Tutorial for High Throughput pathway interpretation and analysis

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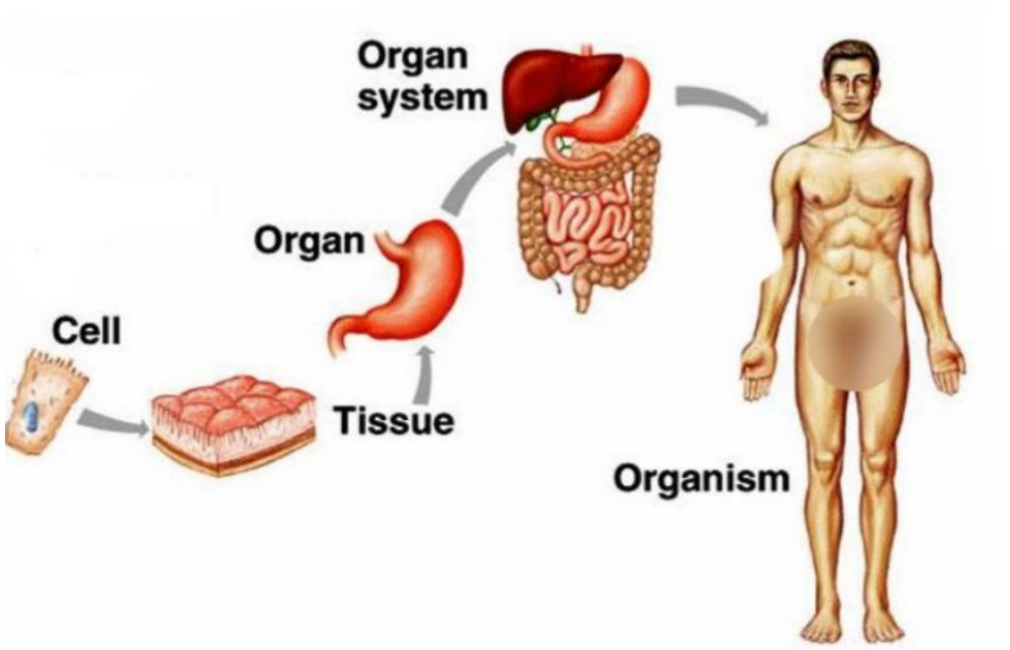
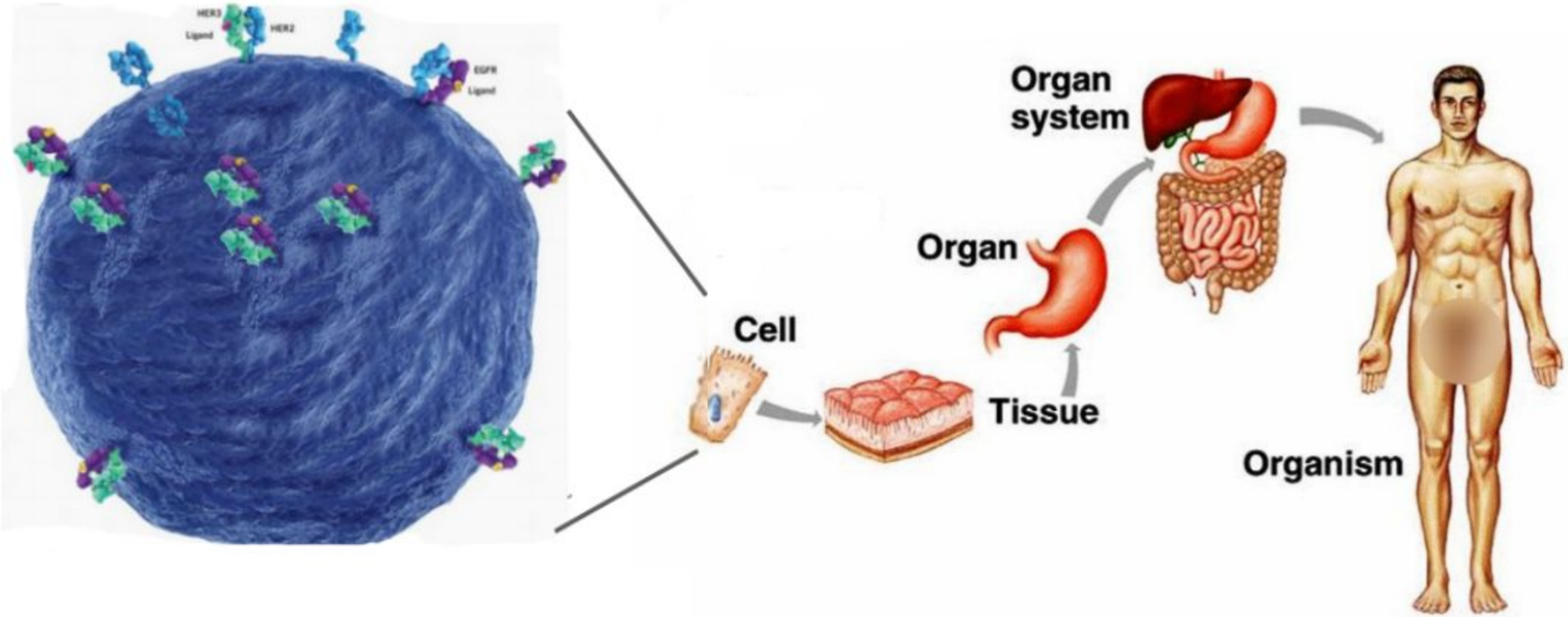
Introduction

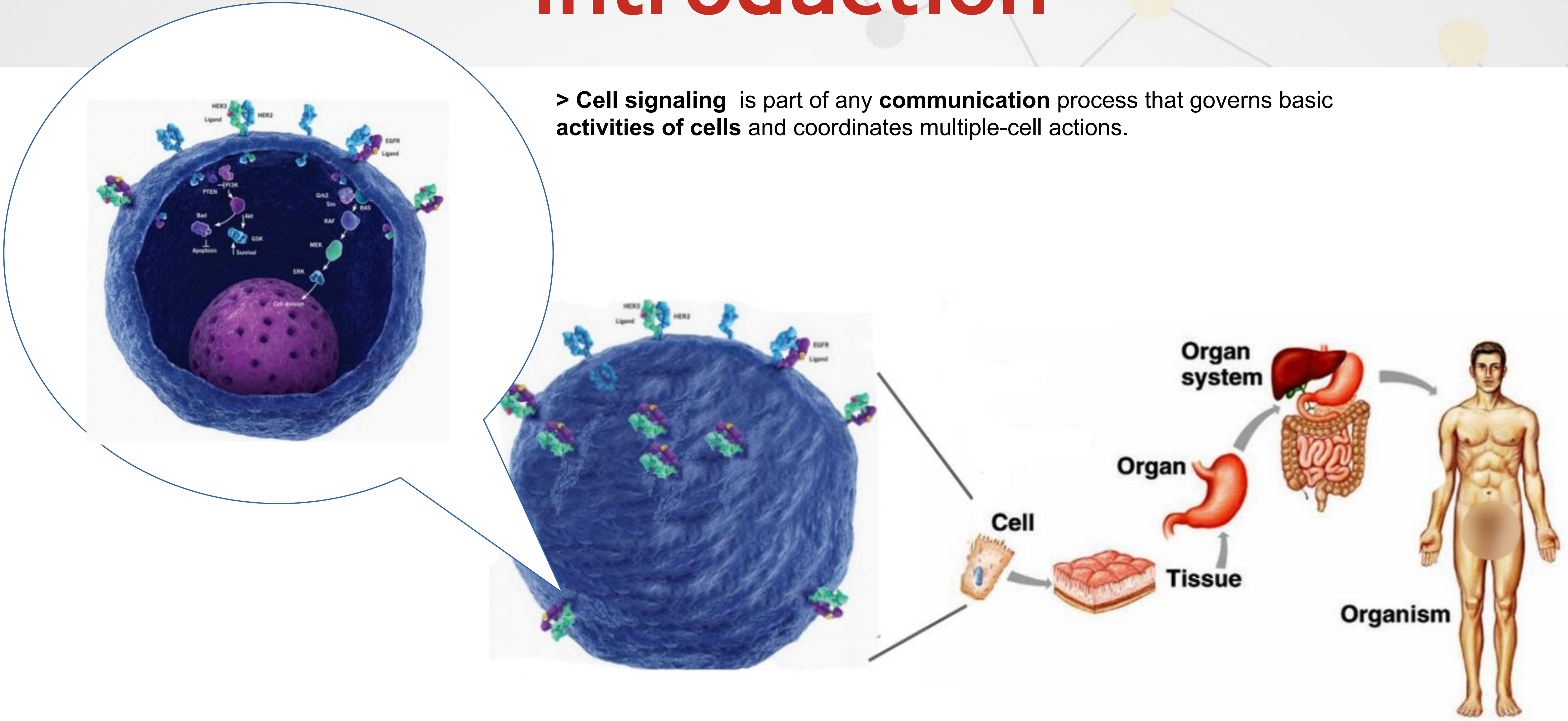


Introduction

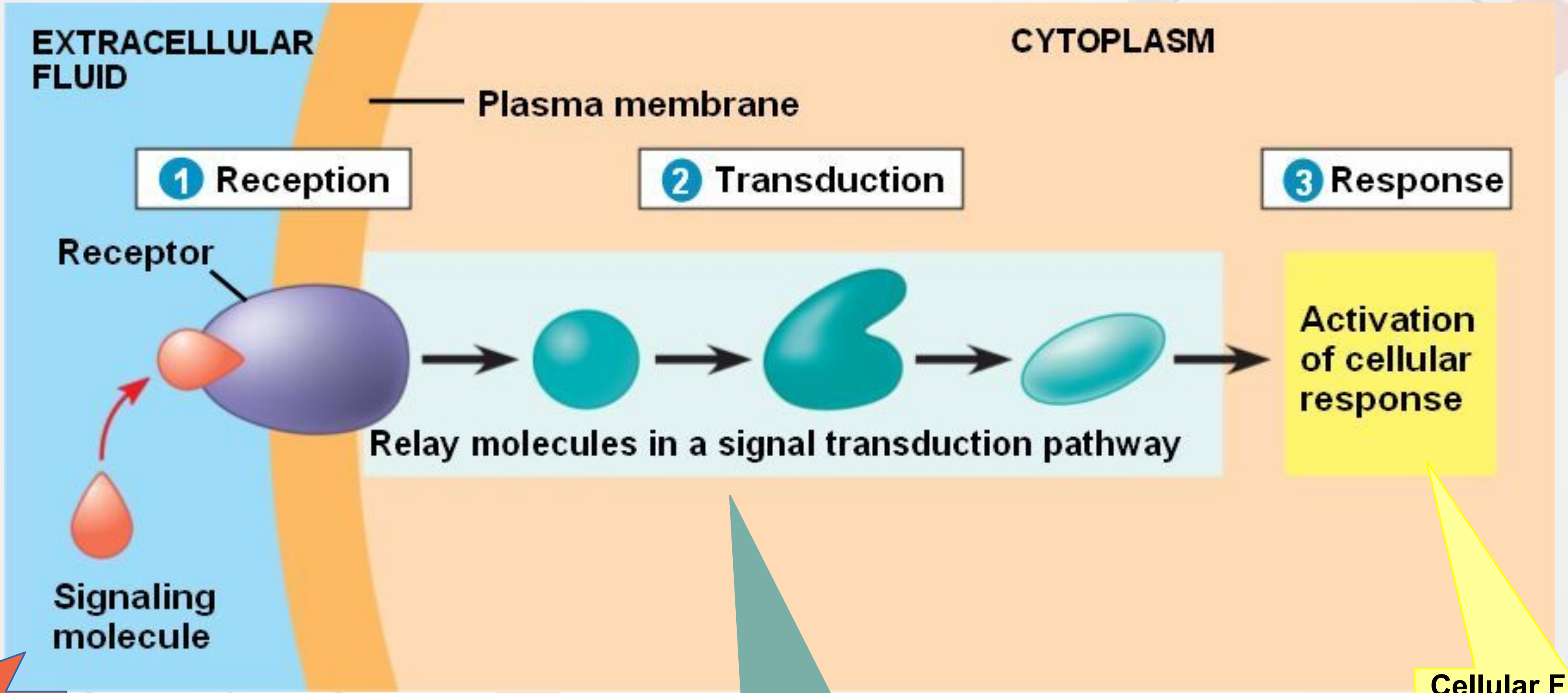


Introduction

> **Cell signaling** is part of any **communication** process that governs basic **activities of cells** and coordinates multiple-cell actions.



Signaling pathway



Chemical signals

- Hormones
- Neurotransmiters
- Growth factors
- Cytokines
- Drugs

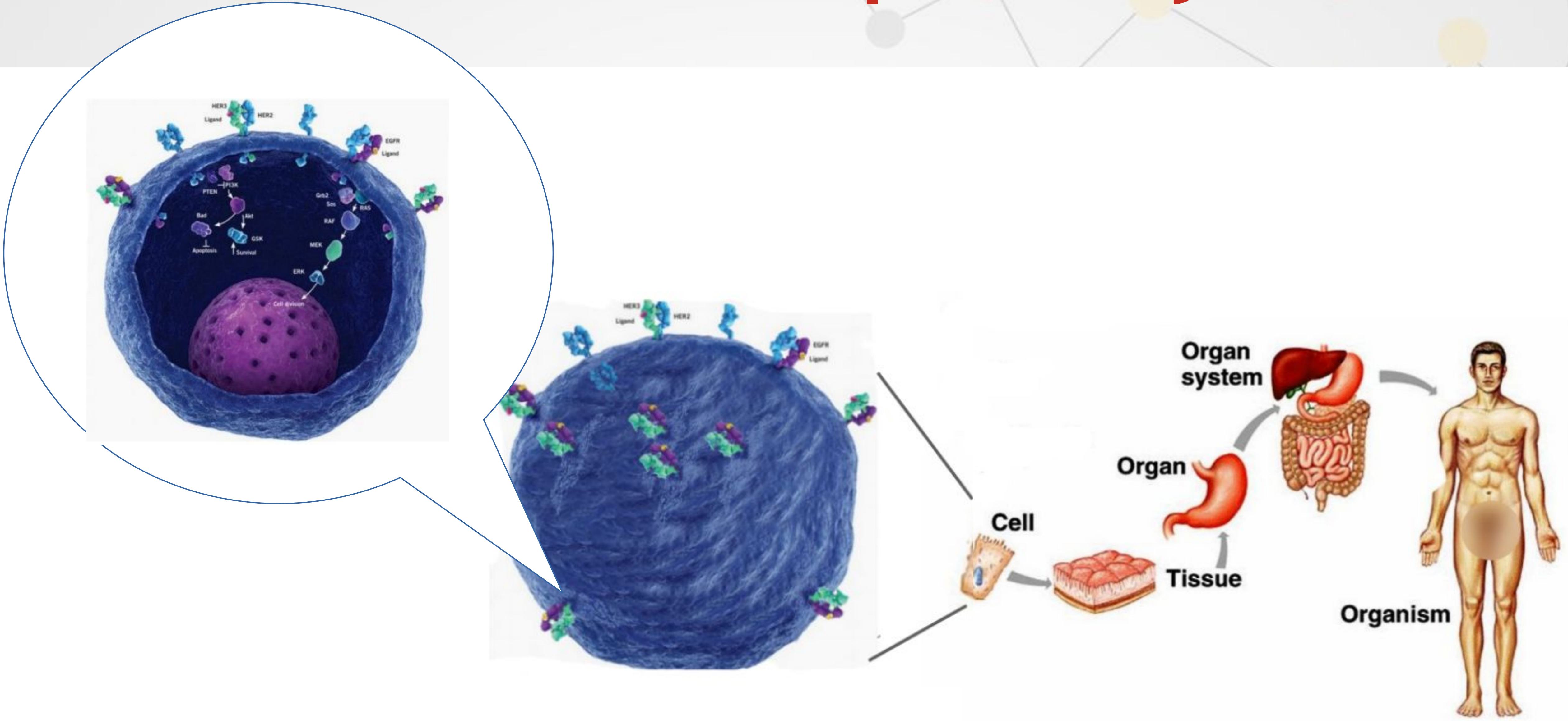
Activation & Inhibition

- Phosphorilation
- Dephosphorilation
- Glycosylation
- Ubiquitination
- Methylation

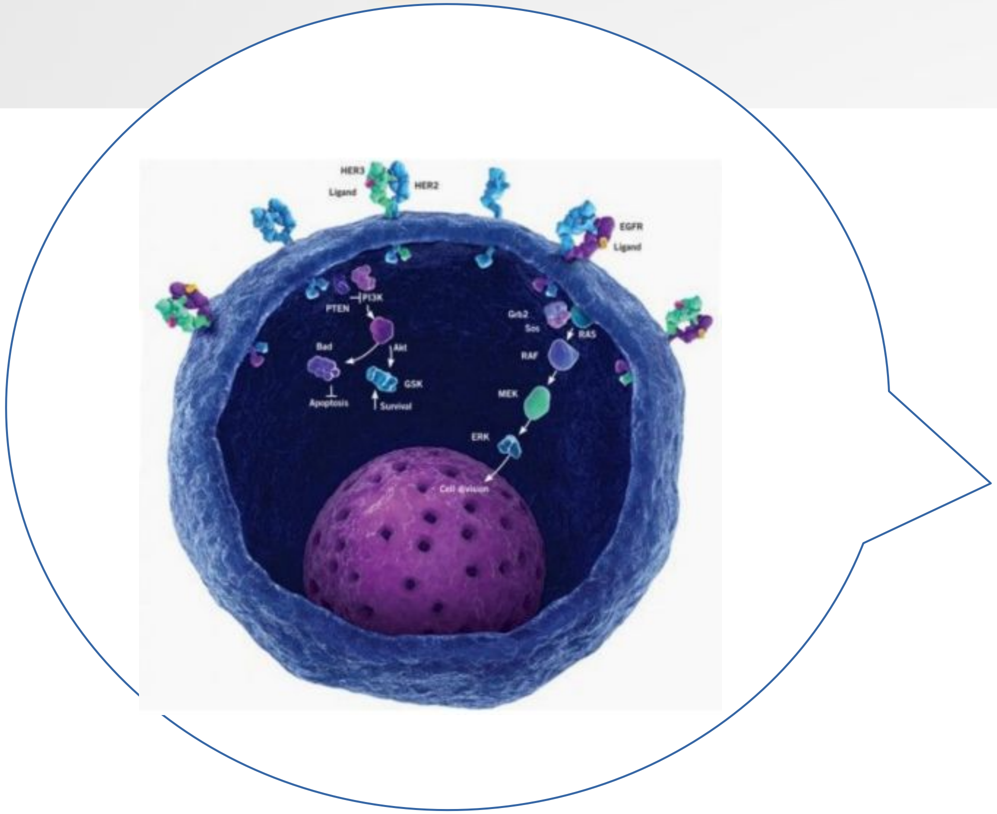
Cellular Function

- Apoptosis
- Survival
- Growth
- Migration
- Proliferation

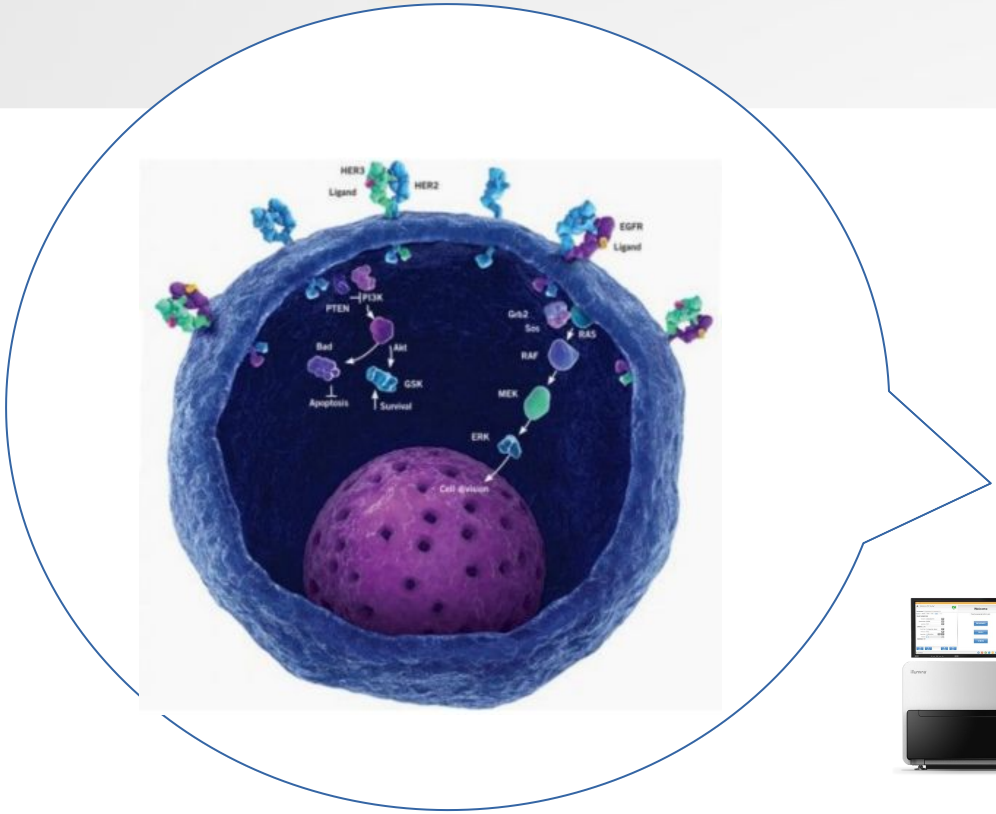
From cell to pathways

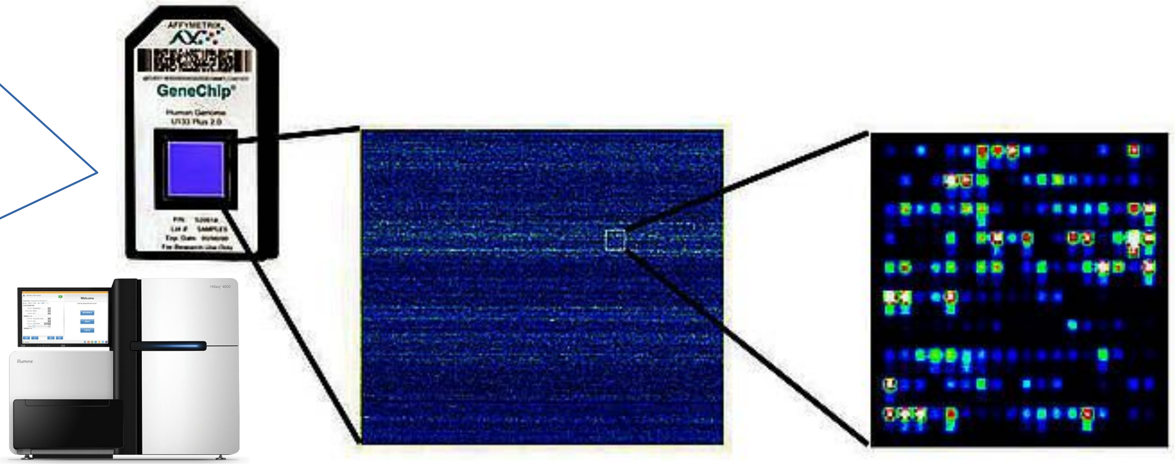


From cell to pathways

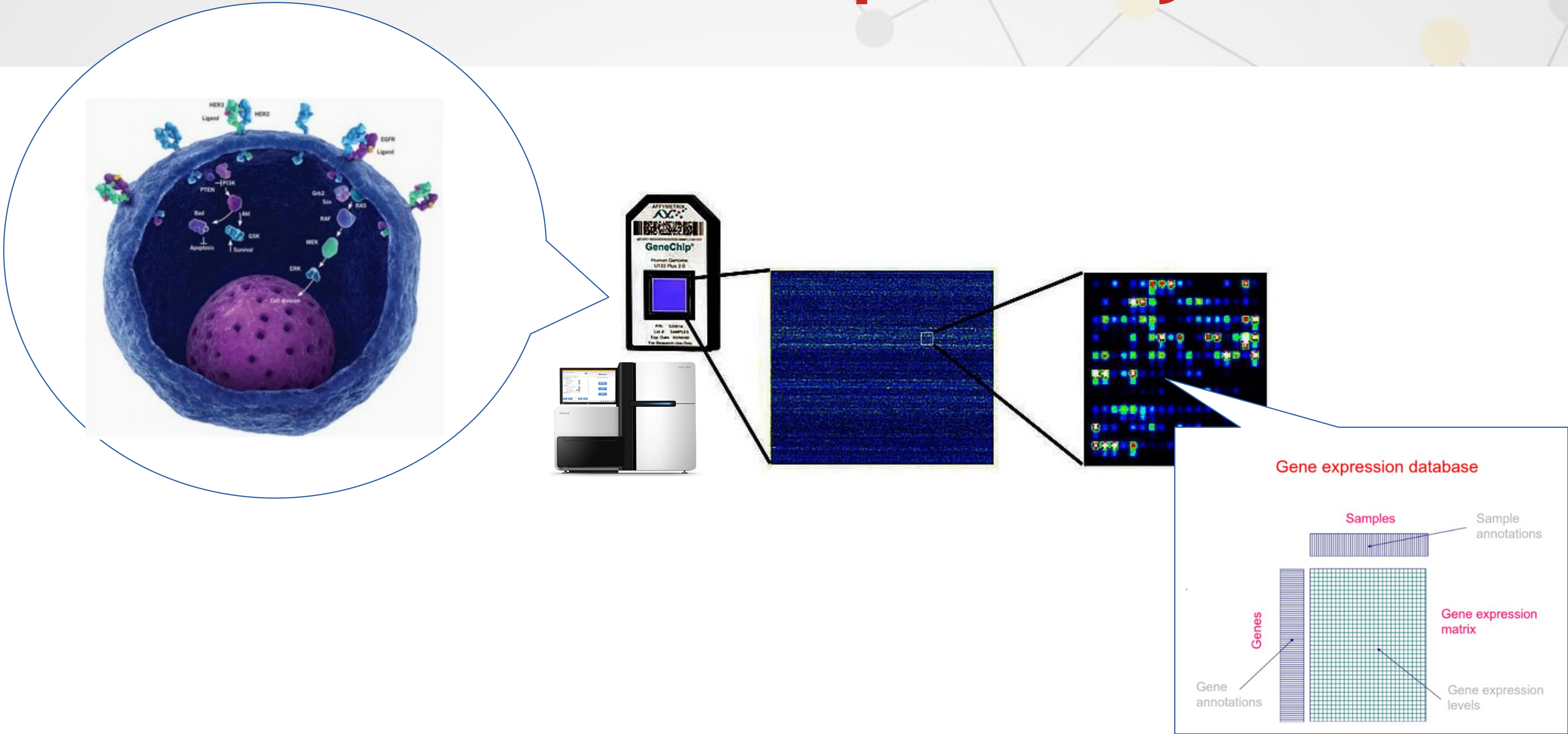


From cell to pathways





From cell to pathways



Gene expression database

Samples

Sample annotations

Genes

Gene expression matrix

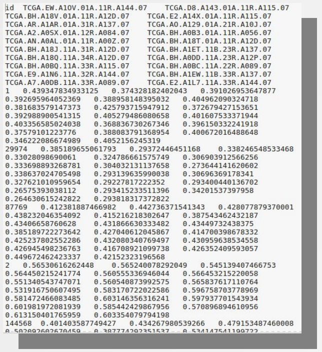
Gene annotations

Gene expression levels

Overview / Our aim

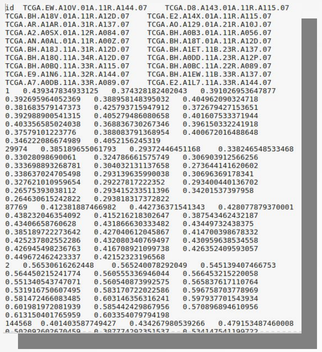
Case Vs Controls

Raw Data

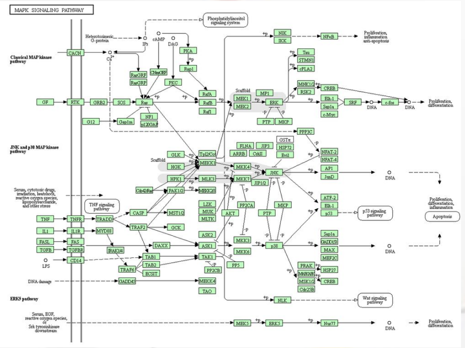


Normalized genes

Case Vs Controls



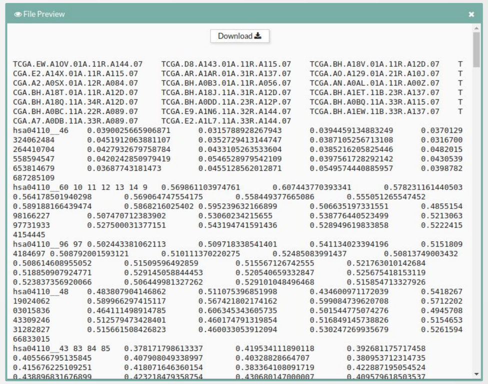
Signaling pathways /circuits



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

Case Vs Controls

Activity

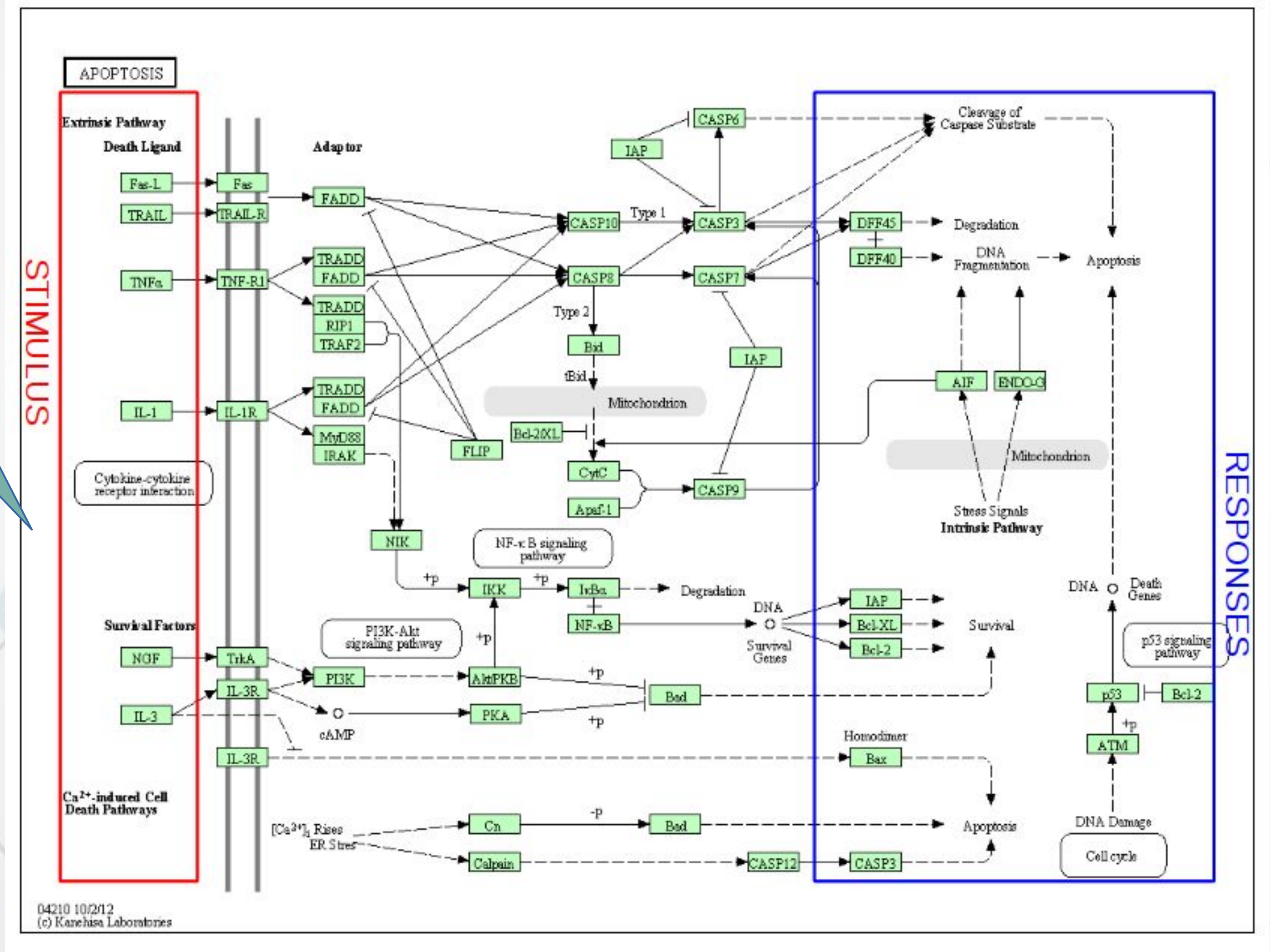


We seek for a **simple transformation** from individual **gene expression** profiles to profiles of **circuit activity** (and functional activity).

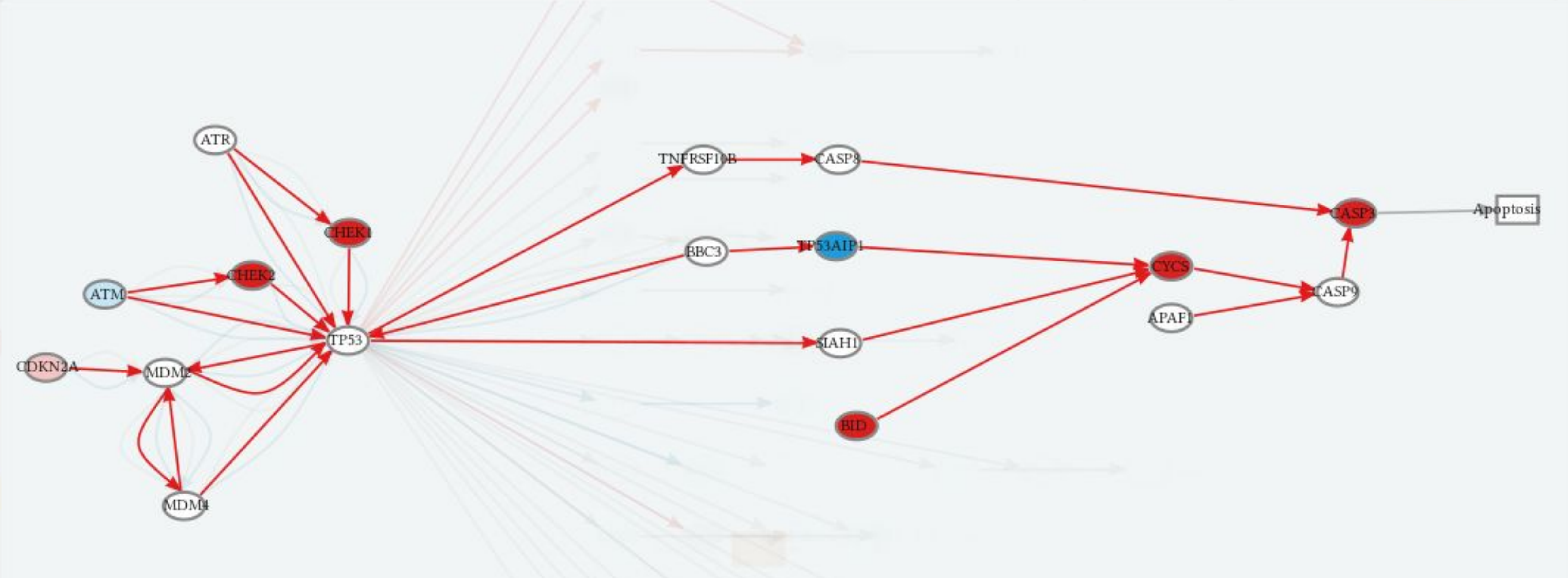
“Torture the data, and it will confess to anything.”
– Ronald Coase

Pathways layout

Take pathways information



Meaningful subpathways

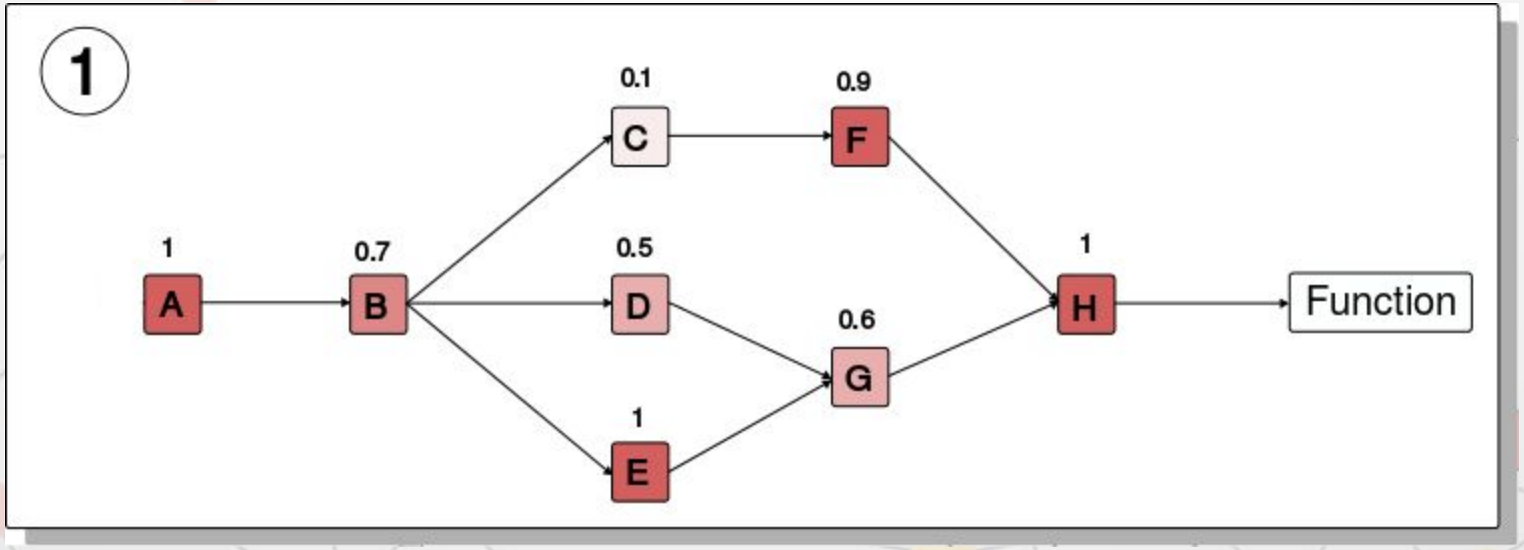


Effector subpathway

> **Subpathway** including any node from any **receptor** to **one effector protein**

Computing the signal

1) Compute a **node score** based on the expression.

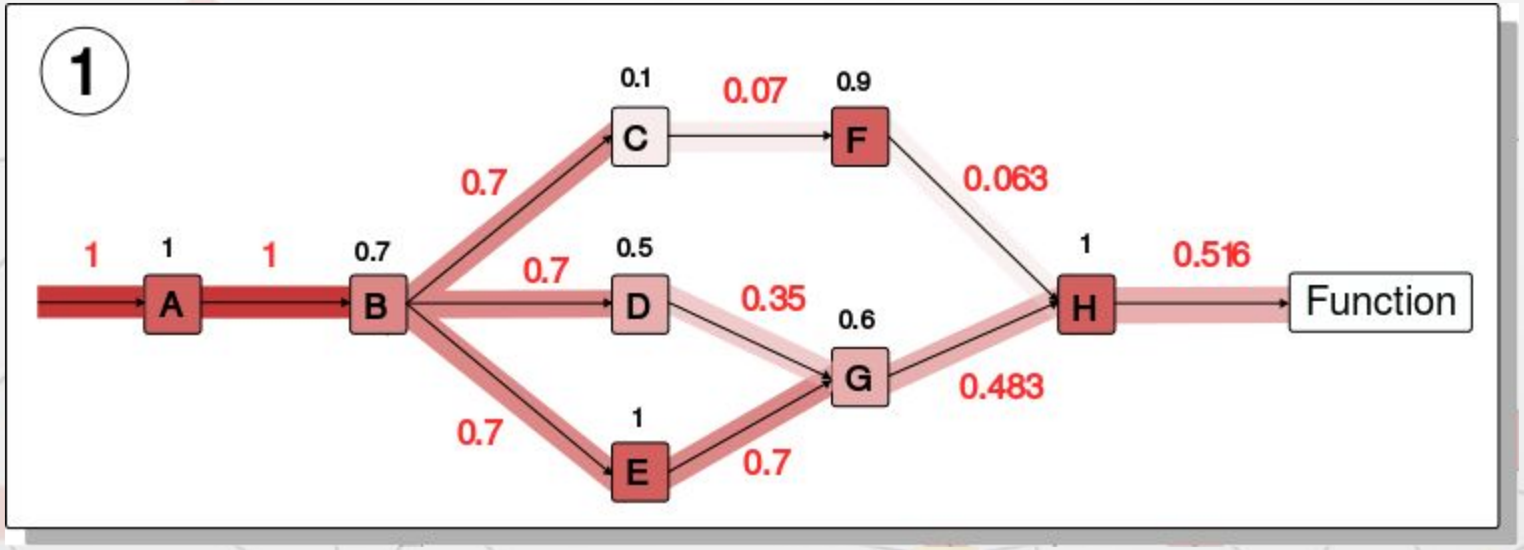


Computing the signal

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

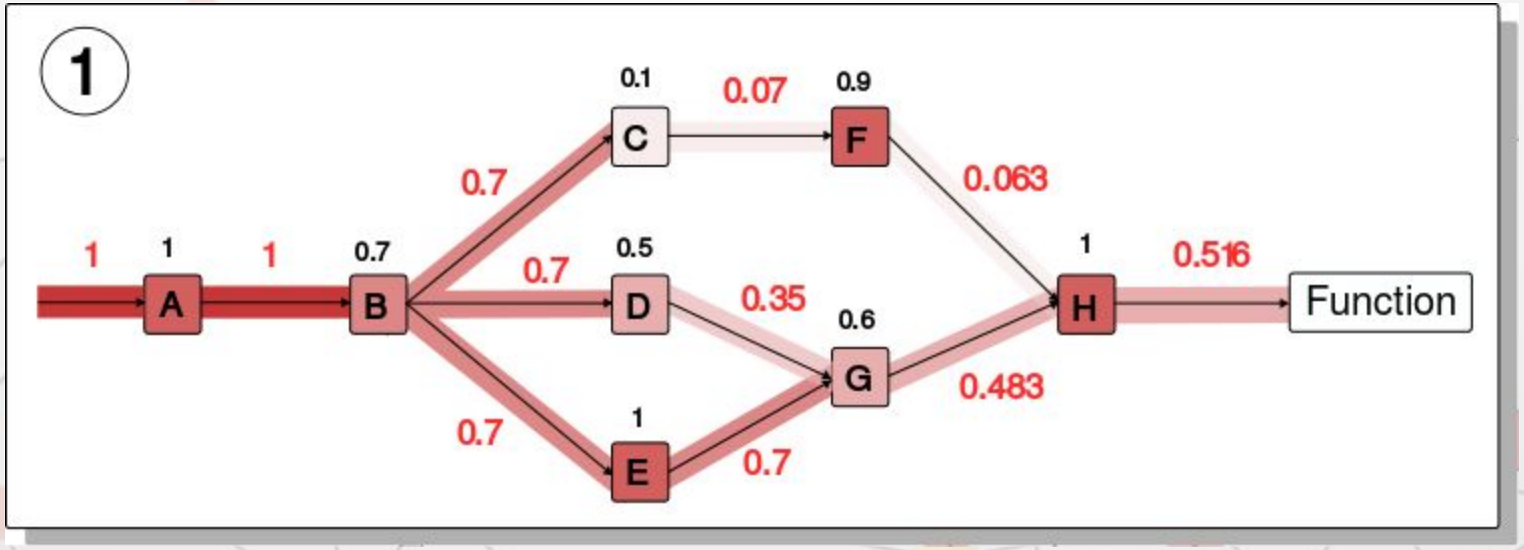
$$S_n = v_n \cdot \left(1 - \prod_{s_i \in A} (1 - s_i)\right) \cdot \prod_{s_j \in I} (1 - s_j)$$

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

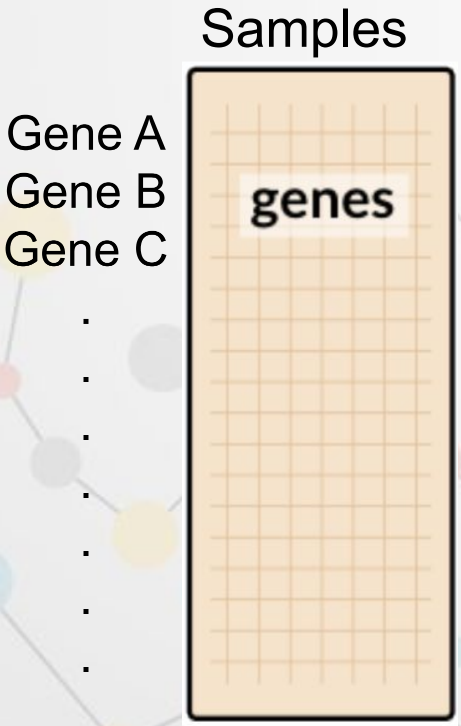


Signal values

1) Input signal **1** in any **input node**
2) Compute the signal through **each node iteratively**
3) **Loops** can be processed
4) **Subpathway signal**: last node signal



Functional annotation


Samples

Gene A
Gene B
Gene C
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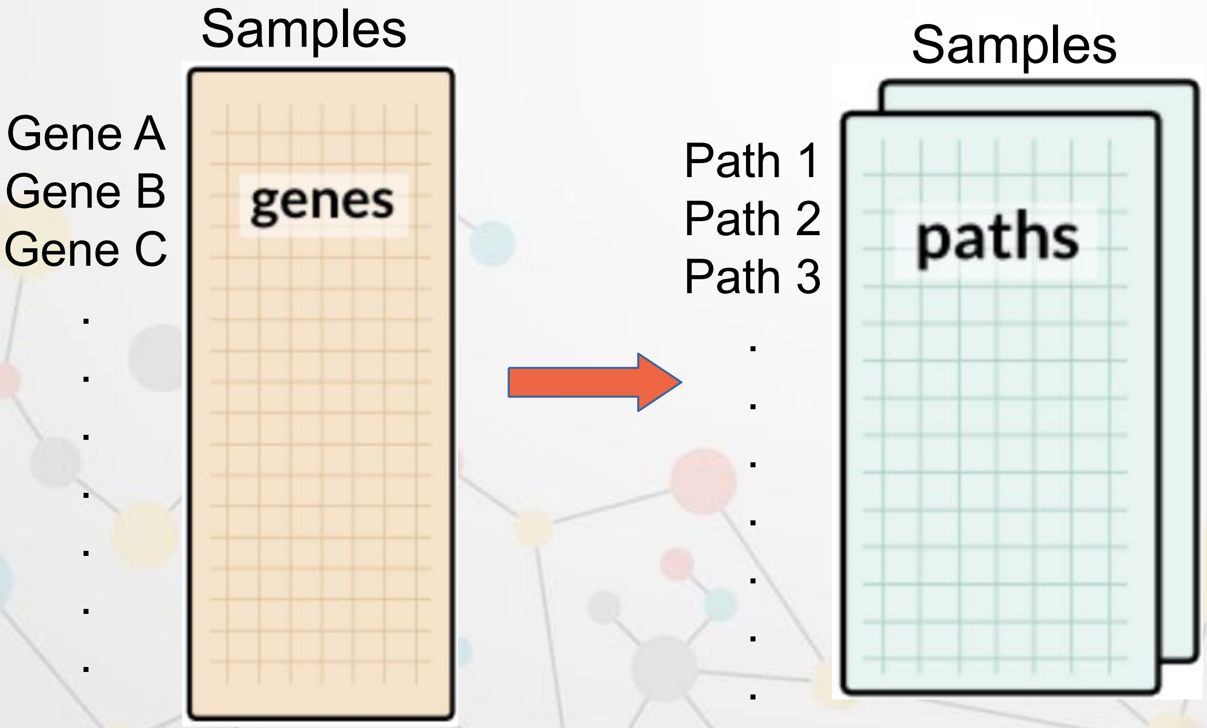
Functional annotation

1) Estimate effector proteins activation



Samples

Gene A
Gene B
Gene C
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genes

Samples

Path 1
Path 2
Path 3
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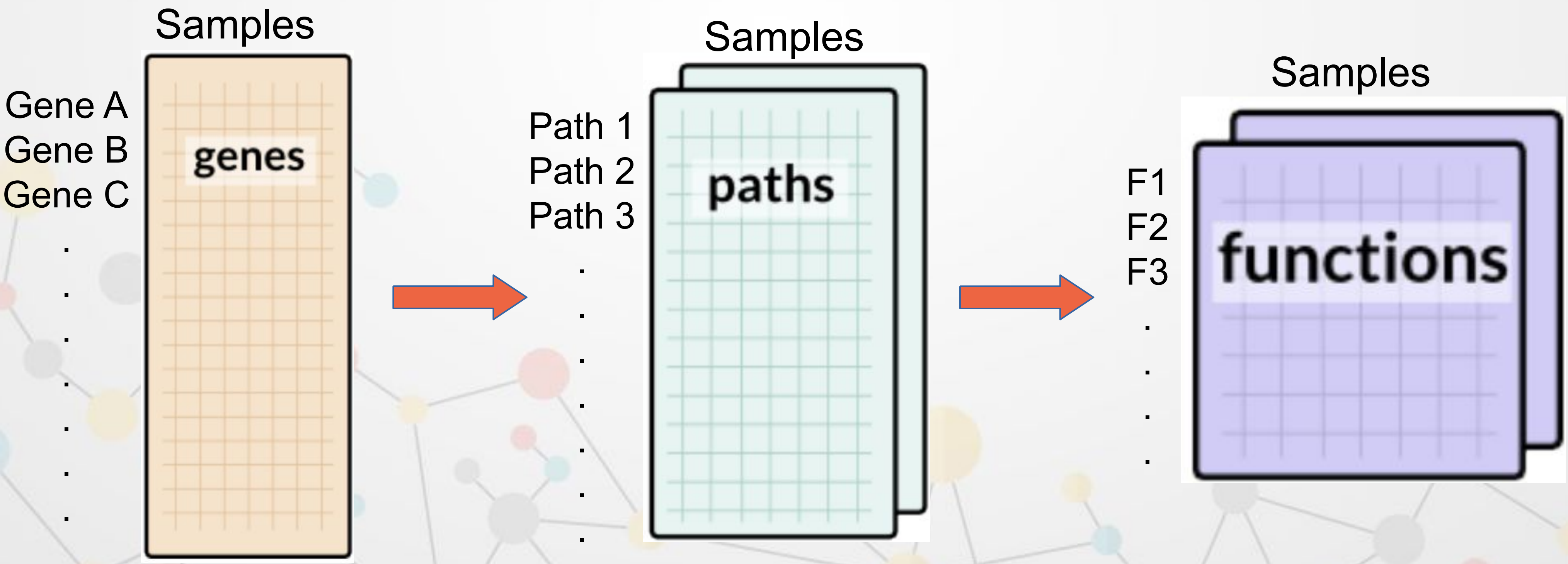
paths

Functional annotation

1) Estimate effector proteins activation
2) Annotate effector proteins functions



Samples

Gene A
Gene B
Gene C
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genes

Samples

Path 1
Path 2
Path 3
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paths

Samples

F1
F2
F3
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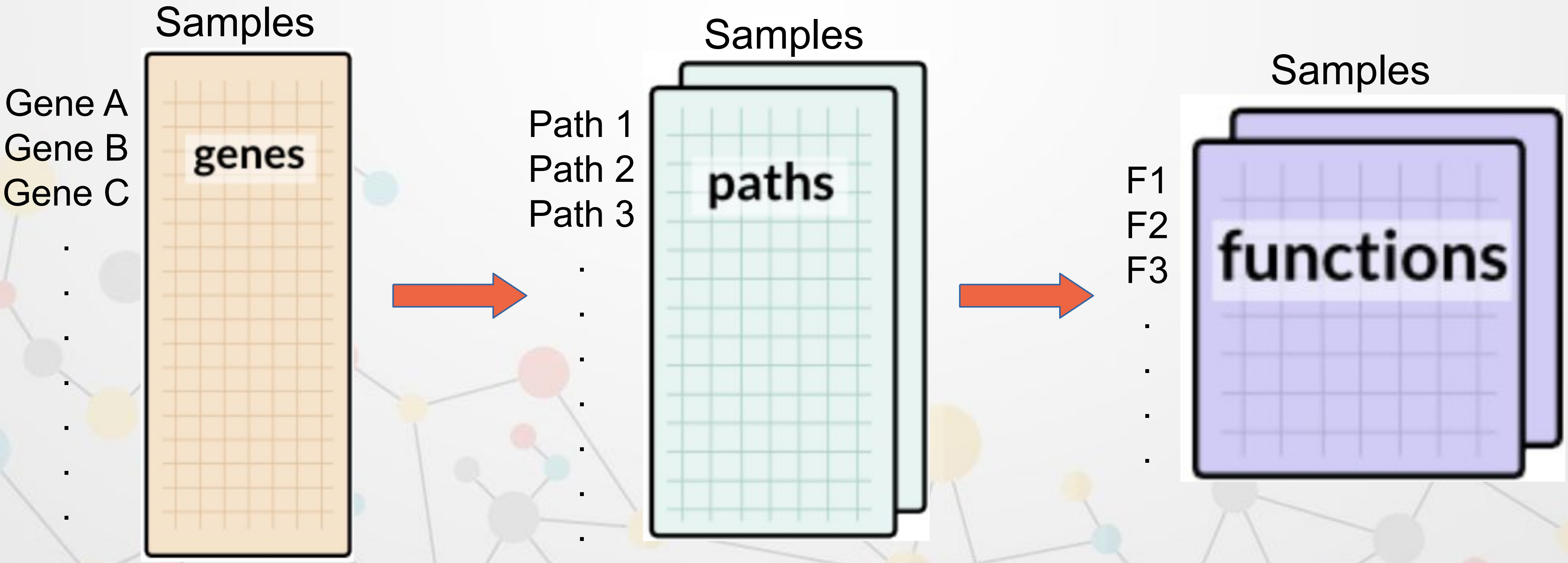
functions

Functional annotation

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



Samples

Gene A
Gene B
Gene C
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Samples

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F1
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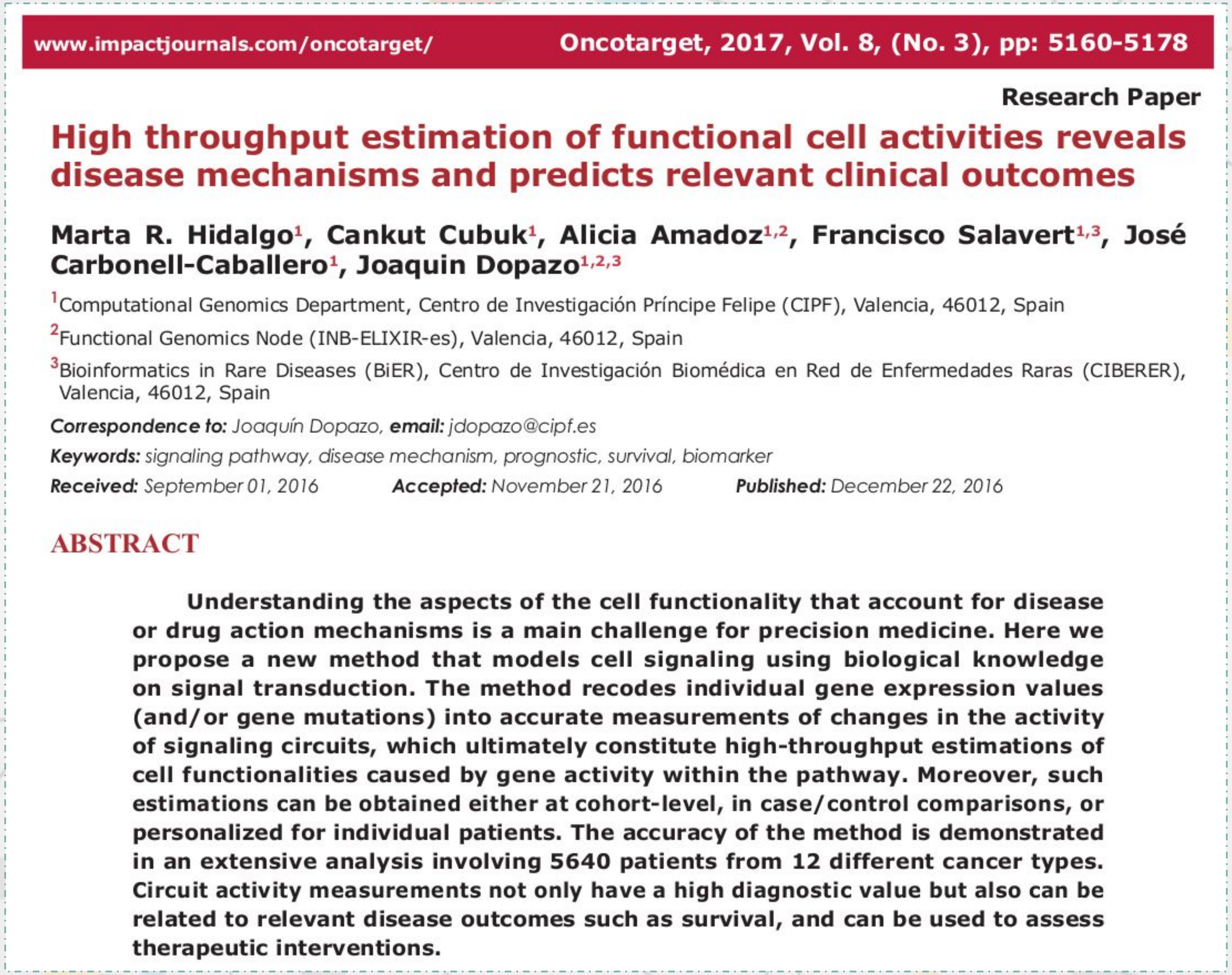

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 3), pp: 5160-5178

Research Paper

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

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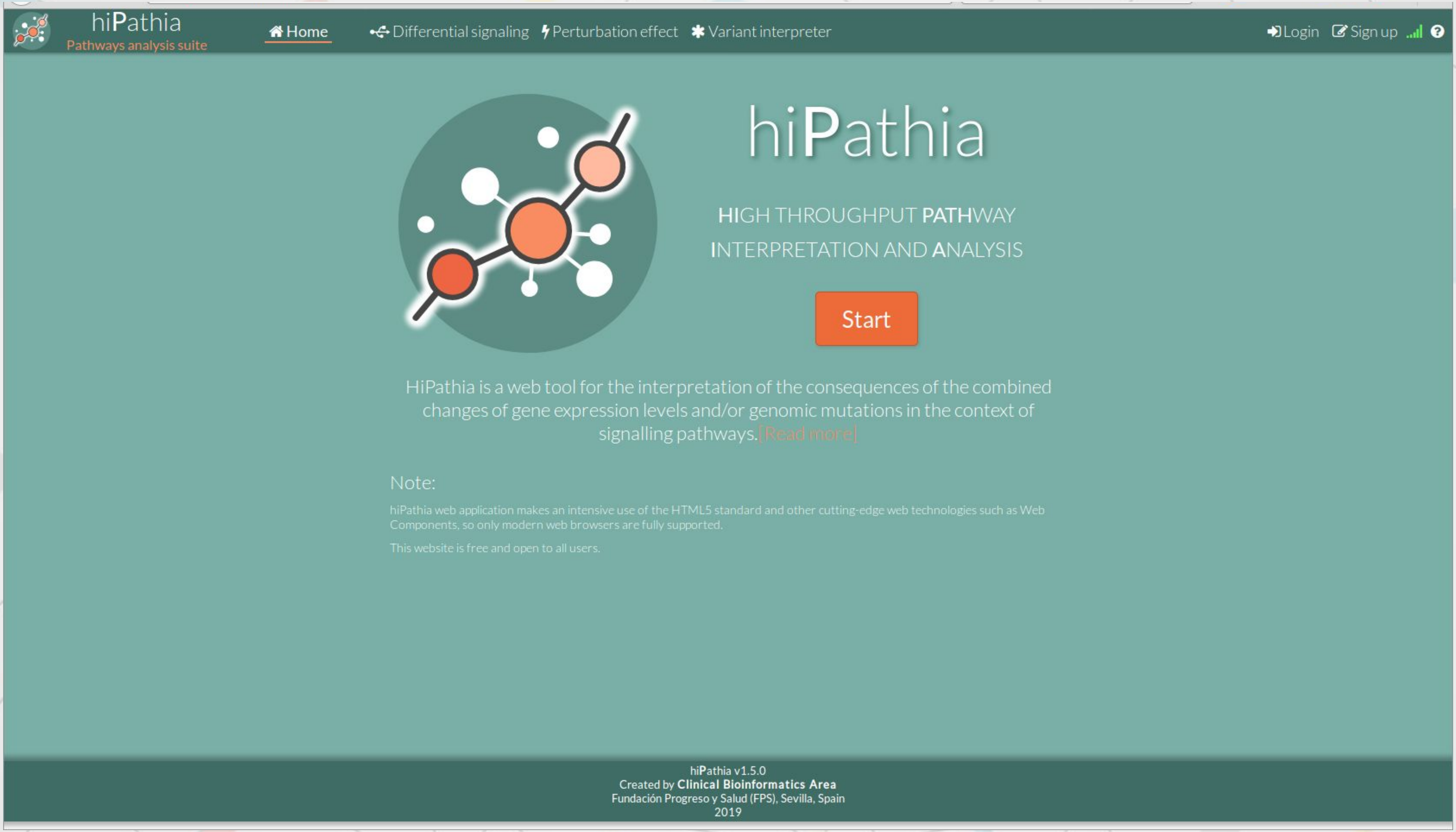
Keywords: *signaling pathway, disease mechanism, prognostic, survival, biomarker*

Received: *September 01, 2016* ***Accepted:*** *November 21, 2016* ***Published:*** *December 22, 2016*

ABSTRACT

Understanding the aspects of the cell functionality that account for disease or drug action mechanisms is a main challenge for precision medicine. Here we propose a new method that models cell signaling using biological knowledge on signal transduction. The method recodes individual gene expression values (and/or gene mutations) into accurate measurements of changes in the activity of signaling circuits, which ultimately constitute high-throughput estimations of cell functionalities caused by gene activity within the pathway. Moreover, such estimations can be obtained either at cohort-level, in case/control comparisons, or personalized for individual patients. The accuracy of the method is demonstrated in an extensive analysis involving 5640 patients from 12 different cancer types. Circuit activity measurements not only have a high diagnostic value but also can be related to relevant disease outcomes such as survival, and can be used to assess therapeutic interventions.



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.[Read more]

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.

This website is free and open to all users.

hiPathia v1.5.0
Created by **Clinical Bioinformatics Area**
Fundación Progreso y Salud (FPS), Sevilla, Spain
2019

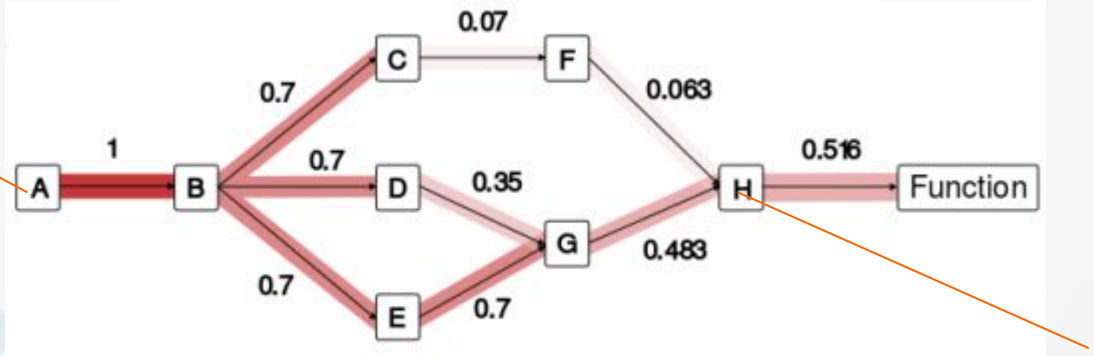
Case study: Breast Cancer

1) We will work with a **Breast Cancer** dataset from the repository The **Cancer Genome Atlas:** http://hipathia.babelomics.org/doc/doku.php?id=worked_example_differential_example

Perturbation effect tool

In our model, signal transduction is usually modulated through all nodes between a **membrane receptor** and an **effector protein**

Membrane Receptor

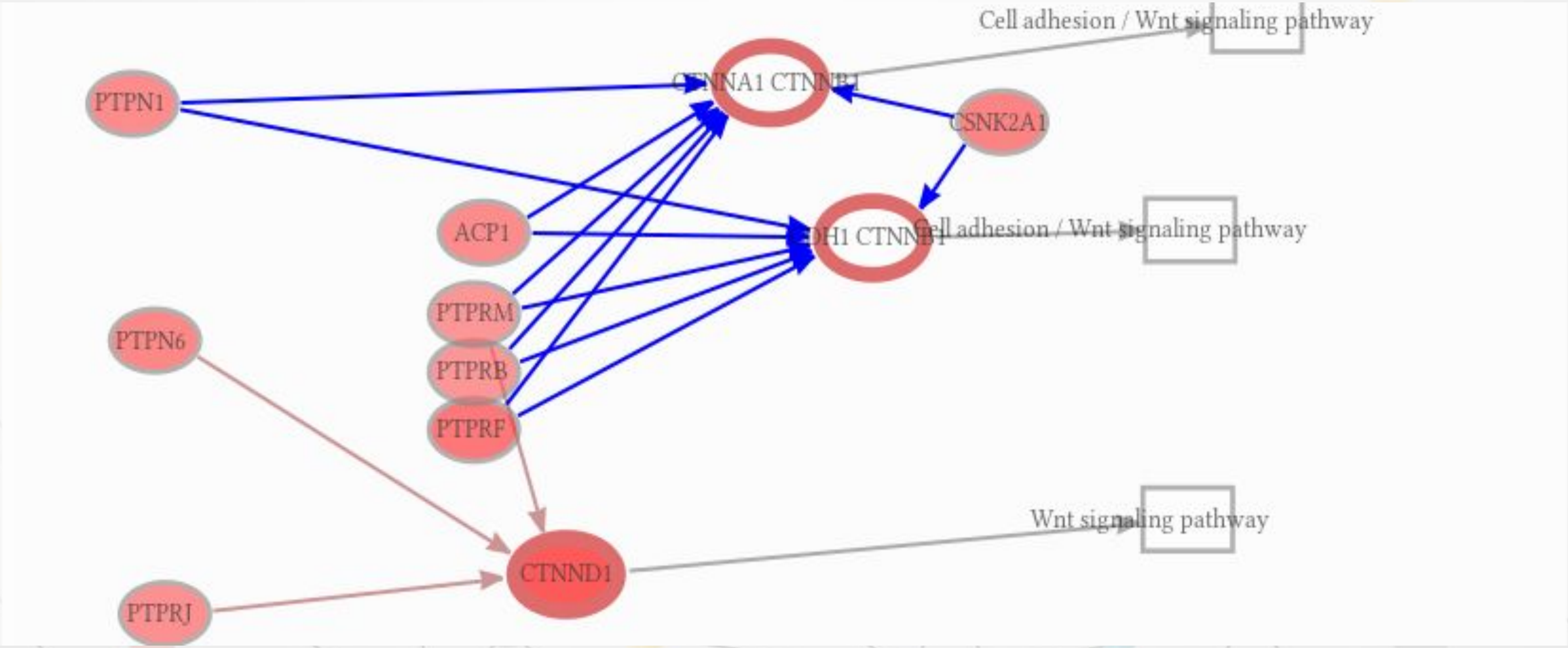


Effector protein

Intracellular signaling proteins

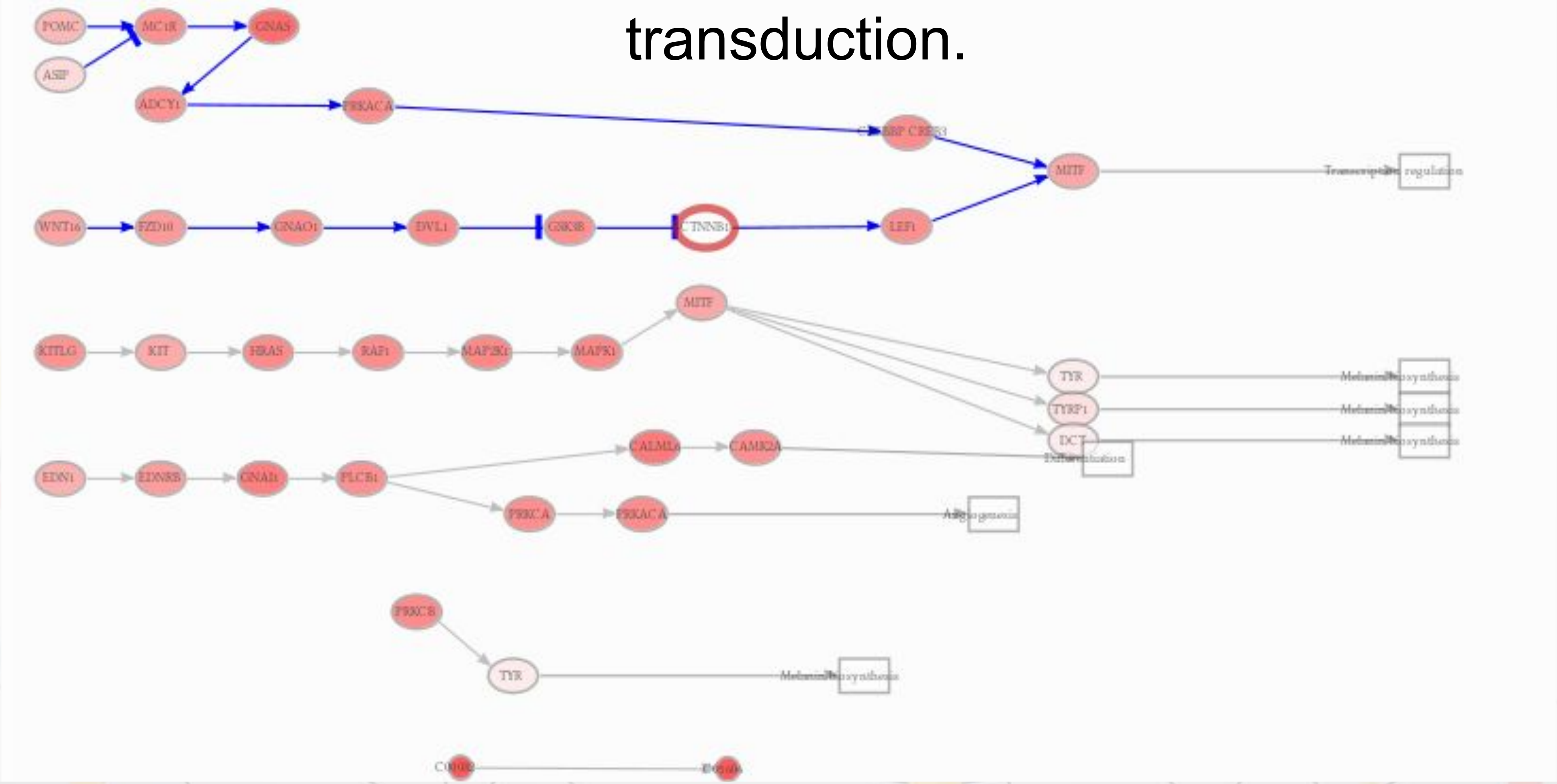
Perturbation effect tool

This approach offers a powerful framework to design targeted therapies with minimum resources.



Perturbation effect tool

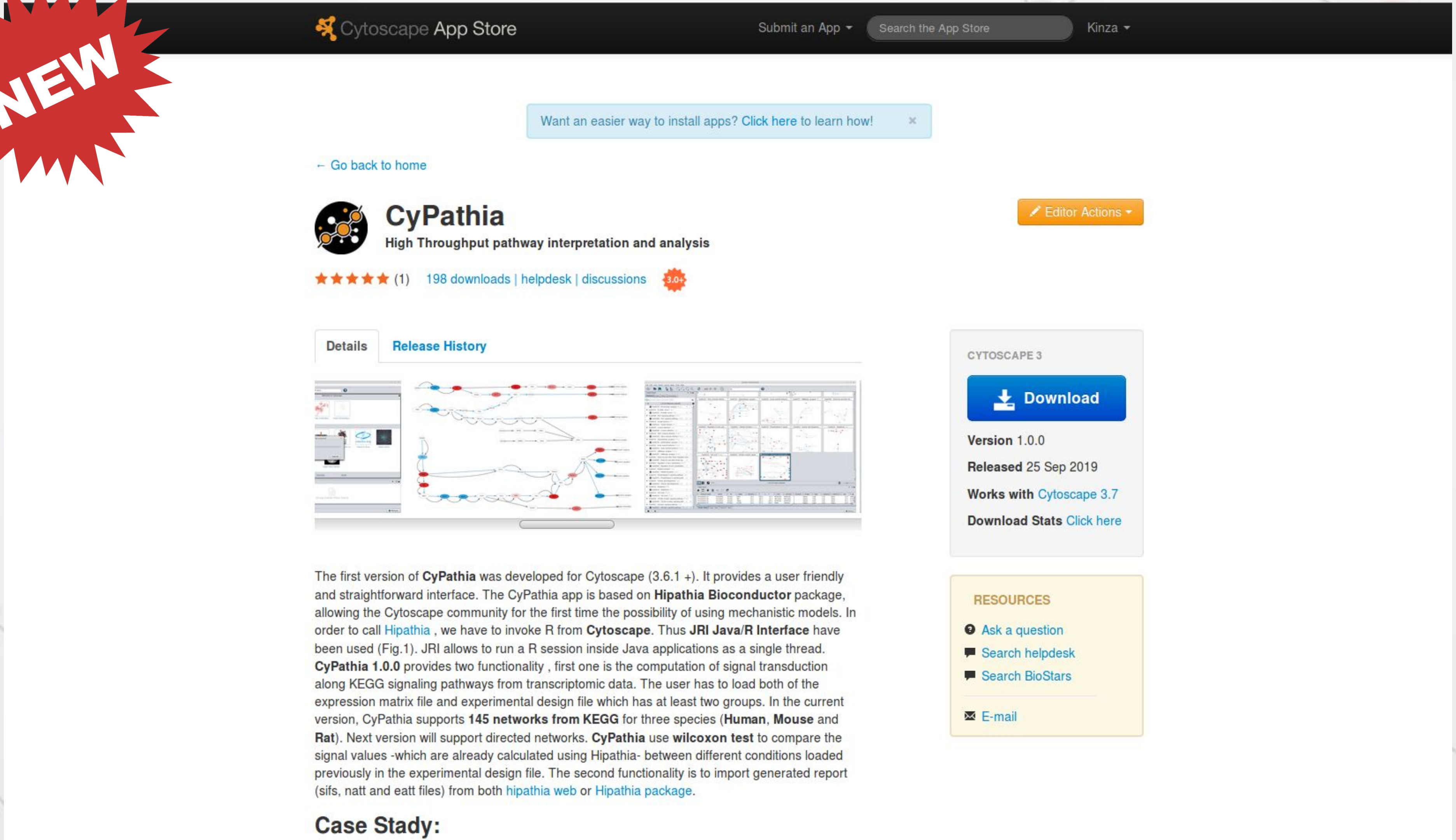
We can use the same machinery t**o virtually explore the consequences of knocking out** (or overexpress) a gene in signal transduction.



CyPathia

The signal propagation model has been implemented also for **Cytoscape community**

NEW



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CyPathia

High Throughput pathway interpretation and analysis

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CYTOSCAPE 3

Version 1.0.0

Released 25 Sep 2019

Works with Cytoscape 3.7

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RESOURCES

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- Search helpdesk
- Search BioStars
- E-mail

The first version of **CyPathia** was developed for Cytoscape (3.6.1 +). It provides a user friendly and straightforward interface. The CyPathia app is based on **Hipathia Bioconductor** package, allowing the Cytoscape community for the first time the possibility of using mechanistic models. In order to call Hipathia , we have to invoke R from **Cytoscape**. Thus **JRI Java/R Interface** have been used (Fig.1). JRI allows to run a R session inside Java applications as a single thread. **CyPathia 1.0.0** provides two functionality , first one is the computation of signal transduction along KEGG signaling pathways from transcriptomic data. The user has to load both of the expression matrix file and experimental design file which has at least two groups. In the current version, CyPathia supports **145 networks from KEGG** for three species (**Human**, **Mouse** and **Rat**). Next version will support directed networks. **CyPathia** use **wilcoxon test** to compare the signal values -which are already calculated using Hipathia- between different conditions loaded previously in the experimental design file. The second functionality is to import generated report (sifs, natt and eatt files) from both hipathia web or Hipathia package.

Case Stady:

@ClinicalBioinfo