Software Tools & Techniques
Cell/Biodynamics Simulation Project of Kyoto University
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Project Introduction

Cell/Biodynamics Simulation Project
www.biosim.med.kyoto-u.ac.jp

- Leader: Prof. Noma
- Main Targets
  - Development of a comprehensive ventricular cell model: Kyoto Model
    - Membrane excitation, excitation contraction coupling, volume regulation, beta signalling, energy metabolism, etc.
  - Simulation of cardiac tissue & heart
    - Excitation propagation, mechanics, circulation dynamics, etc.

Software Packages

- **simBio** by Dr. Sarai
  - Cell model simulator in use
- **DynaBioS** by Dr. Hori, Dr. Lu
  - Platform for biosimulator in use
- **Cell modelling environment**
  - Editor and simulator under development, to be the next-generation system

**simBio**
www.sim-bio.org

- Java package for biological simulation
  - Solver of ordinary differential equations
- Object-oriented model composition similar to CellML
  - Each model component is coded as a class Reactor (component in CellML)
- COR can convert CellML files into simBio codes

**DynaBioS**
www.dynabios.org

- Component-based architecture
- Event-driven architecture
- User-described system behaviour
- FEM solver
- Cell Simulator
- 3D Viewer

- LV motion simulator
Cell Modelling Environment

Concept

- **Purpose**
  - Efficient development and utilization of cell physiology models
- **Flexibility**
  - Functionally separated tools & formats
- **Usability**
  - Abstract & semantic representation
  - Intelligent assistance of user operation
- **Compatibility**
  - Convertible formats from/to CellML files
  - Use of CellML repository as a model library

Model Representation

- Three functionally separated formats
  - Component file
    - Mathematical declaration of a model component
  - Structure file
    - Anatomical hierarchy & composition of a model
  - Values file
    - Values of model variables
- Conversion between a set of three files and a CellML file possible

Developing Methods

- **Cell Model Ontology:**
  - ontology on physiology models
  - For integrated processing of models
- **PEPML:**
  - Physiology Experimental Protocol ML
  - Generic representation with ontology
- **Simulation method of model equations**
  - Analysis and optimization of calculation procedure with graph theory

Cell Model Ontology
Ontology for Physiology Models

- Existing ontologies: GO, BioPAX, etc.
  - Knowledge about substances
    - Anatomical classification
    - Genome information
    - Proteome information
  - Cell Model Ontology (CMO)
    - Knowledge about cellular functions
    - Functional dependence
    - Relationships between substances and functions

Why is CMO needed?

- Cell physiology models refer to the same cellular component or function with different names;
  - (Physiological) function name
    - (Biochemical) substance name
  - Historical aliases & abbreviations
- Model components and variables have general functional relationships.
  - For integrated and semantic processing of physiology models, an ontology is needed.

Ontology

- Function: rapid component of delayed rectifier potassium current
  - Generator substance: hERG channel
    - hERG → Abbr. human ether-a-go-go related gene
  - Transports: potassium
  - Symbol: $I_{K}$
- Function: sarcolemmal calcium pump current
  - Generator substance: plasma membrane Ca-ATPase
    - Abbr. → PMCA
  - Depends on: internal calcium concentration
  - ...

Utilities using CMO

- Identification of CellML with the ontology
  - Assign an ID of CMO to each component and variable in CellML files.
- Cell structure editor
  - Edit the composition of a model with intelligent assistance

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Identification of CellML

- Append a cmo:id attribute to a CellML element
  `<component name="fast_sodium_current" cmo:id="520">
  `<variable name="Nai" cmo:id="211" .../>
- Estimation method
  - Lexical keyword matching of the name
  - Analysis of inclusion relationships
- Results
  - Achieves about 80% correct estimations
- Future work
  - Analysis of anatomical locations & mathematical equations

Cell Structure Editor

- Graphical editor of a model structure with importing components from existing CellML files
- Intelligent assist using CMO
  - restricted allocation to the anatomical hierarchy
  - intelligent addition of required variables
  - automatic connection of components and variables
  - extraction of focused components
Current Status of CMO

- Specification:
  - not fixed yet
- Data:
  - Only several entities and limited attributes
- Users and Applications:
  - Finding
- Collaborators WANTED!

Experimental Protocol

- All physiology experiments are performed according to experimental protocols
- Application of protocol

PEPML

- Physiology Experimental Protocol Markup Language
- A generic representation format of experimental protocols
  - Separate from models
  - Multiple protocols – single model
  - Independent of models by using CMO
    - Single protocol – multiple models
  - Procedural ↔ Declarative, CellML

Structure of PEPML

```xml
<protocol>
  <event id="event1">
    <condition>
      <and>
        <ge>
          <time />
          <literal value="10.0" units="ms" />
        </ge>
        <eq>
          <variable ref="cmo:x" />
          <variable ref="cmo:m" />
        </eq>
      </and>
    </condition>
    <action>
      <set_value>
        <variable ref="cmo:y" />
        <add>
          <literal value="1.0" />
          <sin><time /></sin>
        </add>
      </set_value>
      <add_value>
        <variable ref="cmo:z" />
        <literal value="4.0" />
      </add_value>
    </action>
  </event>
</protocol>
```

Simulation Method

\[ y = 1.0 + \sin(t) \]
\[ z = 4.0 \]
Model Equations

- Formulation of physiology models
  - Differential Algebraic Equations
    - Differential equation: \( \frac{dy}{dt} = f(x) \)
    - Algebraic equation: \( x = g(p) \)
  - Include simultaneous algebraic equations:
    - Chemical & dynamical equilibrium
    - Conservation
- Generic simulation of model equations
  → analysis of calculation procedure

Analysis of Calculation Procedure

- Purpose:
  - Extraction of simultaneous equations
  - Determination of calculation sequence
- Method:
  - Structure analysis of equations with graph theory
    - [Murota 1980]
    - Vertex: variable, Directed-edge: dependence
  - Adapting for physiology models

Optimization of Equations

- General equation forms of models can be optimized

<table>
<thead>
<tr>
<th>Original</th>
<th>Optimized</th>
</tr>
</thead>
<tbody>
<tr>
<td>([Ca][CaX][-][Ca])</td>
<td>([Ca][-][CaX])</td>
</tr>
<tr>
<td>([X][X][-][CaX])</td>
<td>([X][-][CaX])</td>
</tr>
<tr>
<td>([Ca][X][K][CaX])</td>
<td>([Ca][X][-][K][CaX])</td>
</tr>
</tbody>
</table>

- Develop a method to search equation transformations on the graph of model equations

Requests for CellML

- Keep CellML software independent
  - Functions for particular software to be optional, supplemental and separable
  - Not interleave software dependents into CellML
  - But import CellML into software specific formats
- Because
  - CellML repository can be a model library for general use (including other utilities than simulator)

Declaration of Published Model

- Describe models as-is in public CellML files
  - Model description to be declarative (not procedural)
  - Without any transformations of equation for numerical calculation

E.G. Original
\( [B][X][K][BX]\)
\( [B][BX][B][X][BX][X] \)

Transformed
\( [BX][-][b+\sqrt{b^2-4ac}]^2 \)

- Because
  - Transformations cause semantic information lost
  - Transformed equation: no more than quadratic formula
  - Extensions / Imports get impossible
Summary

- simBio
- DynaBioS
- Cell Modelling Environment
  - Model Representation Formats
  - Cell Model Ontology
  - PEPML
  - Method to analyze calculation procedure

Thank you!