

# Modeling and Simulating Hybrid SBML Models

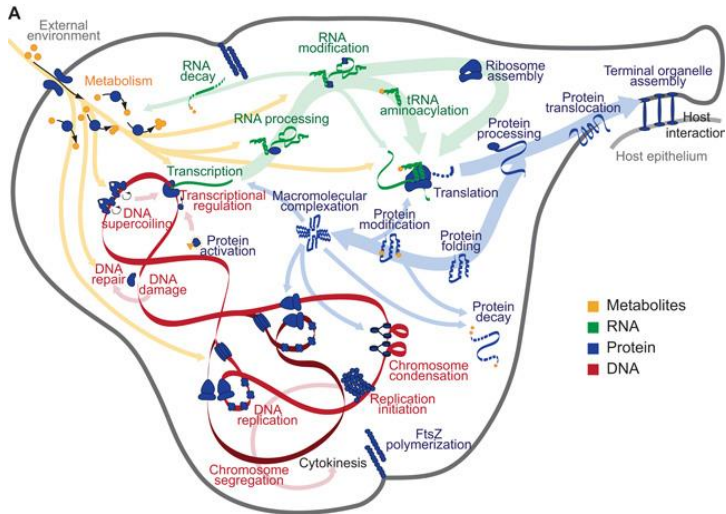
Leandro H. Watanabe and Chris J. Myers

University of Utah

COMBINE 2016

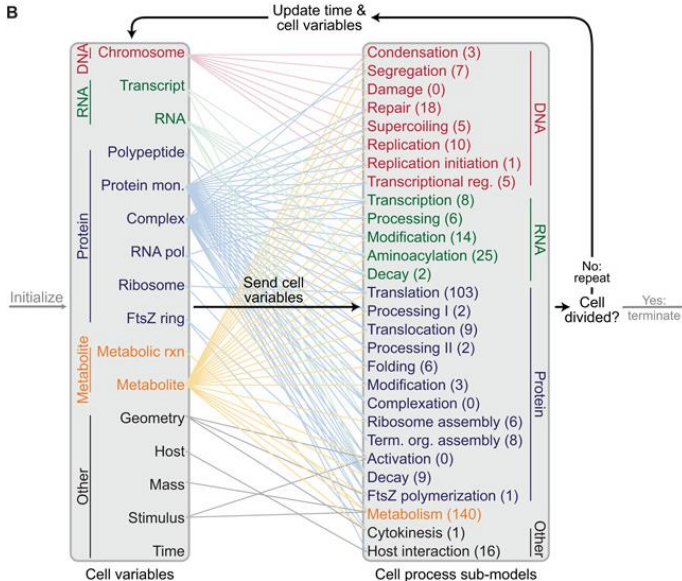
September 22, 2016

# Whole-Cell Model



Courtesy of  
Karr et al.,  
*Cell*, 2012

# Whole-Cell Analysis Method



Courtesy of  
Karr et al.,  
*Cell*, 2012

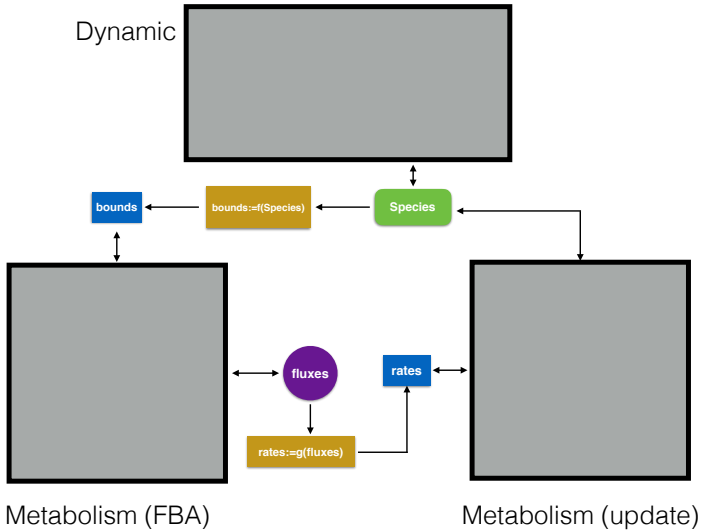
# Whole-Cell Workshops

- Location
  - Rostock, Germany (March, 2015).
  - Salt Lake City, USA (October, 2015).
- Goal: recode MATLAB code to systems biology standards, such as:
  - Systems Biology Markup Language (SBML).
  - Simulation Experiment Description Markup Language (SED-ML).
  - Systems Biology Graphical Notation (SBGN).
- One challenge faced was to encode hybrid models using these standards.

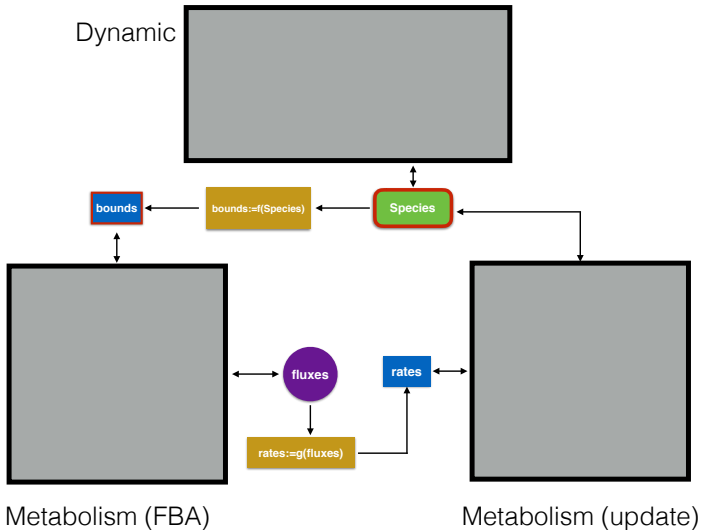
# Approaches To Encode Hybrid Models

- Approach one: use SBML to encode each process individually and use SED-ML to pass data around.
- Approach two: use SBML and its hierarchical composition package to encode the entire hybrid model in SBML.

# Proposed Hybrid Model

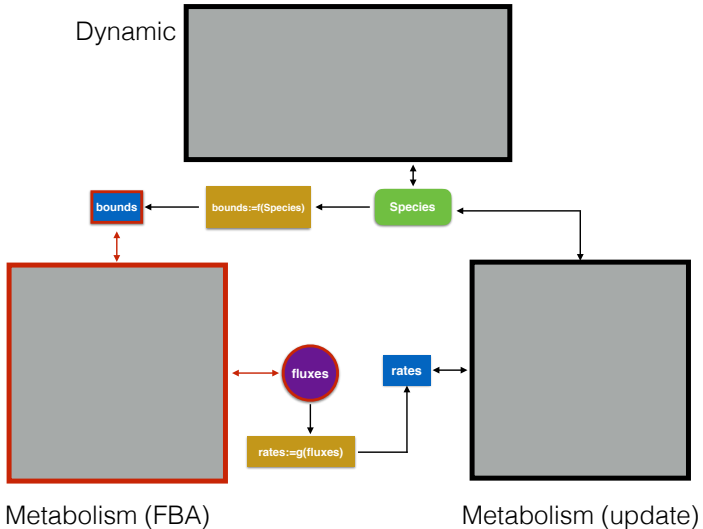


# Proposed Hybrid Model



Initialize variables.

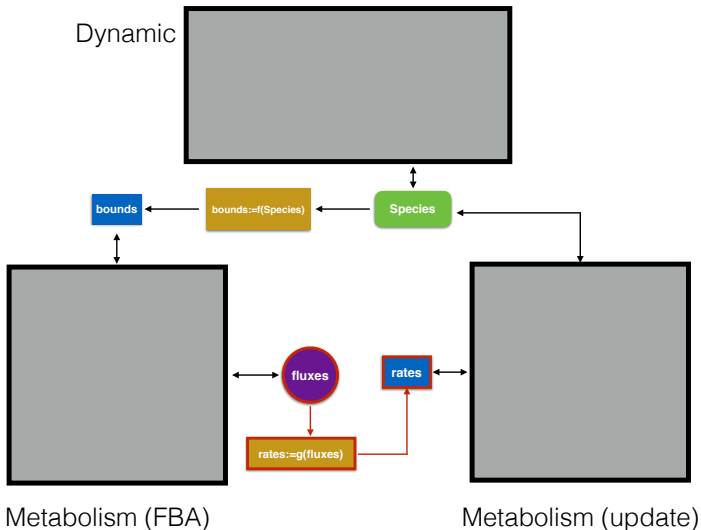
# Proposed Hybrid Model



Perform FBA in the corresponding submodel.

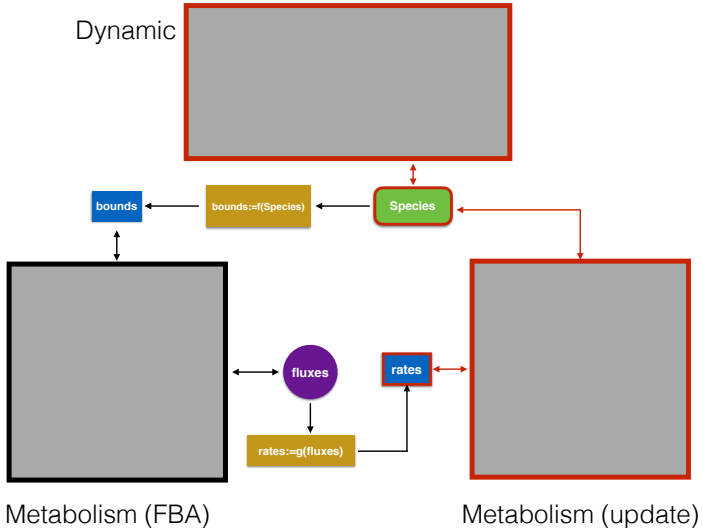


# Proposed Hybrid Model



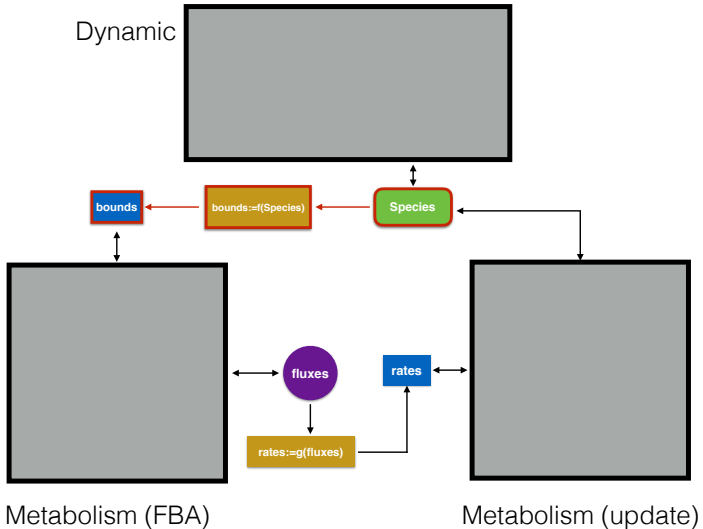
Update the fluxes and assign them to parameters.

# Proposed Hybrid Model



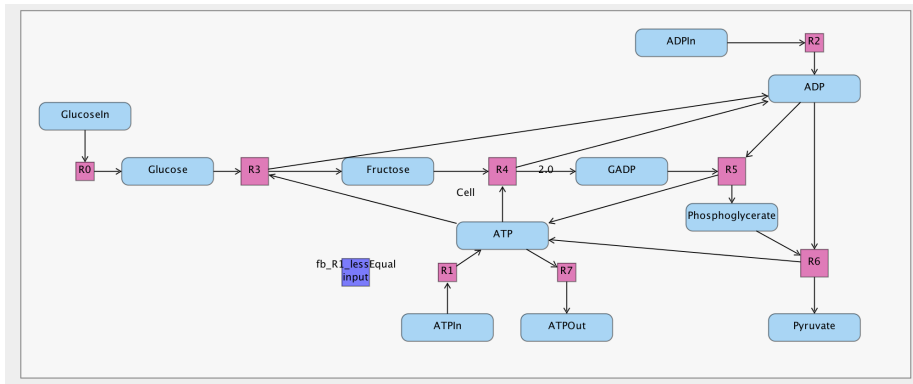
Perform dynamic update in all submodels other than FBA.

# Proposed Hybrid Model

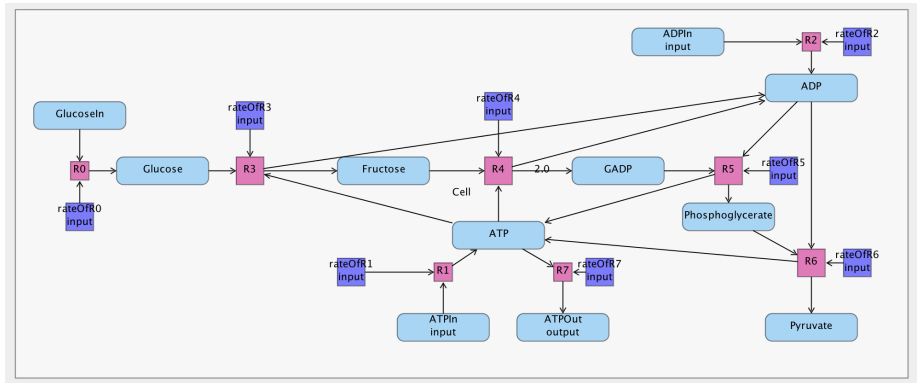


Compute the updated flux bounds for the FBA submodel.

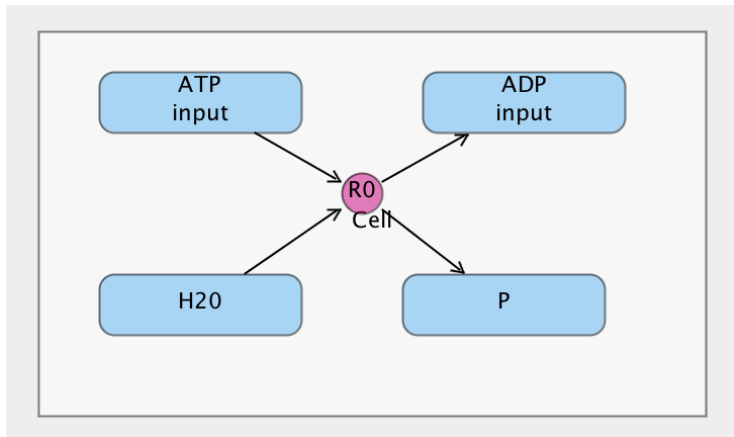
# Simple Example: Glycolysis FBA



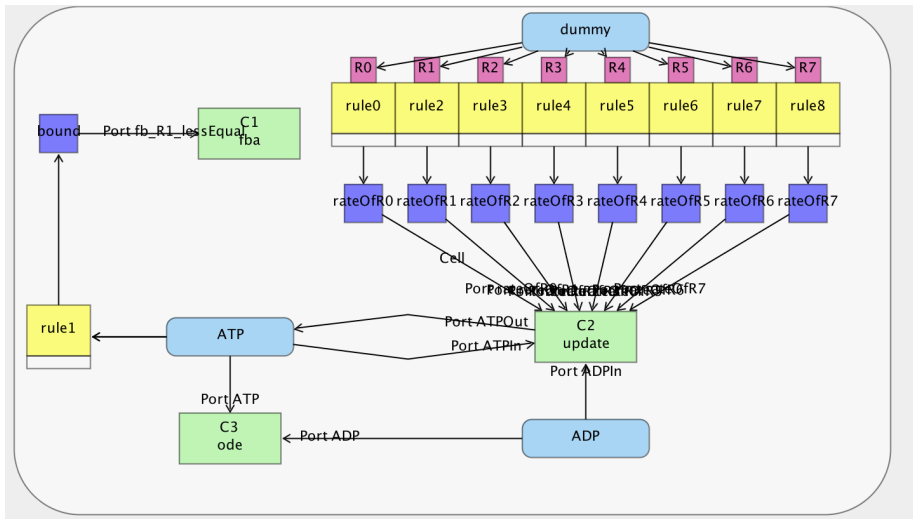
# Simple Example: Glycolysis Update



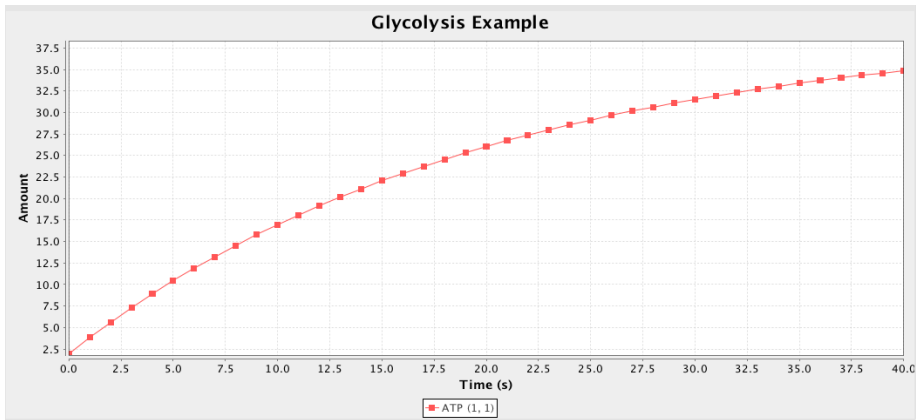
# Simple Example: Metabolite Consumed



# Simple Example: Putting It All Together

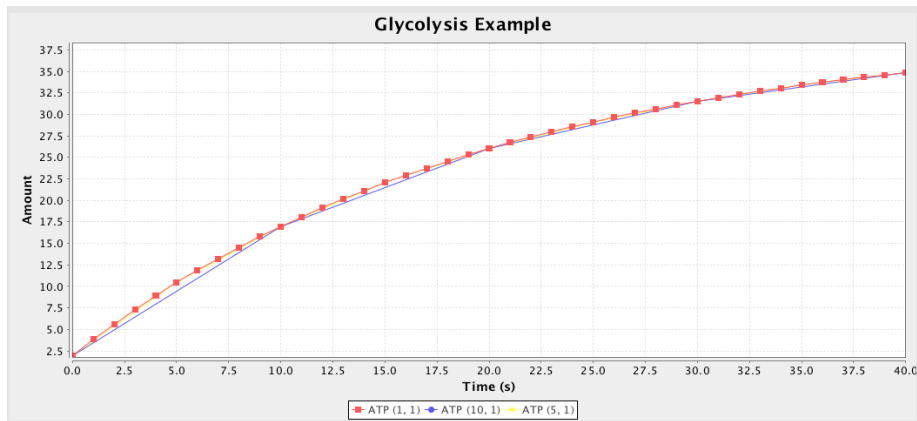


# Simple Example: Results

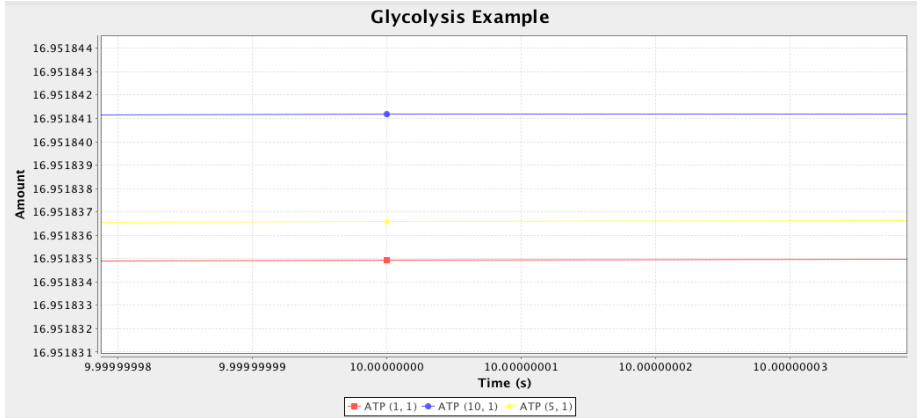




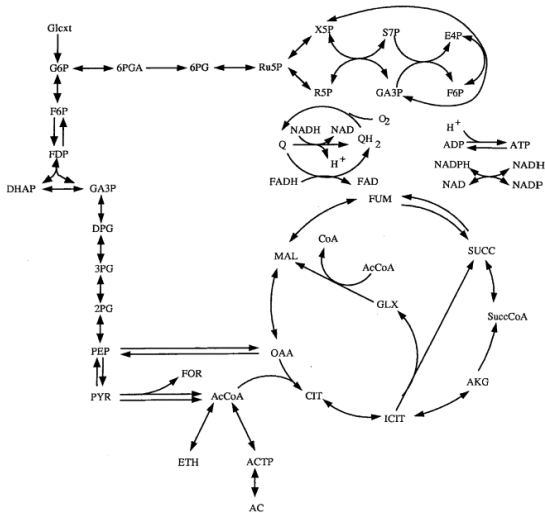
# Simple Example: Different Update Times



# Simple Example: Error

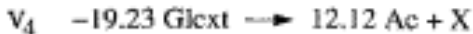
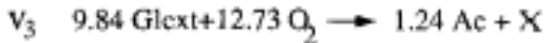
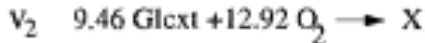
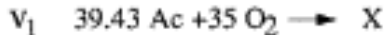
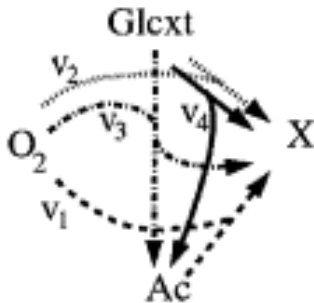


## DFBA Example: Diauxic Growth in E. Coli



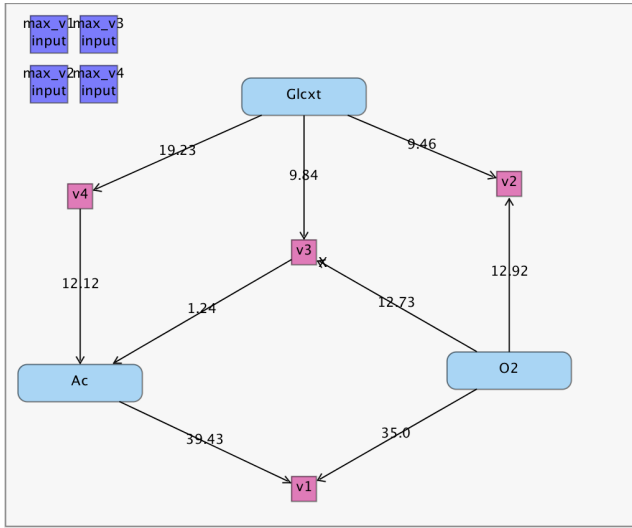
Courtesy of Mahadevan et al., *Biophys*, 2002

# DFBA Example: Simplified Pathway

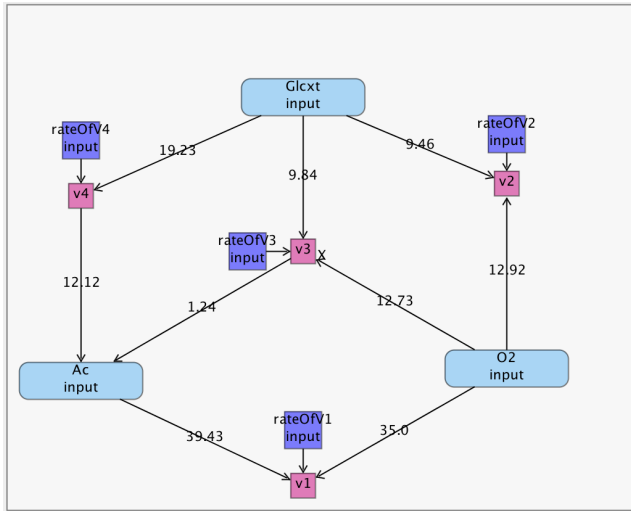


Courtesy of Mahadevan et al., *Biophys*, 2002

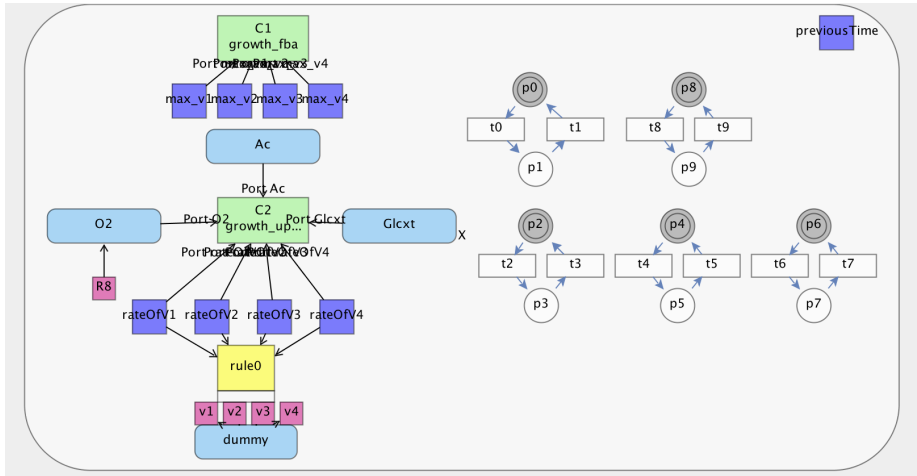
# DFBA Example: Metabolism



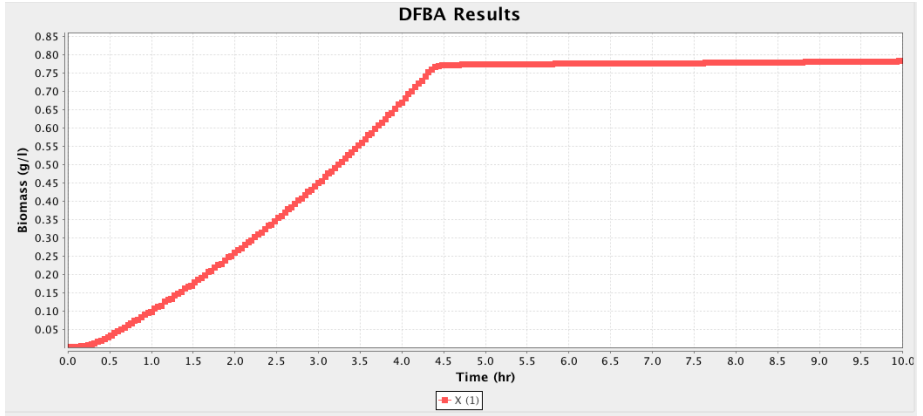
# DFBA Example: Update



# DFBA Example: Top-Level Model



# DFBA Example: Results





# Conclusion

- We proposed a way to encode hybrid models in SBML.
- Need to further explore other update methods (step size, adaptive, etc).
- Test on larger models (e.g. whole-cell model).
- Future extensions:
  - Different standards such as CellML.
  - Different variations (e.g. SSA + ODE)

# Acknowledgments

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