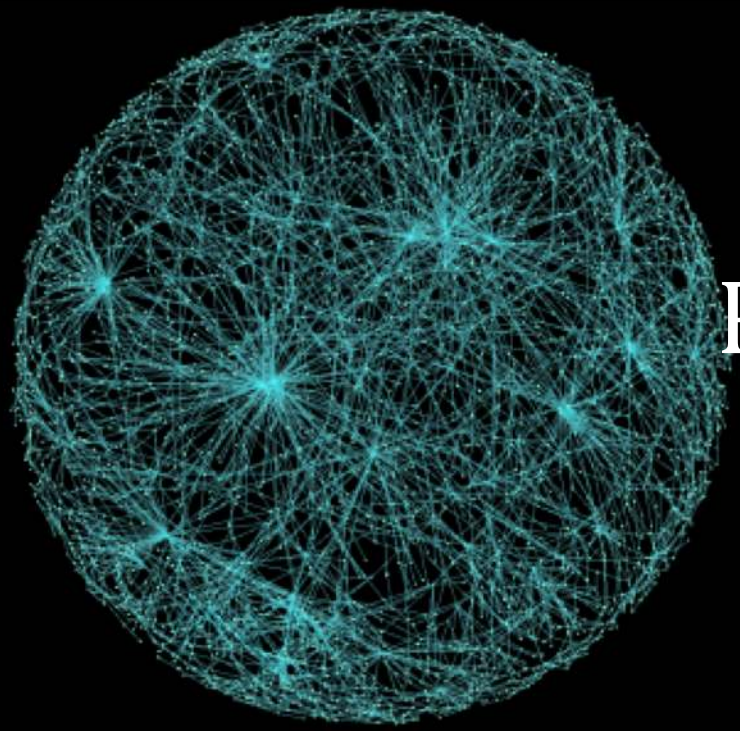
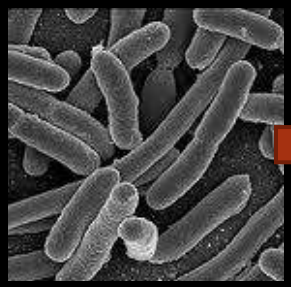
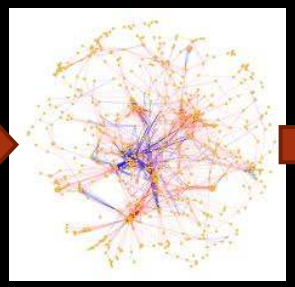
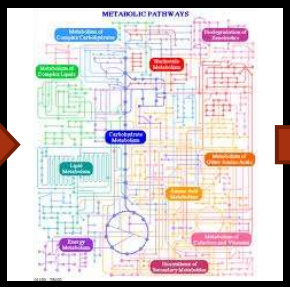


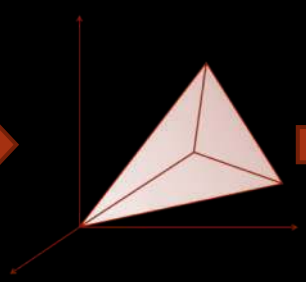
Réseau et modélisation métabolique

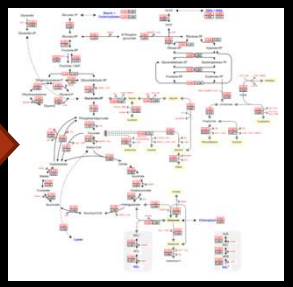






$$Kv = 0$$





Sommaire

- Métabolisme et réseaux métaboliques
- Reconstruction métabolique
- Fondamentaux de la modélisation métabolique
- Elementary flux modes
- Prise en compte de la thermodynamique
- Flux Balance Analysis & Flux Variance Analysis

Métabolisme et réseaux métaboliques

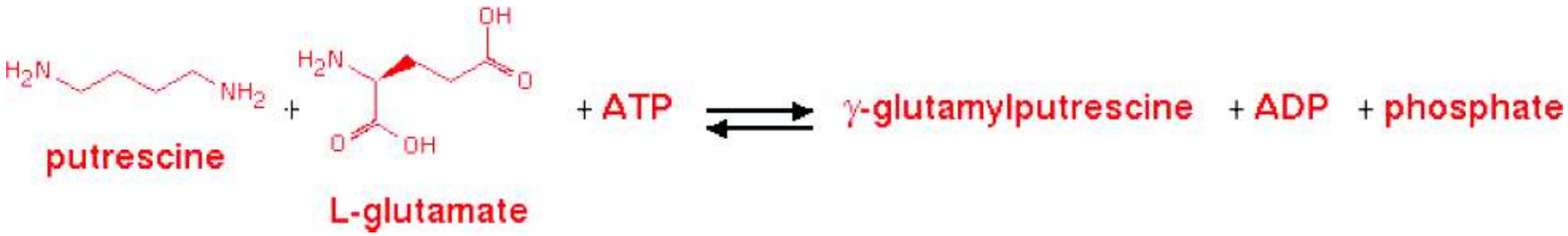
Définitions

- Métabolisme :

« Ensemble des réactions biochimiques ayant lieu dans une cellule »

Provost,A. (2006) Metabolic design of dynamic bioreaction models. 206.

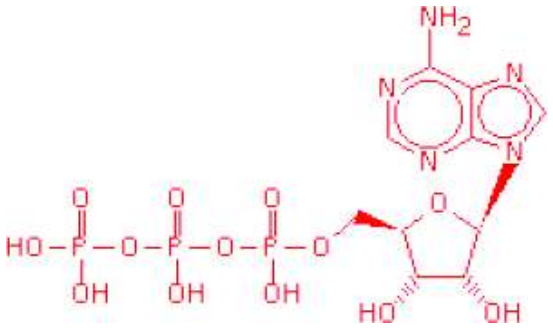
Réaction biochimique



Attributs:

- ✓ Réversibilité
- ✓ Spontanée/Catalysée/Inhibée
- ✓ Constante d'équilibre
- ✓ Cinétique (vitesse)

Métabolites



Attributs :

- Structure
- Poids moléculaire
- Charge
- Activation ou l'inhibition de réactions (difficilement connu)

Enzymes

Les enzymes sont composées par une ou plusieurs protéines et accélèrent la vitesse d'une réaction (voire la rends possible)

Attributs :

- Séquences protéiques (acides aminés)
- Structure
- Activité catalytique (paramètres cinétiques)
- ➔ classifiées pas un EC number

Ec number

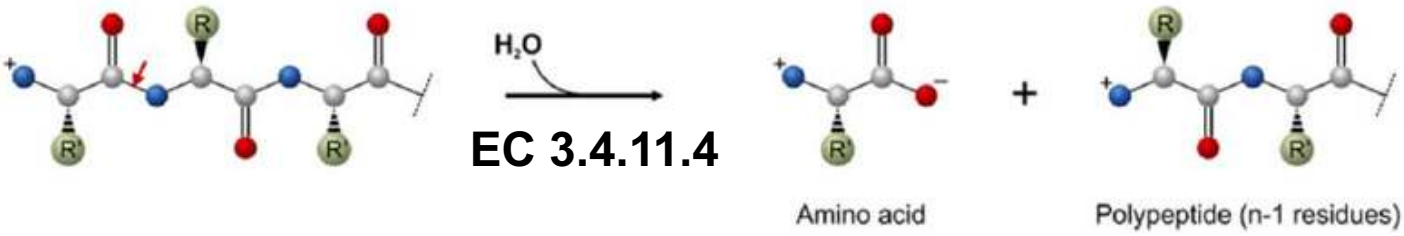
EC number = Enzyme Commission Number

Classification hiérarchique pour les enzymes, basée sur les **réactions chimiques qu'elles catalysent.**

Les nombres représentent **progressivement une classification plus fine** de l'enzyme

Ec number

Tripeptide aminopeptidase



EC 3 **Hydrolases**: enzymes that use water to break up some other molecule

EC 3.4 Hydrolases that act on **peptide bonds**

EC 3.4.11 Hydrolases that cleave off the **amino-terminal amino acid from a polypeptide**

EC 3.4.11.4 Hydrolases that cleave off the amino-terminal end **from a tripeptide**

Définitions

- Métabolisme :

« Ensemble des réactions biochimiques ayant lieu dans une cellule »

- Ces réactions s'organisent en réseau.

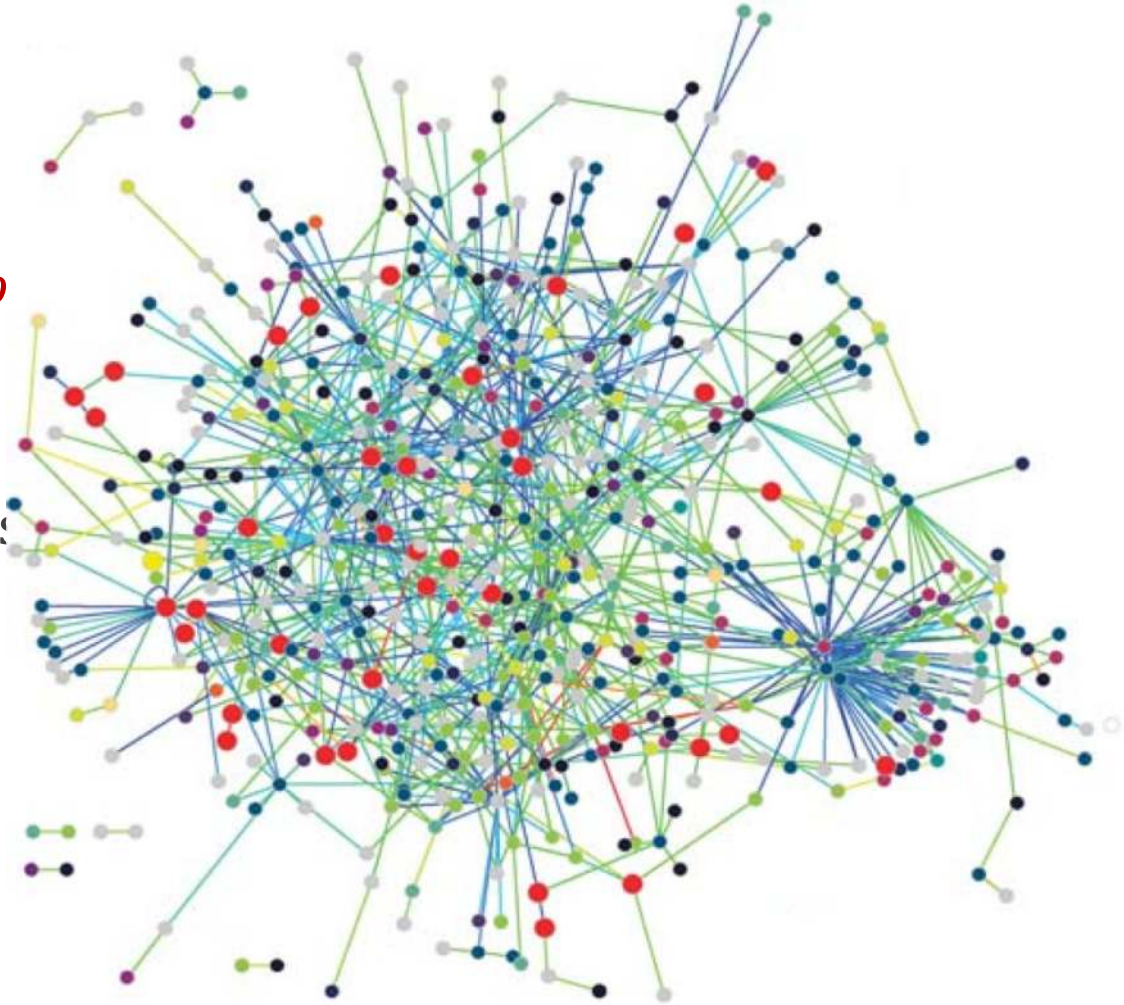
Provost,A. (2006) Metabolic design of dynamic bioreaction models. 206.

Définitions

- Métabolisme :

  « Ensemble des réactio

- Ces réactions s'organis



Provost,A. (2006) Metabolic design of dynamic bioreaction models. 206.

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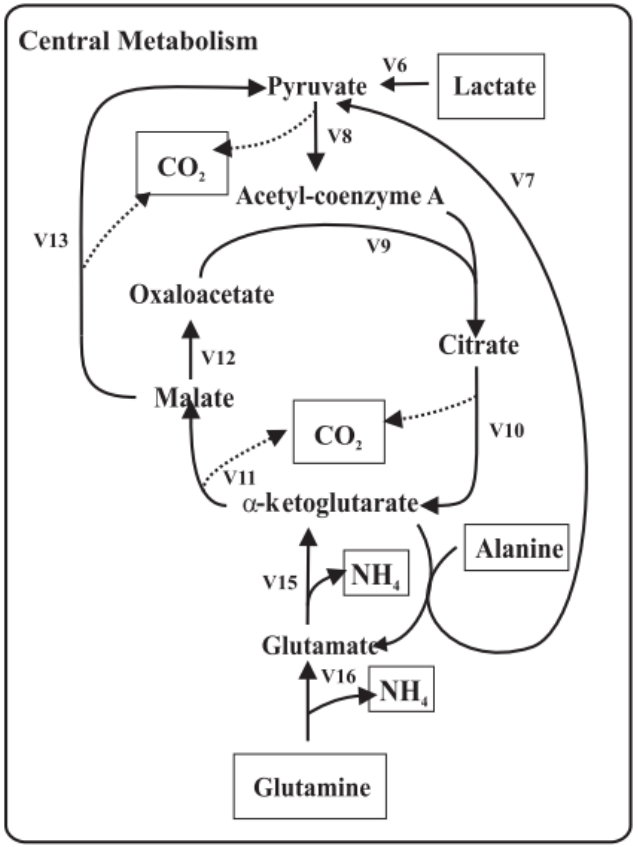


Provost,A. (2006) Metabolic design of dynamic bioreaction models. 206.

Définitions

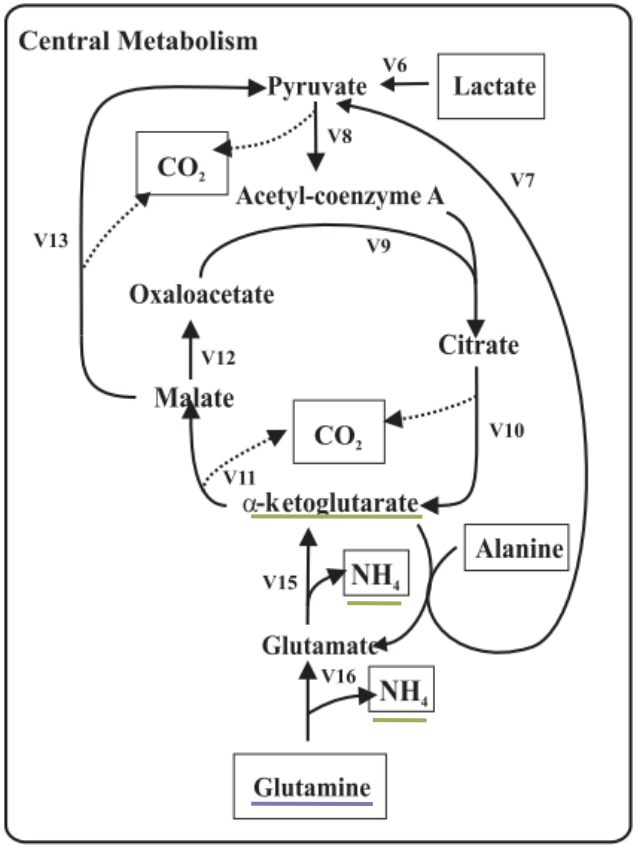
- Métabolisme :

  « Ensemble des réactions biochimiques c
  cellule »

- Ces réactions s'organisent en réseau.

- Chemin métabolique :

« Ensemble ordonné de réactions biochimiques conduisant à la production de produit(s) finaux à partir de subtrat(s)»



Provost,A. (2006) Metabolic design of dynamic bioreaction models. 206.

Définitions

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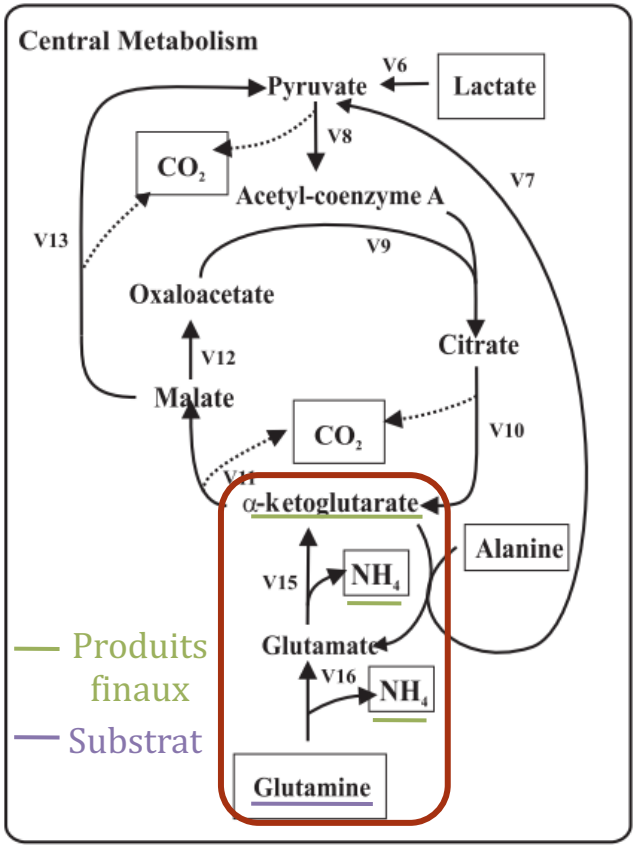

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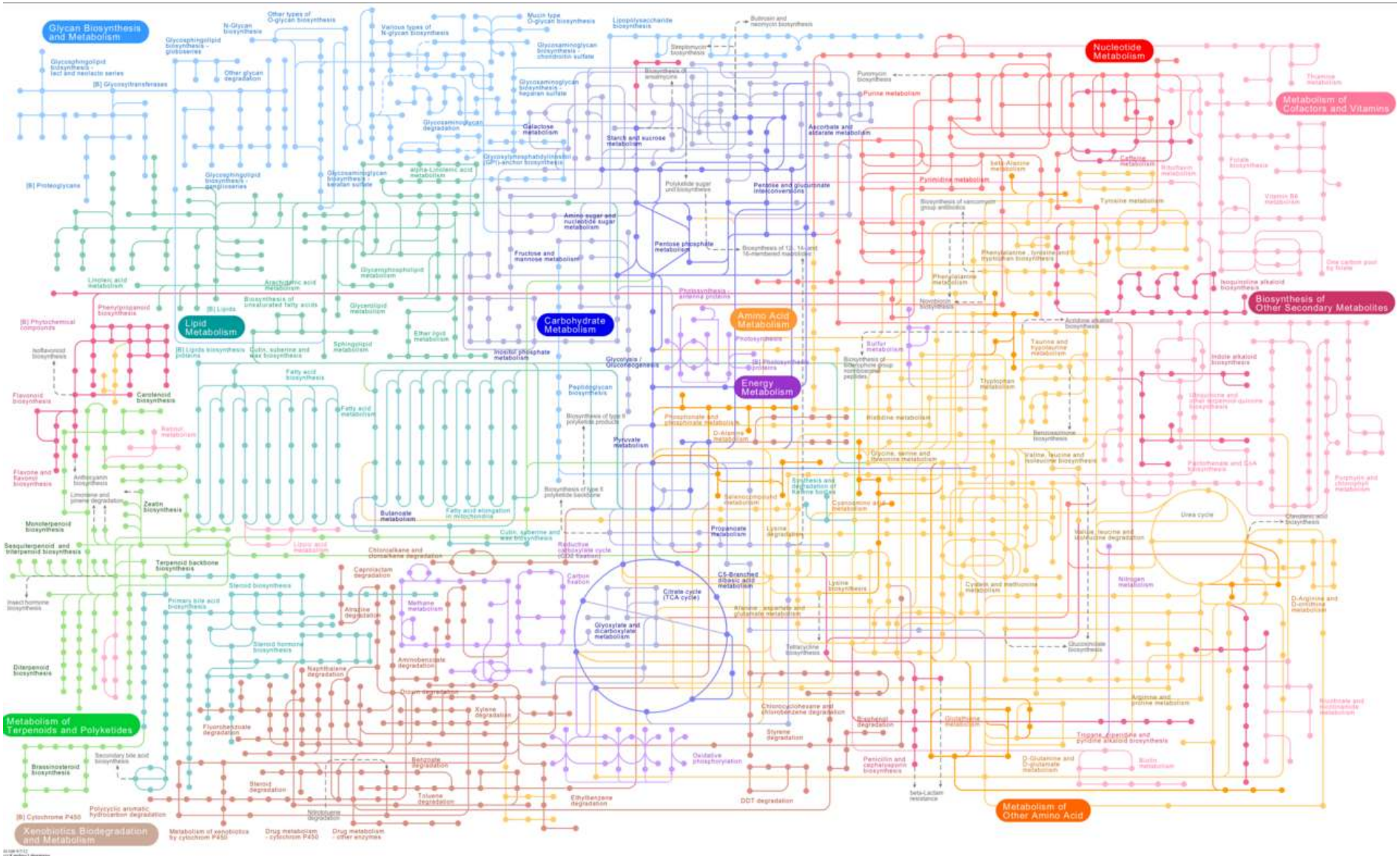
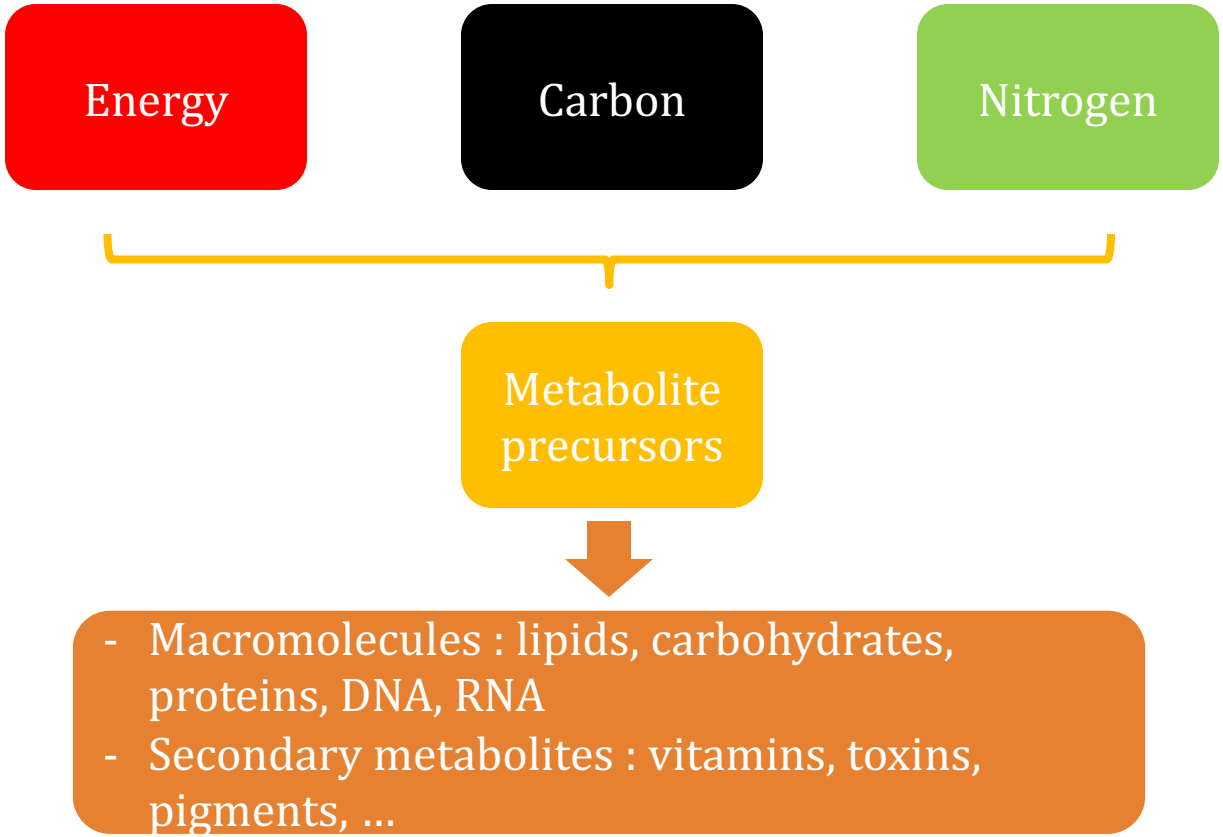
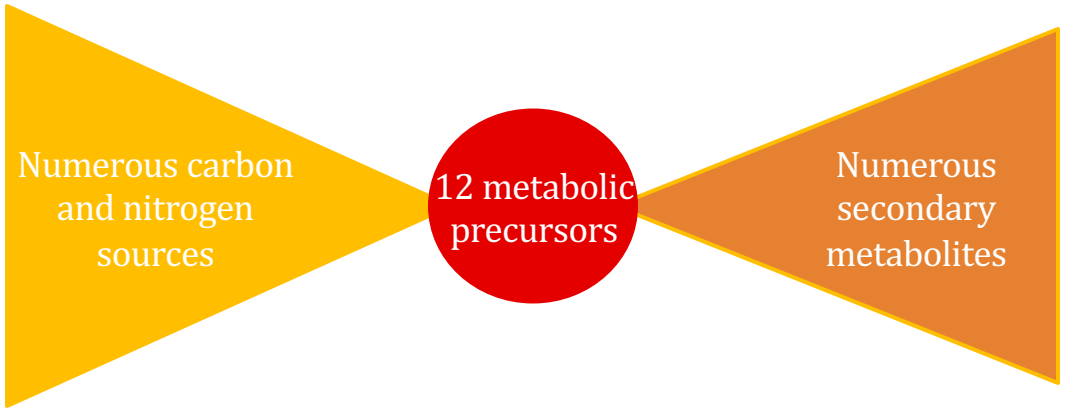


 Ogata,H. et al. (1999) KEGG: Kyoto Encyclopedia of Genes and Genomes. *Nucleic acids research*, **27**, 29–34.

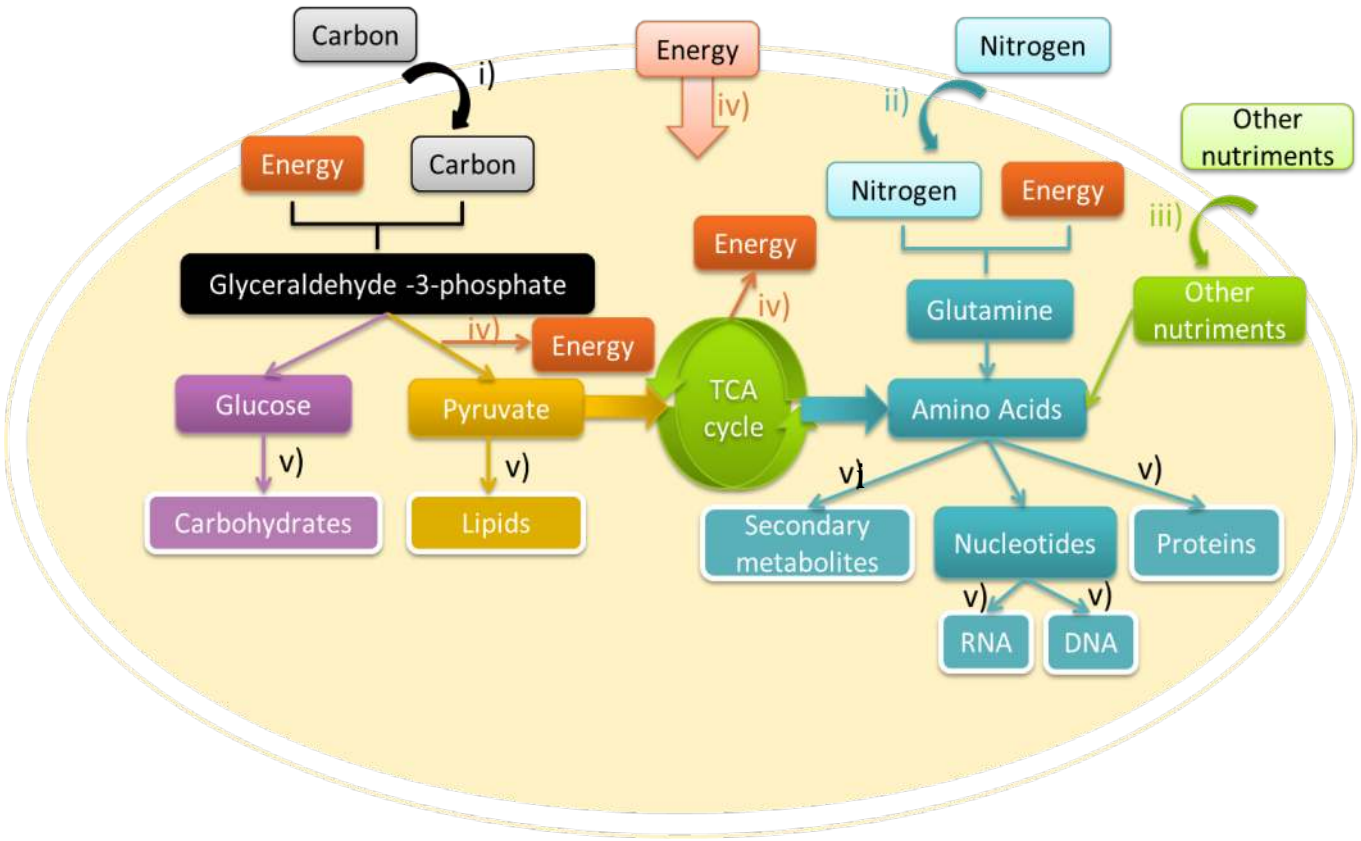
Un vue schématisée du métabolisme



Structure en noeud papillon (bow-tie)



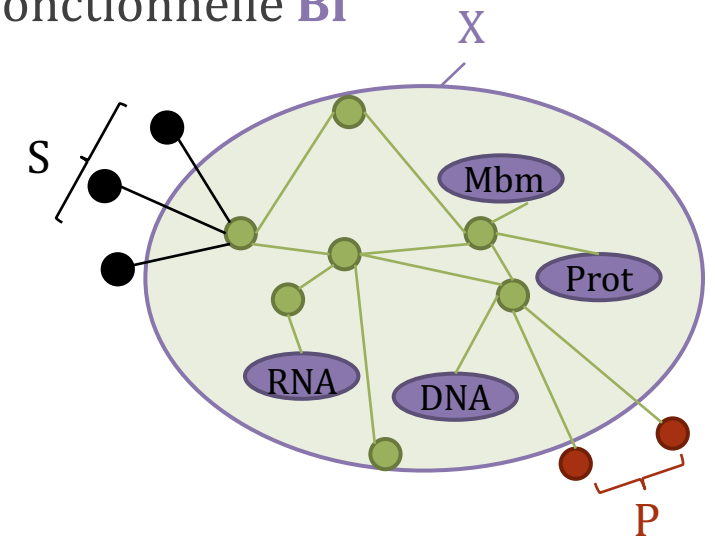
Une vue globale…



i) Carbon assimilation
ii) Nitrogen assimilation
iii) Assimilation of other nutrients
iv) Energy production
v) Macromolecule synthesis
vi) Synthesis of secondary metabolites

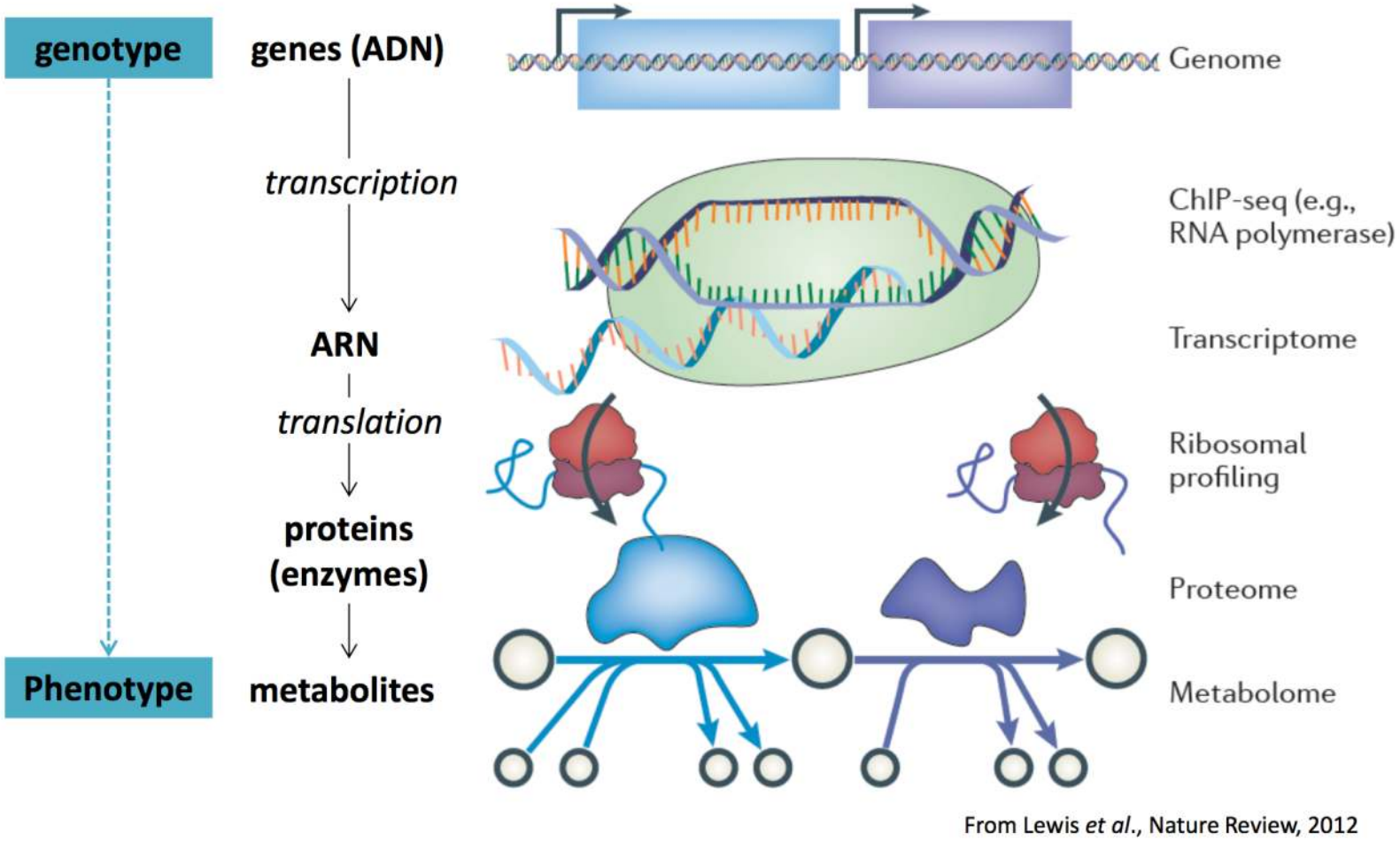
Schéma du métabolisme d'un organisme

- Métabolites externes M_{ext} : **substrats S** et **produits P**
- **Biomasse fonctionnelle Bf** : macromolécules nécessaires au fonctionnement de la cellule (lipides membranaires, protéines, ADN, ARN)
- **Métabolites intracellulaires M_{int}** : intermédiaires dans la transformation des substrats **S** en produits **P** et en biomasse fonctionnelle **Bf**



Biomasse totale X = C + Bf

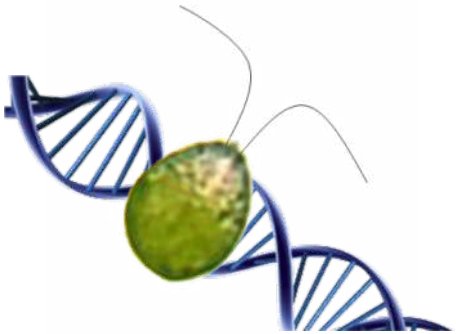
Le métabolisme : au plus proche de la physiologie



From Lewis *et al.*, Nature Review, 2012

A quoi sert l'étude du métabolisme

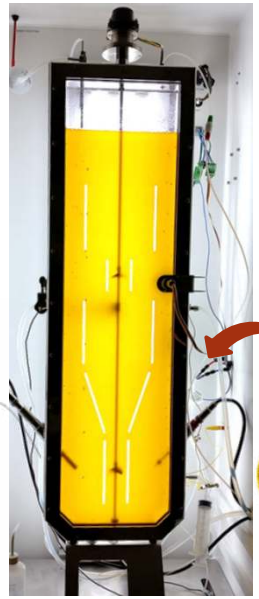
- L'étude du métabolisme permet de :
  - faire le lien entre le génome et la physiologie



Genome

?

Nitrogen replete



Nitrogen starvation

Physiology

A quoi sert l'étude du métabolisme

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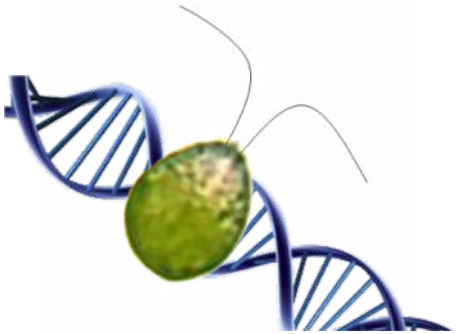

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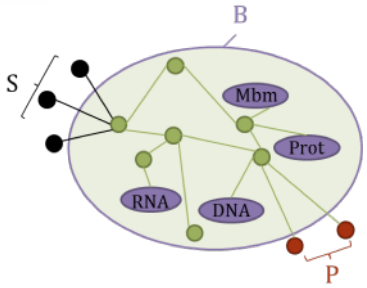
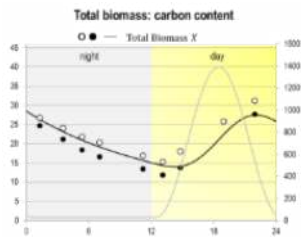
?



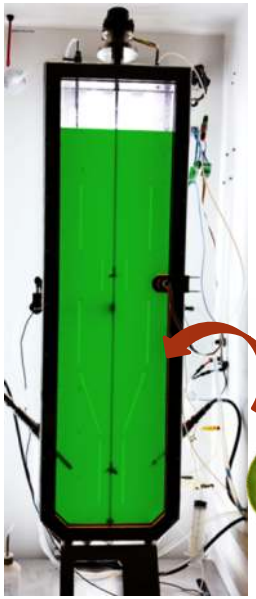
Metabolism

+

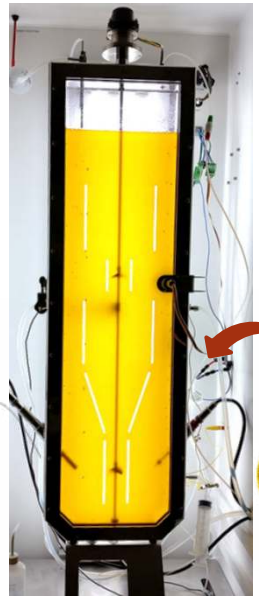


$$\frac{dM}{dt} = K.v.B$$

Mathematical Model



Nitrogen replete



Nitrogen starvation

Physiology

A quoi sert l'étude du métabolisme

- L'étude du métabolisme permet de :
  - faire le lien entre ce qui est observé (macroscopique) et ce qui se passe dans la cellule (intracellulaire)
  - mieux comprendre les mécanismes intracellulaires et le comportement d'une cellule/d'un organisme/d'un écosystème sous différents environnement

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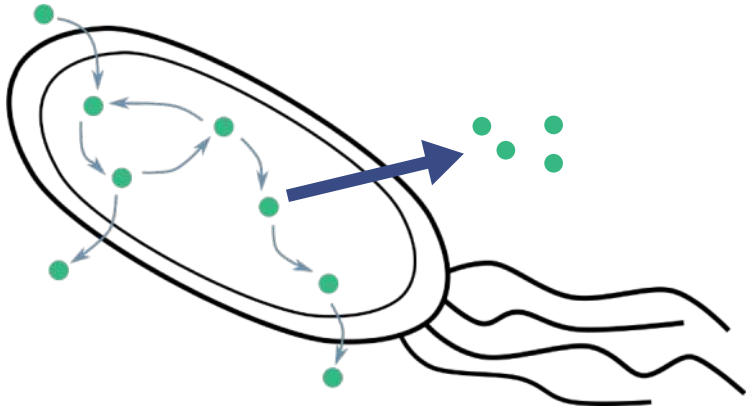
  - mieux comprendre les mécanismes intracellulaires et le comportement d'une cellule/d'un organisme/d'un écosystème sous différents environnement
  - prédire des rendements de production de molécules d'intérêt

Exemple: production de biocarburants, vitamines, protéines par des souches microbiennes telles que e *E. coli*



A quoi sert l'étude du métabolisme

- L'étude du métabolisme per
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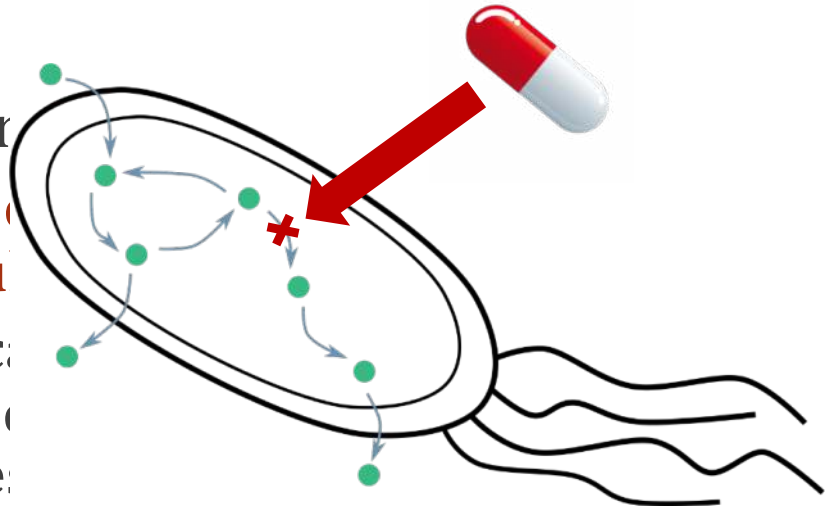
    ce qui se passe dans la cellu
  - mieux comprendre les méc
    comportement d'une cellul
    écosystème sous différente
  - prédire des rendements de
    d'intérêt
  - d'aider à modifier le réseau métabolique (suppression/ ajout de gène) pour synthétiser ou inhiber la production d'une molécule



Exemple: prédire des nouvelles drug targets contre *Mycobacterium tuberculosis.*

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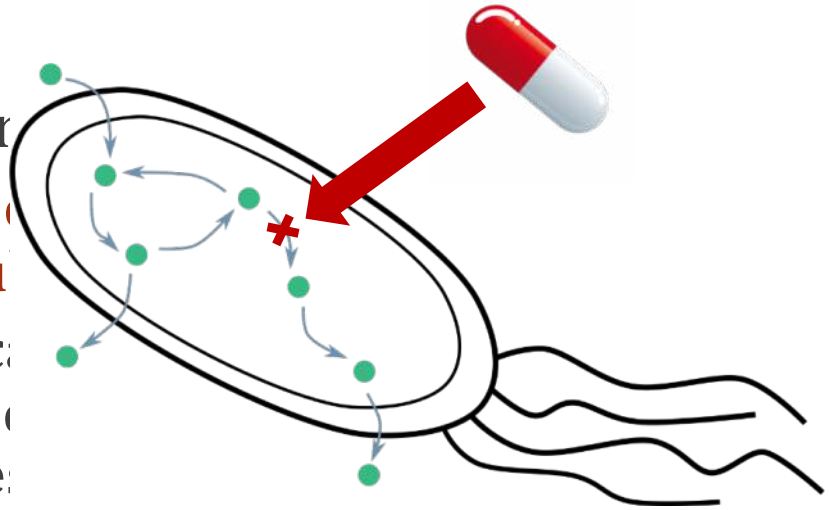
  - …



Exemple: prédire des nouvelles drug targets contre *Mycobacterium tuberculosis.*

Où trouver des réseaux métaboliques?

- Littérature :
  - *Saccharomyces cerevisiae* :

    Duarte,N.C. et al. (2004) Reconstruction and validation of Saccharomyces cerevisiae iND750, a fully compartmentalized genome-scale metabolic model. *Genome research*, **14**, 1298–309.

  - *Escherichia coli* :

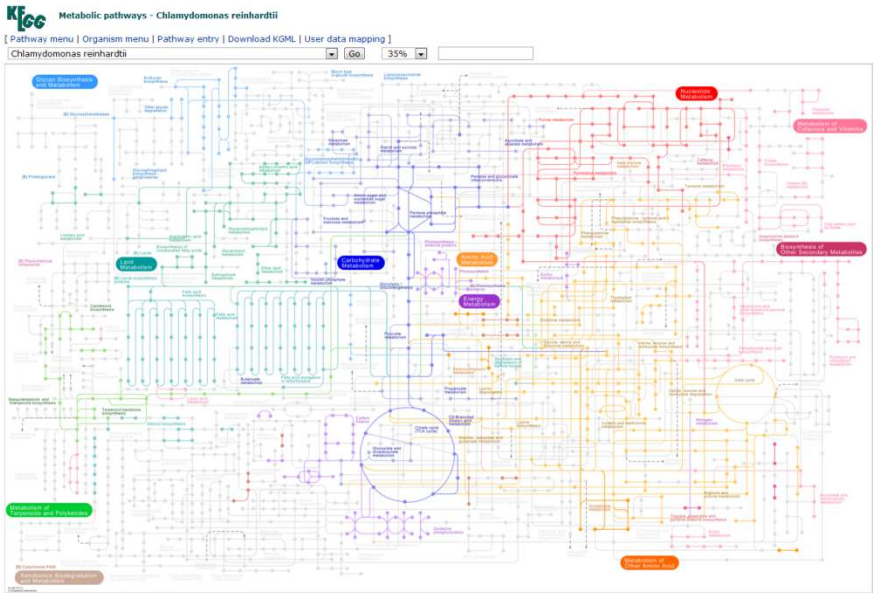
    Orth,J.D. et al. (2011) A comprehensive genome-scale reconstruction of Escherichia coli metabolism--2011. *Molecular systems biology*, **7**, 535.

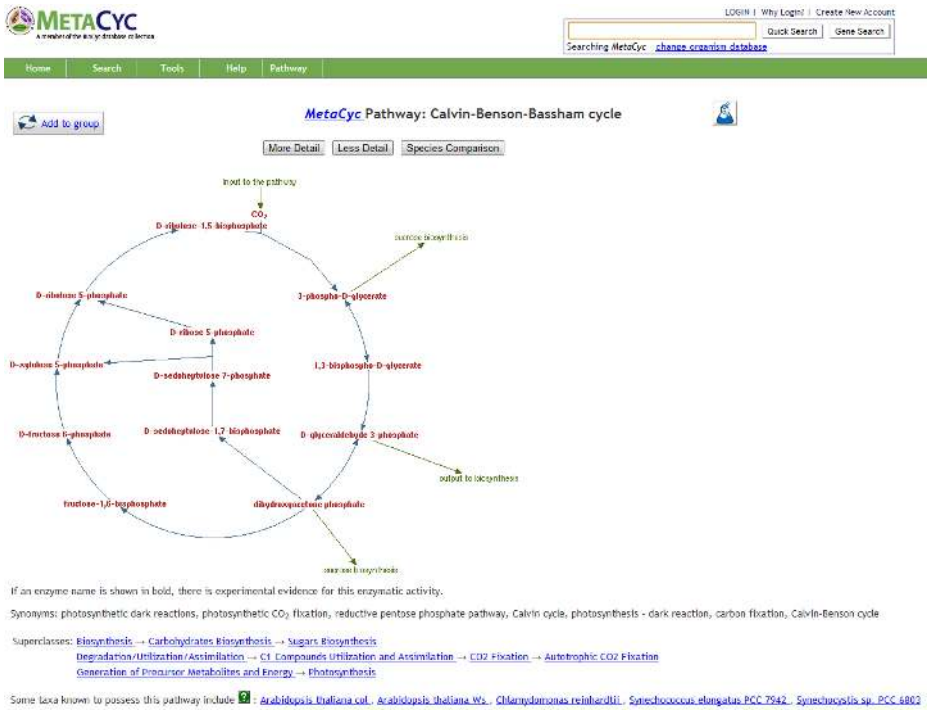
  - *Chlamydomonas reinhardtii :*

    Boyle,N.R. and Morgan,J. a (2009) Flux balance analysis of primary metabolism in Chlamydomonas reinhardtii. *BMC systems biology*, **3**, 4.

Où trouver des réseaux métaboliques?

- A partir de bases de données
  - KEGG[1]
  - MetaCyc[2]
  - …





1, Ogata,H. et al. (1999) KEGG: Kyoto Encyclopedia of Genes and Genomes. *Nucleic acids research*, **27**, 29–34.
2. Karp,P.D. et al. (2000) The EcoCyc and MetaCyc databases. *Nucleic acids research*, **28**, 56–9.

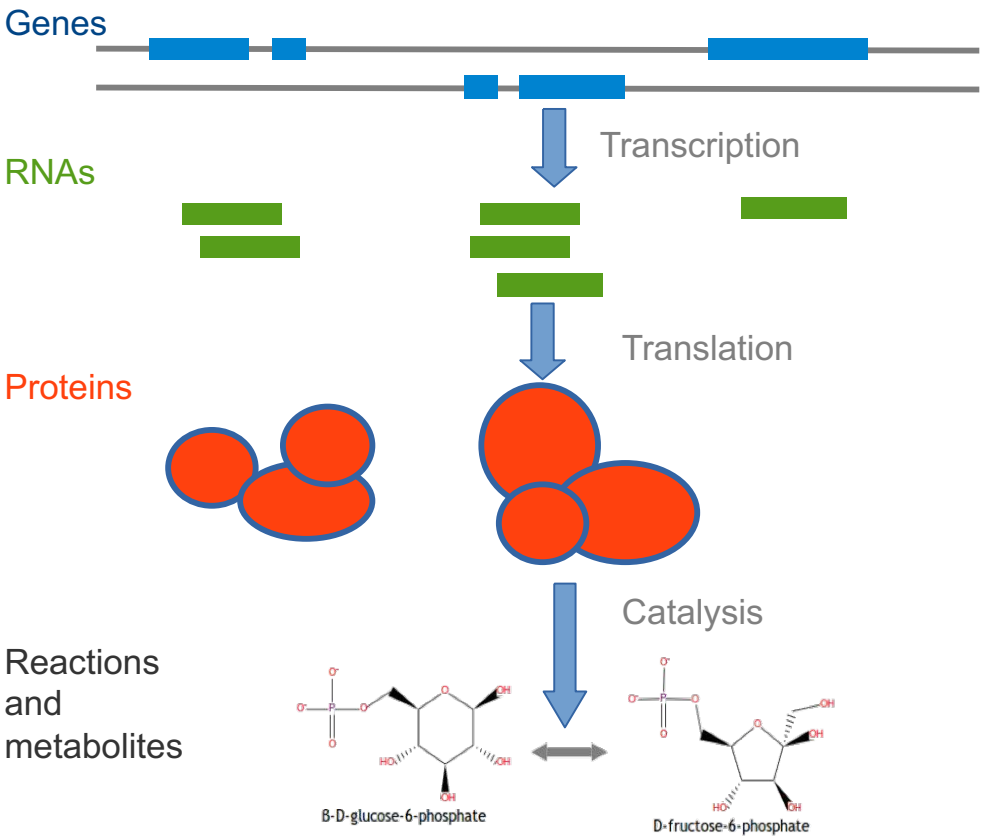
Où trouver des réseaux métaboliques?

- A partir de bases de données
  - KEGG[1]
  - MetaCyc[2]
  - …
- Reconstruction à partir du génome

1, Ogata,H. et al. (1999) KEGG: Kyoto Encyclopedia of Genes and Genomes. *Nucleic acids research*, **27**, 29–34.
2. Karp,P.D. et al. (2000) The EcoCyc and MetaCyc databases. *Nucleic acids research*, **28**, 56–9.

Fondamentaux de la reconstruction métabolique

From genes to reactions



Global view

Sequences and/or annotations → **Automatic reconstruction** → **« Draft network »** → **Curation** → **Metabolic network**

```
>Q2V9N9
MRNTLVSHYQHIIEYRRKSLMGVVFVNYARSFLAGTMALSAVCLN
LNPSYSRVQNFKLKDAGNDPAGILAYHSGIGTVPERFDWNTLDAN
LGIGREAFPVKTDEAGSSRTFLLIRNLARAVAQHDSDTIESELFQ
SVEQRFVDIMQSIQKDPKAEFPRSAVKHLVAGYGAEKYKYSPKLV
ATVARISGITSTSVTLNVCRDVPTYIPNARLIPYACAGVGWGFIG
HLIAGAFLQGVFGSVKHQDIDTDVVAGNISKAASHISSTFRLKNL
>O83055
MGACISVYARFALGCGVFFLHGAVLDGVSRAFSSSAAFSGSAELS
KSSWKLAFPLLPKKGATYTSFSGEDPIWVELSLKGLKVDFESALG
ATLHLYDVSFSVGKDPVFPSNFAQLWTPFITTSYESRSVKYAPGF
SFSSNGIWKSAPSVTSKVKGKGTNSRRMPADPHSKYGLGTEFTLV
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LGLLVAAAKTRNELAAQMRSQSPPGVWEKFEQAVQSLPPITQGKP
VLSVLEQGGFDRVAFDALLIVQWRWISLGAYVASAPTNVFGSMLF
KLVSGLSGGVEARLYIPFTHGLYLEPGSCTPNSTRGKKPQAFVLP
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MLARRPYISLEHGSWPDKRSELVCSCKVLW
```
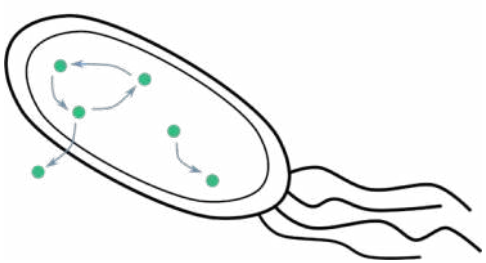
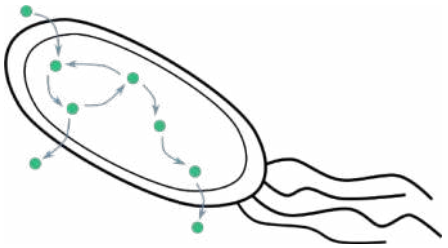





Metabolic network reconstruction: principle

1. Find by orthology (BLASTp) the reactions to propagate

E. Coli

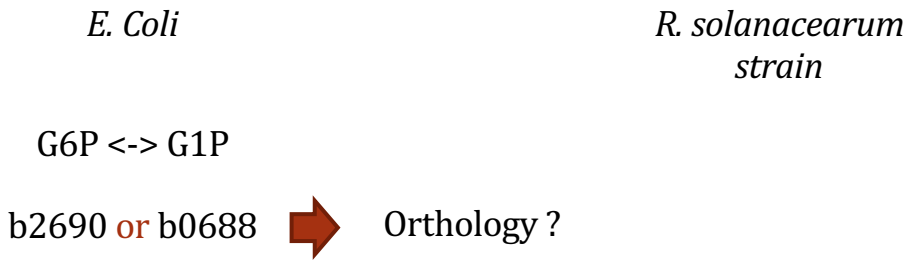
G6P <-> G1P

b2690 or b0688

R. solanacearum strain

Metabolic network reconstruction: principle

1. Find by orthology (BLASTp) the reactions to propagate



Metabolic network reconstruction: principle

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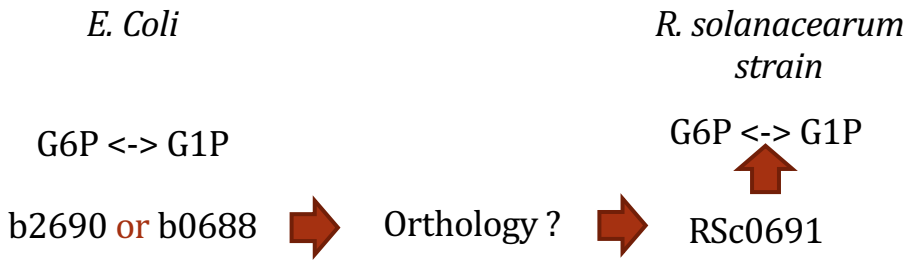

Metabolic network reconstruction: principle

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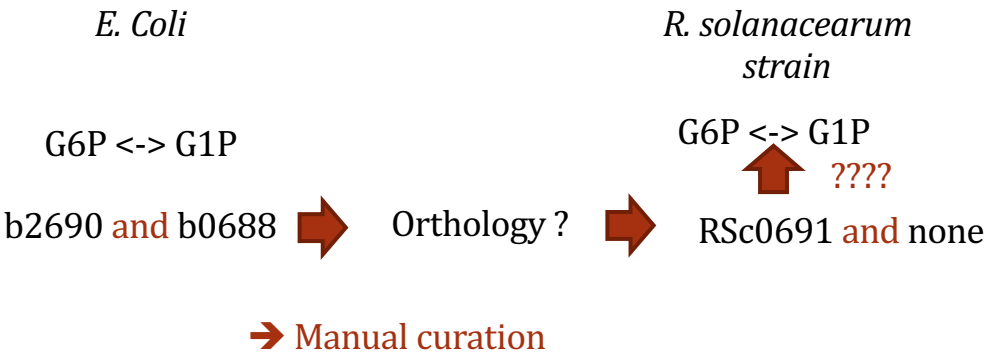


Metabolic network reconstruction: principle

1. Find by orthology (BLASTp) the reactions to propagate
2. Fill the gaps

G1P <--> CARBOHYDRATES + Pi
G1P <-->G6P
G6P <-->F6P

F16P <--> DHAP + GAP
…

Metabolic network reconstruction: principle

1. Find by orthology (BLASTp) the reactions to propagate
2. Fill the gaps

G1P <--> CARBOHYDRATES + Pi
G1P <-->G6P
G6P <-->F6P
?????
F16P <--> DHAP + GAP
…

➔ Manual curation

➔ Search for possible reactions filling the gap in databases

Metabolic network reconstruction: principle

1. Find by orthology (BLASTp) the reactions to propagate
2. Fill the gaps

G1P <--> CARBOHYDRATES + Pi
G1P <-->G6P
G6P <-->F6P
ATP + F6P --> ADP + F16P
F16P <--> DHAP + GAP
…

➔ Manual curation

➔ Verify if the gene catalyzing the reaction is present
or if physiological evidence is in literature
or do the experimental validation

Metabolic network reconstruction: principle

1. Find by orthology (BLASTp) the reactions to propagate
2. Fill the gaps
3. Fix all other issues
   - ✓ Charge of reactions
   - ✓ Sense and reversibility of reactions
   - ✓ Locations of reactions inside the cell
   - ✓ Specific reactions of the organisms
   - ✓ Generic reactions
   - ✓ Blocked reactions
   - ✓ Free food, free energy, etc.
   - ✓ …

Global view

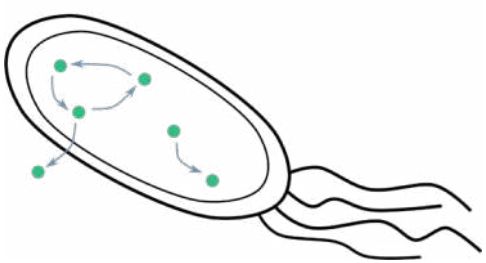
Sequences and/or annotations

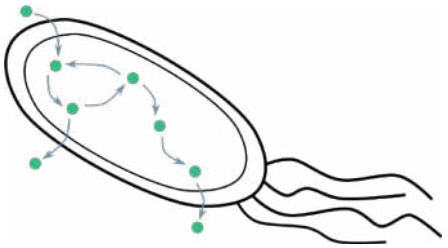
Automatic reconstruction

« Draft network »

Metabolic network

```
>Q2V9N9
MRNTLVSHYQHIIEYRRKSLMGVVFVNYARSFLAGTMALSAVCLN
LNPSYSRVQNFKLKDAGNDPAGILAYHSGIGTVPERFDWNTLDAN
LGIGREAFPVKTDEAGSSRTFLLIRNLARAVAQHDSDTIESELFQ
SVEQRFVDIMQSIQKDPKAEFPRSAVKHLVAGYGAEKYKYSPKLV
ATVARISGITSTSVTLNVCRDVPTYIPNARLIPYACAGVGWGFIG
HLIAGAFLQGVFGSVKHQDIDTDVVAGNISKAASHISSTFRLKNL
>O83055
MGACISVYARFALGCGVFFLHGAVLDGVSRAFSSSAAFSGSAELS
KSSWKLAFPLLPKKGATYTSFSGEDPIWVELSLKGLKVDFESALG
ATLHLYDVSFSVGKDPVFPSNFAQLWTPFITTSYESRSVKYAPGF
SFSSNGIWKSAPSVTSKVKGKGTNSRRMPADPHSKYGLGTEFTLV
GPDQTHHQNKDTVLWNVGARLTLSPGAGFKIVCAFDAGTPYKKGA
LGLLVAAAKTRNELAAQMRSQSPPGVWEKFEQAVQSLPPITQGKP
VLSVLEQGGFDRVAFDALLIVQWRWISLGAYVASAPTNVFGSMLF
KLVSGLSGGVEARLYIPFTHGLYLEPGSCTPNSTRGKKPQAFVLP
TLAAHAWIRPMVSLYGATYGAQGFSYGPGGAAGTVKRNRTFRAGK
MLARRPYISLEHGSWPDKRSELVCSCKVLW
```





Automatic metabolic network reconstruction

- 2 solutions :
  BLAST against a database such as Metacyc or KEGG
  - GET all the possible reactions in the database
  - BUT many false positives, duplicates, gaps in the network, sometimes generic reactions (e.g. lipids), and many problems with update of databases (e.g. change of ids)

- Or,
  BLAST against metabolic network of species phylogenetically close (e.g. *R. eutropha*) or with a high quality metabolic networks (e.g. *E. coli*)
  - LESS reactions to curate, few duplicates, few gaps, metabolic network nearly functional
  - BUT might miss some reactions that are not present in the species of reference chosen, and difficulty to merge the networks if several species of reference (different reaction ids and metabolite ids)

Tools for automatic draft reconstruction against a database

KAAS (KEGG)

- from raw sequences, classifies each gene in a group of KEGG orthologs and returns metabolic maps with highlighted reactions

PRIAM

- from raw sequences, returns a list of potential EC numbers and KEGG metabolic maps with highlighted reactions

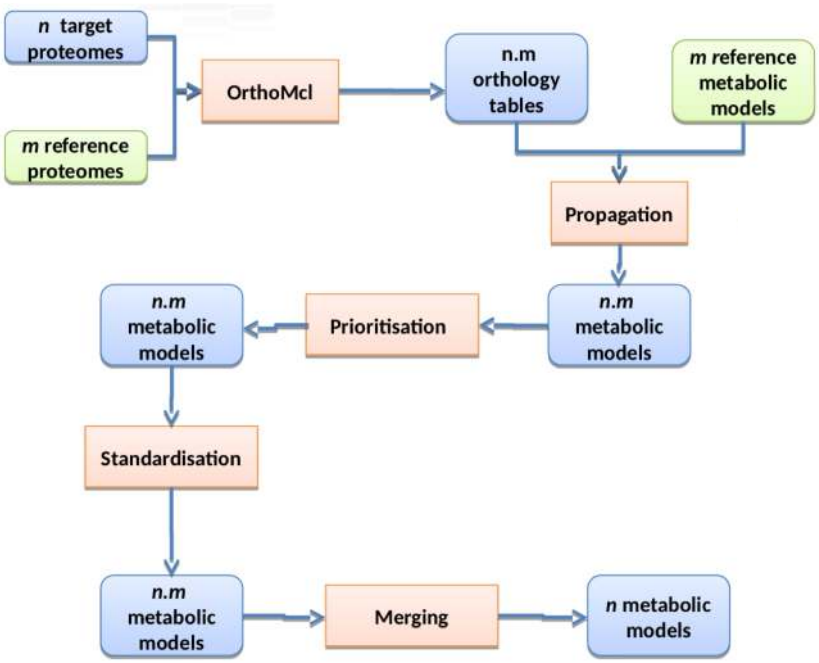
Rast server (TheSeed/ModelSeed)

- from raw sequences, returns a list of potential metabolic scenarios and a draft metabolic model

Pathway-tools (BioCyc)

- from existing annotations, creates a complete Pathway Genome DataBase (PGDB)

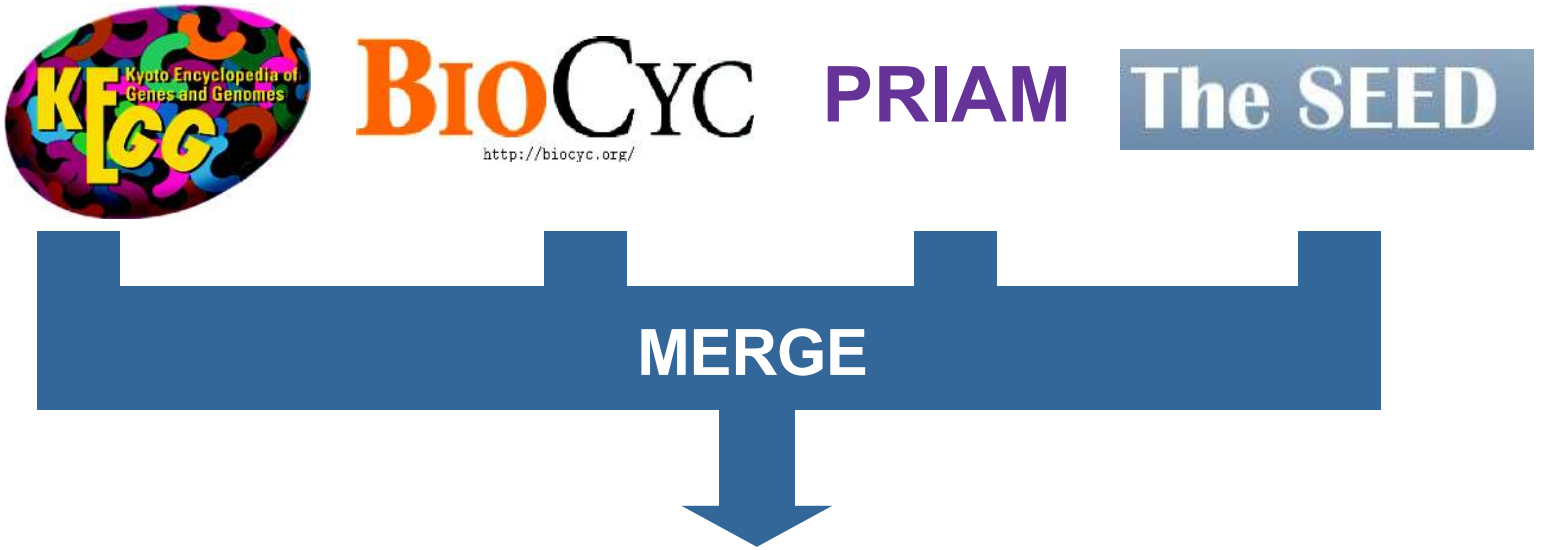
A workflow using few high quality metabolic networks



Developped by Ludovic Cottret

- n= number of species we want the metabolic network
- m = number of reference metabolic networks
- Prioritization = only one version of duplicated reactions is kept, by order preference

Merge several draft reconstructions



Draft reconstruction

One metabolite, several IDs!!!

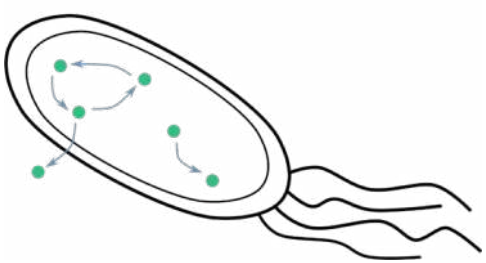
Source	Names	Abbreviations
Shewanella_oneidensis_iSO783(3)	5'-adenylate triphosphate, Adenosine 5'-triphosphate, ATP	atp
Arabidopsis_thaliana_iRS1597(1)	ATP	C00002
Zea_mays_iRS1563(1)	ATP	C00002
Porphyromonas_gingivalis(1)	ATP	atp
Rhizobium_etli(1)	ATP	atp, atp(c)
Neisseria_meningitidis(1)	Adenosine triphosphate	ATP
Clostridium_thermocellum(1)	ATP	atp
Lactobacillus_plantarum_WCFS1(1)	ATP	atp
BiGG(1)	ATP	M_atp_c, M_atp_x, M_atp_e, M_atp_b, M_atp_n, M_atp_r, M_atp_m, M_atp_g, M_atp_v
Methanosarcina_barkeri(1)	ATP	atp
Geobacter_metallireducens(1)	ATP	atp
Geobacter_sulfurreducens(1)	ATP	atp
Salmonella_typhimurium(1)	ATP	atp
Mycoplasma_genitalium(1)	ATP	atp, C00002
Halobacterium_salinarum(1)	ATP	C00002
Acinetobacter_baylyi(1)	atp	ATP
Leishmania_major(1)	ATP	atp, atp[h], atp[m], atp[n], atp[r], atp[v], atp[x]
Streptomyces_coelicolor(1)	ATP	ATP
Corynebacterium_glutamicum(1)	ATP	ATP
Aspergillus_nidulans(1)	ATP	ATP
Mannheimia_succiniciproducens(1)	ATP	ATP
KEGG(3)	ATP, Adenosine 5-triphosphate, Adenosine 5'-triphosphate	C00002, cpd:C00002
Aspergillus_niger(1)	ATP	ATP, ATPe, ATPm
Aspergillus_oryzae(1)	ATP, ATP_	ATP, ATPm, ATPp
Bacillus_subtilis_iBsu1103(3)	ATP, Adenosine 5'-triphosphate,	cpd00002

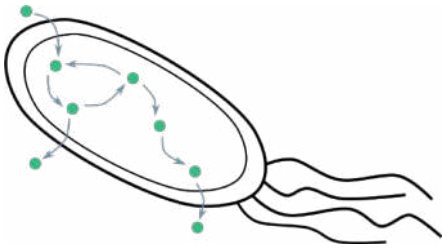
Same problem for reactions IDs!

Global view

Sequences and/or annotations → **Automatic reconstruction** → **« Draft network »** → **Curation** → **Metabolic network**

```
>Q2V9N9
MRNTLVSHYQHIIEYRRKSLMGVVFVNYARSFLAGTMALSAVCLN
LNPSYSRVQNFKLKDAGNDPAGILAYHSGIGTVPERFDWNTLDAN
LGIGREAFPVKTDEAGSSRTFLLIRNLARAVAQHDSDTIESELFQ
SVEQRFVDIMQSIQKDPKAEFPRSAVKHLVAGYGAEKYKYSPKLV
ATVARISGITSTSVTLNVCRDVPTYIPNARLIPYACAGVGWGFIG
HLIAGAFLQGVFGSVKHQDIDTDVVAGNISKAASHISSTFRLKNL
>O83055
MGACISVYARFALGCGVFFLHGAVLDGVSRAFSSSAAFSGSAELS
KSSWKLAFPLLPKKGATYTSFSGEDPIWVELSLKGLKVDFESALG
ATLHLYDVSFSVGKDPVFPSNFAQLWTPFITTSYESRSVKYAPGF
SFSSNGIWKSAPSVTSKVKGKGTNSRRMPADPHSKYGLGTEFTLV
GPDQTHHQNKDTVLWNVGARLTLSPGAGFKIVCAFDAGTPYKKGA
LGLLVAAAKTRNELAAQMRSQSPPGVWEKFEQAVQSLPPITQGKP
VLSVLEQGGFDRVAFDALLIVQWRWISLGAYVASAPTNVFGSMLF
KLVSGLSGGVEARLYIPFTHGLYLEPGSCTPNSTRGKKPQAFVLP
TLAAHAWIRPMVSLYGATYGAQGFSYGPGGAAGTVKRNRTFRAGK
MLARRPYISLEHGSWPDKRSELVCSCKVLW
```





Curation pipeline: a long task…

A draft metabolic network

6 MONTHS TO 2 YEARS

For each reaction check and modify accordingly:

- ✓ GPR
- ✓ Specificity of enzyme (e.g. check domain)
- ✓ Substrates
- ✓ Products
- ✓ Location
- ✓ Reversibility
- ✓ Charge
- ✓ Pathway
- ✓ EC Number
- ✓ …

BRENDA 1987 2019 The Comprehensive Enzyme Information System

METACYC™ UniProt

ChEBI

BiGG ♥

KEGG Kyoto Encyclopedia of Genes and Genomes

PubMed NCBI

Model with “cleaned reactions

Curation pipeline: a long task…

A draft metabolic network

6 MONTHS TO 2 YEARS

For each reaction check and modify accordingly:

- ✓ GPR
- ✓ Specificity of enzyme (e.g. check domain)
- ✓ Substrates
- ✓ Products
- ✓ Location
- ✓ Reversibility
- ✓ Charge
- ✓ Pathway
- ✓ EC Number
- ✓ …

Important: track your decisions/changes!!!!!

BRENDA 1987 2019 The Comprehensive Enzyme Information System

TAcyc™ UniProt

BiGG ♥

KEGG Kyoto Encyclopedia of Genes and Genomes

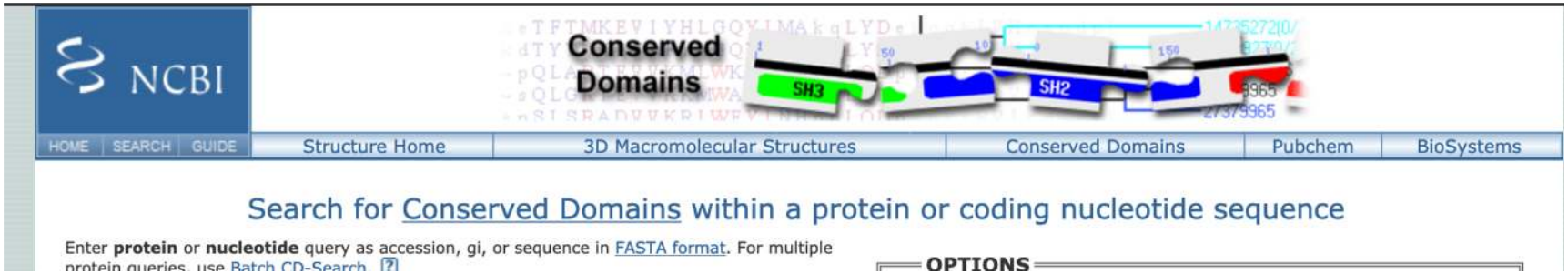
ChEBI

PubMed NCBI

Model with “cleaned reactions”

Enzyme specificity

Ec number	Reaction ID	Reaction Formulae	Match	Base	Gene	Hit id	Hit def	Hit length	e-value	Alignement ler	Coverage	identity	Qualité match
[EC-2.4.2.p]	RXN-14699	1 CMP + 1 phosphate <=> 1 alp	Non	ShotgunProteome									
[EC-2.4.2.p]	RXN-14700	1 UMP + 1 phosphate <=> 1 alp	Non	ShotgunProteome									
[EC-2.4.2.p]	RXN-8800	1 AMP + 1 phosphate => 1 alph	Non	ShotgunProteome									
1.1.1	RXN-12968	1 NAD(P)H + 1 3-oxo-dihomo g	Oui	ShotgunProteome	TIC32-2 (CRv4	gnl|BL_ORD_I	Tisochrysis_lu	361	2.00E-48	294	81	37	Moyen Sur
1.1.1.100	RXN-13443	1 3-oxo-docosapentaenoyl-Co	Oui	ShotgunProteome	CHLNCDRAFT_	gnl|BL_ORD_I	TisoRef-Ass28	304	6.09E-104	253	99	59	Sur
1.14.13.81	RXN-13191	3 NADPH + 2 H+ + 1 magnesium	Oui	ShotgunProteome	CHLREDRAFT_	gnl|BL_ORD_I	Tisochrysis_lu	374	4.10E-90	341	95	41	Moyen Sur
1.14.19	RXN-12755	1 a reduced electron acceptor	Oui	ShotgunProteome	FAD2B (CRv4_	gnl|BL_ORD_I	Tisochrysis_lu	423	3.00E-67	356	86	39	Moyen Sur
1.14.19	RXN-8346	1 a reduced electron acceptor	Oui	ShotgunProteome	FAD2B (CRv4_	gnl|BL_ORD_I	Tisochrysis_lu	423	3.00E-67	356	86	39	Moyen Sur
1.14.19	RXN-8347	1 a reduced electron acceptor	Oui	ShotgunProteome	FAD2B (CRv4_	gnl|BL_ORD_I	Tisochrysis_lu	423	3.00E-67	356	86	39	Moyen Sur
1.14.19	RXN-8350	1 a reduced electron acceptor	Oui	ShotgunProteome	FAD2B (CRv4_	gnl|BL_ORD_I	Tisochrysis_lu	423	3.00E-67	356	86	39	Moyen Sur
1.14.19.3	1.14.19.3-RXN	1 a reduced electron acceptor	Oui	ShotgunProteome	FAD3 (CRv4_A	gnl|BL_ORD_I	Tisochrysis_lu	524	4.00E-21	524	74	25	Très Bordeline
1.14.99	RXN-8389	1 a reduced electron acceptor	Oui	ShotgunProteome	FAD2B (CRv4_	gnl|BL_ORD_I	Tisochrysis_lu	423	3.00E-67	356	86	39	Moyen Sur
1.17.1	RXN-13852	1 H2O + 3 NADP+ + 1 magnesium-protoporphyrin IX 13-monomethyl ester <=> 3 NADPH + 4 H+ + 1 2,4-divinyl protochlorophyllide a											
1.2.1.8	BADH-RXN	1 H2O + 1 betaine aldehyde + 1	Oui	ShotgunProteome	AT3G48170	gnl|BL_ORD_I	Tisochrysis_lu	520	3.2176E-117	500	96	42	Moyen Sur
1.3.1	RXN-12971	1 NADH + 1 dihomo gamma-lin	Non	ShotgunProteome									



GPR

E. Coli

G6P <-> G1P

b2690 and b0688

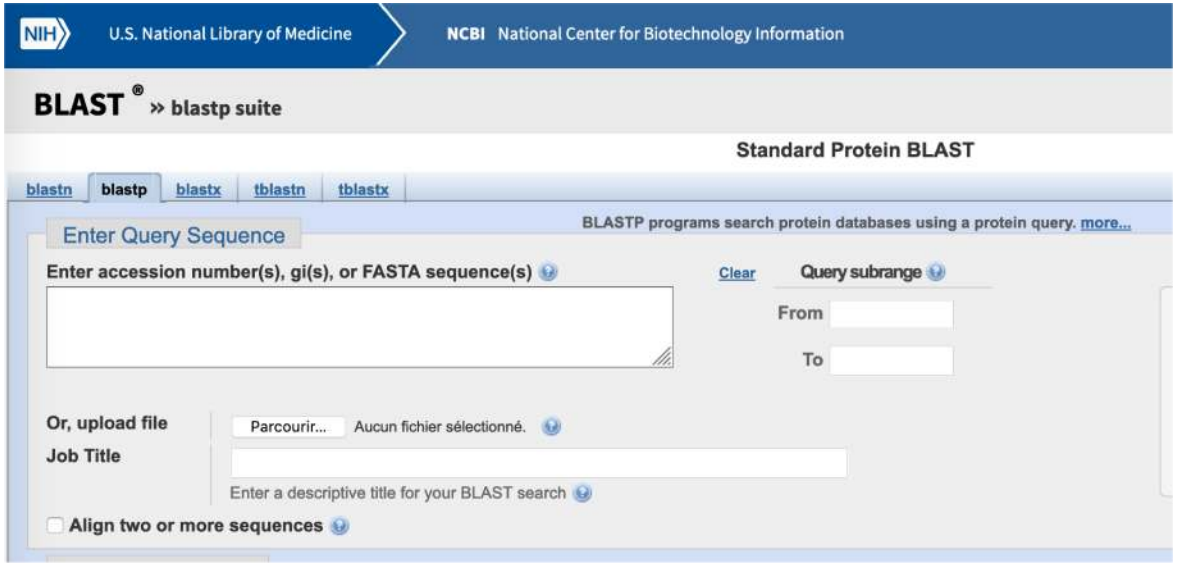
Orthology ?

R. solanacearum strain

G6P <-> G1P

????

RSc0691 and none



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1987 2019
The Comprehensive Enzyme Information System

PubMed

Substrate/Products/Generic reactions

- Problem usually occurring when reconstructing against a database

Reaction:

a (3*R*)-3-hydroxyacyl-[acyl-carrier protein] + $NADP^+$ ← a 3-oxoacyl-[acp] + NADPH + H^+

Unofficial Reactions:

a (3*R*)-3-hydroxyhexanoyl-[acp] + $NADP^+$ ← a 3-oxohexanoyl-[acp] + NADPH + H^+,
a (3*R*)-3-hydroxytetracosanoyl-[acp] + $NADP^+$ ← a 3-oxotetracosanoyl-[acp] + NADPH + H^+,
a (3R,5Z)-3-hydroxydodec-5-enoyl-[acp] + $NADP^+$ ← a (5Z)-3-oxododec-5-enoyl-[acp] + NADPH + H^+,
a (*3R*)-3-hydroxybutanoyl-[acp] + $NADP^+$ ← an acetoacetyl-[acp] + NADPH + H^+,
a (3R)-3-hydroxyglutaryl-[acp] methyl ester + $NADP^+$ ← a 3-oxoglutaryl-[acp] methyl ester + NADPH + H^+,
a (*3R*)-3-hydroxydodecanoyl-[acp] + $NADP^+$ ← a 3-oxododecanoyl-[acp] + NADPH + H^+,
a (3R,9Z)-3-hydroxy-octadec-9-enoyl-[acp] + $NADP^+$ ← a (9Z)-3-oxo-octadec-9-enoyl-[acp] + NADPH + H^+,
a (3*R*,7Z,10Z,13Z,16Z,19Z)-3-hydroxydocosa-7,10,13,16,19-pentaenoyl-[acp] + $NADP^+$ ← a (7Z,10Z,13Z,16Z,19Z)-3-oxodocosa-7,10,13,16,19-pentaenoyl-[acp] + NADPH + H^+,
a (3*R*)-3-hydroxydecanoyl-[acp] + $NADP^+$ ← a 3-oxodecanoyl-[acp] + NADPH + H^+,
a (3*R*)-3-hydroxyoctanoyl-[acp] + $NADP^+$ ← a 3-oxooctanoyl-[acp] + NADPH + H^+,
a (3*R*,7Z)-3-hydroxytetradec-7-enoyl-[acp] + $NADP^+$ ← a (7Z)-3-oxotetradec-7-enoyl-[acp] + NADPH + H^+,
a (3R)-3-hydroxypimeloyl-[acp] methyl ester + $NADP^+$ ← a 3-oxopimeloyl-[acp] methyl ester + NADPH + H^+,
a (3*R*,5Z)-3-hydroxy-tetradec-5-enoyl-[acp] + $NADP^+$ ← a (5Z)-3-oxo-tetradec-5-enoyl-[acp] + NADPH + H^+,
a (3*R*)-3-hydroxytetradecanoyl-[acp] + $NADP^+$ ← a 3-oxotetradecanoyl-[acp] + NADPH + H^+,

Substrate/Products/Generic reactions

- Problem usually occurring when reconstructing against a database

Enzymatic activity: fatty acyl-CoA synthetase (long-chain-fatty-acid—CoA ligase)

a 2,3,4-saturated fatty acid + ATP + coenzyme A → a 2,3,4-saturated fatty acyl CoA + AMP + diphosphate	
EC Number	6.2.1.-
Synonyms	long chain fatty acid CoA-ligase, acyl-activating enzyme, acyl-CoA synthase, fatty acid thiokinase (long-chain), lignoceroyl-CoA synthase, long-chain acyl-CoA synthetase, palmitoyl-CoA synthase, arachidonyl-CoA synthetase, acid:CoA ligase (AMP forming)
Direction	The reaction is physiologically favored in the direction shown.
Alternative Substrates	for a 2,3,4-saturated fatty acid [Comment 1]: decanoate [Kameda81], tridecanoate [Kameda81], laurate [Kameda81], oleate [Kameda81]
Pathways	fatty acid β-oxidation I palmitate biosynthesis II (bacteria and plants) superpathway of fatty acids biosynthesis (*E. coli*)
Credits	Imported from EcoCyc 25-Feb-2019 by Paley S, SRI International
Cofactors or Prosthetic Groups	Mg^{2+} [Samuel70, Kameda81]

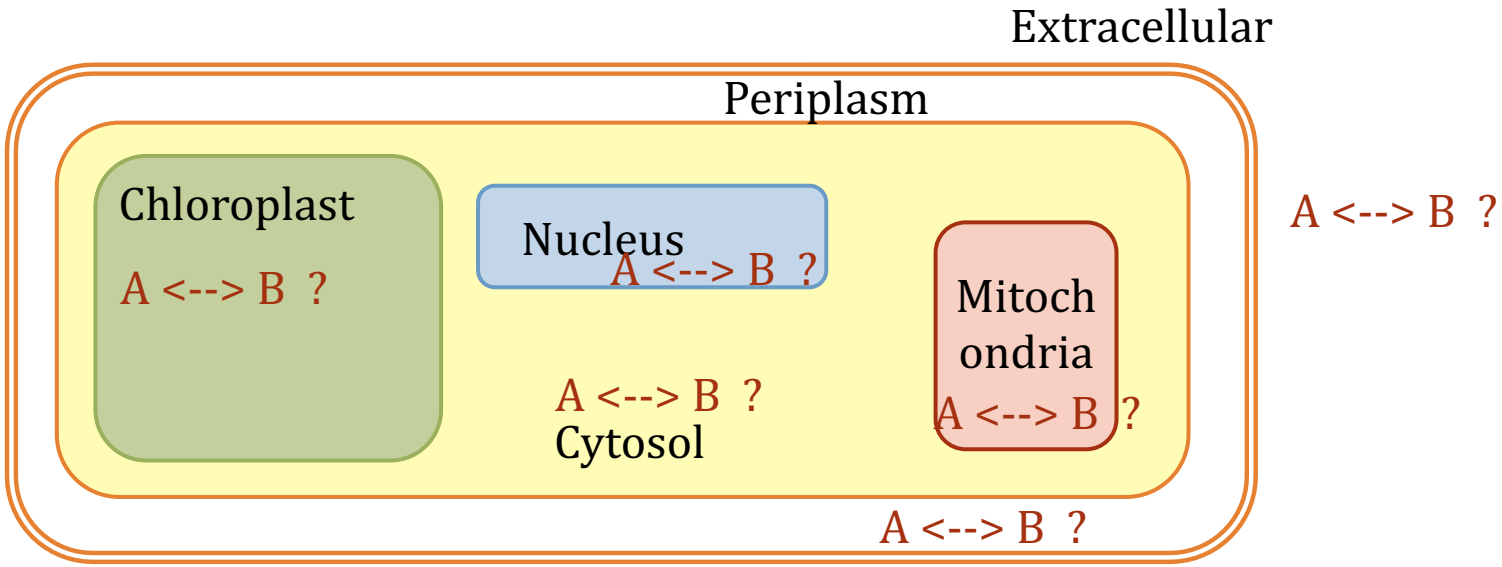
Substrate/Products/Generic reactions

- Problem usually occurring when reconstructing against a database
- Solution:

Select the real substrates by considering which ones are involved in other metabolic processes

Location

- Signatures in the sequences
- Knowledge in phylogenetically closed organisms
- Experimental data (e.g.: proteomics of purified organelle/compartment)



Direction and reversibility

- By considering the direction of the identified metabolic pathways
- Using thermodynamics
- By solving the topological and stoichiometric constraints of the metabolic network

Kümmel, A.; Panke, S. & Heinemann, M. Systematic assignment of thermodynamic constraints in metabolic network models BMC Bioinformatics, 2006, 7, 512

A <--> B ?
A --> B ?
B --> A ?

Charge

- **Check if reaction is balanced:**
  - change stoichiometric coefficients
  - add some missing metabolites (H^+)
  - change the charge of some metabolites

R_G6PDA:
1 M_h2o_c[c] + 1 M_gam6p_c[c] -> 1 M_f6p_c[c] + 1 M_nh3_c[c]

{P=0.0, C=0.0, H=1.0, N=0.0, O=0.0}

On modifie le nh3 en nh4:

1 M_h2o_c[c] + 1 M_gam6p_c[c] -> 1 M_f6p_c[c] + 1 M_nh4_c[c]

{P=0.0, C=0.0, H=0.0, N=0.0, O=0.0}

Curation pipeline: a long task…

A draft metabolic network

6 MONTHS TO 2 YEARS

For each reaction check and modify accordingly:

✓ …

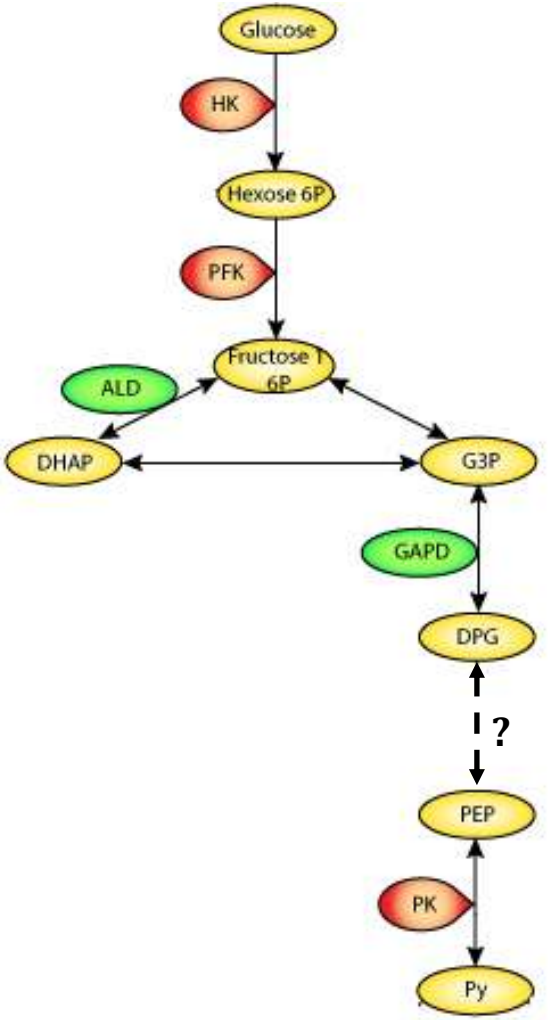
Model with “cleaned reactions”

Gap-filling, addition of transport and generic reactions

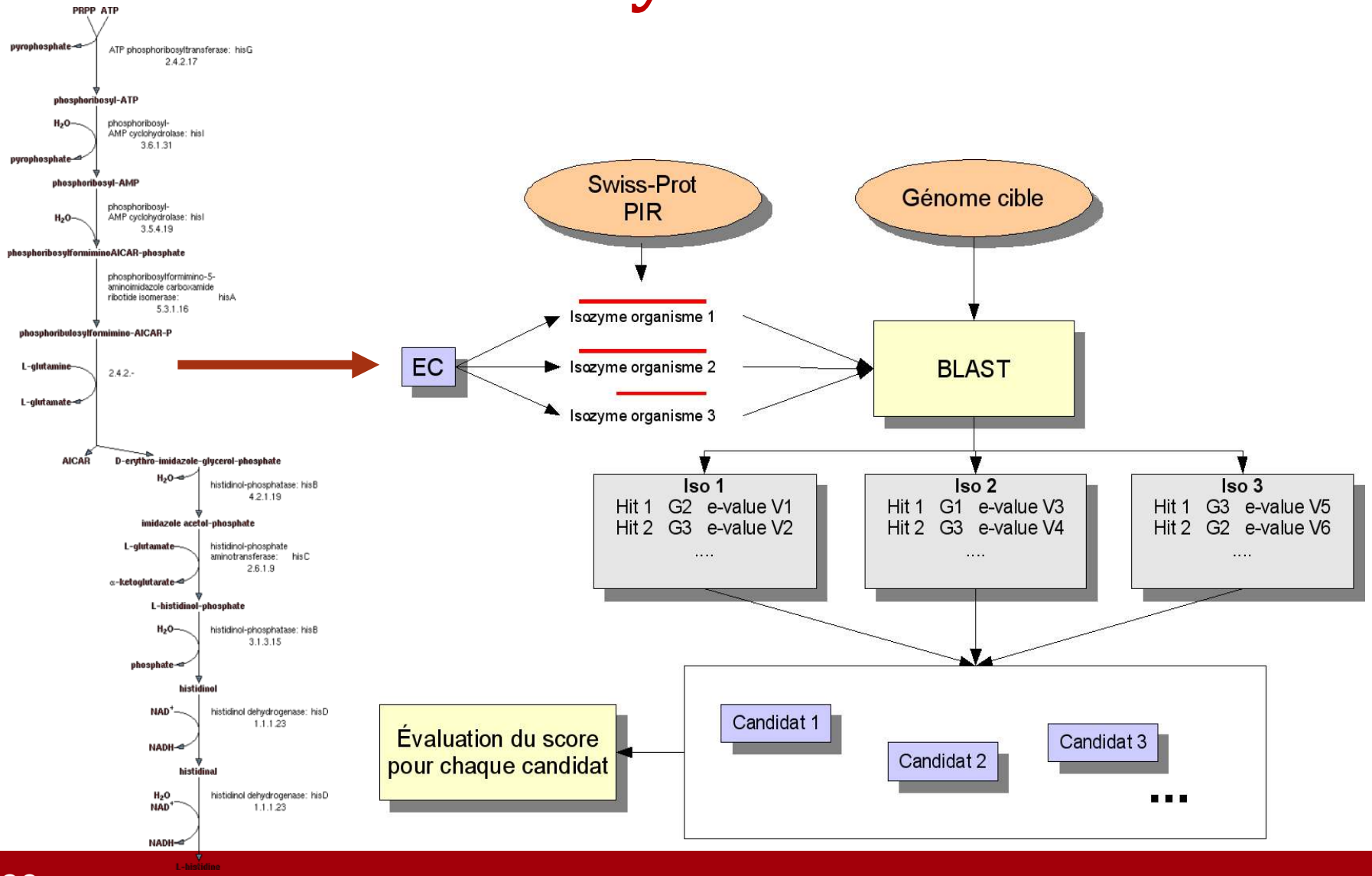
PubMed

Gap filling

1. Identification of missing reactions (graph-based)
2. Fill the gap
   - Manually (literature, blast)
   - Using softwares
     - Pathway Hole Filler
     - Meneco
     - The SEED
     - …



Pathway Hole Filler



Curation pipeline: a long task…

A draft metabolic network

6 MONTHS TO 2 YEARS

For each reaction check and modify accordingly:

- ✓ …

Model with "cleaned reactions

Gap-filling, addition of transport and generic reactions

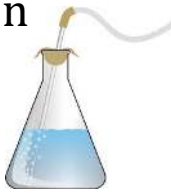
Curated metabolic network

Test

Simulations, comparison to experiments

New version

PubMed



Exchange format

- **SBML, Systems Biology Markeup Language:**
  - a representation format based on XML
  - reaction focused and designed for modelling
  - list of compartments, metabolites, reactions…

SBML: unit definitions

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2" level="2" version="1">
  <model id="iJO1366">
    <listOfUnitDefinitions>
      <unitDefinition id="mmol_per_gDW_per_hr">
        <listOfUnits>
          <unit kind="mole" scale="-3"/>
          <unit kind="gram" exponent="-1"/>
          <unit kind="second" exponent="-1" multiplier="0.00027777777777778"/>
        </listOfUnits>
      </unitDefinition>
    </listOfUnitDefinitions>
```

SBML: compartments

```
<listOfCompartments>
  <compartment id="c" name="Cytoplasm"/>
  <compartment id="e" name="Extracellular"/>
  <compartment id="p" name="Periplasm"/>
</listOfCompartments>
```

SBML: internal metabolites

```
<species id="M_10fthf_c" name="10-Formyltetrahydrofolate" compartment="c">
  <notes>
    <body xmlns="http://www.w3.org/1999/xhtml">
      <p>FORMULA: C20H21N7O7</p>
      <p>CHARGE: -2</p>
    </body>
  </notes>
</species>
```

Each metabolite is duplicated considering their location in the compartments

SBML: external metabolites

```
<species id="M_3amp_b" name="M_3__AMP_C10H12N5O7P" compartment="Extra_organism" charge="-2" boundaryCondition="true"/>
```

boundaryCondition=true indicates that this metabolite can be not balanced but this is the suffix of the metabolite id ("_b", "_e", etc...) that is most often used to distinguish external metabolites.

SBML: reactions

```
<reaction id="R_FDH4pp" name="formate dehydrogenase (quinone-8) (periplasm)" reversible="false">
  <notes>
    <body xmlns="http://www.w3.org/1999/xhtml">
      <p>GENE_ASSOCIATION: ((b3892 and b3893 and b3894) or (b1474 and b1475 and b1476))</p>
      <p>SUBSYSTEM: Oxidative Phosphorylation</p>
      <p>EC Number: 1.2.2.1</p>
    </body>
  </notes>
  <listOfReactants>
    <speciesReference species="M_h_c" stoichiometry="2"/>
    <speciesReference species="M_q8_c"/>
    <speciesReference species="M_for_p"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="M_q8h2_c"/>
    <speciesReference species="M_co2_p"/>
    <speciesReference species="M_h_p"/>
  </listOfProducts>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <ci> FLUX_VALUE </ci>
    </math>
    <listOfParameters>
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      <parameter id="FLUX_VALUE" value="0" units="mmol_per_gDW_per_hr"/>
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    </listOfParameters>
  </kineticLaw>
</reaction>
```

$Q8 + H^+ + Formate \rightarrow Q8H_2 + CO_2 + H^+$

SBML: exchange reactions

```
<reaction id="R_EX_4abut_e_" name="R_4_Aminobutanoate_exchange" reversible="true">
    <notes>
        <html:p>GENE_ASSOCIATION: </html:p>
        <html:p>PROTEIN_ASSOCIATION: </html:p>
        <html:p>SUBSYSTEM: S_</html:p>
        <html:p>PROTEIN_CLASS: </html:p>
    </notes>
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        </math>
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            <parameter id="FLUX_VALUE" value="0.000000" units="mmol_per_gDW_per_hr"/>
            <parameter id="REDUCED_COST" value="-0.021771"/>
        </listOfParameters>
    </kineticLaw>
</reaction>
```

Xylella fastidiosa

Flux Balance Analysis (FBA)
&
Flux Variance Analysis (FVA)

FBA - Hypothèses

- On suppose qu'il y a « croissance équilibrée » :

$$K_{int}.\, v = 0$$

- On contraint le système avec la thermodynamique *:*

$$v_i \geq 0 \; for \; i \; \in Irr$$

- On suppose que le microorganisme optimise certains de ces flux

ex : maximiser la synthèse de biomasse

➔On obtient un problème d'optimisation à résoudre :

$$\max_{v} v_{Bf} \; s.t.$$

$$\begin{cases} K_{int}.\, v = 0 \\ v_i \geq 0 \; for \; i \in Irr \end{cases}$$

FBA

- Pour améliorer la résolution et voir l'impact des conditions expérimentales on peut forcer certains flux à des valeurs fixes. (consommation substrat, excrétion de produits)

$$\max_{v} v_{Bf} \; s.t.$$

$$\begin{cases} K_{int}.v = 0 \\ v_i \geq 0 \; for \; i \in Irr \\ v_s = m_s \end{cases}$$

FBA – Fonction objectives

- La plus courante : linéaire, synthèse de biomasse

$$\max_v v_{Bf}$$

- Fonctions non-linéaires[1] : optimisation de « rendements »

$$\max_v \frac{v_{B_f}}{v_{glucose}}$$

- Fonctions multi-objectives[2] contradictoires

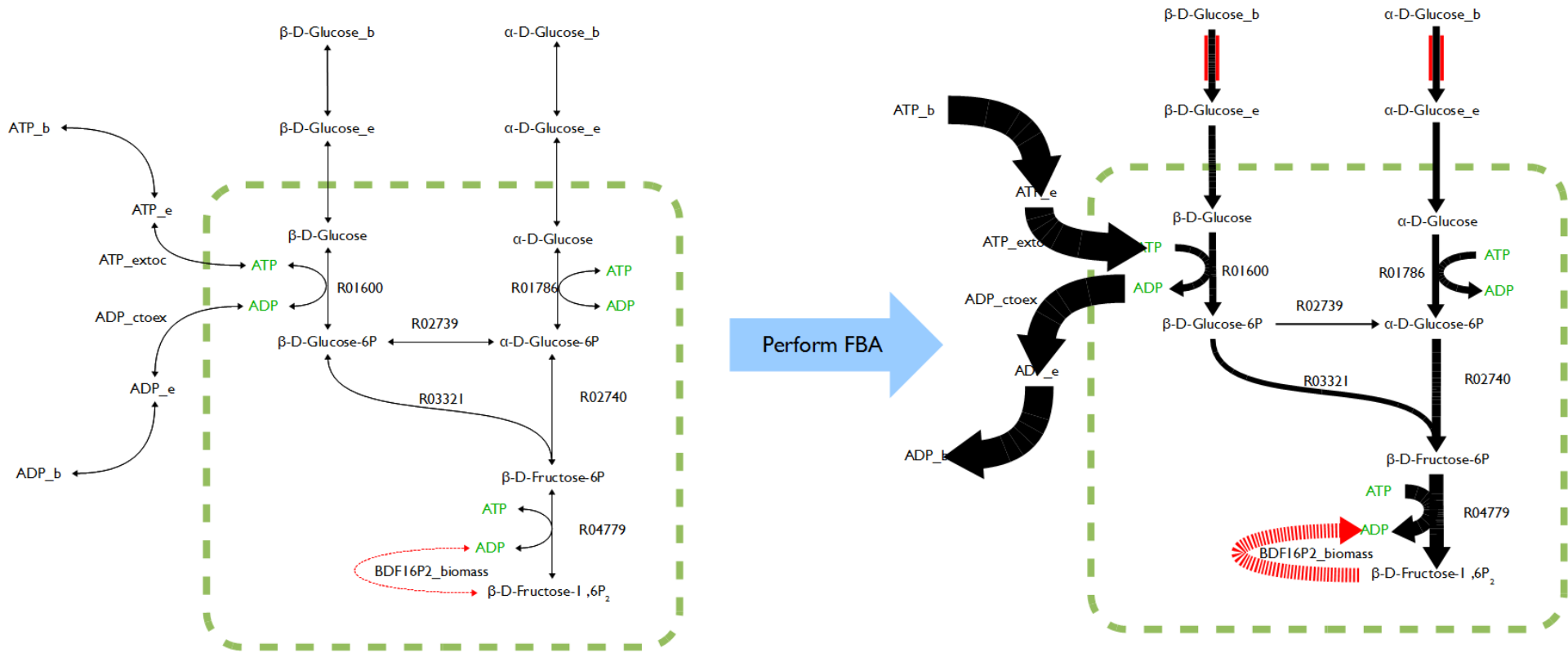
$$\min_v \Sigma_v v \; et \; \max_v \frac{v_{B_f}}{v_{glucose}}$$

- Fonctions multi-objectives pour écosystèmes[3] :

$$\max_v v_{Bf_i} \; pour \; chaque \; organisme \; et$$
$$\max_v v_B \; de \; l'écosystème$$

1. Schuetz,R. et al. (2007)
2. Schuetz,R. et al. (2012)
3. Zomorrodi,A.R. and Maranas,C.D. (2012)

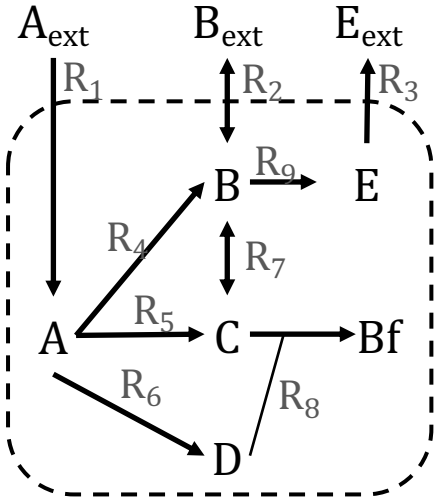
FBA – exemple de résultats



FBA - Application

- Prédire les flux de toutes les réactions intracellulaires
- Comparer la répartition et l'importance des flux entre
  - plusieurs conditions environnementales
  - plusieurs espèces
- Etudier l'impact
  - d'un (plusieurs) flux sur la fonction objective
  - de la suppression d'une ou plusieurs réactions/gènes
  - de l'inhibition ou la catalyse d'une réaction
- Etudier les modifications génétiques/métaboliques à apporter pour optimiser un bioprocédé

FBA – exemple jouet



0 Fonction objective :

1. max v_{R8}
2. max v_{R3}

0 Contraintes :

1. $v_{R1} = 2\ mM.gBf.h^{-1}$ et $v_{R2} \leq 0$ (seulement export de B)
2. puis $v_{R1} = 0\ et\ v_{R2} = 2\ mM.gBf.h^{-1}$

FBA - subtilités

- Un problème d'optimisation linéaire est toujours plus simple à résoudre qu'un problème non-linéaire.

- La valeur optimale de la fonction objective du problème linéaire est toujours unique

- MAIS la solution n'est pas unique i.e. il existe plusieurs répartitions de flux v qui permettent d'atteindre cette valeur optimale

➔ Pour connaître un encadrement de la solution, il faut utiliser le Flux Variance Analysis (FVA)

FVA

- On recherche un encadrement de toutes les solutions au problème FBA
- Pour chaque vitesse de réaction v_{Ri}, on recherche le minimum et le maximum que peut admettre cette réaction, lorsque la fonction objective du problème FBA a atteint sa valeur optimale:

$$\max_{v} v_{Ri} \ \ s.t. \begin{cases} v_{Bf} = v_{opt} \\ K_{int}.v = 0 \\ v_i \geq 0, i \ \in Irr \\ v_s = m_s \end{cases} \qquad \min_{v} v_{Ri} \ \ s.t. \begin{cases} v_{Bf} = v_{opt} \\ K_{int}.v = 0 \\ v_i \geq 0, i \ \in Irr \\ v_s = m_s \end{cases}$$

2000 réactions ➔ 4001 problèmes à résoudre

FBA – FVA outils

- N'importe quel solveur d'optimisation peut être utilisé
  - Gurobi
  - Cplex
  - COBRA
  - …
- Format d'entrée : souvent matriciel

$$\min_x f_{obj} \; s.t. : \begin{cases} A_{eq}.x = b_{eq} \\ A_{ineq}.x \leq b_{ineq} \end{cases}$$

donner

$$f_{obj}, A_{eq}, b_{eq}, A_{ineq}, b_{ineq}$$

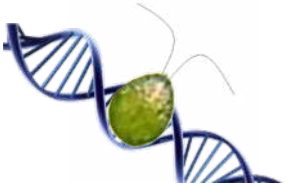
FBA - Extensions

- Dynamic Flux Balance Analysis (DFBA)[1]
  - Le temps est discrétisé : $t_1, \dots, t_n$
  - On suppose la consommation de substrat suivre une cinétique donnée (type Michaelis-Menten)
  - On résout à chaque instant t_i un FBA sur le reste du métabolisme.

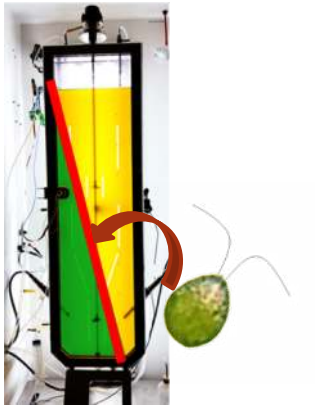
Mahadevan,R. et al. (2002) Dynamic flux balance analysis of diauxic growth in Escherichia coli. *Biophysical journal*, **83**, 1331–1340.

En résumé

Pipeline : from genome to physiology



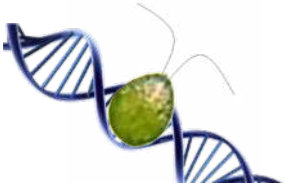
Genome



Experiments

Goal: Understand and predict physiological behaviour from omics data using mathematical models

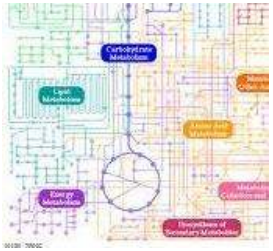
Pipeline : from genome to physiology



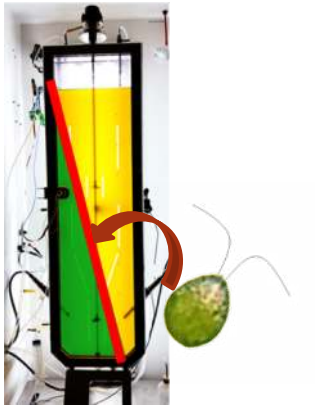
Genome

1

Bioinfo



Metabolic network



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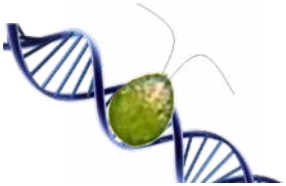
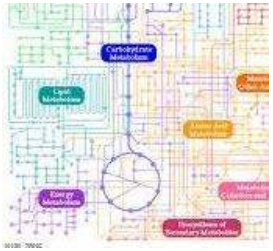


Genome

1

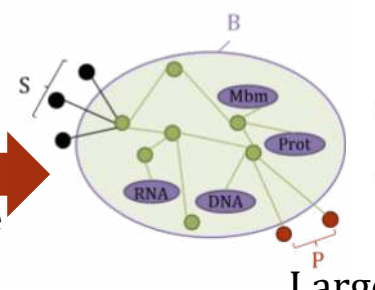
Bioinfo



Metabolic network

2

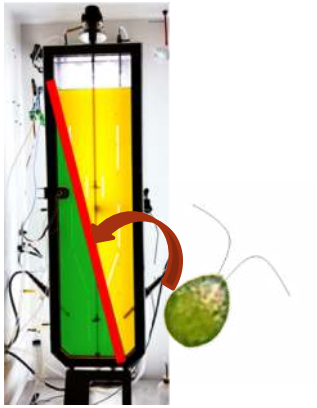
Mass balance



$$\frac{d\begin{pmatrix} S \\ C \\ P \\ B \end{pmatrix}}{dt} = KvB = \begin{pmatrix} K_S \\ K_C \\ K_P \\ K_B \end{pmatrix} vB$$

Large size ODE

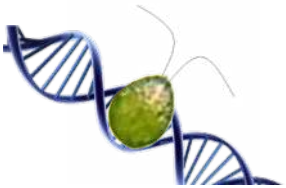
Dynamical system



Experiments

Goal: Understand and predict physiological behaviour from omics data using mathematical models

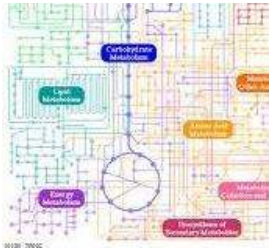
Pipeline : from genome to physiology



Genome

1

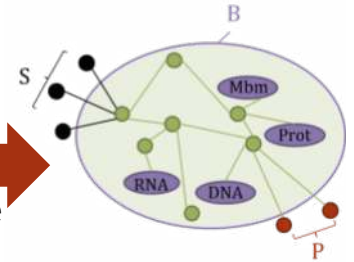
Bioinfo



Metabolic network

2

Mass balance



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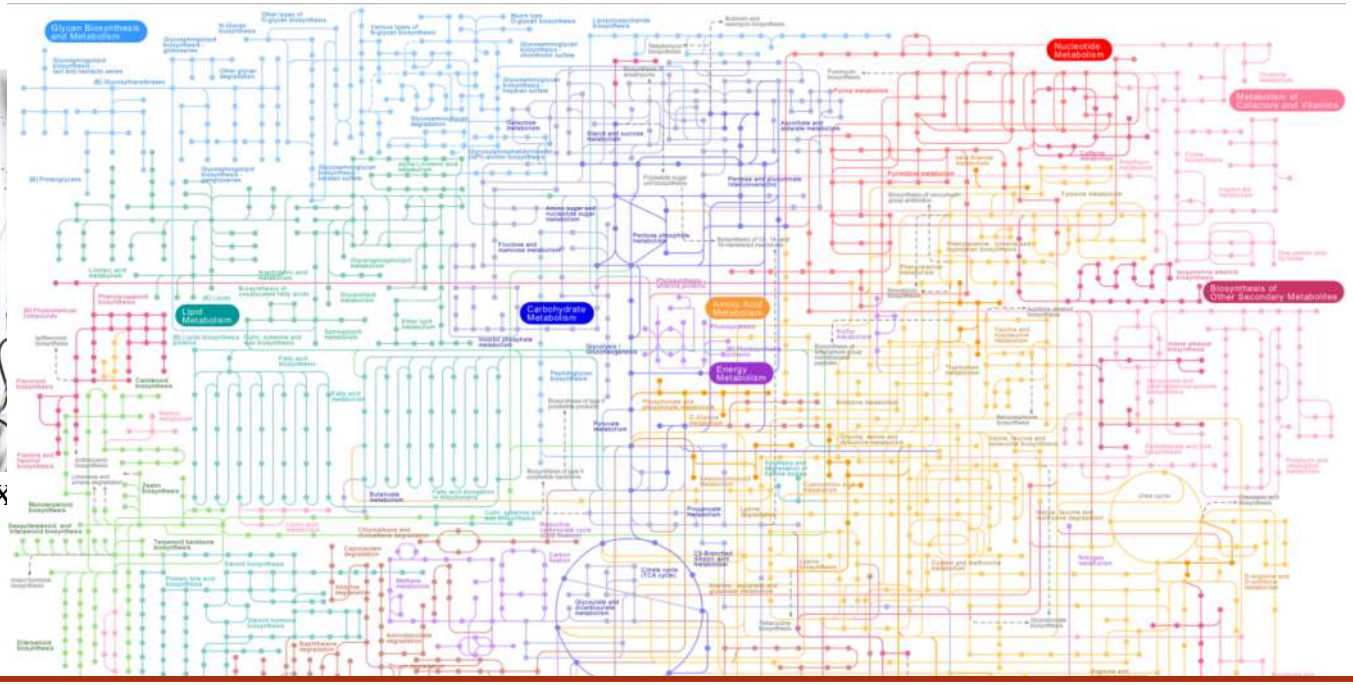
Large size ODE

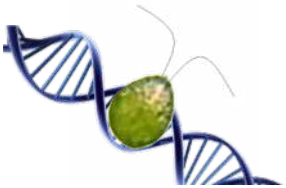
Dynamical system

Ex



Goal: Understand and predict physiological behaviour from omics data using mathematical models

Pipeline : from genome to physiology



Genome

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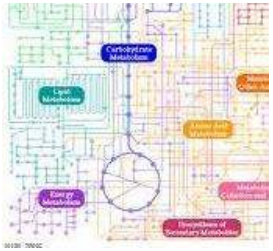
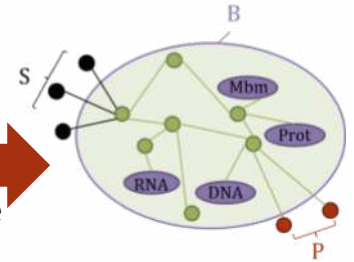
Bioinfo



Metabolic network

2

Mass balance



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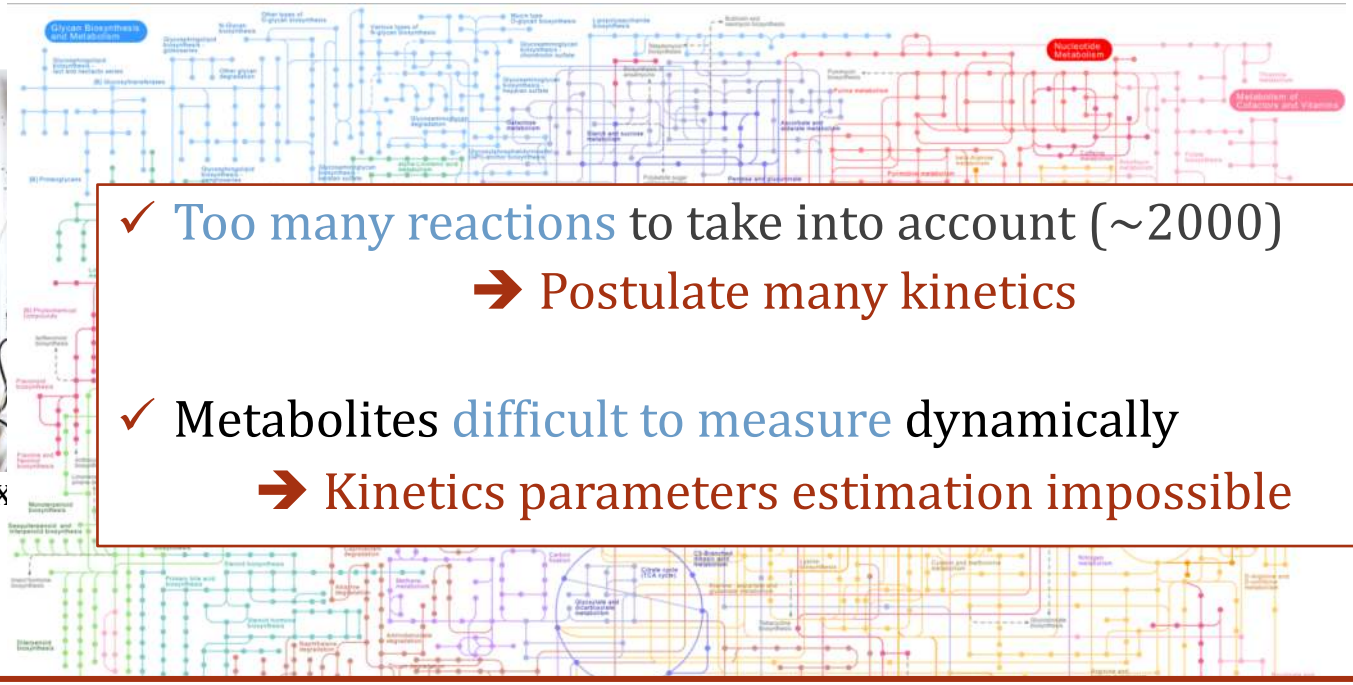
Large size ODE

Dynamical system

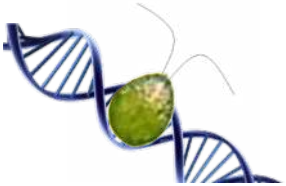


Ex

- ✓ Too many reactions to take into account (~2000)
  - ➔ Postulate many kinetics
- ✓ Metabolites difficult to measure dynamically
  - ➔ Kinetics parameters estimation impossible

Goal: Understand and predict physiological behaviour from omics data using mathematical models

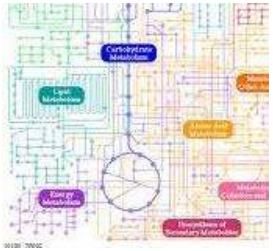
Pipeline : from genome to physiology



Genome

1

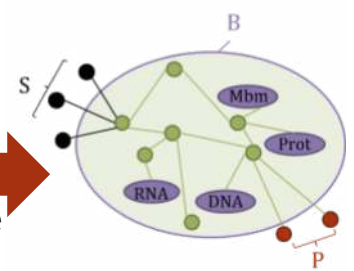
Bioinfo



Metabolic network

2

Mass balance



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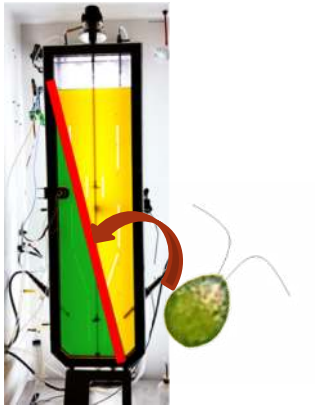
Large size ODE

Dynamical system

3

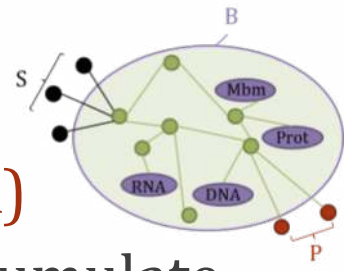
Reduction



Experiments

Goal: Understand and predict physiological behaviour from omics data using mathematical models

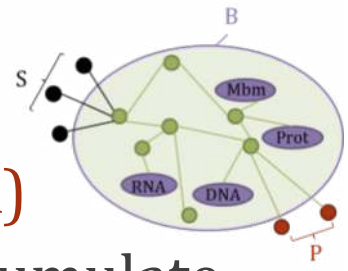
Balanced growth



0 Solution : balanced-growth hypothesis (QSSA)

Internal metabolites C are assumed not to accumulate inside the cell

Balanced growth



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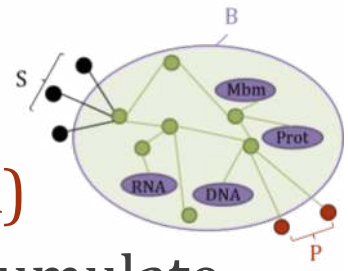
$$K_C v = 0$$

Balanced growth



- Solution : balanced-growth hypothesis (QSSA)

Internal metabolites C are assumed not to accumulate inside the cell

- In this case:

$$K_C v = 0$$

- BUT indeterminate system!

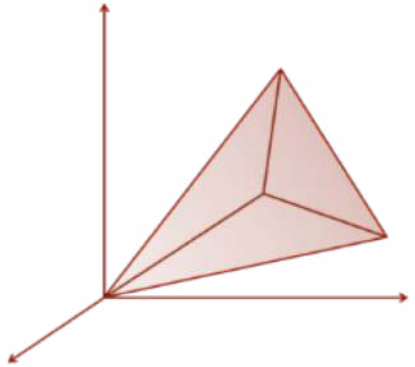
$$\mathrm{n} = \dim(Ker(K_C) \neq 0)$$

Elementary Flux Mode

- The set of solutions

$$\begin{cases} K_C v = 0 \\ v \geq 0 \; if \; v \in Irr \end{cases}$$

is a cone.



Elementary Flux Mode

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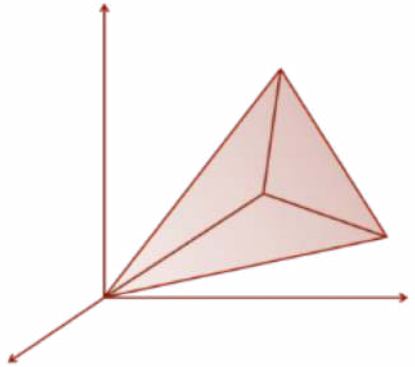

- A cone can be described by a set of non-decomposable vectors named Elementary Flux Modes (EFM)

$$\forall v \in \{EFM\},$$
$$\nexists v' \in C \; tel \text{ que}$$
$$\mathrm{S^c}(v') \overset{\text{def}}{=} \{i | v'_i \neq 0\} \subseteq \mathrm{S^c}(v) \overset{\text{def}}{=} \{i | v_i \neq 0\}$$

Elementary Flux Mode

- The set of solutions

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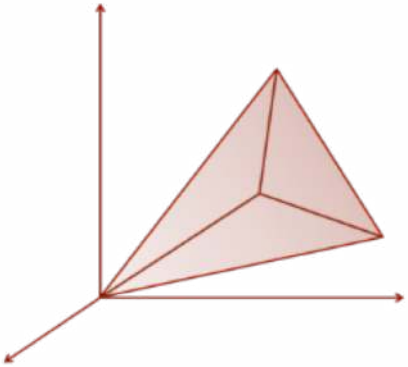

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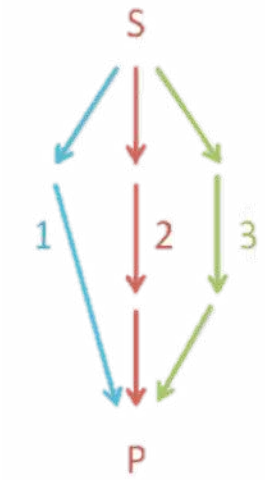
- Each EFM represents a metabolic pathway between a substrate S, a product P and/or biomass B



Elementary Flux Mode

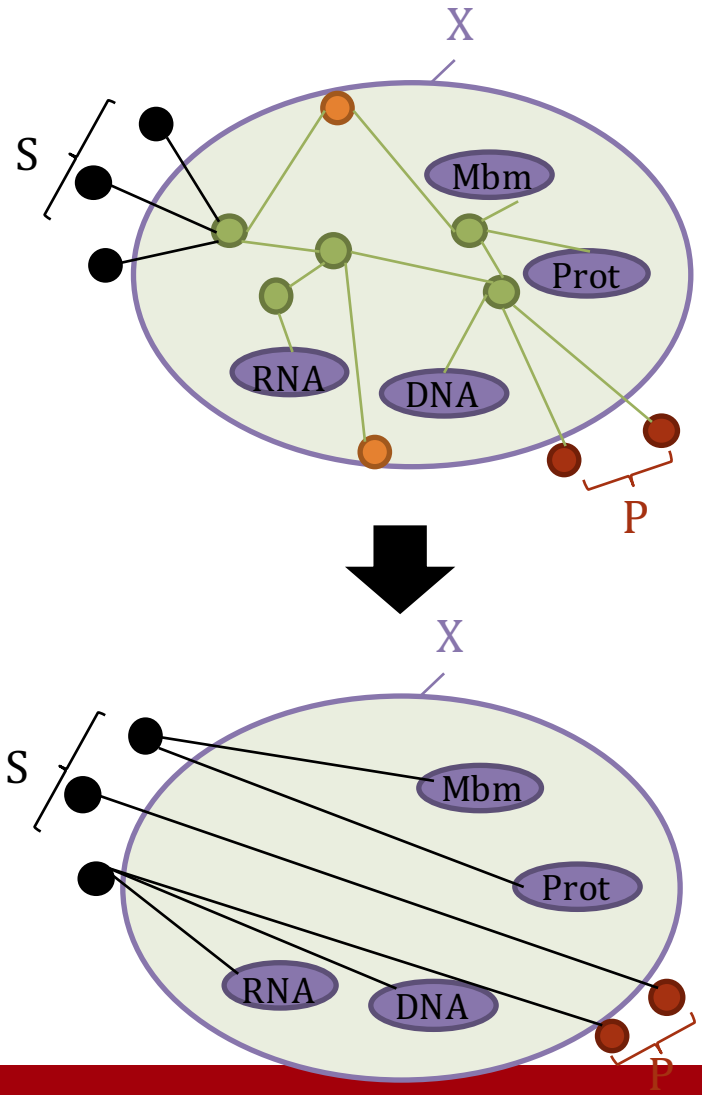
0 The set of EFM is a convex basis of the solution set

$$v_{sol} = E\alpha, \alpha \geq 0$$

$$\rightarrow \frac{d\begin{pmatrix} S \\ C \\ P \\ B \end{pmatrix}}{dt} = KvB \text{ is reduced}^1 \text{ to } \frac{d\begin{pmatrix} S \\ P \\ B \end{pmatrix}}{dt} = K'\alpha B$$

with $K' = K.E$ the stoichiometric matrix of the macroscopic reactions and α their associated kinetics

$$K'_S S \xrightarrow{\alpha} K'_P P + K'_B B$$



1. Klamt and Stelling, 2003, *Trends in biotechnology*

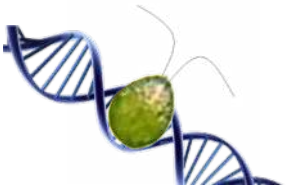
Comparison of classical metabolic approaches

- Unfortunately, the number of EFMs explode exponentially with the size of the network.
  - ➔Too many kinetics α to postulate and estimate

- Solutions:
  - Optimization (maximization of biomass)[1]
  - Reduction of the cone space
    - With experimental data[2]
    - By projection in a smaller space (yield space)[3]
  - Clustering EFMs into families [4]

1. Watson, 1986, *Computer applications in the biosciences: CABIOS*
2. Provost et al., 2006, *Bioprocess and biosystems engineering*
3. Song and Ramkrishna, 2009, *Biotechnology and bioengineering*
4. Song and Ramkrishna, 2010, *Biotechnology and bioengineering*

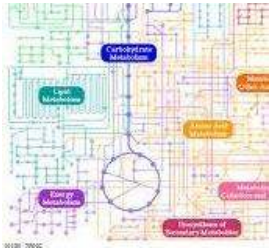
Pipeline : from genome to physiology



Genome

1

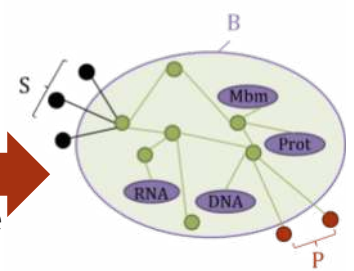
Bioinfo



Metabolic network

2

Mass balance



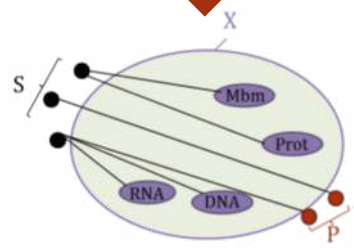
$$\frac{d\begin{pmatrix} S \\ C \\ P \\ B \end{pmatrix}}{dt} = KvB = \begin{pmatrix} K_S \\ K_C \\ K_P \\ K_B \end{pmatrix} vB$$

Large size ODE

Dynamical system

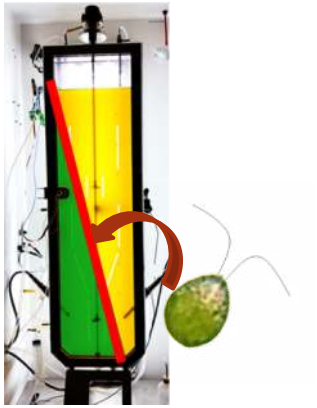
3

Reduction



Small size ODE

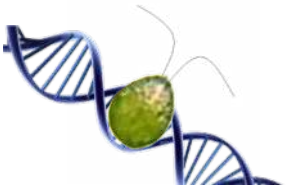
Quasi steady state



Experiments

Goal: Understand and predict physiological behaviour from omics data using mathematical models

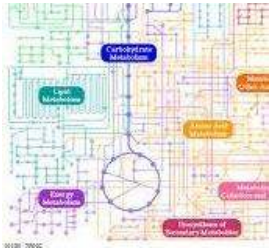
Pipeline : from genome to physiology



Genome

1

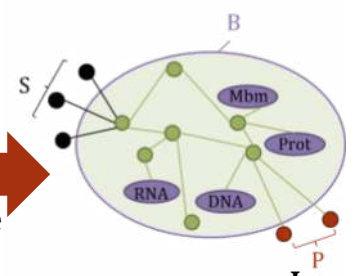
Bioinfo



Metabolic network

2

Mass balance



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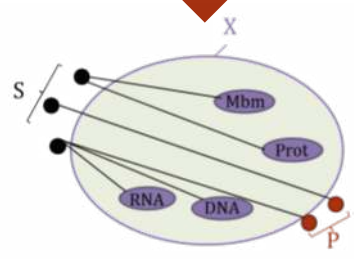
Large size ODE

Dynamical system

3

Reduction

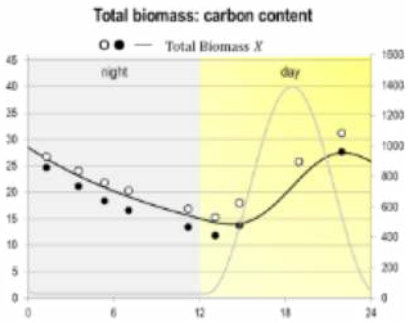


Small size ODE

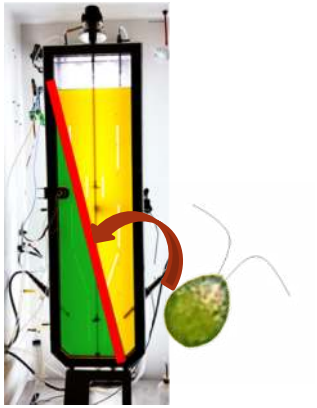
Quasi steady state

Calibration

4



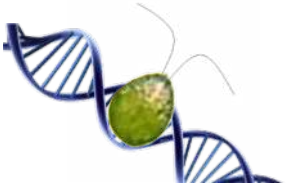
Numerical predictions



Experiments

Goal: Understand and predict physiological behaviour from omics data using mathematical models

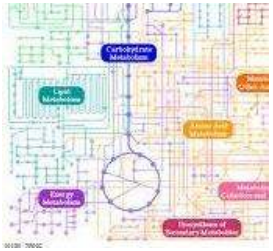
Pipeline : from genome to physiology



Genome

1

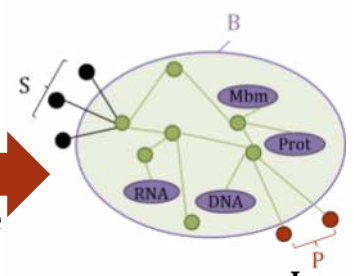
Bioinfo



Metabolic network

2

Mass balance



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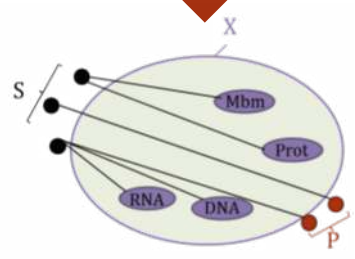
Large size ODE

Dynamical system

3

Reduction

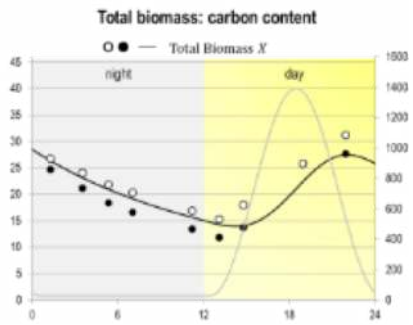


Small size ODE

Quasi steady state

Calibration

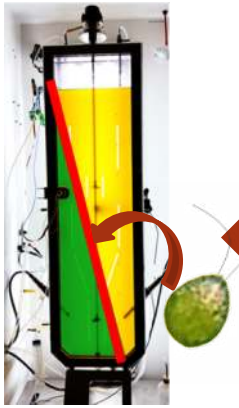
4



Numerical predictions

Validation

5



Experiments

Goal: Understand and predict physiological behaviour from omics data using mathematical models

Perspectives

- Inclure la régulation.
- Construction de nouveaux réseaux
  - nouvelles espèces
  - réseaux plus précis
- Rendre les modèles dynamiques
- Relaxer l'hypothèse de la « balanced growth »?
- Prendre en compte le coût de synthèse des protéines de manière exacte