Practical session on Network modeling

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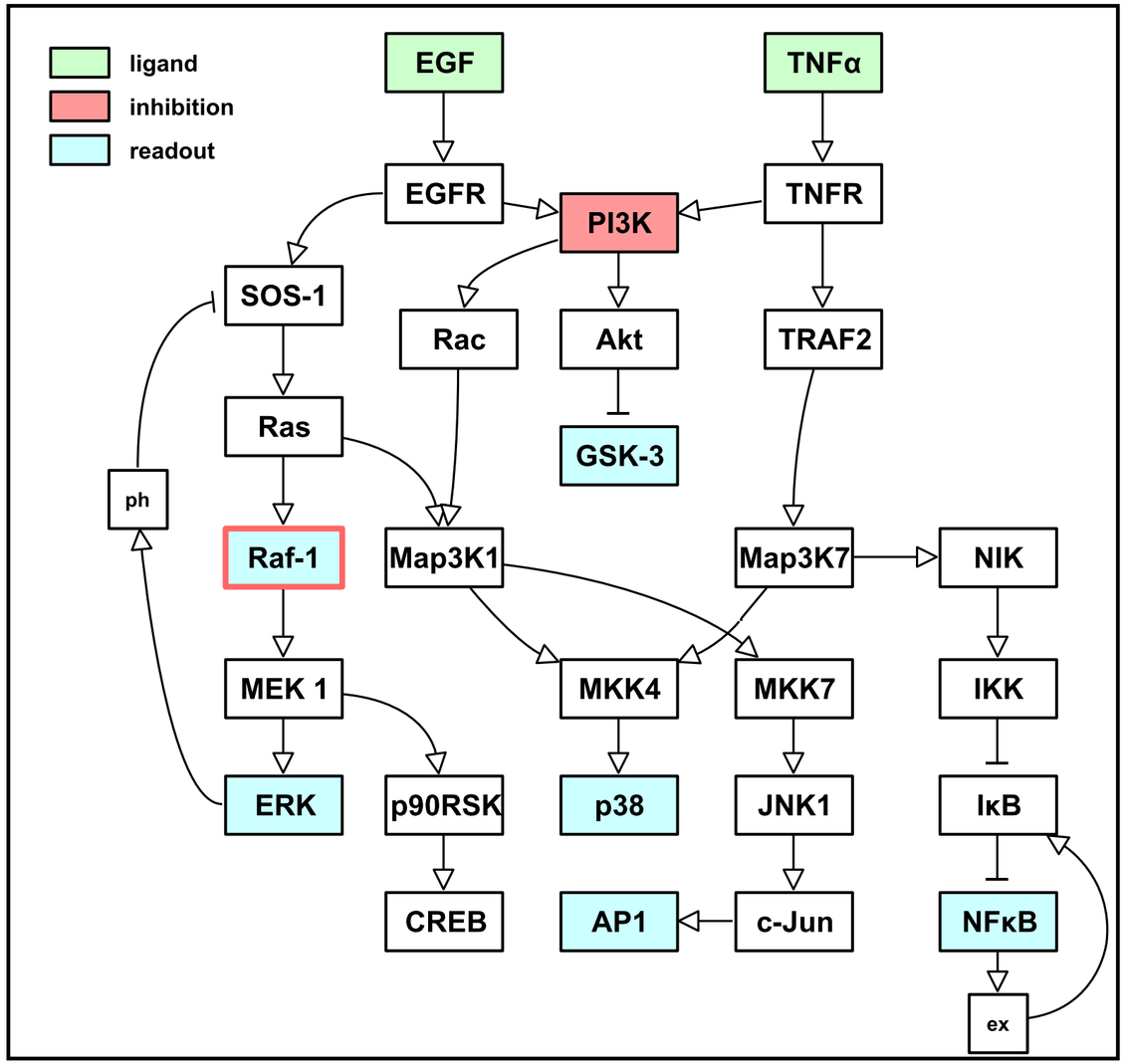
Overview

- Network models
- Perturbation data and Prior knowledge
- Model building cycle
  - Mathematical formulation of the network models
  - Simulation of the models
  - Training model to data
  - Predictions

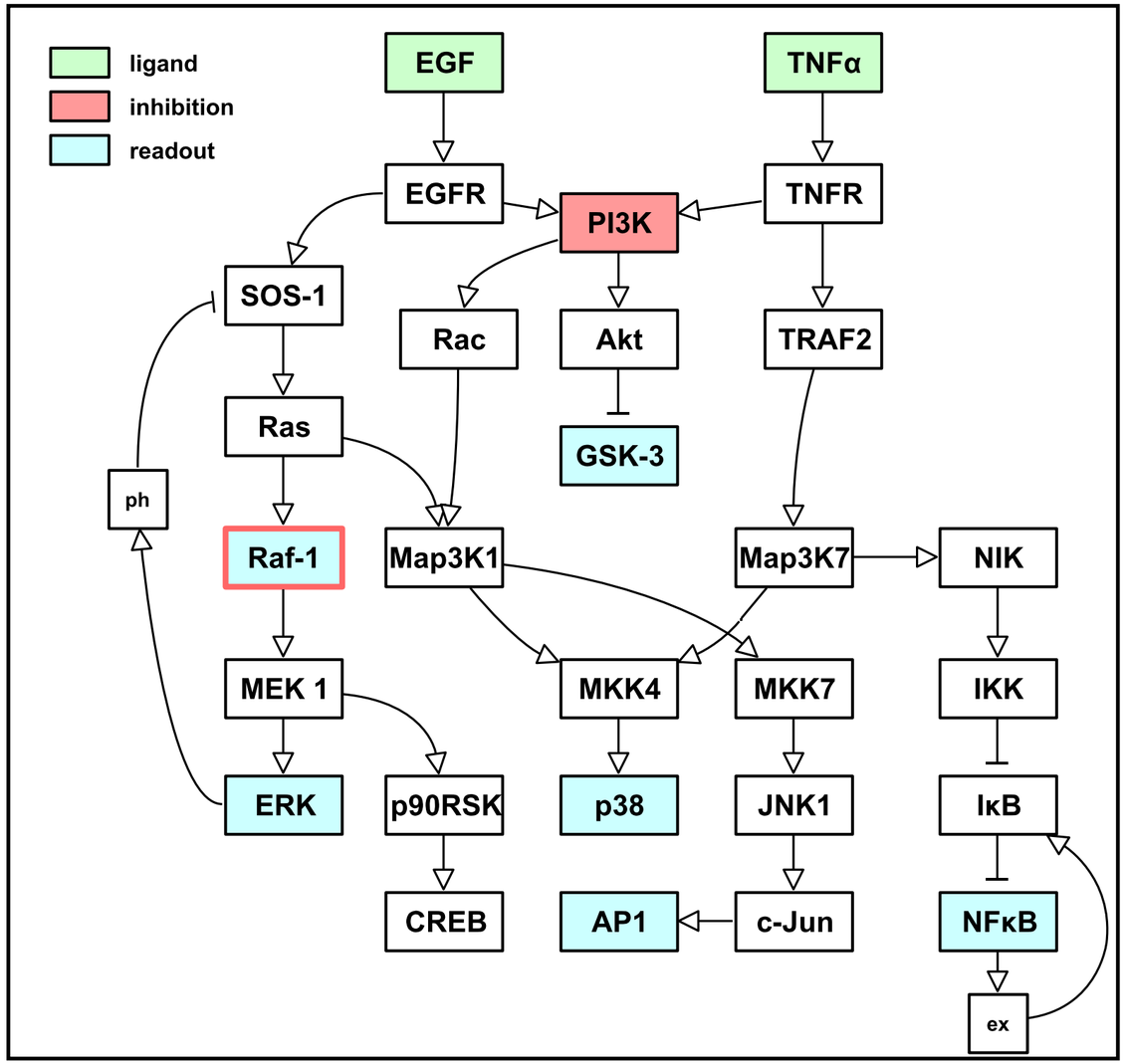
Molecular networks



MacNamara A et al (2012) *Phys Biol*

- What do we see here?

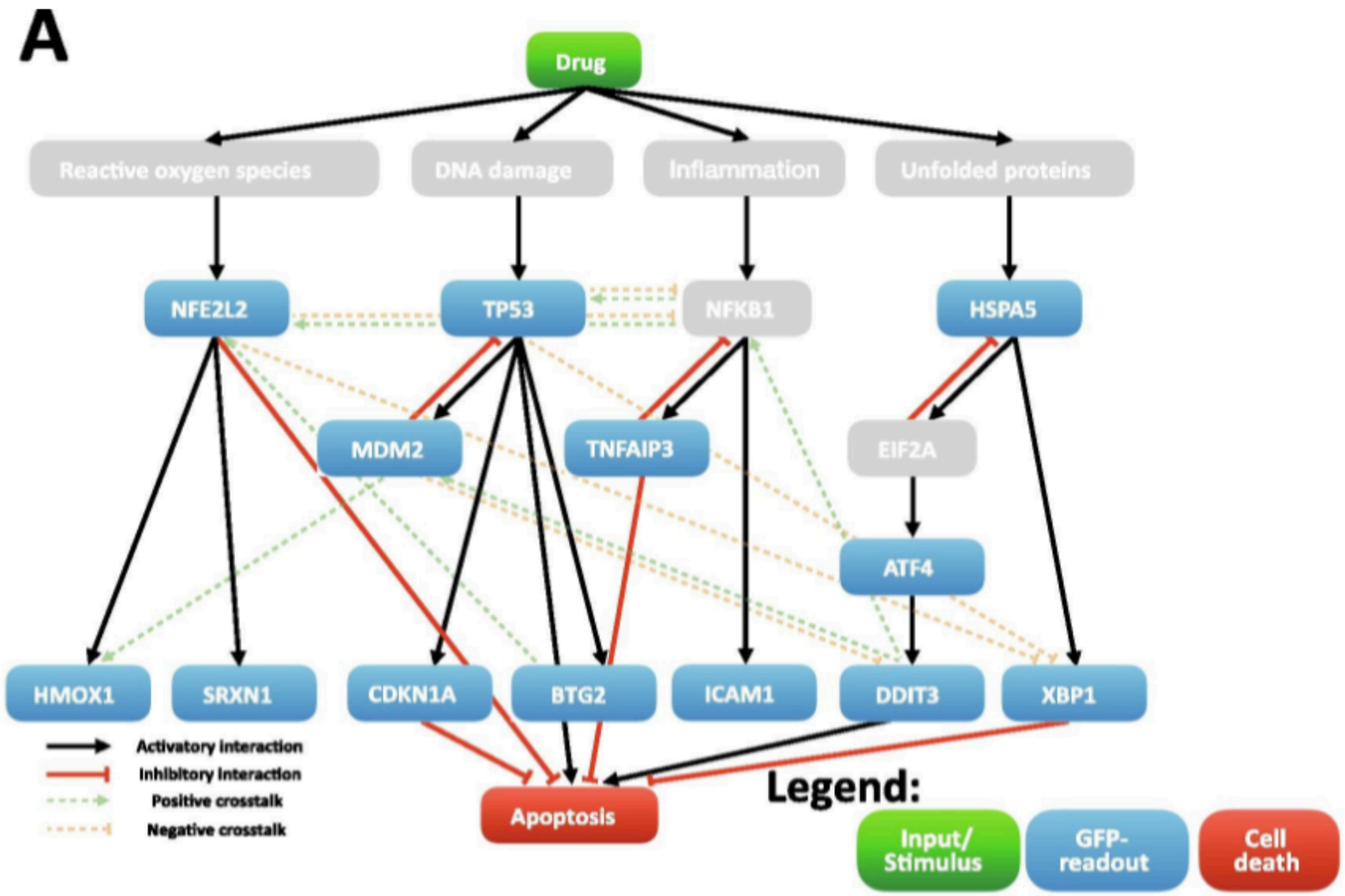
Molecular networks



MacNamara A et al (2012) *Phys Biol*

- Signaling network **model** of EGF and TNFalpha
- Summary of knowledge, experimental observations
- The role of edges:
  - Activation and inhibition
- Feedback loop -> mitigates the initial impulse (in time)
- Huge simplification:
  - Qualitative
  - Many missing interactions and nodes
  - Cellular localisation ignored
  - Complexes not shown

Molecular networks



Wijaya et al (2021) *Biochemical Pharmacology*

What, why and when: network modeling

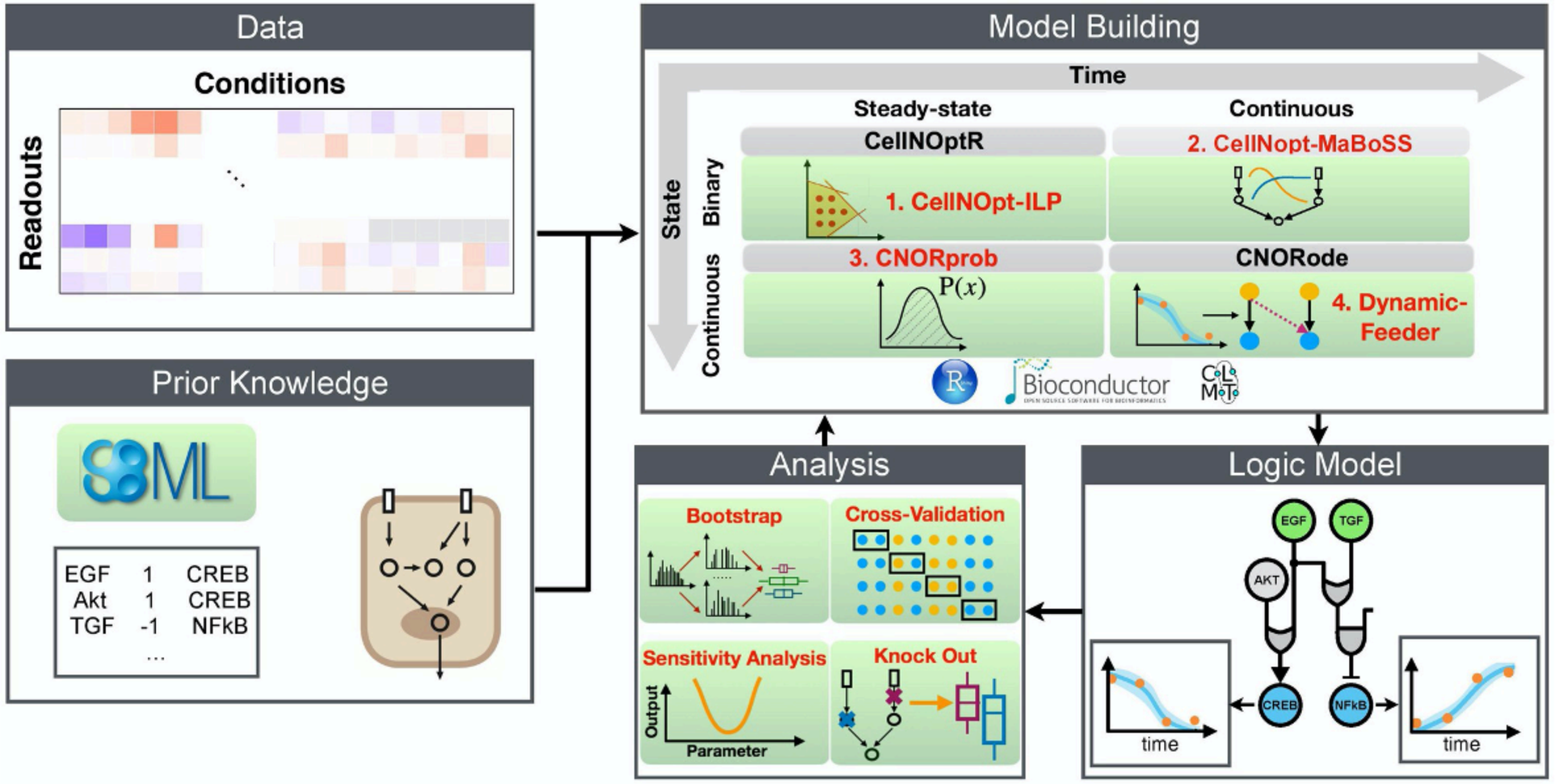
- Network models describe the interplay of molecular markers (signaling transduction)
- Understand/summarize the molecular details of a biological system, a disease or drug action (gain insight)
- We have molecular data to be modeled
  - The activity of signaling molecules are measured
  - Multiple nodes are observed
  - Multiple conditions (perturbations and time)

Software tools

	Simulation w/ continuous states		Simulation w/ Boolean states		Graphical User Interface	Import/export with standards (SBMLqual)	Model fitting / parameter estimation
Tool	*Continuous in time*	*Discrete in time*	*Synchronous updates*	*Asynchronous updates*			
CellNOpt (Terfve et al. 2012)	■	■	■	■	■	■	■
GINsim (Chaouiya, Naldi, and Thieffry 2012)		■	■	■	■	■	
MaBoSS (Stoll et al. 2012)	■	■		■		■	■
FALCON (Landtsheer et al. 2017)		■	■		■		■
BoolNet (Müssel, Hopfensitz, and Kestler 2010)		■	■	■		■	
BooleanNet (Albert et al. 2008)	■	■	■	■			
SQUAD (Di Cara et al. 2007)	■				■		
optPBN (Trairatphisan et al. 2014)		■	■				■
OptimusQual (Dorier et al. 2016)		■		■			■
ViSiBool (Schwab et al. 2018)		■	■		■	■	
GNA (Batt et al. 2012)	■				■	■	
PRUNET (Rodriguez et al. 2015)		■	■		■		■
Odefy (Krumsiek et al. 2010)	■		■			■	
Cell Collective (Helikar et al. 2012)		■	■	■	■	■	
BMA (Benque et al. 2012)		■	■		■	■	

Gjerga, Trairatphisian, Gabor et al (2020) *Bioinformatics*

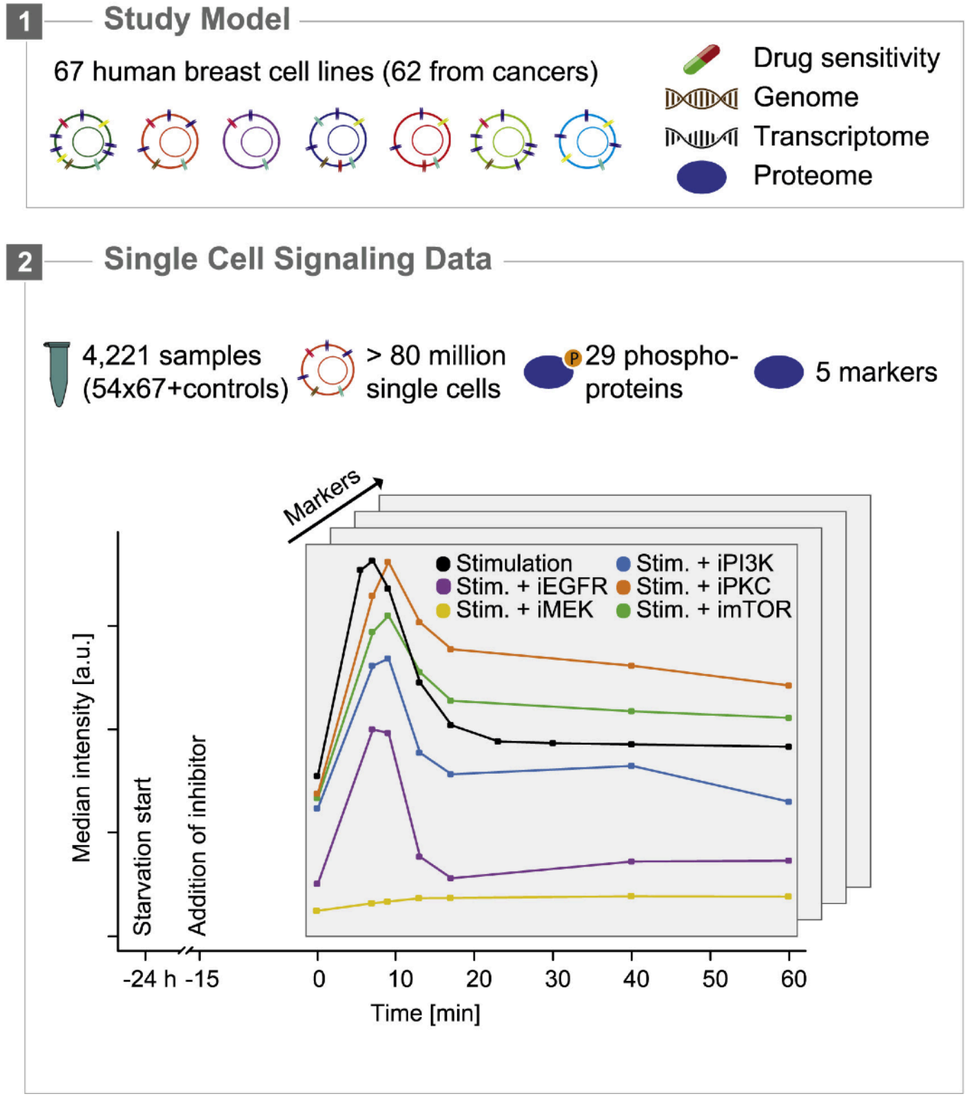
Model building cycle

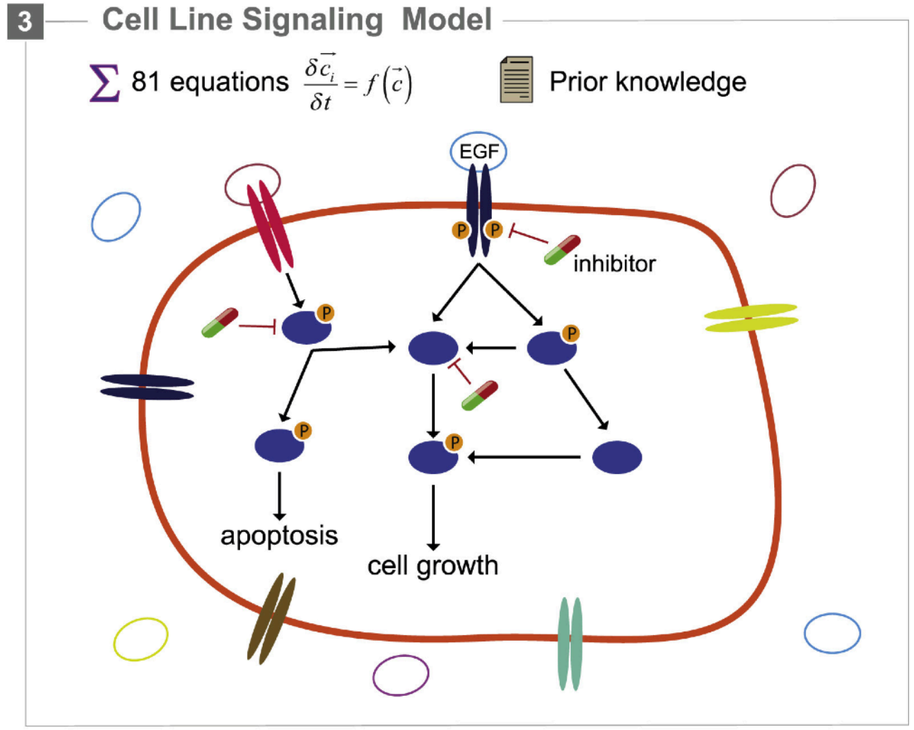


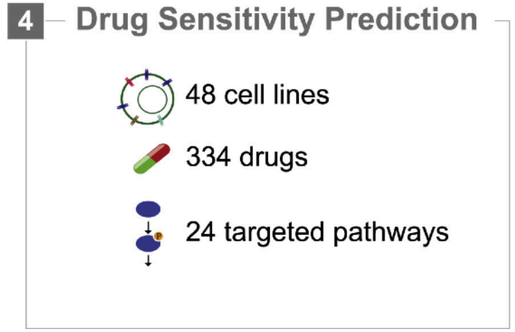
Gjerga, Trairatphisian,
Gabor et al (2020) *Bioinformatics*

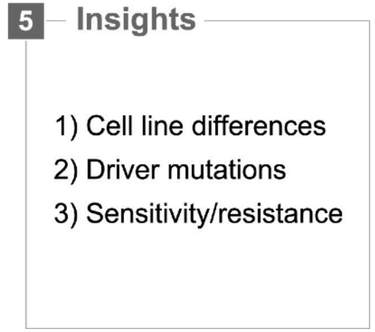
1. Perturbation data

- Let's study some real experiments









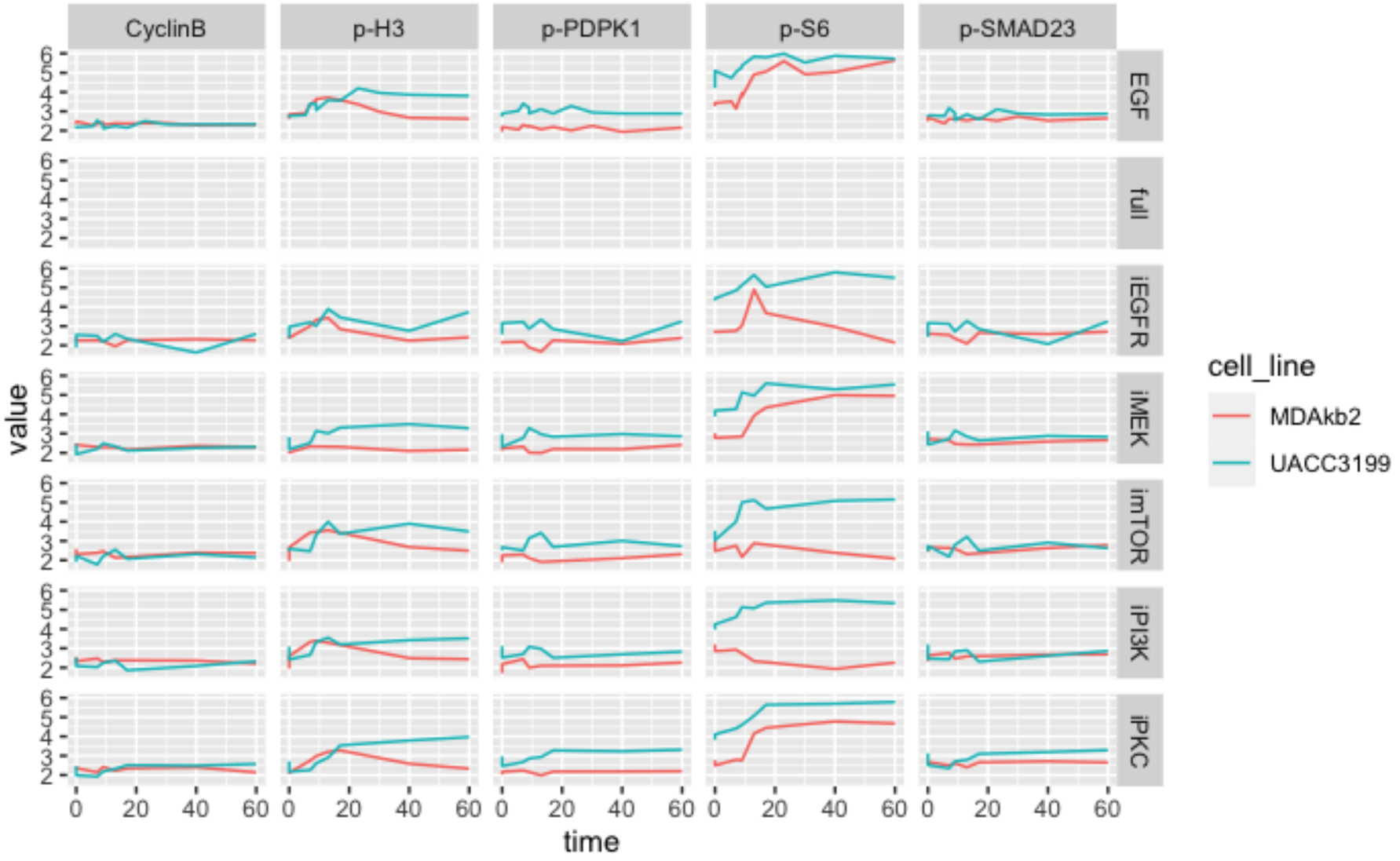
Tognetti, Gabor et al (2021) *Cell systems*

Tasks

- Let’s explore the dynamic data
  - Import data
  - Data formating
  - Comparison of cell lines
  - Visualization signal vs time

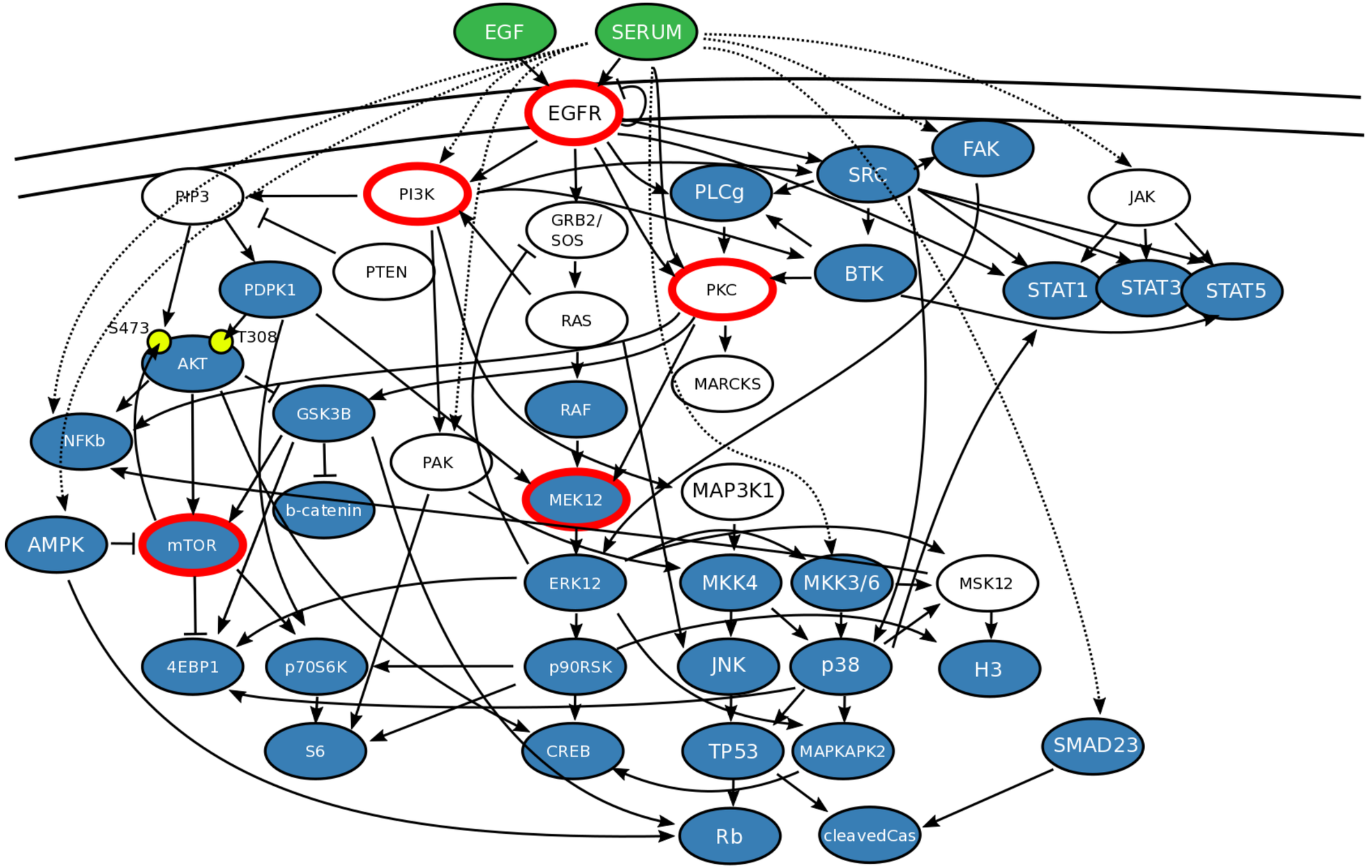
  - Follow R-markdown from GitHub:
    - 01_perturbation_data_exploration.Rmd

Example of two cell-lines (MDAkb2 vs UACC3199)



Can someone explain what happens with

p-S6 in MDAkb2?


EGF
SERUM
EGFR
FAK
SRC
PIP3
PI3K
PLCg
JAK
GRB2/
SOS
PTEN
BTK
PDPK1
PKC
STAT1
STAT3
STAT5
S473
T308
AKT
RAS
MARCKS
GSK3B
RAF
NFKb
PAK
MAP3K1
b-catenin
MEK12
AMPK
mTOR
ERK12
MKK4
MKK3/6
MSK12
4EBP1
p70S6K
p90RSK
JNK
p38
H3
S6
CREB
TP53
MAPKAPK2
SMAD23
Rb
cleavedCas

2. Prior knowledge network (PKN)

- PKN stores known molecular interactions
- What type of interactions do we need to model signaling?
- Where do we find molecular interactions?

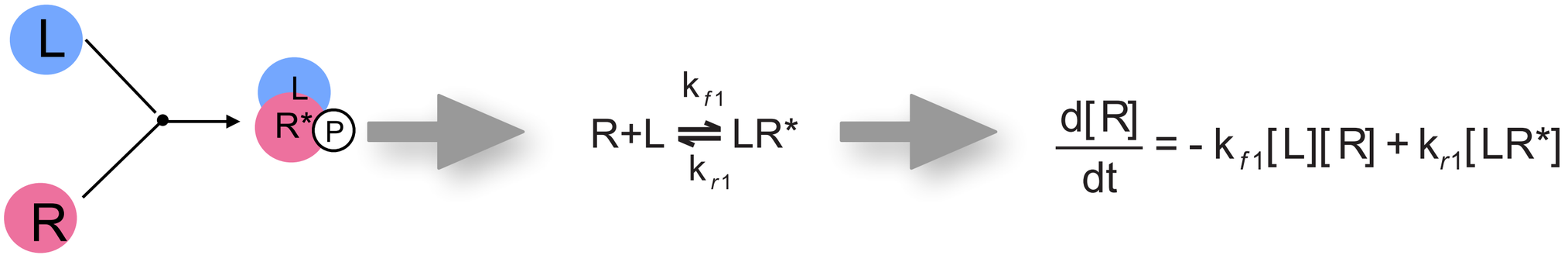
Task 2: finding prior knowledge information

- Try: https://signor.uniroma2.it/
  - Check e.g. MAP2K1 (MEK1)
    - How many partners does MEK1 have?
    - How many known phosphorylation sites does it have?
    - What is the function of phosphorylation on the sites ?

- Can we do this programmatically?
  - Check omnipathdb.org
  - Which other databases are included? (Check the figure)
  - Follow R-markdown from GitHub:
    - 02_prior_knowledge_exploration.Rmd

3. From networks to mathematical models

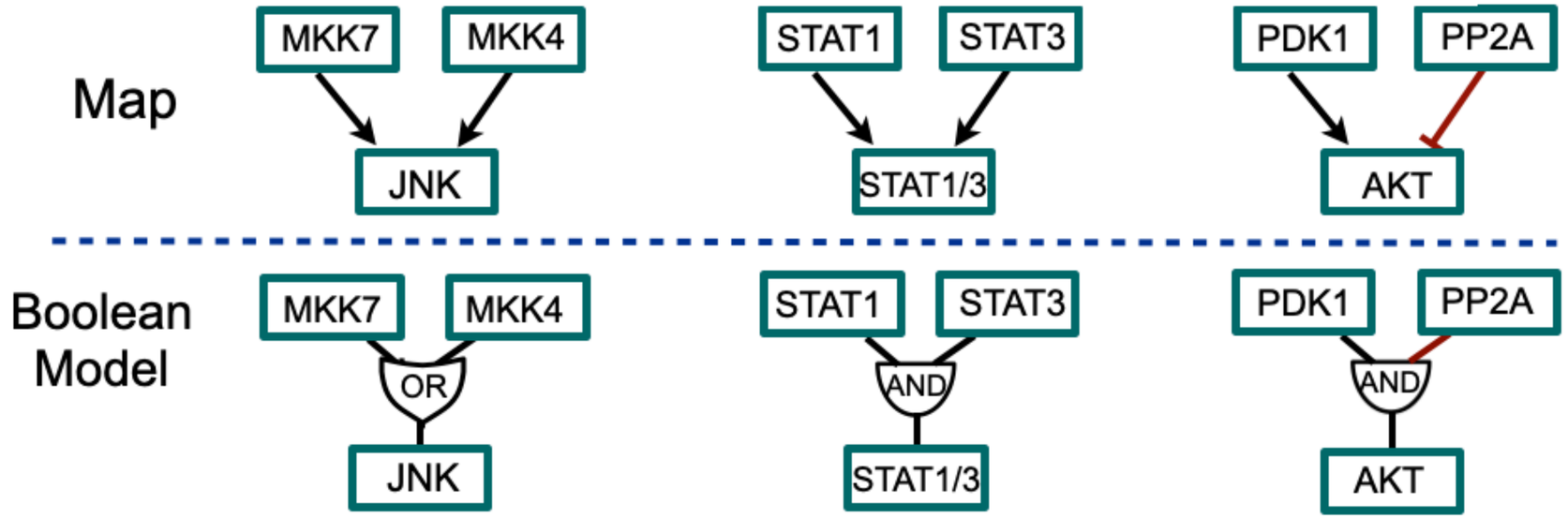
Kinetic model



- Quantitative
  - models the concentration of compounds
- Model format: Ordinary differential equations
- Describes the nodes in time (continuous in time)
- Mass conservation law: consumption & production
- Requires model parameters (k_f1 and k_r1) and initial conditions (R(t=0), L(t=0), LR*(t=0))

3. From networks to mathematical models

Boolean model



- Qualitative:
  - On/off states
- Model format: Boolean models
- Describes the nodes in (quasi) steady state
- No mass conservation -> focuses on causality
- Does not require model parameters, only edges
- There are extensions (fuzzy/probabilistic, logic-based ODEs which are in-between kinetic and Boolean models)

Task 3: Build a toy Boolean model from data and PKN using CellNOpt

- Follow the CellNOpt tutorial
  - 03_basic_Boolean_model.Rmd

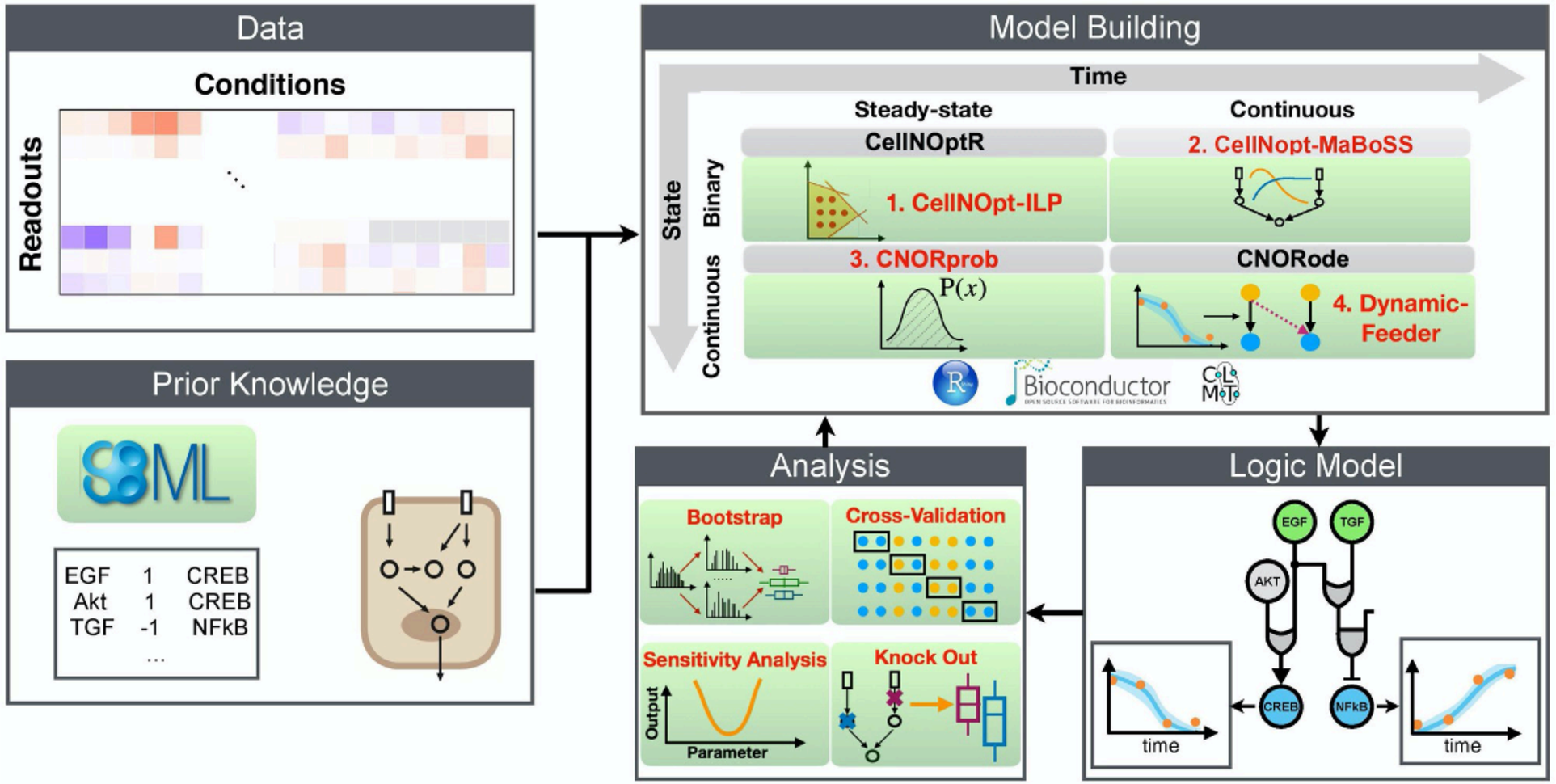
- The tutorial covers:
- On a small network:
  - Load and plot the prior knowledge network
  - Load experimental data and experimental conditions
  - Simulate the model
- Realistic model:
  - Train a model that describes EGF and TNFa signaling to data.

Task 4: Build a logic-ODE model

- Follow the CNORode tutorial
  - 04_logic_ODE_model.Rmd

- The tutorial covers:
  - Intro to Eduati et al (2017) Drug Resistance Mechanisms in Colorectal Cancer Dissected with Cell Type-Specific Dynamic Logic Models, *Cancer Research*
  - Intro to Logic ODE formalism
  - How to import and plot logicODE models and experiments
  - How to optimize logic ODE model
  - Correlation analysis of model parameters and and drug response

Summary


Data
Conditions
Readouts
Prior Knowledge
SBML
EGF 1 CREB
Akt 1 CREB
TGF -1 NFkB
...
Model Building
Time
Steady-state
Continuous
State
Binary
Continuous
CellNOptR
2. CellNopt-MaBoSS
1. CellNOpt-ILP
3. CNORprob
CNORode
P(x)
4. Dynamic-Feeder
Bioconductor
Analysis
Bootstrap
Cross-Validation
Sensitivity Analysis
Output
Parameter
Knock Out
Logic Model
EGF
TGF
AKT
CREB
NFkB
time
time