Dynamic Flux Balance Analysis (DFBA) with SBML (core, comp, fbc)

iBioSim

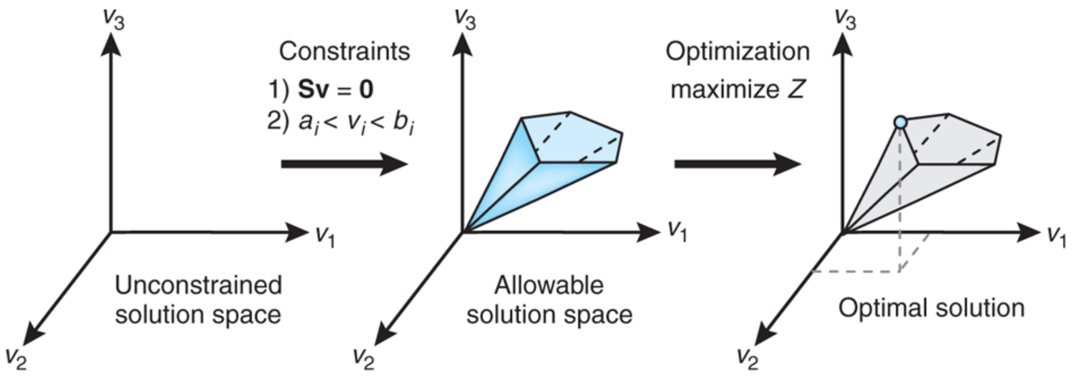
SBML sbmlutils

Leandro Watanabe, Matthias König & Chris Meyers

Dynamic FBA (DFBA)

Coupling of dynamical model parts to steady state networks (FBA)

- Subset of general problem of coupling models with different simulation frameworks
  - Deterministic
  - Constraint-based
  - Logical/boolean models
  - Stochastic simulations



Approaches

- **Coupling of ODE to FBA model**
  - **Direct embedding** of LP-Solver in ODE solver
    - execution in every time step
    - complex implementation (high level expertise on ODE solver design)
    - Stiffness of system at borders of flux-cone
  - **Stationary Optimization Approach** (**SOA**)
    - Iterative stepwise evaluation of FBA problem
    - Assumption: constant solution over step size
  - **Dynamic Optimization Approach (DOA)**
- **Resource allocation** (creating large optimization problem based)
  - Very large optimization problems (explosion of dimensions via time discretization)
  - Dynamic achieved via optimization boundary conditions

DFBA Examples

- **Whole-cell model** (Karr et al)

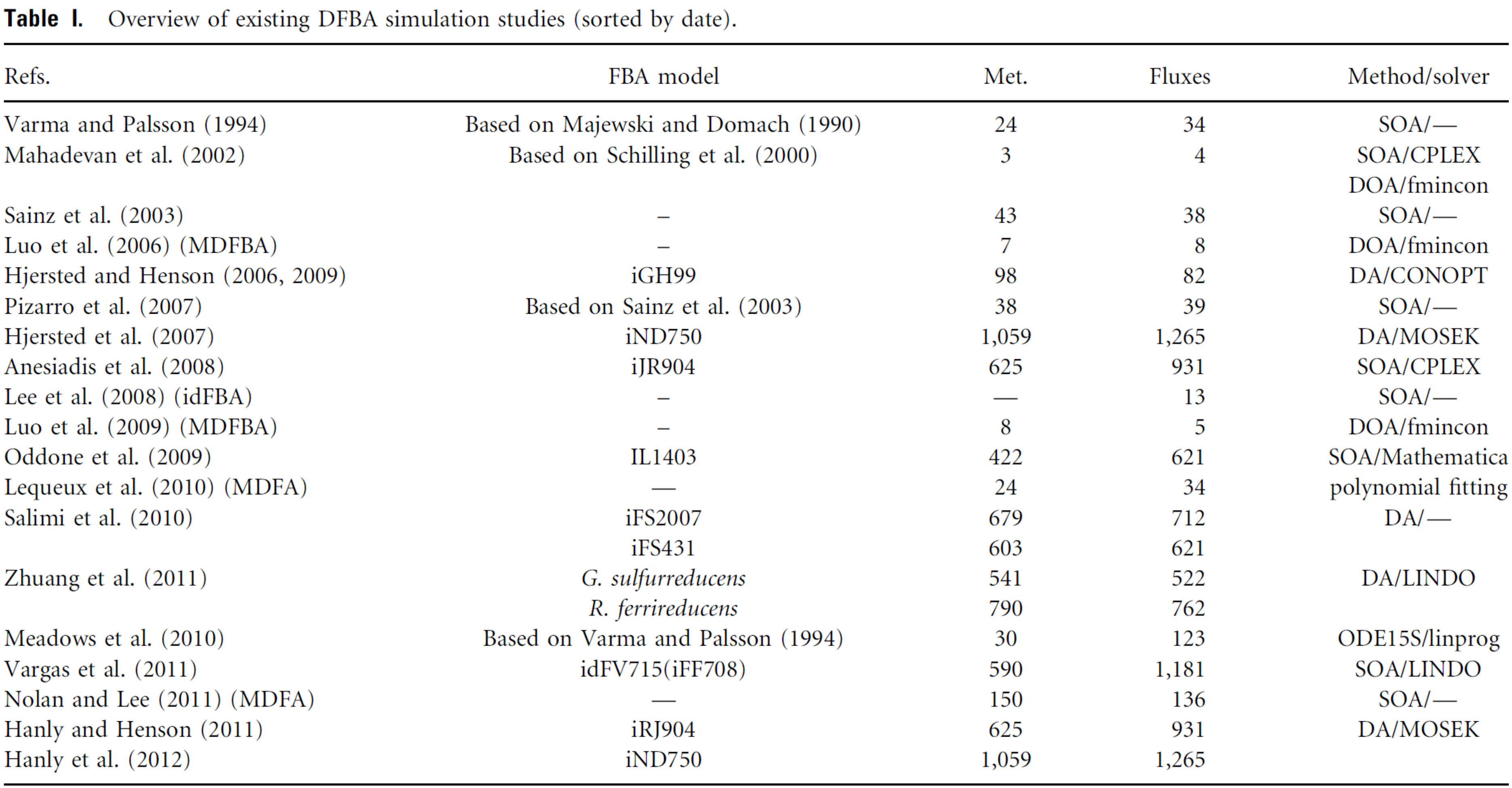


Table I. Overview of existing DFBA simulation studies (sorted by date).

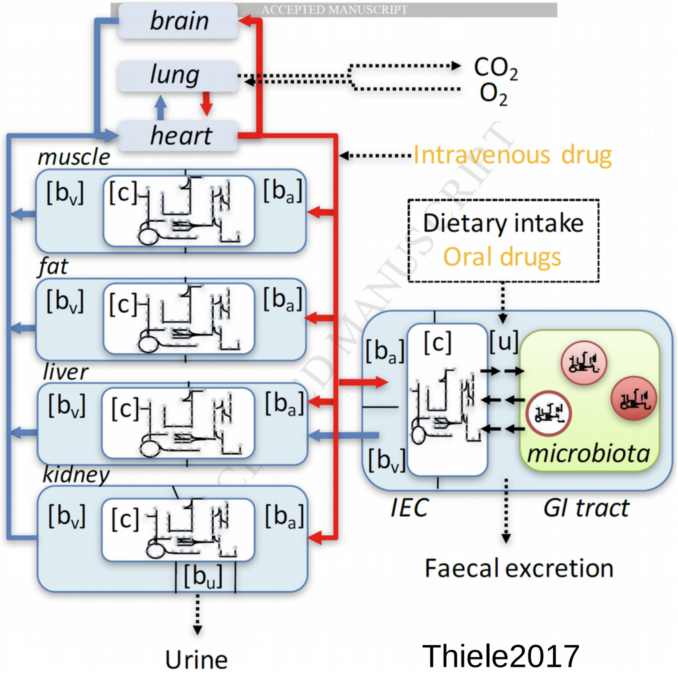
Refs.	FBA model	Met.	Fluxes	Method/solver
Varma and Palsson (1994)	Based on Majewski and Domach (1990)	24	34	SOA/—
Mahadevan et al. (2002)	Based on Schilling et al. (2000)	3	4	SOA/CPLEX
				DOA/fmincon
Sainz et al. (2003)	–	43	38	SOA/—
Luo et al. (2006) (MDFBA)	–	7	8	DOA/fmincon
Hjersted and Henson (2006, 2009)	iGH99	98	82	DA/CONOPT
Pizarro et al. (2007)	Based on Sainz et al. (2003)	38	39	SOA/—
Hjersted et al. (2007)	iND750	1,059	1,265	DA/MOSEK
Anesiadis et al. (2008)	iJR904	625	931	SOA/CPLEX
Lee et al. (2008) (idFBA)	–	—	13	SOA/—
Luo et al. (2009) (MDFBA)	–	8	5	DOA/fmincon
Oddone et al. (2009)	IL1403	422	621	SOA/Mathematica
Lequeux et al. (2010) (MDFA)	—	24	34	polynomial fitting
Salimi et al. (2010)	iFS2007	679	712	DA/—
	iFS431	603	621	
Zhuang et al. (2011)	*G. sulfurreducens*	541	522	DA/LINDO
	R. ferrireducens	790	762	
Meadows et al. (2010)	Based on Varma and Palsson (1994)	30	123	ODE15S/linprog
Vargas et al. (2011)	idFV715(iFF708)	590	1,181	SOA/LINDO
Nolan and Lee (2011) (MDFA)	—	150	136	SOA/—
Hanly and Henson (2011)	iRJ904	625	931	DA/MOSEK
Hanly et al. (2012)	iND750	1,059	1,265	

Applications & Use cases

- **Model embedding**
  - Coupling ODE pathway models to genome-scale metabolic models (liver)
  - Exchange interfaces

- **Whole-body PKPD**
  - Coupling of tissue specific FBA models to whole body PKPD
  - Glucose regulation (liver, muscle, fat, pancreas, stomach)
  - Cori cycle & other multi-tissue physiological cycles
    - Glucose – alanine/pyruvate shuttle

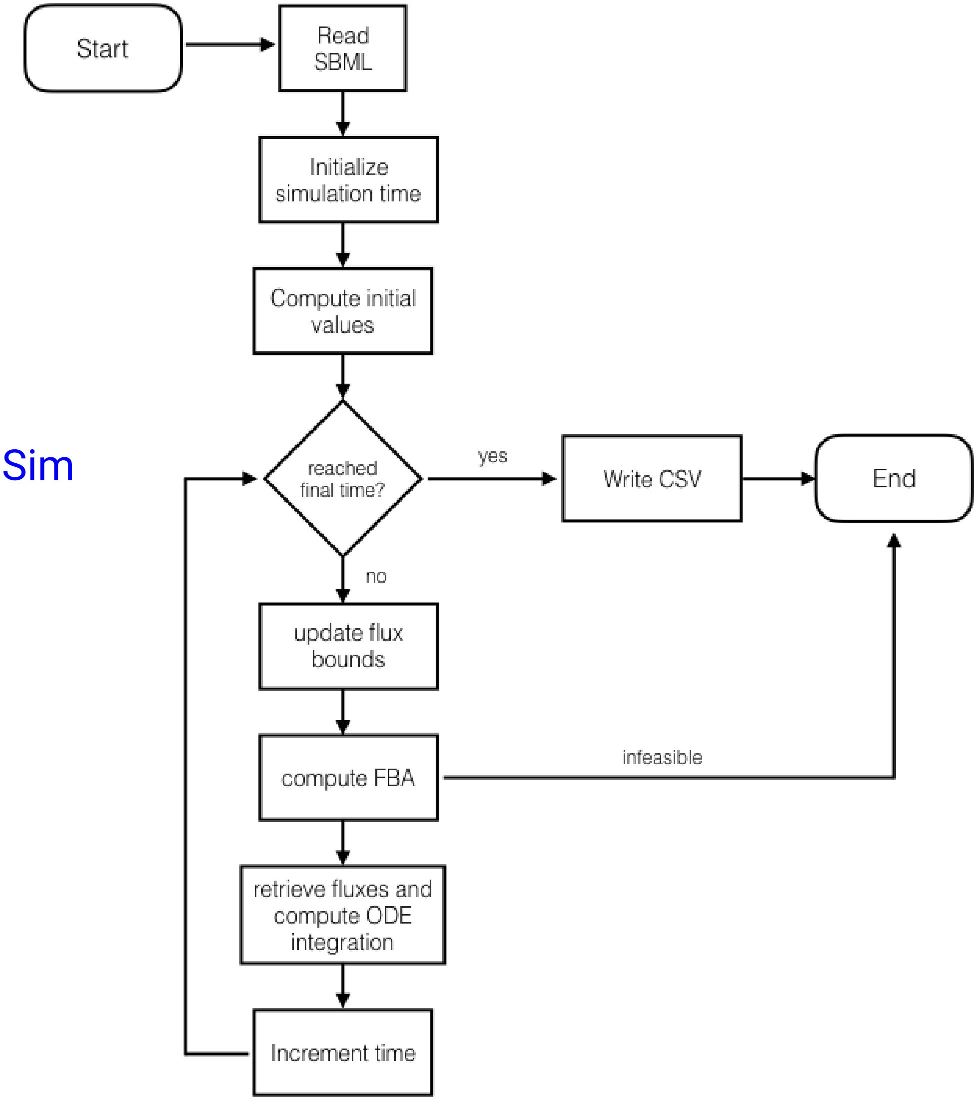
- **Wholecell model**
- **Microbiome, biofilms, ...**



Thiele2017

Simulation Algorithm

- **Implementations**
  sbmlutil
  https://github.com/matthiaskoenig/sbmlutils
  iBioSim
  https://github.com/MyersResearchGroup/iBioSim



SBML encoding

Good description for kinetic and FBA models.
But no description of **how to encode DFBA in SBML?**

- **Core**
  - **Kinetic models**
    Compartments, Parameters, Species, Reactions, RateRules, AssignmentRules, Events, FunctionDefinitions)
- **fbc**
  - **FBA encoding**
    Objective functions, flux bounds, GPR encoding
- **comp**
  - **Coupling of models**
    ExternalModelDefinitions, ModelDefinitions replacements, replacedBy, deletions, ports, submodels

- **Annotation of model components**
  - SBO terms
  - allows automatized coupling

Comp submodels

Splitting problem in clearly defined subproblems with interfaces.

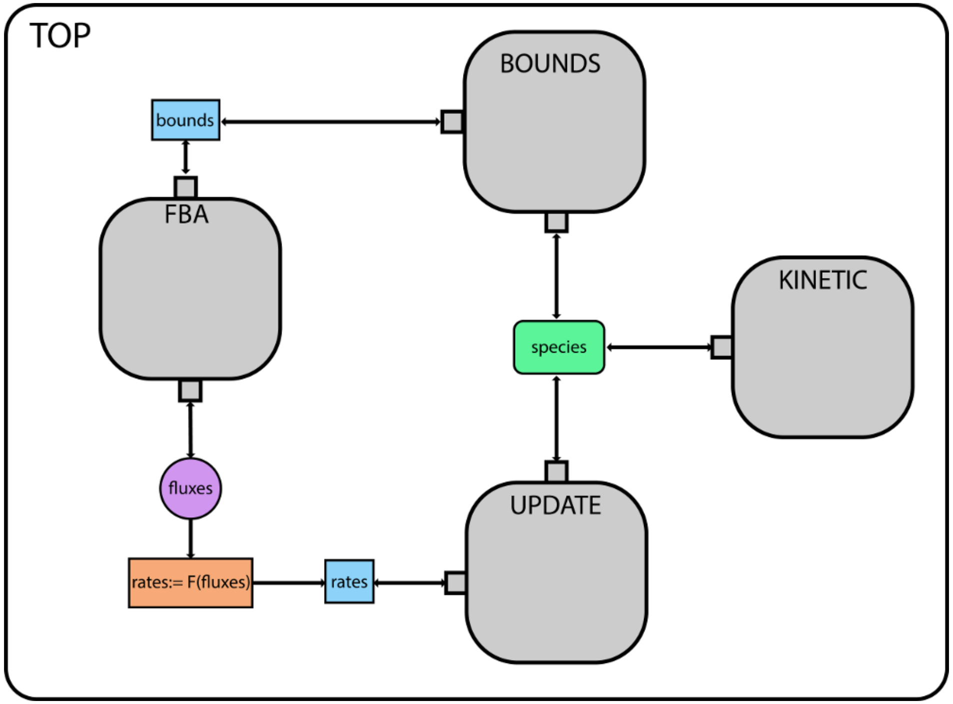
TOP
- (kinetic) equations & coupling of submodels

BOUNDS
- (kinetic) bounds calculation

UPDATE
- (kinetic) update of species with fluxes from FBA

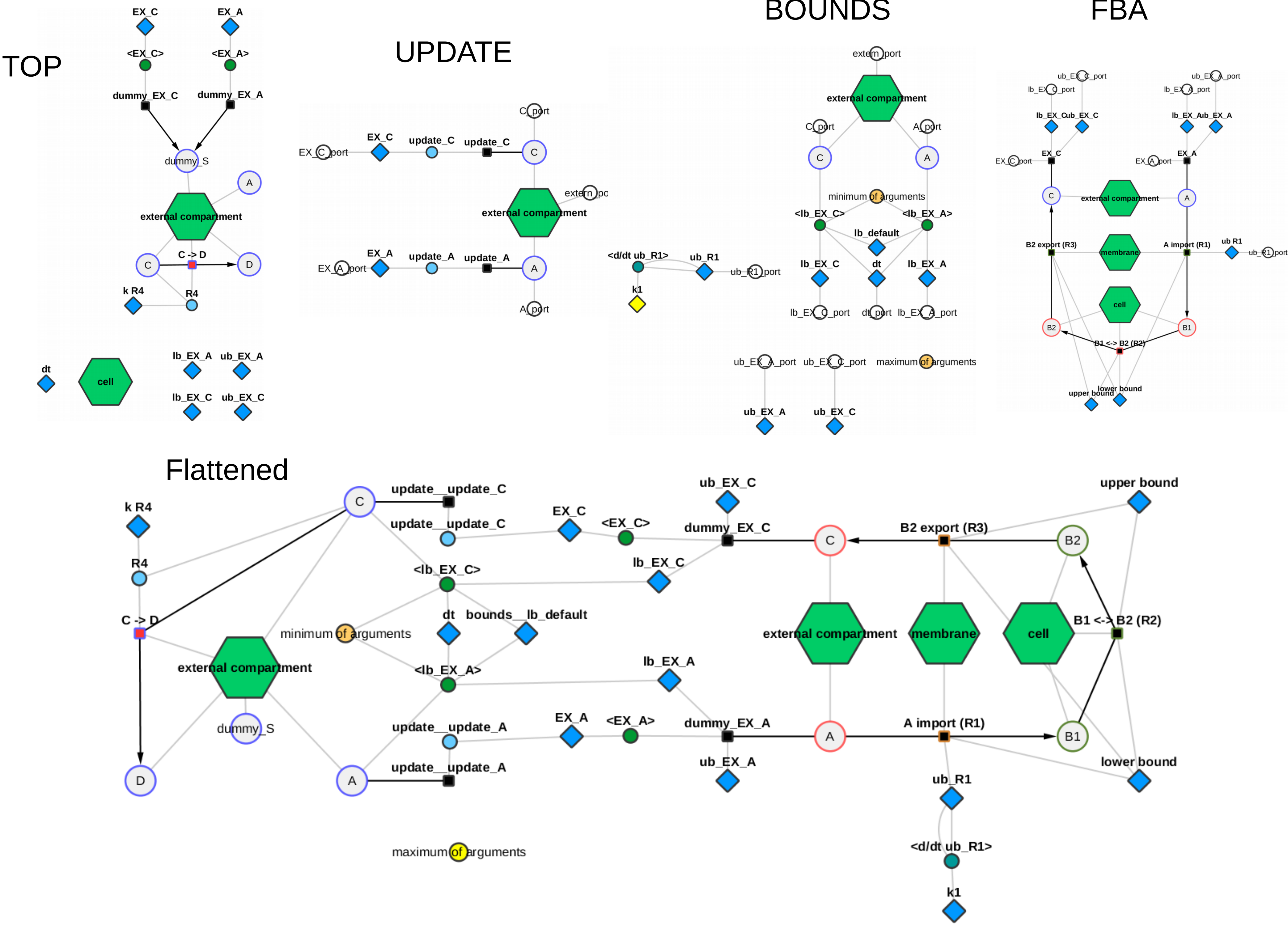
FBA
- (constraint) FBA problem

Interface
- **exchange reactions**
  - What is taken up, what is imported, how unbalanced are metabolites?
- **update kinetics**
  - How does flux change metabolites (scaling by biomass, …)
- **bound kinetics**
  - How do kinetic players effect bounds
- Limiting FBA fluxes via available resources for time step (bounds)



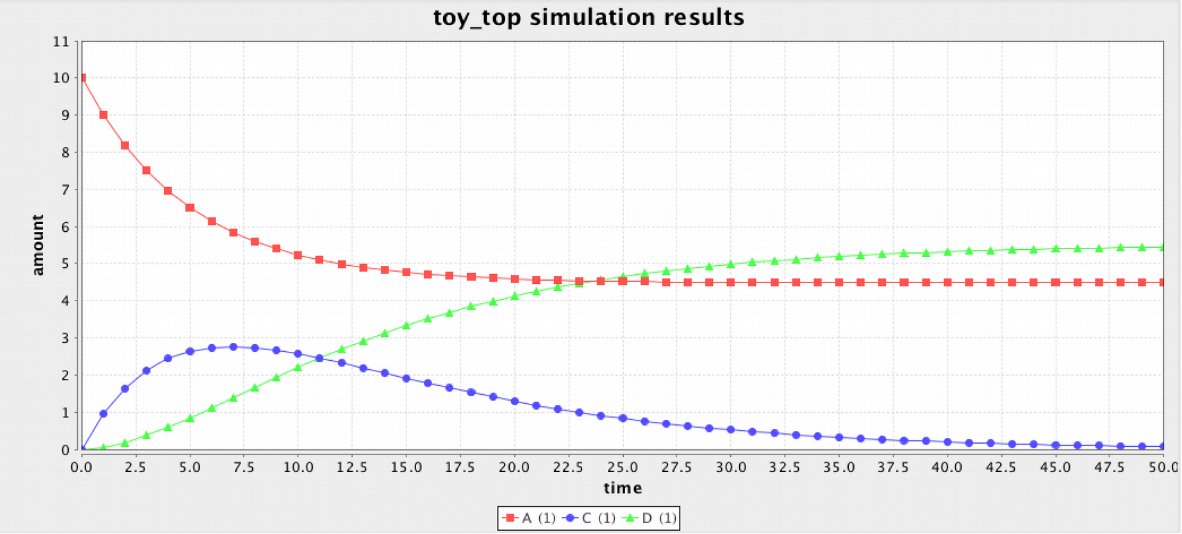
- **dt** (time step)
  - required for bounds update
  - defines steps in DFBA time course

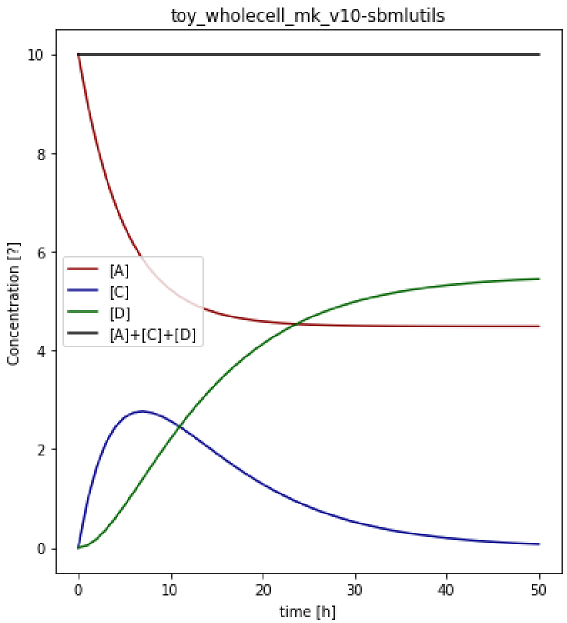
Toy wholecell

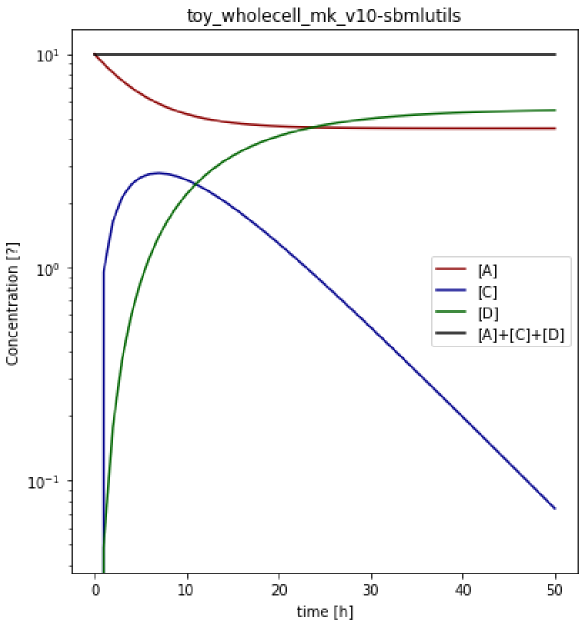


Toy wholecell

- 3 reactions, linear chain
- 2 exchange reactions (A, C)
- **Identical results**

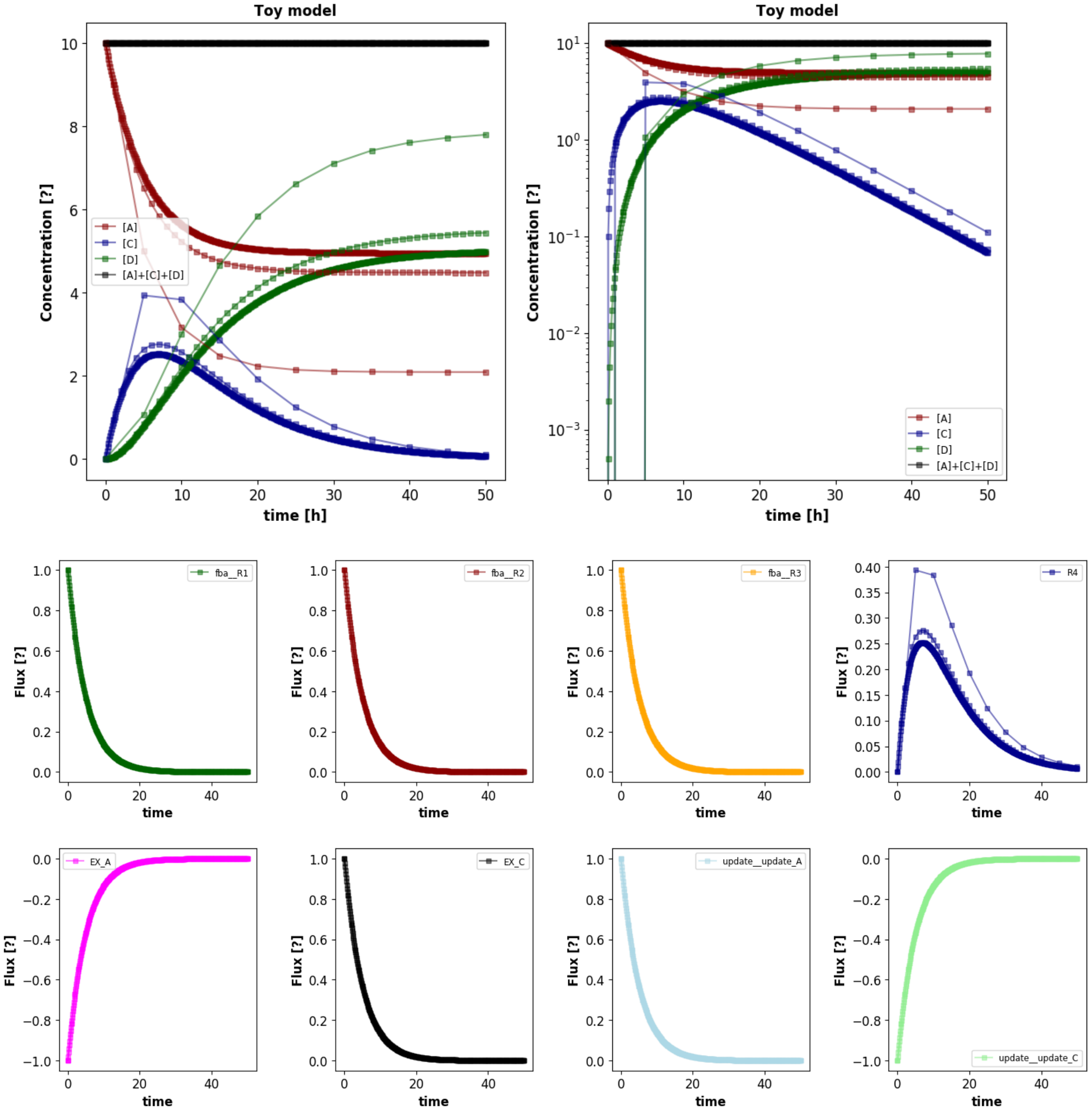






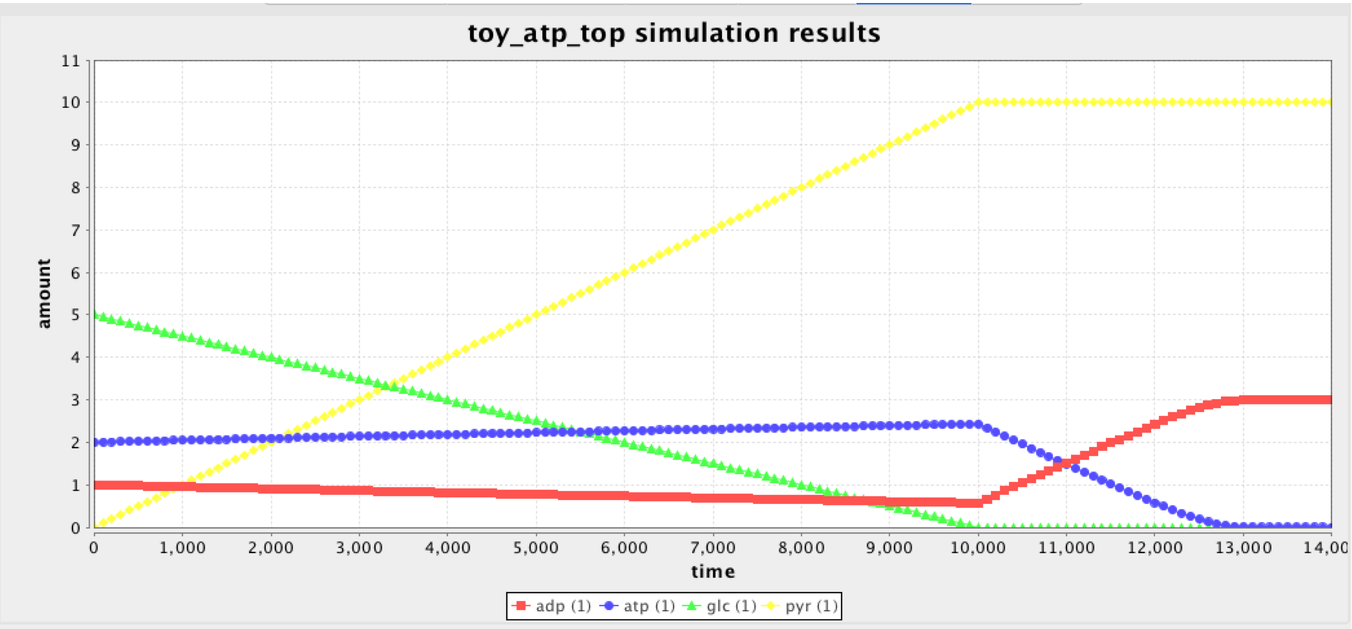
file:///home/mkoenig/git/sbmlutils/sbmlutils/dfba/toy_wholecell/results/v12/index.html

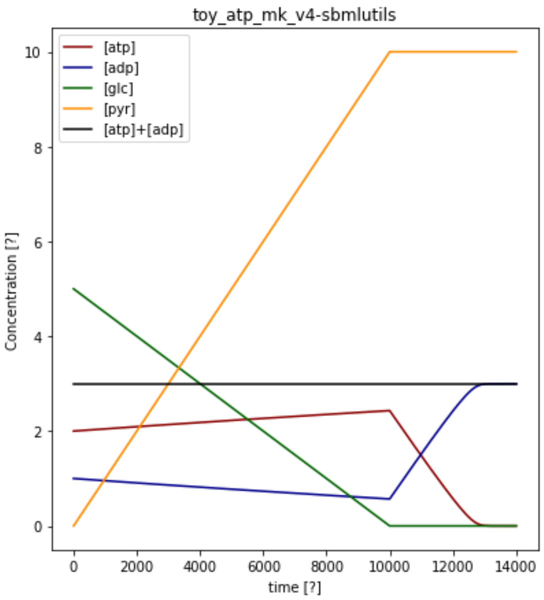
Step size dt [0.1, 1.0, 5.0]

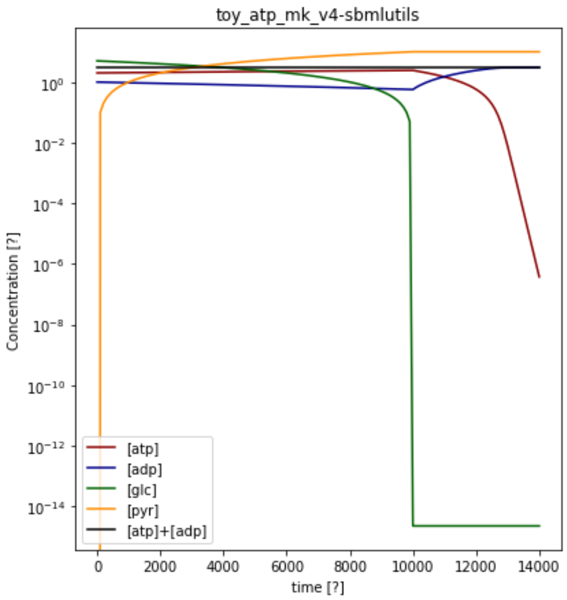


Toy ATP

- Simplified glycolysis







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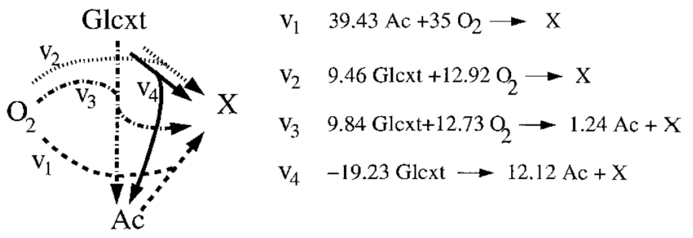
Diauxic growth

Mahadevan2002



v_1 $39.43\ \mathrm{Ac} + 35\ O_2 \longrightarrow X$

v_2 $9.46\ \mathrm{Glcxt} + 12.92\ O_2 \longrightarrow X$

v_3 $9.84\ \mathrm{Glcxt} + 12.73\ O_2 \longrightarrow 1.24\ \mathrm{Ac} + X$

v_4 $-19.23\ \mathrm{Glcxt} \longrightarrow 12.12\ \mathrm{Ac} + X$

FIGURE 2 Simplified metabolic network. The network identified after pathway analysis with glucose, acetate, and oxygen as the input and biomass as the output and selection based on biomass yield is presented above.

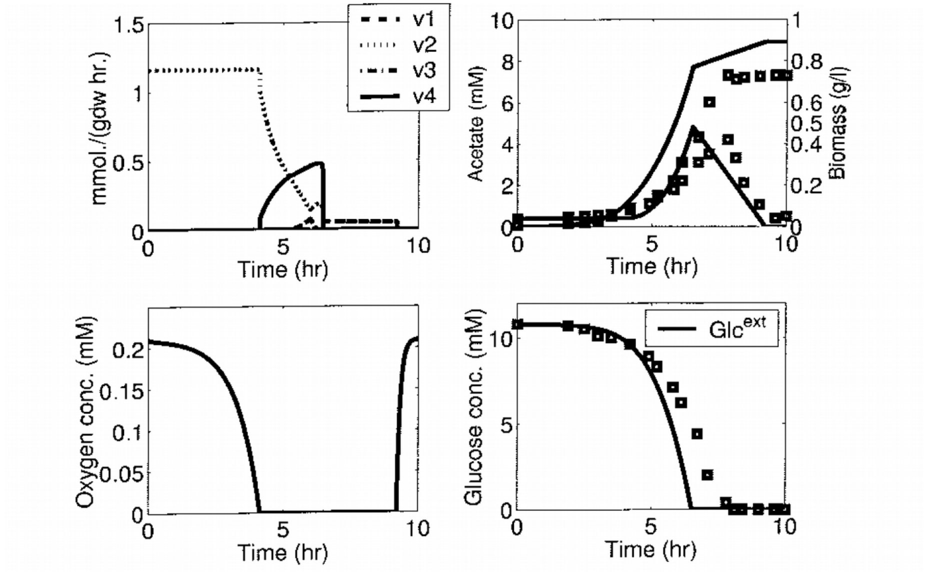
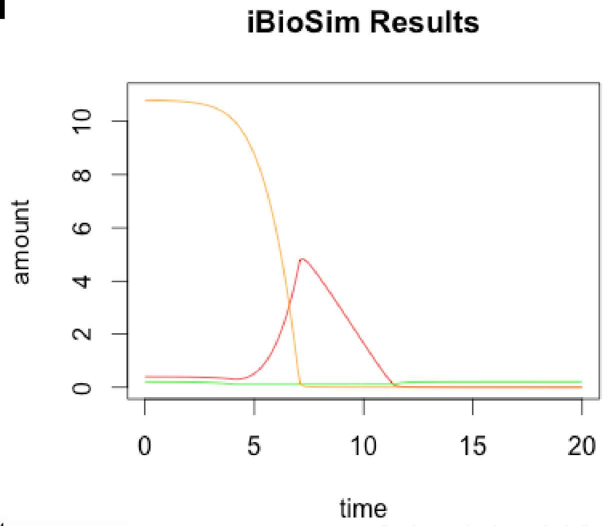
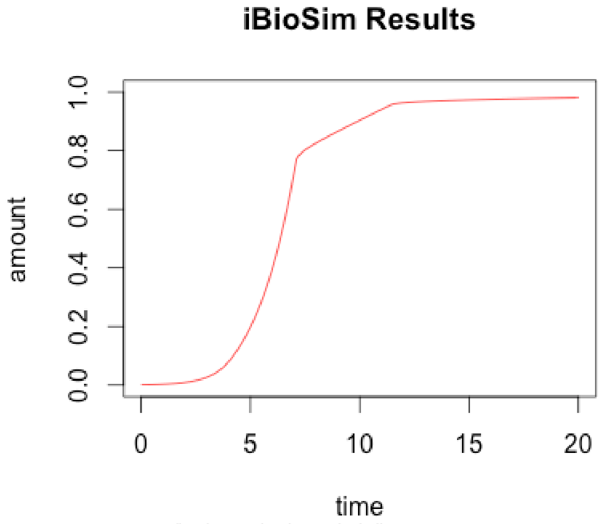
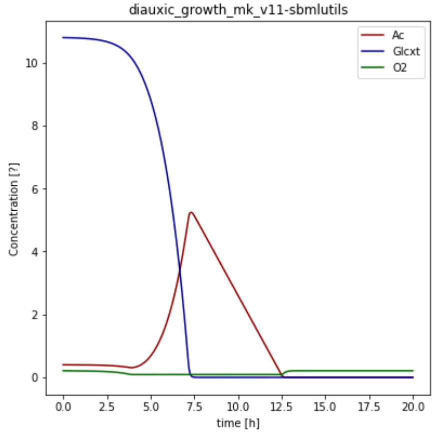
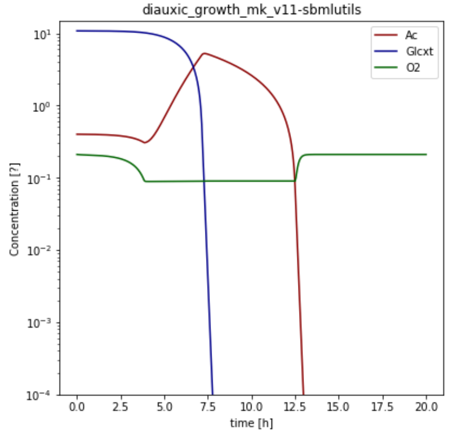


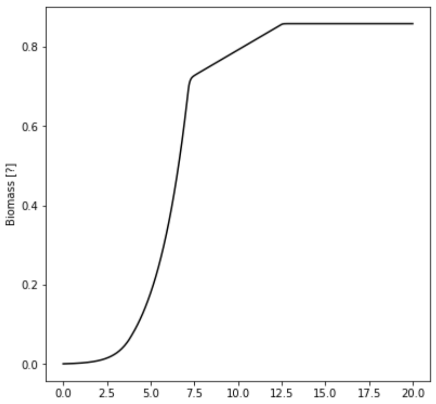
FIGURE 7 Model prediction using SOA for DFBA in the presence of the rate of change of flux constraints for a glucose uptake rate of 11 mmol/gdwhr. Insufficient oxygen uptake rate due to the increased glucose uptake results in the shutting down of the acetate utilization pathway in the initial phase. Glucose, acetate, and biomass concentrations from experimental data are plotted along with the model predictions (Varma and Palsson, 1994b).

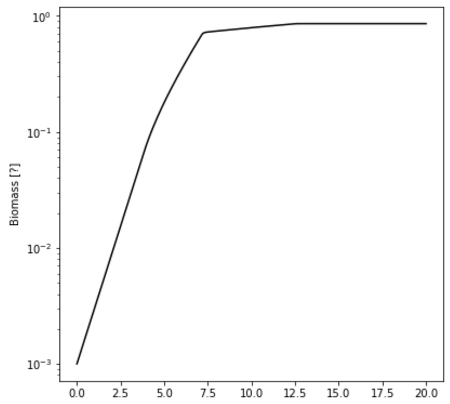






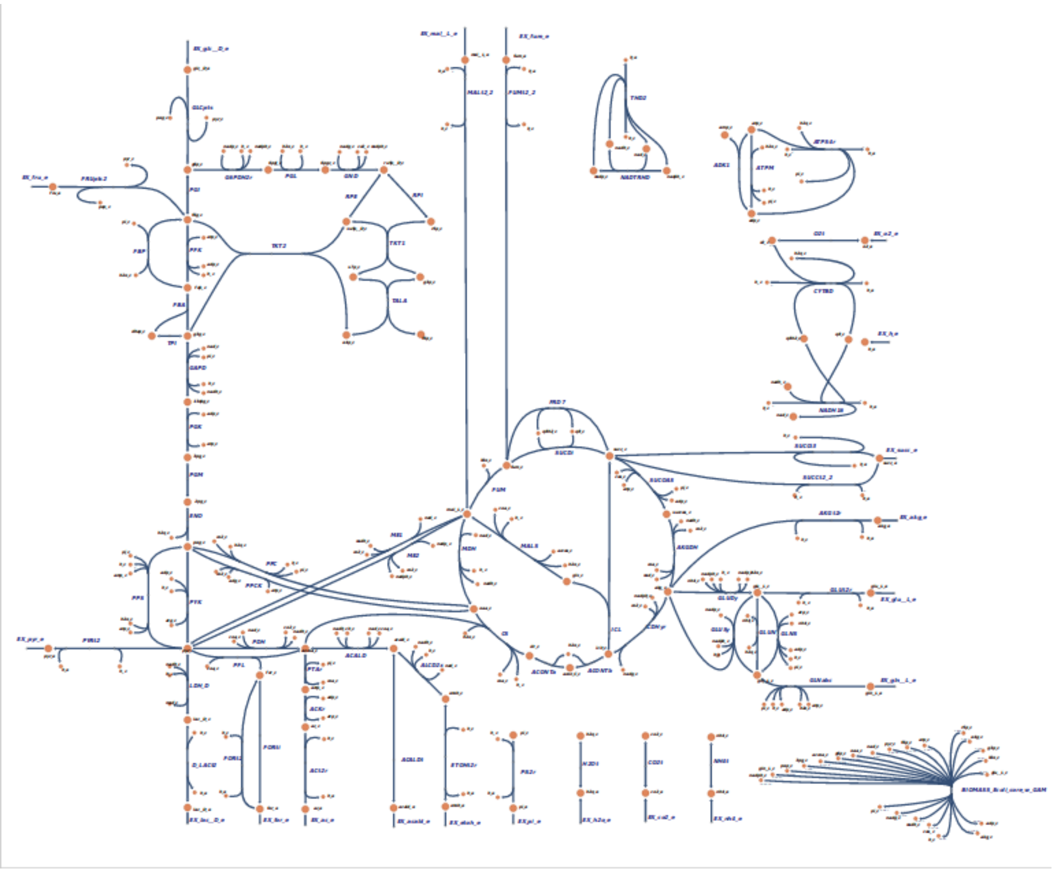




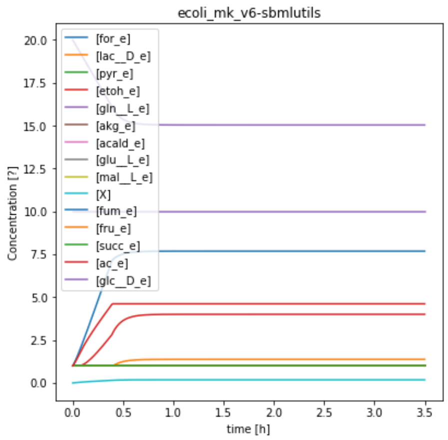


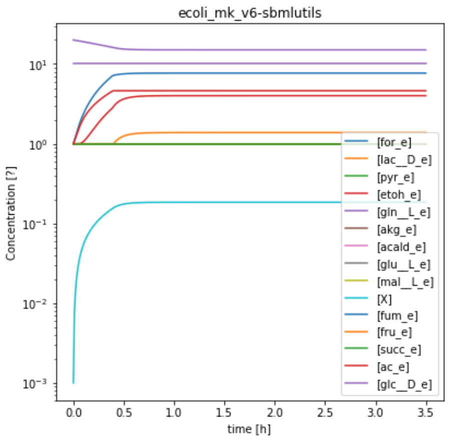
E.coli core (BiGG)

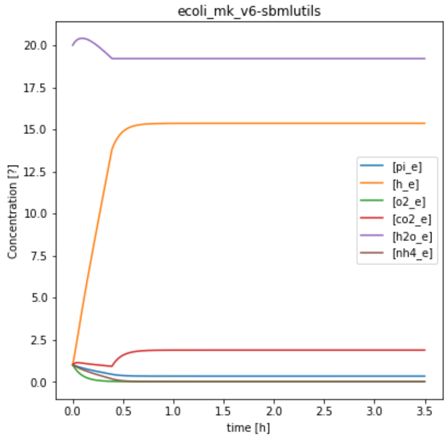
- 95 reactions, 72 metabolites, 137 genes, 4 exchange reactions)
- automatic scripts to generate DFBA models from FBA models (via exchange reactions)

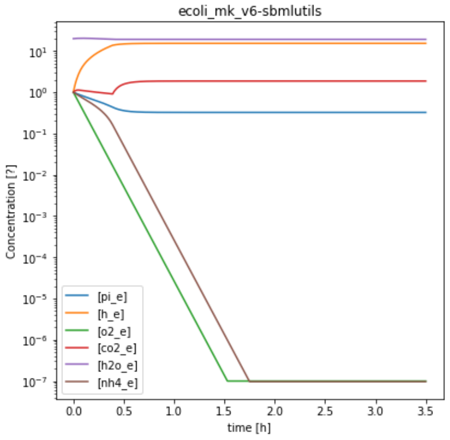


* not-unique, infeasible issues (iBioSim)







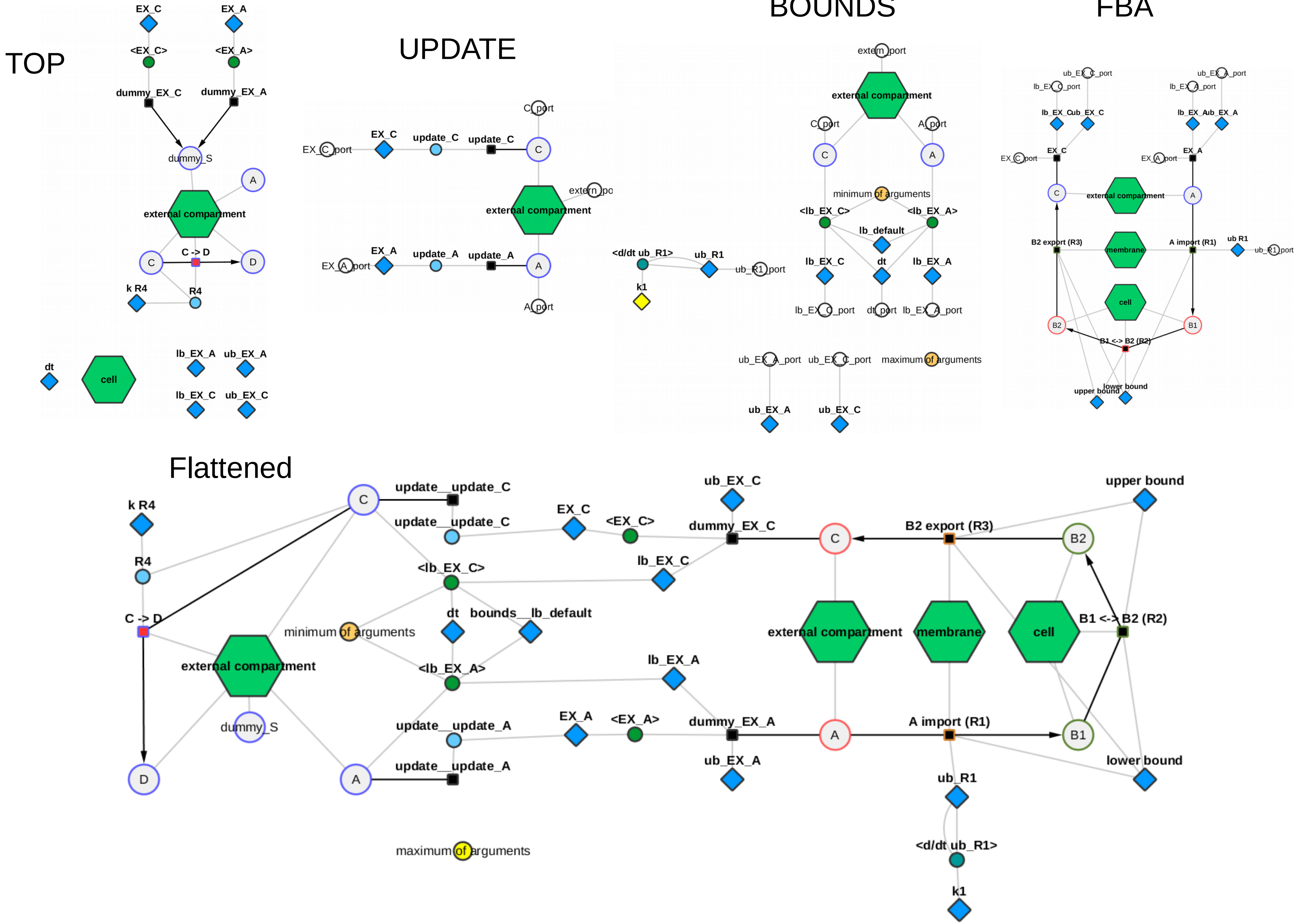


Guidelines for DFBA encoding

https://github.com/matthiaskoenig/dfba

https://github.com/matthiaskoenig/dfba/blob/master/DFBA%20models%20in%20SBML.md

Toy wholecell



Issues & Outlook

- Uniqueness of solutions
  - FVA, sampling from solution space
- Flattening of larger models (memory issues RBC model, flattening slow)
- **Encoding issues in fbc**
  - Additional LP constraints like (v1 + v2 = 10; v1 < v3)
  - More complex optimizations like parsimonous FBA
    - 2 step optimizations
    - Kisao terms
  - Biomass weighting
    - Via conversion factors
- General issues
  - the (in)famous hack: if (c<0): c = 0
  - Only covers

Outlook

- Combine archives (comp files, SED-ML, results)
- Extension to coupling multiple, large FBA models
- Coupling other simulation frameworks

FBC unit challenges

Biomass scaling

- Often FBA fluxes must be scaled with biomass for update of the species in kinetic part (resulted in many unit issues, different flux units)
  - Depends on DFBA model (either biomass weighted results or ot)
  - FBA fluxes per gDW
    - e.g [mmol/h/g]
  - Kinetic fluxes in [mmol/h], not normalized on biomass
  - Biomass species X in [g/l] (other species in [mmol/l]
    - **Scaling factor to convert to amount**
  - Updates via:
    - update_Ac = -pEX_Ac * **X**

Unit challenges

- Reaction flux units defined via units of bounds on reaction

https://docs.google.com/document/d/1KqERrNr7Iptos6cyYekIOkx9L3ZBVb4SWav8vrn4GAY/edit#