

ELIXIR-Omics-Integration-and-Systems-Biology, Sep 9, 2021

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Department of Biotechnology and Biomedicine (DTU Bioengineering)
Computer Aided Biotechnology Group

Constraint-based modeling of metabolism

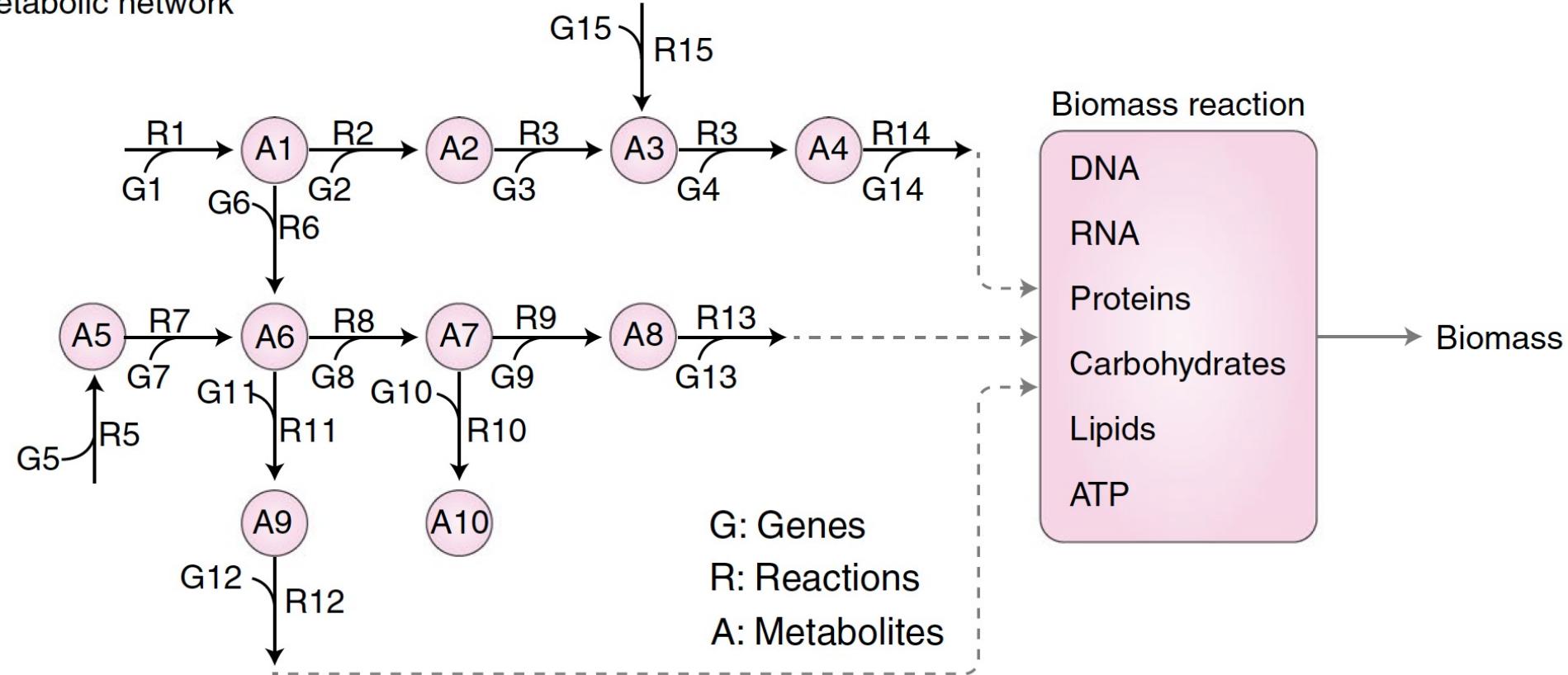
 niso@dtu.dk

What are genome-scale metabolic models
and how are they constructed?

Genome-scale metabolic models (GEMs) 101

Constraint-based modeling aka Genome-scale metabolic modeling (GEMs)

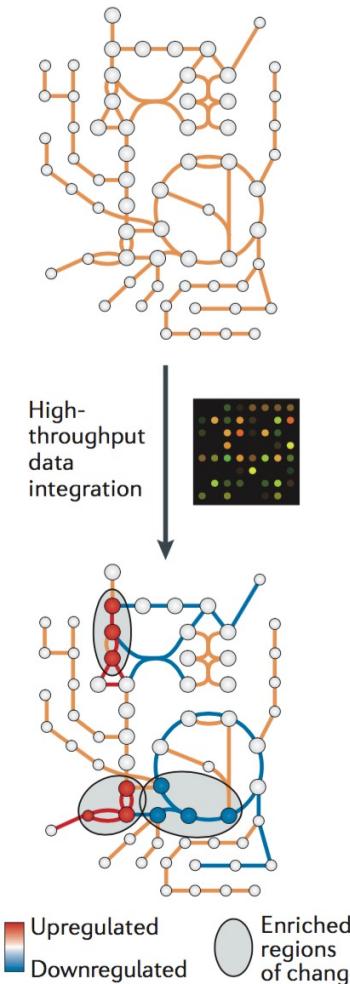
a Metabolic network



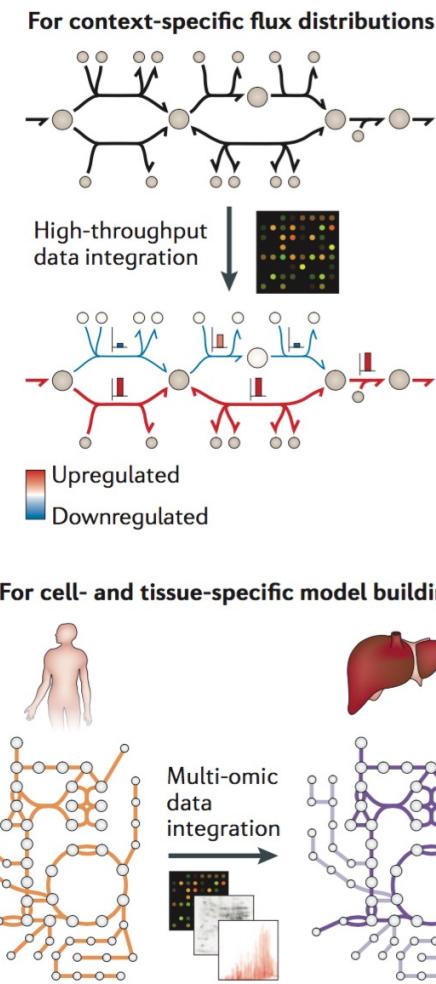
Kumar, M., Ji, B., Zengler, K. & Nielsen, J. Modelling approaches for studying the microbiome. *Nat Microbiol* **4**, 1253–1267 (2019).

Applications of genome-scale metabolic models (GEMs)

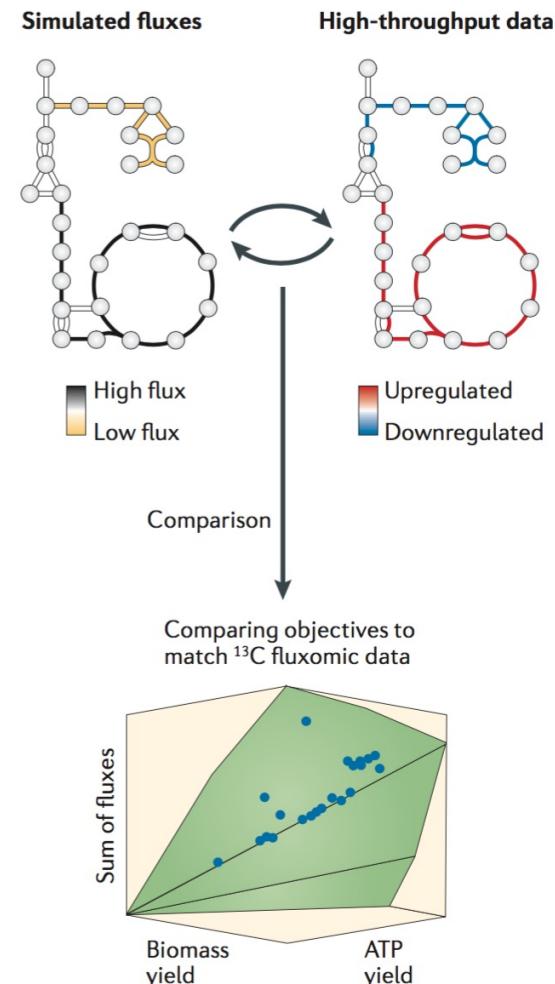
a Topological enrichment



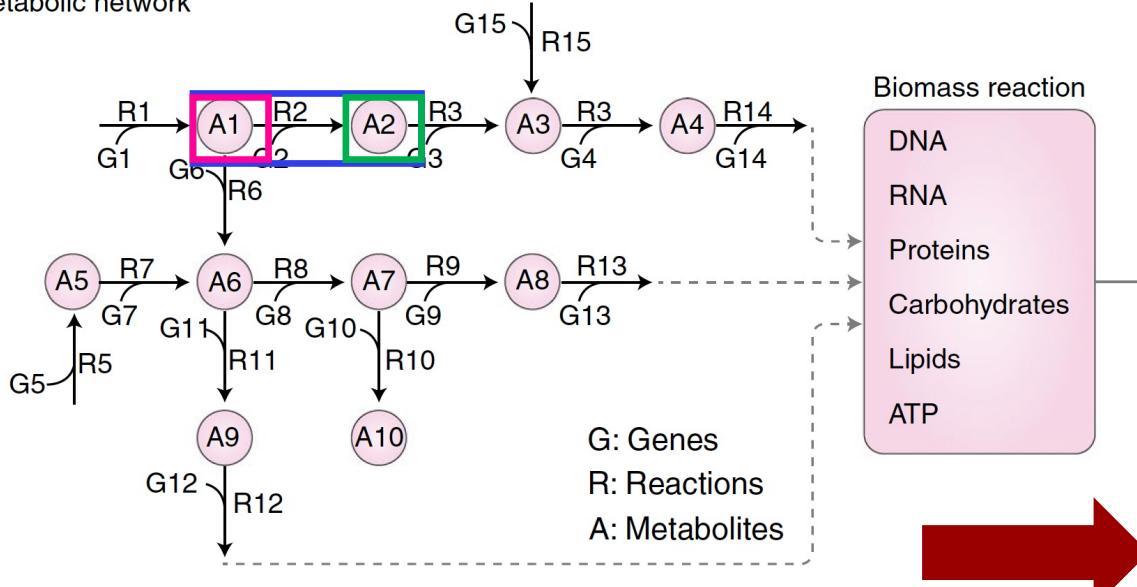
b Constraining the solution space



c Comparison



Constraint-based modeling of metabolism

a Metabolic network**b** Stoichiometric matrix (S)

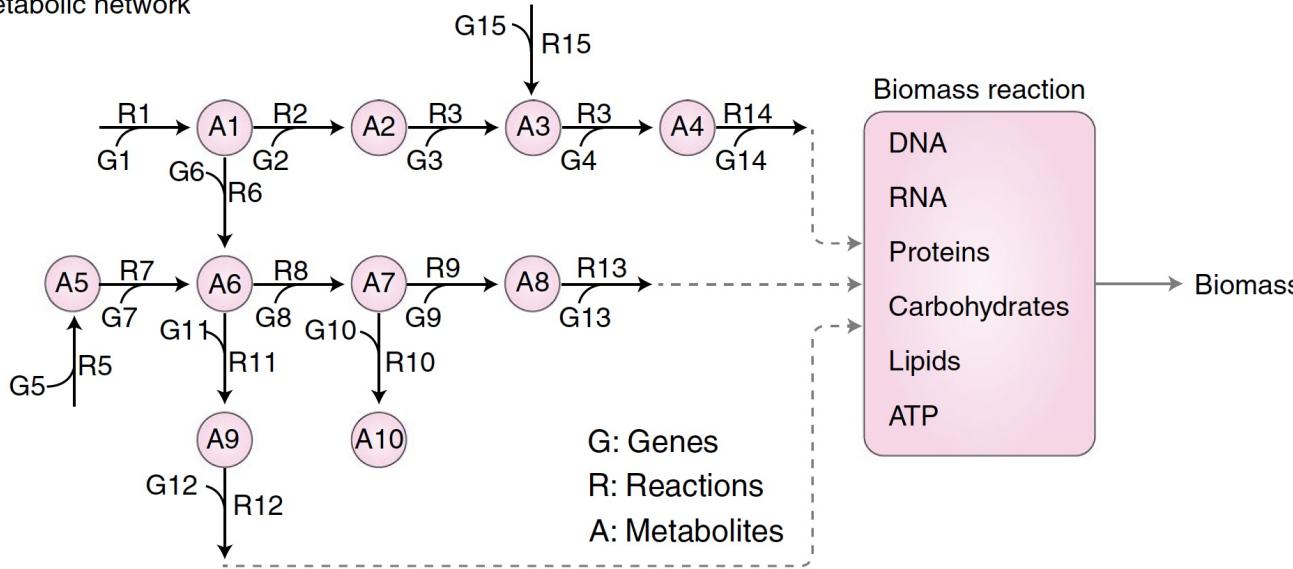
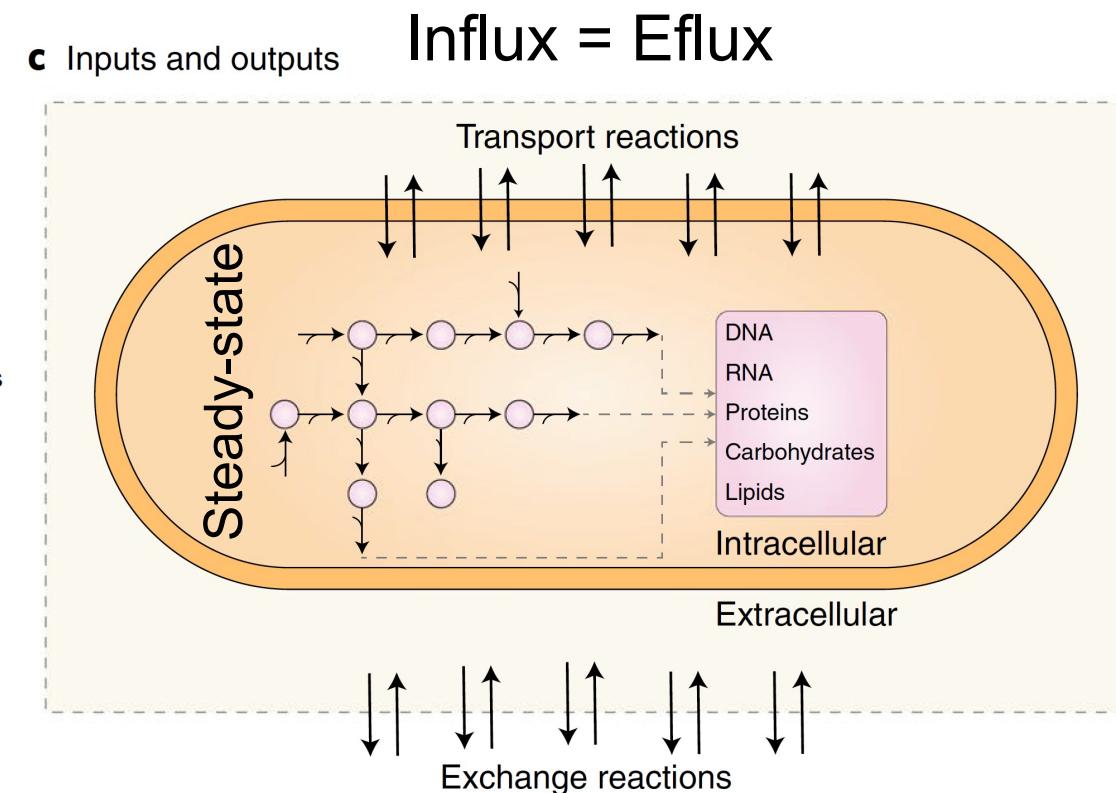
	Reactions														
	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	R12	R13	R14	R15
A1	1	-1	0	0	0	-1	0	0	0	0	0	0	0	0	0
A2	0	1	-1	0	0	0	0	0	0	0	0	0	0	0	0
A3	0	0	1	-1	0	0	0	0	0	0	0	0	0	0	1
A4	0	0	0	1	0	0	0	0	0	0	0	0	0	-1	0
A5	0	0	0	0	-1	0	1	0	0	0	0	0	0	1	0
A6	0	0	0	0	0	1	1	-1	0	0	-1	0	0	0	0
A7	0	0	0	0	0	0	0	0	1	-1	-1	0	0	0	0
A8	0	0	0	0	0	0	0	0	0	1	0	0	-1	0	0
A9	0	0	0	0	0	0	0	0	0	0	1	-1	0	0	0
A10	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0

Encode mathematically

$$\text{ODE} \quad \frac{dx(t)}{dt} = S v(x(t), p, \dots) \xrightarrow{\text{Steady-state assumption}} S v = 0 \quad \text{Linear system of equations}$$

Kumar, M., Ji, B., Zengler, K. & Nielsen, J. Modelling approaches for studying the microbiome. *Nat Microbiol* **4**, 1253–1267 (2019).

Constraint-based modeling of metabolism

a Metabolic network**c** Inputs and outputs

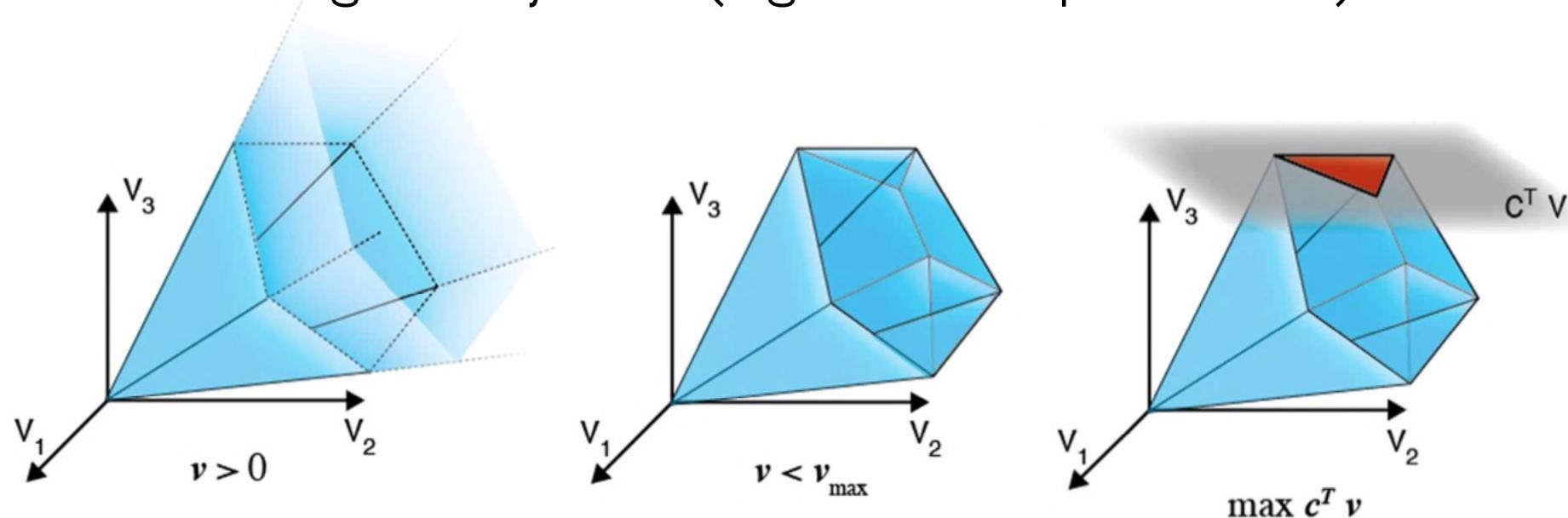
$$\text{ODE } \frac{dx(t)}{dt} = S v(x(t), p, \dots) \xrightarrow{\text{Steady-state assumption}} S v = 0$$

Linear system of equations

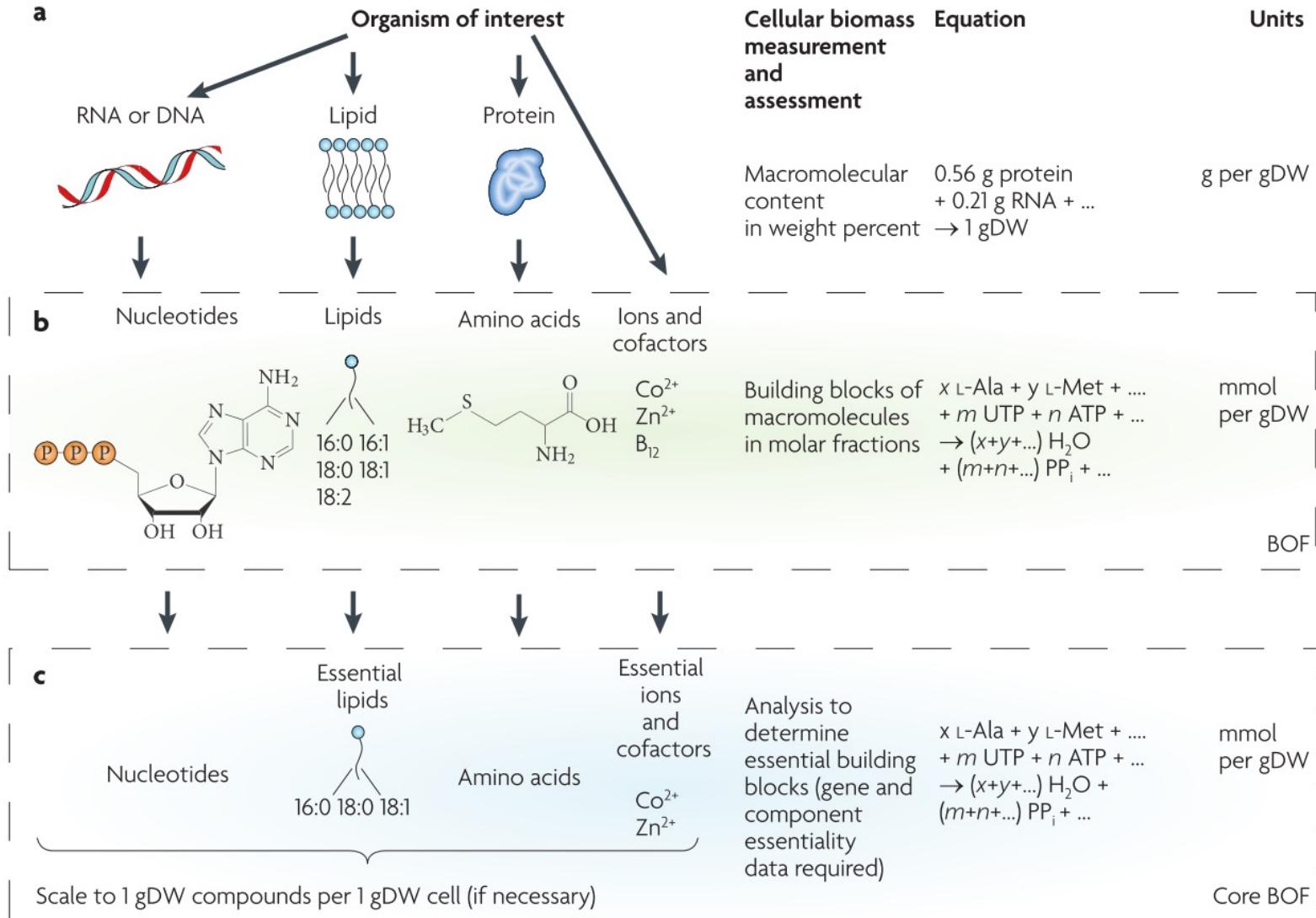
Kumar, M., Ji, B., Zengler, K. & Nielsen, J. Modelling approaches for studying the microbiome. *Nat Microbiol* **4**, 1253–1267 (2019).

Constraint-based modeling: constraints

- Following constraints can be imposed
 - Mass balance: metabolite production and consumption rates are equal ($S v = \mathbf{0}$)
 - Thermodynamics: e.g. irreversibility of reactions
 - Flux capacities: bounds on flux e.g. nutrient uptake rates
- Optimize a biological objective (e.g. biomass production)



Constraint-based modeling: the biomass equation



Feist, A. M., Herrgard, M. J., Thiele, I., Reed, J. L., & Palsson, B. Ø. (2009). Reconstruction of biochemical networks in microorganisms. *Nature Reviews Microbiology*, 7(2), 129–143.
<http://doi.org/10.1038/nrmicro1949>

Constraint-based modeling: flux balance analysis (FBA) problem formulation

Often referred to as
Flux Balance
Analysis (FBA)

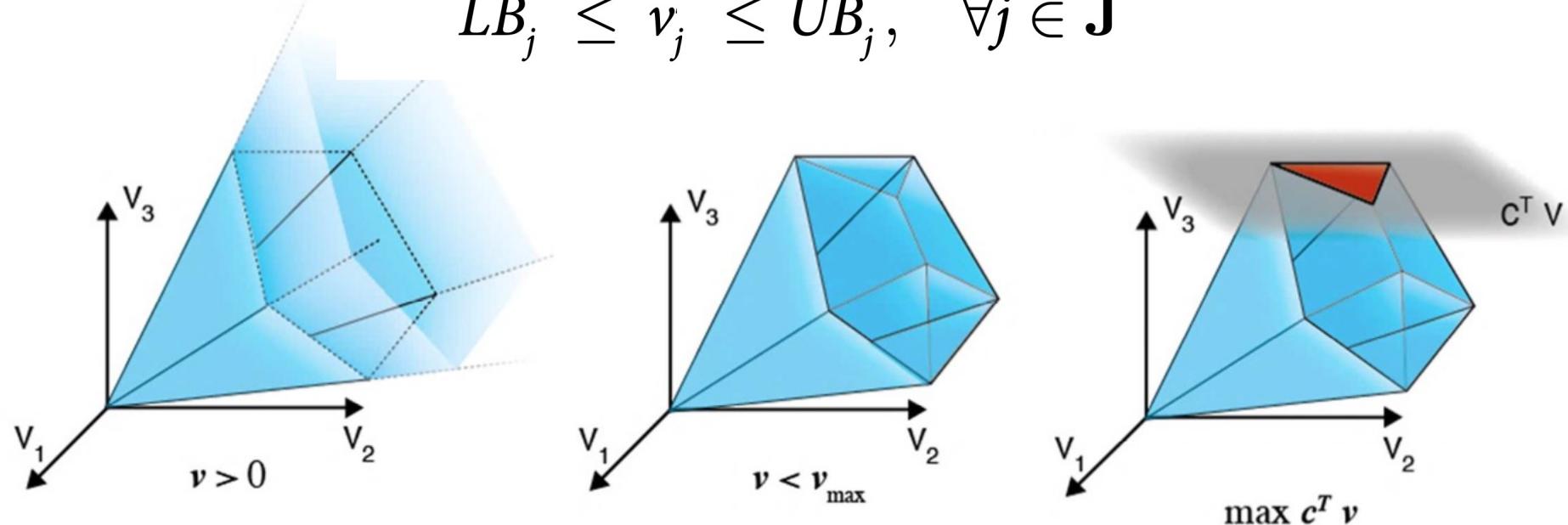
$$\max \quad v_{\text{biomass}}$$

subject to $\sum_{j \in \mathbf{J}} S_{ij} v_j = 0, \quad \forall i \in \mathbf{I}$

Metabolites

$$LB_j \leq v_j \leq UB_j, \quad \forall j \in \mathbf{J}$$

Reactions



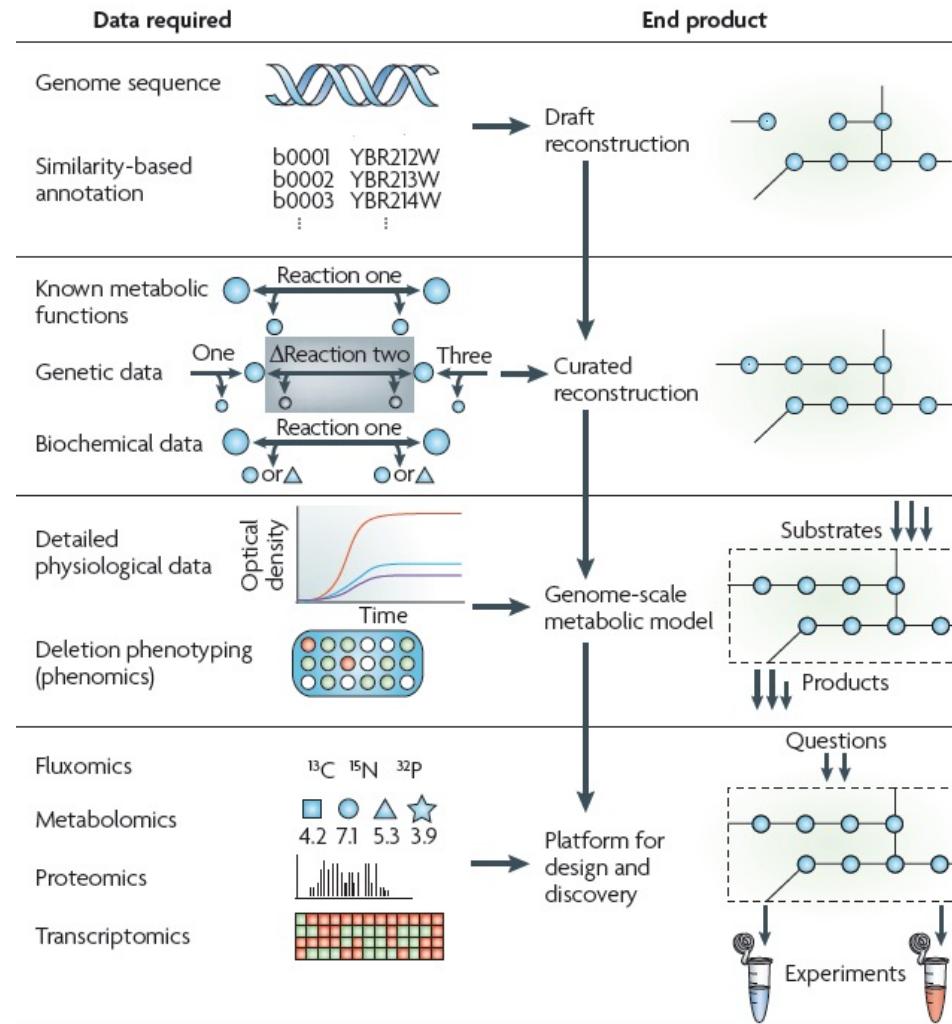
The phases of a genome-scale reconstruction of metabolism

1. Assembly of a draft genome-scale reconstruction

2. Curating the model reconstruction

3. Conversion of the reconstruction into a computational model – Validation

4. Application of the model



Feist et al, 2009, *Nature Reviews Microbiology*, 7:129-143 (p. 130)

Genome-scale metabolic model repositories and reconstruction platforms

Systems Biology Research Group <http://bigg.ucsd.edu/> About Advanced Search Data Access Membrane Validator ▾

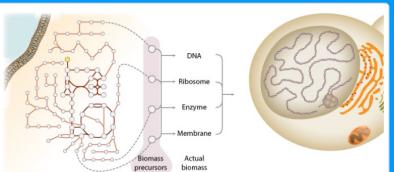
BiGG Models

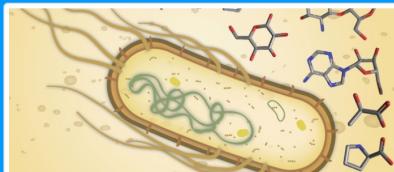
Search the database by model, reaction, metabolite, or gene ?

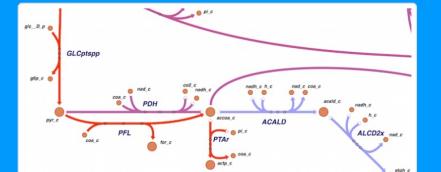
Search

Exclude multi-strain models from search

Latest update Version 1.6: Adds 23 new models & more!

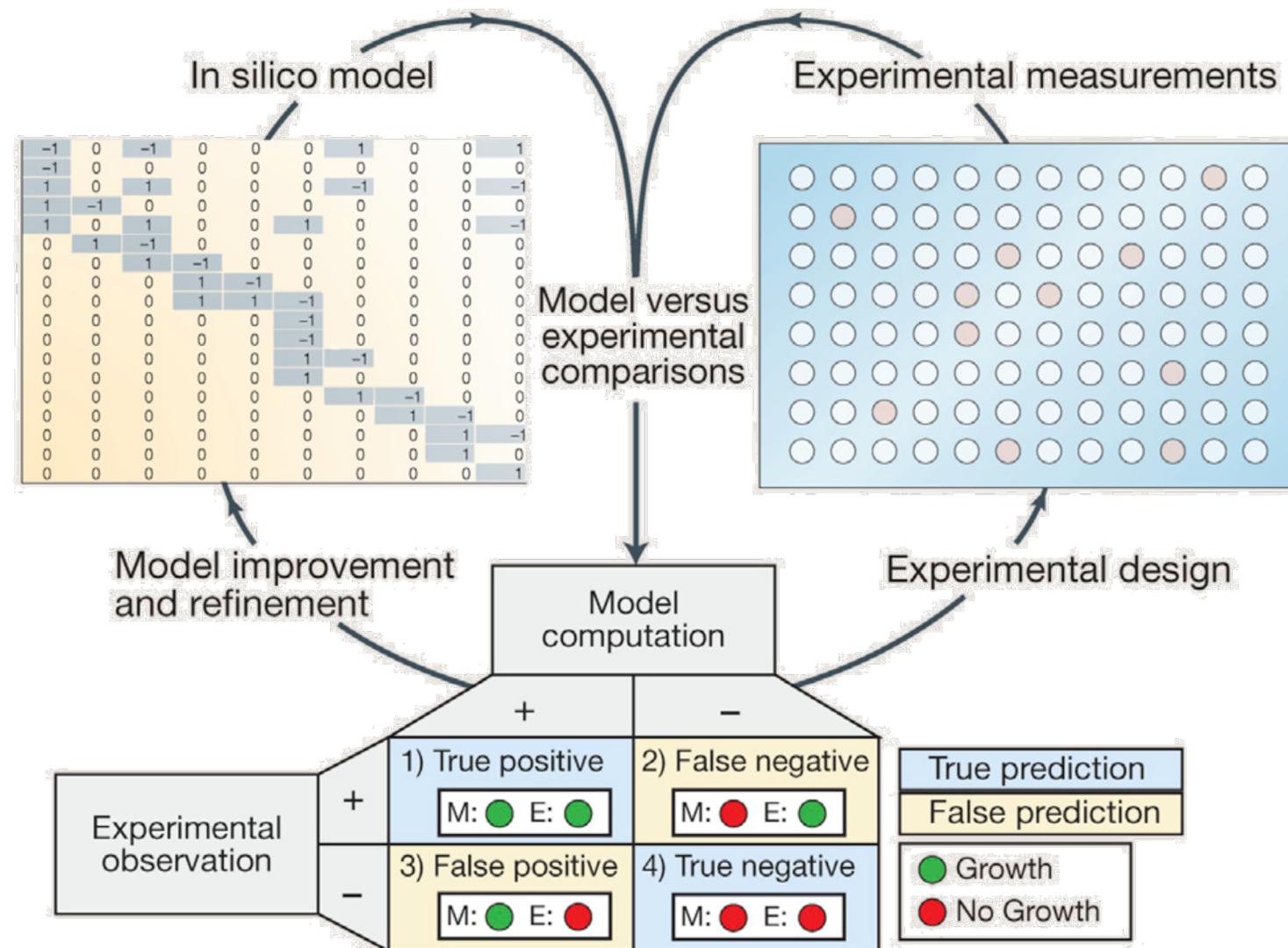

View Models


View Metabolites


View Reactions

- <https://www.kbase.us/>
- <https://metabolicatlas.org/gems/repository>
- <http://www.ebi.ac.uk/biomodels/>
- Many models are also publicly available via GitHub

Iterative improvement of models





<https://github.com/cdanielmachado/carveme>

Genome-scale metabolic model reconstruction with CarveMe

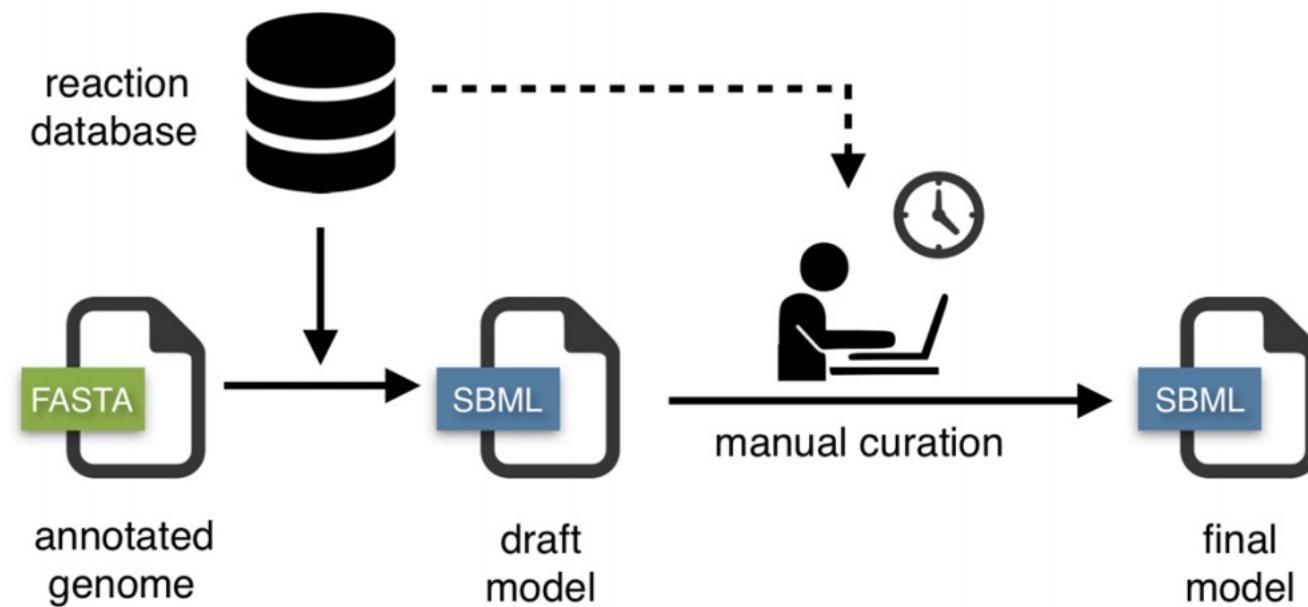
CarveMe is a python-based tool for genome-scale metabolic model reconstruction.

Documentation

For more details please check: <http://carveme.readthedocs.io/>

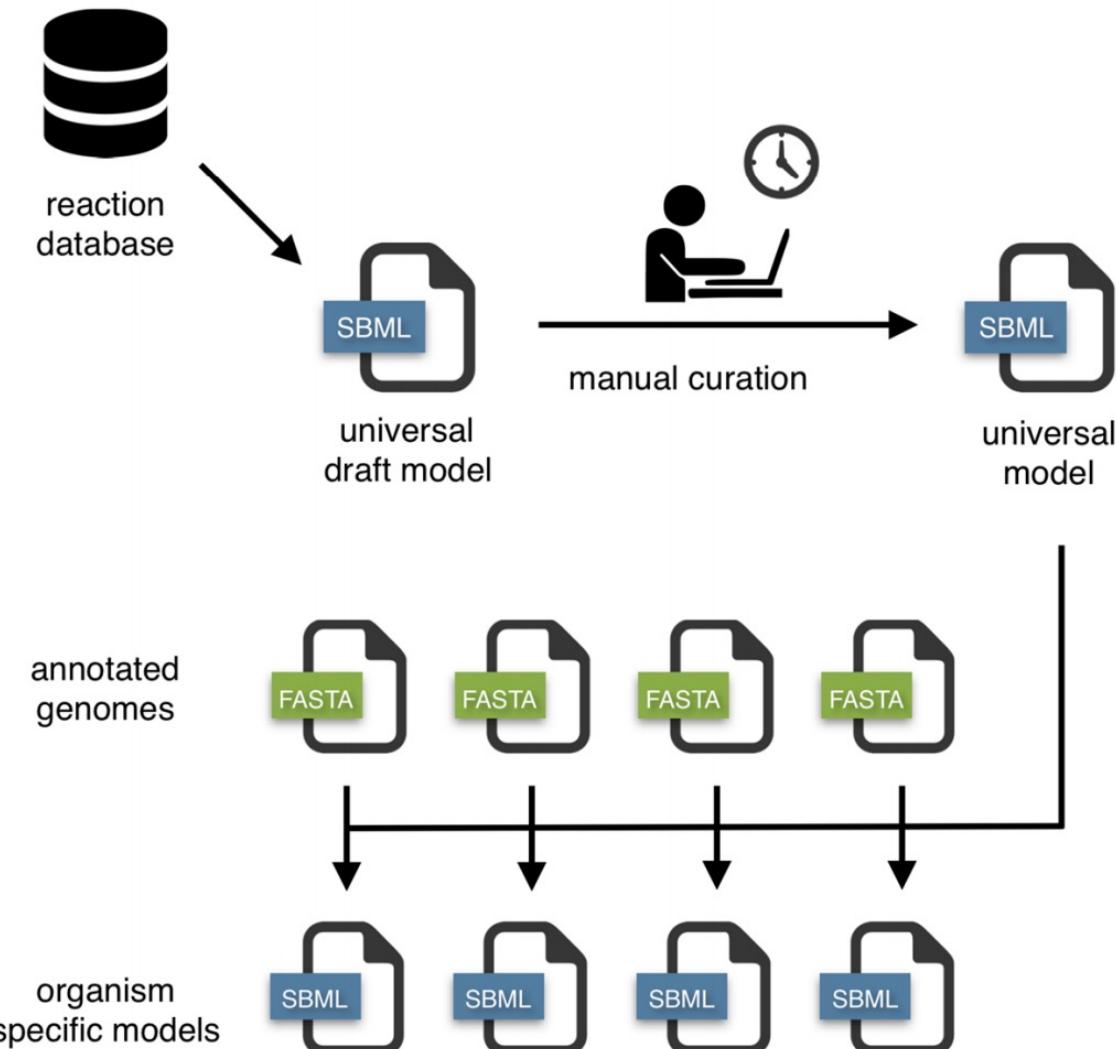
Machado, D., Andrejev, S., Tramontano, M. & Patil, K. R. Fast automated reconstruction of genome-scale metabolic models for microbial species and communities. *Nucleic Acids Res.* **46**, 7542–7553 (2018).

A Classic reconstruction workflow



Machado, D., Andrejev, S., Tramontano, M. & Patil, K. R. Fast automated reconstruction of genome-scale metabolic models for microbial species and communities. *Nucleic Acids Res.* **46**, 7542–7553 (2018).

B CarveMe reconstruction workflow



Machado, D., Andrejev, S., Tramontano, M. & Patil, K. R. Fast automated reconstruction of genome-scale metabolic models for microbial species and communities. *Nucleic Acids Res.* **46**, 7542–7553 (2018).

KBase – Predictive biology



<https://www.kbase.us/>

KBase – Predictive biology

The screenshot shows the KBase Narrative Interface. At the top, there's a header with the KBase logo, a title bar saying "Untitled" and "Created by: Nikolas Sonnenschein (phantomas1234)", and a toolbar with icons for help, kernel, share, save, and a network graph.

The main interface has two tabs: "Analyze" (selected) and "Narratives". The "DATA" section contains a single item: "Marinobacter_adhaerens_HP15 v1" (Genome: Marinobacter adhaerens HP15, 2 minutes ago). A large "Welcome to KBase's Narrative Interface!" box provides an overview of the platform's features, including "Welcome to KBase's Narrative Interface!", "What's a Narrative?", "Take the Tour", "Get Some Data", "Analyze It", "Save and Share Your Narrative", and "Find Documentation". It also includes a "Questions? Bug reports? Contact us!" link and a note about deleting the welcome cell.

The "APPS" section lists several tools under the "Model SEED" category:

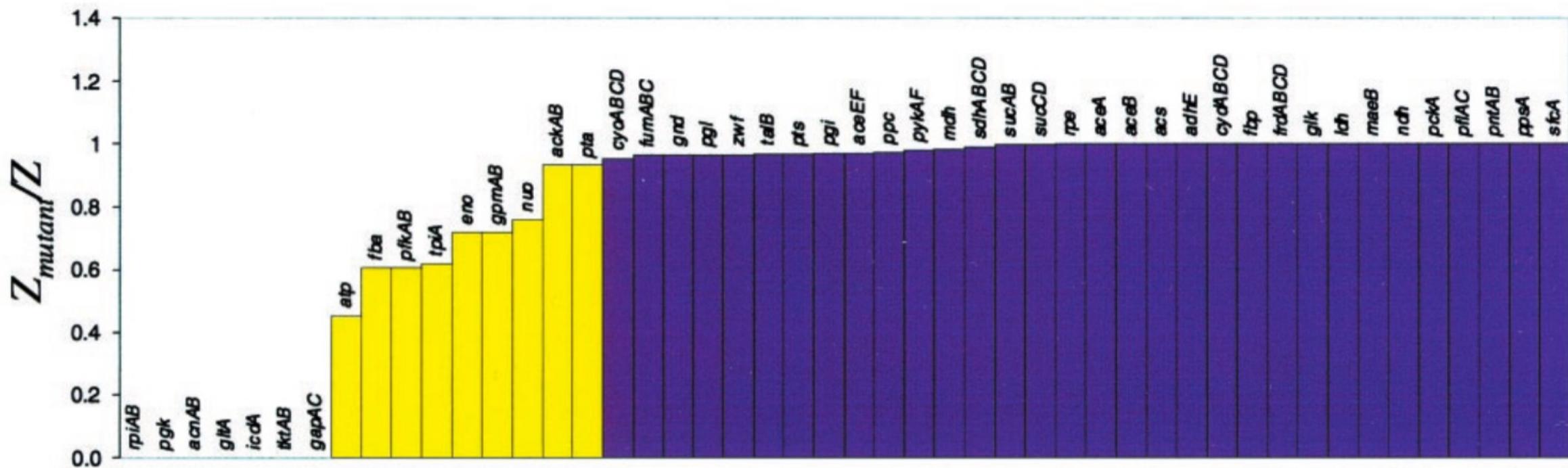
- Build Metabolic Model** (fba_tools v1.7.6): Generating a draft metabolic model based on an annotated genome. Status: Running - started 28s ago. Buttons: View Configure, Info, Job Status, Result.
- Build Multiple Metabolic Models** (fba_tools v1.7.6): Generate a draft metabolic model based on an annotated genome. More options... (link)
- Bulk Download Modeling Objects** (fba_tools v1.7.6): Bulk download modeling objects.
- Check Model Mass Balance** (fba_tools v1.7.6): Check model mass balance.
- Compare FBA Solutions** (fba_tools v1.7.6): Compare FBA solutions.

<https://www.kbase.us/>

Gene essentiality and phenotypic phase planes

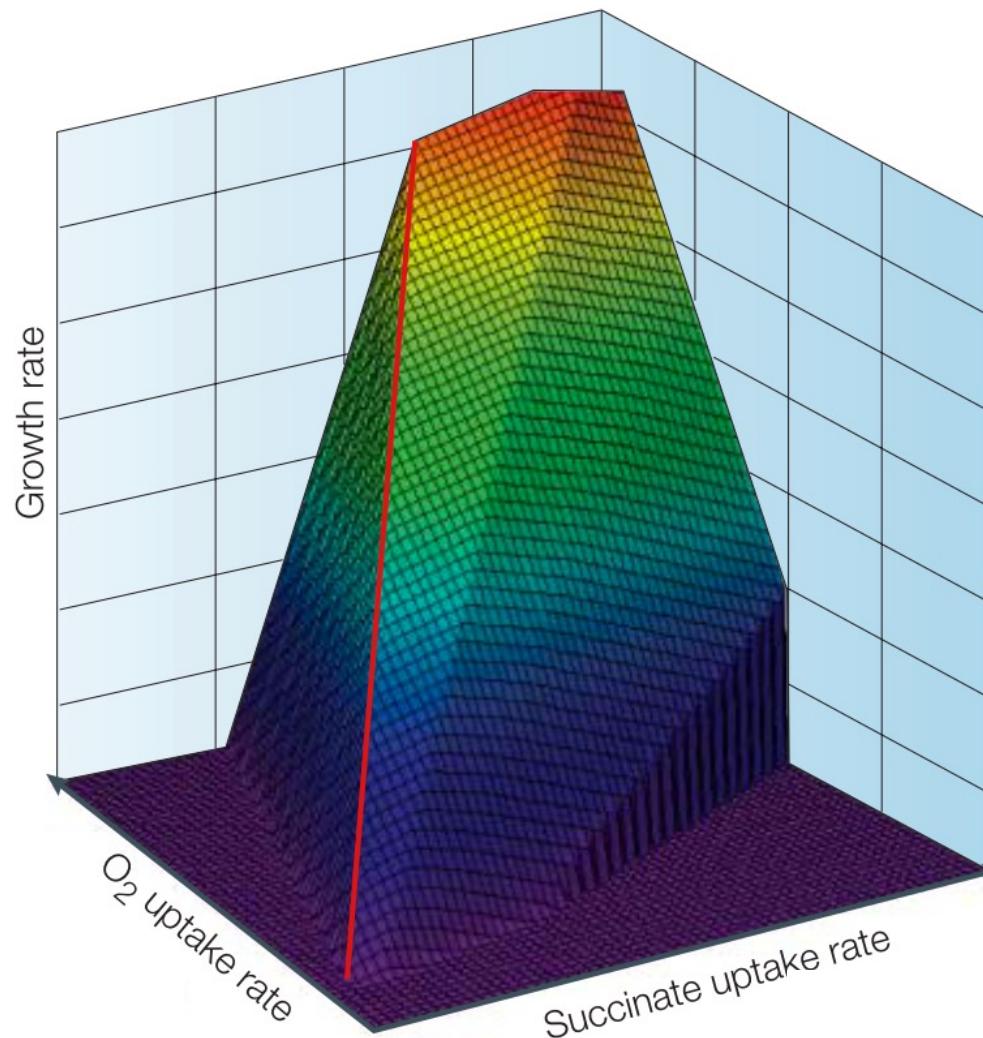
Experimental validation of genome-scale metabolic models

Predict gene essentiality with FBA



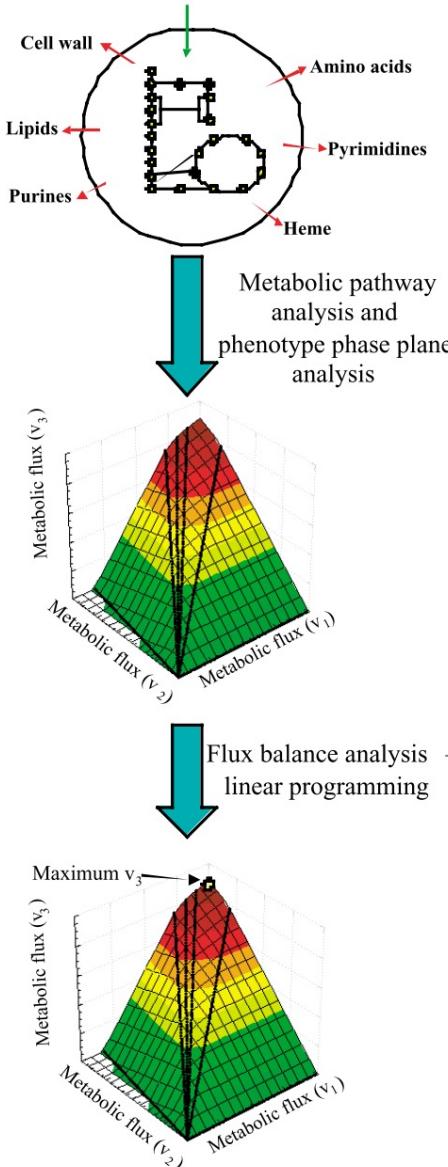
Edwards, J. S., & Palsson, B. Ø. (2000). The Escherichia coli MG1655 in silico metabolic genotype: its definition, characteristics, and capabilities. *Proceedings of the National Academy of Sciences of the United States of America*, 97(10), 5528–5533.

Phenotypic Phase Planes (PPP)

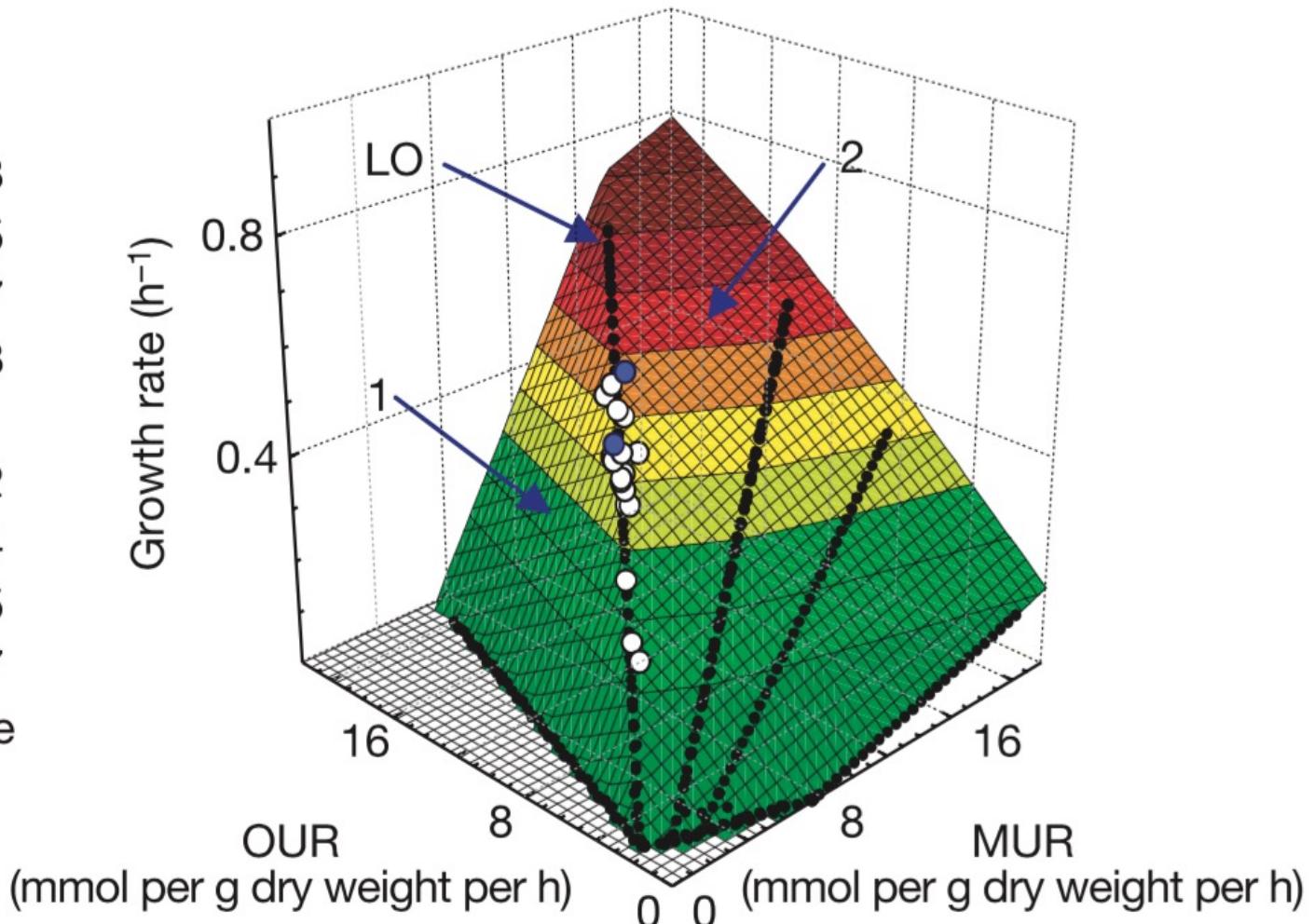
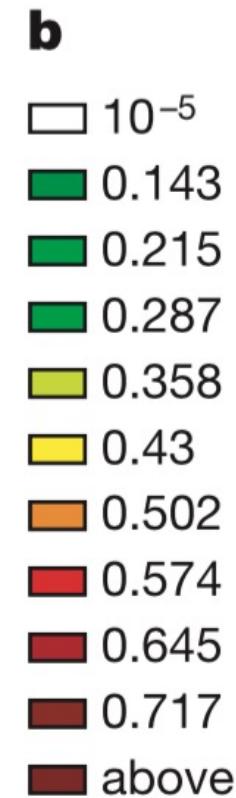


Adaptive laboratory evolution confirms FBA predictions

Phenotypic
Phase
Plane



FBA result
projected

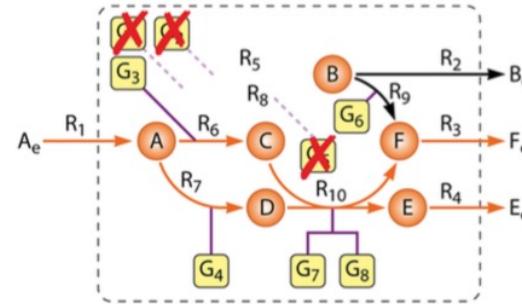
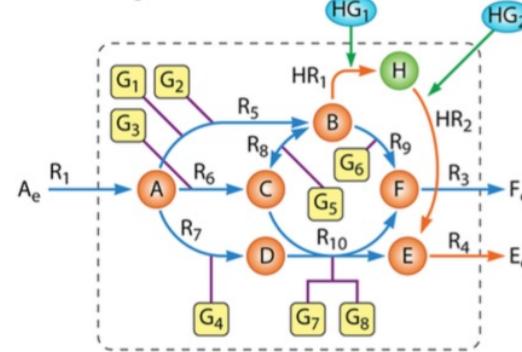
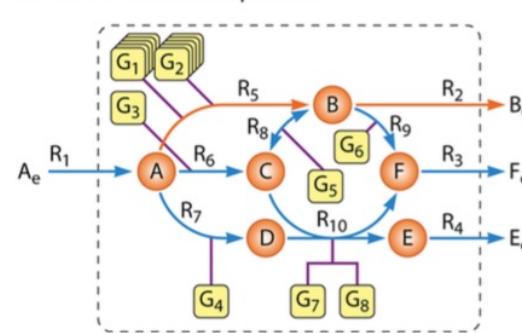
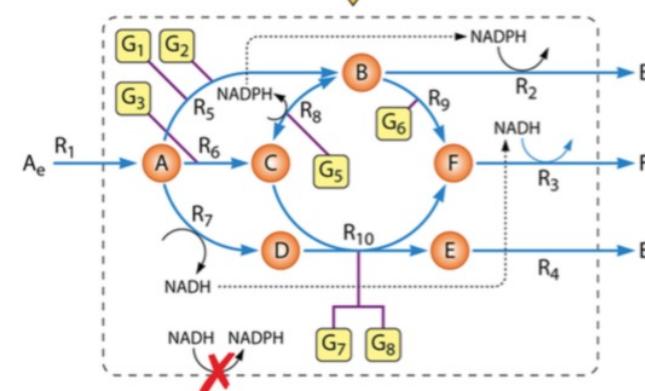
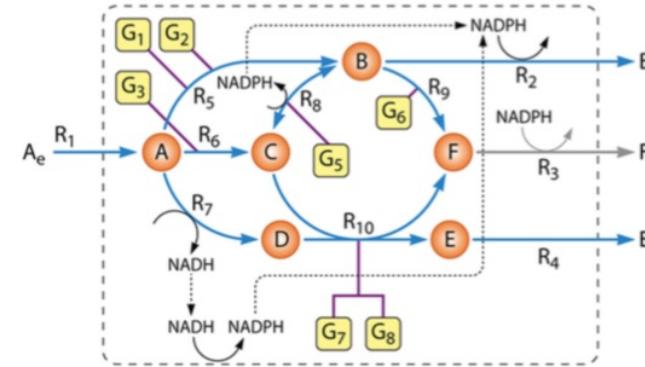


Edwards, J. S., Ibarra, R. U., & Palsson, B. Ø. (2001). In silico predictions of *Escherichia coli* metabolic capabilities are consistent with experimental data. *Nature Biotechnology*, 19(2), 125–130. <http://doi.org/10.1038/84379>

How can constraint-based modeling be applied to strain design?

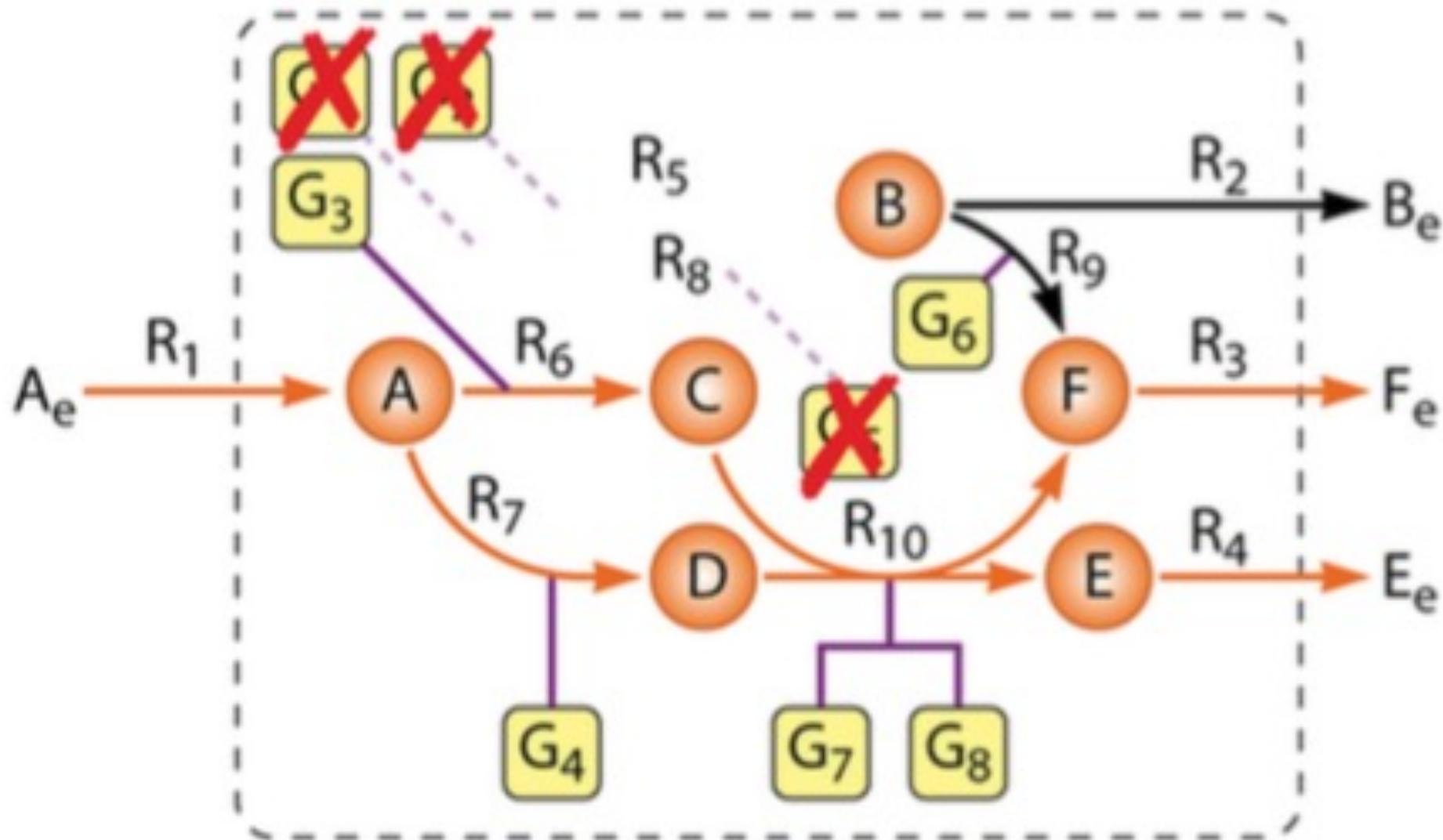
Rational strain engineering with genome-scale metabolic models

Strain engineering operations

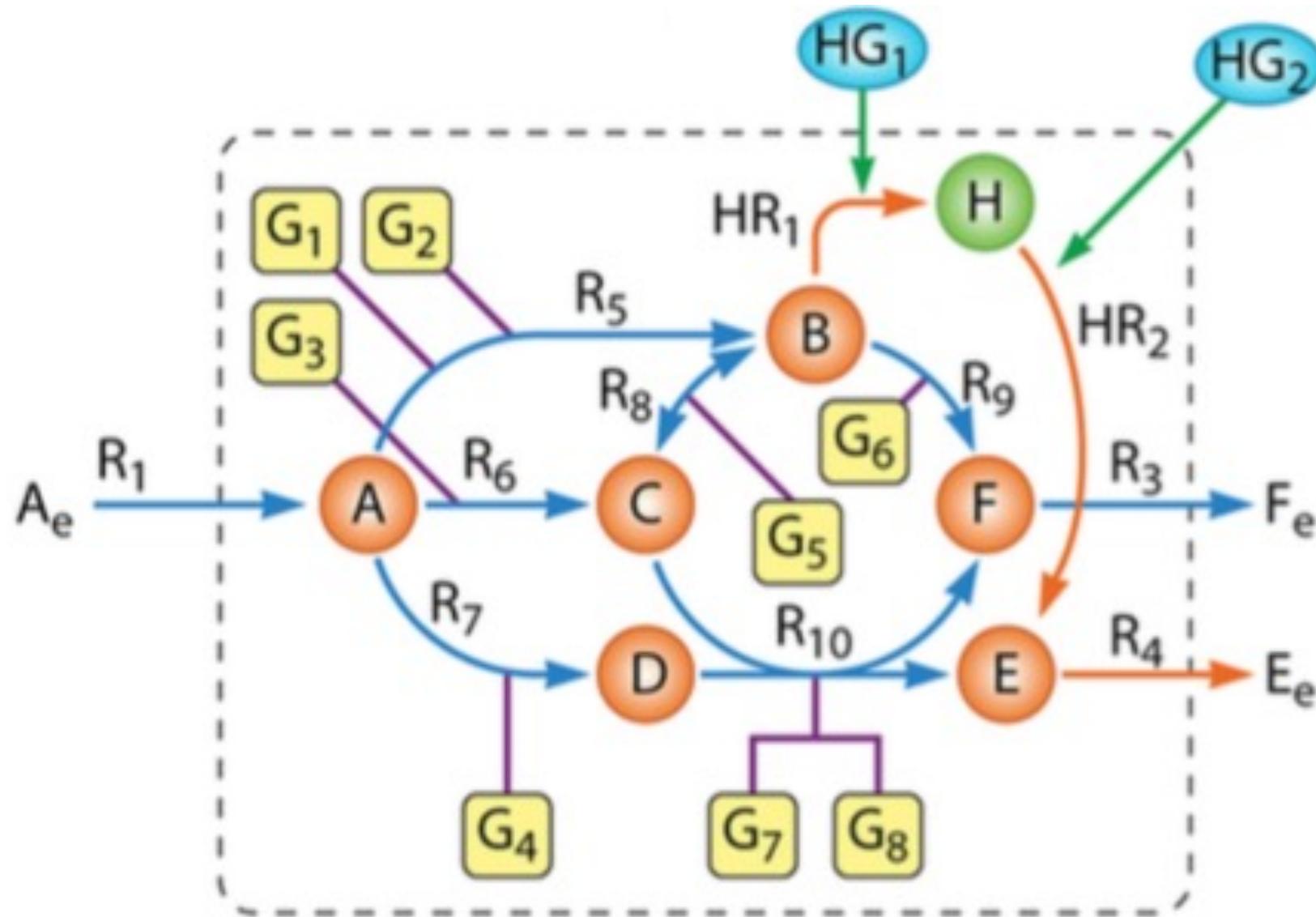
A. Gene deletion**B. Heterologous insertion****C. Gene over/under expression****D. Cofactor specificity modulation**

Maia, P., Rocha, M., & Rocha, I. (2016). In Silico Constraint-Based Strain Optimization Methods: the Quest for Optimal Cell Factories. *Microbiology and Molecular Biology Reviews : MMBR*, 80(1), 45–67. <http://doi.org/10.1128/MMBR.00014-15>

Gene deletions



Heteroloaous insertion



**maximize bioengineering objective
(through gene knockouts)**

subject to

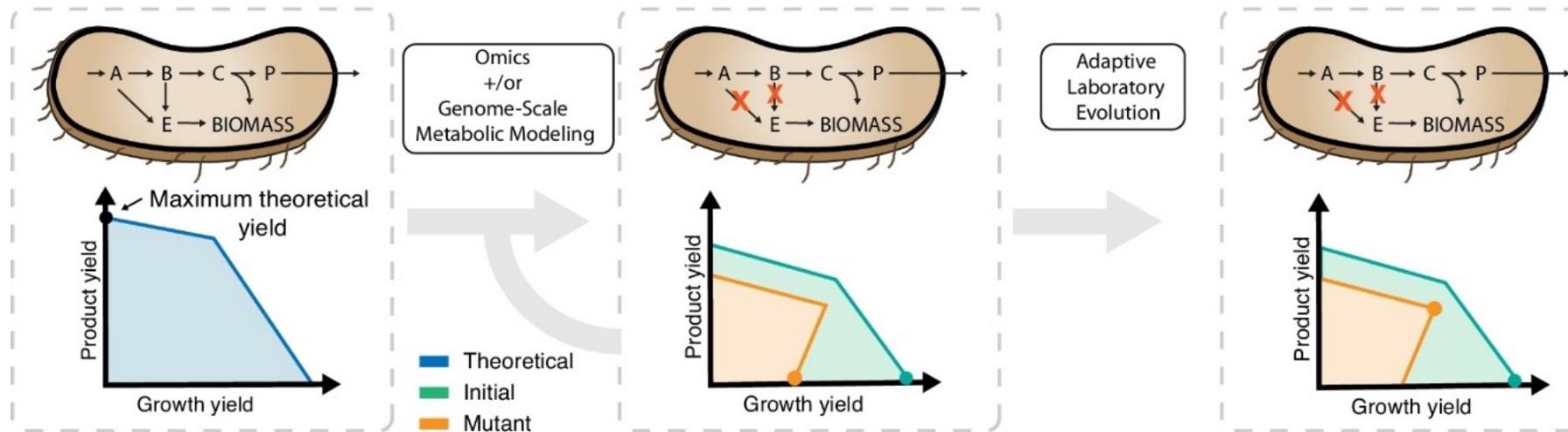
**maximize cellular objective
(over fluxes)**

subject to

- fixed substrate uptake
- network stoichiometry
- blocked reactions identified by outer problem

number of knockouts \leq limit

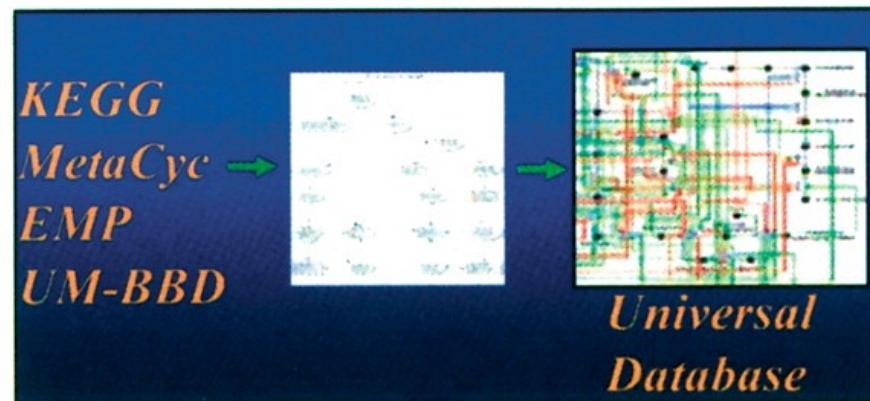
Burgard, Anthony P., Priti Pharkya, and Costas D. Maranas. 2003. "Optknock: A Bilevel Programming Framework for Identifying Gene Knockout Strategies for Microbial Strain Optimization." *Biotechnology and Bioengineering* 84 (6). Department of Chemical Engineering, The Pennsylvania State University, University Park, Pennsylvania 16802, USA.: 647–57.



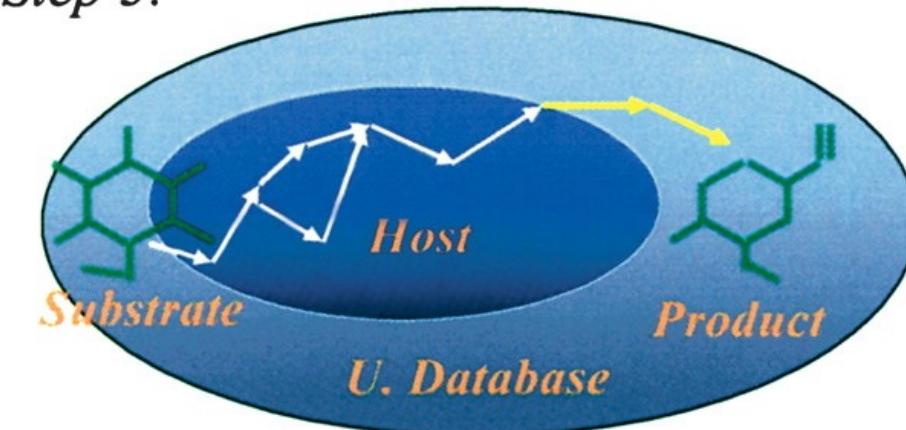
Hansen, Anne Sofie
Lærke, Rebecca M.
Lennen, Nikolaus
Sonnenschein, and
Markus J. Herrgård.
2017. "Systems Biology
Solutions for Biochemical
Production Challenges."
*Current Opinion in
Biotechnology* 45 (June):
85–91.

OptStrain

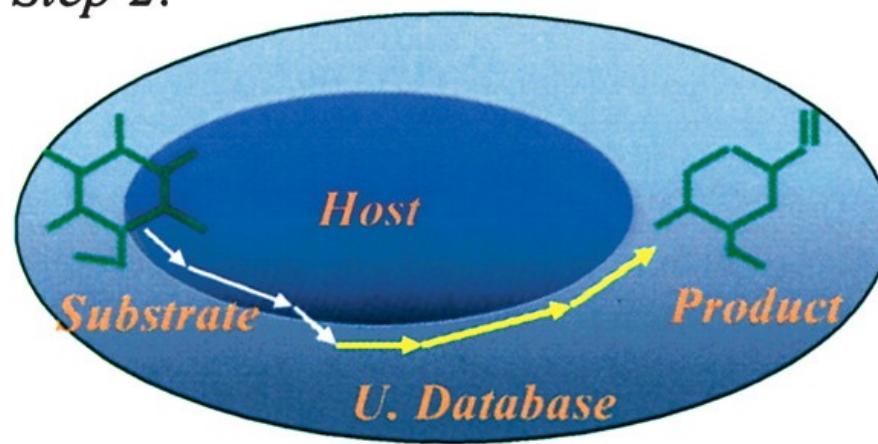
Step 1:



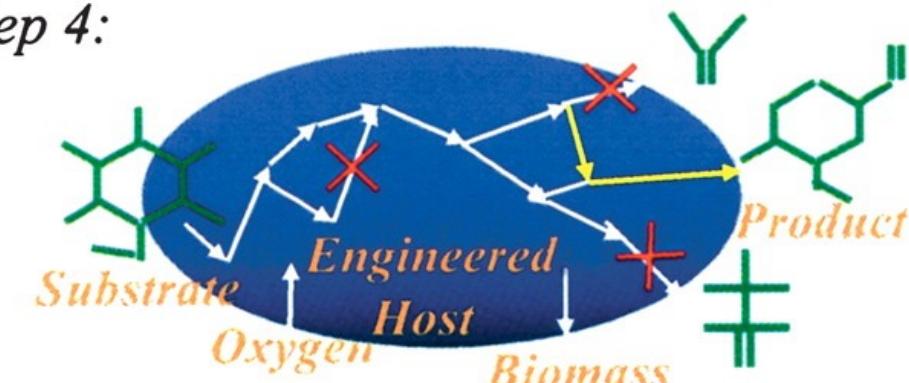
Step 3:



Step 2:



Step 4.



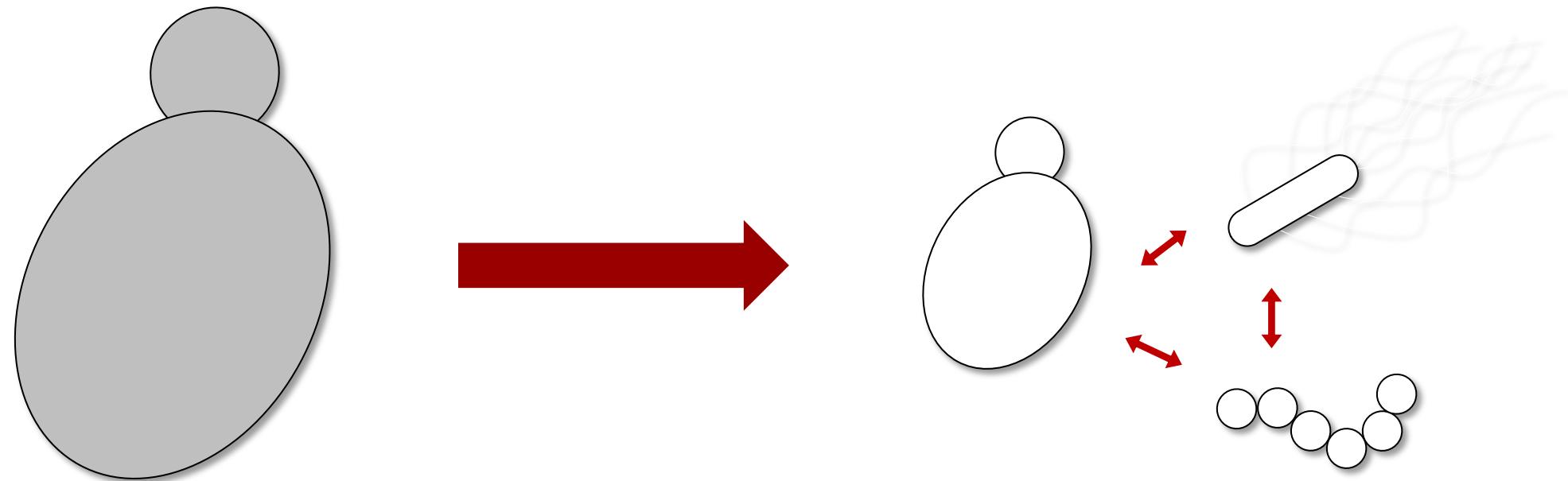
Pharkya, P., Anthony P. Burgard, and C. Maranas. 2004. "OptStrain: A Computational Framework for Redesign of Microbial Production Systems." *Genome Research* 14 (11): 2367-76.



Modeling of microbial communities with genome-scale metabolic models

Microbial community modeling

How can constraint-based metabolic modeling be extended to multiple species?



Different community simulation approaches with GEMs

b

Compartmentalized FBA-based community modelling

Species 1	Species 2
-----------	-----------

Community-level optimization:
max. or min. (Obj. func.)

Obj. func.: Biomass 1 + Biomass 2

c

Multi-level and multi-objective optimization-based community modelling (e.g. OptCom, CASINO)

Species 1	Species 2
-----------	-----------

Species-level optimization: max. or min. (Obj. func.) Species-level optimization: max. or min. (Obj. func.)

Obj. func.: Biomass 1 Obj. func.: Biomass 2

Community-level optimization: max. or min. (Obj. func.)

Obj. func.: a non-linear function of Biomass 1 and Biomass 2

d

Community modelling at steady state for microbiota composition (e.g. cFBA, SteadyCom)

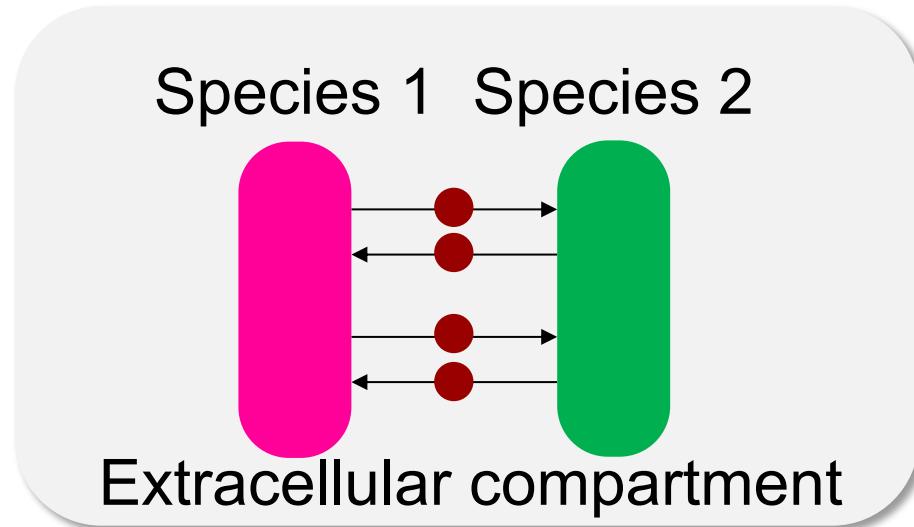
Species 1	Species 2
-----------	-----------

Community-level optimization:
max. or min. (Obj. func.)

Obj. func.: a non-linear function of Biomass 1 and Biomass 2

Additional constraint: Steady state for microbiota composition (constant growth rate across all members of microbial community)

Compartmentalized Flux Balance Analysis



Obj. => weight1 Biomass1 + weight2 Biomass2

- Problems with this approach:
 - Problem 1: How do you pick appropriate weights?
 - Problem 2: units of fluxes in GEMs are usually *mmol gDW⁻¹ h⁻¹*

$$\begin{aligned} & \max \quad v_{biomass}^k \\ \text{subject to} \quad & \sum_{j \in J^k} S_{ij}^k v_j^k = 0, \quad \forall i \in I^k \\ & LB_j^k \leq v_j^k \leq UB_j^k, \quad \forall j \in J^k \end{aligned}$$

Community objective:

$$\max \sum_{k \in K} \alpha^k v_{biomass}^k$$

SteadyCom addresses issues of compartmentalized FBA

RESEARCH ARTICLE

SteadyCom: Predicting microbial abundances while ensuring community stability

Siu Hung Joshua Chan, Margaret N. Simons, Costas D. Maranas*

- Problems with this compartmentalized FBA:
 - Problem 1: How do you pick appropriate weights?
 - Problem 2: units of fluxes v in GEMs are usually $mmol\ gDW^{-1}\ h^{-1}$

Solution to problem 1:

$$v_{biomass}^k = \mu$$

Assume all individual growth rates are equal.

Solution to problem 2:

$$V_j^k = X^k v_j^k$$

Translate metabolic fluxes into aggregate fluxes (mmol/h) by explicitly modeling the biomass X^k (in gDW) of each species.

SteadyCom formulation

$\max \mu \leftarrow$ Maximize community growth rate

subject to

$$\left[\begin{array}{l} \sum_{j \in \mathbf{J}^k} S_{ij}^k V_j^k = 0, \quad \forall i \in \mathbf{I}^k \\ LB_j^k X^k \leq V_j^k \leq UB_j^k X^k, \quad \forall j \in \mathbf{J}^k \\ V_{biomass}^k = X^k \mu \quad \leftarrow \begin{array}{l} \text{Species growth} \\ \text{needs to equal} \\ \text{community} \\ \text{growth} \end{array} \\ X^k \geq 0 \end{array} \right]$$

$\forall k \in \mathbf{K}$

$$u_i^c - e_i^c + \sum_{k \in \mathbf{K}} V_{ex(i)}^k = 0, \quad \forall i \in \mathbf{I}^{com}$$

$$\sum_{k \in \mathbf{K}} X^k = X_0$$

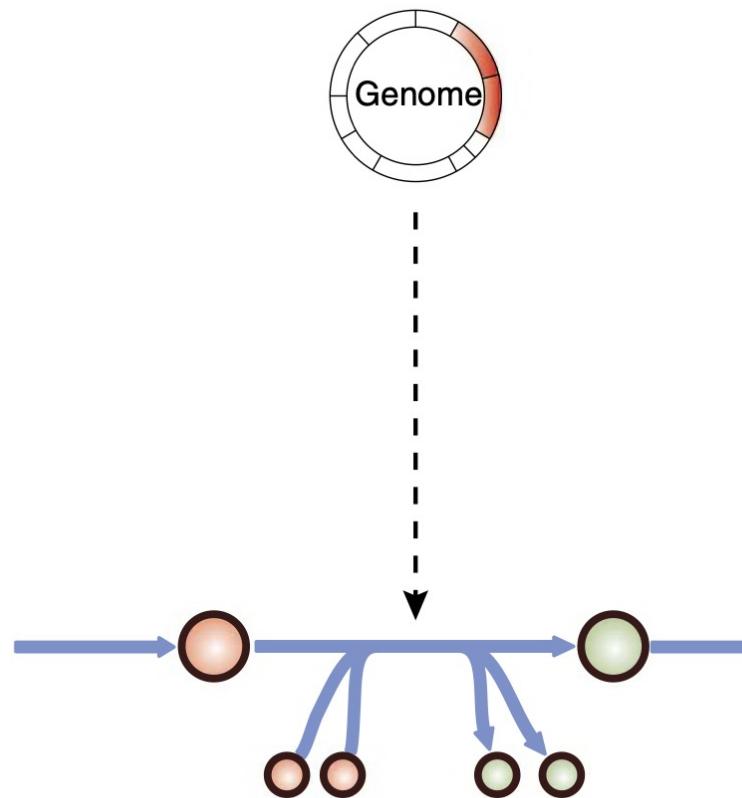
$$\mu, \quad e_i^c \geq 0, \quad \forall i \in \mathbf{I}^{com}$$

(SteadyCom)

Chan, S. H. J., Simons, M. N. & Maranas, C. D.
SteadyCom: Predicting microbial abundances while
ensuring community stability. *PLoS Comput. Biol.* **13**,
e1005539 (2017).

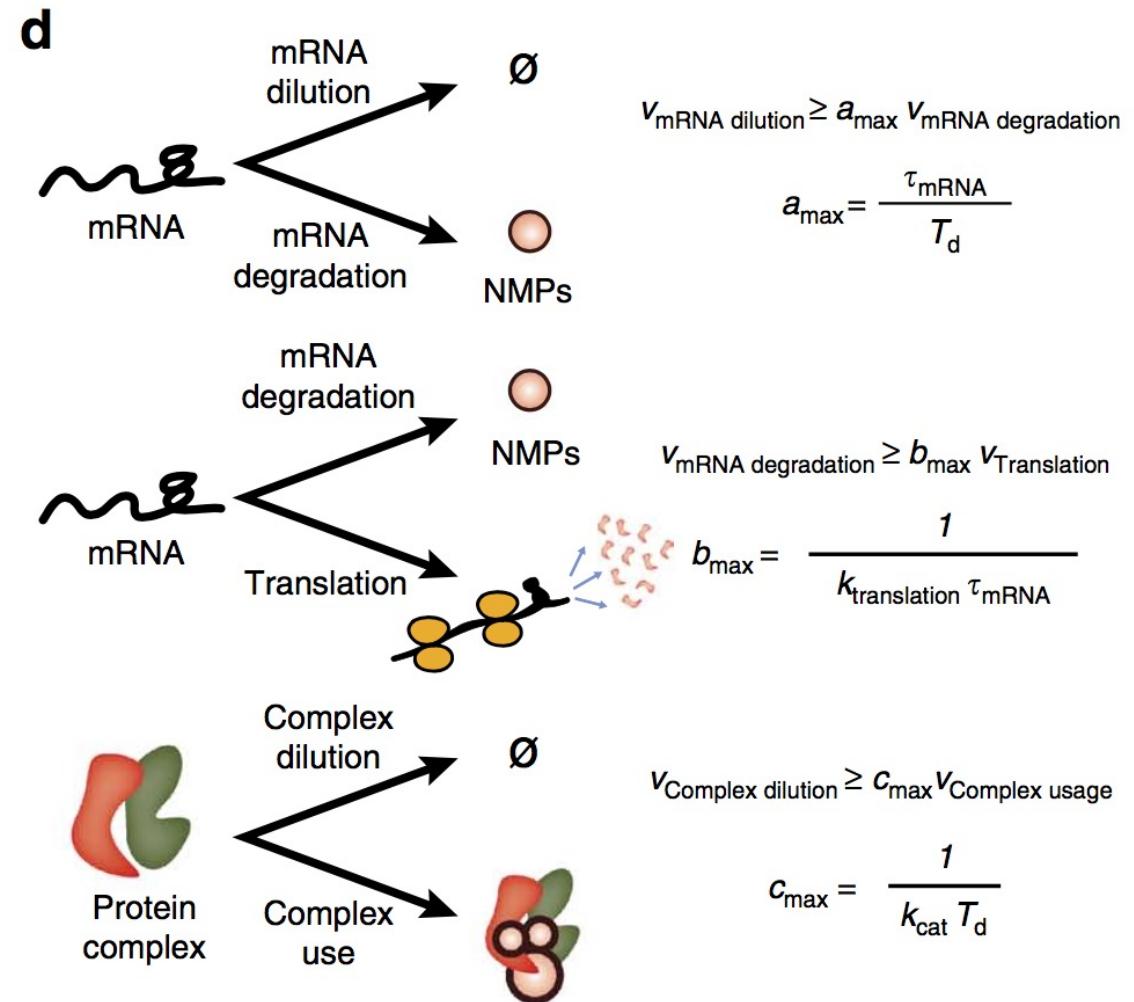
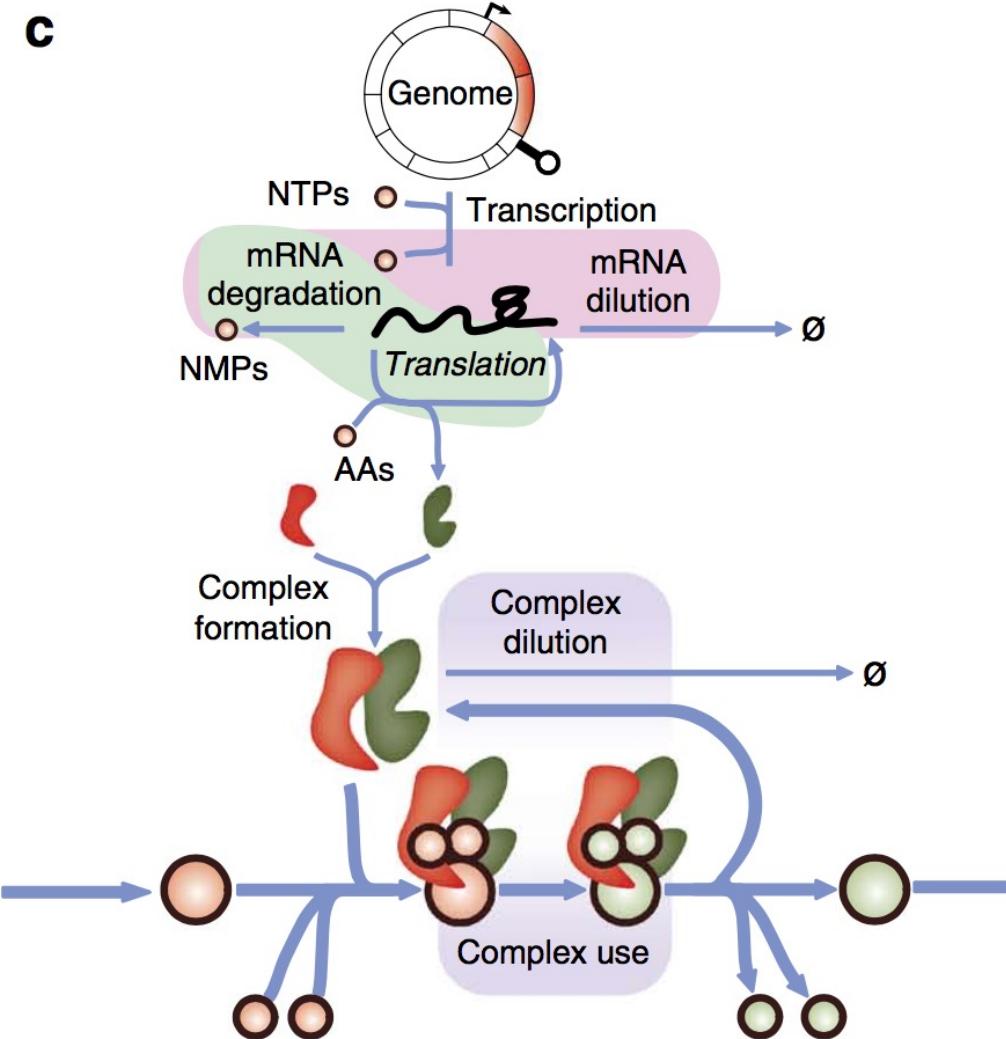
Advanced modeling approaches based on genome-scale models

Conventional genome-scale metabolic model



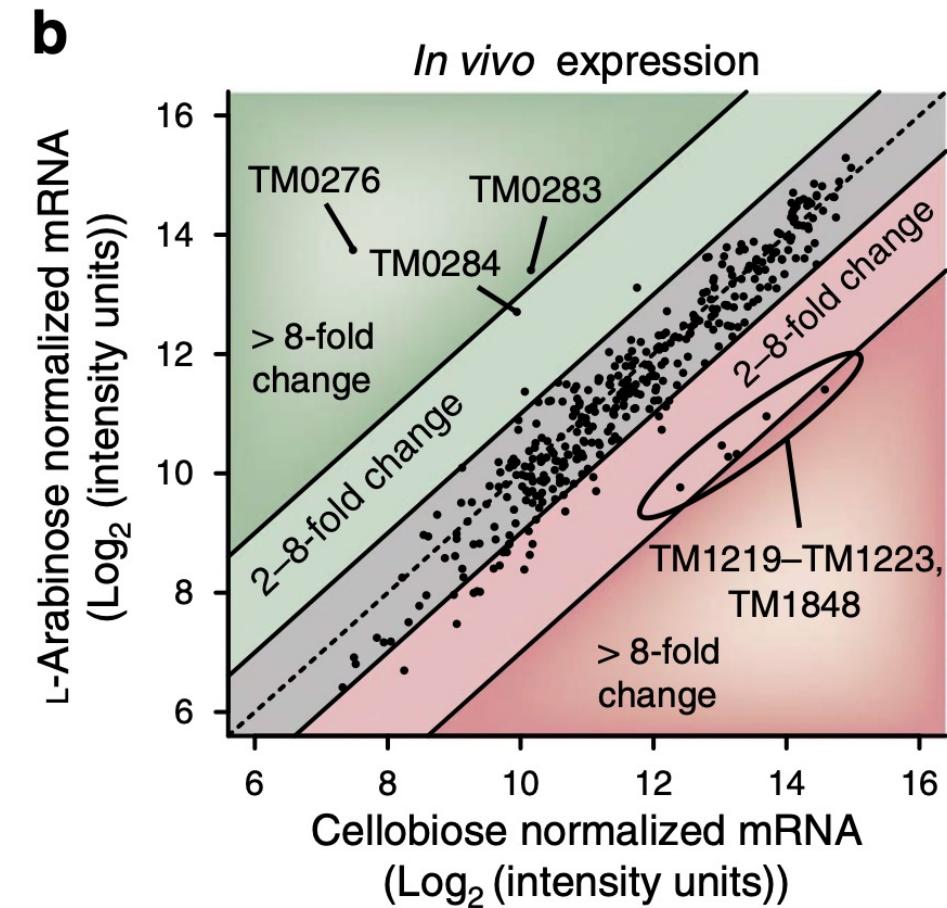
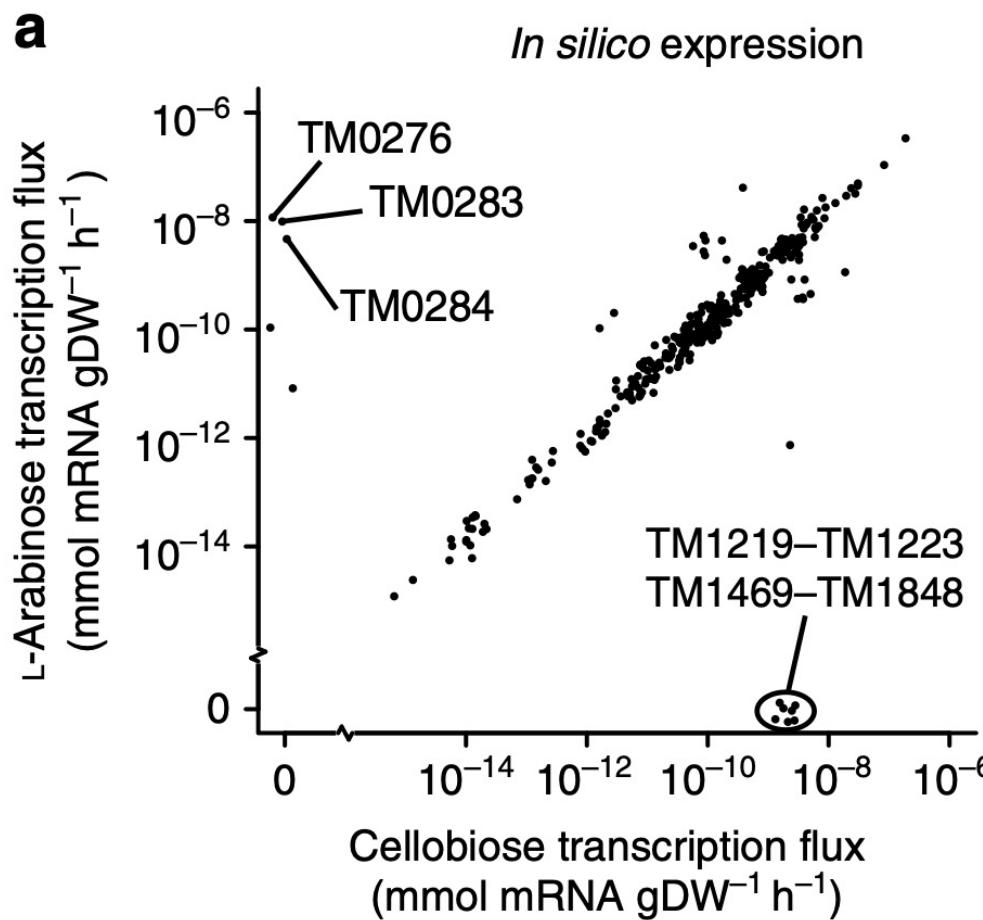
Lerman, J. A., Hyduke, D. R., Latif, H., Portnoy, V. A., Lewis, N. E., Orth, J. D., Schrimpe-Rutledge, A. C., Smith, R. D., Adkins, J. N., Zengler, K. & Palsson, B. Ø. *c Nat. Commun.* **3**, 929 (2012).

Metabolism and macromolecular expression (ME) model



Lerman, J. A., Hyduke, D. R., Latif, H., Portnoy, V. A., Lewis, N. E., Orth, J. D., Schrimpe-Rutledge, A. C., Smith, R. D., Adkins, J. N., Zengler, K. & Palsson, B. Ø. *c Nat. Commun.* **3**, 929 (2012).

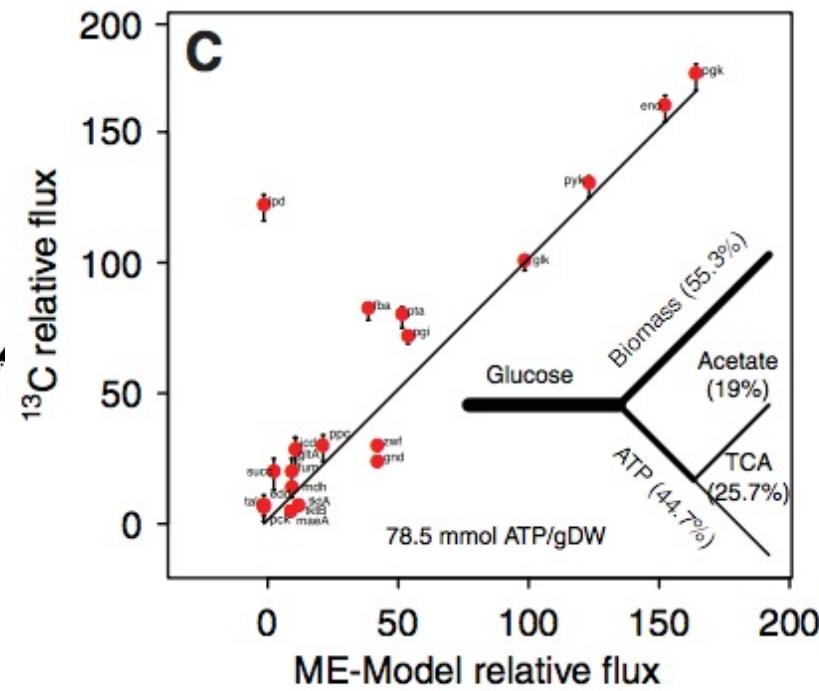
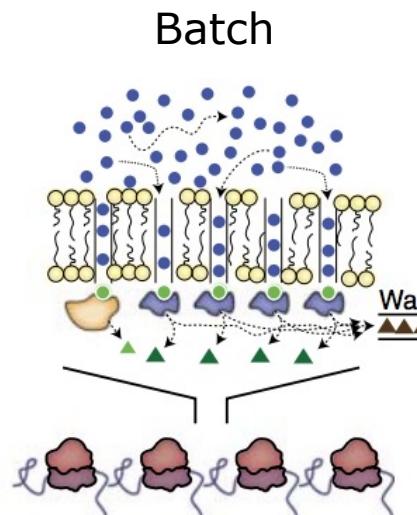
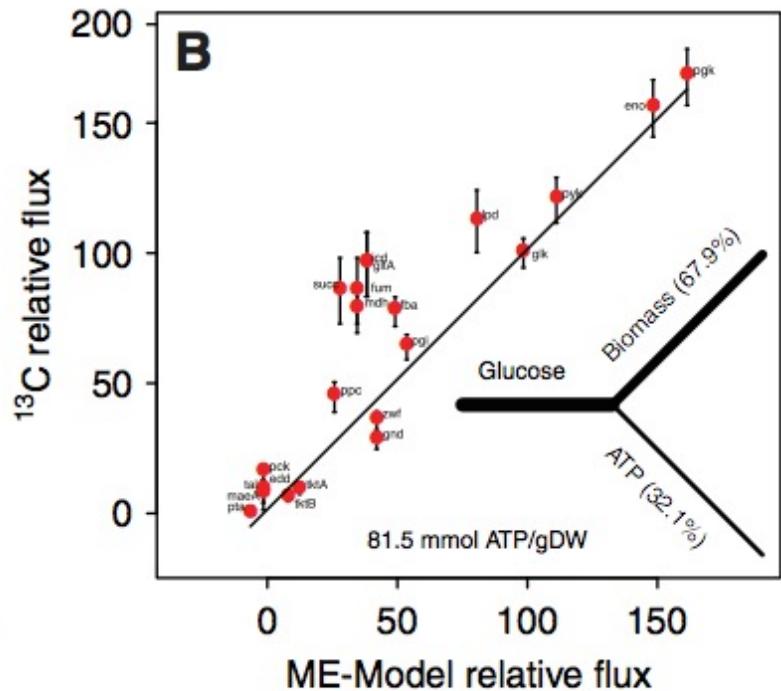
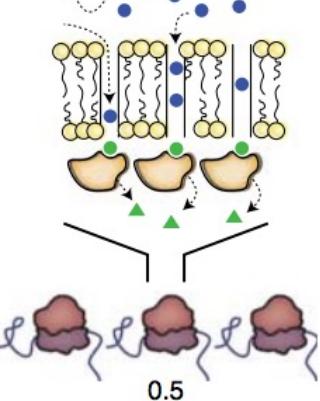
Metabolism and macromolecular expression (ME) model



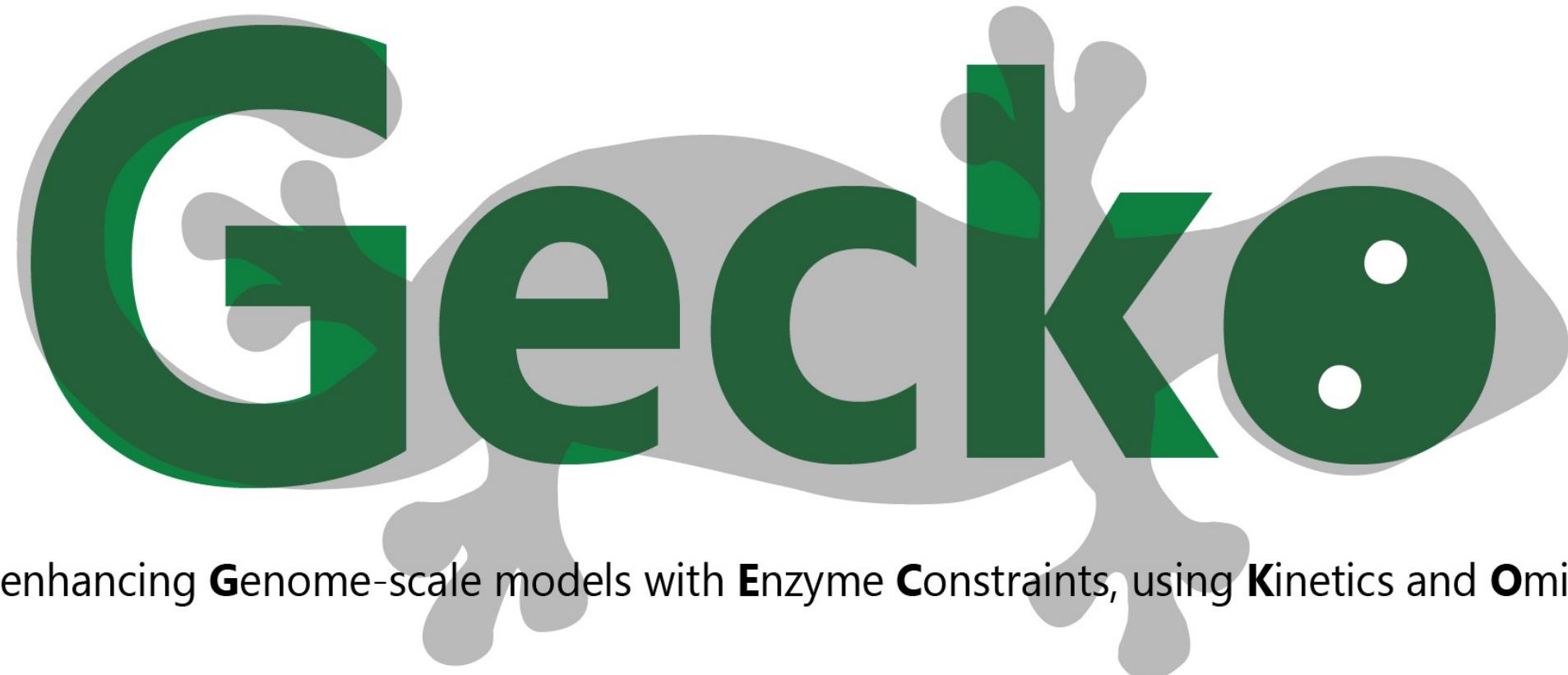
Lerman, J. A., Hyduke, D. R., Latif, H., Portnoy, V. A., Lewis, N. E., Orth, J. D., Schrimpe-Rutledge, A. C., Smith, R. D., Adkins, J. N., Zengler, K. & Palsson, B. Ø. *c Nat. Commun.* **3**, 929 (2012).

Metabolic fluxes under nutrient and proteome limitation

Chemostat



O'Brien, E. J., Lerman, J. A., Chang, R. L., Hyduke, D. R. & Palsson, B. Ø. Genome-scale models of metabolism and gene expression extend and refine growth phenotype prediction. *Mol. Syst. Biol.* **9**, 693 (2013).

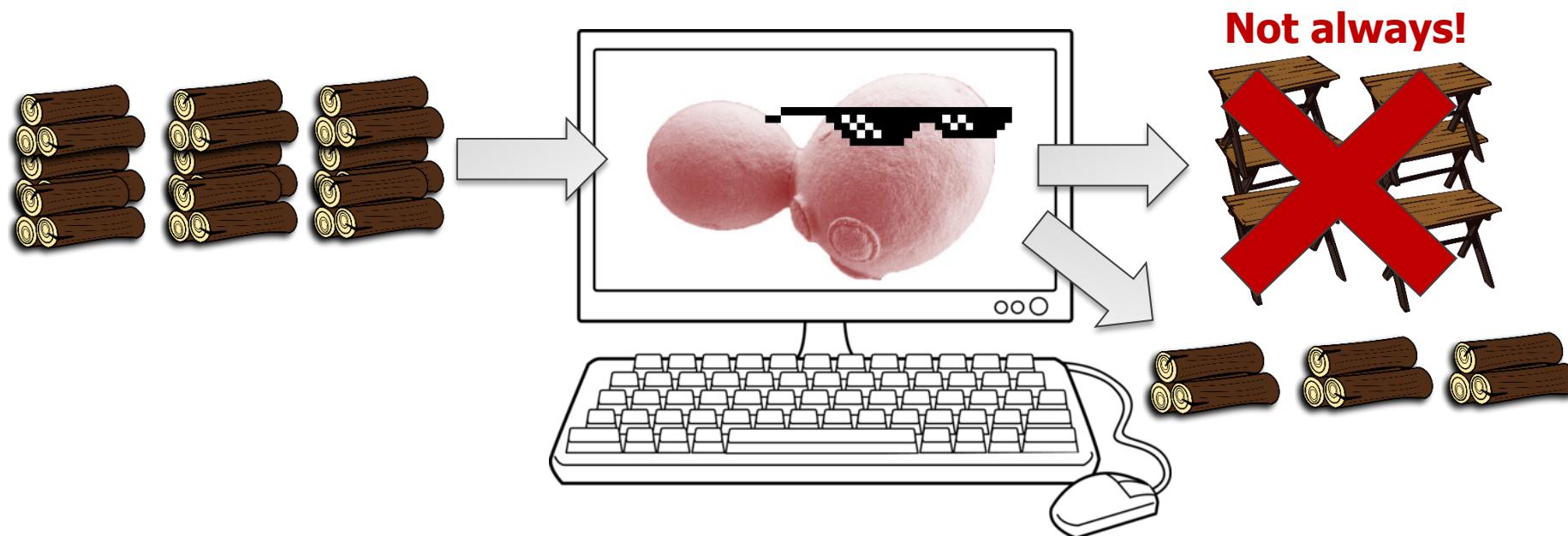


Benjamín J. Sánchez

2020-11-10

Motivation: enzyme limitations in GEMs

Genome-scale models (GEMs) do not account for enzymes' limited capacity:



When is this relevant?

- High energy demand (high growth rate – stress response)
- Inefficient pathways (consumption – production)

Motivation: enzyme limitations in GEMs

Should any reaction have bounds up to $+\infty$?

Should these 2 pathways have reactions with the same bounds?



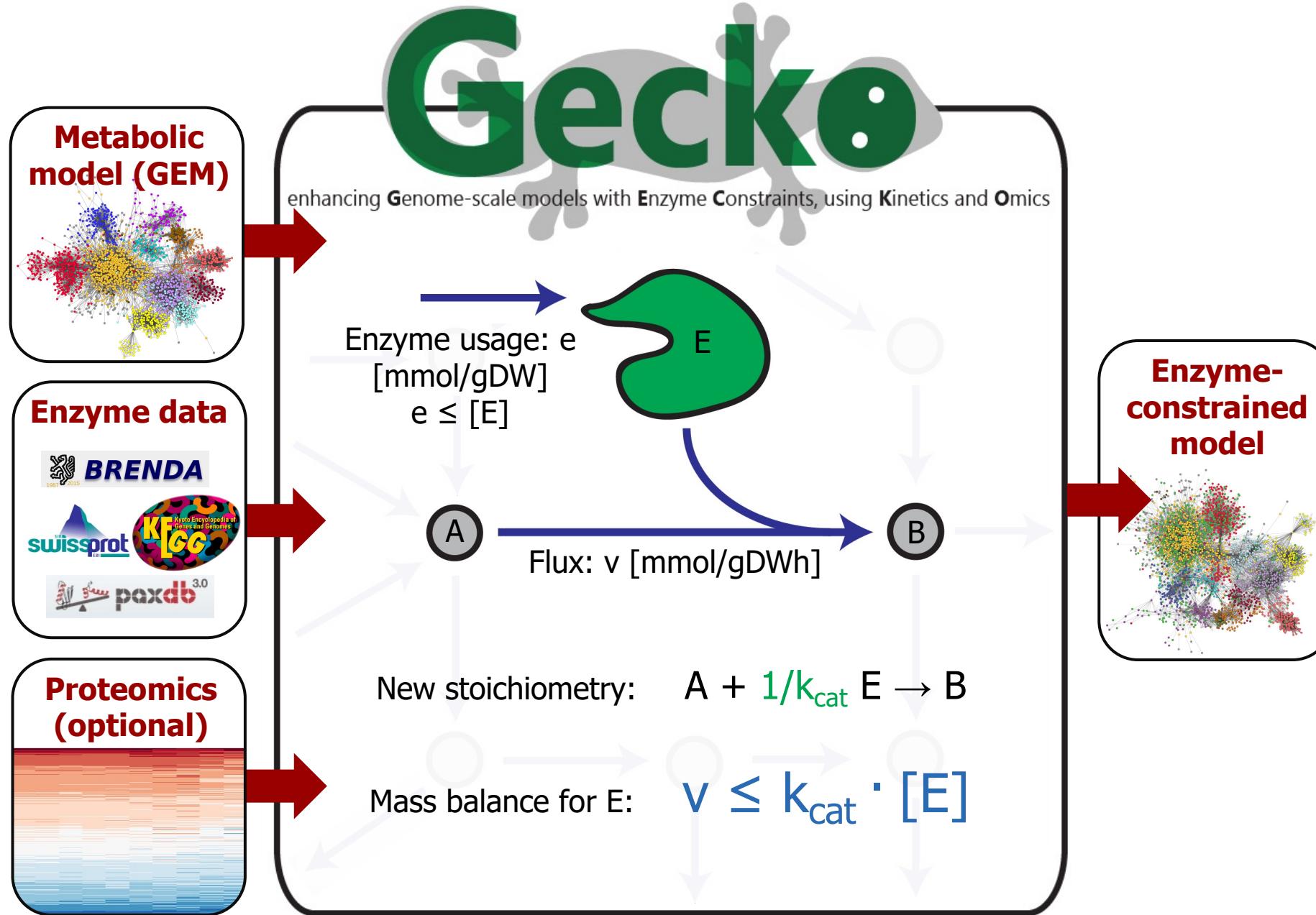
Relationship between enzyme and reaction:

$$\text{Flux of reaction} \longrightarrow v \leq k_{\text{cat}} \cdot [E] \longleftarrow \begin{array}{l} \text{Concentration of enzyme} \\ \text{(from absolute proteomics)} \end{array}$$

\uparrow

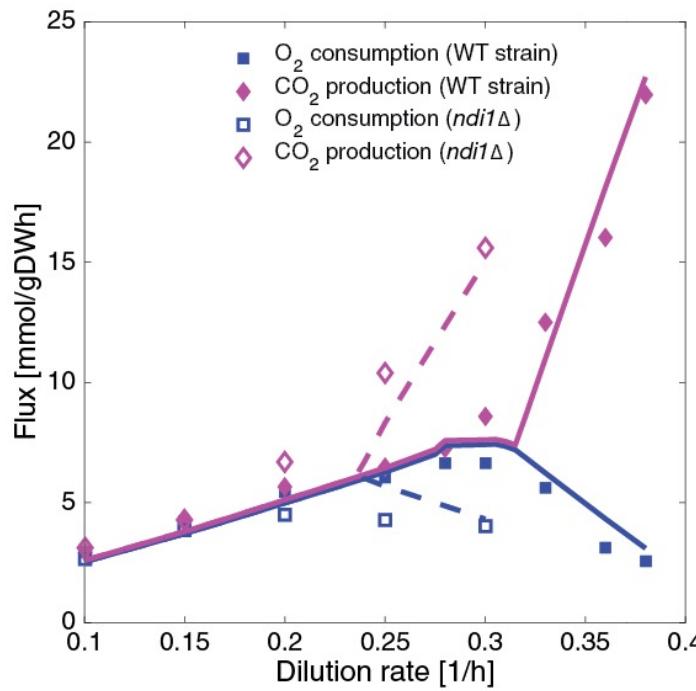
$$\begin{array}{l} \text{Turnover number} \\ \text{(from databases)} \end{array}$$

However: No simple implementation for connecting proteomics to GEMs...

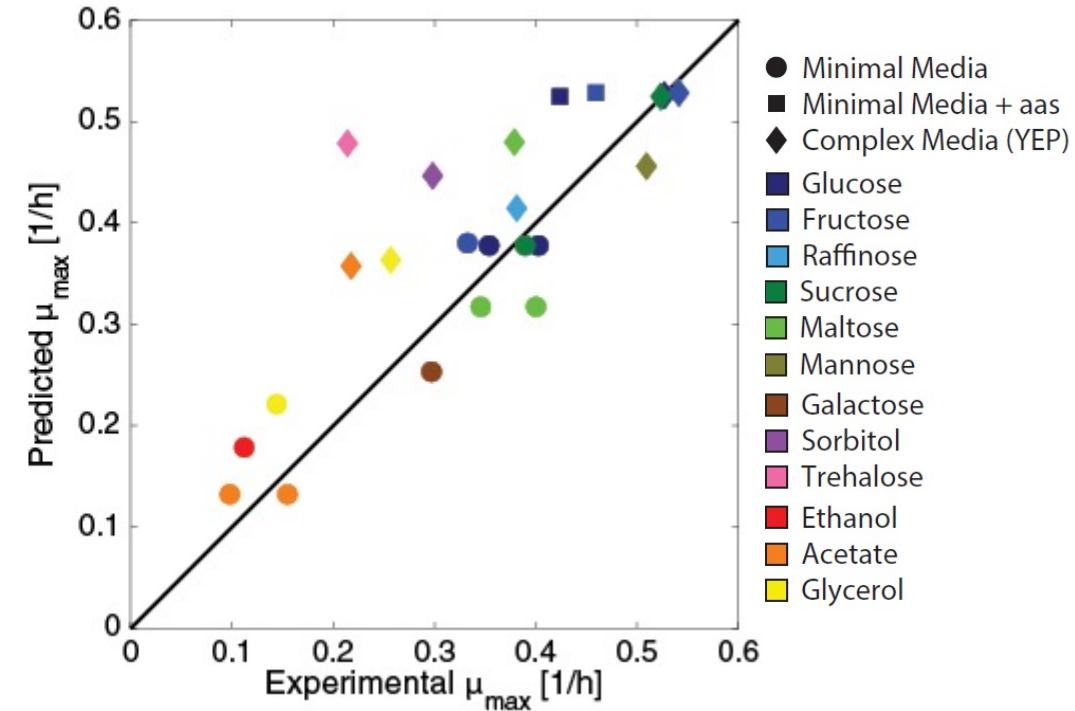


Applications: improving predictions

Respiration/fermentation switch (in WT and knockout): chemostat simulations



Maximum growth rate at different carbon sources: batch simulations



How would these plots look like if we would use a traditional GEM? Discuss.

Applications: integrating proteomics

Proteomic dataset:

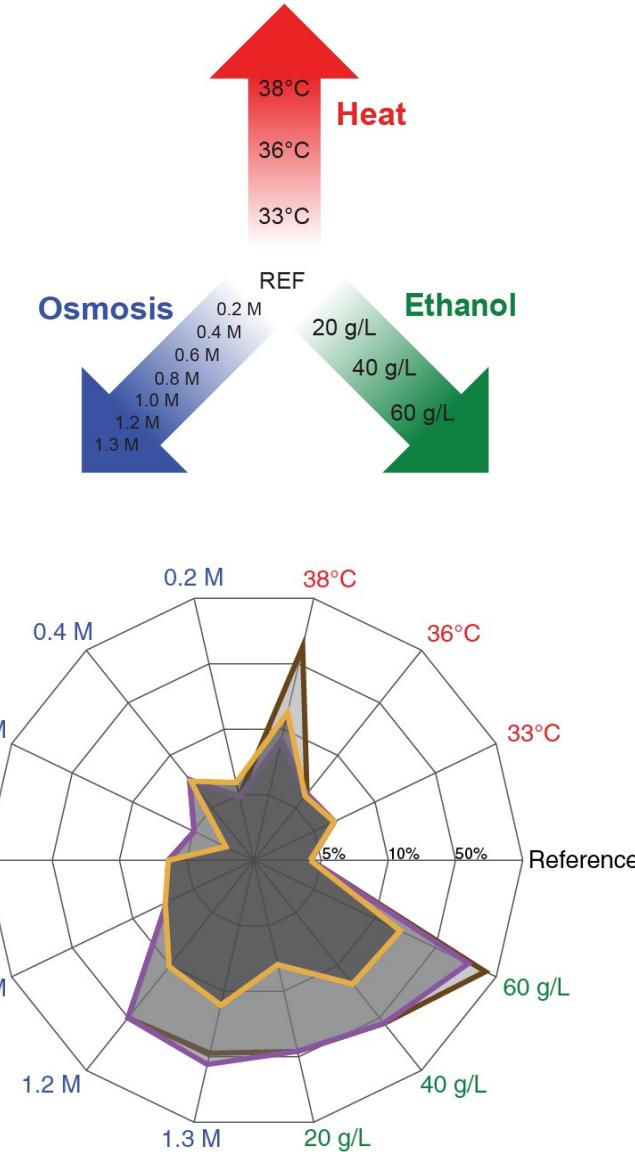
- *S. cerevisiae* grown at 14 different stress conditions
- Glucose-limited aerobic chemostats @ 0.1 1/h

14 condition-specific models:

- Proteomic data as constraints
- Adjusted biomass composition and ATP expenditure

Error [%] in predicting exchange fluxes:

- Yeast7
- ecYeast7 - no proteomic data
- ecYeast7 - with proteomic data



cobraPy, memote, cameo, ...

Software for genome- scale metabolic modelling

cobrapy



models



fluxes



algorithms

<https://opencobra.github.io/cobrapy/>

Star 145 contributors 28 release v0.13.0

cobrapy is a python package that provides a simple interface to metabolic constraint-based reconstruction and analysis.



Moritz



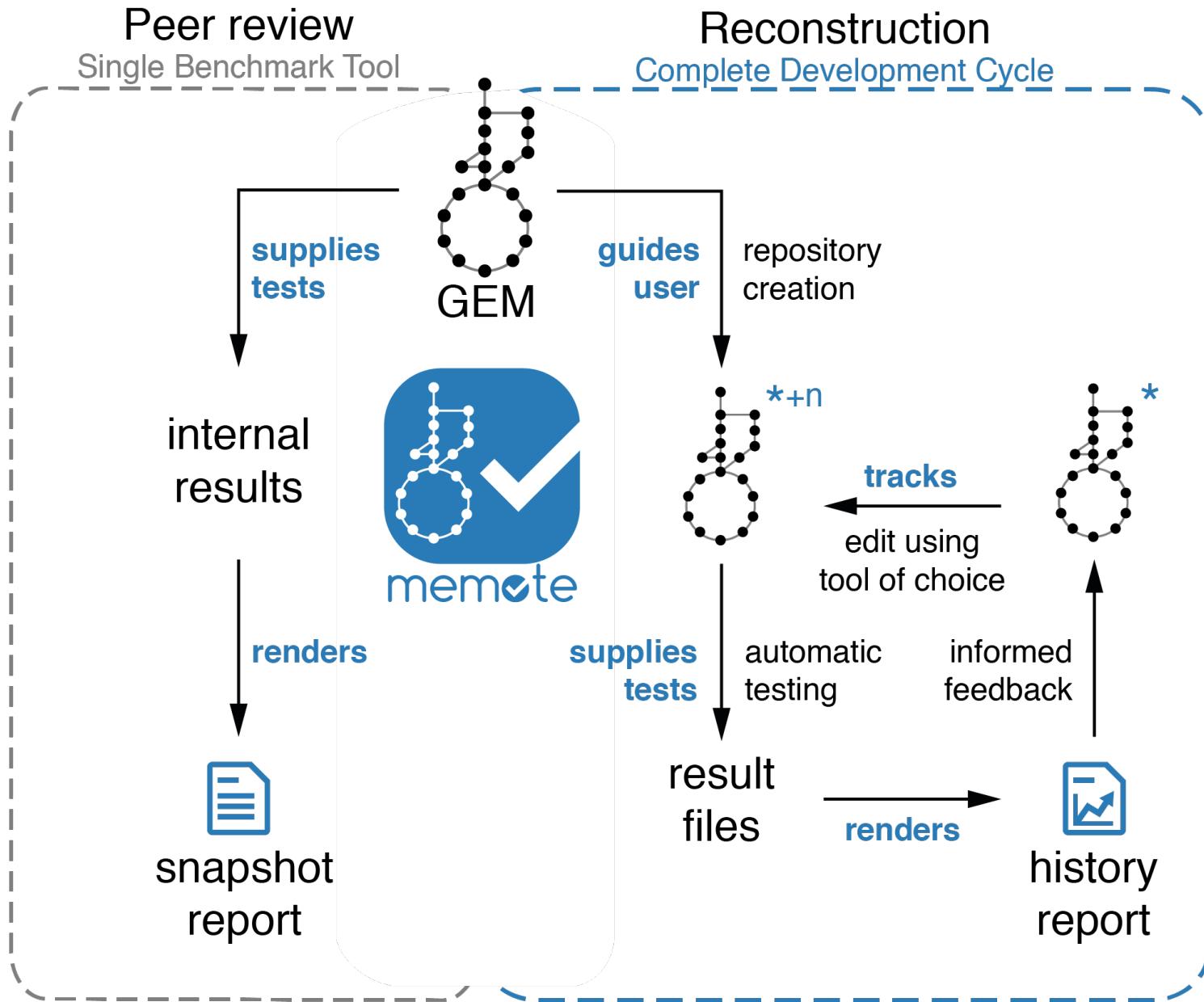
Christian



memote - metabolic model tests

<https://memote.io/>

Workflows



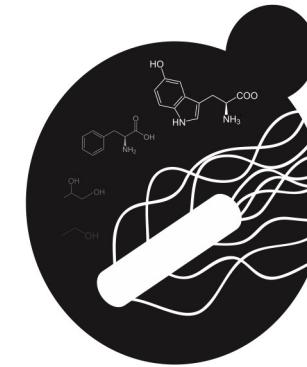
Web interface: memote.io

The screenshot shows a web browser window for 'Memote' at 'memote.io'. The title bar has a blue icon with a checkmark and the word 'Memote'. The address bar shows the URL. The main content area has a blue header with the text 'Upload Your Model'. Below it is a dashed blue rectangular area containing a blue cloud icon with an upward arrow, a 'Choose file' button ('No file chosen'), and the text 'Or Drag It Here.'. To the right of this area is a white box with a blue arrow pointing left, a blue file icon with a checkmark, and the text 'Drag & drop me! ^'. Below this section is a table with columns: Model, Submitted, Expires, Status, View results, and Clear. Two rows of data are shown:

Model	Submitted	Expires	Status	View results	Clear
iKS1317.json	2019-11-18	2019-11-25	Completed	✓ VIEW	trash
449_2018_1900_MOESM2_ESM.xml	2019-11-18	2019-11-25	Completed	✓ VIEW	trash

At the bottom, there is a message 'Hi there!' and a descriptive text: 'Genome-scale metabolic models are tough to understand at a glance. Memote, short for metabolic model tests, is here to change that.'

Cameo

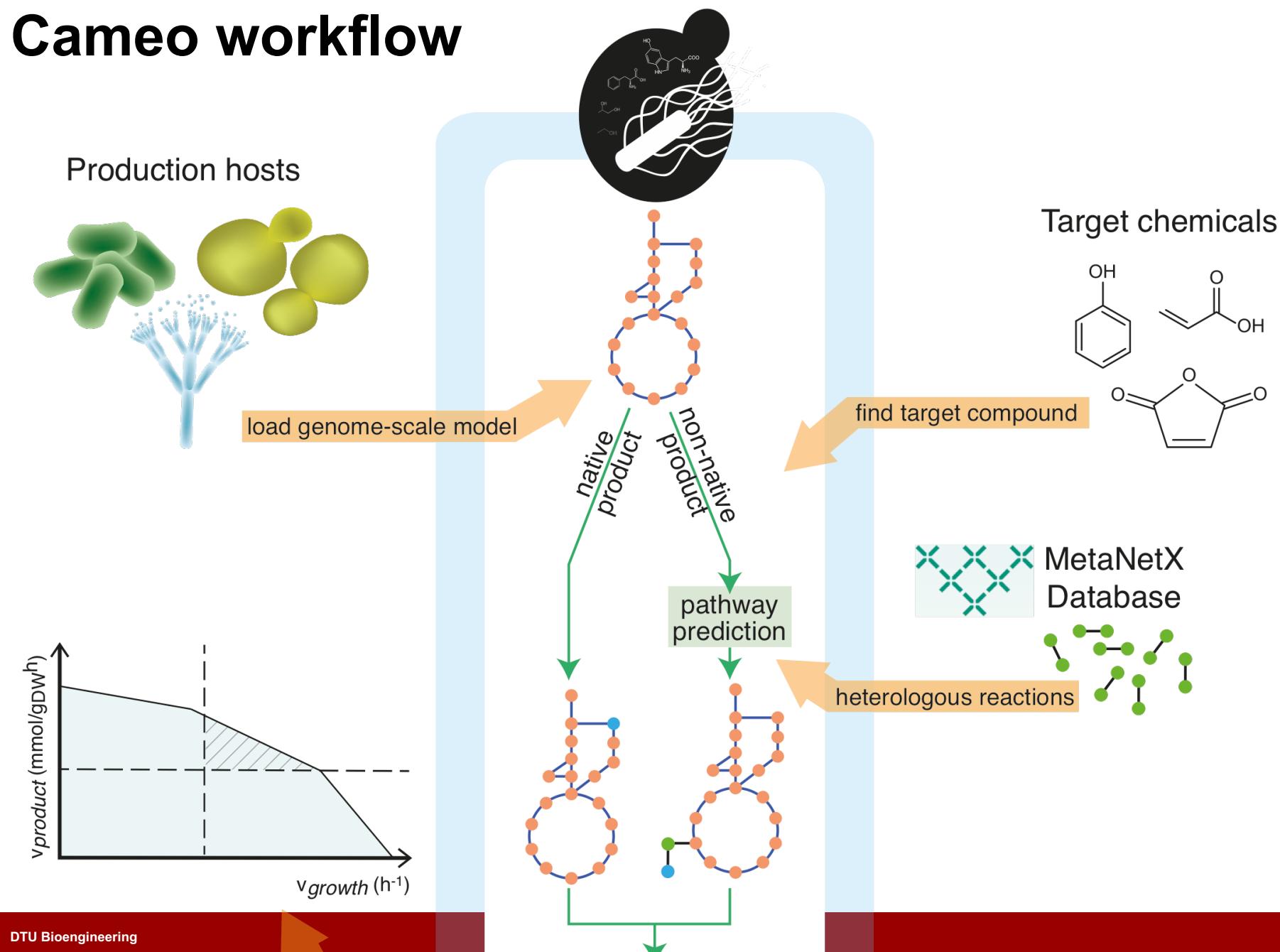


Computer Aided Metabolic Engineering and
Optimization of Cell Factories

<http://cameo.bio>

Cardoso, J. G. R., Jensen, K., Lieven, C., Lærke Hansen, A. S., Galkina, S., Beber, M., Özdemir, E., Herrgård, M. J., Redestig, H. & Sonnenschein, N. Cameo: A Python Library for Computer Aided Metabolic Engineering and Optimization of Cell Factories. *ACS Synth. Biol.* **7**, 1163–1166 (2018).

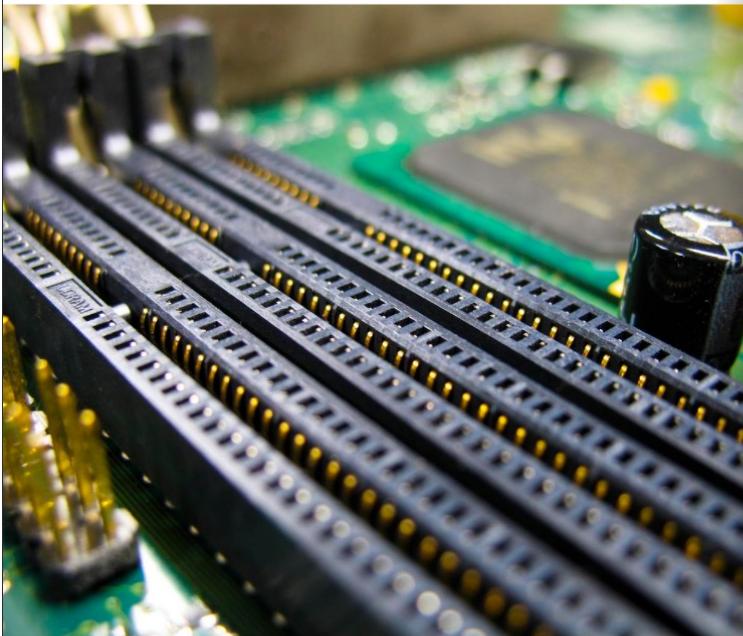
Cameo workflow



Popular Python modeling libraries

Biosustain Magazine

January 2019



SOFTWARE
- can change the world



3 software tools that help industry

Three software tools developed by DTU Biosustain help companies engineer microbes efficiently. So, if you don't know them yet, hang on and learn how big industrial players use the tools to save tons of time.

"This software is amazing and sets the standard for genome-scale modelling."

- Joshua Lerman, Scientist 2, Amyris

Establishing performant cell factories by trial-and-error may possibly lead to frustration and the loss of the single most valuable resource to most people: time. But what if there was a way to eliminate dead-end strategies before spending weeks in the laboratory? Here are three tools that together allow you to do just that.

COBRApy:

COBRApy is a package for constraint-based modelling of metabolic networks written in Python.

The tool strives to become the reference software library for doing genome-scale metabolic modelling by providing the essentials (data structures, simulation methods and model import/export) that others can base their more specialised software tools on.

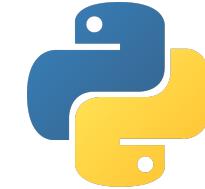
Joshua Lerman, Scientist 2 at the pharmaceutical biotech company **Amyris**, uses COBRApy for a broad range of tasks. For instance, to predict knock-out targets, to find high yield routes to target molecules in yeast, to calculate maximum theoretical yields and productivities and to evaluate which reactions might drain flux off the pathway:

"This software is amazing and sets the standard for genome-scale modelling. COBRApy is a foundational tool for both systems and synthetic biology, and I could not do my work without it," he says.

At the bioinformatics company **Zymergen**, PhD in Chemical Engineering Janet Matsen also uses COBRApy: "When we aim to increase the rate of chemical production, we are really aiming to change the rates of chemical reactions in the cell. Thus, information about fluxes is extremely valuable. COBRApy is the most useful software available to get such information," Janet Matsen says.

She emphasises that it is an extremely valuable tool for them: "Writing an equivalent tool to support our needs would take the time of 1-2 full-time employees." >>

13 - Software tools for industry





Watch 3

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[Contributing](#)
[API Reference](#)

Quick search

Go

geckopy <https://geckopy.readthedocs.io/en/latest/>

CI-CD passing

Genome-scale model Enzyme Constraints, using Kinetics and Omics in python.

By combining kcets and proteomics measurement, geckopy allows for improving the modeling capabilities in genome-scale models.

Based on [Sánchez et al., 2017](#).

Check <https://github.com/SysBioChalmers/GECKO> for the matlab counterpart.

Overview

Load a model.

```
import geckopy

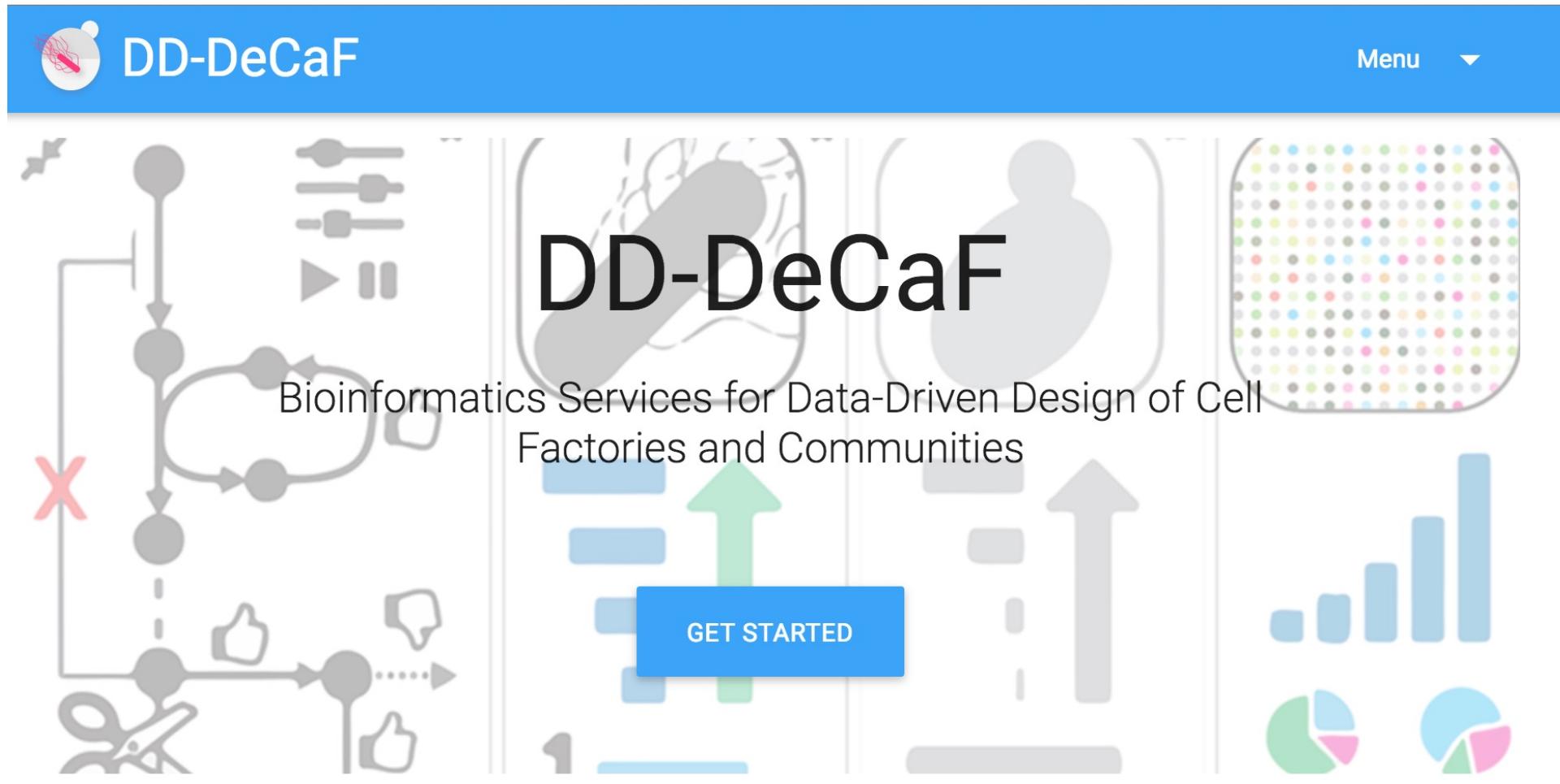
model = geckopy.io.read_sbml_ec_model("tests/data/eciML1515.xml.gz")
model.optimize()
```

Add copy number experimental data.

```
import pandas as pd
from geckopy.experiment import from_copy_number

raw_proteomics = pd.read_csv("tests/data/ecoli_proteomics_schmidt2016S5.tsv")
exp_model = from_copy_number(
    model,
    index=raw_proteomics["uniprot"],
    cell_copies=raw_proteomics["copies_per_cell"],
    stdev=raw_proteomics["stdev"],
    vol=2.3,
    dens=1.105e-12,
    water=0.3,
)
exp_model.optimize()
```

Data-Driven Design of Cell Factories and Communities



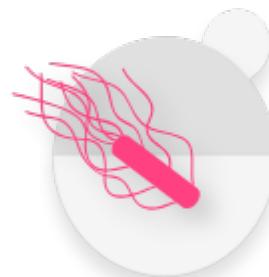
The screenshot shows the DD-DeCaF website homepage. At the top, there is a blue header bar with the text "DD-DeCaF" and a "Menu" button. Below the header, there is a large central graphic featuring a brain-like structure, a person silhouette, and various icons related to bioinformatics and data analysis. A prominent "GET STARTED" button is centered in the middle of the graphic. To the left of the main graphic, there is a smaller diagram showing a flowchart with nodes and arrows, some marked with a red "X". On the bottom left, there is a small European Union flag icon. The text "Bioinformatics Services for Data-Driven Design of Cell Factories and Communities" is displayed in the center of the main graphic area.



The project has received funding from
the European Union's Horizon 2020
research and innovation programme
under grant agreement No 686070

<http://dd-decaf.eu/>

Caffeine – Computer-Aided Cell Factory Design



The image shows three mobile devices (a large tablet and two smartphones) displaying the Caffeine platform interface. The interface includes a sidebar with project management, an interactive metabolic map, and detailed results for specific jobs.

Large Device (Tablet):

- Left Sidebar:** Projects (Homo sapiens, test, iCore, co-factor-swap, Caffeine Testing, antibiotics, optgene-results, tmp, ergothioneine, 2ndary-metabolites, test-project), Home, Interactive Map, Design, Jobs, Designs, Projects, Maps, Models.
- Central Area:** Metabolic map showing fluxes (purple bars) across various pathways and metabolites. A legend indicates Flux (min to max), No flux (dashed lines), Not in the model (red squares), and Measured flux (purple squares).
- Top Right:** STAGING @ 075cb00a, LOG OUT.

Smartphone 1 (Left):

- Top:** Caffeine, LOG OUT.
- Middle:** Organism: Escherichia coli, Model: IJO1366, Conditions: Anaerobic. Product: vanillin. Started: 29 Jul 2019, 13:51. Completed: 29 Jul 2019, 14:25.
- Bottom:** Results table with columns: Manipulations, Heterologous reactions, Knockouts, and Fitness [Production/Growth/Carbon uptake].

Smartphone 2 (Right):

- Top:** Caffeine, LOG OUT.
- Middle:** Organism search bar (e.g., Escherichia coli), NEW ORGANISM button. Options listed: Crictellus griseus, Escherichia coli, Corynebacterium glutamicum, Saccharomyces cerevisiae, Pseudomonas putida.
- Bottom:** Rows per page: 10, 1-10 of 61.

☰ Caffeine

LOG IN

- Home
- Interactive Map
- Design
- Jobs
- Designs
- Projects
- Maps
- Models

Getting started

- [Login \(optional\)](#)
- [Interactive cell factory design and omics data integration](#)
- [Computational cell factory design](#)
- [Assessing the capabilities of cell factories](#)
- [Uploading data](#)

Welcome to our cell factory design and analysis platform! We develop the platform as part of the [DD-DeCaF](#) project with the goal to put model-guided and data-driven design into practice in industrial biotechnology. The platform will enable the following key technologies:

- Metagenomics-enabled design of novel enzymes and biochemical pathways.
- Omics data-driven design of cell factories for the production of chemicals and proteins.
- Analysis and design of microbial communities relevant to human health, industrial biotechnology and agriculture.

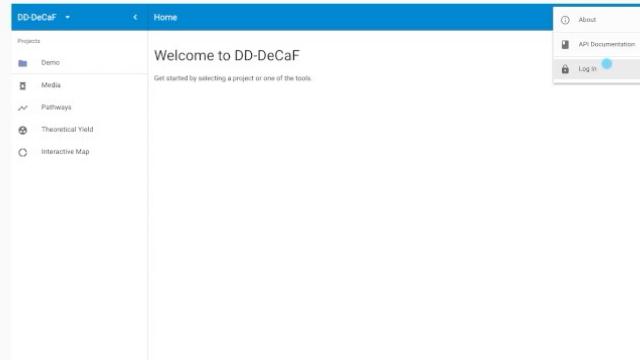
With this interactive web application, we target primarily non-expert users that have a need to analyze omics data and compute strains designs. An advance programming interface is provided for expert users ([API docs](#)) enabling them deviate from the default workflows and perform custom analyses.

The platform is currently in **beta** and tested primarily with Google Chrome. If you'd like to stay up-to-date with new releases, please [subscribe](#) to our quarterly newsletter. We will be eternally grateful for feedback in case you miss features or you encountered a problem (for now please drop us a message at niso@biosustain.dtu.dk).

The following sections provide an overview of what you can currently do on platform. Have fun!

Login (optional)

You can log in [here](#) or by navigating to the menu in the upper right-hand corner. We support sign-on through a number of social media platforms. Alternatively, you can [contact](#) us for an account.



Logging in is optional, (you can browse public domain data and run simulations) but necessary for uploading your own data.

Interactive cell factory design and omics data integration

Caffeine exercise

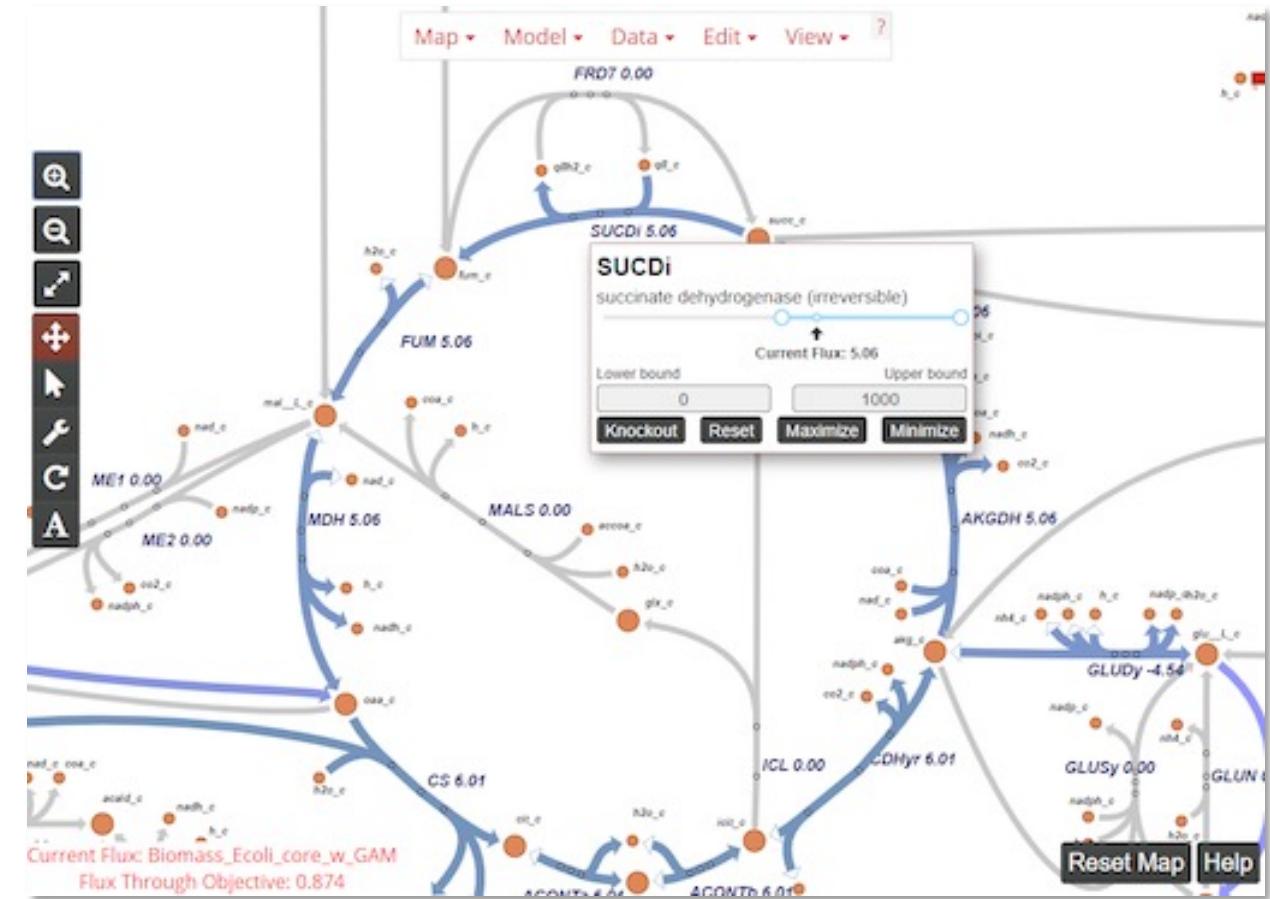
- Go to <https://caffeine.dd-decaf.eu/>
- Select the interactive pathway map in the menu (the default model being loaded is a model of *E. coli*)
 1. Change the carbon source from glucose to pyruvate. How does the growth rate change?
 2. Can *E. coli* grow anaerobically on pyruvate?
 3. How about growing anaerobically on glucose?
 4. Try to kill *E. coli* by knocking out reactions or genes.

Hints:

- Use <https://sbrg.github.io/escher-fba/#/app> as a backup solution if Caffeine is slow
- You can change model parameters when you hover over graphical elements in the map
- You can search on the map by pressing Ctrl+F (or Cmd+F on a Mac)

Modeling LP - Example 2 – Gene knockouts

<https://sbrg.github.io/escher-fba/#/app>



King, Z. A., Dräger, A., Ebrahim, A., Sonnenschein, N., Lewis, N. E. & Palsson, B. Ø. Escher: A Web Application for Building, Sharing, and Embedding Data-Rich Visualizations of Biological Pathways. *PLoS Comput. Biol.* **11**, e1004321 (2015).

Thank you for your attention!

Questions?