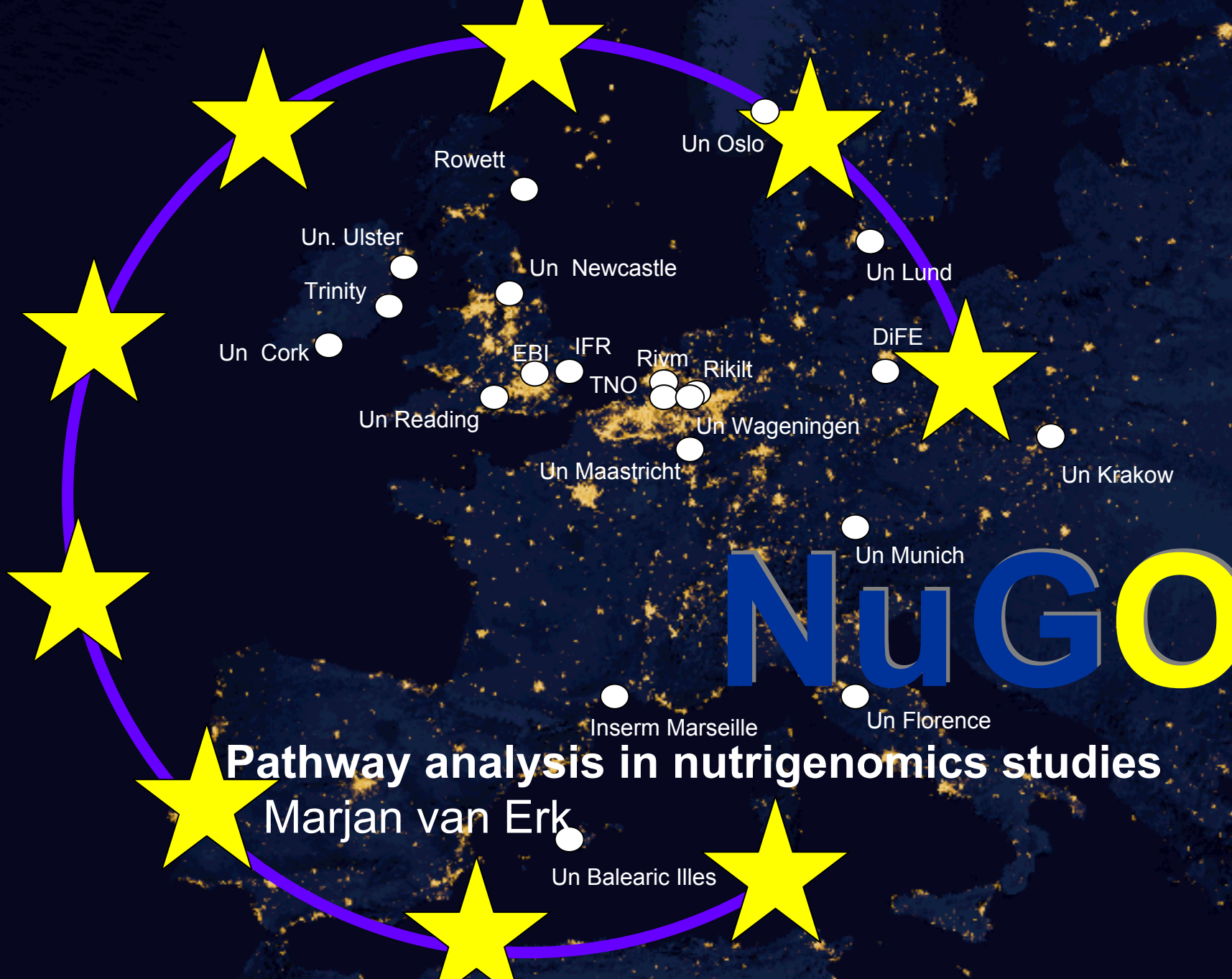
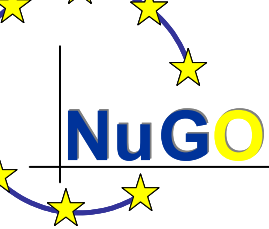




NuGO

Pathway analysis in nutrigenomics studies

Marjan van Erp



- The European Nutrigenomics Organisation
- Network of nutritionists interested in or working in genomics (22 partners, 11 countries)
- Funded by European Union (6 years)
- WP7: Bioinformatics and Systems biology
Analysis and interpretation of data from genomics studies



WP 7 Bioinformatics and Systems Biology

Published or modified on 2005/04/25 by [van Erk, Marian](#)

Welcome to Bioinformatics and Systems Biology

This is the 'homepage' of WP7, giving you a clear overview of the activities within WP7.

WP7 new work description:

See [Workpackage description WP7 2005-mid 2006 version 070205](#)

See also the discussion on long term objectives (e.g. creation of new workpackages [WP7 long term objectives](#))

Do you want to learn more about statistics for microarray analysis?

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Link to [response to 'call for dataset'](#)

Link to [call for dataset: data Roche](#)

WEBEX: <http://nugo.webex.com>

WP7 Description & Objectives

[Workpackage description WP7 2005-mid 2006 version 070205](#)

[Workpackage description WP7 2004-mid 2005](#)

NuGO Stat Toolbox (Statistical Bioinformatics)

A review of statistical methods for nutrigenomics research that NuGO members can use to guide themselves through the use of design issues, array normalization issues and to help them to find analysis tools (e.g. R/Bioconductor) for their particular research purposes.

See also [inventory of statistical issues](#)

NuGO Path Toolbox (biological bioinformatics)

Goal: to make pathway mapping tools more accessible to the NuGO community and assist members in how to apply these to their datasets.

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For discussions: [discussion on pathway mapping/network visualisation](#)
What are the pathways most relevant to nutrition research? Share your thought at [Post your pathway!](#)

Discussion folder

[WP7 Bioinformatics discussion folder:](#)

Discussion on experimental design, data (pre)processing for

Why pathway analysis?

Biochemical Pathways

Genes / proteins do not function alone, but they function together in pathways and processes !!!

Why pathway analysis?

Measured effects in nutrition studies are generally small (e.g. 2-fold change in gene expression, or less), in contrast to toxicological or pharmacological studies.

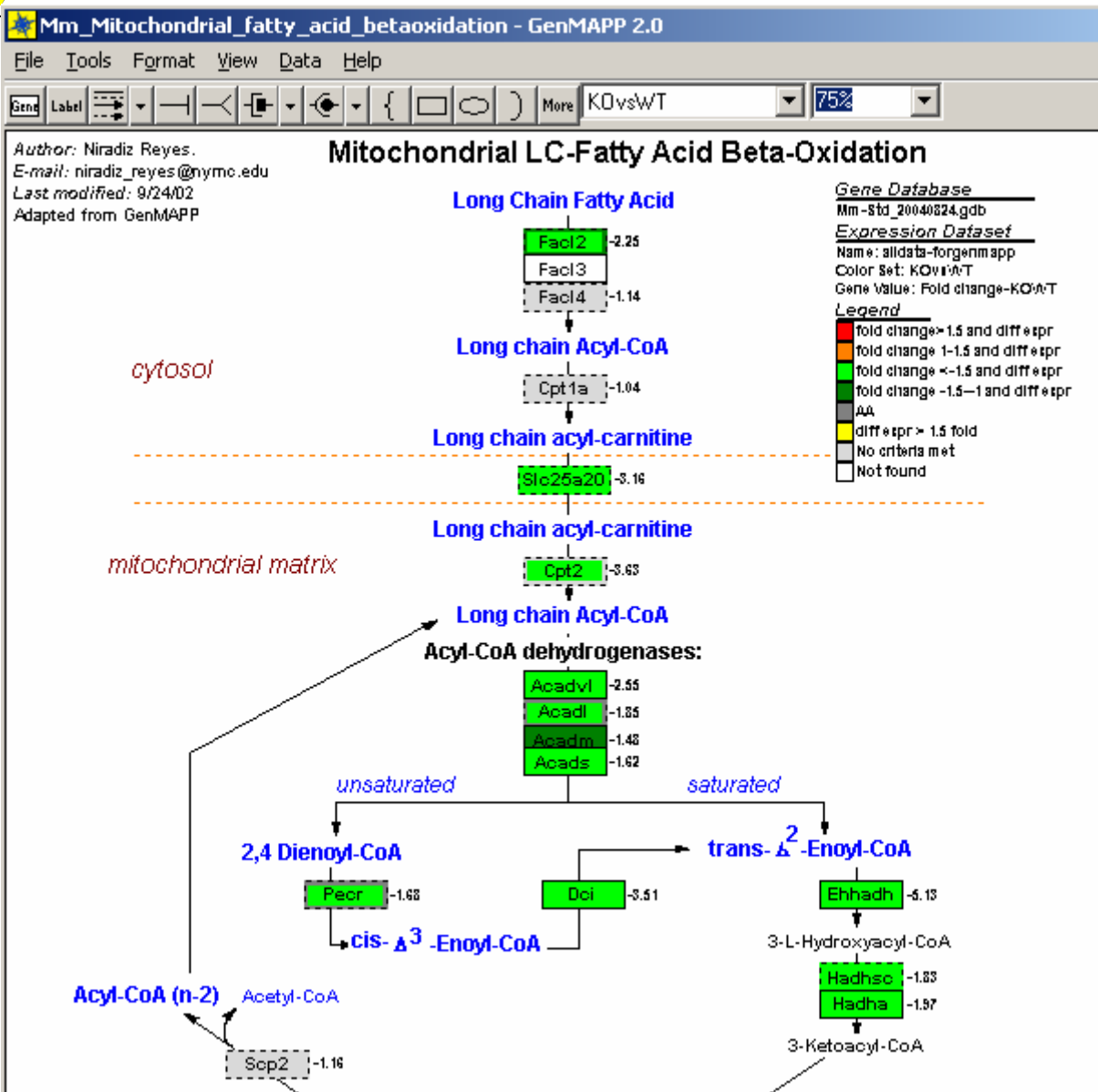


Fewer (significantly) changed genes

How relevant are small expression changes?

BUT: Multiple small expression changes in a pathway may be very important !!

Example from GenMAPP



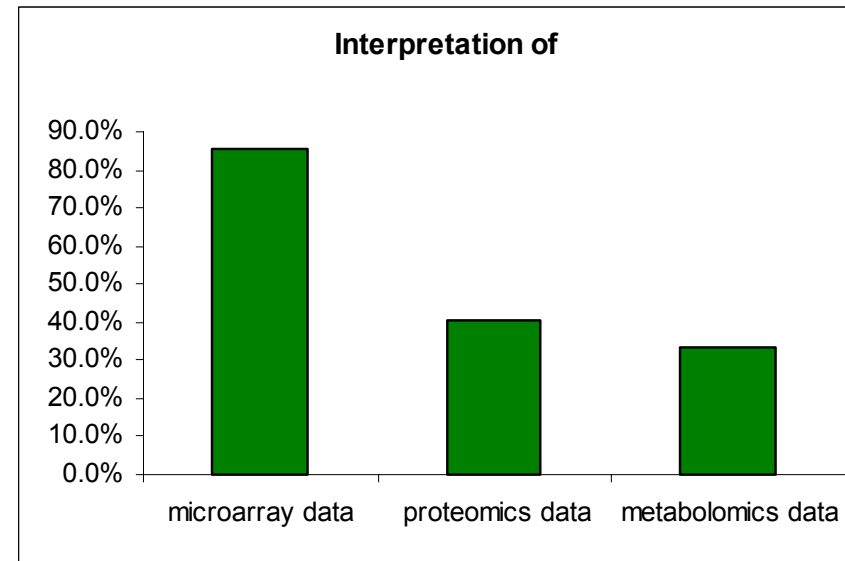
Why pathway analysis?

- Functional genomics is not only about **GENES** (transcriptomics, microarrays).
- ***Proteomics***: large scale measurement of protein expression (2D gel electrophoresis, mass spectrometry)
- ***Metabolomics***: large scale measurement of metabolites in cells, body fluids etc (NMR, mass spectrometry)
- **Systems biology** approach: analyze gene, protein and metabolite data simultaneously.

Analysis, interpretation? Use pathway analysis!

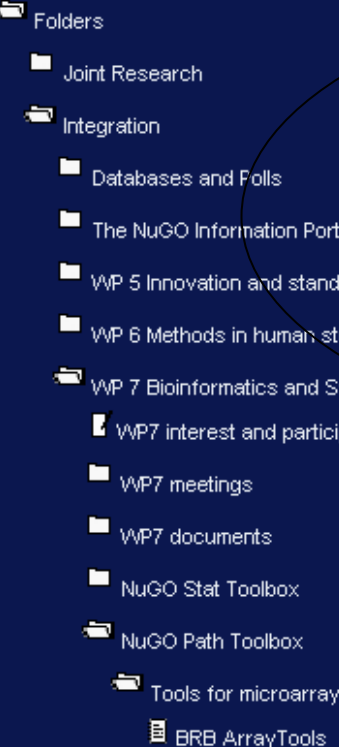


Questionnaire:
Mainly interest in
interpretation of microarray
data



Focus on pathway analysis as tool for biological interpretation of data from microarray experiments:

- What pathway analysis tools are available?
- What are pathways relevant in nutrition research?



/ Folders / Integration / WP 7 Bioinformatics and Systems Biology / NuGO Path Toolbox / Tools for microarray analysis

Tools for microarray analysis

Published or modified on 2004/12/02 by [van Erk, Marian](#)

This folder lists some of the (freely available) tools available for microarray data analysis.

Please let me know if the tools that are listed are useful and if there are other tools that you think should be listed here.

Marjan van Erk

Pathway Analysis:

[GenMAPP \(Gene MicroArray Pathway Profiler\)](#) : visualisation of gene expression data in pathways

[ArrayXPath](#) : visualisation of gene expression data in pathways

[Bio Resource for Array Genes](#) : visualisation of gene expression data in pathways

[KEGG](#)

[BioCarta](#)

[BioCyc: database on pathways and genomes](#)

[CGAP-pathway analysis](#)

commercial tools for Pathway Analysis:

GeneGO: <http://www.genego.com/about/products.shtml#metacore>

Ingenuity Pathways: <http://www.ingenuity.com>

PathwayAssist: <http://www.ariadnegenomics.com/products/pathway.html>

Other tools:

NEW: [GOToolBox](#): analysis based on Gene Ontology

[BRB ArrayTools](#): visualisation and statistical analysis of gene expression data

[the Expression Analysis Systematic Explorer \(EASE\)](#): functional group analysis using gene ontology categories

[Onto-Tools](#): collection of tools, including functional group analysis using gene ontology categories.

[BiGCaT Tools library](#)

NEW: [iHOP text mining tool](#): to navigate literature for information on genes/proteins

Nucleic Acids Research special issue of July 2004 contains an elaborate inventory of webserver for computational analysis of DNA, RNA and proteins: http://nar.oupjournals.org/content/vol32/suppl_2/

All articles are freely available.

→ NuGO PathToolbox

- Which pathways are relevant in nutrition research?
 - Pathway analysis tools contain 'general' pathways, what about nutrition-specific pathway information?
- ↓
- Improvement of pathways by using information/knowledge from NuGO experts !

Folders

- Joint Research
- Integration
 - Databases and Polls
 - The NuGO Information Port
 - WP 5 Innovation and stand
 - WP 6 Methods in human st
 - WP 7 Bioinformatics and S
 - WP7 interest and partici
 - WP7 meetings
 - WP7 documents
 - NuGO Stat Toolbox
 - NuGO Path Toolbox
 - NuGO Path Developmen
 - WP7 Bioinformatics disc

 / Folders / [Integration](#) / [WP 7 Bioinformatics and Systems Biology](#)

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 Published or modified on 2005/04/25 by [van Erk, Marjan](#)

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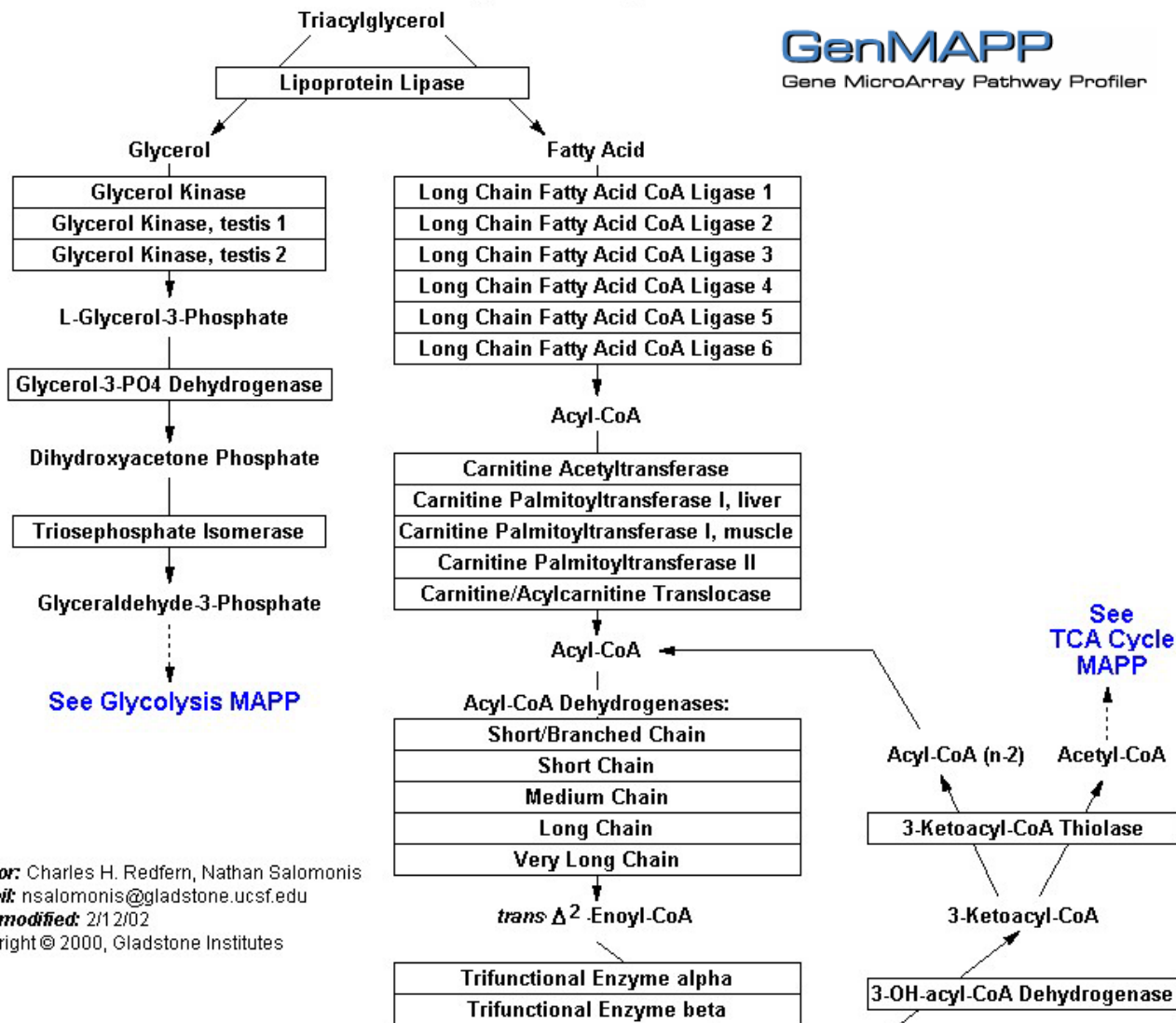
[WP7 Bioinformatics discussion folder:](#)

Discussion on experimental design, data (pre)processing for

Fatty Acid Degradation

GenMAPP

Gene MicroArray Pathway Profiler

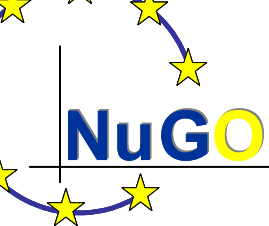


Author: Charles H. Redfern, Nathan Salomonis

E-mail: nsalomonis@gladstone.ucsf.edu

Last modified: 2/12/02

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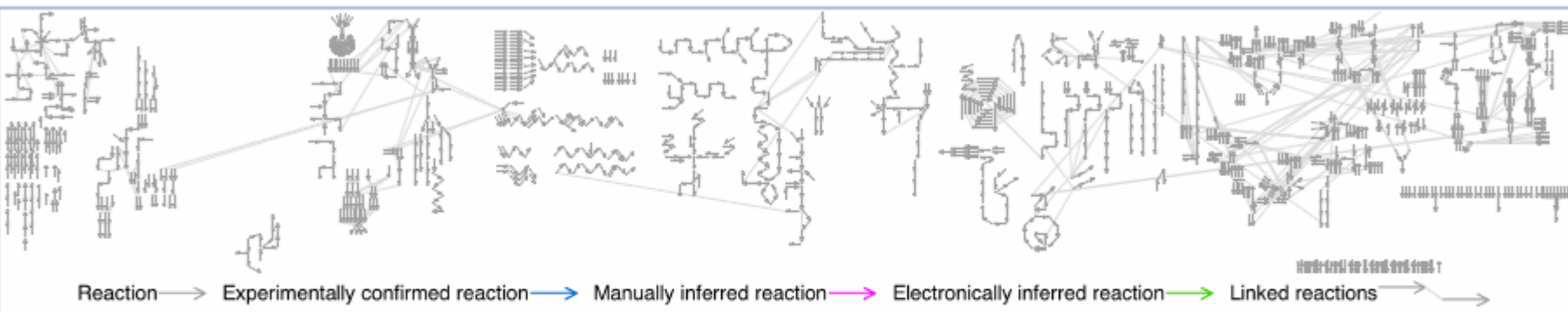


Pathway database

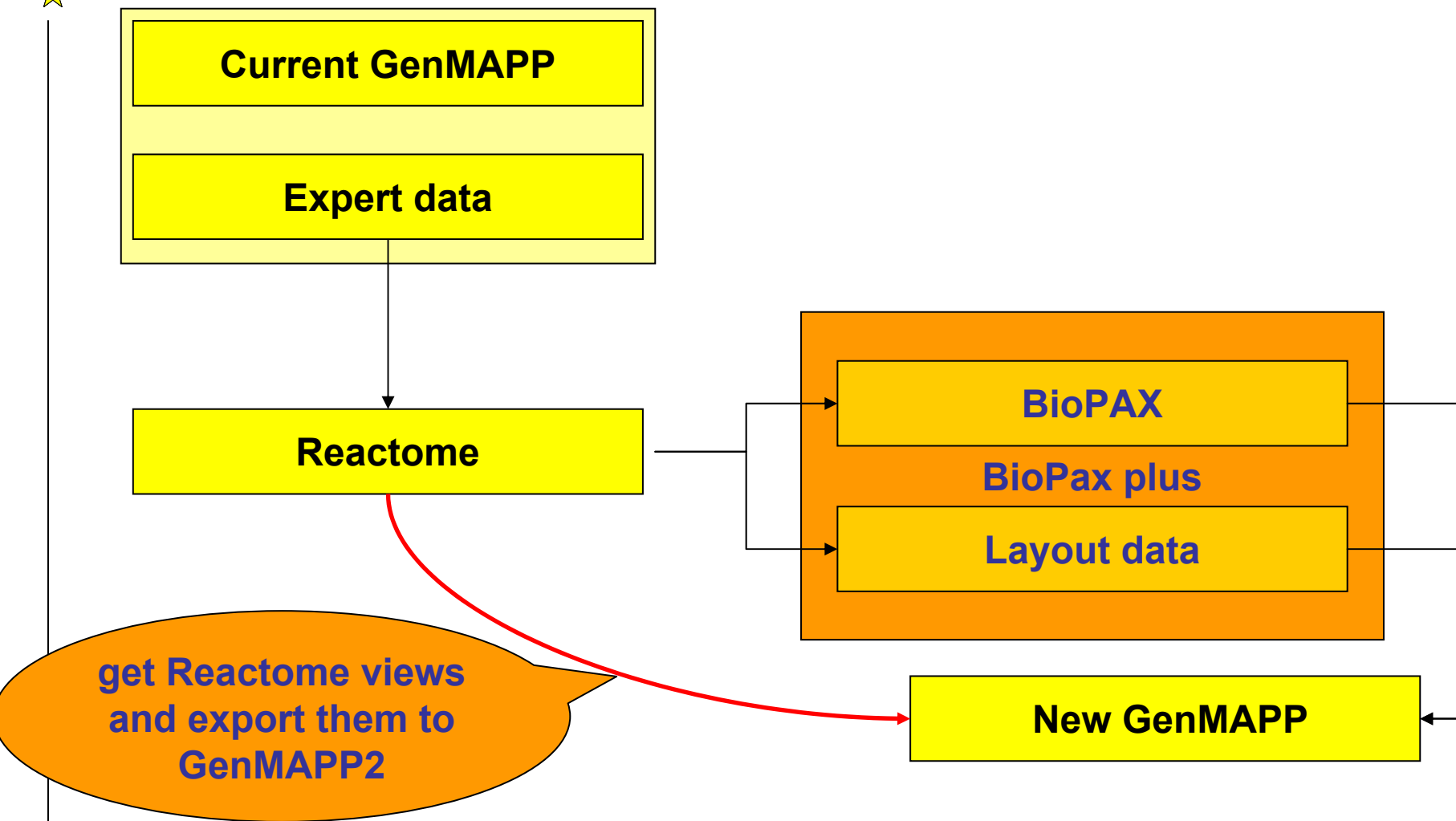
How to store 'NuGO expert pathway information' so that it can be used in a flexible manner?

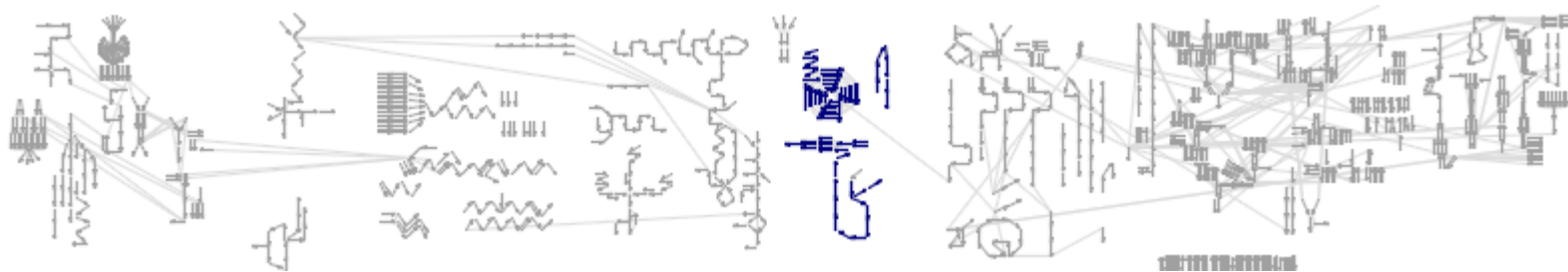
Reactome: reaction database; an international public repository, with a curation team and a peer review system for approval of the pathways

Reactome - a knowledgebase of biological processes



Apoptosis Hsa Mmu Rno Gga Fru Dre	Cell Cycle Checkpoints Hsa Mmu Rno Gga Fru Dre	Cell Cycle, Mitotic Hsa Mmu Rno Gga Fru Dre	DNA Repair Hsa Mmu Rno Gga Fru Dre
DNA Replication Hsa Mmu Rno Gga Fru Dre	Gene Expression Hsa Mmu Rno Gga Fru Dre	Hemostasis Hsa Mmu Rno Gga Fru Dre	Insulin receptor mediated signalling Hsa Mmu Rno Fru Dre





Lipid metabolism pathways

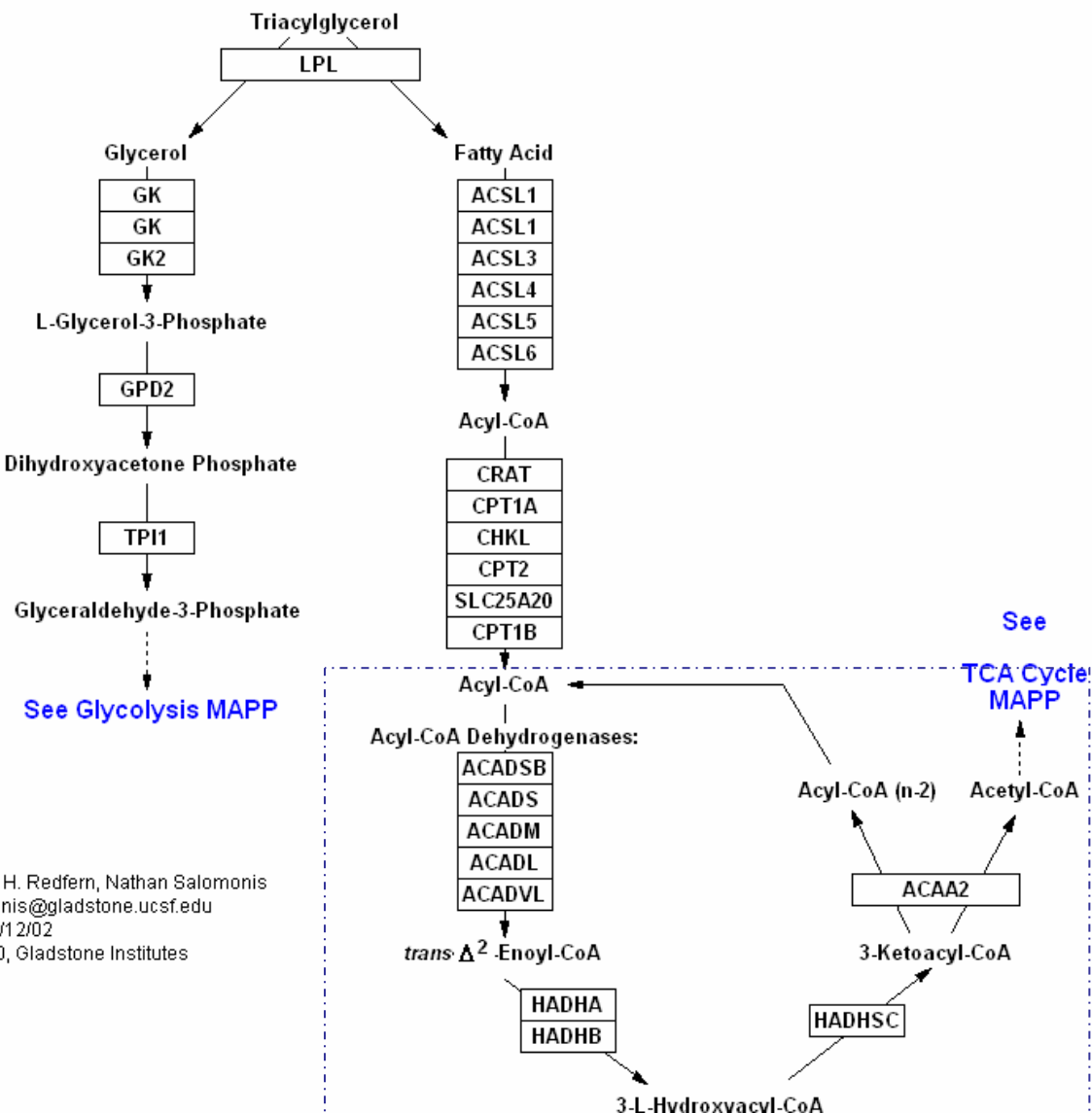
Compare expert pathway, GenMAPP map and pathway in Reactome

No cell compartments, e.g.
mitochondria
Pathway not up-to-date

Reactome:
Focus on
mitochondrial beta-
oxidation

Author: Charles H. Redfern, Nathan Salomonis
E-mail: nsalomonis@gladstone.ucsf.edu
Last modified: 2/12/02
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Fatty Acid Degradation



Reactome (eventbrowser) - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Reload Home Search Favorites Media

Address <http://www.reactome.org/cgi-bin/eventbrowser>

[R](#) [About](#) [TOC](#) [User Guide](#) [Data Model](#) [Schema](#) [Extended search](#) [PathFinder](#) [SkyPainter](#) [Download](#) [Link](#)

Find everything with ALL of the words in Homo sapiens

Found 9 matches:

- ☐ 2,4-dienoyl-CoA reductase, mitochondrial precursor [mitochondrial matrix] **UEGMK**
- ☐ 3,2-trans-enoyl-CoA isomerase, mitochondrial precursor [mitochondrial matrix] **UEGMK**
- ☐ Acyl-CoA dehydrogenase, long-chain specific, mitochondrial precursor [mitochondrial matrix] **UEGM**
- ☐ Acyl-CoA dehydrogenase, medium-chain specific, mitochondrial precursor [mitochondrial matrix] **UEGMM**
- ☐ Acyl-CoA dehydrogenase, short-chain specific, mitochondrial precursor [mitochondrial matrix] **UEGMM**
- ☐ Acyl-CoA dehydrogenase, very-long-chain specific, mitochondrial precursor [mitochondrial matrix] **UEGM**
- ☐ short chain 3-hydroxyacyl-CoA dehydrogenase monomer [mitochondrial matrix] **UEGMKK**
- ☐ Trifunctional enzyme alpha subunit [mitochondrial matrix] **UEGMMM**
- ☐ Trifunctional enzyme beta subunit [mitochondrial matrix] **UEGMMK**

View selected instances as list of display names

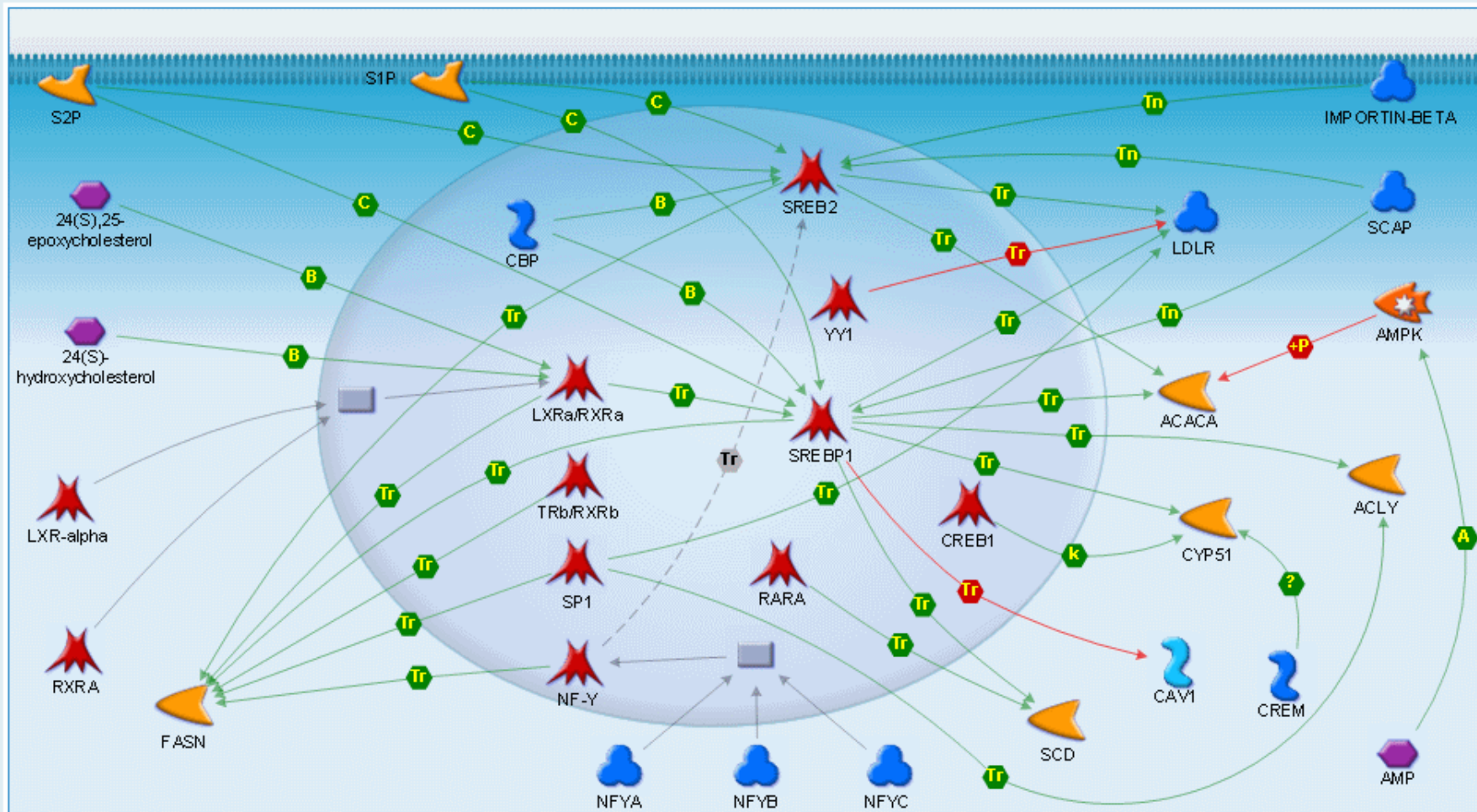
- Transport of fatty acids, e.g. into cell, into mitochondrion
- Transcription regulation of lipid metabolism genes
PPARs
SREBPs
- Pathways / networks around target genes (from literature)

Example: *transcription regulation*

Regulation of lipid metabolism via LXR, NF-Y and SREBP

[View experiments order](#)

[LEGEND](#)



From MetaCore (GeneGO)



- How to get from simple list of genes with significantly changed level of expression to (small) list of significantly effected pathways?

Results Ranked by Z Score and P value

Local Results

Mm_Mitochondrial_fatty_acid_betaoxidation	10/13 76.9%, 13/16 81.2%	z score = 7.128
Mm_Fatty_acid_metabolism	21/47 44.7%, 47/66 71.2%	z score = 6.864
Mm_Fatty_Acid_Degradation	9/16 56.2%, 16/19 84.2%	z score = 5.384
Mm_Fatty_acid_biosynthesis_path_2_	4/4 100%, 4/10 40%	z score = 5.351
Mm_Synthesis_and_degradation_of_ketone_bodies	3/3 100%, 3/7 42.9%	z score = 4.633
Mm_Circadian_Exercise	15/44 34.1%, 44/48 91.7%	z score = 4.467
Mm_Pantothenate_and_CoA_biosynthesis	5/9 55.6%, 9/30 30%	z score = 3.966
Mm_Valine_leucine_and_isoleucine_degradation	9/26 34.6%, 26/44 59.1%	z score = 3.497
Mm_Benzoate_degradation_via_hydroxylation	3/5 60%, 5/47 10.6%	z score = 3.256
Mm_Bile_acid_biosynthesis	8/24 33.3%, 24/43 55.8%	z score = 3.165
Mm_Heme_Biosynthesis	4/9 44.4%, 9/9 100%	z score = 2.948
Mm_Butanoate_metabolism	8/26 30.8%, 26/69 37.7%	z score = 2.895
Mm_Steroid_Biosynthesis	5/13 38.5%, 13/14 92.9%	z score = 2.887
Mm_Arginine_and_proline_metabolism	9/34 26.5%, 34/85 40%	z score = 2.547
Mm_Tryptophan_metabolism	12/53 22.6%, 53/100 53%	z score = 2.336
Mm_Lysine_degradation	8/31 25.8%, 31/69 44.9%	z score = 2.316
Mm_gamma_Hexachlorocyclohexane_degradation	8/33 24.2%, 33/51 64.7%	z score = 2.115
Mm_Fatty_Acid_Synthesis	3/9 33.3%, 9/11 81.8%	z score = 1.93
Mm_Alkaloid_biosynthesis_I	2/5 40%, 5/38 13.2%	z score = 1.891
Mm_Complement_Activation_Classical	4/15 26.7%, 15/16 93.8%	z score = 1.705

MAPPFinder:
Pathways ranked by z-score

Nu

Path
differ

MetaCore (commercial program for pathway analysis)

Maps list - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Home Search Favorites Media

Address http://localaccess.genego.com/cgi/view_maps.cgi?filter=GeneSpring#s_110

Maps

MetaCore (new version): Pathways ranked by p-value

Statistic for genes

Check all

Uncheck all

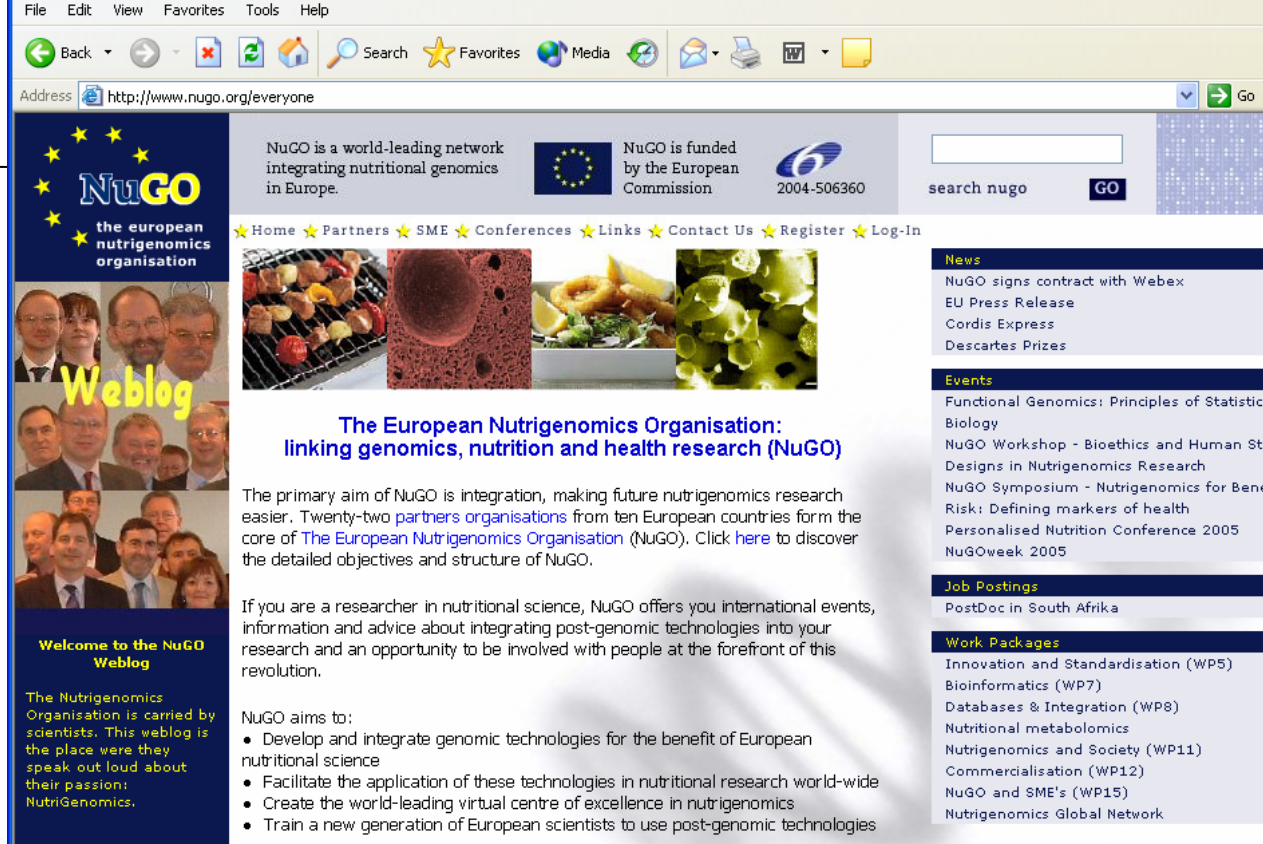
Invert

#	Folder Map name	Processes	p-Value	Expressed	All	Ratio	Ex
1.	Cell signaling/Cell cycle control	cell cycle	7.075e-08				
1.	Cdc25 Regulation of Cell Cycle		5.122e-08	9	54	16.67%	
2.	Cell Cycle Regulation by Brca1		1.540e-05	6	39	15.38%	
3.	Anaphase Promoting Complex (APC) Regulation		8.272e-05	6	52	11.54%	
4.	DNA Damage Responses Involved In Inhibition Of CDK1 During G2		1.354e-04	5	36	13.89%	
5.	ATM signaling		6.421e-03	4	53	7.55%	
6.	Role of ATM, cdc25 and Chk in response to DNA damage		7.866e-03	5	88	5.68%	
7.	S-phase DNA Damage Response		9.918e-03	4	60	6.67%	
8.	Regulatory Cascade of Cyclin Gene Expression		5.116e-02	2	26	7.69%	
2.	Function groups/Growth factors	intracellular receptor-mediated signaling pathway	5.920e-05				
1.	Signaling pathway mediated by PDGF		7.798e-03	4	56	7.14%	
2.	Epidermal Growth Factor signaling pathway		8.297e-03	4	57	7.02%	
3.	EGFR signaling via RAS-family GTPases		8.356e-03	3	30	10.00%	
4.	TGF-beta Receptor Signaling		9.918e-03	4	60	6.67%	
5.	ERBB-family signaling		3.295e-02	3	50	6.00%	
6.	HGF signaling pathway		4.787e-02	3	58	5.17%	
7.	IGF-RI signaling		8.051e-02	3	72	4.17%	
8.	Cross-talk VEGF and angiopoietin 1 signaling		9.937e-02	2	38	5.26%	
9.	VEGF signaling and activation		1.175e-01	2	42	4.76%	

- What are the methods available / used for calculating statistical significance of pathways in microarray datasets?
- Also fit for other nutritional genomics (systems biology) studies?
- Which of these methods do we want to implement or can we implement?
- Develop own tools for assessing statistical significance of pathways in microarray datasets?

NuGO

www.nugo.org



File Edit View Favorites Tools Help

Address <http://www.nugo.org/everyone>

NuGO
the european nutrigenomics organisation

NuGO is a world-leading network integrating nutritional genomics in Europe.

NuGO is funded by the European Commission

2004-506360

search nugo **GO**

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Weblog

The European Nutrigenomics Organisation: linking genomics, nutrition and health research (NuGO)

The primary aim of NuGO is integration, making future nutrigenomics research easier. Twenty-two [partners organisations](#) from ten European countries form the core of [The European Nutrigenomics Organisation \(NuGO\)](#). Click [here](#) to discover the detailed objectives and structure of NuGO.

If you are a researcher in nutritional science, NuGO offers you international events, information and advice about integrating post-genomic technologies into your research and an opportunity to be involved with people at the forefront of this revolution.

Welcome to the NuGO Weblog

The Nutrigenomics Organisation is carried by scientists. This weblog is the place where they speak out loud about their passion: **NutriGenomics**.

News

- NuGO signs contract with Webex
- EU Press Release
- Cordis Express
- Descartes Prizes

Events

- Functional Genomics: Principles of Statistical Biology
- NuGO Workshop - Bioethics and Human Studies in Nutrigenomics Research
- NuGO Symposium - Nutrigenomics for Better Health
- Risk: Defining markers of health
- Personalised Nutrition Conference 2005
- NuGOweek 2005

Job Postings

- PostDoc in South Africa

Work Packages

- Innovation and Standardisation (WP5)
- Bioinformatics (WP7)
- Databases & Integration (WP8)
- Nutritional metabolomics
- Nutrigenomics and Society (WP11)
- Commercialisation (WP12)
- NuGO and SME's (WP15)
- Nutrigenomics Global Network

People involved:

Duccio Cavalieri (Un of Firenze), Rob Stierum (TNO), Chris Evelo (BiGCaT), Rachel van Haaften (BiGCaT), Philippe Rocca-Serra (EBI), Sander Kersten (WUR)