Analysis and visualization of experiment data in the context of biological networks and classification hierarchies

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    1. Experiment data
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    3. Classification hierarchies
    4. Alternative identifiers
3. Methods
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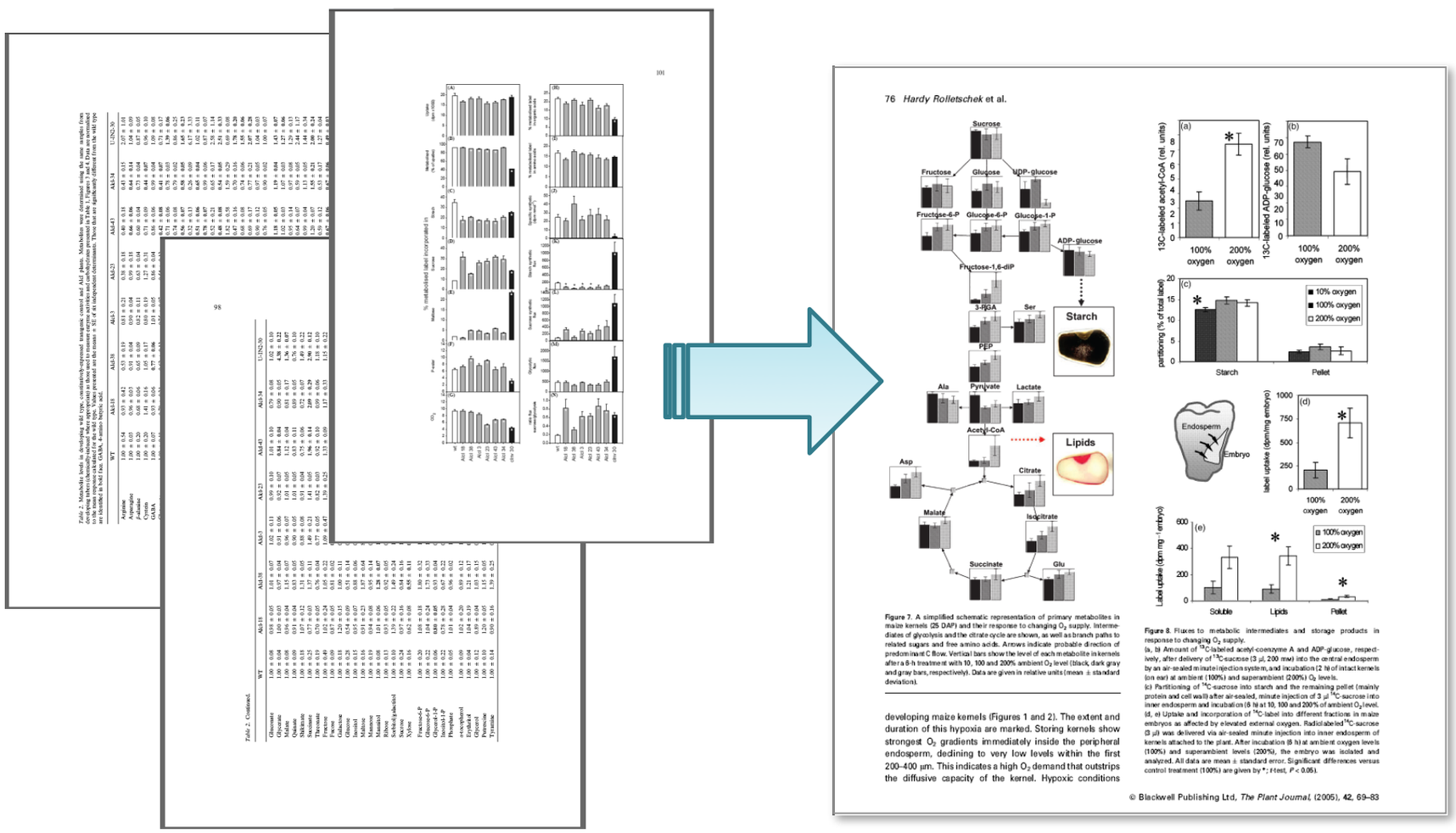
Motivation

- High-throughput analysis techniques create difficult to handle large datasets
- Bioinformatics tools are essential for visualization and analysis, many tools exist but they are often specific for certain domains or linked to specific databases



76 *Hardy Rolletschek* et al.

developing maize kernels (Figures 1 and 2). The extent and duration of this hypoxia are marked. Storing kernels show strongest O_2 gradients immediately inside the peripheral endosperm, declining to very low levels within the first 200–400 μm. This indicates a high O_2 demand that outstrips the diffusive capacity of the kernel. Hypoxic conditions

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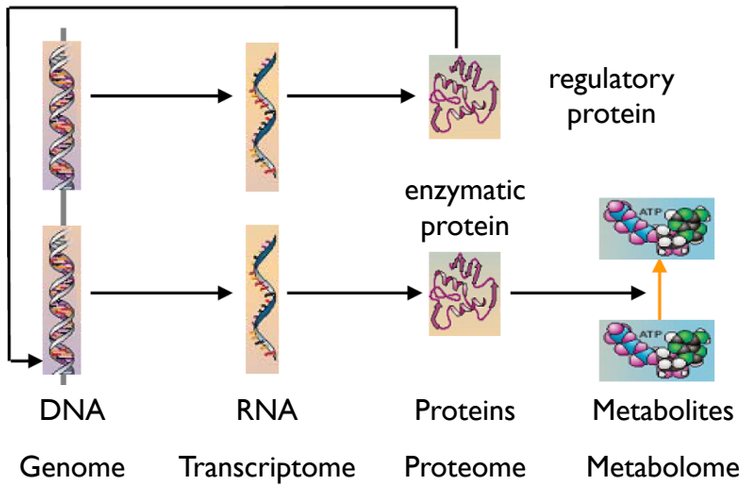
Data representation: experiment data

- Different "-omics" areas, e.g. proteomics and metabolomics, different (high-throughput) analysis techniques

- Data stored in databases or files

- Sometimes standardizied representation e.g. MIAME/MAGE for expression data, PEDRo for proteomics, ArMet for metabolite data

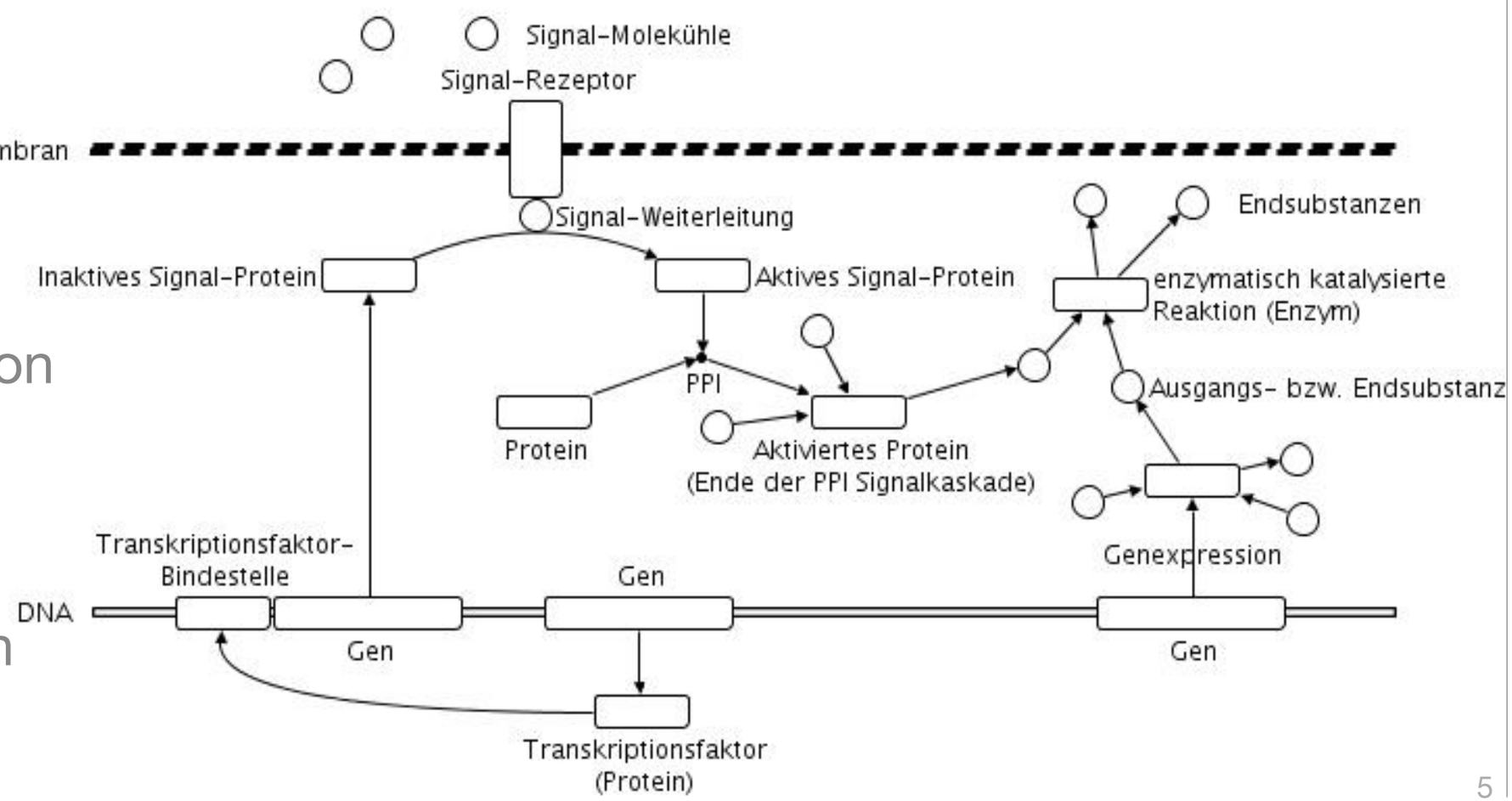
- Often unstructured (spreadsheet files, text files)



Data representation: biological networks

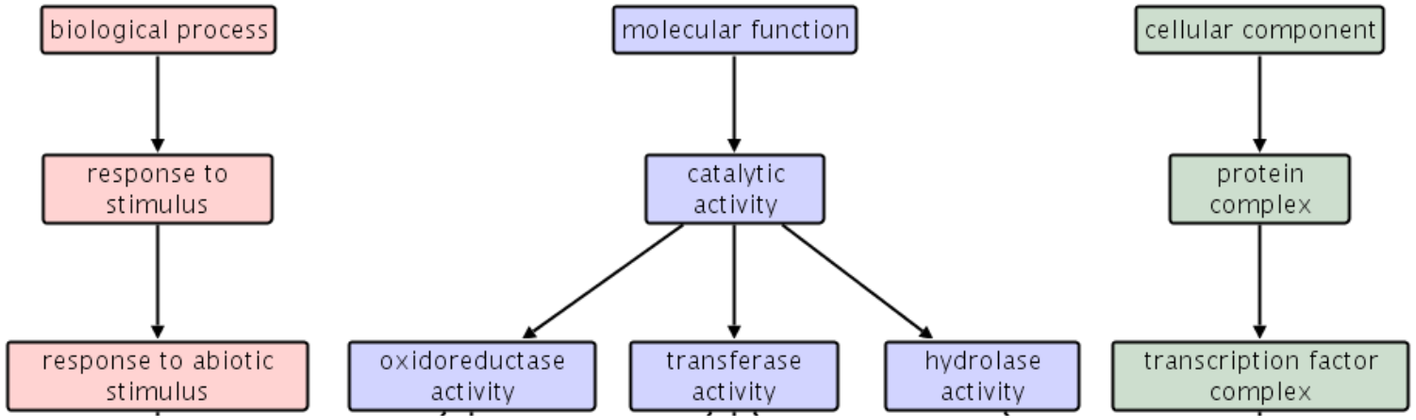
- Different biological domains and networks exist
- All of these networks are related or interconnected
- Use of general directed/undirected/mixed graph structure, node/edge attributes make identification of element type, visualization and analysis possible

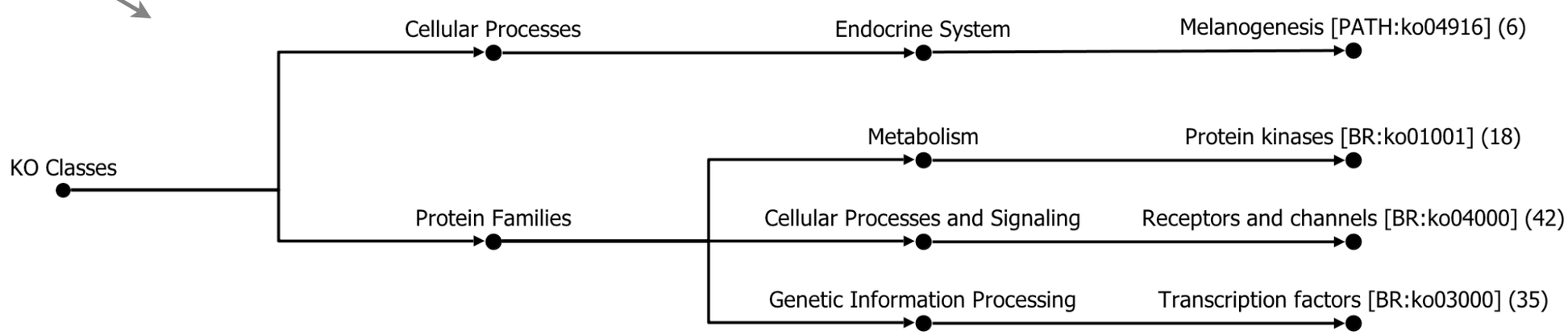
- PPI
- Biochemical reaction networks
- KEGG Pathways
- Signal transduction
- … and more



Data representation: classification hierarchies

- Classification hierarchies / ontologies are defined terms with hierarchical relationships
- Can be modelled as directed acyclic graphs or as trees
- Examples
  - Gene Ontology
  - KEGG Brite
  - MapMan





Data representation: alternative identifiers

- Knowledge about identifiers, synonyms, associated genes or general annotations

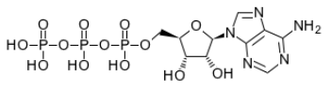
- Examples

  - KEGG Compound database contains compound names, synonyms and chemical formulas

  - ExPASy Enzyme database for enzyme names and synonyms

  - KEGG KO database contains orthologue genes, their gene IDs, names and links to other databases

COMPOUND: C00002

Entry	C00002 Compound
Name	ATP; Adenosine 5'-triphosphate
Formula	C10H16N5O13P3
Mass	506.9957
Structure	

ExPASy Home page | Site Map | Search ExPASy | Contact us | Swiss-Prot | ENZYME

Search ENZYME for Go Clear

NiceZyme View of ENZYME: EC 1.1.1.1

Official Name

Alcohol dehydrogenase.

Alternative Name(s)

Aldehyde reductase.

Reaction catalysed

An alcohol + NAD(+) <=> an aldehyde or ketone + NADH

Cofactor(s)

Zinc or iron.

Comment(s)

- Acts on primary or secondary alcohols or hemiacetals.
- The animal, but not the yeast, enzyme acts also on cyclic secondary alcohols.

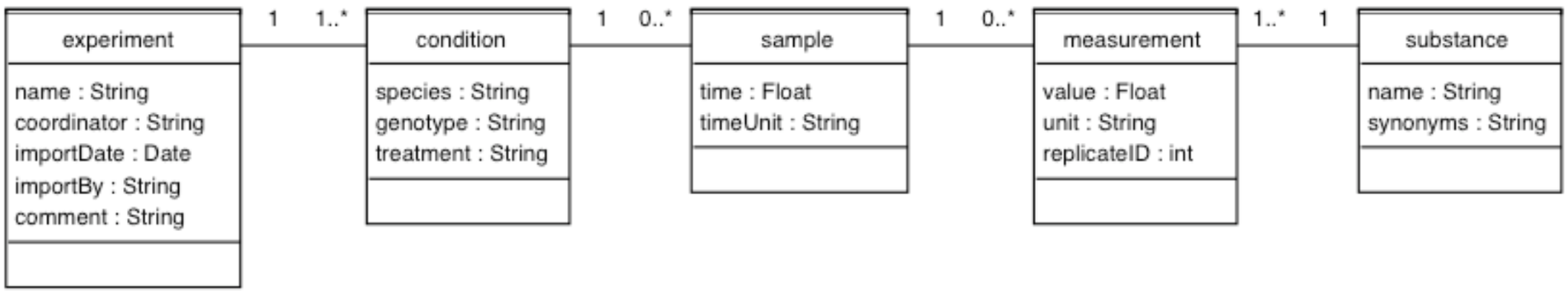
ORTHOLOGY: K00001

Help

Entry	K00001 KO
Name	E1.1.1.1, adh
Definition	alcohol dehydrogenase
Class	Metabolism; Carbohydrate Metabolism; Glycolysis / Gluconeogenesis [PATH:ko00010] Metabolism; Lipid Metabolism; Fatty acid metabolism [PATH:ko00071] Metabolism; Lipid Metabolism; Bile acid biosynthesis [PATH:ko00120] Metabolism; Lipid Metabolism; Glycerolipid metabolism [PATH:ko00561] Metabolism; Amino Acid Metabolism; Tyrosine metabolism [PATH:ko00350] Metabolism; Xenobiotics Biodegradation and Metabolism; 3-Chloroacrylic acid degradation [PATH:ko00641] Metabolism; Xenobiotics Biodegradation and Metabolism; 1- and 2-Methylnaphthalene degradation [PATH:ko00624] Metabolism; Xenobiotics Biodegradation and Metabolism; Metabolism of xenobiotics by cytochrome P450 [PATH:ko00980] BRITE hierarchy

Methods: data mapping

- General data model for experiment data



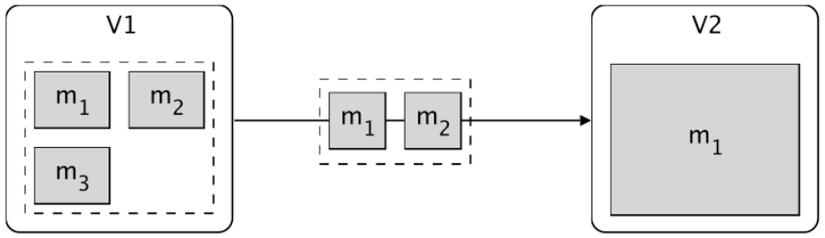
- General data model (mapping-graph) for biological networks and classification hierarchies

- Function for connecting experiment data with mapping-graph

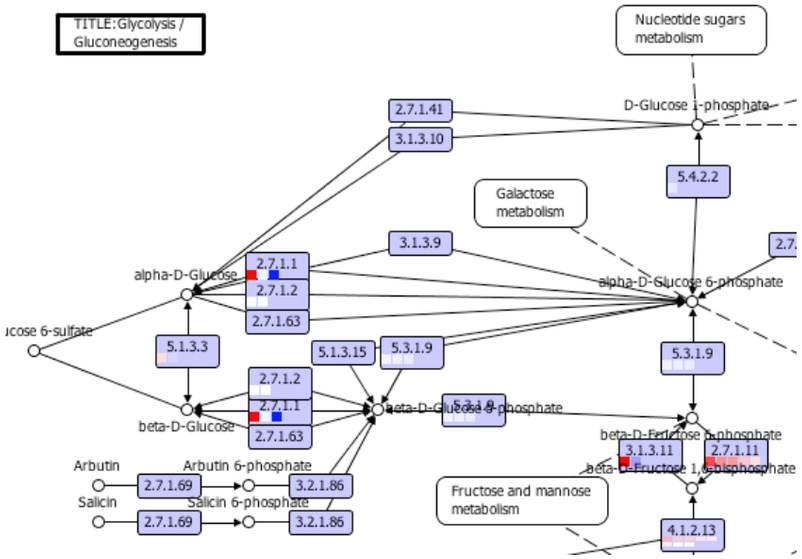
  - Consideration of alternative identifiers for graph *nodes and edges* and alternative identifiers or annotations for experiment data *substances*

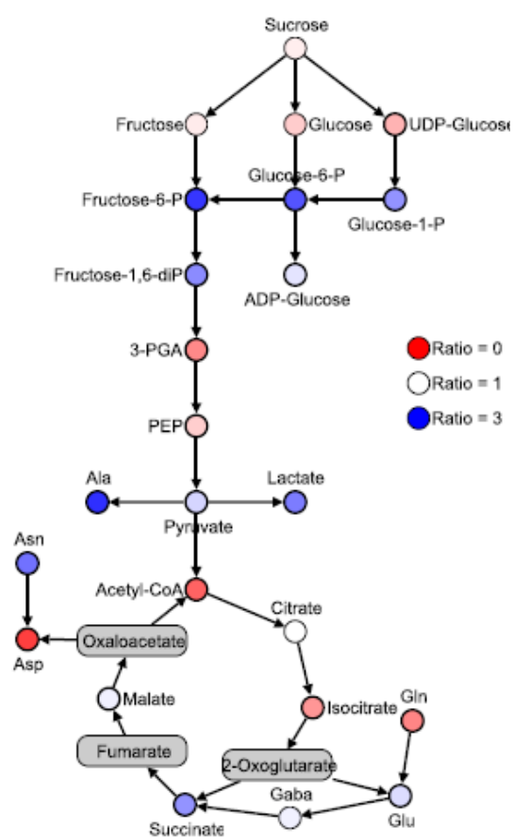
Methods: network integrated data visualization

- Multiple experiment datasets may be mapped to a single graph element, the same dataset may be mapped to multiple graph nodes

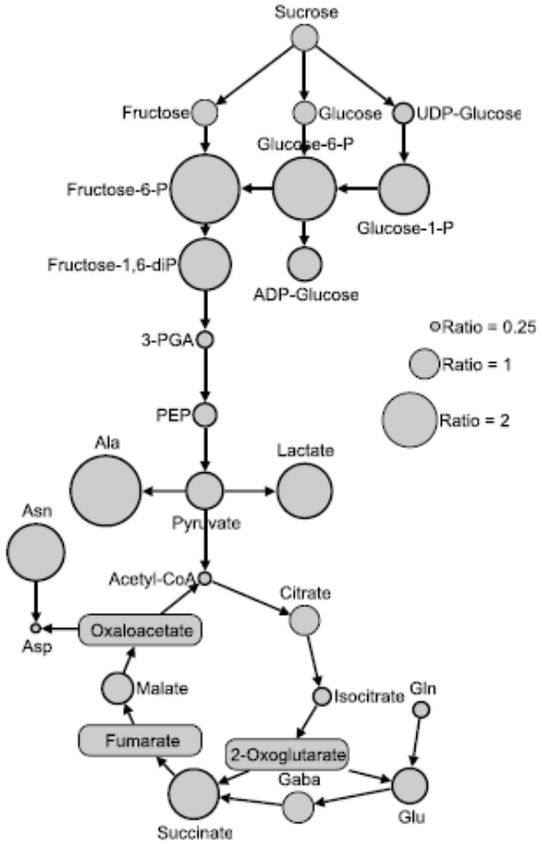


- Mapped data may can be visualized in different ways

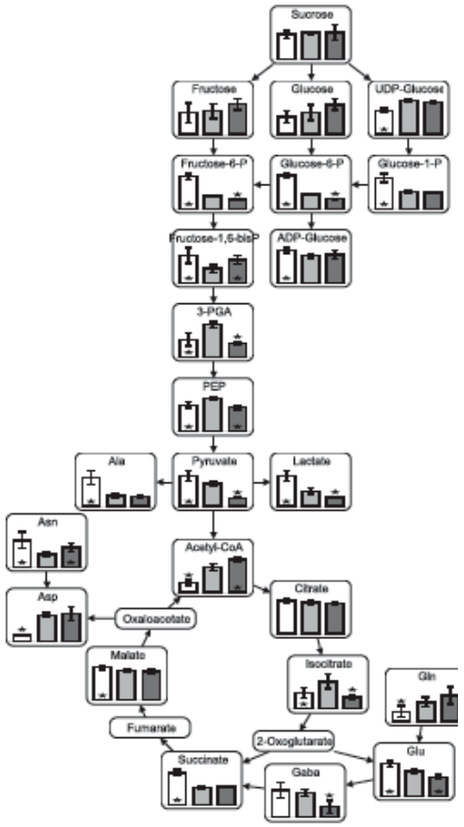




Color-coding
(or "heatmaps")



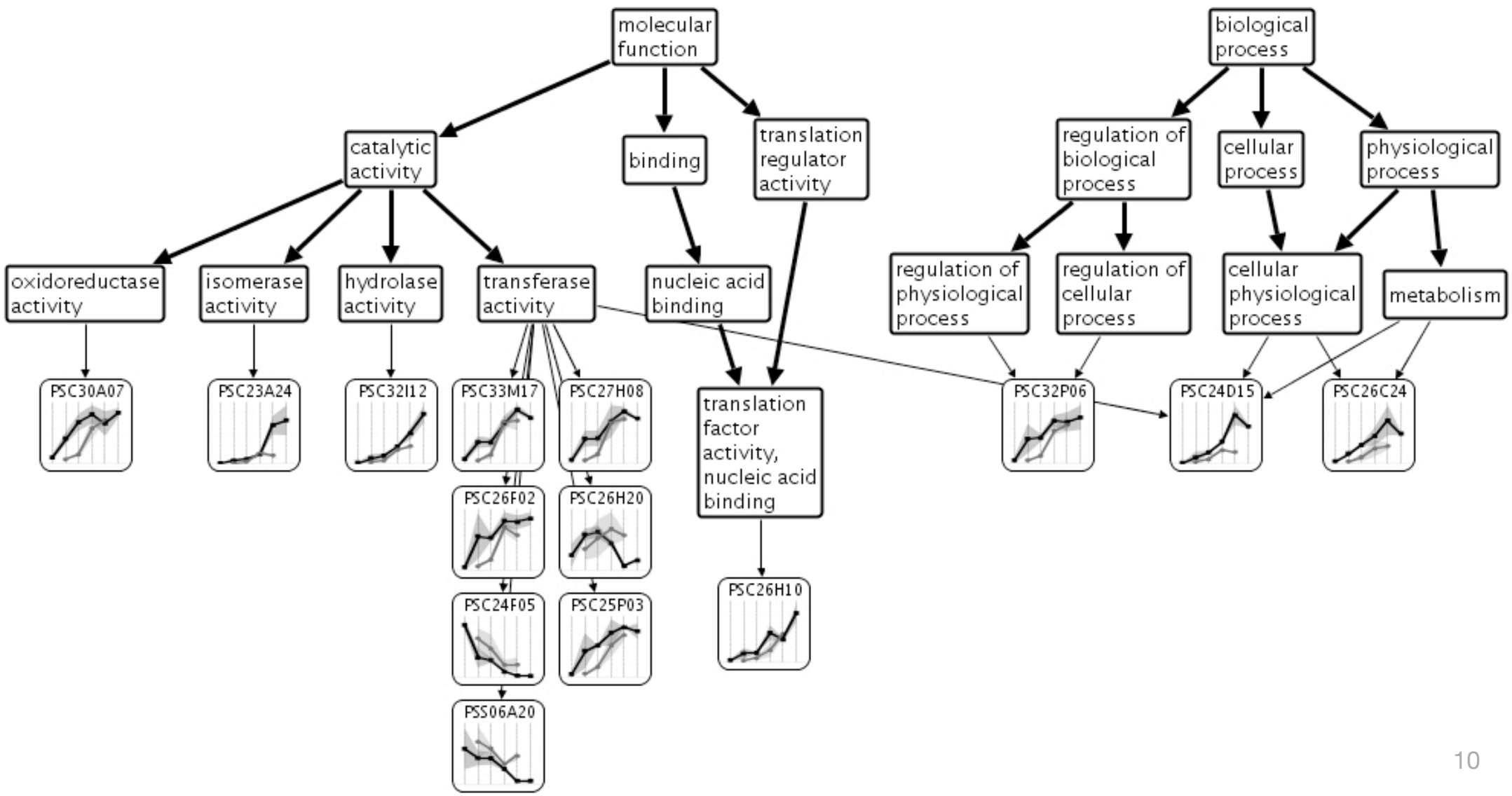
Shape-coding



Diagrams

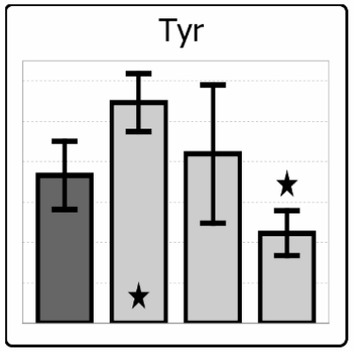
Methods: network integrated data visualization

- For data visualization in context of classification hierarchies, leaf-nodes for experiment data are created and connected to classification nodes

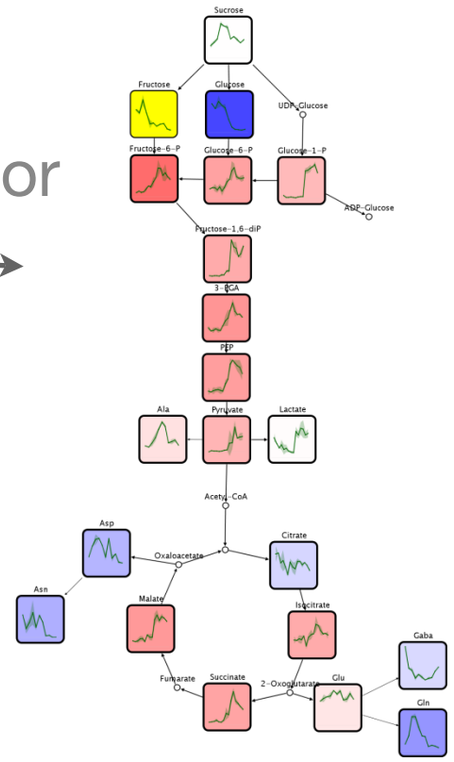


Methods: data analysis (statistics)

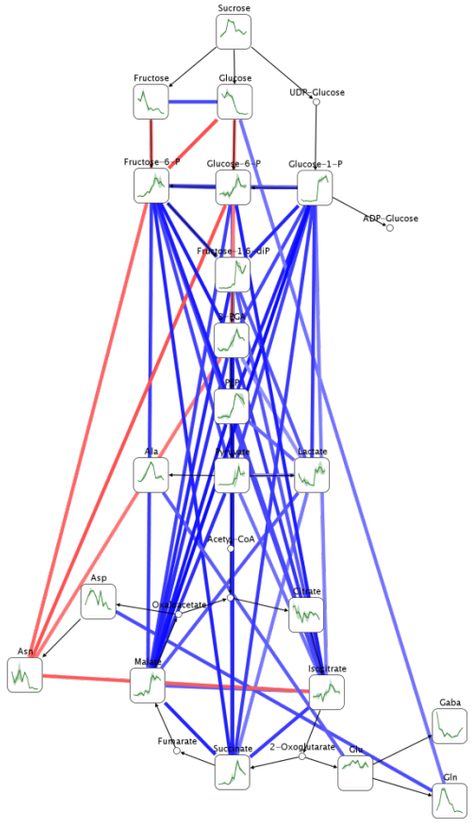
- Statistic tests to compare sample average values (e.g. *t*-Test, U-test, ratio comparison)



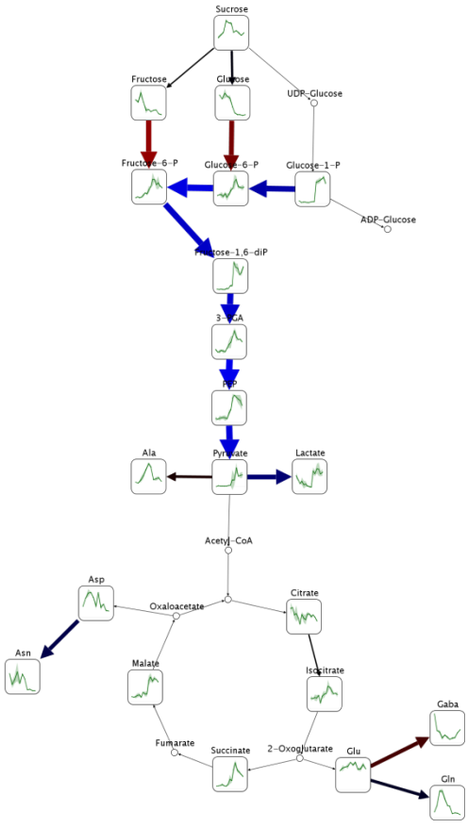
- Detect/remove outliers (Grubbs' test)
- Check for normal distribution (David quick test)
- Correlate time series or replicate data (using Pearson or Spearman correlation)



1:n



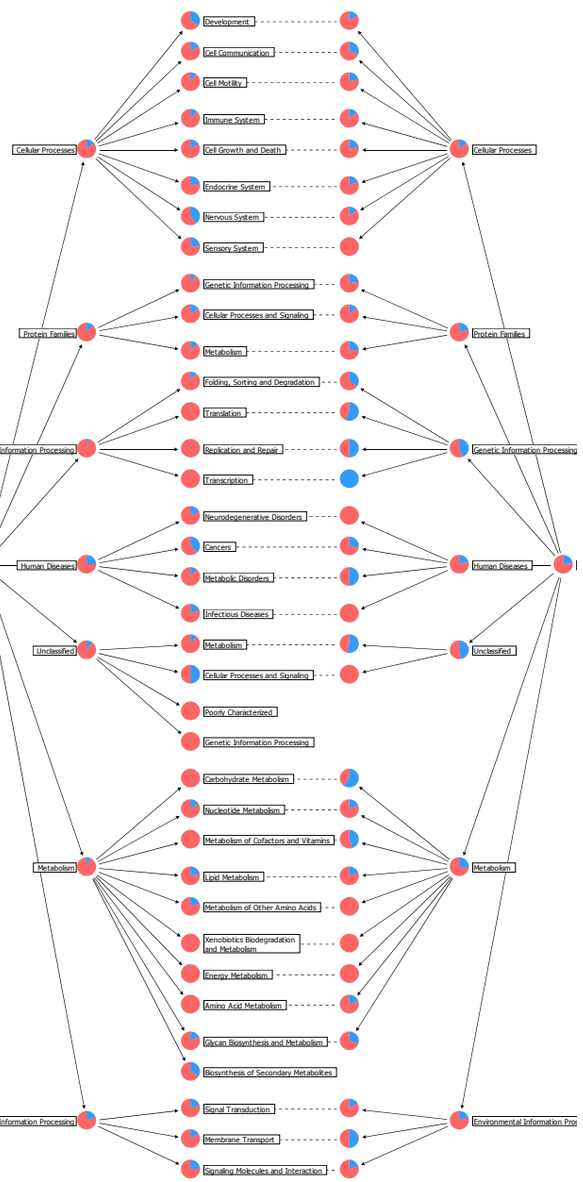
n:n



along path

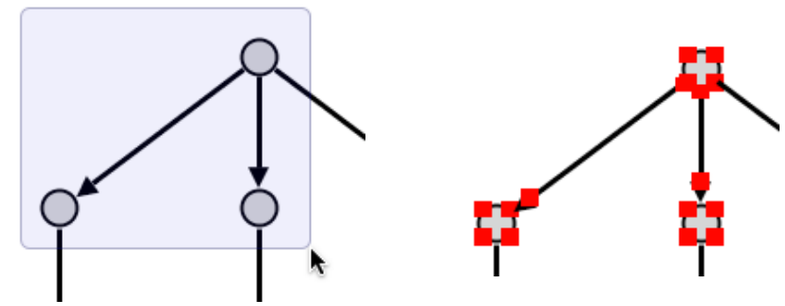
Methods: data analysis (statistics)

- Group data (e.g. up/down regulated genes), calculate histogram

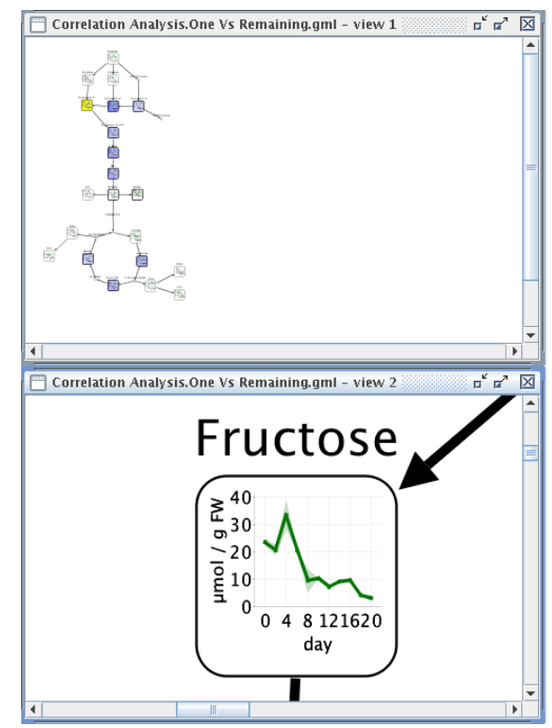


Methods: navigation and interaction

- Support for several interaction techniques
  - Direct selection
    Selection of a set of objects which are highlighted for visual investigation or which are the argument of a subsequent user interaction



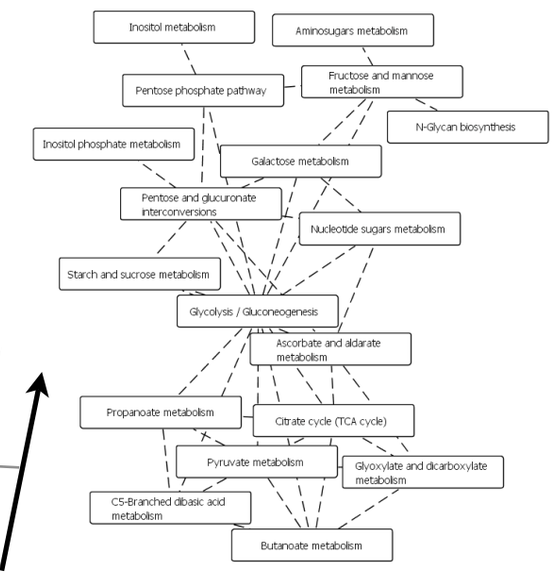
  - Details on demand
    Expansion of the visualization to show more details of a object, show/hide details of a visualization
  - Overview and detail
    A overview of data and a marked region is shown in one view, a second view shows the objects of the highlighted region in more detail

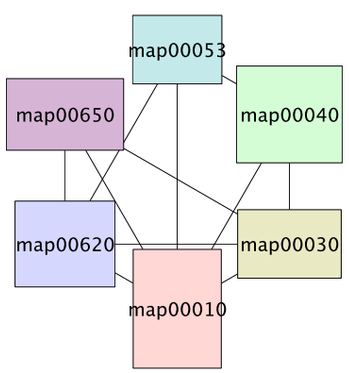


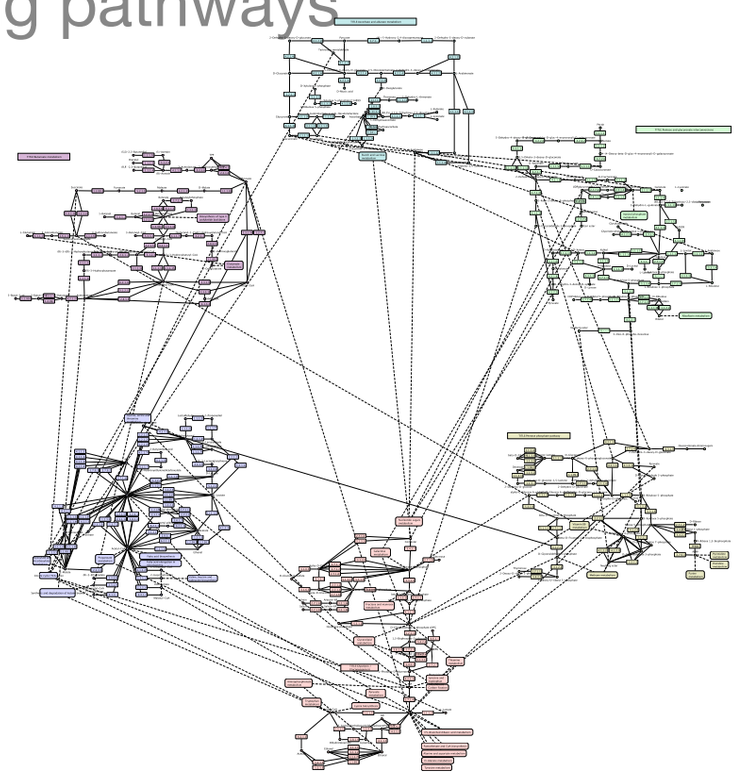
  - Dynamic queries
    Specification and combination of search-criteria for nodes/edges
  - Direct manipulation
    Modification of visualization attributes directly inside the view (node position, edge bends, node size)
  - Attribute walk
    Beginning with the current selection all nodes/edges with the same attribute values are added to the selection

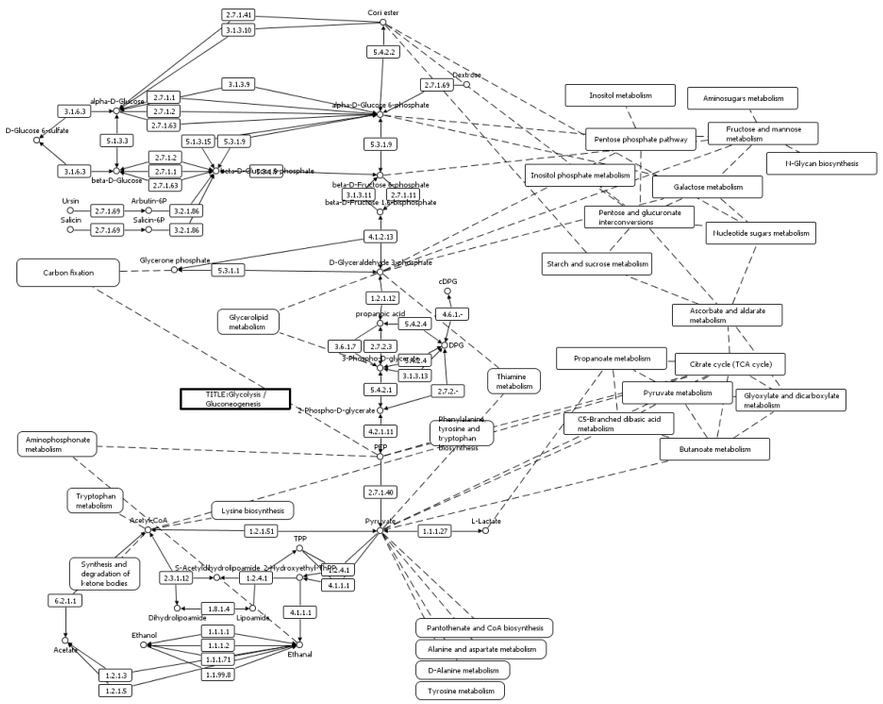
Methods: navigation and interaction

- (KEGG) Pathway navigation techniques
  - Extending the overview
  - Collapsing pathways
  - Arranging pathways



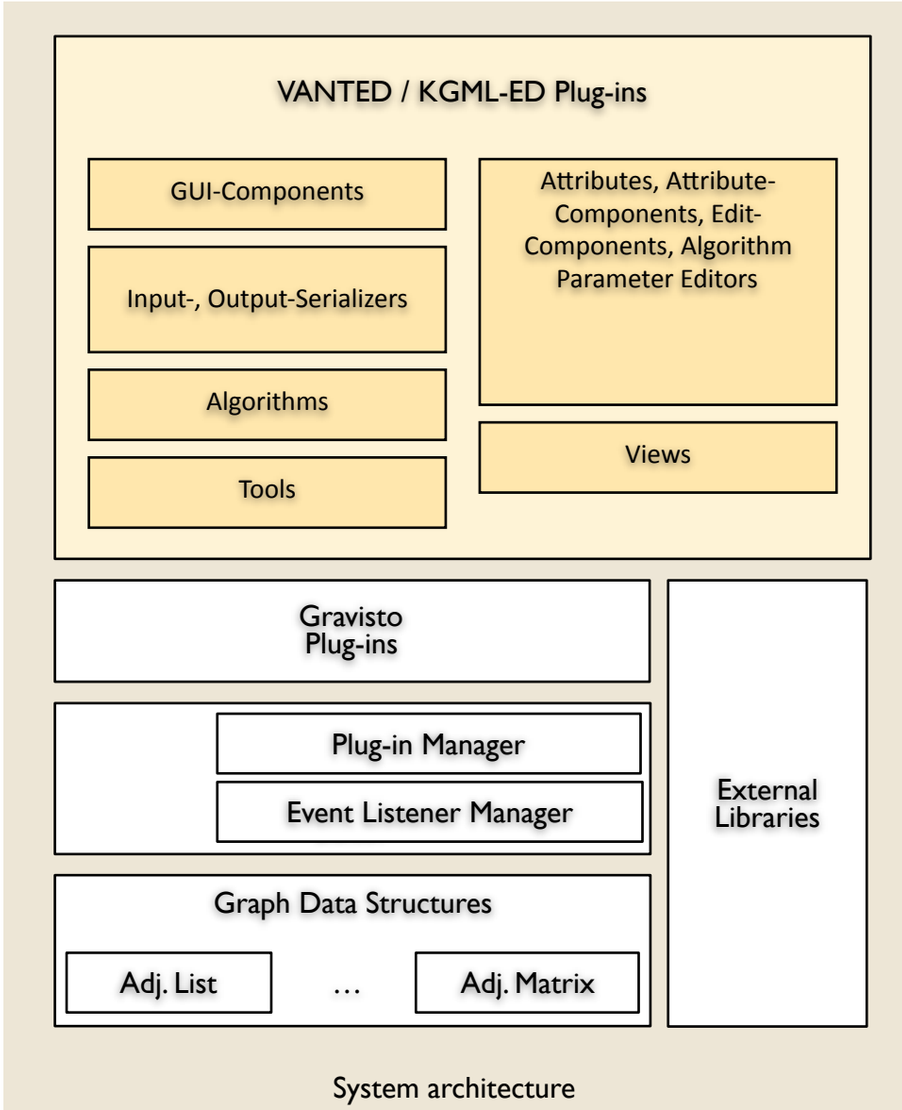






Implementation

- Implemented as open-source Java application
- VANTED is based on the extensible graph library and editor Gravisto, developed at University of Passau, Germany
- Systems architecture
  - Plugin-based extension mechanism
    - New ability to create plugin-jars, which are automatically loaded
    - Information about new/updated plugins via integrated RSS reader
  - Model-View-Controler concept
  - Observer design pattern for event management



System architecture

Implementation

- Development environment
  - Java 1.5 or higher, IDE: Eclipse, Mac/Linux/Windows
- Availability
  - Java Webstart (single-click installation and start)
    - http://vanted.ipk-gatersleben.de
  - Binary download (ZIP file, Mac OS X dmg image
    - http://sourceforge.net/projects/vanted
  - Complete source code
    - CVS Server at SourceForge

Example use cases

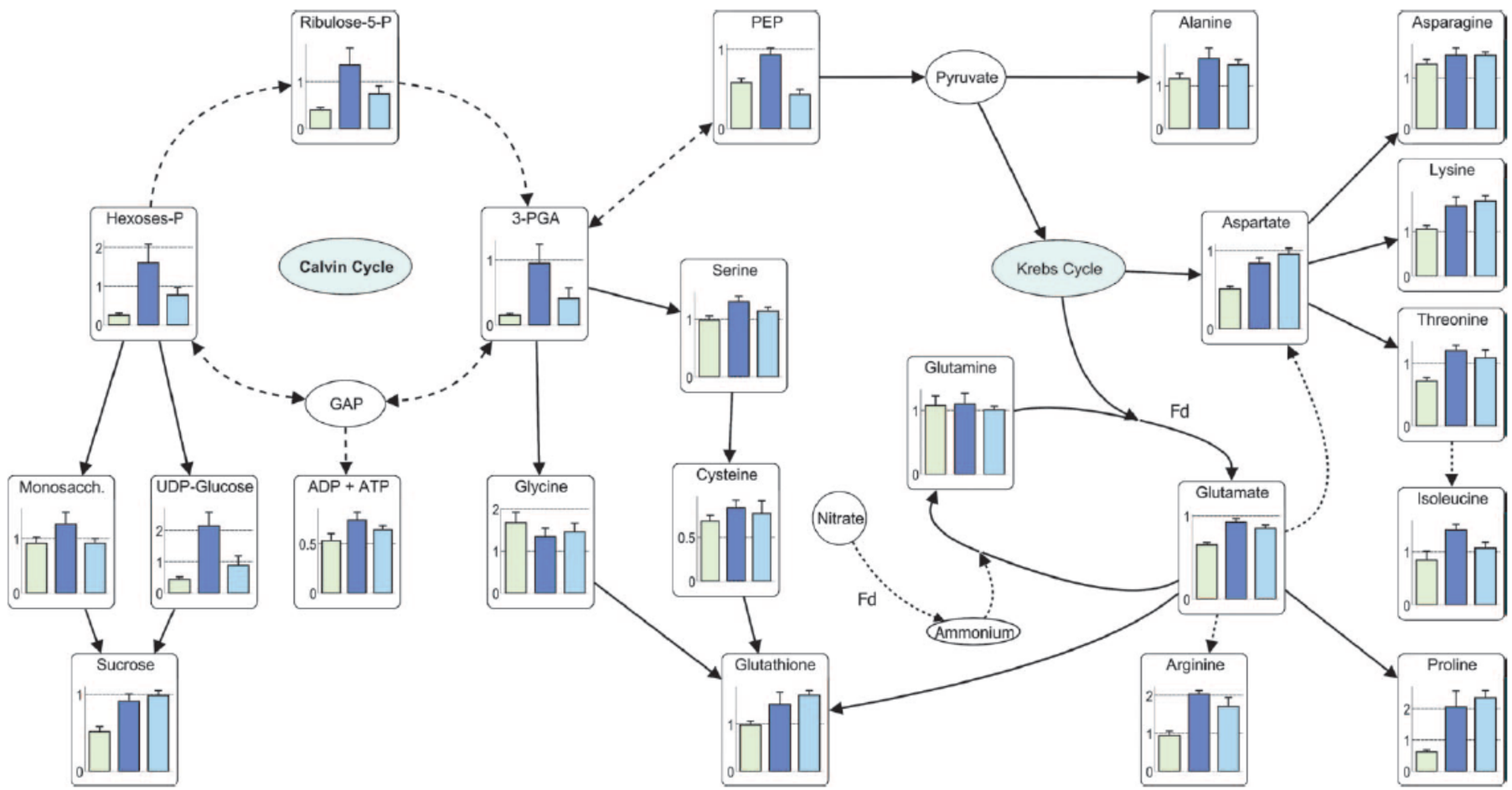
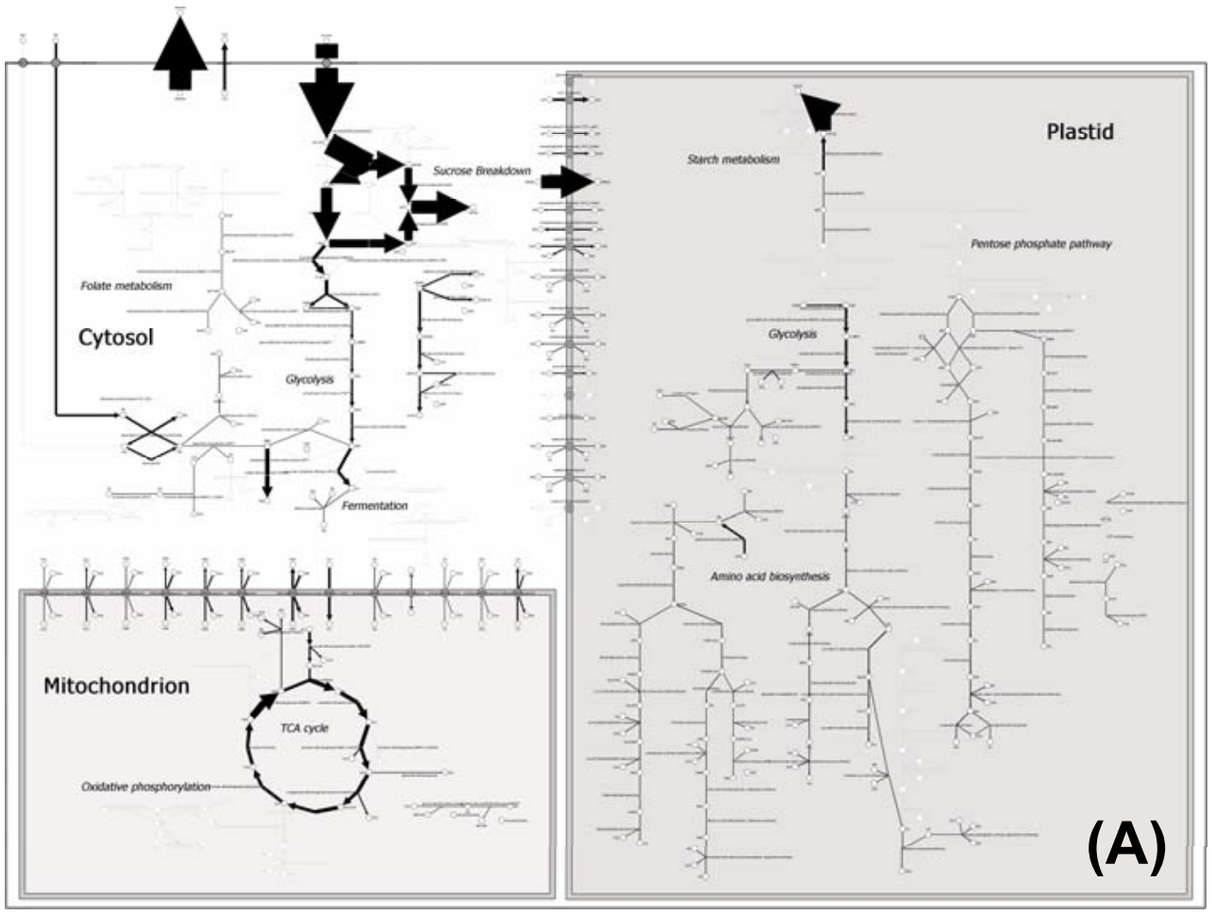
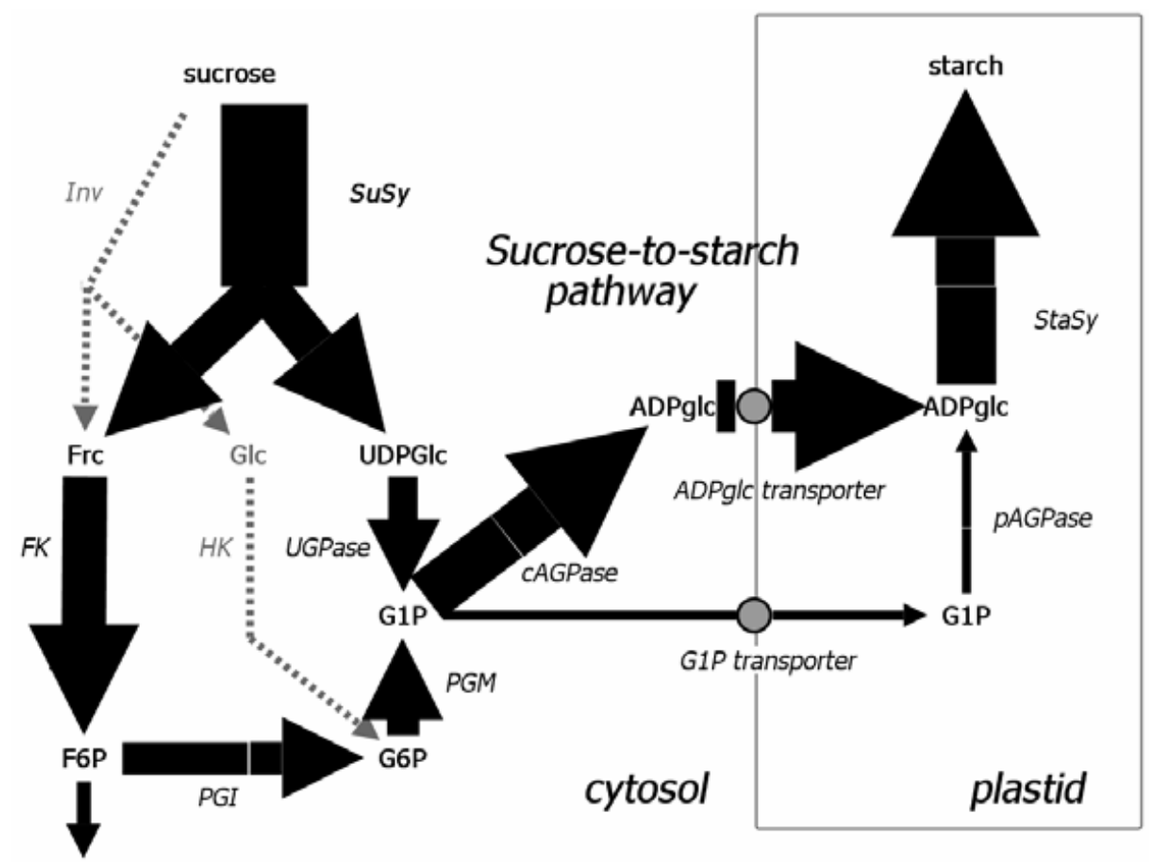


Fig. 4. Relative metabolite changes in iron-starved and control plants. Four-week-old plants were transferred to hydroponic Hoagland solution supplemented with either $FeSO_4$-EDTA or $CaCO_3$ (pH 8.0). Leaf material was harvested after 29 days, and the corresponding metabolites were measured as described in *Materials and Methods*. Depicted are the ratios ± SE of metabolite contents between Fe-starved and -replete plants of WT (green bars), *pfld*5-8 (blue bars), and *pfld*4-2 (light blue bars) lines (n = 8–10 independent plants). The graph was created by using the visualization system Vanted (38).

Tognetti et al. (2007): Enhanced plant tolerance to iron starvation by functional substitution of chloroplast ferredoxin with a bacterial flavodoxin. Proc. Natl. Acad. Sci. USA

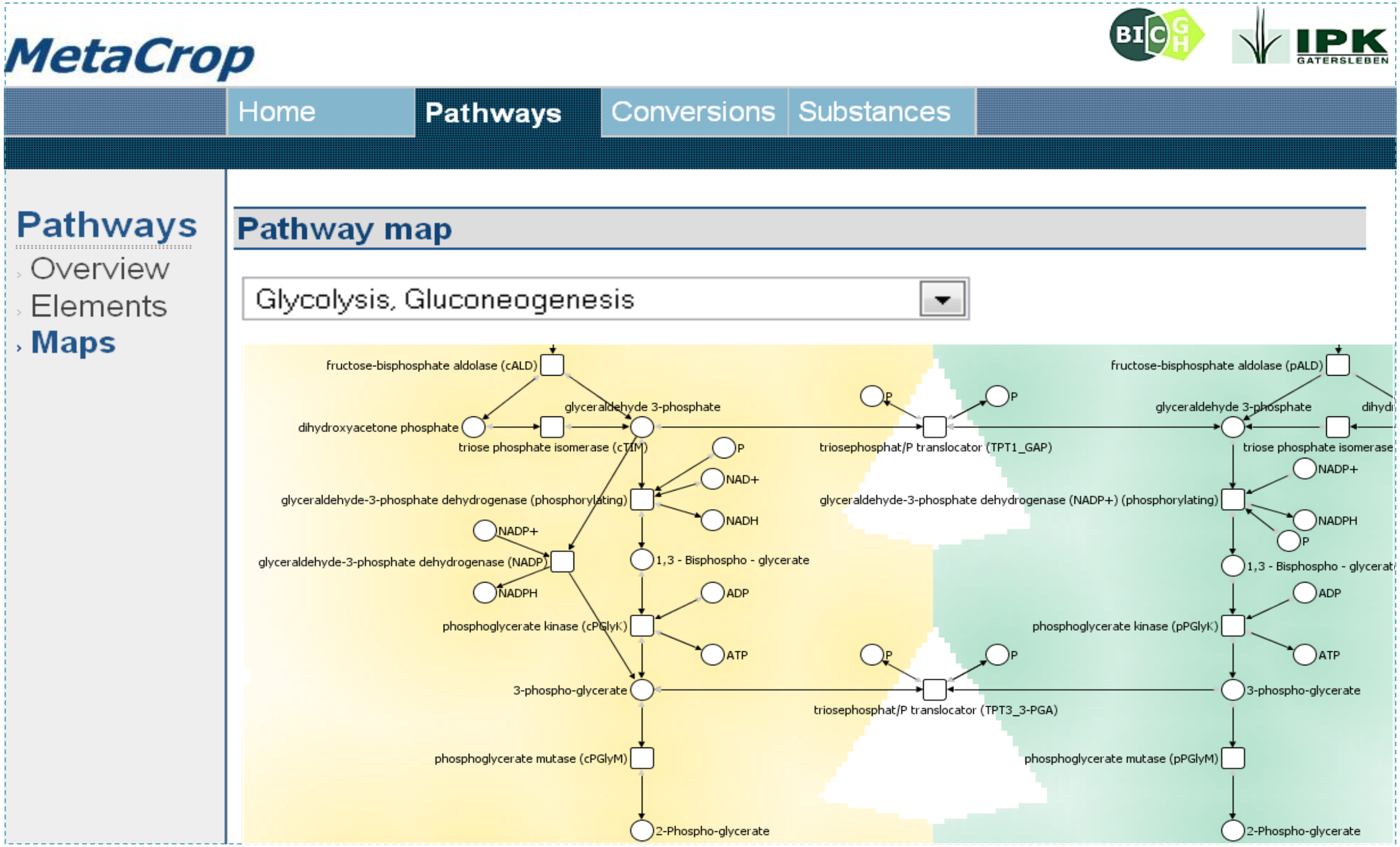
Example use cases





Grafahrend-Belau et al. (2008): Towards Systems Biology of Developing Barley Grains: a Framework for Modeling Metabolism. Proceedings Workshop on Computational Systems Biology (WCSB'08). *TICPS Series* 41: 41-44.

Example use cases



Grafahrend-Belau et al. (2008): MetaCrop – A detailed database for crop plant metabolism. Nucleic Acids Research

Thank you for your attention!

Literature (selection)

DBE information system

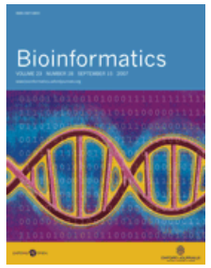
- Borisjuk, Hajirezaei, Klukas, Rolletschek, Schreiber (2004): Integrating data from biological experiments into metabolic networks with the DBE information system. In Silico Biology

VANTED

- Junker, Klukas, Schreiber (2006): VANTED: A system for advanced data analysis and visualization in the context of biological networks.
  BMC Bioinformatics

KEGG pathway navigation

- Klukas and Schreiber (2007): Dynamic exploration and editing of KEGG pathway diagrams.
  Bioinformatics



Internet

- http://vanted.ipk-gatersleben.de
- http://kgml-ed.ipk-gatersleben.de