

# Large-scale Models and Mixed-Mode Simulation for SBML

Kouichi Takahashi  
Takeshi Sakurada

Institute for Advanced Biosciences,  
Keio Univ.

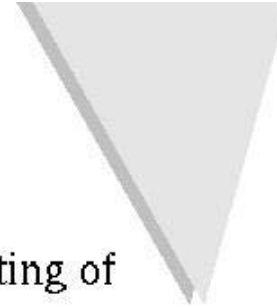


## Purpose

- Add Support for Large-scale Modeling (LM)
  - **Improve Scalability**
- Based on the LM support, support Mixed-Mode models (MM)
  - **Improve flexibility**

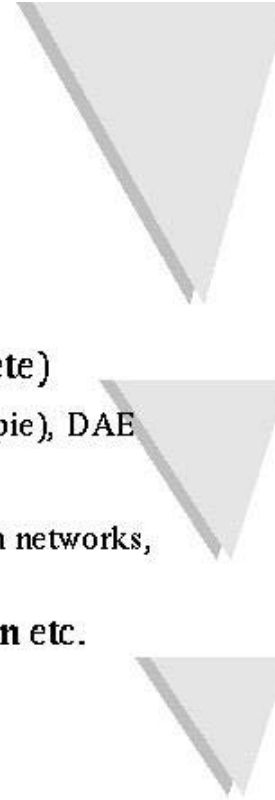
## Why LM?

- Cells are complicated entities consisting of numerous components
- many subsystems / subcompartments:
  - **mitochondria, chlooplasts, lysosomes, ERs, vesicles...**
  - **approx.  $10^{1-2}$  (prokaryotes) –  $10^{2-4}$  (eukaryotes) subcompartments.**
  - More subsystems if mixed-mode.



## Why MM?

- There is no universal algorithm
  - **metabolism (typically continuous)**
    - -> DAE, diffusion-reaction, S-System
  - **signal transduction (continuous / discrete)**
    - -> stochastic algorithms (StochSim, Gillespie), DAE
  - **Gene expression (typically discrete)**
    - -> SRM Object-model(E-CELL), Boolean networks, S-System
  - **Others: DNA Replication, Cell division etc.**
    - -> Discrete event driven etc..
- Different time-scales

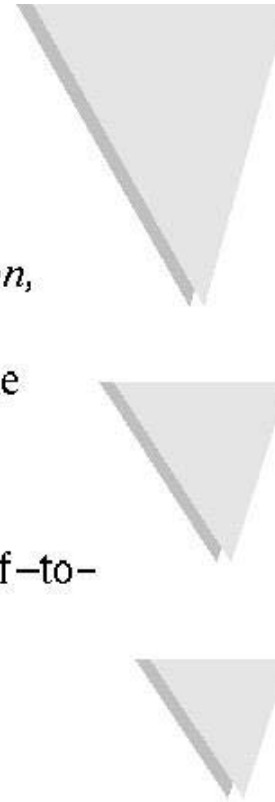


## **What's required for LM?**

- **Prevent lengths of lists from being directly proportional to the size of the model**
- **Define systematic component identifier for structured models**
- **Make it easier to walk-around in large models**
- **Make it modular and structured:**
  - localize data, cut-and-paste submodels

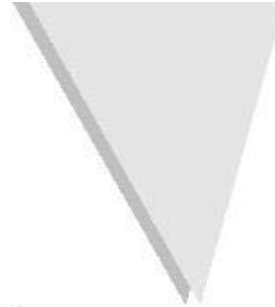
## Problems in level 1

- Sizes of lists (lists of *Specie*, *Reaction*, *Compartment*, *Parameter*, *Rule*) in *Model* are directly proportional to the size of the cell model
  - **not scalable**
- Direction of model description is leaf-to-root mode, not root-to-leaves
  - *Compartment::outside*
  - **not good for model exploration and description of very large models**



## LM Support Proposal

- Move lists (specie, parameter, rule, reaction) from *Model* to *Compartment*
- *Model* have a rootCompartment
- Add sub-compartment list to *Compartment*
- (remove Compartment::outside ?)
- Should break compatibility with level 1: Regular-mode / LM mode ?



# LM support Class Diagram

## Model

name: SName {use="optional"}  
UnitDefinition: UnitDefinition[0..\*]  
rootCompartment: Compartment[1]

## Compartment

name: SName  
volume: double{use="default" value="1"}  
units: SName {use="optional"}  
specie: Specie[0..\*]  
reaction: Reaction[0..\*]  
parameter: Parameter[0..\*]  
compartment: compartment[0..\*]  
rule: Rule[0..\*]



# Component identifiers

## Compartment specifier:

/ -> rootCompartment  
/CELL0/CYTOPLASM -> Cytoplasm in the first  
cell in the model  
../ -> relative outside

## Component specifier:

Species:/CYTOPLASM/MT0:ATP -> ATP in the first mitochondria  
Reaction:/MEMBRANE:SodiumPump -> Na pump on the membrane

## Property specifier:

Species:/CYTOPLASM:ATP::concentration  
Reaction:/MEMBRANE:SodiumPump::reactant[0]

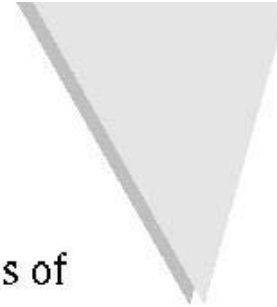


# What's needed for MM?

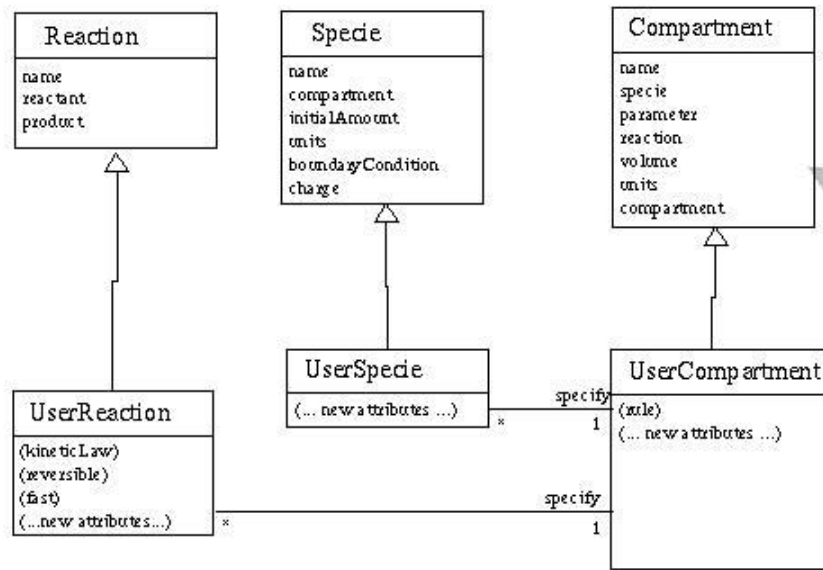
- **Algorithm modularity**
- **Interface / implementation isolation**
  - algorithm-independent interface base classes
  - user-definable subclasses

## MM Support Proposal

- Allow users to define their subclasses of *Compartment*, *Specie* and *Reaction*
- A subclass of *Compartment* represent an algorithm, specifying what classes of *Specie* and *Reaction* should be used
- Minimize signatures of the three base classes



# MM support Class Diagram



## **Suggested schedule**

- **MM depends on LM**
- **SBML level-2: add LM support**
- **SBML level-3 or later: MM support**