A novel method to describe and share complex mathematical models of cellular physiology

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Background

- **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.**

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The Problem

- **How do model authors:**
  - describe such complex models?
  - share them with colleagues and the scientific community?
  - reuse bits and pieces of existing models?
  - publish them?
- **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.**

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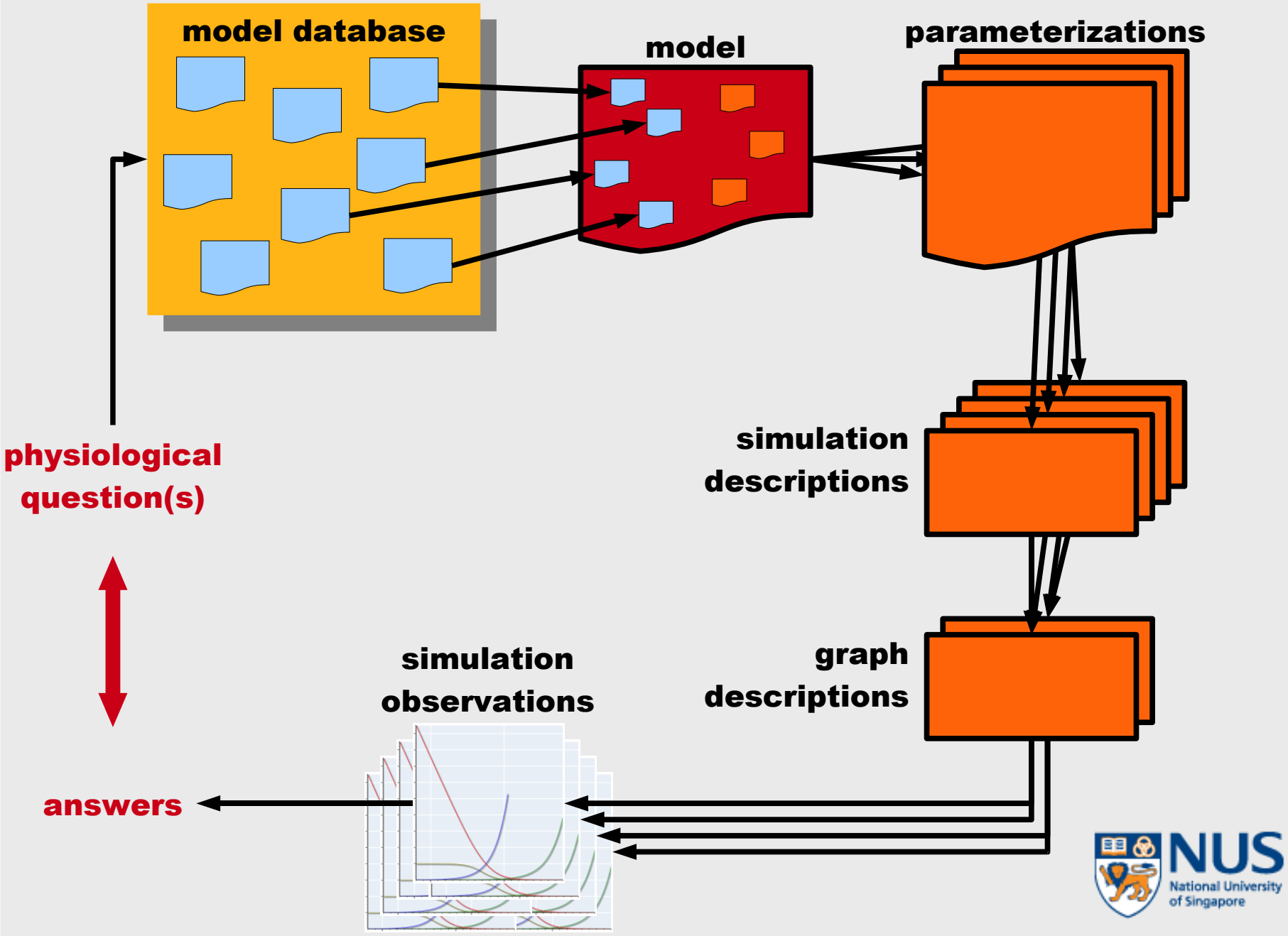
Our solution

- Annotated CellML models....

http://www.cellml.org


model database
model
parameterizations
physiological question(s)
simulation descriptions
graph descriptions
simulation observations
answers
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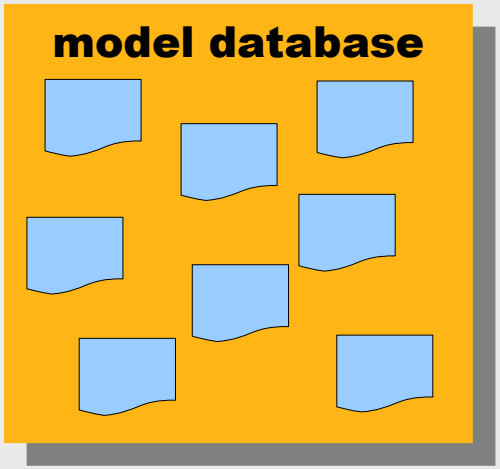
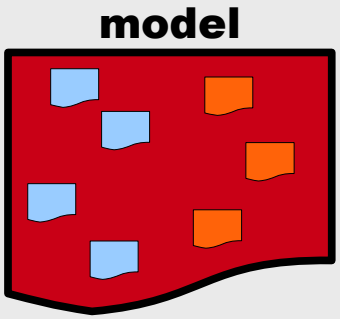
Model repositories



- Freely available & online model repositories.
- Contain models described in standard formats.
- Curated to various levels of “correctness”.
- Examples:
  - http://www.cellml.org/models/
  - http://www.biomodels.net/biomodels/

New models and model components



- **Answering novel questions generally requires the development of new models in combination with existing models:**
  - reparameterizing existing models;
  - combining existing models;
  - altering the dynamics of certain components of the model;
  - extending models to include new behaviour.

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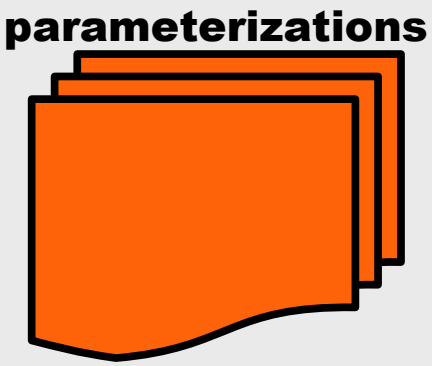
Model parameterization



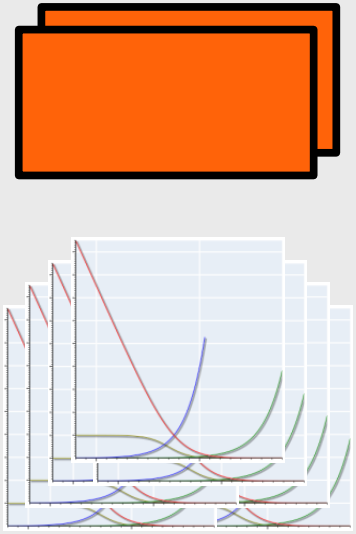
- Each mathematical model may be parameterized for many different scenarios.
- Specializing generic mathematical model for specific purpose.

Description of numerical simulations

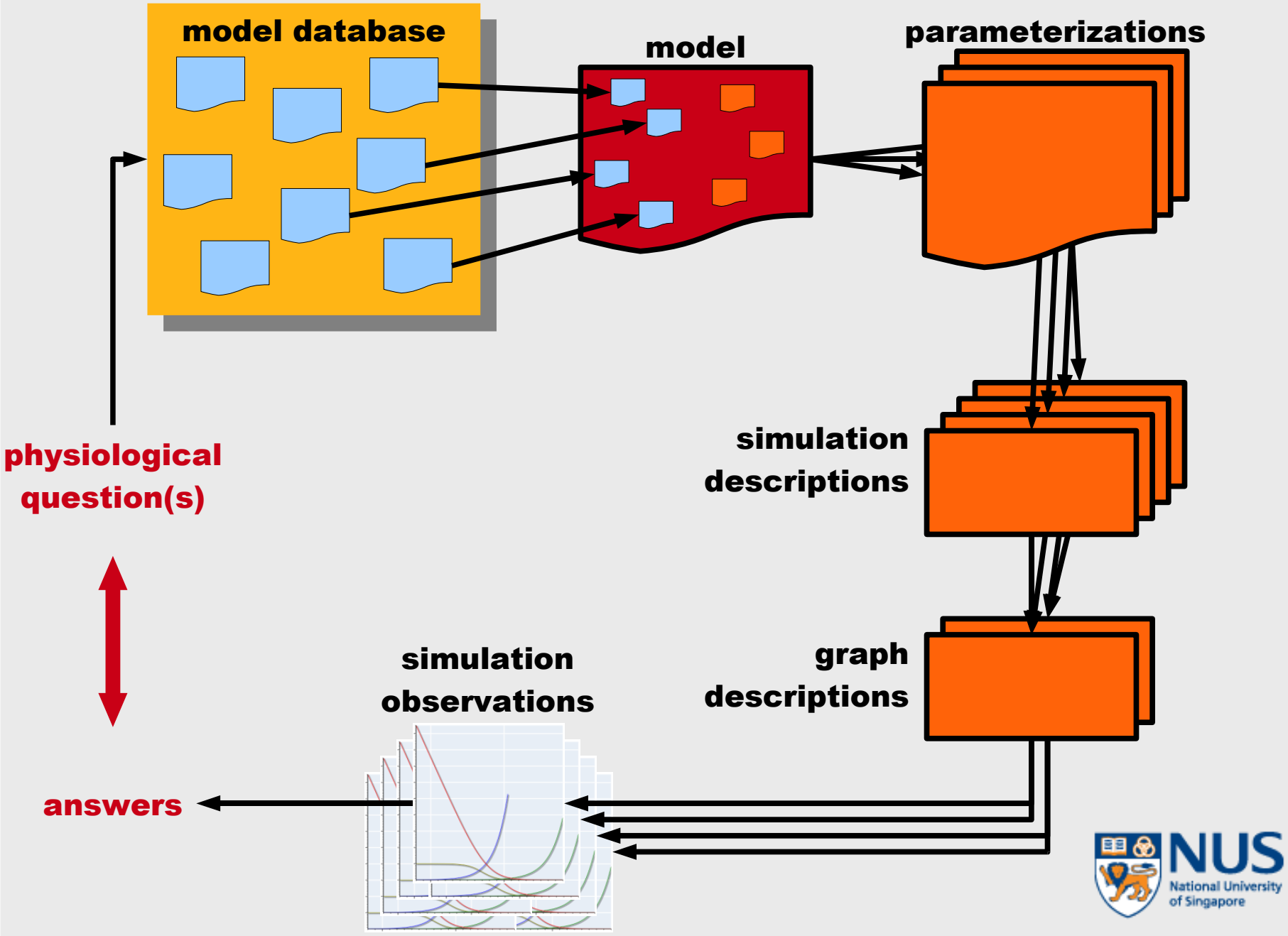
- **Each parameterized model instantiated into one or more simulation.**
- **Simulation metadata:**
  - numerical methods;
  - associated parameters;
  - links to required model and variable(s);
  - general annotations.

Description of simulation outputs

graph descriptions



- **Want to extract specific observations from simulation results.**
- **Graphing metadata:**
  - reference specific 'x' and 'y' variables from specified simulations;
  - range of interest;
  - graphical properties (colours, glyphs, line width, etc.).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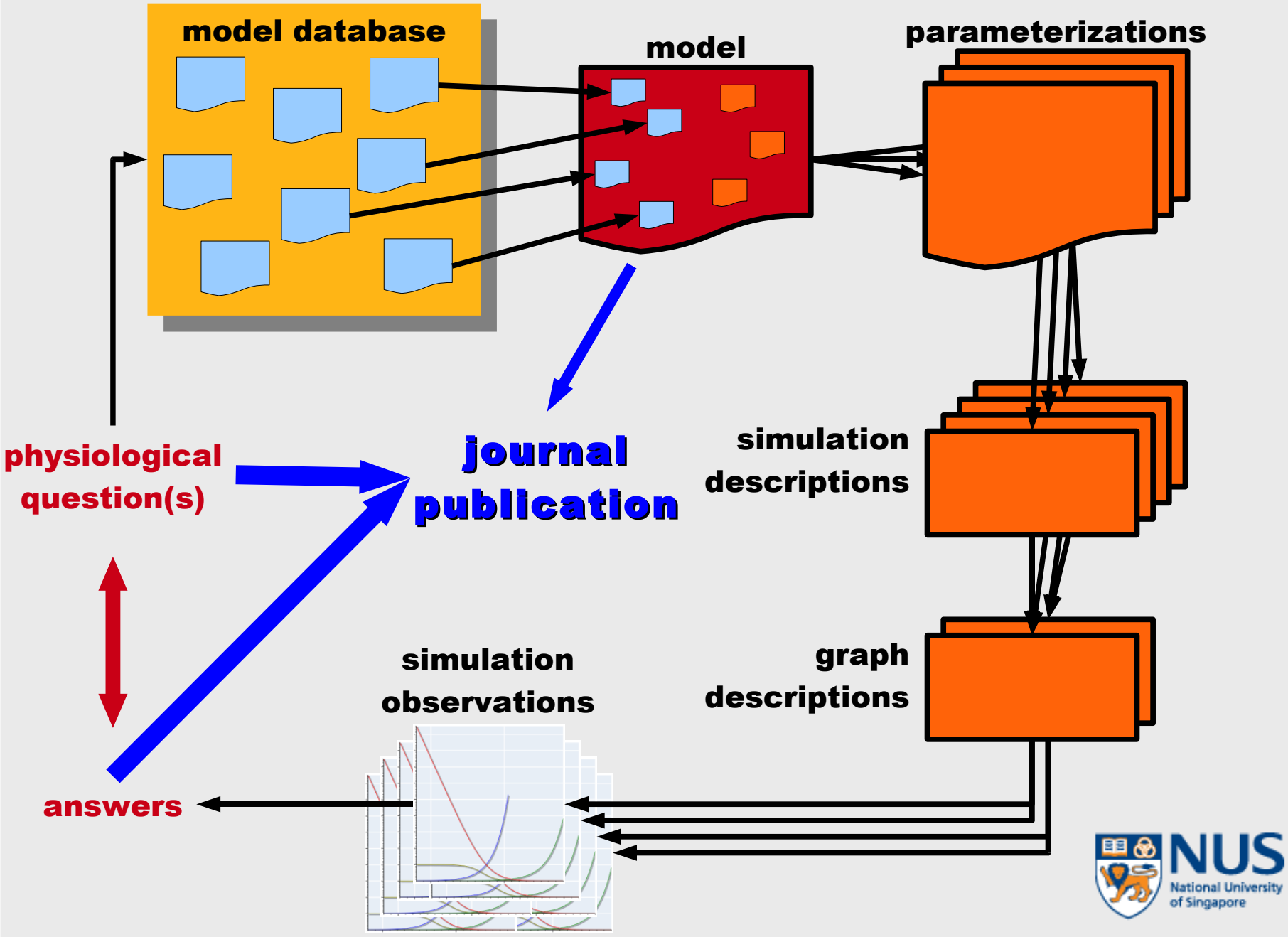
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Human usage

- 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.

Reference Description of a HH-based Modelling Study - Mozilla Firefox

File Edit View History Bookmarks Tools Help

Reference Description of a HH-based Modelling Study

David Nickerson (2008-07-16)

Help

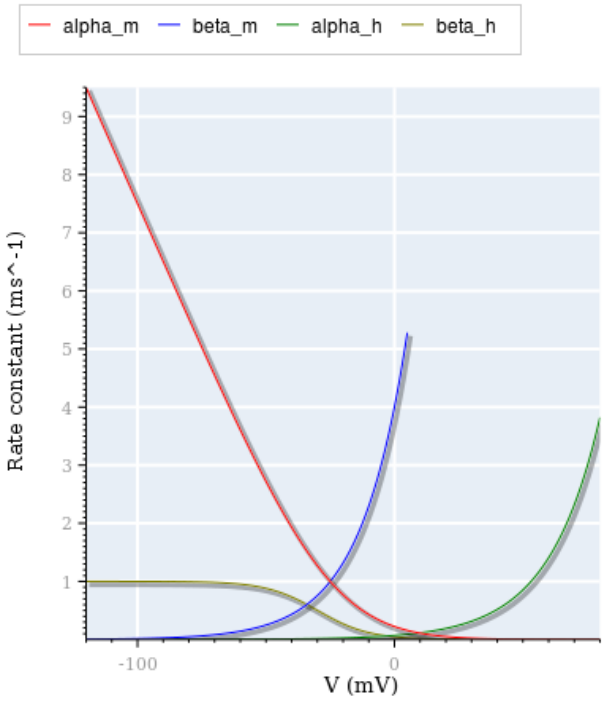
- Reference Description of a HH-based Modelling Study
  - Model Validation
    - Sodium Channel Kinetics Validation
      - INa Gating Rates
      - INa Steady State Gating Kinetics
    - Potassium Channel Kinetics Validation
      - IK Gating Rates
      - IK Steady State Gating Kinetics
    - Voltage 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

Generated by: CellMLSimulator (version: CellMLSimulator 0.3.0-devel-json - revision 132M - Thu Aug 14 18:14:54 SGT 2008) at Monday 01,September,2008 04:11:05 PM SGT

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

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

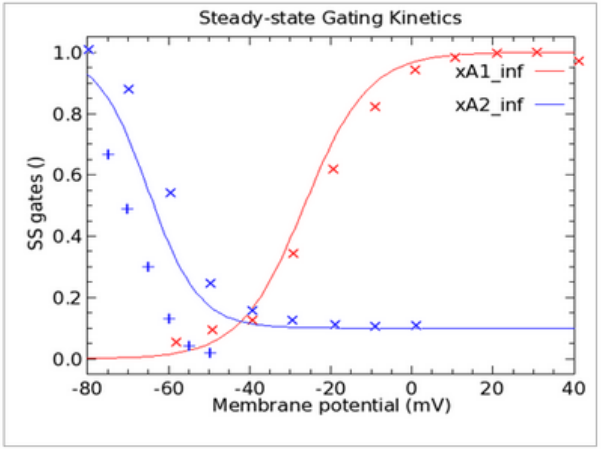
$$I_{KA} = G_{KA} x_{A1} x_{A2} (V_m - E_K)$$ DESCRIPTION

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



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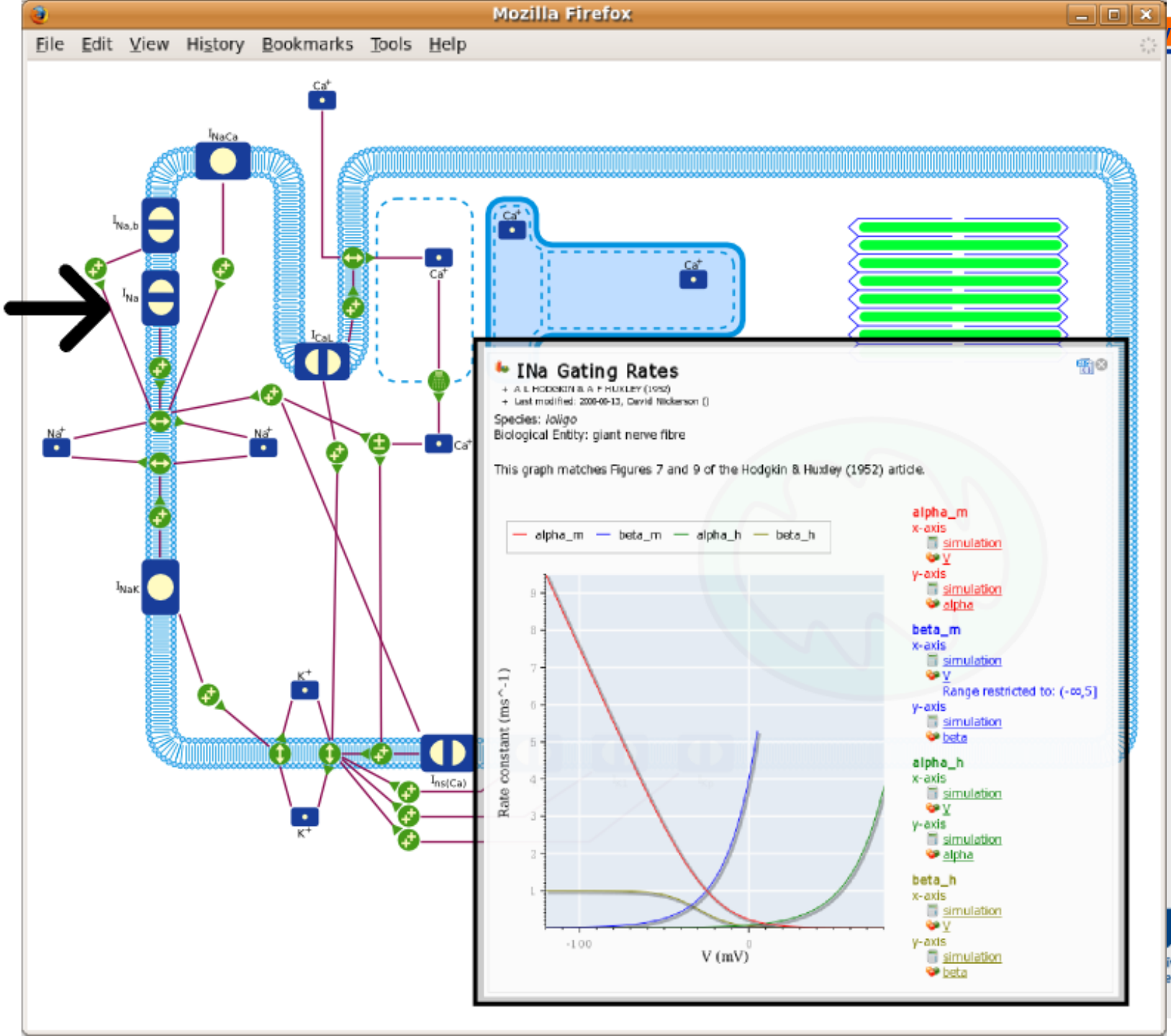
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INa Gating Rates
Species: loligo
Biological Entity: giant nerve fibre
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alpha_m beta_m alpha_h beta_h
Rate constant (ms^-1)
V (mV)
alpha_m
x-axis
simulation
V
y-axis
simulation
alpha
beta_m
x-axis
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

References

- 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

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