Program No. 814.16

We have developed a software suite for the creation, simulation, and dissemination of epithelial cell models. The suite, known as GET (Generalized Epithelial Transport), is freely available under an open-source license at: http://get.readthedocs.org. GET consists of a model creation tool, a simulation tool, and a server that provides access to some functionality from these tools via web services. The server also provides access to data from the Physiome Model Repository. The GET framework makes use of standard community file formats to store mathematical model and numerical simulation information in order to ensure users are able to reuse, reproduce, and exchange their work with other software tools, repositories, and scientists. The mathematical models are encoded in the CellML format (http://cellml.org) and the SED-ML format (http://sed-ml.org) is used to encode descriptions of the computational simulation experiments. The development of the GET suite has led to proposals for extensions to both the CellML and SED-ML specifications in order to meet the requirements of the epithelial cell models.

AUCKLAND BIOENGINEERING INSTITUTE
THE UNIVERSITY OF AUCKLAND NEW ZEALAND

VPR The Virtual Physiological Rat Project www.virtualrat.org

Computational Tools for the Creation, Simulation and Dissemination of Epithelial Cell Models

David Nickerson[1] <http://about.me/david.nickerson>, Kirk Hamilton[2], Daniel Beard[3], Peter Hunter[1]
[1]Auckland Bioengineering Institute, University of Auckland and [2]Department of Physiology, University of Otago, New Zealand
[3]Medical School, University of Michigan, Ann Arbor, MI, USA

Introduction

We are developing a suite of tools that will provide a generalized framework for the creation, simulation, and dissemination of epithelial transport models. We are also creating a library of reusable 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 spans spatial scales from small molecules and membrane transporters, through to whole cell models; and ranges from generic passive transport descriptions through to models of specific transport proteins.

Collaborative, reproducible, and open science

Community standards and ontologies 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 – making them available to the widest possible audience for reuse.

By making use of distributed version control systems to manage the encoded data (Miller *et al* 2011; Yu *et al* 2011), users are able to share their work with collaborators while maintaining accurate provenance records.

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.

GET <http://get.readthedocs.org>

Our suite of tools are collectively known as GET (Generalised Epithelial Transport). 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).

Creation

GET creator is the tool within the GET suite which focuses on the automated creation of epithelial cell models via the assembly of constituent components from the GET library. In this manner, users are able to rapidly create customized epithelial cell models which capture the level of detail they require for their specific investigation. Through the incorporation of knowledge about the modules available in the library, GET creator is able to automatically define the glue which binds the generic modules together (*i.e.,* summing all fluxes of a particular molecule through a given membrane).

Simulation

GET simulator is the simulation engine for the GET framework. While whole epithelial cell models can be encoded in CellML and those models can be simulated by standard CellML-capable simulation tools, in most cases that will not be the full experiment the user desires to run. Instead, the method described by Latta *et al* (1984) has been implemented in GET simulator in order to solve for mass and charge conservation. Our implementation of the Latta *et* al (1984) algorithm takes advantage of our knowledge of the epithelial cell model to make use of standard CellML simulation tools for those parts of the model amenable to such.

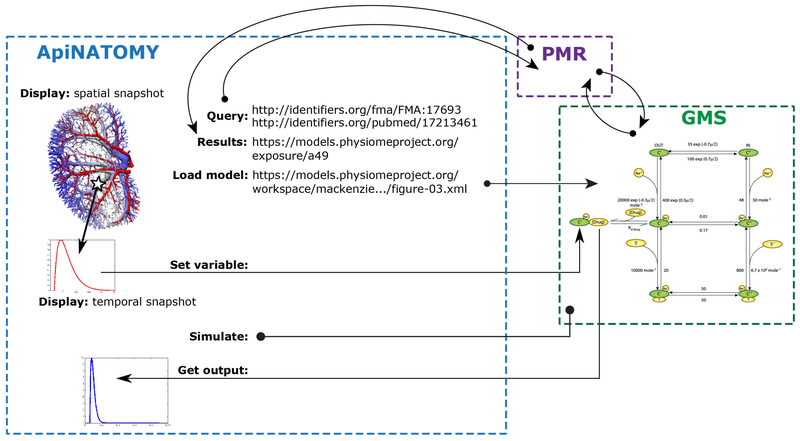
Dissemination

The GET 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. Models in the GET library are housed in the Physiome Repository (PMR, http://models.physiomeproject.org; Yu *et al* (2011)). Examples of generic models are available [1] and annotated transporters [2-5].

GET Model Server (GMS)

The GMS is a prototype web server providing access to the GET suite of tools via standard web services. These services are specific to the GET framework, but as the project develops common tools will be extracted out as proposed features to be implemented as part of the software which runs the Physiome Repository.

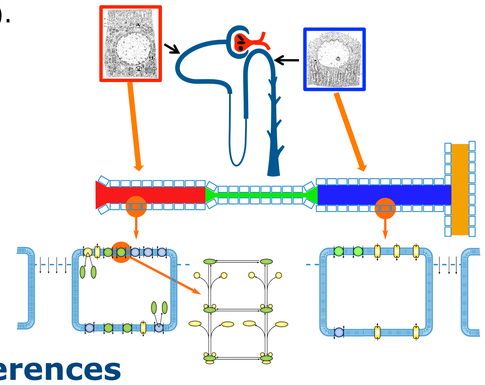
An example demonstrating the use of GMS as part of the Open Physiology workflow (http://open-physiology.org; de Bono *et al* (2015)) is shown to the right. This example illustrates the applicability of the GET suite beyond the field of epithelial cell models.



Illustrative example of the interaction between ApiNATOMY, PMR web services, and the GMS. Using standard identifiers (in this example the FMA term for the renal proximal tubule and a PubMed ID for a specific paper), ApiNATOMY is able to query the PMR metadata repository for relevant CellML models. The model of interest is selected and GMS is instructed to load the model. As well as setting scalar parameter values, ApiNATOMY is able to use the sampled spatial model field values to drive variables in the GMS executable model to link the CellML model to specific spatial locations in the larger scale model. Following the execution of a simulation in GMS, ApiNATOMY is able to retrieve model variable transients from GMS for presentation to the user.

Future work

We are developing user interfaces which take advantage of the GET suite to provide high-level interfaces for model building, editing, exploration, and simulations. 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).



References

Bradley *et al* 2011, *Prog Biophys Mol Biol*. 107(1): 32-47. doi: 10.1016/j.pbiomolbio.2011.06.015.

de Bono *et al* 2015, *Front. Physiol.* 6(24). doi: 10.3389/fphys.2015.00024

Latta *et al* 1984, *J Membr Biol*. 82(1):67-82. doi: 10.1007/BF01870733.

Miller *et al* 2011, *BMC Bioinformatics*. 14;12:22. doi: 10.1186/1471-2105-12-22.

Yu *et al* 2011, *Bioinformatics* 27(5): 743-744. doi: 10.1093/bioinformatics/btq723

Links

1. https://models.physiomeproject.org/workspace/19f
2. https://models.physiomeproject.org/e/236/
3. https://models.physiomeproject.org/e/233/
4. https://models.physiomeproject.org/e/231/
5. https://models.physiomeproject.org/e/232/

Acknowledgements

Supported by the Virtual Physiological Rat Project, NIH grant P50-GM094503 and Maurice Wilkins Centre for Molecular Biodiscovery.