Methods for Semantic Cell Modelling and Convenient Simulation

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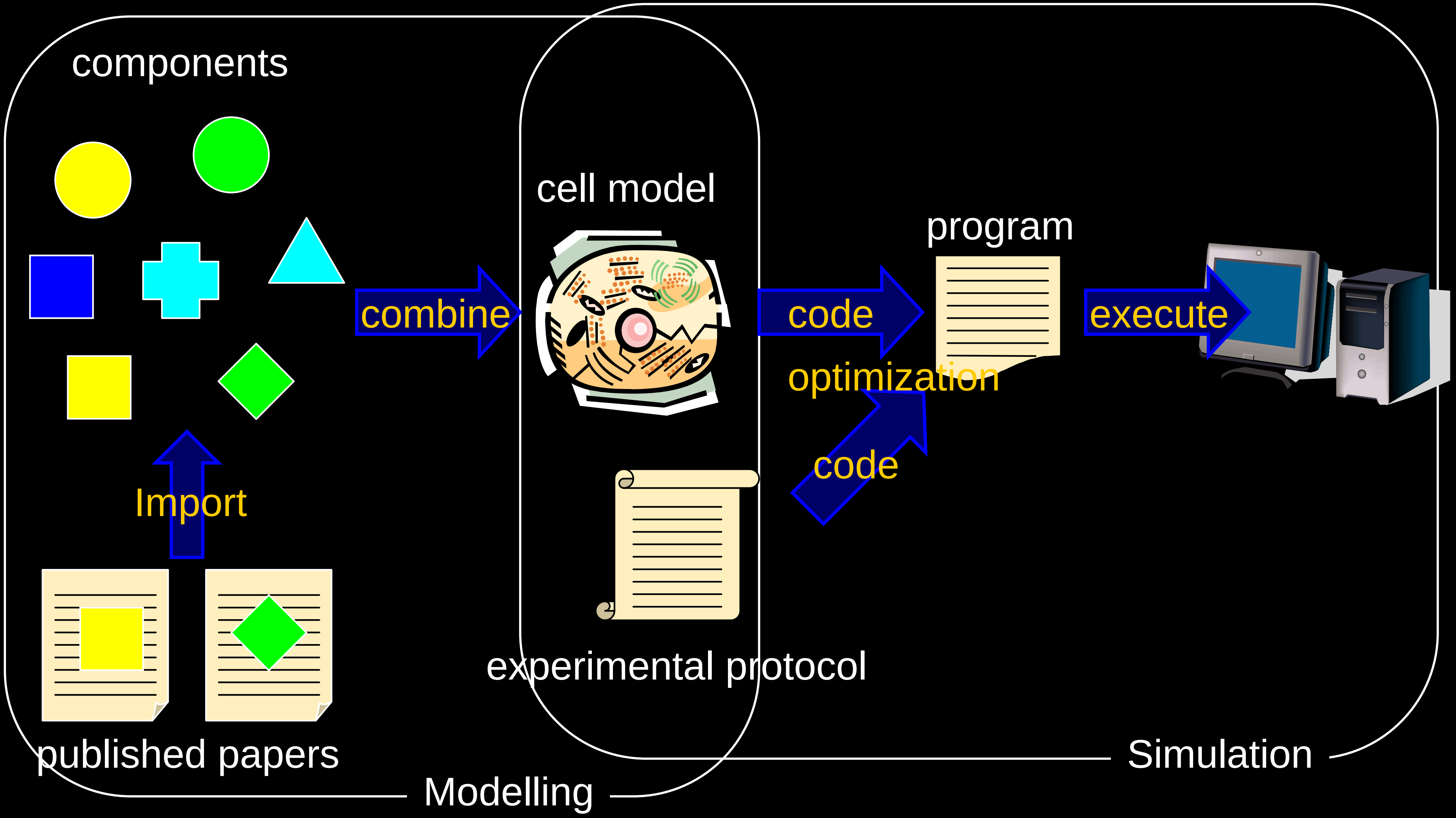
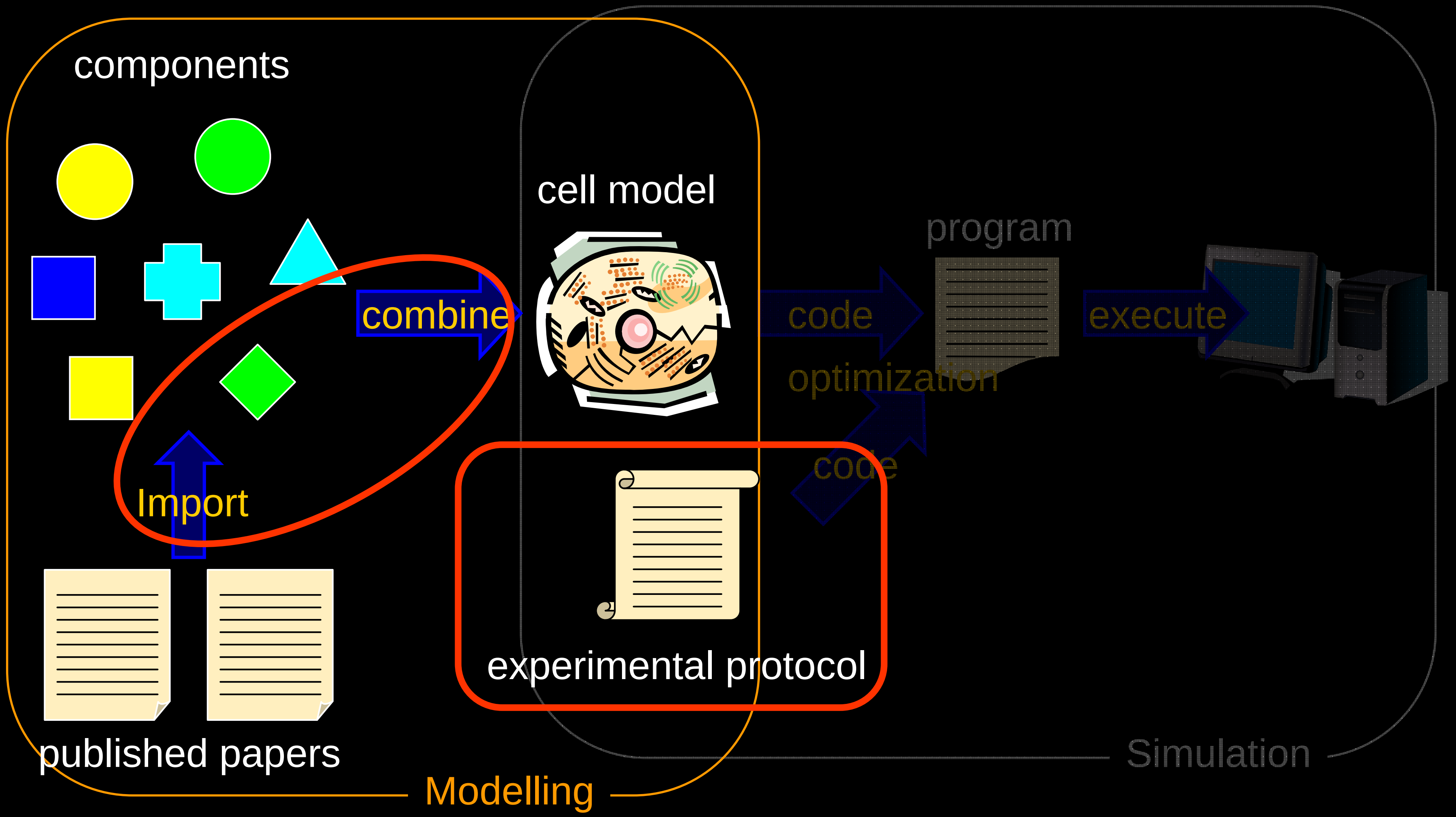
Current Status of Kyoto Model

- Kyoto Model:
  - Comprehensive cardiac myocyte model
  - Recent model published
    - Kuzumoto, et. al. *Prog Biophys Mol Biol*. 2008. doi: 10.1016/j.pbiomolbio.2007.07.005
  - CellML files
    - Being written for several variants of Kyoto Model

Modelling & Simulation



Methods for Modelling



components

combine

Import

published papers

cell model

experimental protocol

Modelling

program

code

execute

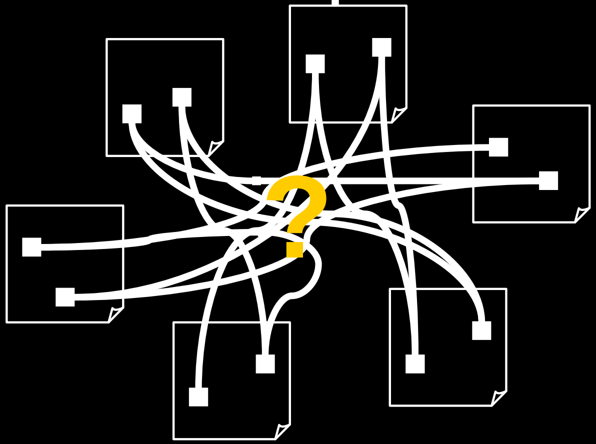
optimization

code

Simulation

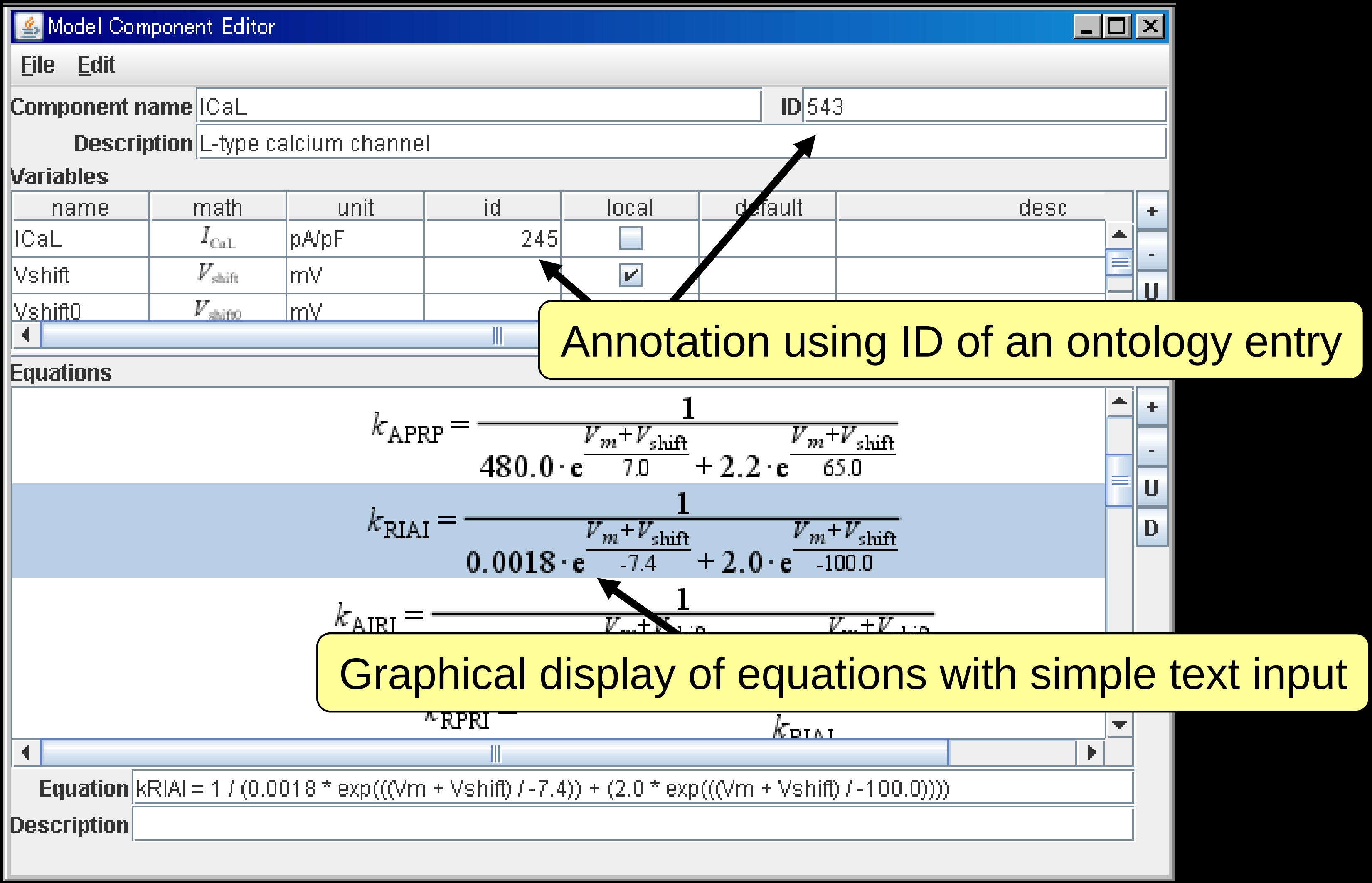
Computer Aided Modelling

- Troublesome task in editing models
  - Composition of components



- Modelling with Ontology
  - Semantic annotation to model components
  - Intelligent assistance using Ontology

Edit of Component



Component name ICaL **ID** 543

Description L-type calcium channel

Variables

name	math	unit	id	local	default	desc
ICaL	I_{CaL}	pA/pF	245	☐		
Vshift	V_{shift}	mV		☑		
Vshift0	V_{shift0}	mV				

Equations

$$k_{\mathrm{APRP}} = \frac{1}{480.0 \cdot e^{\frac{V_m + V_{\mathrm{shift}}}{7.0}} + 2.2 \cdot e^{\frac{V_m + V_{\mathrm{shift}}}{65.0}}}$$

$$k_{\mathrm{RIAI}} = \frac{1}{0.0018 \cdot e^{\frac{V_m + V_{\mathrm{shift}}}{-7.4}} + 2.0 \cdot e^{\frac{V_m + V_{\mathrm{shift}}}{-100.0}}}$$

$k_{\mathrm{AIRI}} =$

$k_{\mathrm{RPRI}} =$

k_{RIAI}

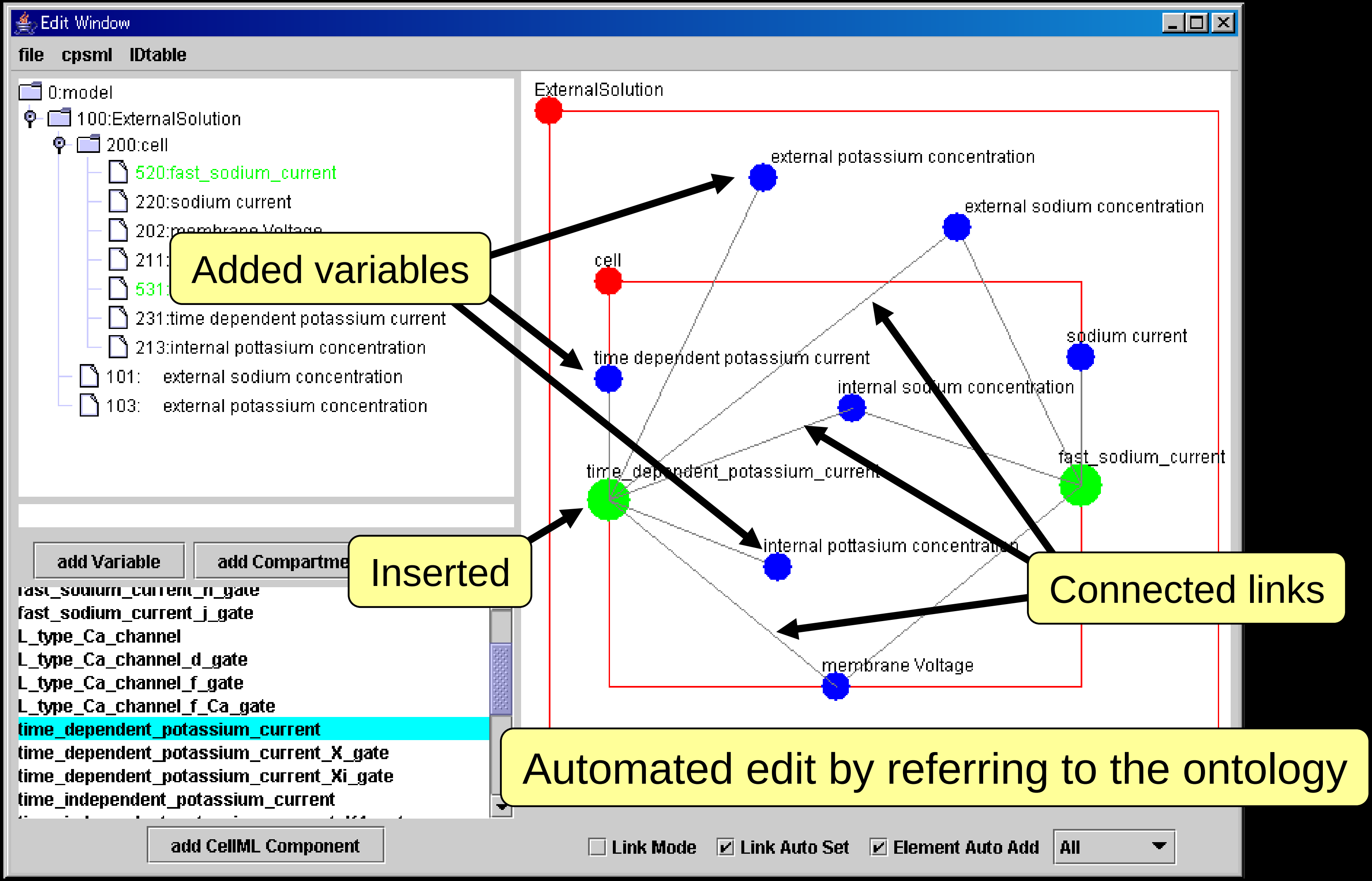
Equation kRIAI = 1 / (0.0018 * exp(((Vm + Vshift) / -7.4)) + (2.0 * exp(((Vm + Vshift) / -100.0))))

Description

Annotation using ID of an ontology entry

Graphical display of equations with simple text input

Composition of Model



0:model
100:ExternalSolution
200:cell
520:fast_sodium_current
220:sodium current
202:membrane Voltage
211:
531:
231:time dependent potassium current
213:internal pottasium concentration
101: external sodium concentration
103: external potassium concentration

fast_sodium_current_j_gate
L_type_Ca_channel
L_type_Ca_channel_d_gate
L_type_Ca_channel_f_gate
L_type_Ca_channel_f_Ca_gate
time_dependent_potassium_current
time_dependent_potassium_current_X_gate
time_dependent_potassium_current_Xi_gate
time_independent_potassium_current

☐ Link Mode ☑ Link Auto Set ☑ Element Auto Add All

Added variables

Inserted

Connected links

Automated edit by referring to the ontology

Convertibility to CellML

- Export to CellML
  - Straightforward conversion
    - Usable as an authoring tool of CellML
- Import from CellML
  - Requires to assign ontology IDs to elements
    - A tool available to intelligently estimate ontology ID

Experimental Protocol

- Simulation needs a model and an experimental protocol

Wet experiment

Experimental protocol

apply

Cell / tissue

Computer simulation

Experimental protocol

apply

Computational model

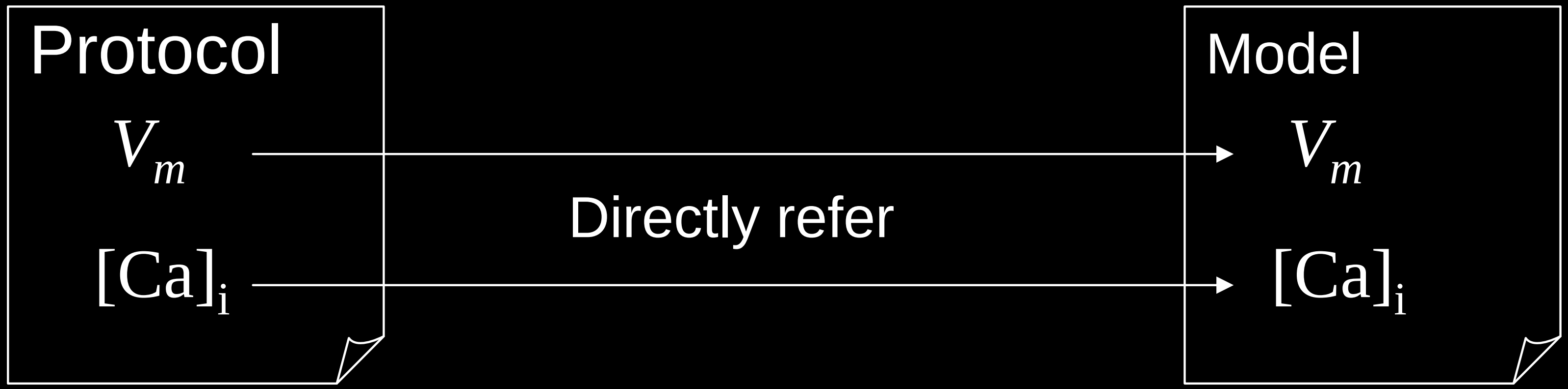
PEPML

- Physiological Experimental Protocol ML
  - XML-based general format
  - Procedural representation

    vs. declarative representation
  - Model independent description using ontologies

Reference of Model Variable

- Without ontology, model-specific



Protocol

V_m

$[\mathrm{Ca}]_i$

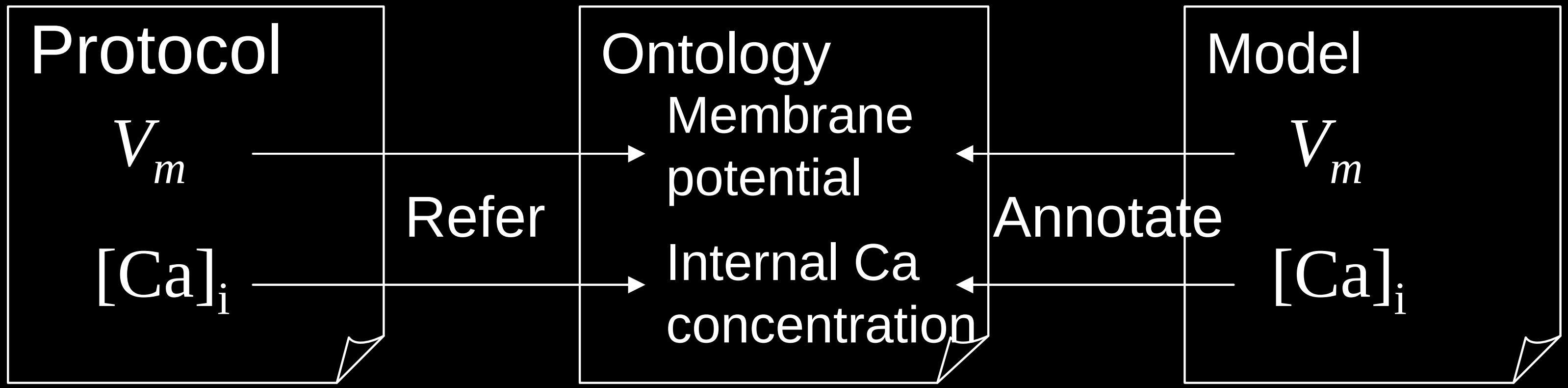
Directly refer

Model

V_m

$[\mathrm{Ca}]_i$

- With ontology, model-independent



Protocol

V_m

$[\mathrm{Ca}]_i$

Refer

Ontology

Membrane potential

Internal Ca concentration

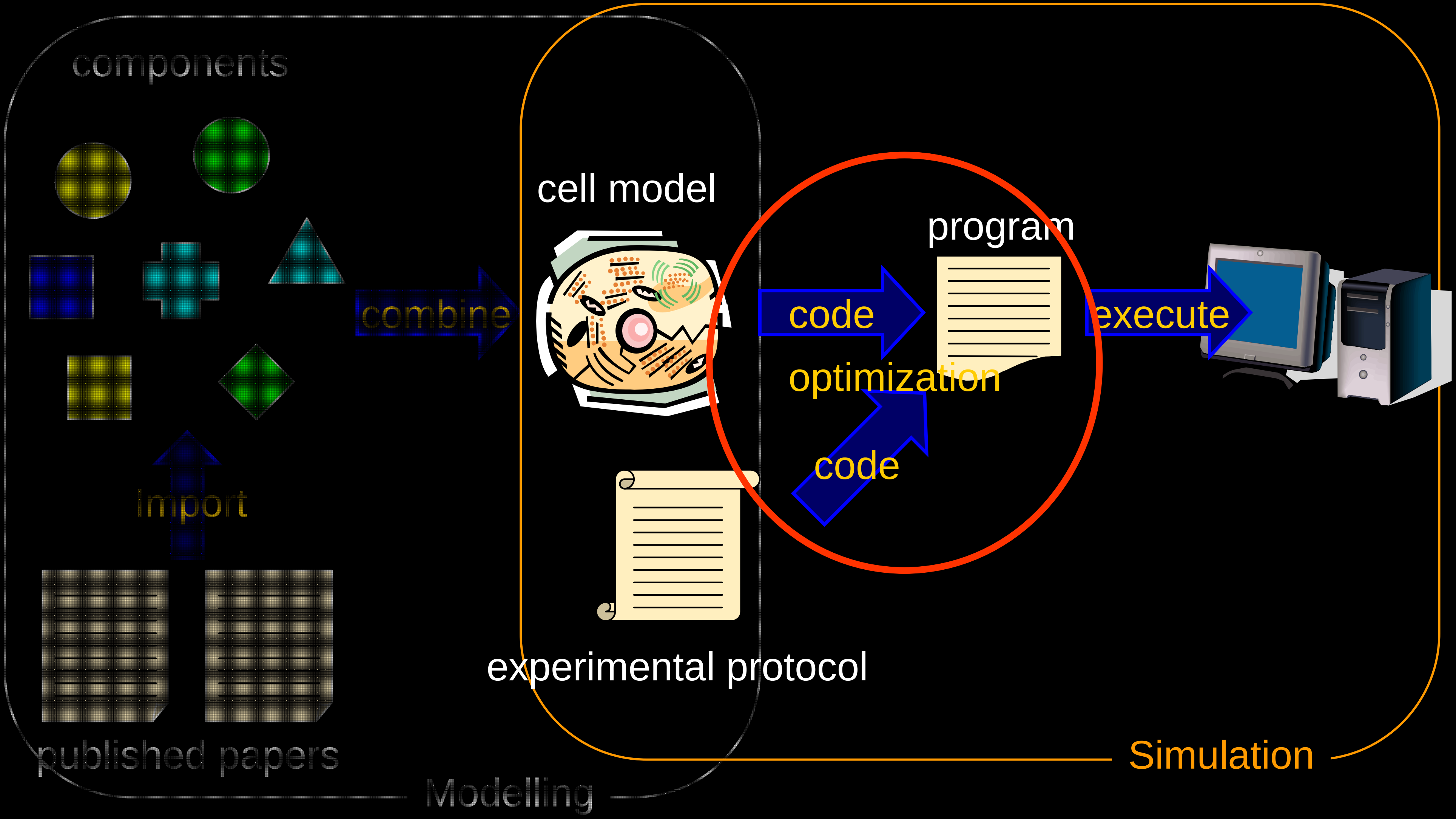
Annotate

Model

V_m

$[\mathrm{Ca}]_i$

Difficulties in Simulation



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Simulation

Boundary Conditions

- Models formulated as DAE:
  - ODE + simultaneous algebraic equations
- Consistent set of boundary conditions for correct simulation of DAE models
  - Which variables are given the values externally?

$$\begin{cases} p \cdot u - (q+a) \cdot v = c \\ (q+a) \cdot u^2 + p \cdot v^2 = d \end{cases}$$

Difficulty

- Difficult to assign consistent boundary conditions to a model with hundreds of variables
- Wrong boundary conditions result in
  - Impossibility of calculation
  - Oblivious unintended calculation

Setup of Boundary Conditions

- Assistance to assign a consistent set of boundary conditions based on graph theory
  - Automatic extraction of candidate variables to be bounded

cyclic AMP metabolism module [Saucerman 2003]

$$[G_{s\alpha GTP}] + [G_{s\alpha GTP} : AC] = [G_{s\alpha GTPtot}]$$

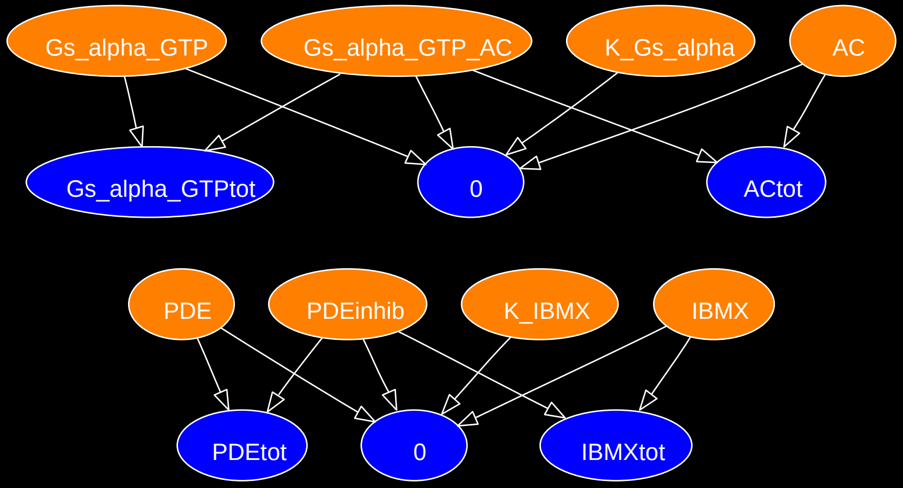
$$[G_{s\alpha GTP} : AC] + [AC] = [AC_{tot}]$$

$$[PDE_{inhib}] + [PDE] = [PED_{tot}]$$

$$[PDE_{inhib}] + [IBMX] = [IBMX_{tot}]$$

$$[G_{s\alpha GTP}][AC] = K_{G_{s\alpha}}[G_{s\alpha GTP} : AC]$$

$$[PDE][IBMX] = K_{IBMX}[PDE_{inhib}]$$

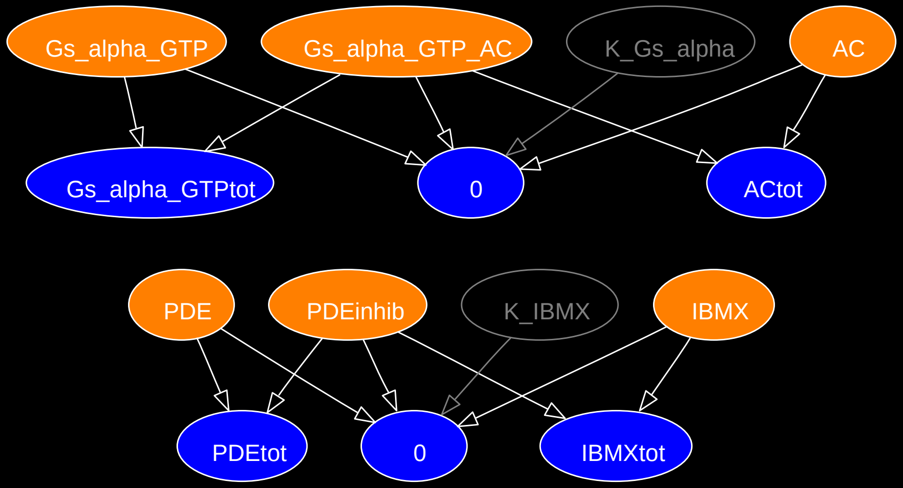


Automatic Optimization

- Optimization of simultaneous equations
  - Reduction of the degree

Original degree: 3+3

$$[G_{s\alpha GTP}]+[G_{s\alpha GTP}:AC]=[G_{s\alpha GTPtot}]$$
$$[G_{s\alpha GTP}:AC]+[AC]=[AC_{tot}]$$
$$[PDE_{inhib}]+[PDE]=[PED_{tot}]$$
$$[PDE_{inhib}]+[IBMX]=[IBMX_{tot}]$$
$$[G_{s\alpha GTP}][AC]=K_{G_{s\alpha}}[G_{s\alpha GTP}:AC]$$
$$[PDE][IBMX]=K_{IBMX}[PDE_{inhib}]$$

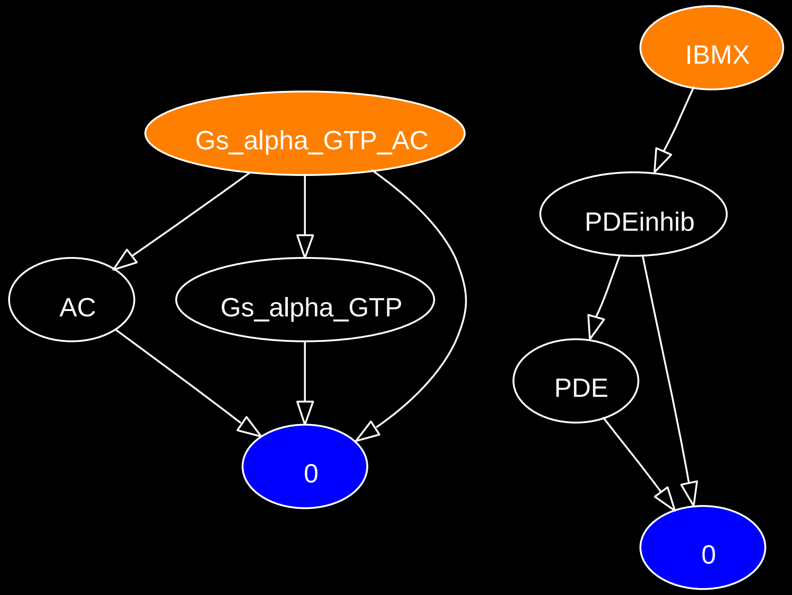


Automatic Optimization

- Optimization of simultaneous equations
  - Reduction of the degree

After optimization degree: 1+1

$$[G_{s\alpha GTP}] = [G_{s\alpha GTPtot}] - \boxed{[G_{s\alpha GTP}:AC]}$$
$$[AC] = [AC_{tot}] - \boxed{[G_{s\alpha GTP}:AC]}$$
$$[G_{s\alpha GTP}][AC] - K_{G_{s\alpha}}\boxed{[G_{s\alpha GTP}:AC]} = 0$$
$$[PDE_{inhib}] = [IBMX_{tot}] - \boxed{[IBMX]}$$
$$[PDE] = [PED_{tot}] - [PDE_{inhib}]$$
$$[PDE]\boxed{[IBMX]} - K_{IBMX}[PDE_{inhib}] = 0$$



Evaluation

- Beta signalling model [Saucerman 2003]
  - Unoptimized naïve math expressions
- Configuration of boundary conditions
  - #Candidates
    - Manual: 3060
    - With the proposed method: 516 (16.9%)
- Optimization of equations
  - Computation time
    - Without optimization: 31.5 [s]
    - With automatic optimization: 20.5 [s] (64.9%)

Conclusion

- Easy modelling and simulation with information technology
  - Modelling with ontology
  - Protocol description format
  - Convenient simulation using graph theory

- Prototype software tools available on

  http://www.biosim.med.kyoto-u.ac.jp/~simayosi/research/tools/

Thank you!