Signaling pathways analysis: HiPathia

Alicia Amadoz

September 30th, 2016

GDA

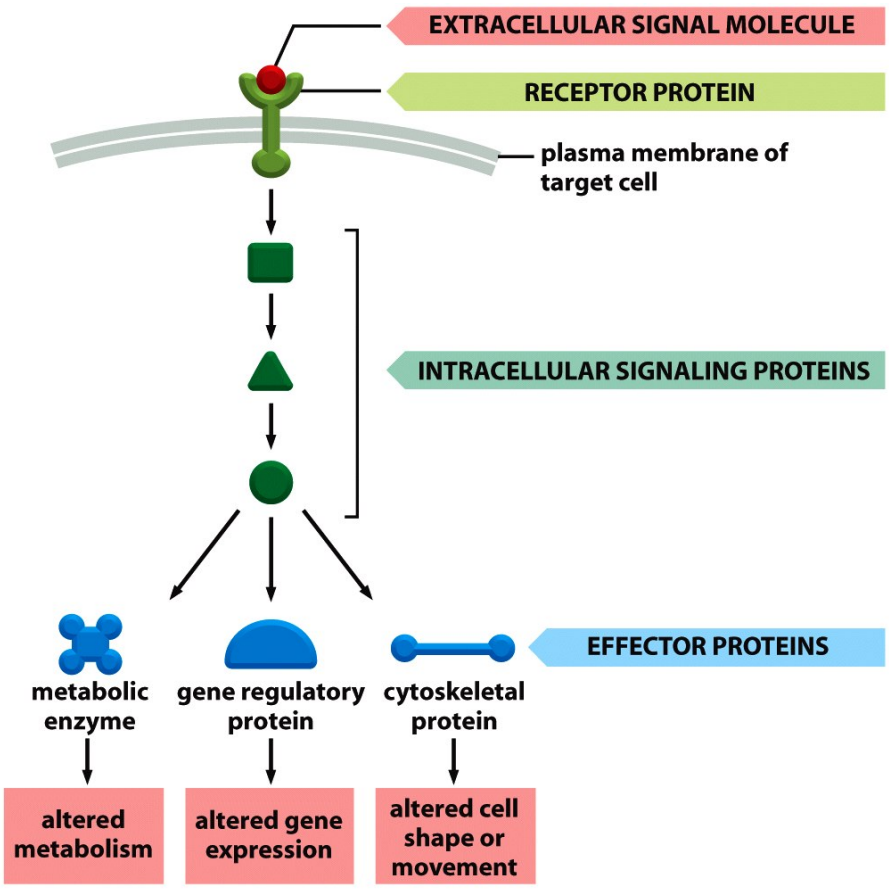
International Course on
Genomic Data Analysis

PRINCIPE FELIPE
CENTRO DE INVESTIGACION

Outline

1. Signaling pathways
   - Methods
2. HiPathia
   - Preprocess
   - Method
3. HiPathia Web Tool
   - Usage
   - Results

Signaling pathways



Signal transduction

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

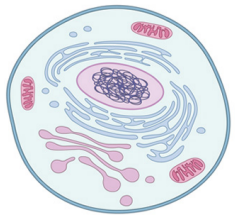
Signaling pathways

Cascades of protein activations and inhibitions

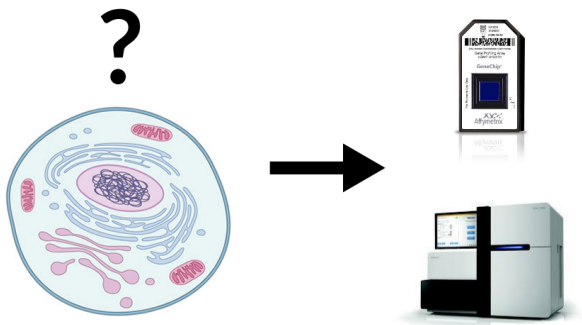
Pathway Methods

From cell to pathways

?

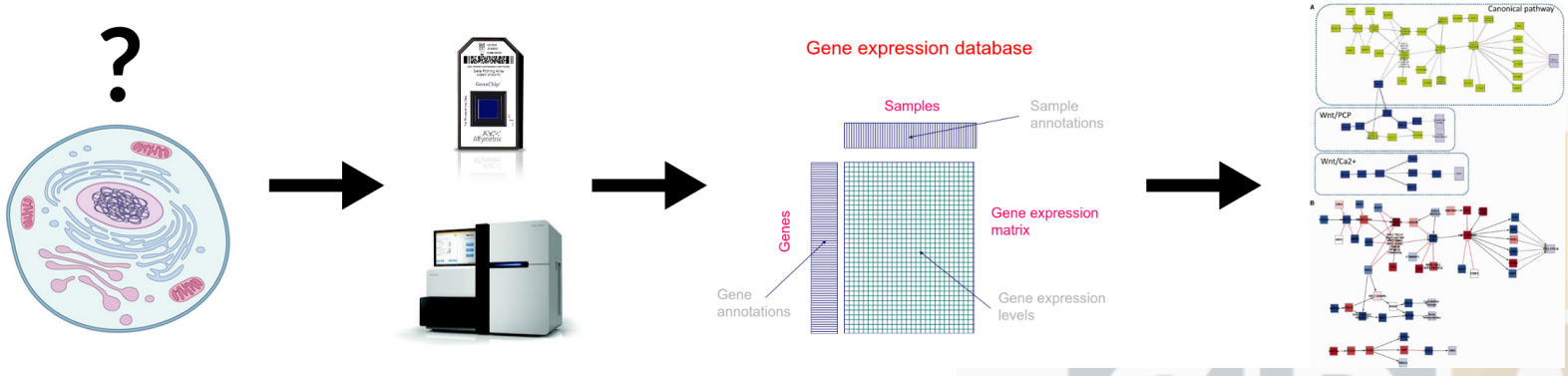


From cell to pathways



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

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

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

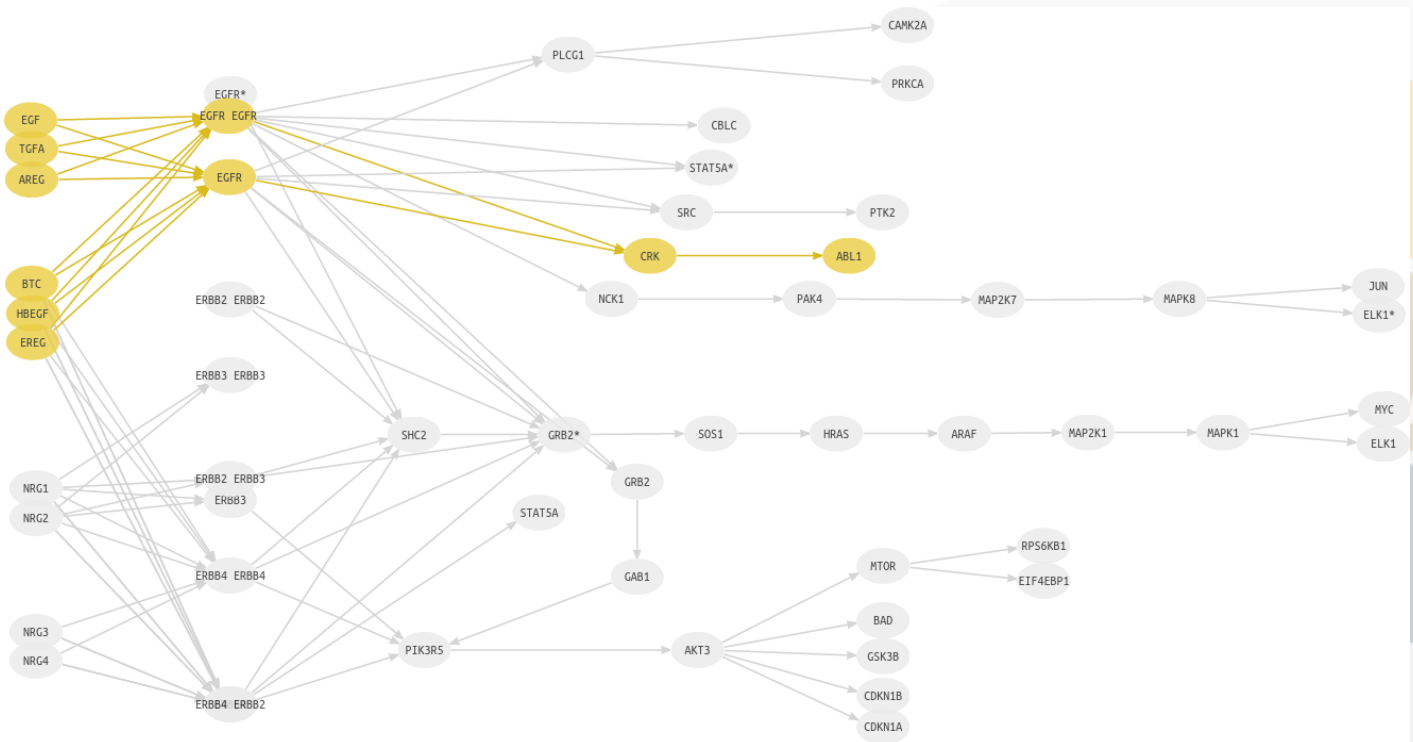
HiPathia

Preprocess

Subpathways

Effector subpathway

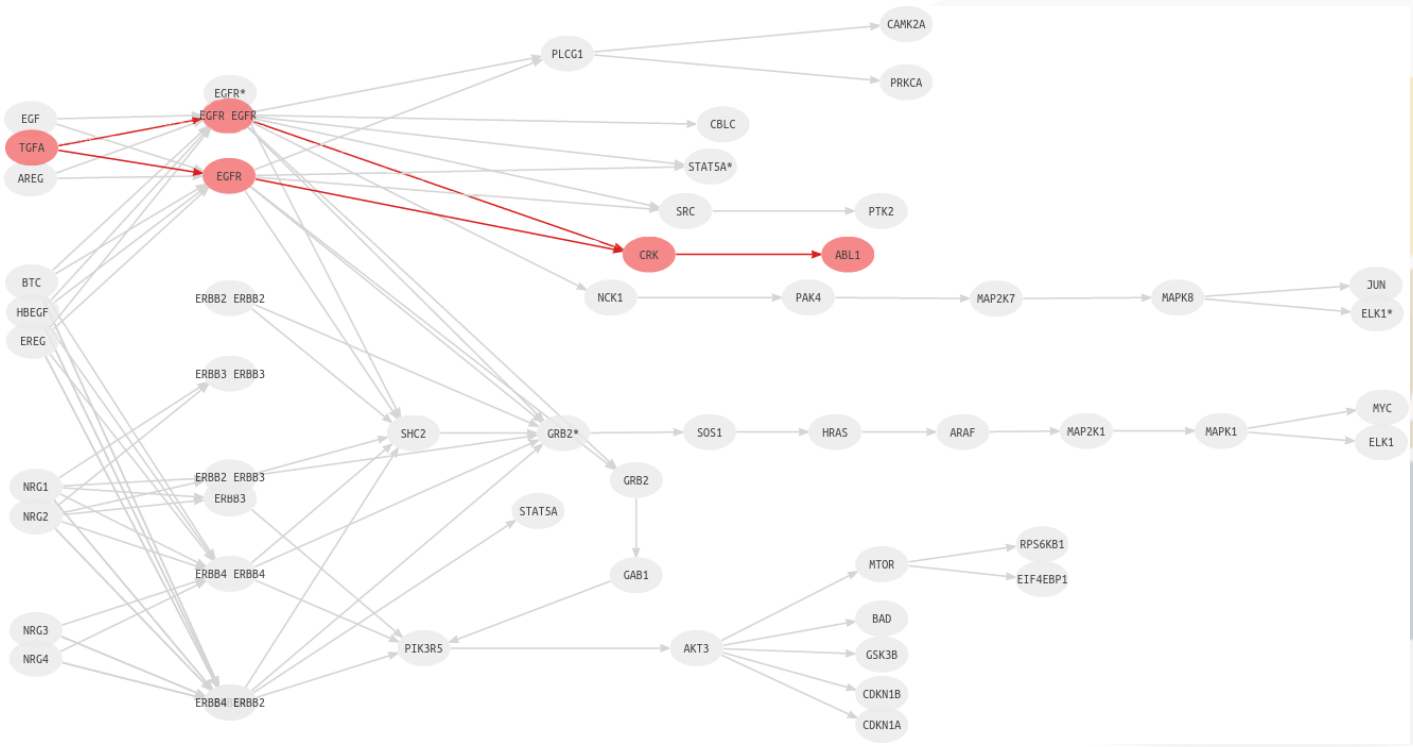
Subgraph of the pathway including any node in a path ending in an effector protein



Subpathways

Decomposed subpathway

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



Normalization

Use normalization pipeline depending on technology

Microarray

- Intensities matrix
- RMA
- quantiles

RNA-Seq

- Counts matrix
- TMM
- log transformation

Normalization

Use normalization pipeline depending on technology

Microarray

- Intensities matrix
- RMA
- quantiles

RNA-Seq

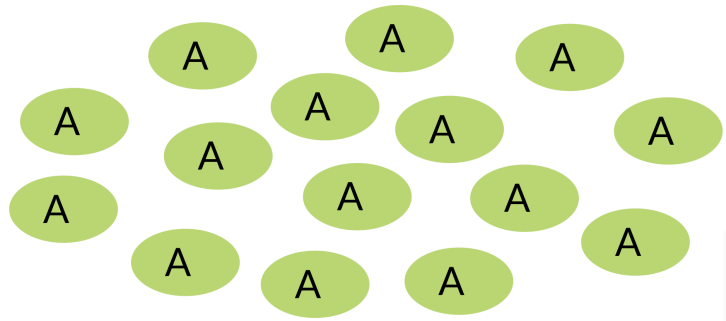
- Counts matrix
- TMM
- log transformation

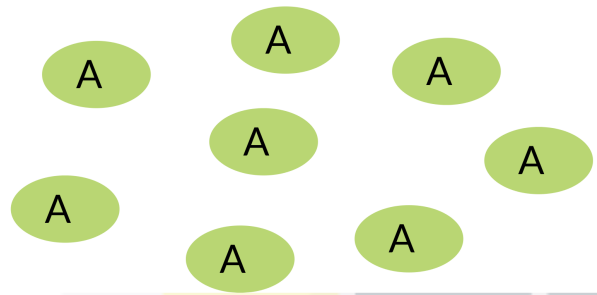
Expression matrix

HiPathia

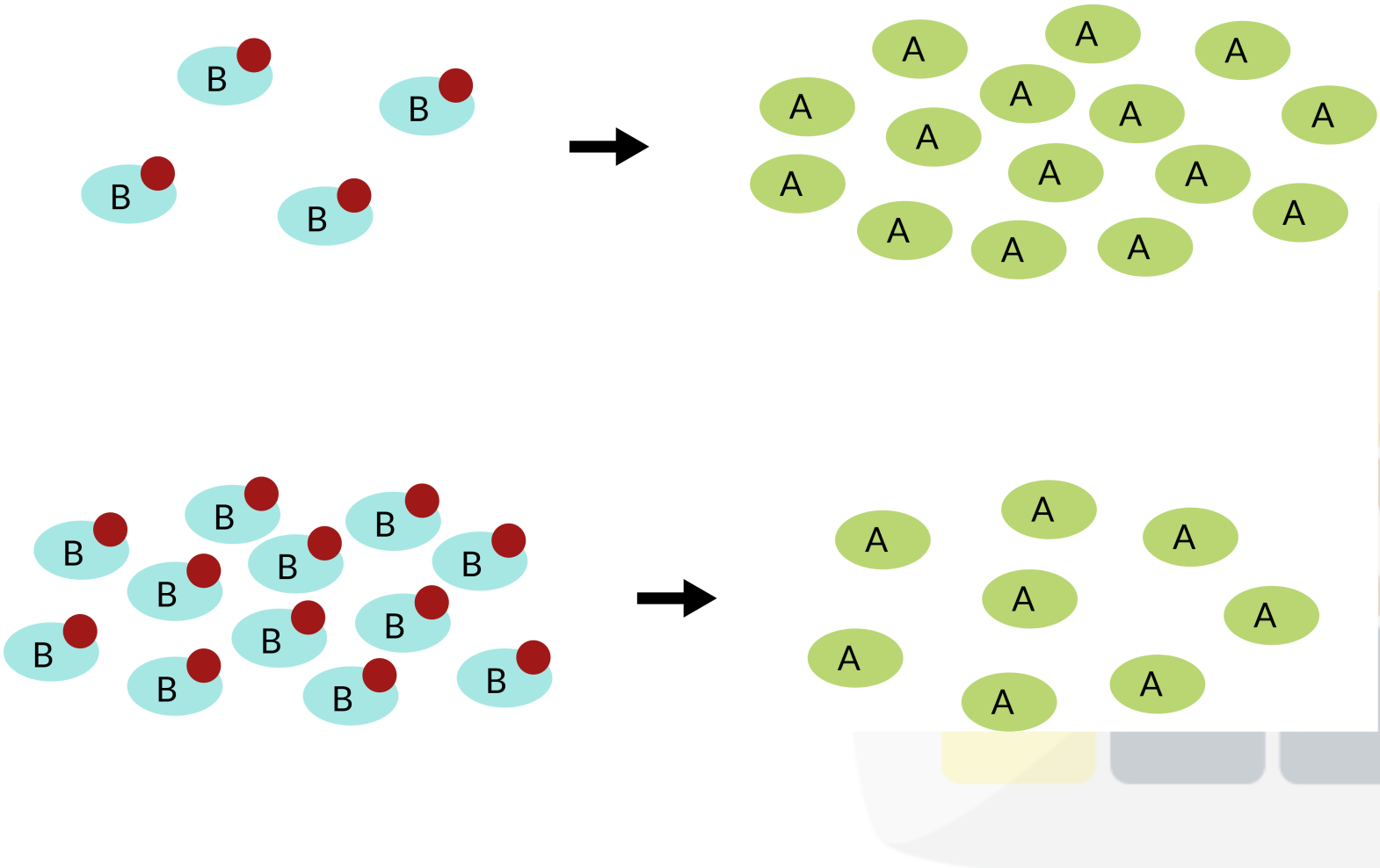
Method

Intuitive idea

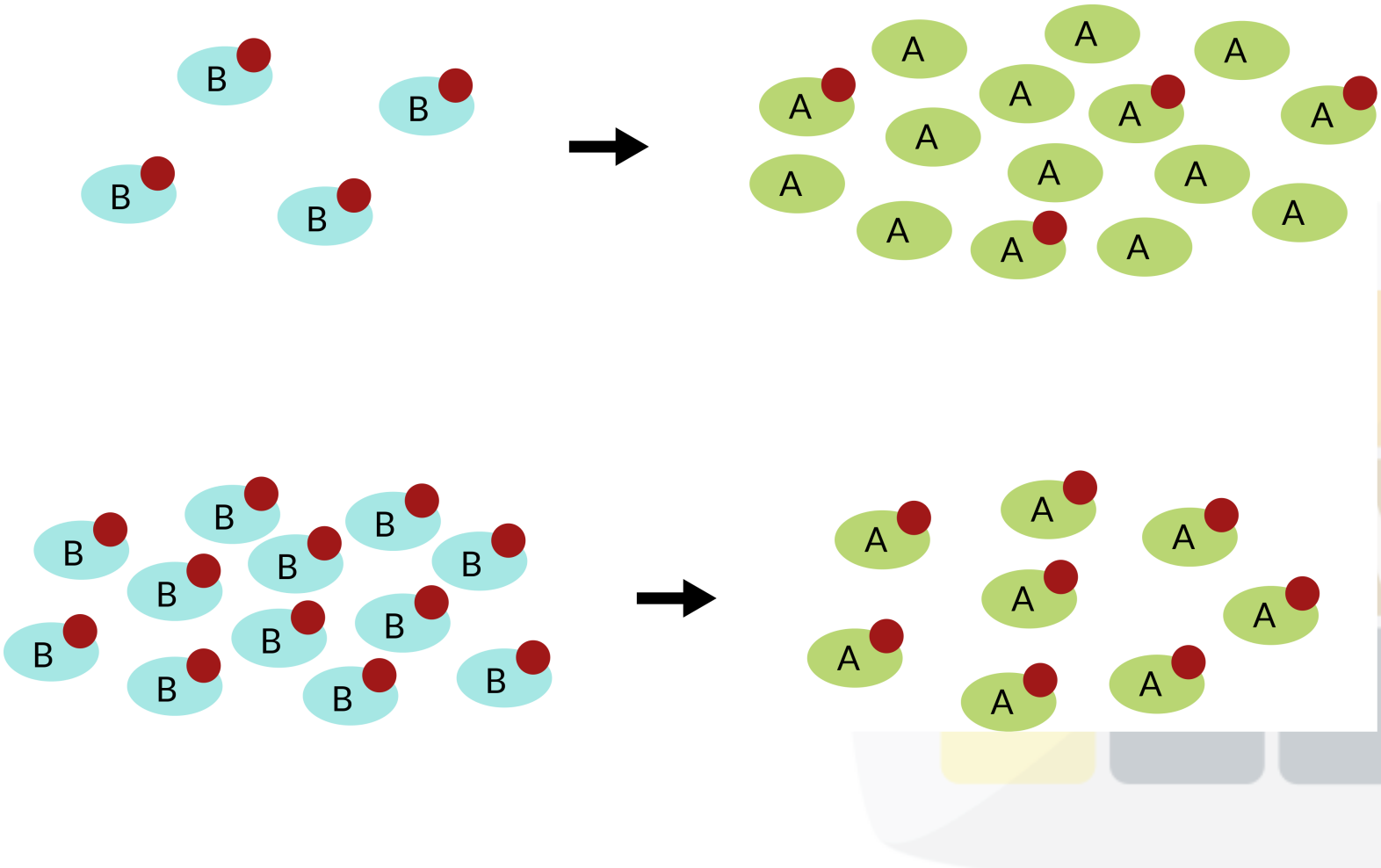




Intuitive idea



Intuitive idea



Computing the signal

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

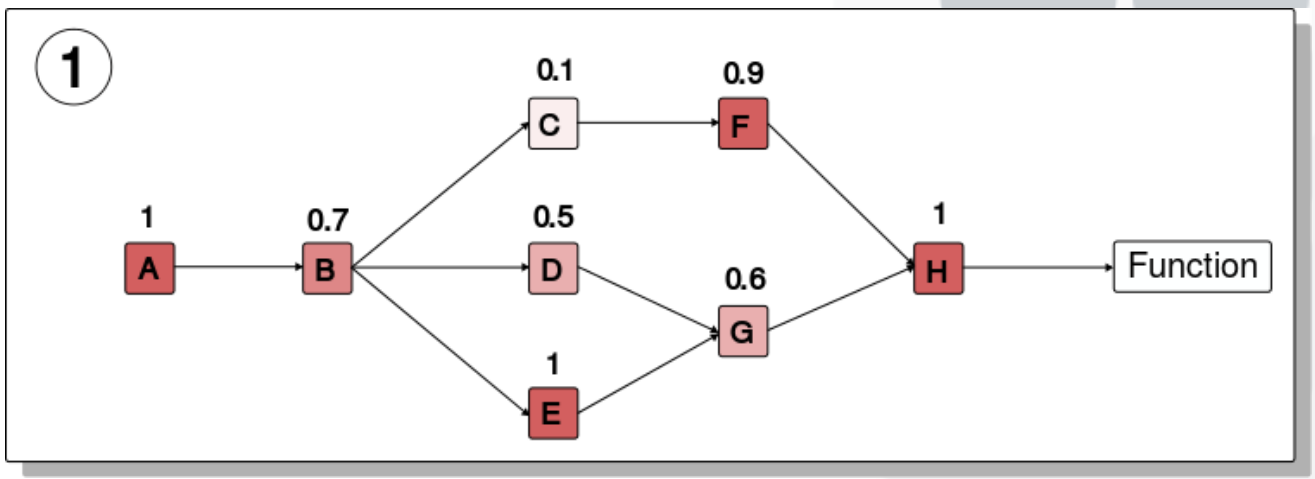
$$S_n = v_n \cdot (1 - \prod_{s_i \in A} (1 - s_i)) \cdot \prod_{s_j \in I} (1 - s_j)$$

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

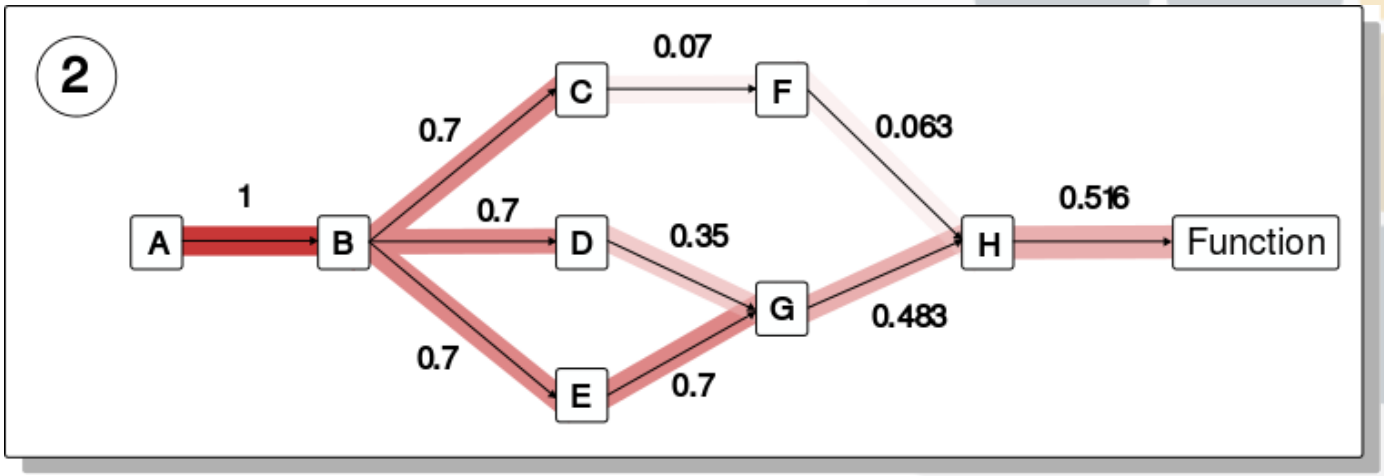
$$S_n = v_n \cdot (1 - \prod_{s_i \in A} (1 - s_i)) \cdot \prod_{s_j \in I} (1 - s_j)$$

S_n: Signal value through n

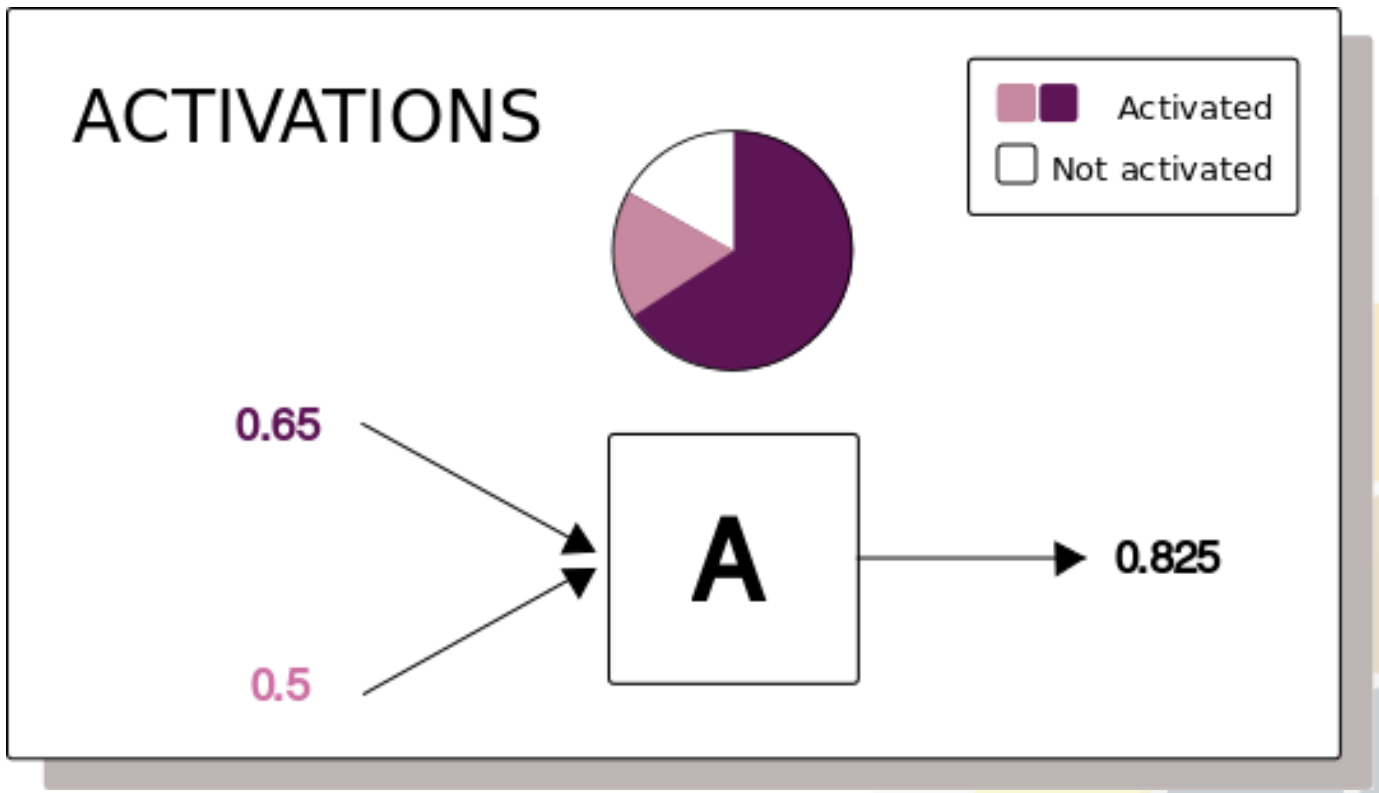
v_n: Node value

A: Activation edges

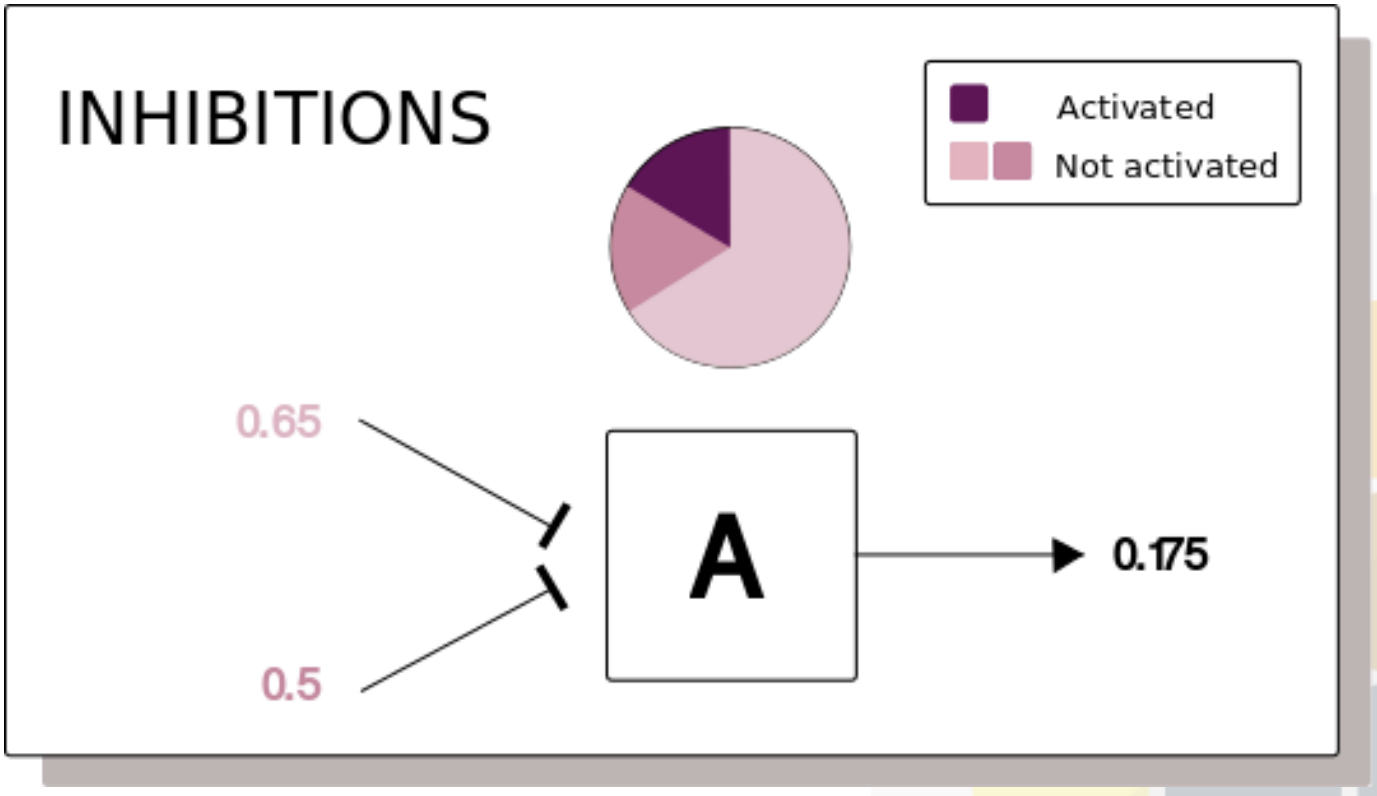
I: Inhibition edges



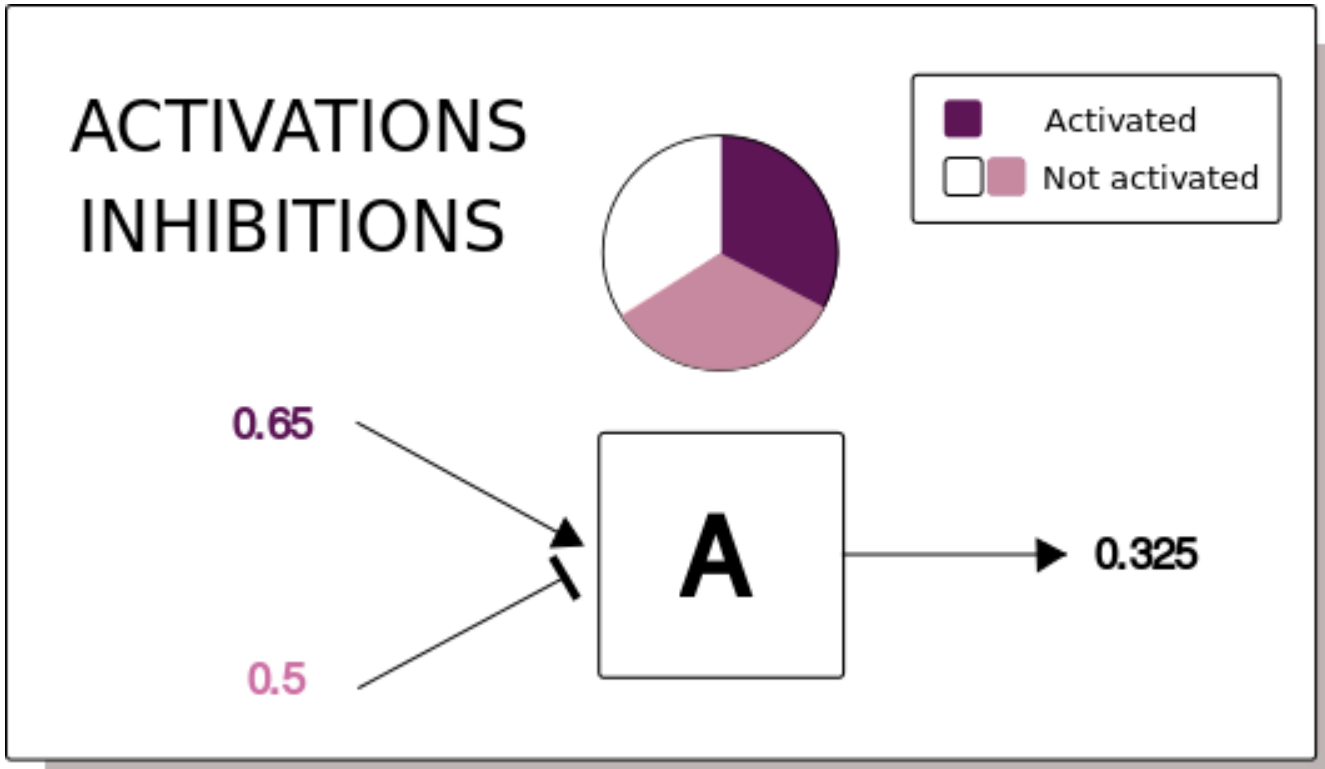
Computing the signal



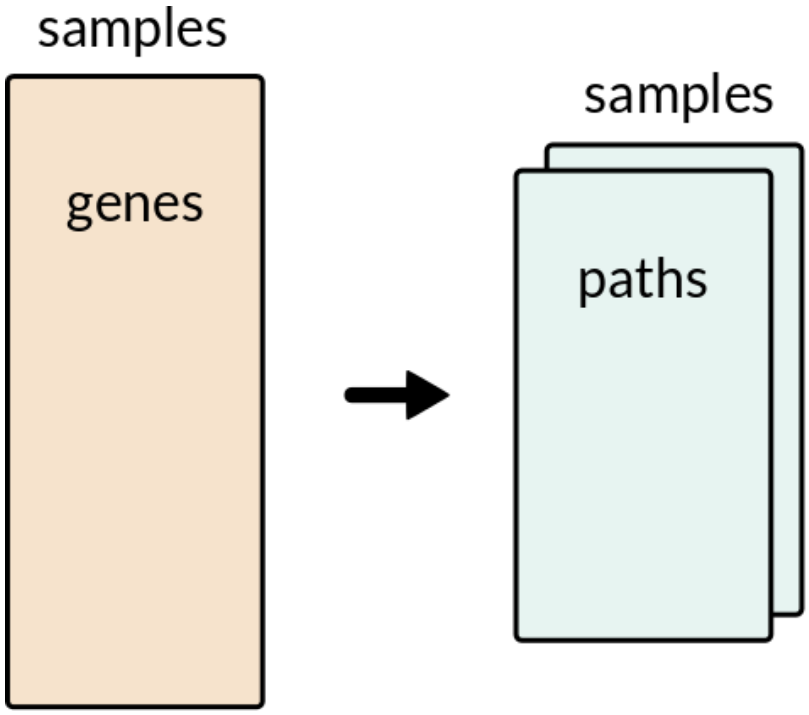
Computing the signal



Computing the signal



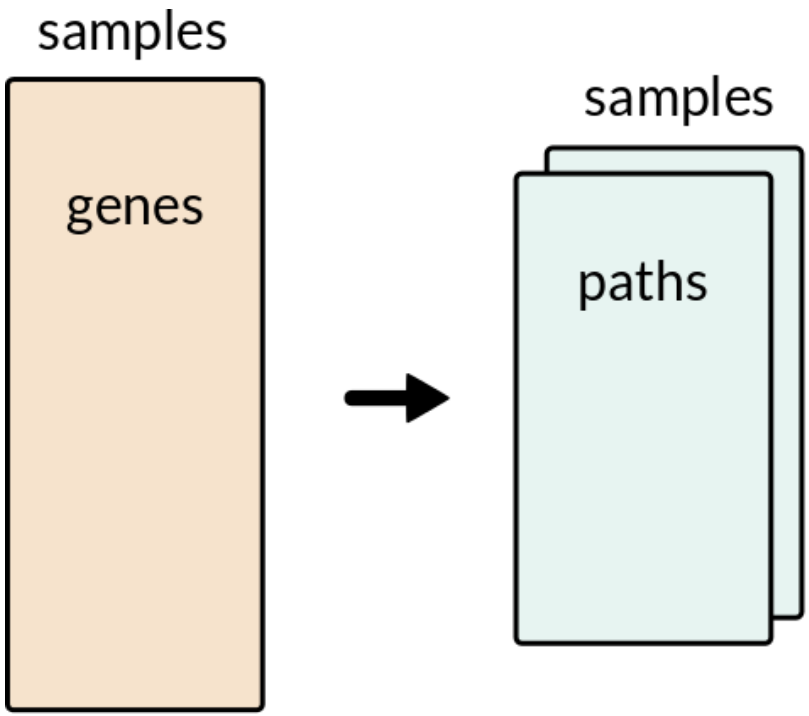
Functional annotation



Functional annotation

We annotate each effector protein to a function

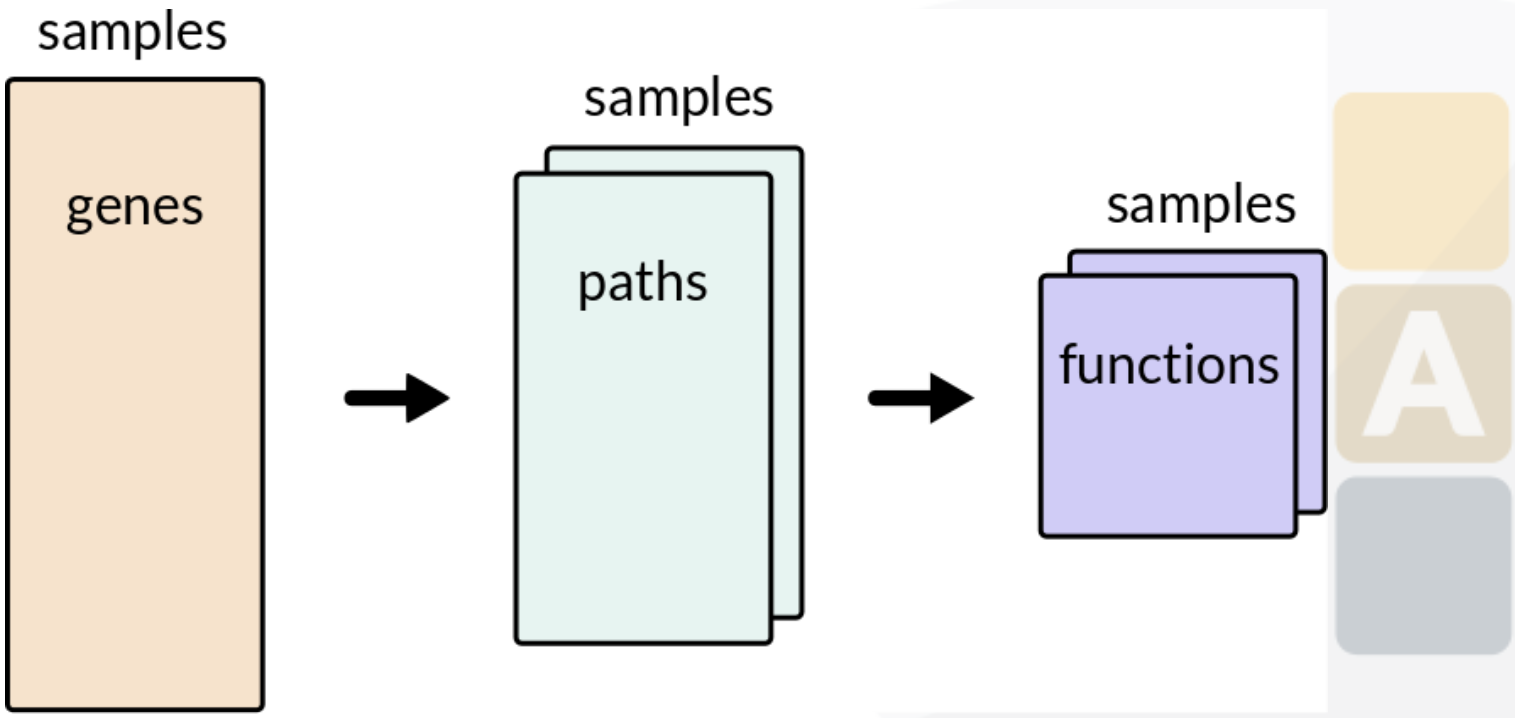
- Uniprot keywords
- GO annotation



Functional annotation

We annotate each effector protein to a function

- Uniprot keywords
- GO annotation



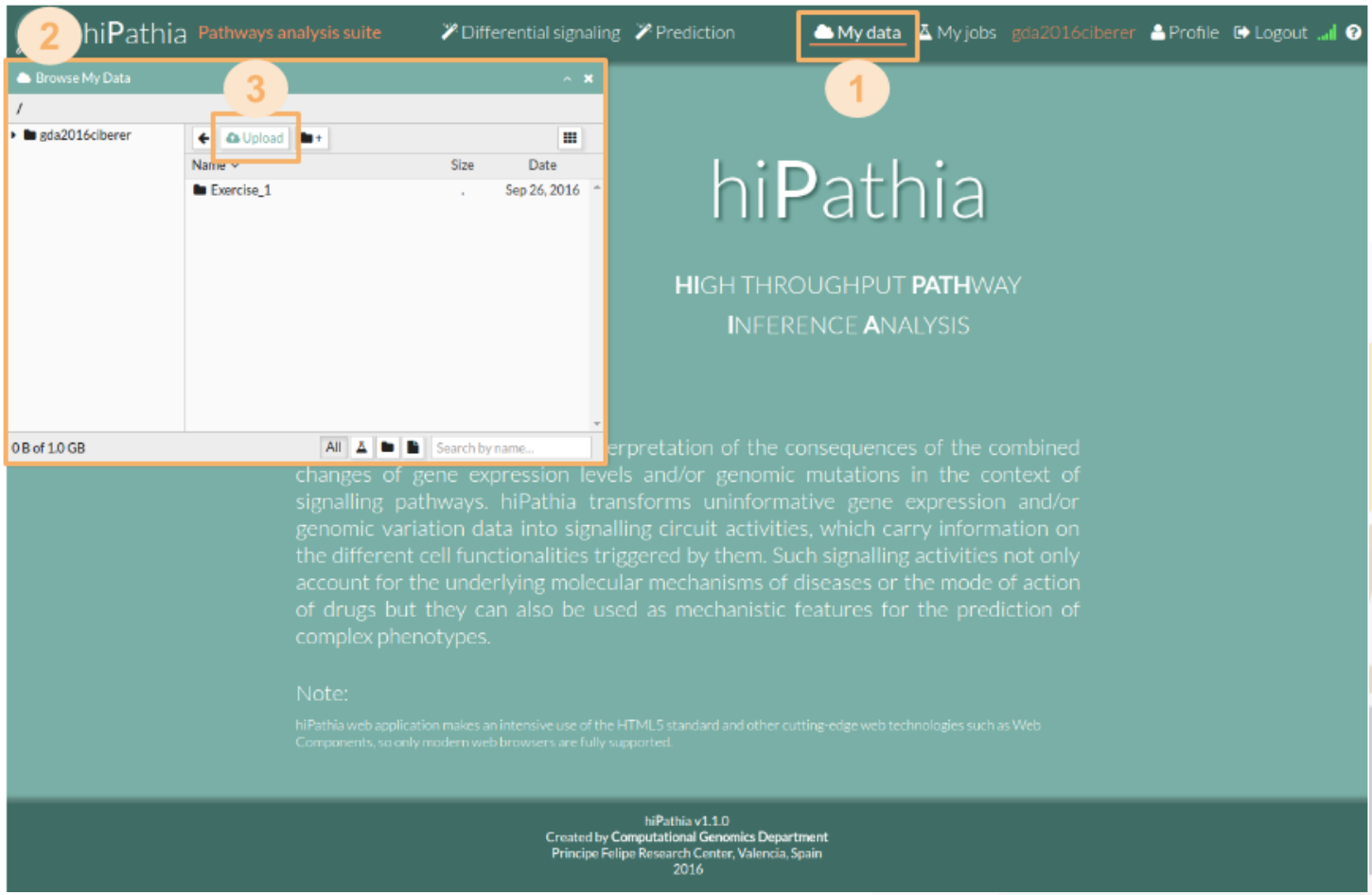
HiPathia

Web tool

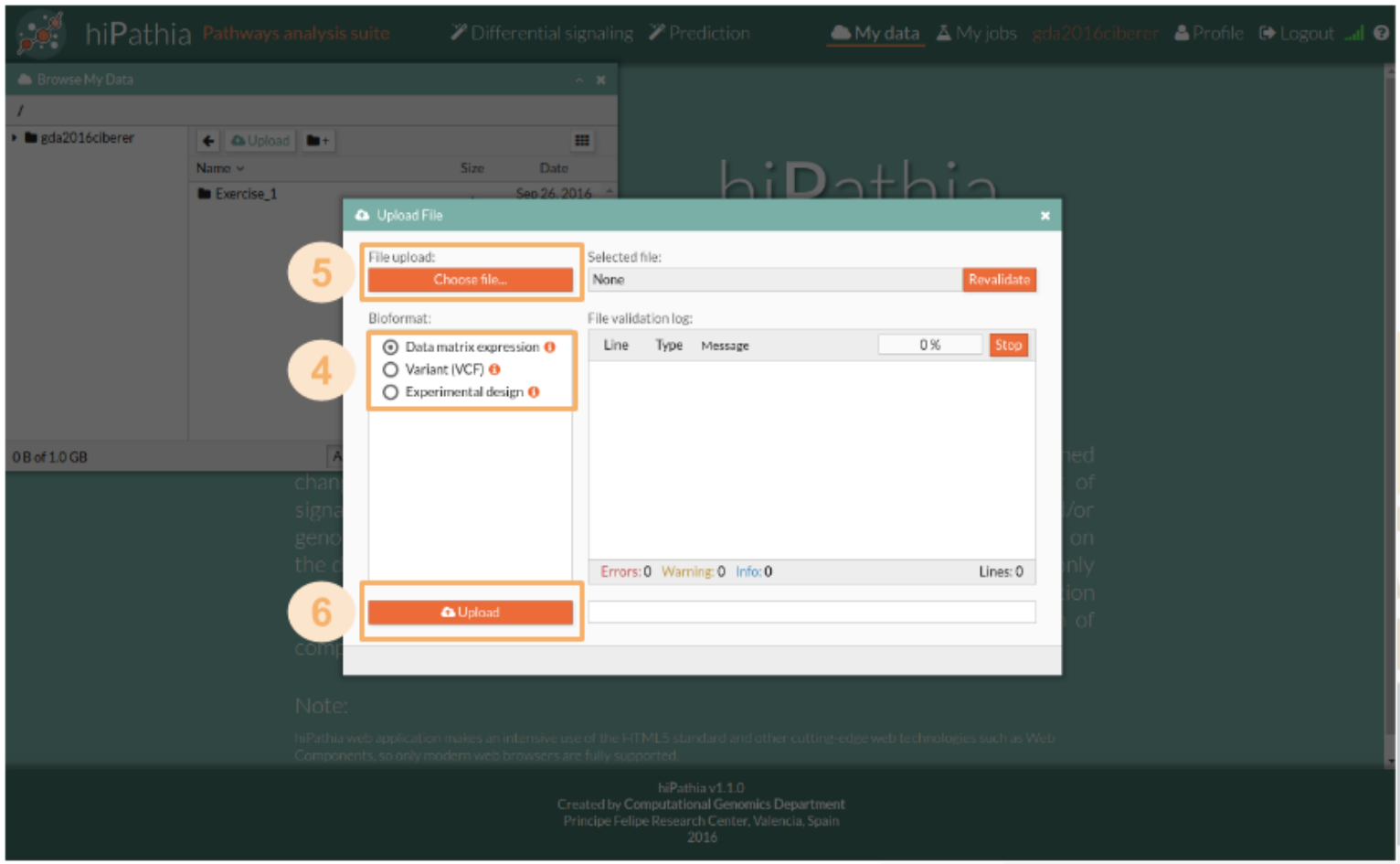
Logging in

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
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

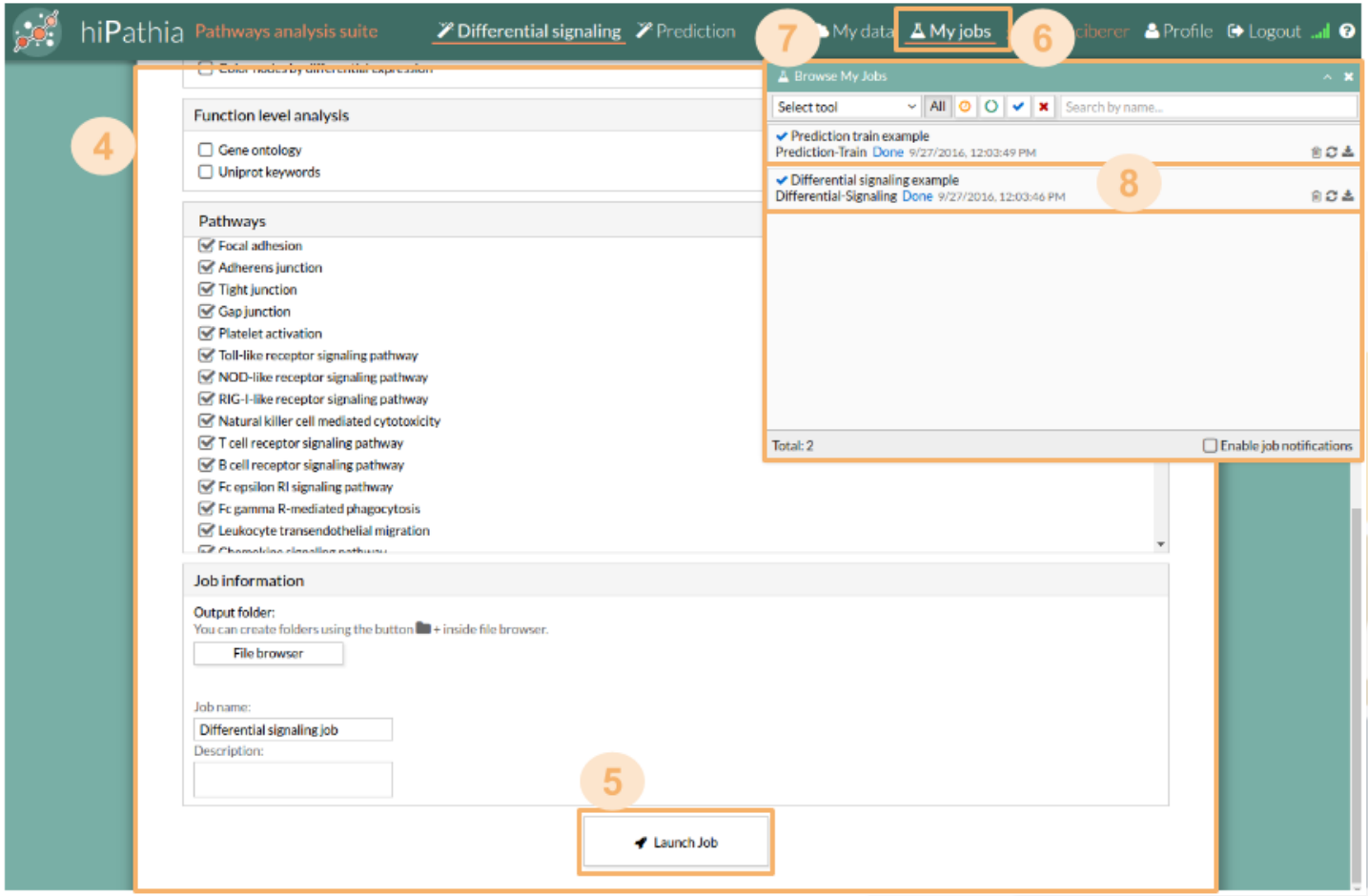
Upload data


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

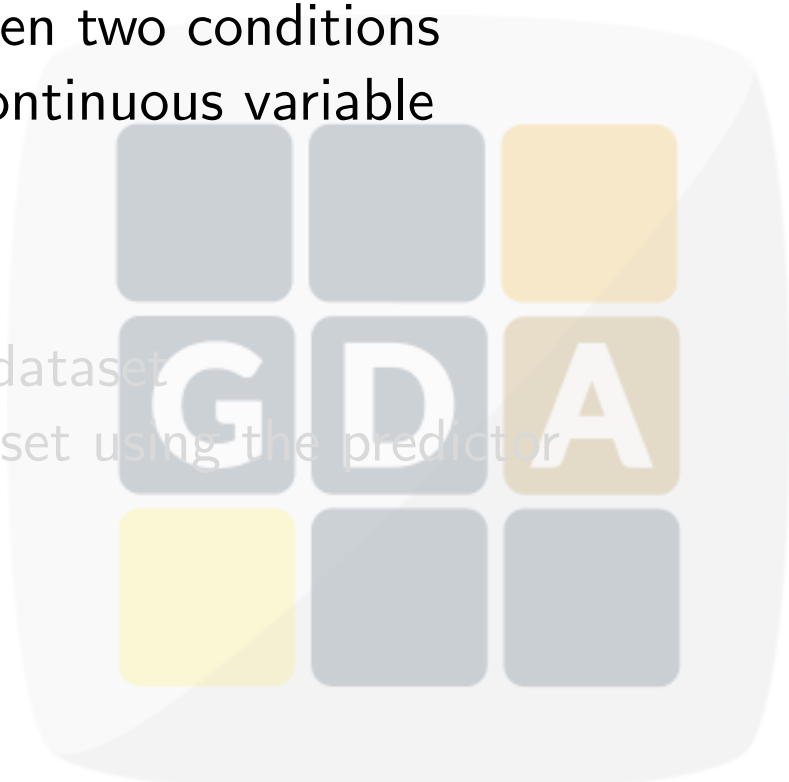
Workflow


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



Tools

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

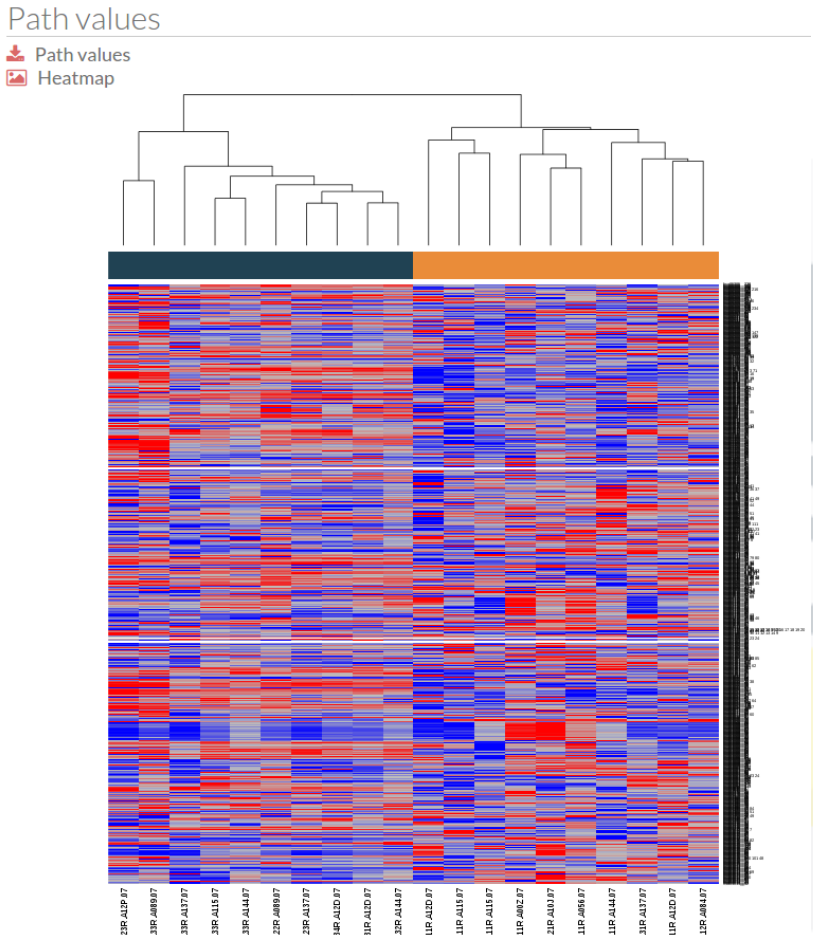
2. **Prediction**
   - Construct a predictor from a dataset
   - Predict classes from new dataset using the predictor

HiPathia

Results

Heatmap

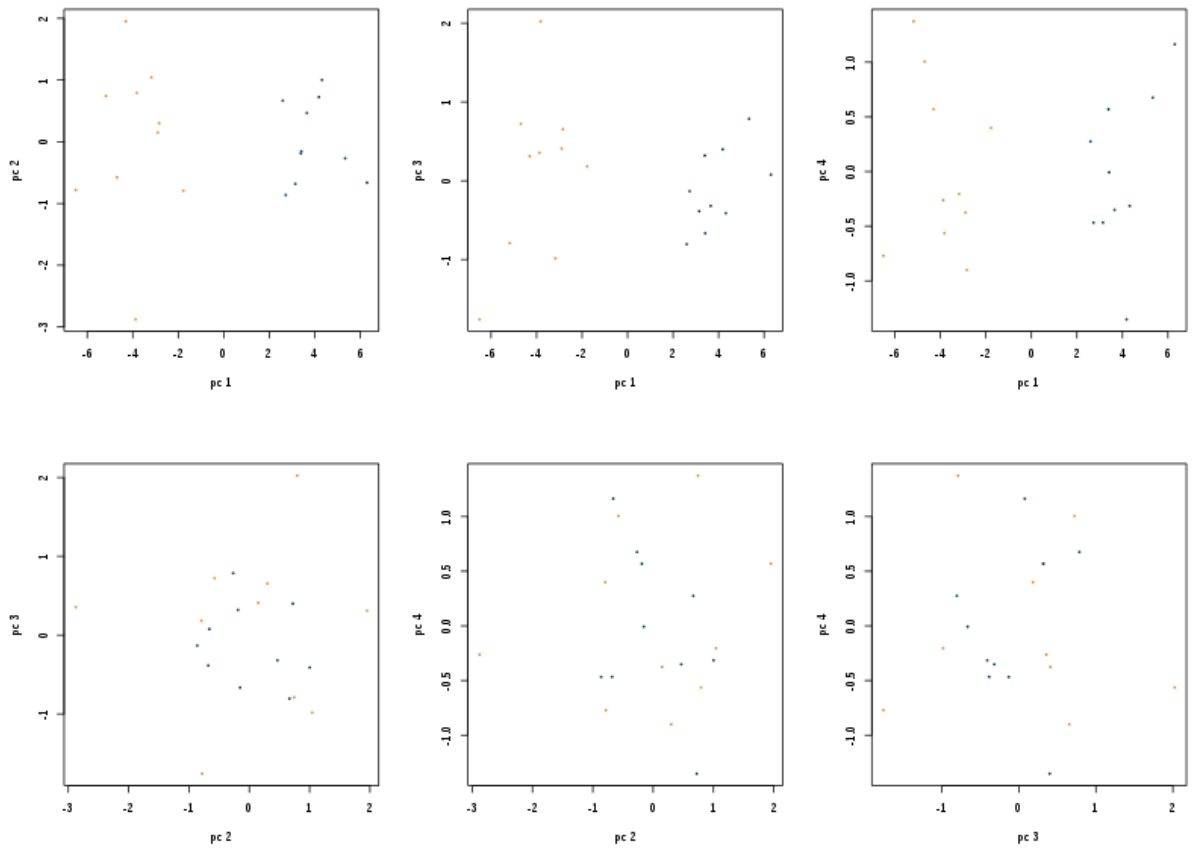
Graphical representation of data where values in a matrix are represented as colors



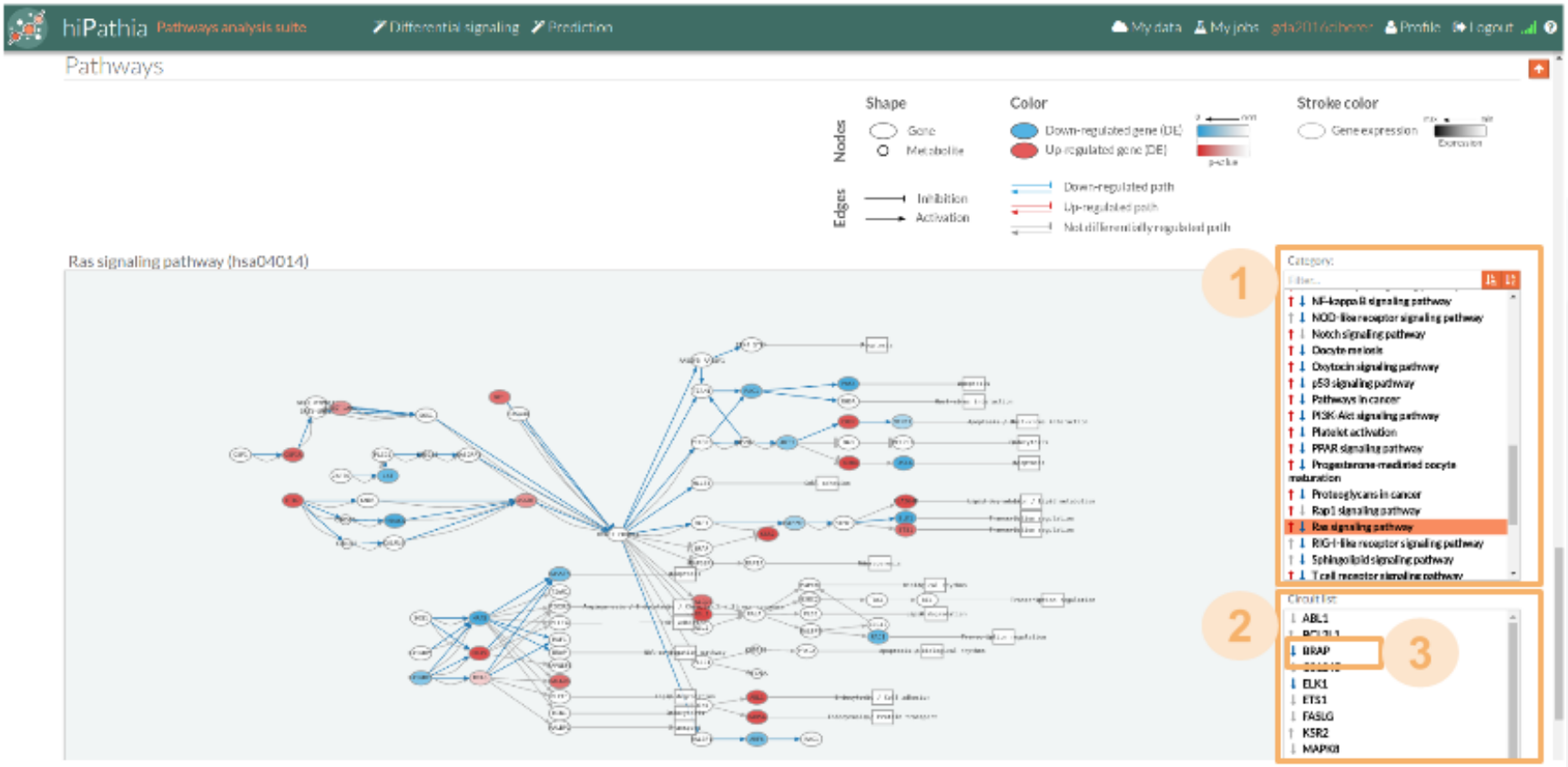
Principal Components Analysis (PCA)

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

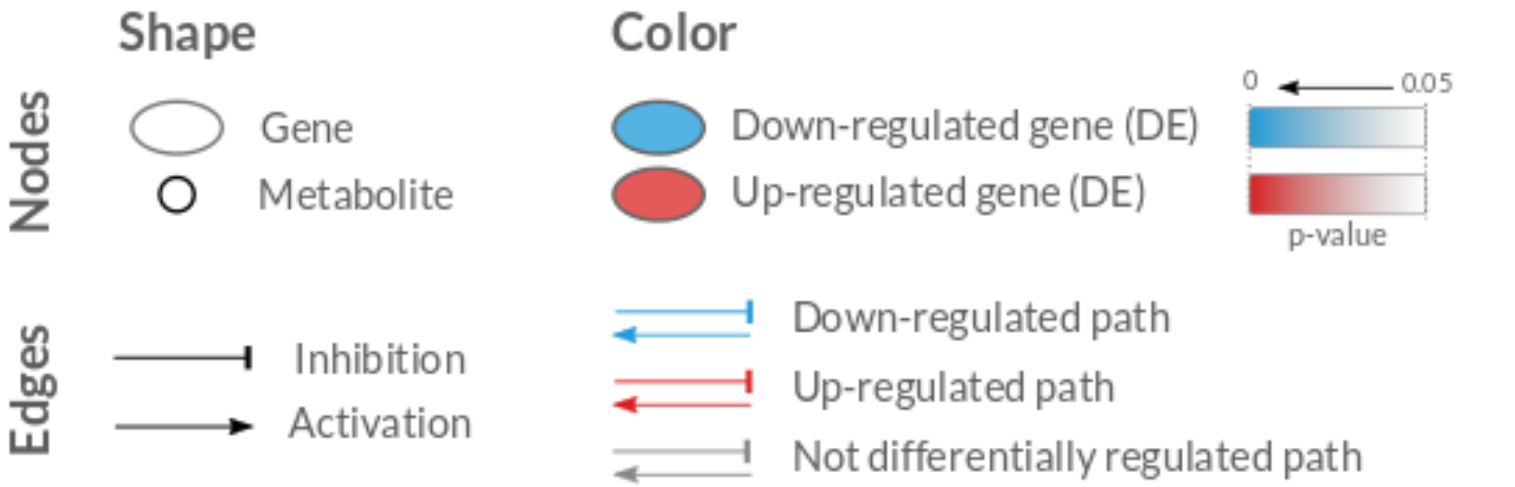
PCA



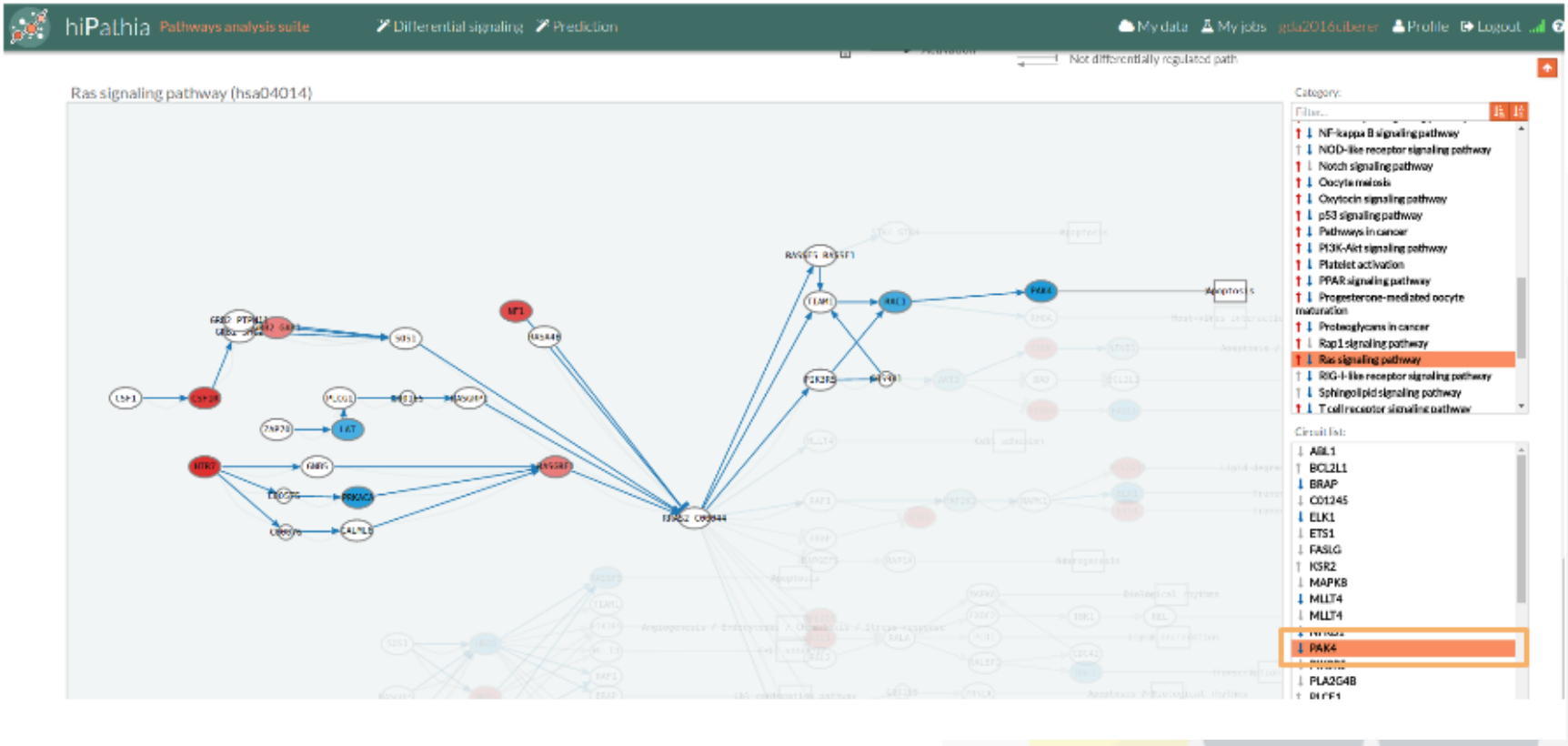
Viewer


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
Circuits:
ABL1
BRAP
ELK1
ETS1
FASLG
KSR2
MAPK8
3

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


hiPathia
Pathways analysis suite
Differential signaling
Prediction
My data
My jobs
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
BRAP
CD1245
ELK1
ETS1
FASLG
KSR2
MAPKB
MLLT4
MLLT4
PAK4
PLA2G4B

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