The Cardiac Electrophysiology Web Lab

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Abstract

Computational modelling of cardiac cellular electrophysiology has a long history, with many models now available for different species, cell types, and experimental preparations. This success brings with it a challenge: how do we assess and compare the underlying hypotheses and emergent behaviours, in order to choose a model as a suitable basis for a new study, or characterize how a particular model behaves in different scenarios?

We have created an online resource for the characterization and comparison of electrophysiological cell models under a wide range of experimental scenarios. The details of the mathematical model (quantitative assumptions and hypotheses formulated as ordinary differential equations) are separated from the experimental protocol being simulated. Each model and protocol is then encoded in computer-readable formats.

A simulation tool runs virtual experiments on models, and a website – https://chaste.cs.ox.ac.uk/FunctionalCuration – provides a friendly interface, allowing users to store and compare results. The system currently contains a sample of 36 models and 23 protocols, including current-voltage curve generation, action potential properties under steady pacing at different rates, restitution properties, block of particular channels, and hypo-/hyper-kalaemia. This resource is publicly available, open source, and free; and we invite the community to use it and become involved in future developments. Those interested in comparing competing hypotheses using models can make a more informed decision; those developing new models can upload them for easy evaluation under the existing protocols, and even add their own protocols.

**Abbreviations.** AP, action potential; APD, action potential duration; NCX, sodium-calcium exchanger; SED-ML, Simulation Experiment Description Markup Language.
Introduction

Mathematical and computational modelling of cardiac electrophysiology has a long history (1, 2). Encoding hypotheses about how systems work in a quantitative form has yielded valuable insights into: cellular behaviour and the roles of different ionic currents (3); the mechanisms behind arrhythmias (4, 5); and treatments such as defibrillation (6). As is the case with mathematical modelling in general, models are developed to represent specific quantitative hypotheses and to answer specific scientific questions. The papers published about new models therefore display behaviour under particular experimental conditions, and draw inferences from that. This is, of course, appropriate and useful.

However, this approach can also be limiting. If we consider that a mathematical model is a quantitatively encoded hypothesis (or set of hypotheses), how can we see which hypothesis is best supported by new data? Within one research group there may be the ability to compare how their own models behave in a wide range of different situations (7), or easily vary their simulations to represent the different experimental scenarios. Nevertheless, there is no automated solution for examining how a particular model behaves under a range of experimental conditions, let alone comparing the behaviours of any of the published models: this technical barrier has resulted in very few papers that compare models/hypotheses being published (with rare exceptions (8, 9)). The need becomes particularly acute as models begin to be used in simulation studies for applications such as drug safety testing (7, 10–12) where we rely on behavioural predictions beyond the ‘normal’ regime in which many models were originally developed and tested.

The challenge has its roots in the publication medium. Traditionally, publishing a model involves displaying the model equations, originally implemented within some computational software, in print form. This makes them difficult to reproduce or extend; indeed often this is impossible without assistance from the original author, whether due to missing information or typographical errors (13, 14). Releasing the source code for the original model implementation helps, and has been done by many groups. However, comparing models available in this form is still extremely challenging, as they have
been written in different programming languages, for different computational platforms, in different formats, and are not readily interoperable.

An excellent effort has encoded many of the action potential models in the CellML format (15–17) – a computer readable definition of the mathematical model equations. This enables the model equations to be shared unambiguously, and code for particular programming languages can be auto-generated from the CellML format.

But despite over 50 years of cardiac modelling, and now hundreds of models and variants for cardiac electrophysiology, there has been nowhere to look up simple model characteristics such as the action potential (AP) waveform at a given pacing rate. There has been no automatic mechanism for checking even the published behaviours ascribed to a model, let alone other potential or expected capabilities. Given this, it is unsurprising that occasionally the curated model descriptions do not always match the original implementations, and we give one example of this below.

We believe a better way forward is provided by the concept of ‘virtual experiments’ (18) – the in silico analogues of wet lab experiments, defined by protocols that crucially can be encoded in a form amenable to processing by a computer program, and applied to different models of a system. This could be seen as an analogue of an experimental protocol which can be followed in different labs to reproduce research findings, a need increasingly recognized as essential in experimental research (19). In earlier work (20) we described how implementing this concept in tools for ‘functional curation’ of models could address some of the challenges described above. In particular, we claimed that being able to examine how models behave in different experimental scenarios helps to guard against potential misuse of models, which could otherwise be encouraged by their already-easy availability.

Here we present the Cardiac Electrophysiology Web Lab – a user-friendly web interface which allows modellers to characterize their (and others’) cardiac electrophysiology models, and to compare a model’s behaviour against that of any other models under a wide range of simulated experimental conditions. It must be emphasized that the Web Lab does not make any judgements as to whether the models behave ‘appropriately’ in a given experiment, or which is ‘best’. Instead, it provides a system to enable careful comparison and analysis of the behaviour of models in multiple virtual experiments.
Methods

To automatically characterize and compare the behaviour of models under different experimental scenarios requires that both models and protocols are described in machine-readable formats. In addition, the details of the protocol need to be separated from the model equations, thus moving us from ‘models of a particular experiment’ to ‘models of the biological system’. Different protocols may then be applied to each model of the system, exercising them in different ways. This approach is shown schematically in Figure 1.

Figure 1: Schematic of the technical infrastructure underlying our website. In the state-of-the-art in model repositories each available model description is actually a model of a particular experimental setup (generally 1Hz pacing in cardiac AP models). In our database, models represent a biological system, and experimental protocols are described separately, and may be applied to any model. Experimental data will be directly comparable with the results of certain protocols.

We utilize the existing CellML format (15) to encode the model descriptions, and the COMBINE Archive (21) to package model and protocol descriptions as well as experiment results. While we are contributing to the development of a community standard format for protocol descriptions (SED-ML, Waltemath et al., 2011b), it does not yet encapsulate all our requirements. In the interim, we have developed our own extensions to this language (20), with a text syntax facilitating understanding and editing of the protocols (23). The techniques required for running experiments using any protocol on any model are detailed in our earlier publications (20, 24); the main features are the use of annotations indicating the physiological meaning of model variables, to
avoid confusion over naming, and automated *units conversions* to ensure mathematically consistent simulations. These simulation tools are built on top of the Chaste libraries for computational biology (25–27).

These tools are exposed to the user via a web interface to provide an installation-free, interactive experience. Behind the scenes a database stores model and protocol descriptions, along with the results of the corresponding experiments: every protocol can be run on every compatible model (i.e. every model containing the biological quantities being probed by the protocol). These descriptions and results may be viewed by anyone, with plots of results rendered in the web browser. In addition, any experiments may be compared, combining their results in a single graphic.

Finally, registered users may upload their own model and protocol descriptions, and run experiments on our servers; these may be kept private, or published for all to see. All the underlying simulation environment, and web portal code, has been released as open source and can be accessed via the web portal, as can the documentation on using the system, uploading your own models, and writing your own protocols.

**Results**

In this section we showcase some of the results that are already available online, to provide an impression of the potential uses, capability and flexibility of the Web Lab. Figure 2 displays the experiment overview table. Results are colour coded according to the experiment’s state: queued; running; inapplicable (the protocol’s required quantities are not present, or not labelled, in the model); failed to run (usually due to numerical instabilities, see below); partially finished (some post-processing was not possible); or successfully finished. Note that we do not compare simulated results against experimental data, and hence the colour coding *does not* represent model ‘correctness’ or ‘agreement with experimental data’ in any sense: it simply indicates to what degree the simulation experiment was able to be run. Accordingly, a model displaying all green results should not be considered as the ‘best’ model.

Below we show some results of individual virtual experiments, highlighting the way different models (or different *hypotheses*) can make very different predictions. This illuminates certain areas that will require careful attention in cardiac electrophysiology modelling.
Figure 2: Overview of the virtual experiments available in our system at the time of writing. See [https://chaste.cs.ox.ac.uk/FunctionalCuration/db.html](https://chaste.cs.ox.ac.uk/FunctionalCuration/db.html) for the current status.

Each square represents the stored results of a single virtual experiment, colour coded according to status. Green indicates that the protocol ran to completion; orange that it did not complete but some of the expected graphs are nevertheless available (so only a subset of the simulations and/or post-processing failed); red that no graphs are available; grey that the model and protocol are incompatible (i.e. the model does not contain some biological feature probed by the protocol); shades of blue indicate a queued or running experiment (no examples shown). Note therefore that colours do not indicate model ‘correctness’ in any sense.
Exploring Model Characteristics

For the first time cardiac electrophysiology researchers can easily examine the action potential waveforms produced by different models. In Figure 3 we present a snapshot of APs for several human ventricular models at both 1Hz and 2Hz.

Figure 3: 1Hz (top) and 2Hz (bottom) steady pacing action potential waveforms for a selection of human ventricular cell models. See https://chaste.cs.ox.ac.uk/q/2015/fc/fig3a and https://chaste.cs.ox.ac.uk/q/2015/fc/fig3b for the Web Lab originals.
One can easily encode more complex protocols, for example S1-S2 or steady-state restitution curves, and compare model behaviours under these protocols, as shown in Figure 4 for the O’Hara 2011 model (28) epi- and endocardial variants.

**Figure 4:** Restitution curves for the O’Hara 2011 model endo- and epicardial variants.

Variation in action potential duration at 90% repolarization is shown for the “S1-S2” protocol with initial stimulus interval S1 set to 1000ms, and for steady-state restitution (in which two paces are analysed and plotted as two lines, to show ‘fork’ or ‘alternans’ at short rates, visible in the endocardial variant). This demonstrates the Web Lab’s ability to run complex protocols with intricate post-processing. See [https://chaste.cs.ox.ac.uk/q/2015/fc/fig4](https://chaste.cs.ox.ac.uk/q/2015/fc/fig4) for the Web Lab original.

Despite a large number of models including dynamic changes in ionic concentrations (first introduced by DiFrancesco and Noble in 1985 (29)), ionic homeostasis would appear to be one of the more controversial areas, as evidenced by the wide variety of model responses (or hypothesis predictions) to alterations of this system. For example, in Figure 5 we present the (steady state) effect on action potential duration (APD) of progressive block of the sodium-calcium exchanger (NCX). The models make a wide
range of predictions, reflecting the current limitations of our knowledge regarding intracellular sodium and calcium homeostasis (30), and an appropriate model for any study involving changes to NCX conductance should therefore be selected carefully. The Web Lab can assist in this by demonstrating how different models behave.

Figure 5: The effect of blockade of the sodium-calcium exchanger (NCX) on steady-state action potential duration (APD) in some human ventricular cell models. Note that, across 0%-80% NCX block some models predict little effect (<5% change); whilst others predict 20% prolongation; and others predict 20% shortening. At 80-100% block the results vary dramatically, with models predicting between 45% prolongation and shortening to as little as 20% of control. See https://chaste.cs.ox.ac.uk/q/2015/fc/fig5 for the Web Lab original.

We have already used the Web Lab to examine recent human ventricular models under drug-induced blockade of certain ion channels. These data formed part of a recent study (31), making this part of the study quick to produce, immediately replicable, and trivial to extend should a novel model be produced (or an existing model be updated).
The model behaviours we have highlighted here are the ‘tip of the iceberg’, and are simply intended to give an impression of the power of the approaches that the Web Lab enables.

**Correcting Errors in Model Encodings**

Discussion of the results of the Decker 2009 model S1-S2 restitution curve (as published in our pilot study (20)) with the senior author Prof. Rudy led us to a careful comparison of our results with those in their original model publication (32). The differences uncovered an error in the CellML implementation of the Decker model which had been present since March 2010 (See http://mirams.wordpress.com/2013/10/22/importance-of-curating-models/ for full details). The CellML file was corrected, and is now providing an accurate representation of the model to the community (https://chaste.cs.ox.ac.uk/q/2015/fc/s1s2). Differences between the original and corrected model versions can be displayed in the Web Lab, using the model comparison tool BiVeS (33, 34); see https://chaste.cs.ox.ac.uk/q/2015/fc/diff for the results. These differences only become apparent when a model is tested in a range of situations, which the Web Lab enables.

**Steady States**

Deterministic electrophysiology models typically tend towards a limit cycle behaviour at a given pacing rate. Many of our protocols examine interventions at this ‘steady state’ rather than after a limited number of paces. In some models we have observed behaviour that is either not the same as that published (the Priebe 1998 model (35), see Figure 6), or seems non-physiological (Aslanidi 2009 atrial model (36)), suggesting that the model equations, or their initial conditions, may require alteration. Non-physiological steady states can often be attributed to ‘drift’ in ionic concentrations due to imbalance when not all currents are accounted for in concentration equations (37). It is useful to be able to distinguish those models that are reaching a limit from those that are continuing to drift, as the latter should not be used in simulations that examine steady state behaviour or run for a long time.
Figure 6: The effect of examining behaviour before and after steady state is reached, for 0% (dashed line), 25%, 50%, 75% and 100% block of the rapid delayed rectifier potassium current (IKr) in the Priebe 1998 model. **Left:** after just one pace at each degree of IKr block, these results are the same as those shown in Priebe et al. (1998). **Right:** the same model after 10000 paces for each degree of IKr block as shown in the Web Lab. Note that even the control action potential varies considerably, and is much longer in the steady state case.

**Discussion**

We have presented a new online resource for users and developers of mathematical models of cardiac electrophysiology. As seen in the previous section, it offers great flexibility in analysing and comparing models under different experimental conditions. This will benefit model users in selecting suitable models for their simulation studies, by ensuring that relevant basic behaviour can be reproduced (for instance, that a model intended for use in simulating arrhythmia has suitable restitution properties). It can also highlight models whose implementations have problems with numerical stability, or those that ‘drift’ to non-physiological regimes.

While we have highlighted some interesting results arising from the experiments already performed, we have deliberately not tried to extract all publishable comparisons from this data before making it available. Instead, we preferred to concentrate on producing a usable public resource for the benefit of the community. Therefore, we welcome and invite others to examine the results for themselves, code up new protocols, and explore what they find.
Despite our efforts to produce reliable virtual experiments with this system, unexpected behaviour may not necessarily reflect a real consequence of the model. Mathematical singularities or other numerical simulation issues may cause the simulated experiment to fail, leading to many of the red boxes in Figure 2. Sometimes the published representation of the model is in error, or its CellML encoding is (as was the case for the Decker 2009 model discussed above). On other occasions the protocol, especially the post-processing section, may need further refinement to account for raw simulation results that fall somewhat outside the expected regime – computing a robust APD that accounts for any shape of AP is surprisingly complex. We invite readers who find any examples of behaviour that do not match other model implementations to contact us and we will attempt to determine the cause. This may, of course, result from a deficiency in our software, although we have an extensive bank of automated software tests to guard against this. In addition, since all the methods and software needed to reproduce results shown in the Web Lab are openly available, the community can examine how the results were produced in full detail.

Our online resource will also be of benefit to model developers. They may upload their in-developement models to the system, keeping them private if needed, in order to evaluate their behaviour against a much wider range of protocols than are typically considered when constructing a new model. If a desired experiment is not already available, the corresponding protocol may be submitted as well. New model versions may be uploaded until the desired set of behavioural characteristics is obtained, and the final model made public when published. The publication could even refer to the stored results as evidence that the model has been thoroughly tested.

Notwithstanding the considerable utility of the existing system, there are many aspects which will require further development as this becomes a hub for researchers working with cardiac electrophysiology models. We particularly encourage users to contribute new models and protocols. We aim to develop a protocol editor in order to ease this task for those without programming experience. In the meantime, users are welcome to suggest what new protocols could be, and we will assist with encoding them.

As noted above, we use annotations indicating the physiological meaning of model variables to form the interface between models and protocols, so that a single protocol...
may be applied to models potentially using different names to represent the same concept. In our database, we thus include copies of models from the CellML repository (17) annotated with terms developed for this purpose. Ideally, these annotations should instead be stored along with the reference versions of the model in the CellML Physiome Model Repository itself, and use community agreed annotations to promote wider interoperability. Related ongoing work is adding more structure to our annotations by defining relationships between terms. This structure can then be used by enhanced tools to provide even more sophisticated interfacing between models and protocols, for instance clamping all extracellular concentrations – without having to specify which ions may be present in the model.

Other enhancements to the tools, and indeed the protocol language, may also be required as new ideas for protocols arise. We are looking at incorporating parameter estimation techniques into this framework, and further automated checking of experiment results could also be investigated (38). It would also be desirable to use a community agreed standard for protocols, rather than our own representation, and so we are proposing features of our new language for incorporation in future versions of the SED-ML standard being developed by the systems biology community (22).

Finally, the most important ingredient that is missing in our current implementation is a direct link to experimental data. Since protocol descriptions should represent experiments that could be performed in a wet lab (39) it is natural to associate corresponding experimental datasets with each protocol. Simulated experimental results could then be compared automatically against these datasets, to reveal the extent to which different models match our current knowledge of the system. While public data repositories for ECG data exist (e.g. www.physionet.org (40)) there is a notable lack of open sources for cell-level data, potentially a serious impediment to progress. Eventually, we envisage model descriptions being associated explicitly with all the data that was originally used to parameterize them. As new data become available, all relevant models could be validated against them, and even re-parameterized automatically to capture the latest experimental results within a quantitative model (18).
Additional Information

Competing interests
None.

Author contributions
JC and GRM devised the system. JC wrote the simulation software. MS and JC wrote the web interface. GRM and JC analysed the results. All authors contributed to writing the manuscript and approved the final version.

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