A tutorial of hipathia, a mechanistic model of pathway activity

Joaquín Dopazo[1]
Marta Hidalgo[2]
Kinza Rian[1]

1. Clinical Bioinformatics Area, Fundación Progreso y Salud, Functional Genomics Node, (INB-ELIXIR-es), Bioinformatics in Rare Diseases (BiER-CIBERER), Sevilla, Spain.

http://www.clinbioinfosspa.es
http://www. babelomics.org
@clinicalbioinfo

2. Unidad de Bioinformática y Bioestadística
Centro de Investigación Príncipe Felipe (CIPF),
Valencia. Spain

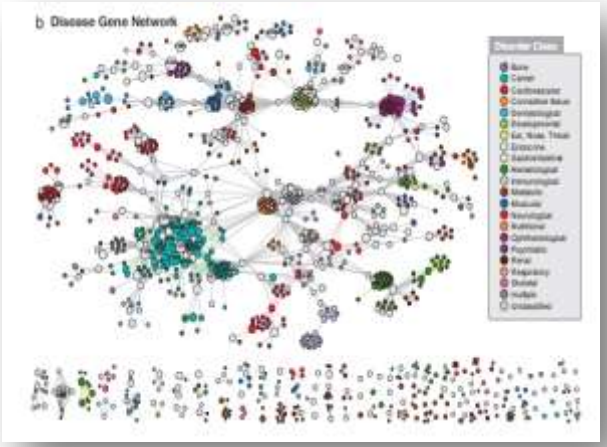
http://bioinfo.cipf.es

3rd Disease Maps Community Meeting.
Paris, 21-22 June 2018

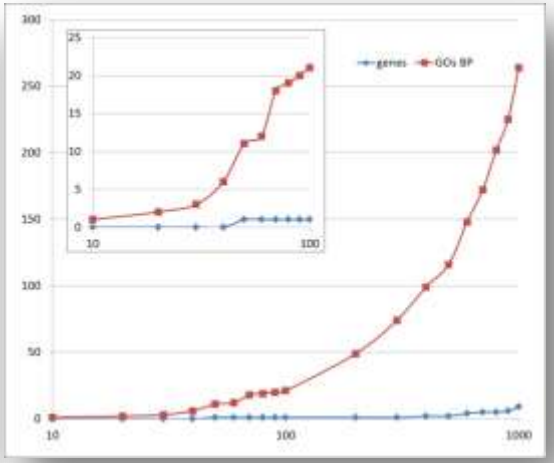
Most human genetic diseases (and almost all traits) have a modular nature

- **Modular nature of genetic diseases: Causative genes** for the same or phenotypically similar diseases may generally reside in the same **biological module**, either a **protein complex** (Lage et al, 2007), a **sub-network** of protein interactions (Lim et al, 2006) , or a **pathway** (Wood et al, 2007)
- We are specifically interested in **signaling pathways** because they describe way in which the cell **trigger actions** in response to stimuli, that is **signaling pathways** account for the **mechanisms** of **cell functionality**

Disease genes are close in the interactome



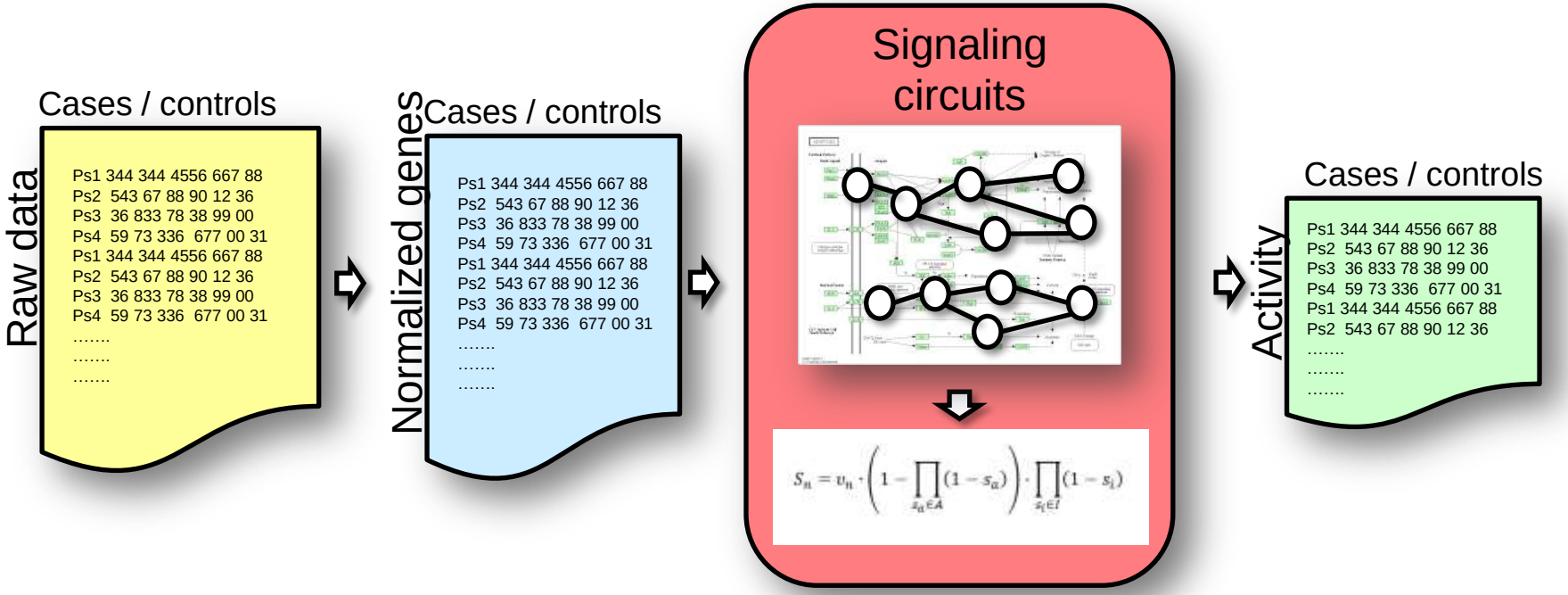
Goh 2007 PNAS



Fernandez, 2013, Orphanet J Rare Dis.

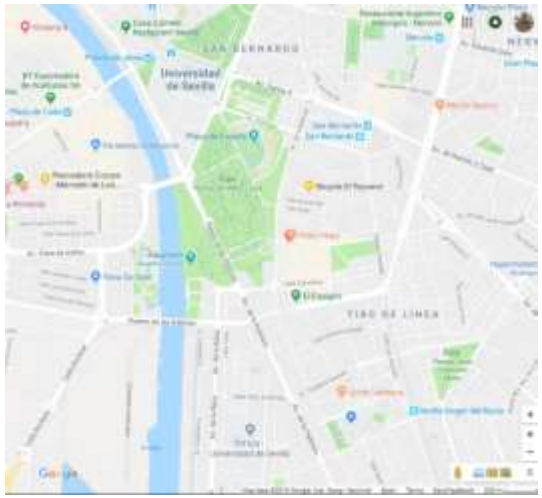
Same disease in different populations is caused by different genes affecting the same functions

Our aim: obtaining estimations on cell signaling activities from affordable gene expression data

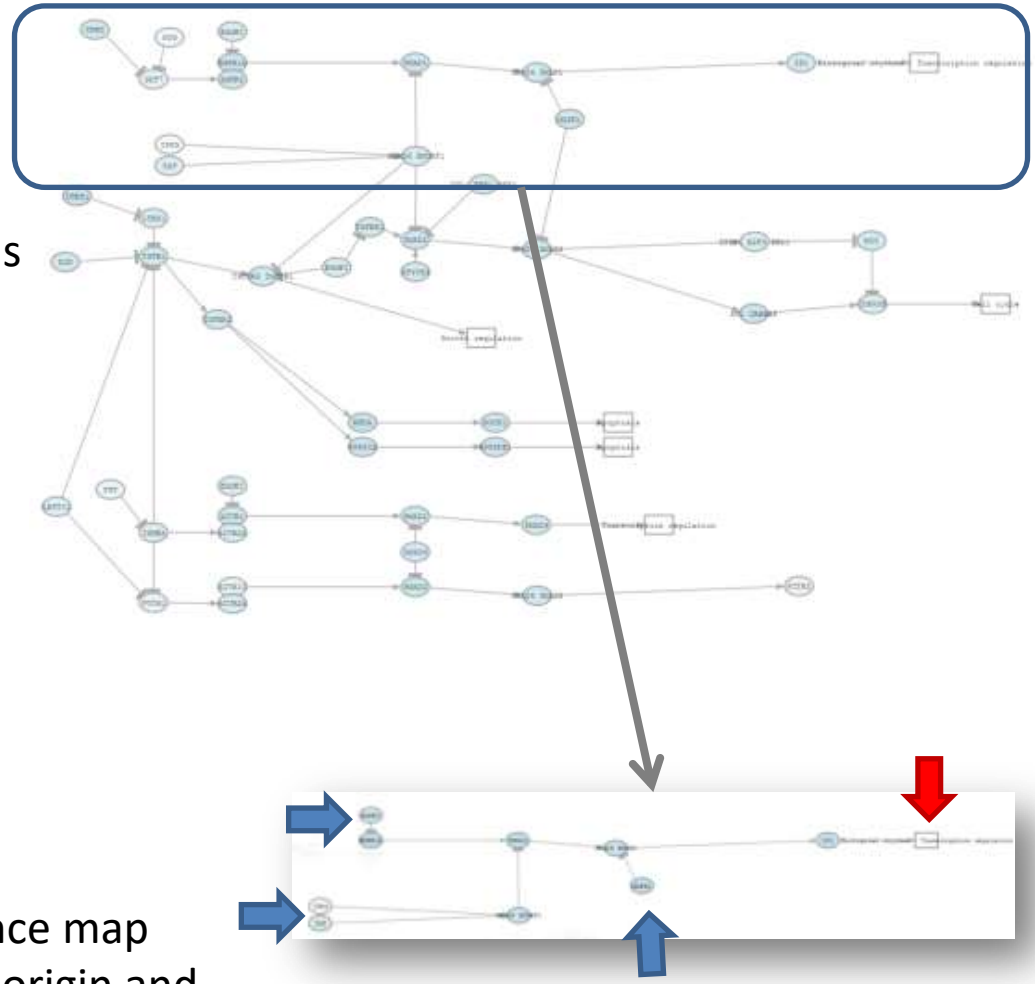


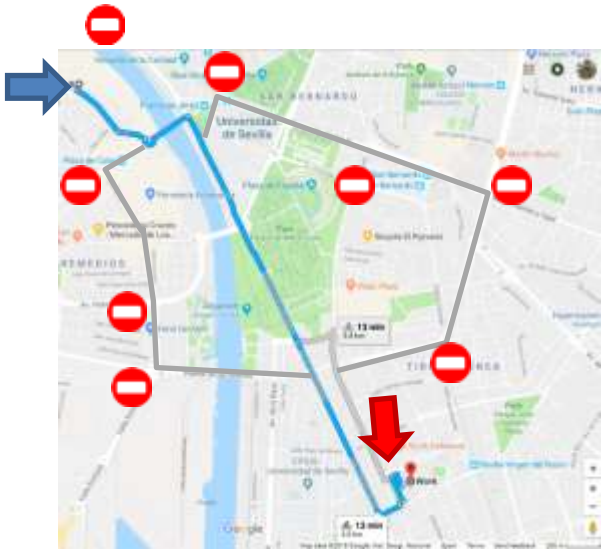
We seek for a simple transformation of raw data (normalization) and an algorithm that result in accurate estimations of signaling circuit activities. It is possible to include mutational profiles in the algorithm (either by integrating them with transcriptomic data or assuming gene expression taken from databases)

Describing the module: on maps and navigation



A map describes connections between elements

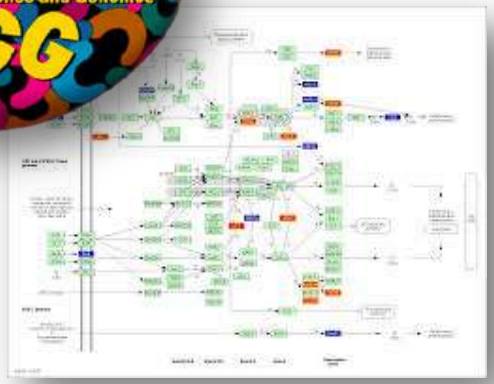




An influence map describes origin and destinations that define processes

Describing the module: Pathways: maps of cell activity (in sickness and in health)

www.genome.jp/kegg



disease-maps.org/

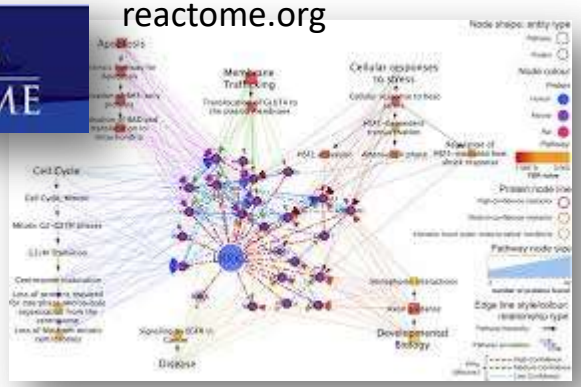
Oncogénesis

Alzheimer

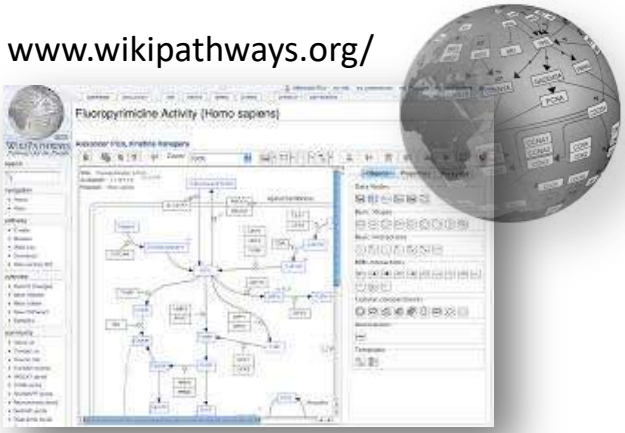
More disease maps…

Parkinson

reactome.org



www.wikipathways.org/

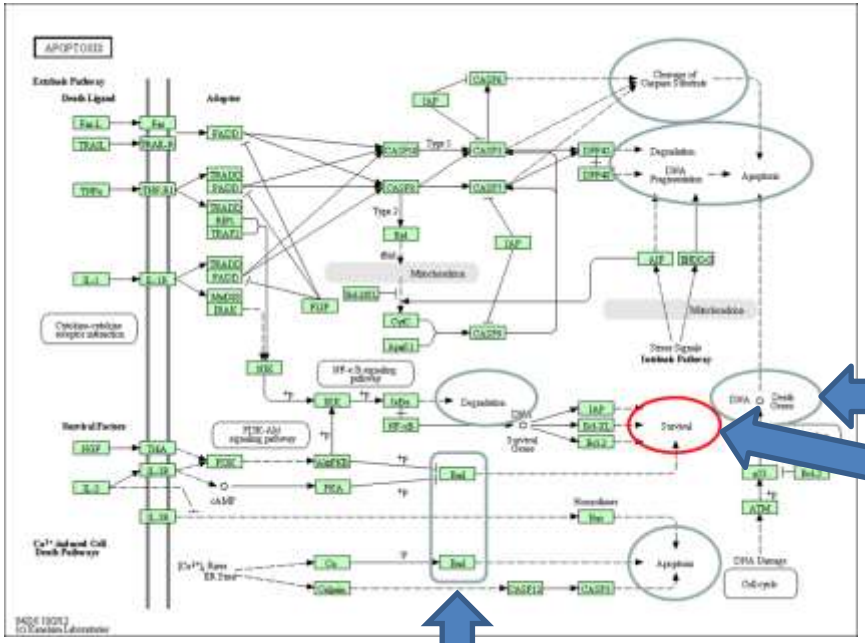


Defining pathway activity

We first need a map: pathways are defined in different repositories (**KEGG**, Reactome, Biocarta, disease maps, etc.)

What pathway level makes a real biological meaning?

Gene → sub-pathway → pathway

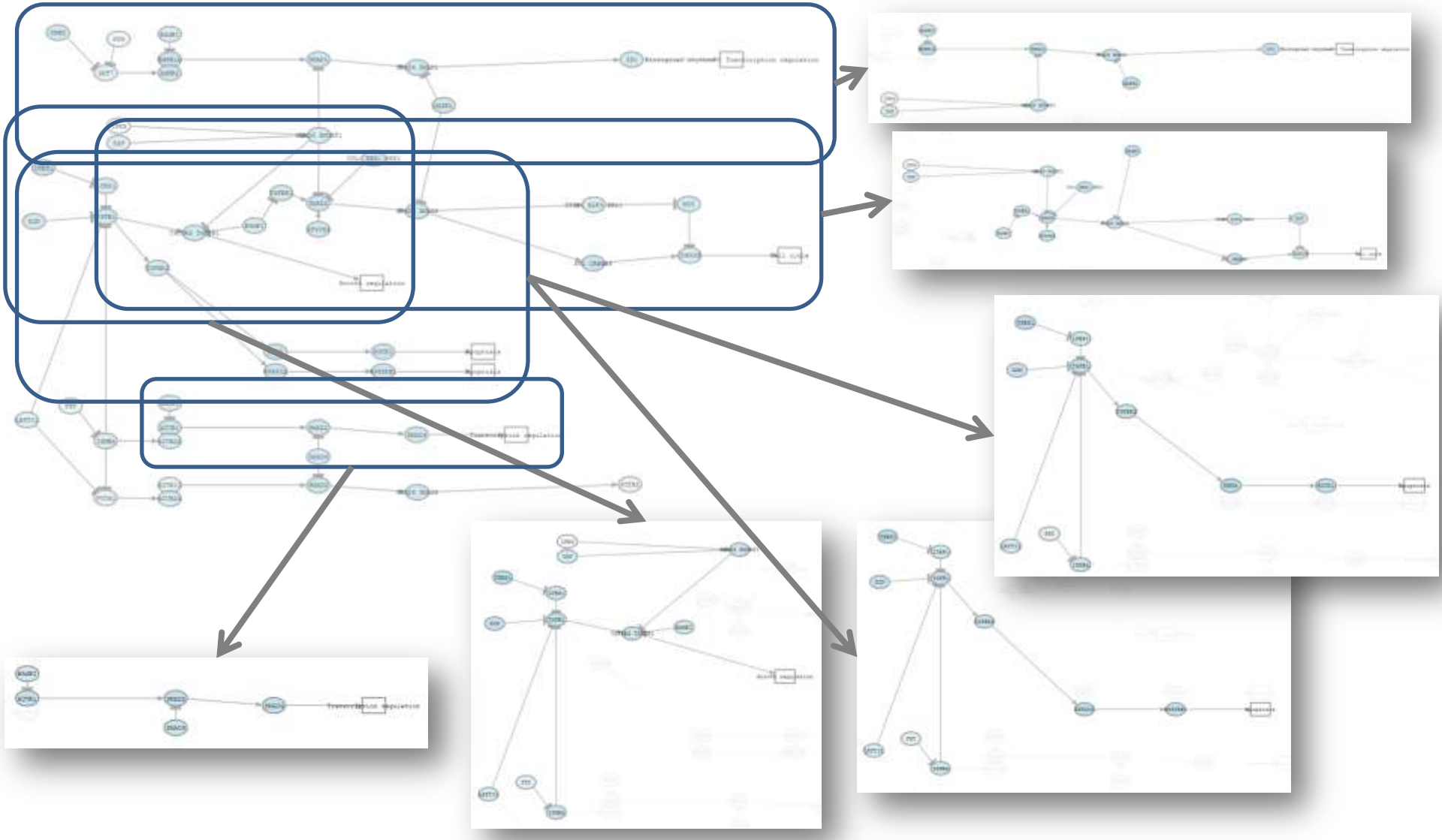


Enrichment methods (pathway-level): Different and often opposite cell behaviors are triggered by the same **pathway**.
E.g.: death and survival

Gene level: The same gene can trigger different (and often opposite) responses, depending on the stimulus

Sub-pathway (elementary circuit) connects stimulus to response

Decomposition of a pathway into their elementary circuits



How realistic are models of pathway activity?

RESEARCH ARTICLE

CANCER

Signaling pathway models as biomarkers: Patient-specific simulations of JNK activity predict the survival of neuroblastoma patients

Dirk Fey,[1] Melinda Halasz,[1] Daniel Dreidax,[2] Sean P. Kennedy,[1] Jordan F. Hastings,[3] Nora Rauch,[1] Amaya Garcia Munoz,[1] Ruth Pilkington,[1] Matthias Fischer,[4,5,6] Frank Westermann,[2] Walter Kolch,[1,7,8] Boris N. Kholodenko,[1,7,8]* David R. Croucher[1,3,9]*

Signaling pathways control cell fate decisions that ultimately determine the behavior of cancer cells. Therefore, the dynamics of pathway activity may contain prognostically relevant information different from that contained in the static nature of other types of biomarkers. To investigate this hypothesis, we characterized the network that regulated stress signaling by the c-Jun N-terminal kinase (JNK) pathway in neuroblastoma cells. We generated an experimentally calibrated and validated computational model of this network and used the model to extract prognostic information from neuroblastoma patient–specific simulations of JNK activation. Switch-like JNK activation mediates cell death by apoptosis. An inability to initiate switch-like JNK activation in the simulations was significantly associated with poor overall survival for patients with neuroblastoma with or without *MYCN* amplification, indicating that patient-specific simulations of JNK activation could stratify patients. Furthermore, our analysis demonstrated that extracting information about a signaling pathway to develop a prognostically useful model requires understanding of not only components and disease-associated changes in the abundance or activity of the components but also how those changes affect pathway dynamics.

Beyond static biomarkers—The activity of signalling networks as an alternate biomarker?

Fey et al., Sci. Signal. 8, ra130 (2015).

Inability of JNK activation (that mediates apoptosis) is associated to bad prognostic, irrespective of *MYCN* amplification status

Problem: ODE can efficiently solve only small systems

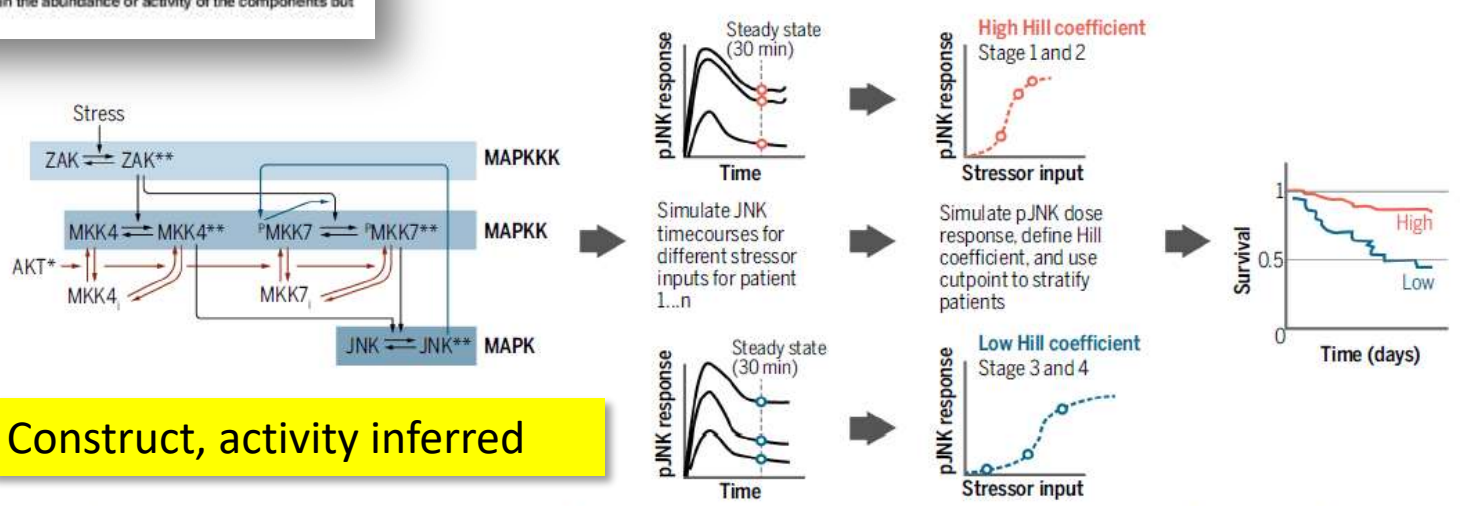
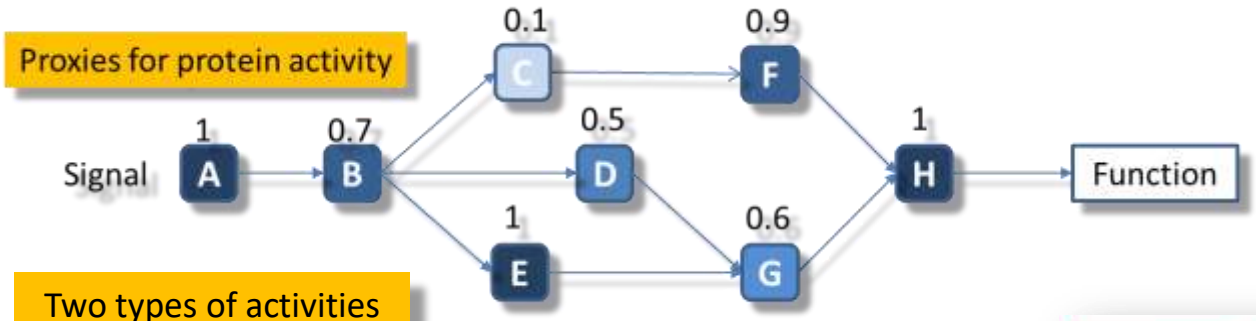
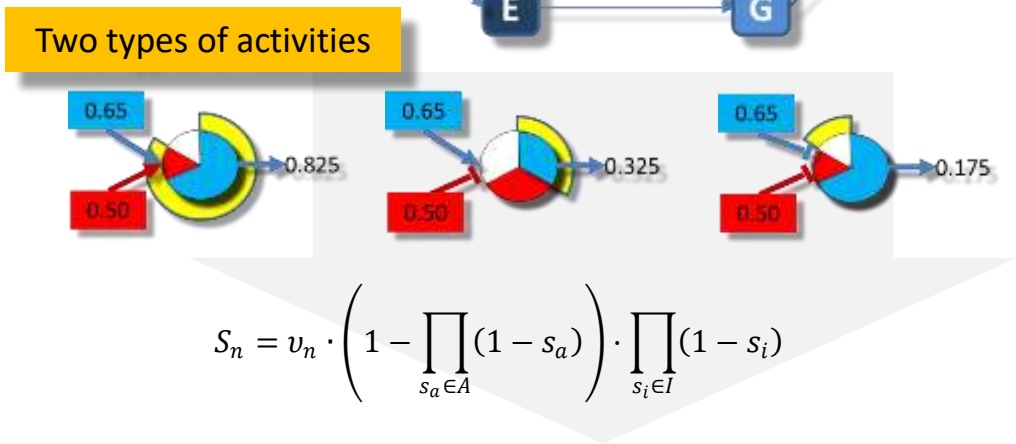


Fig. 1. Using network descriptors of signaling pathway activation potential to predict patient response. After construction of a computational model based on the validated network topology and that reproduces the signaling pathway dynamics, the model can be used to identify network descriptors, such as the Hill coefficient, that are calculated from the dynamic simulation of the activation of a signaling pathway. These in silico biomarkers cannot be directly measured.

Signal propagation models of signaling pathways



From individual gene expression profiles…




www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2016

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[2,3], José Carbonell-Caballero[1], Joaquin Dopazo[1,2,3]

[1]Computational Genomics Department, Centro de Investigación Príncipe Felipe (CIPF), Valencia, 46012, Spain

[2]Functional Genomics Node (INB-ELIXIR-es), Valencia, 46012, Spain

[3]Bioinformatics in Rare Diseases (BIER), Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Valencia, 46012, Spain

Correspondence to: Joaquin Dopazo, **email:** jdopazo@cipf.es

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

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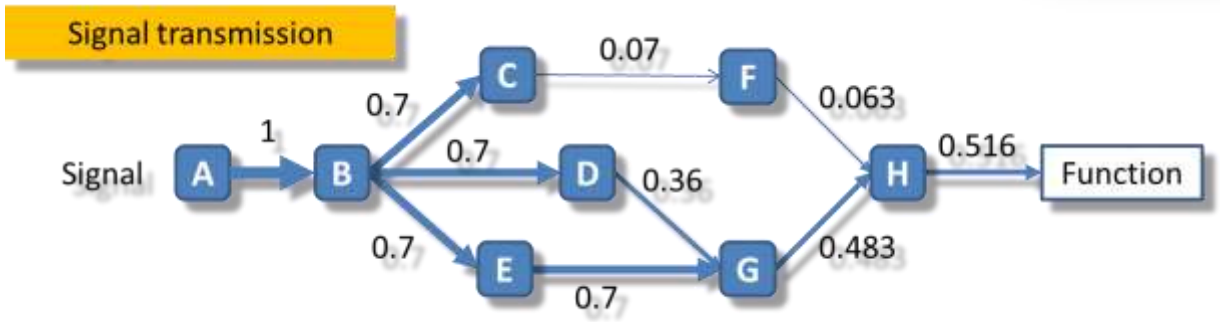


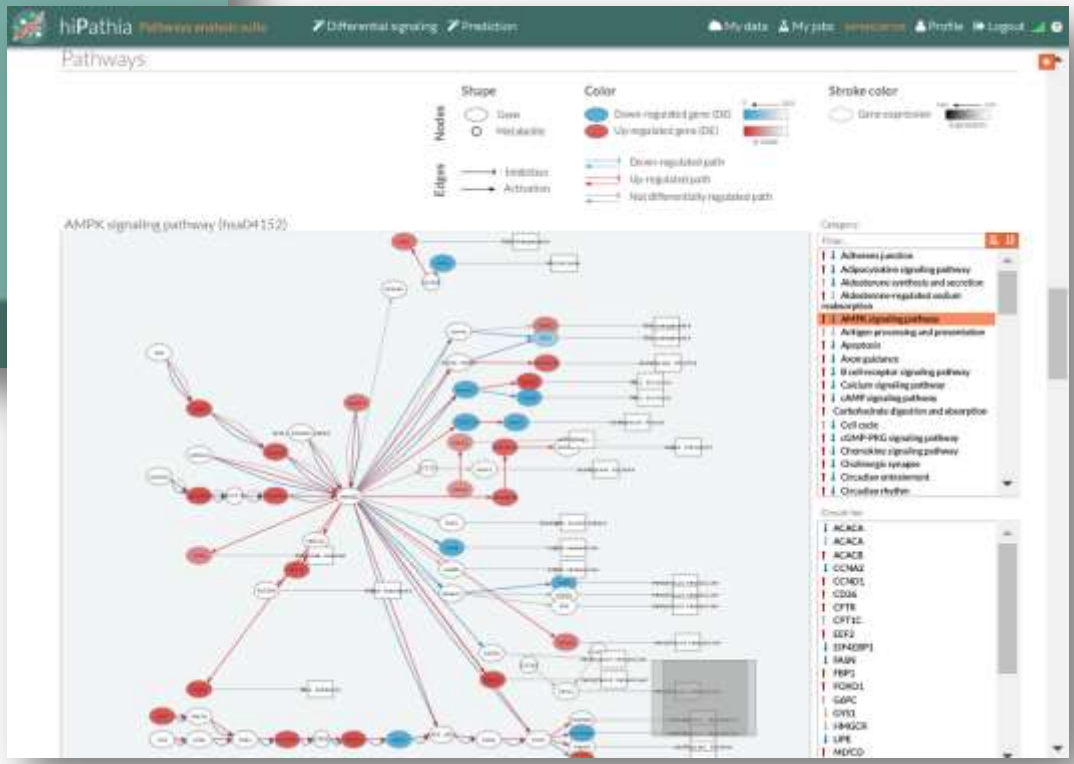
…to profiles of circuit activity (and functional activity)

Are scalable

The hipathia web server

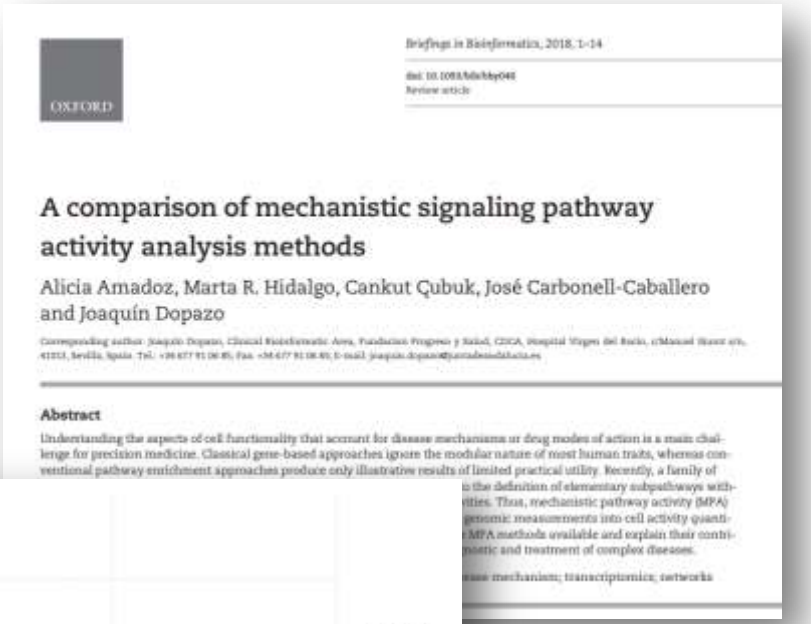
http://hipathia.babelomics.org/

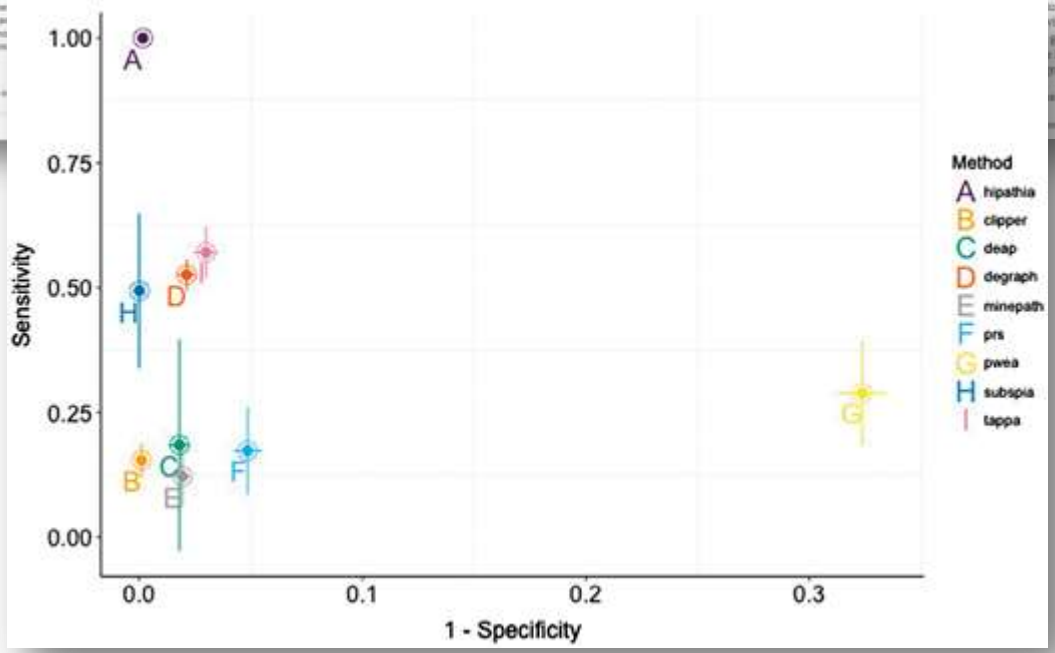
The signal propagation model has been implemented in a web server, hipathia, that allows estimating differential signaling activity between samples



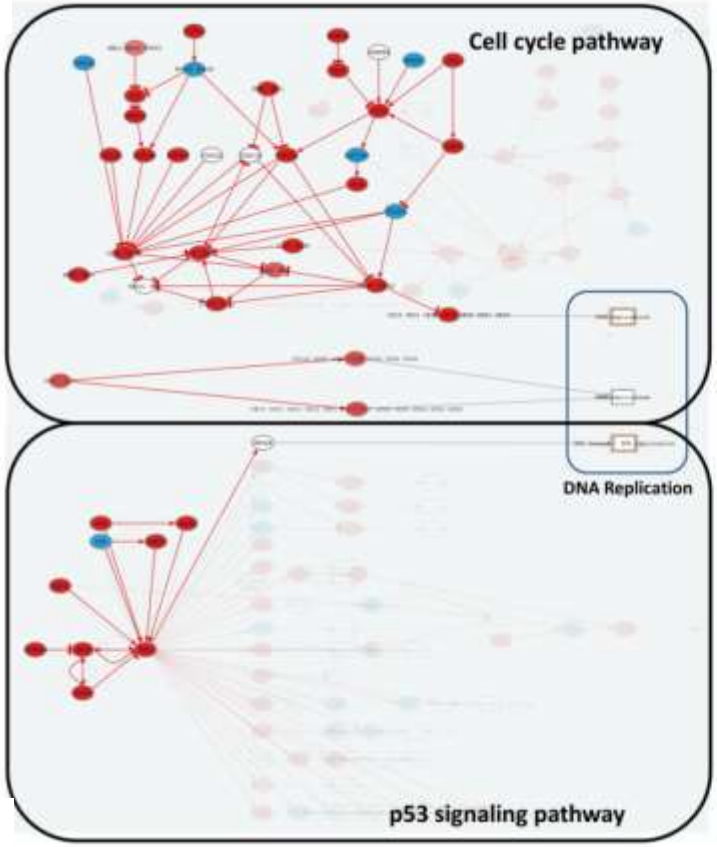
Also, predictors based on signaling activity features can be built

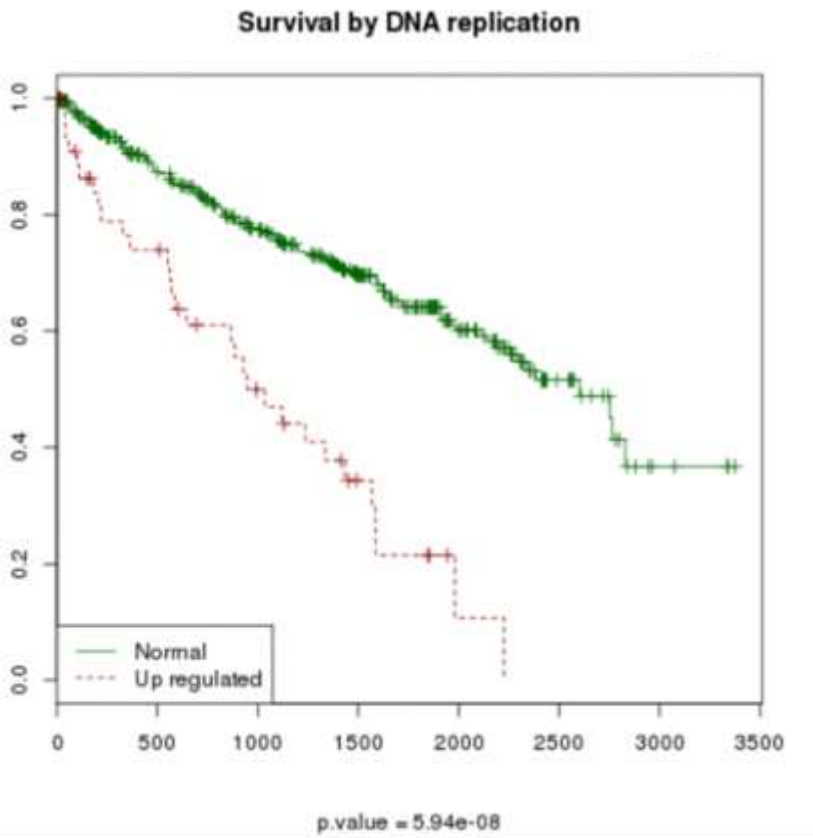
Hipathia has the best sensitivity and specificity rates





Signaling activity trigger cell functions directly related to cancer progression



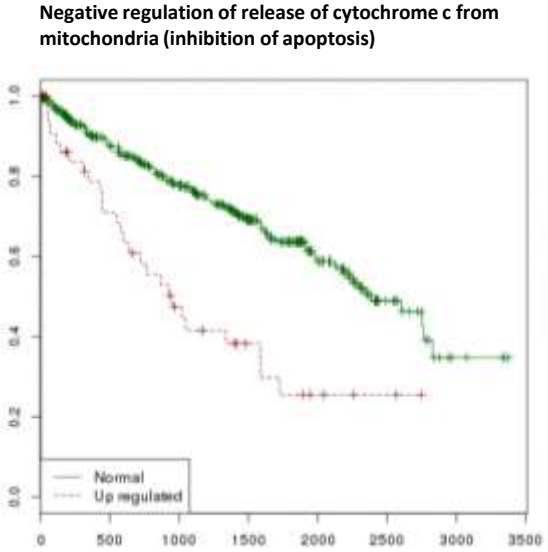


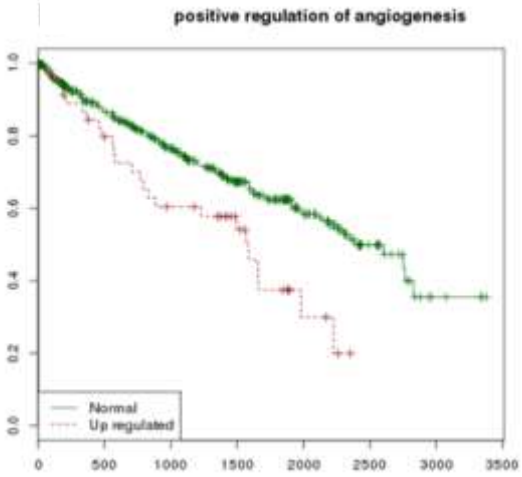
Hidalgo et al., 2017 Oncotarget

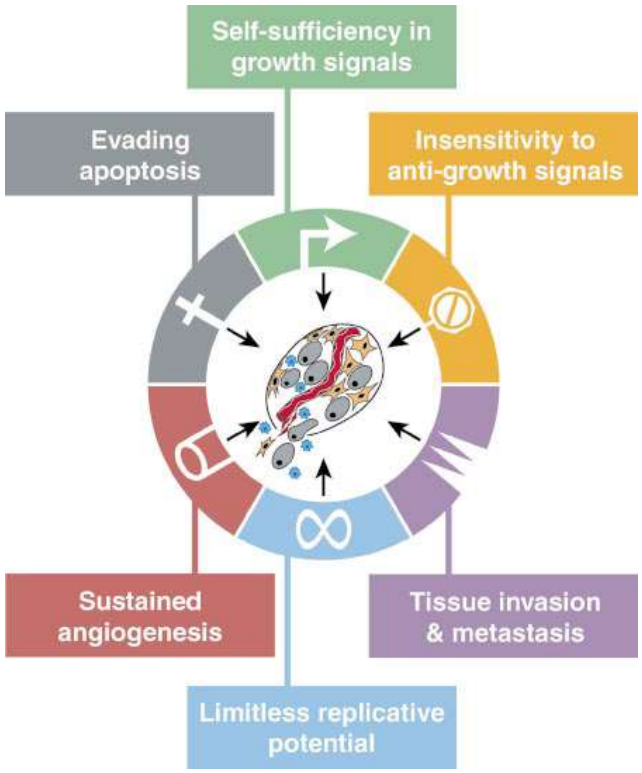
DNA replication= f(gene$_1$, gene$_2$, … gene$_n$)

DNA replication function is a **construct**: the activity is **inferred** not measured

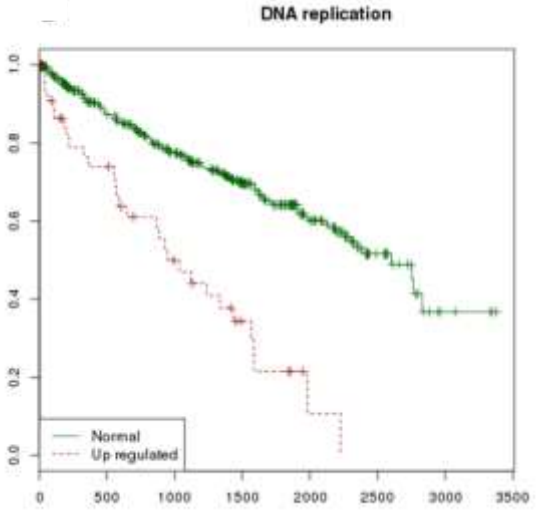
Actually, signal activity triggers all the cancer hallmarks

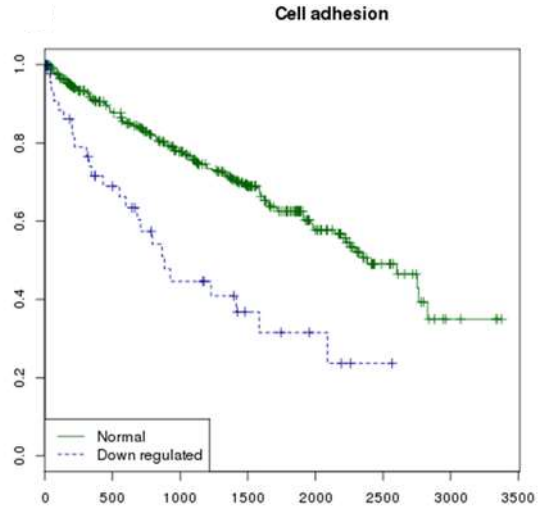






Hanahan, Weinberg, 2011
Hallmarks of cancer: the next generation. Cell 144, 646





Actionable models

The real advantage of models is that, the same way they can be used to convert omics data into measurements of cell functionality that provide information on disease mechanisms and drug MoA, they can be used to test hypothesis such as "*what if I suppress (or over-express) this (these) gen(es)?*" This lead to the concept of **actionable models**.

By **simulating** changes of gene expression/activity it is easy to:

- Directly study of the consequences of induced gene over-expressions or KOs
- Carry out reverse studies of genes that need to be perturbed to change cell functionalities, such as:
  - Reverting the "normal" functional status of a cell
  - Selectively kill diseased cells without affecting normal cells
  - Enhancing or reducing cell functionalities (e.g., apoptosis or proliferation, respectively, to fight cancer)
  - Etc.

Interventions on pathways made easy

Nucleic Acids Research, 2016 1
doi: 10.1093/nar/gkw369

Actionable pathways: interactive discovery of therapeutic targets using signaling pathway models

Francisco Salavert[1,2], Marta R. Hidago[1], Alicia Amadoz[1], Cankut Çubuk[1], Ignacio Medina[3], Daniel Crespo[1], Jose Carbonell-Caballero[1] and Joaquín Dopazo[1,2,4,*]

[1]Computational Genomics Department, Centro de Investigación Príncipe Felipe (CIPF), Valencia, 46012, Spain, [2]Bioinformatics in Rare Diseases (BiER), Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Valencia, 46012, Spain, [3]HPC Service, University Information Services, University of Cambridge, Cambridge, CB3 0RB, UK and [4]Functional Genomics Node, (INB, PRB2, ISCIII) at CIPF, Valencia 46012, Spain

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Freely available software PathAct
http://pathact.babelomics.org/

Tutorial

- **Introduction**
- **Hipathia: differential signaling activity**
- **Pathact: Estimation of the effect of interventions over signaling activity**

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Joaquín Dopazo

Kinza Rian

Marta Hidalgo

Clinical Bioinformatics Area, FPS,
Hospital Virgen del Rocío,
Seville, Spain
http://www.clinbioinfosspa.es

Bioinformatic and Biostatistic Unit, CIPF, Valencia, Spain
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