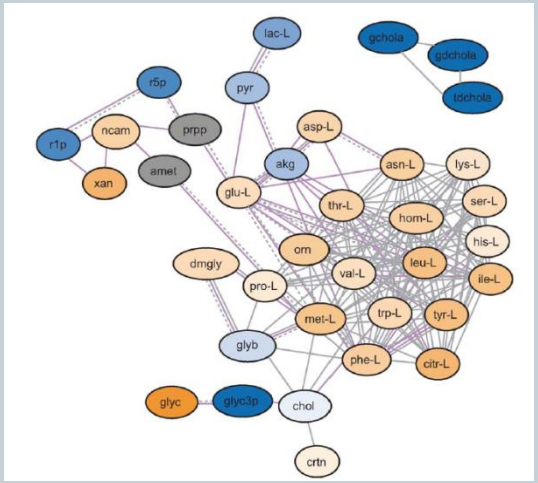
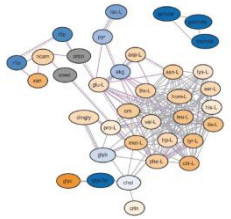
Interpreting Metabolic Profiles Using Unbiased Pathway Model

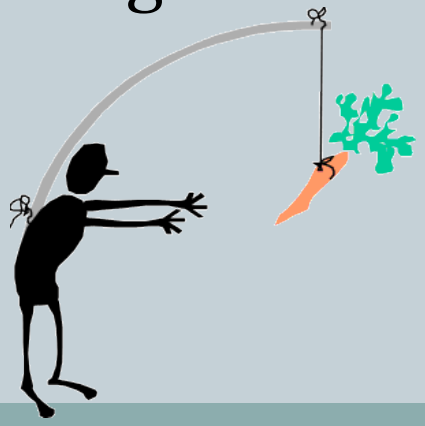
PLOS COMPUTATIONAL BIOLOGY, FEBRUARY 2010



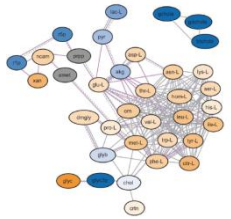
Motivation



- Individuals with the same apparent disease show remarkable variation in prognosis and treatment responsiveness
- Similar disease state can arise from diverse combinations of genetic and environmental factors
- Metabolomics represents a quantitative biologic information from patients

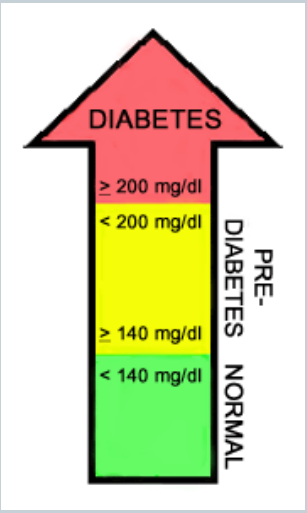


The experiment

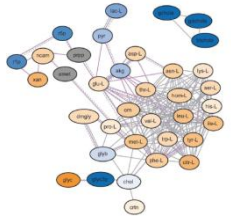


- Oral Glucose Tolerance Test – OGTT
  - 25 individuals with normal glucose tolerance (NGT)
  - 25 individuals with impaired glucose tolerance (IGT)

- Blood samples were drawn fasting and 120 minutes after glucose ingestion
- Mass Spectrometry Analysis



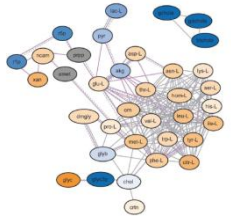
The Naive Analysis



- Identification of significantly changed metabolites
- Pathway enrichment analysis

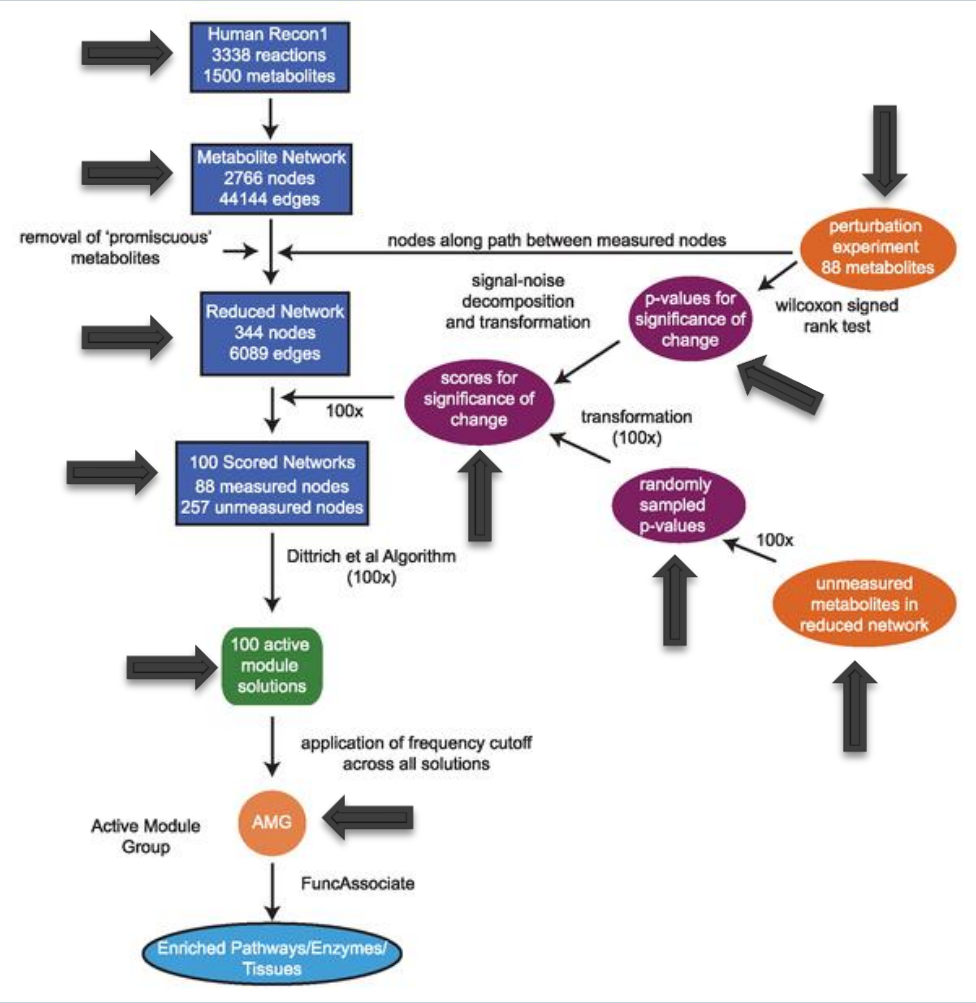
Enrichment solely in NGT for Bile Acid Biosynthesis

Shortcomings

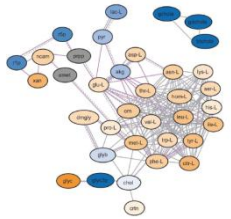


- Sparseness of the metabolome coverage
- Most metabolites are implicated in multiple pathways
- Metabolic vs. Hierarchical regulation
- Physiologic perturbation only affects a subnetwork of metabolites that may not correspond to any of the preconceived pathway definitions

Building Metabolic Reaction Network and Finding Active Module Groups



Characterizing Active Modules of OGTT



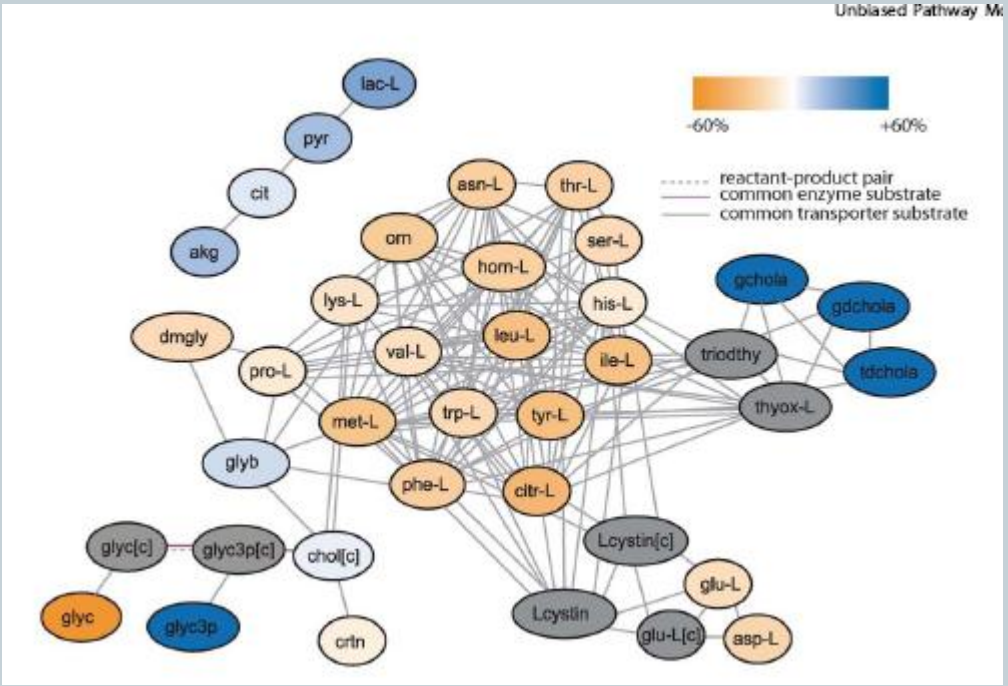
- Enrichment for Glycerophospholipid Metabolism and Glycine, Serine and Threonine Metabolism

The pathways encompass very few of the AMG metabolites

- Using Shlomi *et al. t*issue specific predictions, AMGs showed enrichment for metabolites predicted to be active in kidney and liver

Amino Acids involvement in Glucose Response

- A central cluster of highly interconnected standard and non standard amino acids



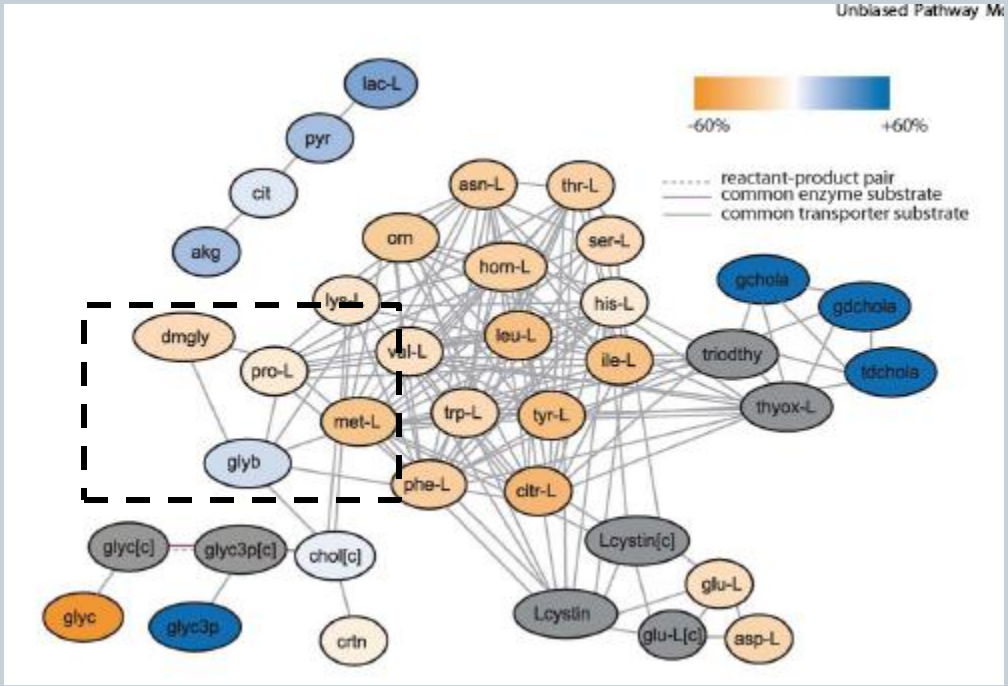
Enrichment for Enzymes and Transporters

Table 1. Enrichment for enzymes and transporters in the NGT and IGT active module groups.

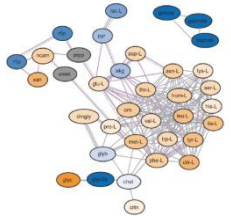
Enzyme or Transporter Family	Enzyme or Transporter Family Member	System	Measured Substrates in Active Module Groups	Reaction	Tissue Distribution
SLC6	SLC6A14*	B(0,+)	Citr-L, Leu-L, Ile-L, Met-L, Lys-L, Val-L, Phe-L, Tyr-L, Trp-L, His-L, Orn-L, Ser-L, (reduced transport for Thr-L, Hom-L, Asn-L, Gln-L)	Facilitated	lung, trachea, salivary gland, mammary gland, pituitary, stomach, colon
SLC6	SLC6A15†	NA	Val-L, Leu-L, Met-L, Ile-L	Facilitated	brain
SLC6	SLC6A19*	B(0)	Citr-L, Leu-L, Ile-L, Phe-L, Trp-L, Tyr-L, Gln-L, Met-L, Asn-L, Hom-L, Thr-L, Ser-L	Facilitated	kidney, intestine
SLC3/SLC7	SLC7A1†	y+	Lys-L, Arg-L, Orn-L, His-L	Facilitated	Ubiquitous except liver
SLC3/SLC7	SLC7A2†	y+	Lys-L, Arg-L, Orn-L, His-L	Facilitated	liver, skeletal muscle, pancreas
SLC3/SLC7	SLC7A3†	y+	Lys-L, Arg-L, Orn-L, His-L	Facilitated	thymus, overy, testis, brain
SLC3/SLC7	SLC3A2/SLC7A5*	L	Tyr-L, Phe-L, Trp-L, Leu-L, Ile-L, Val-L, His-L, Citr-L	Exchange	brain, ovary, testis, placenta
SLC3/SLC7	SLC3A2/SLC7A8†	L	Citr-L, Gln-L, Leu-L, Ile-L, Met-L, Val-L, Phe-L, Thr-L, Asn-L, Trp-L, Ser-L, Tyr-L, Hom-L	Exchange	kidney, intestine, brain, placenta, ovary, testis, muscle, epithelium
SLC3/SLC7	SLC3A1/SLC7A9*	b(0,+)	Lys-L, Val-L, Orn-L, Met-L, Ile-L, Leu-L	Exchange	kidney, intestine, lung, placenta, brain, liver, endothelium
SLC43	SLC43A1*	L	Val-L, Ile-L, Citr-L, Leu-L, Phe-L, Met-L	Facilitated	kidney
SLC43	SLC43A2*	L	Val-L, Ile-L, Citr-L, Leu-L, Phe-L, Met-L	Facilitated	kidney
SLC38	SLC38A4†	A	Met-L, Lys-L, His-L, Arg-L, Asn-L, Ser-L	Facilitated	liver, skeletal muscle, kidney, pancreas
SLCO1	SLCO1A2†	NA	taurochenodeoxycholate, glycocholate, glycochenodeoxycholate	Facilitated	brain, kidney, liver, ciliary body
SLCO1	SLCO1B1†	NA	taurochenodeoxycholate, glycocholate, glycochenodeoxycholate	Facilitated	liver
SLCO1	SLCO1B3†	NA	taurochenodeoxycholate, glycocholate, glycochenodeoxycholate	Facilitated	liver

Amino Acids involvement in Glucose Response

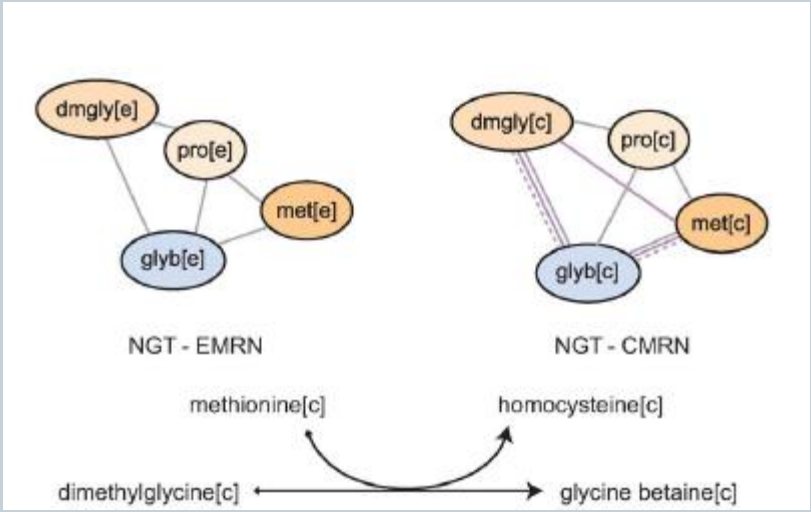
- A central cluster of highly interconnected standard and non standard amino acids



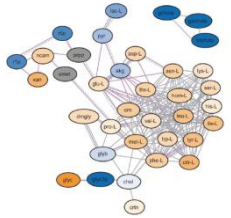
A Role For the Osmoregulatory Transporter SLC6A12 in the Glucose Response



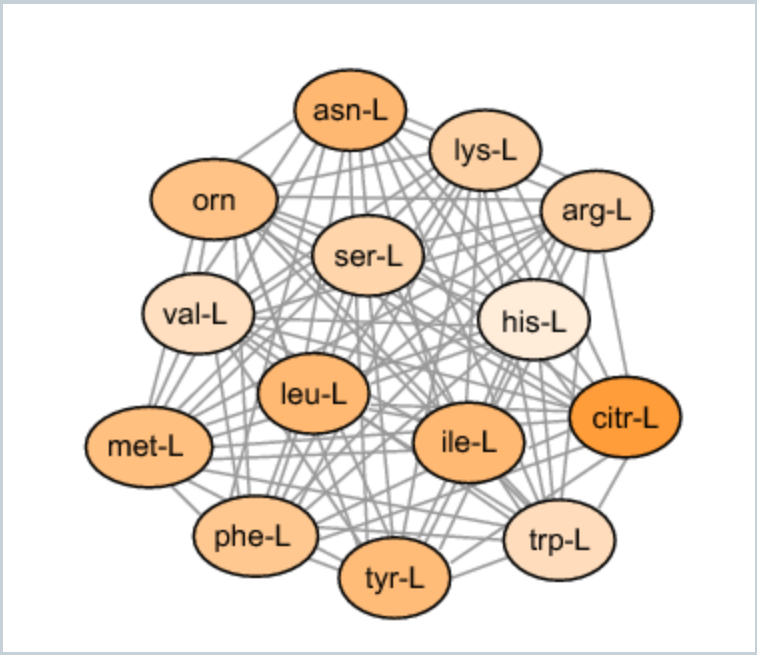
- The purpose of this coupling is to maintain cell osmolarity in face of the amino acid/glucose influx brought about by insulin



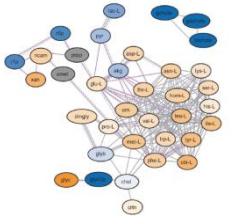
Comparison of NGT and IGT

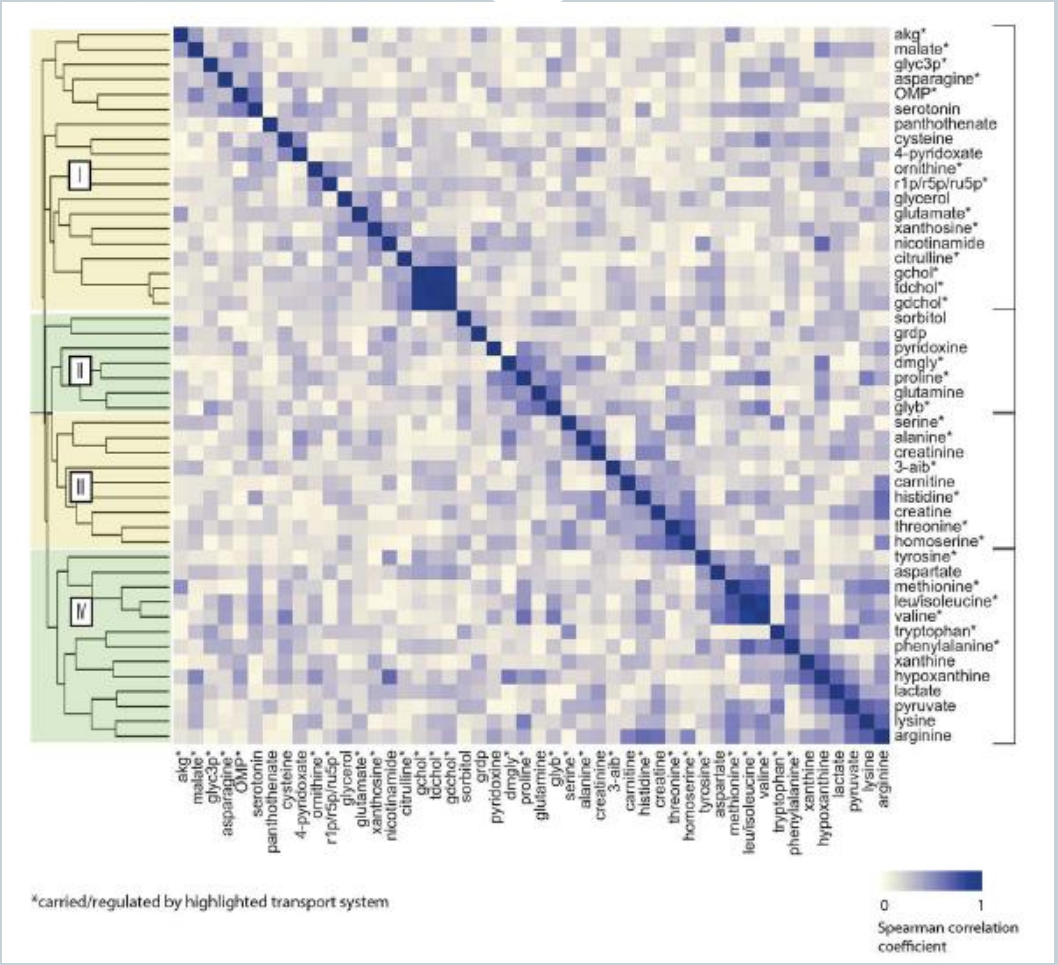


- Glucose and/or insulin-stimulated changes appear to have been blunted in the IGT group

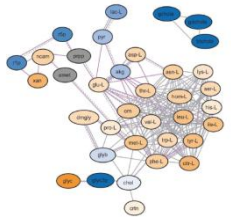


Changed Metabolites Cluster According to Transporter Activity



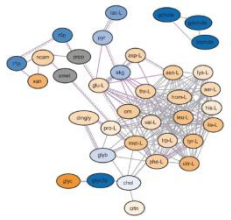


Limitations



- Measurements of additional metabolites may show other more convincing pathways
- Considering all significant changes equivalently
- Alteration in metabolic flux within the cell
- Significantly changed metabolites that are not closely linked are unlikely to appear in AMGs

Summary



- A different method for integrating high throughput data with metabolic model
- Identification of relationships among changed metabolites
- Highlighting the importance of specific solute carriers
- Comparison between NGT and IGT supported blunted glucose stimulated activities in IGT