HiPathia
Models of signaling pathway activity

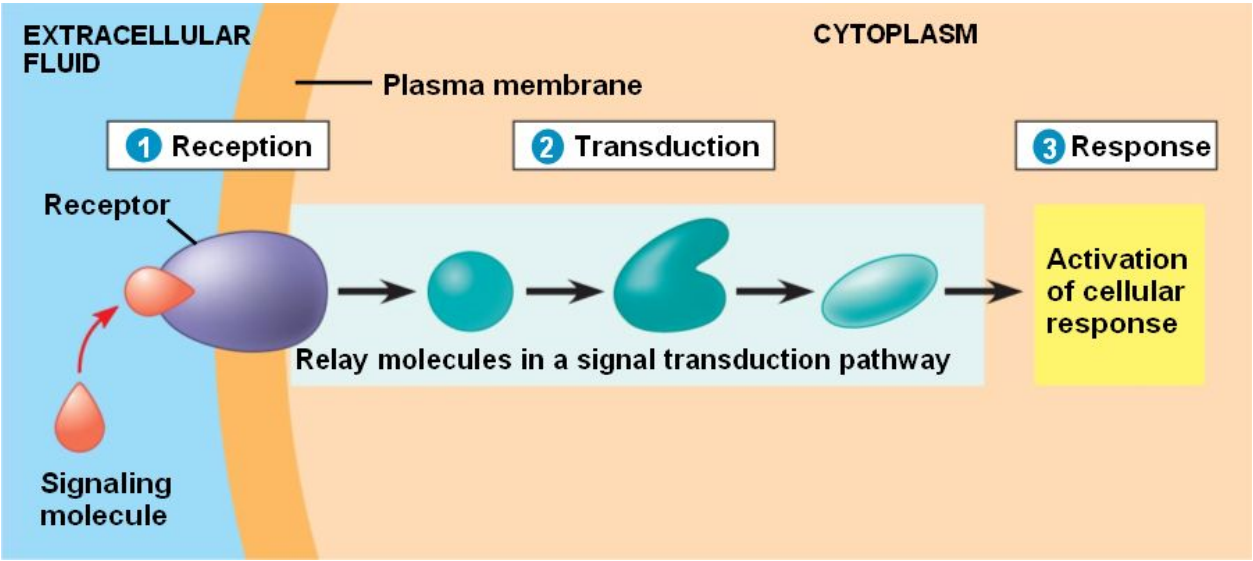
Marta R. Hidalgo

March 10th, 2016

GDA
International Course on
Genomic Data Analysis

PRINCIPE FELIPE
CENTRO DE INVESTIGACION

Signaling pathways



Chemical signals

- Hormones
- Neurotransmiters
- Growth factors
- Cytokines
- Drugs

Activation & Inhibition

- Phosphorilation
- Dephosphorilation
- Glycosylation
- Ubiquitination
- Methylation

Cellular Function

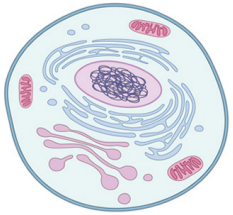
- Apoptosis
- Survival
- Growth
- Migration
- Proliferation

HiPathia

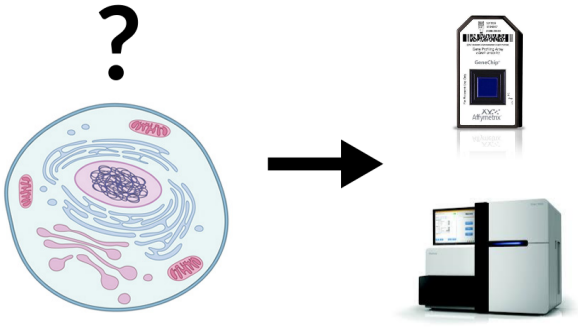
Method

From cell to pathways

?



From cell to pathways



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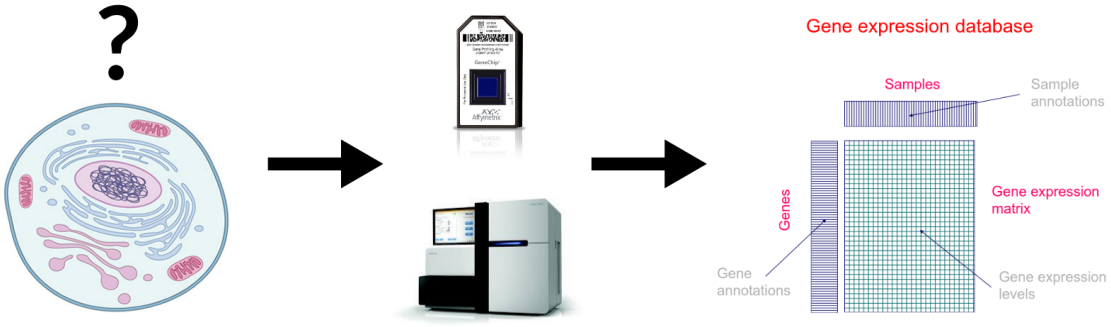

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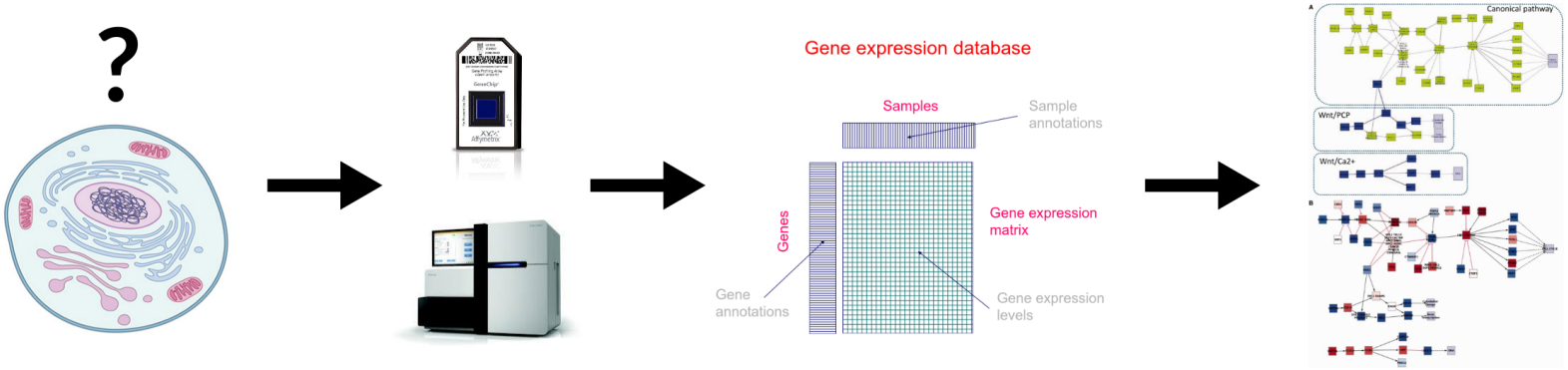

Pathway methods

- **DEGraph**: Based on DE
- **Clipper**: 2 test method
- **SPIA**: Impact factor
- **Sub-SPIA**: Find subnetwork by DE and apply SPIA
- **HiPathia**: Computes signal for each sample

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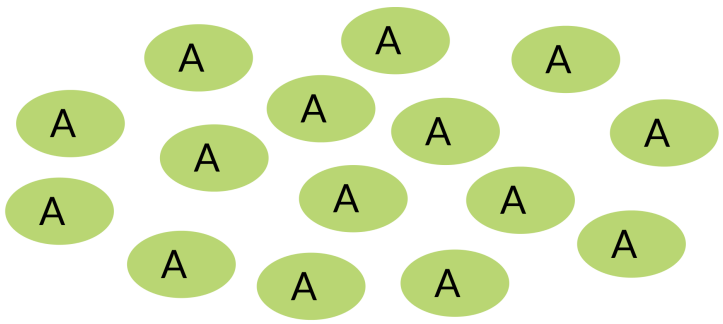
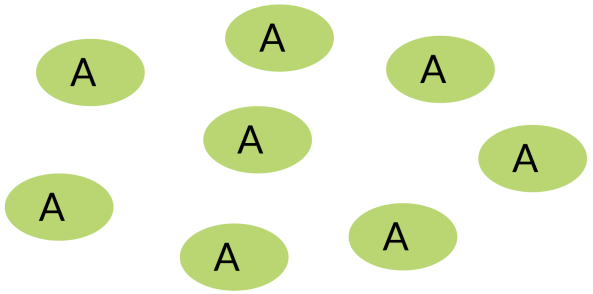
Intuitive idea





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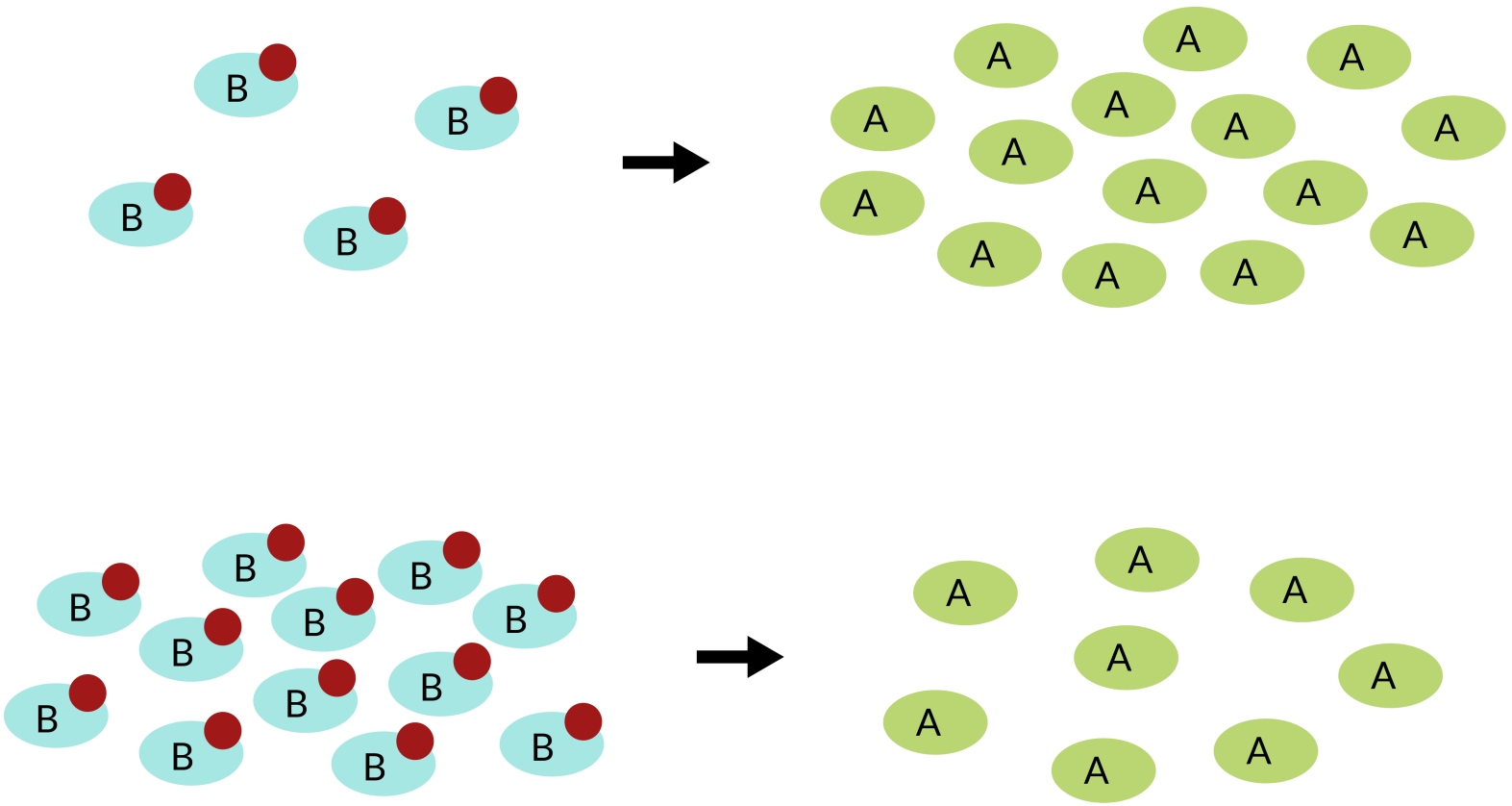
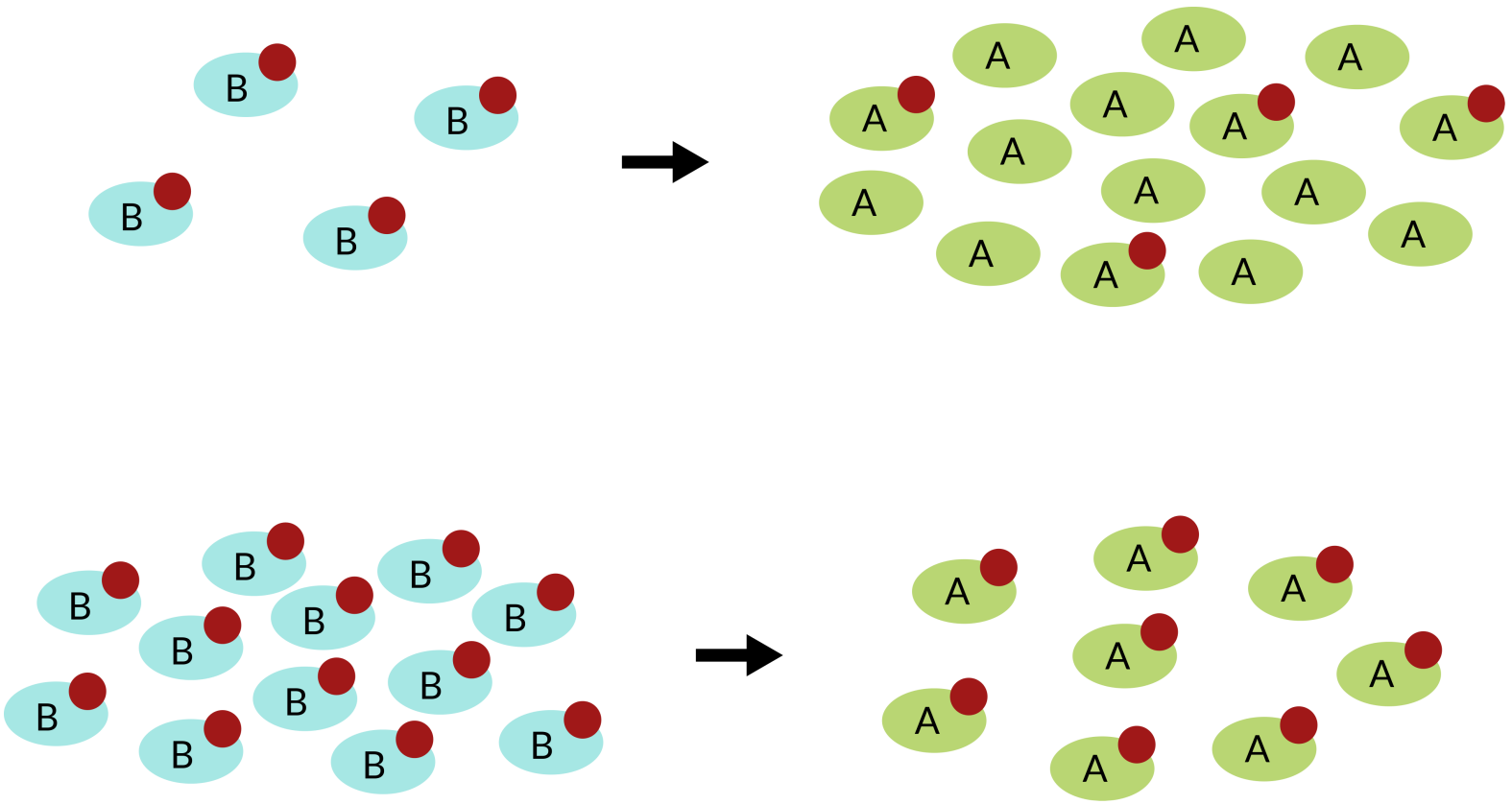
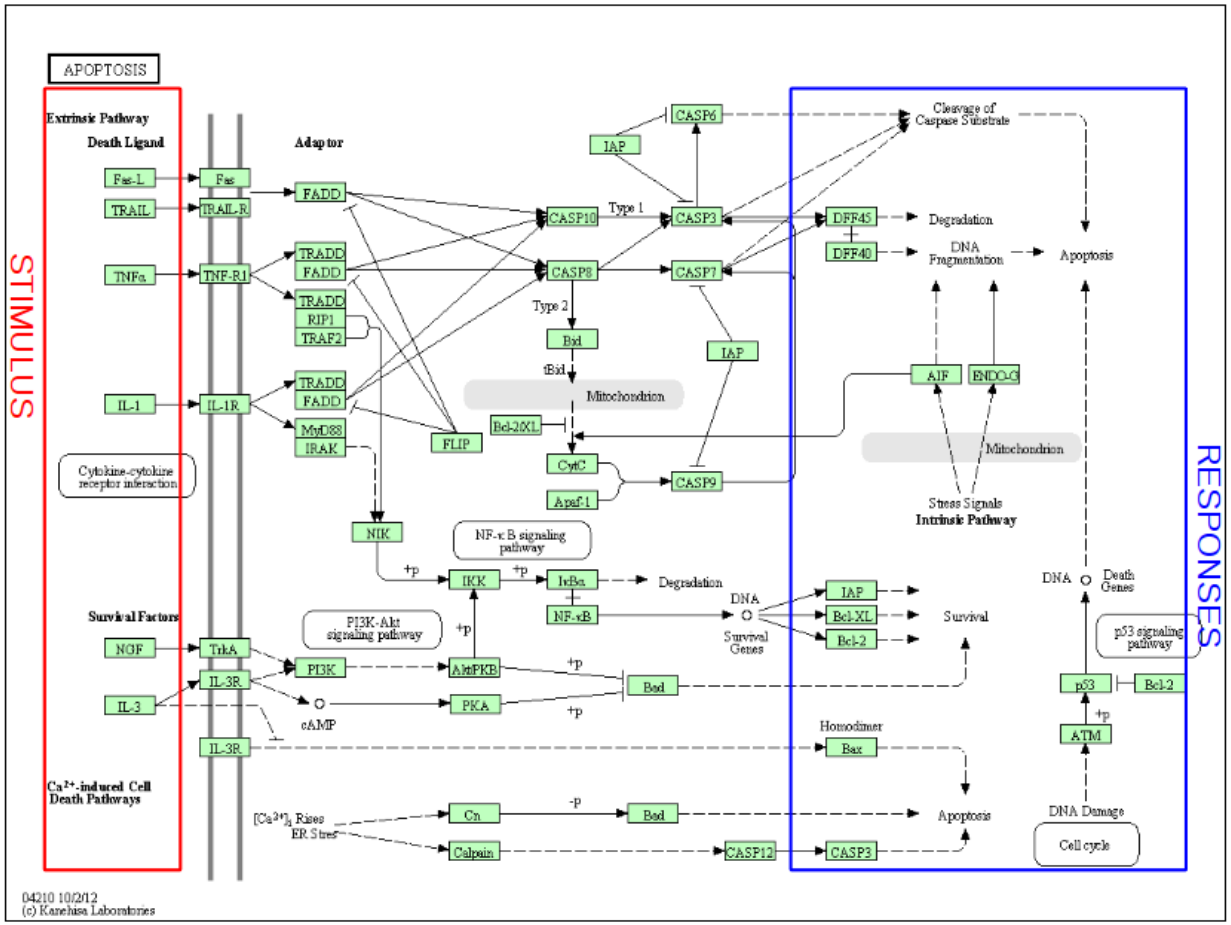


Intuitive idea



Pathways layout

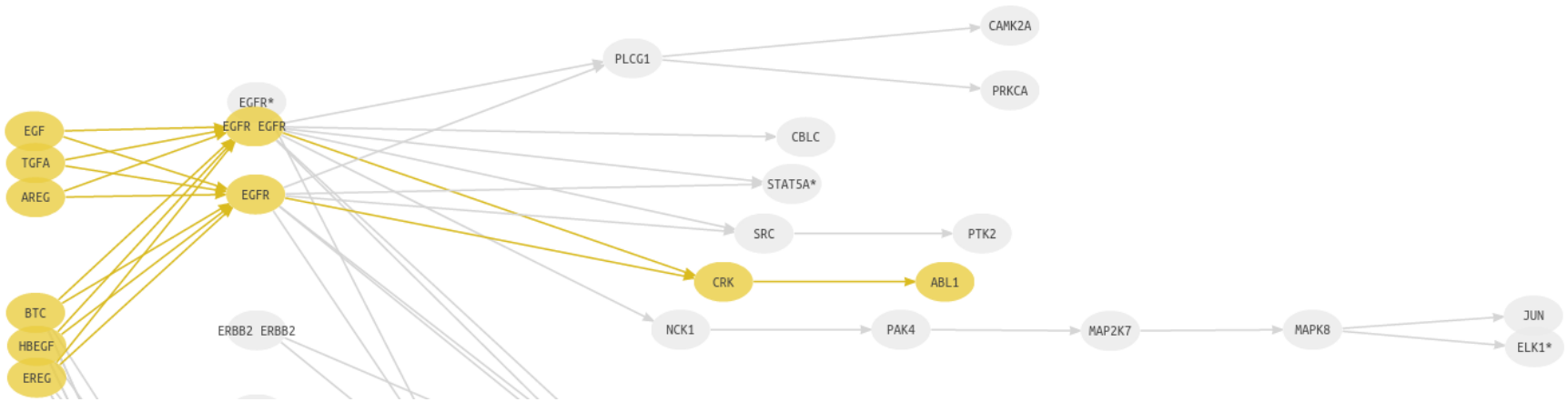
Take pathways information from KEGG, www.kegg.jp



Meaningful subpathways

Effector subpathway

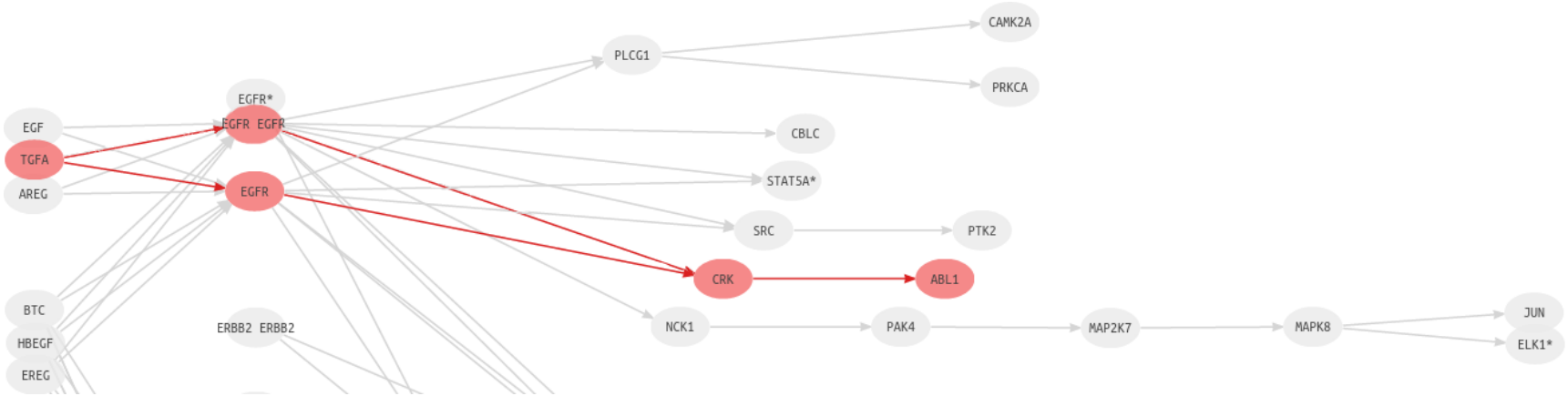
Subpathway including any node from any receptor to one effector protein



Meaningful subpathways

Decomposed subpathway

Subpathway including any node from one receptor to one effector protein



Computing the signal

1. Compute a node score based on the expression
2. Compute signal passing through each node n

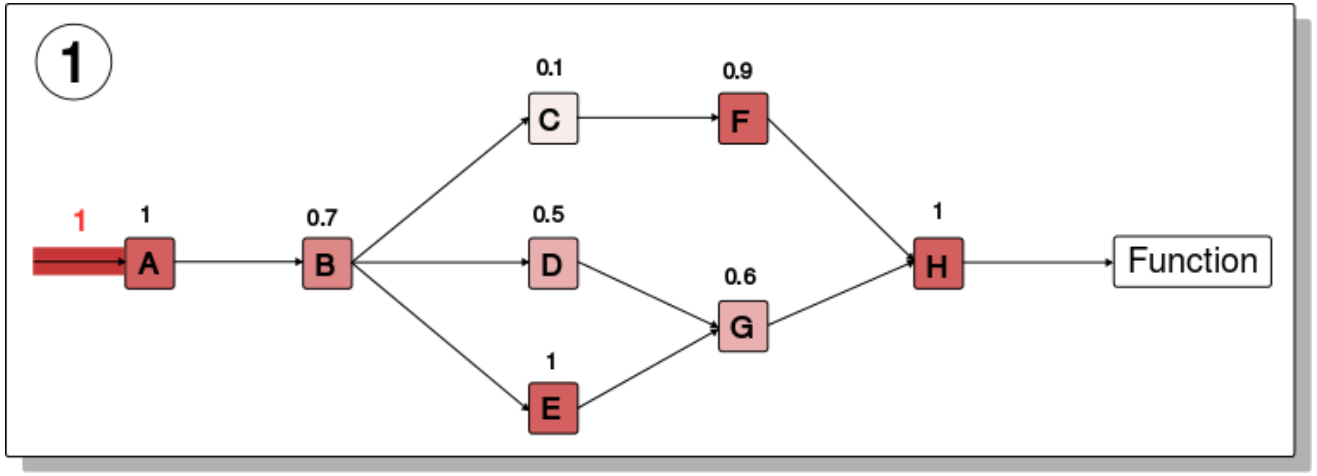
$$S_n = v_n \cdot \left(1 - \prod_{s_i \in A} (1 - s_i)\right) \cdot \prod_{s_j \in I} (1 - s_j)$$

S_n: Signal value through n

v_n: Node value

A: Activation edges

I: Inhibition edges



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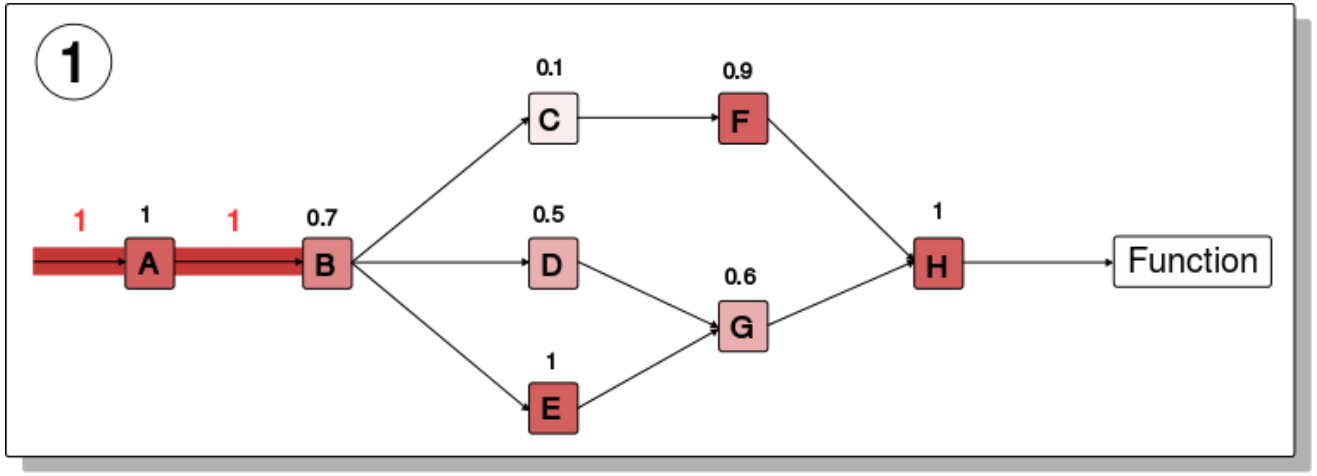

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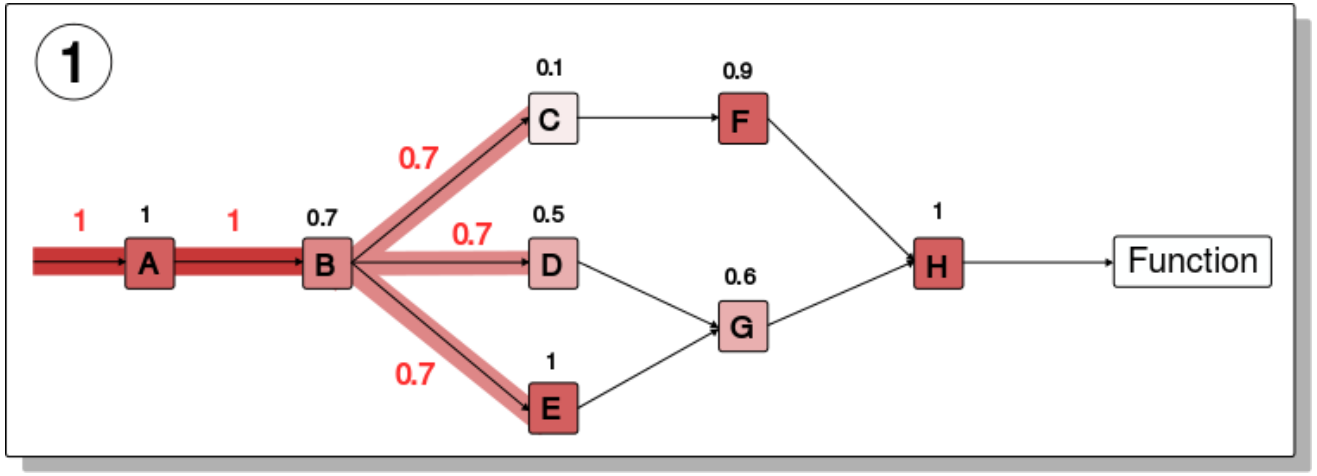

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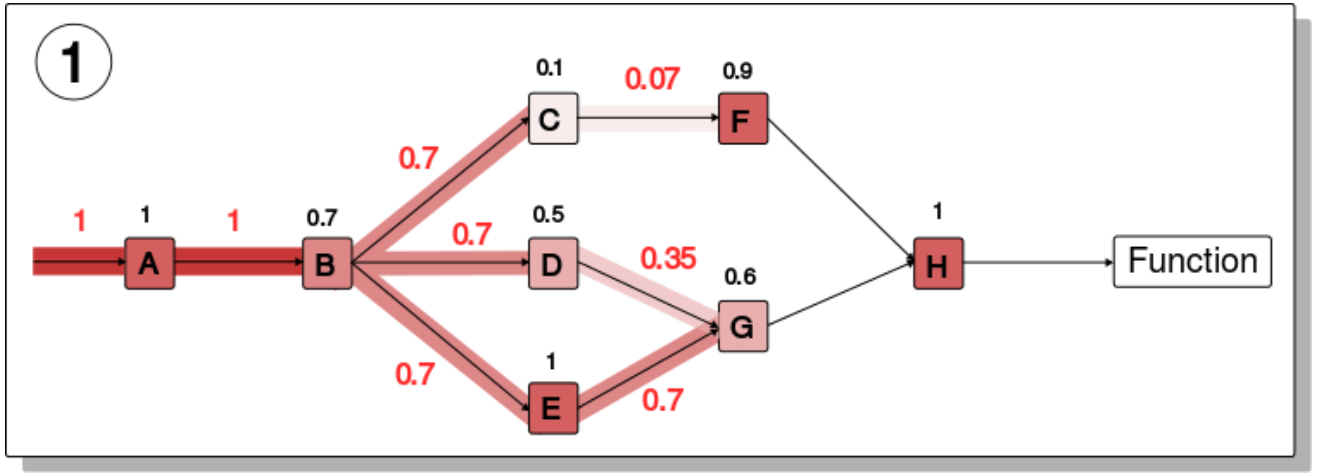

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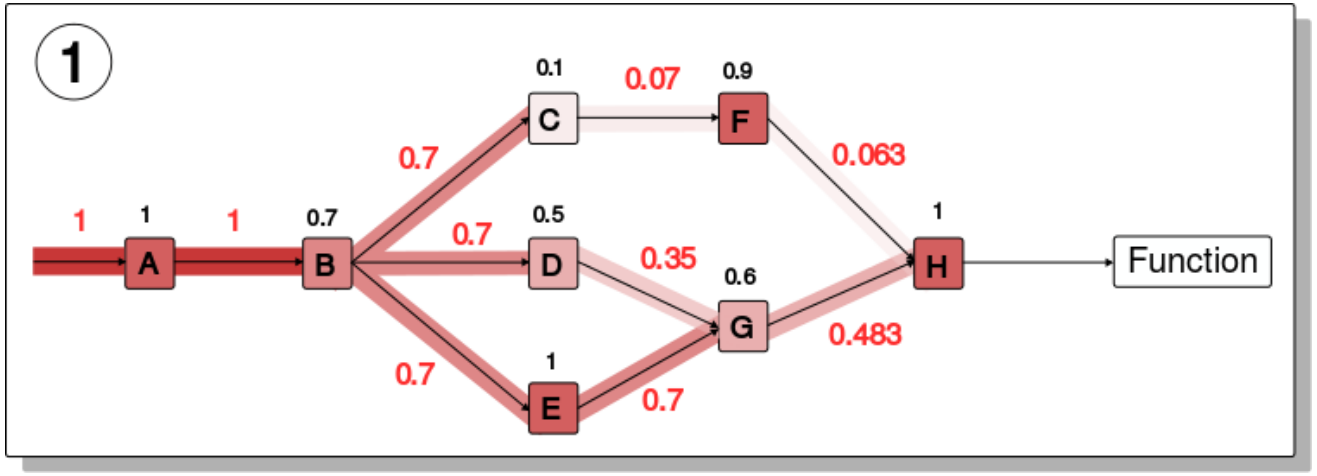

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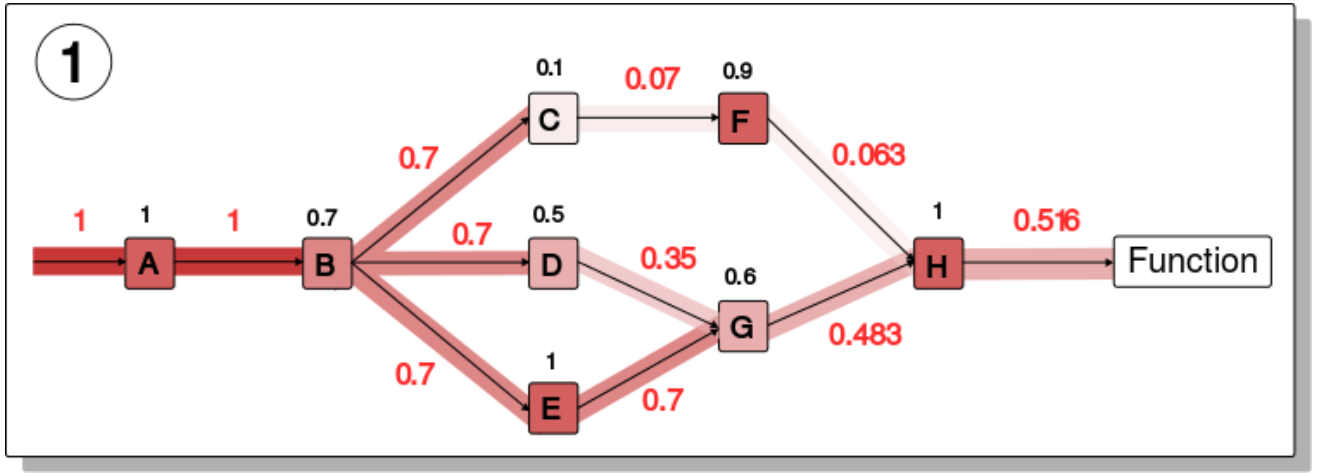

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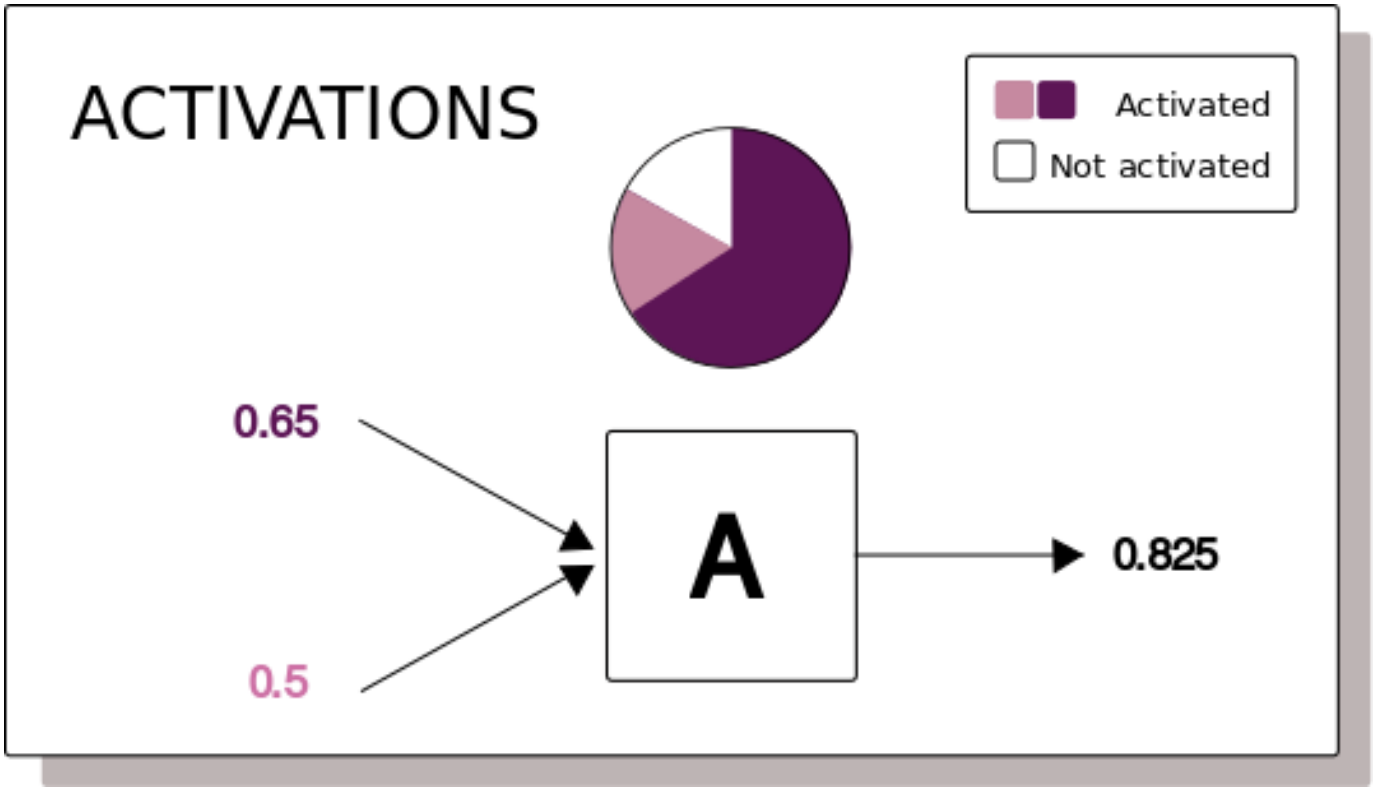

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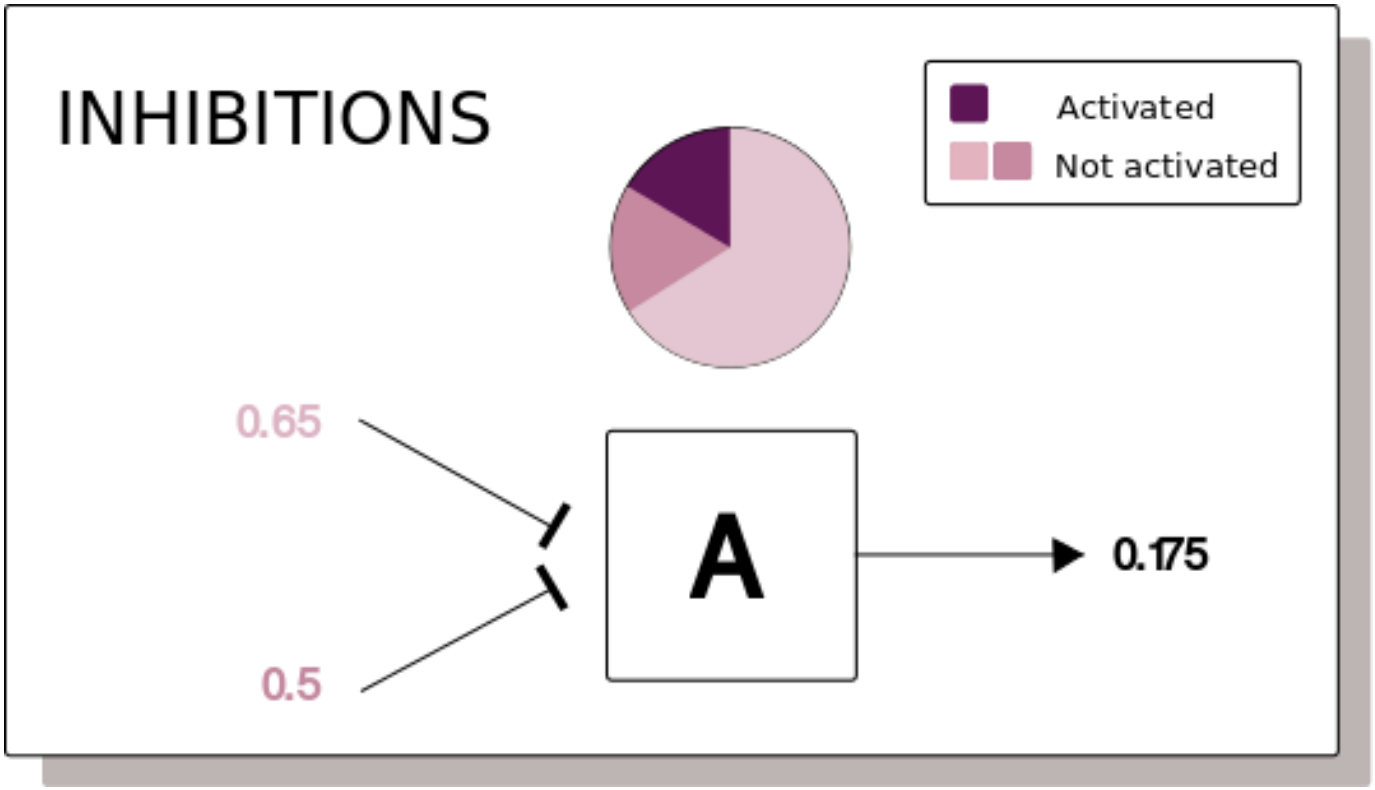

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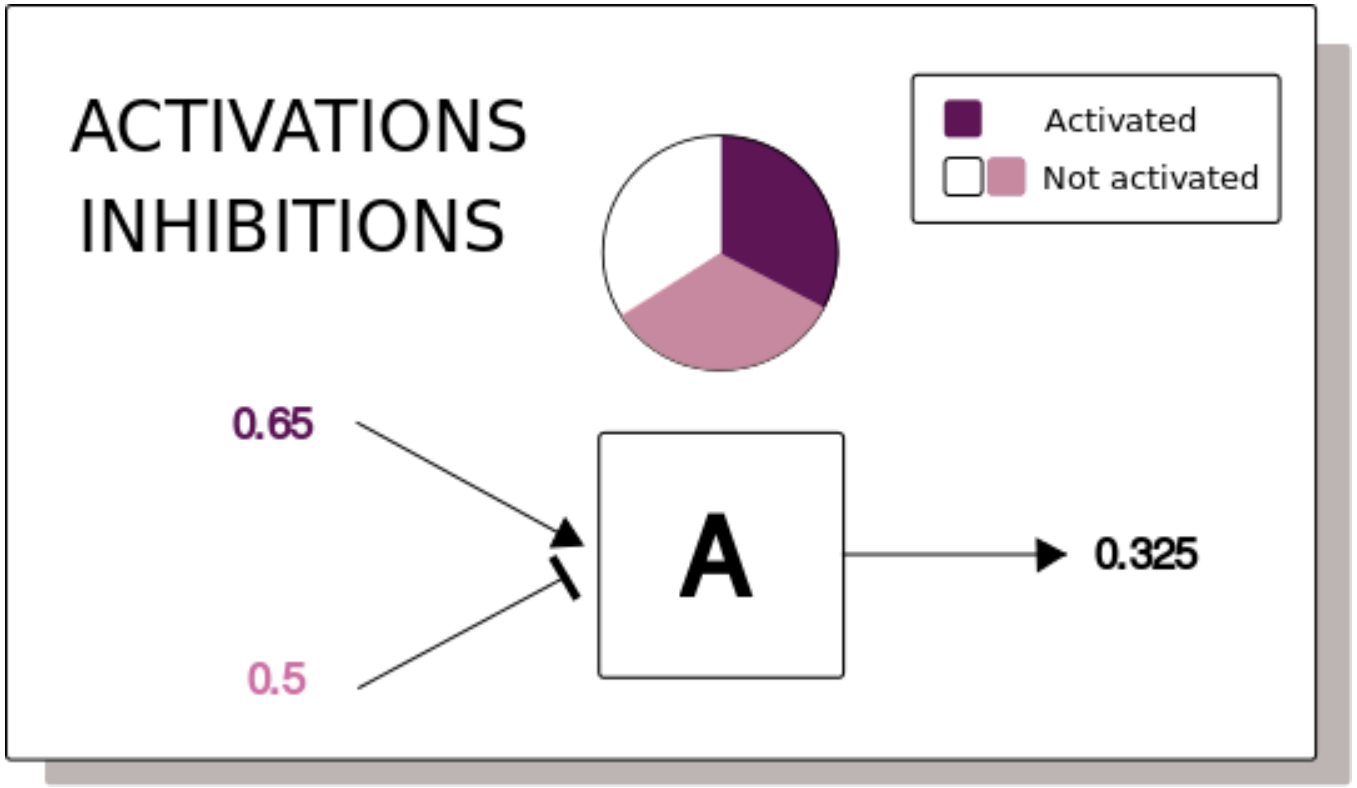
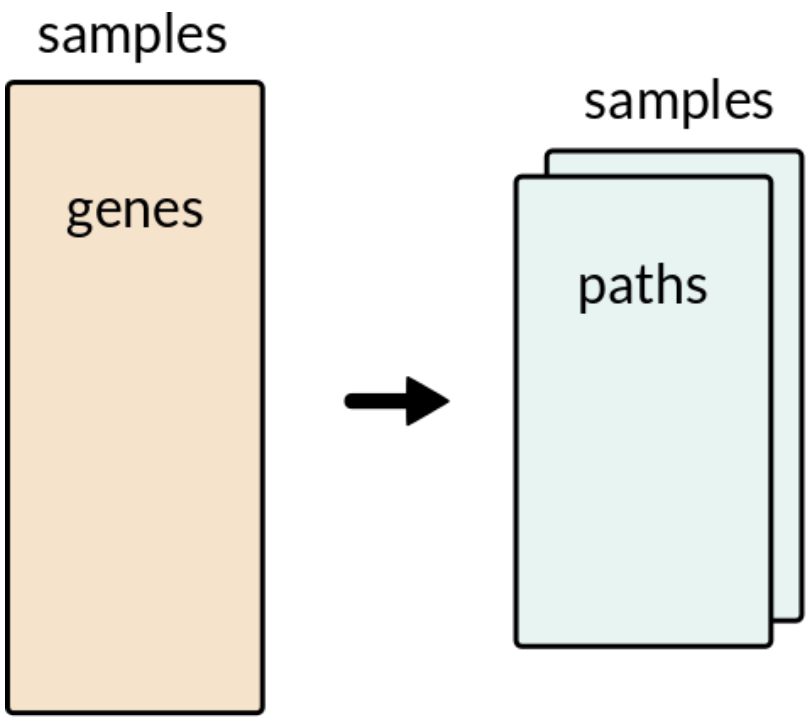


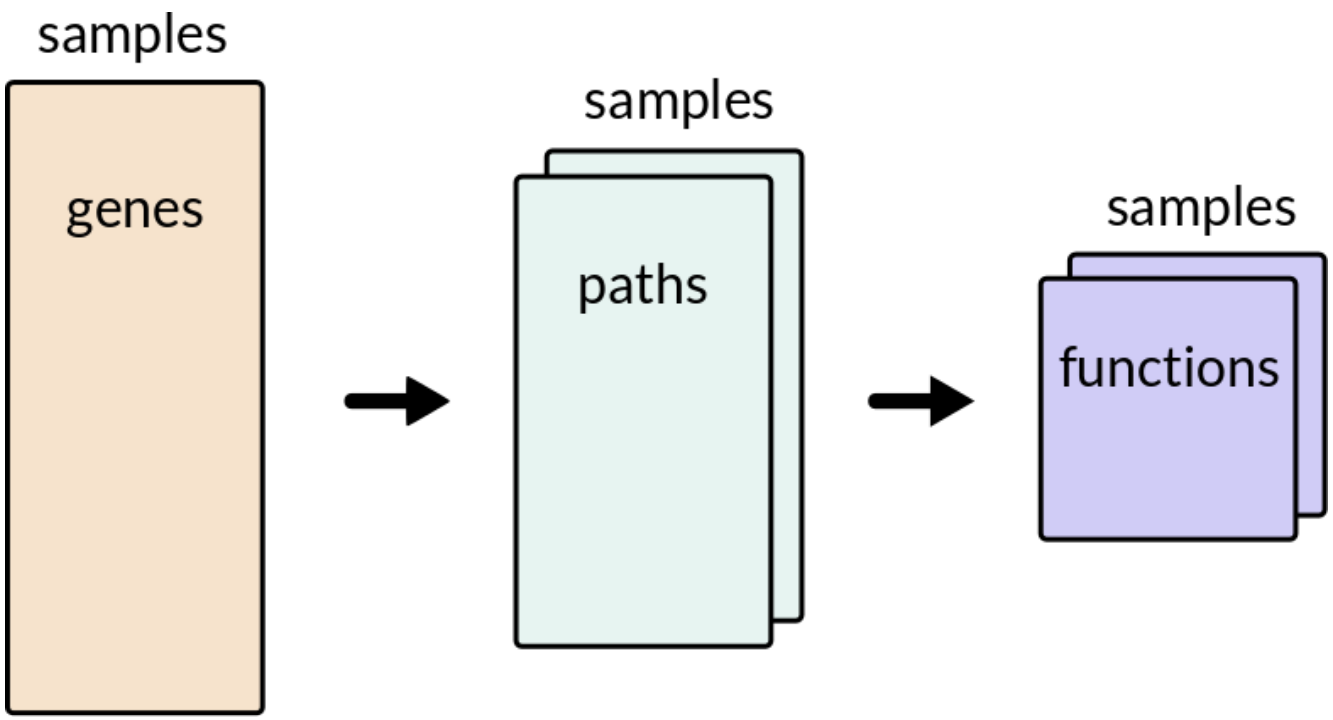
Functional annotation



Functional annotation

We annotate each effector protein to a function

- Uniprot keywords
- GO annotation



HiPathia

Web tool

Logging in

hipathia.babelomics.org

Upload data


2
hiPathia
Pathways analysis suite
Differential signaling
Prediction
My data
My jobs
gda2016ciberer
Profile
Logout
1
Browse My Data
3
/
gda2016ciberer
Upload
Name
Size
Date
Exercise_1
Sep 26, 2016
0 B of 1.0 GB
All
Search by name...
hiPathia
HIGH THROUGHPUT PATHWAY
INFERENCE ANALYSIS
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changes of gene expression levels and/or genomic mutations in the context of
signalling pathways. hiPathia transforms uninformative gene expression and/or
genomic variation data into signalling circuit activities, which carry information on
the different cell functionalities triggered by them. Such signalling activities not only
account for the underlying molecular mechanisms of diseases or the mode of action
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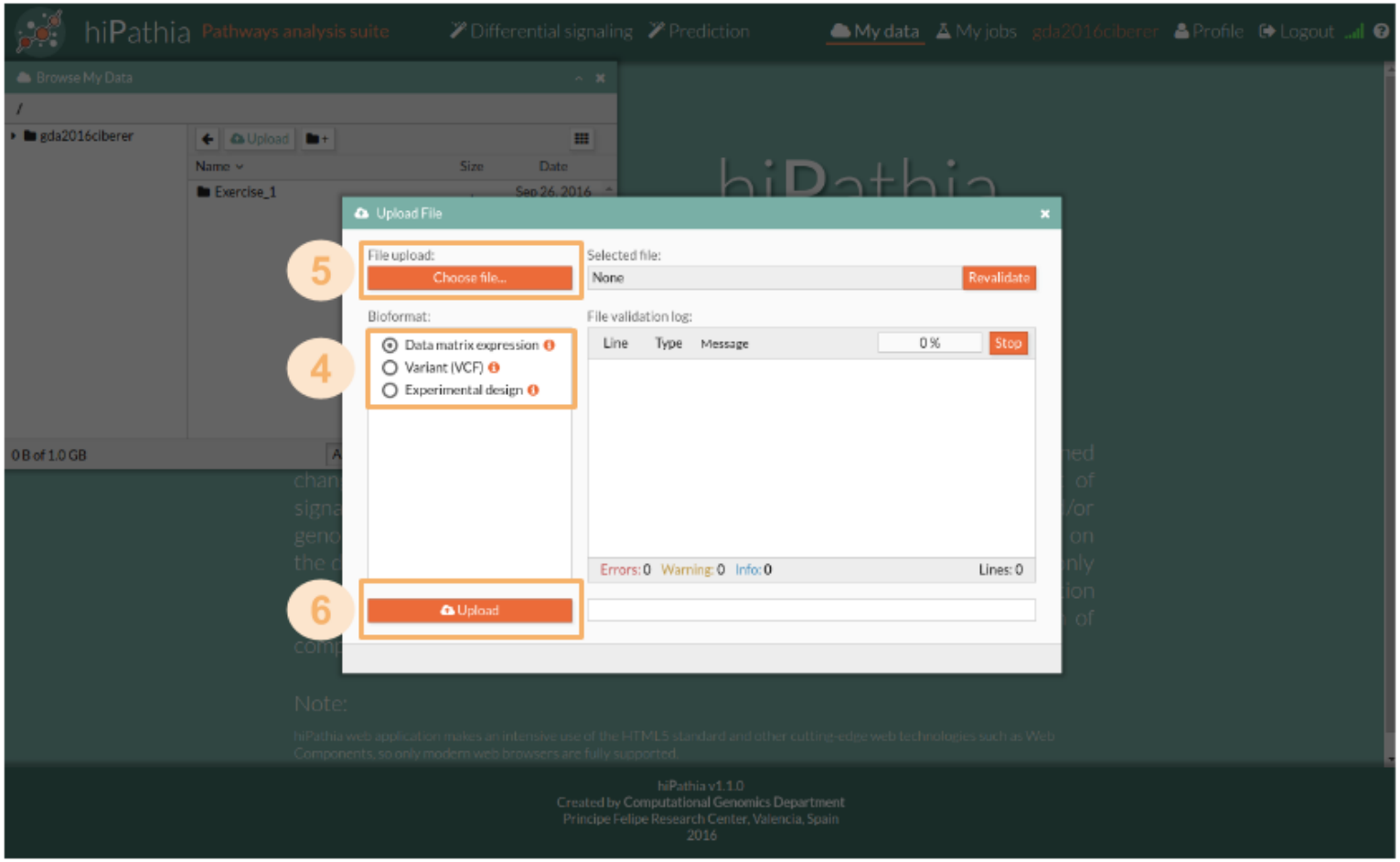
complex phenotypes.
Note:
hiPathia web application makes an intensive use of the HTML5 standard and other cutting-edge web technologies such as Web
Components, so only modern web browsers are fully supported.
hiPathia v1.1.0
Created by Computational Genomics Department
Principe Felipe Research Center, Valencia, Spain
2016

Upload data


hiPathia
Pathways analysis suite
Differential signaling
Prediction
My data
My jobs
gda2016ciberer
Profile
Logout
Browse My Data
gda2016ciberer
Upload
Name
Size
Date
Exercise_1
Sep 26, 2016
0 B of 1.0 GB
Upload File
5
File upload:
Choose file...
Selected file:
None
Revalidate
Bioformat:
4
Data matrix expression
Variant (VCF)
Experimental design
File validation log:
Line
Type
Message
0 %
Stop
Errors: 0
Warning: 0
Info: 0
Lines: 0
6
Upload
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Workflow


2
hiPathia
Pathways analysis suite
Differential signaling
Prediction
3
My data
1
My jobs
gda2016ciberer
Profile
Logout
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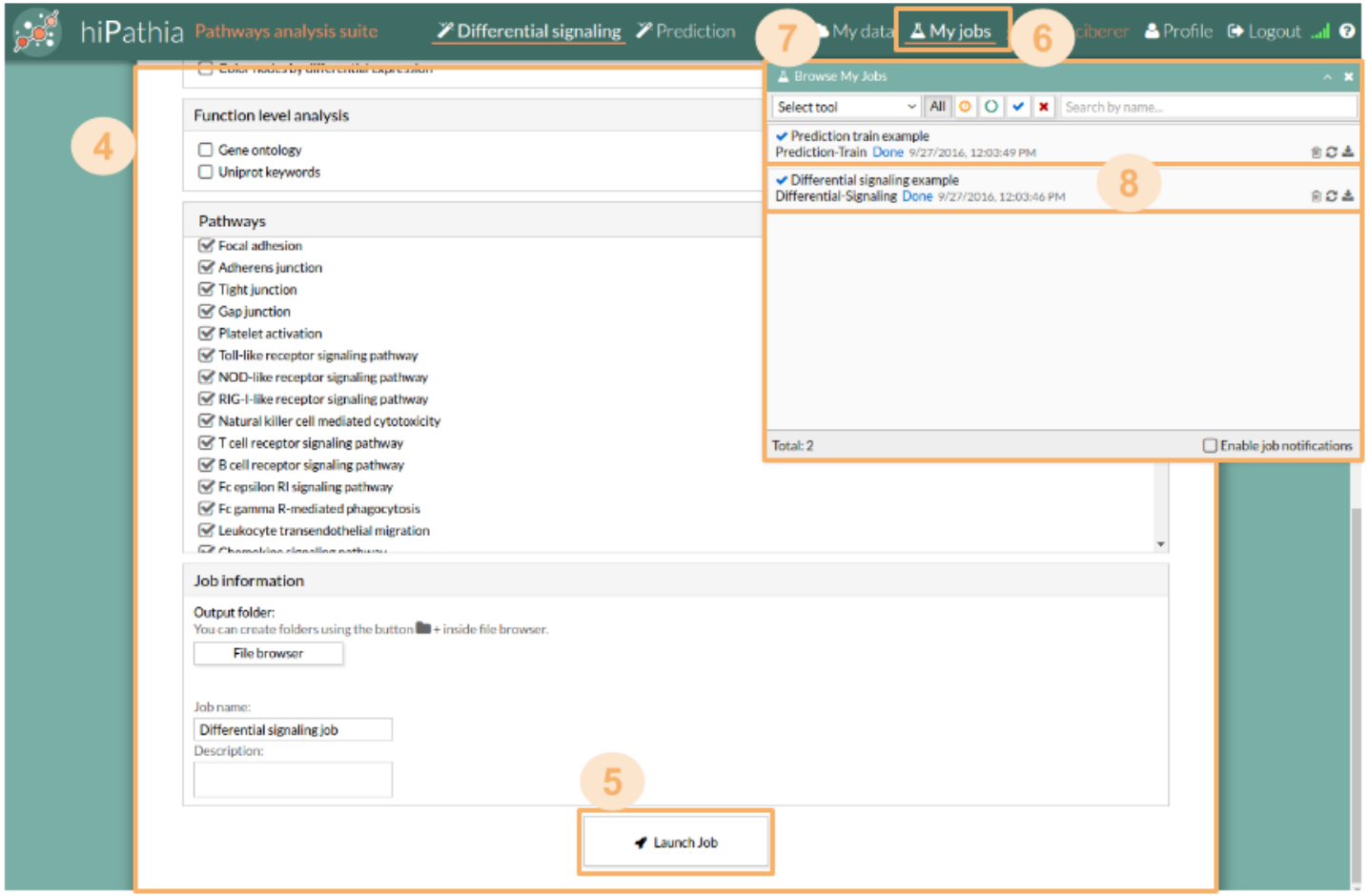
hiPathia Pathways analysis suite
Differential signaling
Prediction
7
My data
My jobs
6
ciberer
Profile
Logout
Browse My Jobs
Select tool
All
Search by name...
Prediction train example
Prediction-Train Done 9/27/2016, 12:03:49 PM
Differential signaling example
Differential-Signaling Done 9/27/2016, 12:03:46 PM
8
Total: 2
Enable job notifications
4
Function level analysis
Gene ontology
Uniprot keywords
Pathways
Focal adhesion
Adherens junction
Tight junction
Gap junction
Platelet activation
Toll-like receptor signaling pathway
NOD-like receptor signaling pathway
RIG-I-like receptor signaling pathway
Natural killer cell mediated cytotoxicity
T cell receptor signaling pathway
B cell receptor signaling pathway
Fc epsilon RI signaling pathway
Fc gamma R-mediated phagocytosis
Leukocyte transendothelial migration
Job information
Output folder:
You can create folders using the button + inside file browser.
File browser
Job name:
Differential signaling job
Description:
5
Launch Job

Tools

1. **Differential signaling**
   - Compare signal activity between two conditions
   - Correlate path value with a continuous variable

2. **Prediction**
   - Construct a predictor from a dataset
   - Predict classes from new dataset using the predictor

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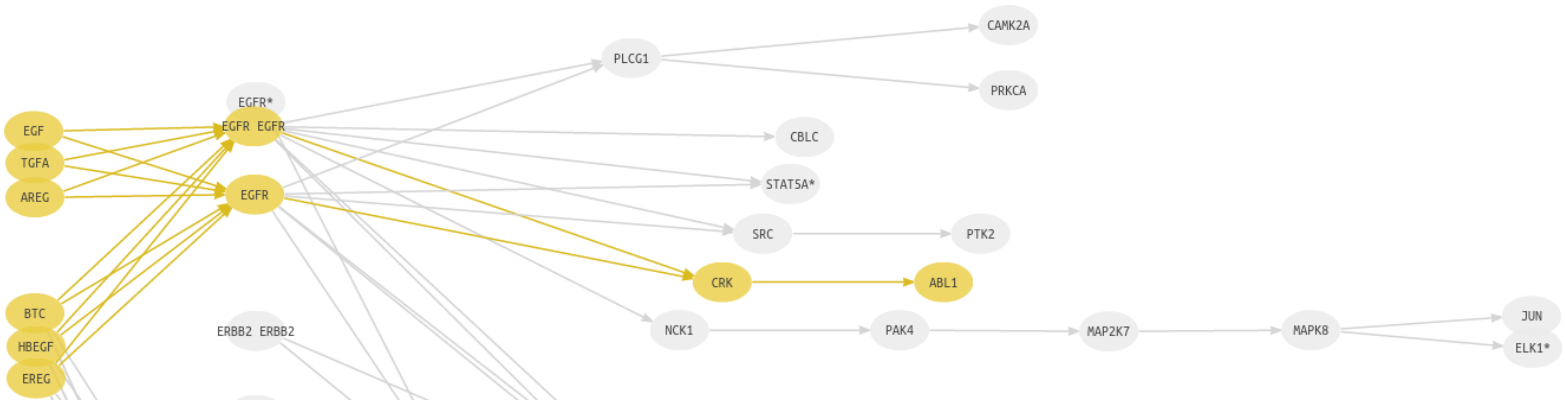
   - Color nodes by differential expression



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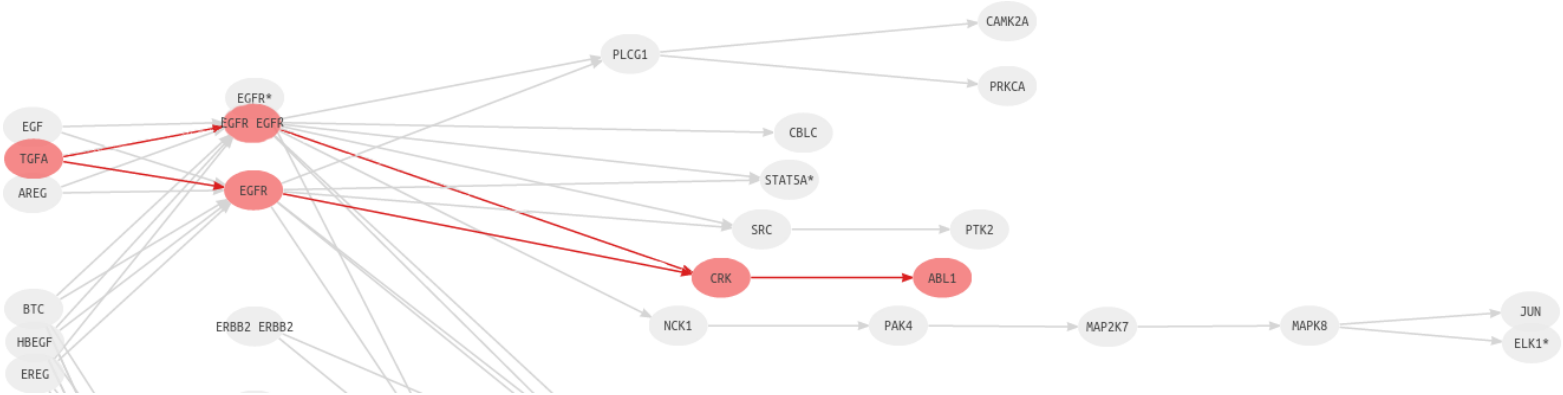

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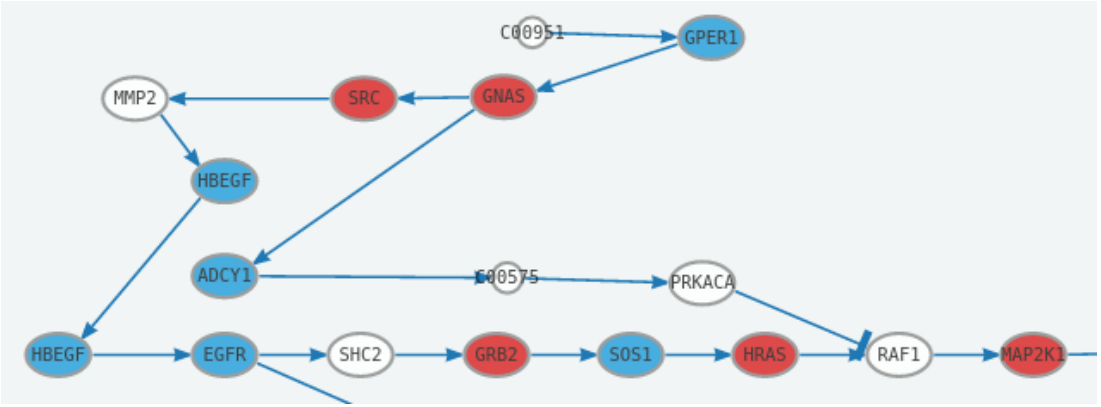


Parameters

1. **Parameters**
   - Decompose paths
   - Color nodes by differential expression

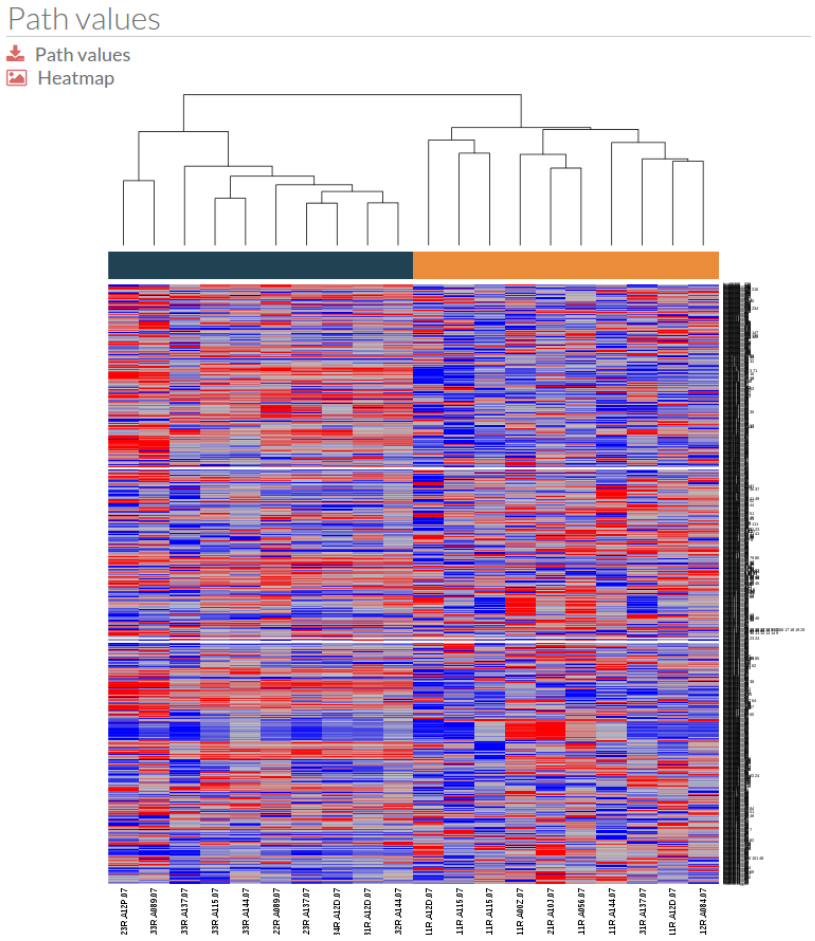
2. **Function level analysis**
   Perform analysis with the following functional annotations:
   - Gene ontology
   - Uniprot keywords

HiPathia

Results

Heatmap

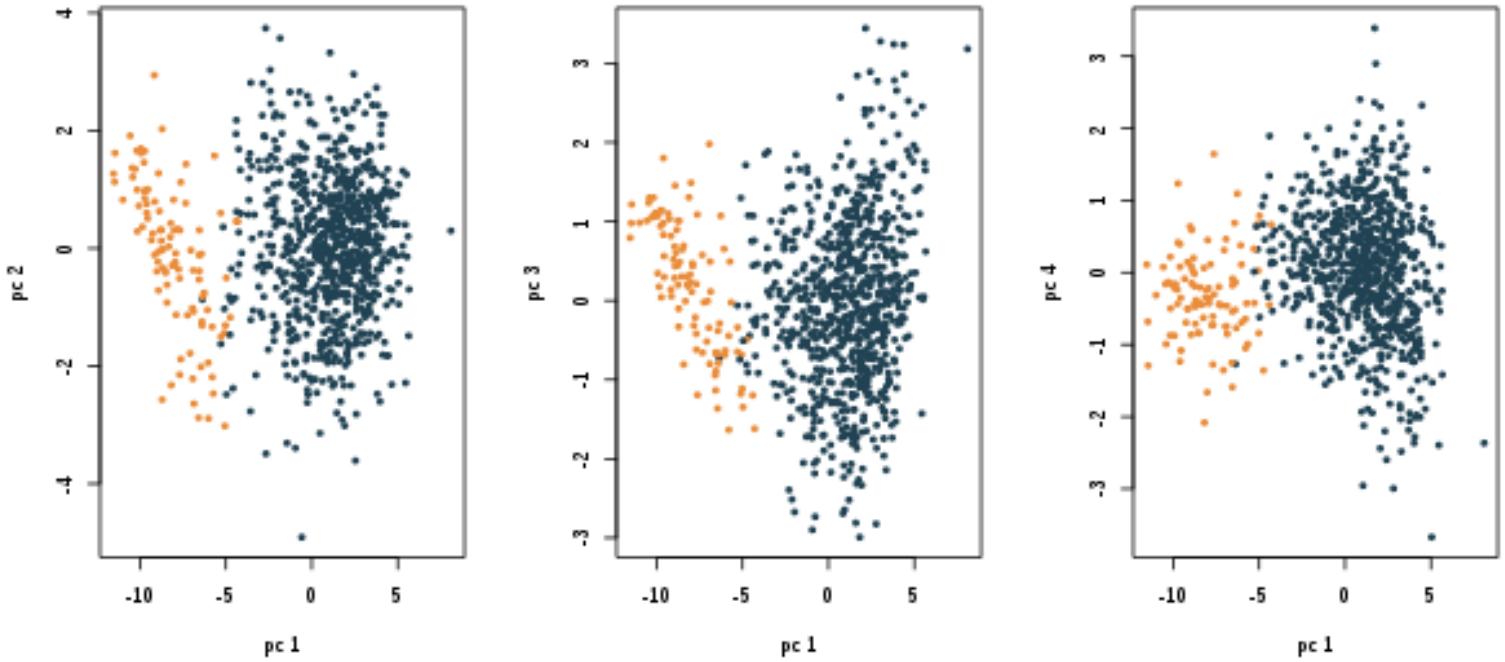
Graphical representation of data where values in a matrix are represented as colors



Principal Components Analysis (PCA)

Statistical procedure to convert a set of observations into a set of values of linearly uncorrelated variables

PCA



Results table

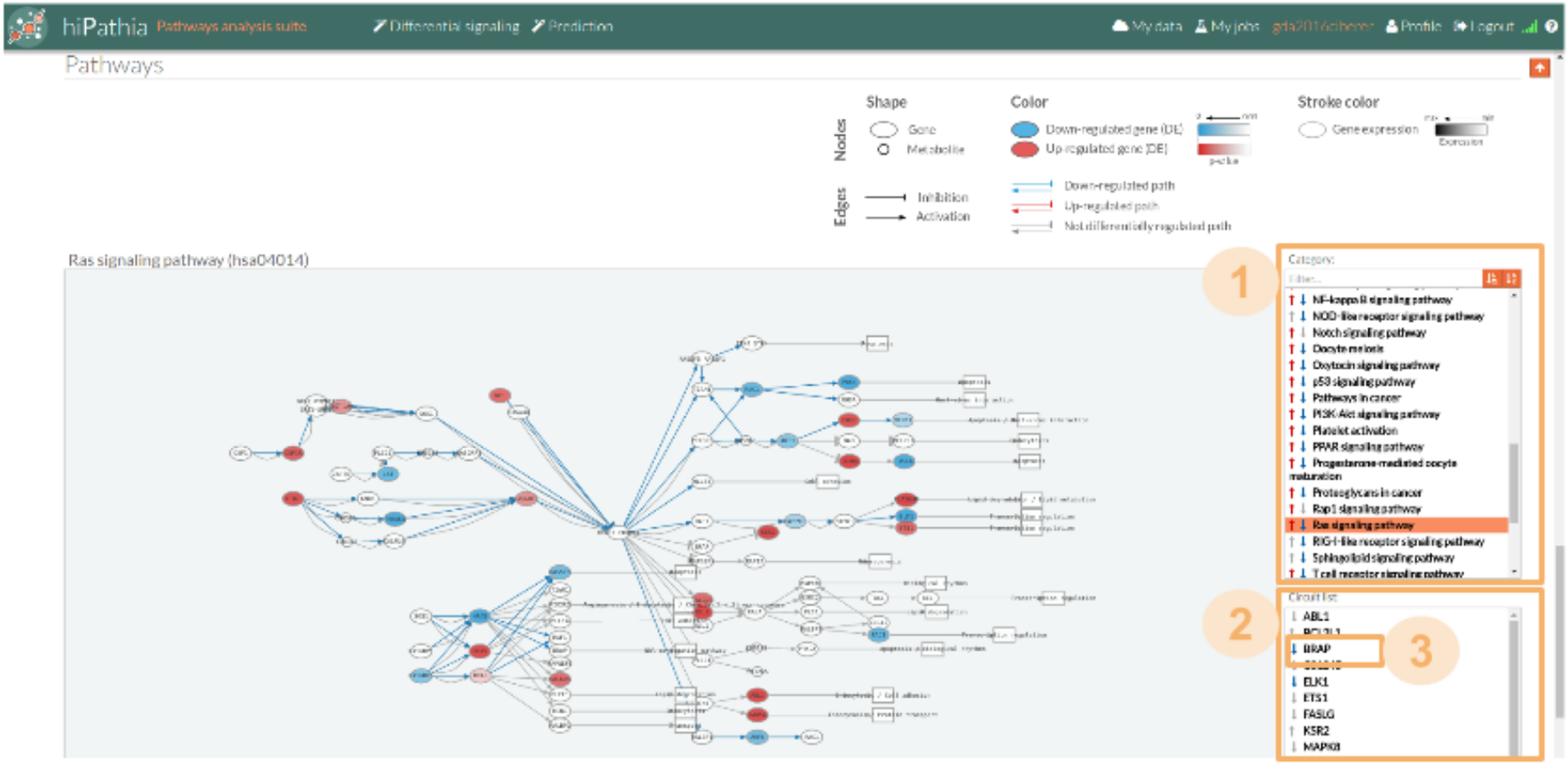
- Table of results for the comparison.
- Ordered by the FDR p-value.

Path significance

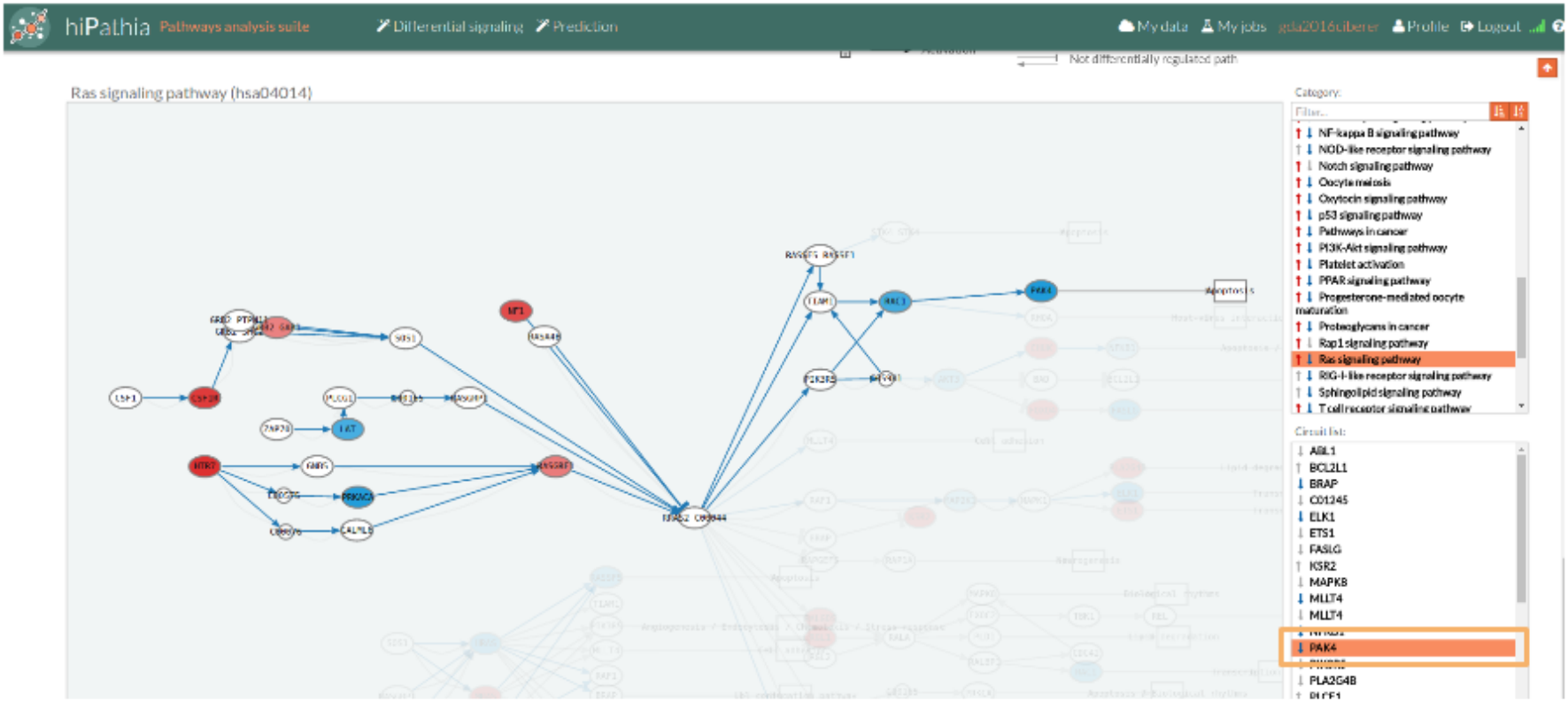
circuit/term	UP/DOWN	statistic	p.value	FDRp.value
ErbB signaling pathway: STAT5A	DOWN	-16.076	0.000	0.000
Adrenergic signaling in cardiomyocytes: SCN1B	DOWN	-15.987	0.000	0.000
Thyroid hormone signaling pathway: RCAN1	DOWN	-15.966	0.000	0.000
cGMP-PKG signaling pathway: PDE2A	DOWN	-15.909	0.000	0.000
cGMP-PKG signaling pathway: C00144	DOWN	-15.786	0.000	0.000
AMPK signaling pathway: LEPR	DOWN	-15.761	0.000	0.000
Hippo signaling pathway: FGF1	DOWN	-15.728	0.000	0.000
Adherens junction: SMAD4 SMAD2	DOWN	-15.727	0.000	0.000
Adipocytokine signaling pathway: PTPN11	DOWN	-15.727	0.000	0.000
p53 signaling pathway: CDK1 CCNB3	UP	15.693	0.000	0.000

« ‹ Page 1 of 102 › » 1 - 10 of 1014

Viewer


hiPathia
Pathways analysis suite
Differential signaling
Prediction
My data
My jobs
Profile
Logout
Pathways
Shape
Color
Stroke color
Nodes
Gene
Metabolite
Down-regulated gene (DE)
Up-regulated gene (DE)
Gene expression
Edges
Inhibition
Activation
Down-regulated path
Up-regulated path
Ras signaling pathway (hsa04014)
1
2
3
Category:
NF-kappa B signaling pathway
NOD-like receptor signaling pathway
Notch signaling pathway
Oocyte meiosis
Oxytocin signaling pathway
p53 signaling pathway
Pathways in cancer
PI3K-Akt signaling pathway
Platelet activation
PPAR signaling pathway
Progesterone-mediated oocyte maturation
Proteoglycans in cancer
Rap1 signaling pathway
Ras signaling pathway
RIG-I-like receptor signaling pathway
Sphingolipid signaling pathway
T cell receptor signaling pathway
Circuit list
ABL1
BRAF
ELK1
ETS1
FASLG
KSR2
MAPK8

Viewer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Not differentially regulated path
Ras signaling pathway (hsa04014)
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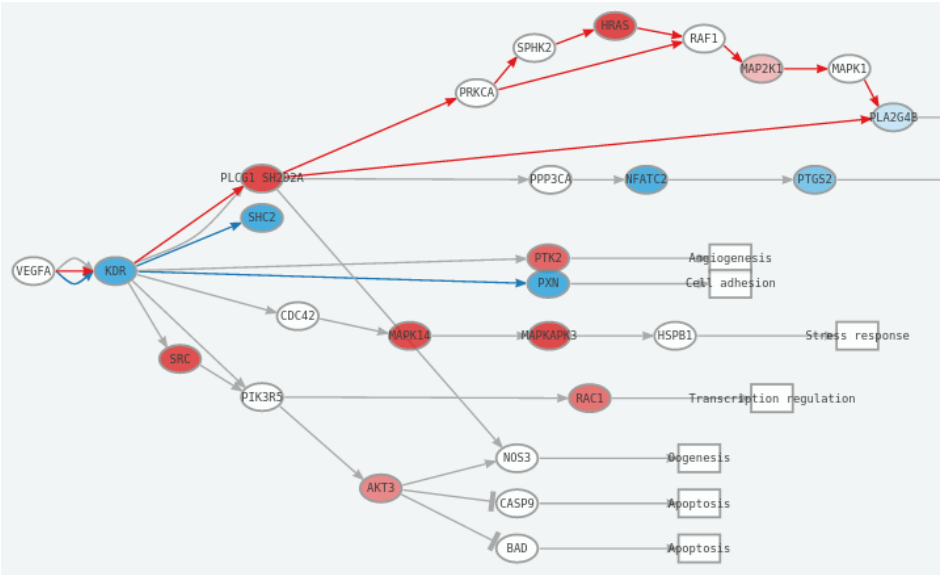
Progesterone-mediated oocyte maturation
Proteoglycans in cancer
Rap1 signaling pathway
Ras signaling pathway
RIG-I-like receptor signaling pathway
Sphingolipid signaling pathway
T cell receptor signaling pathway
Circuit list:
ABL1
BCL2L1
BRAF
CD1245
ELK1
ETS1
FASLG
KSR2
MAPK8
MLLT4
MLLT4
PAK4
PLA2G4B

Viewer


Shape
Color
Nodes
Gene
Metabolite
Down-regulated gene (DE)
Up-regulated gene (DE)
0
0.05
p-value
Edges
Inhibition
Activation
Down-regulated path
Up-regulated path
Not differentially regulated path

Viewer


Shape
Color
Nodes
Gene
Metabolite
Down-regulated gene (DE)
Up-regulated gene (DE)
0
0.05
p-value
Edges
Inhibition
Activation
Down-regulated path
Up-regulated path
Not differentially regulated path

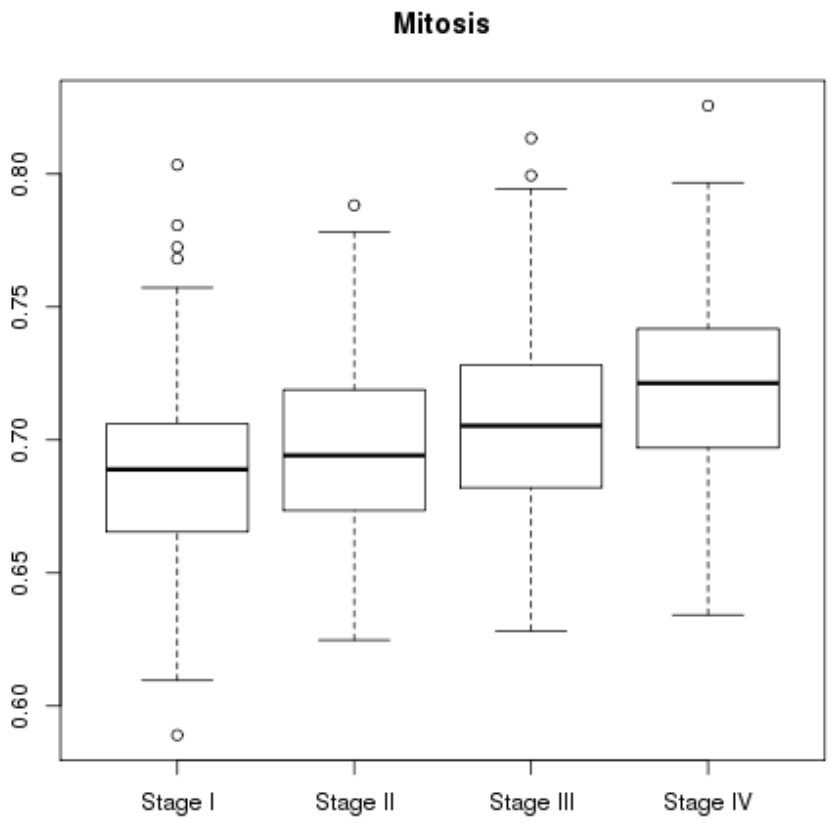

VEGFA
KDR
SHC2
SRC
PLCG1
SH2D2A
PRKCA
SPHK2
HRAS
RAF1
MAP2K1
MAPK1
PLA2G4B
PPP3CA
NFATC2
PTGS2
PTK2
PXN
Angiogenesis
Cell adhesion
CDC42
MAPK14
MAPKAPK3
HSPB1
Stress response
PIK3R5
RAC1
Transcription regulation
AKT3
NOS3
CASP9
BAD
Apoptosis

HiPathia

Further analysis

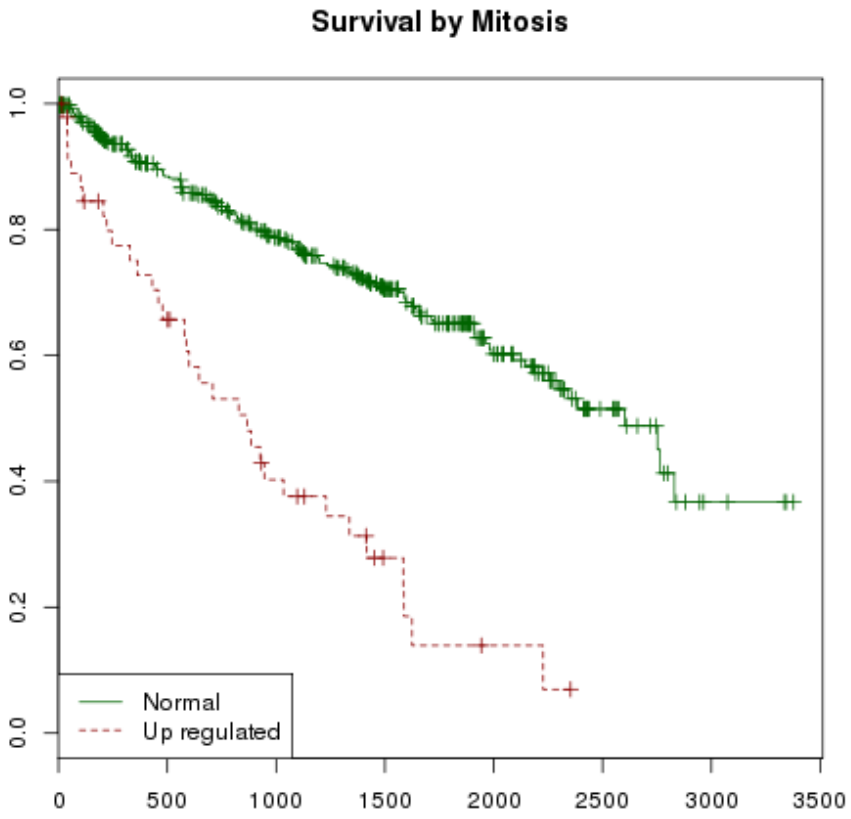
Disease progression analysis

Search for features which increase with the progression of the disease



Survival analysis

Analysis of time duration until one or more events happen



Exercises

HiPathia exercises

Exercise 1

Do the Differential signaling worked example

Exercise 2

Do the Prediction worked example

1. Train a predictor following these steps
2. Test a new dataset following these steps

Exercises 3,4,...

Do the Differential signaling exercises