Virtual Liver
HepatoSys

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN
COMPUTATIONAL SYSTEMS BIOCHEMISTRY

Berlin: Workpackage A, Cellular metabolism
A1.1 Central liver metabolism and its regulation under nutritional challenges

FASIMU: flexible software for flux-balance batch computation in large metabolic networks

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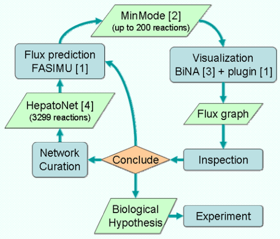
Summary

Flux-balance analysis (FBA) based on linear optimization is widely used to compute metabolic fluxes in large metabolic networks and gains more importance in network curation and structural analysis which requires a computational tool flexible enough to select from the wide variety of FBA algorithms and able to handle batch series.

We present FASIMU, a command line oriented software for the computation of flux distributions using a variety of most common FBA algorithms, including the first available implementation of (i) weighted flux minimization, (ii) fitness maximization for partially inhibited enzymes, and (iii) the concentration-based thermodynamic feasibility constraint. It allows batch computation with varying objectives and constraints suited for network pruning, leak analysis, flux-variability analysis, and systematic probing of metabolic objectives for network curation controlled by an intuitive description file. Input and output supports SBML. FASIMU can work with free (lp_solve and GLPK) or commercial solvers (CPLEX, LINDO). Plugins have been developed to visualize calculated flux distributions in Cytoscape (FluxViz) and BiNA (faBiNA).

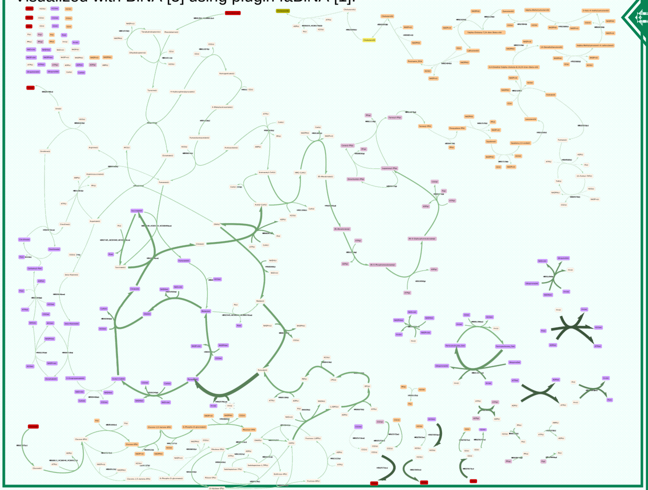
The platform-independent program is an open-source project, freely available at http://www.bioinformatics.org/fasimu under GNU public license, including manual, tutorial, and plugins.

Work flow linking FASIMU computation, visualization and experiment

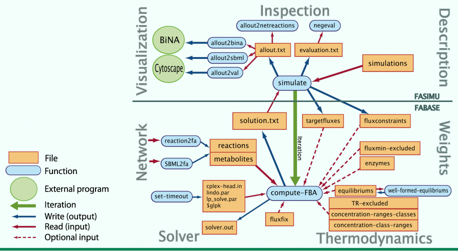


Flux mode producing bile cholesterol

-Computed with FASIMU in HepatoNet [4]
-Visualized with BiNA [3] using plugin faBiNA [1].



Data flow in FASIMU



FBA implementation

Objectives
- Flux minimization [5]
- Fitness maximization [6]
- Biomass maximization [7]
- Network prediction by expression profiles [8]

Constraints
- Thermodynamic constraint based on metabolite concentrations [9]
- Constraining individual fluxes [6]
- Knock-outs (e.g. [10])

Implemented methods

- Flux-variability analysis [12]
- Minimal functional flux modes [2]
- Network pruning [11]
- Leak analysis (similar to [13])

Example script

```
Cholesterol   Cholesterol_bile   -Glucose -O2 +CO2 +H2O
Cholesterol_bile
```

```
source fasimu
opimization-call="compute–FBA –T –F e"
simulate
allout2bina
bina BiNA/Cholesterol.csv
```

Software layout

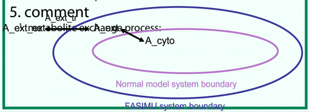
- Runs on LINUX, Windows, MAC, UNIX
- Requires bash, gawk
- Requires external solver (CPLEX, LINDO, GLPK, lp_solve)
- External network visualization helpful
  (BiNA, Cytoscape, CellNetAnalyzer, or SBW)
- Freely available, open source (GPL)
- Can be based on freely available software

Simulation definition

One line per simulation, organized in columns

1. name
2. objective
   - set flux of a process (reaction or metabolite exchange[1])
   - max/minimize a process
   - expression profile pattern
3. constraints
   - explicit boundaries of a process
   - simplified boundaries (+ forward only, - backwards only, % forbidden, = unrestricted)
4. evaluator
   - solution contains process
5. comment

[1] metabolite exchange process:



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