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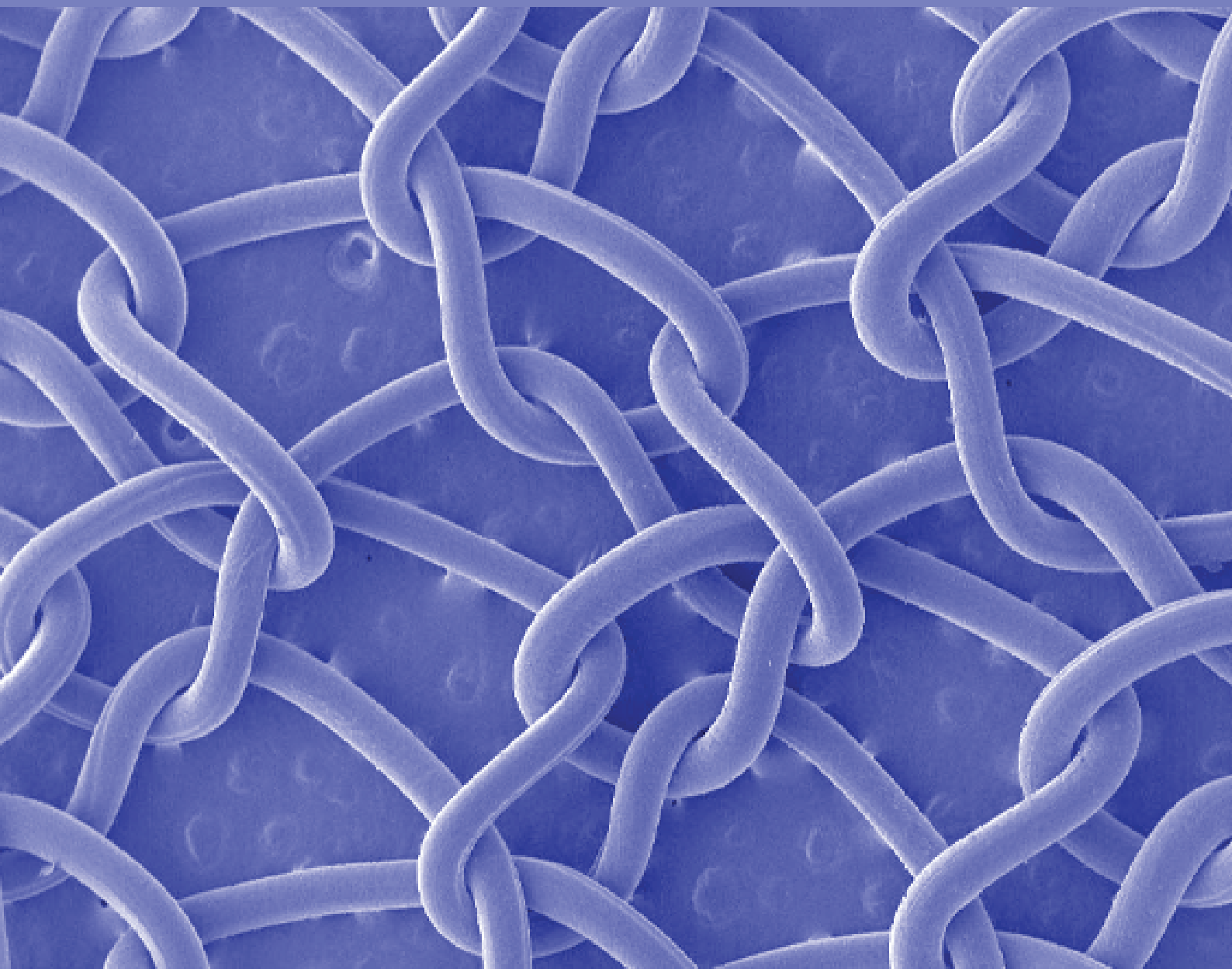

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MATHEMATICAL MODELS: A PRECIOUS TOOL FOR RESEARCH IN PHYSIOLOGY

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"In a few years' time we shall all wonder how we ever managed to do without them (*computer models*) in biological research".
Denis Noble, Science, 2002

ABSTRACT

The use of mathematical models in science has increased in the last decades, since it is clear that they constitute an essential tool for the progress of experimental research.
The main goal of this review is to present to the experimental physiologists some background on the different steps that are usually followed to develop a model. Probably more important, we aim to provide some basic thoughts to highlight the importance and need of mathematical modeling for scientific discovery and progress. The review also recapitulates the evolution of myocyte and Ca^{2+} handling models, the parallel work done in the interpretation of cardiac force generation, the integration of myocyte and force models into mechano-electric representations, and the construction of multi-scale models by assembling ventricular models with the mathematical descriptions of the circulatory system.

Keywords: mathematical models; cardiac myocyte; multiscale models; intracellular calcium

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Is Mathematical Modeling important? Why?

By definition, a model is a simplified representation of a complex system or phenomenon; a hypothetical description of a real intricate entity or process. A mathematical model simulates these systems with equations that describe the relationship between the different components of the model structure and forecast their behavior under specific conditions. Modeling should not merely reproduce the results of the phenomenon being simulated, but serve to understand, predict and postulate the intimate processes or underlying mechanisms that cannot be experimentally assessed or simultaneously evaluated with existing tools.

The usefulness of mathematical models can be fully appreciated through a very simple paradigm, which was wisely utilized in the pioneering work of Hodgkin and Huxley [1]: a mathematical model helps to interpret a given set of experiments and allows the generation of new hypotheses, which should be experimentally tested. The results from these experiments, provide, in turn, feedback to the model, i.e. it is the iterative interaction between experiment and simulation what matters. This process produces a virtuous circle in which the experiments feed the model with data and vice versa, the model supplies information guiding the research, reproducing experimental results, answering questions posed by study observations, identifying the most important players of a given mechanism (and consequently preventing unnecessary and redundant studies) and predicting new results that have to be validated experimentally (Figure 1). Moreover, the ability of simulations to concurrently explore several parameters provides possible physiological explanations that cannot be simultaneously observed in a single experiment.

Figure 1. Main steps in cardiac modeling. A hypothesis originated from experimental observations is modeled by means of mathematical equations. Model validation is performed with selection of adequate parameter values by simulation of experimental results other than those from which the model was built. This process is iteratively repeated until model validation indicates that the model is acceptable for using to predict results based on the original hypothesis. The whole process is repeated for any new model change.

The seminal study by Hodgkin and Huxley in 1952, describing the theory for action potential (AP) generation in the giant squid axon [1], is probably one of the first and best known applications of mathematical modeling to a biological event. This work, which is of paramount importance for the understanding of the mechanisms of AP generation, speaks by itself about how experiment and modeling should be used together to advance knowledge beyond what would be possible with either approach individually. But in addition, it constituted the starting point for innumerable experimental and modeling studies that helped to define the activation mechanisms in excitable cells from a wide range of systems.

Different steps in Mathematical Modeling

The first step in mathematical modeling is a well-devised hypothesis to define a structure or mechanism (Figure 1). This hypothesis, which is based on experimental observations, is expressed by a set of mathematical equations formulating the essential components, pathways, reactions, etc. included in the model, whose complexity depends on the question being asked, and the degree of detail with which the different elements of the model are represented. A key assumption in model design is the number of steps necessary to depict a certain component or pathway. For example, in the cardiac cell, the Na^+ channel current can be described by a single step of voltage-dependent channel conductance or involving numerous steps and compound states as in Markov models. If the aim of the model is to unravel Na^+ channel behavior, this approach is valid. However, if the Na^+ channel is one of the components participating in a more comprehensive mechanism, the need for an elaborate channel description should be evaluated and preferably simplified to clarify the performance of the overall response under analysis. The second step is the selection of model parameter values (channel conductances and reaction rates) associated to ion or chemical compound concentrations, based on direct experimental measurements or estimated through fit of observed data. In the case of simple models it is easier to assess whether model parameters represent physiological situations, whereas this is more demanding when numerous steps with many parameters are involved to represent a single component. Moreover, the effect of parameter changes on model performance is more straightforward the simpler the modeling framework is, and hence the interpretation of modeling predictions. The third step is model validation. This compares model output with experimental results other than the ones used to build the model and evaluates whether the modeling hypothesis matches the real phenomenon. Model changes are then performed to improve the simulation of the observable events, by adjusting the basic structure, the mathematical representations or the parameter values. These steps are iteratively repeated to optimize the model, making it ready for application as a suitable interpretation of a certain physiological mechanism [2]. In these steps it is of utmost importance to consider that equations and parameters must represent structural components and/or physiological behaviors, and not merely reproduce experiments, in order to preserve model consistency. Its final acceptance as a reliable tool for further research is the final step of model consolidation.

Myocyte models

Computational models have been widely used to study cardiovascular physiology in more detail than any other organ system. In this review, we will briefly give an account of the evolution of cardiac models simulating action potential generation, contraction and Ca^{2+} handling in the heart. Mathematical models of the electrical activity of the heart applying the Hodgkin–Huxley equations began with Noble´s 1962 model [3]. His most influential contributions started with his 1960 Nature paper [4] introducing the first mathematical and computational model of a cardiac Purkinje fiber cell, and extended right through to his 2004 study, in collaboration with ten Tusscher and Panfilov, presenting a detailed model of human ventricular cardiomyocyte activity [5]. During this extensive period of more than 50 years, new experimental data supported the development of a more dynamic type of myocyte model, not only by incorporating the main sarcolemmal ion channels, pumps and exchange flow mechanisms but also

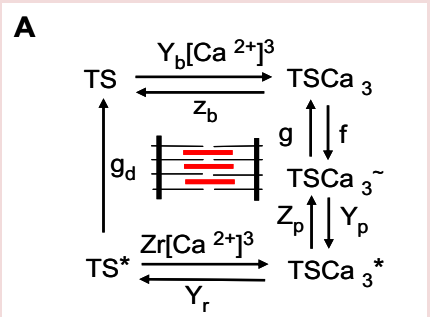
introducing for the first time intracellular Ca^{2+} regulation by the sarcoplasmic reticulum (SR) and Ca^{2+} buffers. The first most accepted representative of this new lineage of models was the Luo and Rudy (LR) model [6], which by the simultaneous representation of the AP and Ca^{2+} transient opened new possibilities in the interpretation of the molecular pathways involved in the physiological response of different normal and pathological conditions. Modeling complexity increased with the incorporation of a mitochondrial model to reproduce ATP generation [7], and other models were adapted to represent the human AP [5, 8, 9]. Parallel to new experimental findings, myocyte model structure was improved with the addition of intracellular CO_2 regulation [10], CaMKII and PKA pathways [11].

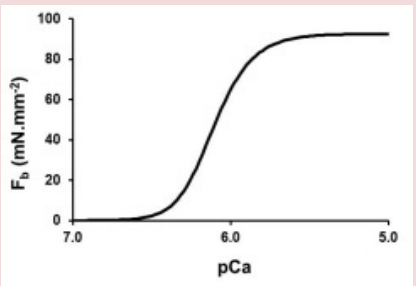
Introducing either experimentally-based or model-fit changes to myocyte parameters, these more complete models were used to represent different normal or pathological conditions, as acidosis [10], post-acidotic arrhythmias [12], heart failure [13], or β-adrenergic stimulation [14]. The limitations of these models reside in part in the fact that they failed to represent myocyte force development. Force models (**See box**) evolved separately from electrical and Ca^{2+} handling representations, and although

Force development models

Since the postulation of the cross-bridge (XB) theory [15, 16], muscle models have been based on the representation of its elementary contractile unit: the sarcomere, where force is generated by the interaction between myosin (thick) and actin (thin) filaments through the myosin XB head. Cross-bridge attachment to the thin filament is enabled by binding of Ca^{2+} to troponin C within a regulatory unit (RU) [18] and each XB acts as an independent force generator. The interpretation of muscle contraction has given rise to different types of models, which may be classified into two main approaches: one in which XB kinetics does not include the Ca^{2+} activation process and another where Ca^{2+} activation is incorporated into the XB RU dynamic scheme. In the first approach postulated by Julian et al. [18], Ca^{2+}-activated XBs could be in either of three states: detached, attached before the power stroke or attached after the power stroke. Using the same basic scheme, Razumova et al. [19] and later Tran [20] extended this model to cardiac cells where an imposed intracellular Ca^{2+} signal activated the RU but free Ca^{2+} concentration did not change as a result of its binding and unbinding to troponin C. It also included cooperativity, a mechanism favoring the process leading to force generation.

The second approach to build cardiac contractile models contemplated Ca^{2+} binding to troponin C in the balance of intracellular Ca^{2+} concentration. This new perspective was based on the four-state RU system to represent force generation postulated by Peterson et al. [21], contemplating two force-developing states: one with Ca^{2+} bound and another without bound Ca^{2+} (**A**). This scheme was further developed including for the first time a XB mechanical structure, with sarcomere length-dependent affinity of XB attachment and XB dynamic behavior [22]. In this model, all attached XBs were represented by an equivalent XB (XBeq), whose elastic structure changed its elongation during muscle shortening or lengthening. Further model complexity with the incorporation of ATP and cooperativity allowed the respective reproduction of the effect of anoxia [23] and a wide range of steady state, like the sigmoidal shape of the force-Ca^{2+} relationship typical of muscle myofilaments (**B**) and twitch contraction experiments [24], enabling the integration of force models with myocyte representations.





some attempts were made to link all aspects involved in the physiology of the cardiac cell, until recently the intracellular Ca^{2+} transient resulting from Ca^{2+} management was not coupled to the mechanical activity, failing to provide an integrated interpretation of excitation-contraction coupling.

The interaction of both models has been used as a more physiological approach to analyze simulated experimental results and the prediction of new hypotheses to be tested in the laboratory (Figure 2A). In this framework, the most significant link between myocyte and contractile models is Ca^{2+} utilization by the contractile apparatus, reproducing the influence of different types of contraction on the Ca^{2+} transient (mechano-electric coupling).

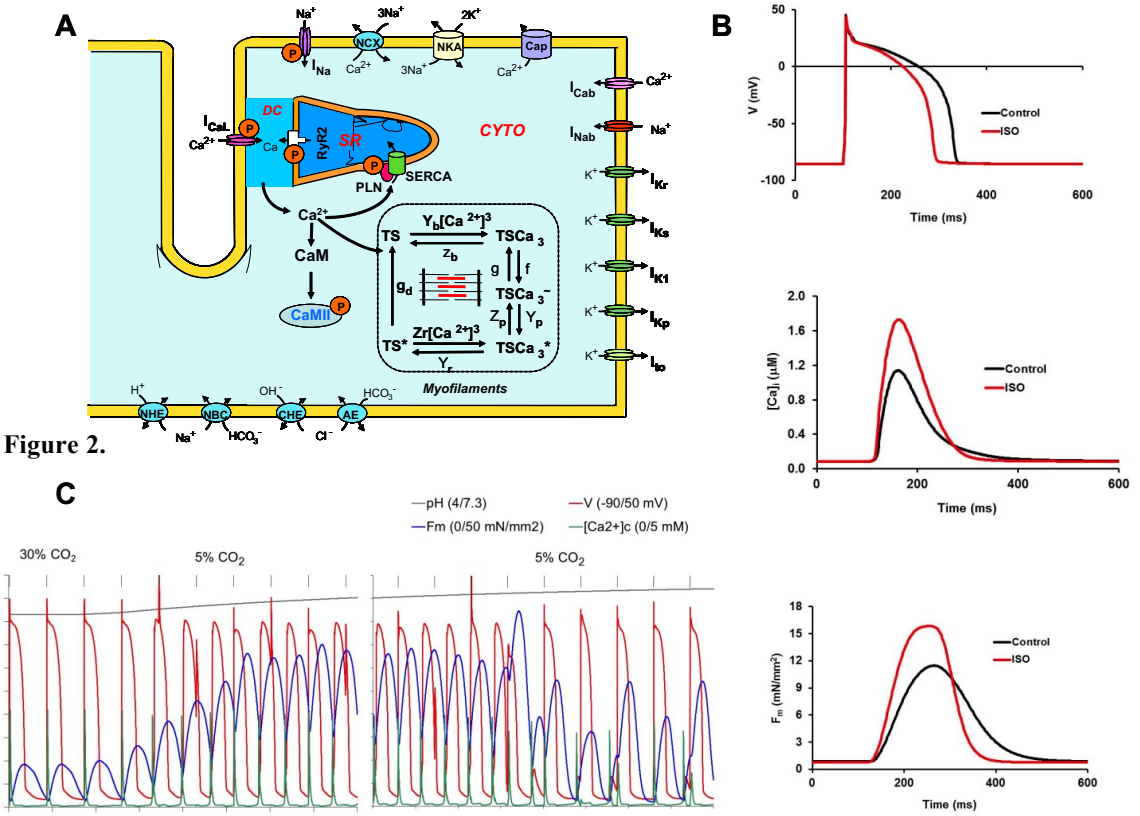


Figure 2.

Myocyte models **A.** The electro-mechanical model depicts sarcolemmal and intracellular ion flows, and myofilament Ca^{2+} management (see box). **B.** Normal and β-adrenergic simulations of voltage, Ca^{2+} transient and force in a rabbit myocyte model (adapted from Negroni et al. [26] using Shannon´s myocyte rabbit model [34]). The model mimics action potential shortening, increased intracellular free [Ca^{2+}] and the positive inotropic and lusitropic effect produced by β-adrenergic stimulation. **C:** Experimentally-observed post-acidotic arrhythmias simulated in the ten Tusscher human myocyte model [12] The model simulates the arrhythmias [spontaneous action potentials (SAP) and delayed afterdepolarizations (DADs) (*arrows*)] that occur when normal pH is restored after a period of acidosis.

Therefore, inclusion of myofilament Ca^{2+} utilization is not only crucial for modeling force generation by the myocyte but is also important for realistic representation of cytosolic Ca^{2+} transients and Ca^{2+} cycling, particularly in the simulation of pathological situations, such as heart failure, in which the reduced myofilament Ca^{2+} sensitivity increases Ca^{2+} overload. This requires balancing intracellular free Ca^{2+} by incorporating myofilament Ca^{2+} utilization as another cytoplasmic Ca^{2+} buffer. Most cardiac models have used Ca^{2+} to activate myofilaments but without the effect of Ca^{2+} utilization on the intracellular free Ca^{2+} generated by the action potential [19], while others have modified their troponin Ca^{2+} buffer equations to express this aspect [7, 25]. On the other hand, a

more direct approach takes into account the fact that the buffer capacity of troponin C changes according to the type of contraction (force generation or shortening), influencing the dynamic of Ca^{2+} transient [23, 26]. Moreover, the relevance of mechano-electric coupling can be appreciated when modeling is used to unravel the interplay between myocyte ion flows and the contractile machinery in situations when both are affected by a certain intervention, as in β-adrenergic stimulation. This is the case of a recent study integrating the Soltis-Saucerman myocyte model [11] with the Negroni-Lascano contraction model [12] to analyze the relative contribution of different phosphorylation targets to the overall mechanical response driven by β-adrenergic stimulation (Figure 2B). This model was able to show that the decrease in myofilament Ca^{2+} sensitivity produced by β-adrenergic stimulation is compensated by the increase in intracellular Ca^{2+}, partially recovering Ca^{2+} binding to Troponin C. It also highlights the essential role of the enhanced cross bridge (XB) cycling in the β-adrenergic increase contractile response [26]. Another mechano-electrical model,- using the modified ten Tusscher human myocyte model coupled to the contractile Negroni-Lascano representation,- was able to reproduce and explain the generation of postacidotic arrythmias observed in isolated rat hearts [12] (Figure 2C). However, these model are still unable to reproduce several steps of excitation-coupling in detail, for instance the regulation of RyR2, by Ca^{2+} and Ca^{2+} buffers and proteins inside the SR or the representation of diastolic events, like arrhythmogenic Ca^{2+} waves propagation.

Multiscale models

A further step in cardiac modeling has been the development of ventricular representations based on different myocyte and myofilament dynamic models to address specific basic science or pathological questions at the organ level. In purely ventricular mechanical models driven by simple schemes to develop intracellular Ca^{2+} transient, different geometrical force-length to pressure-volume transformations have been adopted to represent ventricular function, although it should be borne in mind that these descriptions are elementary approaches to an actual ventricle, constrained in the type of cells and their orientation to develop ventricular pressure. These models, however, have been able to demonstrate that ejecting pressure compared with isovolumic pressure, depends not only on the number of attached XBs (governed by sarcomere length) but also on their elongation (responsible for XB developed force), as shown both in simulated [27, 28] and in experimentally model-fitted ejecting pressure from open-chest dogs [27] (Figure 3A). Numerous other models have coupled a mechanical with an electrical component giving rise to multiscale models of the heart. The mechanical component is based on a myofilament model activated by Ca^{2+} to produce contraction of the whole organ interpreted as an orthotropic elastic material described by equations of continuum mechanics. In this model construction, the electrical component is represented by a cardiac myocyte generating a wave of depolarization propagating throughout the heart according to the conductivity arising from its organization into fibers or laminar sheets. Simulation studies using these more comprehensive models of the heart have been important in revealing the mechanical effects of altered electrical activity and arrhythmogenesis (for review see Trayanova and Rice [29]).

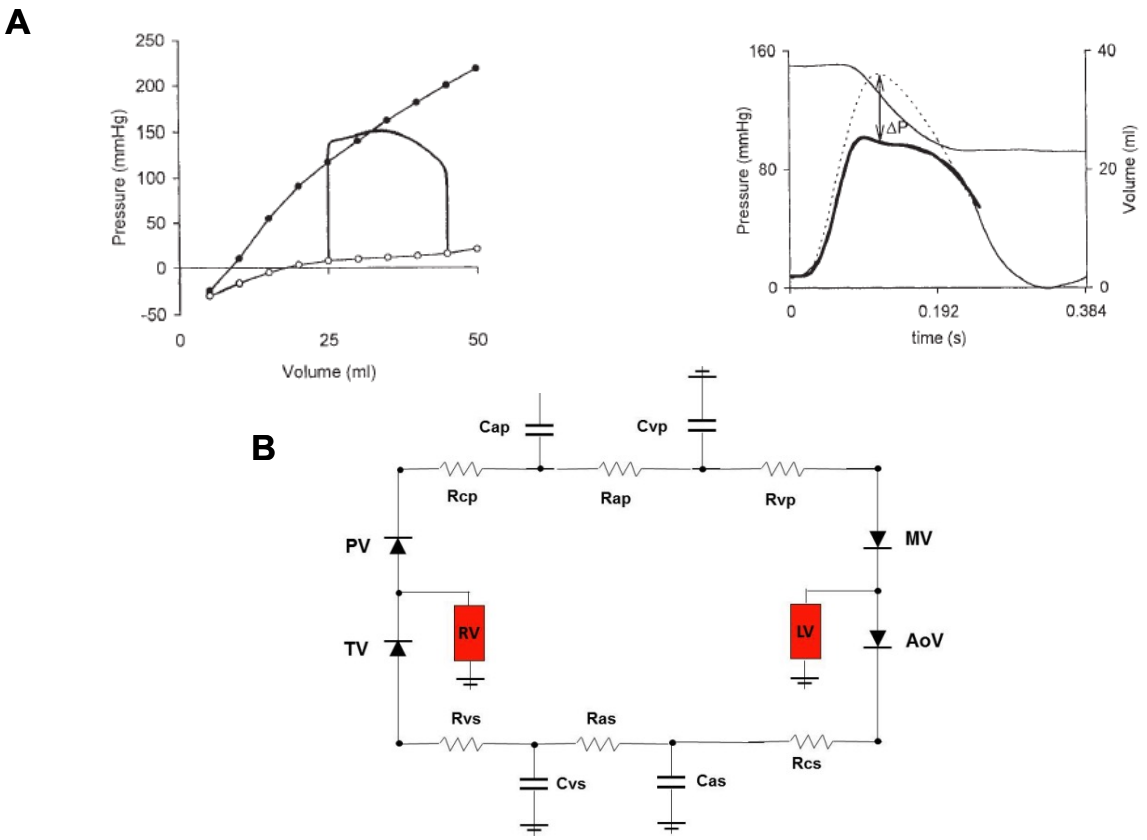


Figure 3. Multisacale models. **A.** Simulations using a ventricular model resulting from force-pressure and length-volume transformation [27]. *Left*: Pressure volume relationship and single beat loop simulations. *Right*: Time course of experimental pressure in open-chest dog (thin line), model fit of ejective pressure (thick line) and simulation of isovolumic pressure (dotted line). **B.** Multiscale model depicting left and right ventricular chambers (LV, RV), with pulmonary and systemic circulatory circuits, represented by a resistive (R)-capacitive Windkessel structure (adapted from Santamore and Burkhoff [30]), where PV, TV, MV and AoV are pulmonary, tricuspid, mitral and aortic valves, Rcp, Rap, Rvp, are pulmonary characteristic, arterial and venous resistances and Cap and Cvp are pulmonary arterial and venous capacitances, and Rvs, Ras, Rcs, Cas and Cvs their systemic counterparts.

The final step in cardiac modeling is the integration of ventricular representations into a model of the cardiovascular system to analyze the impact of molecular changes at the myocyte level on the hemodynamic behaviour of the circulatory system, and in turn that of the peripheral circulation on the heart. In this type of multiscale models the heart acts as a pump responsible for blood flow through a closed-loop circulatory system consisting of a series of resistances and capacitances [30] (Figure 3B). Based on this principle, recent multiscale models have been developed to obtain mechanistic insight into the load dependence of the end-systolic pressure-volume relationship [31], the prediction of atrial or ventricular heart chamber behaviour [31], or the understanding of the electrical, mechanical and hemodynamic interaction in pathological conditions such as heart failure [32].

The ultimate goal of these multiscale representations is the conversion of generic into patient-tailored models to create a diagnostic and therapeutic support for the cardiologist [33]. Using patient-specific data as model input, they would be useful to predict drug effects on the cardiovascular system before their administration to the patients, aiding in the decision-making process of patient care.

Conclusions

In this Mini Review we have attempted to emphasize the importance of modeling in the interpretation and prediction of biological data. As an example, we succinctly reviewed the major steps in the development of cardiac models, ending in the multiscale models. Although the incorporation of biophysical cell models into whole organ models is still emerging, it is important to understand that development of these models is critical for understanding complex phenomena, as following with the example of the heart, atrial and ventricular arrhythmias.

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