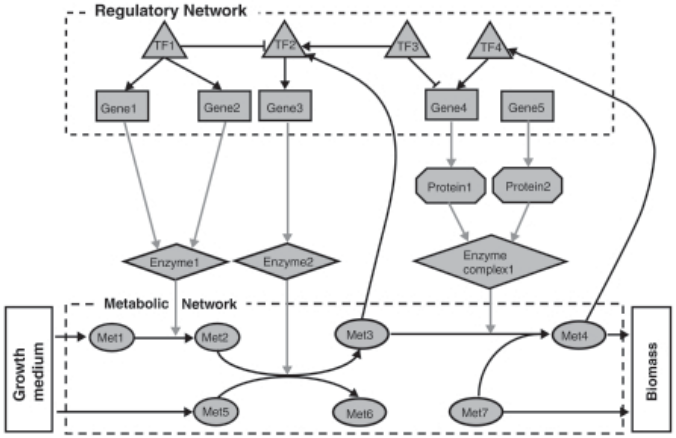
Metabolism and gene regulation

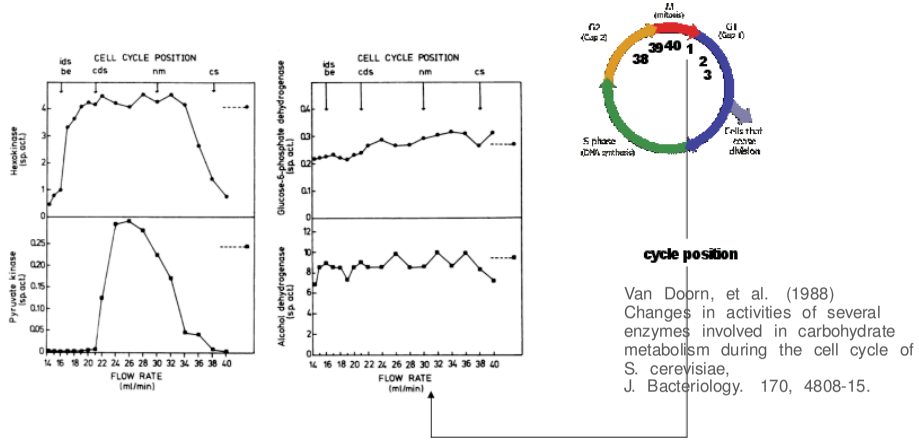


Shlomi et al. 2007

- Gene products/enzymes catalyse reactions.
- Genes are regulated by gene and reaction products.

9. Alterations in metabolism

- Metabolism adapts to changing environments.
- Even in constant environments, metabolism exhibits changes in enzyme activity.
- Significant metabolic alterations during cell cycle.

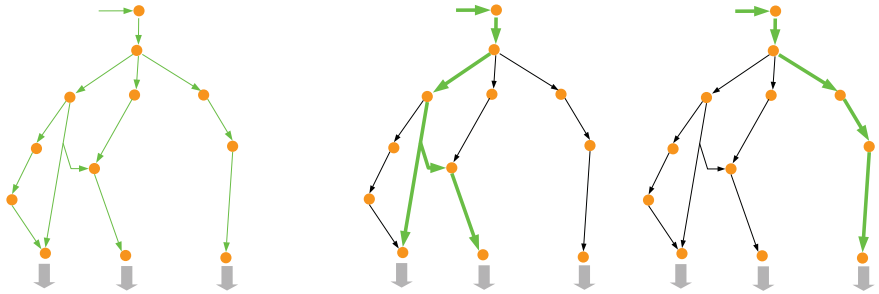


Van Doorn, et al. (1988) Changes in activities of several enzymes involved in carbohydrate metabolism during the cell cycle of S. cerevisiae, J. Bacteriology. 170, 4808-15.

Working hypothesis

Palinkas/Bulik/Bockmayr/Holzhütter 14

Switching between pathways may improve overall efficiency:



The output is produced by a single flux mode, using all reactions.

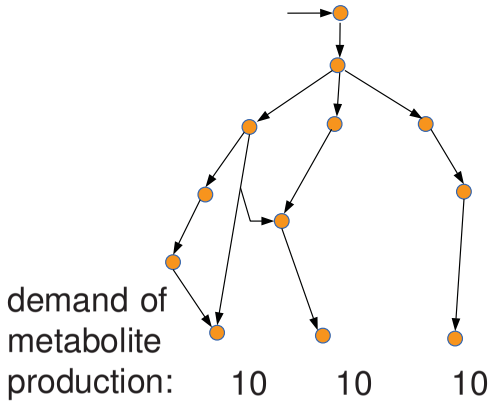
Two consecutive flux modes produce the output with higher flux rates.

When is this possible ?

- Assume metabolic network with internal metabolites $M^{\#}$ and output metabolites M^*, for which there is a demand Γ.
- A flux mode v which is executed for some time $\tau \geq 0$ satisfies the demand if $\tau \cdot S^* v \geq \Gamma$.
- Two flux modes v^1, v^2 which are executed consecutively for time τ_1 resp. τ_2 satisfy the demand if $\tau_1 \cdot S^* v^1 + \tau_2 \cdot S^* v^2 \geq \Gamma$.
- Can we be more efficient with two flux modes v^1, v^2 than with one flux mode v ?
- In an FBA context, this is not possible, since we may always choose $v = \frac{\tau_1}{\tau_1+\tau_2} v^1 + \frac{\tau_2}{\tau_1+\tau_2} v^2$, which has the same efficiency $\tau = \tau_1 + \tau_2$.

Illustrating the principle

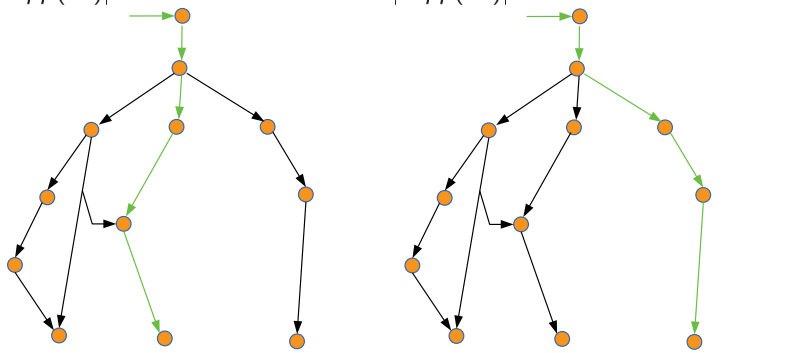
Assume flux bounds $0 \leq v \leq ub/|supp(v)|$, here $ub = 40$.



Illustrating the principle

Assume flux bounds $0 \leq v \leq ub/|supp(v)|$, here $ub = 40$.

$\frac{ub}{|supp(v^1)|} = \frac{40}{5} = 8$ $\frac{ub}{|supp(v^2)|} = \frac{40}{5} = 8$

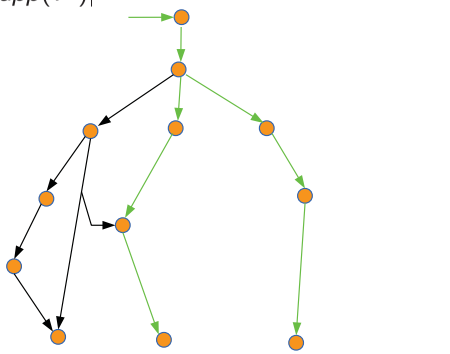


To satisfy demand, need $1.25 \cdot v^1 + 1.25 \cdot v^2$, i.e., $\tau = 2.5$.

Illustrating the principle

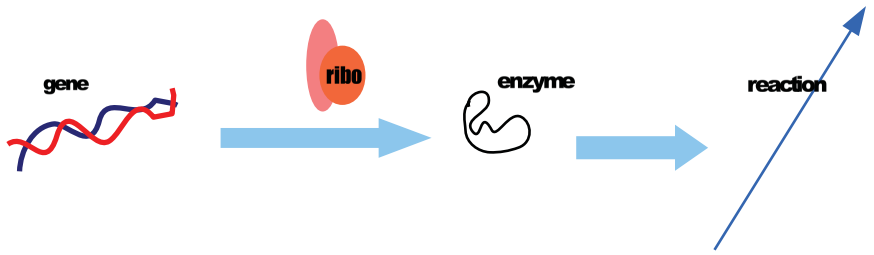
Assume flux bounds $0 \leq v \leq ub/|supp(v)|$, here $ub = 40$.

$\frac{ub}{|supp(v^3)|} = \frac{40}{8} = 5$



To satisfy demand, need $4 \cdot v^3$, i.e., $\tau = 4$.

Modeling approach



gene expression g_j

enzyme amount E_j

reaction flux $v_j \leq kc_j \cdot E_j$

Basic assumption: Total amount of protein in the cell is limited.

Sharing available enzymes

- Synthesis and degradation of i-th enzyme:

$$dE_j/dt = g_j\, ks_j\, A - kd_j\, E_j,$$

where A is the total mass of free amino acids.

- Steady-state condition:

$$E_j = g_j\, A\, \eta_j, \text{ with } \eta_j = ks_j/kd_j.$$

- Assume fixed total mass of amino acids

$$A_{tot} = A + \sum E_i \gamma_i \quad \left[= A + \sum (g_i A \eta_i)\gamma_i = A(1 + \sum g_i \gamma_i \eta_i) \right],$$

where γ_i is the molecular mass of the i-th enzyme.

- Resulting upper bound:

$$v_j \;\leq\; kc_j \cdot E_j = kc_j \cdot A_{tot}\, \frac{g_j \eta_j}{1 + \sum_i g_i \gamma_i \eta_i}$$

Optimizing cellular output

- Internal metabolites $M^{\#}$, output metabolites M^*, all reactions irreversible.
- Assume cell has to produce a certain amount Γ of output metabolites M^*.
- Allow using up to l flux modes $v^1, \ldots, v^l$ in l consecutive time intervals of length $\tau_1, \ldots, \tau_l$.
- Output in k-th time interval: $\tau_k \cdot S^* v^k$
- Goal: Minimize the total time $\tau_1 + \cdots + \tau_l$ needed to produce Γ.
- Lower bounds $lb \geq 0$ (minimum activity of certain reactions).

Non-linear mixed 0-1 optimisation problem

$$\min \sum_{k=1}^{l} \tau_k$$

$$S^{\#} v^k = 0, \qquad \sum_{k=1}^{l} \tau_k\, S^* v^k \geq \Gamma,$$

$$lb_j \;\leq\; v_j^k \;\leq\; kc_j \cdot A_{tot}\, \frac{g_j \eta_j}{1 + \sum_i g_i \gamma_i \eta_i},$$

$$l \in \mathbb{N},\ k = 1, \ldots, l,\ j = 1, \ldots, n,$$

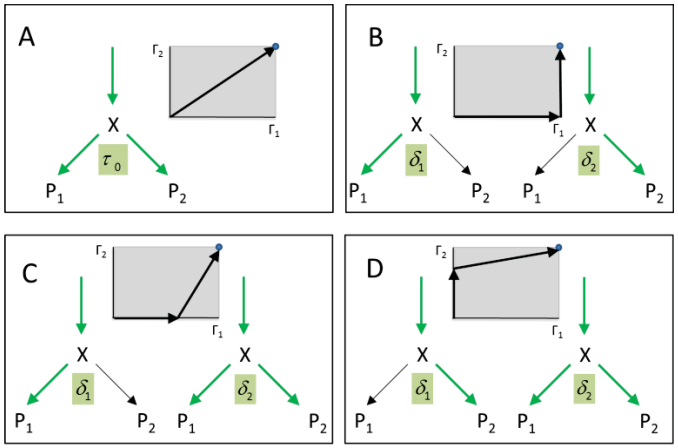
$$\tau_k \in \mathbb{R}_{\geq 0},\ v^k \in \mathbb{R}^n,\ g^k \in \{0,1\}^n.$$

$\rightsquigarrow$ can be reformulated as mixed 0-1 quadratic program (MIQP).

Modeling gene expression levels

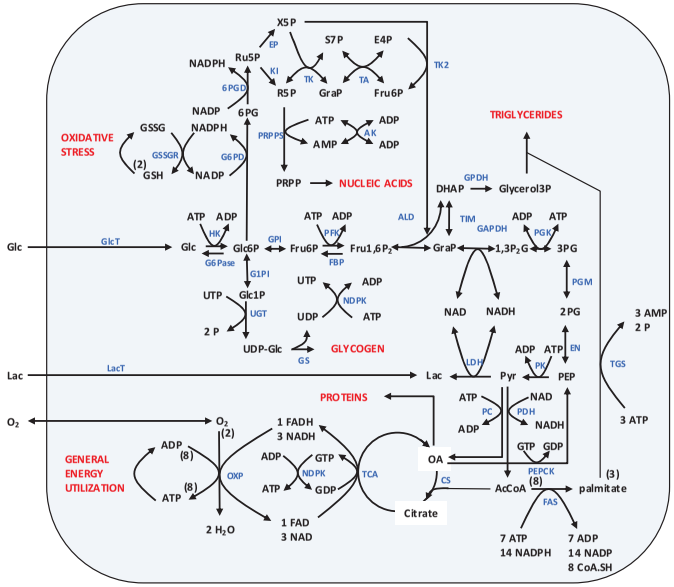
- $g \in [0,1]^n$: fine tuning of genes
  (similar to FBA with Molecular Crowding, cf. Beg et al. 2007)
  $\rightsquigarrow$ feasible region is convex
  $\rightsquigarrow$ no improvement possible through switching
- $g \in \{0,1\}^n$: genes switched on or off individually.
- $g \in U \subset \{0,1\}^n$: genes switched on or off in functional groups,
  $\rightsquigarrow$ biologically more meaningful
  (e.g. common transcription factors)
  $\rightsquigarrow$ may use MinModes (Hoffmann et al. 2006)

Simplistic example



- Improvement by switching depends on parameter values.
- Random sampling gives improvement in 83% of the cases.
- Higher improvement if more protein is spent downstream.

Biomass in central carbon metabolism



Optimal MinMode solutions

Switching MinModes On and Off								
Sub	l	Σ	τ_1	τ_2	τ_3	τ_4	# reaction switches	# active reactions
glc, lac	1	7.405h					0	41
	2	5.544h	2.302h	3.242h			14	29,43
	3	4.805h	2.429h	0.176h	2.201h		26 (14/12)	35,41,29
	4	**4.792h**	**2.214h**	**0.098h**	**0.118h**	**2.362h**	**26 (8/8/10)**	**29,37,41,35**
glc	1	10.700h					0	41
	2	7.967h	0.203h	7.764h			9	38,35
	3	7.631h	0.239h	5.832h	1.559h		11 (8/3)	39,35,32
	4	7.607h	0.071h	1.386h	6.029h	0.121h	14 (4/3/7)	32,32,35,36
lac	1	7.405h					0	41
	2	5.942h	0.728h	5.214h			7	40,35
	3	5.845h	2.688h	2.429h	0.728h		9 (2/7)	33,35,40
	4	5.764h	0.210h	2.688h	2.429h	0.437h	10 (3/2/5)	36,33,35,38