Cardiac Physiome, 17-19th Oct 2013

The Physiome Project and the Virtual Physiological Human

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Auckland Bioengineering Institute

History of Physiome Project

1997 IUPS Physiome Committee

1998 CellML, FieldML

1999 Systems Biology Markup Language

2003 IMAG (NIH, NSF, FDA, NASA, DOE, DOD, ..)

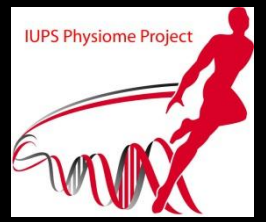
2006 STEP: Strategy for European Physiome

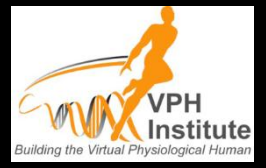
2008 VPH Network of Excellence

2009 Drug Disease Model Resources (DDMoRe)

2010 German Virtual Liver Network

2011 VPH Institute





Physiome colleagues

Jim Bassingthwaighte

Andrew McCulloch

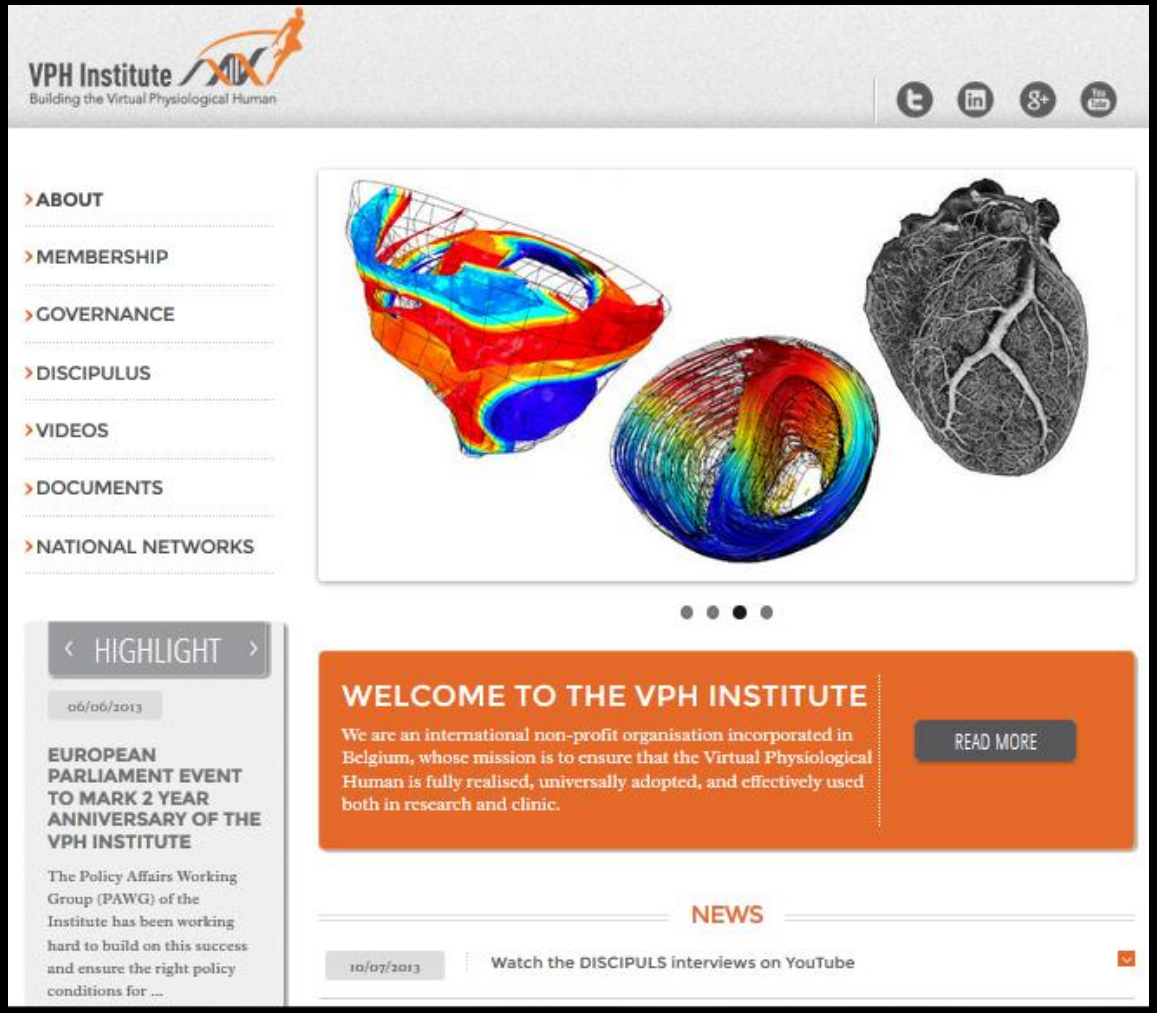
Dan Beard

Nic Smith

Stig Omholt

Adriano Henney

VPH Institute



www.vph-institute.org

Virtual Liver Network

Objective:

- To create a multi-scale dynamic mathematical model that represents, rather than fully replicates human liver physiology, morphology and function
- A model that has a specific focus on application to address the needs of the patient and clinicians.

Steatosis
HGF induced regeneration
LPS induced inflammation
LIAM: Liver Image Analysis-based Modelling

- 9 Workpackages
- 69 Principal Investigators
- 44 Projects
- >200 contributing Scientists
- 36 Independent Institutions
- Mix of academics & industry

Work Package Subject	Projects	
Cellular Metabolism	3	CELL LEVEL
Cellular Signalling	5	
Cross Linking	6	
Cell-Cell Communication	9	TISSUE LEVEL
Liver Lobule	6	
Whole Organ	4	ORGAN LEVEL
Integrated Model	4	
Data Management	3	
Clinical Translation	4	CLINICAL

virtual liver network

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www.virtual-liver.de

A Vision and Strategy for the VPH in 2010 and beyond

Peter Hunter[1,2], Peter V. Coveney[3], Bernard de Bono[4], Vanessa Diaz[5], John Fenner[6], Alejandro F. Frangi[7], Peter Harris[8], Rod Hose[6], Peter Kohl[2], Pat Lawford[6], Keith McCormack[9], Miriam Mendes[3], Stig Omholt[10], Alfio Quarteroni[11], John Skår[12], Jesper Tegner[13], S. Randall Thomas[14], Ioannis Tollis[15], Ioannis Tsamardinos[15], Johannes HGM van Beek[16] and Marco Viceconti[17]

[1] Auckland Bioengineering Institute (ABI), University of Auckland, New Zealand
[2] Department of Physiology Anatomy & Genetics, University of Oxford, UK
[3] Centre for Computational Science, University College London, UK
[4] European Bioinformatics Institute, European Molecular Biology Laboratory, Cambridge, UK

A vision and strategy for the virtual physiological human: 2012 update

Peter Hunter, Tara Chapman, Peter V. Coveney, Bernard de Bono, Vanessa Diaz, John Fenner, Alejandro F. Frangi, Peter Harris, Rod Hose, Peter Kohl, Pat Lawford, Keith McCormack, Miriam Mendes, Stig Omholt, Alfio Quarteroni, Nour Shublaq, John Skår, Karl Stroetmann, Jesper Tegner, S. Randall Thomas, Ioannis Tollis, Ioannis Tsamardinos, Johannes H. G. M. van Beek and Marco Viceconti

Interface Focus 2013 **3**, 20130004, published 21 February 2013

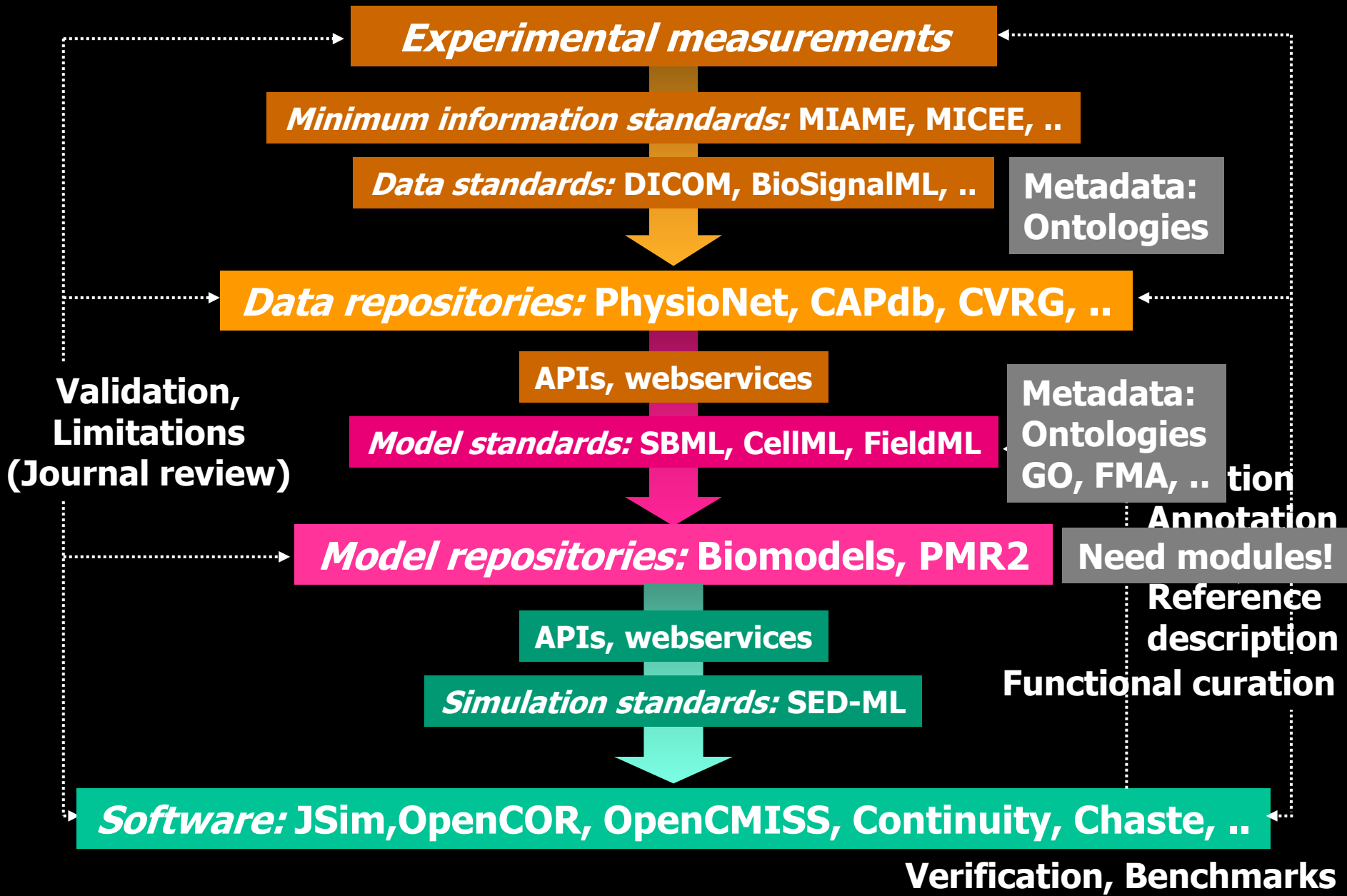
www.vph-noe.eu/images/vph_vision_2011_23dec2010.pdf

To cope with the multi-physics, multi-scale, complexity of human biology we must create reproducible models with modular approaches based upon data and modeling standards

A multi-scale bioengineering approach needs:

- Biophysically based models at every level
  – as much as possible (there's always a black box!)
- Adoption of model and data standards
  – SBML, CellML, FieldML for models
- Automated assembly of multi-scale models
  – molecule to organ(ism)
- Automated model reduction
  – otherwise too expensive

Standards for models, data & software



Note on model publishing

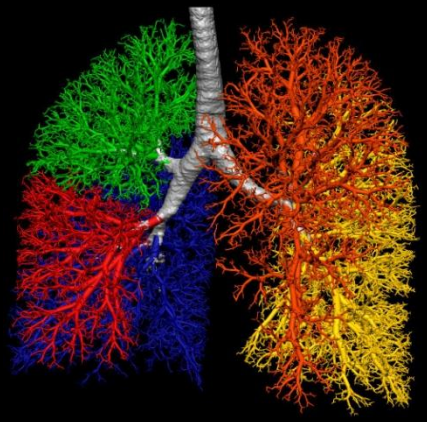
Biophysical Journal

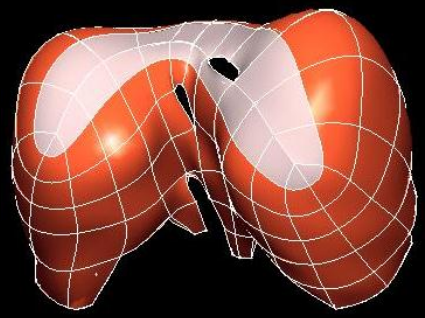
"To assure public access to computational models, authors are strongly encouraged to deposit their models in the CellML Model Repository models.cellml.org/cellml or Biomodels Database www.ebi.ac.uk/biomodels-main/"

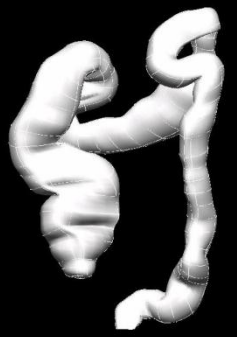
Similarly for many other journals.

Organ system Physiome Projects

Cardiovascular system
Respiratory system
Musculo-skeletal system
Digestive system
Skin (integument)
Urinary system
Lymphoid system
Female reproductive system
Special sense organs
Central nervous system
Endocrine system
Male reproductive system



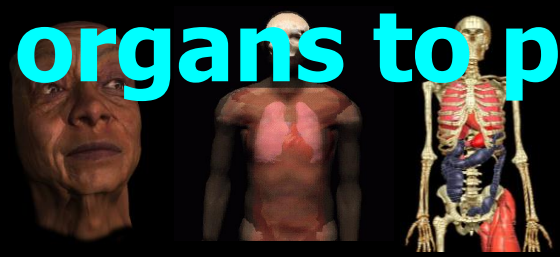




The challenge: organs to proteins

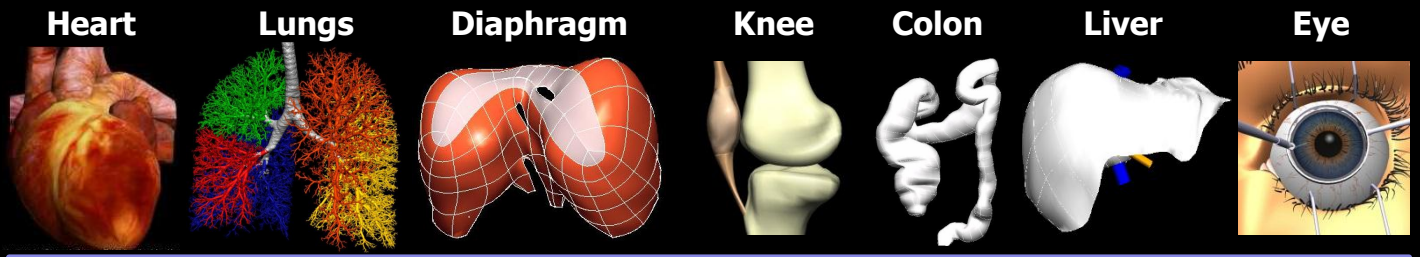
Environment

Organism



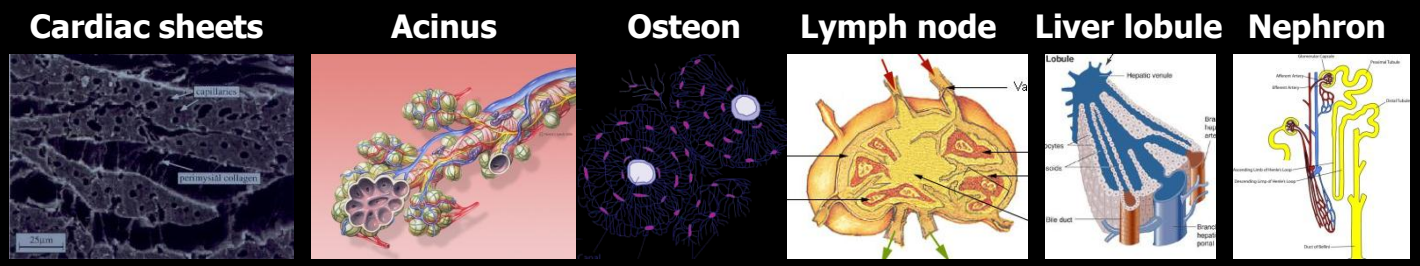
Organ system

Organ

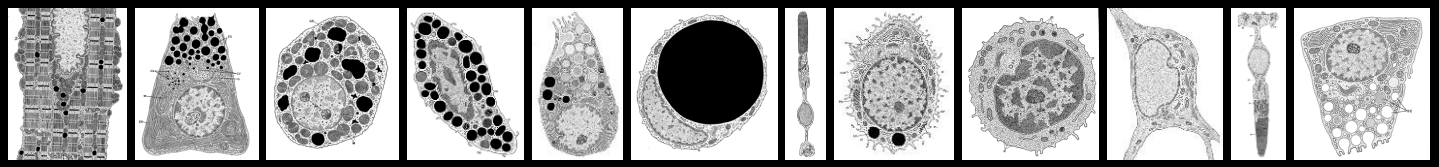


↑ x 1million ↓ 20 generations

Tissue



Cell

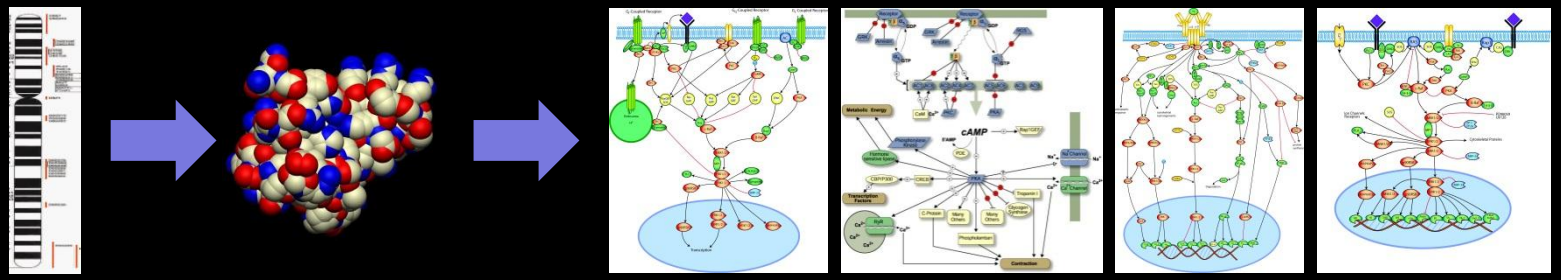


Network

Protein

Gene

Atom



Physiome model repository (PMR)

Tommy Yu

Key features

- Version controlled storage of models
  – They are encapsulated as Workspaces.
- Content management system (CMS) for presentation of models.
  – The set of presentation views is known as Exposures.
- Provides services to store, access and interact with models.
- Links with external web-services to provide semantic reasoning against model metadata across models.

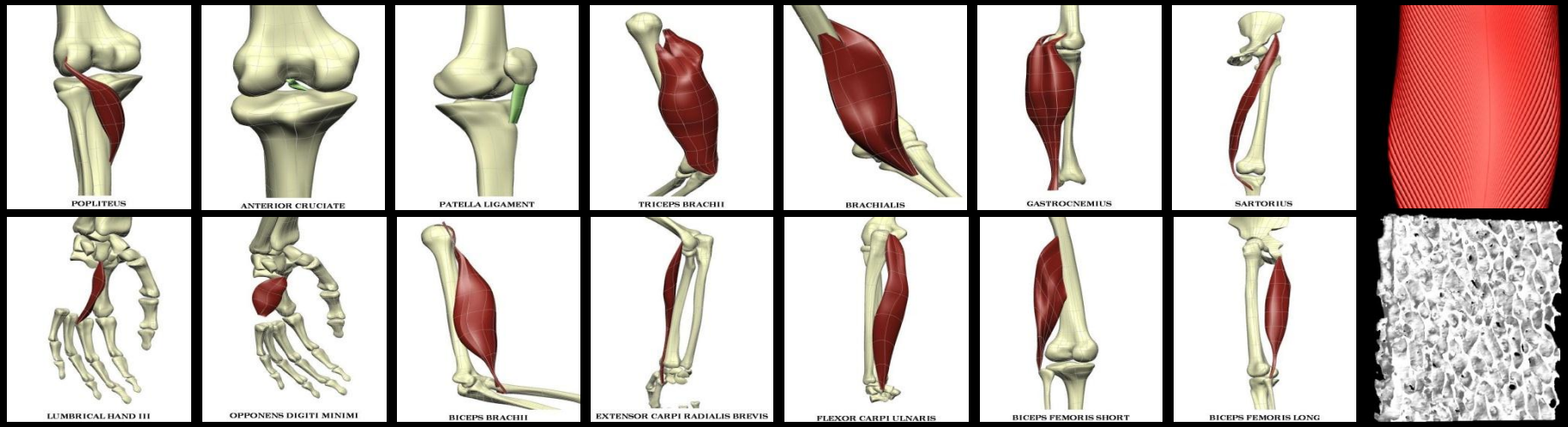
PMR for anatomical models - FieldML

Thor Besier

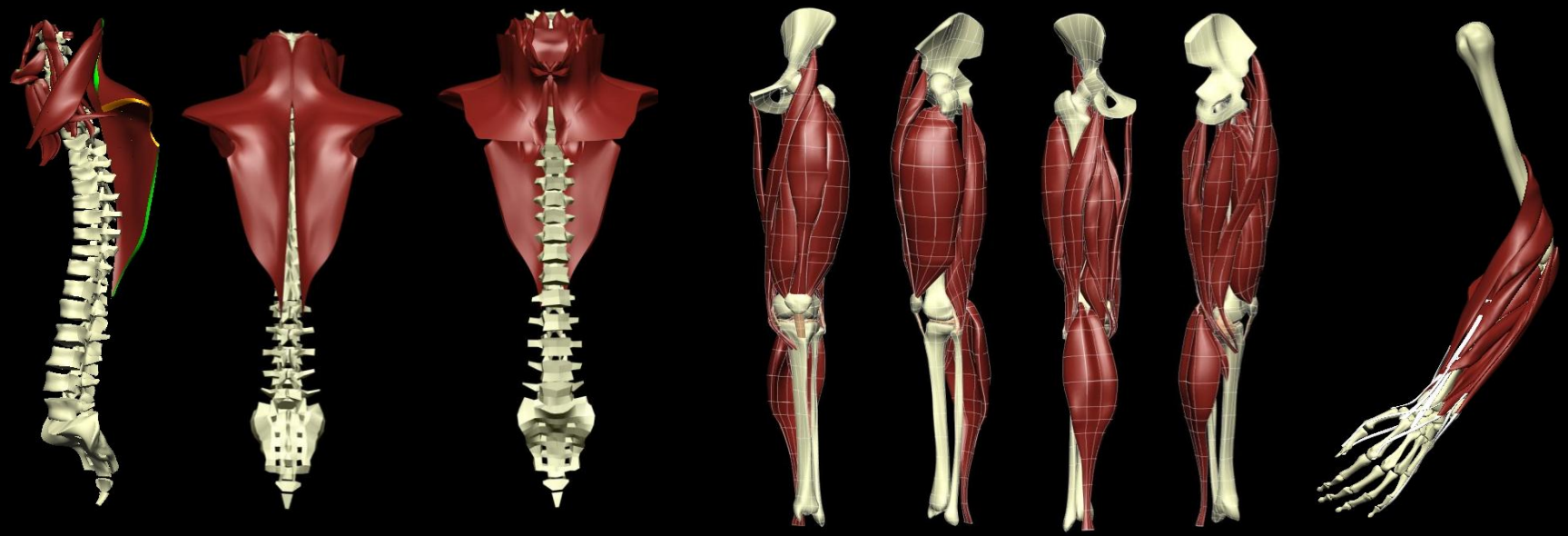
Hugh Sorby

Musculo-skeletal system

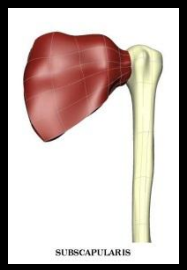
Web-accessible database of generic models (+ tissue structure):

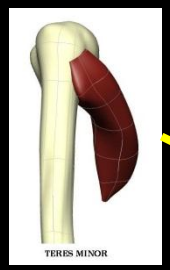


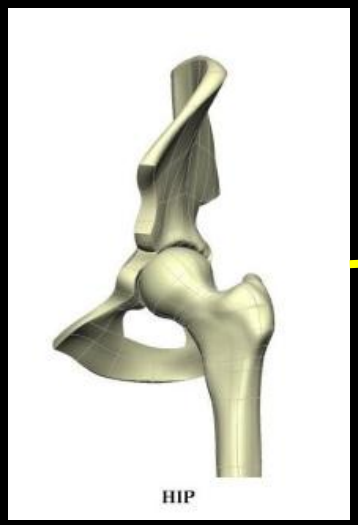
Load generic models into the anatomical component under study:

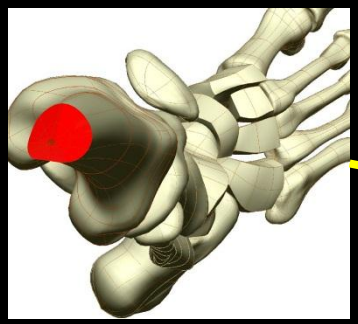


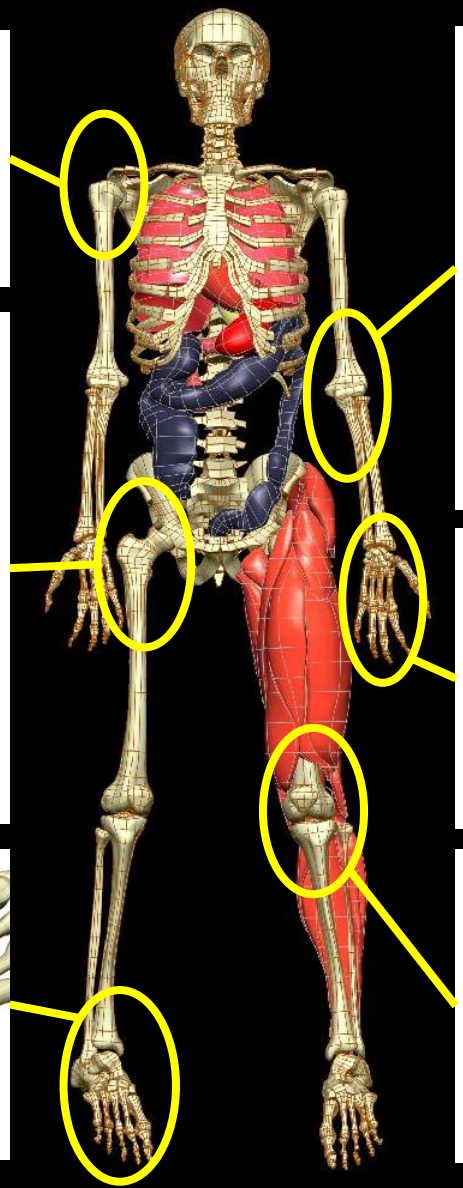
Generic models of the joints

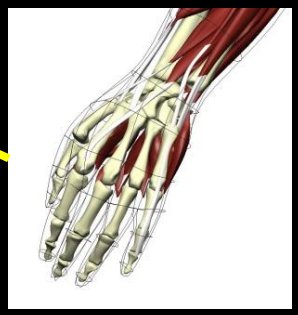


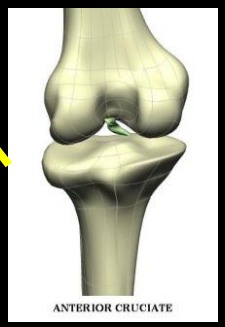








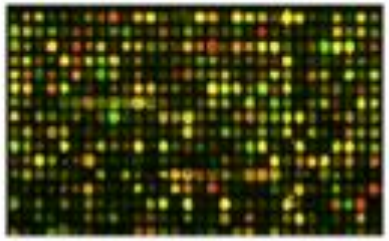




Shim VB, Hunter PJ, Pivonka P, Fernandez JW. A multiscale framework based on the physiome markup languages for exploring the initiation of osteoarthritis at the bone-cartilage interface. IEEE Trans Biomed Eng. 58(12):3532-6, 2011

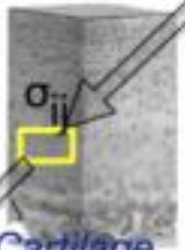
In vivo gene functions

In vivo joint loading



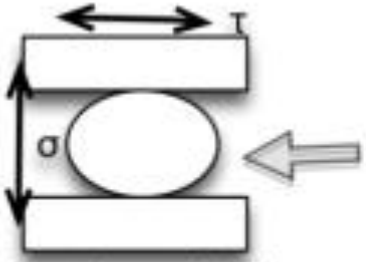
gene expressions of stimulated cells from the device

Knee FE model



Cartilage FE model

Chondrocyte FE model



Application of daily loading signals to cells with a novel device

Multiscale knee model for modelling chondrocyte during daily activities

Population atlases

Alistair Young

www.cardiacatlas.org

Brett Cowan

Cardiac Atlas PROJECT

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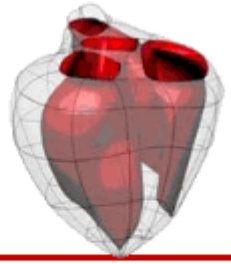
The Cardiac Atlas Project

The Cardiac Atlas Project seeks to establish a structural and functional atlas of the heart. This project is dedicated to combine cardiac modeling and biophysical analysis methods with a structural database for the comprehensive mapping of heart structure and function.



The Cardia Atlas Project is presenting in the

STACOM-CESC'10 workshop @

News

Ethics Essays posted

5/19/10 1:29 AM

We ve posted essays about ethics of data ownership and value on our website The essays are written by Sarah Anderson as part of her student project in Philosophy at the University of Auckland They

CAP XML Model Format

3/8/10 4:13 AM

The Cardiac Atlas Project has released a DTD and XML Schema defining the structure of a model annotation and associated files e g CMGUI exnode files contours The XML Model definition is available

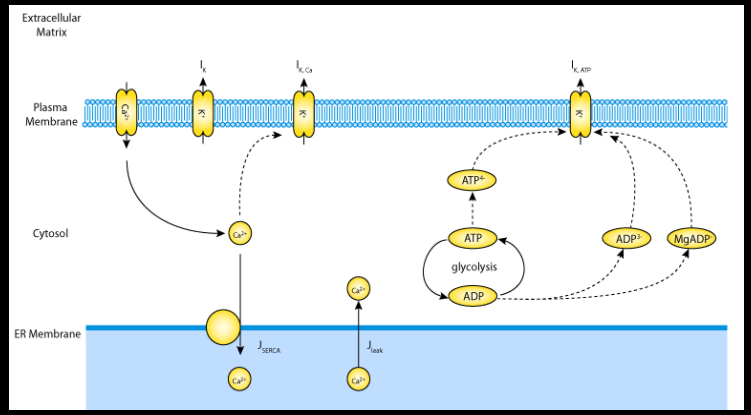
About CAP

Resources

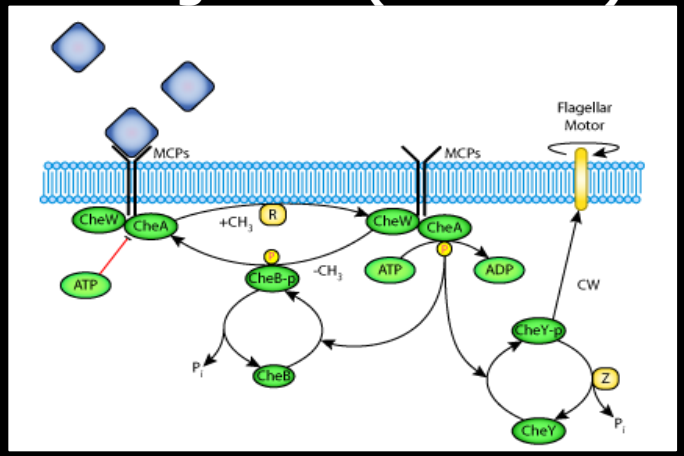
PMR for cell models - CellML

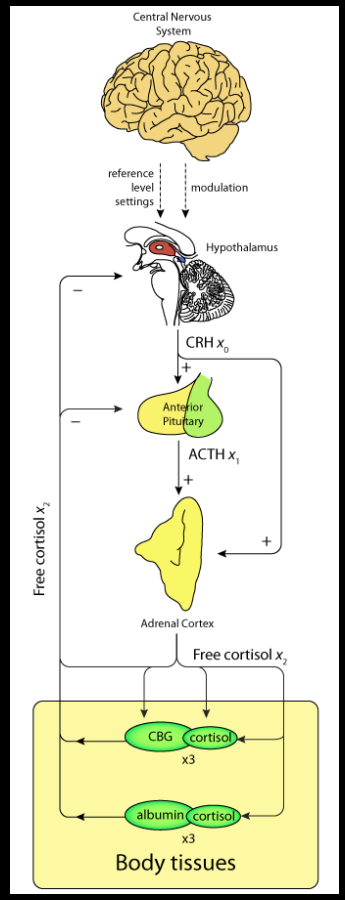
Cuellar AA, Lloyd CM, Nielsen PF, Halstead MDB, Bullivant DP, Nickerson DP, Hunter PJ. An overview of CellML 1.1, a biological model description language. *SIMULATION: Transactions of the Society for Modeling and Simulation*, 79(12):740-747, 2003

Calcium dynamics (63 models)

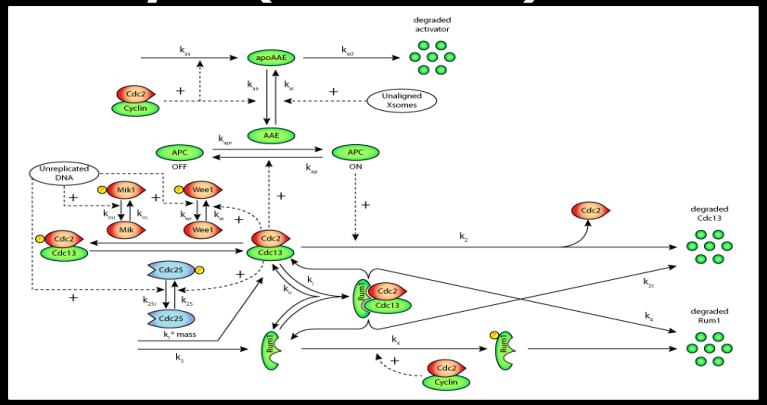


Cell migration (2 models)

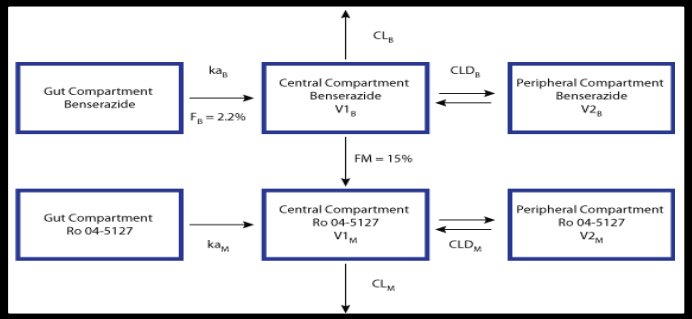




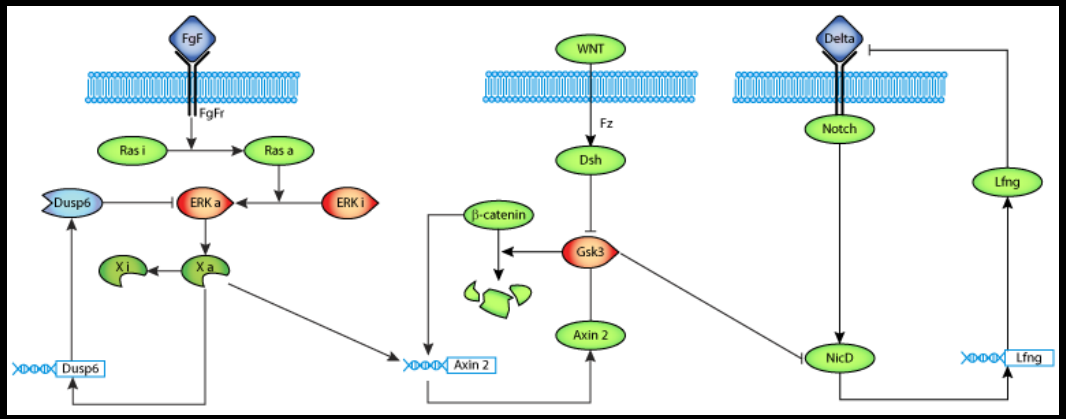
Cell cycle (25 models)



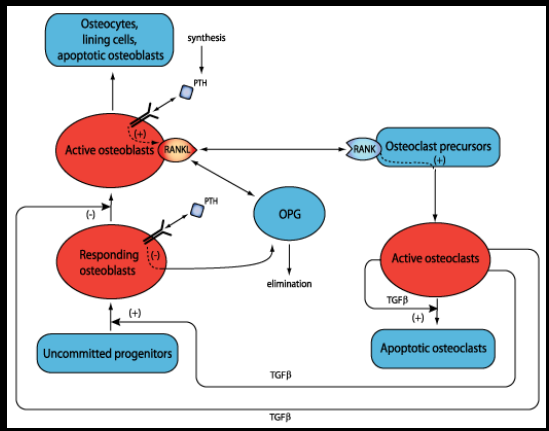
PKPD models (7 models)



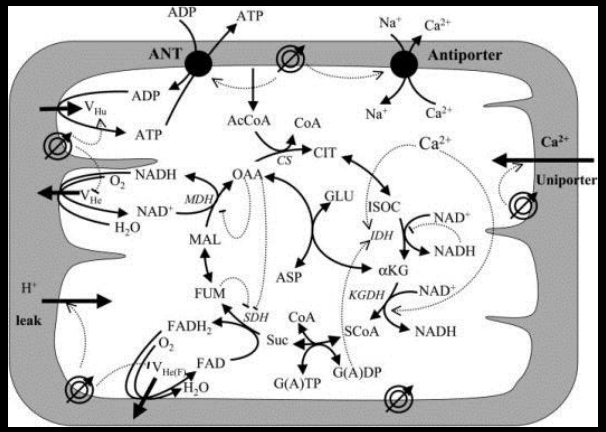
Circadian rhythms (9 models)



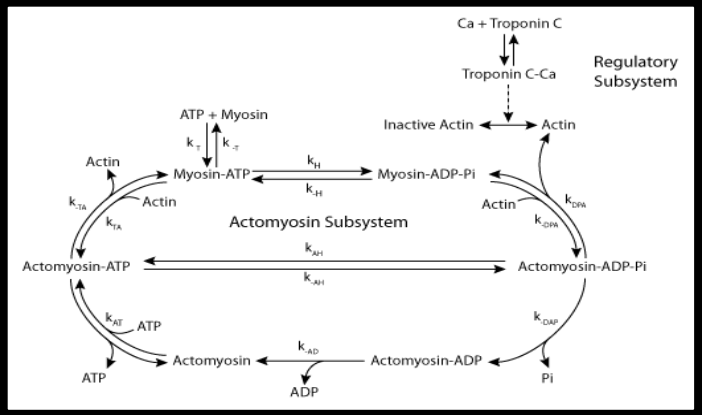
Endocrine system (29)



Metabolism (35 models)

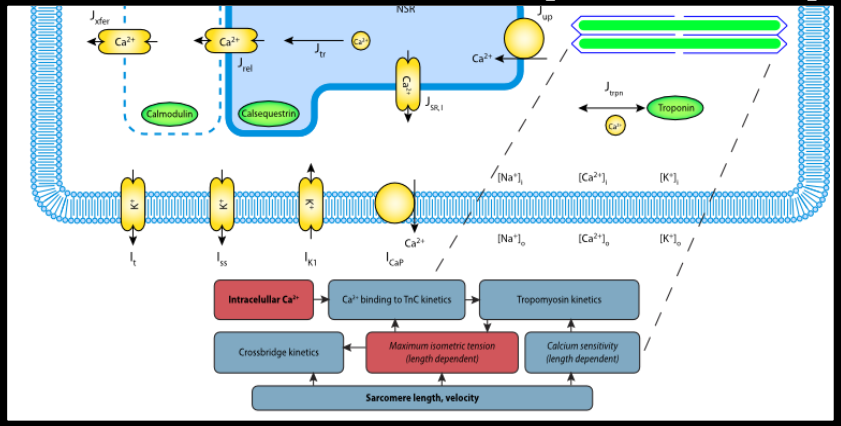


Myofilament mechanics (15)

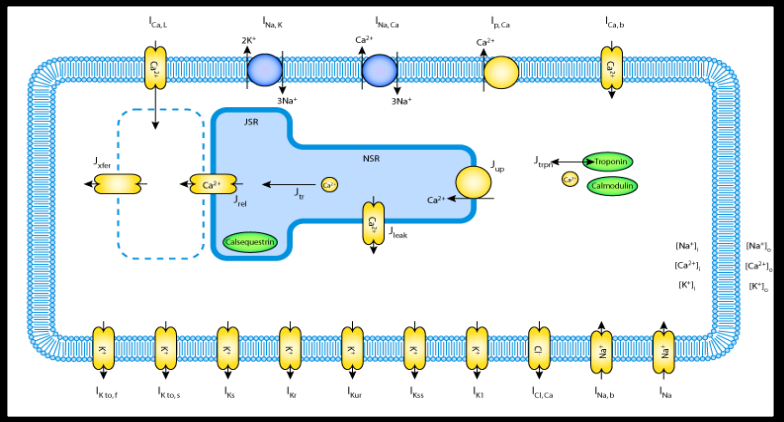


Material constitutive laws

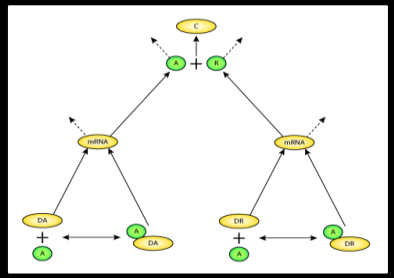
Excitation-contaction (15 models)

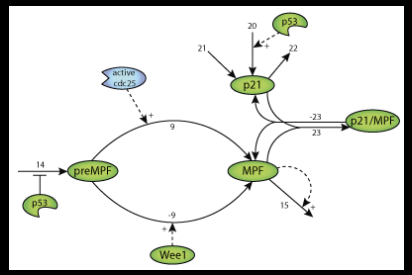


Electrophysiology (117 models)

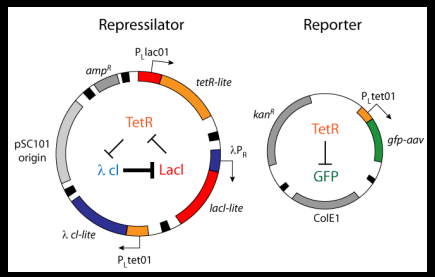


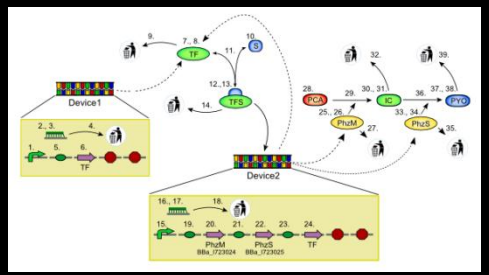
Gene regulation DNA repair (3)



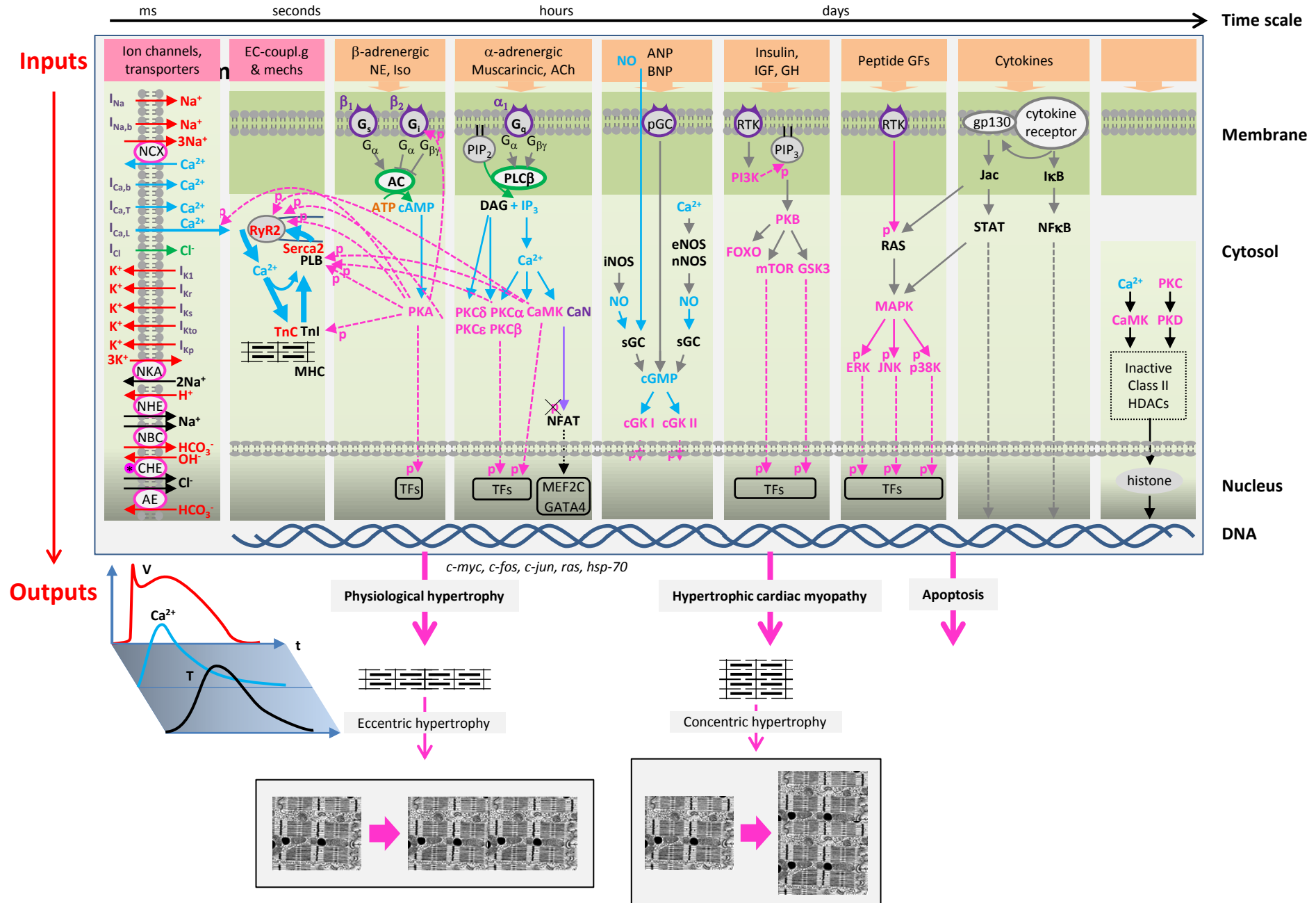


Synthetic biology (5 models)



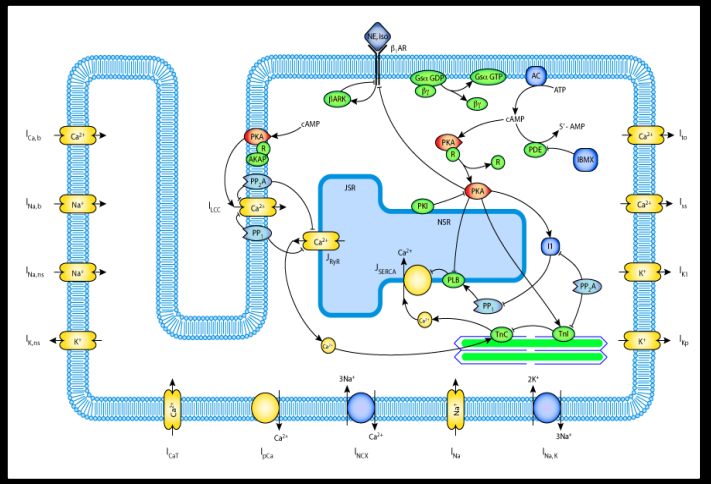


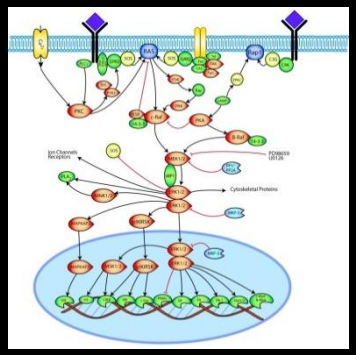
CellML signalling modules for the cardiac myocyte

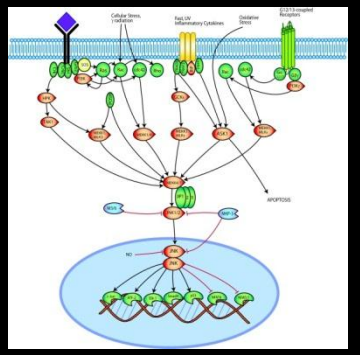


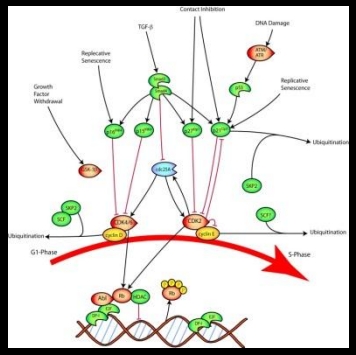
Signaling

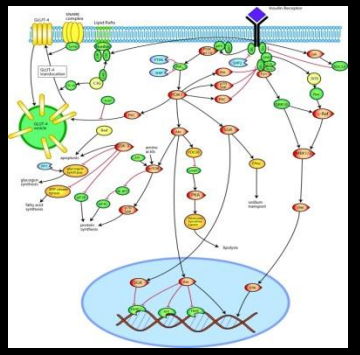
1. cAMP signalling
2. Calcium signalling - via
   - cADP-ribose signalling
   - NAADP signalling
   - Voltage operated channels (VOCs)
   - Receptor operated channels (ROCs)
   - IP_3-Ca^{2+} signalling (via PLC-PIP_2)
   - DAG-PKC signalling (via PLC-PIP_2)
   - PI4-5P_2 signalling
   - Inositol polyphosphate signalling
   - PI3-Kinase signalling
3. NO-cGMP signalling
4. Redox signalling
5. MAP-Kinase signalling
6. NF-kB signalling
7. Phospholipase D (PLD) signalling
8. Sphingomyelin signalling
9. JAK-STAT signalling
10. Smad signalling
11. Wnt signalling
12. Hedgehog signalling
13. Notch signalling
14. ER stress signalling
15. AMP signalling



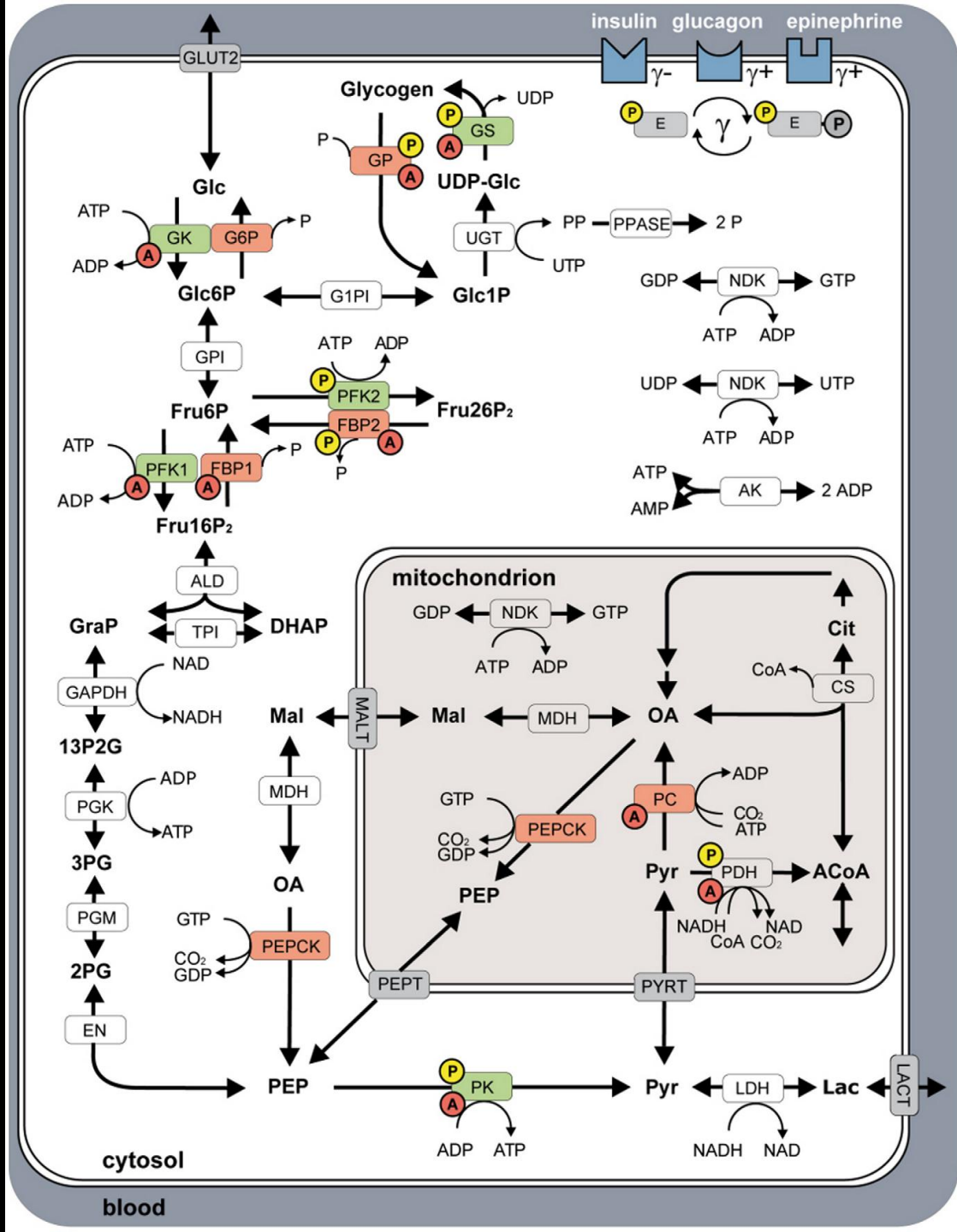


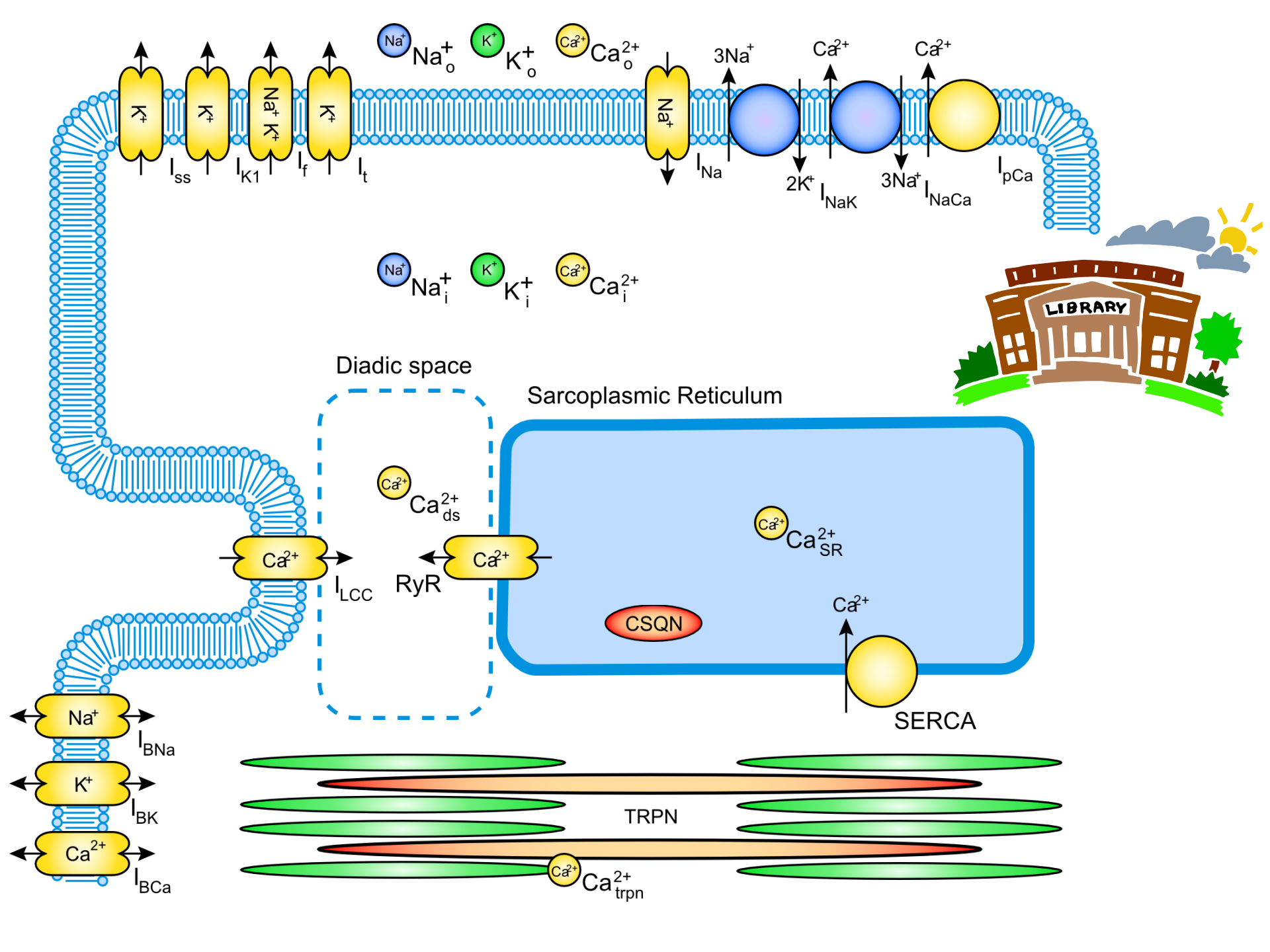






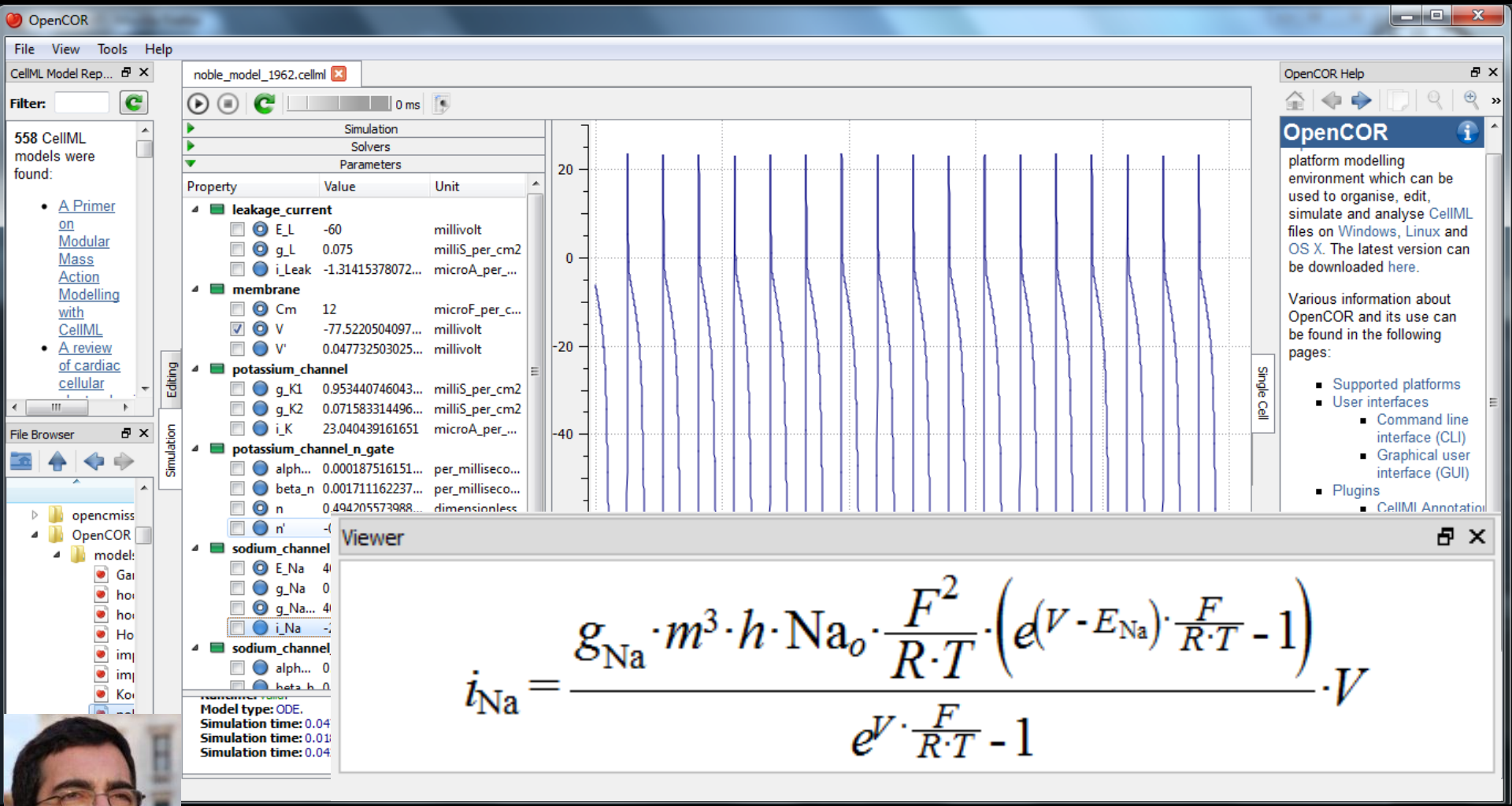
- Glucose transporter (GLUT2)
- Glucokinase (GK)
- Glucose-6 phosphatase (G6Pase)
- Glucose-6-phosphate isomerase (GPI)
- Glucose-1-phosphate 1,6-phosphomutase (G16PI)
- UTP: Glucose-1-phosphate uridylyltransferase (UGT)
- Pyrophosphate phosphohydrolase (PPase)
- Glycogen synthase (GS)
- Glycogen phosphorylase (GP)
- Nucleosid diphosphate kinase (NDK)
- Adenylate kinase (AK)
- Phosphofructo kinase 2 (PFK2)
- Fructo-2,6-bisphosphatase (FBP2)
- Phosphofructo kinase (PFK1)
- Fructose-1,6-bisphosphatase (FBP1)
- Aldolase (ALD)
- Triosephosphate isomerase (TPI)
- D-Glyceraldehyde-3-phosphate: NAD+ oxidoreductase (GAPDH)
- Phosphoglycerate kinase (PGK)
- 3-Phosphoglycerate mutase (PGM)
- Enolase (EN)
- Pyruvate kinase (PK)
- Phosphoenolpyruvate carboxykinase (PEPCK)
- Pyruvate carboxylase (PC)
- Lactate dehydrogenase (LDH)
- Lactate transporter (LACT)
- Pyruvate transporter (PYRT)
- PEP transporter (PEPT)
- Pyruvate dehydrogenase (PDH)
- Citrate synthase (CS)
- Nucleosid diphosphate kinase (NDK)
- Oxalacetate flux (OAAflx)
- Acetyl-CoA flux (ACOAflx)
- Citrate flux (CITflx)




Na^+_o
K^+_o
Ca^{2+}_o
I_{ss}
I_{K1}
I_f
I_t
I_{Na}
$3Na^+$
$2K^+$
I_{NaK}
$3Na^+$
I_{NaCa}
I_{pCa}
Na^+_i
K^+_i
Ca^{2+}_i
LIBRARY
Diadic space
Sarcoplasmic Reticulum
Ca^{2+}_{ds}
Ca^{2+}_{SR}
I_{LCC}
RyR
CSQN
SERCA
I_{BNa}
I_{BK}
I_{BCa}
TRPN
Ca^{2+}_{trpn}

www.cellml.org/tools

→ OpenCOR www.opencor.ws



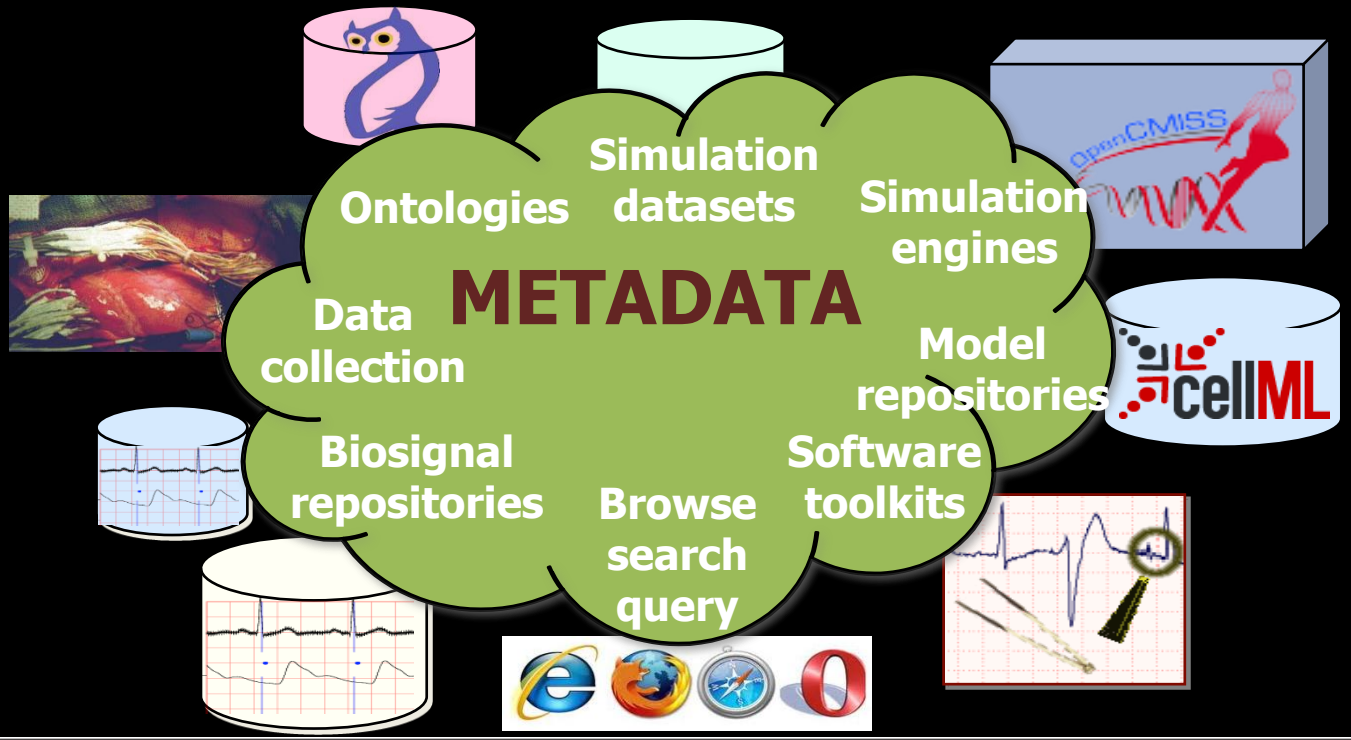
Alan Garny **Run OpenCOR**

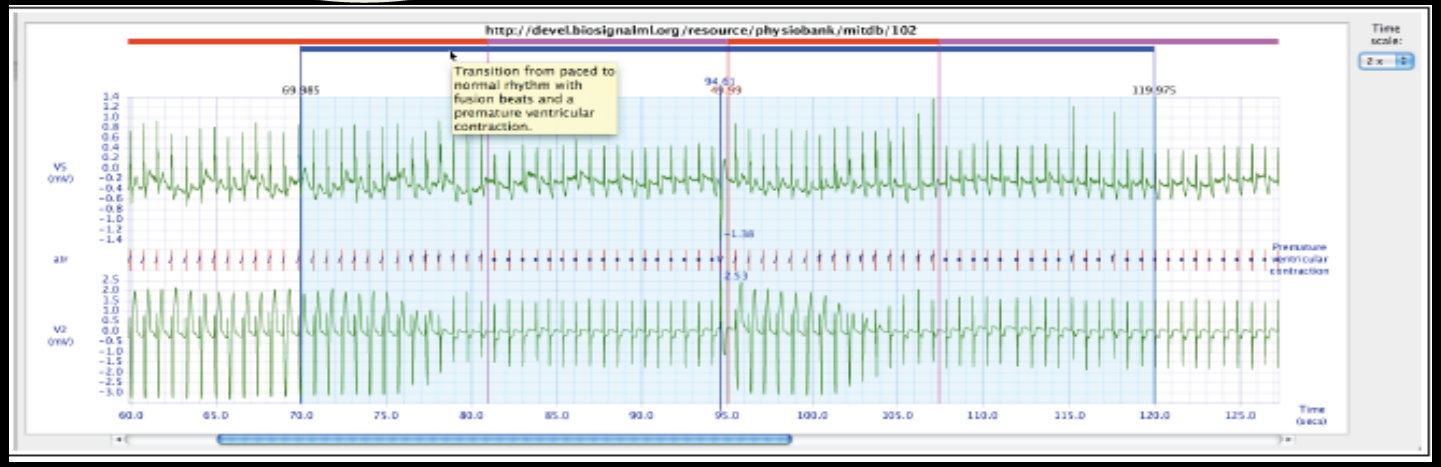
6 month roadmap for OpenCOR

- CellML authoring. This will use the MathML renderer.
- Support for SED-ML (http://sed-ml.org) using Frank Bergmann's API: https://github.com/fbergmann/libSEDML
- Incorporate BioSignalML API
- CellML annotation using composites
- Drag & drop model building

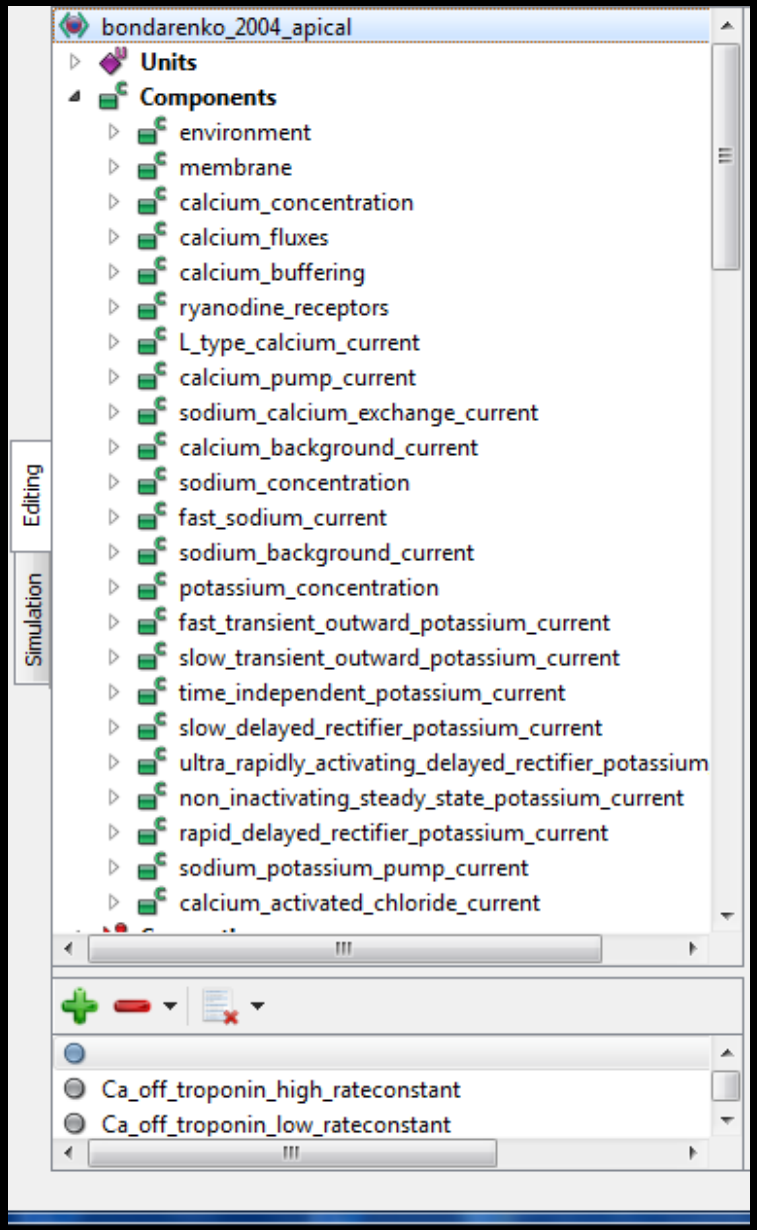
Data standards

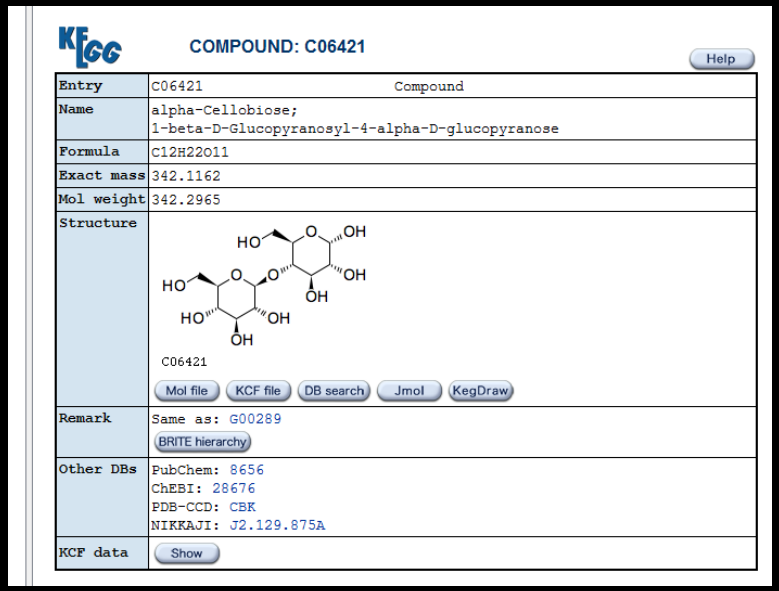
www.BioSignalML.org





Semantic annotation of models





Ontologies:

ChEBI - chemical IDs
GO - cell component
CellType - cells
FMA - anatomy
OPB - biophysics

Annotating CellML models

OpenCOR
- Authoring, curation
- Annotation
- Simulation

OWL knowledge base
Has all reference ontologies.
Chebi - calcium
OPB - concentration
GO (cell cpt) - cytosol
FMA, …
+ units + composites

Ricordo
Reasoning over OWL-KB

SemGen
Reasoning over OWL-KB
→ OPB templates

CellML Model

Metadata (semantics)
Author, publications, etc
Model annotations*

Maths (syntax)
$\frac{dy}{dt} = f(x, ..)$ …

Add new composite & Reclassify
i.e. 'calcium concentration in cytosol' is indexed so x_URI can be found in search

x is *calcium* concentration *in cytosol*
(a property associated with an *entity*)

SparQL queries

MIRIAM

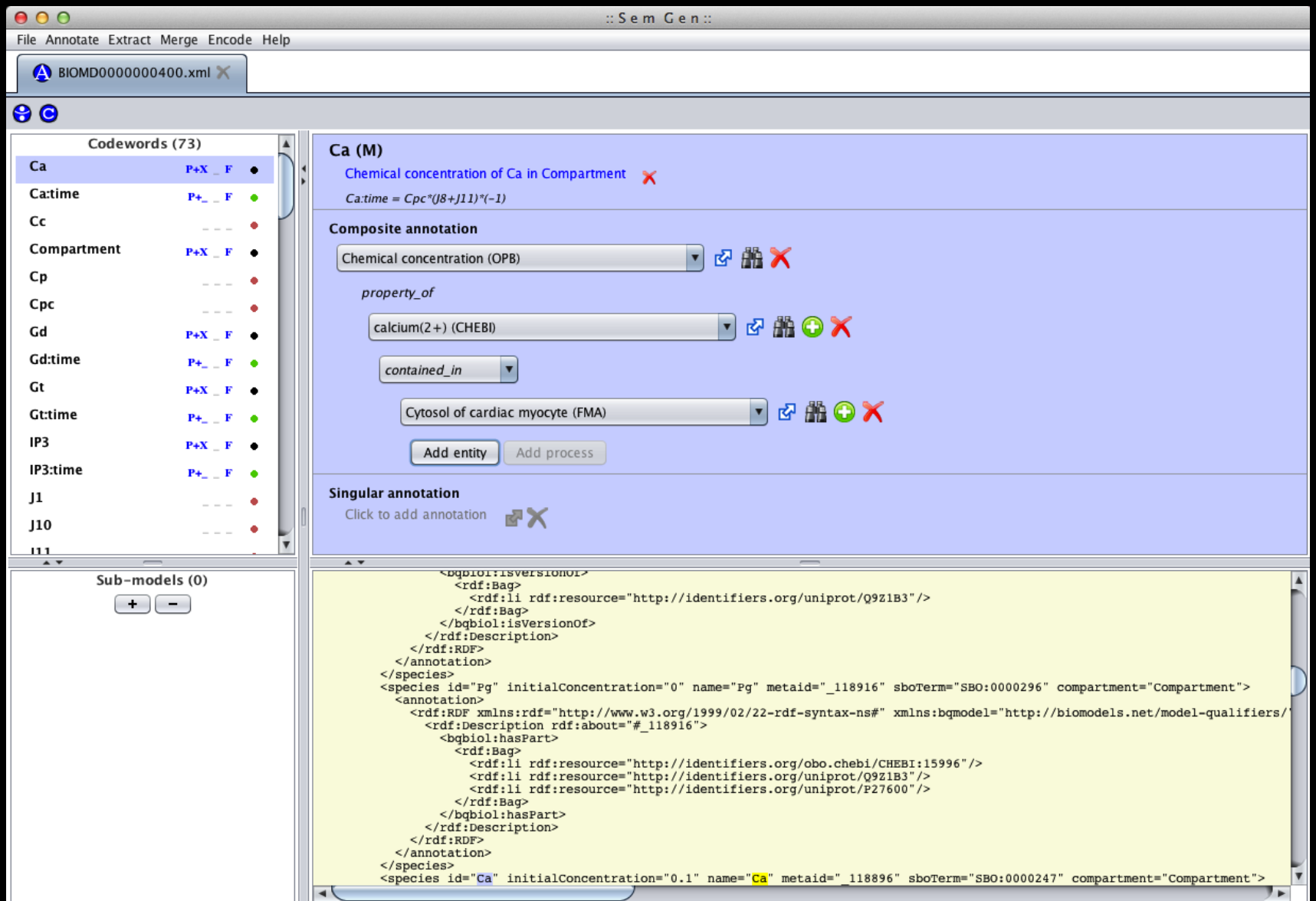
PMR
Mercurial DVS
Imports, provenance

Ricordo RDF Triple store
Stored as RDF triple (3 URIs, one being the relation):
x_URI is_a_computational cpt_for composite_URI

* www.cellml.org/specifications/metadata/mcdraft

Adding Annotations: SemGen

Max Neal



Drag & drop model building

GET: GUI version 3

localhost:9876/get-web/

GET: Generalised Epithelial Transport

Library | Searching

- Small molecules
  - Potassium ion
  - Calcium ion
  - Sodium ion
  - Chloride ion
- Transporters
  - ICaL (TNNP'04)
  - IK1 (TNNP'04)
  - Sodium - glucose cotransporter
  - Sodium pump
  - INa (TNNP'04)
- Whole cell
  - Empty cell

Welcome | New Model...

Some introductory text and documentation might go here one day.

David Nickerson

Created by David Nickerson and Hugh Sorby. Supported by the Virtual Physiological Rat Project, NIH Grant [P50-GM094503]

GET: GUI version 3

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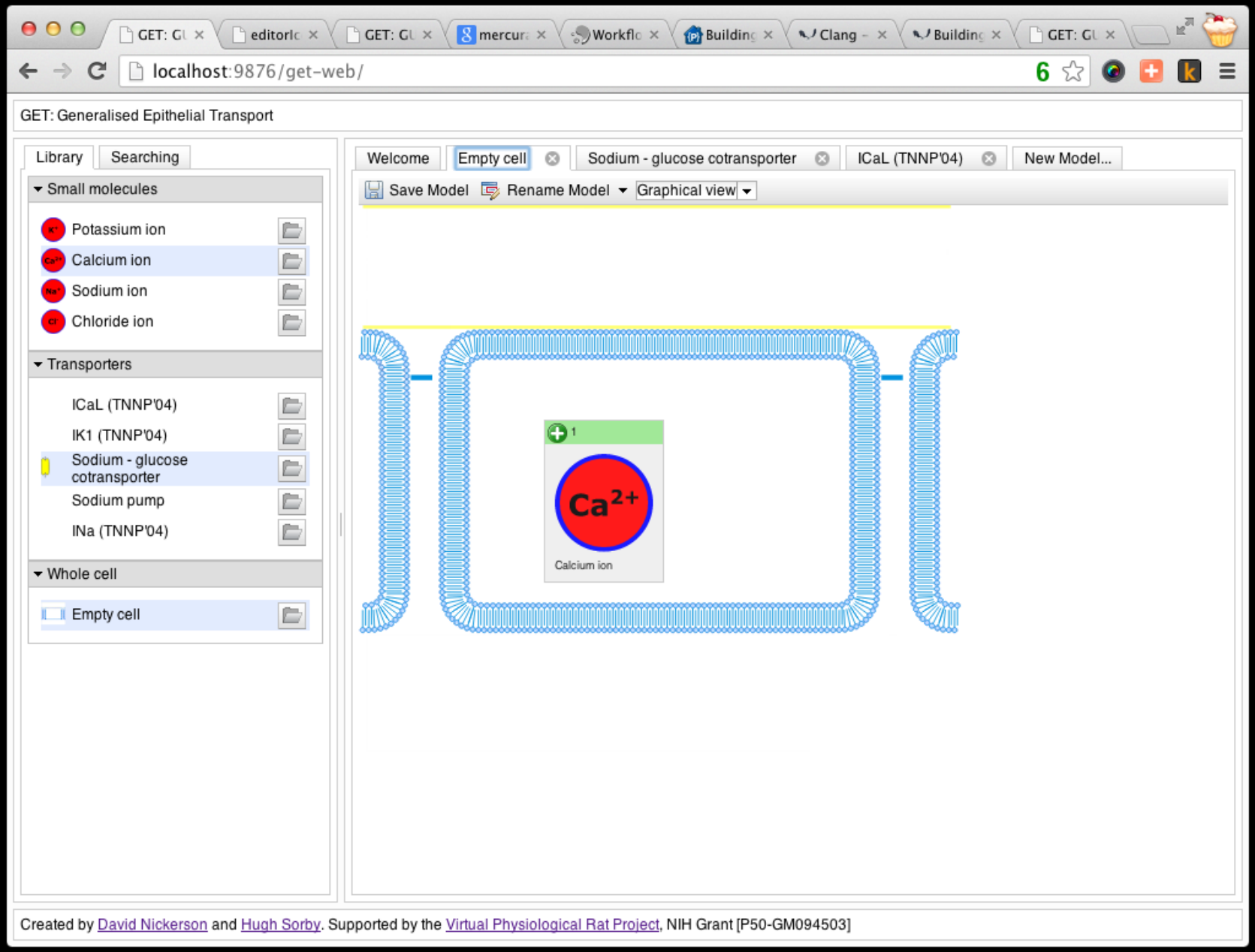
Whole cell
- Empty cell

Welcome | ICaL (TNNP'04) | Empty cell | Sodium - glucose cotransporter | New Model...

Save Model | Rename Model | Graphical view

Created by David Nickerson and Hugh Sorby. Supported by the Virtual Physiological Rat Project, NIH Grant [P50-GM094503]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Graphical view
1
Ca2+
Calcium ion
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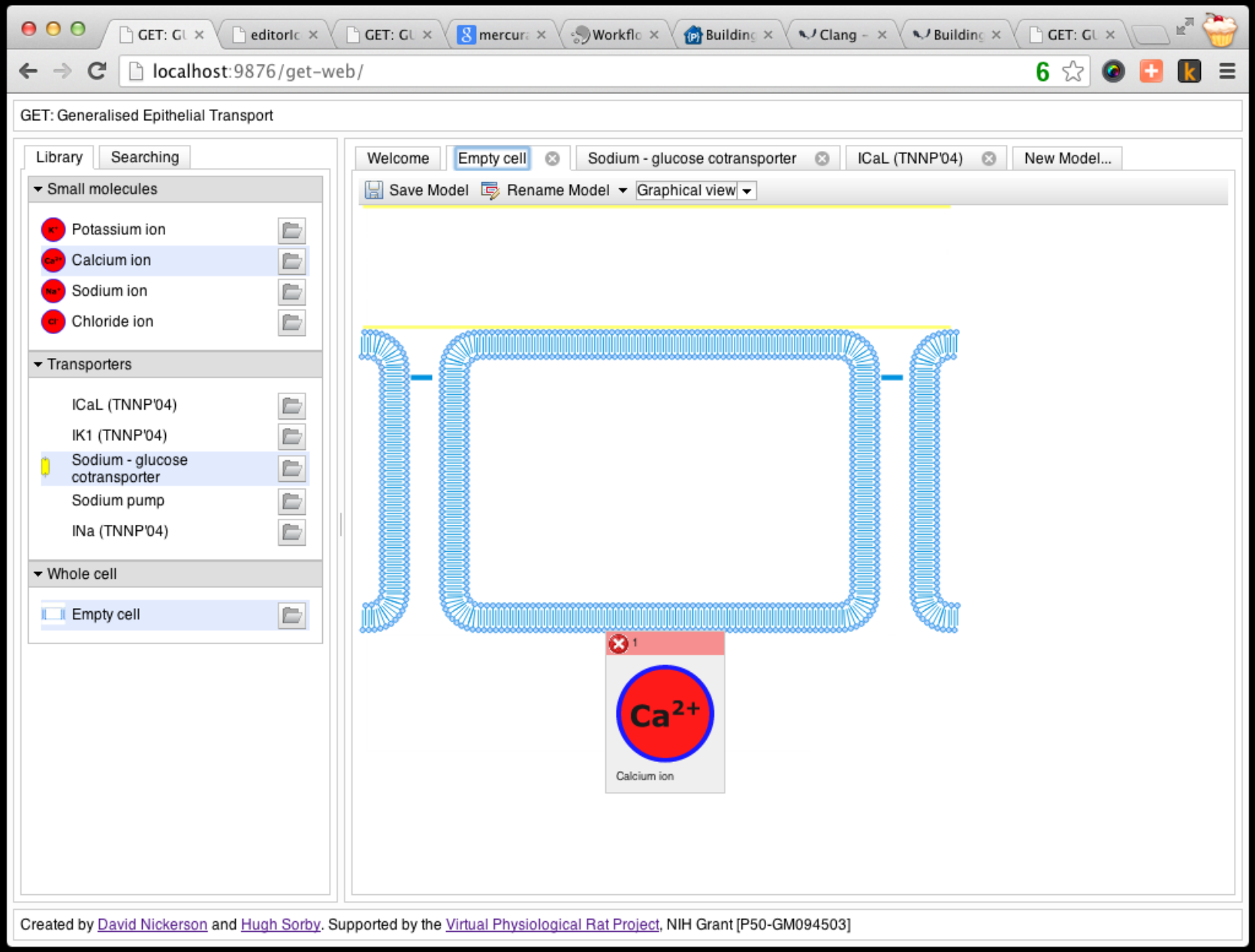
GET: G
editorIc
GET: G
mercur
Workflc
Buildinc
Clang -
Buildinc
GET: G
localhost:9876/get-web/
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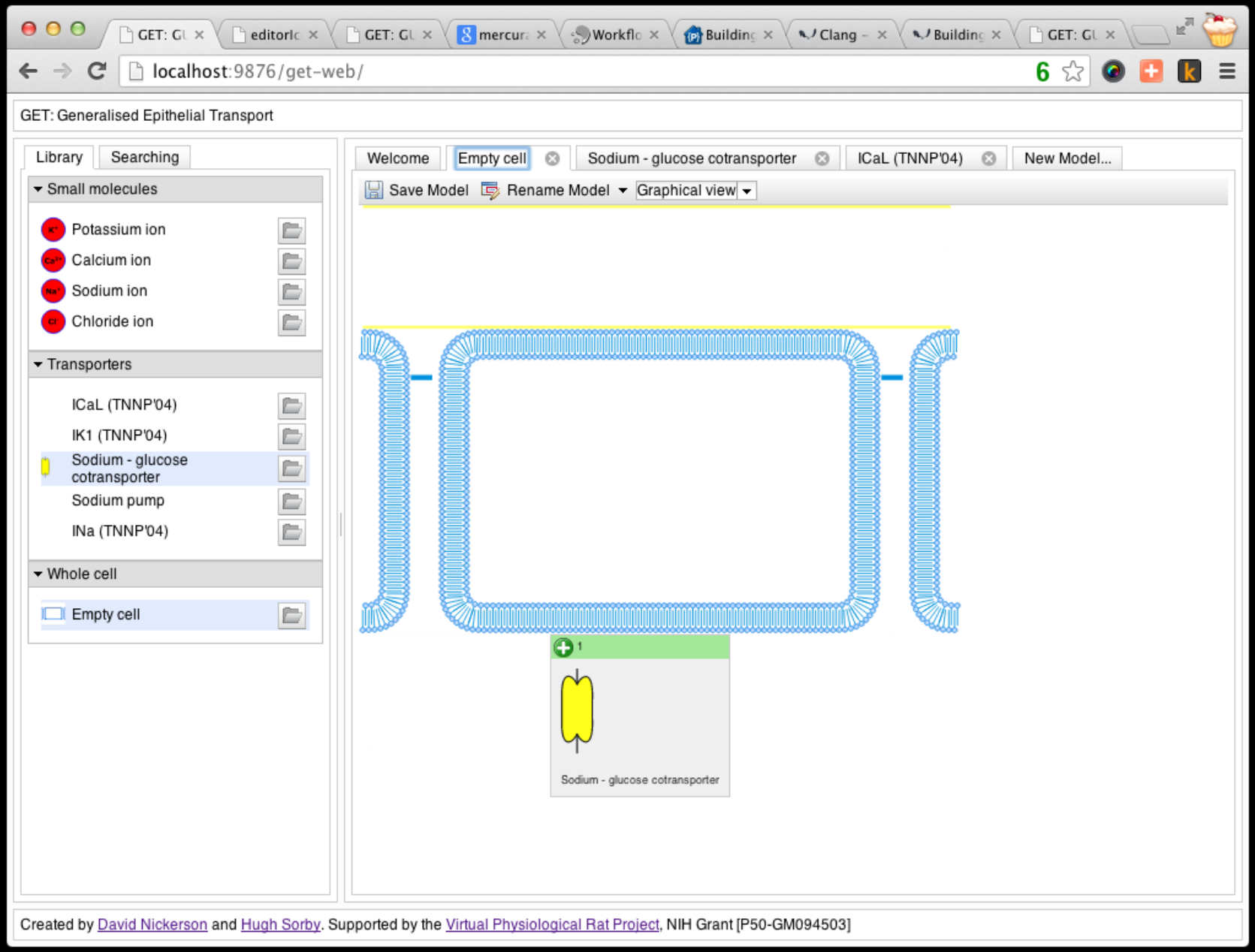
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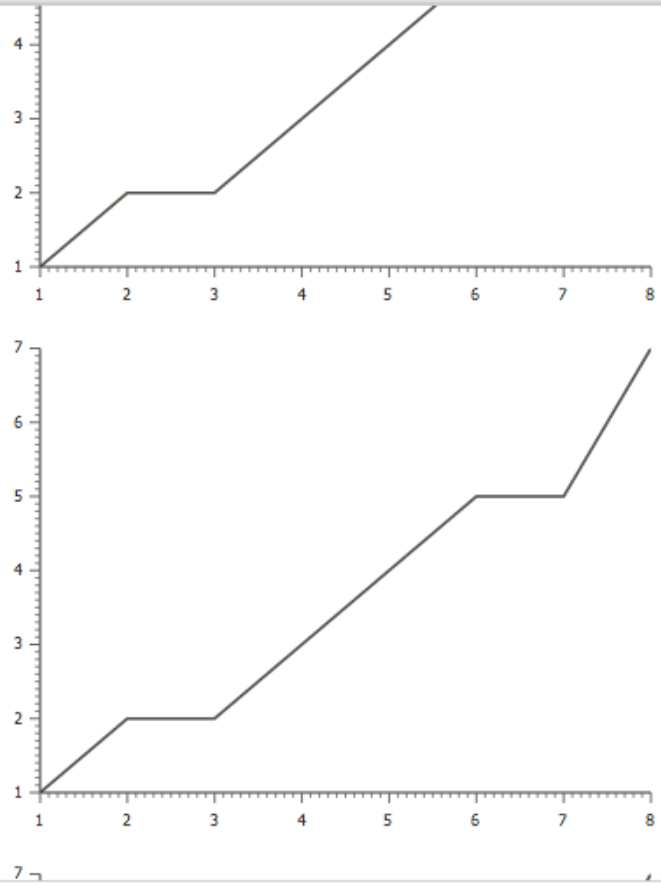
  - Empty cell

Welcome | ICaL (TNNP'04) | Empty cell | Sodium - glucose cotransporter | New Model...

Save Model | Rename Model | Simulation view

Protocols
Generic current-voltage
Calcium clamp
Voltage clamp



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