Course 2851 Principles of Metabolism
Metabolism and endocrinology programme, Karolinska Institutet

Lecture 5

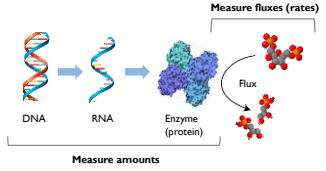
Metabolic networks and fluxes

Roland Nilsson, Ph.D

Department of Medicine, Solna
Center for Molecular Medicine
Karolinska Institutet

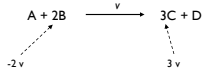
Fluxes describes a cell's metabolic phenotype

But how do we measure them?



Definition

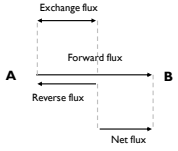
- The *flux (rate)* through a reaction is the *amount of substance processed per unit time*
- Standardized by stoichiometry coefficients



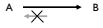
- Expressed per cell or by biomass (total protein in culture, tissue, etc.)

Forward, reverse, net, exchange fluxes

- Most reactions are reversible to some extent, and occur in both directions



Irreversible reaction



Reverse flux = 0
Exchange flux = 0

Reaction at equilibrium

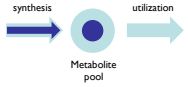
Net flux = 0

Pool sizes are not directly related to fluxes

A pool size is reduced by half. What was the change in flux?

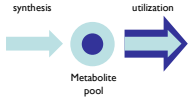
Scenario I

Decreased synthesis initially causes pool to shrink. Flux has *decreased*.



Scenario II

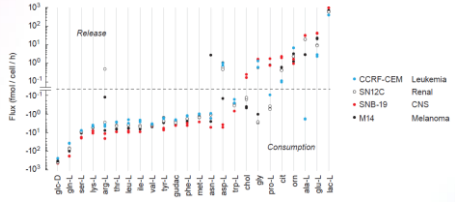
Increased utilization initially causes pool to shrink. Flux has *increased*.



Most metabolites connect to many reactions!

Boundary fluxes: uptake / release of metabolites

- Net flux of metabolite from/to the environment
  - Substrate consumption
  - Accumulation of end products
- Readily measurable

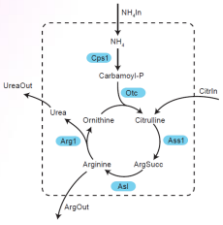


Data from Jain & Nilsson et al, Science 2012

Flux balance analysis

At steady state

Example network: urea cycle



Stoichiometry matrix *S*

	NH4in	Cps1	Otc	Ass1	Asl	Arg1	CitrIn	ArgOut	UreaOut
NH4	1	-1							
Carbamoyl-P		1	-1						
Citrulline			1	-1			1		
ArgSucc				1	-1				
Arginine					1	-1		-1	
Ornithine		-1				1			
Urea						1			-1

$\sum_j S_{ij} v_j \geq 0$ mass balance

$v_j \geq 0$ For irreversible reactions

Example: citrulline

$1 \times v_{Otc} - 1 \times v_{Ass1} + 1 \times v_{CitrIn} = 0$

Metabolic network reconstructions

- Large community projects to gather data on all known metabolic reactions for a given organism

systemsbiology.ucsd.edu

Property	Recon 2
Total number of reactions	7,440
Total number of metabolites	5,063
Number of unique metabolites	2,626
Number of metabolites in extracellular space	642
Number of metabolites in cytoplasm	1,878
Number of metabolites in mitochondrion	754
Number of metabolites in nucleus	165
Number of metabolites in endoplasmic reticulum	570
Number of metabolites in peroxisome	435
Number of metabolites in lysosome	302
Number of metabolites in Golgi apparatus	317
Number of transcripts	2,194
Number of unique genes	1,789
Number of subsystems	99
Number of blocked reactions (% of all reactions)	1,603 (22%)
Number of dead-end metabolites	1,176[2]
Size of S^1 (m, n)	5,063; 7,440
Number of linearly independent mass balances	2,774
Sparsity (% of nonzero entries in S)	0.0837
Number of accomplished metabolic tasks	354
Mapped IEMs (% of all IEMs)	248 (76%)
Number of unique genes causing IEMs	272
Number of IEMs affecting metabolic tasks (% of effective IEMs)	98 (44%)

Thiele et al, Nat Biotech 31:419—425, 2013.

metacyc.org
humancyc.org

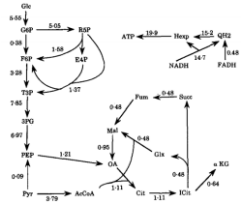
Type of match	Number of proteins
PathoLogic matched by EC number	2,057
PathoLogic matched by name	314
Ambiguous	27
Unmatched by PathoLogic	27,185
Probable enzymes	1,320
Manually matched	625

Romero et al, Genome Biology 6:1-17, 2004 .

Flux balance analysis, variations on a theme

Fluxes at optimal biomass growth

Early application, studied in bioproduction settings

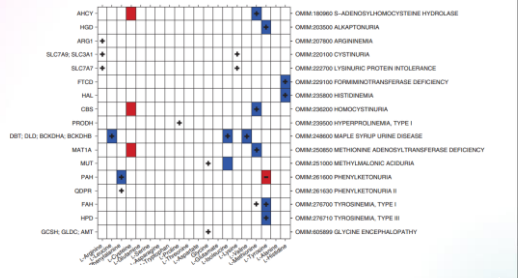


Varma & Palsson, J Theor Biol 165:503-522, 1993.
(*E. Coli*)

Flux balance analysis, variations on a theme

Identifying metabolite biomarkers for genetic disorders

Metabolites overproduced when a reaction is set to zero

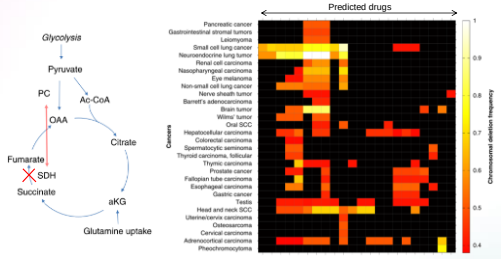


Shlomi et al, Mol Sys Bio 5:263, 2009.

Flux balance analysis, variations on a theme

Synthetic lethality

If one enzyme is lost, what other reactions become required for growth?



Folger et al, Mol Sys Bio 7:501, 2011.

(modified)