CHARITÉ
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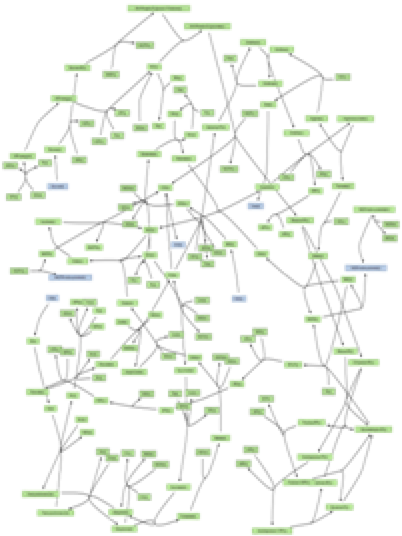
virtual liver
network

ModeScore

Using the flux-balance framework to assess metabolic functions with microarray data

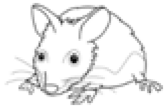


Andreas Hoppe
Institut für Biochemie
Charité – Universitätsmedizin Berlin

COMPUTATIONAL SYSTEMS BIOCHEMISTRY

Outline

- Introduction
- ModeScore method
- TGFβ treatment example
- Statin treatment example



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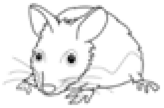
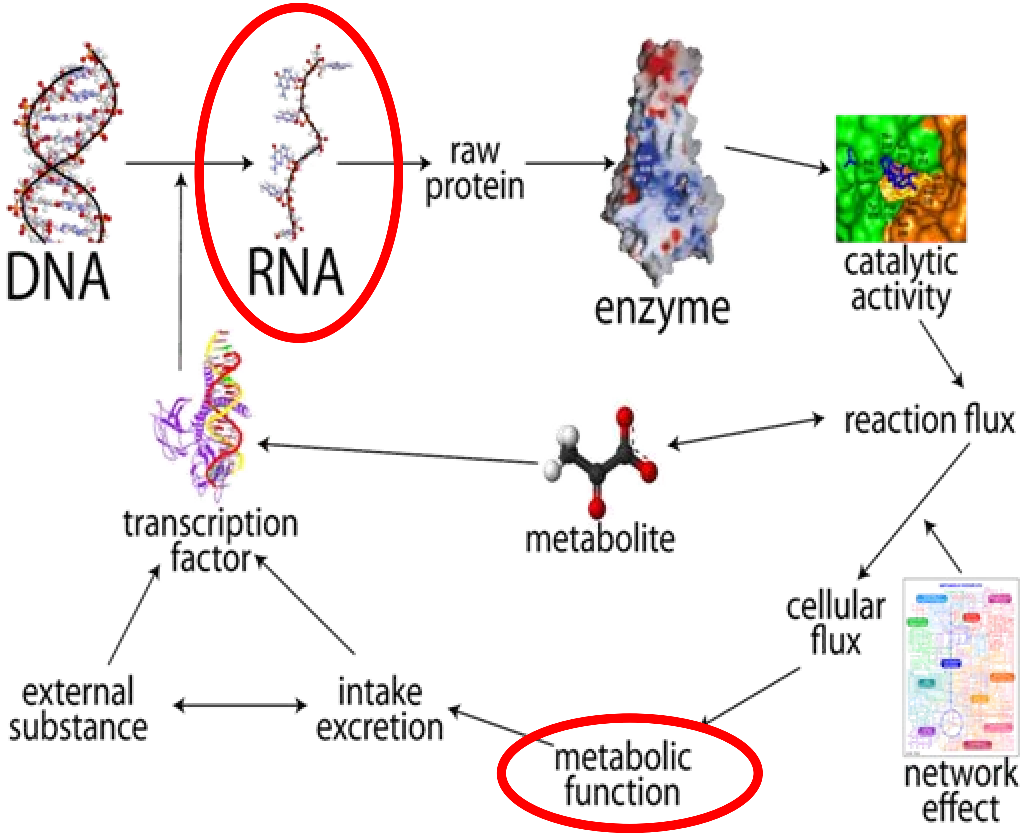


Relating RNA/metabolic functions



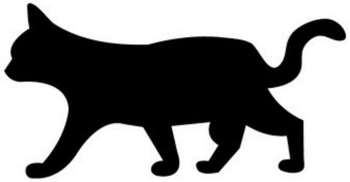
- Many intermediate levels
- many modifying factors
- direct quantitative predictivity low

Gygi et al., 1999, Mol. Cell Biol.

additional information necessary

Hoppe, 2012, Metabolites 2(3).

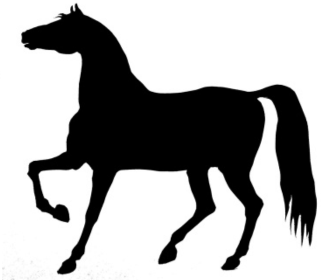
What is this?



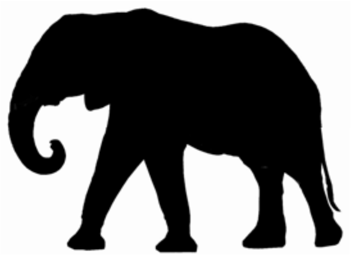
low

low

medium



highest

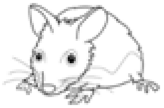


low

Similarity score

Outline

- ○ Introduction
- ○ ModeScore method
- ○ TGFβ treatment example

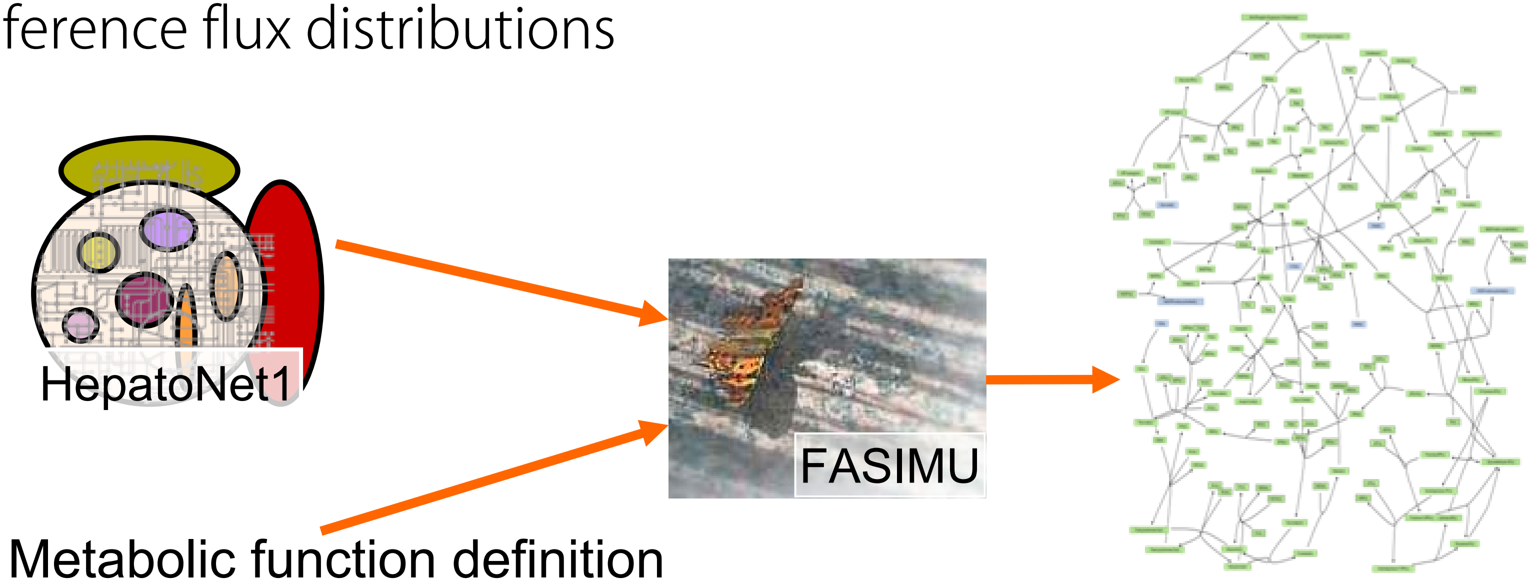


- ○ Statin treatment example

Prediction method

We know
- the way enzymes cooperatively work
- the cell’s metabolic functions

→ reference flux distributions

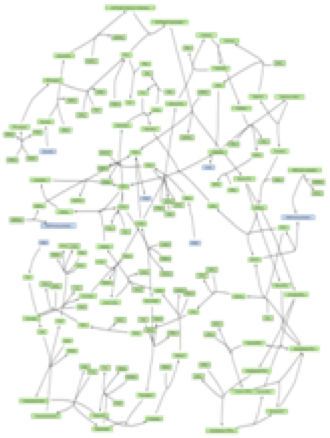


HepatoNet1

FASIMU

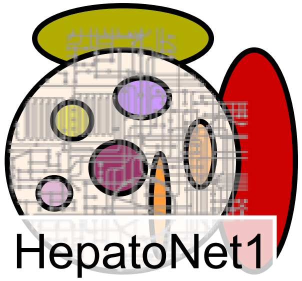
Metabolic function definition

Reference flux mode



Computation of flux distributions

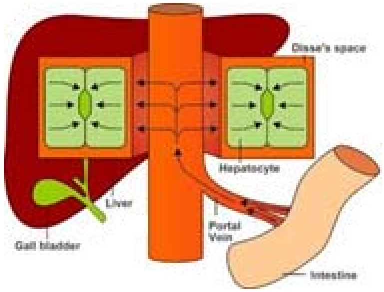
- HepatoNet1
  - Genome-scale Stoichiometric network
  - 2539 reactions, 777 metabolites
  - 8 compartments
  - Gille et al., Mol Syst Biol., (2010) **6**:411.

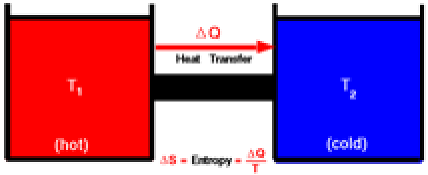


- HepatoNet1b
  - Mouse gene annotations
  - Hoppe et. al., 2012 OASIcs, **26**:1-11. Biomodels MODEL1208060000
- Minimal flux modes
  - elementary functions
  - Hoffmann et al., Genome Informatics, (2006) **17**(1), 195-207.

Computation of flux distributions

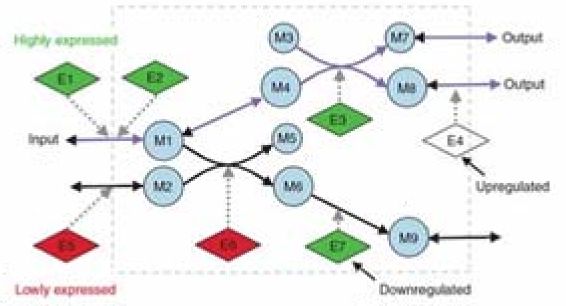
- Functions of hepatocytes
  - main functions: 150/comprehensive set: 1000
  - Hoppe et. al., 2012 OASIcs, **26**:1-11.
- Flux minimization
  - Minimize cellular effort: enzyme, import
  - Holzhütter, Eur J Biochem (2004) **271**, 2905-2922.
- Thermodynamic Realizability
  - Hoppe et al., BMC Syst. Biol., (2007) **1**(1):





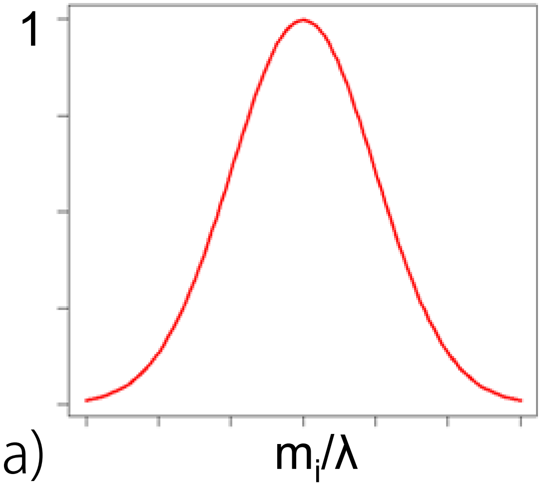
Computation of flux distributions

- Expression-based constraint
  - Shlomi et al., Nat Biotechnol. (2008) **26**(9):1003-10.
  - Huthmacher et al., BMC Syst Biol. (2010) **4**(1):120.



- FASIMU
  - Flexible framework for flux-balance computations
  - Suited for heterogeneous simulation series
  - Hoppe et al., BMC Bioinf., (2011) **12**(1):28.
  - www.bioinformatics.org/fasimu

Prediction method



Assumptions:

- Gene up → flux value up (& vice versa)
- Normal distribution
- Probability maximum: flux/scaling factor λ

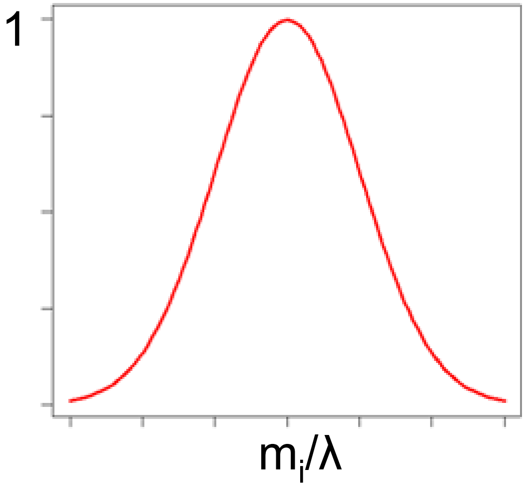
Pattern match

Abundance change — Flux mode

Result

Estimation of function's amplitude of change

Mode set scoring



$\mathsf{Score}(M_k, V) = \frac{\sum_{i \in I_k} w_i \mathsf{score}_i(m_i, v_i)}{\sum_{i \in I_k} w_i}$	total score
$I_k = \{i \mid m_i \neq 0\}$	indices of nonzero values
$w_i = \sqrt{\lvert m_i \rvert \omega_i}$	weights
ω_i	weight adjustment
$\mathsf{score}_i(m_i, v_i) = e^{-\frac{1}{2}\left(2\frac{\lambda v_i - m_i}{\lvert m_i \rvert}\right)^2}$	score component
$M_k = (m_i)_i$	k-th reference mode
$V = (v_i)_i$	relative expression profile
λ chosen such that	$\mathsf{Score}(M_k, V)$ is maximal

ModeScore amplitude *(1/λ)*

- Measures strength of regulation for the function
- Compatible to $\log_2$ fold change
- Cluster point (not average) of gene changes

Contribution scores ($score_i$)

- Measures how good a gene change represents the function's amplitude

ModeScore process

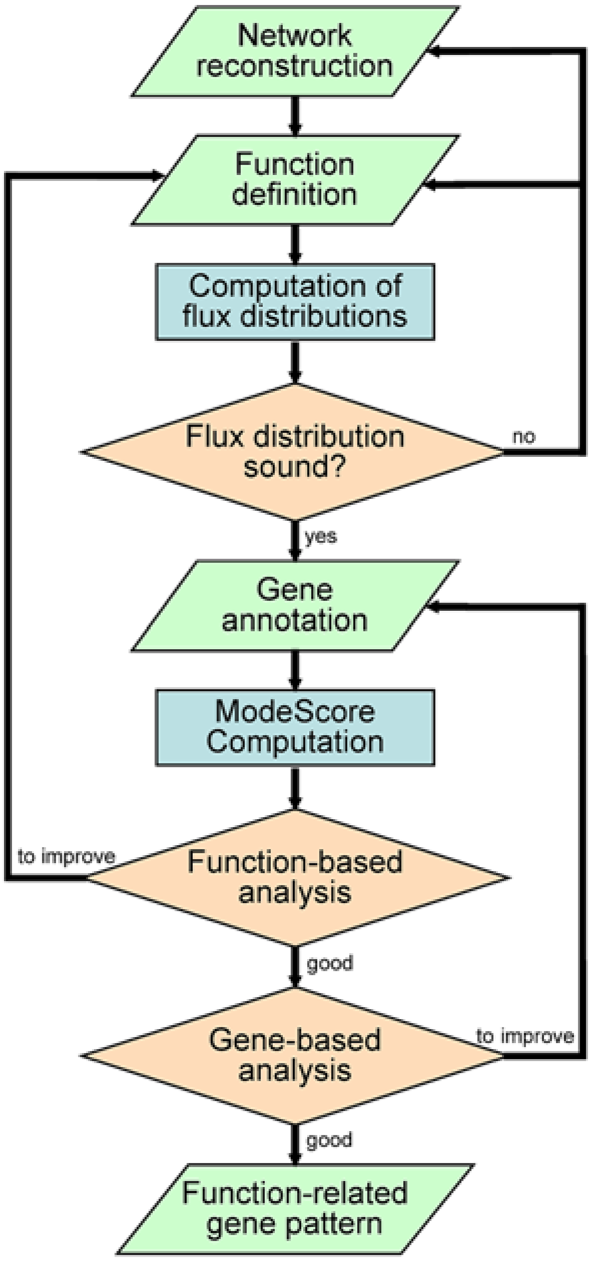
Semi-automatic

- refinement of network, functions, annotations
- scoring/ranking
- manual selection

Selection of changed genes

Testable hypothesis

Hoppe et. al., 2012 OASIcs, **26**:1-11.



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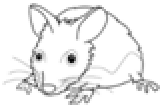
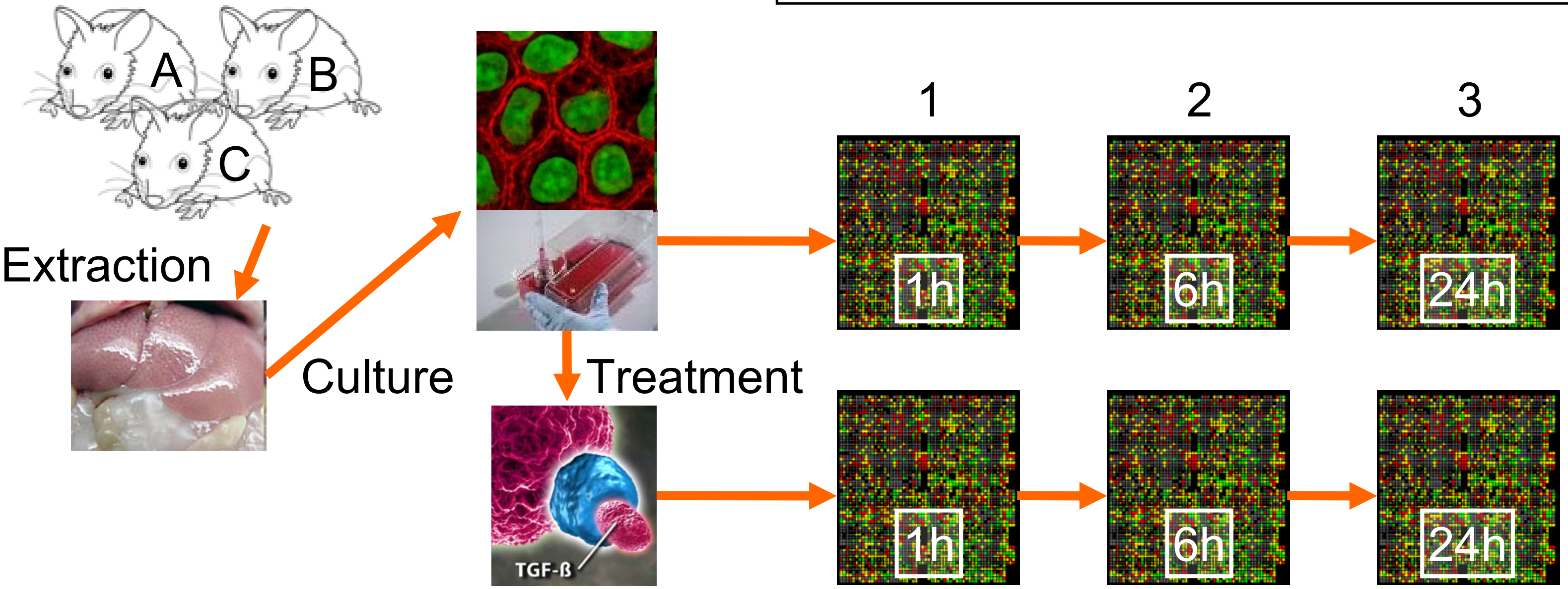


Hepatocyte culture/TGFβ treatment

Iryna Ilkavets
Mannheim

Hoppe et al. 2012, Metabolites **2**(4).
Dooley, 2008, Gastroenterology **135**(2).



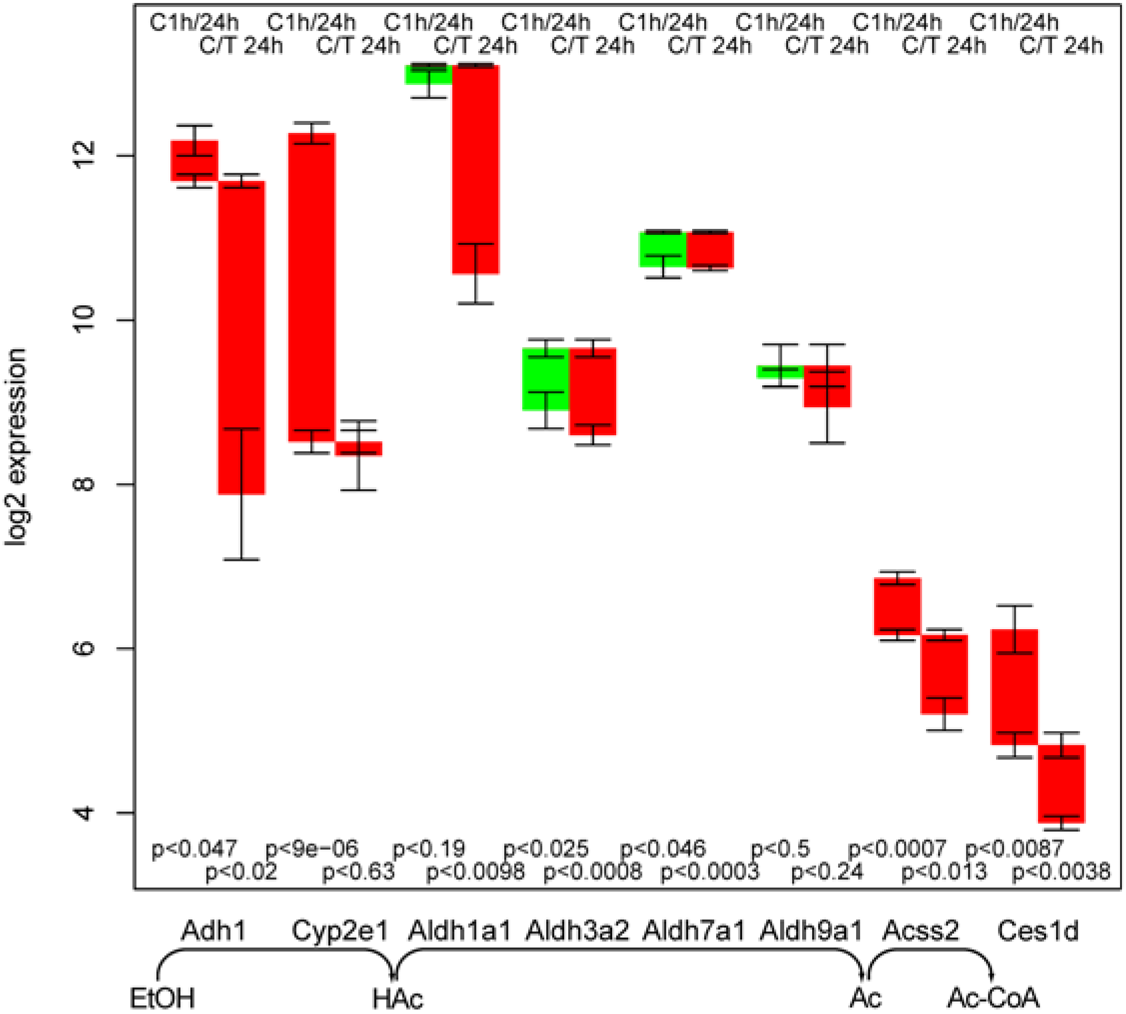
Extraction

Culture

Treatment

1 2 3

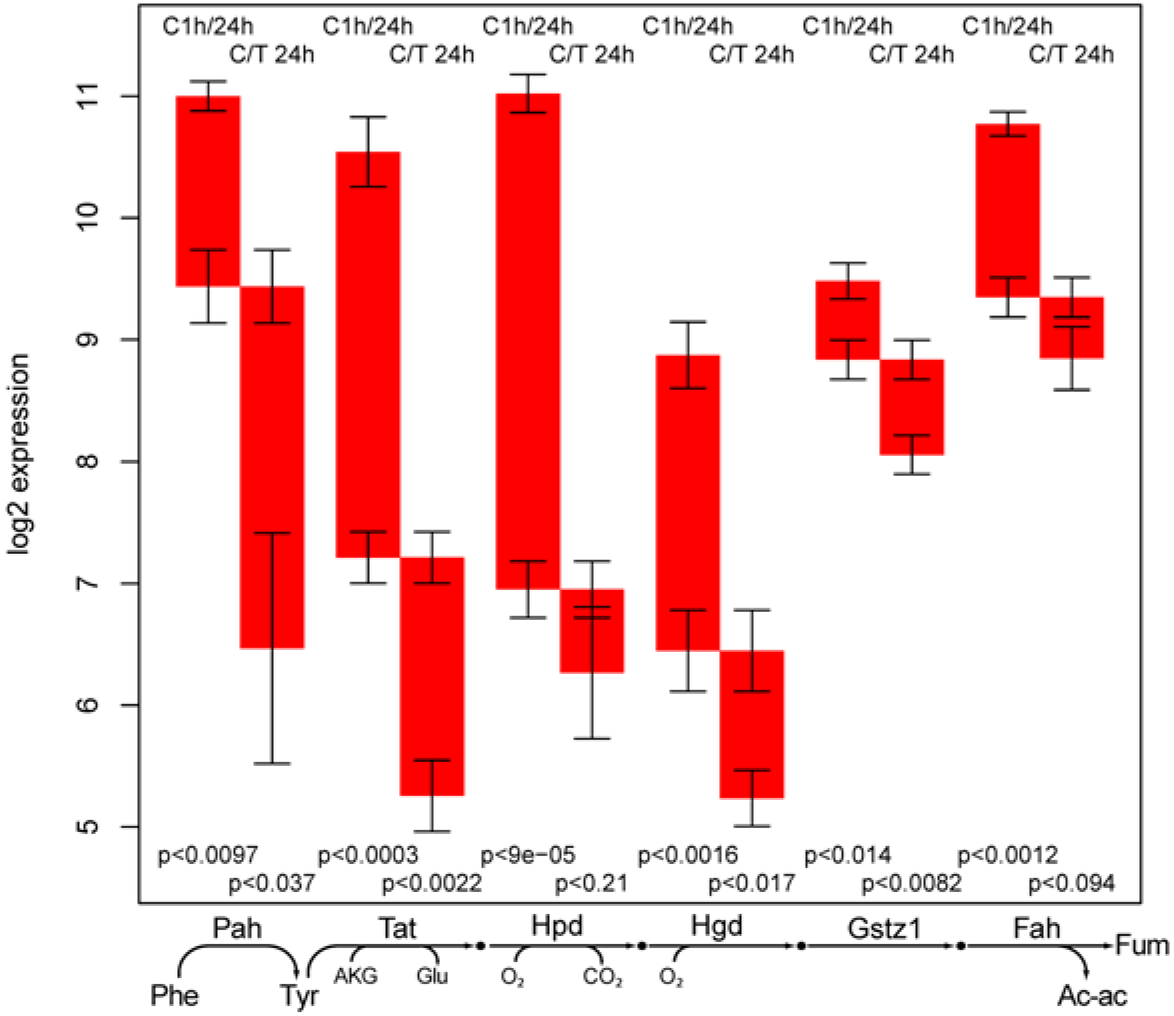
Ethanol degradation



TGFβ down-regulates main isoforms Adh1 Aldh1a1

Isoform

Phenylalanine/Tyrosine degradation



Down-regulation in time

TGFβ enhances

Very consistent

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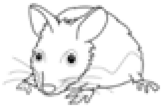
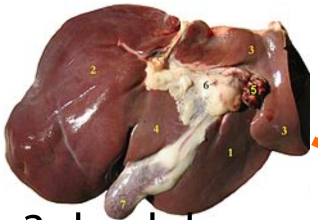


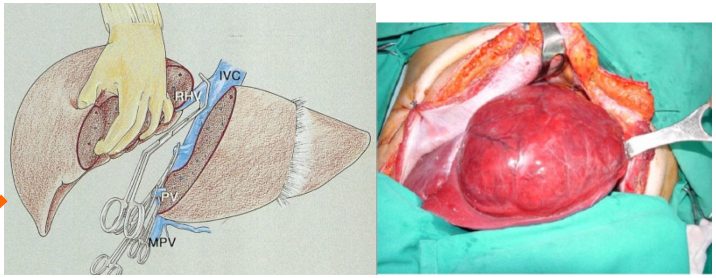
- Statin treatment example

Statin exp.



3 dead donors

A **B** **C**

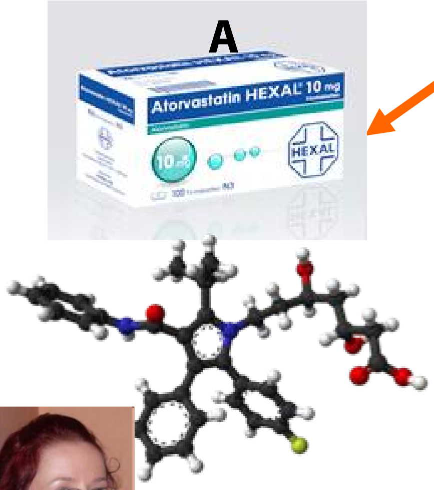


3 donors, lobectomy, liver cancer

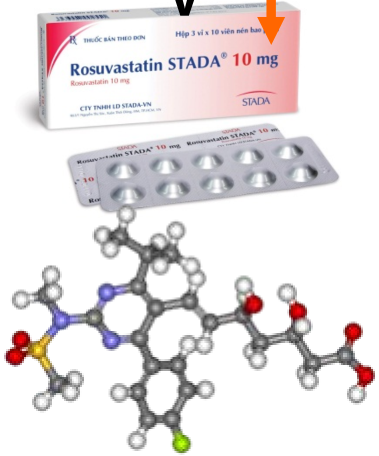
D **E** **F**

cell cultures

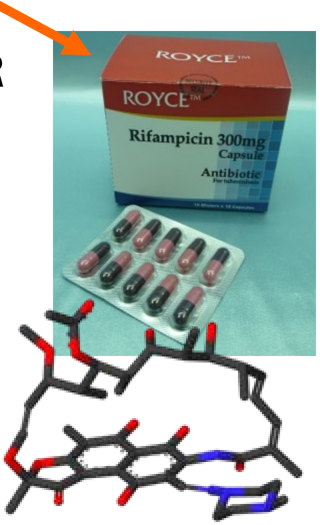
C

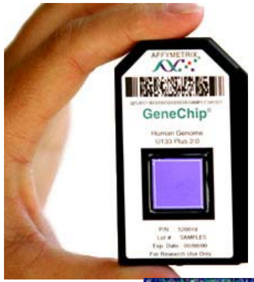


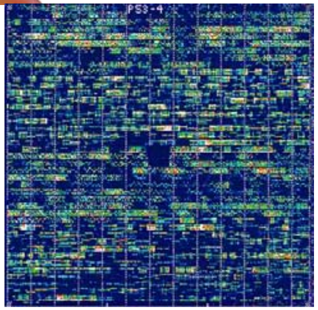
V

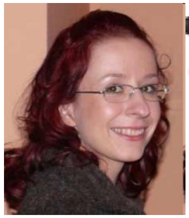


R





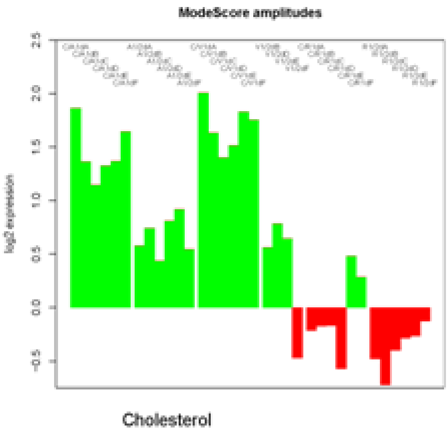




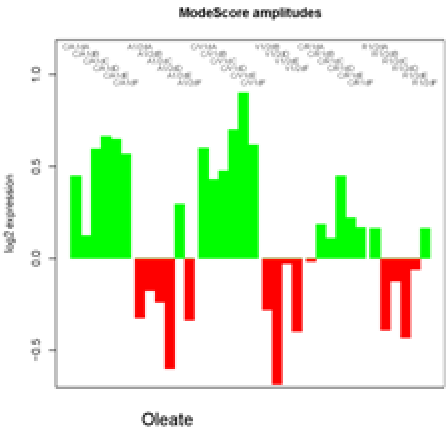
Mateja Hafner
Ljubljana

1d **2d**

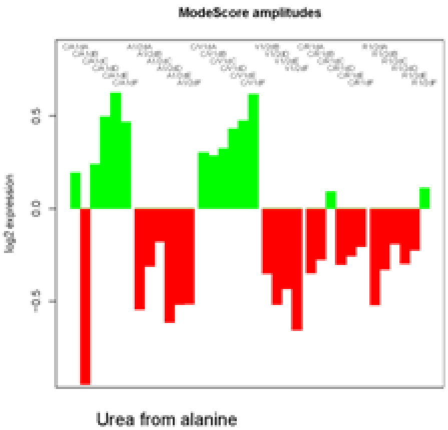
ModeScore analysis, areas of large changes



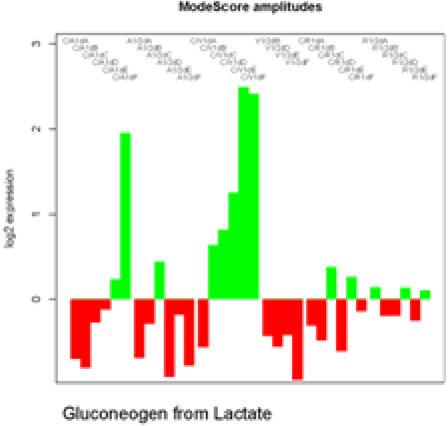
Cholesterol synthesis



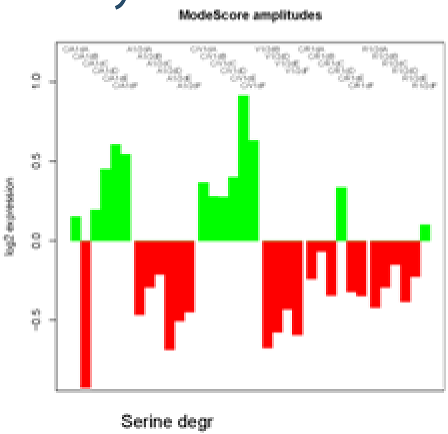
Fatty acid metabolism



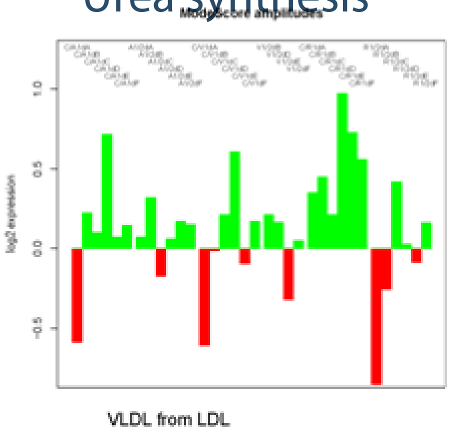
Urea synthesis



Sugar metabolism

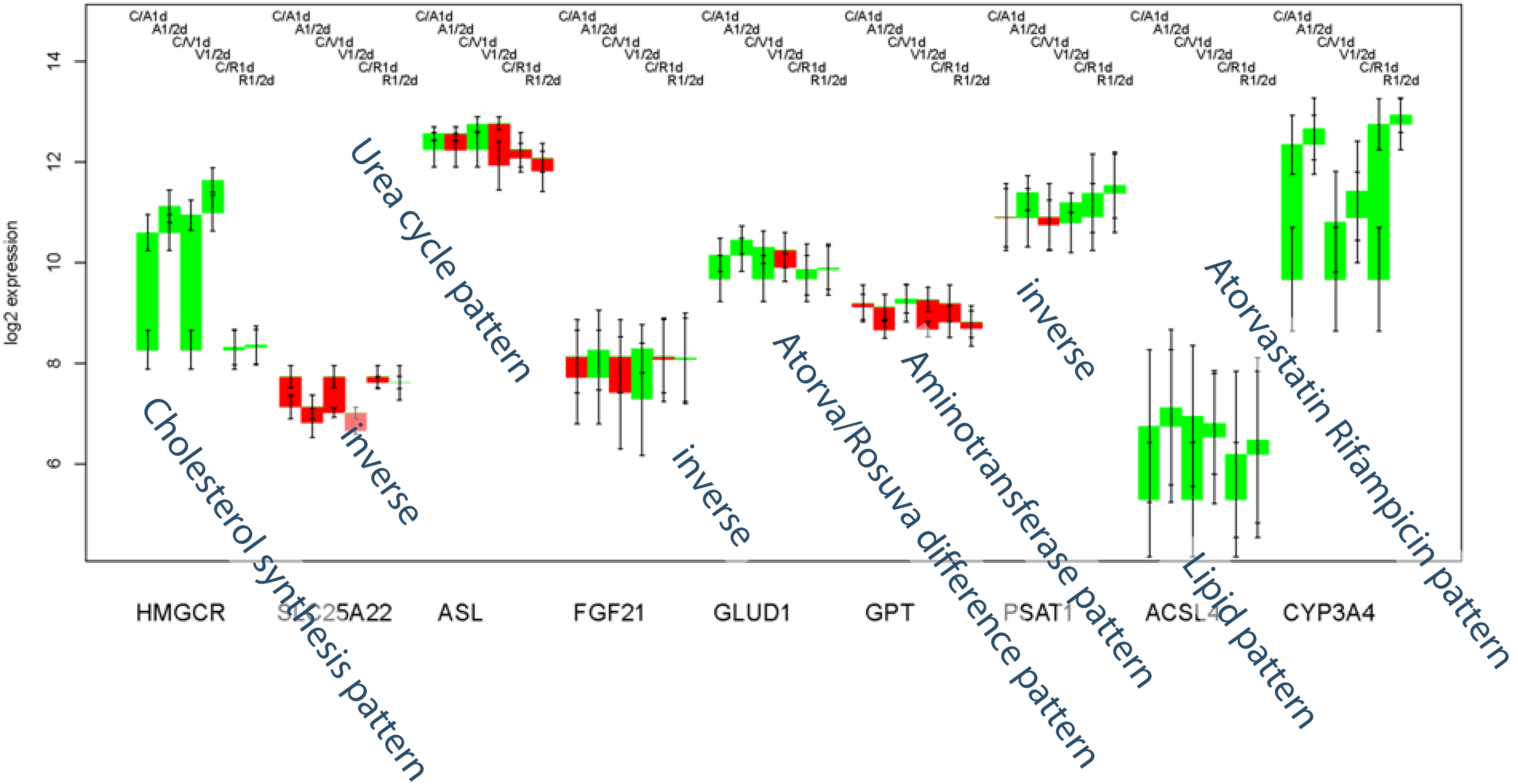


Transamination



Lipoproteins

Patterns of gene changes



Cholesterol synthesis pattern

inverse

Urea cycle pattern

inverse

Atorva/Rosuva difference pattern

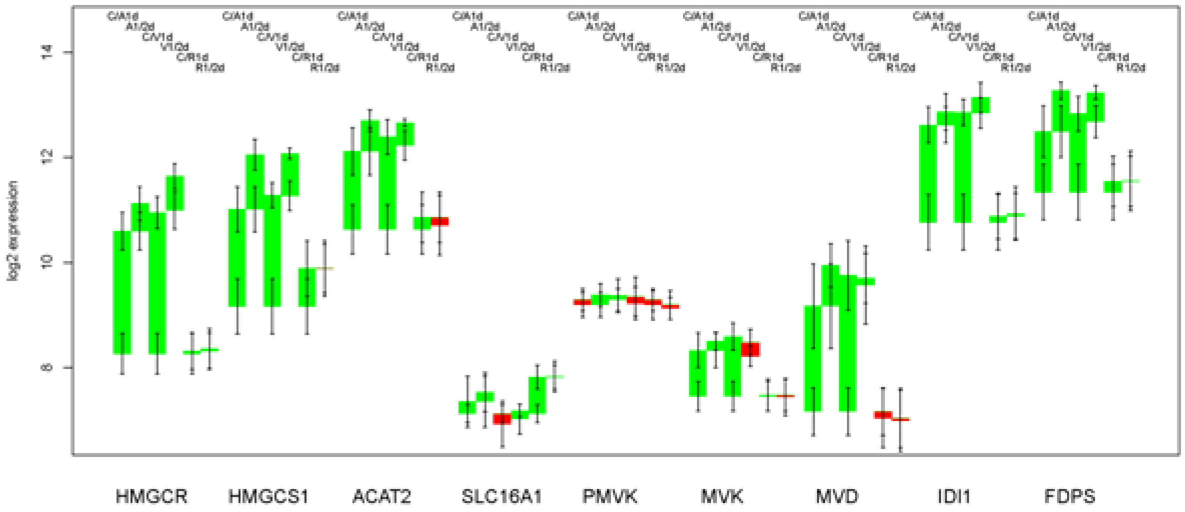
Aminotransferase pattern

inverse

Lipid pattern

Atorvastatin Rifampicin pattern

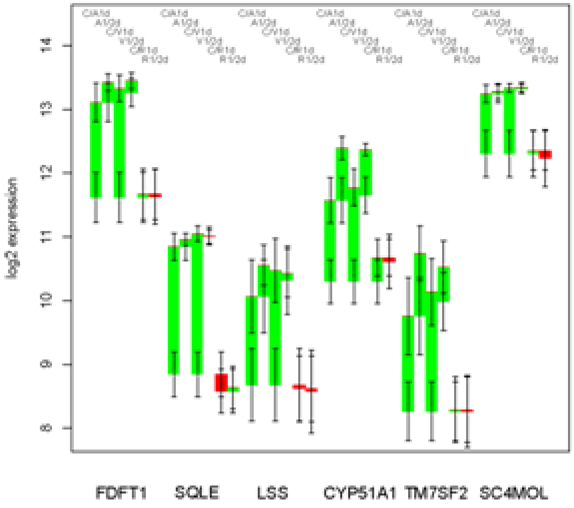
Cholesterol synthesis pattern

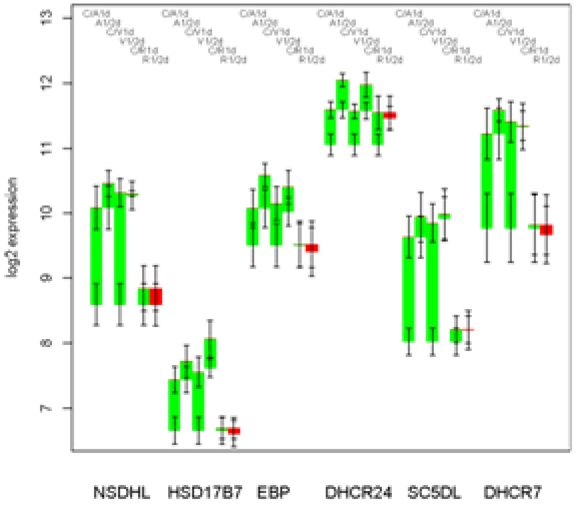


Very consistent

18/21 enyzmes of cholesterol synthesis

Large changes





Pattern definition

Statins:

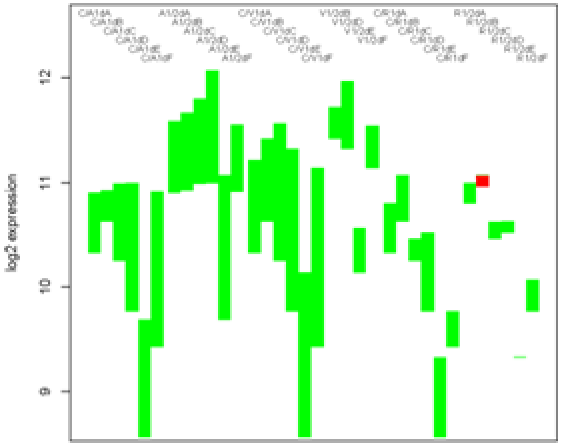
1d strong up

2d (slightly) up

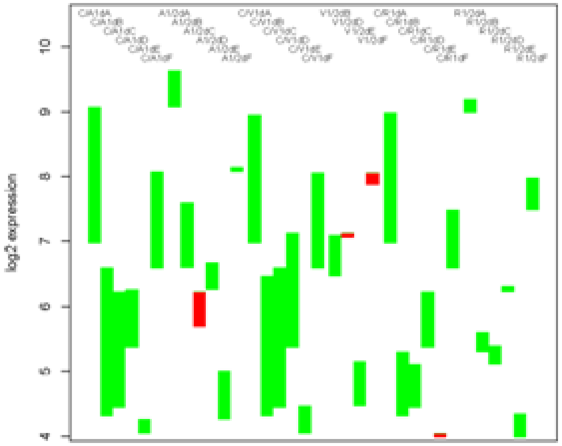
Rifampicin:

minor change

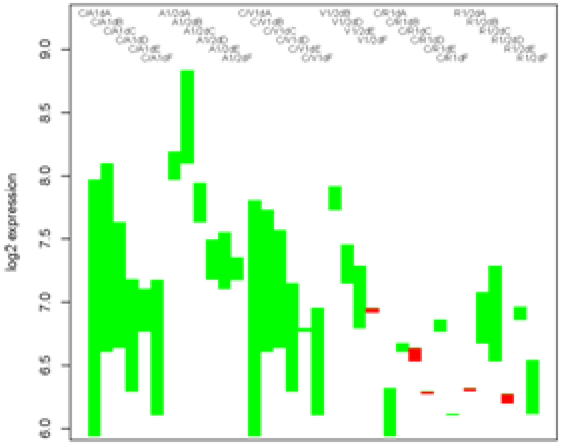
Lipid pattern



SCD δ9 desaturase

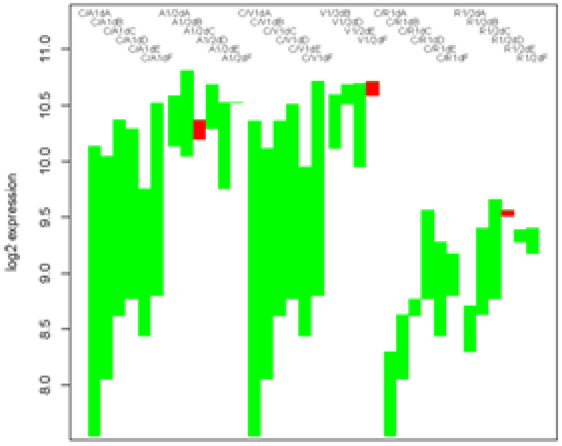


ACSL4 acyl-CoA synthetase



ELOVL2

FA elongases



ELOVL6

Particular enzymes in lipid formation, FA synthesis and degradation

Specific isoforms

Pattern definition

Statins:
- 1d up
- 2d up

Rifampicin:
- up, less than statins

Take-home message

- Gene arrays suitable as hypothesis-finding source
- Flux-balance solutions as scaffold for metabolic function
- ModeScore: prediction of function's regulations
- Hypotheses just based on transcripts:
  - TGFβ, tyrosine degradation down
  - Statins, wide-range regulation effects

Acknowledgements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Steven Dooley
Mannheim


Mateja Hafner
Ljubljana


Damjana Rozman
Ljubljana

www.charite.de/sysbio/people/hoppe
www.bioinformatics.org/fasimu
ModeScore method: Hoppe & Holzhütter, 2012, OASIcs, **26**.
Review on transcript data use: Hoppe, 2012, Metabolites **2**(4).

Implementation

- ModeScore computation
  - data handling: bash/gawk
  - scaling factor optimization: octave
  - table generation: LaTeX
  - bargraphs, t-test: R

virtual liver
network
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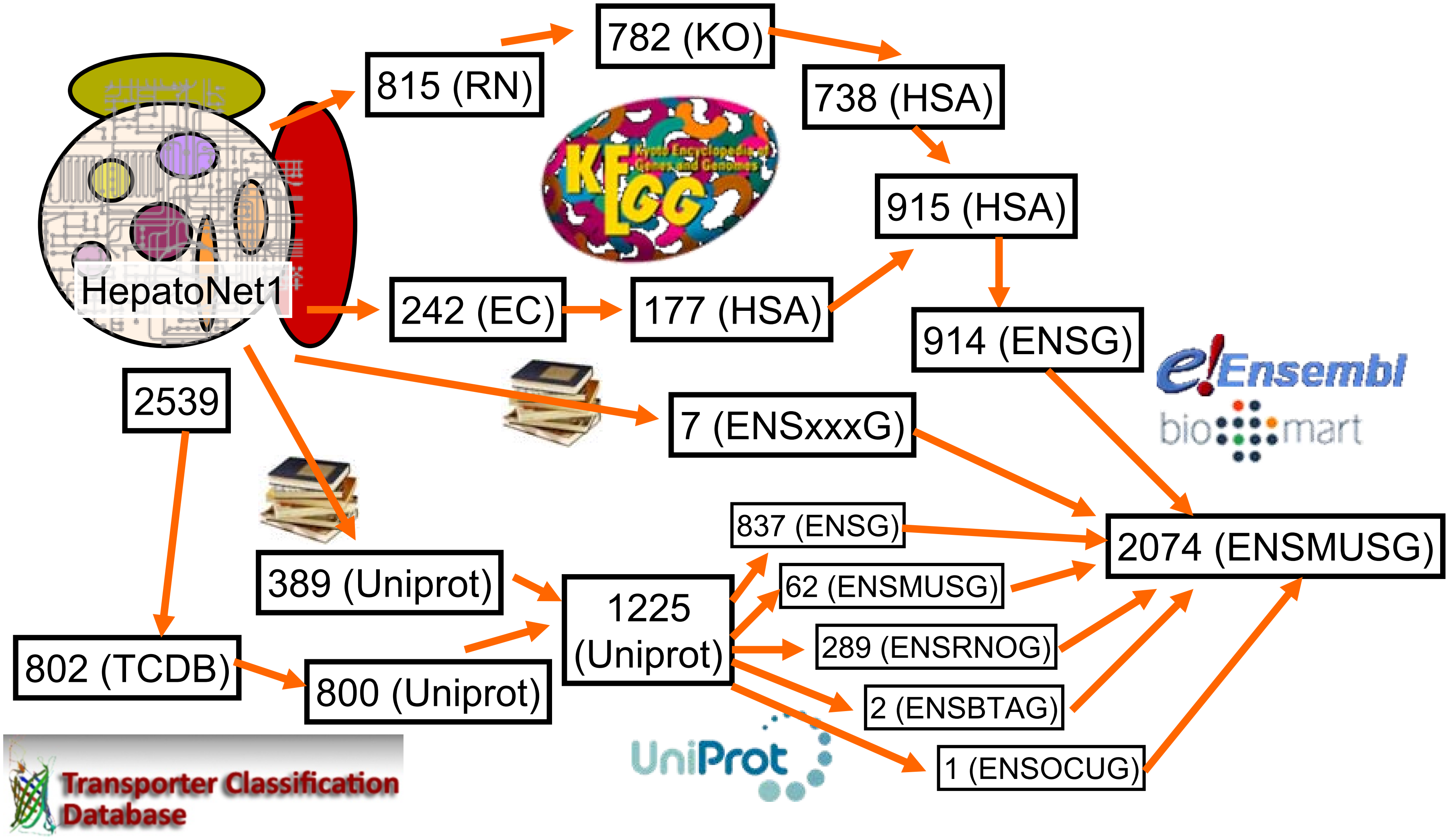
HepatoNet gene annotation



HepatoNet1

815 (RN)

782 (KO)

738 (HSA)

915 (HSA)

242 (EC)

177 (HSA)

914 (ENSG)

2539

7 (ENSxxxG)

389 (Uniprot)

1225 (Uniprot)

837 (ENSG)

62 (ENSMUSG)

289 (ENSRNOG)

2 (ENSBTAG)

1 (ENSOCUG)

2074 (ENSMUSG)

802 (TCDB)

800 (Uniprot)