PathWave Update: Identifying Regulatory Changes in Metabolic Pathways

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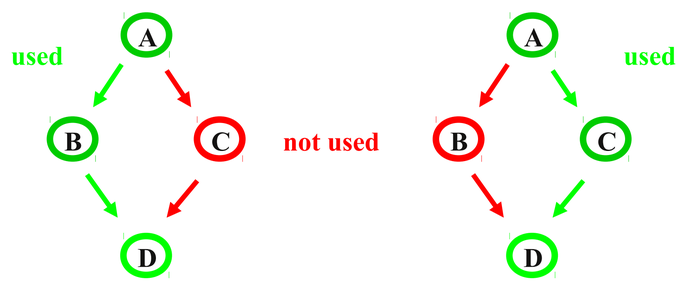
Goal: Finding crucial players in cellular networks for specifically targeting pathogenic cells

normal cell in the human body

pathogenic cell (malignant, virus infected, parasitic)



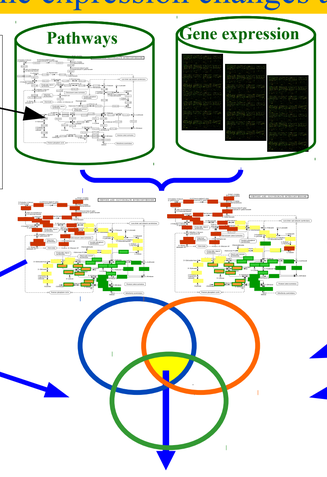
=> targeting C will specifically harm the pathogenic cell

Integrating gene expression changes and pathway information

Extracted from:

1) KEGG (Kanehisa et al., 2008)

2) BiGG (BiochemicalGenetic and Genomic knoledgebase of metabolic reconstructions; Schellenberger et al., 2010)



Data collection by massive parallel methods (e.g. gene expression) and mapping it onto cellular networks

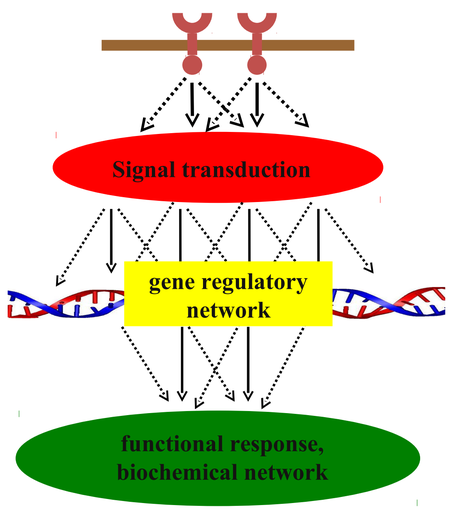
Defining discriminative patterns in gene expression of the disease using wavelet transforms (Schramm et al., 2010a, 2010b)

Discriminative pathways of coordinately expressed genes in the disease

Defining essential nodes in biochemical networks by investigating their topology (Plaimas et al., 2010)

Focus: disease specific drug targets

The three networks



Gene expression profiling by microarrays or transcript sequencing enables observing the pathogenic function of cells on a mesoscopic level. We present PathWave (Schramm et al, 2010a), a tool for analyzing changes in the regulation of metabolism that we applied to neuroblastoma (Schramm et al, 2010a), breast cancer (Schramm et al. 2010b), Alzheimer's disease (Lewis et al, 2010) and oral squamous cell carcinoma (OSCC). In contrast to common enrichment tests, PathWave explicitly takes the network topology of metabolic pathways into account by applying adjusted wavelet transforms on a 2D grid representation of curated pathway maps from the Kyoto Enzyclopedia of Genes and Genomes (KEGG; Kanehisa et al, 2008). This allows to better detect functionally related regulation patterns and identify disease-specific regulatory switches. Here, we present PathWave's basic workflow and briefly discuss current applications and future updates.

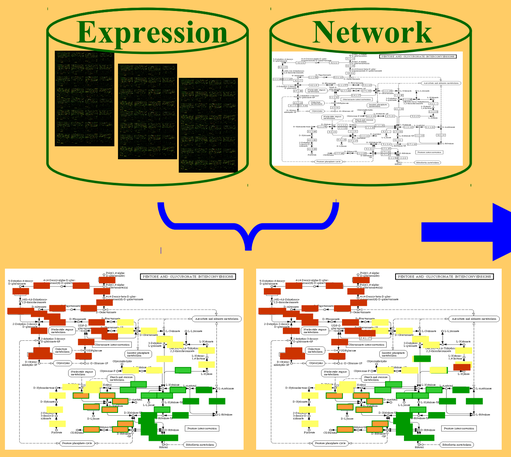
Workflow for defining the relevant pathways

- data collection by massive parallel methods (e.g. gene expression profiling)

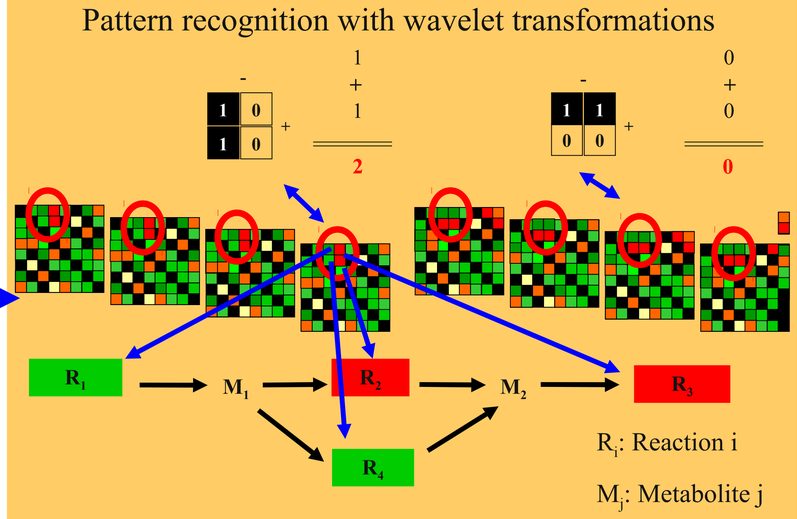
- mapping on a cellular network

=> extracting coherences and incoherences within the network

=> Discovering changes of the system



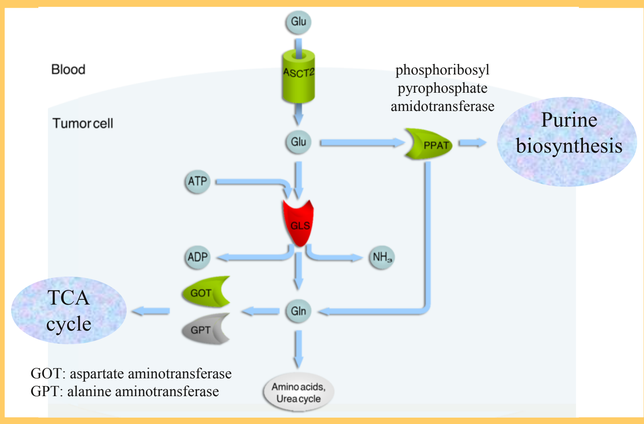
Pattern recognition with wavelet transformations



R_i: Reaction i

M_j: Metabolite j

Example: Switch-like regulation pattern in glutamate metabolism in neuroblastoma (Schramm et al., 2010a)



Some more results (examples) ...

- ***Alzheimer's disease:*** (Lewis et al, 2010) brain regions show distinct changes in metabolic pathways; example: brain regions showing substantially lower metabolic rates also show ***suppression of glycolysis and the TCA cycle***

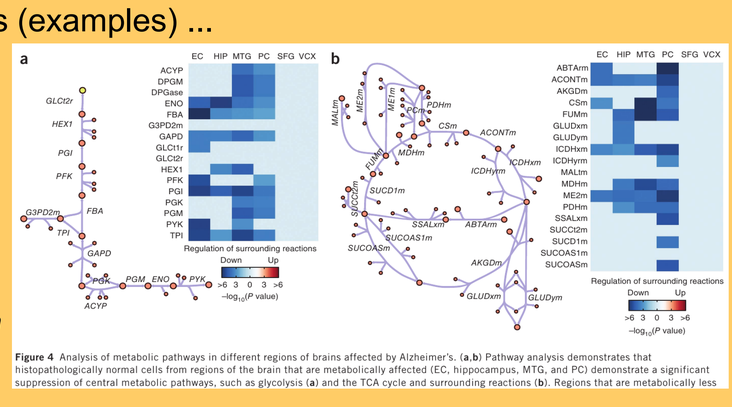


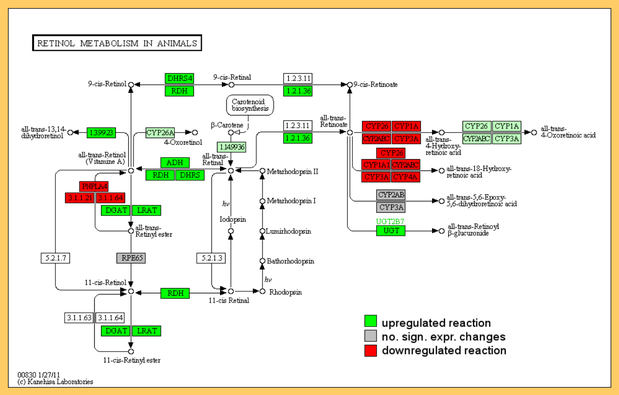
Figure 4 Analysis of metabolic pathways in different regions of brains affected by Alzheimer's. (**a**,**b**) Pathway analysis demonstrates that histopathologically normal cells from regions of the brain that are metabolically affected (EC, hippocampus, MTG, and PC) demonstrate a significant suppression of central metabolic pathways, such as glycolysis (**a**) and the TCA cycle and surrounding reactions (**b**). Regions that are metabolically less

- ***[new] oral squamous cell carcinoma (OSCC):*** 35 OSCC tumors vs. 6 controls (Sticht et al, 2008)

Example:

The *retinol (vitamin A) metabolism* is significantly disregulated.

The regulation pattern observed for single reactions of the pathway may hint at an increased production of retinoic acids (RAs) with reduced CYP-dependent oxidation of RA.



What's new?

- Identification of differentially regulated pathways not only for KEGG, but also for pathways extracted from ***BiGG*** (Biochemical Genetics and Genomics knowledgebase of reconstructed metabolic models; Schellenberger et al, 2010). This has already been applied to Alzheimer's Disease (Lewis et al, 2010)

What is to come? Something new to explore?

- Use of the notion of ***differential co-expression***; complementary to differential expression. Are metabolic reactions affected by a gain/loss of coexpression of the components of the catalyzing enzyme, even if an average differential expression is not observed?

- Application to different data sources: methylation data instead of gene expression data. Can some metabolic switches or differential regulation patterns be explained by ***differential methylation***?

Conclusions.

We presented previous as well as novel results for neuroblastomas, Alzheimer's disease and oral squamous cell carcinomas, obtained using the network-based pattern-recognition-method implemented by PathWave. Our analyses revealed interesting switches and patterns of regulation changes in metabolic pathways. Future research will explore an extension of the method to the analysis of differential co-expression and differential methylation. These extensions, combined with the analysis of differential expression, may provide novel insights into regulatory changes of metabolic pathways.

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