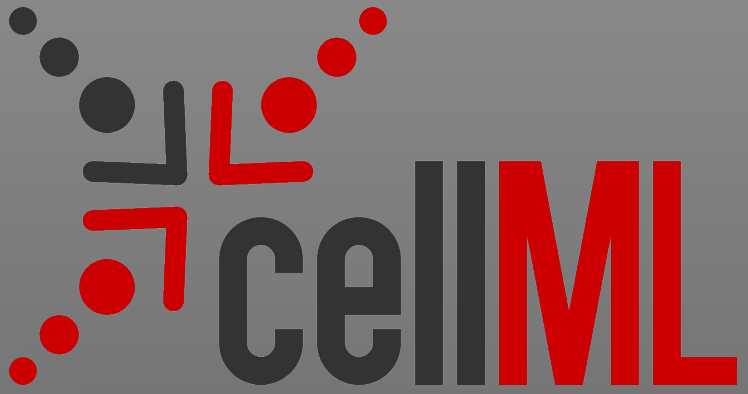
CellML modularity and the Physiome Model Repository

David Nickerson (d.nickerson@auckland.ac.nz)
Catherine Lloyd
Poul Nielsen

AUCKLAND
BIOENGINEERING INSTITUTE
THE UNIVERSITY OF AUCKLAND
NEW ZEALAND
Te Whare Wānanga o Tāmaki Makaurau

Outline

- Introduction to CellML
- Modularity in CellML
- The Physiome [CellML] model repository
- PMR2 – the software behind the repository
- Multiscale modelling



a quick introduction...

What is CellML?

CellML is an XML-based markup language used to describe mathematical models of biological processes

- Equations are expressed in MathML, and metadata are expressed in RDF
- But why is there a need for CellML?

```
<component name="membrane">
    <variable units="millivolt" public_interface="out"
cmeta:id="membrane_V" name="V" initial_value="-86.2" />
    <variable units="joule_per_mole_kelvin" public_interface="out"
name="R" initial_value="8314.472" />
    <variable units="kelvin" public_interface="out" name="T"
initial_value="310" />
    <variable units="coulomb_per_millimole" public_interface="out"
name="F" initial_value="96485.3415" />
    <variable units="microF" public_interface="out" name="Cm"
initial_value="0.185" />
    <variable units="micrometre3" public_interface="out" name="V_c"
initial_value="0.016404" />

    <variable units="millisecond" public_interface="in"
name="time" />
    <variable units="picoA_per_picoF" public_interface="in"
name="i_K1" />
    <variable units="picoA_per_picoF" public_interface="in"
name="i_to" />
    <variable units="picoA_per_picoF" public_interface="in"
name="i_Kr" />
    <variable units="picoA_per_picoF" public_interface="in"
name="i_Ks" />
    <variable units="picoA_per_picoF" public_interface="in"
name="i_CaL" />
    <variable units="picoA_per_picoF" public_interface="in"
name="i_NaK" />
    <variable units="picoA_per_picoF" public_interface="in"
name="i_p_K" />

    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply><eq />
        <apply><diff />
          <bvar><ci>time</ci></bvar>
          <ci>V</ci>
        </apply>
        <apply><times />
          <apply><divide />
            <apply><minus />
              <cn cellml:units="dimensionless">1</cn>
            </apply>
            <cn cellml:units="dimensionless">1</cn>
          </apply>
          <apply><plus /><ci>i_K1</ci>
            <ci>i_to</ci><ci>i_Kr</ci>
            <ci>i_Ks</ci><ci>i_CaL</ci>
            <ci>i_NaK</ci><ci>i_Na</ci>
            <ci>i_b_Na</ci><ci>i_NaCa</ci>
            <ci>i_b_Ca</ci><ci>i_p_K</ci>
            <ci>i_p_Ca</ci><ci>i_Stim</ci>
          </apply>
        </apply>
```

The Underlying Problem?

The Publishing Process

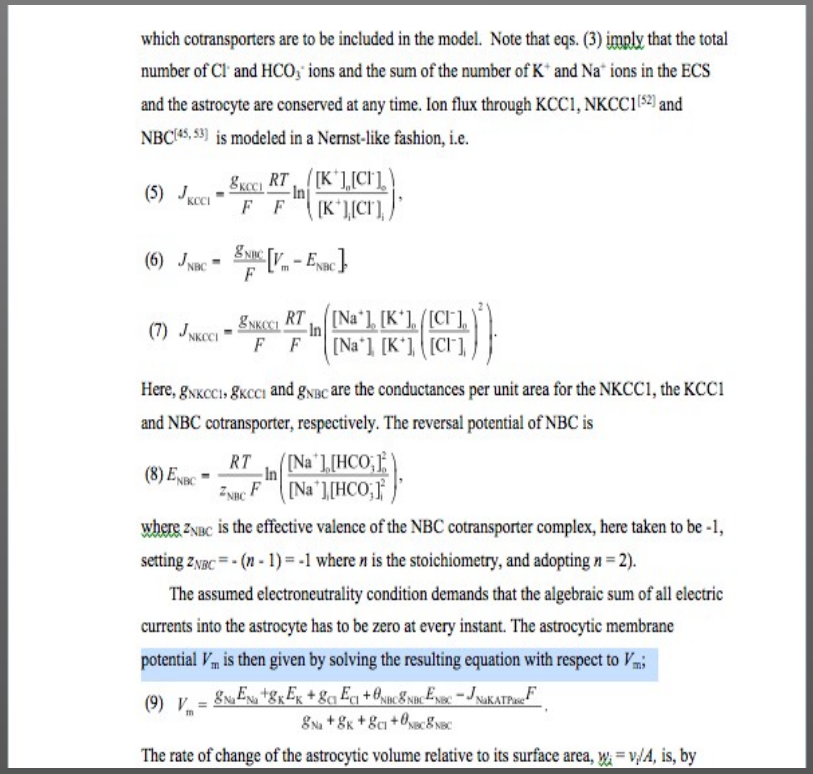
```
%----------Calc the L-type Ca current----------------------

            [CfCa,RevPCa]=
CalcConstantfield(Cai,Cao,2, Vm); %Ca
            [CfK,RevPK] = CalcConstantfield(Ki,Ko,1,
Vm);  %K
            [CfNa,RevPNa] =
CalcConstantfield(Nai,Nao,1, Vm);  %Na
            if (count ==1 && currenttime == 0)
               Va = -74.0078;
            else
               Va = Vm;
            end
            if (count ==0)
              [mcal, hcal,n] =
calcRateConst(1,Va,0,Cai,mcal,hcal,count,dt); %Calc
m and h
              ICaLNa =
(0.00005*PCAL*CfNa)*mcal*hcal;
              ICaLK = (0.001 * PCAL * CfK)*mcal*hcal;
              %ICaLCa = (PCAL * CfCa*mcal*hcal);
%original
              ICaLCa = (PCAL * CfCa*mcal*hcal);
              ICaL = ICaLCa + ICaLK+ICaLNa;
            else
              ICaLNa =
(0.00005*PCAL*CfNa)*mcal*hcal;
              ICaLK = (0.001 * PCAL * CfK)*mcal*hcal;
              ICaLCa = (PCAL * CfCa*mcal*hcal);
              ICaL = ICaLCa + ICaLK+ICaLNa;
              [mcal, hcal] =
calcRateConst(1,Va,0,Cai,mcal,hcal,count,dt); %Calc
m and h
            end
```

model creation

The Underlying Problem?

The Publishing Process



which cotransporters are to be included in the model. Note that eqs. (3) imply that the total number of Cl^- and HCO_3^- ions and the sum of the number of K^+ and Na^+ ions in the ECS and the astrocyte are conserved at any time. Ion flux through KCC1, NKCC1[52] and NBC[45, 53] is modeled in a Nernst-like fashion, i.e.

$$(5)\quad J_{KCC1} = \frac{g_{KCC1}}{F}\frac{RT}{F}\ln\left(\frac{[K^+]_o[Cl^-]_o}{[K^+]_i[Cl^-]_i}\right),$$

$$(6)\quad J_{NBC} = \frac{g_{NBC}}{F}\left[V_m - E_{NBC}\right],$$

$$(7)\quad J_{NKCC1} = \frac{g_{NKCC1}}{F}\frac{RT}{F}\ln\left(\frac{[Na^+]_o}{[Na^+]_i}\frac{[K^+]_o}{[K^+]_i}\left(\frac{[Cl^-]_o}{[Cl^-]_i}\right)^2\right).$$

Here, g_{NKCC1}, g_{KCC1} and g_{NBC} are the conductances per unit area for the NKCC1, the KCC1 and NBC cotransporter, respectively. The reversal potential of NBC is

$$(8)\quad E_{NBC} = \frac{RT}{z_{NBC}F}\ln\left(\frac{[Na^+]_o[HCO_3^-]_o^2}{[Na^+]_i[HCO_3^-]_i^2}\right),$$

where z_{NBC} is the effective valence of the NBC cotransporter complex, here taken to be -1, setting $z_{NBC} = -(n-1) = -1$ where n is the stoichiometry, and adopting $n = 2$).

The assumed electroneutrality condition demands that the algebraic sum of all electric currents into the astrocyte has to be zero at every instant. The astrocytic membrane potential V_m is then given by solving the resulting equation with respect to V_m;

$$(9)\quad V_m = \frac{g_{Na}E_{Na} + g_K E_K + g_{Cl}E_{Cl} + \theta_{NBC}g_{NBC}E_{NBC} - J_{NaKATPase}F}{g_{Na} + g_K + g_{Cl} + \theta_{NBC}g_{NBC}}.$$

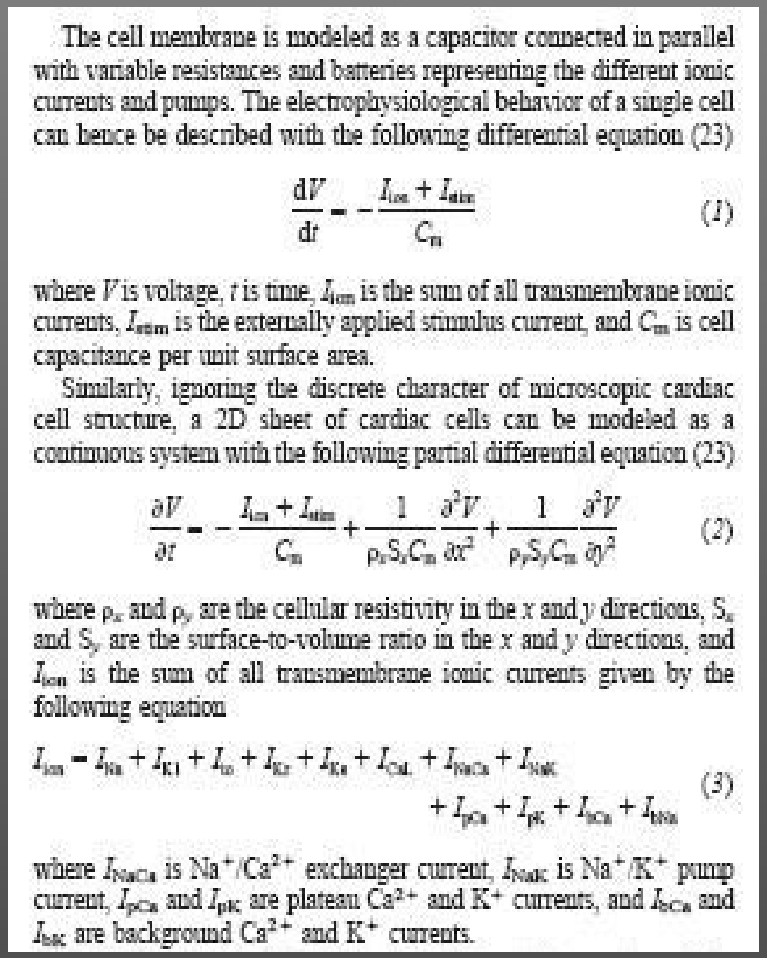
The rate of change of the astrocytic volume relative to its surface area, $w_i = v_i/A$, is, by

model creation

translated into text and equations for publication

The Underlying Problem?

The Publishing Process



The cell membrane is modeled as a capacitor connected in parallel with variable resistances and batteries representing the different ionic currents and pumps. The electrophysiological behavior of a single cell can hence be described with the following differential equation (23)

$$\frac{dV}{dt} = -\frac{I_{ion} + I_{stim}}{C_m} \quad (1)$$

where V is voltage, t is time, I_{ion} is the sum of all transmembrane ionic currents, I_{stim} is the externally applied stimulus current, and C_m is cell capacitance per unit surface area.

Similarly, ignoring the discrete character of microscopic cardiac cell structure, a 2D sheet of cardiac cells can be modeled as a continuous system with the following partial differential equation (23)

$$\frac{\partial V}{\partial t} = -\frac{I_{ion} + I_{stim}}{C_m} + \frac{1}{\rho_x S_x C_m}\frac{\partial^2 V}{\partial x^2} + \frac{1}{\rho_y S_y C_m}\frac{\partial^2 V}{\partial y^2} \quad (2)$$

where ρ_x and ρ_y are the cellular resistivity in the x and y directions, S_x and S_y are the surface-to-volume ratio in the x and y directions, and I_{ion} is the sum of all transmembrane ionic currents given by the following equation

$$I_{ion} = I_{Na} + I_{K1} + I_{to} + I_{Kr} + I_{Ks} + I_{CaL} + I_{NaCa} + I_{NaK} + I_{pCa} + I_{pK} + I_{bCa} + I_{bNa} \quad (3)$$

where I_{NaCa} is Na^+/Ca^{2+} exchanger current, I_{NaK} is Na^+/K^+ pump current, I_{pCa} and I_{pK} are plateau Ca^{2+} and K^+ currents, and I_{bCa} and I_{bK} are background Ca^{2+} and K^+ currents.

model creation

translated into text and equations for publication

reviewed & published

The Underlying Problem?

The Publishing Process

```
 %----------Calc the L-type Ca
current----------------------

              [CfCa,RevPCa]=
CalcConstantfield(Cai,Cao,2, Vm); %Ca
              [CfK,RevPK] =
CalcConstantfield(Ki,Ko,1, Vm);  %K
              [CfNa,RevPNa] =
CalcConstantfield(Nai,Nao,1, Vm);  %Na
              if (count ==1 && currenttime == 0)
                 Va = -74.0078;
              else
                 Va = Vm;
              end
              if (count ==0)
                [mcal, hcal,n] =
calcRateConst(1,Va,0,Cai,mcal,hcal,count,dt);
%Calc m and h
                ICaLNa =
(0.00005*PCAL*CfNa)*mcal*hcal;
                ICaLK = (0.001 * PCAL *
CfK)*mcal*hcal;
                %ICaLCa = (PCAL * CfCa*mcal*hcal);
%original
                ICaLCa = (PCAL * CfCa*mcal*hcal);
                ICaL = ICaLCa + ICaLK+ICaLNa;
              else
                ICaLNa =
(0.00005*PCAL*CfNa)*mcal*hcal;
                ICaLK = (0.001 * PCAL *
CfK)*mcal*hcal;
                ICaLCa = (PCAL * CfCa*mcal*hcal);
                ICaL = ICaLCa + ICaLK+ICaLNa;
                [mcal, hcal] =
calcRateConst(1,Va,0,Cai,mcal,hcal,count,dt);
%Calc m and h
```

model creation

translated into text and equations for publication

reviewed & published

interpreted & implemented

The Underlying Problem?

The Publishing Process

```
 %----------Calc the L-type Ca
current----------------------

              [CfCa,RevPCa]=
CalcConstantfield(Cai,Cao,2, Vm); %Ca
              [CfK,RevPK] =
CalcConstantfield(Ki,Ko,1, Vm);  %K
              [CfNa,RevPNa] =
CalcConstantfield(Nai,Nao,1, Vm);  %Na
              if (count ==1 && currenttime == 0)
                 Va = -74.0078;
              else
                 Va = Vm;
              end
              if (count ==0)
                [mcal, hcal,n] =
calcRateConst(1,Va,0,Cai,mcal,hcal,count,dt);
%Calc m and h
                ICaLNa =
(0.00005*PCAL*CfNa)*mcal*hcal;
                ICaLK = (0.001 * PCAL *
CfK)*mcal*hcal;
                %ICaLCa = (PCAL * CfCa*mcal*hcal);
%original
                ICaLCa = (PCAL * CfCa*mcal*hcal);
                ICaL = ICaLCa + ICaLK+ICaLNa;
              else
                ICaLNa =
(0.00005*PCAL*CfNa)*mcal*hcal;
                ICaLK = (0.001 * PCAL *
CfK)*mcal*hcal;
                ICaLCa = (PCAL * CfCa*mcal*hcal);
                ICaL = ICaLCa + ICaLK+ICaLNa;
                [mcal, hcal] =
calcRateConst(1,Va,0,Cai,mcal,hcal,count,dt);
%Calc m and h
```

model creation

↓ error

translated into text and equations for publication

↓ error

reviewed & published

↓ error

interpreted & implemented

CellML has been developed as a potential solution to the inconsistencies between computational and published models

```
<component name="membrane">
    <variable units="millivolt" public_interface="out" name="V" initial_value="-
86.2" />
    <variable units="microF" public_interface="out" name="Cm"
initial_value="0.185" />
    <variable units="micrometre3" public_interface="out" name="V_c"
initial_value="0.016404" />
    <variable units="millisecond" public_interface="in" name="time" />
    <variable units="picoA_per_picoF" public_interface="in" name="i_K1" />
   <variable units="picoA_per_picoF" public_interface="in" name="i_Ks" />
    <variable units="picoA_per_picoF" public_interface="in" name="i_CaL" />
    <variable units="picoA_per_picoF" public_interface="in" name="i_NaK" />
    <variable units="picoA_per_picoF" public_interface="in" name="i_p_K" />

    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply><eq />
        <apply><diff />
          <bvar><ci>time</ci></bvar>
          <ci>V</ci>
        </apply>
        <apply><times />
          <apply><divide />
            <apply><minus />
              <cn cellml:units="dimensionless">1</cn>
            </apply>
            <cn cellml:units="dimensionless">1</cn>
          </apply>
          <apply><plus /><ci>i_K1</ci>
            <ci>i_to</ci><ci>i_Kr</ci>
            <ci>i_b_Na</ci><ci>i_NaCa</ci>
            <ci>i_b_Ca</ci><ci>i_p_K</ci>
            <ci>i_p_Ca</ci><ci>i_Stim</ci>
          </apply>
        </apply>
      </apply>
    </math>
  </component>
```

The cell membrane is modeled as a capacitor connected in parallel with variable resistances and batteries representing the different ionic currents and pumps. The electrophysiological behavior of a single cell can hence be described with the following differential equation (23)

$$\frac{dV}{dt} = -\frac{I_{ion} + I_{stim}}{C_m} \qquad (1)$$

where V is voltage, t is time, I_{ion} is the sum of all transmembrane ionic currents, I_{stim} is the externally applied stimulus current, and C_m is cell capacitance per unit surface area.

Similarly, ignoring the discrete character of microscopic cardiac cell structure, a 2D sheet of cardiac cells can be modeled as a continuous system with the following partial differential equation (23)

$$\frac{\partial V}{\partial t} = -\frac{I_{ion} + I_{stim}}{C_m} + \frac{1}{\rho_x S_x C_m}\frac{\partial^2 V}{\partial x^2} + \frac{1}{\rho_y S_y C_m}\frac{\partial^2 V}{\partial y^2} \qquad (2)$$

where ρ_x and ρ_y are the cellular resistivity in the x and y directions, S_x and S_y are the surface-to-volume ratio in the x and y directions, and I_{ion} is the sum of all transmembrane ionic currents given by the following equation

$$I_{ion} = I_{Na} + I_{K1} + I_{to} + I_{Kr} + I_{Ks} + I_{CaL} + I_{NaCa} + I_{NaK} + I_{pCa} + I_{pK} + I_{bCa} + I_{bNa} \qquad (3)$$

where I_{NaCa} is Na^+/Ca^{2+} exchanger current, I_{NaK} is Na^+/K^+ pump current, I_{pCa} and I_{pK} are plateau Ca^{2+} and K^+ currents, and I_{bCa} and I_{bK} are background Ca^{2+} and K^+ currents.

Reproduction and provenance

File Edit View History Bookmarks Tools Help

http://www.bioeng.nus.edu.sg/compbiolab/p2/IKA/index.xml

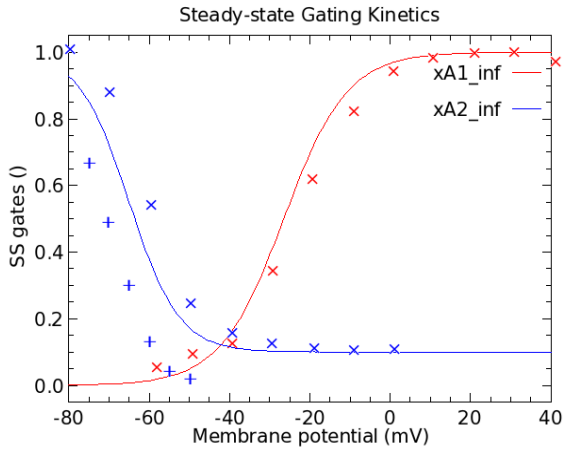
Provenance

Google Provenance Search Bookmarks david....

Practical application of CellM... | Model Reference Description:...

Model Reference Description: Graphs

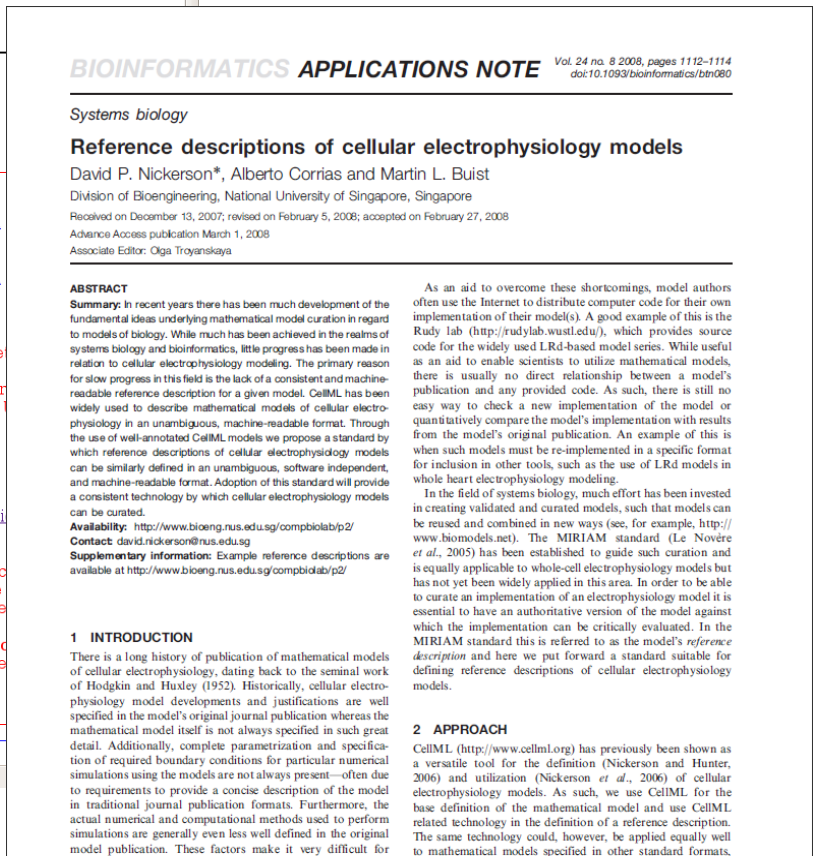
Steady-state Gating Kinetics
Creator: David Nickerson (david.nickerson@nus.edu.sg) Division of Bioengineering, National University of Singapore
Created: 2007-11-27
Publisher: Division of Bioengineering, National University of Singapore



xA1_inf
x-axis
Simulation: ...A-voltage-clamp.xml#simulation
Variable: ...ments/IKA-voltage-clamp.xml#Vm
y-axis
Simulation: ...A-voltage-clamp.xml#simulation
Variable: ...ist/components/IKA.xml#xA1_inf
Experimental Data
IKA steady state activation gating kine
Amberg et al (2002).
Creator: David Nickerson (david.nicker
Division of Bioengineering, National
Singapore
Created: 2007-11-24
Pubmed reference: 12381815
Biological Entity: gastric antrum
Species: mouse
Data source: ...ate-gating-data-activati
header=present]
Comment:
Data used to fit the steady state ac
kinetics of the IKA current in the
(2007) smooth muscle cellular ele
model.
Modification [modified by David Nic
Splitting the combined data into se
for ease of use.
Modified: 2007-11-26

xA2_inf

Done



BIOINFORMATICS APPLICATIONS NOTE Vol. 24 no. 8 2008, pages 1112–1114 doi:10.1093/bioinformatics/btn080

Systems biology

Reference descriptions of cellular electrophysiology models

David P. Nickerson*, Alberto Corrias and Martin L. Buist

Division of Bioengineering, National University of Singapore, Singapore

Received on December 13, 2007; revised on February 5, 2008; accepted on February 27, 2008

Advance Access publication March 1, 2008

Associate Editor: Olga Troyanskaya

ABSTRACT

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

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

Contact: david.nickerson@nus.edu.sg

Supplementary information: Example reference descriptions are available at http://www.bioeng.nus.edu.sg/compbiolab/p2/

1 INTRODUCTION

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

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

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

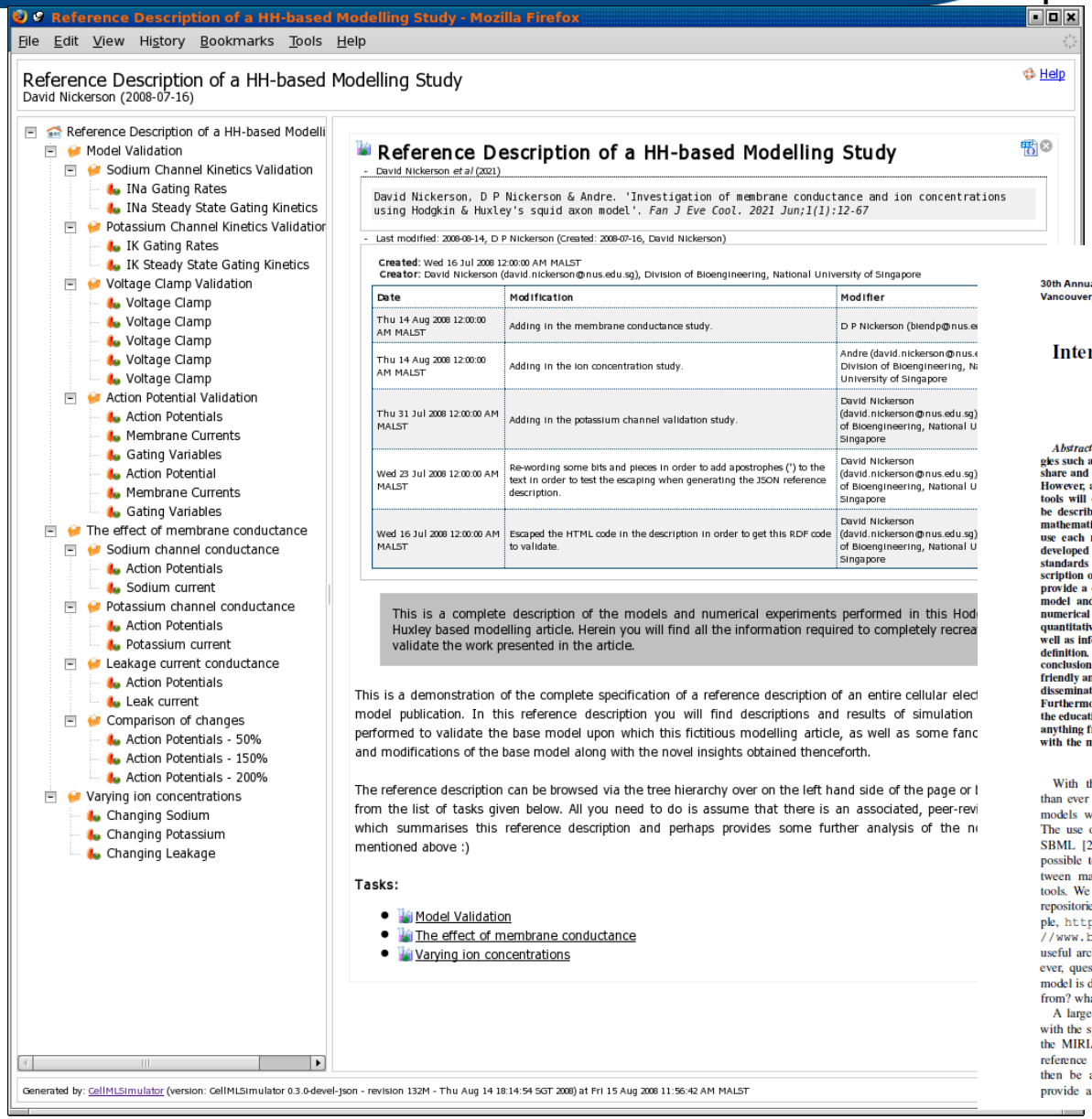
2 APPROACH

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

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

doi:10.1093/bioinformatics/btn080

http://www.bioeng.nus.edu.sg/compbiolab/p3/
http://models.cellml.org/workspace/a1/



30th Annual International IEEE EMBS Conference
Vancouver, British Columbia, Canada, August 20-24, 2008

Interactive reference descriptions of cellular electrophysiology models

David Nickerson and Martin Buist

***Abstract*— With the advent and popularization of technologies such as CellML and SBML it has become relatively easy to share and exchange mathematical models of biological systems. However, as such technology evolves it is inevitable that not all tools will correctly interpret the full range of models able to be described. It is also necessary to completely describe the mathematical models allowing model users to appropriately use each model. To address these issues we have previously developed methods and tools based on community defined standards which allow for the specification of a reference description of a mathematical model. Such reference descriptions provide a comprehensive description of both the mathematical model and the outcomes expected when performing specific numerical simulations using the model. Thus providing for quantitative validation of tool interpretation of a given model as well as informing the model user as to all aspects of the model definition. Further development of this work has led to the conclusion that presenting such reference descriptions in a user friendly and interactive manner provides a powerful tool for the dissemination and understanding of the mathematical model. Furthermore, such a tool is seen as an invaluable teaching aid in the education of biomedical engineers and scientists allowing for anything from a superficial to a very comprehensive interaction with the mathematical model.**

I. INTRODUCTION

With the aid of current technology, it is now easier than ever for mathematical model developers to share their models with collaborators and the scientific community. The use of CellML [1, http://www.cellml.org] or SBML [2, http://sbml.org], for example, makes it possible to exchange mathematical model descriptions between many research groups using independent software tools. We are now seeing the evolution of freely available repositories of curated model descriptions (see, for example, http://www.cellml.org/models/ and http://www.biomodels.net [3]) to provide important and useful archives of model descriptions. There remains, however, questions such as just what a particular mathematical model is describing? where do all the parameter values come from? what data was used to fit this relationship? and so on.

A large step toward addressing these questions was made with the specification of the MIRIAM[1] standard [4]. In part, the MIRIAM standard is based upon the idea of having a reference description of a mathematical model, which can then be annotated with relevant information in order to provide a complete description of the model. Previously, we have presented a method whereby community standards being developed as part of the CellML project can be used to define comprehensive reference descriptions of mathematical models [5]. The outcome of this earlier work provides a machine interpretable description of the mathematical model which includes everything from parameter value sources, to experimental data utilized in model fitting and validation, to the actual graphical outputs included in the peer reviewed publication of the model. We have shown how a static rendering of this model description may be presented to human users in a manner which allows the description to be fully navigated by the user, with examples based on CellML and SBML available at http://www.bioeng.nus.edu.sg/compbiolab/p2.

In addition to questions arising from the model itself, there is also the issue of whether all of the various tools supporting these technologies interpret the mathematical model in exactly the same manner (*cf.* the way in which web pages may look and/or behave differently in different web browsers). As these mathematical model description technologies evolve tool developers are inevitably forced to focus on the developments most relevant to their particular user requirements. Now that tools such as the CellML API (http://www.cellml.org/tools/api) and libSBML [6] are available, the hope is to standardize on such community defined tools for the core interpretation of the models while specific tool developers can build on top of that common foundation to meet their specific requirements. There are currently, however, sufficient independent tools in common usage that there can be no assurance that they all interpret the models in exactly the same manner.

As described above, the method we have presented previously [5] for the specification of comprehensive reference descriptions is a machine interpretable description of the mathematical model. As such, software tools are able to process the entire description and perform various tests upon it. Such tests may include checks on MIRIAM compliance, validity of the model encoding (*e.g.*, SBML or CellML), consistency of physical units. In addition, the reference description includes data obtained from the numerical simulations used as part of the creation of the reference description (*i.e.*, the data used to create the graphs included in the reference description) and links to experimental data

doi:10.1109/IEMBS.2008.4649689

Model exchange and reuse

FAQ 1: why can't we just use MATLAB?

Not the only model description language

- Even where MATLAB is used – as a procedural language it is distinct from the published model
- A CellML model is a pure representation of the maths in the published paper

```
 %----------Calc the L-type Ca
current----------------------

            [CfCa,RevPCa]=
CalcConstantfield(Cai,Cao,2, Vm); %Ca
            [CfK,RevPK] = CalcConstantfield(Ki,Ko,1,
Vm);  %K
            [CfNa,RevPNa] =
CalcConstantfield(Nai,Nao,1, Vm);  %Na
            if (count ==1 && currenttime == 0)
               Va = -74.0078;
            else
               Va = Vm;
            end
            if (count ==0)
              [mcal, hcal,n] =
calcRateConst(1,Va,0,Cai,mcal,hcal,count,dt);
%Calc m and h
              ICaLNa =
(0.00005*PCAL*CfNa)*mcal*hcal;
              ICaLK = (0.001 * PCAL * CfK)*mcal*hcal;
              %ICaLCa = (PCAL * CfCa*mcal*hcal);
%original
              ICaLCa = (PCAL * CfCa*mcal*hcal);
              ICaL = ICaLCa + ICaLK+ICaLNa;
            else
              ICaLNa =
(0.00005*PCAL*CfNa)*mcal*hcal;
              ICaLK = (0.001 * PCAL * CfK)*mcal*hcal;
              ICaLCa = (PCAL * CfCa*mcal*hcal);
              ICaL = ICaLCa + ICaLK+ICaLNa;
              [mcal, hcal] =
calcRateConst(1,Va,0,Cai,mcal,hcal,count,dt);
%Calc m and h
```

FAQ 2: this sounds a lot like SBML, why do both exist?

Historical reasons – both languages were started around 1999/2000 and were unaware the other existed

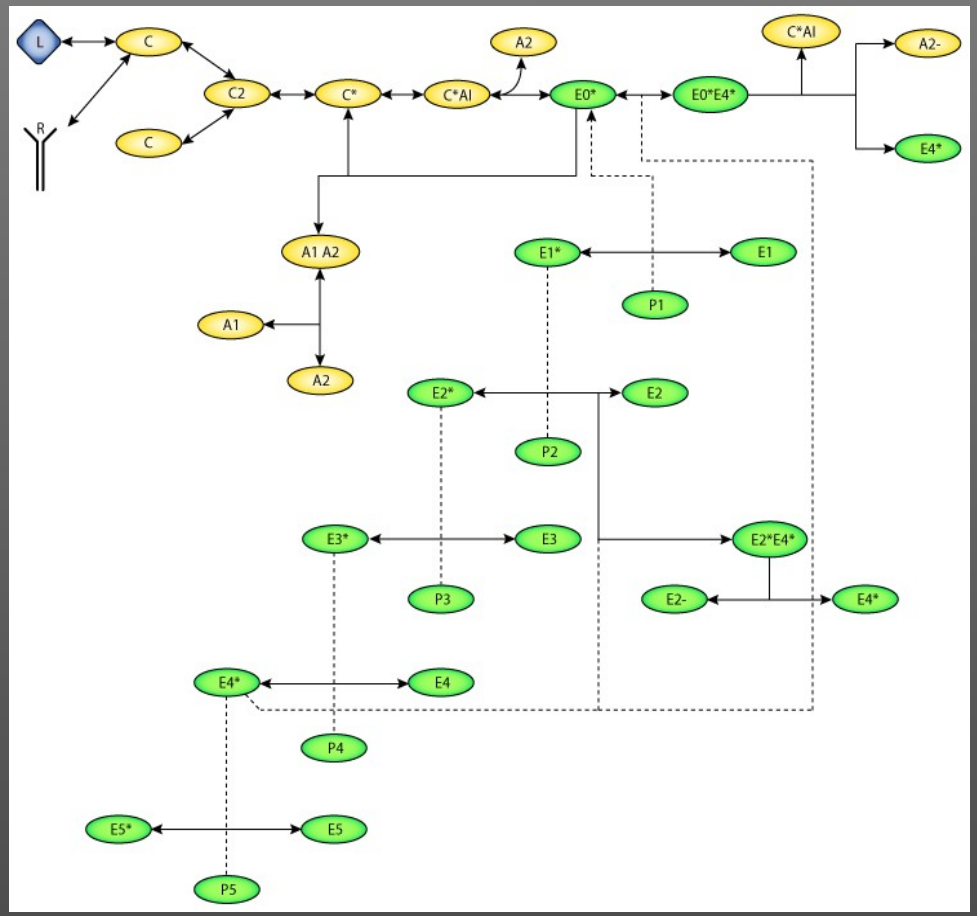
- Functional reasons – SBML and CellML have different emphases:
  - “SBML is designed for representing models of biochemical reaction networks”. *(http://www.sbml.org/)*
  - “The purpose of CellML is to store and exchange computer-based mathematical models”. *(http://www.cellml.org/)*

CellML language features

CellML has a flexible structure and can be used to describe a diverse range of models... including...

CellML language features

CellML has a flexible structure and can be used to describe a diverse range of models... including...

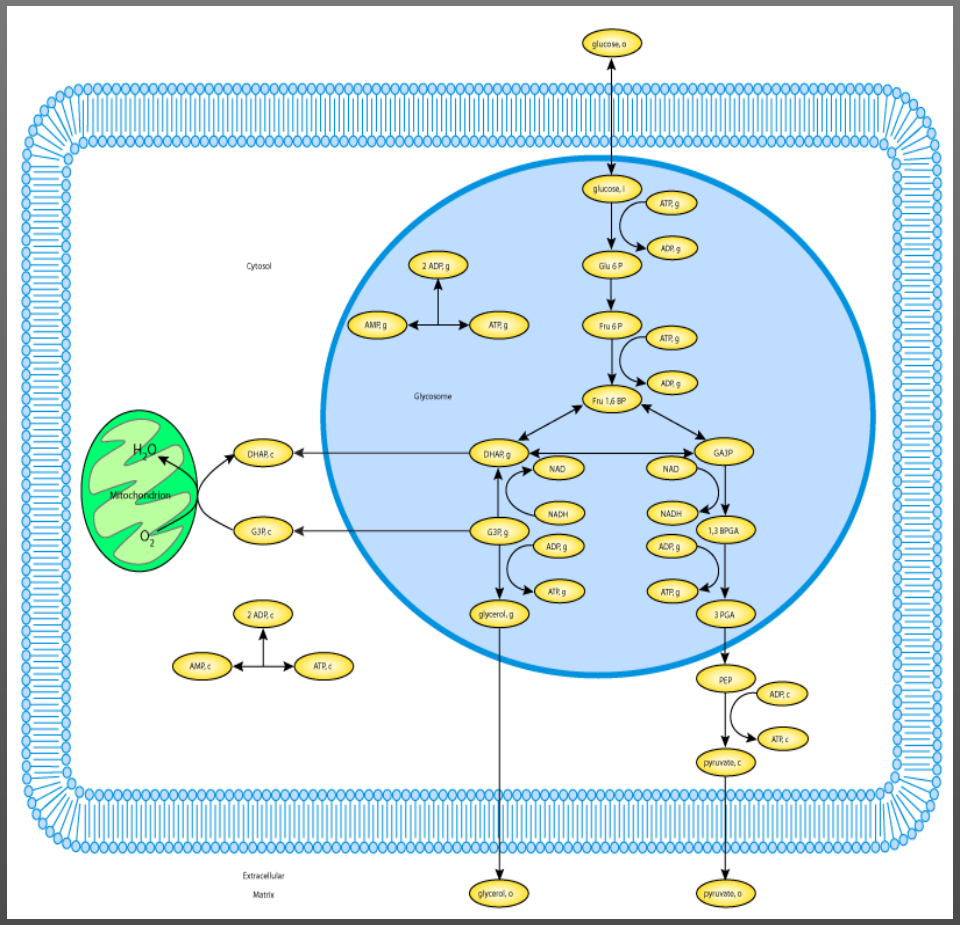


signal transduction

CellML language features

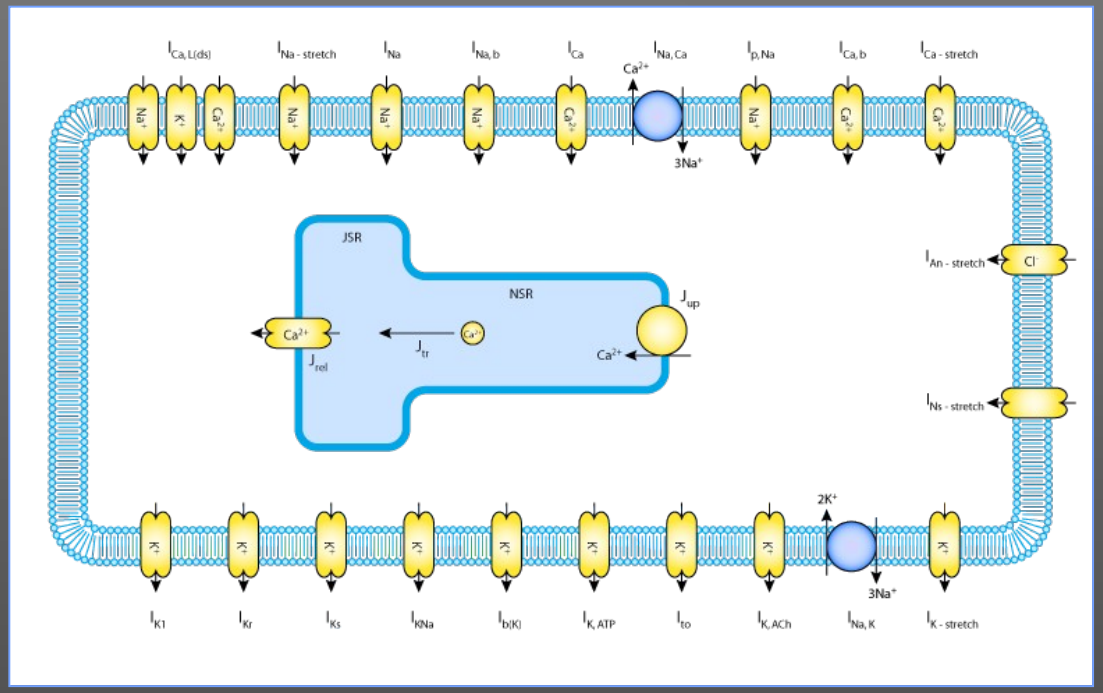
CellML has a flexible structure and can be used to describe a diverse range of models... including...

metabolism



CellML language features

CellML has a flexible structure and can be used to describe a diverse range of models... including...

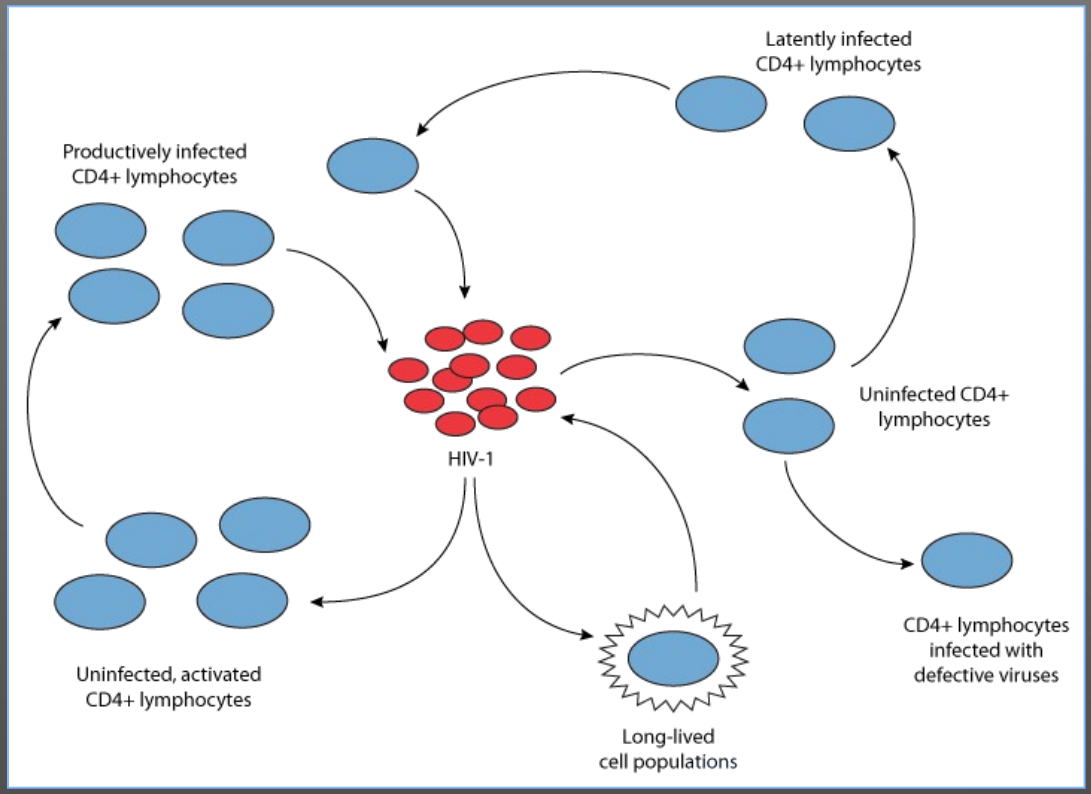


electrophysiology

CellML language features

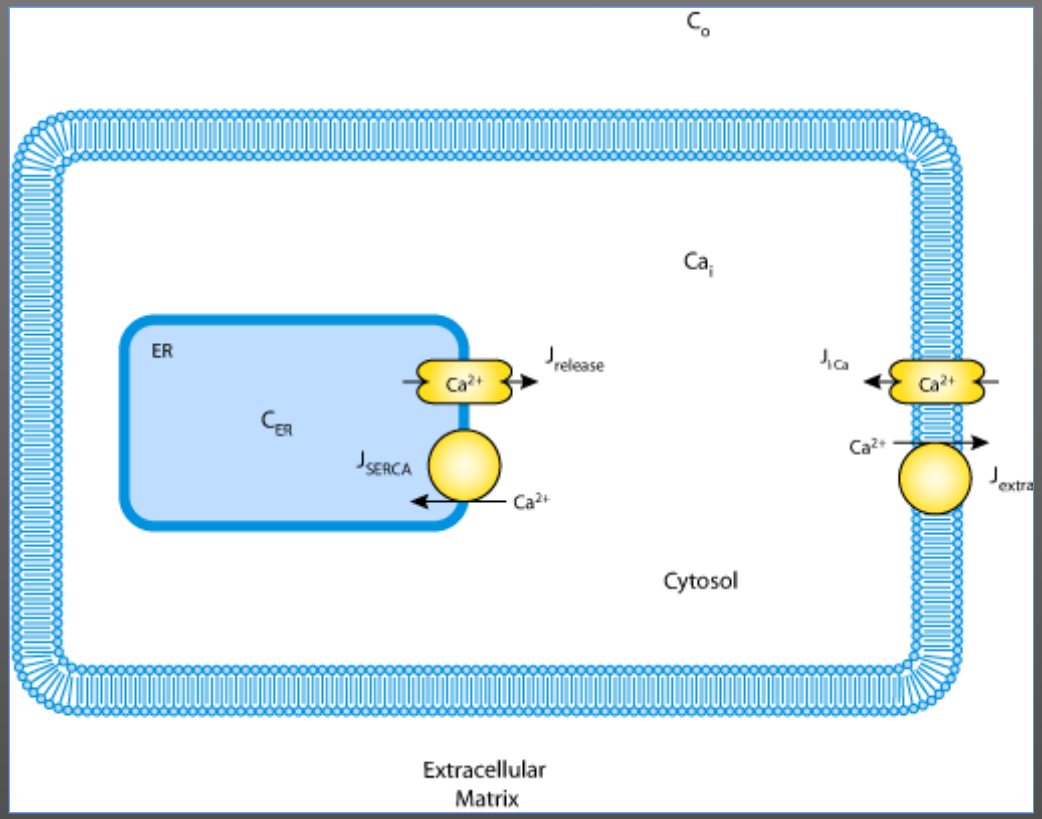
CellML has a flexible structure and can be used to describe a diverse range of models... including...

immunology



CellML language features

CellML has a flexible structure and can be used to describe a diverse range of models... including...

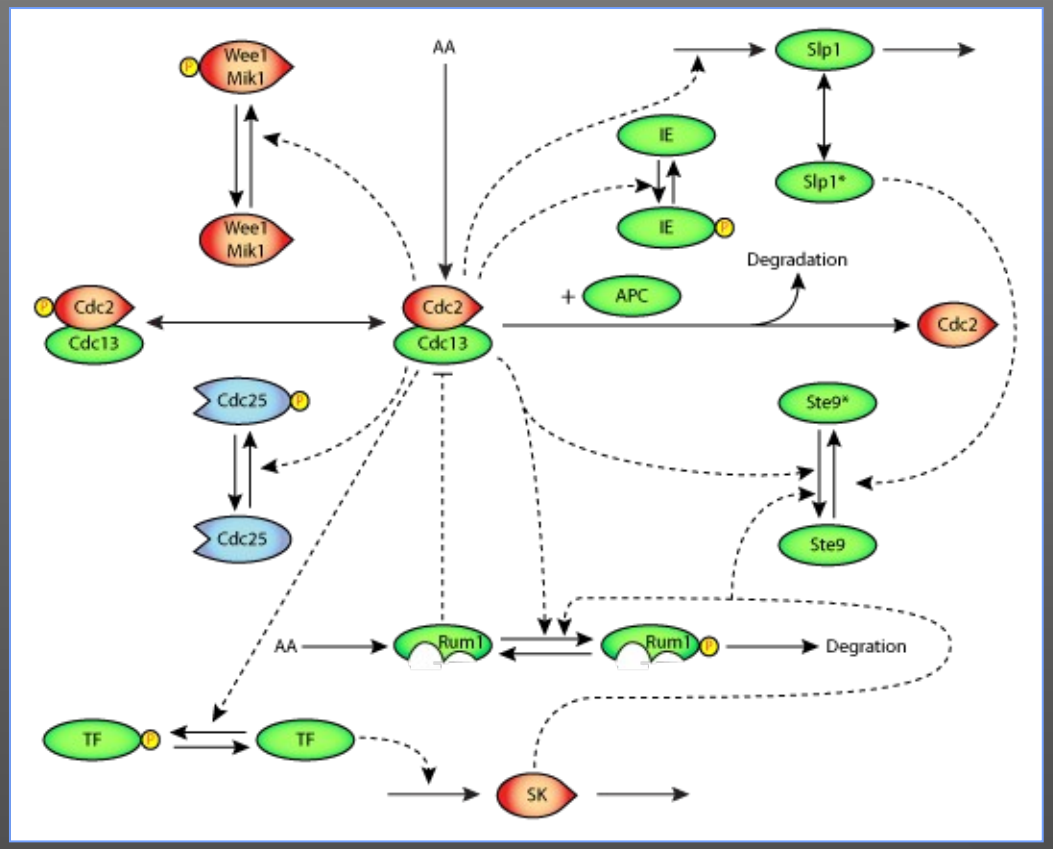


calcium dynamics

CellML language features

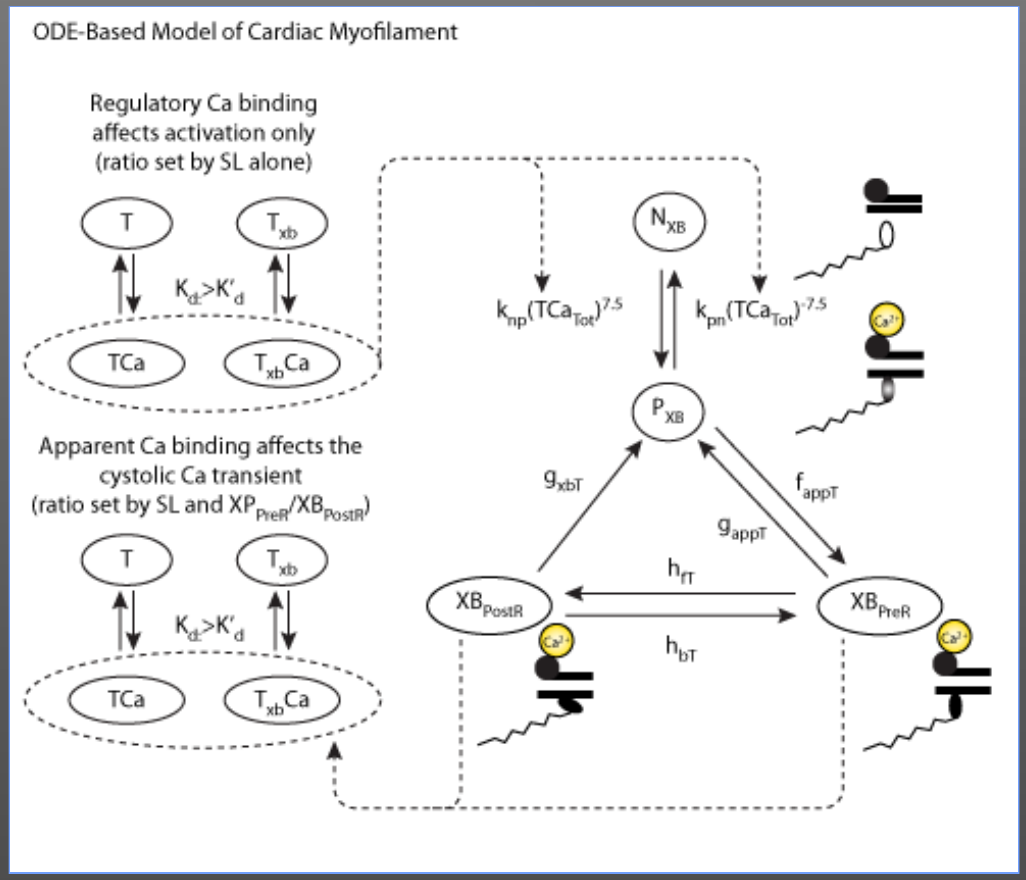
CellML has a flexible structure and can be used to describe a diverse range of models... including...

cell cycle



CellML language features

CellML has a flexible structure and can be used to describe a diverse range of models... including...

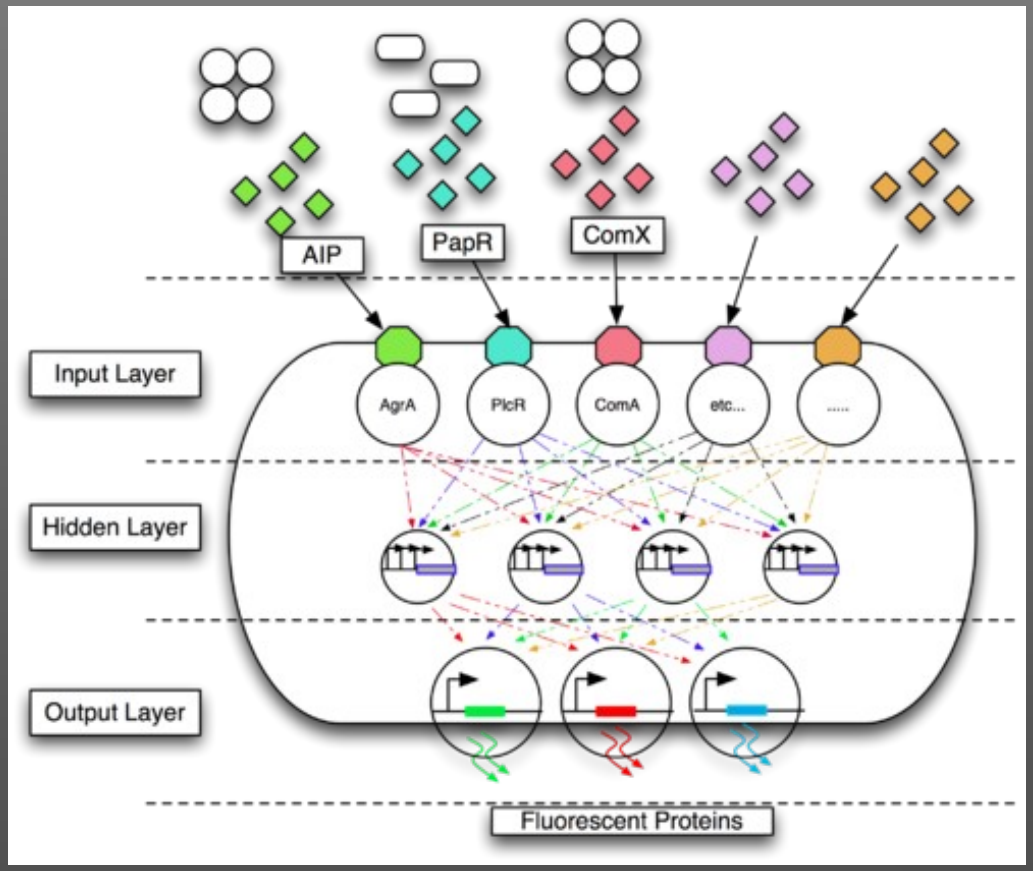


muscle contraction

CellML language features

CellML has a flexible structure and can be used to describe a diverse range of models... including...

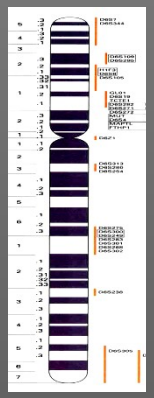
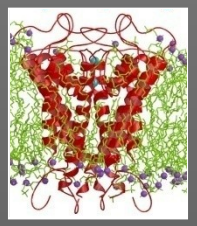
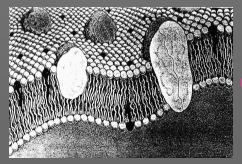
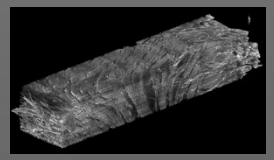
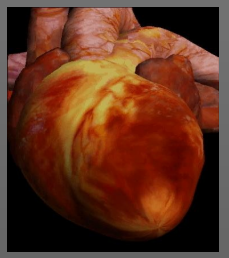
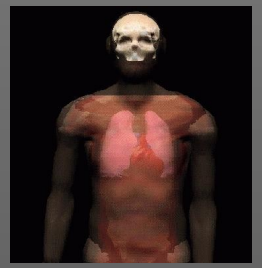
And synthetic biology



Language "limitations"

A question of scale...

Genes → mRNA → Proteins (Lipids, Carbohydrates) → Cell structure-function → Tissue structure-function → Organ structure-function → Clinical medicine

CellML

FieldML + OpenCMISS

Modularity and reuse

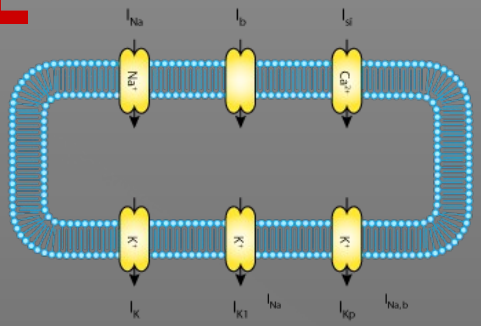
CellML has 2 essential features which promote model exchange and reuse:

CellML has a modular architecture; allowing models to be broken down into "components"

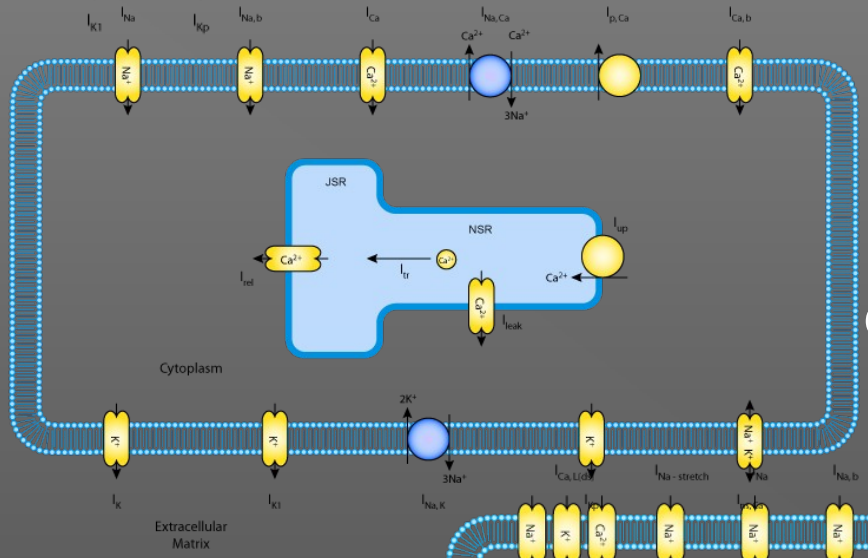
- CellML 1.1 has an "import" feature which allows models to be connected and reused

Model reuse 1: models can evolve over time

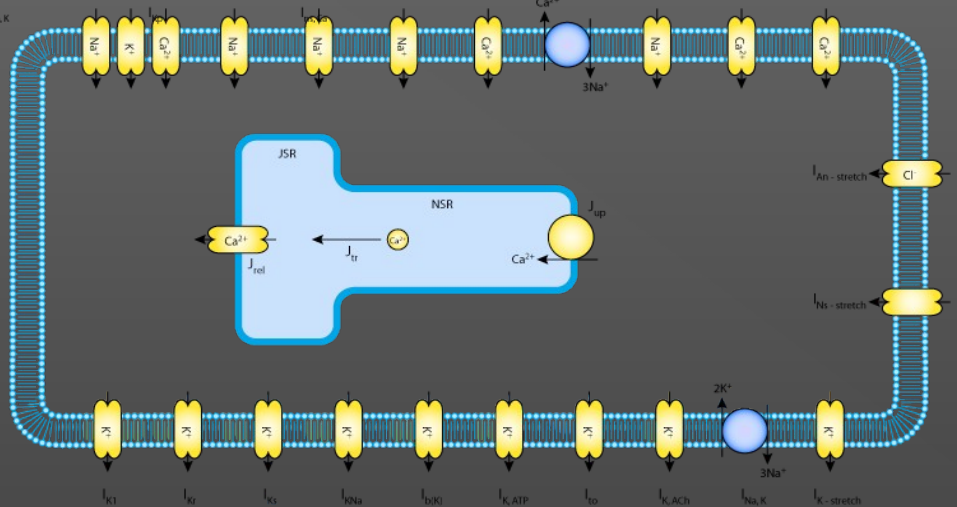
Luo & Rudy I
1991



Luo & Rudy II
1994

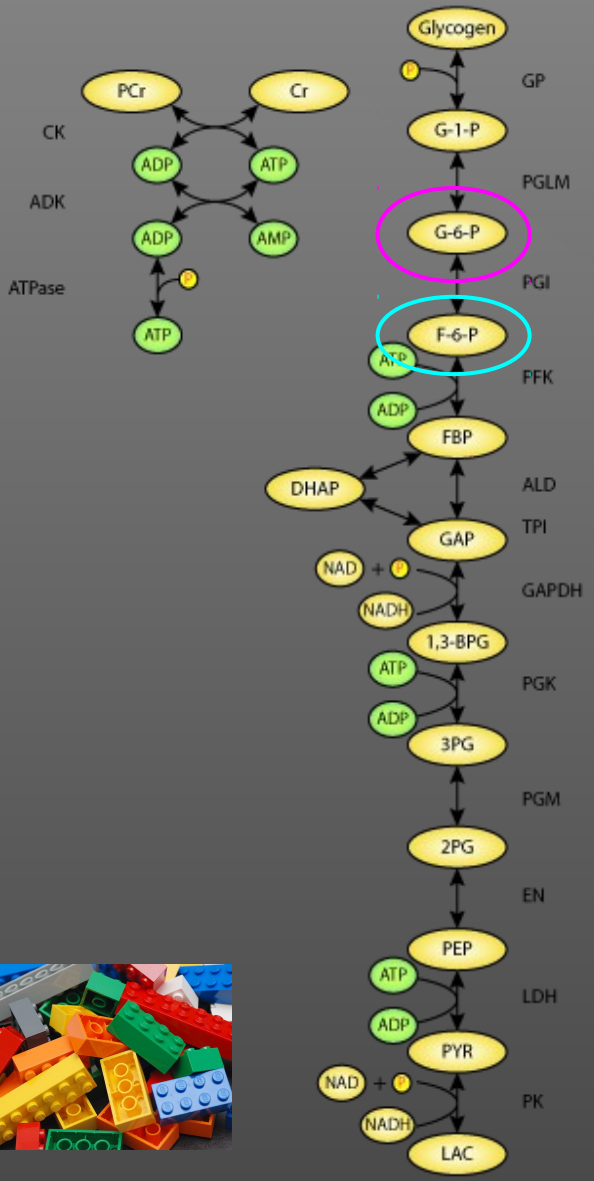


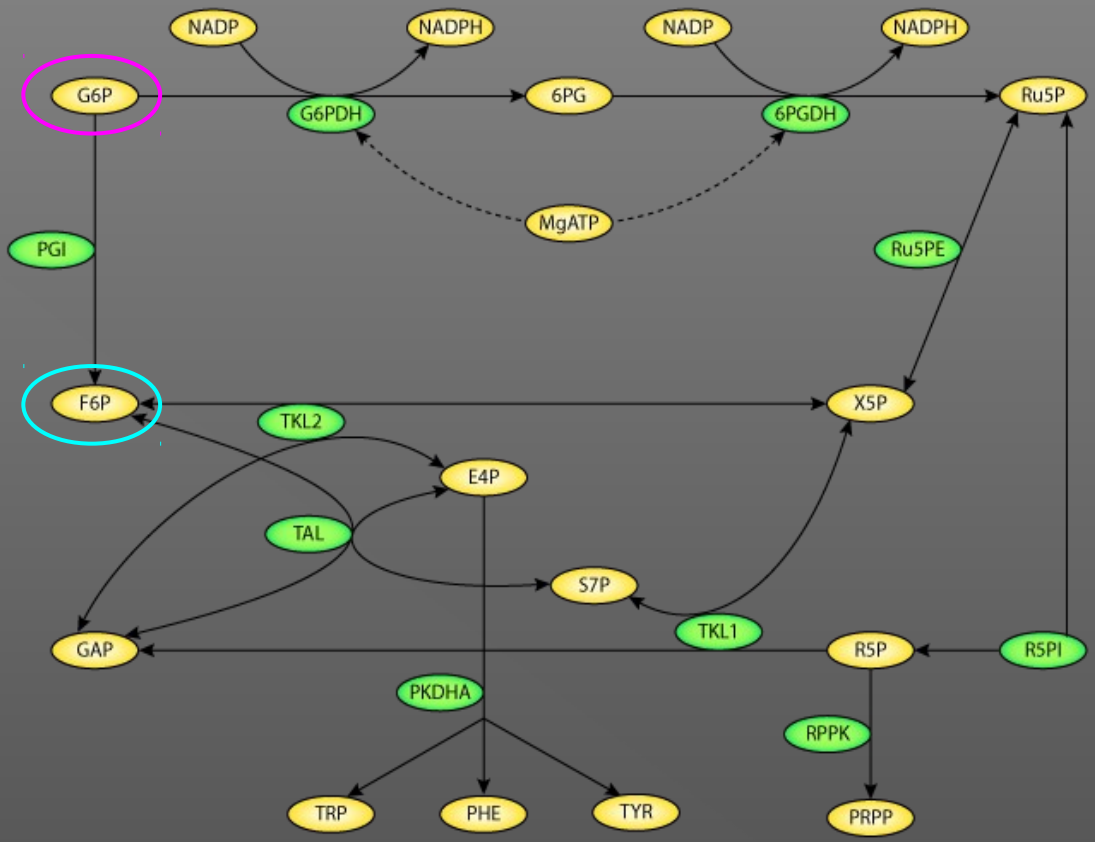
Noble *et al.*
1998



Often biological models are formed from similar components. They can build on each other, becoming increasingly complex over time.

Model reuse 2: models can share entities & processes





Some natural systems have a modular composition. Shared entities or processes can be reused between models.

Model reuse 3: a model with a repeating unit

Faville *et al*. 2009

2 models: cell & pacemaker

the pacemaker is defined once and is imported into the cell 10 times

CellML 1.1 modularity

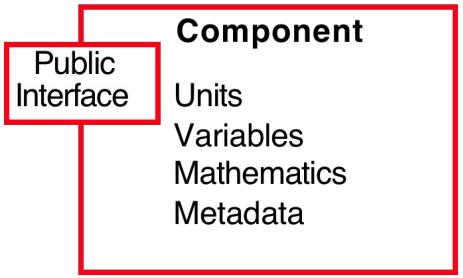
Poul Nielsen

CellML

- CellML is designed to support the definition and sharing of models of biological processes.
- CellML includes information about:
  - Model structure (how the parts of a model are organizationally related to one another);
  - Mathematics (equations describing the underlying biological processes);
  - Metadata (additional information about the model that allows scientists to search for specific models or model components in a database or other repository).
- A public repository of over 500 published signal transduction, electrophysiological, mechanical, and metabolic pathway processes is available at *http://models.cellml.org/*

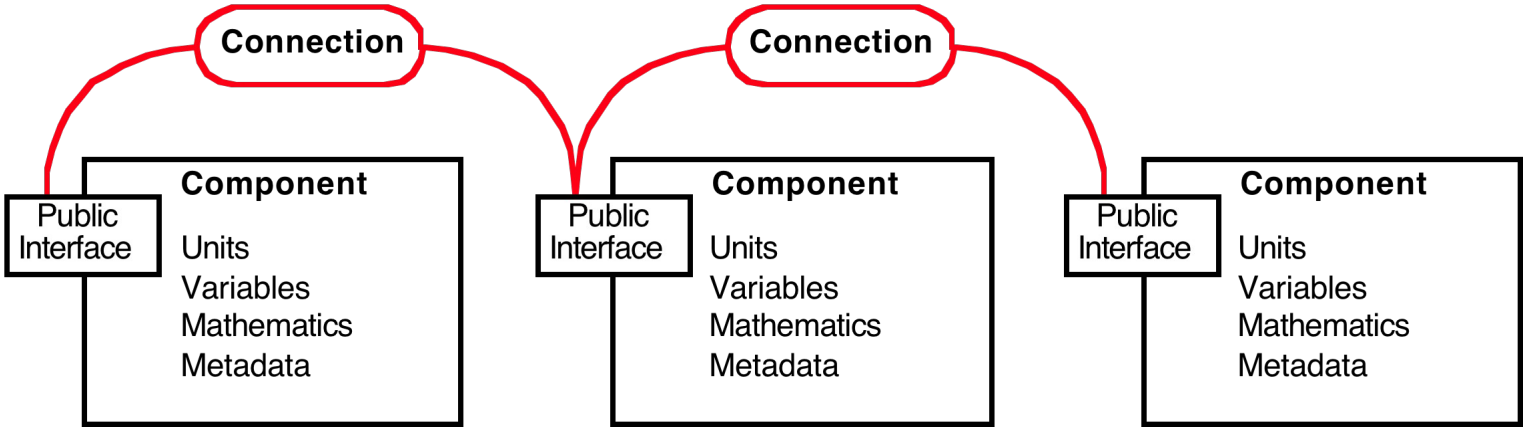
CellML components

- 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.



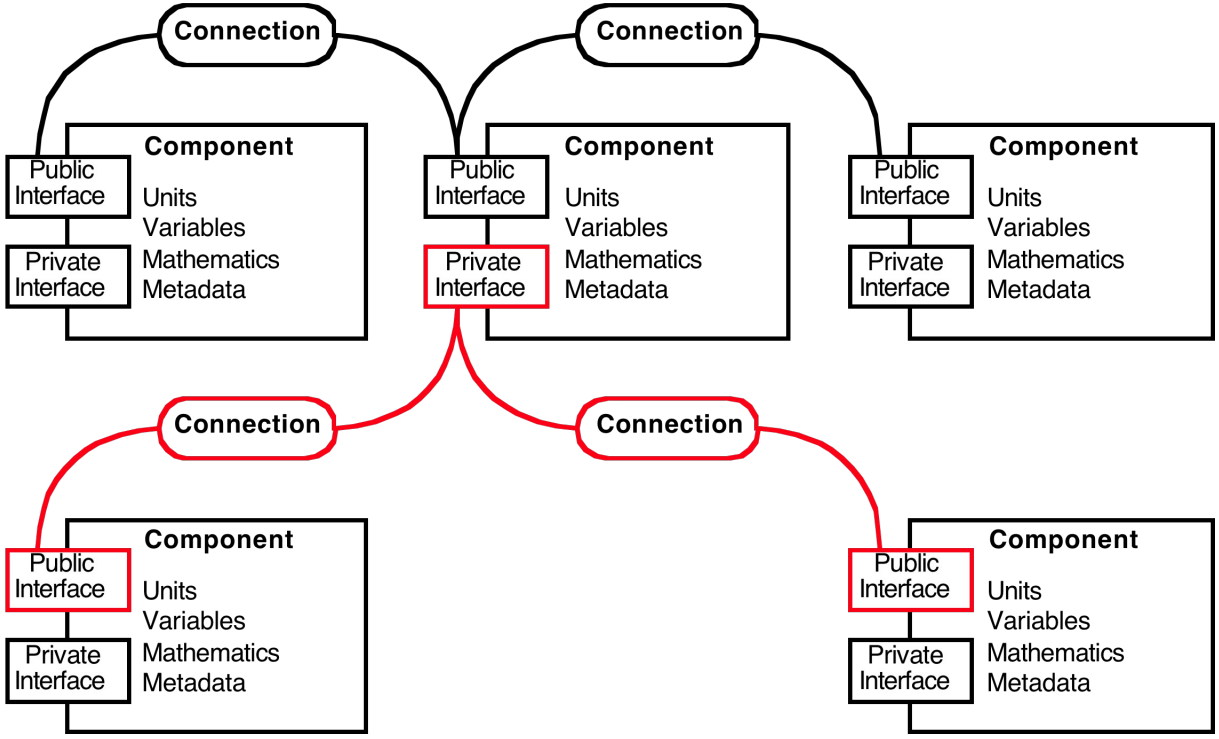
CellML connections

- *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*.



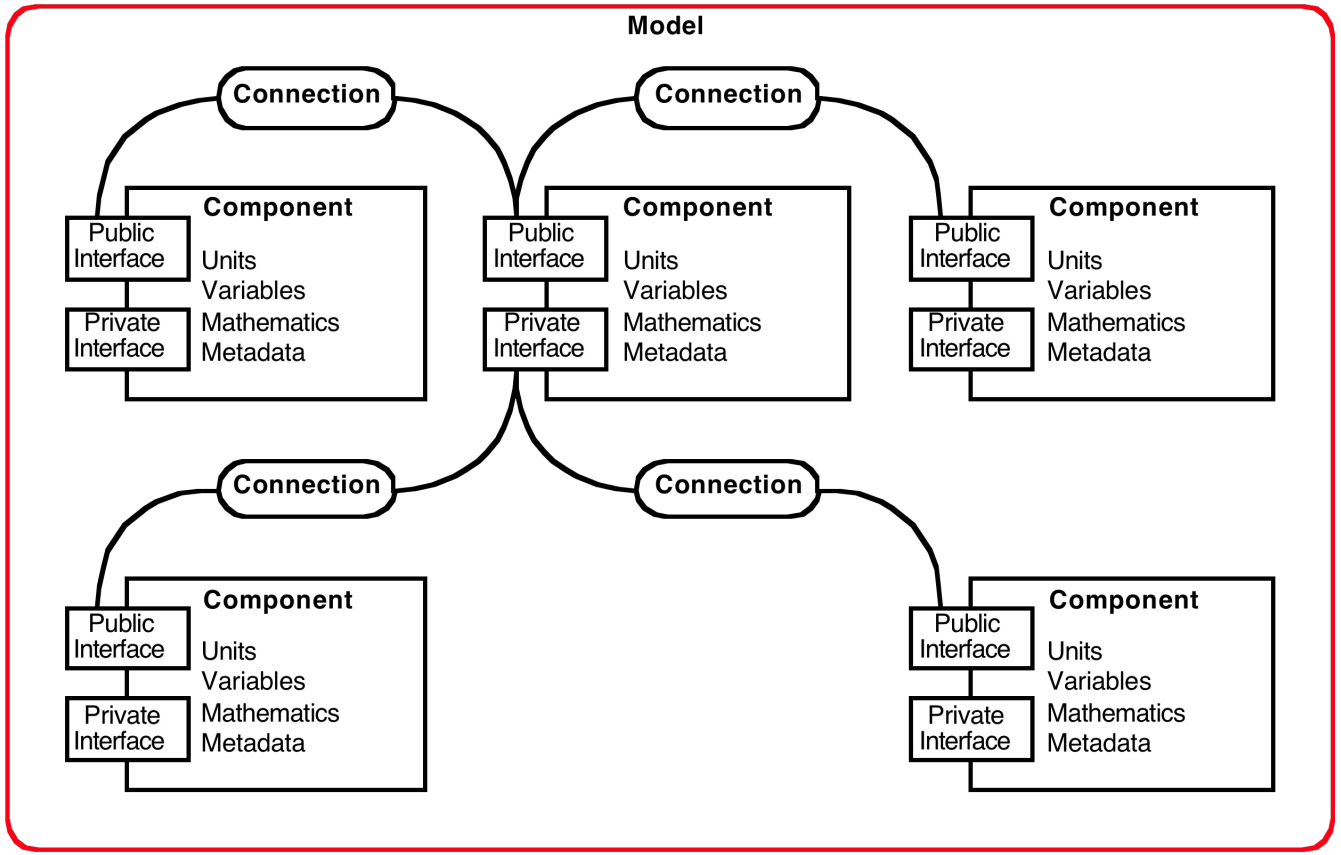
CellML encapsulation

- Encapsulation hierarchies are enabled using *private interfaces*.



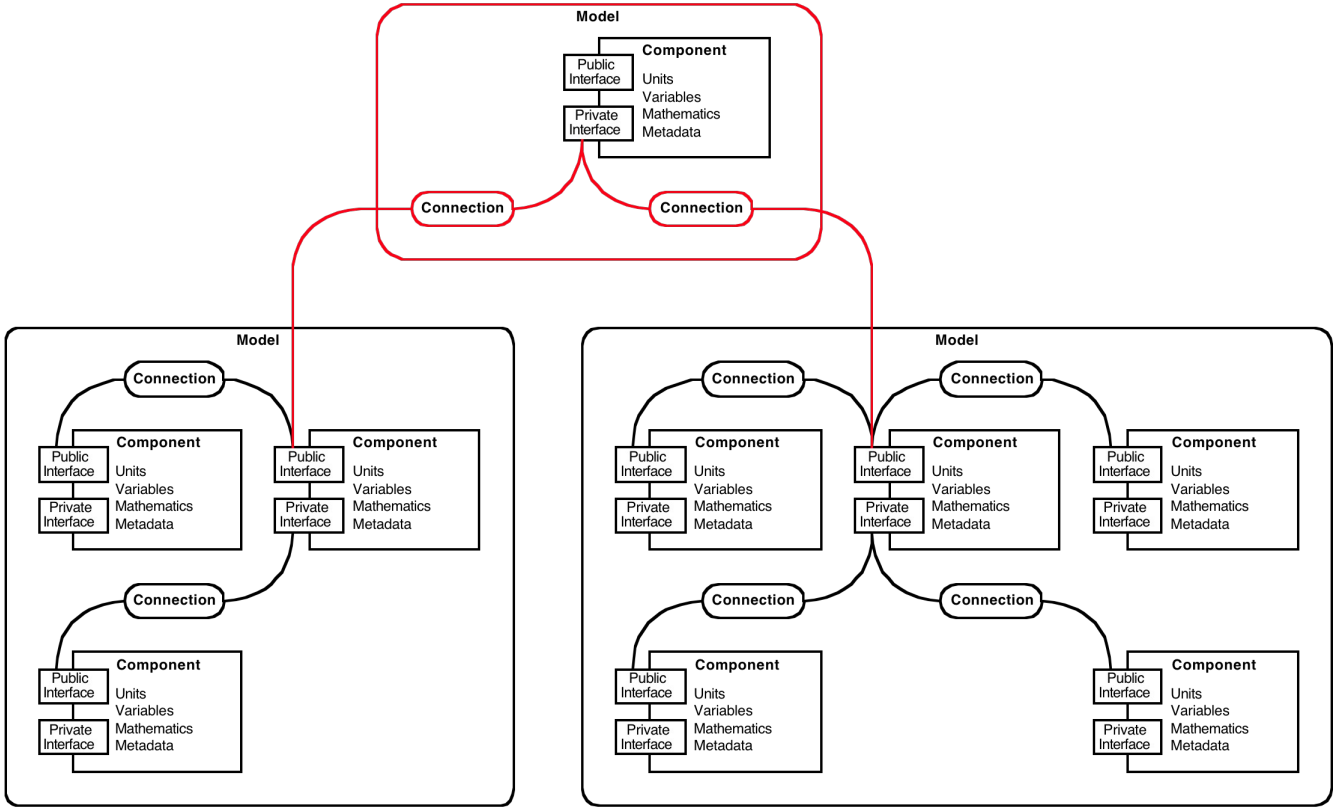
CellML model

•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

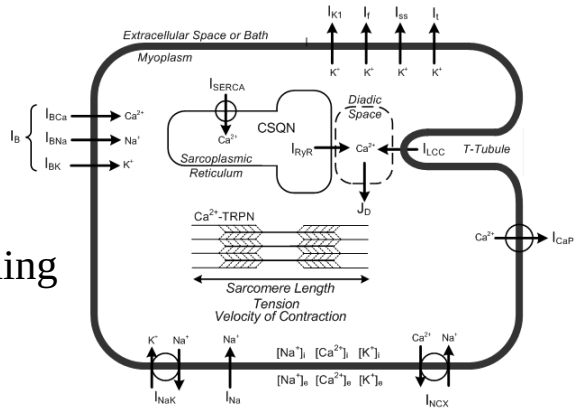
- Model reuse encourages the creation of model libraries.
- This is possible in CellML because there is no distinction between models as stand-alone entities and models as templates.
- Every import creates a new instance of the imported model in the importing model.
- The same model can be imported multiple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

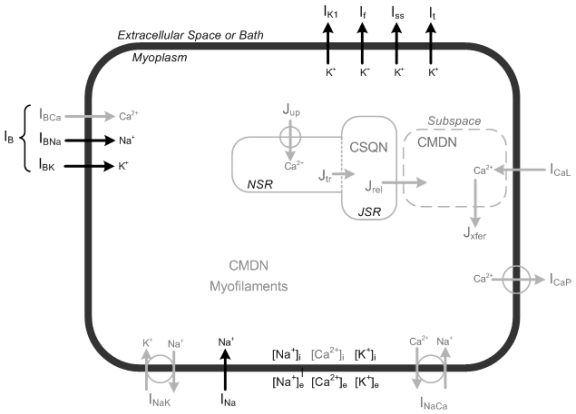
Model libraries

- 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 genericity versus conciseness.

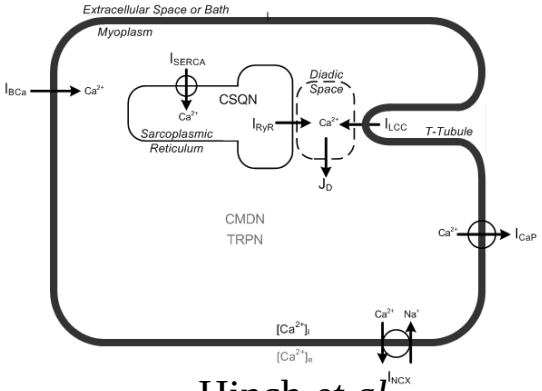
Combine models using CellML import

Terkildsen *et al.*
Integrated model of e-c coupling

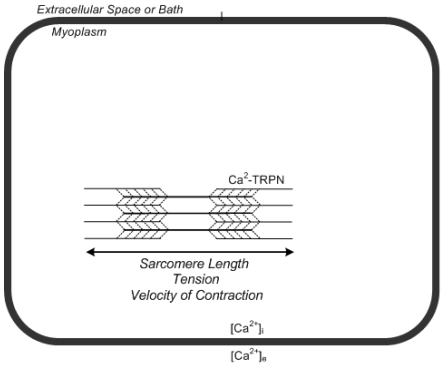




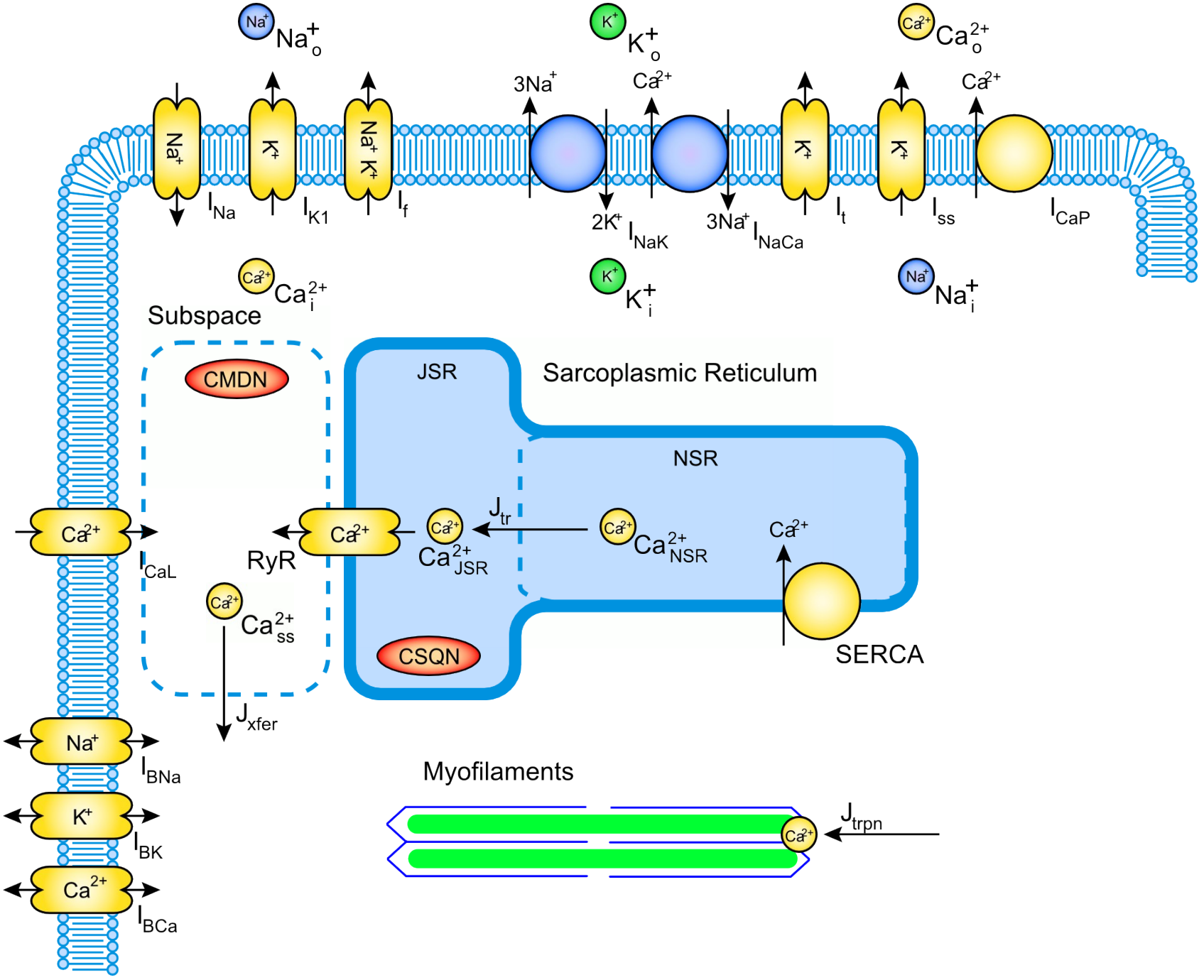
Pandit *et al.*
cardiac action potential

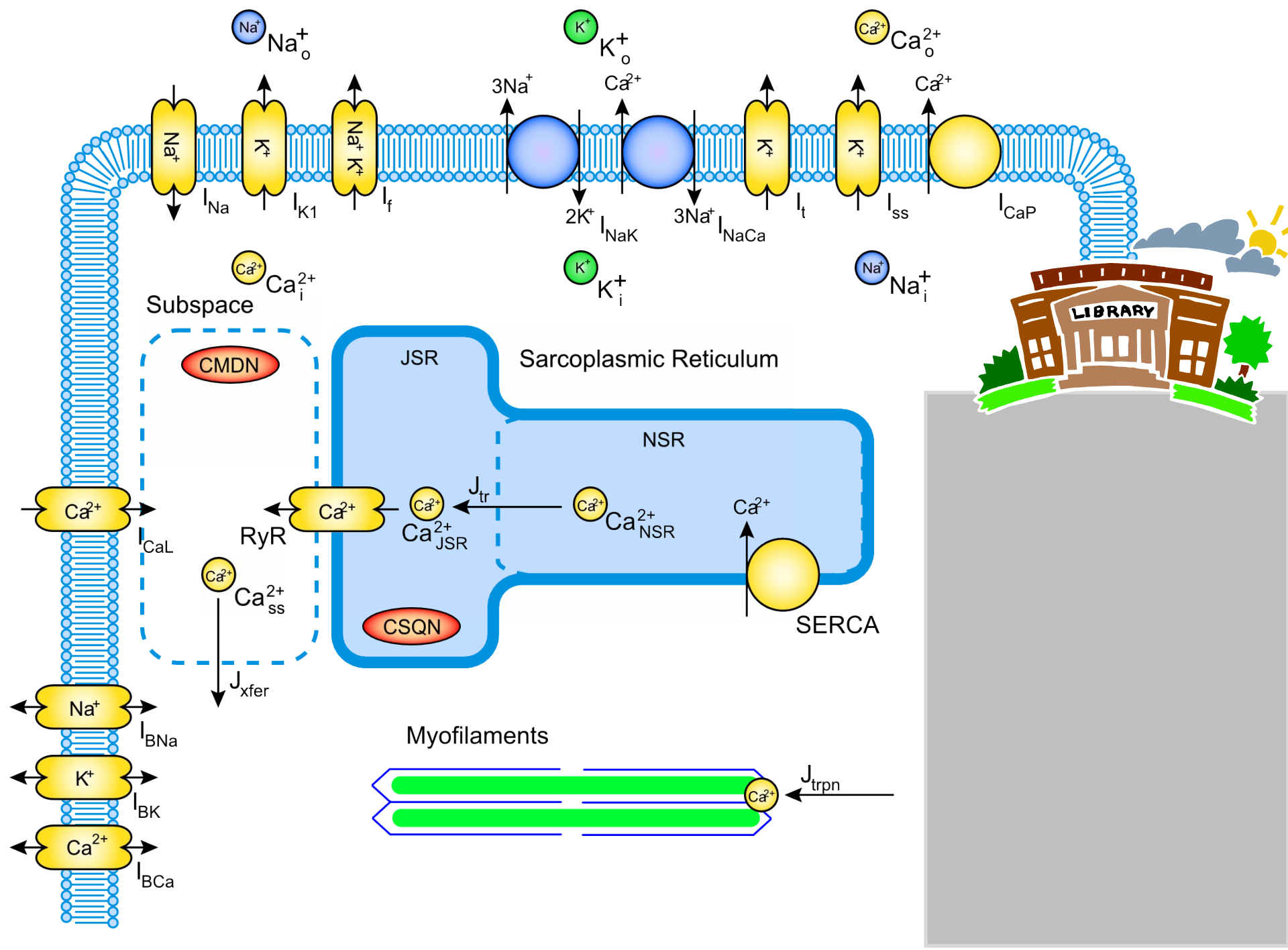


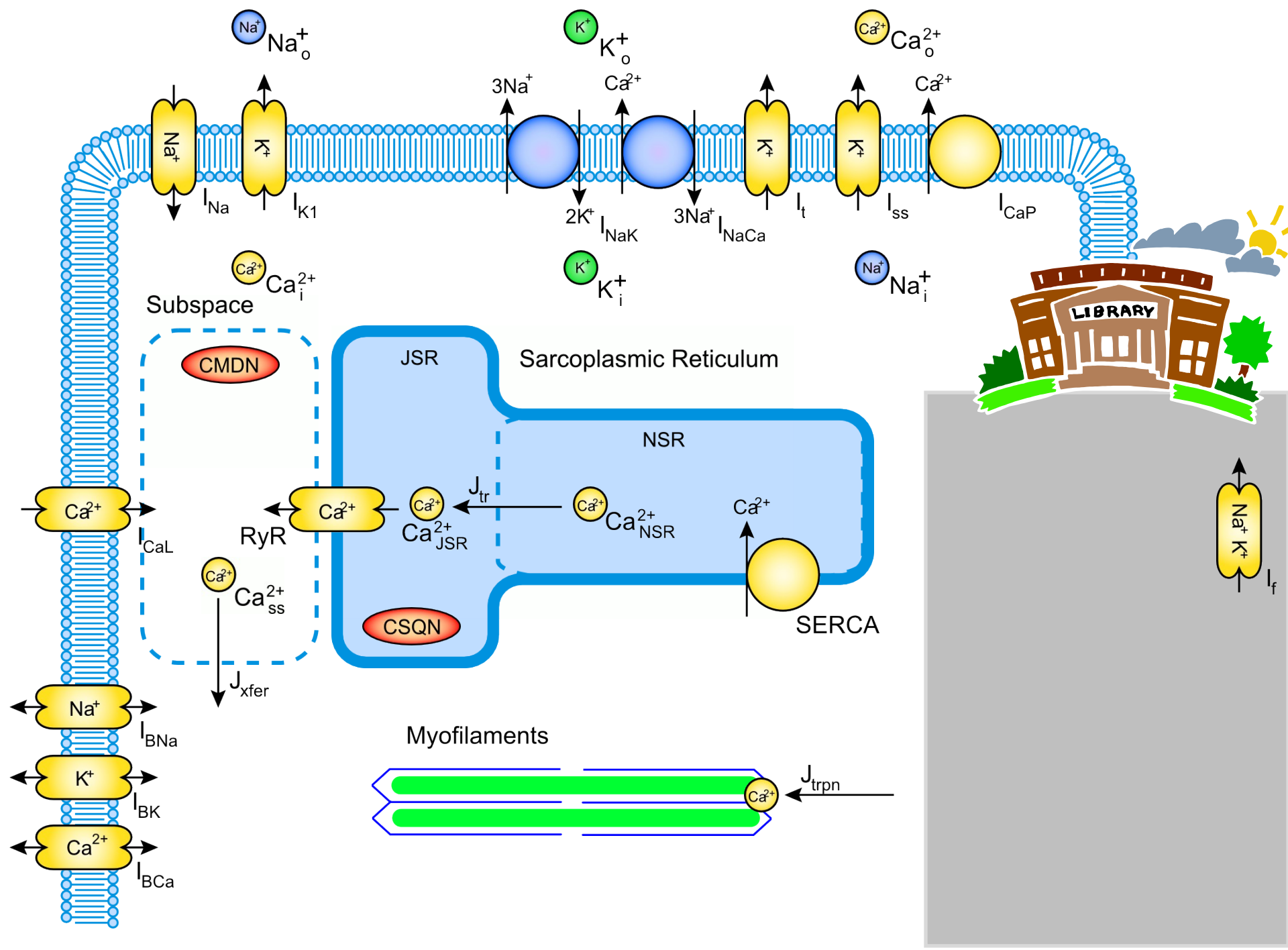
Hinch *et al.*
Ca-induced Ca release

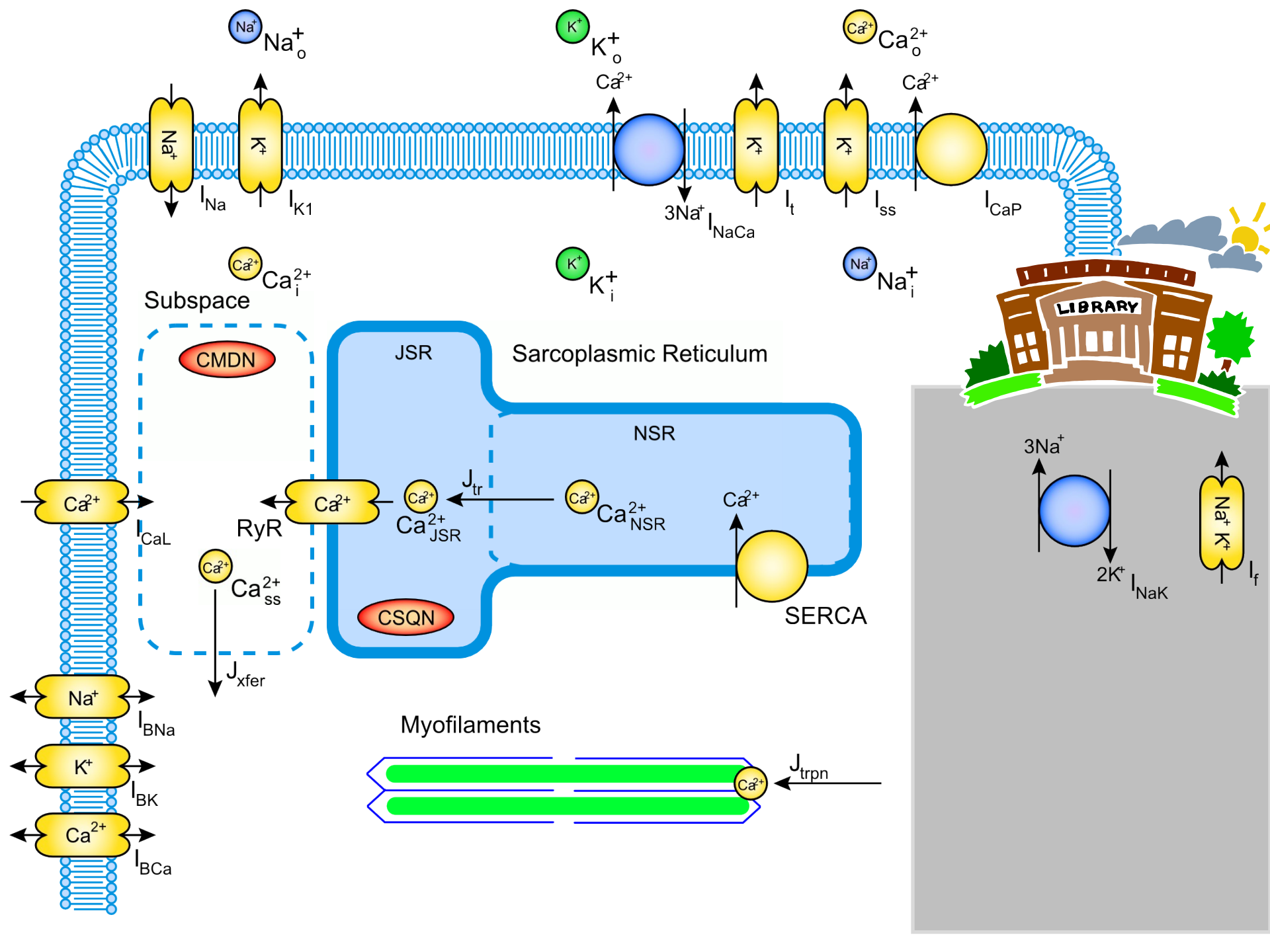


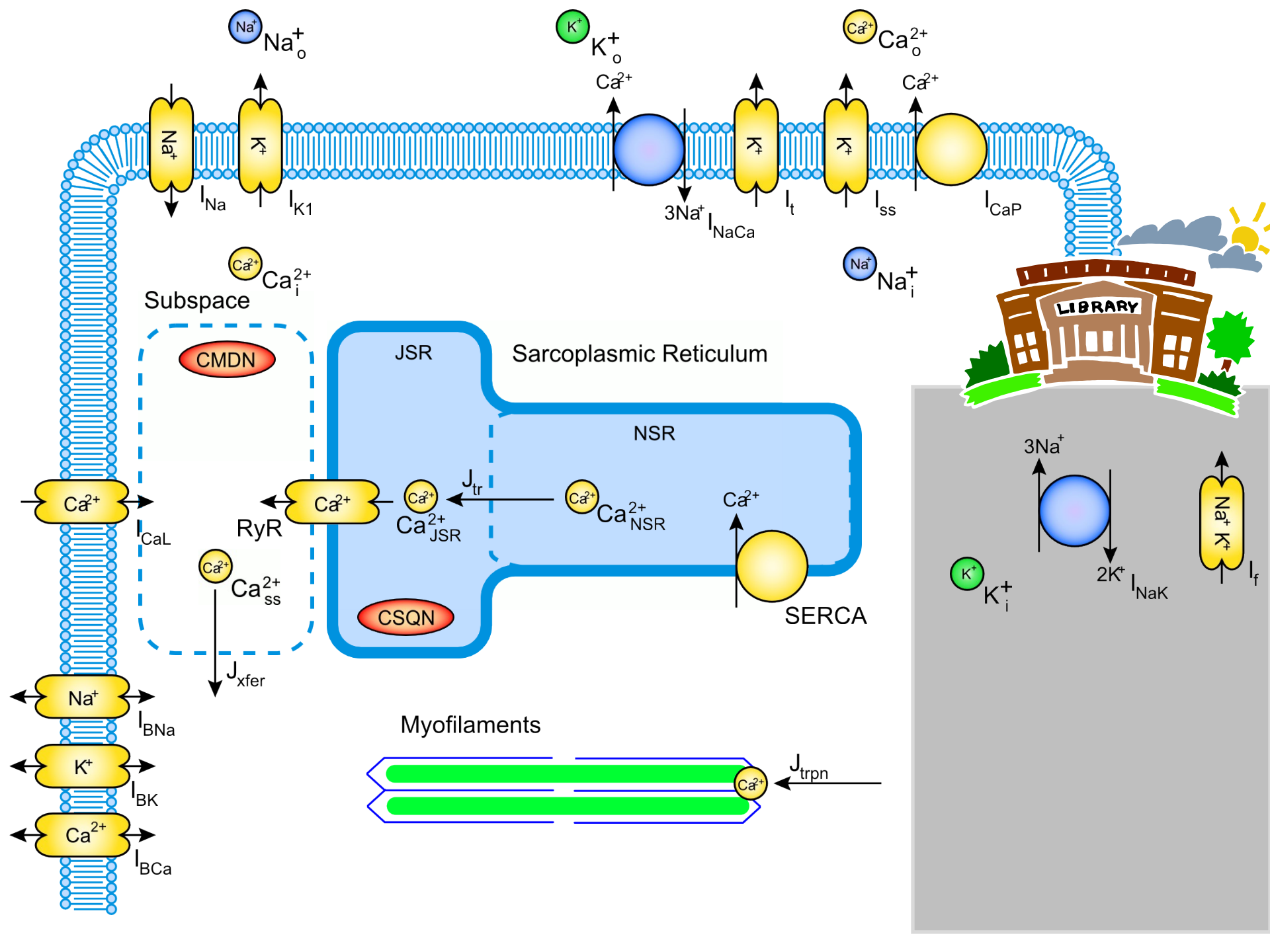
Niederer *et al.*
myofilament mechanics

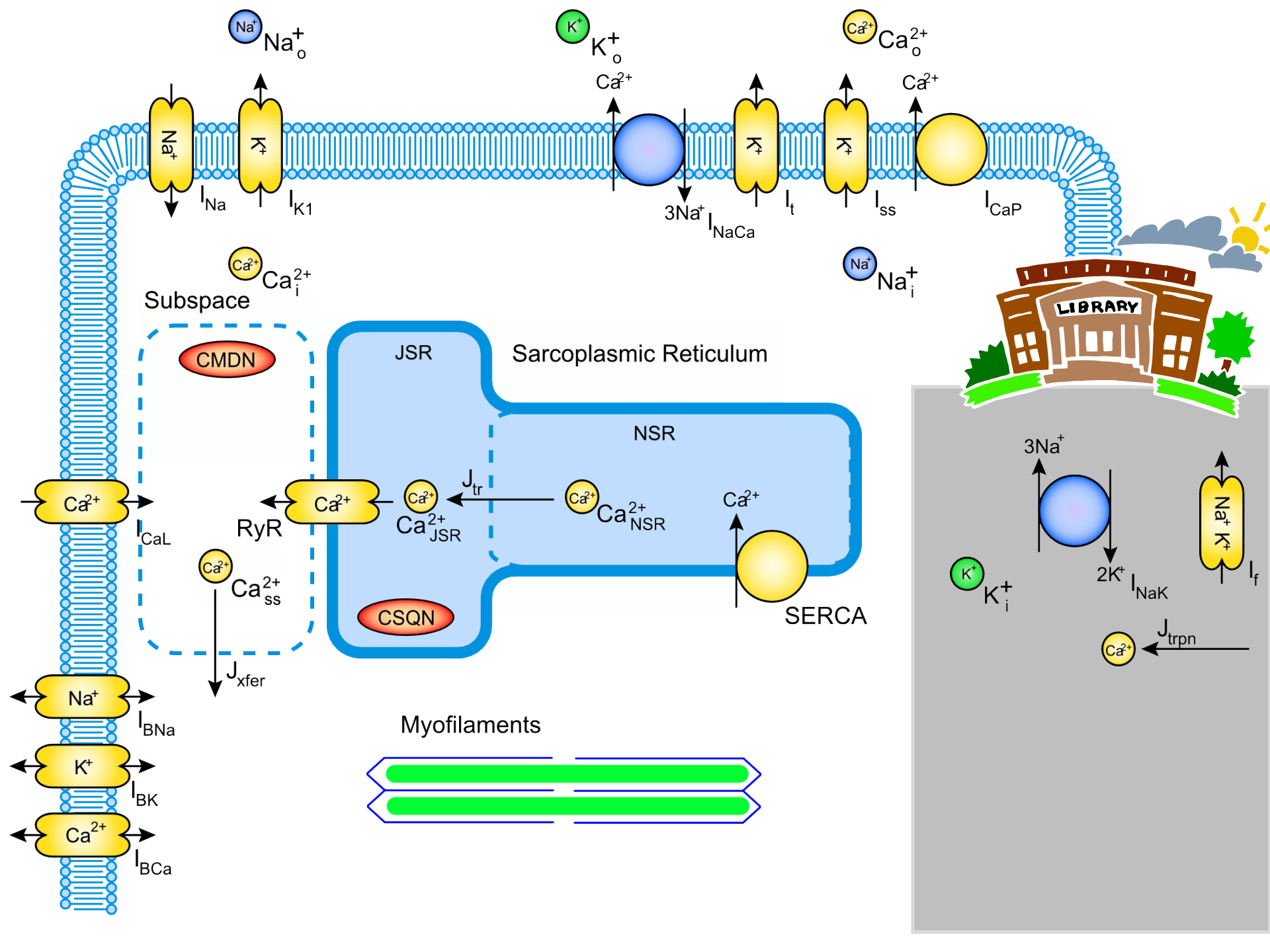

Na^+_o
K^+_o
Ca^{2+}_o
I_{Na}
I_{K1}
I_f
$3Na^+$
$2K^+$
I_{NaK}
$3Na^+$
I_{NaCa}
I_t
I_{ss}
I_{CaP}
Ca^{2+}_i
K^+_i
Na^+_i
Subspace
CMDN
JSR
Sarcoplasmic Reticulum
NSR
J_{tr}
Ca^{2+}_{JSR}
Ca^{2+}_{NSR}
I_{CaL}
RyR
Ca^{2+}_{ss}
J_{xfer}
CSQN
SERCA
I_{BNa}
I_{BK}
I_{BCa}
Myofilaments
J_{trpn}

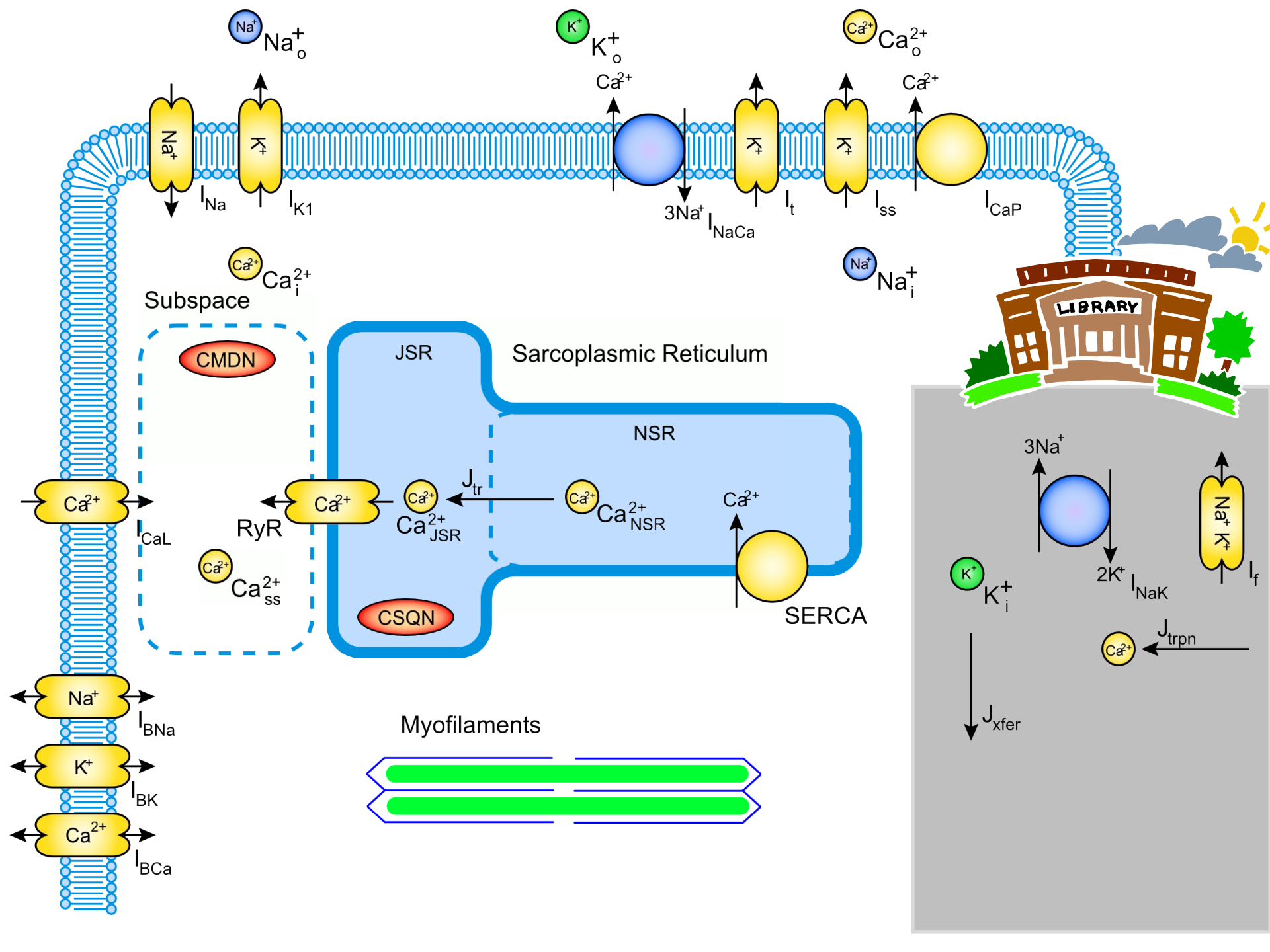

Na^+_o
K^+_o
Ca^{2+}_o
I_{Na}
I_{K1}
I_f
$3Na^+$
$2K^+$
I_{NaK}
$3Na^+$
I_{NaCa}
I_t
I_{ss}
I_{CaP}
Ca^{2+}_i
K^+_i
Na^+_i
Subspace
CMDN
JSR
Sarcoplasmic Reticulum
NSR
J_{tr}
Ca^{2+}_{JSR}
Ca^{2+}_{NSR}
I_{CaL}
RyR
Ca^{2+}_{ss}
J_{xfer}
CSQN
SERCA
I_{BNa}
I_{BK}
I_{BCa}
Myofilaments
J_{trpn}
LIBRARY

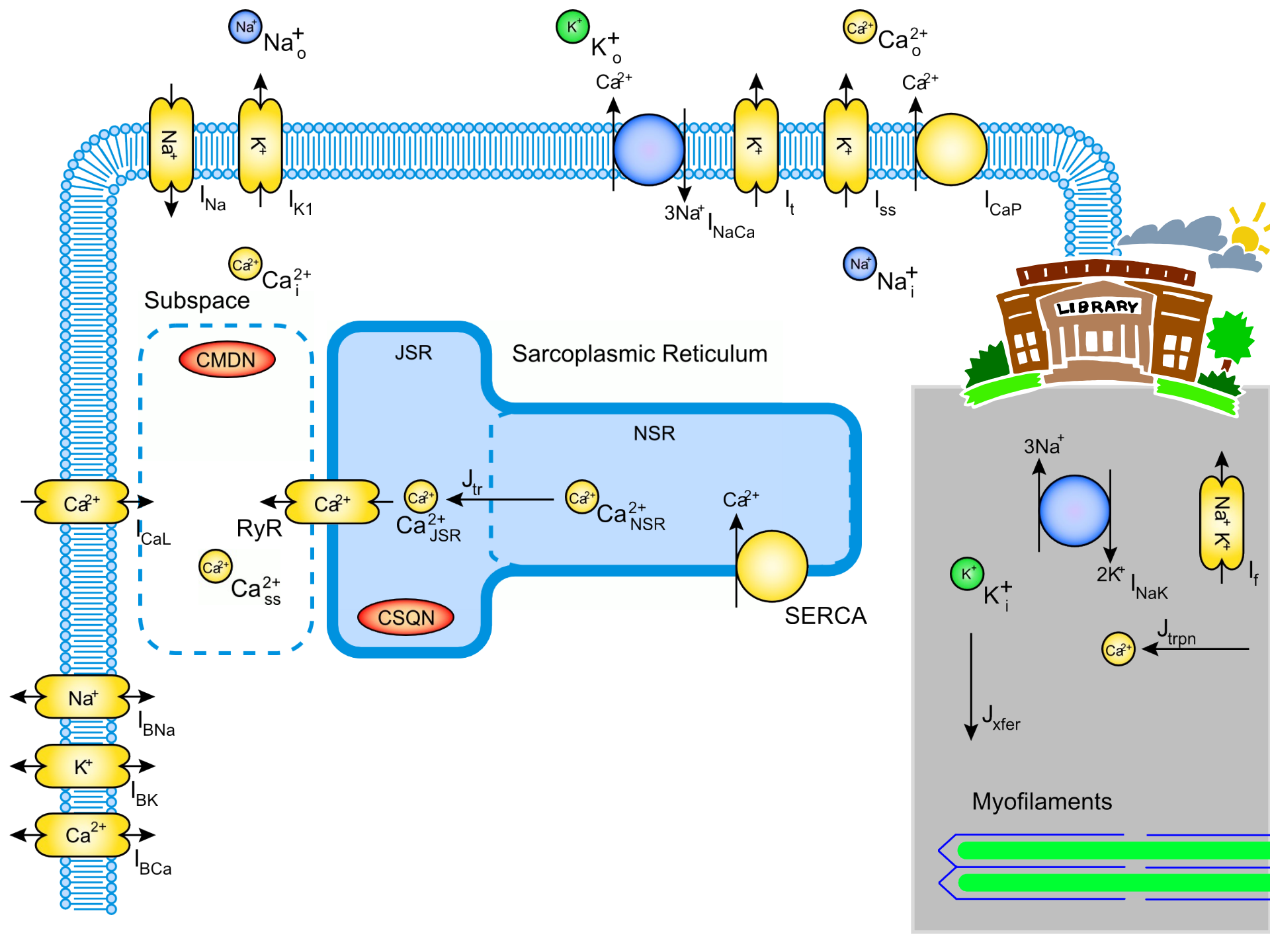

Na^+_o
K^+_o
Ca^{2+}_o
$3Na^+$
Ca^{2+}
I_{Na}
I_{K1}
$2K^+$ I_{NaK}
$3Na^+$ I_{NaCa}
I_t
I_{ss}
I_{CaP}
Ca^{2+}_i
K^+_i
Na^+_i
Subspace
CMDN
JSR
Sarcoplasmic Reticulum
NSR
J_{tr}
Ca^{2+}_{JSR}
Ca^{2+}_{NSR}
RyR
I_{CaL}
Ca^{2+}_{ss}
J_{xfer}
CSQN
SERCA
I_{BNa}
I_{BK}
I_{BCa}
Myofilaments
J_{trpn}
LIBRARY
I_f

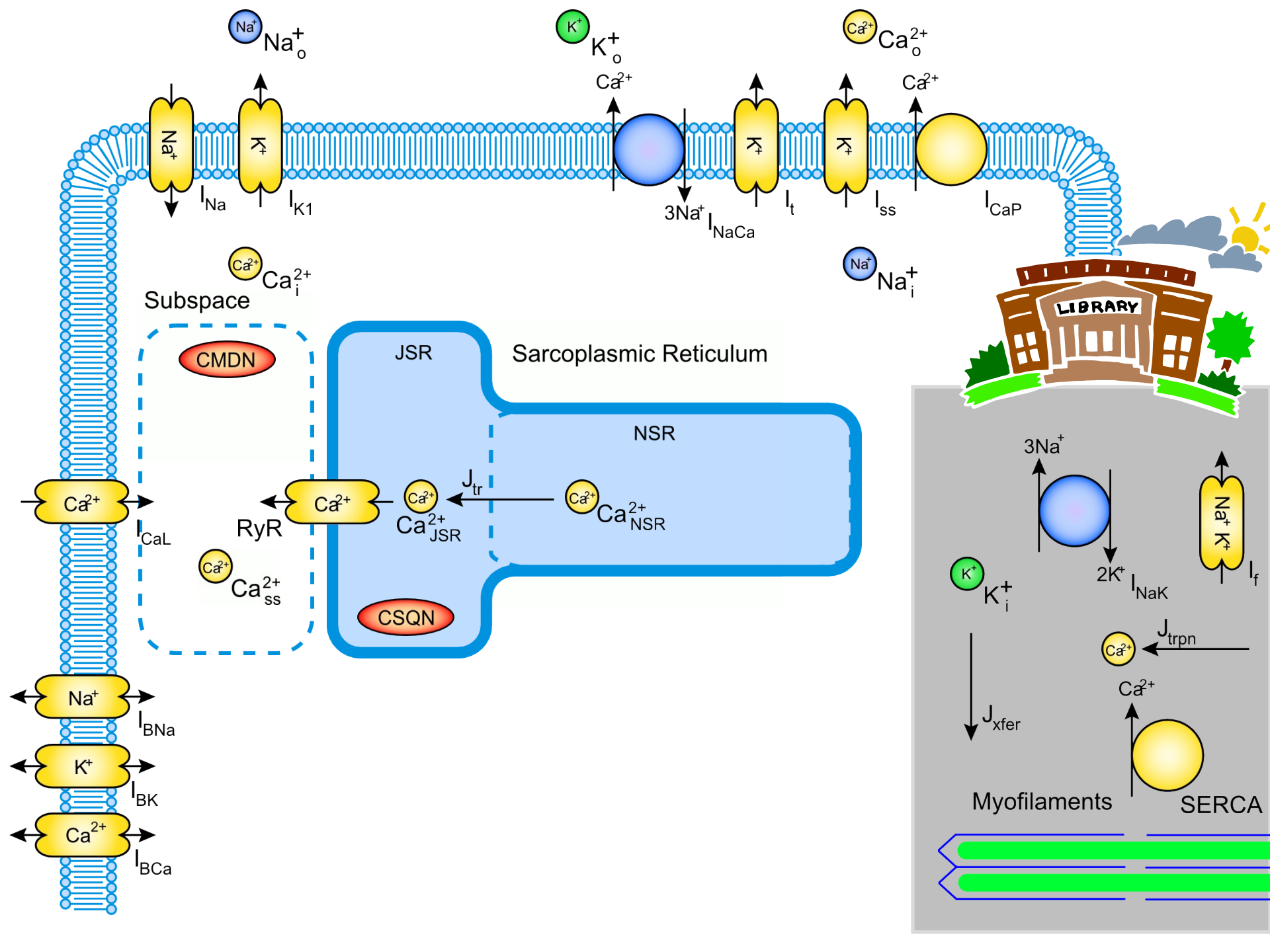

Na^+_o
K^+_o
Ca^{2+}_o
I_{Na}
I_{K1}
$3Na^+$ I_{NaCa}
I_t
I_{ss}
I_{CaP}
Ca^{2+}_i
K^+_i
Na^+_i
Subspace
CMDN
JSR
Sarcoplasmic Reticulum
NSR
J_{tr}
Ca^{2+}_{JSR}
Ca^{2+}_{NSR}
RyR
I_{CaL}
Ca^{2+}_{ss}
J_{xfer}
CSQN
SERCA
I_{BNa}
I_{BK}
I_{BCa}
Myofilaments
J_{trpn}
LIBRARY
$3Na^+$
$2K^+$ I_{NaK}
I_f


Na^+_o
K^+_o
Ca^{2+}_o
I_{Na}
I_{K1}
$3Na^+$ I_{NaCa}
I_t
I_{ss}
I_{CaP}
Ca^{2+}_i
Na^+_i
Subspace
CMDN
JSR
Sarcoplasmic Reticulum
NSR
J_{tr}
Ca^{2+}_{JSR}
Ca^{2+}_{NSR}
RyR
I_{CaL}
Ca^{2+}_{ss}
J_{xfer}
CSQN
SERCA
I_{BNa}
I_{BK}
I_{BCa}
Myofilaments
J_{trpn}
LIBRARY
$3Na^+$
$2K^+$ I_{NaK}
Na^+ K^+
I_f
K^+_i


Na^+_o
K^+_o
Ca^{2+}_o
I_{Na}
I_{K1}
$3Na^+ I_{NaCa}$
I_t
I_{ss}
I_{CaP}
Ca^{2+}_i
Na^+_i
Subspace
CMDN
JSR
Sarcoplasmic Reticulum
NSR
J_{tr}
Ca^{2+}_{JSR}
Ca^{2+}_{NSR}
RyR
I_{CaL}
Ca^{2+}_{ss}
J_{xfer}
CSQN
SERCA
I_{BNa}
I_{BK}
I_{BCa}
Myofilaments
LIBRARY
$3Na^+$
$2K^+ I_{NaK}$
I_f
K^+_i
J_{trpn}


Na^+_o
K^+_o
Ca^{2+}_o
I_{Na}
I_{K1}
$3Na^+$ I_{NaCa}
I_t
I_{ss}
I_{CaP}
Ca^{2+}_i
Na^+_i
Subspace
CMDN
JSR
Sarcoplasmic Reticulum
NSR
J_{tr}
Ca^{2+}_{JSR}
Ca^{2+}_{NSR}
RyR
Ca^{2+}_{ss}
I_{CaL}
CSQN
SERCA
I_{BNa}
I_{BK}
I_{BCa}
Myofilaments
LIBRARY
$3Na^+$
$2K^+$ I_{NaK}
I_f
K^+_i
J_{trpn}
J_{xfer}


Na^+_o
K^+_o
Ca^{2+}_o
I_{Na}
I_{K1}
$3Na^+$ I_{NaCa}
I_t
I_{ss}
I_{CaP}
Ca^{2+}_i
Subspace
Na^+_i
CMDN
JSR
Sarcoplasmic Reticulum
NSR
J_{tr}
Ca^{2+}_{JSR}
Ca^{2+}_{NSR}
I_{CaL}
RyR
Ca^{2+}_{ss}
CSQN
SERCA
I_{BNa}
I_{BK}
I_{BCa}
LIBRARY
$3Na^+$
$2K^+$ I_{NaK}
I_f
K^+_i
J_{trpn}
J_{xfer}
Myofilaments


Na^+_o
K^+_o
Ca^{2+}_o
I_{Na}
I_{K1}
$3Na^+$ I_{NaCa}
I_t
I_{ss}
I_{CaP}
Ca^{2+}_i
Na^+_i
Subspace
CMDN
JSR
Sarcoplasmic Reticulum
NSR
J_{tr}
Ca^{2+}_{NSR}
Ca^{2+}_{JSR}
RyR
I_{CaL}
Ca^{2+}_{ss}
CSQN
I_{BNa}
I_{BK}
I_{BCa}
LIBRARY
$3Na^+$
$2K^+$ I_{NaK}
Na^+ K^+
I_f
K^+_i
J_{trpn}
J_{xfer}
Myofilaments
SERCA

Best practice

- Most useful non-trivial library components describe clearly identifiable biophysical processes.
- Sarala Wimilaratne has given several examples of this approach in her PhD thesis on CellML model visualisation (Cooling 07 GCPR cycle, Hodgkin-Huxley 52, Nobel 62).
- We are compiling a list of best-practice examples based on the experience gained through the process of model decomposition.
- This work is still in its early stages – there is still much to be learned about which approaches offer the best long-term benefits.

Best practice

- Put reusable mathematics in separate components, and use <*import*>s to instantiate these for use where appropriate.
- Use '*_delta*' components to extensibly connect multiple fluxes to species of interest.
- Use separate conversion components for connections where applicable.
- Build coarse-grained components from aggregations of finer-grained, biologically atomic components.
- Define <*units*> at the lowest level possible, <*import*>ing into higher level components as necessary.
- Separate out all parameter values into one or more non-mathematical CellML documents.
- Universal constants should be <*import*>ed from a non-mathematical CellML document (a standard based document on [UC] is recommended).
- If encapsulating, expose all potentially useful values using *public_interface*="*out*".

The CellML Model Repository and Model Curation

Dr Catherine Lloyd
Senior Database Curator
Auckland Bioengineering Institute

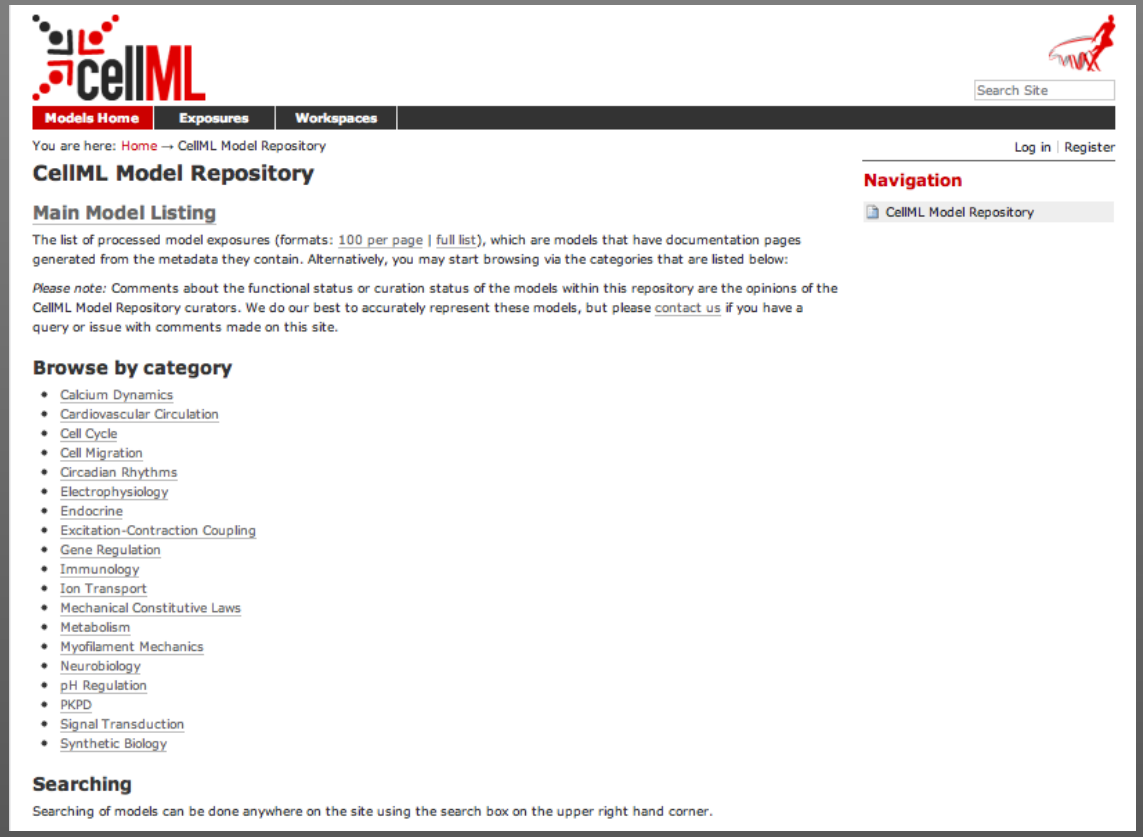
The CellML Model Repository and Model Curation

Physiome

Dr Catherine Lloyd
Senior Database Curator
Auckland Bioengineering Institute

The CellML model repository

http://models.cellml.org



- Began life as a set of test cases
- Today contains >500 models
- Most the models are derived from published papers
- All the models are free for download

cellML

Model categories include

signal transduction

electrophysiology

calcium dynamics

metabolism

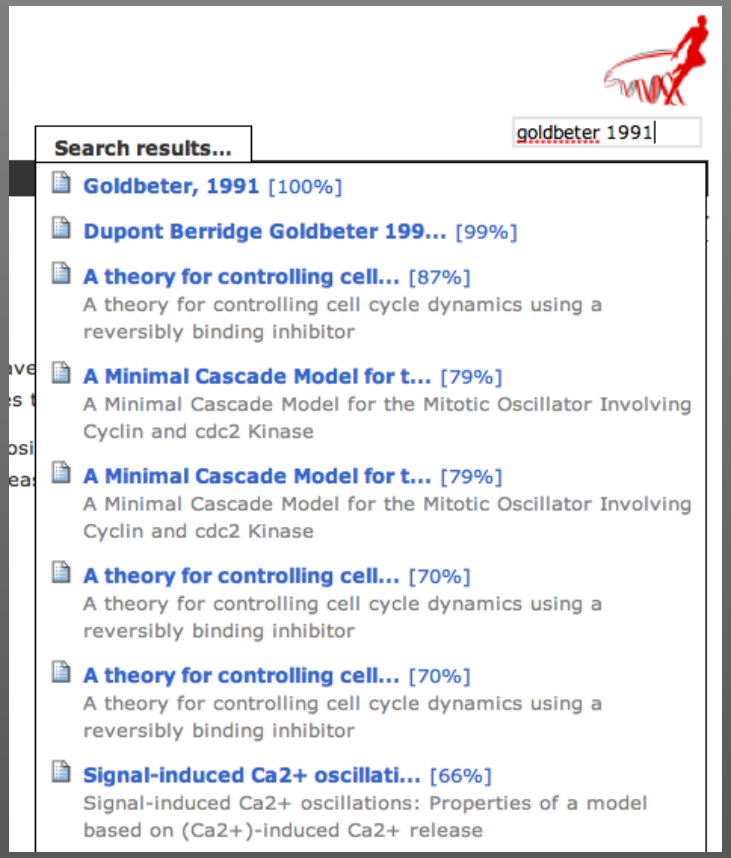
cell cycle

muscle contraction

immunology

synthetic biology

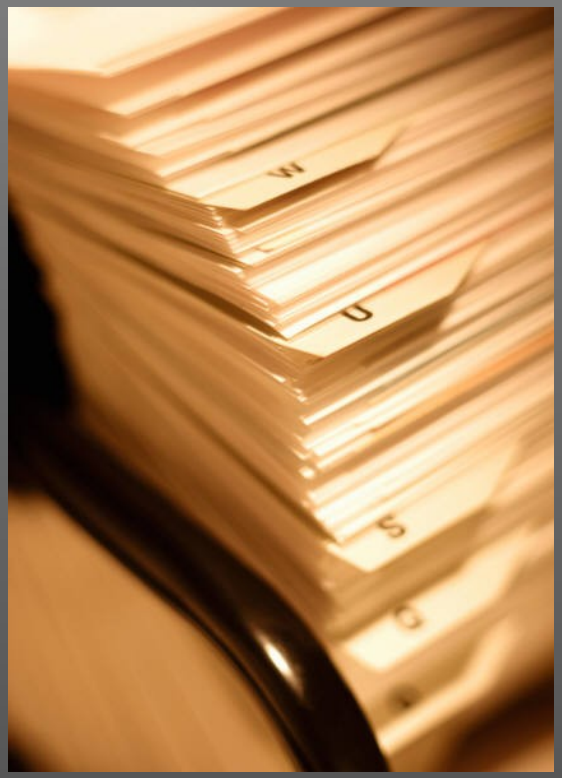
How to find a model



Browse by category

- Calcium Dynamics
- Cardiovascular Circulation
- Cell Cycle
- Cell Migration
- Circadian Rhythms
- Electrophysiology
- Endocrine
- Excitation-Contraction Coupling
- Gene Regulation
- Immunology
- Ion Transport
- Mechanical Constitutive Laws
- Metabolism
- Myofilament Mechanics
- Neurobiology
- pH Regulation
- PKPD
- Signal Transduction
- Synthetic Biology

The repository is more than just a storage system

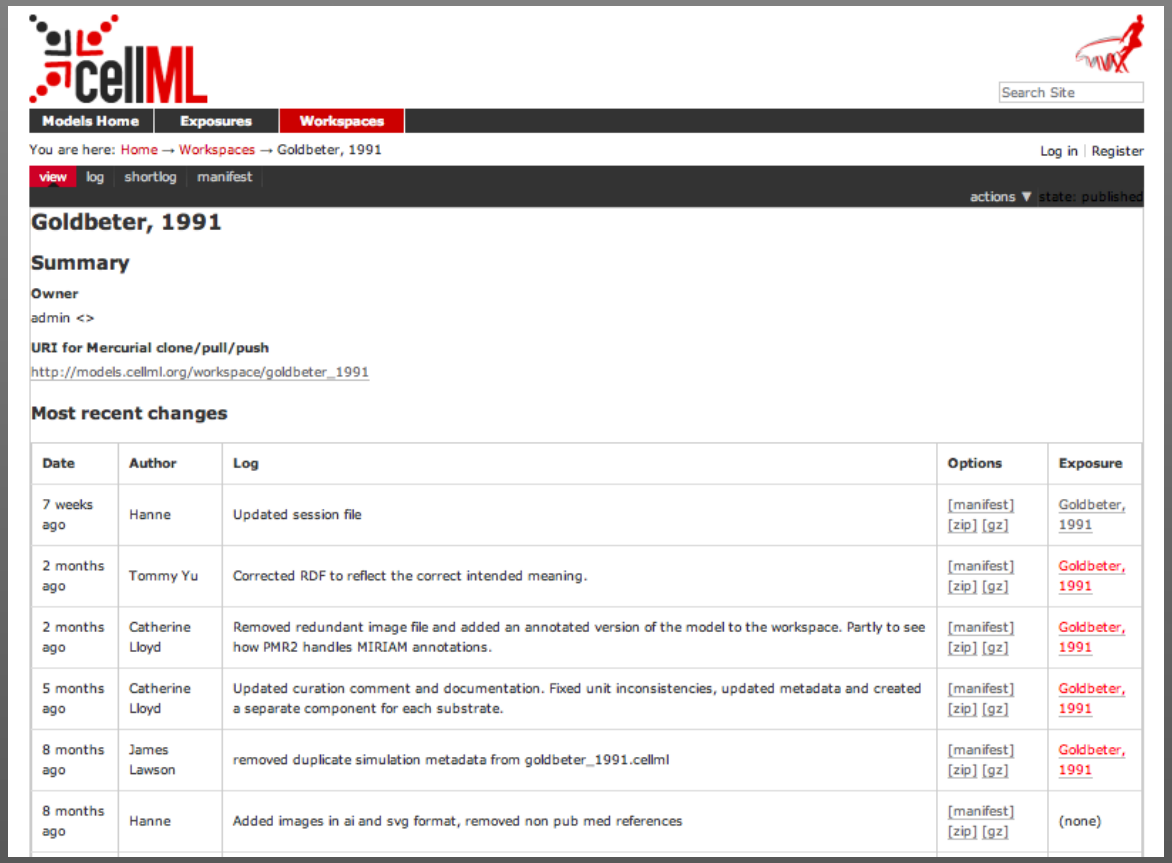


cellML

It's designed to facilitate model exchange and reuse

cellML

Workspace and change-history



cellML

Search Site

Models Home | Exposures | Workspaces

You are here: Home → Workspaces → Goldbeter, 1991

Log in | Register

view | log | shortlog | manifest

actions ▼ state: published

Goldbeter, 1991

Summary

Owner

admin <>

URI for Mercurial clone/pull/push

http://models.cellml.org/workspace/goldbeter_1991

Most recent changes

Date	Author	Log	Options	Exposure
7 weeks ago	Hanne	Updated session file	[manifest] [zip] [gz]	Goldbeter, 1991
2 months ago	Tommy Yu	Corrected RDF to reflect the correct intended meaning.	[manifest] [zip] [gz]	Goldbeter, 1991
2 months ago	Catherine Lloyd	Removed redundant image file and added an annotated version of the model to the workspace. Partly to see how PMR2 handles MIRIAM annotations.	[manifest] [zip] [gz]	Goldbeter, 1991
5 months ago	Catherine Lloyd	Updated curation comment and documentation. Fixed unit inconsistencies, updated metadata and created a separate component for each substrate.	[manifest] [zip] [gz]	Goldbeter, 1991
8 months ago	James Lawson	removed duplicate simulation metadata from goldbeter_1991.cellml	[manifest] [zip] [gz]	Goldbeter, 1991
8 months ago	Hanne	Added images in ai and svg format, removed non pub med references	[manifest] [zip] [gz]	(none)

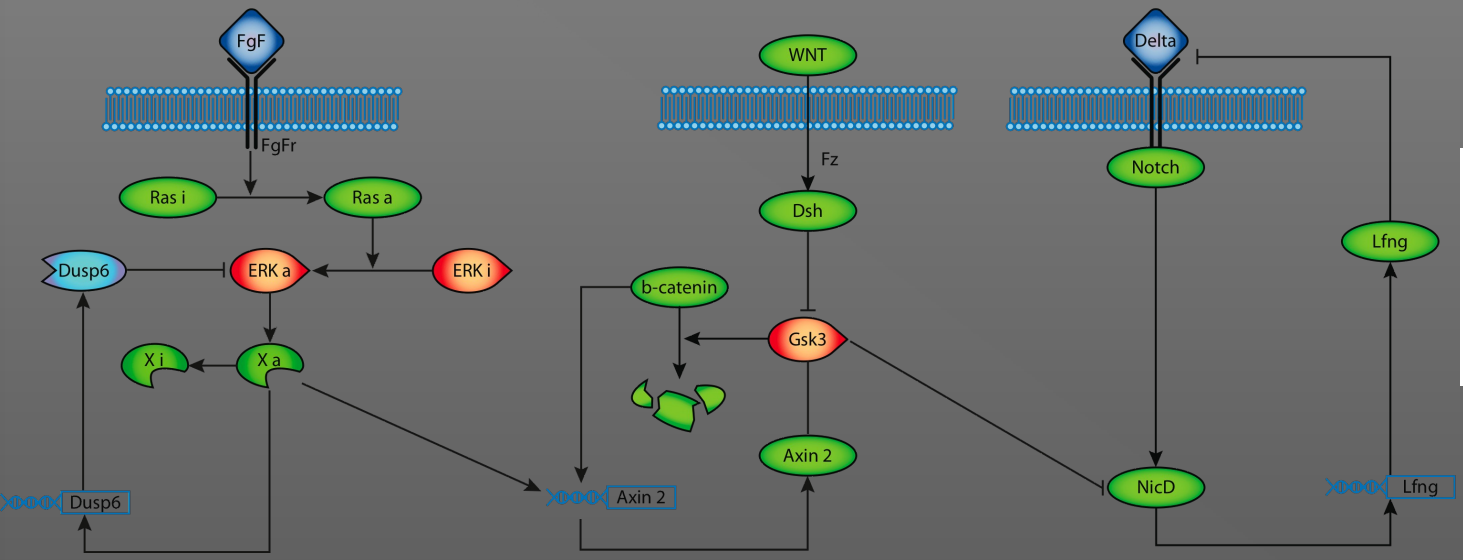
- Each model and its associated files are stored together in a ***workspace***
- Every alteration is recorded and time-stamped to provide a detailed ***change-history***

cellML

Exposure

Goldbeter, Pourquie, 2008

Modeling the segmentation clock as a network of coupled oscillations in the Notch, Wnt and FGF signaling pathways



Model Curation

Curation Status: ★★☆

OpenCell: ★★☆

JSim: ☆☆☆

COR: ★★☆

Modeling the segmentation clock as a network of coupled oscillations in the Notch, Wnt and FGF signaling pathways, Albert Goldbeter and Olivier Pourquie, 2008, *Journal of Theoretical Biology*, 252, 574-585. PubMed ID: 18308339

- Each model entry may be accompanied by an abstract, curation status, citation, and a schematic diagram.

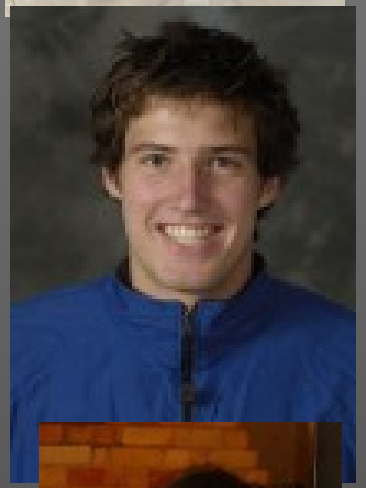
Who is submitting the models?

Curators

- Modellers
- Curators & modellers together





Curation

- Curation involves model validation & annotation
- A star system denotes the curation status of a model
- There's also a more detailed model status comment on display, and the change-history comments recorded in the workspace

Model Status

This CellML model runs in both PCEnv and COR to recreate the published results. The units have been checked and they are consistent. In this particular version of the model couples the Notch, Wnt and FGF signalling pathways together and so uses equations A17 and A18 in the appendix to replace equations A4 and A10 respectively.

Why curate models?

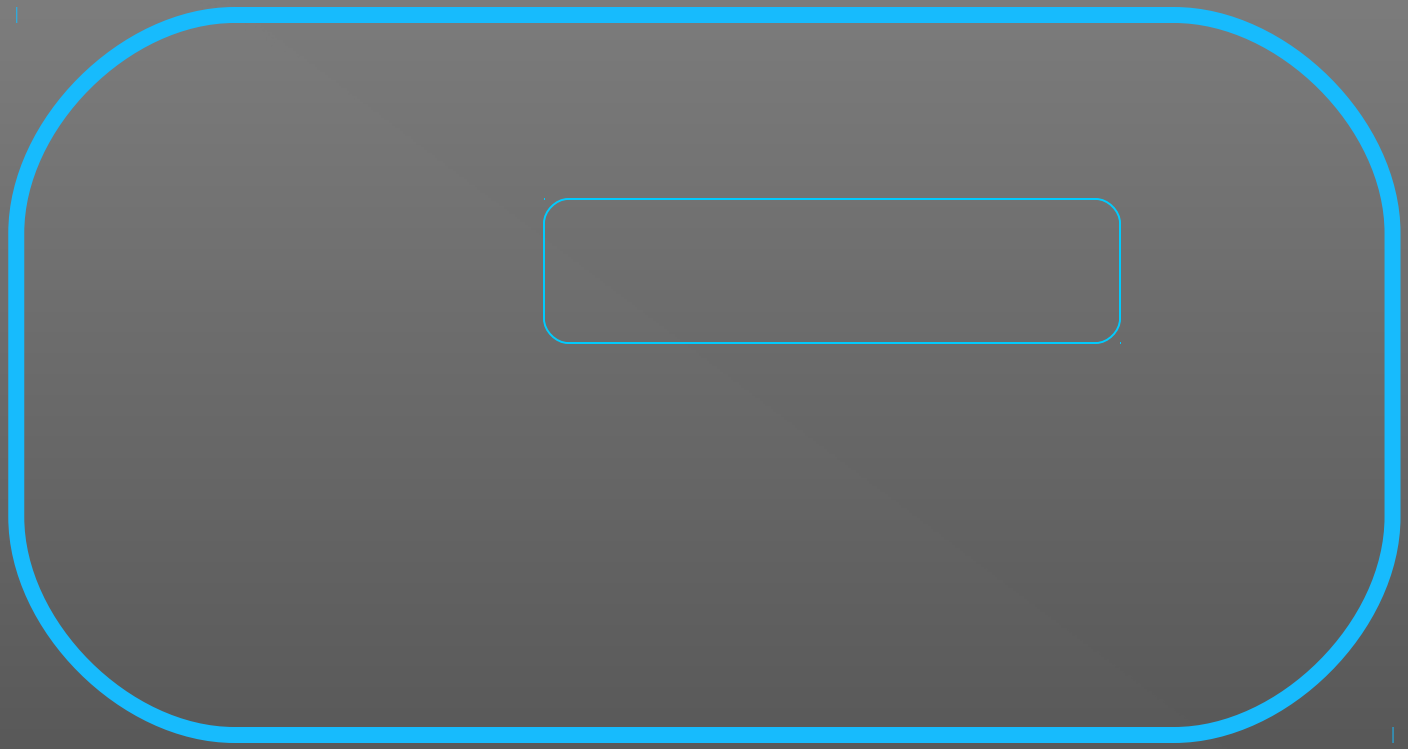
FACT: Of the ~500 models in the repository only a small handful have been directly translated from the published paper into a working CellML model

- QUOTE: *"As anyone who has tried to reproduce a published mathematical model will testify, it's a long, tedious, and generally futile task. Equations are replaced by ambiguous descriptions, parameter values are left undefined and, worst of all, the main author has given up science to set up a vegan cup-cake business."* Dr K. S.

Where are things heading?

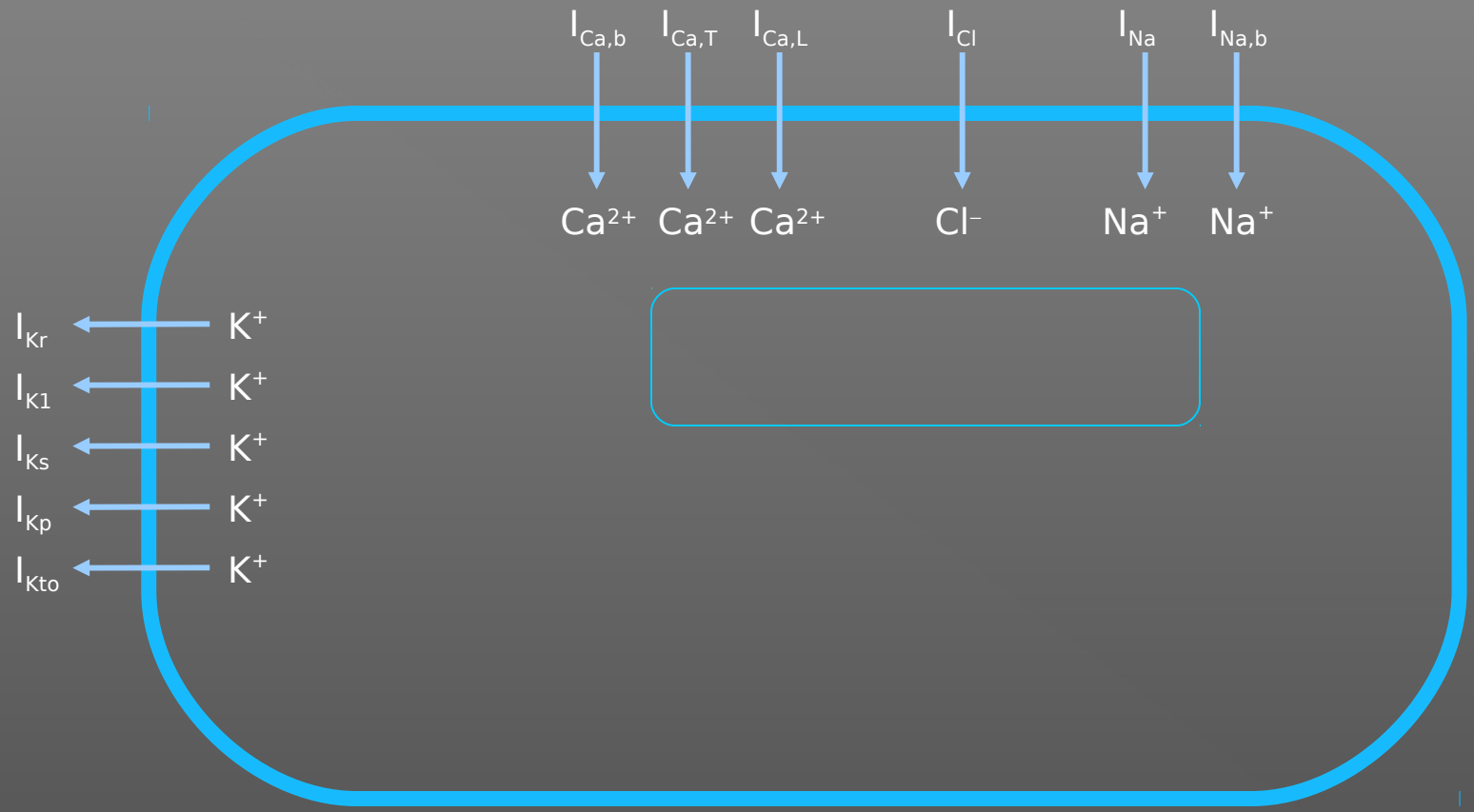
A library of smaller models

A library of smaller models



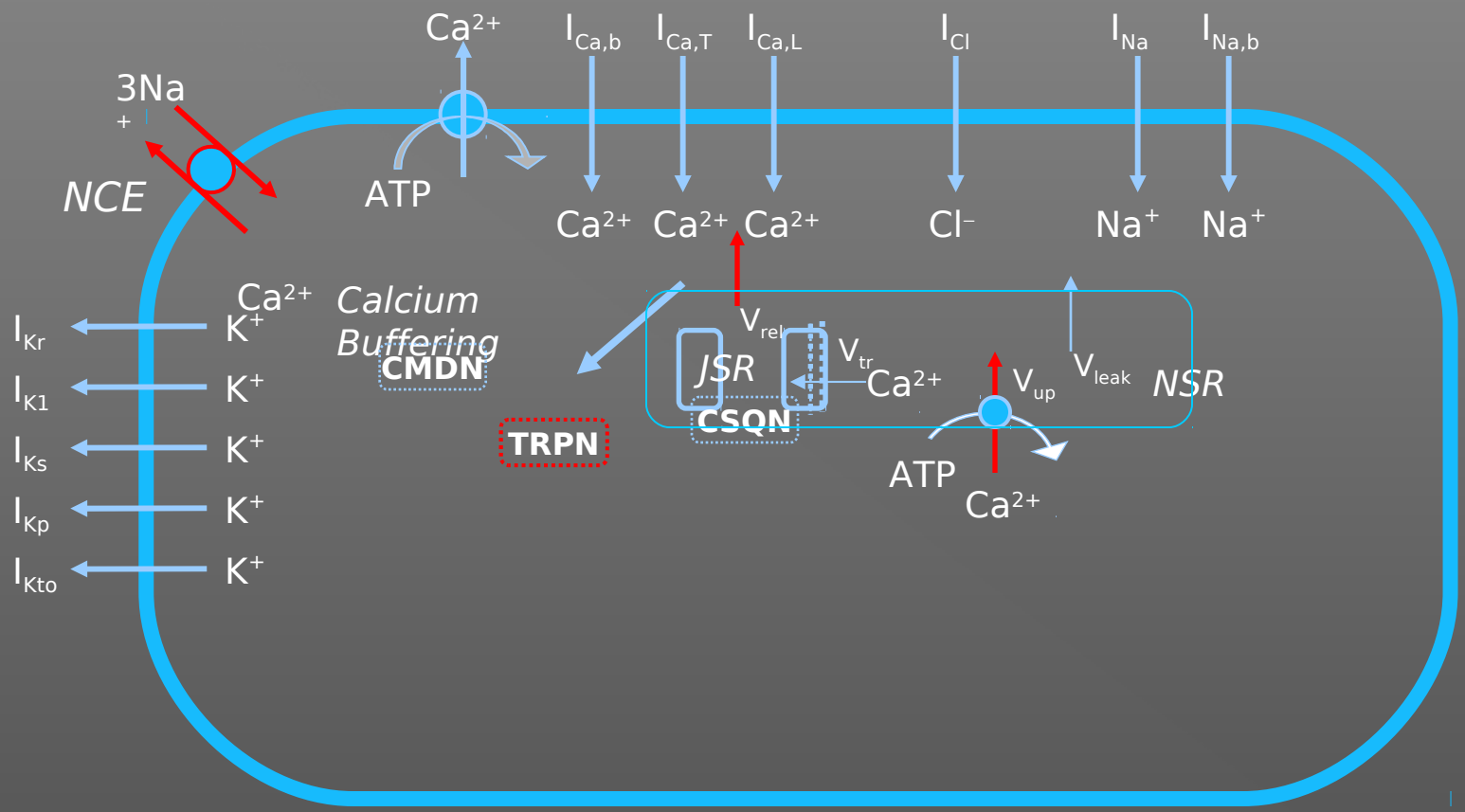
cellML

A library of smaller models



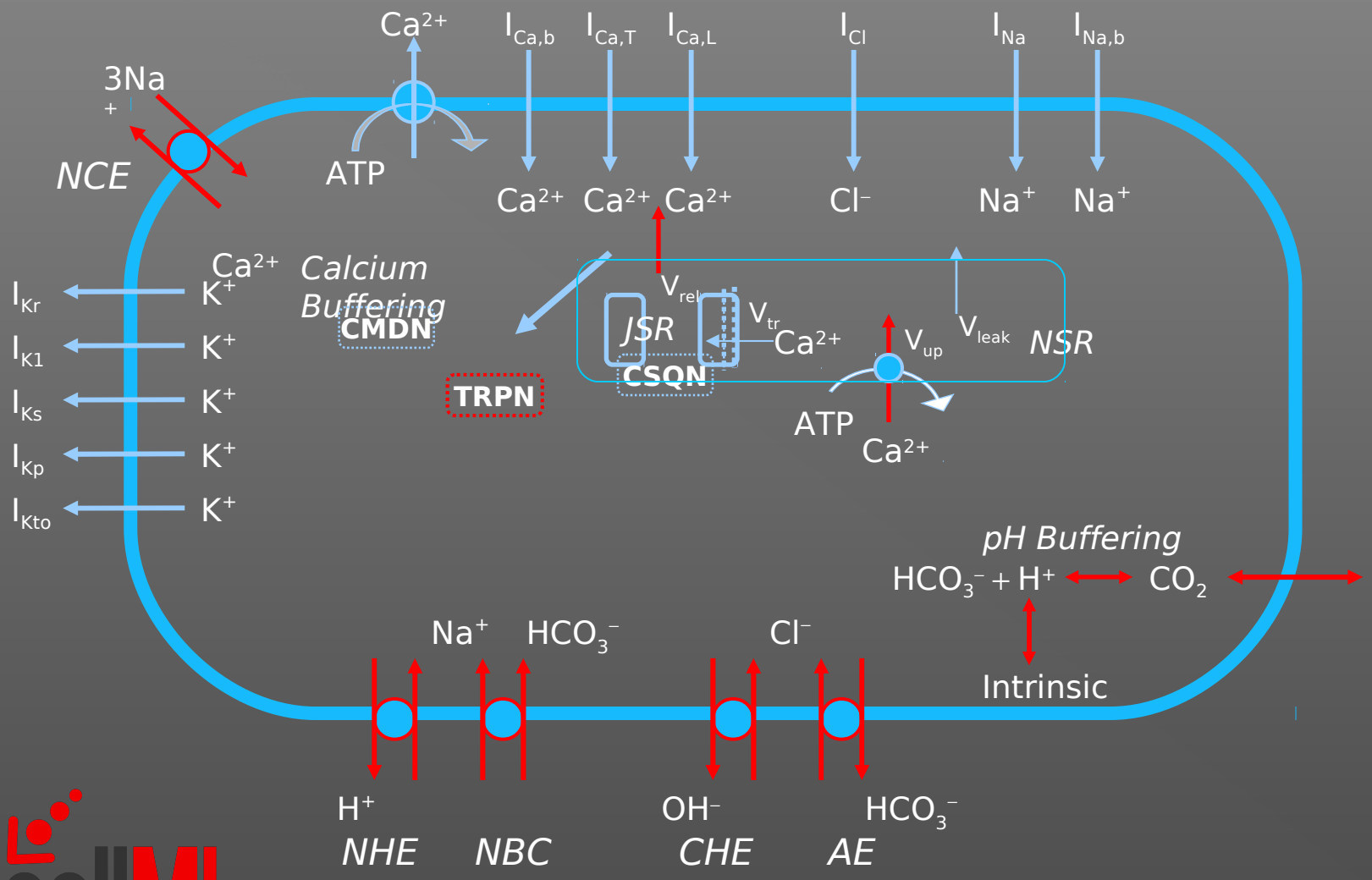
cellML

A library of smaller models



cellML

A library of smaller models



cellML

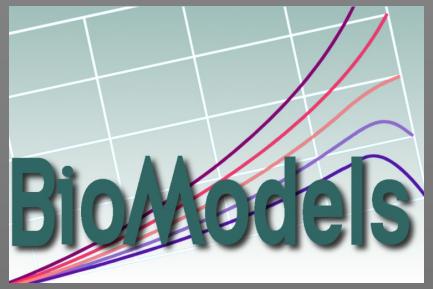
Model annotation

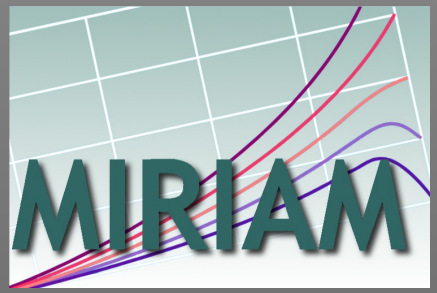
```
<component cmeta:id="M_star" name="M_star">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#M_star">
      <dc:title>M_star</dc:title>
        <dcterms:alternative>fraction of inactive cdc2 kinase</dcterms:alternative>
    </rdf:Description>
  </rdf:RDF>
  <variable units="dimensionless" public_interface="out" name="M_star" cmeta:id="M_M_" >
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/dc/elements/1.1/"
xmlns:dcterms="http://purl.org/dc/terms/" xmlns:bqbiol="http://biomodels.net/biology-qualifiers/" xmlns:bqmodel="http://
biomodels.net/model-qualifiers/">
    <rdf:Description rdf:about="#M_M_">
      <bqbiol:isVersionOf>
        <rdf:Bag>
          <rdf:li rdf:resource="urn:miriam:uniprot:P24033"/>
          <rdf:li rdf:resource="urn:miriam:uniprot:P35567"/>
          <rdf:li rdf:resource="urn:miriam:obo.sbo:sbo%3A0000252"/>
        </rdf:Bag>
      </bqbiol:isVersionOf>
    </rdf:Description>
    </rdf:RDF>
  </variable>
```

- Labelling the models with biological & biophysical data
- Using consistent terms from ontologies
- For improved repository searches, facilitated language interconversion, and model visualisation

cellML

Common curation standards

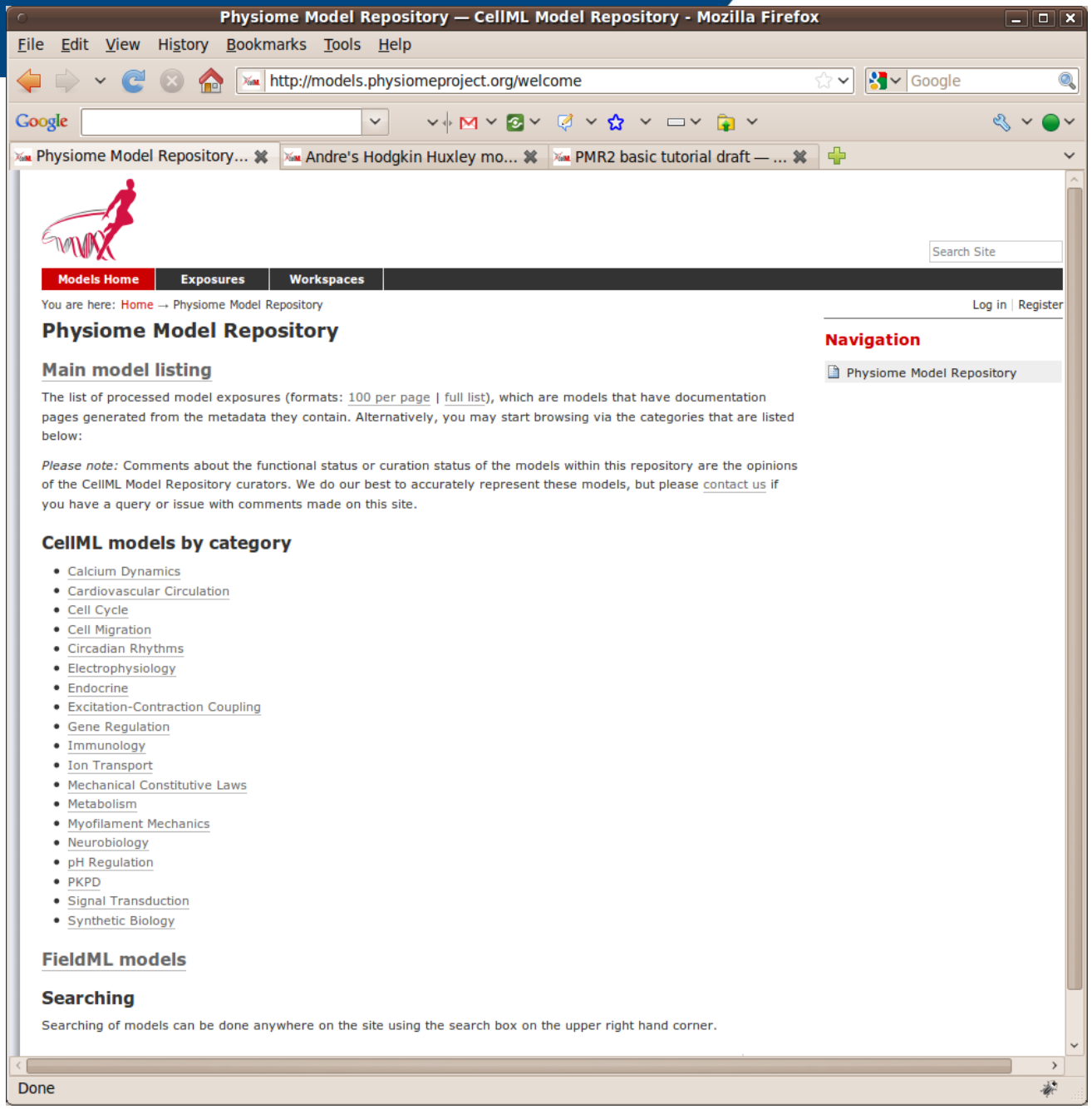


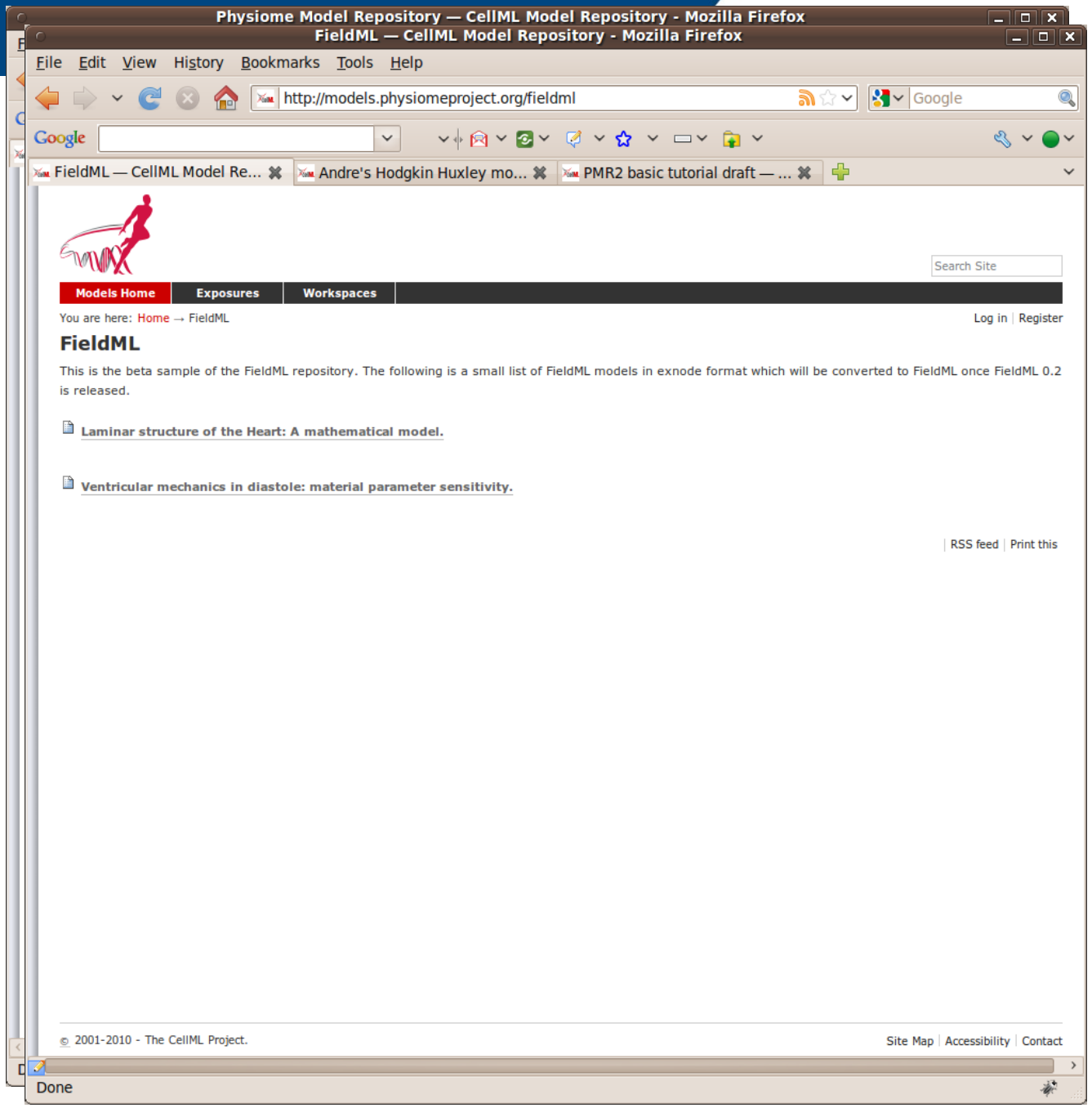


MIRIAM – The Minimal Information Required in the Annotation of Models

- MIRIAM provides a list of criteria a model must satisfy to become fully curated
- By replacing the “stars” with MIRIAM-based “flags” the curation status of a model becomes less ambiguous

Physiome model repository
models.physiomeproject.org


Physiome Model Repository — CellML Model Repository - Mozilla Firefox
File Edit View History Bookmarks Tools Help
http://models.physiomeproject.org/welcome
Google
Physiome Model Repository...
Andre's Hodgkin Huxley mo...
PMR2 basic tutorial draft — ...
Search Site
Models Home
Exposures
Workspaces
You are here: Home → Physiome Model Repository
Log in | Register
Physiome Model Repository
Main model listing
The list of processed model exposures (formats: 100 per page | full list), which are models that have documentation pages generated from the metadata they contain. Alternatively, you may start browsing via the categories that are listed below:
Please note: Comments about the functional status or curation status of the models within this repository are the opinions of the CellML Model Repository curators. We do our best to accurately represent these models, but please contact us if you have a query or issue with comments made on this site.
CellML models by category
Calcium Dynamics
Cardiovascular Circulation
Cell Cycle
Cell Migration
Circadian Rhythms
Electrophysiology
Endocrine
Excitation-Contraction Coupling
Gene Regulation
Immunology
Ion Transport
Mechanical Constitutive Laws
Metabolism
Myofilament Mechanics
Neurobiology
pH Regulation
PKPD
Signal Transduction
Synthetic Biology
FieldML models
Searching
Searching of models can be done anywhere on the site using the search box on the upper right hand corner.
Navigation
Physiome Model Repository
Done


Physiome Model Repository — CellML Model Repository - Mozilla Firefox
FieldML — CellML Model Repository - Mozilla Firefox
File Edit View History Bookmarks Tools Help
http://models.physiomeproject.org/fieldml
Google
FieldML — CellML Model Re...
Andre's Hodgkin Huxley mo...
PMR2 basic tutorial draft — ...
Search Site
Models Home
Exposures
Workspaces
You are here: Home → FieldML
Log in | Register
FieldML
This is the beta sample of the FieldML repository. The following is a small list of FieldML models in exnode format which will be converted to FieldML once FieldML 0.2 is released.
Laminar structure of the Heart: A mathematical model.
Ventricular mechanics in diastole: material parameter sensitivity.
RSS feed | Print this
© 2001-2010 - The CellML Project.
Site Map | Accessibility | Contact
Done

Physiome Model Repository — CellML Model Repository - Mozilla Firefox

FieldML — CellML Model Repository - Mozilla Firefox

Ventricular mechanics in diastole: material parameter sensitivity. — CellML Model Repository - Mozilla Firefox

File Edit View History Bookmarks Tools Help

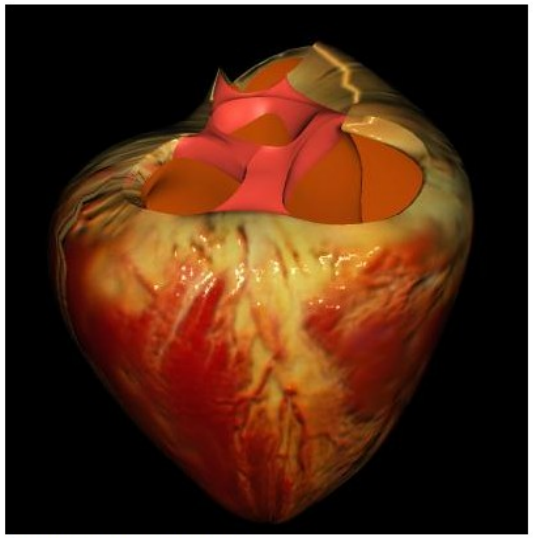
http://models.physiomeproject.org/exposure/fbe9652676c463daa12e046255

Google

Ventricular mechanics in di... | Andre's Hodgkin Huxley mo... | PMR2 basic tutorial draft — ...

Ventricular mechanics in diastole: material parameter sensitivity.

Models of ventricular mechanics have been developed over the last 20 years to include finite deformation theory, anisotropic and inhomogeneous material properties and an accurate representation of ventricular geometry. As computer performance and the computational efficiency of the models improve, clinical application of these heart mechanics models is becoming feasible. One such application is to estimate myocardial material properties by adjusting the constitutive parameters to match wall deformation from MRI or ultrasound measurements, together with a measurement (or estimate) of ventricular pressure. Pigs are now the principal large animal model for these studies and in this paper we present the development of a new three-dimensional finite element model of the heart based on measurements of the geometry and the fibre and sheet orientations of pig hearts. The end-diastolic deformation of the model is computed using the "pole-zero" constitutive law which we have previously used to model the mechanics of passive myocardial tissue specimens. The sensitivities of end-diastolic fibre-sheet material strains and heart shape to changes in the material parameters are computed for the parameters of the pole-zero law in order to assess the utility of the models for inverse material property determination.



The rendered result of this model.

To launch the model, please select Zinc Viewer under navigation on the right.

Model Curation

Curation Status:

Source

Derived from workspace Per Pixel Lighting at changeset 1d31b32abdd7.

Downloads

Complete Archive as .tgz

Download This File

Views available

FieldML Metadata

Source View

Zinc Viewer

Cite this model

License

Navigation

Ventricular mechanics in diastole: material parameter sensitivity.

Done

Ventricular mechanics in diastole: material parameter sensitivity. — CellML Model Repository - Mozilla Firefox

File Edit View History Bookmarks Tools Help

http://models.physiomeproject.org/exposure/fbe9652676c463daa12e046255

Ventricular mechanics in di... | Andre's Hodgkin Huxley mo... | PMR2 basic tutorial draft — ...

Search Site

Models Home | Exposures | Workspaces

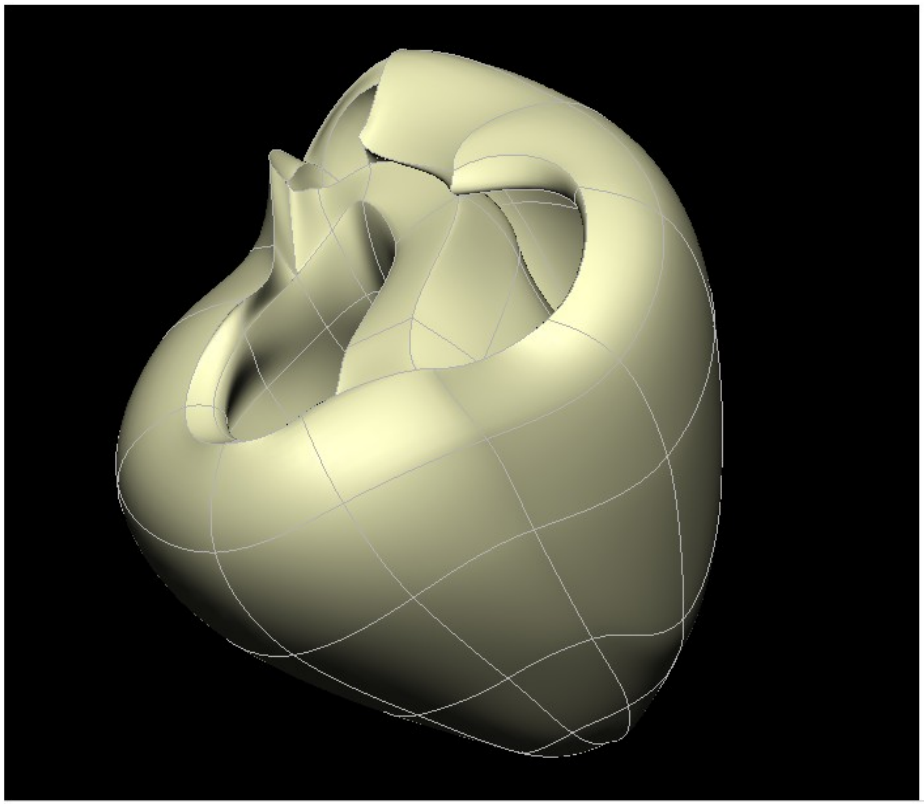
You are here: Home → Exposures → Ventricular mechanics in diastole: material parameter sensitivity. → Ventricular mechanics in diastole: material parameter sensitivity.

Log in | Register

Zinc Viewer

The following viewer requires Mozilla Firefox 1.5 to 3.5, and the Zinc Add-on for Firefox installed.

If you are a user of Firefox 3.6, please see this page for the add-on.



Model Curation

Curation Status:

Source

Derived from workspace Per Pixel Lighting at changeset 1d31b32abdd7.

Downloads

Complete Archive as .tgz

Download This File

Views available

FieldML Metadata

Source View

Zinc Viewer

Cite this model

License

This work is licensed under a Creative Commons Attribution 3.0 Unported License.

Navigation

Ventricular mechanics in diastole: material parameter sensitivity.

Site Map | Accessibility | Contact

Done

Done

PMR2
The software behind the repository

Glossary

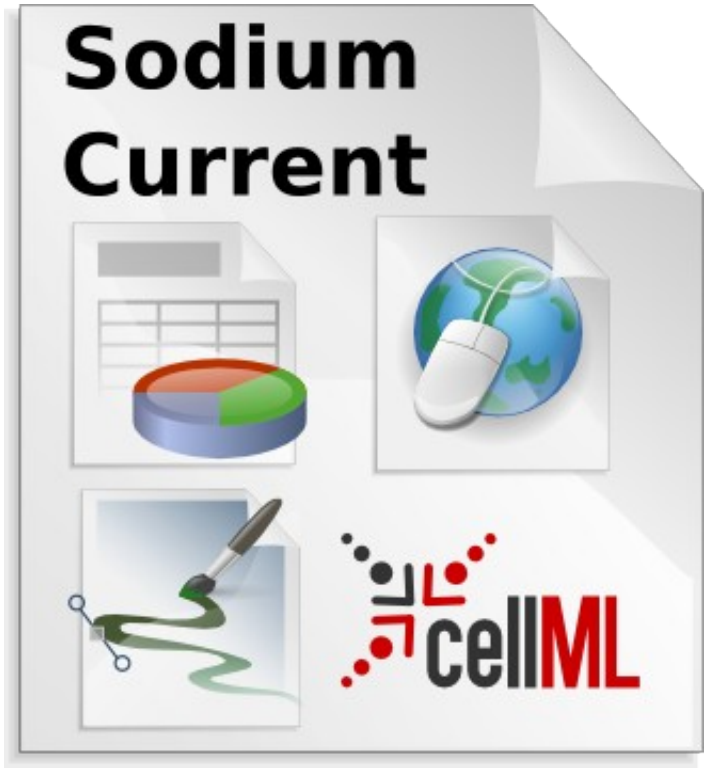
- Workspace – data agnostic mercurial repository
- Changeset – a representation of a single revision of the content of a workspace
- Exposure – a permanent link to a specific changeset with data rendered for the web
- Exposure plug-ins – an extensible framework for rendering workspace content for web presentation
- Plone CMS – workflow manager; user access controls; web presentation; etc.

An example from computational physiology

- Build up a multiscale model of the renal nephron
  - ion transporters, cellular models, segmental models, whole nephron...
- Share the various models with collaborators
- Publish the model along the way

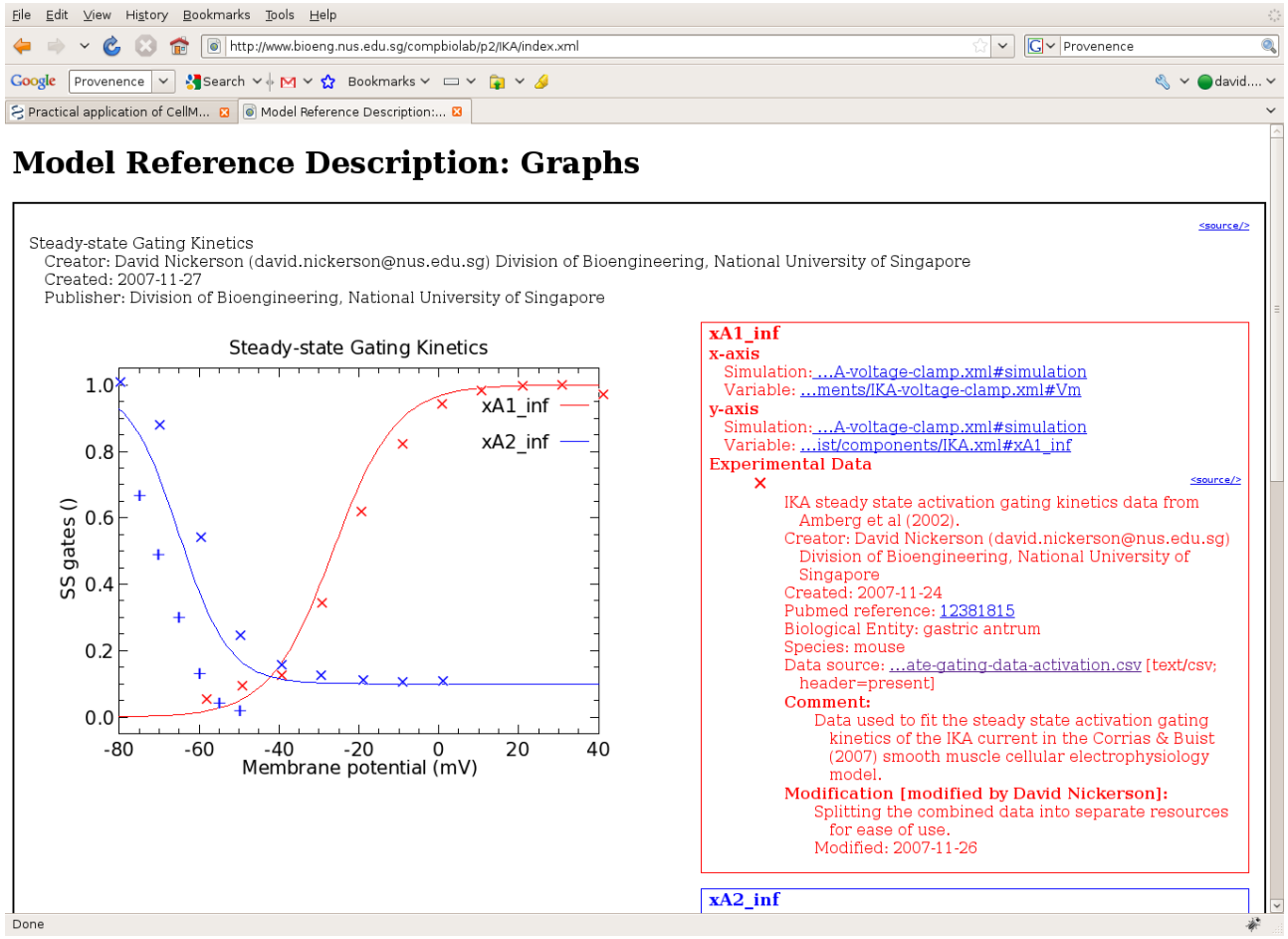
- Disclaimer: not all the following features are implemented/integrated in either language specifications and/or supporting software tools – and such features may change considerably before they are supported.

Membrane transporters



(Workspace)

Membrane transporters



File Edit View History Bookmarks Tools Help

Constituents of the Renal Nephron

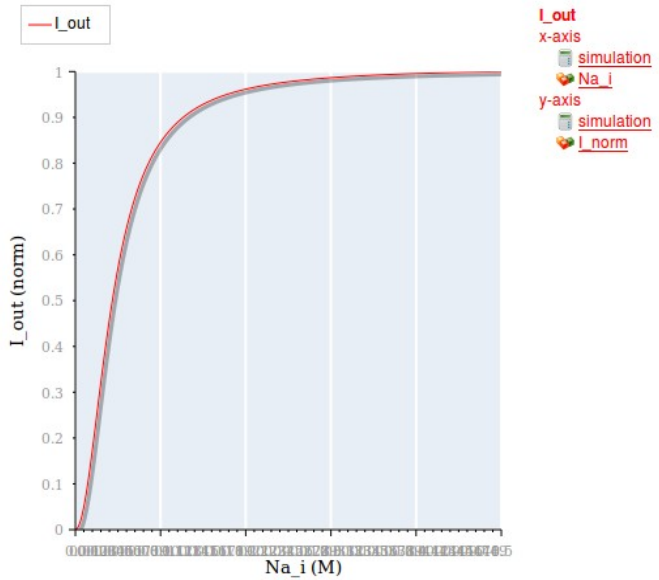
Constituents of the Renal Nephron

David Nickerson (2010-04-19)

Help

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

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



I_out
x-axis
simulation
Na_i
y-axis
simulation
I_norm

I_norm

Units: dimensionless
Defined in math container: Na_i

Na_i

+ Created: 2010-04-21, David Nickerson

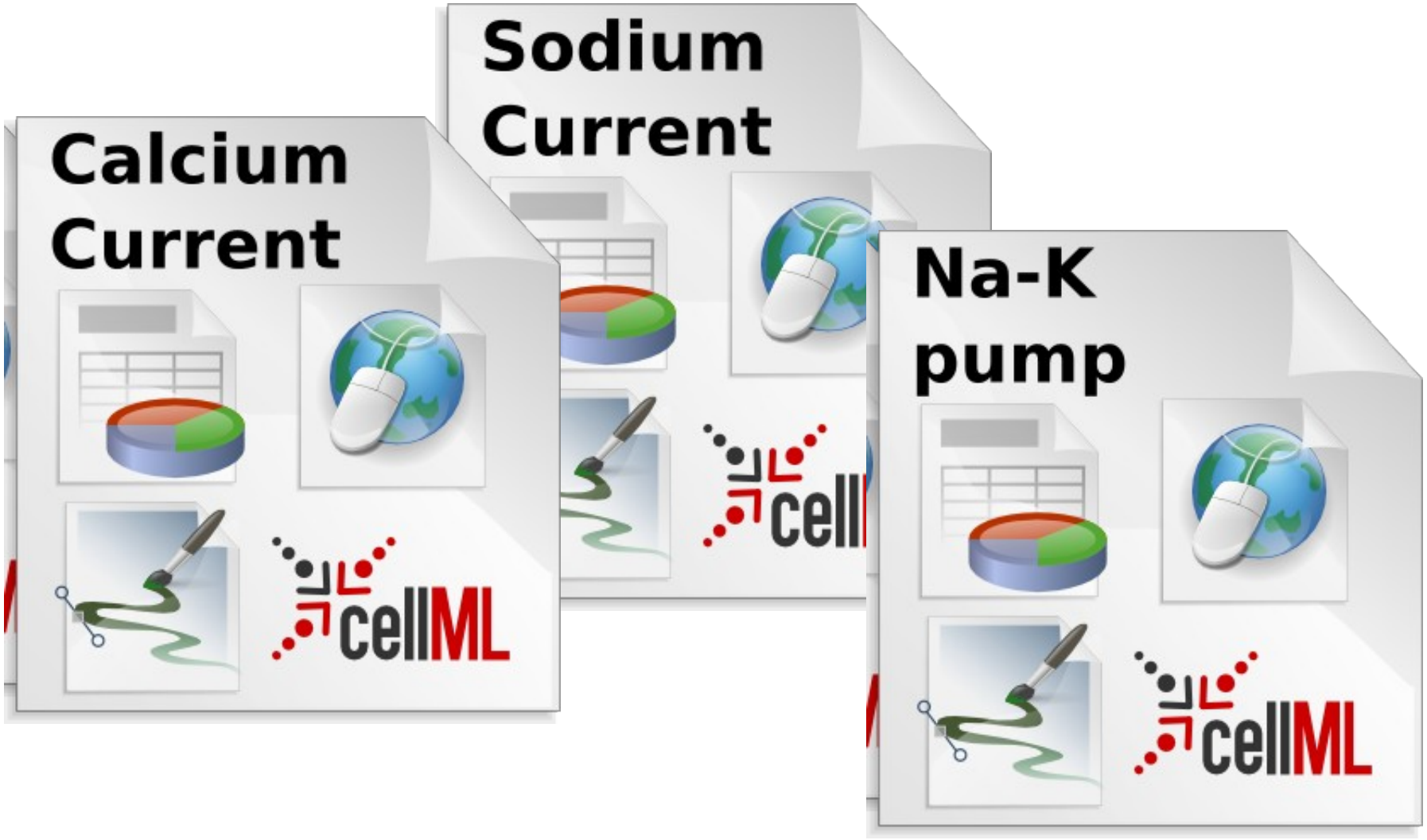
$$\frac{dNa\_i}{dtime} = [1.0e\text{-}3 M\_per\_second]$$

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

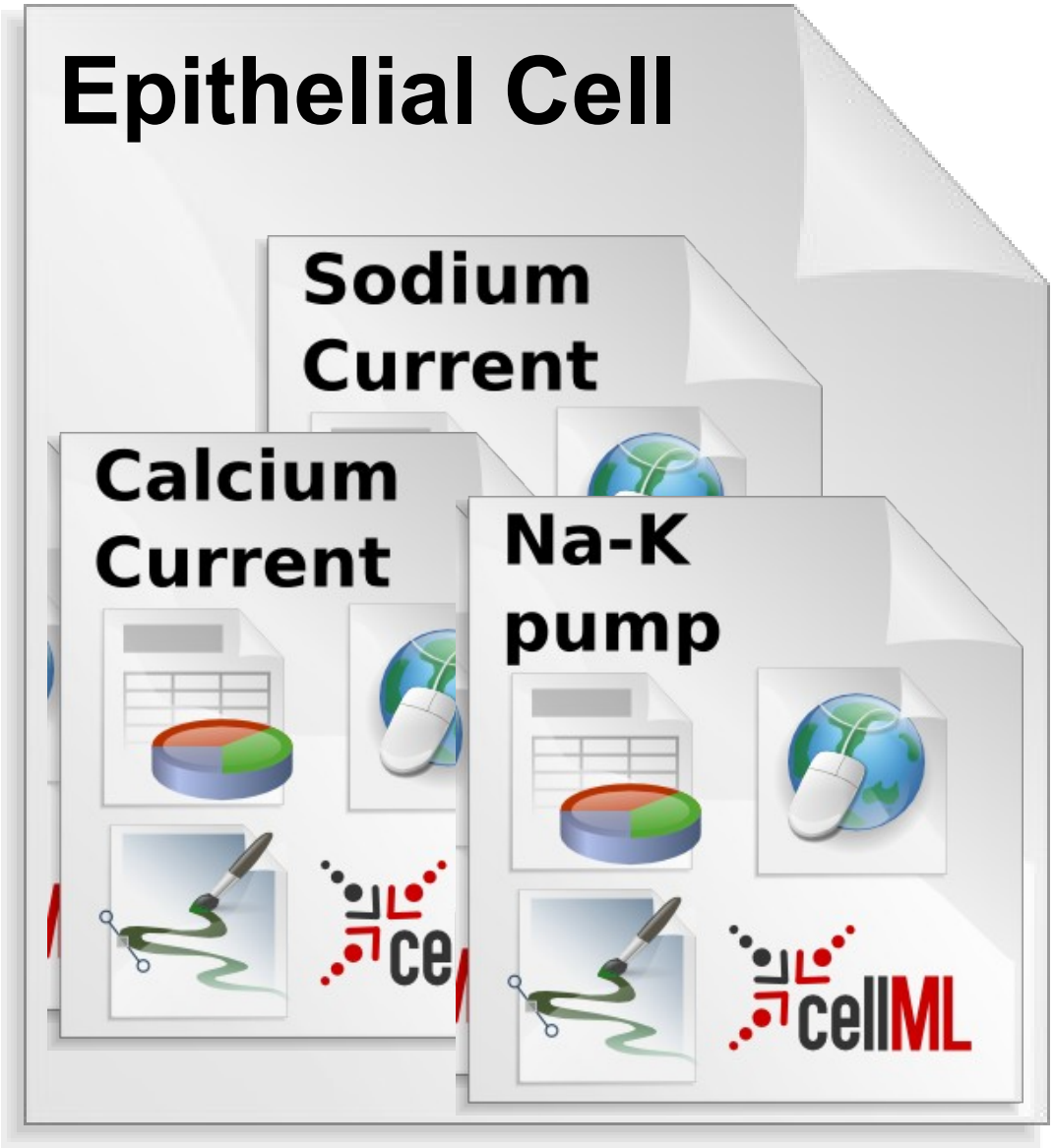
Generated by: CellMLSimulator (version: CellMLSimulator 0.3.0-devel-json - revision 221M - Sat Apr 17 13:07:26 NZST 2010) at Thu 22 Apr 2010 07:56:51 SGT

javascript:;

Membrane transporters



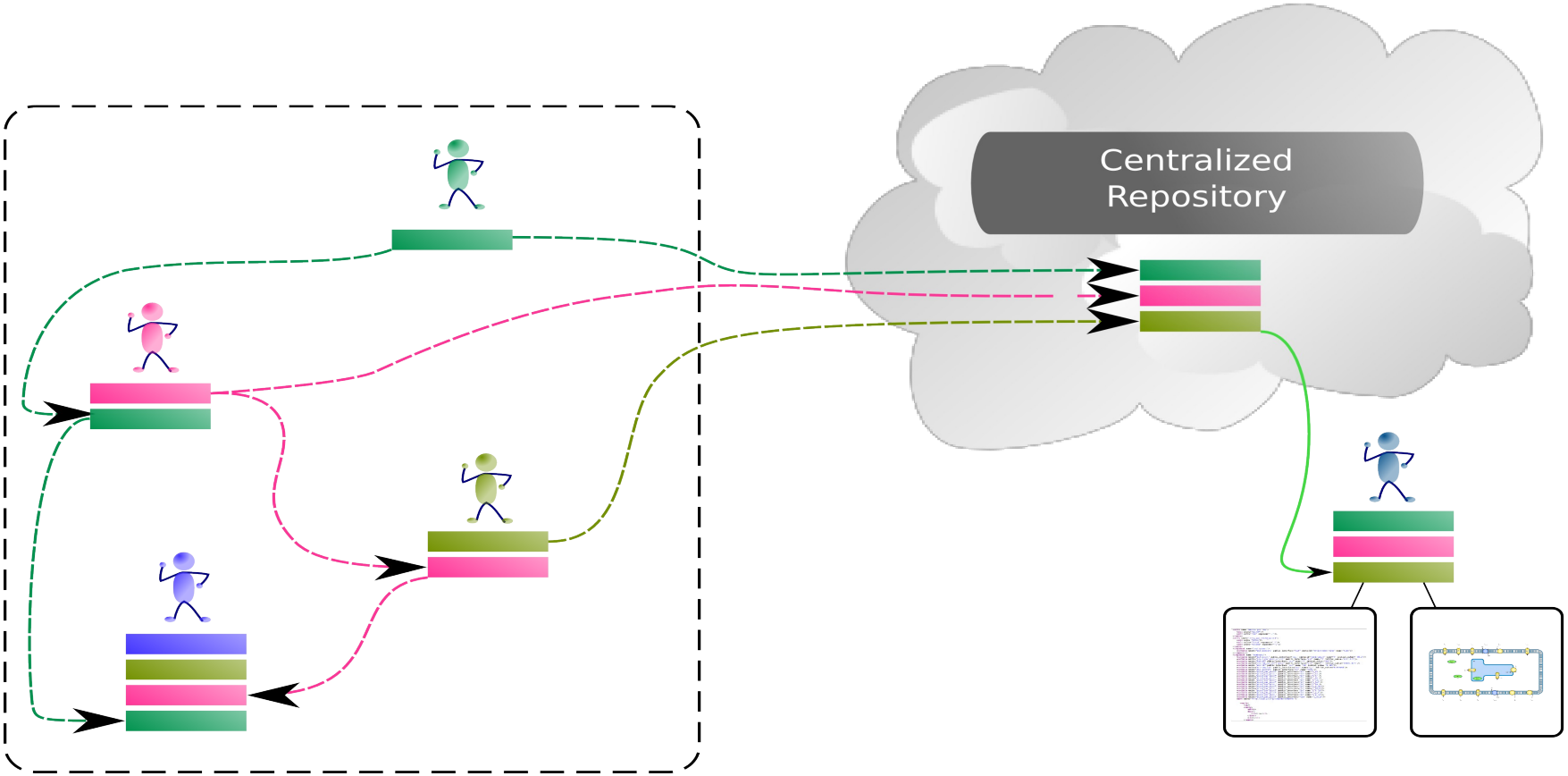
Assemble a cell model



Embedded workspaces

- Intended to manage the separation of modules which are integrated to create a model
- Facilitate the sharing and reuse of model components independently from the source model
- Enables the development of the modules to proceed independently, thus the version of the workspaces embedded is also tracked
- Allows authors to make use of relative URIs when linking data resources providing a file system agnostic method to describe complex module relationships in a portable manner

Collaborative model development



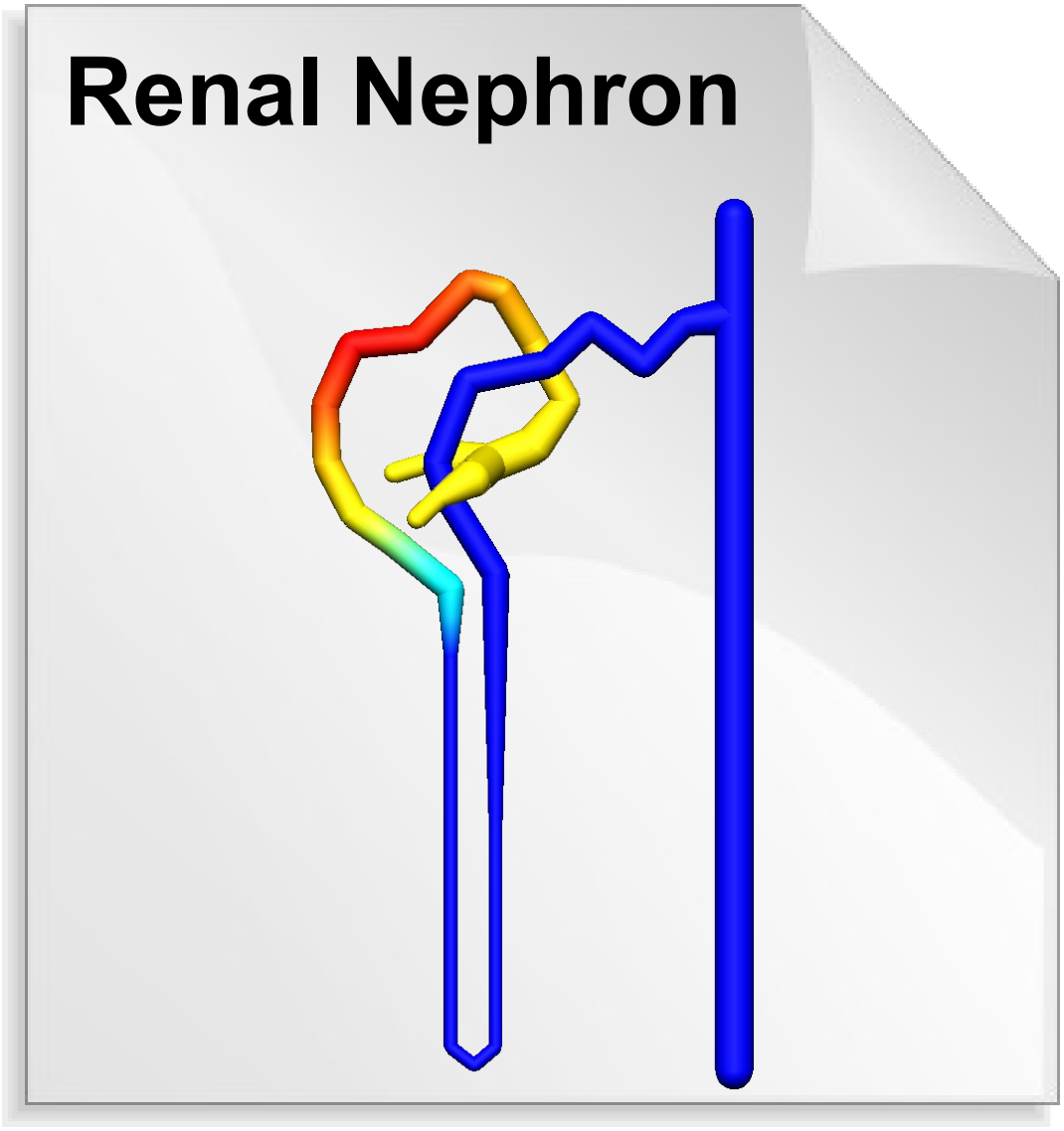
Versioning embedded workspaces

- Workspaces can be embedded at a specific revision or set to track the most recent revision of the source workspace
- Changes made to the source workspace will not affect the embedding workspace until the author explicitly chooses to update the embedded workspace
- Provides the author with the opportunity to review the changesets and make an informed decision regarding alterations to embedded revisions

Data agnostic workspaces

- Generic mercurial repositories
- Can contain any format data (currently relatively unrestricted)
  - CellML, SBML, FieldML, SED-ML, PDF, .doc, ...
- No restriction to models only
  - experimental data, simulation results, generated images, ...

Multiscale models



File Edit View History Bookmarks Tools Help

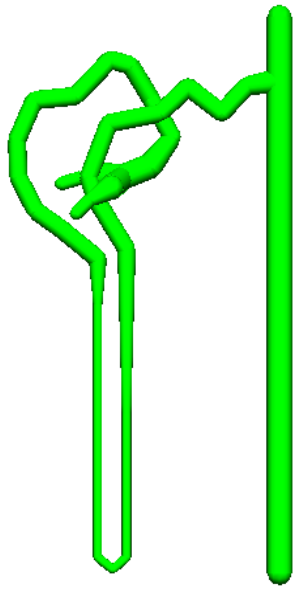
Nephron Interface

The Renal Nephron

Close all

- Nephron
  - Anatomy
    - Efferent Arteriole
    - Afferent Arteriole
    - Glomerulus
    - Proximal Tubule
      - Proximal Convoluted Tu
      - Proximal Straight Tubul
    - Loop of Henle
    - Macula Densa
    - Distal Convoluted Tubule
    - Connecting Tubule
    - Collecting Duct
  - Physiology
    - Efferent Arteriole
    - Afferent Arteriole
    - Glomerulus
    - Proximal Tubule
      - Weinstein et al (2007)
      - Thomas and Dagher (19
    - Loop of Henle
    - Macula Densa
    - Distal Convoluted Tubule
    - Connecting Tubule
    - Collecting Duct
  - Modelling Studies
    - SGLT2 Inhibition
      - Na-glucose cotransport
      - Control
      - Inhibited

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



Nephron

A demonstration renal nephron model interface.

This prototype interface provides the user with an antomical browser, cellular and subcellular transport model database, and some preliminary simulation results for your viewing pleasure. The tree on the left hand side provides the primary overview of the content of this interface, the central pane provides the graphical view where relevant, and this pane shows the details.

David Nickerson

April 2010

Done

File Edit View History Bookmarks Tools Help

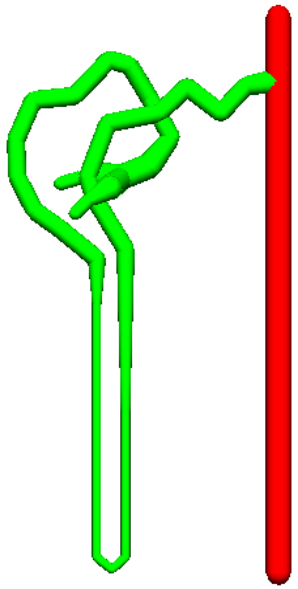
Nephron Interface

The Renal Nephron

Close all

- Nephron
  - Anatomy
    - Efferent Arteriole
    - Afferent Arteriole
    - Glomerulus
    - Proximal Tubule
      - Proximal Convoluted Tu
      - Proximal Straight Tubul
    - Loop of Henle
    - Macula Densa
    - Distal Convoluted Tubule
    - Connecting Tubule
    - Collecting Duct
  - Physiology
    - Efferent Arteriole
    - Afferent Arteriole
    - Glomerulus
    - Proximal Tubule
      - Weinstein et al (2007)
      - Thomas and Dagher (19
    - Loop of Henle
    - Macula Densa
    - Distal Convoluted Tubule
    - Connecting Tubule
    - Collecting Duct
  - Modelling Studies
    - SGLT2 Inhibition
      - Na-glucose cotransport
      - Control
      - Inhibited

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



Collecting Duct

The tubules and ducts that link the nephron tubule with the ureter.

The nephron tubule empties into the collecting duct system, which begins in the medullary ray of the cortex and descends along the axis of the nephron, through the medulla, before draining into a papillary duct. The collecting ducts play a significant role in the 'fine-tuning' of electrolyte and water balance through the hormonal regulation of the permeability of these segments.

In the human cortex, approximately 11 nephron tubules merge into a single cortical collecting duct. As it descends through the medulla, the collecting ducts merge on average about 8 times before draining into the papillary duct.

Related CellML models:

- Weinstein (2002)

Distal Convoluted Tubule

The segment of tubule between the thick ascending limb and the collecting ducts

David Nickerson April 2010

Done 1 Error

File Edit View History Bookmarks Tools Help

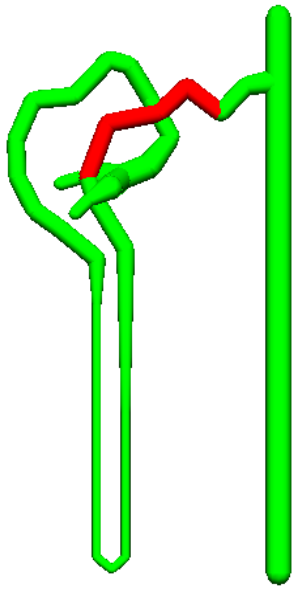
Nephron Interface

The Renal Nephron

Close all

- Nephron
  - Anatomy
    - Efferent Arteriole
    - Afferent Arteriole
    - Glomerulus
    - Proximal Tubule
      - Proximal Convoluted Tu
      - Proximal Straight Tubul
    - Loop of Henle
    - Macula Densa
    - Distal Convoluted Tubule
    - Connecting Tubule
    - Collecting Duct
  - Physiology
    - Efferent Arteriole
    - Afferent Arteriole
    - Glomerulus
    - Proximal Tubule
      - Weinstein et al (2007)
      - Thomas and Dagher (19
    - Loop of Henle
    - Macula Densa
    - Distal Convoluted Tubule
    - Connecting Tubule
    - Collecting Duct
  - Modelling Studies
    - SGLT2 Inhibition
      - Na-glucose cotransport
      - Control
      - Inhibited

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



Distal Convoluted Tubule

The segment of tubule between the thick ascending limb and the collecting ducts.

Sometimes referred to as the early distal tubule. The distal convoluted tubule is located in the cortex where, as per the proximal convoluted tubule, it has a convoluted trajectory through the tissue. The permeability of the distal convoluted tubule resembles that of the thick ascending limb – i.e. virtually impermeable to water and urea but permeable to salt and other electrolytes. Thus as these solutes are reabsorbed, the luminal fluid becomes increasing dilute. This segment is involved in the hormonal regulation of K, Na, Ca and pH.

Related CellML models:

- Weinstein et al (2005)a
- Chang & Fujita (1999)
- Chang and Fujita (2001)

Nephron

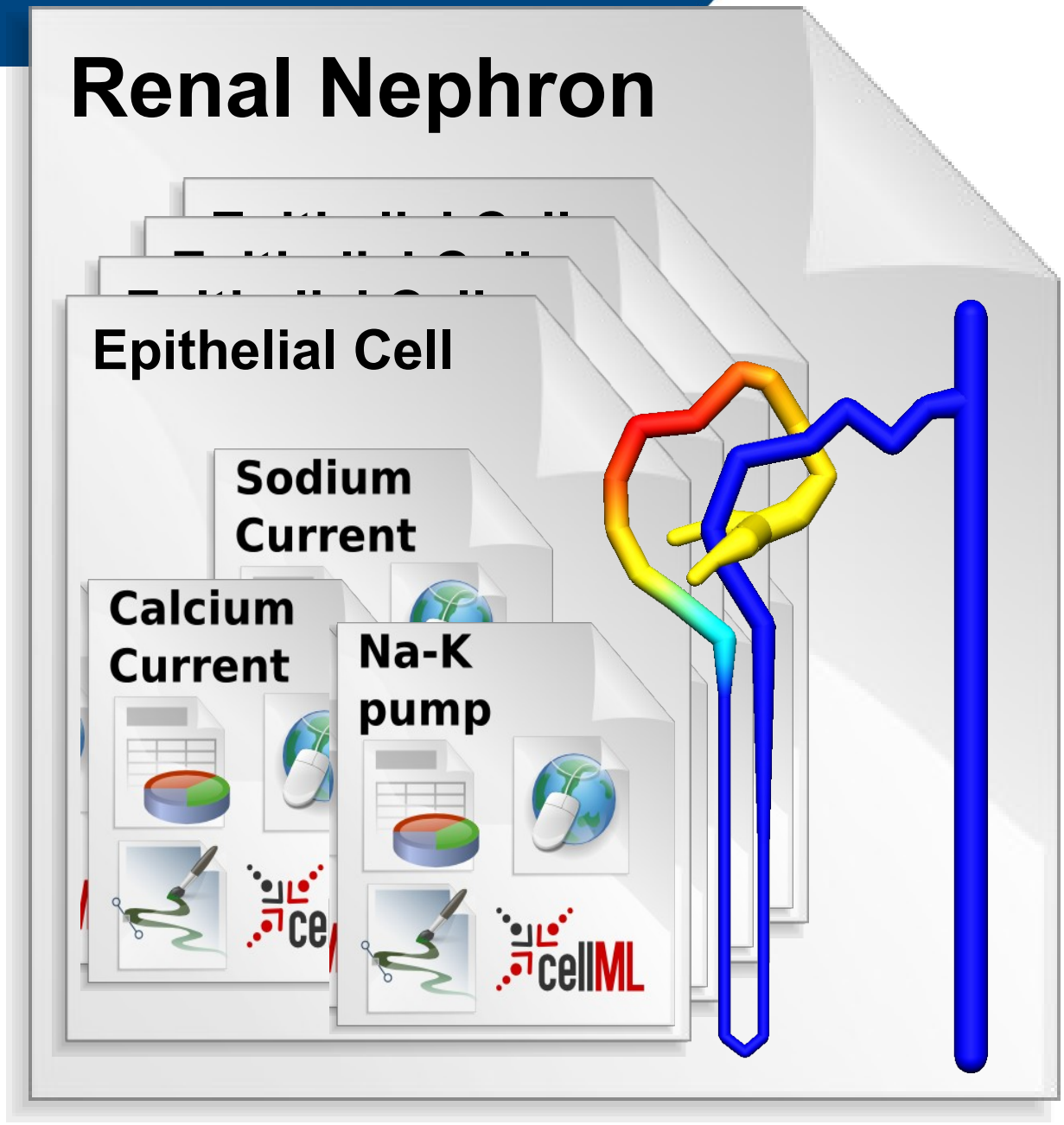
A demonstration renal nephron model interface.

David Nickerson

April 2010

Done

1 Error


Renal Nephron
Epithelial Cell
Sodium Current
Calcium Current
Na-K pump
cellML

File Edit View History Bookmarks Tools Help

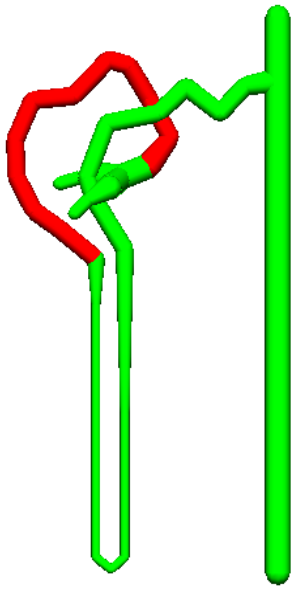
Nephron Interface

The Renal Nephron

Close all

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

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



Proximal Tubule

First of the transporting tubule segments.

From the Bowman's Capsule, the filtered fluid enters the first of the reabsorptive epithelial tubule segments – the proximal tubule. The proximal tubule consists of a convoluted portion and a straight portion. This segment has a high transport activity and is responsible for the bulk of the salt and water reabsorption. Furthermore, the majority of the key organic molecules (glucose and amino acids), as well as other important ions (K, Ca, HCO3), are actively reabsorbed in this segment.

Related CellML models:

- Weinstein et al (2007)
- Thomas and Dagher (1994)

Proximal Convoluted Tubule

Convoluted portion of the Proximal Tubule.

As its name suggests, the proximal convoluted tubule undergoes a convoluted trajectory through the cortical region of the kidney, primarily the cortical labyrinth.

Nephron

David Nickerson April 2010

Done

File Edit View History Bookmarks Tools Help

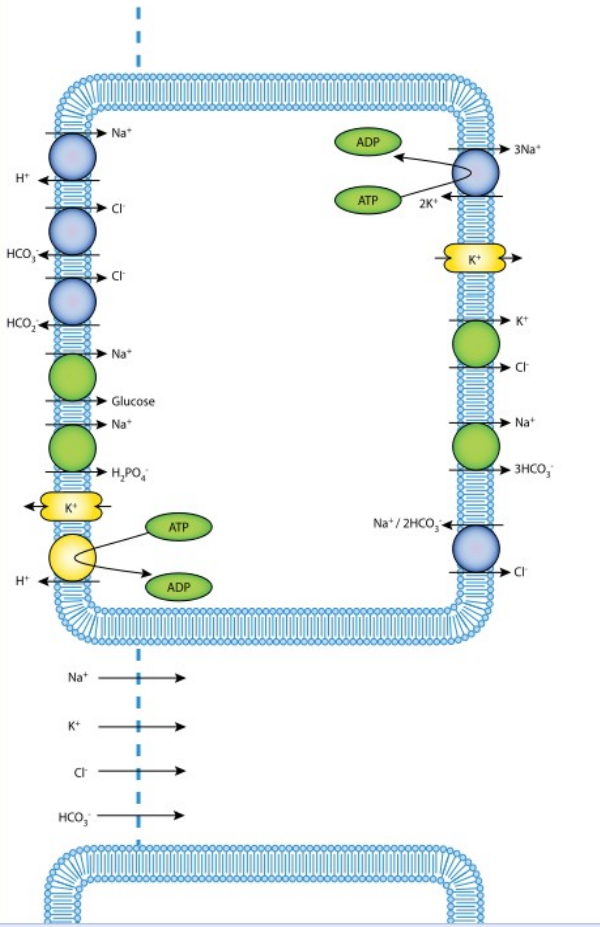
Nephron Interface

The Renal Nephron

Close all

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

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

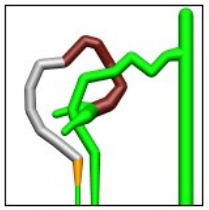


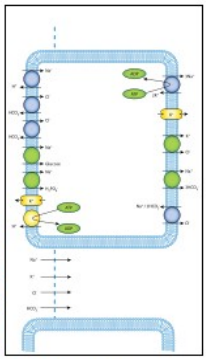
Related CellML models:

- Weinstein et al (2007)
- Thomas and Dagher (1994)

Weinstein et al (2007)

Flow-dependent transport in a mathematical model of rat proximal tubule. *Am J Physiol Renal Physiol* **292**: F1164-F1181, 2007.





proximal convoluted tubule whole cell model. The Na-glucose cotransporter is further refined using models for SGLT1 and SGLT2 in varying densities in the different segments of the proximal tubule.

Proximal Convoluted Tubule

Convoluted portion of the Proximal Tubule.

File Edit View History Bookmarks Tools Help

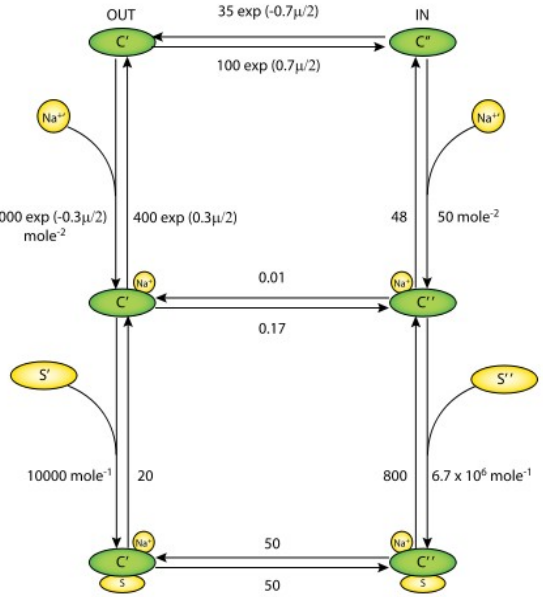
Nephron Interface

The Renal Nephron

Close all

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

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



Na-glucose cotransporter

Refined Na-glucose cotransporter models, SGLT1 and SGLT2.

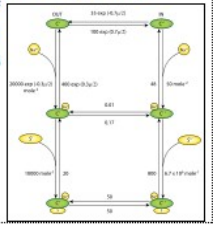
In this study, we utilize the Weinstein et al (2007) proximal tubule model extended through the inclusion of a spatial distribution of the SGLT1 and SGLT2 Na-glucose cotransporter models.

Mackenzie et al (1996)

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

CellML model repository

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



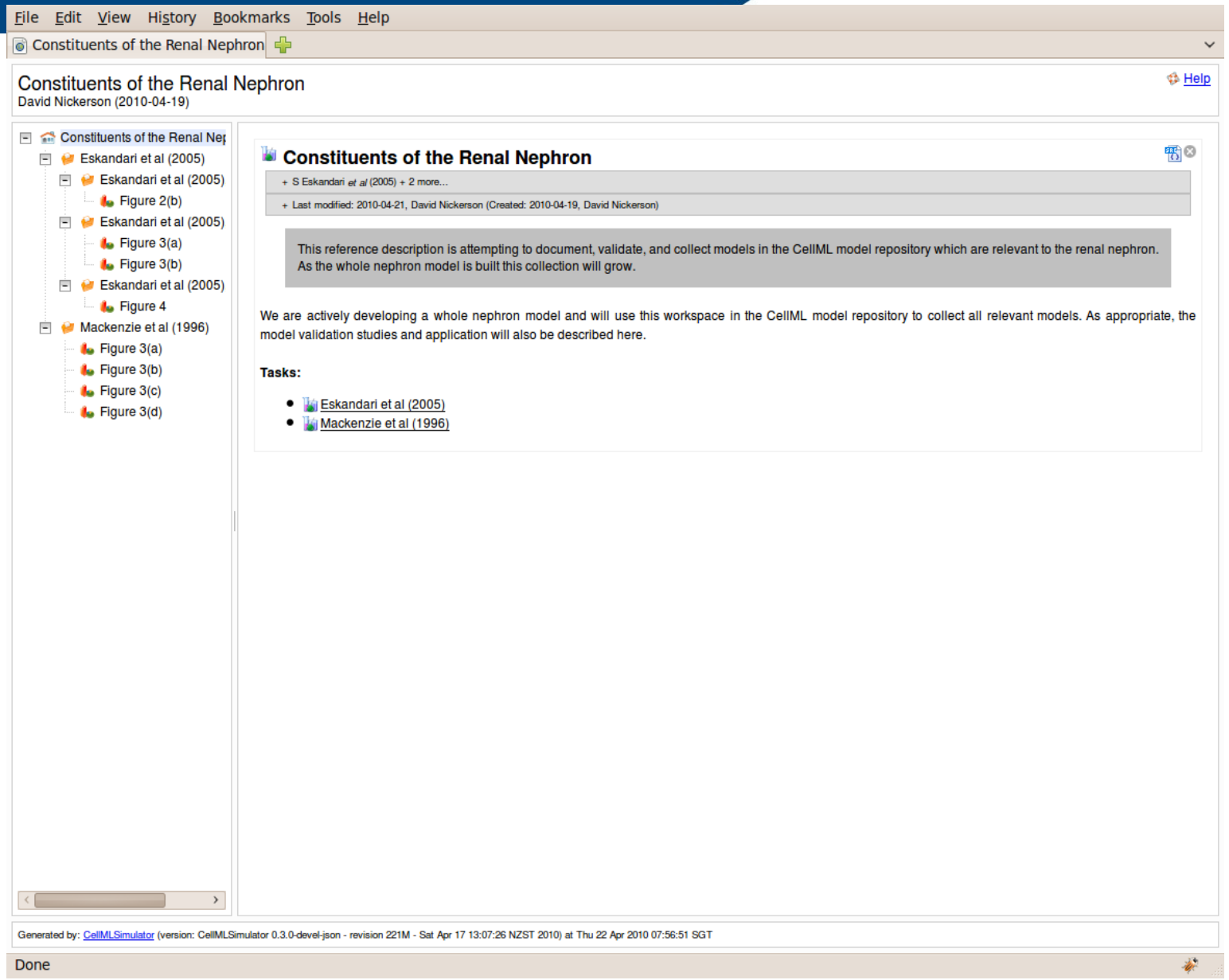
Proximal Tubule

First of the transporting tubule segments.

David Nickerson

April 2010

Done


File Edit View History Bookmarks Tools Help
Constituents of the Renal Nephron
Constituents of the Renal Nephron
David Nickerson (2010-04-19)
Help
Constituents of the Renal Nep
Eskandari et al (2005)
Eskandari et al (2005)
Figure 2(b)
Eskandari et al (2005)
Figure 3(a)
Figure 3(b)
Eskandari et al (2005)
Figure 4
Mackenzie et al (1996)
Figure 3(a)
Figure 3(b)
Figure 3(c)
Figure 3(d)
Constituents of the Renal Nephron
+ S Eskandari et al (2005) + 2 more...
+ Last modified: 2010-04-21, David Nickerson (Created: 2010-04-19, David Nickerson)
This reference description is attempting to document, validate, and collect models in the CellML model repository which are relevant to the renal nephron. As the whole nephron model is built this collection will grow.
We are actively developing a whole nephron model and will use this workspace in the CellML model repository to collect all relevant models. As appropriate, the model validation studies and application will also be described here.
Tasks:
Eskandari et al (2005)
Mackenzie et al (1996)
Generated by: CellMLSimulator (version: CellMLSimulator 0.3.0-devel-json - revision 221M - Sat Apr 17 13:07:26 NZST 2010) at Thu 22 Apr 2010 07:56:51 SGT
Done

File Edit View History Bookmarks Tools Help

Constituents of the Renal Nephron

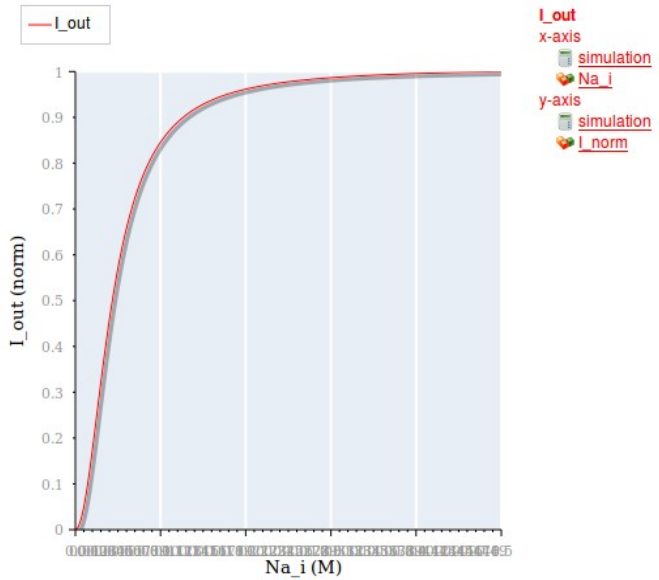
Constituents of the Renal Nephron

David Nickerson (2010-04-19)

Help

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

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



I_out
x-axis
simulation
Na_i
y-axis
simulation
I_norm

I_norm

Units: dimensionless
Defined in math container: Na_i

Na_i

+ Created: 2010-04-21, David Nickerson

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

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

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

javascript:;

File Edit View History Bookmarks Tools Help

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

Google

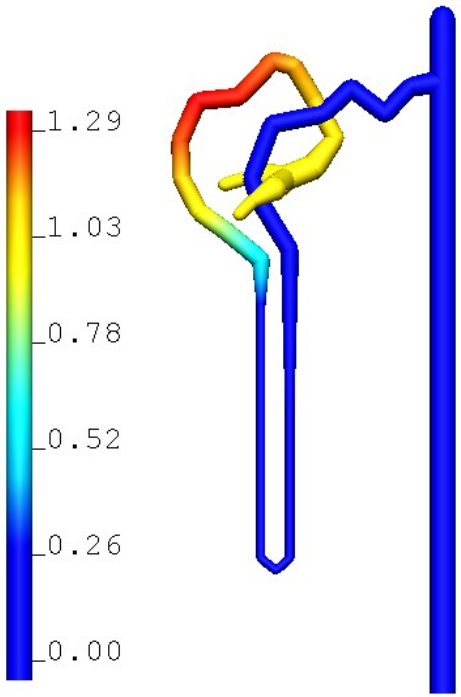
Nephron Interface

The Renal Nephron

Close all

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

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



Inhibited

The altered glucose concentration observed when SGLT2 is inhibited.

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

Na-glucose cotransporter

Refined Na-glucose cotransporter models, SGLT1 and SGLT2.

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

SGLT2 Inhibition

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

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

David Nickerson

April 2010

Done

OpenCMISS

- Connecting variables in CellML models to field components in a finite element model
  - Prototype for linking CellML and FieldML models?
- Allows information to flow in both directions
  - Field values can be controlled by the CellML model and CellML model variables can be controlled by field components
- Will have the ability to make use of many different CellML models which can be simulated independently
- Each CellML model may be replicated many millions of times for large scale problems
  - Distributed computing, GPUs, FPGAs, ...

Acknowledgements

"Team CellML"













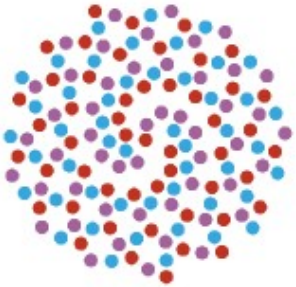

Acknowledgements

THE UNIVERSITY OF AUCKLAND

NEW ZEALAND

Te Whare Wānanga o Tāmaki Makaurau

wellcome trust



MAURICE WILKINS CENTRE

FOR MOLECULAR BIODISCOVERY