# Linking transcription and metabolism

## Infer metabolic changes from RNA expression

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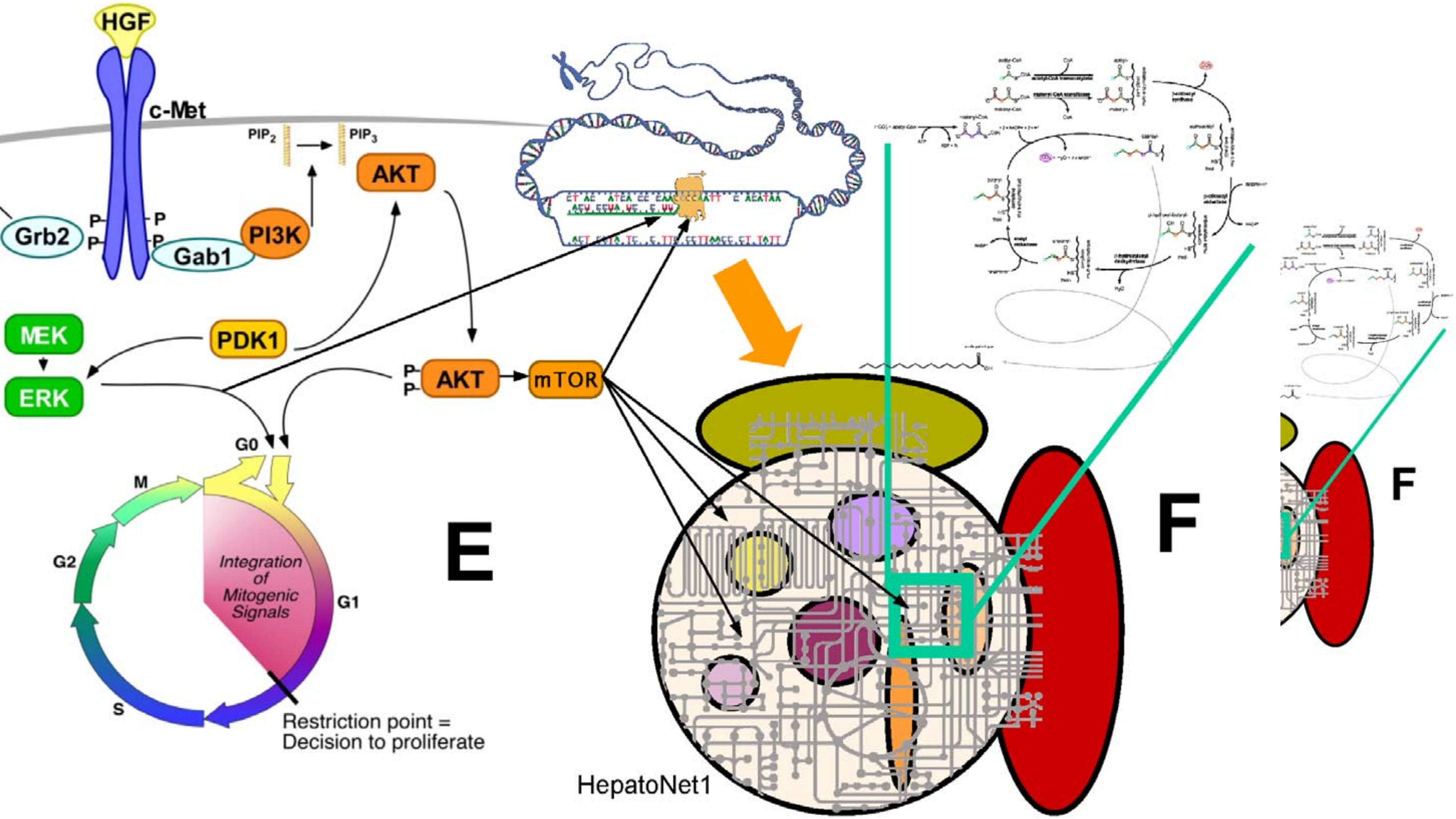
# Integrative model



# Questions

a) Which metabolic functions are strongly affected by HGF?

b) What are the key regulation points?

c) What is the metabolic basis for increased lipid production?

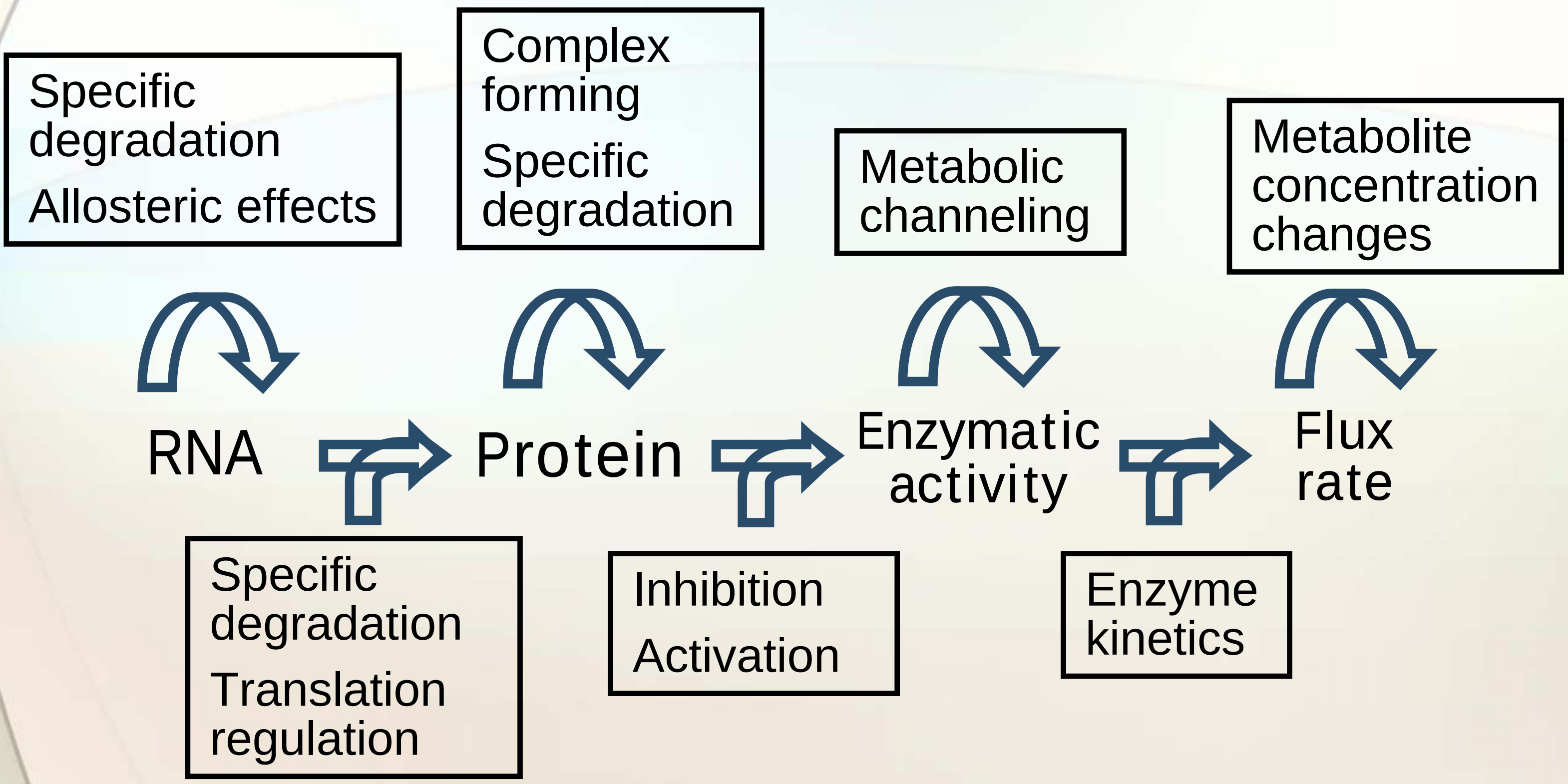
Data: RNA profiles by time/treatment

Approach: ModeScore

# RNA-metabolism chain

RNA ⇒ Protein ⇒ Enzymatic activity ⇒ Flux rate

# RNA-metabolism chain



Specific degradation

Allosteric effects

Complex forming

Specific degradation

Metabolic channeling

Metabolite concentration changes

RNA

Protein

Enzymatic activity

Flux rate

Specific degradation

Translation regulation

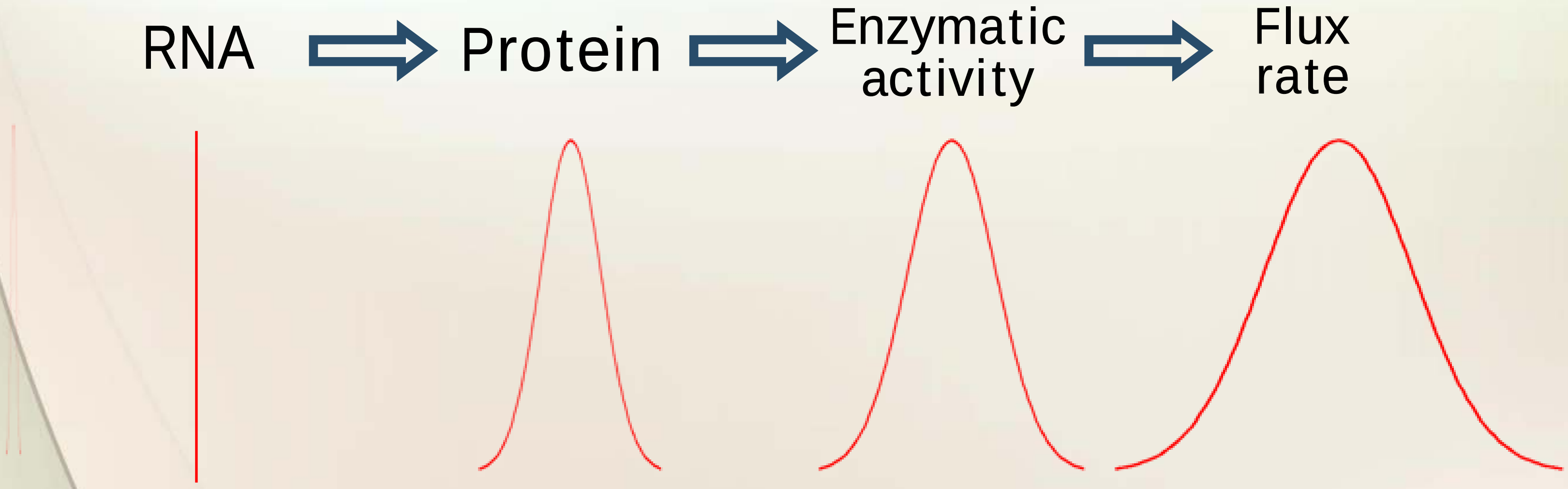
Inhibition

Activation

Enzyme kinetics

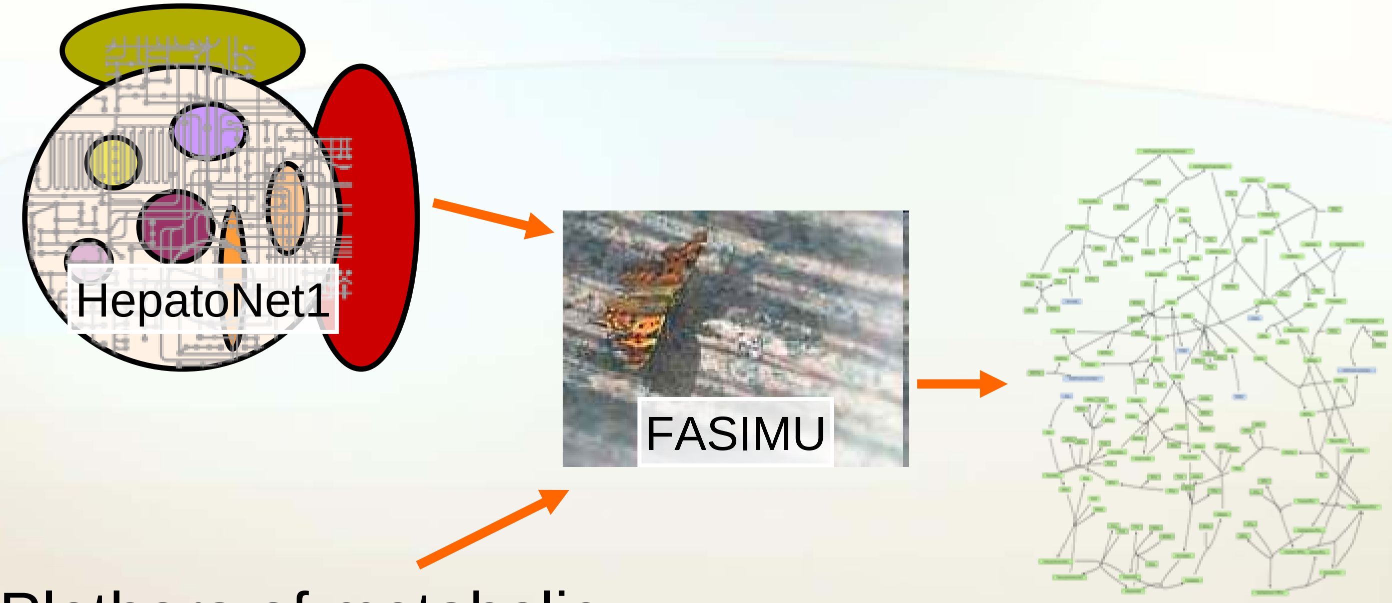
# RNA-metabolism chain

- Probability field
- Normal distribution



RNA ⇒ Protein ⇒ Enzymatic activity ⇒ Flux rate

# Representative flux modes



Plethora of metabolic functions

Reference flux modes

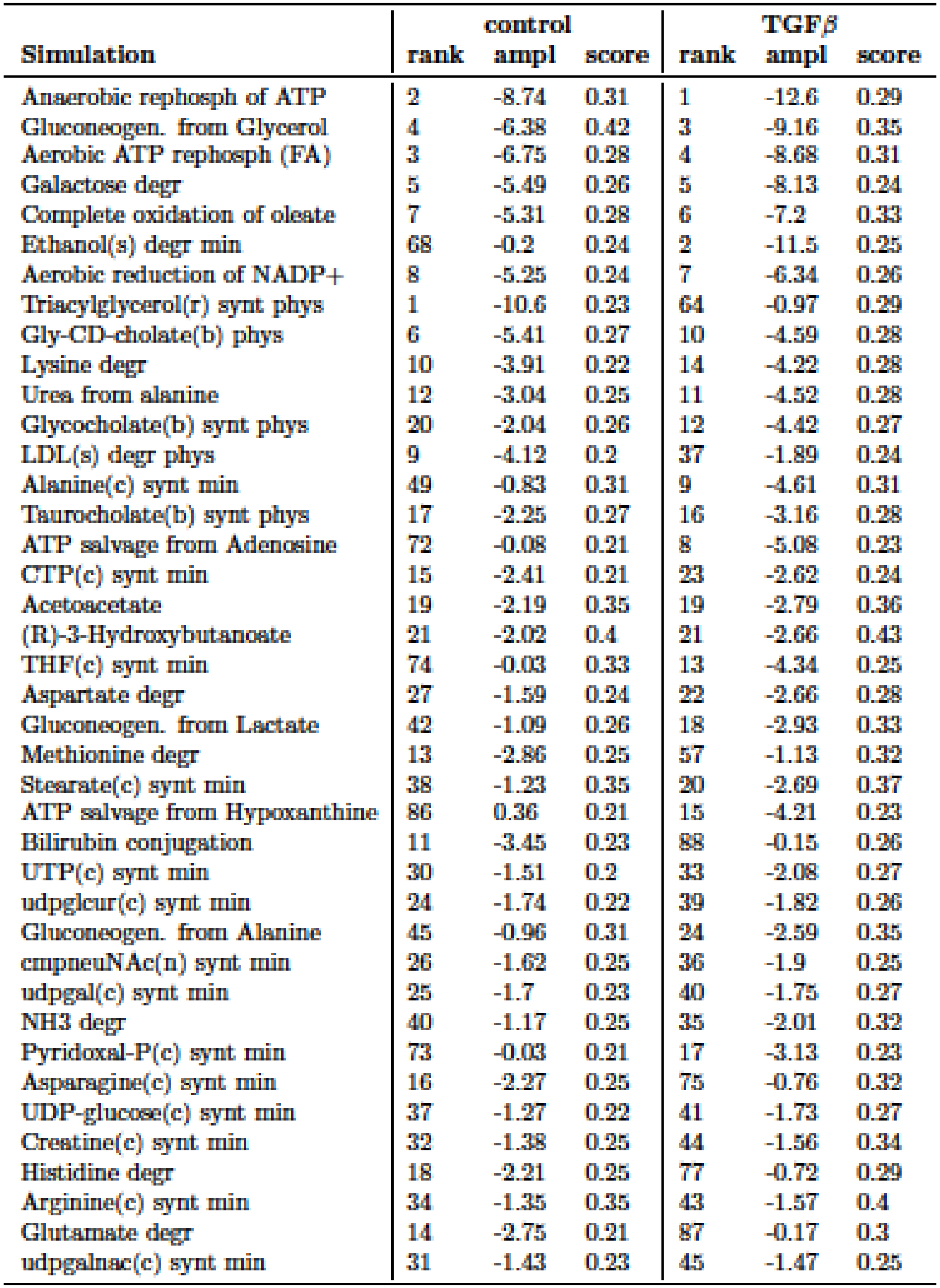
HepatoNet1 … , Gille et al., 2010, Mol Syst Biol
FASIMU … Hoppe et al., 2011, BMC Bioinf

# a) Function change prediction

- matches relative RNA profile with reference mode
- predicts **amplitude** of regulation
- gives confidence **score**

→ Ranking list (by amplitude)

Data from Ilkavets, Dooley



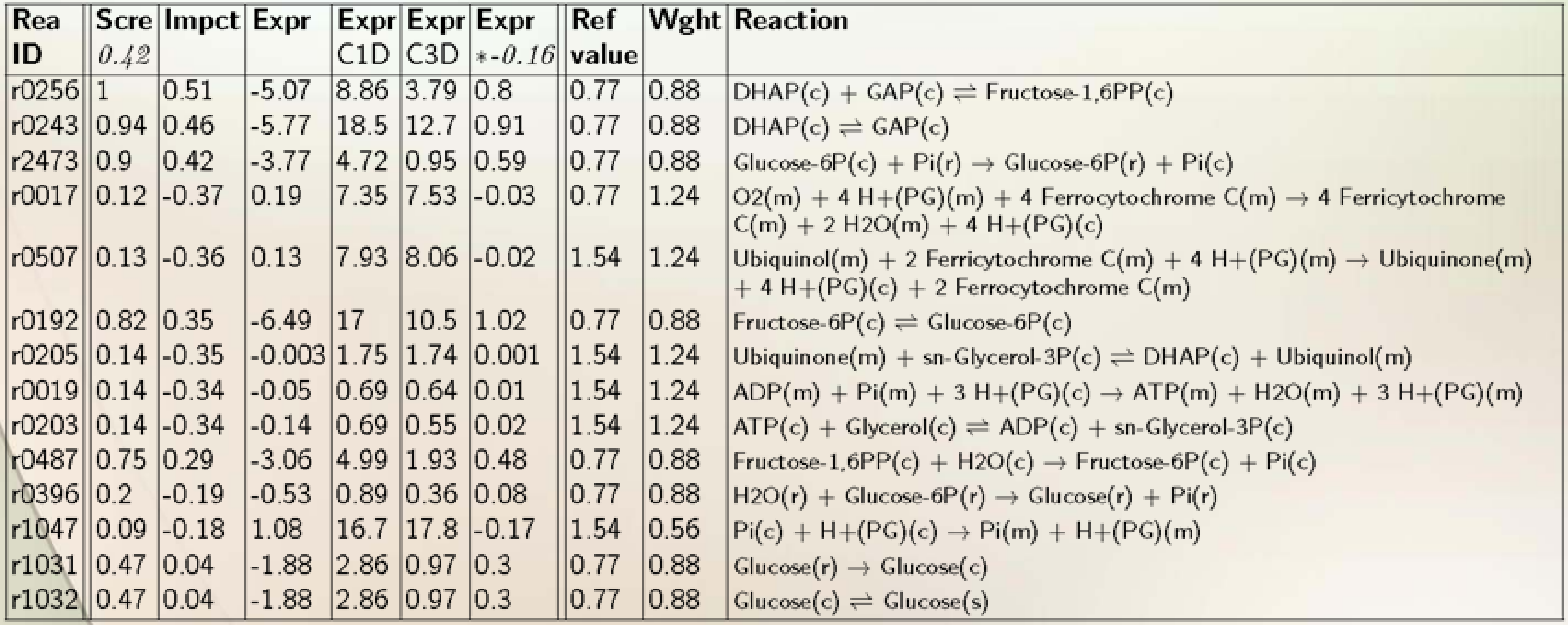
| Simulation | control rank | control ampl | control score | TGF$\beta$ rank | TGF$\beta$ ampl | TGF$\beta$ score |
|---|---|---|---|---|---|---|
| Anaerobic rephosph of ATP | 2 | -8.74 | 0.31 | 1 | -12.6 | 0.29 |
| Gluconeogen. from Glycerol | 4 | -6.38 | 0.42 | 3 | -9.16 | 0.35 |
| Aerobic ATP rephosph (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 |

# b) Regulation points

- Contribution of individual reactions
- Expression difference of individual genes

→Prediction of regulation points

Glyconeogenesis from Glycerol



| 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) |

virtual liver network

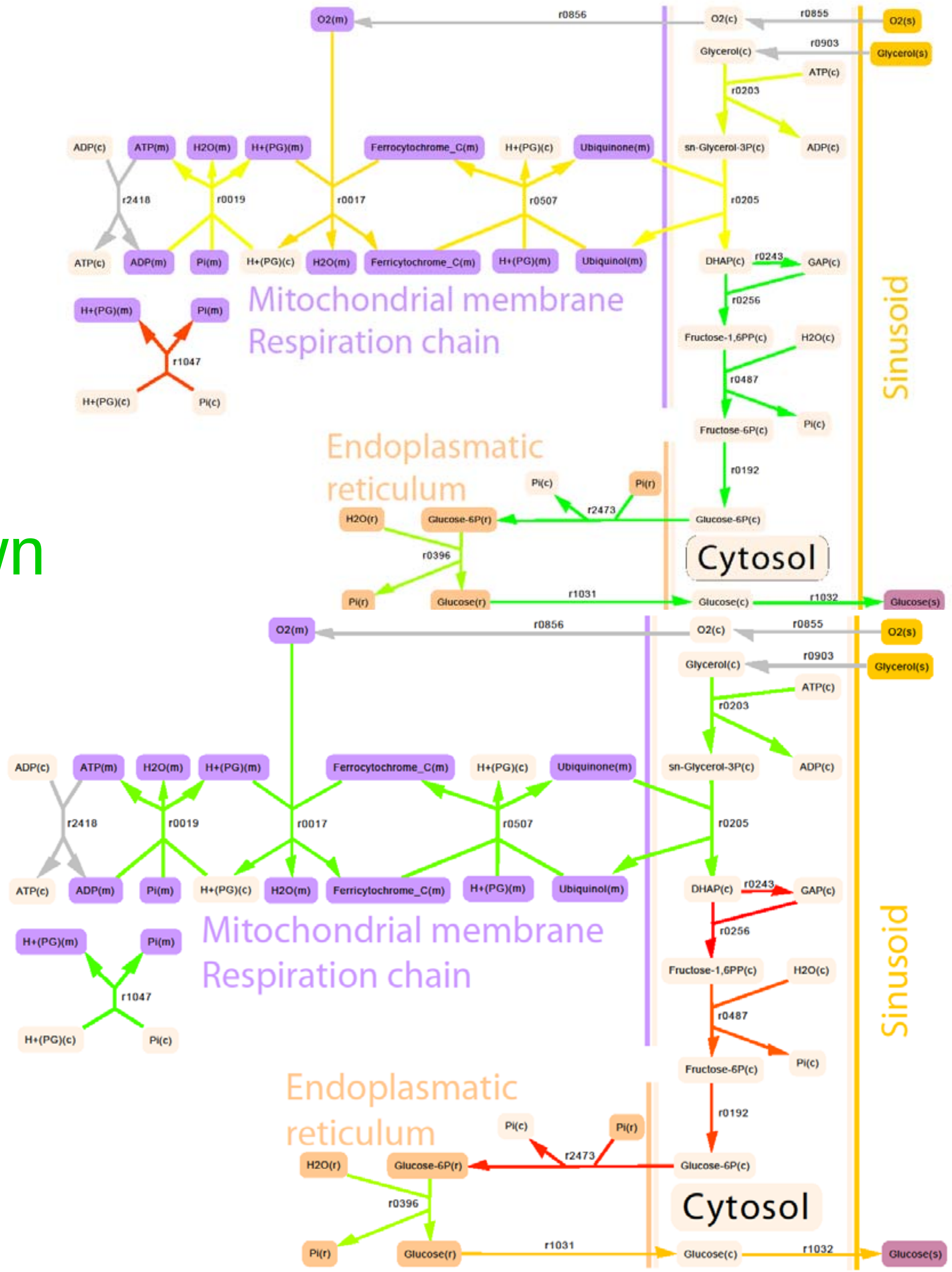
# Glyconeogenesis from Glycerol

Expression change:

up / unchanged / down

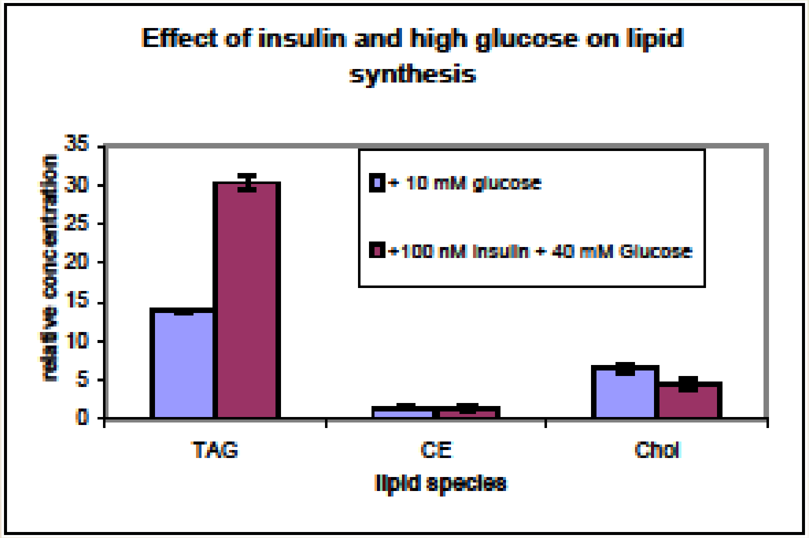
Score:

high / medium / low



# c) Lipid metabolism

- Increased lipid formation (confirmed)
- Focused analysis of lipid-related functions
- Alternative flux scenarios
- Wet lab analysis: Gebhardt, Schiller, Shevchenko



# Summary/Outlook

- ModeScore: Quantitative assessment of metabolic regulation by RNA profiles
- Allows comparative analysis of HGF effect
- In silico predictions
- Focus on lipid metabolism: testing flux scenarios with RNA profiles