virtual liver
network

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

ModeScore

A new algorithm to infer metabolic activity changes from RNA expression

Andreas Hoppe, Charité Universtitätsmedizin Berlin
Computational systems biochemistry group

COMPUTATIONAL SYSTEMS BIOCHEMISTRY

Contents

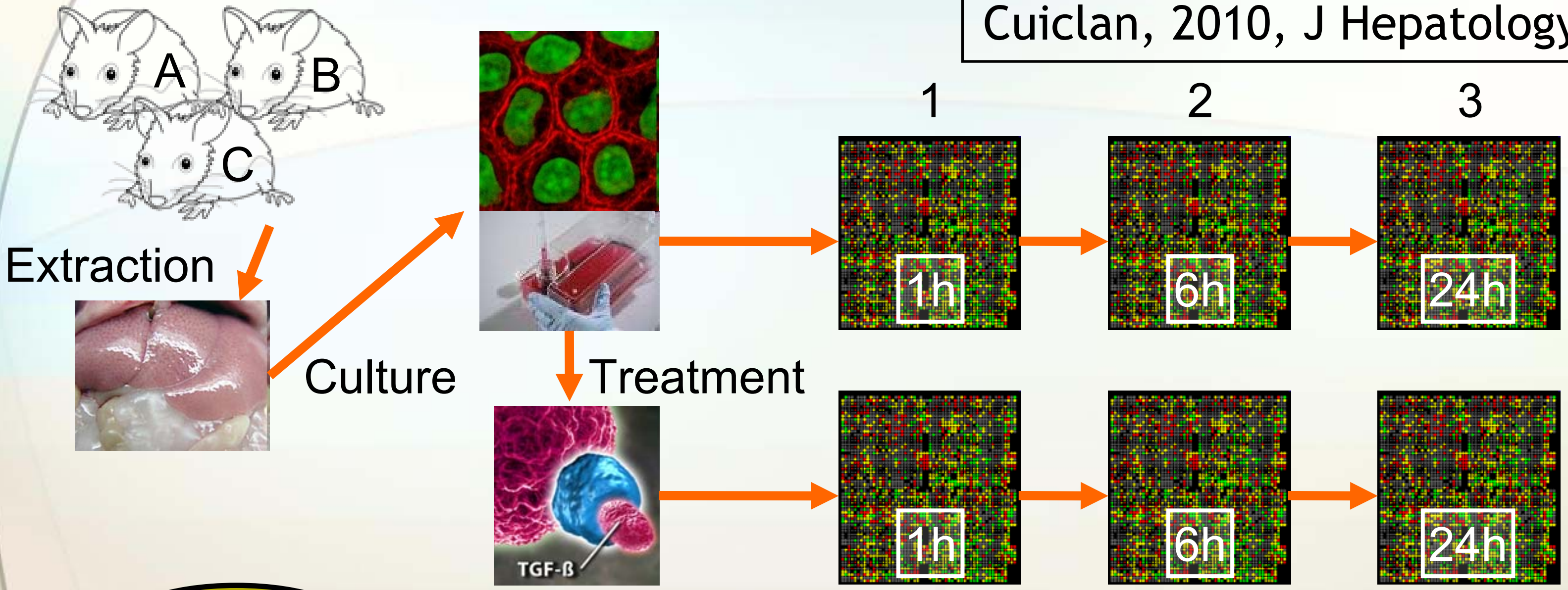
- Introductionary example
- ModeScore concept
- Results

Contents

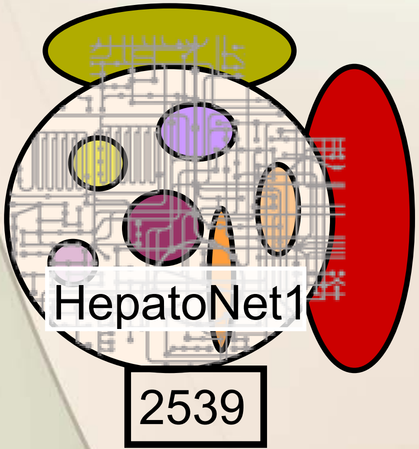
- Introductionary example
- ModeScore concept
- Results

Hepatocyte culture

Dooley, 2008, Gastroenterology
Godoy, 2009, Hepatology
Cuiclan, 2010, J Hepatology

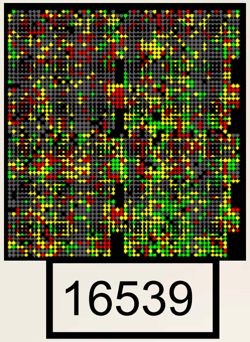

A
B
C
Extraction
Culture
Treatment

Ilkavets, Dooley


HepatoNet1
2539

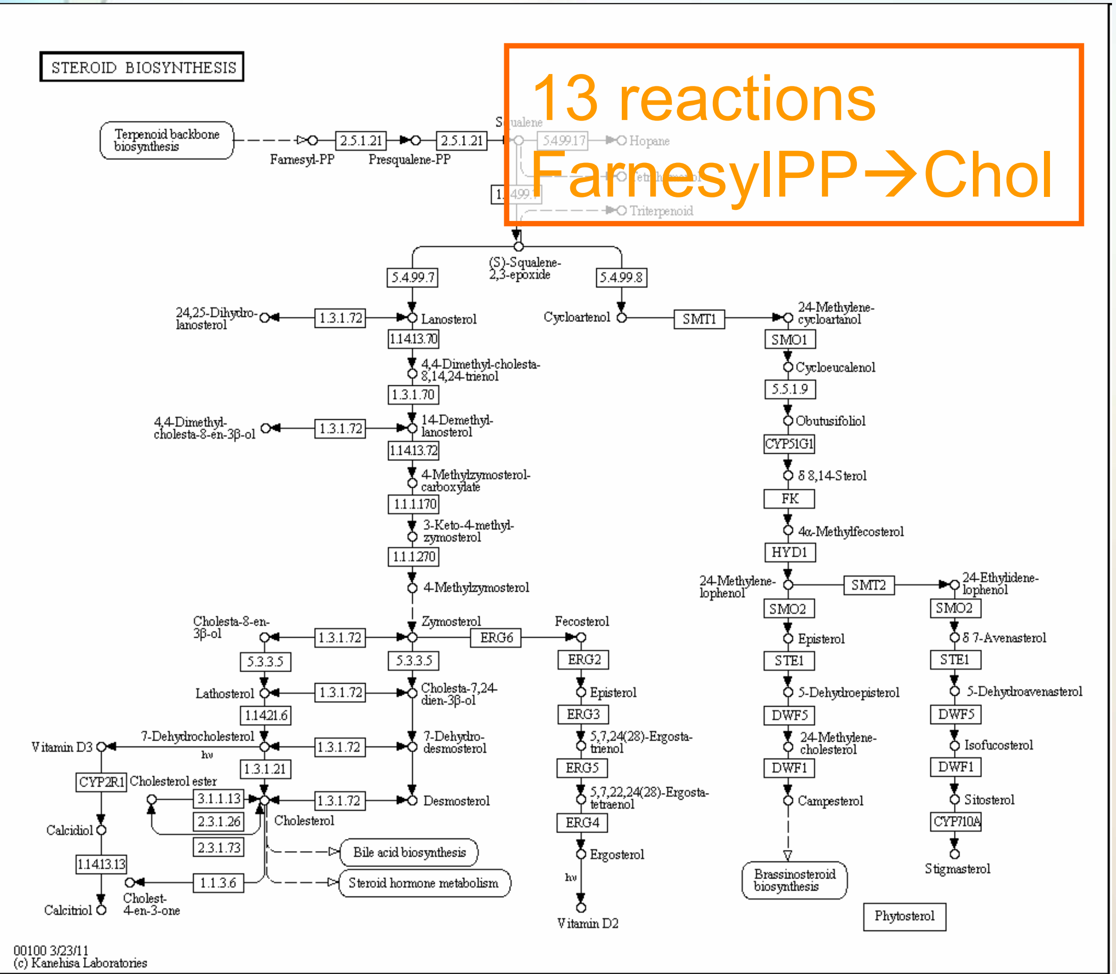
2039/2539 reactions covered (80%)

788/16539 spots covered (4.8%)

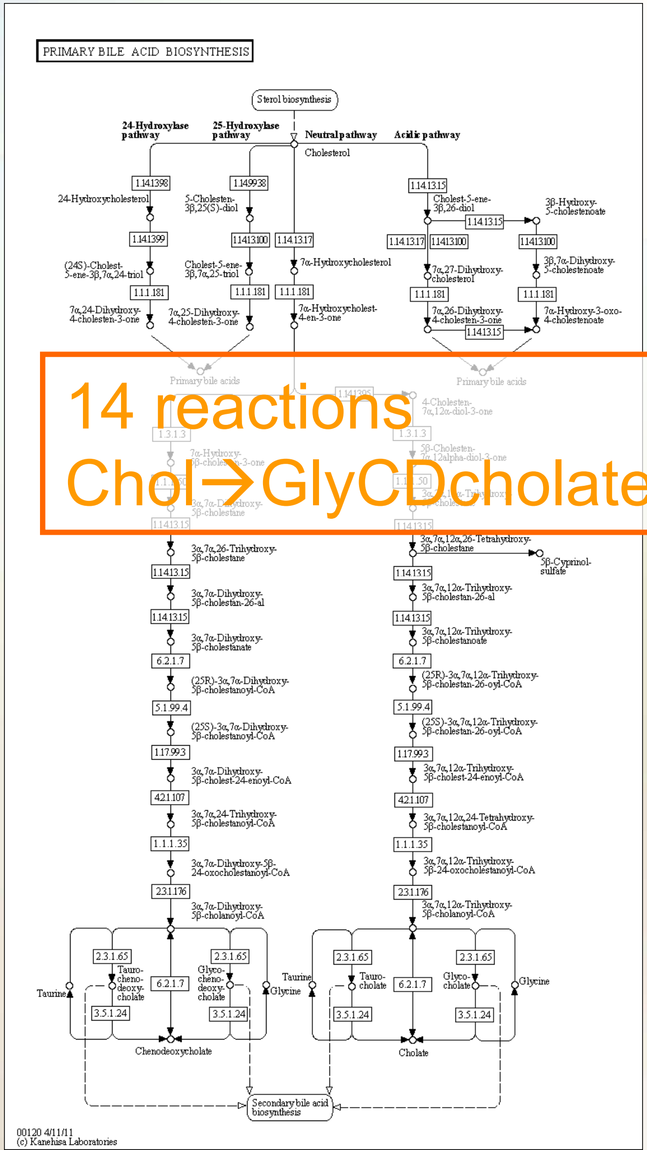

16539

Impact on bile acid production

- KEGG maps



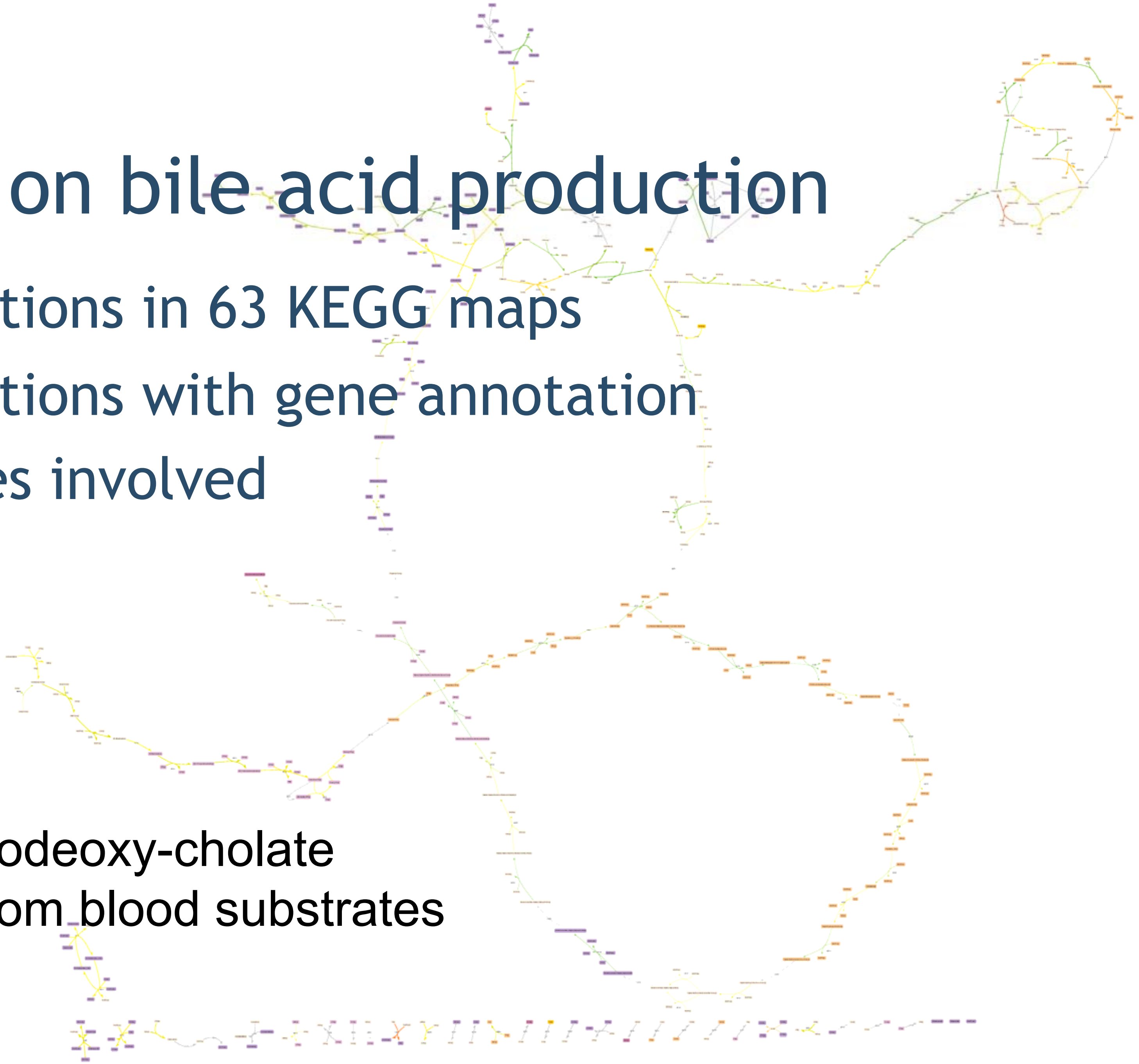
13 reactions
FarnesylPP→Chol



14 reactions
Chol→GlyCDcholate

Impact on bile acid production

- 146 reactions in 63 KEGG maps
- 103 reactions with gene annotation
- 203 genes involved



Glyco-chenodeoxy-cholate
synthesis from blood substrates

Impact on bile acid production

- Production reduced but residual activity
- Activity prediction → on in all profiles

GIMME …, Becker & Palsson, 2008, PLoS Comput Biol
Active subnetworks …, Shlomi et al., 2008, Nat Biotechnol
Huthmacher et al., 2010, BMC Syst Biol

→ More sensitive, quantitative, relative

- How does it compare to the strength of regulation of other functions?

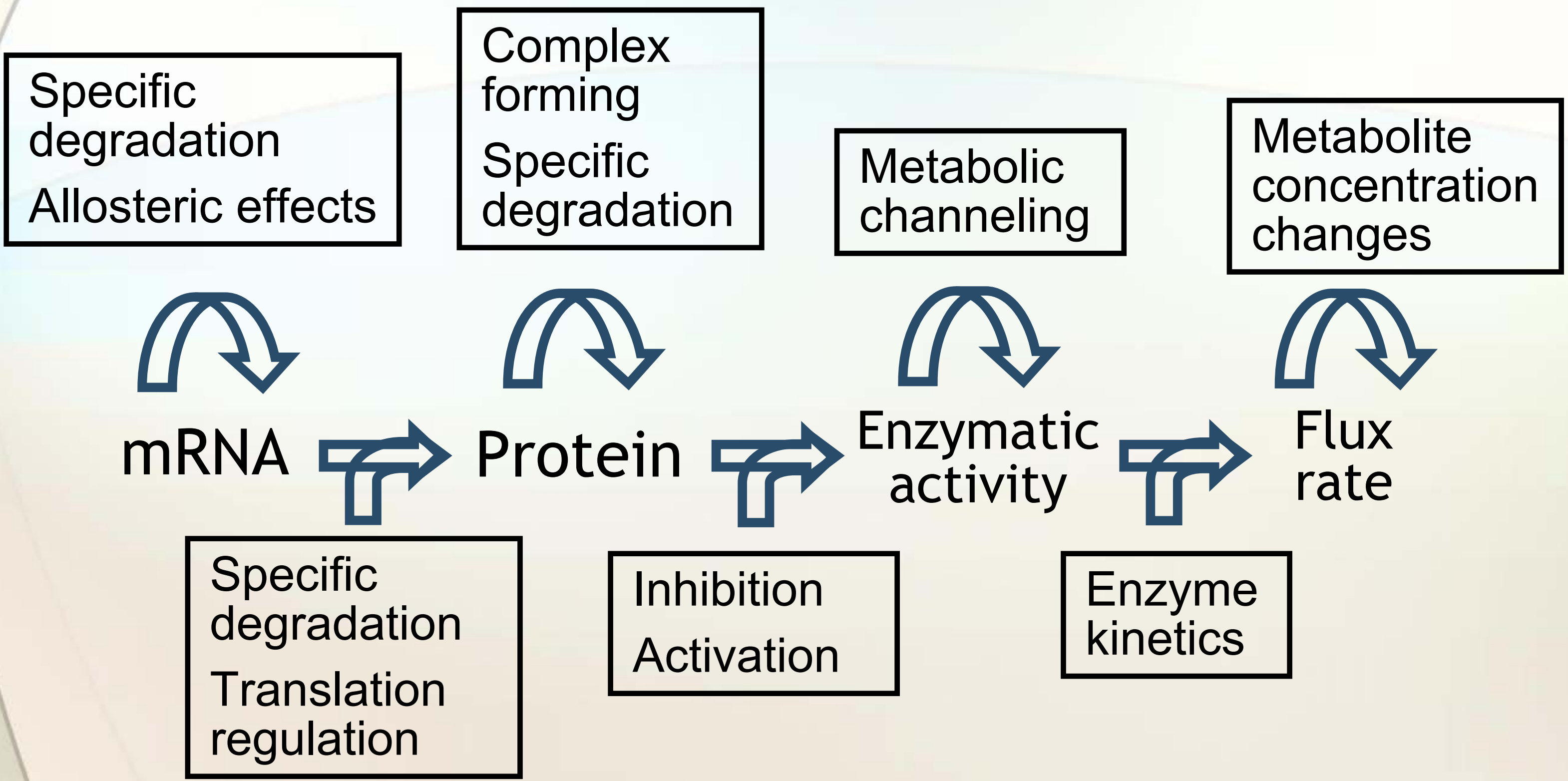
Contents

- Introductionary example
- ModeScore concept
- Results

RNA-metabolism chain

mRNA ⇒ Protein ⇒ Enzymatic activity ⇒ Flux rate

RNA-metabolism chain



Specific degradation

Allosteric effects

Complex forming

Specific degradation

Metabolic channeling

Metabolite concentration changes

mRNA

Protein

Enzymatic activity

Flux rate

Specific degradation

Translation regulation

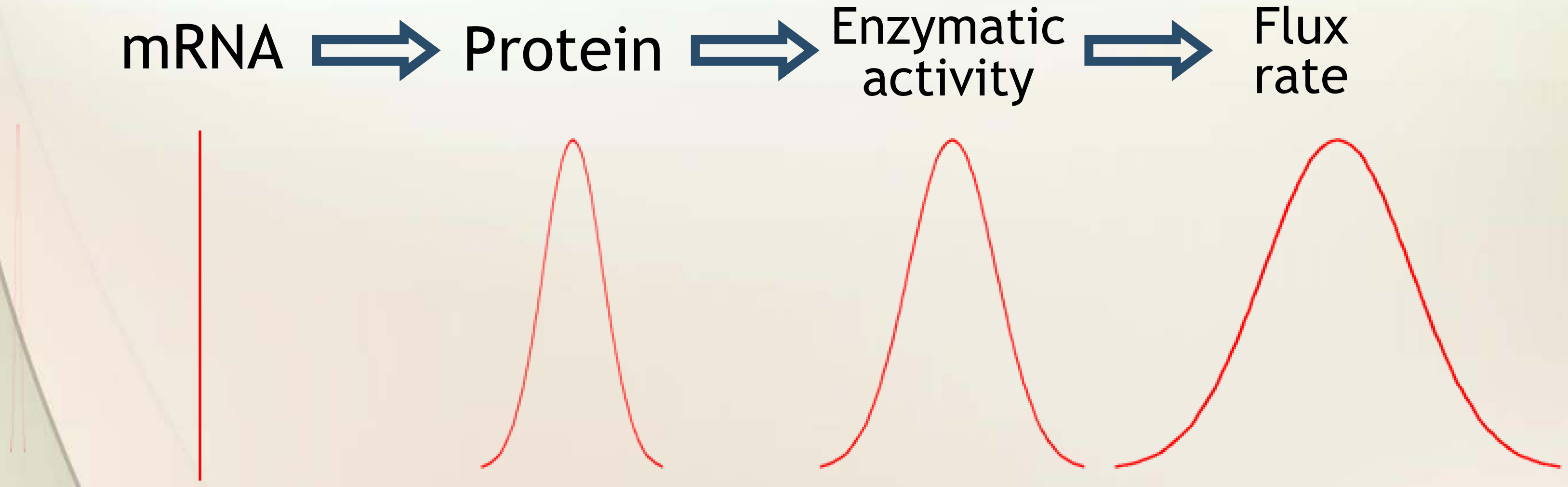
Inhibition

Activation

Enzyme kinetics

RNA-metabolism chain

- Probability field
- Normal distribution



mRNA ⇒ Protein ⇒ Enzymatic activity ⇒ Flux rate

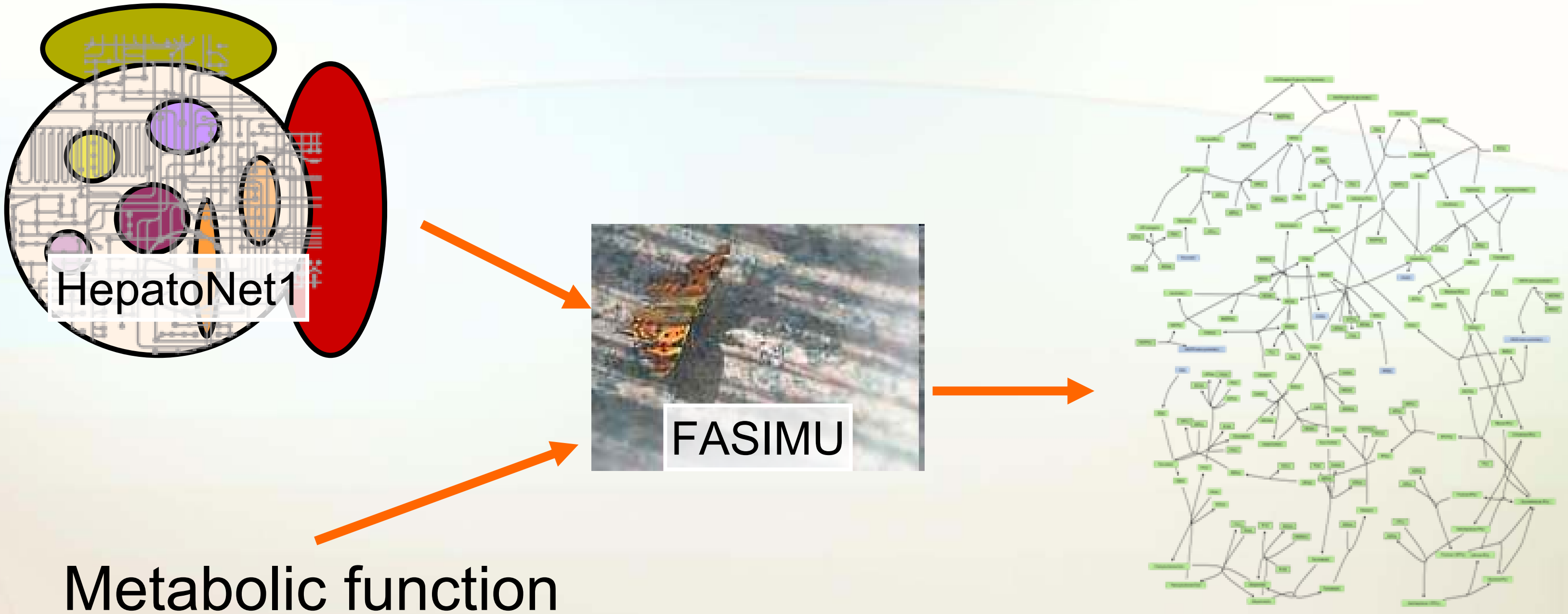
Scoring paths

- Mamitsuka group
- There:
  - Ranking co-expression
  - Using linear reaction chains (KEGG RPAIRS)

Mining active patterns … , Mamitsuka et al., SIGKDO Explorations 2003.

PathRanker … Hancock et al., 2010, Bioinf

Representative flux modes

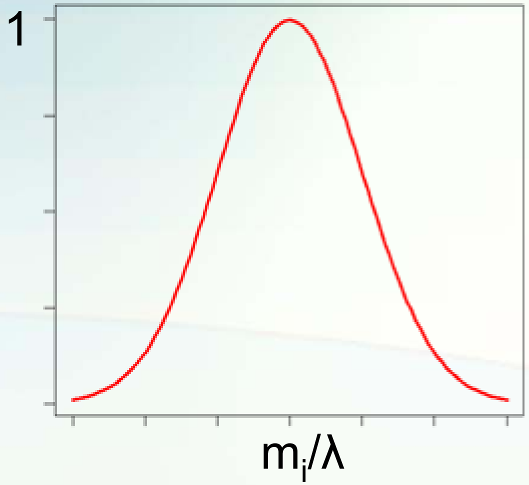


Metabolic function definition

Reference flux mode

HepatoNet1 … , Gille et al., 2010, Mol Syst Biol
FASIMU … Hoppe et al., 2011, BMC Bioinf

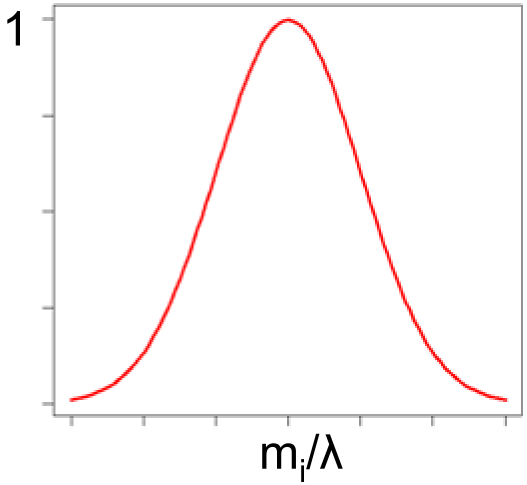
Pattern match: Profile — Mode



Assumption:

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

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

$$I_k = \{i |\, m_i \neq 0\}$$ indices of nonzero values

$$w_i = \sqrt{|m_i| \omega_i}$$ weights

$$\omega_i$$ weight adjustment

$$\mathsf{score}_i(m_i, v_i) = e^{-\frac{1}{2}\left(2\frac{\lambda v_i - m_i}{|m_i|}\right)^2}$$ score component

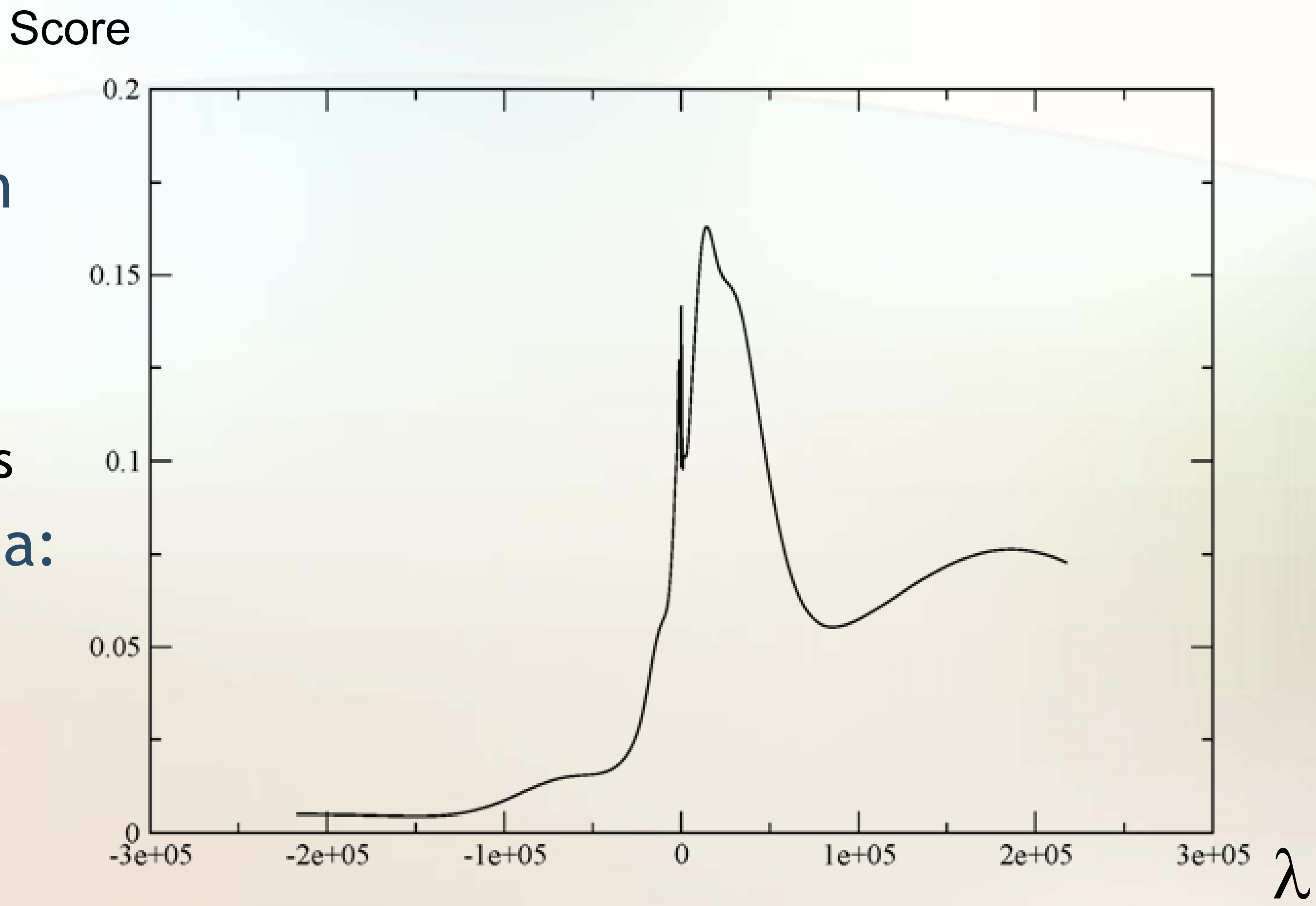
$$M_k = (m_i)_i$$ k-th reference mode

$$V = (v_i)_i$$ relative expression profile

λ chosen such that $\mathsf{Score}(M_k, V)$ is maximal

Optimization of scaling factor

- Optimization
  - Explicit derivation
  - Maxima of components
- Local maxima: alternative matches



Measures

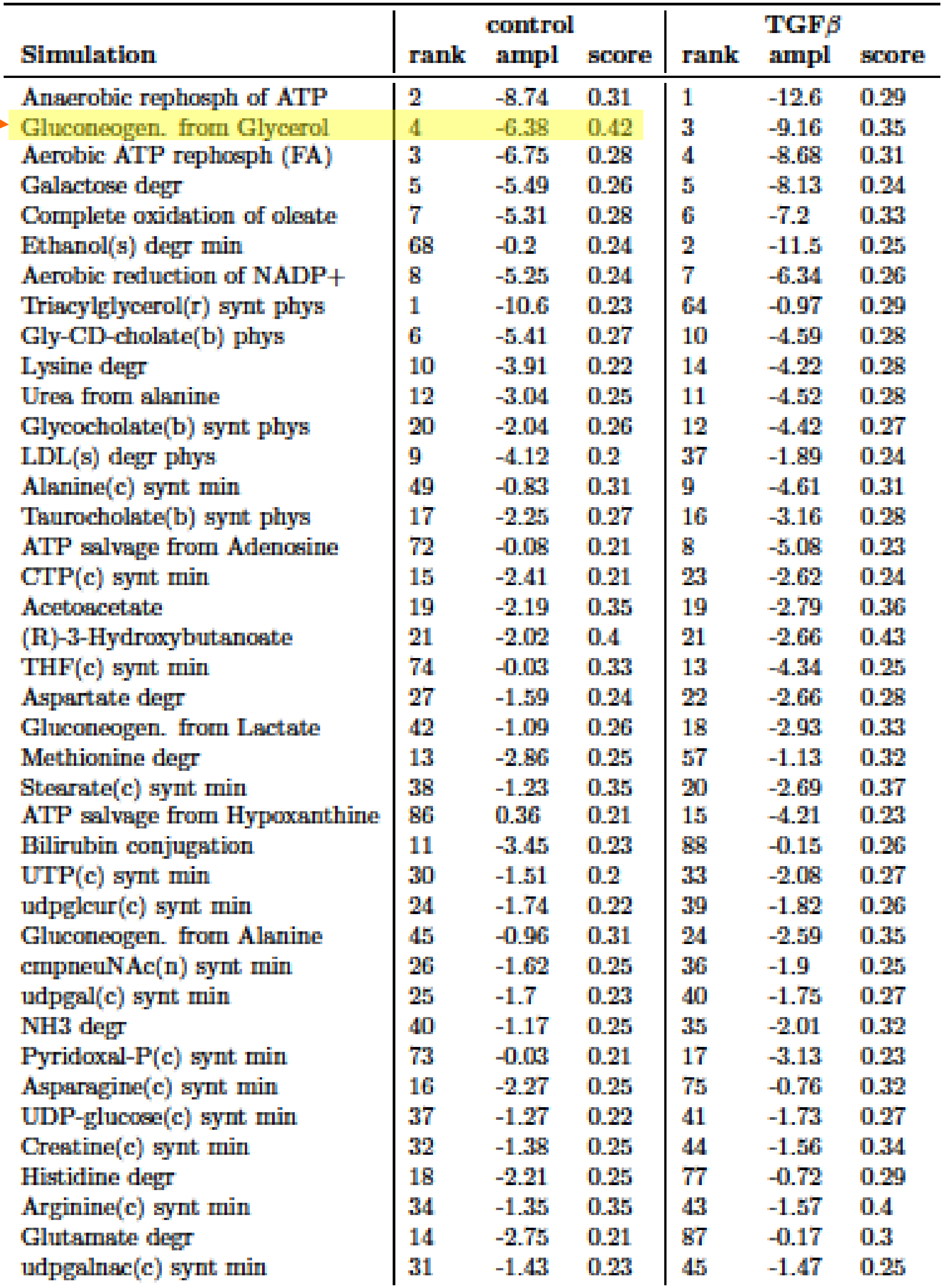
- Score … significance of match
- Amplitude $1/\lambda$
  - measures strength of regulation
- Impact
  - of an individual reaction to the match
  - $\text{Impact}=(\text{score}_i-\text{Score})*\text{weight}_i$

Contents

- Introductionary example
- ModeScore concept
- Results

Top scorers

- List of most downregulated functions
- Filter: mRNA → potentially most interesting functions



Simulation	control			TGFβ		
	rank	ampl	score	rank	ampl	score
Anaerobic rephosph of ATP	2	-8.74	0.31	1	-12.6	0.29
Gluconeogen. from Glycerol	4	-6.38	0.42	3	-9.16	0.35
Aerobic ATP rephosph (FA)	3	-6.75	0.28	4	-8.68	0.31
Galactose degr	5	-5.49	0.26	5	-8.13	0.24
Complete oxidation of oleate	7	-5.31	0.28	6	-7.2	0.33
Ethanol(s) degr min	68	-0.2	0.24	2	-11.5	0.25
Aerobic reduction of NADP+	8	-5.25	0.24	7	-6.34	0.26
Triacylglycerol(r) synt phys	1	-10.6	0.23	64	-0.97	0.29
Gly-CD-cholate(b) phys	6	-5.41	0.27	10	-4.59	0.28
Lysine degr	10	-3.91	0.22	14	-4.22	0.28
Urea from alanine	12	-3.04	0.25	11	-4.52	0.28
Glycocholate(b) synt phys	20	-2.04	0.26	12	-4.42	0.27
LDL(s) degr phys	9	-4.12	0.2	37	-1.89	0.24
Alanine(c) synt min	49	-0.83	0.31	9	-4.61	0.31
Taurocholate(b) synt phys	17	-2.25	0.27	16	-3.16	0.28
ATP salvage from Adenosine	72	-0.08	0.21	8	-5.08	0.23
CTP(c) synt min	15	-2.41	0.21	23	-2.62	0.24
Acetoacetate	19	-2.19	0.35	19	-2.79	0.36
(R)-3-Hydroxybutanoate	21	-2.02	0.4	21	-2.66	0.43
THF(c) synt min	74	-0.03	0.33	13	-4.34	0.25
Aspartate degr	27	-1.59	0.24	22	-2.66	0.28
Gluconeogen. from Lactate	42	-1.09	0.26	18	-2.93	0.33
Methionine degr	13	-2.86	0.25	57	-1.13	0.32
Stearate(c) synt min	38	-1.23	0.35	20	-2.69	0.37
ATP salvage from Hypoxanthine	86	0.36	0.21	15	-4.21	0.23
Bilirubin conjugation	11	-3.45	0.23	88	-0.15	0.26
UTP(c) synt min	30	-1.51	0.2	33	-2.08	0.27
udpglcur(c) synt min	24	-1.74	0.22	39	-1.82	0.26
Gluconeogen. from Alanine	45	-0.96	0.31	24	-2.59	0.35
cmpneuNAc(n) synt min	26	-1.62	0.25	36	-1.9	0.25
udpgal(c) synt min	25	-1.7	0.23	40	-1.75	0.27
NH3 degr	40	-1.17	0.25	35	-2.01	0.32
Pyridoxal-P(c) synt min	73	-0.03	0.21	17	-3.13	0.23
Asparagine(c) synt min	16	-2.27	0.25	75	-0.76	0.32
UDP-glucose(c) synt min	37	-1.27	0.22	41	-1.73	0.27
Creatine(c) synt min	32	-1.38	0.25	44	-1.56	0.34
Histidine degr	18	-2.21	0.25	77	-0.72	0.29
Arginine(c) synt min	34	-1.35	0.35	43	-1.57	0.4
Glutamate degr	14	-2.75	0.21	87	-0.17	0.3
udpgalnac(c) synt min	31	-1.43	0.23	45	-1.47	0.25

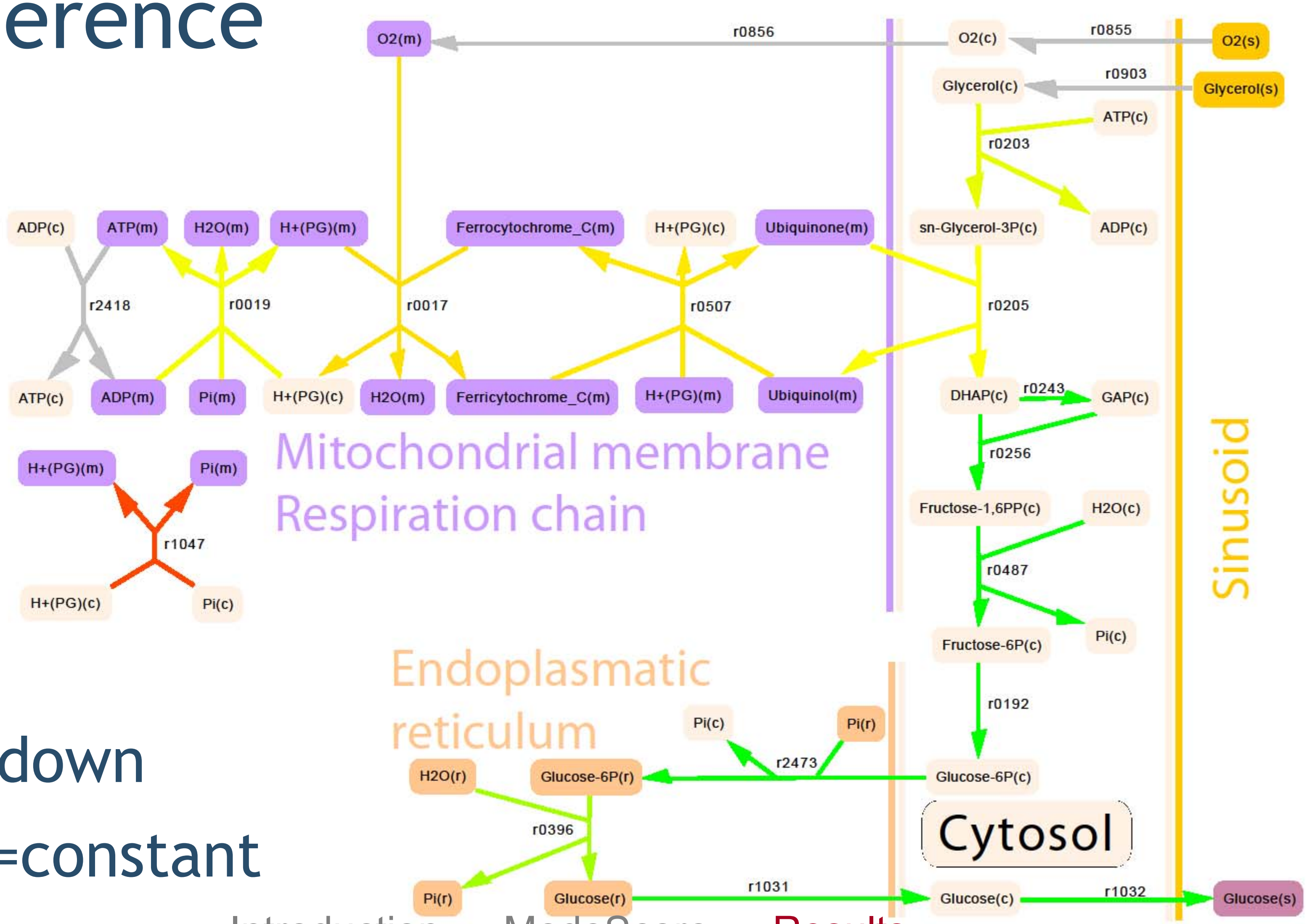
Single reaction chart

- Contribution of individual reactions

→Prediction of regulation points

- Mode: Glyconeogenesis from Glycerol:
  - Amplitude: -6.38 … high
  - Score: 0.42 … highly significant

Expression difference

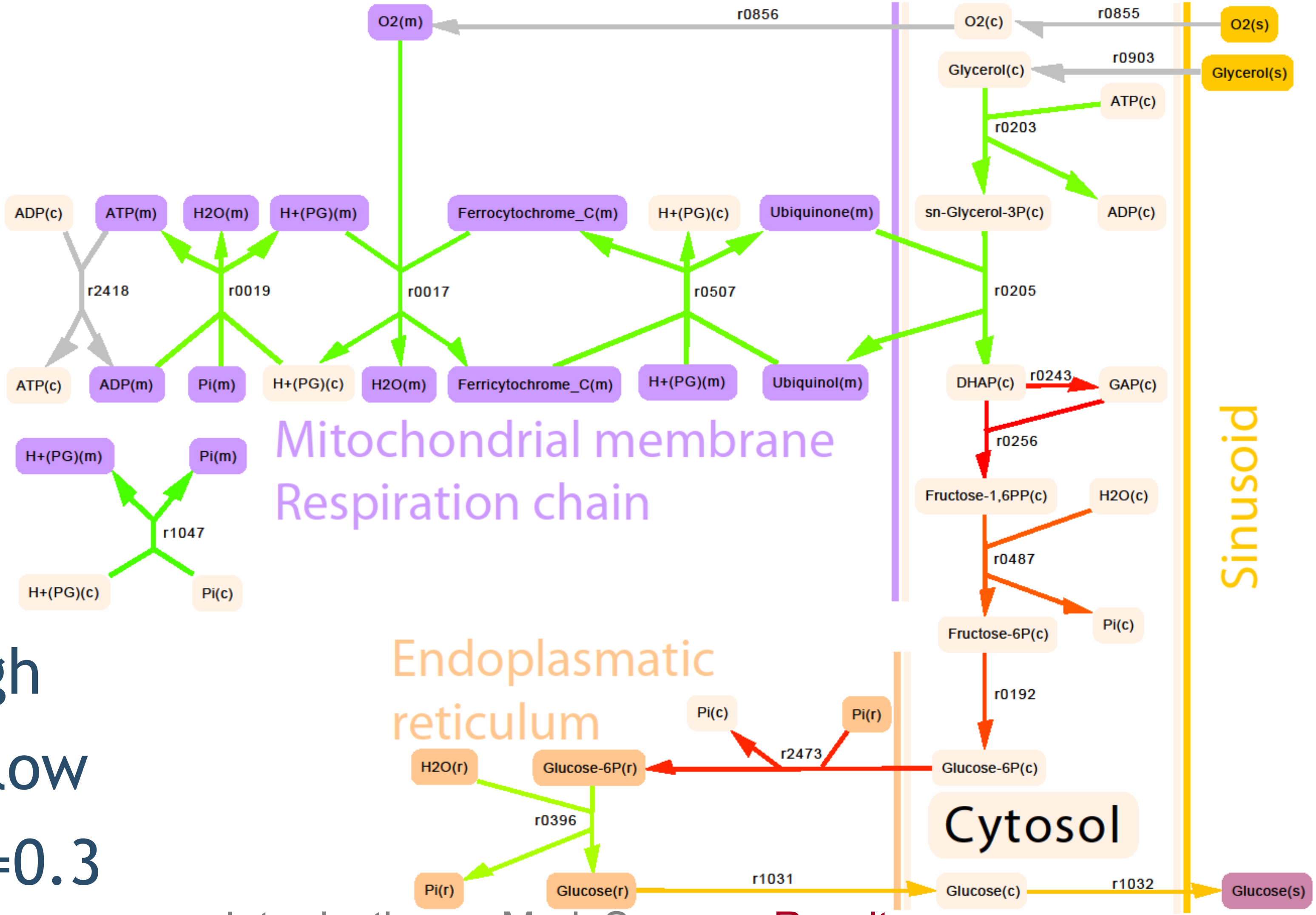


red=up

green=down

yellow=constant

Score



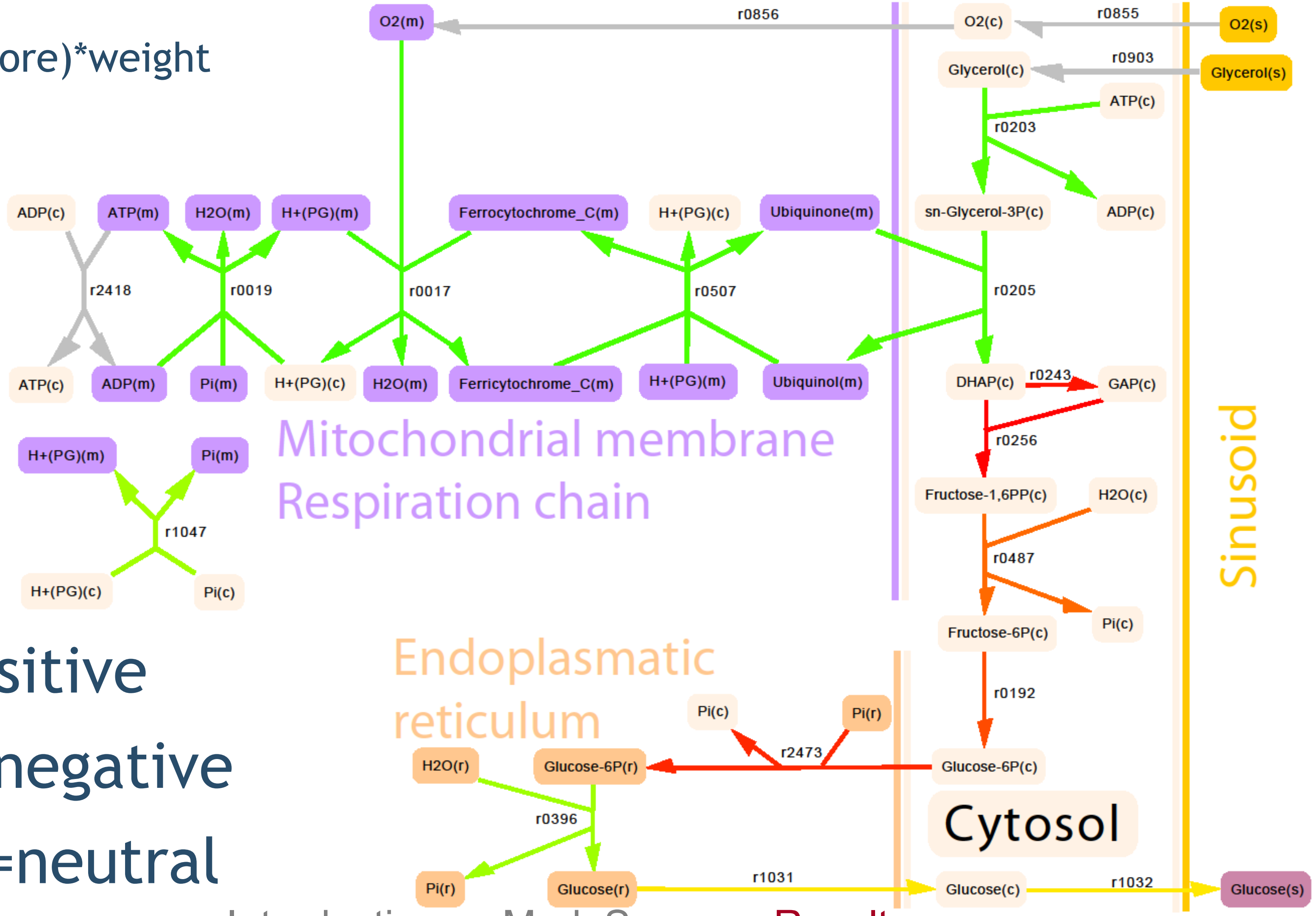
red=high

green=low

yellow=0.3

Impact

$=(\text{score}_i - \text{Score}) * \text{weight}$

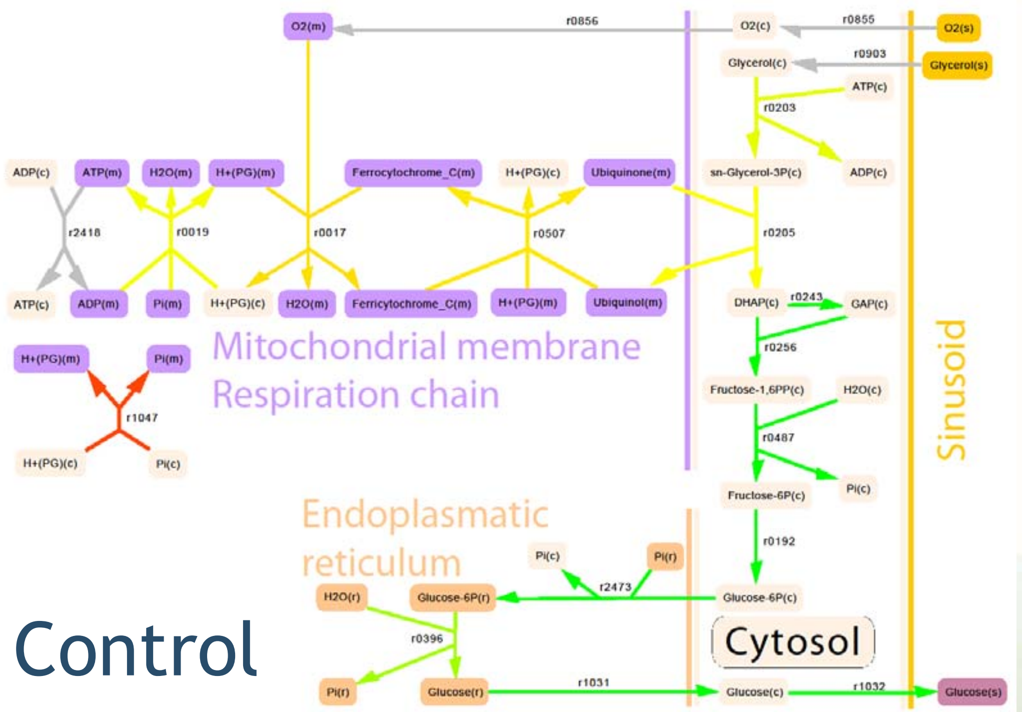


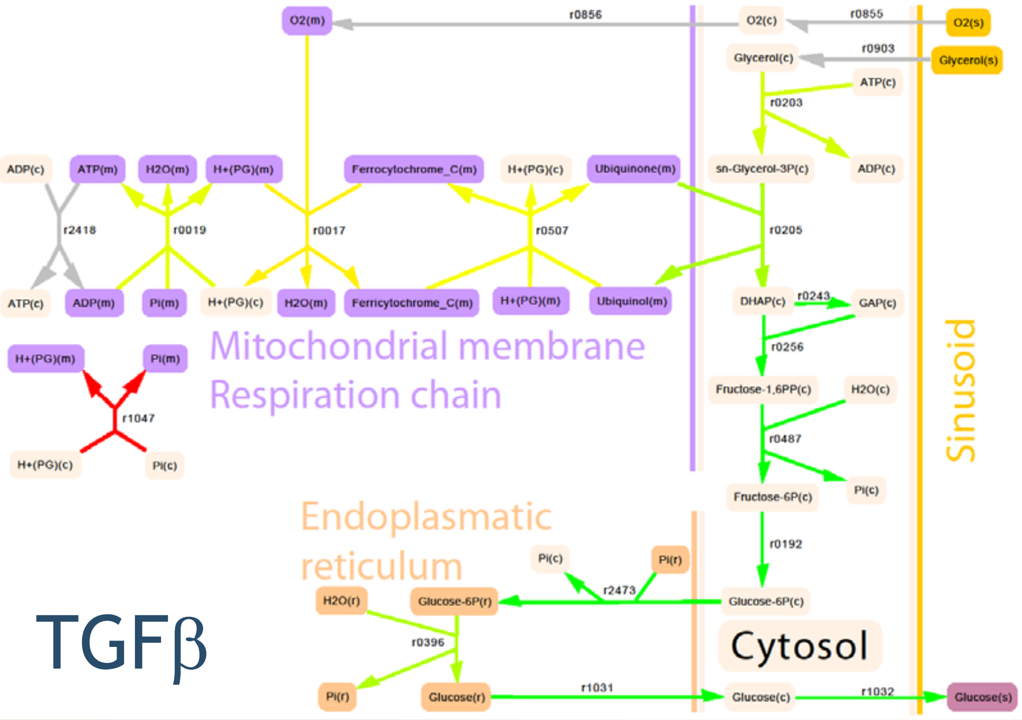
red=positive

green=negative

yellow=neutral

Expression comparison


Control


TGFβ

red=positive
green=negative
yellow=neutral

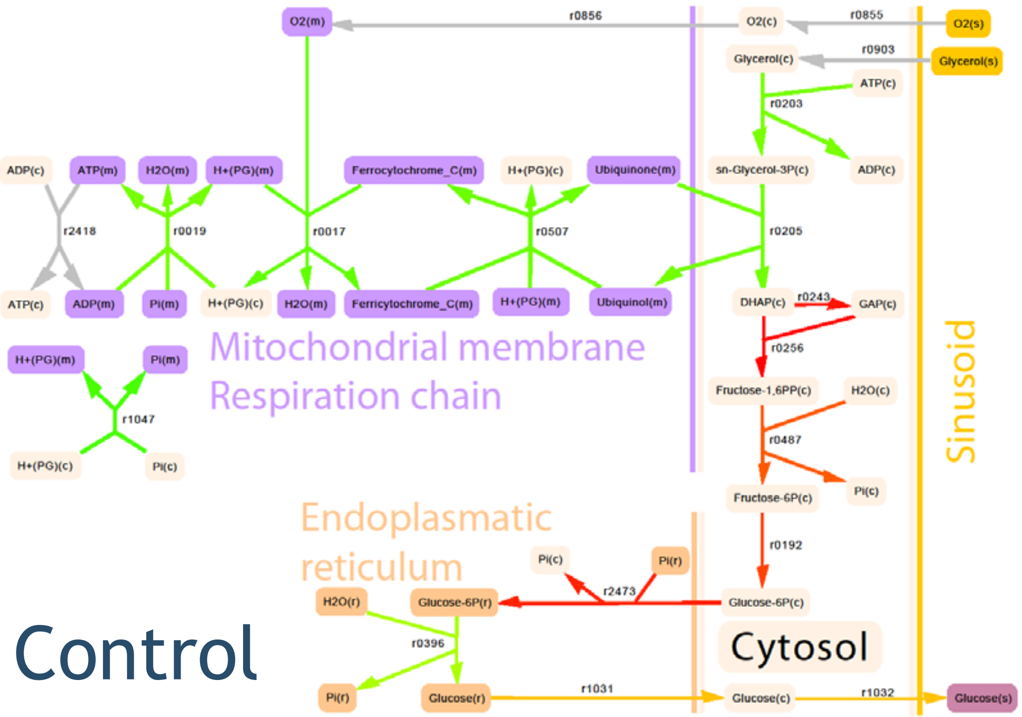
virtual liver
network

Score comparison

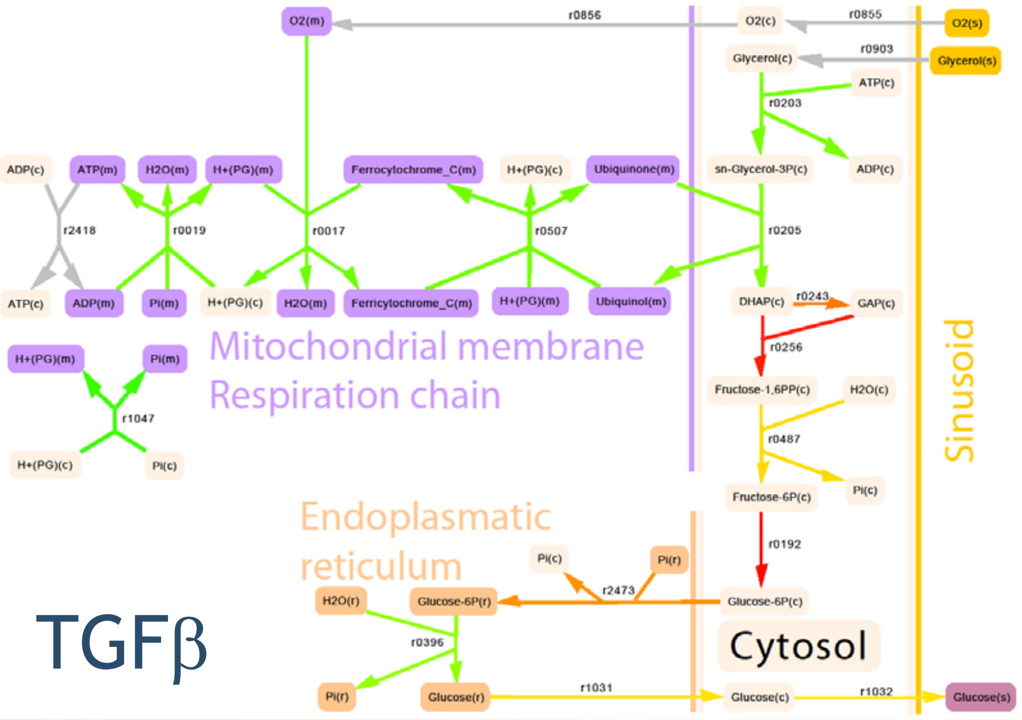
red=high

green=low

yellow=0.3

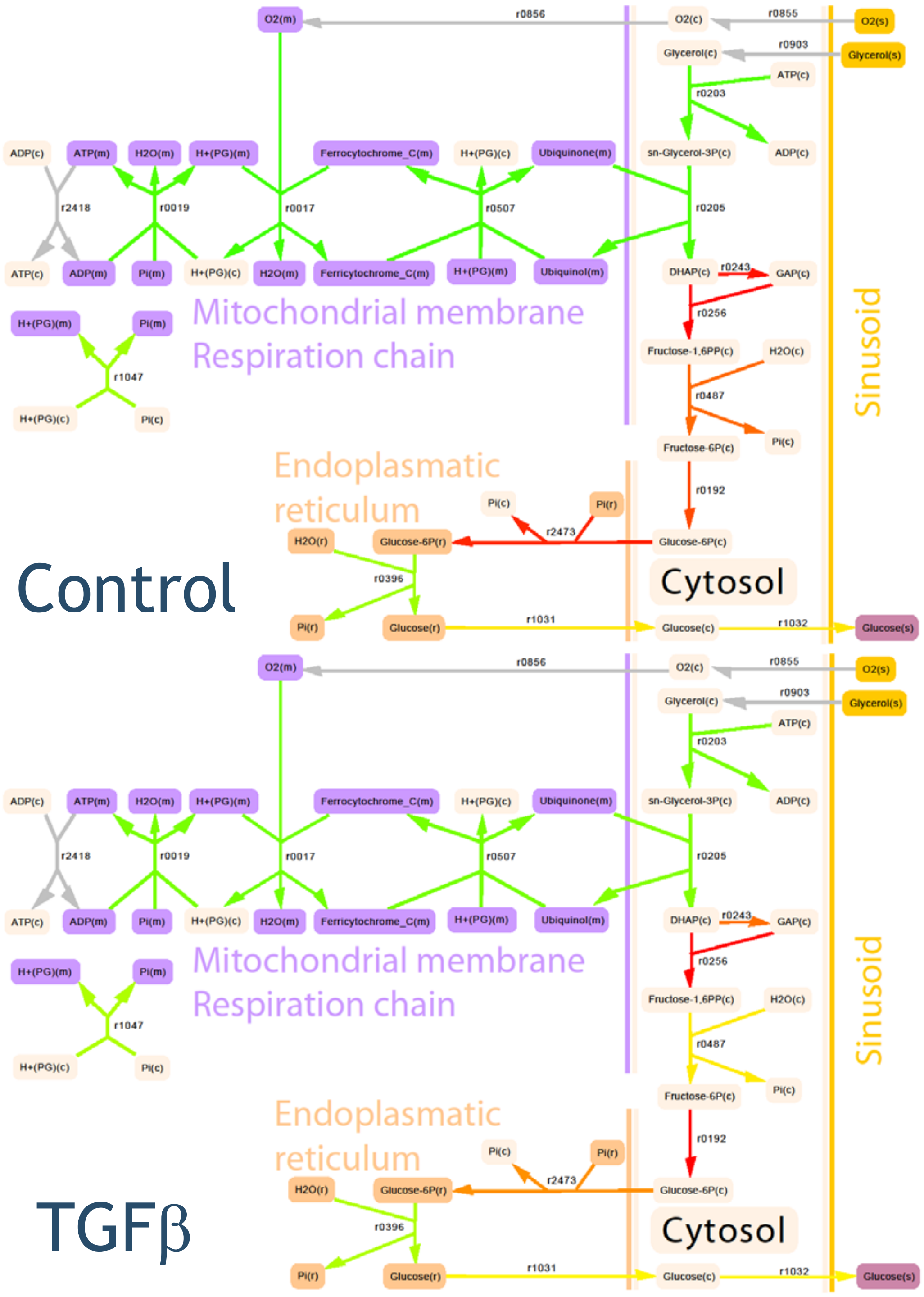


Control



TGFβ

Impact comparison



red=positive

green=negative

yellow=neutral

Findings

- Typical Hepatic functions downregulated, enhanced by TGFβ
  - Urea, bile acid synthesis
  - AA conversion, Bilirubin conjugation
  - Glycolysis, Gluconeogenesis, β-oxidation
- Ethanol degradation downregulated in TGFβ (unaffected by culture)
- TAG synthesis downregulation less for TGFβ

Cuiclan, 2010, J Hepatology

Summary

- Quantitative assessment of regulation by RNA
- Very few parameters
- Filter for potentially
  - most affected metabolic function
  - regulated reaction / gene
- modeset-score in FASIMU 2.3.0 to be released. www.bioinformatics.org/fasimu

Acknowledgements

- Hermann-Georg Holzhütter, Sabrina Hoffmann, Carola Huthmacher (Berlin)
- Iryna Ilkavets, Steven Dooley (Mannheim)
- Sebastian Vlaic (Jena)

The end

Single reaction chart

- Contribution of individual reactions
- Expression difference of individual genes

→Prediction of regulation points

Rea ID	Scre *0.42*	Impct	Expr	Expr C1D	Expr C3D	Expr *∗-0.16*	Ref value	Wght	Reaction
r0256	1	0.51	-5.07	8.86	3.79	0.8	0.77	0.88	DHAP(c) + GAP(c) ⇌ Fructose-1,6PP(c)
r0243	0.94	0.46	-5.77	18.5	12.7	0.91	0.77	0.88	DHAP(c) ⇌ GAP(c)
r2473	0.9	0.42	-3.77	4.72	0.95	0.59	0.77	0.88	Glucose-6P(c) + Pi(r) → Glucose-6P(r) + Pi(c)
r0017	0.12	-0.37	0.19	7.35	7.53	-0.03	0.77	1.24	O2(m) + 4 H+(PG)(m) + 4 Ferrocytochrome C(m) → 4 Ferricytochrome C(m) + 2 H2O(m) + 4 H+(PG)(c)
r0507	0.13	-0.36	0.13	7.93	8.06	-0.02	1.54	1.24	Ubiquinol(m) + 2 Ferricytochrome C(m) + 4 H+(PG)(m) → Ubiquinone(m) + 4 H+(PG)(c) + 2 Ferrocytochrome C(m)
r0192	0.82	0.35	-6.49	17	10.5	1.02	0.77	0.88	Fructose-6P(c) ⇌ Glucose-6P(c)
r0205	0.14	-0.35	-0.003	1.75	1.74	0.001	1.54	1.24	Ubiquinone(m) + sn-Glycerol-3P(c) ⇌ DHAP(c) + Ubiquinol(m)
r0019	0.14	-0.34	-0.05	0.69	0.64	0.01	1.54	1.24	ADP(m) + Pi(m) + 3 H+(PG)(c) → ATP(m) + H2O(m) + 3 H+(PG)(m)
r0203	0.14	-0.34	-0.14	0.69	0.55	0.02	1.54	1.24	ATP(c) + Glycerol(c) ⇌ ADP(c) + sn-Glycerol-3P(c)
r0487	0.75	0.29	-3.06	4.99	1.93	0.48	0.77	0.88	Fructose-1,6PP(c) + H2O(c) → Fructose-6P(c) + Pi(c)
r0396	0.2	-0.19	-0.53	0.89	0.36	0.08	0.77	0.88	H2O(r) + Glucose-6P(r) → Glucose(r) + Pi(r)
r1047	0.09	-0.18	1.08	16.7	17.8	-0.17	1.54	0.56	Pi(c) + H+(PG)(c) → Pi(m) + H+(PG)(m)
r1031	0.47	0.04	-1.88	2.86	0.97	0.3	0.77	0.88	Glucose(r) → Glucose(c)
r1032	0.47	0.04	-1.88	2.86	0.97	0.3	0.77	0.88	Glucose(c) ⇌ Glucose(s)

Weight function

- High flux – high importance
    - avoid single dominant reaction
    - avoid $\lambda \approx 0$
    - empirical: $\sqrt{v}$
- Lumped reactions – increased weight

Zero score / steepness

- Zeroscore … for scaling factor $\lambda=0$
- Score≈*zeroscore* ⇒ Ambiguous
- Depends on steepness *s*
- here: *zeroscore*=0.13