Flux Coupling Analysis, Part I

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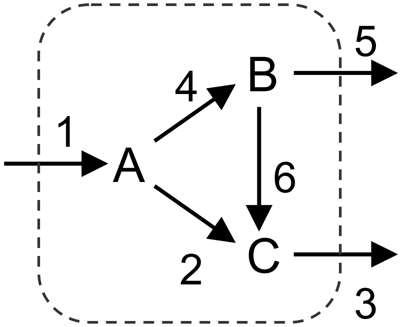
Definitions (1)

- A metabolic network (made by "reconstruction")



- Stoichiometric matrix ($m \times n$)

$S =$

	1	2	3	4	5	6
A	1	-1	…			
B	0	0	…			
C	0	1	…			

- v : Flux vector; v_i : Flux through reaction i

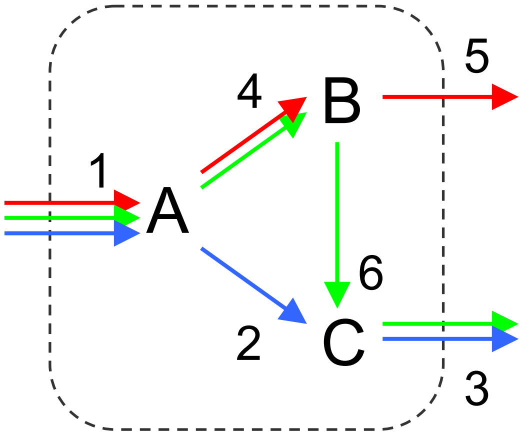
Definitions (2)

- In constraint-based modeling of metabolic networks, it is usually assumed that steady state condition holds:
- $S.v = 0$ (Stoichiometric constraints)
- $\forall i \in Irr : v_i \geq 0$ (Thermodynamic constraints)

Definitions (3)

- An "elementary mode" in a metabolic network can be defined as a steady state flux distribution involving a minimal set of reactions.

	1	2	3	4	5	6
V^1 =	1	0	0	1	1	0
V^2 =	1	0	1	1	0	1
V^3 =	1	1	1	0	0	0

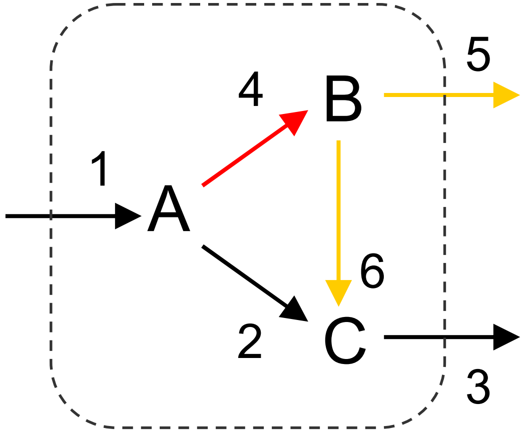


Definitions: Coupled Reactions

- $i \xrightarrow{=0} j$: for all steady state flux vectors v, $v_i=0$ implies $v_j=0$

(directionally coupled)

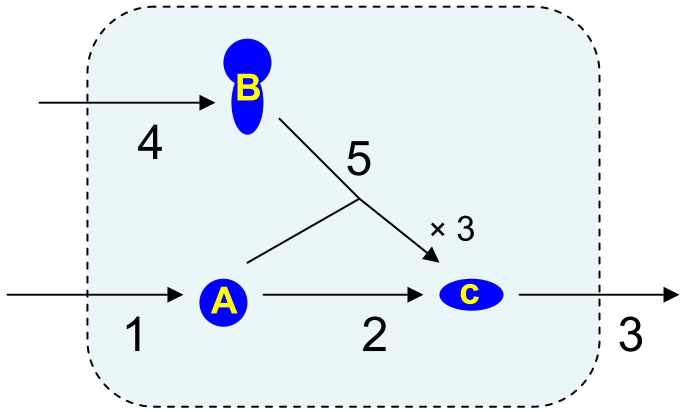
- $4 \xrightarrow{=0} 5$
- $4 \xrightarrow{=0} 6$



Definitions: Coupled Reactions

- $\boldsymbol{i} \overset{=0}{\leftrightarrow} \boldsymbol{j}$: for all steady state flux vectors $\boldsymbol{v}$, $v_i=0$ implies $v_j=0$ and vice versa

(partially coupled)



1	2	3	4	5

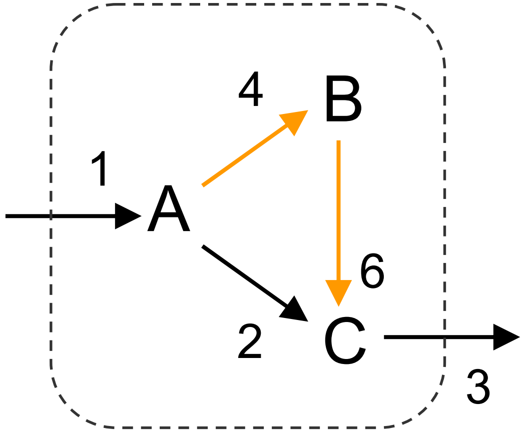
$V^1 = (1,1,1,0,0)$

$V^2 = (1,0,3,1,1)$

Definitions: Coupled Reactions

- $\boldsymbol{i} \Leftrightarrow \boldsymbol{j}$: for all steady state flux vectors $\boldsymbol{v}$, when v_i and v_j are nonzero, $v_i/v_j = \mathrm{const.}$
  (fully coupled)

- 4 ⇔ 6



Definitions: Coupled Reactions

- In metabolic networks, flux coupling is biologically important because functionally related reactions are usually coupled to each other.
- When two fluxes are not coupled, they are “uncoupled”.

Flux coupling and EFMs

Theorem 1

Let N be a metabolic network with flux cone C and set of elementary modes E. For any two reactions i and j, the following are equivalent:

- For all $v \in C$, $v_i = 0$ implies $v_j = 0$.
- For all $e \in E$, $e_i = 0$ implies $e_j = 0$.

Flux coupling and EFMs II

Corollary

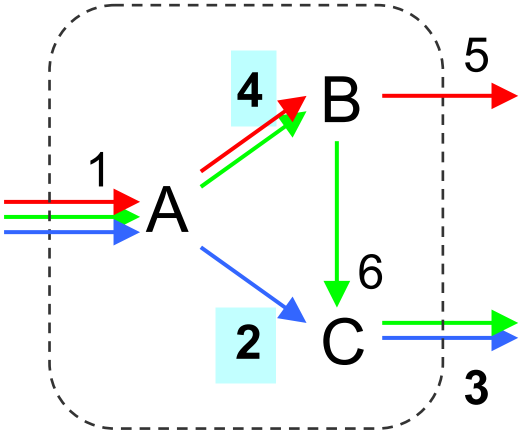
Let i, j be two non-blocked reactions in a metabolic network N with set of elementary modes E.

- i is directionally coupled to j if and only if for all $e \in E$, $e_i = 0$ implies $e_j = 0$.
- i and j are partially coupled if and only if for all $e \in E$, $e_i = 0$ implies $e_j = 0$ and vice versa.
- i and j are fully coupled if and only if there exists a constant $c \neq 0$ such that for all $e \in E$, $e_j = c \cdot e_i$.

Definitions: Uncoupled Reactions

- $\boldsymbol{i} \overset{\text{M.E.}}{\longleftrightarrow} \boldsymbol{j}$: i and j never appear in the same elementary mode (mutually exclusive)

- $2 \overset{\text{M.E.}}{\longleftrightarrow} 4$

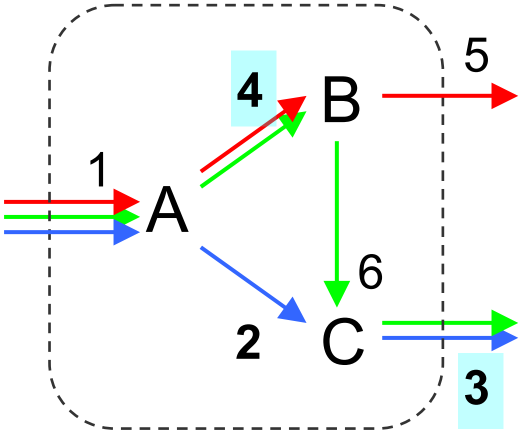


Definitions: Uncoupled Reactions

- $\boldsymbol{i} \overset{\text{S.C.}}{\longleftrightarrow} \boldsymbol{j}$: i and j are uncoupled, but they are not mutually exclusive

  (sometimes coupled)

- $3 \overset{\text{S.C.}}{\longleftrightarrow} 4$

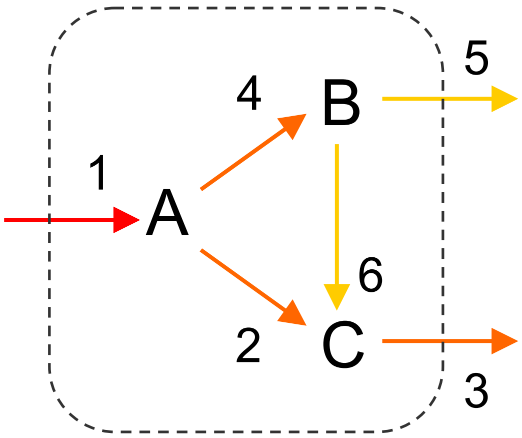


Motivation

- When a metabolic network is “reconstructed”, some reactions might be missing compared to the actual network.
- Do these missing reactions influence the results of flux coupling analysis?

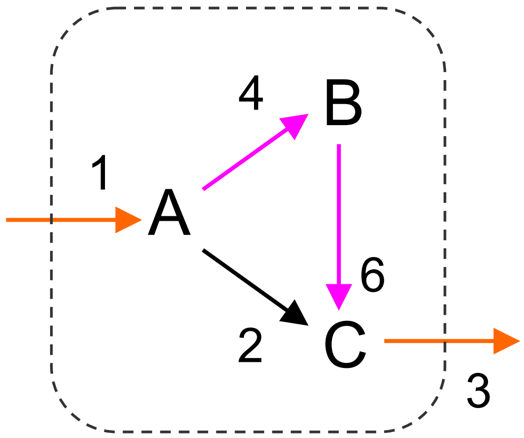
Flux coupling analysis and missing reactions (1)

- $1 \overset{=0}{\longrightarrow} 3$
- $4 \overset{=0}{\longrightarrow} 6$
- $3 \overset{\text{S.C.}}{\longleftrightarrow} 4$



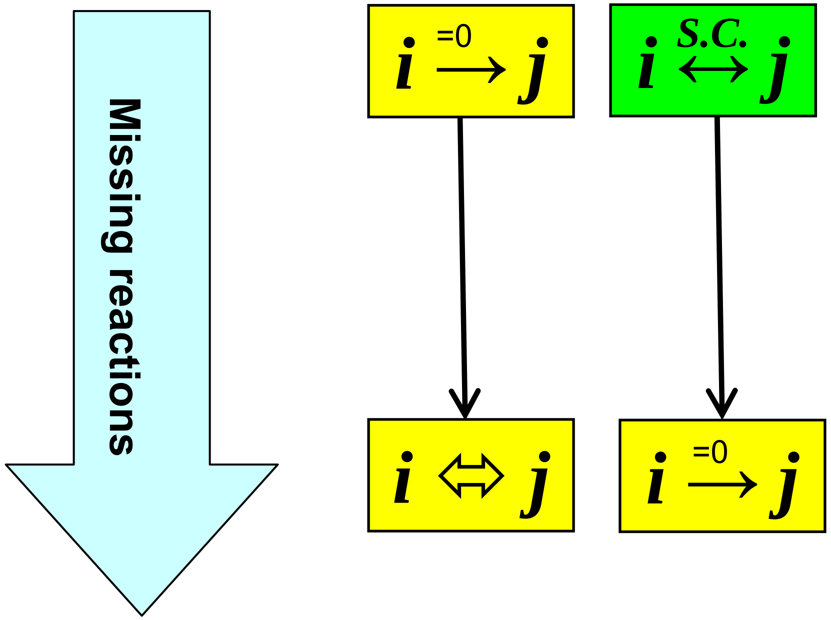
Flux coupling analysis and missing reactions (2)

- $\mathbf{1 \Leftrightarrow 3}$
- $\mathbf{4 \Leftrightarrow 6}$
- $\mathbf{3 \xrightarrow{=0} 4}$



Flux coupling analysis and missing reactions (3)

- Some possible changes in flux coupling due to missing reactions in the network

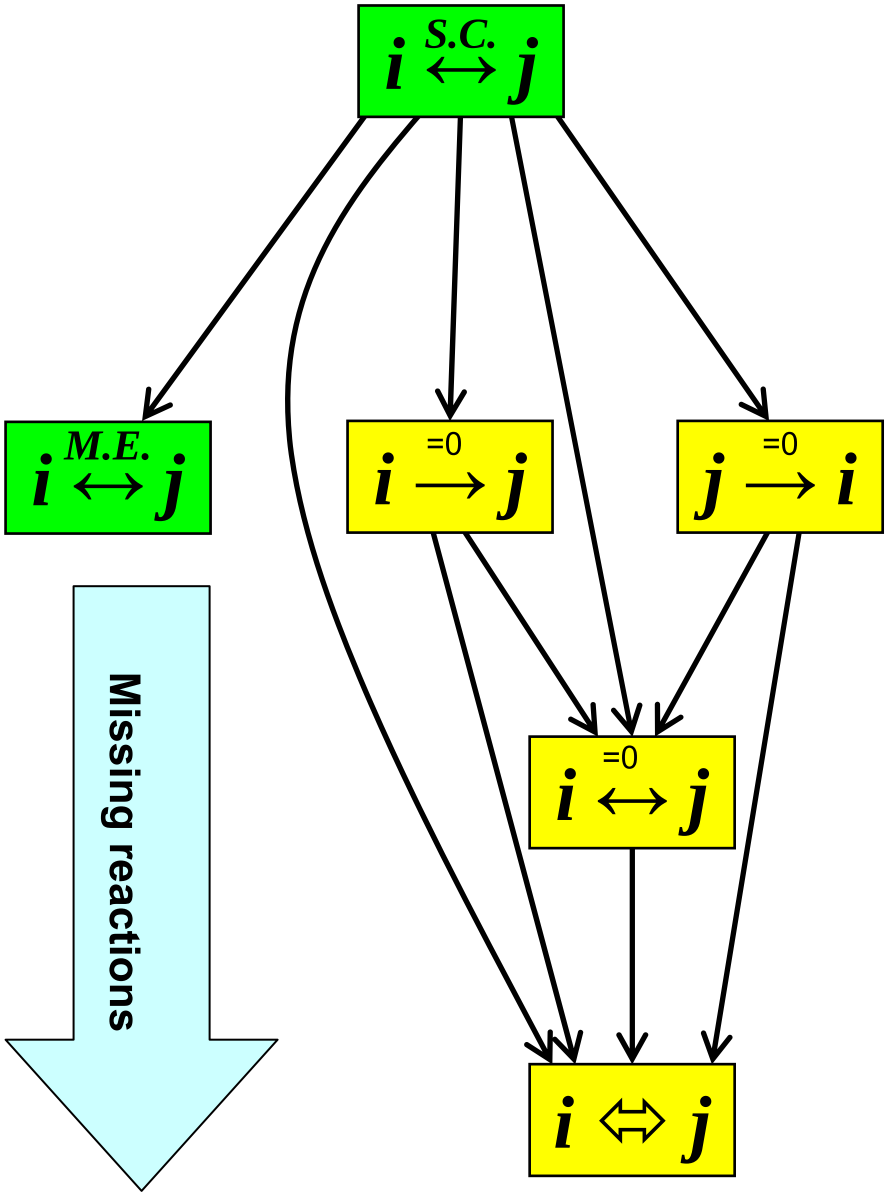


Flux coupling analysis and missing reactions (4)

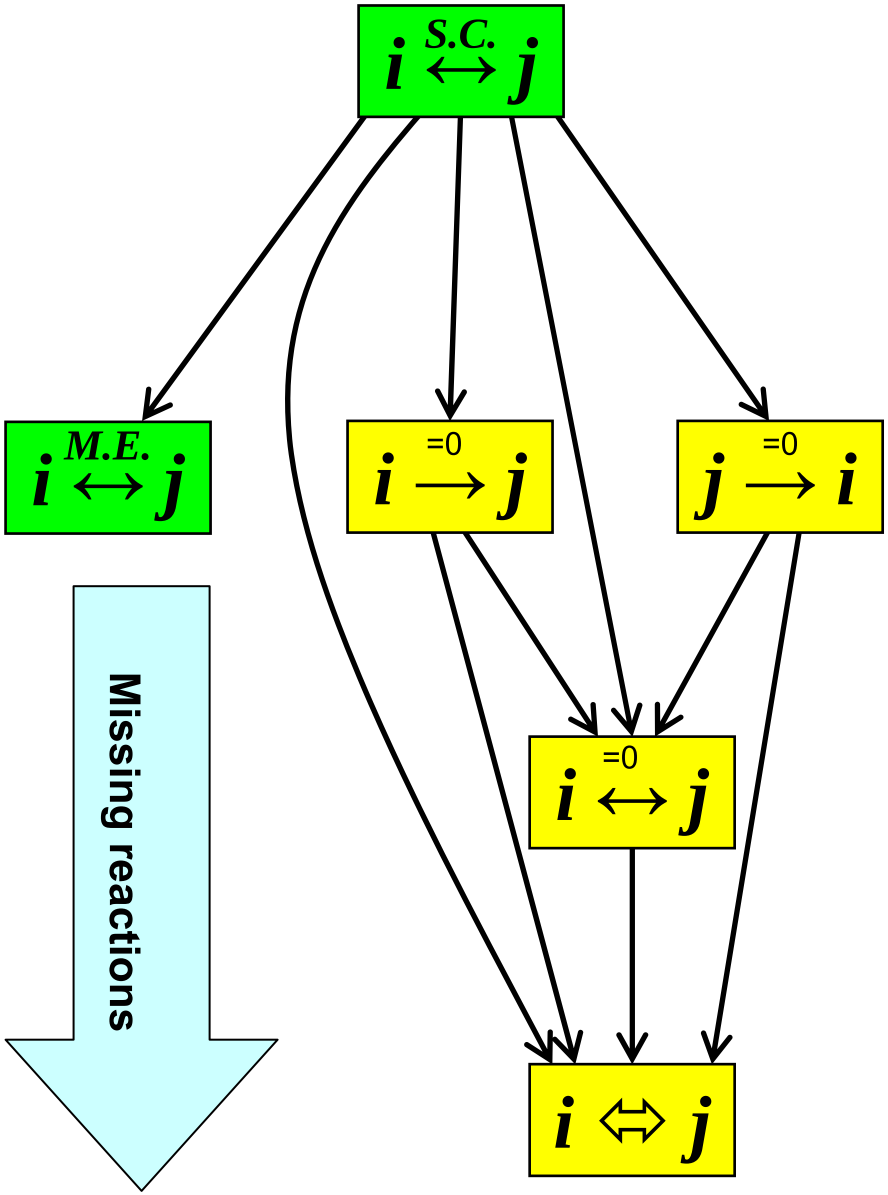
- If some reactions are not included in metabolic networks, flux coupling relations in the smaller network may be different from flux coupling relations in actual (complete networks).

- What relations in complete metabolic networks can convert to other relations in an incomplete network?

- Arrow from R_1 to R_2: having R_1 in actual network, but having R_2 in an incomplete network
- Yellow : Coupling
- Green : Uncoupling



- Uncoupled reaction pairs might be detected as coupled when networks are incomplete.



Conclusion

- Two reactions might be uncoupled in a complete network, but due to missing reactions (lack of knowledge) they might be detected wrongly as coupled.

- If two reactions are uncoupled in an incomplete network, they are certainly uncoupled in the actual (complete) networks.

Test case 1

- Comparing two versions of *E. coli* network
- Computing the number of changes in coupling relations

Changes in flux coupling and uncoupling relations between two E.coli metabolic models.

Change in the coupling type	frequency	Change in the coupling type	frequency
F $\Rightarrow$ P	12	P $\Rightarrow$ F	0
F $\Rightarrow$ D	1169	D $\Rightarrow$ F	0
F $\Rightarrow$ U	763	U $\Rightarrow$ F	0
P $\Rightarrow$ D	0	D $\Rightarrow$ P	0
P $\Rightarrow$ U	0	U $\Rightarrow$ P	0
D $\Rightarrow$ U	241	U $\Rightarrow$ D	2

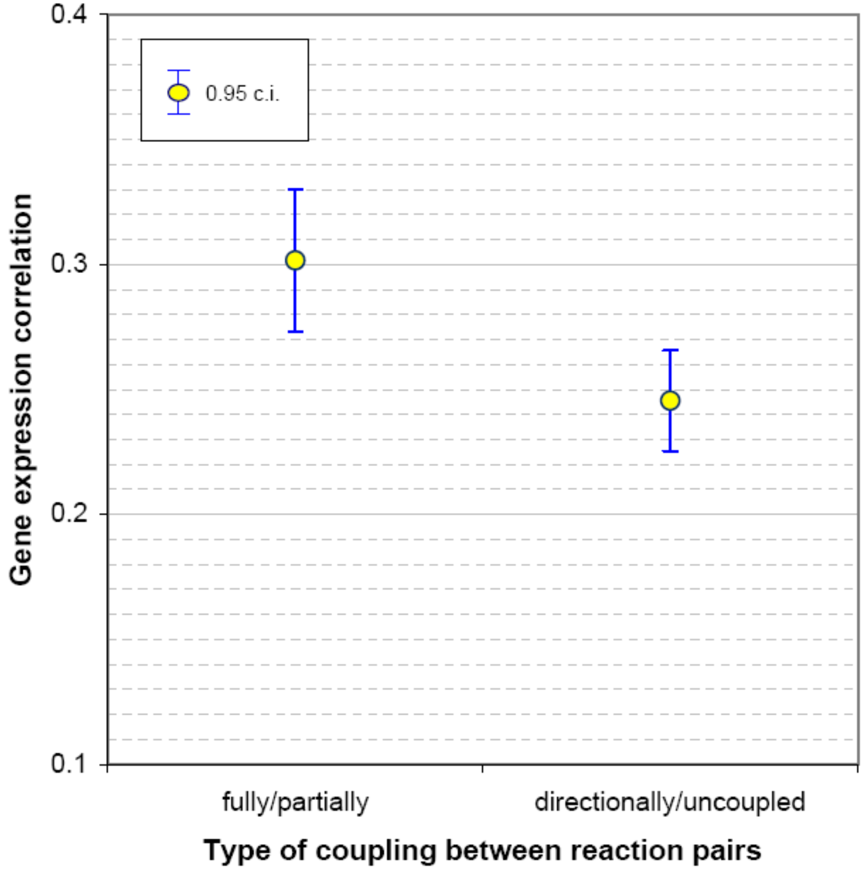
Test case 2

- Correlation between fully-coupled reactions and the co-expression of their corresponding genes (based on an older version of *E. coli* network)
- The analysis was repeated for the new version of *E. coli* network.

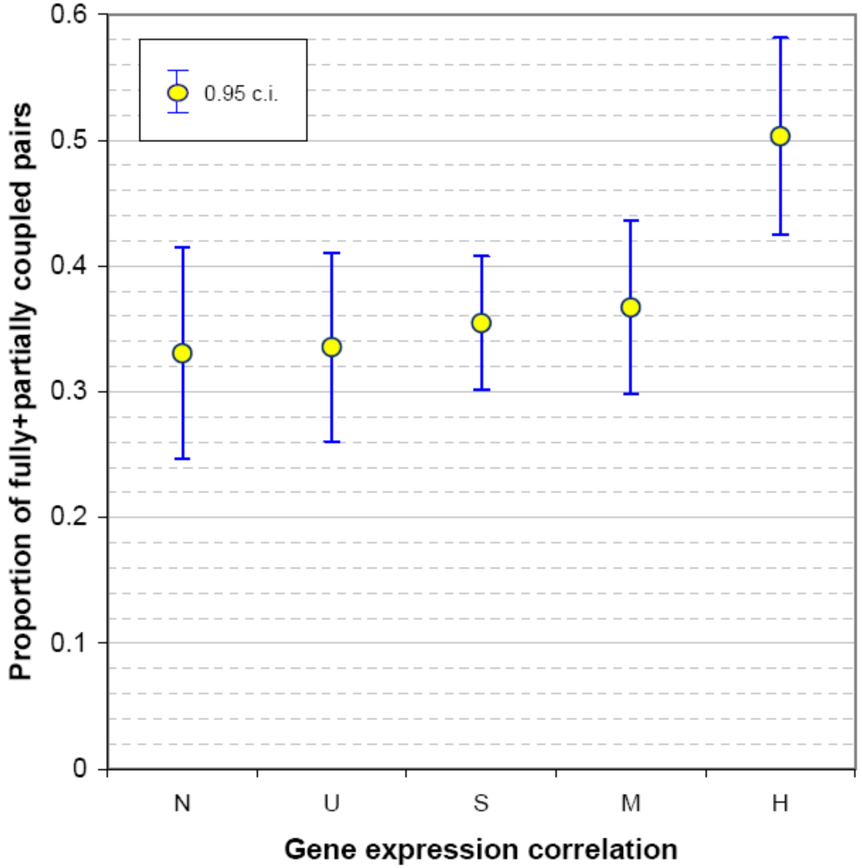
Test case 2

- Coupling relations of the “fully-coupled” reactions in the old network were updated.
- Some “fully-coupled” reactions now become directionally-coupled or even uncoupled.
- The pairs that are still fully coupled in the recent version of *E. coli* network, show higher gene expression correlations.

A


0.4
0.3
0.2
0.1
0.95 c.i.
Gene expression correlation
fully/partially
directionally/uncoupled
Type of coupling between reaction pairs

B


0.6
0.5
0.4
0.3
0.2
0.1
0
0.95 c.i.
Proportion of fully+partially coupled pairs
N
U
S
M
H
Gene expression correlation