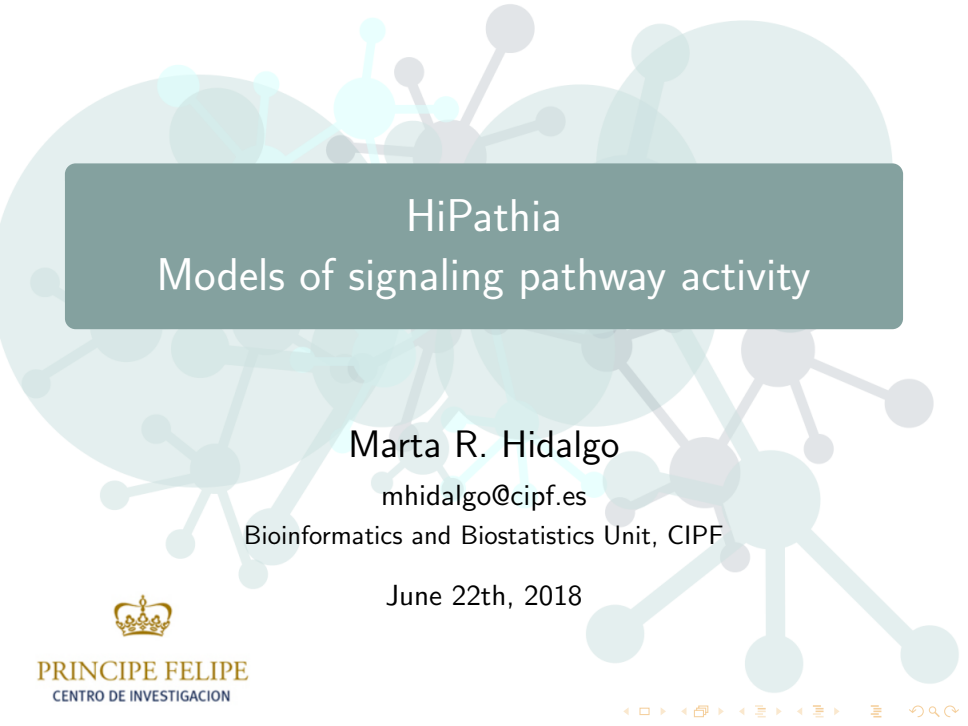




# HiPathia

## Models of signaling pathway activity

Marta R. Hidalgo

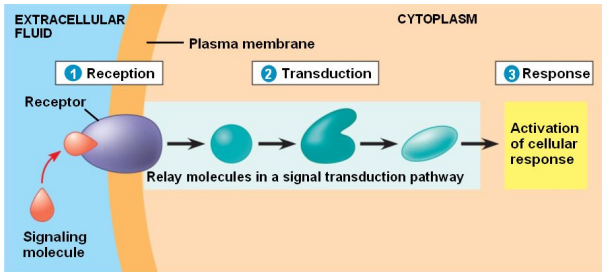
[mhidalgo@cipf.es](mailto:mhidalgo@cipf.es)

Bioinformatics and Biostatistics Unit, CIPF

June 22th, 2018



# Signaling pathways



## Chemical signals

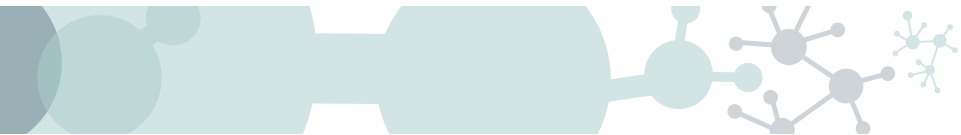
- Hormones
- Neurotransmitters
- Growth factors
- Cytokines
- Drugs

## Activation & Inhibition

- Phosphorilation
- Dephosphorilation
- Glycosylation
- Ubiquitination
- Methylation

## Cellular Function

- Apoptosis
- Survival
- Growth
- Migration
- Proliferation



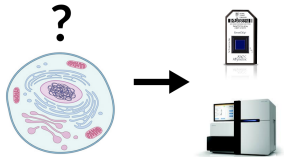
# Pathway Analysis

HiPathia

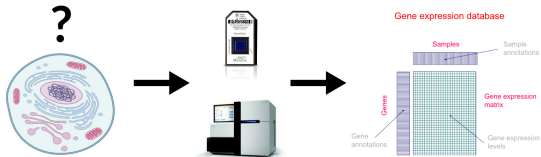
# From cell to pathways



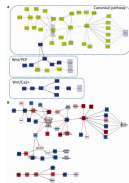
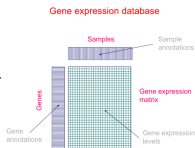
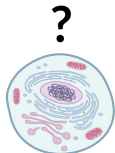
# From cell to pathways



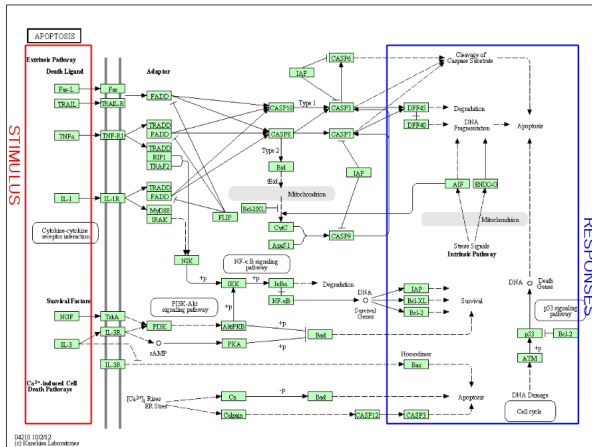
# From cell to pathways



# From cell to pathways



## Take pathways information

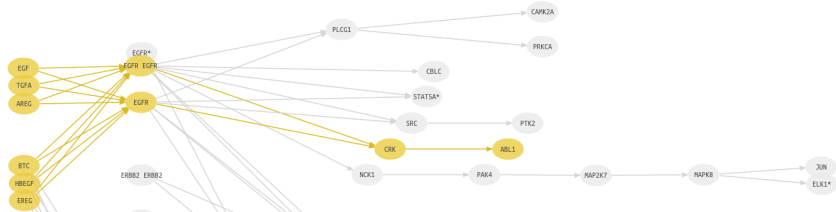




# Meaningful subpathways

## 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  $n$

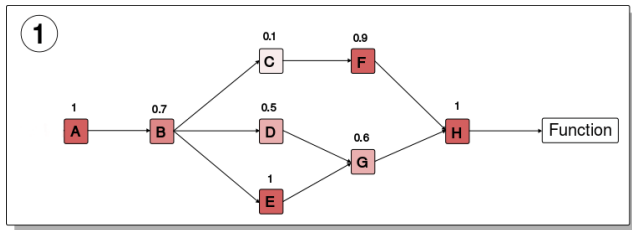
$$S_n = v_n \cdot \left(1 - \prod_{s_i \in A} (1 - s_i)\right) \cdot \prod_{s_j \in I} (1 - s_j)$$

$S_n$ : Signal value through  $n$

$v_n$ : Node value

$A$ : Activation edges

$I$ : Inhibition edges



# Computing the signal

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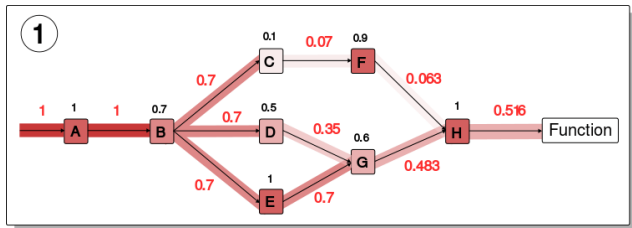
$$S_n = v_n \cdot \left(1 - \prod_{s_i \in A} (1 - s_i)\right) \cdot \prod_{s_j \in I} (1 - s_j)$$

$S_n$ : Signal value through  $n$

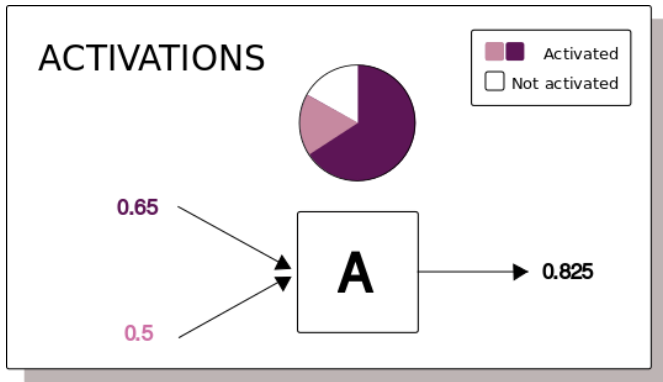
$v_n$ : Node value

$A$ : Activation edges

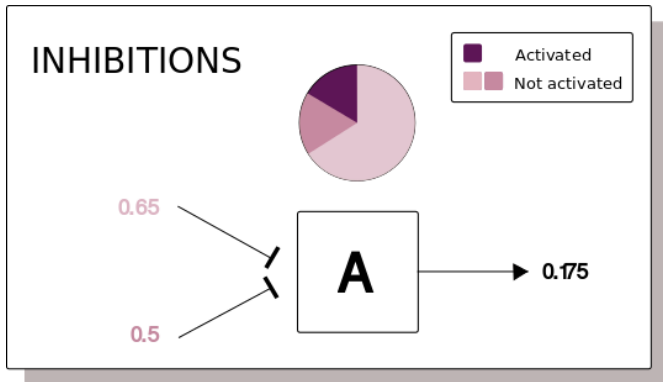
$I$ : Inhibition edges



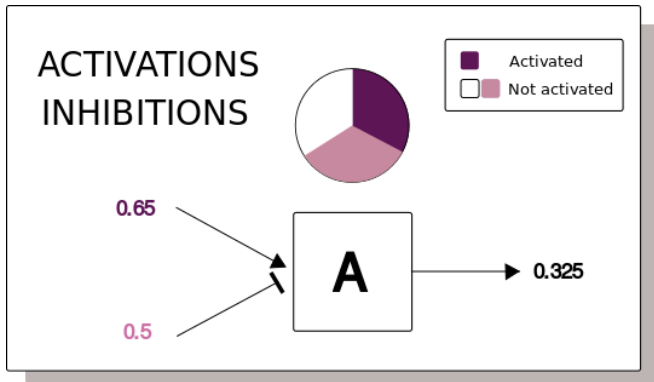
# Computing the signal



# Computing the signal

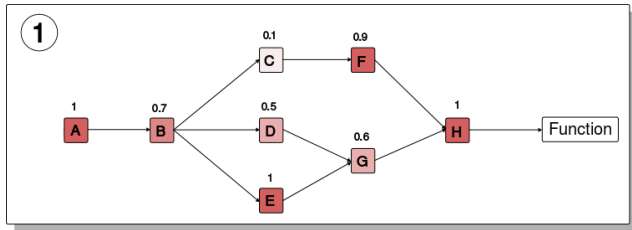


# Computing the signal



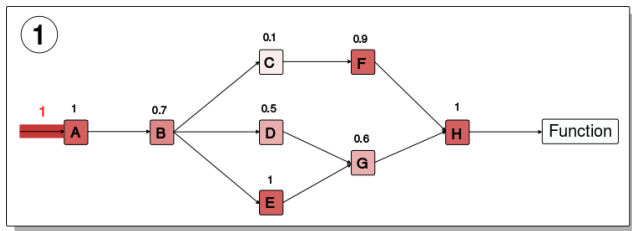
# Signal values

- 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

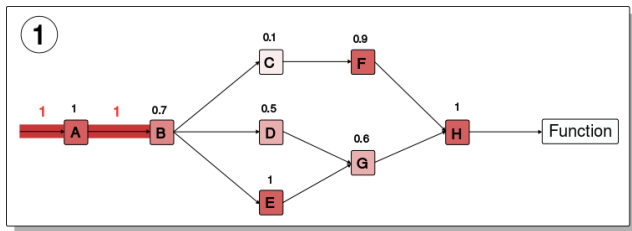
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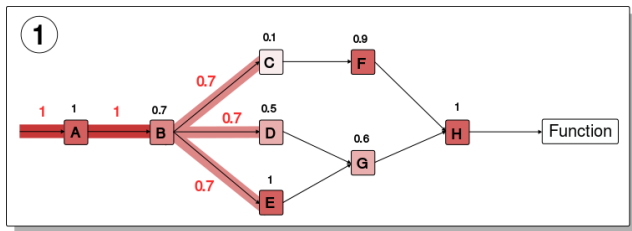
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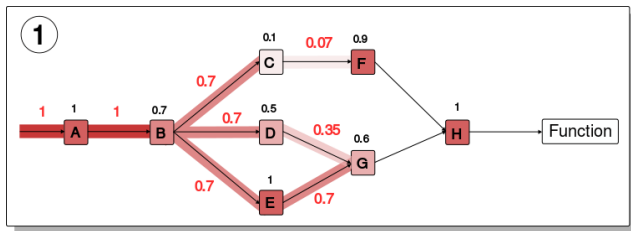
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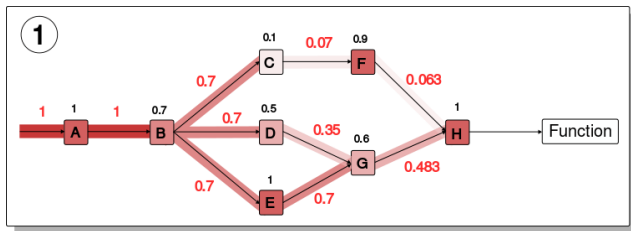
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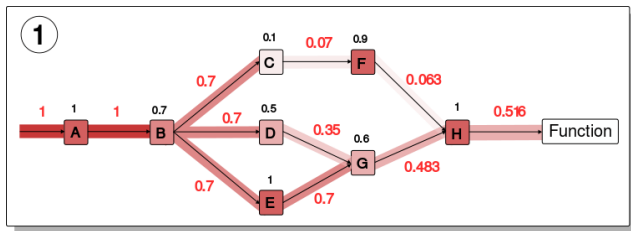
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# Functional annotation

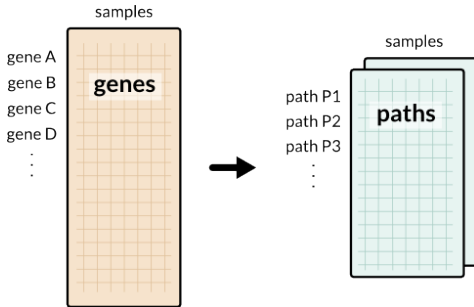


- 1 Estimate effector proteins activation
- 2 Annotate effector proteins functions
  - Uniprot keywords
  - GO annotation

|        | samples                 |
|--------|-------------------------|
| gene A | <div><b>genes</b></div> |
| gene B |                         |
| gene C |                         |
| gene D |                         |
| ⋮      |                         |

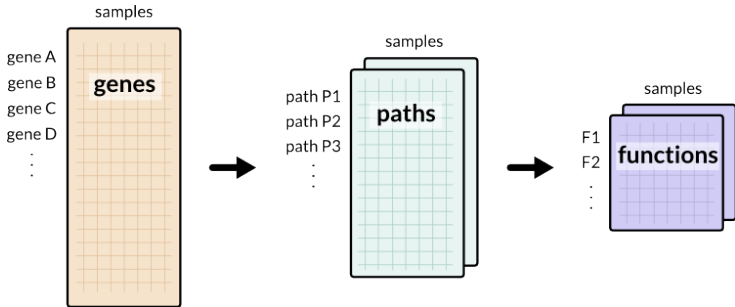
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# Functional annotation

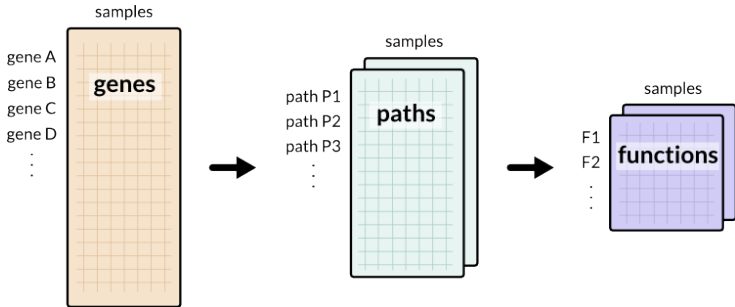
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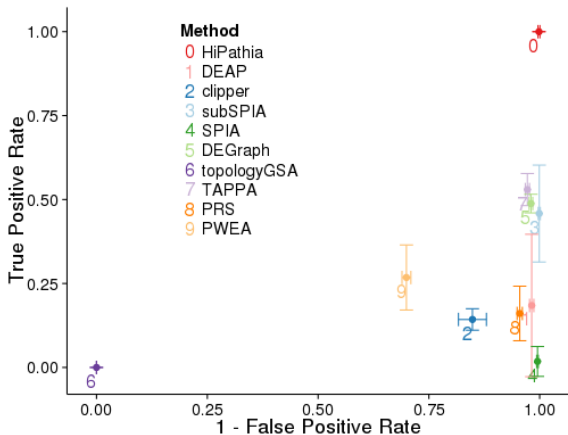


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# Method comparison



# Hipathia Web Tool

[hipathia-course.clinbioinfospa.es](http://hipathia-course.clinbioinfospa.es)

hiPathia Pathways analysis suite Differential signaling Prediction Login Sign up

## 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