closed, open (O), and inactivated (fast (F) or slow (S)). The structure of the channel is changed with the addition with the KPQ mutation. **c** | Effects of a channel inhibitor compound on the Na⁺ channel current. The current is calculated by: the channel conductance (g_{Na}); proportion of channels in the open (P_o), fast-inactivated or slow-inactivated states; voltage across the cell membrane (V_m); Nernst potential for Na⁺ (E_{Na}); and the proportion of channels that are not inhibited by the compound (γ). The proportion of channels that are not inhibited by the compound is defined by a Hill equation with cooperativity (n) and the half-inhibition concentration (IC_{50}).

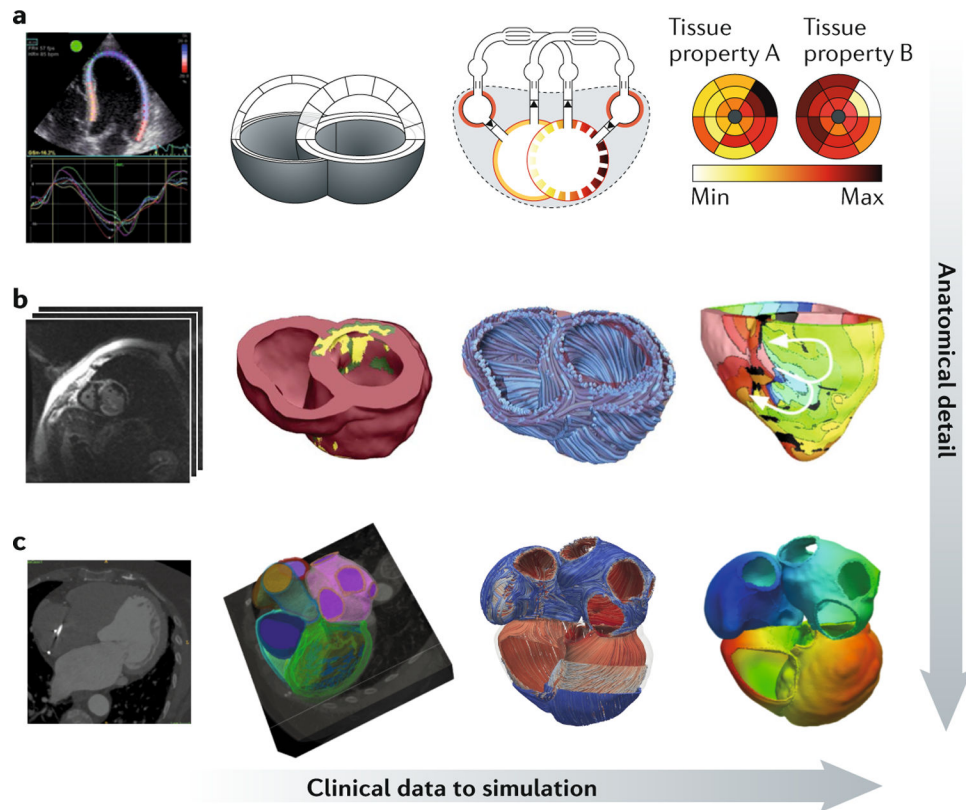


Fig. 3. Linking clinical data to computer models of the heart with increasing levels of anatomical detail.

a | Left to right: echocardiography strain measurements are used to constrain a simplified anatomical model, linked to a closed-loop cardiovascular system representation that can generate model predictions of tissue properties. **b** | Left to right: multimodality MRI data (cine, late gadolinium enhancement, anatomical) can be used to create anatomical models of the ventricles, highlighting structural remodelling (shown in the middle image with labels for viable tissue (pink), border zone (green) and infarct (yellow)); fibre fields can be added to the model and simulations of arrhythmia performed. **c** | Left to right: cardiac CT data segmented to label ventricular and atrial myocardium; fibre fields are generated across the four cardiac chambers, and simulations of atrial and ventricular physiology are performed. Max, maximum; Min, minimum. Part **b** is adapted from REF.⁹⁵, Springer Nature Limited.