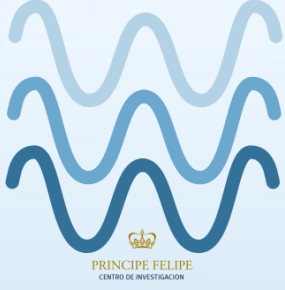
HiPathia
Models of signaling pathway activity

Marta R. Hidalgo
Unidad de Bioinformática y Bioestadística



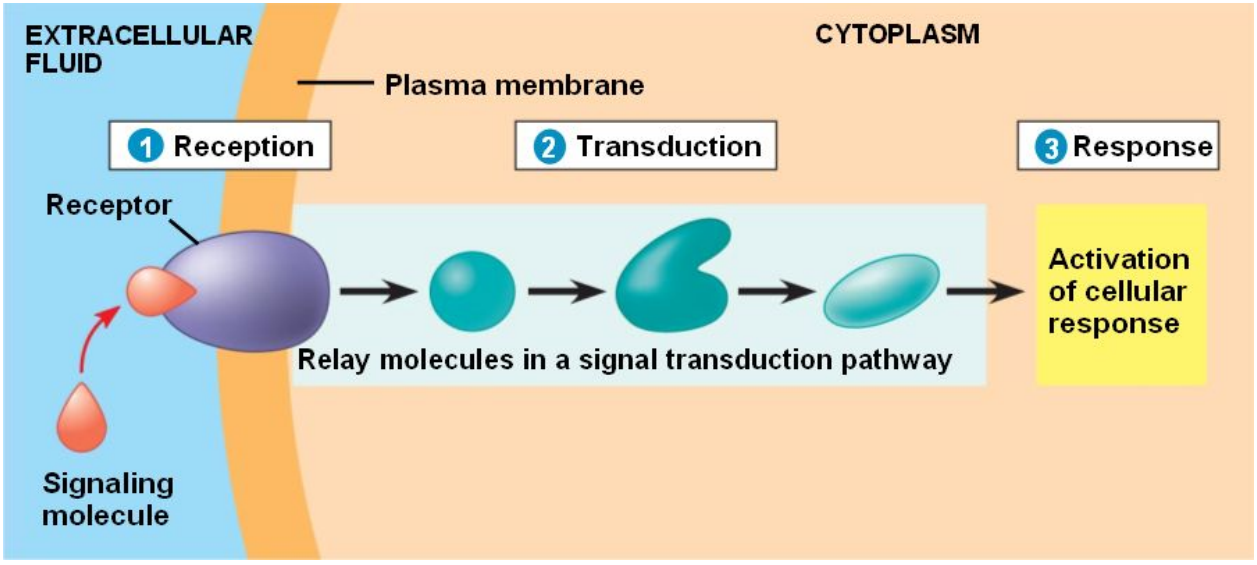
WODA
WEB-BASED OMICS DATA ANALYSIS


Unidad de Bioinformática y Bioestadística

PRINCIPE FELIPE
CENTRO DE INVESTIGACION

CSIC
CONSEJO SUPERIOR DE INVESTIGACIONES CIENTÍFICAS

Signaling pathways



Chemical signals

- Hormones
- Neurotransmiters
- Growth factors
- Cytokines
- Drugs

Activation & Inhibition

- Phosphorilation
- Dephosphorilation
- Glycosylation
- Ubiquitination
- Methylation

Cellular Function

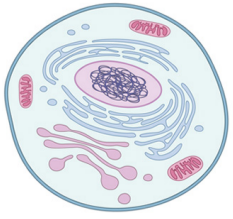
- Apoptosis
- Survival
- Growth
- Migration
- Proliferation

Pathway Analysis

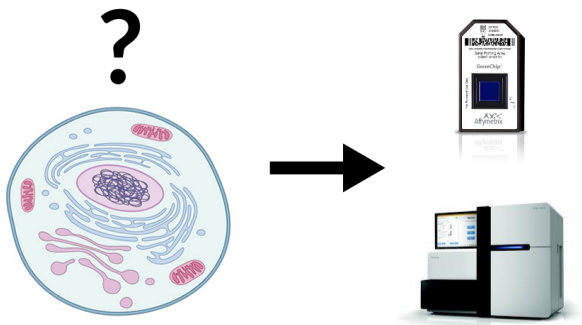
Methods

From cell to pathways

?

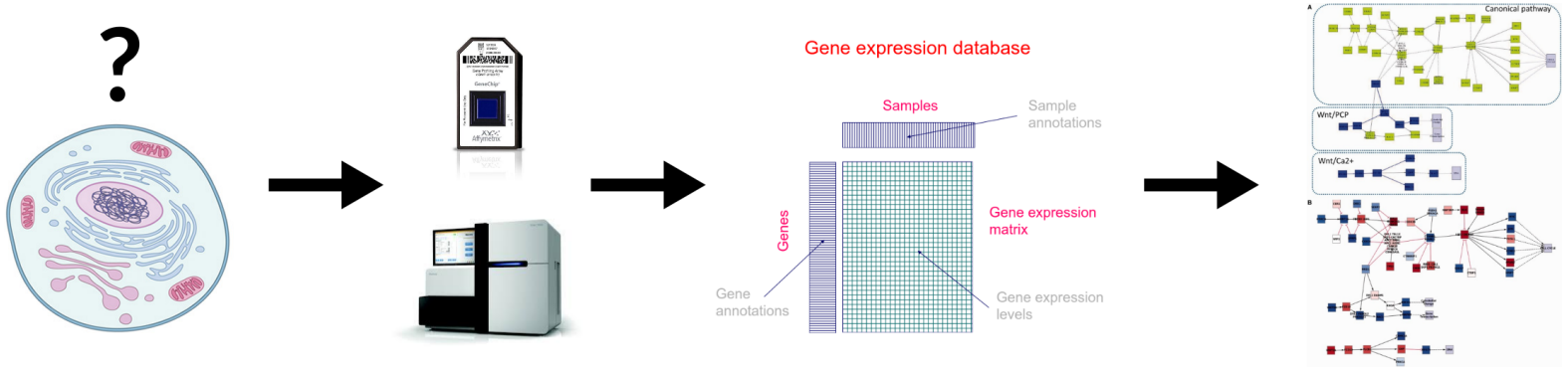


From cell to pathways



From cell to pathways

From cell to pathways



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

The Annals of Applied Statistics
2012, Vol. 6, No. 2, 561–600
DOI: 10.1214/11-AOAS528

MORE POWER VIA GRAPH-STRUCTURED TESTS FOR DIFFERENTIAL EXPRESSION OF GENE NETWORKS

BY LAURENT JACOB, PIERRE NEUVIAL AND SANDRINE DUDOIT

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

Published online 21 September 2012 *Nucleic Acids Research, 2013, Vol. 41, No. 1* ***e19***
doi:10.1093/nar/gks866

Along signal paths: an empirical gene set approach exploiting pathway topology

Paolo Martini[1], Gabriele Sales[2], M. Sofia Massa[3], Monica Chiogna[4] and Chiara Romualdi[2,*]

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

BIOINFORMATICS ORIGINAL PAPER Vol. 25 no. 1 2009, pages 75–82
doi:10.1093/bioinformatics/btn577

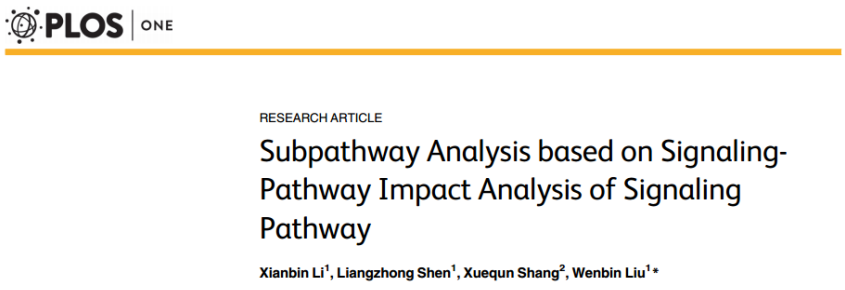
Systems biology

A novel signaling pathway impact analysis

Adi Laurentiu Tarca[1,2], Sorin Draghici[1,*], Purvesh Khatri[1], Sonia S. Hassan[2], Pooja Mittal[2], Jung-sun Kim[2], Chong Jai Kim[2], Juan Pedro Kusanovic[2] and Roberto Romero[2]

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



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

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 3), pp: 5160-5178

Research Paper

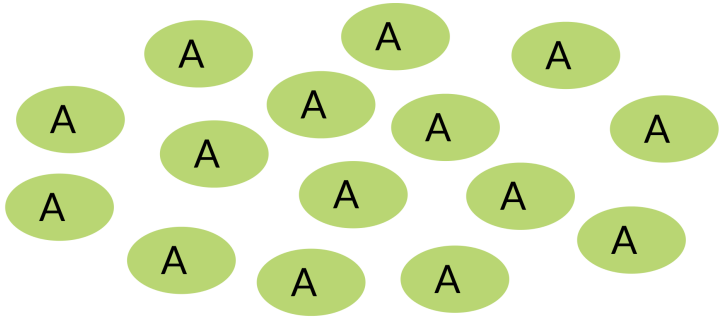
High throughput estimation of functional cell activities reveals disease mechanisms and predicts relevant clinical outcomes

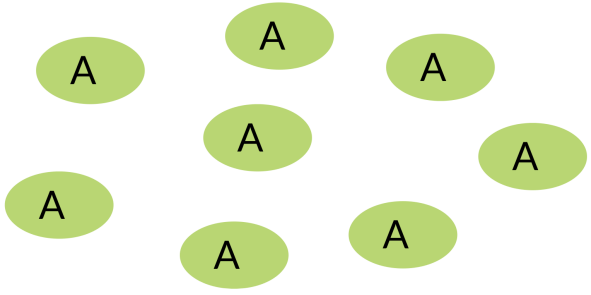
Marta R. Hidalgo[1], Cankut Cubuk[1], Alicia Amadoz[1,2], Francisco Salavert[1,3], José Carbonell-Caballero[1], Joaquin Dopazo[1,2,3]

Pathway Analysis

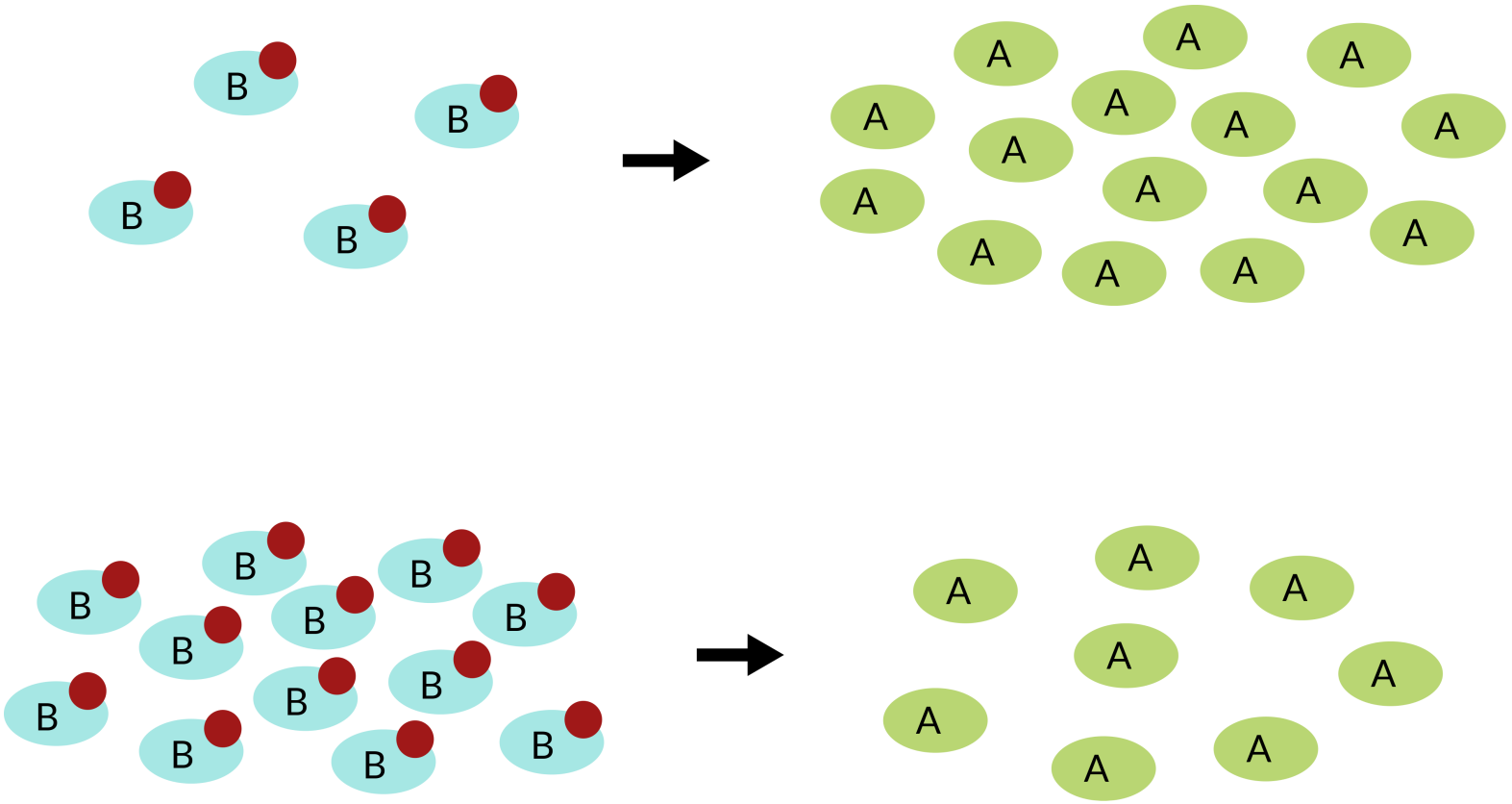
HiPathia

Intuitive idea

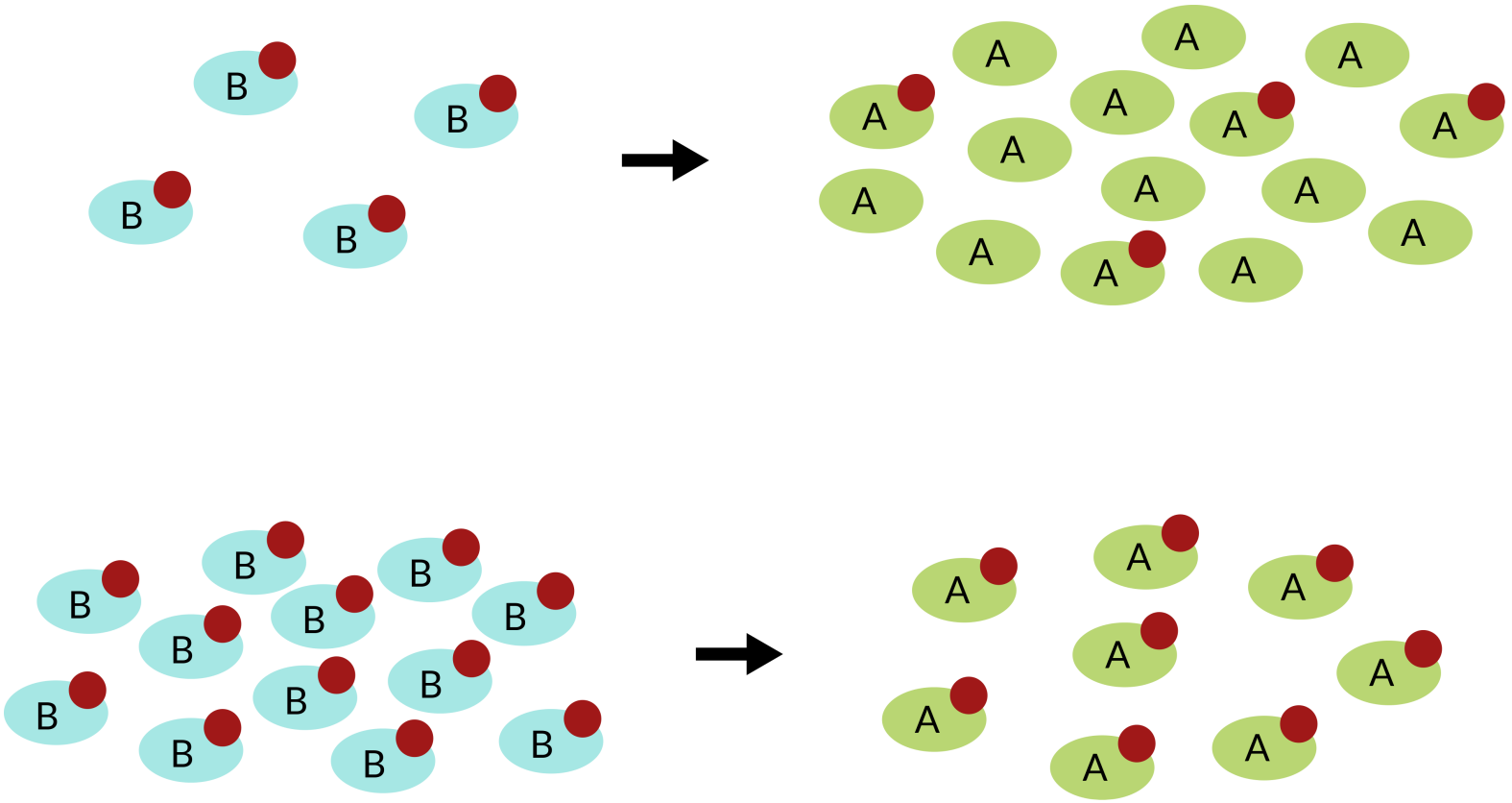




Intuitive idea

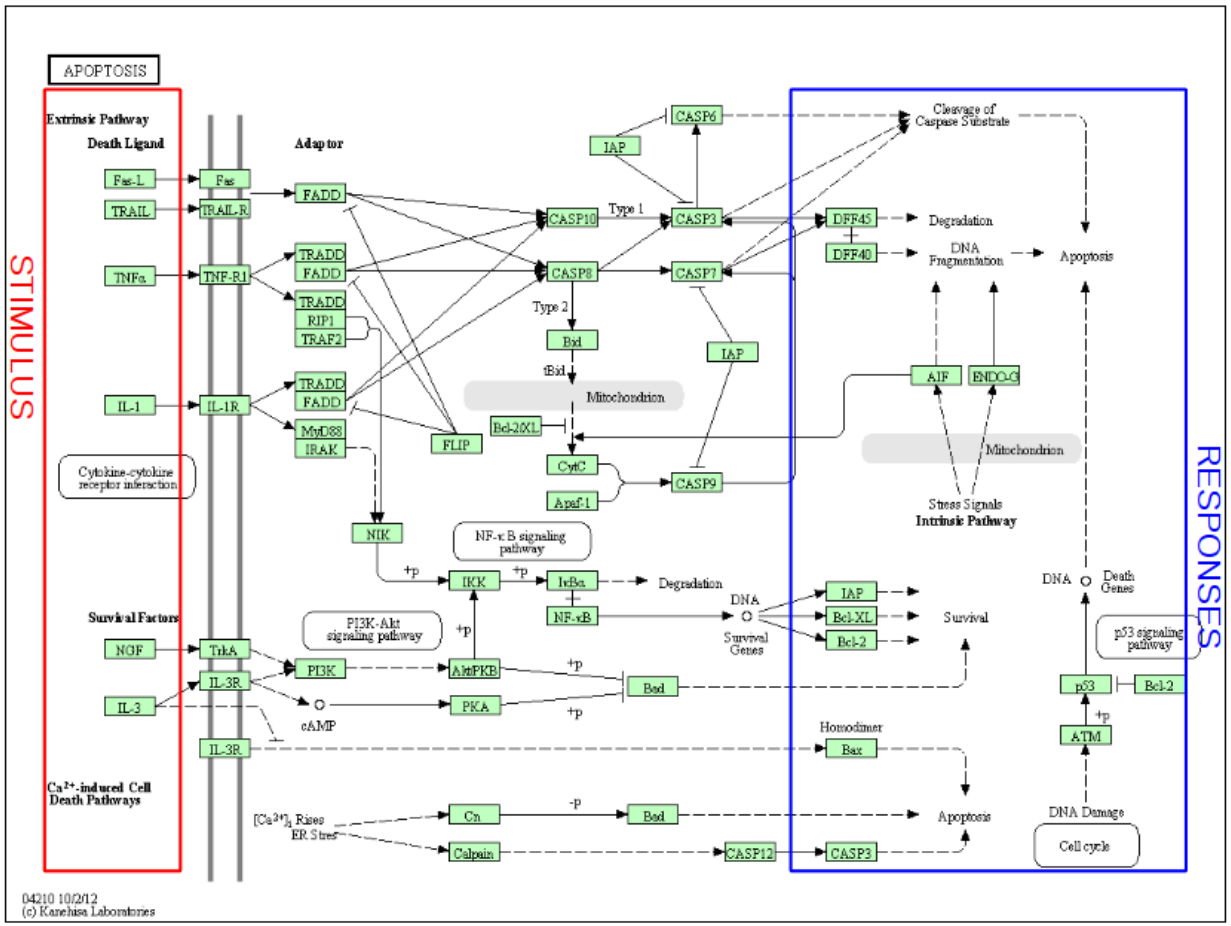


Intuitive idea



Pathways layout

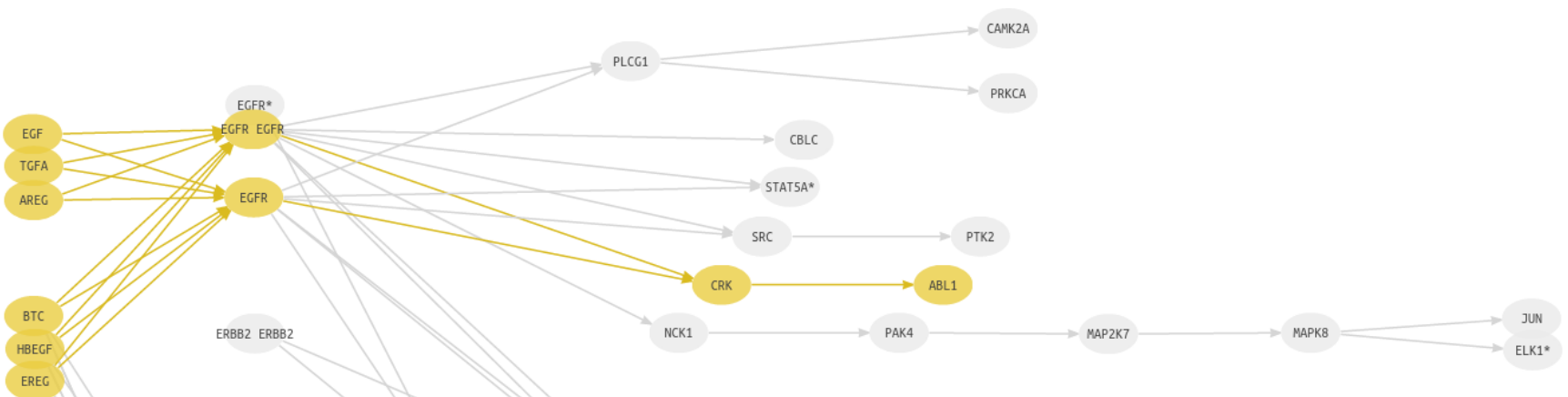
Take pathways information from KEGG, www.kegg.jp



Meaningful subpathways

Effector subpathway

Subpathway including any node from any receptor to one effector protein

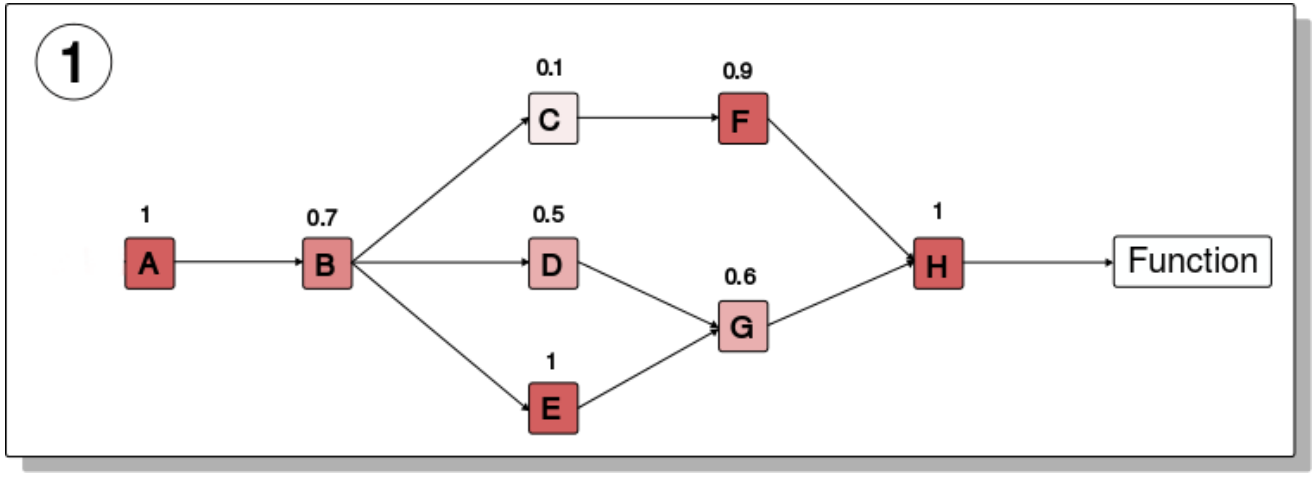


Computing the signal

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

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

S_n: Signal value through n
v_n: Node value
A: Activation edges
I: Inhibition edges



Computing the signal

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

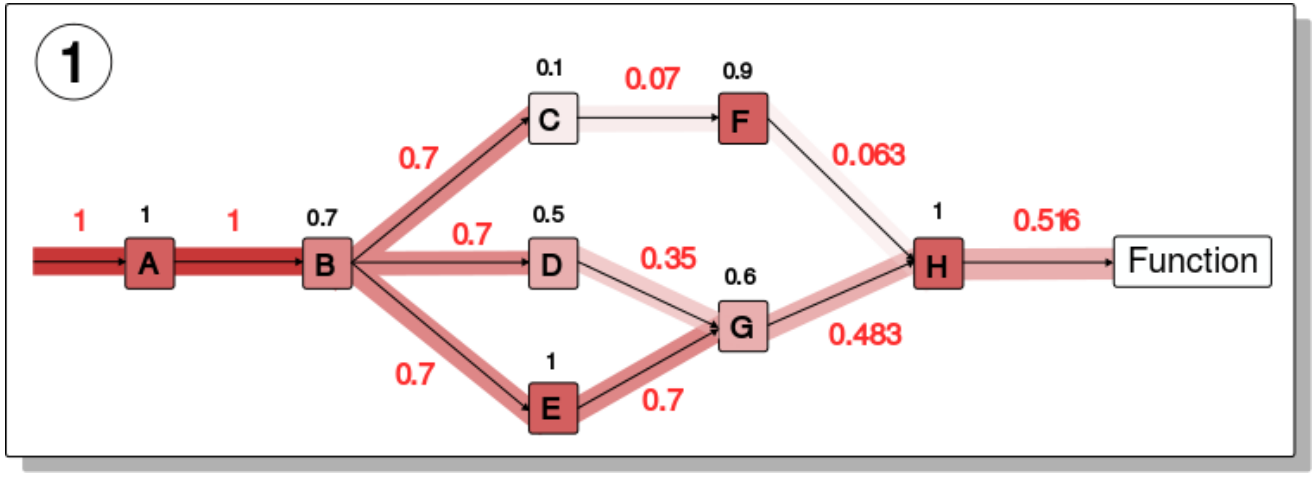
$$S_n = v_n \cdot (1 - \prod_{s_i \in A} (1 - s_i)) \cdot \prod_{s_j \in I} (1 - s_j)$$

S_n: Signal value through n

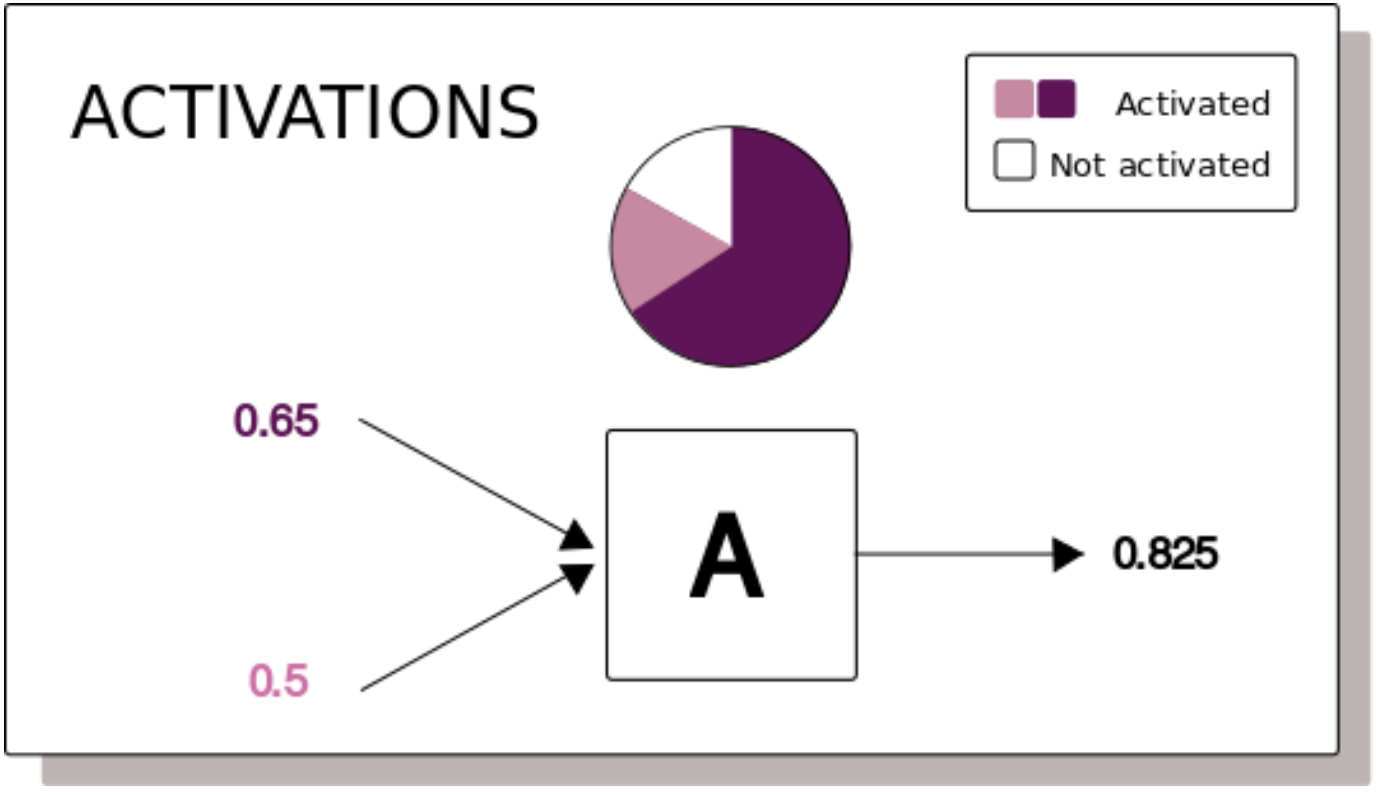
v_n: Node value

A: Activation edges

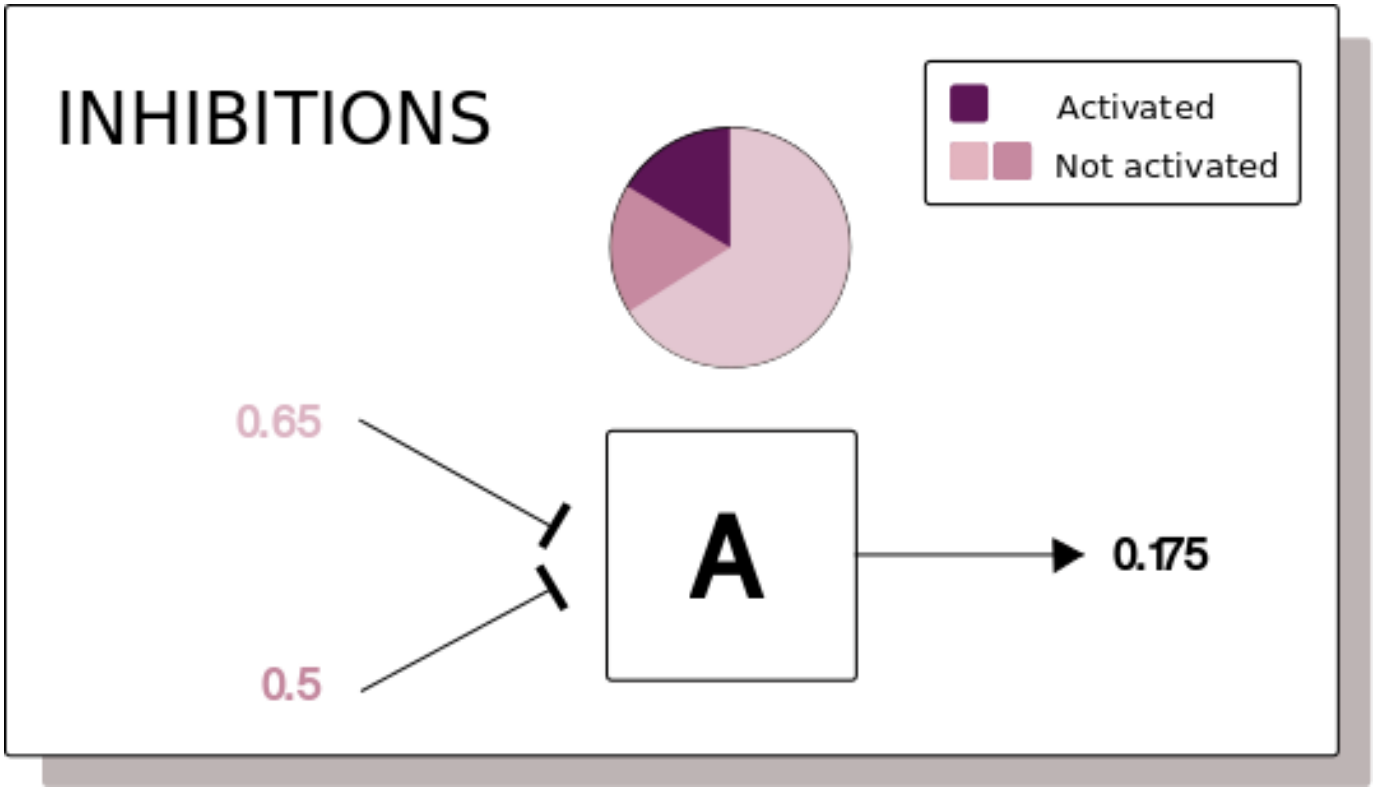
I: Inhibition edges



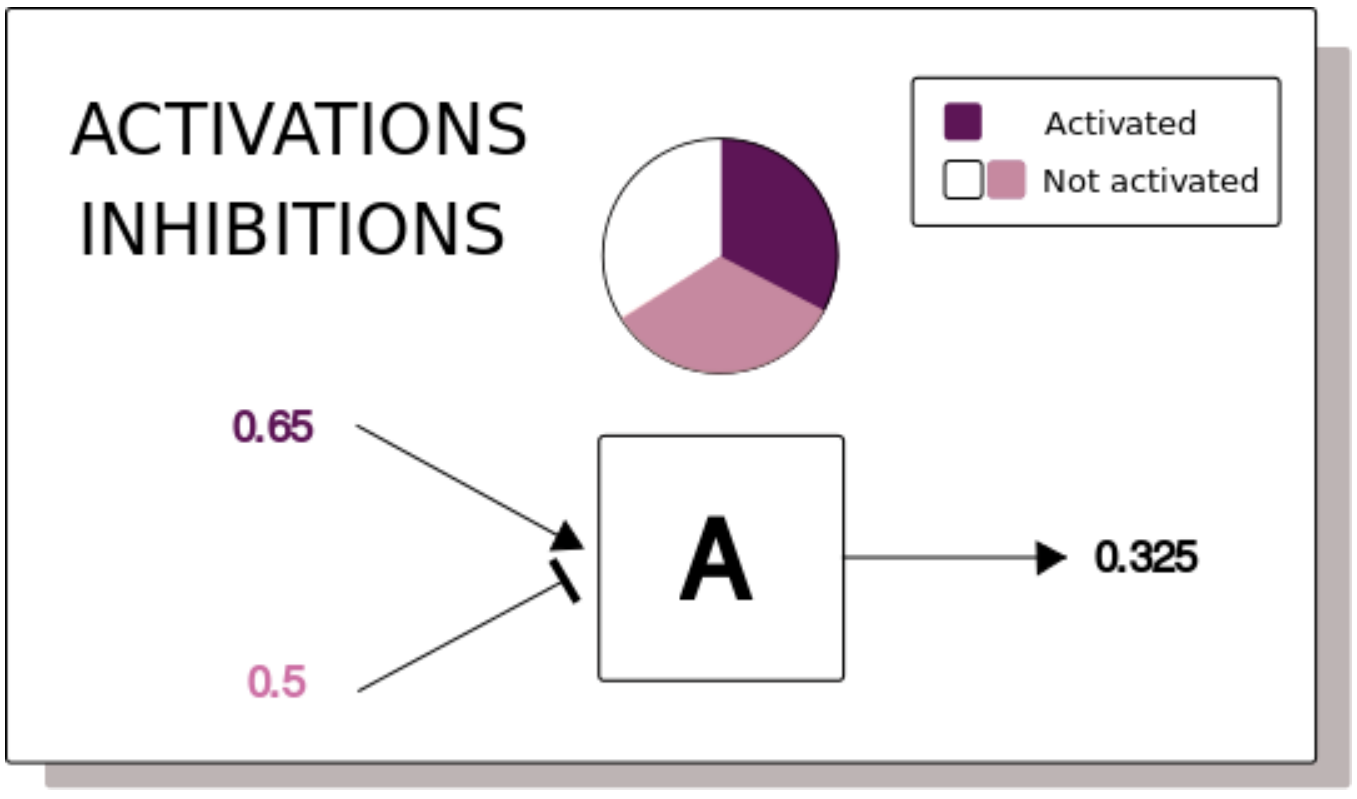
Computing the signal



Computing the signal

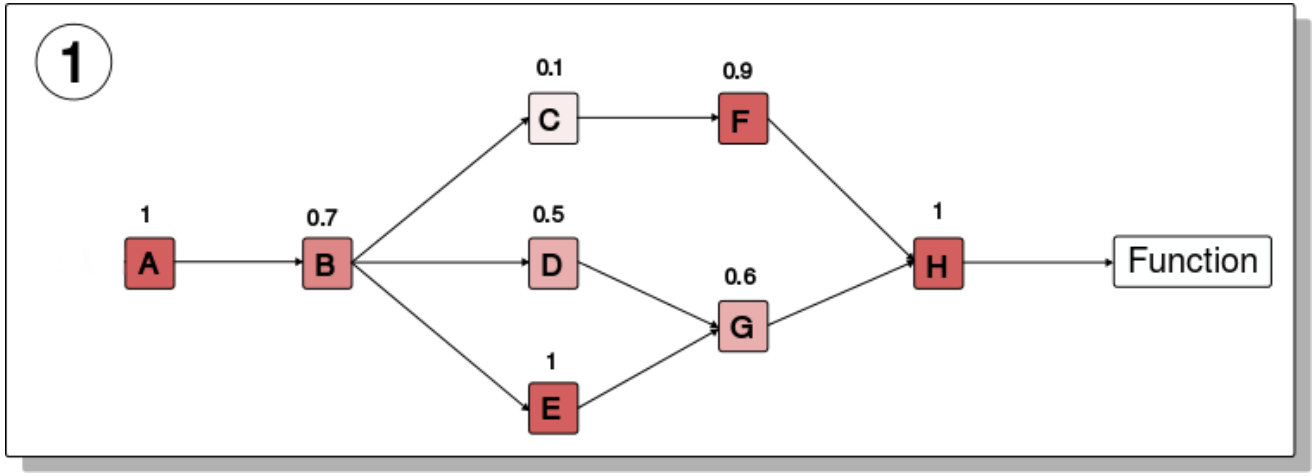


Computing the signal



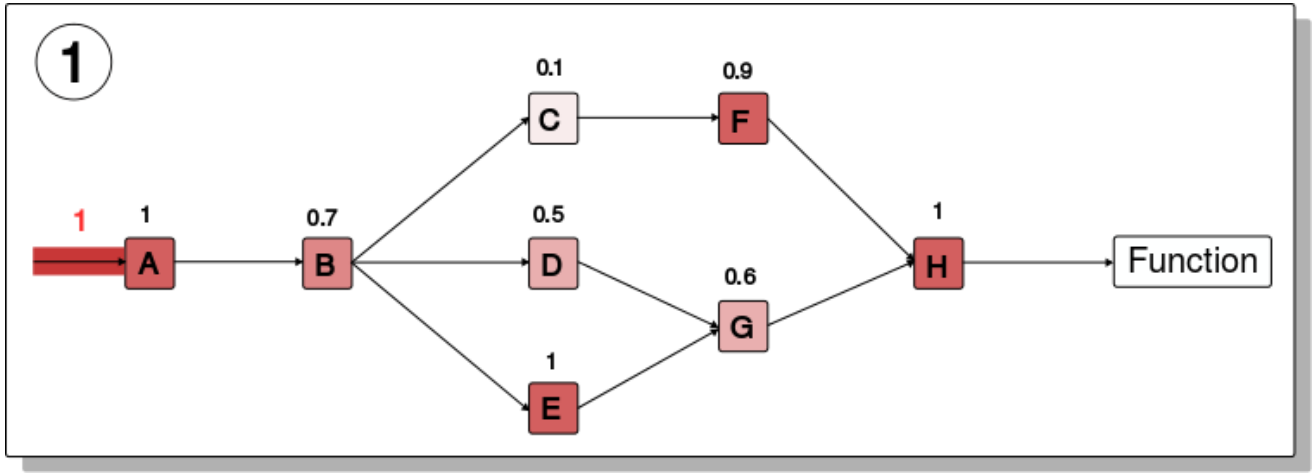
Signal values

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



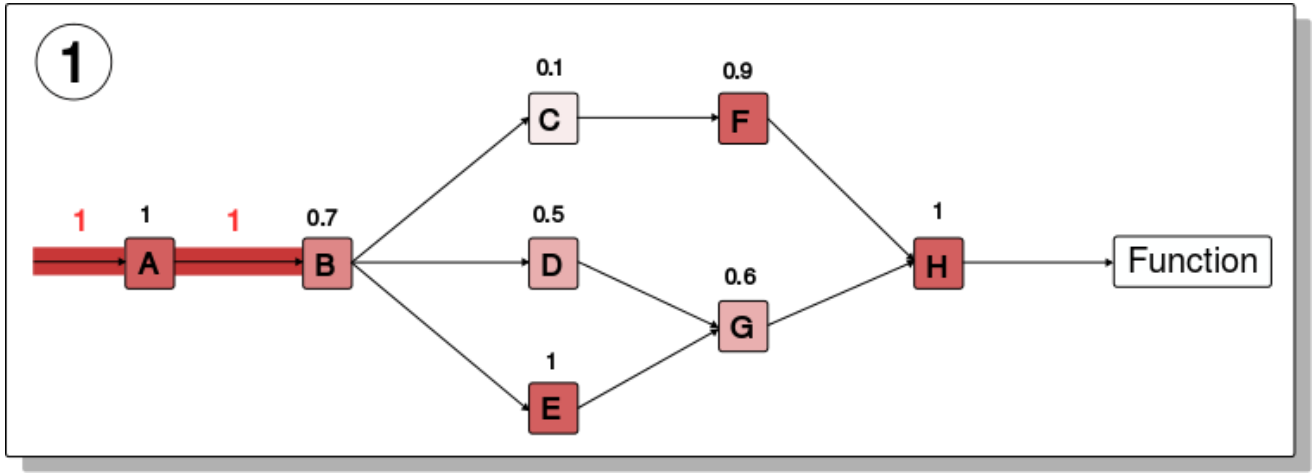
Signal values

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



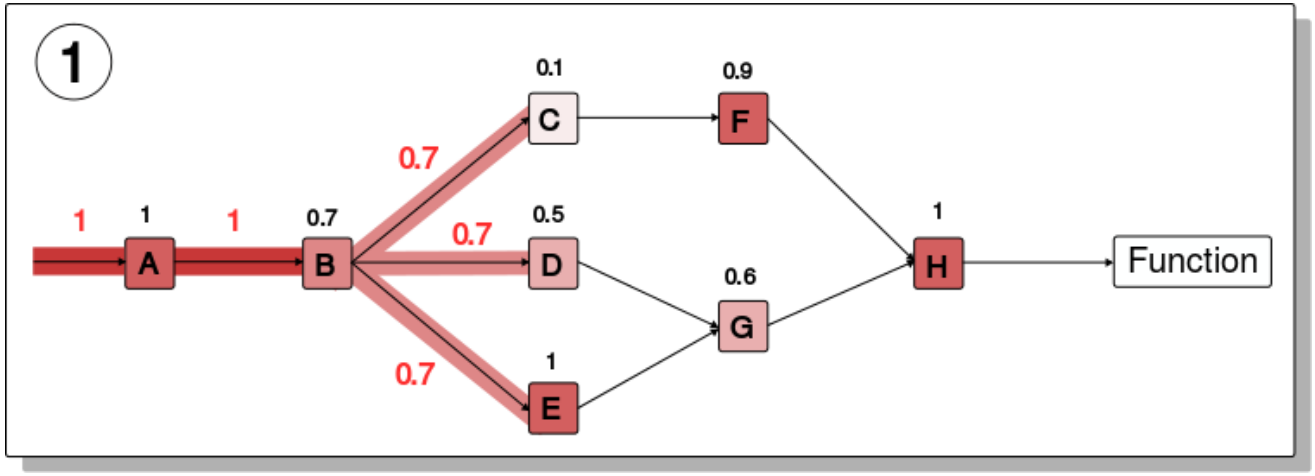
Signal values

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



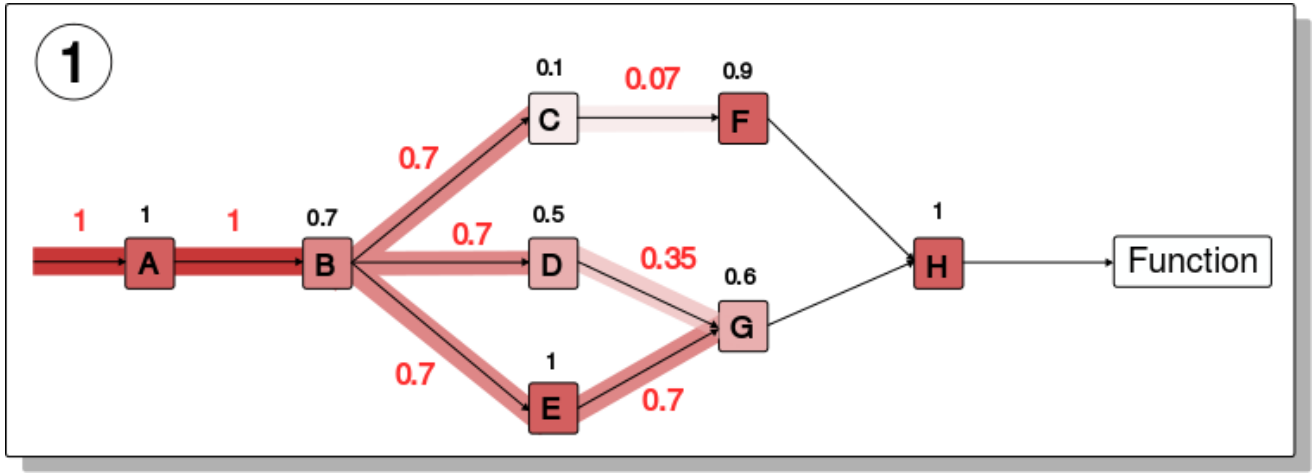
Signal values

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



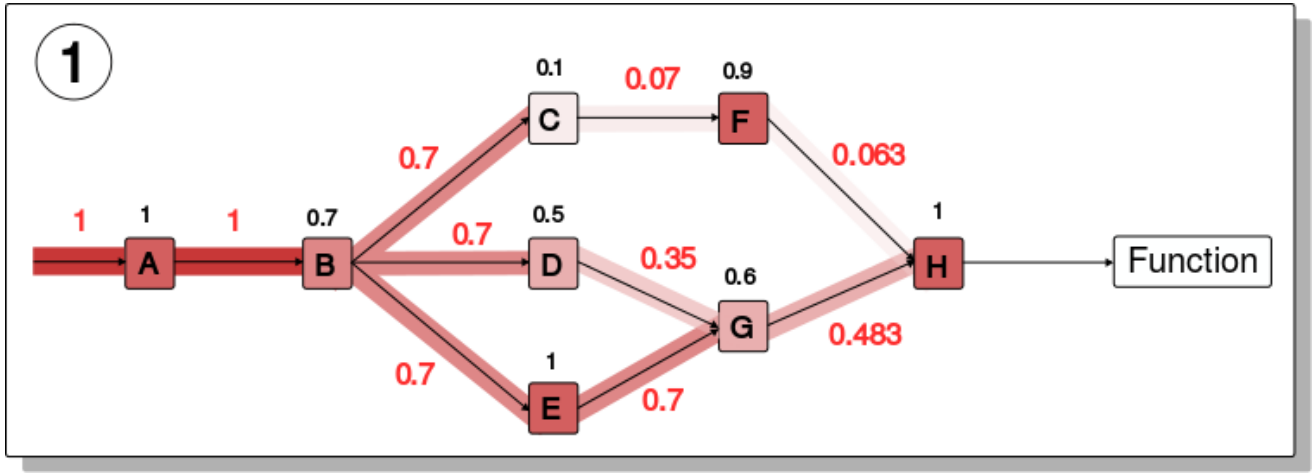
Signal values

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



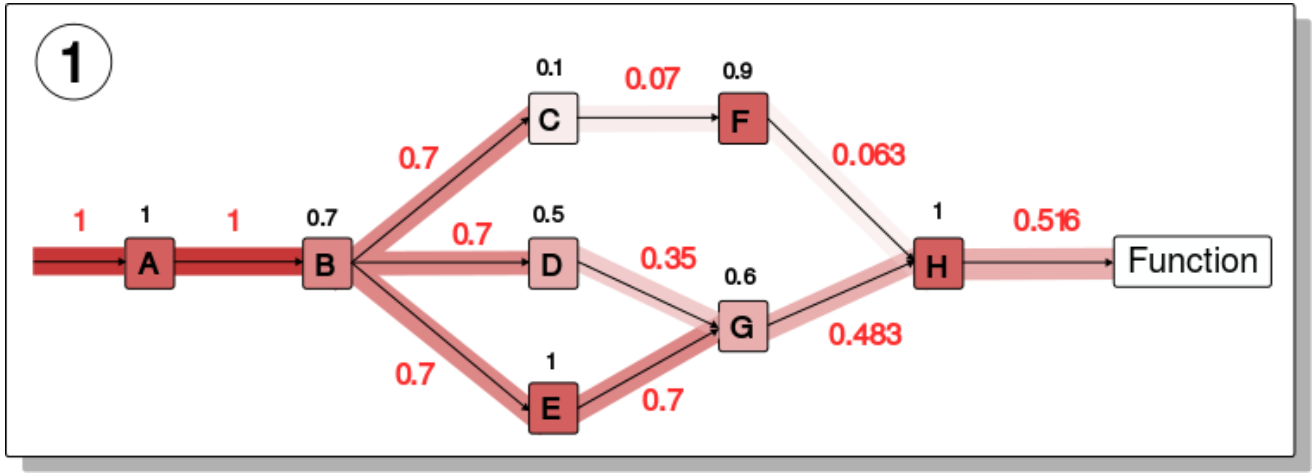
Signal values

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



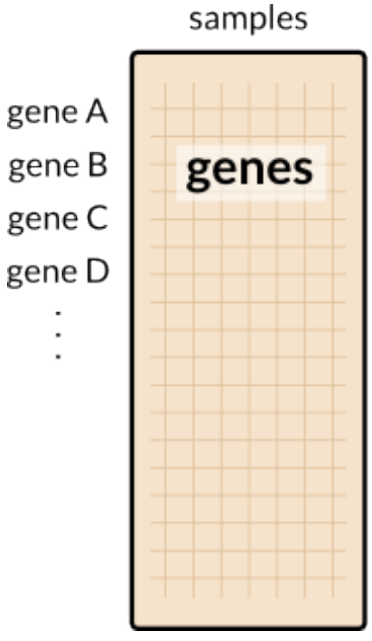
Signal values

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



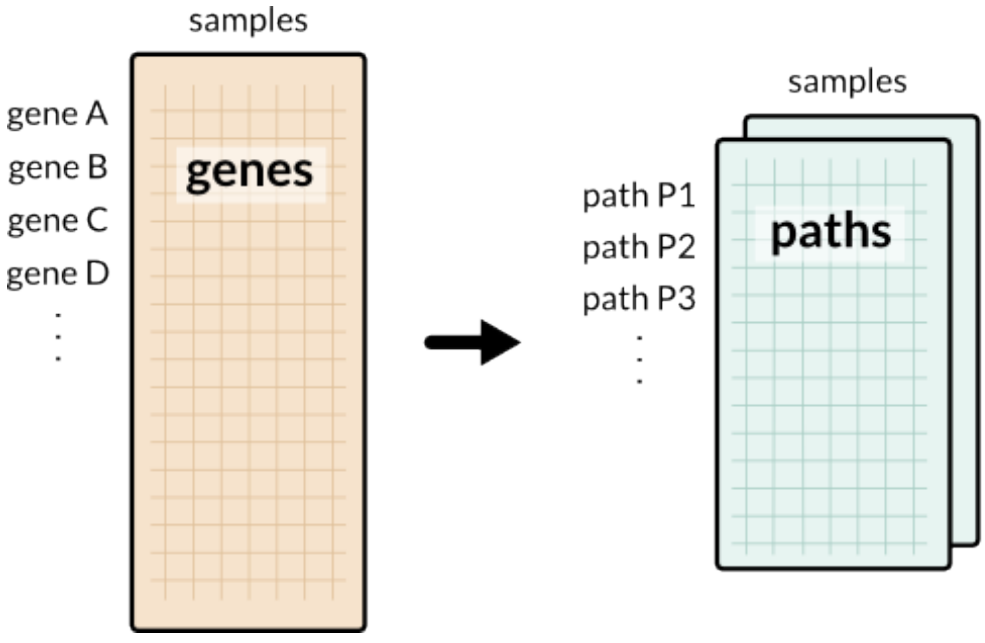
Functional annotation

1. Estimate effector proteins activation
2. Annotate effector proteins functions
   - Uniprot keywords
   - GO annotation



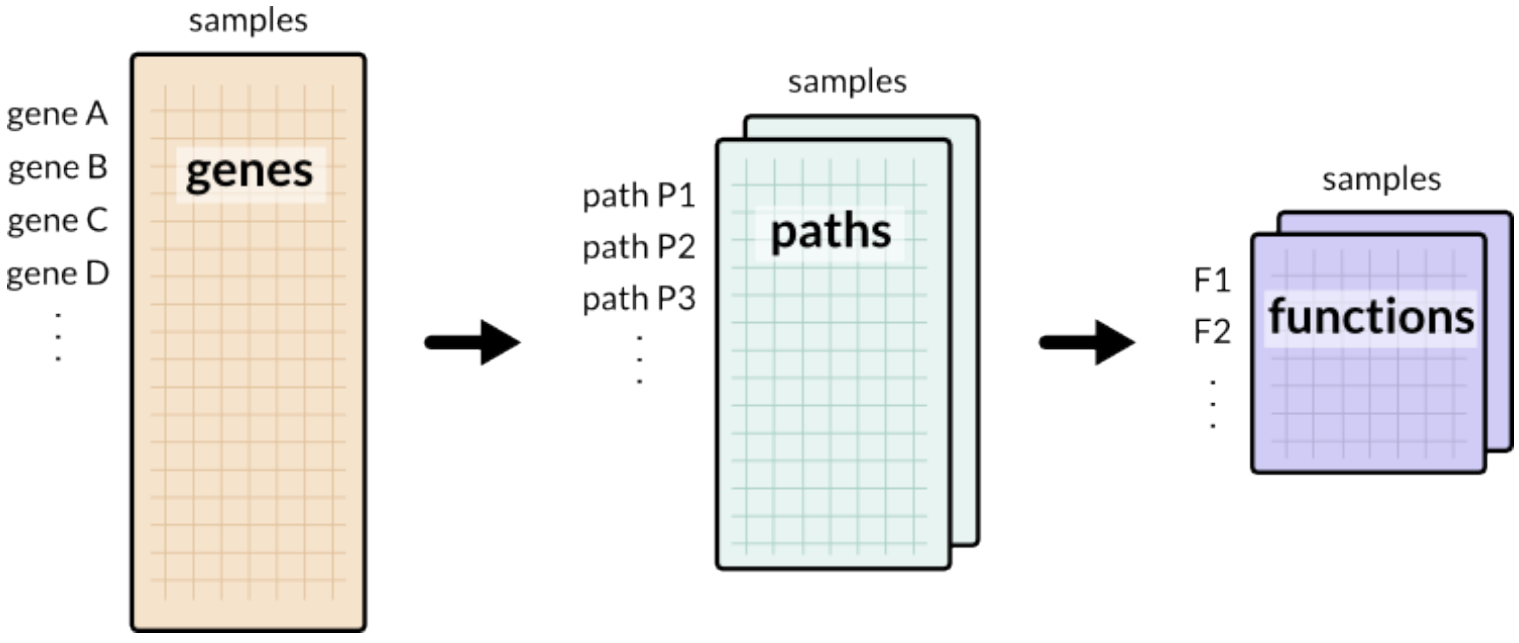
Functional annotation

1. Estimate effector proteins activation
2. Annotate effector proteins functions
   - Uniprot keywords
   - GO annotation



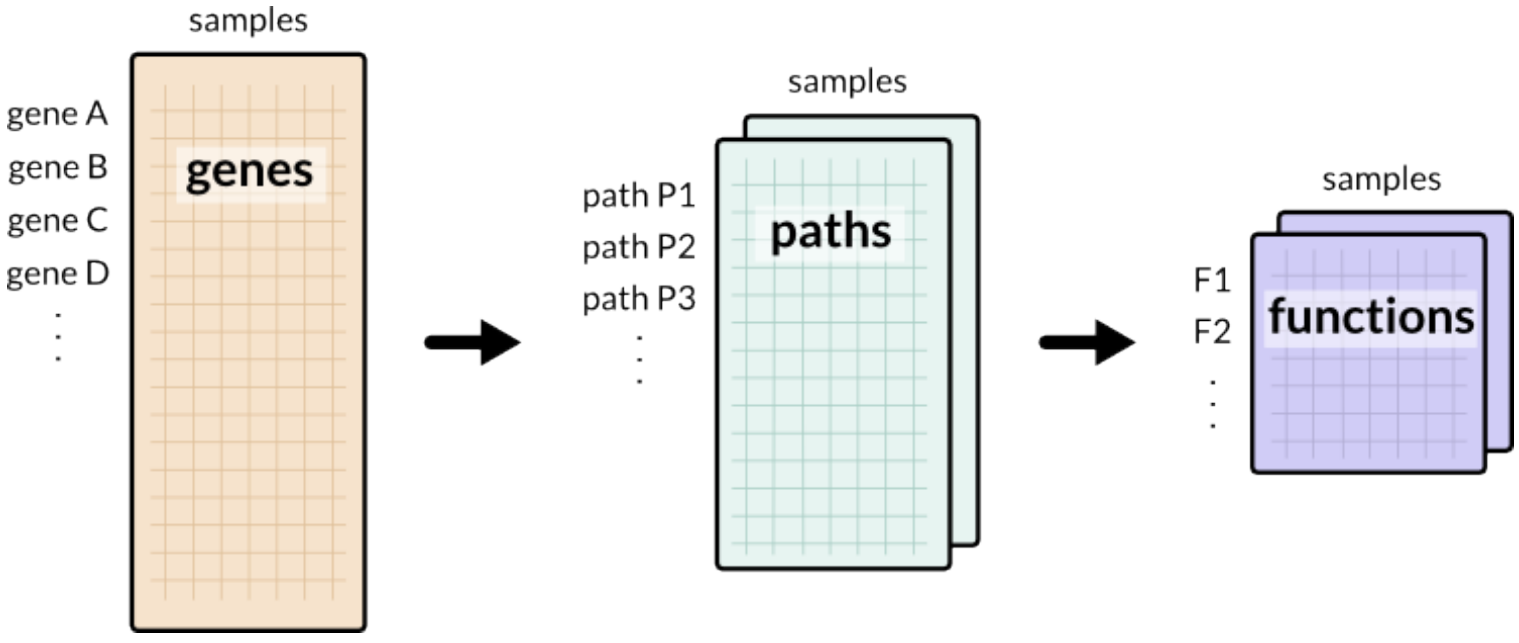
Functional annotation

1. Estimate effector proteins activation
2. Annotate effector proteins functions
   - Uniprot keywords
   - GO annotation

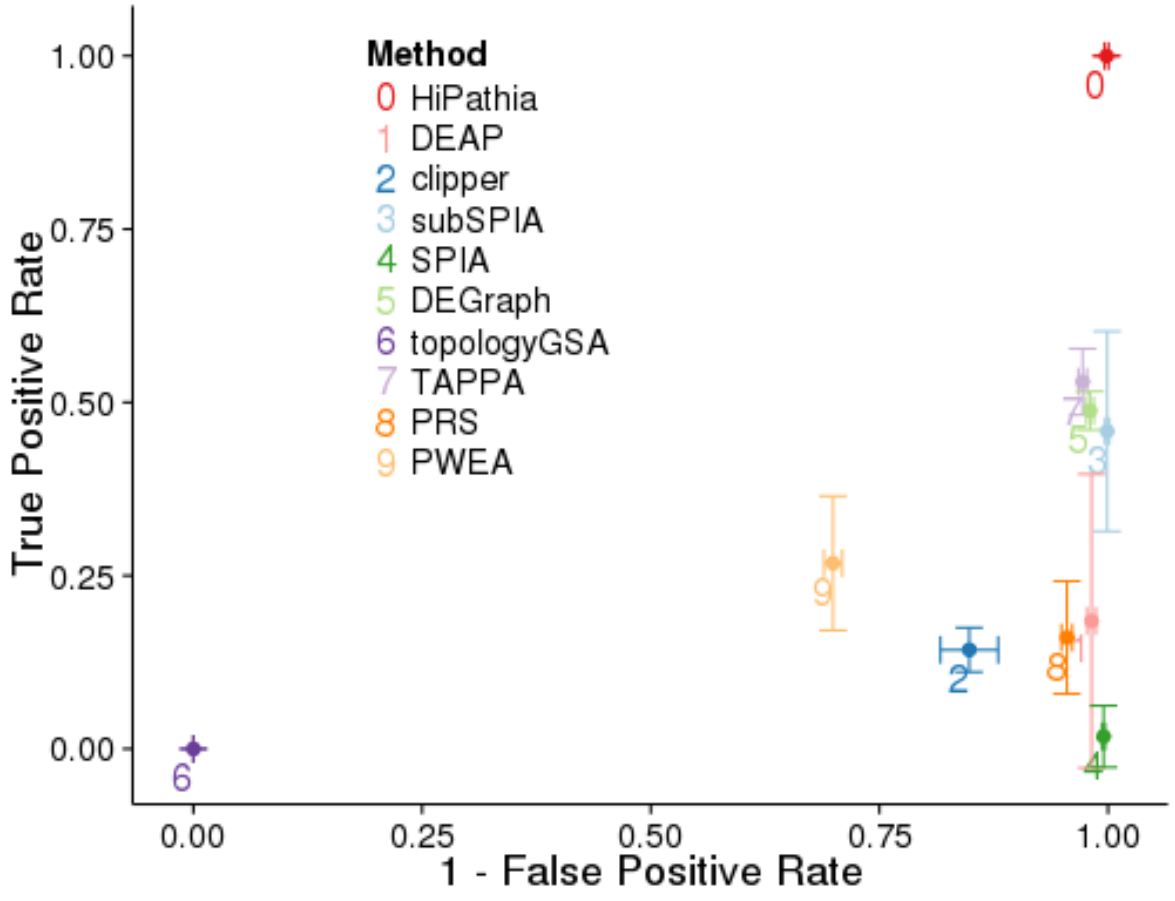


Functional annotation

1. Estimate effector proteins activation
2. Annotate effector proteins functions
   - Uniprot keywords
   - GO annotation



Method comparison



HiPathia

Differential expression tool

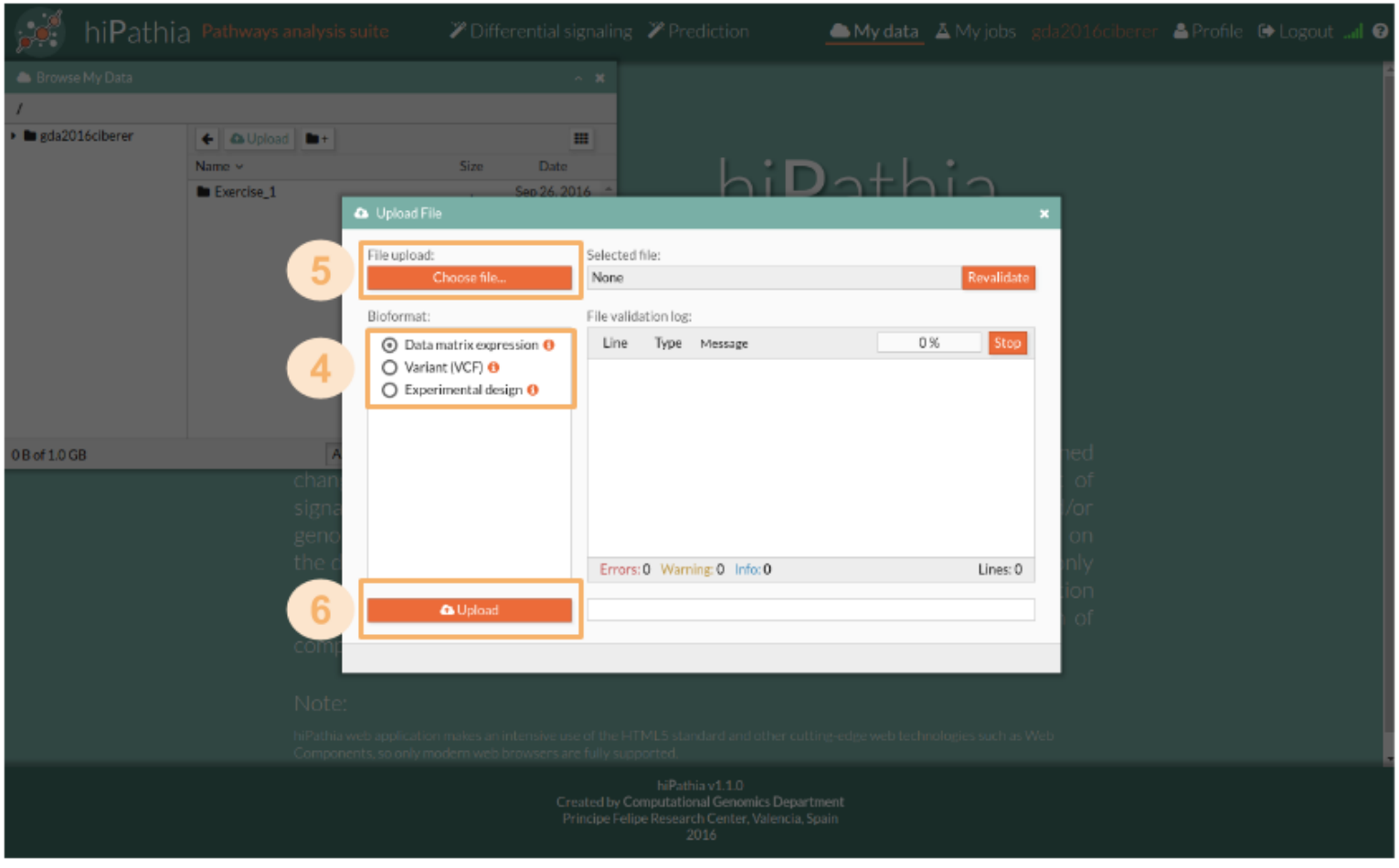
Logging in

hipathia2.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
erpretation of the consequences of the combined 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 of drugs but they can also be used as mechanistic features for the prediction of 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

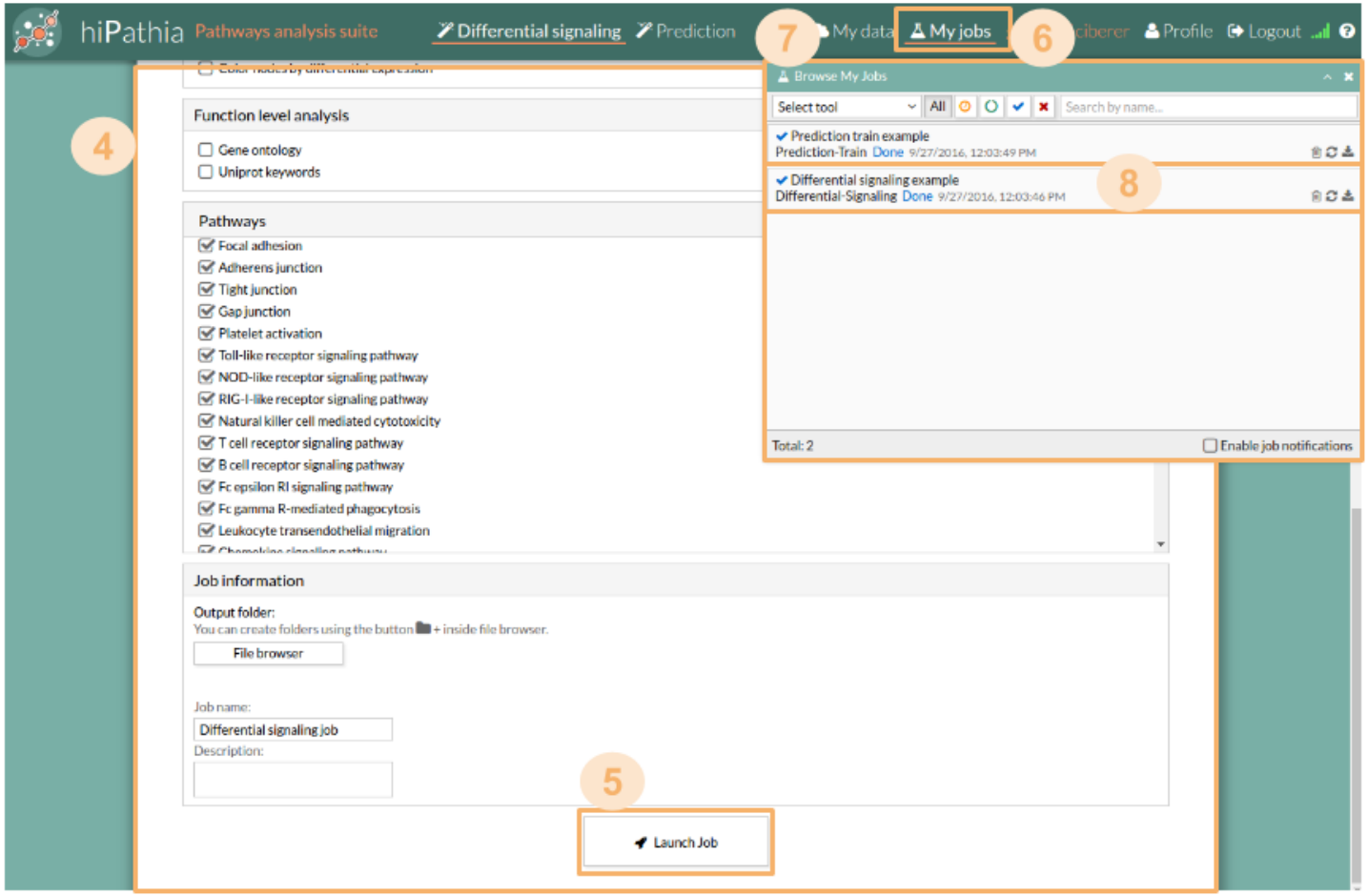
Upload data


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
Note:
hiPathia v1.1.0
Created by Computational Genomics Department
Principe Felipe Research Center, Valencia, Spain
2016

Workflow


2
hiPathia
Pathways analysis suite
Differential signaling
Prediction
3
My data
1
My jobs
gda2016ciberer
Profile
Logout
Browse My Data
/
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
erpretation of the consequences of the combined 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 of drugs but they can also be used as mechanistic features for the prediction of 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

Workflow


hiPathia
Pathways analysis suite
Differential signaling
Prediction
My data
My jobs
ciberer
Profile
Logout
7
6
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
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

Tools

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

2. **Perturbation effect**
   - Predict effects of gene overexpressions and KOs
   - Predict drug effects

Tools

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

2. **Perturbation effect**
   - Predict effects of gene overexpressions and KOs
   - Predict drug effects

Formular details

1. **Species**: *hsa*, *mmu*, *rno*

2. **Parameters**
   - Paired
   - Unadjusted

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

Formular details

1. **Species**: *hsa*, *mmu*, *rno*

2. **Parameters**
   - Paired
   - Unadjusted

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

Formular details

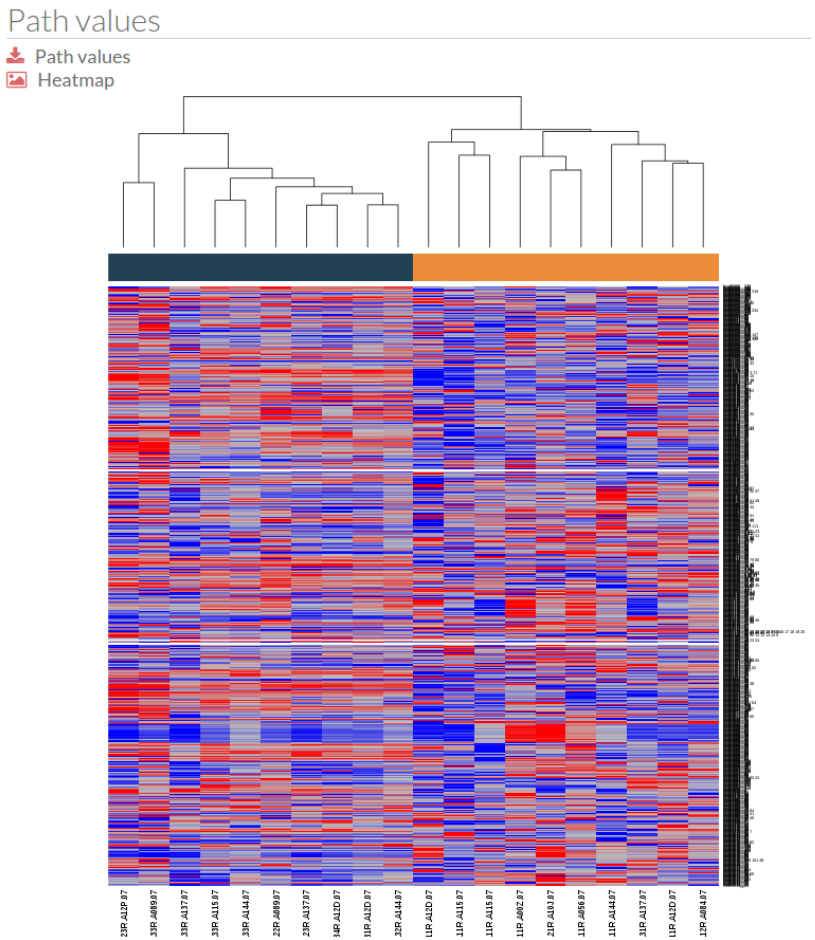
1. **Species**: *hsa*, *mmu*, *rno*

2. **Parameters**
   - Paired
   - Unadjusted

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

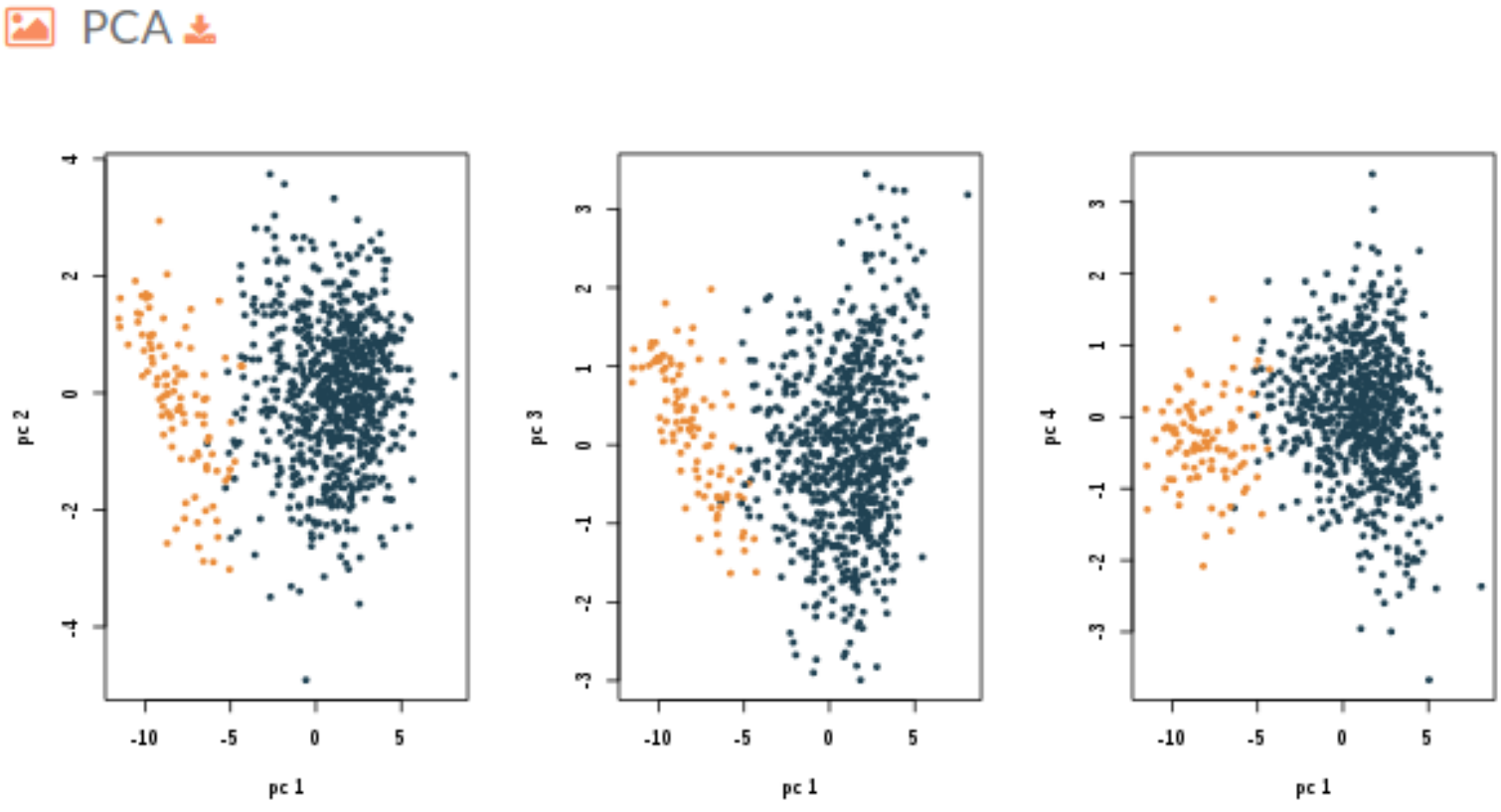
Heatmap

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



Results table

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

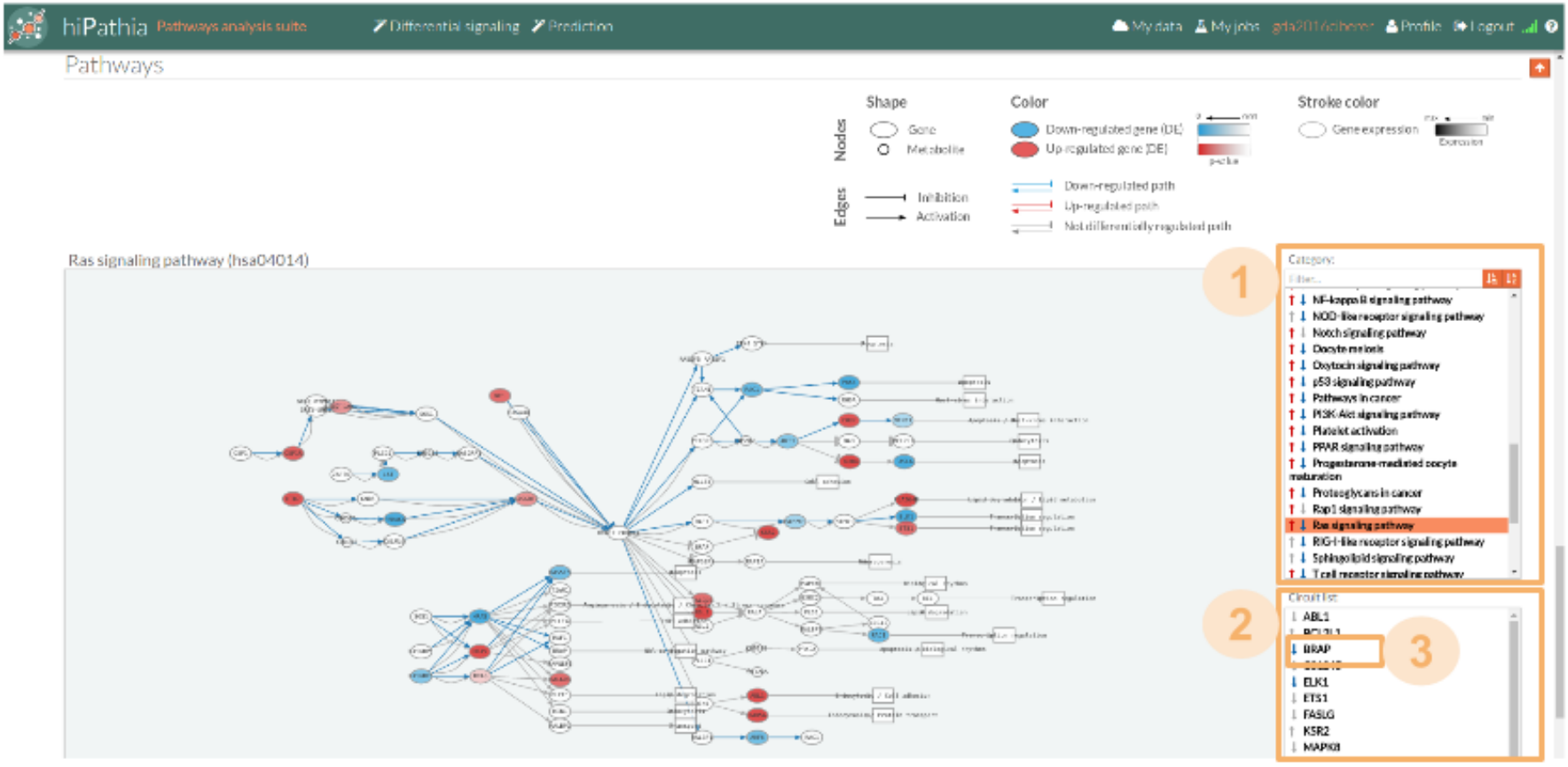
Path significance

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

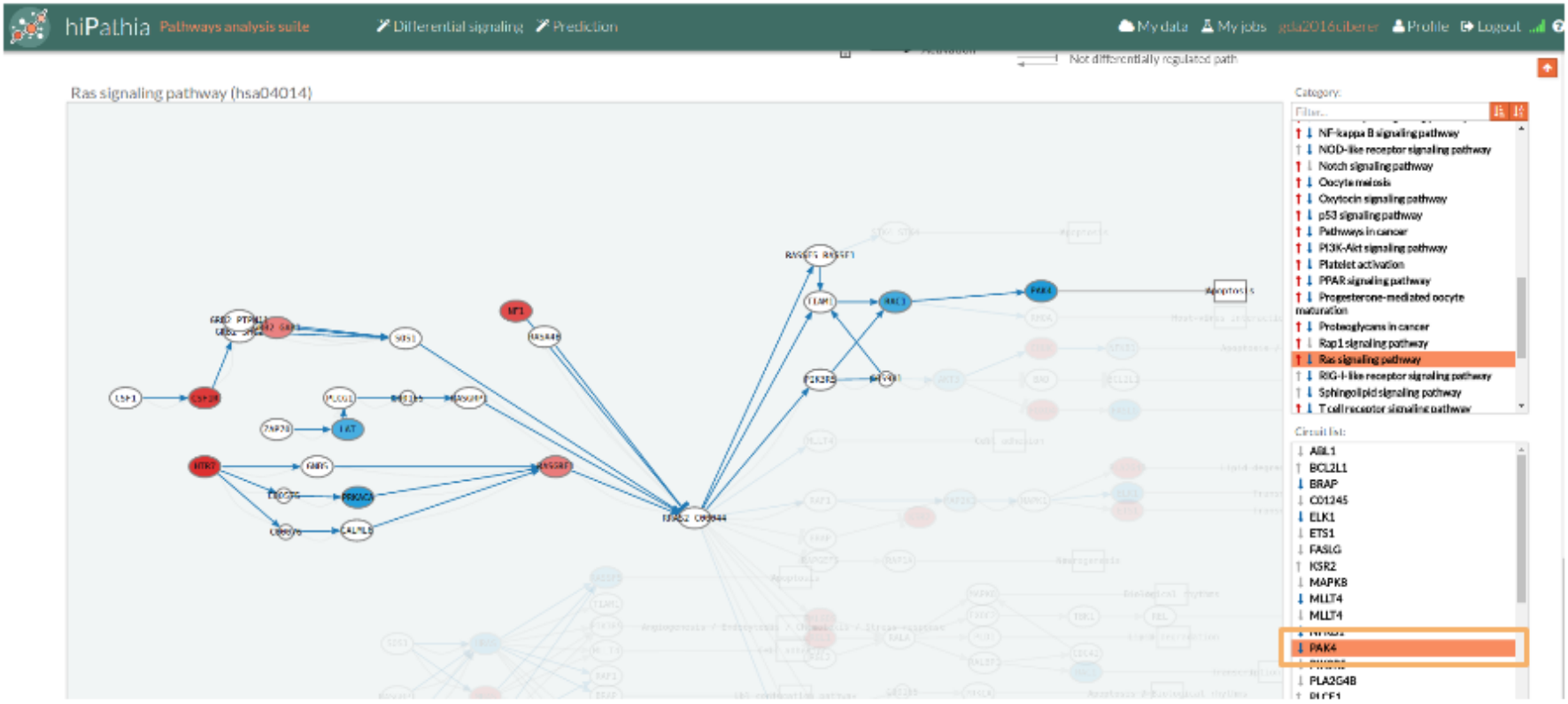
« ‹ Page 1 of 102 › »

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
Not differentially regulated path
Ras signaling pathway (hsa04014)
1
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
2
Circuit list:
ABL1
BRAF
3
ELK1
ETS1
FASLG
KSR2
MAPK8

Viewer

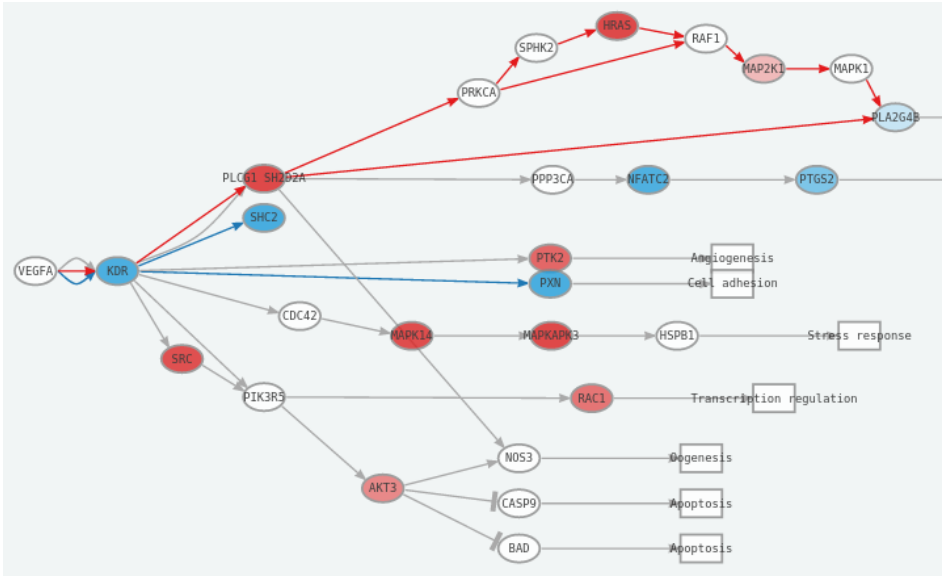

hiPathia
Pathways analysis suite
Differential signaling
Prediction
My data
My jobs
gda2016ciberer
Profile
Logout
Not differentially regulated path
Ras signaling pathway (hsa04014)
Category:
NF-kappa B signaling pathway
NOD-like receptor signaling pathway
Notch signaling pathway
Oocyte meiosis
Oxytocin 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
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

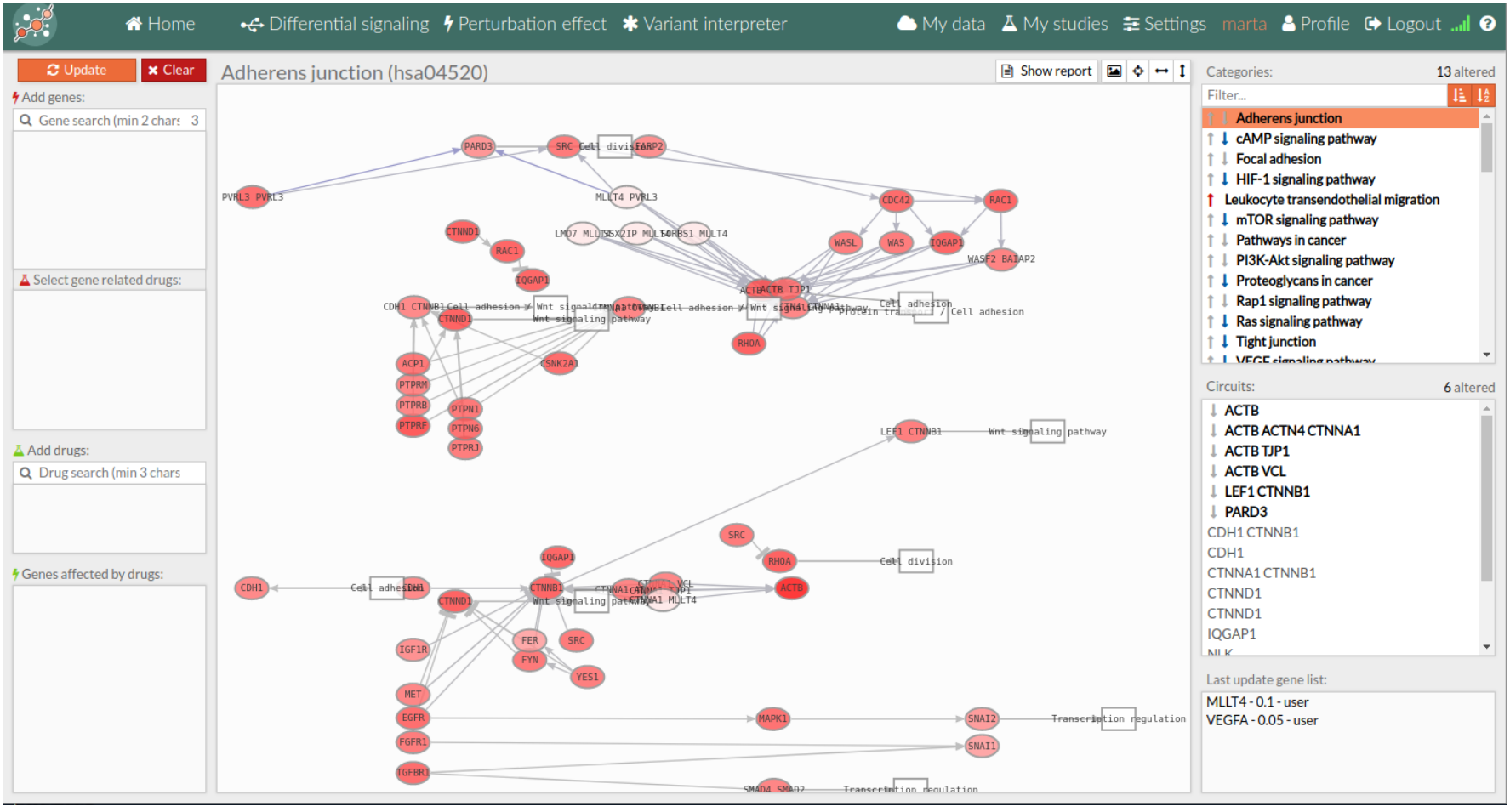

Nodes
Shape
Gene
Metabolite
Color
Down-regulated gene (DE)
Up-regulated gene (DE)
0
0.05
p-value
Edges
Inhibition
Activation
Down-regulated path
Up-regulated path
Not differentially regulated path


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

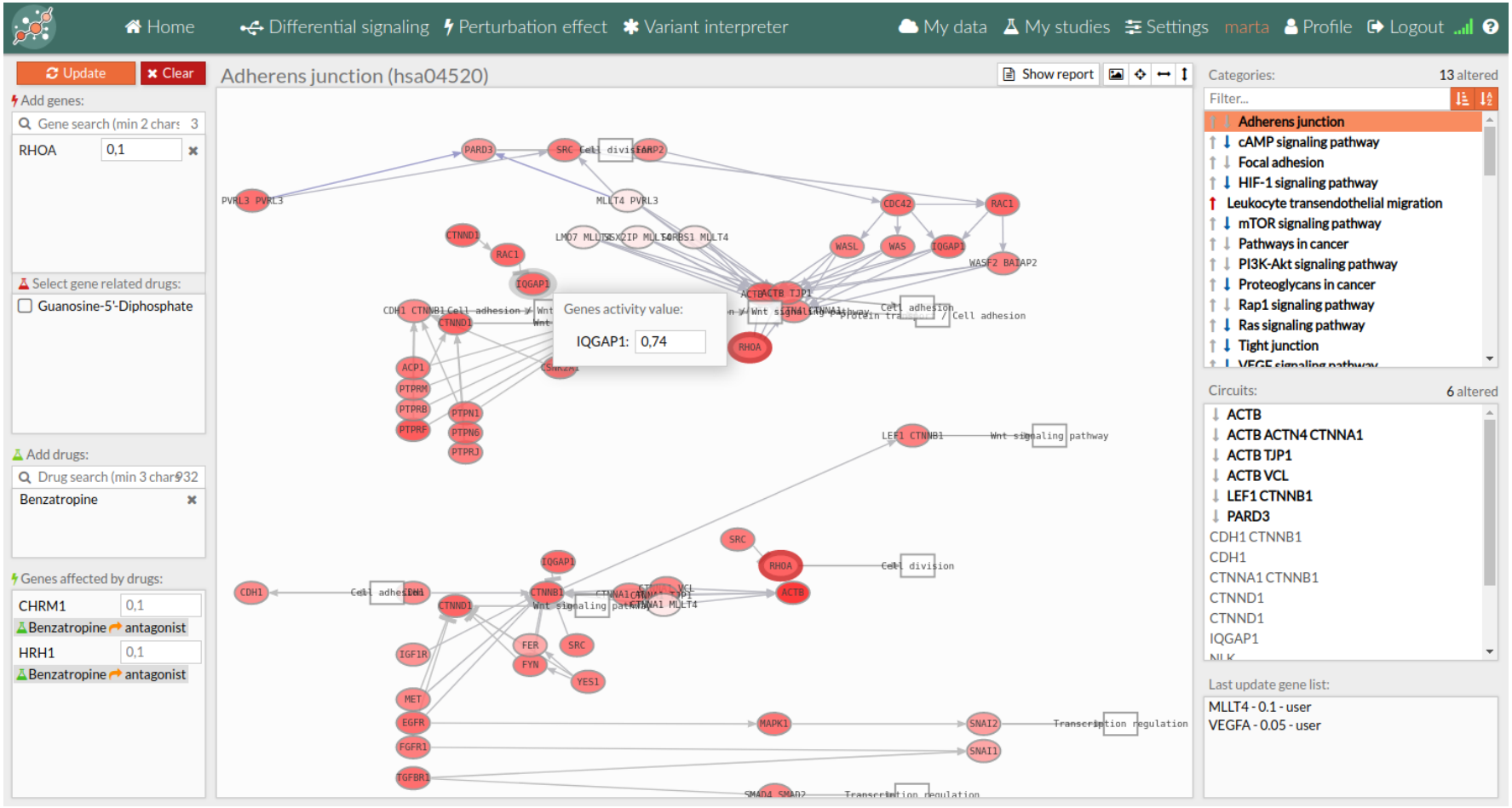
HiPathia

Perturbation effect tool

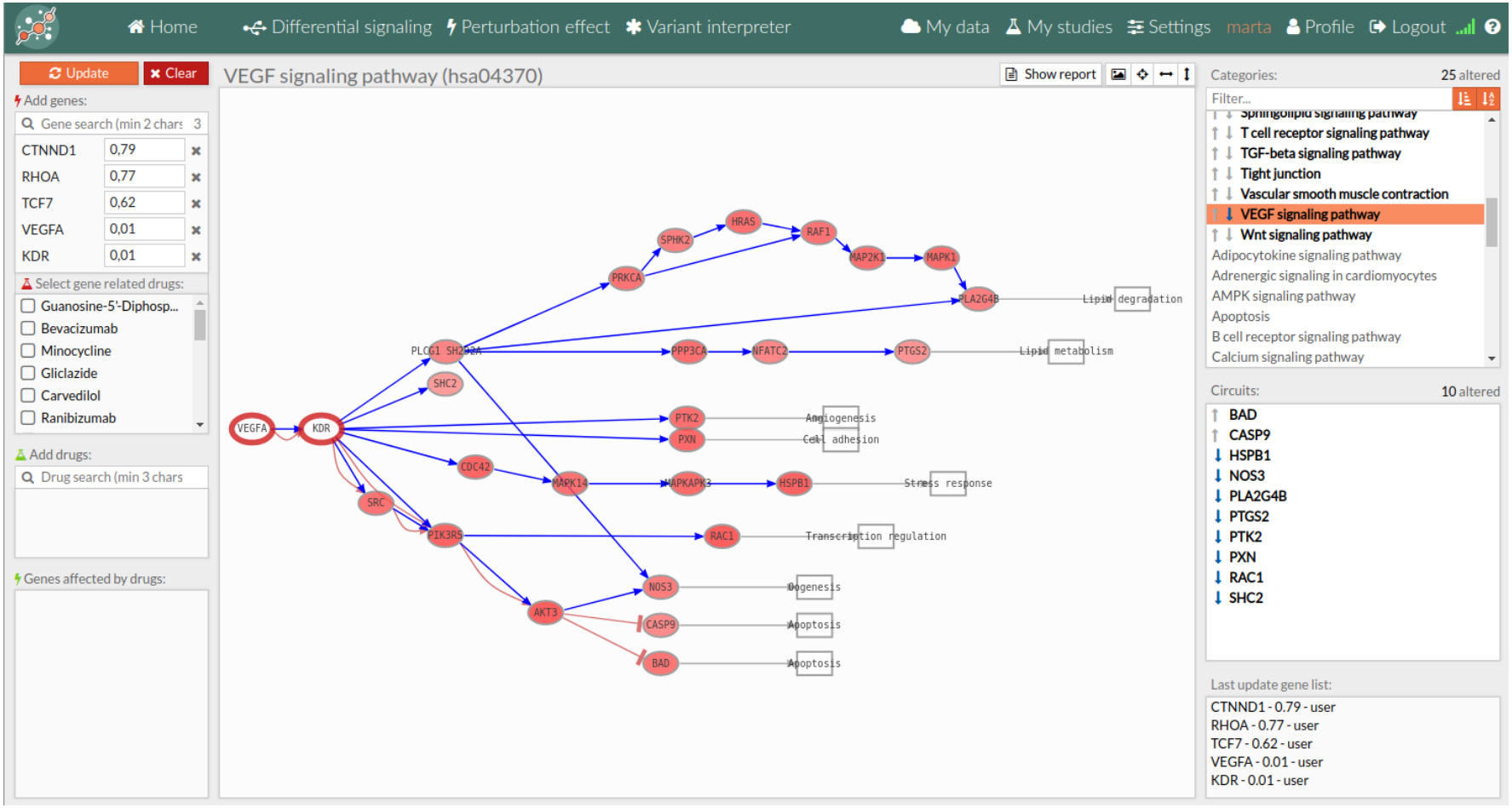
Perturbation effect



Perturbation effect



Perturbation effect

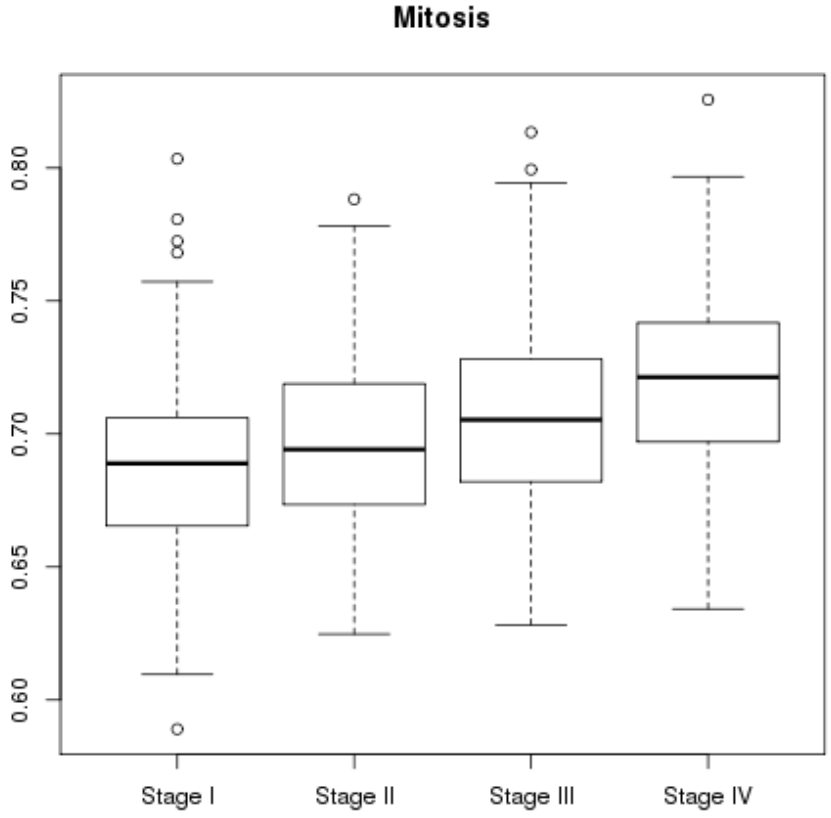


HiPathia

Further analysis

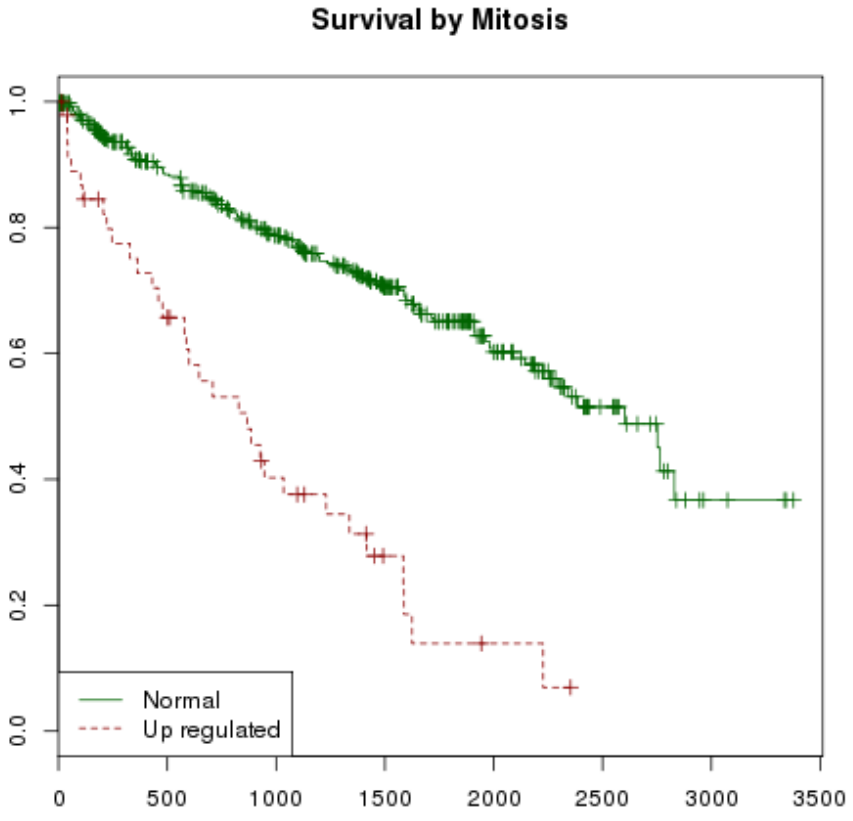
Disease progression analysis

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 Perturbation effect worked example

Further exercises

Do the Differential signaling exercises