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ENDOGENOUS METABOLIC PROFILING AS A FUNDAMENT FOR PERSONALIZED THERANOSTICS

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About AcureOmics AB

- **Founded September 2007**, Umeå, Sweden
- **SME** participating in several EU funded projects/collaborations
- Core expertise
  - **Chemometrics**
    - Philosophy
    - Applications
  - **Metabolomics**
    - Planning experiments
    - Metabolic profiling – Metabolomics platform
    - Multivariate data analysis
    - Workshops/Courses in “omics” related to biological systems

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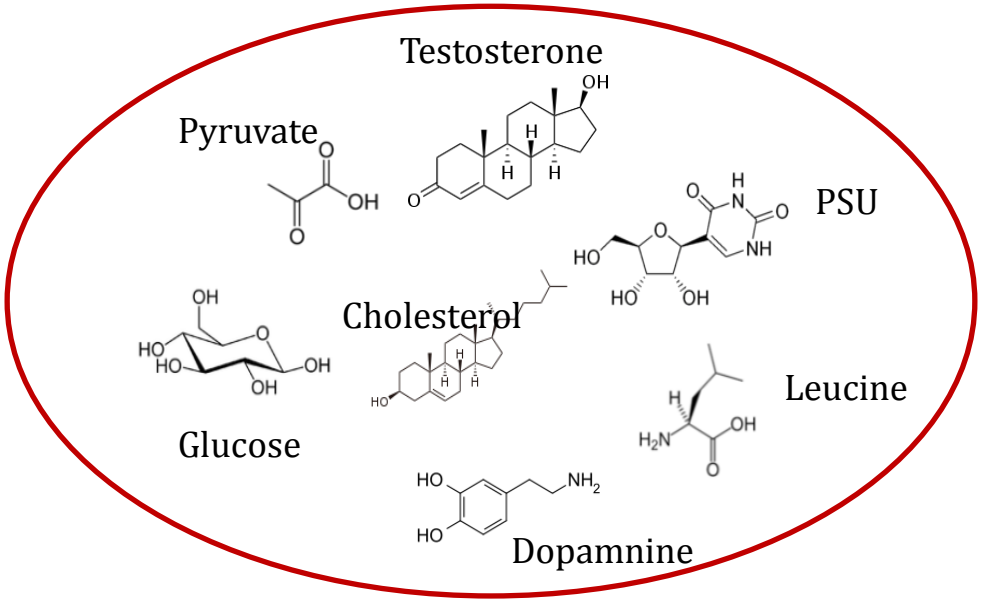
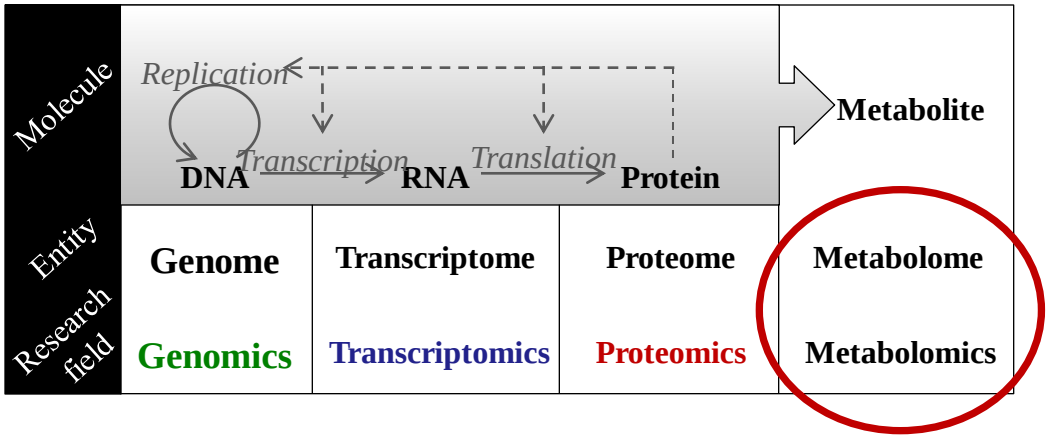
METABOLOMICS

Detailed studies of the ”metabolome”





Genotype → **Phenotype**

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Chemometrics

extract information when studying complex systems

Define the aim

- What do we want?
- What is known already / what more knowledge is needed?

Selection of objects (samples, time points, experiments)

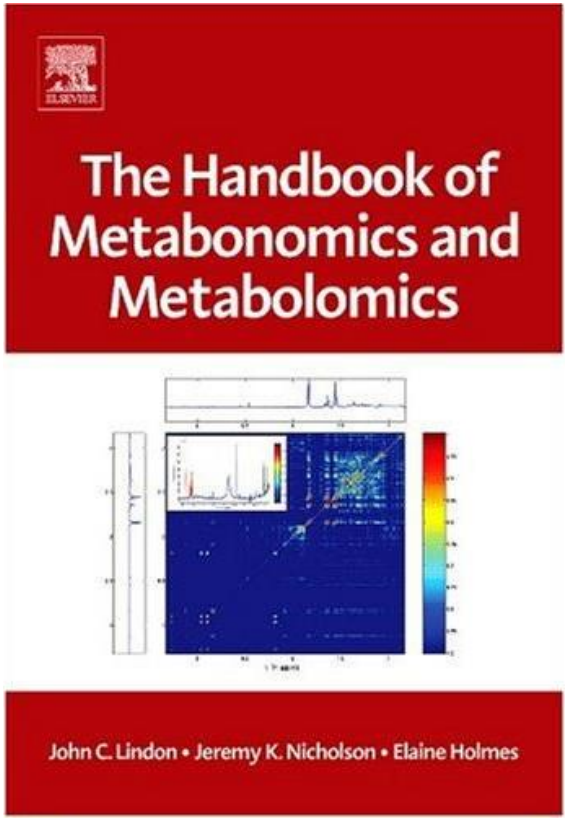
- Design of Experiments (DOE)
- Multivariate design (MVD)

Sample preparation and characterisation

- Experimental protocol (*e.g.* GCMS, Microarray)
- Data processing (*e.g.* normalisation)

Evaluation/Validation of collected data

- Exploratory analysis
- Interpretation & Visualization



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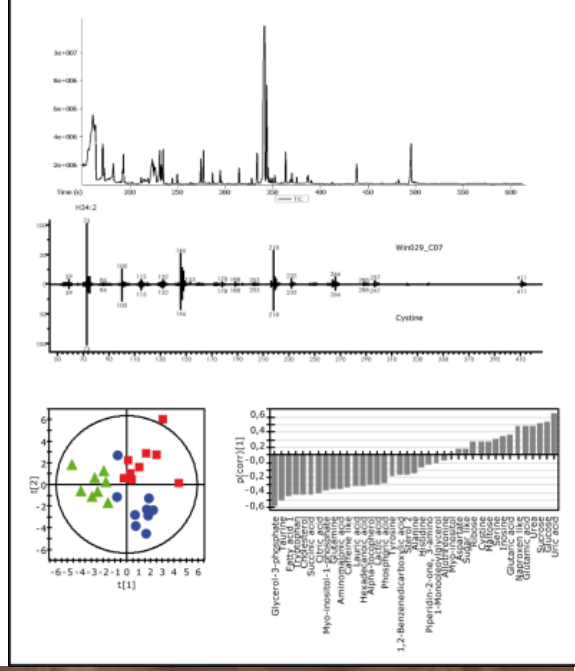
Mass spectrometry based metabolomics platform

One of Europe's best equipped laboratories

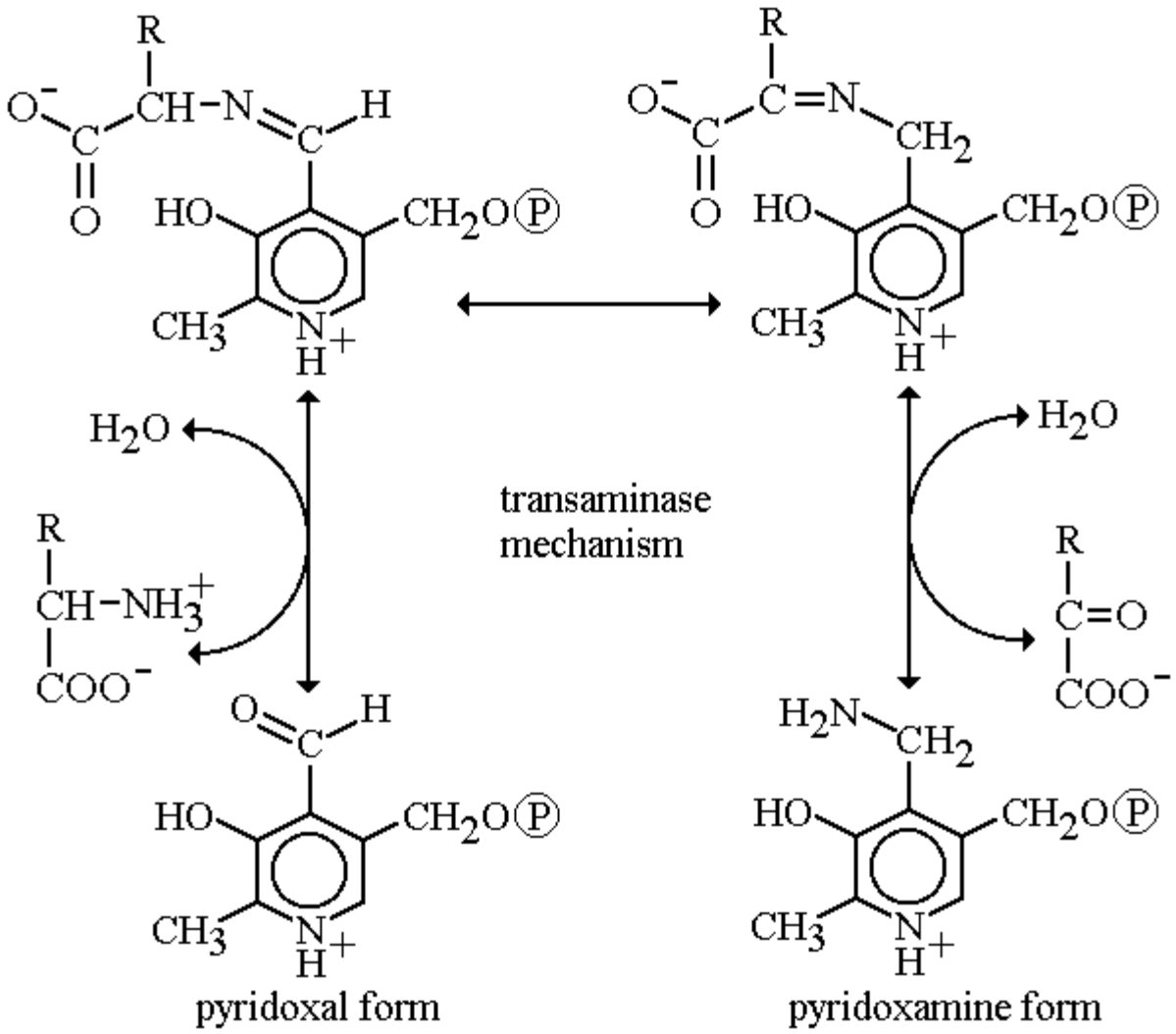
Chromatogram generation
Metabolite identification
Modelling
Biochemistry
Pathways analysis



RA: Comparison of the human case and animal models

- Great overlap of metabolites between humans and animals
  - Different metabolites show overlap in different animal models
  - Allows for identification of relevant animal models
  - Selection of model system for treatment studies

BM	Human Rheumatoid Arthritis	Mouse Collagen Induced Arthritis	Rat Adjuvant Induced Arthritis	Mouse Collagen Induced Arthritis
Aspartate	↓	na	na	↑
myo-insoitol	↑	?	?	na
Alpha-tocopherol	↑	↓	↓	na
Phosphoric acid	↑	0/↓	↓	↑
Proline	↓	na	na	↓
Ornithine	↓	↓	↓	↓
Tyrosine	↓	↓	↓	↓
Glycine	↓	↓	↑	↑
Valine	na	↓	↓	↓
Glyceric acid	↓	↑	↑	↑
Isoleucine	↓	0/↓	↓	↓
Phenylalanine	↑	na	na	↓
Asparagine	↓	↓	↓	↑
Lysine	↓	↓	?	↑
Serine	↓	↓	↓	↑
Pyroglutamic acid	↓	?	↓	na
Cysteine	na	↓	↓	↓
Cholesterol	↑	↑	↓/?	↓
Tryptophan	↓	↓	↓	↓
Urea	↓	↓/?	↓	↓
Glucose	↑	↑/?	↑	↓
Malic Acid	↓	↓	↓	↓
Hexadecanoic acid	na	↓	↓	↓
Linoleic acid	↑	↓	0/↑	↓
Oleic acid	↑	↓	↓	↑
Creatinine	na	↓	↑	↑
Sterol	↓	na	na	↓
Glycerol-3-phosphate	↓	na	na	↓


transaminase
mechanism
pyridoxal form
pyridoxamine form

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RA: Comparison of therapies in rat AIA model

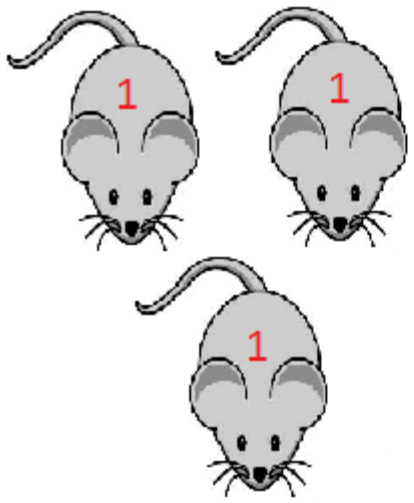
- Metabolites levels are affected by administered therapeutics
  - New drug (X) restore levels in more metabolites compared to MTX*
  - Useful in development of novel drugs
  - Tool in clinical studies to verify therapeutic effect in clinical studies
  - Concomitant development of novel drug and diagnostic test, theranostics?

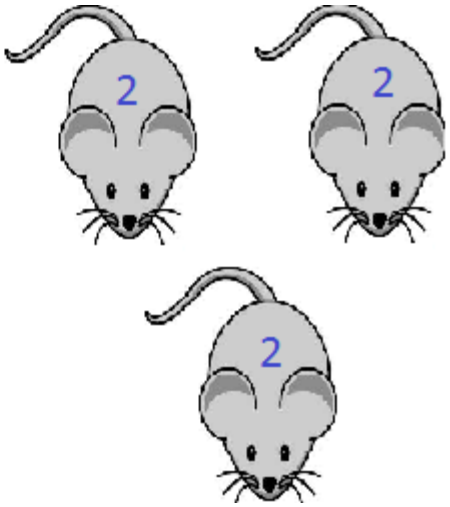
BM	Vehicle	MTX	AP1010	X 1mg	X 3mg	X 10mg
Phosphoric acid	0/↑	↓	↑	↓	0/↓	↓
Ornithine	0/↑/?	0/?	↑	0	↑	↑
Tyrosine	↓	0/↑	↑	0/↑	0/↓	↑
Valine	0	↑	↑	↓	↑	↑
Glyceric acid	↑	↑	↓	↑	↑	↑
Isoleucine	0	0/↓	↑	↓	0/↓	↑
Phenylalanine	0/↓	↑	↑	0/↓	↑	↑
Asparagine	↑	0/↑	↑	0/↓	↑	0/↑
Lysine	↑	0/?	?	↑	↑	↑
Serine	0/↑	↑	↓	0/↓	↑	↑
Pyroglutamic acid	0	↓	0/↑/?	↑	↑	↓
Cysteine	↓	↓	↑	↓	↓	↓
Cholesterol	↓	↓	↑	↓	0/↑	0/↑
Tryptophan	↓	↓	↑	↓	↓	↓
Malic Acid	↑	↑	↑	0/↑	↑	↑
Hexadecanoic acid	↓	0/↓	↓	↓	↓	↓
Linoleic acid	↓	↓	↓	↓	↓	↓
Oleic acid	↓	↓	↓	↓	↓	↓
Creatinine	↑	↑	↑	↑	↑	↑

*MTX, methotrexate

Introduction

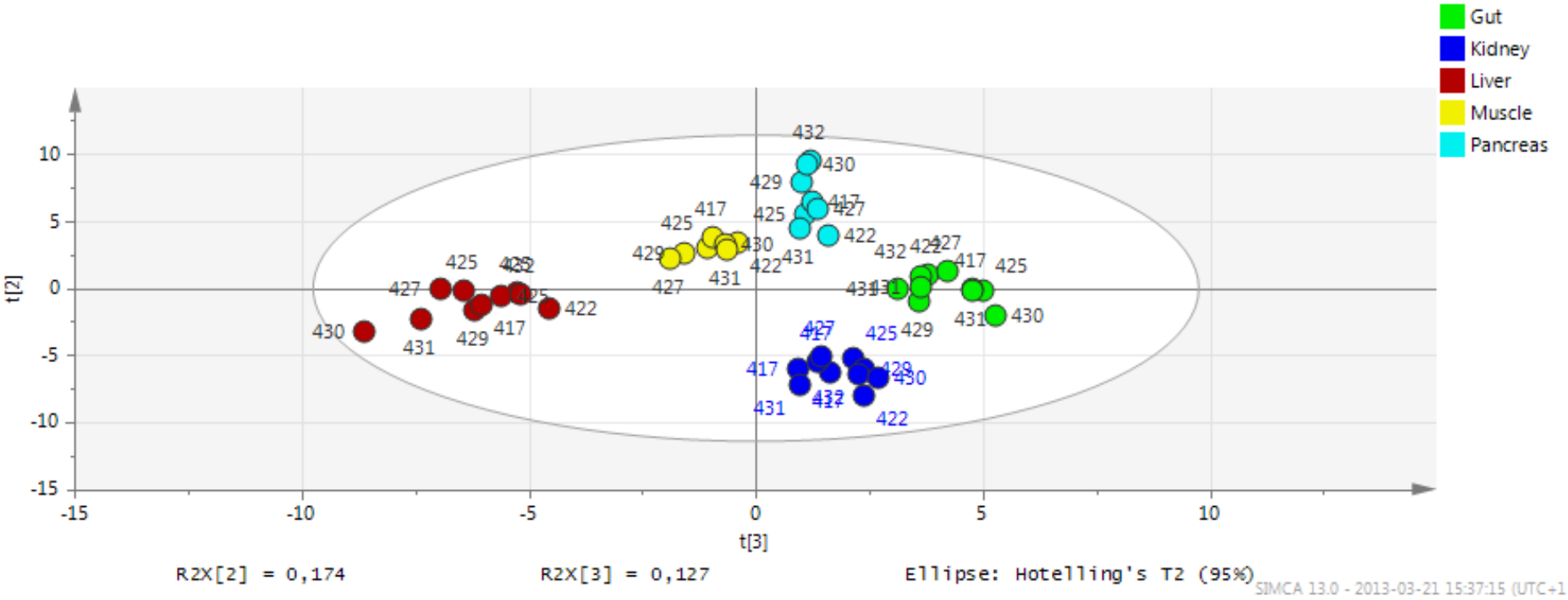
- MODY5 - Maturity onset diabetes of the young
- Heterogeneous mutants (HNF1b+/–)
- Plasma samples day 1, 3 and 5
- Urine and Feces collected each day.
- Compartments
  - Gut
  - Kidney
  - Liver
  - Muscle
  - Pancreas
- Divided into Group 1 and 2





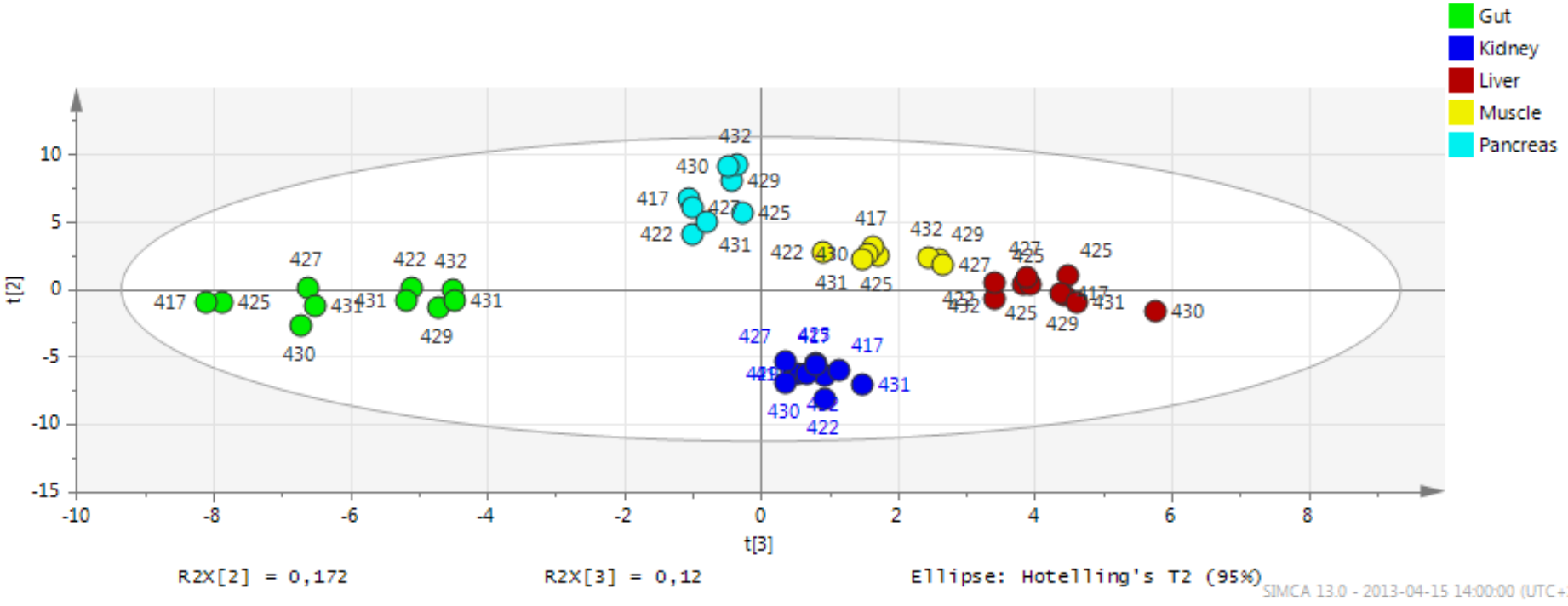
PCA

- Principal component analysis (PCA)
- Model of the greatest separation between observations
- PCA Score plot, five different compartments, group 1 samples



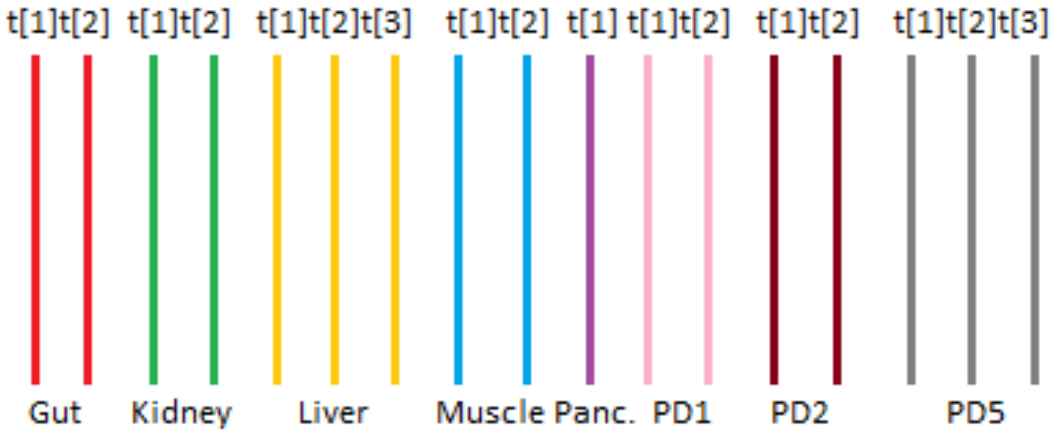
PLS

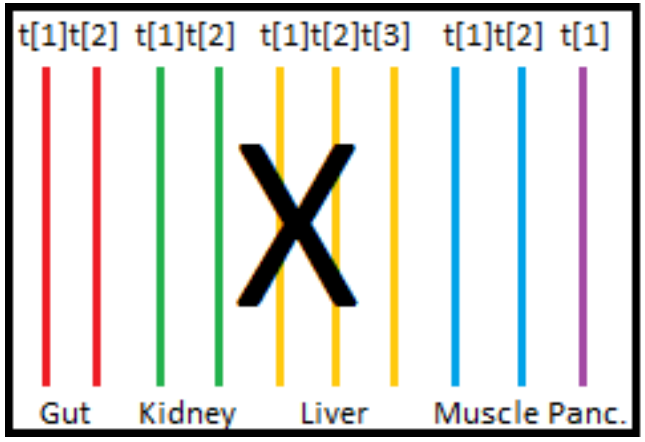
- Partial least squares projection to latent structures (PLS)
- Model of maximum covariation between X and Y
- Quantitative relationship between X and Y
- PLS Score plot five different compartments, group 1 samples

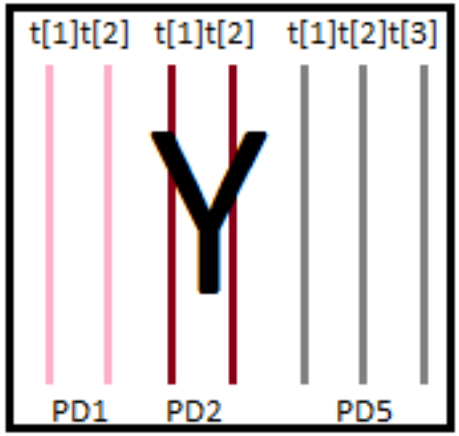


Hierarchical modelling

- Collecting PCA Score vectors
- PLS with Plasma Day1, 3 and 5 as Y vectors

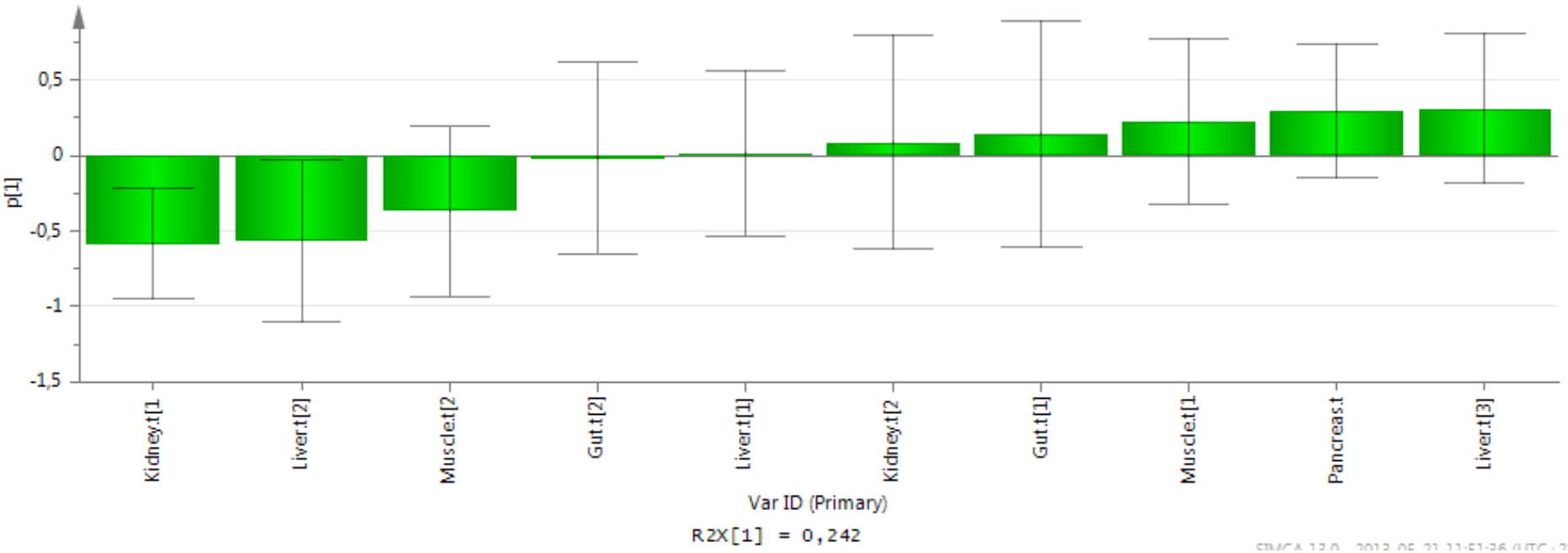






Hierarchical modelling

- Liver and Kidney affect the levels of Plasma metabolites



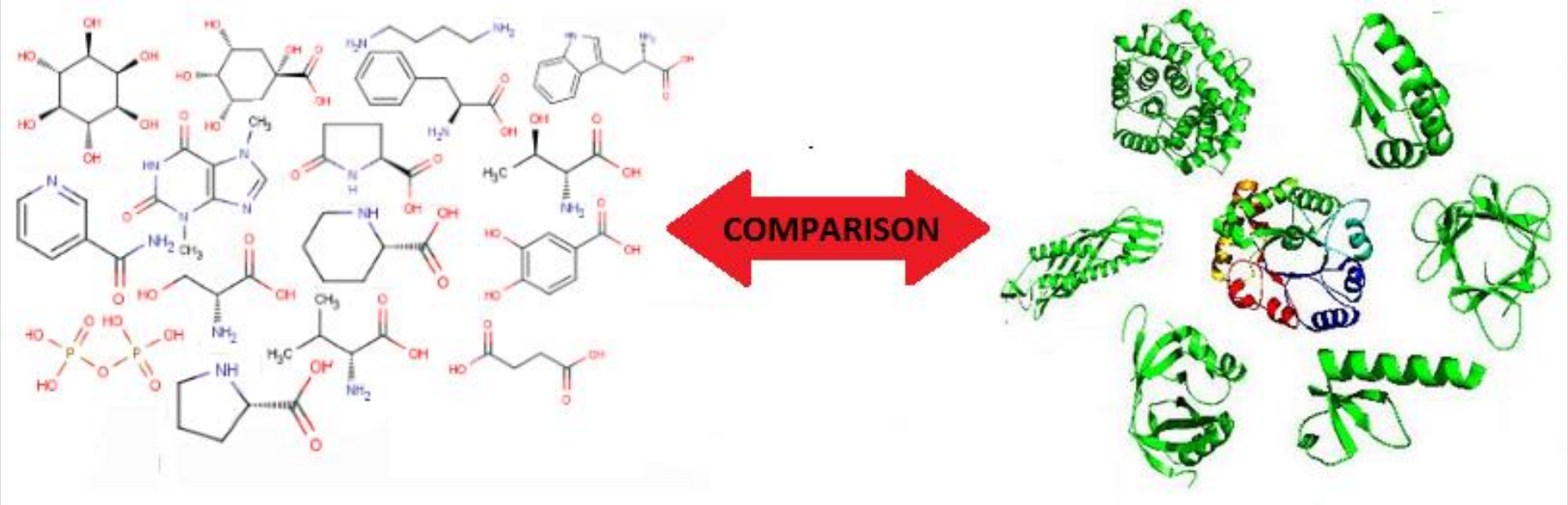
Results

- Liver consumes plasma aromatic amino acids, TCA-cycle metabolites and Cholesterol
- Liver release Xanthine metabolism metabolites and branched amino acids to the plasma.

- Kidney consumes plasma fatty acids, amino acids and carbohydrates
- Kidney releases Cholesterol and AMP to the plasma

Future work

- Metabolomics on Urine samples
- Compare Metabolomics and Proteomics



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Thank you for listening!