

# **CellML, SED-ML, and the Physiome Model Repository**

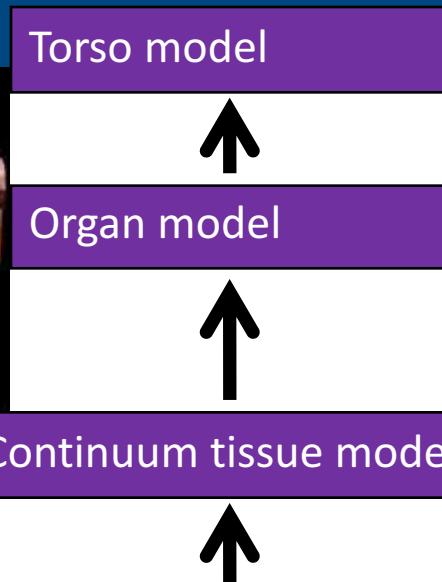
David Nickerson  
Auckland Bioengineering Institute  
University of Auckland  
New Zealand



**AUCKLAND  
BIOENGINEERING  
INSTITUTE**



# Cardiac Physiome

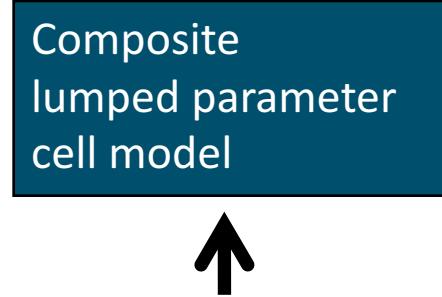


Myocardial activation  
 Ventricular wall mechanics  
 Ventricular blood flow  
 Heart valve mechanics  
 Coronary blood flow  
 Neural control



Discrete tissue structure model

Calcium transport models  
 Myofilament mechanics  
 Signal pathway models  
 Metabolic pathway models  
 Gene regulation models

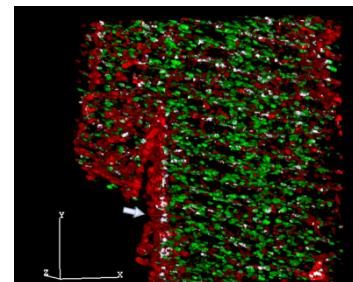
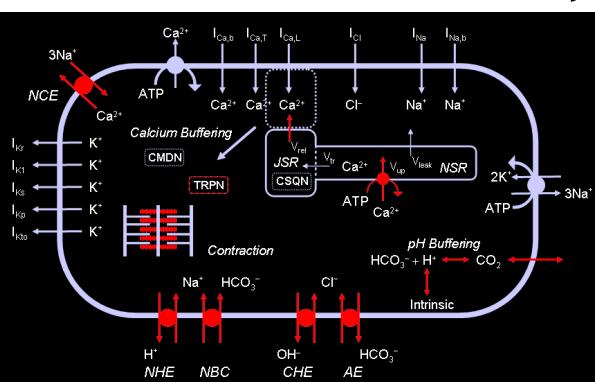


Hodgkin-Huxley type ion channel model

Markov ion channel model

↑

3D cell model



3D protein model

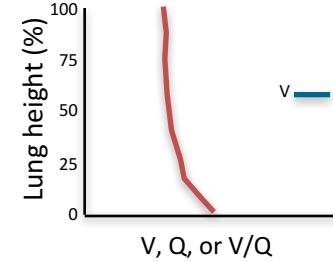
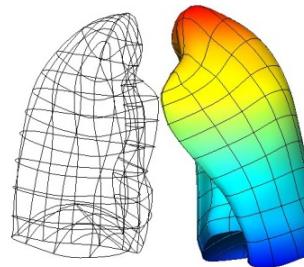
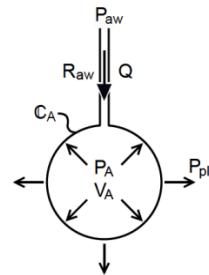
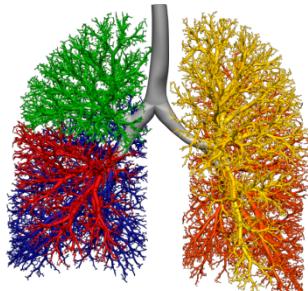
$\uparrow$  (KCNQ1+KCNE1)

Coarse grained MD model

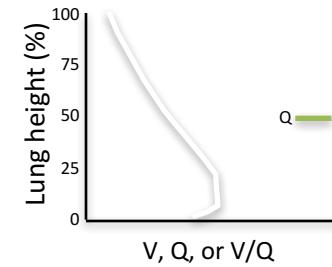
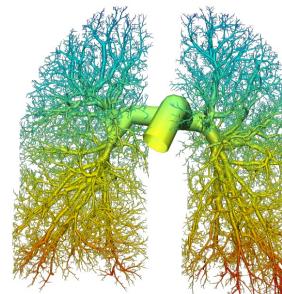
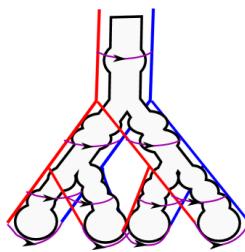
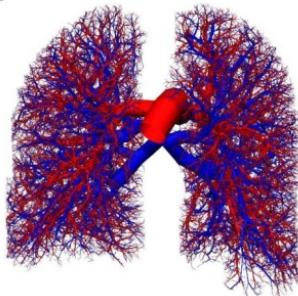
Molecular dynamics model

Quantum mechanics model

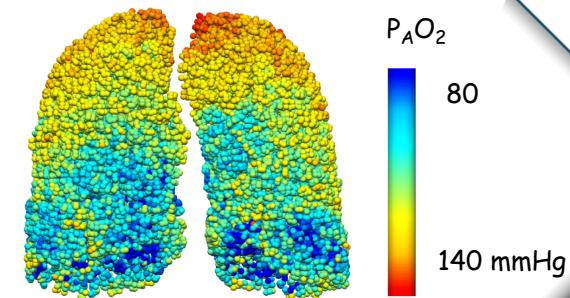
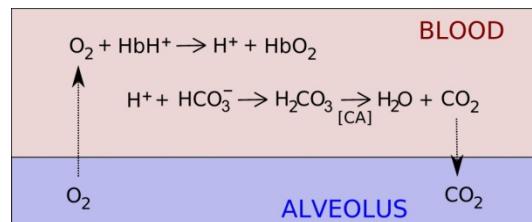
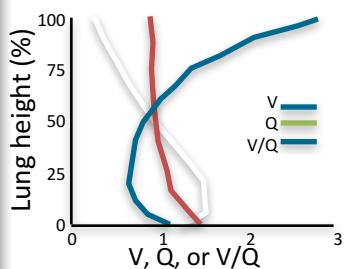
# Respiratory system



Structure-based model + airway resistance + tissue elasticity = ventilation distribution



Vessel resistance + capillary recruitment + hydrostatic pressure = perfusion distribution

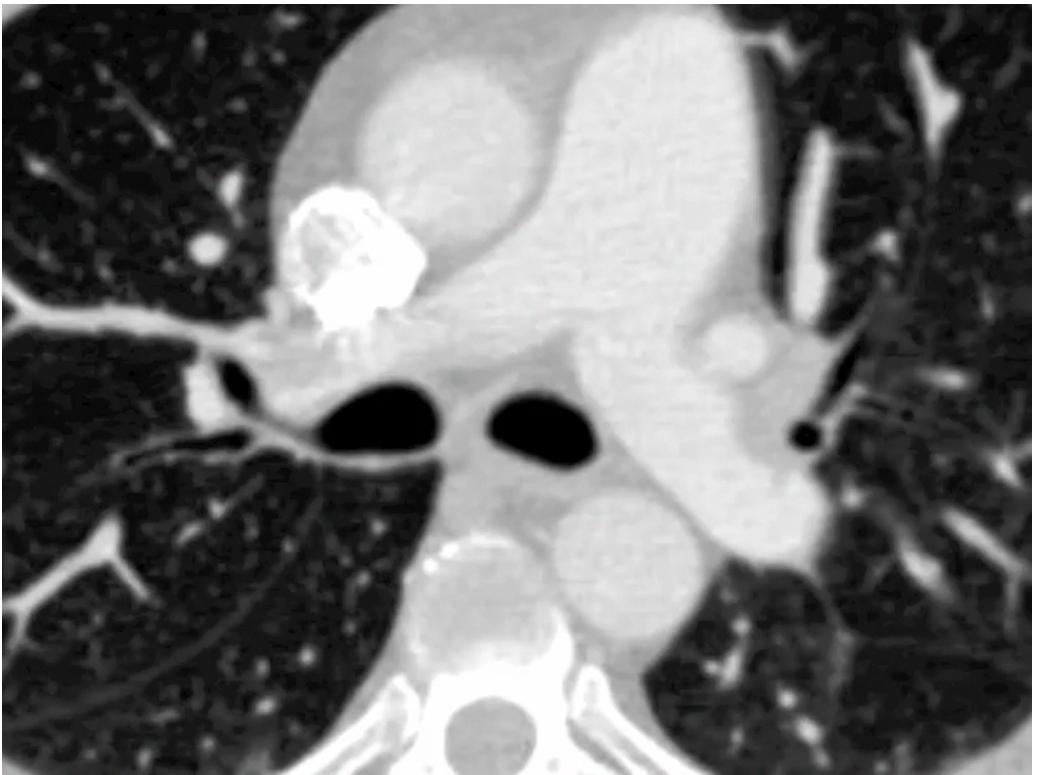
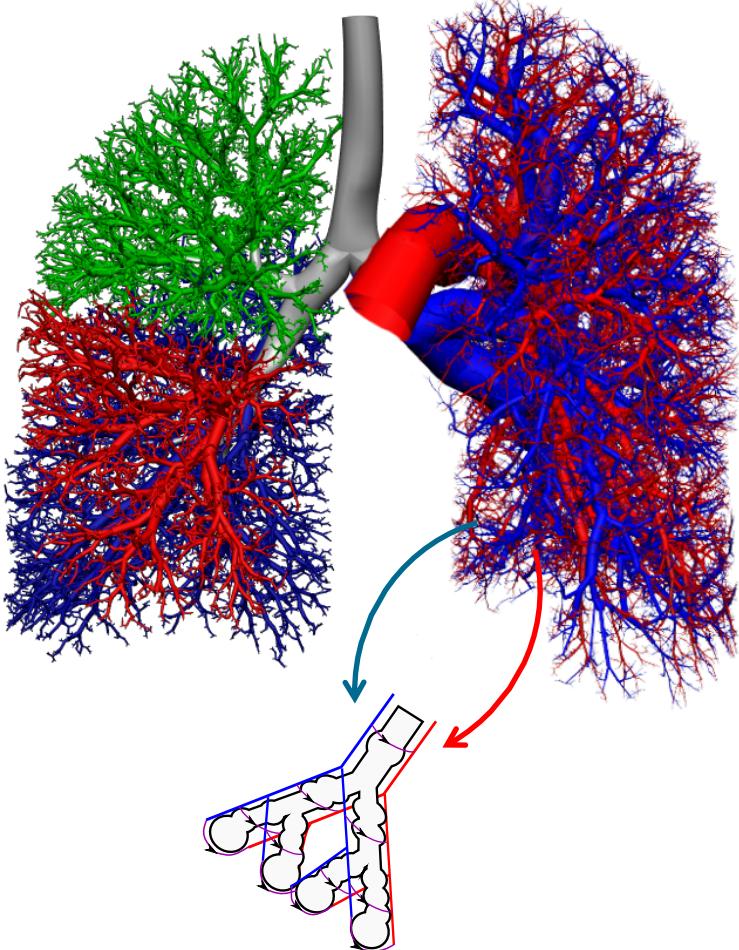


V/Q distribution + model for biophysics of oxygen exchange = arterial & venous blood gases

# Multi-scale models for ventilation, perfusion & gas exchange



Merryn  
Tawhai

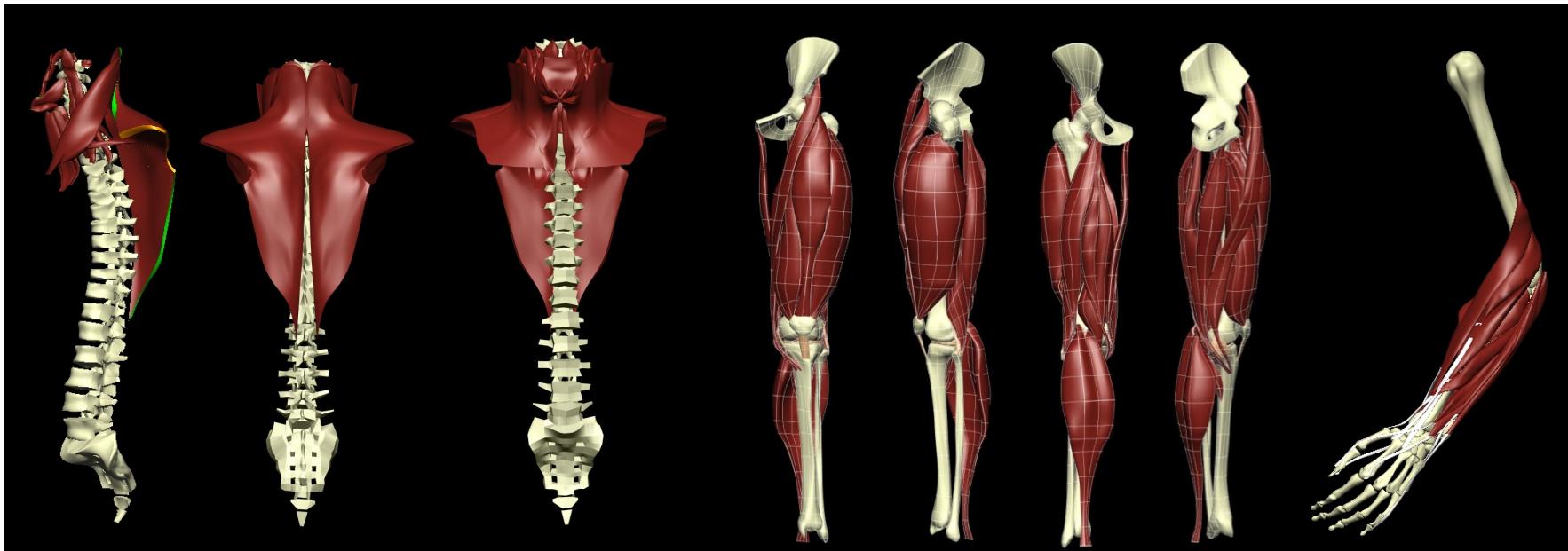
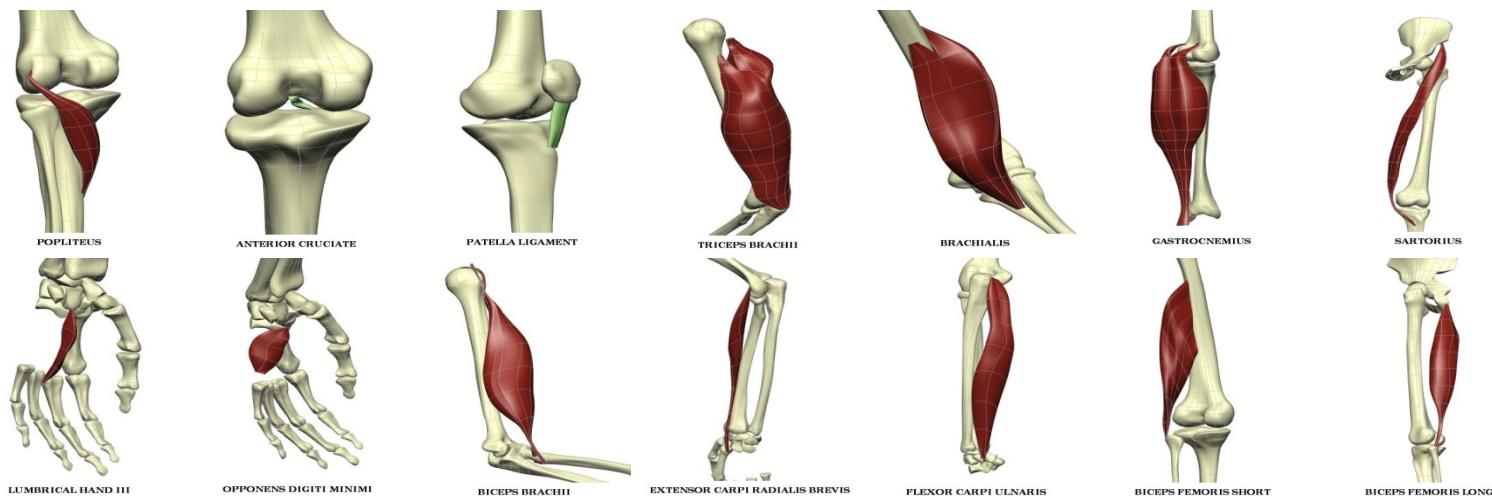


Tawhai MH, Clark AR, Donovan GM, Burrowes KS. Computational modeling of airway & pulmonary vascular structure & function: development of a 'Lung Physiome'. *Critical Reviews in BME*, 2011.

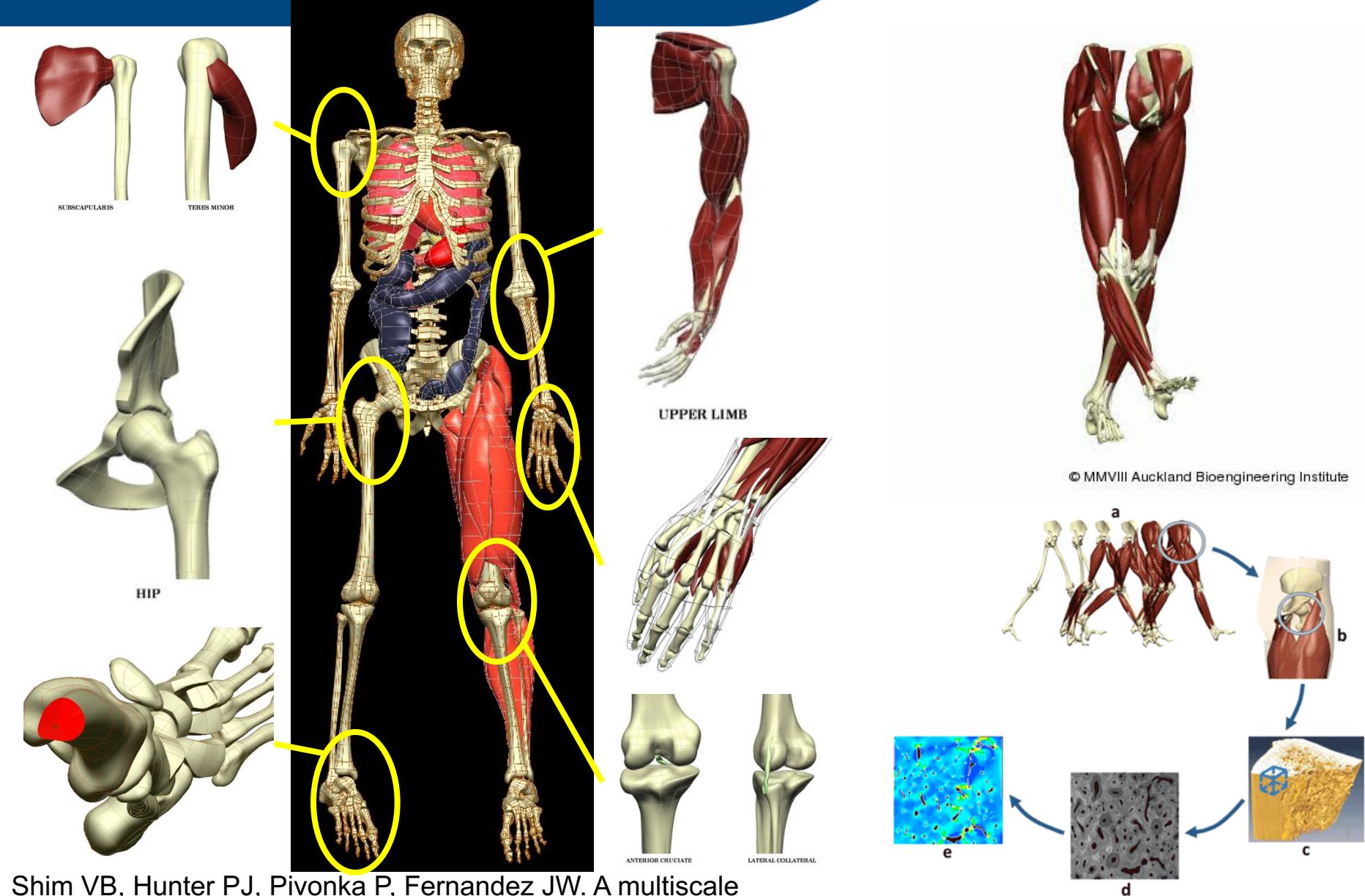
# Musculo-skeletal system



Thor  
Besier

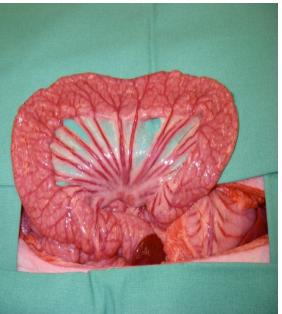
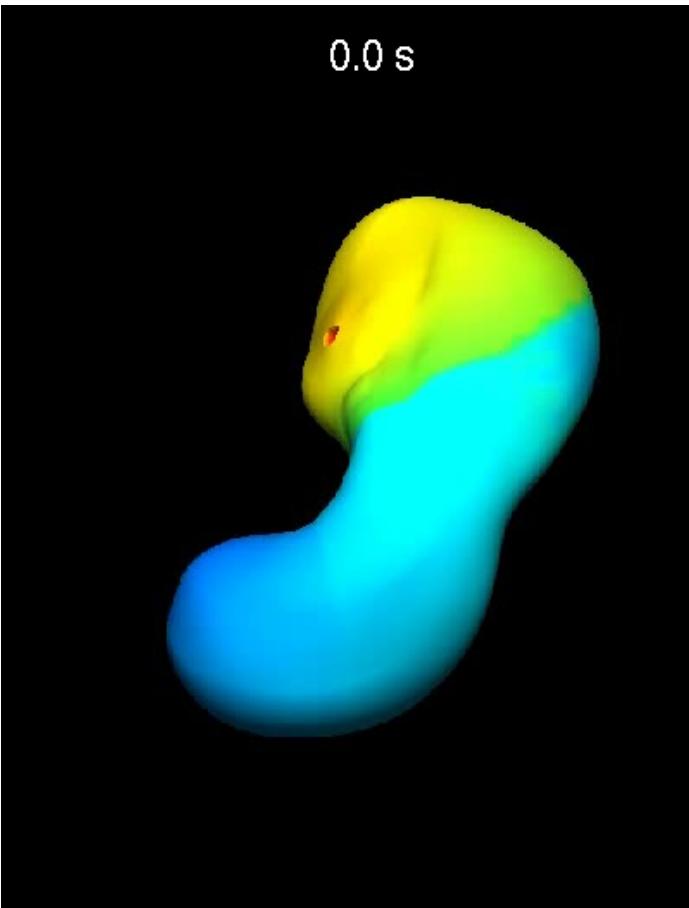
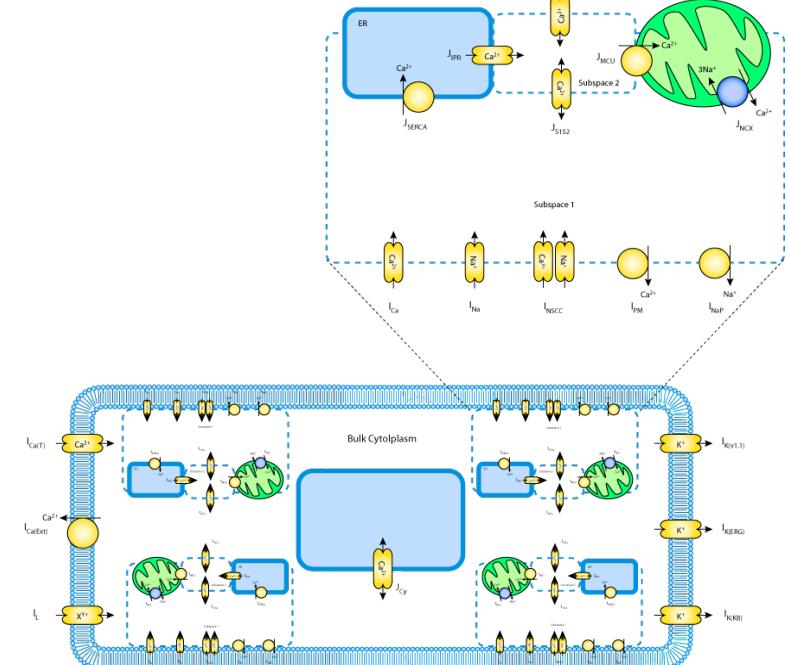
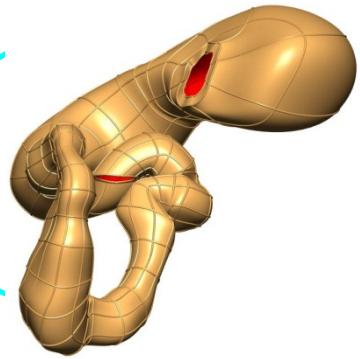
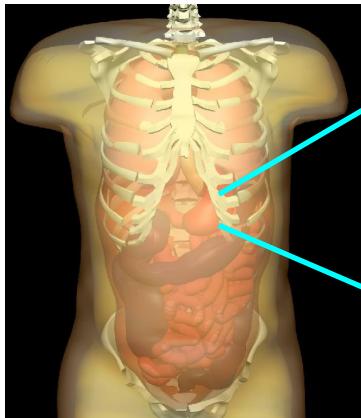


# Generic models of the joints



Shim VB, Hunter PJ, Pivonka P, Fernandez JW. A multiscale framework based on the physiome markup languages for exploring the initiation of osteoarthritis at the bone-cartilage interface. IEEE Trans Biomed Eng. 58(12):3532-6, 2011

# Digestive system: stomach

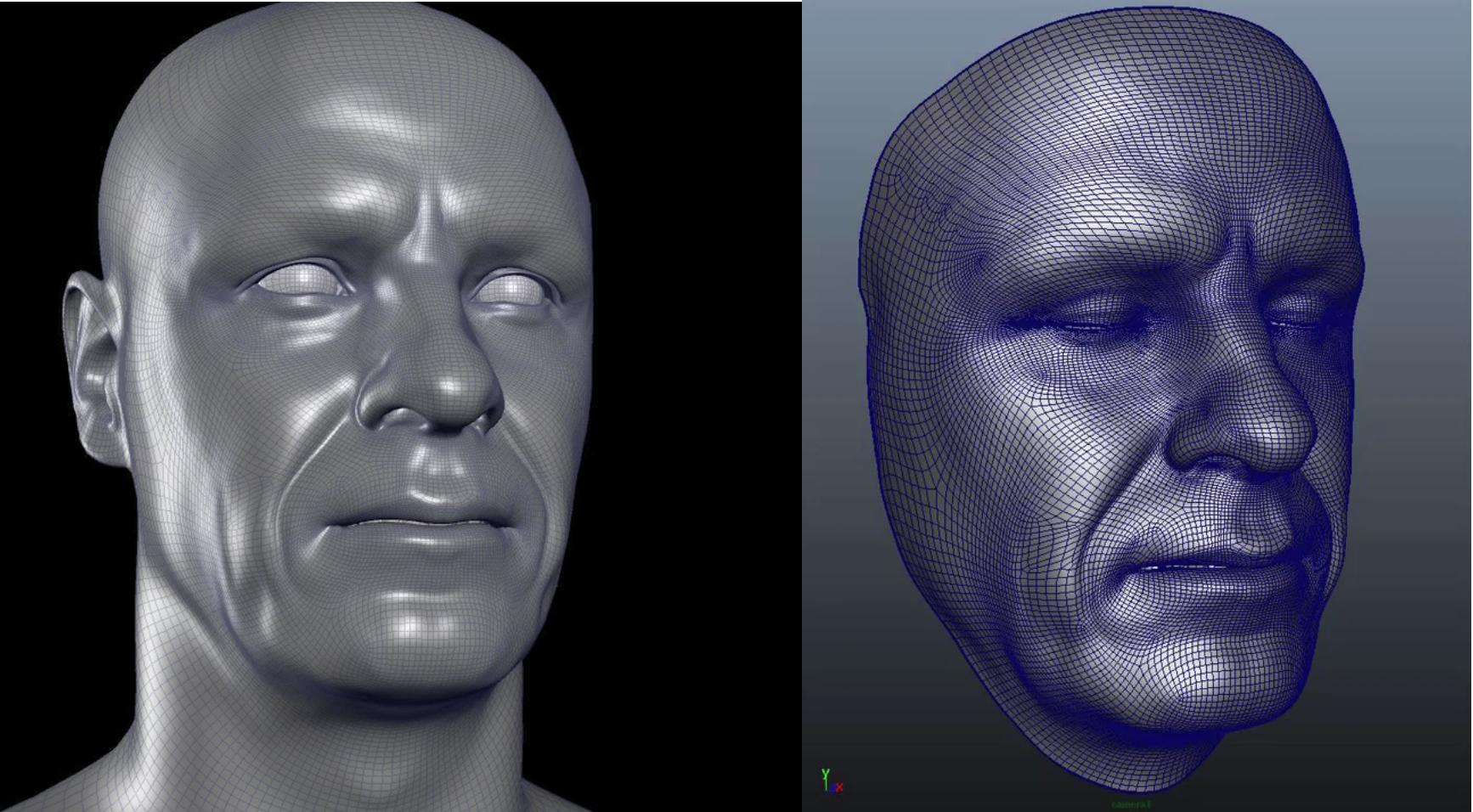


 Leo Cheng

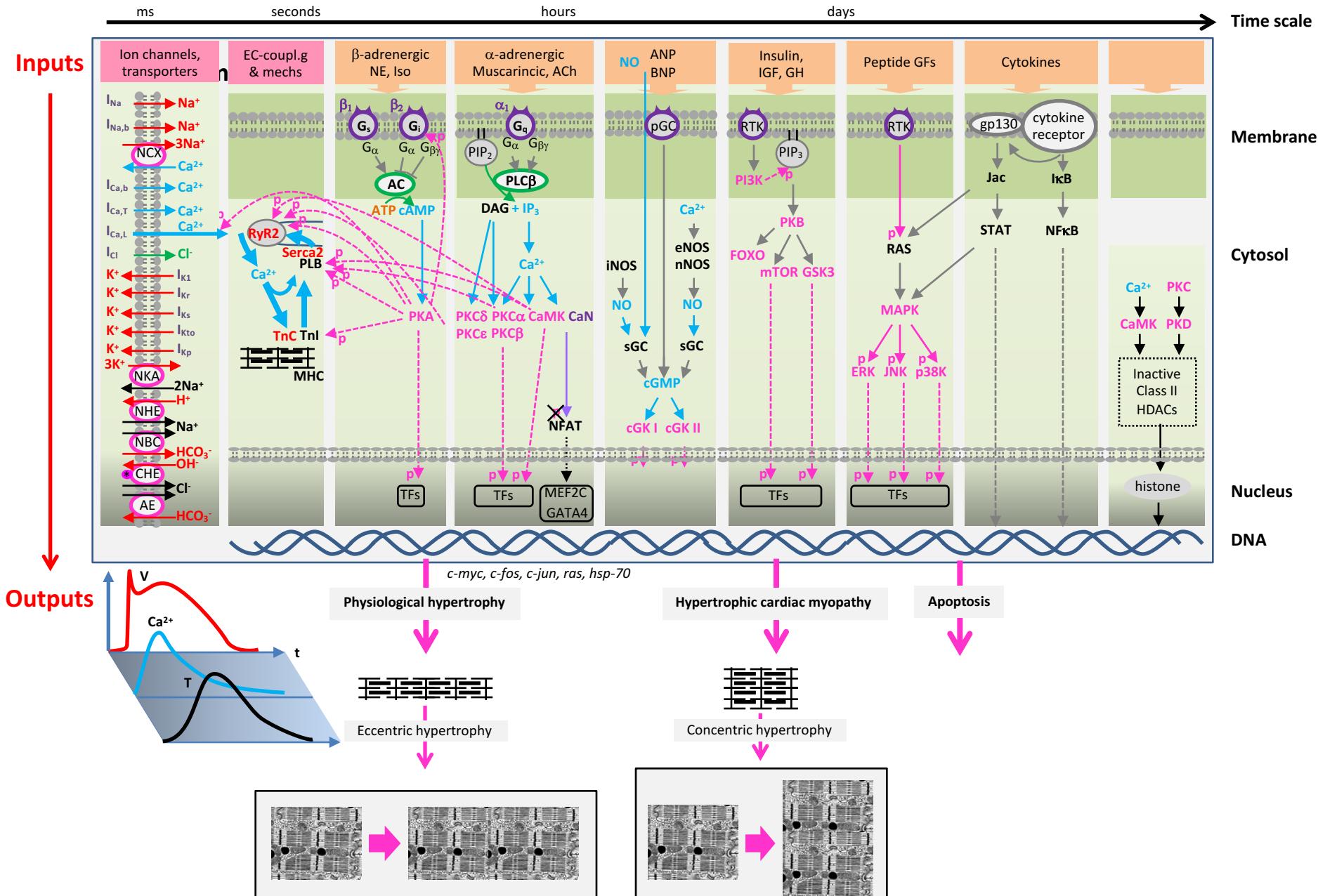
Faville et al. *BiophysJ.* 96, 4834-4852, 2009. Biophysically based mathematical modeling of interstitial cells of Cajal slow wave activity generated from a discrete unitary potential basis.

# Lab for Animate Technologies

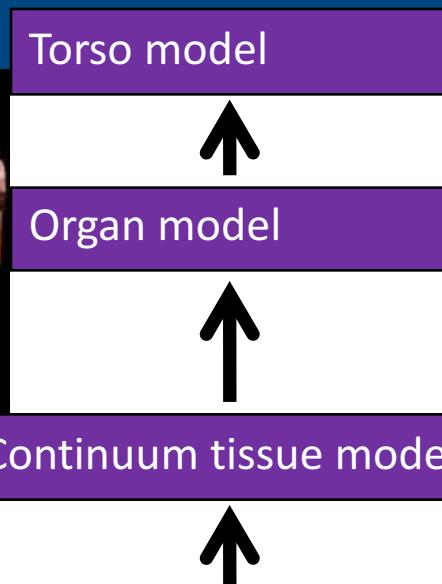
Mark  
Sagar



# CellML signalling modules for the cardiac myocyte



# Cardiac Physiome

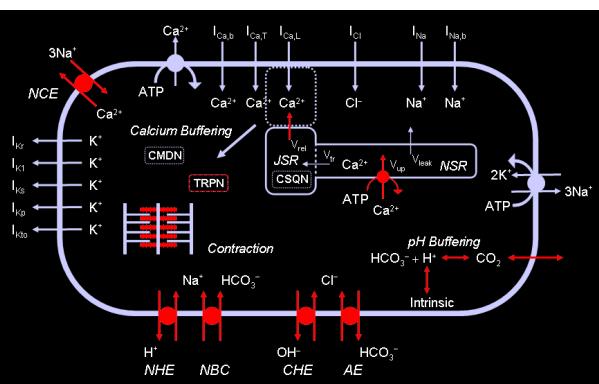


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Discrete tissue structure model

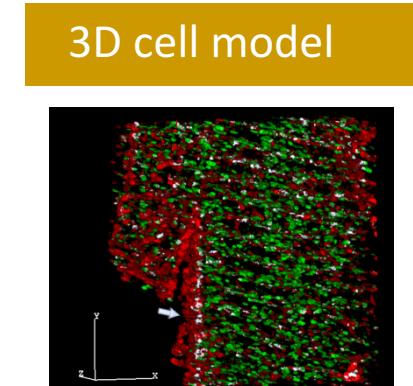
Calcium transport models  
Myofilament mechanics  
Signal pathway models  
Metabolic pathway models  
Gene regulation models



Composite lumped parameter cell model

Hodgkin-Huxley type ion channel model

Markov ion channel model



3D cell model

3D protein model  
(KCNQ1+KCNE1)

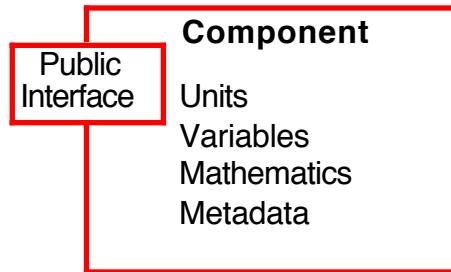
Coarse grained MD model

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Quantum mechanics model

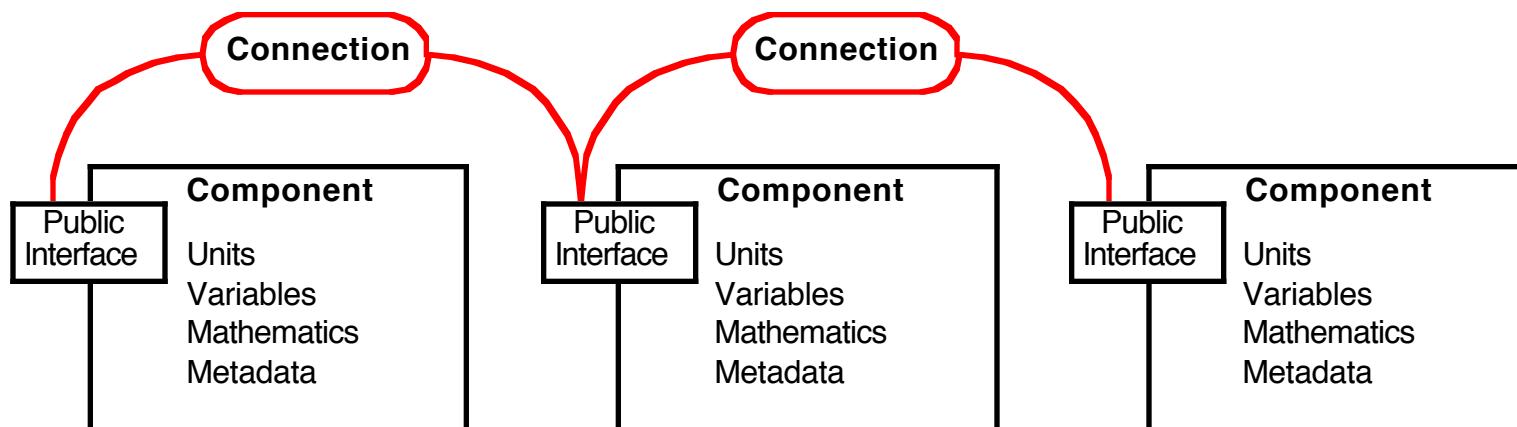
# CellML components

- CellML has a simple structure based upon connected *components*.
- Components abstract concepts by providing well-defined interfaces to other components.
- Components encapsulate concepts by hiding details from other components.



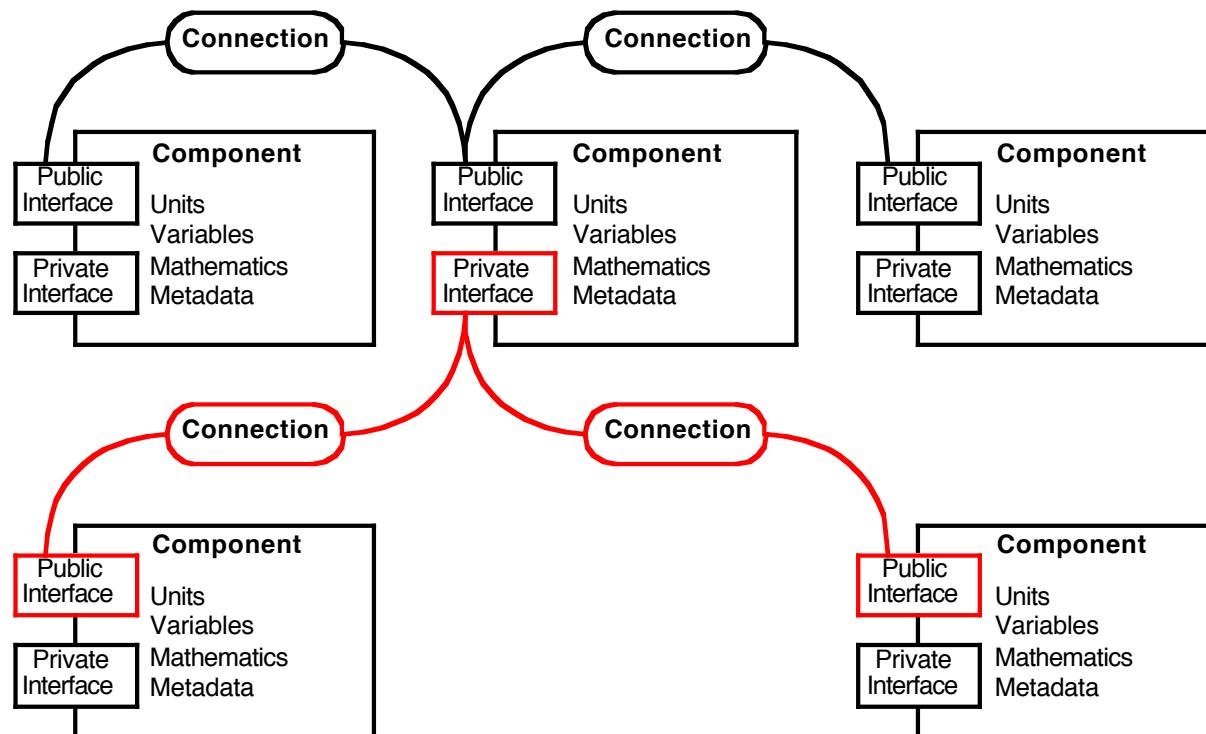
# CellML connections

- *Connections* provide the means for sharing information by associating variables visible in the interface of one component with those in the interface of another component.
- Consistency is enforced by requiring that all variables be assigned appropriate physical *units*.



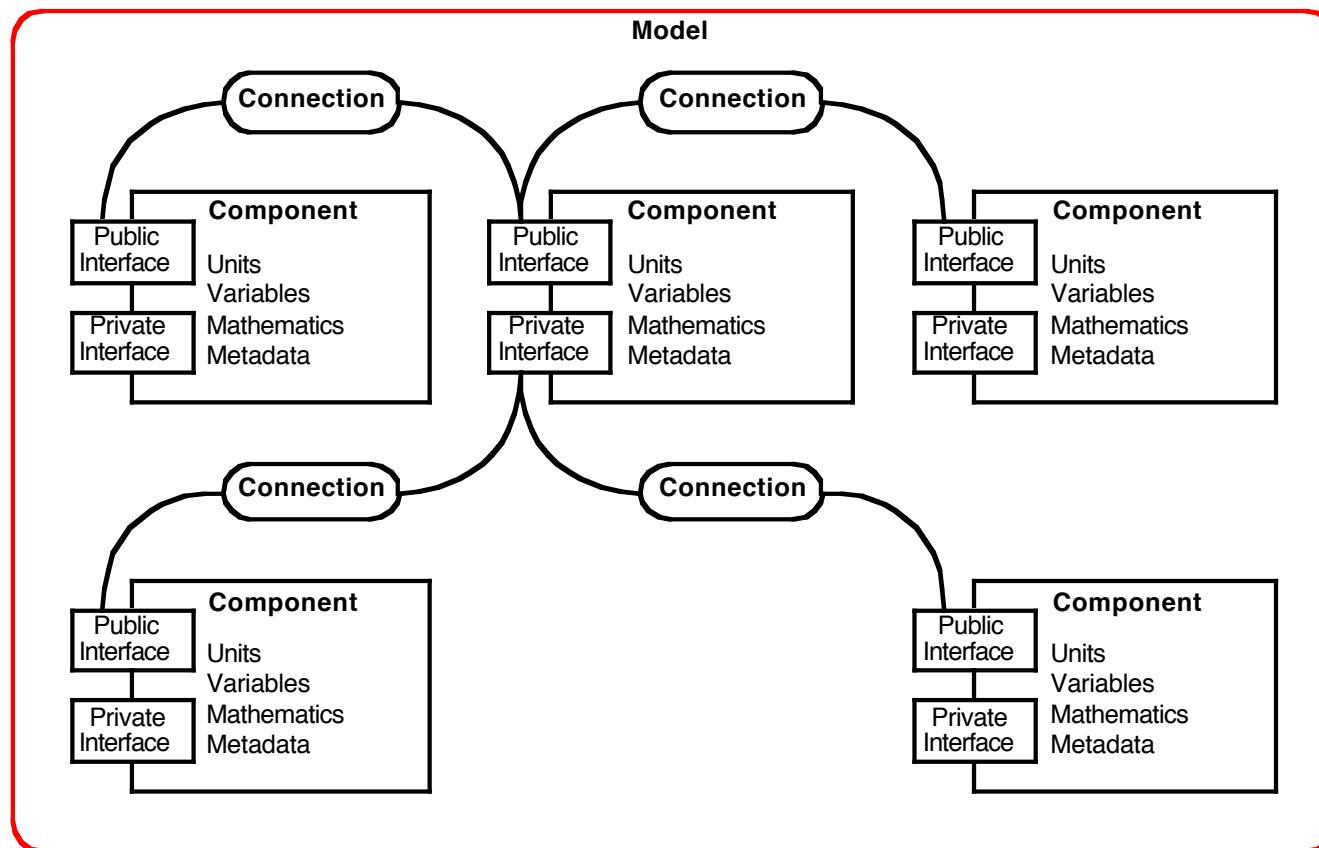
# CellML encapsulation

- Encapsulation hierarchies are enabled using *private interfaces*.



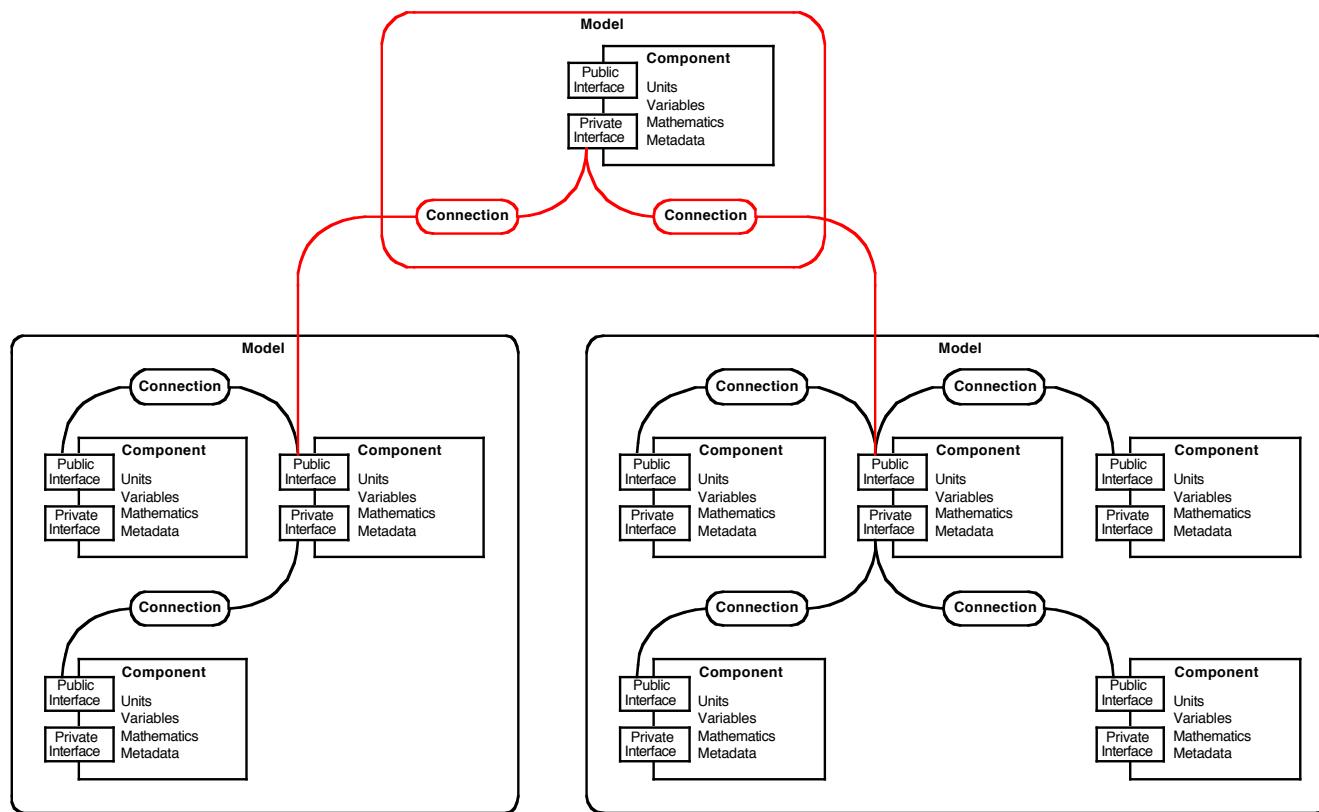
# CellML model

- A *model* is the root element for a CellML document. It is a container for components, connections, units, and metadata.



# CellML import

- Model reuse is enabled by the *import* element.
- New models may thus be constructed by combining existing models into model hierarchies.



# Model libraries

- Model reuse encourages the creation of model libraries.
- This is possible in CellML because there is no distinction between models as stand-alone entities and models as templates.
- Every import creates a new instance of the imported model in the importing model.
- The same model can be imported multiple times to create separate instances (with distinct identifiers) within the importing model.

# Model libraries

- Obvious candidates for reuse are existing CellML 1.0 models available in the model repository.
- Other candidates are the decomposition of existing models by identifying reusable generic (sub)models.
- These generic models are then formulated as new library models, making them available as basic building blocks for import into larger models.
- Useful generic models include collections of:
  - units (complicated combinations, non-SI definitions)
  - constants (codata fundamental physical constants)
  - processes (integrators, reactions, rate relations, ion channels, ...)
- Sometimes difficult to balance generality versus conciseness.

# Combine models

*Exp Physiol* 93.7 pp 919–929

919

## Experimental Physiology

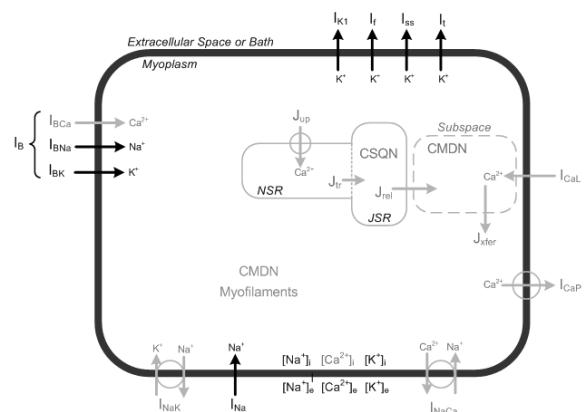
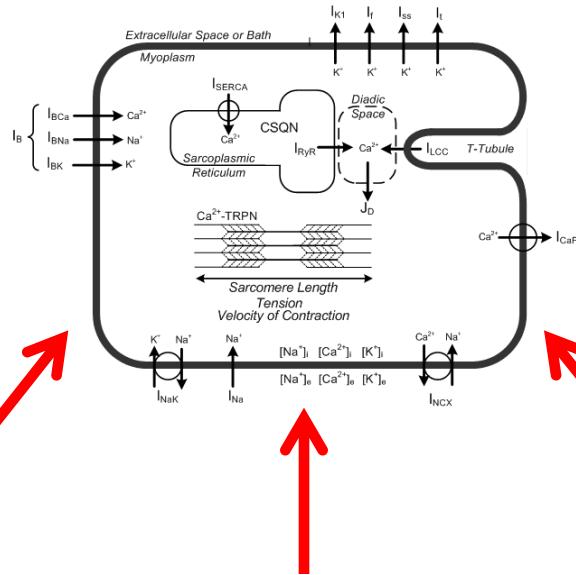
### Using Physiome standards to couple cellular functions for rat cardiac excitation–contraction

Jonna R. Terkildsen<sup>1</sup>, Steven Niederer<sup>2</sup>, Edmund J. Crampin<sup>1,3</sup>, Peter Hunter<sup>1</sup> and Nicolas P. Smith<sup>2</sup>

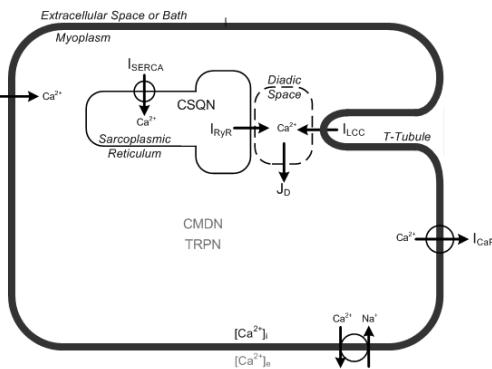
<sup>1</sup>Auckland Bioengineering Institute and <sup>3</sup>Department of Engineering Science, University of Auckland, Auckland, New Zealand

<sup>2</sup>Computing Laboratory, University of Oxford, Oxford, UK

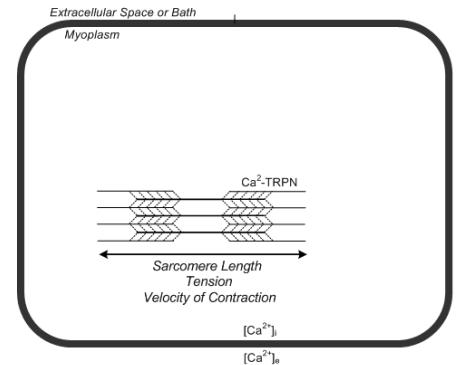
Terkildsen et al.  
coupled e-c + Ca



Pandit et al.  
cardiac action potential



Hinch et al.  
Ca-induced Ca  
release



Niederer et al.  
myofilament  
mechanics

# Extend/enhance models

Progress in Biophysics and Molecular Biology 98 (2008) 38–51

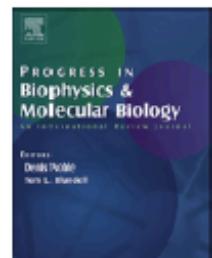


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Progress in Biophysics and Molecular Biology

journal homepage: [www.elsevier.com/locate/pbiomolbio](http://www.elsevier.com/locate/pbiomolbio)

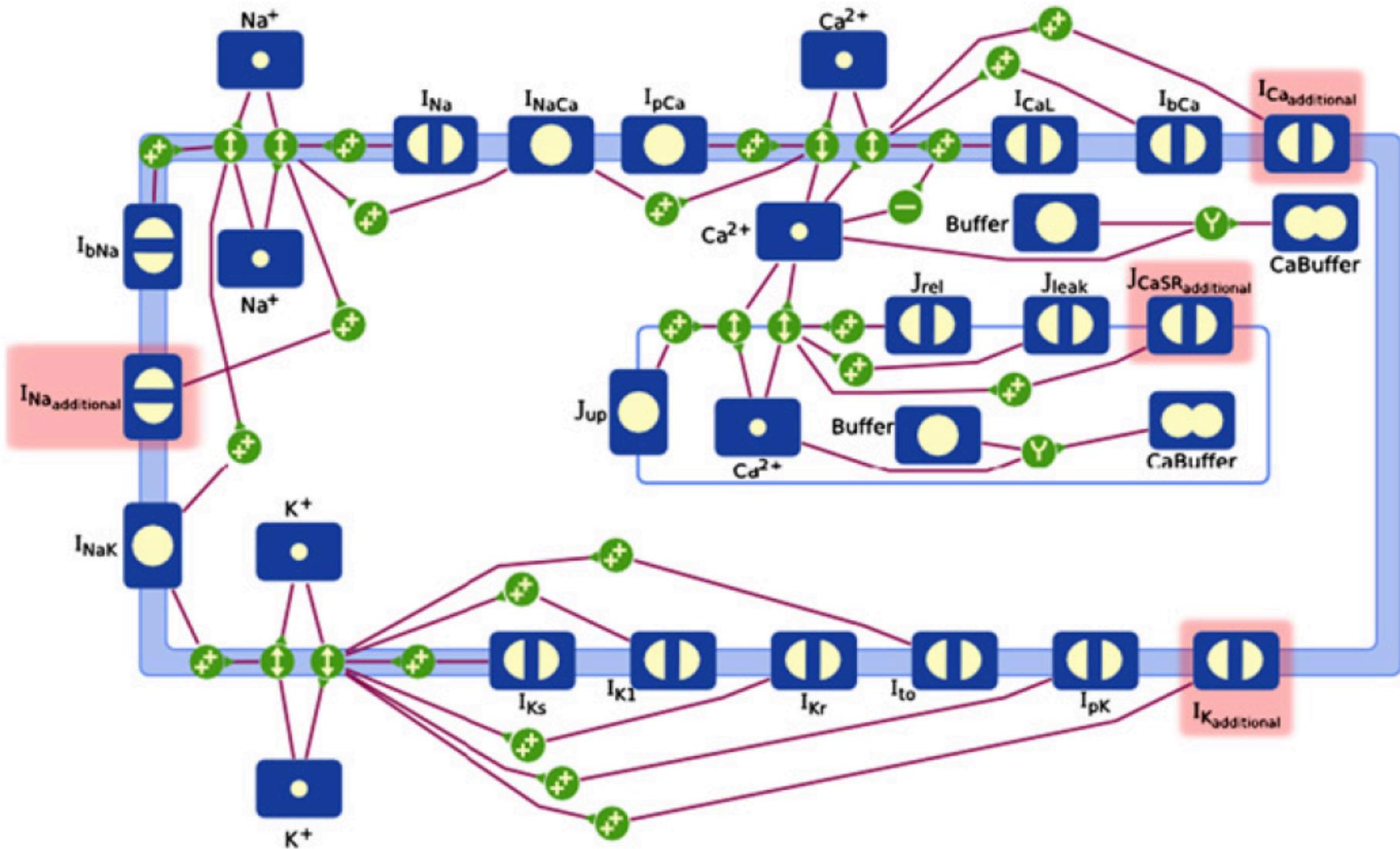


Review

Practical application of CellML 1.1: The integration of new mechanisms into a human ventricular myocyte model

David Nickerson\*, Martin Buist

*Division of Bioengineering, Faculty of Engineering, National University of Singapore, Singapore*





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White Paper

## Modular modelling with Physiome standards

Michael T. Cooling , David P. Nickerson, Poul M. F. Nielsen,  
Peter J. Hunter

First published: 29 August 2016 [Full publication history](#)

DOI: 10.1113/JP272633 [View/save citation](#)

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[Funding Information](#)

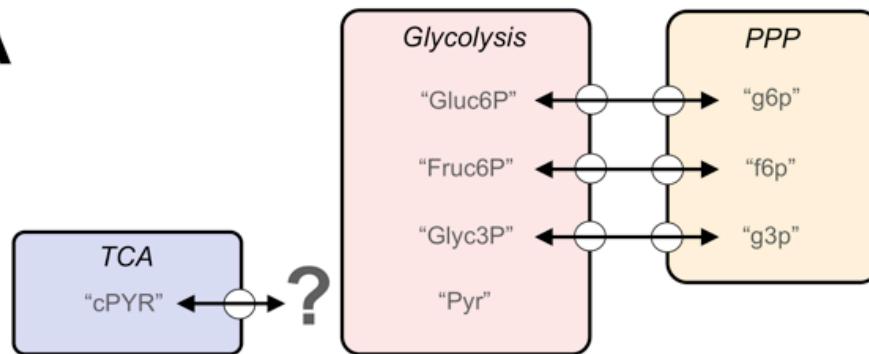
Early View



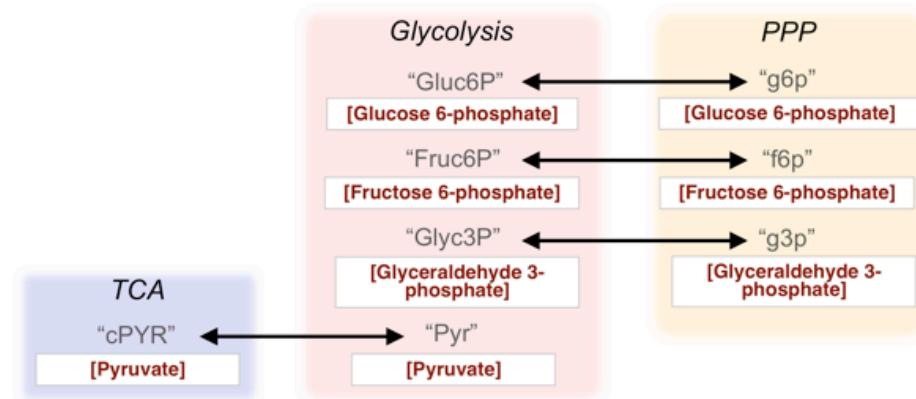
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in an issue

# Annotation

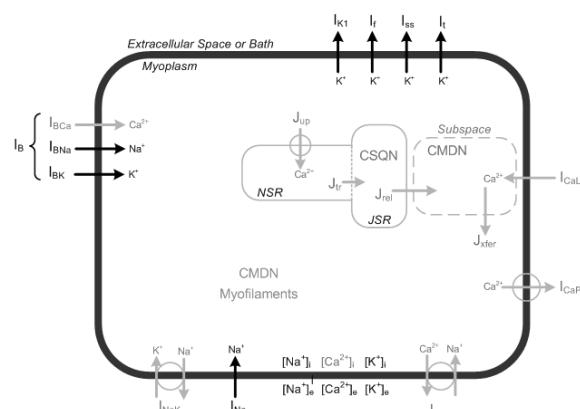
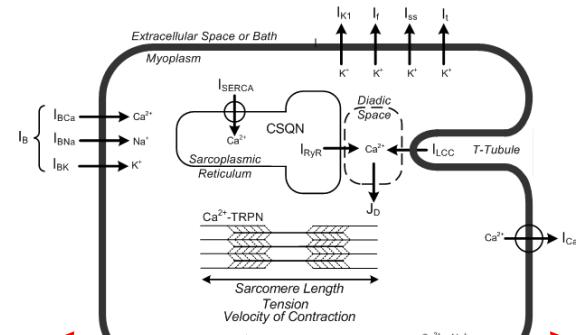
A



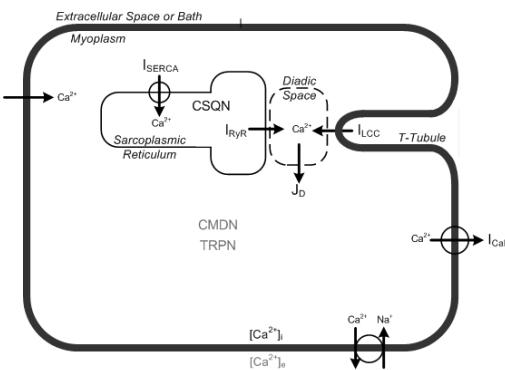
B



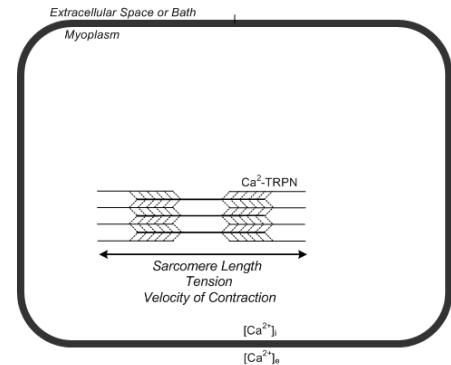
Terkildsen et al.  
coupled e-c + Ca



Pandit et al.  
cardiac action potential



Hinch et al.  
Ca-induced Ca  
release

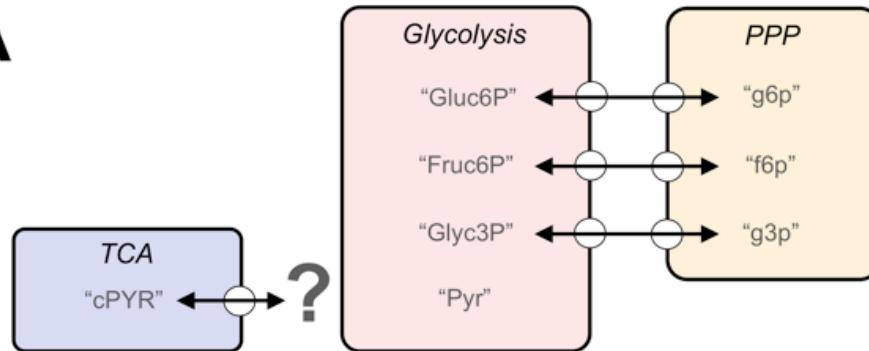


Niederer et al.  
myofilament  
mechanics

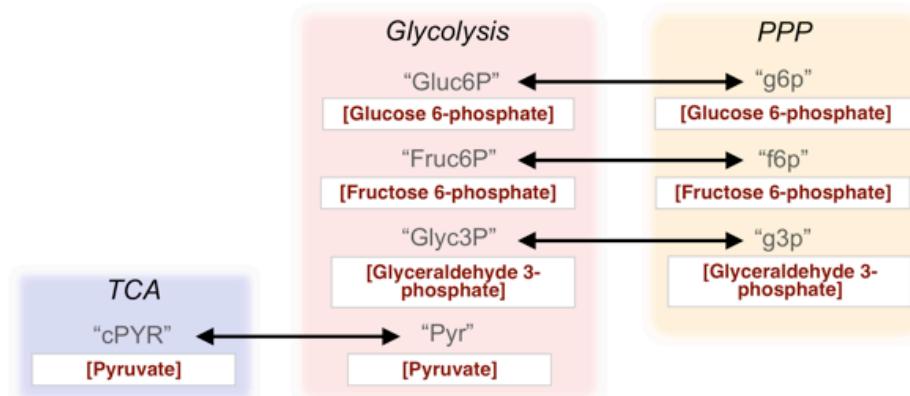
# Black box modularity vs. white box modularity

- The traditional model of modularity (black box) employed in the realm of computer software design is not appropriate here.
- Black box modularity consists of predefined inputs and outputs and no transparency on what is going on inside the box.
- What we need is white box modularity where key state variables and parameters in the model are annotated exposing any one of these to connection with another model.

A



B

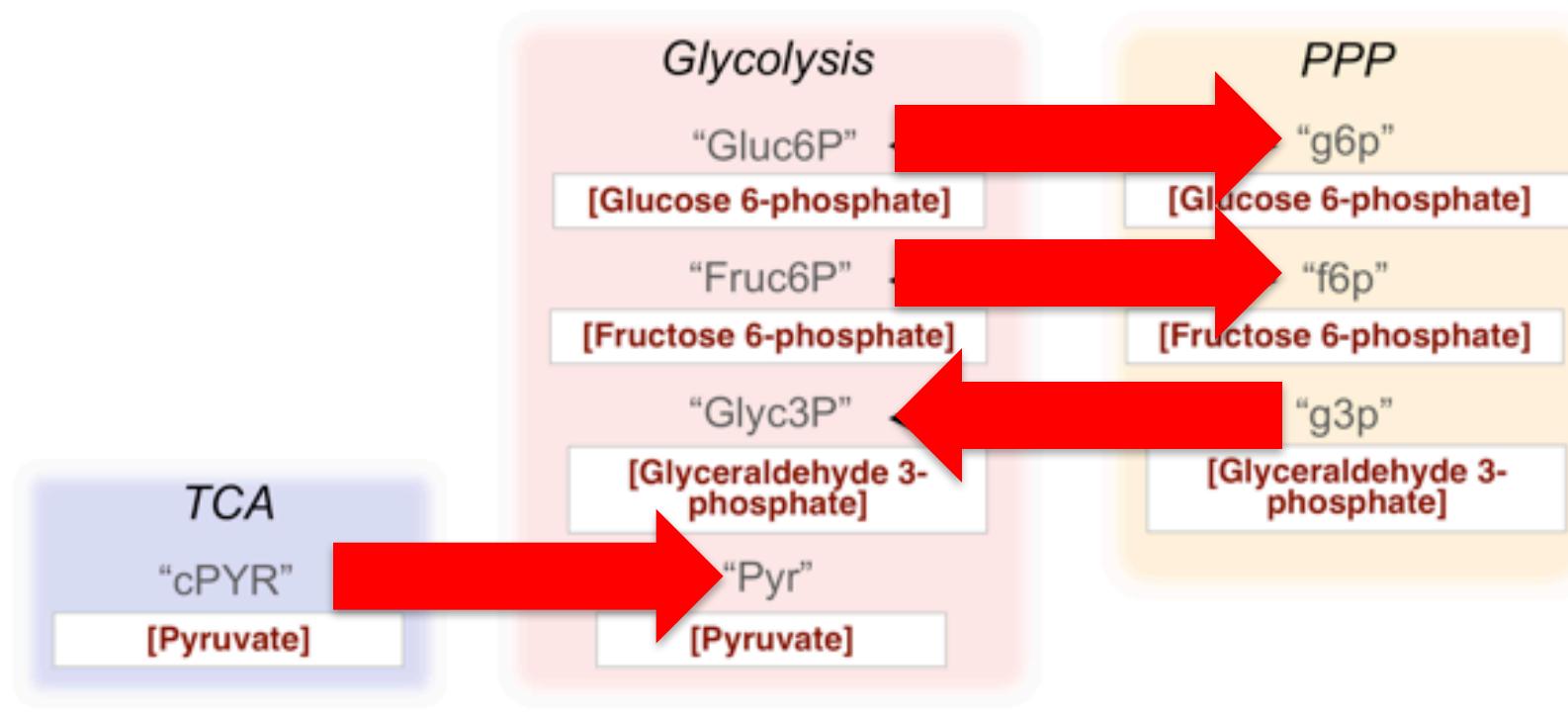


A) Black box modularity with no information on what is inside the box. B) We can see that cPYR is equivalent to Pyr using white box modularity. From Neal ML et al. PLoS Comp Bio, 2014 (in review).

# Black box modularity vs. white box modularity

## CellML 1.1

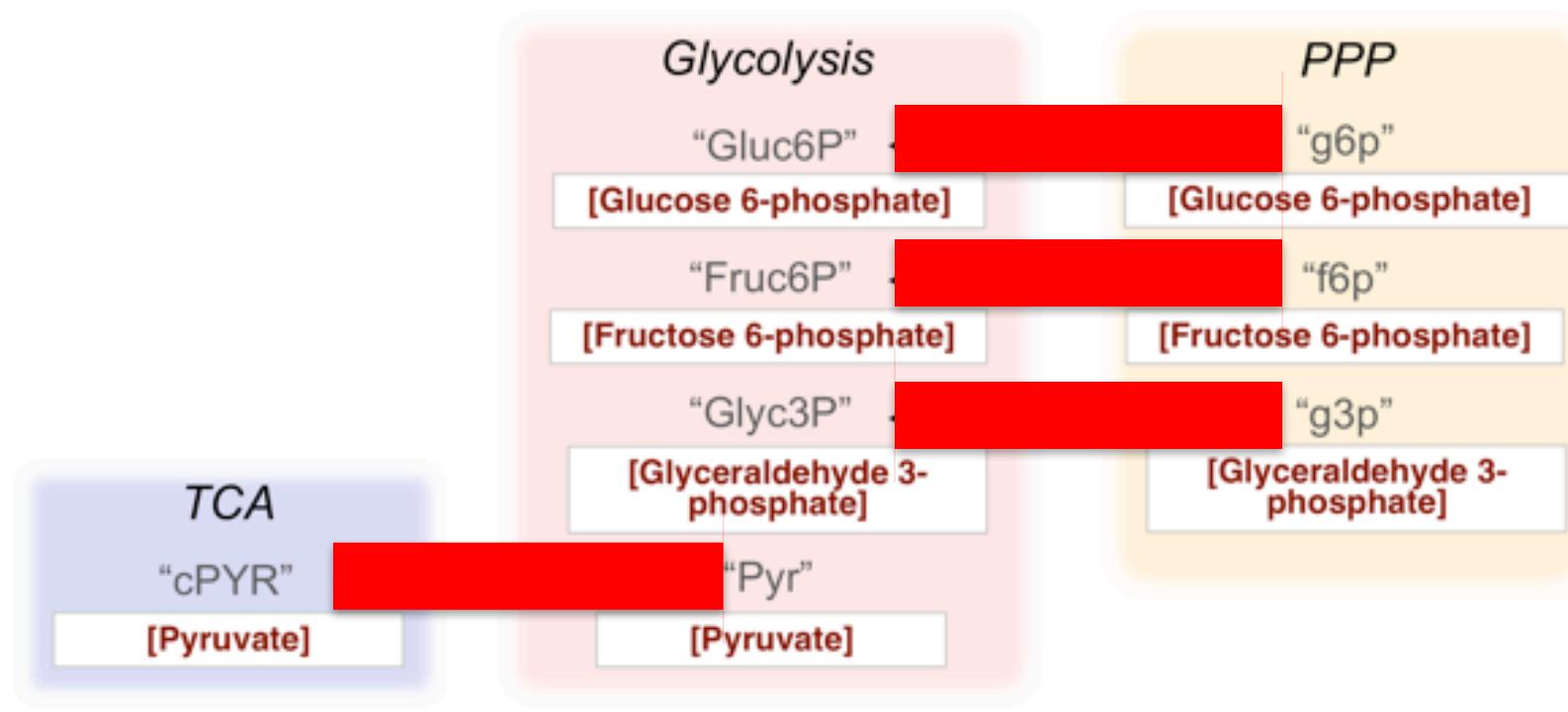
B



# Black box modularity vs. white box modularity

## CellML 2.0

B

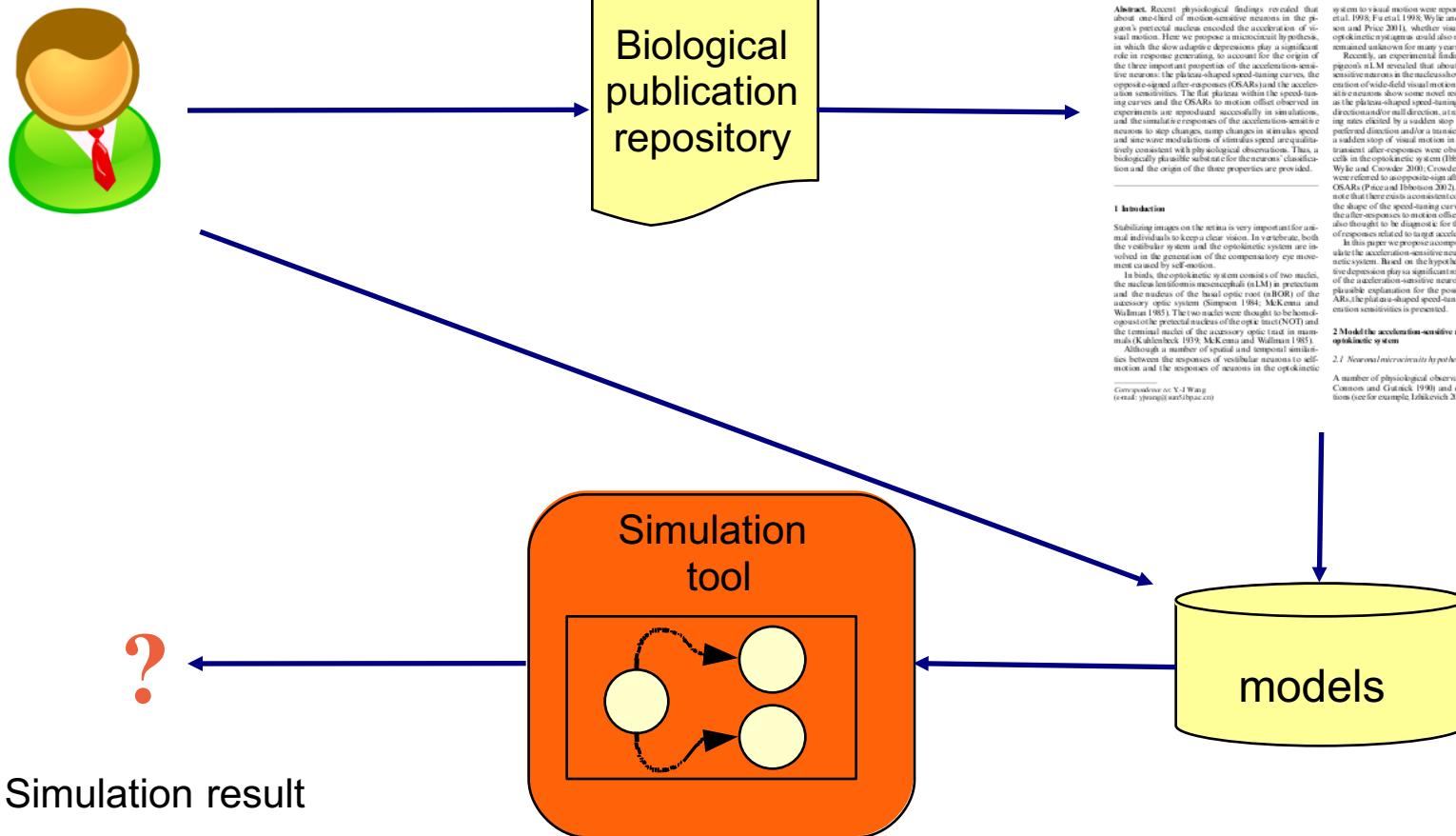




# SED-ML Motivation

Biol Cybern 95: 245–260 (2006)  
DOI 10.1007/s00422-005-0580-5  
© Springer-Verlag 2006

Biological  
Cybernetics



## Modeling the acceleration sensitive neurons in the pigeon optokinetic system

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<sup>1</sup>School of Life Sciences and Biotechnology, Institute of Biophysics, Chinese Academy of Sciences,  
15 Datun Road, Beijing 100101, P.R. China  
<sup>2</sup>Graduate School, Chinese Academy of Sciences, Beijing 100039, P.R. China

Received: 12 October 2004 / Accepted: 24 January 2005 / Published online: 24 March 2005

**Abstract.** Recent physiological findings revealed that most macular of the acceleration-sensitive neurons in the pigeons' optic nerve could encode the direction of visual motion. Here we propose a microcircuit hypothesis in which the slow adapting responses play a significant role in response generation to account for the origin of the direction selectivity of the acceleration-sensitive neurons: the plateau-shaped speed-tuning curves, the opponent-coded after-exposures (OSARs) and the acceleration sensitivities. The speed-tuning curves, the OSARs and the after-exposures curves and the OSARs to motion offset observed in experiments are reproduced successfully in simulations, and the properties of the direction selectivity of the acceleration-sensitive neurons to step changes, ramp changes in stimulus speed are qualitatively consistent with physiological observations. Thus, a biologically plausible substitute for the neurons' classical model and the origin of the three properties are provided.

### 1 Introduction

Stabilizing images on the retina is very important for animal individuals to keep a clear vision. In vertebrates, both the vestibular system and the optokinetic system are involved in the control of the compensatory eye movement caused by self-motion.

In birds, the optokinetic system consists of two nuclei, the nodulus/lentulus nucleus (NLN) of the cerebellum and the nucleus of the avian optic root (aOR) of the accessory optic system (Simpson 1984; McKenna and Wolfman 1985). The two nuclei were thought to be homologous to the pretectal nucleus and the terminal nucleus of the accessory optic tract in mammals (Kühnenbeck 1939; McKenna and Wolfman 1985). The NLN and the aOR are the primary sites of activities between the responses of vestibular neurons to self-motion and the responses of neurons in the optokinetic

system to visual motion were reported (Miles 1984; Wyllie et al. 1991; Friesen 1998; Wyllie and Crowder 2001; Higo et al. 2001). The direction selectivity of neurons involved in optokinetic system again should respond to acceleration remained unknown for many years.

Recently, an experimental finding (Gao et al. 2004) in pigeons (Columba livia) that about one-third of motion-sensitive neurons in the macula showed sensitivity to acceleration of wide-field visual motion. The acceleration-sensitive neurons were found to have a similar shape such as the plateau-shaped speed-tuning curves in the preferred direction and/or null direction, an instant inhibition in firing rate and a transient excitation evoked by the preferred direction and/or a transient excitation evoked by a sudden stop of visual motion in the null direction. The transient after-exposures were observed in seconds (Li et al. 2004; Gao et al. 2004; Gao and Li 2005; Li et al. 2006; Wyllie and Crowder 2010; Crowder and Wyllie 2011) and were referred to as opposite-sign after-exposures, for short, OSARs. The finding was considered to be significant to note that there exists a consistent correspondence between the shape of the speed-tuning curves and the presence of the OSARs. The direction selectivity of the neurons was also thought to be diagnostic for the presence or absence of responses related to target acceleration or deceleration.

In this paper, we propose a microcircuit hypothesis

which the acceleration-sensitive neurons in pigeon optokinetic system. Based on the hypothesis that the slow adapting responses play a significant role in shaping responses of the neurons to visual motion, a plausible explanation for the possible origin of the OSARs, the plateau-shaped speed-tuning curve and the acceleration sensitivities is presented.

### 2 Model of the acceleration-sensitive neurons in pigeon optokinetic system

#### 2.1 Neural microcircuit hypothesis

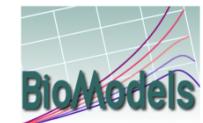
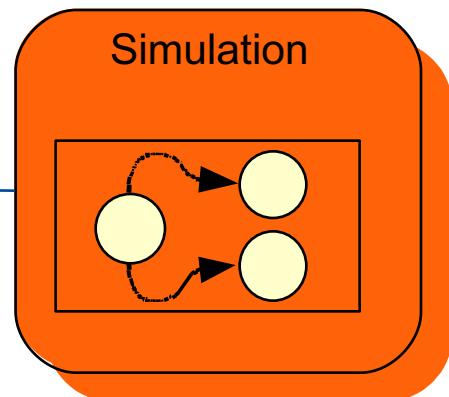
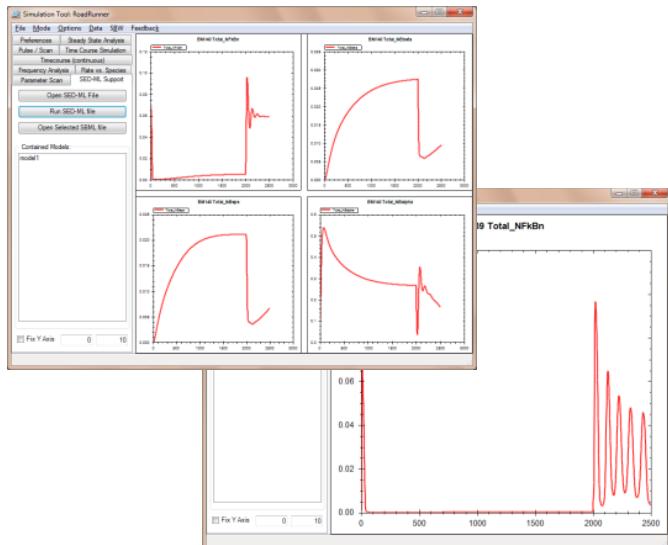
A number of physiological observations (see for example Couston and Grönkjaer 1990) and computational simulations (see for example Lohkamp 2003) have demonstrated

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(e-mail: ywang@ioz.ac.cn)

# SED-ML Motivation



BIOMD0000000139 , BIOMD0000000140

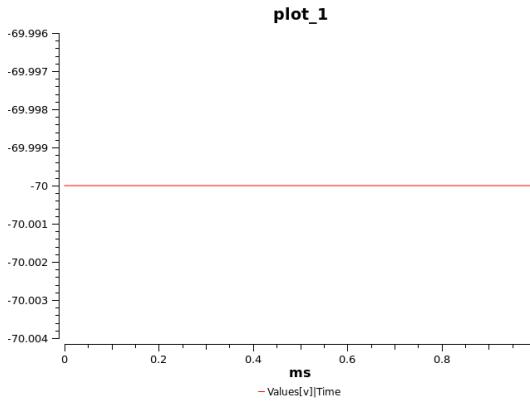


Systems Biology  
Workbench

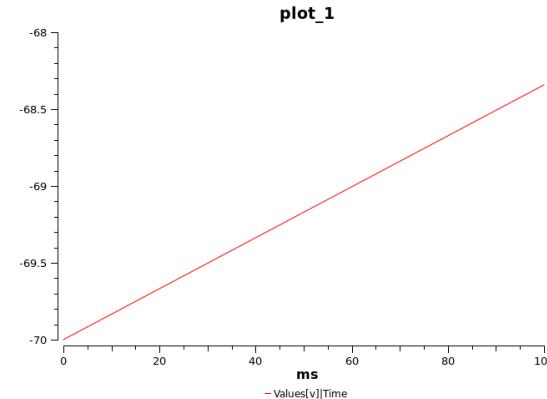
# Example

First attempt to run the model, measuring the spiking rate  $v$  over time

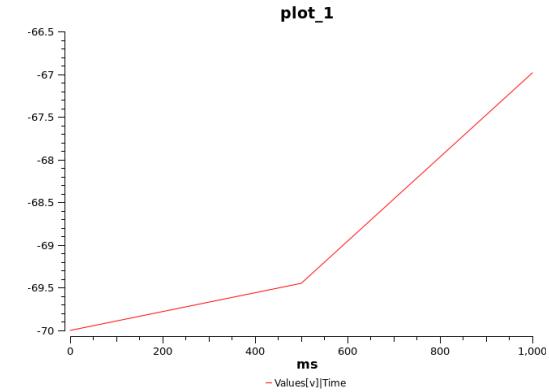
- „ load SBML into the simulation tool COPASI
- „ use parametrisation as given in the SBML file
- „ define output variables ( $v$ )
- „ run the time course



1 ms (standard)



100ms



1000ms

# Example

Second attempt to run the model, adjusting simulation step size and duration

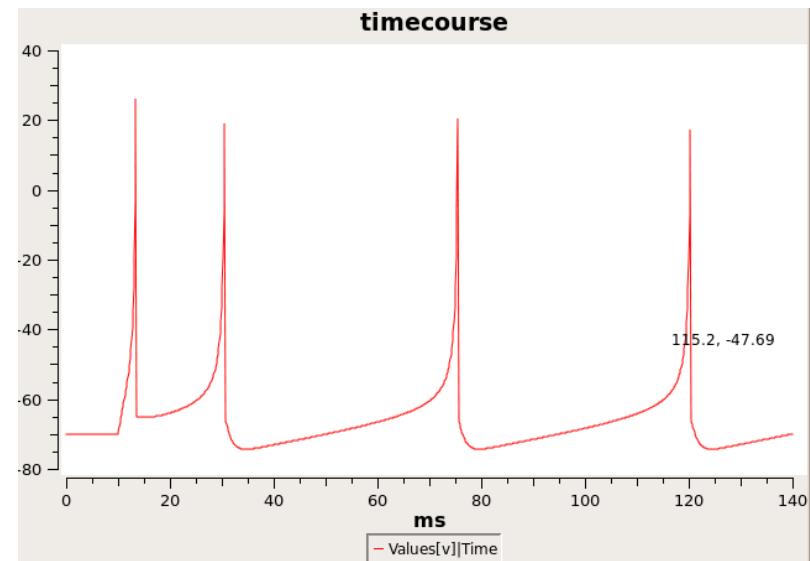
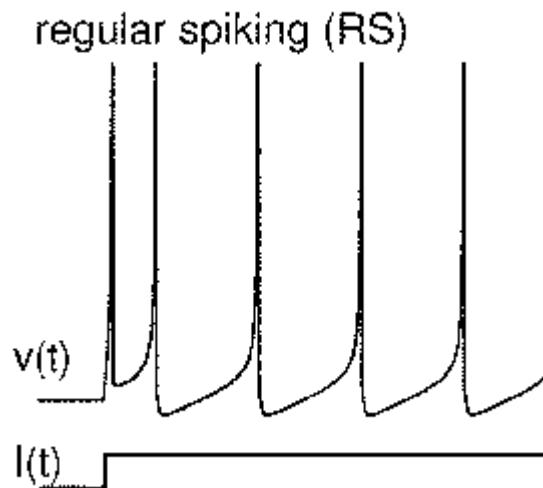


Fig.: COPASI simulation, duration: 140ms, step size: 0.14

# Example

Third attempt to run the model, updating initial model parameters

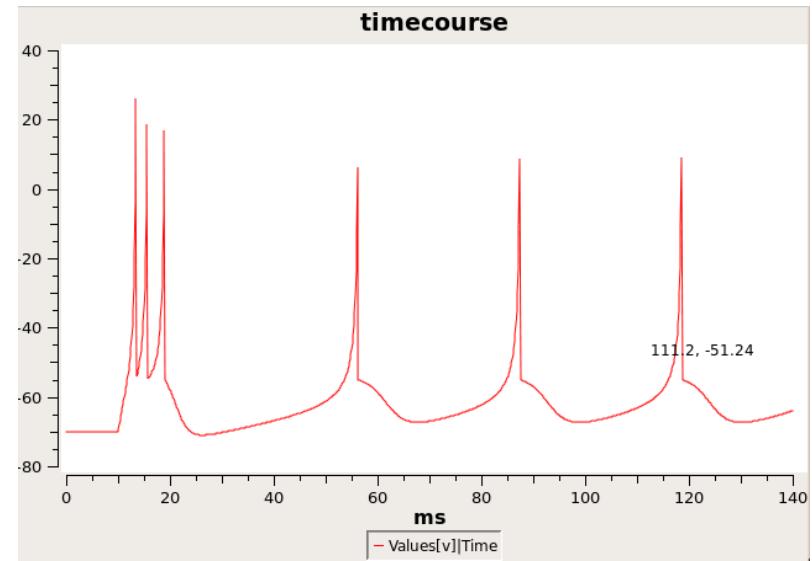
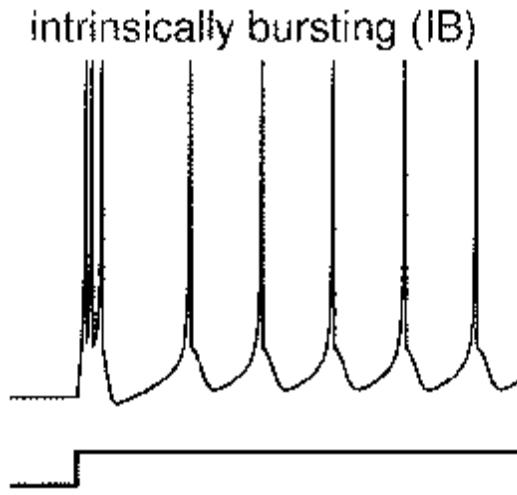


Fig.: COPASI, adjusted parameter values  
( $a=0.02$ ,  $b=0.2$   $c=-55$ ,  $d=4$ )

# Example

www.cellml.org/community/ Workshop Programme -- Cel The Lorenz Attractor, a class The ORd human ventricular The CellML project team -- C

models.cellml.org/e/71/view

 cellML

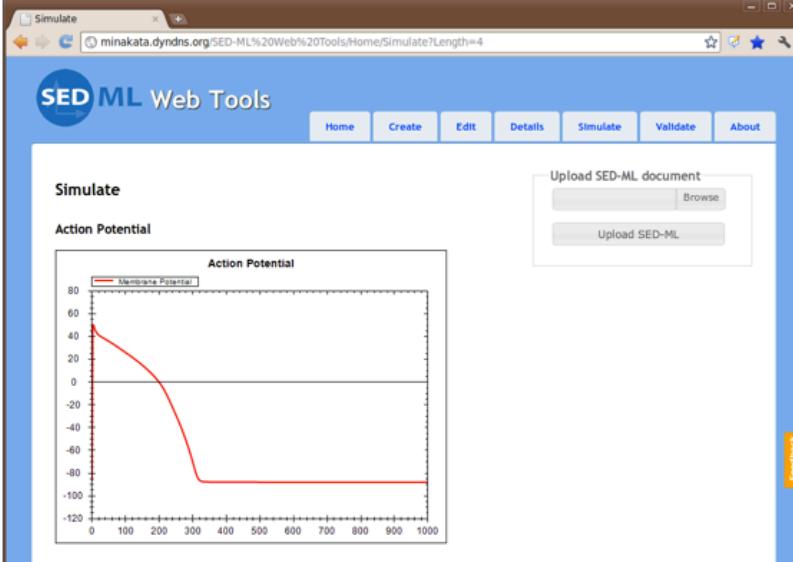
Models Home Exposures Documentation

You are here: Home > Exposures > The ORd human ventricular action potential model

**The ORd human ventricular action potential model**

This workspace houses a CellML 1.0 encoding of the 2011 O'Hara, Virág, Varró, & Rudy 2011 human cardiac ventricular action potential model (ORd). The original article is available at: <http://www.ncbi.nlm.nih.gov/pubmed/21637795>. This model was encoded based on the Matlab version of the code available from: <http://rudylab.wustl.edu/research/cell/>.

The CellML 1.0 encoding of the ORd model was contributed by Steven Niederer. While the units in the CellML encoding are not yet perfect, it is a match for the Matlab code and matches the simulation output for a single beat perfectly. The figure below shows the output of the simulation experiment `action-potential.xml` encoded in SED-ML using the original version of the model from Steve. This output is generated by running the simulation experiment using the SED-ML Web Tools.



Log in | Register

**Model Curation**

Curation Status: 

---

**Source**

Derived from workspace [An encoding of the human ORd model by Steve Niederer](#) at changeset [a96ef0c61614](#).

---

**Downloads**

 Complete Archive as .tgz

---

**Navigation**

 Ohara\_Rudy\_2011.cellml

 action-potential.xml

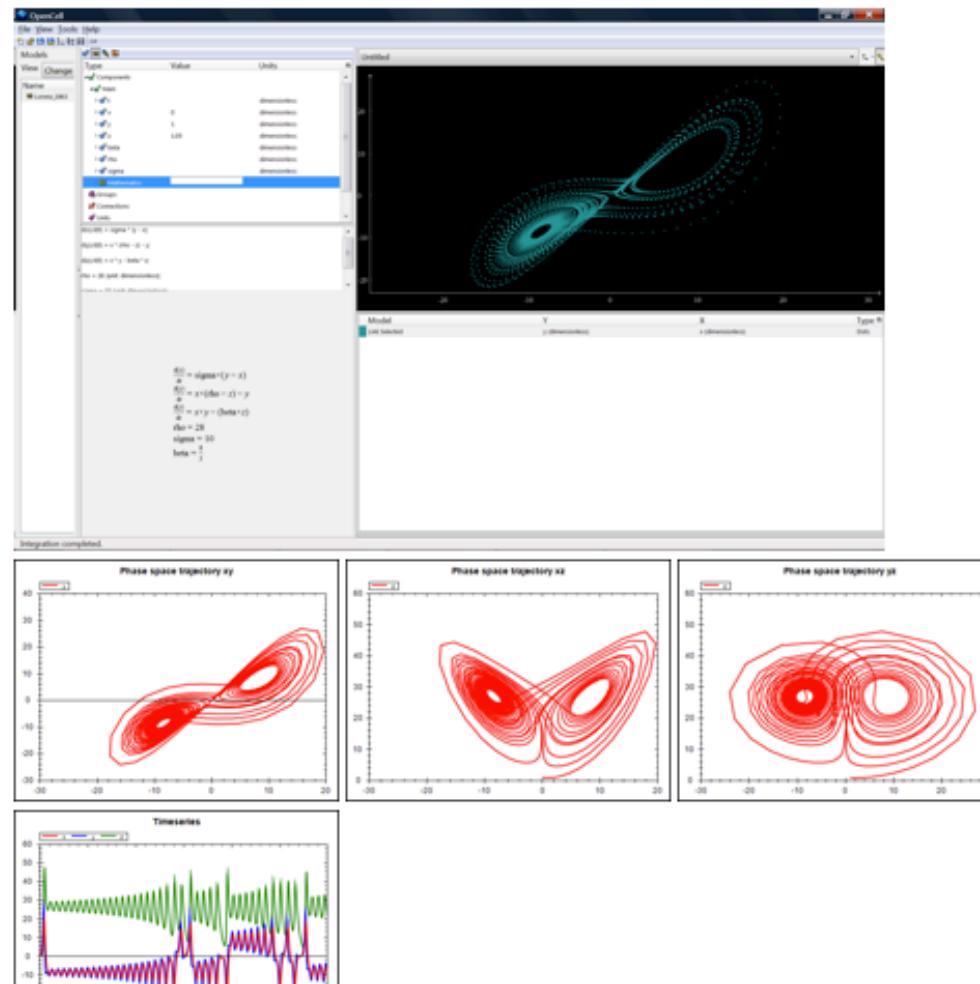


You are here: [Home](#) > [Exposures](#) > The Lorenz Attractor, a classical mathematical model

## The Lorenz Attractor, a classical mathematical model

This workspace houses a CellML encoding of the 1963 Lorenz model which became a well-known demonstration of deterministic chaos. The original article DOI is [10.1175/1520-0469\(1963\)020<0130:DNF>2.0.CO;2](https://doi.org/10.1175/1520-0469(1963)020<0130:DNF>2.0.CO;2). This model was encoded based on the Octave code available in the related [Wikipedia article](#).

An [OpenCell 0.8 session file](#) is available. [SED-ML](#) can also be used to simulate this model, the simulation description is in [Lorenz\\_1963\\_sedml.xml](#), and the simulation experiment can be run using the [SED-ML Web Tools](#). The figures below show the results from using [SED-ML](#).



### Model Curation

Curation Status:



OpenCell:



### Source

Derived from workspace

[Deterministic Nonperiodic Flow](#) at changeset [1cdf5c612924](#).

### Downloads

 Complete Archive as .tgz

### Navigation

 [The Lorenz Attractor, a classical mathematical model](#)

# SED-ML Level 1 Version 1

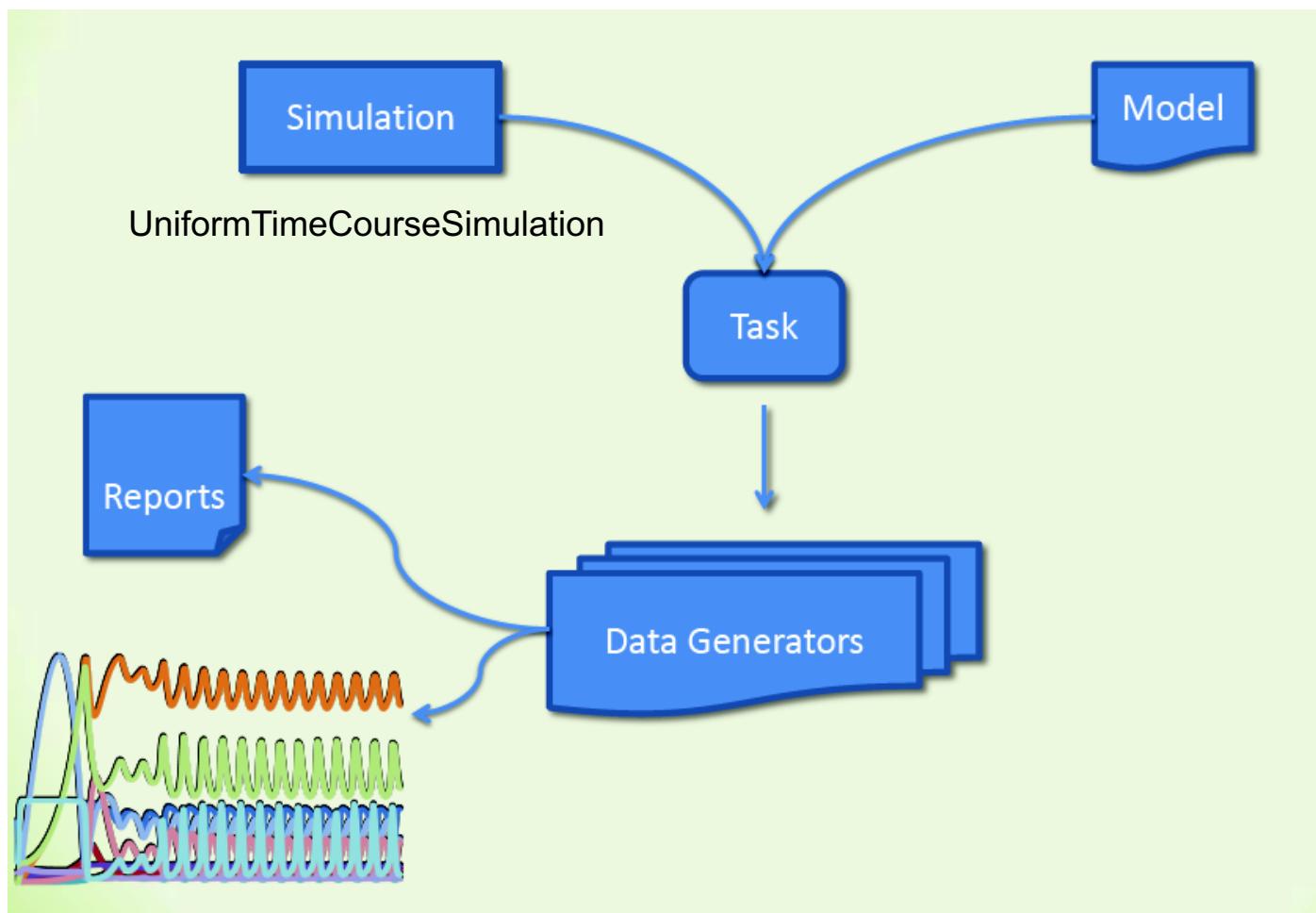
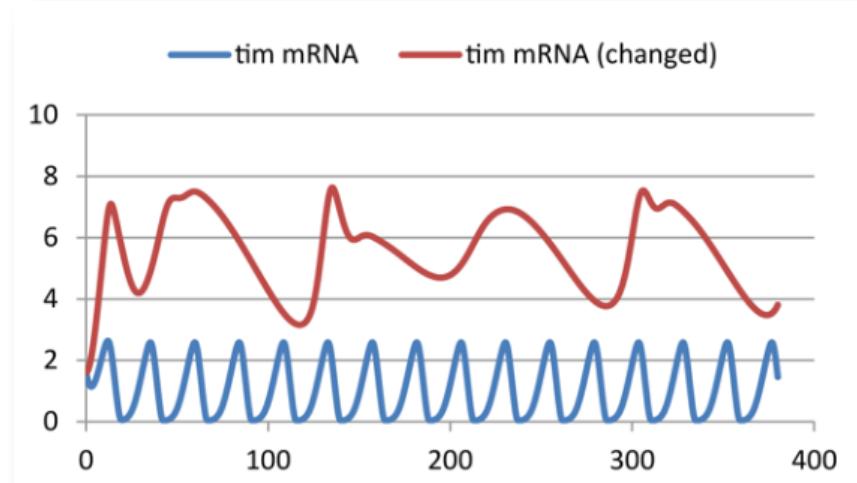
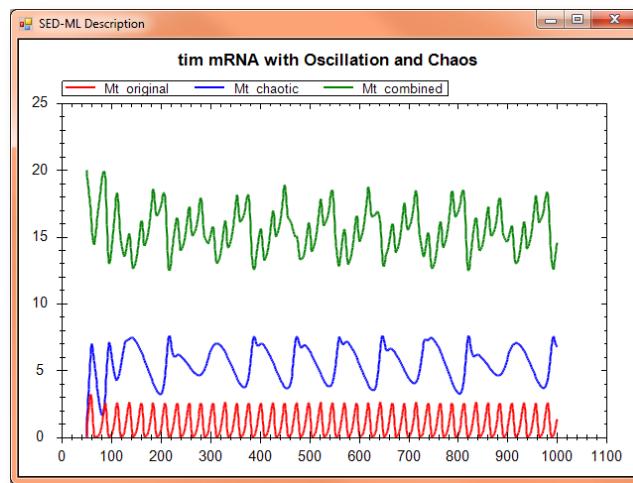


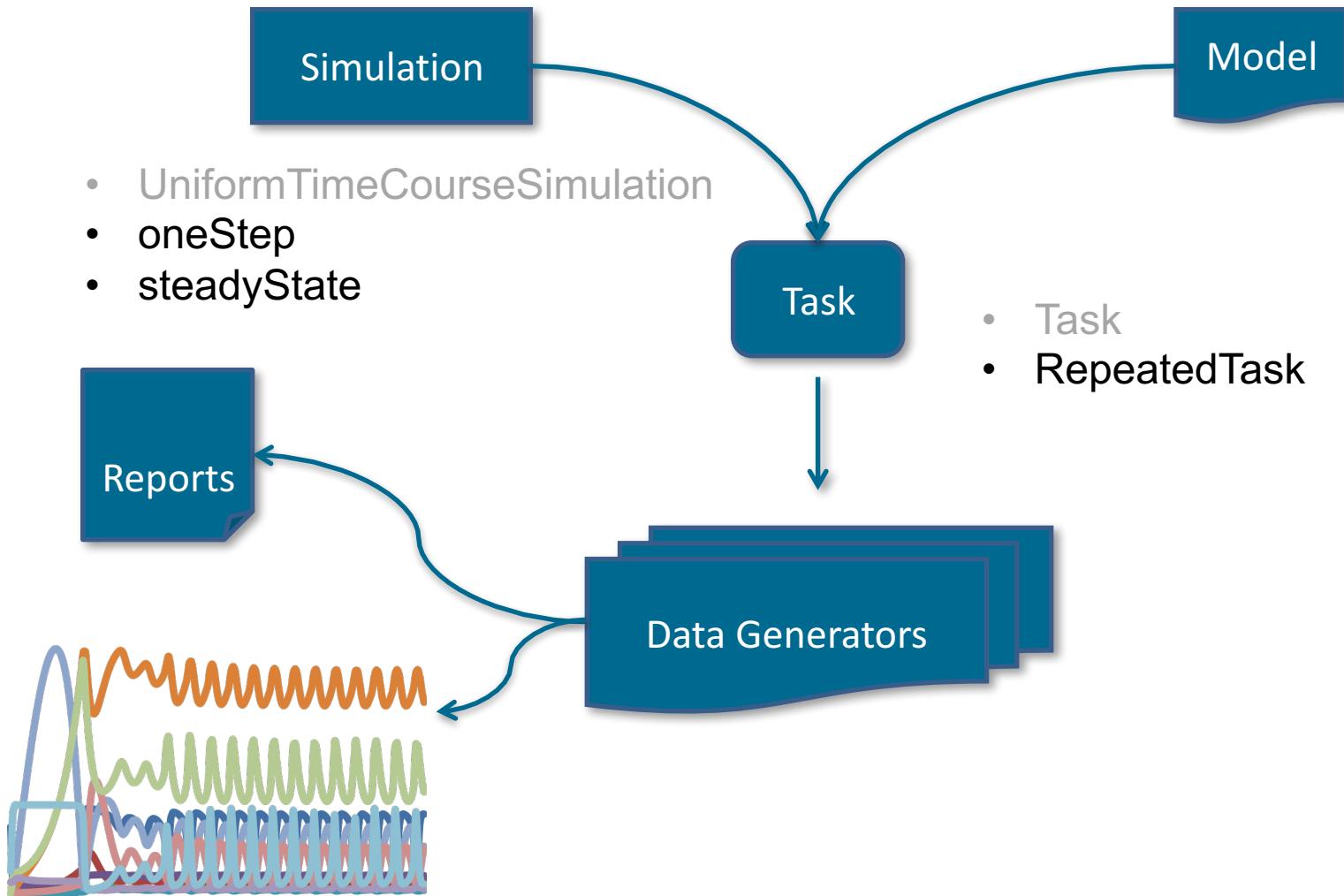
Figure: SED-ML structure (*Waltemath et al., 2011*)

# SED-ML Level 1 Version 1

- Carry out multiple time course simulations
- Collect results from these simulations
- Combine results from these simulations
- Report / Graph the results

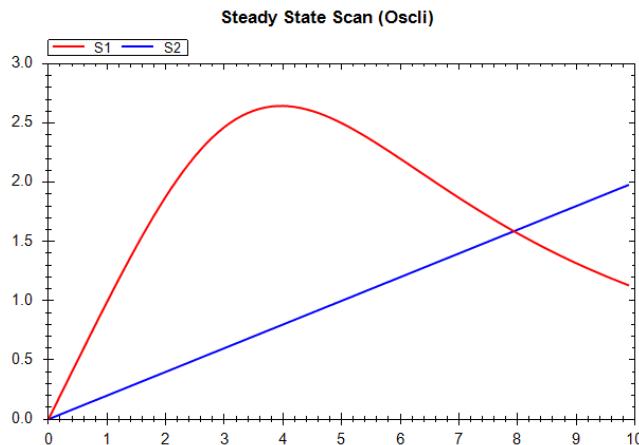


# SED-ML Level 1 Version 2

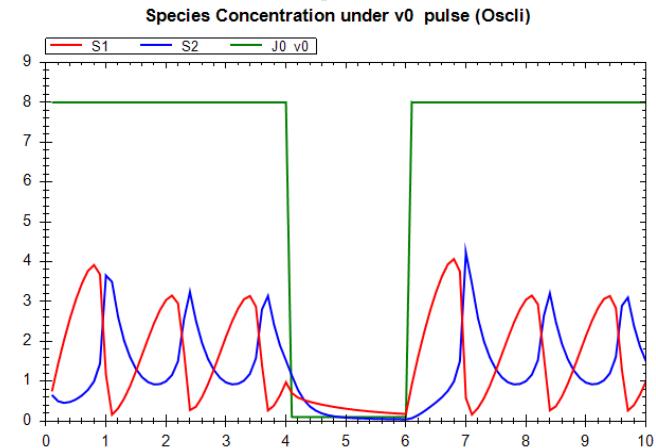


# SED-ML Level 1 Version 2

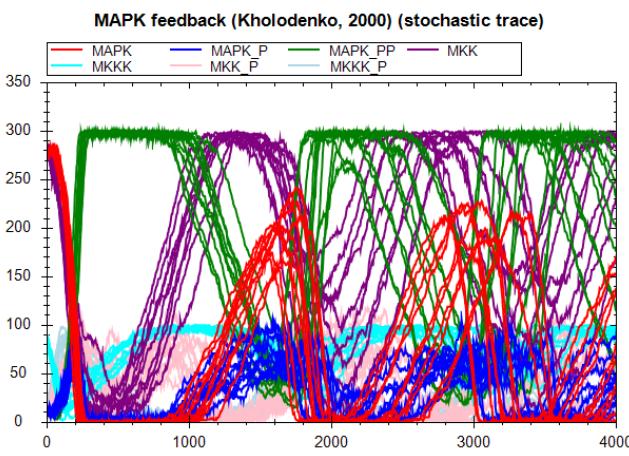
## Parameter Scan



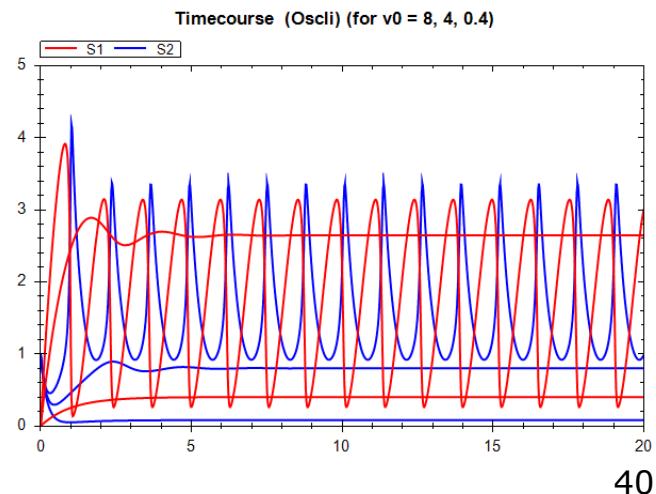
## Pulse Experiments



## Repeated Stochastic Traces



## Time Course Parameter Scan



# SED-ML L1V3 draft

- Focus on the integration of “data” with SED-ML, e.g.,
  - experimental data for use in model fitting, parameter estimation
  - simulation data for testing implementations
- Adoption of NuML as standard data description format
  - <https://github.com/NuML/NuML>
  - XML description of underlying data (initially CSV).
  - provides a common data abstraction layer for SED-ML to utilise.

# Tool support

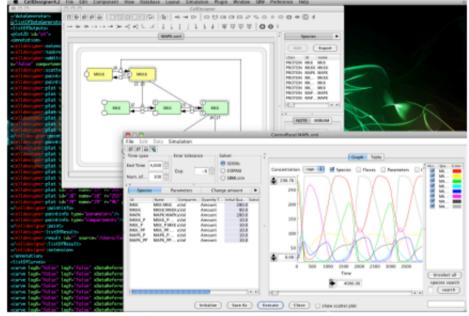
**SED ML** Simulation Experiment Description Markup Language

Home Specifications Information Showcase Contact Editors

**SED-ML Showcase**

On this page we present a number of tools created by the SED-ML community. You will find libraries as well as end user applications. If you would like your software tool to be listed here please fill out the [survey](#).

[Play Slideshow](#) [← Previous](#) [Next →](#)



**CellDesigner**

CellDesigner is software for modeling and simulation of biochemical and gene regulatory networks, originally developed by the Systems Biology Institute in Japan. While CellDesigner itself is a sophisticated structured diagram editor, it enables users to directly integrate various tools, such as built-in SBML ODE Solver, COPASI, SBMLSimulator and SBW-powered simulation/analysis modules. CellDesigner runs on various platforms such as Windows, Mac OS X and Linux, and is freely available from <http://celldesigner.org/>.

Tool 1 of 12



sed-ml.org

- <http://sed-ml.sourceforge.net/showcase.html>
- Please add your tools!

# SED-ML Breakouts

- Tuesday 1:30pm – 5:00pm
  - Review current status of SED-ML L1V3
- Thursday 1:30pm – 3:00pm
  - SED-ML with qualitative models
- Friday 1:30pm – 3:00pm
  - New/extended output types



**[models.physiomeproject.org](https://models.physiomeproject.org)**

# PMR Overview

- Desire to support collaborative, identifiable, and discoverable archiving of computational models.
- The atomic unit of information storage in PMR is the **workspace**.
  - Each workspace is a self-contained version controlled repository with user configurable access control.
  - Every revision throughout the history of a workspace has a persistent and resolvable identifier.
- Specific revisions of a workspace can be promoted for special presentation in the PMR web interface and given their own URL – these are known in PMR as **exposures**.
- Specific resources can be flagged for indexing in RDF triple store.

# Usage stats

- May 2016
  - 940 workspaces in PMR
  - of which 273 are private
  - average 1600 visitors per month (approximately 33% are new visitors)

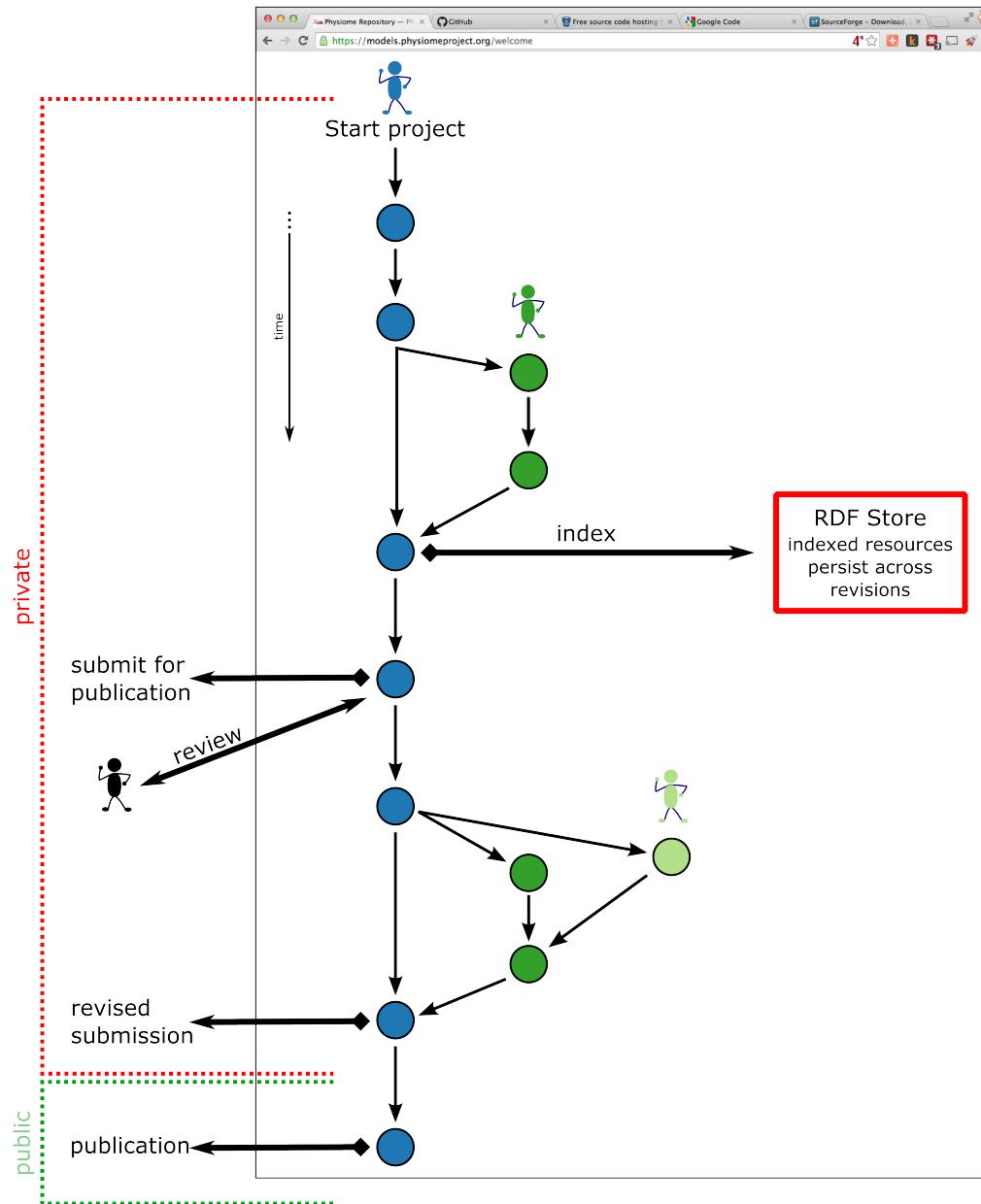
# Publication transition

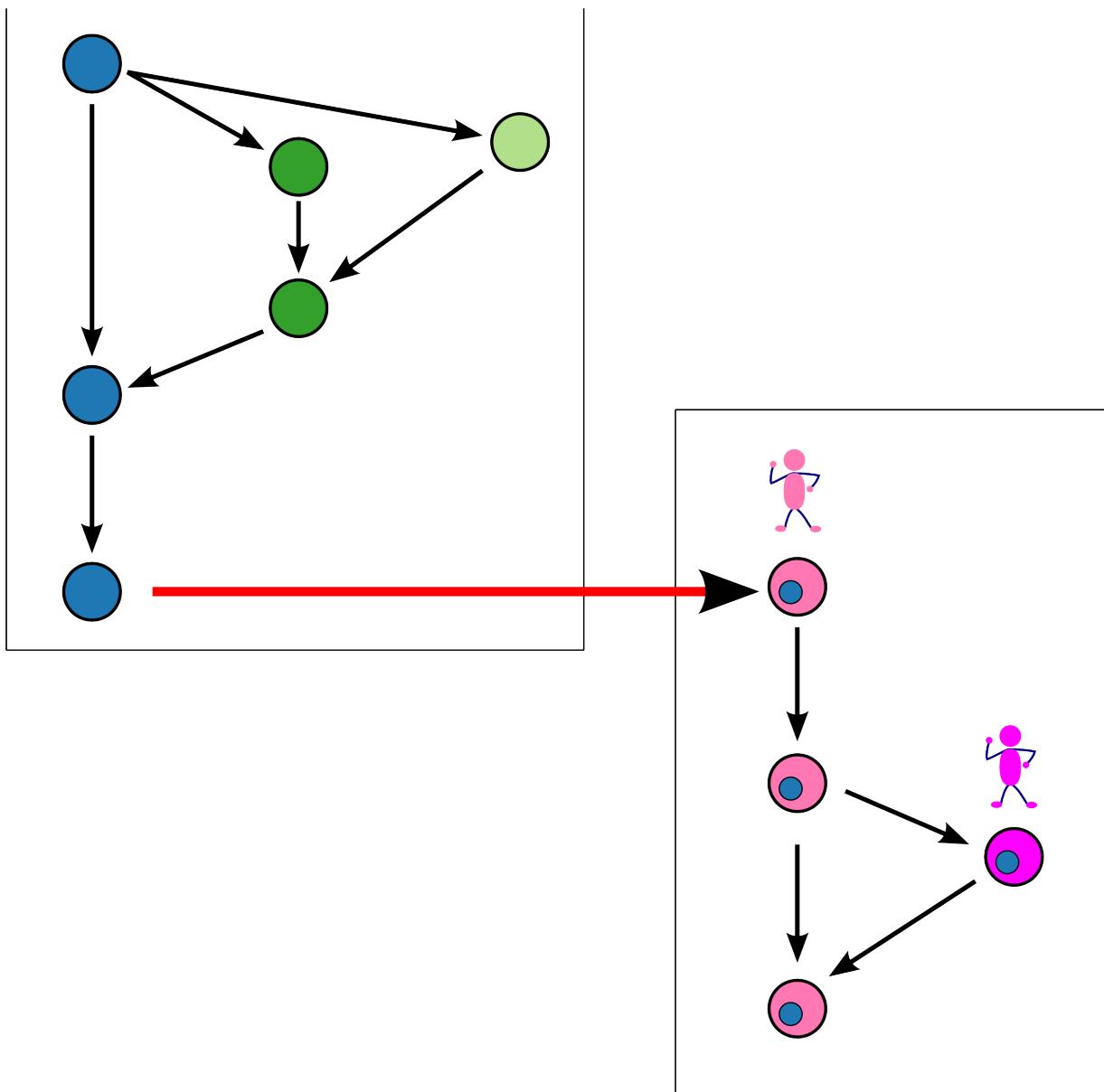
- Everything private by default.
- Users can share directly with collaborators (read and/or write permissions).
  - DVCS allows this to happen outside of PMR regardless (e.g., GitHub or BitBucket)
- Users submit workspaces and exposures for publication if they want them publicly accessible (read only)
  - curators perform cursory checks
- Once published, exists “forever”
  - can be **expired** to indicate newer content available

# Managing modularity and reuse

- How do you keep track of your modules?
- What happens if someone changes one of the modules you rely on?
- How do you share your hierarchical model?
- How do you make your hierarchical model available to others for further application and re-use?

### PMR2 instance





Modularity and reuse demo nickerso / modularity-and

https://models.physiomeproject.org/workspace/1c0

Search Site

David Nickerson

Models Home My Workspaces Exposures Documentation

You are here: Home / Workspaces / Modularity and reuse demonstration

View Edit History Fork Synchronize Exposure Rollover RDF Indexing Sharing Layout Actions ▾ State: Private ▾

## Modularity and reuse demonstration

### Exposure Information

No simplified view available for this workspace as no related exposures were found.

### Workspace Summary

**Description**  
A workspace to demonstrate the usage of modules and embedded workspaces.

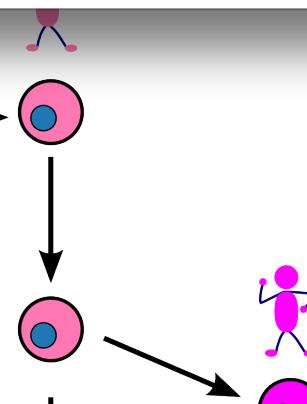
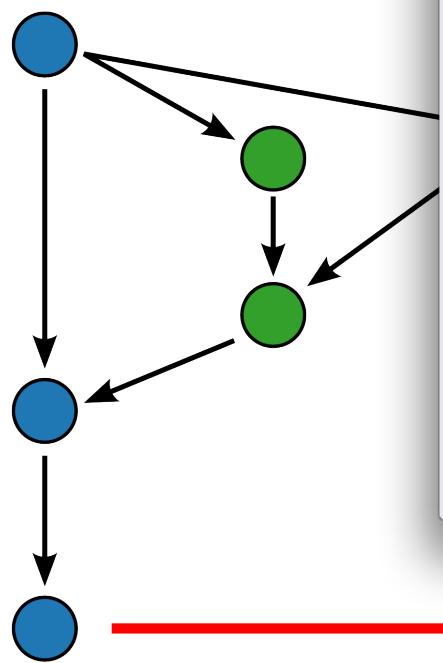
**Owner**  
David Nickerson <david.nickerson@gmail.com>

**URI for mercurial clone/pull/push**  
<https://models.physiomeproject.org/workspace/1c0>

### Files

Filename	Size	Date	Options
derivative-approximation			[browse]
parabolic-approximation			[browse]
sine-function			[browse]
.hgsub	234	2014-09-17 22:57 +1000	[browse]
.hgsubstate	186	2014-09-17 22:57 +1000	[browse]
sin-approximations-sedml.xml	2934	2014-09-17 22:57 +1000	[browse]
sin-approximations.xml	2452	2014-09-17 22:57 +1000	[browse]

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Modularity and reuse demo nickerso / modularity-and-reuse

Atlassian, Inc. [US] https://bitbucket.org/nickerso/modularity-and-reuse/src

4<sup>h</sup> 4 stars + k 🌐 ⚡ 🔍

Bitbucket Dashboard Teams Repositories Create owner/repository ? 🔍

## Source

default | modularity-and-reuse /

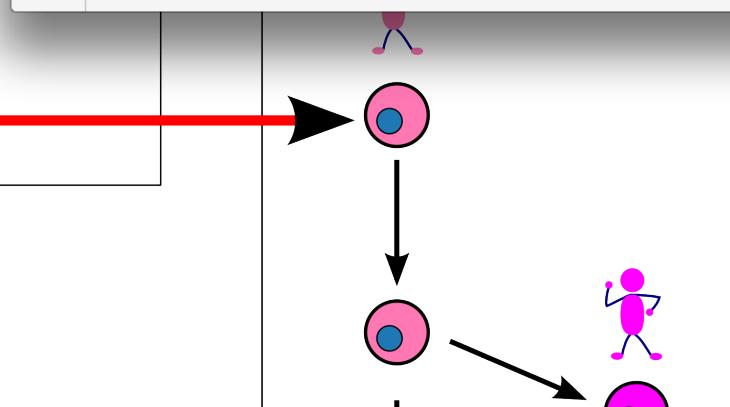
+ New file

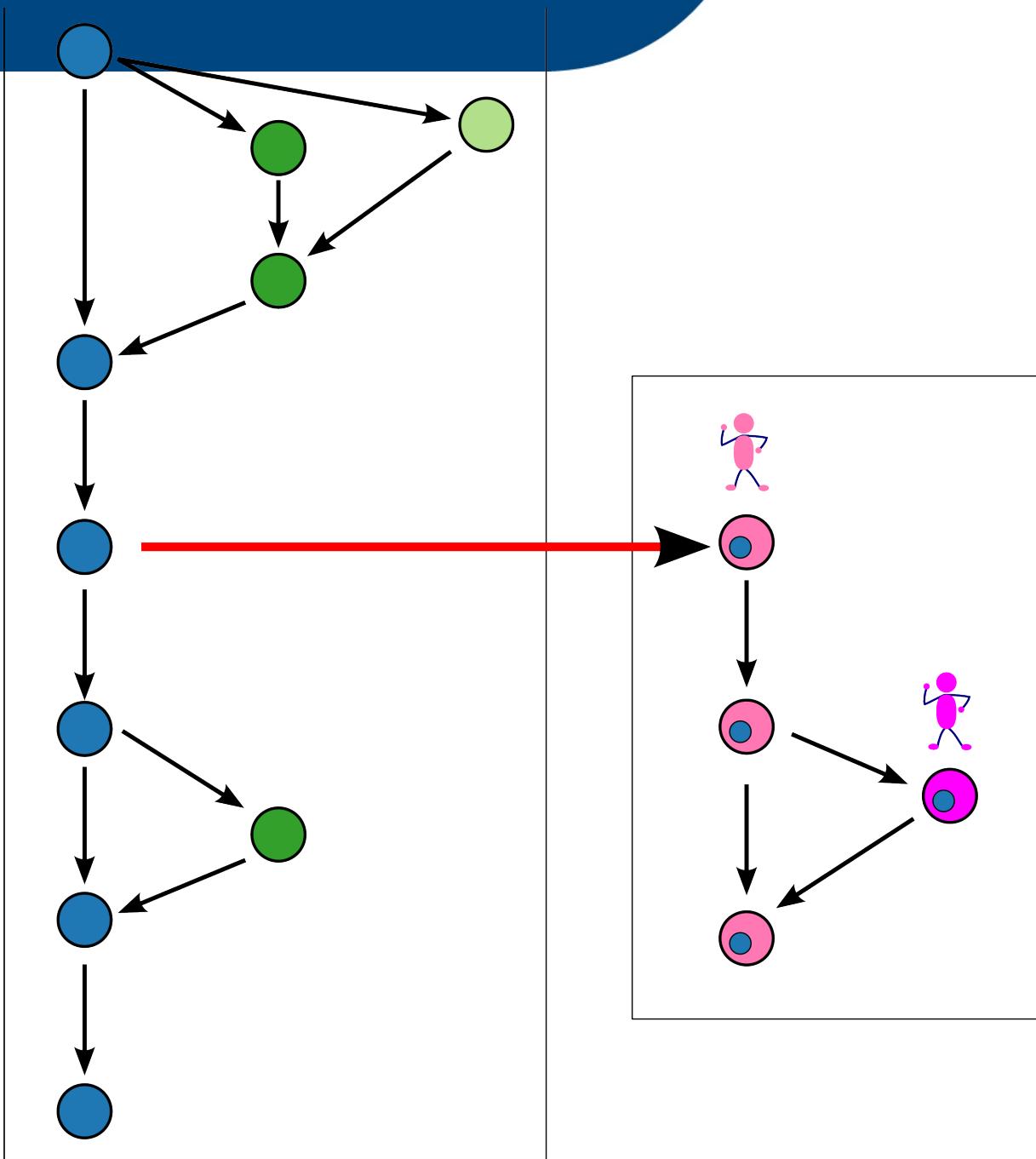
- derivative-approximation [819e3df4b41b]
- parabolic-approximation [0fd92176693f]
- sine-function [416e54e55a76]

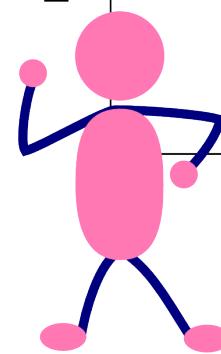
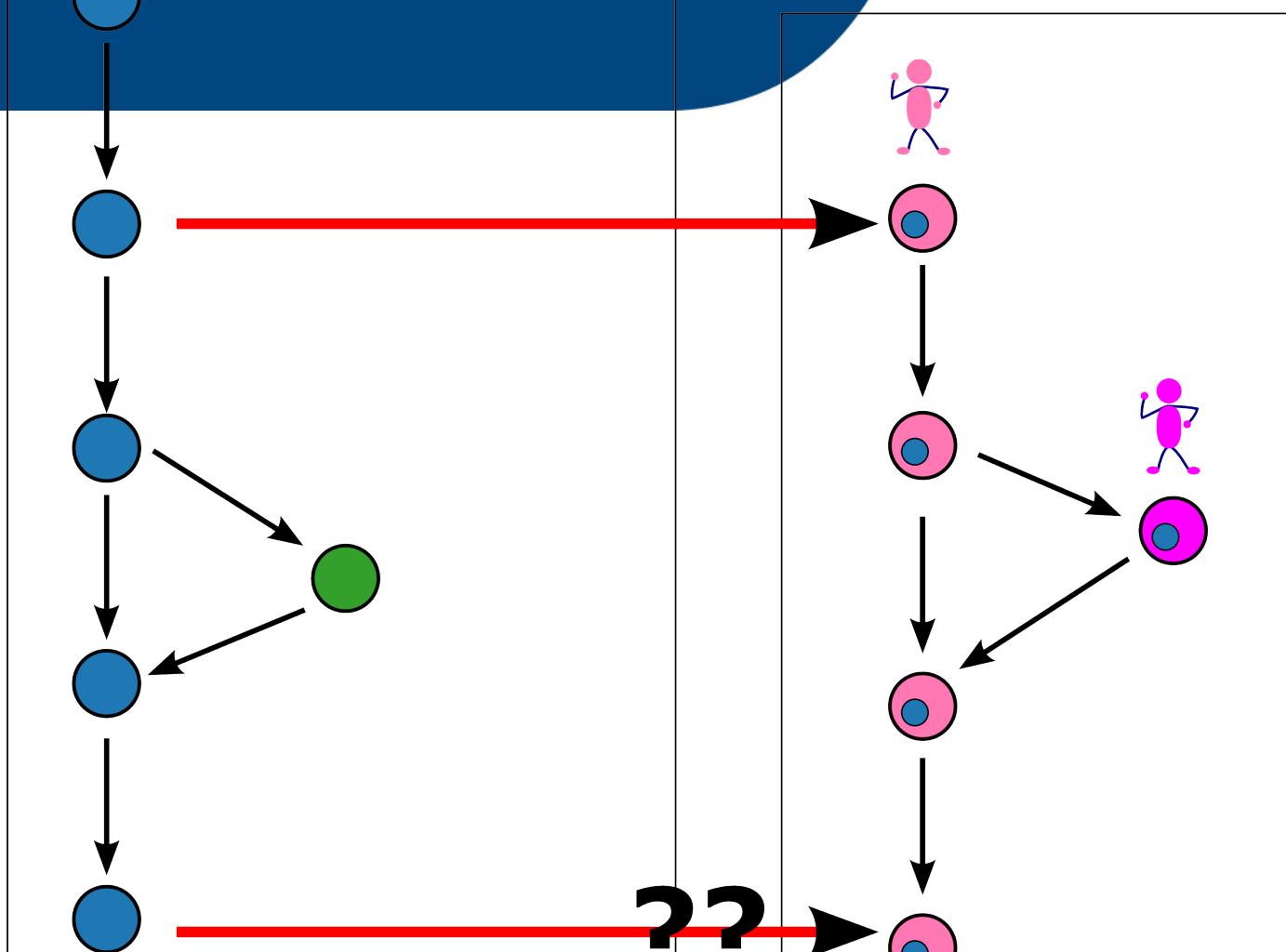
File	Size	Last modified	Description
.hgsub	234 B	an hour ago	embedding derivation and parabolic sin(x) approximation example model
.hgsubstate	186 B	an hour ago	embedding derivation and parabolic sin(x) approximation example model
sin-approximations-sedml.xml	2.9 KB	45 minutes ago	adding a SED-ML document describing a simple time course simulation
sin-approximations.xml	2.4 KB	45 minutes ago	adding the top-level model which imports each of the sin(x) models from the

Blog · Support · Plans & pricing · Documentation · API · Server status · Version info · Terms of service · Privacy policy  
JIRA · Confluence · Bamboo · Stash · SourceTree · HipChat

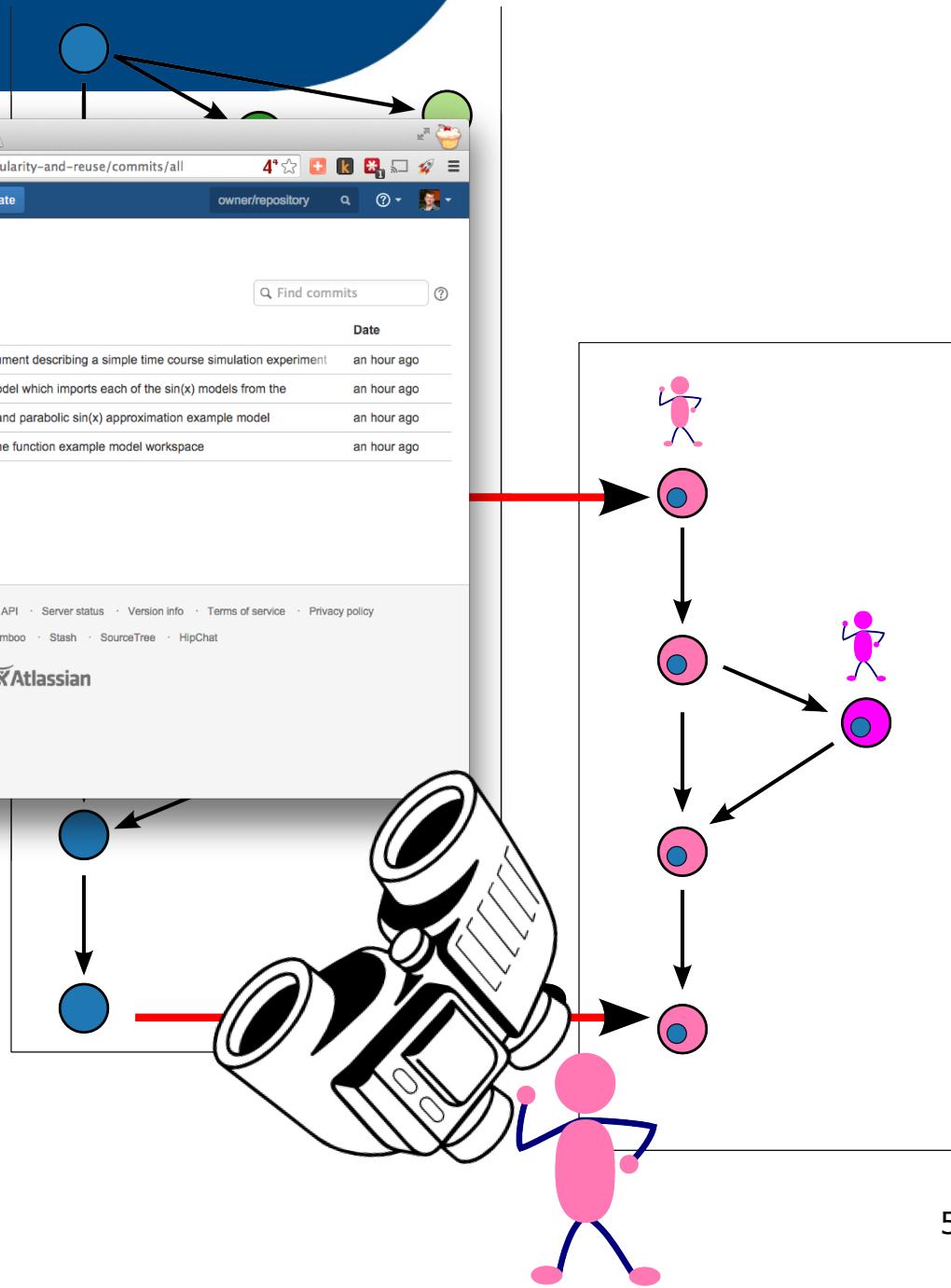
Atlassian

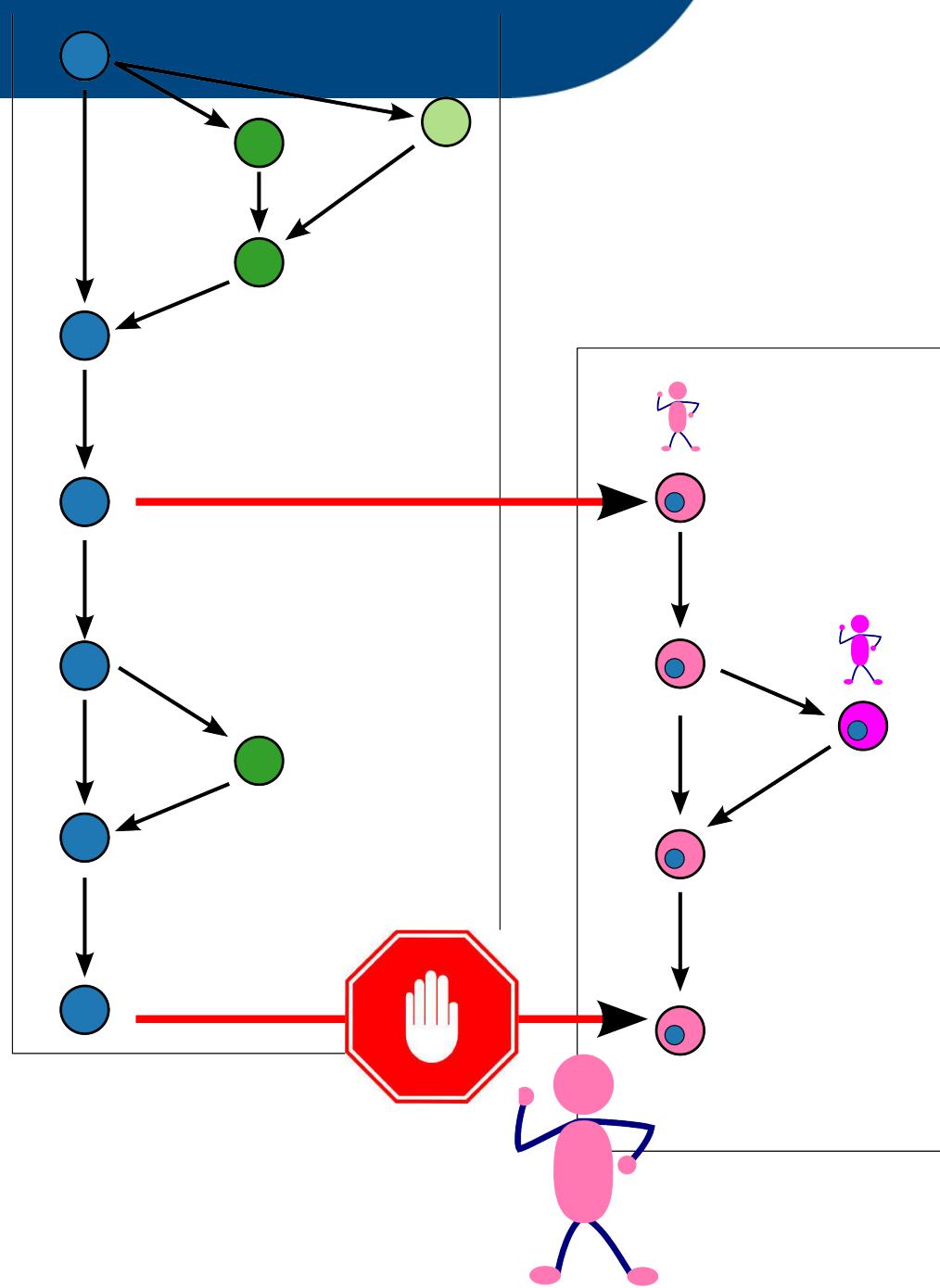


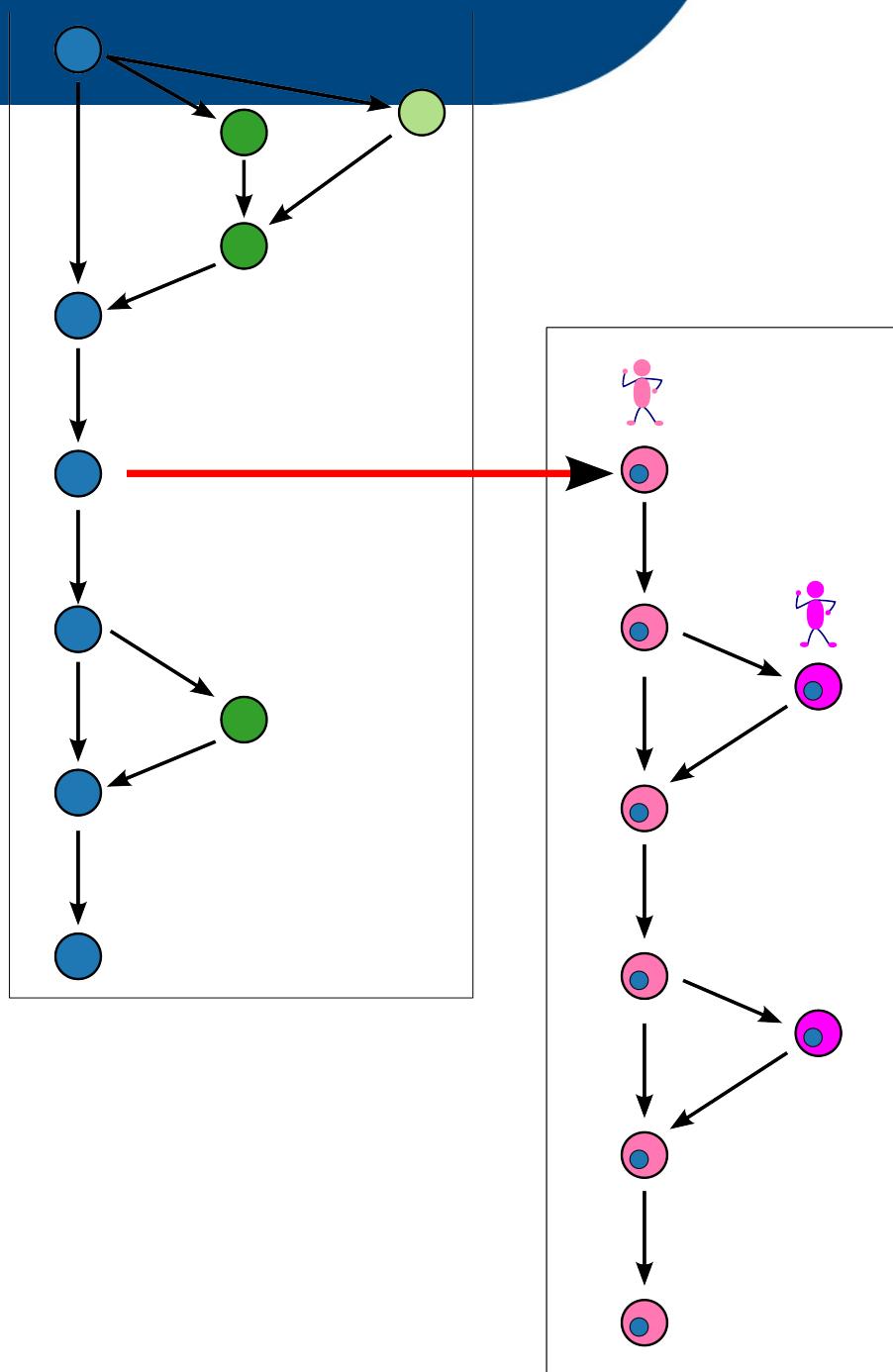


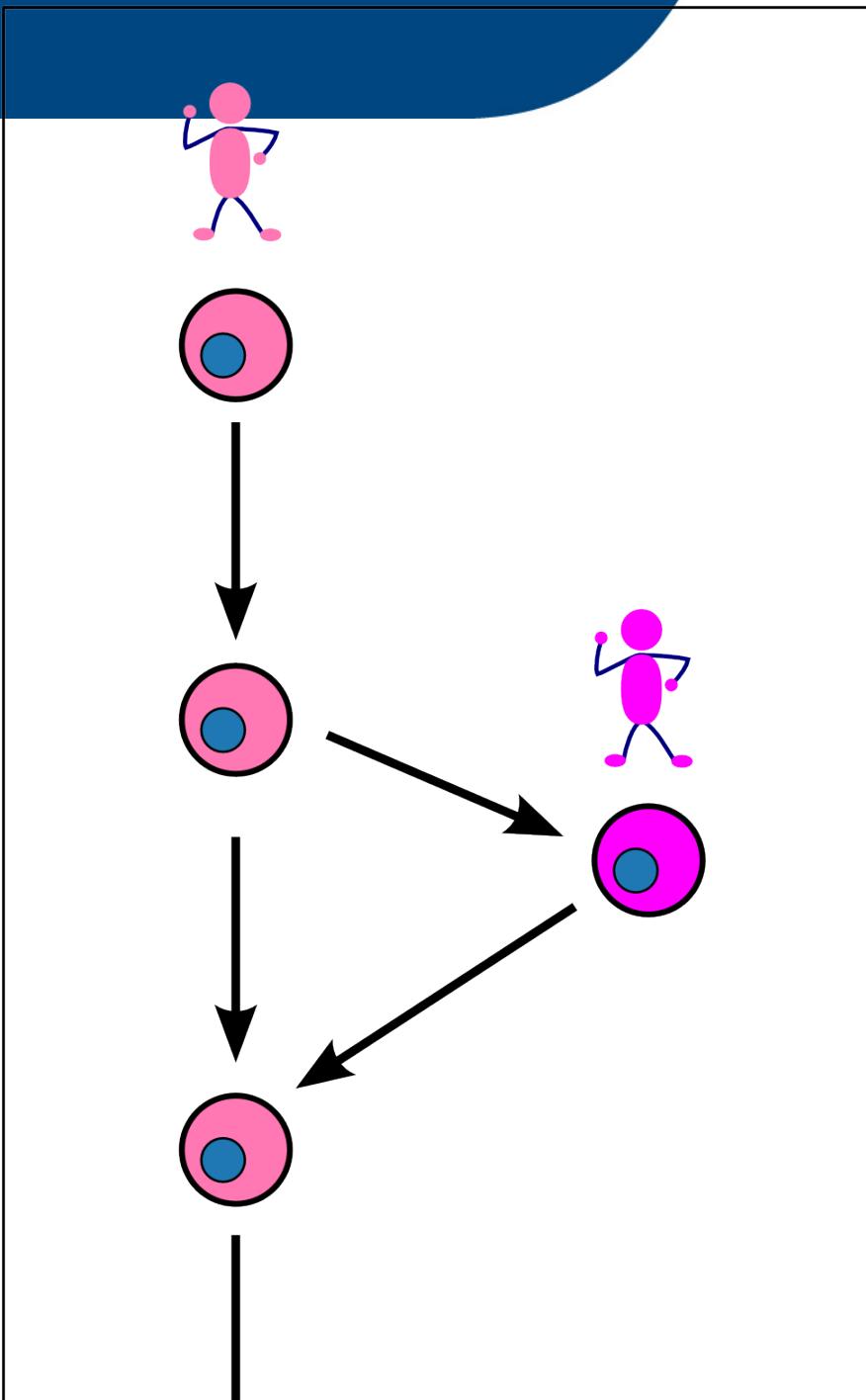


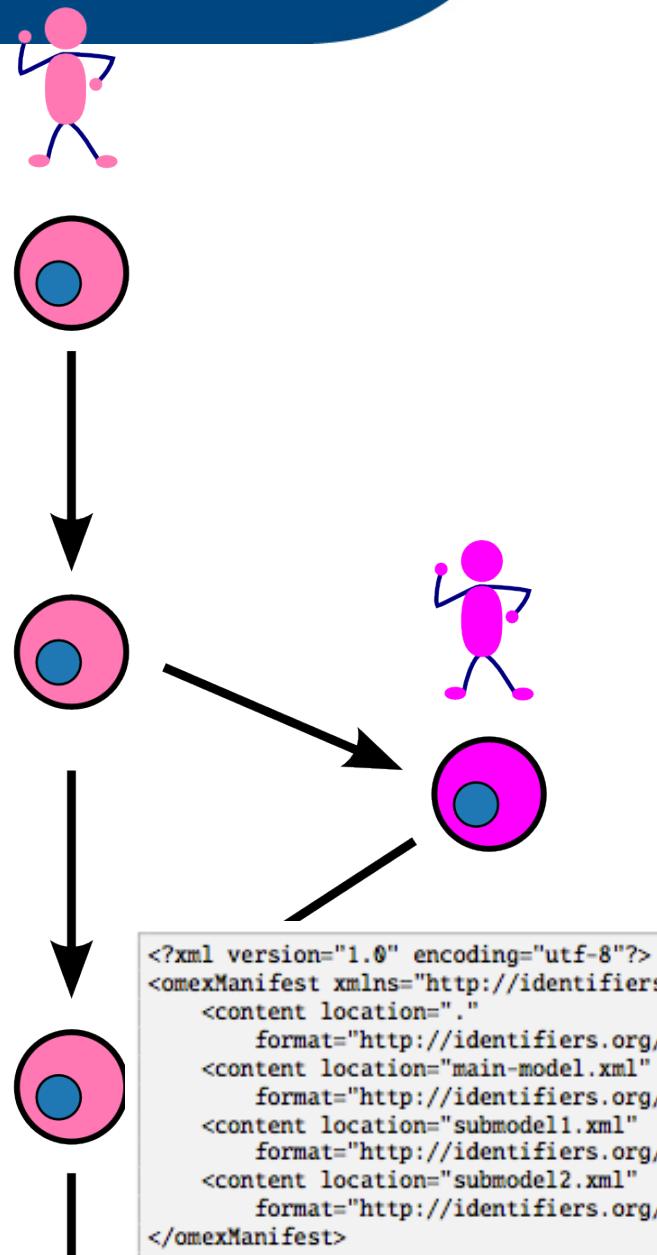
Author	Commit	Message	Date
David Nickerson	7ae00d9	adding a SED-ML document describing a simple time course simulation experiment	an hour ago
David Nickerson	1fc61e3	adding the top-level model which imports each of the sin(x) models from the	an hour ago
David Nickerson	1d71b0c	embedding derivation and parabolic sin(x) approximation example model	an hour ago
David Nickerson	40cfab5	embedding MathML sine function example model workspace	an hour ago

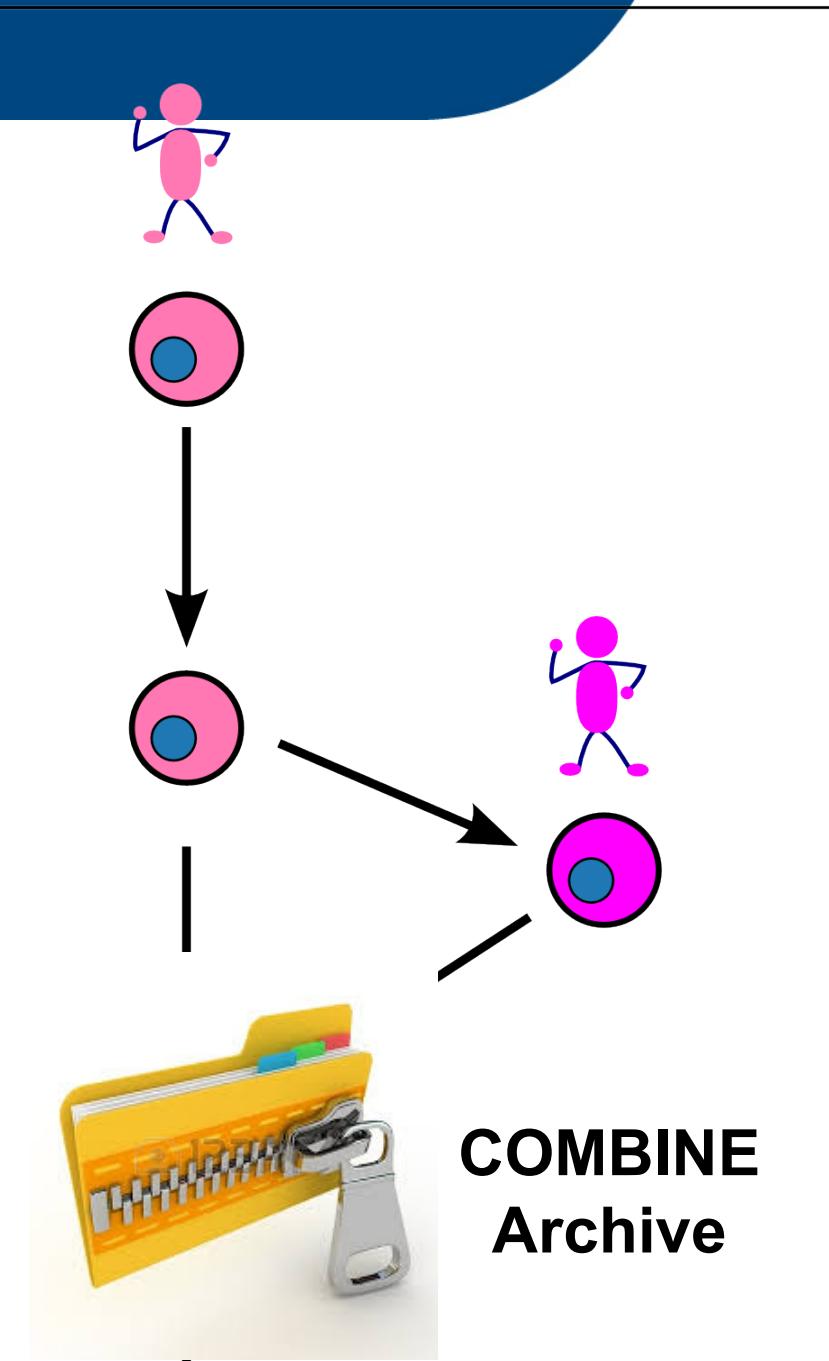












# Recent additions to PMR

The screenshot shows a web browser window with the URL [https://models.physiomeproject.org/protein\\_modules](https://models.physiomeproject.org/protein_modules). The page features a logo of a red stick figure running over a wavy line, followed by a search bar and a star icon. A navigation bar at the top includes links for 'Models Home' (highlighted in red), 'Exposures', and 'Documentation'. Below the navigation, a breadcrumb trail indicates the user is at 'Home / Protein Modules'. The main content area is titled 'Protein Modules' and lists several entries, each with a number and a brief description:

- 25D**  
HH potassium ion channel model
- 25D**  
HH sodium ion channel model
- 28F**  
A kinetic model of Na<sup>+</sup>/H<sup>+</sup> exchanger (NHE3)
- 290**  
A kinetic model of Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> exchanger (AE1)
- 293**  
A kinetic model of V-type H<sup>++</sup>-ATPase (proton pump)
- 294**  
A kinetic model of Na<sup>+</sup>/K<sup>+</sup>-ATPase (sodium-potassium pump)
- 295**  
A kinetic model of Na<sup>+</sup>/HCO<sub>3</sub><sup>-</sup> cotransporter (NBC)

**Chang, Fujita, 1999**  
A kinetic model of the thiazide-sensitive Na-Cl cotransporter

**Eskandari, Wright, Loo,**  
Kinetics of the Reverse Mode of the Na<sup>+</sup>/Glucose Cotransporter

**Mackenzie, Loo, Panayotova-Heiermann, Wright,**  
Biophysical Characteristics of the Pig Kidney Na/Glucose Cotransporter SGLT2 Reveal a Common Mechanism for SGLT1 and SGLT2



Search Site

Models Home

Exposures

Documentation

Log in

You are here: [Home](#) / [Exposures](#) / Na+/H+ Exchanger (NHE3) Model

## Na+/H+ Exchanger (NHE3) Model

### Annotations

#### Described by

A kinetically defined Na+/H+ antiporter within a mathematical model of the rat proximal tubule, A.M. Weinstein, 1995, *The Journal of General Physiology*, **105**, 617-641. DOI: [10.1085/jgp.105.5.617](https://doi.org/10.1085/jgp.105.5.617)

#### Protein

Sodium/hydrogen exchanger 3

#### Located in

Proximal convoluted tubule

Apical plasma membrane

Epithelial cell of proximal tubule

### Workspace Status

This workspace contains several instances of the Weinstein model. There is the general description of the mathematical model and then that model instantiated into specific simulation experiments to reproduce each of the original figures. These models can be browsed via the *Navigation* panel in the right hand column.

- NHE3 Model is the general NHE3 model and can be imported to use in any other model.
- NHE3 Model - Figure 2 illustrates the effect of external pH on Na<sup>+</sup> influx.
- NHE3 Model - Figure 3A illustrates the effect of external pH on the Michaelis constant of Na<sup>+</sup> flux.
- NHE3 Model - Figure 3B illustrates the effect of external pH on the Michaelis constant of Na<sup>+</sup> flux.
- NHE3 Model - Figure 4A illustrates the effect of external pH on competitive inhibition by NH<sub>4</sub><sup>+</sup>.
- NHE3 Model - Figure 4B illustrates the effect of external pH on competitive inhibition by NH<sub>4</sub><sup>+</sup>.

### Source

Derived from workspace Cation/H+ Exchanger at changeset 7b31eb3e8a44.

### Collaboration

To begin collaborating on this work, please use your git client and issue this command:

```
git clone https://models.physio
```

### Downloads

Complete Archive as .tgz

### Navigation

[NHE3 Model](#)

[NHE3 Model - Figure 2](#)

[NHE3 Model - Figure 3A](#)

[NHE3 Model - Figure 3B](#)

[NHE3 Model - Figure 4A](#)

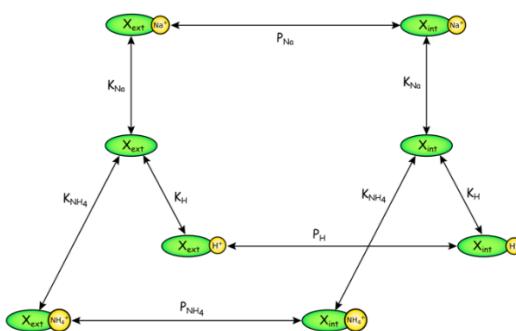
[NHE3 Model - Figure 4B](#)

## NHE Gene Family

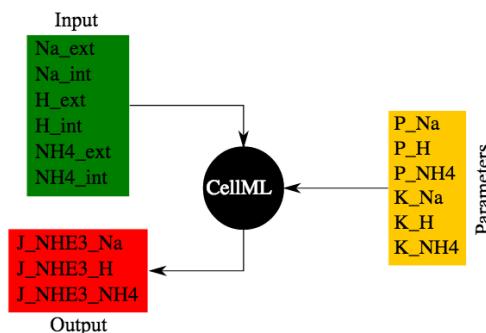
The mammalian NHE gene family (SLC9 family) is comprised of nine isoforms which are categorised by cellular localisation. There are two main categories for these isoforms: NHE1, NHE2, NHE3, NHE4 and NHE5 which reside primarily on the plasma membrane and NHE6, NHE7, NHE8 and NHE9 which locate primarily on intracellular organelles. NHE1 and NHE2 are located at the basolateral and apical membrane of renal tubule cells respectively. NHE3 is present at the apical membrane of proximal tubule. NHE4 is located mostly in renal medulla. NHE5 and NHE6 are present in the kidney, but the exact location of them are not determined yet.

### Model Structure

This transporter mediates the one-for-one exchange of  $\text{Na}^+$  for  $\text{H}^+$  and its activity is enhanced by cytosolic acidosis. Previously, linear nonequilibrium thermodynamics (NET) has been used for modelling the NHE3. In this method, there is a linear relation between NHE3 flux and the transmembrane electrochemical potential differences of  $\text{Na}^+$  and  $\text{H}^+$  and the kinetics are all defined by calculating a transport coefficient using the overall rate of  $\text{Na}^+$  reabsorption. In this work, the NHE3 model has been represented using the approach of Heinz with the assumption of equilibrium binding and one-for-one exchange of  $\text{Na}^+$  for  $\text{H}^+$ . This model consists of four parameters which are transporter density,  $\text{Na}^+$  and  $\text{H}^+$  affinity and the  $\text{Na}^+:\text{H}^+$  permeation rates. These are calculated in a least-squares fit to the kinetic parameters defined experimentally (Aronson et al., 1983). This model includes the  $\text{NH}_4^+$  transport and competitive binding. An internal  $\text{H}^+$  modifier site is also implemented in NHE3 model to increase transport beyond the expected kinetic by representing as a velocity effect of  $\text{H}^+$  binding to a single site (Aronson et al., 1982).



The figure above represents the kinetic scheme for NHE3. The carrier, X, can be oriented toward the external ( $X_{\text{ext}}$ ) or internal ( $X_{\text{int}}$ ) side of the membrane and bound to one of three ions,  $\text{Na}^+$ ,  $\text{H}^+$ , or  $\text{NH}_4^+$ . It is assumed that cation binding is faster than translocation of the carrier-ion complex, therefore the concentration of the loaded carrier at each side is defined by equilibrium binding constants,  $K_{\text{Na}}$ ,  $K_{\text{H}}$ , and  $K_{\text{NH}_4}$ . The carrier is assumed to be symmetric, so the binding constants are the same for either side of the membrane. Translocation constant for the loaded carrier occurs based on rate coefficients,  $P_{\text{Na}}$ ,  $P_{\text{H}}$ , and  $P_{\text{NH}_4}$ . Also translocation does not happen for empty carrier.



### Downloads

- [Download This File](#)
- [Complete Archive as .tgz](#)

### Views Available

- [Documentation](#)
- [Model Metadata](#)
- [Model Curation](#)
- [Mathematics](#)
- [Generated Code](#)
- [Cite this model](#)
- [Source View](#)
- [Launch with OpenCOR](#)



### Tools

- [Compare...](#)

### License

The terms of use/license for this work is unspecified.

### Navigation

- [NHE3 Model](#)
- [NHE3 Model - Figure 2](#)
- [NHE3 Model - Figure 3A](#)
- [NHE3 Model - Figure 3B](#)
- [NHE3 Model - Figure 4A](#)
- [NHE3 Model - Figure 4B](#)

OpenCOR

Weinstein\_1995\_NHE3.cellml

CellML Annotation
CellML Text
Raw CellML
Raw SED-ML
Raw Text

$$J_{NHE3_{Na}} = \frac{x_T}{\sigma} \cdot \left( P_{Na} \cdot P_H \cdot \left( \alpha_{int_{Na}} \cdot \beta_{ext_H} - \alpha_{ext_{Na}} \cdot \beta_{int_H} \right) + P_{Na} \cdot P_{NH4} \cdot \left( \alpha_{int_{Na}} \cdot \gamma_{ext_{NH4}} - \alpha_{ext_{Na}} \cdot \gamma_{int_{NH4}} \right) \right)$$

```

var x_T: mM {init: 1.0};
var sigma: per_s;
var P_Na: per_s;
var P_H: per_s;
var P_NH4: per_s;
var P0_Na: per_s {init: 1.6e-3};
var P0_H: per_s {init: 0.48e-3};
var P0_NH4: per_s {init: 1.6e-3};
var K_Na: mM {init: 30.0};
var K_H: mM {init: 72e-6};
var K_NH4: mM {init: 27.0};
var K_I: mM {init: 1.0e-6};
var f_m: dimensionless {init: 0.0};
var f_M: dimensionless {init: 2.0};
var alpha_ext_Na: dimensionless;
var alpha_int_Na: dimensionless;
var beta_ext_H: dimensionless;
var beta_int_H: dimensionless;
var gamma_ext_NH4: dimensionless;
var gamma_int_NH4: dimensionless;

alpha_ext_Na = Na_ext/K_Na;
alpha_int_Na = Na_int/K_Na;
beta_ext_H = H_ext/K_H;
beta_int_H = H_int/K_H;
gamma_ext_NH4 = NH4_ext/K_NH4;
gamma_int_NH4 = NH4_int/K_NH4;
P_Na = P0_Na * (f_M * H_int + f_m * K_I) / (H_int + K_I);
P_H = P0_H * (f_M * H_int + f_m * K_I) / (H_int + K_I);
P_NH4 = P0_NH4 * (f_M * H_int + f_m * K_I) / (H_int + K_I);
sigma = (1{dimensionless}) + alpha_ext_Na + beta_ext_H + gamma_ext_NH4) * (P_Na * alpha_int_Na + P_H * beta_int_H + P_NH4 * gamma_int_NH4) + (1{dimensionless}) + alpha_int_Na + beta_int_H + gamma_int_NH4) * (P_Na * alpha_int_Na + P_H * beta_int_H + P_NH4 * gamma_int_NH4);
J_NHE3_Na = x_T / sigma * (P_Na * P_H * (alpha_ext_Na * beta_ext_H - alpha_ext_Na * beta_int_H) + P_Na * P_NH4 * (alpha_int_Na * gamma_ext_NH4 - alpha_ext_Na * gamma_int_NH4));
J_NHE3_H = x_T / sigma * (P_Na * P_H * (alpha_ext_Na * beta_int_H - alpha_int_Na * beta_ext_H) + P_H * P_NH4 * (beta_int_H * gamma_ext_NH4 - beta_ext_H * gamma_int_NH4));
J_NHE3_NH4 = x_T / sigma * (P_Na * P_NH4 * (alpha_ext_Na * gamma_int_NH4 - alpha_int_Na * gamma_ext_NH4) + P_H * P_NH4 * (beta_ext_H * gamma_int_NH4 - gamma_ext_NH4 * beta_int_H));
J_NHE3_Na_Max = x_T * P_Na * P_H / (P_Na + P_H);

enddef;
enddef;

```

Line: 53, Col: 43 INS



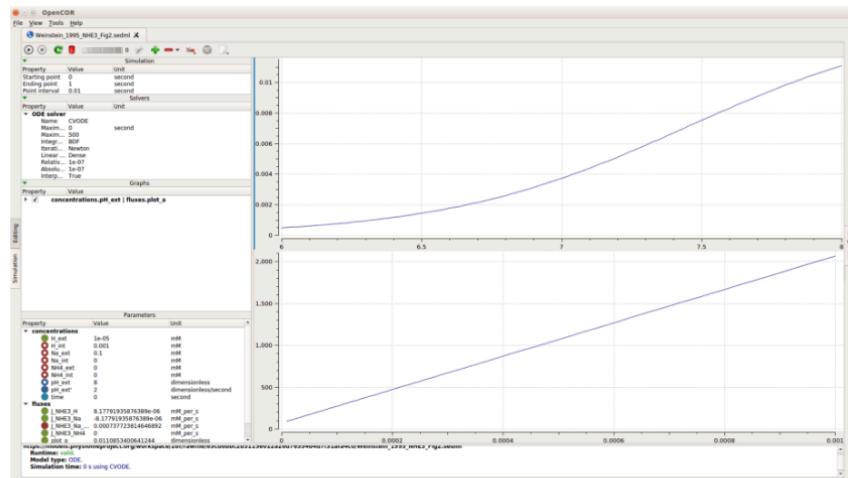
You are here: [Home](#) / [Exposures](#) / [Na+/H+ Exchanger \(NHE3\) Model](#) / NHE3 Model - Figure 2

## NHE3 Model - Figure 2

### Figure 2

This is the general mathematical model for the NHE3 model with modifications to enable simulations which are capable of reproducing Figure 2 in the original paper. The simulation experiment for this model can be obtained by loading the corresponding SED-ML document into OpenCOR and executing the simulation. The results of which are shown below. A rendering of the mathematical model itself is available [here](#).

In Figure 2, the  $\text{Na}^+$  influx is computed for a range of external pH when  $\text{NH}_4^+$  is not present. Internal and external  $\text{Na}^+$  concentrations are fixed at 0.0 and 0.1 mM; internal pH is 6; and external pH is varied from 6 to 8. (top)  $\text{Na}^+$  flux is shown as a function of the external pH. (bottom) Reciprocal flux is shown as a function of the external  $\text{H}^+$  concentration.



A screenshot illustrating the results when the associated SED-ML document is loaded into OpenCOR and the simulation executed.

This can be reproduced directly from the repository by choosing the [Launch with OpenCOR](#) link from the [Views Available](#).

### Source

Derived from workspace Cation/H+ Exchanger at changeset 7b31eb3e8a44.

### Collaboration

To begin collaborating on this work, please use your git client and issue this command:

```
git clone https://models.phys
```

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### Tools

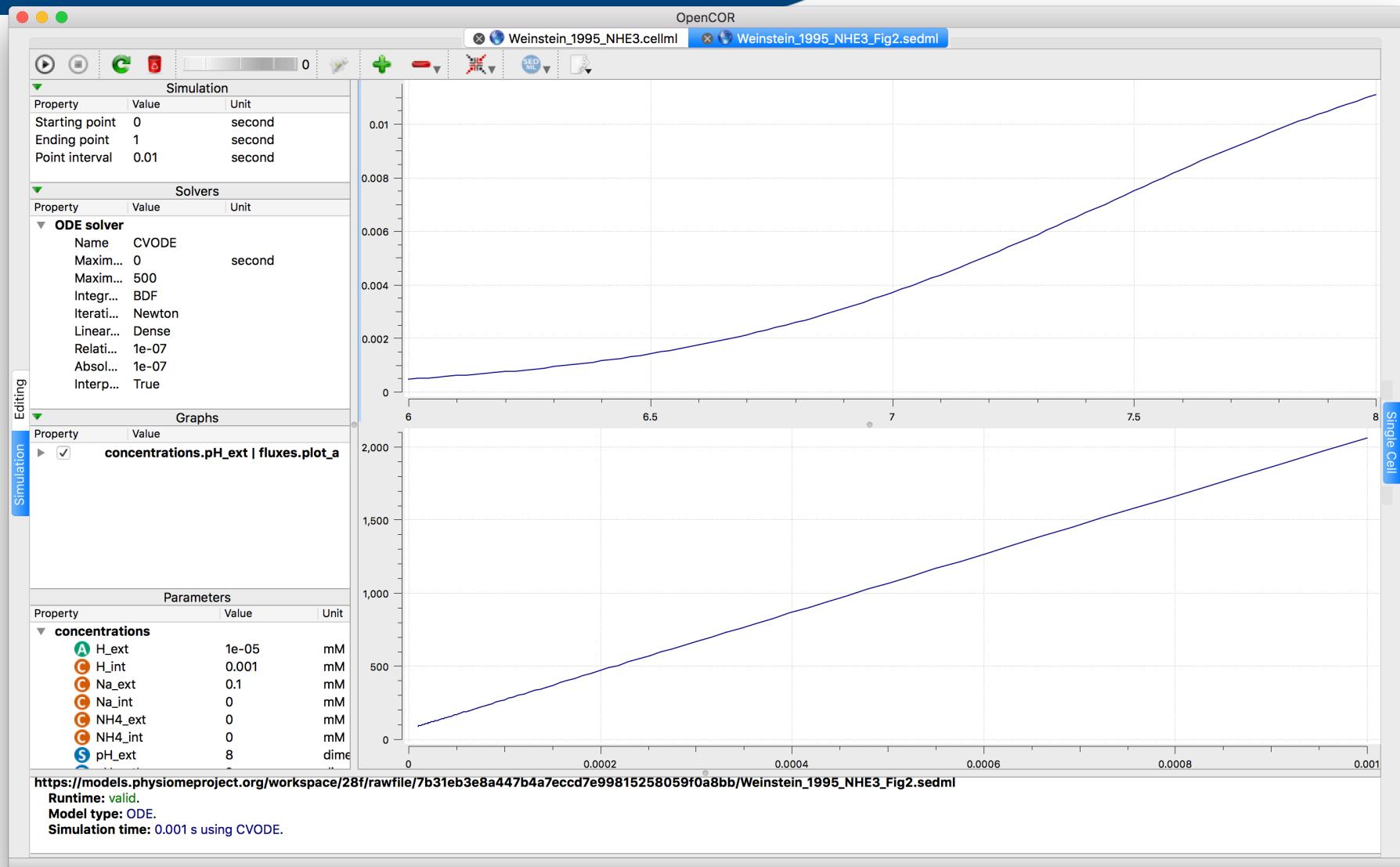
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# Acknowledgements



Frank Bergmann



Dagmar Waltemath



Tommy Yu &  
the ABI  
software team



Peter  
Hunter

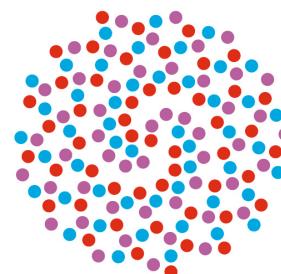


# Acknowledgements



The Virtual Physiological  
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