

INT3007 Systems Biology Introduction to Metabolic Modeling

Marian Breuer

7rd of November 2022

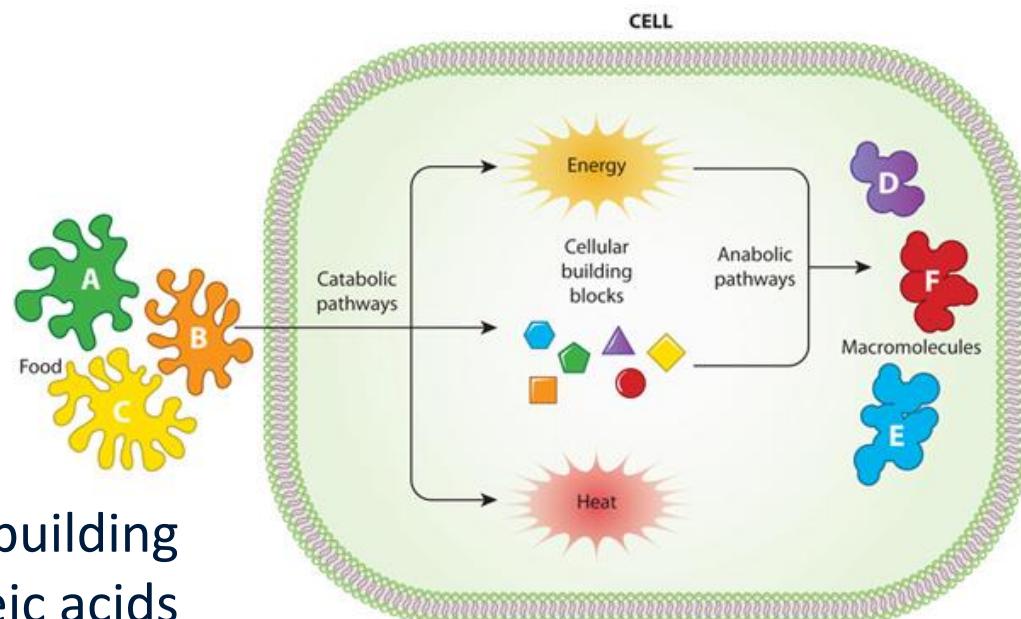


Metabolism

Metabolism is the set of life-sustaining chemical transformations within the cells of organisms.

Purpose of metabolism

- Extraction of energy
- Storage of fuels
- Synthesis of important building blocks (proteins, lipids, nucleic acids & carbohydrates → growth)
- Elimination of waste

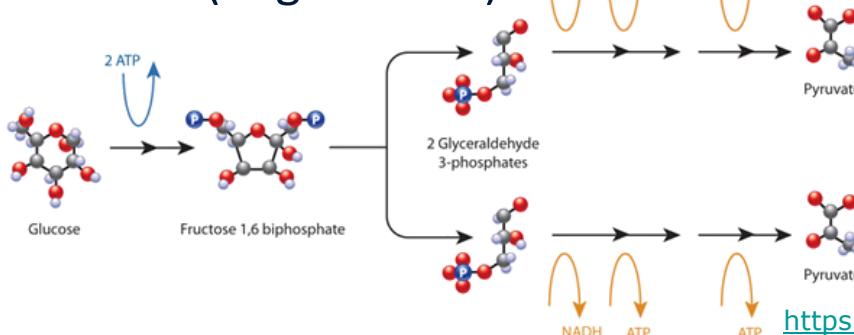


<https://en.wikipedia.org/wiki/Metabolism>

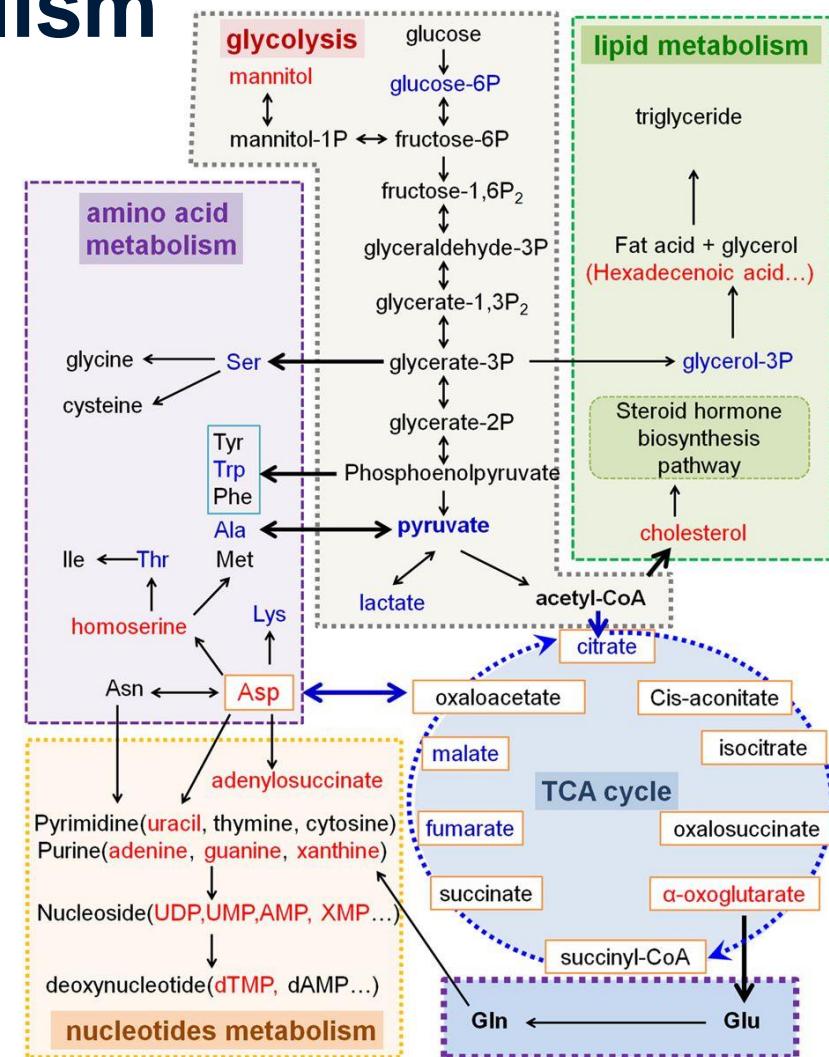
<https://www.nature.com/scitable/topicpage/cell-metabolism-14026182>

Components of metabolism

- Connected reactions:
product of one reaction → substrate for next reaction
- Catalyzed by **enzymes**
- Activity tuned according to immediate needs or changes in environment
 - Example: Presence/absence of oxygen
- Co-ordinated series of chemical reactions: **metabolic pathway**
- Goal: create a new molecule (biosynthesis), or break down a molecule (degradation)



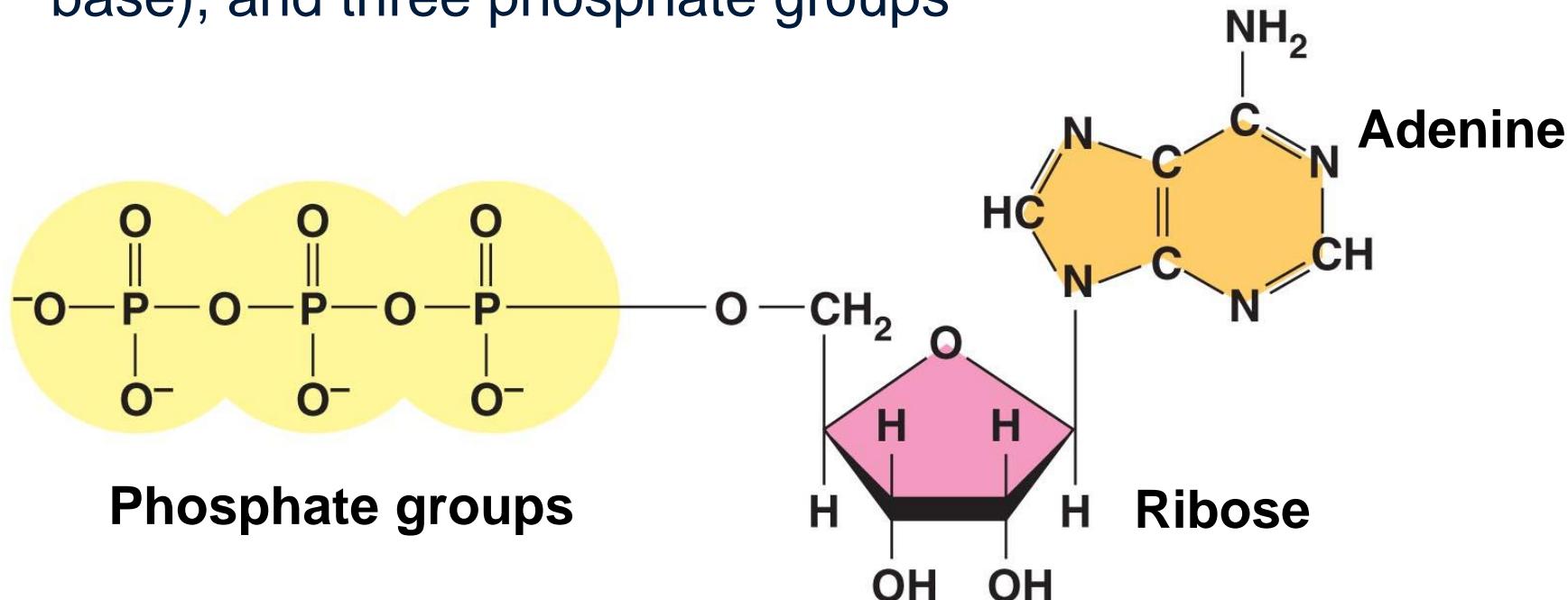
Metabolism



<https://www.nature.com/scitable/topicpage/cell-metabolism-14026182>

ATP as energy currency

- **ATP (adenosine triphosphate)** is the main cellular energy currency
- ATP is composed of ribose (a sugar), adenine (a nitrogenous base), and three phosphate groups

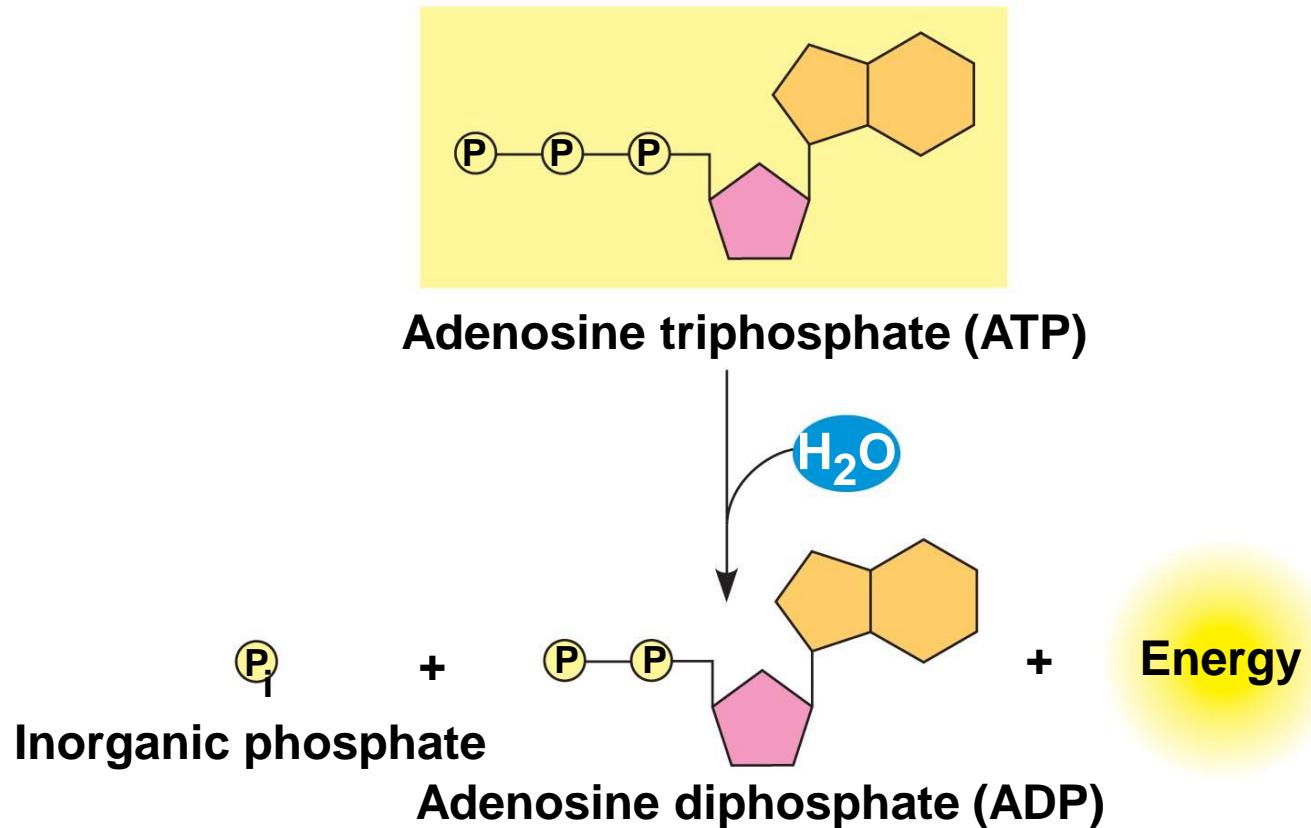


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Fig. 8-8

ATP as energy currency

Energy is released by **hydrolysis** of a phosphate bond



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Fig. 8-9

ATP as energy currency

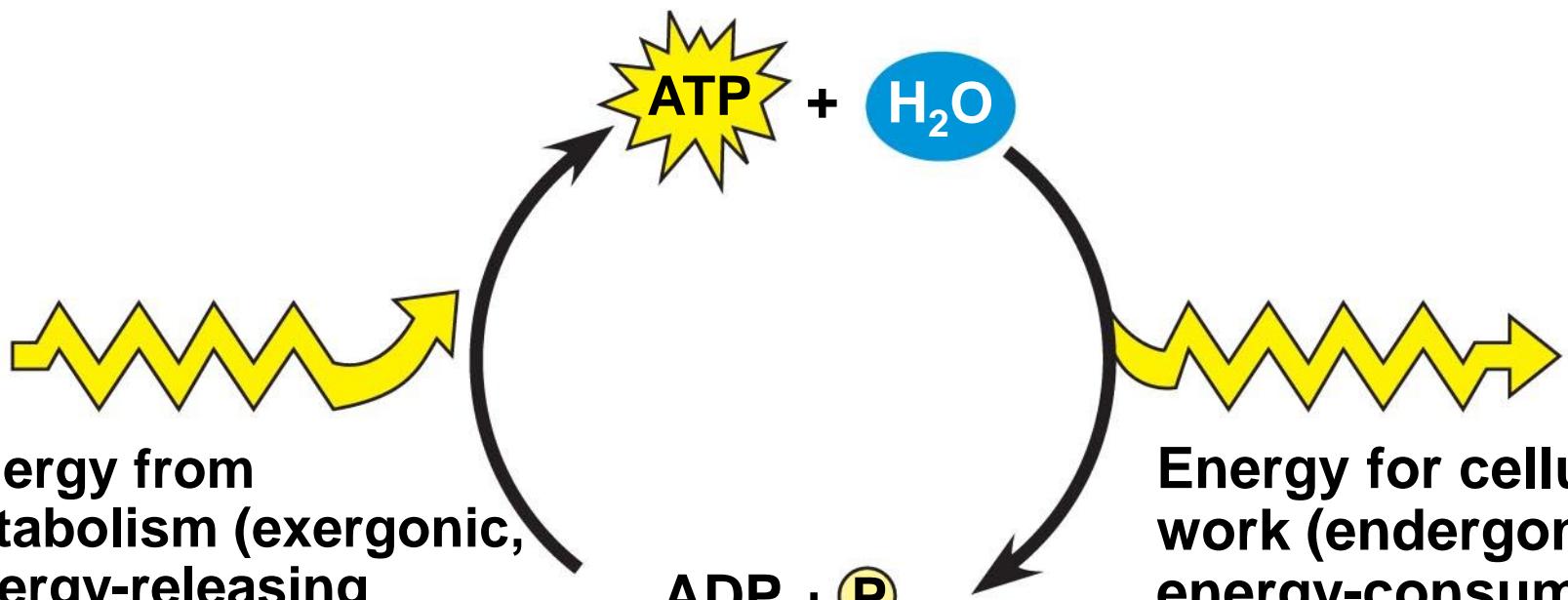
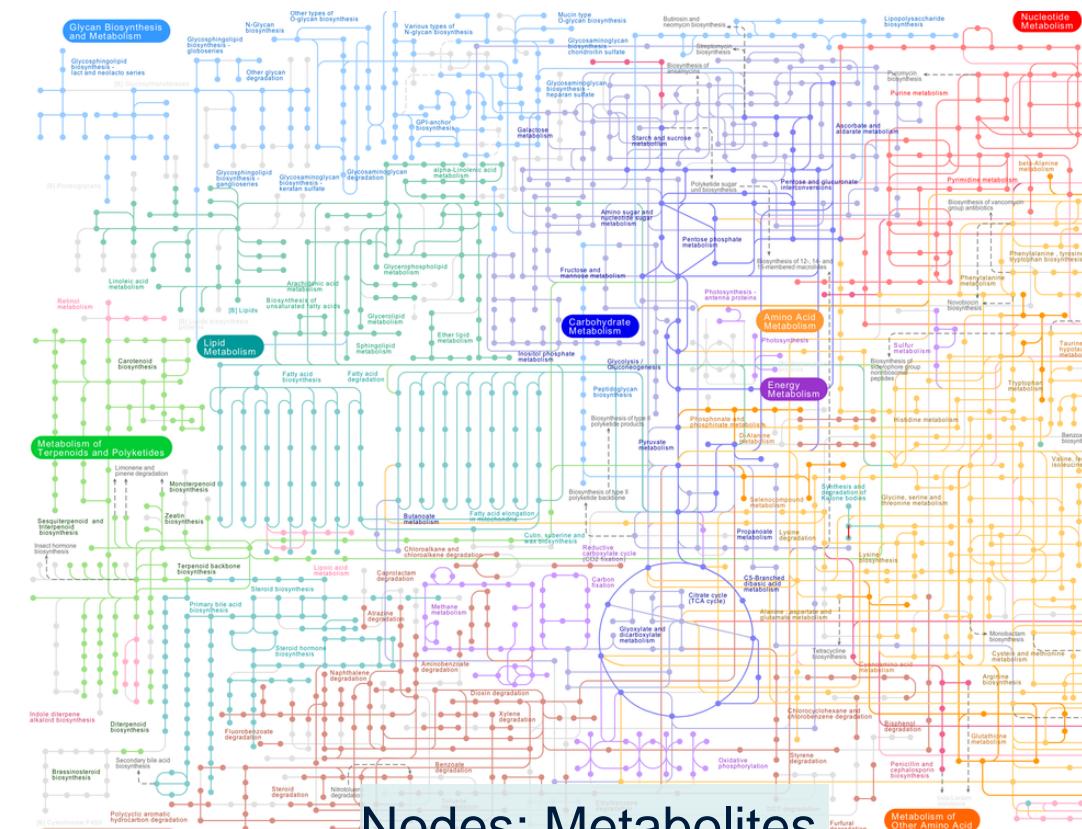


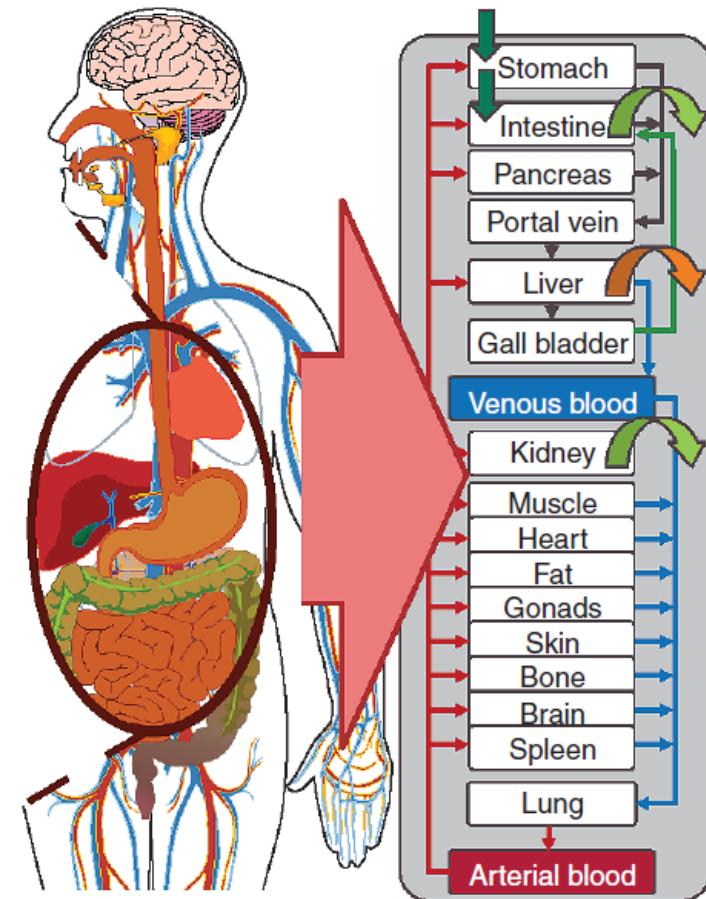
Fig. 8-12

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Metabolism as a network

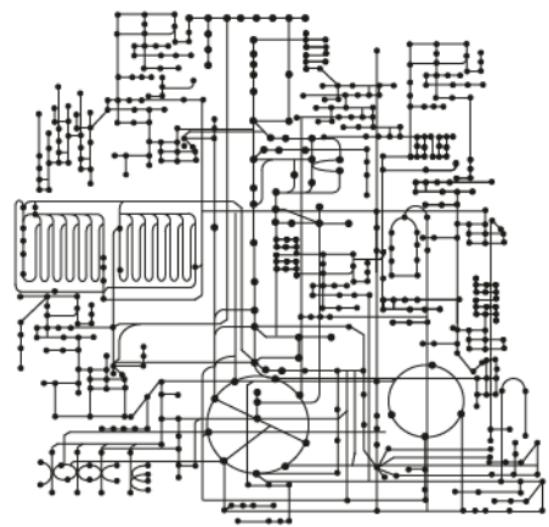


Nodes: Metabolites
Edges: Reactions

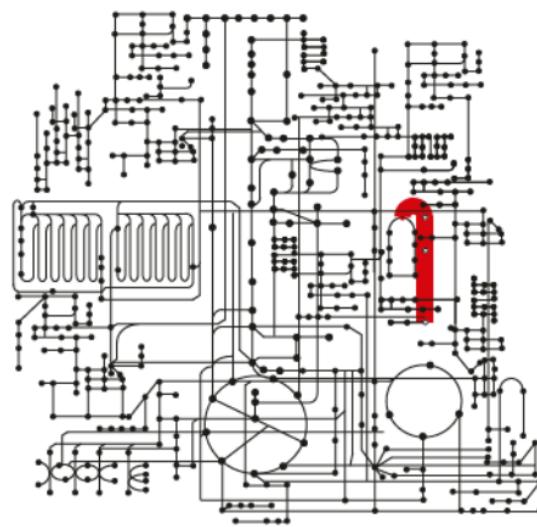


Role of metabolism in health and disease

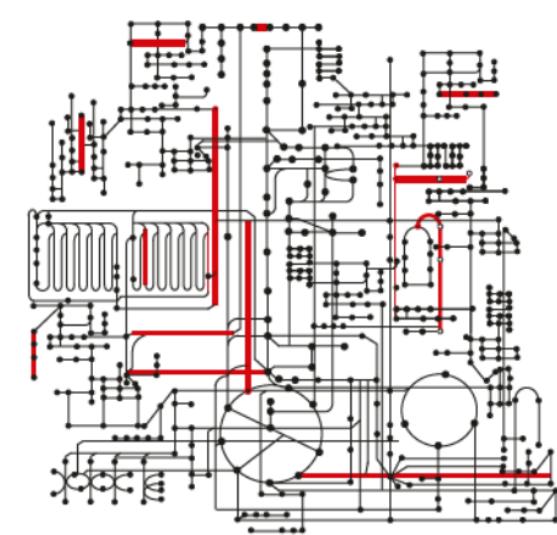
Wild type



Mendelian disorder



Complex disease



Lanpher et al. *Nat. Rev. Gen.* 2006, 7, 449.

Role of metabolism in health and disease

Table 1 | Examples of large- and small-molecule Mendelian inborn errors of metabolism*

Molecule/pathway affected	Representative disease	OMIM #	Clinical presentation	Management options
<i>Large-molecule diseases</i>				
Complex lipid degradation	Gaucher disease Type I	230800	Hepatomegaly, splenomegaly, bony lesions, acid β-glucuronidase deficiency.	Enzyme replacement; substrate reduction.
Mucopolysaccharidoses	MPS I (Hurler syndrome)	607014	Corneal clouding, mental retardation, hernias, dysostosis multiplex, hepatosplenomegaly. Elevated urine excretion of glycosaminoglycans, α-L-iduronidase activity deficient.	Bone marrow transplantation. Enzyme replacement.
Glycogen storage diseases	GSD1A (Von Gierke disease)	232200	Hepatomegaly, pancreatitis, hypoglycaemia, hyperlipidaemia, hyperuricaemia, lactic acidosis. Liver adenomas and hepatocellular carcinomas.	Avoid hypoglycaemia and acidosis with continuous feeding or supplementation with uncooked cornstarch. Liver transplantation for carcinoma or adenoma.
Peroxisomal diseases	Zellweger syndrome	214100	Dysmorphic features, hepatomegaly, polymicrogyria, severe mental retardation. Pimecolic aciduria, elevated long-chain fatty acids. Death usually in first year.	Symptomatic.
<i>Small-molecule diseases</i>				
Amino-acid-metabolism disorders	Phenylketonuria	261600	Microcephaly, pale pigmentation, mental retardation (if untreated). Teratogenic effects on foetuses of affected mothers (if untreated).	Phenylalanine-restricted diet.
Urea-cycle disorders	Ornithine transcarbamoylase deficiency	311250	Hyperammonaemia, vomiting, coma. Episodic hyperammonaemia. X-chromosome-linked inheritance.	Acute: detoxification with dialysis, nitrogen scavengers. Long-term: protein restriction, nitrogen supplementation, arginine supplementation, nitrogen scavengers. Liver transplantation.
Organic acid-metabolism disorders	Methylmalonic aciduria	251000	Mental retardation, episodic acidosis, hyperammonaemia, stroke-like episodes, progressive renal failure, neutropenia, cardiomyopathy.	Dietary restriction of propiogenic amino acids; carnitine supplementation. Consider liver transplantation.
Monosaccharides	Galactosaemia	230400	Progressive symptoms after start of milk feeding. Vomiting, jaundice, liver failure, sepsis, cataracts.	Lactose free, galactose-restricted diet.
Pyruvic-acid and lactic-acid metabolism disorders	Pyruvate carboxylase deficiency	266150	Psychomotor retardation, lactic acidosis, hypotonia.	Carbohydrate restricted diet. Cofactor supplementation.
Fatty-acid metabolism	Medium-chain acyl-CoA dehydrogenase deficiency	201450	Episodic hypoketotic hypoglycaemia. Decompensation with fasting or illness.	Avoid fasting and catabolic stress. Carnitine supplementation.
Purine- and pyrimidine-metabolism disorders	Adenosine deaminase deficiency	102700	Severe combined immune deficiency (SCID).	Bone marrow transplant.
Cholesterol biosynthetic disorders	Smith-Lemli-Opitz syndrome	270400	Dysmorphic features, midline malformations, severe psychomotor retardation.	Cholesterol supplementation. Consider HMG-CoA reductase inhibitors.
Vitamin and cofactors-metabolism defects	Biotinidase deficiency	253260	Metabolic acidosis, neurologic impairment, seizures, skin and hair defects.	Biotin supplementation.
Heme synthesis	Acute intermittent porphyria	176000	Abdominal colic, episodic events mimicking acute abdomen, polyneuropathy.	Avoid triggers. Treat acute attacks with IV glucose and hemin preparations.
Copper- and iron-transport disorders	Wilson disease	277900	Chronic liver disease, cirrhosis, psychiatric disease. Neurological deterioration.	Avoid copper in diet. D-penicillamine. Consider liver transplantation.

Lanpher et al. *Nat. Rev. Gen.* 2006, 7, 449.

Maastricht Centre for Systems Biology (MaCSBio)

How to study metabolic networks?

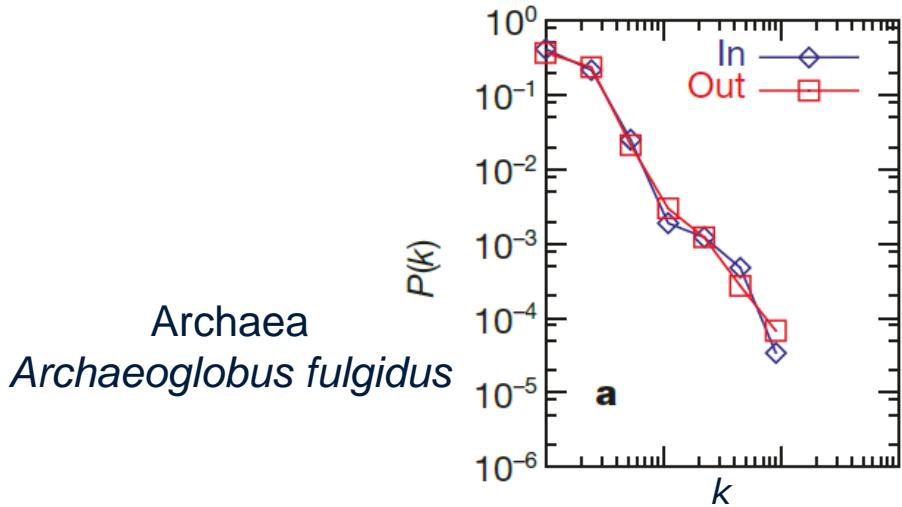
Can study network connectivity

Maastricht Centre for Systems Biology (MaCSBio)

Node connectivity of metabolic networks

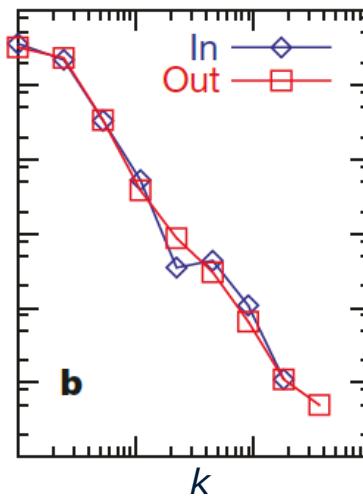
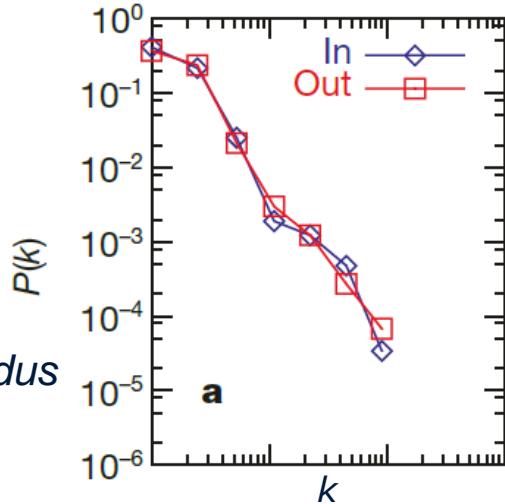
Jeong et al. *Nature* 2000, **407**, 651.

Node connectivity of metabolic networks

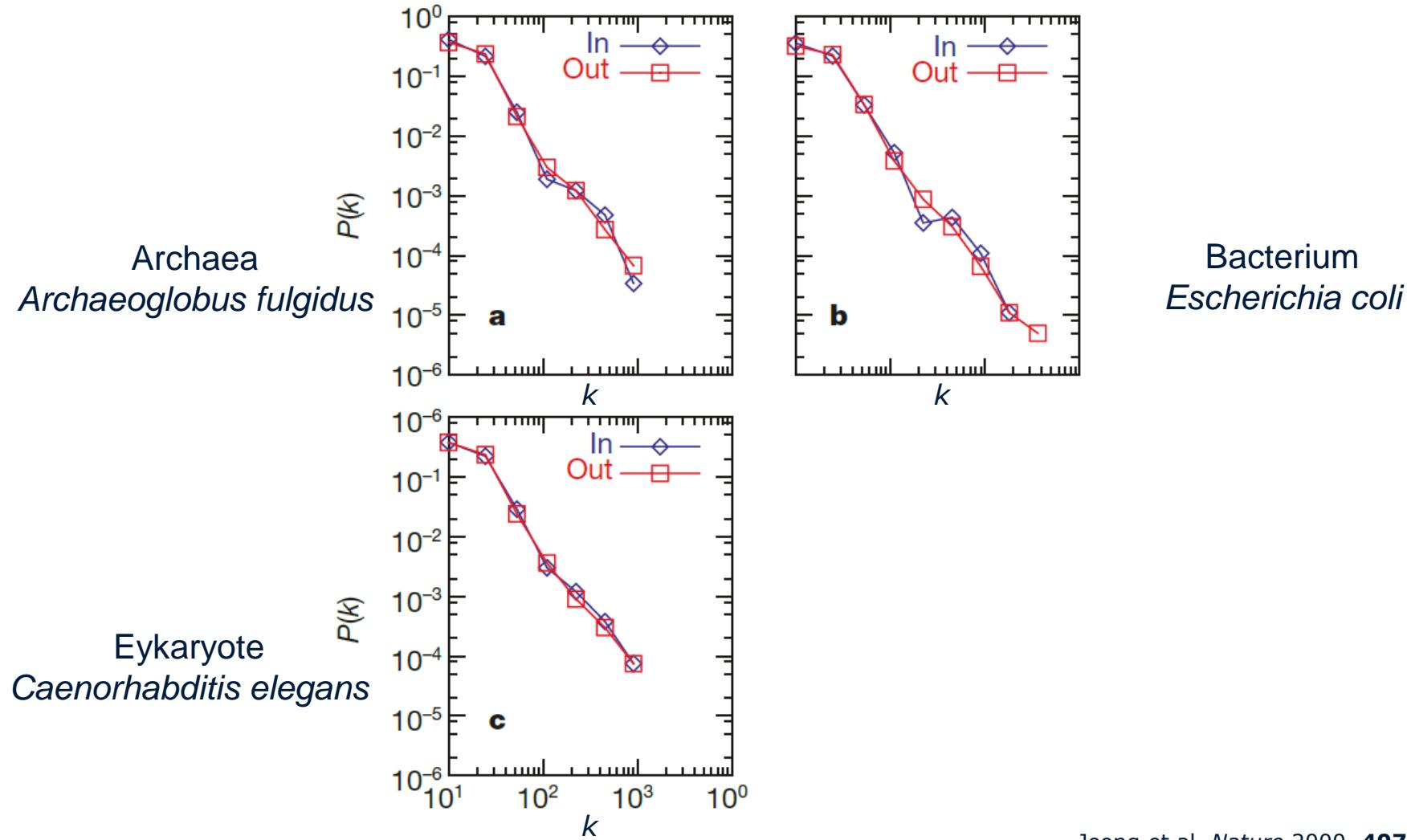


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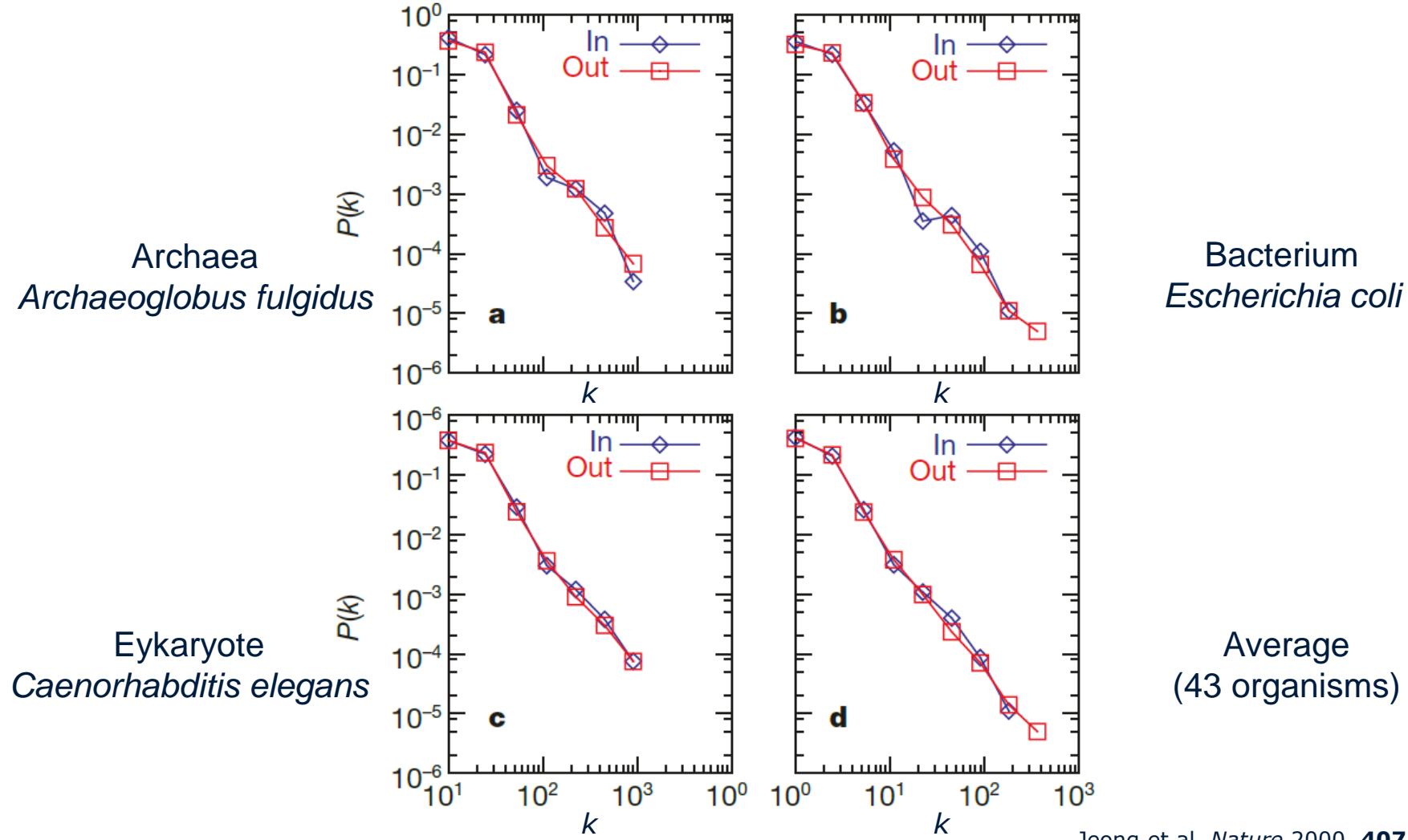


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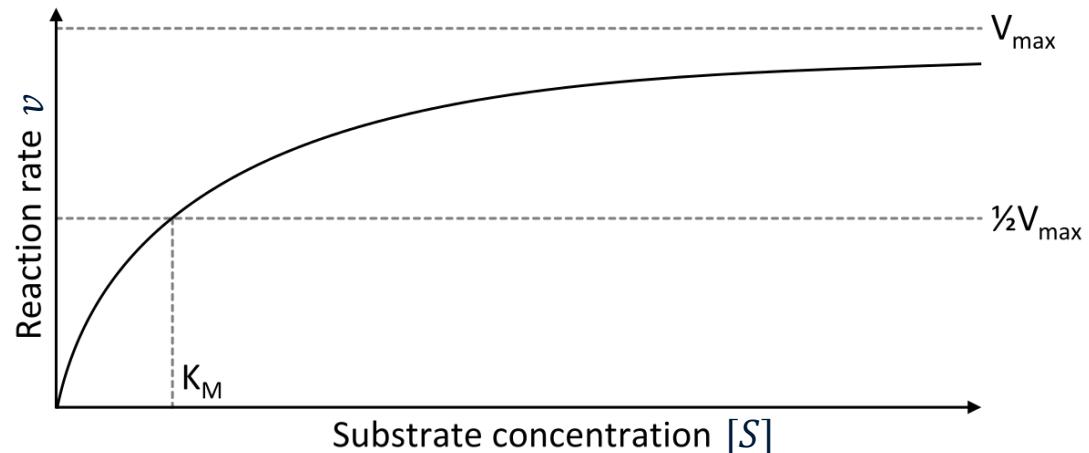
How to study metabolic networks?

What else do we know about the network?

- Metabolic reactions are catalyzed by **enzymes**
- **Reaction rates** (“fluxes”) describe how much product is formed per time
- Enzyme reaction rates are governed by **rate laws**

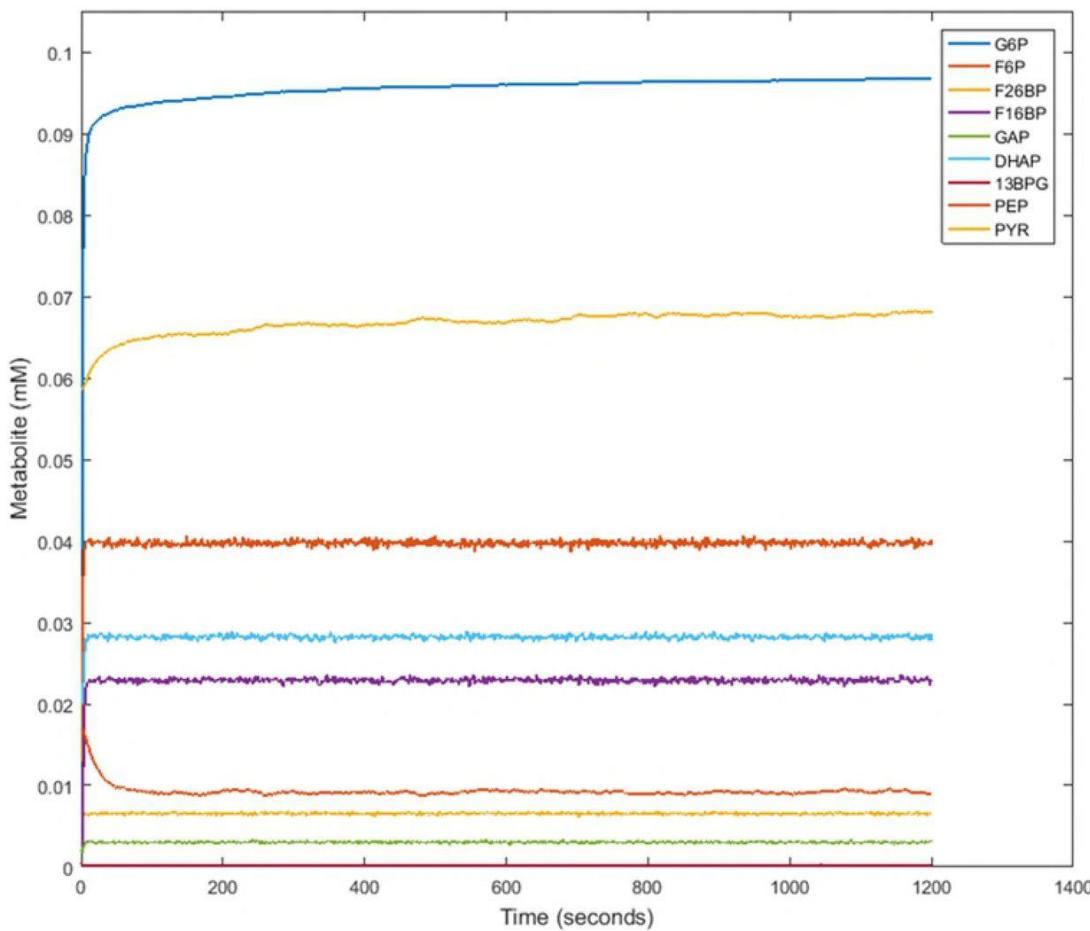
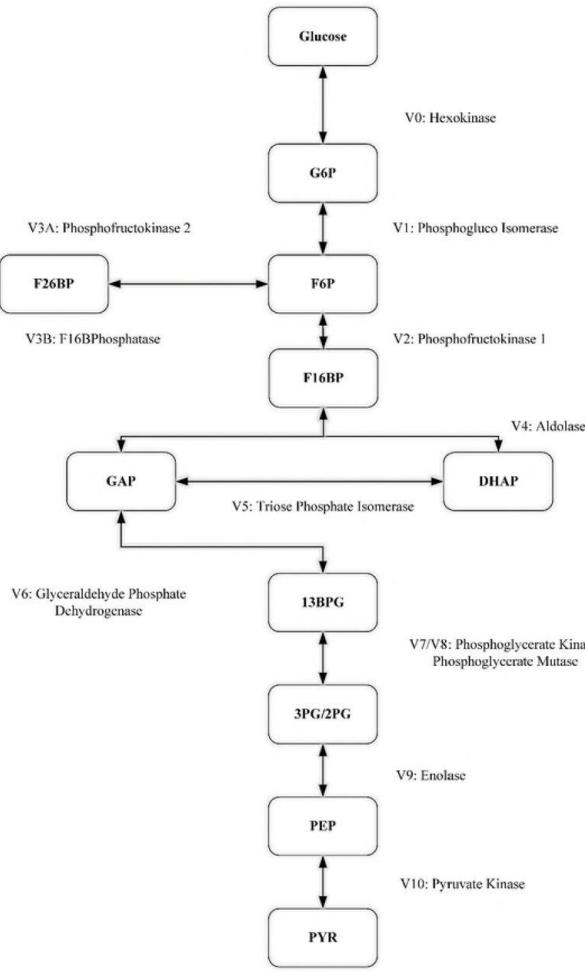
E.g. Michaelis-Menten kinetics:

$$v = \frac{V_{max} [S]}{K_M + [S]}$$



Dynamic modeling

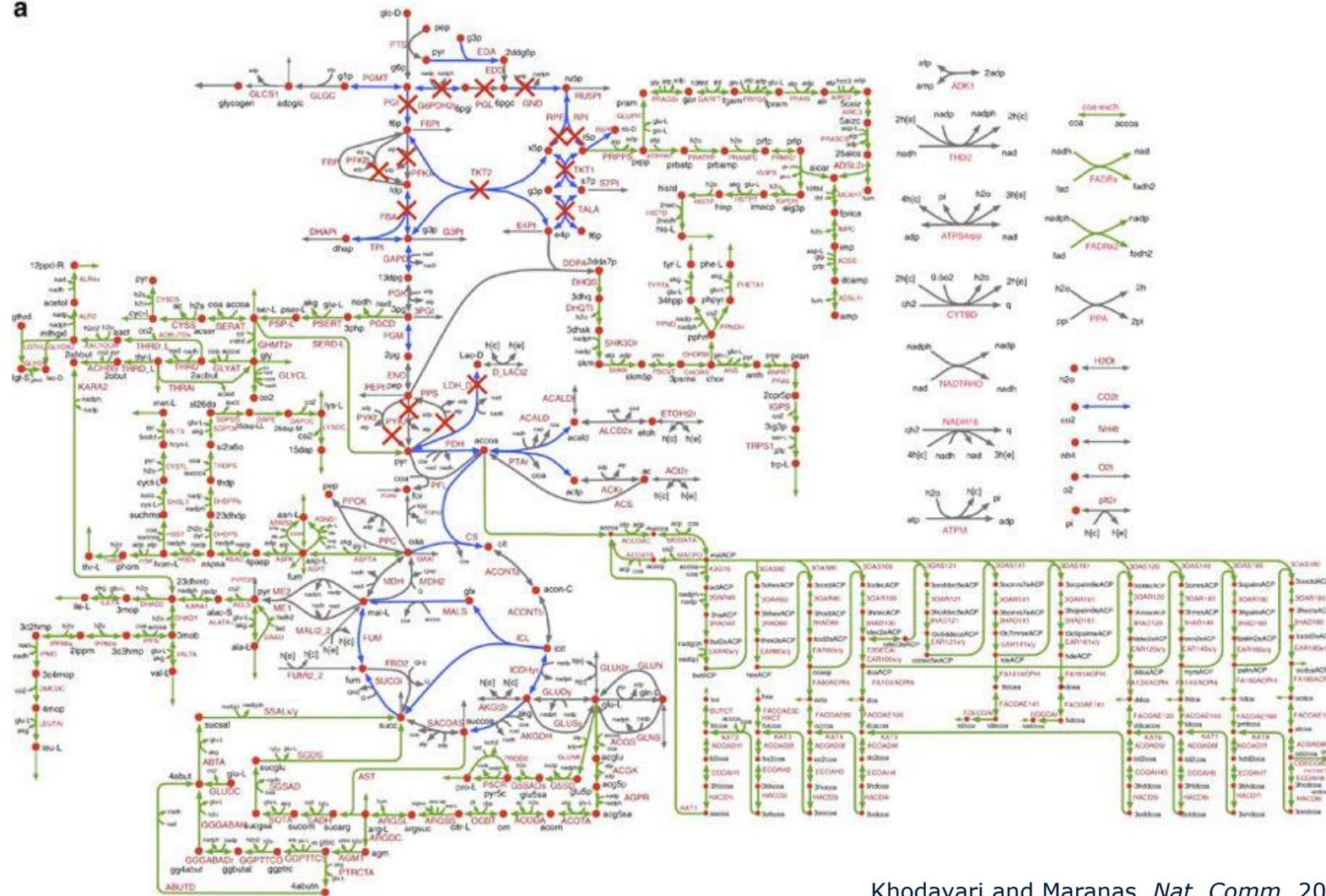
Rate laws of single steps allow time course simulations of pathways



Clement et al. *bioRxiv* 2018. doi: 10.1101/336677

Can you simulate a genome-scale network?

a



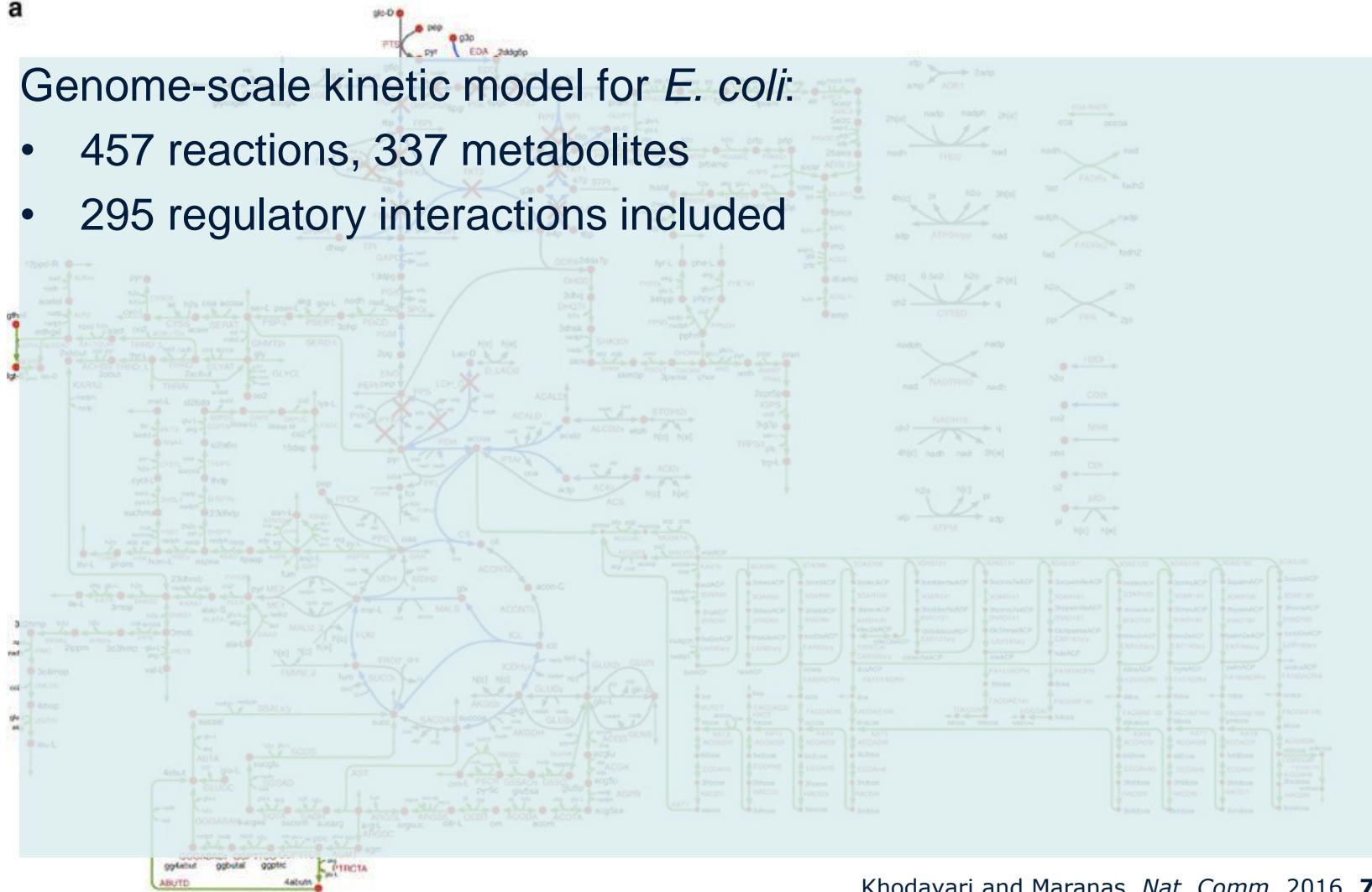
Khodayari and Maranas. *Nat. Comm.* 2016, 7, 13806.

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Genome-scale kinetic model for *E. coli*:

- 457 reactions, 337 metabolites
- 295 regulatory interactions included



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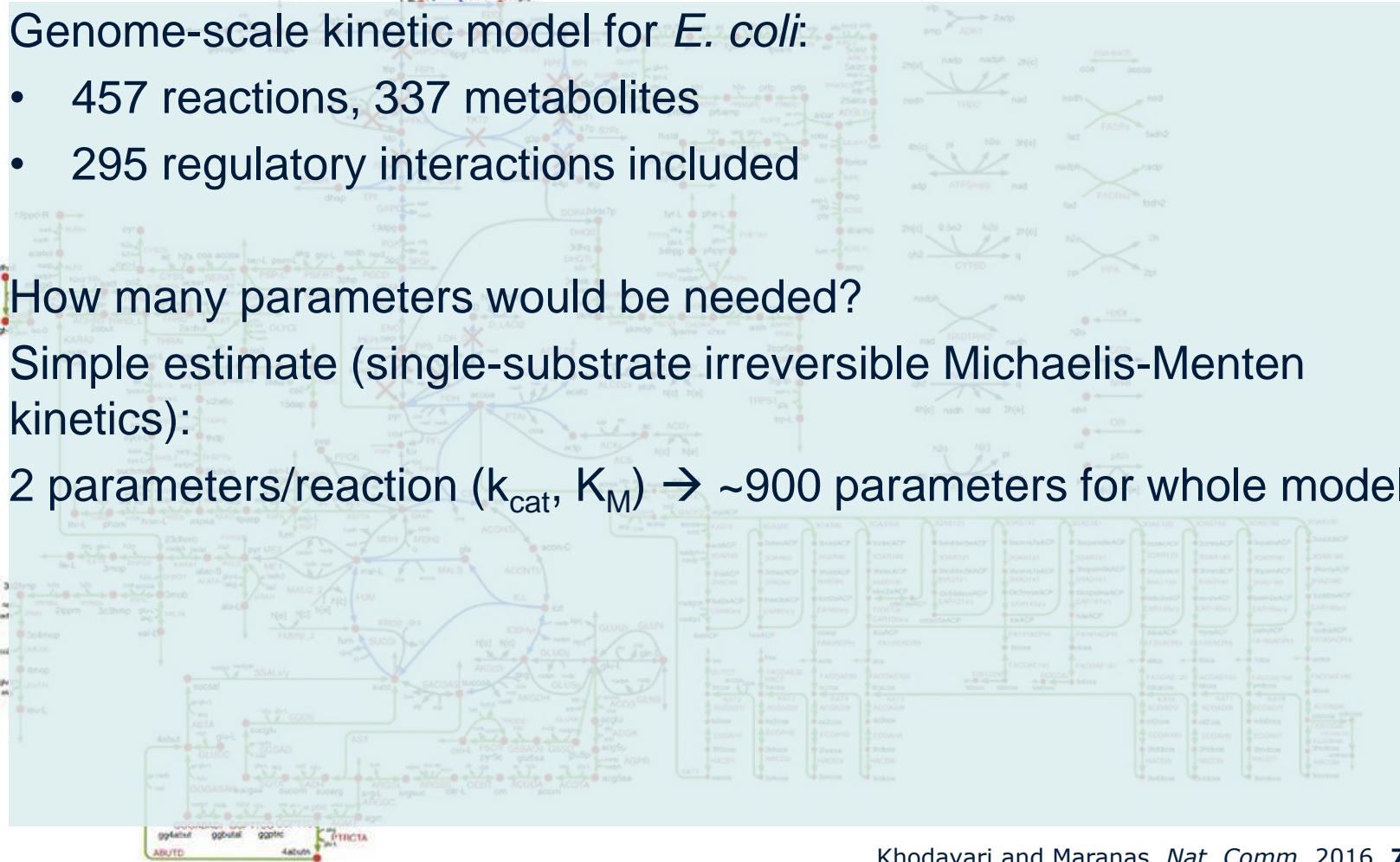
Genome-scale kinetic model for *E. coli*:

- 457 reactions, 337 metabolites
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How many parameters would be needed?

Simple estimate (single-substrate irreversible Michaelis-Menten kinetics):

2 parameters/reaction (k_{cat} , K_M) \rightarrow ~900 parameters for whole model



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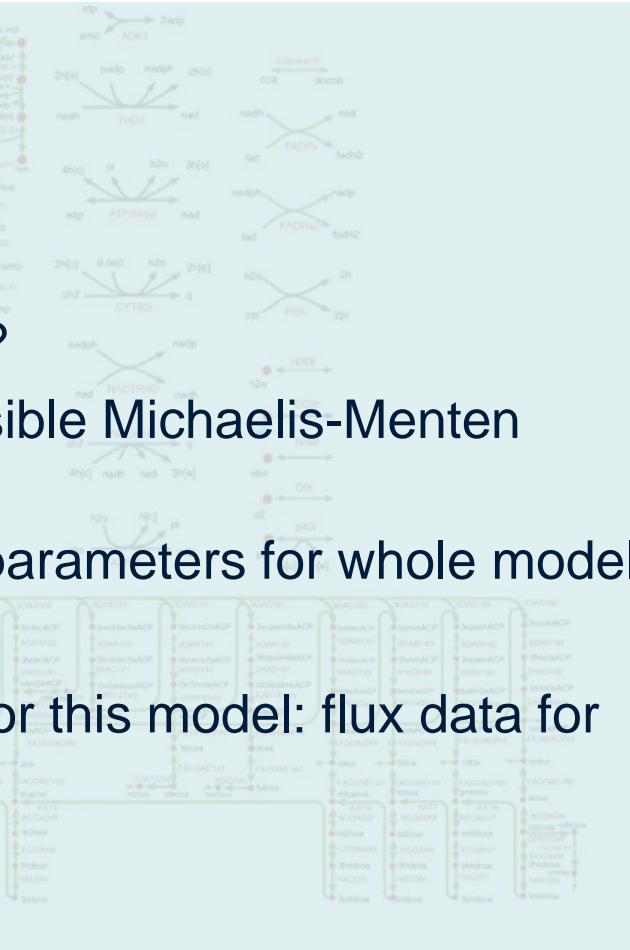
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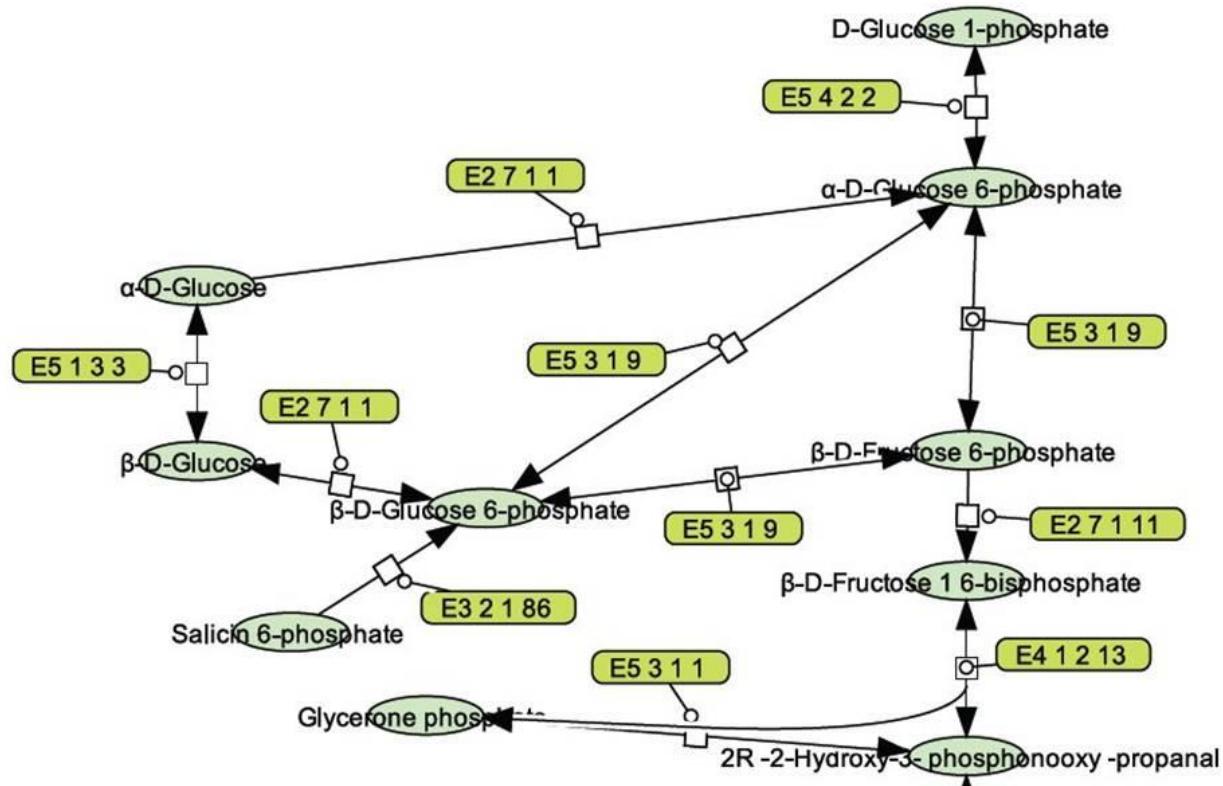
\rightarrow Requires extensive amounts of data (for this model: flux data for numerous gene deletions)

\rightarrow Infeasible for most metabolic networks

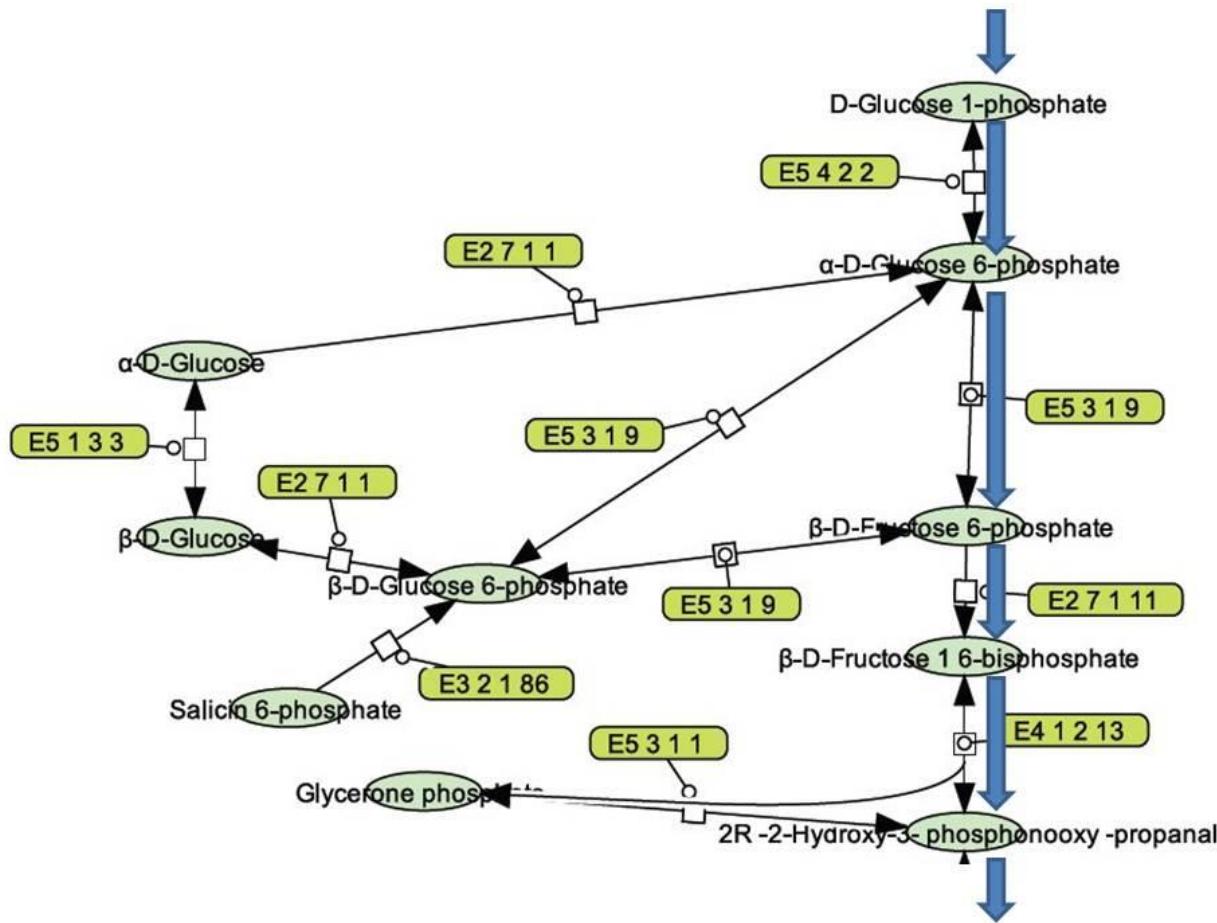


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So how to model metabolic fluxes without kinetic information?



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Only stoichiometry is required to predict possible *steady states*

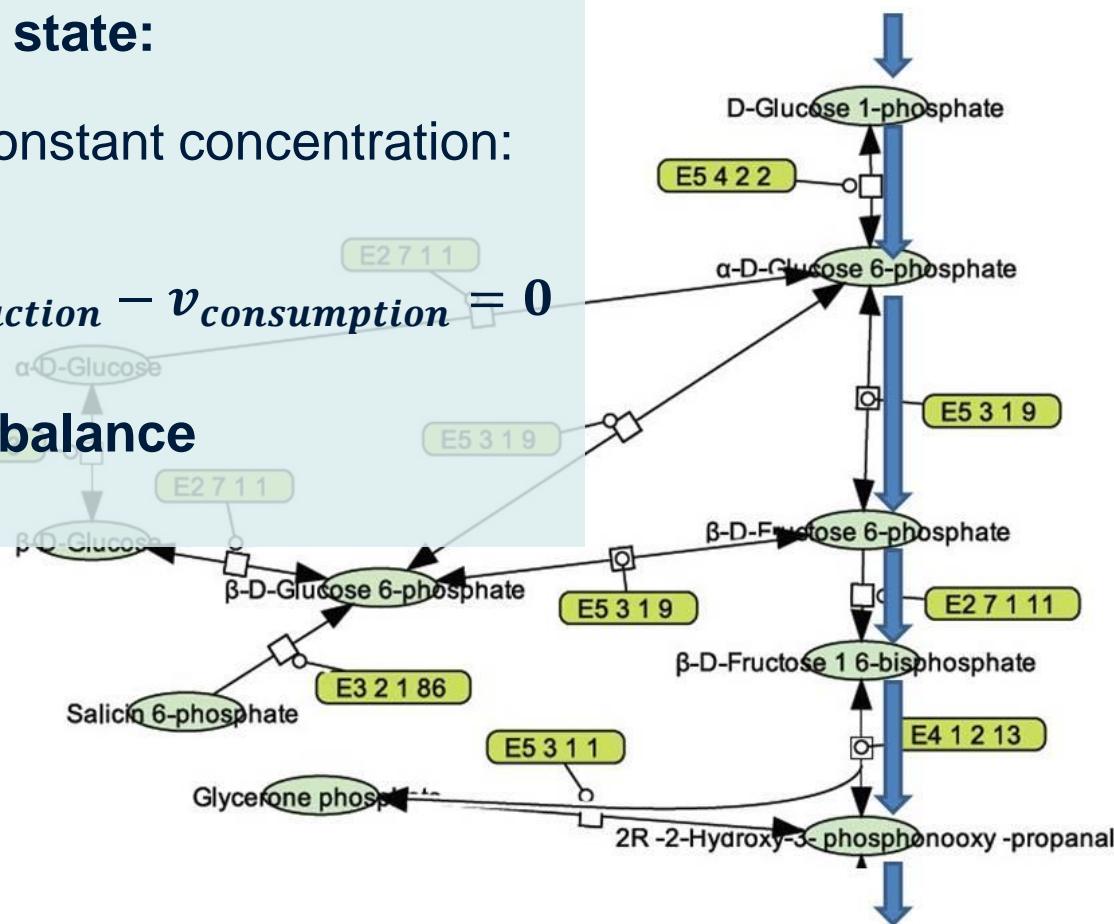
So how to model metabolic fluxes without kinetic information?

Steady state:

Each metabolite has constant concentration:

$$\frac{d[\text{metabolite}]}{dt} = v_{\text{production}} - v_{\text{consumption}} = 0$$

→ Mass balance



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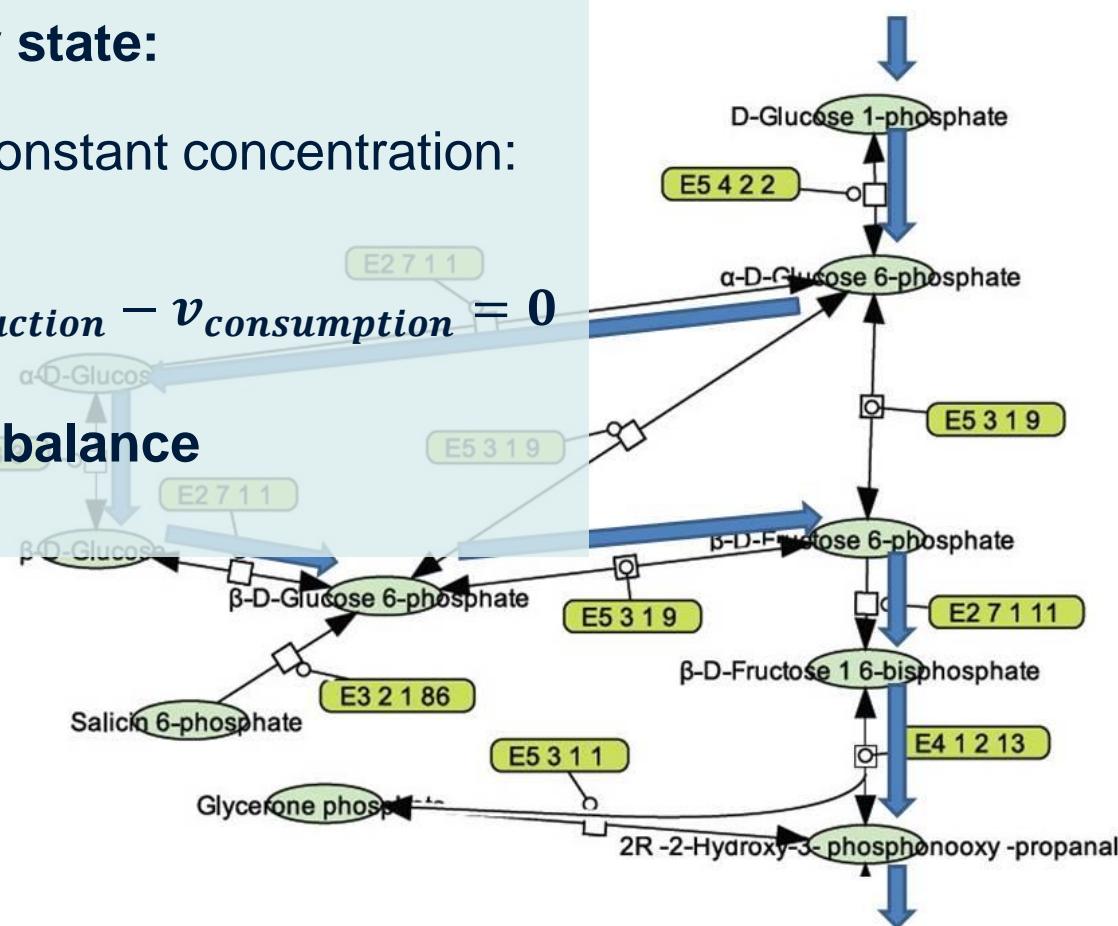
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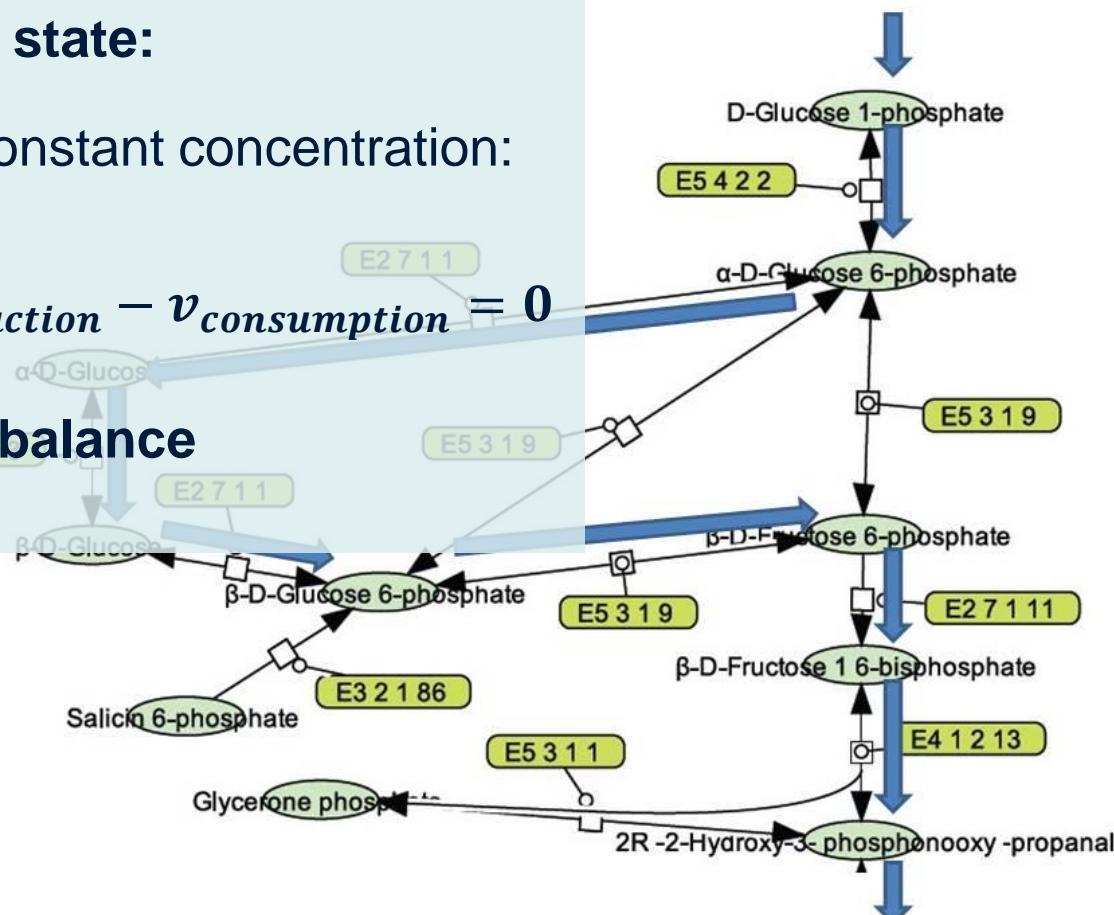
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Possible steady state

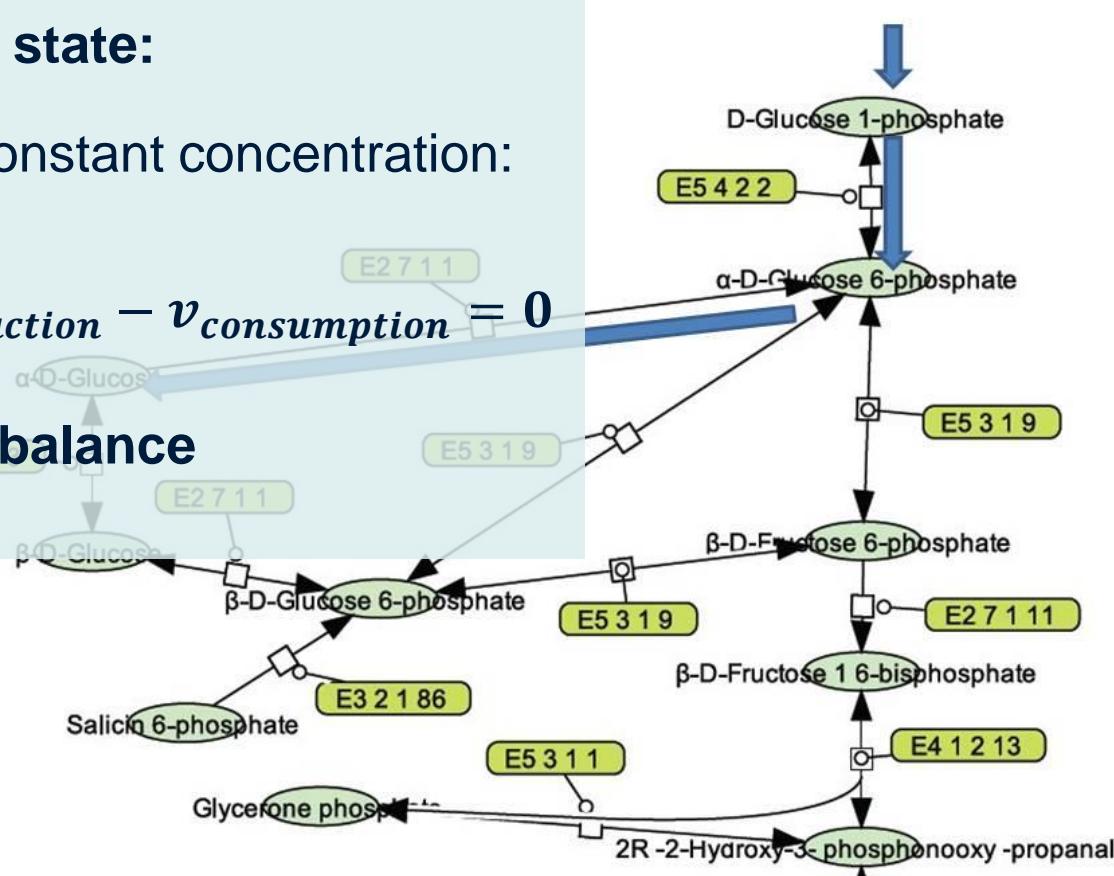
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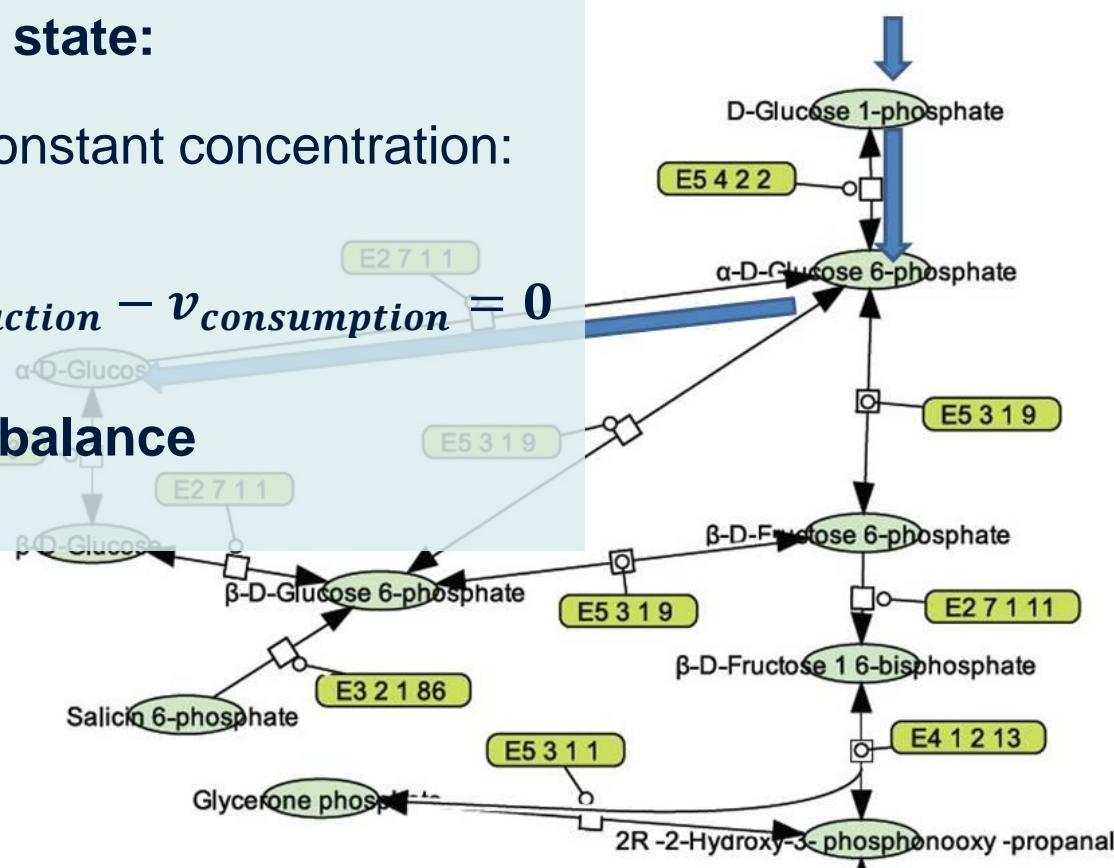
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Not a possible steady state

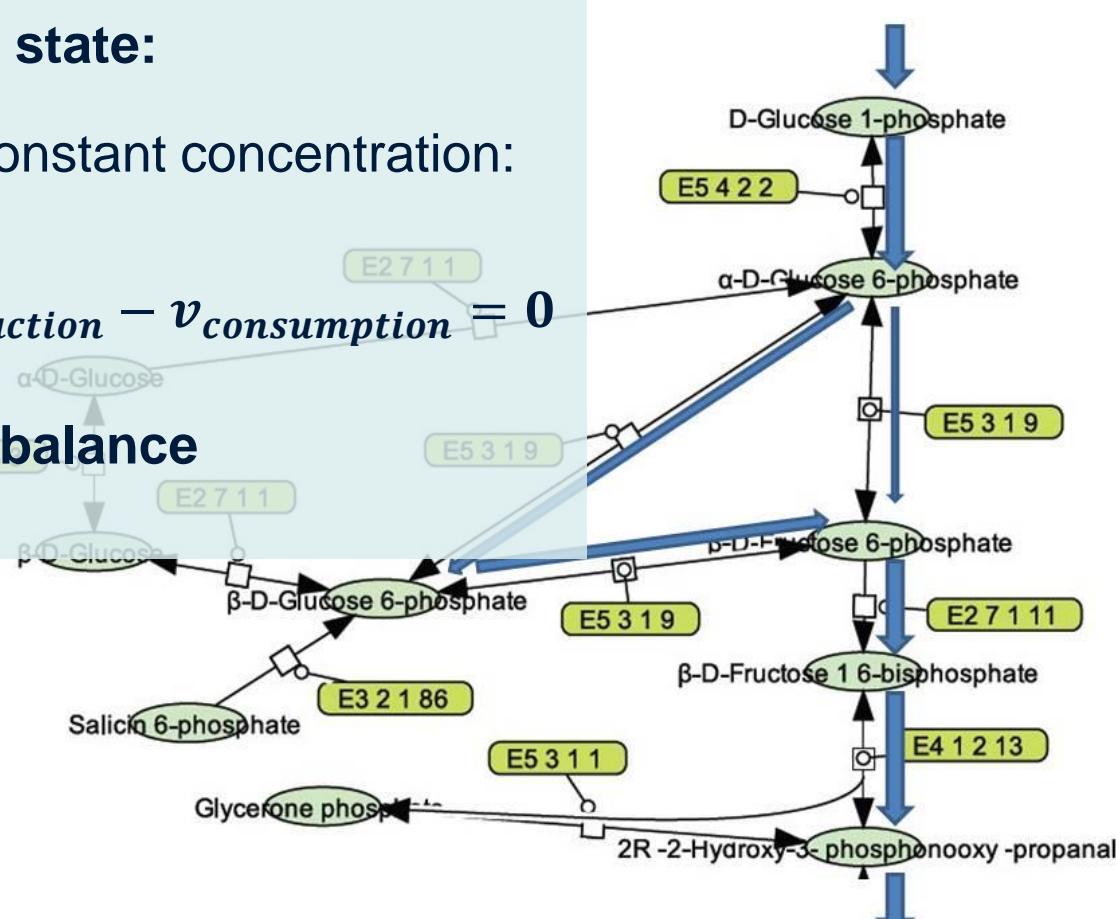
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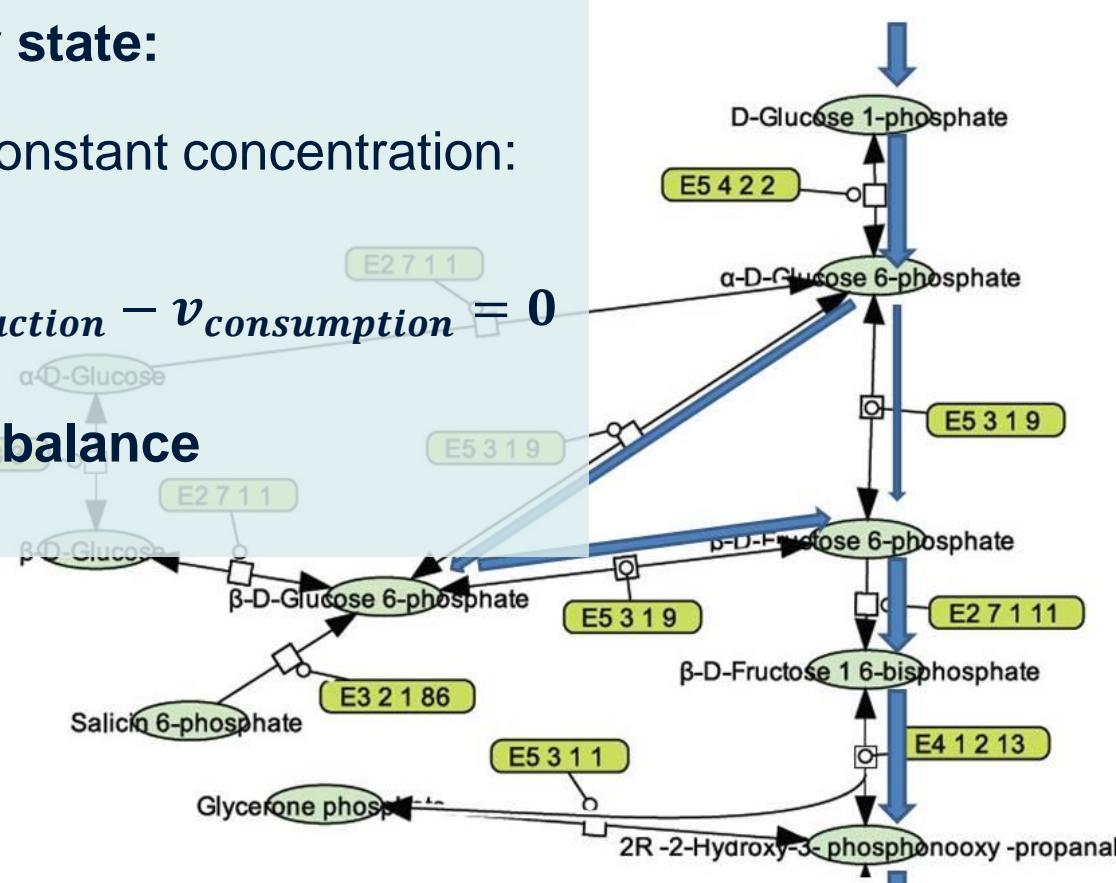
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Steady state:

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→ Mass balance



Modeling of network steady states based on mass balance constraints: **Constraint-based modeling**

So what can you learn from the possible steady states?

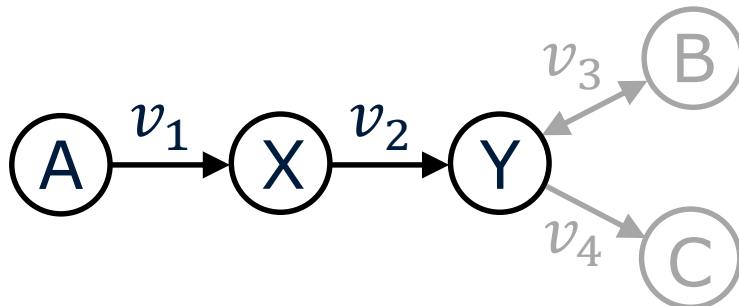
Can study possible phenotypes, e.g.:

How much ATP could a cell produce under different conditions?

[ONLINE DEMO]

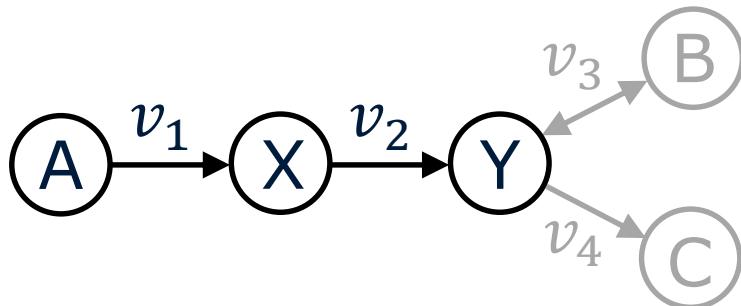
escher.github.io/escher-demo/knockout

Toy system – Mass balance



v_1, \dots, v_4 : Reaction rates/"fluxes"
(Conversion rates of reactants
with unit stoichiometry)

Toy system – Mass balance



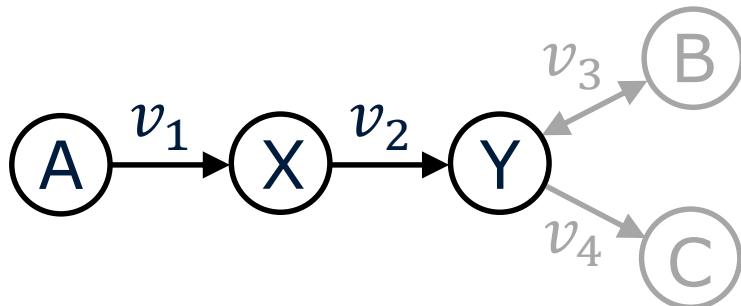
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Mass balance for X:

$$\frac{d[X]}{dt} = v_1 - v_2 = 0$$

$$\rightarrow v_1 = v_2$$

Toy system – Mass balance



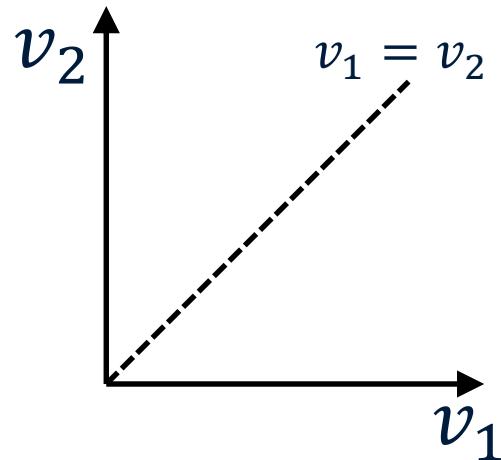
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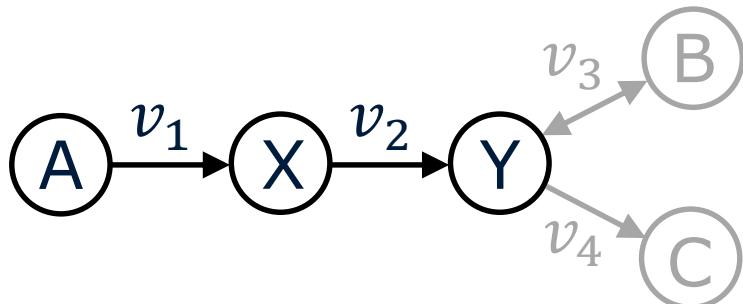
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Possible solutions:



Toy system – Mass balance

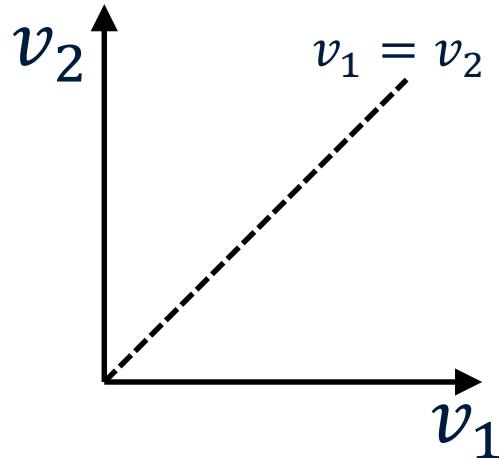


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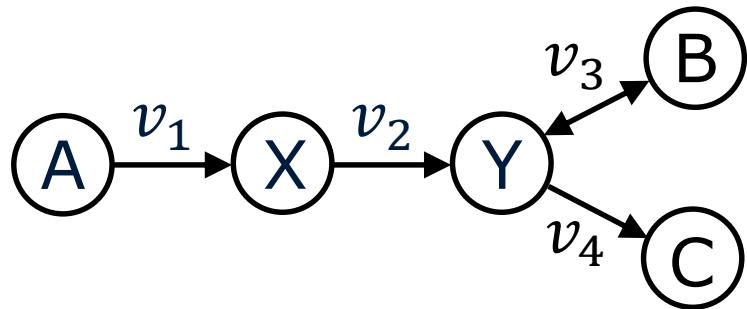
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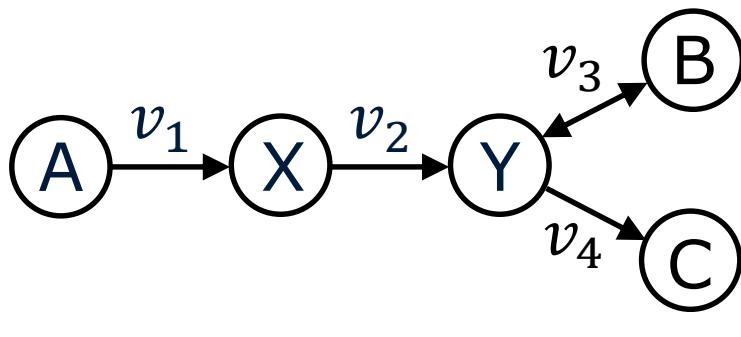
Solution vector:
Steady-state "flux vector"

$$\vec{v} = \begin{pmatrix} v_1 \\ v_2 \end{pmatrix} = \begin{pmatrix} v_1 \\ v_1 \end{pmatrix} = v_1 \cdot \begin{pmatrix} 1 \\ 1 \end{pmatrix} = c \cdot \begin{pmatrix} 1 \\ 1 \end{pmatrix}$$

Toy system – Mass balance



Toy system – Mass balance

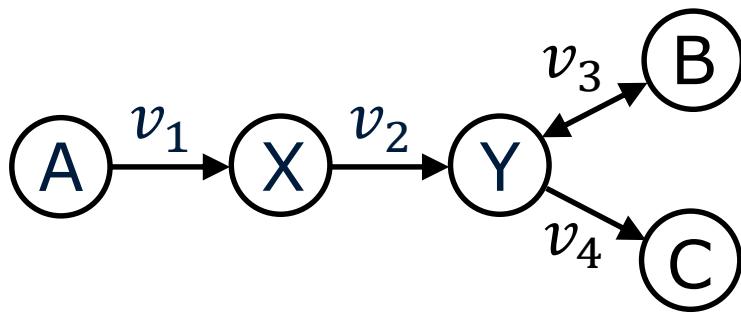


Mass balances for X,Y:

$$\frac{d[X]}{dt} = v_1 - v_2 = 0$$

$$\frac{d[Y]}{dt} = v_2 - v_3 - v_4 = 0$$

Toy system – Mass balance



Mass balances for X,Y:

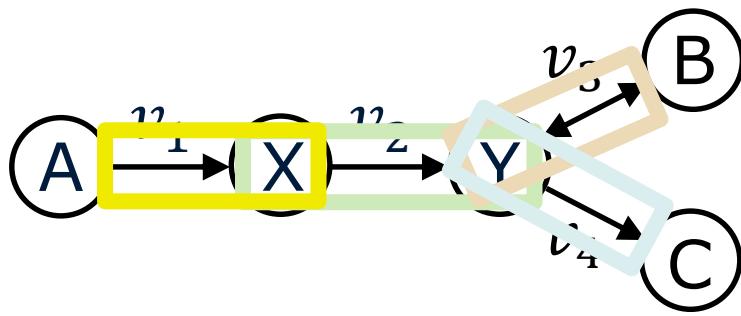
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Matrix notation:

$$\begin{pmatrix} \frac{d[X]}{dt} \\ \frac{d[Y]}{dt} \end{pmatrix} = \begin{pmatrix} 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & -1 \end{pmatrix} \cdot \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}$$

Toy system – Mass balance



Mass balances for X,Y:

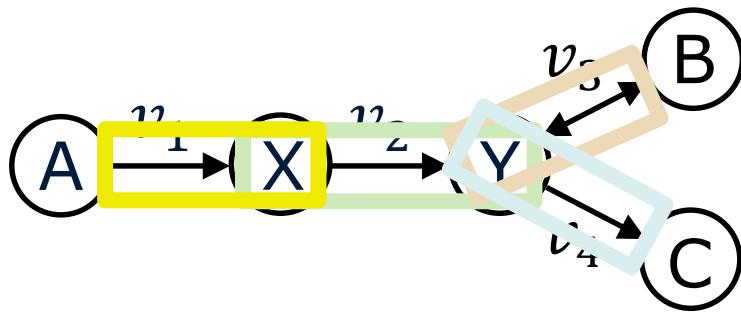
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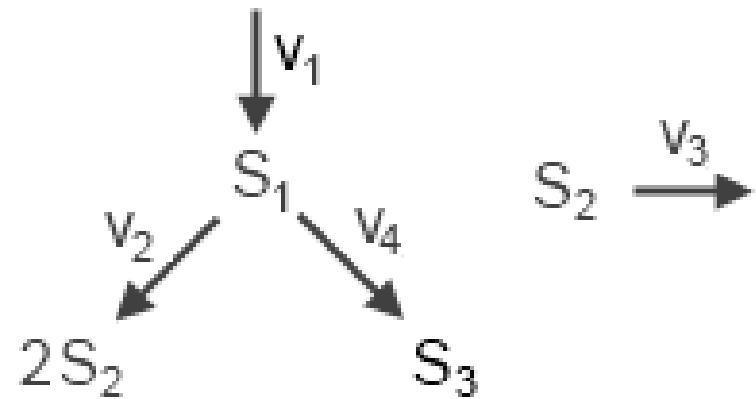
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Stoichiometric matrix S:

- Dimensions: $m * r$ (for m metabolites and r reactions)
 - Each column contains stoichiometry of one reaction
- Stoichiometric matrix contains structure of network

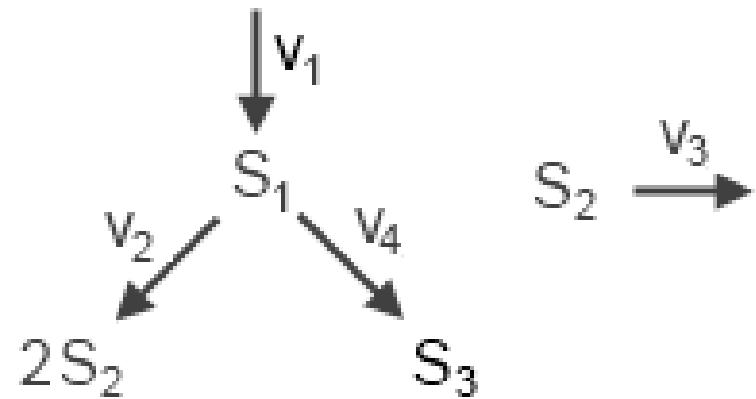
Constructing the stoichiometric matrix



	v₁	v₂	v₃	v₄
S₁				
S₂				
S₃				

Example from: http://www.bio-physics.at/wiki/index.php?title=Stoichiometric_Matrix

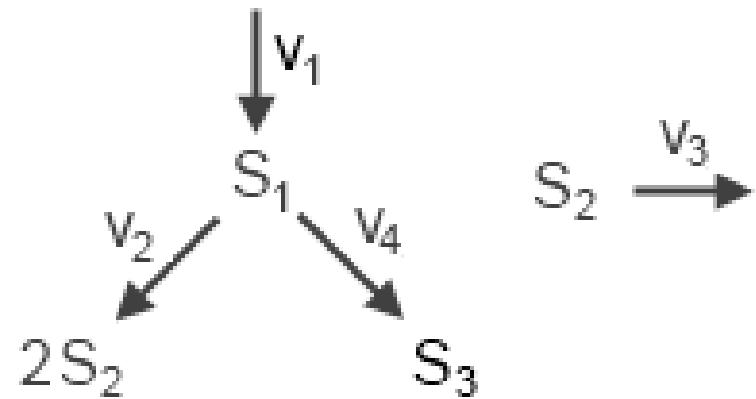
Constructing the stoichiometric matrix



	v₁	v₂	v₃	v₄
S₁	+1			
S₂	0	-1		
S₃	0	1		

Example from: http://www.bio-physics.at/wiki/index.php?title=Stoichiometric_Matrix

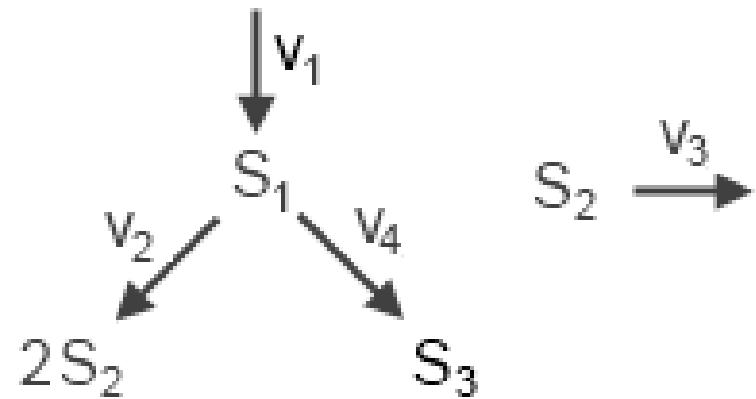
Constructing the stoichiometric matrix



	v₁	v₂	v₃	v₄
S₁	+1	-1		
S₂	0	+2		
S₃	0	0		

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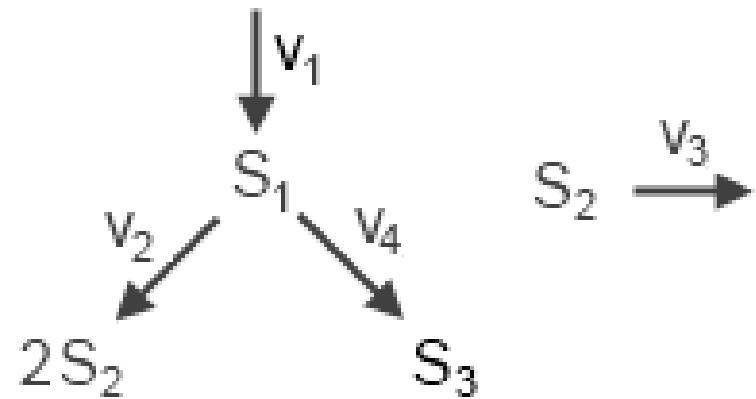
Constructing the stoichiometric matrix



	v₁	v₂	v₃	v₄
S₁	+1	-1	0	
S₂	0	+2	-1	
S₃	0	0	0	

Example from: http://www.bio-physics.at/wiki/index.php?title=Stoichiometric_Matrix

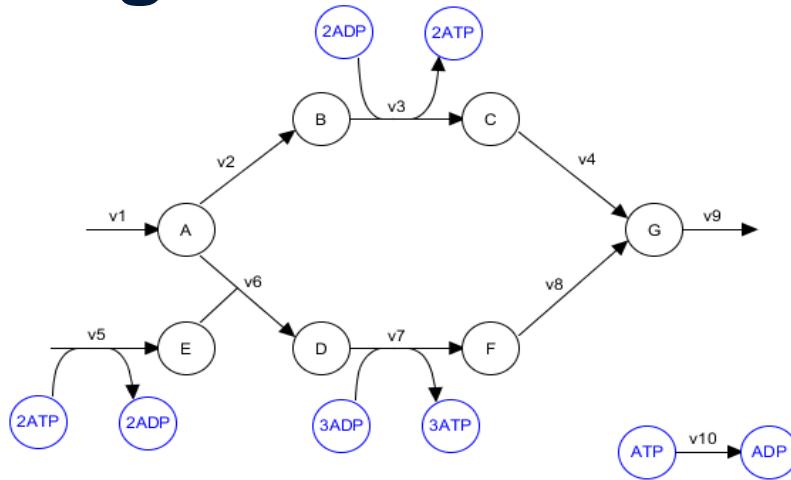
Constructing the stoichiometric matrix



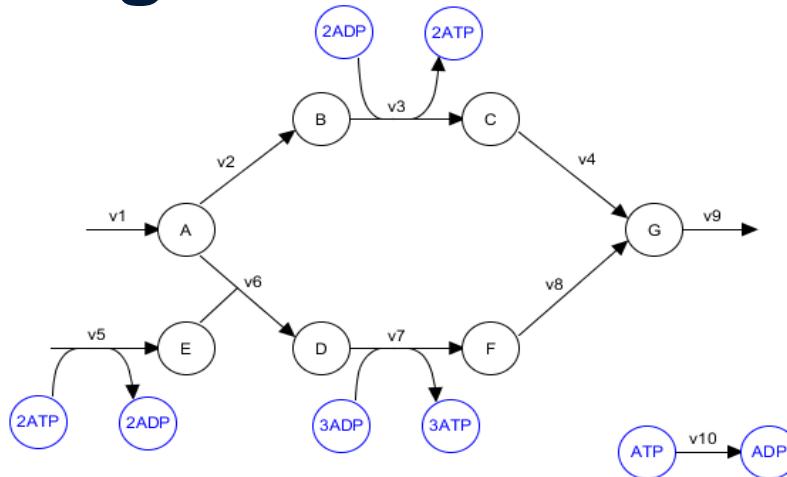
	v₁	v₂	v₃	v₄
S₁	+1	-1	0	-1
S₂	0	+2	-1	0
S₃	0	0	0	1

Example from: http://www.bio-physics.at/wiki/index.php?title=Stoichiometric_Matrix

Constructing the stoichiometric matrix

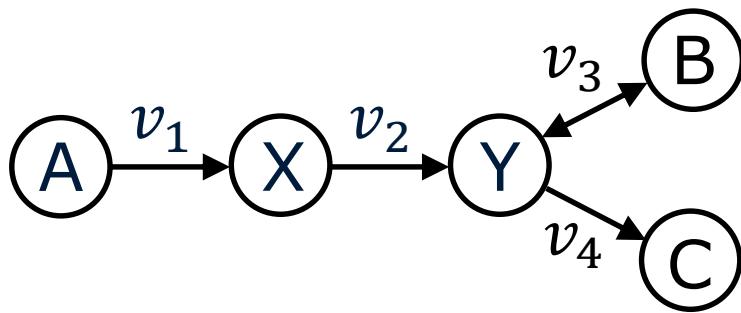


Constructing the stoichiometric matrix



Metabolites\Reactions	v1	v2	v3	v4	v5	v6	v7	v8	v9	v10
A	1	-1	0	0	0	-1	0	0	0	0
B	0	1	-1	0	0	0	0	0	0	0
C	0	0	1	-1	0	0	0	0	0	0
D	0	0	0	0	0	1	-1	0	0	0
E	0	0	0	0	1	-1	0	0	0	0
F	0	0	0	0	0	0	1	-1	0	0
G	0	0	0	1	0	0	0	1	-1	0
ADP	0	0	-2	0	2	0	-3	0	0	1
ATP	0	0	2	0	-2	0	3	0	0	-1

Toy system – Mass balance



Mass balances for X,Y:

$$\frac{d[X]}{dt} = v_1 - v_2 = 0$$

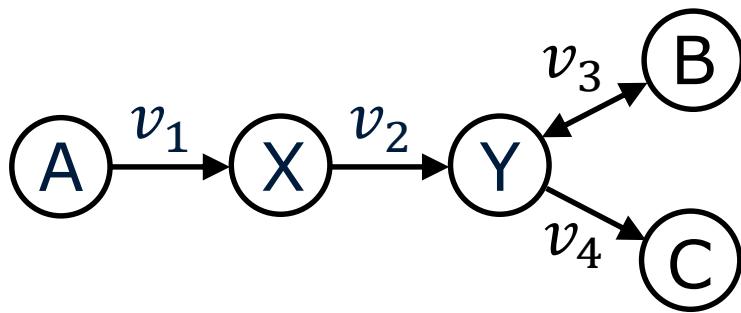
$$\frac{d[Y]}{dt} = v_2 - v_3 - v_4 = 0$$

Matrix notation:

$$\begin{pmatrix} \frac{d[X]}{dt} \\ \frac{d[Y]}{dt} \end{pmatrix} = \begin{pmatrix} 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & -1 \end{pmatrix} \cdot \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}$$

Vector of concentration changes (mx1) Stoichiometric matrix (mxn) Reaction flux vector (nx1)

Toy system – Mass balance



Mass balances for X,Y:

$$\frac{d[X]}{dt} = v_1 - v_2 = 0$$

$$\frac{d[Y]}{dt} = v_2 - v_3 - v_4 = 0$$

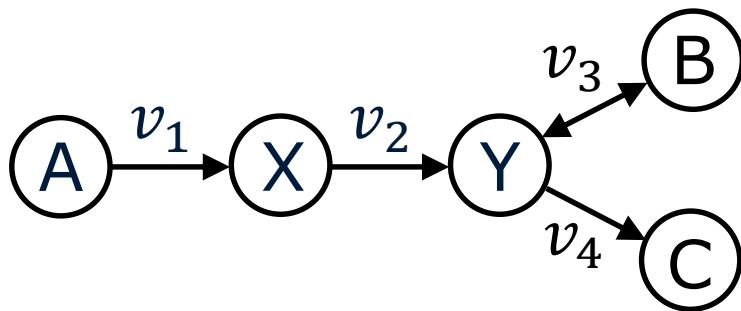
Matrix notation:

$$\begin{pmatrix} \frac{d[X]}{dt} \\ \frac{d[Y]}{dt} \end{pmatrix} = \begin{pmatrix} 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & -1 \end{pmatrix} \cdot \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}$$

Vector of concentration changes (mx1) Stoichiometric matrix (mxn) Reaction flux vector (nx1)

In general: $\dot{\vec{c}} = S \cdot \vec{v} = \vec{0}$

Toy system – Mass balance



Mass balances for X,Y:

$$\frac{d[X]}{dt} = v_1 - v_2 = 0$$

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Matrix notation:

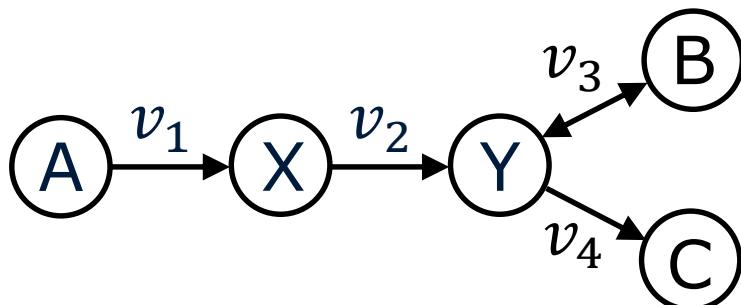
$$\begin{pmatrix} \frac{d[X]}{dt} \\ \frac{d[Y]}{dt} \end{pmatrix} = \begin{pmatrix} 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & -1 \end{pmatrix} \cdot \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}$$

Vector of concentration changes (mx1) Stoichiometric matrix (mxn) Reaction flux vector (nx1)

In general: $\dot{\vec{c}} = S \cdot \vec{v} = \vec{0}$

→ Steady-state flux vectors form the **null space** of the stoichiometric matrix.

Toy system – Mass balance



Mass balances for X,Y:

$$\frac{d[X]}{dt} = v_1 - v_2 = 0$$

$$\frac{d[Y]}{dt} = v_2 - v_3 - v_4 = 0$$

Solution vector:

$$\vec{v} = c_1 \cdot \begin{pmatrix} 1 \\ 1 \\ 0 \\ 1 \end{pmatrix} + c_2 \cdot \begin{pmatrix} 0 \\ 0 \\ 1 \\ -1 \end{pmatrix}$$

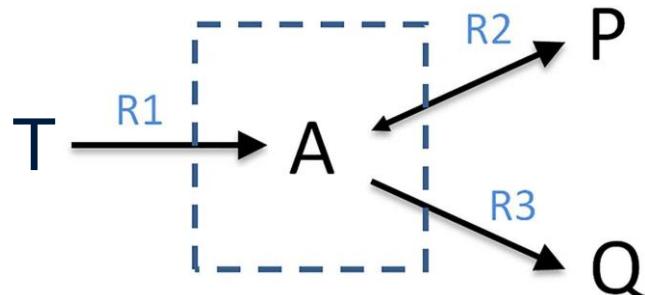
$$\begin{pmatrix} \frac{d[X]}{dt} \\ \frac{d[Y]}{dt} \end{pmatrix} = \begin{pmatrix} 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & -1 \end{pmatrix} \cdot \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}$$

Vector of concentration changes (mx1) Stoichiometric matrix (mxn) Reaction flux vector (nx1)

$$\text{In general: } \dot{\vec{c}} = S \cdot \vec{v} = \vec{0}$$

→ Steady-state flux vectors form the **null space** of the stoichiometric matrix.

Constrained solution space



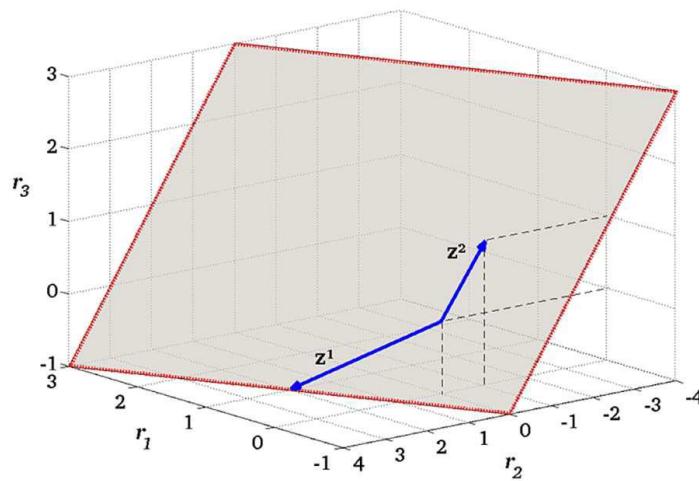
$$S \cdot \vec{v} = 0$$

Stoichiometric matrix

$$S = \begin{pmatrix} 1 & -1 & -1 \\ R1 & R2 & R3 \end{pmatrix}$$

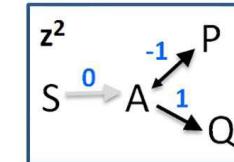
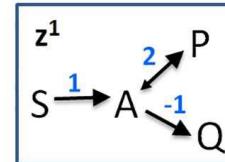
Possible solutions: $\vec{v} = c_1 \cdot \begin{pmatrix} 1 \\ 2 \\ -1 \end{pmatrix} + c_2 \cdot \begin{pmatrix} 0 \\ -1 \\ 1 \end{pmatrix}$

Resulting solution space:



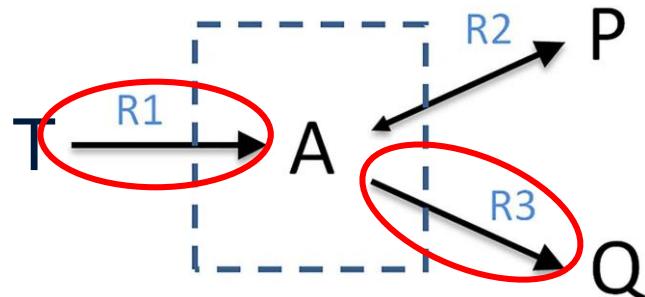
Basis vectors

	z^1	z^2
r_1	1	0
r_2	2	-1
r_3	-1	1



Klamt et al. *PLOS Comp. Biol.* 2017, **13**, e1005409.

Constrained solution space

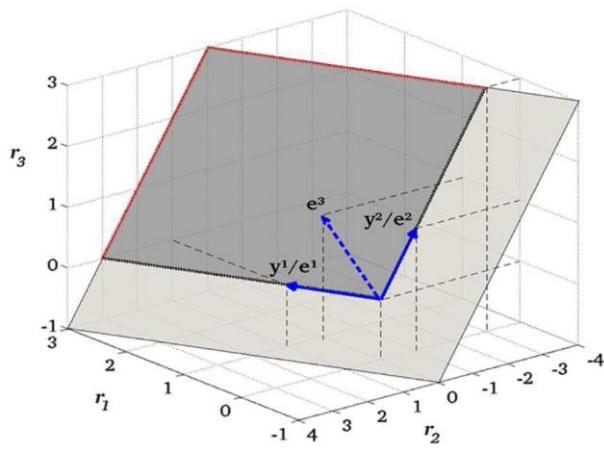


Some reactions are irreversible!

$$r_i \geq 0$$

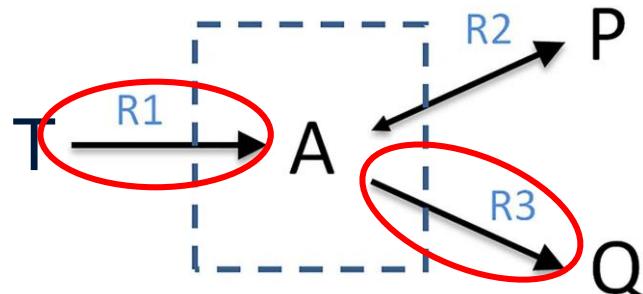
$$S \cdot \vec{v} = 0$$

Resulting **solution space**:



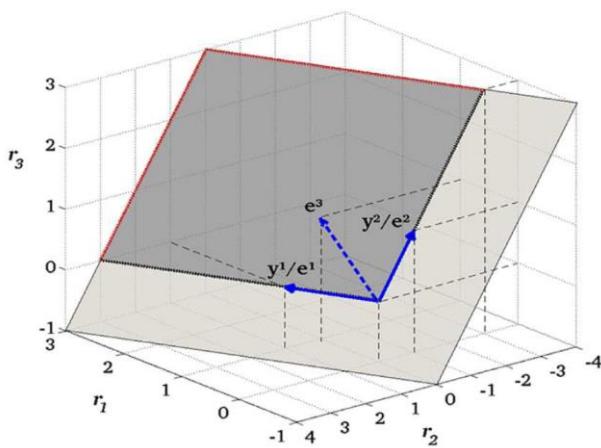
Klamt et al. *PLOS Comp. Biol.* 2017, **13**, e1005409.

Constrained solution space



$$S \cdot \vec{v} = 0$$

Resulting **solution space**:



Some reactions are irreversible!

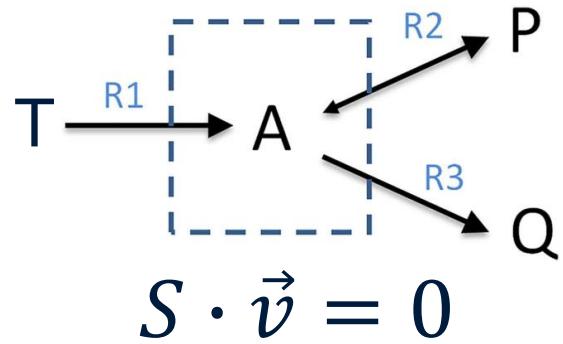
$$r_i \geq 0$$

Examples:

- Oxidation reactions
- ATP consumption

Klamt et al. *PLOS Comp. Biol.* 2017, **13**, e1005409.

Constrained solution space

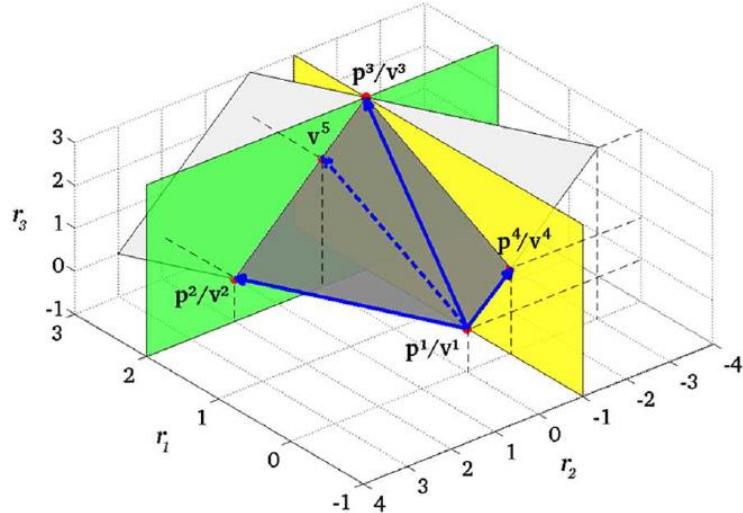


Some reactions might have upper/lower bounds:

$$r_i^{lb} \leq r_i \leq r_i^{ub}$$

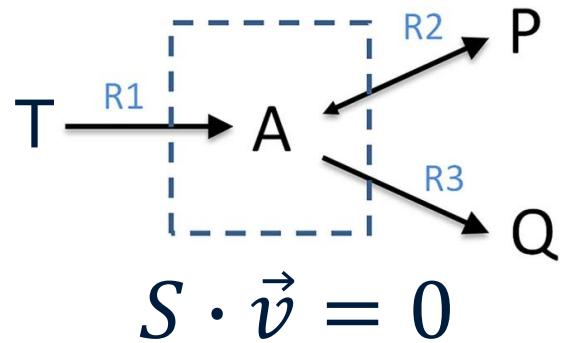
e.g.:

$$r_1 \leq 2, r_2 \geq -1$$

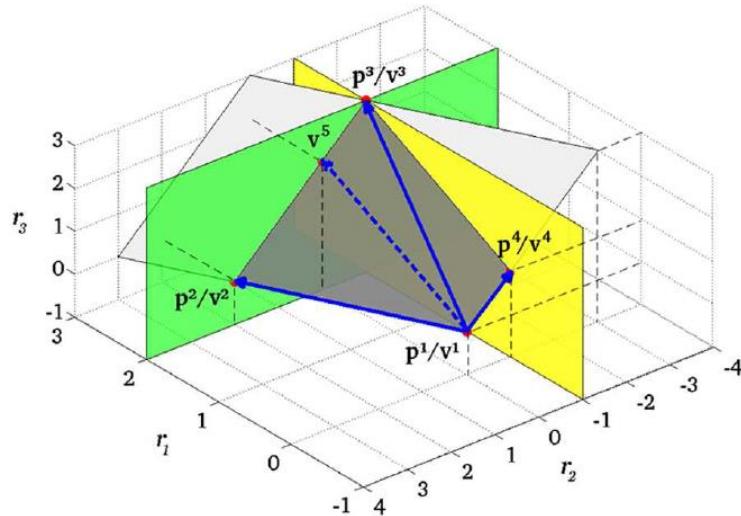


Klamt et al. *PLOS Comp. Biol.* 2017, **13**, e1005409.

Constrained solution space



Resulting **solution space**:



Some reactions might have upper/lower bounds:

$$r_i^{lb} \leq r_i \leq r_i^{ub}$$

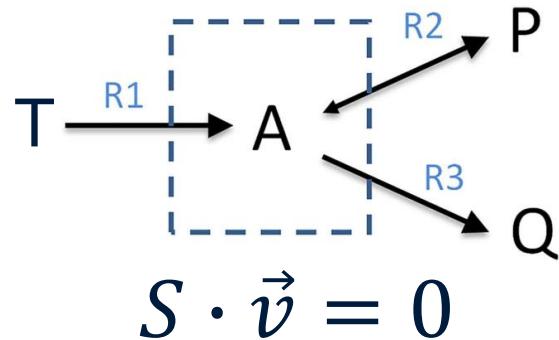
e.g.:

$$r_1 \leq 2, r_2 \geq -1$$

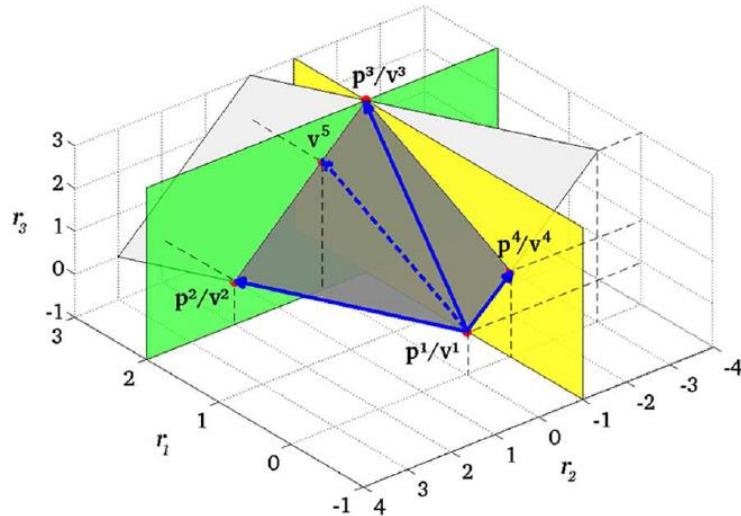
Examples:

- Sugar uptake
- Oxygen uptake

Analyzing the constrained solution space



Solution space:



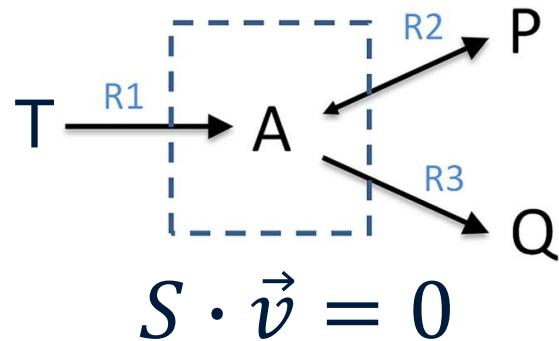
So which of these possible steady states does the cell pick...?

Some cells (e.g. bacteria) might have a simple **objective**:
 E.g. maximal ATP production

→ Solution space tells us maximal possible value!

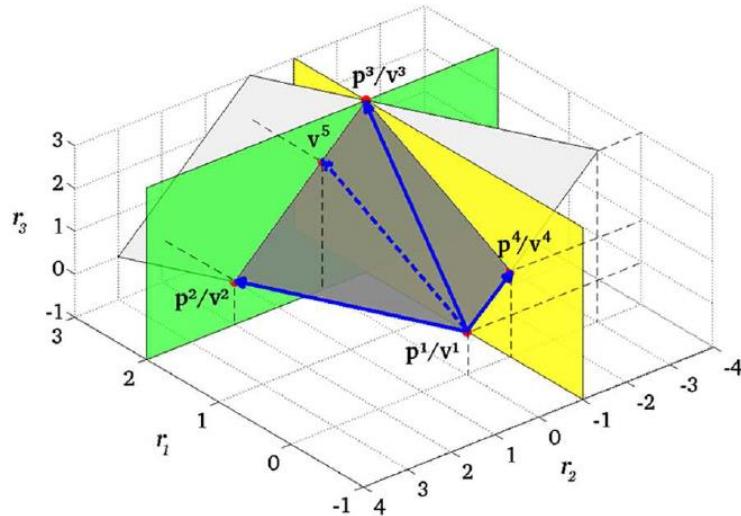
Figures: Klamt et al. *PLOS Comp. Biol.* 2017, **13**, e1005409.

Analyzing the constrained solution space



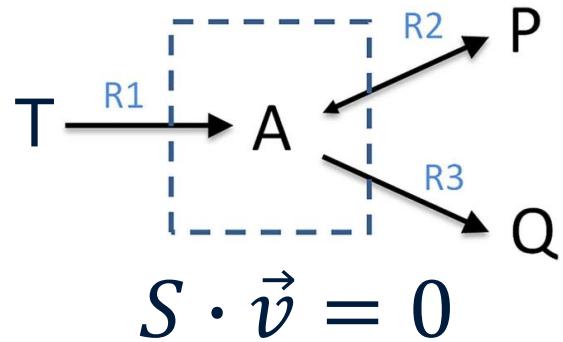
E.g., which steady state would maximize flux through $R3$?

Solution space:



Figures: Klamt et al. *PLOS Comp. Biol.* 2017, **13**, e1005409.

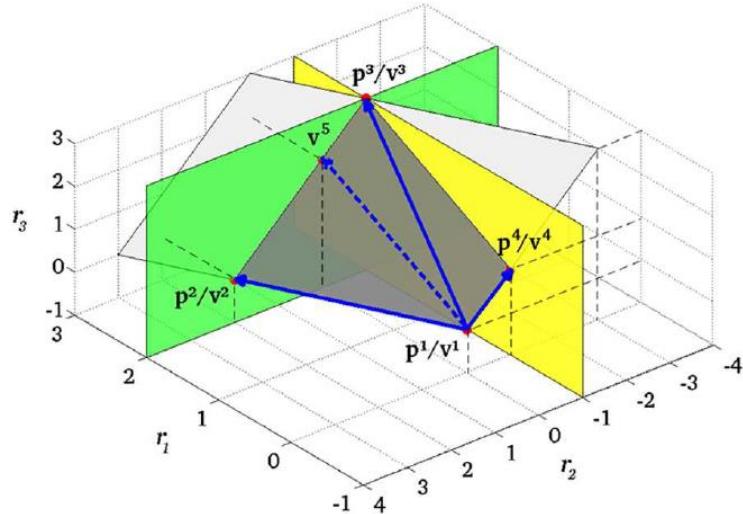
Analyzing the constrained solution space



E.g., which steady state would maximize flux through $R3$?

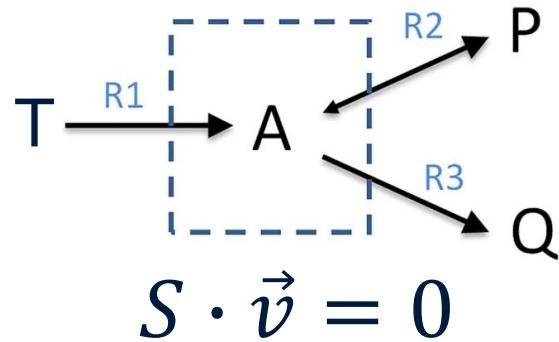
$$\vec{v}_{opt} = \begin{pmatrix} 2 \\ -1 \\ 3 \end{pmatrix}$$

Solution space:

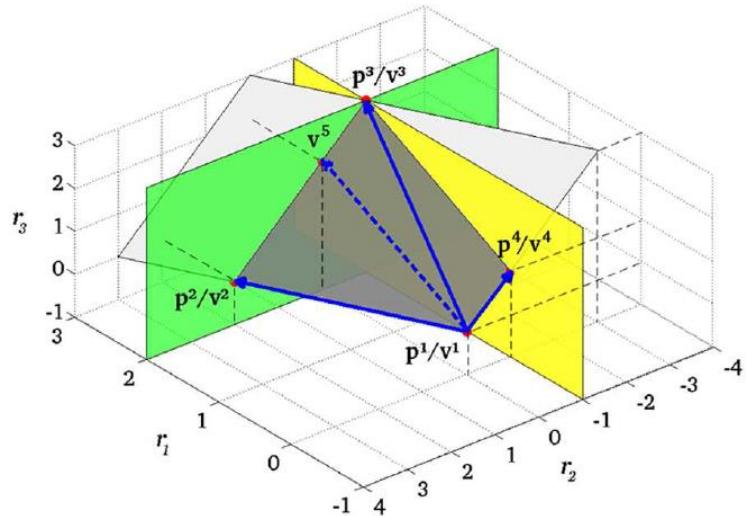


Figures: Klamt et al. *PLOS Comp. Biol.* 2017, **13**, e1005409.

Analyzing the constrained solution space



Solution space:



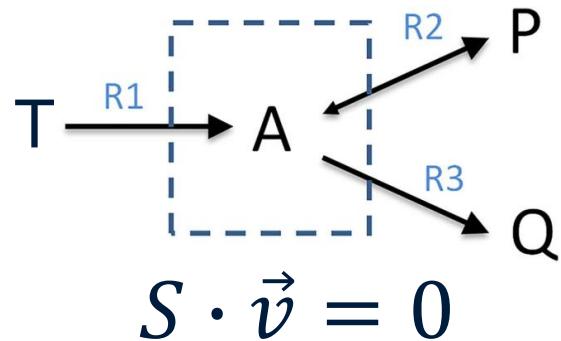
E.g., which steady state would maximize flux through R_3 ?

$$\vec{v}_{opt} = \begin{pmatrix} 2 \\ -1 \\ 3 \end{pmatrix}$$

Flux Balance Analysis:
Predicting a flux steady state by maximizing an **objective function** (here: r_3).

Figures: Klamt et al. *PLOS Comp. Biol.* 2017, **13**, e1005409.

Analyzing the constrained solution space

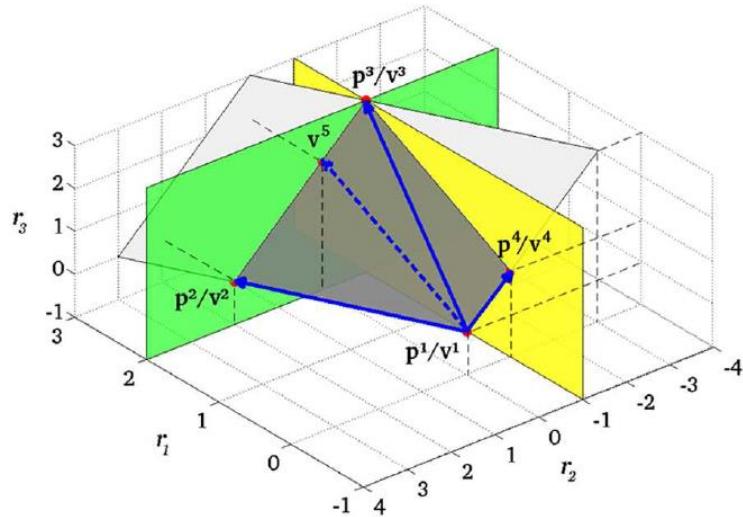


Can now also study different conditions:

Assume $r_2 = 0$

- Could be: Gene defect, drug

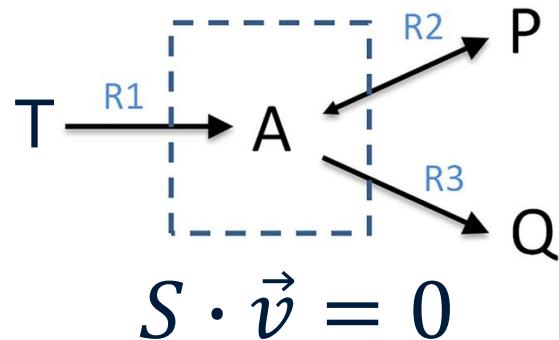
Solution space:



Which steady state would now maximize flux through R3?

Figures: Klamt et al. *PLOS Comp. Biol.* 2017, **13**, e1005409.

Analyzing the constrained solution space

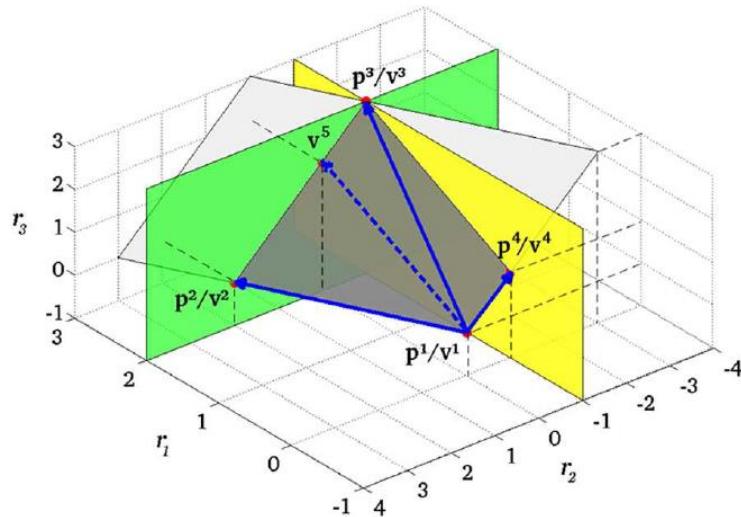


Can now also study different conditions:

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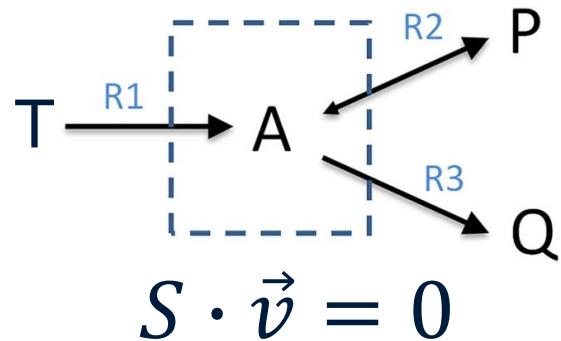


Which steady state would now maximize flux through R3?

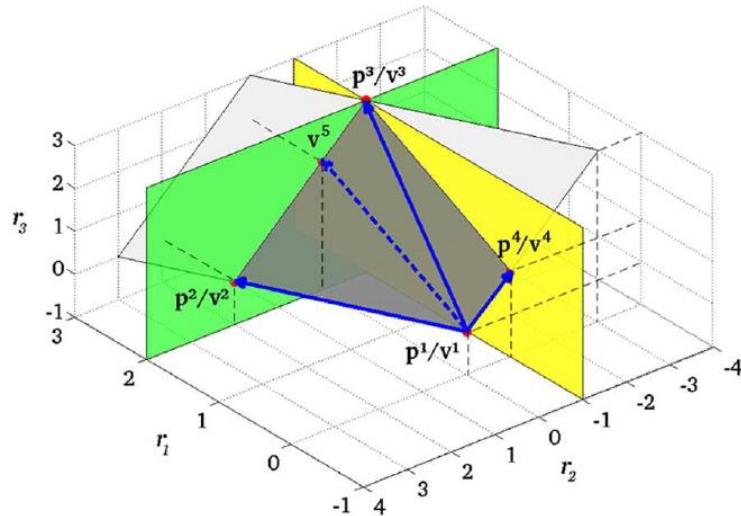
$$\vec{v}_{opt} = \begin{pmatrix} 2 \\ 0 \\ 2 \end{pmatrix}$$

Figures: Klamt et al. *PLOS Comp. Biol.* 2017, **13**, e1005409.

Analyzing the constrained solution space



Solution space:



Today's tutorial:

- Simple metabolic network
- Constructing stoichiometric matrix
- Studying reaction fluxes under steady state
- Calculating maximal ATP production under different conditions

Figures: Klamt et al. *PLOS Comp. Biol.* 2017, **13**, e1005409.

Elements of a constraint-based model

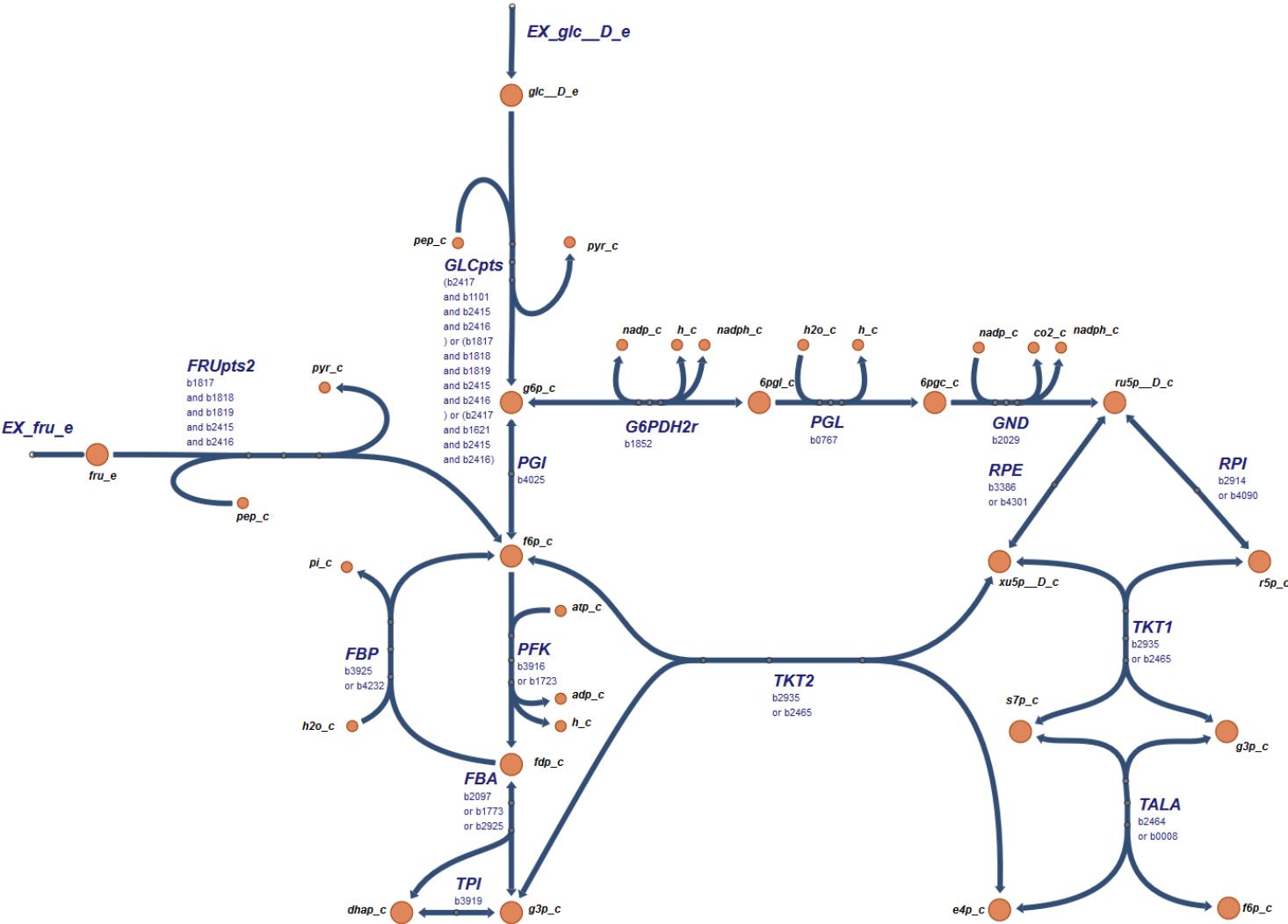


Figure: ESCHER (escher.github.io).

Elements of a constraint-based model

Metabolites

Reactions

Stoichiometry

Directionality of reactions
(thermodynamic considerations)

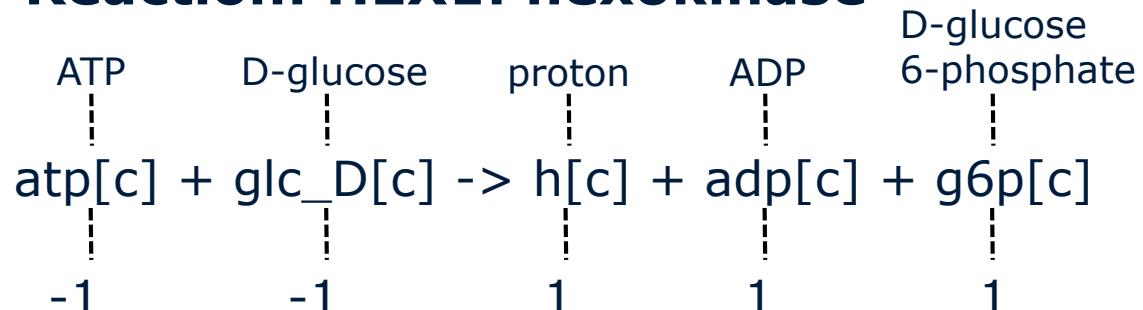
Enzymes
(catalysing a reaction)

Gene-Protein-Reaction
rules

Mass- and charge-balance
of reactions

Compartmentalisation

Reaction: HEX1: hexokinase



\rightarrow vs. $<=>$, irreversible vs. reversible

Hexokinase 1, 2, 3, or 4 (glucokinase)
catalyze the reaction

(3098) or (3099) or (3101) or (2645)...

Gene number for hexokinase 1

Glucose transport from extracellular space to cytosol



Figure: ESCHER (escher.github.io).

How to construct a genome-scale constraint-based model?

The screenshot shows the NCBI Entrez Gene search interface. The search bar contains the query `txid511145[Organism:noexp] AND metab*`. The results summary indicates 1721 hits. A detailed view of the first two results is shown:

- 1: csdE**: predicted Fe-S metabolism protein [*Escherichia coli* str. K12 substr. MG1655]. Other Aliases: b2811, ECK2807, JW2780, yedK. Annotation: NC_000913.2 (2942564..2943007). GeneID: 947274.
- 2: ucpA**: predicted oxidoreductase, sulfate metabolism protein [*Escherichia coli* str. K12 substr. MG1655]. Other Aliases: b2426, ECK2421, JW5394, vfeF.

A table summarizes the gene information:

Gene alias	Locus name	EntrezGene function
csdE	b2811	predicted Fe-S metabolism protein
ucpA	b2426	predicted oxidoreductase, sulfate metabolism protein
yjjX	b4394	thiamin metabolism associated protein

Annotations for **csdE** and **ucpA** are expanded, showing their primary source (ECOCYC:G7455 and EcoGene:EG13083 respectively), locus tag, and gene type (protein coding).

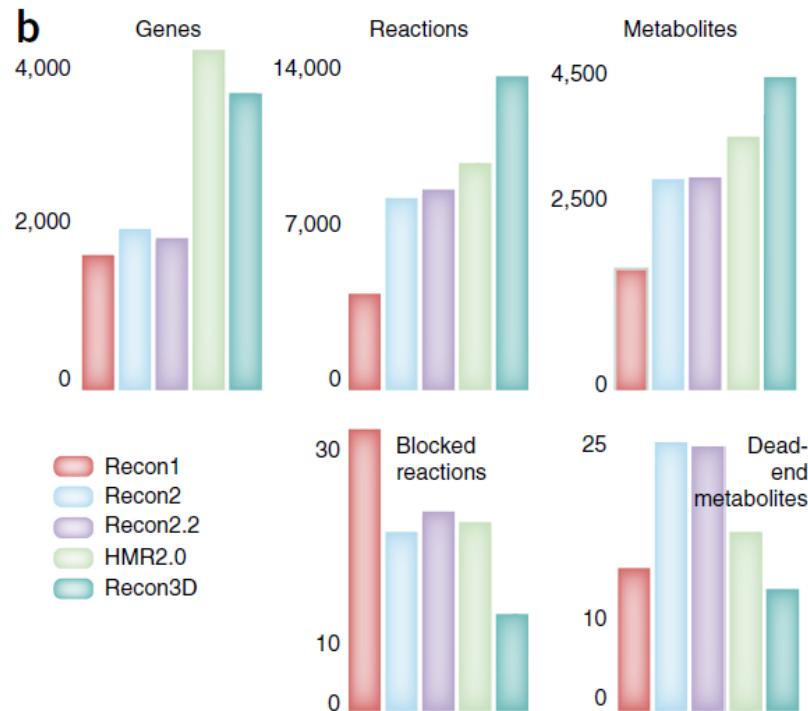
Annotations for **csdE** and **ucpA** are highlighted with boxes, and arrows point from these annotations to the corresponding entries in the table above.

Thiele and Palsson. *Nat. Protocols* 2010, **5**, 93.

How to construct a genome-scale constraint-based model?

Recon3D enables a three-dimensional view of gene variation in human metabolism

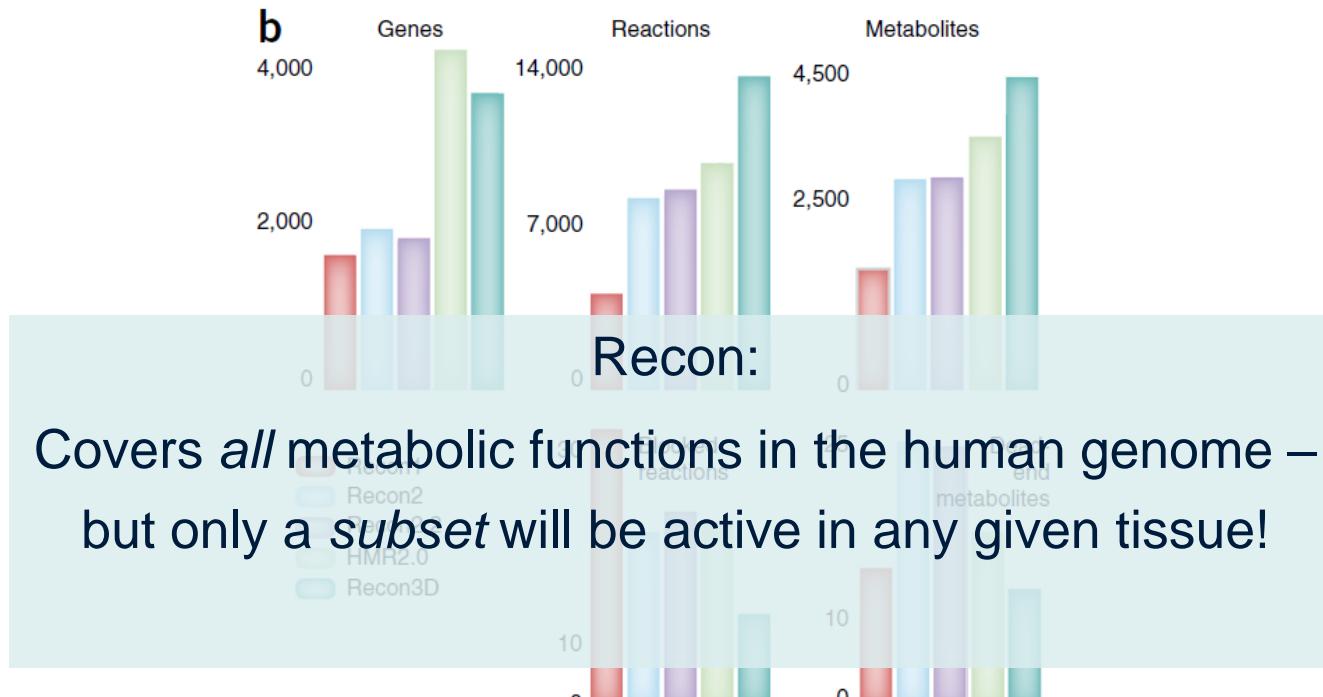
Elizabeth Brunk^{1,2} , Swagatika Sahoo^{3,11}, Daniel C Zielinski¹, Ali Altunkaya^{4,5} , Andreas Dräger⁶ , Nathan Mih¹, Francesco Gatto^{1,7} , Aylant Nilsson⁷ , German Andres Preciat Gonzalez³ , Maike Kathrin Aurich³, Andreas Prlic⁴, Anand Sastry¹, Anna D Danielsdottir³, Almut Heinken³, Alberto Noronha³, Peter W Rose⁴, Stephen K Burley^{4,8}, Ronan M T Fleming^{3,9} , Jens Nielsen^{2,7} , Ines Thiele³ & Bernhard O Palsson^{1,2,10} 



How to construct a genome-scale constraint-based model?

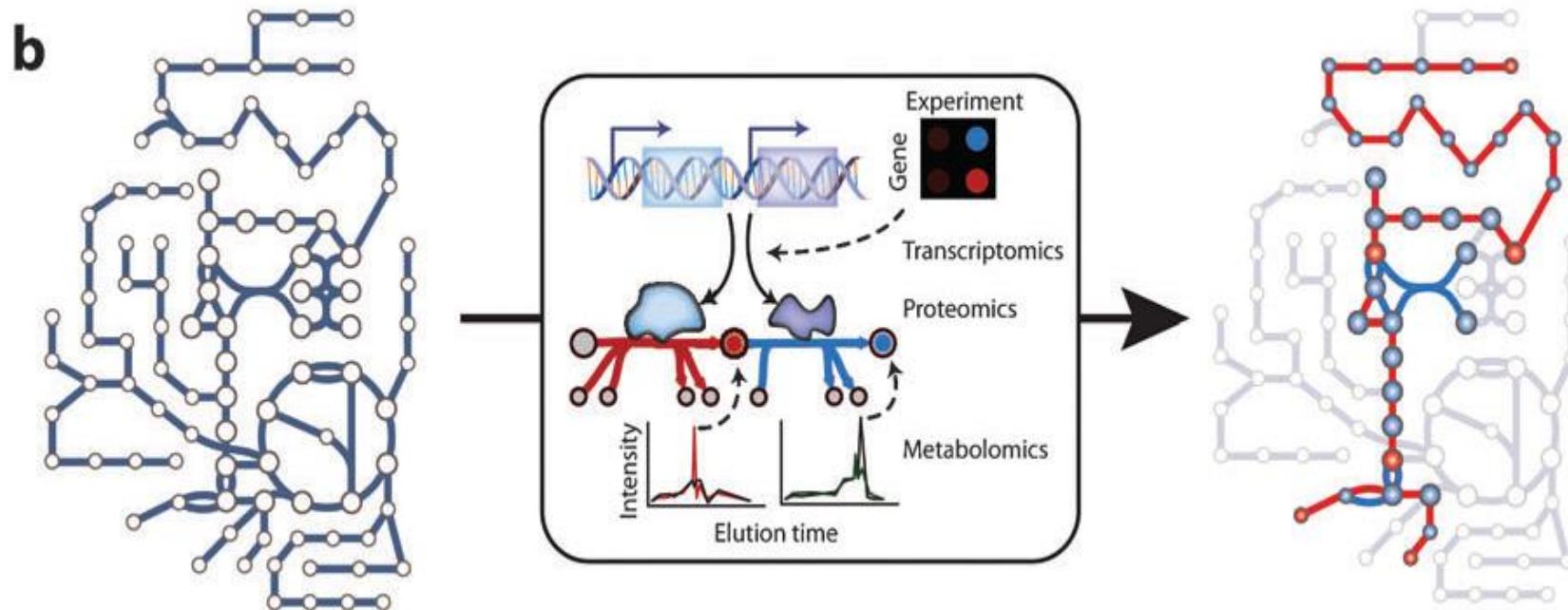
Recon3D enables a three-dimensional view of gene variation in human metabolism

Elizabeth Brunk^{1,2} , Swagatika Sahoo^{3,11}, Daniel C Zielinski¹, Ali Altunkaya^{4,5} , Andreas Dräger⁶ , Nathan Mih¹, Francesco Gatto^{1,7} , Aylant Nilsson⁷ , German Andres Preciat Gonzalez³ , Maike Kathrin Aurich³, Andreas Prlic⁴, Anand Sastry¹, Anna D Danielsdottir³, Almut Heinken³, Alberto Noronha³, Peter W Rose⁴, Stephen K Burley^{4,8}, Ronan M T Fleming^{3,9} , Jens Nielsen^{2,7} , Ines Thiele³ & Bernhard O Palsson^{1,2,10} 



How to construct a genome-scale constraint-based model?

Gene expression data allows to construct network for a specific cell type (e.g. hepatocyte) or condition (e.g. cancer)



Hyduke D.R. et al. *Molecular BioSystems* 2013, **9**, 167.

Maastricht Centre for Systems Biology (MaCSBio)

Modeling human metabolic networks

Can predict steady states in human networks under different conditions

Thursday's practical:

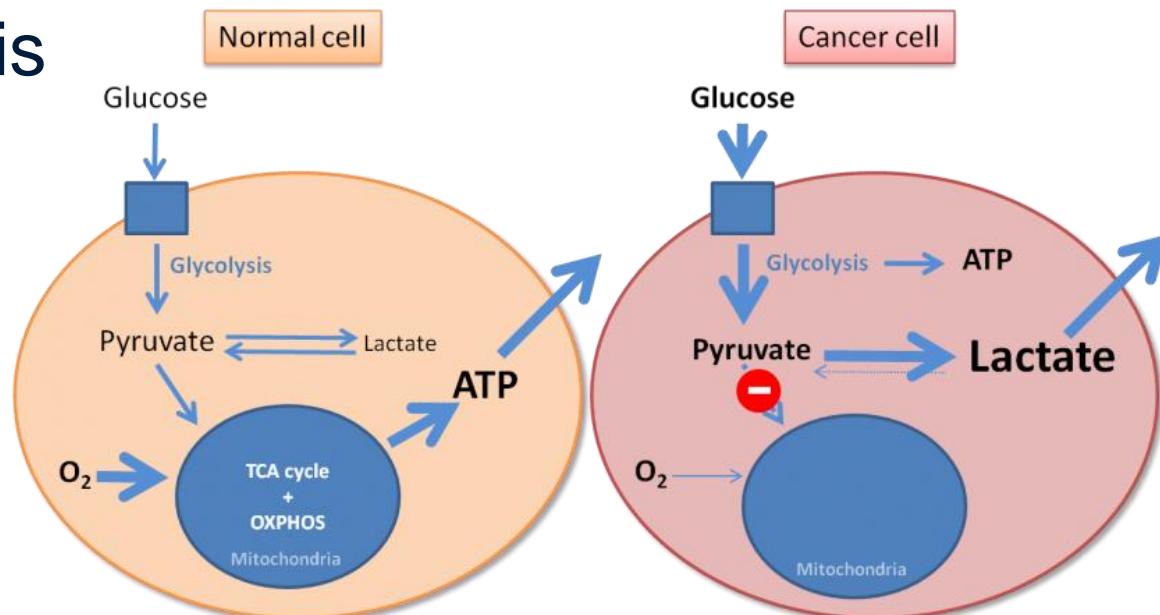
Normal vs. cancer metabolism

→ Warburg effect

Modeling human metabolic networks

Warburg effect:

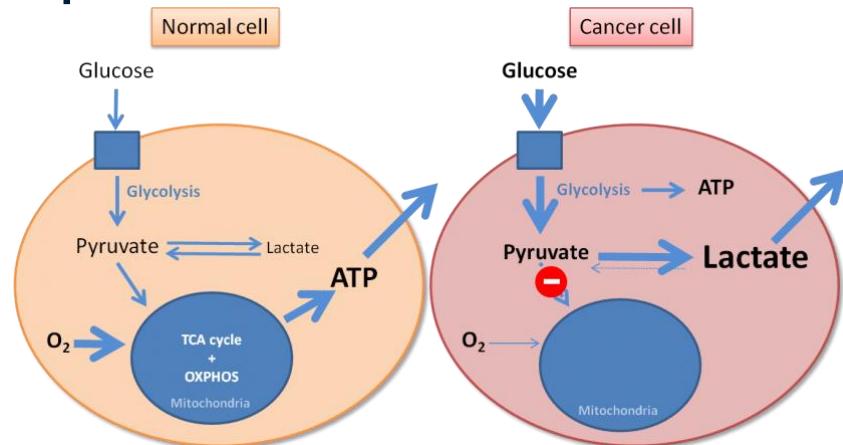
- Normal cells: ATP primarily from OXPHOS
 - Most cancer cells: high rate of glycolysis + lactic acid fermentation, even when O_2 is present
- Aerobic glycolysis



Modeling human metabolic networks

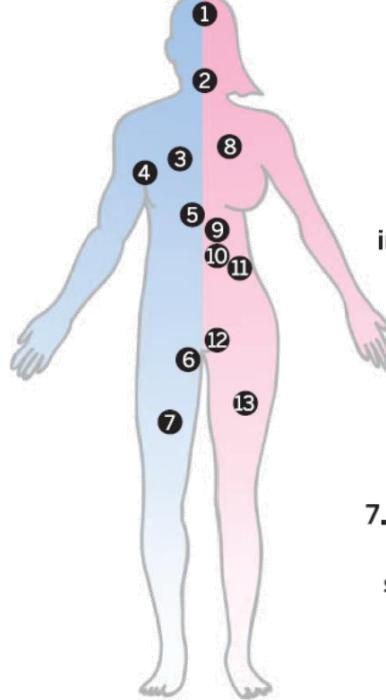
Thursday's practical:

- Calculate and visualize fluxes in a healthy metabolic network
- Construct a cancer metabolic network by removing genes not expressed
- Calculate fluxes in cancer-specific network and compare to healthy case

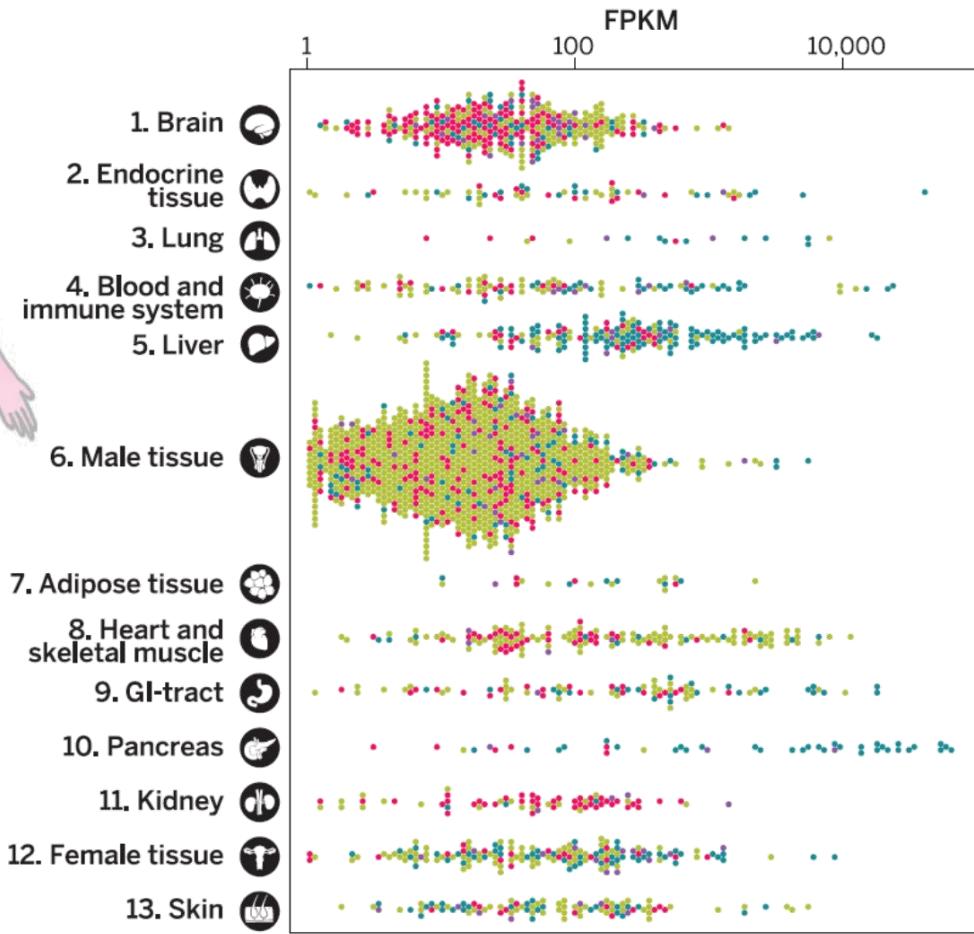


Constructing condition-specific networks

Gene expression is continuous!



- soluble
- membrane
- secreted
- membrane and secreted isoforms

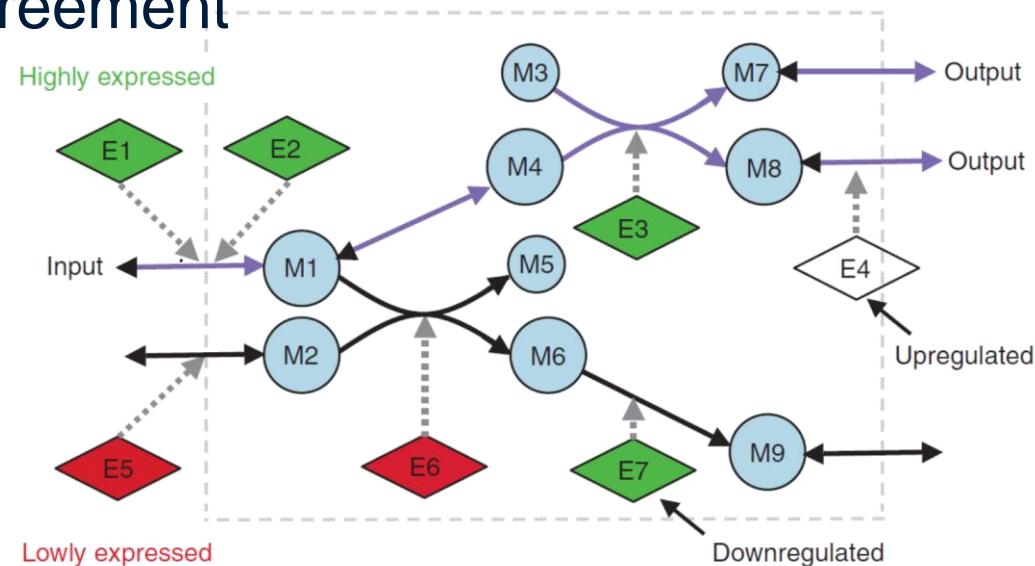
Uhlen et al. *Science* 2015, **347**, 1260419.

Constructing condition-specific networks

Possibilities to deal with continuous gene expression data:

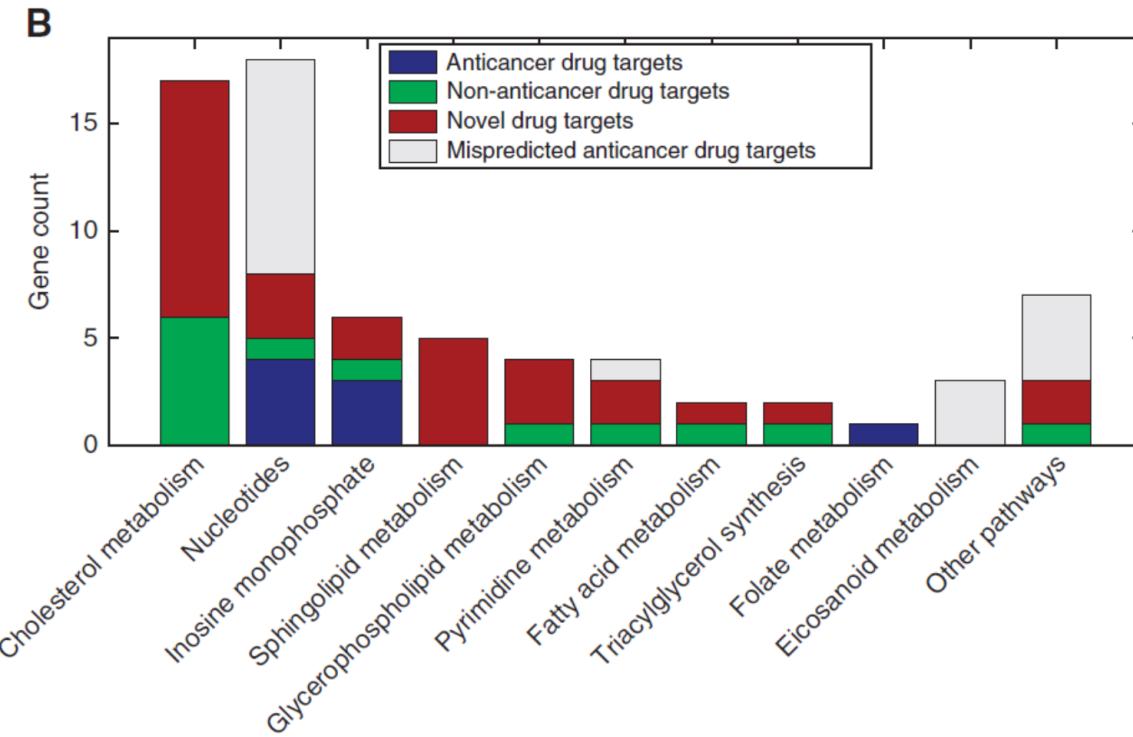
iMAT:

- Group genes into relatively high/medium/low expression
- Find network structure and flux state that maximizes agreement with data



Biomedical applications of human condition-specific networks

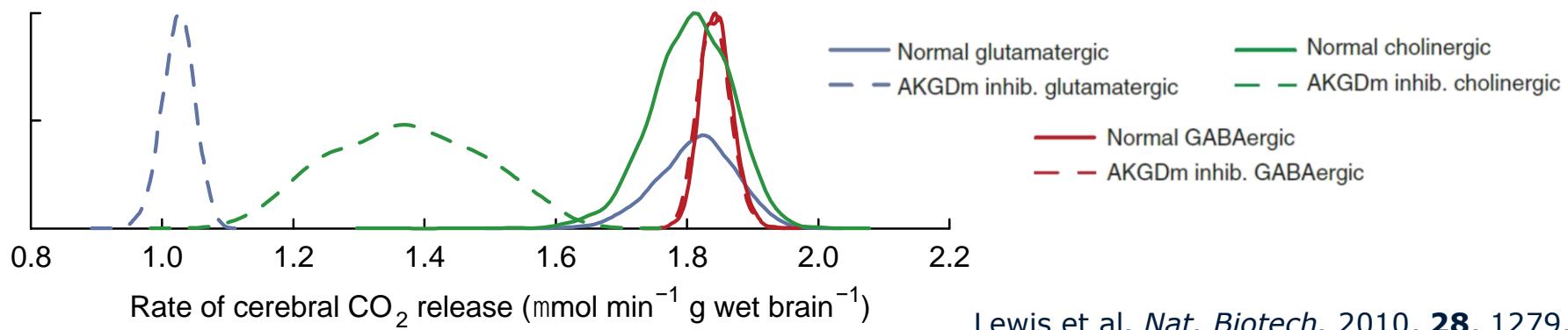
Predicting selective drug targets in cancer through metabolic networks



Biomedical applications of human condition-specific networks

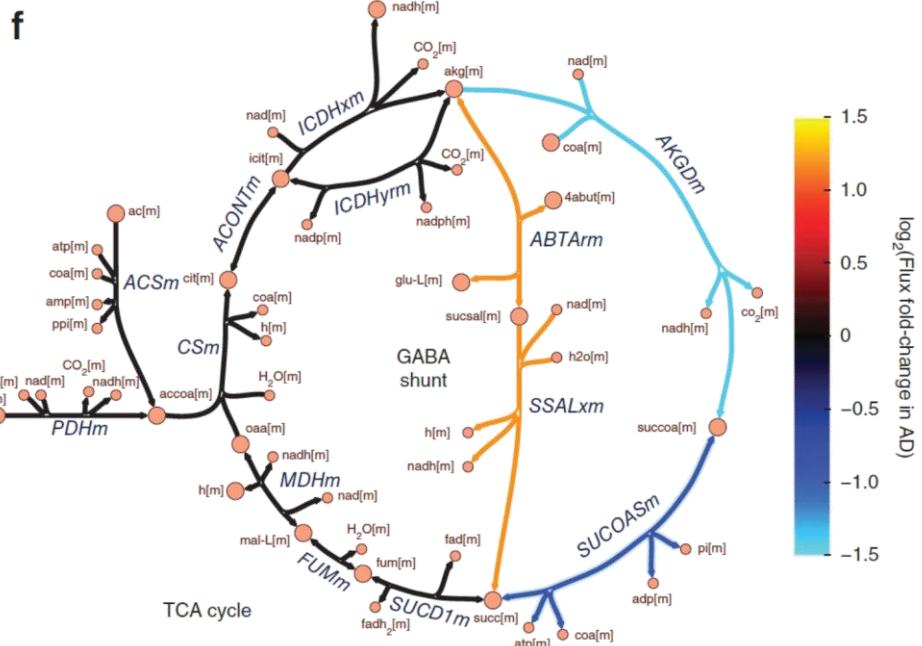
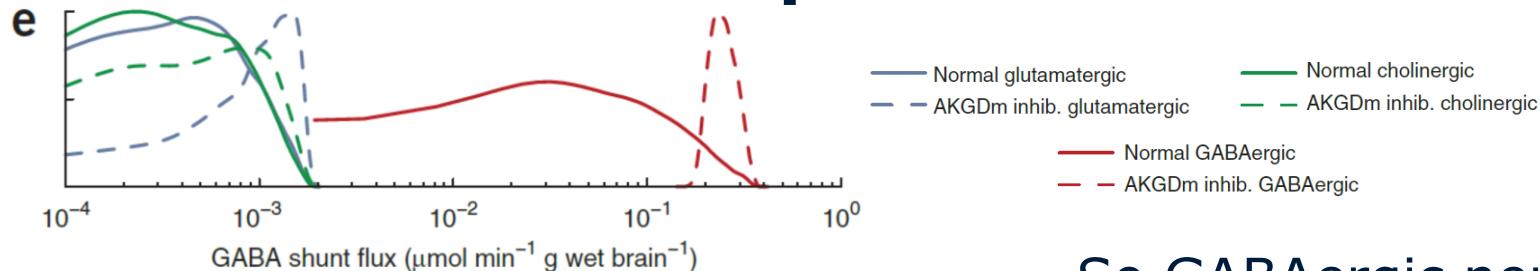
Flux space sampling:

- Calculating distributions of possible fluxes for reactions of interest
- Comparing distributions between networks
→ Identify reaction activity difference



Lewis et al. *Nat. Biotech.* 2010, **28**, 1279.

Biomedical applications of human condition-specific networks



So GABAergic neurons have higher GABA shunt flux – but why?

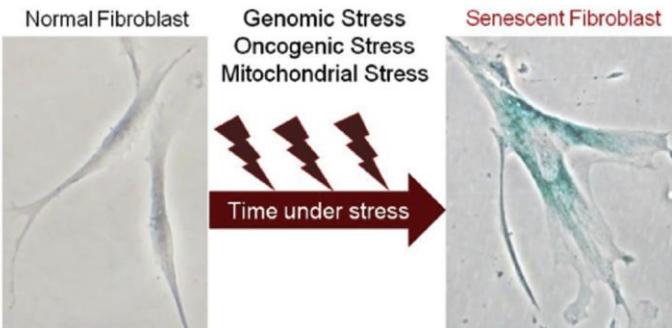
→ *In silico* removal of reactions: Glutamate decarboxylase (GAD) suggested to be key enzyme

Lewis et al. *Nat. Biotech.* 2010, **28**, 1279.

Project opportunities at MaCSBio

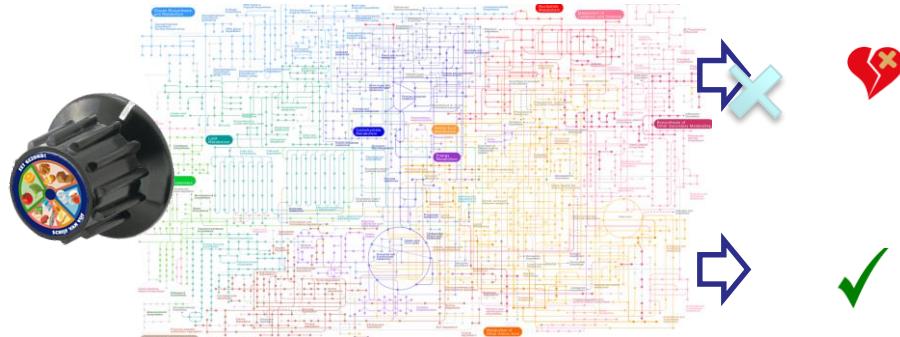
BTR projects in genome-scale metabolic modeling

Cellular senescence

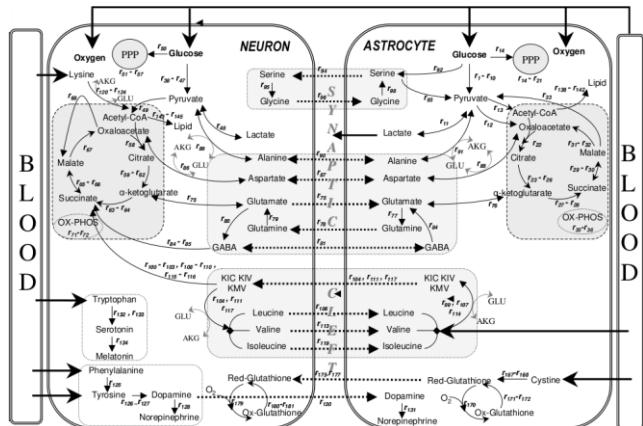


Nacarelli et al. Mol. Cell. Endocrinol. 2017, 455, 83.

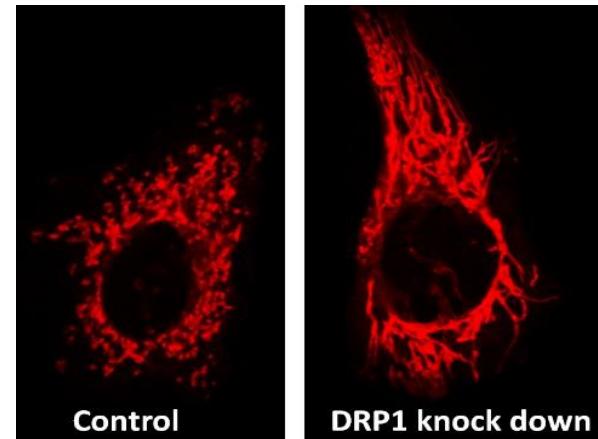
Heart disease



Glial cells



Fibroblasts



Project opportunities at MaCSBio

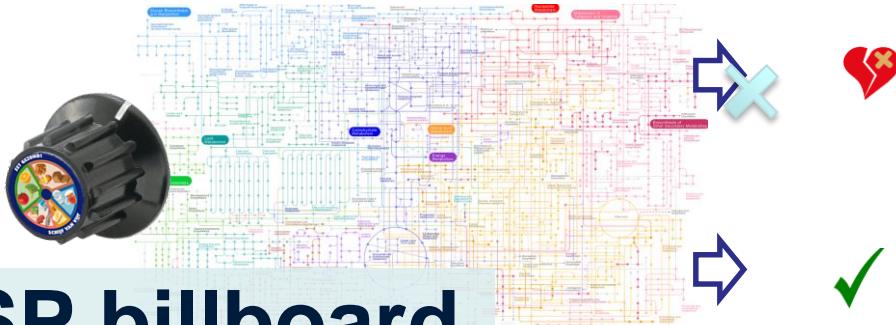
BTR projects in genome-scale metabolic modeling

Cellular senescence



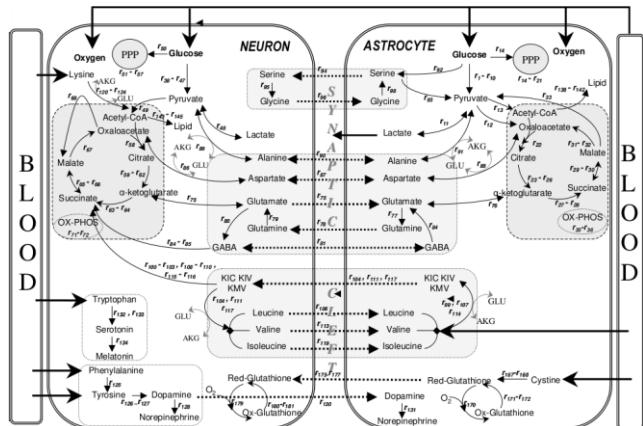
Nacarelli et al. Mol. Cell. Endocrinol. 2014; 345: 81.

Heart disease

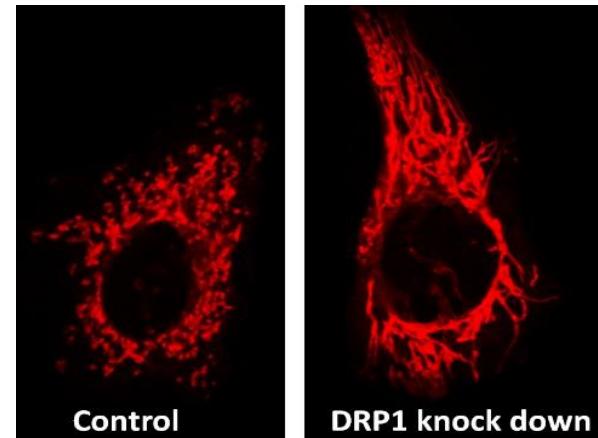


Check MSP billboard

Glial cells



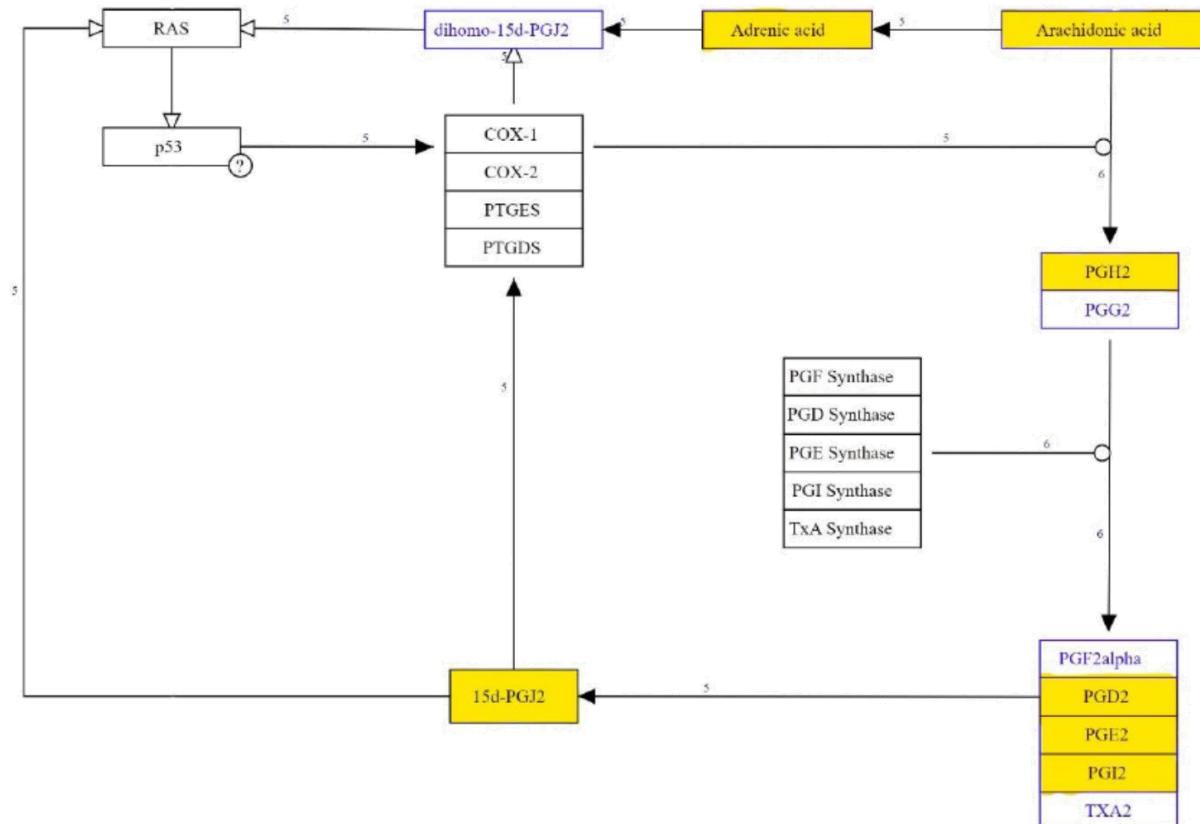
Fibroblasts



Project opportunities at MaCSBio

This project period:

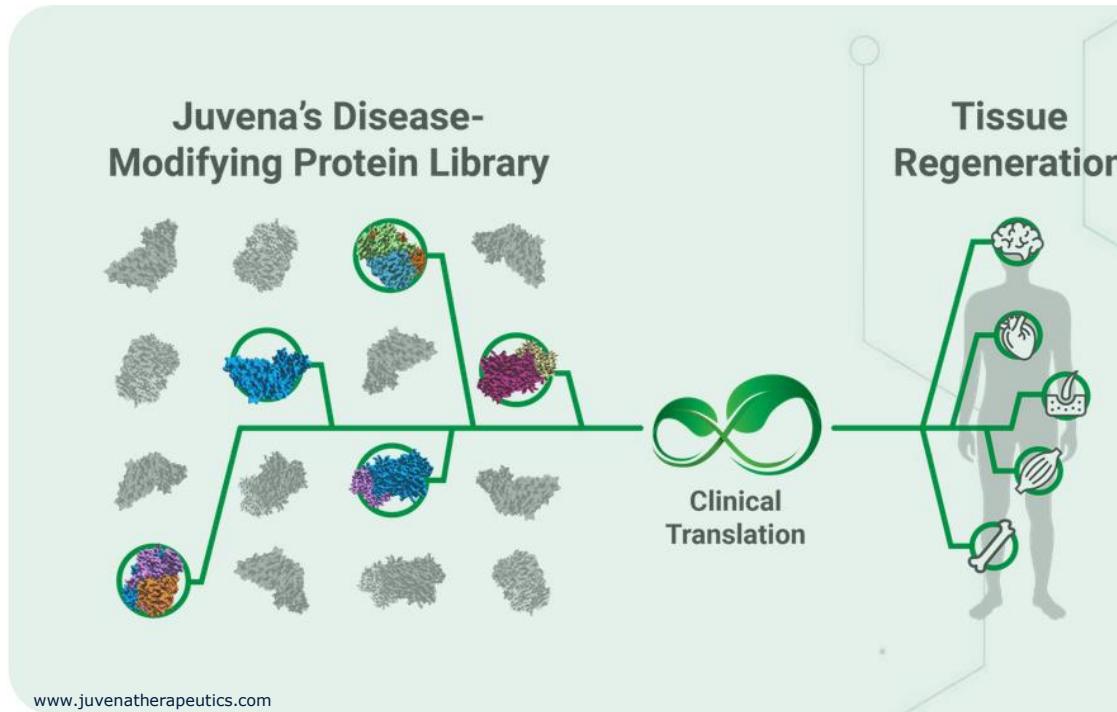
Curating metabolic pathways in human metabolic networks



MaCSBio Lecture Series seminar

Mapping Secreted Proteins to Unmet Medical Needs

Dr. Thach Mai, Juvena Therapeutics, Nov 28 2022



Registration: www.maastrichtuniversity.nl/register-macsbio-lecture-series