

ICSB 2017 Workshop: DD-DeCaF, cobrapy, escher and cameo

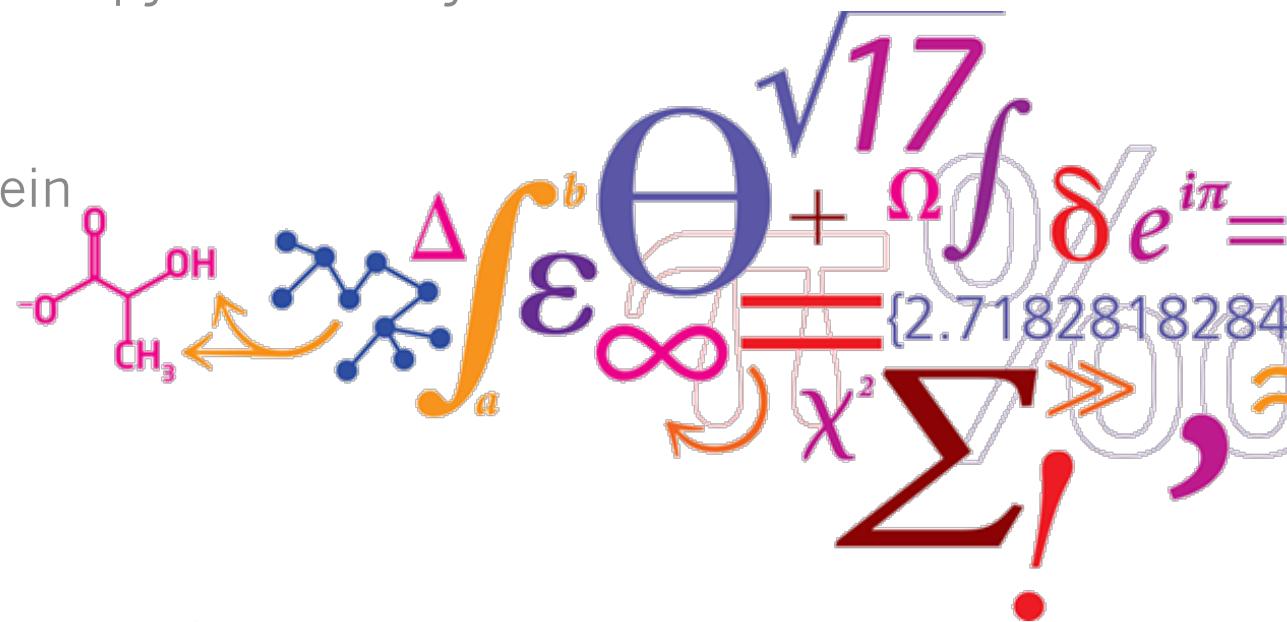
A tutorial on metabolic flux modeling using
packages from the cobrapy community

Henning Redestig

Nikolaus Sonnenschein

Moritz Beber

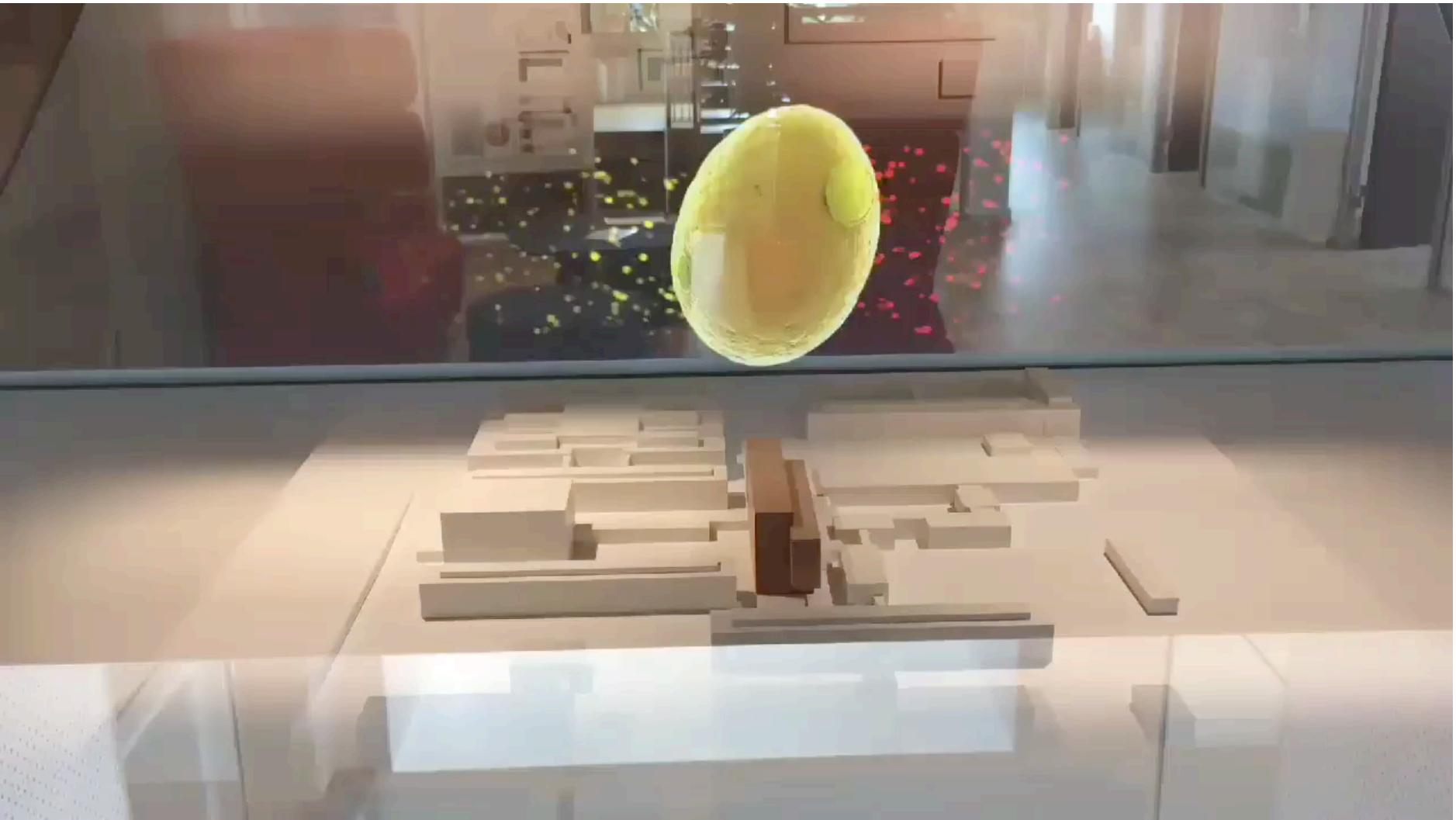
Christian Lieven



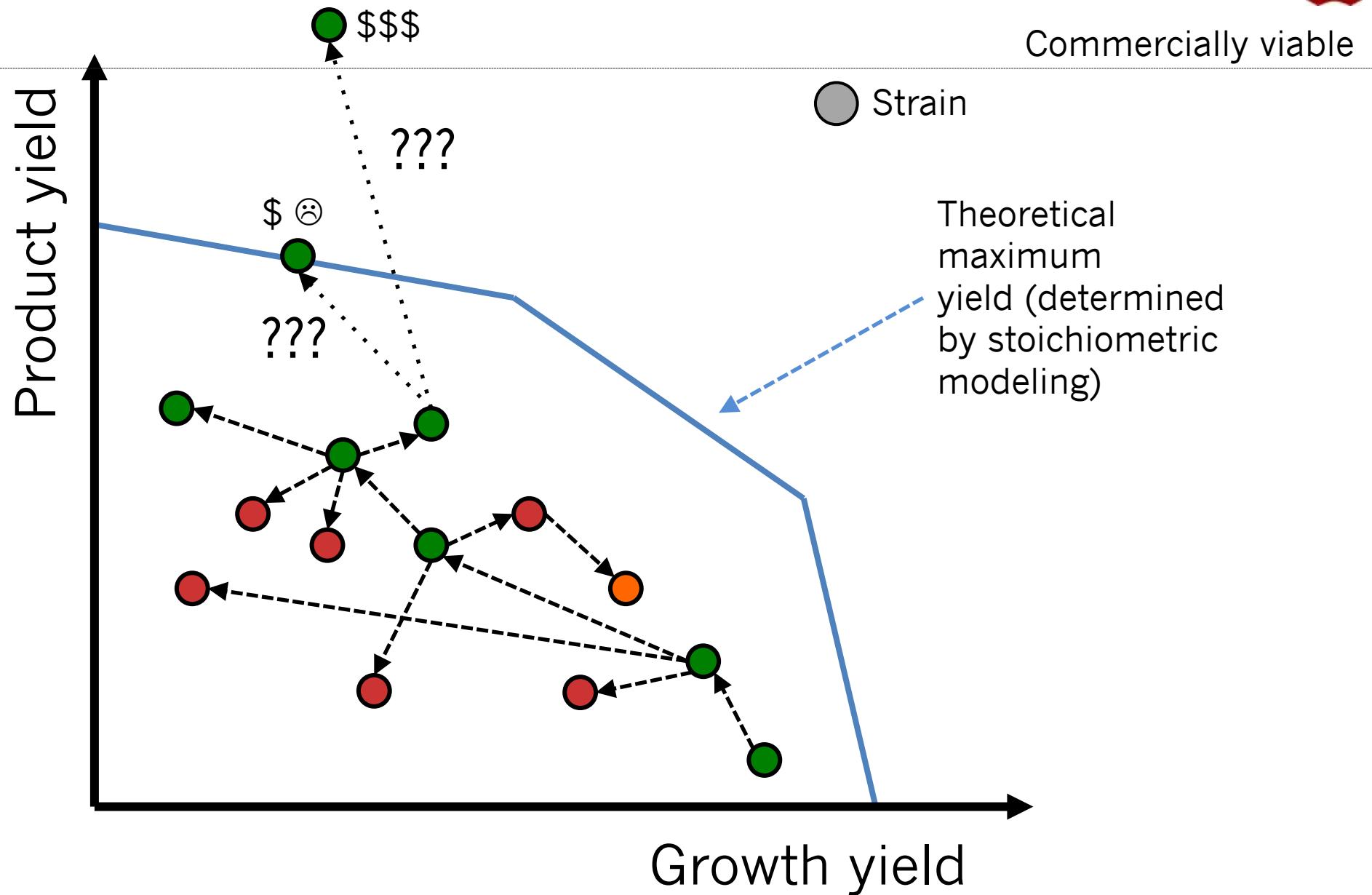
DTU Biosustain

The Novo Nordisk Foundation Center for Biosustainability

NNF Center for Biosustainability



The strain engineering problem



The problem with traditional metabolic engineering

Commercial:

Product titre > 10 g/L
>25 FTE for >5 years
Cost >\$50M

Academic:

Product titre < 100 mg/L
2 FTE for 3 years
Cost \$1M



Valley of Death

Bridging the valley of death

Lab automation



Omics



Commercial:

Product titre > 10 g/L
Cost <\$20M

Academic:

Product titre < 100 mg/L
2 FTE for 3 years
Cost \$1M

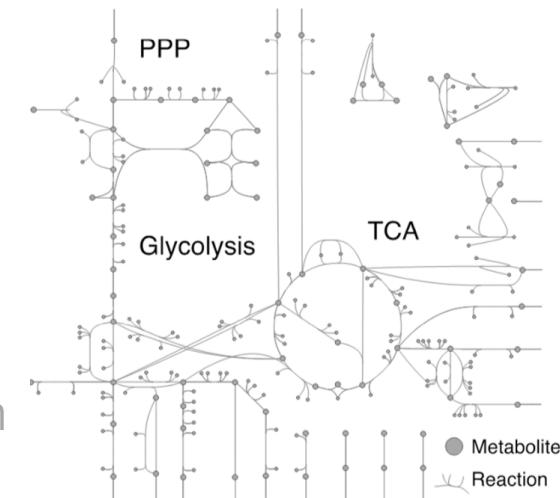


Valley of Death



Systems biology
guided design

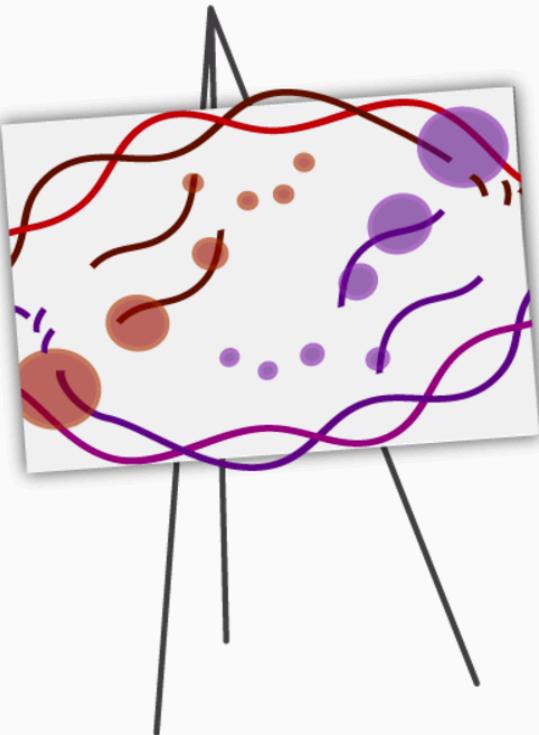
Metabolic pathway



Metabolite

Reaction

SOFTWARE TOOLS TO BE COVERED IN THIS WORKSHOP



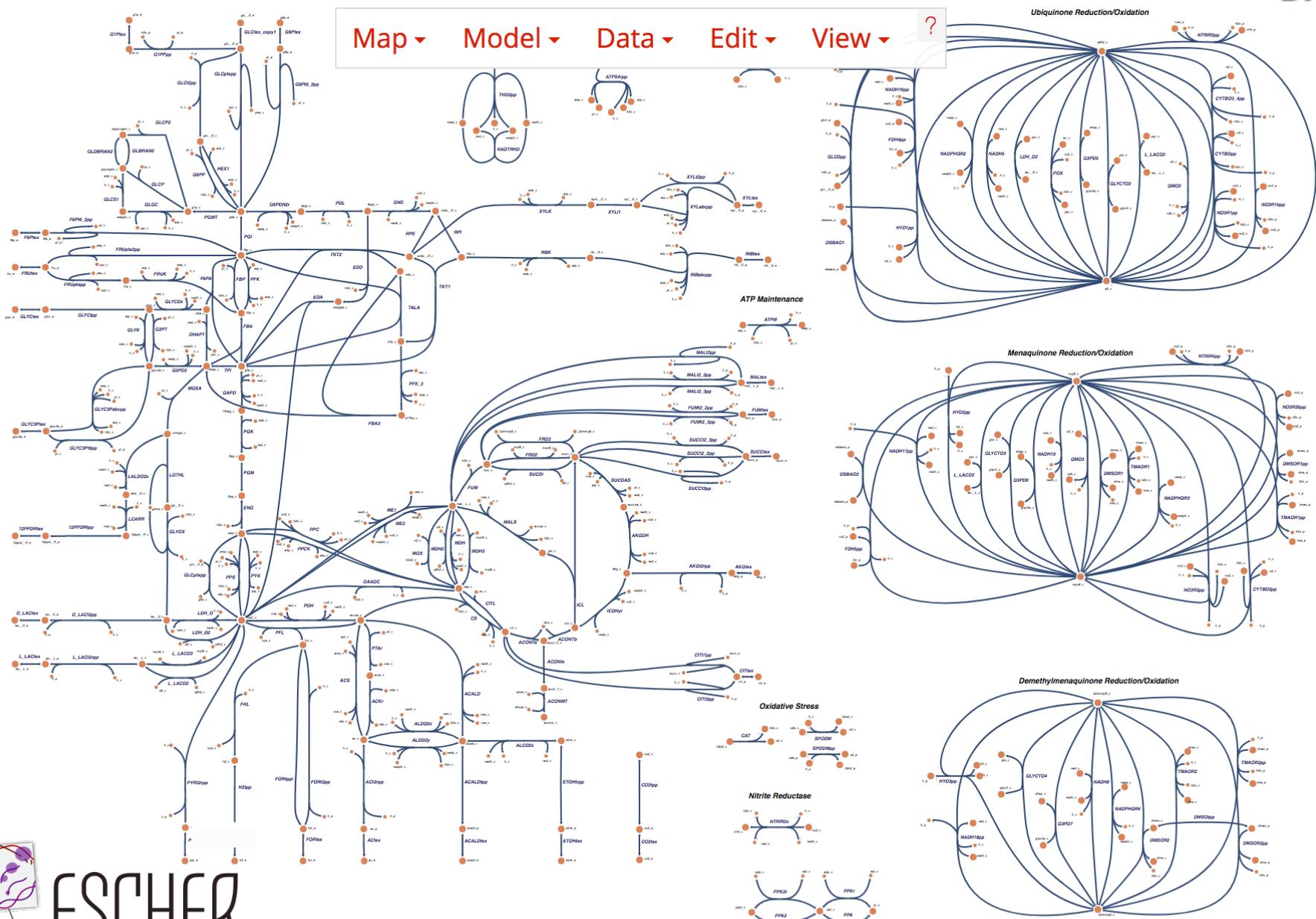
ESCHER

*Build, share, and embed visualizations of
biological pathways.*



Developed by Zachary King

UC San Diego



ESCHER

*Build, share, and embed visualizations of
biological pathways.*

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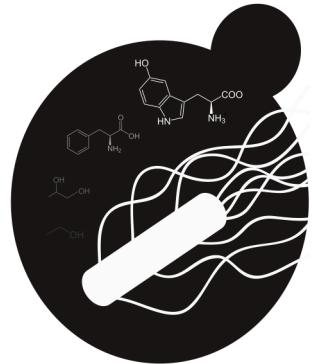
90

contributors 24

release v0.6.1

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

Cameo

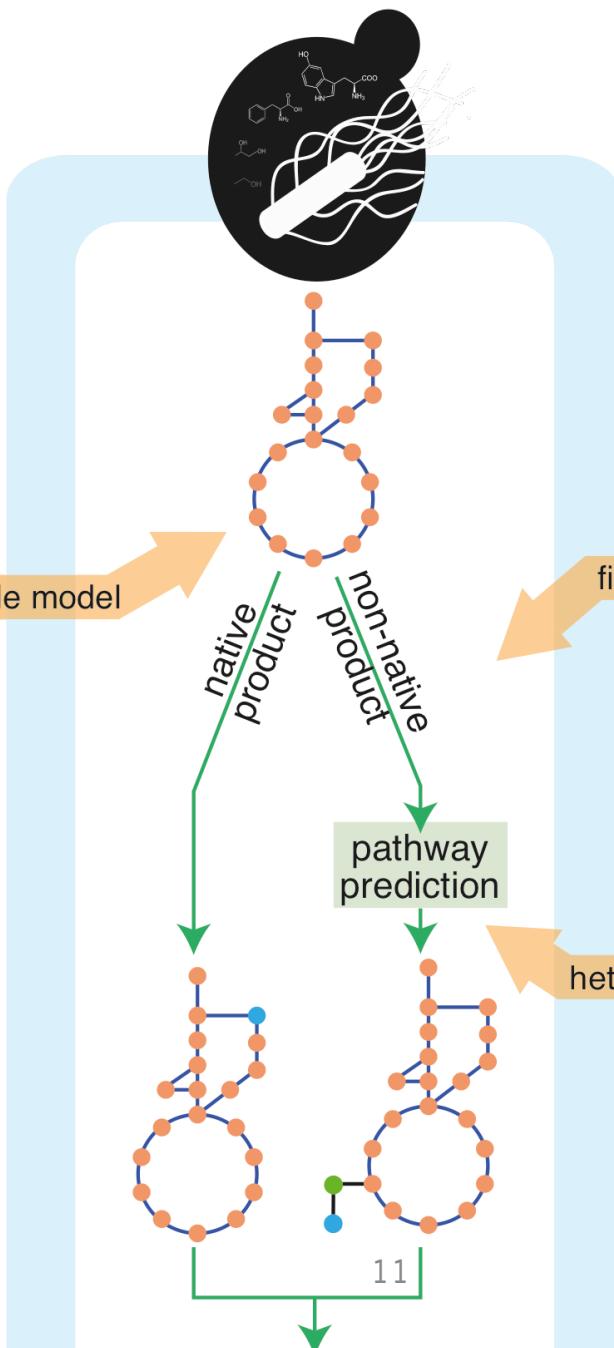
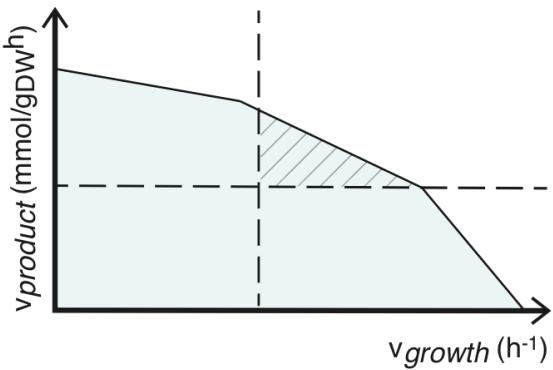
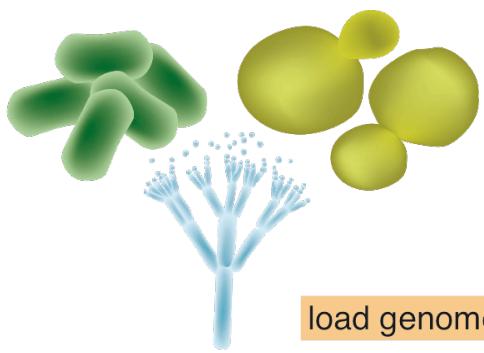


Computer Aided Metabolic Engineering
and Optimization of Cell Factories

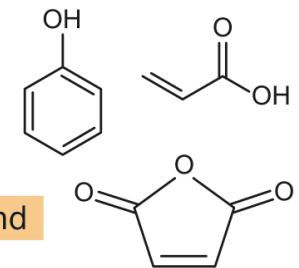
<http://cameo.bio>

Workflow

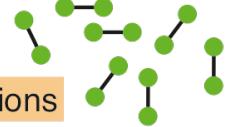
Production hosts



Target chemicals



MetaNetX
Database



http://try.cameo.bio

jupyter

Files Running Clusters

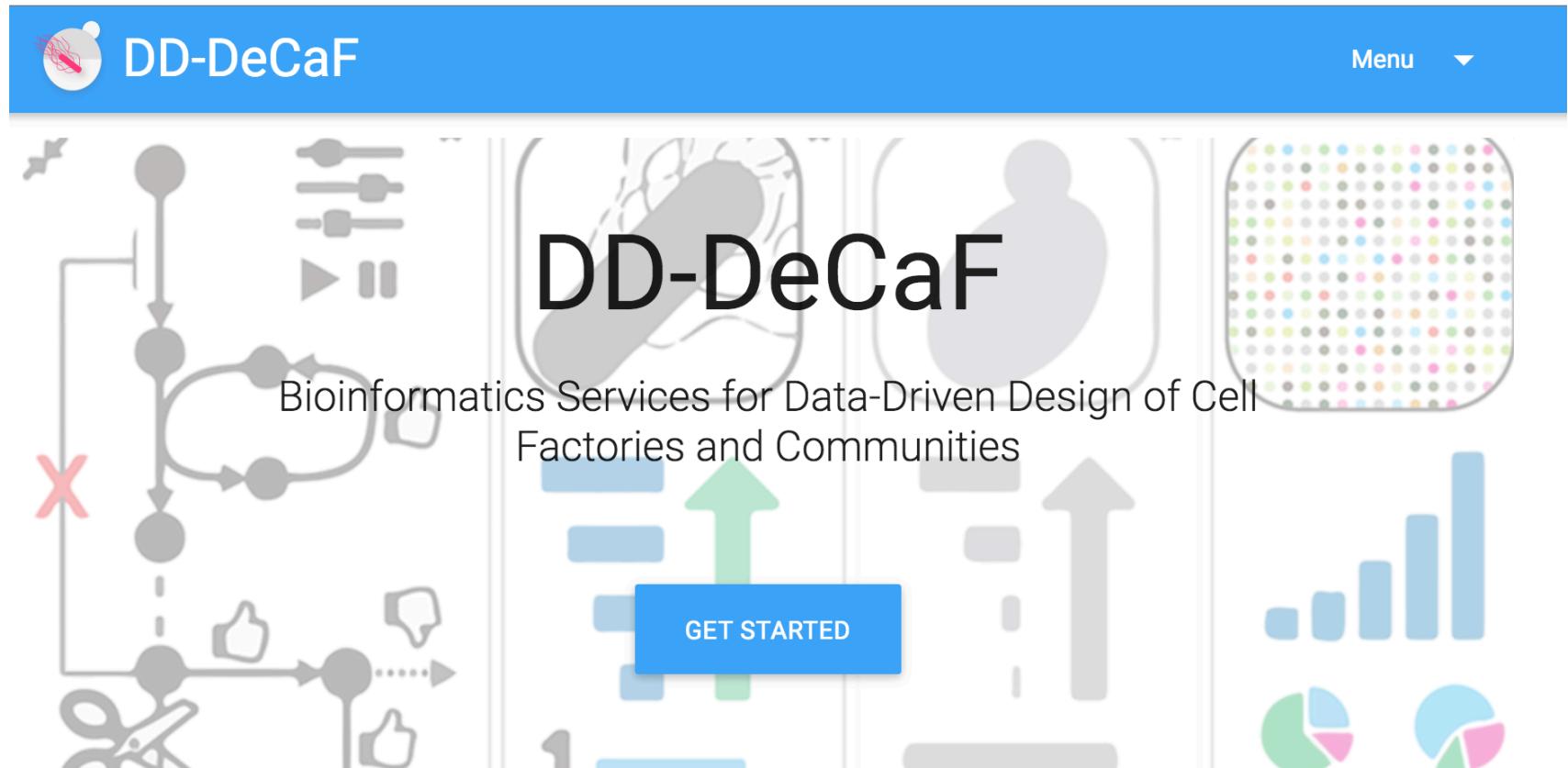
Select items to perform actions on them.

Upload New

<input type="checkbox"/>	
<input type="checkbox"/>	Advanced-SynBio-for-Cell-Factories-Course
<input type="checkbox"/>	data
<input type="checkbox"/>	images
<input type="checkbox"/>	other
<input type="checkbox"/>	util
<input type="checkbox"/>	01-quick-start.ipynb
<input type="checkbox"/>	02-import-models.ipynb
<input type="checkbox"/>	03-simulate-models.ipynb
<input type="checkbox"/>	04-analyze-models.ipynb
<input type="checkbox"/>	05-predict-gene-knockout-strategies.ipynb
<input type="checkbox"/>	06-predict-gene-modulation-targets.ipynb
<input type="checkbox"/>	07-predict-heterologous-pathways.ipynb
<input type="checkbox"/>	08-high-level-API.ipynb
<input type="checkbox"/>	09-vanillin-production.ipynb
<input type="checkbox"/>	11-multiprocess.ipynb
<input type="checkbox"/>	12-advanced-usage-of-heuristic-optimization.ipynb
<input type="checkbox"/>	index.ipynb
<input type="checkbox"/>	Dockerfile
<input type="checkbox"/>	LICENSE
<input type="checkbox"/>	README.md
<input type="checkbox"/>	test_notebooks.sh

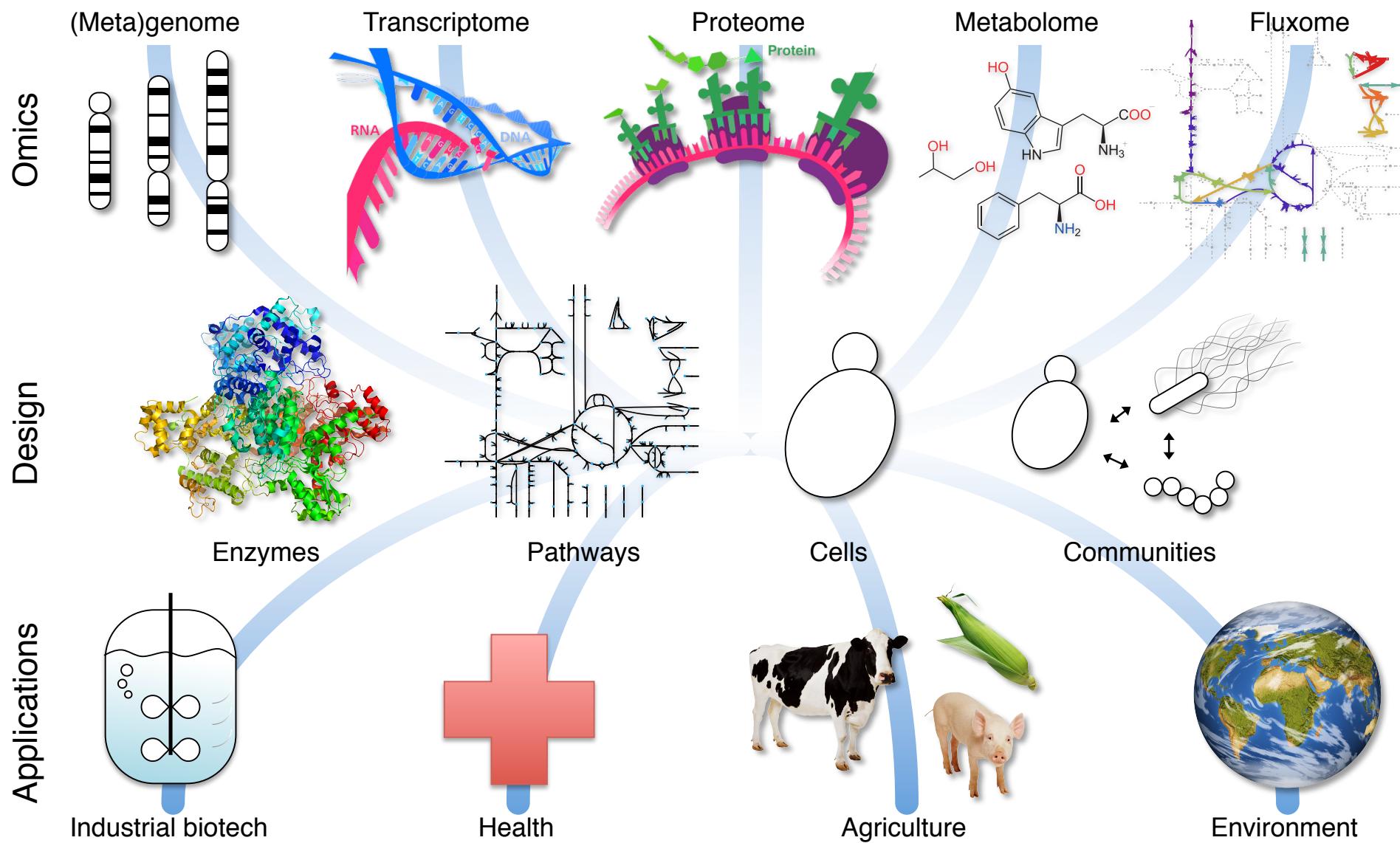
H2020: Data-Driven Design of Cell Factories and Communities

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



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

Horizon 2020: Data-Driven Design of Cell Factories and Communities

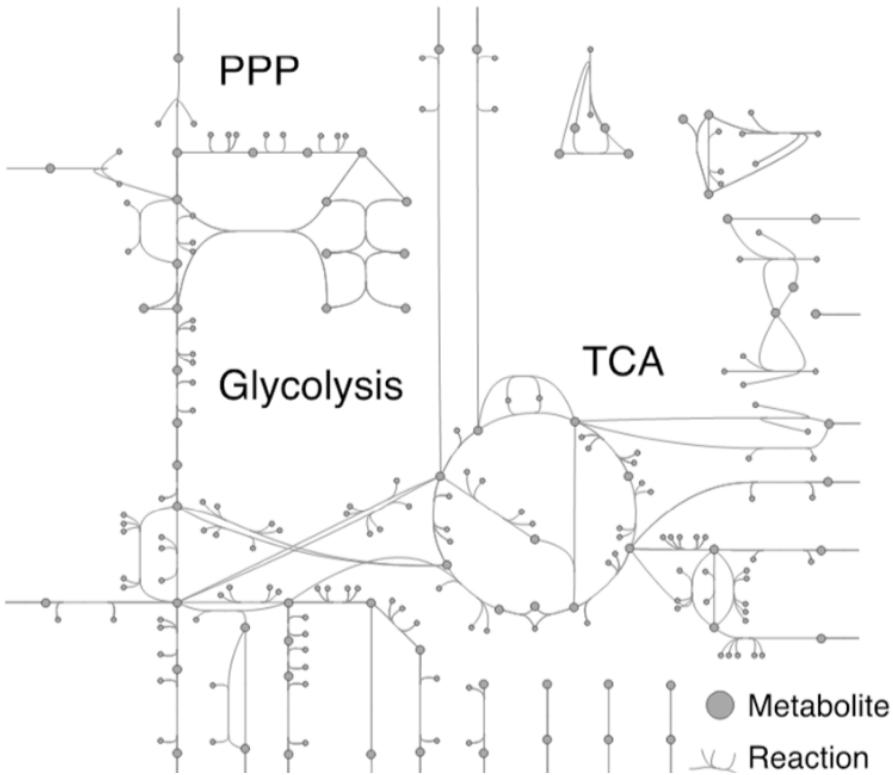


CONSTRAINT-BASED MODELING

Flux balance analysis: derivation

a

Metabolic pathway

**b**

Stoichiometric matrix

		Reactions								
		a	b	c	d	e	f	g	h	i
Metabolites		0	0	-1	-2	1	...			
		0	0	0	0	-1	...			
a		-1	1	0	0	0	0	...		
b		0	-1	0	1	0	0	...		
c		1	0	0	1	0	0	...		
d	
e	
f	
g	
h	
i	

$= S$

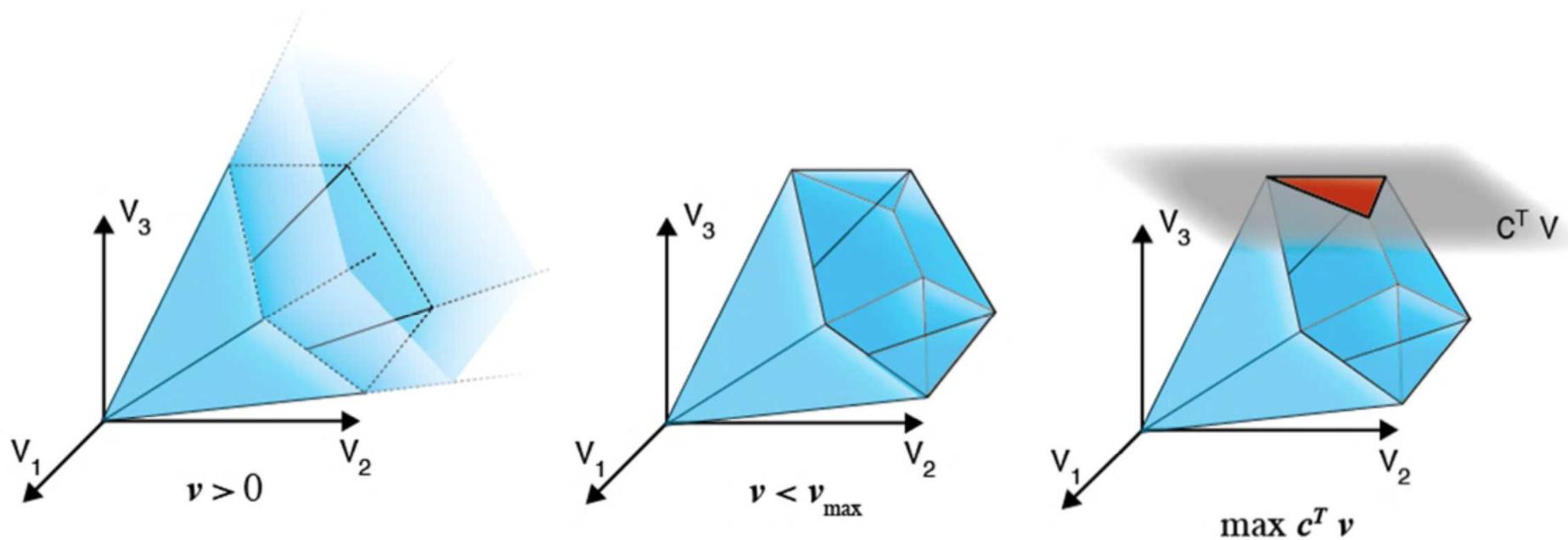
$\begin{matrix} c & \xleftarrow{a} & d & \xleftarrow{a} & e & \xleftarrow{a} & f & \xleftarrow{a} & g & \xleftarrow{a} & h \\ e & \xrightarrow{a} & c & \xrightarrow{a} & d & \xrightarrow{a} & e & \xrightarrow{a} & f & \xrightarrow{a} & g \\ & & & & & & & & & & \end{matrix}$

 $\begin{matrix} a & + & b & = & c \\ & & & & \end{matrix}$

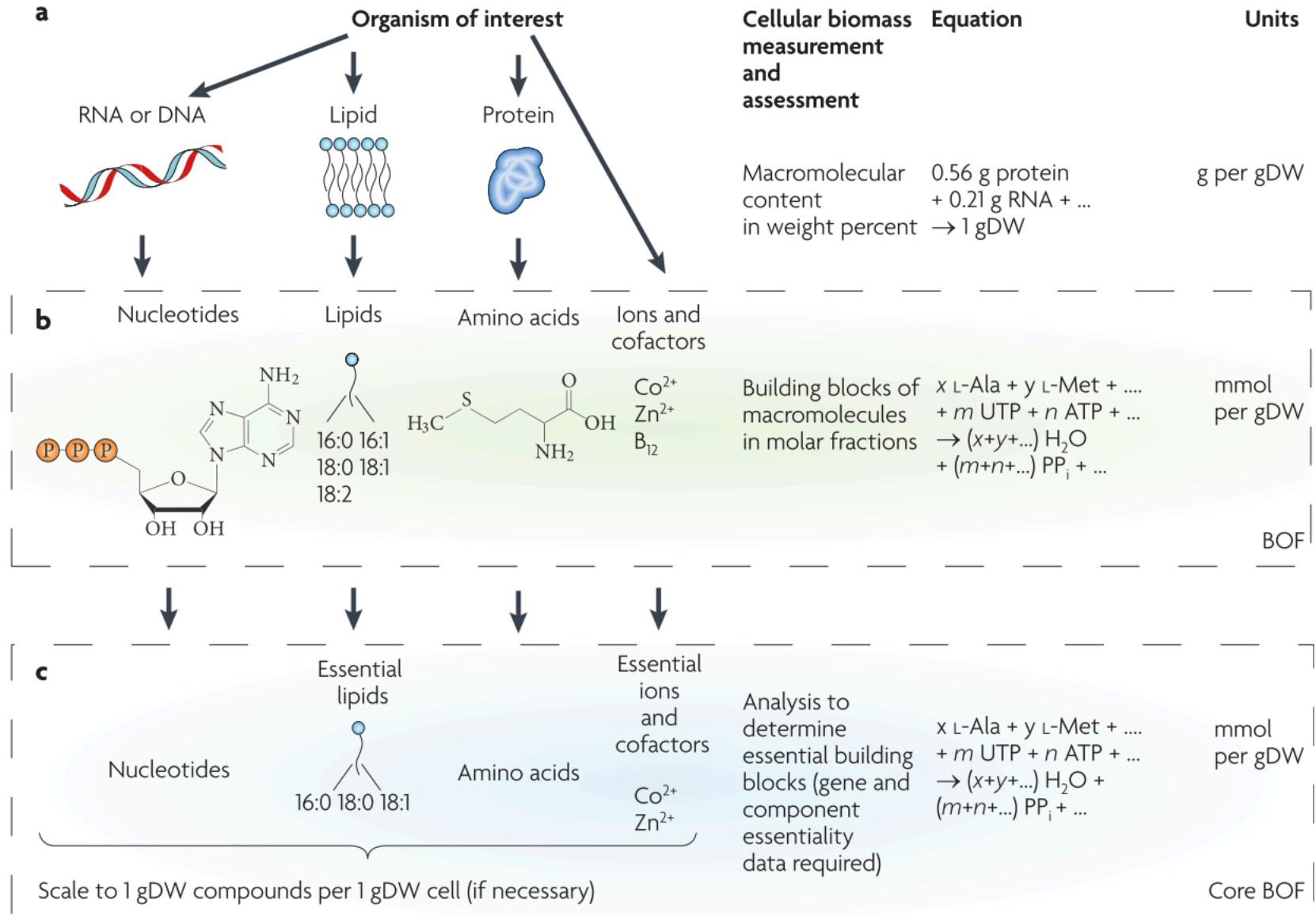
$$\frac{dx(t)}{dt} = S v = 0, \dots)$$

Flux balance analysis: constraints

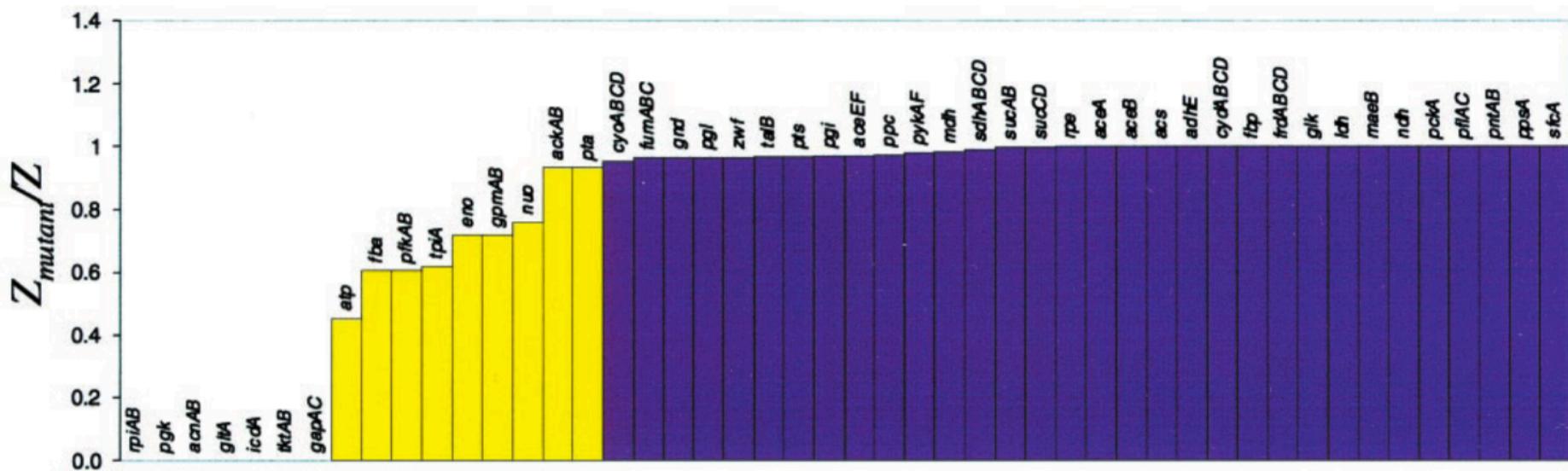
- Following constraints can be superimposed
 - Mass balance: metabolite production and consumption rates are equal ($s^T v = 0$)
 - Thermodynamics: e.g. irreversibility of reactions
 - Flux capacities: bounds on flux e.g. nutrient uptake rates
- Optimize a biological objective (e.g. biomass production)



The biomass equation

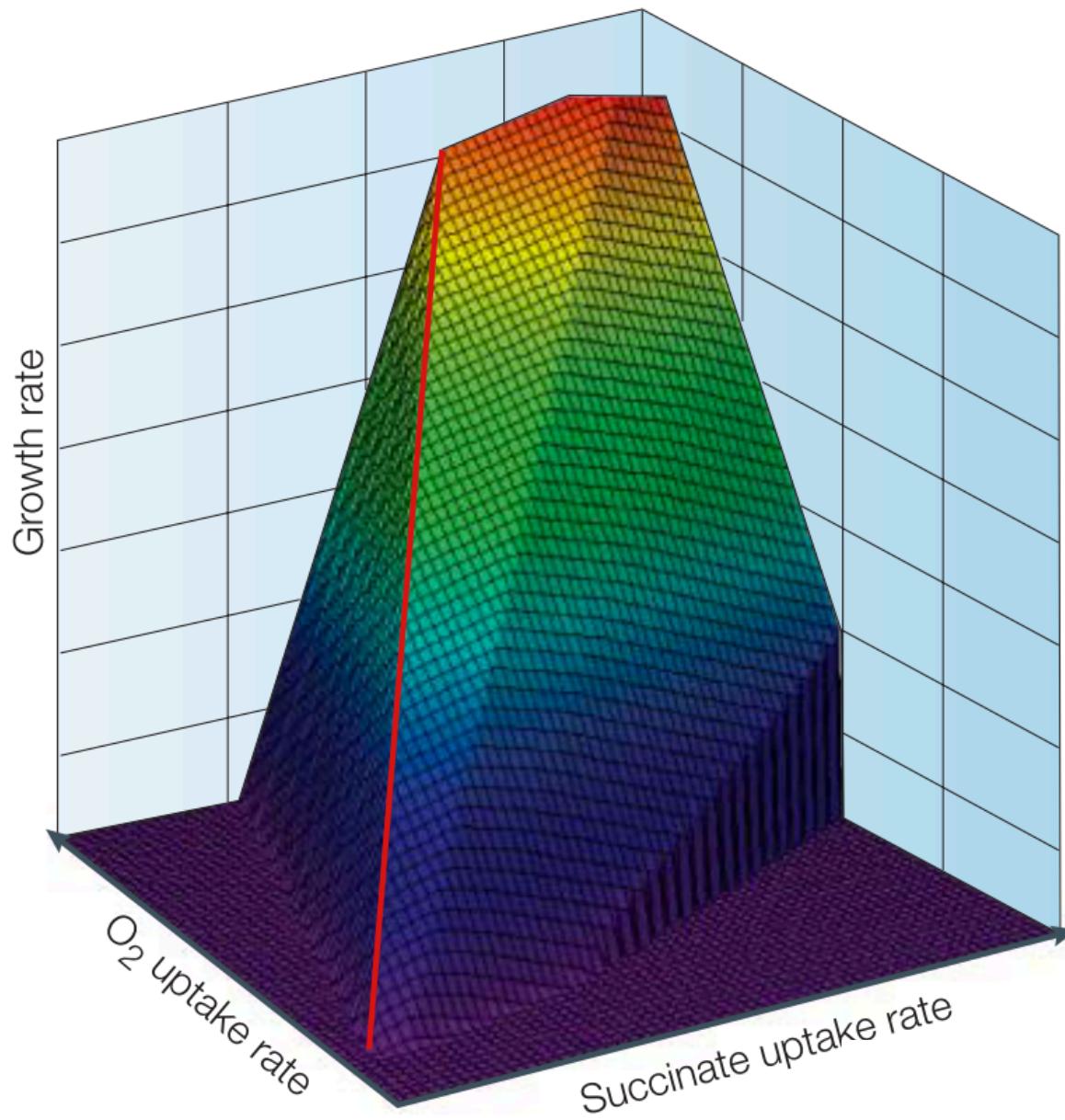


Predict gene essentiality with FBA

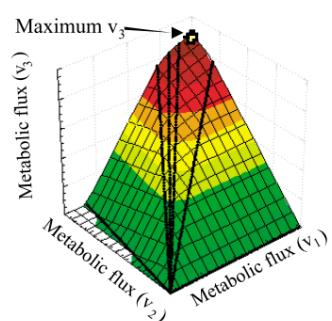
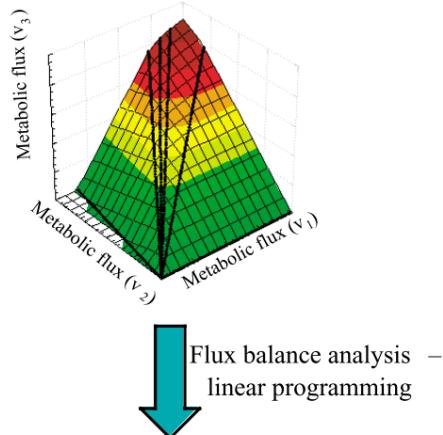
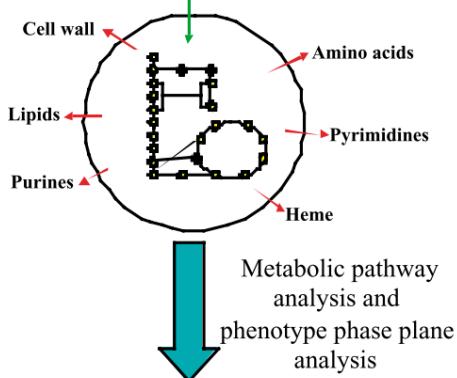


Edwards, J. S., & Palsson, B. Ø. (2000). The *Escherichia coli* MG1655 in silico metabolic genotype: its definition, characteristics, and capabilities. *Proceedings of the National Academy of Sciences of the United States of America*, 97(10), 5528–5533.

Phenotypic Phase Planes (PPP)

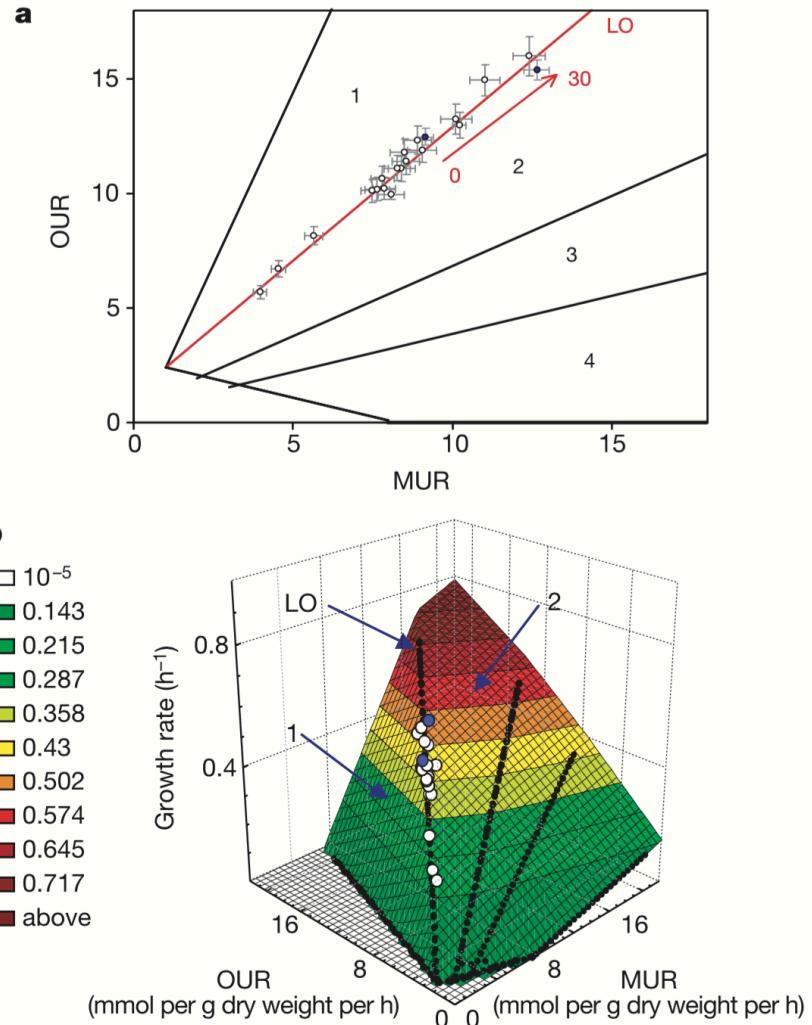


Adaptive laboratory evolution confirms FBA predictions



Phenotypic Phase Plane

FBA result projected

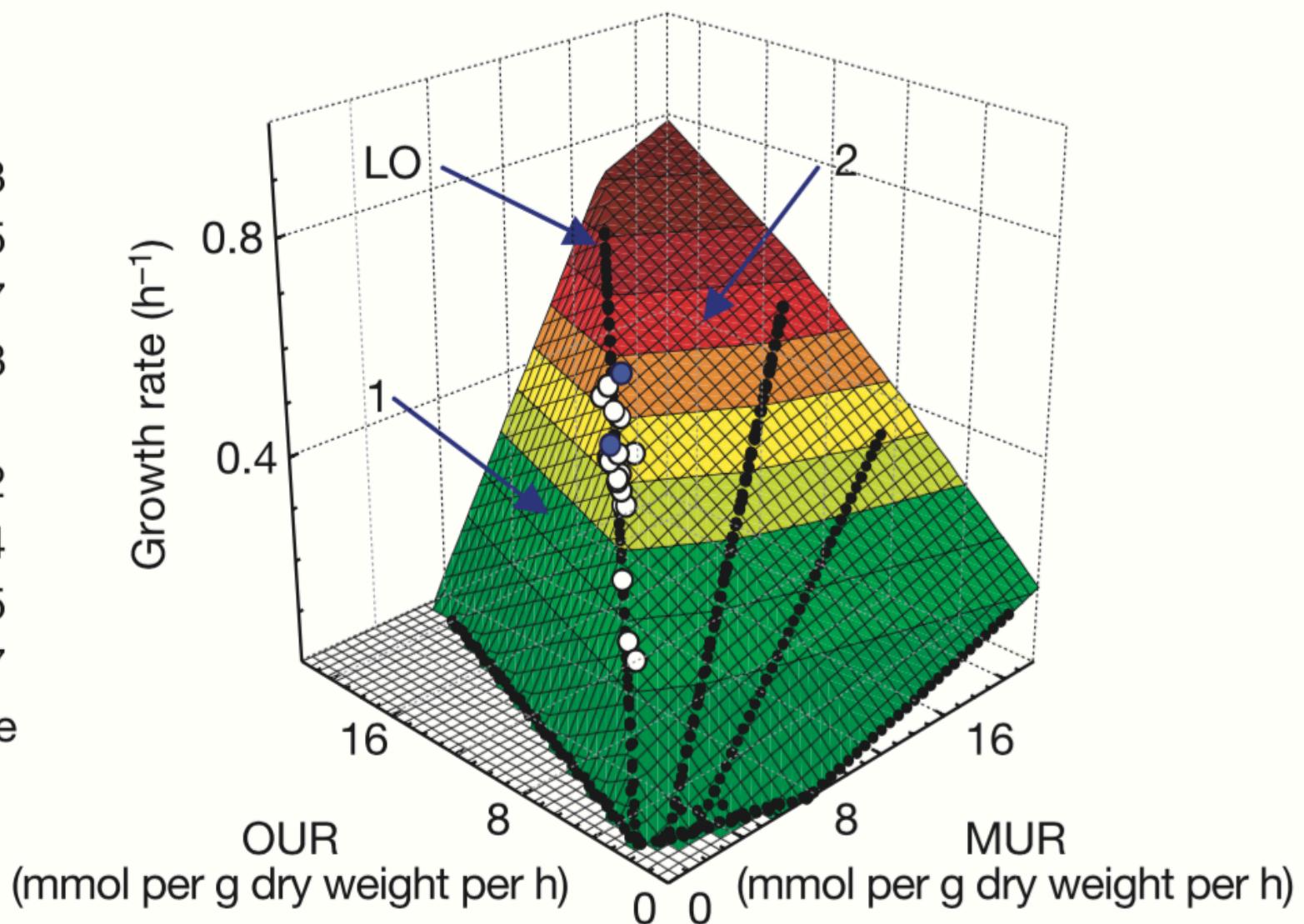


Edwards, J. S., Ibarra, R. U., & Palsson, B. Ø. (2001). In silico predictions of *Escherichia coli* metabolic capabilities are consistent with experimental data. *Nature Biotechnology*, 19(2), 125–130. <http://doi.org/10.1038/84379>

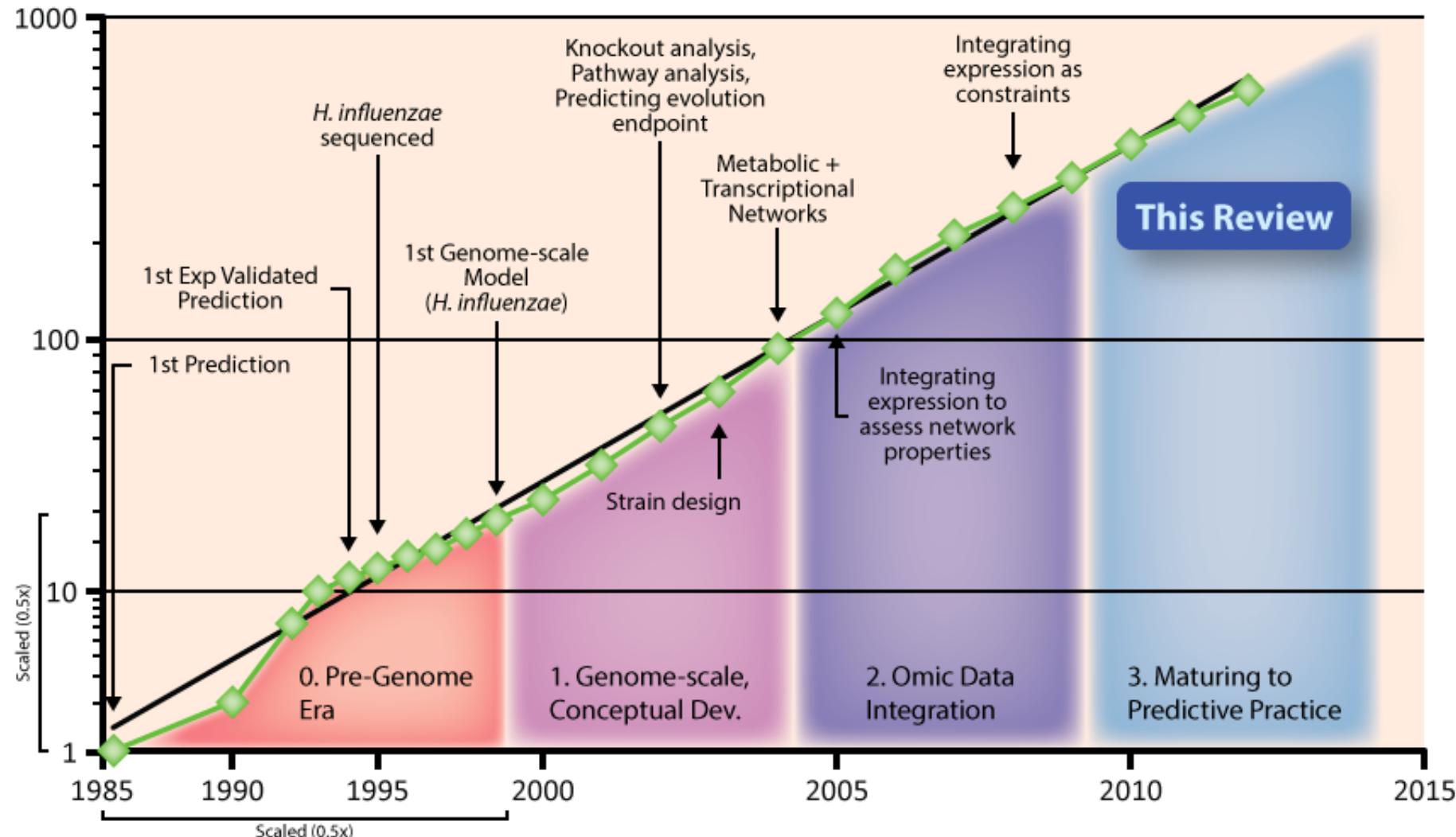
Adaptive laboratory evolution confirms

b

- 10⁻⁵
- 0.143
- 0.215
- 0.287
- 0.358
- 0.43
- 0.502
- 0.574
- 0.645
- 0.717
- above



Success of the field



A Bordbar, JM Monk, ZA King, BO Palsson
Nature Reviews Genetics 15 (2), 107-120

WORKSHOP DETAILS



software carpentry



Software carpentry + Computational
cell factory engineering course (2016)

Workshop schedule

Time	Topic
9:00	(45 min) Demonstration of the DD-DeCaF platform
15 min	Break
10:00	(45 min) Gentle introduction to programming in Python using Jupyter notebooks
15 min	Break
11:00	(1 h) Modeling metabolic flux using cobrapy
1 h	Lunch
13:00	(1 h) Modeling metabolic flux using cobrapy (continued)
15 min	Break
14:15	(1 h) Model and data visualization with Escher
15 min	Break
15:30	(1 h 30 min) Computational strain design using cameo
17:00	Finish

Workshop materials and server

- Workshop materials
 - <https://github.com/DD-DeCaF/icsb-tutorial>
- Workshop JupyterHub
 - No installation hassle of software
 - <https://workshop.dd-decaf.eu>
 - You will need to create a GitHub account if you don't already have one