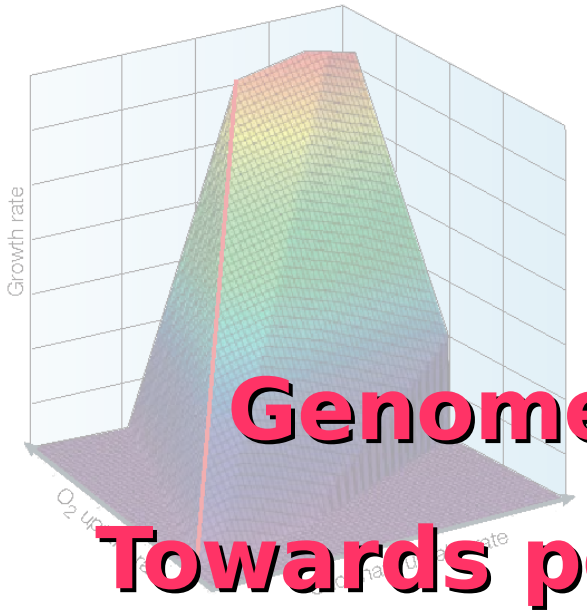

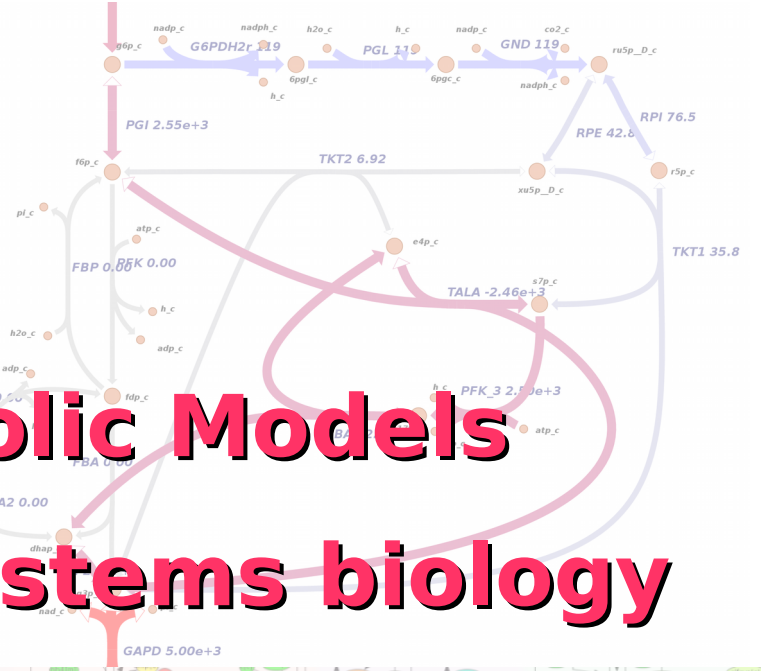

Genome-Scale Metabolic Models

Towards personalised systems biology

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              <ci> A </ci>
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        </kineticLaw>
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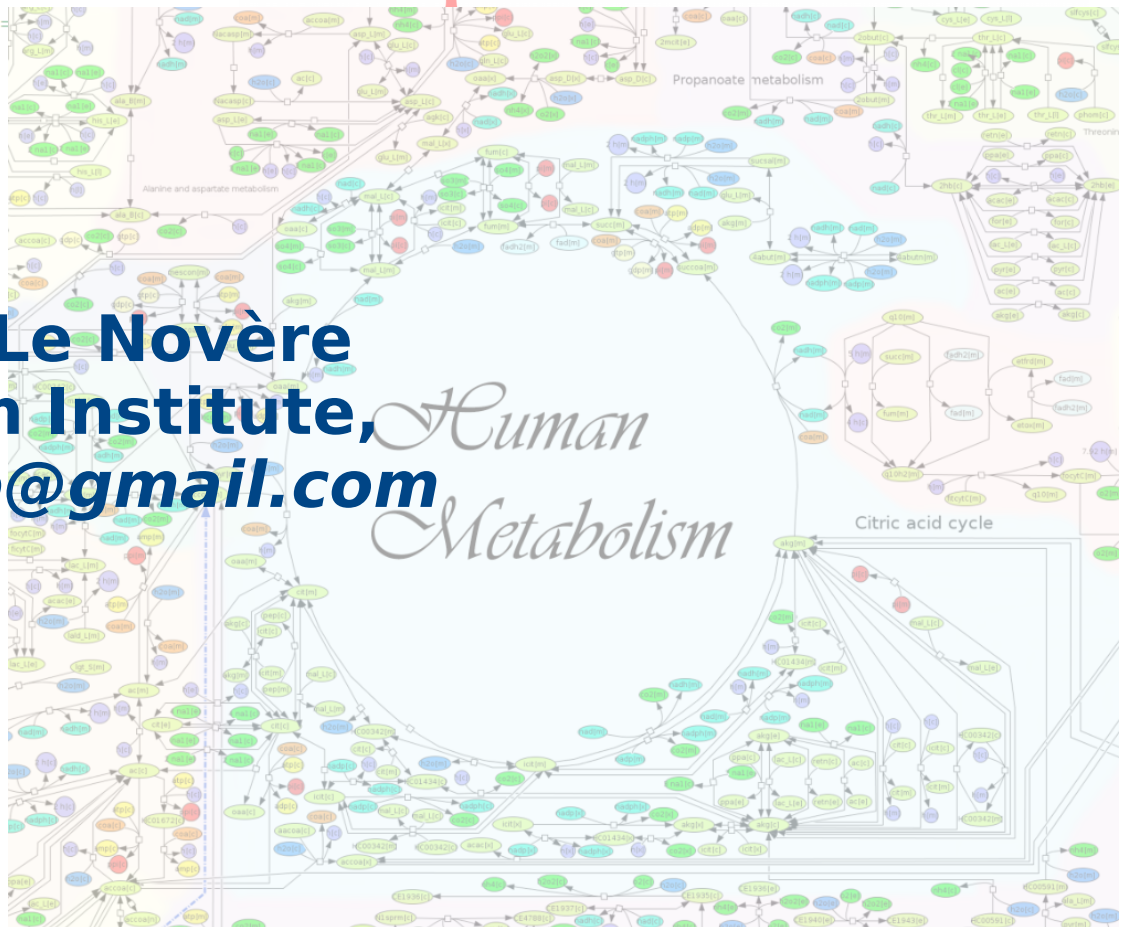
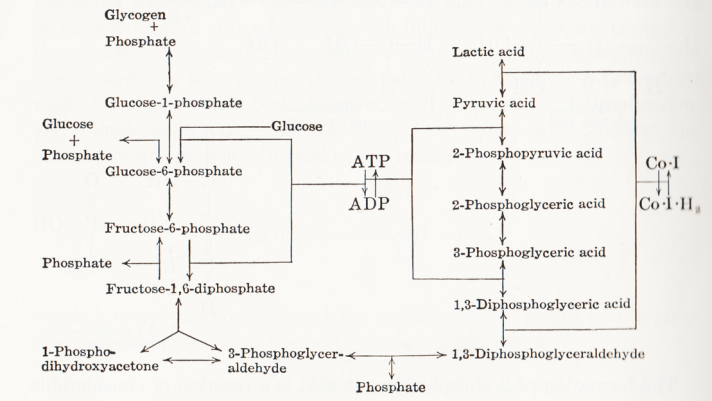
    </listOfReactions>
  </model>
</sbml>
```

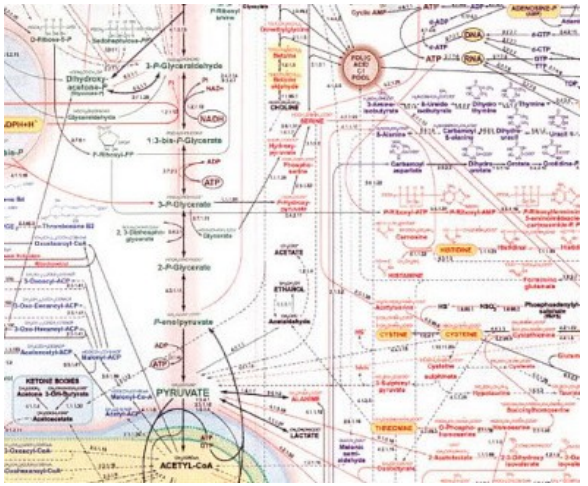
Nicolas Le Novère
Babraham Institute,
n.lenovere@gmail.com



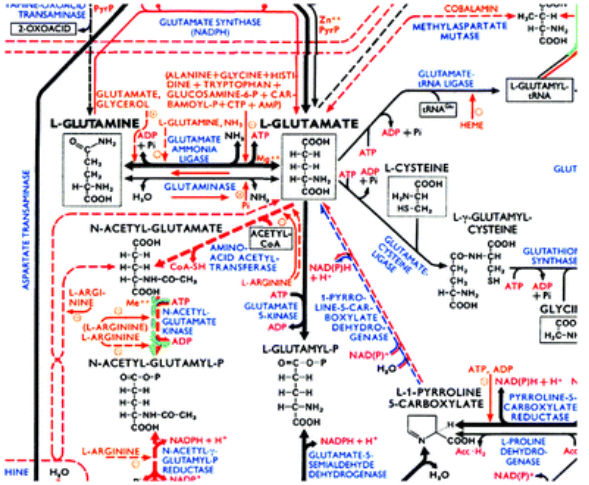
Gortner (1949)



Nicholson (1970)



Michal (1984)



“Hand drawing” on paper

⟶ no software-based browsing, processing and analysis

⟶ no validation of mass-balance, charge balance

⟶ no verification that pathways can actually carry fluxes

J. theor. Biol. (1989) **141,** 515–528

Metabolic Dynamics in the Human Red Cell. Part I—A Comprehensive Kinetic Model

ABHAY JOSHI† AND BERNHARD O. PALSSON‡

Department of Chemical Engineering, The University of Michigan, Ann Arbor, MI 48109-2136, *U.S.A.*

(*Received* 7 *March* 1989, *and accepted in revised form* 19 *May* 1989)

First attempt at a Comprehensive model of metabolism

J. theor. Biol. (1992) **154,** 421–454

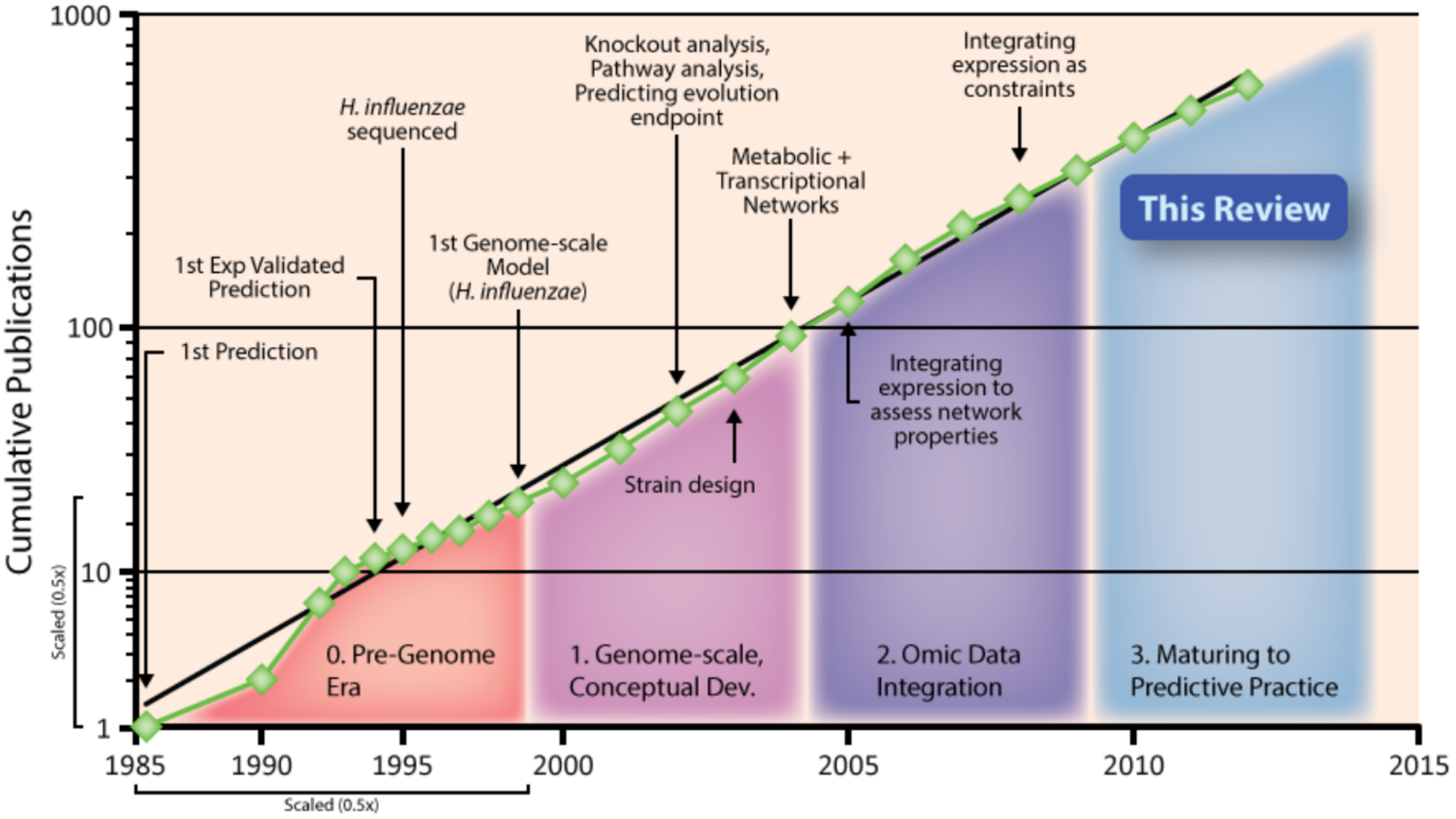
Network Analysis of Intermediary Metabolism using Linear Optimization. I. Development of Mathematical Formalism

JOANNE M. SAVINELL† AND BERNHARD O. PALSSON‡

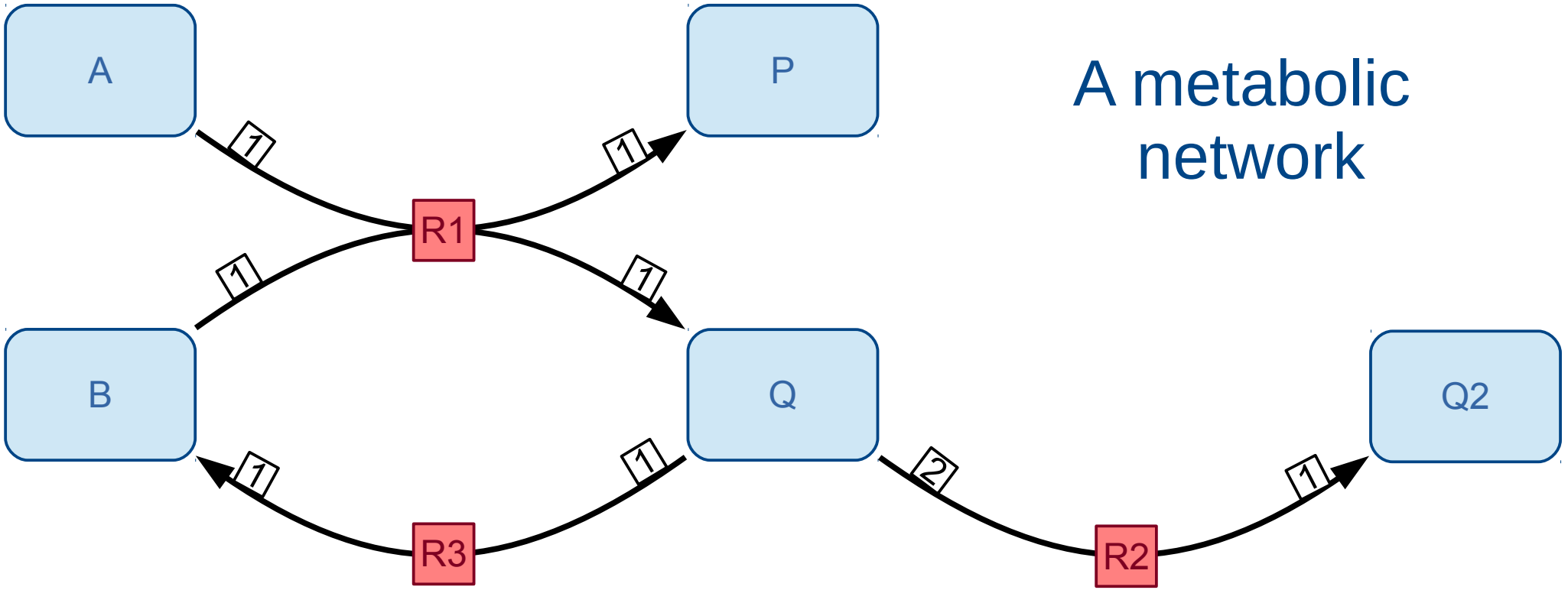
Department of Chemical Engineering, The University of Michigan, Ann Arbor, MI 48109-2136, *U.S.A.*

(*Received on* 12 *November* 1990, *Accepted on* 13 *September* 1991)

Development of constraint-based modeling

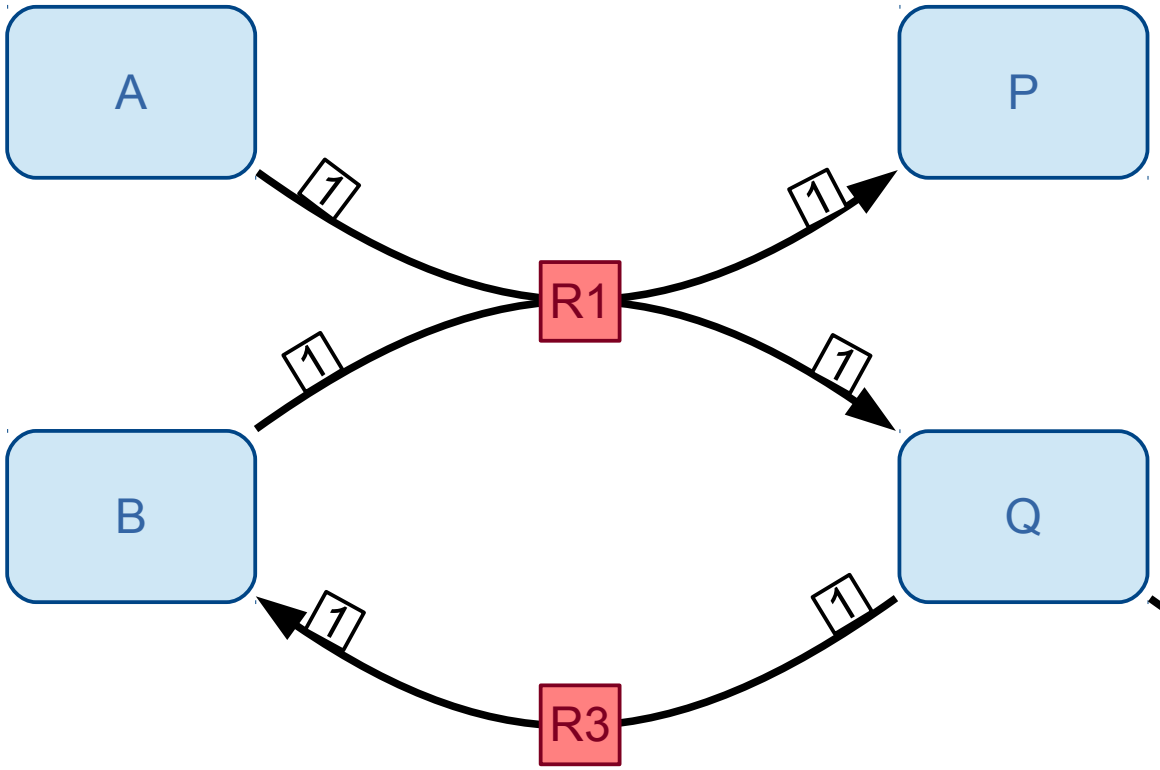


Bordbar et al (2014) *Nat Rev Genet* 15: 107-120
http://systemsbiology.ucsd.edu/cobra-predictions



A metabolic network

$$
\begin{aligned}
\dot{A} &= -1 \times V_1 \\
\dot{B} &= -1 \times V_1 + 1 \times V_3 \\
\dot{P} &= +1 \times V_1 \\
\dot{Q} &= +1 \times V_1 - 2 \times V_2 - 1 \times V_3 \\
\dot{Q2} &= +1 \times V_2
\end{aligned}
$$



A metabolic network

$$
\begin{aligned}
\dot{A} &= \begin{bmatrix} -1 \times V_1 & & +1 \times V_3 \end{bmatrix} \\
\dot{B} &= \begin{bmatrix} -1 \times V_1 & & +1 \times V_3 \end{bmatrix} \\
\dot{P} &= \begin{bmatrix} +1 \times V_1 & & \end{bmatrix} \\
\dot{Q} &= \begin{bmatrix} +1 \times V_1 & -2 \times V_2 & -1 \times V_3 \end{bmatrix} \\
\dot{Q}2 &= \begin{bmatrix} & +1 \times V_2 & \end{bmatrix}
\end{aligned}
$$

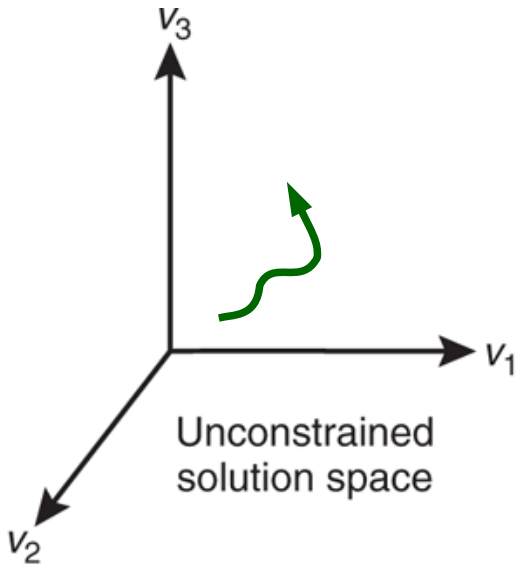
Stoichiometry matrix

	R1	R2	R3
A	-1	0	0
B	-1	0	1
P	1	0	0
Q	1	-2	-1
Q2	0	1	0

S	Reaction 1	Reaction 2	Reaction 3	Reaction 4	....	Reaction n
Metabolite 1	-1	-1	0	0	...	1
Metabolite 2	0	-1	0	-2	...	0
Metabolite 3	-1	1	-1	0	...	0
...	...	...	...	...	...	...
Metabolite m	2	0	1	0	...	0

$$\mathbf{S} \times \mathbf{v} = \dot{\mathbf{x}}$$

$$\begin{pmatrix} \text{Flux 1} \\ \text{Flux 2} \\ \text{Flux 3} \\ \text{Flux 4} \\ \dots \\ \text{Flux n} \end{pmatrix} = \begin{pmatrix} \text{d[M1]/dt} \\ \text{d[M2]/dt} \\ \text{d[M3]/dt} \\ \dots \\ \text{d[Mm]/dt} \end{pmatrix}$$



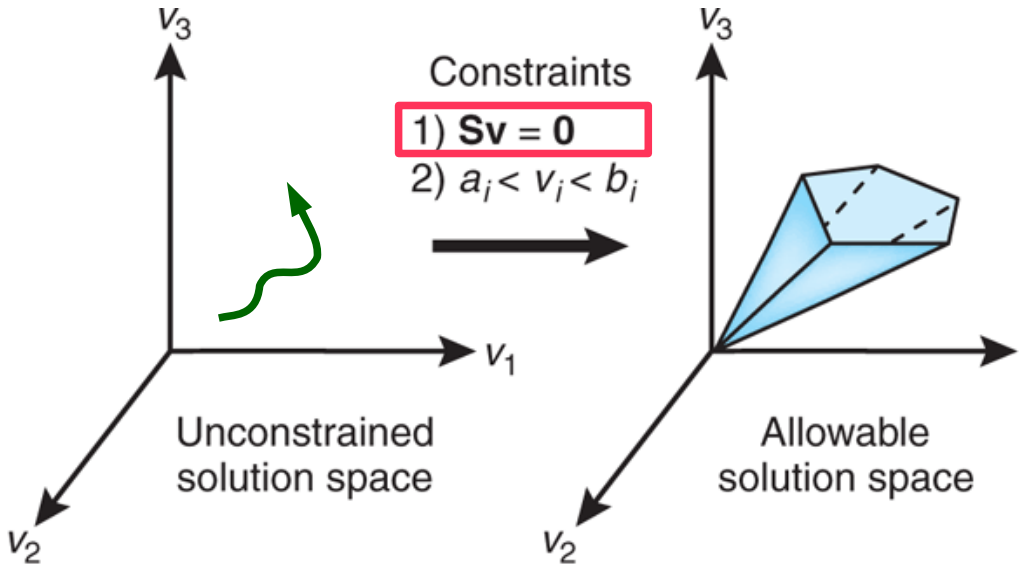
S	Reaction 1	Reaction 2	Reaction 3	Reaction 4	…	Reaction n
Metabolite 1	-1	-1	0	0	...	1
Metabolite 2	0	-1	0	-2	...	0
Metabolite 3	-1	1	-1	0	⋯	0
...	...	...	...	...	...	...
Metabolite m	2	0	1	0	...	0

$$\mathbf{S} \times \mathbf{v} = 0$$

v:
- Flux 1
- Flux 2
- Flux 3
- Flux 4
- ...
- Flux n

Steady-states

More reactions than reactants = underdetermined (more variables than equations)



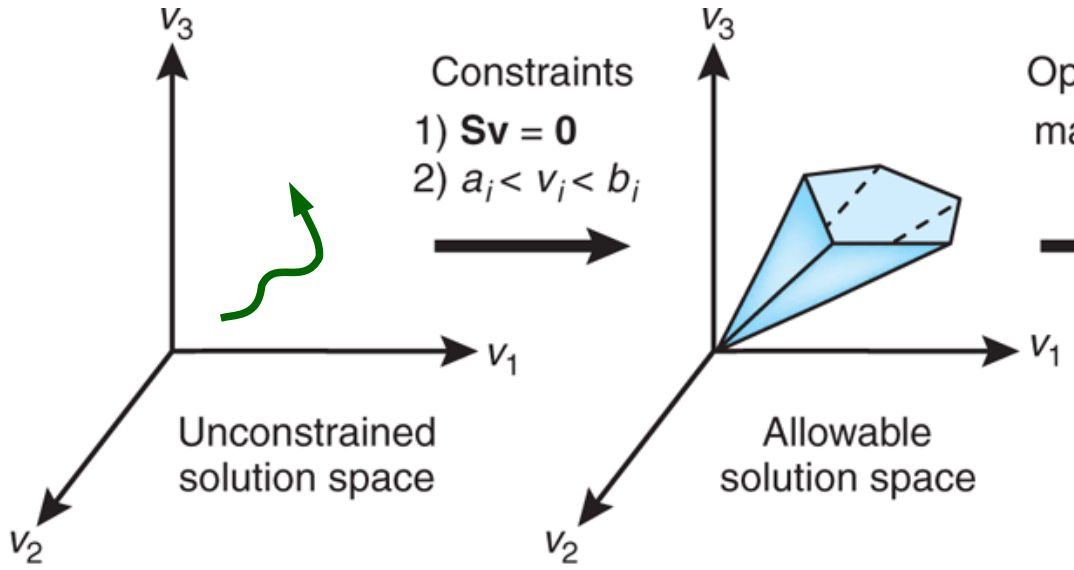
S	Reaction 1	Reaction 2	Reaction 3	Reaction 4	…	Reaction n
Metabolite 1	-1	-1	0	0	...	1
Metabolite 2	0	-1	0	-2	...	0
Metabolite 3	-1	1	-1	0	⋯	0
...	...	...	...	...	...	...
Metabolite m	2	0	1	0	...	0

$$\mathbf{S} \times \mathbf{v} = 0$$

$\mathbf{v}$ = Flux 1, Flux 2, Flux 3, Flux 4, ..., Flux n

Steady-states

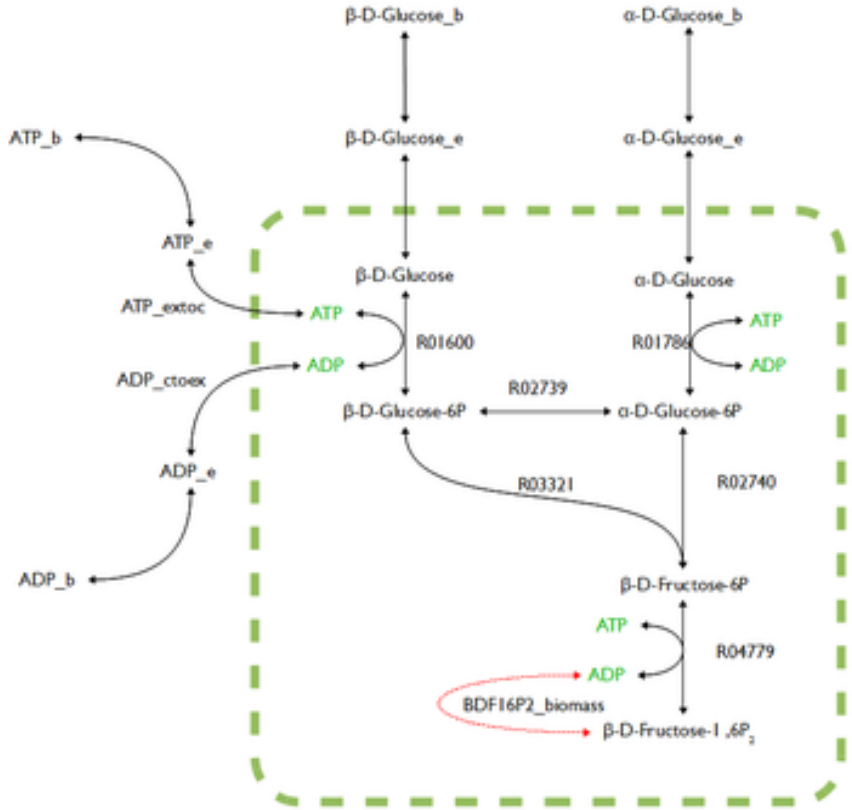
More reactions than reactants = underdetermined (more variables than equations)



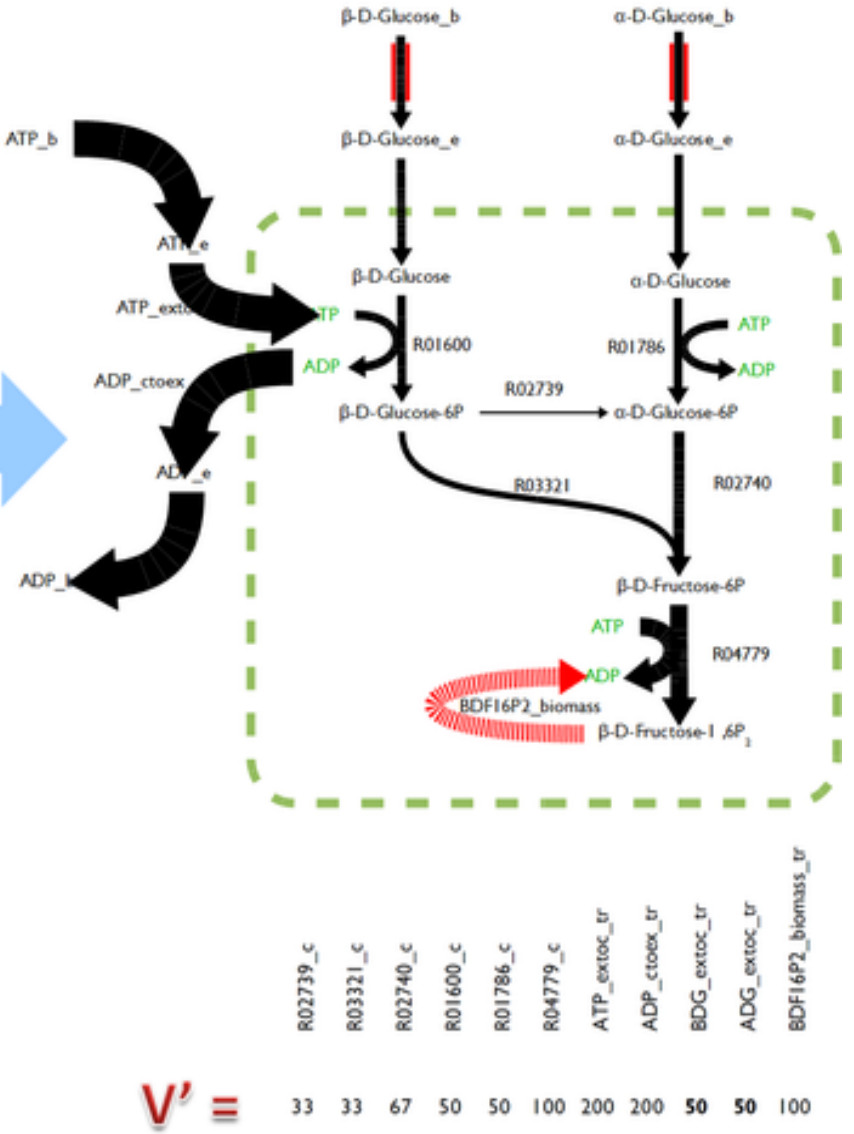
Choose an objective function
(e.g. maximise biomass
ATP production
Cell cycling
Pluripotency?)

Solve using
Linear programming

Application of Flux Balanced Analysis

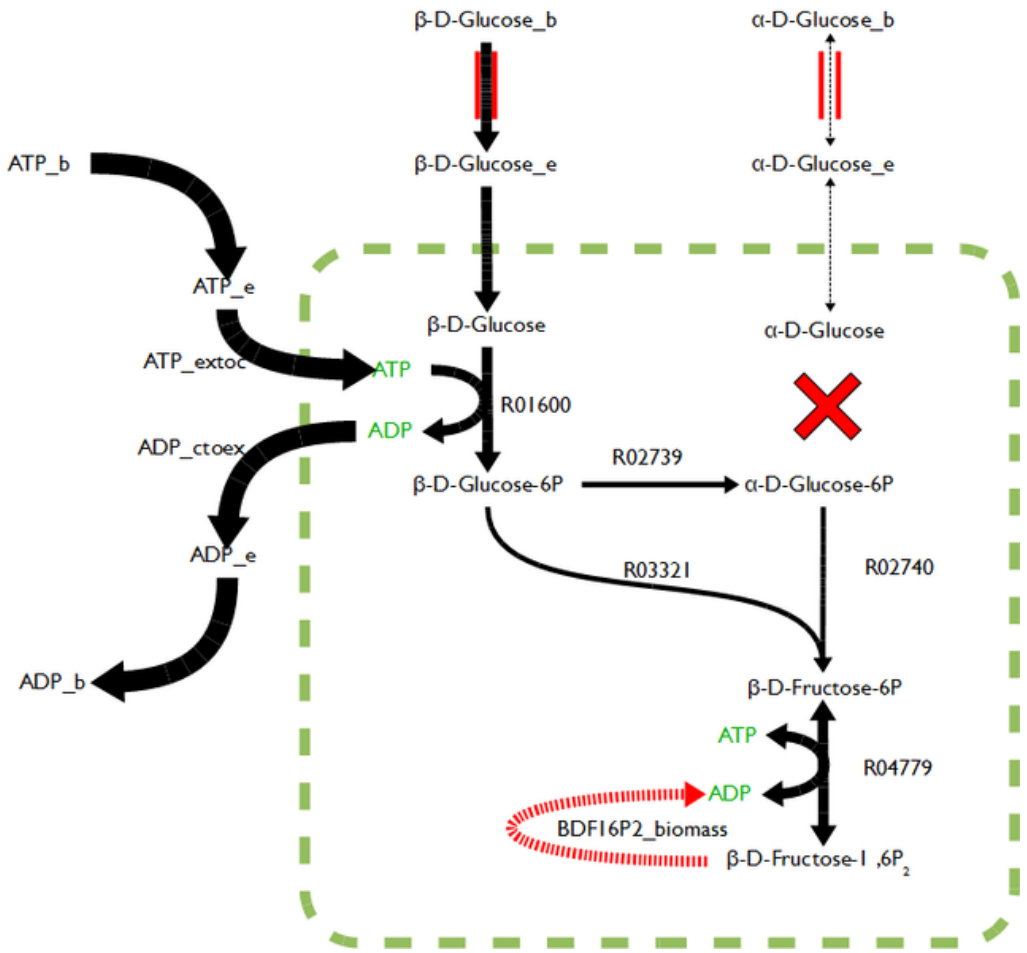


Perform FBA

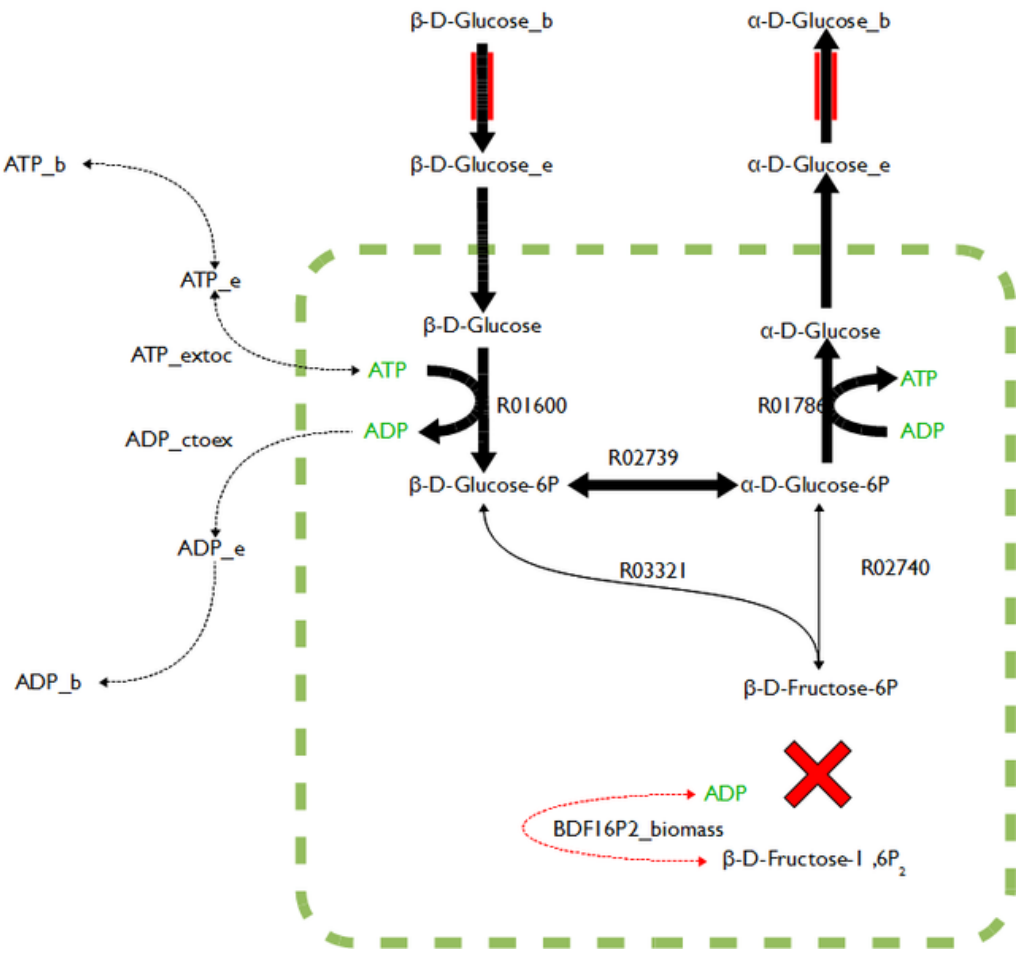


	R02739_c	R03321_c	R02740_c	R01600_c	R01786_c	R04779_c	ATP_extoc_tr	ADP_ctoex_tr	BDG_extoc_tr	ADG_extoc_tr	BDF16P2_biomass_tr
V′ =	33	33	67	50	50	100	200	200	**50**	**50**	100

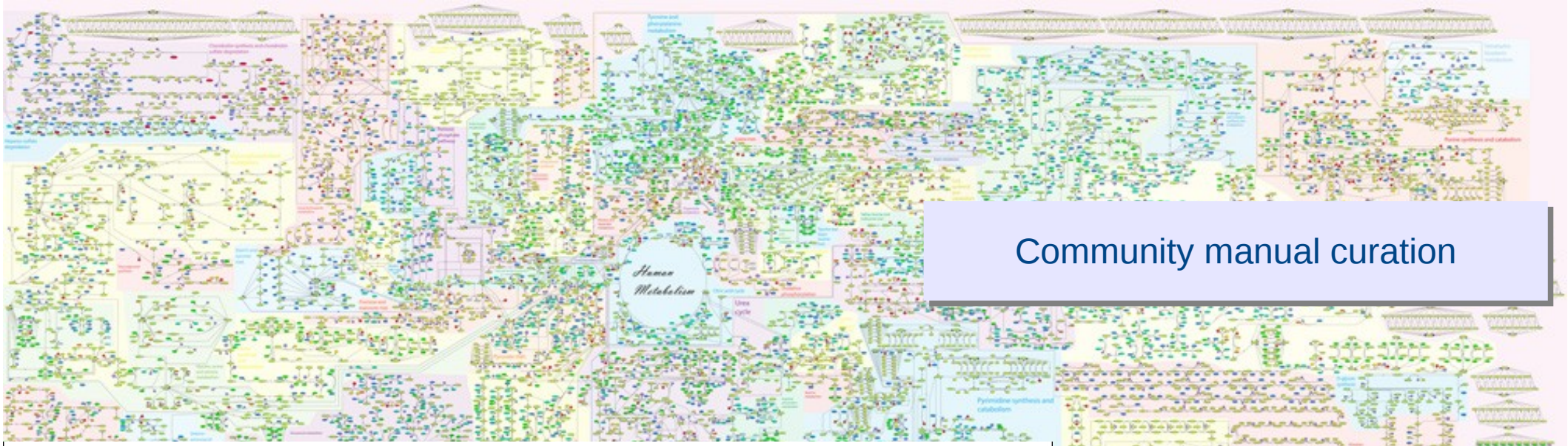
FBA after perturbations



Non-lethal mutation



lethal mutation



Community manual curation

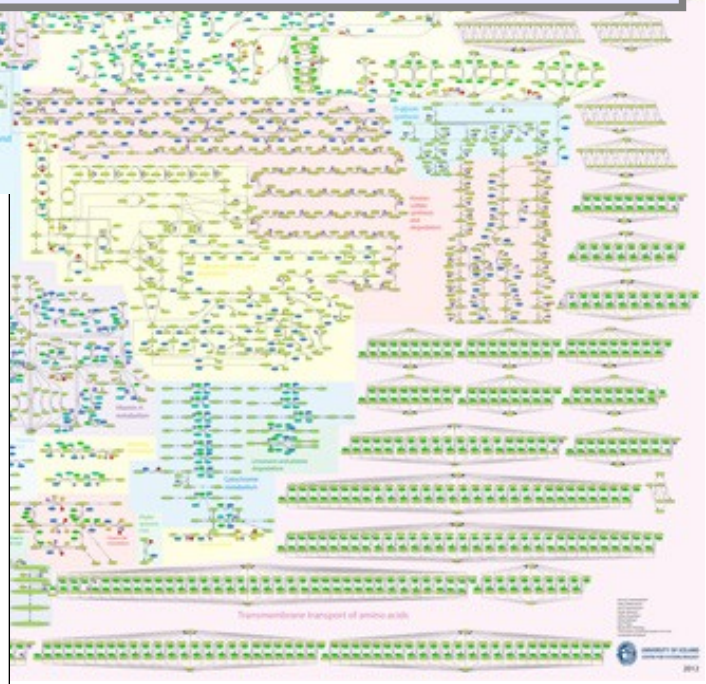
A community-driven global reconstruction of human metabolism

Ines Thiele[1,2,37], Neil Swainston[3,4,37], Ronan M T Fleming[1,5], Andreas Hoppe[6], Swagatika Sahoo[1], Maike K Aurich[1], Hulda Haraldsdottir[1], Monica L Mo[7], Ottar Rolfsson[1], Miranda D Stobbe[8,9], Stefan G Thorleifsson[1], Rasmus Agren[10], Christian Bölling[6], Sergio Bordel[10], Arvind K Chavali[11], Paul Dobson[12], Warwick B Dunn[3,13], Lukas Endler[14], David Hala[15], Michael Hucka[16], Duncan Hull[4], Daniel Jameson[3,4], Neema Jamshidi[7], Jon J Jonsson[5], Nick Juty[17], Sarah Keating[17], Intawat Nookaew[10], Nicolas Le Novère[17,18], Naglis Malys[3,19,20], Alexander Mazein[21], Jason A Papin[11], Nathan D Price[22], Evgeni Selkov, Sr[23], Martin I Sigurdsson[1], Evangelos Simeonidis[22,24], Nikolaus Sonnenschein[25], Kieran Smallbone[3,26], Anatoly Sorokin[21,27], Johannes H G M van Beek[28–30], Dieter Weichart[3,31], Igor Goryanin[21,32], Jens Nielsen[10], Hans V Westerhoff[3,28,33,34], Douglas B Kell[3,35], Pedro Mendes[3,4,36] & Bernhard Ø Palsson[1,7]

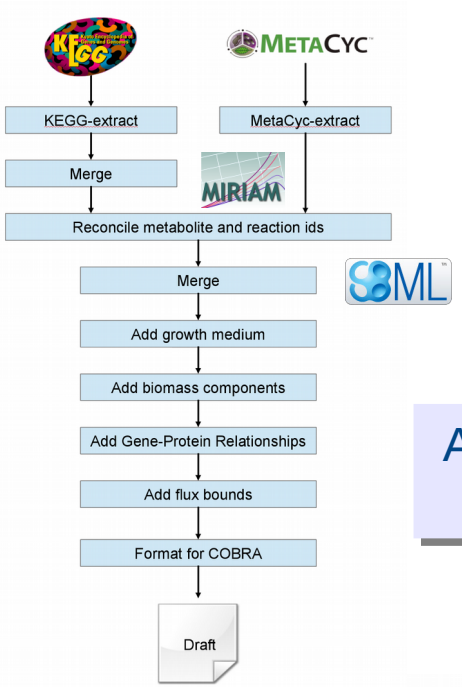
Multiple models of human metabolism have been reconstructed, but each represents only a subset of our knowledge. Here we describe Recon 2, a community-driven, consensus 'metabolic reconstruction', which is the most comprehensive representation of human metabolism that is applicable to computational modeling. Compared with its predecessors, the reconstruction has improved topological and functional features, including ~2× more reactions and ~1.7× more unique metabolites. Using Recon 2 we predicted changes in metabolite biomarkers for 49 inborn errors of metabolism with 77% accuracy when compared to experimental data. Mapping metabolomic data and drug information onto Recon 2 demonstrates its potential for integrating and analyzing diverse data types. Using protein expression data, we automatically generated a compendium of 65 cell type–specific models, providing a basis for manual curation or investigation of cell-specific metabolic properties. Recon 2 will facilitate many future biomedical studies and is freely available at http://humanmetabolism.org/.

npg

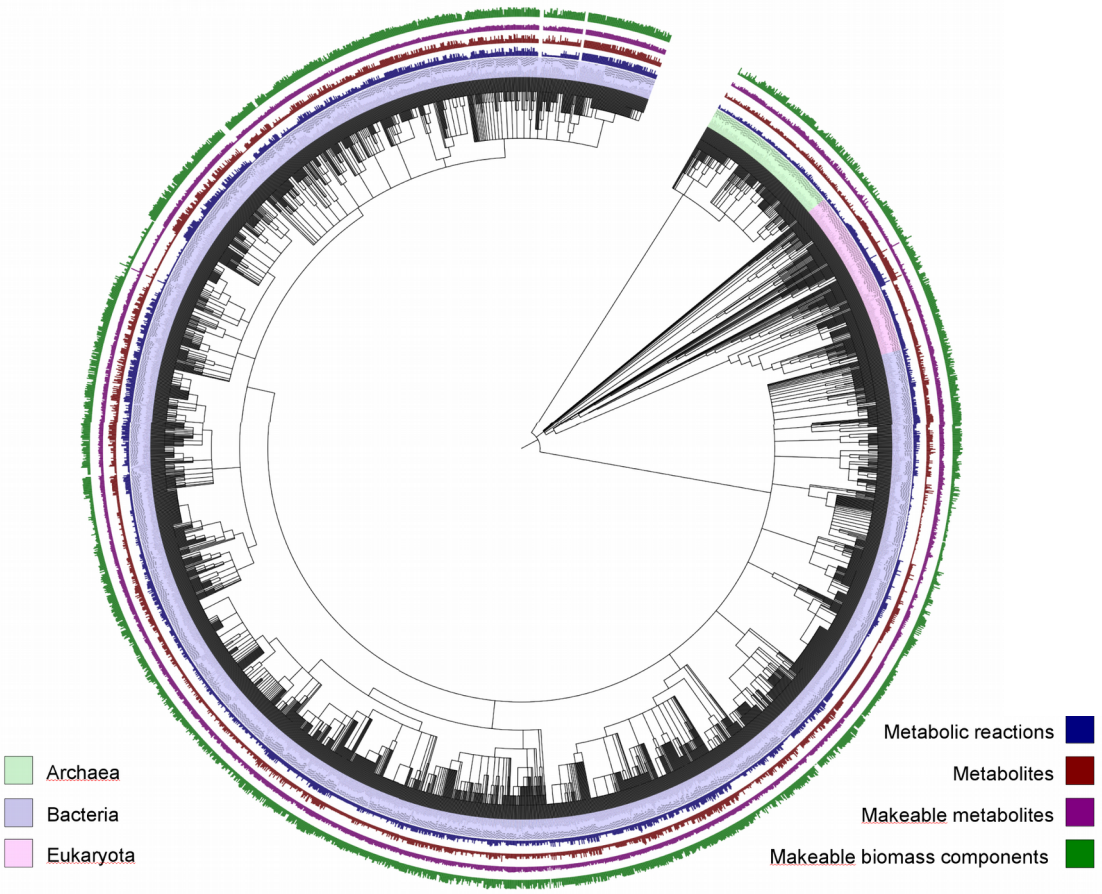
An understanding of metabolism is fundamental to comprehending the phenotypic behavior of all living organisms, including humans, where metabolism is integral to health and is involved in much of human disease. High quality, genome-scale 'metabolic reconstructions' are at the heart of bottom-up systems biology analyses and represent the entire network of metabolic reactions that a given organism is known to exhibit[1]. The metabolic-network reconstruction procedure is now well-established[2] and has been applied to a growing number of model organisms[3]. Metabolic reconstructions allow for the conversion of biological knowledge into a mathematical format and the subsequent computation of physiological states[1,4,5] to address a variety of scientific and applied questions[3,6]. Reconstructions enable network-wide mechanistic investigations of the genotype-phenotype relationship. A high-quality reconstruction of the metabolic network is thus



- 8 compartments
- 5 063 metabolites
- 2 194 proteins
- 7 440 reactions



Automated reconstruction
>2600 species



Büchel *et al. BMC Systems Biology* 2013, **7**:116
http://www.biomedcentral.com/1752-0509/7/116

BMC Systems Biology

RESEARCH ARTICLE Open Access

Path2Models: large-scale generation of computational models from biochemical pathway maps

Finja Büchel[1,2†], Nicolas Rodriguez[1,3†], Neil Swainston[4†], Clemens Wrzodek[2†], Tobias Czauderna[5], Roland Keller[2], Florian Mittag[1,2], Michael Schubert[1], Mihai Glont[1], Martin Golebiewski[6], Martijn van Iersel[1], Sarah Keating[1], Matthias Rall[2], Michael Wybrow[7], Henning Hermjakob[1], Michael Hucka[8], Douglas B Kell[4,9], Wolfgang Müller[6], Pedro Mendes[4,10,11], Andreas Zell[2], Claudine Chaouiya[12], Julio Saez-Rodriguez[1], Falk Schreiber[5,13], Camille Laibe[1], Andreas Dräger[2,14] and Nicolas Le Novère[1,3*]

Abstract

Background: Systems biology projects and omics technologies have led to a growing number of biochemical pathway models and reconstructions. However, the majority of these models are still created *de novo*, based on literature mining and the manual processing of pathway data.

Results: To increase the efficiency of model creation, the Path2Models project has automatically generated mathematical models from pathway representations using a suite of freely available software. Data sources include KEGG, BioCarta, MetaCyc and SABIO-RK. Depending on the source data, three types of models are provided: kinetic, logical and constraint-based. Models from over 2 600 organisms are encoded consistently in SBML, and are made freely available through BioModels Database at http://www.ebi.ac.uk/biomodels-main/path2models. Each model contains the list of participants, their interactions, the relevant mathematical constructs, and initial parameter values. Most models are also available as easy-to-understand graphical SBGN maps.

Conclusions: To date, the project has resulted in more than 140 000 freely available models. Such a resource can tremendously accelerate the development of mathematical models by providing initial starting models for simulation and analysis, which can be subsequently curated and further parameterized.

Keywords: Modular rate law, Constraint based models, Logical models, SBGN, SBML

Background

Since the discovery of the set of biochemical transformations known as the Embden-Meyerhof-Parnas glycolysis pathway in the early twentieth century, the concepts of pathways and networks have become useful and ubiquitous tools in the understanding of biochemical processes. Biochemical pathways provide a qualitative representation of chains of molecular interactions and chemical reactions that are known to take place in cells. Such interactions result in changes in the concentration, state or location of chemical entities. Pathways aim at providing a detailed representation of this biochemical reality, based on observations of the reactions. As such, the elucidation of biochemical pathways is being dramatically sped up with the efforts of molecular biology and biochemistry research, and particularly with the recent appearance of high-throughput omics technologies.

The definition of biochemical pathways is largely arbitrary, as in practice they are interlinked and interdependent in the functioning cell. Nevertheless, it is convenient to partition these pathways into different types such as signaling pathways, metabolic networks, gene regulatory networks, etc. With the growing number and complexity of biochemical pathways, a number of public databases

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Full list of author information is available at the end of the article

SBML.org — The Systems Biology Markup Language

Welcome to the portal for the **Systems Biology Markup Language** (**SBML**), a free and open interchange format for computer models of biological processes. SBML is useful for models of metabolism, cell signaling, and more. It **continues to be evolved and expanded** by an international community.

For the curious

What *is* SBML? Read our **introduction**, then perhaps browse the **mailing lists**, the **FAQ**, and the **SBML Level 3 package activities** to glimpse what's happening with SBML today.

For modelers

Looking for software that supports SBML? Our **software guide** lists over **280** systems. Are you instead looking for models? Visit **BioModels Database**, where you can find hundreds!

For software developers

Want to support SBML in your software? Read our **intro** and then the **specifications** to understand SBML in depth, then check our **libraries**, **test resources**, and also **3rd-party software**.

No matter how you use SBML, we invite you to sign up for news updates either through our **RSS feed**, our **Twitter feed**, or one of the **mailing lists**, and get involved with **community efforts** to help improve SBML. You can also call attention to your project's support of SBML by displaying the **SBML logo**.

SBML would not have been possible without support from **many agencies and organizations**, as well as contributions from many motivated individuals, including the **major contributors** who are shaping SBML Level 3.

SBML News

GSOC 2018 SBML projects

(13 Feb.'18) There are a number of **potential SBML-related projects** available in GSOC this year.

Deviser 1.0 released

(8 Feb.'18) Deviser is a code generation system for SBML Level 3 packages

JSBML 1.3.1 released

(19 Dec.'17) Tons of new features and bug fixes

Older news ...

Community News

Tellurium 2.0

(16 Oct.'17) Version 2.0 of Tellurium adds a Notebook facility and improved SED-ML and COMBINE Archive handling.

SED-ML L1v3

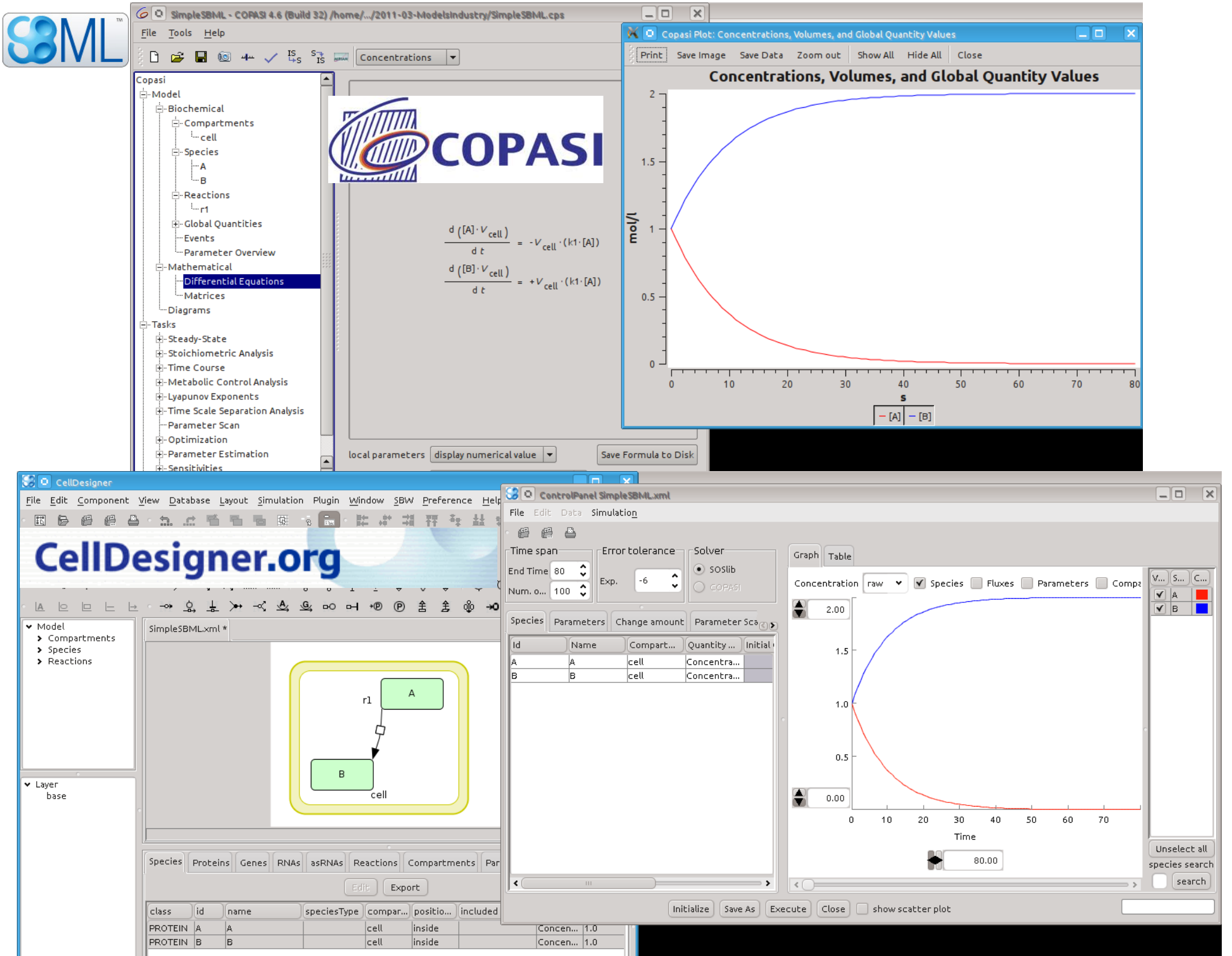
(9 Oct.'17) The SED-ML Editors have released a new version of SED-ML Level 1.

BioModels platform released

(9 Oct.'17) The developers of BioModels Database have released a new platform.

Older news ...

You can **tell us what to announce**.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Parameter Overview
Mathematical
Differential Equations
Matrices
Diagrams
Tasks
Steady-State
Stoichiometric Analysis
Time Course
Metabolic Control Analysis
Lyapunov Exponents
Time Scale Separation Analysis
Parameter Scan
Optimization
Parameter Estimation
Sensitivities
COPASI
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display numerical value
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Print Save Image Save Data Zoom out Show All Hide All Close
Concentrations, Volumes, and Global Quantity Values
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SOSlib
COPASI
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Id Name Compart... Quantity ... Initial
A A cell Concentra...
B B cell Concentra...
Graph Table
Concentration raw
Species Fluxes Parameters Compa
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Time
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V... S... C...
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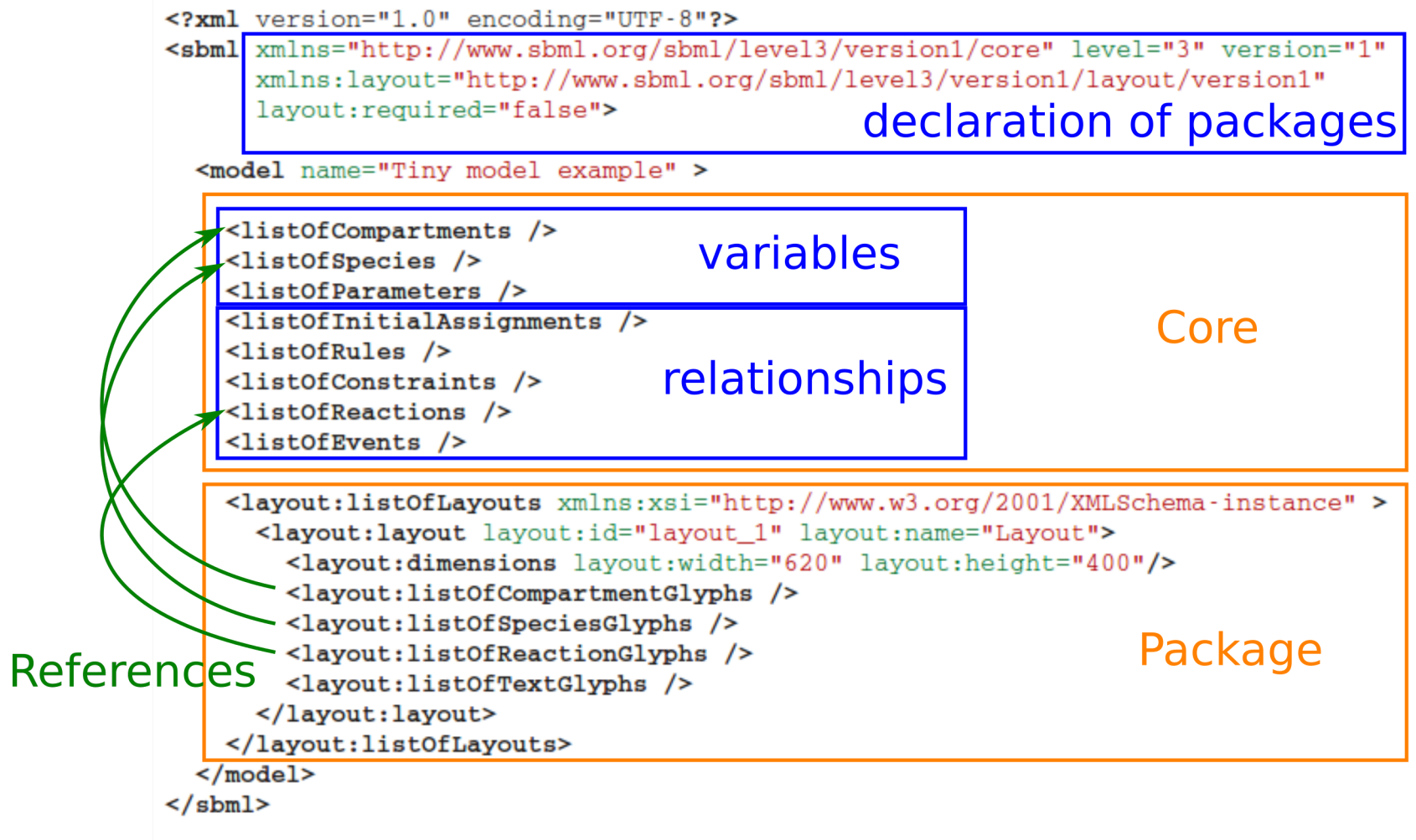
B
Unselect all
species search
search
Initialize Save As Execute Close show scatter plot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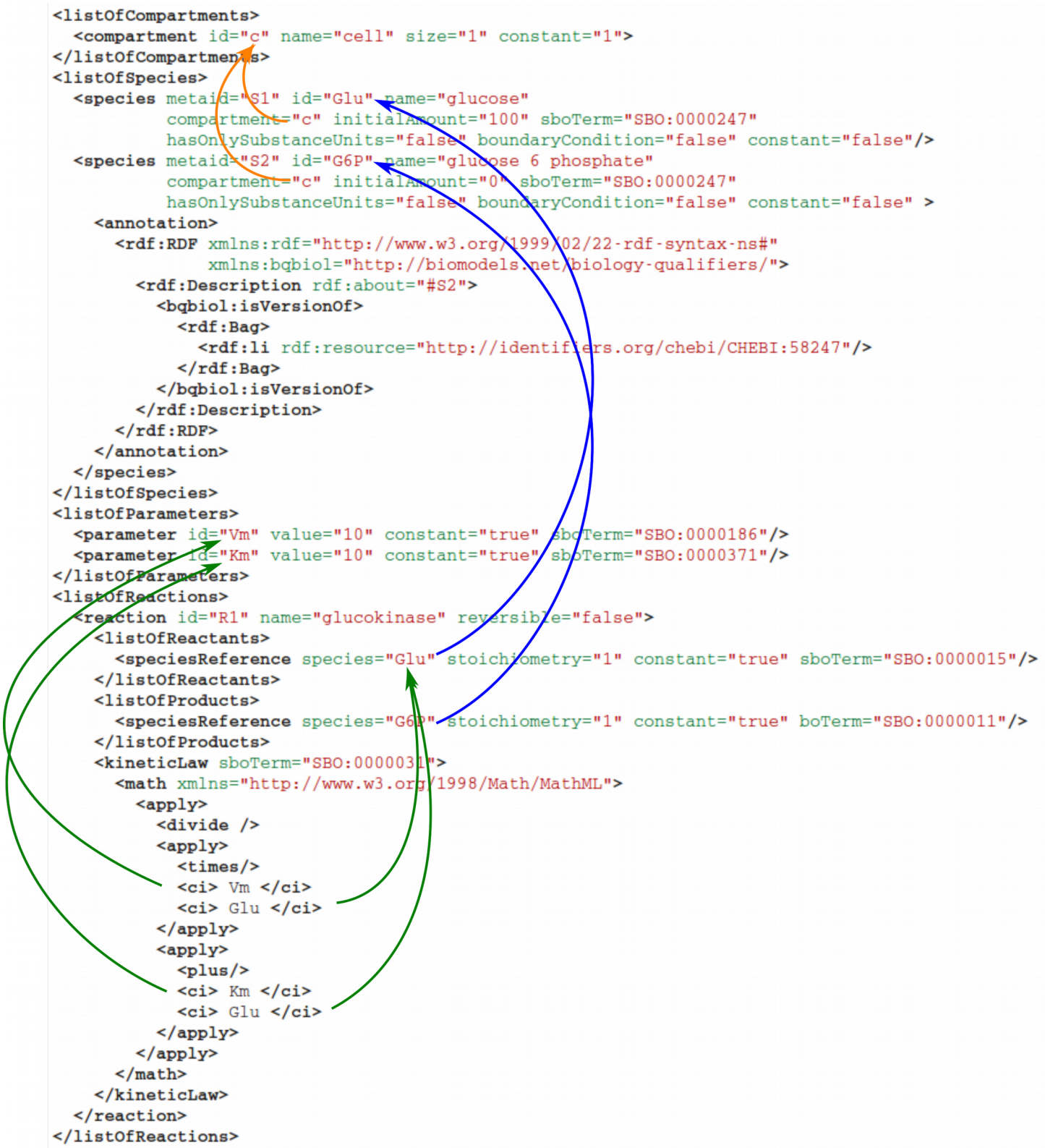
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Do genome-scale models need exact solvers or clearer standards?

Ali Ebrahim, Eivind Almaas, Eugen Bauer, Aarash Bordbar, Anthony P Burgard, Roger L Chang, Andreas Dräger, Iman Famili, Adam M Feist, Ronan MT Fleming, Stephen S Fong, Vassily Hatzimanikatis, Markus J Herrgård, Allen Holder, Michael Hucka, Daniel Hyduke, Neema Jamshidi, Sang Yup Lee, Nicolas Le Novère, Joshua A Lerman, Nathan E Lewis, Ding Ma, Radhakrishnan Mahadevan, Costas Maranas, Harish Nagarajan, Ali Navid, Jens Nielsen, Lars K Nielsen, Juan Nogales, Alberto Noronha, Csaba Pal, Bernhard O Palsson, Jason A Papin, Kiran R Patil, Nathan D Price, Jennifer L Reed, Michael Saunders, Ryan S Senger, Nikolaus Sonnenschein, Yuekai Sun, Ines Thiele

Author Affiliations

DOI 10.15252/msb.20156157 | Published online 14.10.2015
Molecular Systems Biology (2015) 11, 831

SBML Level 3 Package Specification

SBML Level 3 Package: Flux Balance Constraints ('fbc')

Brett G. Olivier
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VU University Amsterdam
Amsterdam, NH, The Netherlands

Frank T. Bergmann
fbergmann@caltech.edu
Computing and Mathematical Sciences
California Institute of Technology
Pasadena, CA, US

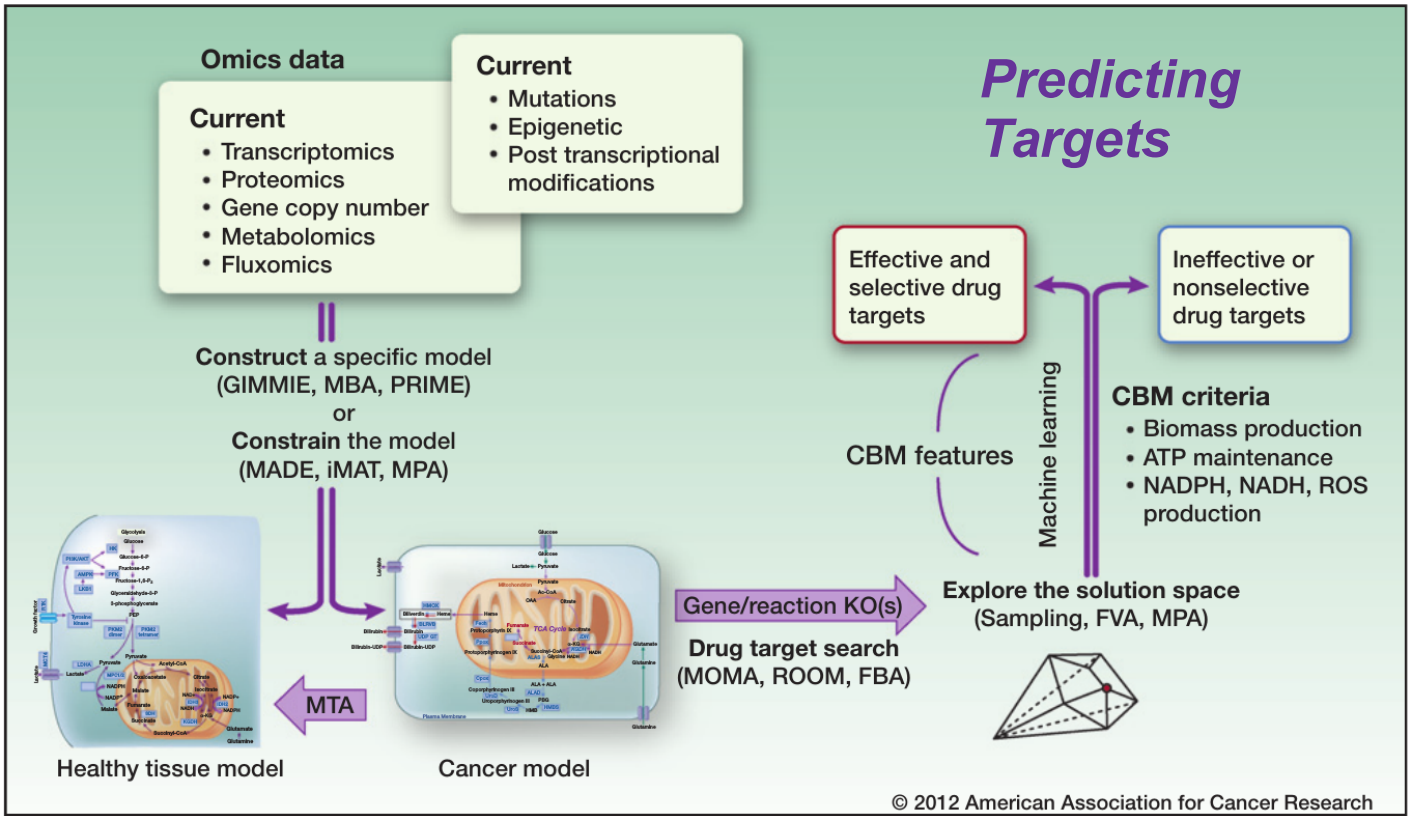
Version 2, Release 1

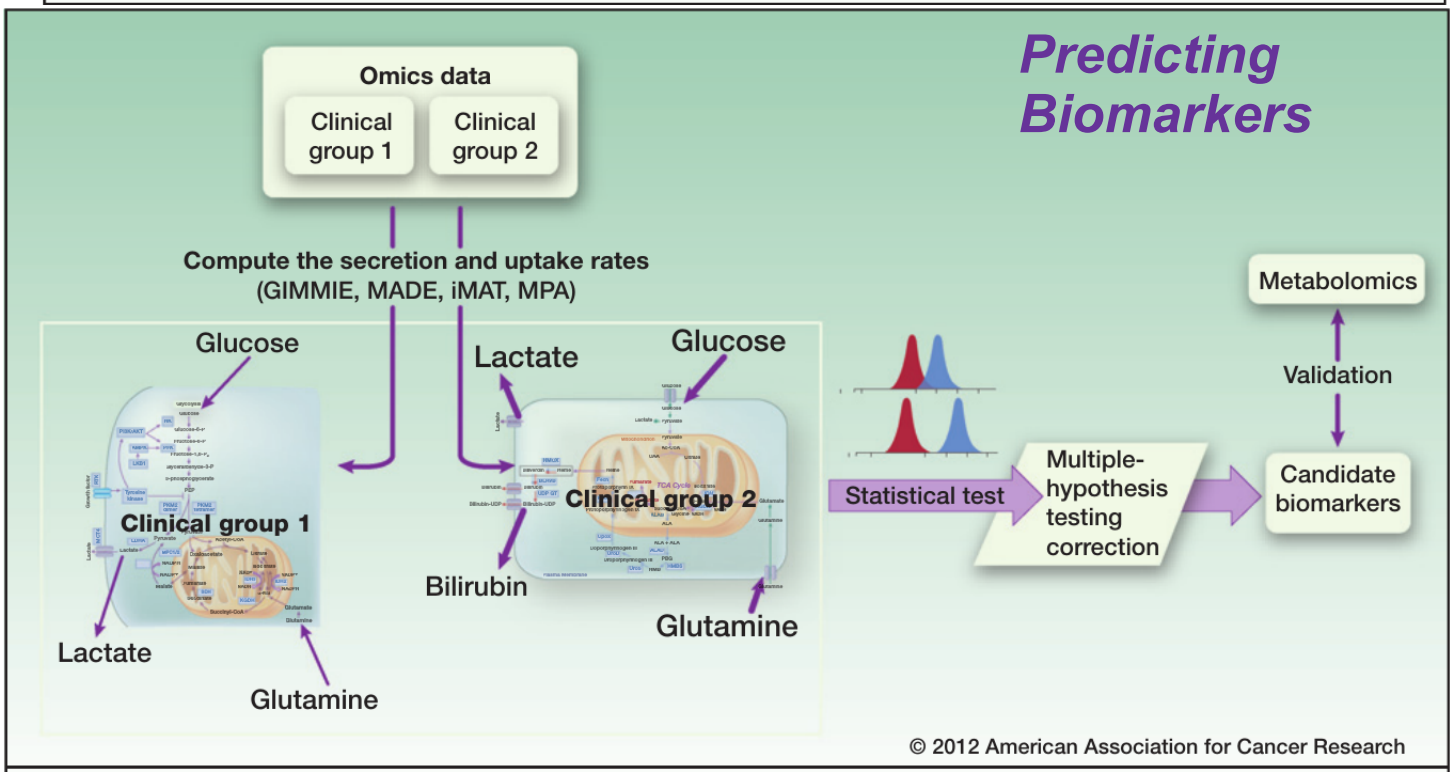
September 12, 2015

Jerby and Ruppin (2012)
Clin Cancer Res

Systematically perturb a given system

Compare two systems





Using gene expression to fix the boundaries

2009

OPEN ACCESS Freely available online

PLoS COMPUTATIONAL BIOLOGY

Interpreting Expression Data with Metabolic Flux Models: Predicting *Mycobacterium tuberculosis* Mycolic Acid Production

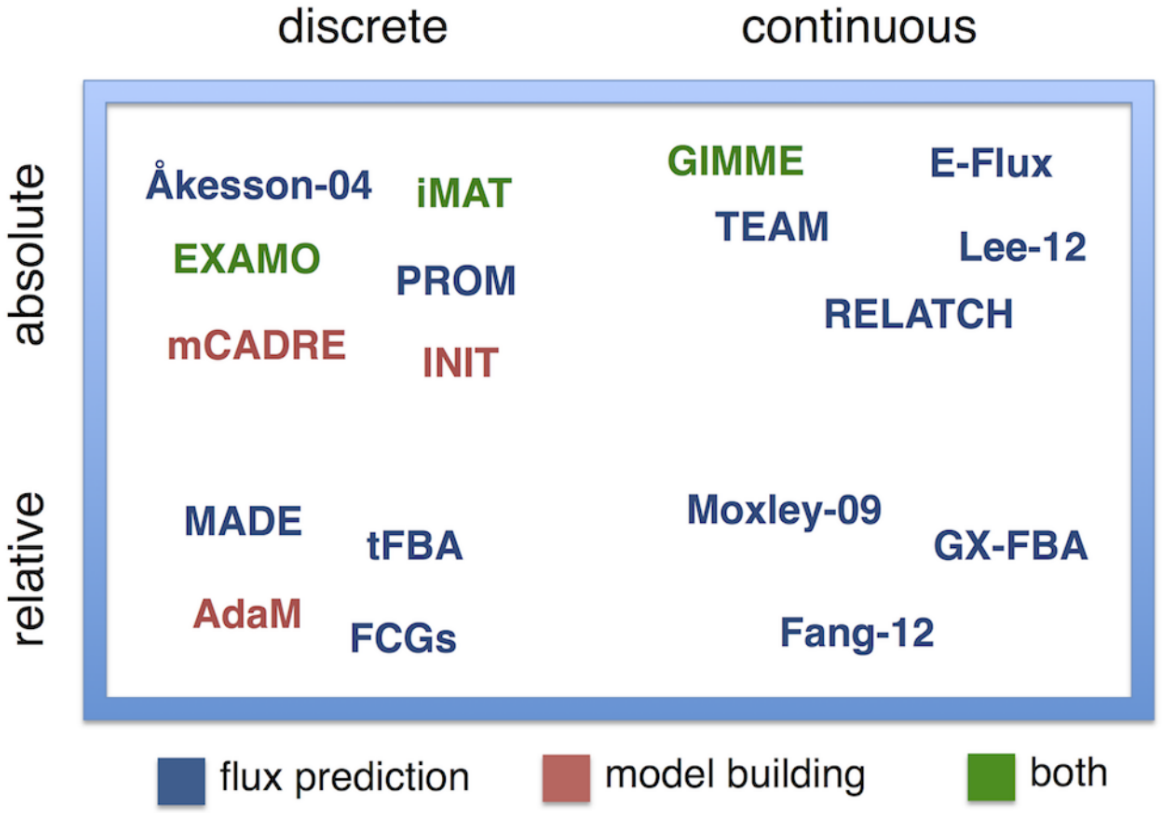
Caroline Colijn[1,3,5]*, Aaron Brandes[1], Jeremy Zucker[2], Desmond S. Lun[1,7], Brian Weiner[1], Maha R. Farhat[4], Tan-Yun Cheng[6], D. Branch Moody[6], Megan Murray[3], James E. Galagan[1,8]

1 Broad Institute of MIT and Harvard, Cambridge, Massachusetts, United States of America, **2** Department of Genetics, Harvard Medical School, Boston, Massachusetts, United States of America, **3** Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, United States of America, **4** Department of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Boston, Massachusetts, United States of America, **5** Department of Engineering Mathematics, University of Bristol, Bristol, United Kingdom, **6** Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, United States of America, **7** Phenomics and Bioinformatics Research Centre, School of Mathematics and Statistics, and Australian Centre for Plant Functional Genomics, University of South Australia, Mawson Lakes, South Australia, Australia, **8** Department of Biomedical Engineering and Department of Microbiology, Boston University, Boston, Massachusetts, United States of America

Abstract

Metabolism is central to cell physiology, and metabolic disturbances play a role in numerous disease states. Despite its importance, the ability to study metabolism at a global scale using genomic technologies is limited. In principle, complete genome sequences describe the range of metabolic reactions that are possible for an organism, but cannot quantitatively describe the behaviour of these reactions. We present a novel method for modeling metabolic states using whole cell measurements of gene expression. Our method, which we call E-Flux (as a combination of flux and expression), extends the technique of Flux Balance Analysis by modeling maximum flux constraints as a function of measured gene expression. In contrast to previous methods for metabolically interpreting gene expression data, E-Flux utilizes a model of the underlying metabolic network to directly predict changes in metabolic flux capacity. We applied E-Flux to *Mycobacterium tuberculosis*,

Two types of approaches



Use gene expression data to determine flux bounds,

Then optimise

Minimize difference between gene expression data and fluxes during optimisation

OPEN ACCESS Freely available online

PLOS COMPUTATIONAL BIOLOGY

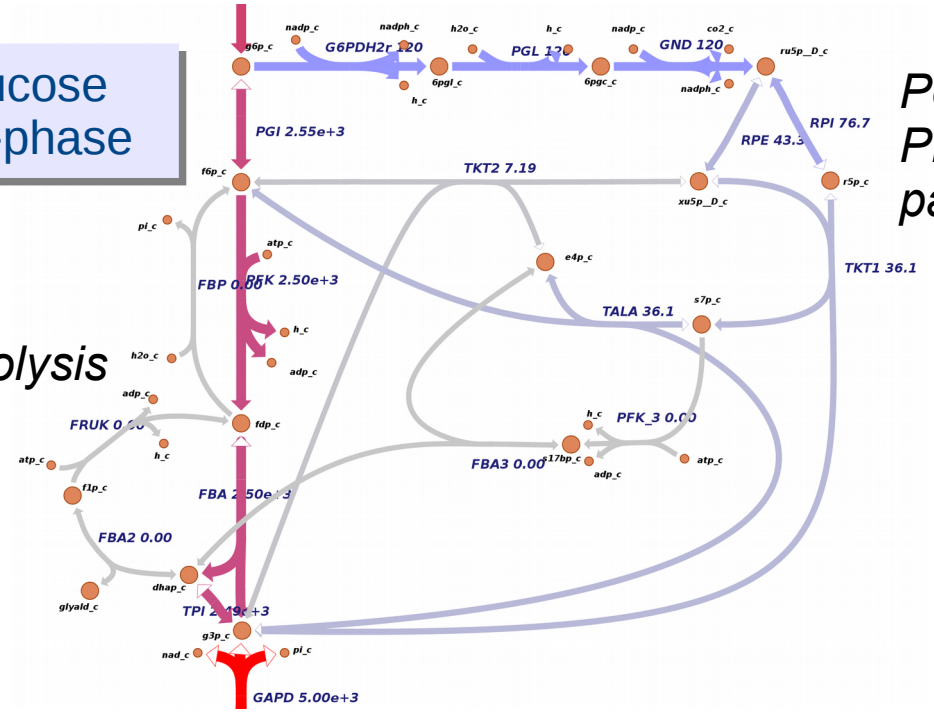
Systematic Evaluation of Methods for Integration of Transcriptomic Data into Constraint-Based Models of Metabolism

2014

Daniel Machado, Markus Herrgård*

The Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark, Horsholm, Denmark

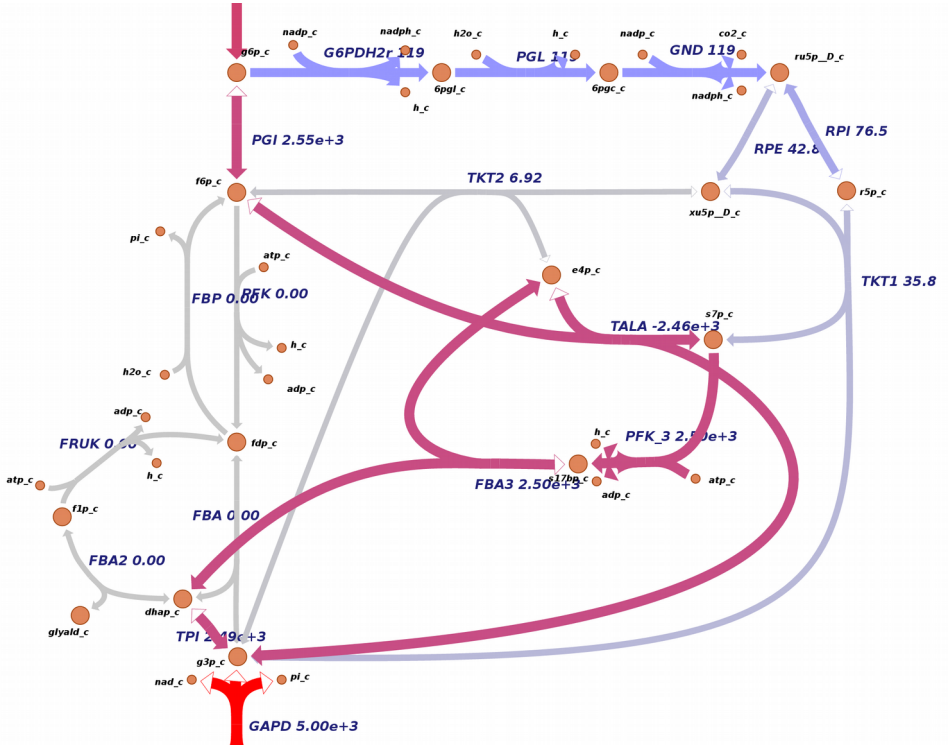
Glucose
Log-phase

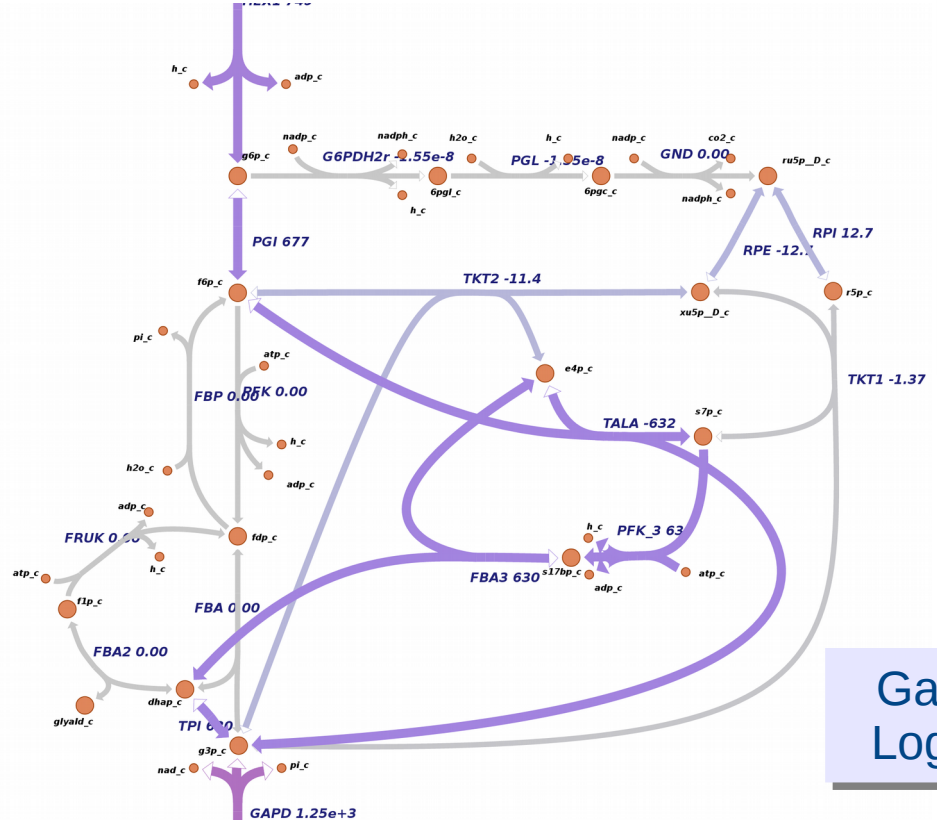


Pentose Phosphate pathway

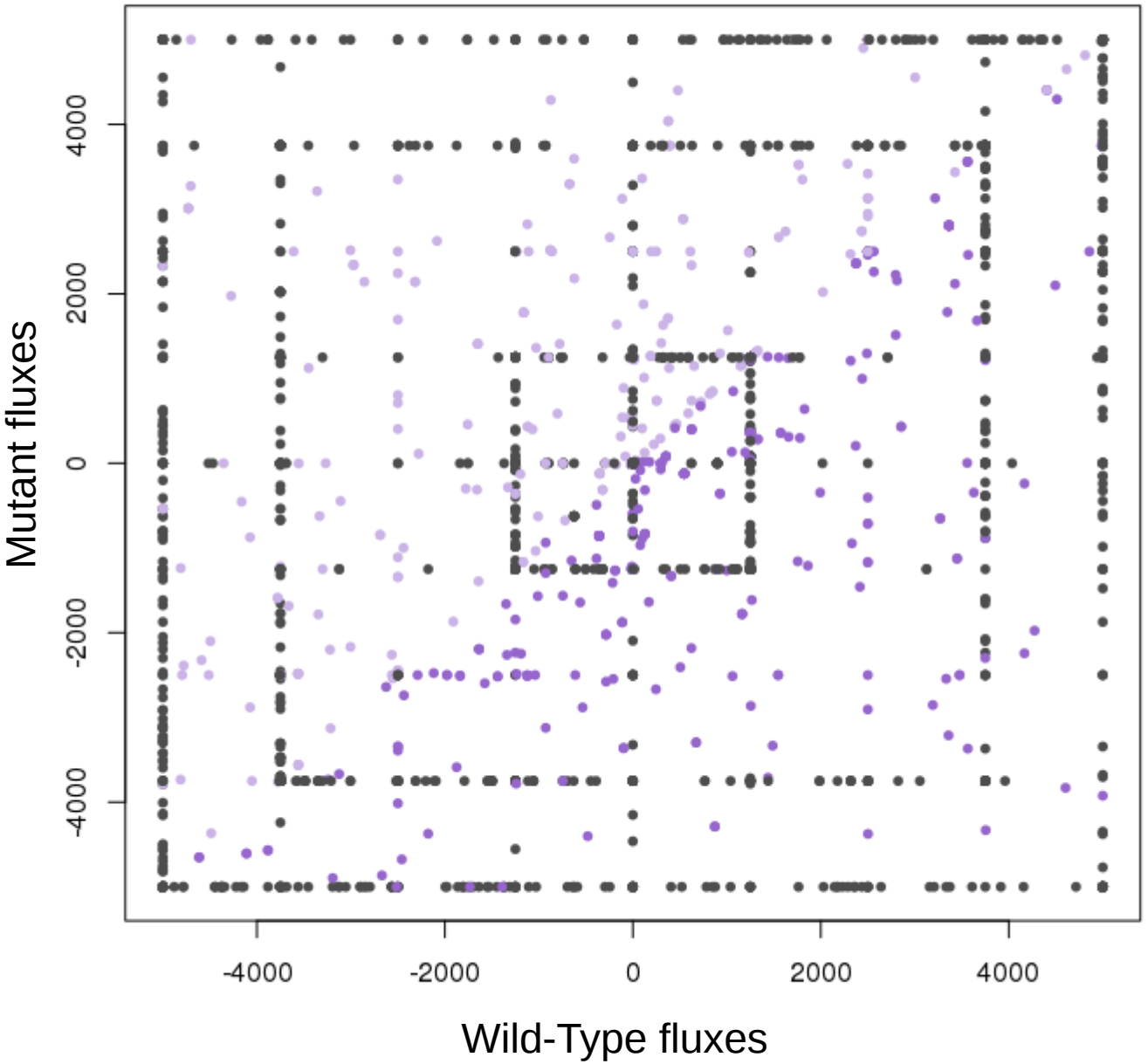
glycolysis

Glucose
48 h





Galactose
Log-phase


Mutant fluxes
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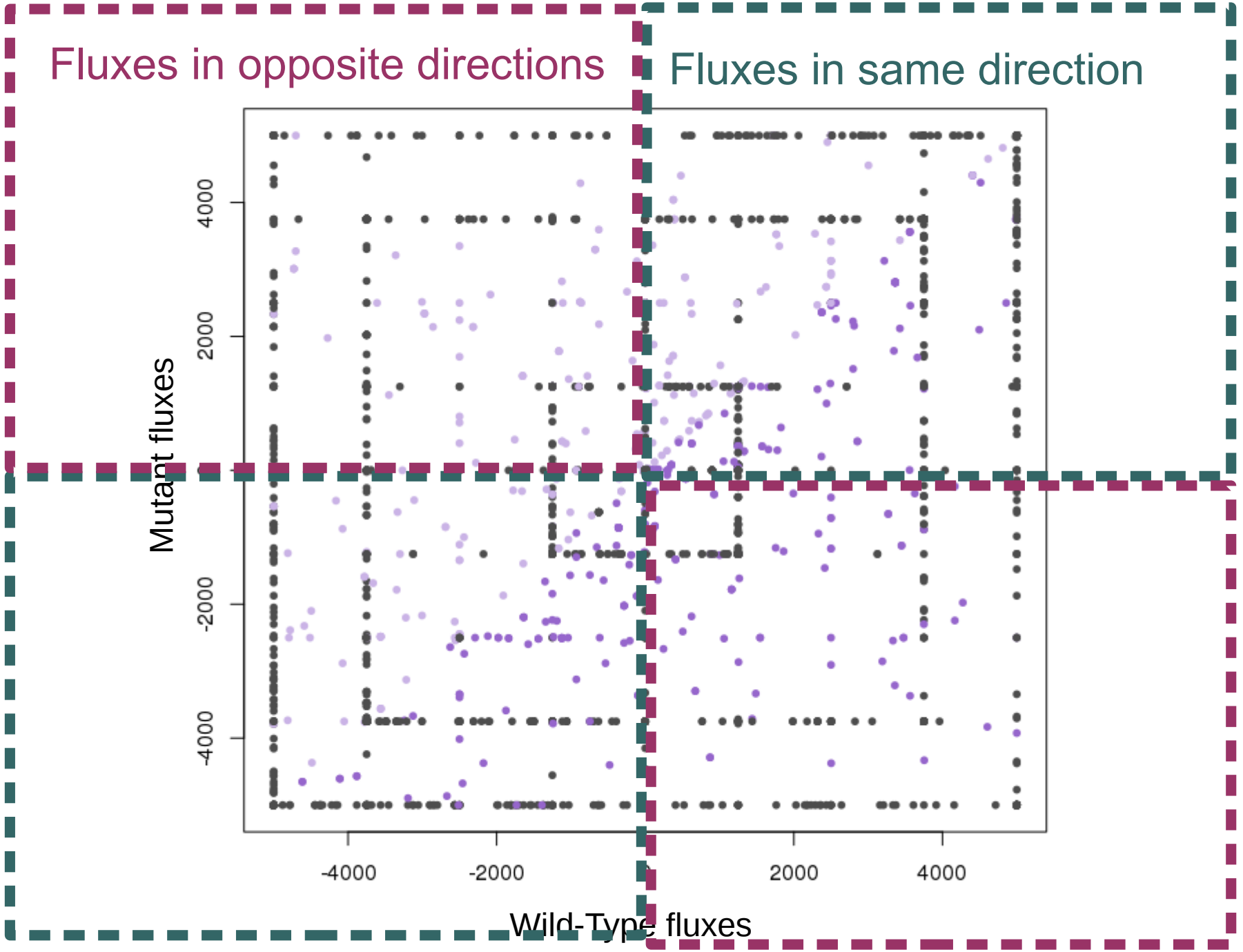
2000
0
-2000
-4000
-4000
-2000
0
2000
4000
Wild-Type fluxes


Fluxes in opposite directions
Fluxes in same direction
Mutant fluxes
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2000
-2000
-4000
-4000
-2000
2000
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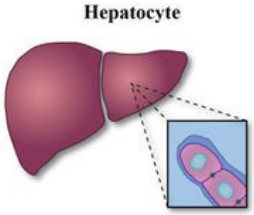
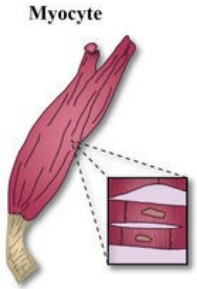
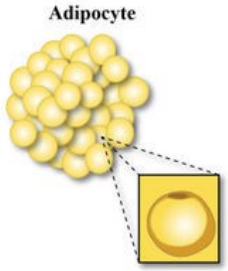
Wild-Type fluxes



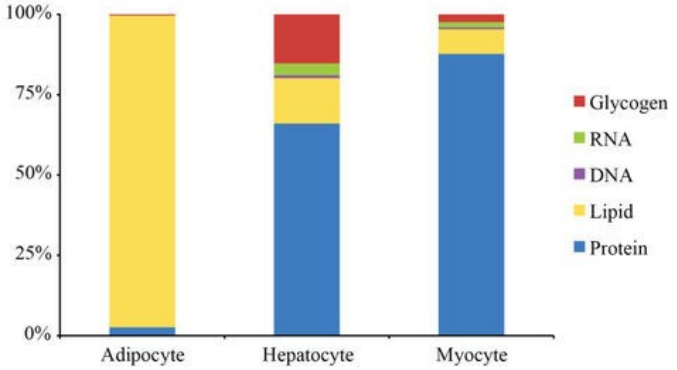


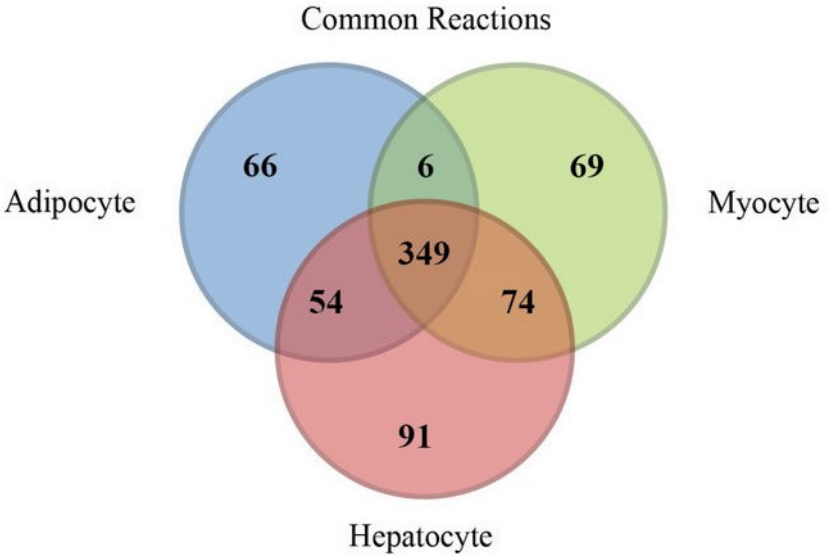


Tissue-Specific Properties

	Adipocyte	Hepatocyte	Myocyte
Transcripts	819	928	971
Proteins	788	898	942
Intracellular Reactions	587	705	656
Gene Associated Reactions	79.7%	81.1%	81.9%
Metabolites	493	589	539
in vitro growth rate (1/h)	0.014	0.035	0.013
Min carbon uptake required for *in vitro* growth rate (mmol C/ gDW/h)	6.15	6.99	6.02
Max ATP Yield (mmol/cell gDW/h/ mmol glucose)	0.44	0.47	0.51
Max NADH Yield (mmol/cell gDW/h/ mmol glucose)	5.80	6.21	6.77

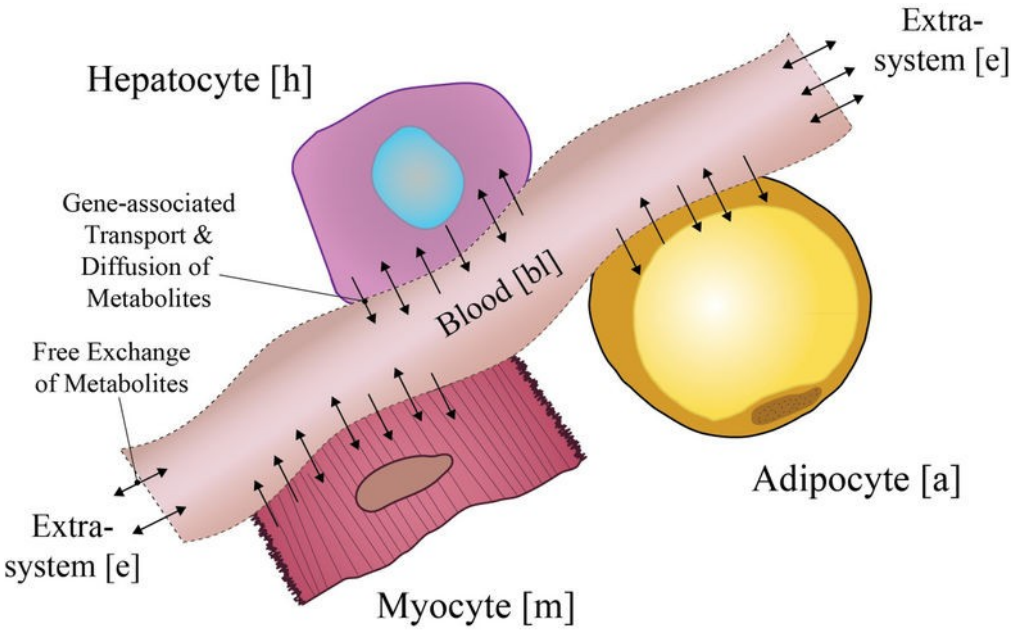
Individual Cell Composition





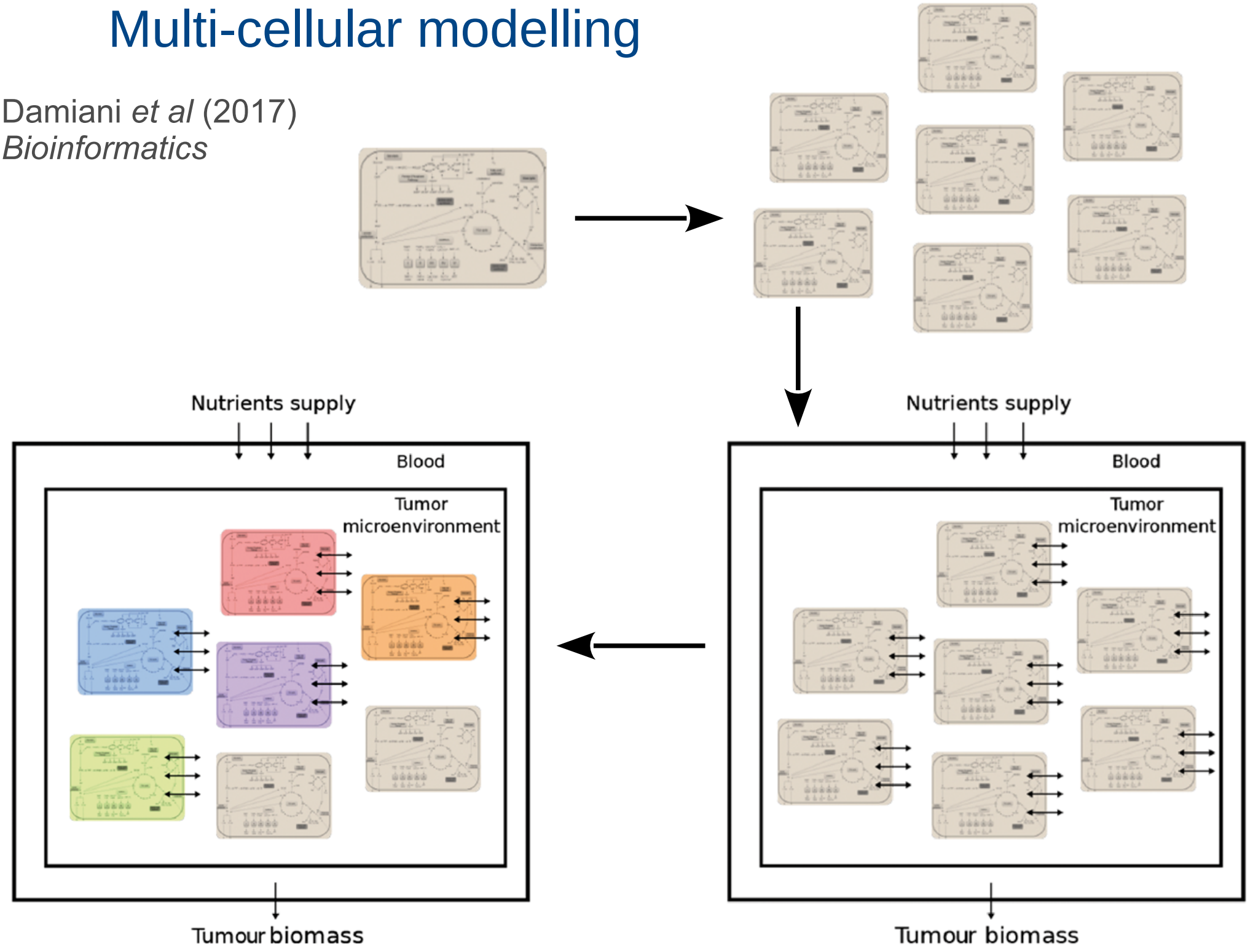
Multi-tissue modeling

Bordbar et al (2011)
BMC Systems Biol



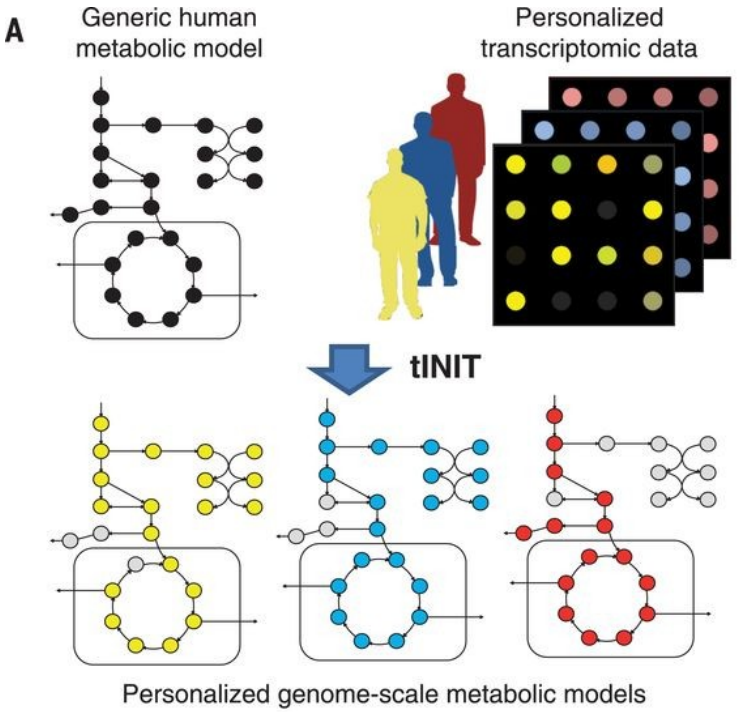
Multi-cellular modelling

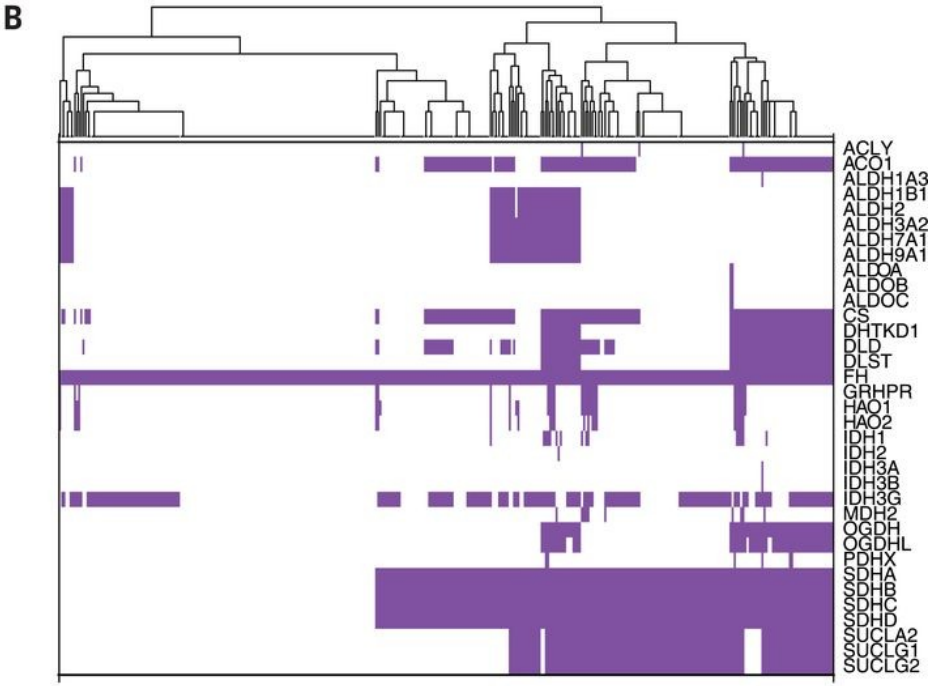
Damiani *et al* (2017)
Bioinformatics

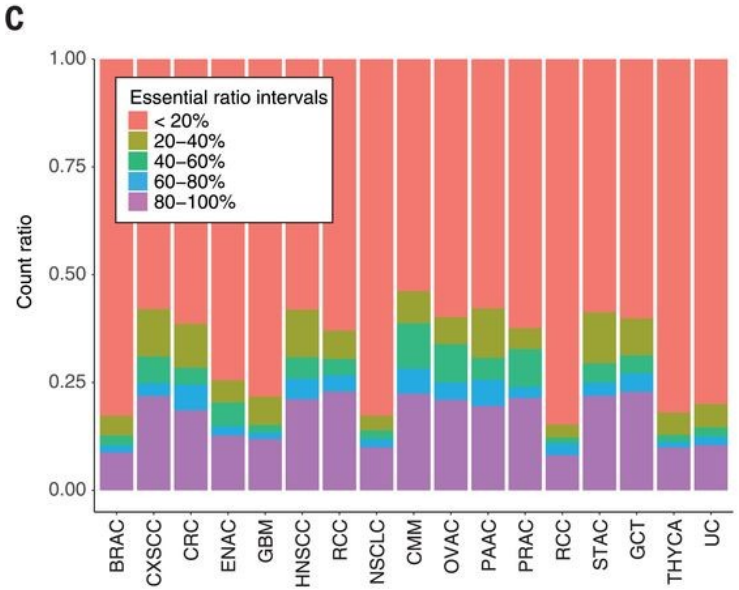


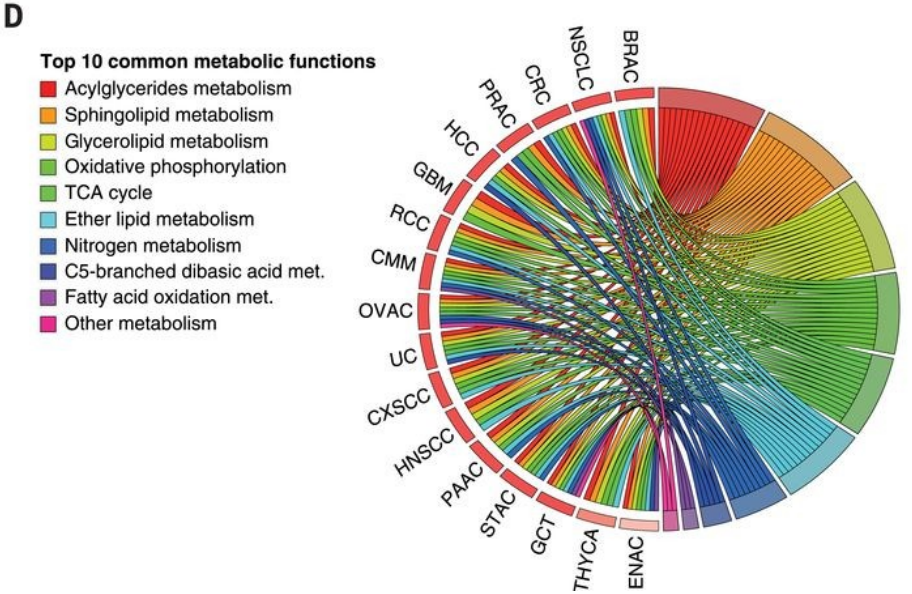
Patient-derived modelling

Uhlen *et al* (2018)
BMC Systems Biol









Try the new BioModels platform (beta)

BioModels Database

Search

Advanced

BioModels Database is a repository of computational models of biological processes. Models described from literature are manually curated and enriched with cross-references. All models are provided in the Public Domain. More information about BioModels Database can be found in the FAQ.

Models published in the literature

Browse

Manually curated (641 models)

Non curated (1008 models)

Patient-derived genome-scale metabolic models (6753 models)

Alternative access

Gene Ontology classification

Gene Ontology tree

Advanced search

Models automatically generated from pathway resources (Path2Models)

Browse

Metabolic (112,898 models)

Non-metabolic (27,531 models)

Whole genome metabolism (2,641 models)

Alternative access

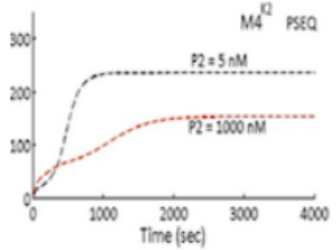
Dedicated search

Taxonomy

Model of the month

February 2018

Sarma and Ghosh 2012 used ODE models to demonstrate that signal processing characteristics are determined by the topological design of the kinases and phosphatases in MAPK cascade.



Access this model of the month.

News

21 August 2017 Patient-derived genome-scale metabolic models

BioModels now hosts 6753 models derived from biological samples collected from patients.

26 June 2017 31st release of BioModels

We are extremely happy to announce the 31st release of BioModels. The resource now provides 1640 literature-based models and 143,070 models automatically generated from pathway resources. For more information, please refer to the release notes.

16 January 2017 Metabolic network and logical models

Archives of metabolic network and logical models

Uhlén2017 - TCGA-3C-AAAU-01A - Breast Invasive Carcinoma (female, 56 years)

Download this model | View the Model of the Month entry for this model | Send feedback

Model information

Identifier:	MODEL1707110684	**Age at diagnosis:**	56	**Format:**	SBML L2V3
Original model:	MODEL1707110684.xml.origin	**Gender:**	female	**Submission:**	17 Aug 2017 16:12:32 UTC
Publication:	10.1126/science.aan2507	**Disease:**	Breast Invasive Carcinoma	**Last modified:**	17 Aug 2017 16:12:21 UTC
Submitter:	Adil Mardinoglu	**Primary disease site:**	breast	**Published:**	17 Aug 2017 16:12:32 UTC

Annotations

is	*BioModels*	MODEL1707110684
isDerivedFrom	*BioModels*	MODEL1402200003
hasTaxon	*Taxonomy*	Homo sapiens
isDerivedFrom	*Genomic Data Commons Data Portal*	6e7d5ec6-a469-467c-b748-237353c23416
hasProperty	*Experimental Factor Ontology*	1000307
hasProperty	*PATO*	female

Notes

This is a whole genome metabolism model of a female patient diagnosed at the age of 56 years with Breast Invasive Carcinoma affecting the patient's breast.

This model was automatically generated by tINIT (Agren, R., et al. (2014). Identification of anticancer drugs for hepatocellular carcinoma through personalized genome-scale metabolic modeling. Mol Syst Biol; 10(3), 721.) using information coming from the sample TCGA-3C-AAAU-01A from GDC Portal (Initial release 1.0, accessed via GDC API) and, where relevant, augmented with metabolic pathway information extracted from Human Metabolic Atlas.

This model has been produced by Human Pathology Atlas project (Uhlen, M., et al.; A pathology atlas of the human cancer transcriptome. Science.) and is currently hosted on BioModels Database and identified by MODEL1707110684.

To cite BioModels, please use: V Chelliah et al; BioModels: ten-year anniversary. Nucleic Acids Res 2015; 43 (D1): D542-D548.

Welcome to BioModels

BioModels is a repository of mathematical models of biological and biomedical systems. It hosts a vast selection of existing literature-based physiologically and pharmaceutically relevant mechanistic models in standard formats. Our mission is to provide the systems modelling community with reproducible, high-quality, freely-accessible models published in the scientific literature. More information about BioModels can be found in the FAQ.

Recently published

- Signaling_class_5
- Sier2017_E2_combined
- Figure4C
- Sier et al_2017_estrogen PBPK_simple
- Tiemann2011_PhenotypeTransitions
- Figure4D
- Sier2017_estrogen_PBPK_GSMN

Recently accessed

- DeCaluwe2016 - Circadian Clock
- Switching behaviour of PP2A inhibition by ARPP-16 - mutual inhibitions
- Araujo2016 - Positive feedback in Cdk1 signalling keeps mitotic duration short and constant
- Mufudza2012 - Estrogen effect on the dynamics of breast cancer
- Musante2017 - Switching behaviour of PP2A inhibition by ARPP-16 - mutual inhibitions and PKA inhibits MAST3 and dominant negative effect
- Uhlén2017 - TCGA-F2-6879-01A - Pancreatic Adenocarcinoma (male, 58 years)
- Musante2017 - Switching behaviour of PP2A inhibition by ARPP-16 - mutual inhibitions and PKA inhibits MAST3

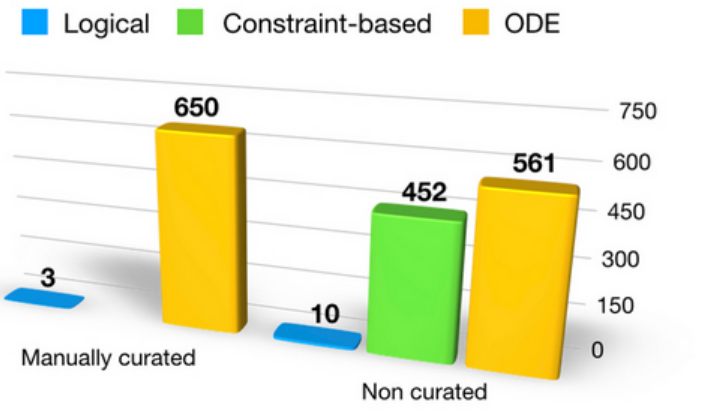
Features

What is available in BioModels?

Two branches
- ☑ Manually curated
- ☑ Non curated

Model formats
- ☑ SBML
- ☑ CellML
- ☑ Matlab
- ☐ ...

Modelling approaches
- ☑ Ordinary Differential Equation
- ☑ Logical
- ☑ Constraint-based
- ☐ ...

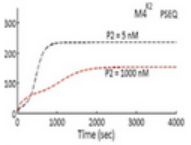


Acknowledgements

EMBL | BBSRC bioscience for the future | AgedBrainSYSBIO | imi | SEVENTH FRAMEWORK PROGRAMME

Model of the month

February, 2018



Sarma and Ghosh 2012 used ODE models to demonstrate that signal processing characteristics are determined by the topological design of the kinases and phosphatases in MAPK cascade.

Access this model of the month | View all Model of the Month entries

News

Patient-derived genome-scale metabolic models
BioModels now hosts 6753 models derived from biological samples collected from patients.
21 Aug 2017 at 10:00

31st release of BioModels
We are extremely happy to announce the 31st release of BioModels!
26 Jun 2017 at 02:20

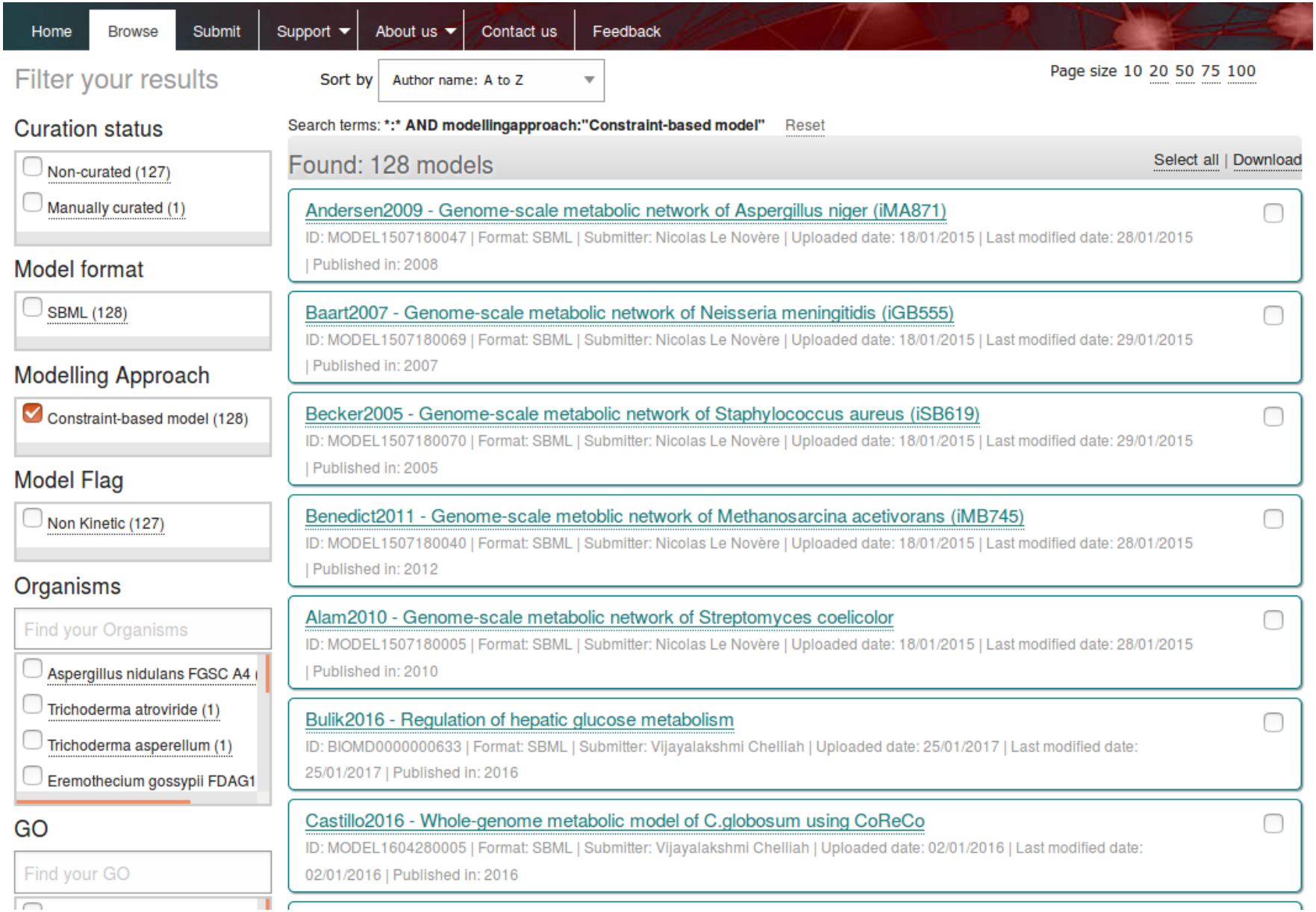
Metabolic networks and logical models have been published
The metabolic network and logical models hosted in the literature-based branch of BioModels can now be downloaded from our FTP server.
16 Jan 2017 at 04:15

Mechanistic models on neurodegenerative disease processes published
The paper, entitled Mechanistic models on neurodegenerative disease processes, available from CPT:PSP
09 Jan 2017 at 09:03

BioModels Release on 9th January 2017
BioModels now provides 1603 literature-based models. It includes 624 curated and 979 non-curated models
09 Jan 2017 at 10:41

more

Help


Home
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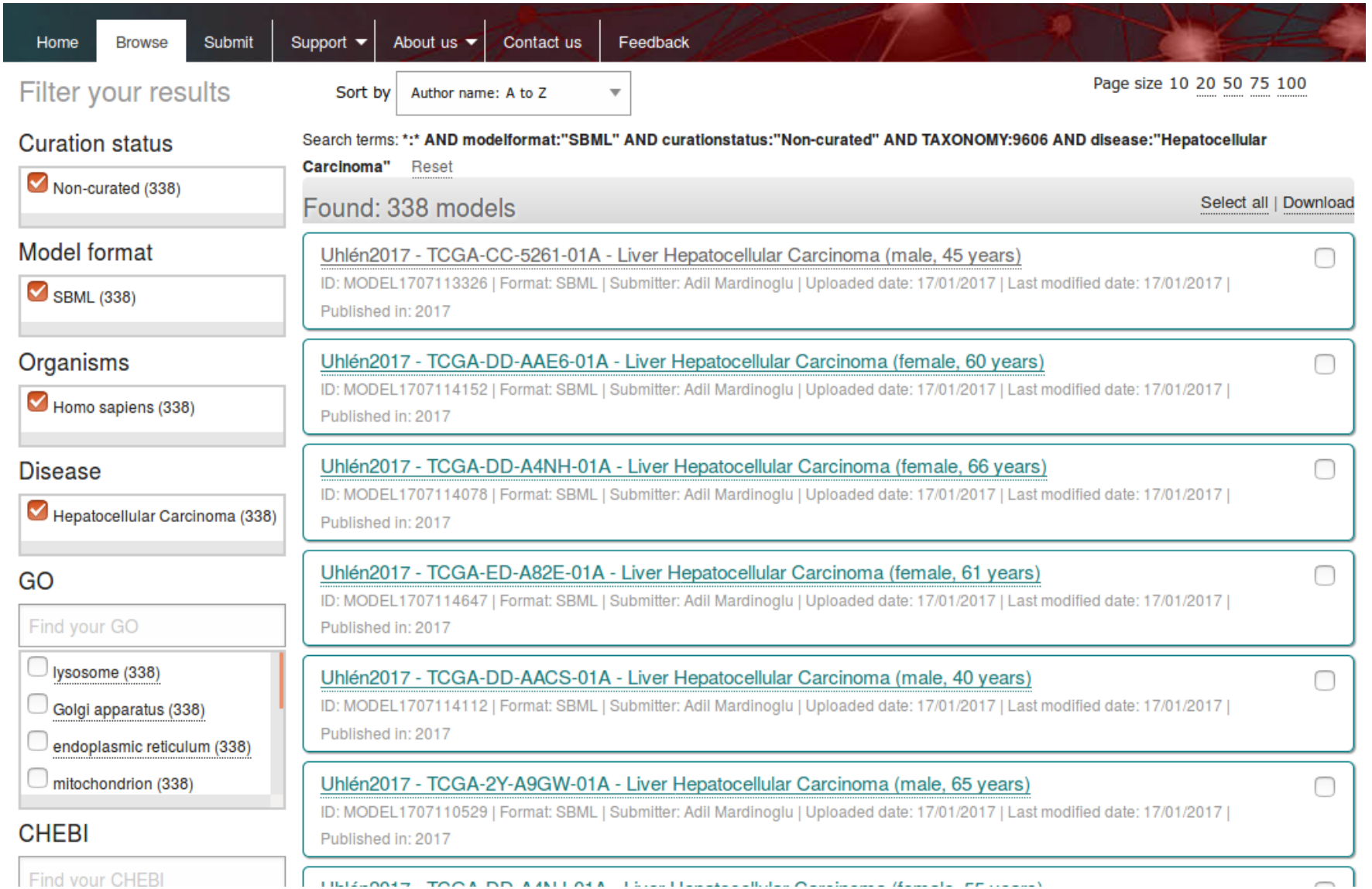
Contact us
Feedback
Filter your results
Sort by
Author name: A to Z
Page size 10 20 50 75 100
Curation status
Non-curated (127)
Manually curated (1)
Model format
SBML (128)
Modelling Approach
Constraint-based model (128)
Model Flag
Non Kinetic (127)
Organisms
Find your Organisms
Aspergillus nidulans FGSC A4
Trichoderma atroviride (1)
Trichoderma asperellum (1)
Eremothecium gossypii FDAG1
GO
Find your GO
Search terms: *:* AND modellingapproach:"Constraint-based model"
Reset
Found: 128 models
Select all | Download
Andersen2009 - Genome-scale metabolic network of Aspergillus niger (iMA871)
ID: MODEL1507180047 | Format: SBML | Submitter: Nicolas Le Novère | Uploaded date: 18/01/2015 | Last modified date: 28/01/2015 | Published in: 2008
Baart2007 - Genome-scale metabolic network of Neisseria meningitidis (iGB555)
ID: MODEL1507180069 | Format: SBML | Submitter: Nicolas Le Novère | Uploaded date: 18/01/2015 | Last modified date: 29/01/2015 | Published in: 2007
Becker2005 - Genome-scale metabolic network of Staphylococcus aureus (iSB619)
ID: MODEL1507180070 | Format: SBML | Submitter: Nicolas Le Novère | Uploaded date: 18/01/2015 | Last modified date: 29/01/2015 | Published in: 2005
Benedict2011 - Genome-scale metoblic network of Methanosarcina acetivorans (iMB745)
ID: MODEL1507180040 | Format: SBML | Submitter: Nicolas Le Novère | Uploaded date: 18/01/2015 | Last modified date: 28/01/2015 | Published in: 2012
Alam2010 - Genome-scale metabolic network of Streptomyces coelicolor
ID: MODEL1507180005 | Format: SBML | Submitter: Nicolas Le Novère | Uploaded date: 18/01/2015 | Last modified date: 28/01/2015 | Published in: 2010
Bulik2016 - Regulation of hepatic glucose metabolism
ID: BIOMD0000000633 | Format: SBML | Submitter: Vijayalakshmi Chelliah | Uploaded date: 25/01/2017 | Last modified date: 25/01/2017 | Published in: 2016
Castillo2016 - Whole-genome metabolic model of C.globosum using CoReCo
ID: MODEL1604280005 | Format: SBML | Submitter: Vijayalakshmi Chelliah | Uploaded date: 02/01/2016 | Last modified date: 02/01/2016 | Published in: 2016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Curation status
Non-curated (338)
Model format
SBML (338)
Organisms
Homo sapiens (338)
Disease
Hepatocellular Carcinoma (338)
GO
Find your GO
lysosome (338)
Golgi apparatus (338)
endoplasmic reticulum (338)
mitochondrion (338)
CHEBI
Find your CHEBI
Search terms: *:* AND modelformat:"SBML" AND curationstatus:"Non-curated" AND TAXONOMY:9606 AND disease:"Hepatocellular Carcinoma"
Reset
Found: 338 models
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Uhlén2017 - TCGA-CC-5261-01A - Liver Hepatocellular Carcinoma (male, 45 years)
ID: MODEL1707113326 | Format: SBML | Submitter: Adil Mardinoglu | Uploaded date: 17/01/2017 | Last modified date: 17/01/2017 |
Published in: 2017
Uhlén2017 - TCGA-DD-AAE6-01A - Liver Hepatocellular Carcinoma (female, 60 years)
ID: MODEL1707114152 | Format: SBML | Submitter: Adil Mardinoglu | Uploaded date: 17/01/2017 | Last modified date: 17/01/2017 |
Published in: 2017
Uhlén2017 - TCGA-DD-A4NH-01A - Liver Hepatocellular Carcinoma (female, 66 years)
ID: MODEL1707114078 | Format: SBML | Submitter: Adil Mardinoglu | Uploaded date: 17/01/2017 | Last modified date: 17/01/2017 |
Published in: 2017
Uhlén2017 - TCGA-ED-A82E-01A - Liver Hepatocellular Carcinoma (female, 61 years)
ID: MODEL1707114647 | Format: SBML | Submitter: Adil Mardinoglu | Uploaded date: 17/01/2017 | Last modified date: 17/01/2017 |
Published in: 2017
Uhlén2017 - TCGA-DD-AACS-01A - Liver Hepatocellular Carcinoma (male, 40 years)
ID: MODEL1707114112 | Format: SBML | Submitter: Adil Mardinoglu | Uploaded date: 17/01/2017 | Last modified date: 17/01/2017 |
Published in: 2017
Uhlén2017 - TCGA-2Y-A9GW-01A - Liver Hepatocellular Carcinoma (male, 65 years)
ID: MODEL1707110529 | Format: SBML | Submitter: Adil Mardinoglu | Uploaded date: 17/01/2017 | Last modified date: 17/01/2017 |
Published in: 2017

Uhlén2017 - TCGA-CC-5261-01A - Liver Hepatocellular Carcinoma (male, 45 years)

Overview | Files | History

Short description

This is a whole genome metabolism model of a male patient diagnosed at the age of 45 years with Liver Hepatocellular Carcinoma affecting the patient's liver.

This model was automatically generated by tINIT (Agren, R., et al. (2014). Identification of anticancer drugs for hepatocellular carcinoma through personalized genome-scale metabolic modeling. Mol Syst Biol; 10(3), 721.) using information coming from the sample TCGA-CC-5261-01A from GDC Portal (Initial release 1.0, accessed via GDC API) and, where relevant, augmented with metabolic pathway information extracted from Human Metabolic Atlas.

This model has been produced by Human Pathology Atlas project (Uhlen, M., et al.; A pathology atlas of the human cancer transcriptome. Science.) and is currently hosted on BioModels Database and identified by MODEL1707113326.

To cite BioModels, please use: V Chelliah et al; BioModels: ten-year anniversary. Nucleic Acids Res 2015; 43 (D1): D542-D548.

Format

SBML (L2V3)

Related Publication

A pathology atlas of the human cancer transcriptome.

Uhlen M, Zhang C, Lee S, Sjöstedt E, Fagerberg L, Bidkhori G, Benfeitas R, Arif M, Liu Z, Edfors F, Sanli K, von Feilitzen K, Oksvold P, Lundberg E, Hober S, Nilsson P, Mattsson J, Schwenk JM, Brunnström H, Glimelius B, Sjöblom T, Edqvist PH, Djureinovic D, Micke P, Lindskog C, Mardinoglu A, Ponten F

Science (New York, N.Y.) , 8/ 2017 , Volume 357 , Issue 6352

Metadata information

hasTaxon	*Taxonomy* Homo sapiens
isDerivedFrom	1ad7f17e-b3b8-40e9-aab8-5a17e0aec408 *BioModels Database* MODEL1402200003
is	MODEL1707113326
hasProperty	*PATO* male *Human Disease Ontology* hepatocellular carcinoma
Curation status	non-curated
Original model(s)	http://identifiers.org/biomodels.db/MODEL1402200003

Help

Nucleic Acids Research, 2006, Vol. 34, Database issue ***D689–D691***
doi:10.1093/nar/gkj092

BioModels Database: a free, centralized database of curated, published, quantitative kinetic models of biochemical and cellular systems

Nicolas Le Novère*, Benjamin Bornstein[1], Alexander Broicher, Mélanie Courtot, Marco Donizelli, Harish Dharuri[2], Lu Li, Herbert Sauro[2], Maria Schilstra[3], Bruce Shapiro[1], Jacky L. Snoep[4] and Michael Hucka[5]

Li *et al. BMC Systems Biology* 2010, **4**:92
http://www.biomedcentral.com/1752-0509/4/92

BMC Systems Biology

DATABASE Open Access

BioModels Database: An enhanced, curated and annotated resource for published quantitative kinetic models

Chen Li[1], Marco Donizelli[1], Nicolas Rodriguez[1], Harish Dharuri[2], Lukas Endler[1], Vijayalakshmi Chelliah[1], Lu Li[1], Enuo He[1,2], Arnaud Henry[1], Melanie I Stefan[1], Jacky L Snoep[3], Michael Hucka[2], Nicolas Le Novère[1] and Camille Laibe*[1]

D542–D548 *Nucleic Acids Research, 2015, Vol. 43, Database issue* *Published online 20 November 2014*
doi: 10.1093/nar/gku1181

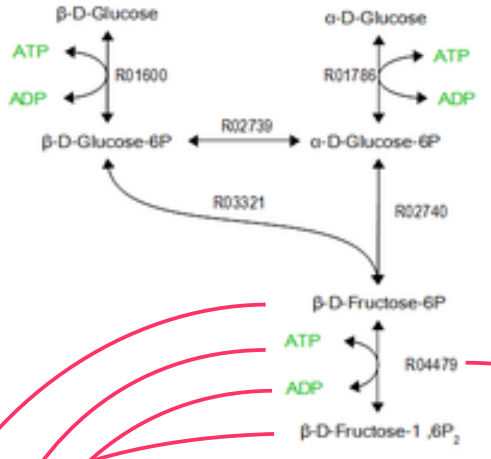
BioModels: ten-year anniversary

Vijayalakshmi Chelliah[1,*,†], Nick Juty[1,†], Ishan Ajmera[1], Raza Ali[1], Marine Dumousseau[1], Mihai Glont[1], Michael Hucka[2], Gaël Jalowicki[1], Sarah Keating[1], Vincent Knight-Schrijver[1,3,4], Audald Lloret-Villas[1], Kedar Nath Natarajan[1], Jean-Baptiste Pettit[1], Nicolas Rodriguez[1,3], Michael Schubert[1], Sarala M. Wimalaratne[1], Yangyang Zhao[1], Henning Hermjakob[1], Nicolas Le Novère[1,3] and Camille Laibe[1]

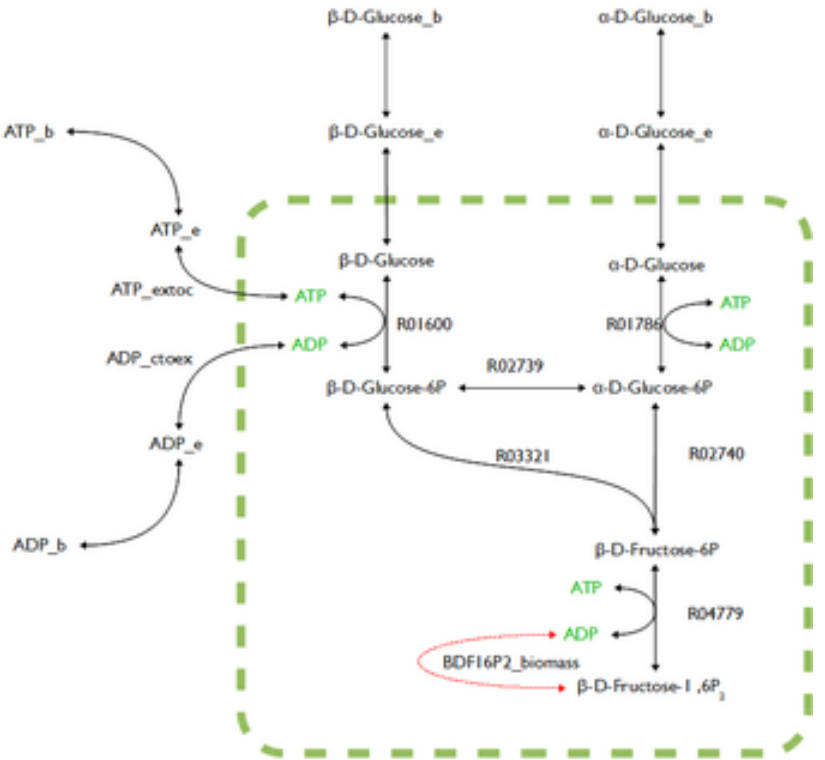
D1248–D1253 *Nucleic Acids Research, 2018, Vol. 46, Database issue* *Published online 2 November 2017*
doi: 10.1093/nar/gkx1023

BioModels: expanding horizons to include more modelling approaches and formats

Mihai Glont[1], Tung V. N. Nguyen[1], Martin Graesslin[2], Robert Hälke[3], Raza Ali[1], Jochen Schramm[2], Sarala M. Wimalaratne[1], Varun B. Kothamachu[1,4], Nicolas Rodriguez[4], Maciej J. Swat[1], Jurgen Eils[2], Roland Eils[2], Camille Laibe[1], Rahuman S. Malik-Sheriff[1,*], Vijayalakshmi Chelliah[1], Nicolas Le Novère[4,*] and Henning Hermjakob[1,*]



Prepare for FBA



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C00002	0	0	0	-1	-1	-1
C00008	0	0	0	1	1	1
C00221	0	0	0	-1	0	0
C00267	0	0	0	0	-1	0
C00668	-1	0	-1	0	1	0
C01172	1	-1	0	1	0	0
C05345	0	1	1	0	0	-1
C05378	0	0	0	0	0	1

	R02739_c	R03321_c	R02740_c	R01600_c	R01786_c	R04779_c	ATP_extoc_tr	ADP_ctoex_tr	BDG_extoc_tr	ADG_extoc_tr	BDF16P2_biomass_tr
C00002[c]	0	0	0	-1	-1	-1	1	0	0	0	0
C00002[e]	0	0	0	0	0	0	-1	0	0	0	0
C00008[c]	0	0	0	1	1	1	0	-1	0	0	1
C00008[e]	0	0	0	0	0	0	0	1	0	0	0
C00221[c]	0	0	0	-1	0	0	0	0	1	0	0
C00221[e]	0	0	0	0	0	0	0	0	-1	0	0
C00267[c]	0	0	0	0	-1	0	0	0	0	1	0
C00267[e]	0	0	0	0	0	0	0	0	0	-1	0
C00668[c]	-1	0	-1	0	1	0	0	0	0	0	0
C01172[c]	1	-1	0	1	0	0	0	0	0	0	0
C05345[c]	0	1	1	0	0	-1	0	0	0	0	0
C05378[c]	0	0	0	0	0	1	0	0	0	0	-1

FBA + logic model

2001

J. theor. Biol. (2001) **213,** 73–88
doi:10.1006/jtbi.2001.2405, available online at http://www.idealibrary.com on IDEAL®

Regulation of Gene Expression in Flux Balance Models of Metabolism

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**Department of Bioengineering, University of California, San Diego, La Jolla, CA 92093-0412, U.S.A.*
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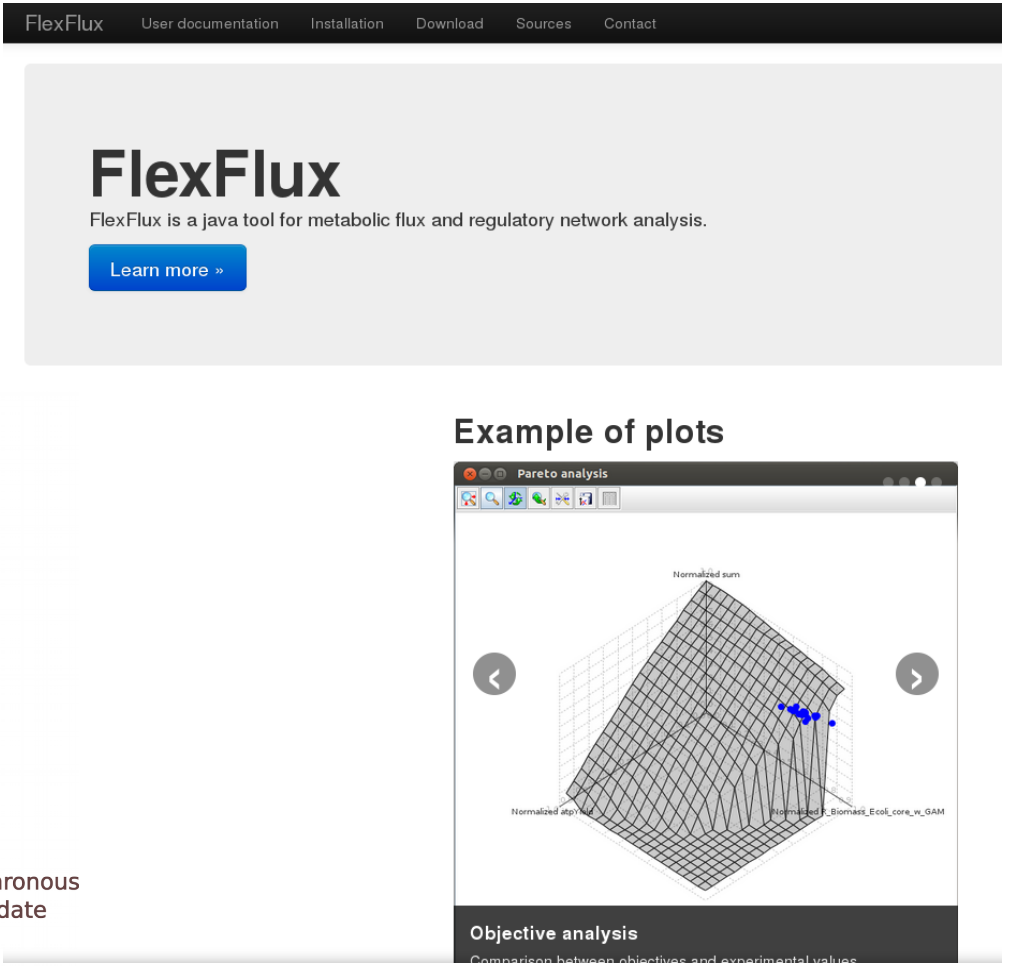
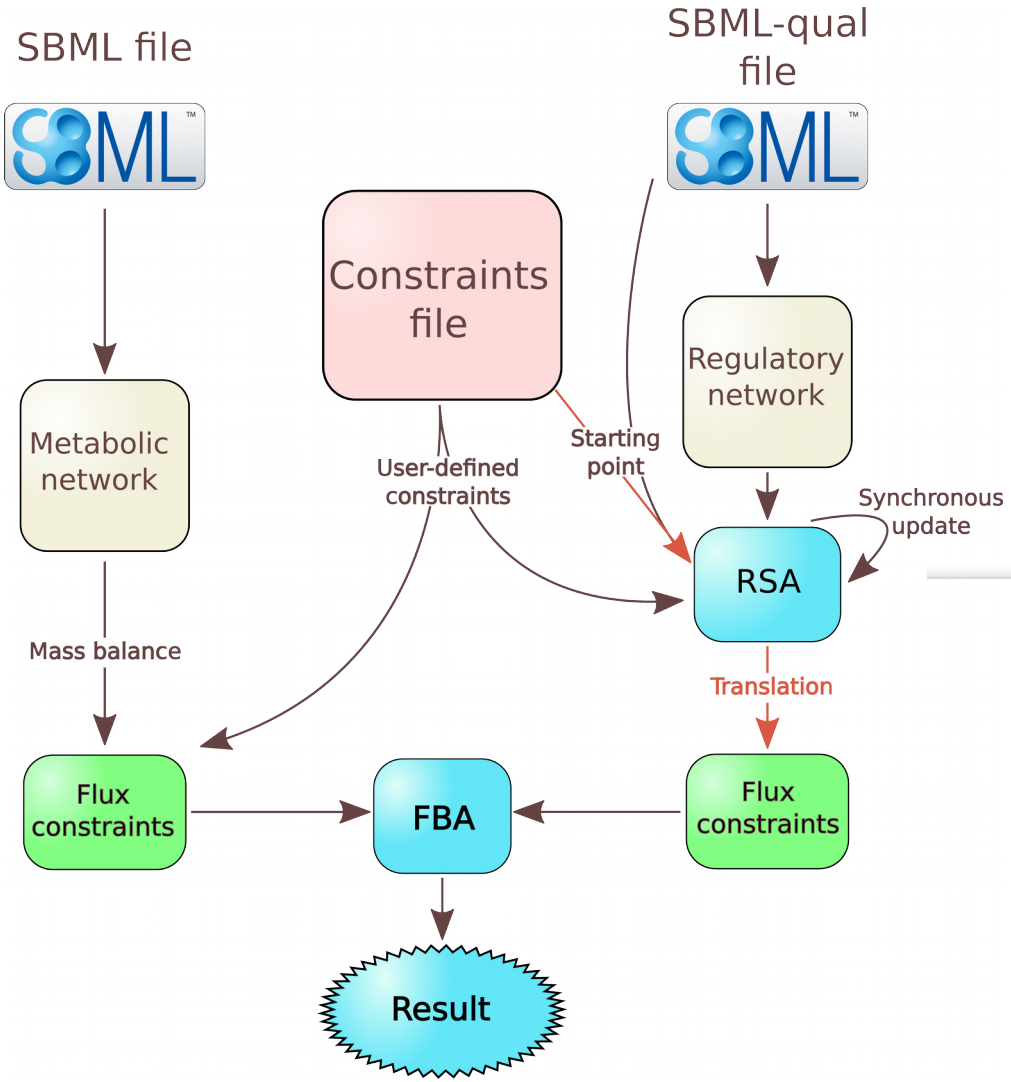
(*Received on* 6 *March* 2001, *Accepted in revised form on* 19 *July* 2001)

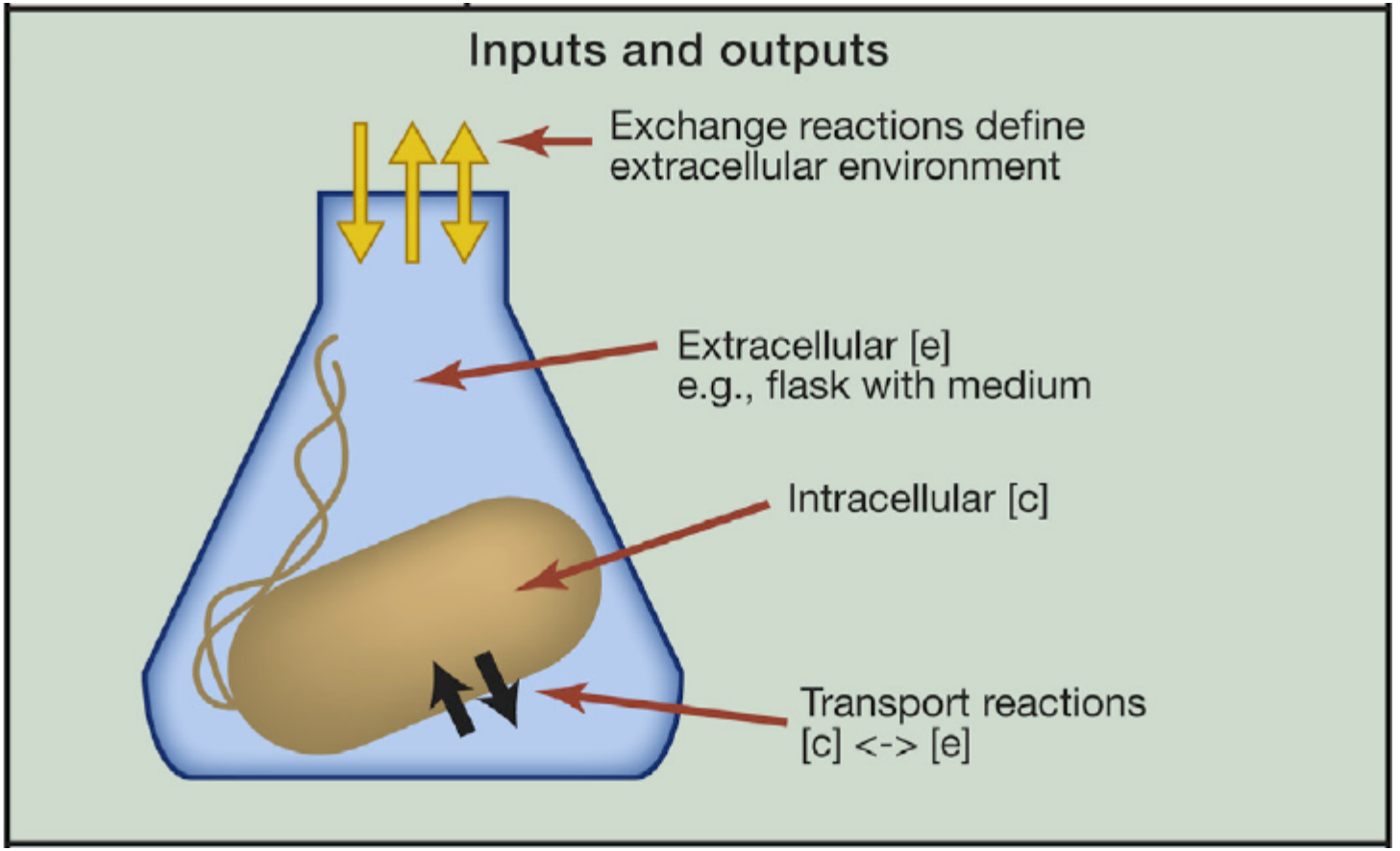
Genome-scale metabolic networks can now be reconstructed based on annotated genomic data augmented with biochemical and physiological information about the organism. Mathematical analysis can be performed to assess the capabilities of these reconstructed networks. The constraints-based framework, with flux balance analysis (FBA), has been used successfully to predict time course of growth and by-product secretion, effects of mutation and knock-outs, and gene expression profiles. However, FBA leads to incorrect predictions in situations where regulatory effects are a dominant influence on the behavior of the organism. Thus, there is a need to include regulatory events within FBA to broaden its scope and predictive capabilities. Here we represent transcriptional regulatory events as time-dependent constraints on the capabilities of a reconstructed metabolic network to further constrain the space of possible network functions. Using a simplified metabolic/regulatory network, growth is simulated under various conditions to illustrate systemic effects such as catabolite repression, the aerobic/anaerobic diauxic shift and amino acid biosynthesis pathway repression. The incorporation of transcriptional regulatory events in FBA enables us to interpret, analyse and predict the effects of transcriptional regulation on cellular metabolism at the systemic level.

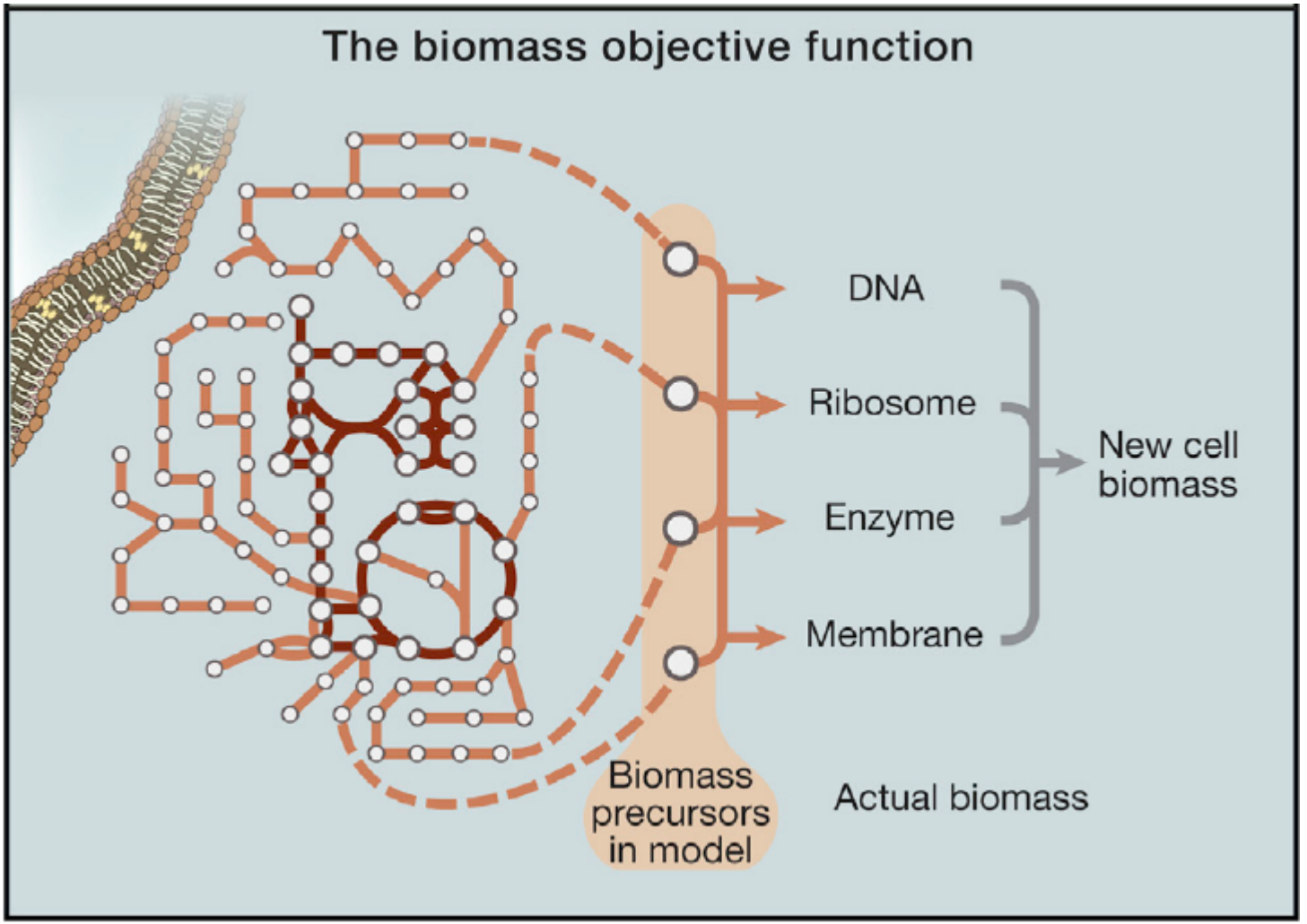




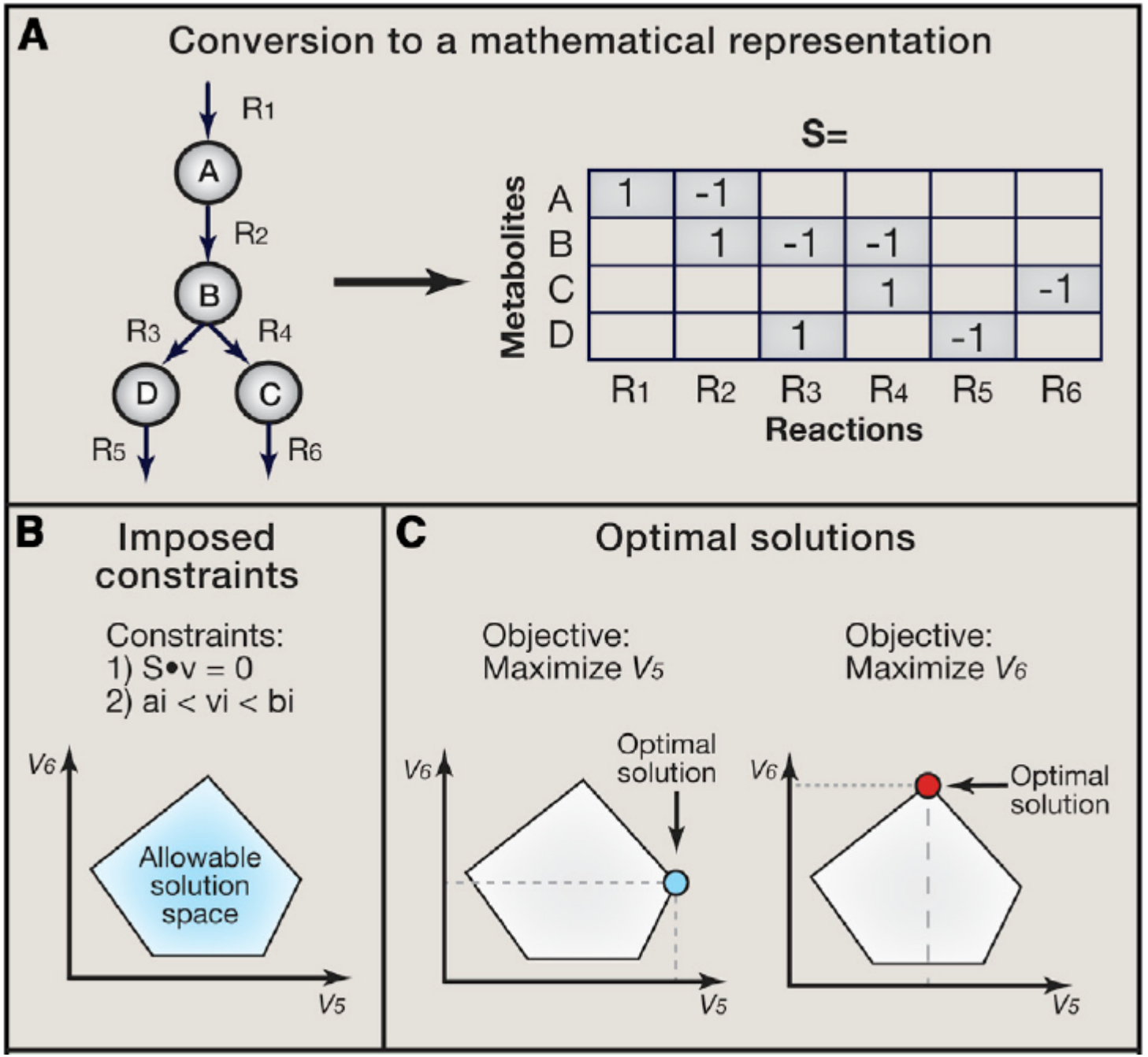
Example of plots

Lucas Marmiesse (Toulouse)


Inputs and outputs
Exchange reactions define extracellular environment
Extracellular [e]
e.g., flask with medium
Intracellular [c]
Transport reactions
[c] <-> [e]

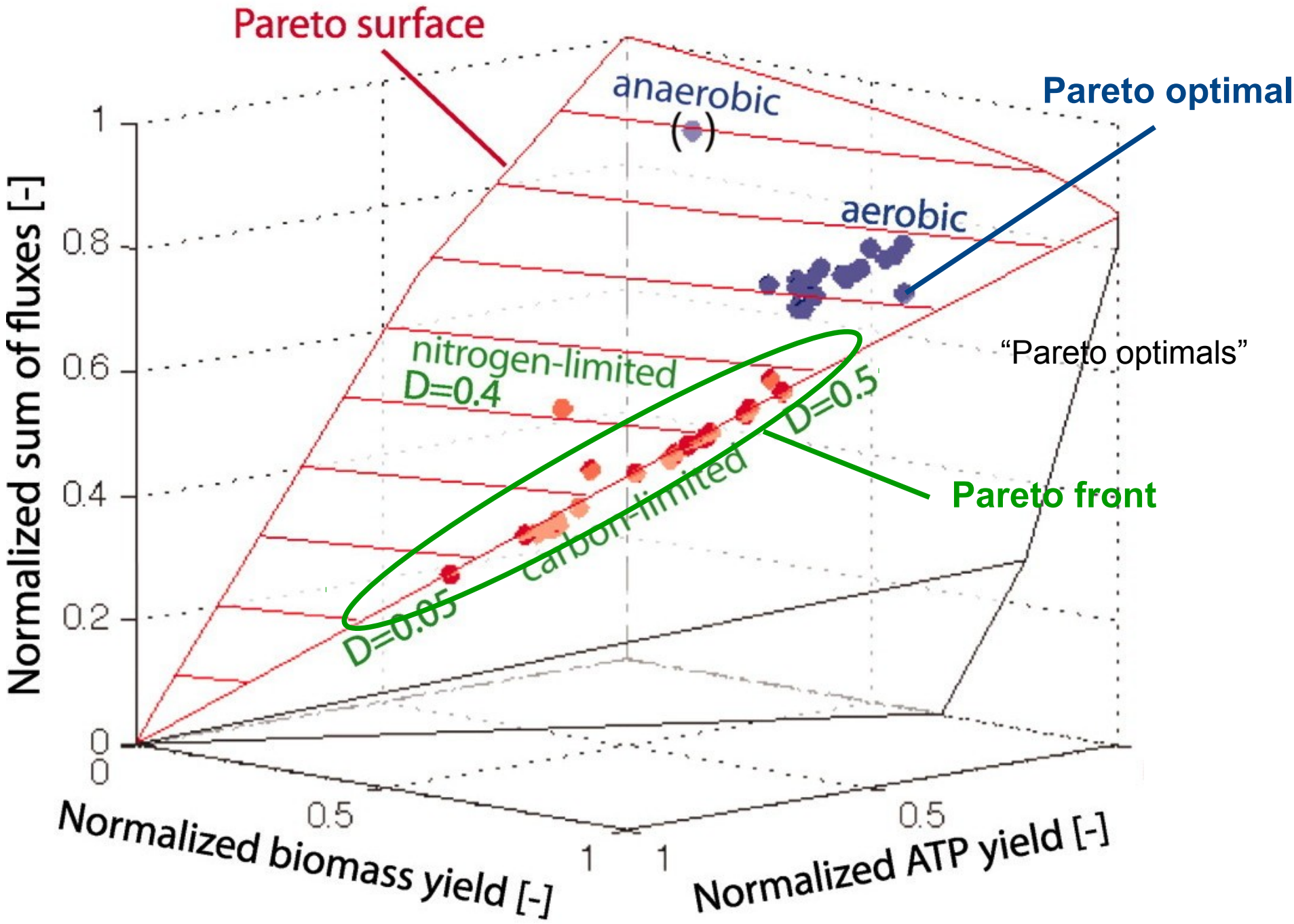

The biomass objective function
DNA
Ribosome
Enzyme
Membrane
New cell biomass
Biomass precursors in model
Actual biomass

Different objectives → different solutions



An objective generally involve a combination of several fluxes and/or outputs,
And will also provide several solutions ("Pareto optimals")

Vilfredo Pareto (1848-1923)


Pareto surface
anaerobic
(·)
Pareto optimal
aerobic
nitrogen-limited
D=0.4
D=0.5
carbon-limited
Pareto front
D=0.05
"Pareto optimals"
Normalized sum of fluxes [-]
1
0.8
0.6
0.4
0.2
0
0
0.5
1
Normalized biomass yield [-]
1
0.5
Normalized ATP yield [-]