Bridging experiments, models and simulations: an integrative approach to validation in computational cardiac electrophysiology

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Carusi A, Burrage K, Rodríguez B. Bridging experiments, models and simulations: an integrative approach to validation in computational cardiac electrophysiology. Am J Physiol Heart Circ Physiol 303: H144–H155, 2012. First published May 11, 2012; doi:10.1152/ajpheart.01151.2011.—Computational models in physiology often integrate functional and structural information from a large range of spatiotemporal scales from the ionic to the whole organ level. Their sophistication raises both expectations and skepticism concerning how computational methods can improve our understanding of living organisms and also how they can reduce, replace, and refine animal experiments. A fundamental requirement to fulfill these expectations and achieve the full potential of computational physiology is a clear understanding of what models represent and how they can be validated. The present study aims at informing strategies for validation by elucidating the complex interrelations among experiments, models, and simulations in cardiac electrophysiology. We describe the processes, data, and knowledge involved in the construction of whole ventricular multiscale models of cardiac electrophysiology. Our analysis reveals that models, simulations, and experiments are intertwined, in an assemblage that is a system itself, namely the model-simulation-experiment (MSE) system. We argue that validation is part of the whole MSE system and is contingent upon 1) understanding and coping with sources of biovariability; 2) testing and developing robust techniques and tools as a prerequisite to conducting physiological investigations; 3) defining and adopting standards to facilitate the interoperability of experiments, models, and simulations; and 4) understanding physiological validation as an iterative process that contributes to defining the specific aspects of cardiac electrophysiology the MSE system targets, rather than being only an external test, and that this is driven by advances in experimental and computational methods and the combination of both.

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Over the last 50 years there have been huge advances in mathematical models and simulation tools and techniques used in a number of areas of physiology, leading to more sophisticated models able to include more fine-grained biophysical detail, a greater number of variables, more complex sets of equations, and a greater level of integration. Perhaps the most advanced area of computational physiology is computational cardiac electrophysiology, concerned with the investigation of the electrical activity of the heart. Computational models of cardiac electrophysiology are multiscale both spatially and temporally and integrate information across subcellular, cellular, tissue, and organ levels (with spatial scales ranging from nanometers to meters and temporal scales from picoseconds to years). Multiscale cardiac modeling and simulation have been crucial in improving our understanding of ionic mechanisms of normal and abnormal heart rhythm, electrotherapy, and the electrocardiogram. Over 40 mathematical models of the electrical excitation in single cardiac cells are now available (see www.cellml.org). Three-dimensional anatomical models of the cardiac ventricles and atria have also been constructed [see, for

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instance, the following studies (2, 3, 11, 14, 31, 47, 60, 65, 72, 77, 83a, 91, 96, 99, 102, 110, 111)]. Simulations using sophisticated software and numerical techniques have been conducted to investigate the effect of drugs, disease, or mutations at the ionic level on the electrical activity of the human heart (66, 77, 96, 107, 110). Similar progress has also been seen in areas of computational physiology related to organs such as lung, kidney, liver, and brain. However, at this point, progress in validating integrated multiscale whole organ models is more patchy. While different levels are validated separately, the integration of a multiscale model presents new challenges to validation, and relatively few studies go on to attempt validation at the whole organ level (14, 81, 96, 111). Our aim is to contribute to an understanding of validation of whole organ models in cardiac electrophysiology, and for this it is necessary to understand what is the nature of the multiscale model that is being validated.

While the term “model” is often used, with an assumption that there is a common definition of it, there is in fact a wide variety of understandings of what a model is in the scientific community, as was shown in interviews with scientists (1). The philosophy of science and of modeling also analyzes this term in different ways. Traditionally the two most common conceptions of models in the philosophical literature have been 1) the representational view (according to which models accurately or realistically capture features of the domain in question) and 2) the instrumentalist view (according to which models are heuristic tools for probing systems). More recently this distinction has been questioned, and different accounts have been given of the ways in which the representational and instrumentalist view of models might be related (61). The understanding of the term “model” has not been analyzed in the field of computational physiology. In this setting, a common view of models is that they are, “by definition, simplified representations of reality” (50). However, this view does not inform the criteria for construction, use, and validation of models. This article is an attempt to define the pragmatic framework of cardiac electrophysiology and identify the important conceptual and methodological challenges that arise in bridging models, simulations, and experiments.

In cardiac electrophysiology (and computational physiology, in general), the question of what models represent and how they can be validated is made more difficult by the fact that models and simulations are multiscale, spanning a range of spatial scales (at least from $10^{-9}$ to $10^{0}$ m, from protein complexes to whole human) and temporal scales (at least $10^{-7}$ to $10^{8}$ s, to capture behavior from ion channel opening to disease development and aging) (82, 93). It is therefore difficult to identify one entity that can be considered the model or representation source. Indeed, this is especially true in multiscale settings, in which models can be regarded as ensembles or combinations of functional and structural models at different levels from the ionic to the whole organ. We claim that a more insightful view of the nature of modeling and simulating requires an understanding of the whole process of constructing models and simulations. Therefore, we analyze the stages of the construction of computational cardiac electrophysiology models and simulations from the ionic to the whole organ level showing how they form an interrelated system in which no part can be isolated from the others. Our main aim is to inform strategies for validation by highlighting the complex relationships among models, experiments, and simulations in cardiac electrophysiology. We then discuss implications of this analysis for validation and prediction. This article does not, however, intend to be a thorough review of the studies published in computational cardiac electrophysiology and therefore the list of referenced articles is necessarily incomplete. The reader can refer to previously published reviews of specific areas of computational cardiac electrophysiology [such as, for example, the following studies (17, 25, 41, 87, 99)].

Multiscale Models and Simulations in Cardiac Electrophysiology

In the following sections, we describe the process underlying the development of multiscale models and simulations in cardiac electrophysiology from the subcellular to the whole organ level. While other authors have touched on some of the aspects that we bring together in this article and, in particular, the interaction between simulation and experiments, these authors have focused more on cell models (67, 68) or systems biology approaches (50, 58b) at levels below the organ level. Our contribution is to probe all levels of scale but with a particular emphasis on whole organ models in cardiac electrophysiology.

Equations. Cardiac electrophysiology concerns the study of the electrical activity of the heart under both normal and abnormal conditions. The construction of the models involves a complex iteration between models, simulations, and experiments, spanning multiple spatiotemporal levels, as schematized in Fig. 1. At the whole organ or tissue level, electrical propagation in cardiac tissue is often simulated using the bidomain equations or alternative simplified formulations such as the monodomain, Eikonal, or graph-based models (51, 105). In a human heart, the myocardium consists of the order of $10^{10}$ cells, and it is not computationally feasible to simulate, in a bottom up fashion, the electrical propagation through this number of cells. Instead the bidomain model represents a middle out approach, which arises by assuming a homogenization principle in which the smallest unit is a block of cells. The bidomain model consists of two partial differential equations based on the assumption that cardiac tissue is a continuum, which behaves electrically as two domains, the intracellular and the extracellular media. The bidomain equations relate intracellular and extracellular electrical potential to current flow at each tissue node. Each of the two media is modeled as an anisotropic network of resistors, with the intracellular and extracellular networks being connected at each node point by the cellular membrane. Two fundamental laws are used: Ohm’s law (to relate electrical potential to flow of transmembrane, intracellular, and extracellular currents) and Kirchhoff’s law (for conservation of charge).

Perhaps the most complicated term in cardiac electrophysiology models is the nonlinear term representing the cellular dynamics accounting for transmembrane and subcellular currents [see, for example, the following studies (21, 26, 30, 39, 40, 54, 55, 58, 67, 70, 92)]. From the electrophysiological point of view, the cellular membrane acts as an electrical isolator, which hosts proteins of transmembrane ionic transport, functioning as ion channels, exchangers, and pumps. Therefore, at the cellular level, membrane electrical properties are modeled as a capacitor in parallel with a nonlinear term accounting for the conductivities of transmembrane proteins including ion
channels, exchangers, and pumps (46). Equations are based on knowledge of the biophysical processes underlying ionic transport, but uncertainty regarding understanding of underlying those biophysical processes means that often several mathematical formulations could be used in the models. In those cases, often the equation that allows best fit between simulation results and experimental data with similar conditions imposed is chosen.

Multiplicity of cellular models in cardiac electrophysiology is also due to a compromise between complexity, computability, and knowledge (67). In view of the great complexity of measuring and modeling ionic currents, an alternative approach is also adopted to model cardiac action potential dynamics, consisting of simplified or phenomenological models (18, 33, 106). The equations in this type of model aim at capturing morphology and rate-dependent properties of specific action potentials without including a detailed description of specific ionic currents. This has the advantage of a reduced number of equations and parameters to be identified with the limited information obtained from experimental recordings.

Parameter values. Whereas the mathematical framework described above is generic for cardiac tissue, the models are aimed at being specific, for example, of a particular animal species or spatial location within the heart (for example, dog vs. rabbit, atria vs. ventricles). Data obtained from wet-laboratory experiments are the means whereby the generic and abstract mathematical equations are related to specific and particular cardiac physiological features and processes (1, 26, 30, 34, 39, 40, 70, 54, 55, 58, 79). Parameter values in the models are obtained directly from experimental measurements (when possible) or indirectly by minimizing the difference between simulated and measured experimental behavior using similar conditions in both cases. Parameters are linked to the specific conditions and experimental models in which the measurements were performed (such as animal species and location of origin of the preparation, temperature, solutions, measurement technique, etc.). A clear account of conditions and techniques used in the experiments for model development and validation is therefore particularly important and needs to be clearly described and linked to each model (80).

As novel experimental findings are obtained, equations and parameters in the models are updated and new models are developed with novel and improved features but also aspects inherited from previous models (64, 67, 83, 86). Parameters in the equations describing ionic current kinetics are estimated from voltage-clamp recordings in isolated cells, which often involve pharmacological block of ionic currents other than the one of interest. These measurements have two main limitations. First, drug block is often nonspecific and therefore ionic current measurements include contamination from other currents. Second, cells used in voltage-clamp experiments have undergone an aggressive isolation procedure that damages the cell membrane and results in a decrease in numbers of ion channels (109). For modeling purposes, it is assumed that the dynamics of ionic channels are not affected by the isolating procedure. But in fact, the current conductance (that is the product of unitary conductance and whole cell number of channels) is decreased in isolated cells with respect to tissue. This is due to the decrease in channel numbers caused by damage during the isolation procedure (109). Thus, if current conductance in the models is estimated from isolated cell voltage clamp recordings, its value will be underestimated with respect to the one present in intact tissue. Therefore, modelers often choose to estimate the current conductance indirectly, by measuring the effect of block of the ionic current under investigation on electrophysiological properties in tissue preparations (26, 70, 95, 79). Differences in the interpretation of the experimental data and the information they provide on model parameters can explain some of the differences observed in models targeting similar aspects of cardiac electrophysiology, as for example seen in models of the human ventricular action potential (21, 40, 70) or the rabbit ventricular action potential (58, 86, 92). Furthermore, the blurring between single cell and tissue levels both in model building and experimental procedures is an important issue that is often overlooked but becomes more apparent when viewed in the context of an model-simulation-experiment (MSE) system, as this article makes clear.
At the whole organ and tissue level, important parameters in the bidomain equations are the intracellular and extracellular conductivity tensors, which include two important pieces of information: fiber architecture and conductivity. Fiber architecture, which is the local direction of the conductivity tensor at all points of the model, is usually incorporated into tissue models by extracting information from histological or diffusion tensor-MRI images using image processing algorithms or using a mathematical rule that relates fiber rotation at a particular location with distance to the surfaces of the ventricular wall (43, 51, 77, 103, 111). Conductivity values along and across fibers are indirectly determined to yield the conduction velocities in all directions and are measured experimentally in tissue (44).

An important aspect in parameter estimation in cardiac electrophysiology is the high degree of interspecies, intersubject, temporal, and spatial variability in experiments (79, 83, 84, 86, 90). Equations and parameters are obtained based on experimental data from a variety of preparations and experiments often from a number of different laboratories. In experiments, different samples are used to achieve statistical significance and usually average values of a particular property are used to fit the data for model construction. Variability among the different recordings, measured as standard deviation or standard error of the mean, is largely ignored in the construction of cardiac electrophysiology models. This raises important questions about what models represent, with important consequences in the definition of how the comparison between simulations and experiments needs to be performed for validation purposes from the ionic to the whole-organ level.

Anatomically based meshes of the heart. The equations and parameter values described above allow simulation of electrophysiological function in cardiac tissue. The spatial characteristics of the tissue (such as its geometry) are defined by the mesh, which is part of tissue or whole organ models. As illustrated in Fig. 2, the representation of the anatomy of the upper or lower chambers of the heart (whole atria or whole ventricles models) is obtained from imaging modalities such as MRI and histology using segmentation techniques to obtain a binary image that defines the boundaries of the cardiac tissue (11, 75, 76, 97, 102, 111). The binary image is then used to generate a volumetric mesh by applying a discretization process in space necessary to conduct the simulations, as described in the next section. Thus the underlying tissue model is a discrete one composed of cells (the cardiac tissue), which is turned into a continuous model (the bidomain model), and finally turned back into a discrete model required to conduct the computer simulations. The anatomically based volumetric mesh comprises the elements or points in the cardiac domain over which the solution to the bidomain equation is calculated. The volumetric mesh is therefore defined by the image-based anatomy and the numerical method used in the simulations to solve the bidomain equations. To resolve the spatial scales of the electrophysiological dynamics, human ventricular meshes can contain over thirty million fine elements (60, 65, 72, 110). Thus the mesh is a mediation between the models and simulations, as explained further below.

Simulations. As illustrated in the previous section, models and simulations are intertwined in the model construction process. At the ionic and cellular level, equations and parameters are determined by minimization of the difference between simulation results and mean experimental values. At the tissue and whole organ level, the numerical method required to conduct the simulations determines how tissue meshes are discretized into smaller spatial steps, impacting the anatomical model. The mesh spatial resolution is determined to achieve convergence of numerical algorithms and has no relationship with the size of the cells.

Simulation complexity is addressed in various ways, all of which involve a trade-off between efficiency, robustness, and accuracy within the numerical routines. There are subtle interplays between spatial and temporal resolutions, and these interplays vary from method to method. Without a good understanding of these dynamics, it is possible to get unstable behavior or numerical artefacts (22, 24, 73) that would affect simulations results, and therefore model construction. An important implication of the intertwining of models and simulations identified here is that a first requirement for model validation is the robustness and accuracy of the simulation techniques used in the model construction process.

Simulations in cardiac electrophysiology are conducted for three main purposes: 1) to build the models themselves and determine equations and parameter values; 2) for model validation by comparing simulation results with independent experimental
data sets (not used in model construction); 3) to investigate the novel electrophysiological phenomena under study.

Simulations are also defined by the stimulation protocols and conditions imposed. In the case of 1) and 2), simulation conditions aim at mimicking the conditions applied in the experimental data sets used in model construction and validation, respectively. In the case of 3), simulation conditions, including equations, parameters, meshes and stimulation protocols, need to be designed based on the hypotheses to be tested and phenomena to be investigated.

Models as Representations? The MSE System

From this overview of the different stages of the construction of a representing system, with the variety of inputs, techniques, and interplay between different factors, it is clear that there is not, in fact, a model that can be described as a representation. If there is a representation at all, this role can only be assigned to the whole assemblage of experiments, models, and simulations with the different subsidiary processes that go into building it: the MSE system. The process of constructing the MSE system consists of the following stages.

First, the mathematical formulation including equations and parameter values for membrane kinetics is determined by background assumptions, existing knowledge, and hypotheses about the biophysical functioning of ion channels and assumptions about best fit between experimental data and simulation results. Already at this stage, there is an abstraction in that only what is believed to be relevant for the cardiac electrophysiological model is extracted.

Second, the mesh mediates between models (in the form of parameterized equations) and simulations since it allows for the solving of the equations on a tissue domain in the computational simulation. The mesh also allows for the visual representation of the model and visual interpretation of the simulation results in spatial and temporal terms.

Third, the simulation techniques are a three-way negotiation among computational tractability, existing knowledge of the target domain, and the model in the form of equations. There is no clear line to be drawn between the models (in the form of equations, parameters, and meshes) and the simulations, since there is feedback between the simulations and the models, as well as feed-forward from the equations to the simulations.

Fourth, at the same time, a hypothetical target domain, which consists of the specific aspects of cardiac electrophysiology under investigation, is constructed from the information extracted from experimental data, relative to the accuracy of the experimental techniques. This construction is the way in which the basis for a representational relationship is established, since this is the way in which the MSE system reproduces the relevant features of cardiac electrophysiology undergoing investigation and that make up the target domain. It is important to notice that the whole process of building the MSE system integrates different sources of data and finally goes beyond anything that is available from experimental data in an attempt at a systems-level/multiscale reconstruction.

Therefore, the use of modeling and simulation as a research tool already targets specific aspects of cardiac electrophysiology (the target domain), by considering a background of assumptions and specific research questions. This is illustrated in the diagram presented in Fig. 3. Representation is achieved through the process of modeling and simulating, building on existing experimental data and assumptions based on existing knowledge. Several stages of the process of modeling and simulating extract information from this target domain to try to reinstantiate in the MSE system some of the relevant aspects of cardiac electrophysiology, chosen based on the underlying hypotheses. Other stages of the process make up for the limitations of specific experimental data sets and go beyond it by integrating experimental data from ionic to tissue level obtained using a variety of experimental techniques. A process of iteration takes place between a background consisting of prior knowledge, available techniques and assumptions, extraction of information, and refinement of the background to integrate and expand existing knowledge.

The need for using different techniques to obtain information at different levels comes from the need to address the limitations of each of the experimental data sets used in the definition of the MSE system at each level of integration, as discussed in Parameter values. Integration is not a new ability for the life sciences. Experimental and clinical electrophysiologists have always integrated different sources of knowledge and information, using a variety of techniques and practices, both explicit and tacit. Sometimes the result is a conceptual model, often rendered in the form...
of diagrams. What is aimed for with a computational integrative model is a model that can be manipulated directly to make and test predictions. MSE computational physiology systems allow novel ways to interact and probe the electrophysiological system to expand knowledge.

While clearly it is possible to take the MSE system apart and to decompose it into its parts, the way in which it functions is as a system itself, consisting of equations, parameter values, and simulation techniques and output, where each part interacts with the others and with experiments, under the umbrella of the scientific questions or hypotheses to be tested (Fig. 3). When it comes to validation, it is crucial that the whole MSE system be validated, as this is proof that the representation has hit its target and the representational relation holds.

The multiscaled MSE allows us to address questions at a level that is higher than the components that make up the MSE. Even when each of the levels is separately validated, different strategies for validation must be used for the integration of different levels in the multiscale whole organ model. For example, Occam’s principle must be applied at each level to avoid parameter accumulation. However, this balance between a simple representation fit for purpose and the increasing complexity of multiscaled MSEs is not just a computational issue but raises several crucial philosophical and methodological issues.

**Implications for Validation**

Whereas models, tools, and research environments in cardiac electrophysiology have gone through profound changes in the last 50 years, the criteria of validation of simulation results are still not as clear as they could be. For example, 50 years ago, Noble wrote, “It can be seen that the general shape of the action potential (A) corresponds very closely to that observed experimentally in Purkinje fibers” (66). Here, it is implicit that representation occurs by means of qualitative correspondence. However, as modeling and simulating techniques develop, we must ask the question whether the relationship of representation should be understood in quantitative or in qualitative terms or both. This is crucial for our understanding of what it means for models to be described as representations and also to measure the success of a model in targeting a domain. This is a question that imposes itself particularly forcefully in the case of multiscale whole organ models where the complexity is such that we may need different ways of balancing qualitative and quantitative outputs. Few studies raise this important issue (108).

The process of validation is therefore one which needs to consider the MSE system against the background of its construction to be able to interpret the results of the attempted validation and to evaluate those results. This is no different from any other experimental science, including wet-laboratory experimental biology, where the interpretation of experiment results depends on a precise knowledge and often firsthand familiarity with the entire history of the samples, starting from the choice of animal model to all the techniques used for producing and experimenting on samples.

Physiological validation of computational models is performed by comparison to independent experimental data sets not used in the construction of the MSE system. Figure 4 illustrates examples of studies providing a comparison between simulations and experiments at the single cell level and at the whole ventricular level. The comparison can be performed in two ways (and often a combination of both): 1) quantitatively, by checking that the value for a specific electrophysiological property (such as action potential duration) in simulations is within the range reported in experiments [see, for example, the following studies (26, 54, 55, 70, 84, 100, 104)] or 2) qualitatively, by observing the outcome of a particular intervention (for example, a certain drug block leads to abnormalities in repolarization or reentry) (26, 55, 70, 88, 108). The perceived robustness of these two modes of validation is a very important issue that requires further reflection and that, however, goes beyond the scope of this article.

The multiscale nature of models in cardiac electrophysiology often results in the data sets for construction and for validation being acquired at different levels and therefore in different preparations and using different techniques (78, 81). As a consequence, the multiscale models and in particular those spanning the ionic to the whole ventricular level are often constructed from experiments using a variety of techniques and preparations. Each experimental technique involves a modification of the preparation with respect to its in vivo state (for example, the isolation procedure). Therefore, a challenge for validation is to obtain the appropriate knowledge of the specific

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Fig. 4. Examples of comparison between simulation and experimental results for validation at the single cell and whole ventricular levels. A: human action potentials obtained from stochastic simulations and experimental micro-electrode recordings under control conditions and following block of the rapid component of the delayed rectifying current ($I_{Kr}$) [adapted with permission from Pueyo et al. (79)]. The comparison shows agreement between simulations and experiments (qualitative validation), and the occurrence of early afterdepolarizations following $I_{Kr}$ block (quantitative validation). B: comparison of the activation sequence on the epicardial surface of the rabbit ventricles (anterior and posterior views), obtained from computer simulations using a rabbit whole ventricular model with specialized conduction system (left) and optical mapping recordings (right) [adapted with permission from Bordas et al. (14)]. The pattern of activation is qualitatively similar in simulations and experiments (qualitative validation), and activation times in simulations are in range with the experimentally obtained ones (quantitative validation).
conditions that were applied in the experiments. Uncertainty in that respect could be greatly reduced by a precise definition of experimental conditions (such as temperature, solution compositions, preparation, and recording technique) and adoption of standards and criteria for electrophysiological experiments [as described in Quinn et al. (80)]. Furthermore, each recording procedure introduces artefacts in the electrophysiological measurements, and, therefore, comparison of experiments and simulations must always take this distortion into account. This is not always possible due to uncertainty concerning how experimental procedures affect the recordings. However, an example can be found in the investigation of the role of photon scattering in optical mapping recordings of the electrical activity of the heart (8, 9, 10 45). Allowing for photon scattering in the simulations not only achieves a better match between experiments and simulations, but it allows quantifying distortion because of photon scattering and it helps in the interpretation of optical mapping recordings.

Clearly, minimizing the complexity of the model would also minimize the sources of variability, artefacts, and errors involved in the MSE system, resulting in a more straightforward validation. It is important to ensure that the multiscale models are no more complex than necessary, although it is not at all trivial to make this judgment. Even if we could validate models separately for each of the levels of the multiscale model, there is inevitably a further level of complexity in the integration of levels, and it is difficult, if not impossible, to draw the boundaries of this complexity in advance.

In the validation process, the interpretation of correspondences or lack thereof is not straightforward either. If there is a match, it is possible that the MSE system has captured the specific features of cardiac electrophysiology relevant to the question under investigation. Then, the next stage is to perform simulations for investigating a hypothesis. If there is not a match, it is important to identify the possible reasons for the lack of a match to improve the MSE system, and by it, our knowledge. Thus it is only by placing model development in the context of the MSE that we can gain insight into what questions a particular model answers best.

Validation rarely shows up absolute failure or success at finding a match. As we have mentioned before, the MSE system incorporates models for the separate levels that are usually independently validated, which contributes to defining their representational content. Importantly, the lack of a match is not necessarily a negative outcome. As Noble (67) points out, “it is one of the functions of models to be wrong,” and failures can sometimes be more productive than successes. Failures have the potential to teach us more about the MSE system because they bring to light its underlying assumptions. A case in point was the failure of the so-called McAllister-Noble-Tsien model (58a). It was partly designed to deal with multiple components of potassium currents in cardiac Purkinje fibers, but it was shown to be inconsistent with what was known about ion depletion and accumulation in extracellular space. However, its failure led to the development of the first ventricular cell model by Beeler and Reuter (6).

Another example of “success in failure” was the lack of quantitative match between experimental and simulated voltage values obtained following the application of electric shocks in the study of Rodríguez et al. (81). It led to the hypothesis that the lower values in electrical potentials recorded on the surface of the heart in the experiments compared with the simulations were due to the distortion introduced by photon scattering effects in optical mapping recordings. Subsequent combined experimental and computational investigations showed that this was indeed the case (10), thus helping in the interpretation of optical mapping recordings and our understanding of the response of cardiac tissue to electric shocks.

Advances in our understanding of the MSE system require the evaluation of the possible reasons for the lack of match between experiments and simulations, which can be summarized as follows.

First, the lack of appropriate comparability between the experimental ensemble has informed the construction of the MSE system and the one used for validation. The description of the model can be too broad, encompassing different possible scenarios in cardiac electrophysiology, given the existence of high biological variability, illustrated in Fig. 5. For example, aspects of an MSE system for rabbit ventricular electrophysiology might have been based on experimental data for young rabbits, whereas validation is attempted using data obtained in old rabbit preparations showing significant age-related differences in electrophysiology and function. Alternatively, crucial experimental conditions including temperature or solution concentrations may not be adequately reproduced in the simulations.

Second, numerical techniques and software used in the simulations could be unstable, resulting in erroneous results, and therefore the lack of match might not be explained physiologically but technically (22, 24, 73).

Third, our definition of match may be too stringent. A quantitative match is evaluated using error tolerances (such as the maximum difference between simulation and experimental results), defined by the end user, and therefore varying error tolerances might provide different outcomes for the validation. Even when identical targets are aimed at, stochastic events would rule out arriving at precisely identical targets in every respect (52, 79, 94). This would need to be considered in the definition of the validation criteria and the interpretation of the validation output.

Fourth, the MSE system lacks cardiac electrophysiology features crucial for the question under investigation. This may indicate that a different mode of integration of data or knowledge must be tried, or it may be that the integration reveals unexpected aspects (67). The MSE system should be understood as a dynamic process, evolving through iterations over time between experimental, clinical, and computational investigations. The progress depends very much on the improvement of the experimental techniques that are geared toward the MSE system and the understanding of their limitations in obtaining an accurate description of specific cardiac electrophysiology aspects.

Given the analysis presented above, we propose that the MSE system can be considered a representational instrument with interrelated instrumental and representational aspects determined by the research question. The interrelation between these aspects is conditional: if the technical and representational aspects are validated, then the MSE system can be used as an instrument to investigate the research question. Therefore, the outcome of validation should be viewed as against both of these roles of the whole MSE system.
From this discussion, we can highlight the importance of the following aspects for validation.

First, variability. The better we understand sources of variability, the more specific our MSE systems can be of specific scenarios in cardiac electrophysiology [see Goaillard et al. (38) for discussion of variability and the need to obtain as much data as possible from a single data source]. Furthermore, error tolerances in validation need to be related to the variability observed in the experimental results. Sources of electrophysiological variability are multiscale, spanning a wide range of spatiotemporal scales (Fig. 5). As shown in various studies, sensitivity analysis can unravel causes and implications of variability in specific properties, as illustrated in the following studies (84, 86, 89, 90).

Second, robustness of techniques and tools. A necessary condition for validation is the robustness of numerical techniques and software used as they are implicated in model construction and simulation. Therefore, the development of tested software [such as the Chaste and CMISS software environments (15, 74)] should be regarded as crucial.

Third, standards. Given the dynamic interplay between components in the MSE system, it is vital that there be interoperability at the modeling, simulation, and experimental levels. This is reflected in the development of CellML, SBML, and FieldML for model encoding, repositories, and databases (5, 23, 36); the development of SED-ML for encoding simulation experiments; and recent work on the development of minimum information standards for electrophysiological experiments (80). All of these developments are vital when building the dynamic components inherent in the MSE system.

Fourth, physiological validation. Rather than one considering the representation to be a static relationship existing between independently existing model on one hand and reality on the other, it is more helpful to think of the relationship between the MSE system and its target domain as an ongoing dynamic process of iteration and adjustment. The dynamics of the iterative process are driven by advances in both experimental and computational techniques as well as investigations on their combined use in cardiac electrophysiology research. The process is driven both by consistency and inconsistencies in the MSE system, which is both the match and the lack of match between simulations and experiments (or success and failure in validation). The iterative nature of this process is clear from the evolution of single cell electrophysiology models of different types and species, which has often resulted in families of several generations of models. As new experimental data and techniques become available, inconsistencies between computational model predictions and experiments result in refinement and improved knowledge of the corresponding MSE system.

With respect to whole organ models, the process of iteration between experiments and simulations has been crucial, for example, to improving the understanding of important human health phenomena such as the dynamics of ventricular fibrillation (15, 24, 97), the most dangerous type of lethal arrhythmia, and the success and failure of electrical defibrillation, the only effective therapy against sudden cardiac death (98). In both cases, whole ventricular electrophysiology simulations were successfully combined with clinical and experimental methods to bring two important advantages. First, the high spatiotemporal resolution data on the three-dimensional electrophysiological activity of the ventricles obtained from the simulations overcome limitations of clinical or experimental recordings, which are often restricted to low spatiotemporal resolution and/or just the surface of the heart. Second, computer models and simulations provide the ability to dissect the relative importance of different factors, which result in the identification of key properties such as the minimal action potential duration for ventricular fibrillation (96, 97) or ventricular anatomy and structure for defibrillation (81, 98). These novel findings could point toward new avenues for the preven-
tion of ventricular fibrillation, both pharmacologically and electrically.

Future research is expected to continue this iterative process of coconstruction of the MSE system in human electrophysiology driven by recent technical developments for the characterization of human cardiac electrophysiology, including gene expression screening, in vitro optical mapping recordings (32, 37, 56), and noninvasive electrocardiographic imaging (27, 28). This coincides with the availability of advanced computational tools for complex multiscale simulations and improvement in computer power. Those advances are likely to change the landscape of cardiac electrophysiology and to result in novel ways of coconstructing the human electrophysiology MSE system and with it our knowledge of cardiac electrophysiology. The current maturity of the MSE system in cardiac electrophysiology opens up new perspectives for the potential of computational cardiac electrophysiology for the refinement, reduction, and replacement of animal experiments in research as well as in industrial applications such as drug development (29, 35, 59, 89).

Conclusions

Our analysis of the computational modeling and simulation process for research in cardiac electrophysiology reinforces the importance of developing strategies for validation informed by the following key aspects: 1) understanding sources of variability to inform valid ways of comparing experiments and simulations; 2) technically testing the robustness and accuracy of tools and techniques; 3) developing and adopting the standards for models, simulations, and experiments; and 4) understanding physiological validation as a dynamics process driven by new developments both in experimental and computational methods. In addition, a thorough examination of the process of modeling and simulating in cardiac electrophysiology highlights the intricate ways in which models, simulations, and experiments are intertwined and the important implications this has in the identification of models as representations and their validation. We show that if anything could qualify as having representational status, it is not just the model, rather it is the whole system of models, simulations, and experiments. This operates as an assemblage, i.e., the MSE system that progressively constructs the specific electrophysiological aspects it aims to represent, at the same time as it is itself constructed. How the MSE system is constructed is crucial to the question of what it represents and how it is validated. New strategies for validation need to pay more attention to the complex interrelationships between each part of the MSE system to fully realize the added value of the integrative approach provided by the MSE system. Since it allows us to query the target systems in different ways than is possible using experimental techniques, the MSE system highlights aspects of cardiac electrophysiology that are otherwise invisible and can reveal limitations and inconsistencies in our knowledge of cardiac electrophysiology and associated recording techniques.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

A.C., K.B., and B.R. conception and design of research; A.C., K.B., and B.R. interpreted results of experiments; A.C., K.B., and B.R. prepared figures; A.C., K.B., and B.R. drafted manuscript; A.C., K.B., and B.R. edited and revised manuscript; A.C., K.B., and B.R. approved final version of manuscript.

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