What team CellML is up to with SED-ML...

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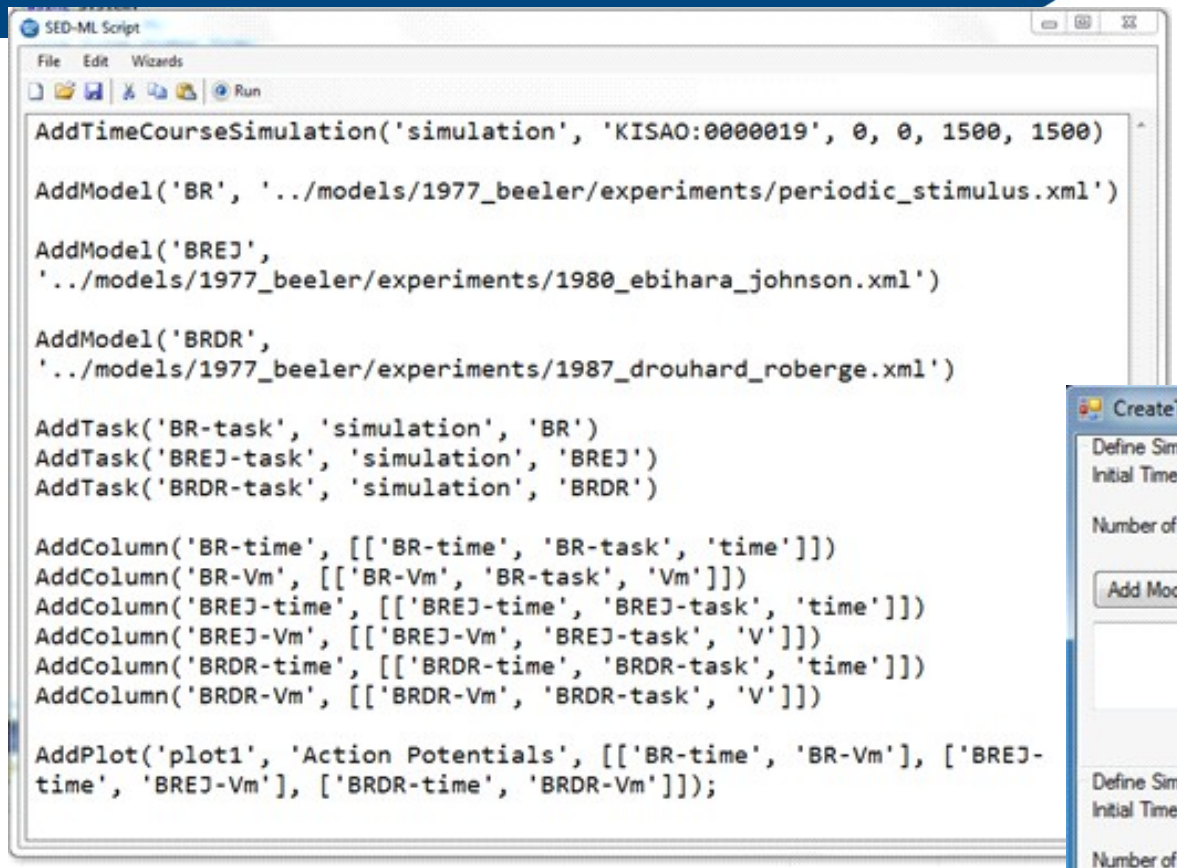
Te Whare Wānanga o Tāmaki Makaurau


SED-ML Script
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AddModel('BREJ',
'../models/1977_beeler/experiments/1980_ebihara_johnson.xml')
AddModel('BRDR',
'../models/1977_beeler/experiments/1987_drouhard_roberge.xml')
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AddTask('BREJ-task', 'simulation', 'BREJ')
AddTask('BRDR-task', 'simulation', 'BRDR')
AddColumn('BR-time', [['BR-time', 'BR-task', 'time']])
AddColumn('BR-Vm', [['BR-Vm', 'BR-task', 'Vm']])
AddColumn('BREJ-time', [['BREJ-time', 'BREJ-task', 'time']])
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AddColumn('BRDR-time', [['BRDR-time', 'BRDR-task', 'time']])
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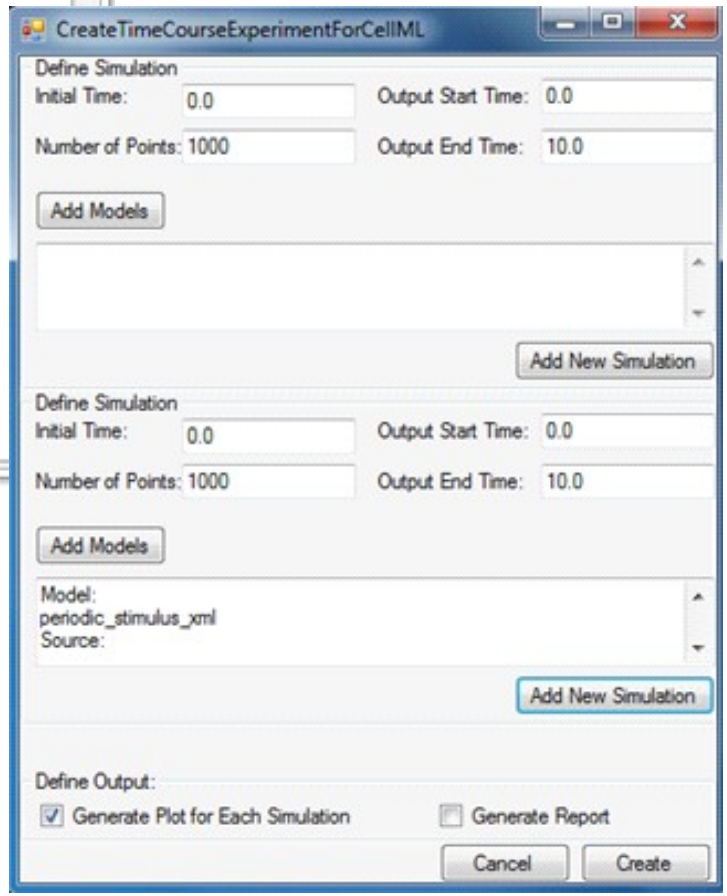
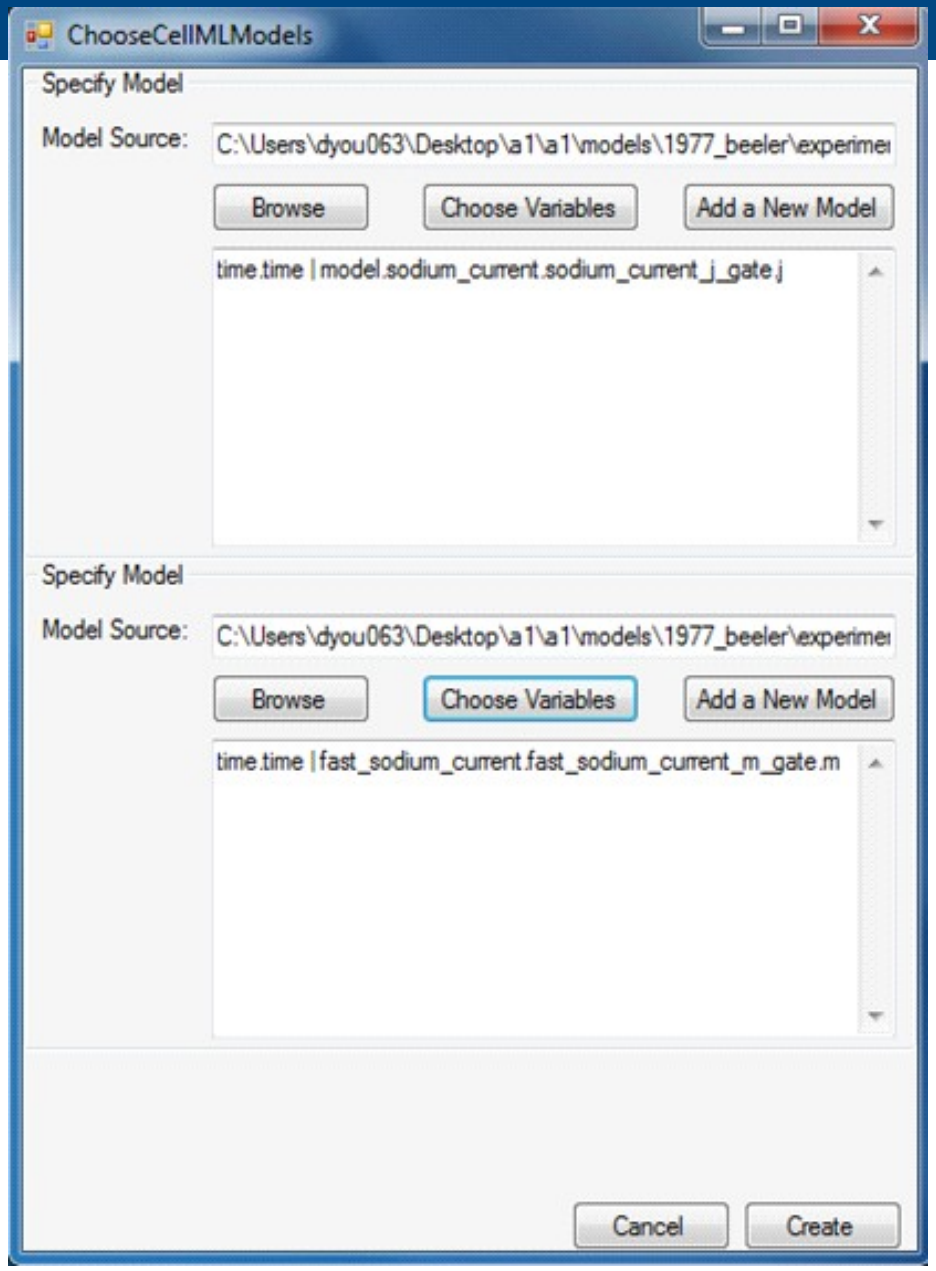
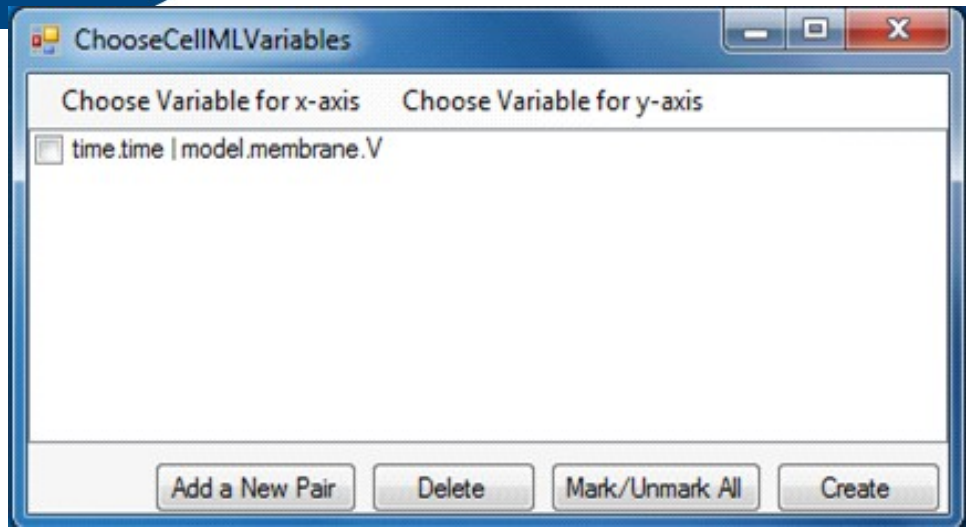
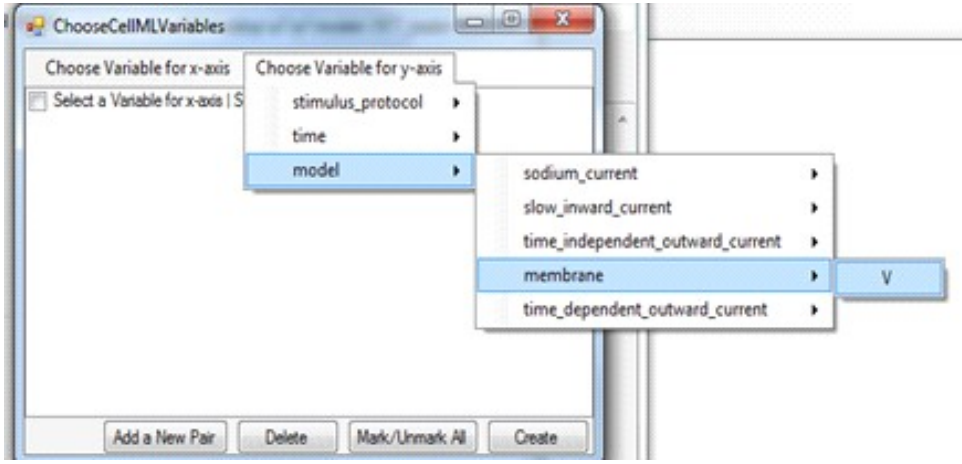
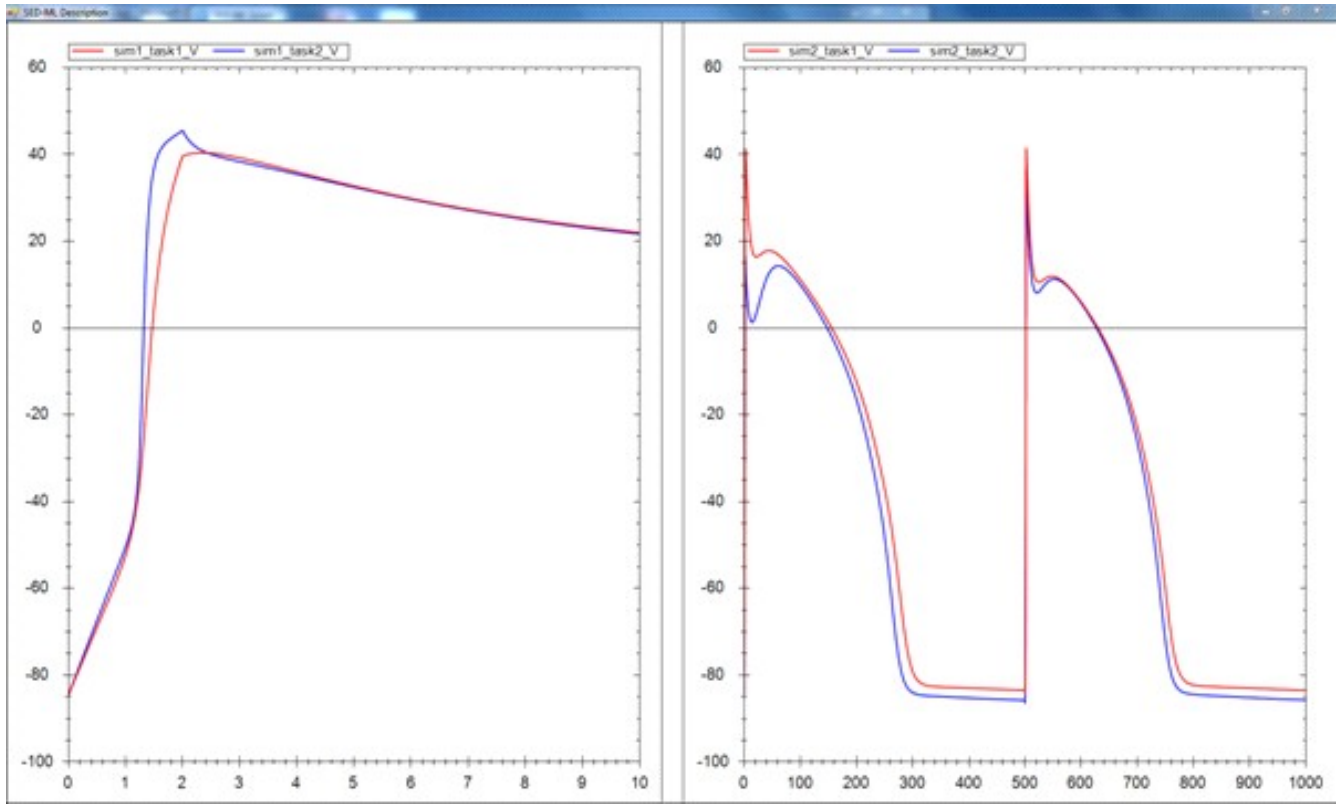

CreateTimeCourseExperimentForCellML
Define Simulation
Initial Time: 0.0
Output Start Time: 0.0
Number of Points: 1000
Output End Time: 10.0
Add Models
Add New Simulation
Define Simulation
Initial Time: 0.0
Output Start Time: 0.0
Number of Points: 1000
Output End Time: 10.0
Add Models
Model:
periodic_stimulus_xml
Source:
Add New Simulation
Define Output:
Generate Plot for Each Simulation
Generate Report
Cancel
Create


ChooseCellMLModels
Specify Model
Model Source:
C:\Users\dyou063\Desktop\a1\a1\models\1977_beeler\experimer
Browse
Choose Variables
Add a New Model
time.time | model.sodium_current.sodium_current_j_gate.j
Specify Model
Model Source:
C:\Users\dyou063\Desktop\a1\a1\models\1977_beeler\experimer
Browse
Choose Variables
Add a New Model
time.time | fast_sodium_current.fast_sodium_current_m_gate.m
Cancel
Create


ChooseCellMLVariables
Choose Variable for x-axis
Choose Variable for y-axis
time.time | model.membrane.V
Add a New Pair
Delete
Mark/Unmark All
Create


ChooseCellMLVariables
Choose Variable for x-axis
Choose Variable for y-axis
Select a Variable for x-axis | S
stimulus_protocol
time
model
sodium_current
slow_inward_current
time_independent_outward_current
membrane
time_dependent_outward_current
V
Add a New Pair
Delete
Mark/Unmark All
Create


SED-ML Description
sim1_task1_V
sim1_task2_V
60
40
20
0
-20
-40
-60
-80
-100
0
1
2
3
4
5
6
7
8
9
10
sim2_task1_V
sim2_task2_V
60
40
20
0
-20
-40
-60
-80
-100
0
100
200
300
400
500
600
700
800
900
1000

An actual use-case

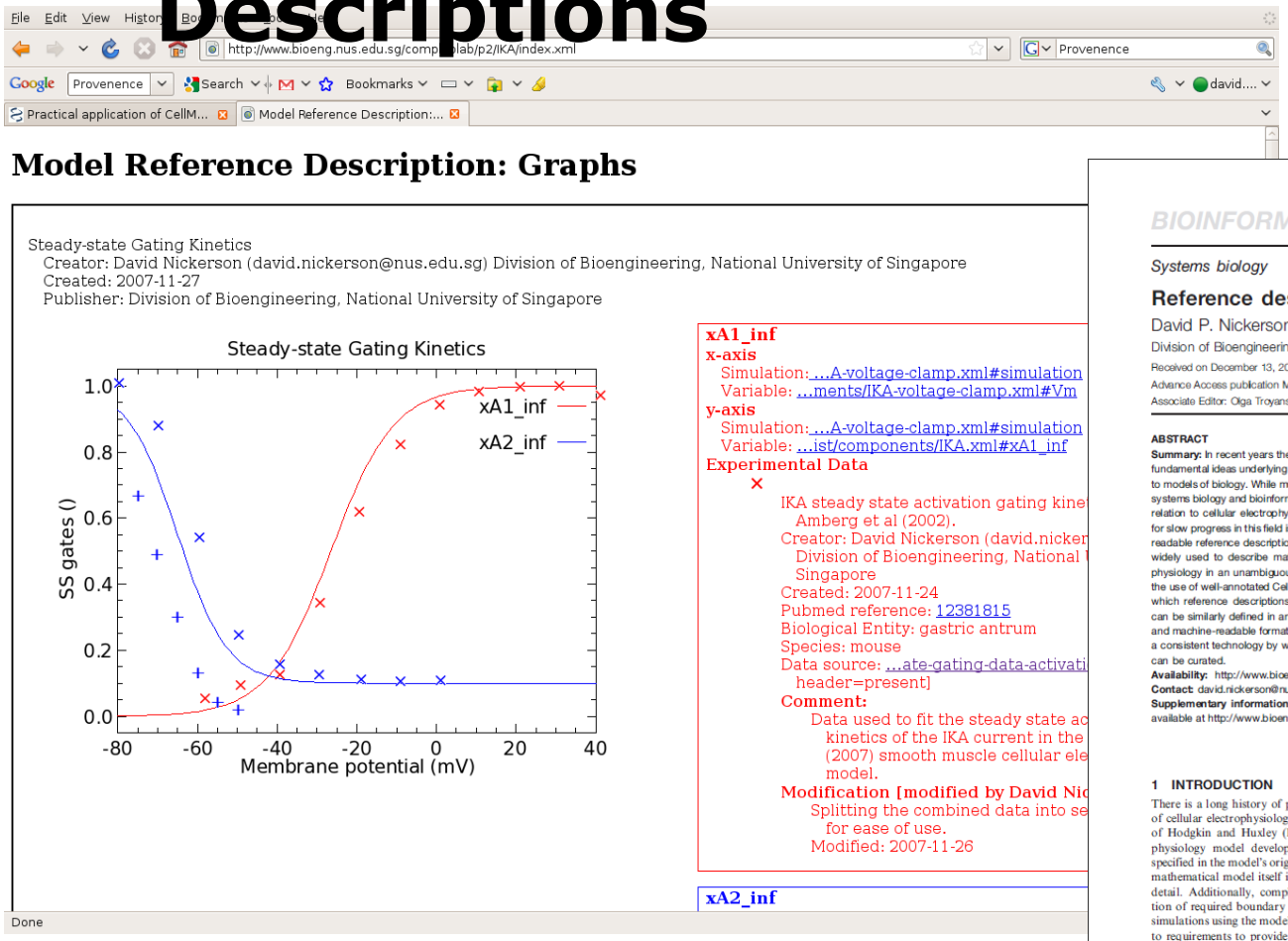
- Need to run simulations of models in which there are one or more “random” variables.
- Not really part of the model description (?)
  - But maybe should be achieved using 

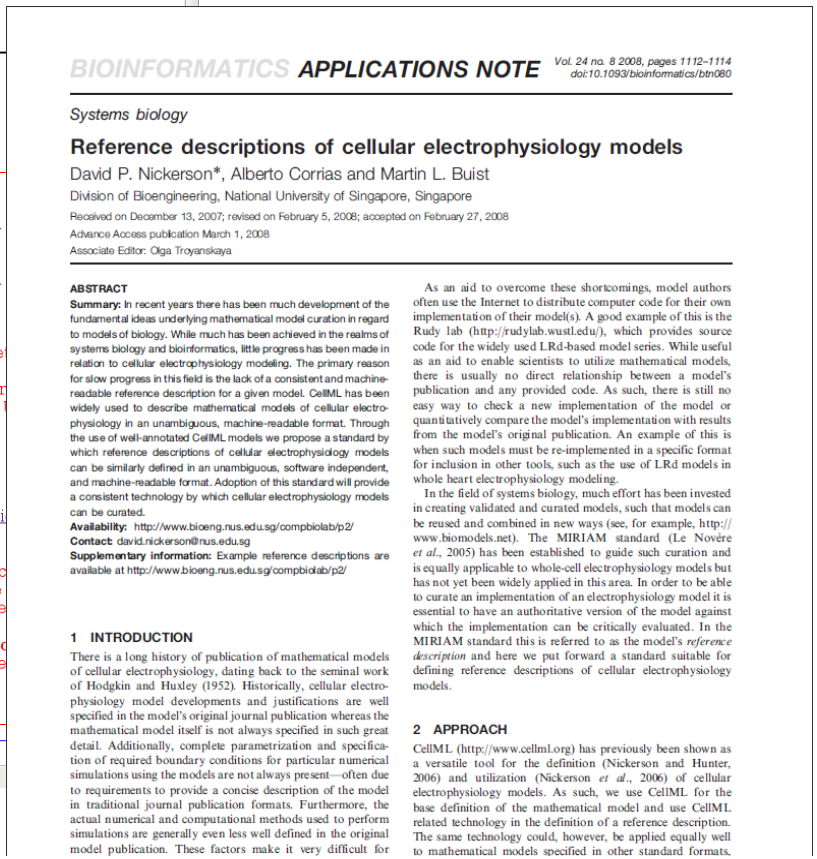
- Led to SProS (SED-ML Processing Service)
  - SED-ML object model interface specified in IDL
  - Transformed into C++ (and other language bindings)
  - Implemented as a CellML API service

SProS status

- IDL file exists
- C++ implementation with unit tests covering the complete object model
- Currently sitting on the **`implement-xpath`** branch http://cellml-api.hg.sourceforge.net/hgweb/cellml-api/cellml-api/file/8cb195c32157
- Uses the CellML API DOM implementation
- Requires an XPath implementation which also uses this DOM implementation...
- Implementation progress currently stopped until after the next release of the CellML API.

CellMLSimulator & Reference Descriptions

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doi:10.1093/bioinformatics/btn080

Systems biology

Reference descriptions of cellular electrophysiology models

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ABSTRACT

Summary: In recent years there has been much development of the fundamental ideas underlying mathematical model curation in regard to models of biology. While much has been achieved in the realms of systems biology and bioinformatics, little progress has been made in relation to cellular electrophysiology modeling. The primary reason for slow progress in this field is the lack of a consistent and machine-readable reference description for a given model. CellML has been widely used to describe mathematical models of cellular electrophysiology in an unambiguous, machine-readable format. Through the use of well-annotated CellML models we propose a standard by which reference descriptions of cellular electrophysiology models can be similarly defined in an unambiguous, software independent, and machine-readable format. Adoption of this standard will provide a consistent technology by which cellular electrophysiology models can be curated.

Availability: http://www.bioeng.nus.edu.sg/compbiolab/p2/
Contact: david.nickerson@nus.edu.sg
Supplementary information: Example reference descriptions are available at http://www.bioeng.nus.edu.sg/compbiolab/p2/

1 INTRODUCTION

There is a long history of publication of mathematical models of cellular electrophysiology, dating back to the seminal work of Hodgkin and Huxley (1952). Historically, cellular electrophysiology model developments and justifications are well specified in the model's original journal publication whereas the mathematical model itself is not always specified in such great detail. Additionally, complete parametrization and specification of required boundary conditions for particular numerical simulations using the models are not always present—often due to requirements to provide a concise description of the model in traditional journal publication formats. Furthermore, the actual numerical and computational methods used to perform simulations are generally even less well defined in the original model publication. These factors make it very difficult for

As an aid to overcome these shortcomings, model authors often use the Internet to distribute computer code for their own implementation of their model(s). A good example of this is the Rudy lab (http://rudylab.wustl.edu/), which provides source code for the widely used LRd-based model series. While useful as an aid to enable scientists to utilize mathematical models, there is usually no direct relationship between a model's publication and any provided code. As such, there is still no easy way to check a new implementation of the model or quantitatively compare the model's implementation with results from the model's original publication. An example of this is when such models must be re-implemented in a specific format for inclusion in other tools, such as the use of LRd models in whole heart electrophysiology modeling.

In the field of systems biology, much effort has been invested in creating validated and curated models, such that models can be reused and combined in new ways (see, for example, http://www.biomodels.net). The MIRIAM standard (Le Novère *et al.*, 2005) has been established to guide such curation and is equally applicable to whole-cell electrophysiology models but has not yet been widely applied in this area. In order to be able to curate an implementation of an electrophysiology model it is essential to have an authoritative version of the model against which the implementation can be critically evaluated. In the MIRIAM standard this is referred to as the model's *reference description* and here we put forward a standard suitable for defining reference descriptions of cellular electrophysiology models.

2 APPROACH

CellML (http://www.cellml.org) has previously been shown as a versatile tool for the definition (Nickerson and Hunter, 2006) and utilization (Nickerson *et al.*, 2006) of cellular electrophysiology models. As such, we use CellML for the base definition of the mathematical model and use CellML related technology in the definition of a reference description. The same technology could, however, be applied equally well to mathematical models specified in other standard formats.

http://www.bioeng.nus.edu.sg/compbiolab/p2/

doi:10.1093/bioinformatics/btn080

File Edit View History Bookmarks Tools Help

file:///home/andre/projects/zinc/NephronInterface/interface.html

Google

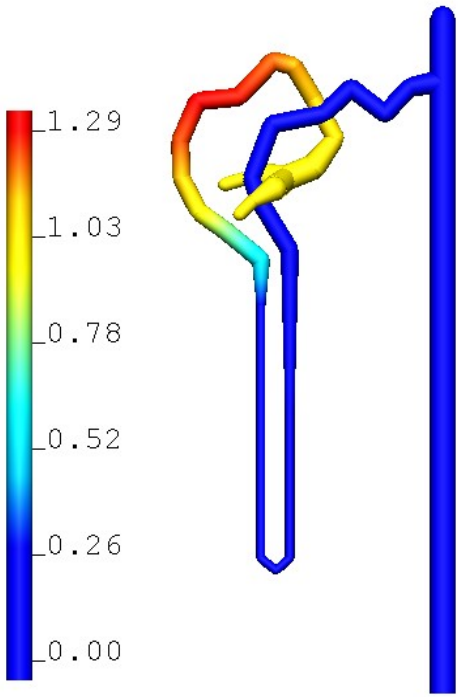
Nephron Interface

The Renal Nephron

Close all

- Nephron
  - Anatomy
  - Physiology
  - Modelling Studies
    - SGLT2 Inhibitio
      - Na-glucose c
      - Control
      - Inhibited

Input mode: Display | Reset view | nephron | segment | cell | protein



Inhibited

The altered glucose concentration observed when SGLT2 is inhibited.

These results show the altered glucose concentration in the proximal tubule when the control SGLT2 mode is inhibited, as would be the case if the drug dapagliflozin was applied to inhibit SGLT2 activity.

Na-glucose cotransporter

Refined Na-glucose cotransporter models, SGLT1 and SGLT2.

In this study, we utilize the Weinstein et al (2007) proximal tubule model extended through the inclusion of a spatial distribution of the SGLT1 and SGLT2 Na-glucose cotransporter models.

SGLT2 Inhibition

The selective inhibition of the Na-glucose cotransporter, SGLT2, by the drug Dapagliflozin.

Inhibition of SGLT2 is emerging as an effective treatment of type 2 diabetes. The drug

David Nickerson

April 2010

Done

File Edit View History Bookmarks Tools Help

Nephron Interface

The Renal Nephron

Close all

- Nephron
  - Anatomy
    - Efferent Arterio
    - Afferent Arterio
    - Glomerulus
    - Proximal Tubul
      - Proximal Co
      - Proximal Str
    - Loop of Henle
    - Macula Densa
    - Distal Convolut
    - Connecting Tub
    - Collecting Duct
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    - Efferent Arterio
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    - Loop of Henle
    - Macula Densa
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    - Connecting Tub
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    - SGLT2 Inhibitio
      - Na-glucose
      - Control
      - Inhibited

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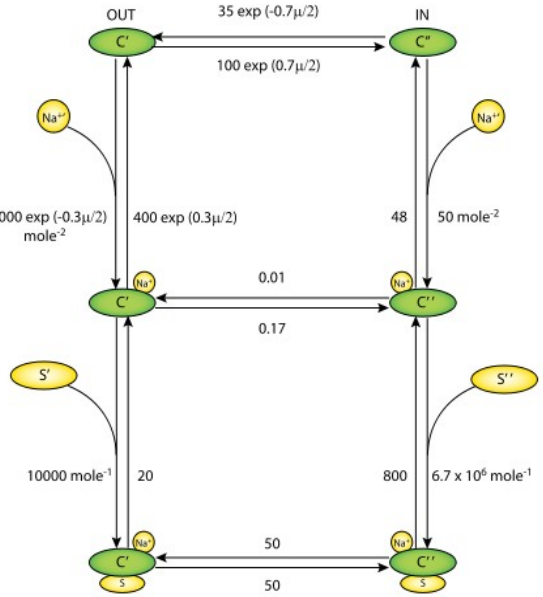

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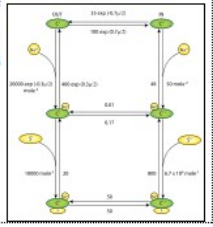
Mackenzie et al (1996)

Biophysical Characteristics of the Pig Kidney Na+/Glucose Cotransporter SGLT2 Reveal a Common Mechanism for SGLT1 and SGLT2. *J Biol Chem* **271**: 32678-32683, 1996.

CellML model repository

A complete description of this model is available and will be intergrated into this interface as future work.



Proximal Tubule

First of the transporting tubule segments.

David Nickerson

April 2010

Done

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Constituents of the Renal Nephron

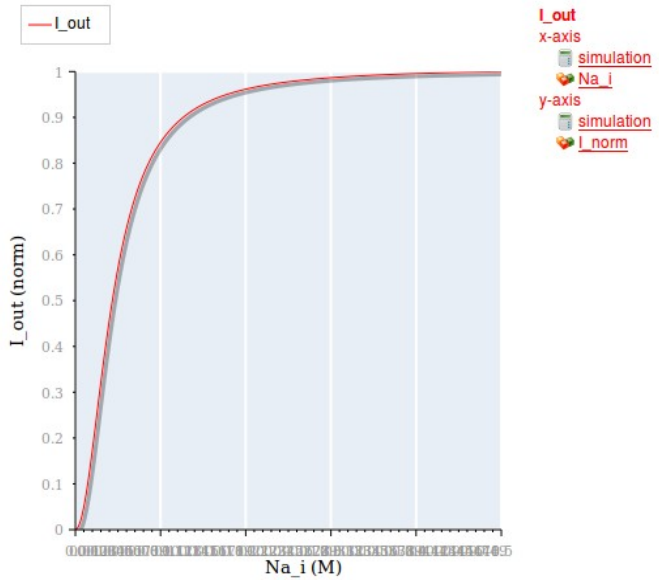
Constituents of the Renal Nephron

David Nickerson (2010-04-19)

Help

- Constituents of the Renal Nep
  - Eskandari et al (2005)
    - Eskandari et al (2005)
      - Figure 2(b)
    - Eskandari et al (2005)
      - Figure 3(a)
      - Figure 3(b)
    - Eskandari et al (2005)
      - Figure 4
  - Mackenzie et al (1996)
    - Figure 3(a)
    - Figure 3(b)
    - Figure 3(c)
    - Figure 3(d)

Reproduction of figure 4 from Eskandari et al (2005).



I_out
x-axis
simulation
Na_i
y-axis
simulation
I_norm

I_norm

Units: dimensionless
Defined in math container: Na_i

Na_i

+ Created: 2010-04-21, David Nickerson

$$\frac{dNa\_i}{dtime} = [1.0e\text{-}3 M\_per\_second]$$

$$I\_norm = I\_NaGl\_SS / [6.29510065e\text{-}06 uA]$$

Generated by: CellMLSimulator (version: CellMLSimulator 0.3.0-devel-json - revision 221M - Sat Apr 17 13:07:26 NZST 2010) at Thu 22 Apr 2010 07:56:51 SGT

javascript:;

CellMLSimulator plans

- Migrate from CellML simulation and graphing metadata (plus custom annotations) to SED-ML
- SED-ML for multiscale models?
- libSedML vs jlibSedML vs Andre's C++ libSedML vs SProS...