HiPathia
Models of signaling pathway activity

Marta R. Hidalgo

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Bioestadística

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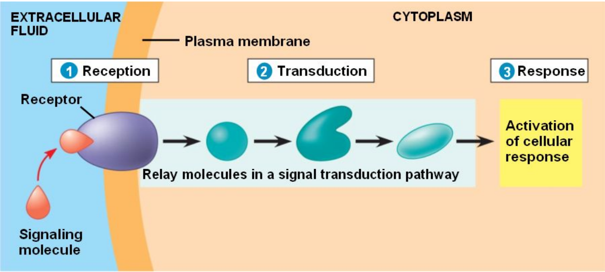
WODA
WEB-BASED OMICS DATA ANALYSIS

Signaling pathways



Chemical signals

- Hormones
- Neurotransmiters
- Growth factors
- Cytokines
- Drugs

Activation & Inhibition

- Phosphorilation
- Dephosphorilation
- Glycosylation
- Ubiquitination
- Methylation

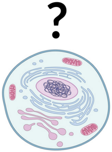
Cellular Function

- Apoptosis
- Survival
- Growth
- Migration
- Proliferation

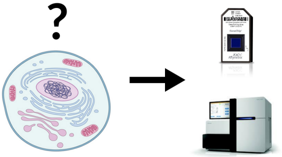
Pathway Analysis

Methods

From cell to pathways

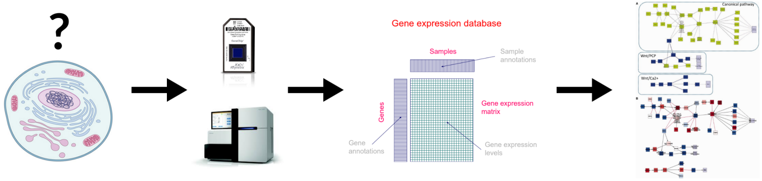


From cell to pathways



From cell to pathways

From cell to pathways



Gene expression database

Samples

Sample annotations

Genes

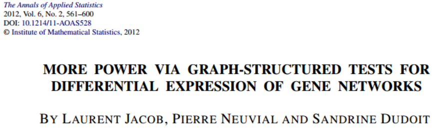
Gene expression matrix

Gene annotations

Gene expression levels

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
© Institute of Mathematical Statistics, 2012

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

BY LAURENT JACOB, PIERRE NEUVIAL AND SANDRINE DUDOIT

Pathway methods

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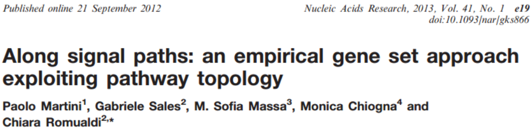

Published online 21 September 2012

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

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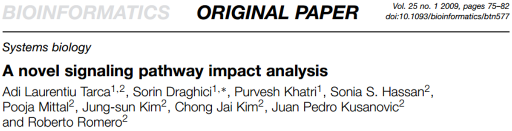

BIOINFORMATICS **ORIGINAL PAPER** Vol. 25 no. 1 2009, pages 75–82
doi:10.1093/bioinformatics/btn577

Systems biology

A novel signaling pathway impact analysis

Adi Laurentiu Tarca[1,2], Sorin Draghici[1,*], Purvesh 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]

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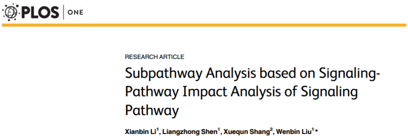

PLOS | ONE

RESEARCH ARTICLE

Subpathway Analysis based on Signaling-Pathway Impact Analysis of Signaling Pathway

Xianbin Li[1], Liangzhong Shen[1], Xuequn Shang[2], Wenbin Liu[1]*

Pathway methods

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

Research Paper

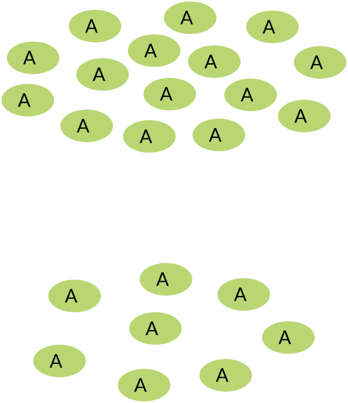
High throughput estimation of functional cell activities reveals disease mechanisms and predicts relevant clinical outcomes

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

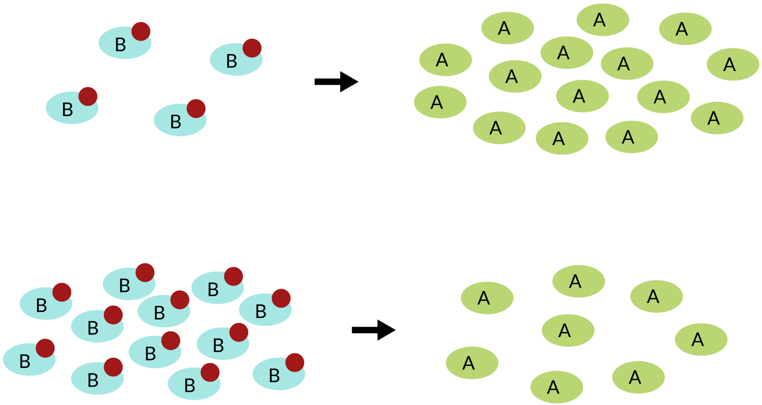
Pathway Analysis

HiPathia

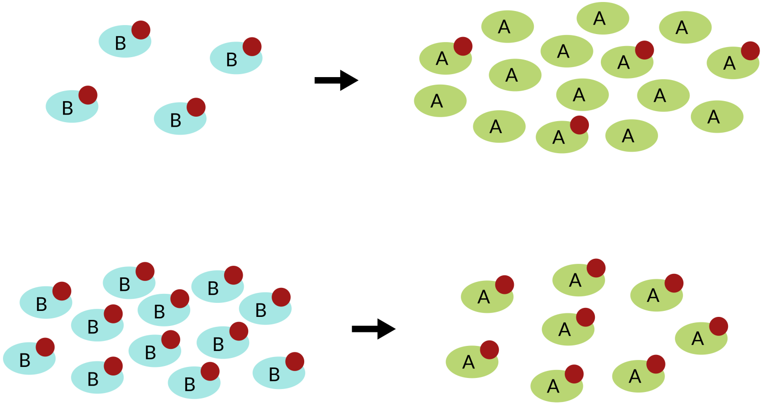
Intuitive idea



Intuitive idea

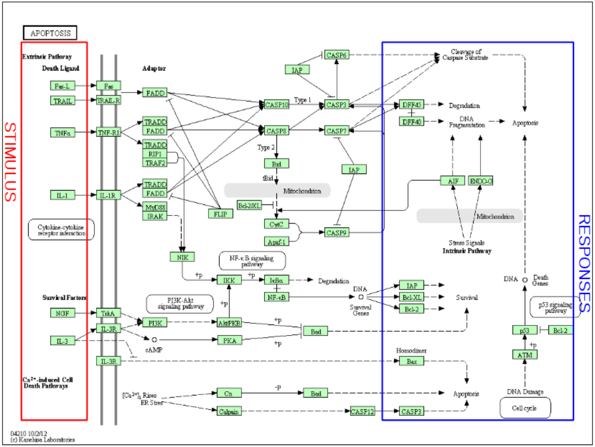


Intuitive idea



Pathways layout

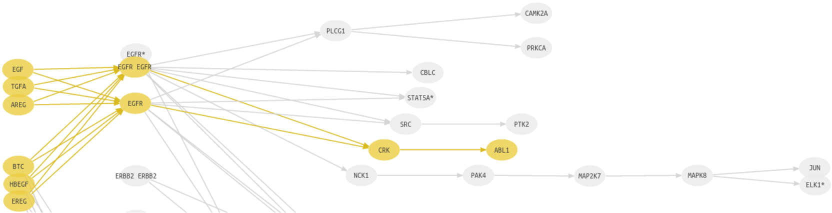
Take pathways information from KEGG, www.kegg.jp



Meaningful subpathways

Effector subpathway

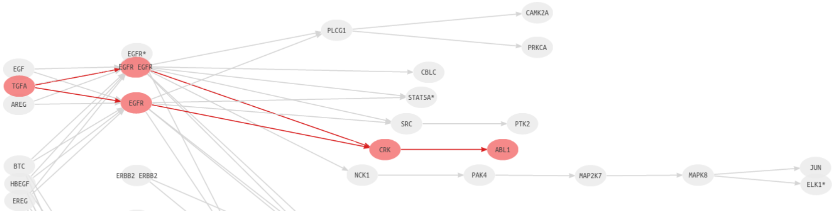
Subpathway including any node from any receptor to one effector protein



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

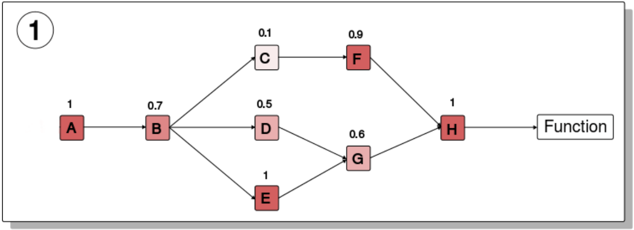
$$S_n = v_n \cdot (1 - \prod_{s_i \in A}(1-s_i)) \cdot \prod_{s_j \in I}(1-s_j)$$

S_n: Signal value through n

v_n: Node value

A: Activation edges

I: Inhibition edges



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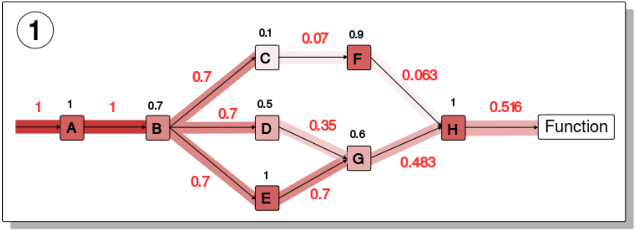

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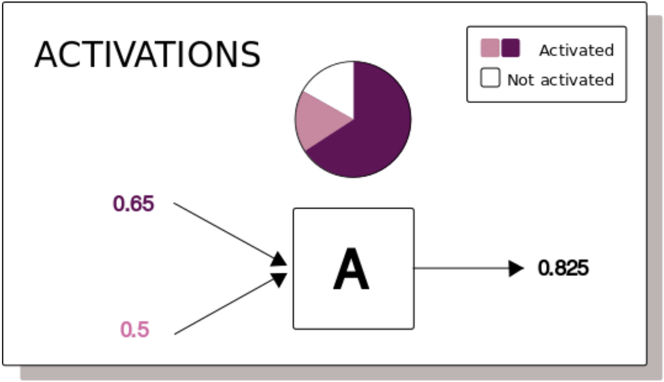

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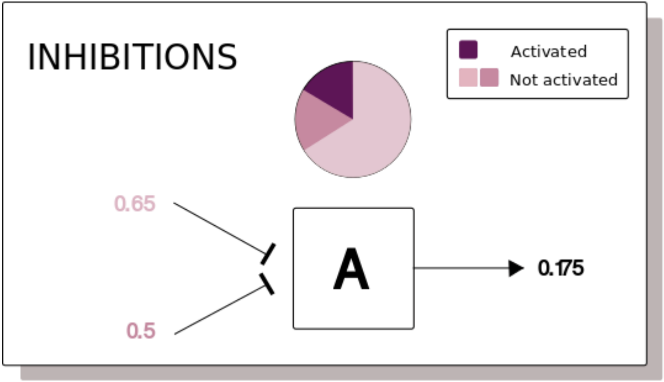
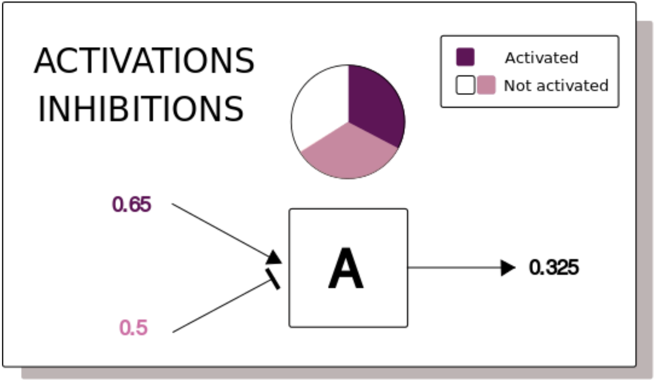
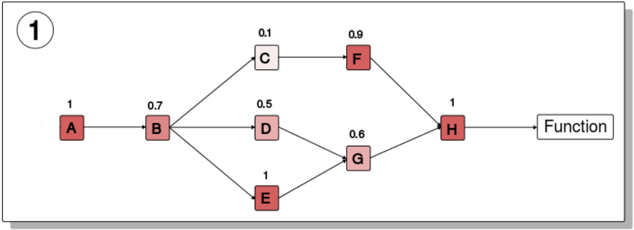


Computing the signal



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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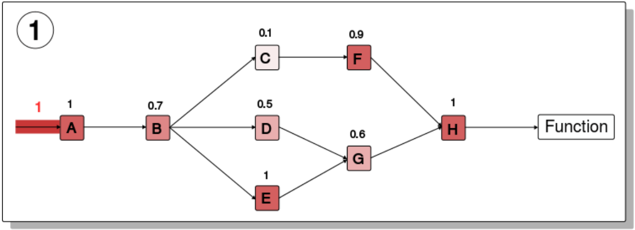

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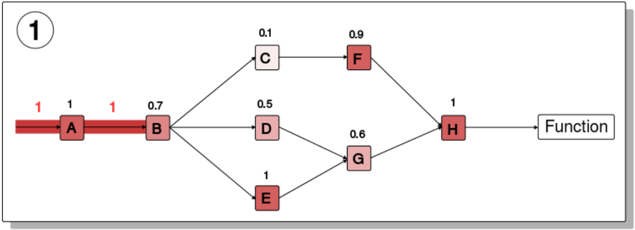

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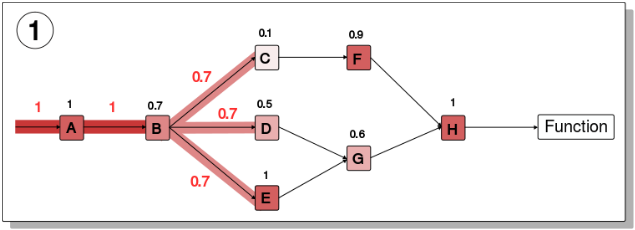

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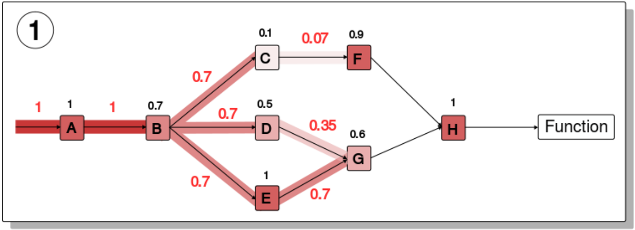

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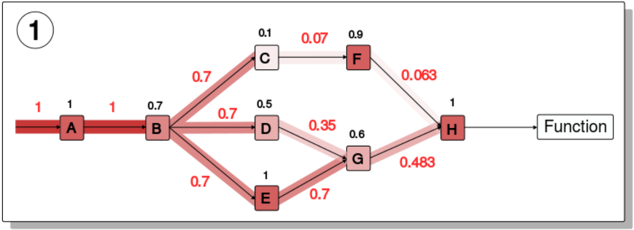

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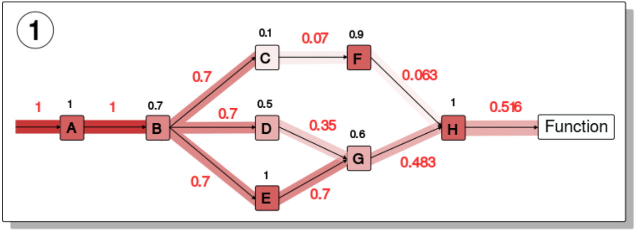
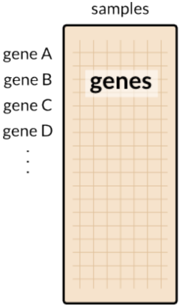


Functional annotation

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



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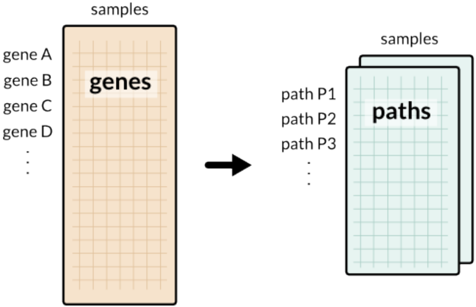

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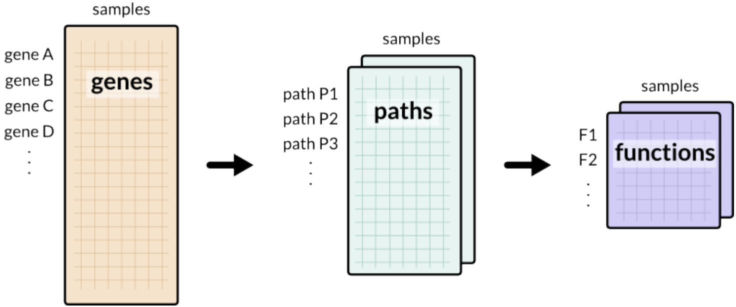
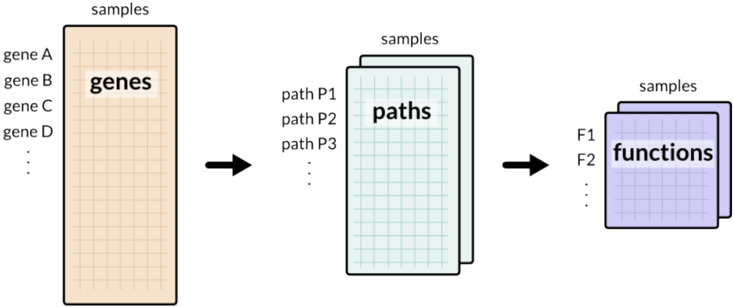


Functional annotation

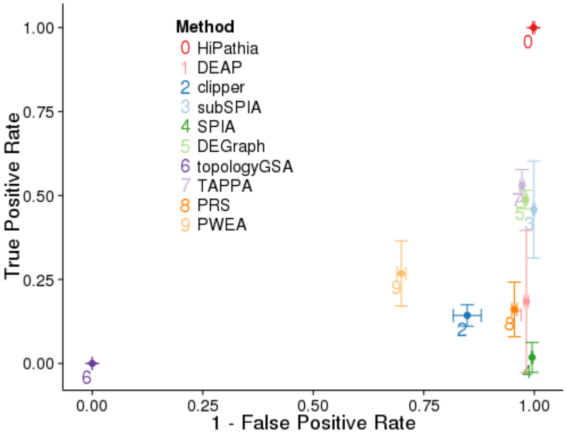
① Estimate effector proteins activation

② Annotate effector proteins functions

- Uniprot keywords
- GO annotation



Method comparison



HiPathia

Web tool

Logging in

hipathia2.babelomics.org

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 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

HIGH THROUGHPUT PATHWAY INFERENCE ANALYSIS

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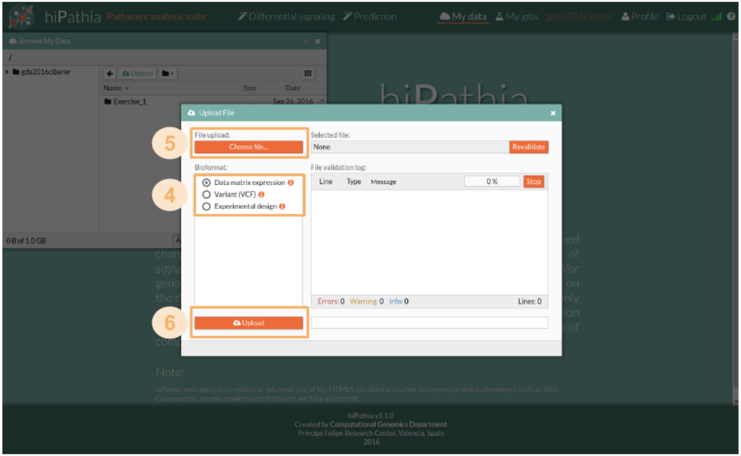

File upload:

Selected file: None

Bioformat:

- ● Data matrix expression
- ○ Variant (VCF)
- ○ Experimental design

File validation log:

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

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Workflow

hiPathia

HIGH THROUGHPUT PATHWAY
INFERENCE ANALYSIS

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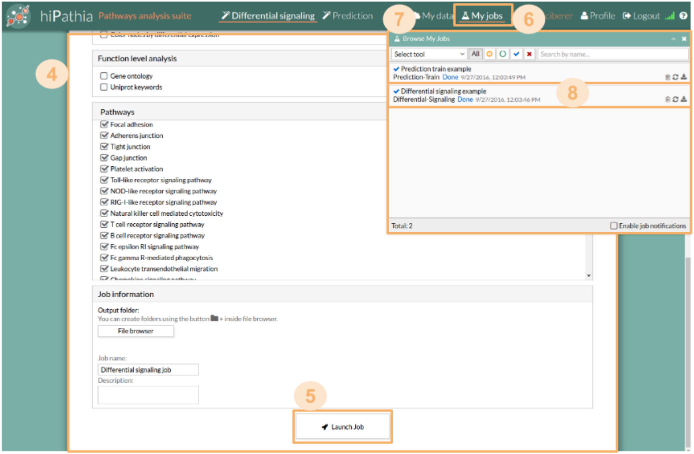

Function level analysis

☐ 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.

Job name: Differential signaling job
Description:

✓ 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

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
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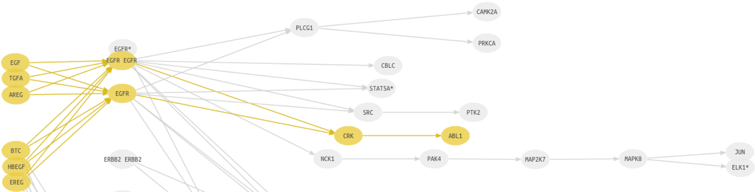
Parameters

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



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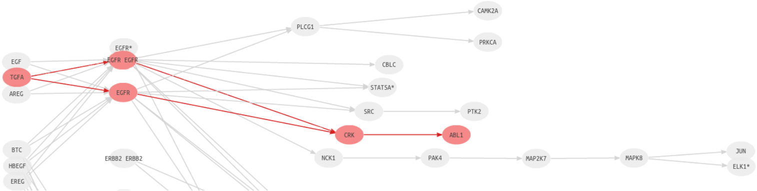

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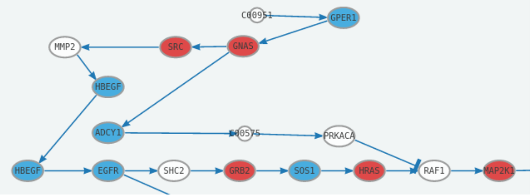


Parameters

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

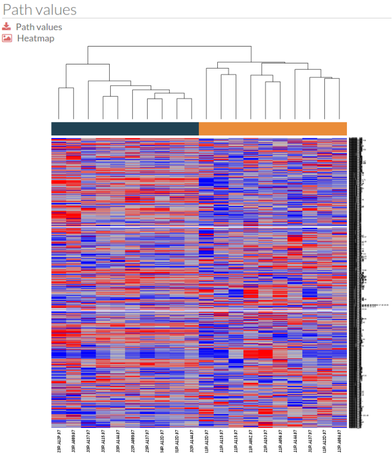
2. **Function level analysis**
   Perform analysis with the following functional annotations:
   - Gene ontology
   - Uniprot keywords

HiPathia

Results

Heatmap

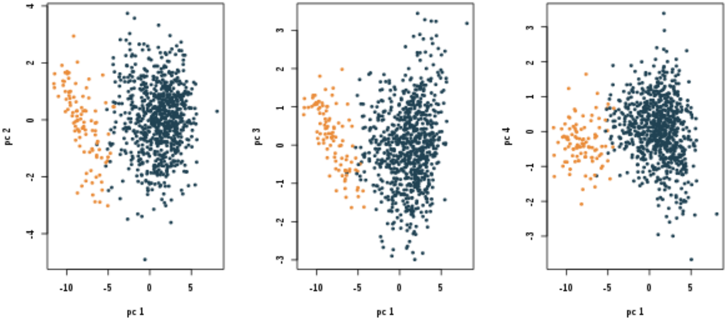
Graphical representation of data where values in a matrix are represented as colors



Principal Components Analysis (PCA)

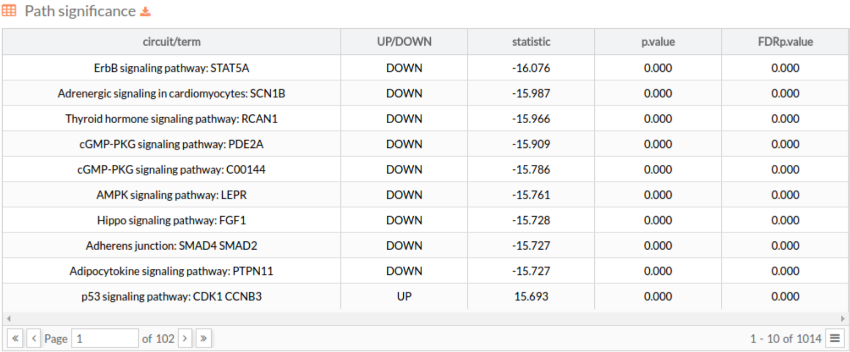
Statistical procedure to convert a set of observations into a set of values of linearly uncorrelated variables

PCA



Results table

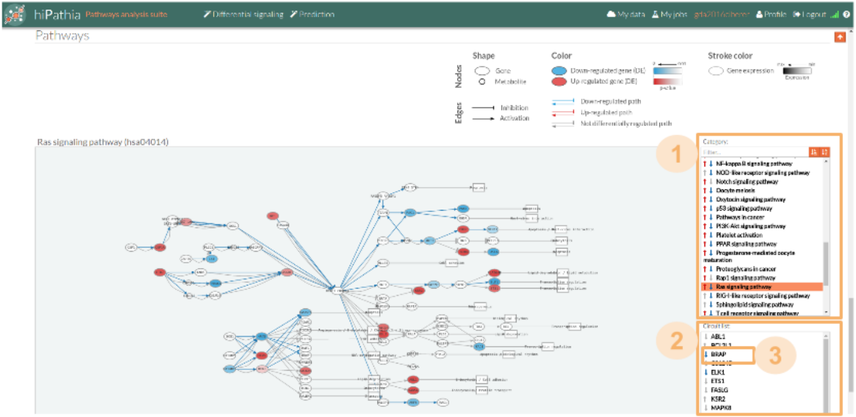
- Table of results for the comparison.
- Ordered by the FDR p-value.



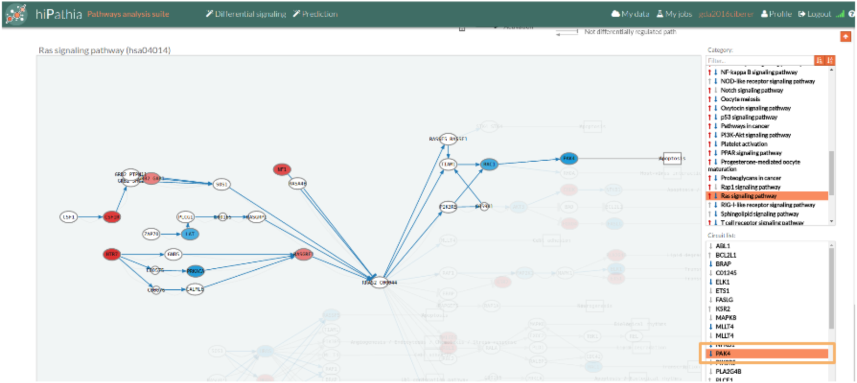
Path significance

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

Viewer


hiPathia Pathways analysis suite
Differential signaling
Prediction
My data
My jobs
Profile
Logout
Pathways
Shape
Nodes
Gene
Metabolite
Edges
Inhibition
Activation
Color
Down-regulated gene (DE)
Up-regulated gene (DE)
p-value
Down-regulated path
Up-regulated path
Not differentially regulated path
Stroke color
Gene expression
Expression
Ras signaling pathway (hsa04014)
1
Category:
Filter...
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
BCL2L1
BRAP
3
ELK1
ETS1
FASLG
KSR2
MAPK8

Viewer



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:

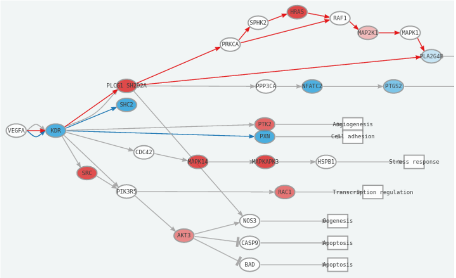
- ↓ ABL1
- ↑ BCL2L1
- ↓ BRAP
- ↓ C01245
- ↓ ELK1
- ↓ ETS1
- ↓ FASLG
- ↑ KSR2
- ↓ MAPK8
- ↓ MLLT4
- ↓ MLLT4
- ↓ PAK4
- ↓ PLA2G4B

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

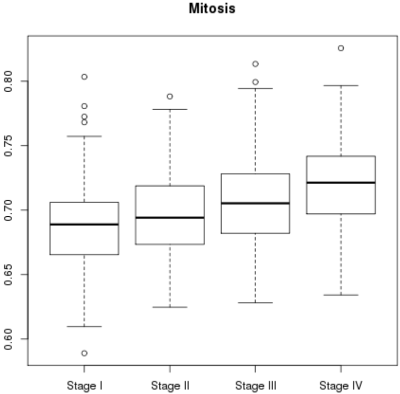

VEGFA
KDR
PLCG1
SH2D2A
SHC2
SRC
PIK3R5
CDC42
PRKCA
SPHK2
HRAS
RAF1
MAP2K1
MAPK1
PLA2G4B
PPP3CA
NFATC2
PTGS2
PTK2
PXN
Angiogenesis
Cell adhesion
MAPK14
MAPKAPK3
HSPB1
Stress response
RAC1
Transcription regulation
AKT3
NOS3
Oogenesis
CASP9
Apoptosis
BAD
Apoptosis

HiPathia

Further analysis

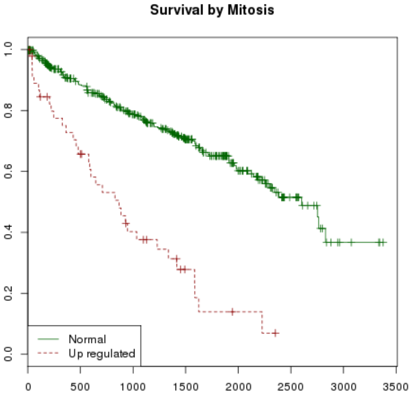
Disease progression analysis

Search for features which increase with the progression of the disease



Survival analysis

Analysis of time duration until one or more events happen



Neuroblastoma

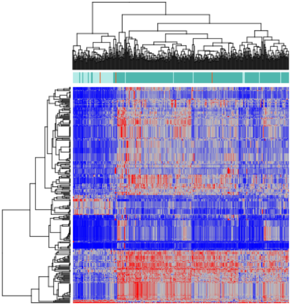
- Tumor derivado de células primitivas del sistema nervioso simpático
- Poca supervivencia para pacientes de alto riesgo
    - Estadio de la enfermedad
    - Edad del paciente
    - Amplificación de MYCN

Comparación MYCN - No MYCN

Comparación de expresión entre individuos con y sin amplificación de MYCN

Pacientes con MYCN:

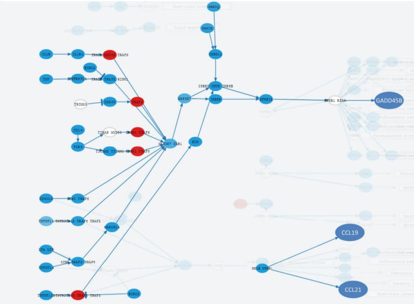
- inhibición de apoptosis a través de la ruta JNK [Fey, Sci Signal 2015]
- problemas de reparación de ADN



Hidalgo et al. 2018, Biology Direct

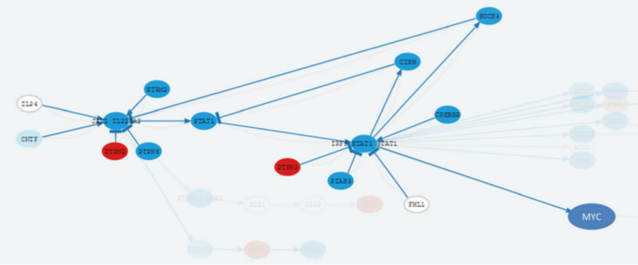
Inhibición ruta JNK

Circuit (Pathway and effector protein)	Status	FDR *p*-value	GO ID	GO Definition
Ras signaling pathway: MAPK8	DOWN	4.31E-29	GO:0007254	JNK cascade
Fc epsilon RI signaling pathway: MAPK8	DOWN	1.23E-15	GO:0007254	JNK cascade
cAMP signaling pathway: MAPK8	DOWN	4.72E-08	GO:0007254	JNK cascade
Apoptosis: GADD45G	DOWN	1.07E-29	GO:0046330	positive regulation of JNK cascade
MAPK signaling pathway: MAP 4 K2	DOWN	1.68E-24	GO:0046330	positive regulation of JNK cascade
NF-kappa B signaling pathway: CCL19	DOWN	2.36E-22	GO:0046330	positive regulation of JNK cascade
NF-kappa B signaling pathway: GADD45B	DOWN	3.83E-21	GO:0046330	positive regulation of JNK cascade
NF-kappa B signaling pathway: CCL21	DOWN	8.43E-16	GO:0046330	positive regulation of JNK cascade
p53 signaling pathway: GADD45G	UP	1.70E-07	GO:0046330	positive regulation of JNK cascade



Reparación de ADN

Circuit (Pathway and effector protein)	Status	FDR p-value	GO ID	GO Definition
Jak-STAT signaling pathway: MYC	DOWN	1.94E-32	GO:2001022	positive regulation of response to DNA damage stimulus
MAPK signaling pathway: MYC	DOWN	1.39E-26	GO:2001022	positive regulation of response to DNA damage stimulus
ErbB signaling pathway: MYC	DOWN	7.15E-24	GO:2001022	positive regulation of response to DNA damage stimulus
Wnt signaling pathway: MYC	DOWN	7.78E-22	GO:2001022	positive regulation of response to DNA damage stimulus
Hippo signaling pathway: MYC	DOWN	7.12E-13	GO:2001022	positive regulation of response to DNA damage stimulus
Jak-STAT signaling pathway: MYC	DOWN	1.94E-32	GO:0006338	chromatin remodeling
MAPK signaling pathway: MYC	DOWN	1.39E-26	GO:0006338	chromatin remodeling
ErbB signaling pathway: MYC	DOWN	7.15E-24	GO:0006338	chromatin remodeling
Wnt signaling pathway: MYC	DOWN	7.78E-22	GO:0006338	chromatin remodeling
Hippo signaling pathway: MYC	DOWN	7.12E-13	GO:0006338	chromatin remodeling



Supervivencia

Supervivencia en pacientes de NB

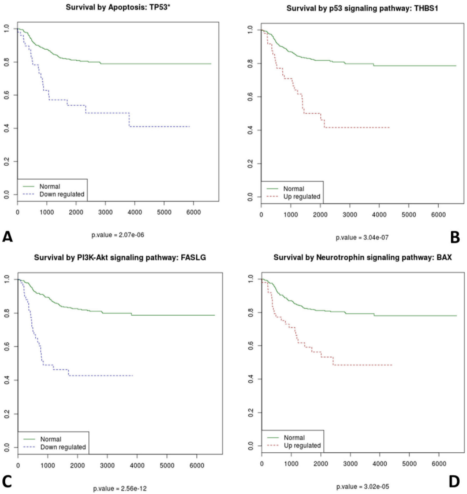
- 10% más UP contra resto
- 10% más DOWN contra el resto

- Kaplan-Meyer plots
- X^2 test

Supervivencia

Inhibición apoptosis

Metástasis



Angiogénesis

Evasión sistema inmune

Hipathia

hiPathia

HIGH THROUGHPUT PATHWAY
INFERENCE ANALYSIS

- hipathia.babelomics.org/
- Paquete Bioconductor Hipathia
- Contacta con nosotros! ubb@cipf.es

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