REVIEW ARTICLE

Computational cardiac physiology for new modelers: origins, foundations, and future

Jussi T. Koivumäki[1] | Johan Hoffman[2] | Mary M. Maleckar[3] | Gaute T. Einevoll[4,5,6] | Joakim Sundnes[3*]

[1]Faculty of Medicine and Health Technology, and Centre of Excellence in Body-on-Chip Research, Tampere University, Tampere, Finland

[2]Division of Computational Science and Technology, KTH Royal Institute of Technology, Sweden

[3]Computational Physiology Department, Simula Research Laboratory, Oslo, Norway

[4]Centre for Integrative Neuroplasticity, University of Oslo, Oslo, Norway

[5]Department of Physics, University of Oslo, Oslo, Norway

[6]Department of Physics, Norwegian University of Life Sciences, Ås, Norway

Correspondence
Joakim Sundnes,
DepartmentComputational Physiology Department, Simula Research Laboratory, Lysaker, Norway
Email: sundnes@simula.no

Funding information
Academy of Finland Center of Excellence in Body-on-Chip Research, Pirkanmaa regional fund of the Finnish Cultural Foundation (grant numbers 50171514 and 50201322), the Horizon 2020 Research and Innovation Programme (grant number 945539), the Norwegian Research Council, (grant numbers 309762 and 248828), and the Swedish Research Council (grant number 2018-04854).

Mathematical models of the cardiovascular system have come a long way since they were first introduced in the early 19th century. Driven by a rapid development of experimental techniques, numerical methods and computer hardware, detailed models that describe physical scales from the molecular level up to organs and organ systems have been derived and used for physiological research. Mathematical and computational models can be seen as condensed and quantitative formulations of extensive physiological knowledge, and are used for formulating and testing hypotheses, interpreting and directing experimental research, and have contributed substantially to our understanding of cardiovascular physiology. However, in spite of the strengths of mathematics to precisely describe complex relationships, and the obvious need for the mathematical and computational models to be informed by experimental data, there still exist considerable barriers between experimental and computational physiological research.

In this review we present a historical overview of the development of mathematical and computational models in cardiovascular physiology, including the current state of the art. We further argue for why a tighter integration is needed between experimental and computational scientists in physiology, and point out important obstacles and chal-

lenges that must be overcome in order to fully realize the synergy of experimental and computational physiological research.

KEYWORDS
mathematical modeling, cardiovascular physiology, computer models

1 | INTRODUCTION

The aim of this review is to promote and facilitate a tighter integration between experimental and computational physiological research. Detailed computational models describing multiscale physiological processes - ranging from the molecular level to organs and organ systems - have become indispensable research tools in recent decades, as enabled by the rapid development of both experimental techniques and computer technology. However, in spite of the obvious strengths of mathematics in formulating and testing physiological hypotheses, and the equally obvious need for computational research to be guided and driven by experimental data, there are still considerable barriers between experimental and computational physiology. While these barriers may come in many forms, limited interdisciplinary understanding and lack of effective communication across fields is usually a key factor. In the present review, we aim to explain and demystify important concepts of computational physiology and scientific computing, hoping to make *in silico* physiology more accessible to researchers most familiar with *in vivo* and *in vitro* experimental research. Figure 1 provides a graphic illustration of the terms and concepts included here, with font size indicating the relative importance of each term. While we make no attempt to provide an in-depth explanation of all of these, our aim is to open up some black boxes and to provide content and context to the jargon and buzzwords of computational science. Focusing on cardiovascular research, we present a historical overview of the important contributions of mathematics and computations in physiology, and explain key terms of scientific computing and their relevance. We also draw some parallels between computational efforts in studies of the heart and the brain, aiming to identify tools and practices that should be shared between these communities for their mutual benefit. Hopefully, this review may facilitate essential communication between scientific disciplines.

Computational Modeling & Simulation are commonly used for formulating and testing hypotheses, interpreting, and even directing experimental research, and have contributed substantially to progress in physiological research [1]. This is particularly true of the cardiovascular system, where mathematical models have been used in groundbreaking basic science and translational research in the cardiovascular field, see, e.g., [2, 3], and have even provided new clinical methods in the form of *in silico* medicine [4]. Models offer essential tools to further mechanistic understanding of physiological processes. Examples of particular importance include the case where state-of-the-art experimental methods are insufficient to resolve the desired information (e.g., the flow of ions within a subdomain of an intact cell), a scenario wherein data is overly sparse for mechanistic conclusions (e.g., a limited number of patients with a given pathology or few clinical measurements), or to provide efficacy and safety for repeated testing (e.g., as part of clinical trials for new pharmacological compounds). Therefore, multi-scale computational cardiac models may serve several roles in research, and have served as knowledge integrators, permitting the development of conceptual models relying upon diverse sources of information. Additionally, these have enabled mechanism-driven experimental design, as models permit precise isolation of individual variables, a scenario often extremely difficult to achieve *in vitro* due to the complexity and interdependencies of biological systems. Thus mathematics can serve as an "alternative mi-

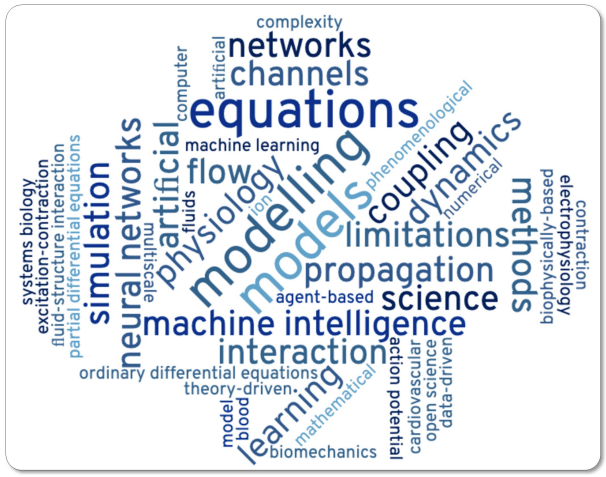

FIGURE 1 Word cloud illustration of the concepts and terminology covered in this review. Font size indicates the relative emphasis within the scope. The aim of this review is to provide a brief introduction to these terms, in order to facilitate interdisciplinary communication as well as motivate further reading.

croscope" – a supplementary tool to see where systems confound and current experimental technologies cannot yet clarify. Computational cardiac models can additionally operate as hypothesis generators; there are several notable cases for which a physiological phenomenon was first observed *in silico*, often years before it was achieved in an experimental setting [5]. Finally, as *in silico* models keep improving, they have the potential to provide insights that are not available via current experimental methods, be these enabled by, for example, advanced imaging techniques or animal models. Beyond the cutting-edge, the benefits of using computational modeling in cardiac research and cardiology are pragmatic. Computer models based on physical principles effectively encode and represent centuries of scientific knowledge, which may be immensely useful in data-driven research based on statistical methods and machine learning. The models may offer a modest, often predictable expense in development and use, enabling cost-savings for projects [6], and can also be employed together with traditional experimental methods, enabling attention to the responsible use of animal models [7].

Despite these key advantages of applications of computational modeling and recent inclusion into both the biomedical science and health domains, much wider knowledge and adoption in cardiovascular research would be beneficial. Shared competence in computational cardiac modeling will continue to deepen insight and accelerate knowledge in cardiovascular physiology, as well as create downstream benefits in cardiology care. In this review we aim to present and discuss the current state of the art in computational cardiac physiology, including its potential clinical applications. The potential for clinical applications, as well as the clinical utility of improved understanding of cardiac (patho-)physiology, have been important drivers for the development of computational physiology models. The clinically motivated development of fundamental physiological models makes it difficult to clearly separate *computational physiology* and *computational medicine*, and we will therefore address both. We mainly focus on the classical style of physiology models that are derived from physical principles and theory, but for context and perspective, we also touch upon relevant data-driven methods such as machine learning. The remainder of the review is organized as follows. In Section 2.1, we explain what we mean by computational modeling and give a brief introduction to key concepts of modeling as well as fundamental cardiac physiology. Section 3 summarizes the current state of the art in

cardiovascular modeling and provides a brief summary of alternative and supplementary model frameworks, including machine learning, as well as methods for assessing the quality of model results. Section 4 outlines a number of key barriers to further exploitation of computational models, while Section 5 delineates possible directions to overcome these barriers and presents brief concluding remarks.

2 | MODEL FOUNDATIONS

2.1 | Foundations of mathematical and computational modeling

The term model can have many different meanings in the context of medicine and biology. Here, we restricted our attention to mathematical and computational models, that is, models defined by a system of equations or a well-defined set of rules (i.e., an algorithm) and are intended to describe some biomedical phenomenon. Even with this restriction, there are numerous and vastly different categories of these models. For instance, statistical models embody certain assumptions on the statistical properties of observed data, biophysical models aim to describe the underlying mechanisms that give rise to such observations, while phenomenological models aim to describe an observed phenomenon with a simplified set of mathematical relations and parameters, not necessarily aiming to capture the underlying physics. Although this nomenclature and classification of models is relevant and useful in many cases, the borders between the model classes are not sharp. Many biophysical models include model components of a statistical or phenomenological nature, and phenomenological models can often be viewed as simplified biophysical models. Although all three modeling approaches have been used with success in medical research, statistical models are by far the most ubiquitous, being a cornerstone of both clinical and experimental research.

In recent years, these traditional modeling approaches have been supplemented by machine learning (ML) and artificial intelligence (AI), which have had a massive impact on many fields and are emerging as important tools in medicine as well. In terms of model categorisation, many ML methods are examples of classical statistical models, while artificial neural networks (ANNs) can be viewed as a distinct category of statistical models: biologically-inspired computer models used for tasks such as prediction or classification (see, e.g., [8, 9]). In certain ANN *architectures*, these may popularly be termed "deep learning" models. The emerging success of ML methods has also increased the relevance of another categorisation of modeling approaches: that of *data-driven* versus *theory-driven* modeling. The typical example of a data-driven model is an ML algorithm with no built-in knowledge or assumptions of the underlying physics, which is *trained* on empirical data to give predictive capabilities. On the other hand, a typical theory-driven model involves a mathematical formulation that describes the underlying physics, for instance, a biophysical model of an excitable membrane, where all variables and parameters have a physical interpretation. In reality, the border between these categories is blurred, since theory-driven models often include *constitutive relations* based solely on empirical data, and data-driven models may be informed or constrained by physical reasoning (see, e.g. [10, 11]).

In this review, we will mainly focus on the huge and largely unrealized potential of theory-driven models, used on their own for hypothesis testing or clinical decision support, or as a supplement to ANNs and other ML methods. The latter application, effectively combining classical theory-driven models with modern ML, is an emerging sub-field which is particularly promising for reducing training data requirements by encoding established information into ML techniques. Typical examples of theory-driven models are electrophysiology models derived from fundamental laws such as Maxwell's equations and Kirchhoff's laws, tissue mechanics and fluid flow models based on Newton's laws of motion, and biochemical transitions described by the fundamental principles of chemistry. Such models have a long history in physiology and medicine, including models of blood flow derived centuries ago (e.g., [12]), and detailed models of neurons [13] and muscle mechanics [14] dating back to the 1950s. However, the potential of such modeling

has increased substantially in the last 3-4 decades, driven by rapid advances in computing power, numerical methods, medical imaging, and experimental techniques. Patient-specific and clinically-driven models have been active areas of research for at least two decades, see, for instance [15, 16, 17, 6, 18, 19], but there are still relatively few examples (e.g., [4]) of direct clinical use of computational models. The purpose of this review is to advance this situation by presenting and discussing the state of the art and the success stories of computational models in medicine, as well as the important challenges and obstacles towards increased use in cardiovascular research and in clinical settings.

Common to most of these biophysically based models is their formulation in terms of differential equations: mathematical relations between unknown functions and their derivatives, i.e., between *physical quantities* and their *rate of change*. A simple example is the relationship between position, velocity, and acceleration in kinematics, and how these relate to forces through Newton's second law. Because of the complexity of the processes involved, relevant models in physiology tend to be complex systems of partial differential equations (PDEs) that relate spatial variations of physical quantities to their temporal dynamics. The most important of these models in the context of cardiovascular physiology include the bidomain model coupled to cell electro-chemistry models, for describing cardiac electrophysiology [20]; soft tissue continuum mechanics models describing the deformation of blood vessels and the heart muscle [21, 22]; and Navier-Stokes equations describing the flow of blood [23]. All of these models are complex systems of nonlinear PDEs, which are impossible to solve analytically, and need to be solved using numerical methods and computers. These computational tools have evolved immensely over the last few decades, and this evolution has been an important driver for a rapid increase in complexity, realism, and relevance of physiological models that can be derived and studied.

2.2 | From differential equations to algorithms and software.

A challenge of dealing with increasingly complex physiological models is that the fundamental equations, and therefore the underlying physics, tend to be hidden inside black boxes of complex algorithms and software. Model users are often left with the choice of either trusting the models, with little insight into the underlying computations, or of diving deep into the details of complex numerical software tools. Neither of these solutions is very satisfying, and it should be a key goal for computational software developers to include appropriate documentation as well as thorough verification and validation of software tools. Such measures, discussed in more detail below, will allow non-technical and new users to gain the necessary insight and trust without having to perform an in-depth assessment of numerical and algorithmic details.

Nevertheless, some degree of fundamental knowledge about numerical methods and software is, of course, valuable for any user of such tools. An introduction to numerical methods is well beyond the scope of this text, but in this paragraph, we provide a brief explanatory presentation of the fundamental ideas common to all computational software. Mathematically, classical solutions to differential equations come in the form of mathematical formulae that solve the equations of interest, and typically offer the quantity or quantities of interest as a function of space and time. However, the analytical treatment of differential equations is based on the concept of infinity, which is an ill-suited concept for a computer, which deals only with finite numbers. As a concrete example, consider a model (i.e., a differential equation) describing blood flow in an artery, for which the solution is the fluid velocity and pressure in every point inside the vessel. Since there are infinitely many points, the solution is infinite-dimensional, and ideally we would aim to find mathematical formulae that specify the velocity and pressure as functions of position and time. However, for most realistic and relevant models such formulae is impossible to find, and the solution must instead rely on numerical methods based on finite numbers, which construct *approximate* solutions to the equations. Common to all such methods is that the solution is approximated as a parameterized mathematical function, e.g., $u = f(t, x, \lambda)$,

where t is time, x is the spatial coordinates, and $\lambda = \lambda_i, i = 1, \ldots, n$ is a list of parameters. The n parameters are then determined so that u approximates the true solution u_{exact} for all values of x and t.

Depending on the choice of solution method, i.e., the choice of the approximation function $u = f(t, x, \lambda)$, the parameters λ_i may or may not have a physical interpretation. In commonly applied engineering methods such as finite element, finite volume, and finite difference methods, these parameters actually represent approximate values of the solution in discrete points in space and time. We then have $\lambda_i = u_i$, where u_i are approximates to the true solution u_{exact} in discrete points, corresponding to nodes in a mesh that approximates the physical domain of interest, see Figure 4 for an example. While it is somewhat unusual in these methods to view the discrete solution values u_i as parameters in an approximating function, formulating the methods in this general way is useful to see the relation between all the methods, and in particular the commonalities between classical engineering methods and emerging methods such as deep learning. Other relevant methods include spectral methods, which approximate the solution as a weighted sum of predefined mathematical functions, or deep neural networks, where the parameters represent the *weights* and *biases* of the activation functions [24].

Methods for determining the parameters λ fall into three categories: (i) minimization methods, where the approximation is selected from a finite dimensional approximation space as the function which minimizes a residual, that is, the degree to which a function fails to satisfy the differential equation; (ii) projection methods, where the approximation is obtained by orthogonal projection, as the function for which the residual is orthogonal to the finite dimensional approximation space; or (iii) collocation methods, where the approximation is determined to be exact in a finite number of collocation points. A least squares method is an example of a minimization method, a Galerkin finite element method is a projection method, and a finite difference method is an example of a collocation method. See, for instance, [25] for a comprehensive overview of computational methods.

The accuracy of the solution depends on the number of parameters used in the approximating function, often referred to as the solution's *degrees of freedom*. In finite element and finite difference methods, increasing the number of degrees of freedom involves increasing the density of nodes in the mesh, which allows for improved accuracy of the geometrical representation as well as that of the solution itself. In spectral methods, increasing the number of degrees of freedom means that we approximate the solution using a richer set of mathematical functions, while in the case of a deep neural network, it means to increase the number of layers in the network or the number of nodes in each layer. In all cases, the result of more degrees of freedom is a potentially more accurate solution, at the cost of increased computational effort. Accurate simulations of complex physical phenomena may require billions of degrees of freedom and the computational expense can be substantial. In such cases, it becomes essential to utilize efficient numerical methods that run on powerful computational hardware. The complexity of deriving and implementing such methods is a significant obstacle towards more widespread use of detailed computational models in cardiovascular research. Increasing the availability of reliable and well documented computational software tools is an important step for advancing the use of biophysical models, and in particular for advancing their use among researchers and clinicians without formal training in mathematics or scientific computing. Such software tools are being developed for a number of cardiovascular modeling applications, and many of them are made freely available to the research community (see, e.g., [26, 27, 28, 29, 30, 31]). However, although many of these packages have been developed over several decades and are highly capable and feature-rich, most of them are still lacking in documentation and user-friendliness and have a very steep learning curve for non-expert users. These topics will be discussed in more detail below.

2.3 | Anatomical and physiological background

Here, we offer an overview of heart anatomy and the physiological processes that are the main targets in computational cardiovascular modeling. A more nuanced and detailed presentation can be found in, for instance [32, 33] and the reviews cited in this section.

In spite of all of its emotional connotations, the heart's fundamental function is that of a mechanical pump that drives blood through the circulatory system. The heart consists of four chambers; the smaller left and right atria (LA and RA, respectively) and the larger left and right ventricles (LV and RV, respectively). From the lungs, i.e., the pulmonary circulation, oxygen-rich blood enters the LA, is pumped into the LV, and then out into the systemic circulation through the aorta. At the capillaries of the systemic circulation, the blood perfuses tissue to deliver nutrients and remove waste. Deoxygenated blood returns to the heart via the venous system into the RA, the RV and back to the lungs through the pulmonary circulation. This flow of blood is driven by the rhythmic contraction and relaxation of the heart muscle tissue, in combination with valves at the openings in and out of the ventricles to keep the blood flowing in the correct direction. During the relaxation phase, known as *diastole*, the cavity pressures in both ventricles drop below the venous pressures, causing the inlet valves to open and the ventricles to fill with venous blood. Then, as the heart tissue contracts, known as *systole*, the cavity pressures increase, first causing the inlet valves to close, and then the outlet valves to open when the pressures rise above the arterial pressure. The pressure differences between the ventricles and arteries then drive the blood flow into the arterial system. Pressure differences in the cardiovascular system are also reflected in the overall anatomy of the heart. The resistance of the systemic circulation is much higher than that of the pulmonary circulation, and, consequentially, the pressure needed to drive the flow into the body's arteries is much higher. The cavity pressure in the LV is therefore higher than that in the RV, and, thus, the LV is the thickest and strongest muscle in the heart. The movement of the heart is constrained by connections to surrounding tissues and organs, though between the pericardium (the fibrous connective tissue surrounding most of the heart) and the outer layer (epicardium) of the heart, a thin film of pericardial fluid allows the movement of the heart to be almost frictionless [34].

The contraction of the myocardium is initiated and regulated by an electrical signal originating in the *sino-atrial (SA) node*, which is a collection of so-called pacemaker cells (which generate their own action potentials; see next paragraph) located in the RA. From the SA node, the electrical signal first propagates through the atria to trigger their contraction, then enters the ventricles through the *atrio-ventricular (AV) node*, and then propagates quickly through the ventricles via the bundle of His and the Purkinje system (see e.g., [32] for a detailed illustration and explanation of this specialized cardiac conduction system). At the end of the Purkinje cells, the signal enters the cardiomyocytes (CMs, cardiac muscle cells), and is conducted through the rest of the cardiac muscle by the auto-excitability of these CMs, as explained below.

CMs are excitable cells, just like neurons and other muscle cells, meaning that they respond to an electrical stimulus by going through an *action potential (AP)*. At rest, the interior of CMs are negatively charged compared with the surrounding domain, giving rise to a transmembrane potential difference close to -90mV (for e.g., ventricular CMs). During the AP, the membrane quickly depolarizes, then stays at approximately zero (0) potential difference for a while (100-300 millseconds in human CMs; the plateau phase), and then returns to the negative resting potential (via a process known as repolarization). This cycle is achieved via membrane channel proteins, principally voltage-gated ion channels permeable to specifically sodium, calcium and potassium ions, as well as a number of ion pumps and exchangers. While all of these ions are crucial for the excitability of the cells, calcium plays a special role in CMs and other muscle cells as the trigger for contraction. During the plateau phase of the AP, calcium flows into the cell through the cell membrane, which triggers a release of more calcium from a complex intracellular storage system known as the

sarcoplasmic reticulum (SR) [35]. This process, known as calcium-induced-calcium-release, gives a tenfold increase in the intracellular calcium concentration, which triggers the contractile apparatus of the CMs. The main contractile units of the CMs, called sarcomeres, are made up of overlapping thick and thin filaments. The increase in intracellular calcium concentration causes calcium to bind to dedicated proteins (troponin C) on the thin filaments, which allows the formation of *crossbridges* between the thin and thick filaments that make up the sarcomeres, which are the main contractile units of the myocytes. The resulting cross-bridge cycling, where cross-bridges continuously attach, twist, and detach, cause the individual sarcomeres and the entire myocyte to shorten.

The CMs constitute independent excitable and contractile units, and substantial knowledge about the heart's function has been extracted from studies and models of individual cells. However, the function of the heart results from the coordinated action of billions of cells, and many important aspects of its function can only be studied and understood at the tissue- and organ scale. CMs have cylindrical shape, and are organized in a fibre-like structure, which gives the heart tissue direction-dependent (anisotropic) electrical and mechanical properties. While excitation and contraction occurs at the level of the individual heart cell, the cells are both electrically and mechanically coupled, and they can be viewed as a functional syncytium, meaning that their micro- and ultrastructure allow them to function as a continuously excitable and contractile tissue. This property is conveniently utilized in models of both electrophysiology and mechanics, as will be summarized in subsequent sections. Electrical conduction through the tissue takes the form of a sharp wavefront of depolarization, which is typically modeled as a *reaction-diffusion* process described by the bidomain equations, as briefly mentioned above.

The excitation-contraction coupling process described for individual myocytes above, initiated by the AP and resulting in myocardial contraction, governs the development of *active force* in the muscle. However, the overall mechanical state of the heart additionally depends on its passive properties. The stress in the myocardium (force per area) is set up by both the elastic force counteracting material stretching during contraction and the active force generated from the cross-bridge cycling. Even at the most relaxed phase of the heart cycle, some stress remains from the previous contraction and the low cavity pressure in early diastole. Thus, the heart and the cardiovascular system at large is a system which is always loaded, and continuously adapting.

3 | STATE OF THE ART

A primary goal of this review is to motivate and facilitate increased collaboration between experimental and computational physiologists. As such, it is useful to give a brief overview of the state of the art in computational cardiac physiology, focusing on the status of models for individual components of the cardiovascular system, ranging from models for ion channels and CM electrophysiology to tissue mechanics and blood flow. Advances in medical imaging and experimental methods have been central to the development of increasingly complex and detailed models of the cardiovascular system. A few examples of image based modeling are provided in Figure 2, which illustrates the close link between computational models and imaging on all spatial scales.

3.1 | Models of ion channel and cell electrophysiology

As CM electrophysiology has many similarities with neuronal cells, the basis for modeling has been drawn from the pioneering squid giant axon work of Hodgkin and Huxley [13]. The first CM model by Noble [36] predicted the AP in a generic mammalian Purkinje cell model based on three currents: sodium, potassium, and a background current. Since then, the number of models describing the specifics of different species and CM types has grown steadily [37].

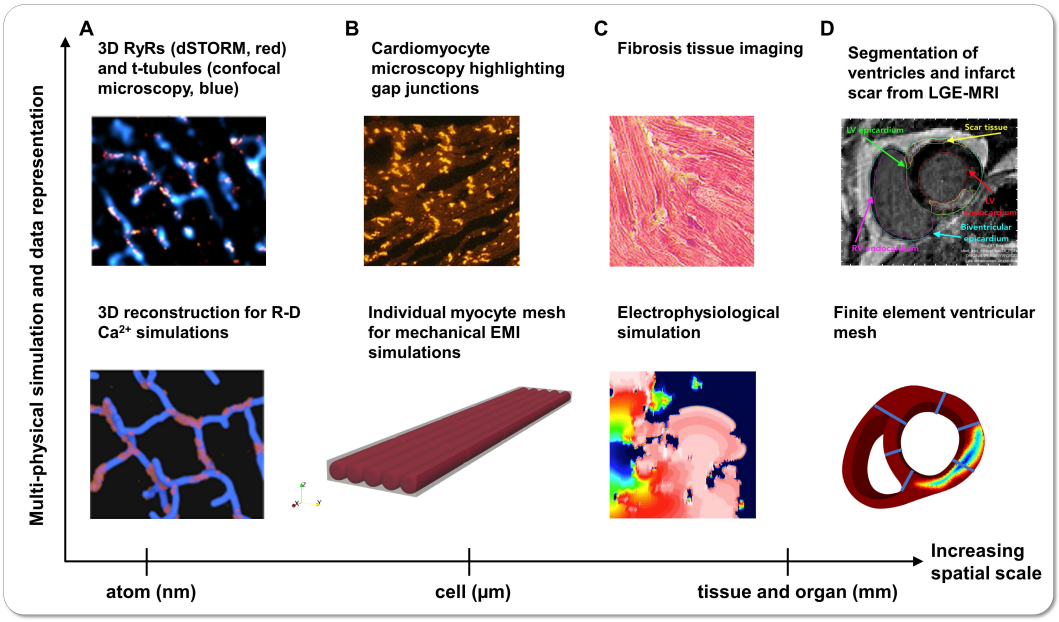

FIGURE 2 Examples of linking imaging and functional data to computational models and simulations at different biophysical scales. A) 3D direct stochastic optical reconstruction microscopy (dSTORM) imaging of Ryanodine receptors (RyRs) combined with confocal imaging of transverse tubules (T-tubules), and corresponding 3D mesh for reaction diffusion (R-D) simulations for calcium ions. B) Labeled imaging of gap junctions in a cardiomyocyte, and the analogous mesh for mechanical simulations using the so-called EMI model that represents explicitly the extracellular Space (E), cell membrane (M) and intracellular space (I) of a collection of cardiomyocytes. C) Light microscopic imaging of cardiac fibrotic tissue, and an electrophysiological simulation (membrane voltage displayed) based on that geometrical mesh. D) Segmentation of ventricles and infarct scar from late gadolinium enhanced (LGE) magnetic resonance imaging (MRI), and visualization of the damaged tissue in a finite element mesh.

However, for decades there was cross-species parameter inheritance [38]. This was common also for the early human ventricular cardiomyocyte (hV-CM) models [39, 40, 41], but more recent ventricular cell models have been based fully on human data [42, 43]. A full species coherence in source of parameters is yet to be reached in the atrial, sinoatrial, and induced pluripotent stem cell-derived (hiPSC-CM) models, for reviews, see e.g., [44, 45, 46].

While the Hodgkin-Huxley channel gating formalism remains widely used in CM electrophysiology models, recent models are increasingly replacing it with more general Markov chain models, that may more readily be linked to the underlying protein function. A Markov model consists of a set of states that correspond to different protein configurations, for example, the open and closed state of an ion channel. A set of equations which describe the transitions between these states can depend on, for instance, ion concentrations, membrane voltage (V_m), temperature, or drug concentrations. When a channel is in the open state, it allows specific ions to flow through and carry electrical current, driven by the electrical potential difference and concentration difference across the membrane. A fundamental concept for describing the ion movement is the reversal potential, i.e., the Nernst equilibrium potential for ion X (E_X), which is the membrane potential for which the net flux of ion X is zero. A membrane voltage $V_m \neq E_X$ will drive electrical current through the open ion channels. The most common model for calculating the current is a linear model based on Ohm's law, i.e., $I_X = g_X(V_m, time)(V_m - E_X)$, where I_X is the current carried by ion X and g_X is the conductivity of the given channel. However, some ion currents are better described by the more complex and nonlinear Goldman–Hodgkin–Katz equation [47, 48]. For a comprehensive review of this topic, see, e.g., [49].

CMs contain a large number of different ion channels, pumps, and exchangers, and the composition varies between different species as well as between different regions of the heart. The extent to which this complexity is accounted for in a mathematical CM model ranges from phenomenological to mechanistically detailed models. For example, the ventricular CM model by Fenton and Karma [50] contains only three prototypical transmembrane currents: a fast inward Na^+, slow inward Ca^2+, and slow outward K^+. Despite its simplicity, the model can still reproduce "higher level" features of electrophysiological data, such as AP morphology and conduction velocity restitution. At the other end of the complexity spectrum is, for example, the O'Hara et al. [42] hV-CM model that describes 1) unique properties of close to 20 different ion channels, pumps and exchangers, 2) fluxes and concentrations of Na^+, Ca^2+ and K^+ in three different intracellular compartments, and 3) even some aspects of enzymatic signalling. The principle of AP simulation is exactly the same in these two very different CM models; calculating the net transmembrane flux of ions gives the time course of V_m. The iterative nature of model development is demonstrated well in the case of the O'Hara et al. hV-CM model [42]. After its publication in 2011, this model has been updated and extended to include features such as cellular myofilament mechanics [51], beta-adrenergic regulation of ion transporters [52], improved prediction accuracy of drug-induced arrhythmias [53], physiologically accurate balance of de-/repolarizing currents [54], and more detailed intracellular Ca2+ dynamics [55].

3.2 | Modelling action potential propagation

As noted above, the structure of CMs and their coupling allows the cardiac tissue to be modeled as a functional syncytium, thereby neglecting the discrete and cell-based nature of the process (for a review see, e.g., [56]). A continuous description of cardiac tissue can be obtained by homogenizing the discrete representation as a resistor network [57], where CMs are coupled diffusively via V_m [58]. While recent work has highlighted applications and mechanisms that require a representation of the tissue's discrete nature [59, 60, 61], a continuum approximation remains the standard for tissue-scale cardiac electrophysiology. The reference model is the *bidomain model* [62], which assumes continuous and overlapping extra- and intracellular spaces, as well as a continuous and spatially distributed cell membrane. The model is derived from first principles: conservation of charge in these domains in combination with known properties

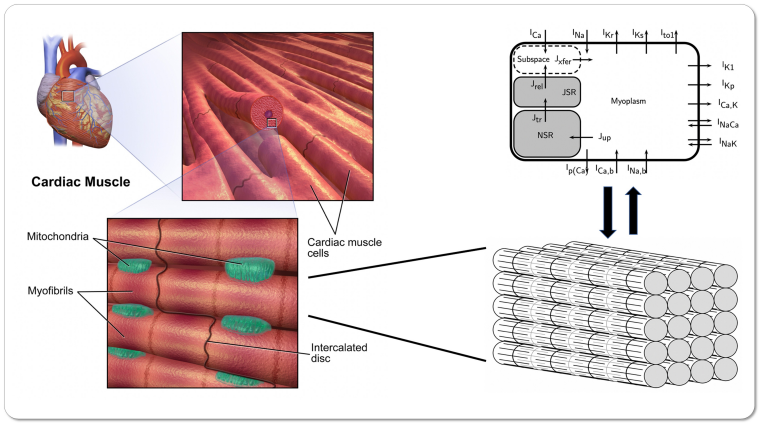

FIGURE 3 Illustration of the multiscale nature of cardiac electro-mechanics models. The functional units of the heart tissue are the cardiomyocytes, which in turn are filled with bundles of contractile units called myofibrils (bottom right). The contraction of the myofibrils is controlled by calcium concentration within the cardiomyocyte, in turn controlled by the electrical activation of the cell membrane, which is driven by the opening and closing of highly specific ion channels in this membrane. State-of-the-art electro-mechanics models describe the two-way coupling between electrophysiology and mechanics on the cellular level, and how these integrate to define the function of the complete organ. (Figure adapted from *https://commons.wikimedia.org/wiki/User:BruceBlaus*)

of current across the membrane, i.e., the CM membrane models outlined above. A popular simplification of the model is the *monodomain model*, which assumes equal ratios of anisotropy between the intra- and extracellular spaces. Models with more domains have also been derived. For example, [63] expanded the bidomain model to include a third domain representing cardiac fibroblasts. However, the standard bi- and monodomain models remain, by far, the most widely used, and capture many important characteristics of cardiac electrophysiology.

3.3 | Models for cell- and tissue contraction

The force generation in muscle cells results from a complex interplay of thin and thick filaments, and mathematical models for these processes date back to the seminal works of Hill in the 1930s [64], and Huxley in the 1950s [14]. The Hill muscle model is a phenomenological model providing a fairly simple relation between developed force and the velocity of shortening, and is widely used in musculo-skeletal models and cardiac models alike. Huxley's models, on the other hand, provide a detailed description of the formation of cross-bridges between thin and thick filaments, and how the cross-bridge formation and consequent force development depend on muscle length and shortening velocity. Although being a huge contribution to the fundamental understanding of muscle cell mechanics, and still having wide utility in physiological research, Huxley's models are generally considered too complex and computationally demanding to be used in tissue-level mechanics models. Intermediate models have been derived that aim to describe the underlying physics using a lumped approach based on ordinary differential equations (ODEs), and avoid the extensive complexity of the Huxley type of models. Important contributions in this category include the so-called HMT model and subsequent developments [22, 65]. These models are structurally similar to the ODE-based models for cell electrophysiology in Section 3.1, and describe the dynamics of calcium binding the thin filaments, exposing the binding sites for cross-bridges, and the subsequent cross-bridge formation and force development. The important

force-velocity relationship is captured by a phenomenological model of Hill type. More recent model approaches aim to capture even more of the underlying physics, by describing the cross-bridges as linear springs, where the developed force is the product of the spring stiffness and the cross-bridge distortion [66, 67]. Arguably, the most influential model of this kind in the cardiac modeling community is that of Rice et al [67], which was deliberately developed to faithfully capture as much physical detail as possible while retaining a computationally efficient ODE-based framework. The overall model is a mix of biophysical and phenomenological components, and is readily coupled with both cell level electrophysiology and tissue level mechanics models. More recent models have been derived and adapted to experimental data from various species, most notably human [68]. As noted in Section 2.3, the deformation of the heart muscle results from the interplay between the active contraction of the cardiomyocytes and the passive mechanical properties of the tissue. The dynamics of the tissue is described within the framework of continuum mechanics, or more specifically within *nonlinear solid mechanics*, see, e.g., [69] for a detailed overview. Building on the well established framework of continuum mechanics means that models and solvers can exploit vast amounts of tools and theory developed over several decades. Typically, the mechanics model itself is a fairly standard version of an fundamental mechanics law called Cauchy's first equation of motion, which expresses balance of internal and external forces. However, application of such models in a realistic scenario is challenged by complex geometries, dynamic boundary conditions, strongly nonlinear material behavior, as well as the dynamic and adaptive behavior of living tissue. Figure 3 illustrates the multiscale nature of cardiac electro-mechanics models. The electrical and mechanical behavior of the complete organ is governed by sub-cellular structures such as ion channels and sarcomeres. An interesting historical overview of the development of cardiac mechanics models can be found in [70].

3.4 | Fluid dynamics and fluid-structure interaction.

The Navier-Stokes equations is a system of nonlinear PDEs that models the fluid dynamics of the cardiovascular system, in which the velocity and pressure of the blood is determined by its density, viscosity and the external forces acting on the blood volume. The tissue mechanics of blood vessels also influences the velocity and pressure of the blood flow, a coupled system of nonlinear PDEs, referred to as fluid-structure interaction. In the chambers of the heart and the larger blood vessels, the macroscopic blood flow is often approximated to be Newtonian, i.e. assuming a linear relationship between stress and strain. But in the smaller blood vessels, the nonlinear nature of the blood must be taken into consideration, while on the other hand the 3D Navier-Stokes equations often can be reduced to 1D or 0D models [71].

Blood flow and the stiffness of the vessel walls is not the only fluid-structure interaction in the cardiovascular system. The blood flow in the heart represents another fluid-structure interaction problem to model. The endocardium is in contact with the blood inside the chambers, and the function of the heart valves relies on the interplay between the blood and the leaflets. Fluid-structure interaction simulations are both used to study the native valves, and to optimize the design of prosthetic heart valves, see e.g. [72, 73, 74].

Idealized models of blood flow in the heart can be used to improve diagnosis and treatment, see e.g. [75], and computational modeling also enables sensitivity studies with respect to the different parts and parameters of the flow system, see [76]. A more direct clinical application of computational methods is patient-specific simulations, where computational models are tailored to individual patients based on data from medical imaging [2]. To date, a majority of the patient-specific cardiovascular simulations have focused on the left ventricle of the heart, see e.g [77, 78, 79, 80, 81, 82], but there also many other studies, addressing e.g., abdominal aortic aneurysms [83] or coronary artery disease [4].

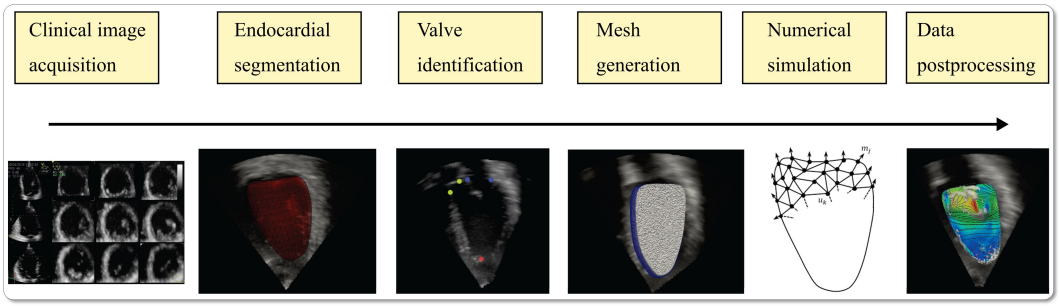

FIGURE 4 Illustration of a pathway for patient-specific simulation of the blood flow in the left ventricle of the heart, with all the steps from clinical image acquisition to data post-processing (reprinted from Larsson et al. [82]). The steps described from left to right are: (i) acquisition of ultrasound images (echocardiography), (ii) segmentation of the left ventricle endocardium for a series of time instants, (iii) identification of the mitral and aortic valves, (iv) generation of a 3D tetrahedral mesh of the left ventricle which is deformed over the cardiac cycle according to the segmented endocardium, (v) finite element simulation of the blood flow in the left ventricle, (vi) visualization and analysis of the simulation data.

3.5 | Multiscale and multiphysics models

The components of the cardiovascular system are of course tightly interconnected, and the model components outlined above should, in principle, not be viewed in isolation. However, all models are simplifications, and the ability to isolate individual mechanisms and sub-systems is one of the main strengths of mathematical and computational models. Consequently, significant insight can be gained from studying individual system components using isolated models as outlined above. The majority of developed cell models concern only electrophysiology and neglect cell contraction, nearly all simulations studies based on the bidomain model completely neglect the deformation of the heart, and most whole-heart mechanics models include very crude representations of both electrophysiology and blood flow. Such simplifications are important for reducing the computational cost of the models, and for facilitating analysis and interpretation of results, by reducing the overall model complexity and isolating the mechanisms under study. It should also be noted that, even with these simplifications, most of the models discussed in this review describe complex processes occurring on a wide range of spatial and temporal scales. As such, most of the models could be correctly classified as multiscale and multiphysics models, although the latter term is usually reserved for models that couple electrophysiology and mechanics.

Significant exemptions where the individual model components cannot be viewed in isolation exist. The most well-known case may be the study of mechano-electric feedback (MEF) mechanisms on the cell- and organ-levels, which clearly require a degree of two-way coupling between the electrophysiology and mechanics models [84]. The potential role of MEF in arrhythogenesis has been an important driver for this development, and a number of research groups have developed advanced models of coupled electro-mechanics, see for instance [85, 86, 87, 88, 89, 90, 91, 92]. Similarly, the development of fluid-structure interaction (FSI) models that couple tissue mechanics with blood flow has mainly been driven by investigations of valve mechanics. Valvular disorders are common and represent a substantial clinical problem [93]. The healthy function of the heart valves relies on a complex interplay between the valve leaflets, blood flow, and surrounding tissues. Capturing all these details in a computational model leads to extremely challenging FSI problems. However, such complexity is needed to answer clinically relevant questions, and this has driven the further development of advanced and complex models [94, 95, 74, 96, 93, 97, 98].

A similar clinical or scientific driver has been more difficult to identify in the coupling of tissue electro-mechanics with detailed models of blood flow, and the literature contains relatively few such models. Significant exemptions are the multiphysics heart model implemented in the Alya code from Barcelona supercomputing center [99], and the University of Tokyo multiphysics model of the heart implemented in the UTHeart code [100, 101].

3.6 | Alternative model frameworks and concepts

In this review, we have focused our attention on mathematical and computational models and broadly introduced model classifications in terms of statistical and biophysical models, or, equivalently, data-driven and theory-driven models. As noted, we have devoted the review primarily to biophysically-based modeling approaches for the cardiovascular system, underpinned by complex systems of nonlinear differential equations. However, although differential equations are ubiquitous in physics and science, there are other relevant mathematical formalisms for computational modeling of the cardiovascular system and its cells and tissues. A few examples will be offered here to orient the reader and to suggest further reading.

Machine learning (ML) in cardiovascular medicine was introduced in Section 2.1 above. In the context of alternative model formulations, the most noteworthy subset of ML methods may be artificial neural networks (ANN). These are models based on initially bio-mimetic neural networks, in which layers of "neurons" are activated, and the connections between neurons are described by "weights" - the strength of connections - that are updated through an optimization process as the network "learns" a given task. ANN architectures which use multiple layers of artificial neurons to learn from the data have come to be known as *deep learning*. In recent years, deep learning has offered revolutionary improvement to a wide variety of tasks in biological and biomedical research, including image processing and classification, genomic analysis, drug discovery, and risk prediction, among others, with a focus on utilizing large and disparate data sets ("big" and multi-modal data). In cardiovascular research, deep learning has increasingly been used for predictive clinical tasks, see e.g. [102], and has also been combined with other mathematical formalisms, including biophysical models, to both improve predictive capabilities of models and to lend mechanistic insight into the system at hand [103, 104]. Also notably, *agent-based modeling (ABM)* [105] is a class of models used to simulate the actions and interactions of many autonomous agents (which could be individuals, or themselves organizational units) as a way to assess and predict the emergence of higher-level phenomena in complex systems. ABM have been used, for example, to model blood vessels and blood flow [106], particularly during growth and remodeling, and may be combined with reaction-diffusion systems (continuum approaches) as described by partial differential equations [107, 108]. More broadly, this class of models is widely used in healthcare research and has been used to model preventative interventions in at-risk populations over time [109].

Systems biology is a diverse and broadly defined field that takes an integrative rather than singular, reductionist view, and may avail itself of the integration of multiple models and modeling approaches appropriate for the system being studied. As such, most of the physiological models introduced in this review can be defined as systems biology models, which aim to explain how components and mechanisms interact and function together in cells and tissues. However, although systems biology is often defined in a way that includes models on all physical scales, the term is more commonly used for models describing systems and interactions on the scale of genes and proteins. Furthermore, *systems medicine* (https://www.casym.eu) approaches in cardiovascular healthcare are designed to systematically integrate diverse and multimodal data, including regulatory RNAs and DNA, proteins, metabolites as well as knowledge from cell biology, animal experiments and human phenotypic and clinical data [110]. These integrative research approaches rely heavily upon the use of omics-based science, bioinformatics, and network theory, additionally using medical informatics to uncover mechanisms and to improve patient care [111]. Relevant mathematical formalisms

include those already presented, as well as data-based models which help tease meaning out of high-throughput, multi-modality data. Relevant, timely examples include e.g. *probabalistic graphical models* (Bayesian networks, Boolean networks) used e.g. in computational network biology [112] and *weighted correlation network analysis* as used primarily in genomics analysis. Probabalistic graphical models encode multivariate probability distributions of large numbers of random variables that interact with one another, making use of theory from both statistics and computer science, and have additionally been used to assess cardiovascular disease risk [113]. Weighted correlation network analysis, also known as weighted gene co-expression network analysis (WGCNA), is a widely-used method for biological network and particularly genomic analysis. It is based on pairwise correlations between variables, e.g. [114], and has recently been used to identify specific modules and hub genes related to coronary artery disease [115]. For a broader survey of models in biomedicine, the authors refer the reader to, e.g., [116].

3.7 | What level of detail is needed in a model, and how do we know how good it is?

Even from the very brief overview provided above, the complexity of the cardiovascular system is easily appreciated. The system's overall function is driven by a finely tuned network of biophysical processes, creating a multi-physics and multi-scale system which is challenging to fully understand. It is natural to ask whether all these details need to be captured and described in detail for a model to be useful. Fortunately, the answer is no, as the required level of biophysical detail is strongly dependent on the application at hand. Indeed, the ability to precisely describe complex processes and their interactions is one of the key strengths of mathematical models. As such, models are useful for understanding complex systems and for integrating processes from the sub-cellular scale to the complete organ system; a task which may be virtually impossible without the use of models. Multi-scale models of such biophysical detail may be extremely useful in fundamental research, to advance our understanding of how the cardiovascular system works, and, for instance, for predicting the effect of pharmacological interventions on cardiovascular function, see, e.g., [117, 118, 119, 120, 121, 122]. However, for many tasks such fine-grained detail is not needed, and there may not even be sufficient data available for constraining the model parameters. An important example is the development of patient specific models of cardiac mechanics and electrophysiology, for use in the clinic. The purpose of such models is typically to support diagnosis to predict a disease trajectory or optimize an intervention, and the available parameterisation data is usually severely limited. Tuning the models to such a specific task, by sacrifizing some biophysical detail to ease parameter fitting and interpretation, may be highly appropriate and necessary, see, e.g., [123].

If we accept that models cannot capture all biophysical detail, and that they need to be selected and tuned for the specific task at hand, how can we assess the quality of the models and ensure that the results are reliable and accurate? Such questions are essential in all model-based research, and in particular if models are used to support clinical decisions on actual patients. There are several tools that can be used to assess the trustworthiness of model results. Sensitivity analysis and uncertainty quantification (UQ) [124] can be used to quantify the sensitivity of a model's output to uncertainty in parameters and input variables. Many parameters in biological models are difficult to measure accurately, they may vary considerably between species and individuals, and may even change over time for the same individual. If the confidence intervals or other statistical properties of the input parameters are known, UQ is used to calculate the corresponding properties for the output quantities of interest. UQ is starting to make inroads in the computational physiology community, with applications in neurophysiology [125, 126, 127] as well as cardiovascular physiology [128, 129, 130, 131]. Such analysis is still not as widespread as it probably should be, given the substantial uncertainty and natural variation inherent in biological systems. However, the more general topic of *model validation* is getting increasingly relevant in the physiological modelling literature. While UQ may be

one component of model validation, the most common understanding of the term model validation is some form of comparing the models predictions with data that was not used to derive the model or fit its parameters. Such a comparison is, in principle, very simple to perform, but in reality it is usually more challenging. There is often limited data available for model development and parameter fitting, which makes it difficult to exclude high quality data from the development process. Furthermore, all models have a limited domain of validity, and it is challenging to precisely define the set of applications and input-parameter values for which a model is considered validated. We will discuss these topics below, and refer the reader to [132] for further on-topic reading.

4 | LIMITATIONS, CHALLENGES, AND OPEN QUESTIONS

We have briefly reviewed key basics of cardiac physiology, as well as several classes of mathematical models that are used to model cardiac physiology. As indicated above, the models' level of detail and realism is increasing rapidly, and the models can be seen as compact and quantitative condensations of vast amounts of physiological knowledge. While their usage in general physiological research is also increasing, one may wonder why they are not even more widespread. Physiology is about studying and understanding the mechanisms of living organisms, and one may argue that advanced computer models are essential tools in the field. Furthermore, while the potential of cardiovascular simulations for clinical applications is widely accepted by the research community, and comprehensive patient-specific models were published more than a decade ago [17], actual examples of their use in the clinical setting are fairly few and far between.

To understand the causes for the slow uptake of computer models, it is important to outline common pitfalls of mathematical models and computational simulations.

4.1 | Barriers to full exploitation of biophysics-based models in physiological research

Often, models "fail" - that is - fail to offer the desired insight into a physiological phenomenon - because the model type or choice is inappropriate for the task. This may be due to operator error, because of an uninformed or mistaken choice, failure to solve the model equations with sufficient accuracy, or lack of empirical data to successfully parameterize and constrain the model. Furthermore, models are often developed for a single application, or to generate mechanistic insight and test a hypothesis in a single context. While biophysically-detailed models could, in principle, describe many analogous applications, they often do not generalize well out of the box. Typically, a parameter set that makes the model accurately predict experiments in one situation, does not give accurate predictions in another situation. A goal of future cardiovascular modeling should be to work toward developing models with improved generalizability with well-defined and well understood limitations and parameterizations.

Considering challenges in terms of subcultures of science, can also be wise when crafting interdisciplinary projects. For instance, full appreciation of the challenges, time, and effort both experimental and computational work requires will help weigh the costs and benefits of use of a variety of model types. We offer more detail on these challenges with respect to the employ of biophysics-based models in physiological research, below.

It is also a rather common view in physiology that although models include a fair amount of biophysical detail, they are much farther from the "real thing" in comparison to, for example, *in vitro* models. There is, of course, no way around the fact that biology will always be more complex than the knowledge accumulated in the models. Furthermore, often times, the level of complexity in computational models has to be limited due to the practical considerations of the computational load. However, it is worthwhile to consider another point of view. Although models are often developed

and refined to ever increase their physiological detail and accuracy, they serve a purpose also in more rudimentary implementations. That is, if a model includes all the mechanisms thought to be underlying a particular physiological function yet it does not replicate experimental findings, that is a clear indication that the theoretical/conceptual model is faulty. In the famous words of Richard Feynman, "what I cannot create, I do not understand."

Although we argue that even simple models can lead to important insight, lack of biological detail and accuracy represents a significant barrier towards broader use of models in physiology. In this context, it is important to review the factors that limit the realism and accuracy of current physiological models. Besides computational load, the level of complexity and mechanistic detail of biophysics-based models is limited by the access to and applicability of experimental data for model fitting, especially in the case of human data. Existing state-of-the-art models are based on physical first principles, and offer a mechanistic and robust description of cardiovascular physiology. However, many of the models include constitutive relations containing parameters that need to be measured or estimated. Typical such parameters may include the conductance and density of a specific ion channel, the conductivity of cardiac tissue, and mechanical properties of blood vessels and cardiac muscle. Most of these parameters are impossible or very difficult to measure *in vivo* and need to be estimated from other observations such as medical images and ECGs, or inferred from *in vitro* experiments which are limited both by access to cells and tissue and by how closely they represent *in vivo* conditions. The advent of hiPSC-based approaches has solved some of the challenges related to access of human cardiac cells and tissue, although the engineered cardiomyocytes have phenotypes that do not quite match the native ones. In spite of these challenges, the applicability of experimental data for modelling purposes could be improved rather straightforwardly with a bit more profound inter-disciplinary knowledge. There have already been significant efforts to allow models to guide the design of experiments [133, 134, 135, 136, 137], and to develop novel measurement protocols that would be information-rich from the modelling perspective, while also being efficient to use in the wet lab.

Last, but not least, the inherent complexity of available computational models represents a significant obstacle towards widespread adoption by the biomedical research community. Many research groups develop and distribute state-of-the-art modelling tools, which are made freely available for use by the research community either as open or closed source software. However, most of these tools have a steep learning curve and are not developed or documented for use by researchers with limited computational backgrounds. Even high-end commercial software tools have limitations in this area. For instance, widely used software for computational fluid dynamics simulations of blood may be relatively simple to use for non-experts, and provides simulations that look reasonable, but assessing the quality and accuracy of the simulation still requires expert technical knowledge [138]. Although much progress has been made in recent years, both commercial tools and open, community-led software has much potential for improvement in terms of model standardization, interoperability, and documentation. Efforts such as the MIRIAM (Minimal information required in the annotation of models) and MIASE (Minimum Information About a Simulation Experiment) guidelines [139, 140], markup languages like SED-ML [141], CellML [142], and others, are community-led efforts for improving the reproducibility of computational modelling. Together with ongoing open-source software development efforts, including openCARP [26], Chaste [27], lifeV [30], CRIMSON [143], and OpenCMISS [144], the operability of models is being slowly, but steadily, extended beyond the traditional in-house expert users.

4.2 | What if we had unlimited data and computational resources?

In the previous sections we have introduced a number of detailed mathematical models of cardiovascular physiology, covering spatial scales from ion channels and sarcomeres to the whole organ. We have also reviewed a number of challenges in computational modeling, and repeatedly referred to the lack of experimental data and limited computational

power as two of the most important obstacles for more widespread use of models. In this context, it is interesting to ask what modelers could do in the absence of these limitations. The question is clearly hypothetical, but attempting to answer it may still provide useful insight about where the field is moving.

First addressing the computational power, removing this limitation would allow us to solve models of arbitrary detail and complexity in a reasonable time frame. But how would this impact the field in terms of new insight and new opportunities? First, reduced computation times will dramatically increase the utility of existing models for research and clinical work. Many existing models, for instance, the bidomain model describing electrophysiology reviewed earlier, can be solved with the accuracy and robustness required for widespread research and clinical use. However, the solution often takes several hours on a supercomputer or large cluster, obviously limiting the use of the models for many clinical timescales.

Second, a huge benefit may arise from the ability to run multiple instances of existing models, for parameter estimation, uncertainty quantification, and sensitivity analysis. Such analyses are crucial for assessing the models' quality and reliability, and may dramatically increase the predictive power and insight gained. Furthermore, improved capability to explore variability would help us to better understand this fundamental feature of biology. Sampling-based methods such as Monte-Carlo simulations [145, 146] and the so-called *population of models* approach [147, 44] offer simple and powerful tools for the analyses, but these methods typically require running the baseline model up to several hundred times. Their use is therefore currently limited to simplified and less computationally demanding models.

Thirdly and finally, abundant computing power would open the possibility for entirely new model concepts and frameworks, capturing more biophysical detail and with higher spatial and temporal resolution. Examples of emerging concepts include tissue models with spatially resolved cells [148, 61], models of cardiovascular growth and remodeling over several months [149, 150, 151], and advanced multiphysics models that capture interactions across the entire cardiovascular system [100, 101, 99]. All of these models exist, but the computational demand represents a serious obstacle to further exploration and exploitation. The same is true for a detailed model of hemodynamics. It is impossible today to realistically represent individual blood cells in a macroscopic model, due to a lack of both data to specify constitutive relations and the computational power to resolve all (sometimes turbulent) scales in the blood flow. If this were possible, that would offer a bridge from macroscopic flow structures in the heart and larger vessels, such as vortices and shear layers, to the mechanical stimuli experienced by individual blood cells and endothelial cells. Such simulations would, for example, be able to enhance the understanding of flow-induced thrombosis. Apart from turbulent flow in the chambers of the heart, the geometry of the chambers generate coupled flow on multiple scales, for example, through the fine geometric details of the trabeculae carneae. A full spatio-temporal resolution of this multiscale problem is still out of reach [152].

5 | PERSPECTIVE AND OUTLOOK

In this review, we have thus far provided an introduction to mathematical and computational modeling in cardiovascular physiology, offered historical context, as well as an overview of the state of the art for different physiological components and at different spatio-temporal scales. Below, we consider bleeding-edge efforts in cardiovascular research and medicine employing computational and mathematical modeling, and offer conjectures regarding promising new research initiatives and their potential next steps.

5.1 | Translational cardiac model applications, computational cardiology and personalised medicine

Personalised medicine supported by computational modeling, see for instance [153] for an overview of methods, has also emerged in cardiology. This potential application of models, with the vision of creating a "digital twin" on which various therapeutic options can be explored, remains a key driver for research in computational cardiovascular physiology. Personalised models that accurately represents each patient's heart and/or disease may offer the ability to integrate existing patient data, to design new and optimal personal treatment plans, and potentially to guide care in real time. Wide adoption of such virtual patient models likely presents the core of next-generation cardiology care for many pathologies, and integrated commercial, clinical, and academic research efforts at the international level towards this end are ongoing. For an example workflow wherein patient data is used to create a computational model for individualized simulation, see Figure 4. This kind of data assimilation, where model parameters are adapted to match certain measurements from patients or experimental data, has been an active research field for decades. A related approach, which may be just as relevant from a clinical perspective, is to use models for regularizing or augmenting sparse and noisy data. For instance, many data-driven approaches, in particular ANNs, require huge volumes of training data, which is often difficult or impossible to obtain in the medical field. Combining such data-driven techniques with physics-based models effectively encodes established knowledge into the model, thereby reducing the training data requirement substantially and potentially increasing the applicability of the models. Physics-informed neural networks (PINNs) and physics-based data augmentation are examples of active research areas at the interface between data science and classical physiological modeling.

A key use case for computational cardiovascular modeling is the rapid translation of research for commercial and/or clinical applications. Examples, as highlighted in the following paragraphs, may include drug development/ preclinical screening; device development and testing, ranging from e.g. pacemakers to blood pumps and artificial valves), and use of model-derived or supported cardiovascular risk indices in the clinic. More details regarding notable community-driven coordinating bodies and efforts contributing to this translational impact follows below. The Cardiac Physiome Society (https://www.cardiacphysiome.org/), incorporated and convening for several decades, has the mission of "promoting integrative multi-scale simulation and analysis of cardiac physiology in health and disease, spanning the full breadth of cardiac functions and all scales of biological organization from molecule to patient". The Society aims to encourage and facilitate international collaboration, cooperation, sharing, exchange, and interoperability in basic, translational and clinical research data, models and technology development. The Virtual Physiological Human (VPH) - an effort synonymous with *in silico* medicine and the use of a digital twin - is a field that encompasses the use of individualised physiology-based computer simulations in all aspects of the prevention, diagnosis, prognostic assessment, and treatment of a disease and development of a biomedical product. The VPH Initiative (VPHi), incorporated into an Institute since 2011 (https://www.vph-institute.org/), has been aligned for decades with many international research efforts broadly focused in computational cardiovascular physiology and medicine. There are additionally many current efforts to combine computational cardiology and personalised medicine with powerful, emerging machine learning and artificial intelligence techniqiues, e.g. the PROCardio Norwegian Center for Research-Based Innovation, aimed to improved patient diagnostics and prognostics (https://www.heart-sfi.no/); the SimCardioTest (https://www.inria.fr/en/simcardiotest-consortium-hearts) project aims to accelerate the adoption of digital simulation for the design of cardiac drugs and medical devices. A notable example of personalised cardiovascular simulation currently in the clinic is the FDA-approved use of fractional flow reserve in computational fluid dynamics models for coronary artery disease, determining the ratio between the maximal achievable blood flow in a diseased coronary artery, and the maximal flow in a normal coronary artery, as based on computed tomography imaging of the

coronary vasculature [4].

Virtual patient models also serve personalised cardiac medicine in their ability to capture inter-patient variability. These represent tools for rapidly developing personalised treatment protocols over large virtual cohorts using virtual trials, as well as the opportunity to safely design and optimize clinical trials of pharmaceutical compounds or key cardiac devices, facilitating validation and approvals for advances in cardiac care and cardiac safety. The aforementioned VPHi was a major partner in the 2-year EU funded Avicenna project (https://www.vph-institute.org/avicenna.html), which led to a published roadmap (https://avicenna-isct.org/roadmap/) outlining a strategy for *in silico* clinical trials, with large focus on cardiovascular medicine in addition to other application areas in physiology. The Comprehensive in vitro Proarrhythmia Assay, a novel in vitro/in silico paradigm to detect ventricular proarrhythmic liability (CiPA, https://cipaproject.org/) for pharmacological development pipelines [154], is now firmly in use in several international regulatory settings, with an application focus in cardiac-safe commercial drug development.

5.2 | Brain-heart axis: shared goals, research questions, and methodological exchange

Although mathematical models have been developed for virtually every process in the human body, see, e.g., [155], the cardiovascular system and the nervous system stand out in terms of both invested effort and progress. While these systems share many common modeling challenges, the research communities are largely disjointed, and both sub-fields could benefit from increased interaction and exchange of tools and ideas. In this section we discuss some of the key similarities and differences, and point to significant research initiatives in computational neurophysiology that could inspire similar efforts in the cardiovascular field.

From a cellular point of view, the heart and brain share several key features. Both consist of electrically excitable cells and fire action potentials, albeit that the action potential in heart cells is about a factor hundred slower than in nerve cells. This similarity is reflected in the use of Hodgkin-Huxley style ion-channel current models when modeling cellular excitation. This common modeling foundation is reflected in the similar challenges facing the modeling in the two domains. A joint challenge is inverse modeling, that is, fitting the parameters of the model so that it accounts for experimental data. This problem is not only ill-posed in the sense that many combinations of model parameters can fit the data, it is also made more difficult in that some of the model parameters may change over time. The density of various ion channels, a key model parameter in electrophysiological modeling, is, for example, under the control of the cellular mechanisms that dynamically modulate gene transcription.

It bears mention that, although the links between neurological and cardiovascular disorders are well known [156], this path is to a great extent unexplored. Computational modelling is a very potential approach to shed light on that path, as it enables integration of data and mechanistic insights from these two realms. For example, the pleiotropic effects genetic variants that impact both neuronal and cardiac cellular excitability have been explored recently in the context of schizophrenia and cardiac pacemaking [157].

There are, however, also clear differences. The mechanical tissue properties of the heart are critical for the heart's function. In the brain, the tissue is not supposed to move, and mechanical properties are mainly of interest when studying mechanical brain trauma. Likewise, fluid flow is less central for brain function, even though modelling of blood flow through the brain vasculature is important for understanding brain metabolism [158]. Another key difference is that unlike in the heart, there are non-local interactions between cells in the brain. The nerve cells send pulse-like all-or-nothing signals to each other via axons. These long and thin cable-like protrusions make direct connections between cells that can be many centimeters apart. In contrast, heart cells only signal to each other via changes in concentrations of ions and molecules in their shared extracellular space. Thus, only rather local interactions are possible. This makes the electrical network in the brain immensely more complicated than in the heart, allowing for a much richer behavior.

This allows for the much richer dynamics required in efficient information processing compared to the the relatively simple pumping action of the heart. In computational brain science most effort has gone into trying to understand this information processing, and a host of simplified neuron and network models have been introduced to make this endeavor computationally and conceptually tractable [159].

To address the complexity of the brain several large scale projects have been initiated, both for data collection and modeling. In terms of modeling, two projects stand out. In the Human Brain Project, an EU Flagship project started in 2013, a key goal is to develop an infrastructure for large-scale neural network simulation and comparison of model predictions with experiments. This digital and distributed infrastrucure, labeled EBRAINS (ebrains.eu), will be a part of ESFRI, that is part of the strategically supported European research infrastructure. At the Allen Institute for Brain Science, the Mindscope program is developing large-scale network models for the mouse brain based on unprecedented amounts of neurobiological data recorded in house with an industrial-style lab approach [160]. Another interesting initiative in the neuroscience field is the establishment of the International Brain Laboratory where more than twenty research groups in US and Europe have created a joint virtual laboratory for experimental and theoretical investigations of brainwide circuits for complex behavior (https://www.internationalbrainlab.com/). In contrast, while there exist many national and international longer-term center-based efforts in cardiovascular sciences, including modeling, the heart field lacks nucleating efforts similar in scope and depth to those in the computational neuroscience field, as outlined above. As efforts at this level help to drive progress, particularly around community-driven, open-science focused tool sharing, the cardiovascular modeling community would do well to focus efforts in this direction and to learn from the good practices in use in computational neuroscience.

5.3 | Concluding remarks

In this review, we have aimed to offer the reader a comprehensive overview of cardiovascular computer simulations, including their origins, to context, foundations, and physiological and computational background. We have offered a succinct but thorough view of the state of the art, and have presented arguments for closer interaction between modellers and experimental scientists. Finally, we have tried to capture the essence of current limitations and matters of debate in this field, followed by musings on directions for expansions and where things are headed.

While the main focus of our review has been on how science and physiological knowledge can benefit from a widespread use of computations, the natural next step is for personalised computational models to become an integral part of healthcare and clinical practice. In the not-so-far future, indeed, the following scenario may become reality. Consider a patient, Maria, 65 years of age, who has recently been diagnosed with hypertension, but is otherwise in good health. While her mother and grandmother unfortunately developed heart failure and accompanying quality of life issues in their old age, for Maria, it may be different. Her cardiac digital twin has incorporated all the general, genetic, and specifically heart-related information from her doctor visits over the years, and is continuously updated following new scans and treatments. After discussing with her health care providers, Maria has made herself familiar with her own health data and her digital twin and she is happy with the added knowledge these tools bring in terms of monitoring her heart health. Her physician consults this comprehensive, integrative model before meeting with Maria, and so feels confident of the best way to monitor and treat her patient in a timely fashion.

While this vision may seem still firmly in the realm of science fiction, translation and integration of cardiovascular computational models into basic science and even clinical realms are rapidly becoming reality. It is our hope that, through further technological advancement in software and hardware, open science practices, and wide cultural adoption, computer modeling in the cardiovascular sciences can continue to accelerate discovery and to improve critical cardiovascular healthcare.

Conflict of interest

The authors have no conflicts of interest to declare.

references

[1] Neumaier A. In: Kallrath J, editor. Mathematical Model Building Boston, MA: Springer US; 2004. p. 37–43. https://doi.org/10.1007/978-1-4613-0215-5_3.

[2] Chabiniok R, Wang VY, Hadjicharalambous M, Asner L, Lee J, Sermesant M, et al. Multiphysics and multiscale modelling, data–model fusion and integration of organ physiology in the clinic: ventricular cardiac mechanics. Interface focus 2016;6(2):20150083.

[3] Kassab G, Guccione J. Editorial: Mathematical Modeling of Cardiovascular Systems: From Physiology to the Clinic. Frontiers in Physiology 2019;10:1259. https://www.frontiersin.org/article/10.3389/fphys.2019.01259.

[4] Taylor CA, Fonte TA, Min JK. Computational fluid dynamics applied to cardiac computed tomography for non-invasive quantification of fractional flow reserve: scientific basis. Journal of the American College of Cardiology 2013;61(22):2233–2241.

[5] Roth BJ. Bidomain modeling of electrical and mechanical properties of cardiac tissue. Biophysics Reviews 2021;2(4):041301. https://doi.org/10.1063/5.0059358.

[6] Niederer SA, Lumens J, Trayanova NA. Computational models in cardiology. Nature Reviews Cardiology 2019;16(2):100–111.

[7] Langley G, Adcock I, Busquet F, Crofton K, Csernok E, Giese C, et al. Towards a 21st-century roadmap for biomedical research and drug discovery: Consensus report and recommendations. Drug Discovery Today 2016 10;22.

[8] Ching T, Himmelstein DS, Beaulieu-Jones BK, Kalinin AA, Do BT, Way GP, et al. Opportunities and obstacles for deep learning in biology and medicine. Journal of The Royal Society Interface 2018;15(141):20170387.

[9] Esteva A, Robicquet A, Ramsundar B, Kuleshov V, DePristo M, Chou K, et al. A guide to deep learning in healthcare. Nature medicine 2019;25(1):24–29.

[10] Poirot MG, Bergmans RH, Thomson BR, Jolink FC, Moum SJ, Gonzalez RG, et al. Physics-informed deep learning for dual-energy computed tomography image processing. Scientific reports 2019;9(1):1–9.

[11] Sahli Costabal F, Yang Y, Perdikaris P, Hurtado DE, Kuhl E. Physics-informed neural networks for cardiac activation mapping. Frontiers in Physics 2020;8:42.

[12] Poiseuille JLM. Recherches sur les causes du mouvement du sang dans les vaisseaux capillaires. C R Acad Sci 6 1835;.

[13] Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. The Journal of Physiology 1952;117(4):500–544.

[14] Huxley AF. Muscle structure and theories of contraction. Prog Biophys Biophys Chem 1957;7:255–318.

[15] Saber NR, Wood NB, Gosman A, Merrifield RD, Yang GZ, Charrier CL, et al. Progress towards patient-specific computational flow modeling of the left heart via combination of magnetic resonance imaging with computational fluid dynamics. Annals of biomedical engineering 2003;31(1):42–52.

[16] Löhner R, Cebral J, Soto O, Yim P, Burgess JE. Applications of patient-specific CFD in medicine and life sciences. International journal for numerical methods in fluids 2003;43(6-7):637–650.

[17] Aguado-Sierra J, Krishnamurthy A, Villongco C, Chuang J, Howard E, Gonzales MJ, et al. Patient-specific modeling of dyssynchronous heart failure: a case study. Progress in biophysics and molecular biology 2011;107(1):147–155.

[18] Boyle PM, Zghaib T, Zahid S, Ali RL, Deng D, Franceschi WH, et al. Computationally guided personalized targeted ablation of persistent atrial fibrillation. Nature biomedical engineering 2019;3(11):870–879.

[19] Stella S, Vergara C, Maines M, Catanzariti D, Africa PC, Dematté C, et al. Integration of activation maps of epicardial veins in computational cardiac electrophysiology. Computers in Biology and Medicine 2020;127:104047.

[20] Tung L. A bidomain model for describing ischemic myocardial D-C potentials. PhD thesis, Massachusetts Institute of Technology, Cambridge; 1978.

[21] Holzapfel GA, Gasser TC, Ogden RW. A new constitutive framework for arterial wall mechanics and a comparative study of material models. Journal of elasticity and the physical science of solids 2000;61(1):1–48.

[22] Hunter PJ, McCulloch AD, Ter Keurs H. Modelling the mechanical properties of cardiac muscle. Progress in biophysics and molecular biology 1998;69(2-3):289–331.

[23] Peskin CS. Numerical analysis of blood flow in the heart. Journal of computational physics 1977;25(3):220–252.

[24] Raissi M, Perdikaris P, Karniadakis GE. Physics-informed neural networks: A deep learning framework for solving forward and inverse problems involving nonlinear partial differential equations. Journal of Computational Physics 2019;378:686–707.

[25] Hoffman J. Methods in Computational Science. SIAM; 2021.

[26] OpenCARP;. See *https://opencarp.org/*.

[27] Chaste;. See *https://www.cs.ox.ac.uk/chaste/*.

[28] Pulse;. See *https://github.com/ComputationalPhysiology/pulse*.

[29] Continuity;. See *https://continuity.ucsd.edu/*.

[30] LifeV;. See *https://bitbucket.org/lifev-dev/lifev-release/wiki/Home*.

[31] CircAdapt;. See *http://www.circadapt.org/*.

[32] Katz AM. Physiology of the Heart. Lippincott Williams & Wilkins; 2010.

[33] Silverthorn DU. Human physiology. Jones & Bartlett Publishers; 2015.

[34] Fritz T, Wieners C, Seemann G, Steen H, Dössel O. Simulation of the contraction of the ventricles in a human heart model including atria and pericardium. Biomechanics and modeling in mechanobiology 2014;13(3):627–641.

[35] Marks AR, et al. Calcium cycling proteins and heart failure: mechanisms and therapeutics. The Journal of clinical investigation 2013;123(1):46–52.

[36] Noble D. A modification of the Hodgkin–Huxley equations applicable to Purkinje fibre action and pace-maker potentials. Journal of Physiology 1962;160:317–352. `https://doi.org/10.1113/jphysiol.1962.sp006849`, journal Article.

[37] Fink M, Niederer SA, Cherry EM, Fenton FH, Koivumäki JT, Seemann G, et al. Cardiac cell modelling: Observations from the heart of the cardiac physiome project. Progress in Biophysics and Molecular Biology 2011;104(1-3):2–21. `https://doi.org/10.1016/j.pbiomolbio.2010.03.002`, journal Article.

[38] Niederer SA, Fink M, Noble D, Smith NP. A Meta Analysis of Cardiac Electrophysiology Computational Models. Experimental Physiology 2009;94:486–495. `https://doi.org/10.1113/expphysiol.2008.044610`, journal Article.

[39] Priebe L, Beuckelmann DJ. Simulation Study of Cellular Electric Properties in Heart Failure. Circulation Research 1998 Jun;82(11):1206–1223. http://circres.ahajournals.org/content/82/11/1206.

[40] ten Tusscher KHWJ, Noble D, Noble PJ, Panfilov AV. A model for human ventricular tissue. AJP - Heart and Circulatory Physiology 2004;286(4):H1573–1589. https://doi.org/10.1152/ajpheart.00794.2003, journal Article.

[41] Iyer V, Mazhari R, Winslow RL. A computational model of the human left-ventricular epicardial myocyte. Biophysical Journal 2004;87(3):1507–1525. https://doi.org/10.1529/biophysj.104.043299, journal Article.

[42] O'Hara T, Virág L, Varró A, Rudy Y. Simulation of the Undiseased Human Cardiac Ventricular Action Potential: Model Formulation and Experimental Validation. PLoS Comput Biol 2011 May;7(5):e1002061. https://doi.org/10.1371/journal.pcbi.1002061.

[43] Trovato C, Passini E, Nagy N, Varró A, Abi-Gerges N, Severi S, et al. Human Purkinje in silico model enables mechanistic investigations into automaticity and pro-arrhythmic abnormalities. Journal of Molecular and Cellular Cardiology 2020 May;142:24–38. http://www.sciencedirect.com/science/article/pii/S0022282820300833.

[44] Vagos M, Herck V, M IG, Sundnes J, Arevalo HJ, Edwards AG, et al. Computational Modeling of Electrophysiology and Pharmacotherapy of Atrial Fibrillation: Recent Advances and Future Challenges. Frontiers in Physiology 2018;9:1221. https://doi.org/10.3389/fphys.2018.01221.

[45] Fenton FH, Cherry EM. Models of cardiac cell. Scholarpedia 2008;3(8):1868. https://doi.org/10.4249/scholarpedia.1868, journal Article.

[46] Paci M, Koivumäki JT, Lu HR, Gallacher DJ, Passini E, Rodriguez B. Comparison of the Simulated Response of Three in Silico Human Stem Cell-Derived Cardiomyocytes Models and in Vitro Data Under 15 Drug Actions. Frontiers in Pharmacology 2021;12. https://www.frontiersin.org/articles/10.3389/fphar.2021.604713/full?&utm_source=Email_to_authors_&utm_medium=Email&utm_content=T1_11.5e1_author&utm_campaign=Email_publication&field=&journalName=Frontiers_in_Pharmacology&id=604713, publisher: Frontiers.

[47] Goldman DE. POTENTIAL, IMPEDANCE, AND RECTIFICATION IN MEMBRANES. Journal of General Physiology 1943 Sep;27(1):37–60. https://rupress.org/jgp/article/27/1/37/12030/POTENTIAL-IMPEDANCE-AND-RECTIFICATION-IN-MEMBRANES, publisher: The Rockefeller University Press.

[48] Hodgkin AL, Katz B. The effect of sodium ions on the electrical activity of the giant axon of the squid. The Journal of Physiology 1949;108(1):37–77. https://physoc.onlinelibrary.wiley.com/doi/abs/10.1113/jphysiol.1949.sp004310, _eprint: https://physoc.onlinelibrary.wiley.com/doi/pdf/10.1113/jphysiol.1949.sp004310.

[49] Hille B. Ion channels of excitable membranes. Sinauer Associates, Inc.; 2001.

[50] Fenton F, Karma A. Vortex dynamics in three-dimensional continuous myocardium with fiber rotation: Filament instability and fibrillation. Chaos: An Interdisciplinary Journal of Nonlinear Science 1998 Mar;8(1):20–47. https://aip.scitation.org/doi/10.1063/1.166311.

[51] Adeniran I, Hancox JC, Zhang H. Effect of cardiac ventricular mechanical contraction on the characteristics of the ECG: A simulation study. Journal of Biomedical Science and Engineering 2013 Dec;06(12):47. http://www.scirp.org/journal/PaperInformation.aspx?PaperID=41405&#abstract, number: 12 Publisher: Scientific Research Publishing.

[52] Dai L, Zang Y, Zheng D, Xia L, Gong Y. Role of CaMKII and PKA in Early Afterdepolarization of Human Ventricular Myocardium Cell: A Computational Model Study. Computational and Mathematical Methods in Medicine 2016;2016:4576313. https://doi.org/10.1155/2016/4576313.

[53] Dutta S, Chang KC, Beattie KA, Sheng J, Tran PN, Wu WW, et al. Optimization of an In silico Cardiac Cell Model for Proarrhythmia Risk Assessment. Frontiers in Physiology 2017;8. https://www.frontiersin.org/articles/10.3389/fphys.2017.00616/full.

[54] Tomek J, Bueno-Orovio A, Passini E, Zhou X, Minchole A, Britton O, et al. Development, calibration, and validation of a novel human ventricular myocyte model in health, disease, and drug block. eLife 2019 Dec;8:e48890. https://doi.org/10.7554/eLife.48890.

[55] Bartolucci C, Passini E, Hyttinen J, Paci M, Severi S. Simulation of the Effects of Extracellular Calcium Changes Leads to a Novel Computational Model of Human Ventricular Action Potential With a Revised Calcium Handling. Frontiers in Physiology 2020;11. https://doi.org/10.3389/fphys.2020.00314, publisher: Frontiers.

[56] Plonsey R, Barr RC. Impulse Propagation. In: Plonsey R, Barr RC, editors. Bioelectricity: A Quantitative Approach Boston, MA: Springer US; 2007.p. 155–186. https://doi.org/10.1007/978-0-387-48865-3_6.

[57] Neu JC, Krassowska W. Homogenization of syncytial tissues. Critical Reviews in Biomedical Engineering 1993;21(2):137–199.

[58] Keener J, Sneyd J. Mathematical Physiology: I: Cellular Physiology. 2 ed. Interdisciplinary Applied Mathematics, New York: Springer-Verlag; 2009. https://www.springer.com/gp/book/9780387758466.

[59] Weinberg SH. Ephaptic coupling rescues conduction failure in weakly coupled cardiac tissue with voltage-gated gap junctions. Chaos: An Interdisciplinary Journal of Nonlinear Science 2017 Aug;27(9):093908. https://aip.scitation.org/doi/abs/10.1063/1.4999602, publisher: American Institute of Physics.

[60] Hichri E, Abriel H, Kucera JP. Distribution of cardiac sodium channels in clusters potentiates ephaptic interactions in the intercalated disc. The Journal of Physiology 2018;596(4):563–589. https://physoc.onlinelibrary.wiley.com/doi/abs/10.1113/JP275351, _eprint: https://physoc.onlinelibrary.wiley.com/doi/pdf/10.1113/JP275351.

[61] Jæger KH, Edwards AG, McCulloch A, Tveito A. Properties of cardiac conduction in a cell-based computational model. PLOS Computational Biology 2019 May;15(5):e1007042. https://doi.org/10.1371/journal.pcbi.1007042.

[62] Henriquez CS. Simulating the electrical behavior of cardiac tissue using the bidomain model. Critical Reviews in Biomedical Engineering 1993;21(1):1–77.

[63] Sachse FB, Moreno AP, Seemann G, Abildskov JA. A model of electrical conduction in cardiac tissue including fibroblasts. Annals of Biomedical Engineering 2009;37(5):874–889. https://doi.org/10.1007/s10439-009-9667-4, journal Article.

[64] Hill AV. The heat of shortening and the dynamic constants of muscle. Proceedings of the Royal Society of London Series B-Biological Sciences 1938;126(843):136–195.

[65] Niederer S, Hunter P, Smith N. A quantitative analysis of cardiac myocyte relaxation: a simulation study. Biophysical journal 2006 Jan;http://linkinghub.elsevier.com/retrieve/pii/S000634950672358X.

[66] Razumova MV, Bukatina AE, Campbell KB. Stiffness-distortion sarcomere model for muscle simulation. Journal of Applied Physiology 1999;87(5):1861–1876.

[67] Rice JJ, Wang F, Bers DM, de Tombe PP. Approximate Model of Cooperative Activation and Crossbridge Cycling in Cardiac Muscle Using Ordinary Differential Equations. Biophysical Journal 2008 Sep;95(5):2368–2390.

[68] Land S, Park-Holohan SJ, Smith NP, Dos Remedios CG, Kentish JC, Niederer SA. A model of cardiac contraction based on novel measurements of tension development in human cardiomyocytes. Journal of molecular and cellular cardiology 2017;106:68–83.

[69] Holzapfel AG. Nonlinear solid mechanics. John Wiley & Sons, Inc.; 2000.

[70] Niederer SA, Campbell KS, Campbell SG. A short history of the development of mathematical models of cardiac mechanics. Journal of molecular and cellular cardiology 2019;127:11–19.

[71] Xiao N, Humphrey JD, Figueroa CA. Multi-scale computational model of three-dimensional hemodynamics within a deformable full-body arterial network. Journal of computational physics 2013;244:22–40.

[72] Kamensky D, Hsu MC, Schillinger D, Evans JA, Aggarwal A, Bazilevs Y, et al. An immersogeometric variational framework for fluid–structure interaction: Application to bioprosthetic heart valves. Computer methods in applied mechanics and engineering 2015;284:1005–1053.

[73] Toma M, Jensen MØ, Einstein DR, Yoganathan AP, Cochran RP, Kunzelman KS. Fluid–structure interaction analysis of papillary muscle forces using a comprehensive mitral valve model with 3D chordal structure. Annals of biomedical engineering 2016;44(4):942–953.

[74] Spühler JH, Jansson J, Jansson N, Hoffman J. 3D fluid-structure interaction simulation of aortic valves using a unified continuum ALE FEM model. Frontiers in physiology 2018;9:363.

[75] Chan BT, Lim E, Chee KH, Osman NAA. Review on CFD simulation in heart with dilated cardiomyopathy and myocardial infarction. Computers in Biology and medicine 2013;43(4):377–385.

[76] Seo JH, Vedula V, Abraham T, Lardo AC, Dawoud F, Luo H, et al. Effect of the mitral valve on diastolic flow patterns. Physics of fluids 2014;26(12):121901.

[77] Doenst T, Spiegel K, Reik M, Markl M, Hennig J, Nitzsche S, et al. Fluid-dynamic modeling of the human left ventricle: methodology and application to surgical ventricular reconstruction. The Annals of thoracic surgery 2009;87(4):1187–1195.

[78] Mangual JO, Kraigher-Krainer E, De Luca A, Toncelli L, Shah A, Solomon S, et al. Comparative numerical study on left ventricular fluid dynamics after dilated cardiomyopathy. Journal of biomechanics 2013;46(10):1611–1617.

[79] Khalafvand S, Zhong L, Ng E. Three-dimensional CFD/MRI modeling reveals that ventricular surgical restoration improves ventricular function by modifying intraventricular blood flow. International journal for numerical methods in biomedical engineering 2014;30(10):1044–1056.

[80] Moosavi MH, Fatouraee N, Katoozian H, Pashaei A, Camara O, Frangi AF. Numerical simulation of blood flow in the left ventricle and aortic sinus using magnetic resonance imaging and computational fluid dynamics. Computer methods in biomechanics and biomedical engineering 2014;17(7):740–749.

[81] Doost SN, Ghista D, Su B, Zhong L, Morsi YS. Heart blood flow simulation: a perspective review. Biomedical engineering online 2016;15(1):1–28.

[82] Larsson D, Spühler JH, Petersson S, Nordenfur T, Colarieti-Tosti M, Hoffman J, et al. Patient-specific left ventricular flow simulations from transthoracic echocardiography: robustness evaluation and validation against ultrasound Doppler and magnetic resonance imaging. IEEE transactions on medical imaging 2017;36(11):2261–2275.

[83] Biasetti J, Hussain F, Gasser TC. Blood flow and coherent vortices in the normal and aneurysmatic aortas: a fluid dynamical approach to intra-luminal thrombus formation. Journal of The Royal Society Interface 2011;8(63):1449–1461.

[84] Quinn TA, Kohl P. Cardiac mechano-electric coupling: acute effects of mechanical stimulation on heart rate and rhythm. Physiological reviews 2021;101(1):37–92.

[85] Usyk TP, LeGrice IJ, McCulloch AD. Computational model of three-dimensional cardiac electromechanics. Computing and visualization in science 2002;4(4):249–257.

[86] Gurev V, Lee T, Constantino J, Arevalo H, Trayanova NA. Models of cardiac electromechanics based on individual hearts imaging data. Biomechanics and modeling in mechanobiology 2011;10(3):295–306.

[87] Land S, Niederer SA, Smith NP. Efficient computational methods for strongly coupled cardiac electromechanics. IEEE Transactions on Biomedical Engineering 2011;59(5):1219–1228.

[88] Wall ST, Guccione JM, Ratcliffe MB, Sundnes JS. Electromechanical feedback with reduced cellular connectivity alters electrical activity in an infarct injured left ventricle: a finite element model study. American Journal of Physiology-Heart and Circulatory Physiology 2012;302(1):H206–H214.

[89] Shavik SM, Wall ST, Sundnes J, Burkhoff D, Lee LC. Organ-level validation of a cross-bridge cycling descriptor in a left ventricular finite element model: effects of ventricular loading on myocardial strains. Physiological reports 2017;5(21):e13392.

[90] Costabal FS, Concha FA, Hurtado DE, Kuhl E. The importance of mechano-electrical feedback and inertia in cardiac electromechanics. Computer methods in applied mechanics and engineering 2017;320:352–368.

[91] Strocchi M. An electromechanics four-chamber heart model for cardiac resynchronisation therapy response prediction and optimisation. PhD thesis, King's College London; 2021.

[92] Augustin CM, Gsell MA, Karabelas E, Willemen E, Prinzen FW, Lumens J, et al. A computationally efficient physiologically comprehensive 3D–0D closed-loop model of the heart and circulation. Computer Methods in Applied Mechanics and Engineering 2021;386:114092.

[93] Zamorano J, Lancellotti P, Pierard L, Pibarot P. Heart Valve Disease: State of the Art. Springer International Publishing; 2019. https://books.google.no/books?id=Le69DwAAQBAJ.

[94] Prot V, Skallerud B, Holzapfel G. Transversely isotropic membrane shells with application to mitral valve mechanics. Constitutive modelling and finite element implementation. International journal for numerical methods in engineering 2007;71(8):987–1008.

[95] Votta E, Caiani E, Veronesi F, Soncini M, Montevecchi FM, Redaelli A. Mitral valve finite-element modelling from ultrasound data: a pilot study for a new approach to understand mitral function and clinical scenarios. Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences 2008;366(1879):3411–3434.

[96] Sacks MS, Drach A, Lee CH, Khalighi AH, Rego BV, Zhang W, et al. On the simulation of mitral valve function in health, disease, and treatment. Journal of biomechanical engineering 2019;141(7).

[97] Lee JH, Rygg AD, Kolahdouz EM, Rossi S, Retta SM, Duraiswamy N, et al. Fluid–structure interaction models of bioprosthetic heart valve dynamics in an experimental pulse duplicator. Annals of biomedical engineering 2020;48(5):1475–1490.

[98] Roy R, Warren E, Xu Y, Yow C, Madhurapantula RS, Orgel JP, et al. Functional grading of a transversely isotropic hyperelastic model with applications in modeling tricuspid and mitral valve transition regions. International Journal of Molecular Sciences 2020;21(18):6503.

[99] Santiago A, Aguado-Sierra J, Zavala-Aké M, Doste-Beltran R, Gómez S, Arís R, et al. Fully coupled fluid-electromechanical model of the human heart for supercomputers. International journal for numerical methods in biomedical engineering 2018;34(12):e3140.

[100] Watanabe H, Sugiura S, Kafuku H, Hisada T. Multiphysics simulation of left ventricular filling dynamics using fluid-structure interaction finite element method. Biophysical journal 2004;87(3):2074–2085.

[101] Hosoi A, Washio T, Okada Ji, Kadooka Y, Nakajima K, Hisada T. A multi-scale heart simulation on massively parallel computers. In: SC'10: Proceedings of the 2010 ACM/IEEE International Conference for High Performance Computing, Networking, Storage and Analysis IEEE; 2010. p. 1–11.

[102] Krittanawong C, Virk HUH, Bangalore S, Wang Z, Johnson KW, Pinotti R, et al. Machine learning prediction in cardiovascular diseases: a meta-analysis. Scientific Reports 2020;10(1):16057. https://doi.org/10.1038/s41598-020-72685-1.

[103] Buccino AP, Kordovan M, Ness TV, Merkt B, Häfliger PD, Fyhn M, et al. Combining biophysical modeling and deep learning for multielectrode array neuron localization and classification. Journal of neurophysiology 2018;120(3):1212–1232.

[104] Godoy EJ, Lozano M, Garcia-Fernandez I, Sebastian R. Combining Biophysical Modeling and Machine Learning to Predict Location of Atrial Ectopic Triggers. In: 2018 Computing in Cardiology Conference (CinC), vol. 45 IEEE; 2018. p. 1–4.

[105] An G, Mi Q, Dutta-Moscato J, Vodovotz Y. Agent-based models in translational systems biology. Wiley Interdisciplinary Reviews: Systems Biology and Medicine 2009;1(2):159–171.

[106] Bora Ş, Evren V, Emek S, Çakırlar I. Agent-based modeling and simulation of blood vessels in the cardiovascular system. Simulation 2019;95(4):297–312.

[107] Keshavarzian M, Meyer CA, Hayenga HN. Mechanobiological model of arterial growth and remodeling. Biomechanics and modeling in mechanobiology 2018;17(1):87–101.

[108] Kleinstreuer N, Dix D, Rountree M, Baker N, Sipes N, Reif D, et al. A computational model predicting disruption of blood vessel development. PLoS computational biology 2013;9(4):e1002996.

[109] Li Y, Kong N, Lawley MA, Pagán JA. AN AGENT-BASED MODEL FOR IDEAL CARDIOVASCULAR HEALTH. Decision Analytics and Optimization in Disease Prevention and Treatment 2018;p. 241.

[110] Kramer F, Just S, Zeller T, New perspectives: Systems medicine in cardiovascular disease. BioMed Central Ltd.; 2018. https://doi.org/10.1186/s12918-018-0579-5.

[111] Lee LY, Pandey AK, Maron BA, Loscalzo J. Network medicine in Cardiovascular Research . Cardiovascular Research 2020 nov;https://academic.oup.com/cardiovascres/advance-article/doi/10.1093/cvr/cvaa321/5962174.

[112] Ni Y, Müller P, Wei L, Ji Y. Bayesian graphical models for computational network biology. BMC Bioinformatics 2018 mar;19(3):63. https://doi.org/10.1186/s12859-018-2063-z.

[113] Gupta A, Slater JJ, Boyne D, Mitsakakis N, Béliveau A, Druzdzel MJ, et al. Probabilistic Graphical Modeling for Estimating Risk of Coronary Artery Disease: Applications of a Flexible Machine-Learning Method. Medical Decision Making 2019 nov;39(8):1032–1044. https://pubmed.ncbi.nlm.nih.gov/31619130/.

[114] Presson AP, Yoon NK, Bagryanova L, Mah V, Alavi M, Maresh EL, et al. Protein expression based multimarker analysis of breast cancer samples. BMC Cancer 2011;11(1):230. https://doi.org/10.1186/1471-2407-11-230.

[115] Zheng PF, Chen LZ, Guan YZ, Liu P. Weighted gene co-expression network analysis identifies specific modules and hub genes related to coronary artery disease. Scientific Reports 2021 dec;11(1):6711. https://doi.org/10.1038/s41598-021-86207-0.

[116] Ledzewicz U, Schättler H, Friedman A, Kashdan E. Mathematical Methods and Models in Biomedicine; 2013.

[117] Mirams GR, Cui Y, Sher A, Fink M, Cooper J, Heath BM, et al. Simulation of multiple ion channel block provides improved early prediction of compounds' clinical torsadogenic risk. Cardiovascular Research 2011;91(1):53–61. https://doi.org/10.1093/cvr/cvr044.

[118] Li Z, Ridder BJ, Han X, Wu WW, Sheng J, Tran PN, et al. Assessment of an In Silico Mechanistic Model for Proarrhythmia Risk Prediction Under the CiPA Initiative. Clinical Pharmacology & Therapeutics 2019;105(2):466–475. https://onlinelibrary.wiley.com/doi/abs/10.1002/cpt.1184.

[119] Doste R, Bueno-Orovio A. Multiscale modelling of β-adrenergic stimulation in cardiac electromechanical function. Mathematics 2021;9(15):1785.

[120] Heijman J, Sutanto H, Crijns HJ, Nattel S, Trayanova NA. Computational models of atrial fibrillation: achievements, challenges, and perspectives for improving clinical care. Cardiovascular Research 2021;117(7):1682–1699.

[121] Kosta S, Dauby PC. Frank-Starling mechanism, fluid responsiveness, and length-dependent activation: Unravelling the multiscale behaviors with an in silico analysis. PLoS computational biology 2021;17(10):e1009469.

[122] Cheng L, Qiu Y, Schmidt BJ, Wei GW. Review of applications and challenges of quantitative systems pharmacology modeling and machine learning for heart failure. Journal of Pharmacokinetics and Pharmacodynamics 2021;p. 1–12.

[123] Finsberg H, Xi C, Zhao X, Tan JL, Genet M, Sundnes J, et al. Computational quantification of patient-specific changes in ventricular dynamics associated with pulmonary hypertension. American Journal of Physiology-Heart and Circulatory Physiology 2019;317(6):H1363–H1375.

[124] Smith RC. Uncertainty quantification: theory, implementation, and applications, vol. 12. Siam; 2013.

[125] Halnes G, Ulfhielm E, Ljunggren EE, Kotaleski JH, Rospars JP. Modelling and sensitivity analysis of the reactions involving receptor, G-protein and effector in vertebrate olfactory receptor neurons. Journal of Computational Neuroscience 2009;27(3):471.

[126] Valderrama AT, Witteveen J, Navarro M, Blom J. Uncertainty propagation in nerve impulses through the action potential mechanism. The Journal of Mathematical Neuroscience 2015;5(1):1–9.

[127] Tennøe S, Halnes G, Einevoll GT. Uncertainpy: a python toolbox for uncertainty quantification and sensitivity analysis in computational neuroscience. Frontiers in neuroinformatics 2018;12:49.

[128] Osnes H, Sundnes J. Uncertainty analysis of ventricular mechanics using the probabilistic collocation method. IEEE transactions on biomedical engineering 2012;59(8):2171–2179.

[129] Brault A, Dumas L, Lucor D. Uncertainty quantification of inflow boundary condition and proximal arterial stiffness–coupled effect on pulse wave propagation in a vascular network. International journal for numerical methods in biomedical engineering 2017;33(10):e2859.

[130] Mirams GR, Niederer SA, Clayton RH. The fickle heart: uncertainty quantification in cardiac and cardiovascular modelling and simulation. Philosophical Transactions of the Royal Society A 2020;378.

[131] Campos J, Sundnes J, Dos Santos R, Rocha B. Uncertainty quantification and sensitivity analysis of left ventricular function during the full cardiac cycle. Philosophical Transactions of the Royal Society A 2020;378(2173):20190381.

[132] Whittaker DG, Clerx M, Lei CL, Christini DJ, Mirams GR. Calibration of ionic and cellular cardiac electrophysiology models. WIREs Systems Biology and Medicine 2020;12(4):e1482. https://wires.onlinelibrary.wiley.com/doi/abs/10.1002/wsbm.1482.

[133] Lei CL, Clerx M, Whittaker DG, Gavaghan DJ, De Boer TP, Mirams GR. Accounting for variability in ion current recordings using a mathematical model of artefacts in voltage-clamp experiments: Modelling patch clamp artefacts. Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences 2020 jun;378(2173).

[134] Ortega FA, Butera RJ, Christini DJ, White JA, Dorval AD. Dynamic clamp in cardiac and neuronal systems using RTXI. Methods in Molecular Biology 2014;1183:327–354.

[135] Cooper J, Scharm M, Mirams GR. The Cardiac Electrophysiology Web Lab. Biophysical Journal 2016 jan;110(2):292–300.

[136] Brown TR, Krogh-Madsen T, Christini DJ. Illuminating Myocyte-Fibroblast Homotypic and Heterotypic Gap Junction Dynamics Using Dynamic Clamp. Biophysical Journal 2016 aug;111(4):785–797.

[137] Beattie KA, Hill AP, Bardenet R, Cui Y, Vandenberg JI, Gavaghan DJ, et al. Sinusoidal voltage protocols for rapid characterisation of ion channel kinetics. Journal of Physiology 2018 may;596(10):1813–1828.

[138] Steinman D. Computational modeling and flow diverters: a teaching moment. American Journal of Neuroradiology 2011;32(6):981–983.

[139] Minimal information required in the annotation of models (MIRIAM);. See *http://co.mbine.org/standards/miriam)*.

[140] Minimum information about a simulation experiment (MIASE);. See *http://co.mbine.org/standards/miase*.

[141] Simulation experiment description ML;. See *http://sed-ml.org/*.

[142] CellML;. See *https://www.cellml.org/*.

[143] Crimson;. See *http://www.crimson.software/)*.

[144] OpenCMISS;. See *http://opencmiss.org/*.

[145] Eck VG, Donders WP, Sturdy J, Feinberg J, Delhaas T, Hellevik LR, et al. A guide to uncertainty quantification and sensitivity analysis for cardiovascular applications. International journal for numerical methods in biomedical engineering 2016;32(8):e02755.

[146] Pathmanathan P, Cordeiro JM, Gray RA. Comprehensive uncertainty quantification and sensitivity analysis for cardiac action potential models. Frontiers in physiology 2019;10:721.

[147] Sarkar AX, Christini DJ, Sobie EA. Exploiting mathematical models to illuminate electrophysiological variability between individuals. The Journal of physiology 2012;590(11):2555–2567.

[148] Tveito A, Jæger KH, Lines GT, Paszkowski Ł, Sundnes J, Edwards AG, et al. An evaluation of the accuracy of classical models for computing the membrane potential and extracellular potential for neurons. Frontiers in computational neuroscience 2017;11:27.

[149] Klepach D, Lee LC, Wenk JF, Ratcliffe MB, Zohdi TI, Navia JL, et al. Growth and remodeling of the left ventricle: a case study of myocardial infarction and surgical ventricular restoration. Mechanics research communications 2012;42:134–141.

[150] Lee LC, Sundnes J, Genet M, Wenk JF, Wall ST. An integrated electromechanical-growth heart model for simulating cardiac therapies. Biomechanics and modeling in mechanobiology 2016;15(4):791–803.

[151] Niestrawska JA, Augustin CM, Plank G. Computational modeling of cardiac growth and remodeling in pressure overloaded hearts—Linking microstructure to organ phenotype. Acta biomaterialia 2020;106:34–53.

[152] Sacco F, Paun B, Lehmkuhl O, Iles TL, Iaizzo PA, Houzeaux G, et al. Evaluating the roles of detailed endocardial structures on right ventricular haemodynamics by means of CFD simulations. International journal for numerical methods in biomedical engineering 2018;34(9):e3115.

[153] Chase JG, Preiser JC, Dickson JL, Pironet A, Chiew YS, Pretty CG, et al. Next-generation, personalised, model-based critical care medicine: a state-of-the art review of in silico virtual patient models, methods, and cohorts, and how to validation them. Biomedical engineering online 2018;17(1):1–29.

[154] I C, H H. Comprehensive in vitro Proarrhythmia Assay, a novel in vitro/in silico paradigm to detect ventricular proarrhythmic liability: a visionary 21st century initiative. Expert opinion on drug safety 2014;13(6):745–758. https://pubmed.ncbi.nlm.nih.gov/24845945/.

[155] Keener J, Sneyd J. Mathematical physiology, 2nd edn, vols 1 & 2. Springer, New York; 2009.

[156] Bernardi J, Aromolaran KA, Aromolaran AS. Neurological Disorders and Risk of Arrhythmia. International Journal of Molecular Sciences 2021;22:188. https://www.mdpi.com/1422-0067/22/1/188.

[157] Mäki-Marttunen T, Lines GT, Edwards AG, Tveito A, Dale AM, Einevoll GT, et al. Pleiotropic effects of schizophrenia-associated genetic variants in neuron firing and cardiac pacemaking revealed by computational modeling. Translational Psychiatry 2017;7(11):5. https://www.nature.com/articles/s41398-017-0007-4.

[158] Gagnon L, Smith AF, Boas DA, Devor A, Secomb TW, Sakadžić S. Modeling of cerebral oxygen transport based on in vivo microscopic imaging of microvascular network structure, blood flow, and oxygenation. Frontiers in computational neuroscience 2016;10:82.

[159] Gerstner W, Kistler WM, Naud R, Paninski L. Neuronal dynamics: From single neurons to networks and models of cognition. Cambridge University Press; 2014.

[160] Billeh YN, Cai B, Gratiy SL, Dai K, Iyer R, Gouwens NW, et al. Systematic integration of structural and functional data into multi-scale models of mouse primary visual cortex. Neuron 2020;106(3):388–403.