Semantic annotation in the Physiome Model Repository

David Nickerson

Auckland Bioengineering Institute

Auckland, New Zealand

COMBINE 2019

https://doi.org/10.17608/k6.auckland.8858654

Physiome Model Repository

- https://models.physiomeproject.org
- Over 800 public workspaces
  - Each independently version controlled
  - Persistent releases of specific versions (exposure)
  - Many different types of biology and mathematics
  - Proteins through to whole organ and larger scale
- Historically CellML (+SED-ML) models
- Modularity and reuse
- Consistency between browser and tool integration
  - content type negotiation
  - REST

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PMR Semantics

- User indicates the resources they would like indexed
  - Within a workspace (~COMBINE archive)
  - Some smarts in extracting RDF from CellML models
  - Various RDF serialization formats supported
- Versioning
  - Workspace – latest version
  - Exposures
- SPARQL endpoint
  - Read-only
  - Permissions filter

https://doi.org/10.17608/k6.auckland.8858654

Why do we annotate?

- Comprehension

https://doi.org/10.17608/k6.auckland.8858654

Models Home | My Workspaces | Exposures | Documentation

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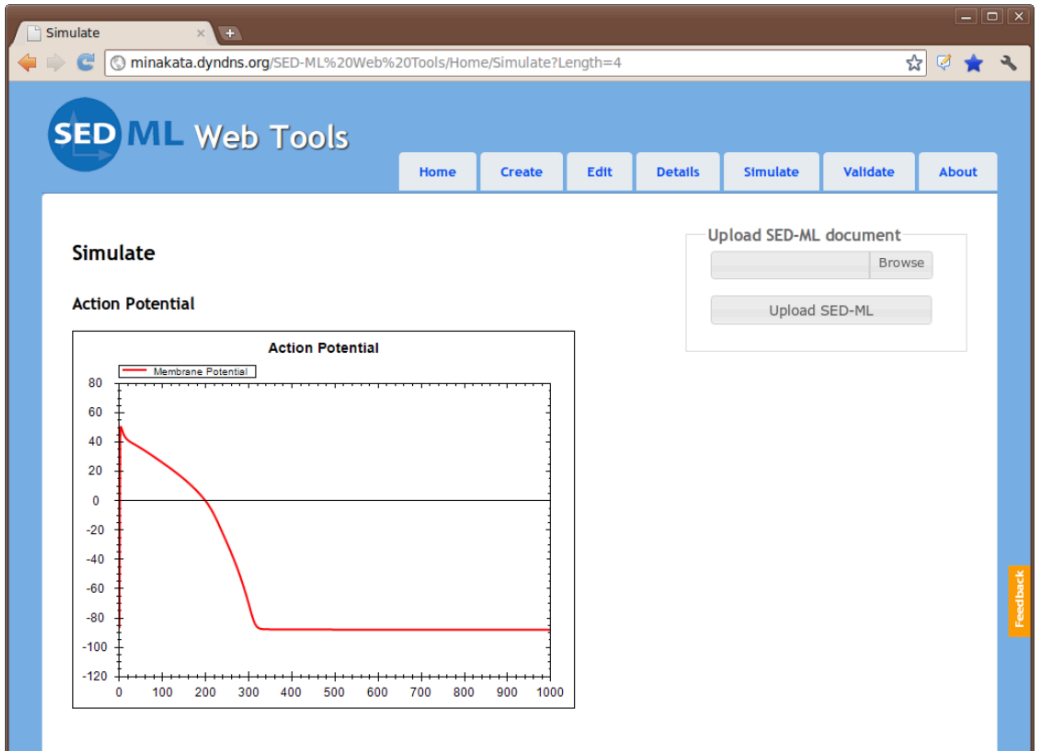
Contents | View | Wizard | Sharing — State: Published

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.



$$\frac{d}{d\,time}(CaMKt) = aCaMK\ CaMKb\ (CaMKb + CaMKt) - (bCaMK\ CaMKt)$$

Component: intracellular_ions

$$cmdnmax = \begin{cases} cmdnmax\_b1.3 \text{ if } celltype = 1 \\ cmdnmax\_b \text{ otherwise} \end{cases}$$

$$\frac{d}{d\,time}(nai) = \frac{(-(INa+INaL+3INaCa\_i+3INaK+INab))\ Acap\ cm}{F\ vmyo} + \ldots$$

$$\frac{d}{d\,time}(nass) = \frac{(-(ICaNa+3INaCa\_ss))\ cm\ Acap}{F\ vss} - JdiffNa$$

$$\frac{d}{d\,time}(ki) = \frac{(-(Ito+IKr+IKs+IK1+IKb+Istim-(2\ INaK)))\ cm\ Acap}{F\ vmyo}$$

$$\frac{d}{d\,time}(cai) = Bcai\left(\left(\frac{(-(IpCa+ICab-(2INaCa\_i)))\ cm\ Acap}{2F\ vmyo}\right.\right.$$

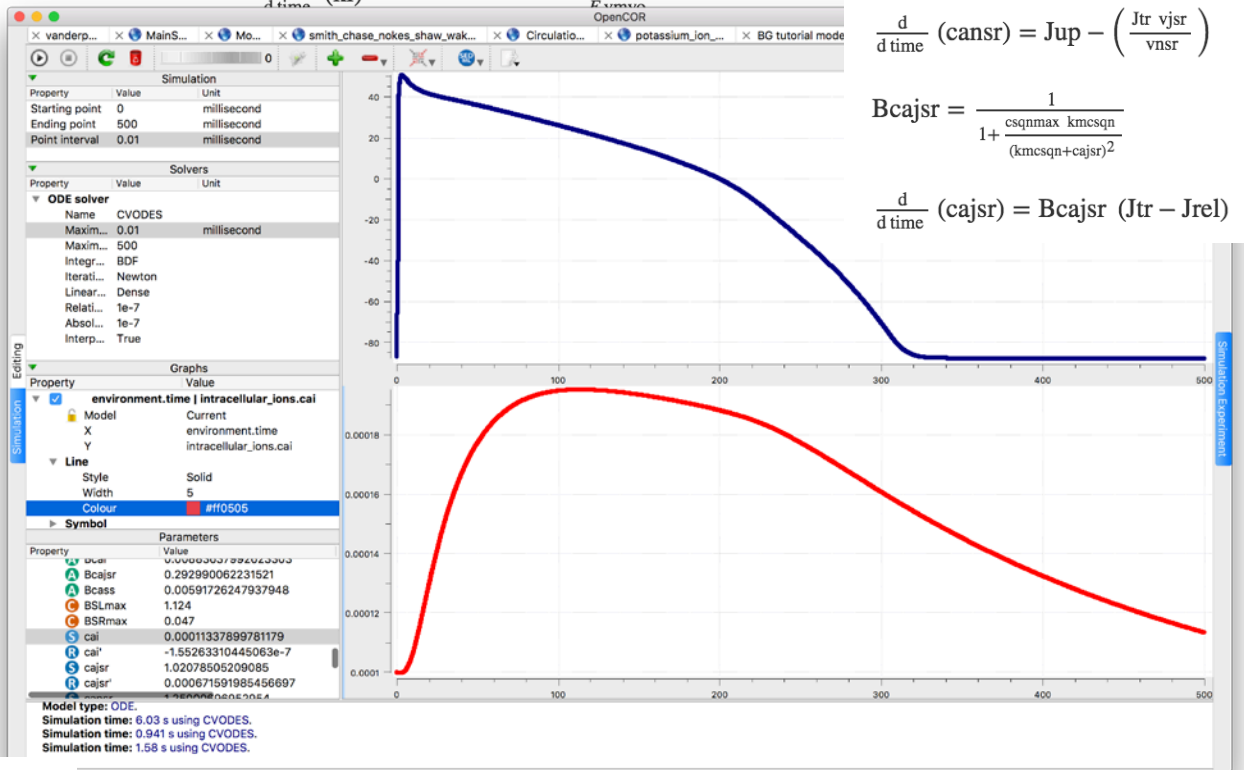
$$Bcass = \frac{1}{1+\frac{BSRmax\ KmBSR}{(KmBSR+cass)^2}+\frac{BSLmax\ KmBSL}{(KmBSL+cass)^2}}$$

$$\frac{d}{d\,time}(cass) = Bcass\left(\frac{(-(ICaL-(2INaCa\_ss)))\ cm\ Acap}{2F\ vss} + \ldots\right.$$

$$\frac{d}{d\,time}(cansr) = Jup - \left(\frac{Jtr\ vjsr}{vnsr}\right)$$

$$Bcajsr = \frac{1}{1+\frac{csqnmax\ kmcsqn}{(kmcsqn+cajsr)^2}}$$

$$\frac{d}{d\,time}(cajsr) = Bcajsr\ (Jtr - Jrel)$$



https://models.physiomeproject.org/e/71

https://doi.org/10.17608/k6.auckland.8858654

Generated Code

The following is matlab code generated by the CellML API from this CellML file. (Back to language selection)

The raw code is available.

```
function [RATES, ALGEBRAIC] = computeRates(VOI, STATES, CONSTANTS)
    global algebraicVariableCount;
    statesSize = size(STATES);
    statesColumnCount = statesSize(2);
    if ( statesColumnCount == 1)
        STATES = STATES';
        ALGEBRAIC = zeros(1, algebraicVariableCount);
    else
        statesRowCount = statesSize(1);
        ALGEBRAIC = zeros(statesRowCount, algebraicVariableCount);
        RATES = zeros(statesRowCount, statesColumnCount);
    end
    ALGEBRAIC(:,3) = 1.00000./(1.00000+exp((STATES(:,1)+87.6100)./7.48800));
    RATES(:,18) = (ALGEBRAIC(:,3) - STATES(:,18))./CONSTANTS(:,44);
    ALGEBRAIC(:,4) = 1.00000./(1.00000+exp((STATES(:,1)+93.8100)./7.48800));
    RATES(:,19) = (ALGEBRAIC(:,4) - STATES(:,19))./CONSTANTS(:,96);
    ALGEBRAIC(:,1) = 1.00000./(1.00000+exp( - (STATES(:,1)+CONSTANTS(:,32))./CONSTANTS(:,33)));
    ALGEBRAIC(:,14) = 1.00000./( CONSTANTS(:,36).*exp((STATES(:,1)+CONSTANTS(:,34))./CONSTANTS(:,35))+ CONSTANTS
(:,37).*exp( - (STATES(:,1)+CONSTANTS(:,38))./CONSTANTS(:,39)));
    RATES(:,11) = (ALGEBRAIC(:,1) - STATES(:,11))./ALGEBRAIC(:,14);
    ALGEBRAIC(:,2) = 1.00000./(1.00000+exp((STATES(:,1)+CONSTANTS(:,40))./CONSTANTS(:,41)));
    ALGEBRAIC(:,15) = 1.00000./( 1.43200e-05.*exp( - (STATES(:,1)+1.19600)./6.28500)+ 6.14900.*exp((STATES(:,1)+
0.509600)./20.2700));
    RATES(:,12) = (ALGEBRAIC(:,2) - STATES(:,12))./ALGEBRAIC(:,15);
    ALGEBRAIC(:,16) = 1.00000./( 0.00979400.*exp( - (STATES(:,1)+17.9500)./28.0500)+ 0.334300.*exp((STATES(:,1)+
5.73000)./56.6600));
    RATES(:,13) = (ALGEBRAIC(:,2) - STATES(:,13))./ALGEBRAIC(:,16);
    ALGEBRAIC(:,5) = 1.00000./(1.00000+exp( - (STATES(:,1) - 14.3400)./14.8200));
    ALGEBRAIC(:,18) = 1.05150./(1.00000./( 1.20890.*(1.00000+exp( - (STATES(:,1) - 18.4099)./29.3814)))+3.50000./
(1.00000+exp((STATES(:,1)+100.000)./29.3814)));
    RATES(:,20) = (ALGEBRAIC(:,5) - STATES(:,20))./ALGEBRAIC(:,18);
    ALGEBRAIC(:,7) = 1.00000./(1.00000+exp( - (STATES(:,1)+3.94000)./4.23000));
```

Source

Derived from workspace An encoding of the human ORd model by Steve Neiderer at changeset 2593df010620.

Collaboration

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

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

Downloads

Download This File

Complete Archive as .tgz

Views Available

Documentation

Model Metadata

Mathematics

Generated Code

Cite this model

Source View

Launch with OpenCOR

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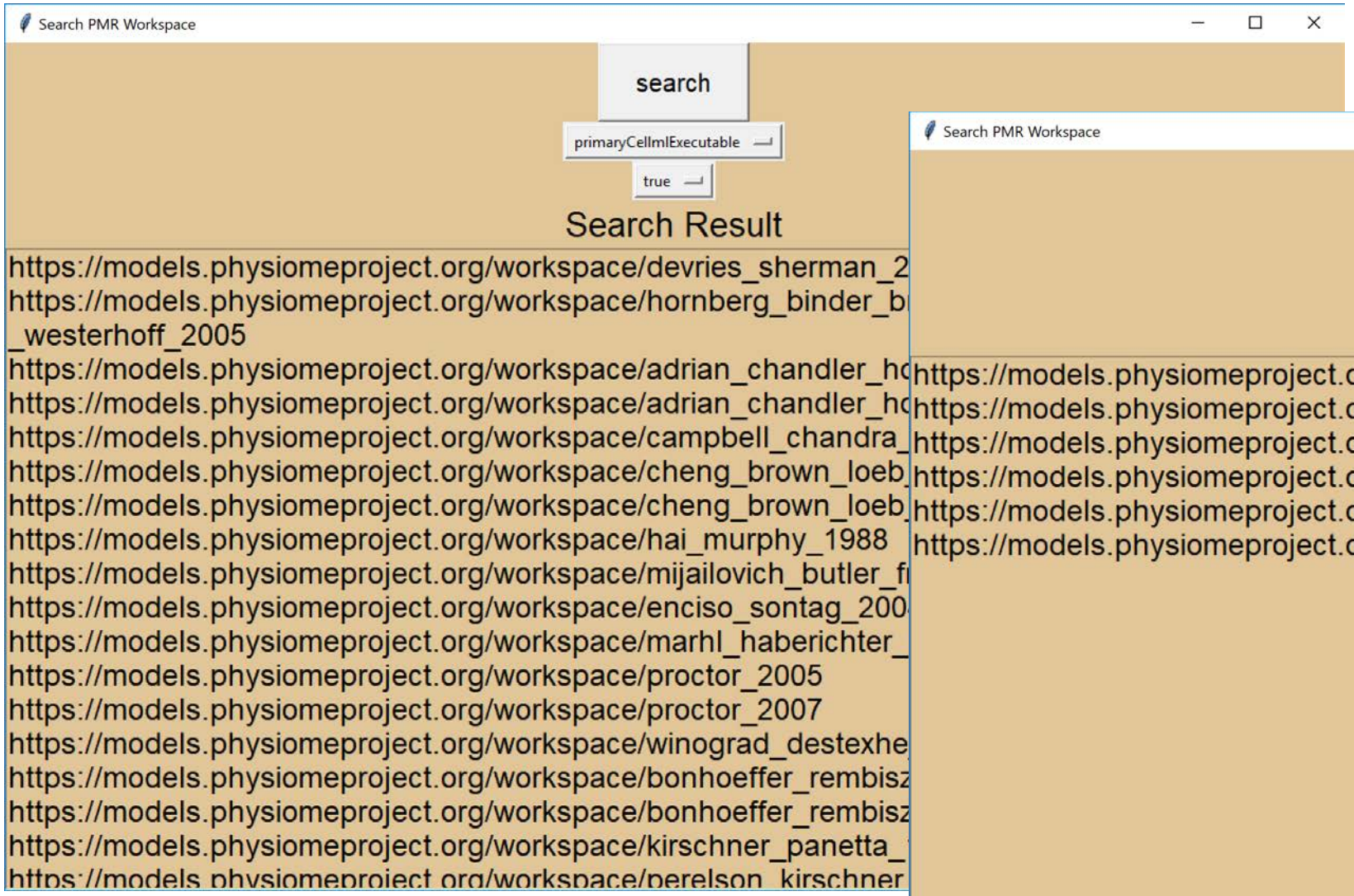
License

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


Search PMR Workspace
search
primaryCellmlExecutable
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Search Result
https://models.physiomeproject.org/workspace/devries_sherman_2
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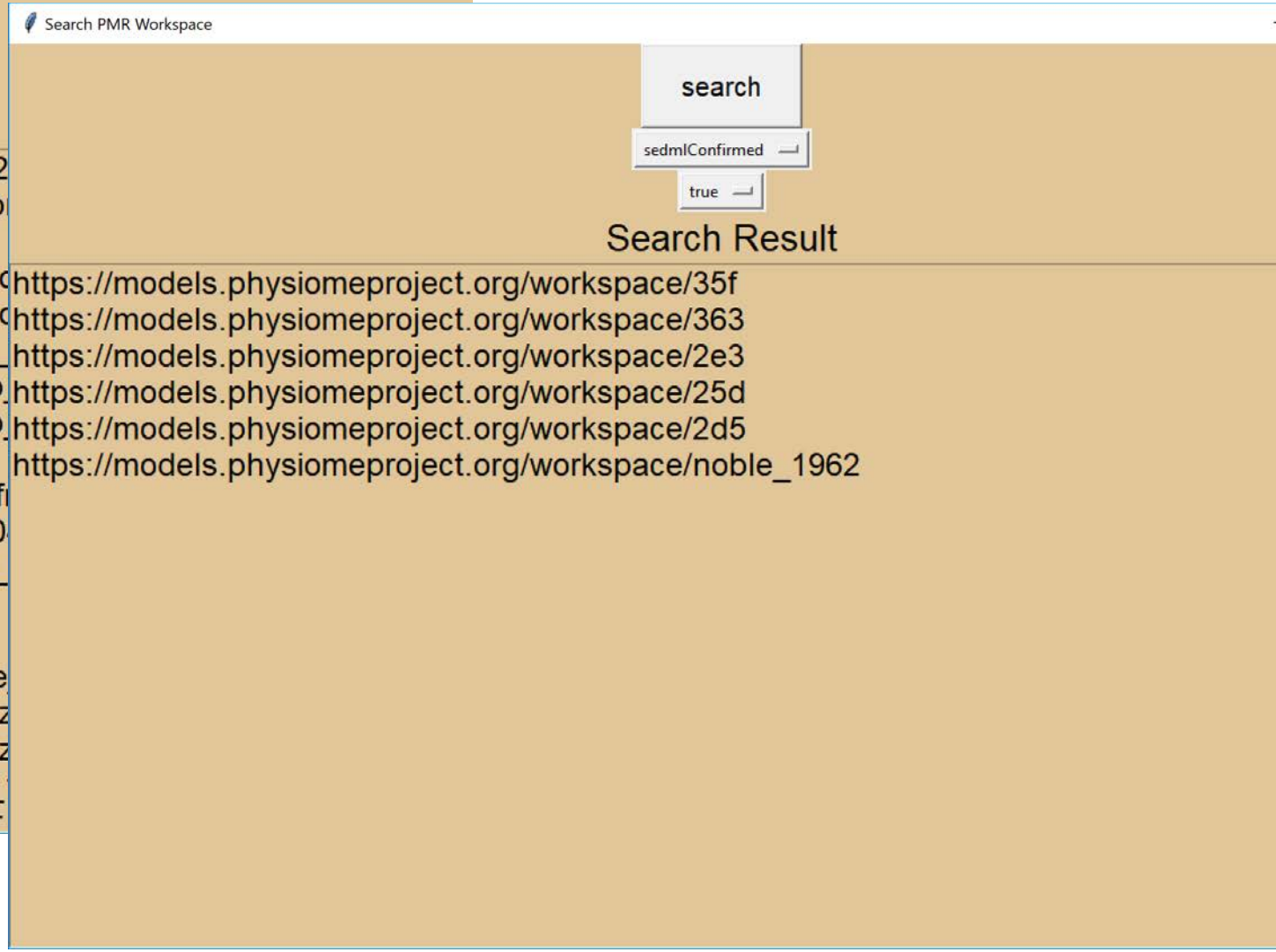
Search PMR Workspace
search
sedmlConfirmed
true
Search Result
https://models.physiomeproject.org/workspace/35f
https://models.physiomeproject.org/workspace/363
https://models.physiomeproject.org/workspace/2e3
https://models.physiomeproject.org/workspace/25d
https://models.physiomeproject.org/workspace/2d5
https://models.physiomeproject.org/workspace/noble_1962

Why do we annotate?

- Comprehension
- Modularity and reuse

https://doi.org/10.17608/k6.auckland.8858654

The Journal of Physiology

J Physiol 000.0 (2016) pp 1–15

WHITE PAPER

Modular modelling with Physiome standards

Michael T. Cooling[1], David P. Nickerson[1], Poul M. F. Nielsen[1,2] and Peter J. Hunter[1]

[1]Auckland Bioengineering Institute, the University of Auckland, New Zealand
[2]Department of Engineering Science, the University of Auckland, New Zealand

Key points

- The complexity of computational models is increasing, supported by research in modelling tools and frameworks. But relatively little thought has gone into design principles for complex models.
- We propose a set of design principles for complex model construction with the Physiome standard modelling protocol CellML.
- By following the principles, models are generated that are extensible and are themselves suitable for reuse in larger models of increasing complexity.
- We illustrate these principles with examples including an architectural prototype linking, for the first time, electrophysiology, thermodynamically compliant metabolism, signal transduction, gene regulation and synthetic biology.
- The design principles complement other Physiome research projects, facilitating the application of virtual experiment protocols and model analysis techniques to assist the modelling community in creating libraries of composable, characterised and simulatable quantitative

OPEN ACCESS Freely available online

PLOS | COMPUTATIONAL BIOLOGY

Perspective

A Reappraisal of How to Build Modular, Reusable Models of Biological Systems

Maxwell L. Neal[1]*, Michael T. Cooling[2], Lucian P. Smith[1], Christopher T. Thompson[3], Herbert M. Sauro[1], Brian E. Carlson[4], Daniel L. Cook[5], John H. Gennari[6]

1 Department of Bioengineering, University of Washington, Seattle, Washington, United States of America, **2** Auckland Bioengineering Institute, University of Auckland, Auckland, New Zealand, **3** Department of Physiology, Medical College of Wisconsin, Milwaukee, Wisconsin, United States of America, **4** Department of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, Michigan, United States of America, **5** Department of Physiology and Biophysics, University of Washington, Seattle, Washington, United States of America, **6** Department of Biomedical Informatics and Medical Education, University of Washington, Seattle, Washington, United States of America

PLOS | ONE

RESEARCH ARTICLE

Semantics-Based Composition of Integrated Cardiomyocyte Models Motivated by Real-World Use Cases

Maxwell L. Neal[1]*, Brian E. Carlson[2], Christopher T. Thompson[2], Ryan C. James[1], Karam G. Kim[1], Kenneth Tran[3], Edmund J. Crampin[4,5,6,7], Daniel L. Cook[8], John H. Gennari[1]

1 Department of Biomedical Informatics and Medical Education, University of Washington, Seattle, Washington, United States of America, **2** Department of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, MI, United States of America, **3** Auckland Bioengineering Institute, The University of Auckland, Auckland, New Zealand, **4** Systems Biology Laboratory, Melbourne School of Engineering, University of Melbourne, Victoria, Australia, **5** ARC Centre of Excellence in Convergent Bio-Nano Science and Technology, Melbourne School of Engineering, University of Melbourne, Victoria, Australia, **6** School of Mathematics and Statistics, University of Melbourne, Victoria, Australia, **7** School of Medicine, University of Melbourne, Victoria, Australia, **8** Department of Physiology and Biophysics, University of Washington, Seattle, WA, United States of America

Bioinformatics, 2018, 1–3
doi: 10.1093/bioinformatics/bty829
Advance Access Publication Date: 26 September 2018
Applications Note

OXFORD

Systems biology

SemGen: a tool for semantics-based annotation and composition of biosimulation models

Maxwell L. Neal [1,*], Christopher T. Thompson[2], Karam G. Kim [3], Ryan C. James[3], Daniel L. Cook[3], Brian E. Carlson [2] and John H. Gennari [3]

[1]Seattle Children's Research Institute, Center for Global Infectious Disease Research, Seattle, WA 98109, USA, [2]Department of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, MI 48109, USA and [3]Department of Biomedical Informatics and Medical Education, University of Washington, Seattle, WA 98195, USA

*To whom correspondence should be addressed.

Associate Editor: Jonathan Wren

Received on April 16, 2018; revised on September 9, 2018; editorial decision on September 19, 2018; accepted on September 24, 2018

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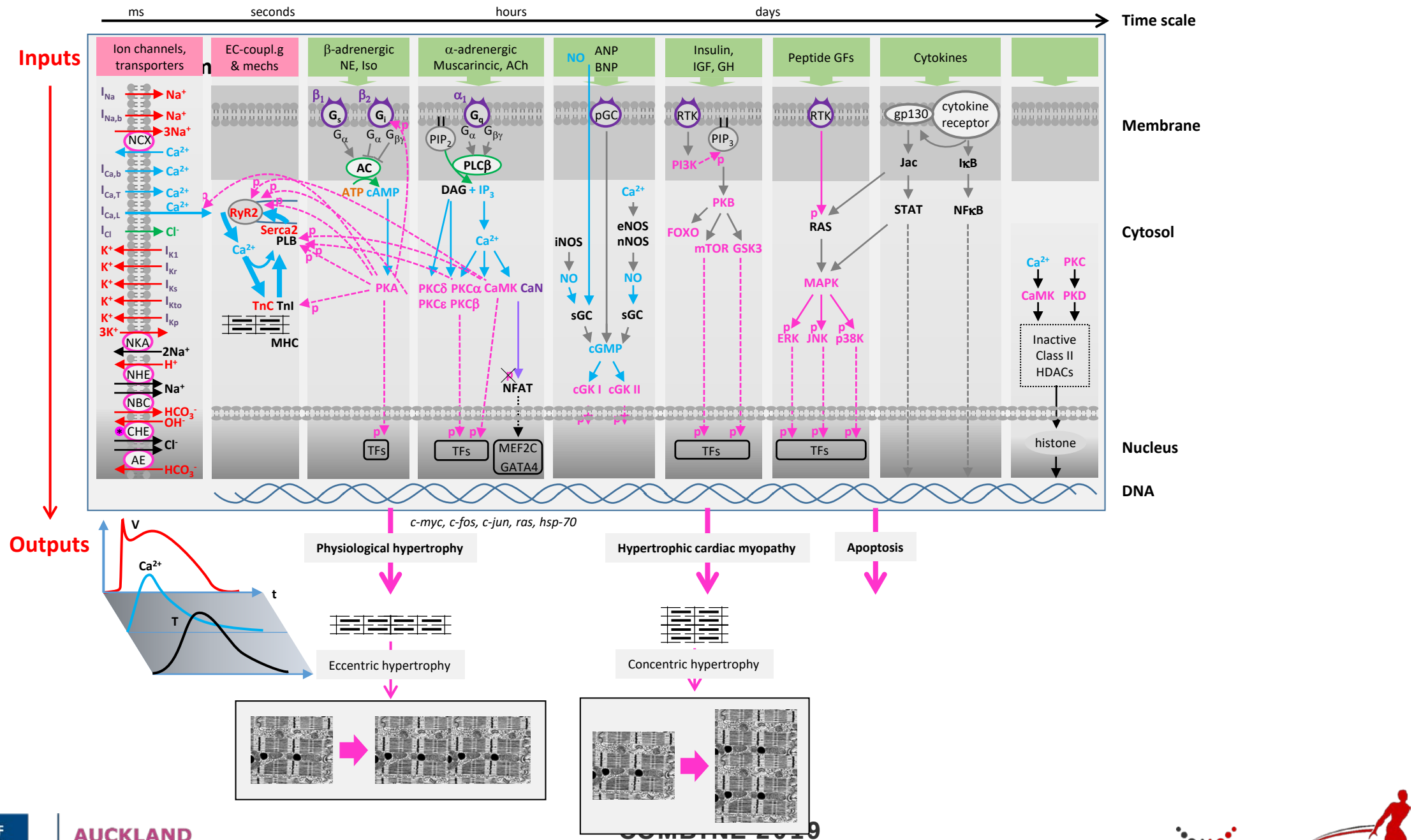
6.auckland.8858654

cellML



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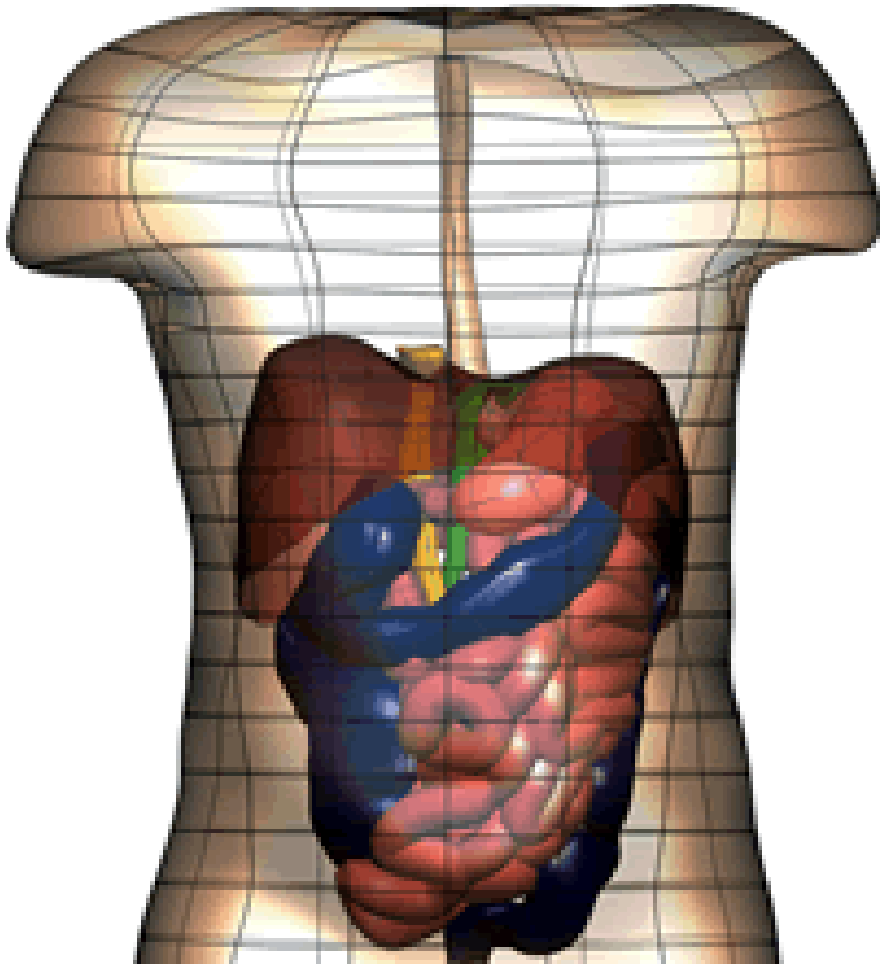

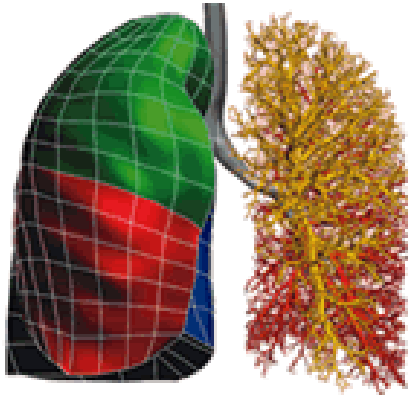

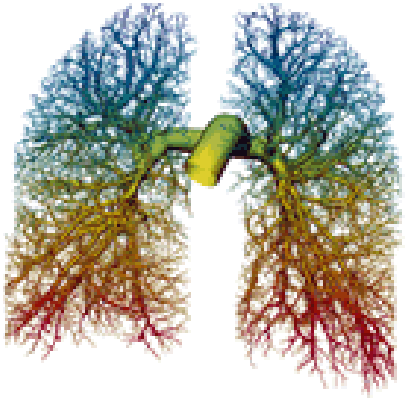

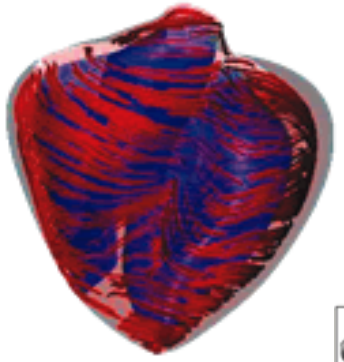

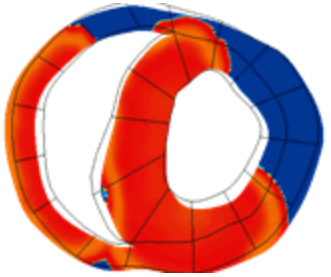

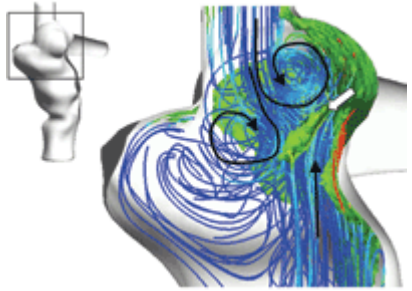

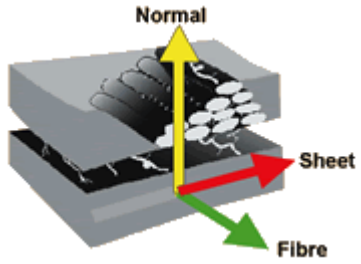

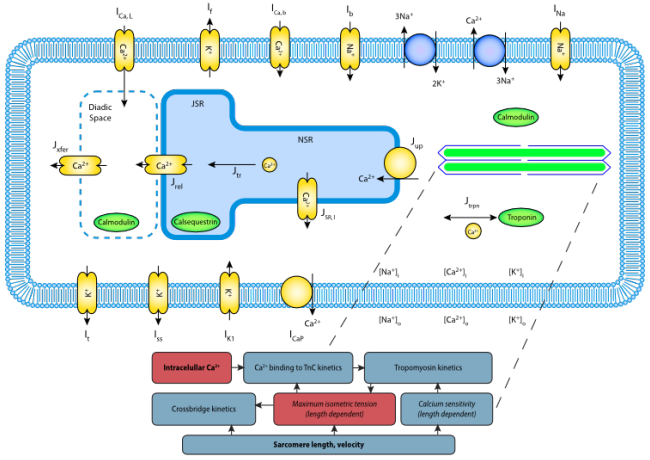

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cellML

Why do we annotate?

- Comprehension
- Modularity and reuse
- Search

Model Annotation and Discovery with the Physiome Model Repository

Dewan M. Sarwar [1], Reza Kalbasi [1], John H. Gennari [2], Brian E. Carlson [3], Maxwell L. Neal [4], Bernard de Bono [1], Koray Atalag [1], Peter J. Hunter [1] and David P. Nickerson [1,*]

[1] Auckland Bioengineering Institute, University of Auckland, Auckland, New Zealand
[2] Department of Biomedical Informatics and Medical Education, University of Washington, Seattle, Washington, USA
[3] Molecular & Integrative Physiology, University of Michigan, Ann Arbor, Michigan, USA and
[4] Center for Global Infectious Disease Research, Seattle Children's Research Institute, Seattle, Washington, USA

https://github.com/dewancse/model-discovery-tool

Recommender System

sodium/hydrogen exchanger 3 is a **Kidney** model. It is located in **proximal convoluted tubule, epithelial cell of proximal tubule, apical plasma membrane.**

Model: weinstein_1995.cellml#NHE3.J_NHE3_Na
Biological Meaning: Flux of Na+ from luminal to cytosol through apical plasma membrane

Species: Rattus norvegicus

Gene: Slc9a3

Protein: sodium/hydrogen exchanger 3

Recommendations/suggestions based on existing models in PMR

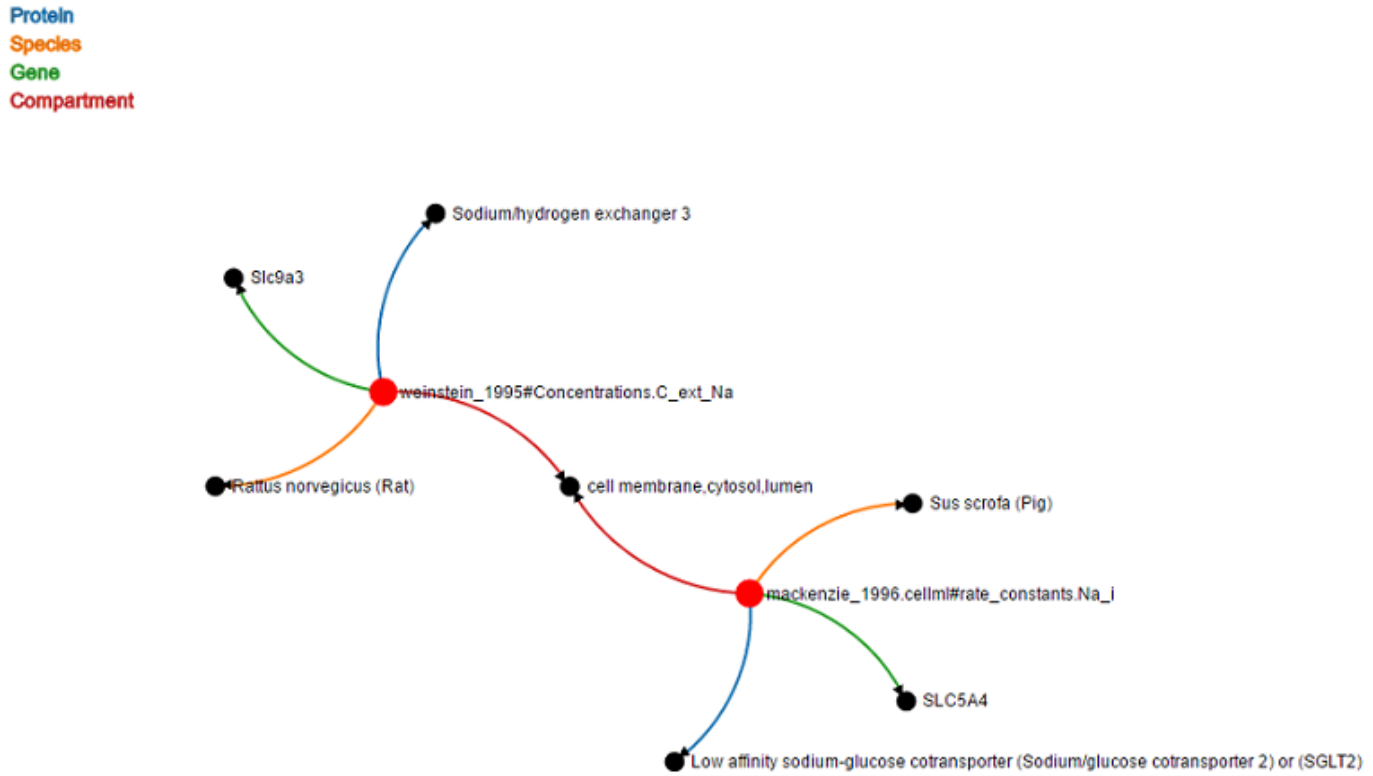
Basolateral membrane model

- sodium/hydrogen exchanger 3 (human)
- low affinity sodium-glucose cotransporter (mouse)
- sodium/potassium-transporting ATPase subunit alpha-1 (rat)

Alternative model of sodium/hydrogen exchanger 3
Not Exist

Kidney model in PMR
sodium/hydrogen exchanger 3 (human)
low affinity sodium-glucose cotransporter (mouse)
sodium/glucose cotransporter 1 (human)

Close Save




```
Identity Matrix:  #
#
#  Percent Identity  Matrix - created by Clustal2.1
#
#

     1: sp|Q9ET37|S5A4A_MOUSE  100.00   22.86   17.86   21.86
     2: sp|P48764|SL9A3_HUMAN   22.86  100.00   19.15   89.49
     3: sp|P06685|AT1A1_RAT     17.86   19.15  100.00   18.20
     4: sp|P26433|SL9A3_RAT     21.86   89.49   18.20  100.00
```

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Why do we annotate?

- Comprehension
- Modularity and reuse
- Search
- Do cool stuff

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Machine Learning

- Add something about how cool ML is and why we should be using it.
- Insert latest buzz word here.
- TensorFlow.
- ICSB tutorial.
- How does this relate to annotation?

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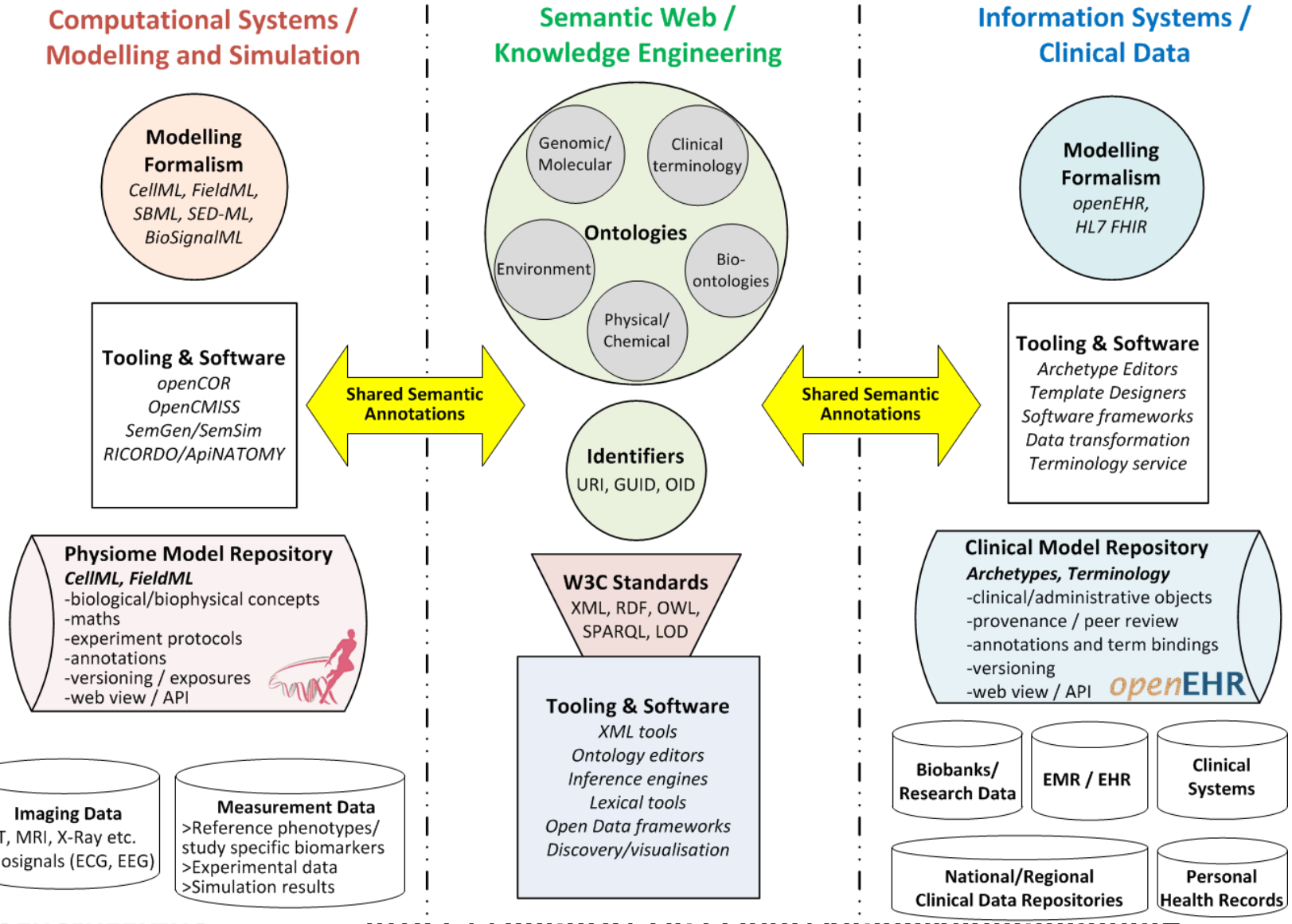
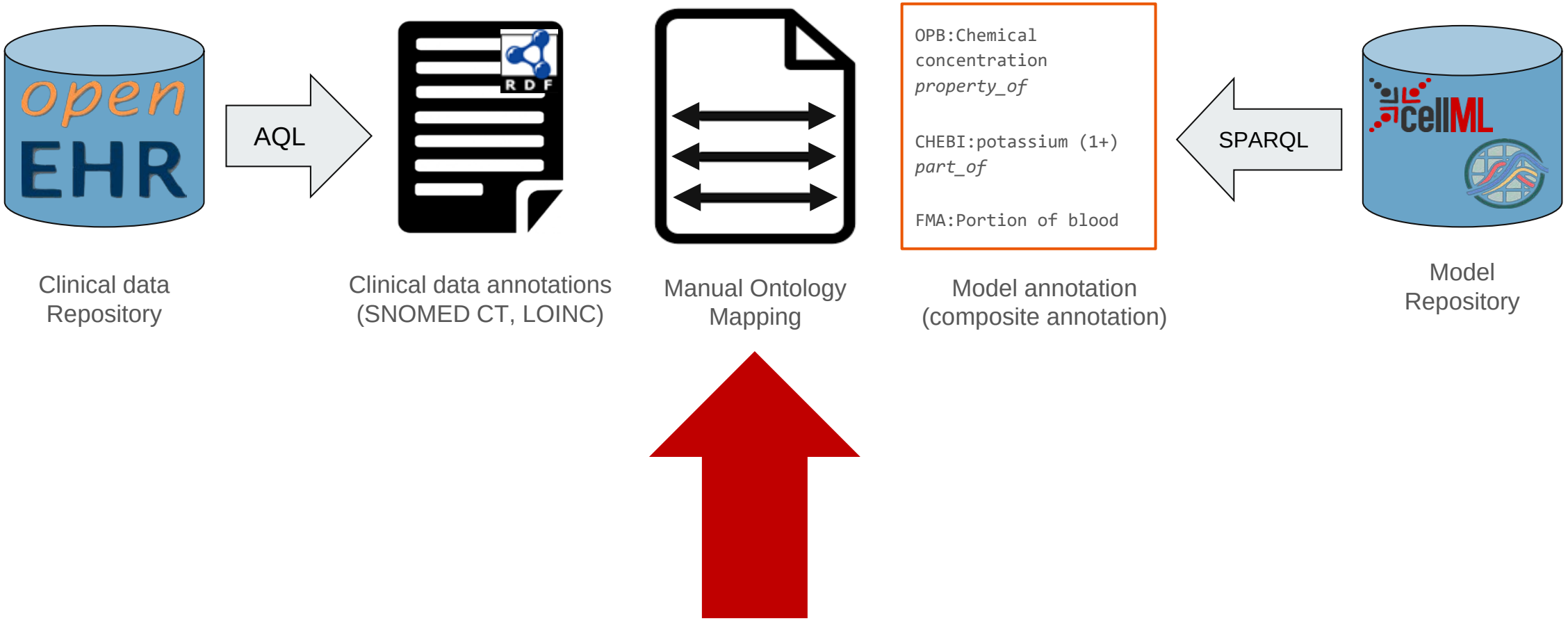
Link to (clinical) data





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Epithelial Modelling Platform

https://github.com/dewancse/epithelial-modelling-platform

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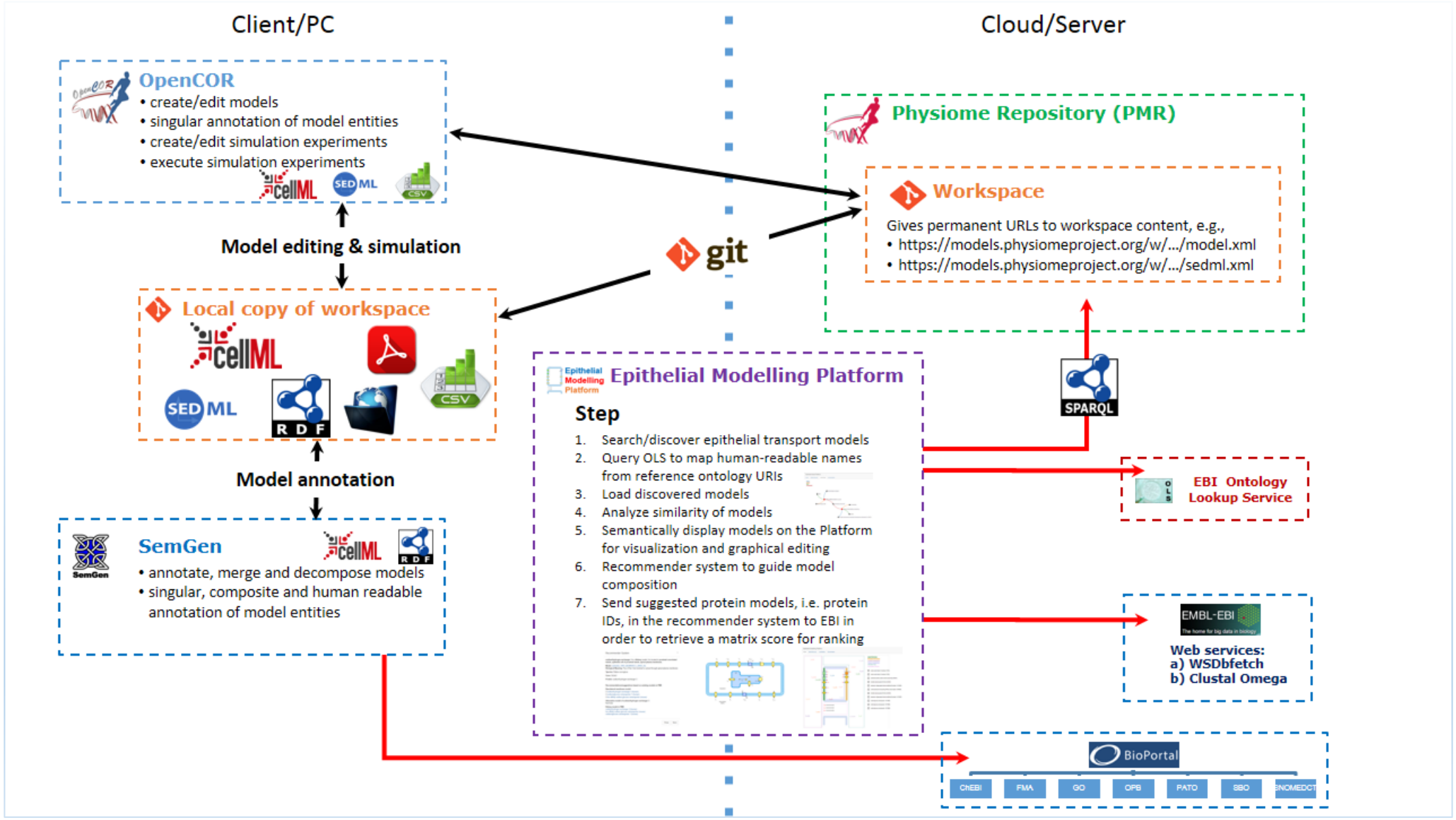

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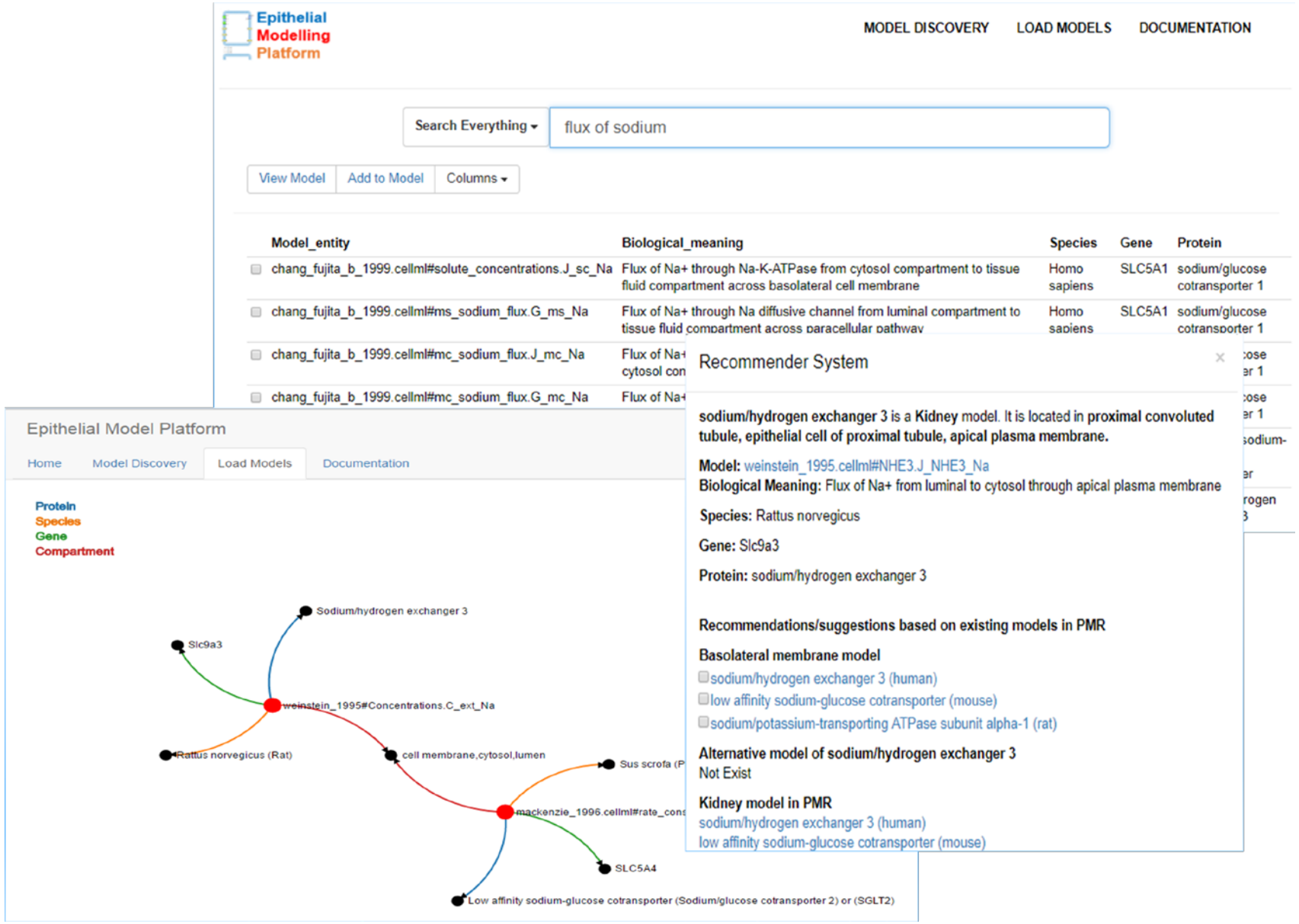

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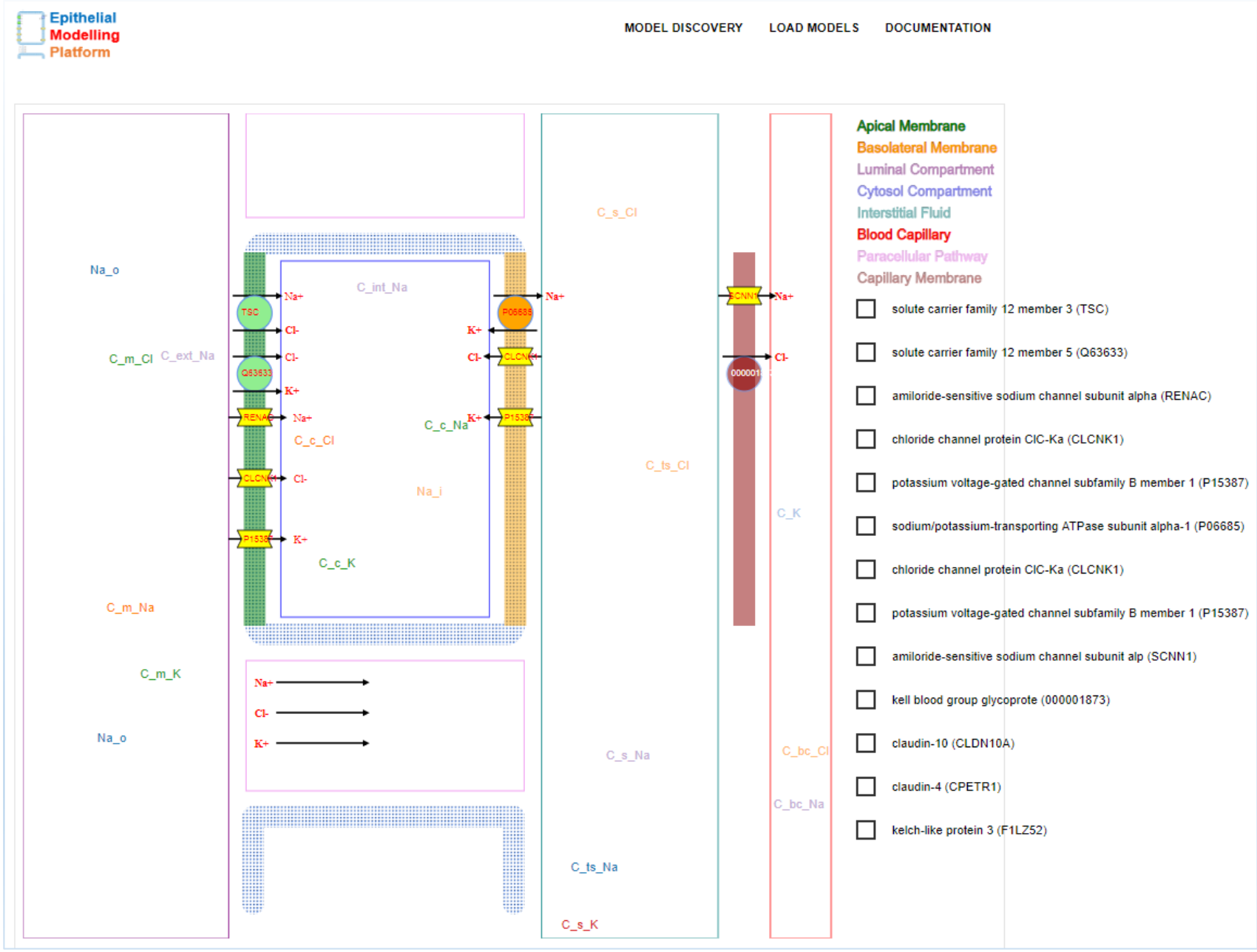

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Model + Data = Verification?

- Given a semantic description of the protocol used to generate some data
  - Experimental context
  - Simulation experiments
- Known model characteristics (and capabilities?)
  - Query for data that has similar characteristics
- Generate SED-ML to apply dataset's protocol to model and execute it
  - Can compare model predictions to data
  - Gives some measure of confidence that the model might not be unusable?

https://doi.org/10.17608/k6.auckland.8858654

CRBM journal curation service

- Work with journals to improve reproducibility
- Help develop common curation practices
  - Domain specific curation vs general curation
  - Curation != validation
- Measuring reproducibility
  - FAIR metrics and associated pitfalls?
- Annotation
  - Non-standard model formats
  - Simulation results (SourceData figure panels?)

https://doi.org/10.17608/k6.auckland.8858654

Acknowledgements

- Dewan Sarwar
- Koray Atalag
- Bernard de Bono
- Tommy Yu
- Peter Hunter

- ABI Physiome Group

Aotearoa Foundation

SPARC

CENTER FOR REPRODUCIBLE BIOMEDICAL MODELING

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cellML