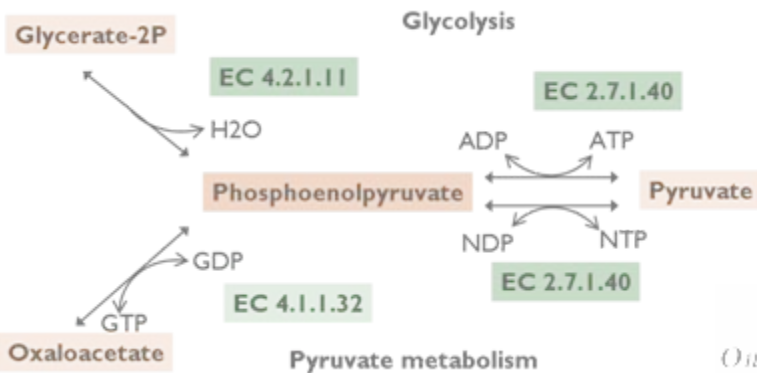
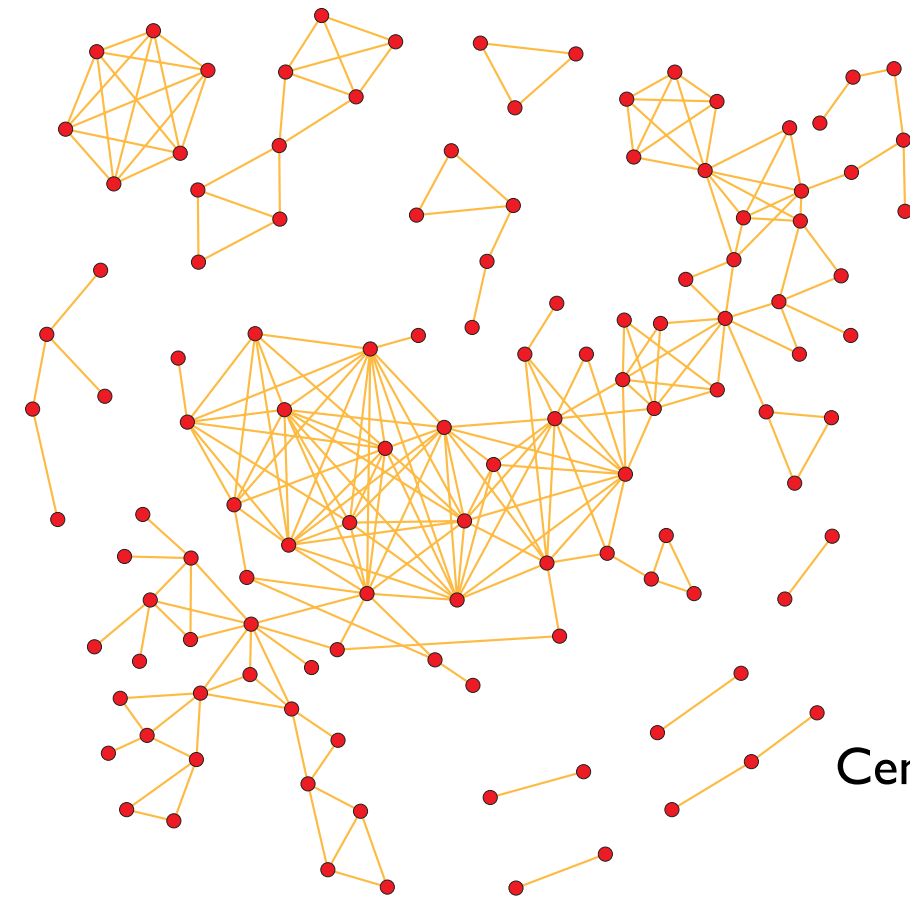


Metabolomic links of human diseases

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Department of physics
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International workshop and conference for network sciences
(NetSci 2007)
New York Hall of Science, May 20-25, 2007



Human genome annotation for diseases

Some disorders are associated with gene mutation



AGAT deficiency

GATM

EC 2.1.4.1

L-arginine + glycine →
L-ornithine + guanidinoacetate

S-Adenosyl-L-methionine + guanidinoacetate →
S-Adenosyl-L-homocysteine + Creatine

Creatine deficiency

Mental retardation
Language disorder
Epilepsy

Homo sapiens [Build 36.2 \(Current\)](#) [BLAST The Human Genome](#)

Chromosome: [1](#) [2](#) [3](#) [4](#) [5](#) [6](#) [7](#) [8](#) [9](#) [10](#) [11](#) [12](#) [13](#) [14](#) [[15](#)] [16](#) [17](#) [18](#) [19](#) [20](#) [21](#) [22](#) [X](#) [Y](#) [MT](#)

Query: [GATM](#) [\[clear\]](#)

Master Map: [OMIM Morbid](#) [Summary of Maps](#) [Maps & Options](#)

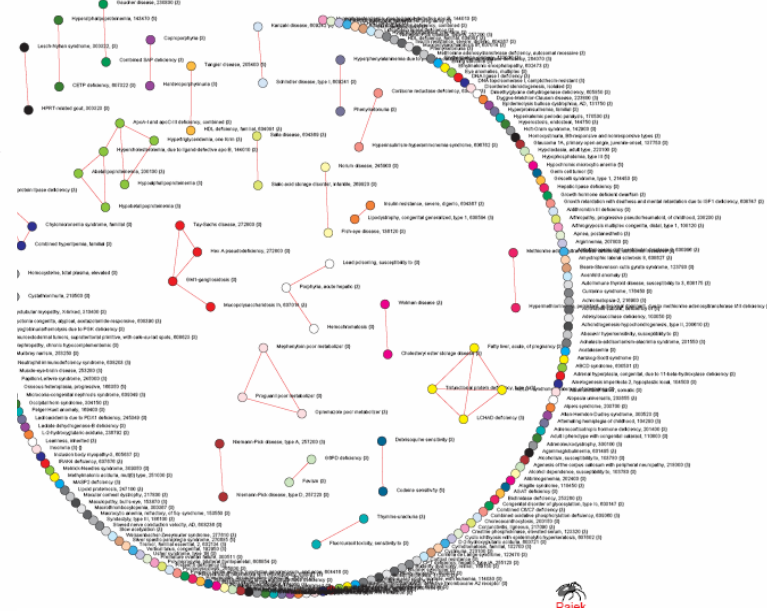
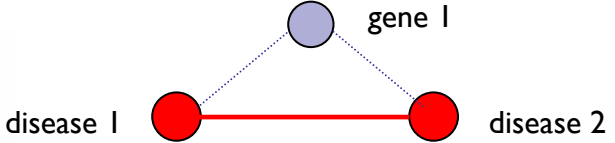
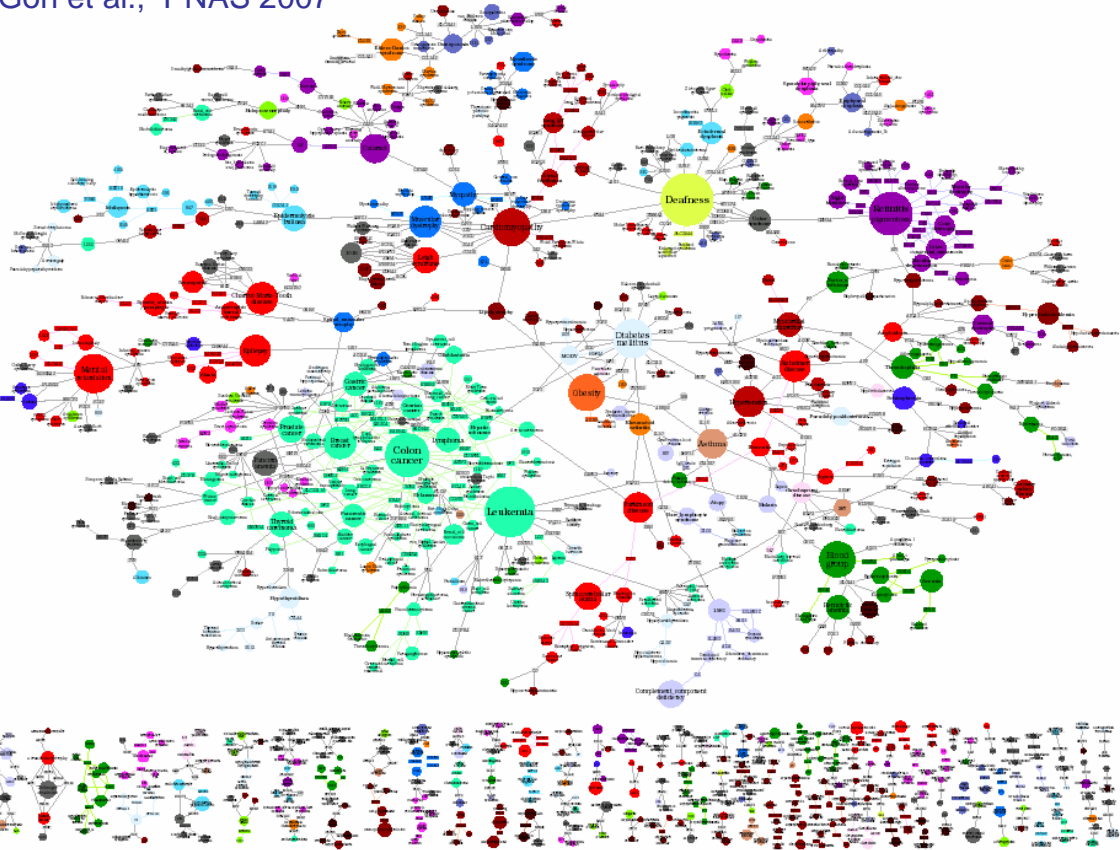
Region Displayed: [15q15.3-15q21.1](#)

Genes_seq	Pheno	Genes_cyto	Morbid	MM Number	Symbol	GeneID	Disease
LCMT2		LCMT2		603805	TGM6	9333	Peeling skin syndrome, acral type, 609796
ADAL		ADAL		604360	SPG11	23442	Spastic paraplegia-11
ZNF690		ZNF690		607036	IVD	3712	Isovaleric acidemia, 243500
76P		76P		607465	CDAN1	146059	Anemia, congenital dyserythropoietic, type I, 224120
TP53BP1		TP53BP1		177070	EPB42	2038	Spherocytosis, hereditary, Japanese type
MAP1A		CATSPER2P1		606440	STRC	161497	Deafness, autosomal recessive 16, 603720
HISPPD2A		FRTS		602860	BUB1B	701	Colorectal cancer, 114500
CKMT1B		HISPPD2B		604114	PLCB2	5330	Platelet PLC beta-2 deficiency
STRC		MAP1A		605419	SCZD10	63944	Schizophrenia, 181500
		HISPPD2A		606759	DUOX2	50506	Hypothyroidism, congenital, due to DUOX2 deficiency, 607200
		HCL3		134600	FRTS	65211	Fanconi renotubular syndrome
		MOPCB2		602360	GATM	2628	AGAT deficiency
		SPG11		604432	SCA11	10977	Spinocerebellar ataxia-11
		B2MR		602099	ALS5	255	Amyotrophic lateral sclerosis-5, juvenile recessive
		SCZD10		600839	SLC12A1	6557	Barter syndrome, type 1, 601678
		CKMT1B		114240	CAPN3	825	Muscular dystrophy, limb-girdle, type 2A, 253600
		STRC		605981	UBR1	197131	Johanson-Blizzard syndrome, 243800
		CATSPER2					
		LOC554224					
		CKMT1A					
		LOC554225					
		LOC440278					
		PDIA3					
		ELL3					
		SERF2					
		SERINC4					
		HYPK					
		MFAP1					
		MDR76					
		LOC728758					
		ACTBP7					
		SCZD10					
		SCA11					
		EDMD5					

Genetic links of human diseases

Diseases associated with a common gene's mutation or a common module's breakdown may be developed together in a patient

Goh et al., PNAS 2007



1286 diseases, 1534 links,
Largest connected component 875
Clustering of the disease in the same class

Poor connectivity of metabolic diseases
217 metabolic diseases
Largest component 6

Human genome and metabolic network

www.genome.jp/kegg

 **Homo sapiens (human): 5313** Help

Entry	5313	CDS	H.sapiens
Gene name	PKLR		
Definition	pyruvate kinase, liver and RBC [EC:2.7.1.40]		
Orthology	KO: K00873 pyruvate kinase		
Pathway	PATH: hsa00010 Glycolysis / Gluconeogenesis PATH: hsa00230 Purine metabolism PATH: hsa00620 Pyruvate metabolism PATH: hsa00710 Carbon fixation PATH: hsa04910 Insulin signaling pathway PATH: hsa04930 Type II diabetes mellitus PATH: hsa04950 Maturity onset diabetes of the young		

25736 genes

959 full EC numbers for enzymes

1493 reactions

1258 compounds

 **ENZYME: 2.7.1.40** Help

Entry	EC 2.7.1.40	Enzyme
Name	pyruvate kinase; phosphoenolpyruvate kinase; phosphoenol transphosphorylase	
Class	Transferases; Transferring phosphorus-containing groups; Phosphotransferases with an alcohol group as acceptor BRITE hierarchy	
Sysname	ATP:pyruvate 2-O-phosphotransferase	
Reaction(IUBMB)	ATP + pyruvate = ADP + phosphoenolpyruvate [RN:R00200]	
Reaction(KEGG)	R00200.	

Metabolic pathways and diseases

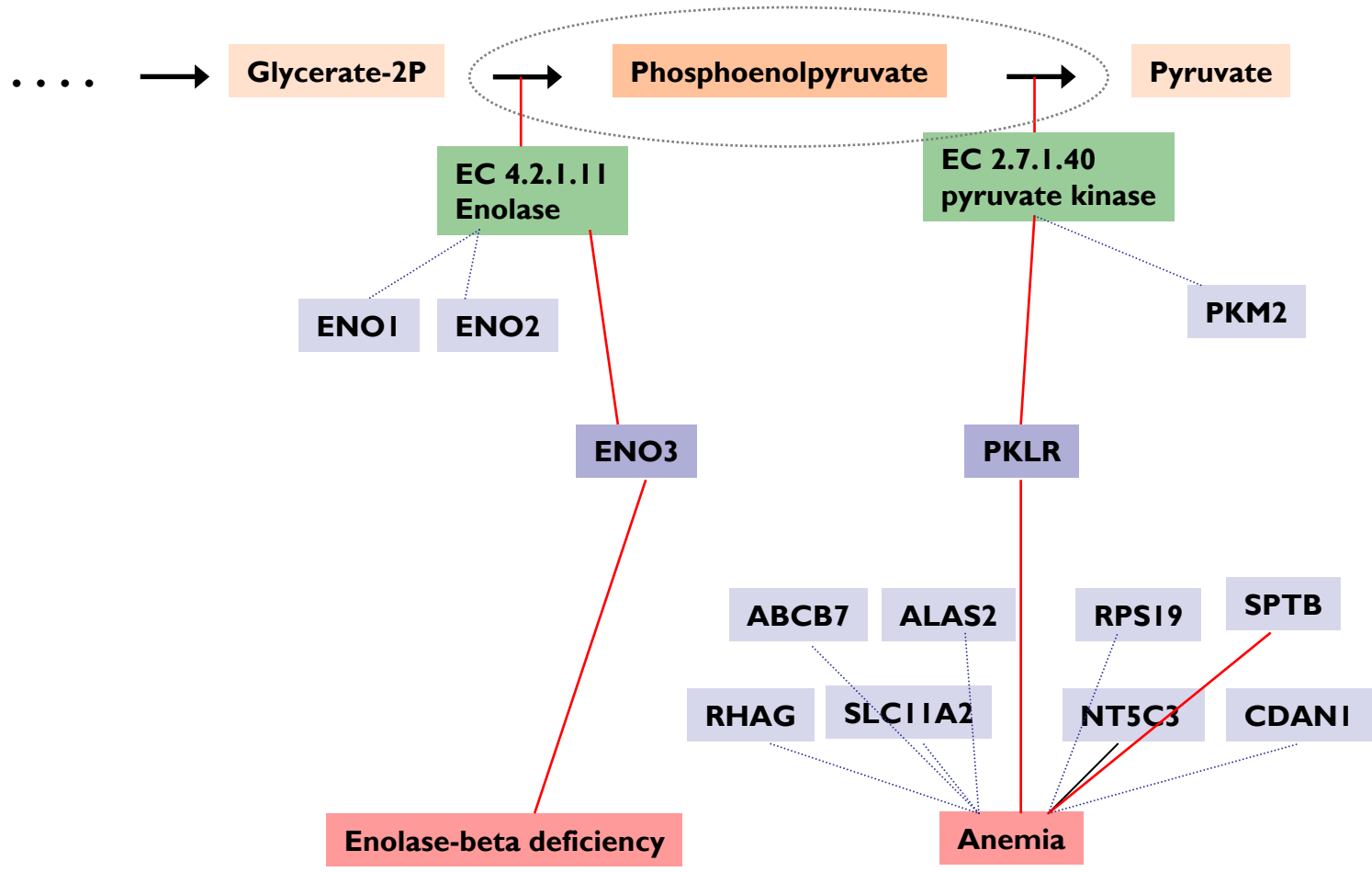
Metabolome

Enzymome

Genome

Diseasome

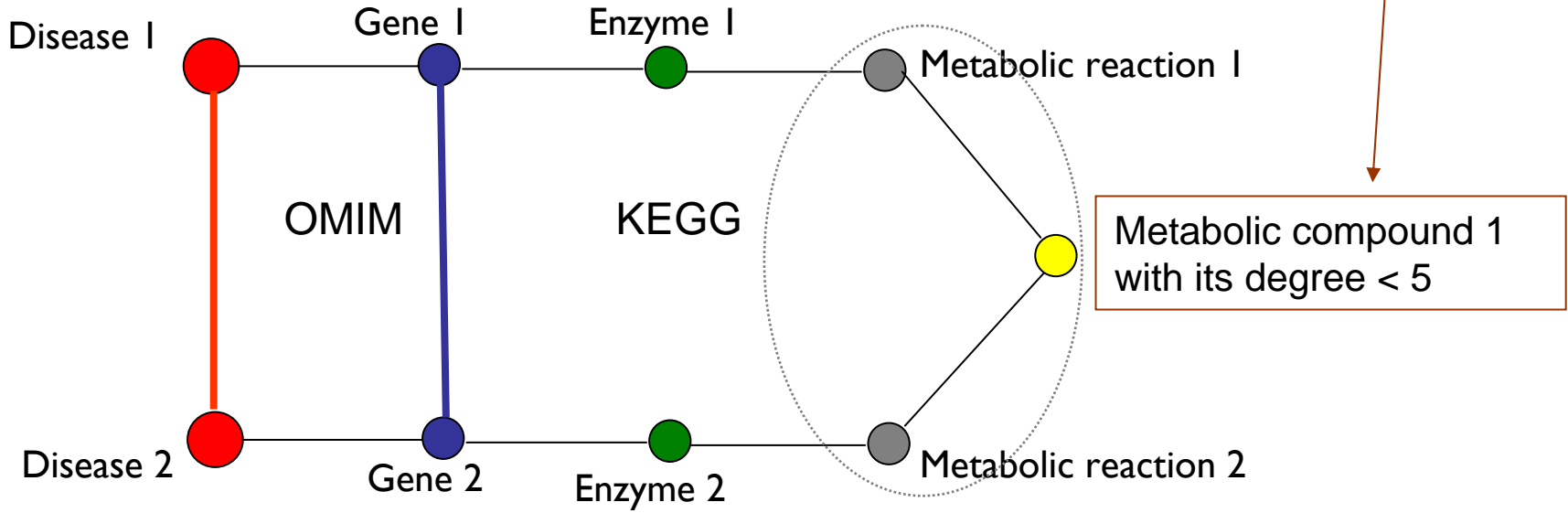
[Glycolysis]



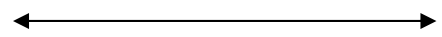
Metabolomic links

Connectivity of the metabolism is projected onto the gene space and disease space

Only the metabolic compounds with small degree are considered for constructing these metabolic links since a perturbation of one reaction is not expected to affect 'hub' compounds. The presented results are, however, still valid even if we include All the metabolic compounds to construct the metabolic links.



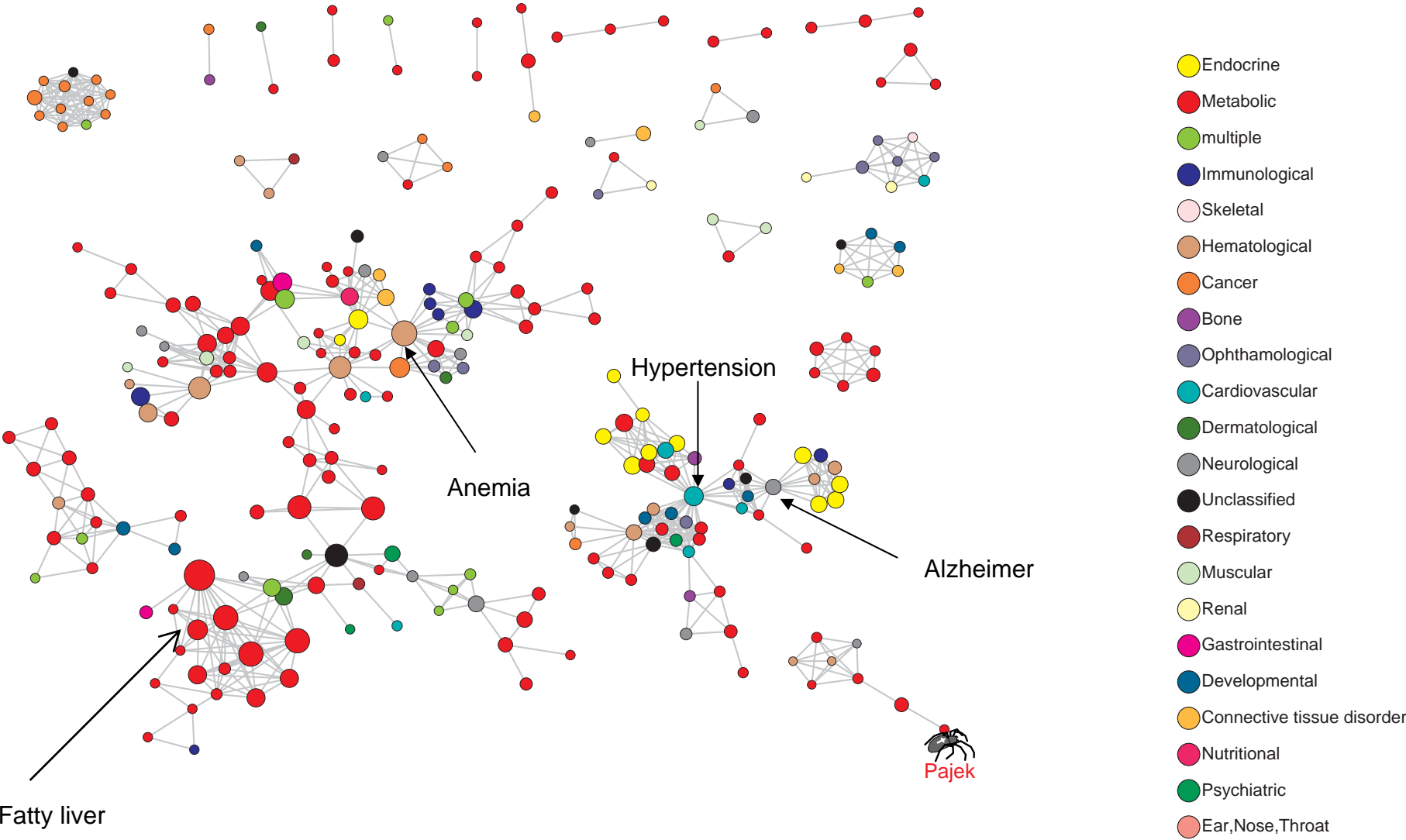
Disease



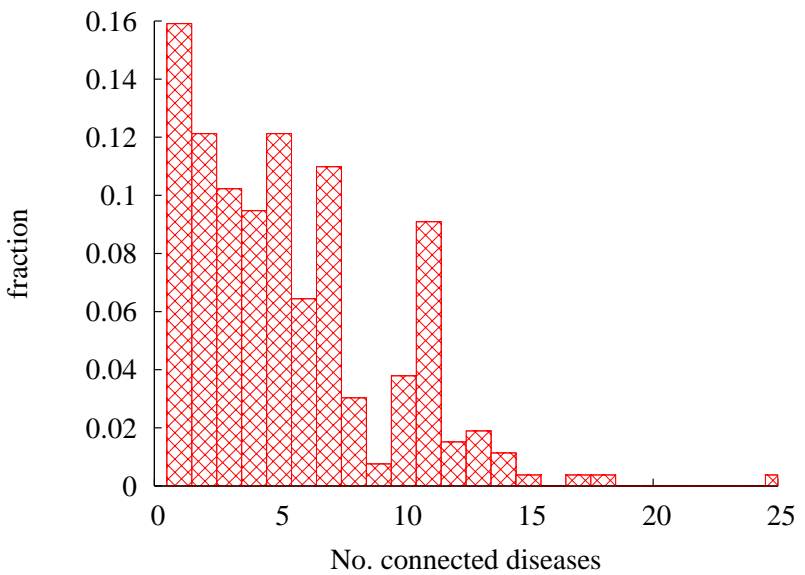
A segment of a metabolic pathway:
Adjacent reactions

Disease network

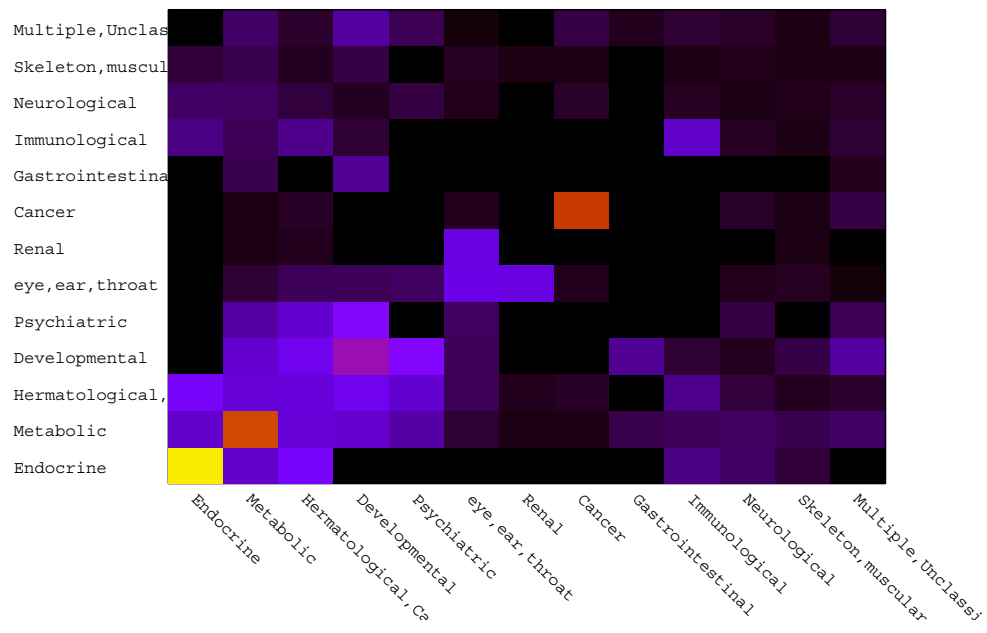
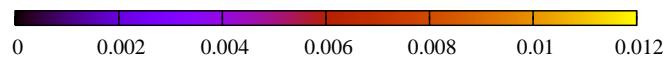
264 diseases 714 metabolomic links
Largest connected component includes 118 diseases
Second largest one includes 50 diseases



Link distribution

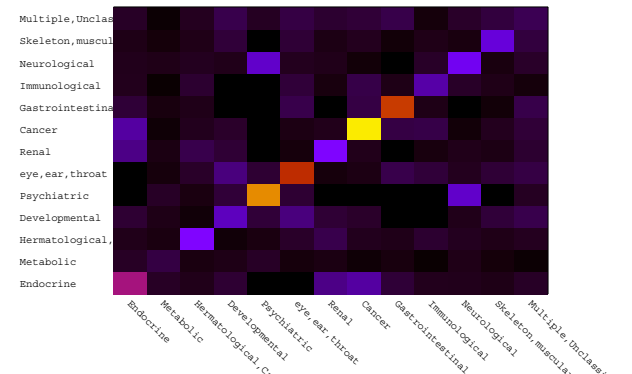
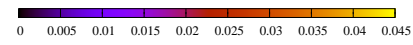


Fraction of connected pairs



Disease	Class	Degree
Hypertension, diastolic, resistance to	Cardiovascular	25
Anemia, congenital dyserythropoietic, type I	Hematological	18
Warfarin resistance	Hematological	17
Hemolytic anemia due to adenylate kinase deficiency	Hematological	15
Alzheimer disease-1, APP-related	Neurological	14
Tolbutamide poor metabolizer	Unclassified	14
Trifunctional protein deficiency, type 1	Metabolic	14
Coronary artery disease, autosomal dominant	Cardiovascular	13
Diabetes mellitus	Endocrine	13
HELLP syndrome, maternal, of pregnancy	Metabolic	13
LCHAD deficiency	Metabolic	13
Fatty liver, acute, of pregnancy	Metabolic	13
Mucopolysaccharidosis 1h	Metabolic	12
GM1-gangliosidosis	Metabolic	12
Nucleoside phosphorylase deficiency, immunodeficiency due to	Immunological	12
Myoneurogastrointestinal encephalomyopathy syndrome	multiple	12
Virilization, maternal and fetal, from placental aromatase deficiency	Developmental	11
Meningioma	Cancer	11
Bannayan-Riley-Ruvalcaba syndrome	Unclassified	11
Aromatase deficiency	Metabolic	11

Cf. Genetic links



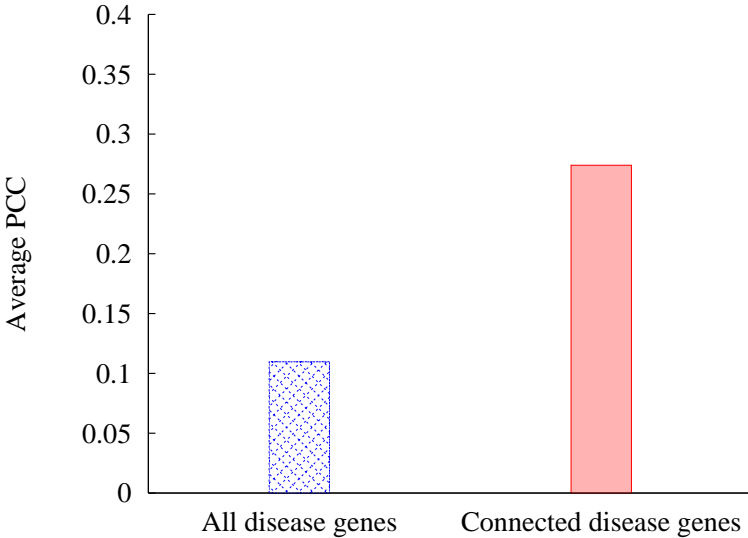
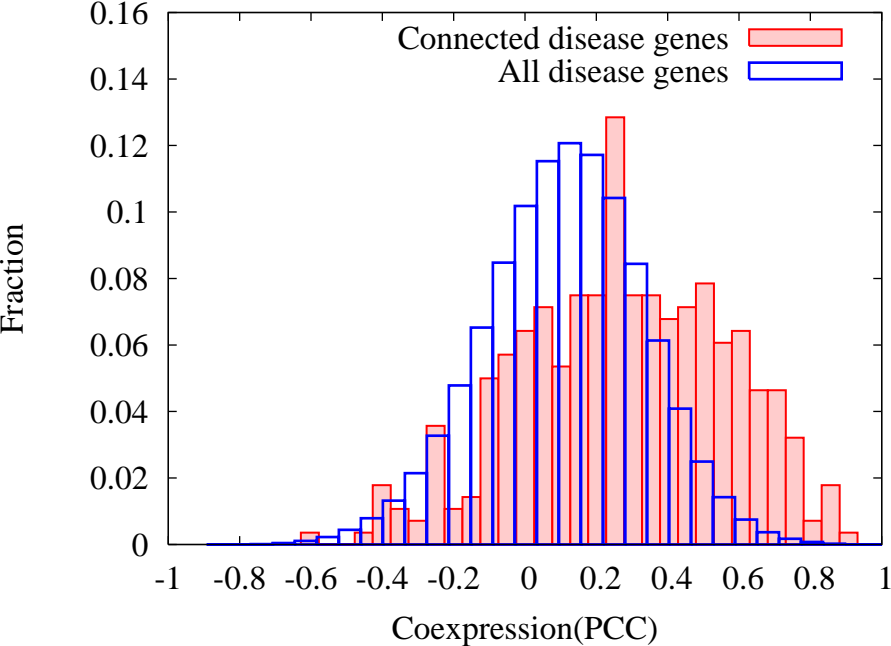
Coherence of the human genes connected by metabolomic links

We computed Gene-gene coexpression of 20655 genes in 36 normal tissues reported in Ge et al. Genomics 2005

$$PCC_{ij} = \frac{\frac{1}{N} \sum_k (s_{ik} - \langle s \rangle_i)(s_{jk} - \langle s \rangle_j)}{\sqrt{\frac{1}{N} \sum_k (s_{ik} - \langle s \rangle_i)^2 \frac{1}{N} \sum_k (s_{jk} - \langle s \rangle_j)^2}}$$

s_{ik} = Logarithm of the expression level of a gene i in tissue

$N = 36$ (Number of tissues)



Cf. Yeast genes also exhibit such coherence along the metabolomic links
Kharchenko et al., Molecular systems biology, 2005

Comorbidity of human diseases connected by metabolomic links

Comorbidity : Co-occurrence of two or more disorders in an individual at a given time

Dataset
13,039,018 inpatients
32,341,348 visits from 1990 to 1993
Up to 10 diseases diagnosed for each visit

Phi-correlation : a measure of comorbidity for a pair of diseases

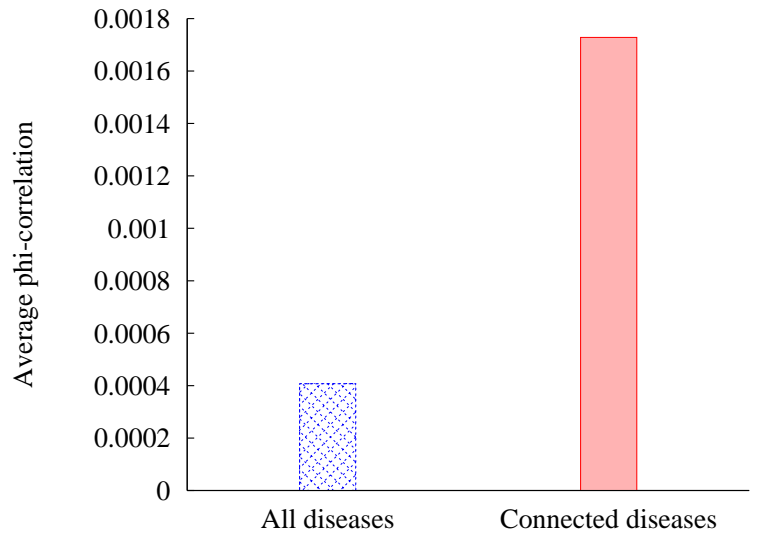
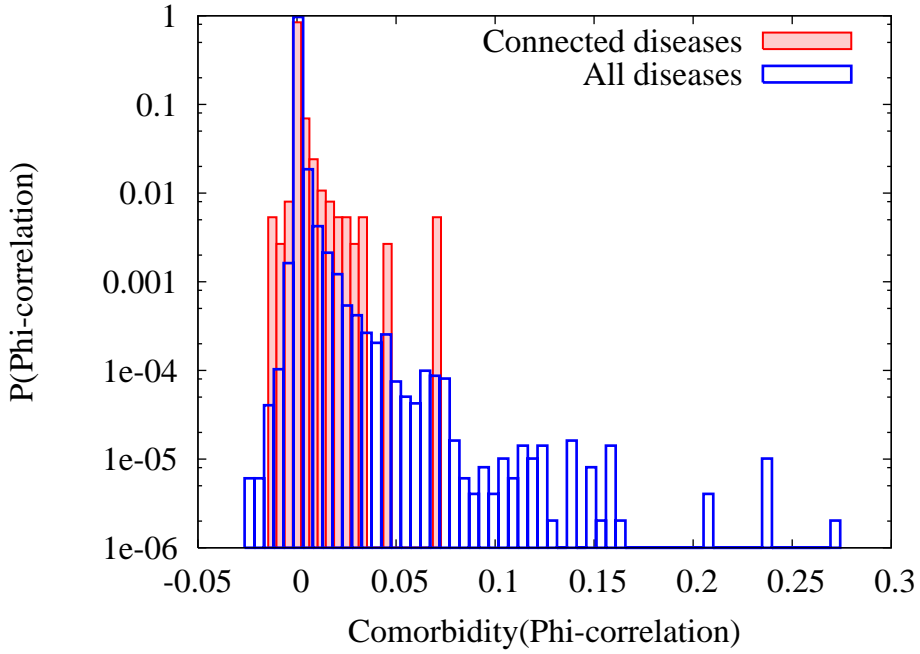
	Don't have disease j	have disease j
Don't have disease i	A	B
have disease i	C	D

$$\phi_{ij} = \frac{AD - BC}{\sqrt{(A + B)(C + D)(A + C)(B + D)}}$$

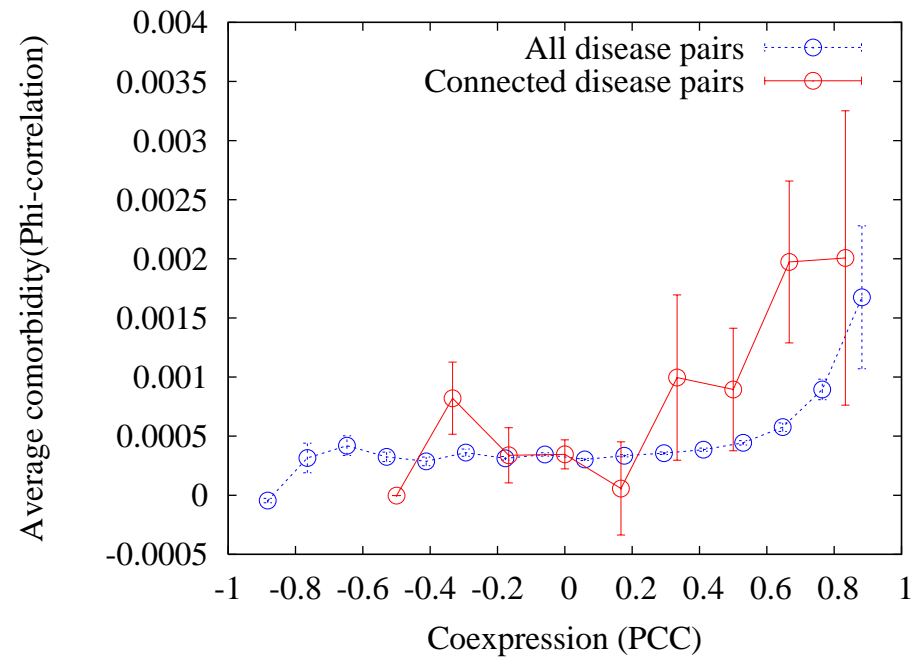
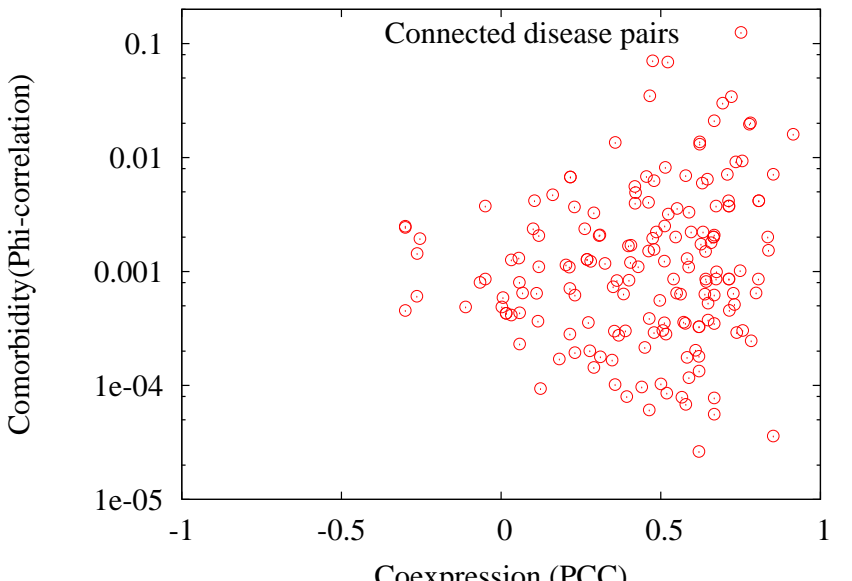
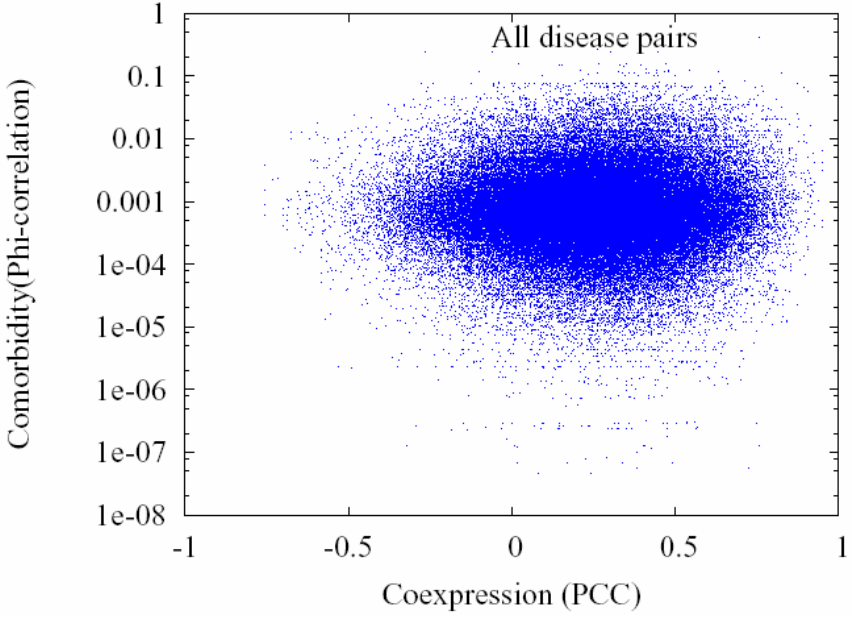
= 1 if B=C=0
= -1 if A=D=0

Comorbidity of human diseases connected by metabolomic links

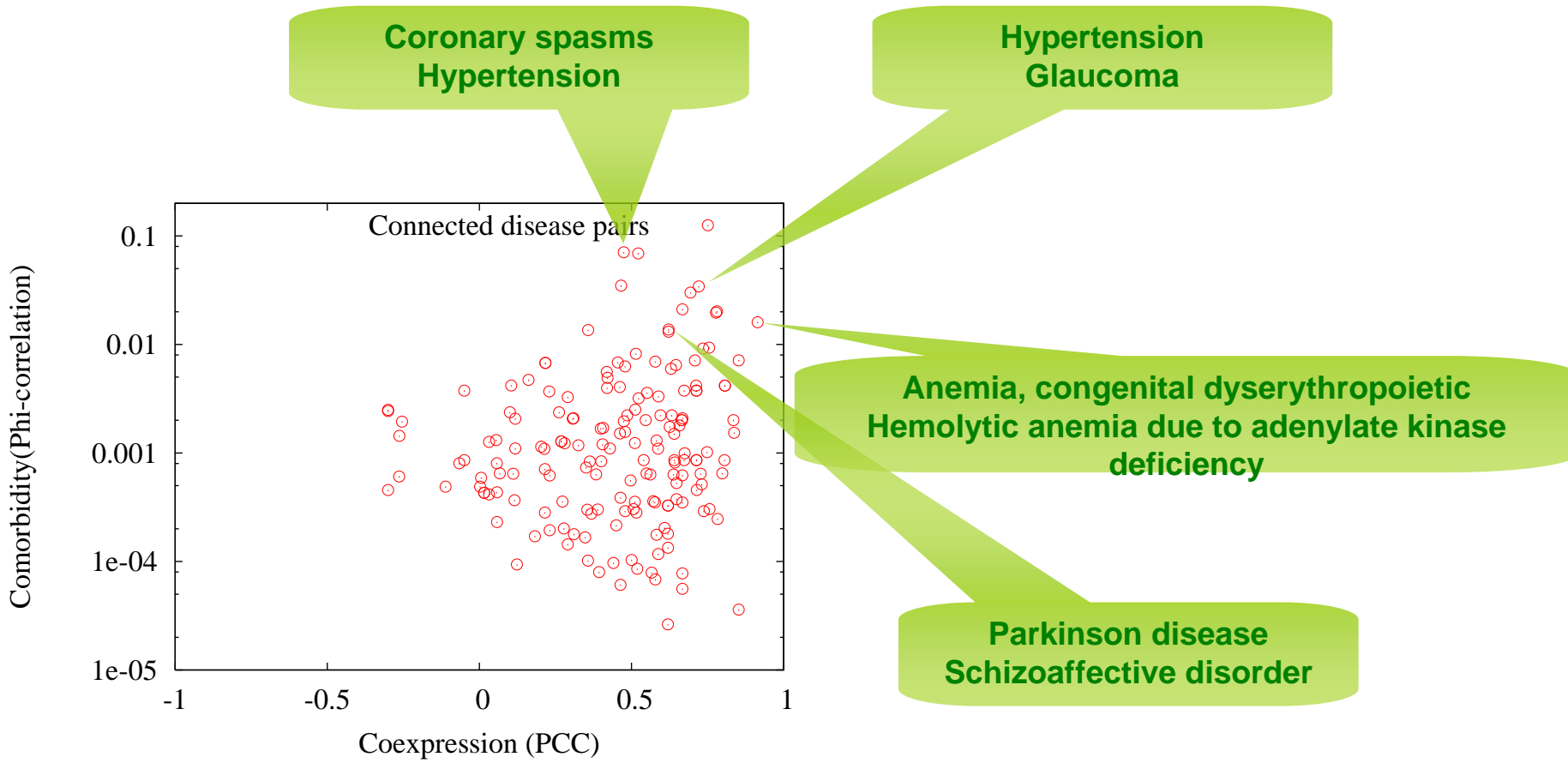
We computed the phi-correlation for all genetic disorders we considered using the disease dataset



Correlation of gene coexpression and comorbidity



Pairs of connected diseases with high comorbidity and high co-expression



Summary and outlook

Compiling the association of metabolic pathways and human diseases, we suggested a network of human diseases connected by the metabolomic links.

Connected diseases are characterized by the high co-expression of their associated genes and the high comorbidity, validating the metabolomic links

Metabolic pathways can be annotated for the diseases, which can be enriched by the comorbidity data and the gene co-expression.

Co-Sets:

*reactions the fluxes of which are coupled in the metabolic network
Recently Palsson group reconstructed human metabolic network including transport and exchange reactions*

Case study:

Pathophysiology of metabolic diseases (Oltvai group, U. Pittsburgh)