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LA METABOLOMIQUE ET SES APPLICATIONS EN BIOLOGIE: POURQUOI, COMMENT, BUT ET PERSPECTIVES

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Institut national
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Aix*Marseille université

BIOMET

Le mot métabolisme provient du grec "μεταβο–λισμο× " (metabo-lismo), qui signifie "changement."

Concept du metabolisme par Ibn al-Nafis (1213–1288):
« *Le corps et ses partis sont en état perpétuel de dissolution et de reconstitution, de sorte qu'ils subissent inévitablement un changement permanent* »

Quelques définitions…..

Métabolite
Est une molécule organique <1500 Da détectable dans un organisme, incluant des molécules d'origine endogènes ou exogènes, issus des micro-organismes

Le Métabolome
Est un terme utilisé pour la première fois par Olivier et al en 1998 pour décrire un **ensemble de métabolites** synthétisés par un organisme

La Métabolomique
A été formulée par Oliver Fiehn et est définie par une **analyse complète non sélective** dans laquelle tous les métabolites d'un système biologique sont identifiés et quantifiés

La Métabonomique
Est définie par la **mesure quantitative de la réponse métabolique** multiparamétrique des systèmes vivants à un stimuli ou une altération génétique (Jeremy Nicholson)

Profilage des métabolites
Implique l'identification et la quantification d'un **ensemble ou d'une classe prédéfinis** de métabolites d'identités connus ou inconnus et appartenant à des voies métaboliques particulières.

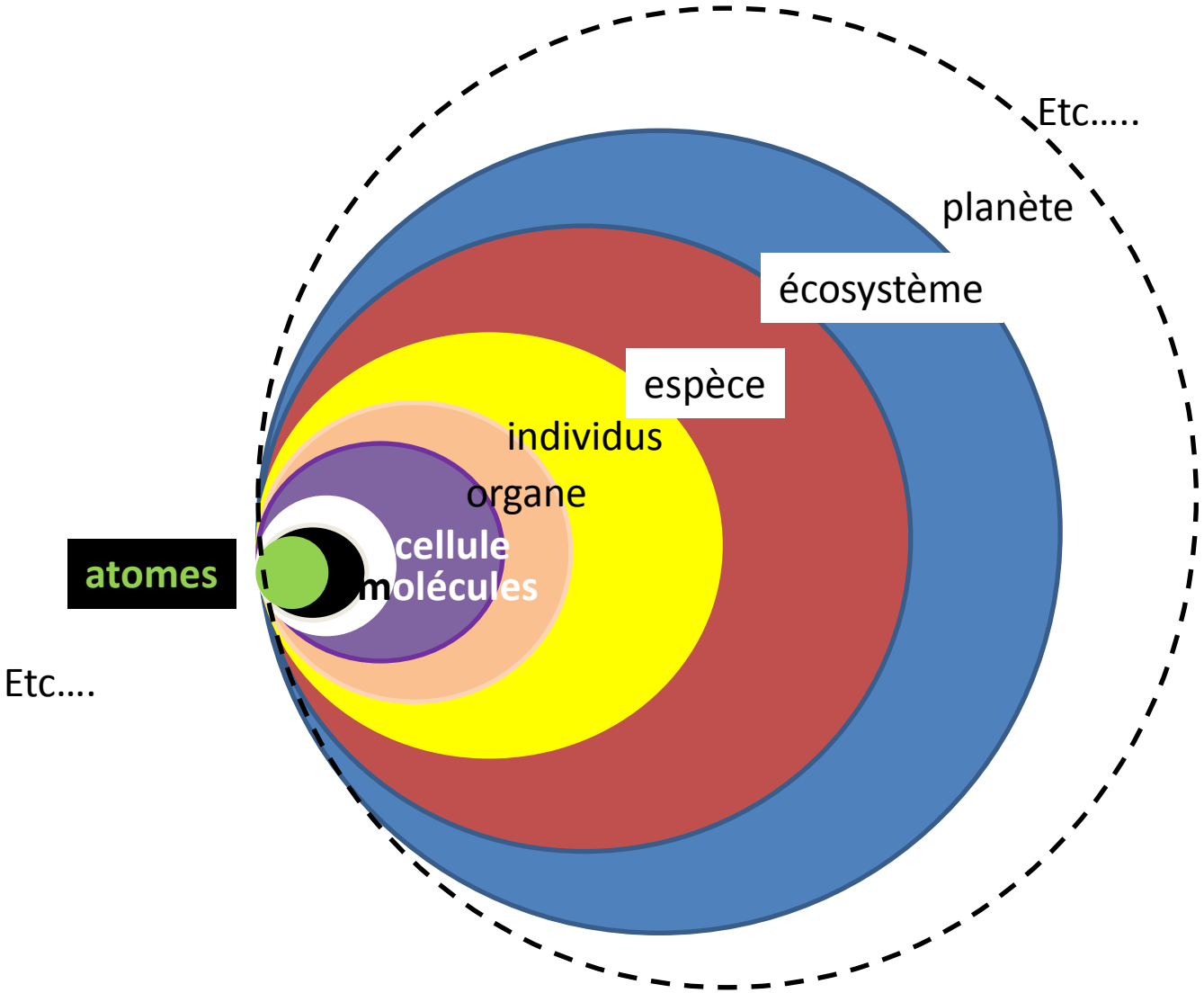
Le métabolome représente l'ultime réponse d'un organisme à une altération génétique, une pathologie, une exposition à un toxique ou toute cause environnementale. Le métabolome d'un système peut ainsi à la fois permettre de lire la signature biologique d'une réponse adaptative ou pathologique, et également être le vecteur de cette réponse. Ce dernier aspect souligne l'implication directe du métabolome dans le déterminisme des phénotypes

OPINION

2020 visions

For the first issue of the new decade, *Nature* asked a selection of leading researchers and policy-makers where their fields will be ten years from now. We invited them to identify the key questions their disciplines face, the major roadblocks and the pressing next steps. Visit go.nature.com/htW8uM to respond and to add your vision.

Les petites molécules sont présentent dans tous les systèmes…



systèmes gigognes

Le Metabolome est Connecté à tous les autres "Omes"

- Small molecules (i.e. AMP, CMP, GMP, TMP) are the primary constituents of the genome & transcriptome
- Small molecules (i.e. the 20 amino acids) are the primary constituents of the proteome
- Small molecules (i.e. lipids) give cells their shape, form, integrity and structure
- Small molecules (sugars, lipids, AAs, ATP) are the source of all cellular energy
- Small molecules serve as cofactors and signaling molecules for both the proteome and the genome
- *The genome & proteome largely evolved to catalyze the chemistry of small molecules*

Qing-zhao Wang · Chan-yuan Wu · Tao Chen · Xun Chen · Xue-ming Zhao

Integrating metabolomics into systems biology framework to exploit metabolic complexity: strategies and applications in microorganisms

Appl Microbiol Biotechnol (2006) 70: 151–161
DOI 10.1007/s00253-005-0277-2

Physiologia Plantarum 132: 162–175. 2008

Plant metabolomics and its potential application for human nutrition

Robert D. Hall[a,b,*], Inge D. Brouwer[c] and Melissa A. Fitzgerald[d]

Metabolomics tools for identifying biomarkers for neuropsychiatric diseases

Neurobiology of Disease 35 (2009) 165–176

Metabolomics in human nutrition: opportunities and challenges

Am J Clin Nutr 2005;82:497–503

Emerging high-throughput approaches to analyze bioremediation of sites contaminated with hazardous and/or recalcitrant wastes

Biotechnology Advances 26 (2008) 561–575

Applications of Metabolomics in Agriculture

Richard A. Dixon,† David R. Gang,‡ Adrian J. Charlton,§ Oliver Fiehn,# Harry A. Kuiper,|| Tracey L. Reynolds,⊥ Ronald S. Tjeerdema,⊗ Elizabeth H. Jeffery,△ J. Bruce German,× William P. Ridley,*,⊥ and James N. Seiber◇

High-Throughput Technique for Comprehensive Analysis of Japanese Green Tea Quality Assessment Using Ultra-performance Liquid Chromatography with Time-of-Flight Mass Spectrometry (UPLC/TOF MS)

J. Agric. Food Chem. 2008, 56, 10705–10708

8984 *J. Agric. Food Chem.* 2006, *54*, 8984–8994

Metabolomics in monitoring kidney transplants

Wishart, David S

Current Opinion in Nephrology & Hypertension:
November 2006 - Volume 15 - Issue 6 - p 637-642

Metabonomic modeling of drug toxicity

Hector C. Keun *

Pharmacology & Therapeutics 109 (2006) 92 – 106

Metabonomics in pharmaceutical R & D

John C. Lindon, Elaine Holmes and Jeremy K. Nicholson

FEBS Journal **274** (2007) 1140–1151

Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease

Zeneng Wang[1,2], Elizabeth Klipfell[1,2], Brian J. Bennett[3], Robert Koeth[1], Bruce S. Levison[1,2], Brandon DuGar[1], Ariel E. Feldstein[1,2], Earl B. Britt[1,2], Xiaoming Fu[1,2], Yoon-Mi Chung[1,2], Yuping Wu[4], Phil Schauer[5], Jonathan D. Smith[1,6], Hooman Allayee[7], W. H. Wilson Tang[1,2,6], Joseph A. DiDonato[1,2], Aldons J. Lusis[3] & Stanley L. Hazen[1,2,6]

7 APRIL 2011 | VOL 472 | NATURE | 57

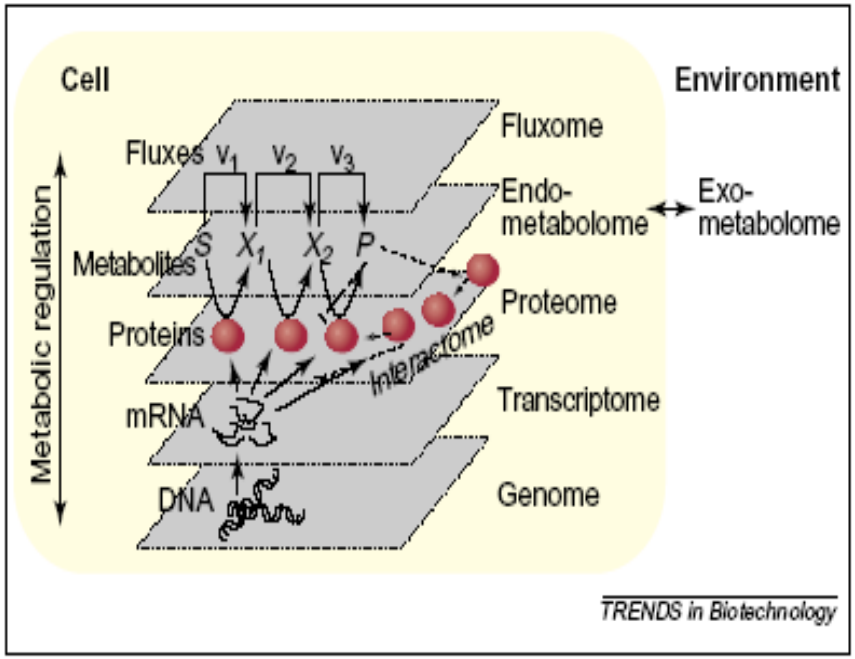
Regulation of floral scent production in petunia revealed by targeted metabolomics

Phytochemistry 62 (2003) 997–1008

Metabolomic Profiling for Identification of Novel Potential Biomarkers in Cardiovascular Diseases

Journal of Biomedicine and Biotechnology
Volume 2011, Article ID 790132, 9 pages

Comment j'en suis arrivé à la métabolomique… et autres omiques



contexte pro-athérogène

Hamsters adultes

Régime CROQUETTES

+ 20% lipides (0,12% cholestérol)

12 semaines

Croquettes

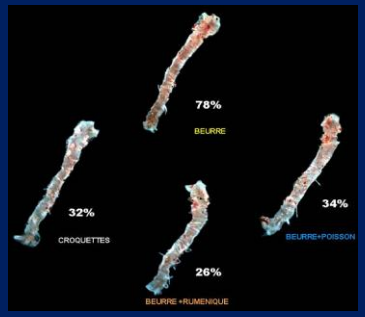
Beurre
(rum énique: 0,1%)

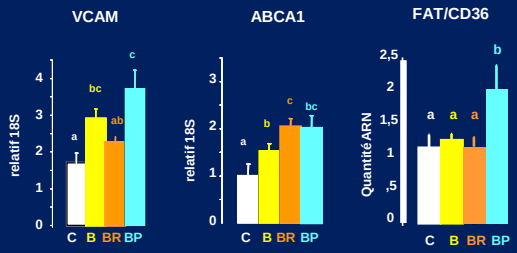
Beurre
+
rum énique
(qsp 1%)

Beurre
+
Huile de Poisson
(1%)

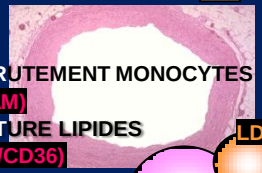
les stries lipidiques (dépôts d'esters de cholestérol) **marqueurs circulants** (lipoprotéines, paraoxonase, apo SAA) **expression gènes cibles** (VCAM-1, ABCA-1, COX2, cytokines, PPARs,…)

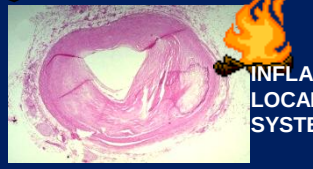
Valeille, K. et al, AJP, 2005





ATHEROSCLEROSE





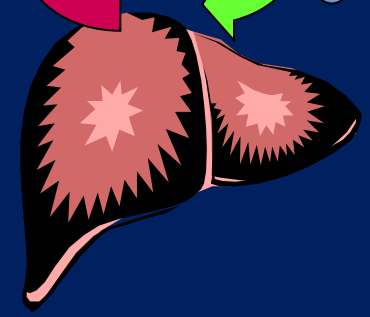
RECRUTEMENT MONOCYTES
(VCAM)
CAPTURE LIPIDES
(FAT/CD36)

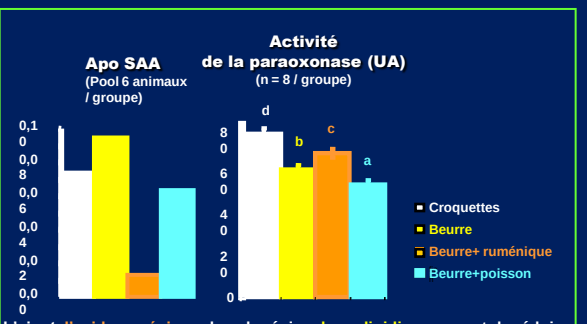
INFLAMMATION
LOCALE: TNFα, COX-2, IL1β
SYSTEMIQUE: apoSAA

LDL
VLDL

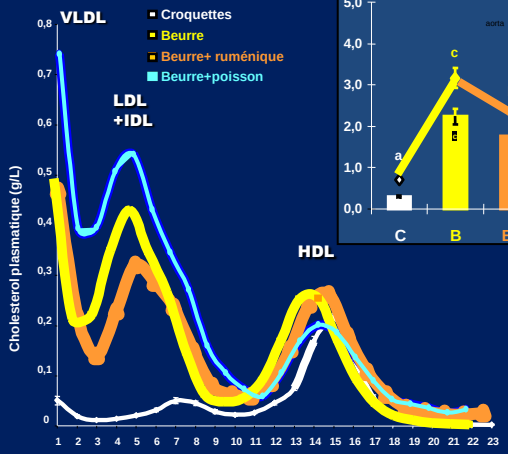
TRANSPORT
CHOLESTEROL

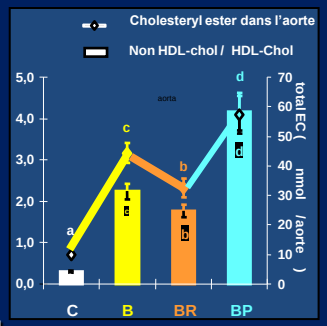
EFFLUX CHOLESTEROL
(ABCA1)
DETOXICATION LDLox
(PARAOXONASE)
HDL

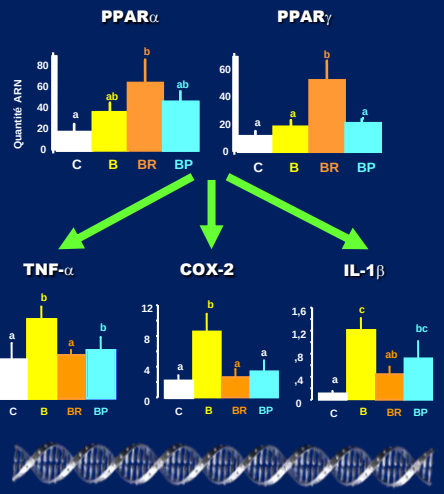




L'ajout d'acide ruménique dans le régime hyperlipidique permet de réduire le statut inflammatoire (apoSAA) et tend à normaliser l'activité de détoxication des LDL oxydées (activité paraoxonase du plasma). L'ajout d'huile de poisson n'apporte aucun bénéfice.





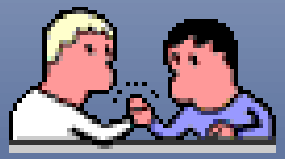


Valeille, K. et al, AJP, 2005

Conclusions

L' acide ruménique dans la matière grasse laitière est anti-athérogène (hamster hyperlipidémique)

↘ importance des dépôts lipidiques (EC)

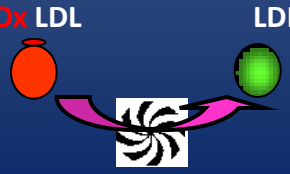


Systémique: ↘ nonHDL-CH/HDL-CH

Local: ↗ Efflux chol (ABCA1)

↘ Recrutement des monocytes

↘ inflammation

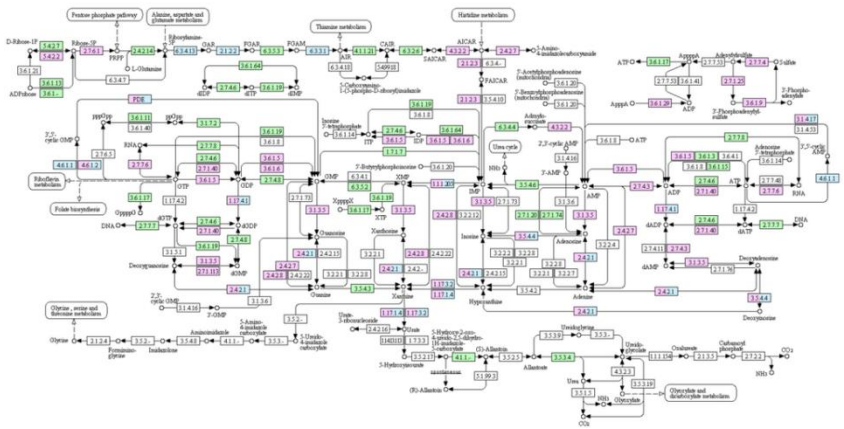


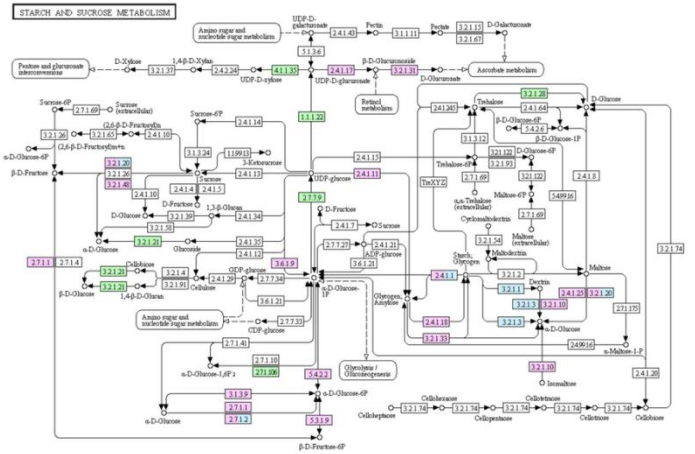
↗ Détoxication des oxLDL

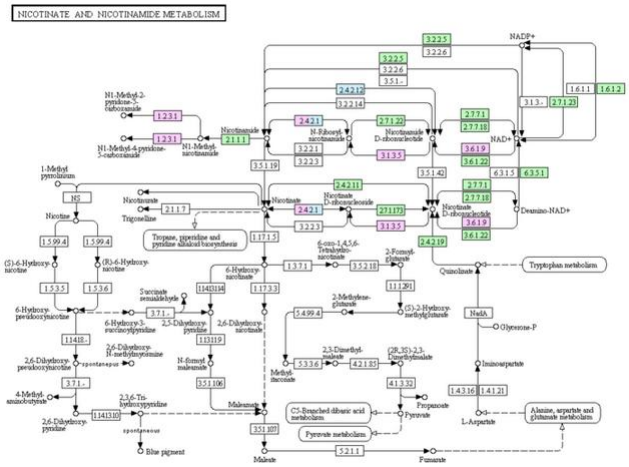
Est-ce suffisant?

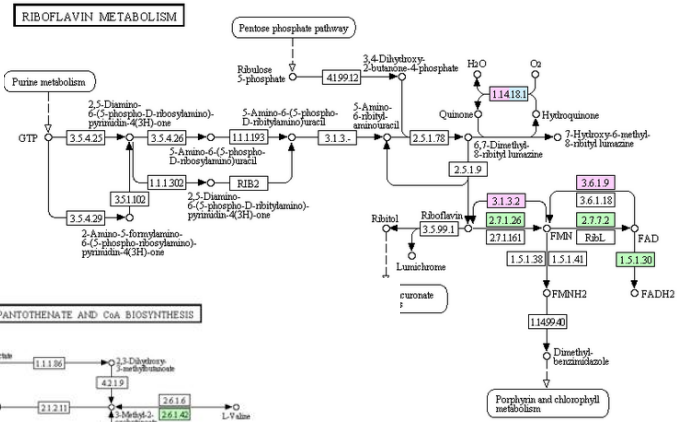
Oui et non

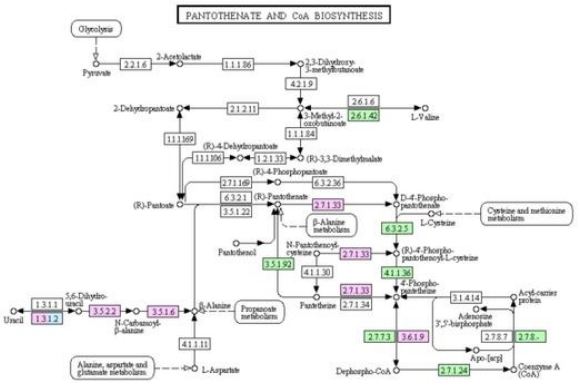
Mécanisme moléculaires de la calcification artérielle (KEGG H01002)



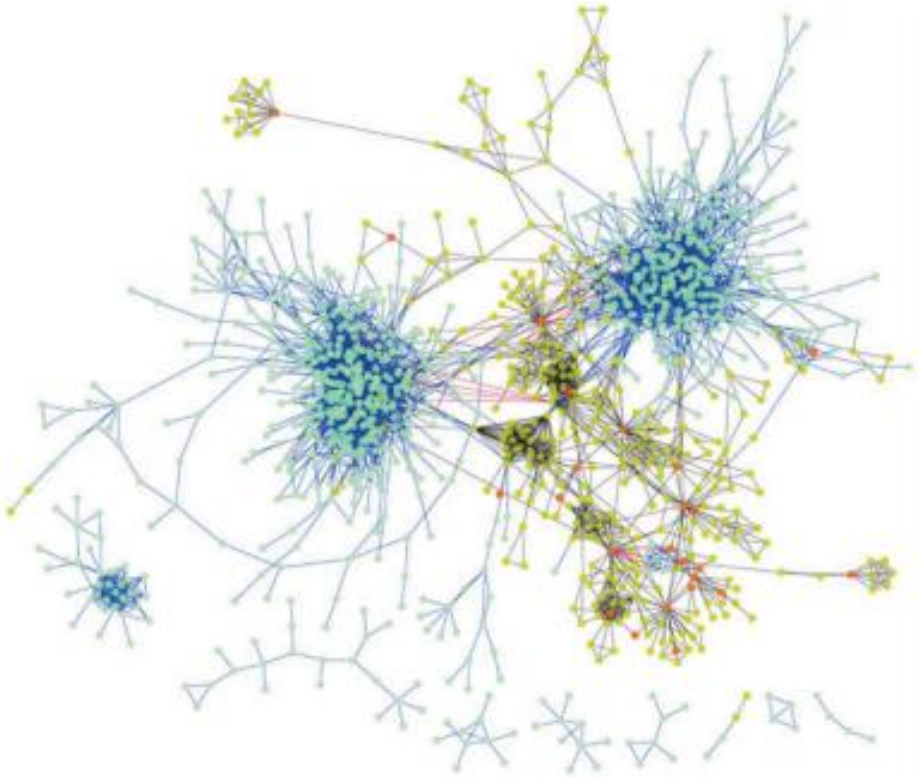




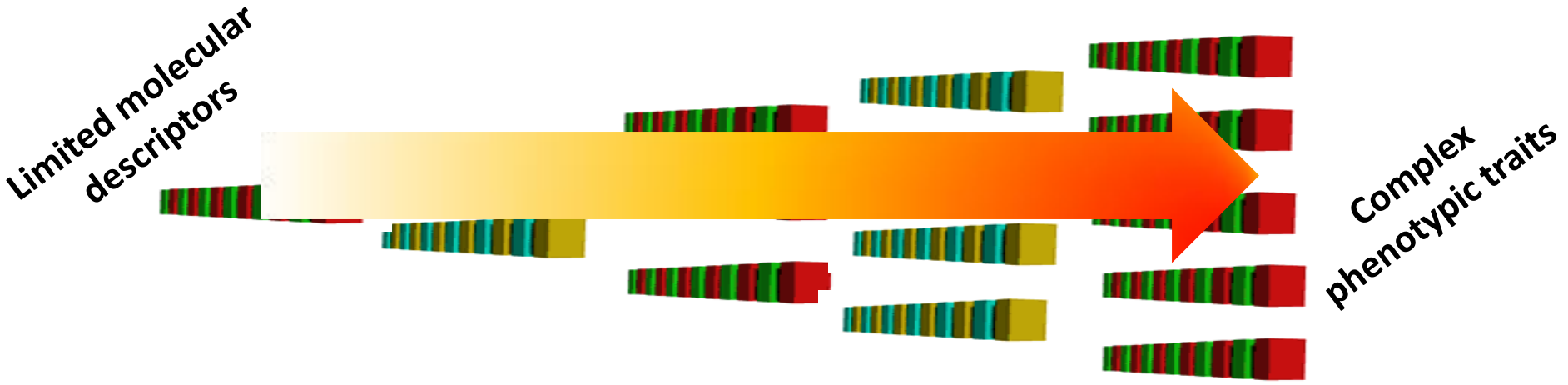




Réseau des gènes liés au sexe impliqués dans l'athérogénèse (composante sexuelle)
Reconstitution « in silico » partir des données de la littérature



Diez D, Wheelock AM, Goto S, et al. The use of network analyses for elucidating mechanisms in cardiovascular disease. Mol Biosyst 2010;6:289-304.

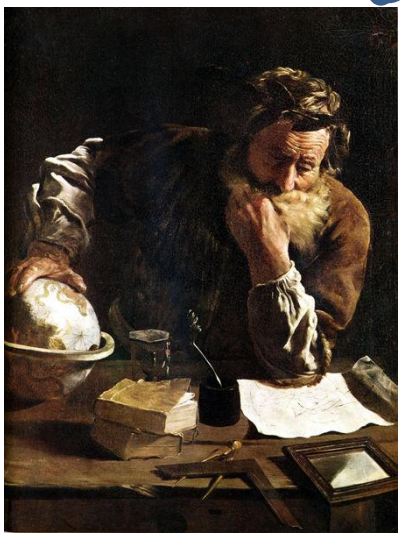


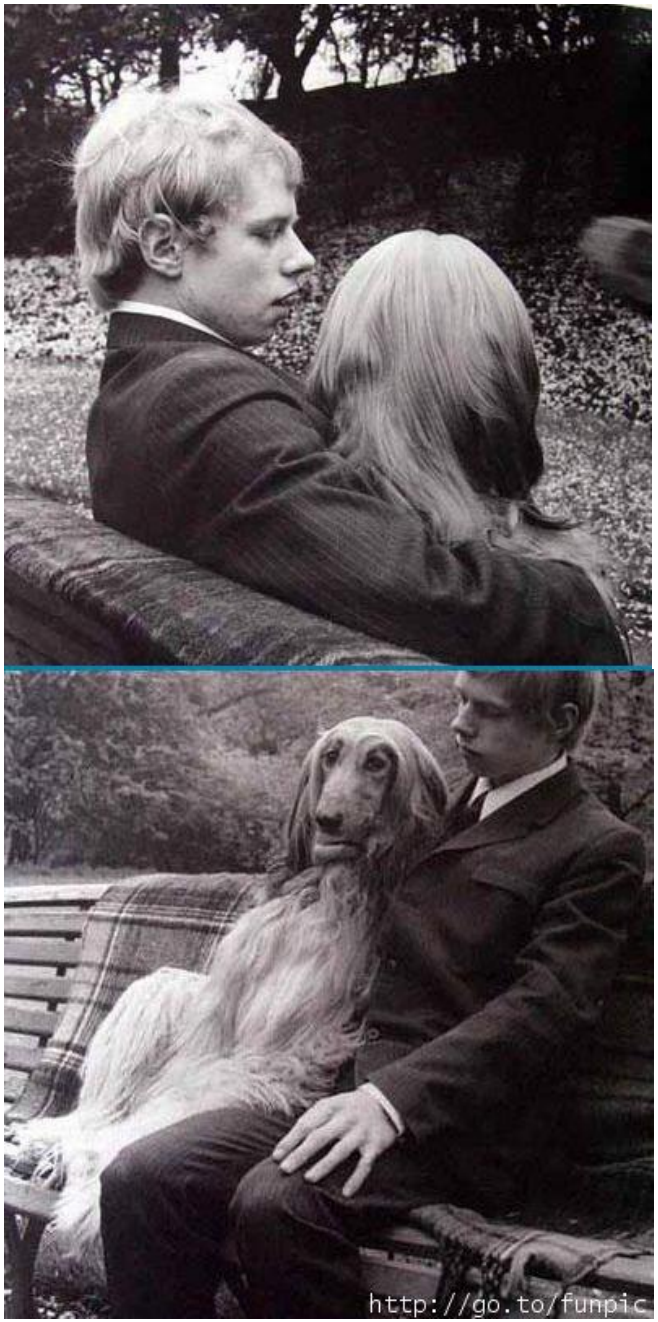
Blood lipids, CRP…

CVD, diabetes…

« conventional » so-called bottom-up strategies: explain complex phenotypes with only few targeted molecular descriptors

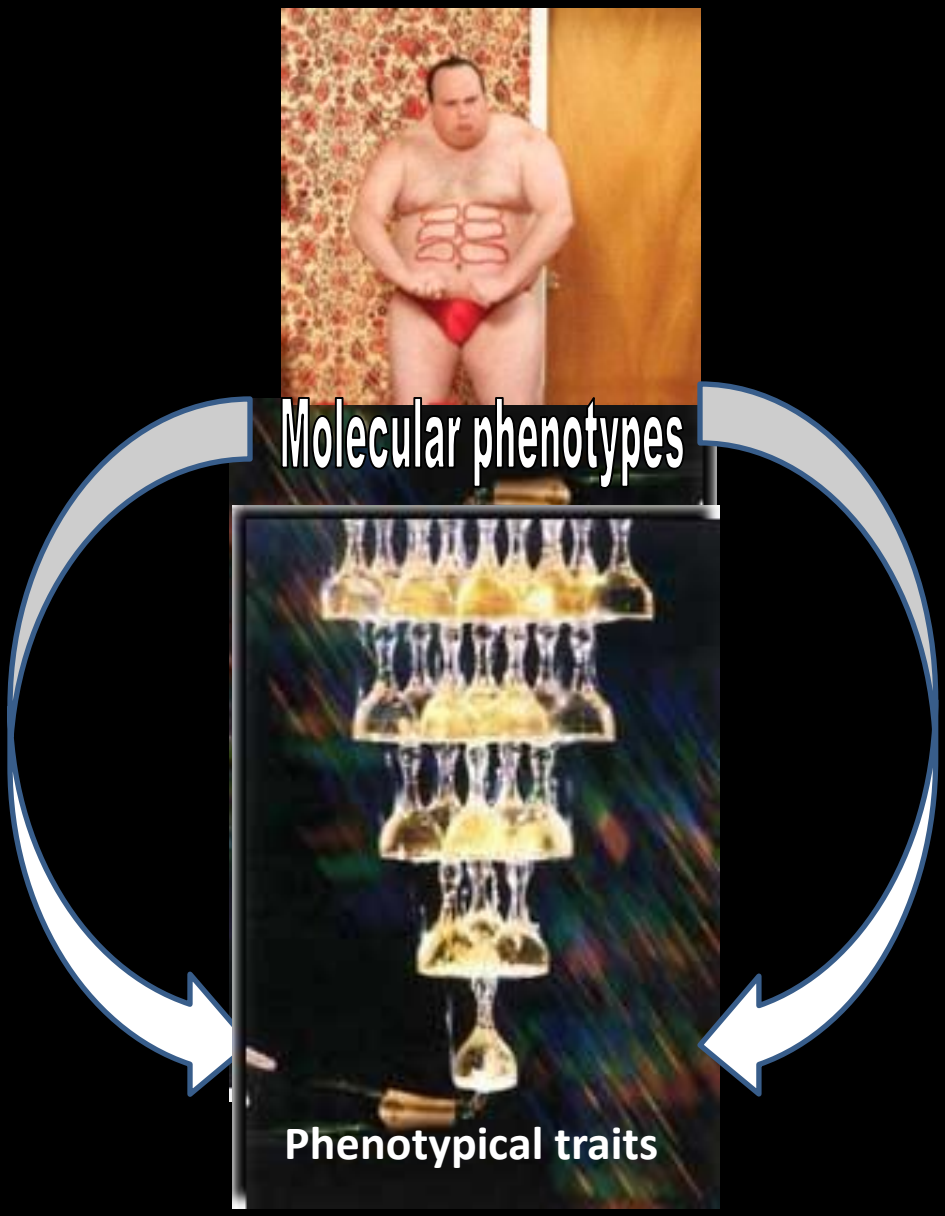
Reality is much complex than anticipated…..



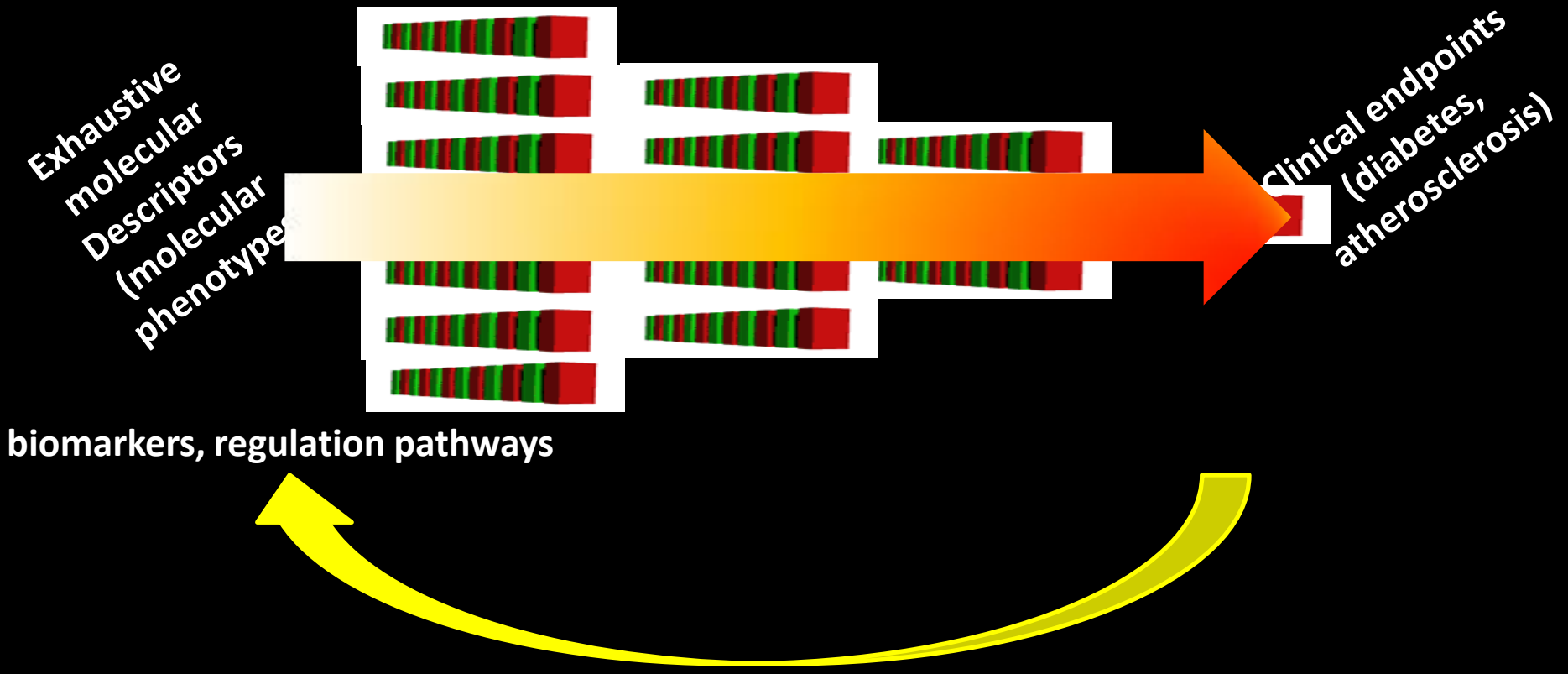


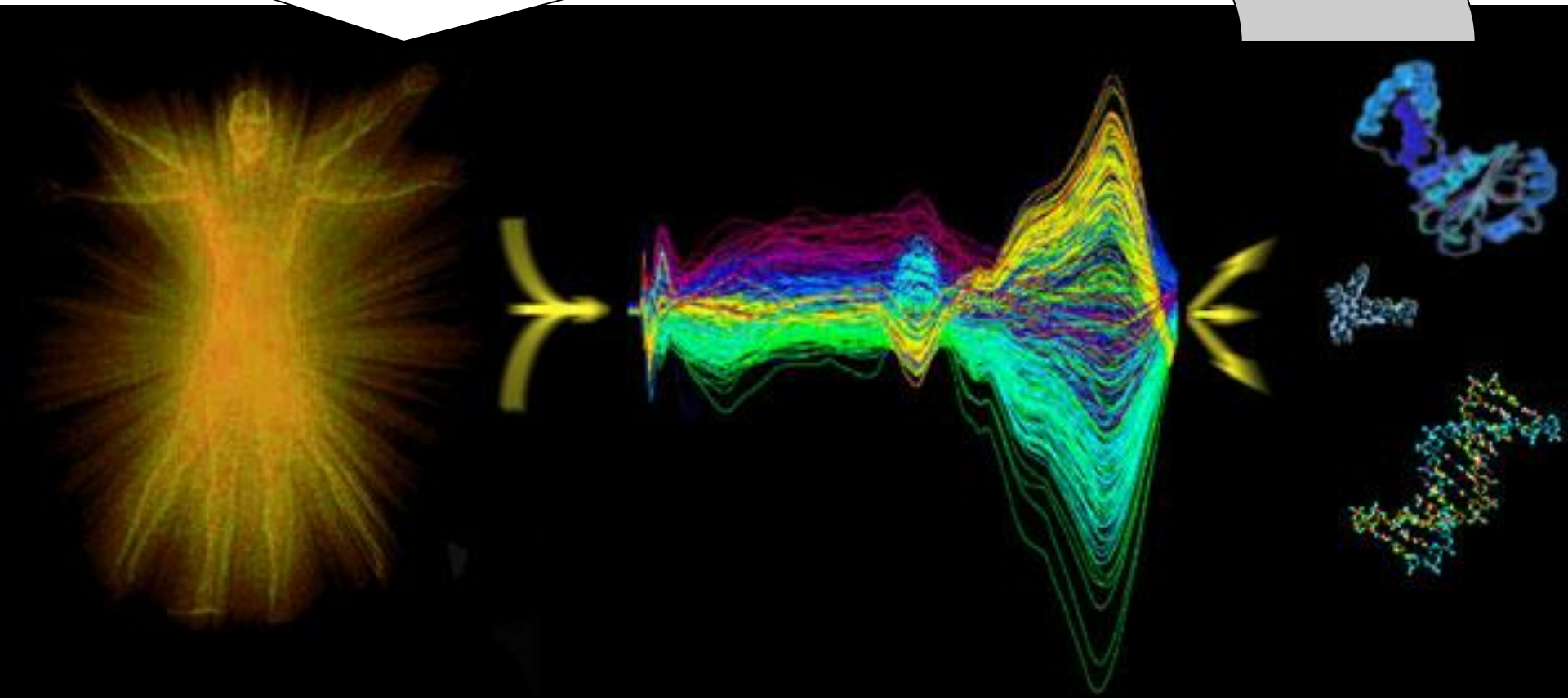
Need to adress the molecular basis of phenotypes

the « top down » approach…..



The top-down approach



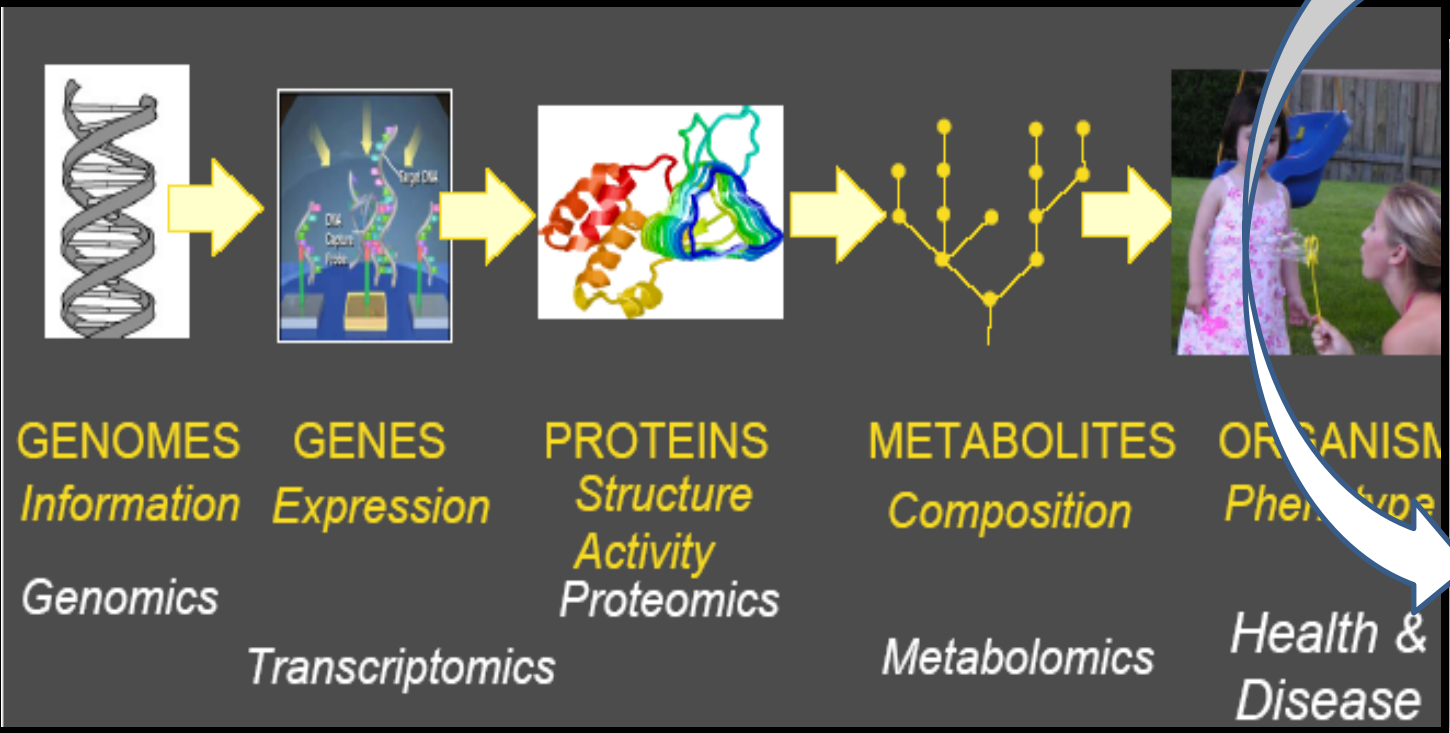


http://masspec.scripps.edu/index.php

Need to assess the molecular basis of phenotypes

the « omic» answer…..

Molecular phenotypes



<u>Contrairement au transcriptome ou au protéome, le métabolome représente l'ultime réponse d'un organisme</u> <u>à une altération</u> génétique, une pathologie, une exposition à un toxique ou à tout autre facteur susceptible de perturber son fonctionnement.

La métabolomique (en santé) pour

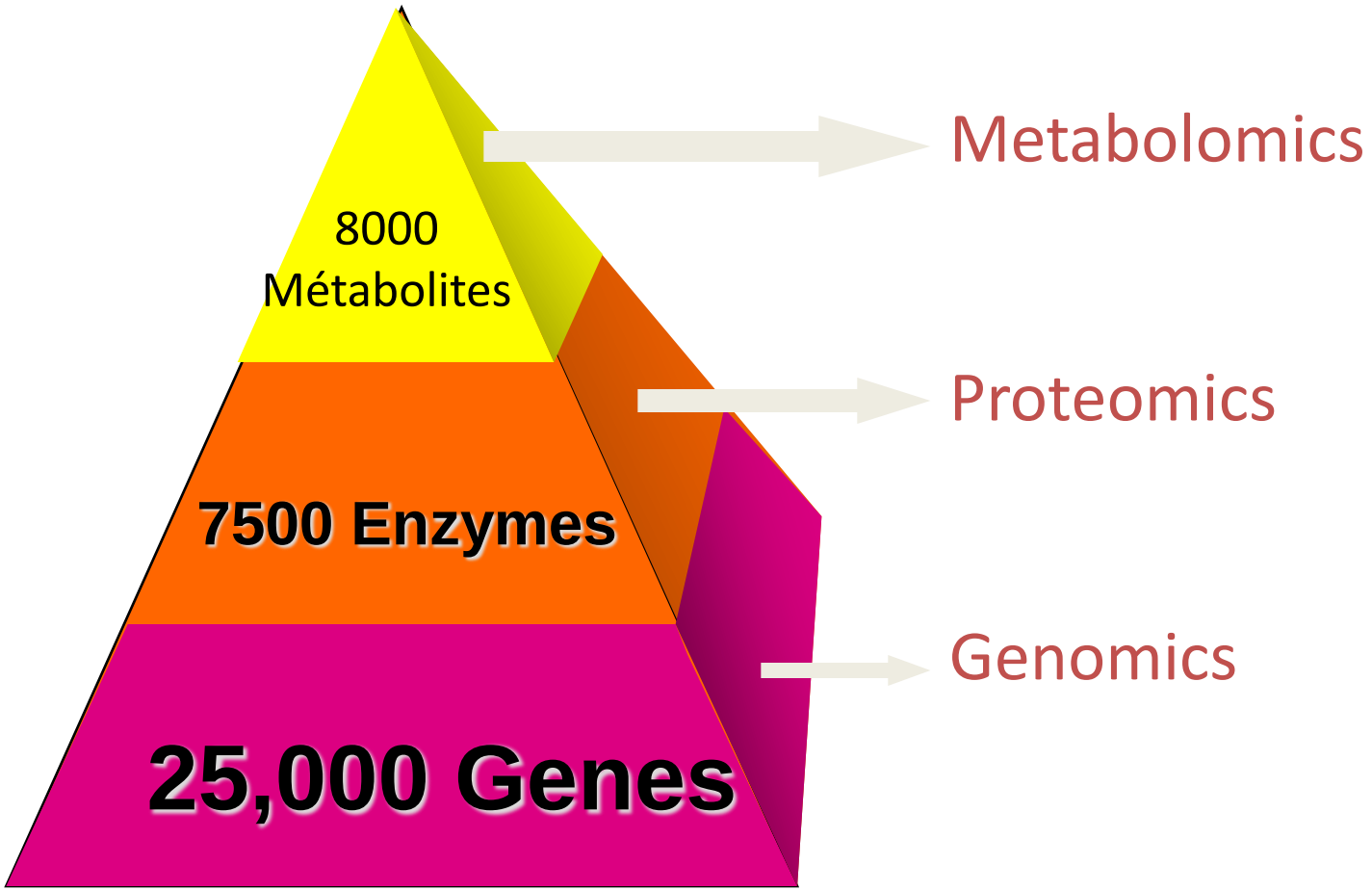
la découverte de biomarqueurs et détecter l'insoupçonnable

cartographier les voies métaboliques (mécanismes, flux)

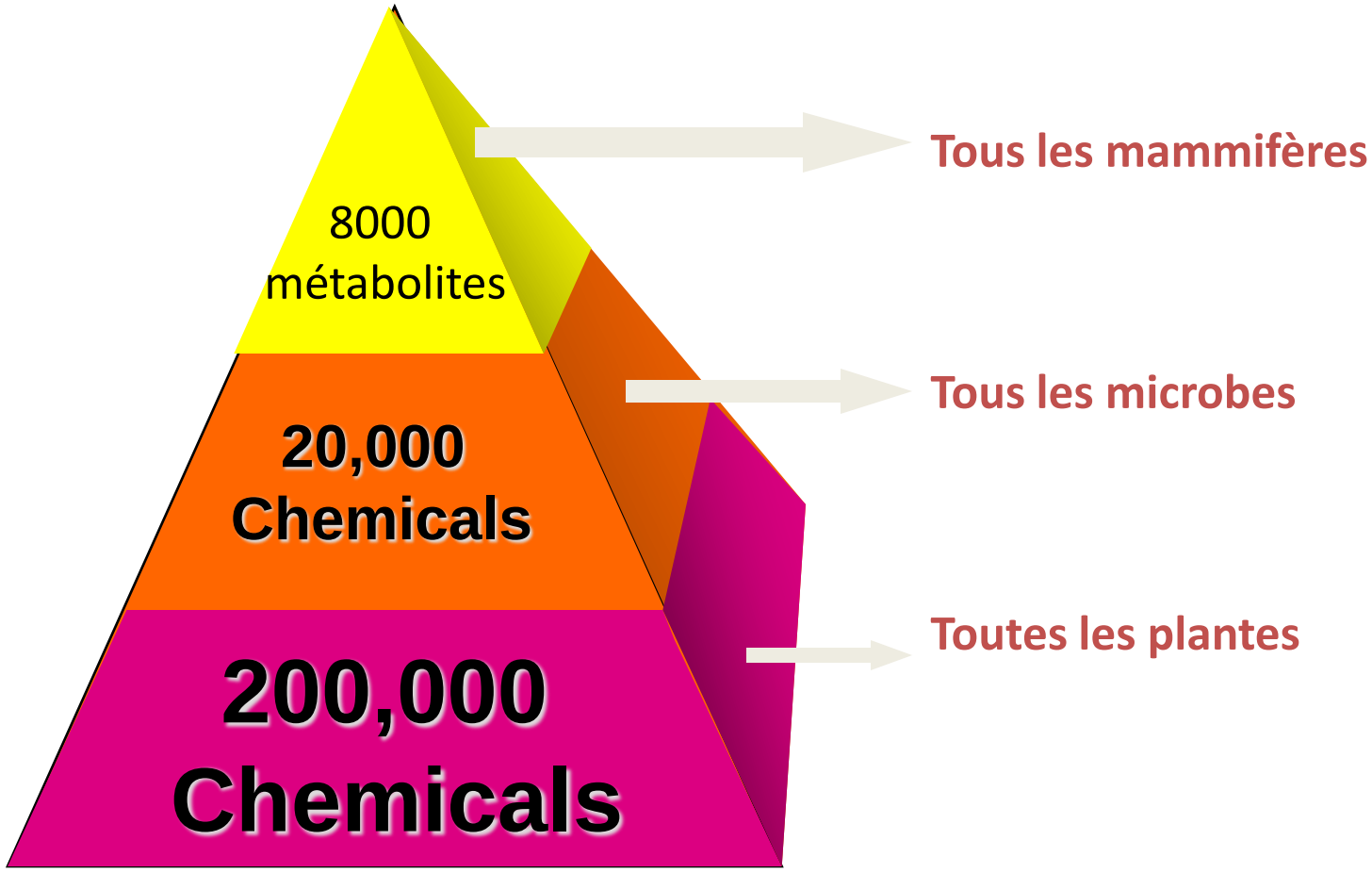
« marché des biomarqueurs sont évalués à 694 millions de $ en 2008, montant qui pourrait atteindre 2,2 milliards de $ en 2015, avec des perspectives de croissance annuelle de l'ordre de 12 à 13,5 %. »

History

- The first paper was titled, “Quantitative Analysis of Urine Vapor and Breath by Gas-Liquid Partition Chromatography”, by Robinson and Pauling in 1971.
- Many of the bioanalytical methods used for metabolomics have been adapted (or in some cases simply adopted) from existing biochemical techniques.
- Human Metabolome project – first draft of human metabolome in 2007


8000
Métabolites
7500 Enzymes
25,000 Genes
Metabolomics
Proteomics
Genomics

Differents Metabolomes



Pourquoi la métabolomique est difficile?

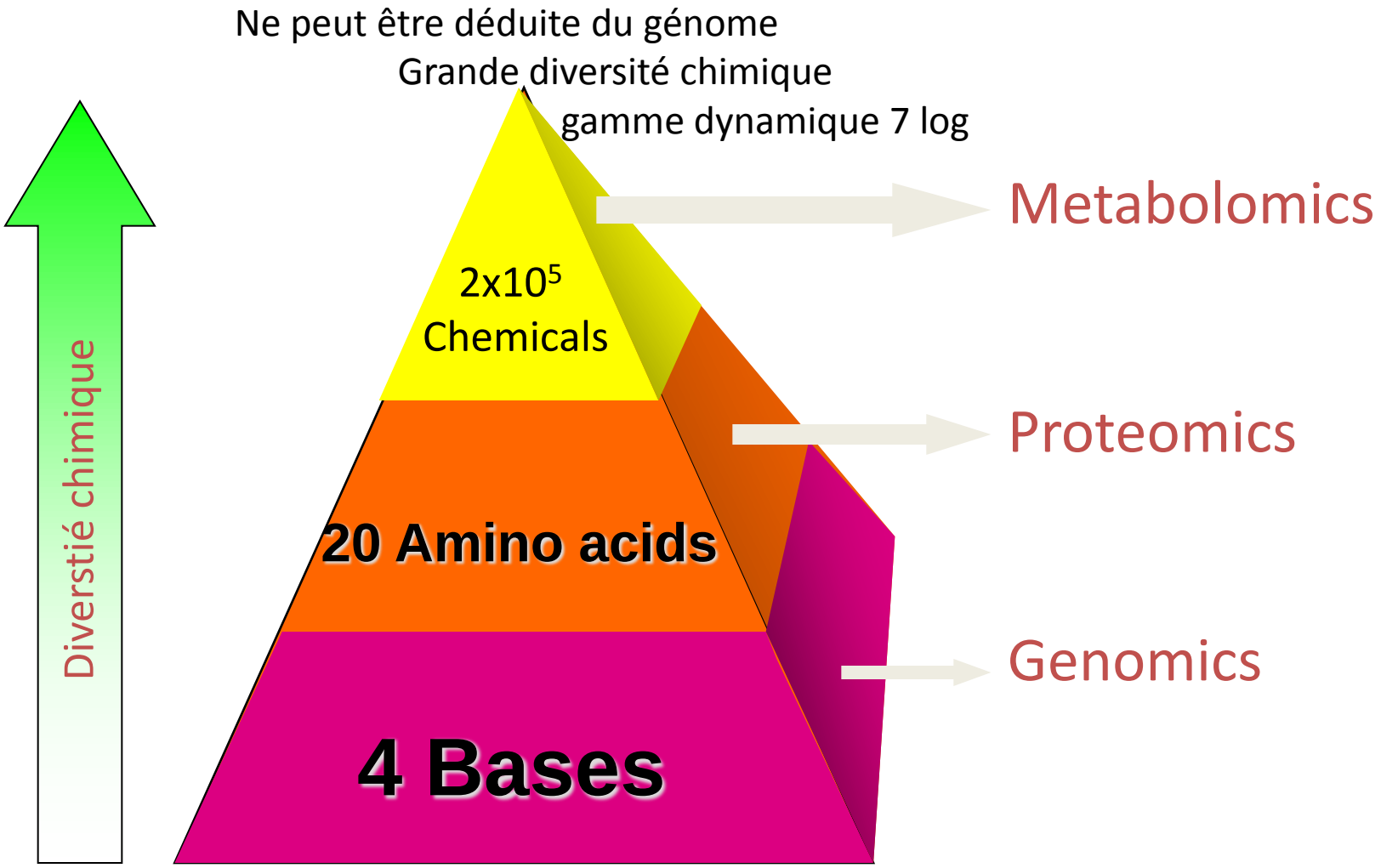
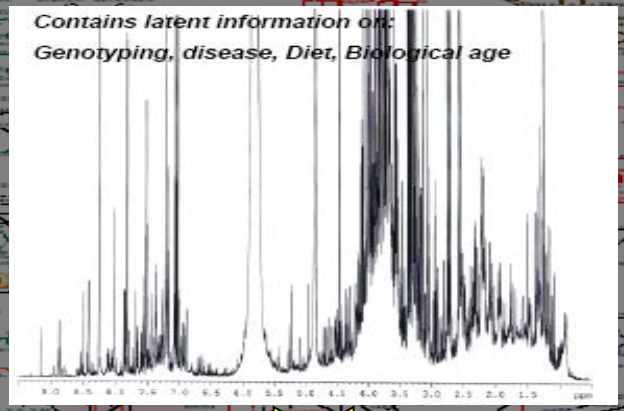


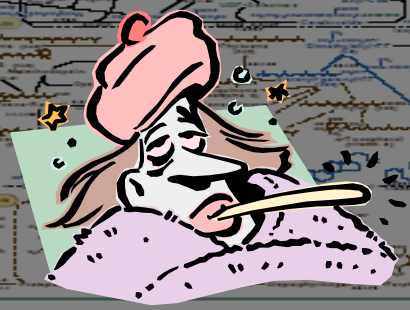
Plate-formes:
NMR
LC/MS
GC/MS

Sang, urines,
extrait tissulaire



Data acquisition

MVA
bioinformatic



Data mining

La métabolomique: quelle infrastructure…..

Chimistes

Machine(s)

Biologistes

Ingénieurs
Chercheurs
Cliniciens
Technicien

réseau

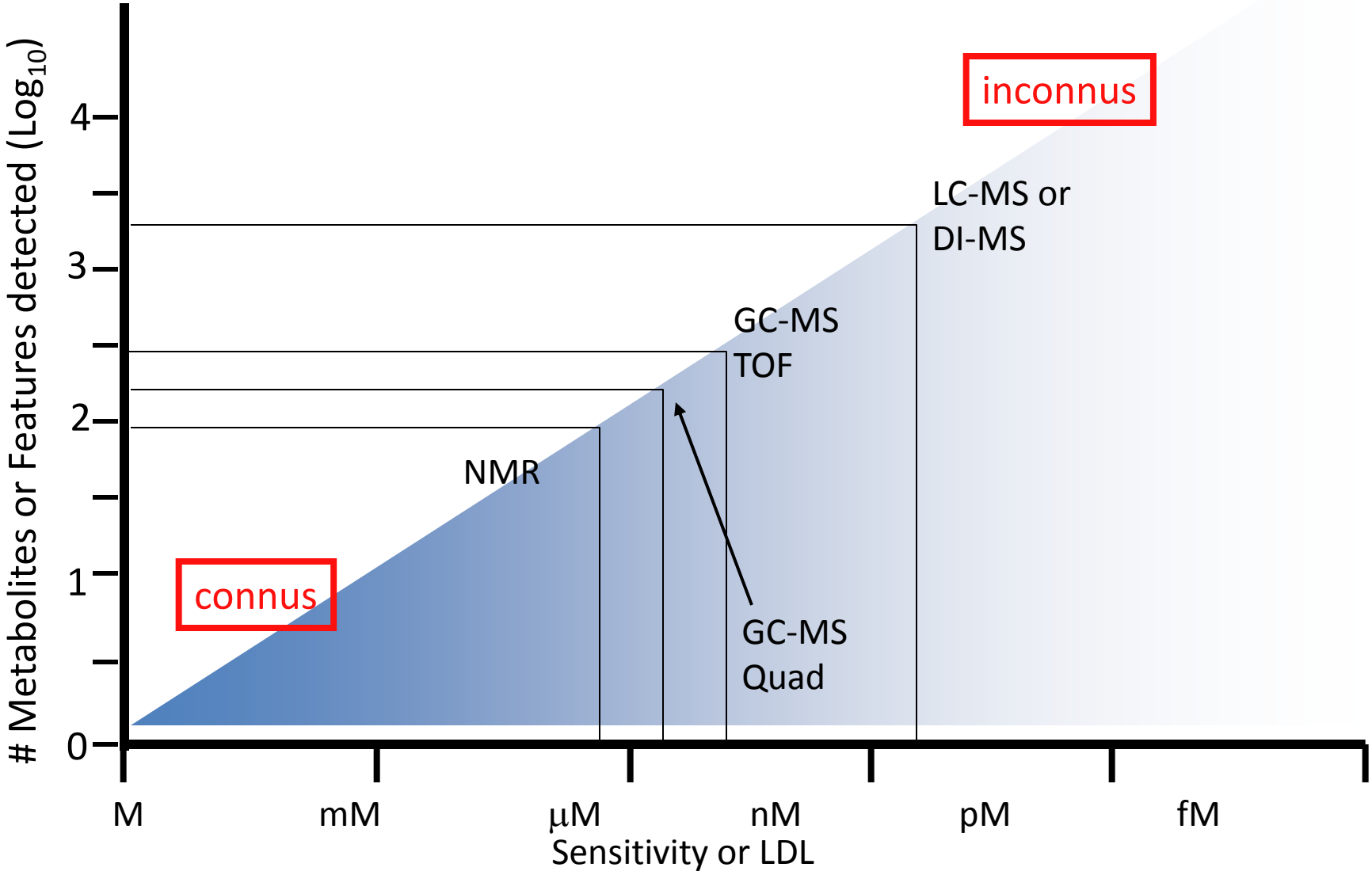
Bioinformatique

Statisticiens

Quels sont les outils de la métabolomique?

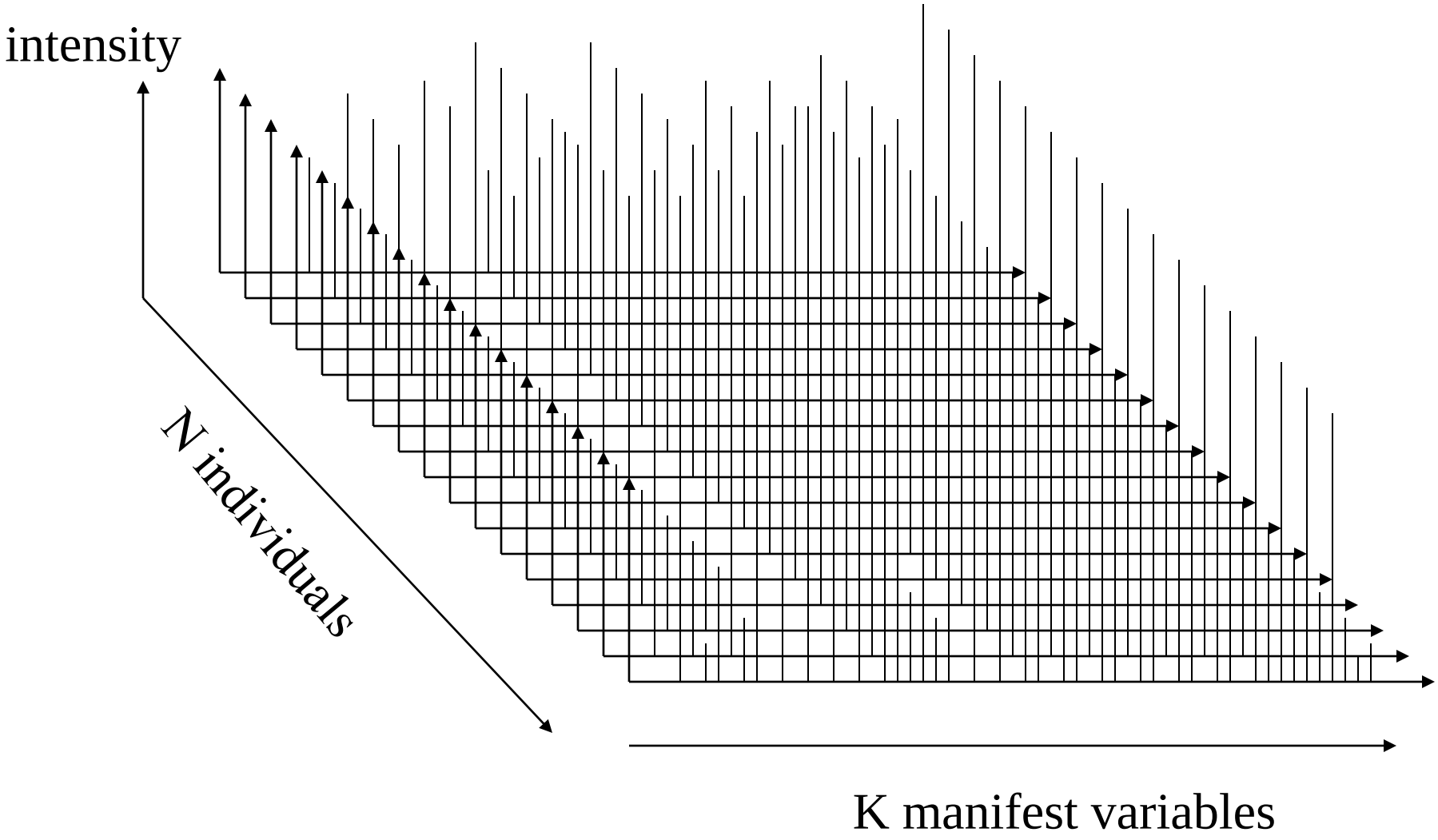
outils	avantages	défauts
RMN	Robustesse et reproductibilité	Recouvrement sensibilité
GC-MS GC X GC TOF	sensibilité	dérivation
LC-MS	sensibilité	stabilité

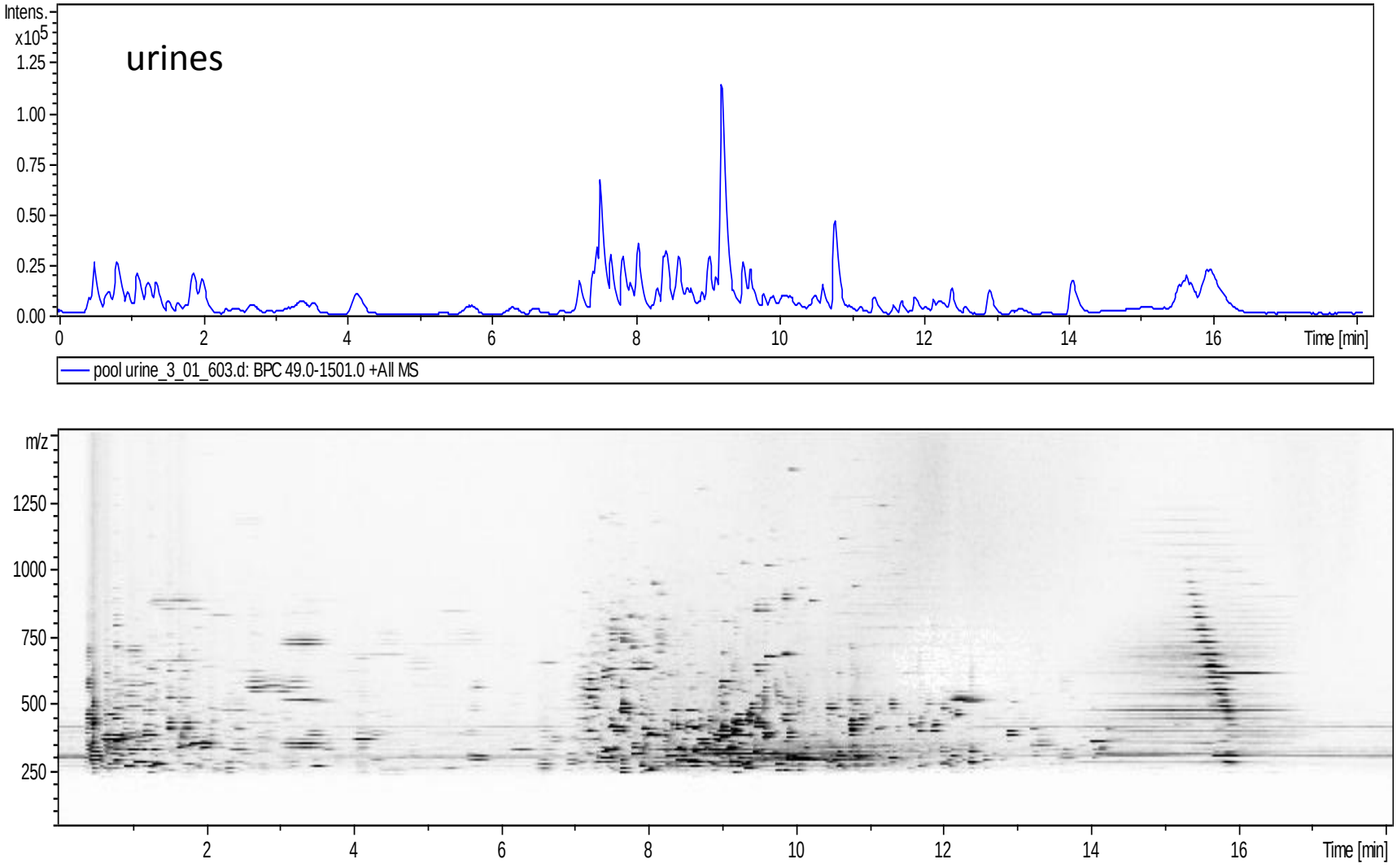
Technologie & Sensibilité

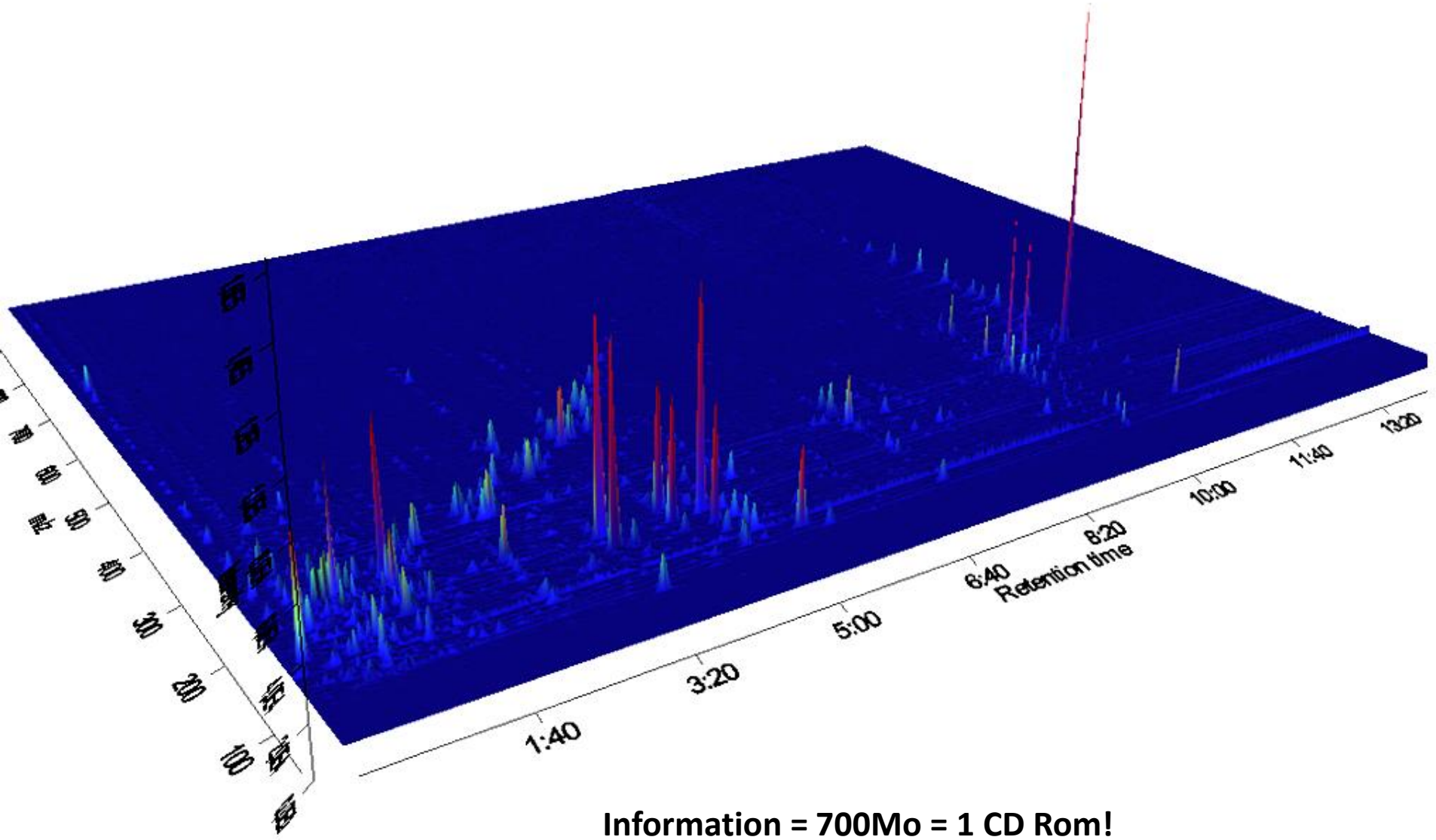


Que peut-on mesurer?

- NMR-based metabolomics (~50 metabolites identified/quantified, μM sensitivity)
- GC-MS based metabolomics (~70 metabolites identified/quantified, <μM sensitivity)
- DI-MS based metabolomics (160 metabolites identified/quantified, nM sensitivity)
- LC-MS based metabolomics (300 metabolites identified/quantified, nM sensitivity)
- Lipidomics (3000 lipids identified and semi-quantified, nM sensitivity)
- Specialty phytochemical, nutrient, drug and pesticide analysis (mostly HPLC, nM sensitivity)


intensity
N individuals
K manifest variables


urines
Intens.
x10^5
1.25
1.00
0.75
0.50
0.25
0.00
0
2
4
6
8
10
12
14
16
Time [min]
pool urine_3_01_603.d: BPC 49.0-1501.0 +All MS
m/z
1250
1000
750
500
250
2
4
6
8
10
12
14
16
Time [min]

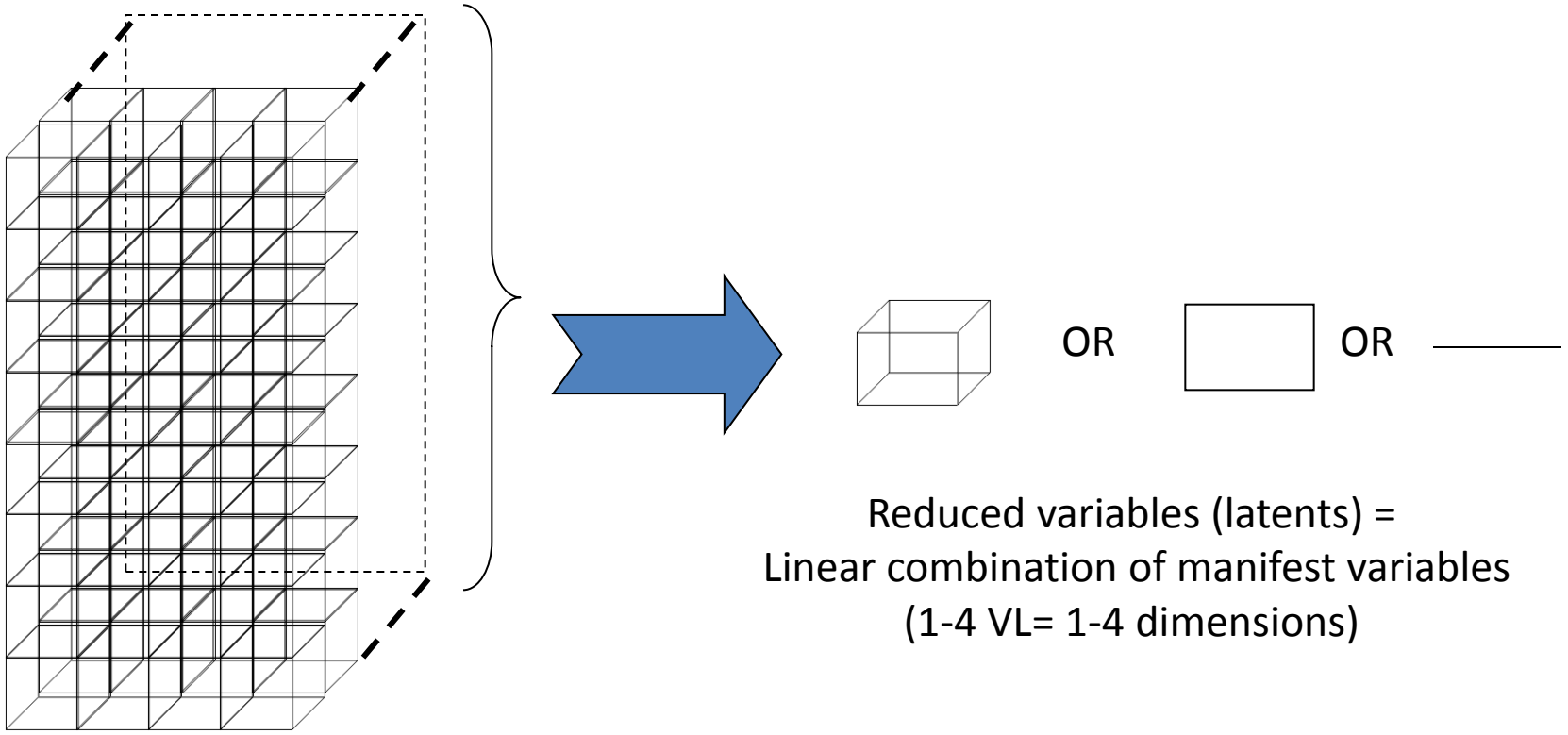


Information = 700Mo = 1 CD Rom!

1 variable = 1 dimension

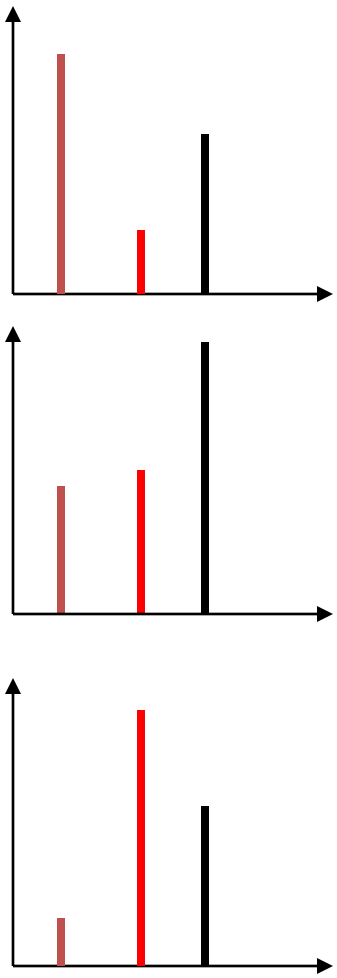
1000 variables = 1000 dimensions

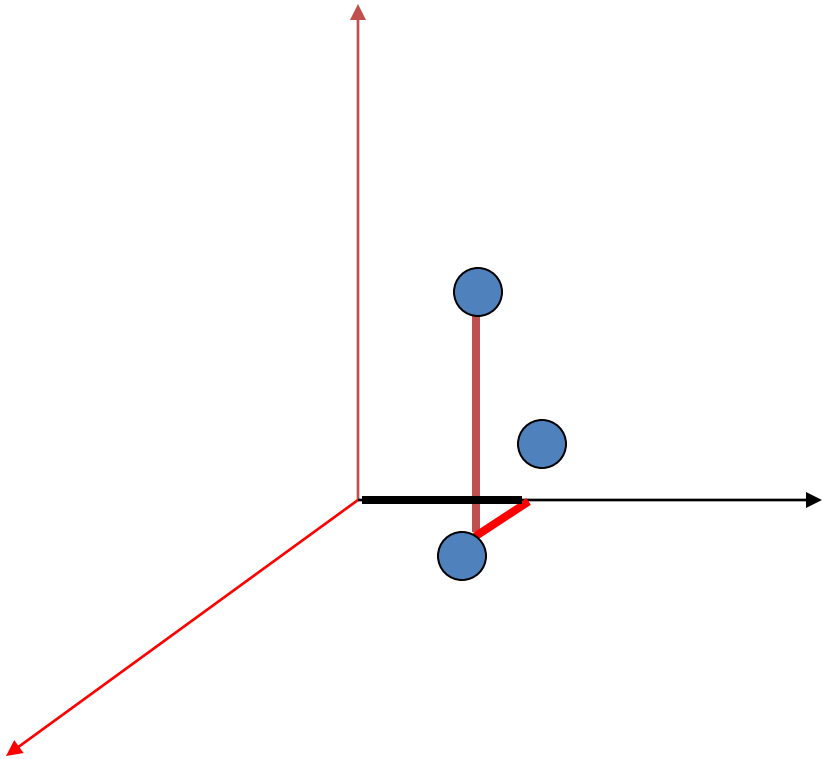
GOAL= REDUCTION WITHOUT LOSING INFORMATION

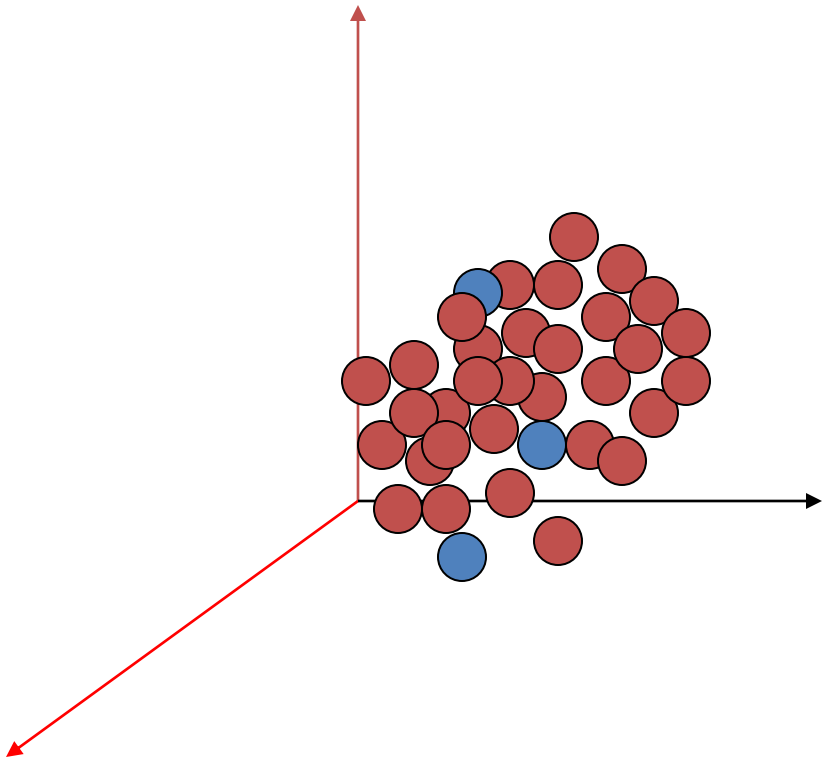


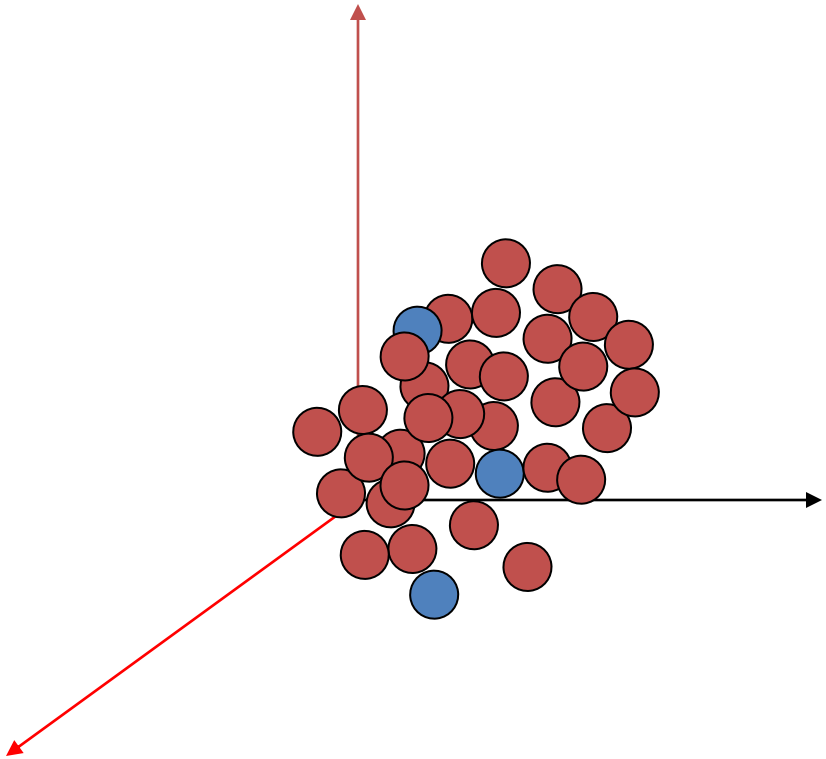
Reduced variables (latents) =
Linear combination of manifest variables
(1-4 VL= 1-4 dimensions)

K manifest variables = k dimensional space
(Hyperspace)

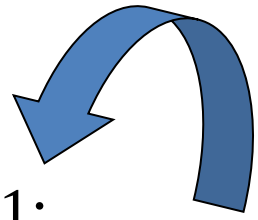






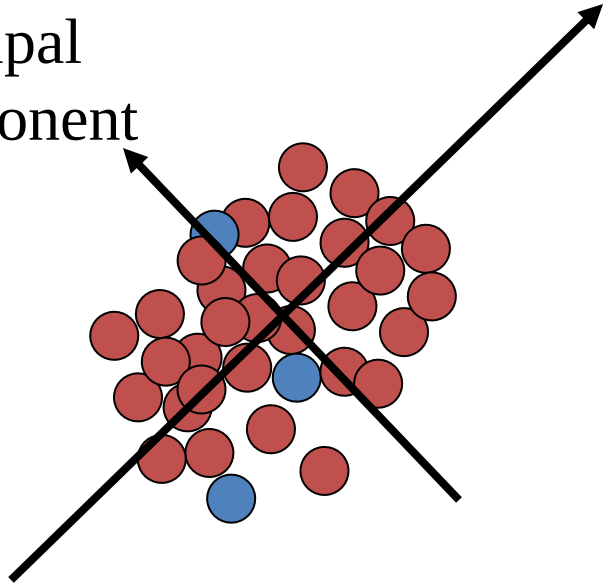


Orthogonal to PC1:
Max of variance

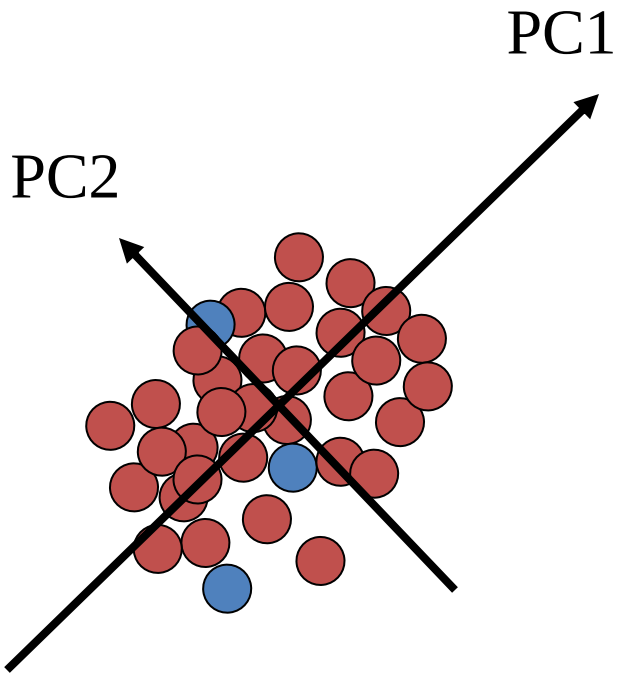


Second
principal
component

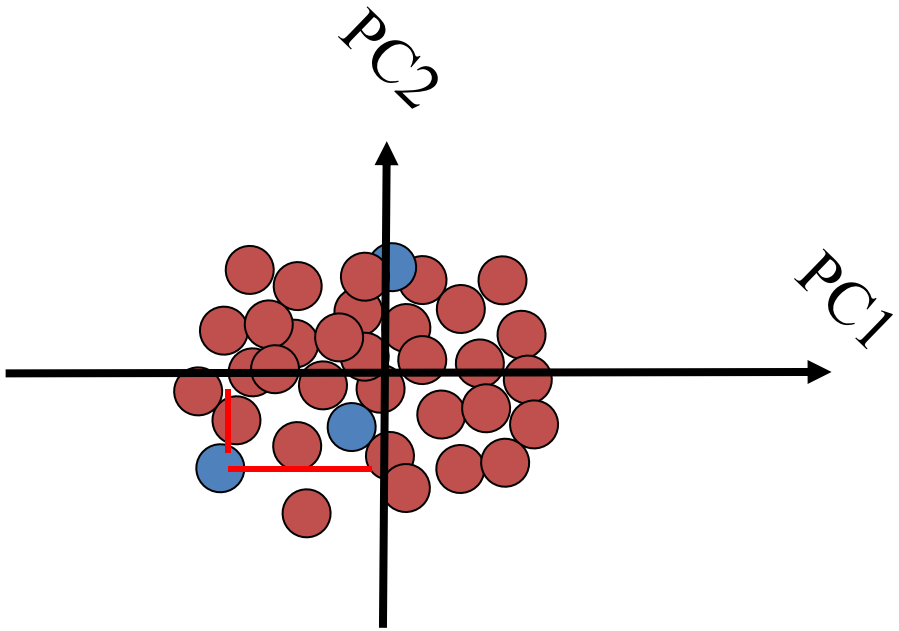
1ère principal
component

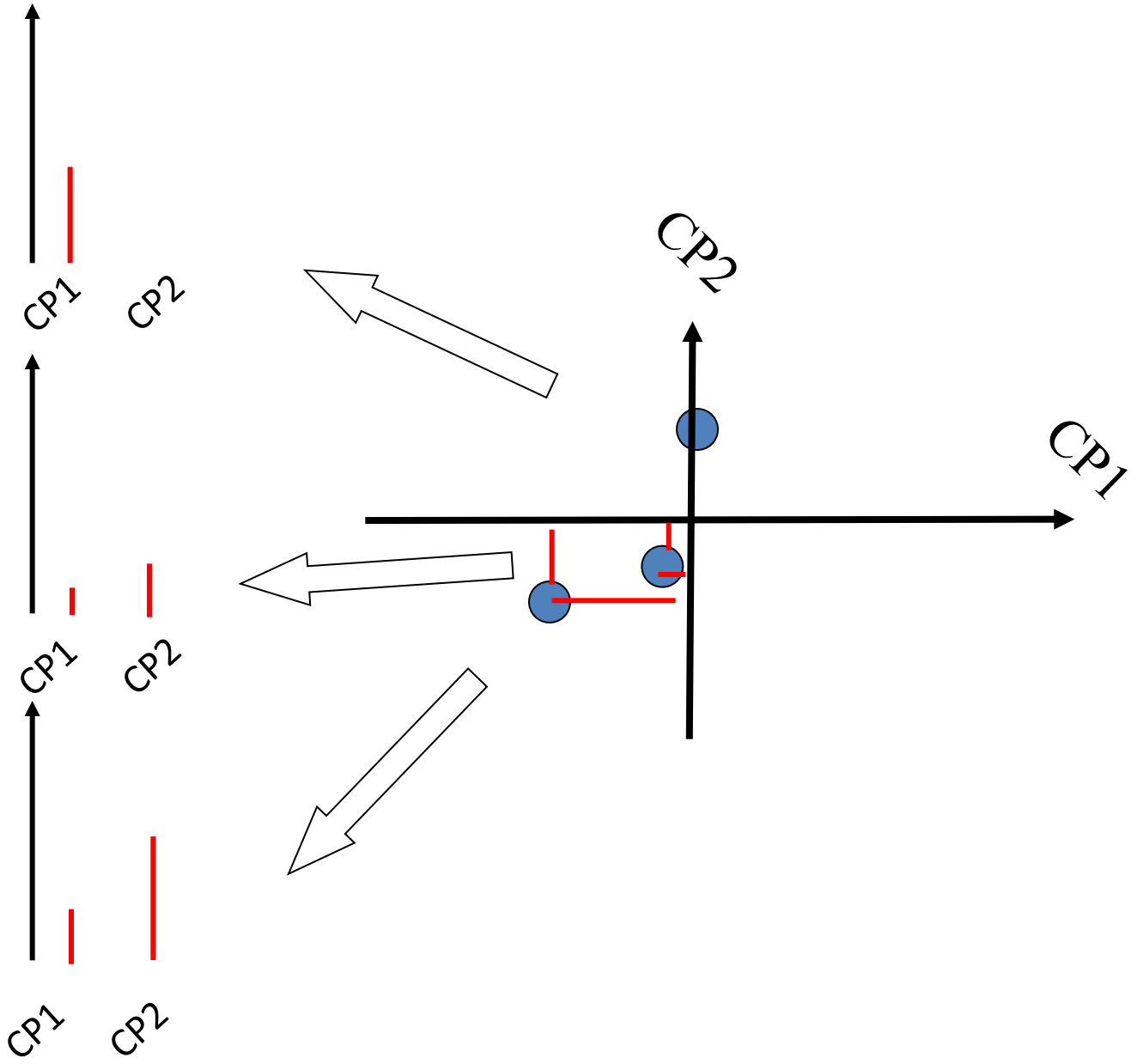


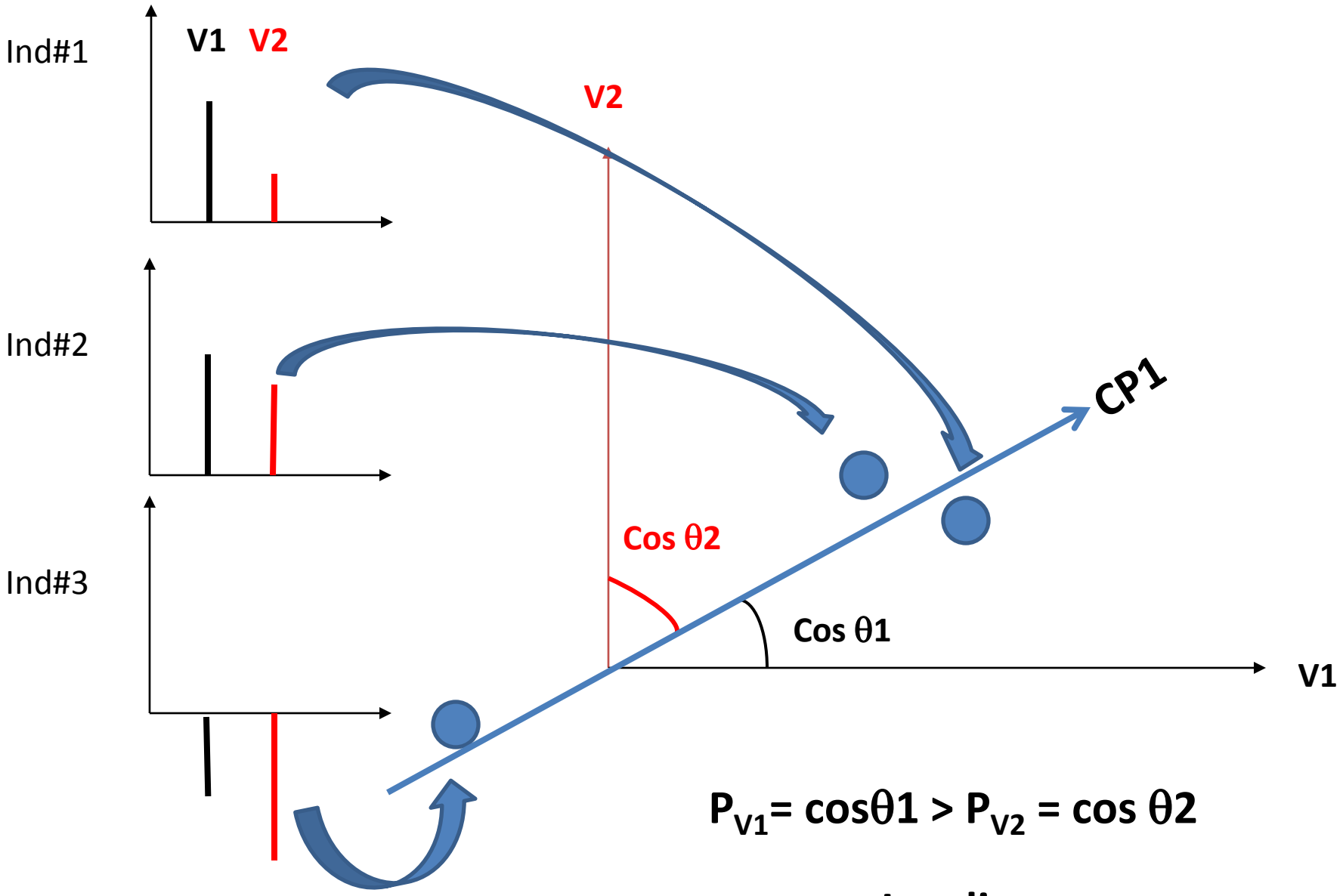
Axis of maximal deviation


PC1
PC2

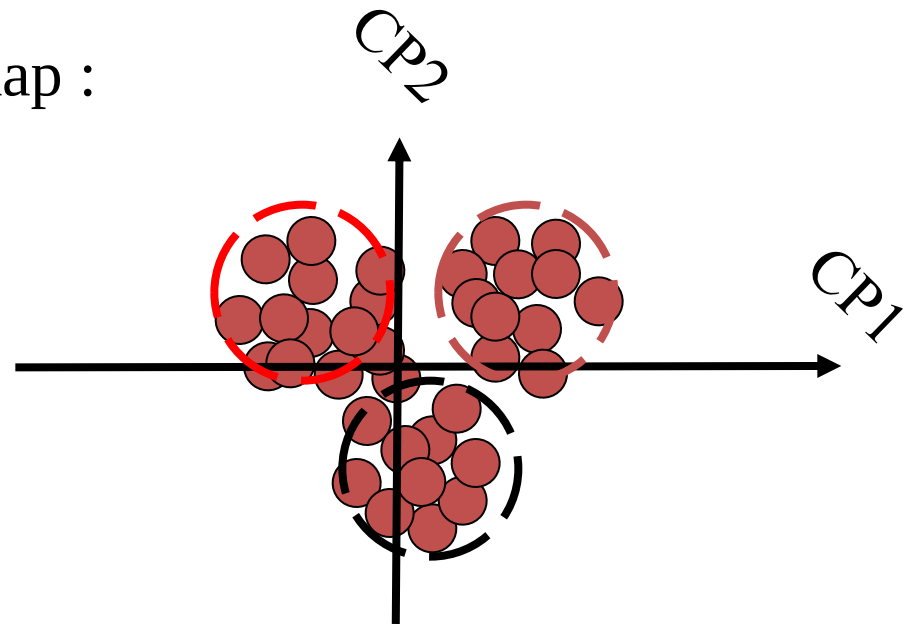
Observations map or « score plot »



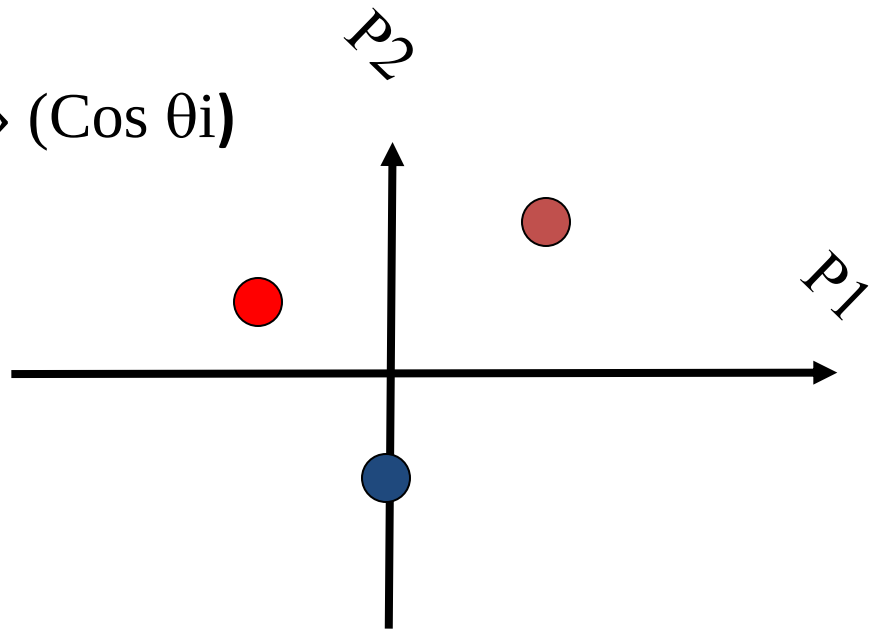

CP1
CP2
CP1
CP2
CP1
CP2
CP2
CP1


Ind#1
V1
V2
V2
Ind#2
CP1
Cos θ2
Ind#3
Cos θ1
V1
P_{V1}= cosθ1 > P_{V2} = cos θ2
« Loadings »

observations map :
« Score plot »



variables map :
« loading plot » (Cos θi)



Pour aller plus loin….

Metabolomics (2014) 10:361–374
DOI 10.1007/s11306-013-0598-6

REVIEW ARTICLE

Reflections on univariate and multivariate analysis of metabolomics data

Edoardo Saccenti · Huub C. J. Hoefsloot · Age K. Smilde · Johan A. Westerhuis · Margriet M. W. B. Hendriks

Environmental and Molecular Mutagenesis 54:542–557 (2013)

Review Article

Deciphering the Complex: Methodological Overview of Statistical Models to Derive OMICS-Based Biomarkers

Marc Chadeau-Hyam,[1*] Gianluca Campanella,[1] Thibaut Jombart,[2] Leonardo Bottolo,[3] Lutzen Portengen,[4] Paolo Vineis,[1,5] Benoit Liquet,[6] and Roel C.H. Vermeulen[4,7]

Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease

Zeneng Wang[1,2], Elizabeth Klipfell[1,2], Brian J. Bennett[3], Robert Koeth[1], Bruce S. Levison[1,2], Brandon DuGar[1], Ariel E. Feldstein[1,2], Earl B. Britt[1,2], Xiaoming Fu[1,2], Yoon-Mi Chung[1,2], Yuping Wu[4], Phil Schauer[5], Jonathan D. Smith[1,6], Hooman Allayee[7], W. H. Wilson Tang[1,2,6], Joseph A. DiDonato[1,2], Aldons J. Lusis[3] & Stanley L. Hazen[1,2,6]

7 APRIL 2011 | VOL 472 | NATURE

50 cas avec 3 ans suivi (infarctus, AVC, mort)
50 témoins

Métabolomique LC MS plasma
= 2000 analytes mesurés

40 analytes fortement discriminants

Cohorte 1 = cohorte d'apprentissage

50 cas avec 3 ans suivi (infarctus, AVC, mort)
50 témoins

Métabolomique LC MS plasma
= 2000 analytes mesurés

40 analytes fortement discriminants

Cohorte 2 indépendante = cohorte de validation

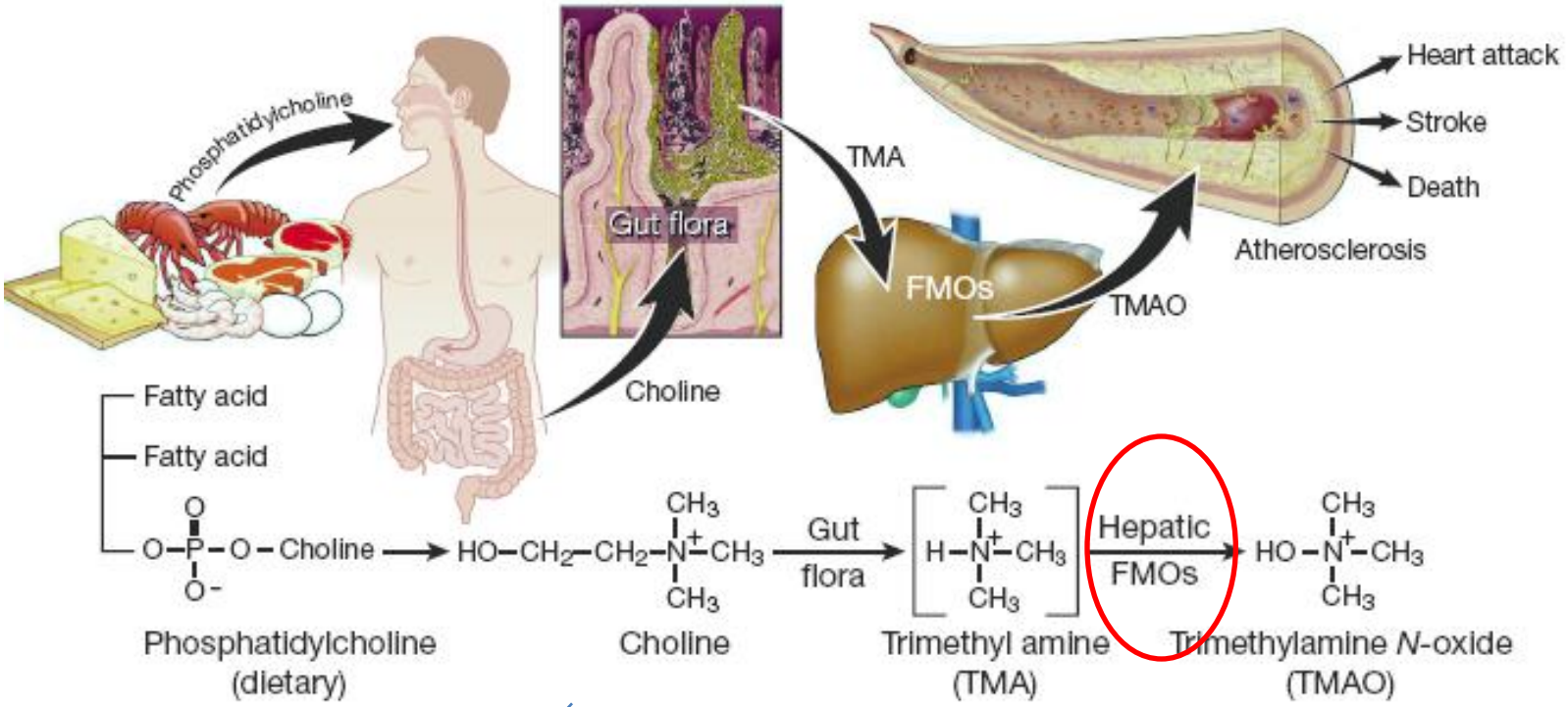
25 cas avec 3 ans suivi (infarctus, AVC, mort)
25 témoins

Métabolomique LC MS plasma
= 2000 analytes mesurés

24 analytes fortement discriminants

18 analytes en commun
Top 3 = choline, betaine, trimethyloxyde amine (TMAO)

choline, betaine, trimethyloxyde amine (TMAO)= Métabolites de la phosphatidylcholine

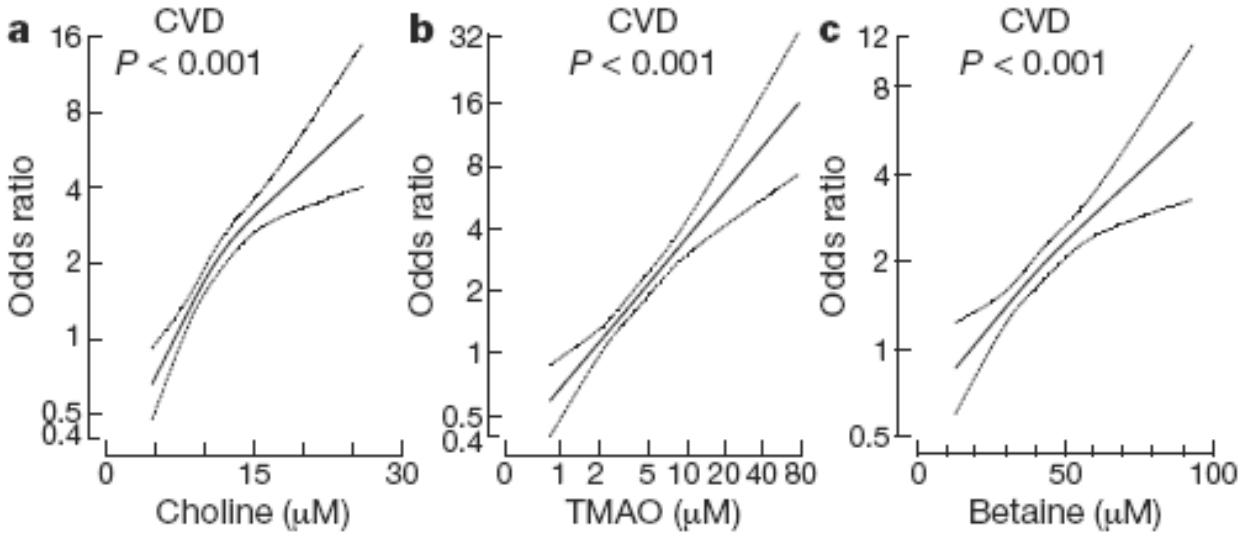


bétaine

Validation sur modèle souris athéromateux:

- nourris avec ou sans choline
- Nourris avec ou sans TMAO
- Traités aux antibiotiques
- Cohortes humaines 1876 sujets avec angiographies

Dosage des métabolites « athérogènes » dans une cohorte de 1876 sujets à pathologie cardiovasculaire variable (angiographie)



Implication = nouveaux marqueurs du risque cardiovasculaire, indépendant des marqueurs lipidiques classiques

Identifications de cibles thérapeutiques: flore intestinale, FMOs hépatique

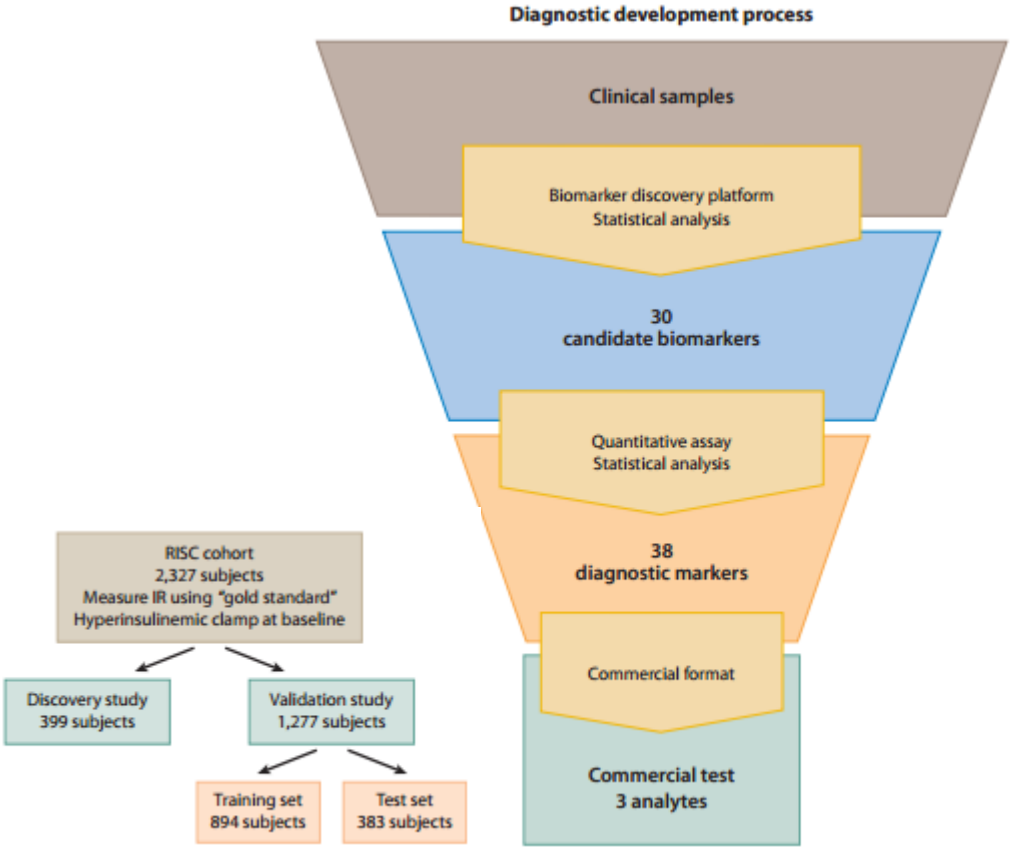
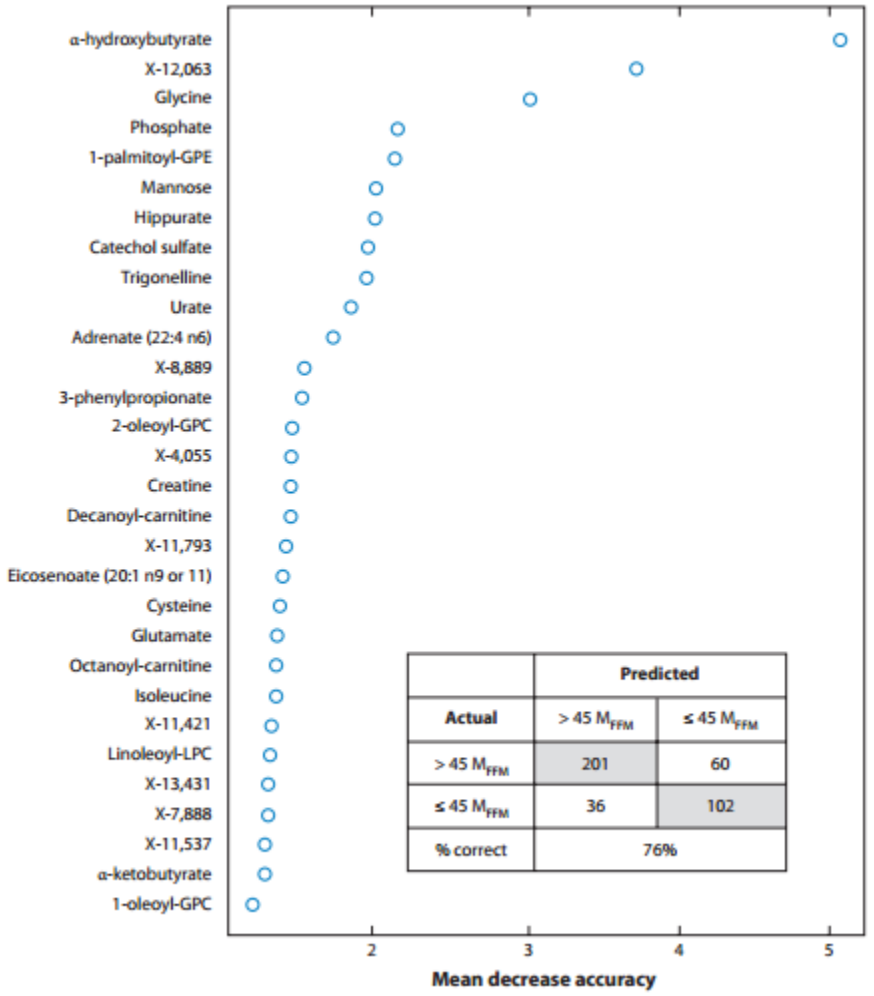


Table 1 Biomarker candidates

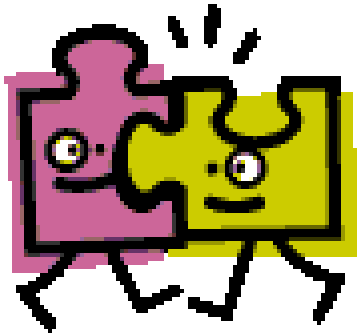
2-hydroxybutyrate	Linoleic acid	Stearate
3-hydroxybutyrate	Linolenic acid	Threonine
3-methyl-2-oxo-butyric acid	Margaric acid	Isovalerylcarnitine
3-phenylpropionate	Octanoyl carnitine	Linoleoyl-LPC
Catechol sulfate	Oleic acid	1,5-anhydroglucitol
Creatine	Oleoyl-LPC	Stearoyl-LPC
Decanoyl carnitine	Palmitate	1-palmitoyl-GPE
Docosatetraenoic acid	Palmitoleic acid	Octanoylcarnitine
Glutamic acid	Palmitoyl-LPC	alpha-ketobutyrate
Glycine	Serine	Cysteine



	Predicted	
Actual	> 45 M_{FFM}	≤ 45 M_{FFM}
> 45 M_{FFM}	201	60
≤ 45 M_{FFM}	36	102
% correct	76%	

Milburn MV, Lawton KA. Application of metabolomics to diagnosis of insulin resistance. Annu Rev Med 2013;64:291-305.

Couplage avec autres omiques

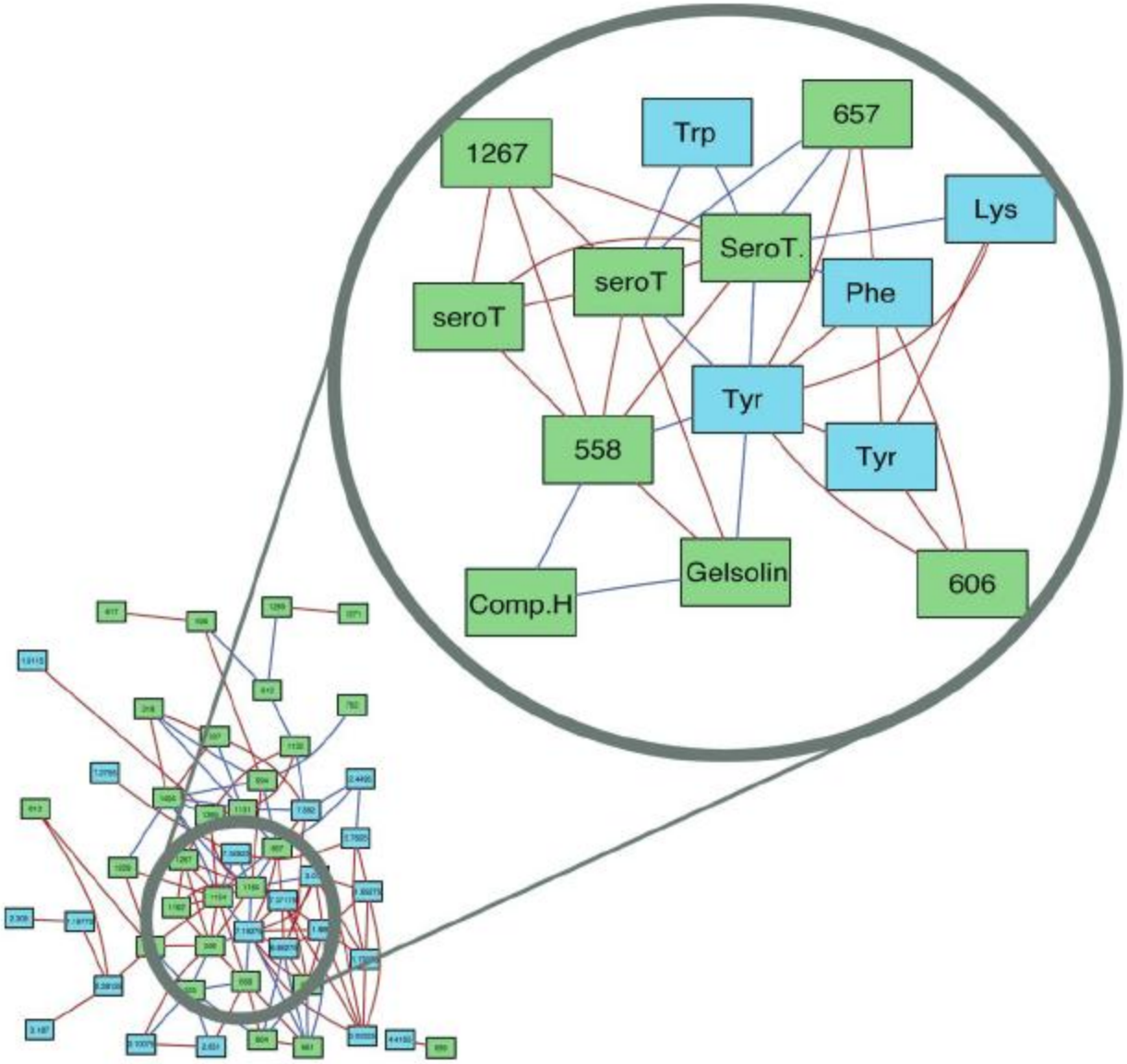


research articles Journal of proteome research

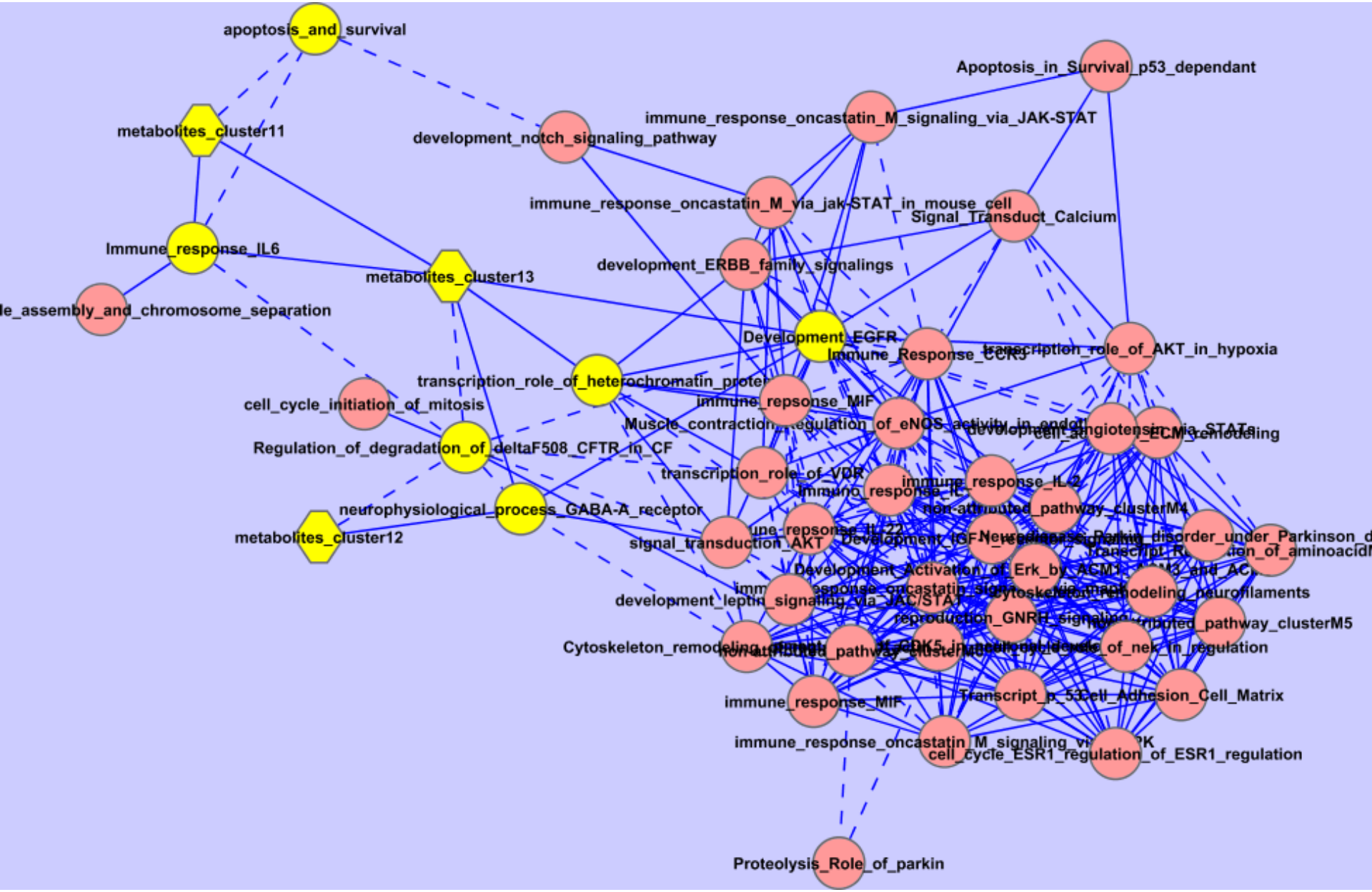
Statistically Integrated Metabonomic−Proteomic Studies on a Human Prostate Cancer Xenograft Model in Mice

Mattias Rantalainen,[†] Olivier Cloarec,[†] Olaf Beckonert,[†,#] I. D. Wilson,[‡] David Jackson,[§] Robert Tonge,[§] Rachel Rowlinson,[§] Steve Rayner,[§] Janice Nickson,[§] Robert W. Wilkinson,[∥] Jonathan D. Mills,[∥] Johan Trygg,[*,⊥] Jeremy K. Nicholson,[†] and Elaine Holmes[*,†]

Multiple correlations between metabolites and proteins were found, including associations between serotransferrin precursor and both tyrosine and 3-D-hydroxybutyrate. Additionally, a correlation between decreased concentration of tyrosine and increased presence of gelsolin was also observed. This approach can provide enhanced recovery of combination candidate biomarkers across multi-omic platforms, thus, enhancing understanding of in vivo model systems studied by multiple omic technologies


1267
Trp
657
Lys
SeroT.
seroT
Phe
seroT
Tyr
558
Tyr
Gelsolin
606
Comp.H

Subnetwork of strongly interacting pathways to metabolites clusters



Proteasome Subunits mRNA Expressions Correlate With Male BMI: Implications for a Role in Obesity

Obesity (2009) **17,** 1044–1049.

Adipose Tissue IL-6 Content Correlates with Resistance to Insulin Activation of Glucose Uptake both *in Vivo* and *in Vitro*

The Journal of Clinical Endocrinology & Metabolism 87(5):2084–2089

Conjugated Linoleic Acid Supplementation Reduces Adipose Tissue by Apoptosis and Develops Lipodystrophy in Mice

DIABETES, VOL. 49, SEPTEMBER 2000

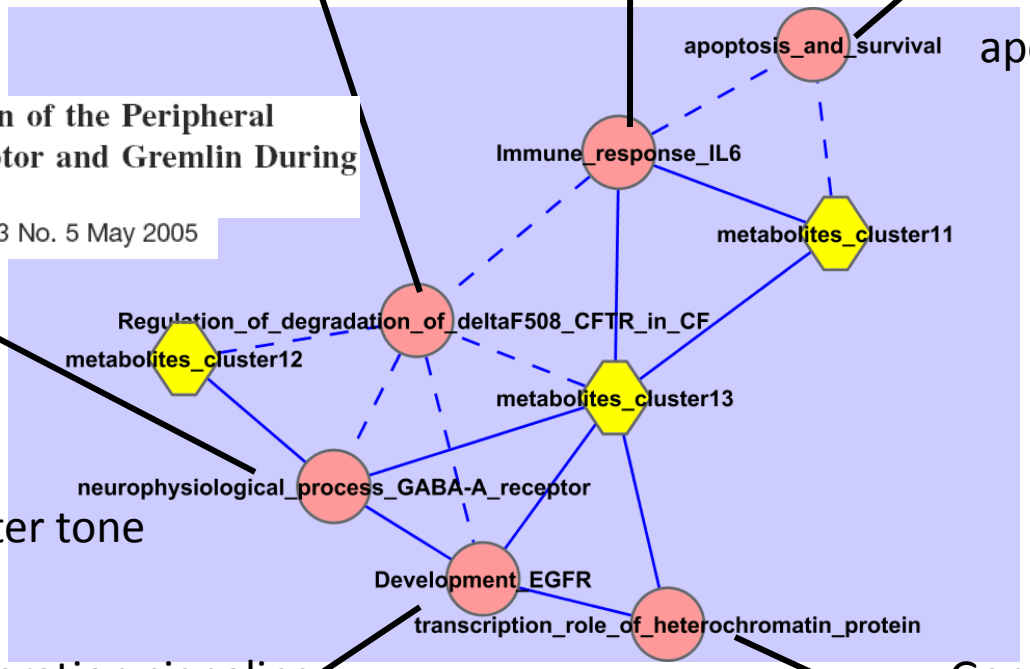
Differential Expression of the Peripheral Benzodiazepine Receptor and Gremlin During Adipogenesis

OBESITY RESEARCH Vol. 13 No. 5 May 2005

Proteasome & ER stress

Inflammation

apoptosis



Major impact of CLA on adipocytes

Neurotransmiter tone

Cell proliferation signaling

Gene regulation

EGFR Tyrosine Kinase Inhibitor (PD153035) Improves Glucose Tolerance and Insulin Action in High-Fat Diet–Fed Mice

DIABETES, VOL. 58, DECEMBER 2009

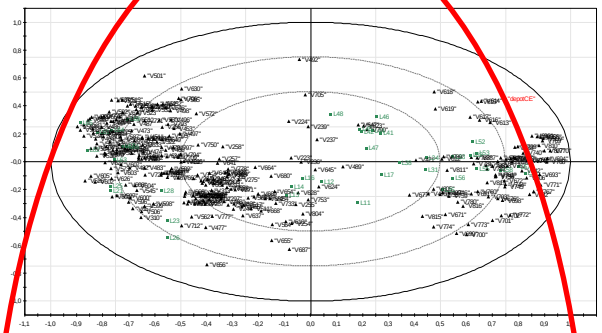
Site-dependent differences in both prelamin A and adipogenic genes in subcutaneous adipose tissue of patients with type 2 familial partial lipodystrophy

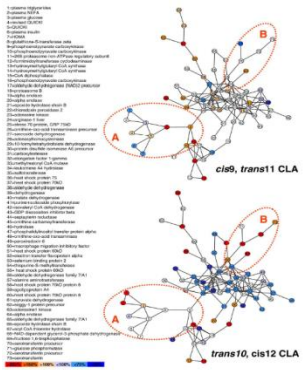
J Med Genet 2009;**46**:40–48.

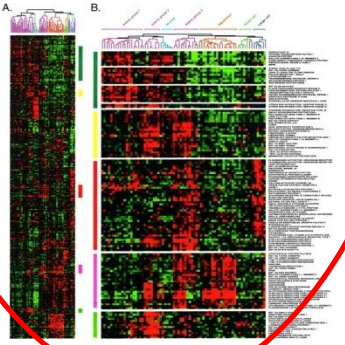
métabolome

protéome

transcript me



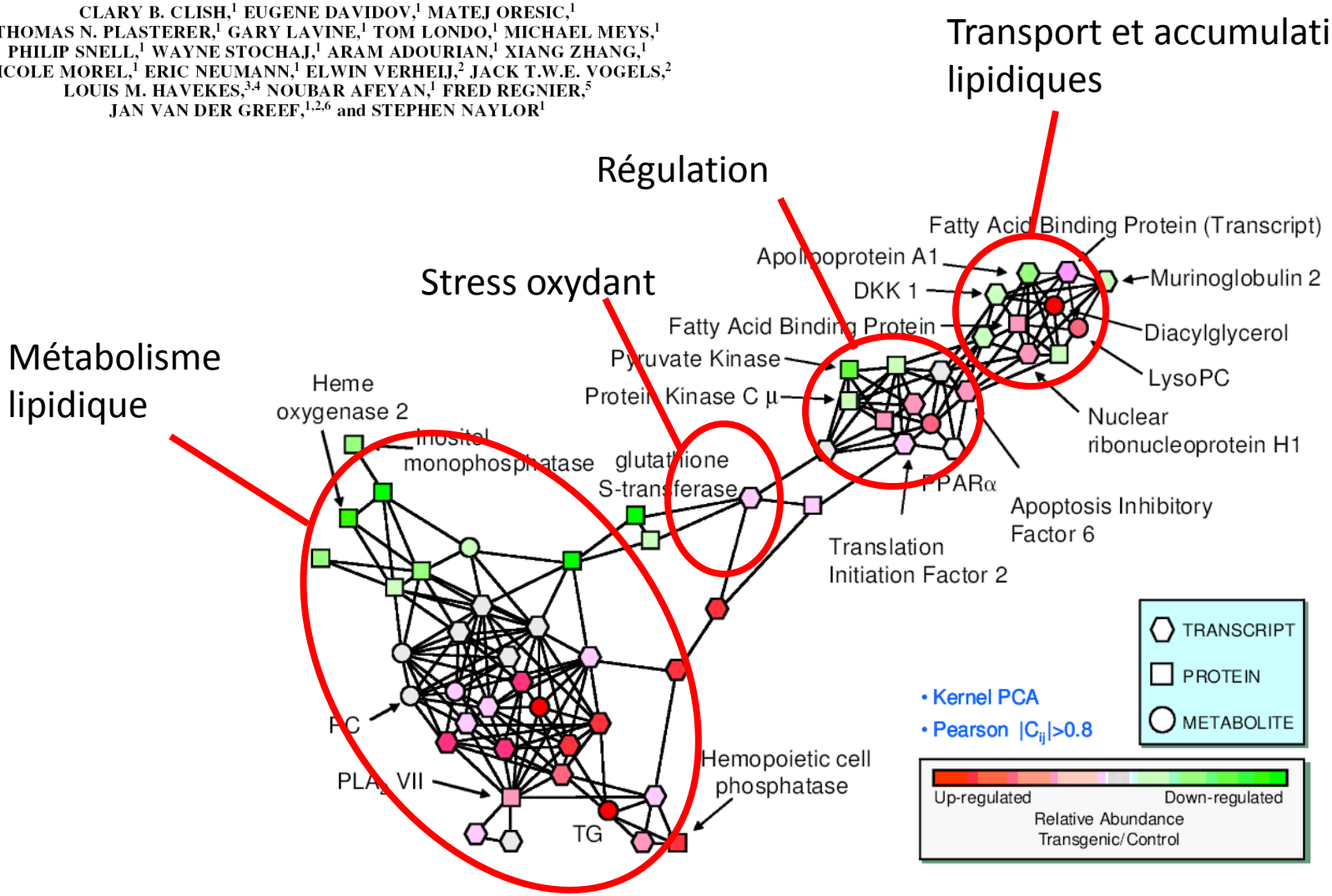




OMICS A Journal of Integrative Biology
Volume 8, Number 1, 2004

Integrative Biological Analysis of the APOE*3-Leiden Transgenic Mouse

CLARY B. CLISH,[1] EUGENE DAVIDOV,[1] MATEJ ORESIC,[1]
THOMAS N. PLASTERER,[1] GARY LAVINE,[1] TOM LONDO,[1] MICHAEL MEYS,[1]
PHILIP SNELL,[1] WAYNE STOCHAJ,[1] ARAM ADOURIAN,[1] XIANG ZHANG,[1]
NICOLE MOREL,[1] ERIC NEUMANN,[1] ELWIN VERHEIJ,[2] JACK T.W.E. VOGELS,[2]
LOUIS M. HAVEKES,[3,4] NOUBAR AFEYAN,[1] FRED REGNIER,[5]
JAN VAN DER GREEF,[1,2,6] and STEPHEN NAYLOR[1]



Evaluer l'impact athérogénique de différentes matières grasses laitières anhydres +/-décholestérolisées et appauvries en AGS

MGLA std

67%

MGLA déchol & dé-sat

41%

MGLA déchol + colza

37%

MGLA std + colza

37%

Palme natif + colza

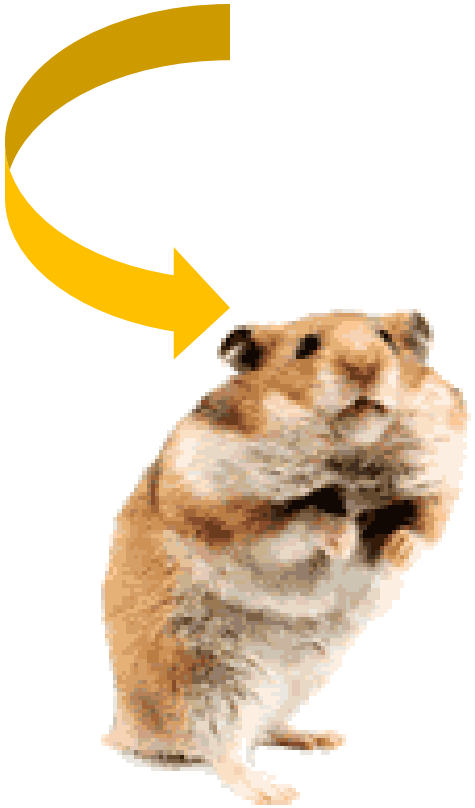
37%

20% fat (by weight), en régime semi-synthétique

X 12 semaines

Athérogénèse (Cholesteryl-ester aorte)

Régimes tests



Metabolome plasmatique n=701 (LCMS)

Metabolome urines n=1224 (LCMS)

Chimie du sang =26 (biochimie: TG, Chol, HDLC, LDLC,…)

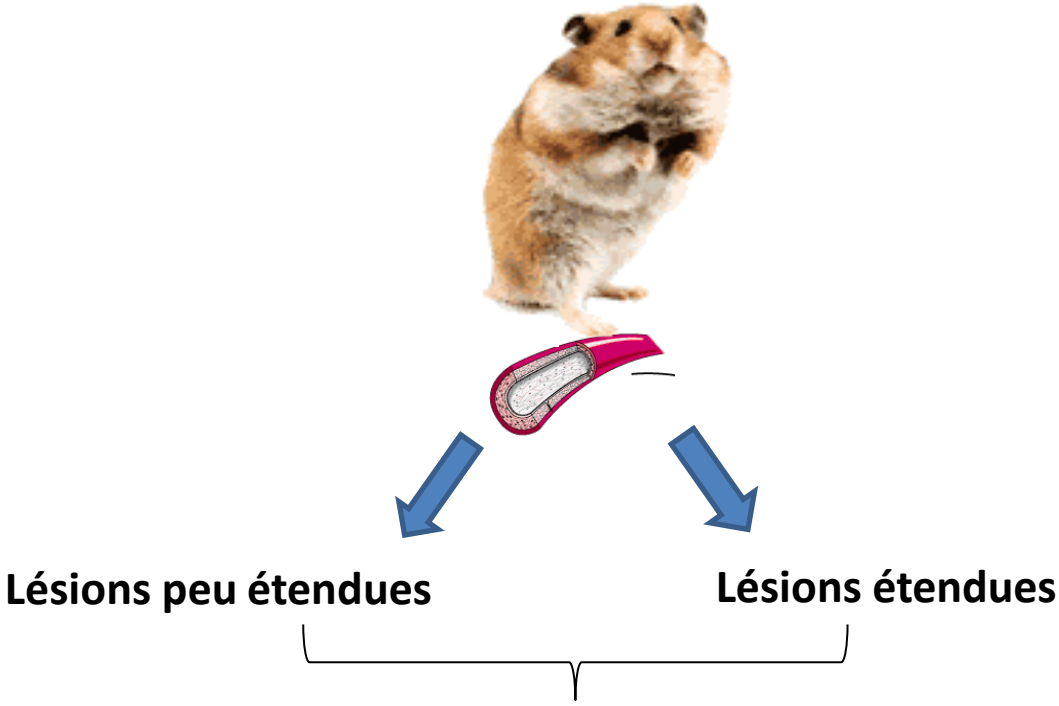
Acides gras foie & classes lipidiques du plasma n=124 (fast-GC)

Expression gènes foie et sang n=44 (QPCR)

Total = 1666 variables biologiques/hamster + 1 (mesure indice athérogénicité)

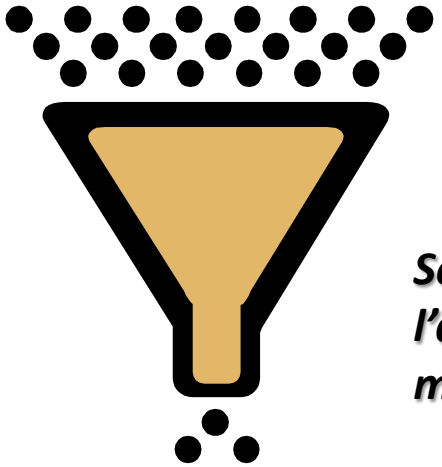
But

- **identifier des biomarqueurs prédictifs de l'athérogénèse sensibles aux régimes;**



Marqueurs biologiques des lésions (*f*(régimes)?)

1666 variables biologiques/hamster



Sélection selon critère VIP de l'analyse discrimante multivariée PLS

127 variables biologiques discriminantes

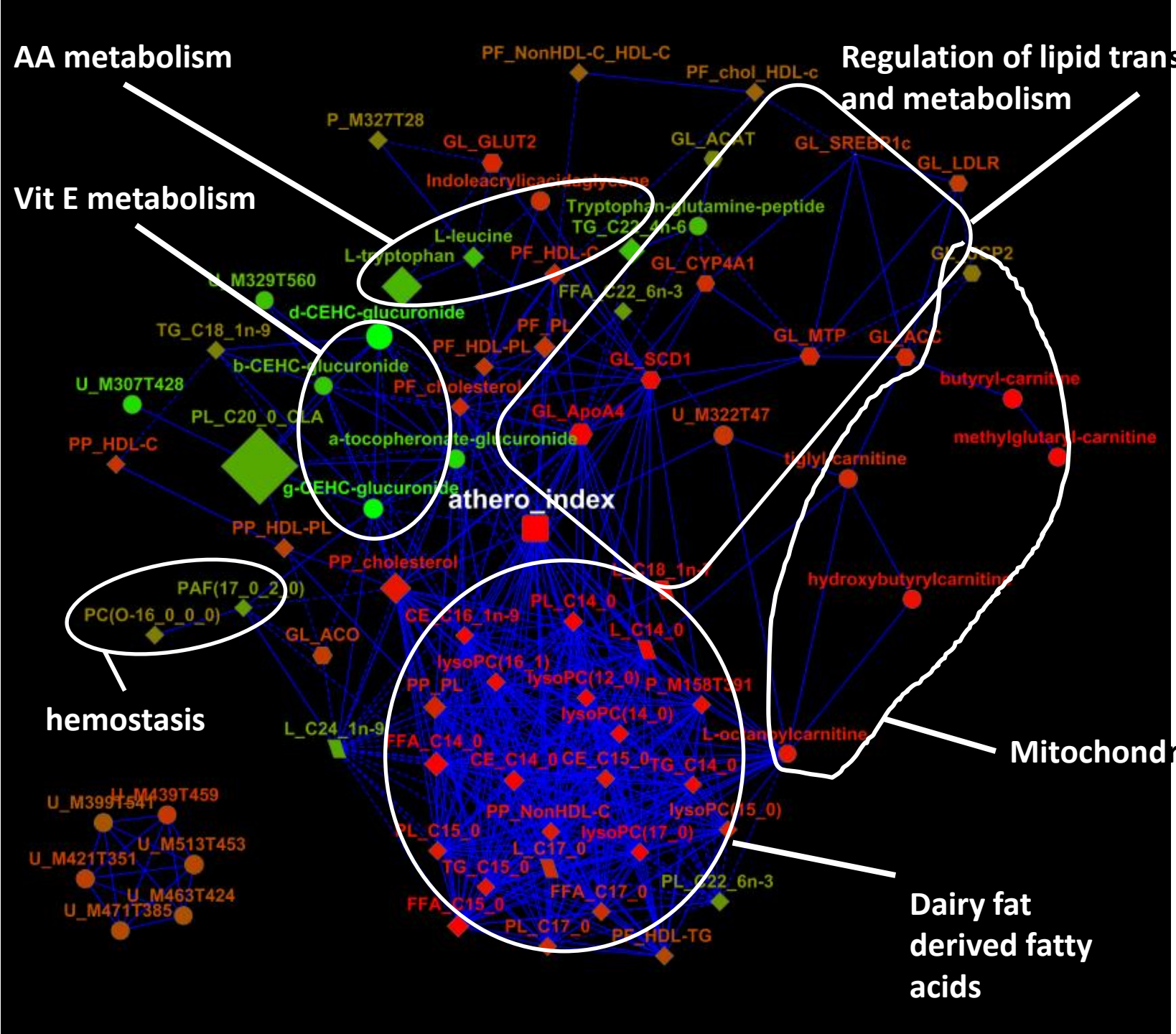
38 métabolome urine

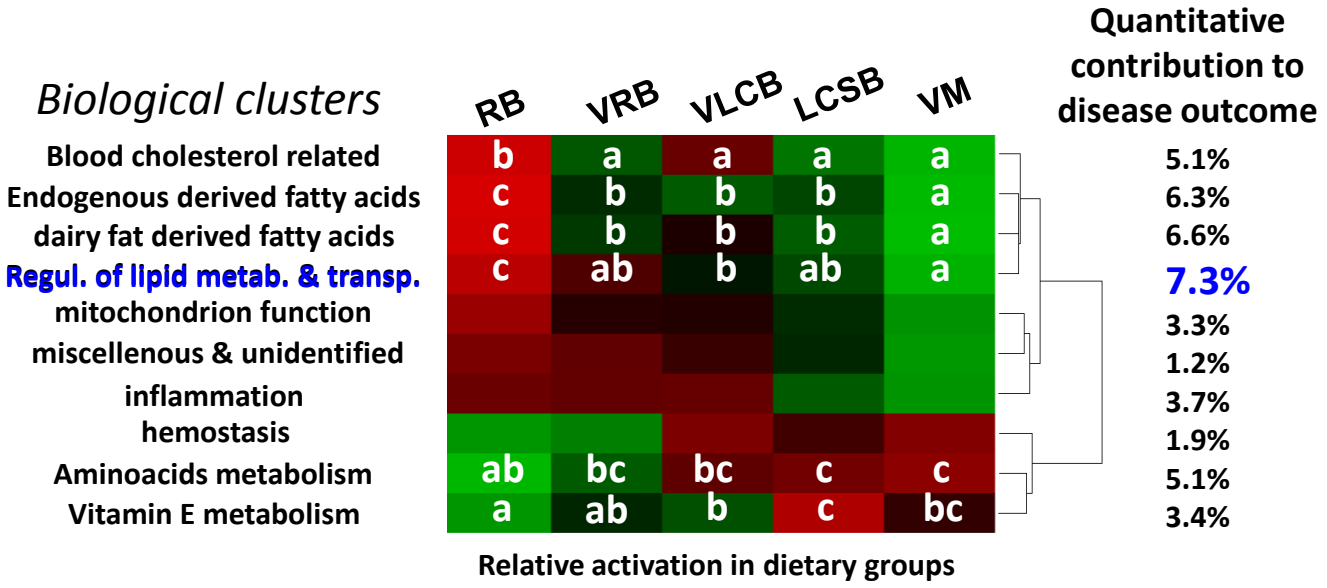
38 metabolome plasma

23 acides gras (PL, CE, TG, Lipides totaux)

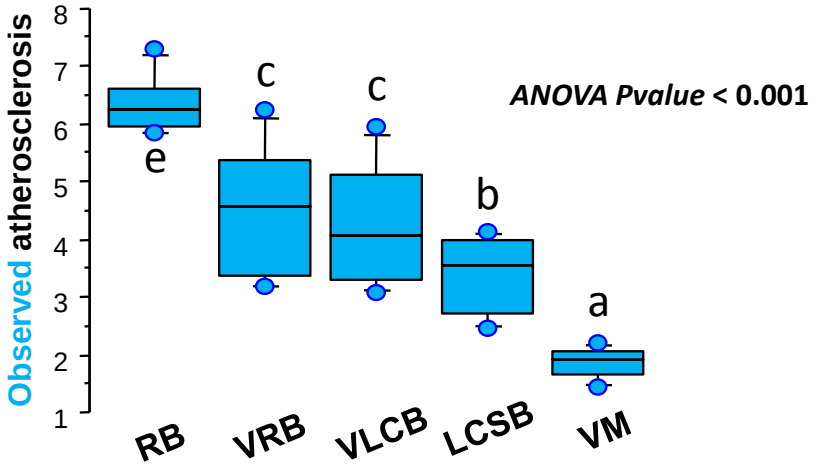
12 biochimie sang

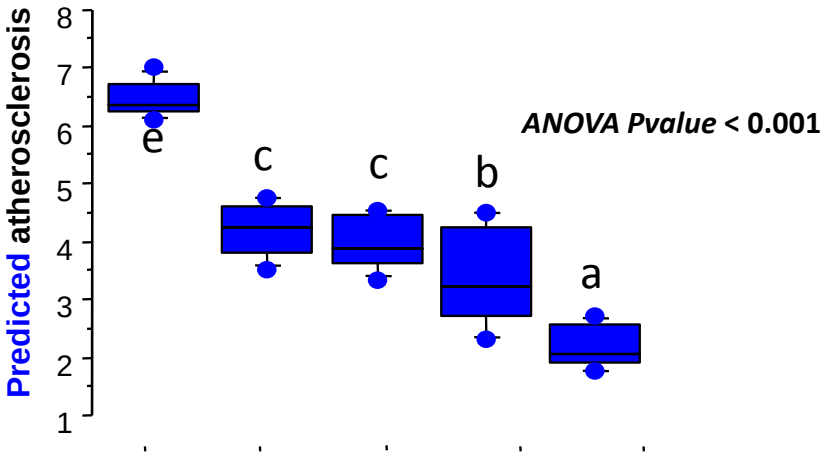
16 gènes

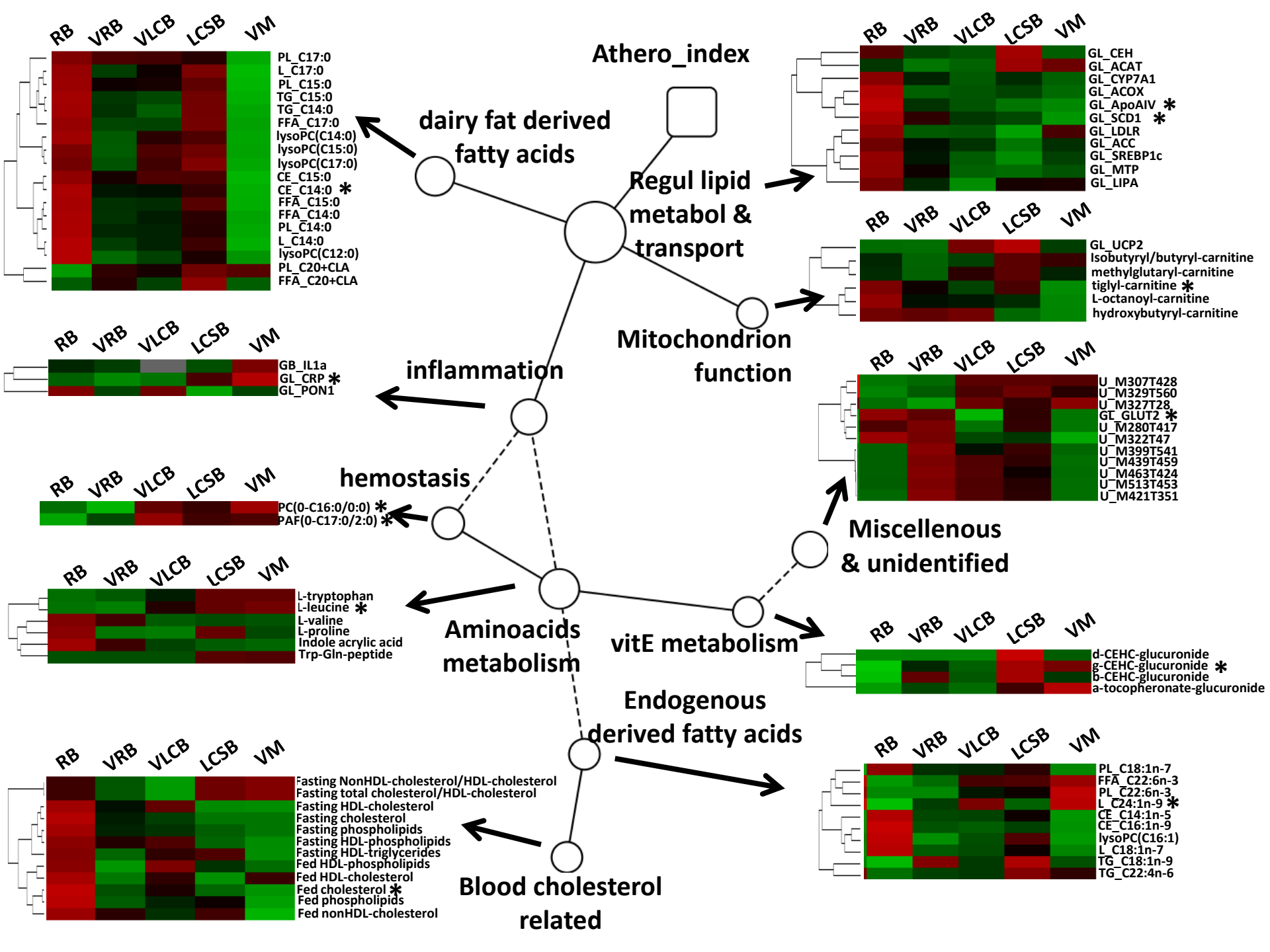

AA metabolism
Vit E metabolism
hemostasis
Regulation of lipid transport and metabolism
Mitochondrion function
Dairy fat derived fatty acids
athero_index
PF_NonHDL-C_HDL-C
PF_chol_HDL-c
P_M327T28
GL_GLUT2
GL_ACAT
GL_SREBP1c
GL_LDLR
Indoleacrylicacidglycine
Tryptophan-glutamine-peptide
TG_C22_4n-6
L-leucine
L-tryptophan
PF_HDL-C
GL_CYP4A1
GL_SCP2
U_M329T560
FFA_C22_6n-3
d-CEHC-glucuronide
TG_C18_1n-9
PF_PL
PF_HDL-PL
GL_MTP
GL_ACC
b-CEHC-glucuronide
GL_SCD1
U_M307T428
PF_cholesterol
butyryl-carnitine
PL_C20_0_CLA
GL_ApoA4
U_M322T47
a-tocopheronate-glucuronide
methylglutaryl-carnitine
PP_HDL-C
tiglylcarnitine
g-CEHC-glucuronide
PP_HDL-PL
PP_cholesterol
hydroxybutyrylcarnitine
PAF(17_0_2_0)
PL_C14_0
PC(O-16_0_0_0)
CE_C16_1n-9
L_C14_0
GL_ACO
lysoPC(16_1)
PP_PL
lysoPC(12_0)
P_M158T391
lysoPC(14_0)
L_C24_1n-9
L-octanoylcarnitine
FFA_C14_0
CE_C14_0
CE_C15_0
TG_C14_0
U_M399T541
U_M439T459
PP_NonHDL-C
lysoPC(15_0)
U_M513T453
PL_C15_0
lysoPC(17_0)
U_M421T351
L_C17_0
TG_C15_0
PL_C22_6n-3
U_M463T424
FFA_C17_0
FFA_C15_0
U_M471T385
PL_C17_0
PF_HDL-TG



Predicted Atherogenicity = 0.108091*[***dairy fat derived fatty acids***] + 0.152669*[***endogenous derived fatty acids***] - 0.0340185*[**mitochondrion function**] + 0.173429*[***regul. Lipid metabol. Trans.***] - 0.0751566*[***vitaminE metabolism***] - 0.153142*[***hemostasis***] - 0.110269*[***aminoacids metabolism***] + 0.110269*[***blood cholesterol related***]+ 0.231903*[***inflammation***] - 0.00456344*[***miscellenous & unidentified***] + **4.06731**.






Athero_index
dairy fat derived fatty acids
Regul lipid metabol & transport
Mitochondrion function
inflammation
hemostasis
Aminoacids metabolism
Miscellenous & unidentified
vitE metabolism
Endogenous derived fatty acids
Blood cholesterol related
RB VRB VLCB LCSB VM
PL_C17:0
L_C17:0
PL_C15:0
TG_C15:0
TG_C14:0
FFA_C17:0
lysoPC(C14:0)
lysoPC(C15:0)
lysoPC(C17:0)
CE_C15:0
CE_C14:0 *
FFA_C15:0
FFA_C14:0
PL_C14:0
L_C14:0
lysoPC(C12:0)
PL_C20+CLA
FFA_C20+CLA
GL_CEH
GL_ACAT
GL_CYP7A1
GL_ACOX
GL_ApoAIV *
GL_SCD1 *
GL_LDLR
GL_ACC
GL_SREBP1c
GL_MTP
GL_LIPA
GL_UCP2
Isobutyryl/butyryl-carnitine
methylglutaryl-carnitine
tiglyl-carnitine *
L-octanoyl-carnitine
hydroxybutyryl-carnitine
GB_IL1a
GL_CRP *
GL_PON1
U_M307T428
U_M329T560
U_M327T28
GL_GLUT2 *
U_M280T417
U_M322T47
U_M399T541
U_M439T459
U_M463T424
U_M513T453
U_M421T351
PC(0-C16:0/0:0) *
PAF(0-C17:0/2:0) *
L-tryptophan
L-leucine *
L-valine
L-proline
Indole acrylic acid
Trp-Gln-peptide
d-CEHC-glucuronide
g-CEHC-glucuronide *
b-CEHC-glucuronide
a-tocopheronate-glucuronide
Fasting NonHDL-cholesterol/HDL-cholesterol
Fasting total cholesterol/HDL-cholesterol
Fasting HDL-cholesterol
Fasting cholesterol
Fasting phospholipids
Fasting HDL-phospholipids
Fasting HDL-triglycerides
Fed HDL-phospholipids
Fed HDL-cholesterol
Fed cholesterol *
Fed phospholipids
Fed nonHDL-cholesterol
PL_C18:1n-7
FFA_C22:6n-3
PL_C22:6n-3
L_C24:1n-9 *
CE_C14:1n-5
CE_C16:1n-9
lysoPC(C16:1)
L_C18:1n-7
TG_C18:1n-9
TG_C22:4n-6

Quelques applications en sélection cultivars, origine produits, qualité

Table 1. A selection of metabolomic studies on common foods summarizing the purpose of these studies, the methodologies used and the major conclusions reached

Purpose	Plant/food	Sample preparation	Analysis	Data analysis	Outcome	Reference
Metabolite diversity/ breeding	Raspberries	Acetic acid/acetonitrile	DIMS-LC-MS	PCA	Variation attributed to anthocyanins	Stewart et al. [26]
Metabolite diversity/ breeding	Tomatoes	MeOH with H_2O/ chloroform partition	GC-MS	PCA	Identification of 889 metabolic loci, metabolites associated with yield trait	Schauer et al. [24]
Metabolite diversity/ breeding	Potatoes	MeOH with H_2O/ chloroform partition	GC-MS	PCA Correlation	Detected variation between cultivars and landraces	Dobson et al. [27, 28]
Geographic origin	Grapes/wine	95% EtOH	NMR	PCA/PLS-DA	Grapes from different regions can be distinguished	Son et al. [69]
Geographic origin	Coffee	MeOH/H_2O	GC-FID/LCMS	PCA	Samples from Asia, Africa, and S. America could be distinguished	Choi et al [35]
Geographic origin	Green tea	Hot H_2O	NMR	PCA/OPLS-DA	Growing region with high temperature, rainfall and sun increased the anine concentrations	Lee et al. [70]
Geographic origin	Olive oil	SPME	GC-MS	Linear discriminant analysis	Distinguished from different productions areas within a region	Cavaliere et al. [36]
Quality	Green tea	MeOH/H_2O/chloroform	GC-MS/LC-MS	PCA/OPLS-DA	Tea grown on greater shade had higher umami and less astringency and these attributes were related to sugars, amino acid and phenolics	Ku et al. [71]
Postharvest disorder	Apples		GC-MS			Rudell et al. [38]
Sensory	Tomatoes	Lyophilisation/SPME/ extraction H_2O:MeOH	GC-MS and LC-MS	PCA/PLS (with validation)		Thissen et al. [21]
Sensory	Wine/grapes	Wine directly added to NMR tubes	NMR	PCA/PLS-DA	Metabolites related to sun/shade treatments and mouth-feel parameters	Rochfort et al. [39]
GM assessment	Tomatoes	80% MeOH/H_2O	GC-MS, LC-MS, CE-MS	ANOVA/PCA	GM lines were within traditional cultivar variation	Kusano et al. [41]

Characterization and classification of Western Greek olive oils according to cultivar and geographical origin based on volatile compounds

Eirini Pouliarekou[a], Anastasia Badeka[a], Maria Tasioula-Margari[a], Stavros Kontakos[b], Francesco Longobardi[c], Michael G. Kontominas[a,*]

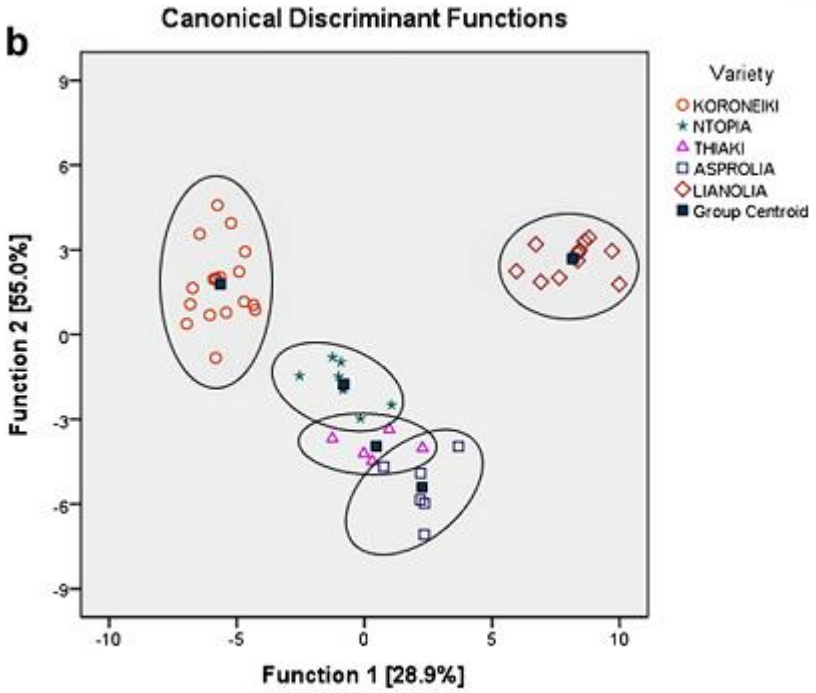
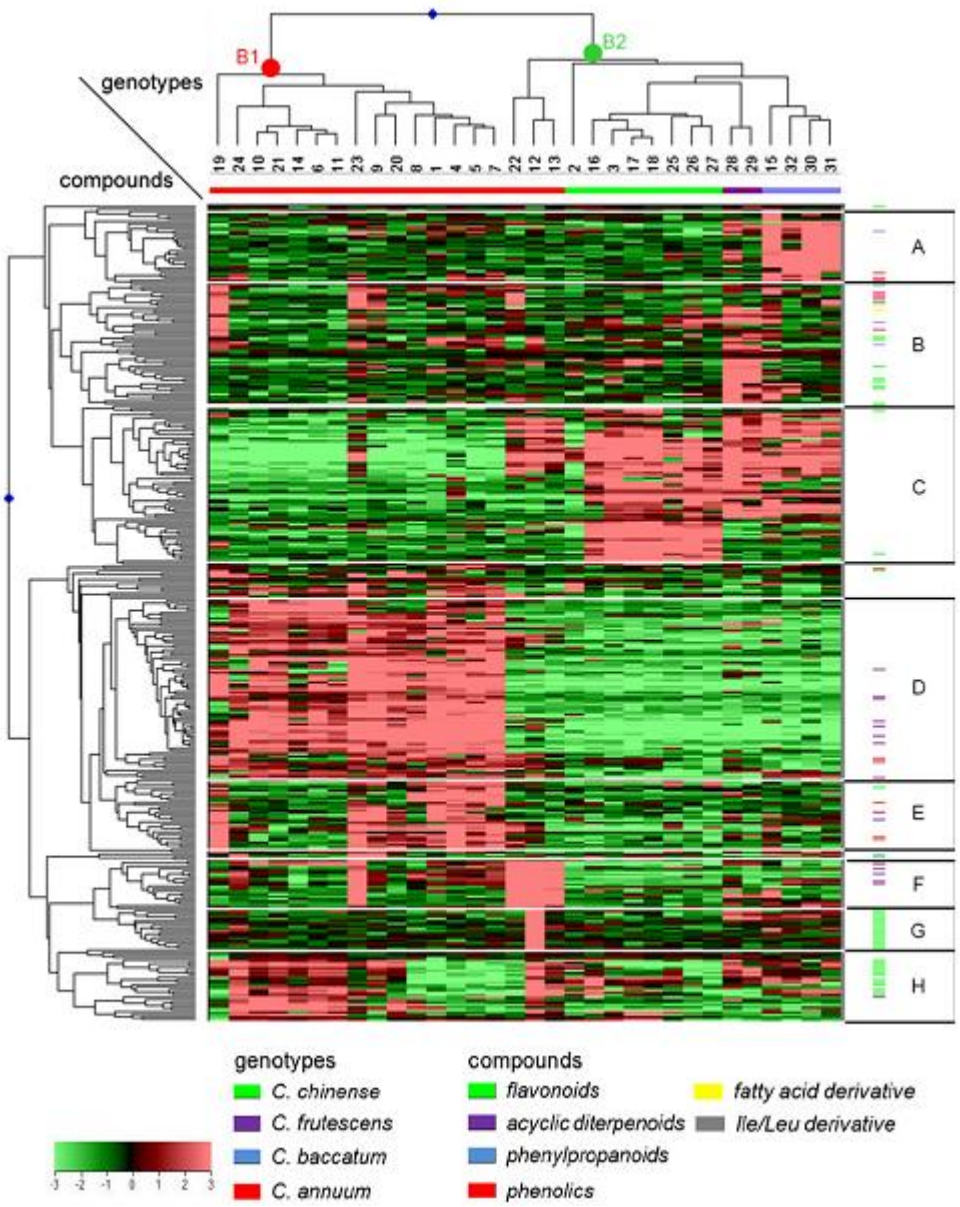


Fig. 3. Classification of olive oil samples from Western Greece according to cultivar using (a) 53 variables and (b) 19 variables.

Metabolomics and molecular marker analysis to explore pepper (*Capsicum* sp.) biodiversity

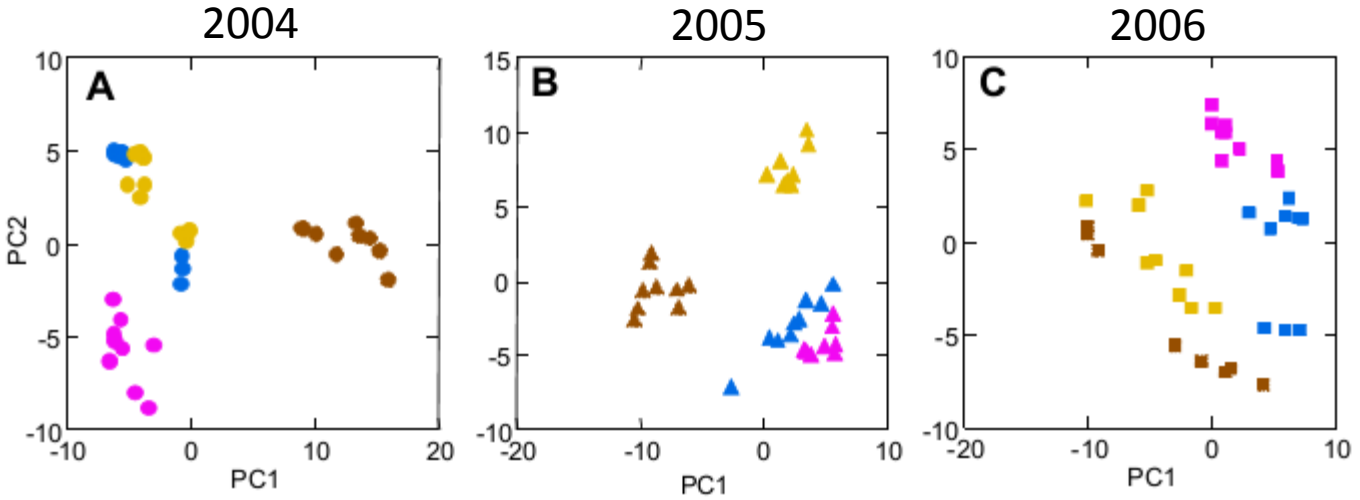
Yuni Wahyuni · Ana-Rosa Ballester · Yury Tikunov · Ric C. H. de Vos · Koen T. B. Pelgrom · Awang Maharijaya · Enny Sudarmonowati · Raoul J. Bino · Arnaud G. Bovy

Metabolomics (2013) 9:130–144



Metabolite profiling of maize grain: differentiation due to genetics and environment

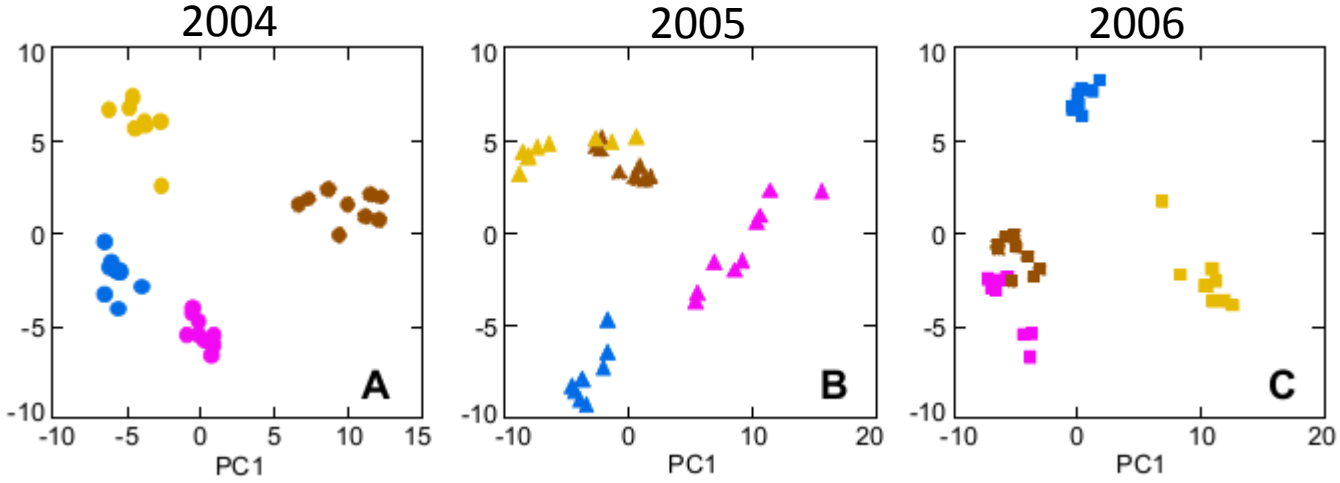
Richard M. Röhlig · Joachim Eder · Karl-Heinz Engel



Cultivar Amadeo x

LOCATION
- Mittich
- Reith
- Strassmoos
- Thann

Géo x temps



1 localisation x
- Flavi
- Lukas
- Pontos
- Shorty

Cult x temps

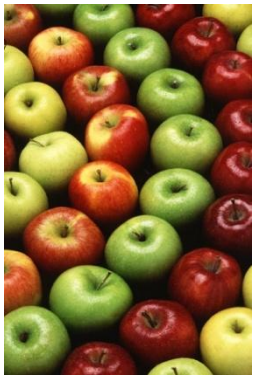
Apple Peels, from Seven Cultivars, Have Lipase-Inhibitory Activity and Contain Numerous Ursenoic Acids As Identified by LC-ESI-QTOF-HRMS

micrOTOF QII mass spectrometer

Tony K. McGhie,* Sébastien Hudault, Rona C. M. Lunken, and John T. Christeller

Table 3. Relative Amount of Each Compound Measured Normalized to Total Peak Area

no.	compound name	average	'Braeburn'	'Granny Smith'	'Sciros'	O.P. 'Red Field'	'Cripps Pink'	'Fuji'	'Scilate'
1	dihydroxy-urs-12-en-28-oic acid	0.13	0.14	0.00	0.22	0.24	0.07	0.12	0.07
2	unknown	1.64	1.37	0.13	0.53	1.24	6.39	0.73	0.59
3	unknown	0.76	0.44	1.21	0.48	2.14	0.53	0.26	0.26
4	unknown	1.76	1.04	1.60	1.77	4.65	1.26	0.73	1.01
5	trihydroxy-urs-12-en-28-oic acid	2.48	2.03	1.88	0.63	0.49	4.10	3.16	5.34
6	trihydroxy-urs-12-en-28-oic acid	0.11	0.28	0.01	0.26	0.24	0.00	0.00	0.00
7	unknown	2.50	1.00	1.91	3.63	6.64	0.75	0.77	2.49
8	unknown	3.45	2.75	2.56	3.07	5.14	4.18	3.34	2.56
9	tetrahydroxy-urs-12-en-28-oic acid	1.26	5.28	0.08	1.16	1.68	0.38	0.20	0.23
10	unknown	0.93	1.25	0.88	0.35	1.84	0.74	0.78	0.64
11	3-oxo-1,19α-dihydroxy-urs-12-en-28-oic acid (annurcoic acid)	8.39	12.32	5.08	9.27	8.90	8.79	6.40	7.80
12	unknown	3.35	5.22	3.35	1.02	5.69	2.77	3.35	2.04
13	unknown	2.25	3.44	2.33	1.34	3.30	1.49	2.29	1.62
14	3-oxo-1α-hydroxy-urs-12-en-28-oic acid	2.14	4.91	1.25	2.02	1.98	2.21	1.21	1.55
15	3β-*p*-coumaroyloxy-dihydroxy-urs-12-en-28-oic acid	1.54	1.53	0.17	0.23	0.51	1.70	2.60	4.01
16	3β,19α-dihydroxy-urs-12-en-28-oic acid (pomolic acid)	1.86	1.73	1.66	1.96	1.78	1.69	1.62	2.65
17	3-oxo-hydroxy-urs-12-en-28-oic acid	3.69	5.38	4.98	5.45	2.74	2.58	2.21	3.20



	'Braeburn'	'Granny Smith'	'Sciros'	O.P. 'Red Field'	'Cripps Pink'	'Fuji'	'Scilate'
total ursenoic acids peak area	3,630,859	3,110,778	4,243,395	4,381,954	4,207,580	4,753,673	3,507,671
% lipase inhibition	39	71	60	64	70	60	50

27	unknown	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
28	oxo-urs-12-en-28-oic acid	0.59	0.90	0.61	0.81	0.51	0.37	0.49	0.51
29	unknown (dihydroxy-urs-12-en-28-oic acid)	1.91	3.13	1.73	2.38	1.86	1.39	1.59	1.35
30	oxo-urs-12-en-28-oic acid	1.96	3.21	2.04	3.39	1.33	1.16	1.29	1.49
31	3-oxo-hydroxy-urs-12-en-28-oic acid	2.56	8.63	0.00	0.00	2.21	2.01	3.28	1.79
32	3-oxo-hydroxy-urs-12-en-28-oic acid	2.04	0.00	1.93	2.97	2.57	1.94	2.15	2.42
33	3β-?-*p*-coumaroyloxy-hydroxy-urs-12-en-28-oic acid	2.00	1.08	1.94	2.83	1.21	1.49	2.94	2.31
34	3β-*trans*-*p*-coumaroyloxy-2α-hydroxy-urs-12-en-28-oic acid	6.34	3.67	4.94	8.94	4.18	5.29	8.95	7.65
35	3β-*cis*-*p*-coumaroyloxy-2α-hydroxy-urs-12-en-28-oic acid	4.35	1.33	7.18	5.76	2.32	3.55	6.05	4.46
36	oxo-urs-12-en-28-oic acid	2.83	3.39	4.29	4.20	2.25	1.63	2.06	2.50
37	3β-hydroxy-lup-20(29)-en-28-oic acid (betulinic acid)	6.03	3.80	9.62	5.85	4.92	6.76	5.33	6.85
38	3β-hydroxy-urs-12-en-28-oic acid (ursolic acid)	5.41	4.48	8.56	5.36	3.95	5.56	4.55	6.45
39	unknown	1.29	0.31	0.00	0.07	4.40	2.65	0.12	1.00
40	unknown	2.26	1.05	3.74	1.90	1.79	2.63	2.26	2.80
41	unknown	6.49	3.78	9.76	6.10	5.40	7.19	6.12	7.85
42	3β-hydroxy-urs-12-en-28-ol (uvaol)	5.06	1.53	6.42	2.53	3.23	5.70	11.70	3.12
43	unknown	1.70	0.86	1.39	1.36	1.25	2.40	1.97	2.60
	total ursenoic acids peak area		3,630,859	3,110,778	4,243,395	4,381,954	4,207,580	4,753,673	3,507,671
	% lipase inhibition		39	71	60	64	70	60	50

Metabolomics-Driven Nutraceutical Evaluation of Diverse Green Tea Cultivars

Yoshinori Fujimura[1☯], Kana Kurihara[2☯], Megumi Ida[2], Reia Kosaka[2], Daisuke Miura[1], Hiroyuki Wariishi[1,2,3], Mari Maeda-Yamamoto[4], Atsushi Nesumi[4], Takeshi Saito[5], Tomomasa Kanda[5], Koji Yamada[2], Hirofumi Tachibana[1,2,3]*

Analyse métabolomique de différents cultivars de thé vert

Test biologique (dysfonction vasculaire in vitro) des différents cultivars de thé vert

Cultivars biologiquement actifs/non actifs

Métabolites discriminants des cultivars

Métabolites associés à l'activité biologique

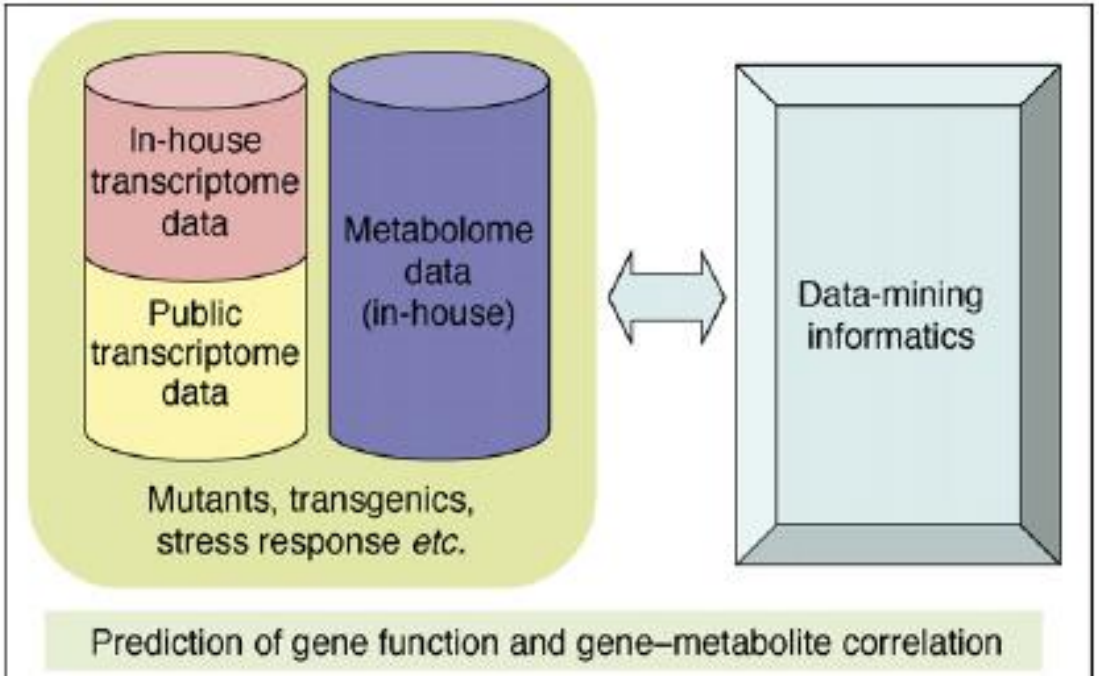
Cultivars possédant les métabolites actifs

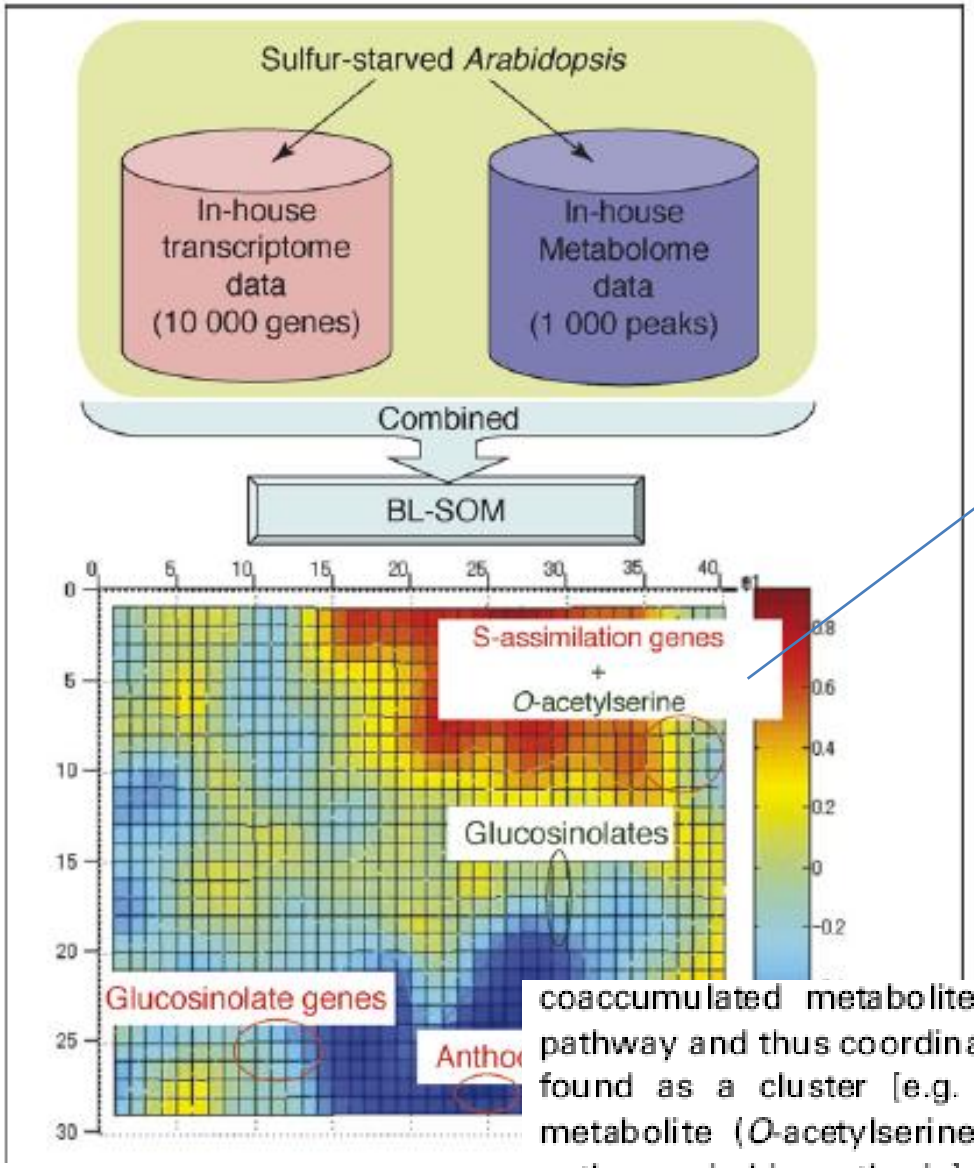
Validation = transfert de l'activité biologique par ajout des métabolites suspectés actifs à un cultivar initialement inactif (ex: importance bio THEANIN)

Decoding genes with coexpression networks and metabolomics – 'majority report by precogs'

TRENDS in Plant Science Vol.13 No.1

Kazuki Saito[1,2], Masami Y. Hirai[1] and Keiko Yonekura-Sakakibara[1]





Co-expression de gènes associés à l'assimilation du souffre avec O-acetylsérine

Fonction de gènes inconnus

coaccumulated metabolites. A set of genes involved in the same metabolic pathway and thus coordinately regulated under the sulfur-starved condition were found as a cluster [e.g. genes of glucosinolate biosynthesis, genes and a metabolite (*O*-acetylserine) of the sulfur assimilation pathway and genes of anthocyanin biosynthesis]. These clusters contained novel genes for enzymes and transcription factors to be further characterized [17,20]. *O*-Acetylserine, an intermediary and regulatory metabolite of the sulfur assimilation pathway, was found in the same cluster as the genes of this pathway [17].

CRIBIOM, une plate-forme de criblage biologique

Méthodes de production/formulation

cultivars

Process industriel

Qualité/ingeniering

Produits/molécules
d'intérêts santé

Signature biologique &
caractéristiques moléculaires

Système biologique intégré

Stress
(agression, drogue,
nutriments)

Gènes (réponse amont)

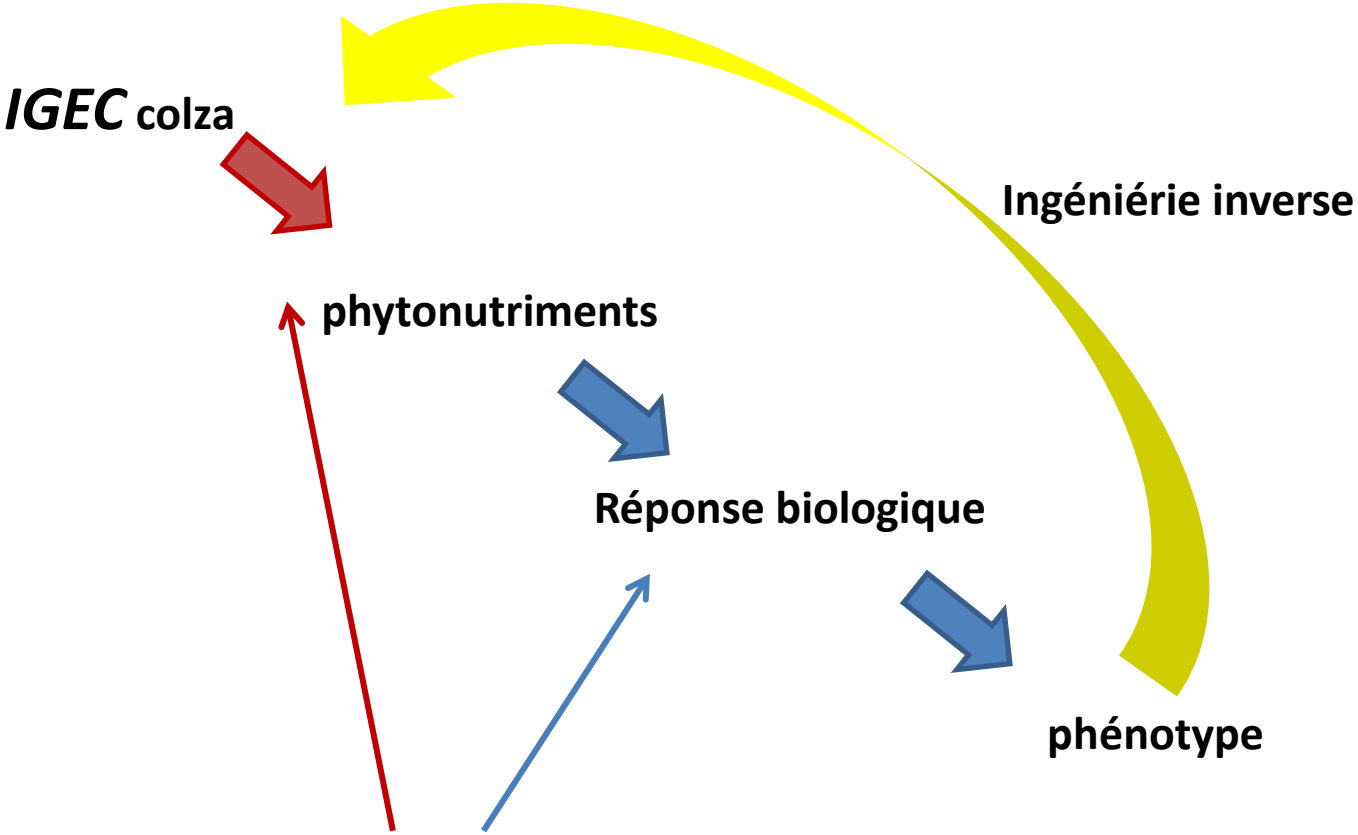
protéines

Métabolites (réponse aval)

Réponse adaptative

Projet « Polygone »

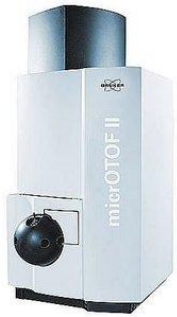
Onidol, PIVERT, U-Caen, AMU
GENESYS/SAS PIVERT



« omiques »

CRIBIOM

Métabolomique et lipidomique



LC QTOF

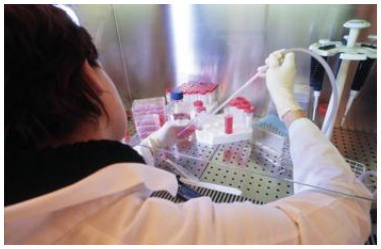
GCMS

LC orbitrap

fastGCFID

Plate-formes expérimentales

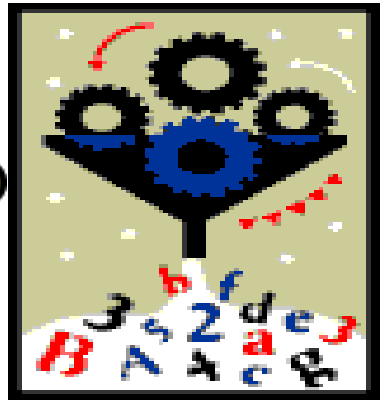
animalerie



Cultures cellulaires

Bioinformatique, statistiques et modélisation in silico

MS Nutrition
La solution quantitative



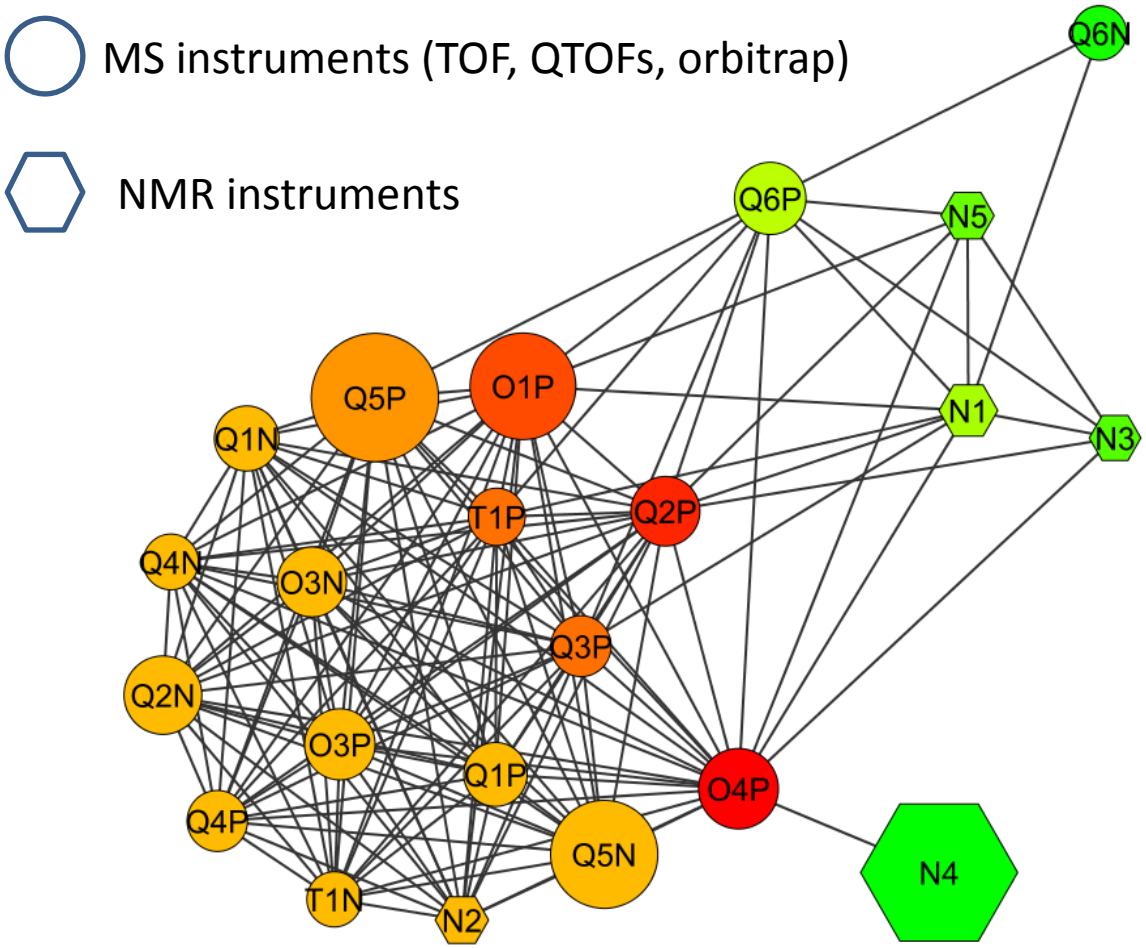
Transcriptomique

Plate forme microarray (IFR)

QPCR

Quels sont les éléments qui fragilisent encore le développement de la métabolomique?

Reproductibilité inter-plateforme et standardisation

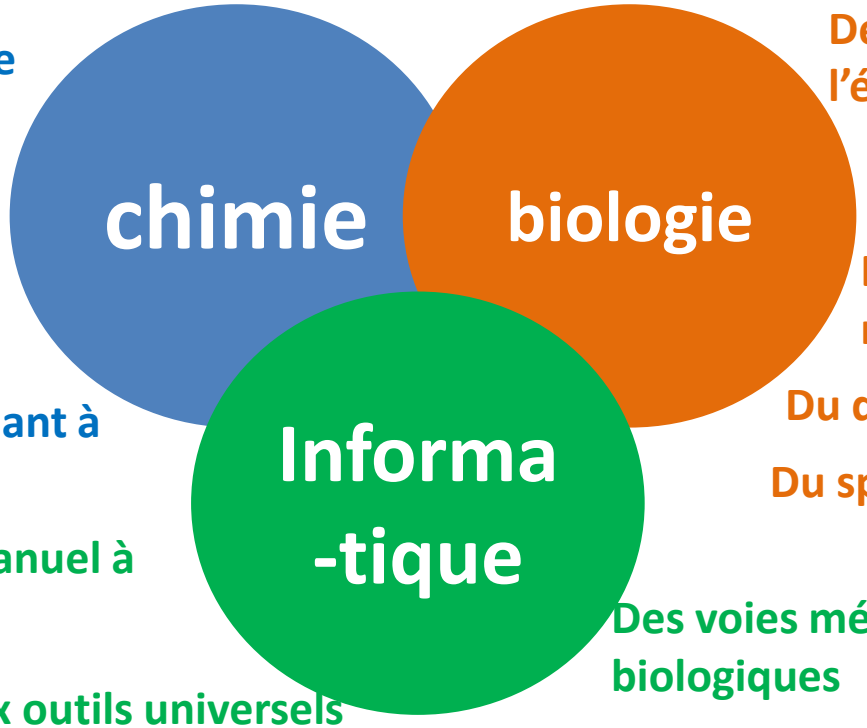


MetabO RinG

Despite a large differences in the number of features among the instruments, the heterogeneity in the analytic conditions and data post-processing, the spectral information within (NMR and MS) and across methods (NMR vs MS) was highly converging (from 64% to 91% on average). No effect of the MS configuration (TOF, QTOF, Orbitrap) was noticed

Facteurs humains: scepticisme et conservatisme des biologistes, formation insuffisante

Les progrès à attendre



De l'identification manuelle à l'identification automatique à haut débit

Du relatif au quantitatif

Du statique au dynamique

De centaines de composés à des milliers

De la preuve de principe à la routine

De l'instrument dépendant à l'universel

De l'interrogation manuel à l'automatisation

Des outils maisons aux outils universels

D'un accès restreint à un accès universel (visualisation)

De la découverte à la validation de nouveaux biomarqueurs

Des biomarqueurs individuels aux biomarqueurs multiplexes

Des petites cohortes à l'épidémiologie

Du laboratoire R&D à la clinique

Du groupe au metabotype individuel

Du descriptif au mécanistique

Du spectral à l'imagerie

Des voies métaboliques aux fonctions biologiques

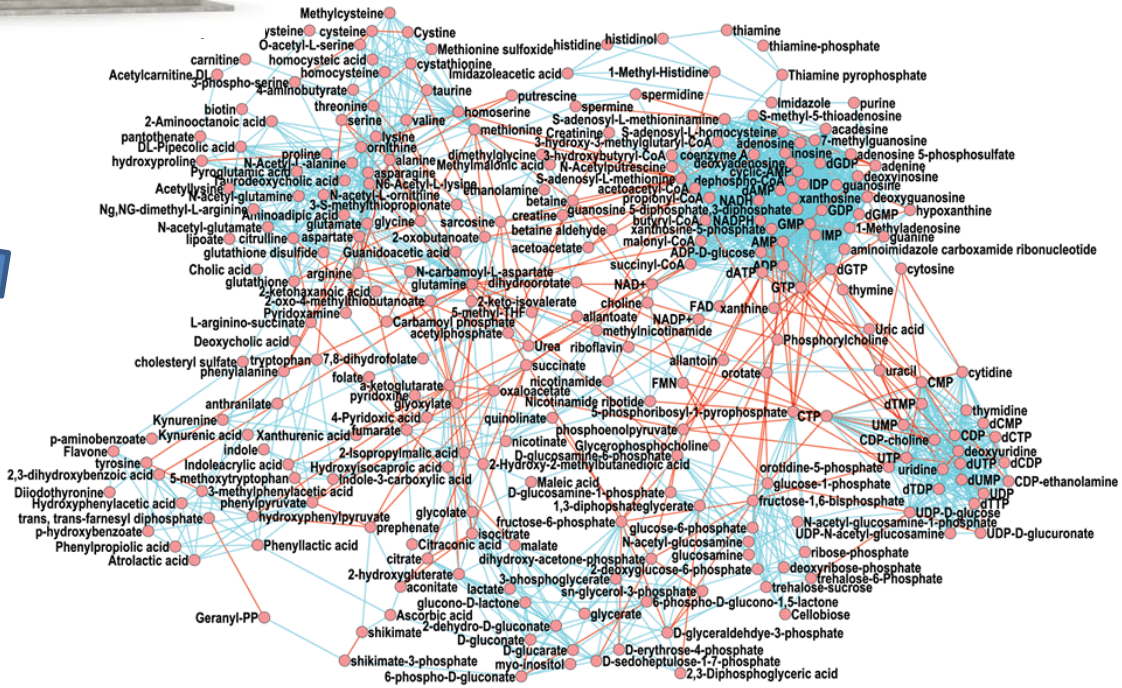
Des statistiques à l'intégration au text-mining et à l'interprêtation

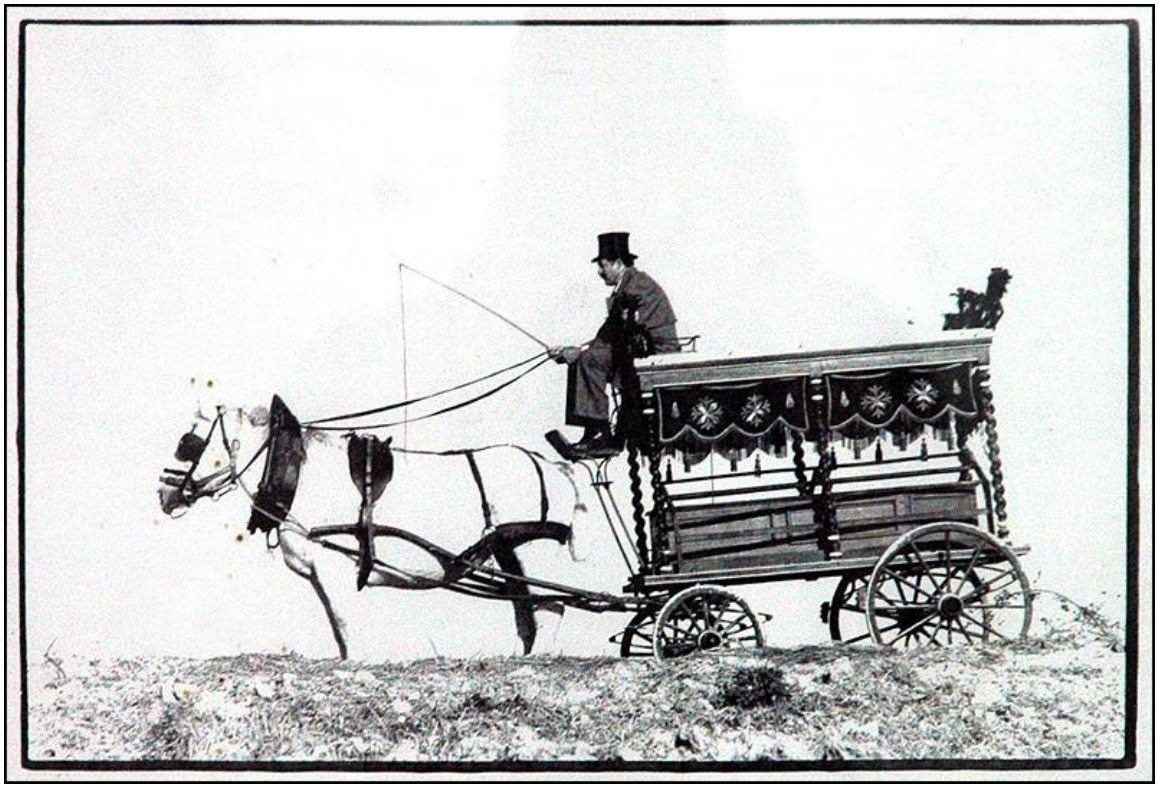
De la métabolomique à l'intégration omique

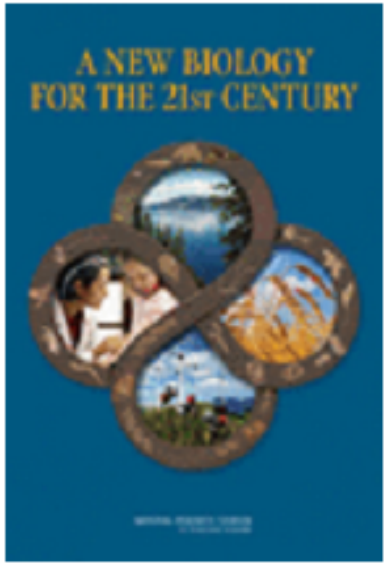
Spectro de masse

Banque de données

Identifier et annoter







A New Biology for the 21st Century

Committee on a New Biology for the 21st Century: Ensuring the United States Leads the Coming Biology Revolution; National Research Council

ISBN: 0-309-14489-2, 112 pages, 6 x 9, (2009)


Que pensez-vous de la métabolomique?
A: Très bien
B: Bien
C: Moyen
D: À supprimer