

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

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Dynamic FBA (DFBA)

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

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

Approaches

- **Resource allocation** (creating large optimization problem based)
 - Very large optimization problems
 - Dynamic achieved via optimization boundary conditions like $\text{biomass}(24\text{h}) = k * \text{biomass}(0\text{h})$ in combination with resource variables
 - Coupling to arbitrary ODEs not possible
- **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)**
 - **Dynamic Optimization Approach (DOA)**

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)	<i>G. sulfurreducens</i>	541	522	DA/LINDO
	<i>R. ferrireducens</i>	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

- **Circadian Liver metabolism**

- Coupling circadian blood metabolite & gene/protein expression patterns to FBA model of liver metabolism (HepatoNet1)

- **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

- **Model embedding**

- Coupling ODE pathway models to genome-scale metabolic models (liver)

SBML

De facto standard for Systems Biology Models (ODE, FBA, mixed compartments)

- Good description for kinetic and FBA models, but no implementation of DFBA in standard
- Core language (core) & extension packages
 - **core**
Kinetic models
 - Compartments, Parameters, Species, Reactions, RateRules, AssignmentRules, Events, FunctionDefinitions)
 - **fbc**
FBA encoding
 - objective functions, upper & lower bounds, GPR encoding
 - **comp**
Coupling of models
 - ExternalModelDefinitions, ModelDefinitions replacements, replacedBy, deletions, ports, submodels,

Encoding

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

TOP

- kinetic part & coupling of submodels

BOUNDS

- kinetic bounds calculation

UPDATE

- kinetic update of species from FBA

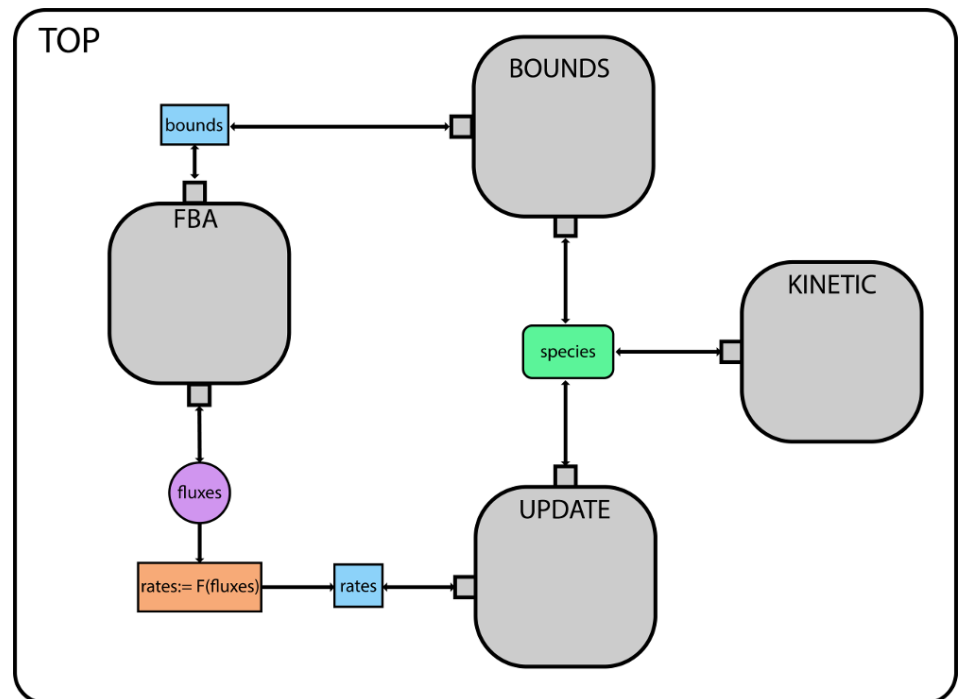
FBA

- FBA problem (interface via exchange reactions)

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Interface

- **exchange reactions**
(boundaryCondition=True species)
 - What is taken up, what is imported, how unbalanced are metabolites?
- **update kinetics**
 - How does flux effect metabolites (scaling by biomass, ...)
- **bound kinetics**
 - How do kinetic players effect bounds & resource limitation of FBA



Simulation Algorithm

- **Implementations**

- sbmlutils

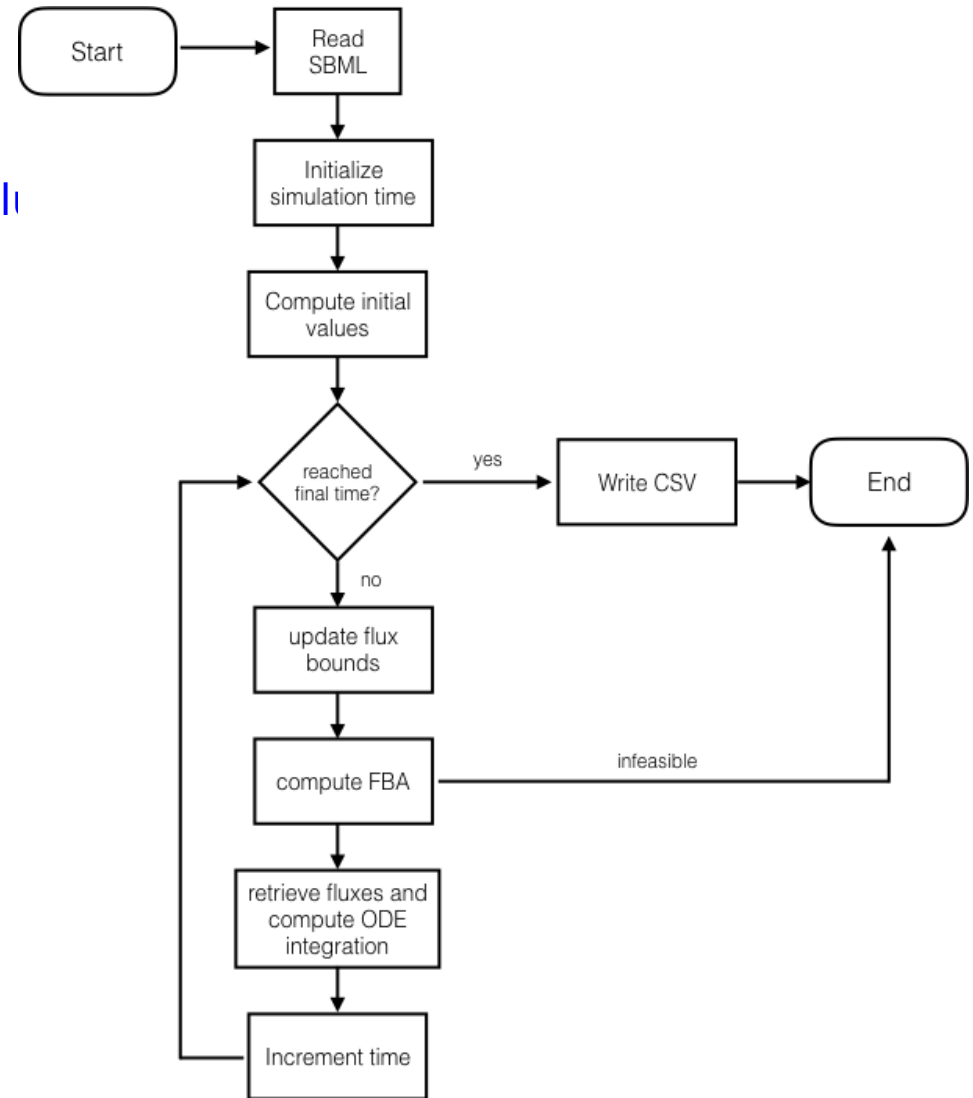
- <https://github.com/matthiaskoenig/sbmlutils>

- iBioSim

- <http://www.async.ece.utah.edu/ibiosim>

- **Challenges**

- standardized encoding of DFBA models
 - uniqueness of FBA solutions
 - bounds limitations based on species amounts/concentrations
 - the (in)famous hack
 - if ($c < 0$): $c = 0$



Example Models

Toy model

- 3 reactions, linear chain, 2 exchange reactions

Diauxic growth

- 4 effective reactions, 4 exchange reactions

E.coli core

- 95 reactions, 72 metabolites, 137 genes, 4 exchange reactions
- http://bigg.ucsd.edu/models/e_coli_core
- https://escher.github.io/builder/index.html?enable_editing=true&map_name=e_coli_core.Core%20metabolism

