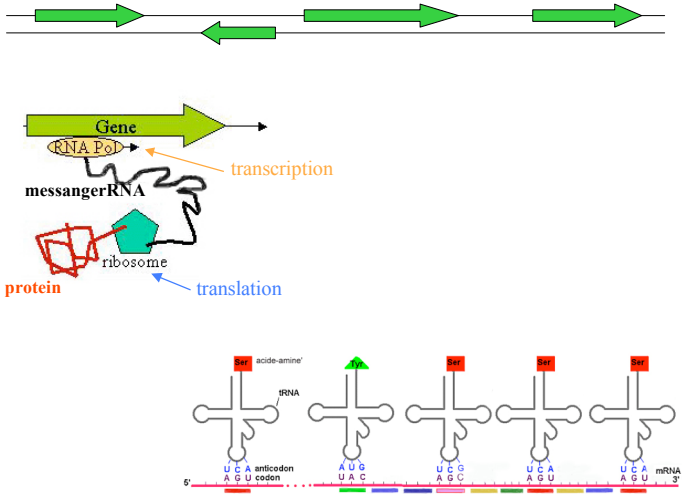
M2 - BIM

EVOL

Algorithme de recherche de biais des codons dans les génomes, espaces de genes et espaces d'organismes

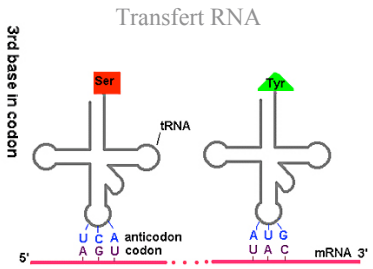
Alessandra Carbone
Université Pierre et Marie Curie



Redundancy of the genetic code

2nd base in codon

1st base in codon	U	C	A	G	3rd base in codon
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	STOP	STOP	A
	Leu	Ser	STOP	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G



Bias on codon usage & preferred codons

In *E.coli* and other organisms that reproduce rapidly

high tRNA number
high expression

correlated to (experimentally)

codon preference

Codon preference and tRNA : Ikemura, 1985; Bennetzen and Hall, 1982; Bulmer, 1987; Gouy and Gautier, 1982
tRNA and elongation rate : Varenne *et al.*, 1984.
High expression and codon preference : Grantham *et al.*, 1980; Wada *et al.*, 1990; Sharp and Li, 1987; Sharp *et al.*, 1986; Médigue *et al.*, 1991; Shields and Sharp, 1987; Sharp *et al.*, 1988; Stenico *et al.*, 1994.

Visualisation of genes in a genome and identification of their codon bias

$g = [x_{1,g}\ x_{2,g} \ldots x_{64,g}]$ $x_{i,g}$ relative frequency of codon i in g

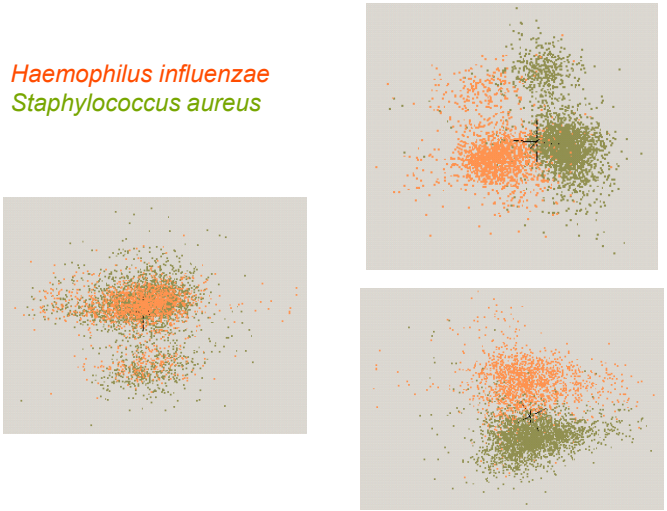
Vector normalisation:

$(x_{i,g} - \underline{x}_i) / \sigma_i$ $\underline{x}_i$ mean of frequencies $x_{i,g}$
σ_i standard deviation of $x_{i,g}$

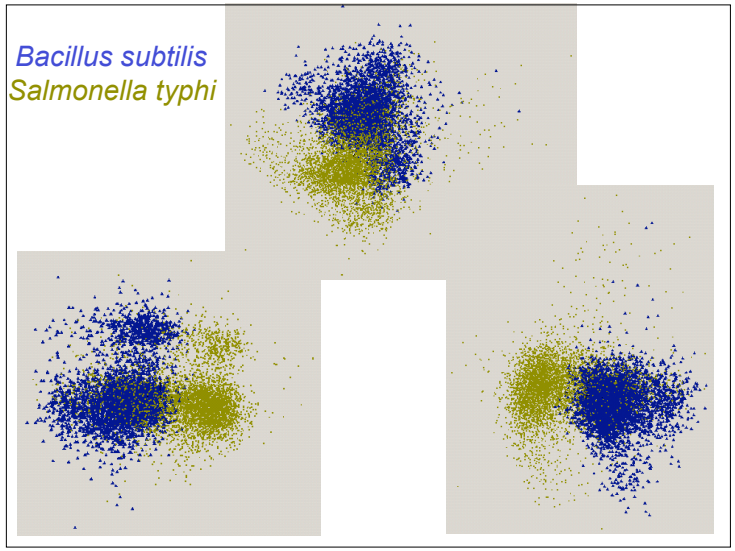
Normalized vectors and PCA are used to "see"

- organisms in codon space
- genes and functions

Haemophilus influenzae
Staphylococcus aureus



Bacillus subtilis
Salmonella typhi

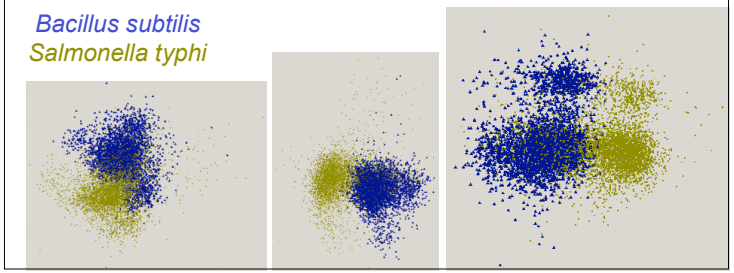


$g = [x_{1,g}\ x_{2,g} \ldots x_{64,g}]$ $x_{i,g}$ relative frequency of codon i in g

Vector normalisation:

$(x_{i,g} - \underline{x}_i) / \sigma_i$ $\underline{x}_i$ mean of frequencies $x_{i,g}$
σ_i standard deviation of $x_{i,g}$

Bacillus subtilis
Salmonella typhi

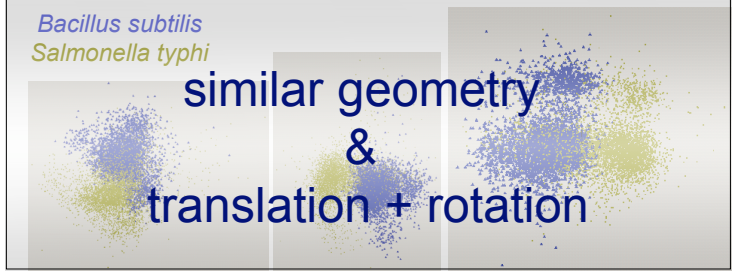


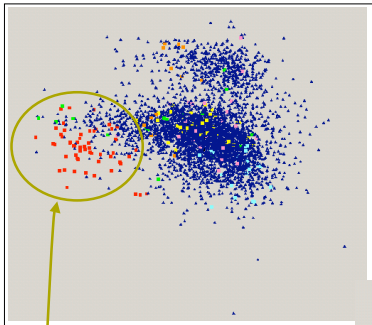
$g = [x_{1,g}\ x_{2,g} \ldots x_{64,g}]$ $x_{i,g}$ relative frequency of codon i in g

Vector normalisation:

$(x_{i,g} - \underline{x}_i) / \sigma_i$ $\underline{x}_i$ mean of frequencies $x_{i,g}$
σ_i standard deviation of $x_{i,g}$

Bacillus subtilis
Salmonella typhi

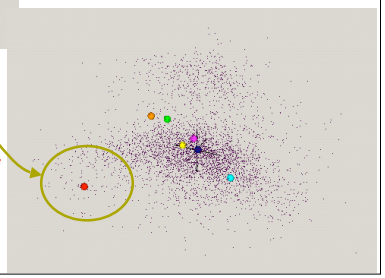




Ribosomal proteins
ATP binding proteins
IS proteins
NADH proteins
Flagellar biosynthesis proteins
Lipoproteins, membrane proteins, transport proteins

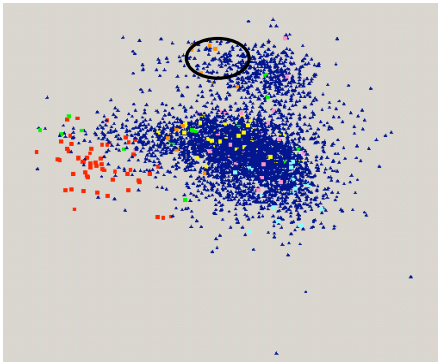
Proteins codifying for "translation", glycolysis …

They are the most expressed in *E.coli*

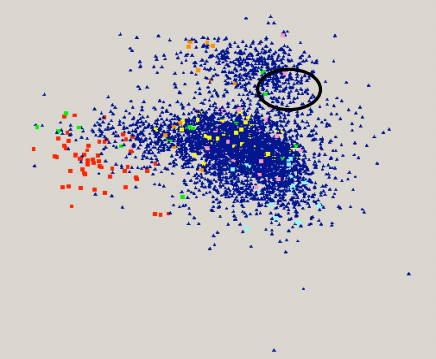


E.coli

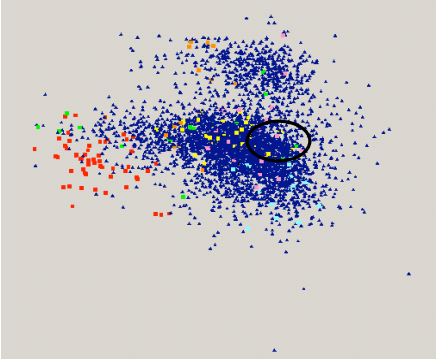
How to define "codon bias" and how to search for highly biased genes in an automatic manner?



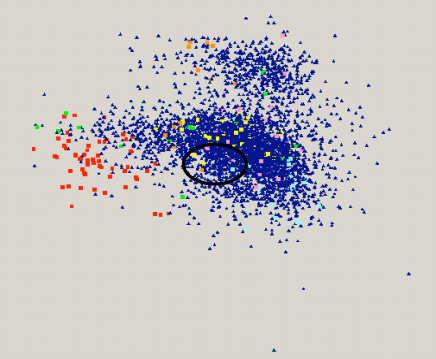
How to define “codon bias” and how to search for highly biased genes in an automatic manner?



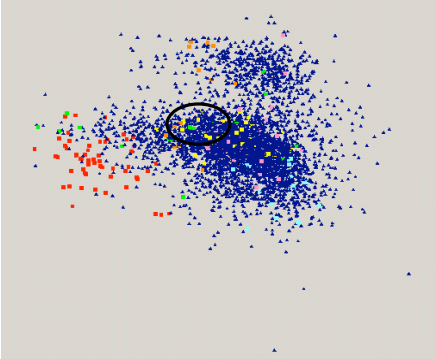
How to define “codon bias” and how to search for highly biased genes in an automatic manner?



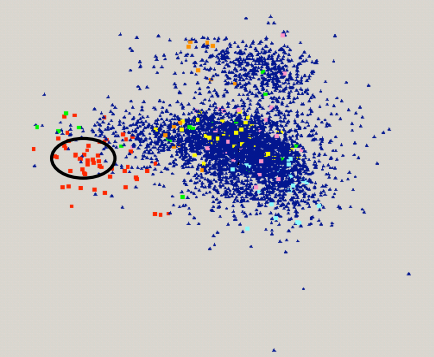
How to define “codon bias” and how to search for highly biased genes in an automatic manner?

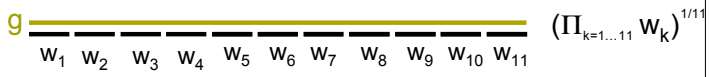


How to define “codon bias” and how to search for highly biased genes in an automatic manner?



How to define “codon bias” and how to search for highly biased genes in an automatic manner?





$$CAI(g) = (\Pi_{k=1...L} w_k)^{1/L}$$ (Sharp & Li, 1987)

Codon Adaptation Index

L number of codons in g

w_k $\frac{\text{frequency of the } k^{th} \text{ codon of g in S}}{\text{frequency of the dominant synonymous codon in S}}$

proteines codifying for “translation”, glycolysis …

Let S be a set of genes and g be a gene

$$CAI(g) = (\Pi_{k=1...L} w_k)^{1/L}$$ (Sharp & Li, 1987)

Codon Adaptation Index

L number of codons in g

w_k $\frac{\text{frequency of the } k^{th} \text{ codon of g in S}}{\text{frequency of the dominant synonymous codon in S}}$

proteines codifying for “translation”, glycolysis …

Let S be a set of genes and g be a gene

$$CAI(g) = (\Pi_{k=1...L} w_k)^{1/L}$$ (Sharp & Li, 1987)

Codon Adaptation Index

L number of codons in g

w_k $\frac{\text{frequency of the } k^{th} \text{ codon of g in S}}{\text{frequency of the dominant synonymous codon in S}}$

we compute S

Let S be a set of genes and g be a gene

$$SCCI(g) = (\Pi_{k=1\ldots L}\, w_k)^{1/L}$$

Self Consistent Codon Index

L number of codons in g

w_k $\dfrac{\text{frequency of the } k^{th} \text{ codon of g in S}}{\text{frequency of the dominant synonymous codon in S}}$

we compute S

Let S be a set of genes and g be a gene

$$SCCI(g) = (\Pi_{k=1\ldots L}\, w_k)^{1/L}$$

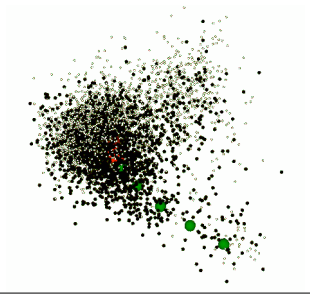
Self Consistent Codon Index

Self consistency condition

SCCI values on genes in S are **maximal** :
SCCI(G/S) ≤ SCCI(S), G is the set of all genes

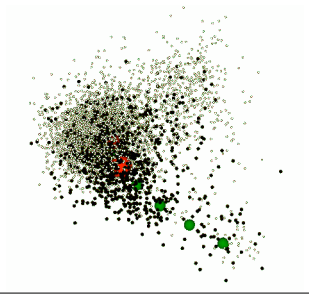
Idea of the algorithm:

- Compute the weight of the codons over the whole genome and compute afterwards SCCI values for all genes
- Select the 50% of genes with the highest SCCI value
- Repeat the iteration and select the 25% of the genes
- and so on… until we arrive to the 1% of genes in the original set.
- … then repeat the iteration on the 1% of genes with highest SCCI until convergence is reached.



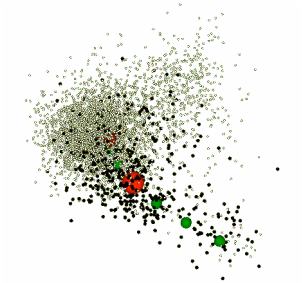
Idea of the algorithm:

- Compute the weight of the codons over the whole genome and compute afterwards SCCI values for all genes
- Select the 50% of genes with the highest SCCI value
- Repeat the iteration and select the 25% of the genes
- and so on… until we arrive to the 1% of genes in the original set.
- … then repeat the iteration on the 1% of genes with highest SCCI until convergence is reached.



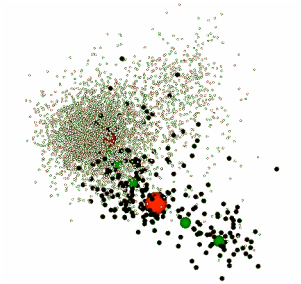
Idea of the algorithm:

- Compute the weight of the codons over the whole genome and compute afterwards SCCI values for all genes
- Select the 50% of genes with the highest SCCI value
- Repeat the iteration and select the 25% of the genes
- and so on… until we arrive to the 1% of genes in the original set.
- … then repeat the iteration on the 1% of genes with highest SCCI until convergence is reached.



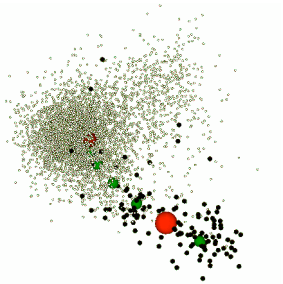
Idea of the algorithm:

- Compute the weight of the codons over the whole genome and compute afterwards SCCI values for all genes
- Select the 50% of genes with the highest SCCI value
- Repeat the iteration and select the 25% of the genes
- and so on… until we arrive to the 1% of genes in the original set.
- … then repeat the iteration on the 1% of genes with highest SCCI until convergence is reached.



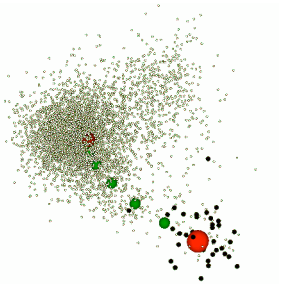
Idea of the algorithm:

- Compute the weight of the codons over the whole genome and compute afterwards SCCI values for all genes
- Select the 50% of genes with the highest SCCI value
- Repeat the iteration and select the 25% of the genes
- and so on… until we arrive to the 1% of genes in the original set.
- … then repeat the iteration on the 1% of genes with highest SCCI until convergence is reached.



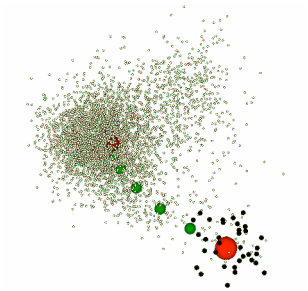
Idea of the algorithm:

- Compute the weight of the codons over the whole genome and compute afterwards SCCI values for all genes
- Select the 50% of genes with the highest SCCI value
- Repeat the iteration and select the 25% of the genes
- and so on… until we arrive to the 1% of genes in the original set.
- … then repeat the iteration on the 1% of genes with highest SCCI until convergence is reached.



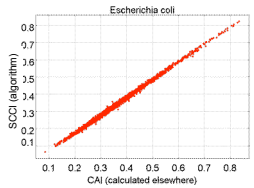
Idea of the algorithm:

- Compute the weight of the codons over the whole genome and compute afterwards SCCI values for all genes
- Select the 50% of genes with the highest SCCI value
- Repeat the iteration and select the 25% of the genes
- and so on… until we arrive to the 1% of genes in the original set.
- … then repeat the iteration on the 1% of genes with highest SCCI until convergence is reached.



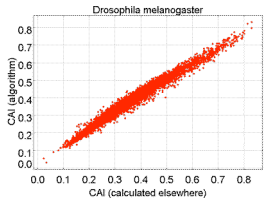
S found by the algorithm: *E.coli*

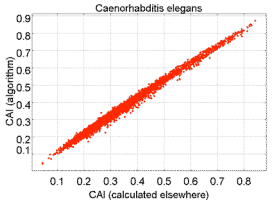
(*E.coli* reproduce rapidly)

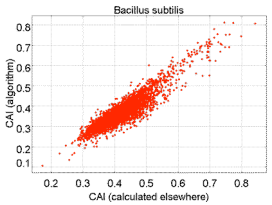


Gene	Annotation
tufA	protein chain elongation factor EF-Tu
tufB	protein chain elongation factor EF-Tu
tsf	protein chain elongation factor EF-Ts
fusA	GTP-binding protein chain elongation factor EF-G
mopA	chaperonin GroEL
dnaK	heat shock protein DnaK
cspA	cold shock protein 7.4
tig	trigger factor
ompA	outer membrane protein
ompX	outer membrane protein
ompC	outer membrane protein
lpp	murein lipoprotein
pal	peptidoglycan-associated lipoprotein
yaiU	putative flagellin structural protein
yfiD	putative formate acetyltransferase
eno	diadenosine tetraphosphatase
tpiA	triosephosphate isomerase
pgk	phosphoglycerate kinase
gapA	glyceraldehyde-3-phosphate dehydrogenase A
fba	fructose-bisphosphate aldolase class II
pykF	pyruvate kinase I
pflB	formate acetyltransferase 1
ahpC	alkyl hydroperoxide reductase C22 subunit
sodA	superoxide dismutase SodA
tktA	transketolase 1/2 isozyme
rpoC	RNA polymerase beta prime subunit
rpsI	30S ribosomal subunit protein S9
rpsA	30S ribosomal subunit protein S1
rpsB	30S ribosomal subunit protein S2
rpsC	30S ribosomal subunit protein S3
rpsU	30S ribosomal subunit protein S21
rplA	50S ribosomal subunit protein L1
rplY	50S ribosomal subunit protein L25
rplI	50S ribosomal subunit protein L9
rplL	50S ribosomal subunit protein L7/L12
rplC	50S ribosomal subunit protein L3
rpmE	50S ribosomal subunit protein L31
rplB	50S ribosomal subunit protein L2
rplK	50S ribosomal subunit protein L11
rpmI	50S ribosomal subunit protein A
rpmA	50S ribosomal subunit protein L27
rplD	50S ribosomal subunit protein L4, regulates expression of S10 operon

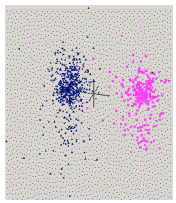
Validation for other fast growing organisms





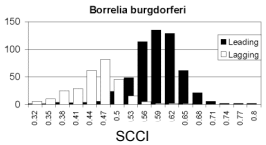


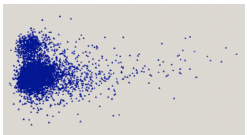
SCCI : a universal measure



Borrelia burgdorferi

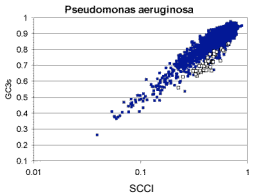
Strand bias





Pseudomonas aeruginosa

GC3 bias



The set of biased genes

- is **unique** (for the organisms we checked, ~210)
- **exists** also for organisms that do not have an evolutionary tendency explained with translational pressure.

For **any** bacteria we can compute:

+ dominant bias: strand bias, GC3, AT, ...
+ numerical criteria to determine the strength of translational bias

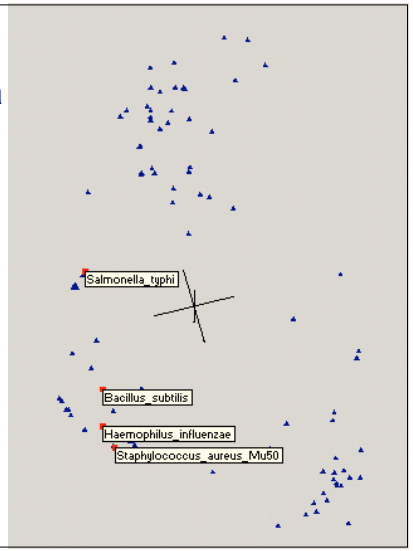
Random version of the algorithm

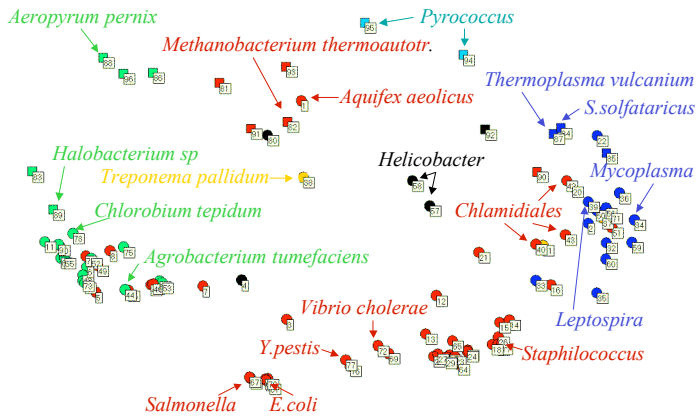
- Choose randomly the 1% of genes in G
- Compute weights and CAI values
- Select the 1% of genes with the highest CAI
- Repeat the iteration until convergence

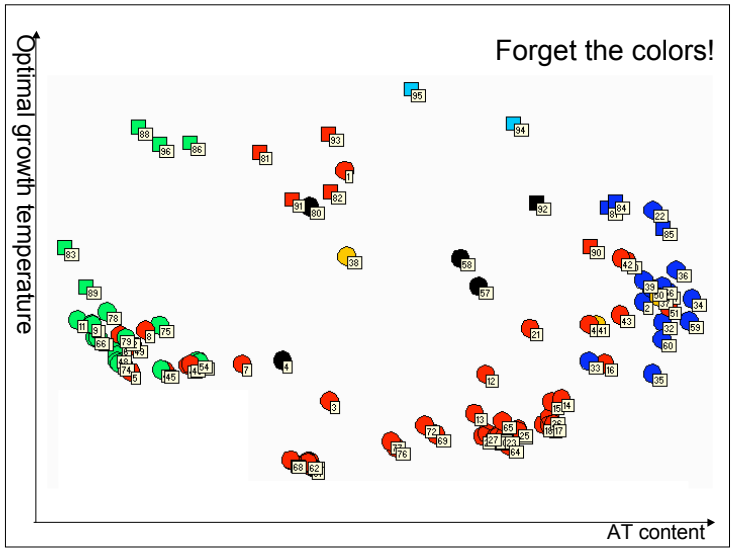
Bacteria and Archaea in SCCI codon space

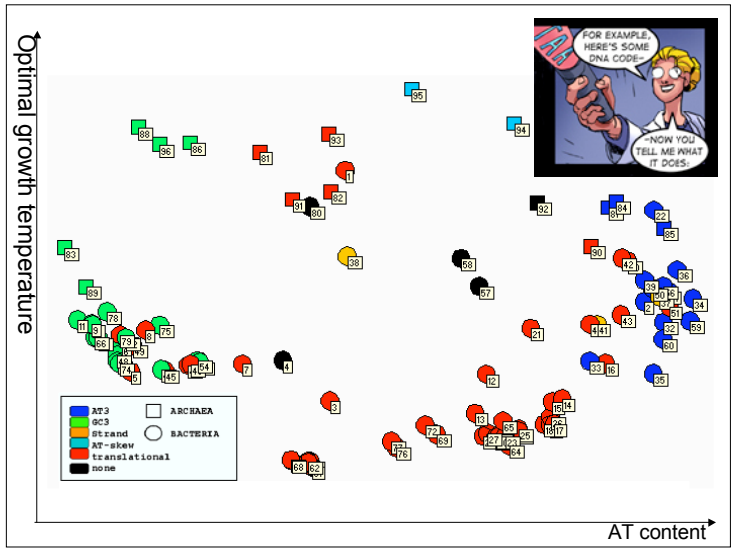
An organism is a 64-dim vector where

coordinate
=
SCCI codon weight



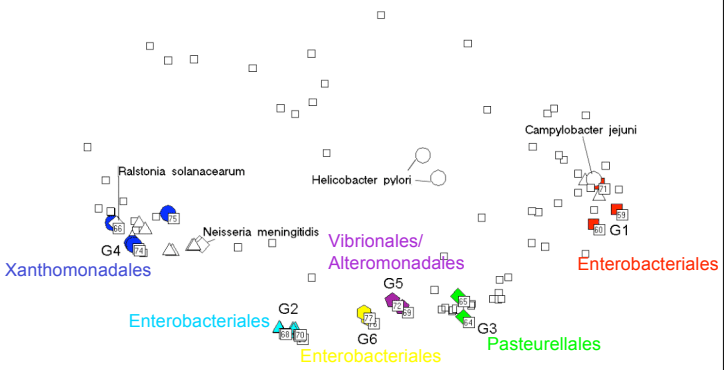






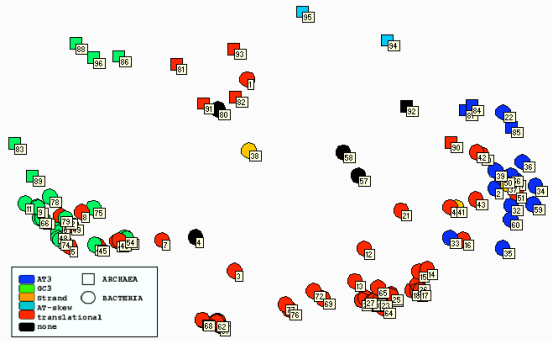
Can we exploit the geometry of the space to derive functional characteristics of groups of organisms?

Phylogenetically related families : γ-proteobacteria



Similar physiology and habitat

Organisms at small distance: similar physiology and habitat



Environmental clusters :

soil bacteria
enterics
symbions

spore formers
small intercellular pathogens
small extracellular pathogens

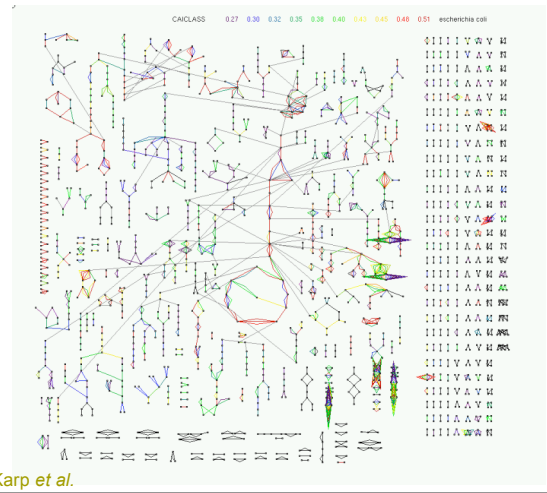
Coherence in the organisms space based on SCCI

Can we use this signal to deduce some more biological information ?

Can we determine the most important **metabolic networks** in a (translationally biased) organism ?

Metabolic networks

E.coli



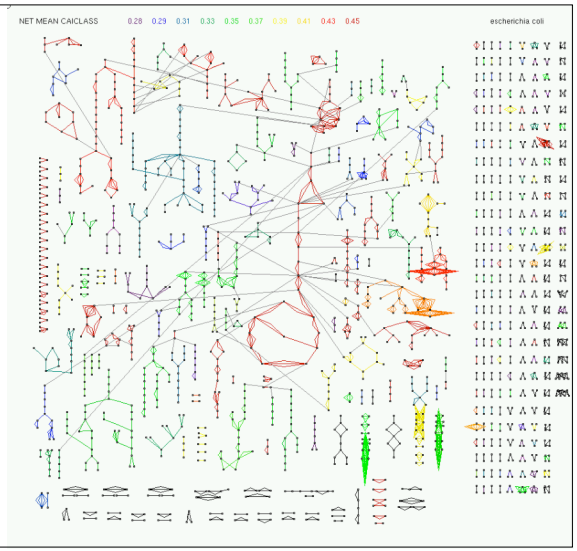
EcoCyc network, P.Karp *et al.*

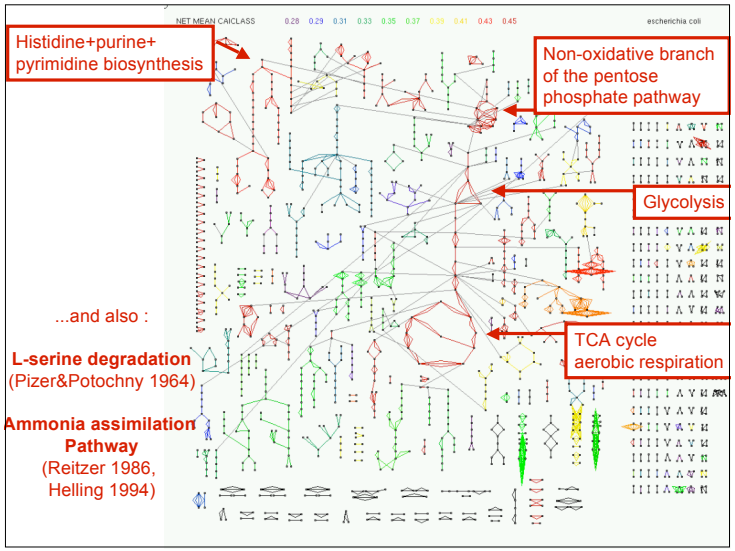
Pathway Index

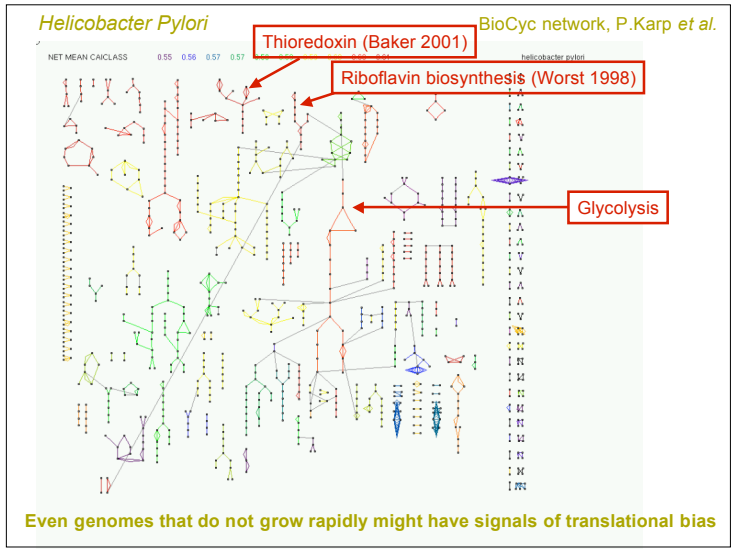
PI(P)
=
mean SCCI(g)
g∈P

Relative Pathway Index

RPI(P)
=
$(PI(P)-\mu_M)/\sigma_M$







Metabolic pathways essential to *Mycobacterium tuberculosis*

Essential to *M.tuberculosis* **but not** to other bacteria

Biotin synthesis	(Norman et al. 1994)
Chorismate biosynthesis	(Parish and Stoker 2002)
Aspargine degradation	(Sassetti et al. 2003)
Pyridoxal 5'phosphate biosynthesis	(Sassetti et al. 2003)
Valine degradation	(Sassetti et al. 2003)
Leucine biosynthesis	(Sassetti et al. 2003)
ppGpp	(Primm et al. 2000)

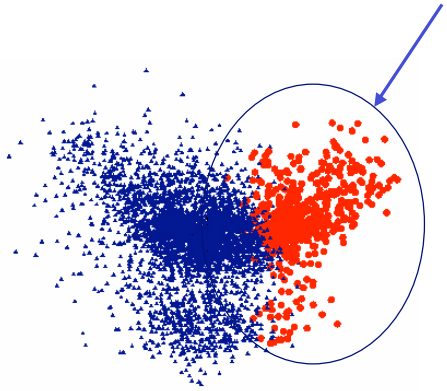
Coherence in the organisms space based on SCCI

Can we use this signal to deduce some more biological information ?

We determined the most important **metabolic networks** in a (translationally biased) organism

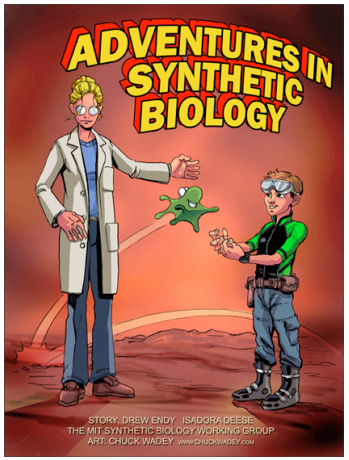
Can we determine genes belonging to **minimal gene sets** ?

Are these genes among the **most essential** ?



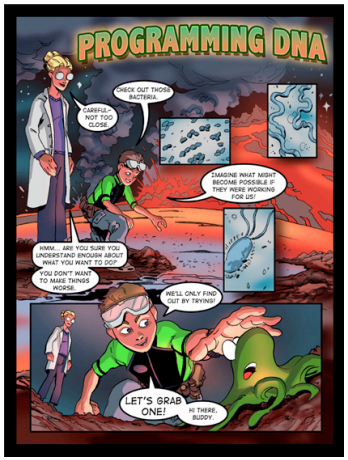
A parenthesis on synthetic biology

1st step



Genome synthesis

2nd step



Genome programming

Craig Venter, November 2002

Synthesis of a bacterial genome

the chromosome will be inserted in a living cell (whose genetic material has been removed) to verify if it can direct normal functional activities of the organism.

Clyde Hutchison, 1999 (*Science* 286, 2165-2169):
Gene knock out (517) of *Mycoplasma genitalium* (580kb), and estimation of how many genes are necessary to life over 517: about 300 to survive.

Eckard Wimmer, 2002 (*Science* 297, 1016-1018):
Synthesis of a poliovirus that infects cells! (~7500b)

Venter, Hutchison, Smith, 2008 (*Science* 319, 1215-1220)
Synthesis of *Mycoplasma genitalium*

Search for a minimal genome

Why to do this :

Add genes to transform *Mycoplasma* in a "useful" bacteria

Remedy against environmental pollution, new industrial chemical substances production, insuline production…

To search for a minimal set is not easy…

Experiments : transposomal mutagenesis & RNA silencing

B.subtilis	*M.genitalium*	*H.influenzae*	*E.coli*
300 genes/~4000 (Itaya, 1995) **248** genes/~4100 (Kobayashi, 2003)	**265** genes / 482 (Hutchison et al., 1999) **382** genes / 482 (Hutchison et al., 2006)	**670** genes/ ~1272 (Akerley et al. 2002)	**620** genes / 3746 (Gerdes et al. 2003) **234** genes / 2994 (Hashimoto et al. 2005)
S.cerevisiae	*C.elegans*	*S.aureus*	*S.pneumoniae*
1105 genes/ 5916 (Giaever et al. 2002)	**1722** genes/ 19427 (Kamath et al. 2003)	**150** genes (Yi et al. 2001)	**110** genes (Thanassi et al. 2002)

Comparative genomics

2 genomes	34 genomes	100 genomes	147 genomes
256 genes (Mushegian & Koonin 1996)	**80** genes (Harris et al 2003)	**60** genes (Koonin et al. 2003)	**35** genes (Charlebois & Doolittle 2004)

Number of genes in the minimal set depends on

Experiments:

- life/environmental conditions of the organism during the experiment
  → bacteria live in very good lab conditions

Computational detection of sequence homology:

- parameters and tools to detect homologies
  → there are genomes with more than 60% of genes with unknown function

Genes relevant to **environmental conditions** are missing

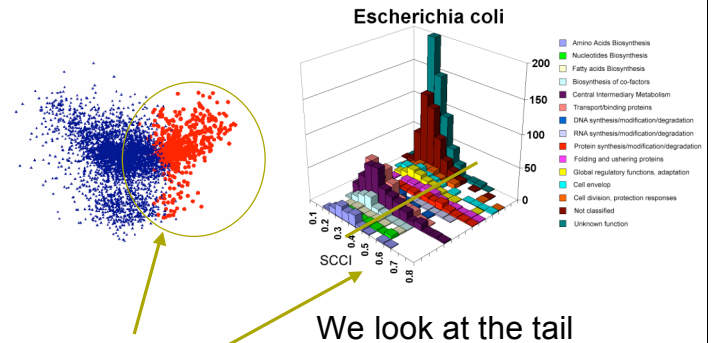
Stress response genes are missing

Genes with **uncharacterized functions** are missing

Genes in minimal gene sets

$SCCI(g) > \mu+\sigma$

- Genes with uncharacterised function
- Genes dependent on specific environmental conditions
- Stress response genes
- Highly expressed genes (belonging to most species)
- Non-orthologous genes



Core genes

We look at the tail

SCCI(g) > $\mu+\sigma = 0.42$

Map of core genes of 27 organisms (based on 200 most biased genes)

	Aci	Bha	Bsu	Bth	Bba	Cdi	Efa	Eca	Eco	Hin	Lpl	Lla	Mac	Pmu	Plu	Pab	Sty	Sat	Son	Sfl	Sag	Smu	Spn	Spy	Syn	Vch	Ype
INFORMATION STORAGE AND PROCESSING																											
J Translation and associated functions																											
ribosomal proteins (including subunits)	49	65	48	34	11	49	49	41	45	46	50	53	39	51	47	49	47	46	48	44	52	46	51	52	22	53	51
elongation factors	5	4	4	4	1	4	4	5	5	5	4	4	2	5	5	3	5	5	6	5	5	4	6	5	3	7	3
initiation factors	2	2	1	1	3	1		1	1	1	1	1	2	2	2	3	1	1	1	1	2	2		2		2	2
aminoacyl-transfer-RNA-synthetases	1		2	13	5	5	5	7	9	6	6	8	6	6	9	5	7	7	7	11	6	7	11	9		10	2
polyribonucleotide nucleotidyltransferase	1	1			1		1	1	1	1		1	2	1	1		1	1	1	1			1			1	1
ribosome recycling/releasing/binding factors	1		1	1			1		2	1	1			1	2		1	1	1	1	2	1	1	1		1	1
K Transcription																											
cold shock proteins	2	1	3	5		1	1	2	3		3	2		2	3		3	3	2	3	1			1		3	7
RNA polymerase	3	1	4	1	1	3	3	4	5	3	5	5	2	3	4	4	3	3	3	5	6	4	4	5	5	4	4
transcription antiterminator					1	1	1		1	1	1	1		1	1		1	1		1		1					
trascription terminator					1		1					1		1			2	2	1	1			1	1		2	1
L DNA replication, recombination and repair																											
Bacterial nucleoid DNA-binding protein	1	1	1				1	2	1		1			1	1		1	1		2			1	1		2	2
RNA helicase					1	1	1	1		1	1	1			1		1	1		1	1			1	1	1	1
single-strand binding protein					1			1	1						1		1	1		1		1		1			1
Recombination protein					1			1			1				1		1			1	1			1			1
CELLULAR PROCESSES AND SIGNALING																											
D Cell division and chromosome partitioning																											
cell division proteins							1	1			1	1			1	1	1	1			2	2	1				1
O Posttranslational modification, protein turnover, chaperons																											
chaperone proteins	3	3	3	2	3	4	3	3	2	3	3	3	2	3	5		3	3	3	3	1	2	3	2	4	5	3
peptidyl-prolyl cis-trans isomerase	2	1	1	1	2	1		3	3	3		1	2	2	3		3	3	3	3				1	1	2	3
thioredoxin	1	3	1	1			1				1	2	2		1	1			1		1	1	2	1	2	1	
alkyl hydroperoxide reductase protein			1	2			1	1	1							1		1	2	1	1	1		1		1	1
trigger factor	1	1	1	1			1	1	1	1	1	1		1	1		1	1	1	1	1	1	1	1	1	1	1
Clp protease			1	1		2	1	1	1		1	1										2	1		1		
ribose-phosphate pyrophosphokinase		1	1	1		1			1					1			1	1	1							1	
cell division							1				1	1			1		1		1			1		1	2		1
M Cell envelop biogenesis, outer membrane																											
channel forming, conductance	1			1		1			1					1			1	1		1	1	1		1			
lipoproteins					1			2	1	1				1	2		3	2	2	2						2	2
outer membrane proteins								4	5	4				3	3		8	7	9	5						6	7
N Cell mobility and secretion																											
secretory proteins	1				2	1	1	2	3	2				3	3		3	4	3	4	2				1		2
flagellin proteins		1	2	1	1			1							1	3			1							1	3
membrane GTP-binding proteins	1			1	1	1		1			1	1			1		1	1		1							
P Inorganic ion transport and metabolism																											
superoxide dismutase	1	1	1	1		1	1	1	2	1		1		1	1		1	1	1	2	1	1	1	1	1	1	1
phosphate binding proteins		2			1			3	2		1	1					3	3		2		1		1	2	1	1
metal-ion binding proteins		4		2						2			1	4	1						2		2	1			

	Aci	Bha	Bsu	Bth	Bba	Cdi	Efa	Eca	Eco	Hin	Lpl	Lla	Mac	Pmu	Plu	Pab	Sty	Sat	Son	Sfl	Sag	Smu	Spn	Spy	Syn	Vch	Ype
METABOLISM																											
C Energy production and conversion																											
hydratase	2	1	1				1		1	1	1			1	1		1	1	1	1							
dehydrogenases	7	8	5	10	7	7	6	5	6	5	5	6	14	6	5	6	6	4	11	5	2	3	5	5	3	6	6
membrane-bound ATP-synthase	4	3	2	3	2	5	2	4	3	4	3	3	3	5	4	3	3	3	4	3	3	2	2	3	3	4	3
succinyl-CoA synthetase	2	2		1				2	3						2	1	2	2	4	3						2	2
ferredoxin	2	2	1	1									5		1	1					1				2		1
other reductases								2	3	2			2	1				1	1	3	1					2	2
cytochrome oxidases	2			1			1									1		2	2	1						1	
cytochrome		1	1				2			1	3			1	3		1		1	6	1				5		
inorganic pyrophosphatase	1	1			1	1	1	1	1	1	1			1	1	1	1	1	1	1	1	1	1	1		1	1
phosphate acetyltransferase			1	1			1	1	1	1	1		1	1	1		1	1		1		1	1	1		1	1
formate acetyltransferase								1	1	1	1	1		1	1		1	1	1	1	1	1	1	1		1	1
acetate kinase				1		1	1	1	1	1	1		1	1	1		1	1		1	1			1		1	1
flavodoxin										1	1	1		1					1	1	1	1	1	1		1	1
G Carbohydrate transport and metabolism																											
enolase	1	1	1	1	1	1	1	1	1	1	1	1		1	1		1	1	1	1	1	1	1	1	1	1	1
1,6-bisphosphate aldolase	1	1	1	1		1	1	1	1	1	1	1		1	2		1	1	1	1	1	2	2	2	2	2	2
glyceraldehyde-3-phosphate dehydrogenase	1	1	1	2	1	1	1	1	1	1	1	2		1	1	1	1	1	1	2	2	1	2	1	1	1	1
inositol-1-monophosphatase	1								1	1	1			1	1		1	1	1	1							
transketolase	1		1	1				2	1	1				2	1		1	1	1	1	1	1	1	1	2	1	
transporter (ABC and others)		3							1		3	2	4	1	3				2	1		7	3		3	2	
PTS system		2	2	2			2	2	5	1	8	6				5	6		4	9	13	12	9		3	2	
triosephosphate isomerase		1	1	1			1	1	1	1	1	1		1	1		1	1		1	1		1	1		1	1
phosphoglycerate kinase/mutase		1	2	1	1	1	2	2	2	2	2	2	2		2	1	3	3		3	3	2	3	1	2	3	
pyruvate kinase			1	1	1		1	1	1	1	1	1	1	1	1	1	1	1		1	1		1	1		1	1
6-phosphofructokinase				1				1		1	1	1					1	1		1	1		1	1		1	
glucose-6-phosphate isomerase				1				1		1		2	1				1	1		1	1	1	1	1			1
transaldolase				1							1	1			1	1	1	1		1					1	1	1
6-phosphogluconate dehydrogenase (gnd)								1	1		1	1	1		1	1						1			1	1	1
isomerases										1		1	1			1			1	1	1	2	2	1			
E Amino acids transport and metabolism																											
transporters	1	2			3			1	1	2	1	2	2	1		2	1	2		1	5	4	2			3	1
glutamine synthetase	1	1	1	1	1	1		1	1		1	1	2		1		1	1	1	1	1	1	1		1		1
serine hydroxymethyltransferase	1		1	1		1		1	1	1				1	1	1	1	1	1	1		1					1
aminotransferases	2	1		2	1		1	1	1	2	1	2	2	1	1	4	1	2		1	1		1	1		1	2
ketol-acid reductoisomerase	1	1	1					1	1	1		1	1		1		1	1				1					1
dehydrogenases				3		2		1		2			3		2	3			1			3	2				
synthases	1	1						2				1	4		1	1						2	1		2	1	1
lyases								1	1	2				1	1		1	1		1			1			1	
F Nucleotide transport and metabolism																											
nucleoside diphosphate kinase	1	1					1		1	1			1		1				1	1					1		1
other kinases							1		1	1	1	1	1	1	1		2	2	2	1	1	1	1	1	1	1	1
nucleoside di(tri)phosphate reductase						1	2		1	1	1	1	1	2	2						2	1	1		1		
GMP reductase			1	1		1	1	1	1	1	1		1				1	1	1	1	1	1	1		1	1	
GMP synthase			1	1		1	1	1	1	1	1		1			2	1	1		1	1	1	1				
CTP synthetase	1		1	1			1						1	1					1		1	1				1	
adenylosuccinate synthetase	1			1		1	1	1	1	1				1	1			1	1		1	1					1
transferases			1	2					1		1	2		1		1					1	2		3	1		
purine-nucleoside phosphorylase				2		1		1	1	1		1		1	1		1	1	1	1	1		2			1	1
deoxyribose-phosphate aldolase				1		1			1			1	1		1		1	1		1	1		1				
H Coenzyme metabolism																											
S-adenosylmethionine synthetase	1		1	1	1			1	1	1	1				1		1	1	1	1					1	1	1
I Lipid metabolism																											
acyl carrier protein	1	1	1				1	2	1	1		1		1	1		1	1	2	1	1		1	1	1	1	1
acetylCoA carboxylase	3	2	1			1		2	1	1				2	2		2	2		2						1	2
beta-ketoacyl-acyl carrier protein synthase	1								1	1		1		1			1	1		1		1				1	1

Genes with **specific metabolic functions** are in the tail

Photosynthesis metabolism : *Synechocystis*
- Phycobilisome proteins
- Photosystem I and II
- Fructose-1,6-bisphosphate-aldolase

Methan metabolism : *Methanosarcina acetivorans*
- Methanol-5 hydroxybenzimidazolylcobamideco methyltransferase
- Methyl coenzyme M reductase
- Methylcobamide methyltransferase isozyme M
- Corrinoid proteins
- Ack, Pta, cdhA

Ferrodoxin metabolism : *Pyrococcus abyssi*
- Ferredoxin
- Ferredoxin oxidoreductase
- Keto-valine-ferredoxin oxidoreductase γ-chain

Carbohydrates metabolism : *Streptococcus mutans*
- Transport and metabolism of cellobiose, sucrose, beta-glucoside
- Metabolism of mannitol
- Genes for metabolism of glucose, fructose, mannose, maltose/maltodextrin

Stress response genes are in the tail

Comparison with data from **comparative genomics**

Most represented functional classes of genes issued by comparing *M.genitalium* and *H.influenzae* (Mushegian and Koonin, 1996) **correspond to** most represented functional classes in functional genomic cores

Core genes expected to be essential but **missed** in (Mushegian&Koonin) :

Transcription : Sigma factors (rpo), termination factors (rho), chaperons (hsp90)
Energy metabolism : PTS proteins
Translation : no tRNA nucleotidyltransferase is found (consistently with comparative genomics)

Comparison with **experimental data**

difficult to make

there are no a priori false positives nor false negatives

E.coli:
620 essential genes (Gerdes *et al.*, 2003)
234 essential genes (Hashimoto *et al.*, 2005)

E.coli (Gerdes, 2003) :

620 essential genes over 3746 analyzed ones
520 core genes: 62.5% are essential

Enolase (*eno*) is a core gene and it does not belong to the 620 genes claimed to be essential for *E.coli*

E.coli (Hashimoto et al., 2005) :

234 essential genes, 1890 non-essential, 900 unknown behavior over 2994 analyzed ones (after genome minimization)
520 core genes : 129 essential, 278 non-essential, 53 unknown behavior, 63 deleted after minimization

Most are stress response genes

B.subtilis (Kobayashi et al., 2003) :

248 essential genes
519 core genes : 126 essential

Most genes involved in Embden-Meyerhof-Parnas pathway are core genes in agreement with their unexpected essentiality for (Kobayashi et al. 2003)

Collaborations and references

Algorithm and microbial SCCI codon space :

- **F.Képès,** CNRS & génopole Evry
- **A.Zinovyev**, IHÉS & Institut Curie (Paris)

A. Carbone, A. Zinovyev, F. Képès, Codon adaptation index as a measure of dominating codon bias, *Bioinformatics*, **19**, 2005–2015, 2003.

A. Carbone, F. Képès, A. Zinovyev , Codon Bias Signatures, Organization of Microorganisms in Codon Space, and Lifestyle, *Molecular Biology and Evolution*, **22**, 547–561, 2004.

Metabolic networks comparison :

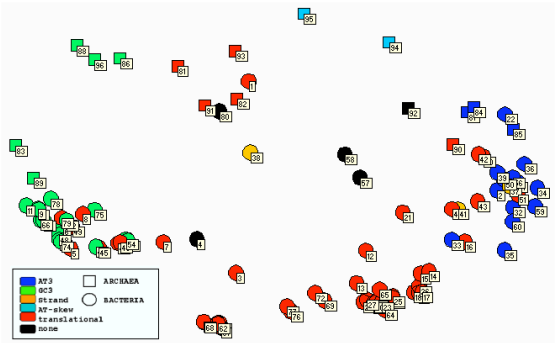
- **D.Madden**, IHÉS & IGI (USA)

A. Carbone, R. Madden, Insights on the Evolution of Metabolic Networks of Unicellular Translationally Biased Organisms from Transcriptomic Data and Sequence Analysis, *Journal of Molecular Evolution*, **59**, 1–25, 2005.

Minimal gene sets :

A.Carbone, Computational prediction of genomic functional cores specific to different microbes, *Journal of Molecular Evolution*, 2006, in press.

Bootstrapping information from translationally biased organisms



translationally biased organisms are everywhere

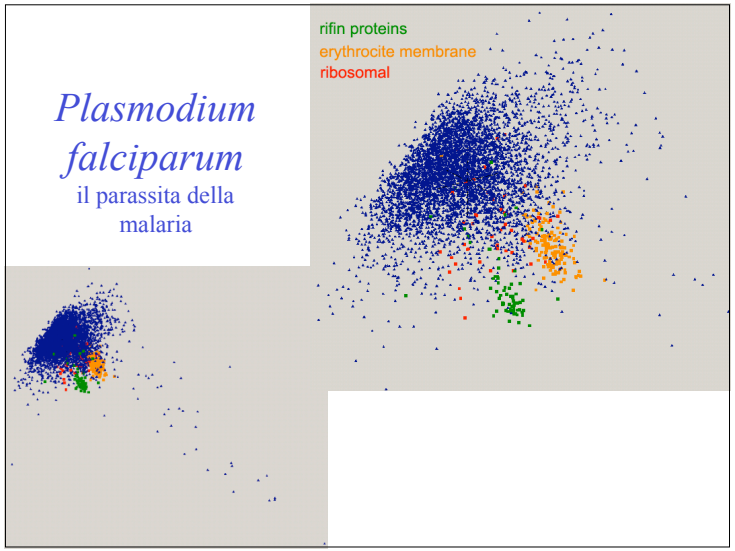
Small genomes : *M.genitalium* and *B.aphidicola*

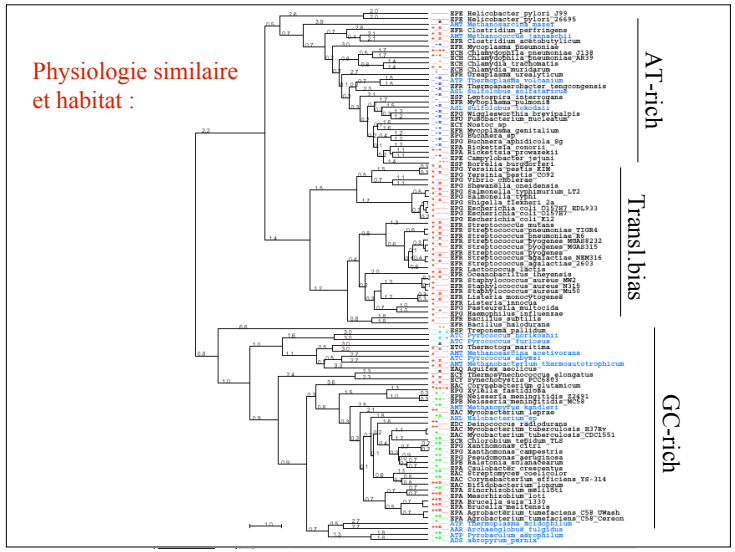
Buchnera aphidicola str Bp	504 coding genes 498 genes homologous to *E.coli* genes

Mycoplasma genitalium	484 coding genes 266 genes homologous to *E.coli* genes

189 genes are shared by *B.aphidicola* and *M.genitalium*

129 of these genes have high SCCI in *E.coli*


Plasmodium falciparum
il parassita della malaria
rifin proteins
erythrocite membrane
ribosomal


Physiologie similaire et habitat :
AT-rich
Transl.bias
GC-rich