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*
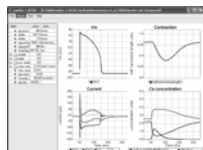 - Editor and simulator under development, to be the next-generation system

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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)
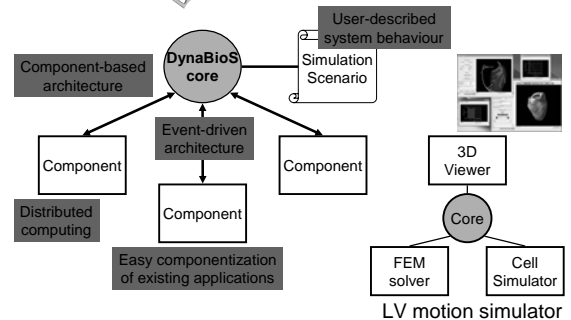- COR can convert CellML files into simBio codes

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DynaBioS   www.dynabios.org

LV motion simulator

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Cell Modelling Environment

System Schema
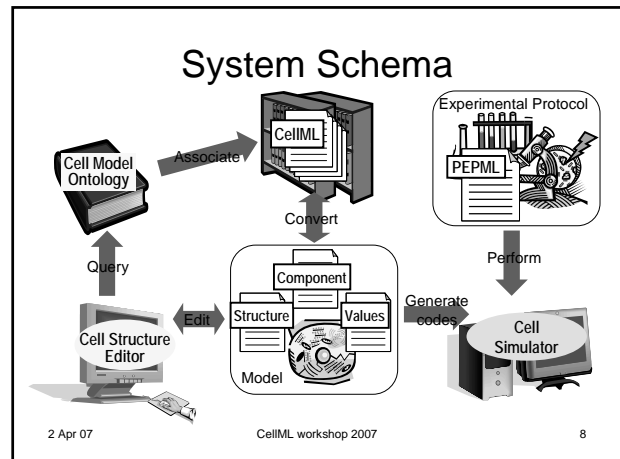

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Concept

- 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

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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

  CellML
  component
  variable
  initial_value
  group
  encapsulation
  containment
  connections

- Conversion between a set of three files and a CellML file possible

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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

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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
    vs. (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_{Kr}
- 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

  DOI: 10.2997/ipsjdc.2.726

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
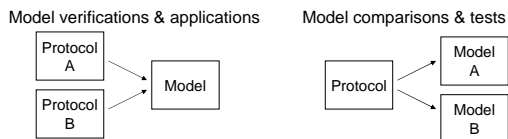- Users and Applications:
  - Finding

- Collaborators WANTED!

PEPML
Physiology Experimental Protocol Markup Language

Experimental Protocol

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

Model verifications & applications

```
Protocol
A          →
              Model
Protocol
B
```

Model comparisons & tests

```
                Model
                A
Protocol   →
                Model
                B
```

PEPML

- 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

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

  (t < 10.0) && (x == m)        y = 1.0 + sin(t)
                                z += 4.0
```

Simulation Method

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Model Equations

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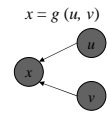 $\rightarrow$ analysis of calculation procedure

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

$x = g(u, v)$

Optimization of Equations

- General equation forms of models can be optimized

Original		Optimized
$[Ca]+[CaX]=[Ca]_t$		$[Ca]=[Ca]_t-[CaX]$
$[X]+[CaX]=[X]_t$	$\Leftrightarrow$	$[X]=[X]_t-[CaX]$
$[Ca]\cdot[X]=K_m[CaX]$		$0=[Ca]\cdot[X]-K_m[CaX]$
Three dimensions		*One dimensions*

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

Requests for CellML

Software Independency

- 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	Transformed
$[B]\cdot[X]=K_m[BX]$	$[BX]=\left(-b+\sqrt{b^2-4c}\right)/2$
$[B]+[BX]=[B]_t, \quad [X]+[BX]=[X]_t$	

- 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!