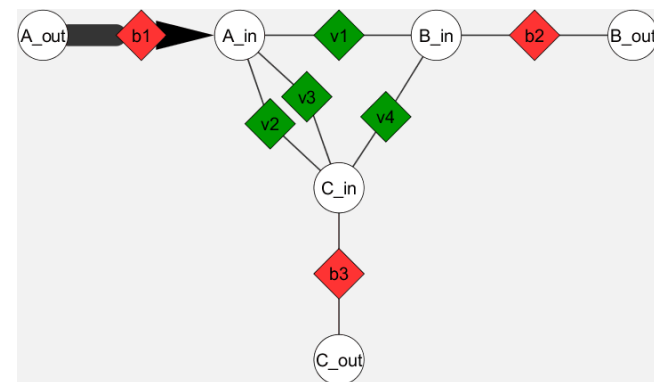



CYFLUXVIZ & CYSBML


Visualization of Constrained-based and Kinetic Model Simulations in Cytoscape




Matthias König

VISUALIZATION IN CYTOSCAPE

- **Cytoscape** ^[1]  **Cytoscape**
 - opensource software platform for visualizing complex networks

- **CySBML** ^[2] 
 - opensource plugin for SBML
 - annotation support

- **CyFluxViz** ^[3] 
 - opensource plugin for flux visualization
 - COBRA integration

[1] Cytoscape: a software environment for integrated models of biomolecular interaction networks. [Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, Amin N, Schwikowski B, Ideker T. Genome Res.](#) 2003 Nov;13(11):2498-504.

[2] Fluxviz - cytoscape plug-in for visualization of flux distributions in networks. [König M, Holzhütter HG. Genome Inform.](#) 2010 Jul;24(1):96-103.

[3] CySBML: a Cytoscape plugin for SBML. [König M, Dräger A, Holzhütter HG. Bioinformatics.](#) 2012 Sep 15;28(18):2402-3. doi: 10.1093/bioinformatics/bts432. Epub 2012 Jul 5.

CYSBML

SBML plugin for Cytoscape based on **JSBML** (*Dräger, et al., 2011*), a free, open-source Java™ library for SBML.



- Supports all versions and levels of SBML
- Handles **SBML Models** and **SBML Qualitative Models**
- Supports **SBML Layout extension** (*Gauges, et al., 2006*)
- Access to **BioModels** via web services (*Li, et al., 2010*)
- Reads **annotations** of the SBML elements and provides access to the annotated resources within the network visualization
- Validation of imported SBML files
- Navigation menu based on SBML structure

 **BioModels.Net**



CYSBML INTERFACE

Interplay
CyFluxViz & NetMatch

CySBML Menu Bar

SBML Navigation Tree

The screenshot displays the CysBML interface with several key components:

- BioModels Import:** A panel on the left for searching BioModels. It includes fields for Name, Person, Publication, ChEBI, and UniProt. A list of 22 BioModels is shown, with the first one selected: **MODEL6624091635** (name: Hoefnagel2002_Glycolysis).
- Network Analysis:** A central panel titled "Network Analysis of path_hsa00450 (undirected)". It displays various network statistics:

Betweenness Centrality	Closeness Centrality	Stress Centrality Distribution
Shared Neighbors Distribution	Neighborhood Connectivity Distribution	
Topological Coefficients	Shortest Path Length Distribution	
Simple Parameters	Node Degree Distribution	Avg. Clustering Coefficient Distribution

Clustering coefficient : 0.0
Connected components : 12
Network diameter : 8
Network radius : 1
Network centralization : 0.069
Shortest paths : 3336 (61%)
Characteristic path length : 4.309
Avg. number of neighbors : 2.081

Number of nodes : 74
Network density : 0.029
Network heterogeneity : 0.976
Isolated nodes : 10
Number of self-loops : 0
Multi-edge node pairs : 0
Analysis time (sec) : 0.077
- SBML Navigation Tree:** A panel on the right showing a tree structure of SBML models. The selected model is **Methylselenol (Methylselenol)**. Below the tree, the species is defined: **Species : Methylselenol (Methylselenol)**. The SBO identifier is **SBO:0000247**. The biological qualifier is **BQB_IS C05703** (urn:miriam:kegg.compound). The chemical structure is shown as CH3-Se-H. The biological qualifier is **BQB_HAS_PROPERTY B01888** (urn:miriam:3dmet). The biological qualifier is **BQB_OCCURS_IN R0958** (urn:miriam:kegg.reaction).

BioModel Import

Integration
NetworkAnalyzer

Annotation Area &
WebLinks

BioModel IMPORT

- SBML BioModels search via
 - identifiers
 - name
 - author
 - publication
 - ChEBI
 - UniProts
- Import multiple models for comparative analysis

The screenshot displays the 'CysBML BioModel Import' window. On the left, a search form has 'glycolysis' entered in the 'Name' field. Below the form is a list of 22 model IDs, with 'BIOMD0000000281' selected. At the bottom left, a 'BioModel Ids' list contains 'BIOMD0000000070' and 'BIOMD0000000071'. On the right, the 'BioModels.Net' logo is shown above the text '22 BioModels found for'. Below this, three model details are displayed in a table-like format.

Name	glycolysis
id	BIOMD0000000172
name	Pritchard2002_glycolysis
authors	[Pritchard L, Kell DB]
pubmed	12180966
encoders	[Lukas Endler, Pedro Mendes]

id	MODEL6624091635
name	Hoefnagel2002_Glycolysis
authors	[Hoefnagel MH, van der Burgt A, Martens DE, Hugenholtz J, Snoep JL]
pubmed	12241048
encoders	[]

id	BIOMD0000000281
name	Chance1960_Glycolysis_Respiration
authors	[CHANCE B, GARFINKEL D, HIGGINS J, HESS B]
pubmed	13692276
encoders	[Lukas Endler, Kieran Smallbone]

id	MODEL1011010000
name	Bruck2008_Glycolysis
authors	[Bruck J, Liebermeister W, Klipp E]
pubmed	19425118
encoders	[Kieran Smallbone, Jozsef Bruck]

id	BIOMD0000000071
name	Bakker2001_Glycolysis
authors	[Helfert S, Estévez AM, Bakker B, Michels P, Clayton C]
pubmed	11415442
encoders	[Jacky L Snoep, Harish Dharuri, Lukas Endler]

id	BIOMD0000000064
----	---------------------------------

CYFLUXVIZ

WHY ANOTHER FLUX VISUALIZATION TOOL?

Feature	CellNet-Analyzer	FBA-SimVis	fa-BINA	Cyto-scape
<i>Network import</i>	—	+	+	+
<i>Flux data import</i>	+	+	+	—
<i>Export flux distribution views</i>	—	+	+	+
<i>Batch export</i>	—	—	+	—
<i>Filtering and subnetwork views</i>	—	—	±	—
<i>Flux mapping on visual attributes</i>	—	+	+	—
<i>Flexible mapping functionality</i>	—	—	±	+
<i>Adaptable mapping functions</i>	—	+	—	+
<i>Batch support for flux distributions</i>	—	—	±	—
<i>Annotation of simulation information</i>	—	—	—	—
<i>Functional enrichment</i>	—	±	±	+

□ Available tools

- lack important functionality
- not flexible enough
- no open source
- no good interface (API)
- no batch capabilities
- only basic mappings
- dependence on simulation tools & methods (FBA vs. Kinetic)

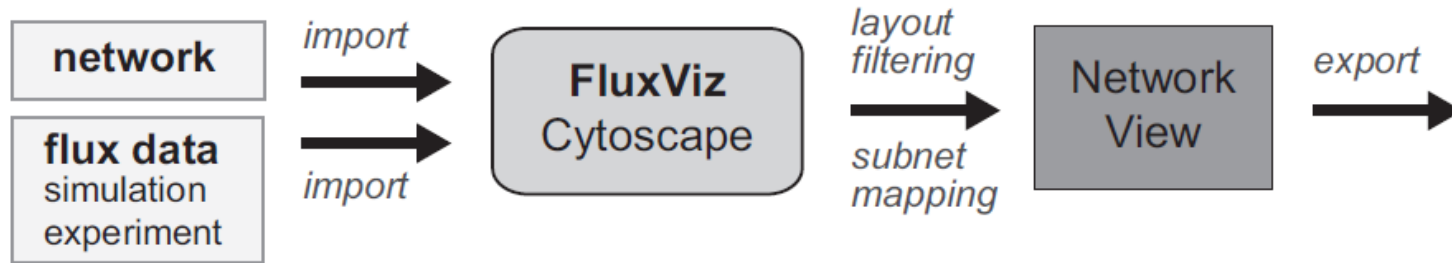
□ Not reinventing the wheel

- **CyFluxViz as visualization Solution in network context**
- **Integration into existing modeling workflow** (only simulation results necessary)

ANOTHER VISUALIZATION TOOL !

Feature	CellNet– Analyzer	FBA– SimVis	fa– BINA	Cyto– scape	Flux– Viz	FluxViz Details
<i>Network import</i>	–	+	+	+	+	many formats (SBML, GML, XGMML, SIF, BioPAX, PSI–MI)
<i>Flux data import</i>	+	+	+	–	+	CSV format, FASIMU val files, Cytoscape attributes
<i>Export flux distribution views</i>	–	+	+	+	+	many formats: PDF, SVG, EPS, JPEG, PNG, BMP
<i>Batch export</i>	–	–	+	–	+	batch export of selected flux distributions in many formats
<i>Filtering and subnetwork views</i>	–	–	±	–	+	flux containing network attribute based subnetworks like compartment/pathway subnetworks flux containing attribute networks
<i>Flux mapping on visual attributes</i>	–	+	+	–	+	all node and edge attributes can be utilized edge size, direction and tooltip are used for standard visualization of fluxes
<i>Flexible mapping functionality</i>	–	–	±	+	+	additional node and edge attributes can be used to represent additional data like for example localization as node color or gene expression as node size.
<i>Adaptable mapping functions</i>	–	+	–	+	+	global settings for all flux distributions vs. local for single flux distributions linear and stepwise linear (flux → edge weight) mappings based on setpoints
<i>Batch support for flux distributions</i>	–	–	±	–	+	batch import and export cycling through flux distributions on the fly generation of flux distribution mapping with consistent layout
<i>Annotation of simu- lation information</i>	–	–	–	–	+	import of simulation information (FASIMU)
<i>Functional enrichment</i>	–	±	±	+	+	many Cytoscape plug–ins available; simple enhancement through plug–in architecture, large community

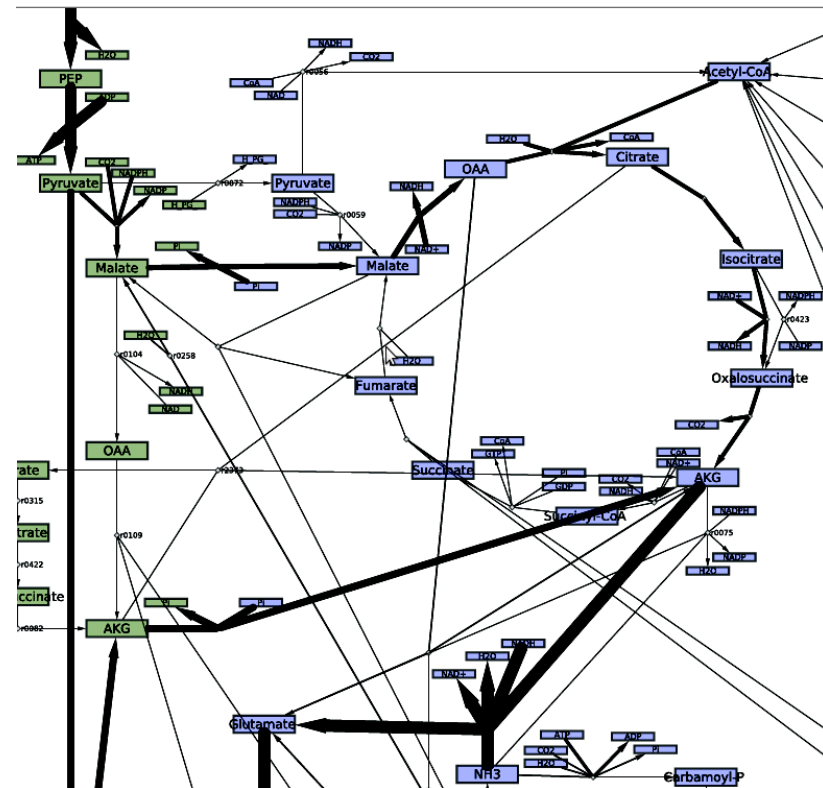
WORKFLOW



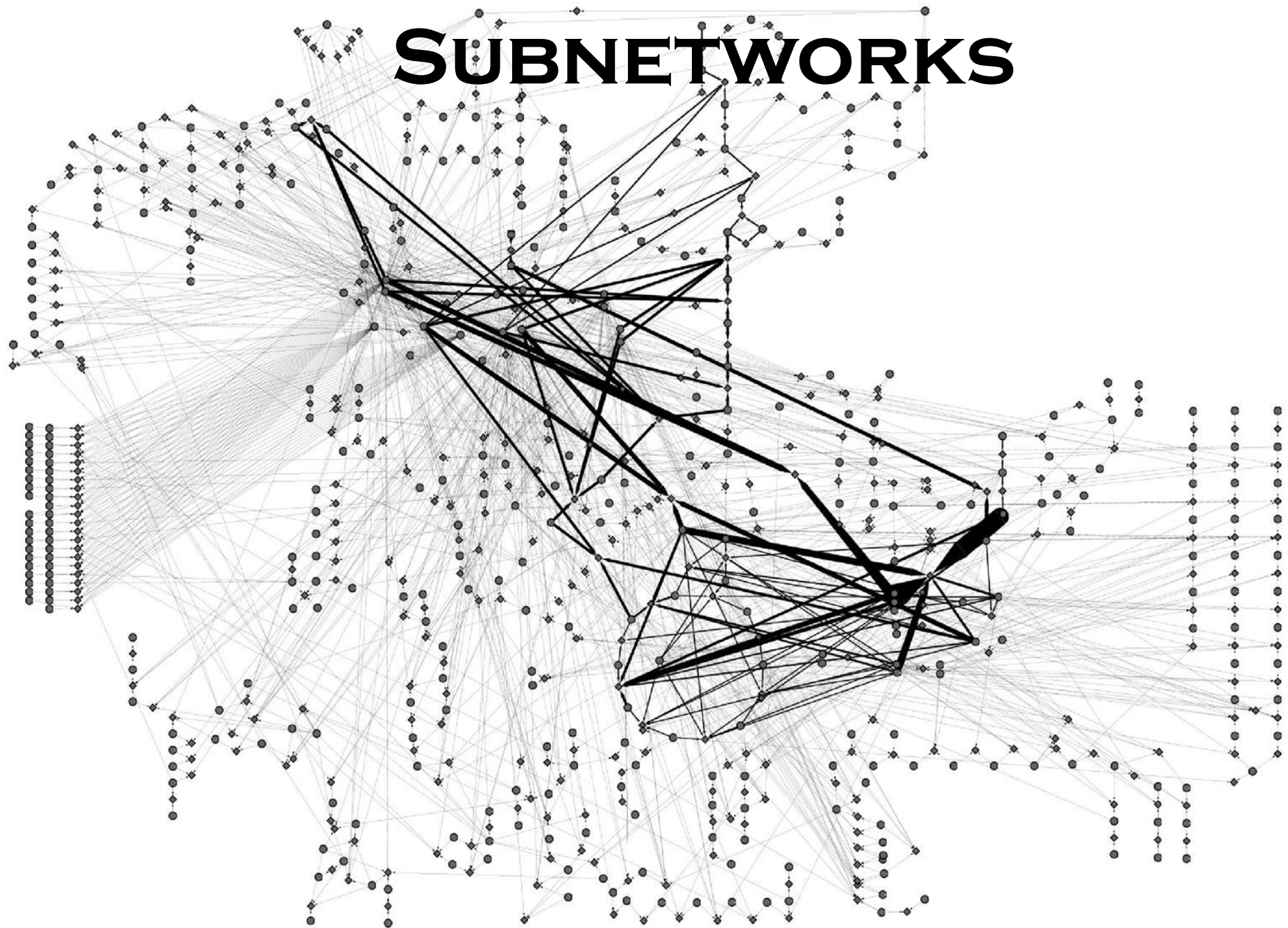
```

<species id="ID_15045_cytosol" name="6-phospho-D-gluconic acid_cytosol"
<species id="ID_15046_cytosol" name="D-ribulose 5-phosphate_cytosol" c

<species id="ID_14103_cytosol" name="D-fructose 6-phosphate [Fru6P]_cy
<species id="ID_14102_cytosol" name="D-glucose 6-phosphate [Glu6P]_cyt
</listOfSpecies>
<listOfReactions>
<reaction id="ID_19899_plasma_membrane" name="GLUT2 [GLUT2]_plasma_mem
<listOfReactants>
<speciesReference species="ID_14148_blood_circulation" stoichiomet
</listOfReactants>
<listOfProducts>
<speciesReference species="ID_14148_cytosol" stoichiometry="1"/>
</listOfProducts>
</reaction>
<reaction id="ID_21210_mito
<listOfReactants>
<speciesReference speci
17257_mitochondrial_matrix -0.033333
<speciesReference speci
17609_cytosol 0.268333
<speciesReference speci
17617_mitochondrial_matrix 0.033333
<speciesReference speci
17645_cytosol 0.268333
</listOfReactants>
17711_mitochondrial_matrix -0.033333
17725_cytosol 0.033333
17725_mitochondrial_matrix -0.033333
17905_cytosol 0.268333
17925_cytosol -0.536667
17950_cytosol -0.536667
</listOfProducts>
18170_cytosol -0.033333
18170_mitochondrial_matrix 0.066667
18274_mitochondrial_matrix -0.033333
18349_cytosol 0.536667
18374_cytosol 0.536667
18688_cytosol 0.268333
18806_cytosol -0.268333
18966_mitochondrial_matrix 0.033333
19002_cytosol -0.503333
19054_cytosol -0.536667
</listOfReactants>
<speciesReference speci
18349_cytosol 0.536667
18374_cytosol 0.536667
18688_cytosol 0.268333
18806_cytosol -0.268333
18966_mitochondrial_matrix 0.033333
19002_cytosol -0.503333
19054_cytosol -0.536667
</listOfProducts>
<speciesReference speci
18349_cytosol 0.536667
18374_cytosol 0.536667
18688_cytosol 0.268333
18806_cytosol -0.268333
18966_mitochondrial_matrix 0.033333
19002_cytosol -0.503333
19054_cytosol -0.536667
</listOfProducts>
</reaction>
  
```

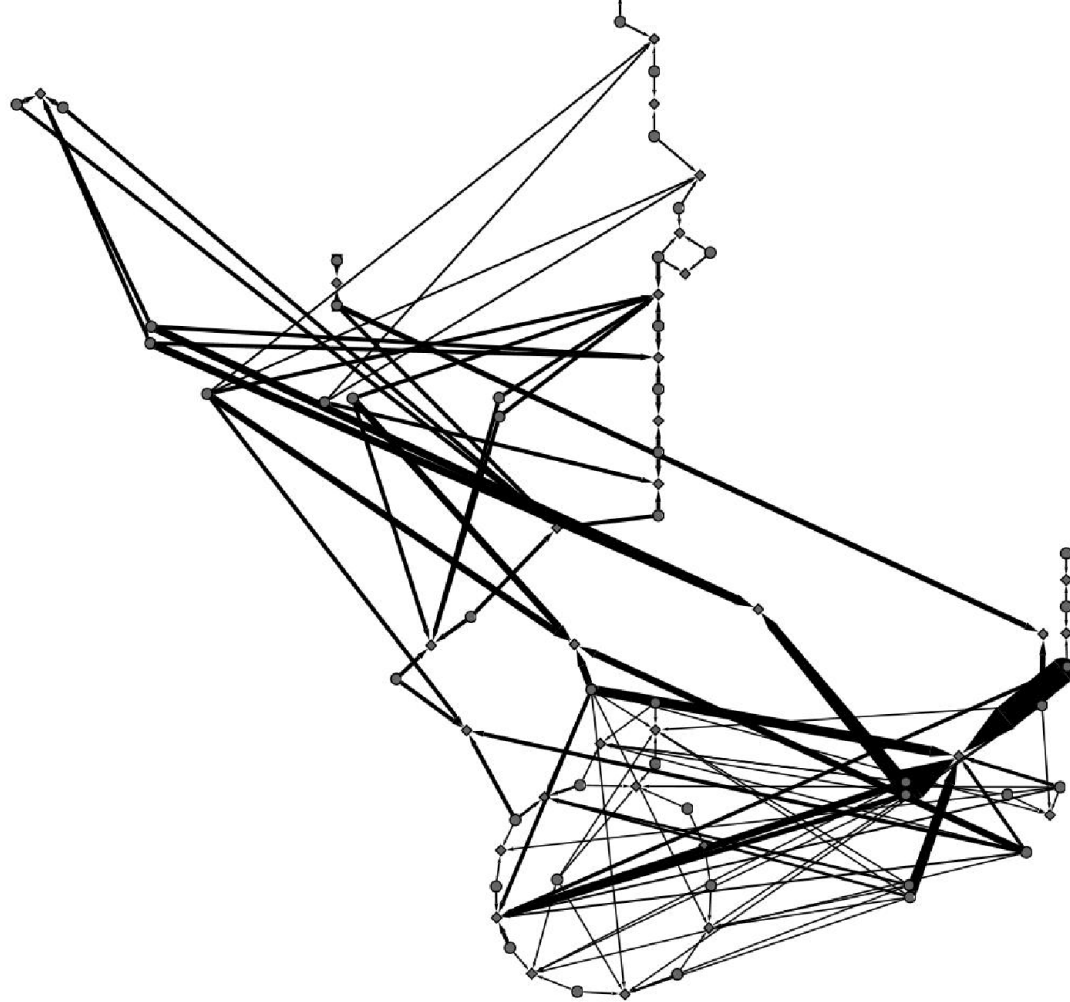


SUBNETWORKS

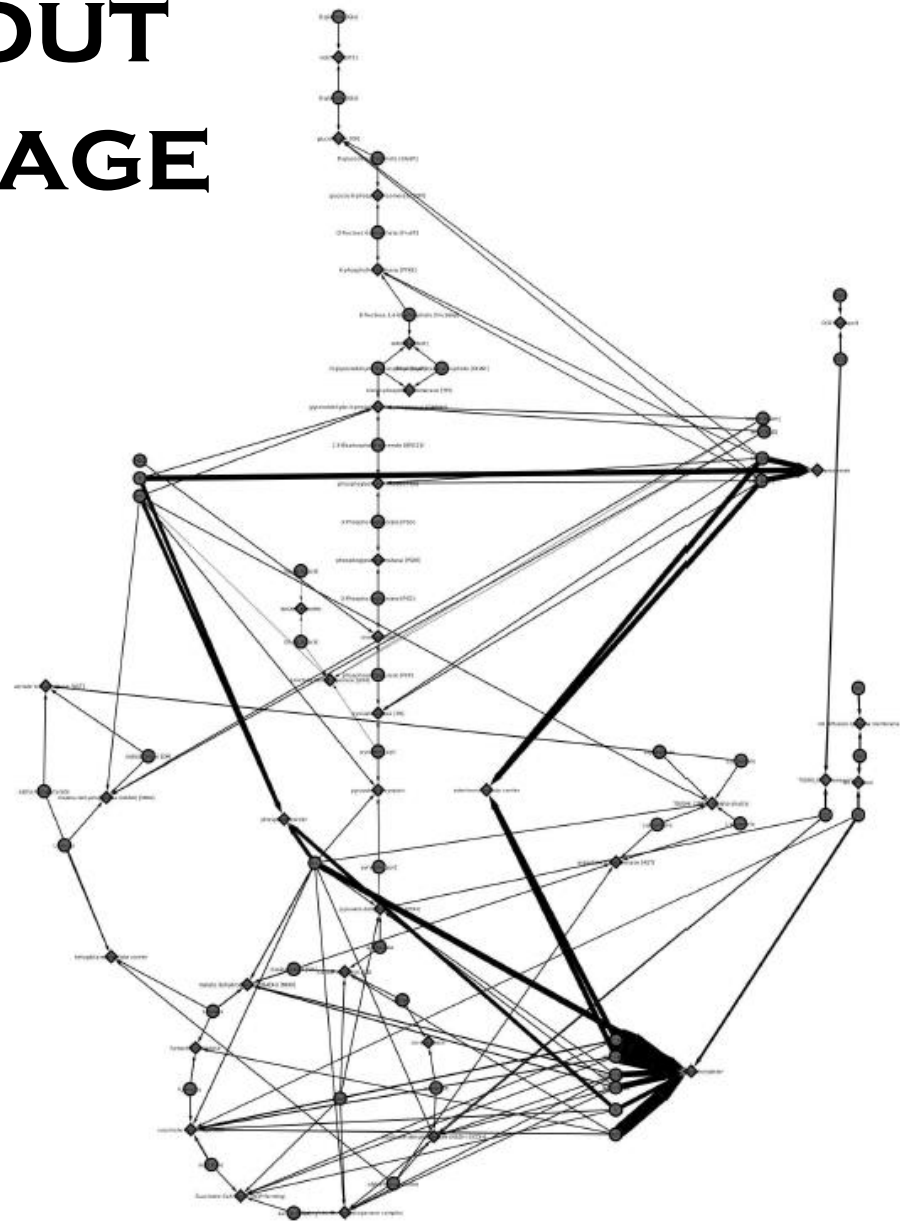
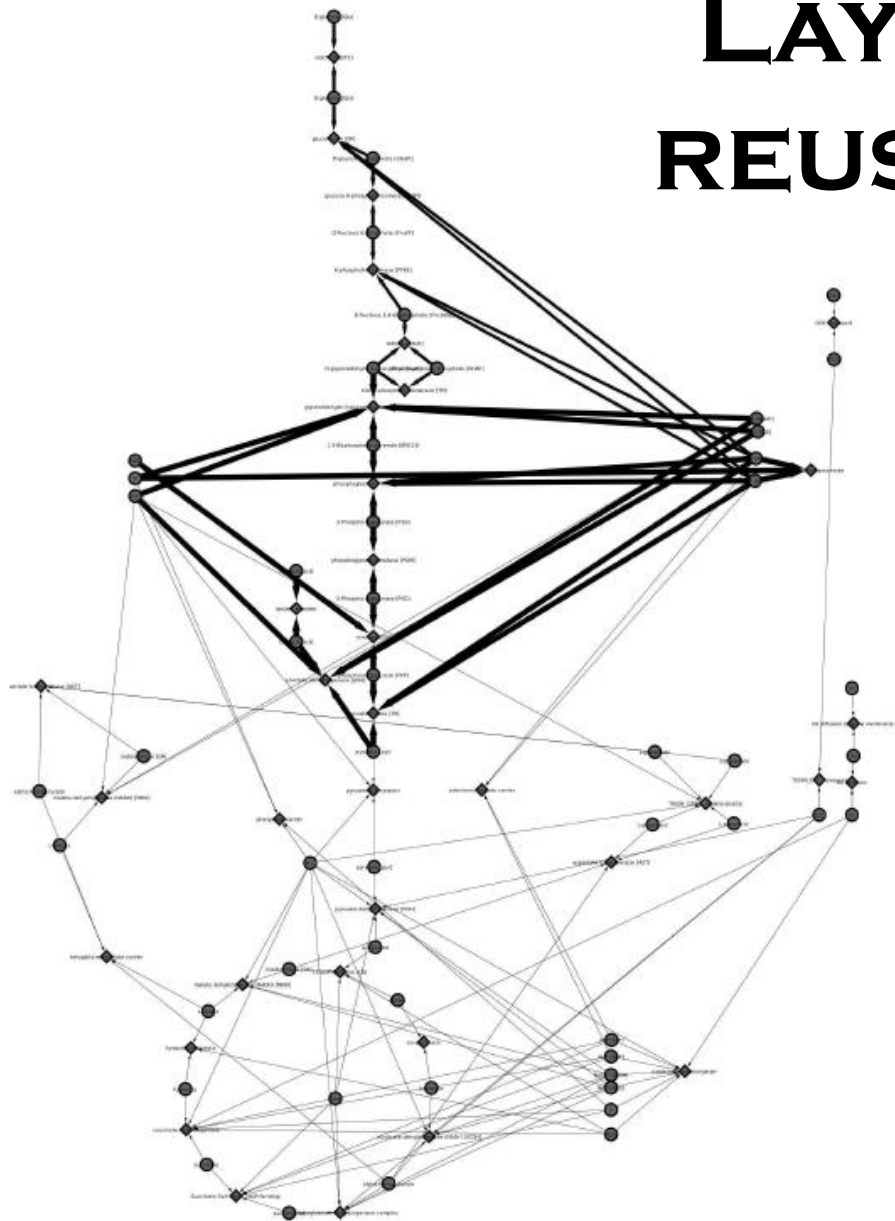


SUBNETWORKS

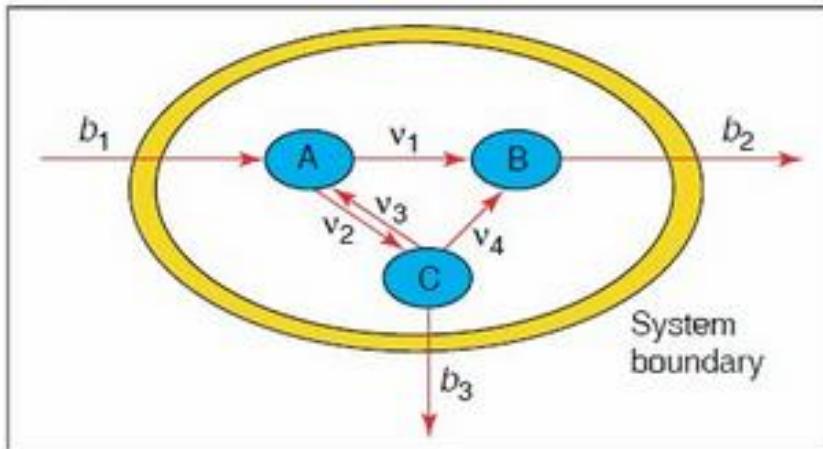
- Arbitrary attributes (flux, localisation)
- Combination criteria



LAYOUT REUSAGE

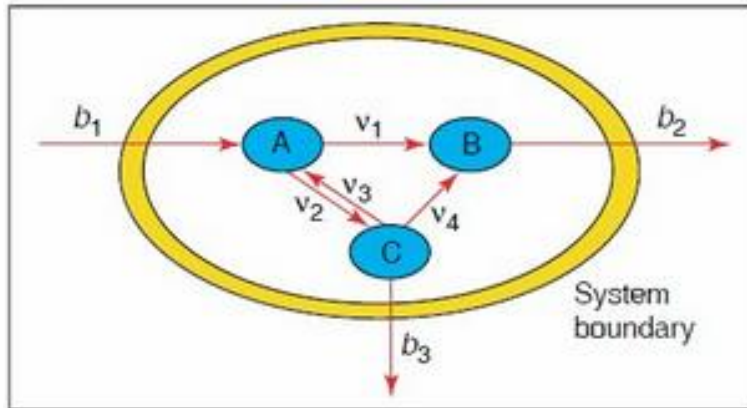


SMALL DEMO NETWORK



```
<listOfCompartments>
  <compartment id="outside" name="Outer Compartment"/>
  <compartment id="inside" name="Inner Compartment"/>
</listOfCompartments>
<listOfSpecies>
  <species id="A_in" name="A_in" compartment="inside"/>
  <species id="B_in" name="B_in" compartment="inside"/>
  <species id="C_in" name="C_in" compartment="inside"/>
  <species id="A_out" name="A_out" compartment="inside"/>
  <species id="B_out" name="B_out" compartment="inside"/>
  <species id="C_out" name="C_out" compartment="inside"/>
</listOfSpecies>
<listOfReactions>
  <reaction id="b1" reversible="false">
    <listOfReactants>
      <speciesReference species="A_out" sboTerm="SBO:0000015"/>
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="A_in" sboTerm="SBO:0000011"/>
    </listOfProducts>
  </reaction>
  <reaction id="b2" reversible="false">
    <listOfReactants>
      <speciesReference species="B_in" sboTerm="SBO:0000015"/>
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="B_out" sboTerm="SBO:0000011"/>
    </listOfProducts>
  </reaction>
  <reaction id="b3" reversible="false">
    <listOfReactants>
      <speciesReference species="C_in" sboTerm="SBO:0000015"/>
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="C_out" sboTerm="SBO:0000011"/>
    </listOfProducts>
  </reaction>
  <reaction id="v1">
    <listOfReactants>
      <speciesReference species="A_in" sboTerm="SBO:0000015"/>
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="B_in" sboTerm="SBO:0000011"/>
    </listOfProducts>
  </reaction>
```

DEMO FBA



SBML Toolbox

reading/writing of SBML models

COBRA Toolbox

constraint-based models in Matlab

Solver for linear programming, mixed integer programming & quadratic programming

GUROBI (free academic license)

CyFluxViz Toolbox

COBRA solutions -> CyFluxViz

```
% read SBML model with default bounds
modelSBML = TranslateSBML('Koenig2012_demo.xml');
defaultBound = 10.0;
[model] = convertSBMLToCobra(modelSBML, defaultBound);

% alter/set reaction bounds (constraints)
% model = changeRxnBounds(model, rxnNameList, boundValue, boundType)
% u - upper, l - lower, b - both
model = changeRxnBounds(model, {'b1', 'b2'}, [1.0, 1.0], {'u', 'u'});

% set objective function
% Maximize the B output
model = changeObjective(model, {'b2'}, [1.0]);

% Add the exchange reactions to the example (otherwise no exchange
% possible -> unbalanced metabolites)
% addExchangeRxn(model,metList,lb,ub)
ex_mets = {'A_out', 'B_out', 'C_out'};
Nex = numel(ex_mets);
lb_ex = -inf*ones(1,Nex);
ub_ex = inf*ones(1, Nex);
model = addExchangeRxn(model, ex_mets, lb_ex, ub_ex);

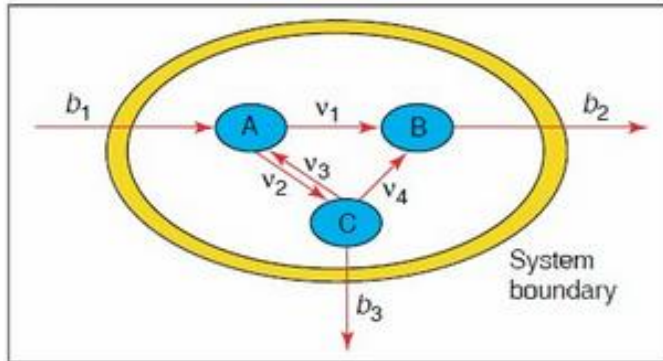
% model overview
cobraModelOverview(model)

% Flux minimization based on Taxicab norm
% 'one' Minimise the Taxicab Norm using LP.
%
% min |v|
% s.t. S*v = b
% c'*v = f
% lb <= v <= ub

sol = optimizeCbModel(model, 'max', 'one')
printFluxVector(model, sol.x, true, false)

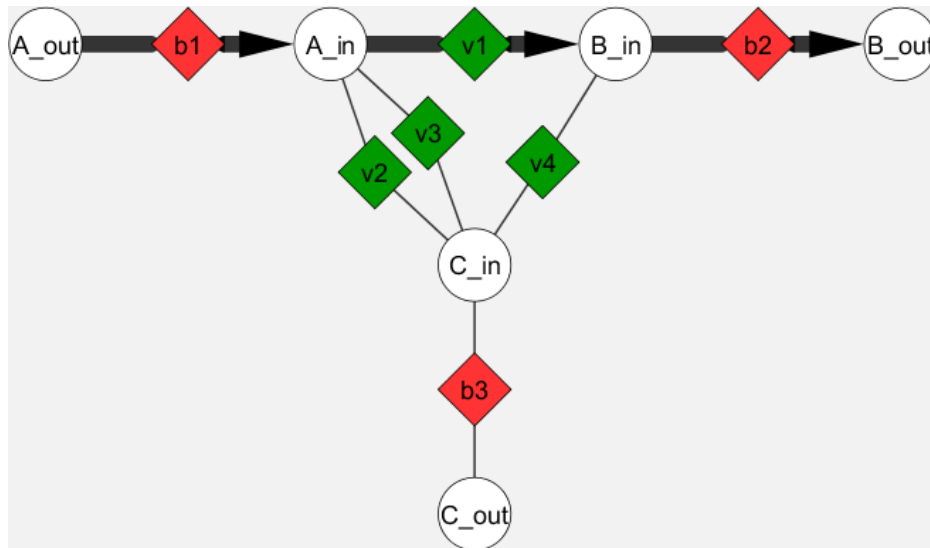
% Generate the output files
simIds{1} = 'FBA_test'
solutions{1} = sol.x;
fluxdata = cobra2fluxdata(modelSBML.id, model, simIds, solutions);
fluxdata2XML(fluxdata, './xml_fluxes/Koenig2012_demo_COBRA_simple.xml')
```


RESULT FBA



```

b1 (A_out -> A_in ) 0 [ 0.0 <-> 1.0] 0.0 ( )
b2 (B_in -> B_out ) 0 [ 0.0 <-> 1.0] 1.0 ( )
b3 (C_in -> C_out ) 0 [ 0.0 <-> 10.0] 0.0 ( )
v1 (A_in <=> B_in ) 1 [-10.0 <-> 10.0] 0.0 ( )
v2 (A_in <=> C_in ) 1 [-10.0 <-> 10.0] 0.0 ( )
v3 (C_in <=> A_in ) 1 [-10.0 <-> 10.0] 0.0 ( )
v4 (C_in <=> B_in ) 1 [-10.0 <-> 10.0] 0.0 ( )
Ex_A_out (A_out <=> ) 1 [-Inf <-> Inf] 0.0 (Ex_A_out)
Ex_B_out (B_out <=> ) 1 [-Inf <-> Inf] 0.0 (Ex_B_out)
Ex_C_out (C_out <=> ) 1 [-Inf <-> Inf] 0.0 (Ex_C_out)
  
```

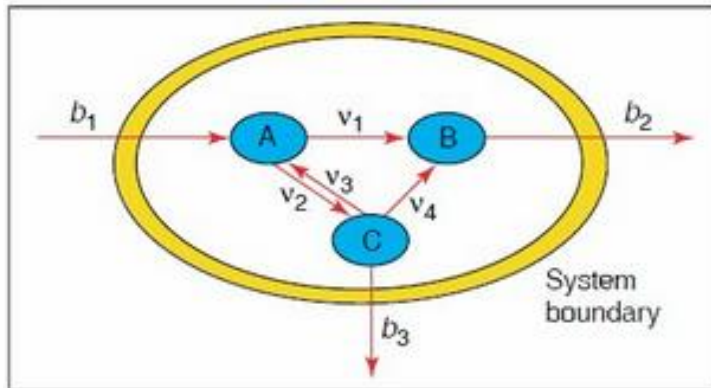


```

sol =
    x: [10x1 double]
    f: 1
    stat: 1
    origStat: -99
    solver: 'gurobi5'
    time: 0.0370

b1  1
b2  1
v1  1
Ex_A_out  -1
Ex_B_out   1
simIds =
  
```

DEMO KINETIC



CyFluxViz Toolbox

Kinetic solutions -> CyFluxViz

```

% Integration
tspan = [0:1:20]; % [sec]
[t,c] = ode15s(@(t,y) Koenig2012_demo_dxdt(t, y), tspan, S0, odeset('RelTol', 1e-6));

% Calculate fluxes
[~, vtmp] = Koenig2012_demo_dxdt(0, S0);
Nv = numel(vtmp);
Nt = numel(t);
v = zeros(Nt, Nv);
for k=1:Nt
    [~, v(k, :)] = Koenig2012_demo_dxdt(t(k), c(k, :));
end
  
```

```

% b1 : A import
Km_A = 1.0; % mM
Vmax_b1 = 5.0; % mM/s
b1 = Vmax_b1/Km_A * (A_out - A_in)/(1 + A_out/Km_A + A_in/Km_A);

% b2 : B export
Km_B = 0.5; % mM
Vmax_b2 = 2.0; % mM/s
b2 = Vmax_b2/Km_B * (B_in - B_out)/(1 + B_out/Km_B + B_in/Km_B);

% b3 : C export
Km_C = 3.0; % mM
Vmax_b3 = 2.0; % mM/s
b3 = Vmax_b3/Km_C * (C_in - C_out)/(1 + C_out/Km_C + C_in/Km_C);

% v1 : C (A_in -> B_in)
Vmax_v1 = 1.0; % [mM/s]
Keq_v1 = 10.0; % []
v1 = Vmax_v1*(A_in - 1/Keq_v1*B_in);

% v2 : C (A_in -> C_in)
Vmax_v2 = 0.5; % [1/s]
v2 = Vmax_v2*A_in;

% v3 : C (C_in -> A_in)
Vmax_v3 = 0.1; % [1/s]
v3 = Vmax_v3*C_in;

% v4 : C (C_in -> B_in)
Vmax_v4 = 0.5; % [mM/s]
Keq_v4 = 2.0; % []
v4 = Vmax_v4*(C_in - 1/Keq_v4*B_in);
  
```

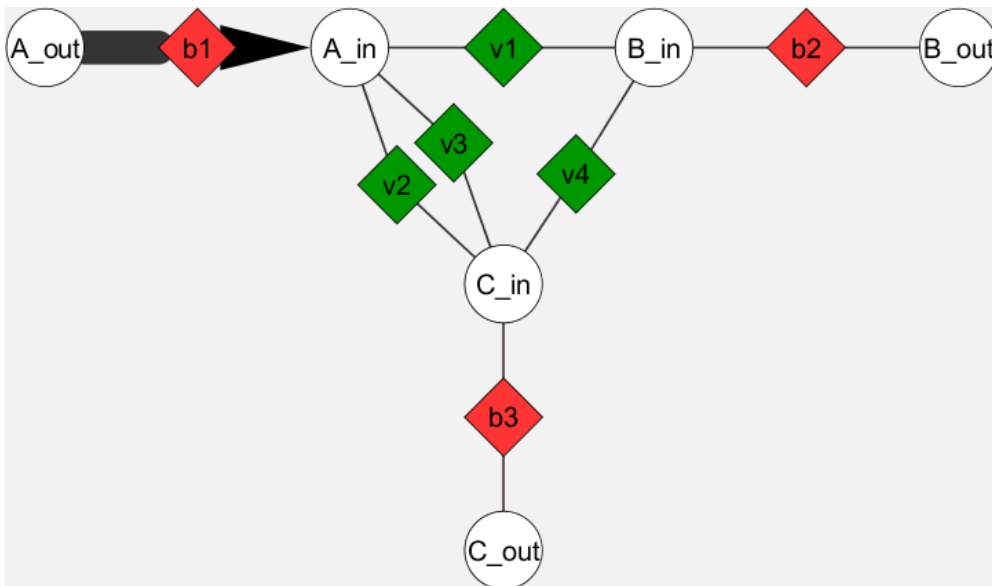
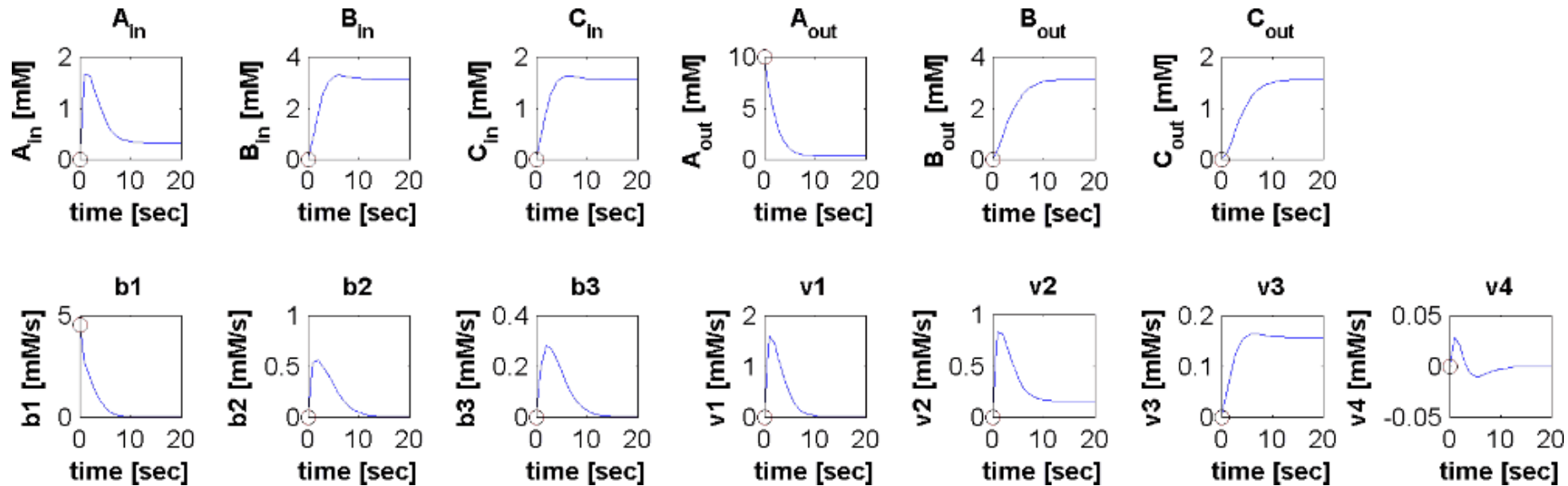
```

% Species and reaction ids
speciesNames = {'A_{in}', 'B_{in}', 'C_{in}', 'A_{out}', 'B_{out}', 'C_{out}'};
speciesIds = {'A_in', 'B_in', 'C_in', 'A_out', 'B_out', 'C_out'};
reactionIds = {'b1', 'b2', 'b3', 'v1', 'v2', 'v3', 'v4'};

% Generate the fluxdata (fluxes & concentrations) for CyFluxViz
fluxdata = kinetic2fluxdata(modelSBML.id, speciesIds, reactionIds, t, c, v);

% Generate the output files
fluxdata2XML(fluxdata, './Koenig2013_demo_Fluxes.xml')
  
```


RESULT KINETIC

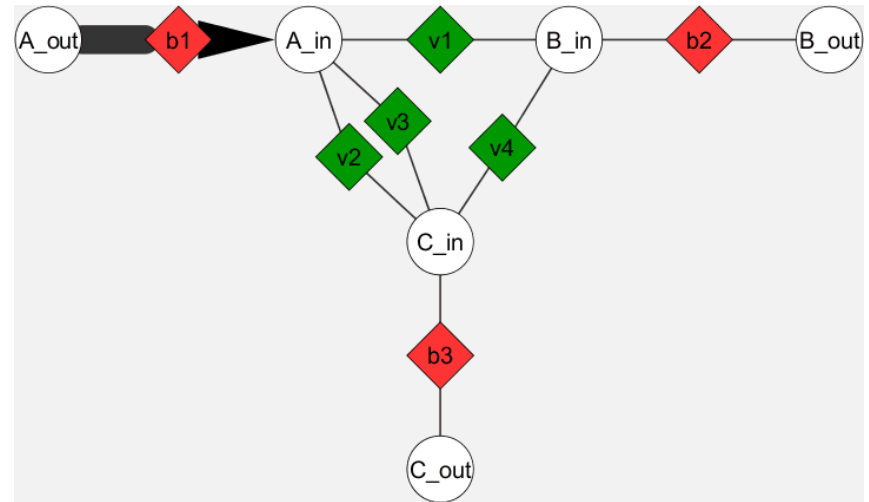


Independent of Simulation Software

- only mapping between SBML species/reaction ids \leftrightarrow numerical values needed
- simple integration into existing workflows

OUTLOOK

- full **support of kinetic simulations** (dynamic visualization with node size changes)
- socket communication
 - **on the fly update** of visualization
- Java & Python exporter
 - easy generation of CyFluxViz files (SBMLSimulator?, Copasi, ...?)
- Cy3 support
- Support FBC package ?



THANKS



- **Andreas Dräger & Prof. Holzhütter**
- **Camille Laibe** (BioModel WebServices) for implementing additional BioModel WebService functionality
- Qual Team and **Finja Büchel, Florian Mittag, and Nicolas Rodriguez** (Qual implementation in JSBML)
- **Sebastian Fröhlich** and **Clemens Wrzodek** (Layout support in JSBML)

Funding: Virtual Liver Network
[grant numbers 0315756 and 0315741].



CYFLUXVIZ FORMAT

```
<?xml version="1.0" encoding="utf-8"?>
<fluxDistributionCollection>
  <listOfFluxDistributions>
    <fluxDistribution id="001_kin_t-0.0" name="001_kin_t-0.0" networkId="Koenig2013_demo" time="0">
      <listOfFluxes>
        <flux fluxValue="4.5455" id="b1" type="nodeFlux"/>
      </listOfFluxes>
      <listOfConcentrations>
        <concentration concentrationValue="0" id="A_in" type="nodeConcentration"/>
        <concentration concentrationValue="0" id="B_in" type="nodeConcentration"/>
        <concentration concentrationValue="0" id="C_in" type="nodeConcentration"/>
        <concentration concentrationValue="10" id="A_out" type="nodeConcentration"/>
        <concentration concentrationValue="0" id="B_out" type="nodeConcentration"/>
        <concentration concentrationValue="0" id="C_out" type="nodeConcentration"/>
      </listOfConcentrations>
    </fluxDistribution>
    <fluxDistribution id="002_kin_t-1.0" name="002_kin_t-1.0" networkId="Koenig2013_demo" time="1">
      <listOfFluxes>
        <flux fluxValue="2.6658" id="b1" type="nodeFlux"/>
        <flux fluxValue="0.54123" id="b2" type="nodeFlux"/>
        <flux fluxValue="0.20157" id="b3" type="nodeFlux"/>
        <flux fluxValue="1.5928" id="v1" type="nodeFlux"/>
        <flux fluxValue="0.83613" id="v2" type="nodeFlux"/>
        <flux fluxValue="0.045324" id="v3" type="nodeFlux"/>
        <flux fluxValue="0.027876" id="v4" type="nodeFlux"/>
      </listOfFluxes>
      <listOfConcentrations>
        <concentration concentrationValue="1.6723" id="A_in" type="nodeConcentration"/>
        <concentration concentrationValue="0.79499" id="B_in" type="nodeConcentration"/>
        <concentration concentrationValue="0.45324" id="C_in" type="nodeConcentration"/>
        <concentration concentrationValue="6.6341" id="A_out" type="nodeConcentration"/>
        <concentration concentrationValue="0.34986" id="B_out" type="nodeConcentration"/>
        <concentration concentrationValue="0.095584" id="C_out" type="nodeConcentration"/>
      </listOfConcentrations>
    </fluxDistribution>
  </listOfFluxDistributions>
</fluxDistributionCollection>
```

USAGE CASE

HepatoNet1:

A comprehensive metabolic network of the human hepatocyte suited for the computational analysis of physiological liver functions, MSB (2010)

