## Introduction

One of the key issues in computational and mathematical biology is the way we integrate models and data. Current approaches are typically ad-hoc and disconnected, and so a completely different strategy is needed. A quantitative model should provide an unambiguous and testable description of a proposed mechanism. However, today models are probably the least reproducible type of research outputs. While some community standards for representing models themselves exist, tasks such as comparing different hypotheses against experimental data, determining a model's suitability or limitations for a particular study, or incremental development of models, are still challenging and often performed inadequately.

*Functional curation* is intended to address this problem. The key underpinning idea is that when mathematical and computational models are being developed and curated the primary goal should be the continuous comparison of model predictions against experimental data. This requires the definition of *virtual experiments* – simulating in the models precisely the same protocols employed in generating the experimental data used to develop or test the models. A repository of knowledge can then be built up as models, protocols and data are curated together.

*Some intro on virtual experiments more generally?*

As was discussed in the VPH-FET roadmap [V2011] there are both technical and societal challenges to achieving such a vision. Given the broad range of models and experiments studied in the life sciences, developing standard formats to represent them is a significant and on-going task. Much development effort is then needed to develop the tool infrastructure around such standards. Perhaps even more challenging however is achieving community uptake. This requires significant progress on usability of solutions, including good documentation and training materials. It also requires that solutions provide added value to researchers, with demonstrator projects by “eager adopters” manifesting the potential impact.

This paper describes our approach to achieving this goal, the progress made in conception and implementation since our initial prototype [C2011a], and some future directions.

## Use-cases

Software or standards development needs to be driven by specific scientific applications if solutions are to be pragmatic, useful, usable, and hence taken up by the community. The benefits of the system need to be demonstrated to potential users through concrete use cases. Our investigation of the requirements for virtual experiments, and our tool development, are therefore grounded in several application areas.

Our primary application area, also considered in [C2011a], is cardiac electrophysiology. It has several features making it well suited to our purposes. Firstly it is a well-developed field, with a variety of models of essentially the same system which may fruitfully be compared. This variety is also expressed through variations in modelling convention [C2011b], which provides challenges for applying a single experiment to multiple models. The post-processing required in typical electrophysiology experiments is also often complex, providing difficult requirements for language design. *cGP provides demonstration of potential.*

Other areas are now starting to be considered, in order to ensure a wider applicability for our approach. These include immunology, synthetic biology, visual psychophysics and neuro coding. A particularly interesting case is discrete cell-based modelling within Chaste [P2009], where the model is encoded by an executable program, rather than in a markup language. This provides additional challenges in interfacing, but may yield a useful approach to bridging with legacy or unusual models.

## Virtual experiments

In defining virtual experiments there is a balance to be struck between a standardised language that is reasonably concise, and hence providing support in many tools is not too difficult, and allowing flexibility for researchers to represent new and varied kinds of experiments. The benefits of standard formats for exchange have been discussed often [e.g. C2010], but there is often also an overhead associated with their use [V2011]. Working with the standards needs to be made easy for end users. We are considering several aspects in addressing this problem.

Firstly, through examining the kinds of experiments required by our scientific applications, we are determining the minimal set of semantic constructs required in a “protocol language” that still allows the largest possible set of common experiments to be encoded. Note that we are not necessarily seeking to encode every possible experiment – unusual or especially complex cases may well be better expressed using general purpose programming languages and/or workflow systems.

Secondly, we argue that there is great value in the protocol language supporting the definition of common generic components that may be parameterised, and hence instantiated for specific scenarios. A library of such components may then be built up, facilitating the creation of new experiment descriptions from these. For example, a common experiment type in cardiac electrophysiology is the voltage clamp, where a single ion channel in the cell membrane is isolated, a potential applied, and the current response analysed. This generic protocol is applied to different ion channels, with different input voltage traces – these would become inputs to a parameterised protocol. Any voltage clamp experiment could then be specified quickly and easily.

Related to this, we have recently added the concept of *nested protocols* to the prototype described in [C2011a]. Here, one protocol may reference another as though it were a model, wrapping model pre-processing, simulation, and post-processing within an outer experiment. This supports uses such as a protocol performing a single pace of a myocyte being embedded within a dynamic steady-state simulation – the single pace is performed repeatedly until the state variable values at the end of each pace converge.

The community standard SED-ML [W2011] has been developed to encode simulation experiments. It is therefore counterproductive to propose a new language. Instead, we are investigating to what extent SED-ML can already support the use-cases we identify, and where it cannot we will submit extension proposals for review by the community.

## Towards a complete framework

Standardised descriptions of virtual experiments are not sufficient in themselves. If there is to be widespread uptake of this approach, these standards need to be embedded within usable tools to provide added benefit to modellers. Building on our prototype tools for executing experiments [C2011a] we are investigating several options.

The middleware framework *sif*(service-oriented interoperability framework) [S2008], was designed to facilitate the sharing and aggregation of data from distributed, heterogeneous data sources. The framework was developed originally to support healthcare applications (see, for example, [S2010a]); in recent years, the focus has turned to Systems Biology applications [S2010b].

The *sif* framework is currently being used to manage the distributed execution of experiments; it is also being used to curate these along with the associated (experimental and simulated) data and models from multiple sources.

*Dagmar’s work on SEMS here.*

Future work will also look at developing plugins for the OpenCOR modelling environment[[1]](#footnote-1) to allow designing and running virtual experiments as an integral part of model development.

## Discussion and conclusions

The description of virtual experiments in standard formats is essential to future progress in VPH research. Only sharing the experimental setups along with the models themselves makes the models truly useful to others, and provides the crucial link to data. This will increase the acceptance and use of realistic and validated models, allowing researchers from different disciplines to share resources and develop new knowledge.

The proposed framework will also enable a richer characterization of the behavioural repertoire of models. By automatically and comprehensively testing multiple models and protocols users can have confidence that the model they have chosen or developed provides a good approximation of the desired physiology. Model comparison under multiple protocols allows the impact of changes in parameter values or model structure to be ascertained in greater detail.

The model development process will also be facilitated. Generic experiment descriptions will allow faster setup of simulation experiments. Continually appraising models against collections of protocols and desired outputs will ensure that desired functionality is not lost. As models, protocols, and data are curated together in open repositories, the store of global knowledge and understanding is increased.

## References

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1. <http://www.opencor.ws/> [↑](#footnote-ref-1)