Signaling pathways analysis

Marta R. Hidalgo

Systems Genomics Lab, CIPF

September 30th, GDA 2015

Outline

Signaling Pathways

Signaling pathways

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
  Databases
  Pathway methods

Preprocess
  Modeling KEGG
  Subpathways
  Normalization

Method
  Computing the signal
  Functional annotation
  Further analysis

Exercises

Signal transduction

Cellular mechanism which allows the cell to respond to different stimuli by means of biochemical reactions

Signaling pathways

Cascades of protein activations and inhibitions

Databases

▶ KEGG

Databases

Signaling pathways
analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods
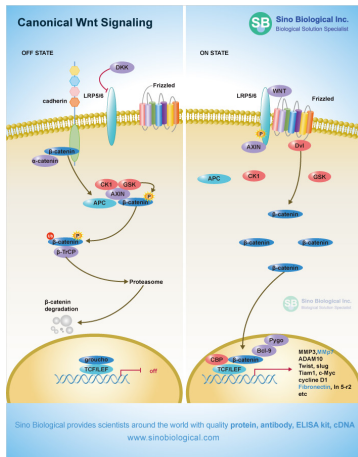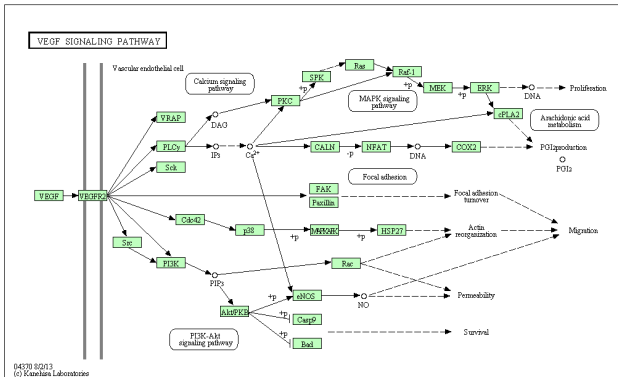
Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
Functional annotation
Further analysis

Exercises

- KEGG
- Reactome

Databases

- ► KEGG
- ► Reactome
- ► Others: WikiPathways,...

WIKIPATHWAYS
Pathways for the People

Pathway methods

- SPIA

Pathway methods

- ▶ SPIA
- ▶ PARADIGM

Pathway methods

- ▶ SPIA
- ▶ PARADIGM
- ▶ Pathifier

Pathway methods

Score per pathway

- ▶ SPIA
- ▶ PARADIGM
- ▶ Pathifier

Pathway methods

Score per pathway

- ▶ SPIA
- ▶ PARADIGM
- ▶ Pathifier

- ▶ SubSPIA

Pathway methods

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
Functional annotation
Further analysis

Exercises

Score per pathway

- ▶ SPIA

- ▶ PARADIGM

- ▶ Pathifier

- ▶ SubSPIA

- ▶ Pathiways

Pathway methods

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
Functional annotation
Further analysis

Exercises

Score per pathway

- ▶ SPIA
- ▶ PARADIGM
- ▶ Pathifier

Score per subpathway

- ▶ SubSPIA
- ▶ Pathiways

Pathway methods

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
Functional annotation
Further analysis

Exercises

Score per pathway

- ▶ SPIA
- ▶ PARADIGM
- ▶ Pathifier

Score per subpathway

- ▶ SubSPIA
- ▶ Pathiways
    - ▶ Probabilistic approach
    - ▶ Only Microarray data
    - ▶ Only processed KEGG pathways

Method

Method

- ▶ Independent from gene expression technology

Method

- Independent from gene expression technology
- Independent from pathway database

Method

- ▶ Independent from gene expression technology
- ▶ Independent from pathway database
  - ▶ SIF + attributes file

Method

- ▶ Independent from gene expression technology
- ▶ Independent from pathway database
  - ▶ SIF + attributes file
  - ▶ Module to process KEGG pathways

Workflow

Input

- ▶ SIF file + attributes
- ▶ Expression matrix

Workflow
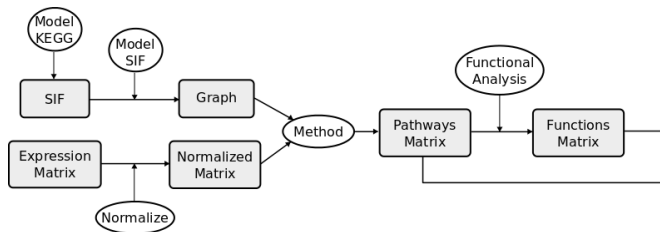
Input

- ▶ SIF file + attributes
- ▶ Expression matrix

Output

- ▶ Pathways matrix
- ▶ Functions matrix
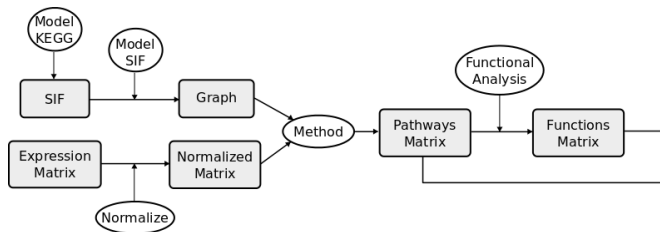
[Signaling pathways analysis

Marta R. Hidalgo](#)

[Signaling pathways](#)
[Databases](#)
[Pathway methods](#)

[Preprocess](#)
[Modeling KEGG](#)
[Subpathways](#)
[Normalization](#)

[Method](#)
[Computing the signal](#)
[Functional annotation](#)
[Further analysis](#)

[Exercises](#)

Preprocess

Modeling KEGG pathways

Modeling KEGG pathways

Nodes

Edges

Modeling KEGG pathways

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
Functional annotation
Further analysis

Exercises
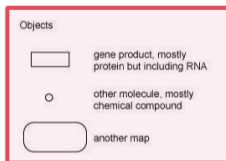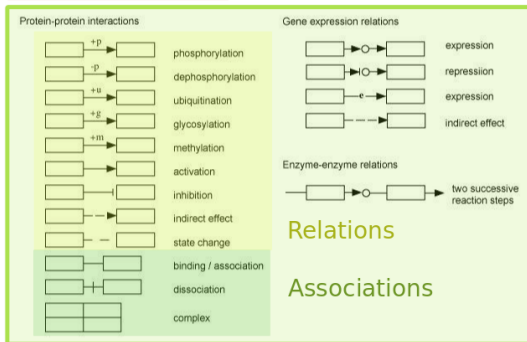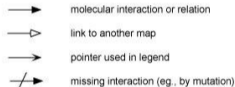
Modeling KEGG pathways

Only activations/inhibitions allowed

Modeling KEGG pathways

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods
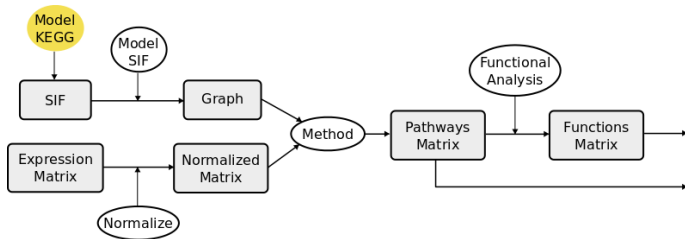
Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
Functional annotation
Further analysis

Exercises

Only activations/inhibitions allowed

- **Relation edges:** Simplified to activation/inhibition

Modeling KEGG pathways

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
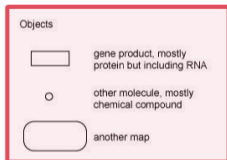Computing the signal
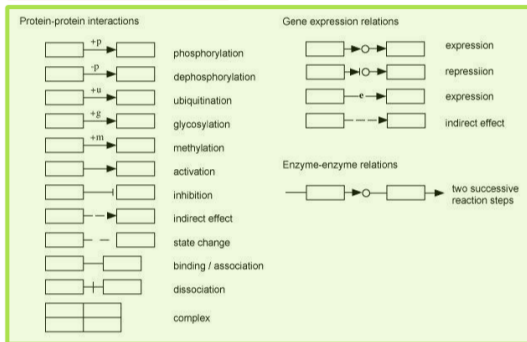Functional annotation
Further analysis

Exercises

Only activations/inhibitions allowed

▶ **Relation edges:** Simplified to activation/inhibition

▶ **Association edges:** The net is modeled to include the information

Modeling KEGG pathways

Plain nodes

Include one node, many genes

Complex nodes

Include different nodes

Modeling KEGG pathways

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
Functional annotation
Further analysis

Exercises

Plain nodes

Include one node, many genes

Complex nodes

Include different nodes

- ▶ Binding/association

Modeling KEGG pathways

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
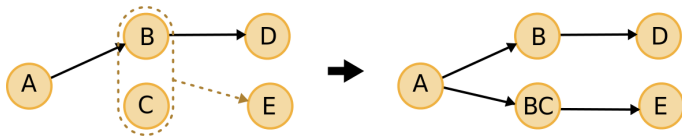Functional annotation
Further analysis

Exercises

Plain nodes

Include one node, many genes

Complex nodes

Include different nodes

- ▶ Binding/association
- ▶ Group

Modeling the graph

Effector subpathways

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
Functional annotation
Further analysis

Exercises

Effector proteins

Last genes of the network, responsibles for performing the corresponding molecular function
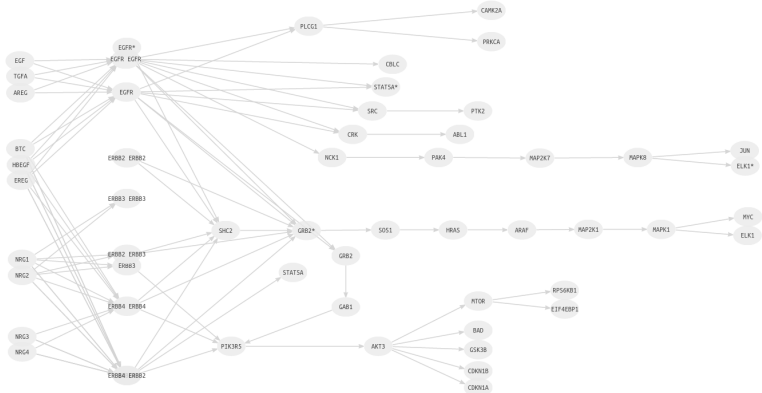
Effector subpathways

Effector subpathway

Subgraph of the pathway including any node in a path
ending in an effector protein

Effector subpathways

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
Functional annotation
Further analysis

Exercises

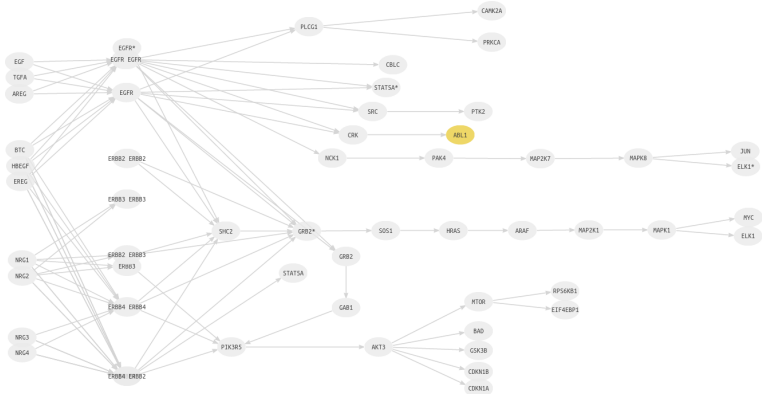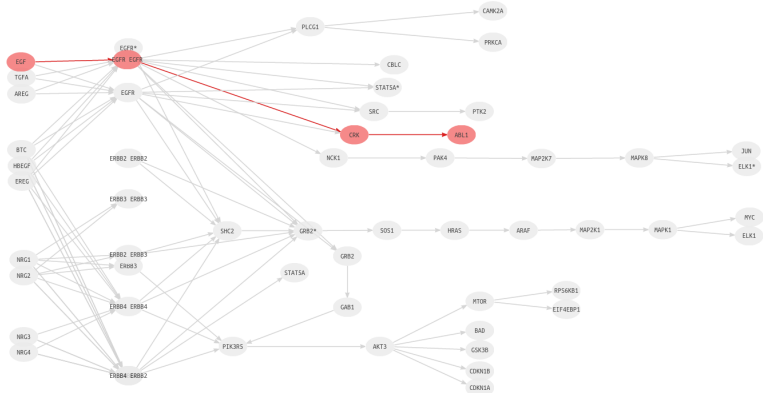## Effector subpathway

Subgraph of the pathway including any node in a path ending in an effector protein

Decomposed subpathways

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
Functional annotation
Further analysis

Exercises

Single subpathway

Subgraph of the pathway including only one input and one output node

Decomposed subpathways

Single subpathway

Subgraph of the pathway including only one input and one output node
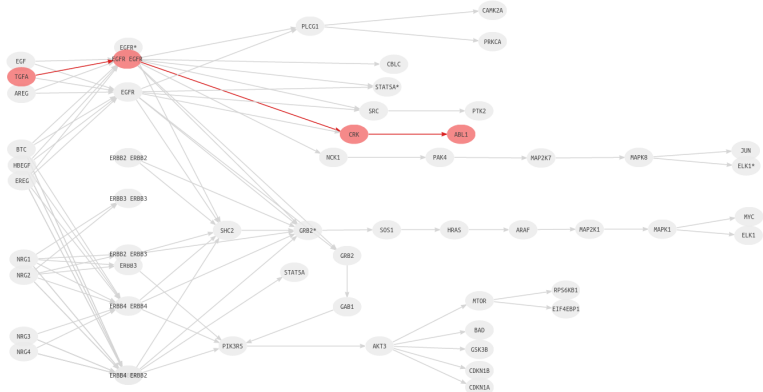
Decomposed subpathways
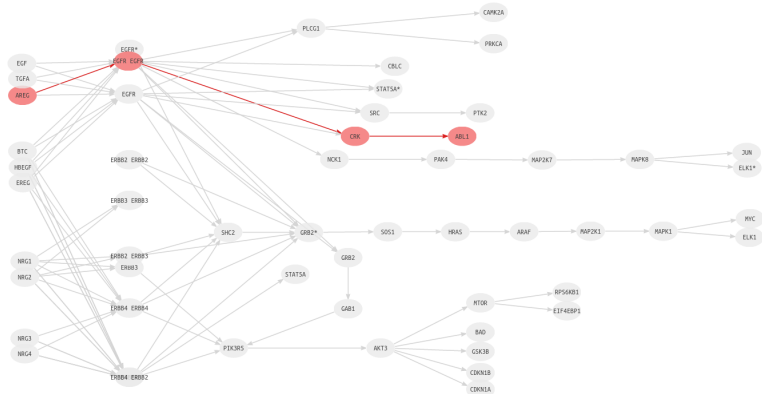
Single subpathway

Subgraph of the pathway including only one input and one output node

Decomposed subpathways

Single subpathway

Subgraph of the pathway including only one input and one output node

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
Functional annotation
Further analysis

Exercises

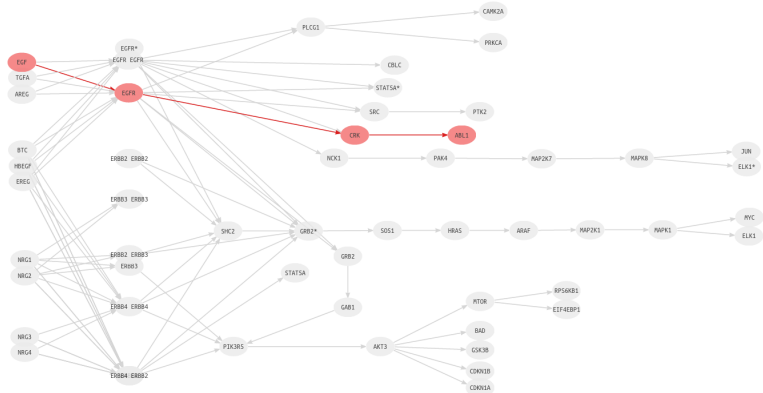# Decomposed subpathways
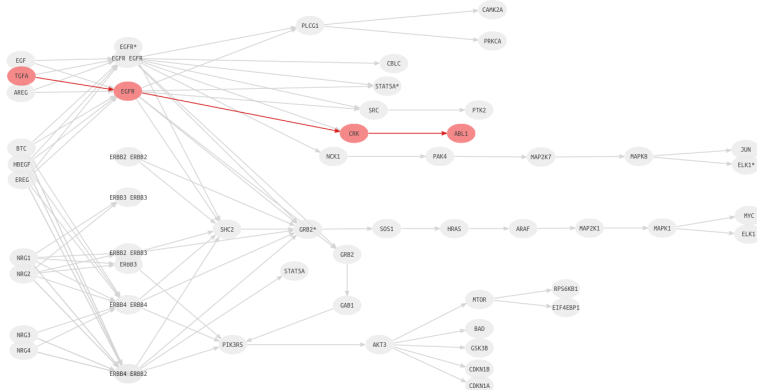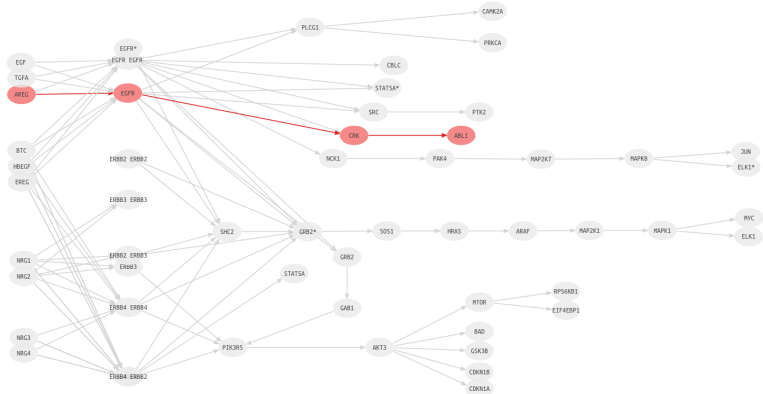
Single subpathway

Subgraph of the pathway including only one input and one output node

Decomposed subpathways

Single subpathway

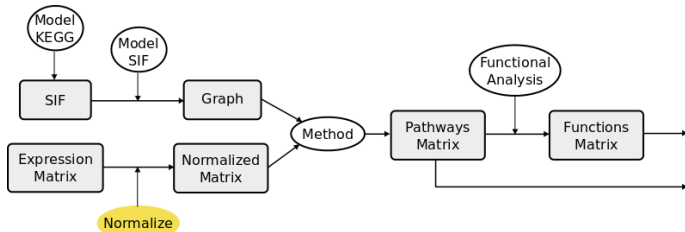Subgraph of the pathway including only one input and one output node

Normalization

Signaling pathways
analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
Functional annotation
Further analysis

Exercises

Normalization

The expression matrix is normalized to [0,1]

Options

- ▶ By quantiles: a quantiles normalization is performed
- ▶ By gene: the normalization is performed by rows
- ▶ Percentil: normalize taking the percentil

Method

Method

Signaling pathways
analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
Functional annotation
Further analysis

Exercises

Method

Signaling pathways
analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
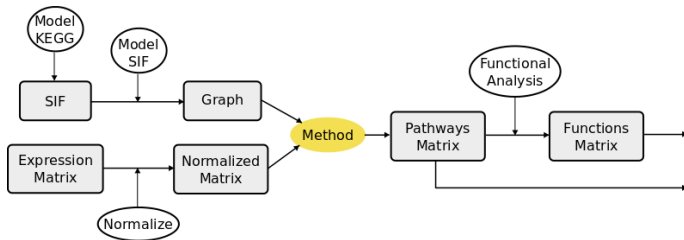Modeling KEGG
Subpathways
Normalization

Method
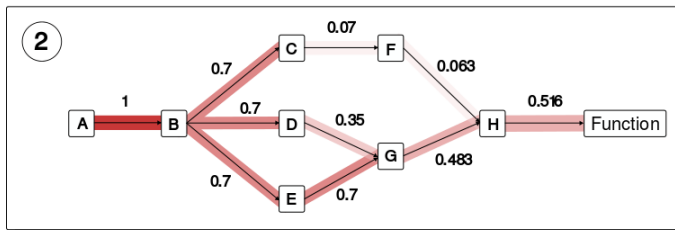Computing the signal
Functional annotation
Further analysis

Exercises

Node values

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
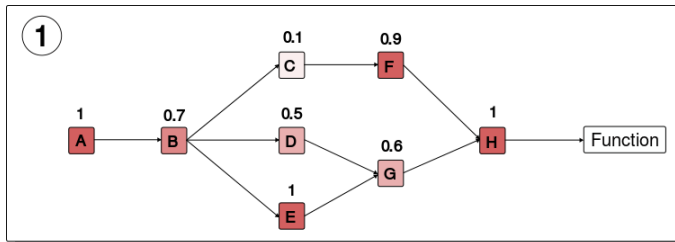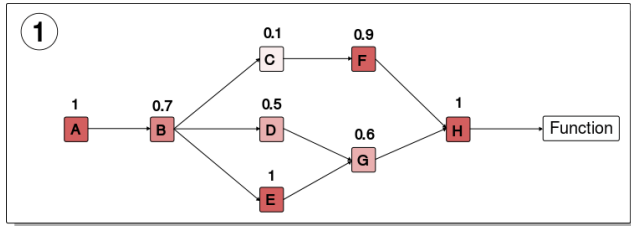Computing the signal
Functional annotation
Further analysis

Exercises

- **Plain nodes:** Percentil 90 of the genes included
- **Complex nodes:** Compute value of each node, take percentil 10

Signal value through a node

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
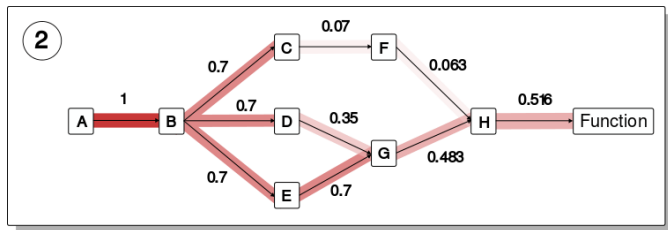Functional annotation
Further analysis

Exercises

For node n

$$S_n = v_n \cdot \left(1 - \prod_{s_i \in A}(1 - s_i)\right) \cdot \prod_{s_j \in I}(1 - s_j)$$
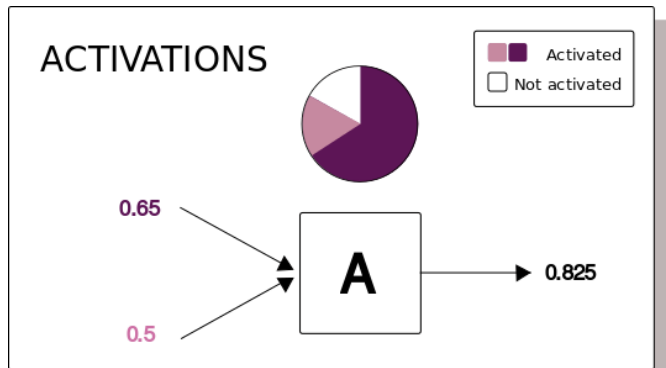
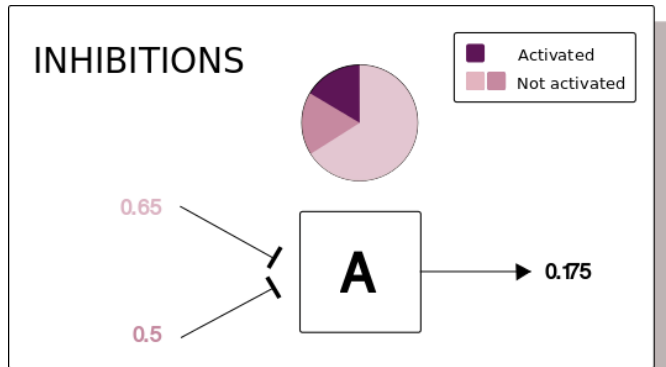S_n: Signal value through n

v_n: Node value

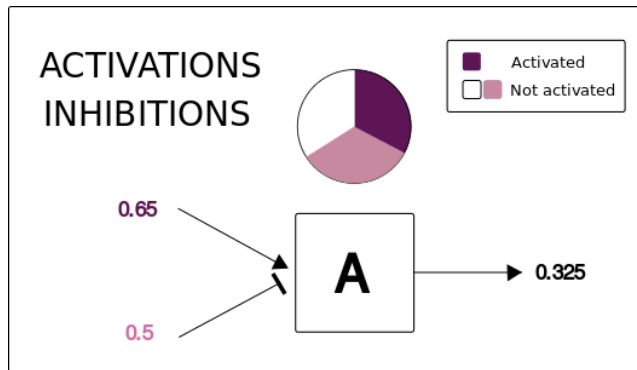A: Activation edges

I: Inhibition edges

Computing the signal

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
Functional annotation
Further analysis

Exercises

Computing the signal

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
Functional annotation
Further analysis

Exercises

Computing the signal

Signal values
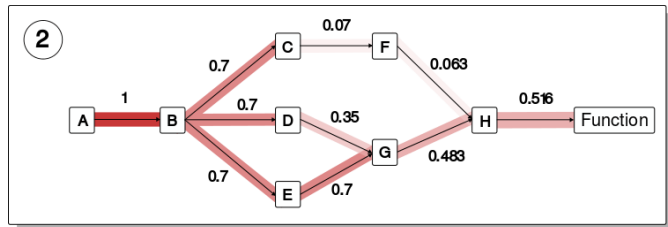
Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
Functional annotation
Further analysis

Exercises

▶ Input signal 1 in any input node

Signal values

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
Functional annotation
Further analysis

Exercises

▶ Input signal 1 in any input node
▶ Compute the signal through each node iteratively
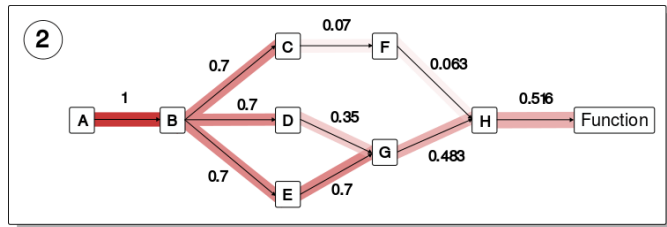
Signal values

- Input signal 1 in any input node
- Compute the signal through each node iteratively
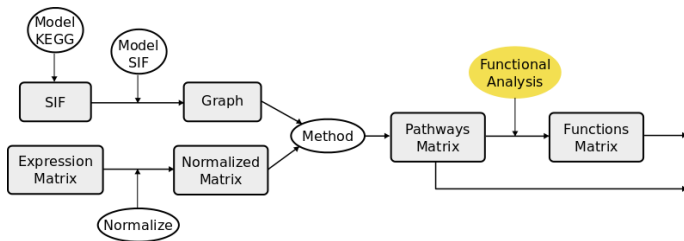- Loops can be processed
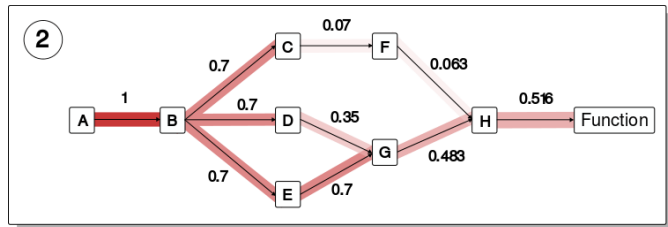
Signal values

- ▶ Input signal 1 in any input node
- ▶ Compute the signal through each node iteratively
- ▶ Loops can be processed
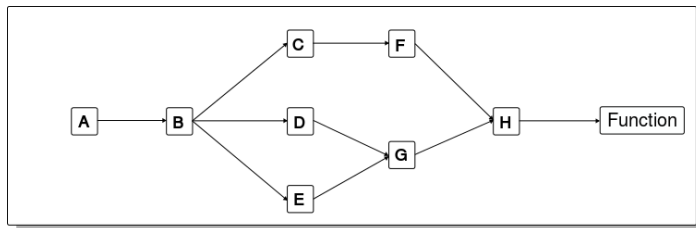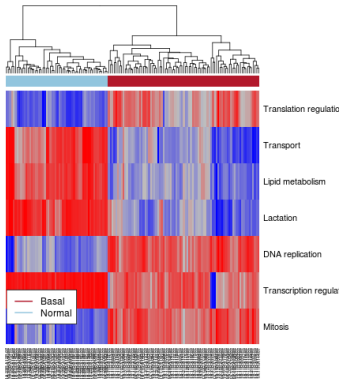- ▶ Subpathway signal: last node signal

Functional annotation

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods
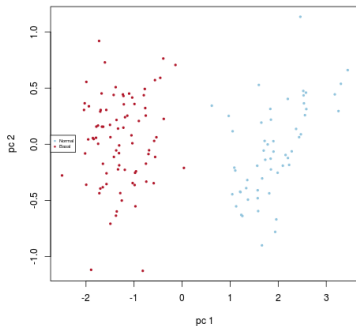
Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
Functional annotation
Further analysis

Exercises
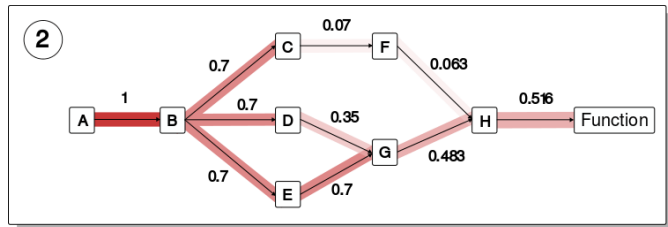
Functional annotation

Subpathway function $\sim$ Effector protein function

- ▶ KEGG annotation
- ▶ Uniprot keywords
- ▶ GO annotation

Further analysis

- Heatmap

Further analysis

- ▶ Heatmap
- ▶ PCA

Further analysis

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods
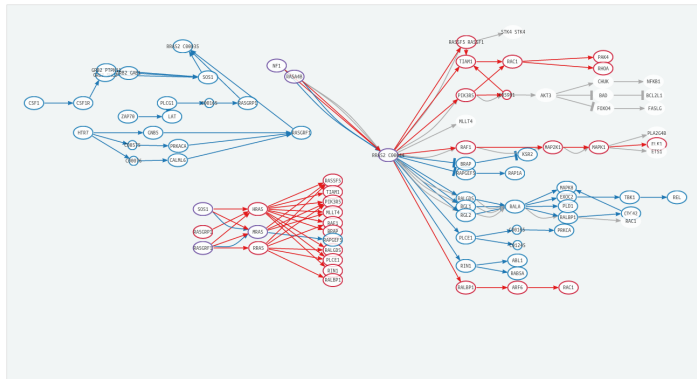
Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
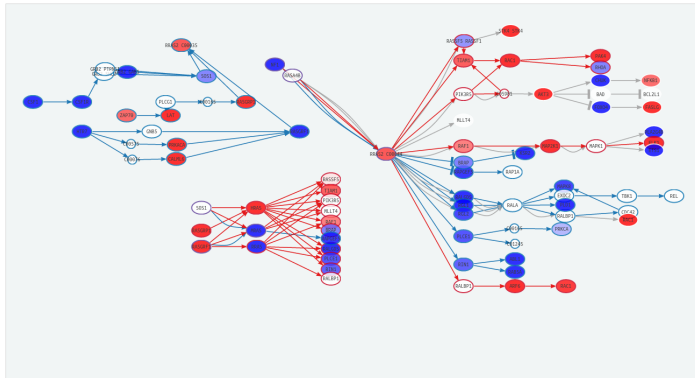Functional annotation
Further analysis

Exercises

- ▶ Heatmap
- ▶ PCA
- ▶ Compare groups: Wilcoxon

Further analysis

- Heatmap
- PCA
- Compare groups: Wilcoxon

Signaling pathways analysis

Marta R. Hidalgo

Signaling pathways
Databases
Pathway methods

Preprocess
Modeling KEGG
Subpathways
Normalization

Method
Computing the signal
Functional annotation
Further analysis

Exercises

Exercises