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We have developed a simulation tool, get-simulator, for performing simulation experiments with user-defined epithelial cell models. Users are able to define their epithelial cell model *de novo* or through the assembly of pre-existing modules. Existing cell models may also be re-used in new simulation experiments. Cell models are encoded in the CellML format (http://cellml.org) and the SED-ML format (http://sed-ml.org) descriptions of the simulation experiments. SED-ML allows a given collection of models to be instantiated into one or more specific computational tasks to be executed in order to generate unambiguously defined outputs. In addition to the models and simulation experiment descriptions themselves, get-simulator makes use of relevant annotations of these source data to enable the automatic generation of executable code for each of the required computational tasks. Following the execution of these tasks, the user is presented with the resulting outputs defined in the SED-ML document. get-simulator and example models are available from https://bitbucket.org/get under a free and open-source license.

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VPR The Virtual Physiological Rat Project www.virtualrat.org

Epithelial cell modeling: standards-based simulation experiments

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Introduction

We are developing a set of tools that will provide a generalized framework for the development and application of epithelial transport models. Where possible, our final user interface will hide the mathematical and computational details from the novice modeler.

We are creating a library of reusable renal epithelial transport models. Users will be able to search this library for appropriate pre-existing models, or templates, to incorporate into their own work. The library includes models from small molecules and membrane transporters, through to whole cell models.

Collaborative, reproducible, and open science

Community standards are used to encode the mathematical models, simulation experiments, and associated biological information and experimental data. Using such standards ensures that models built using our tools are interchangeable with other tools, platforms, and environments.

Our tools make use of distributed version control systems to manage the encoded data (Miller *et al*. 2011). This ensures users are able to share their work with collaborators while maintaining accurate provenance records.

Current prototype implementation of our tools provides custom client-server software. Our aim is to integrate our prototype implementation into the Physiome Model Repository (Yu *et al* 2011). This will enable users to contribute their work to the scientific community at large, providing opportunity for application of such work in novel applications.

Experimental protocols & validation

Simulation experiments can be defined to correspond to specific experimental protocols. Such simulation definitions can be stored in the library as templates ready for application to specific models. If *"expected"* data is associated with the simulation description, we are able to use the data to aid the validation of new models to which the simulation is applied.

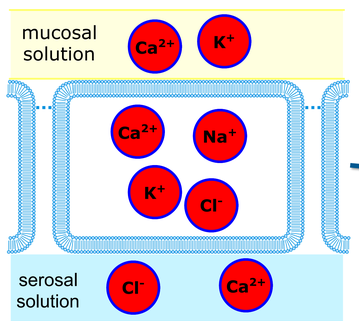
Methods

Our tools and model library make use of CellML (http://cellml.org) to encode the mathematical models and SED-ML (http://sed-ml.org) to encode descriptions of the simulation experiments. Encoded data are annotated with additional information to describe the model beyond the mathematical relationships. Such information may include: the specific biology a given part of a model is representing; the identity of the person who encoded the model; or a link to the published article in which the model was first published (or subsequent publications refining the model).

The model library consists of encoded models designed to be modular and reusable. Complex models may be created through the assembly of existing modules from the model library, and then contributed back to the library for future use. Model annotations are used to guide the user as to appropriate models to use for a given purpose and to automate the model assembly process.

get-creator <https://bitbucket.org/get/get-creator>

In addition to making use of existing whole cell models from the library, users are able to make use of *empty* or template epithelial cell models. From this blank canvas, the user will be able to add the desired collection of molecular species and transport processes from the library to the appropriate compartments and membranes of the template cell model. In the example below, the user is interested in the dynamic concentrations of the ions shown and the passive transport of those ions between the compartments of the model.



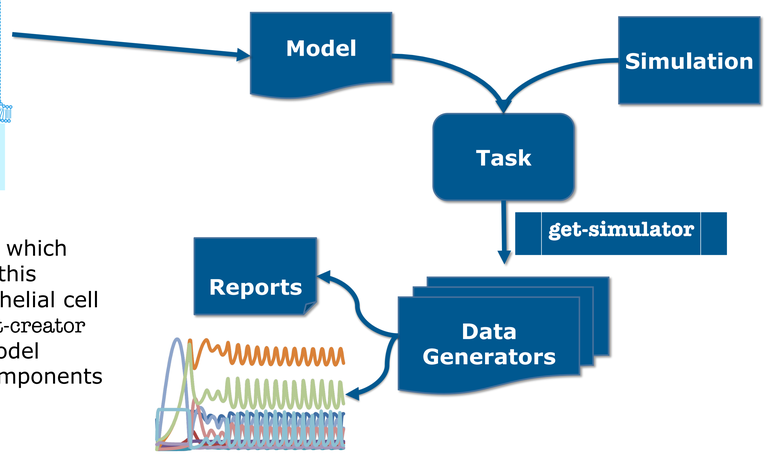
get-creator is the tool in our framework which provides the functionality to automate this process. Users simply describe the epithelial cell model they would like to create and get-creator will create the corresponding CellML model hierarchy which reuses the required components from the model library.

get-simulator <https://bitbucket.org/get/get-simulator>

Latta *et al* (1984) described a general method for performing simulations with epithelial cell models which ensures the conservation of mass and charge. We have implemented this method in get-simulator, using epithelial cell models encoded in CellML.

SED-ML allows us to encode descriptions of the simulations to be executed. These descriptions include the numerical algorithm or method to be used in executing a specific simulation task, using the Kinetic Simulation Algorithm Ontology (KiSAO, Courtot *et al* 2011). We make use of a proposal to extend SED-ML with custom simulation algorithms to enable get-simulator to prototype software support for our simulation experiments.

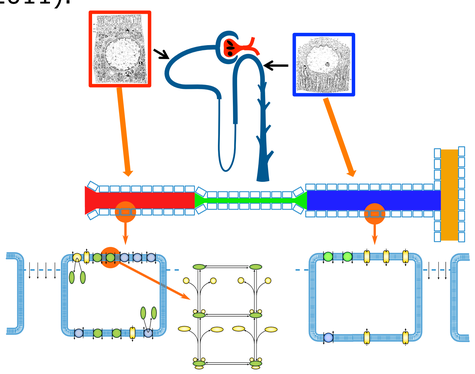
Thus we are able to encode the mathematical models in CellML and the simulation experiments in SED-ML, as shown below. This defines an unambiguous link between simulation results, mathematical model(s), and numerical simulation(s).



Future work

We are developing user interfaces which take advantage of these tools to provide high-level interfaces for model building, editing, exploration, and simulations. See http://bitbucket.org/get for the details.

By making use of accepted community standards to encode and annotate the data in our library, we ensure that models developed using our tools are available for use in other contexts. In particular, we are developing a finite element nephron model which will be able to directly make use of models from the library as shown below. This work is being performed under the OpenCMISS software project (Bradley *et al* 2011).



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