A network-based approach to identify active pathways and drug effects on metabolic syndrome

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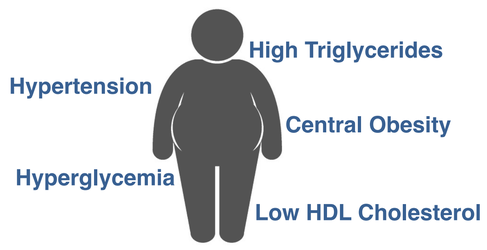
Objectives

A systems biology approach based on **network analysis** was considered to study the underlying **biological processes** deregulated in metabolic syndrome. This approach further provides an adequate background to reflect **drug effects** on metabolic syndrome and for the development of **new therapeutic strategies**.

Metabolic Syndrome



Metabolic syndrome is a **cluster of metabolic disturbances** and increasingly prevalent worldwide [1]. The direct association with type 2 diabetes and cardiovascular diseases entails **serious health implications**.

Methods

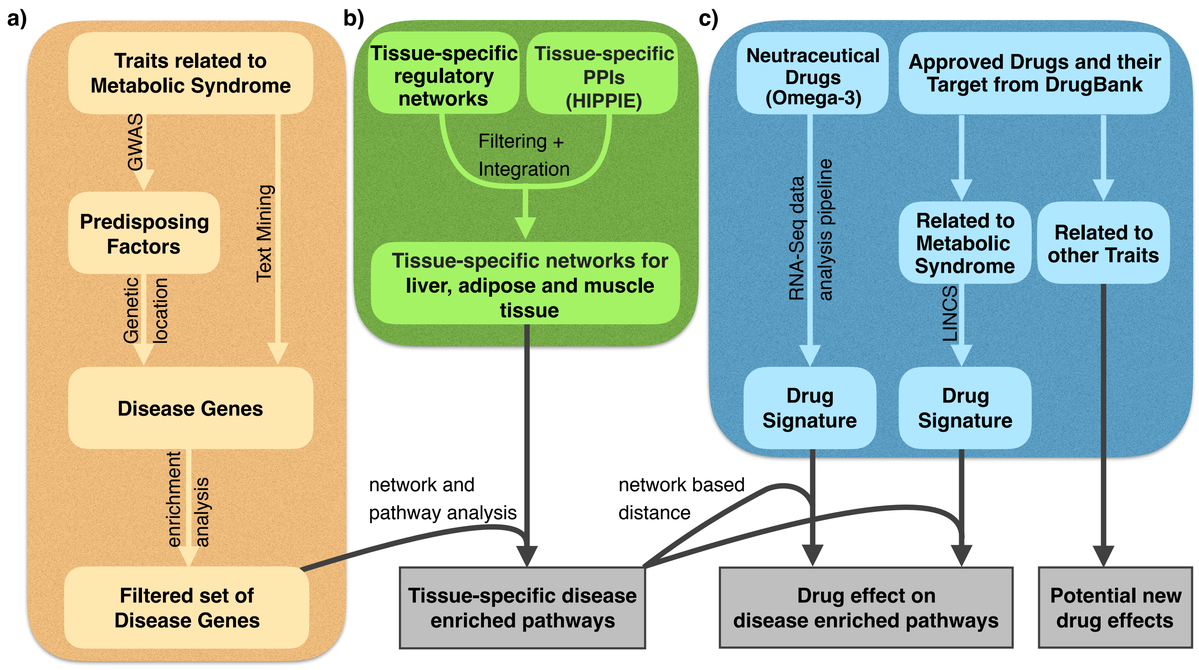
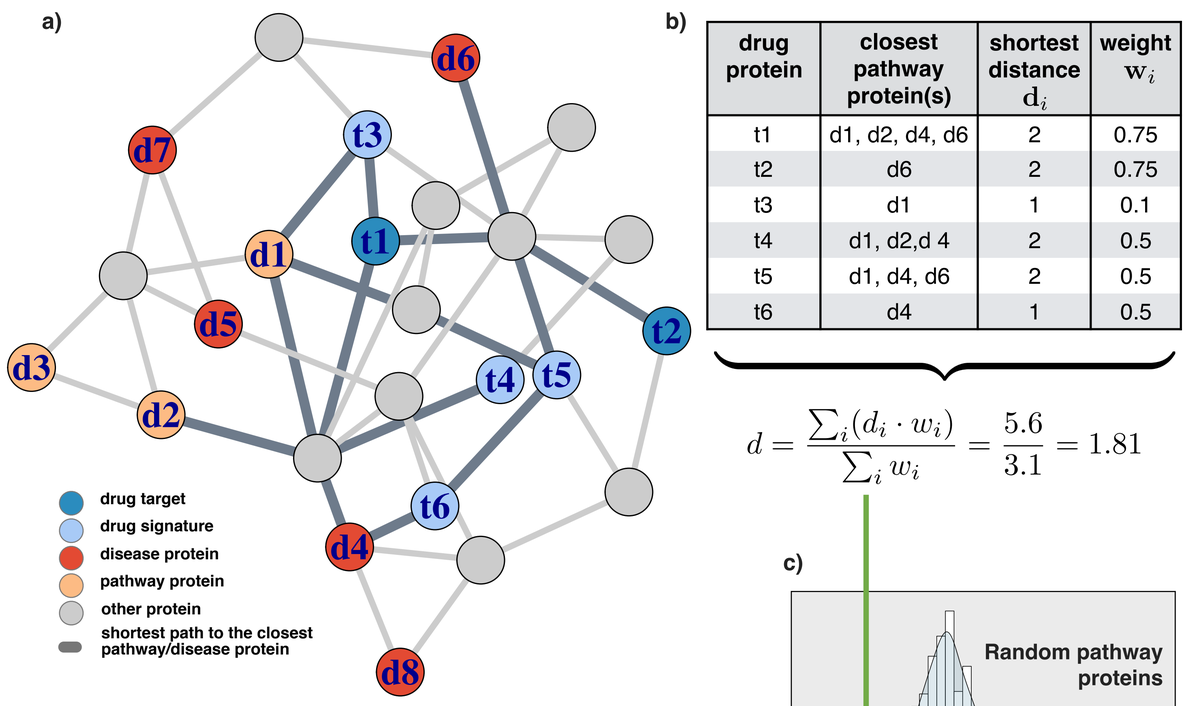


Figure 1. Overview of the proposed approach. **a)** A list of genes associated with **metabolic syndrome** is established [2]. **b) Tissue-specific networks** are constructed by integrating regulatory networks from [3] and PPI networks from HIPPIE db [4]. **c) Drug signatures** are derived from RNA-Seq data or a combination of DrugBank information [5] and LINCS profiles [6].
Integration of these three data sources allows to study **tissue-specific disease enriched pathways**, **drug effects** on these pathways and potential new drug effects in a **drug repurposing** manner.



drug protein	closest pathway protein(s)	shortest distance d_i	weight w_i
t1	d1, d2, d4, d6	2	0.75
t2	d6	2	0.75
t3	d1	1	0.1
t4	d1, d2,d 4	2	0.5
t5	d1, d4, d6	2	0.5
t6	d4	1	0.5

$$d = \frac{\sum_i (d_i \cdot w_i)}{\sum_i w_i} = \frac{5.6}{3.1} = 1.81$$

Figure 2. Network-based drug — disease distance. **a) Network position** and shortest paths between a drug signature (t1 to t6) and a disease enriched pathway (d1 to d8). **b)** Calculation of the **weighted closest distance** d (modified from [7]). **c)** Significant distances are identified by a comparison to a **reference distribution** of distances.

Results

- Identification of **1561 genes** associated with metabolic syndrome.
- Pathway enrichment analysis resulted in **52 disease enriched pathways**, highlighting the importance of the signaling component for the disease **(Table 1)**.
- **2218 approved drugs** were determined from DrugBank [5]; 57 of these drugs have a known application for traits related to metabolic syndrome. **Figure 3** displays the **distances to the disease enriched pathways** for three of these drugs.

PATHWAYS	TISSUE	CATEGORY	DISEASE GENES / PATHWAY GENES	P-VALUE
LIPID DIGESTION, MOBILIZATION, AND TRANSPORT	Liver	Metabolism of Lipids	17/19	3.9e-6
GROWTH FACTOR SIGNALING THROUGH FOXO TF	Liver	Immune System/ Signal Transduction	32/69	1.05e-5
SIGNALING BY NGF	Adipose	Signal Transduction	28/51	0.001
FORMATION OF THE BETA-CATENIN: TCF TRANSACTIVATING COMPLEX	Adipose	Signal Transduction	10/12	0.002
DISEASES OF SIGNAL TRANSDUCTION	Skeletal muscle	Disease	32/57	2.096e-5
SIGNALING BY SCF-KIT	Skeletal muscle	Signal Transduction	23/34	2.096e-5

Table 1. Disease enriched biological pathways in adipose, liver and skeletal muscle tissue. For each network the two most significant disease enriched pathways, their Reactome category [8], the ratio of disease genes and pathway genes as well as the adjusted p-value are displayed.

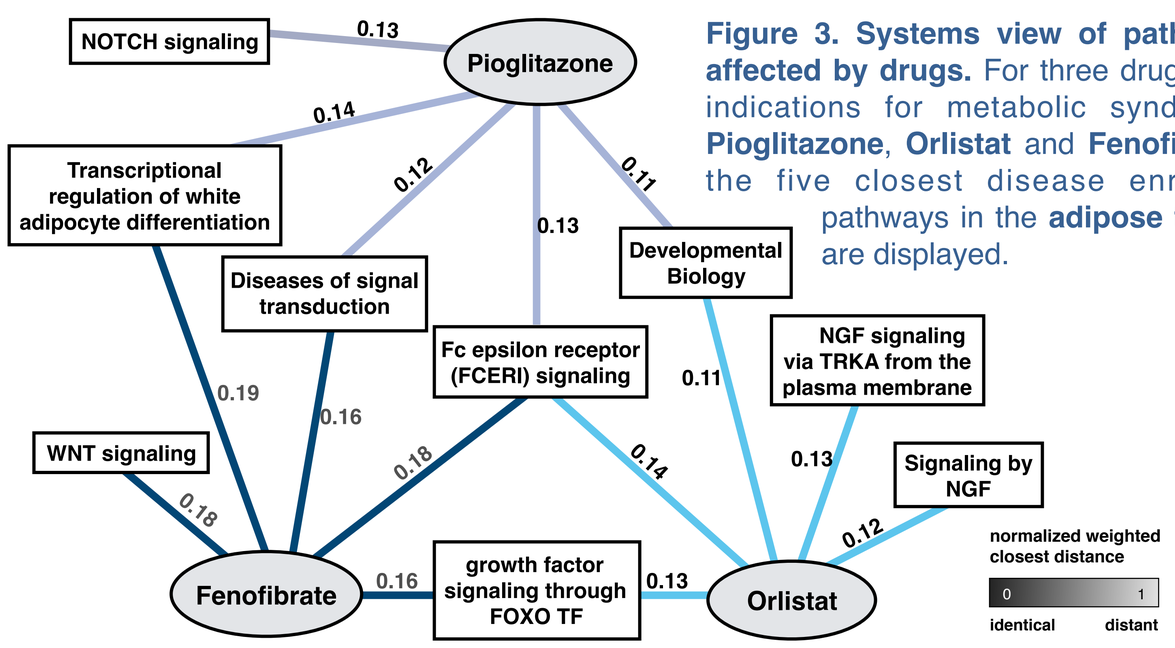


Figure 3. Systems view of pathways affected by drugs. For three drugs with indications for metabolic syndrome, **Pioglitazone**, **Orlistat** and **Fenofibrate**, the five closest disease enriched pathways in the **adipose tissue** are displayed.

Future Work and Perspectives

- Integration of **RNA-Seq** analysis pipeline.
- Application of the pipeline directed towards **drug repurposing**.

References

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