

HiPathia

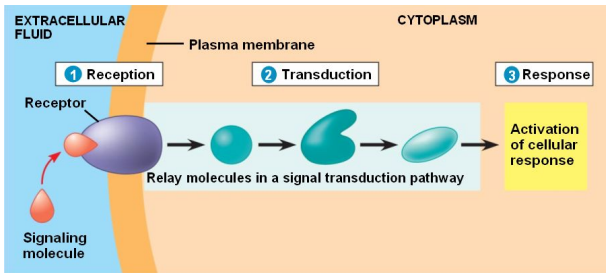
Models of signaling pathway activity

Marta R. Hidalgo
Systems Genomics Lab, CIPF

January 10th, 2019



Signaling pathways



Chemical signals

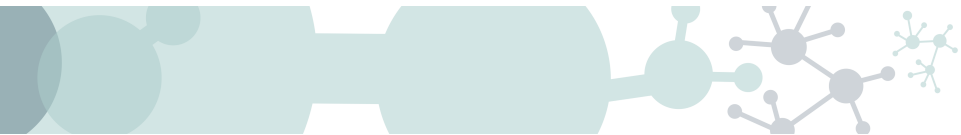
- Hormones
- Neurotransmitters
- Growth factors
- Cytokines
- Drugs

Activation & Inhibition

- Phosphorilation
- Dephosphorilation
- Glycosylation
- Ubiquitination
- Methylation

Cellular Function

- Apoptosis
- Survival
- Growth
- Migration
- Proliferation



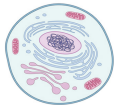
Pathway Analysis

Methods

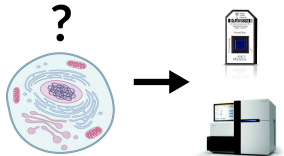
From cell to pathways



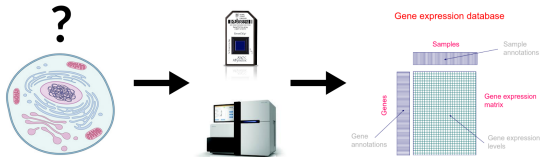
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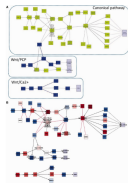
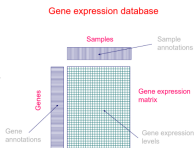
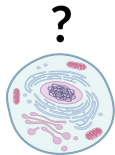
From cell to pathways



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-AOS1252
© Institute of Mathematical Statistics, 2012

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

BY LAURENT JACOB, PIERRE NEUVIAL AND SANDRINE DUDOI

Pathway methods



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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 Martini¹, Gabriele Sales², M. Sofia Massa³, Monica Chiogna⁴ and
Chiara Romualdi^{2,*}**

Pathway methods



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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 Khatri¹, Sonia S. Hassan²,
Pooja Mittal², Jung-sun Kim², Chong Jai Kim², Juan Pedro Kusanovic²
and Roberto Romero²

Pathway methods



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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

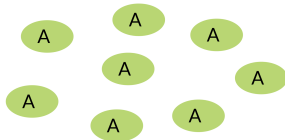
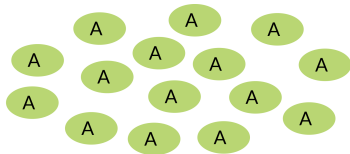
Marta R. Hidalgo¹, Cankut Cubuk¹, Alicia Amadoz^{1,2}, Francisco Salavert^{1,3}, José Carbonell-Caballero¹, Joaquin Dopazo^{1,2,3}



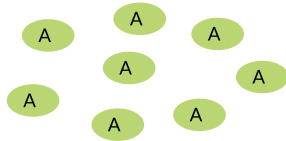
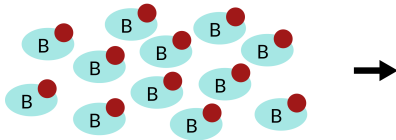
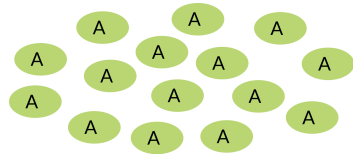
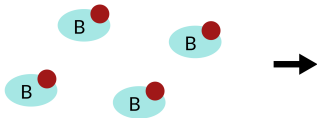
Pathway Analysis

HiPathia

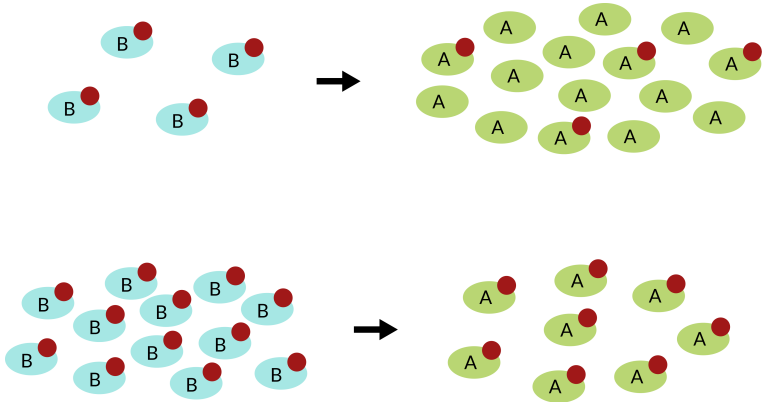
Intuitive idea



Intuitive idea



Intuitive idea

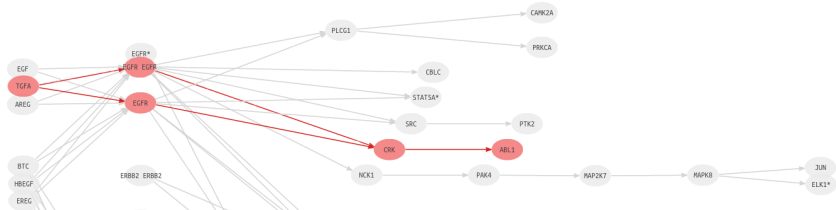


Meaningful subpathways



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

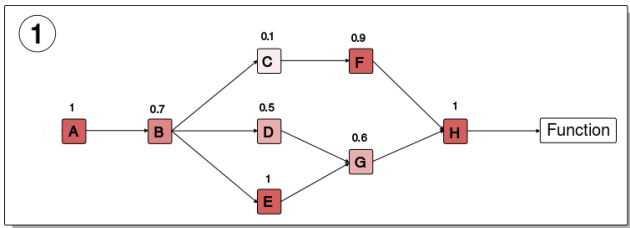
$$S_n = v_n \cdot \left(1 - \prod_{s_j \in A} (1 - s_j)\right) \cdot \prod_{s_j \in I} (1 - s_j)$$

S_n : Signal value through n

v_n : Node value

A : Activation edges

I : Inhibition edges



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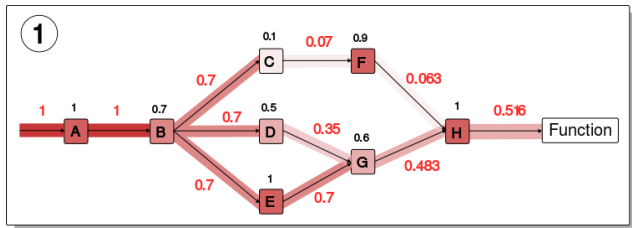
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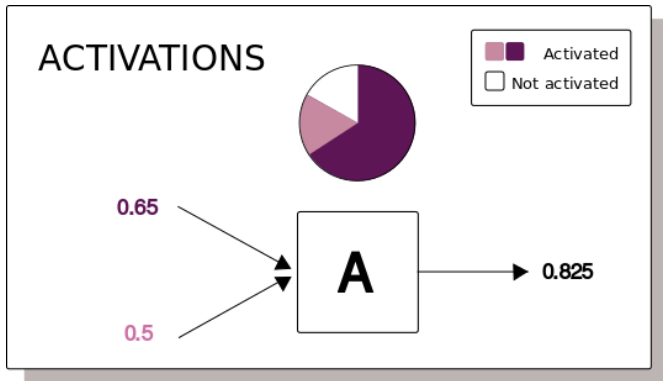
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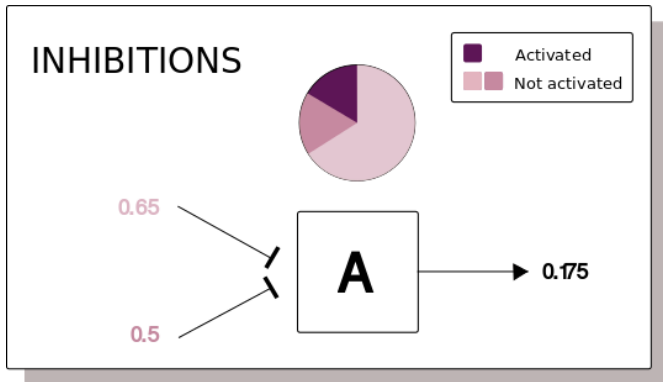
I: Inhibition edges



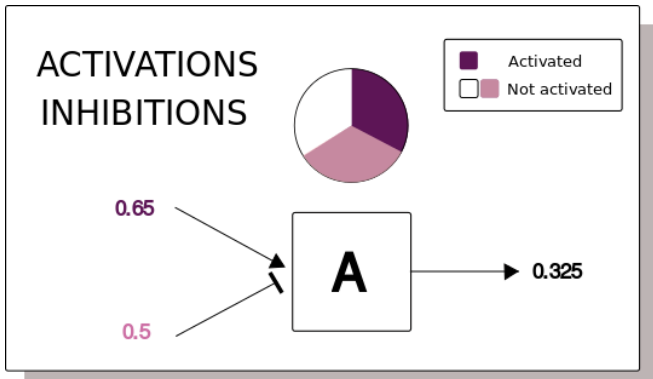
Computing the signal



Computing the signal

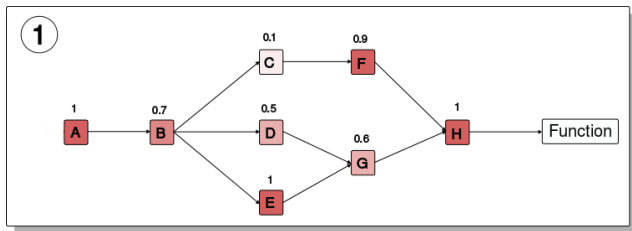


Computing the signal



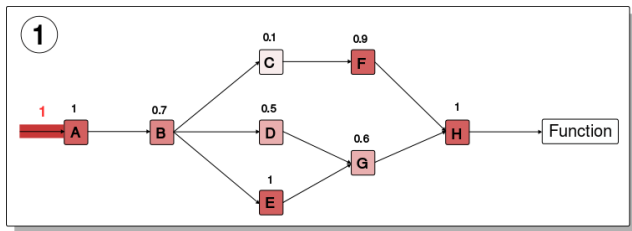
Signal values

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



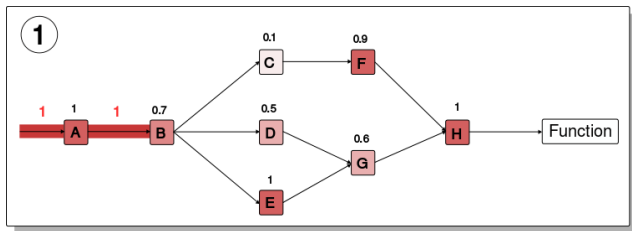
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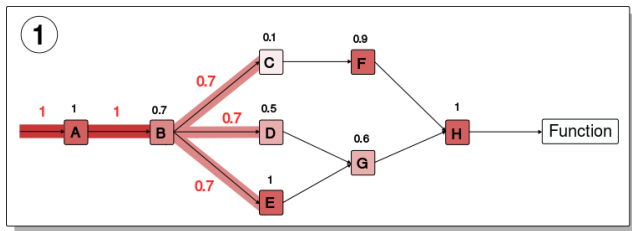
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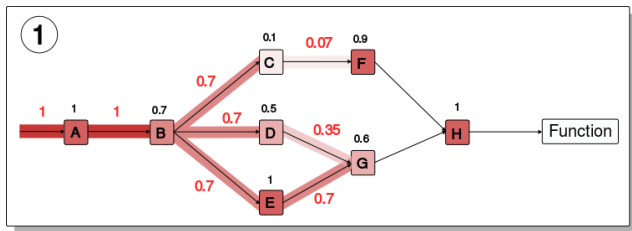
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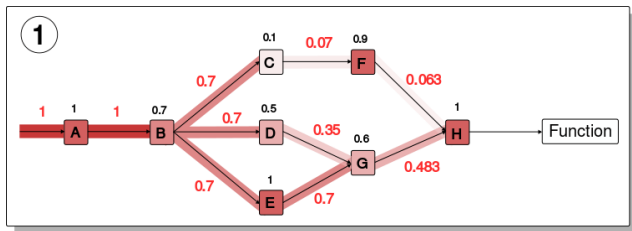
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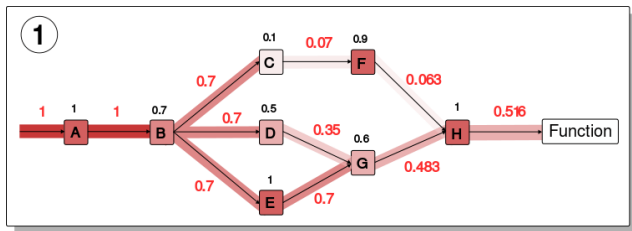
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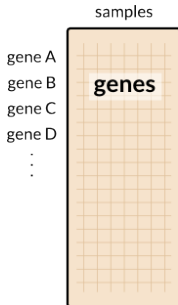
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Functional annotation

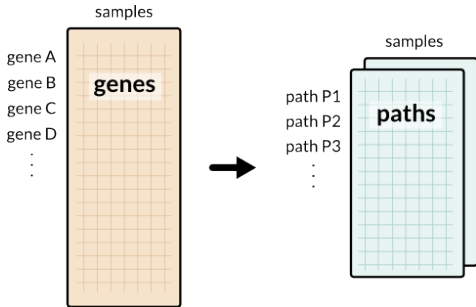


- 1 Estimate effector proteins activation
- 2 Annotate effector proteins functions
 - Uniprot keywords
 - GO annotation



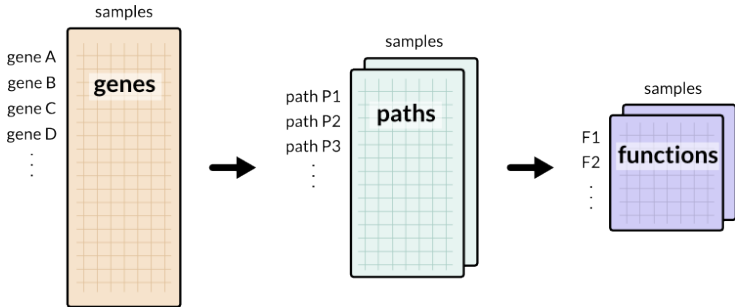
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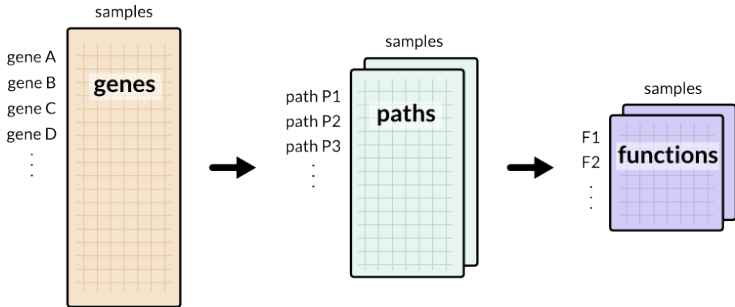
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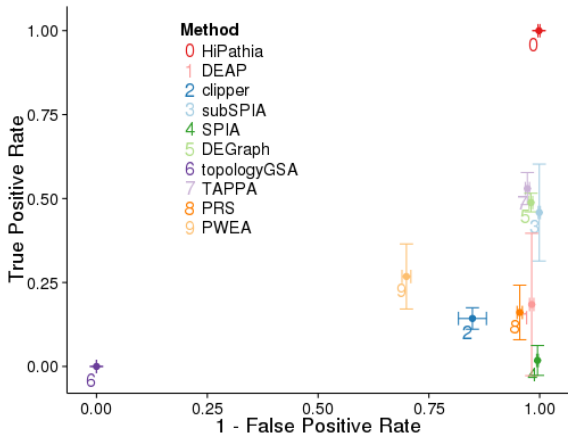


Functional annotation

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Method comparison





HiPathia

Web tool

Logging in

hipathia2.babelomics.org

hiPathia Pathways analysis suite Differential signaling Prediction Login Signup

hiPathia

HIGH THROUGHPUT PATHWAY
INFERENCE ANALYSIS

1 Start

2 3

hiPathia is a web tool for the interpretation 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 HTML 5 (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
Príncipe Felipe Research Center, Valencia, Spain
2016

Upload data

2 hiPathia Pathways analysis suite Differential signaling Prediction My data My jobs gta2016ciberer Profile Logout

3 Upload

1

hiPathia

HIGH THROUGHPUT PATHWAY
INFERENCE ANALYSIS

0B of 1.0 GB All Search by name...

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2016

Upload data

hiPathia Pathways analysis suite

Differential signaling Prediction

My data My jobs gda2016cberer Profile Logout

Browse My Data

gda2016cberer

Upload

Name Size Date

Exercise_1

See 24, 2016

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Príncipe Felipe Research Center, Valencia, Spain
2016

5 File upload: Selected file: None Revalidate

Choose file...

6 Bioformat: File validation log:

Data matrix expression

Variant (VCF)

Experimental design

Line Type Message 0%

Stop

Errors: 0 Warning: 0 Info: 0 Lines: 0

Upload

Workflow

2 hiPathia Pathways analysis suite Differential signaling Prediction My data My jobs gda2016ciberer Profile Logout

3 1

hiPathia

HIGH THROUGHPUT PATHWAY
INFERENCE ANALYSIS

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2016

Workflow

The screenshot shows the hiPathia Pathways analysis suite interface. The top navigation bar includes the hiPathia logo, the text "Pathways analysis suite", and tabs for "Differential signaling" and "Prediction". On the right side of the navigation bar, there are links for "My data", "My jobs", "Libraries", "Profile", and "Logout".

Callout 4 points to the "Function level analysis" section, which contains checkboxes for "Gene ontology" and "UniProt keywords".

Callout 5 points to the "Launch Job" button at the bottom of the "Job information" section.

Callout 6 points to the "My jobs" link in the top navigation bar.

Callout 7 points to the "My data" link in the top navigation bar.

Callout 8 points to the "Differential signaling example" job entry in the "Browse My Jobs" panel. The panel shows a list of jobs with columns for "Select tool", "Job name", and "Status". The "Differential signaling example" job is highlighted, showing it was completed on 1/27/2016 at 12:03:46 PM. The panel also includes a "Total: 2" summary and an "Enable job notifications" checkbox.

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

① Differential signaling

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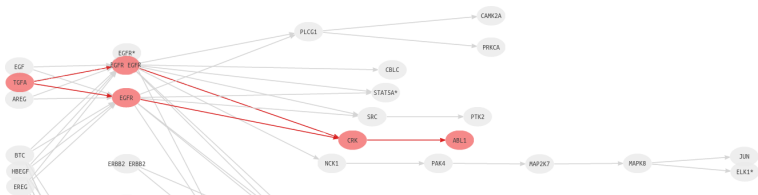
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Parameters

1 Parameters

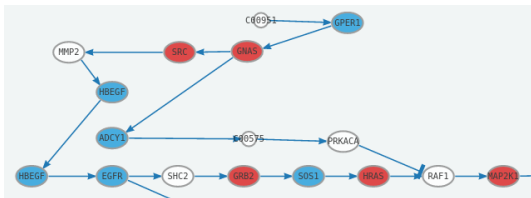
- Decompose paths
- Color nodes by differential expression



Parameters

1 Parameters

- Decompose paths
- Color nodes by differential expression



Parameters

The header features a teal background with overlapping circles on the left and a network diagram on the right. The network diagram consists of several grey nodes connected by lines, with some nodes having smaller grey circles attached to them, resembling a molecular or biological structure.

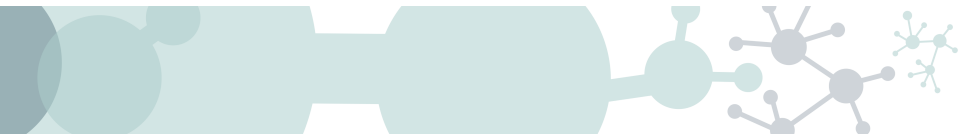
① Parameters

- Decompose paths
- Color nodes by differential expression

② Function level analysis

Perform analysis with the following functional annotations:

- Gene ontology
- Uniprot keywords



HiPathia

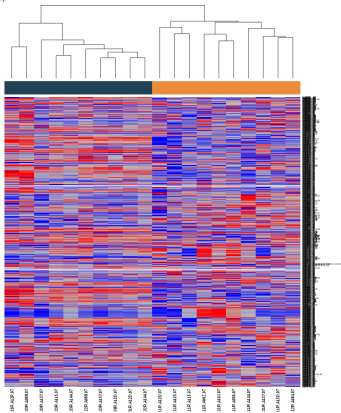
Results

Heatmap

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

Path values

- Path values
- Heatmap

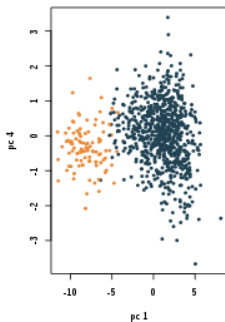
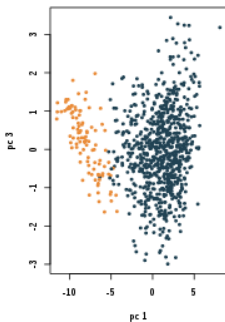
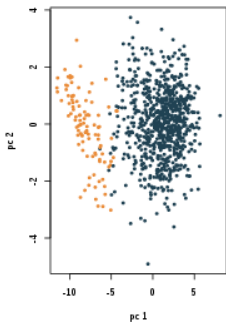


Principal Components Analysis (PCA)



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

Viewer

Pathways

Shape

Nodes

- Gene
- Molecule

Edges

- Inhibition
- Activation

Color

Down-regulated gene (DE)

Up-regulated gene (UE)

Down-regulated path

Up-regulated path

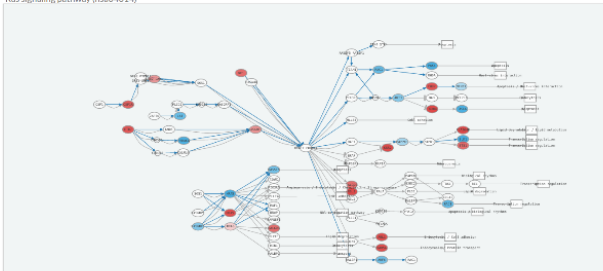
Not differentially regulated path

Stroke color

Gene expression

Expression

Ras signaling pathway (hsa04014)



1

Categories:

- MAPK signaling pathway
- EGFR signaling pathway
- Notch signaling pathway
- Chemokine signaling pathway
- Wnt signaling pathway
- Pathways overview
- PI3K-Akt signaling pathway
- Platelet activation
- PPAR signaling pathway
- Prostaglandin-mediated cyclooxygenase regulation
- Proteoglycan in cancer
- Rap1 signaling pathway
- Ras signaling pathway**
- BCR signaling pathway
- IGF1R signaling pathway
- IGF1R signaling pathway
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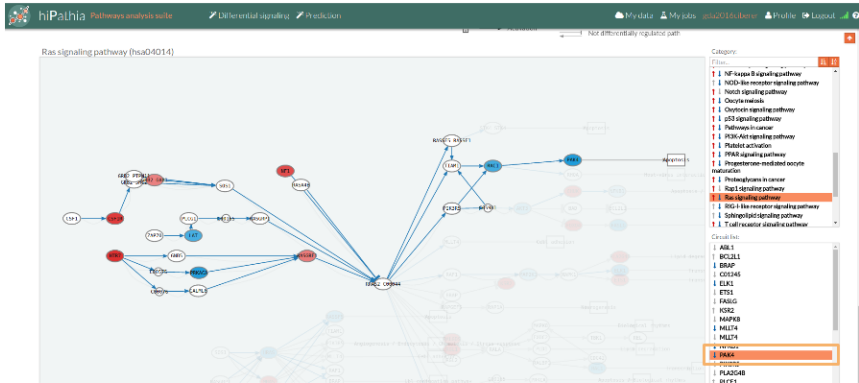
2

Genes:

- ABL1
- BCR
- EGFR
- ERK1
- ERK2
- FABP3
- IRS1
- MAPK1

3

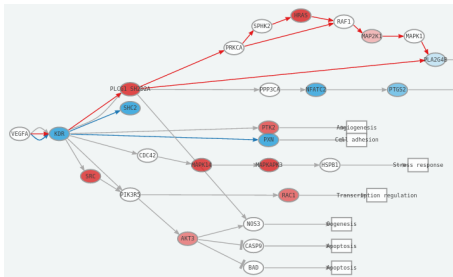
Viewer

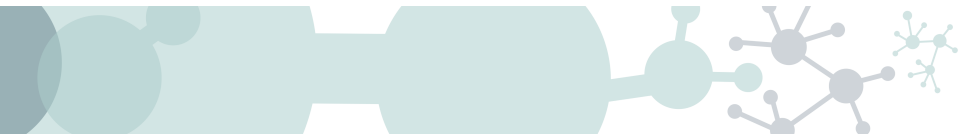


Viewer



Viewer



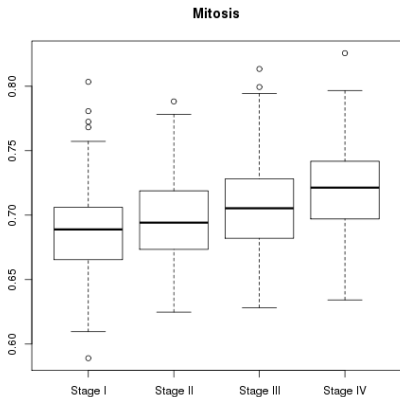


HiPathia

Further analysis

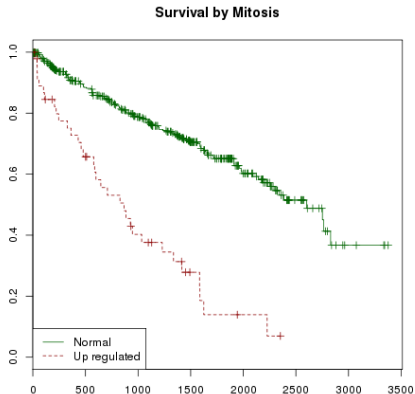
Disease progression analysis

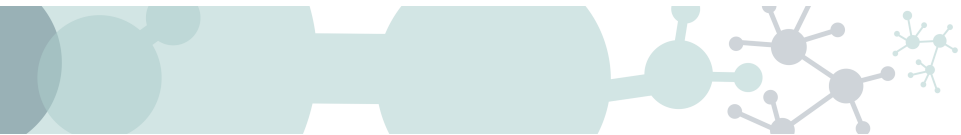
Search for features which increase with the progression of the disease



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](#)