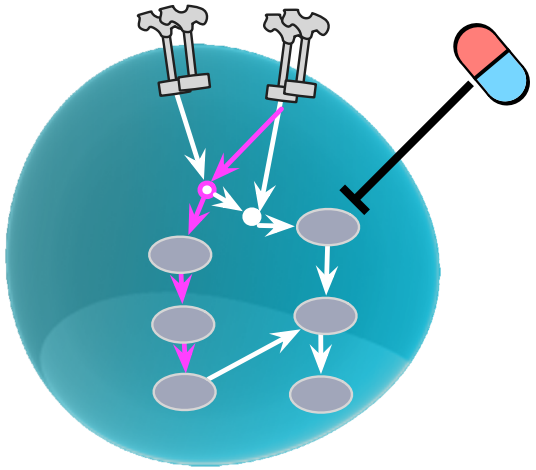
A logic modelling workflow for systems pharmacology



Luis Tobalina

13/07/2018

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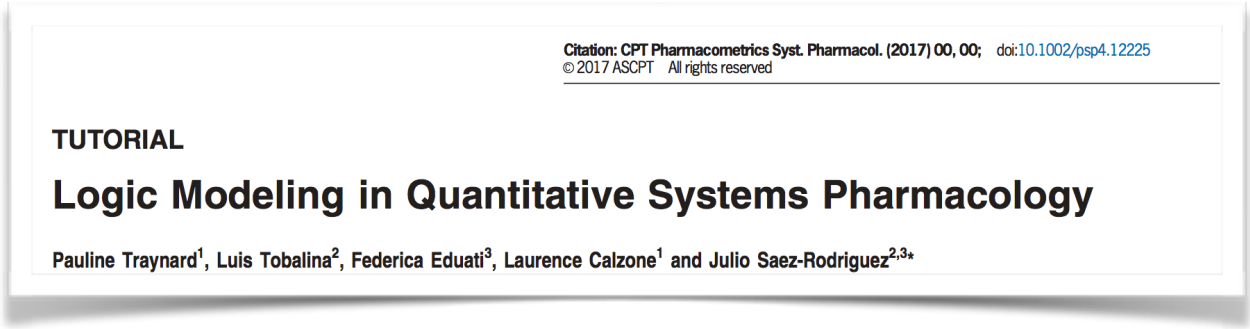
@sysbiomed

Institute for Computational Biomedicine
Heidelberg University & RWTH Aachen

Outline

- Context
- Pipeline
- Network
- Modelling
- Data
- Insights
- Summary



Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 00, 00; doi:10.1002/psp4.12225

TUTORIAL

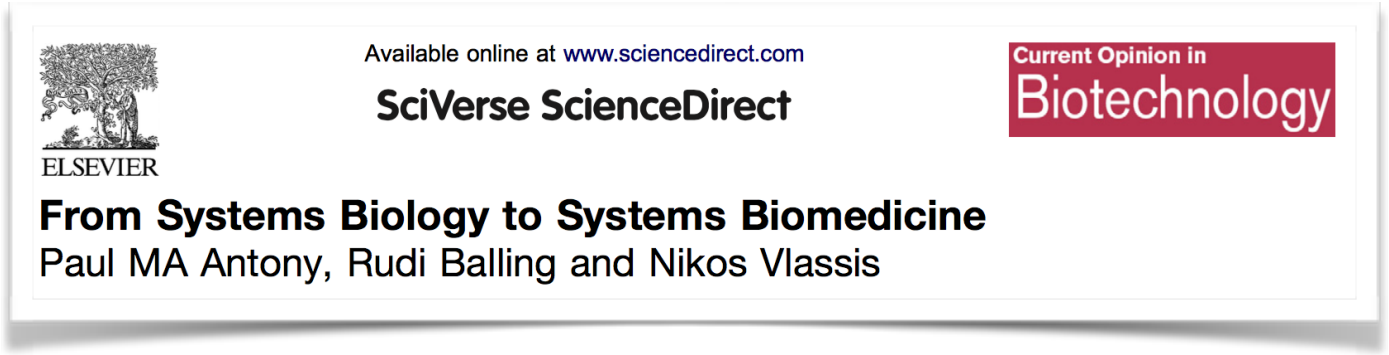
Logic Modeling in Quantitative Systems Pharmacology

Pauline Traynard[1], Luis Tobalina[2], Federica Eduati[3], Laurence Calzone[1] and Julio Saez-Rodriguez[2,3]*

Systems Biomedicine

- Systems Biology examines how cell components interact and form networks and how the networks generate whole cell functions corresponding to observable phenotypes (Palsson, 2006)

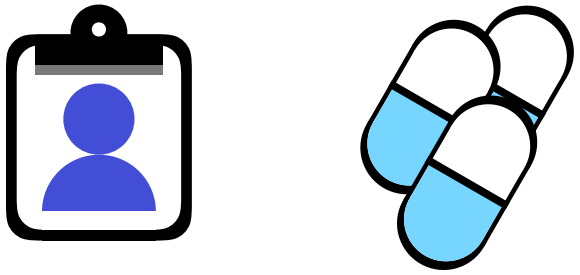
- Systems Biomedicine addresses the challenge of translating insights in biological systems to clinical application



Systems Pharmacology

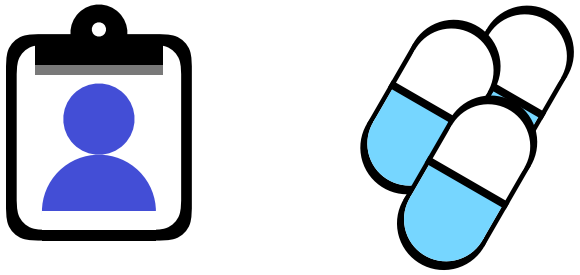
- Systems Pharmacology is the application of the concepts of systems biomedicine to pharmacology in order to understand the full effect of a drug

- Personalised medicine aims to match each patient with their most beneficial treatment



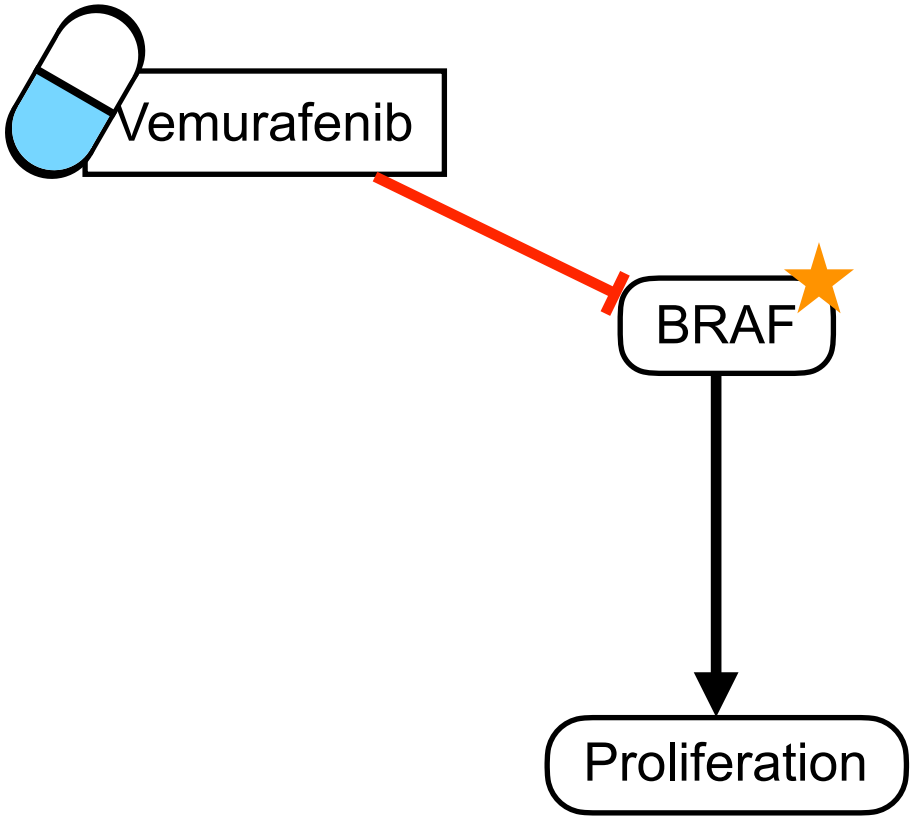
Disease and Therapy

- Identifying key drivers of a disease helps us to design targeted therapies
- Drug combinations may help in diseases driven by several altered proteins
- In diseases like cancer, we also have to address development of resistance to the applied therapy
- Not all the targets are actionable
- Not all the therapies need to target the diseased cell: immunotherapy



Importance of signalling networks

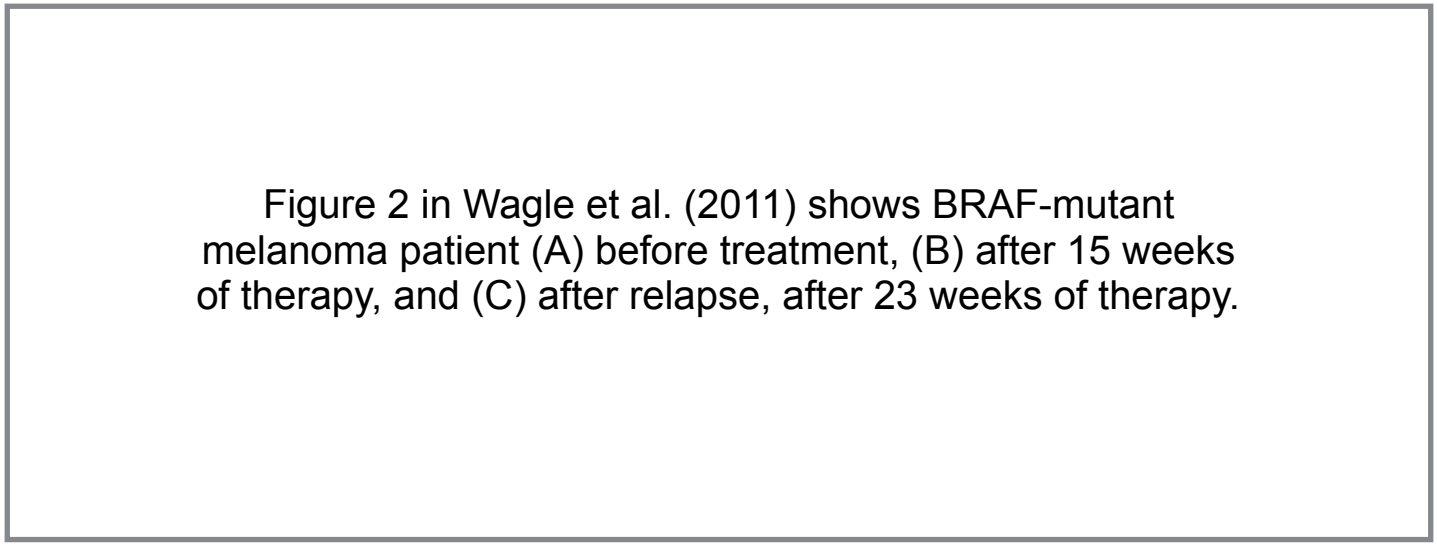
- Melanoma patients with BRAF mutation show response to BRAF inhibitors



Note: simplified interaction diagram

Importance of signalling networks

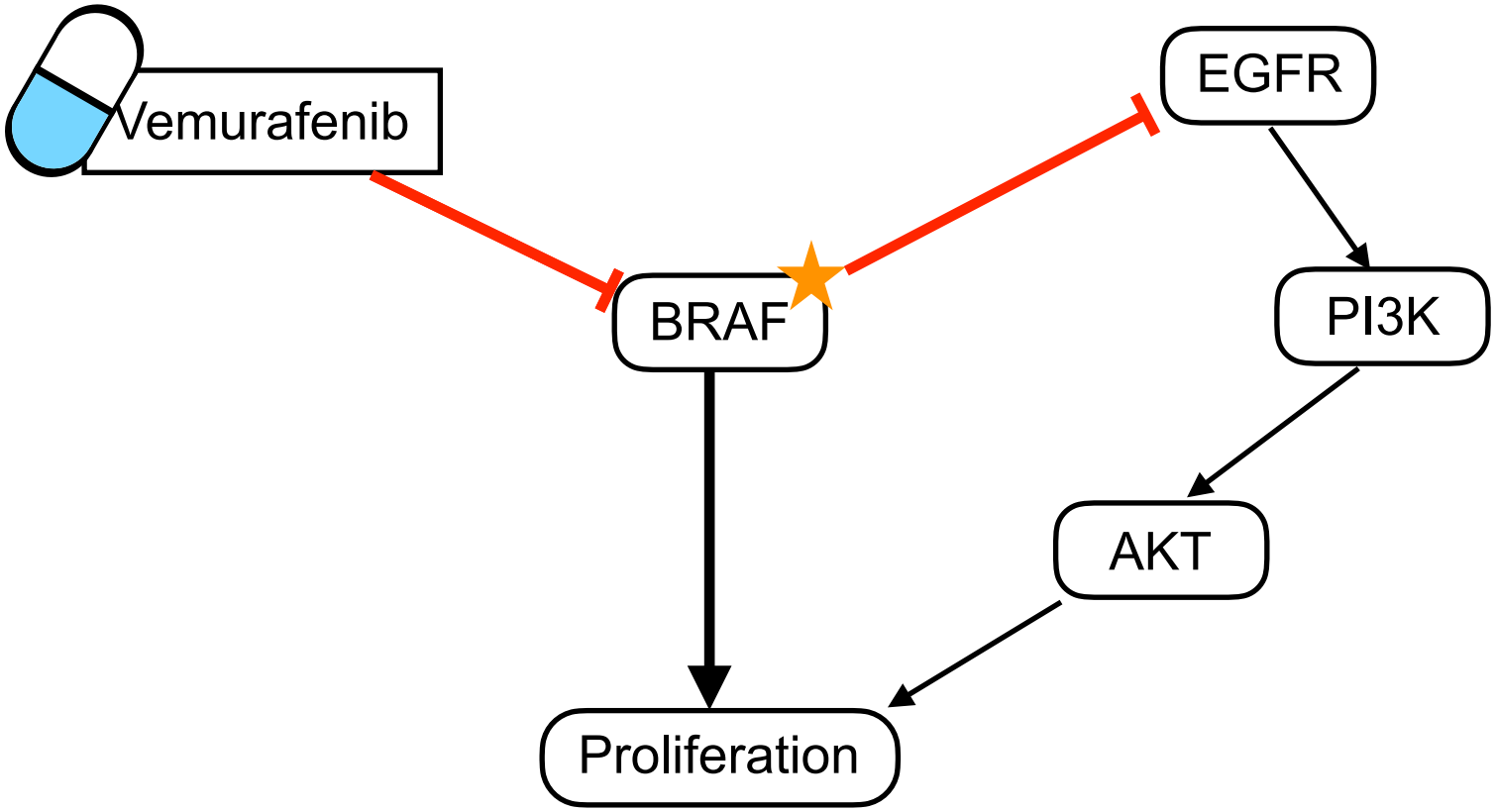
- But resistance to treatment eventually develops, leading to relapse



Wagle et al., *J Clin Inv*, 29:22, 2011

Importance of signalling networks

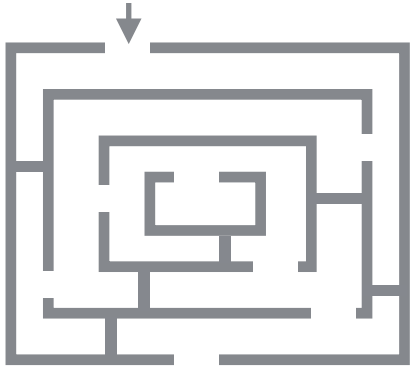
- Colon cancer patients with the same mutation show resistance to treatment because of EGFR feedback loop



Note: simplified interaction diagram

Challenges

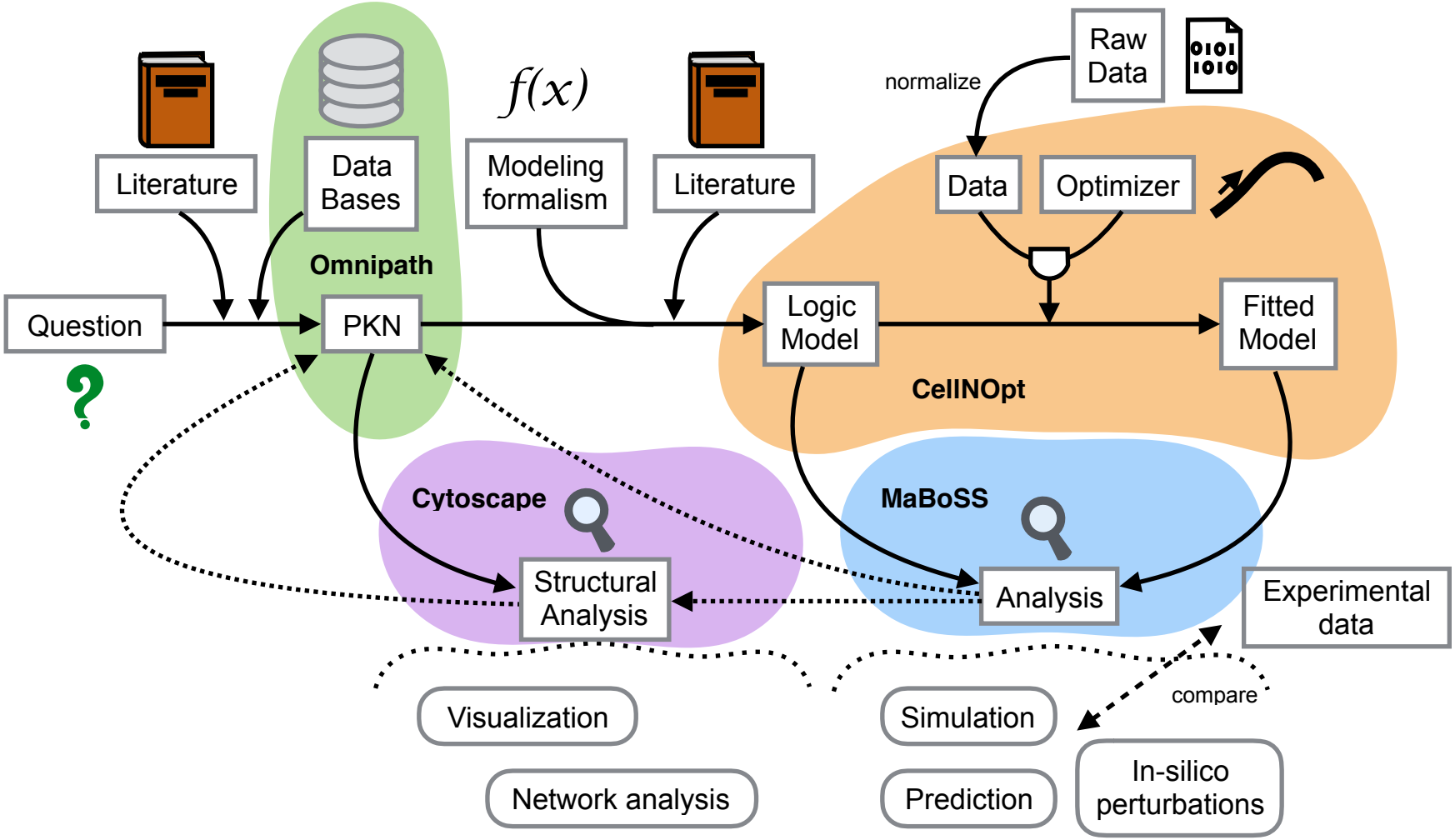
- Biomedical research faces different challenges:
  - Noise
  - Batch effects
  - Small sample size
  - Difficult / Expensive experiments



- Possible ways of dealing with these:
  - Well thought and designed experiments
  - Pool information from different studies
  - Use of prior knowledge
  - Development of mathematical models

$f(x)$

Pipeline overview



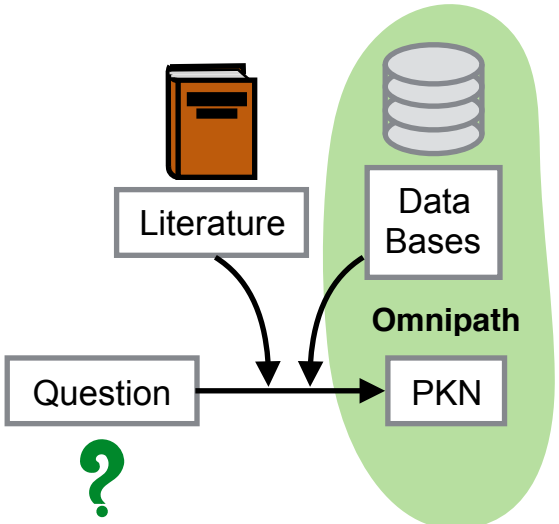
Traynard et al. *CPT: Pharmacometrics & systems pharmacology* 2017

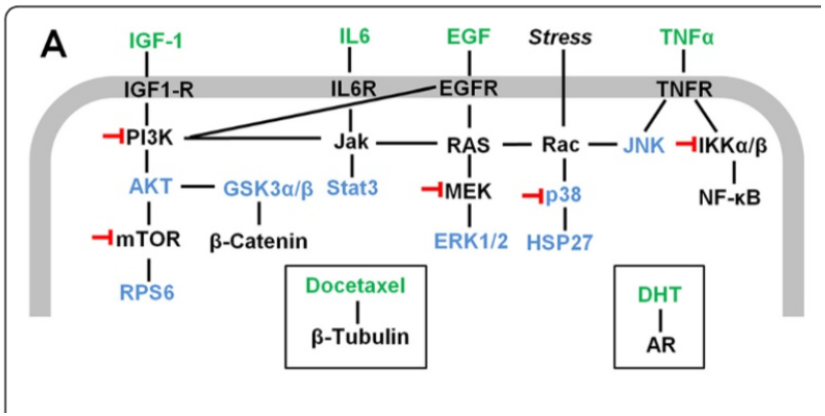
Biological question

- The first step of modelling is to start with a biological question of interest

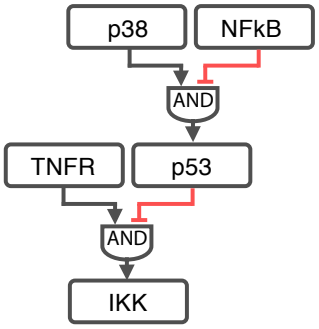
- Example: what are the changes in the phosphoproteomic response to the PI3K pathway when a prostate cancer cell goes from being castration sensitive to castration resistant

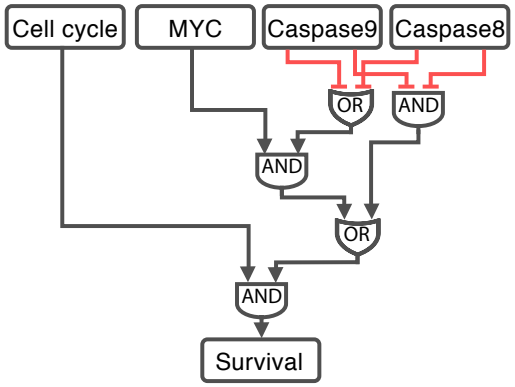
Network model





Lescarbeau and Kaplan *BMC Cancer* 2014, **14**:325
http://www.biomedcentral.com/1471-2407/14/325

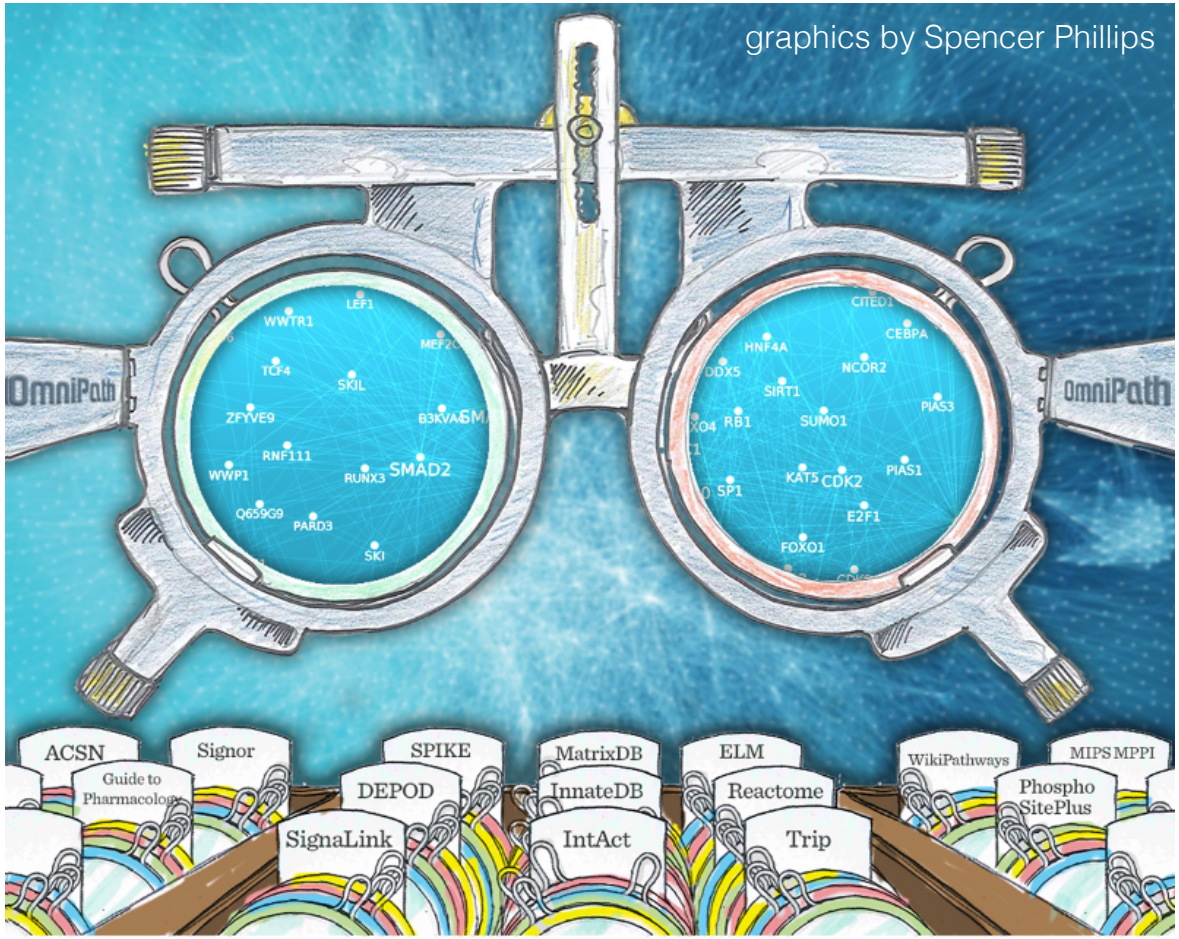




Türei et al. *Nature Methods* 2016

OmniPath

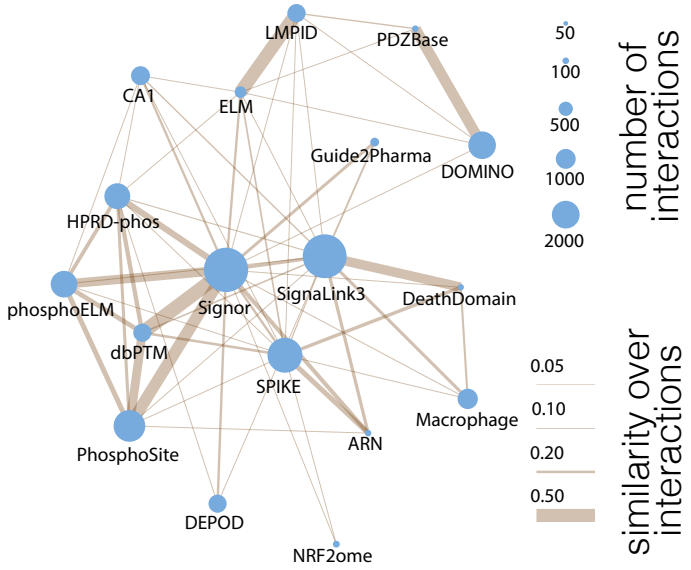
- http://omnipathdb.org



Türei, Korcsmáros & Saez-Rodriguez (2016). Nat Methods, 13(12)966-967.

OmniPath

- OmniPath is a comprehensive collection of literature curated human signaling pathways
- Why Omnipath?

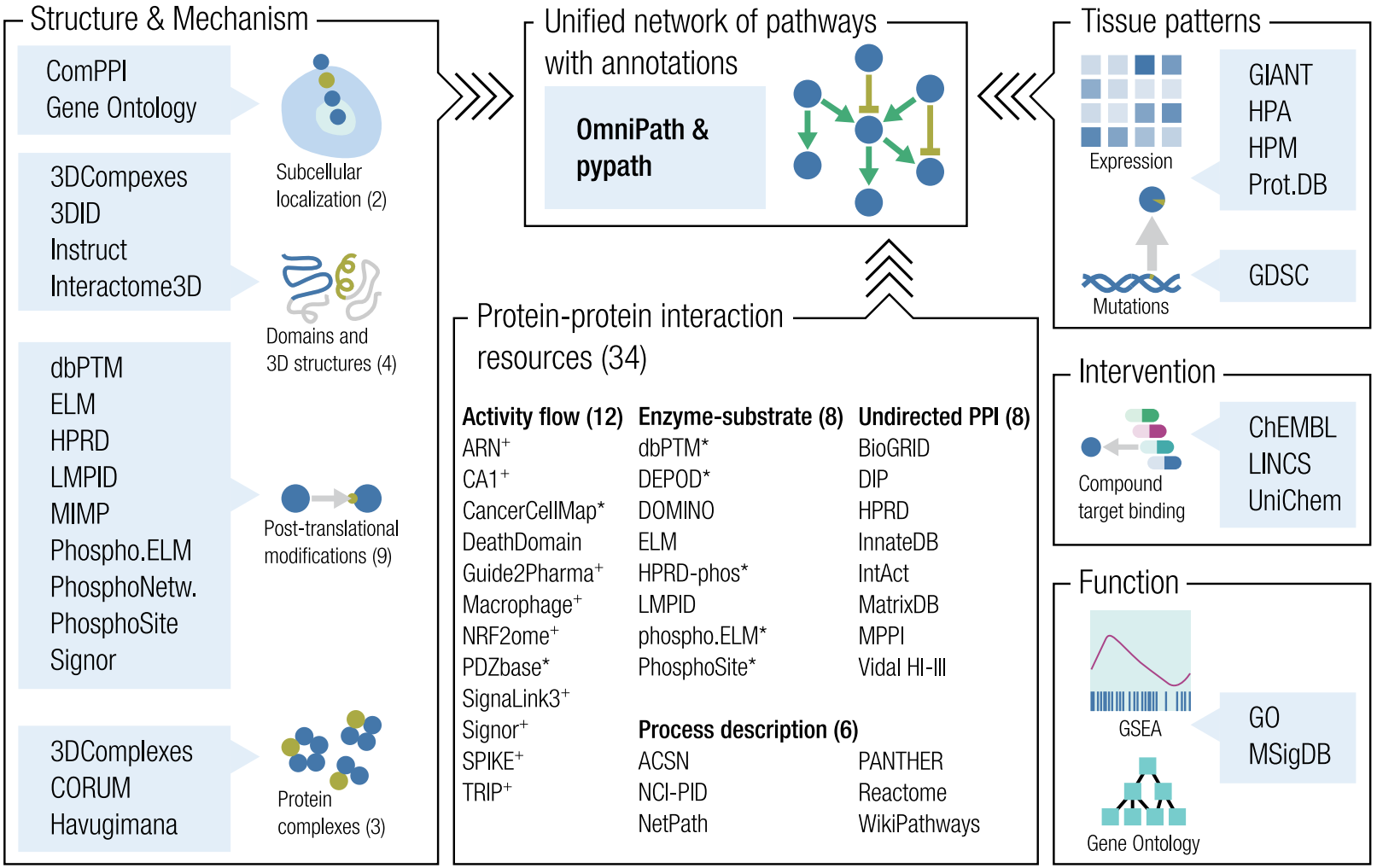


Türei, Korcsmáros & Saez-Rodriguez (2016)

http://omnipathdb.org/

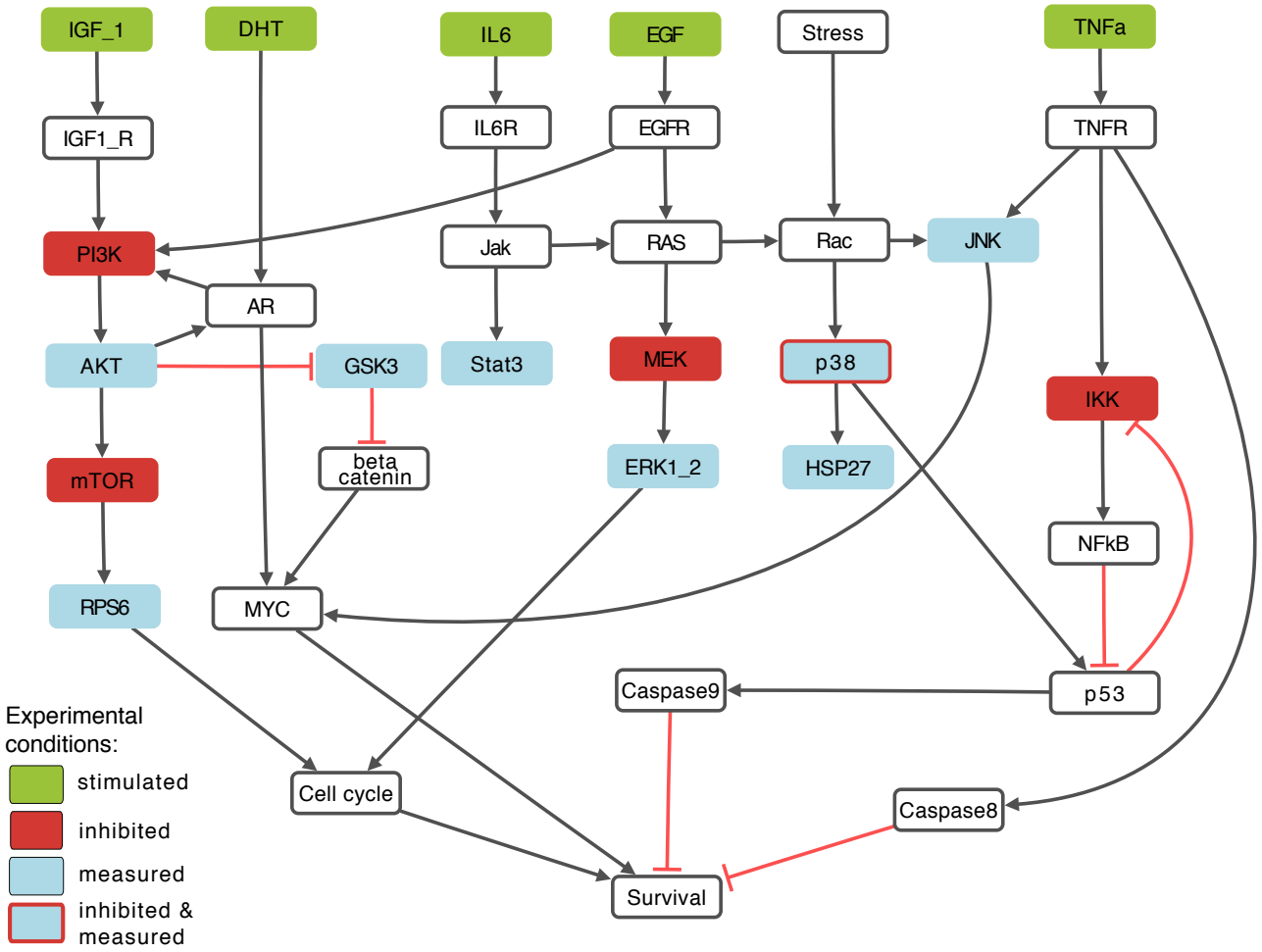
- Available via a webservice or using pypath, a Python module for molecular networks and pathways analysis

OmniPath

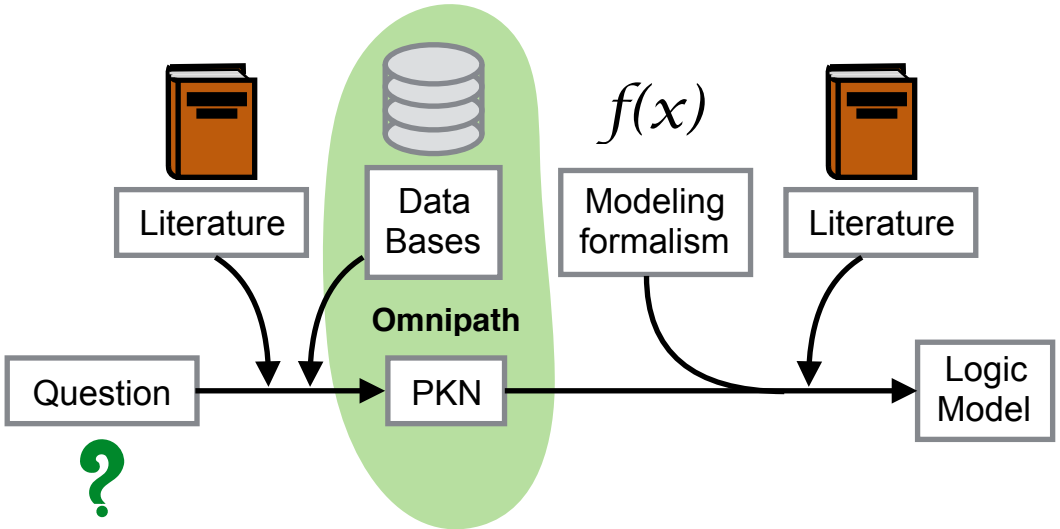


Türei, Korcsmáros & Saez-Rodriguez (2016)

Network model

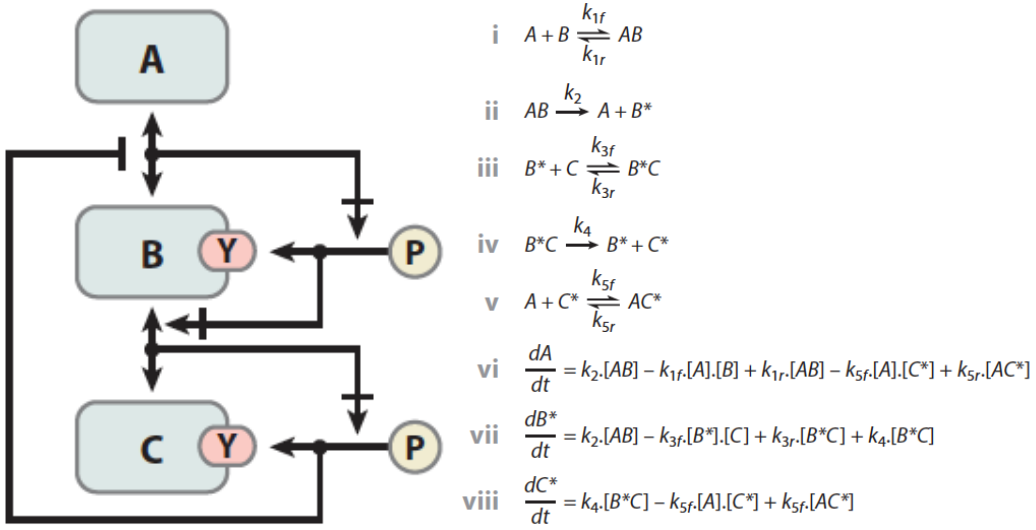


Logic model

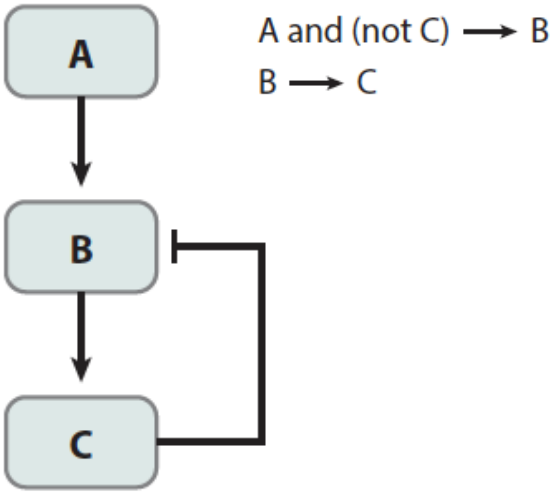

Literature
Data Bases
f(x)
Modeling formalism
Literature
Omnipath
Question
PKN
Logic Model
?

Choice of modelling formalism

Physicochemical modeling



Causal (logic) modelling

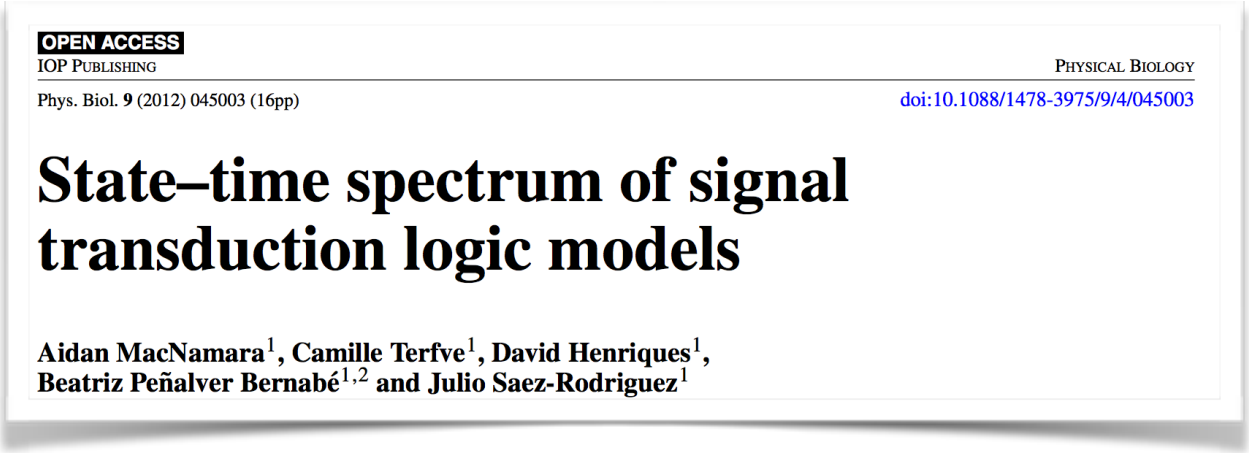


The amount of details to include in the model and the **mathematical formalism** used to describe the process should be **lead by the biological question** (and by available data).

Figures from: Saez-Rodriguez J, et al. *Annual Rev Biomed Eng*, 2015

Variety of formalisms

- Boolean simulation with synchronous updates
- Constrained fuzzy logic
- Simulations with multiple time-scales
- Logic based ODEs
- …



OPEN ACCESS

IOP PUBLISHING — PHYSICAL BIOLOGY

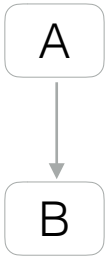
Phys. Biol. **9** (2012) 045003 (16pp) — doi:10.1088/1478-3975/9/4/045003

State–time spectrum of signal transduction logic models

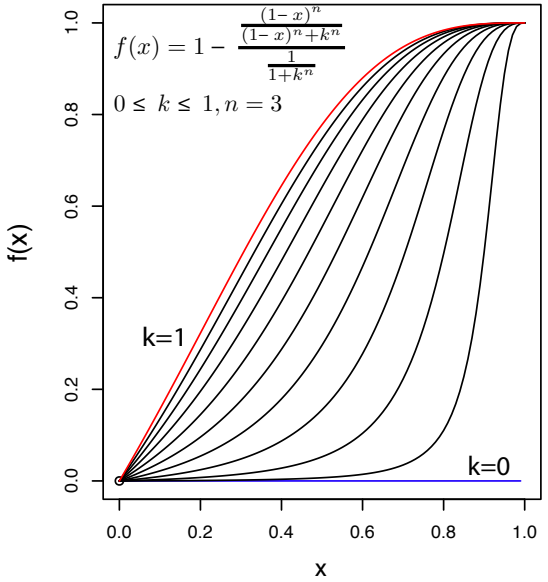
Aidan MacNamara[1], Camille Terfve[1], David Henriques[1], Beatriz Peñalver Bernabé[1,2] and Julio Saez-Rodriguez[1]

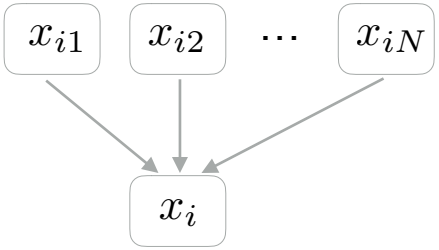
Using logic ODE as modelling formalism

Based on ordinary differential equations derived from logic models using a continuous update function



$$\frac{dx_B}{dt} = \tau_B[f(x_A) - x_B]$$





$$\frac{dx_i}{dt} = \tau_i(B_i(f(x_{i1}), f(x_{i2}), \ldots, f(x_{iN})) - x_i)$$

DM Wittmann, et al., 2009, BMC Systems Biology
F Eduati, 2017, Cancer Research

Using logic ODE as modelling formalism

- Easily interpretable parameters

τ_i is the life-time of species *i*
=0 node not functional
>0 higher functionality

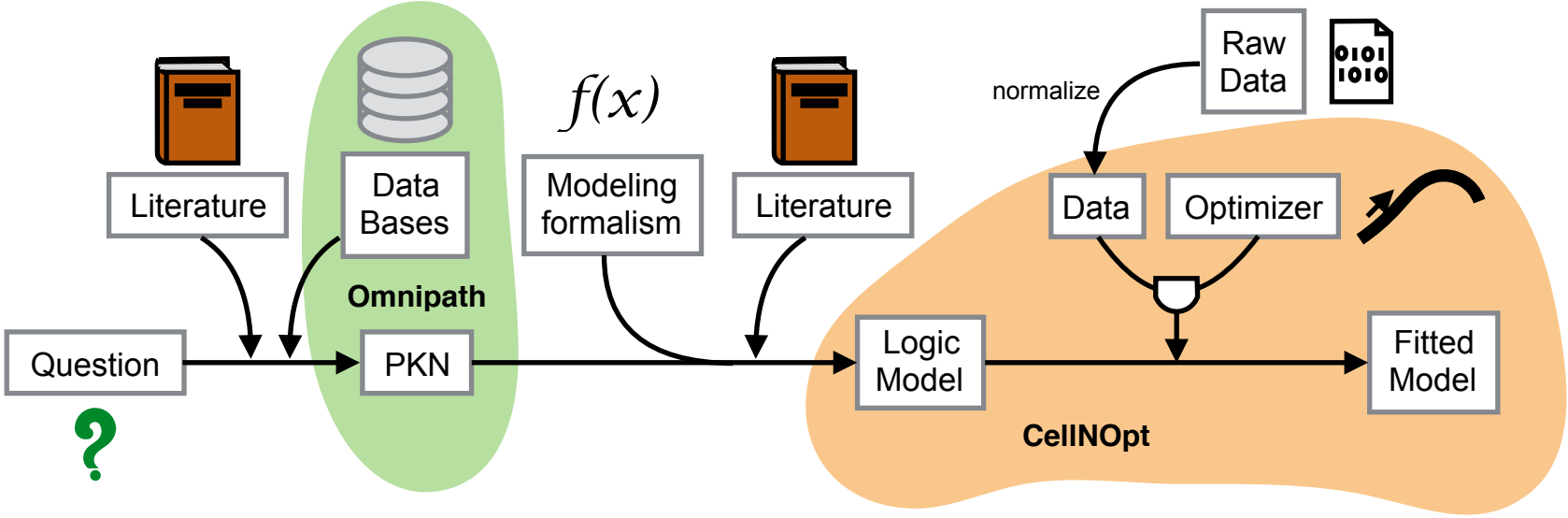
k_{ij} strength of regulation j → i
=0 no edge
>0 stronger interaction

- Direct derivation from logic rules

Generalisation for OR gates

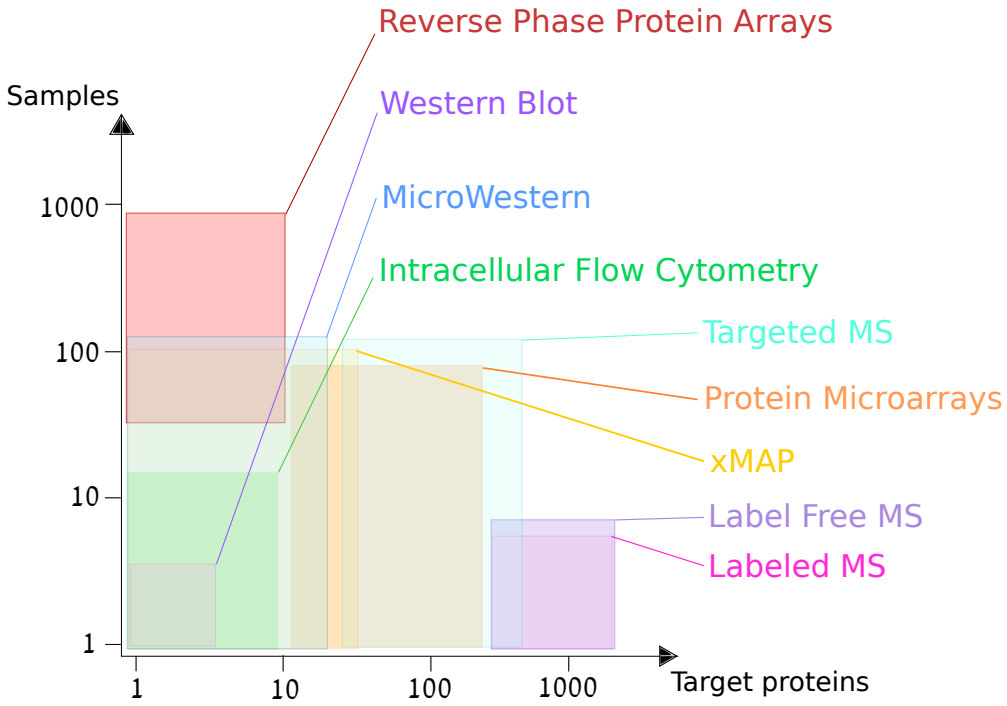
x_1	x_2	$B(f(x_1), f(x_2)) = ...$
0	0	$0(1 - f(x_1))(1 - f(x_2))+$
0	1	$(1 - f(x_1))f(x_2)+$
1	0	$f(x_1)(1 - f(x_2))+$
1	1	$f(x_1)f(x_2)$

Collect data



- Objective: obtain data for training logic models
- Priority: high number of perturbations

Phospho-proteomics to look at signal transduction



Antibody-based methods:

low coverage

many conditions

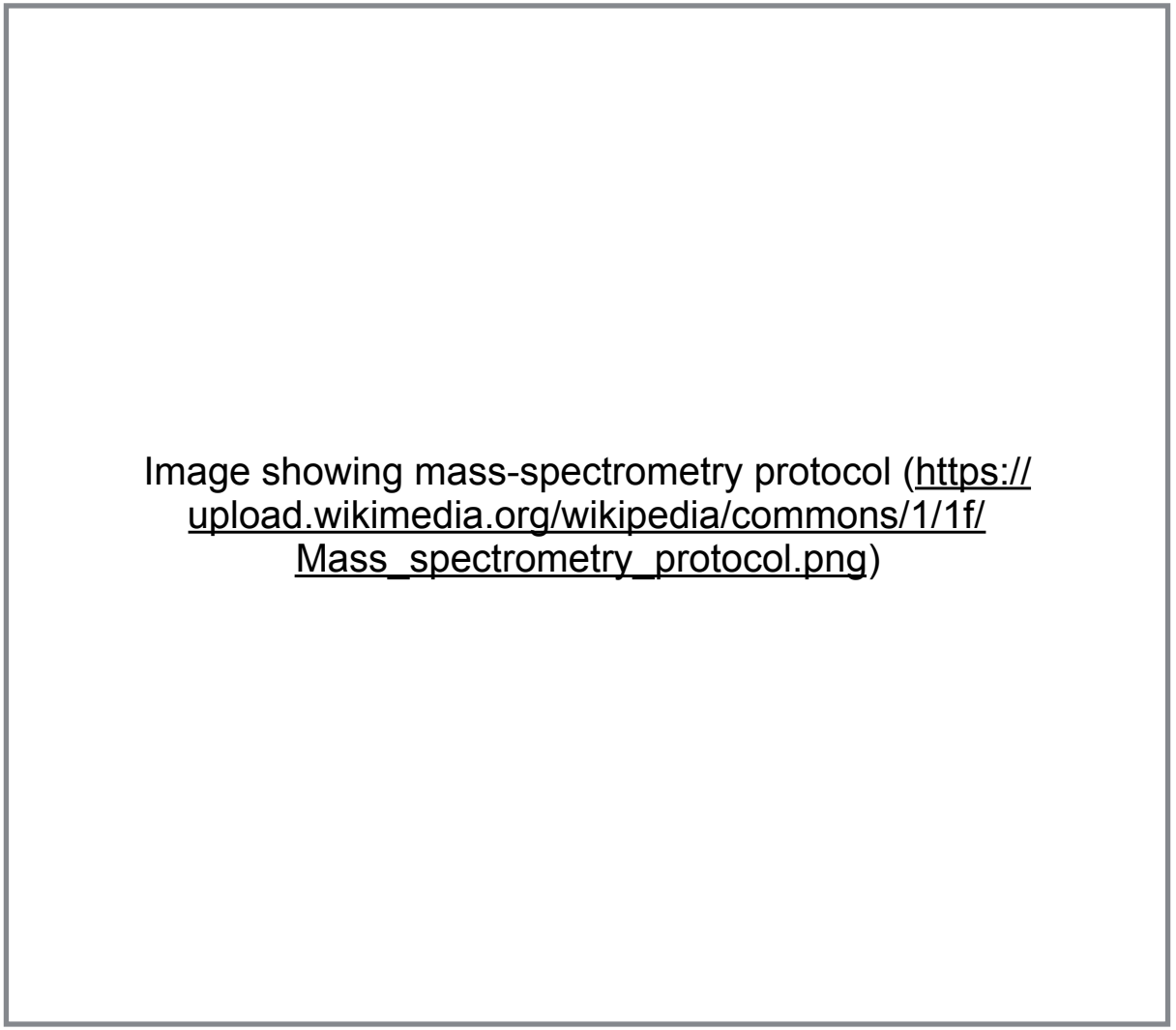
Mass-spectrometry methods:

high coverage

few conditions

Terfve C, Saez-Rodriguez J, *Adv. Syst. Biol.*, 2012
Saez-Rodriguez J, et al. *Annual Rev Biomed Eng*, 2015

Phospho-proteomics



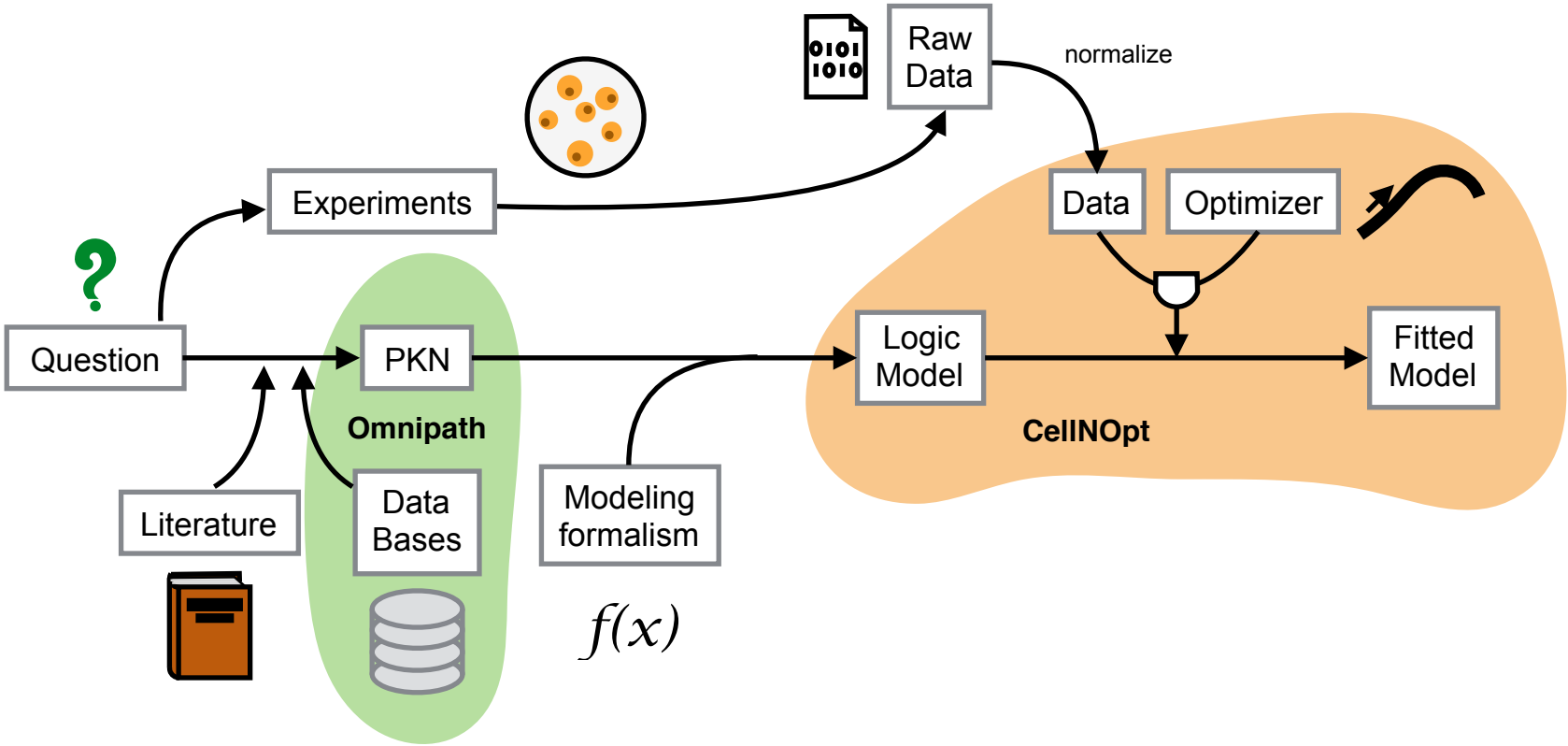
Credit: By Philippe Hupé [CC-BY-SA-3.0 (http://creativecommons.org/licenses/by-sa/3.0)], via Wikimedia Commons

https://pharmchem.ucsf.edu/research/physbio/proteomics

Preparing the data

- Normalisation challenges
  - Boolean logic works with binary values, but measurements are continuous values
  - CellNOpt ODE works with values between 0 and 1
- Coverage challenges
  - Not all the nodes in the model may be covered by the measurements
- Use of derived measurements
  - e.g. Kinase activities

Use data for training models



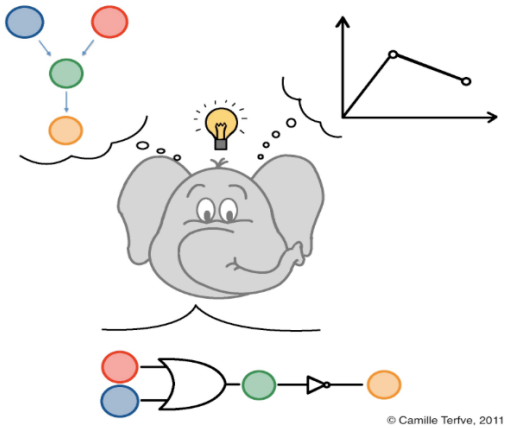
www.cellnopt.org

A flexible pipeline to model protein signalling networks trained to data using various logic formalisms.

CellNOpt packages | *Documentation (model and data sets)* | *Publications* | *For Developers (SVN, etc.)* | *Downloads* | *Contact*

OVERVIEW

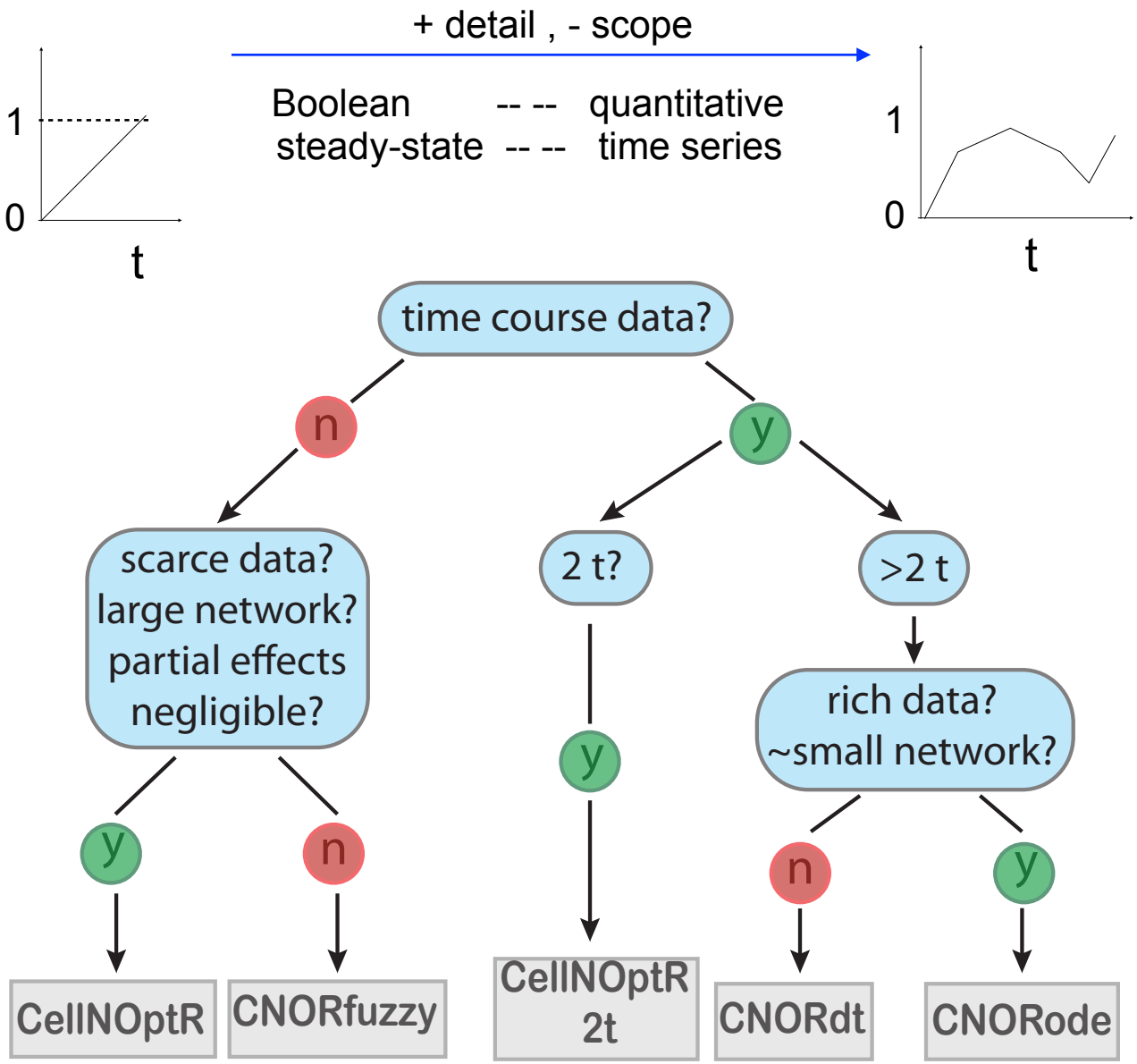
CellNOpt (from CellNetOptimizer; a.k.a. CNO) is a software used for creating logic-based models of signal transduction networks using different logic formalisms (Boolean, Fuzzy, or differential equations). CellNOpt uses information on signaling pathways encoded as a Prior Knowledge Network, and trains it against high-throughput biochemical data to create cell-specific models.



CellNOpt is freely available under GPL license in R and Matlab languages. It can be also accessed through a python wrapper, and a Cytoscape plugin called CytoCopter provides a graphical user interface.

CellNOpt is mainly developed at the Saez-Rodriguez group at the European Bioinformatics Institute (EBI). The project started at the groups of Peter Sorger (Harvard Medical School) and Doug Lauffenburger (M.I.T.). There is a group of CellNOpt developers at different locations.

Broad spectrum of modelling formalism with different level of detail



Terfve C Cokelaer T
MacNamara A Henriques D
Gonçalves E Morris MK
van Iersel M Lauffenburger DA
Saez-Rodriguez J
*BMC Syst Biol, 6:*133, 2012

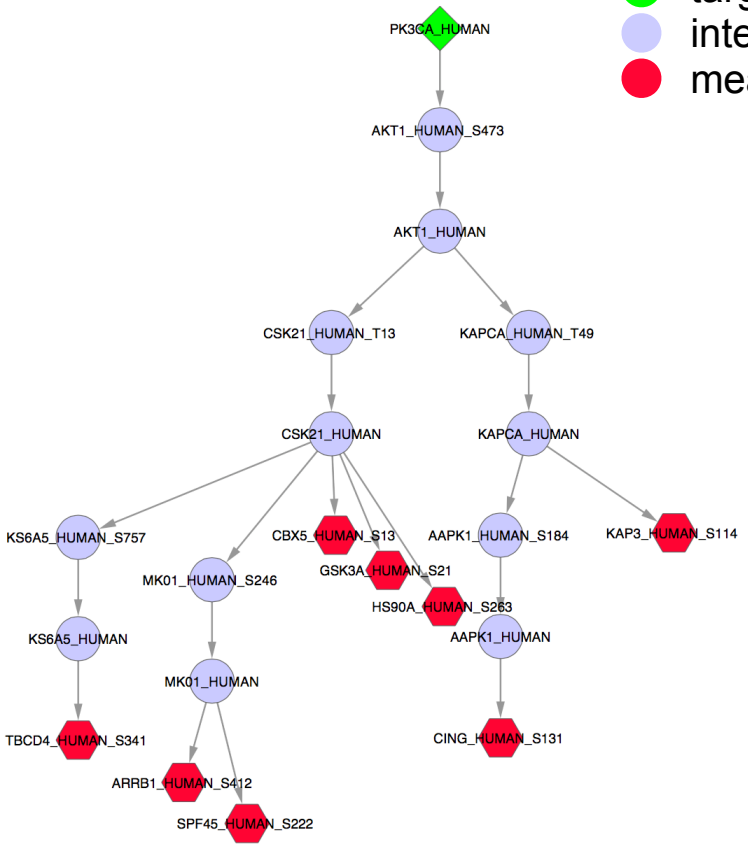
PHONEMeS

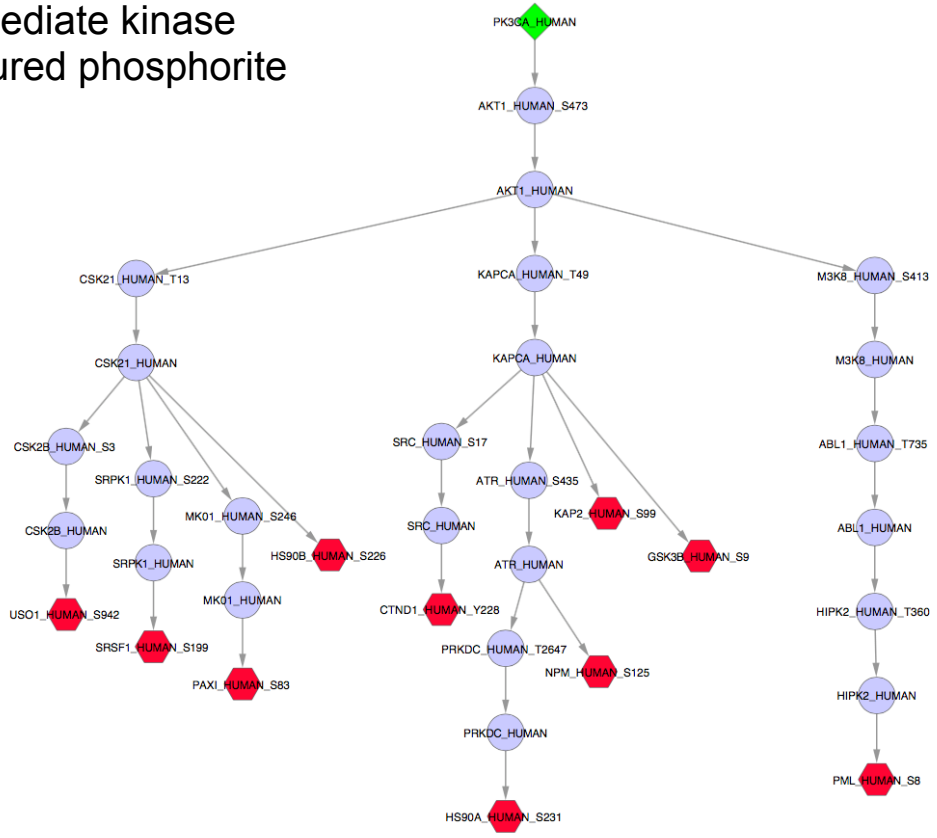
- PHONEMeS (PHOsphorylation NEtworks for Mass Spectrometry) is a method to model signalling networks based on untargeted phosphoproteomics mass spectrometry data and kinase/phosphatase-substrate interactions (Terfve et al. 2015 Nature communications)
- We can use it to combine high-throughput data (SWATH phospho-proteomics) with a large scale background network (e.g. Omnipath)

LNCaP

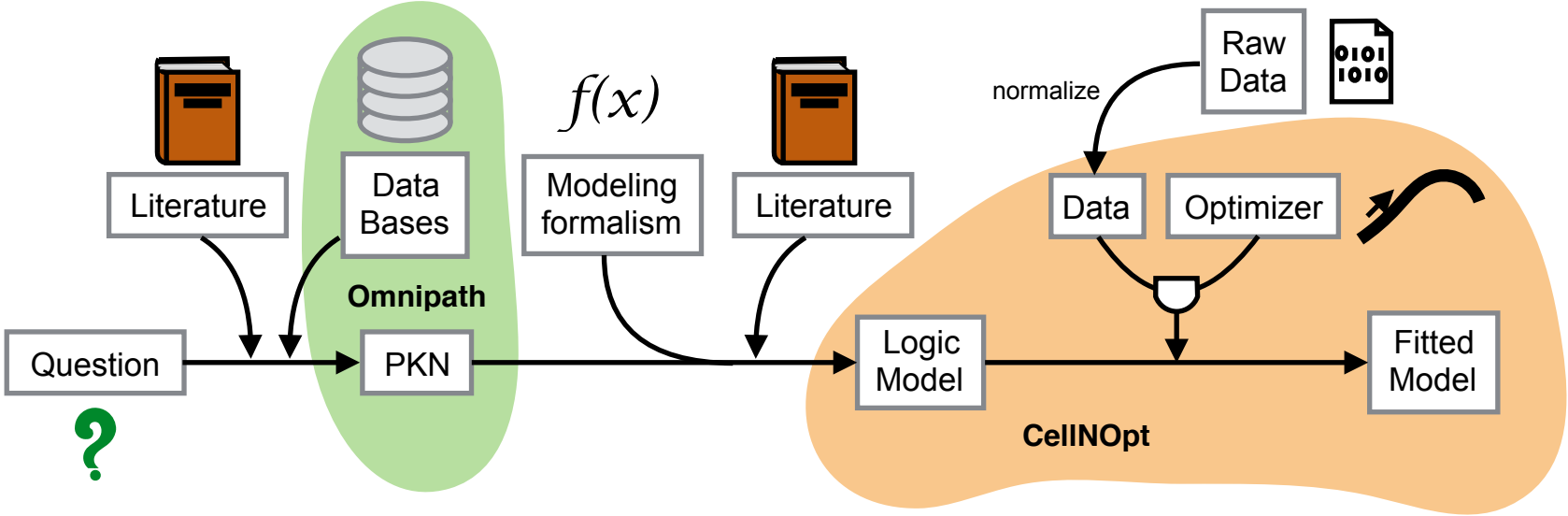
LNCaP-ablated

target kinase
intermediate kinase
measured phosphorite

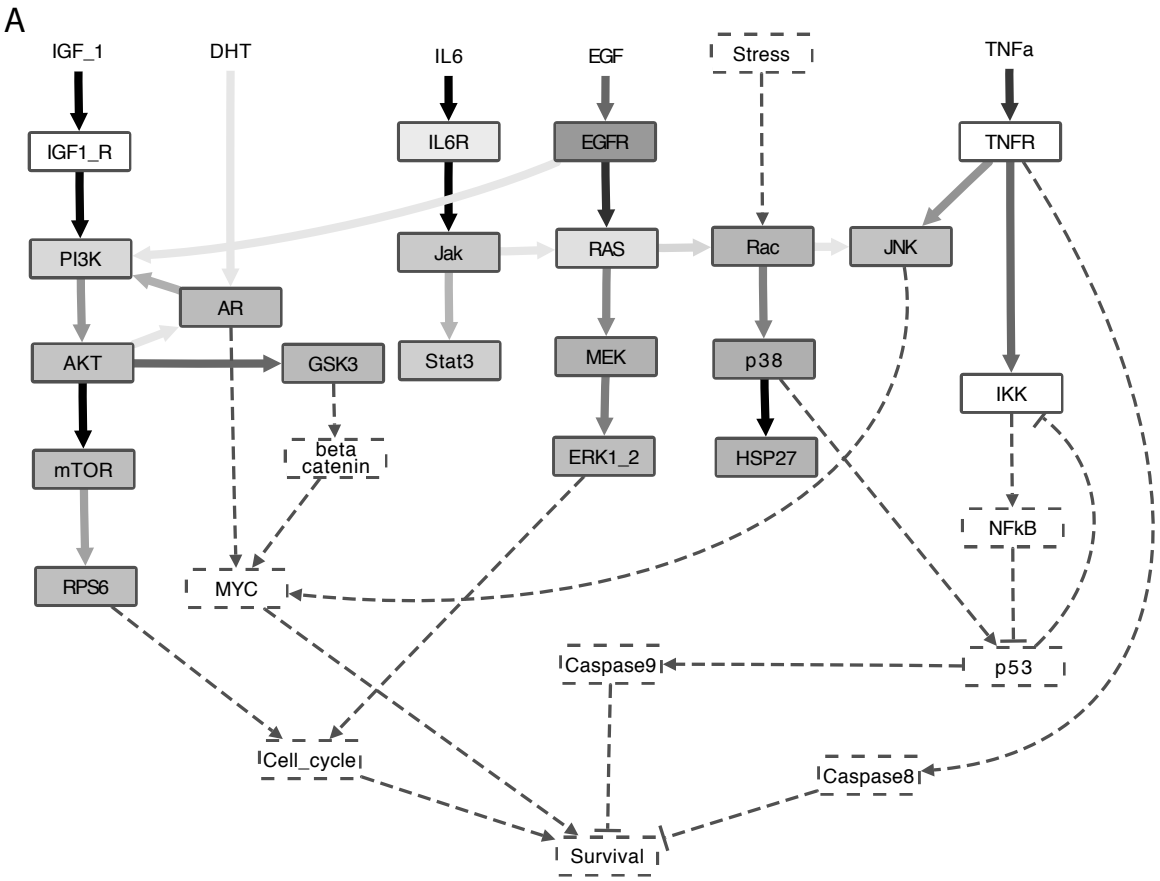


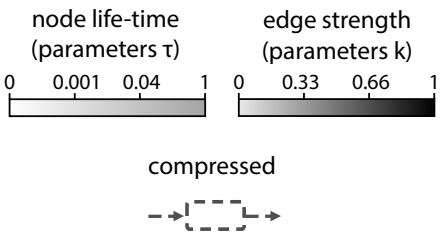


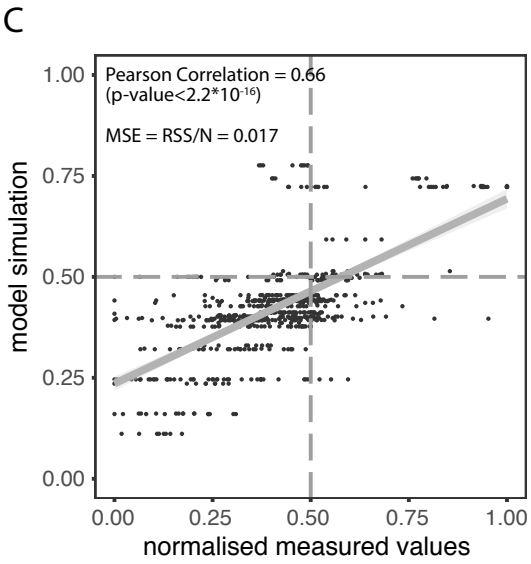
Fitting example



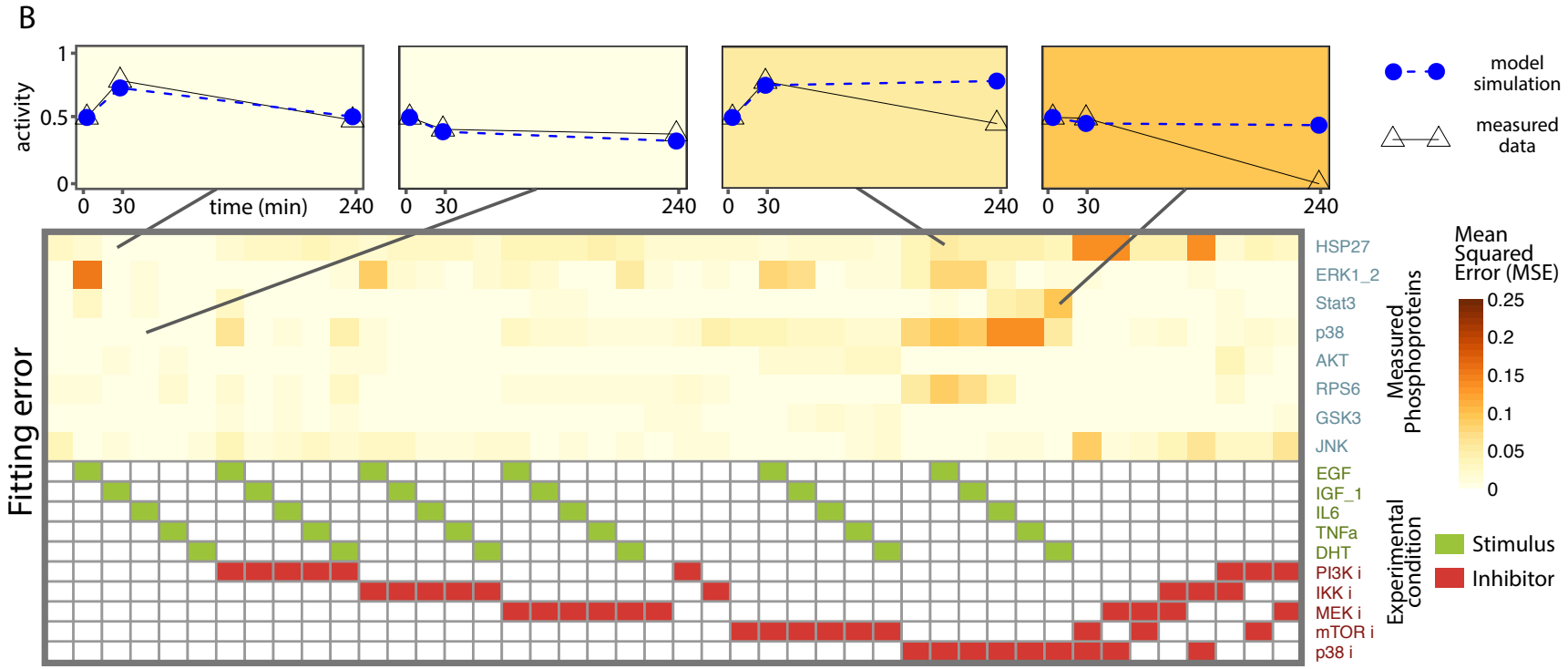
Assessing fitted networks







Assessing fitted networks

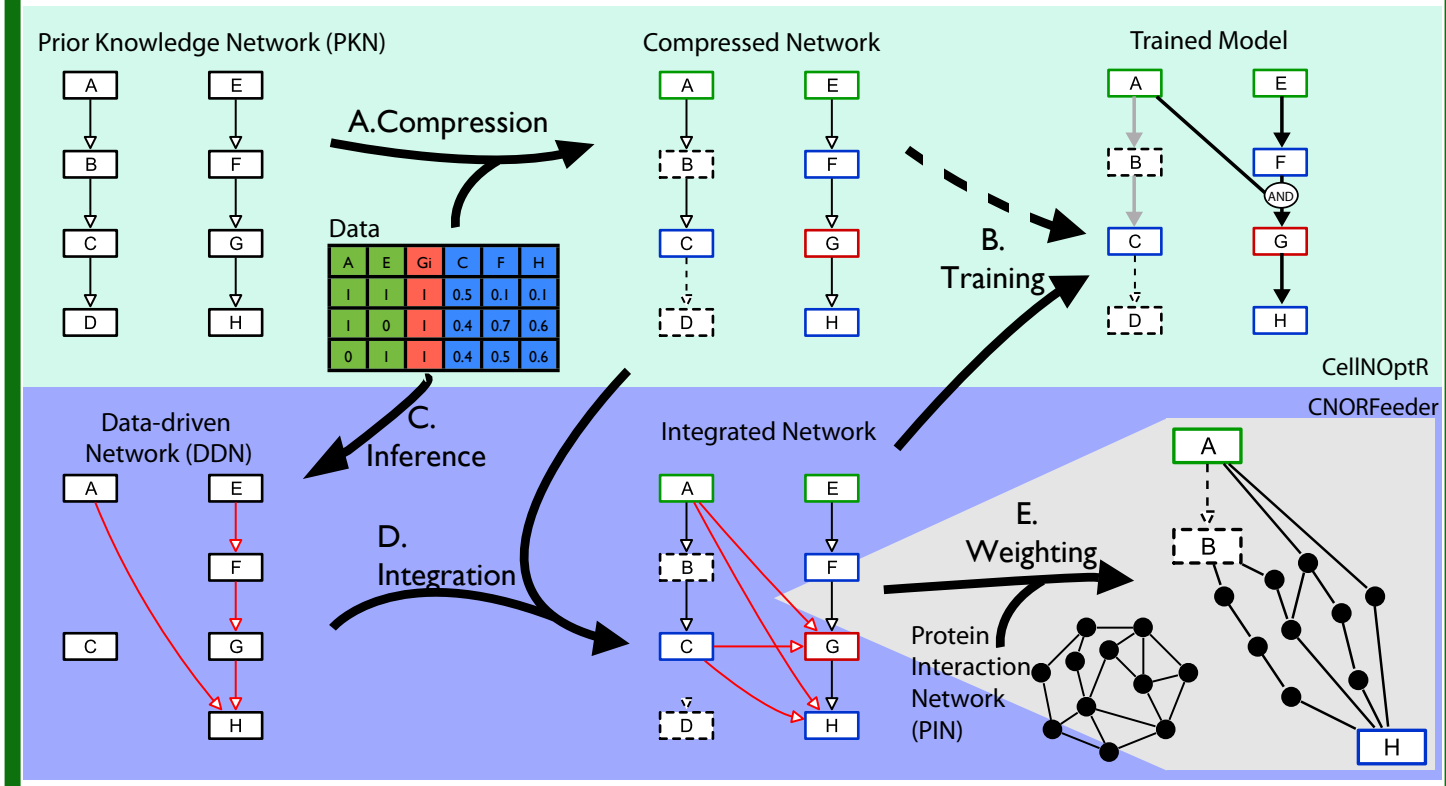


Traynard et al. *CPT: Pharmacometrics & systems pharmacology* 2017

How to deal with incomplete prior knowledge?

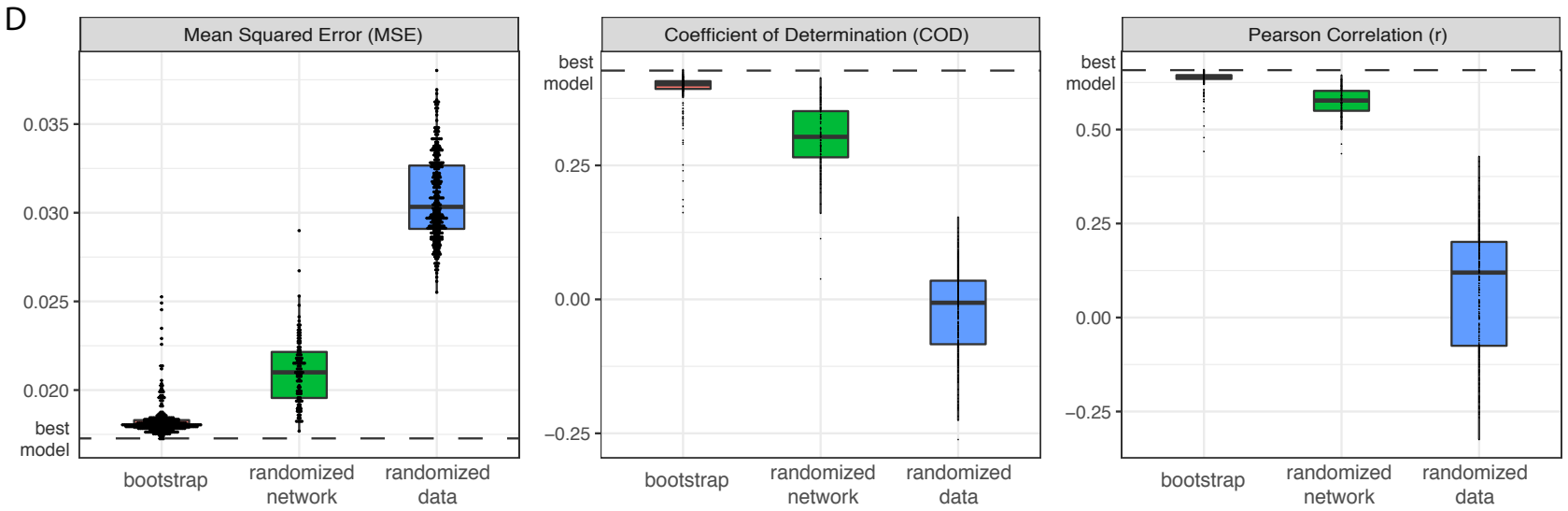
CNOFeed: Link CellNOpt to methods to infer new links

Federica Eduati



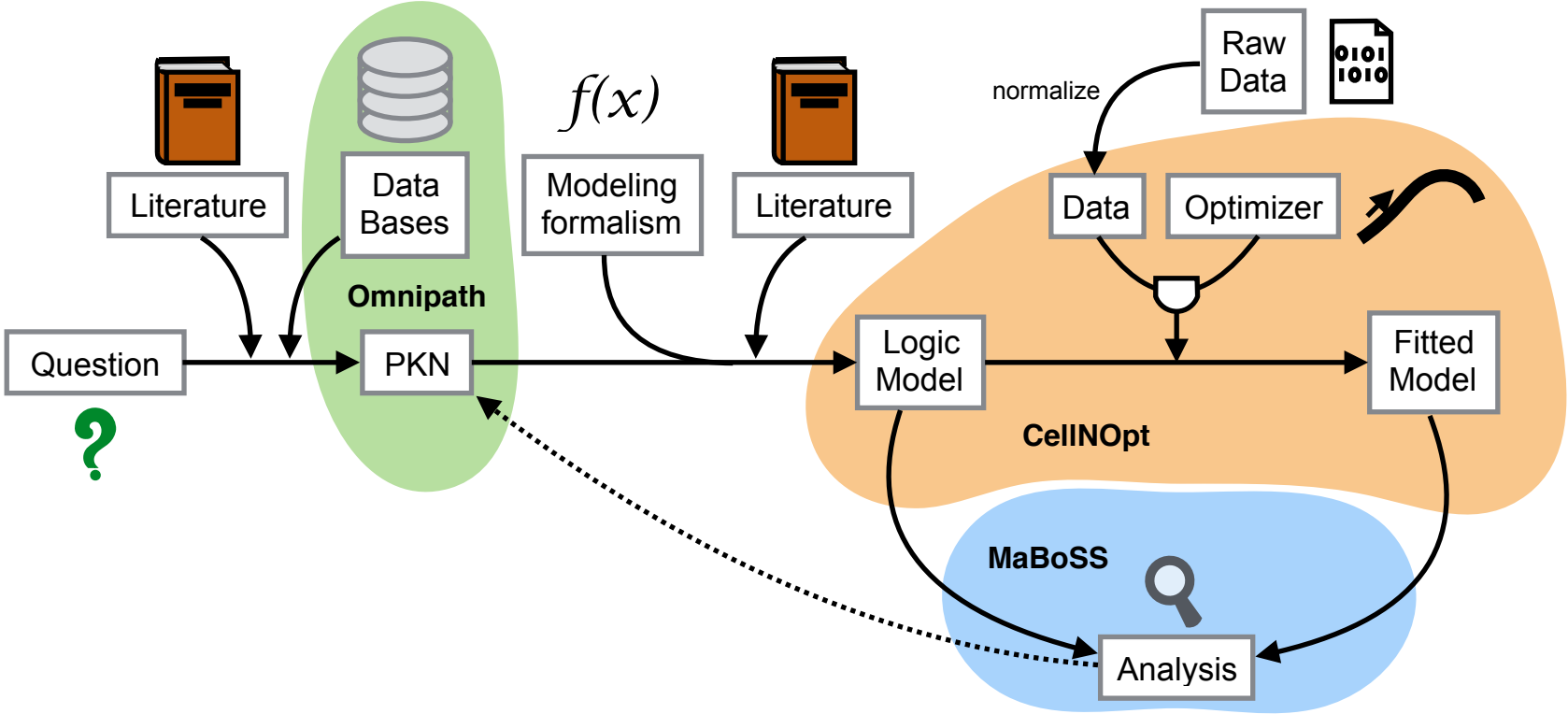
Eduati F, de las Rivas J, di Camilo B, Toffolo G, Saez-Rodriguez J
Bioinformatics 10.1093/bts363, *2012*

Assessing fitted networks



Traynard et al. *CPT: Pharmacometrics & systems pharmacology* 2017

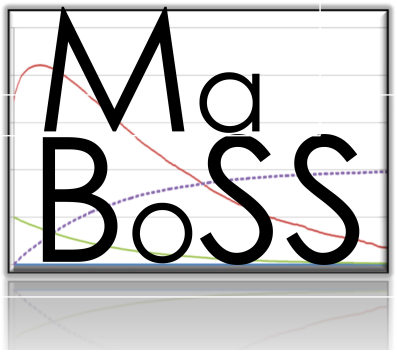
Further analysis



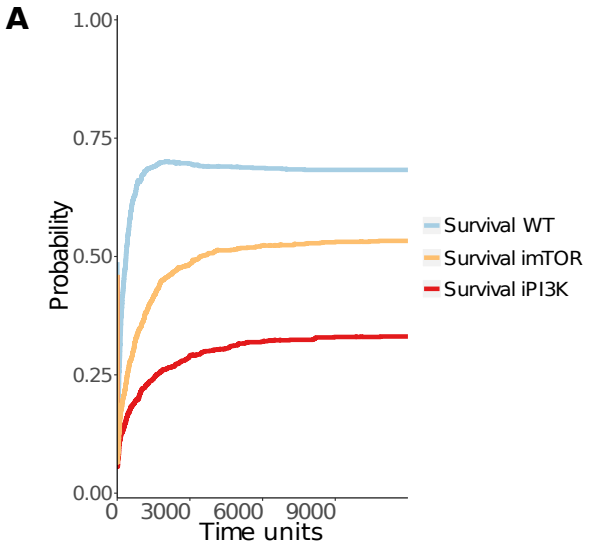
MaBoSS

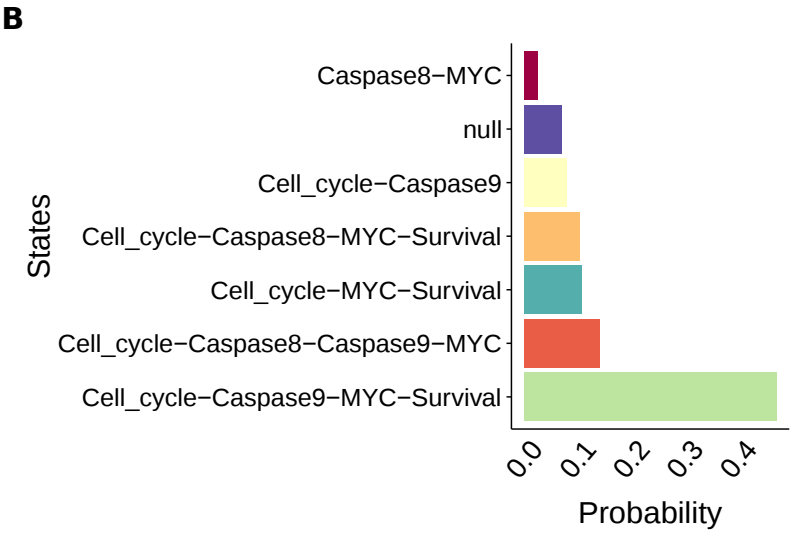
- MaBoSS is a C++ software for simulating continuous/ discrete time Markov processes, applied on a Boolean network
- Given some initial conditions, MaBoSS applies Monte-Carlo kinetic algorithm (or Gillespie algorithm) to the network to produce time trajectories. Time evolution of probabilities are estimated

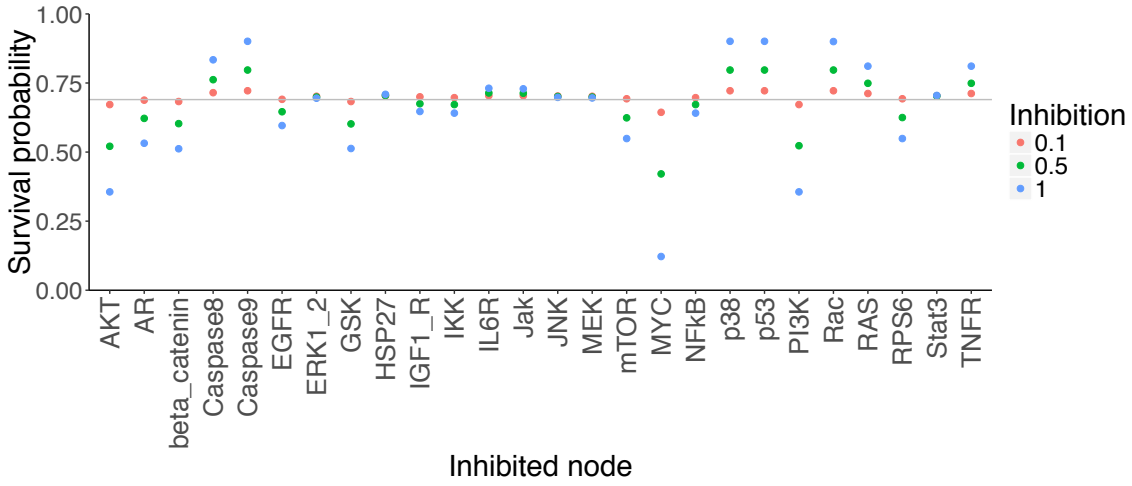
https://maboss.curie.fr

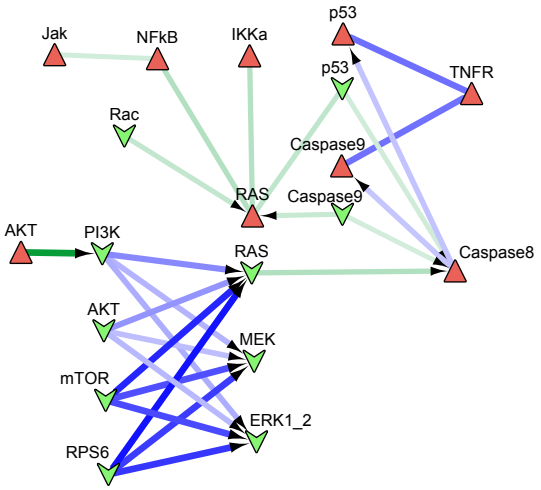


MaBoSS simulations









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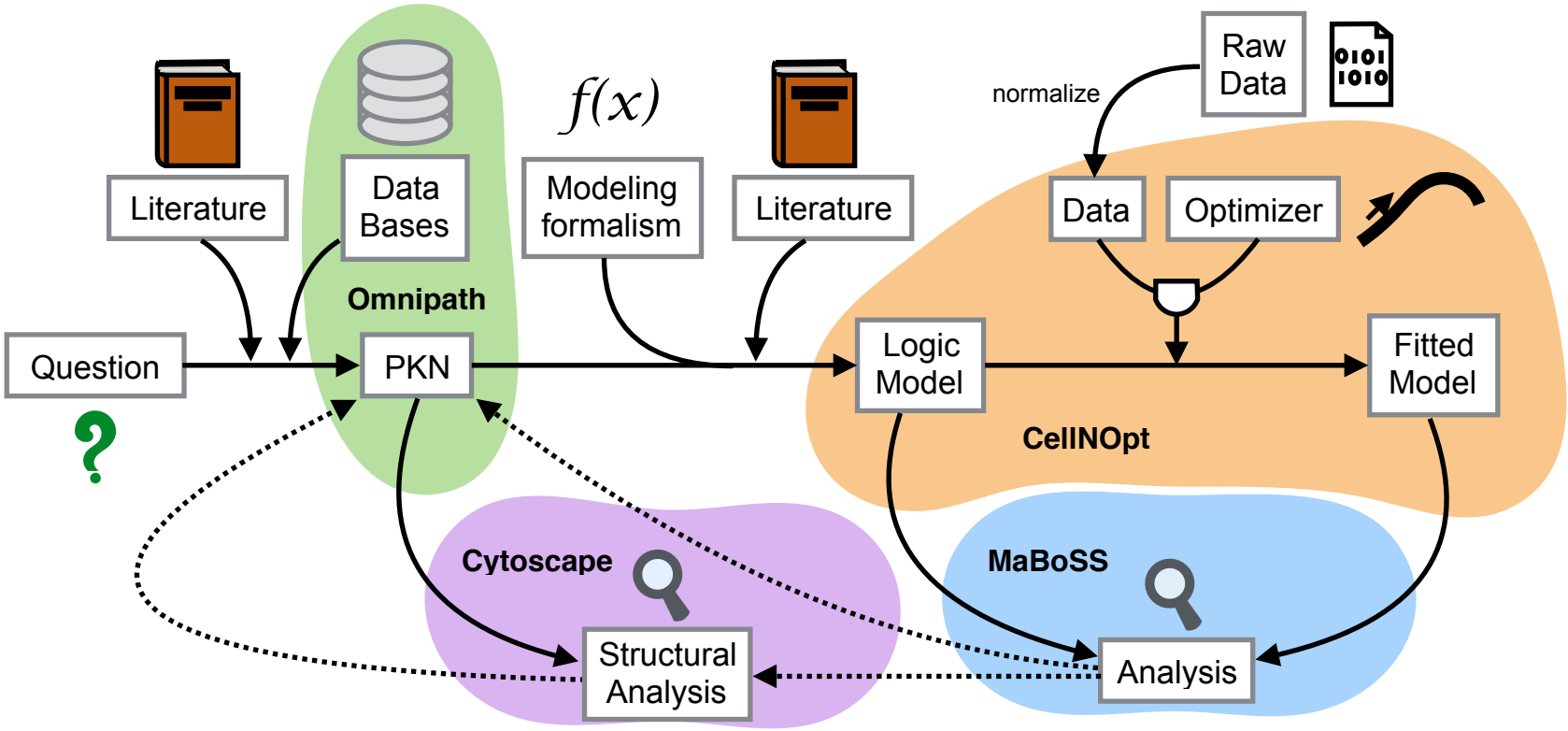
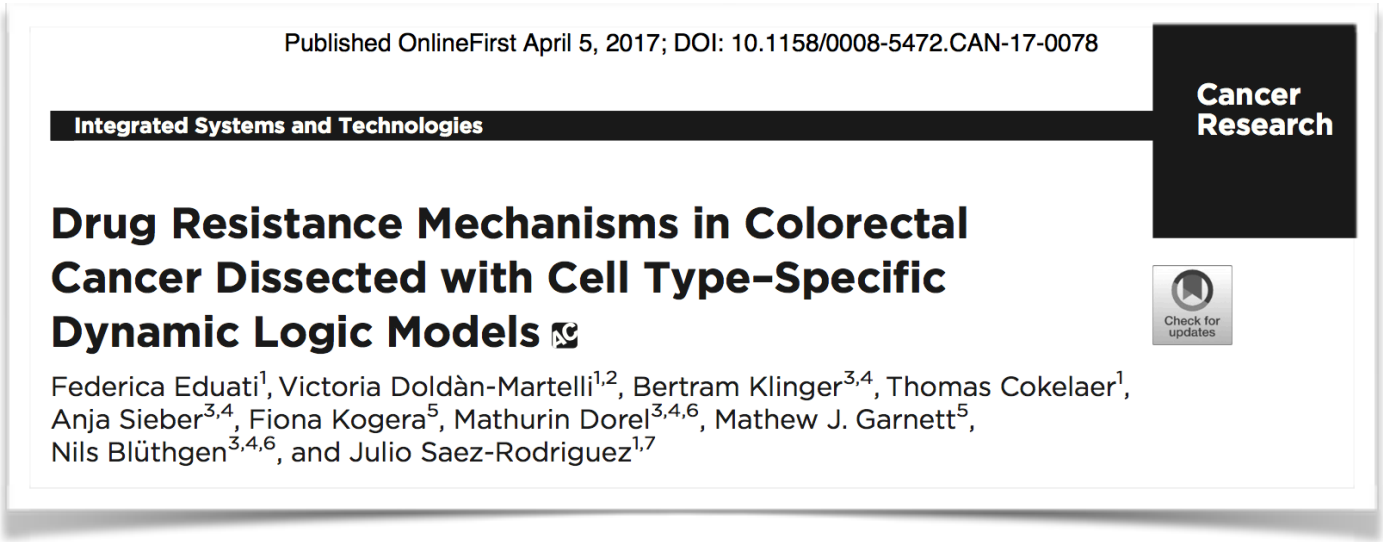
Further analysis



Example in colorectal cancer

- Can we use logic models of signalling networks to understand and target drug resistance?



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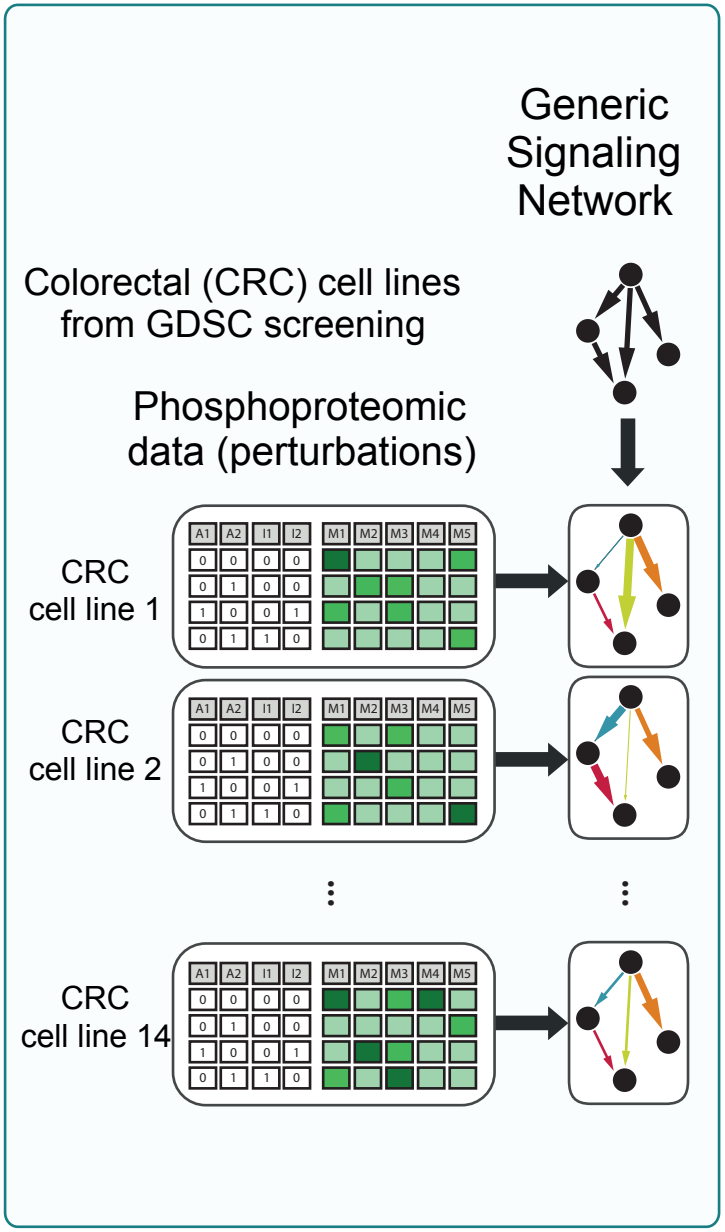
Integrated Systems and Technologies

Cancer Research

Drug Resistance Mechanisms in Colorectal Cancer Dissected with Cell Type–Specific Dynamic Logic Models

Federica Eduati[1], Victoria Doldàn-Martelli[1,2], Bertram Klinger[3,4], Thomas Cokelaer[1], Anja Sieber[3,4], Fiona Kogera[5], Mathurin Dorel[3,4,6], Mathew J. Garnett[5], Nils Blüthgen[3,4,6], and Julio Saez-Rodriguez[1,7]

Dynamic logic models provide mechanistic insight and novel biomarkers



w. N. Bluethgen & M. Garnett

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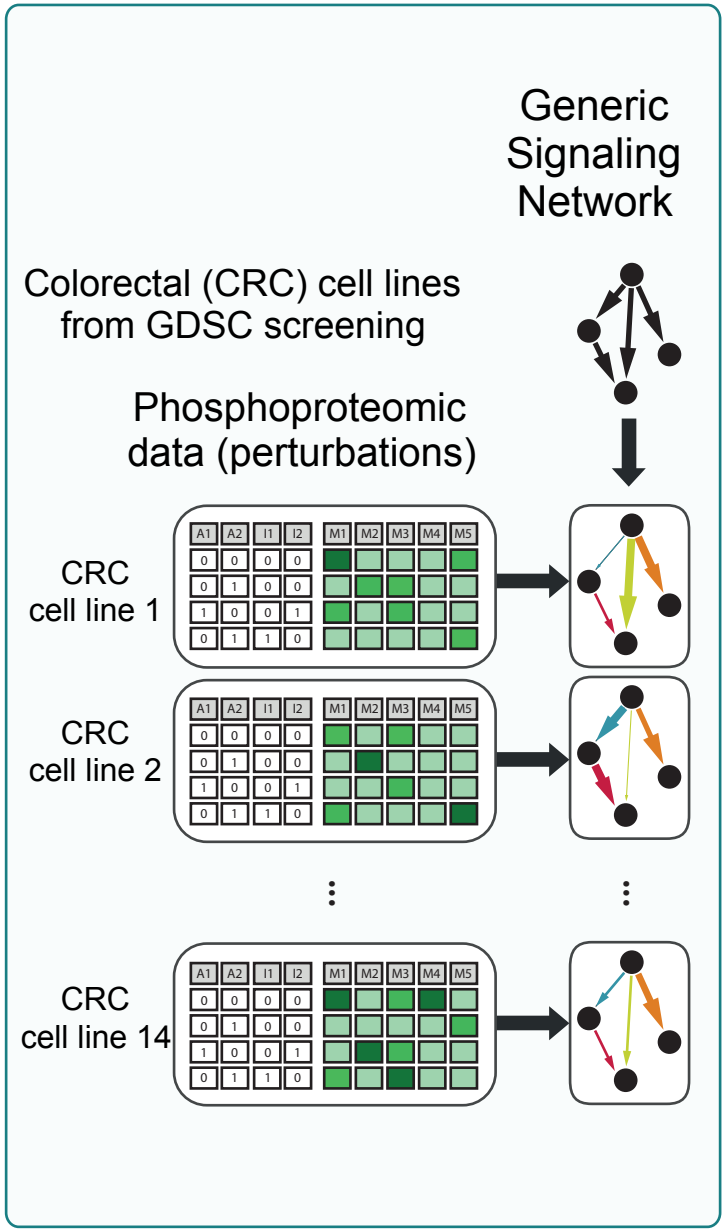

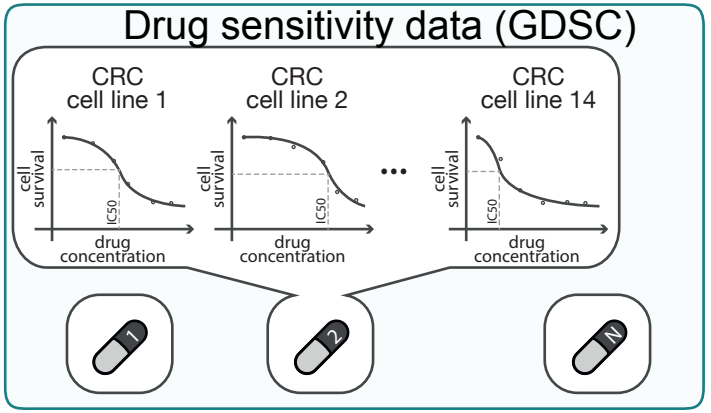

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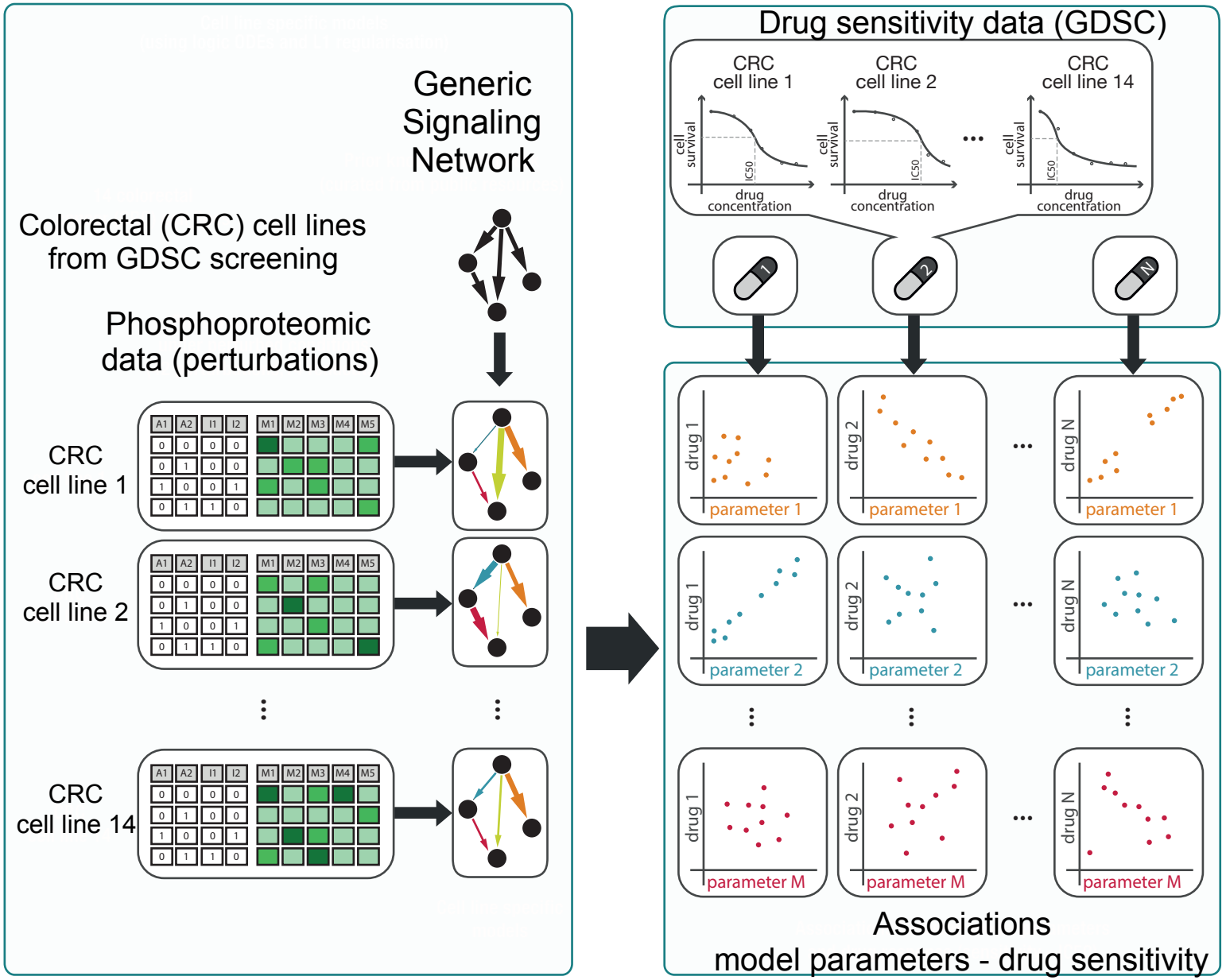

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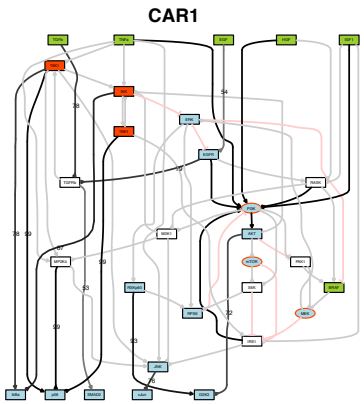
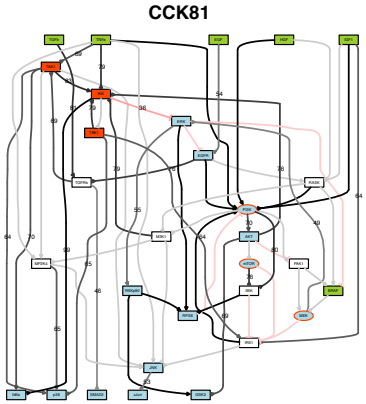
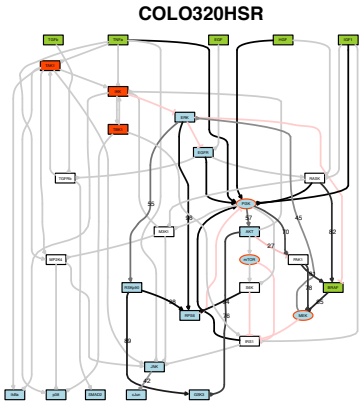
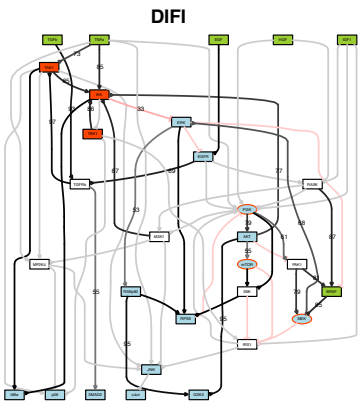
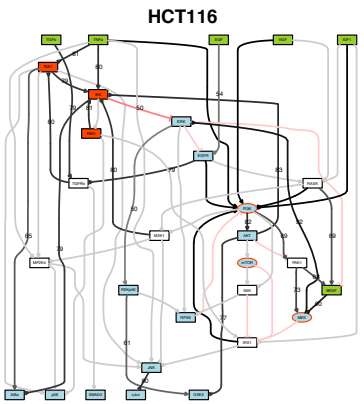
CRC Cell lines specific models

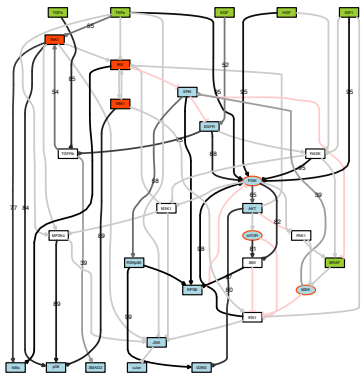


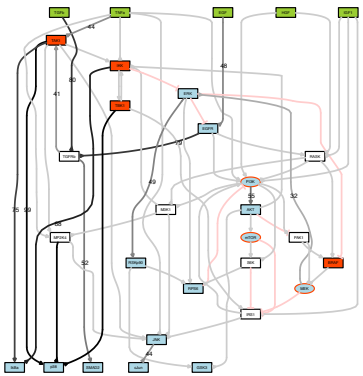


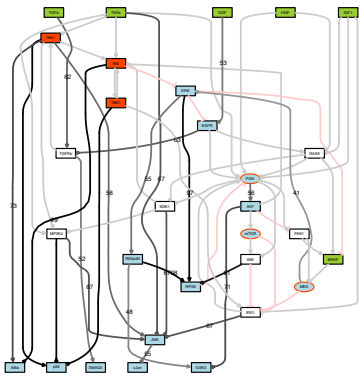


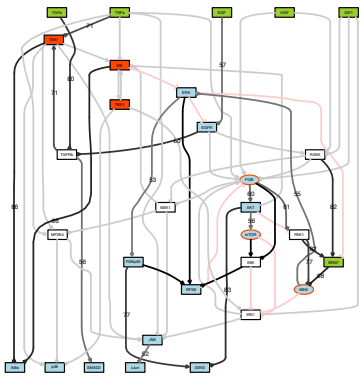


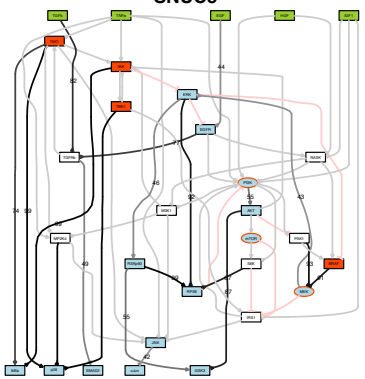


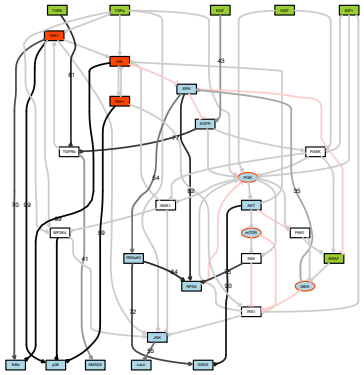


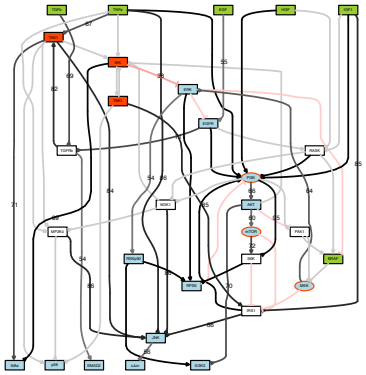


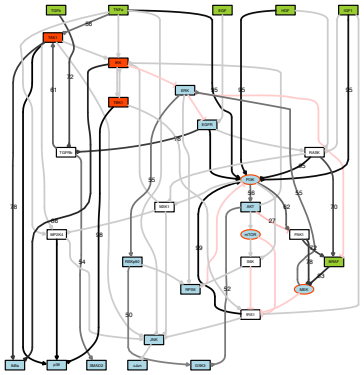


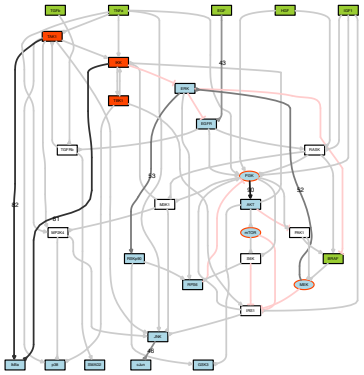












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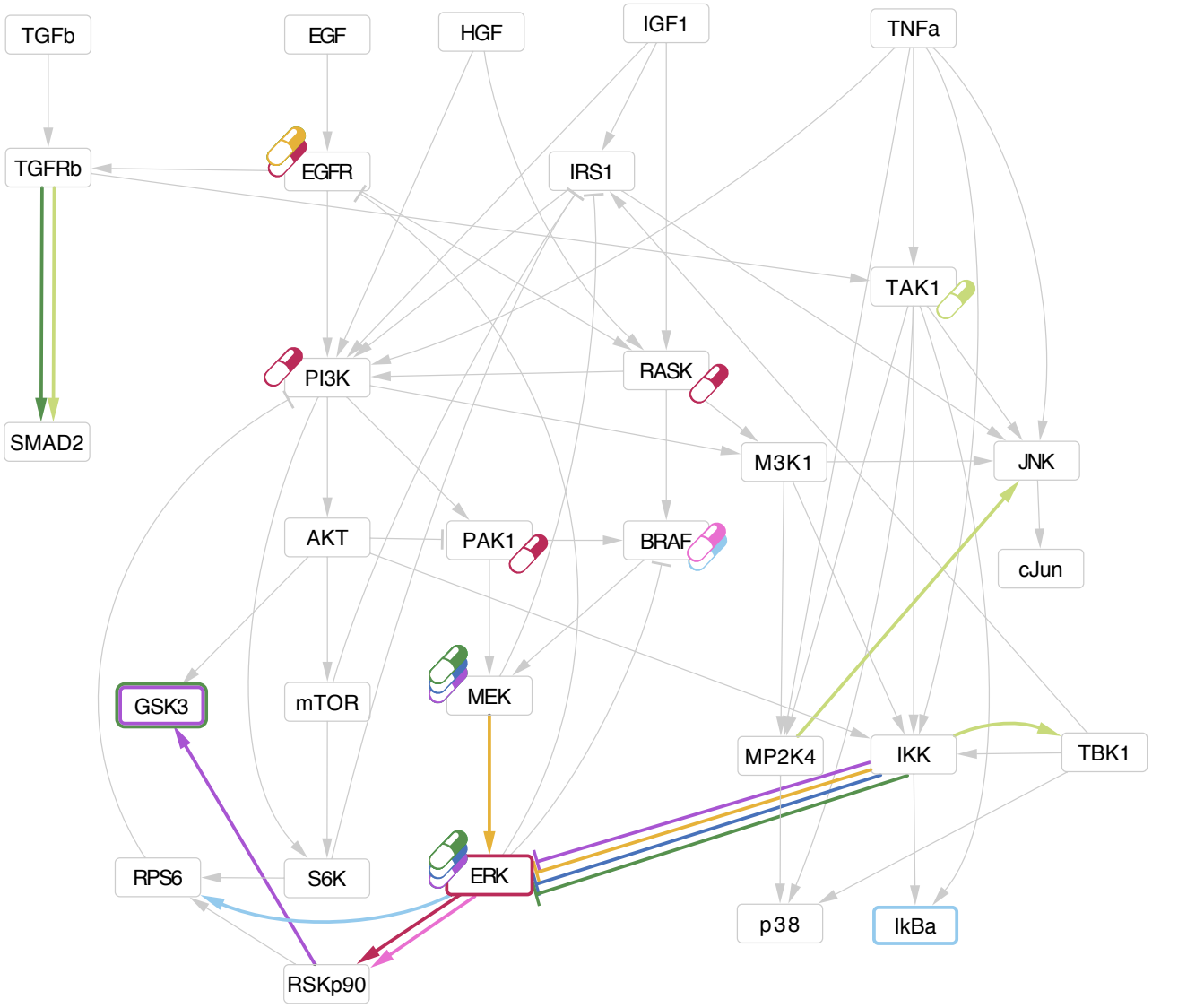
Model-based biomarkers of drug efficacy and resistance



No genetic biomarker

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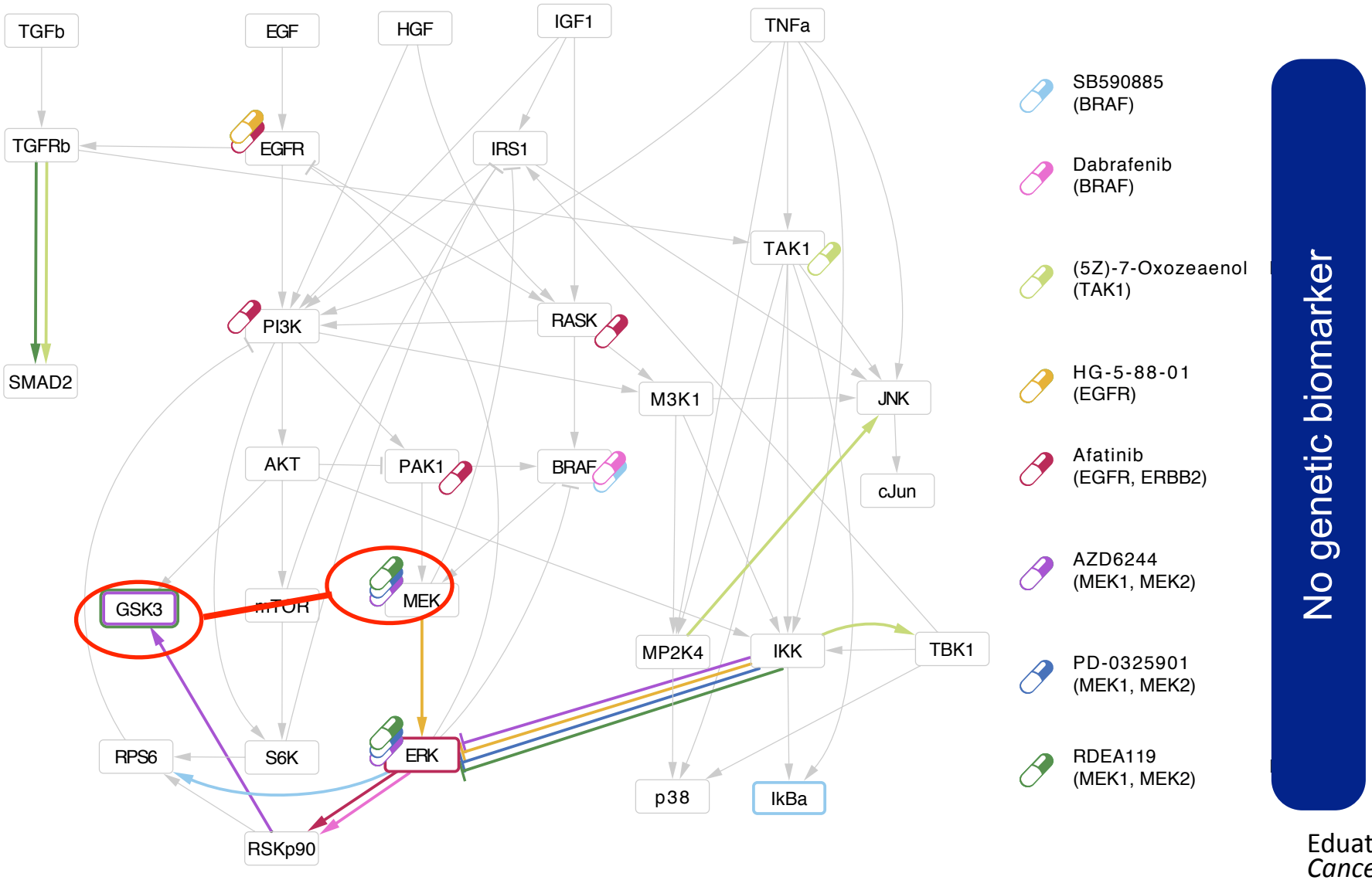

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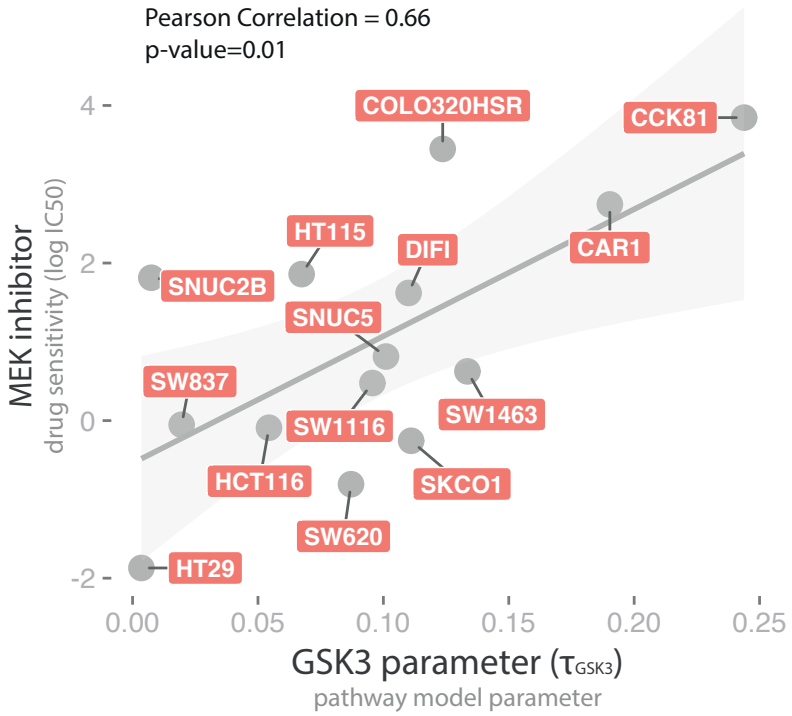
Identified and validated novel biomarkers and a new combination strategy



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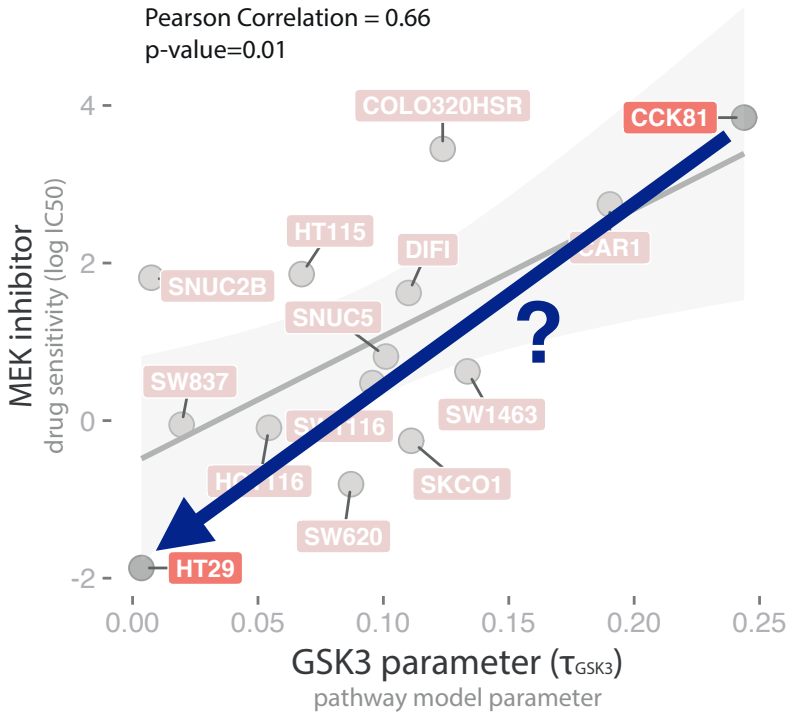

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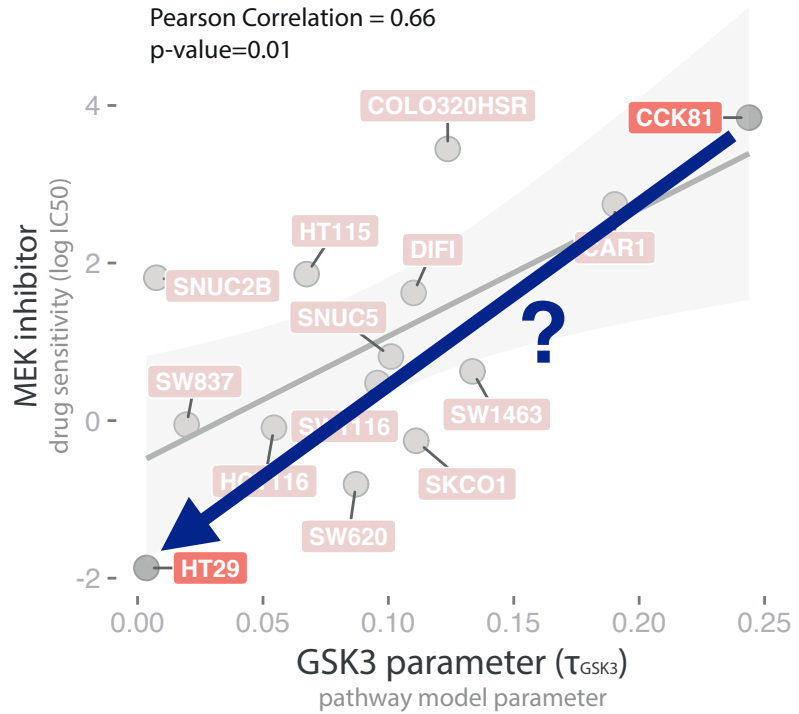

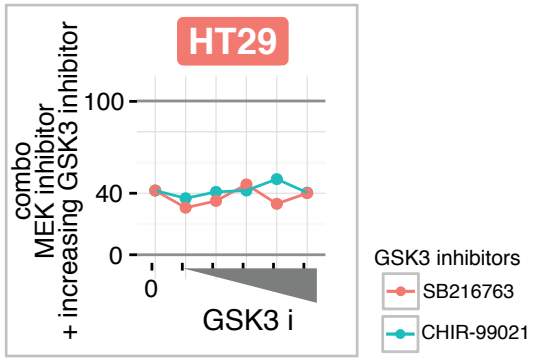

no improved sensitivity when GSK3 is not functional

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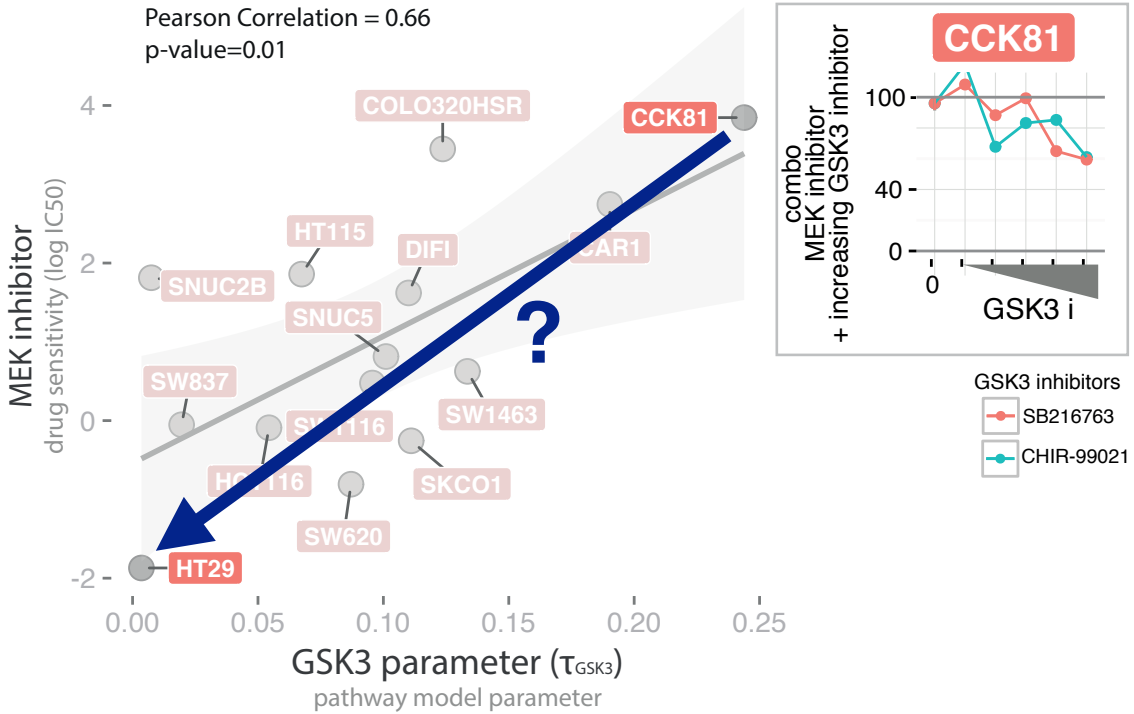
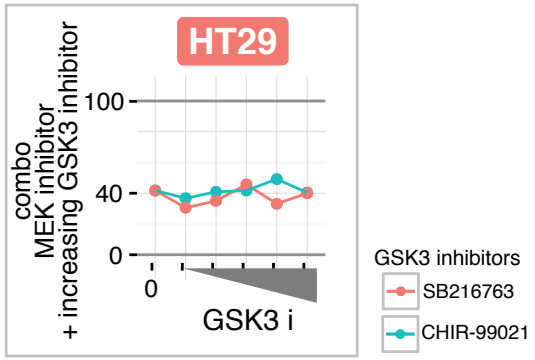


synergistic combo when GSK3 is functional



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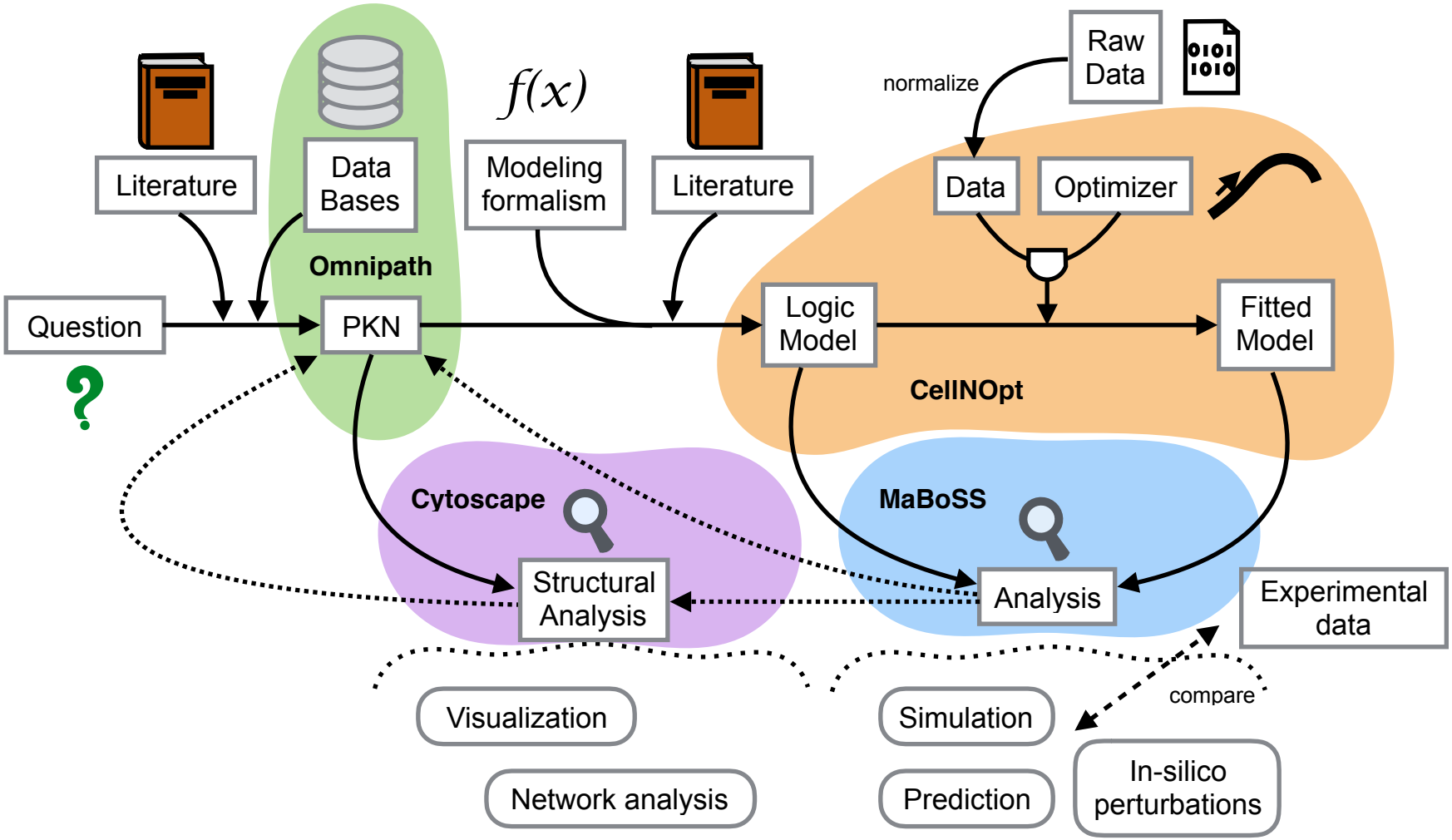
Summary



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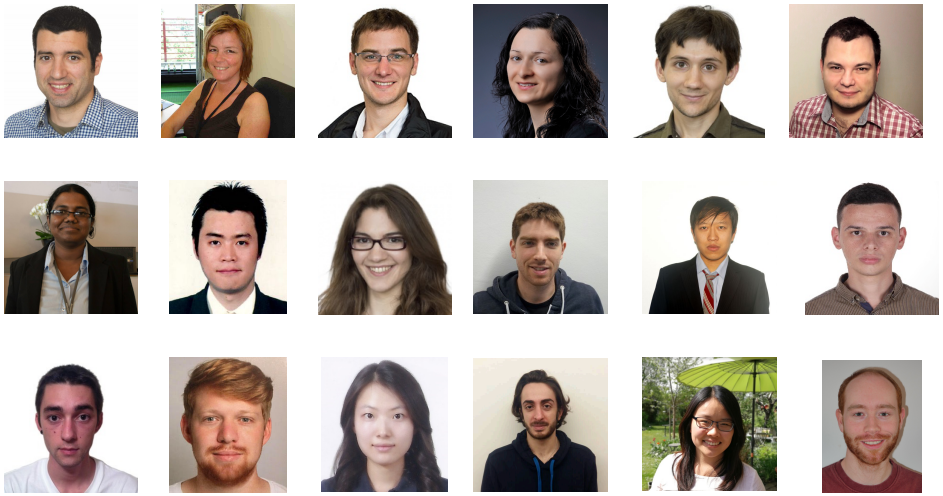
Acknowledgements

Saez-Rodriguez group

Special thanks to:

Julio Saez-Rodriguez
Pauline Traynard
Laurence Calzone
Federica Eduati
Attila Gabor



Collaborators:

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NNPrECISE

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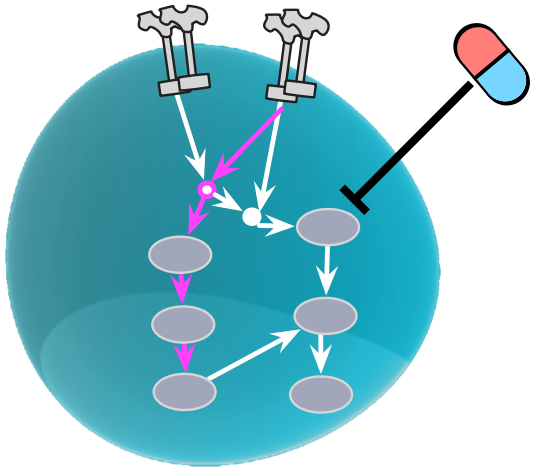
A logic modelling workflow for systems pharmacology



Luis Tobalina

13/07/2018

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