

# Modélisation par contraintes des systèmes métaboliques:

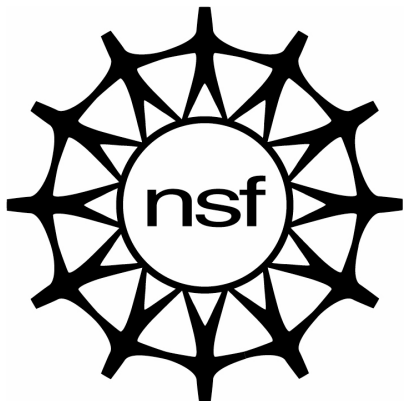
*application in silico, in vivo & in situ*

**Damien Eveillard**

*LINA, Université de Nantes - CNRS*

Rennes, le 29 Novembre 2007

IRISA

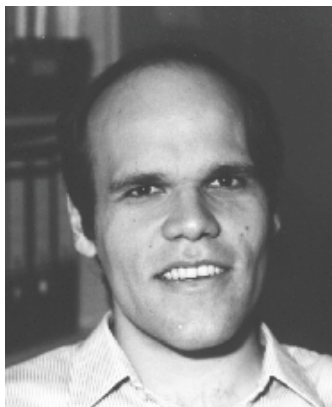
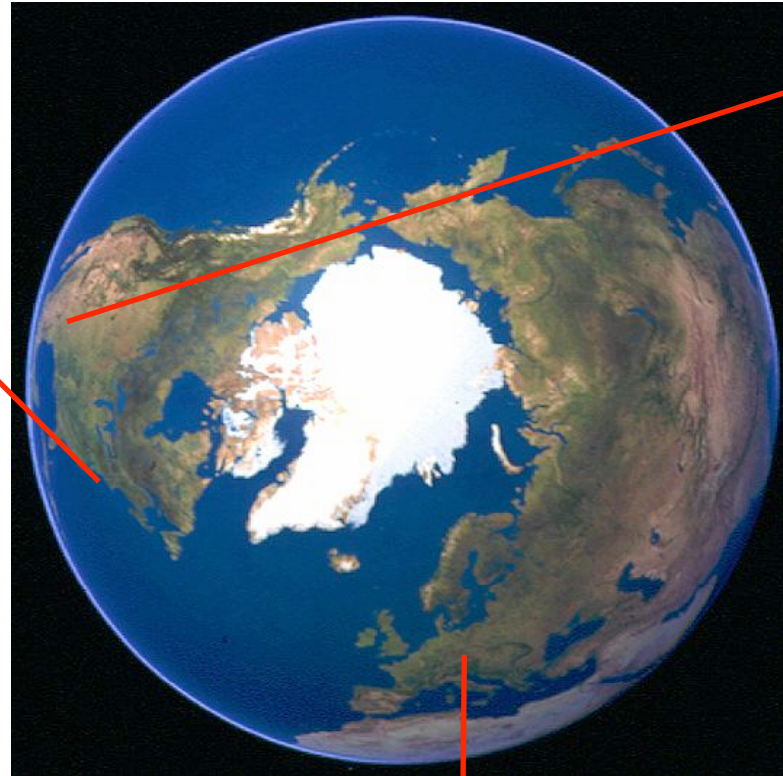




**Bess B. Ward**  
*Princeton University*



**George A. Jackson**  
*Texas A&M University*



**Alexander Bockmayr**  
*Freie Universität Berlin*



**Abdelhalim Larhlimi**  
*Freie Universität Berlin*

Palsson

*Nature Biotechnol. 2000*

« Because biological information is incomplete, it is necessary to take into account the fact that cells are subject to certain constraints that limit their possible behaviors. By imposing these constraints in a model, one can then determine what is possible and what is not, and determine how a cell is likely to behave, but never predict its behavior precisely. »

# Plan de l'exposé

1. Modélisation par contraintes d'un système biologique à l'équilibre

*MMB & RMS*

2. Application sur le réseau métabolique de l'érythrocyte

*Validation & exploitation de modèle*

3. Comprendre les systèmes biologiques non-cultivés

*Vers une nouvelle frontière de "systems biology"*

# Modélisation par contraintes d'un système biologique à l'équilibre

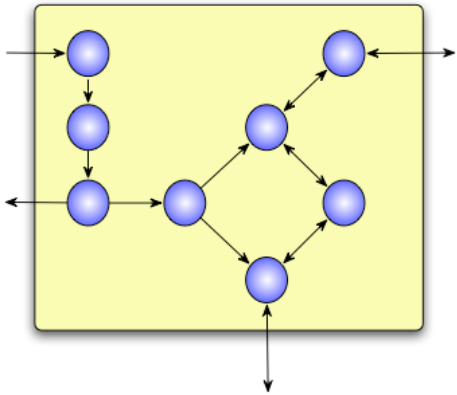
*vers la définition de "Minimal Metabolic Behavior"...*

# Un système de contraintes linéaires

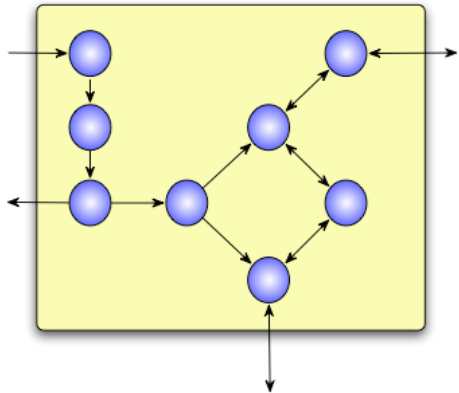
$$\begin{pmatrix} A \rightarrow B \\ B \rightarrow C \\ C \leftrightarrow D \\ \dots \\ T \rightarrow B \end{pmatrix}$$

- Le système des réactions métaboliques est un système de contraintes linéaires
- Application des outils d'optimisation de contraintes

# A l'équilibre de flux...



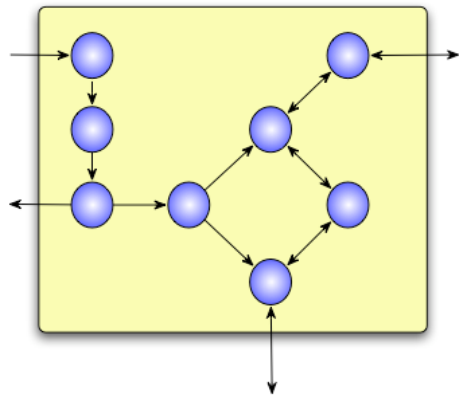
# A l'équilibre de flux...



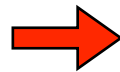
$$S.v = 0$$



# A l'équilibre de flux...



$$S.v = 0$$



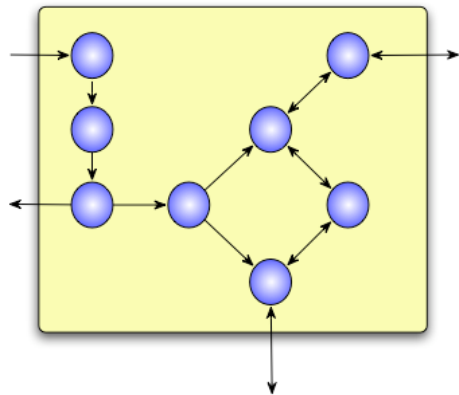
réactions

0	...	0	1
1	...	-1	0
0	...	1	0
...	...	...	...
-1	...	0	-1

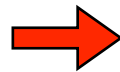
metabolites

matrice  
stoechiométrique

# A l'équilibre de flux...



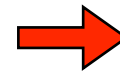
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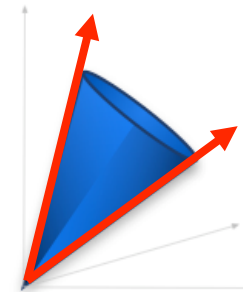
réactions  
metabolites

0	..	0	1
1	..	-1	0
0	..	1	0
..	..	..	..
-1	..	0	-1

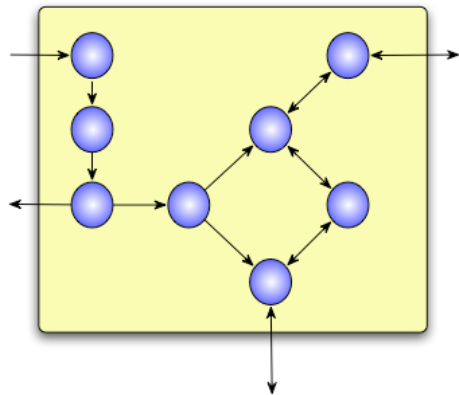
matrice  
stoechiométrique



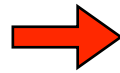
cône de flux



# A l'équilibre de flux...



$$S \cdot v = 0$$

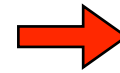


réactions

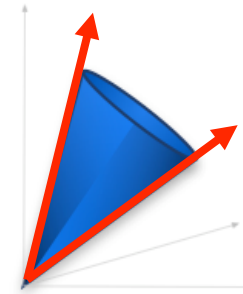
0	..	0	1
1	..	-1	0
0	..	1	0
..	..	..	..
-1	..	0	-1

metabolites

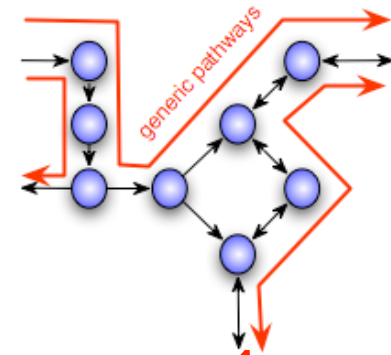
matrice stoechiométrique



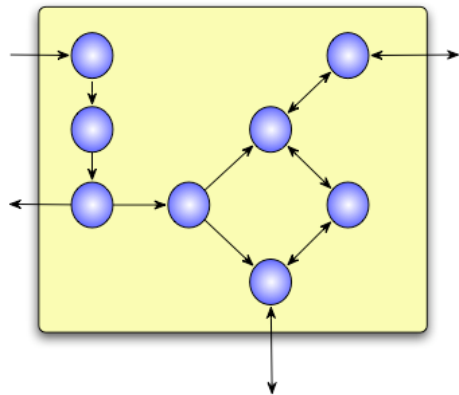
cône de flux



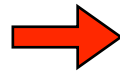
Rayons extrêmes du cône



# A l'équilibre de flux...



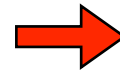
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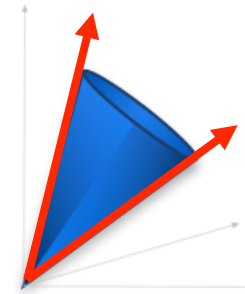
réactions  
metabolites

0	..	0	1
1	..	-1	0
0	..	1	0
..	..	..	..
-1	..	0	-1

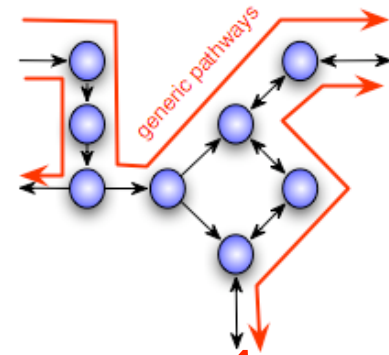
matrice  
stoechiométrique



cône de flux

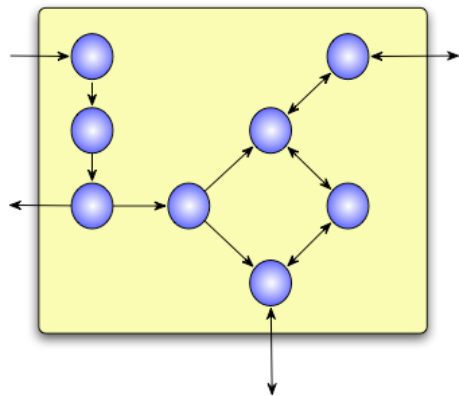


Rayons extrêmes  
du cône

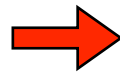


- Mais le cône est *rarement* pointé en biologie

# A l'équilibre de flux...



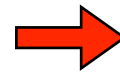
$$S.v = 0$$



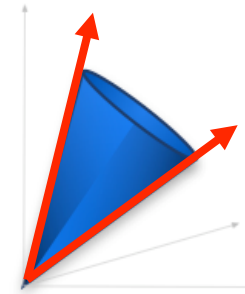
réactions  
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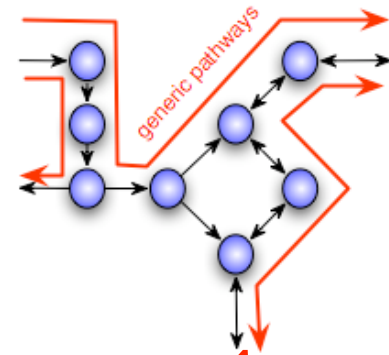
matrice  
stoechiométrique



cône de flux

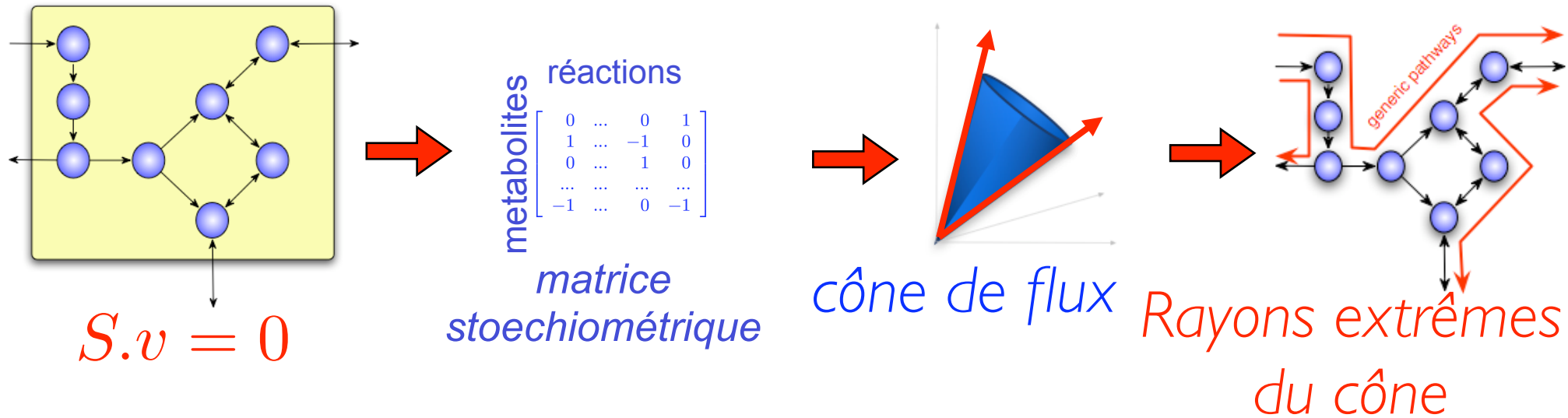


Rayons extrêmes  
du cône



- Mais le cône est *rarement* pointé en biologie
- Calcul complexe et difficile

# A l'équilibre de flux...



- Mais le cône est *rarement* pointé en biologie
- Calcul complexe et difficile
- Différentes approches pour représenter le cône de flux

# Voies extrêmes vs. Modes élémentaires

- Modes élémentaires (EFMs) :  
pas de décomposition  
😊 **Biologie** ☹️ **Calculs**
- Voies extrêmes (EPs) :  
décomposition des réactions  
😊 **Calculs** ☹️ **Biologie**

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Les 2 approches se basent sur les vecteurs générateurs du cône



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Les 2 approches se basent sur les vecteurs générateurs du cône

Différents algorithmes (*FluxAnalyzer, CNA...*)

# Minimal Metabolic Behaviors and Reversible Metabolic Space

- Travail sur un **cône non pointé**
- **Larhlimi & Bockmayr, 2006** proposent une ***description externe***
- Les contraintes sont des inégalités

$$v_i \geq 0, i \in Irr$$

- Recherche des faces minimales propres :  
*Adaptation de l'algorithme de Fukuda (cdd)*

# Minimal Metabolic Behaviors and Reversible Metabolic Space (2)

- Chaque face est définie par des réactions irréversibles

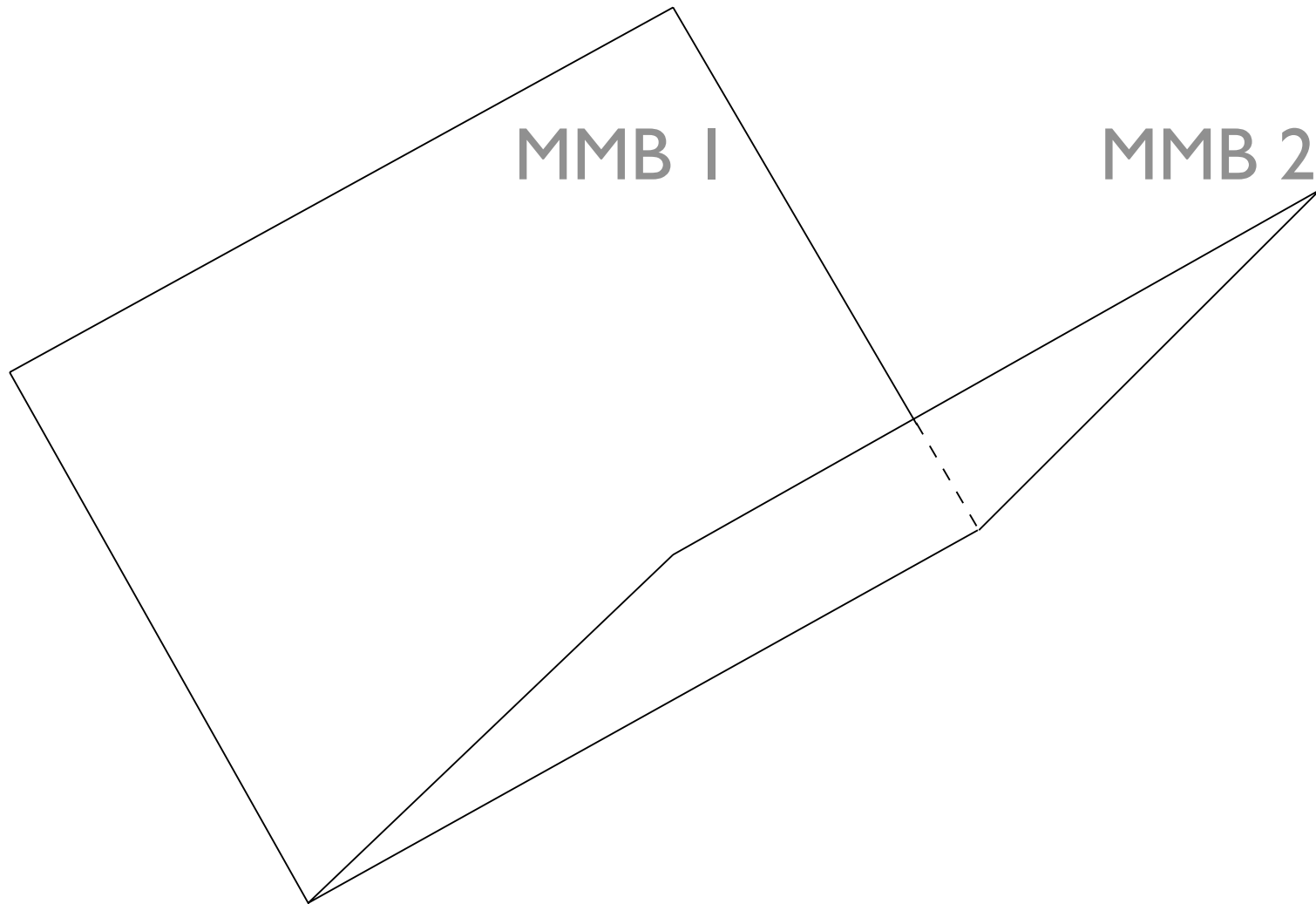
➡ face minimal = comportement métabolique minimal (MMB)

- La base du cône est un espace linéaire

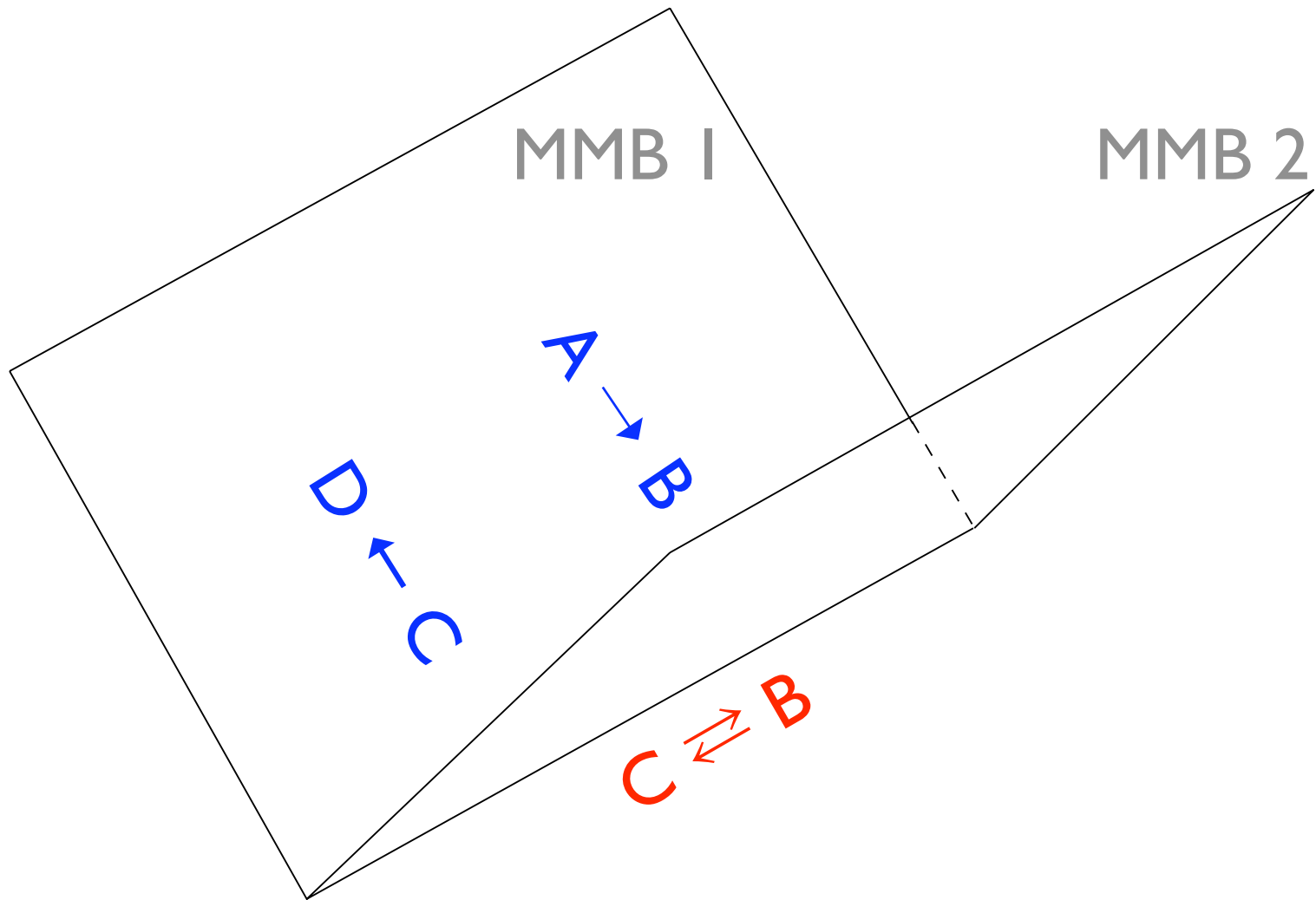
$$A \leftrightarrow B \quad \text{lin.space}(C) \neq \{0\}$$

➡ définie par des réactions réversibles = espace métabolique réversible (RMS)

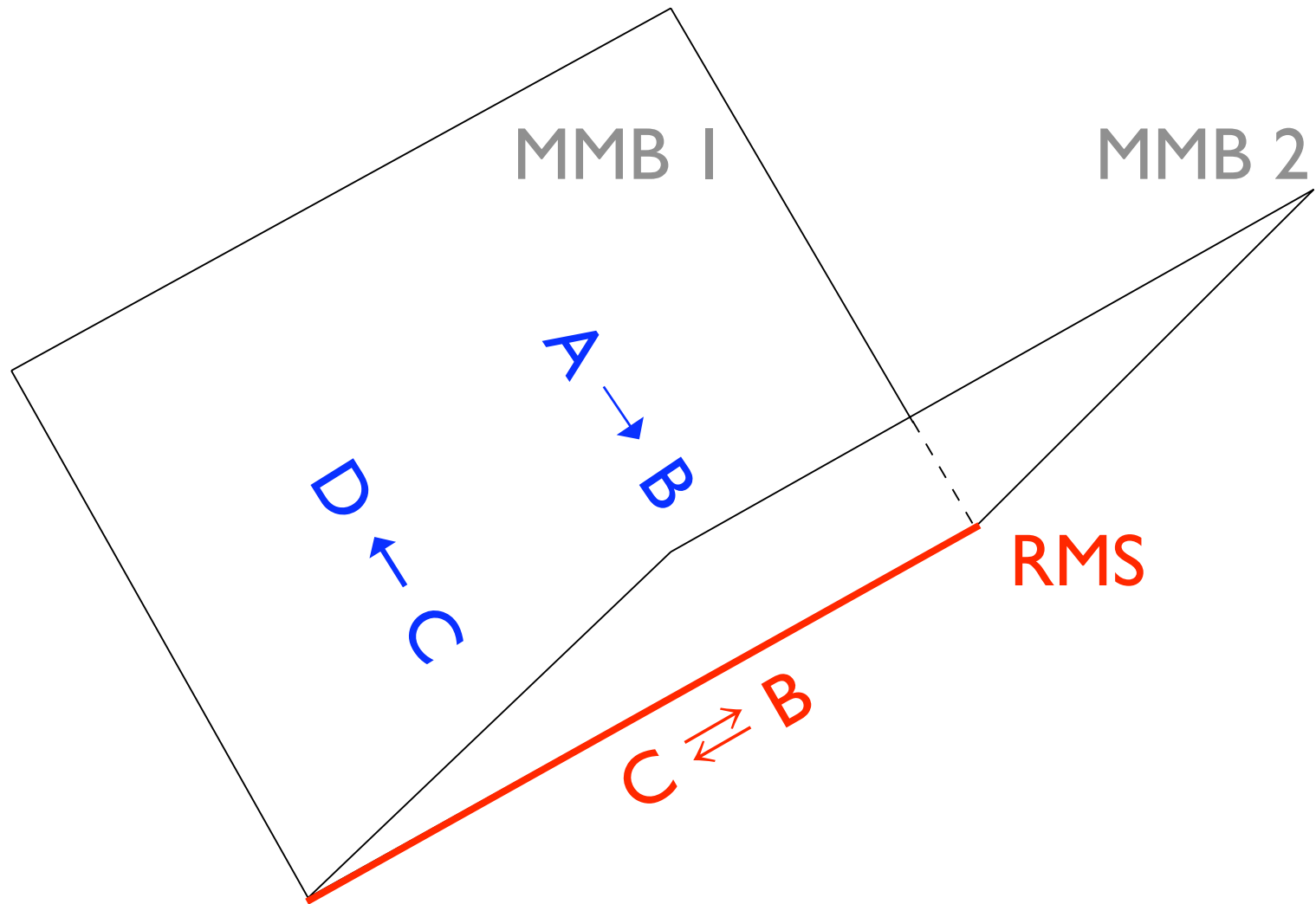
# Un cône non-pointé



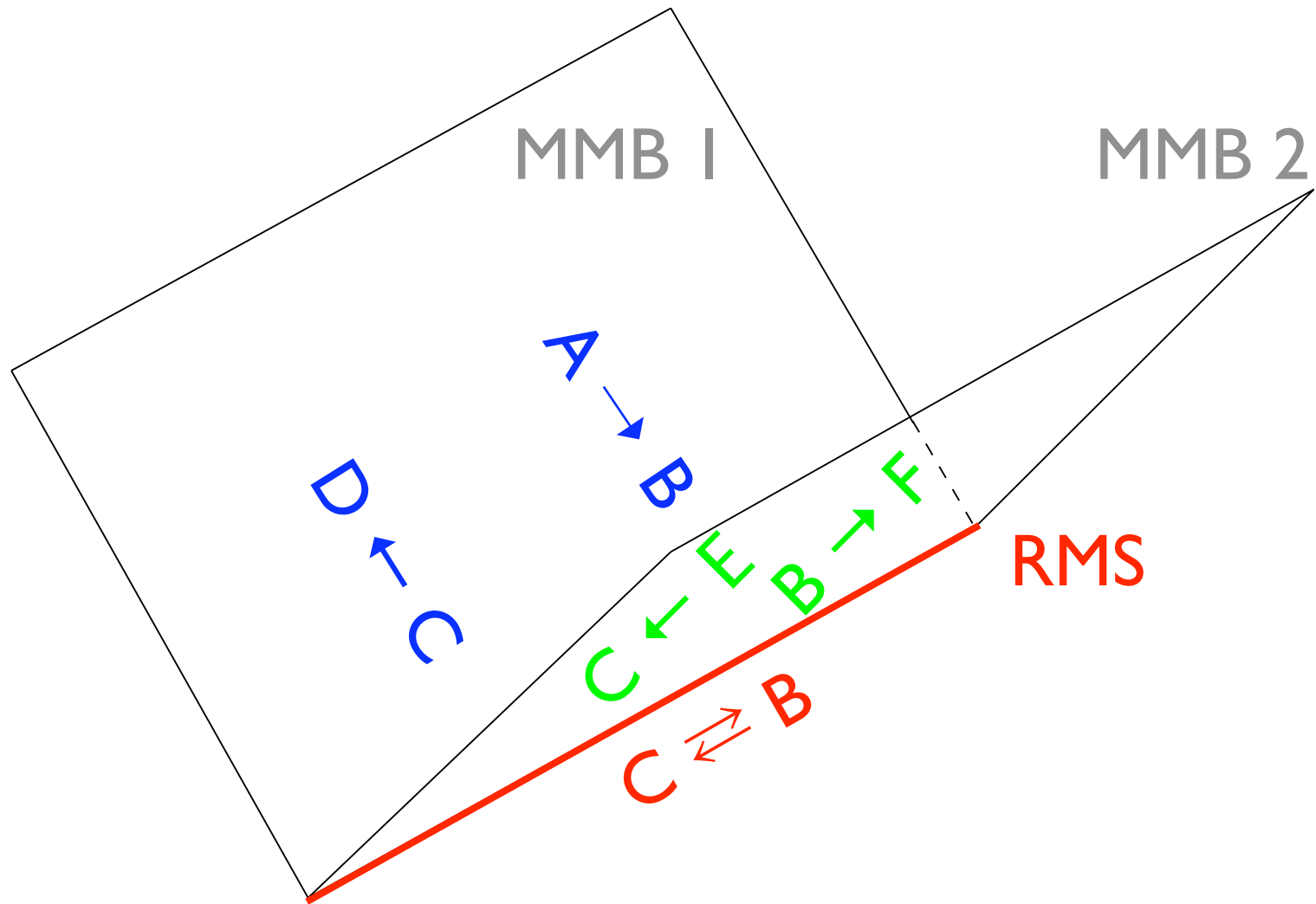
# Un cône non-pointé



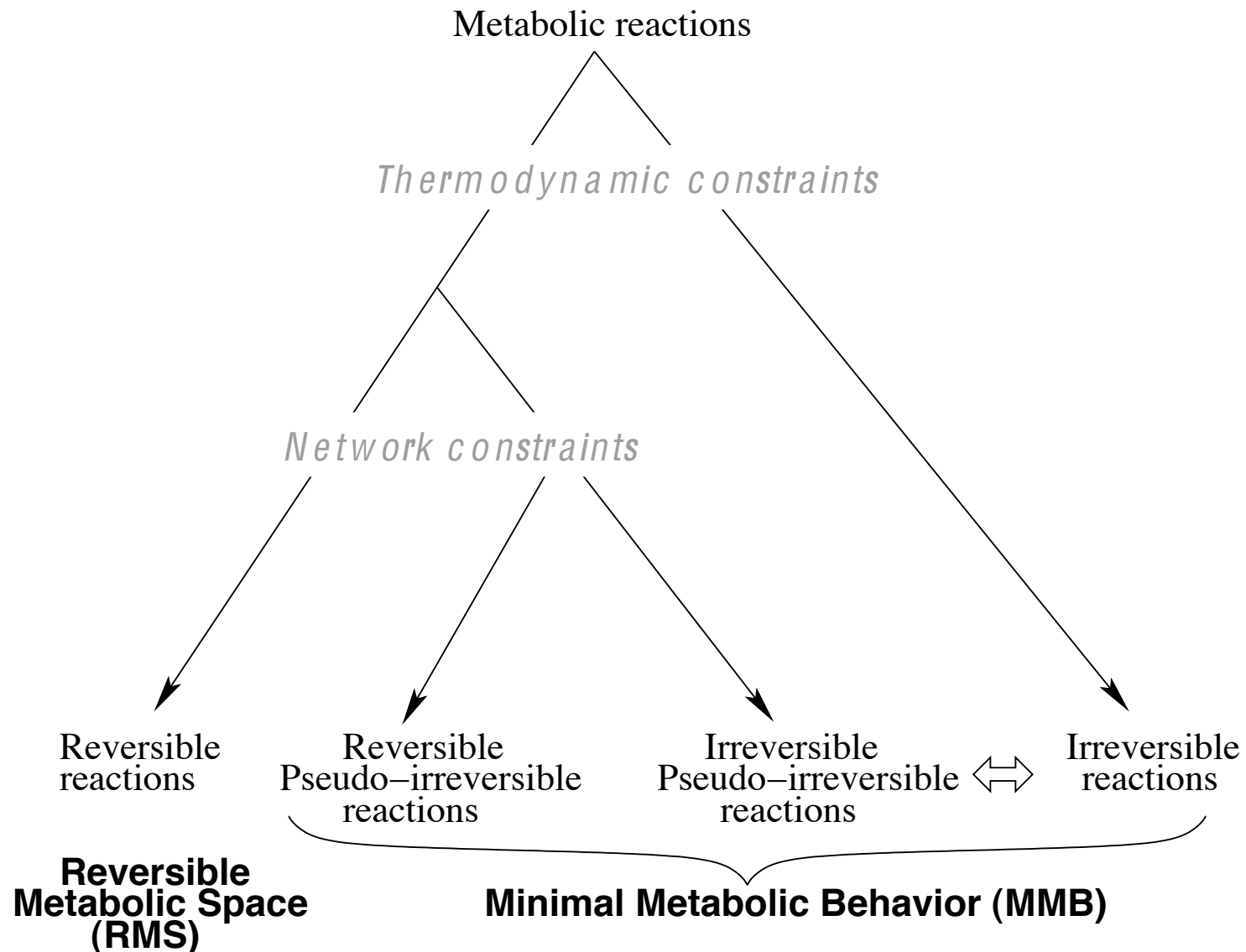
# Un cône non-pointé



# Un cône non-pointé

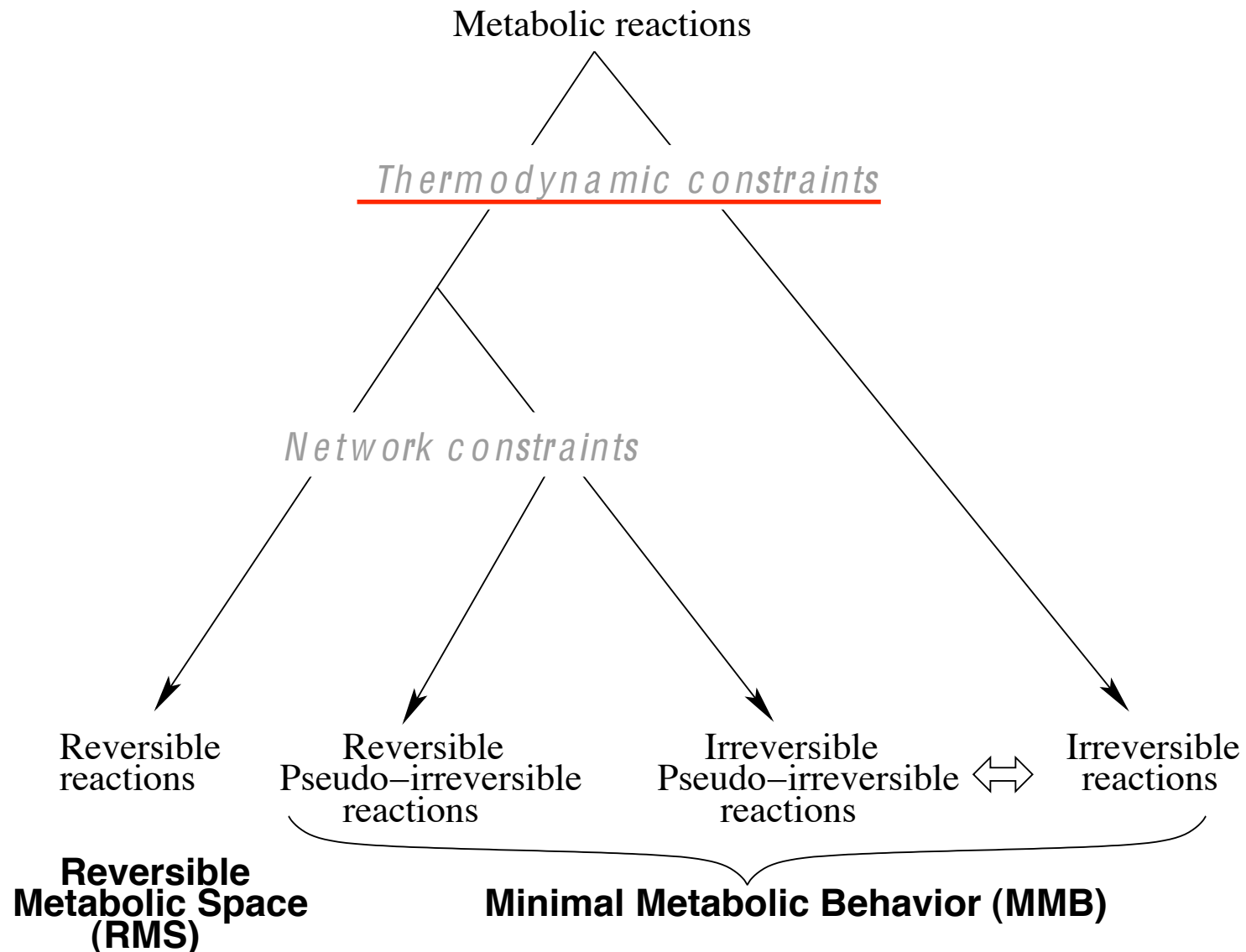


# Les contraintes métaboliques

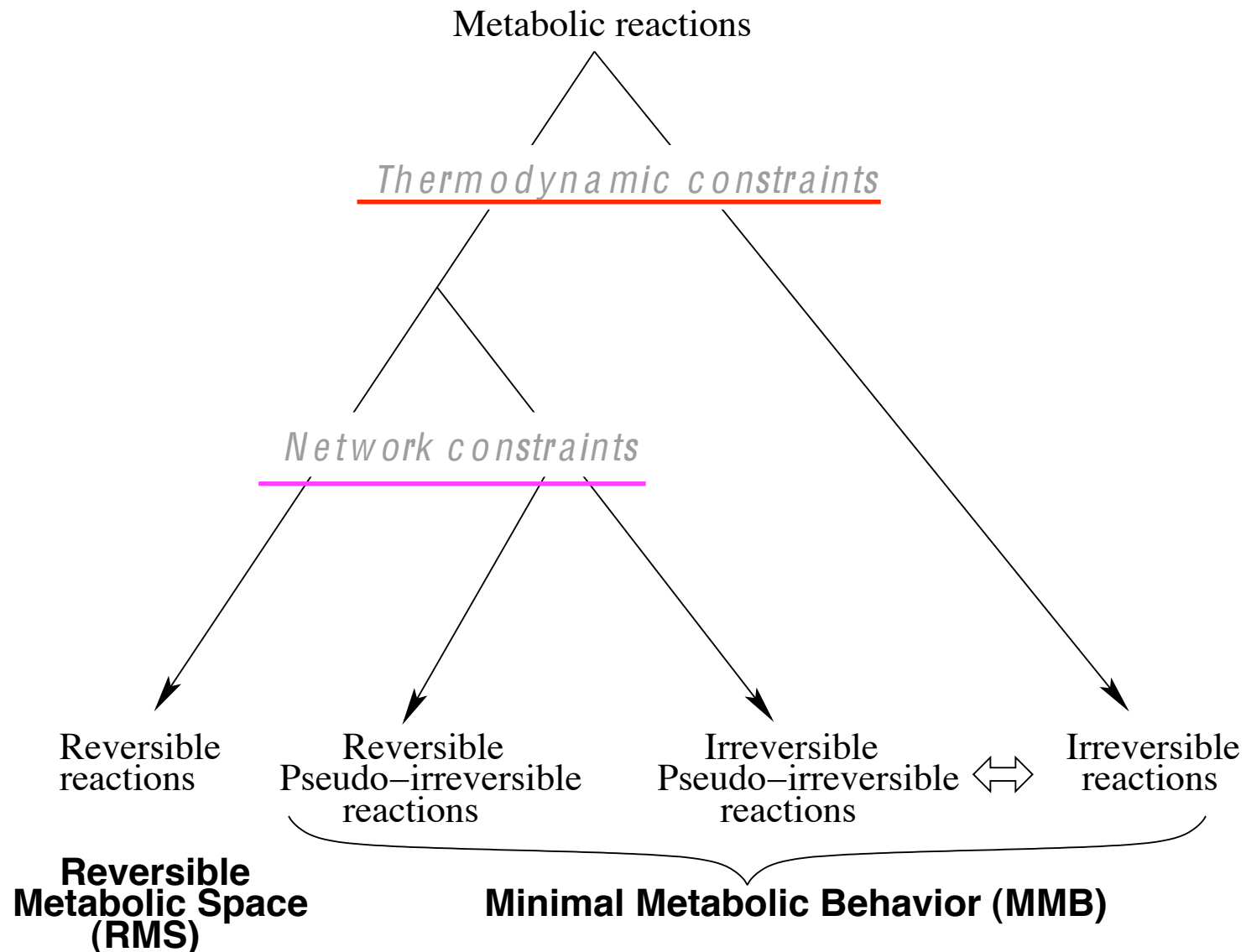




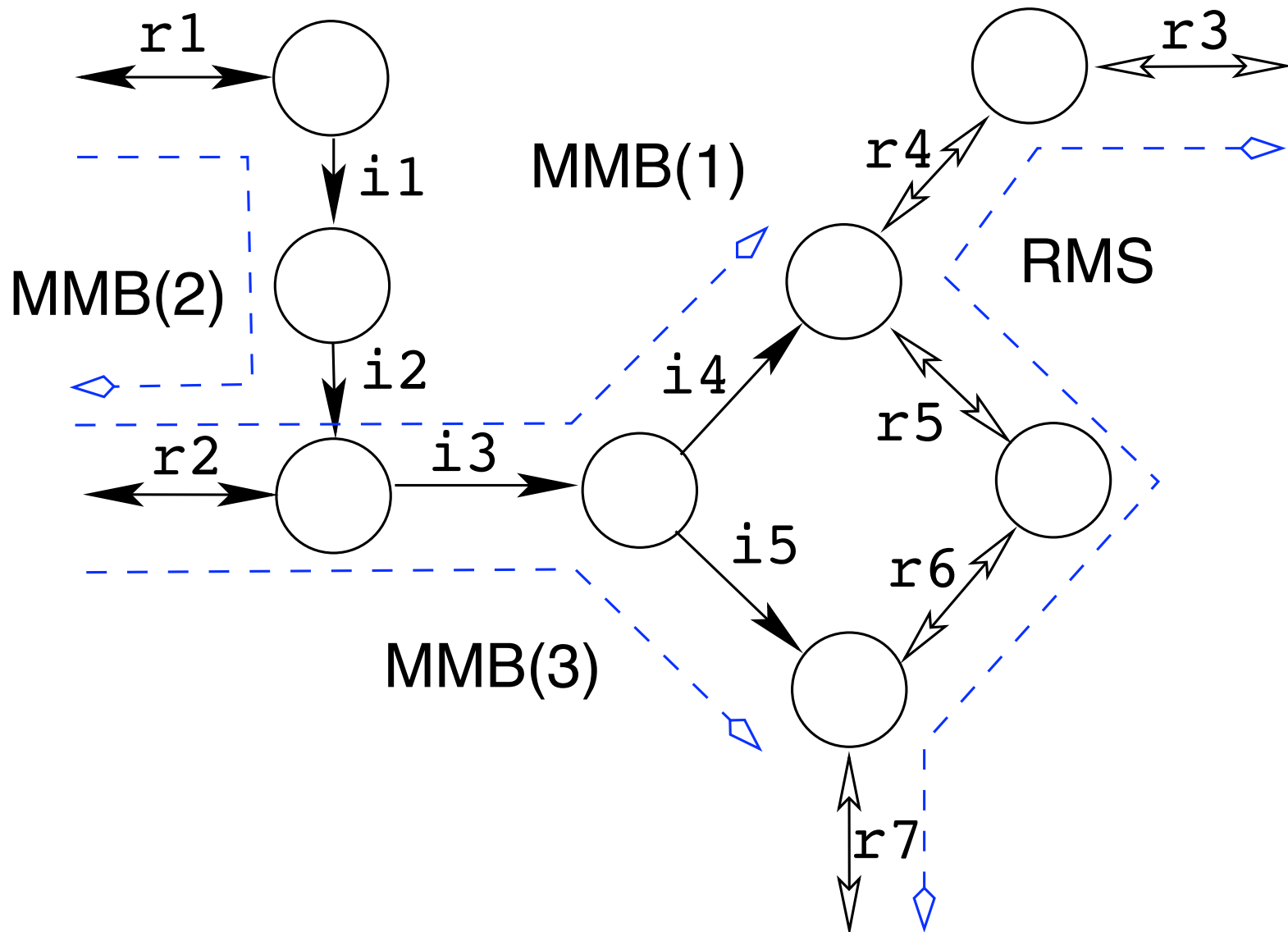
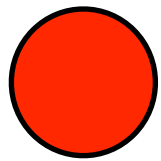
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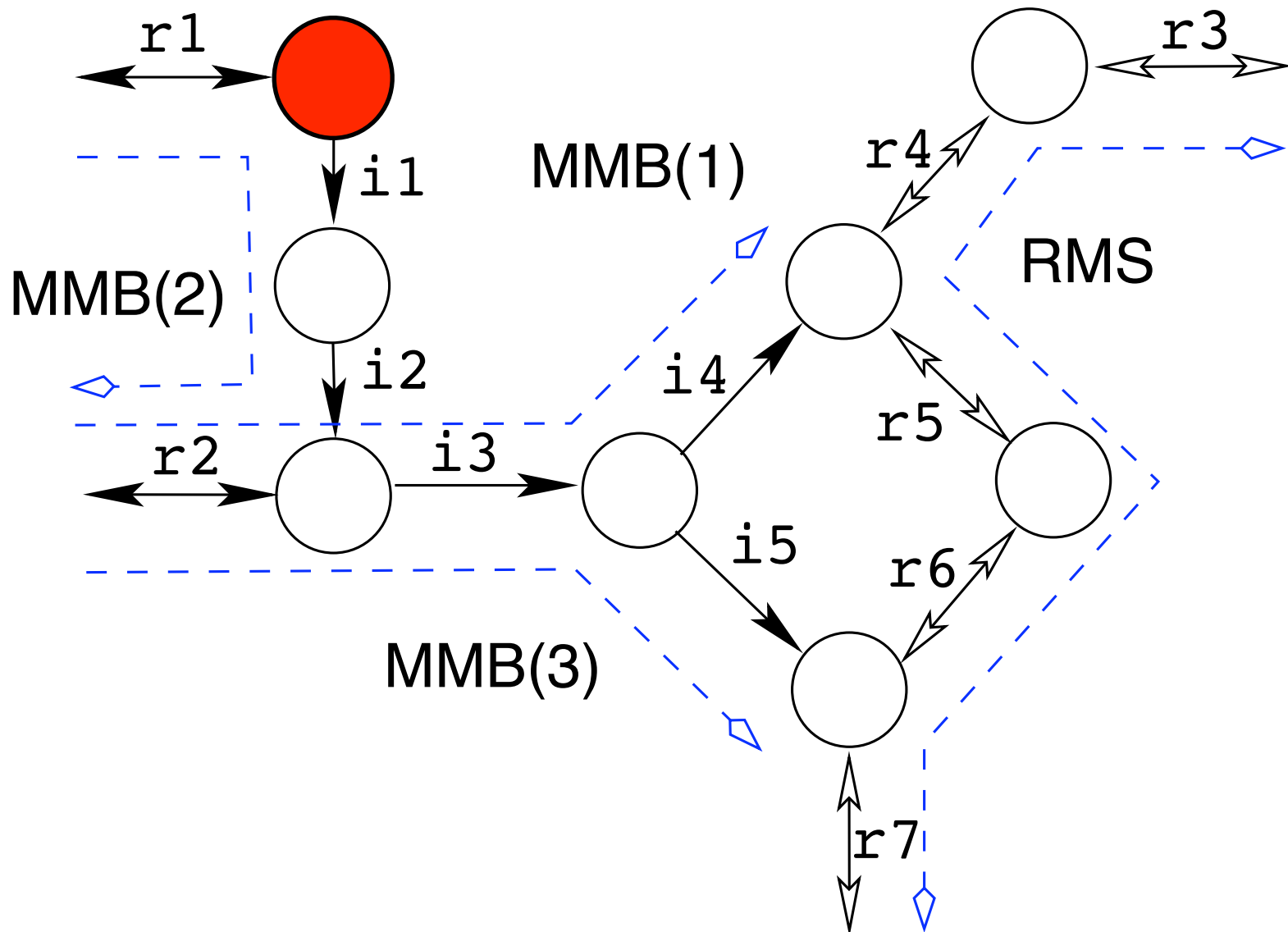
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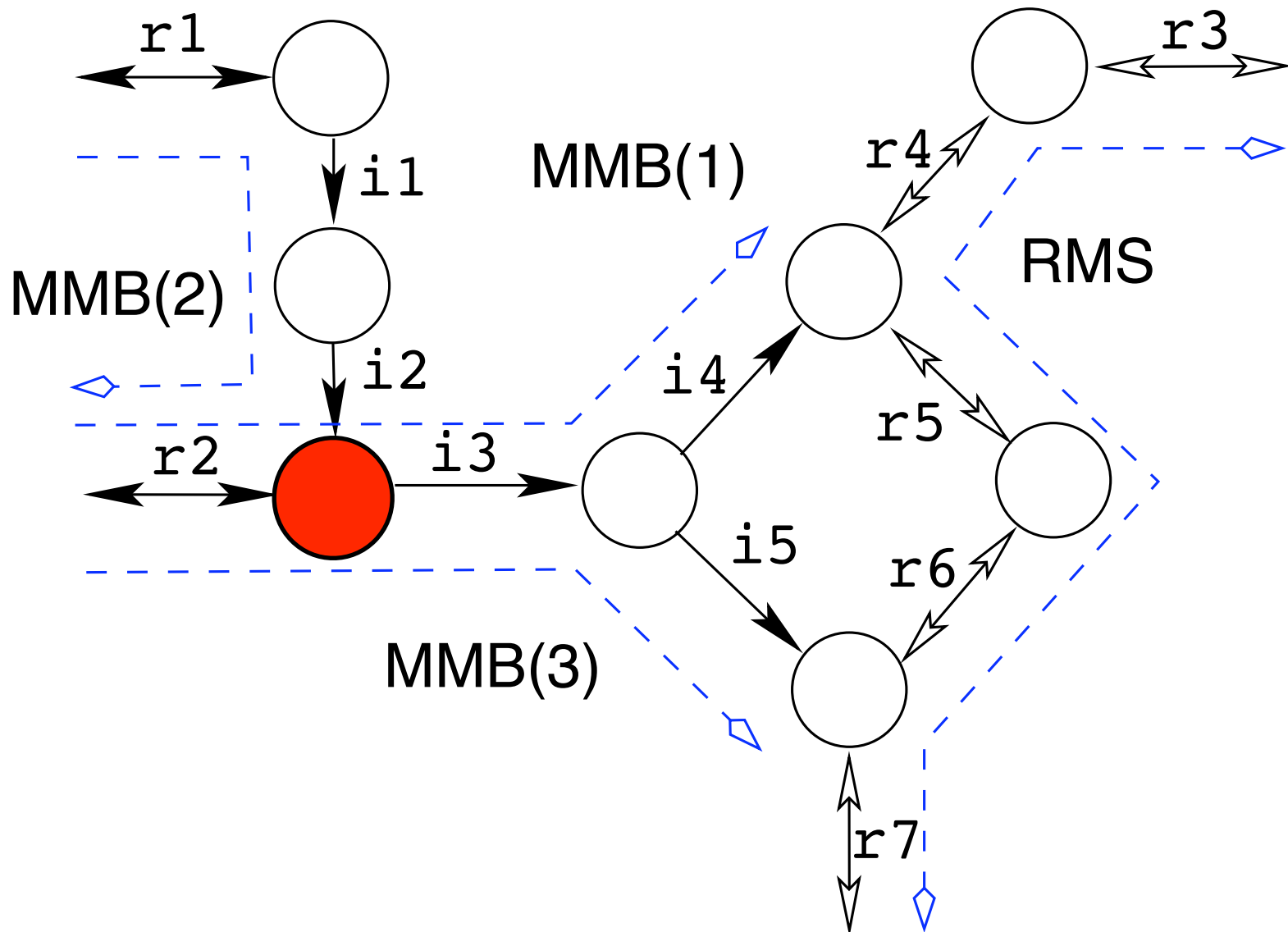
# Exemple de décomposition



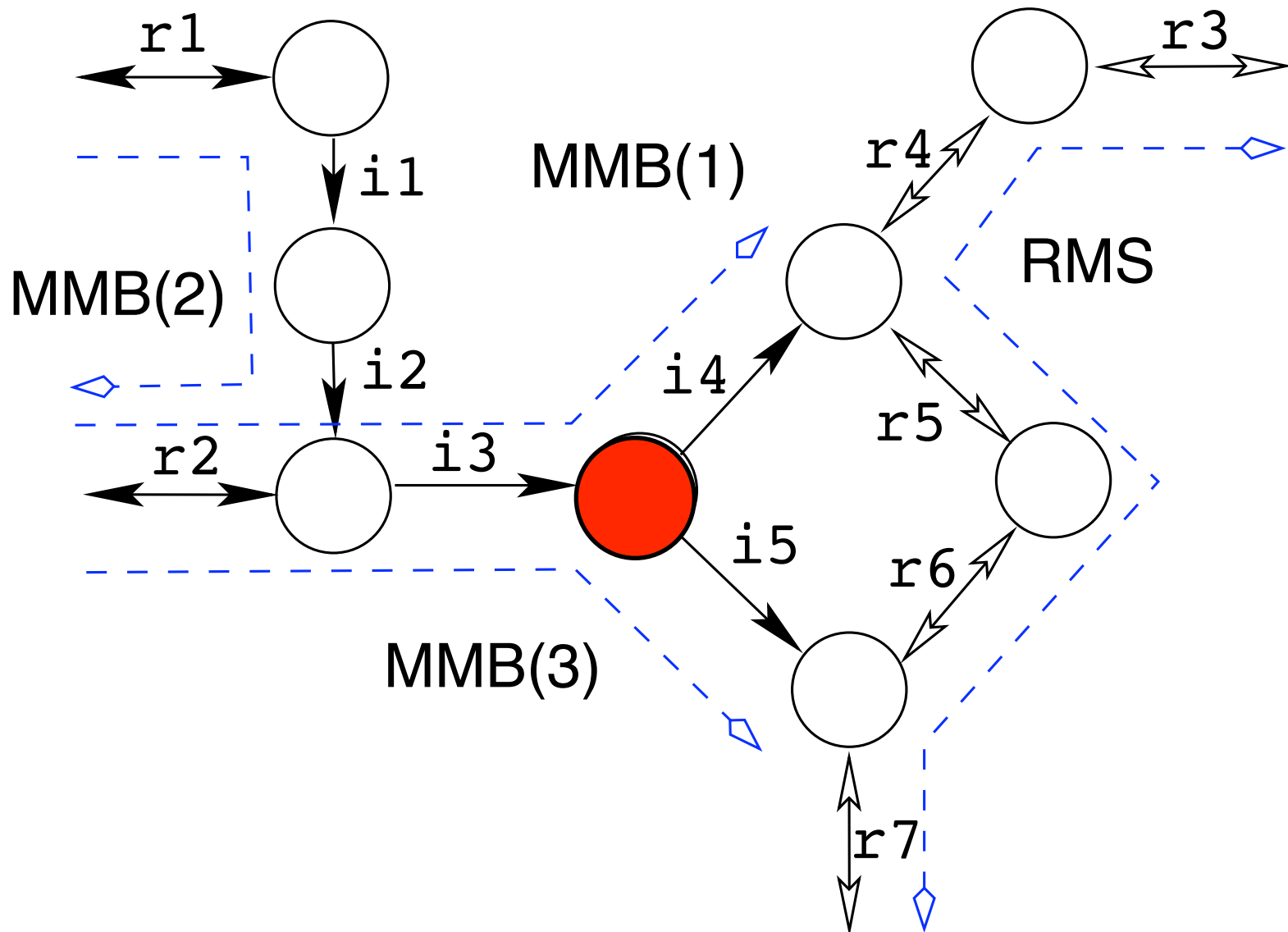
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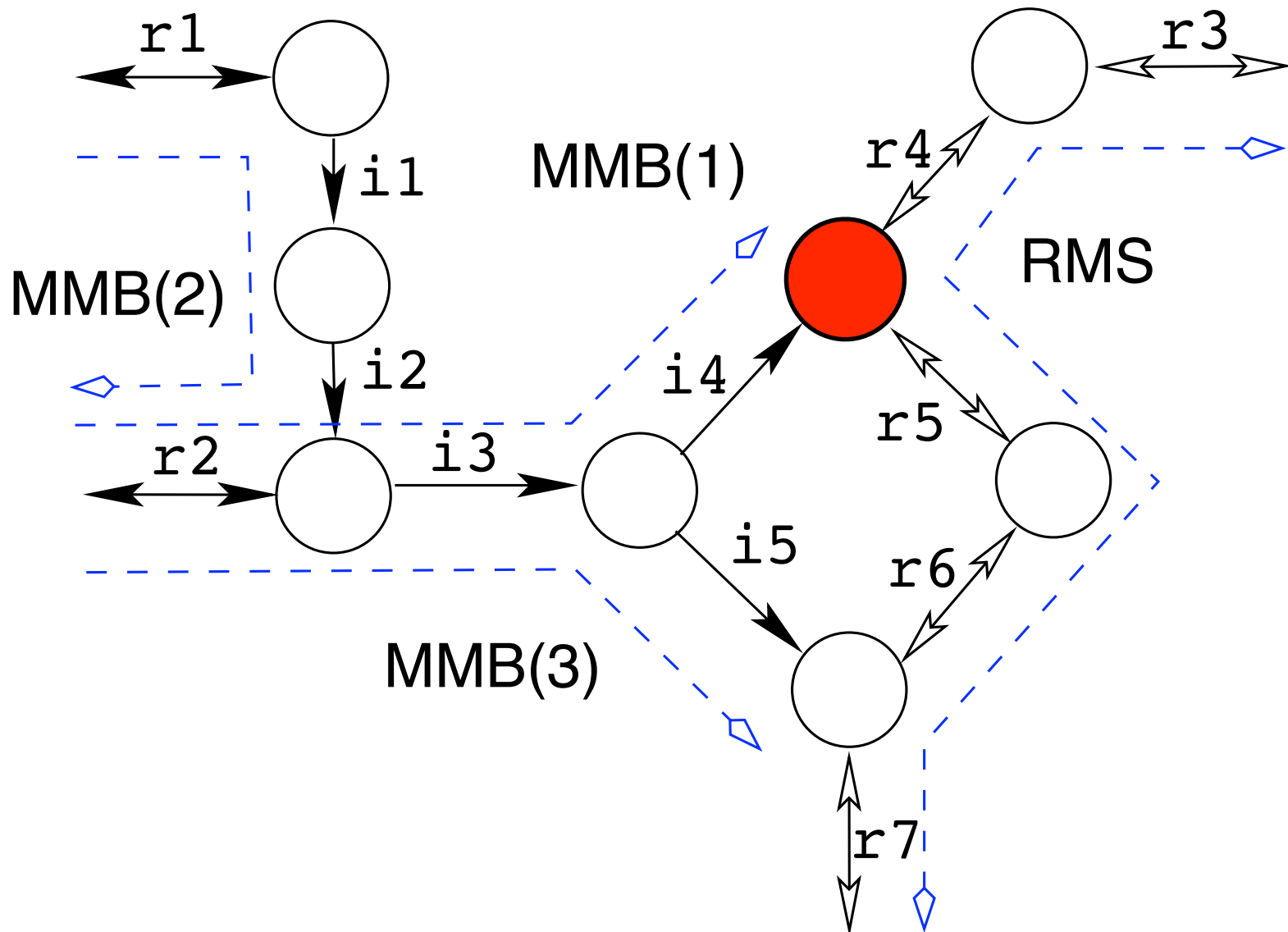
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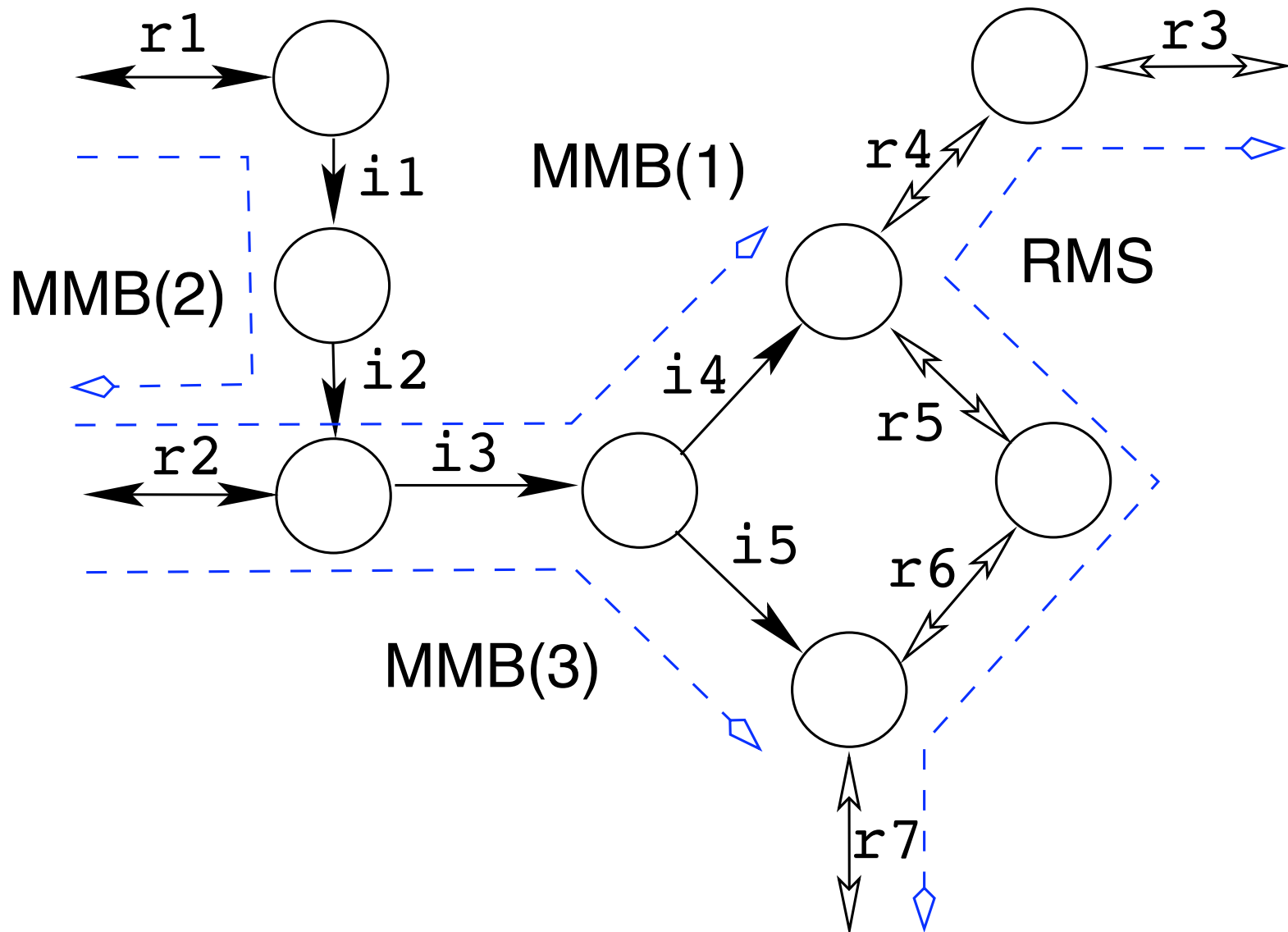
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# Exemple de décomposition

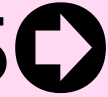


# Exemple de décomposition

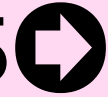




# Application sur KEGG

	Met	RR	RI	MMBs		EFMs	EPs
				#	RMS		
Glycolyse	32	29	18	17	13	19464	1745
TCA <i>cycle citrate</i>	22	25	4	5	12	3870	1588
M. azote	41	14	53	45	9	601	612
Erythrocyte	40	70	50	18	3	48	55  39

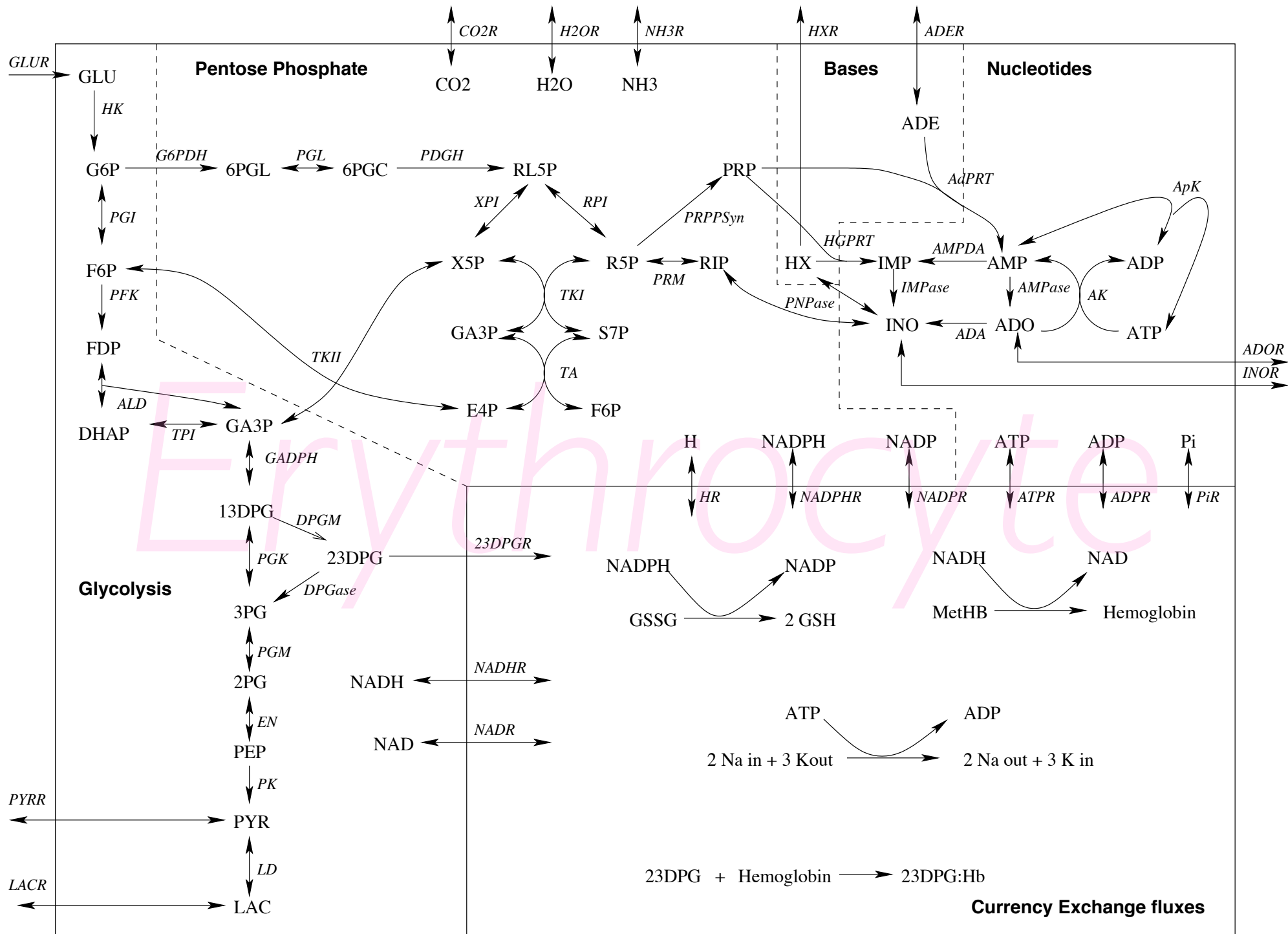
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*Est-ce biologiquement pertinent ?*

# Application sur le réseau métabolique de l'érythrocyte

*Validation & exploitation de modèle...*



# Voies extrêmes vs. Modes élémentaires

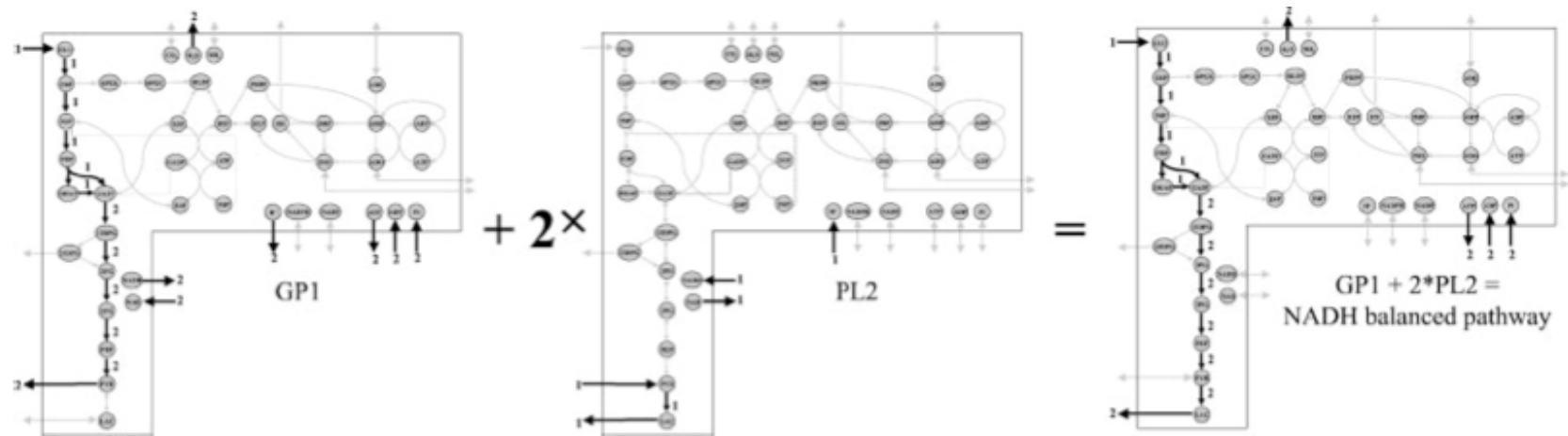
808

Biophysical Journal Volume 83 August 2002 808-818

## Extreme Pathway Analysis of Human Red Blood Cell Metabolism

Sharon J. Wiback and Bernhard O. Palsson

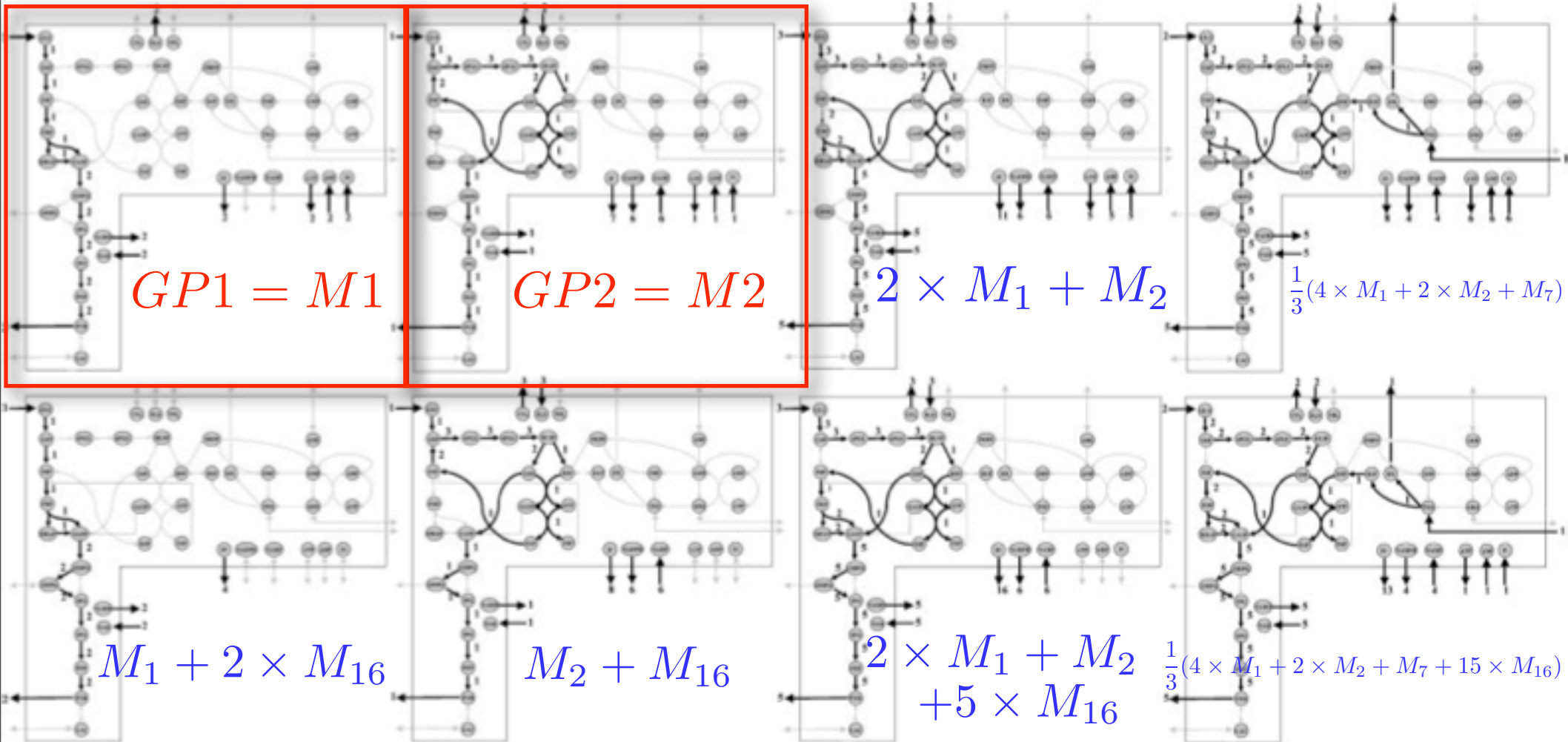
Department of Bioengineering, University of California, San Diego, La Jolla, California 92093 USA



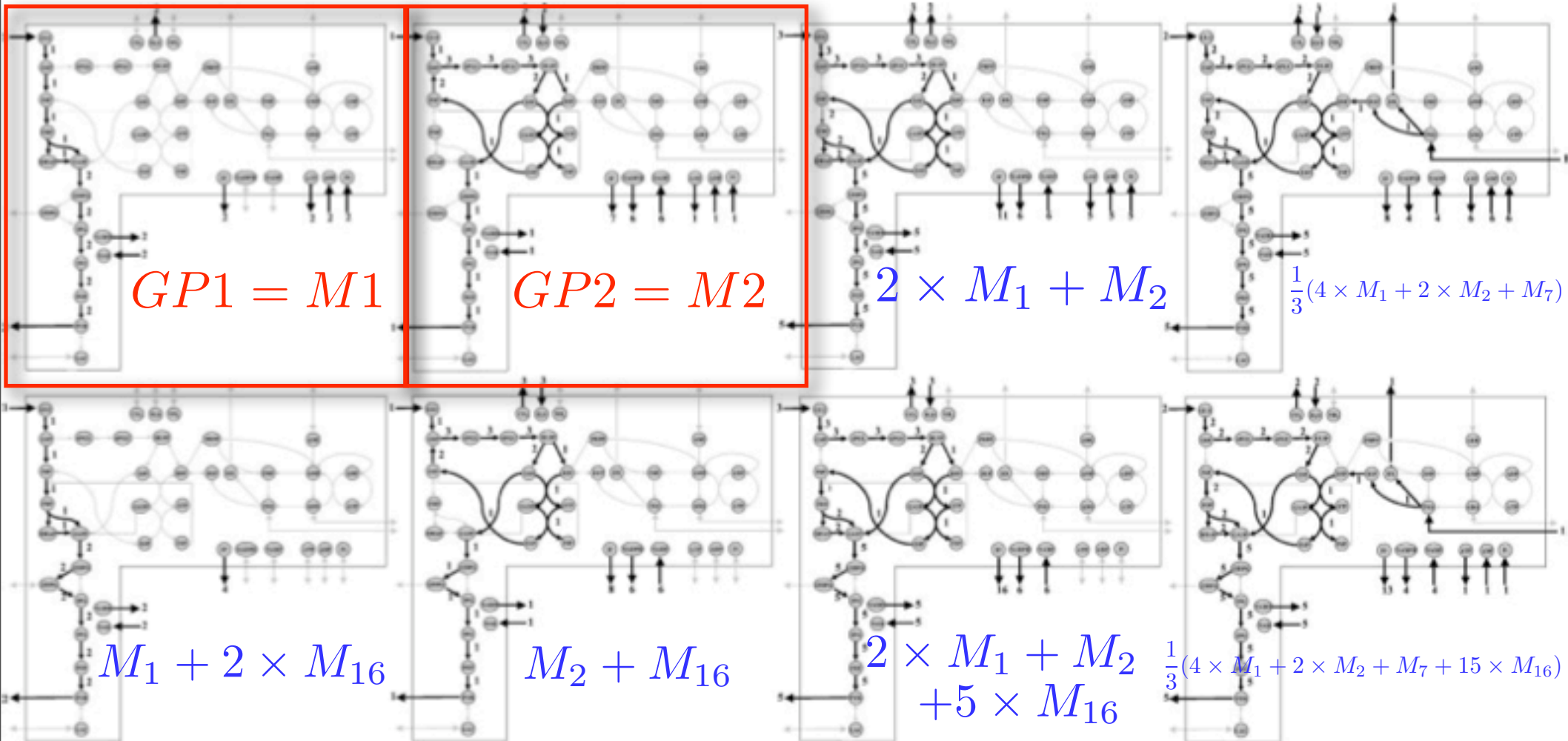
$$GP1 + 2 \times (PL2) = NADH \text{ mode}$$

EfMs sont des combinaisons linéaires de EPs

# Comparaison des pathways



# Comparaison des pathways



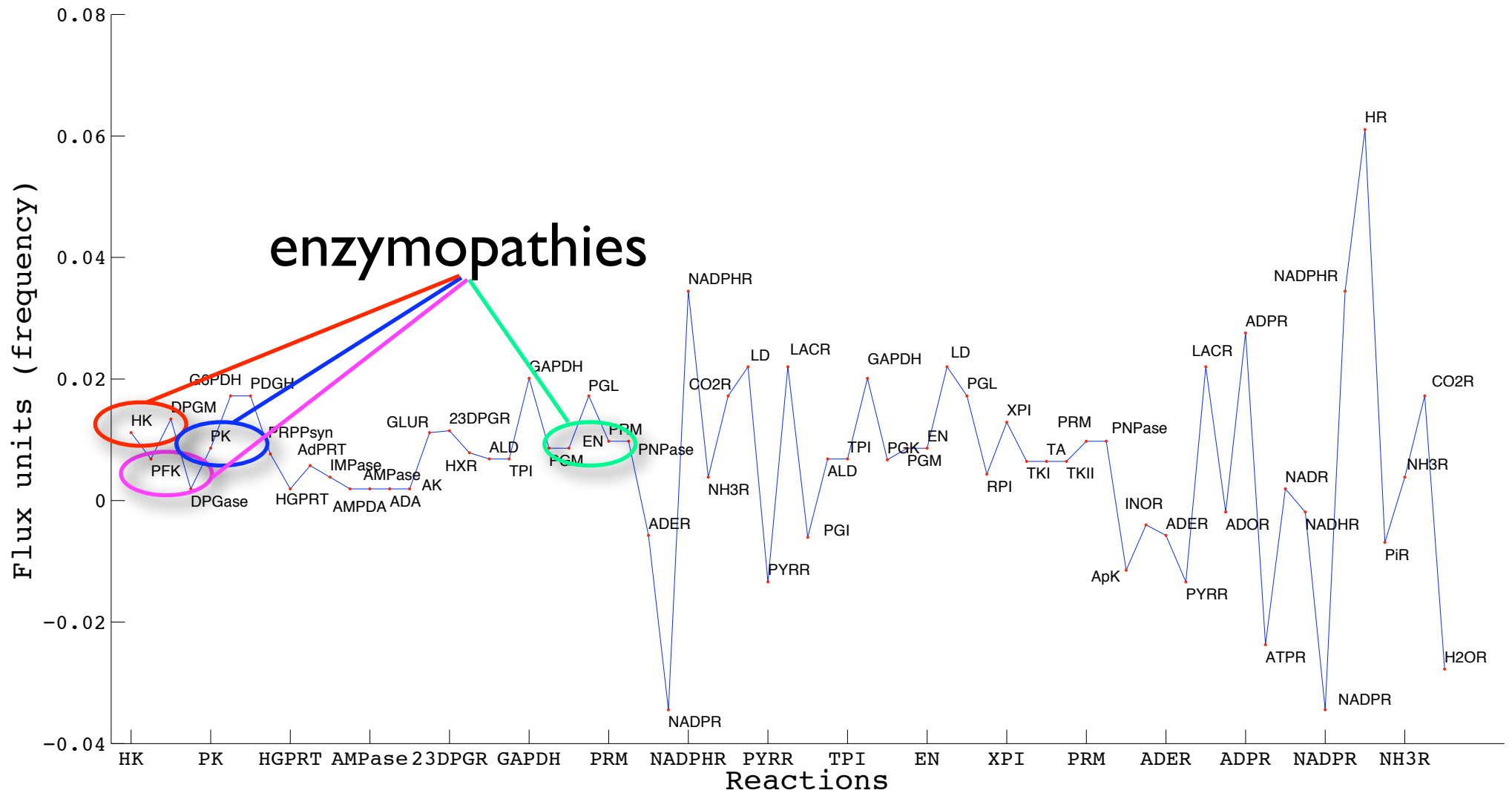
MMB & RMS plus compacts que EP ( $\equiv$  EFM)

pour la même information biologique





*Comme les autres approches...*





# Simulation de Monte-Carlo

2172

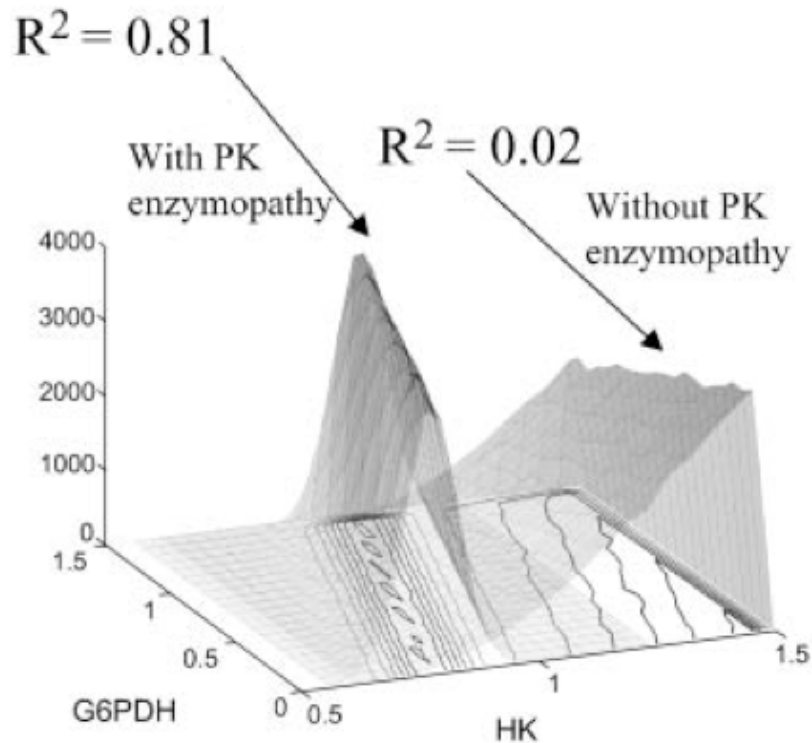
Biophysical Journal Volume 87 October 2004 2172–2186

## Uniform Sampling of Steady-State Flux Spaces: Means to Design Experiments and to Interpret Enzymopathies

Nathan D. Price, Jan Schellenberger, and Bernhard O. Palsson

Department of Bioengineering, University of California at San Diego, La Jolla, California

**ABSTRACT** Reconstruction of genome-scale metabolic networks is now possible using multiple different data types. Constraint-based modeling is an approach to interrogate capabilities of reconstructed networks by constraining possible cellular behavior through the imposition of physicochemical laws. As a result, a steady-state flux space is defined that contains all possible functional states of the network. Uniform random sampling of the steady-state flux space allows for the unbiased



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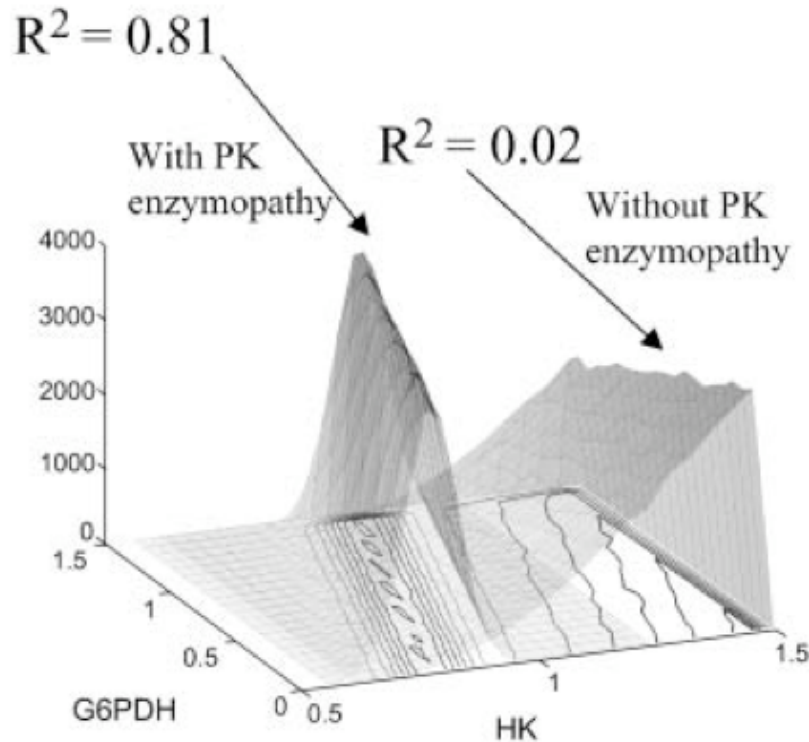
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- Simulation des flux avant et après mutation(s)

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2172

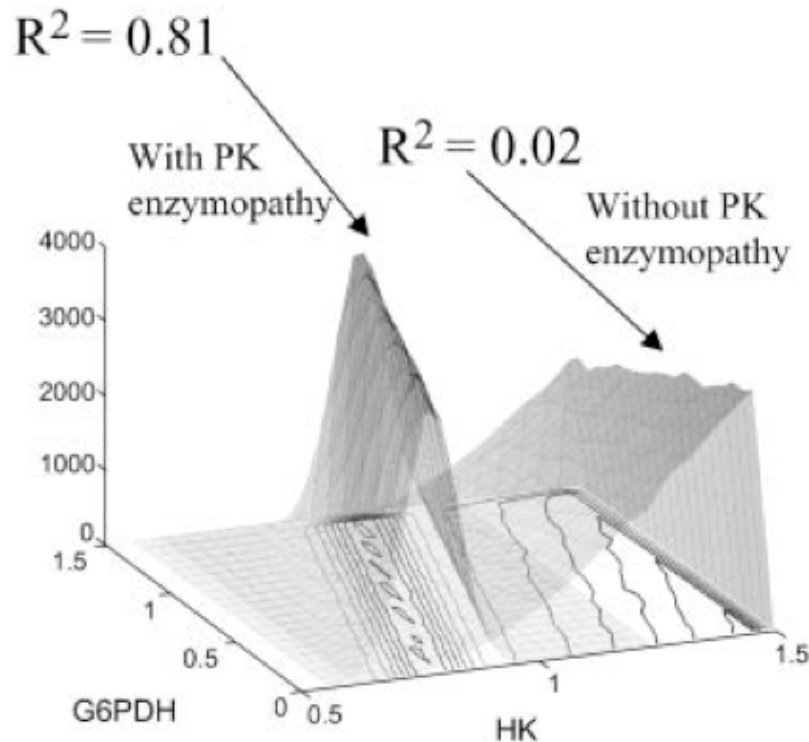
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- Nécessité de connaître certains coefficients

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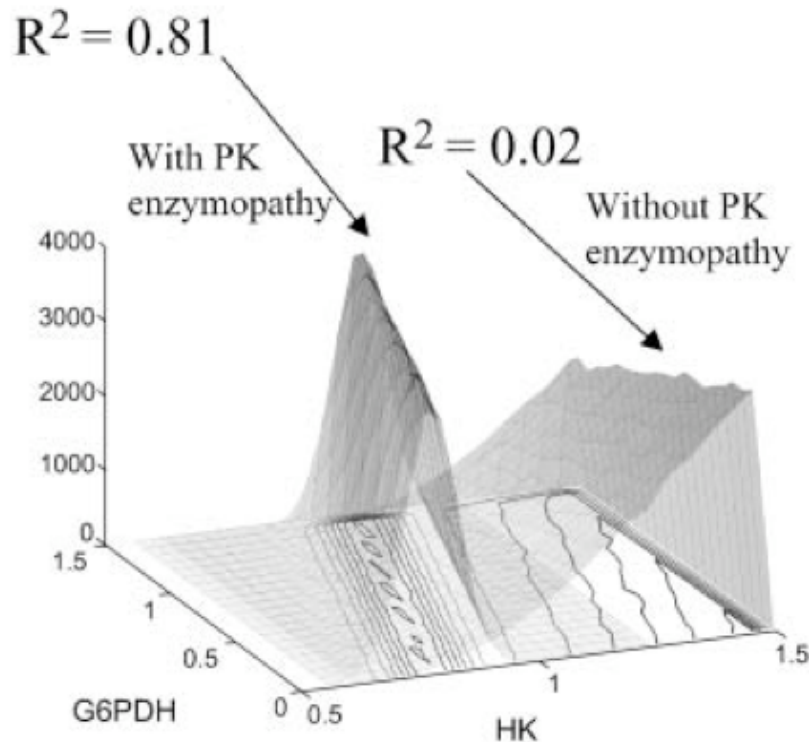
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- Possibilité de raisonner sur les contraintes métaboliques



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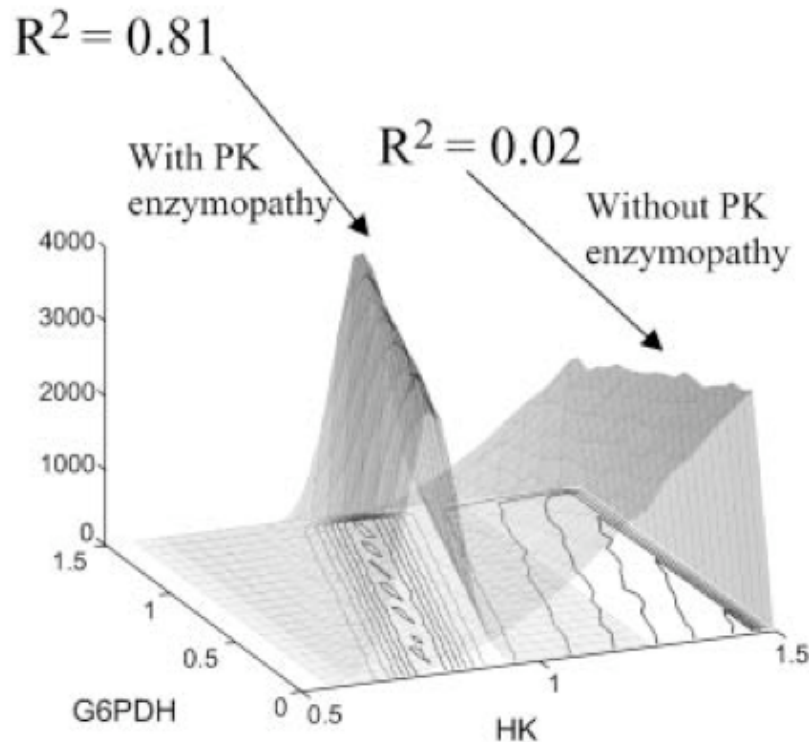
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- Nécessité de connaître certains coefficients
- Possibilité de raisonner sur les contraintes métaboliques

➡ approche qualitative

# Description qualitative des contraintes métaboliques

RCF starting.....

Computing generic pathways.....

The flux cone has 17 MMBS and dimension(RMS) = 1

Classification of reactions.....

The reaction ALD, supposed reversible, is irreversible!!!

The reaction TPI, supposed reversible, is irreversible!!!

The reaction GAPDH, supposed reversible, is irreversible!!!

The reaction PGM, supposed reversible, is irreversible!!!

The reaction EN, supposed reversible, is irreversible!!!

The reaction PGL, supposed reversible, is irreversible!!!

The reaction PNPase, supposed reversible, is irreversible!!!

The reaction PRM, supposed reversible, is irreversible!!!

The reaction ADE, supposed reversible, is irreversible!!!

The reaction NADP, supposed reversible, is irreversible!!!

The reaction NADPH, supposed reversible, is irreversible!!!

The reaction CO2, supposed reversible, is irreversible!!!

The reaction NH3, supposed reversible, is irreversible!!!

Finally There are :

- Irreversible reactions: 31

- Pseudo-irreversible reactions: 14

- Reversible reactions :6

- Blocked reactions :0

Computing pseudo-irreversible reaction dependencies....

Computing reversible reaction dependencies....

Computing irreversible reaction dependencies....



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The reaction NADP, supposed reversible, is irreversible!!!

The reaction NADPH, supposed reversible, is irreversible!!!

The reaction CO2, supposed reversible, is irreversible!!!

The reaction NH3, supposed reversible, is irreversible!!!

Finally There are :

- Irreversible reactions: 31

- Pseudo-irreversible reactions: 14

- Reversible reactions :6

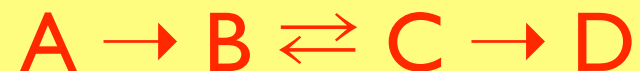
- Blocked reactions :0

Computing pseudo-irreversible reaction dependencies....

Computing reversible reaction dependencies....

Computing irreversible reaction dependencies....

**Réactions réversibles sont  
irréversibles**



# Vers la définition de réactions couplées

- + ADE -> AdPRT
- + PRM -> HGPRT HX PNPase
- + PNPase -> HGPRT HX PRM
- + ALD -> PFK TPI
- + NH3 -> ADA
- + HX ->
- + CO2 -> G6PDH PDGH PGL NADP NADPH
- + 23DPG ->
- + GLC -> HK
- + NADPH -> G6PDH PDGH PGL NADP CO2
- + HGPRT ->
- + NADP -> G6PDH PDGH PGL NADPH CO2
- + PRPPsyn -> AdPRT HGPRT ADE
- + IMPase -> AMPDA HGPRT
- + AdPRT -> ADE
- + AMPDA ->
- + AK ->
- + ADA -> NH3
- + AMPase ->
- + PDGH -> G6PDH PGL NADP NADPH CO2
- + PGL -> G6PDH PDGH NADP NADPH CO2
- + G6PDH -> PDGH PGL NADP NADPH CO2
- + PK -> PGM EN
- + EN -> PK PGM
- + DPGase ->
- + PGM -> PK EN
- + DPGM -> DPGase 23DPG
- + PFK -> ALD TPI
- + GAPDH -> PK 23DPG PGM EN
- + HK -> GLC
- + TPI -> PFK ALD

# Vers la définition de réactions couplées

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- + PRM -> HGPRT HX PNPase
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Réactions associées par les contraintes stoechiométriques et thermodynamiques

**TABLE 2** Effects of simulated enzymopathies in glycolytic enzymes on steady-state flux space

Glycolytic enzymes	$V_{\max}^i$	Constraining?	Systemic $V_{\max}^i$	Systemic $V_{\min}^i$	Restricted $V_{\max}^i$	Percentage of steady-state flux space remaining	Hemolytic anemia?*
Hexokinase (HK)	1.5	Yes	1.50	0.48	0.74	0.02%	Yes
Phosphofructokinase (PFK)	250	No	1.58	0.31	0.63	0.21%	Variable
Triose phosphate isomerase (TPI)	1000	No	1.58	0.31	0.63	0.21%	Yes
Aldolase (ALD)	1000	No	1.58	0.31	0.63	0.21%	Yes
Lactate dehydrogenase (LDH)	1000	No	2.81	0.09	0.77	0.56%	No
Pyruvate kinase (PK)	250	No	3.21	1.17	1.68	0.83%	Yes
Enolase (EN)	1000	No	3.21	1.17	1.68	0.84%	Yes
Phosphoglucosomerase (PGI)	1000	No	1.48	-0.77	-0.21	1.0%	Yes
Phosphoglycerate kinase (PGK)	1000	No	2.91	0.87	1.38	2.2%	Usually
Diphosphoglycerate phosphatase (DPGase)	0.52	Yes	0.52	0.3	0.36	29%	No
Diphosphoglyceromutase (DPGM)	12	No	1.43	0.3	0.58	47%	No

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Résultats cohérents avec les simulations d'enzymopathies (travaux de Palsson et al.)

Simplifier le système

Comment comparer ces réactions

Groupes de réactions + ou - importants ?

# Analyse qualitative

*La théorie :*

- Les réactions irréversibles et pseudo-irréversibles définissent les MMBs
  - ➔ responsable du comportement biologique
- Les réactions réversibles définissent le RMS
  - ➔ flexibilité du système



# Analyse qualitative

*La théorie :*

- Les réactions irréversibles et pseudo-irréversibles définissent les MMBs

modification réaction = modification comportement

- Les réactions réversibles définissent le RMS

 flexibilité du système

# Analyse qualitative

*La théorie :*

- Les réactions irréversibles et pseudo-irréversibles définissent les MMBs

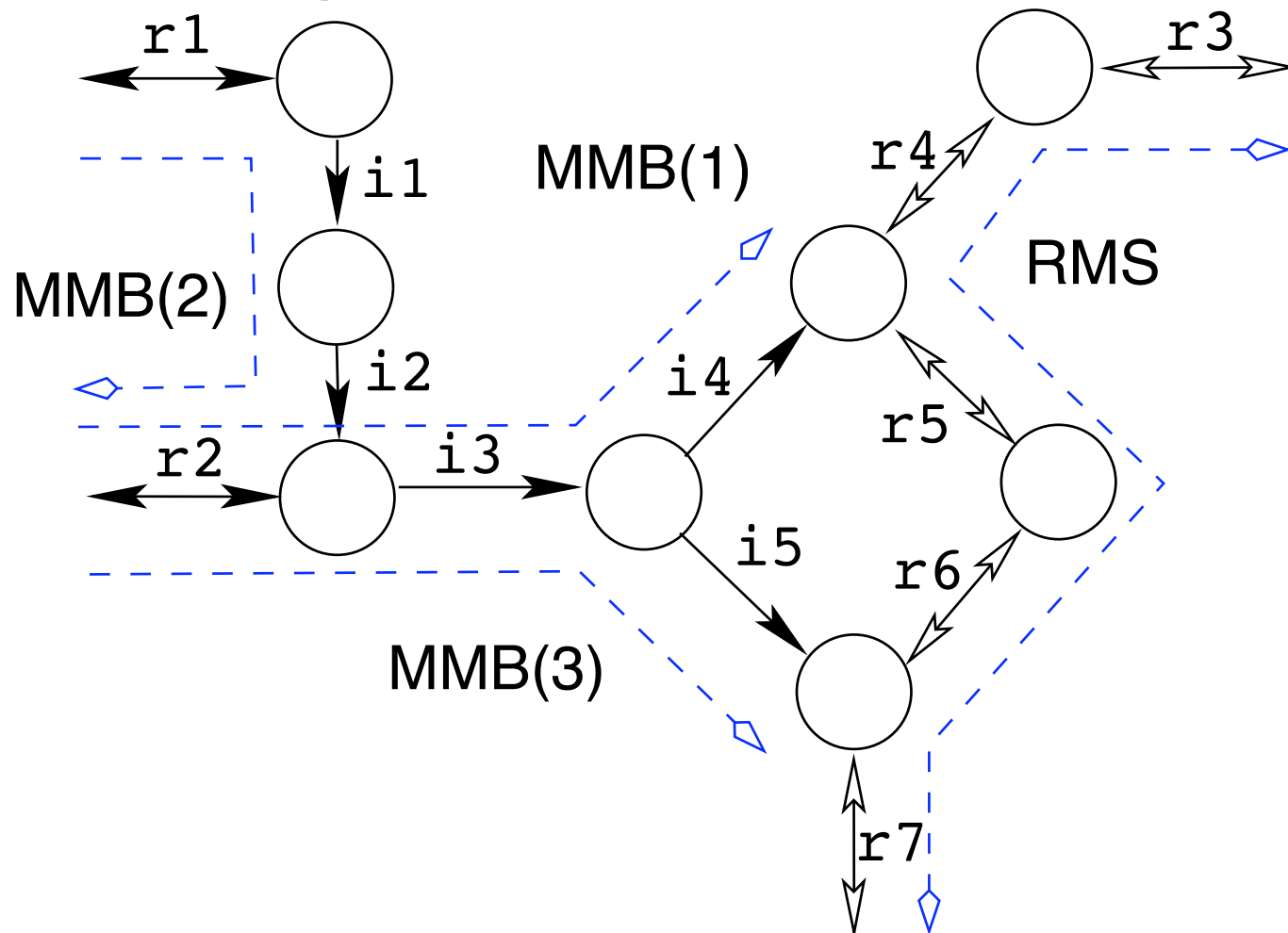
modification réaction = modification comportement

- Les réactions réversibles définissent le RMS

modification réaction = pas forcément modification de comportement

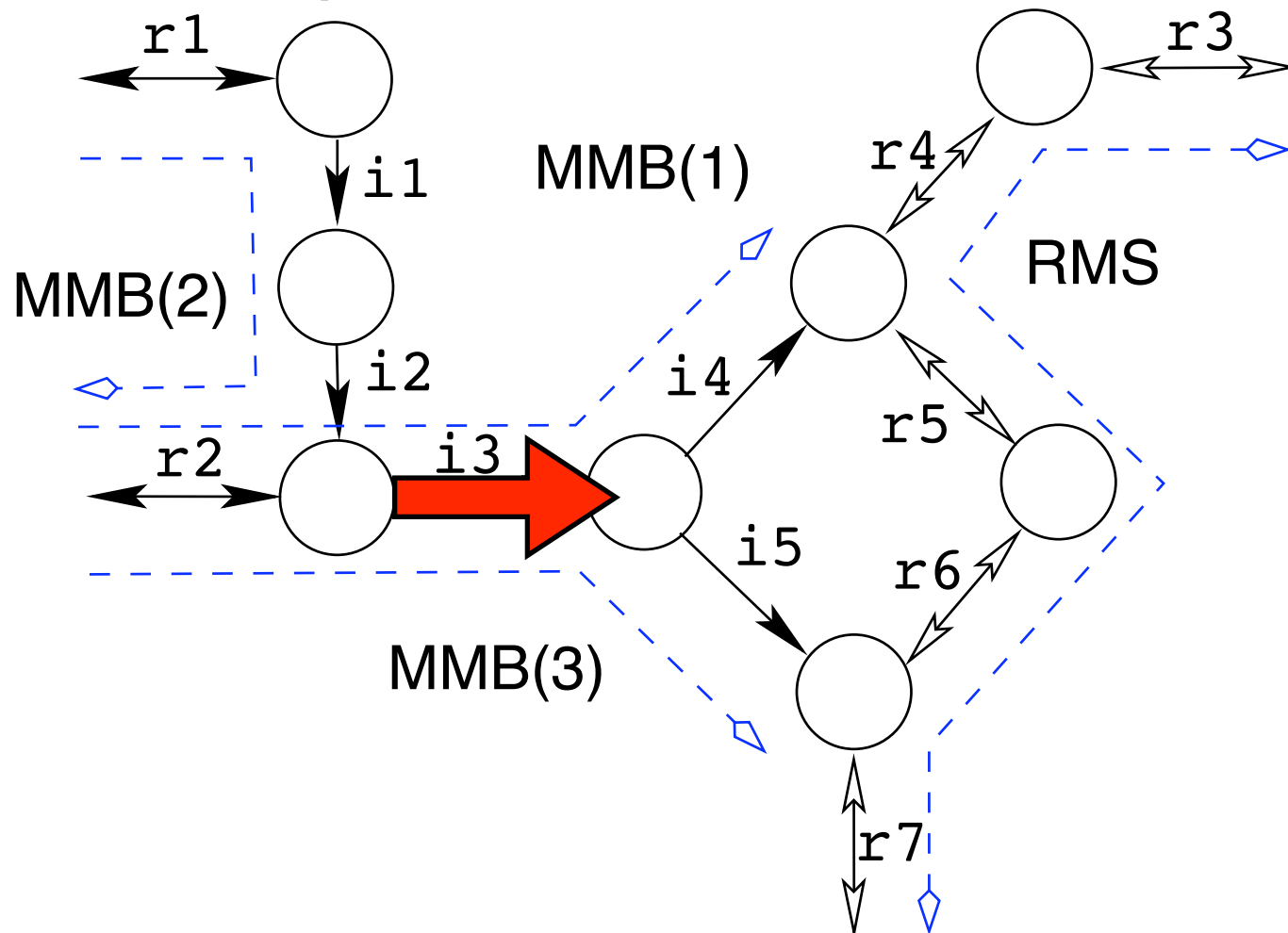
Une réaction irréversible ou pseudo-irréversible est biologiquement importante :

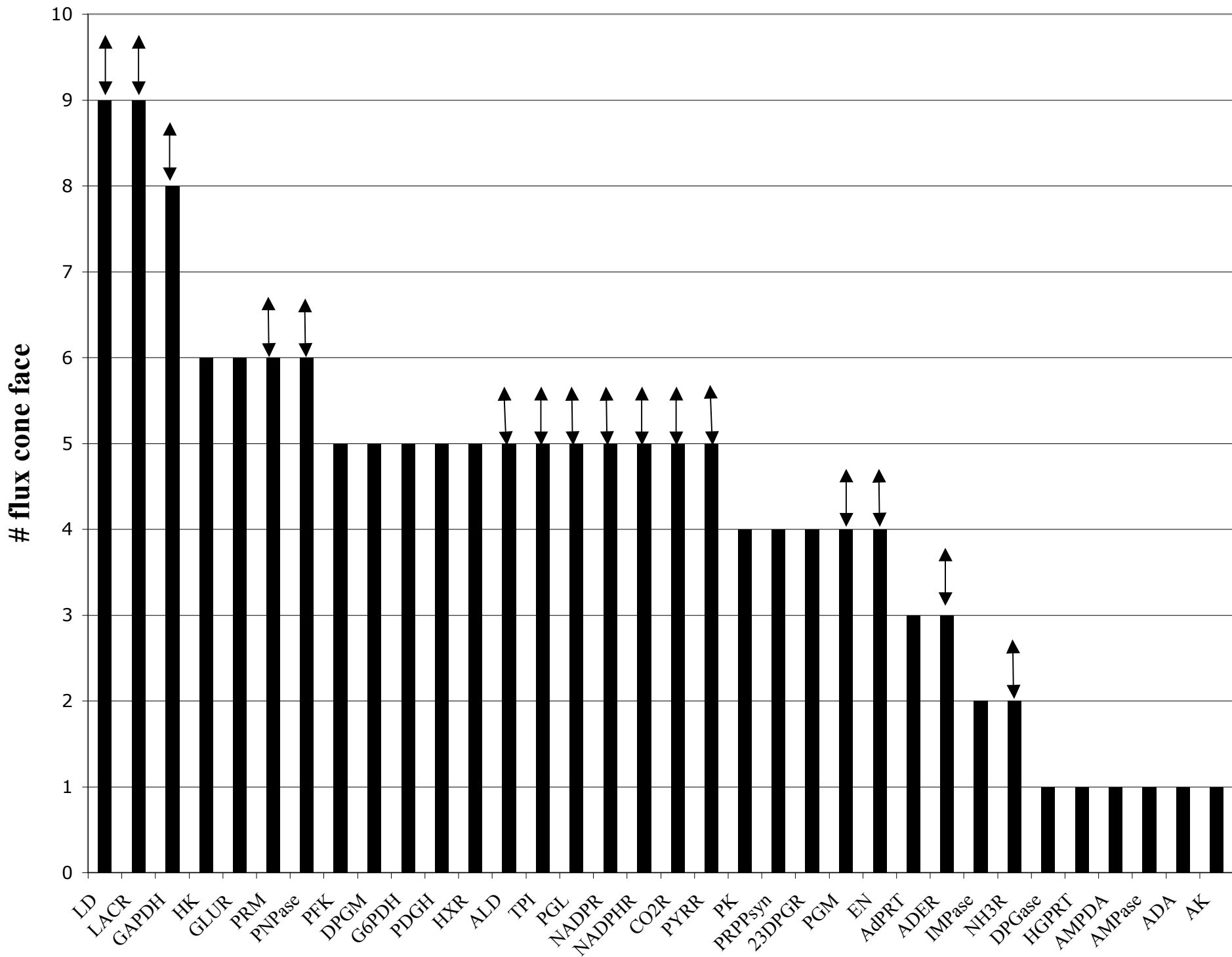
- appartient à un comportement métabolique minimal
- appartient à plusieurs MMBs

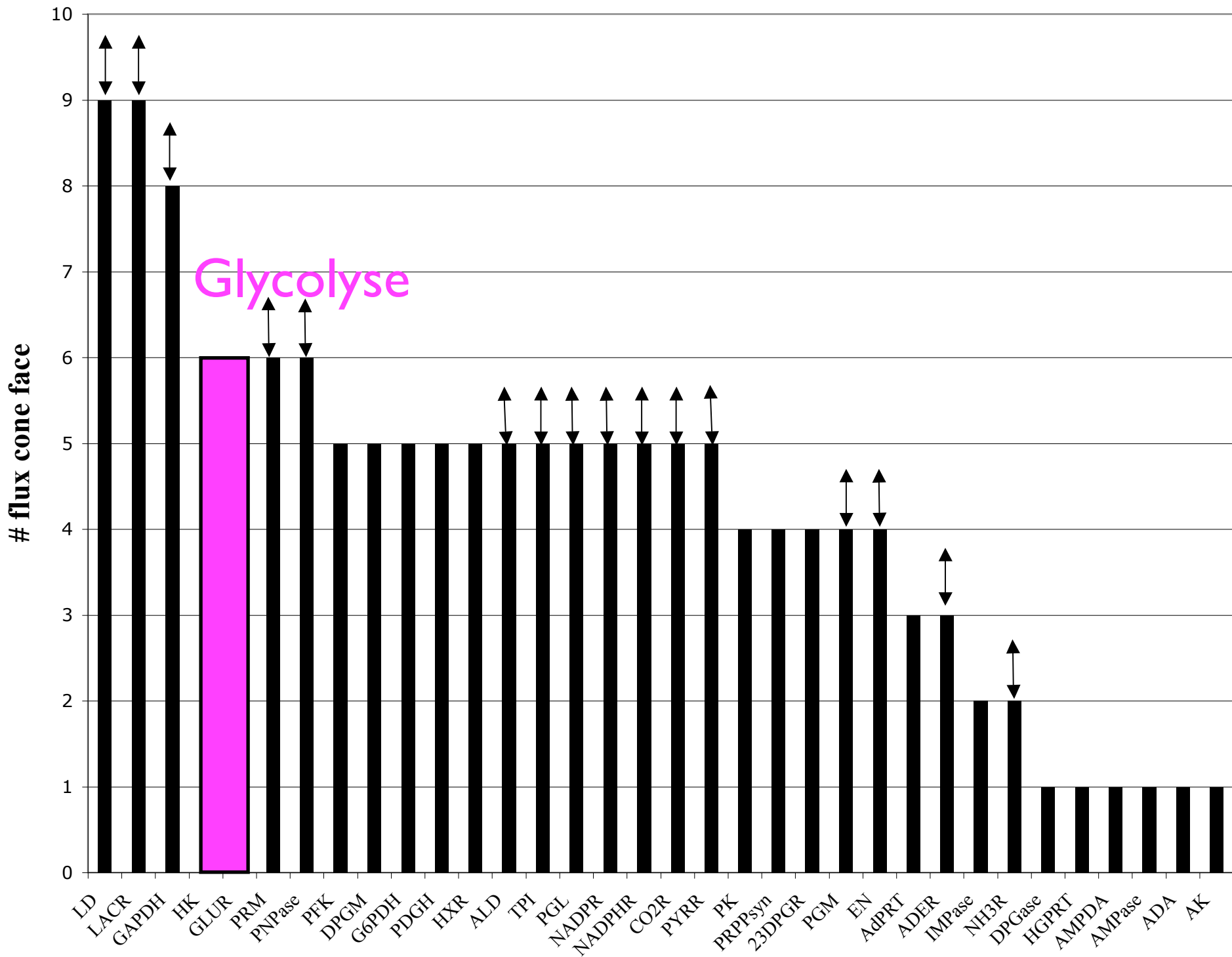


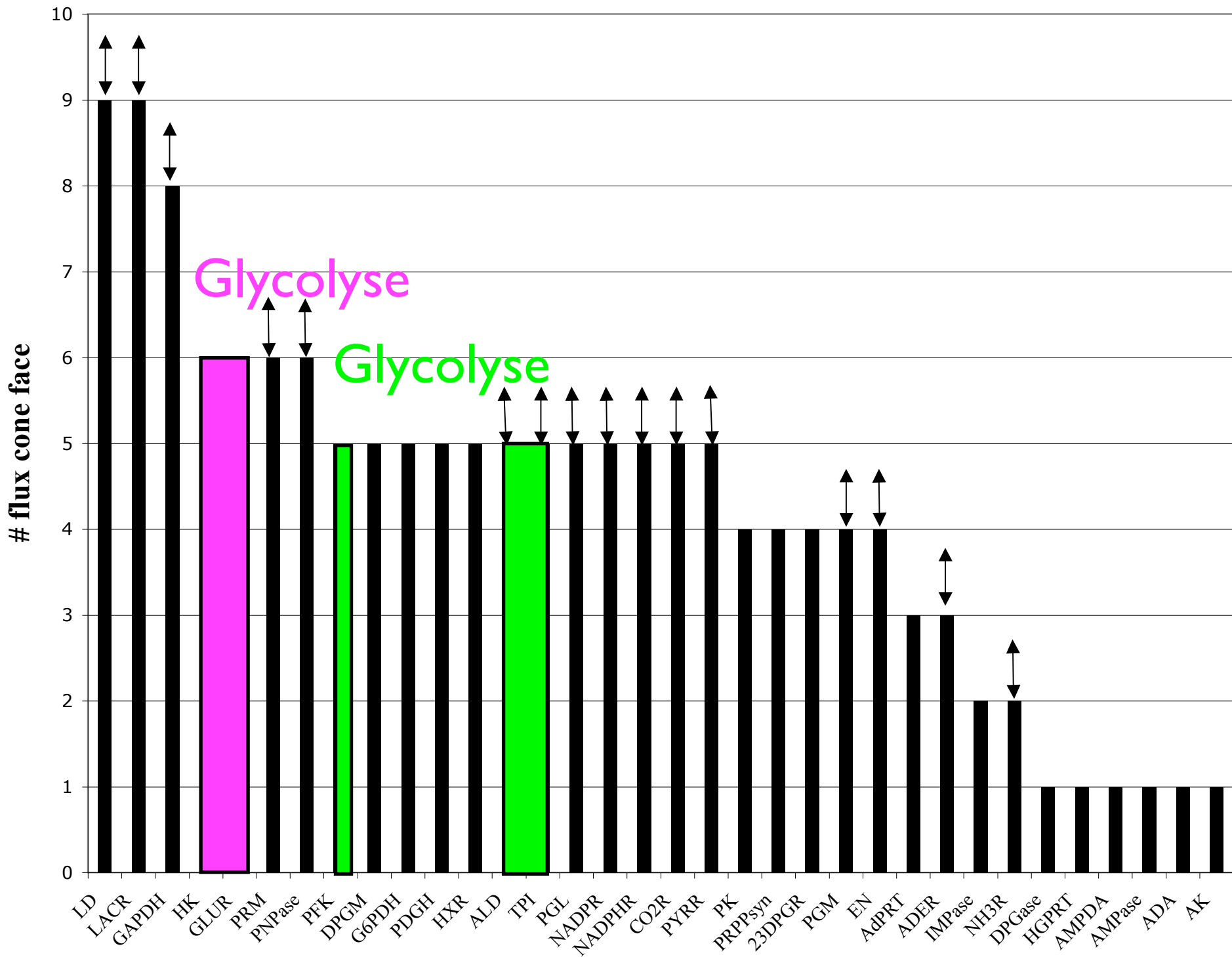
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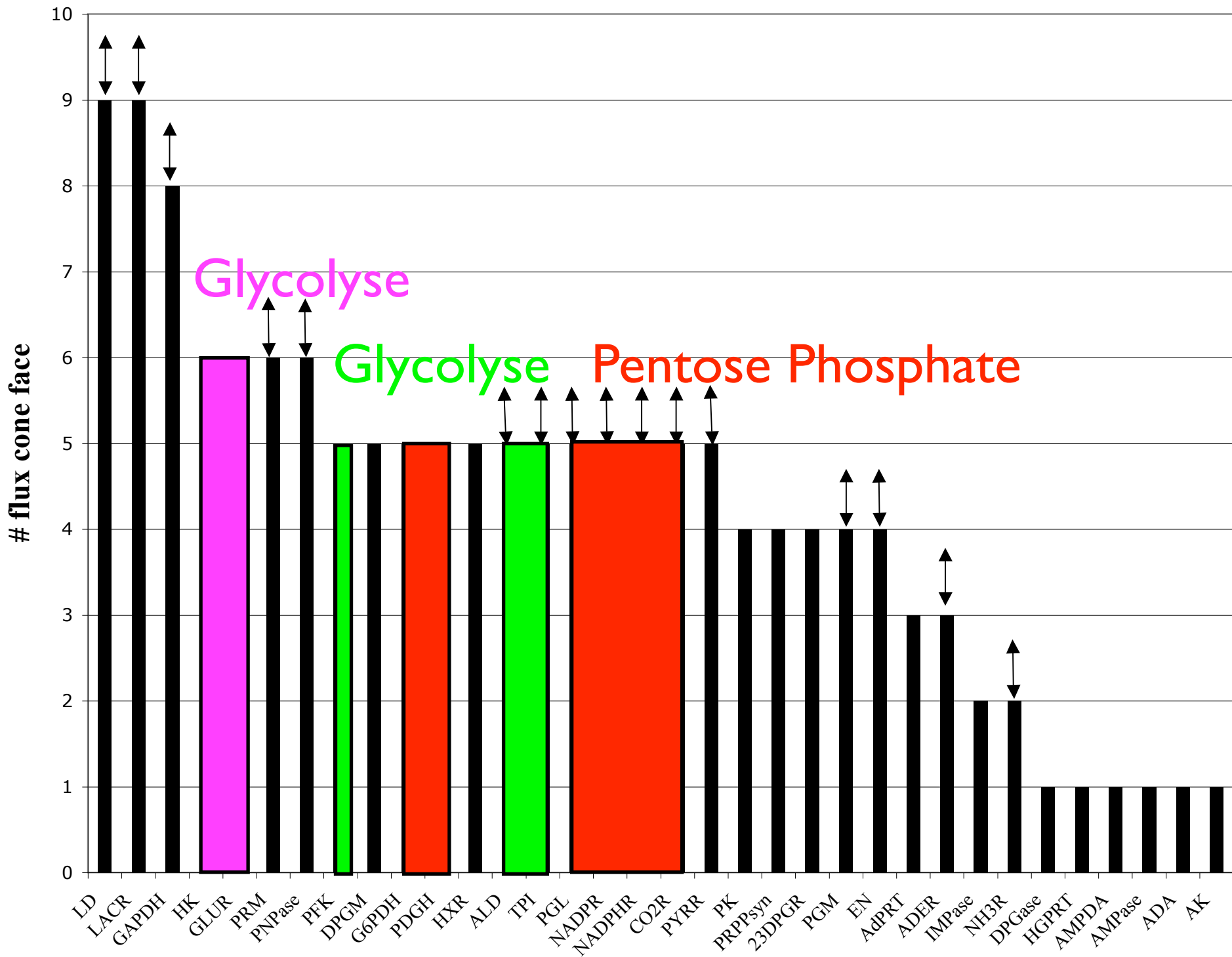
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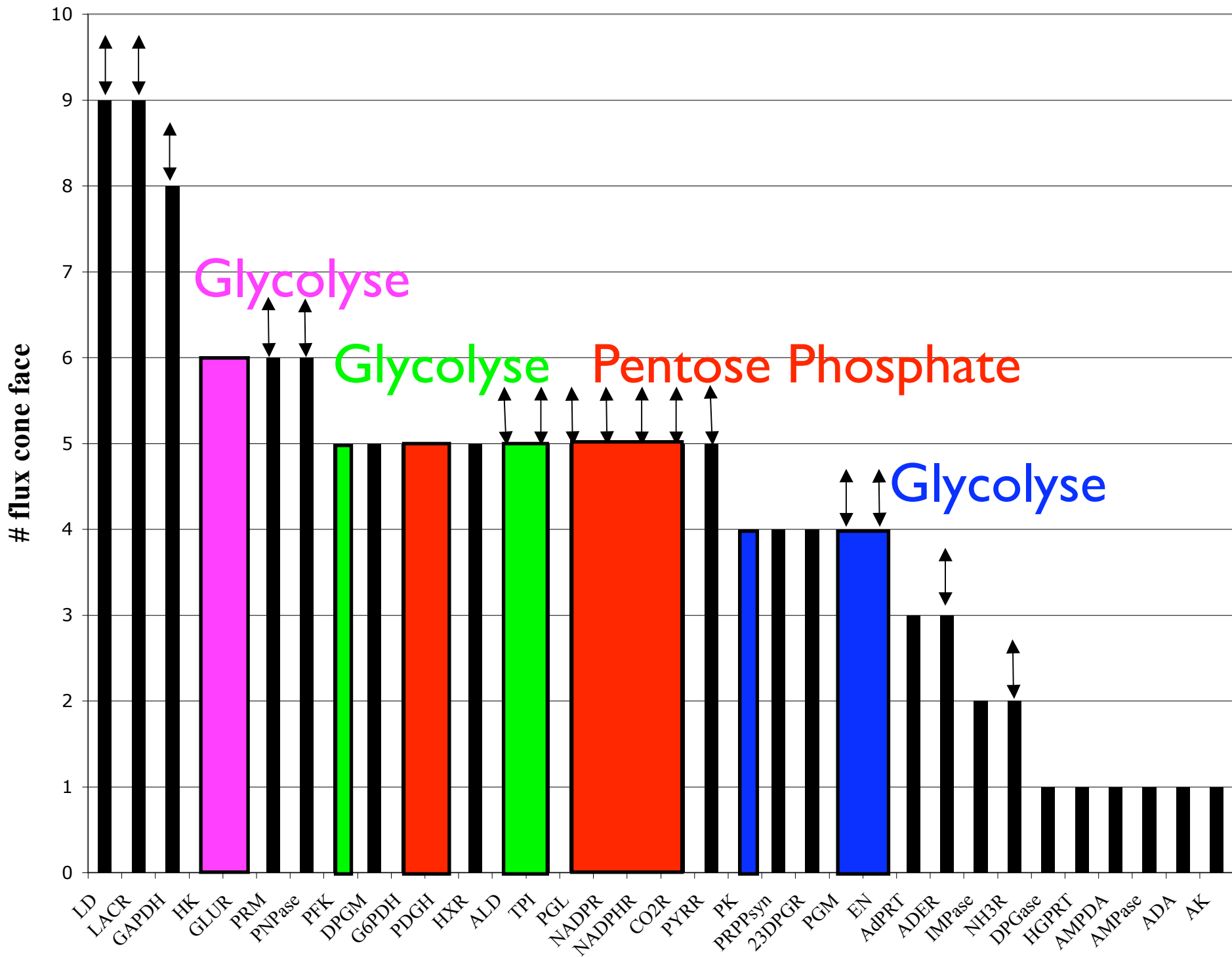


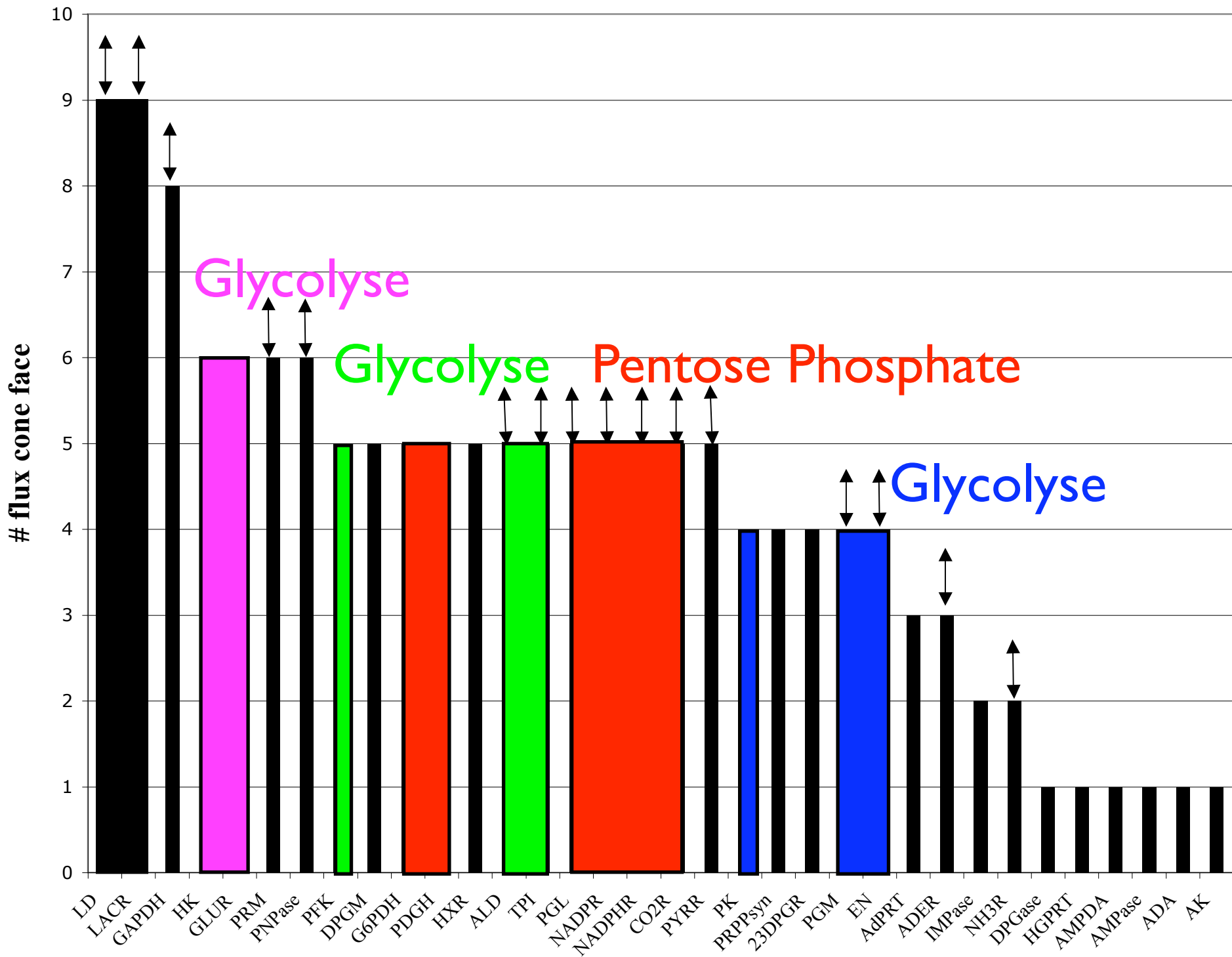


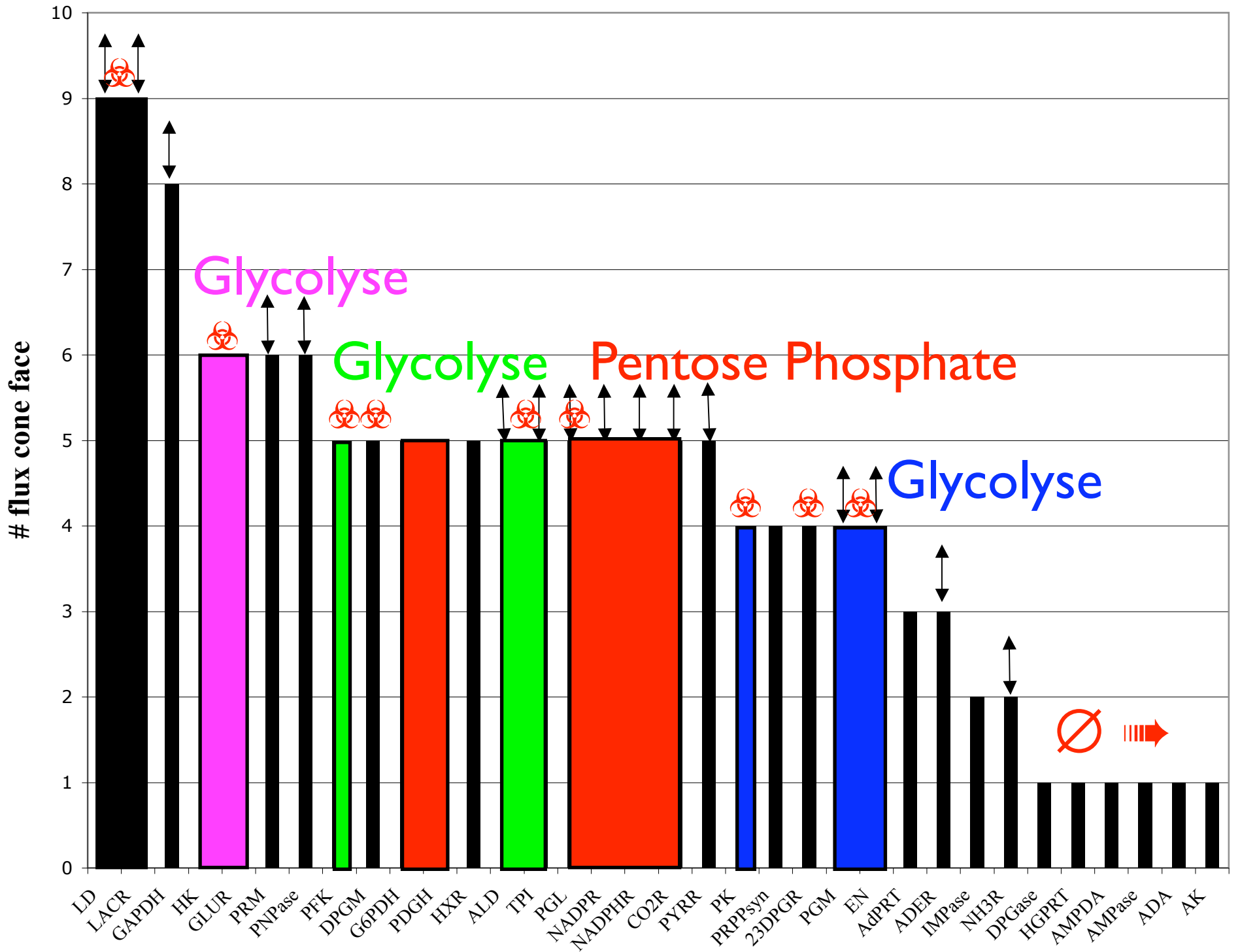


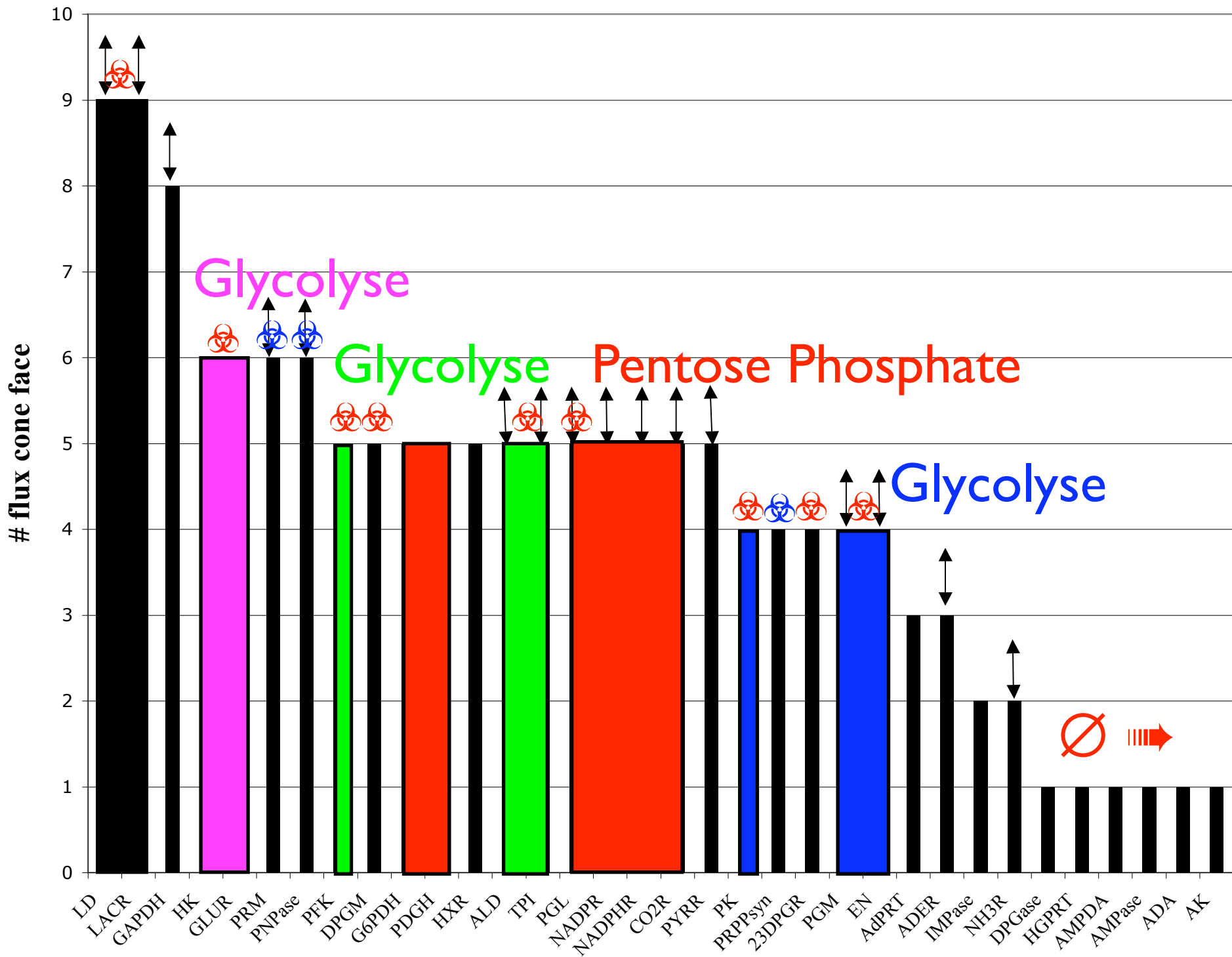












- Juste avec les contraintes métaboliques
- Informations qualitatives seules
- Cohérent mais pas encore de validation :  
besoin de nouvelles expériences sans *a priori*
- Aide à la décision expérimentale mais peut  
être plus... *approfondir le raisonnement*

# Vers une définition de la robustesse

*Kitano (2004) Nature*


« Robustness is the fundamental feature of evolvable complex systems. Its a property that allow a system to maintain its function despite external and internal perturbation.»

# Robustesse c'est...

## ***I. Redondance***

- Plusieurs pathways pour une même fonction  
*(Stelling et al. 2002, Edwards & Palsson, 2000)*
- Redondance des EPs et EFM s'explique par la dimension de RMS

## **2. Flexibilité**

- Plasticité phénotypique (*Wuchty et al. 2003*)
- Directement associé à RMS   
formalisation de la flexibilité
- Potentiel d'évolution/adaptation du système



### **3. Modularité**

- Modules dans le réseau métabolique :  
*modification d'un module sans conséquences sur les autres*
- Etudes comparatives (*Schlosser, 2002*)
- Protéines intra-modulaires très contraintes  
(*Fraser, 2005*)
- **MMB : description modulaire des fonctions métaboliques**

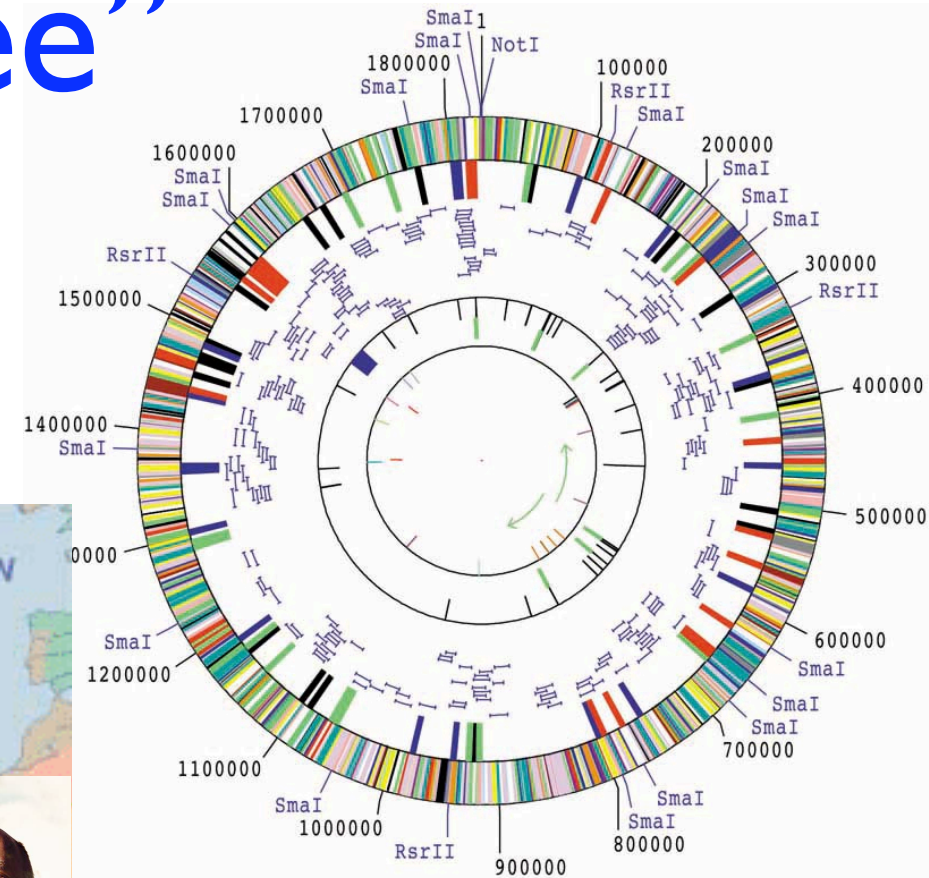
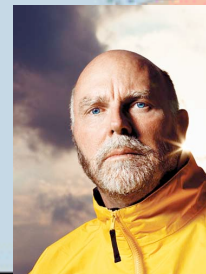
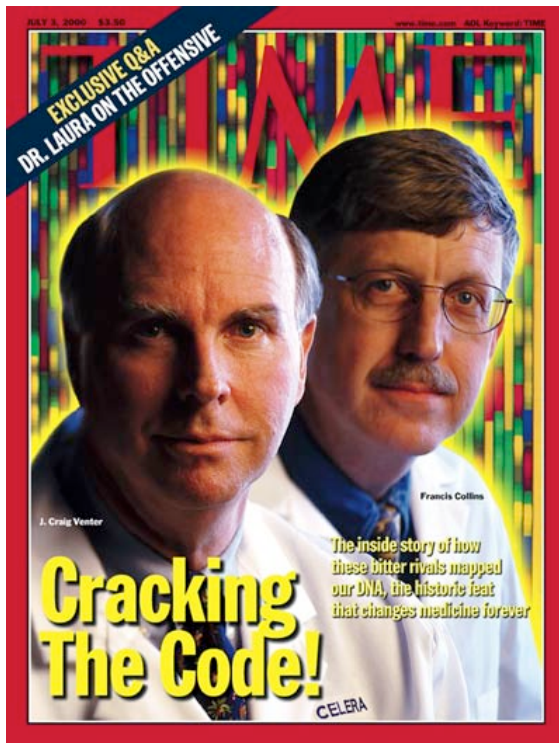
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*modification d'un module sans conséquences sur les autres*
- Etudes comparatives (*Schlosser, 2002*)
- Protéines intra-modulaires très contraintes  
(*Fraser, 2005*)
- MMB : description modulaire des fonctions métaboliques

MMB & RMS : formalisation de la Biologie Intégrative...

Vers une nouvelle frontière  
en  
*“systems biology”*

# Bioinformatique du “non cultivée”



Comprendre la diversité des organismes non cultivés  
➔ Comprendre les contraintes de la biocomplexité

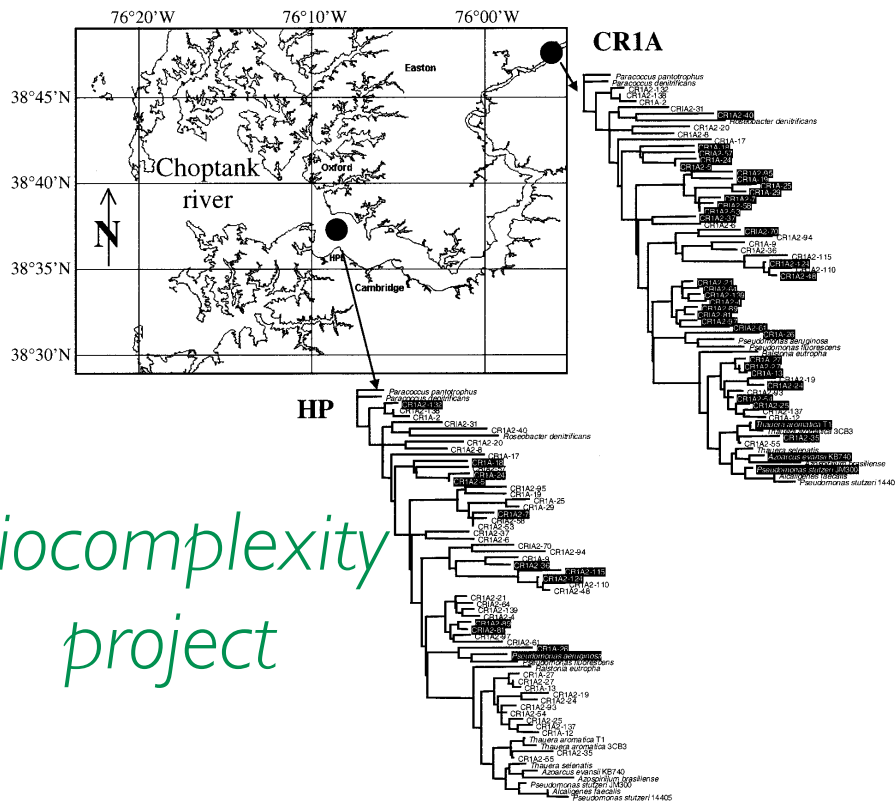


# Comprendre la biodiversité bactérienne

- Variation de la diversité en fonction des paramètres environnementaux

- Comprendre la diversité du non-cultivé

 **nouveaux outils formels**

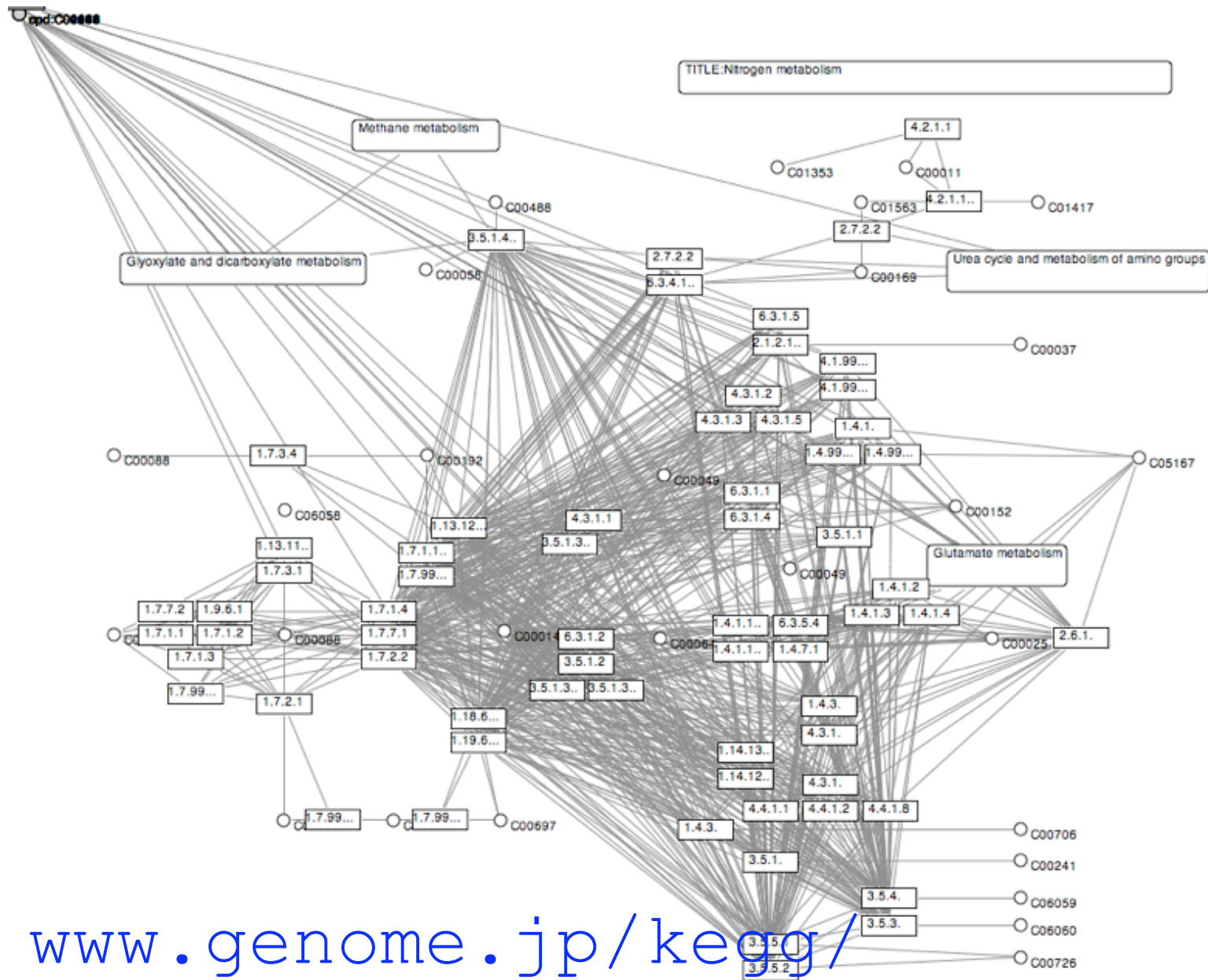


Biocomplexity  
project

Complexité bactérienne dans gradient d'azote...

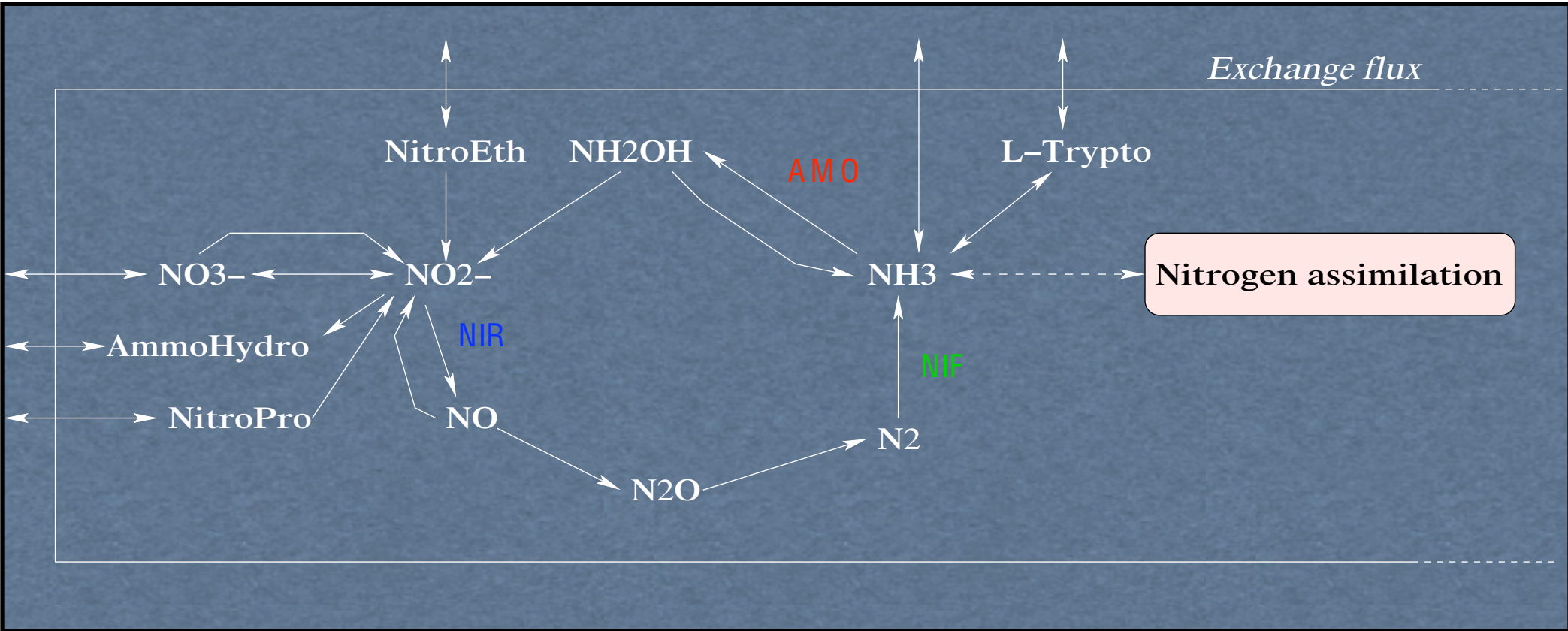


# Le cycle de l'azote comme un *métabolisme*

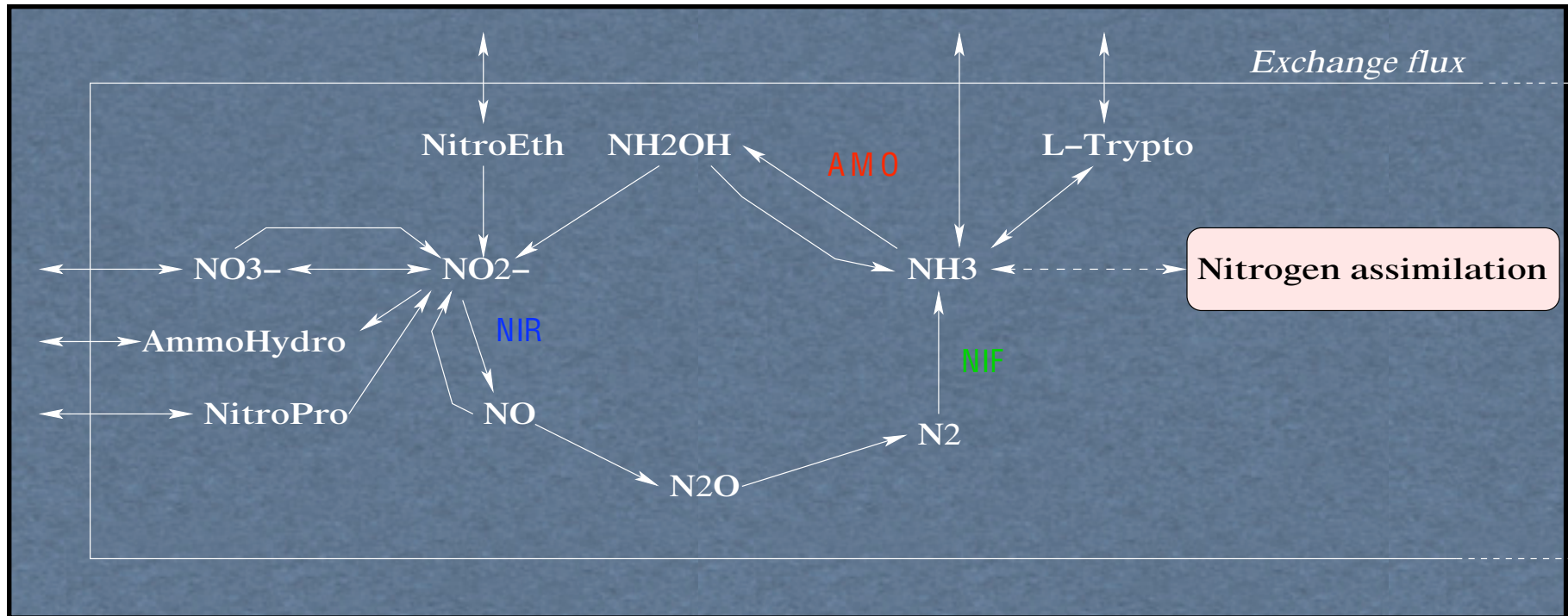




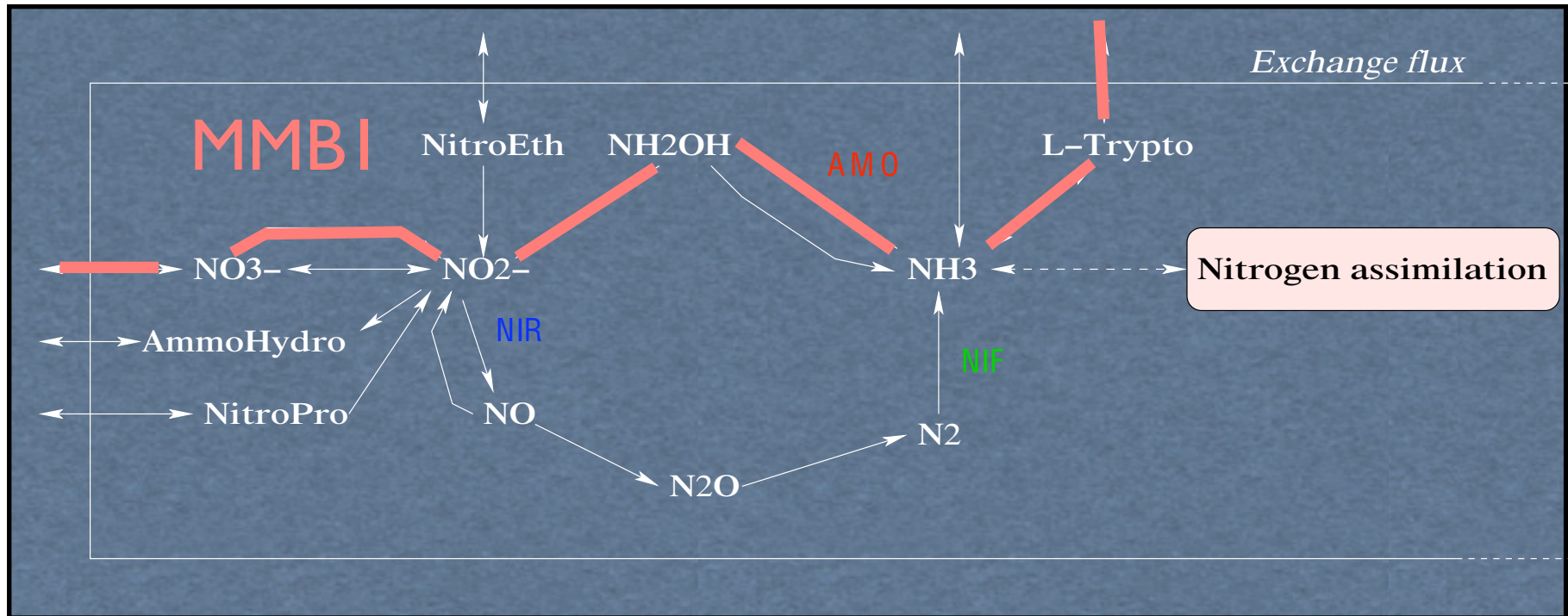




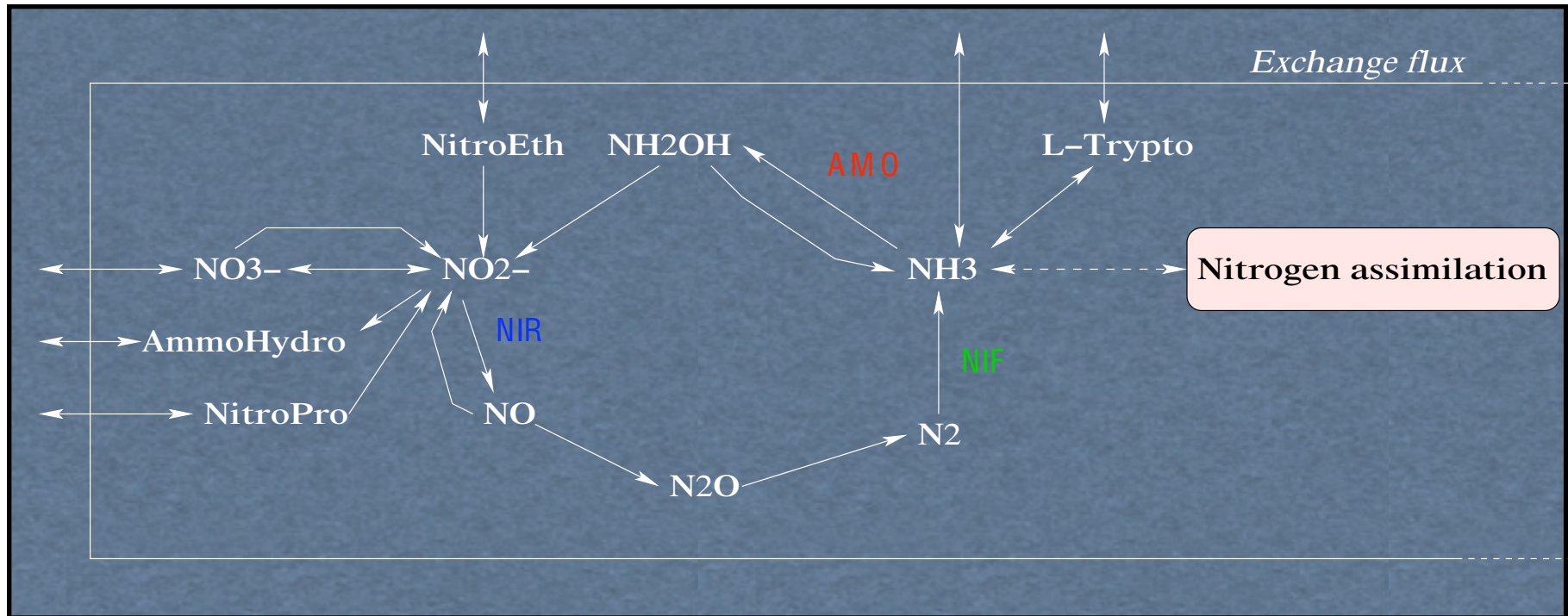
# MMBs du cycle de l'azote



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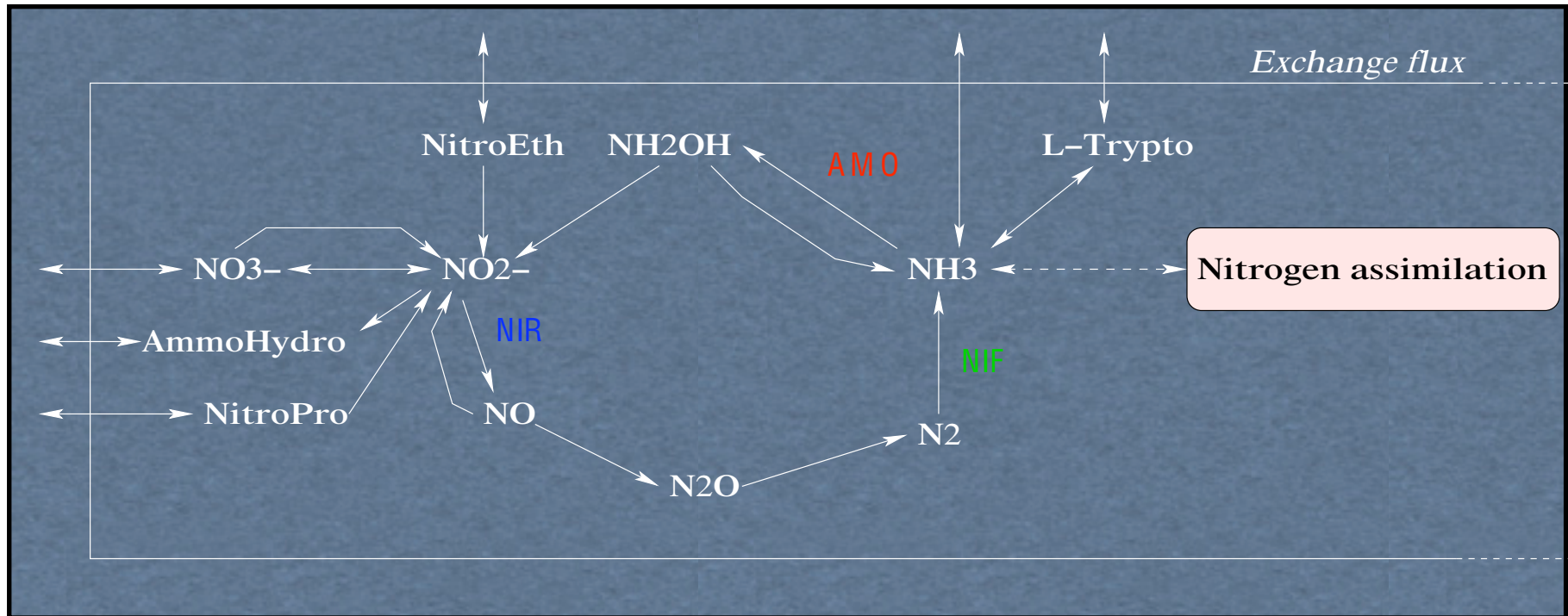
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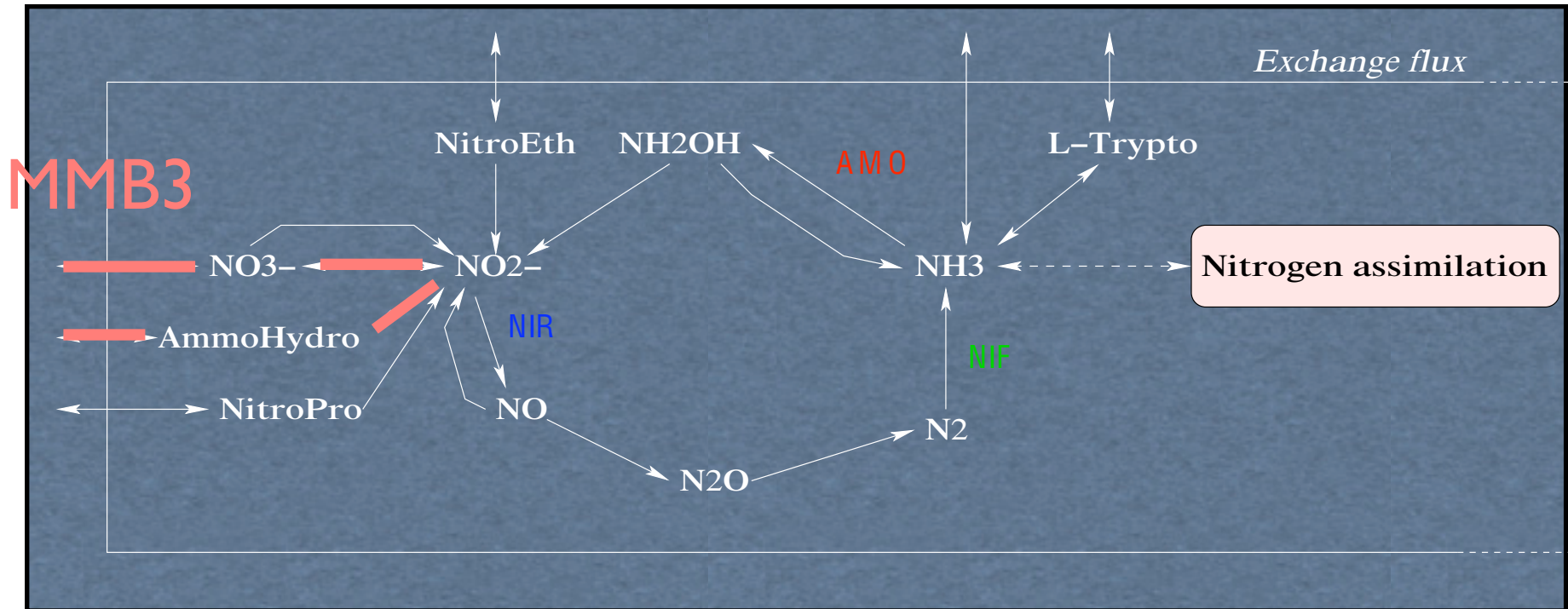




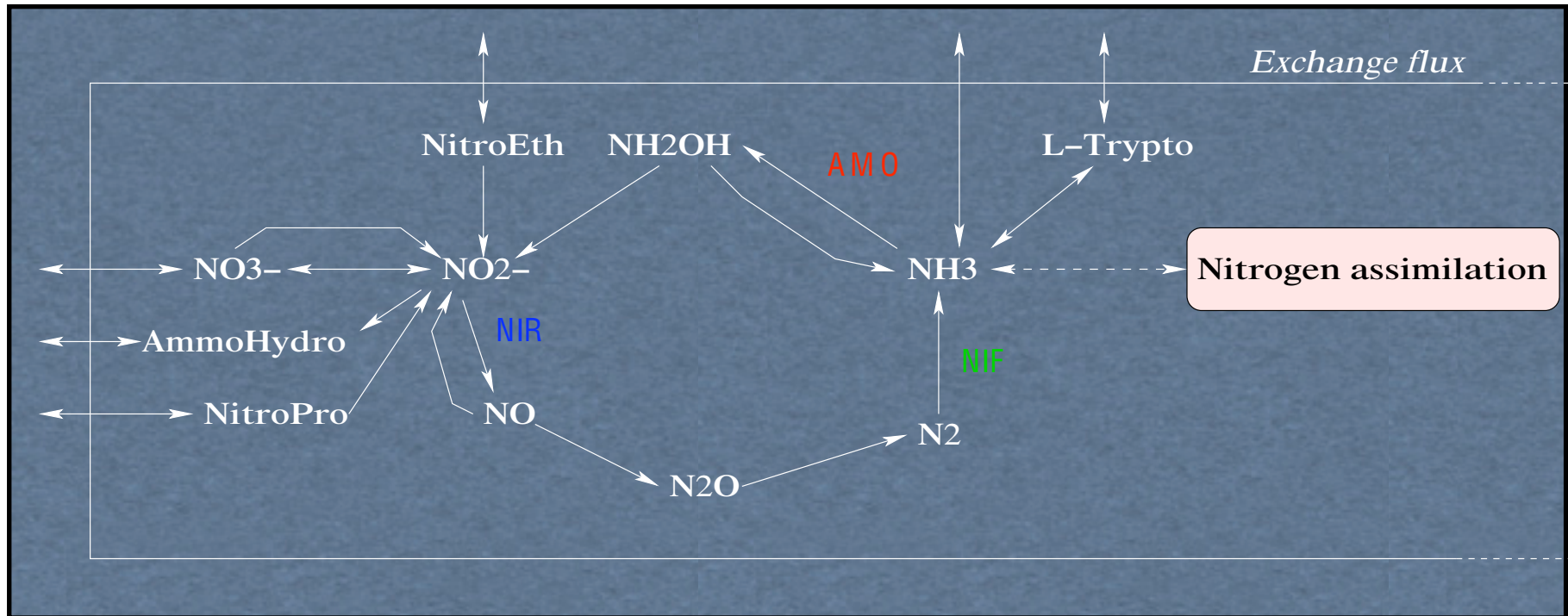
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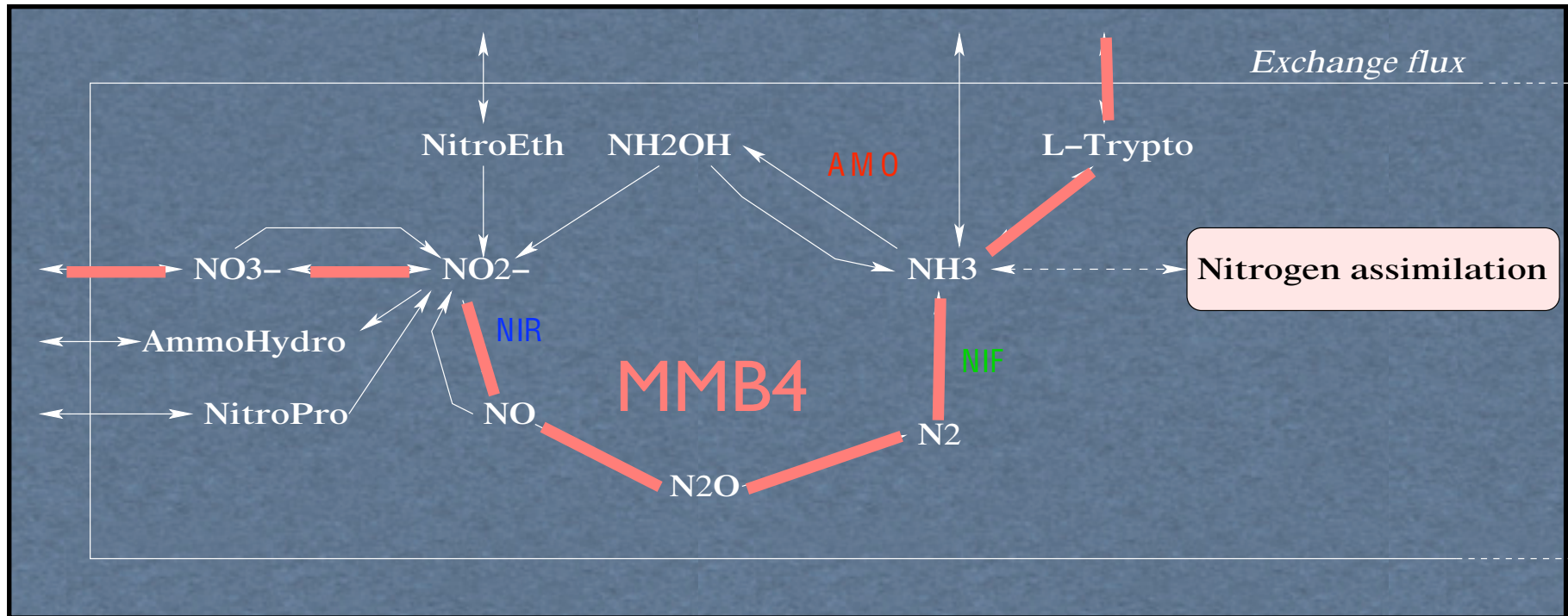


# MMBs du cycle de l'azote

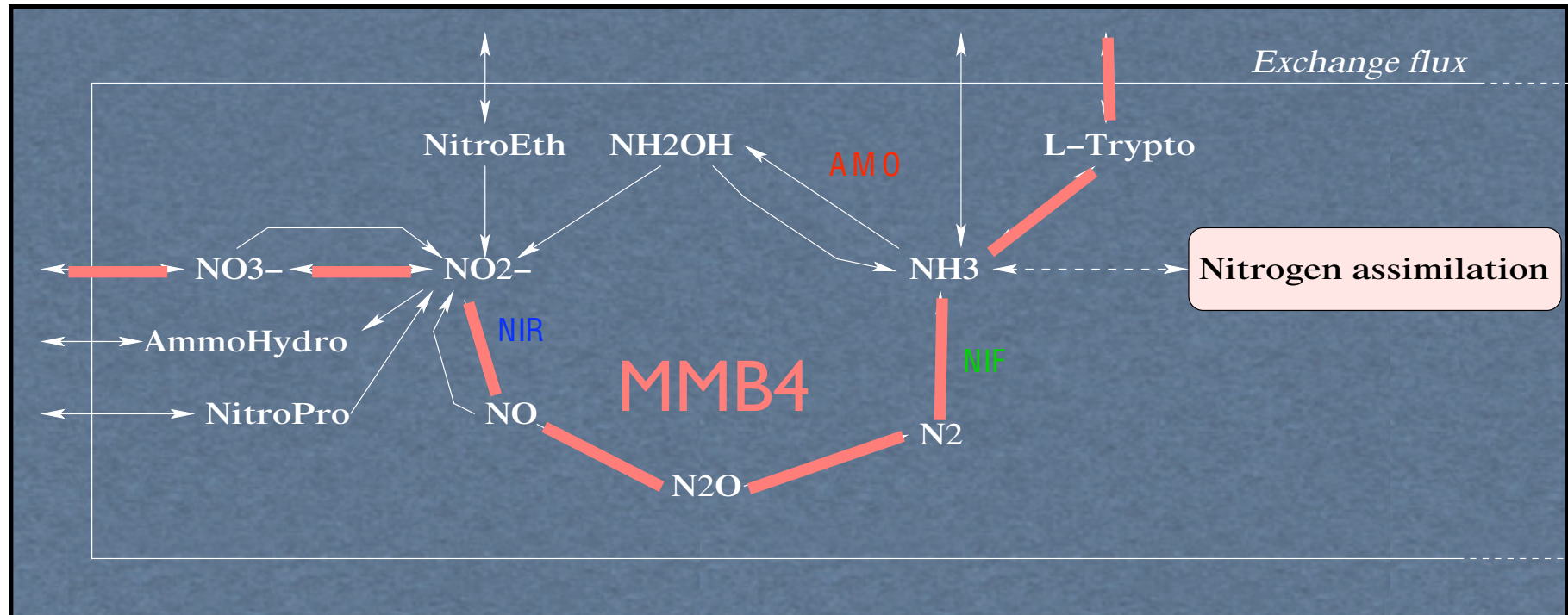




# MMBs du cycle de l'azote

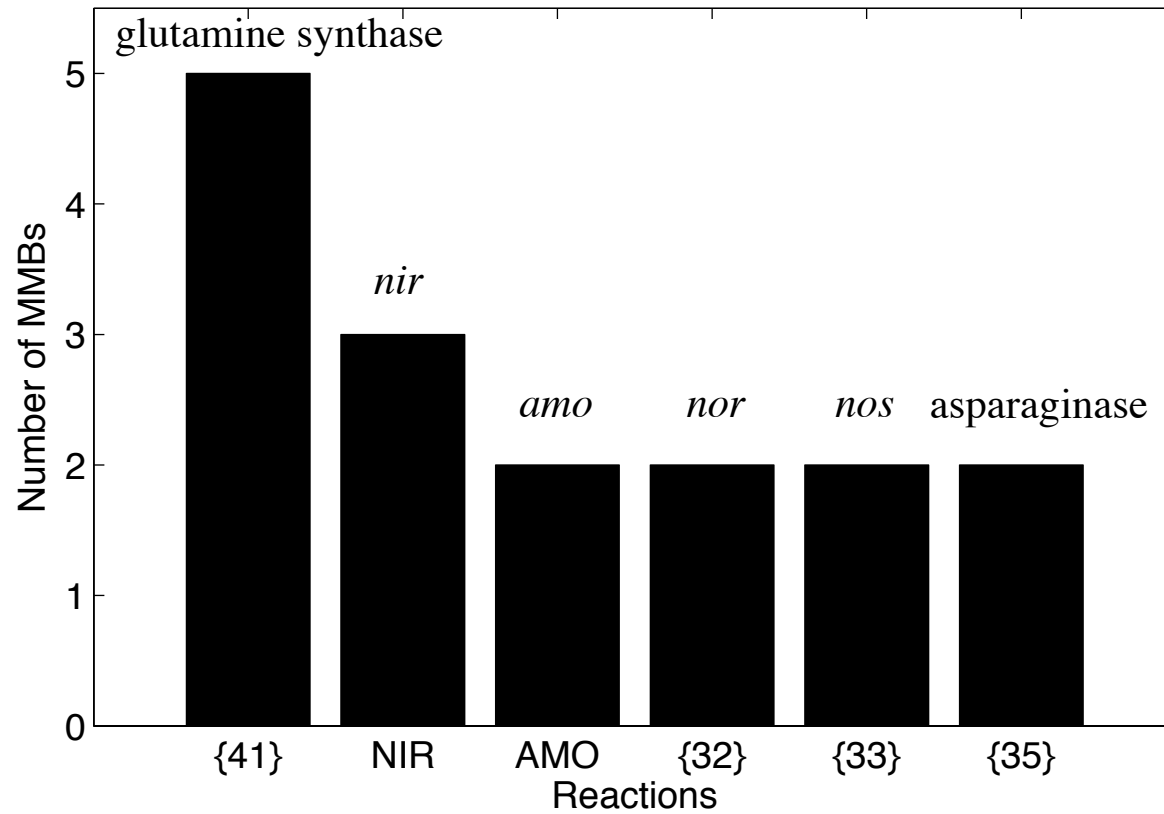


# MMBs du cycle de l'azote

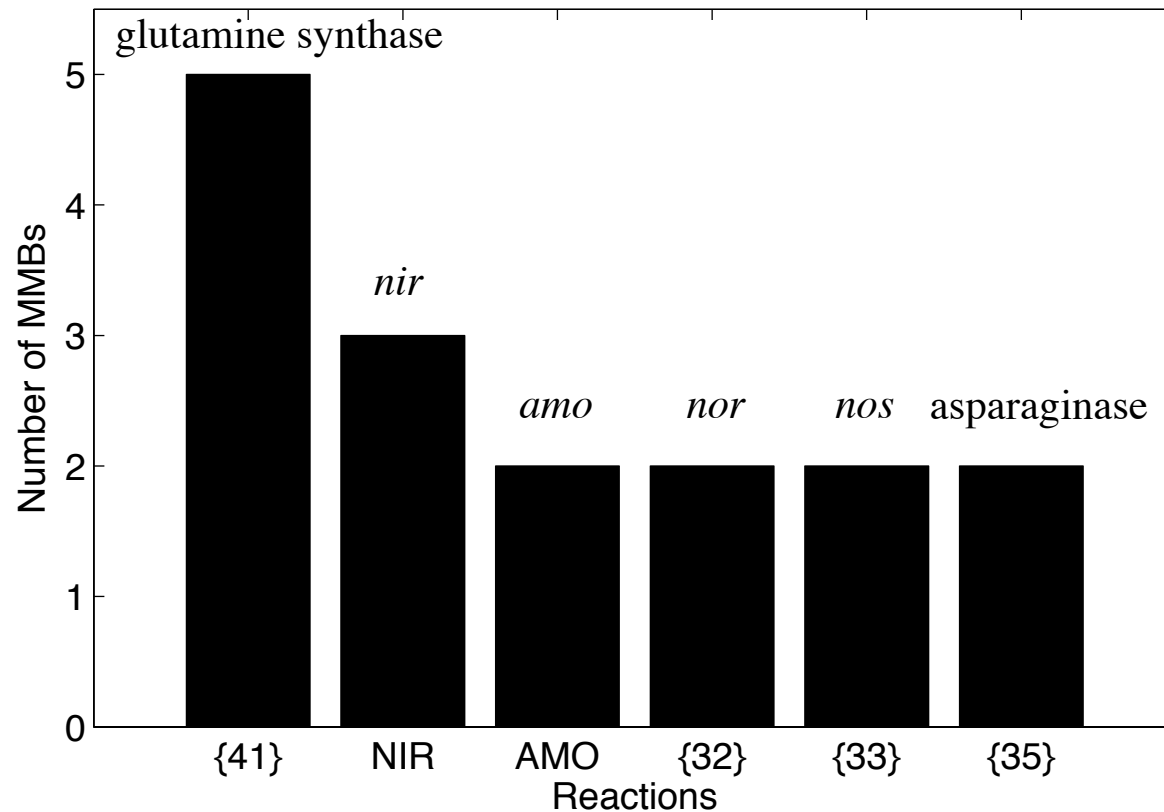


51 MMBs

# Réactions importantes

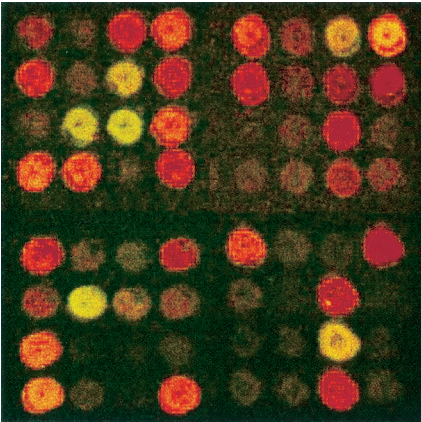


# Réactions importantes



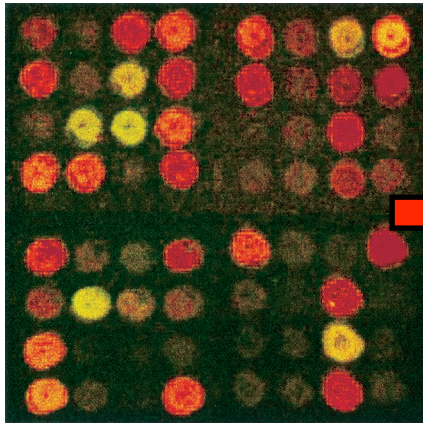
... sont encodées par les gènes fonctionnels  
bactériens

# Distribution des gènes fonctionnels

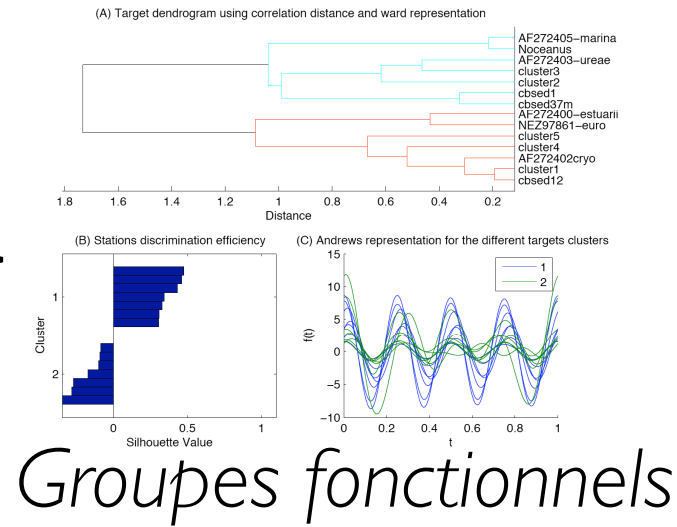
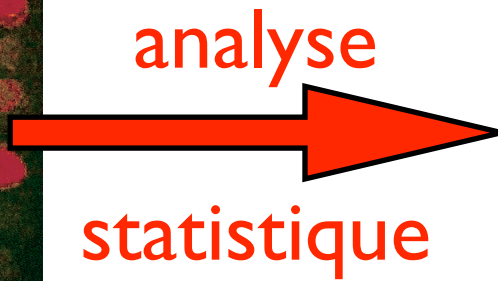


*Puces à ADN*

# Distribution des gènes fonctionnels

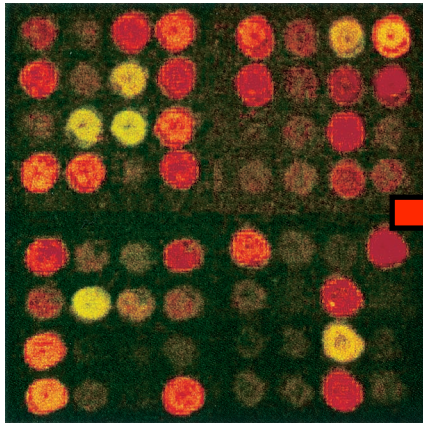


Puces à ADN

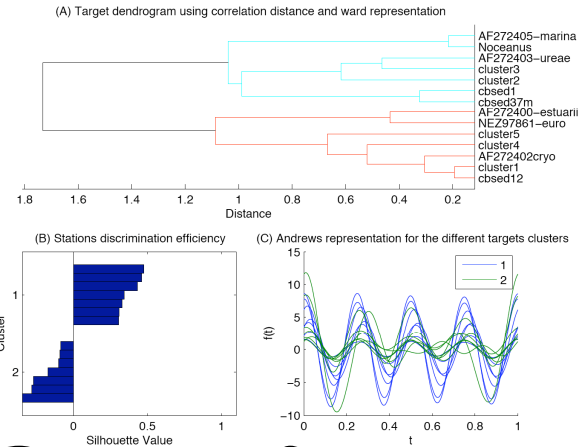
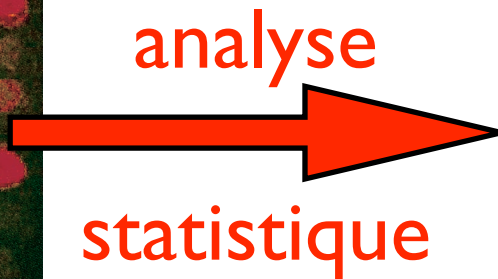


Groupes fonctionnels

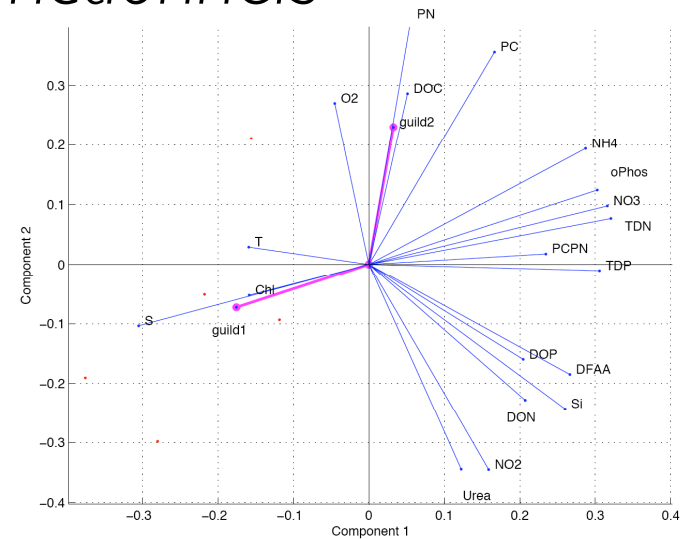
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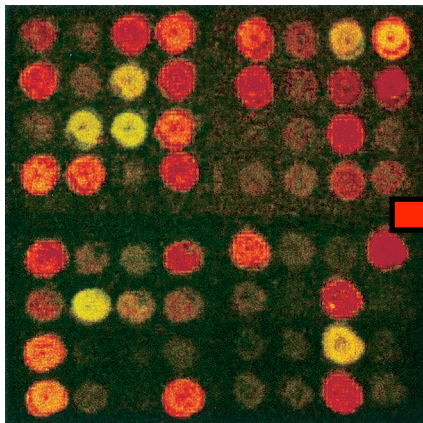
Groupes fonctionnels



Relation des groupes avec les paramètres environnementaux

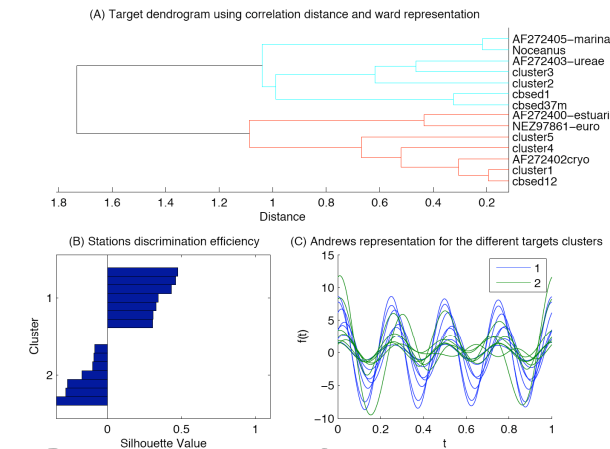


# Distribution des gènes fonctionnels



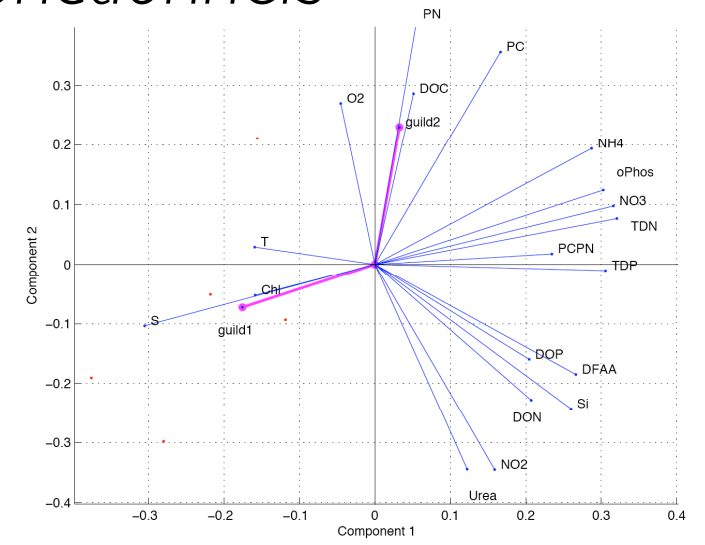
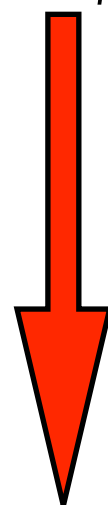
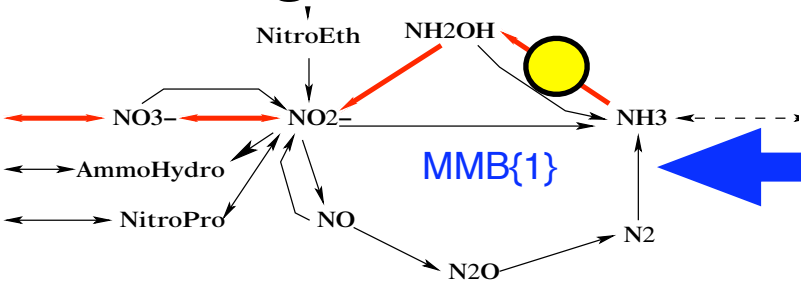
analyse  
statistique

Puces à ADN



Groupes fonctionnels

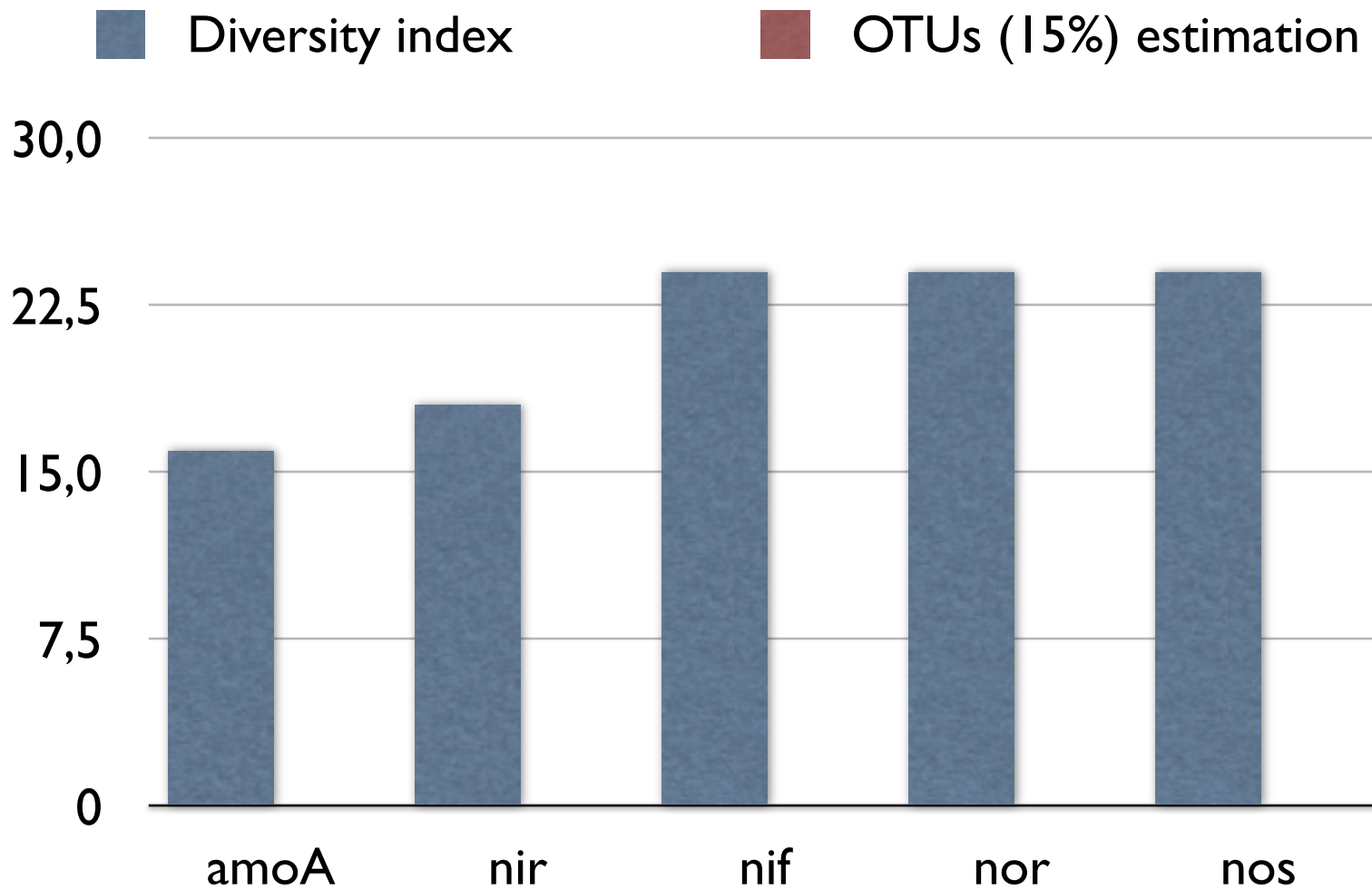
activation gène  
antagoniste NH3 & AA



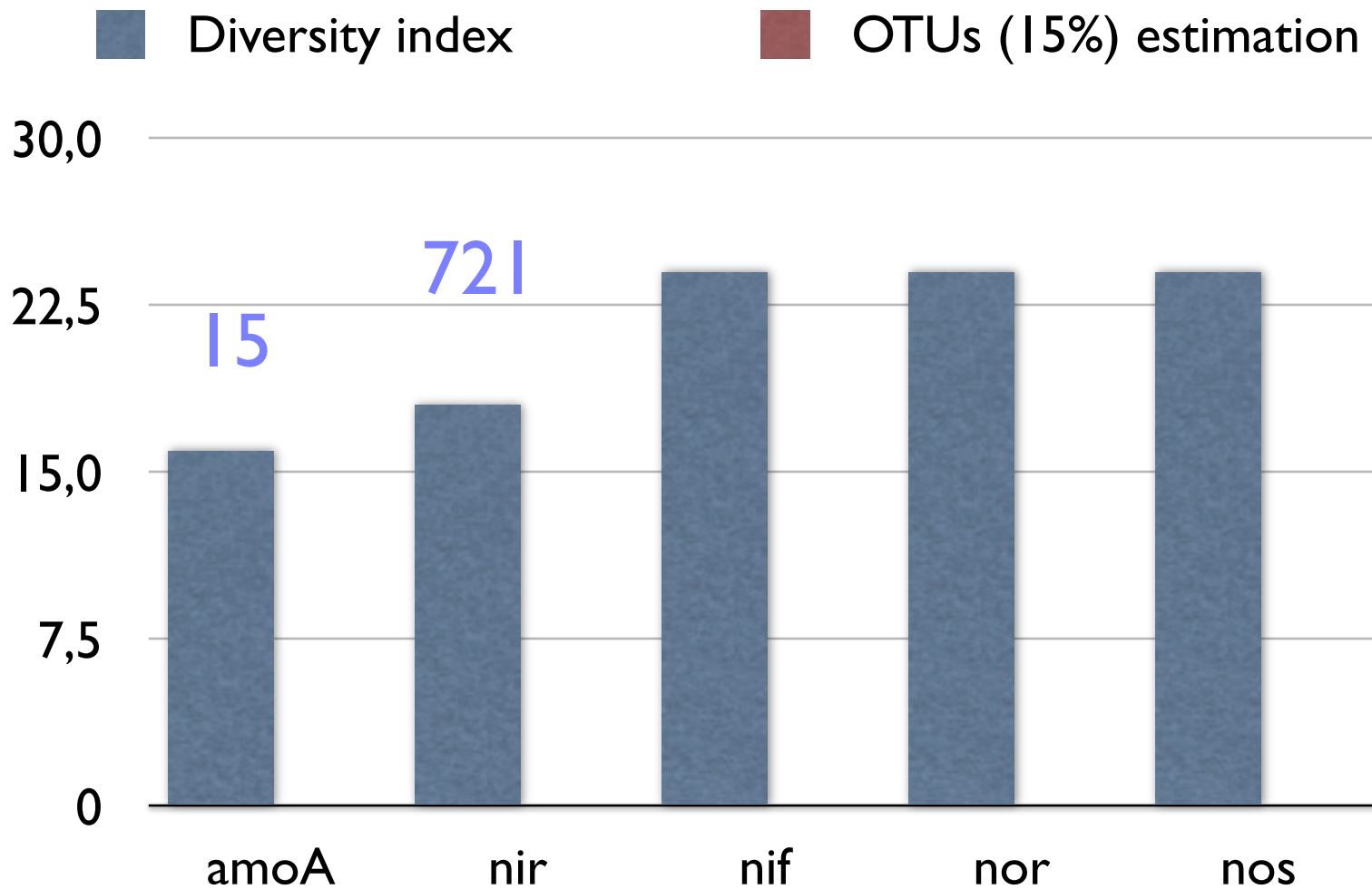
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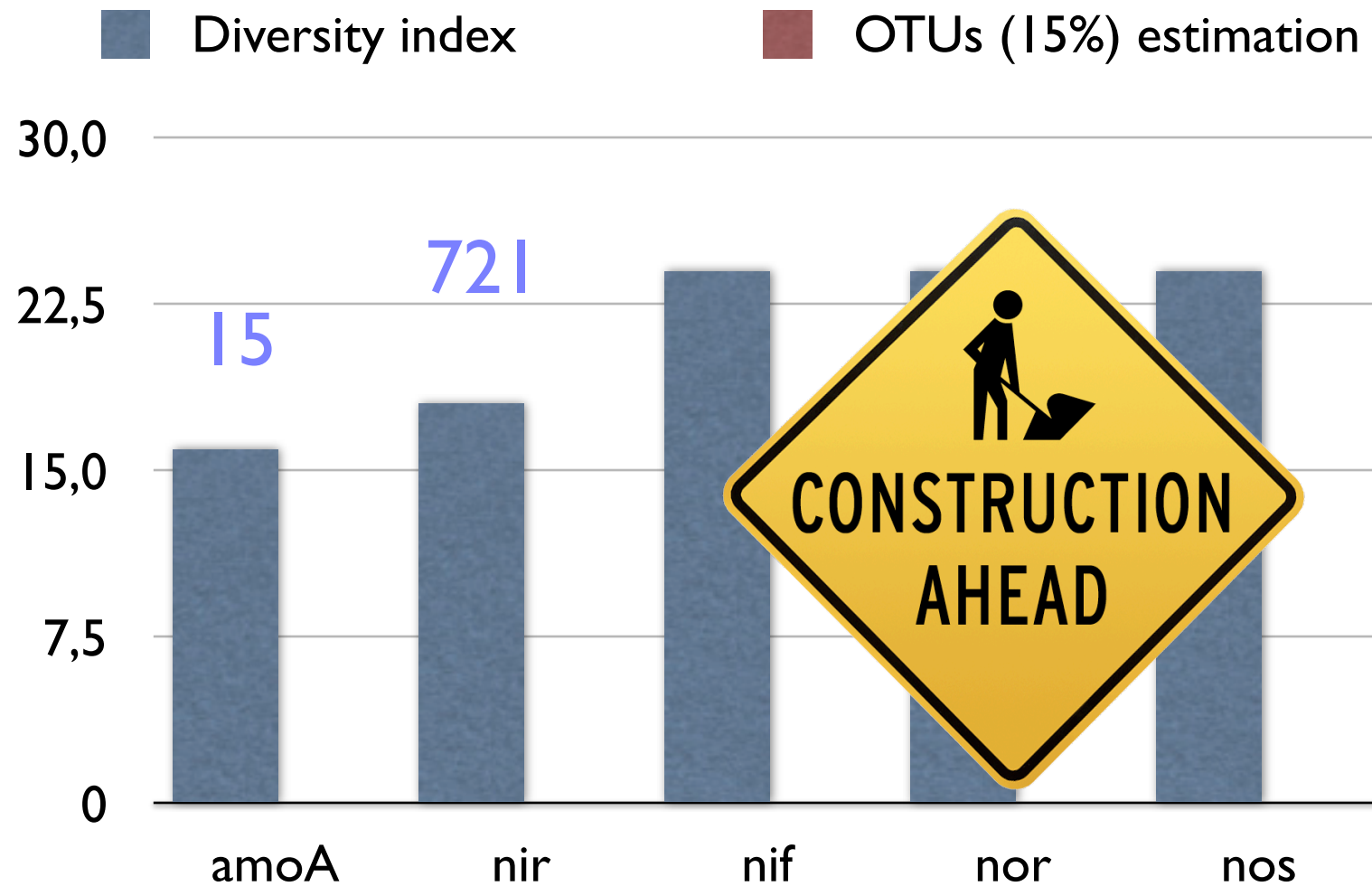
# Index de diversité fonctionnelle



# Index de diversité fonctionnelle



# Index de diversité fonctionnelle



# Conclusions/Perspectives

# Conclusions

1. Théorie unificatrice pour les systèmes biologiques

dynamique (*systèmes hybrides*)

à l'équilibre

2. Vers une **conceptualisation** des concepts de biologie théorique : besoin des sciences formelles

3. Pas seulement simuler mais surtout **raisonner** sur le vivant pour comprendre le

# Perspectives

## 1. Travailler sur la modularité

*Comparaison des modules issus d'algorithmes  
et MMBs*

## 2. Méthodologie de modélisation unificatrice

*Equilibre de flux & dynamique*

## 3. Transcender les échelles expérimentales

génome  $\Leftrightarrow$  métabolome

*⇒ pour une même fonction biologique*

# Perspectives (2)

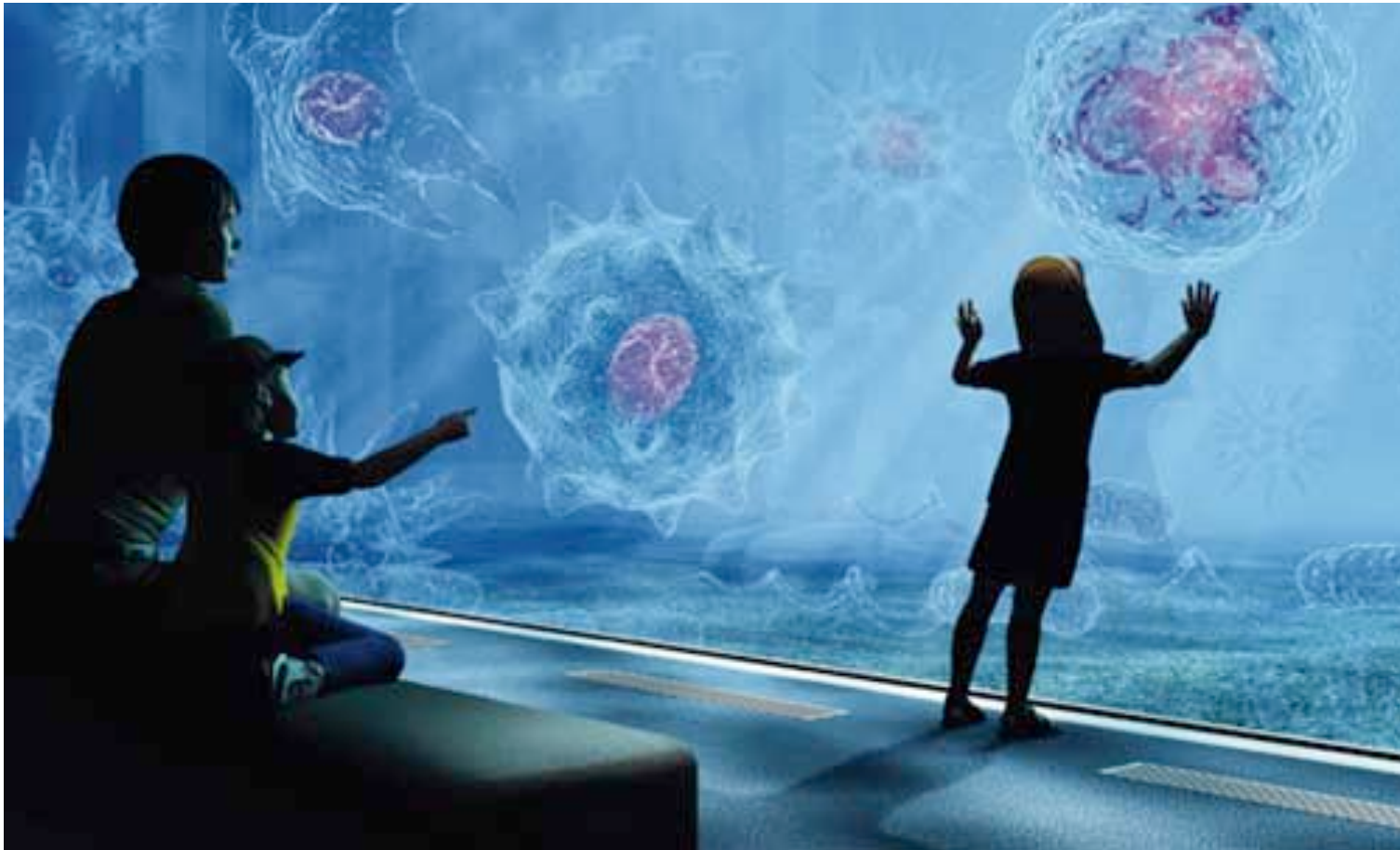
## 4. Des modèles qualitatifs vers des modèles quantitatifs

*couplage contraintes et modélisation statistique*

***Contraintes : base théorique de raisonnement***

*⇒ nouvelle fenêtre sur le vivant*

# Approches par contraintes



pour comprendre la  
biocomplexité