Model publication using physiome standards

David Nickerson & Martin Buist
Division of Bioengineering
National University of Singapore

NUS National University of Singapore

Introduction

- In this age of widespread broadband internet penetration and given the computational power available on most desktops we envision a shift in the publication paradigm for physiome style models.
- Rather than a textural description of a model's development and behaviour, model authors will publish complete descriptions of their models [reference description] and a human readable summary [traditional journal article].

Why?

- **Mathematical models of cellular physiology are rapidly increasing in biophysical detail:**
  - electrophysiology and mechanics;
  - + calcium dynamics;
  - + mitochondrial energetics;
  - + signalling cascades;
  - + ...
- **Models routinely now consist of large systems of differential & algebraic equations and many parameters.**
- **Modelling studies typically require multiple models, each with many parameterizations.**

NUS National University of Singapore

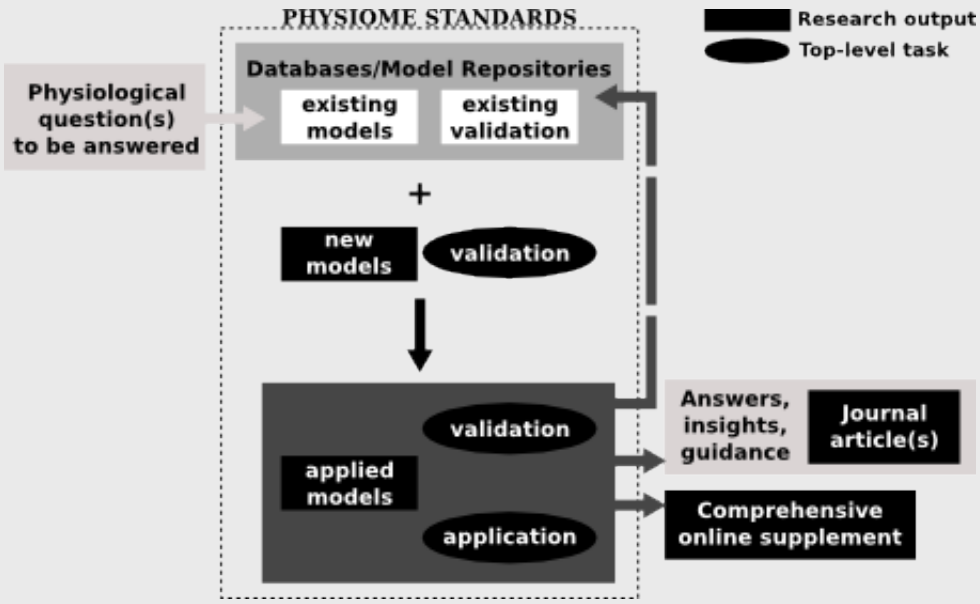
- **Model authors need to:**
  - describe complex models;
  - share them with colleagues and the scientific community;
  - reuse bits and pieces of existing models;
  - publish, publish, publish...
- **Several (almost) independent sub-problems:**
  - the mathematical model(s);
  - parameterizations of the mathematical model(s);
  - instantiation of the models as specific and reproducible computational simulations;
  - extraction of specific “simulation observations” from simulation datasets.
- **Machine vs human interpretation and interaction.**
- **Reusability!**

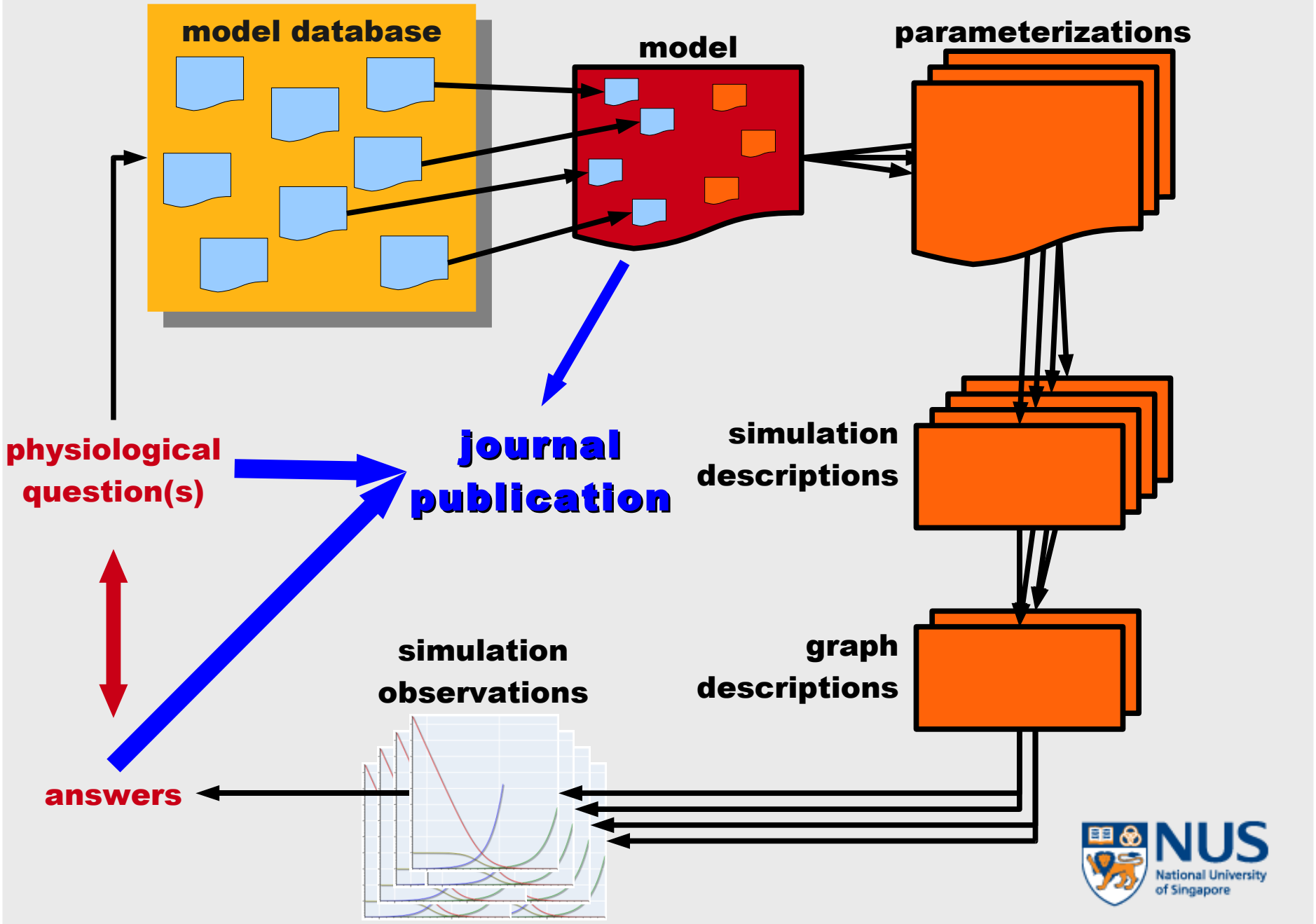
Requirements

- **Machine interpretable model description**
  - the entire model and all supporting data should be available and encoded in suitable formats.
- **Resource annotation**
  - meet the requirements of MIRIAM at the minimum, although the more the better!
- **Experimental observations**
  - every aspect of the model should be backed up either directly with experimental observations or appropriate literature citations.
- **Human usable model presentation**
  - the complete model description must be available to users in familiar and easy-to-use environments.

NUS National University of Singapore

Paradigm summary




model database
model
parameterizations
physiological question(s)
journal publication
simulation descriptions
graph descriptions
simulation observations
answers
NUS
National University of Singapore

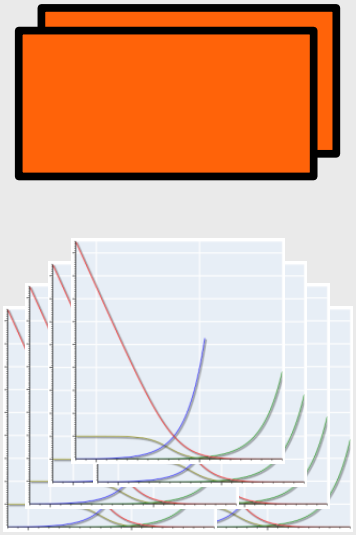
Description of numerical simulations

- **Each parameterized model instantiated into one or more simulation.**
- **Simulation metadata:**
  - numerical methods;
  - associated parameters;
  - links to required model and variable(s);
  - general annotations.

NUS National University of Singapore

Description of simulation outputs

graph descriptions



- **Want to extract specific observations from simulation results.**
- **Graphing metadata:**
  - reference specific variables from specified simulations;
  - range of interest;
  - graphical properties (colours, glyphs, line width, etc.);
  - links to external data.

NUS National University of Singapore

(Andre's) CellML metadata

- **Simulation & graphing metadata:**
  - specification drafts have been prepared, still much to do;
  - somewhat exchangeable between PCEnv (OpenCell) and CellMLSimulator;
  - included in model repository via PCEnv sessions.
  - no linkage between simulation observations (graphs).
- **Tasks:**
  - a basic container to hold lists of child tasks and/or simulation observations;
  - allows the grouping of simulation observations into a logical hierarchy.
- **Analysis**
  - a poorly thought out way to perform analysis of simulation observations.

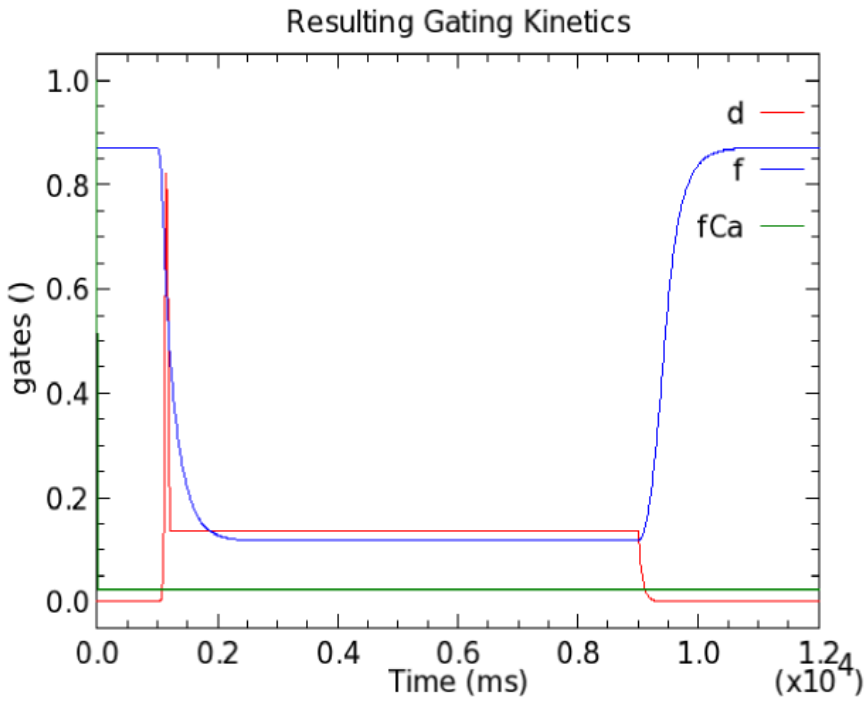
NUS National University of Singapore

Model Reference Description: Graphs - Mozilla Firefox

File Edit View History Bookmarks Tools Help

<source/>

Resulting Gating Kinetics
Creator: David Nickerson (david.nickerson@nus.edu.sg) Division of Bioengineering, National University of Singapore
Created: 2007-09-11
Publisher: Division of Bioengineering, National University of Singapore
Modification [modified by David Nickerson (david.nickerson@nus.edu.sg) Division of Bioengineering, National University of Singapore]:
Adding standard CellML metadata annotations to the graph descriptions.
Modified: 2007-11-22



d
x-axis
Simulation: ...tage-clamp-25mV.xml#simulation
Variable: ...nts/ICa-voltage-clamp.xml#time
y-axis
Simulation: ...tage-clamp-25mV.xml#simulation
Variable: ...as_buist/components/ICaL.xml#d

f
x-axis
Simulation: ...tage-clamp-25mV.xml#simulation
Variable: ...nts/ICa-voltage-clamp.xml#time
y-axis
Simulation: ...tage-clamp-25mV.xml#simulation
Variable: ...as_buist/components/ICaL.xml#f

fCa
x-axis
Simulation: ...tage-clamp-25mV.xml#simulation
Variable: ...nts/ICa-voltage-clamp.xml#time
y-axis
Simulation: ...tage-clamp-25mV.xml#simulation
Variable: ..._buist/components/ICaL.xml#fCa

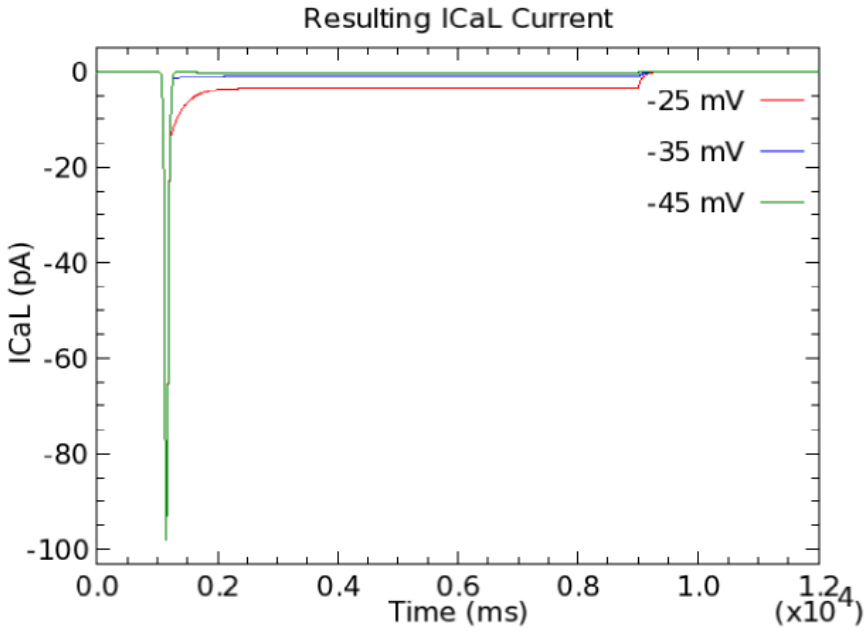
NUS National University of Singapore

Model Reference Description: Graphs - Mozilla Firefox

File Edit View History Bookmarks Tools Help

<source/>

Resulting ICaL Current
Creator: David Nickerson (david.nickerson@nus.edu.sg) Division of Bioengineering, National University of Singapore
Created: 2007-09-11
Publisher: Division of Bioengineering, National University of Singapore
Pubmed reference: 17486452
Comment [created by David Nickerson (david.nickerson@nus.edu.sg) Division of Bioengineering, National University of Singapore]:
This graph partially provides a reproduction of Figure 2(D) from Corrias & Buist (2007).
Created: 2007-11-22
Modification [modified by David Nickerson (david.nickerson@nus.edu.sg) Division of Bioengineering, National University of Singapore]:
Adding standard CellML metadata annotations to the graph descriptions.
Modified: 2007-11-22



-25 mV
x-axis
Simulation: ...tage-clamp-25mV.xml#simulation
Variable: ...nts/ICa-voltage-clamp.xml#time
y-axis
Simulation: ...tage-clamp-25mV.xml#simulation
Variable: ...buist/components/ICaL.xml#ICaL

-35 mV
x-axis
Simulation: ...tage-clamp-35mV.xml#simulation
Variable: ...nts/ICa-voltage-clamp.xml#time
y-axis
Simulation: ...tage-clamp-35mV.xml#simulation
Variable: ...buist/components/ICaL.xml#ICaL

-45 mV
x-axis
Simulation: ...tage-clamp-45mV.xml#simulation
Variable: ...nts/ICa-voltage-clamp.xml#time
y-axis
Simulation: ...tage-clamp-45mV.xml#simulation
Variable: ...buist/components/ICaL.xml#ICaL

NUS National University of Singapore

Reference Description of a HH-based Modelling Study

David Nickerson (2008-07-16)

Help

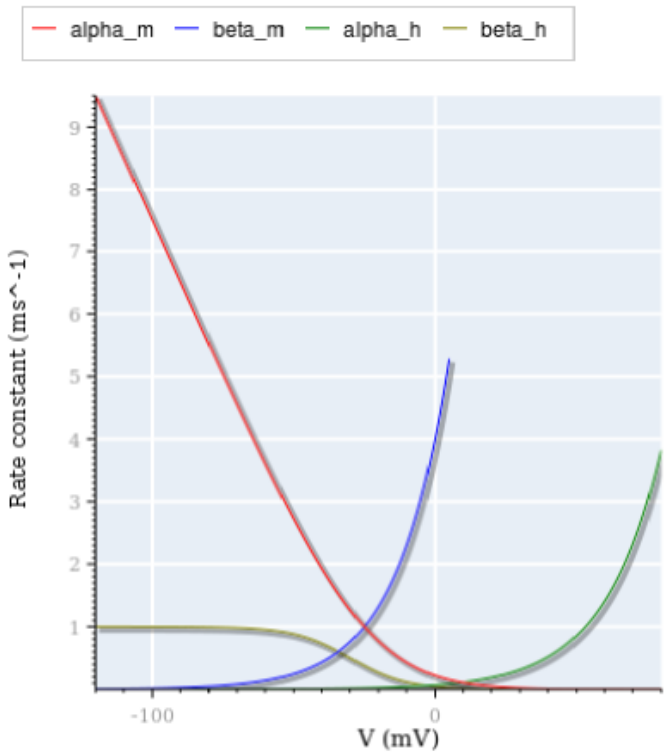
- Reference Description of a HH-based Modelling Study
  - Model Validation
    - Sodium Channel Kinetics Validation
      - INa Gating Rates
      - INa Steady State Gating Kinetics
    - Potassium Channel Kinetics Validation
      - IK Gating Rates
      - IK Steady State Gating Kinetics
    - Voltage Clamp Validation
    - Action Potential Validation
      - Action Potentials
      - Membrane Currents
      - Gating Variables
      - Action Potential
      - Membrane Currents
      - Gating Variables
  - The effect of membrane conductance
    - Sodium channel conductance
      - Action Potentials
      - Sodium current
    - Potassium channel conductance
      - Action Potentials
      - Potassium current
    - Leakage current conductance
      - Action Potentials
      - Leak current
    - Comparison of changes
      - Action Potentials - 50%
      - Action Potentials - 150%
      - Action Potentials - 200%
  - Varying ion concentrations
    - Changing Sodium
    - Changing Potassium
    - Changing Leakage

INa Gating Rates

+ A L HODGKIN & A F HUXLEY (1952)
+ Last modified: 2008-08-13, David Nickerson ()

Species: *loligo*
Biological Entity: giant nerve fibre

This graph matches Figures 7 and 9 of the Hodgkin & Huxley (1952) article.



alpha_m
x-axis
simulation
V
y-axis
simulation
alpha

beta_m
x-axis
simulation
V
Range restricted to: (-∞,5]
y-axis
simulation
beta

alpha_h
x-axis
simulation
V
y-axis
simulation
alpha

beta_h
x-axis
simulation
V
y-axis
simulation
beta

Human usage

- Model descriptions typically consist of many XML documents – works well for software interchange, not so well for human scientists.
- Different people prefer to look at and interact with models in different ways.
- Different applications may be well suited to specific methods of data display.

Customisable "*views*" of the model description.

Current status of CellMLSimulator

- **Understands the current draft simulation and graphing metadata specifications to some extent**
  - only one numerical integrator provided (CVODES);
  - uses HDF5 to store annotated simulation data.
- **Interprets task hierarchies**
  - can determine required simulations needed to supply data required for the described simulation observations (in combination with the HDF5 data file).
- **Includes a JavaScript dojo module to drive the presentation of the comprehensive model description.**
- **http://www.bioeng.nus.edu.sg/compbiolab/p2**
- **http://www.bioeng.nus.edu.sg/compbiolab/p3**
- **http://cellml.sourceforge.net**

NUS National University of Singapore

Mozilla Firefox

File Edit View History Bookmarks Tools Help

$$\frac{dV_m}{dt} = \frac{-1}{C_m}(I_{ion} + I_{stim})$$ DESCRIPTION VALIDATION

$$I_{ion} = I_{CaL} + I_{LVA} + I_{Kr} + I_{KA} + I_{BK} + I_{Kb} + I_{Na} + I_{NSCC}$$ DESCRIPTION

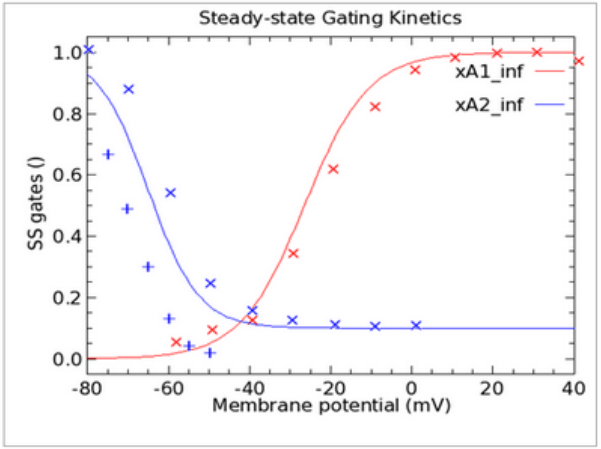
$$I_{KA} = G_{KA} x_{A1} x_{A2} (V_m - E_K)$$ DESCRIPTION

$$\frac{dx_{A1}}{dt} = \frac{x_{A1\infty} - x_{A1}}{\tau_{A1}}$$ DESCRIPTION

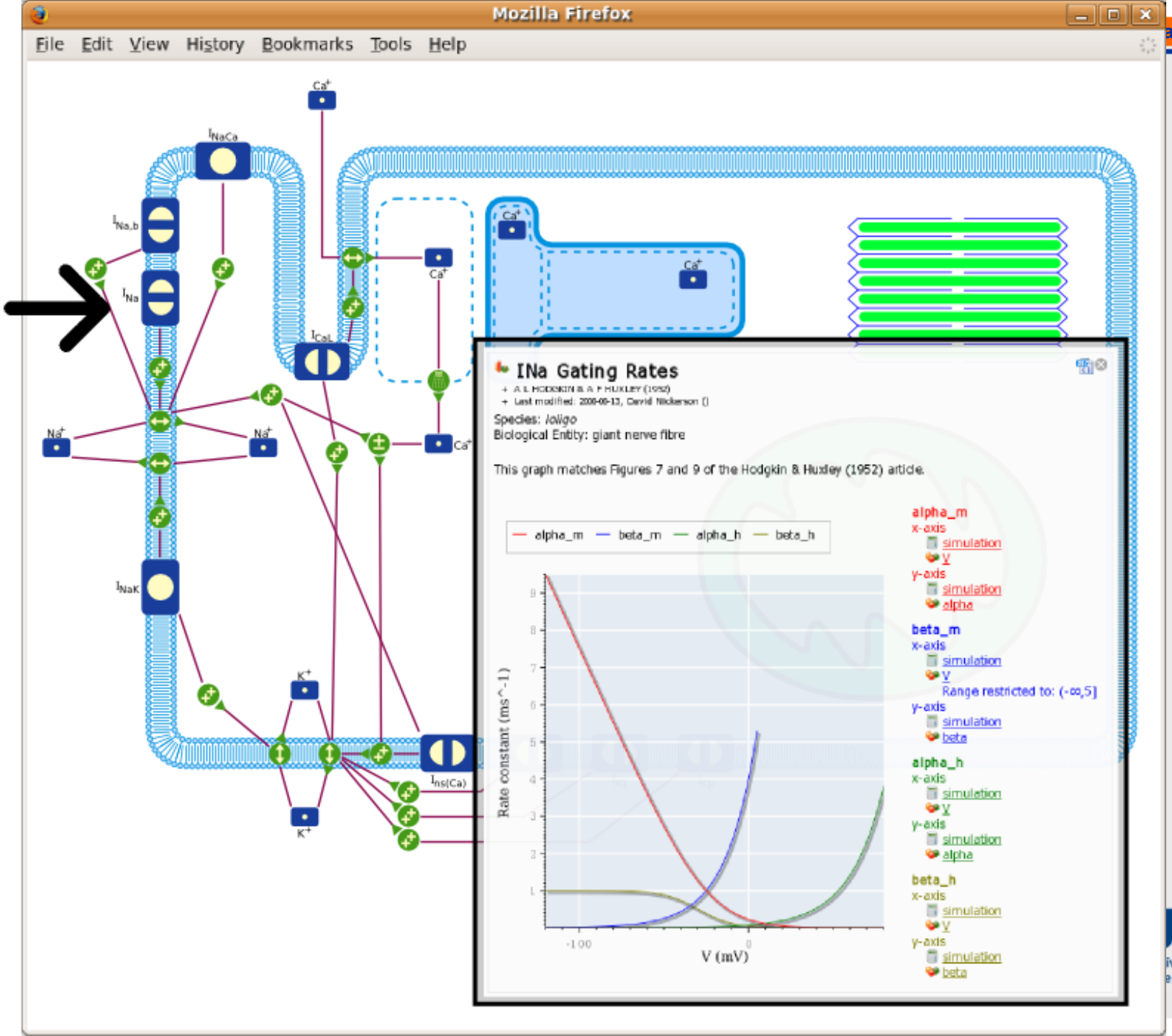
$$x_{A1\infty} = \frac{1}{1 + exp\left(\frac{-(26.5 - V_m)}{7.9}\right)}$$ DESCRIPTION

Steady state value for A-type K+ channel activation, fitted to data from the murine gastric antrum. GET ARTICLE

VALIDATION



NUS National University of Singapore


Mozilla Firefox
File Edit View History Bookmarks Tools Help
INa Gating Rates
Species: loligo
Biological Entity: giant nerve fibre
This graph matches Figures 7 and 9 of the Hodgkin & Huxley (1952) article.
alpha_m
beta_m
alpha_h
beta_h
Rate constant (ms^-1)
V (mV)
-100
0
alpha_m
x-axis
simulation
V
y-axis
simulation
alpha
beta_m
x-axis
simulation
V
Range restricted to: (-∞,5]
y-axis
simulation
beta
alpha_h
x-axis
simulation
V
y-axis
simulation
alpha
beta_h
x-axis
simulation
V
y-axis
simulation
beta

Large scale models

- **Current physiome model encoding formats suitable for large scale models**
  - CellML + FieldML + openCMISS = ?
  - + cmgui = cool movies;
  - proof of concept already exists in CMISS.
- **Core CellML metadata suitable for any (XML?) model encoding format.**
- **CellML simulation metadata provides an excellent foundation on which to extend to the required annotations for other classes of numerical methods/algorithms.**

NUS National University of Singapore

Large scale models

- **CellML graphing metadata works well for extracting observations from simulations performed based on CellML models**
  - can it be extended to handle the spatial aspects of large scale models?
- **Task-based annotation will work across multiple temporal and spatial scales**
  - eg, provides the ability to group cellular model validation, material property fitting, and whole organ models together.

Large scale models

- **Combination of models of different spatial scales or biophysical processes to create large multiscale and multiphysics models**
  - important to unambiguously define and describe connections between models;
  - eg, automated conversion of tissue volume currents and cellular area currents;
  - will require ontological annotation of variables in the CellML models and fields in the FieldML models;
  - eg, coupling electrophysiology and mechanics.

Large scale models

- **Human presentation and interaction**
  - dynamic web-based environments are expected to adapt well to multiscale and multiphysics models;
  - “easy” to navigate through the spatial scales;
  - have used standard web technologies in order that other efforts can be plugged in to the framework;
  - eg, Zinc should slip straight in for the visualisation of and interaction with three-dimensional FieldML models;
  - eg, JavaScript can be used to respond to user input to guide the user through the comprehensive description of a large scale model;
  - eg, web services can be used to connection presentation environments on client machines to high performance computational resources.

NUS National University of Singapore

References

- Nickerson & Buist (2009): *Phil Trans R Soc A* (VPH special issue, in press)
- Nickerson & Buist (2008): *EMBS Conf Proc*:2427–2430
- Nickerson *et al* (2008): *Bioinformatics* 24(8):1112–1114; doi: 10.1093/bioinformatics/btn080
- Nickerson & Buist (2008): *Prog Biophys Mol Biol* 98(1):38–51; doi: 10.1016/j.pbiomolbio.2008.05.006
- http://www.bioeng.nus.edu.sg/compbiolab/p2
- http://www.bioeng.nus.edu.sg/compbiolab/p3

Acknowledgment

- A*STAR BMRC Grant #05/1/21/19/383.

NUS National University of Singapore