

Signaling pathways analysis

Marta R. Hidalgo

Systems Genomics Lab, CIPF

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Signaling pathways
analysis

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Signaling pathways

Databases

Pathway methods

Preprocess

Modeling KEGG

Subpathways

Normalization

Method

Computing the signal

Functional annotation

Further analysis

Exercises

Outline

Signaling pathways

- Databases

- Pathway methods

Preprocess

- Modeling KEGG

- Subpathways

- Normalization

Method

- Computing the signal

- Functional annotation

- Further analysis

Exercises

Signaling pathways
analysis

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Signaling pathways

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- Pathway methods

Preprocess

- Modeling KEGG

- Subpathways

- Normalization

Method

- Computing the signal

- Functional annotation

- Further analysis

Exercises

Signaling Pathways

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analysis

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Pathway methods

Preprocess

Modeling KEGG

Subpathways

Normalization

Method

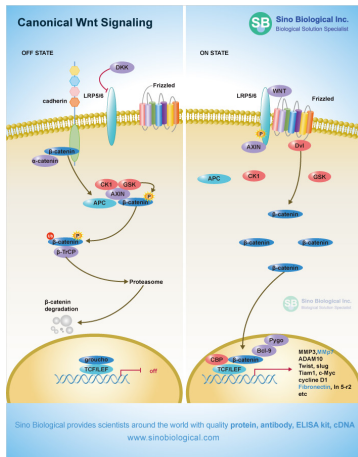
Computing the signal

Functional annotation

Further analysis

Exercises

Signaling pathways



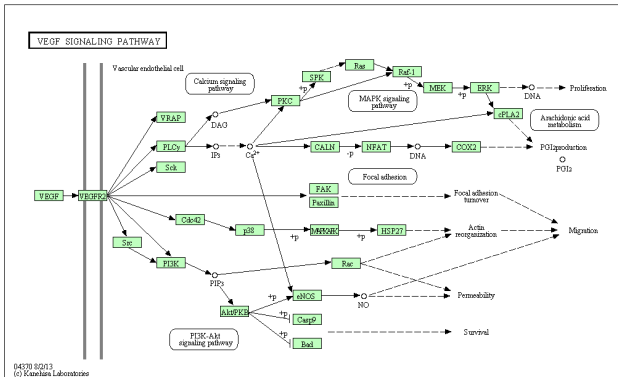
Signal transduction

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

Signaling pathways

Cascades of protein activations and inhibitions

► KEGG



Databases

- ▶ KEGG
- ▶ Reactome

The screenshot shows the Reactome web interface. Several components are highlighted with red boxes and labels:

- Home button**: Located at the top left of the interface.
- Species selector**: A dropdown menu for selecting the species.
- Show/hide**: A button to toggle the visibility of certain elements.
- Diagram key**: A button to view the legend for the pathway diagram.
- Quick tour**: A button to access a guided tour of the interface.
- Zoom/move toolbar**: A set of icons for navigating and zooming the pathway diagram.
- Pathway diagram panel**: The central area displaying a metabolic pathway diagram with various molecules and reactions.
- Search & tools**: A search bar and additional utility buttons.
- Hierarchy panel**: A sidebar on the left showing a hierarchical tree of biological processes.
- Thumbnail**: A small preview image of the current pathway diagram.
- Details panel**: A panel at the bottom showing detailed information about the selected reaction, including its name, identifier, and description.

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Signaling pathways

Databases
Pathway methods

Preprocess

Modeling KEGG
Subpathways
Normalization

Method

Computing the signal
Functional annotation
Further analysis

Exercises

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



WIKIPATHWAYS
Pathways for the People

Pathway methods

▶ SPIA

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analysis

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Signaling pathways

Databases

Pathway methods

Preprocess

Modeling KEGG

Subpathways

Normalization

Method

Computing the signal

Functional annotation

Further analysis

Exercises

Pathway methods

- ▶ SPIA
- ▶ PARADIGM

Signaling pathways
analysis

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Signaling pathways

Databases

Pathway methods

Preprocess

Modeling KEGG

Subpathways

Normalization

Method

Computing the signal

Functional annotation

Further analysis

Exercises

Pathway methods

- ▶ SPIA
- ▶ PARADIGM
- ▶ Pathifier

Signaling pathways
analysis

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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 pathway

- ▶ SPIA
- ▶ PARADIGM
- ▶ Pathifier

- ▶ SubSPIA

Score per pathway

- ▶ SPIA
- ▶ PARADIGM
- ▶ Pathifier

- ▶ SubSPIA
- ▶ Pathways

Score per pathway

- ▶ SPIA
- ▶ PARADIGM
- ▶ Pathifier

Score per subpathway

- ▶ SubSPIA
- ▶ Pathiways

Score per pathway

- ▶ SPIA
- ▶ PARADIGM
- ▶ Pathifier

Score per subpathway

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

Method

Signaling pathways
analysis

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Signaling pathways

Databases

Pathway methods

Preprocess

Modeling KEGG

Subpathways

Normalization

Method

Computing the signal

Functional annotation

Further analysis

Exercises

- ▶ Independent from gene expression technology

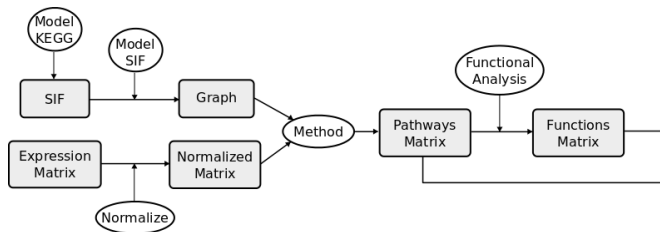
- ▶ Independent from gene expression technology
- ▶ Independent from pathway database

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

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

Input

- ▶ SIF file + attributes
- ▶ Expression matrix

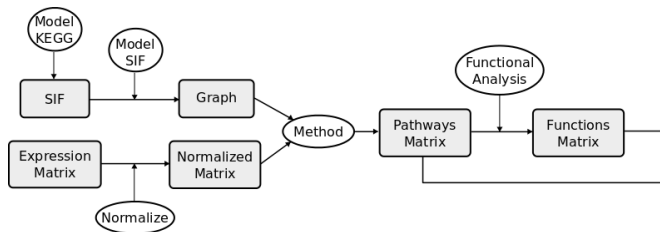


Input

- ▶ SIF file + attributes
- ▶ Expression matrix

Output

- ▶ Pathways matrix
- ▶ Functions matrix



Preprocess

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analysis

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Signaling pathways

Databases

Pathway methods

Preprocess

Modeling KEGG

Subpathways

Normalization

Method

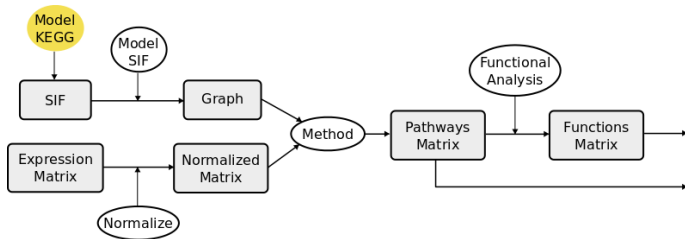
Computing the signal

Functional annotation

Further analysis

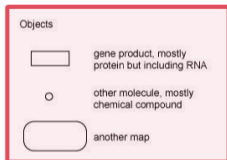
Exercises

Modeling KEGG pathways

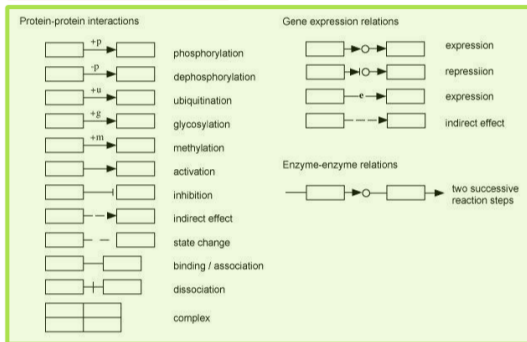
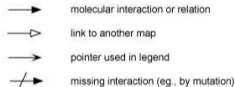


Modeling KEGG pathways

Nodes



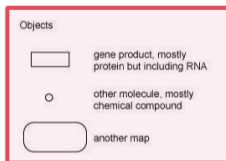
Arrows



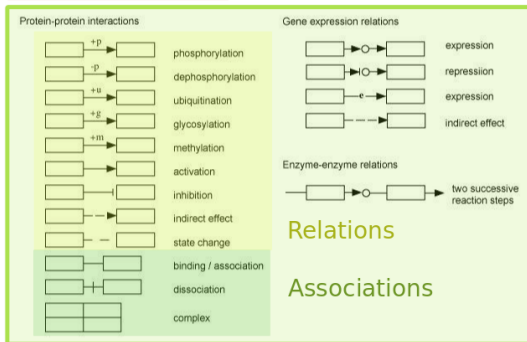
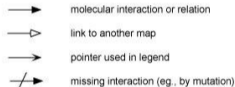
Edges

Modeling KEGG pathways

Nodes



Arrows



Edges

Modeling KEGG pathways

Only activations/inhibitions allowed

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Signaling pathways

Databases

Pathway methods

Preprocess

Modeling KEGG

Subpathways

Normalization

Method

Computing the signal

Functional annotation

Further analysis

Exercises

Modeling KEGG pathways

Signaling pathways
analysis

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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

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

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analysis

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Signaling pathways

Databases

Pathway methods

Preprocess

Modeling KEGG

Subpathways

Normalization

Method

Computing the signal

Functional annotation

Further analysis

Exercises

Modeling KEGG pathways

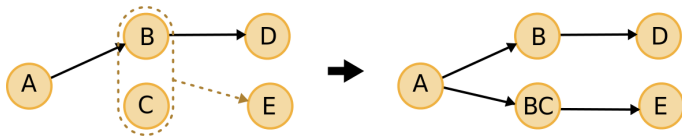
Plain nodes

Include one node, many
genes

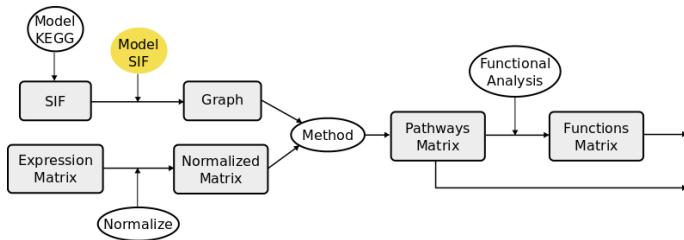
Complex nodes

Include different nodes

- ▶ Binding/association
- ▶ Group



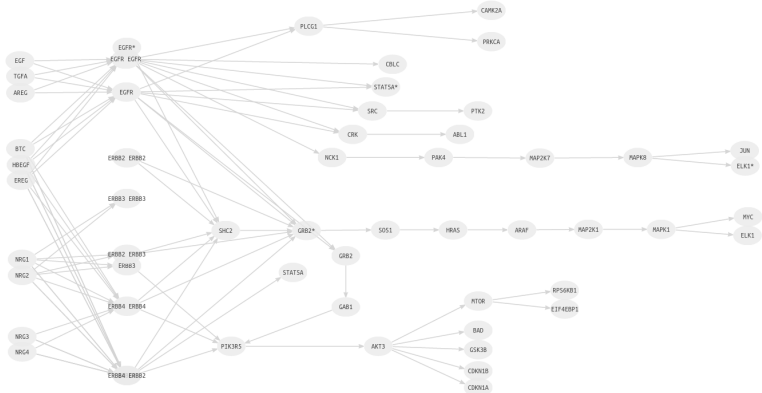
Modeling the graph



Effector subpathways

Effector proteins

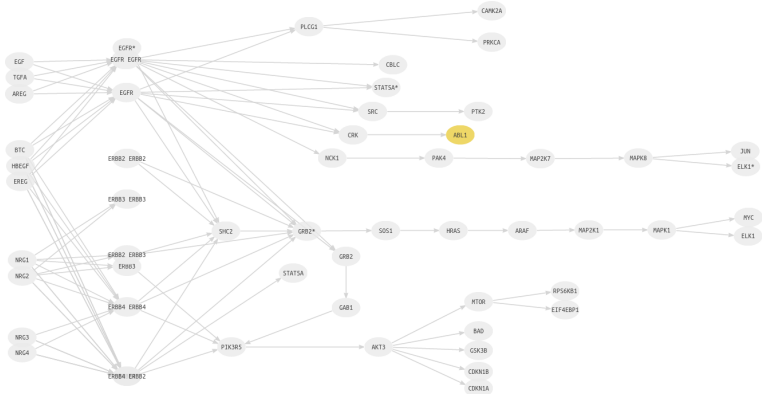
Last genes of the network, responsables for performing the corresponding molecular function



Effector subpathways

Effector subpathway

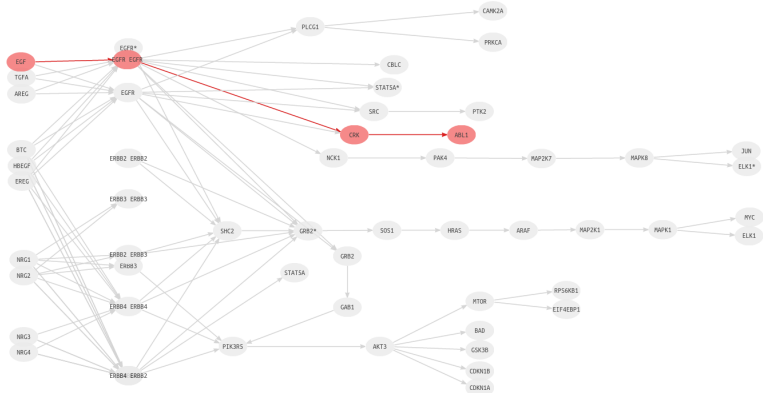
Subgraph of the pathway including any node in a path ending in an effector protein



Decomposed subpathways

Single subpathway

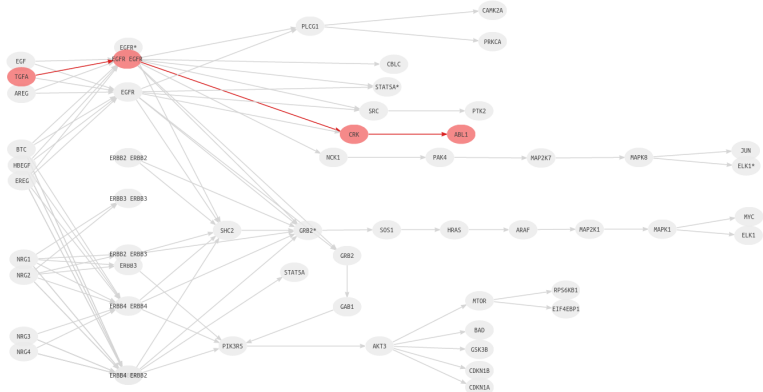
Subgraph of the pathway including only one input and one output node



Decomposed subpathways

Single subpathway

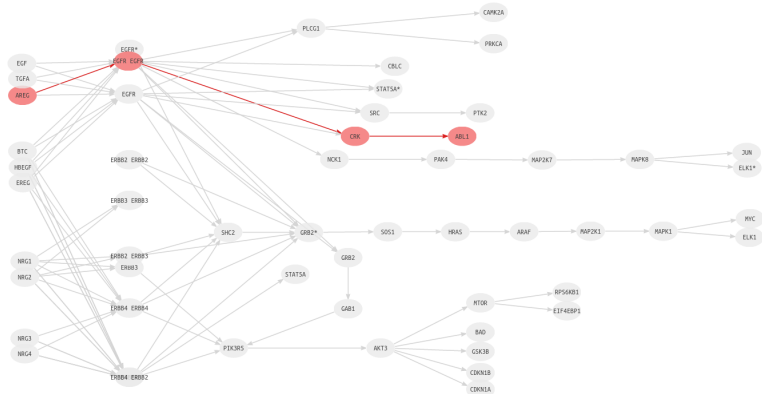
Subgraph of the pathway including only one input and one output node



Decomposed subpathways

Single subpathway

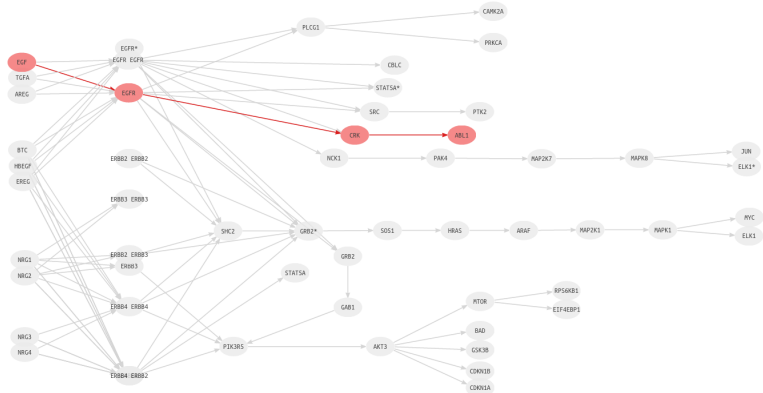
Subgraph of the pathway including only one input and one output node



Decomposed subpathways

Single subpathway

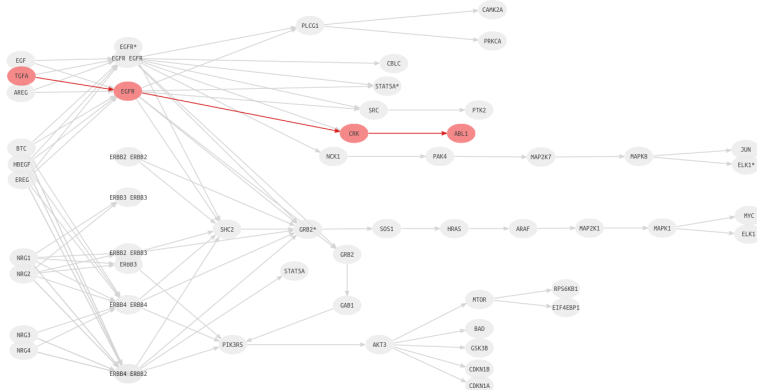
Subgraph of the pathway including only one input and one output node



Decomposed subpathways

Single subpathway

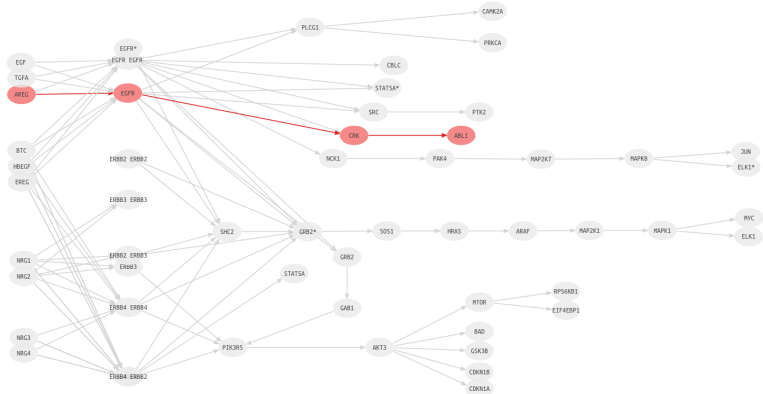
Subgraph of the pathway including only one input and one output node



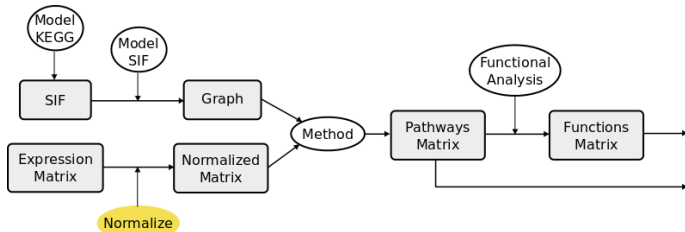
Decomposed subpathways

Single subpathway

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



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

Signaling pathways
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Signaling pathways

Databases

Pathway methods

Preprocess

Modeling KEGG

Subpathways

Normalization

Method

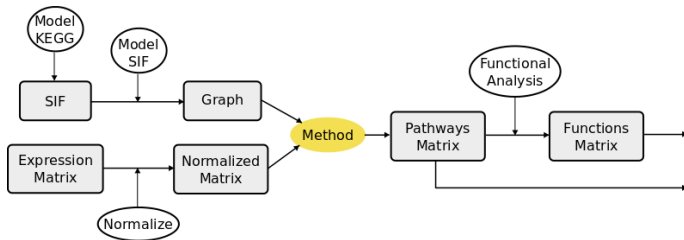
Computing the signal

Functional annotation

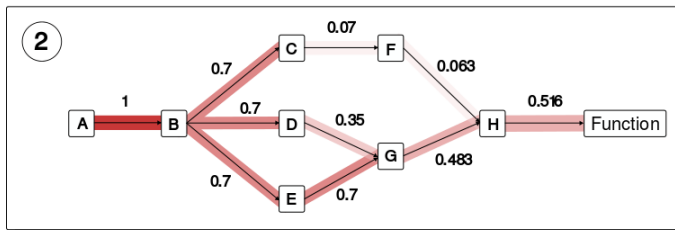
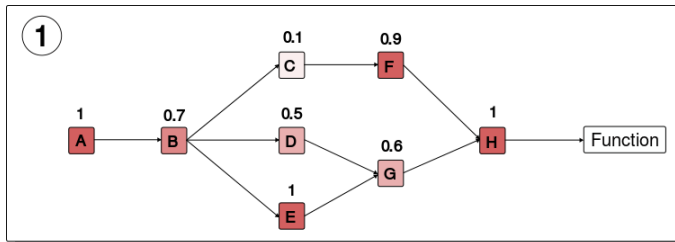
Further analysis

Exercises

Method

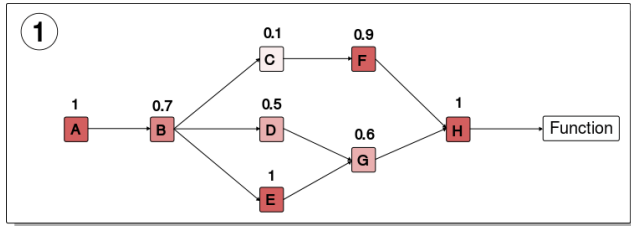


Method



Node values

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



Signal value through a node

For node n

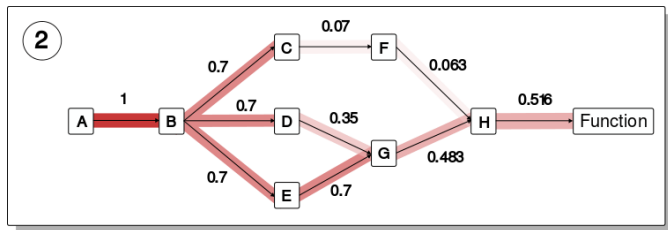
$$S_n = v_n \cdot \left(1 - \prod_{s_i \in A} (1 - s_i)\right) \cdot \prod_{s_j \in I} (1 - s_j)$$

S_n : Signal value through n

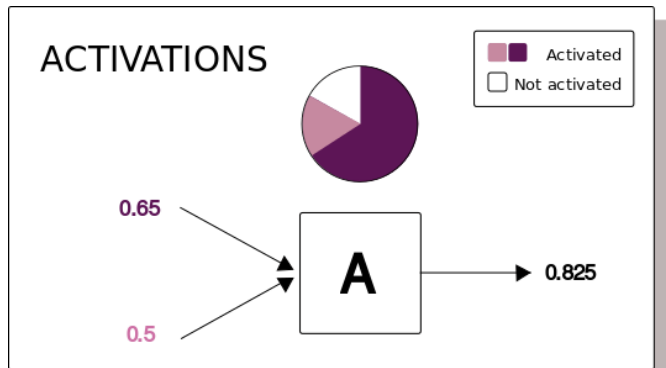
v_n : Node value

A: Activation edges

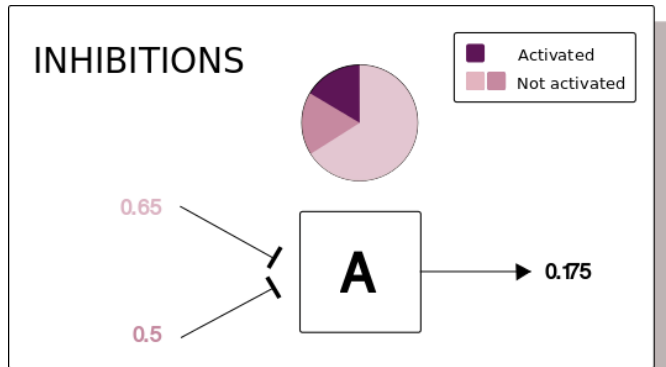
I: Inhibition edges



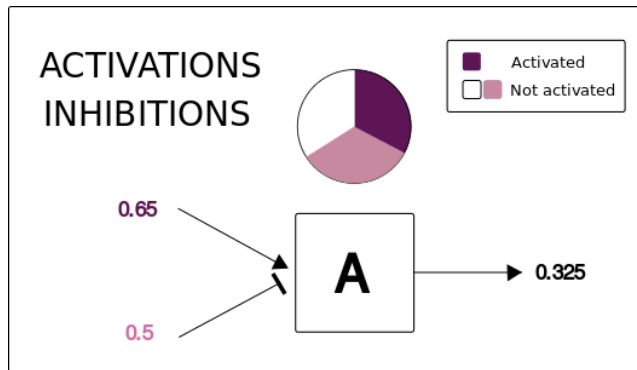
Computing the signal



Computing the signal

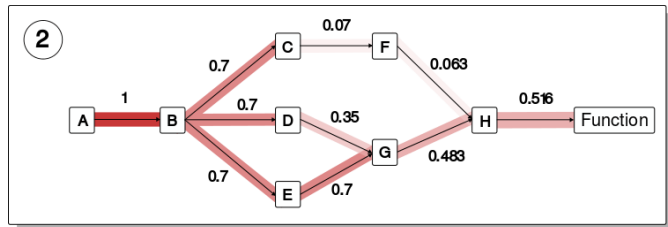


Computing the signal



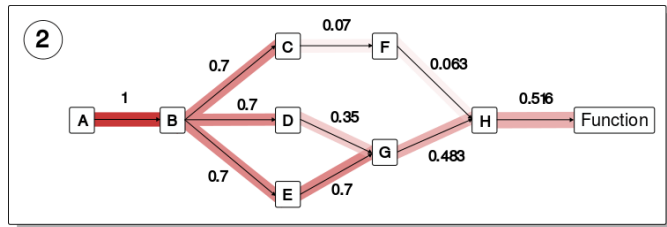
Signal values

- ▶ Input signal 1 in any input node



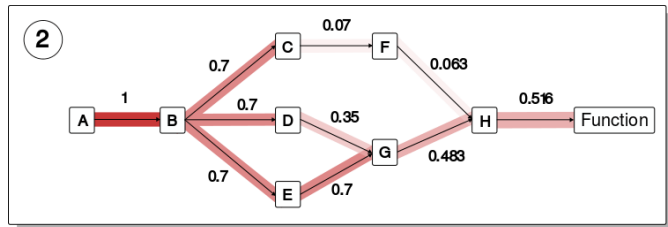
Signal values

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



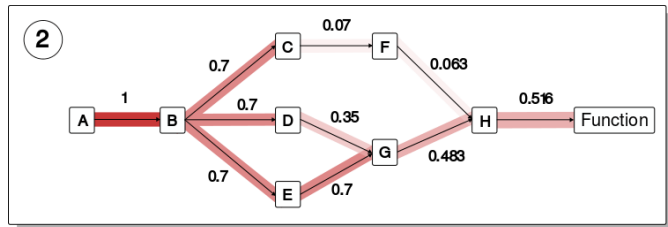
Signal values

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

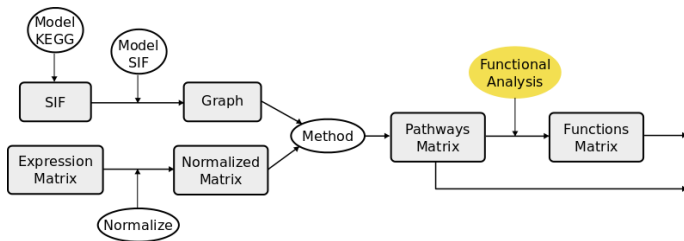


Signal values

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

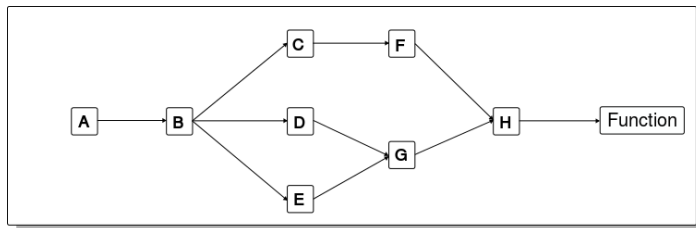


Functional annotation



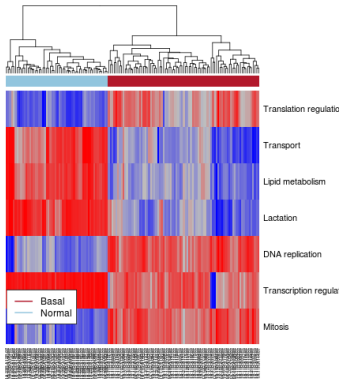
Subpathway function \sim Effector protein function

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



Further analysis

► Heatmap



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Signaling pathways

Databases
Pathway methods

Preprocess

Modeling KEGG
Subpathways
Normalization

Method

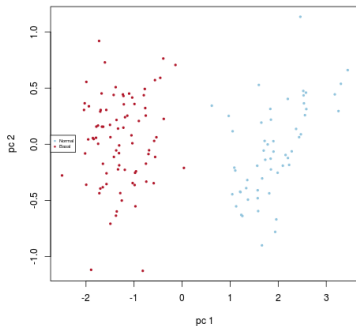
Computing the signal
Functional annotation

Further analysis

Exercises

Further analysis

- ▶ Heatmap
- ▶ PCA



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analysis

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Signaling pathways

Databases
Pathway methods

Preprocess

Modeling KEGG
Subpathways
Normalization

Method

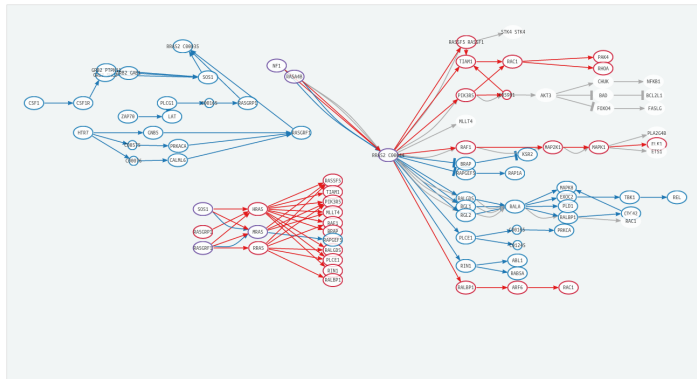
Computing the signal
Functional annotation

Further analysis

Exercises

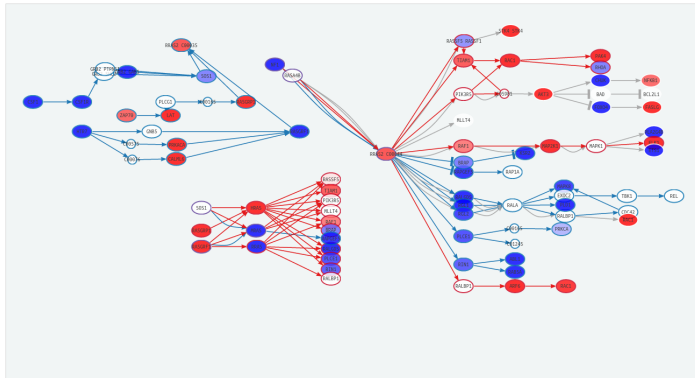
Further analysis

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



Further analysis

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



Exercises

Signaling pathways
analysis

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Signaling pathways

Databases

Pathway methods

Preprocess

Modeling KEGG

Subpathways

Normalization

Method

Computing the signal

Functional annotation

Further analysis

Exercises