Lessons Learned at the Whole Cell Summer School

Chris J. Myers

Whole Cell Model

Theory

Cell

A Whole-Cell Computational Model Predicts Phenotype from Genotype

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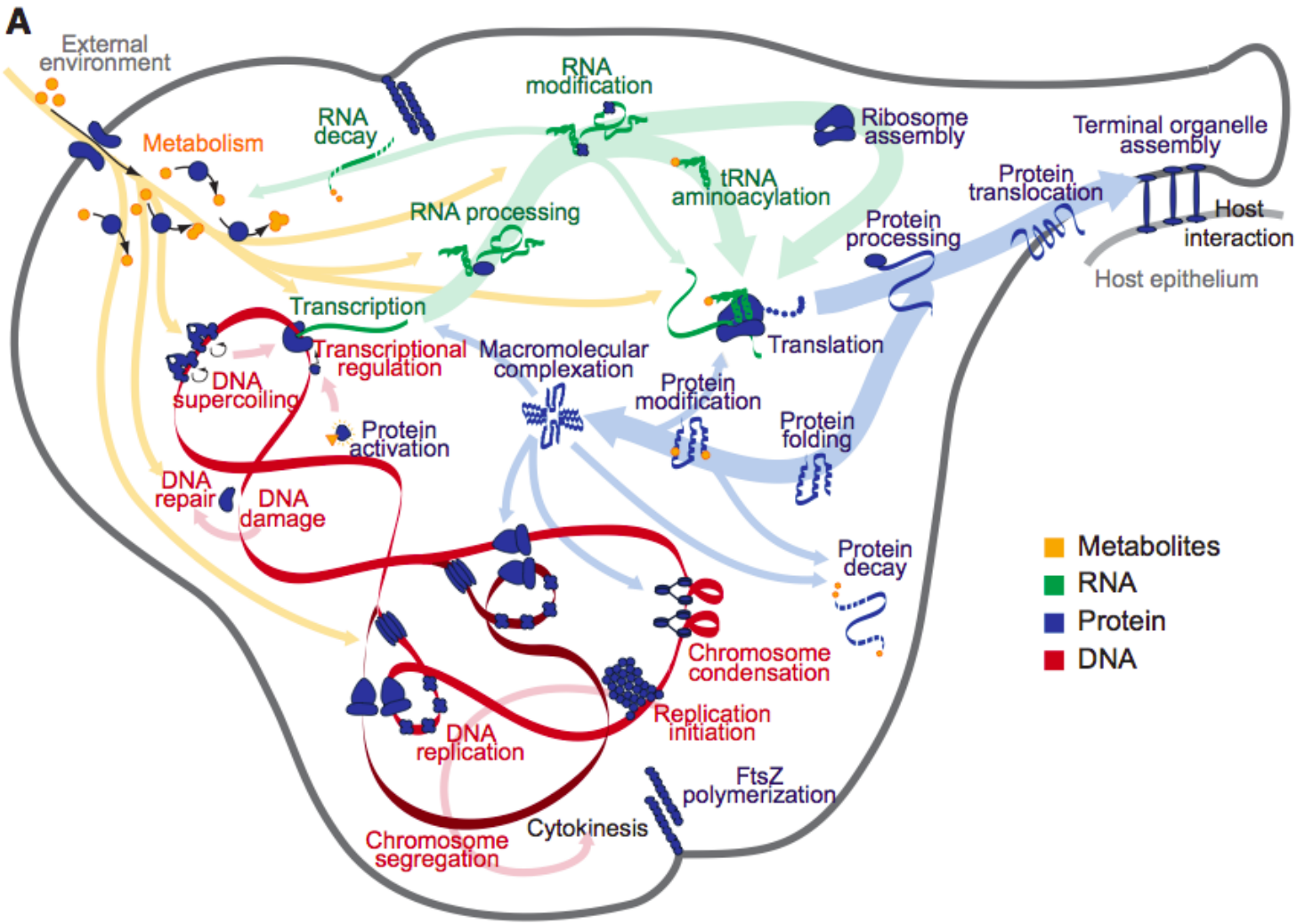
SUMMARY

Understanding how complex phenotypes arise from individual molecules and their interactions is a primary challenge in biology that computational approaches are poised to tackle. We report a whole-cell computational model of the life cycle of the human pathogen *Mycoplasma genitalium* that

First, until recently, not enough has been known about the individual molecules and their interactions to completely model any one organism. The advent of genomics and other high-throughput measurement techniques has accelerated the characterization of some organisms to the extent that comprehensive modeling is now possible. For example, the mycoplasmas, a genus of bacteria with relatively small genomes that includes several pathogens, have recently been the subject of an exhaustive experimental effort by a European consortium to determine

Cell (2012)

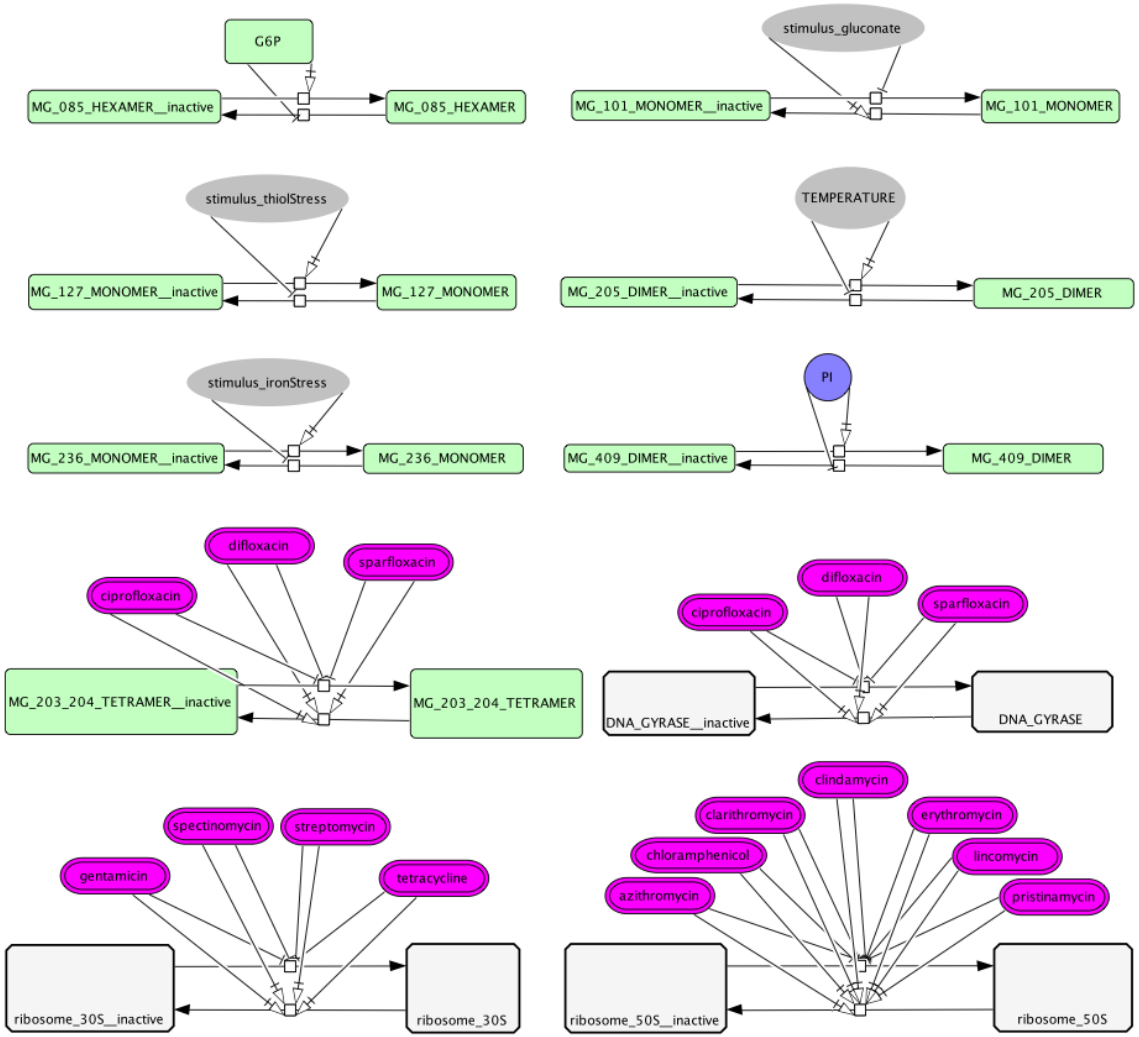
Whole Cell Model Processes



Goals of the Project

- Create an SBGN diagram for each process.
- Produce SBML for each process.
- Write SED-ML to test each process.
- Integrate and test the complete model.

SBGN for Protein Activation



Challenges Converting Matlab to SBML

- Matlab is inherently sequential while SBML is inherently parallel.
- Assignments, conditional behavior, and loops can be done with SBML events, but it can be a bit tricky.
- Random numbers and distributions not yet well supported by SBML (need distributions package).
- Matrices are efficient in Matlab and not well supported by SBML (need arrays package and a way to handle large, sparse matrices).
- Parallel access to mutually exclusive shared variables is difficult (chromosome).

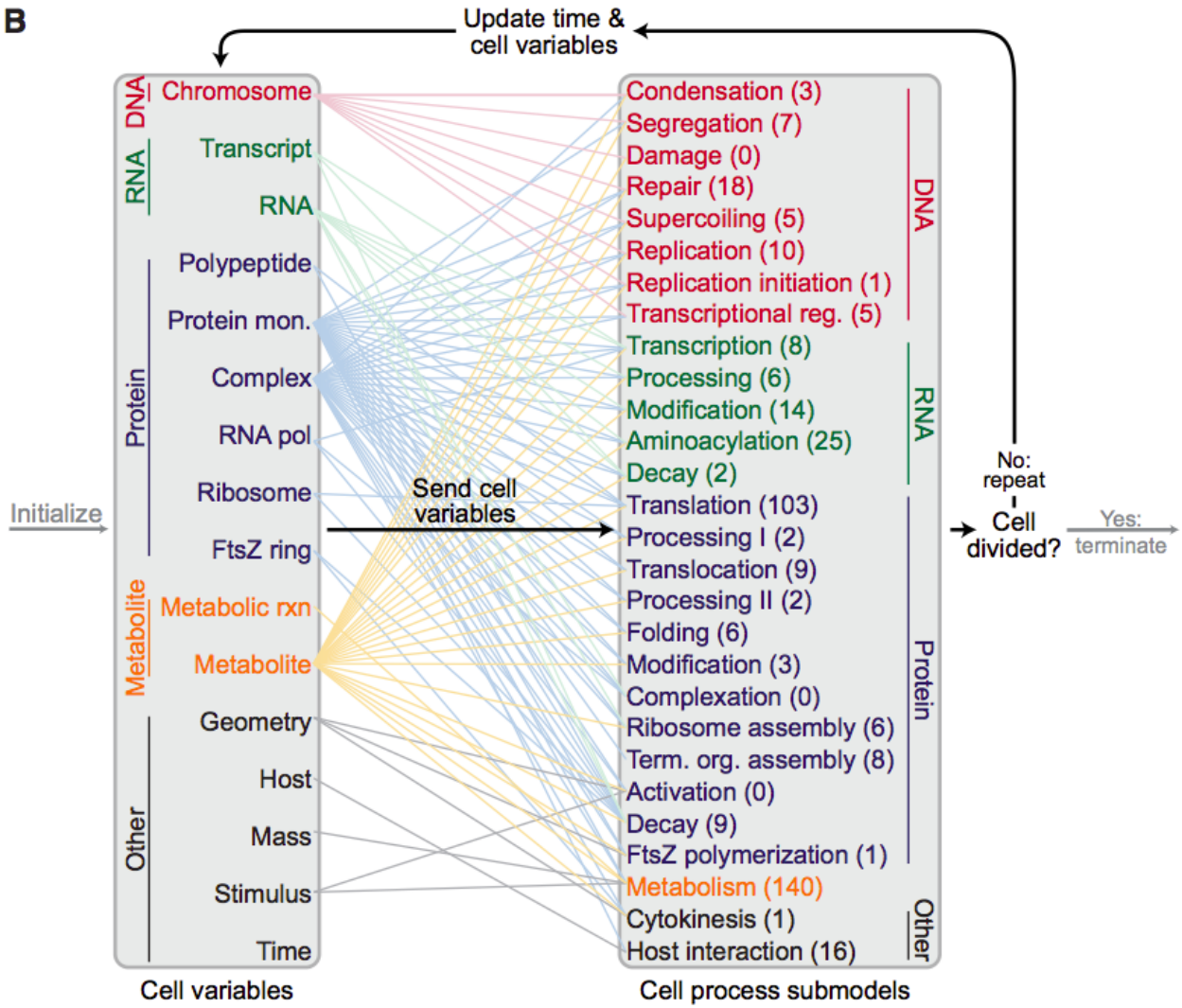
Key Challenge for Each Group

- Replication initiation - need to access shared variable, chromosome.
- Replication - must represent state of 500kb chromosome.
- Transcription - need to track positions of transcription factors and move RNAP along the chromosome, large number of variables.
- Translation - need to track positions of ribosomes on many types of mRNAs, again large number of variables.
- Protein - many small processes, requires random distributions.
- Metabolism - updating bounds between simulation steps.
- DNA damage/repair - accessing shared chromosome state and dealing with randomness.
- Cytokinesis - dealing with randomness.
- Integration - variable sharing.

Integration Team Goals

- Coordinate the development of the interfaces for each process.
- Determine how SED-ML can be used to express the simulation of each process, as well as, the complete model.
- Determine a scheme for variable sharing between the processes.

Whole Cell Model Simulation



Simulation Algorithm

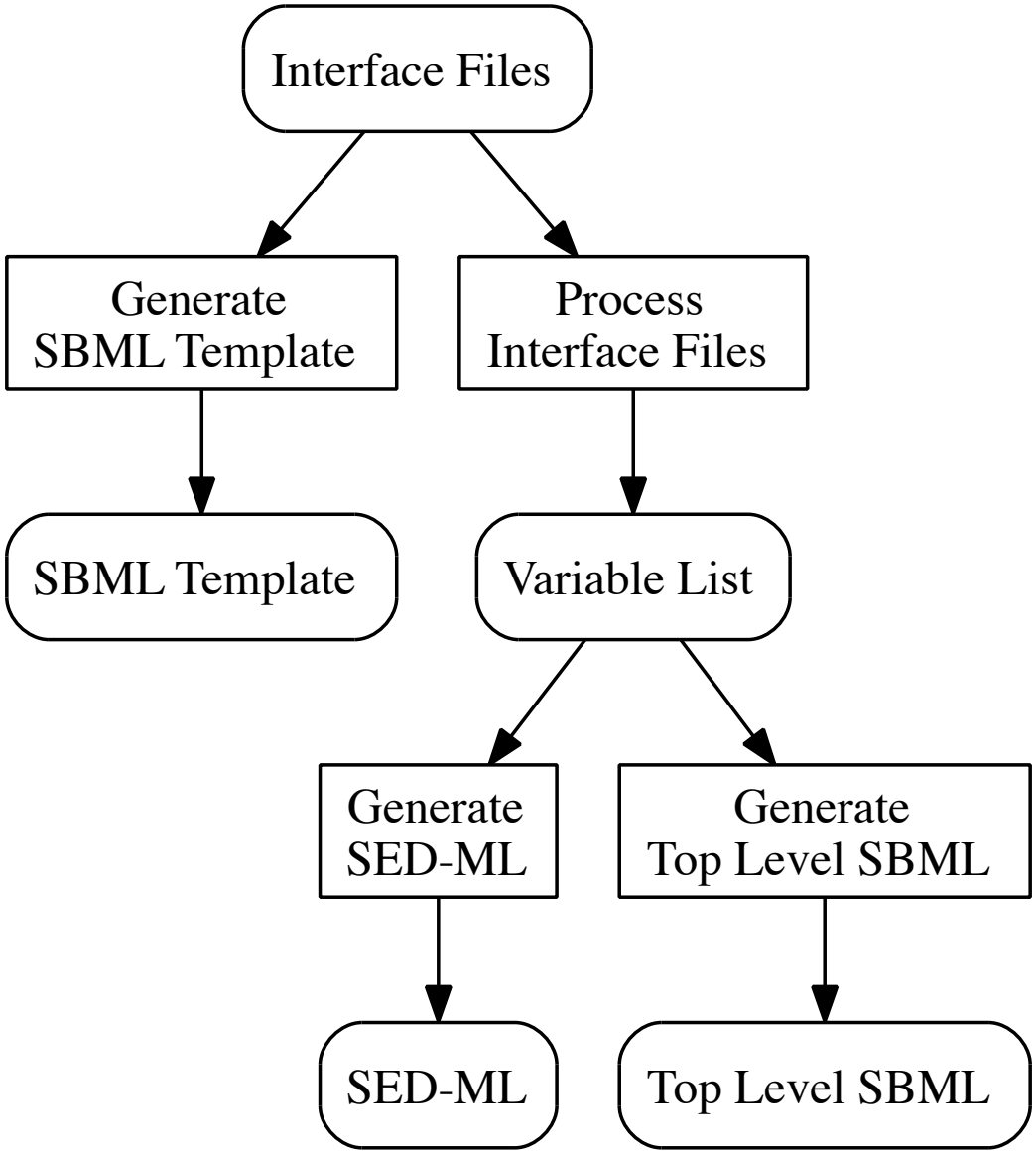
function `RunSimulation(`$S[0]$`)`
  for $t \leftarrow$ `1..tMAX` **do**
    $S[t] \leftarrow S[t-1]$
    for $P_k \leftarrow P_1$ **to** P_p **do**
      $S_k[t] \leftarrow P_k$`.copyFromState(`$S[t]$`)`
      $Req_k \leftarrow P_k$`.require(`$S_k[t]$`)`
    end for
    for $P_k \leftarrow P_1$ **to** P_p **do**
      $R_k \leftarrow Split(R[t], Req_k, Req_1, Req_2, ..., Req_p)$
    end for
    for $P_k \leftarrow Permute(P)$ **do**
      $S_k[t] \leftarrow P_k$`.copyFromState(`$S[t]$`)`
      $(V_k[t]||R_k) \leftarrow P_k$`.evolve((`$V_k[t]||R_k$`))`
      $V[t] \leftarrow P_k$`.copyToState(`$V_k[t]$`)`
    end for
    $S[t] \leftarrow (V[t]||Merge(R_1, R_2, ...R_p))$
  end for
  return S
end function

Shared Variables

Three types of shared variables:

- Metabolites - distributed based upon process requirements.
- Proteins/variables - updated by a few processes.
- Chromosome - requires mutually exclusive access.

Integration Workflow



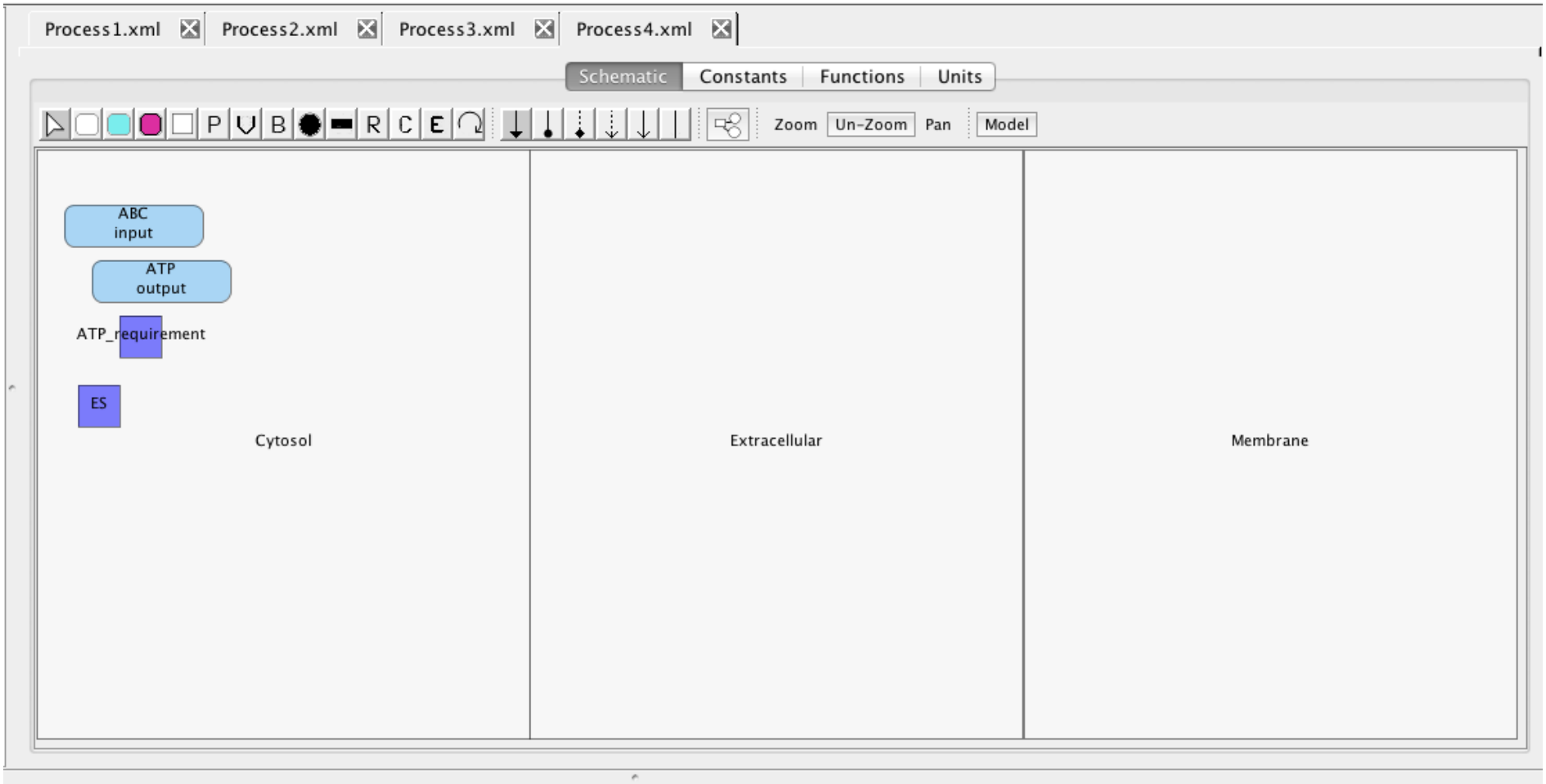
Interface Files

- For each species, must indicate type of access needed:
  - Read-only
  - Read/write
  - Requirement
  - Read-only and requirement
- For each parameter, also must indicate type of access needed:
  - Read-only
  - Read/write
  - Mutually exclusive

Interface Files Example

Process1						
Type	Id	RO	RW	REQ	ROREQ	ME
Metabolite	ATP		X			
Protein	ABC		X			
Parameter	ES		X			
Process2						
Type	Id	RO	RW	REQ	ROREQ	ME
Metabolite	ATP	X				
Protein	ABC		X			
Parameter	ES	X				
Process3						
Type	Id	RO	RW	REQ	ROREQ	ME
Metabolite	ATP			X		
Protein	ABC	X				
Parameter	ES	X				
Process4						
Type	Id	RO	RW	REQ	ROREQ	ME
Metabolite	ATP				X	
Protein	ABC					
Parameter	ES					

SBML Template Example



Variable List Example

species,ATP,Process1(rw),Process2(ro),Process3(req),Process4(roreq)
species,ABC,Process1(rw),Process2(rw),Process3(ro)
param,ES,Process1(rw),Process2(ro),Process3(ro)

SED-ML (no variable sharing)

```
<?xml version="1.0" encoding="UTF-8"?>
<sedML xmlns="http://sed-ml.org/sed-ml/level1/version2" level="1" version="2">
  <listOfSimulations>
    <oneStep id="sim_1" step="1.0">
      <algorithm kisaoID="KISAO:0000035"/>
    </oneStep>
  </listOfSimulations>
  <listOfModels>
    <model id="Process1" language="urn:sedml:language:sbml" source="Process1.xml"/>
    <model id="Process2" language="urn:sedml:language:sbml" source="Process2.xml"/>
    <model id="Process3" language="urn:sedml:language:sbml" source="Process3.xml"/>
    <model id="Process4" language="urn:sedml:language:sbml" source="Process4.xml"/>
  </listOfModels>
  <listOfTasks>
    <task id="tsk_1" modelReference="Process1" simulationReference="sim_1"/>
    <task id="tsk_2" modelReference="Process2" simulationReference="sim_1"/>
    <task id="tsk_3" modelReference="Process3" simulationReference="sim_1"/>
    <task id="tsk_4" modelReference="Process4" simulationReference="sim_1"/>
    <repeatedTask id="main_loop" resetModel="false" range="repeat">
      <listOfRanges>
        <uniformRange id="repeat" start="0" end="1000" numberOfPoints="1000" type="linear" />
      </listOfRanges>
      <listOfSubTasks>
        <subTask order="1" task="tsk_1" />
        <subTask order="2" task="tsk_2" />
        <subTask order="3" task="tsk_3" />
        <subTask order="4" task="tsk_4" />
      </listOfSubTasks>
    </repeatedTask>
  </listOfTasks>
</sedML>
```

SED-ML (variable sharing)

```
<?xml version="1.0" encoding="UTF-8"?>
<sedML xmlns="http://sed-ml.org/sed-ml/level1/version2" level="1" version="2">
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    <oneStep id="sim_1" step="1.0">
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    </oneStep>
  </listOfSimulations>
  <listOfModels>
    <model id="Process1" language="urn:sedml:language:sbml" source="Process1.xml"/>
    <model id="Process2" language="urn:sedml:language:sbml" source="Process2.xml"/>
    <model id="Process3" language="urn:sedml:language:sbml" source="Process3.xml"/>
    <model id="Process3" language="urn:sedml:language:sbml" source="Process4.xml"/>
  </listOfModels>
  <listOfTasks>
    <task id="tsk_1" modelReference="Process1" simulationReference="sim_1"/>
    <task id="tsk_2" modelReference="Process2" simulationReference="sim_1"/>
    <task id="tsk_3" modelReference="Process3" simulationReference="sim_1"/>
    <task id="tsk_4" modelReference="Process4" simulationReference="sim_1"/>
    <repeatedTask id="main_loop" resetModel="false" range="repeat">
      <listOfRanges>
        <uniformRange id="repeat" start="0" end="1000" numberOfPoints="1000" type="linear" />
      </listOfRanges>
```
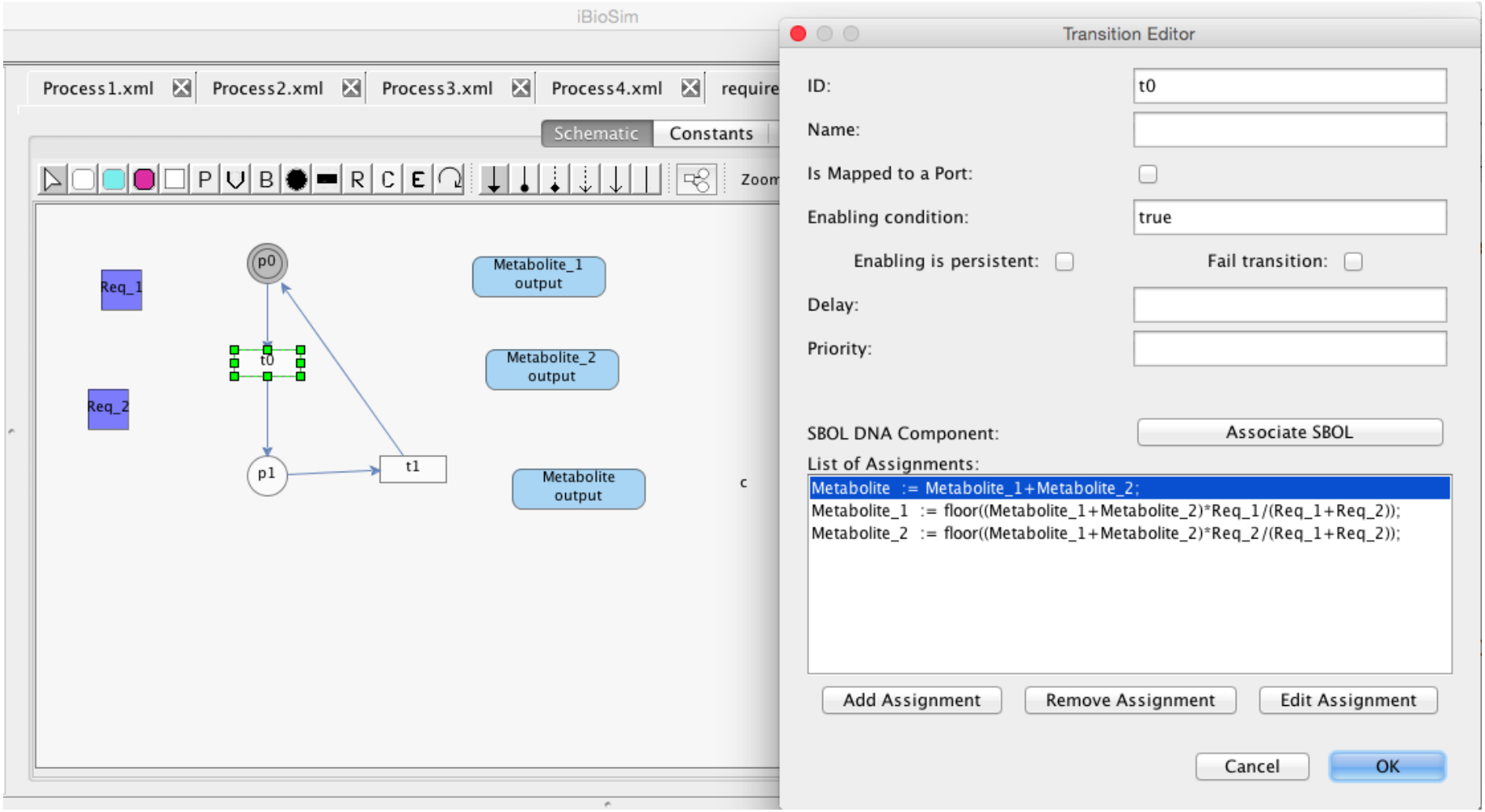
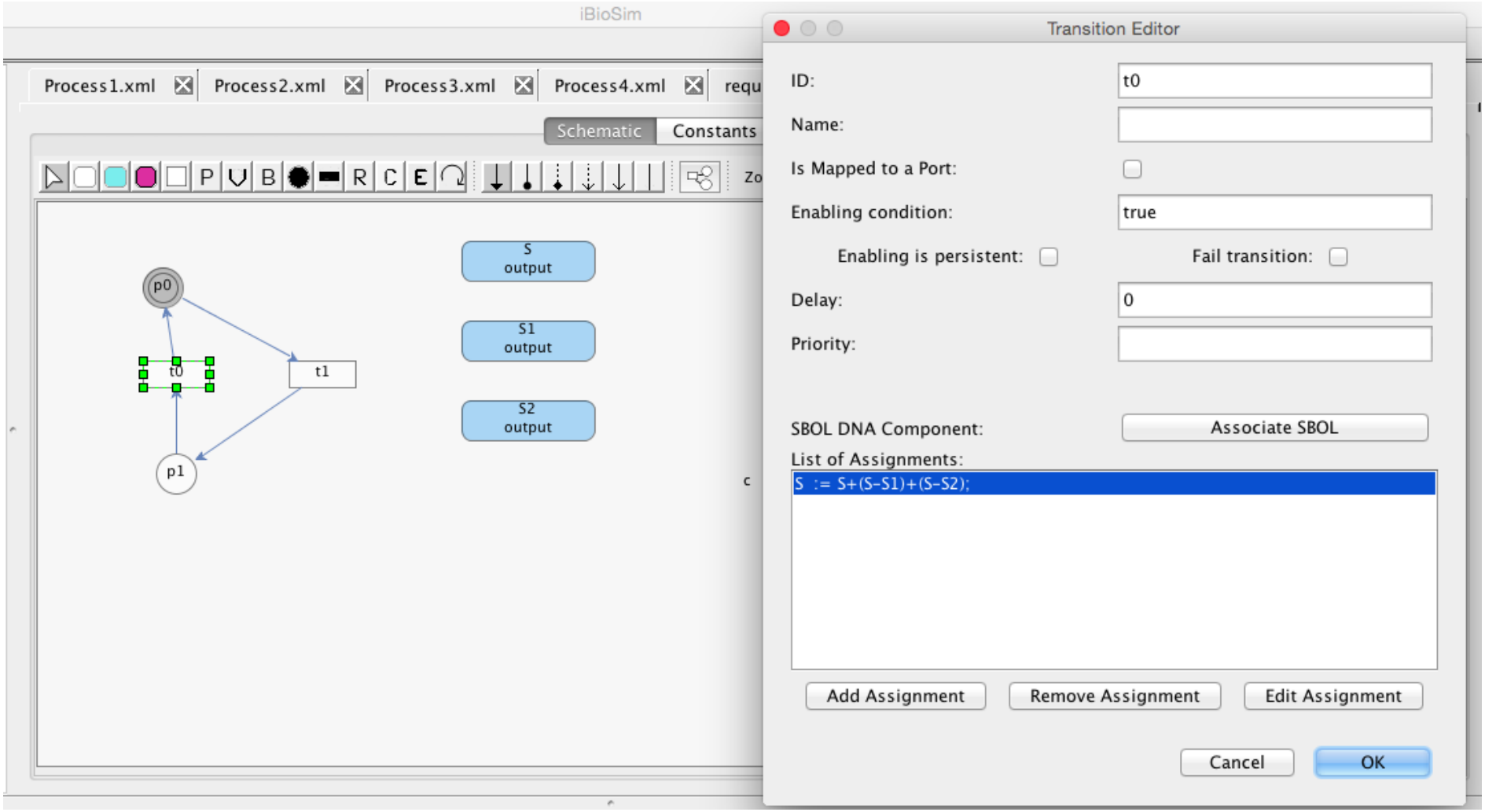

SED-ML (variable sharing)

```
    <listOfChanges>
      <setValue target="/sbml:sbml/sbml:model[@id='Process1']/sbml:listOfSpecies/sbml:species[@id='ATP']"
        modelReference="Process1">
        <math xmlns="http://www.w3.org/1998/Math/MathML">
          <ci> 0 </ci>
        </math>
      </setValue>
      <setValue target="/sbml:sbml/sbml:model[@id='Process2']/sbml:listOfSpecies/sbml:species[@id='ATP']"
        modelReference="Process2">
        <listOfVariables>
          <variable id="sp_1" modelReference="Process1" target="/sbml:sbml/sbml:model[@id='Process1']/
            sbml:listOfSpecies/sbml:species[@id='ATP']"/>
          <variable id="sp_3" modelReference="Process3" target="/sbml:sbml/sbml:model[@id='Process3']/
            sbml:listOfSpecies/sbml:species[@id='ATP']"/>
          <variable id="sp_4" modelReference="Process4" target="/sbml:sbml/sbml:model[@id='Process4']/
            sbml:listOfSpecies/sbml:species[@id='ATP']"/>
        </listOfVariables>
        <math xmlns="http://www.w3.org/1998/Math/MathML">
          <apply><plus/><ci>sp_1</ci><ci>sp_3</ci><ci>sp_4</ci></apply>
        </math>
      </setValue>
      ...
    </listOfChanges>
    <listOfSubTasks>
      <subTask order="1" task="tsk_1" />
      <subTask order="2" task="tsk_2" />
      <subTask order="3" task="tsk_3" />
      <subTask order="4" task="tsk_4" />
    </listOfSubTasks>
  </repeatedTask>
 </listOfTasks>
</sedML>
```

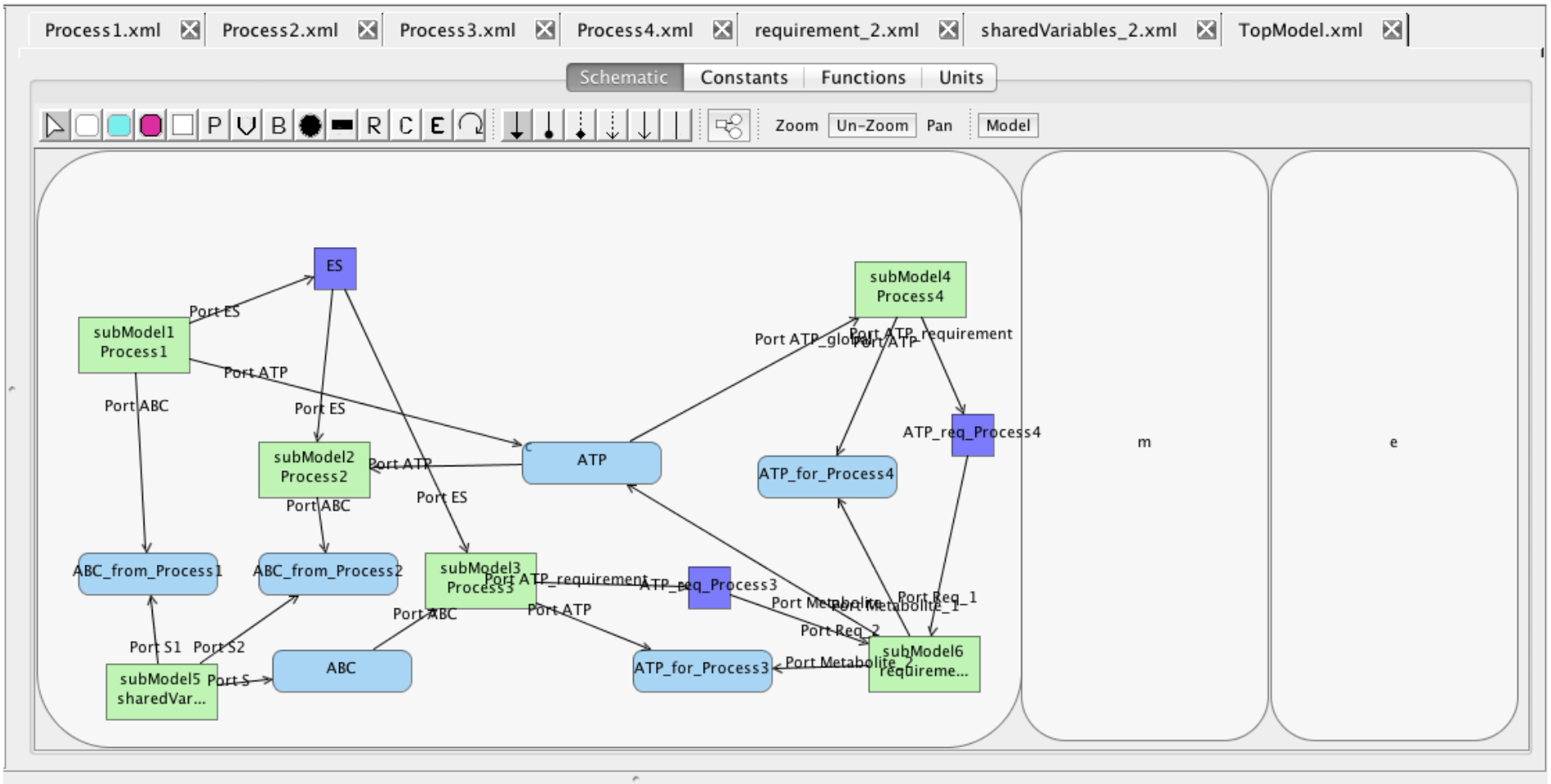
Metabolite Sharing



Species/Parameter Sharing



Top Level SBML



Remaining Integration Tasks

- Develop SBML for mutually exclusive accessed shared variables.
- Finish debugging the scripts.
- Obtain missing interface files.
- Share SBML templates with the other teams.
- Generate top-level SED-ML.
- Generate top-level SBML.
- Test with models provided from other teams.

Lessons Learned by Jonathan Karr

- Lot of work to do to make models more transparent.
- SBML can be more easily human readable.
- SBML more clearly expresses biochemistry, but not if rules are expanded out.
- Stochastic modeling (Gillespie) very similar to many sub-models except far more computationally expensive.
- New thoughts on how to generalize state allocation to chromosome.

SBML Challenges Observed by Jonathan Karr

- Unable to efficiently represent large state spaces.
- Unable to compactly represent template reaction rules.
- Semi-standard because not all packages implemented by all tools.
- SBML files must be paired with specific programs.
- SBML could improve with:
  - Expansion of language to include 1D spatial representation, new construct for chromosome, and other higher-level constructs.
  - New rule-based GUI to enable higher-level description.
  - New simulator to handle large scale models efficiently.

SED-ML/SBGN Observations by Jonathan Karr

- SED-ML useful, but care should be taken in avoiding encoding the model in SED-ML.
- SBGN useful for documentation, but it does not typically produce biologically intutitive diagrams for publication.