Modularity in CellML

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

NUS National University of Singapore

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.**

NUS National University of Singapore

The Problem

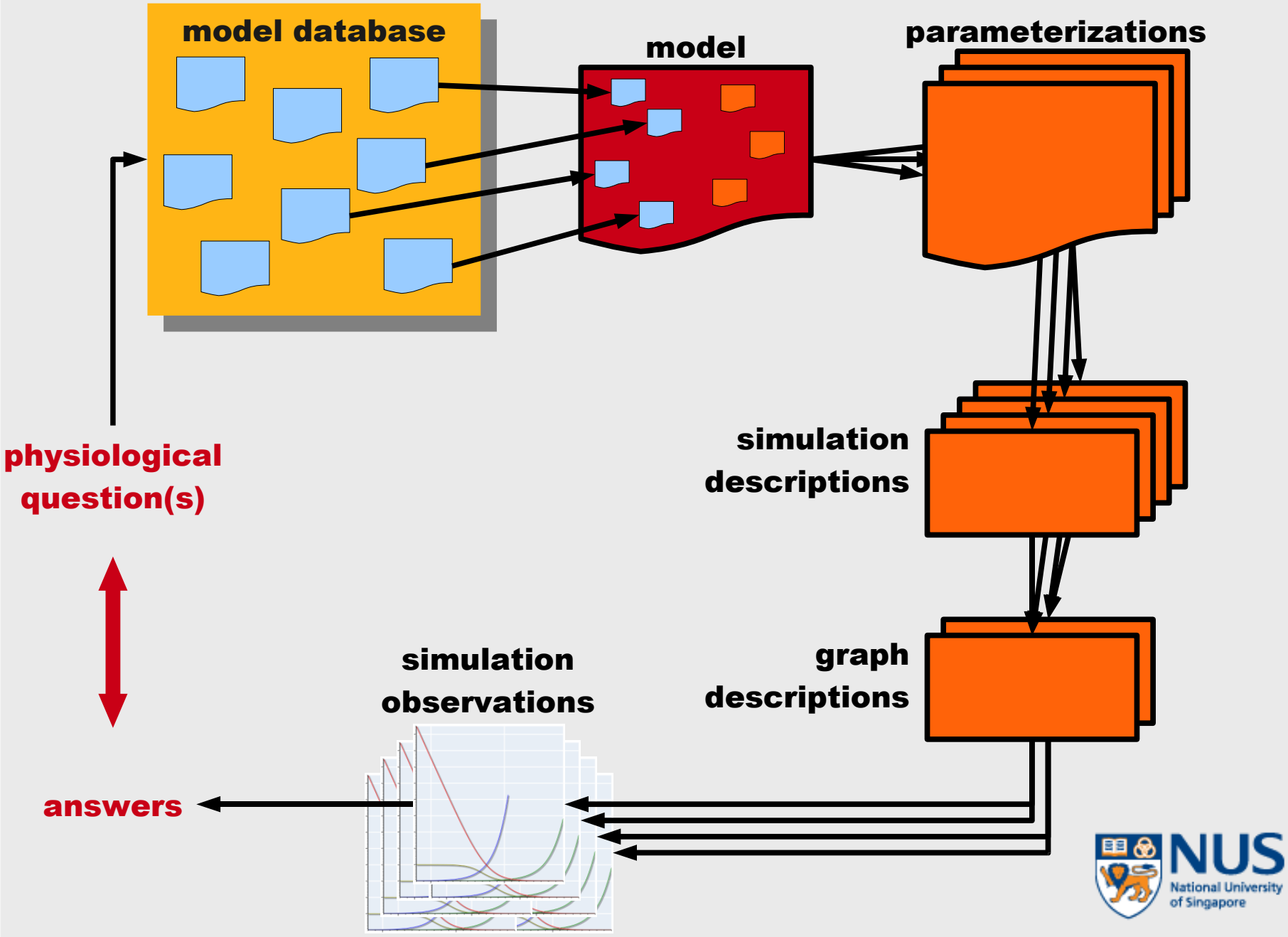
- **How do model authors:**
  - describe such complex models?
  - share them with colleagues and the scientific community?
  - reuse bits and pieces of existing models?
  - publish them?
- **Several (almost) independent sub-problems:**
  - the mathematical model(s);
  - parameterizations of the mathematical 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.**

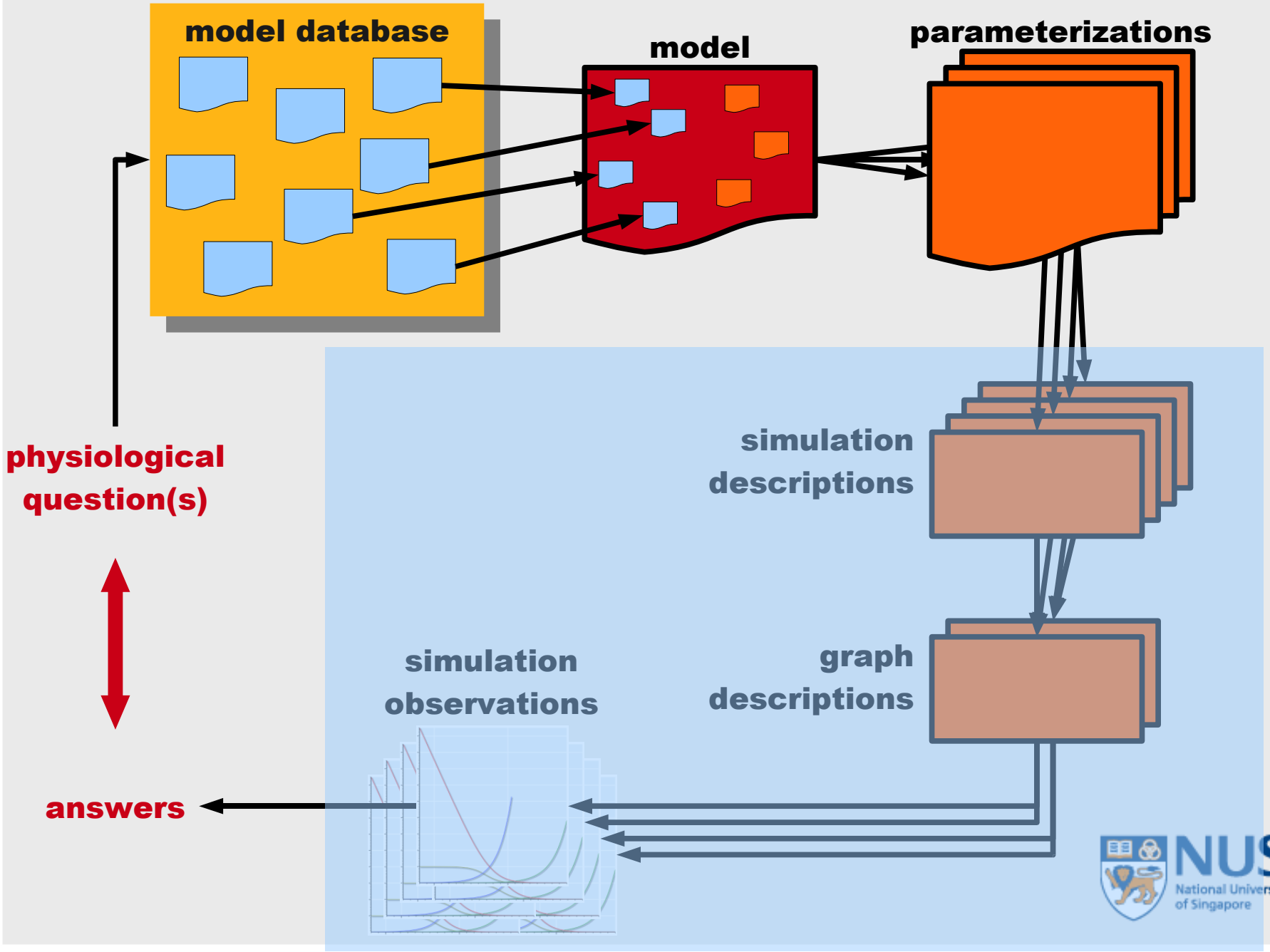
NUS National University of Singapore

Our solution

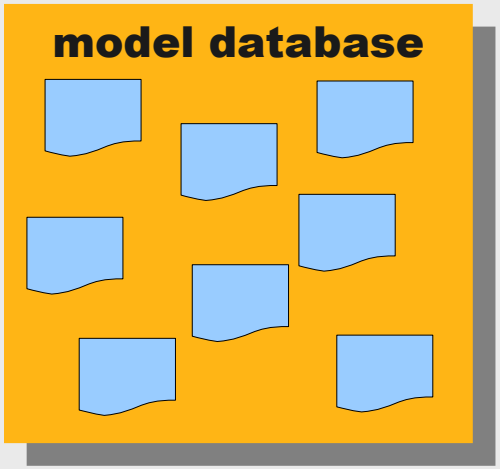
- Annotated CellML models....

http://www.cellml.org


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


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

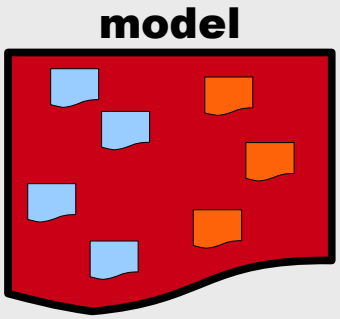
Model repositories



- 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/

NUS National University of Singapore

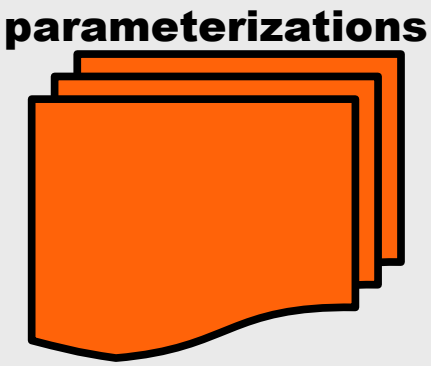
New models and model components



- **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.

NUS National University of Singapore

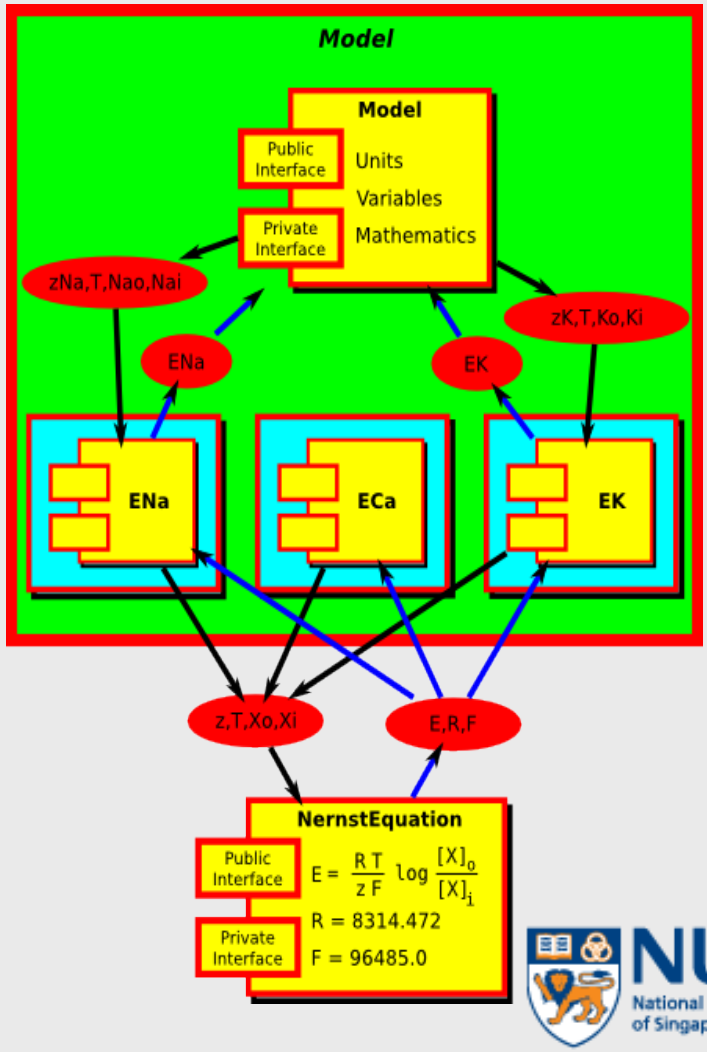
Model parameterization



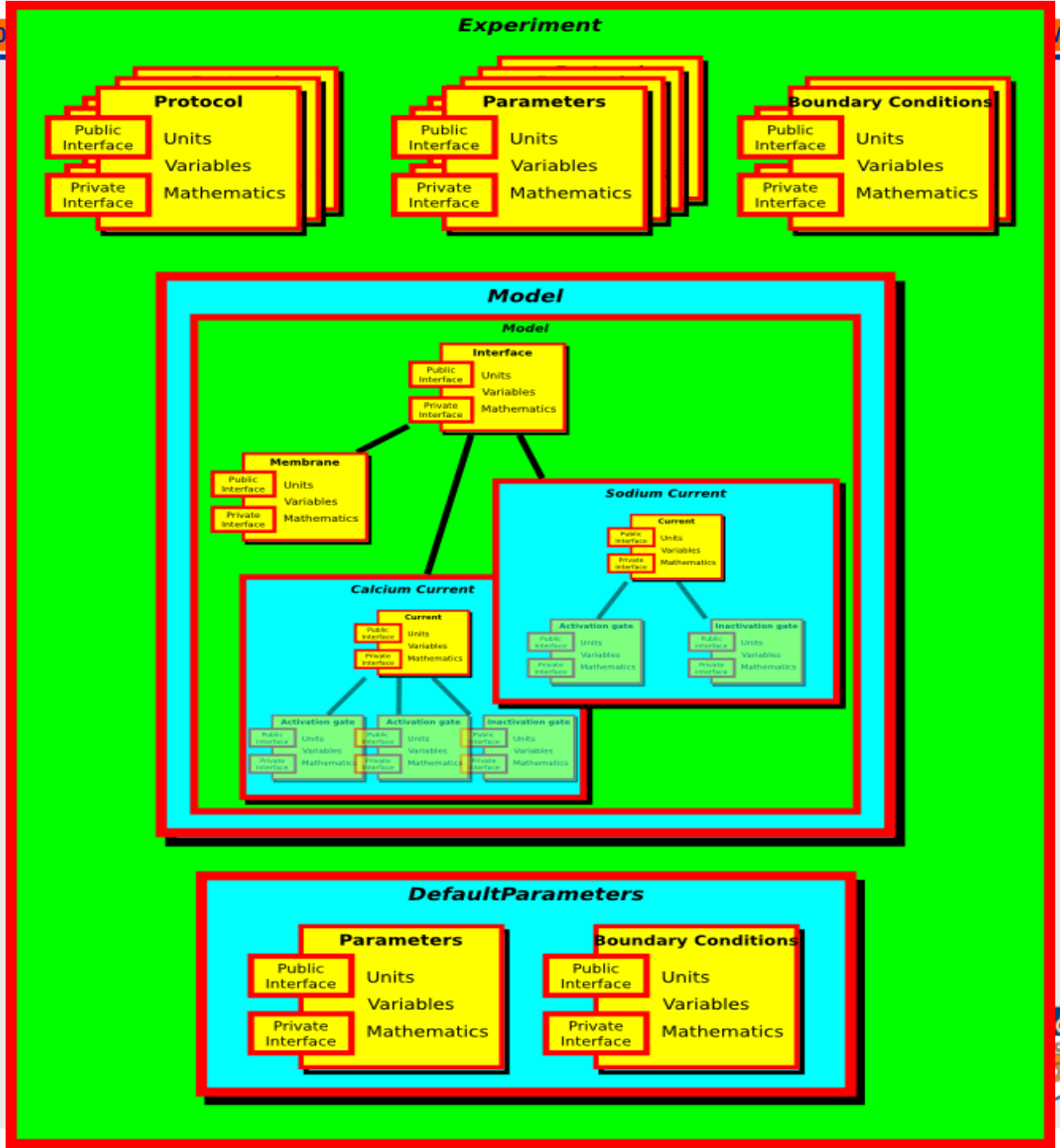
- Each mathematical model may be parameterized for many different scenarios.
- Specializing generic mathematical model for specific purpose.

Mechanics of Modularity in CellML

- **CellML 1.1:**
  - import element;
  - use of variables in setting initial_value attribute.



NUS National University of Singapore


Experiment
Protocol
Public Interface
Private Interface
Units
Variables
Mathematics
Parameters
Public Interface
Private Interface
Units
Variables
Mathematics
Boundary Conditions
Public Interface
Private Interface
Units
Variables
Mathematics
Model
Model
Interface
Public Interface
Private Interface
Units
Variables
Mathematics
Membrane
Public Interface
Private Interface
Units
Variables
Mathematics
Sodium Current
Current
Activation gate
Inactivation gate
Calcium Current
Current
Activation gate
Activation gate
Inactivation gate
DefaultParameters
Parameters
Public Interface
Private Interface
Units
Variables
Mathematics
Boundary Conditions
Public Interface
Private Interface
Units
Variables
Mathematics

Mechanics of Modularity in CellML

- **CellML 1.2 (?):**
  - variable typing, sets:
    - avoid current necessity to recompose model hierarchies to expose species rate variables;
    - simply add new fluxes to the set of all fluxes for that species.

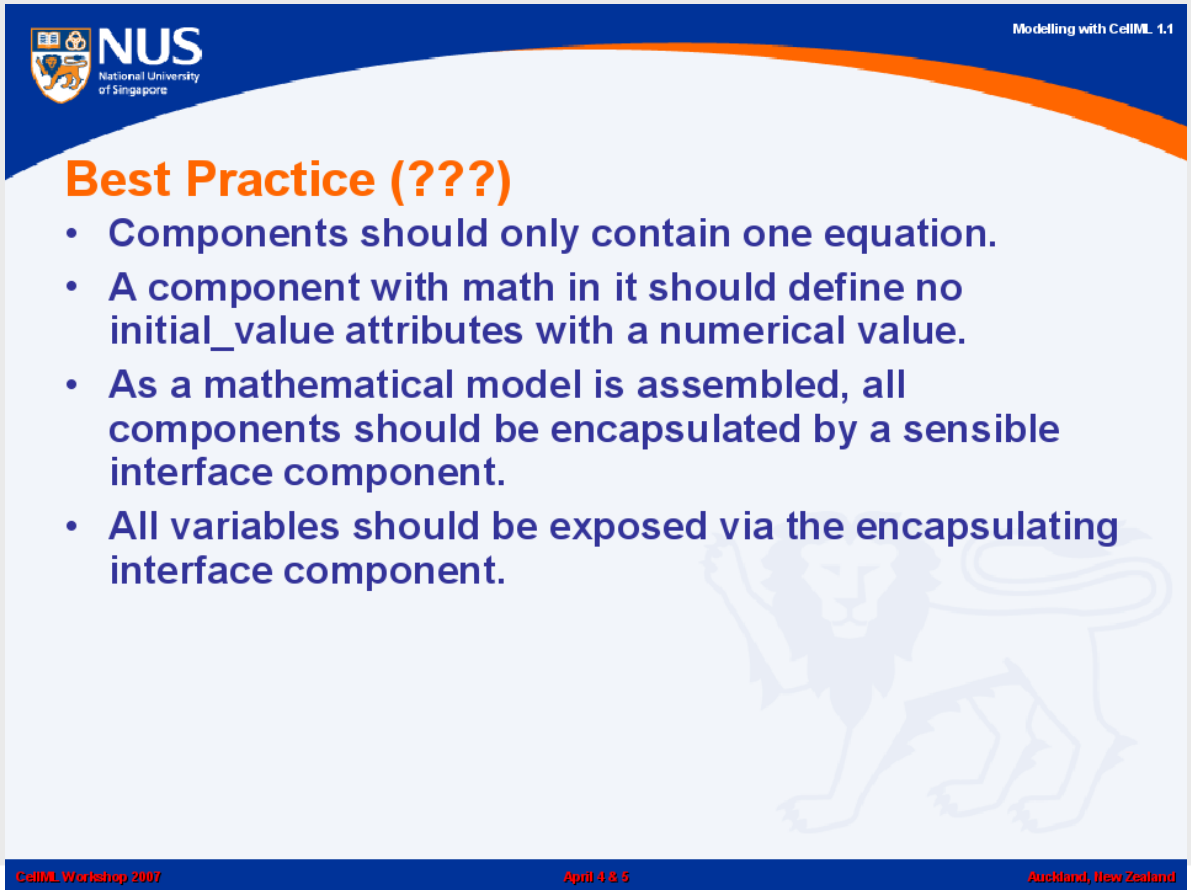
Enhancing Modularity in CellML

- **Model repository (PMR2):**
  - model workspaces;
  - DVCS;
  - curation and authorship;
  - programatic access.
- **Tool support:**
  - C++ API exists and generally works, why aren't people using it?
- **Model component curation:**
  - what does it mean to use a model component outside its original model?
  - annotation? licensing? PMR2...

NUS National University of Singapore

Enhancing Modularity in CellML

- Guidelines on the use of CellML 1.1 to ensure we all create models suitable for re-use by the community wherever possible...



NUS National University of Singapore

References

- Nickerson & Buist (2008): Prog Biophys Mol Biol. 98(1):38–51; doi: 10.1016/j.pbiomolbio.2008.05.006
- http://www.cellml.org/publications

Acknowledgment

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

NUS National University of Singapore