

Defining regulation coefficients

Unraveling the complexity of flux regulation:
A new method demonstrated for nutrient
starvation in *Saccharomyces cerevisiae*

Rossell *et al.* (2006), *PNAS* 103:2166-2171

$$v = v(e, \mathbf{X}, \mathbf{K}) = f(e) \cdot g(\mathbf{X}, \mathbf{K}).$$

$$1 = \frac{\Delta \log f(e)}{\Delta \log J} + \frac{\Delta \log g(\mathbf{X}, \mathbf{K})}{\Delta \log J} = \rho_h + \rho_m.$$

‘hierarchical’

~ metabolic

regulation coefficients

Experimental setup

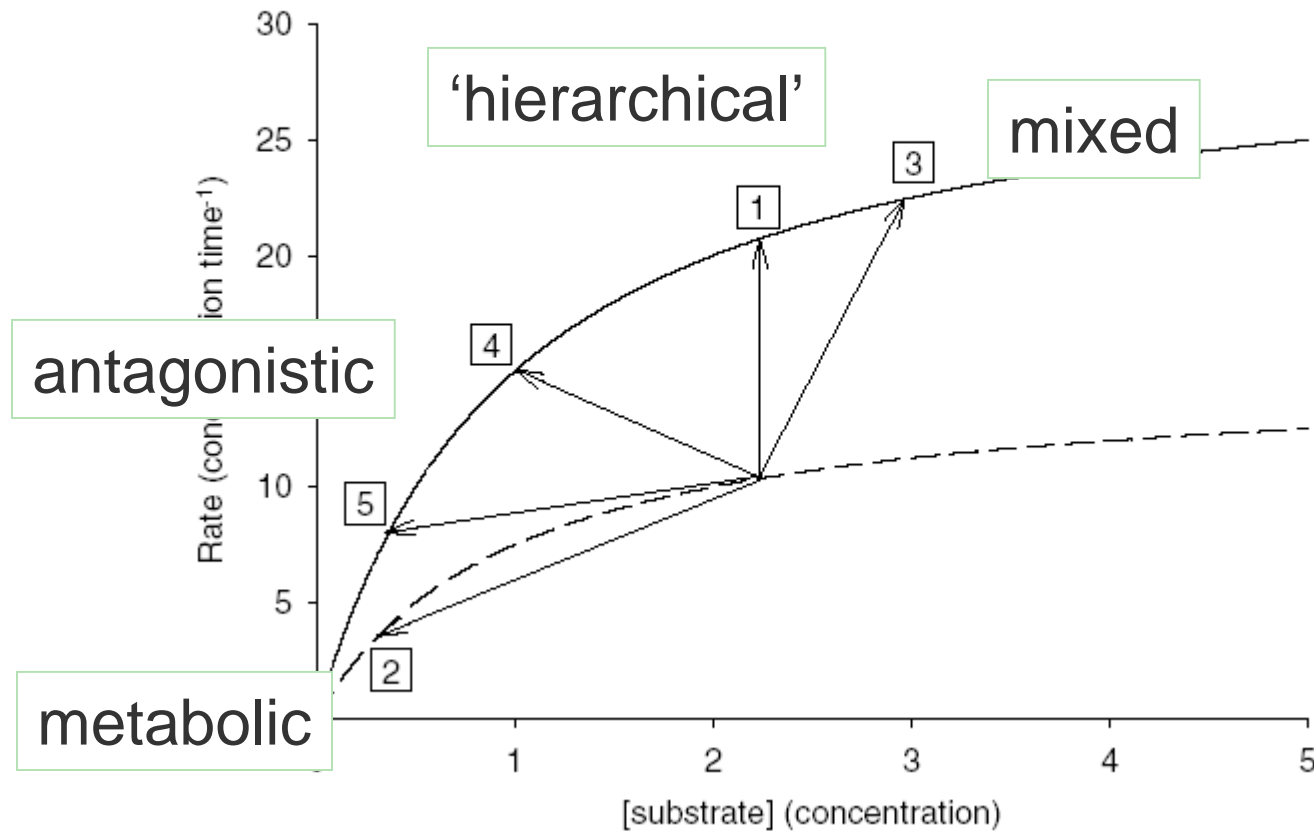
- Yeast grown in synthetic medium + glucose
- N or C starvation for 24 h
- Fluxes measured over 30 min in the presence of glucose
→ $\Delta \log J$
- Enzyme assays
→ $\Delta \log E$

$$\rho_h = \frac{\Delta \log E}{\Delta \log J}$$

$$\rho_m = 1 - \rho_h$$

Different types of regulation

S. Rossell et al. / FEMS Yeast Research 5 (2005) 611–619



Mainly gene regulation

Enzyme	Nitrogen starvation			Carbon starvation		
	ρ_h	SEM	ρ_m	ρ_h	SEM	ρ_m
GLT	1.2	0.1	-0.2	0.4	0.1	0.6
HK	1.0	0.2	0.0	0.1	0.0	0.9
PGI	0.8	0.3	0.2	0.0	0.0	1.0
PFK	0.4	0.2	0.6	0.4	0.4	0.6
ALD	1.1	0.5	-0.1	0.0	0.2	1.0
TPI	0.1	0.9	0.9	-0.4	0.2	1.4
GAPDH	0.7	0.5	0.3	0.1	0.0	0.9
PGK	0.0	0.2	1.0	-0.3	0.1	1.3
PGM	1.0	0.4	0.0	0.0	0.0	1.0
ENO	0.4	0.5	0.6	0.3	0.1	0.7
PK	1.4	0.3	-0.4	0.1	0.0	0.9
PDC	2.3	0.6	-1.3	0.1	0.0	0.9
ADH	1.7	0.4	-0.7	-1.3	0.2	2.3

PDC, pyruvate decarboxylase; PFK, 6-phosphofructokinase; PGI, glucose-6-phosphate isomerase; PGK, phosphoglycerate kinase; PGM, phosphoglycerate mutase; PK, pyruvate kinase; TPI, triose-phosphate isomerase.

Mainly metabolic regulation

Enzyme	Nitrogen starvation			Carbon starvation		
	ρ_h	SEM	ρ_m	ρ_h	SEM	ρ_m
GLT	1.2	0.1	-0.2	0.4	0.1	0.6
HK	1.0	0.2	0.0	0.1	0.0	0.9
PGI	0.8	0.3	0.2	0.0	0.0	1.0
PFK	0.4	0.2	0.6	0.4	0.4	0.6
ALD	1.1	0.5	-0.1	0.0	0.2	1.0
TPI	0.1	0.9	0.9	-0.4	0.2	1.4
GAPDH	0.7	0.5	0.3	0.1	0.0	0.9
PGK	0.0	0.2	1.0	-0.3	0.1	1.3
PGM	1.0	0.4	0.0	0.0	0.0	1.0
ENO	0.4	0.5	0.6	0.3	0.1	0.7
PK	1.4	0.3	-0.4	0.1	0.0	0.9
PDC	2.3	0.6	-1.3	0.1	0.0	0.9
ADH	1.7	0.4	-0.7	-1.3	0.2	2.3

PDC, pyruvate decarboxylase; PFK, 6-phosphofructokinase; PGI, glucose-6-phosphate isomerase; PGK, phosphoglycerate kinase; PGM, phosphoglycerate mutase; PK, pyruvate kinase; TPI, triose-phosphate isomerase.

Mixed regulation

Enzyme	Nitrogen starvation			Carbon starvation		
	ρ_h	SEM	ρ_m	ρ_h	SEM	ρ_m
GLT	1.2	0.1	-0.2	0.4	0.1	0.6
HK	1.0	0.2	0.0	0.1	0.0	0.9
PGI	0.8	0.3	0.2	0.0	0.0	1.0
PFK	0.4	0.2	0.6	0.4	0.4	0.6
ALD	1.1	0.5	-0.1	0.0	0.2	1.0
TPI	0.1	0.9	0.9	-0.4	0.2	1.4
GAPDH	0.7	0.5	0.3	0.1	0.0	0.9
PGK	0.0	0.2	1.0	-0.3	0.1	1.3
PGM	1.0	0.4	0.0	0.0	0.0	1.0
ENO	0.4	0.5	0.6	0.3	0.1	0.7
PK	1.4	0.3	-0.4	0.1	0.0	0.9
PDC	2.3	0.6	-1.3	0.1	0.0	0.9
ADH	1.7	0.4	-0.7	-1.3	0.2	2.3

PDC, pyruvate decarboxylase; PFK, 6-phosphofructokinase; PGI, glucose-6-phosphate isomerase; PGK, phosphoglycerate kinase; PGM, phosphoglycerate mutase; PK, pyruvate kinase; TPI, triose-phosphate isomerase.

Antagonistic regulation

Enzyme	Nitrogen starvation			Carbon starvation		
	ρ_h	SEM	ρ_m	ρ_h	SEM	ρ_m
GLT	1.2	0.1	-0.2	0.4	0.1	0.6
HK	1.0	0.2	0.0	0.1	0.0	0.9
PGI	0.8	0.3	0.2	0.0	0.0	1.0
PFK	0.4	0.2	0.6	0.4	0.4	0.6
ALD	1.1	0.5	-0.1	0.0	0.2	1.0
TPI	0.1	0.9	0.9	-0.4	0.2	1.4
GAPDH	0.7	0.5	0.3	0.1	0.0	0.9
PGK	0.0	0.2	1.0	-0.3	0.1	1.3
PGM	1.0	0.4	0.0	0.0	0.0	1.0
ENO	0.4	0.5	0.6	0.3	0.1	0.7
PK	1.4	0.3	-0.4	0.1	0.0	0.9
PDC	2.3	0.6	-1.3	0.1	0.0	0.9
ADH	1.7	0.4	-0.7	-1.3	0.2	2.3

PDC, pyruvate decarboxylase; PFK, 6-phosphofructokinase; PGI, glucose-6-phosphate isomerase; PGK, phosphoglycerate kinase; PGM, phosphoglycerate mutase; PK, pyruvate kinase; TPI, triose-phosphate isomerase.

How to interpret this complex interplay?

- Different types of regulation can occur in the **same pathway**
- Flux through **same reaction** can be regulated differently, depending on physiological state

However:

- This 'hierarchical' regulation coefficient does not take into account changes in expression of other enzymes
- The latter changes are accounted for indirectly through their effects on metabolism.
- Therefore the relative contributions of gene regulation and metabolic control are not fully separated