Logic models of signalling networks with CellNOpt:

from Boolean logic to differential equations

Julio Saez-Rodriguez

Joint Research Center for Computational Biomedicine

RWTH AACHEN UNIVERSITY

Steps in building (and using) a model

- Set up experiments to extract most information
- Process data efficiently
- Choose type of mathematical model (given data, question, etc)
- Train models to experimental data
- Use models to gain insight

Plato’s allegory of the cave

http://www.zlw-ima.rwth-aachen.de/forschung/

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  - **Measurements** are **shadows**:
    - Phosphorylation = Activation? Which site? How does it affect the regulation of the protein?

Plato's allegory of the cave

- **Cues** are **lights**
  - **Measurements** are **shadows**:
    - Phosphorylation = Activation? Which site? How does it affect the regulation of the protein?
  - Fluorescence=phosphorylation? Signal saturated? Below detection level?

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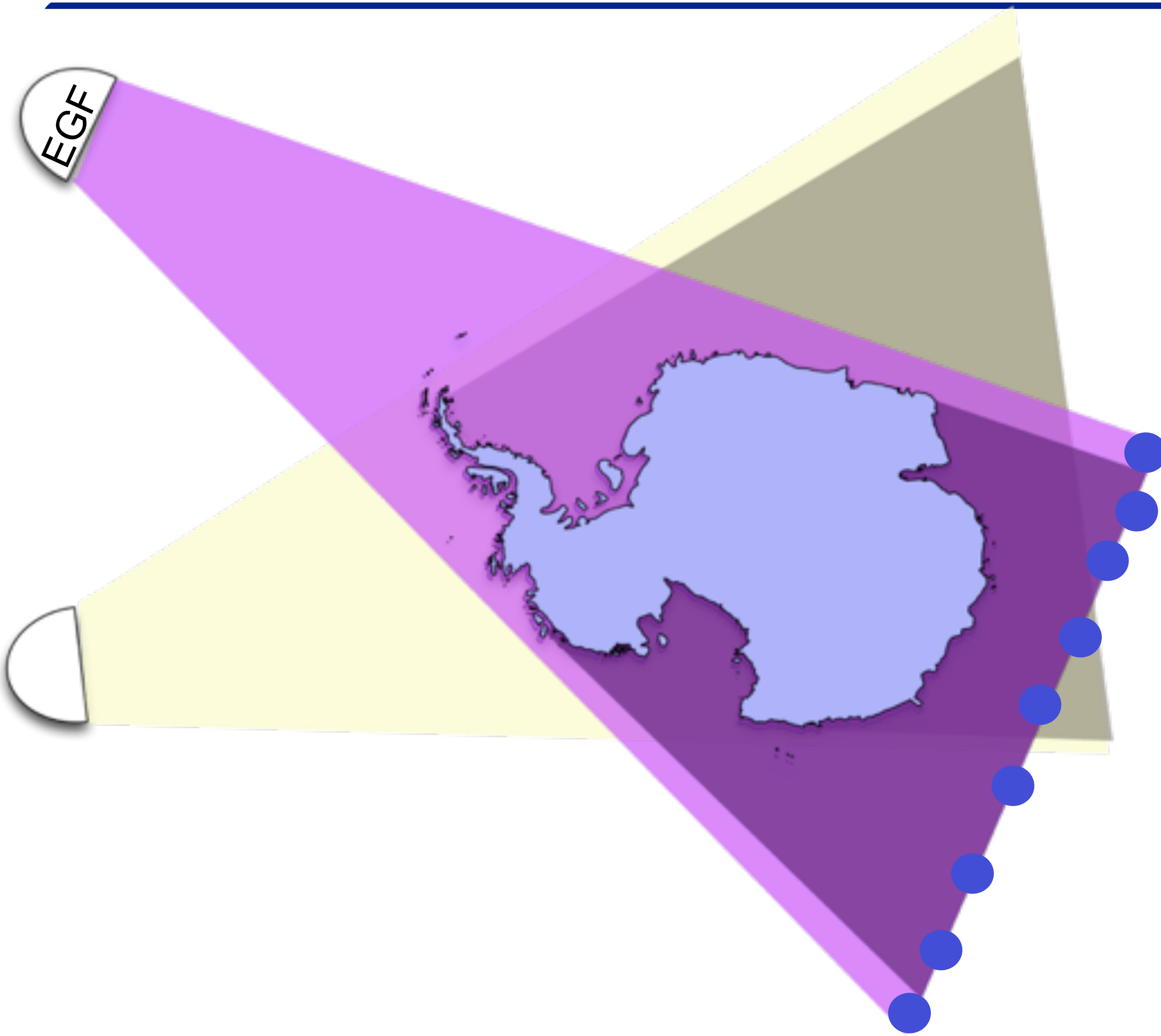
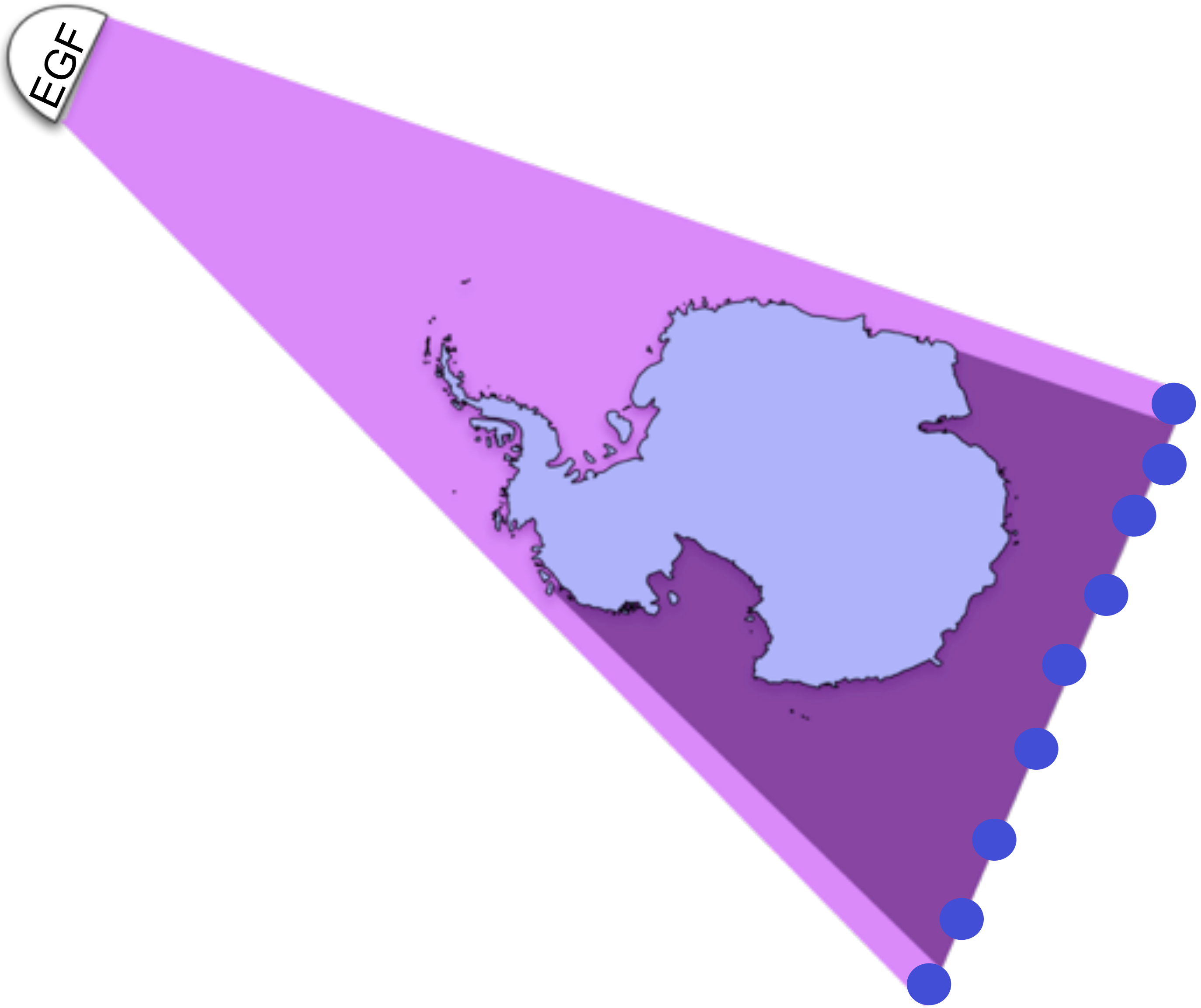
Choosing cues to maximize information



Choosing cues to maximize information



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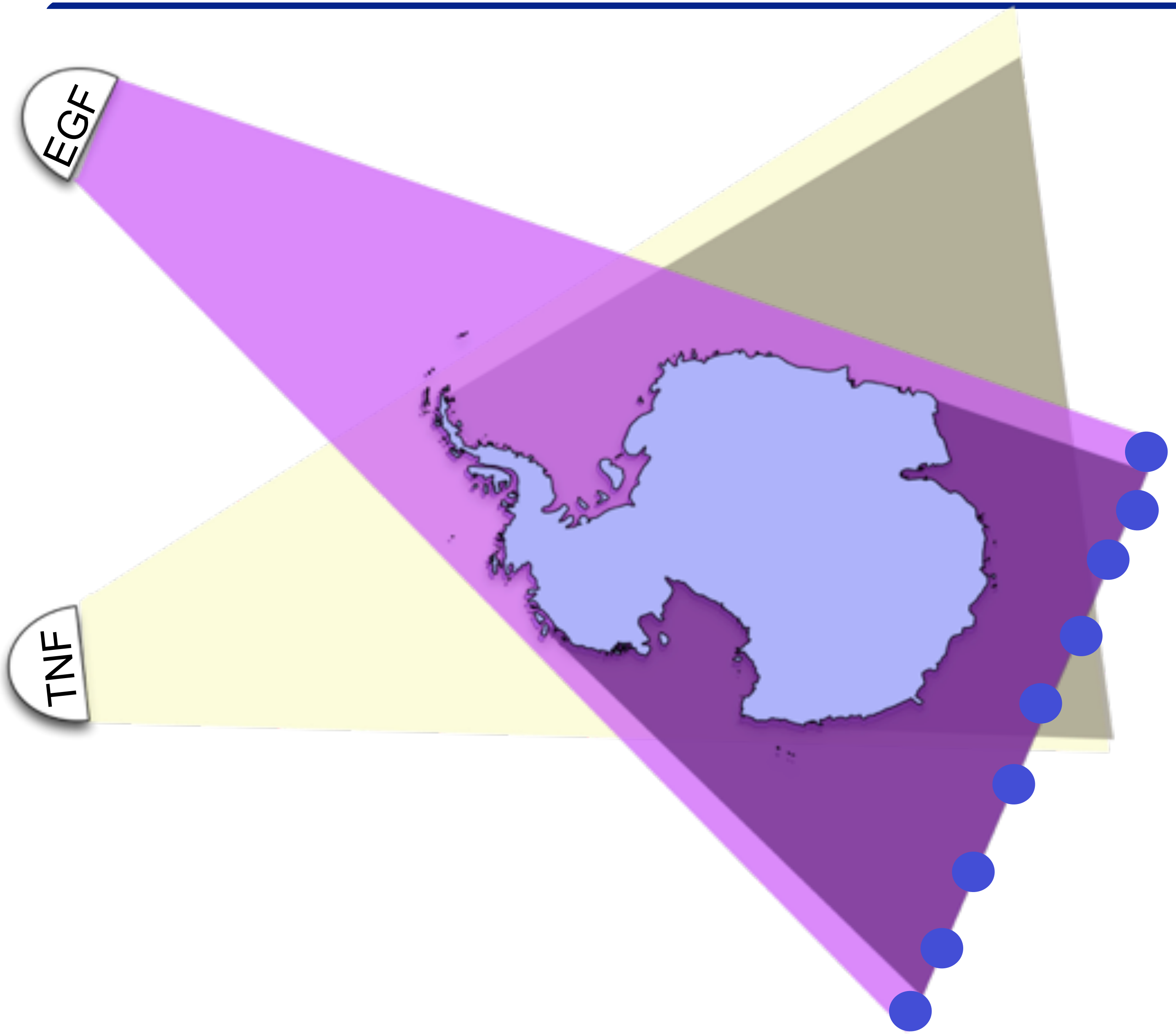

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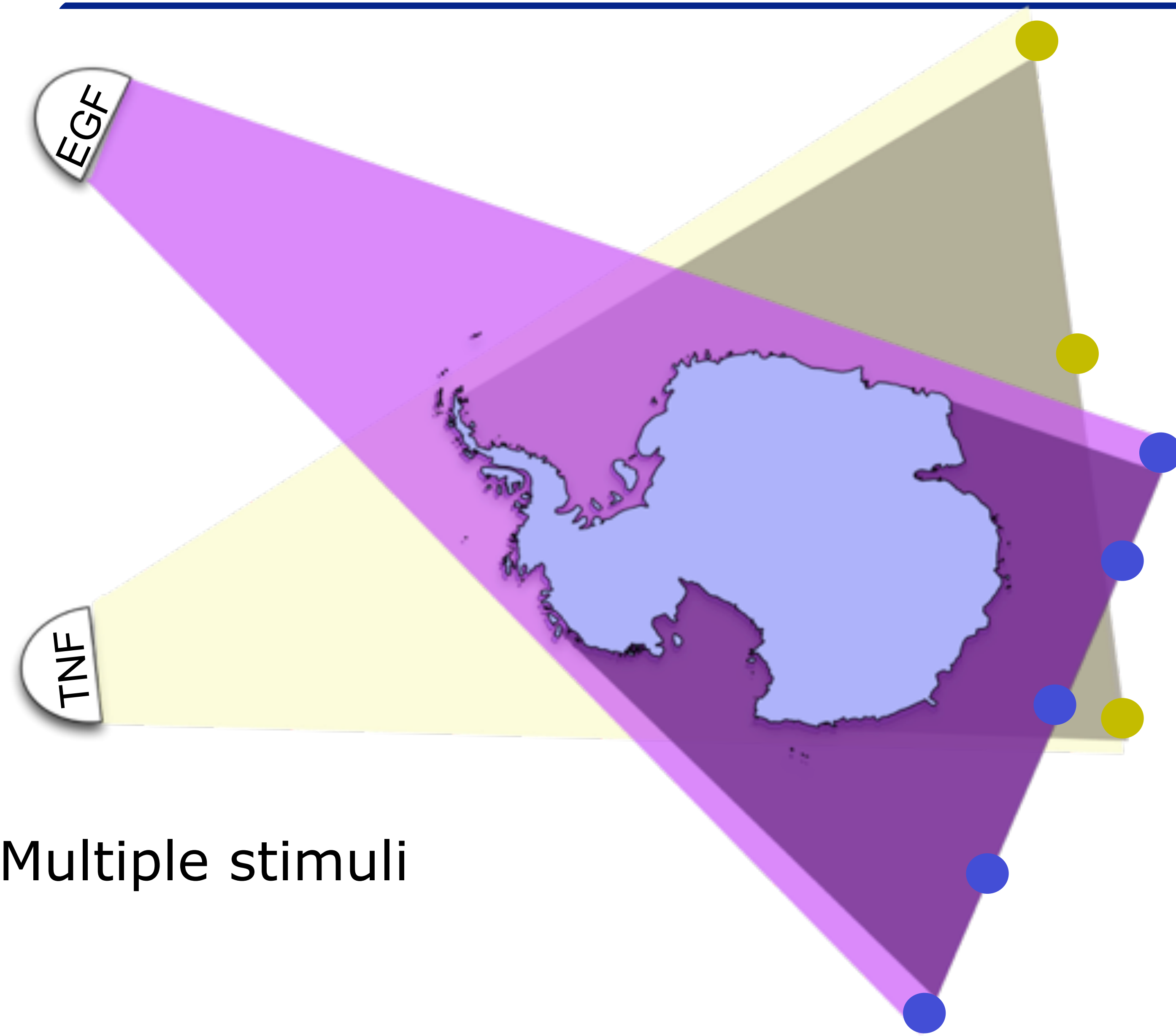
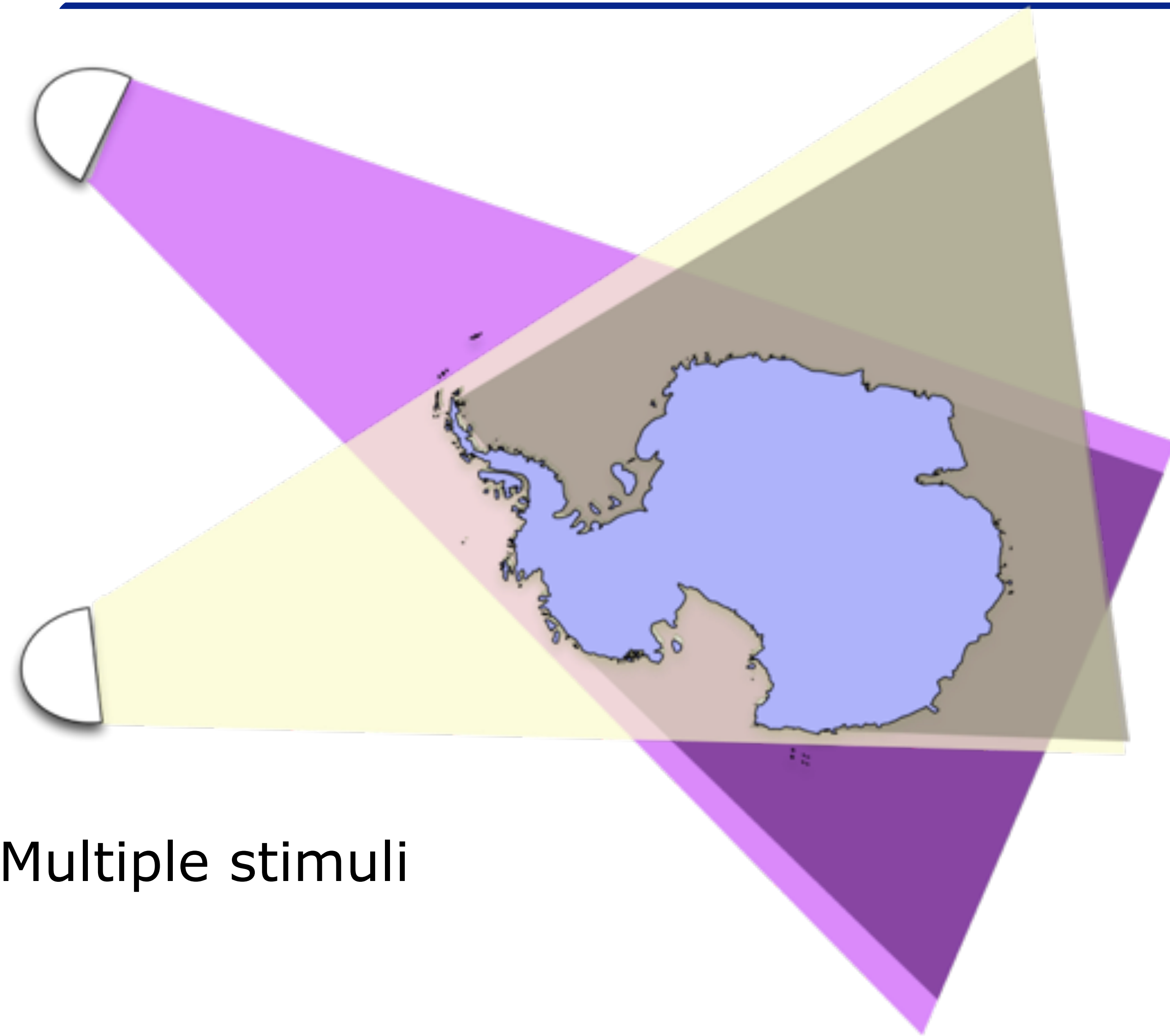


- Multiple stimuli

Choosing cues to maximize information



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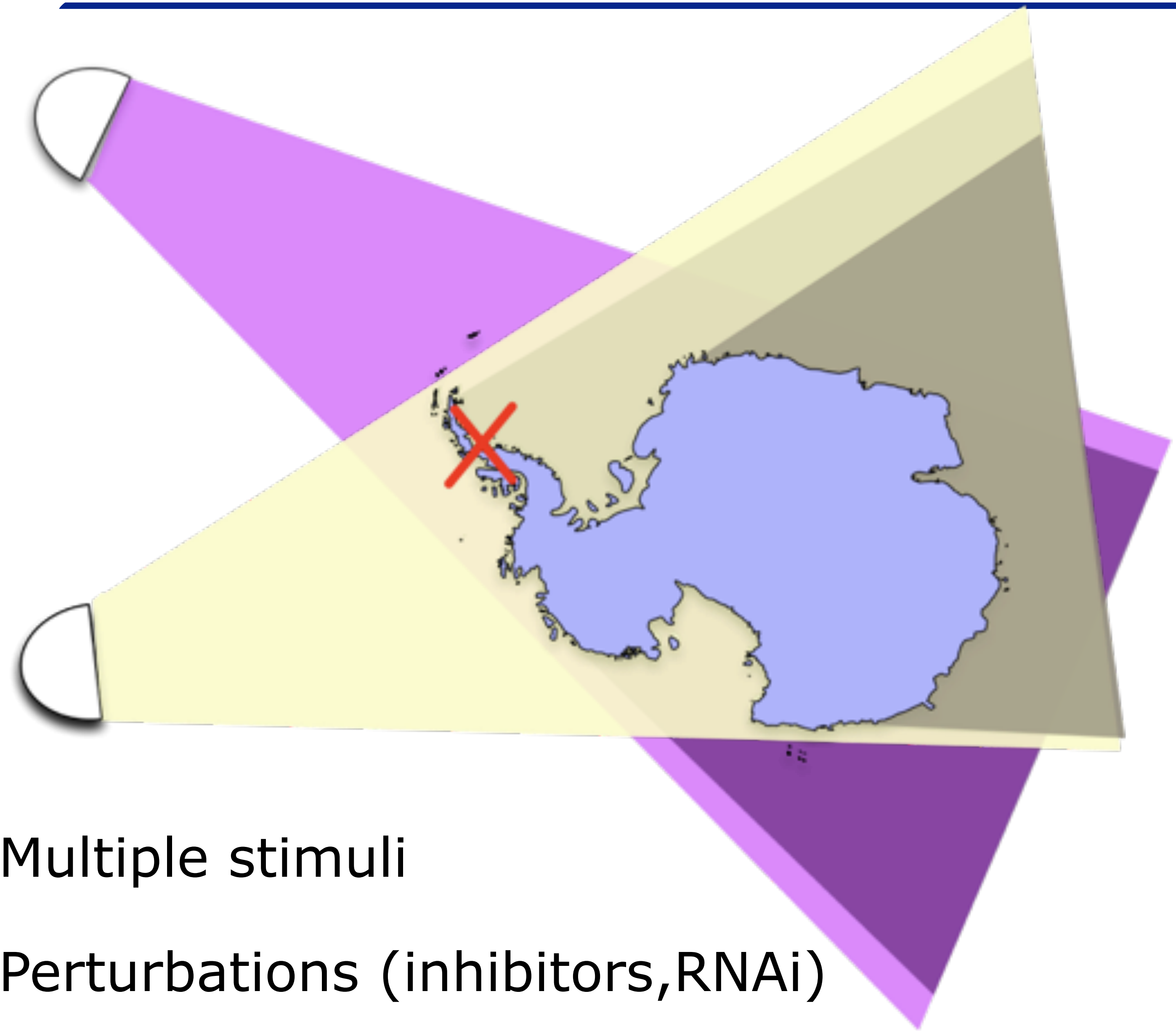
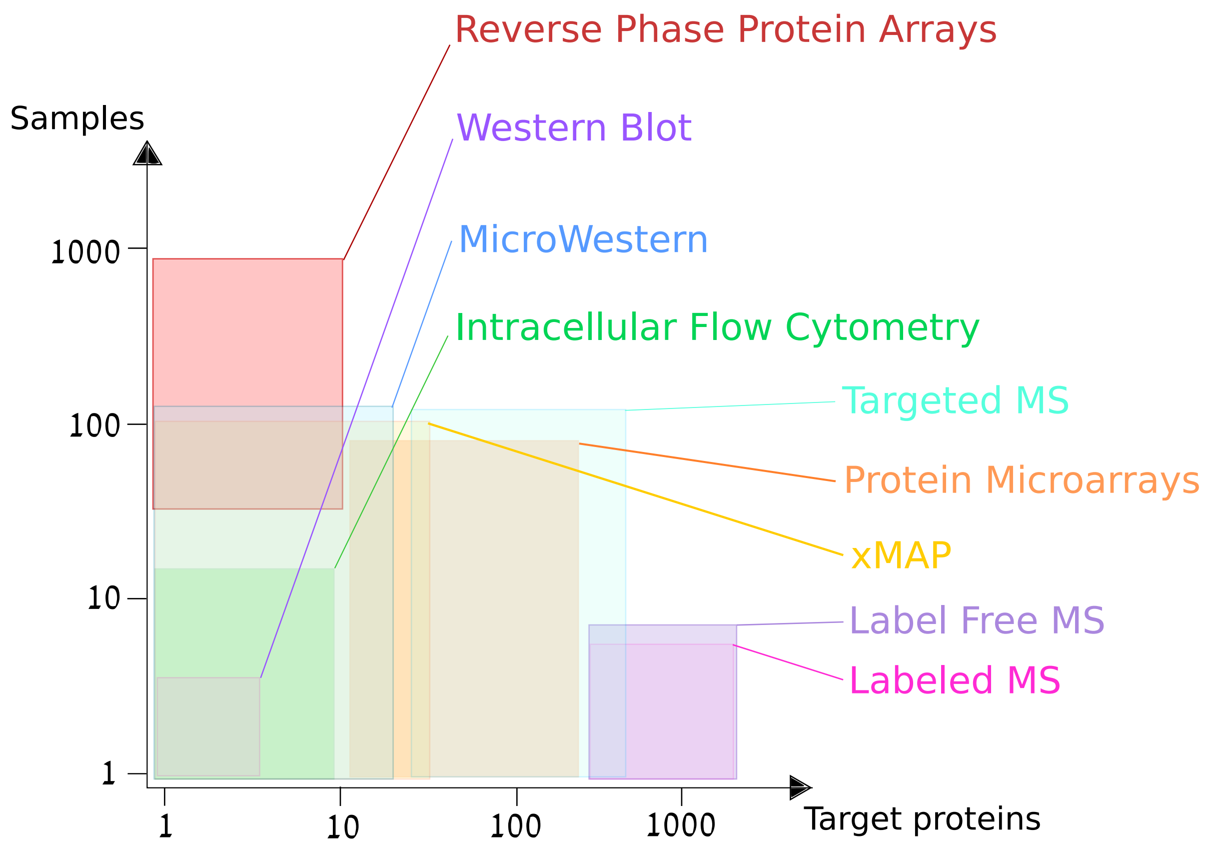


- Multiple stimuli
- Perturbations (inhibitors,RNAi)

To look at signal transduction, proteomics is the natural platform

Different platforms with pros and cons



Terfve C, Saez-Rodriguez J, *Adv. Syst. Biol.*, 2012
Saez-Rodriguez J, MacNamara A, Cook, S, *Annual Rev Biomed Eng*, 2015

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Terfve C, Saez-Rodriguez J, *Advances in Systems Biology, Springer, 736:19-57, 2012*

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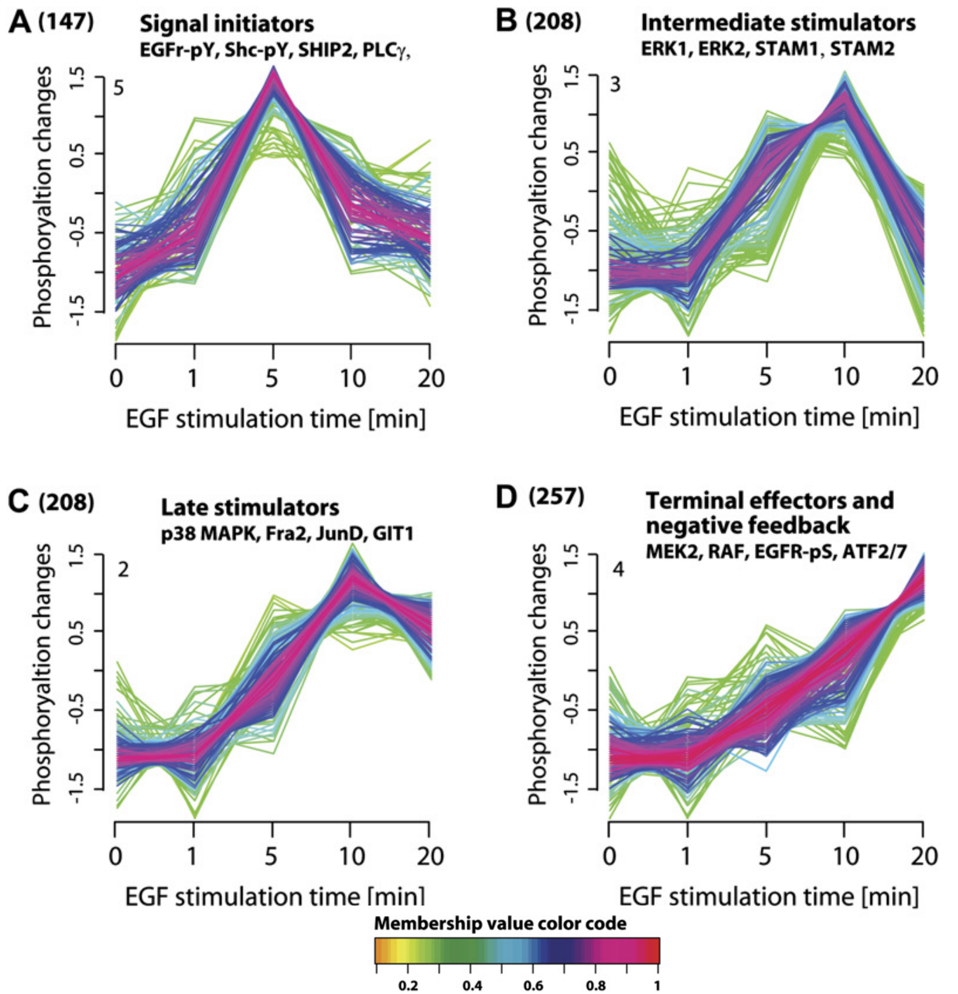
E.g. cluster time series of phosphorylation of peptides upon EGF stimulation to classify them (early/late responders, etc.)



Olsen, J.V. et al., “Global, In Vivo, and Site-Specific Phosphorylation Dynamics in Signaling Networks”, *Cell* 127:635-648, (2006).

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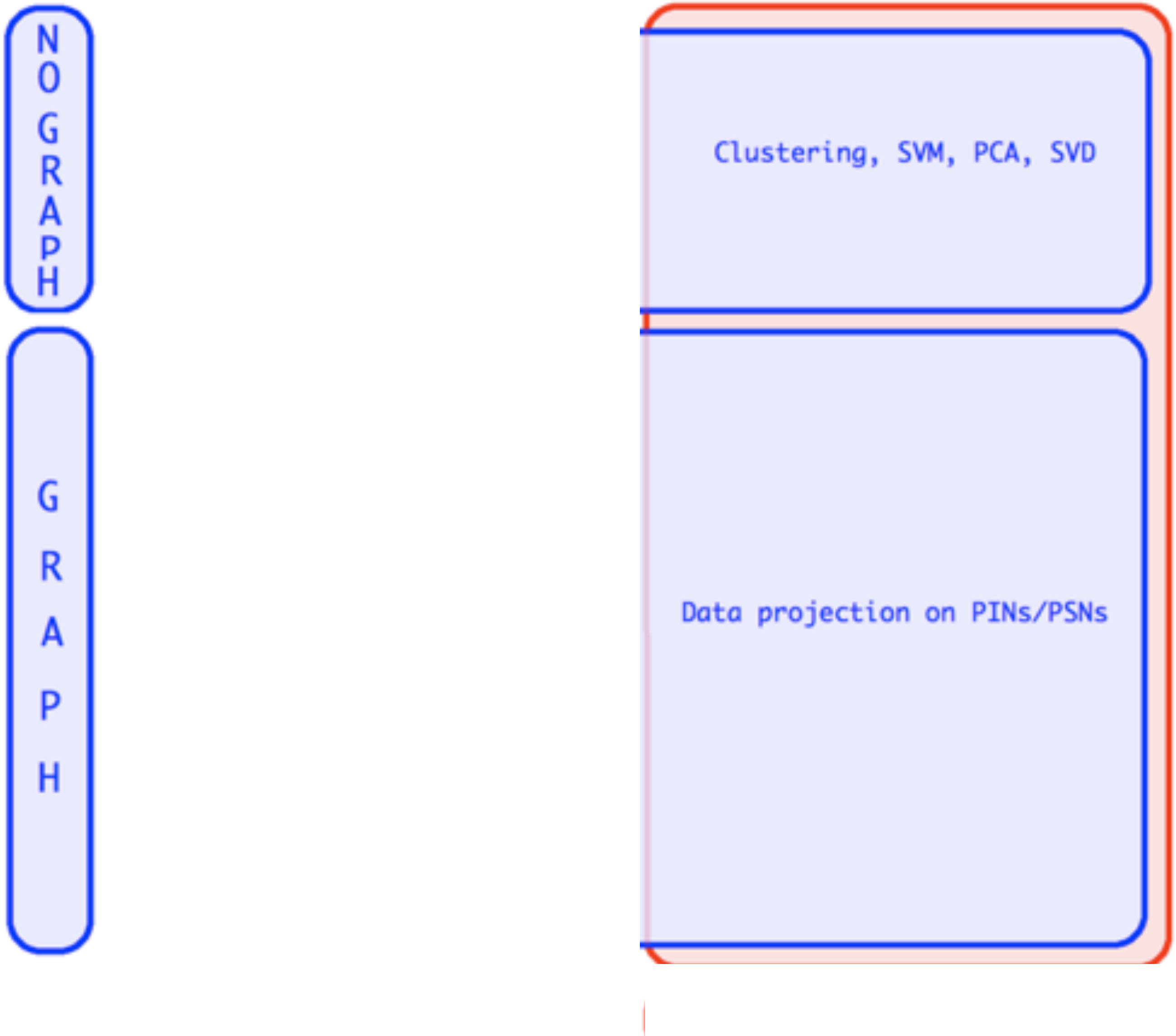
Projection on protein networks helps to put data in molecular context



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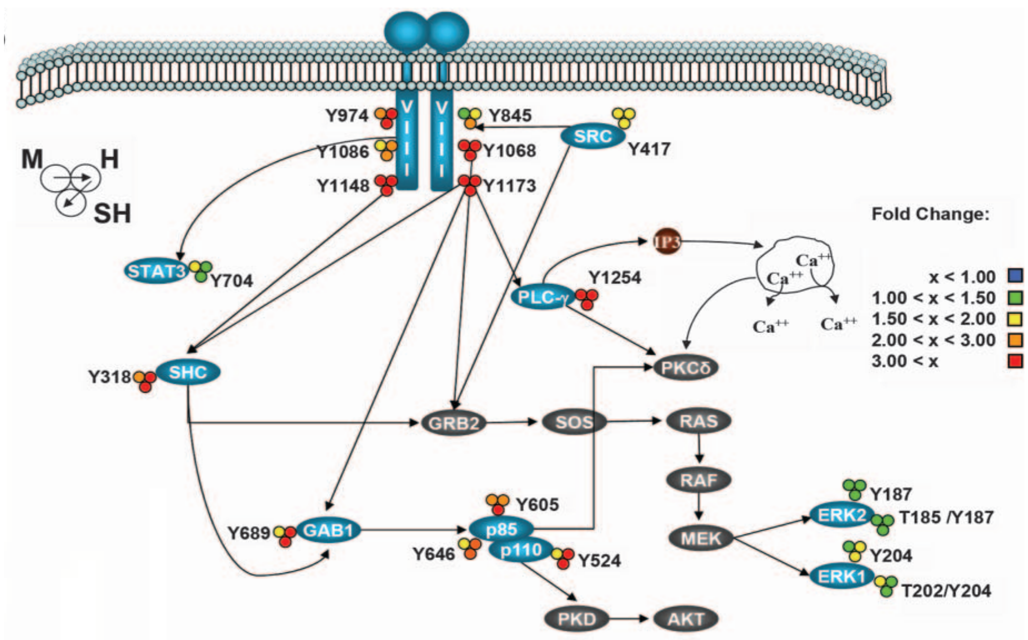
E.g. visualize fold increase in phosphorylation for different Gliobastoma cell lines (with different EGFR expression)



Huang, P. et al., "Quantitative analysis of EGFRvIII cellular signaling networks reveals a combinatorial therapeutic strategy for glioblastoma", PNAS, (2007).

Clustering, SVM, PCA, SVD

Data projection on PINs/PSNs

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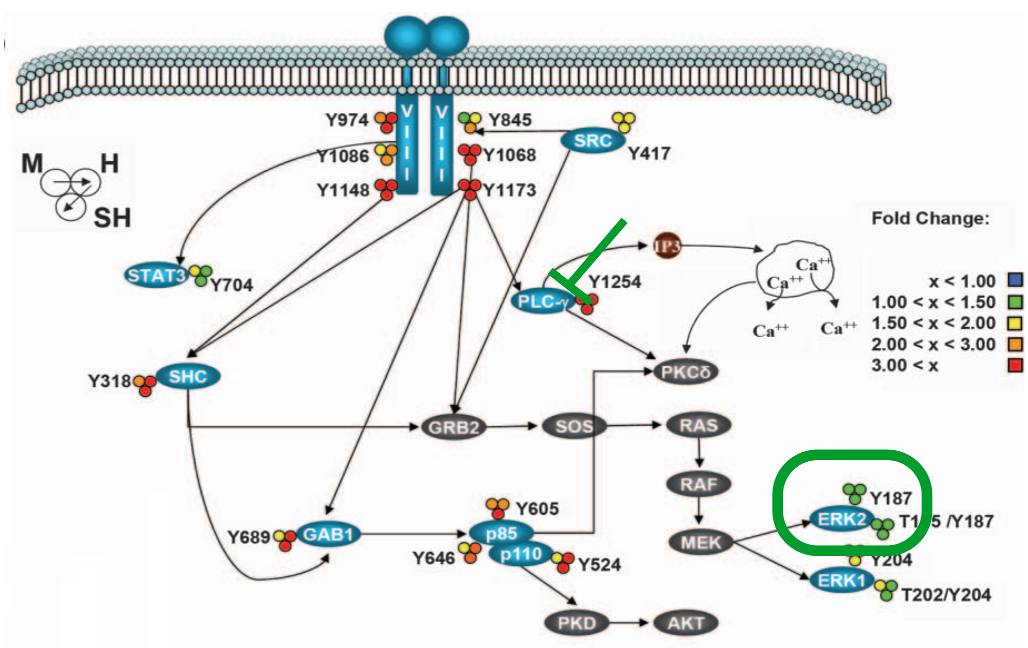
Projection on protein networks helps to put data in molecular context

What would happen on ERK2 if PLCγ is inhibited?

E.g. visualize fold increase in phosphorylation for different Gliobastoma cell lines (with different EGFR expression)



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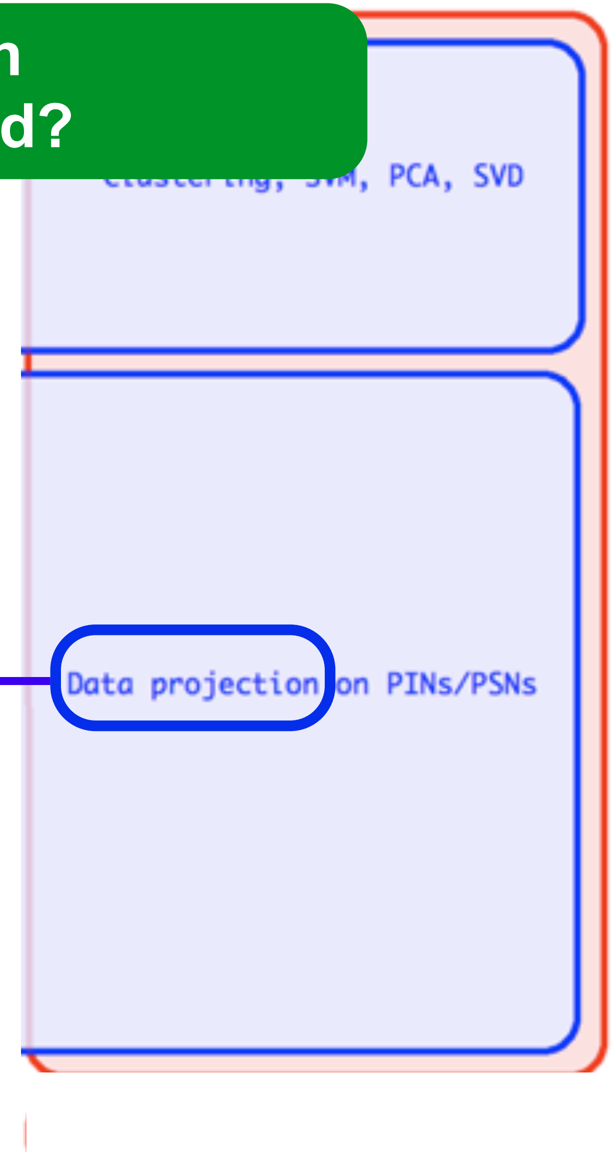
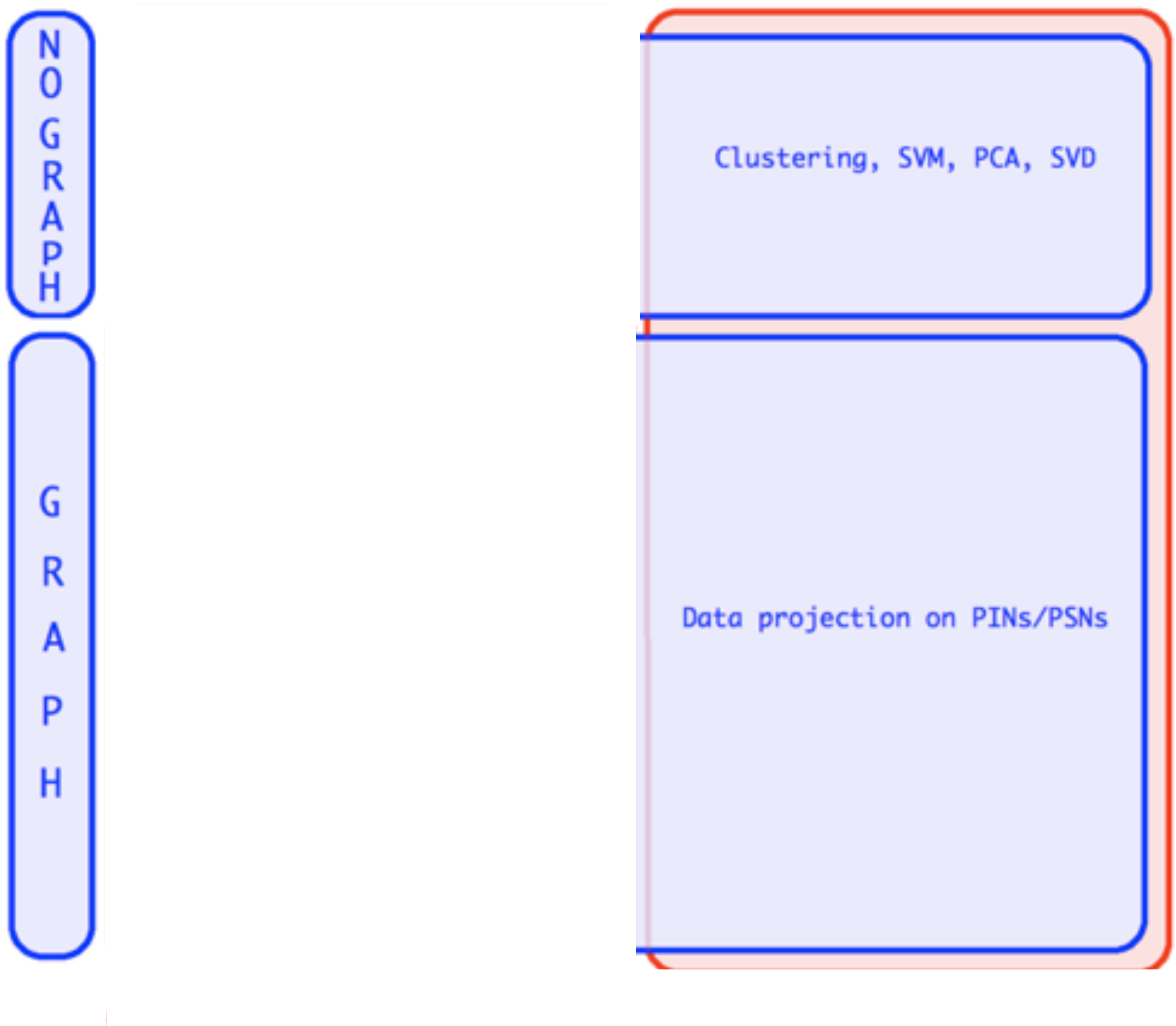


Data-driven predictive models



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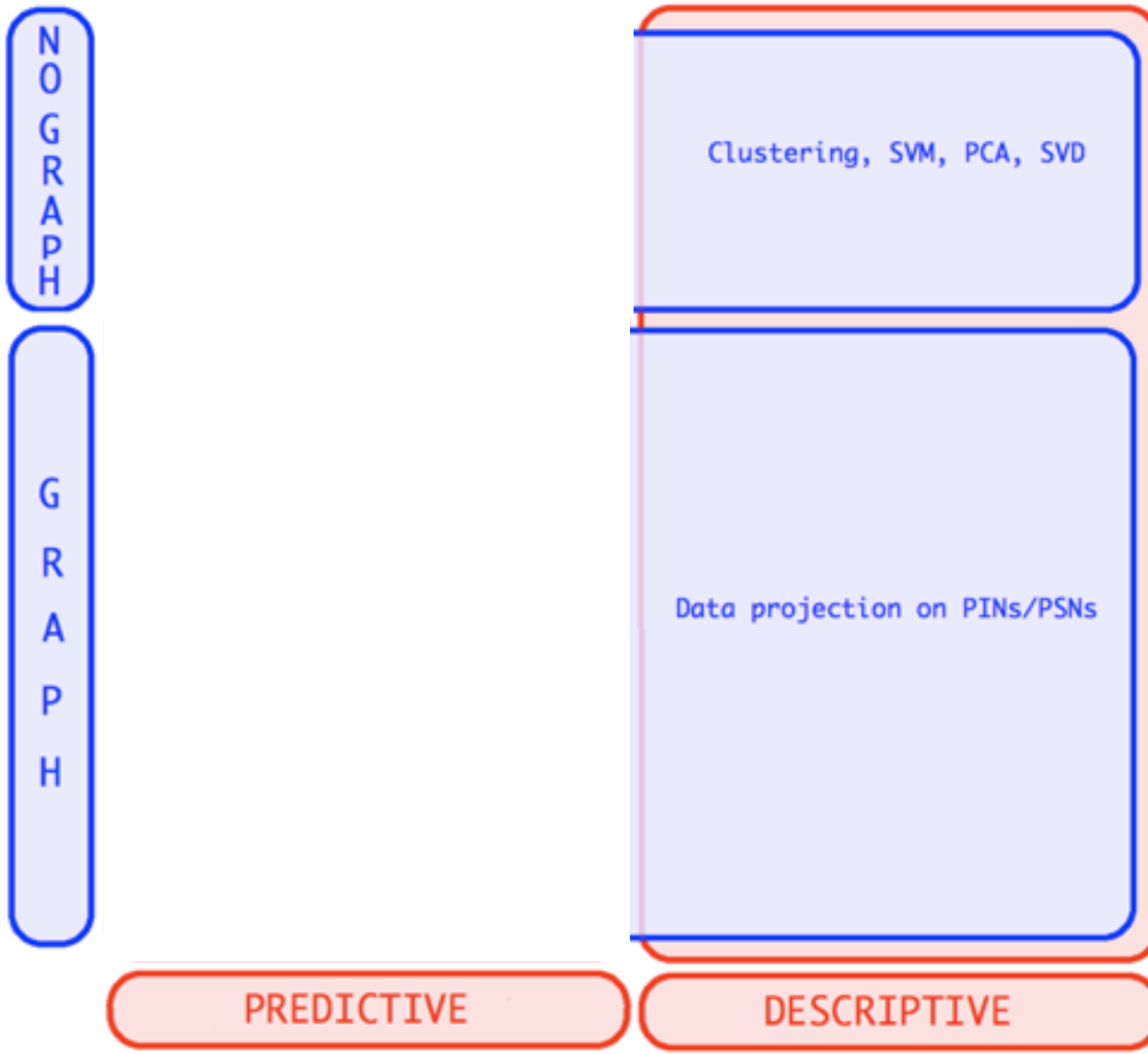

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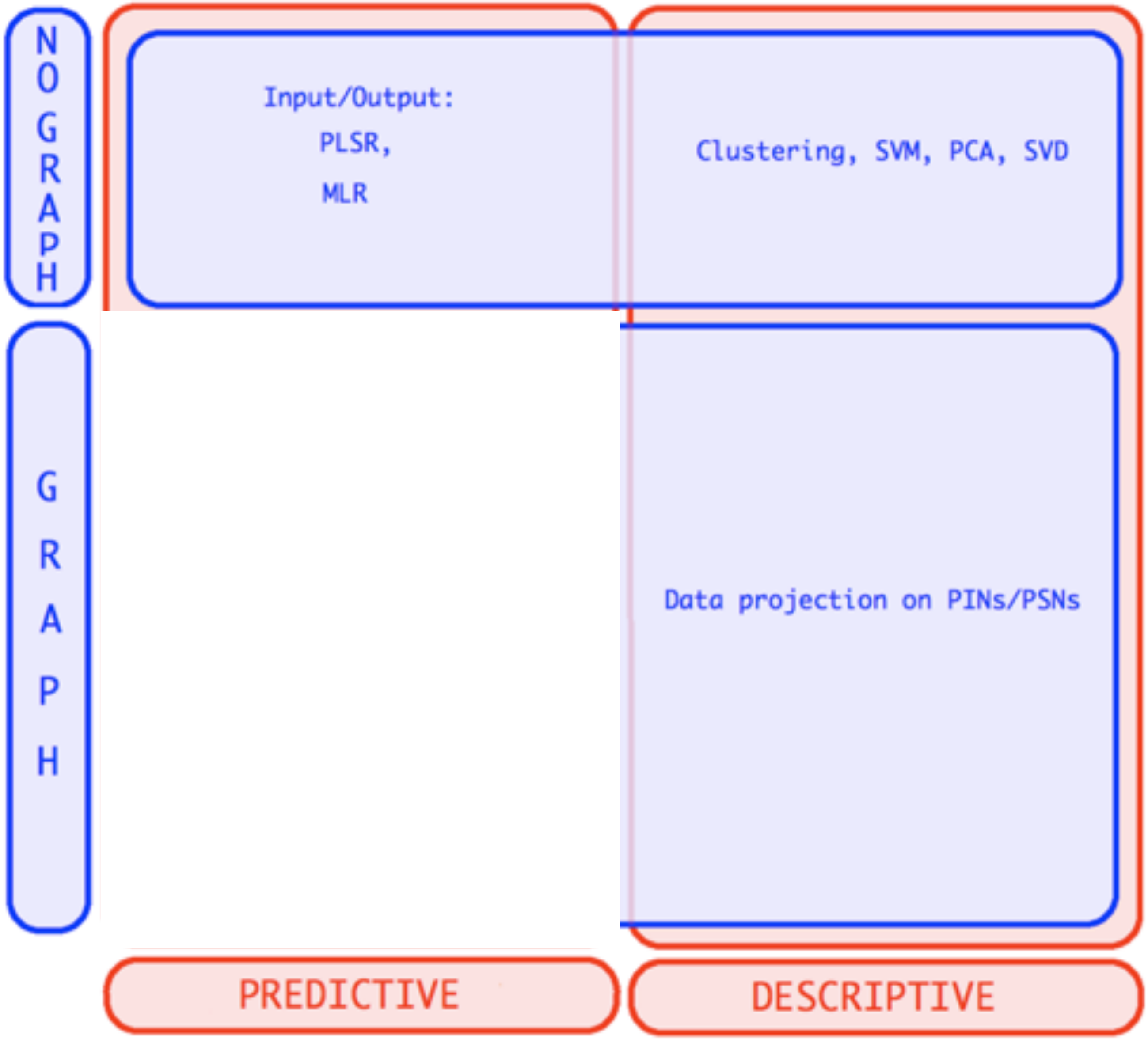

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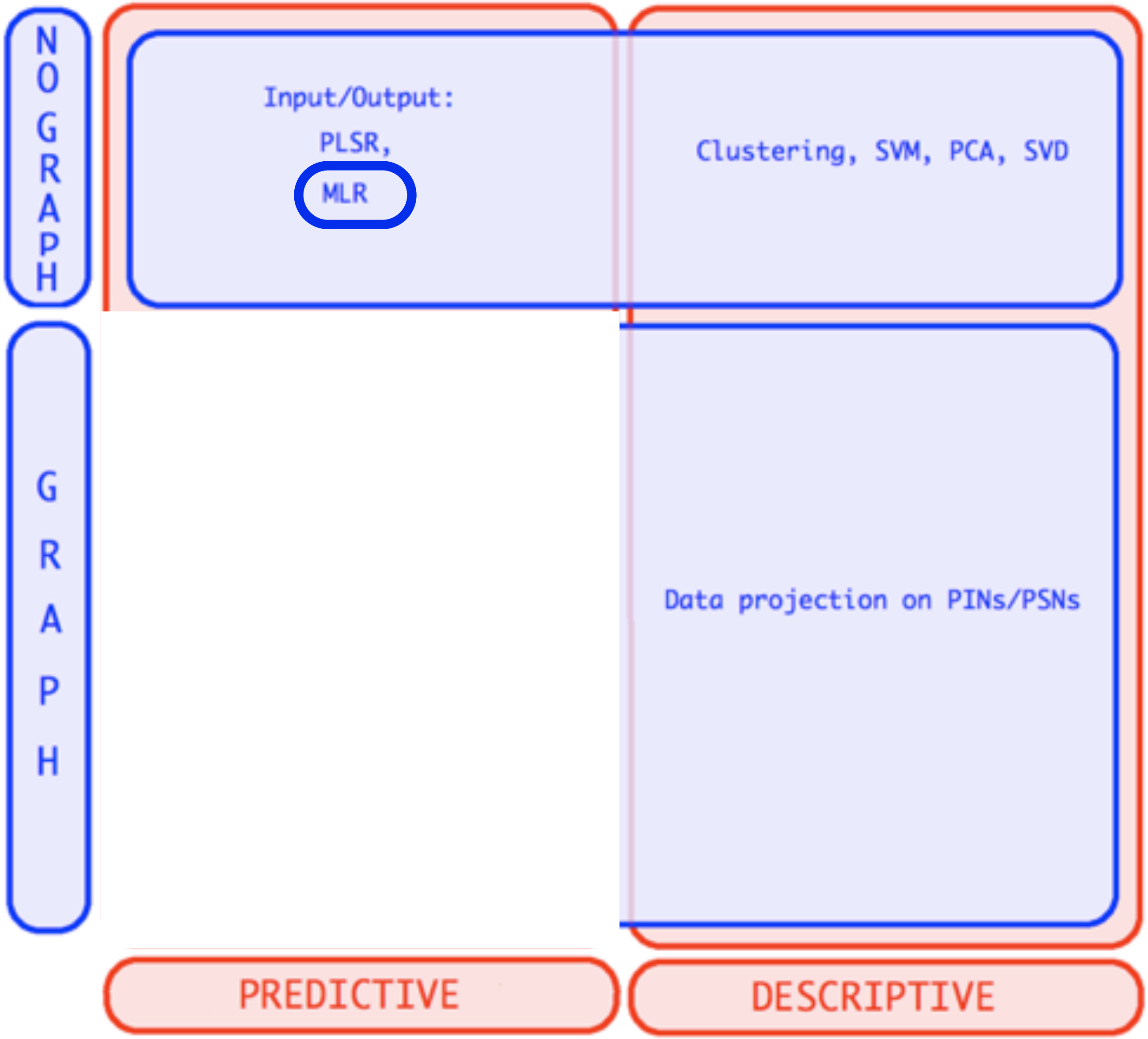

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An example of a perturbation-based high-throughput data sets

Alexopoulos L, Saez-Rodriguez J, Cosgrove B, Lauffenburger DA, Sorger PK, *Mol. Cell. Prot.,* 9, 1849, 2010

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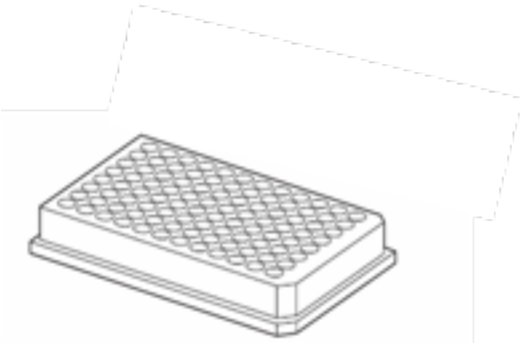

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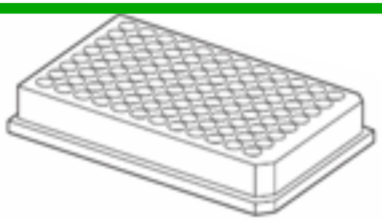
Cue	
	➜ 7 **extracellular ligands**
	➜ 7 specific **chemical inhibitors** (drugs)



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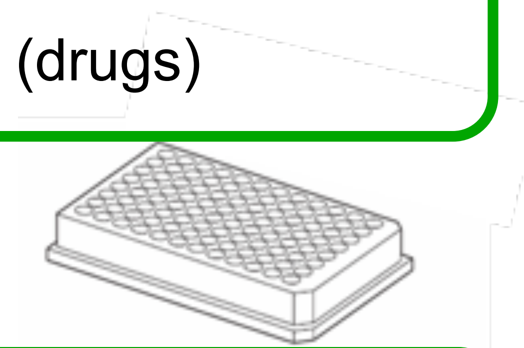

Signal

➜ **Phosphorylation** of 17 key proteins (30 min, 3h)

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An example of a perturbation-based high-throughput data sets

Primary human hepatocytes & HCC cell lines (HepG2, Hep3B, Huh7, Focus)

Cue
- ➜ 7 **extracellular ligands**
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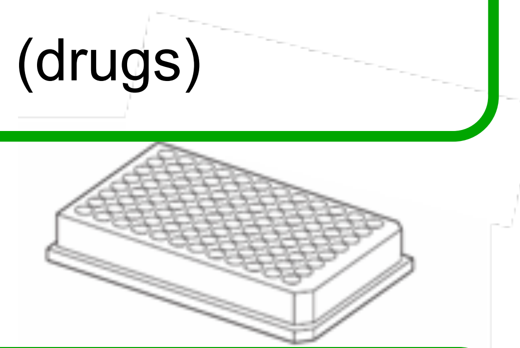

Signal
- ➜ **Phosphorylation** of 17 key proteins (30 min, 3h)

using Luminex/xMAP (bead-based ELISA)

Response
- ➜ **Release** of 20 cytokines (3h, 24h)

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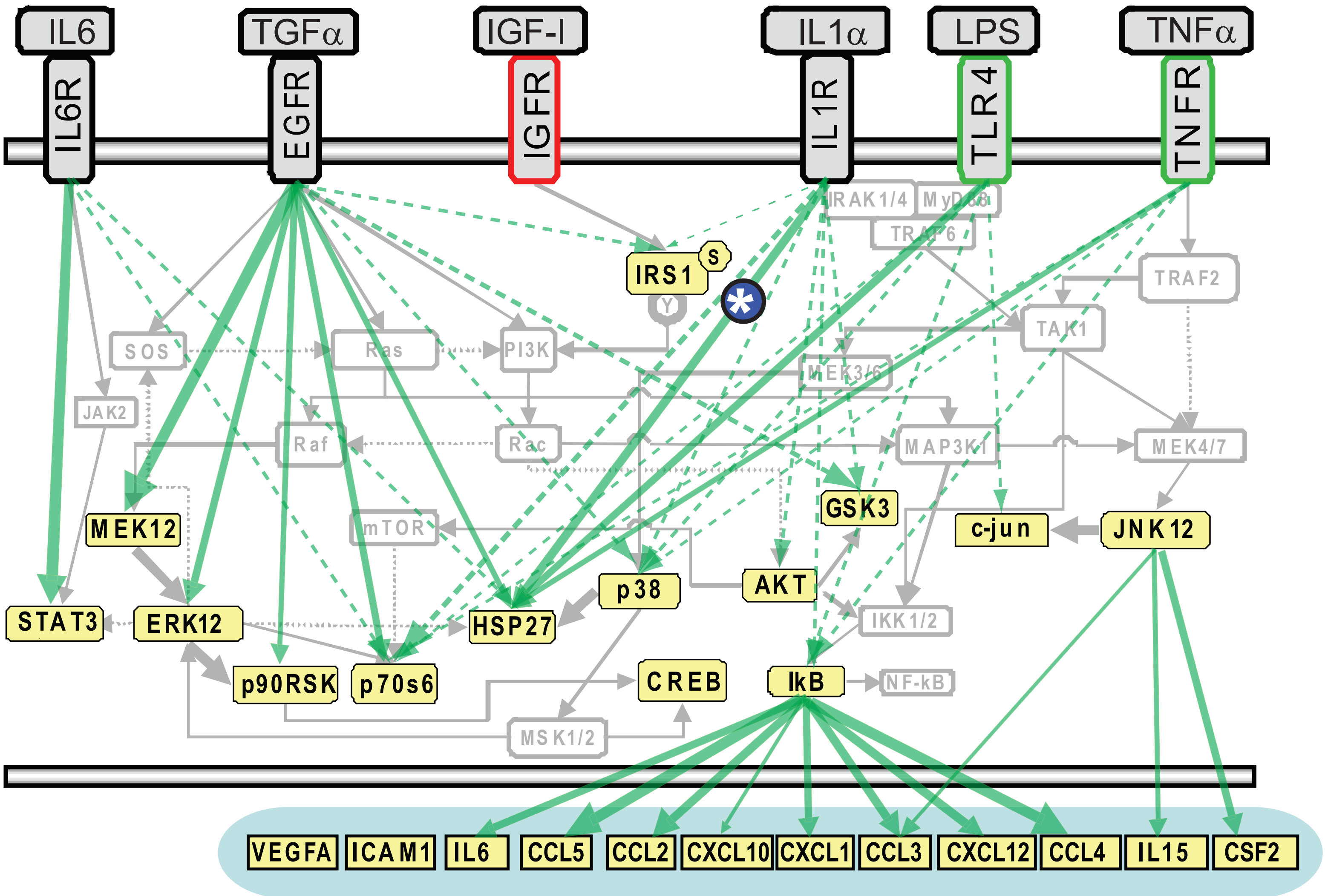
Linear regression uncovers signaling differences between primary & transformed hepatocytes



Draw 30 % strongest weights (correlations) obtained by Multiple Linear Regression

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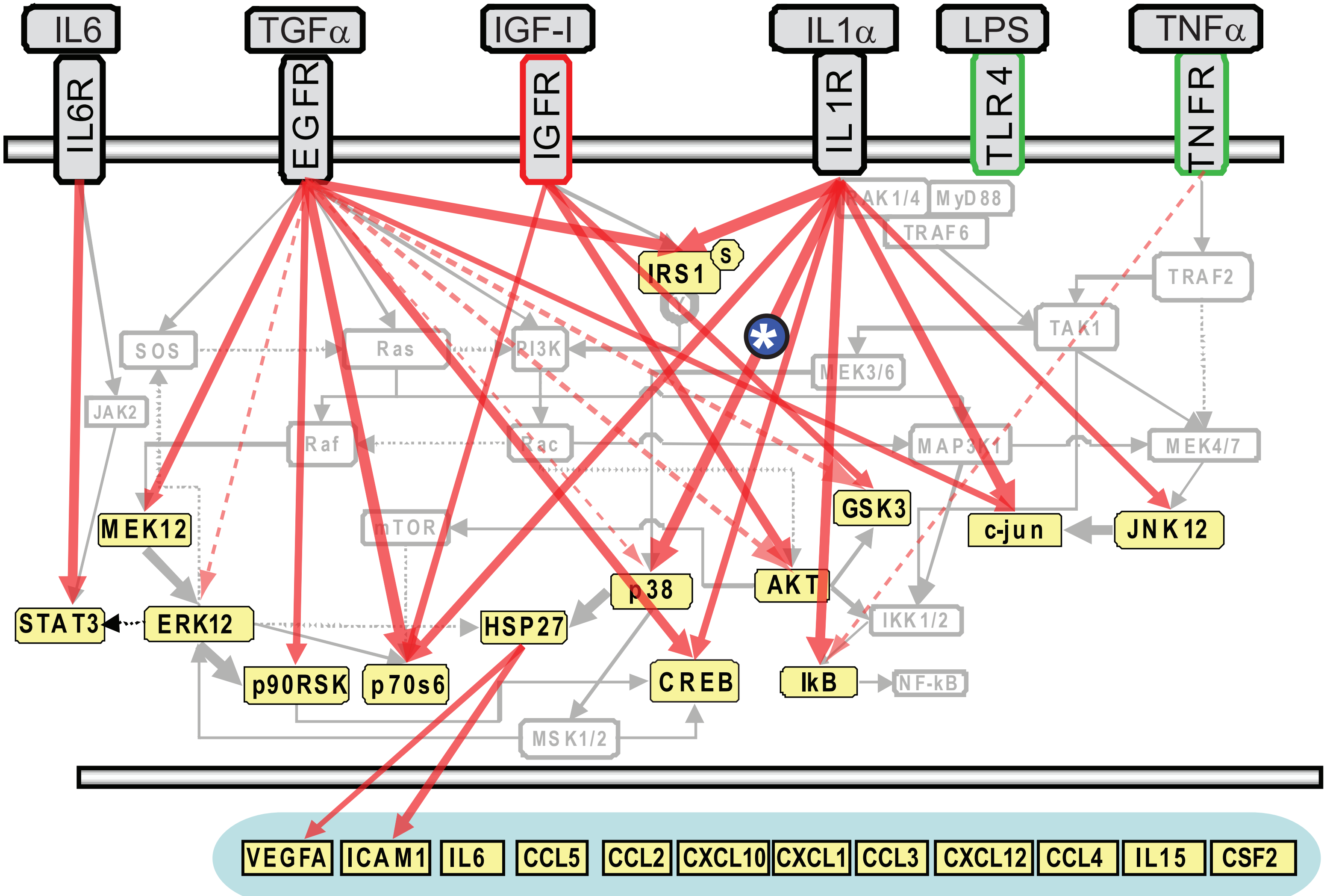

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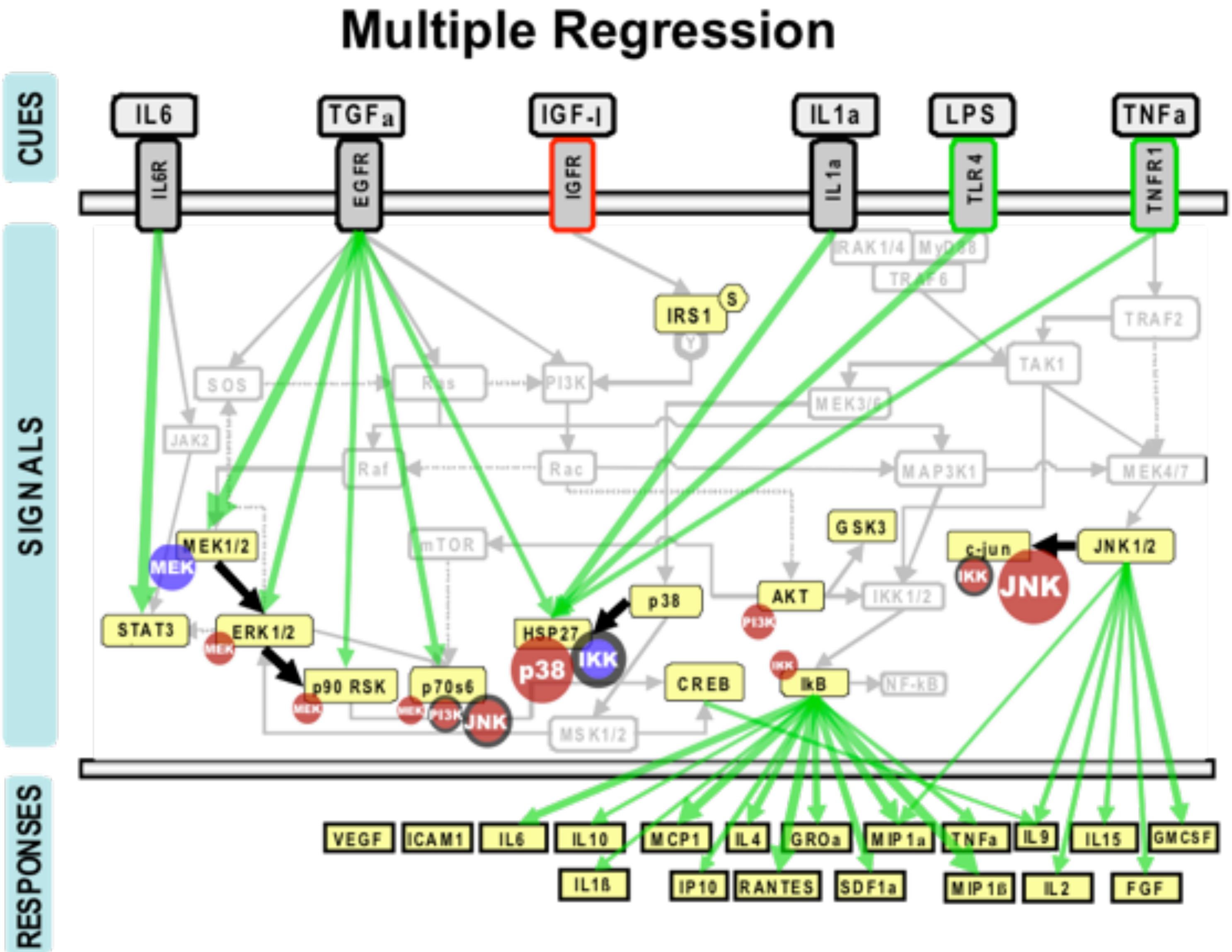
Data-driven approaches useful but provide limited mechanistic insight



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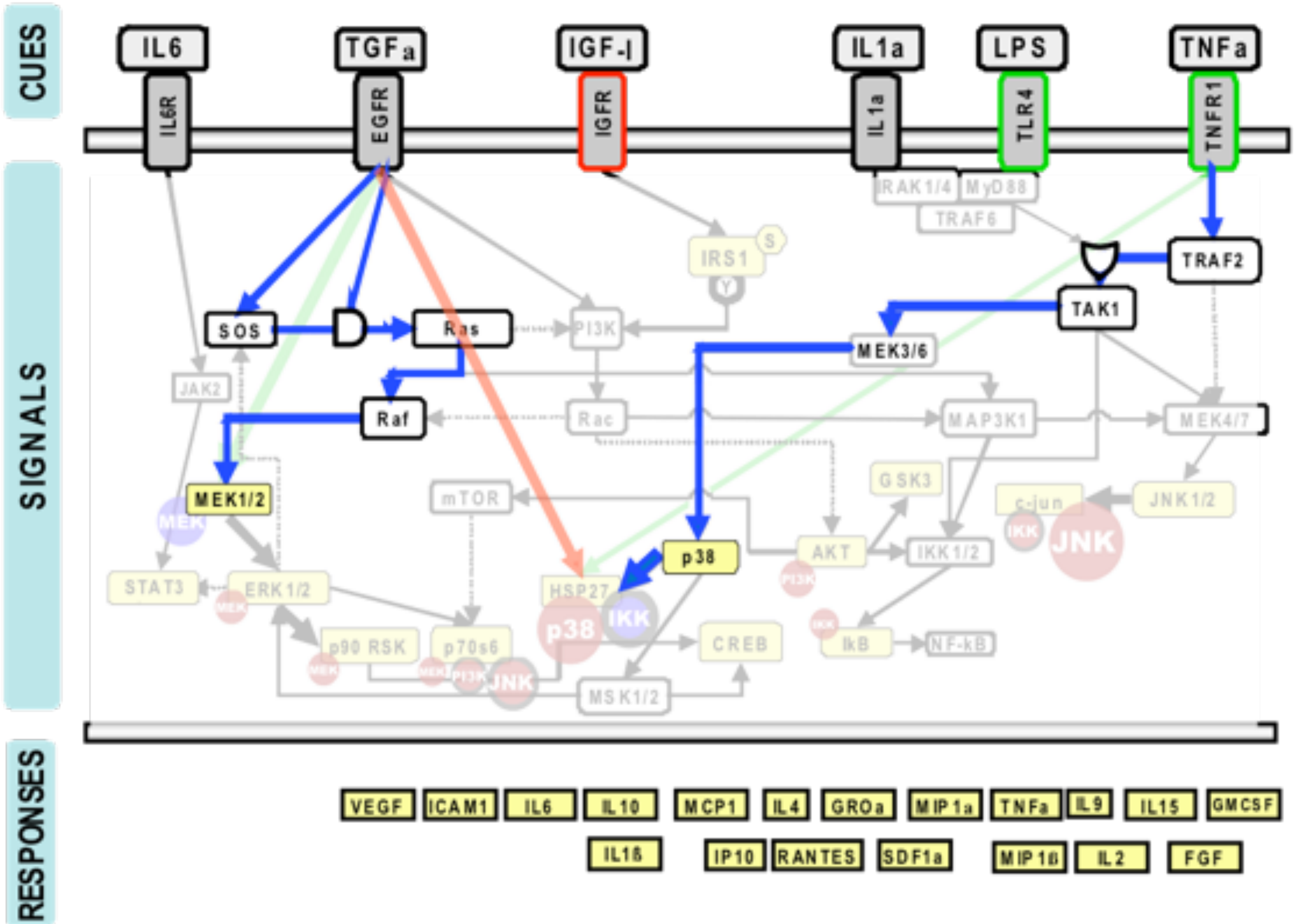

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Mechanistic modelling: Integrating network knowledge with functional data

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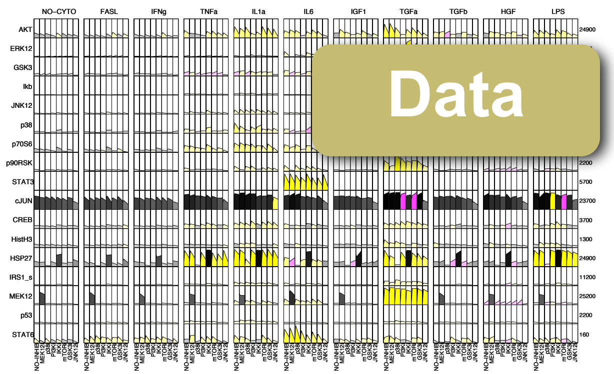
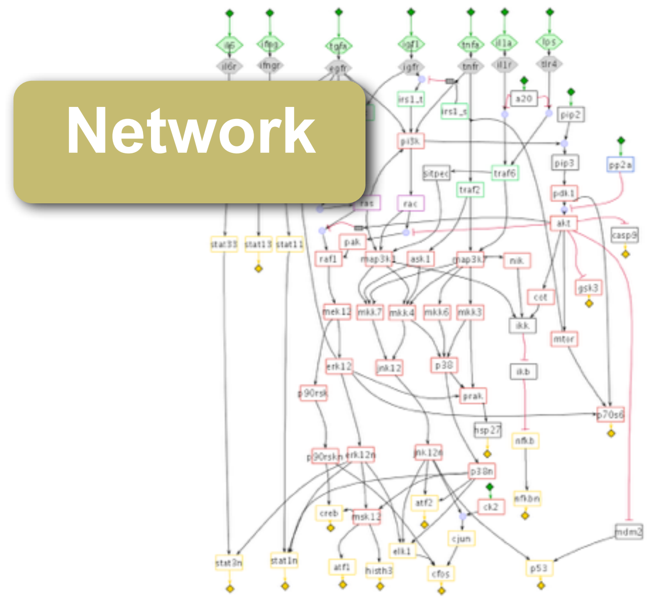
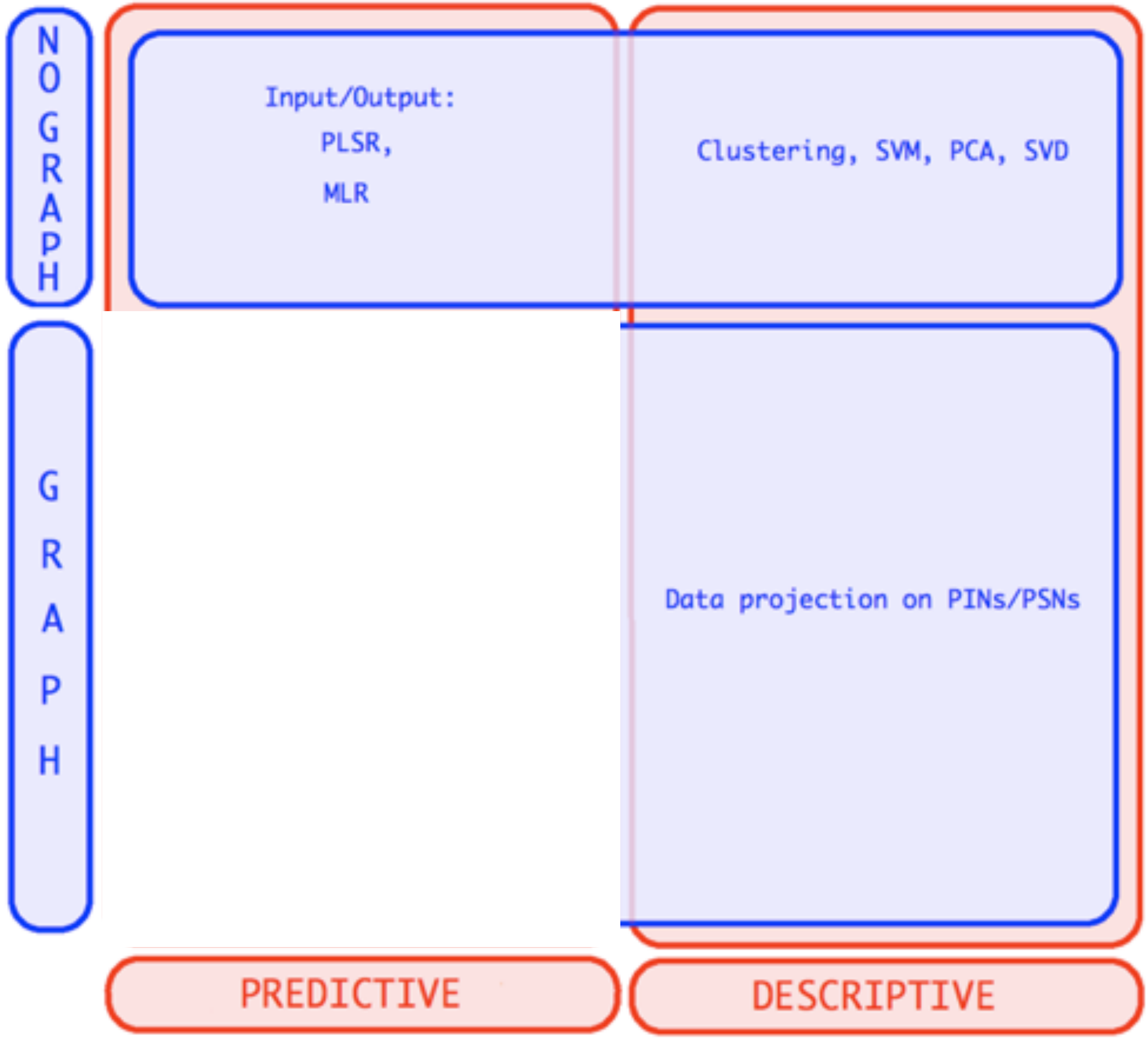




Multiple mechanistic approaches



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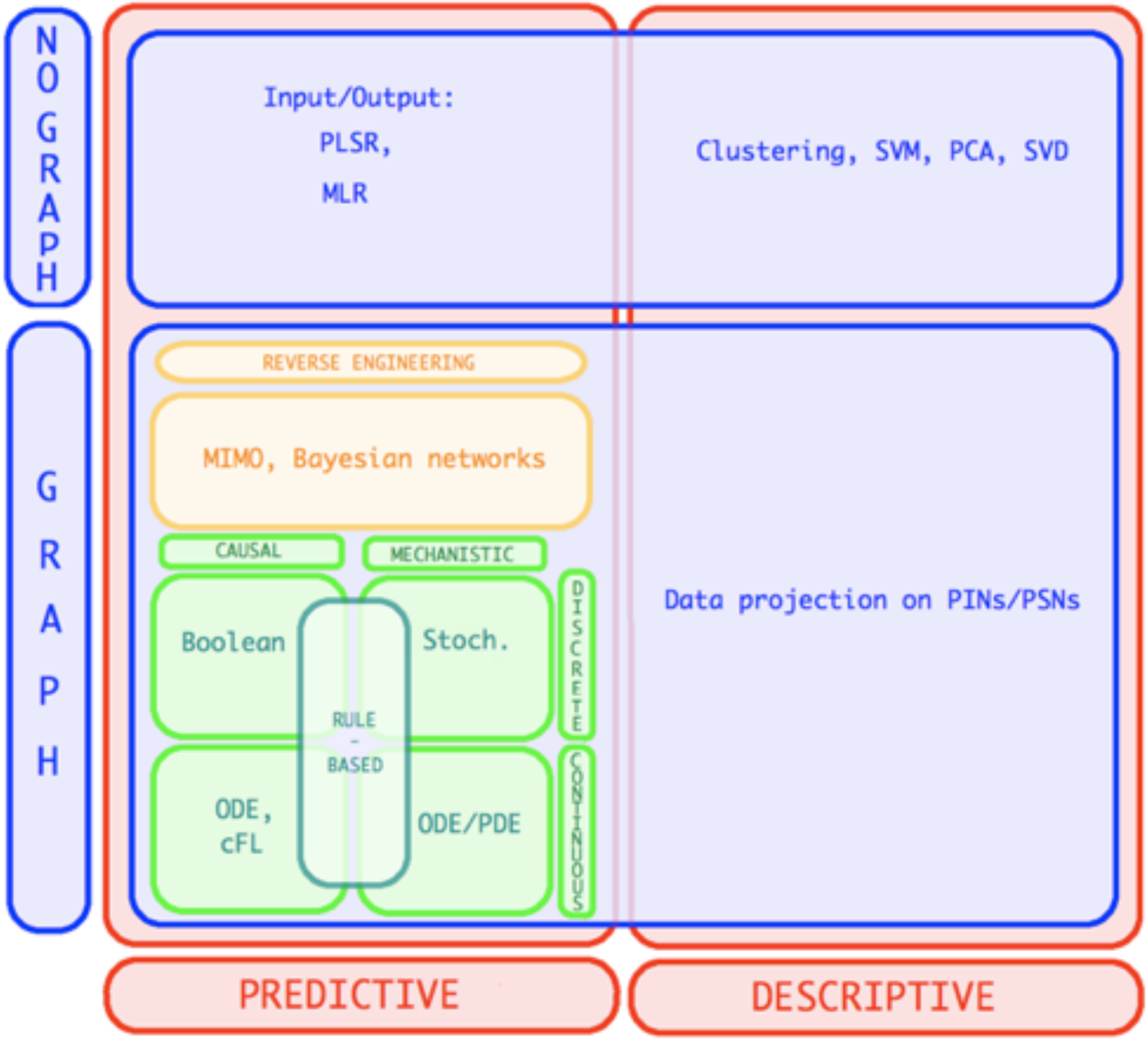

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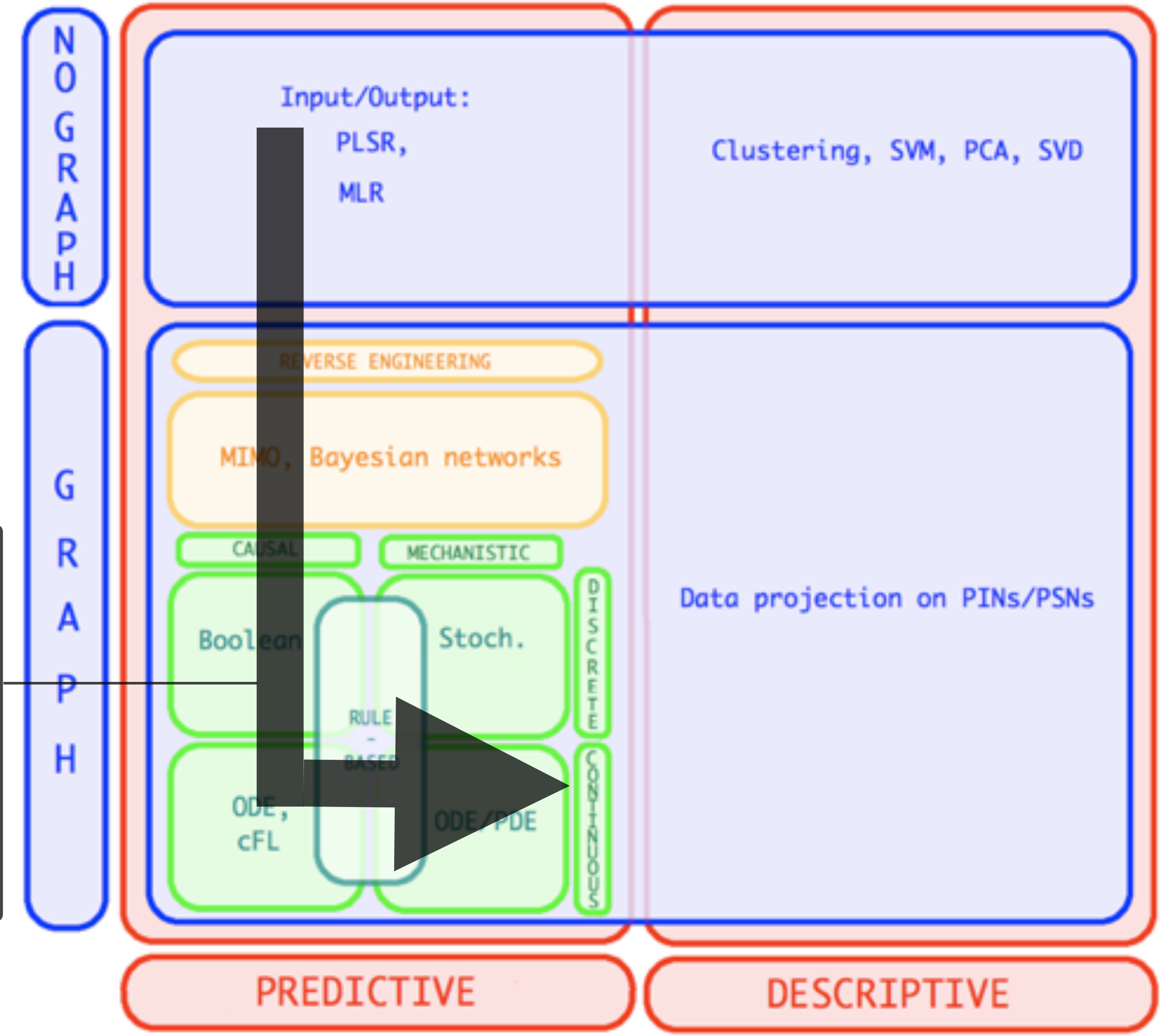

+ Mechanistic insight

+ Prior knowledge & data required

- Model size

+ Harder calibration

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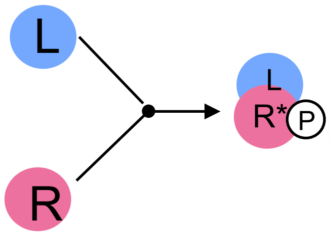
Causal vs. biochemical representation of signal transduction



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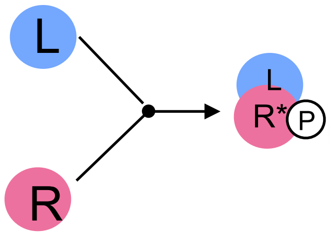
$$\frac{d[R]}{dt} = -k_{f1}[L][R] + k_{r1}[LR^*]$$

Causal vs. biochemical representation of signal transduction

- Natural modeling approach is based on **differential equations** describing underlying biochemistry



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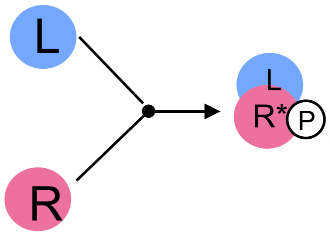

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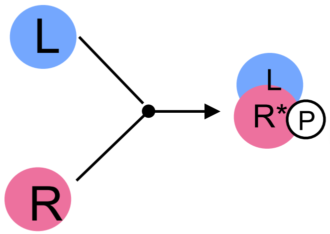

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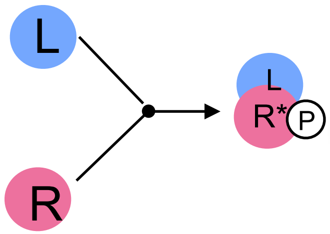

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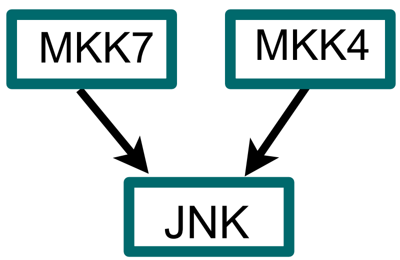

Boolean Model

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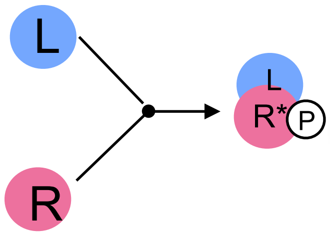

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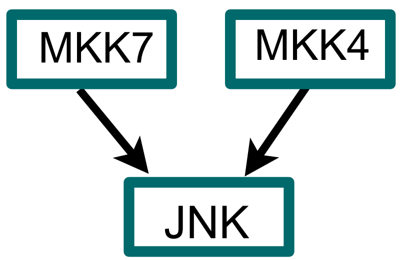

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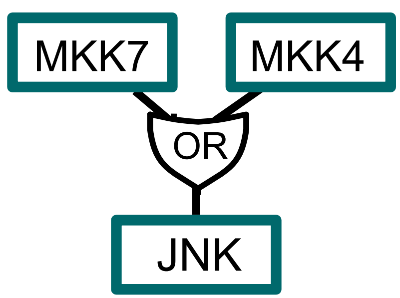

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Causal vs. biochemical representation of signal transduction

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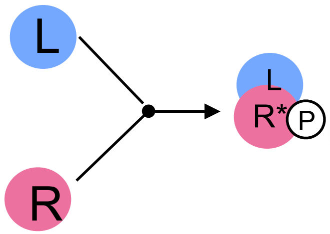

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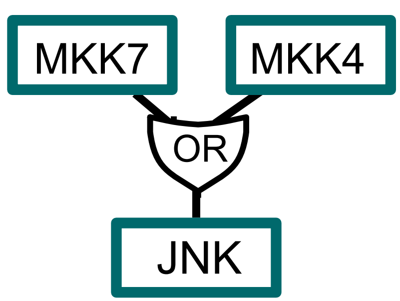

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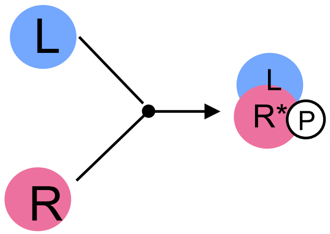

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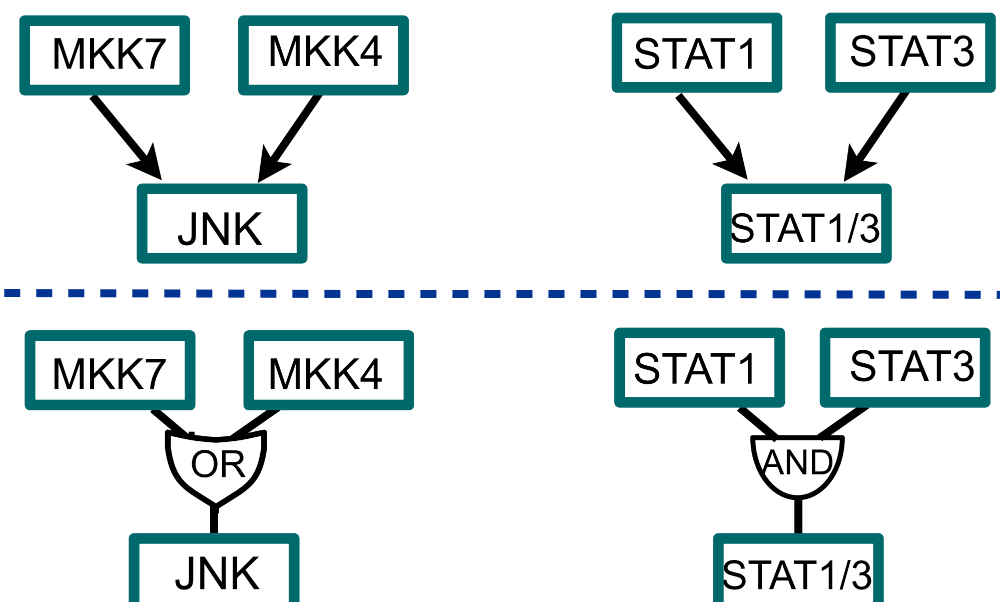

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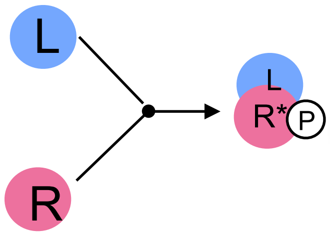

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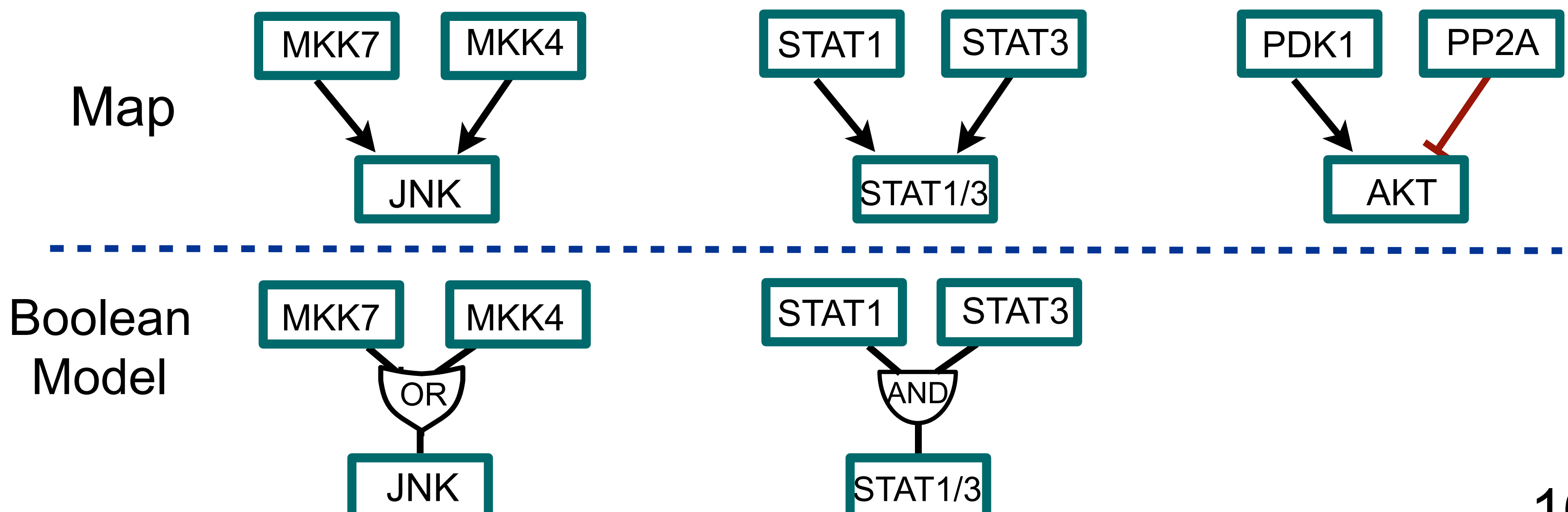

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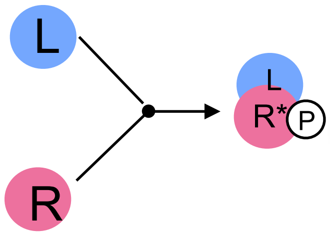
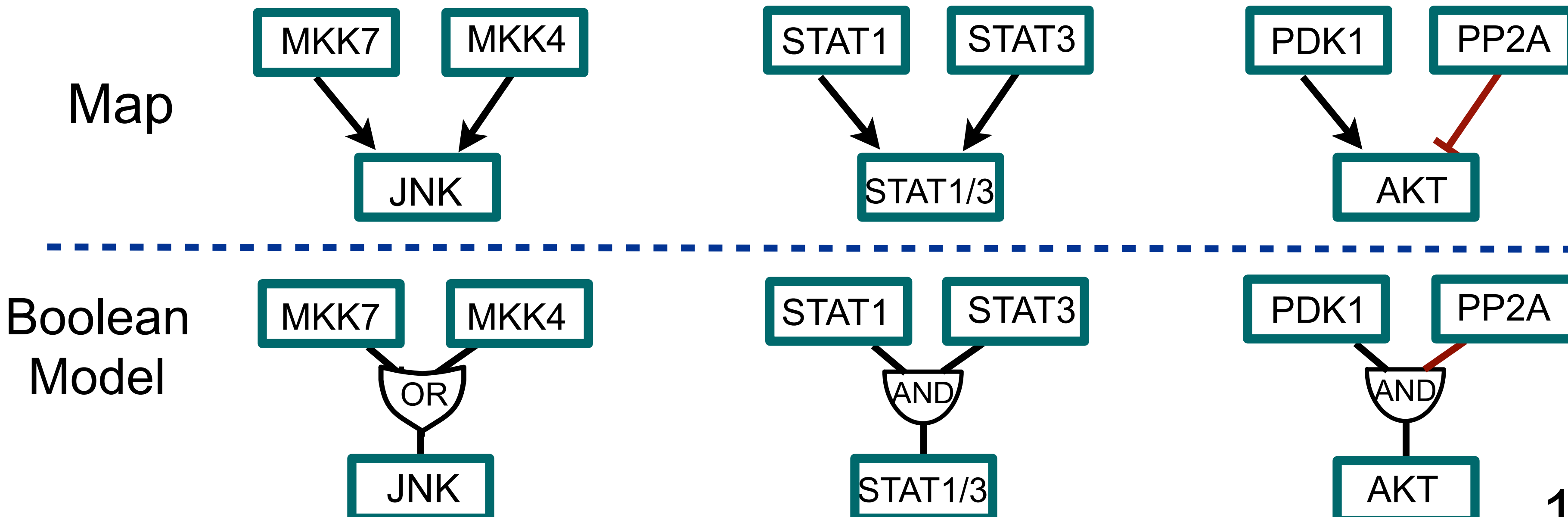
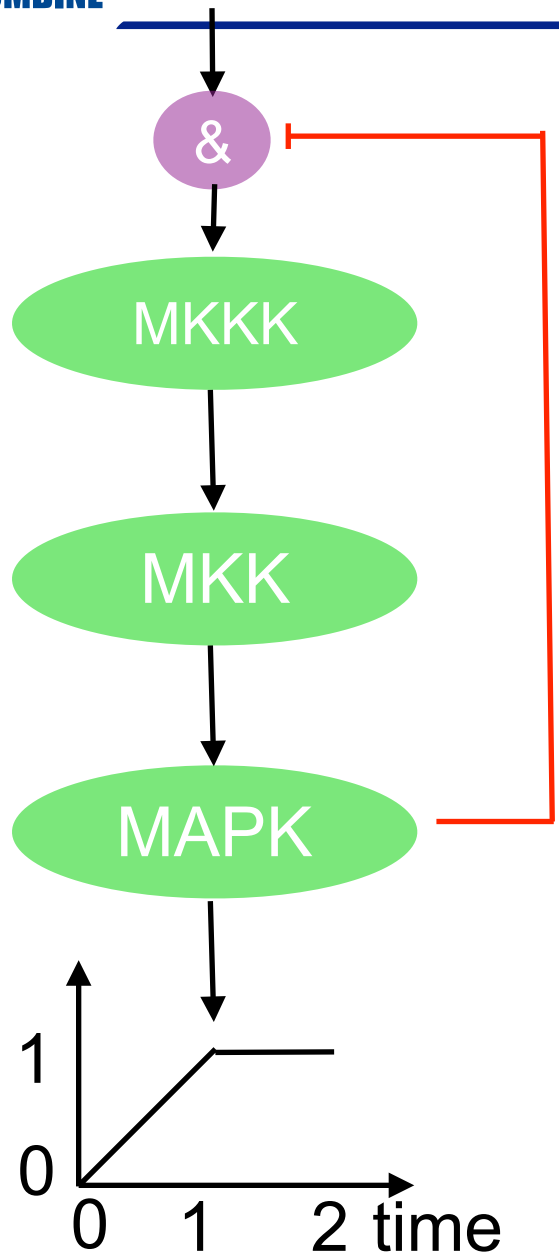


$$R+L \underset{k_{r1}}{\overset{k_{f1}}{\rightleftharpoons}} LR^* \qquad \frac{d[R]}{dt} = -k_{f1}[L][R] + k_{r1}[LR^*]$$

- **If the network is too large** for detailed modeling (parameters to fit, etc.), and not enough molecular information available in pathway maps
  - Boolean (0/1,"ON/OFF") models: **maps + logic gates (AND/OR)**



Causal vs. reaction representation



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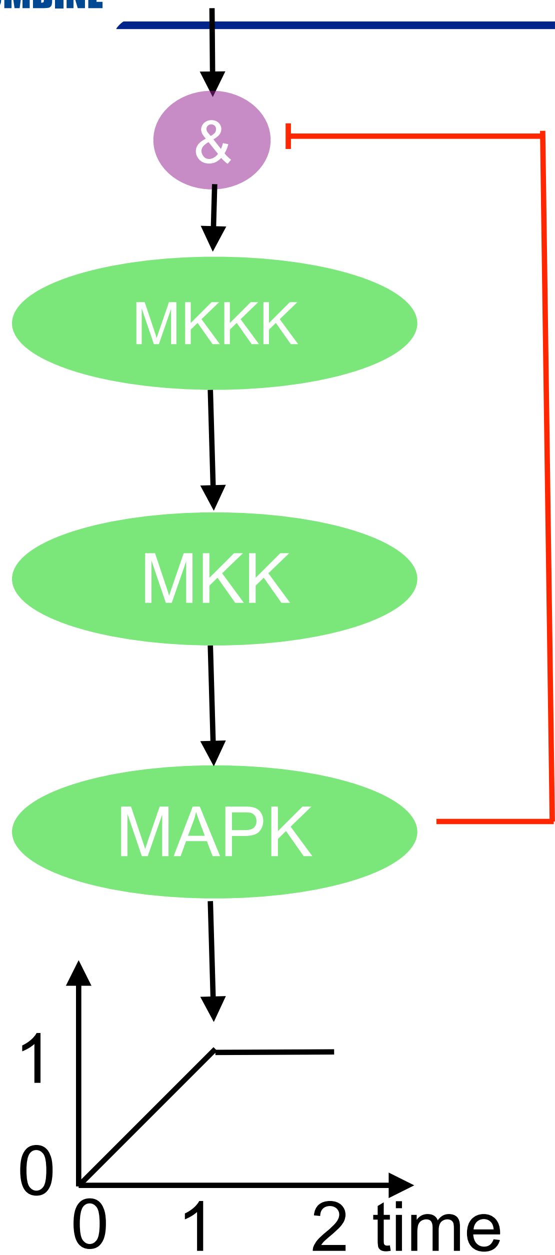
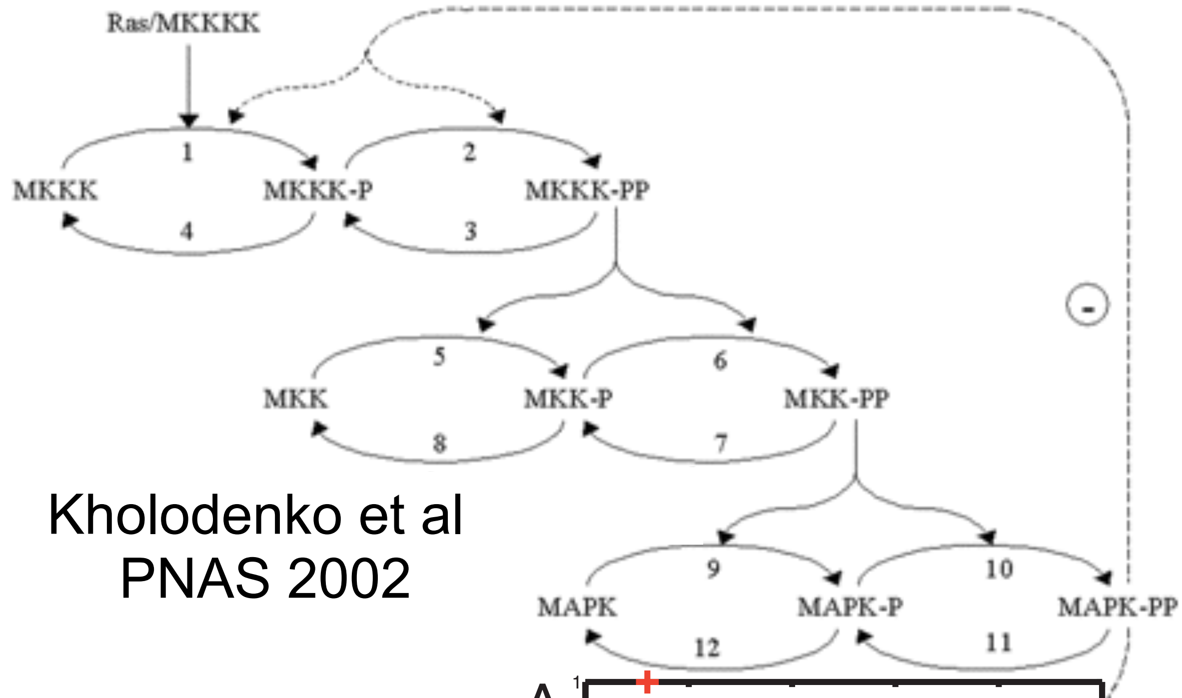
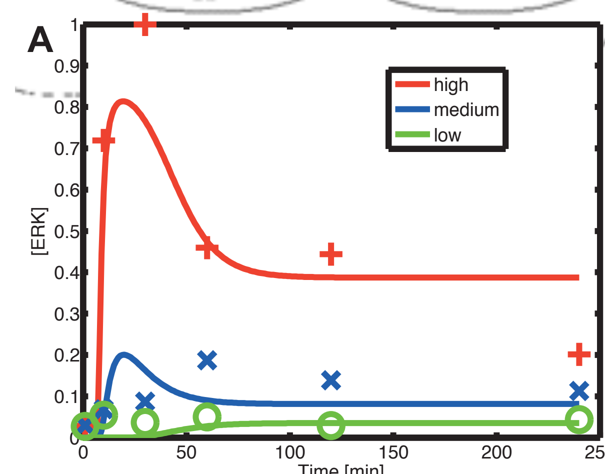




Kholodenko et al
PNAS 2002



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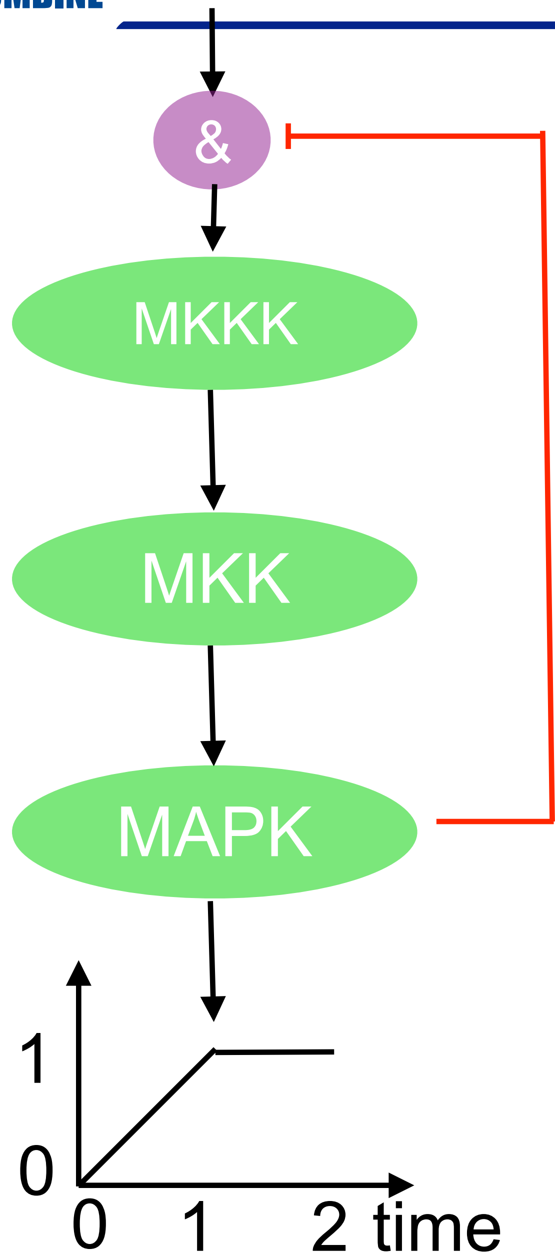
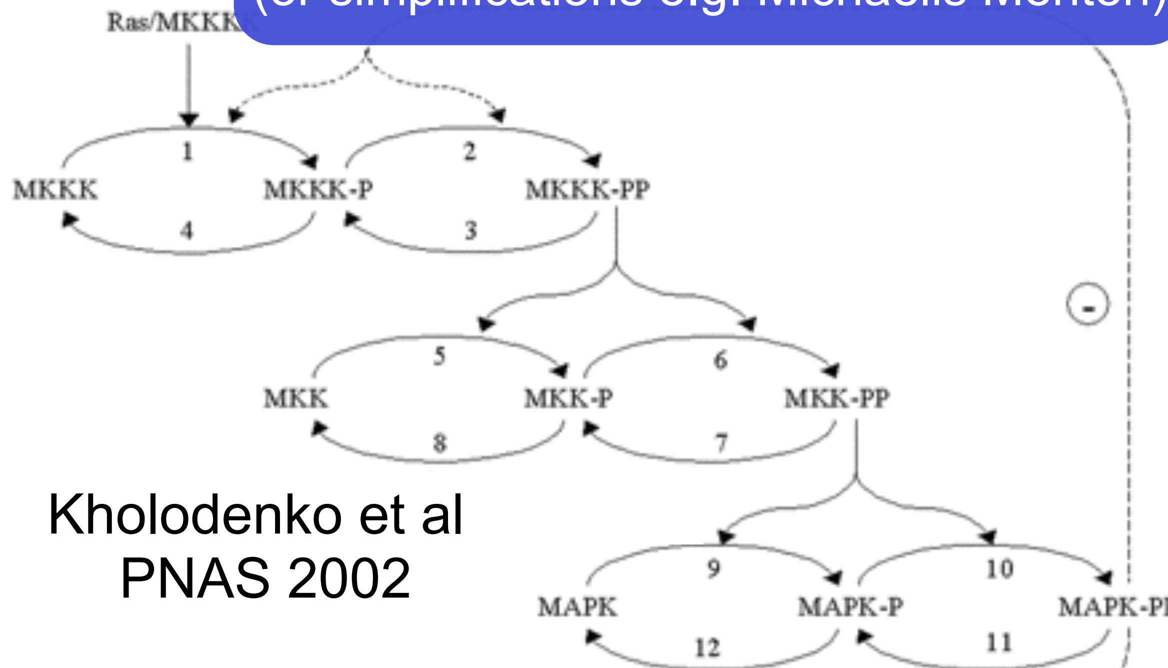


Model reactions with mass action law
(or simplifications e.g. Michaelis Menten)



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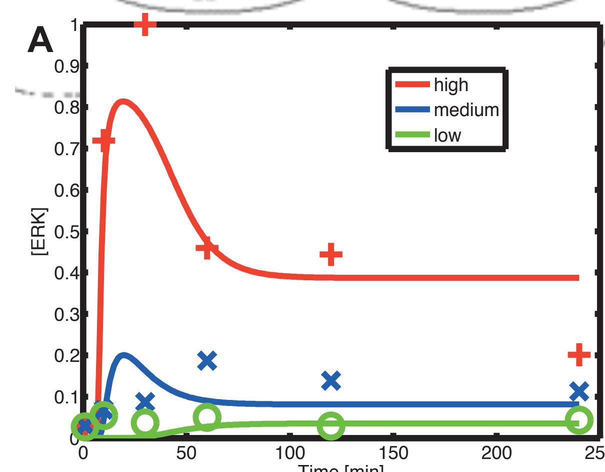

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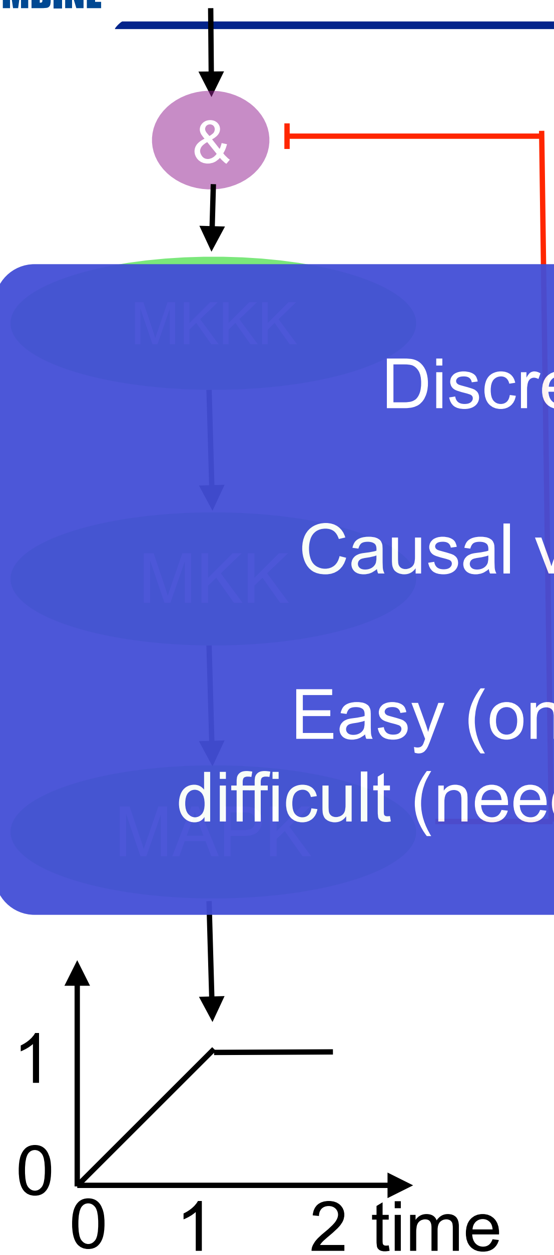

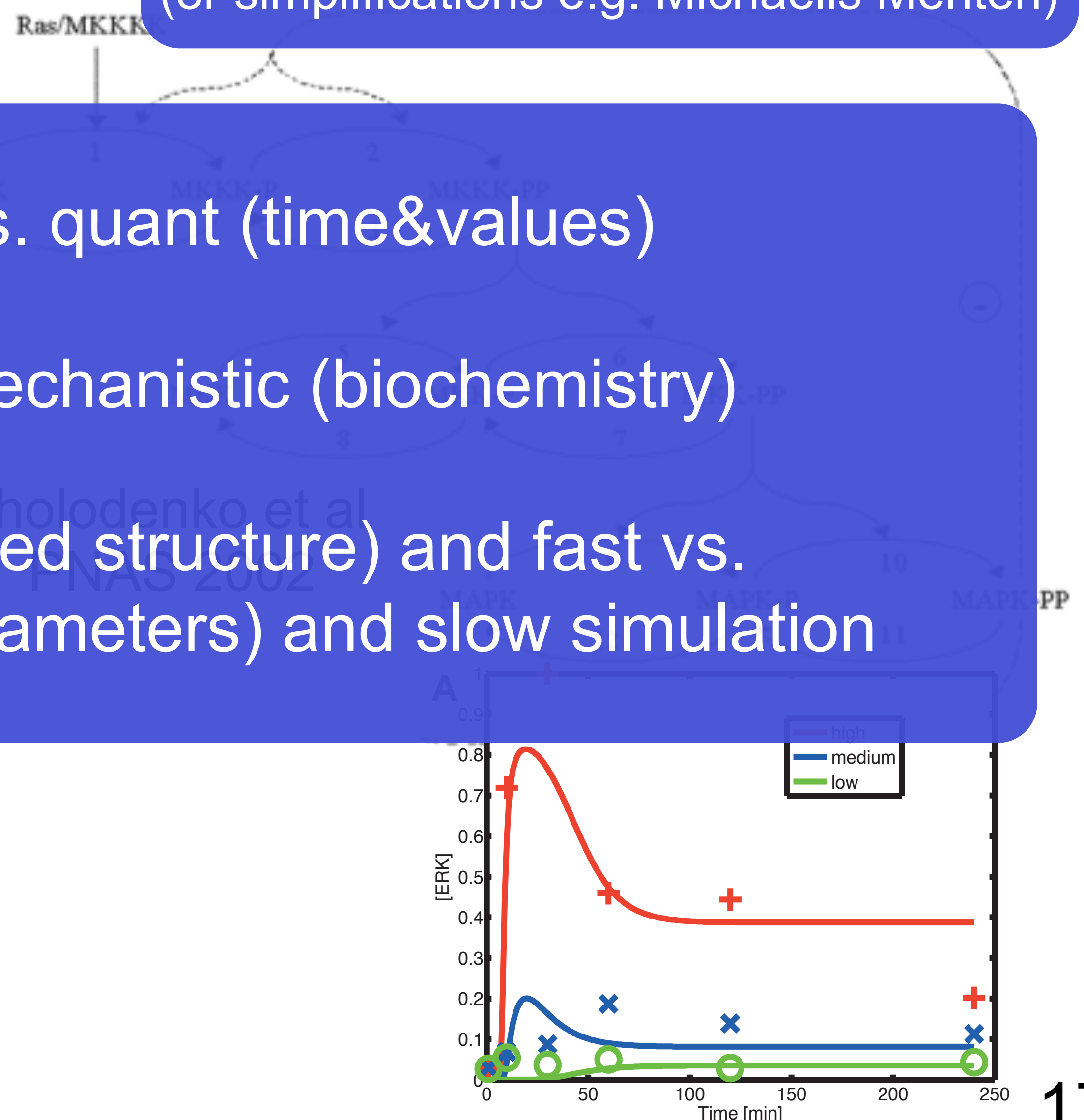

Discrete vs. quant (time&values)

Causal vs. mechanistic (biochemistry)

Easy (only need structure) and fast vs.
difficult (need parameters) and slow simulation

Now Laurence will tell you
all about logic modelling :)

Steps in building (and using) a model

- Set up experiments to extract most information
- Process data efficiently
- Choose type of mathematical model
- Train models to experimental data
- Use models to gain insight

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How to choose model: balance of fit of data and size of model

A good model should describe (and predict) data well and be as simple as possible

Metric $$\theta = \theta_f + \alpha \cdot \theta_S$$

Fit to data

$$\theta_f = \sum_{l=1}^{S} \sum_{K=1}^{M} (\underbrace{Bi_{kl}^{M}}_{\in \{0,1\}} - \underbrace{Bi_{kl}^{E}}_{\in [0,1)})^2$$

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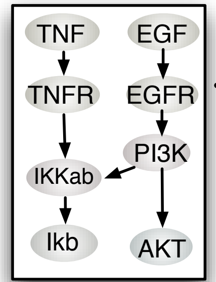
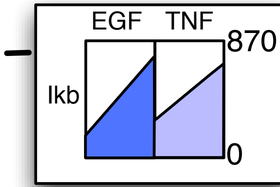
Best model ~ minimum metric
(optimization problem) - can be solved algorithmically

Linking pathway maps to data of signal transduction



Define Pathway Map
from literature/Database

Perform Experiments



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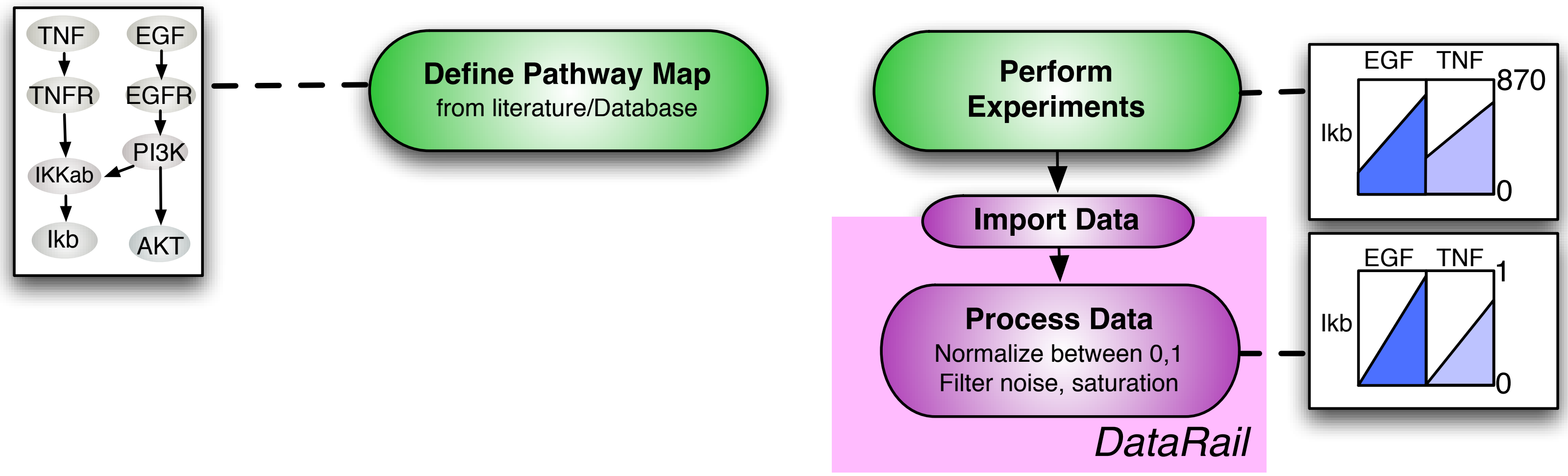

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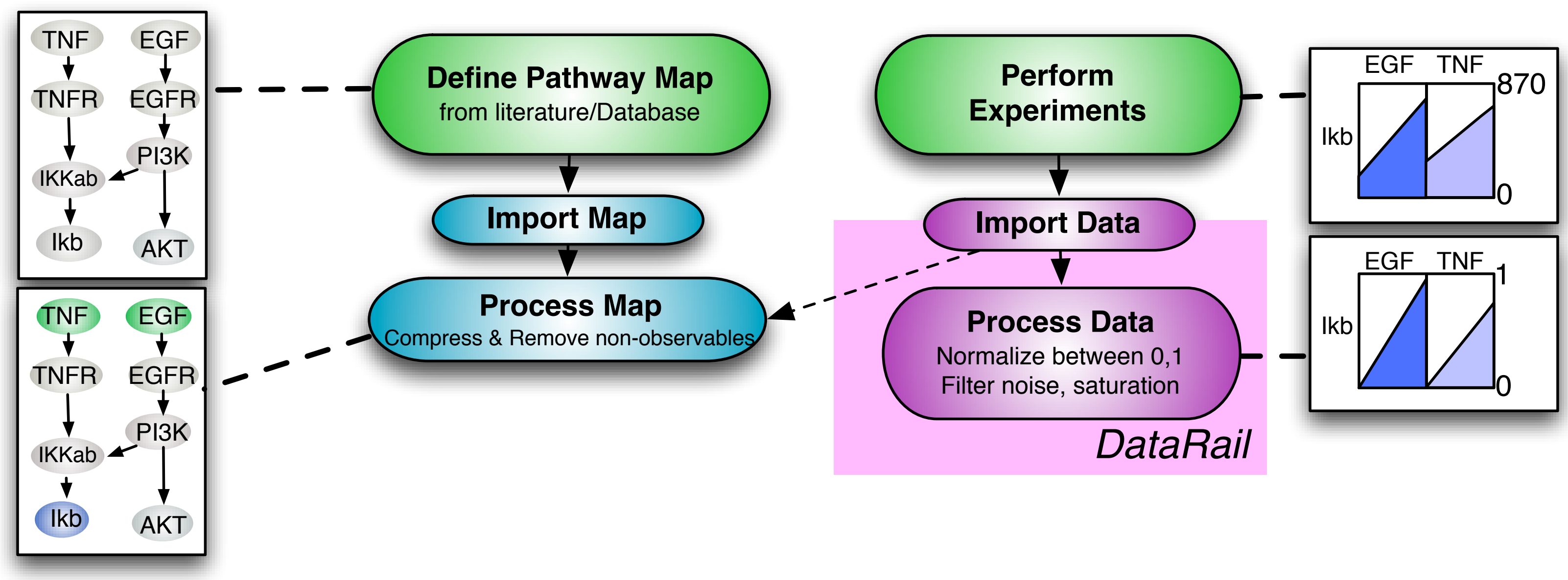

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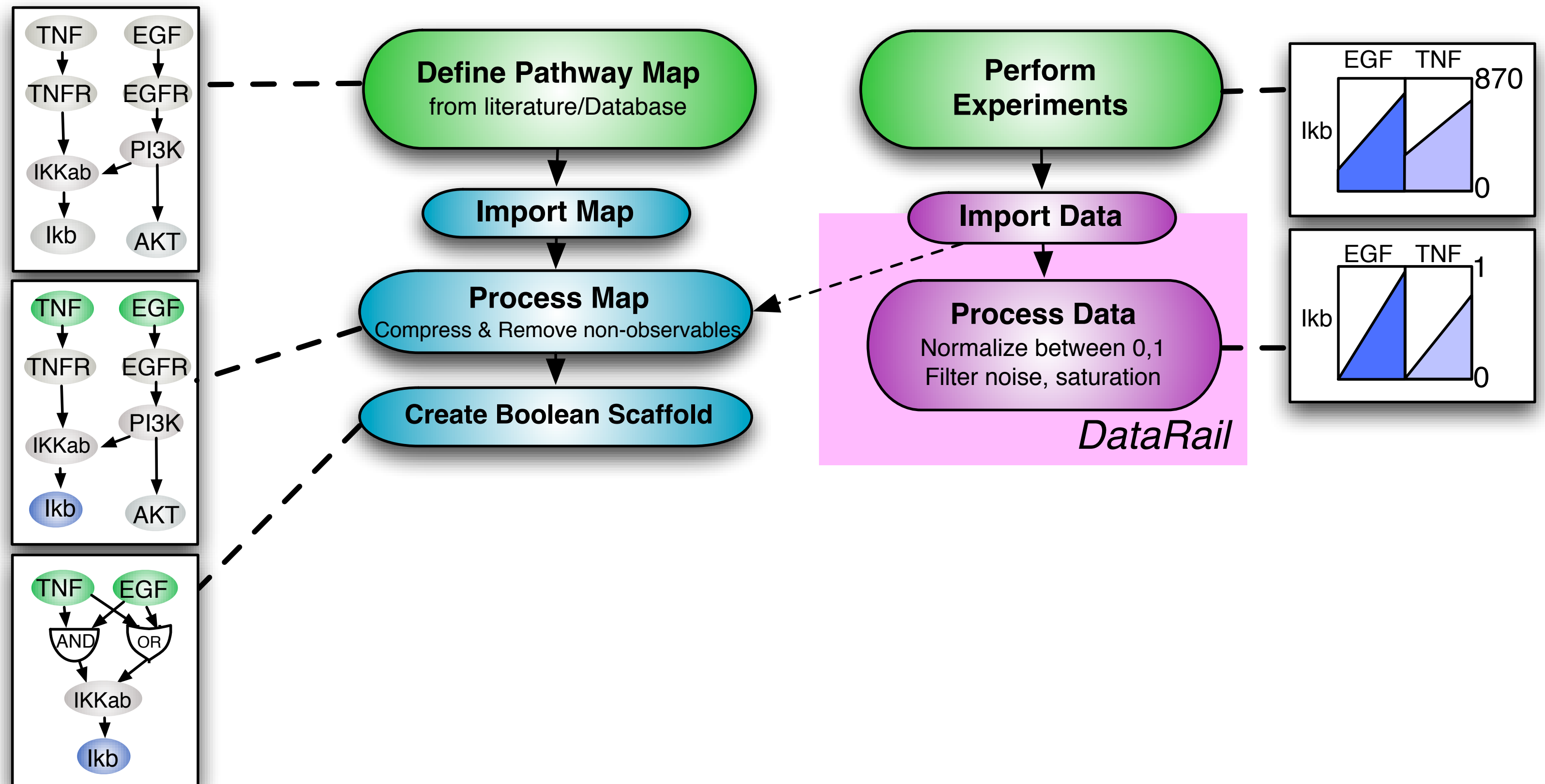

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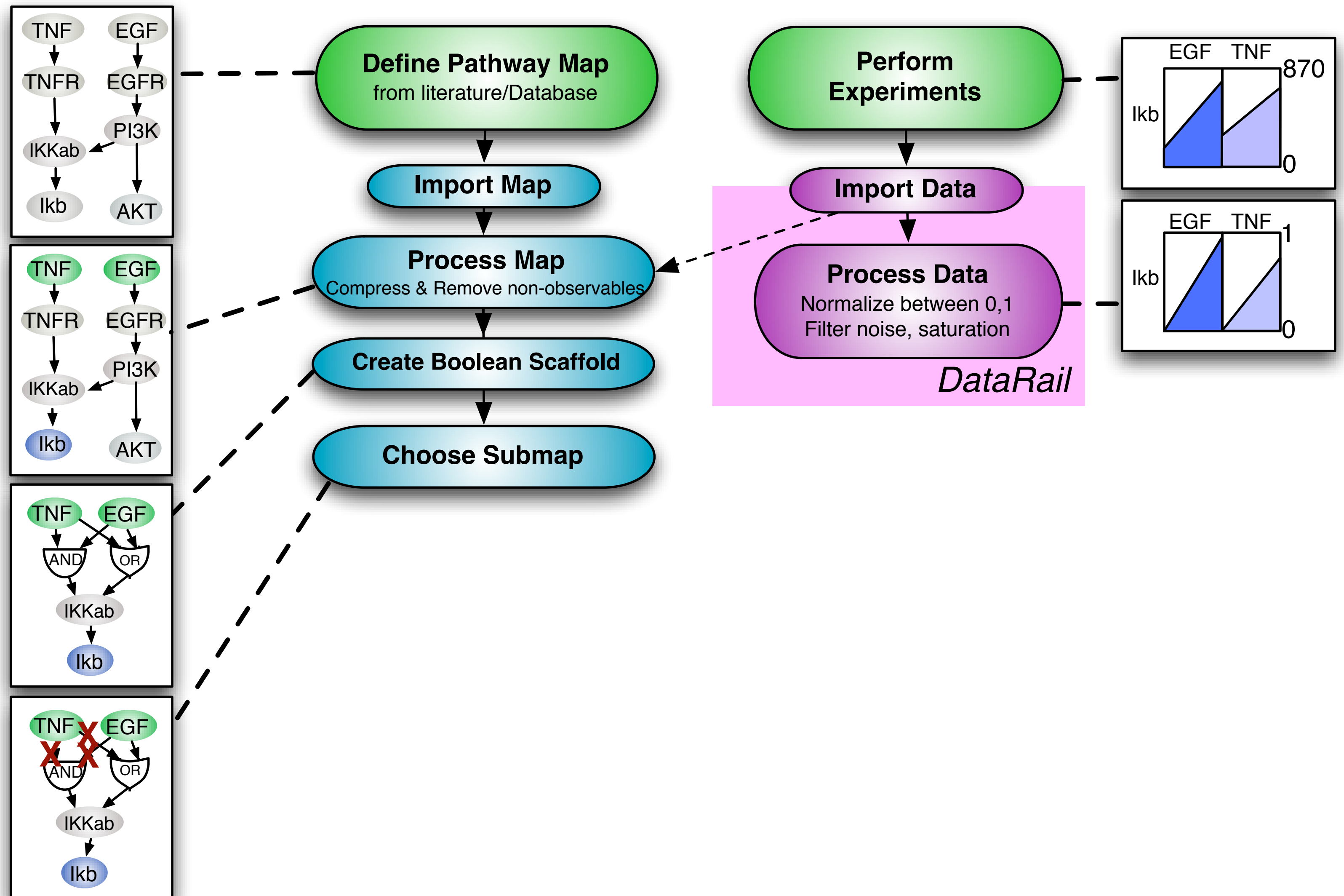

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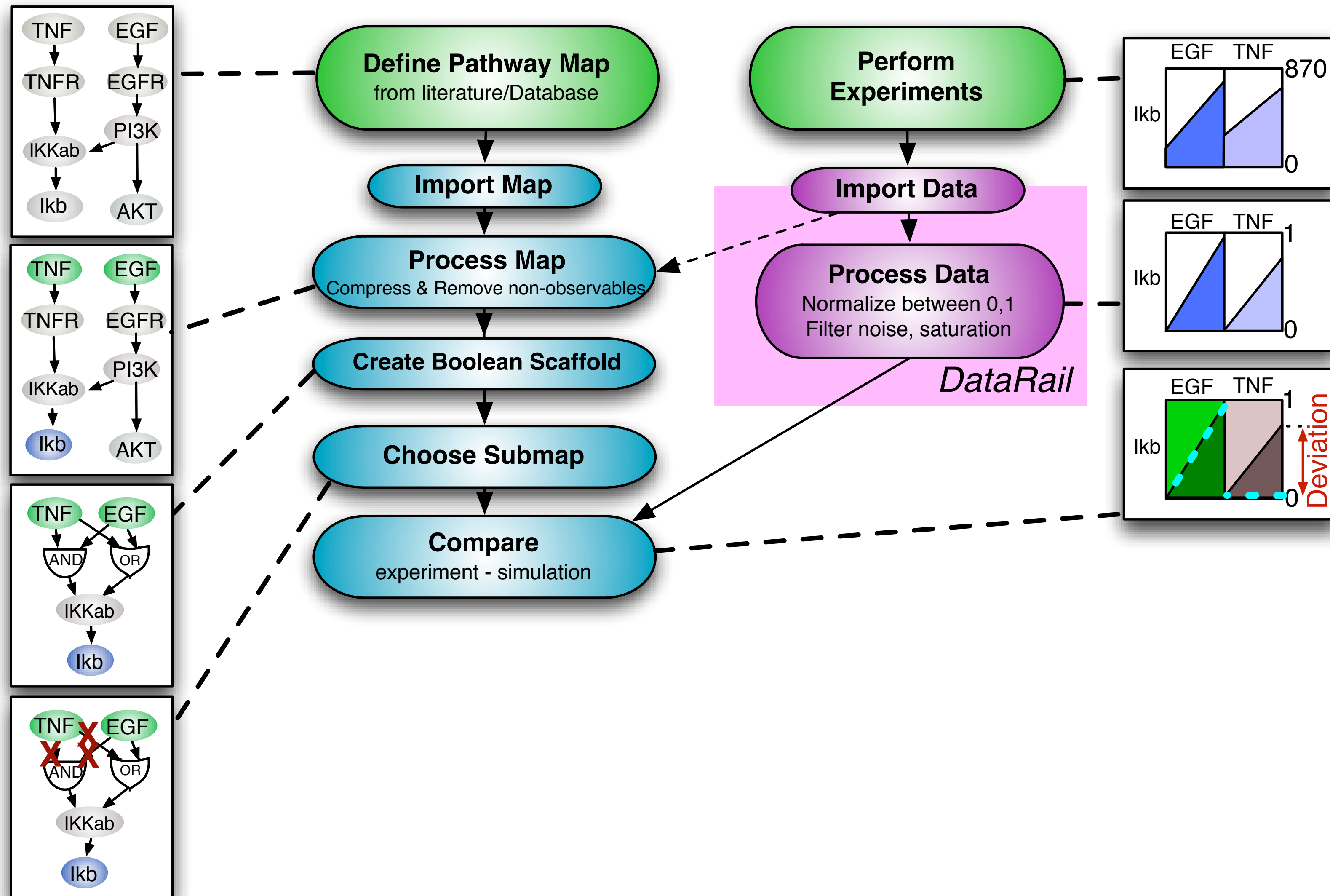

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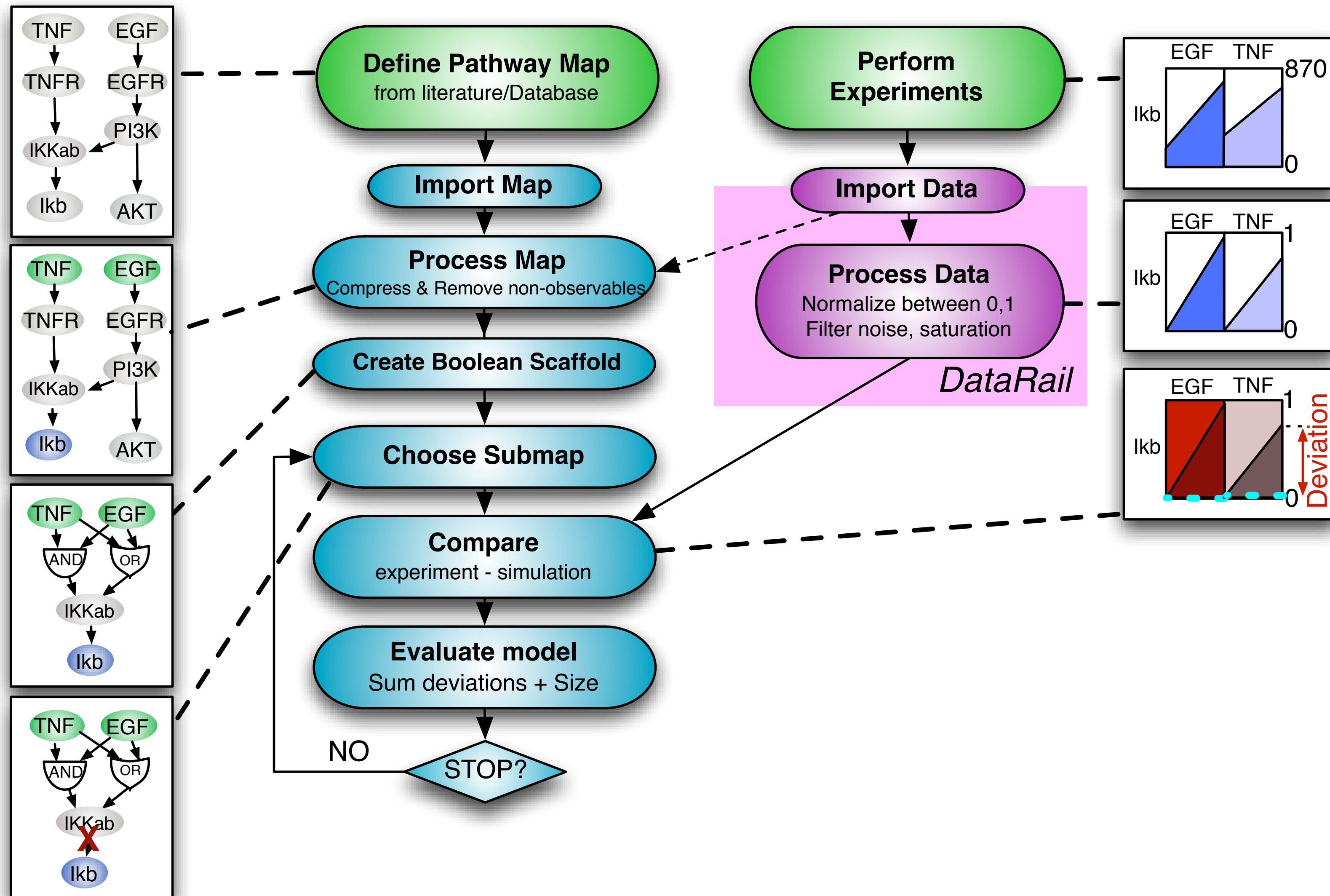

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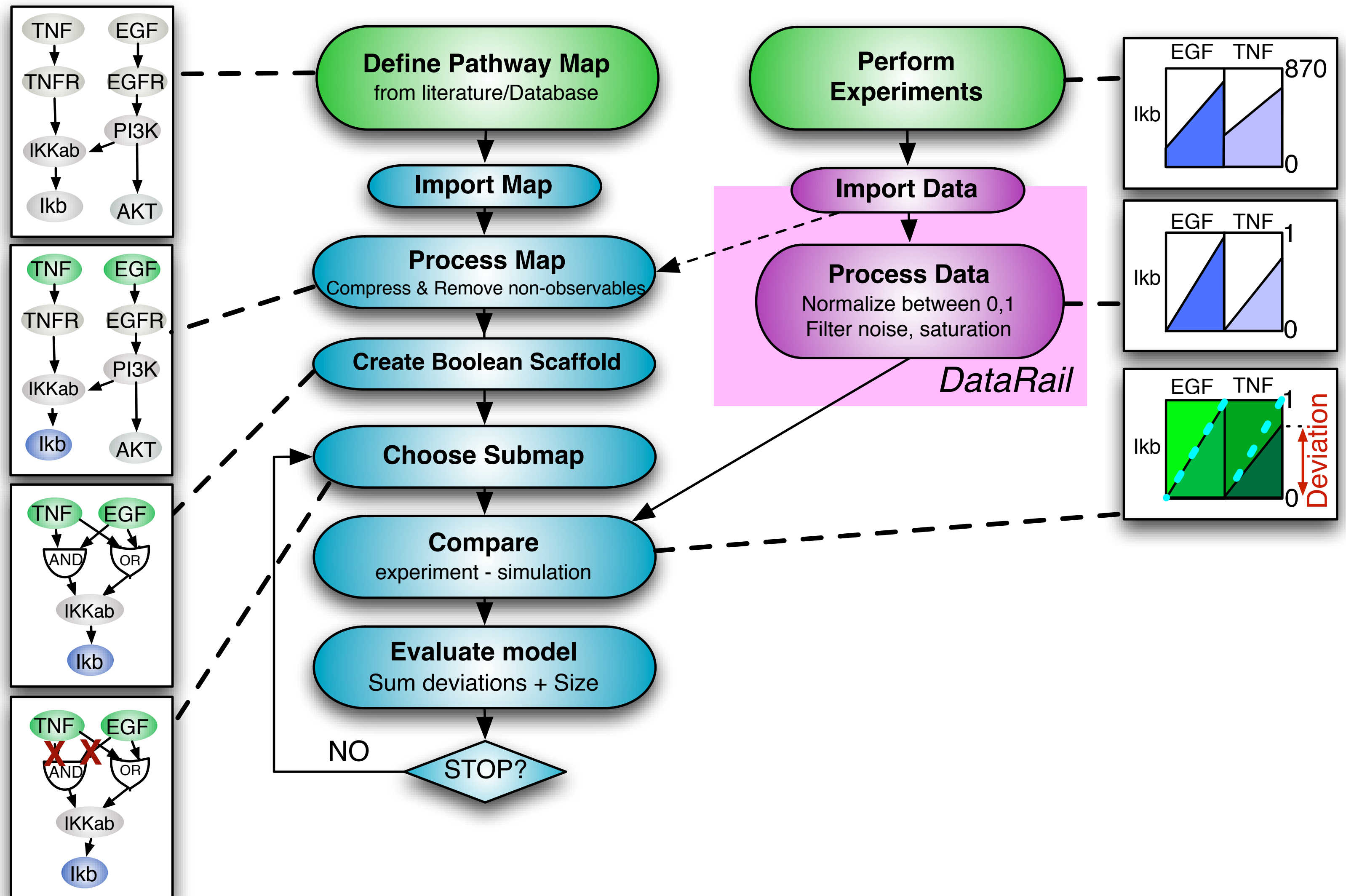

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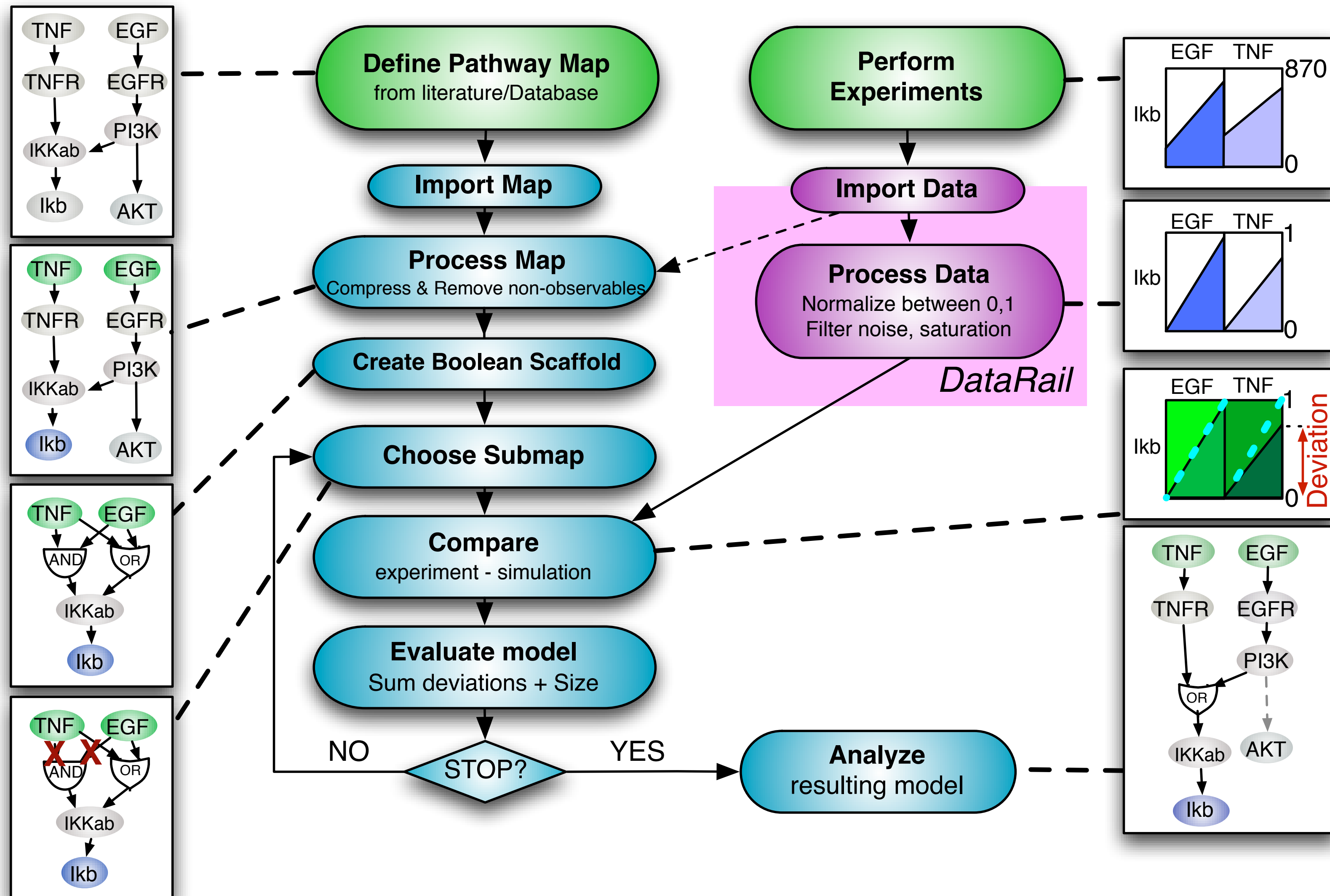

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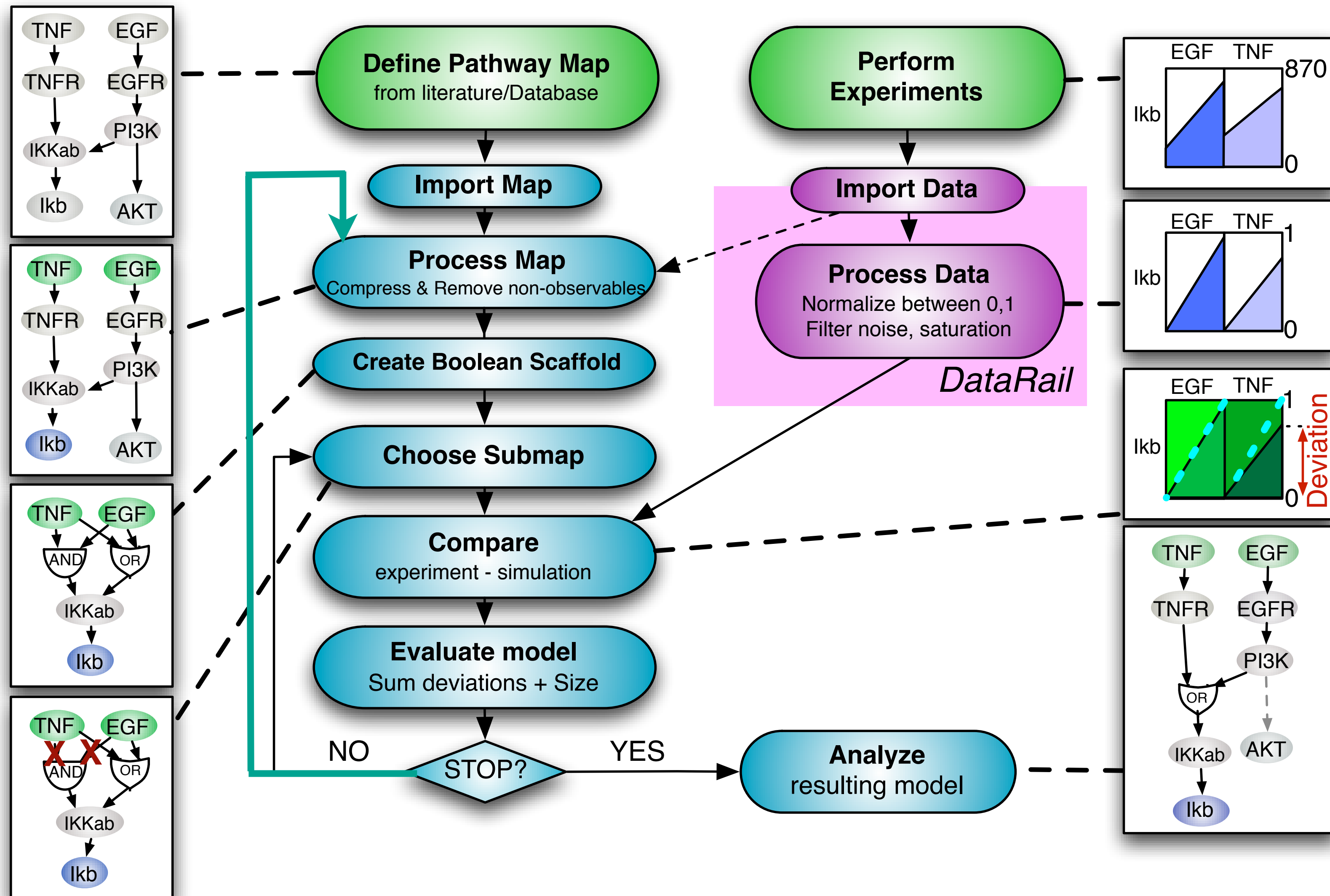


Linking pathway maps to data of signal transduction

Pipeline implemented in

CellNOpt *(for CellNetOptimizer), aka CNO*

a Bioconductor, Python (and Matlab) toolbox

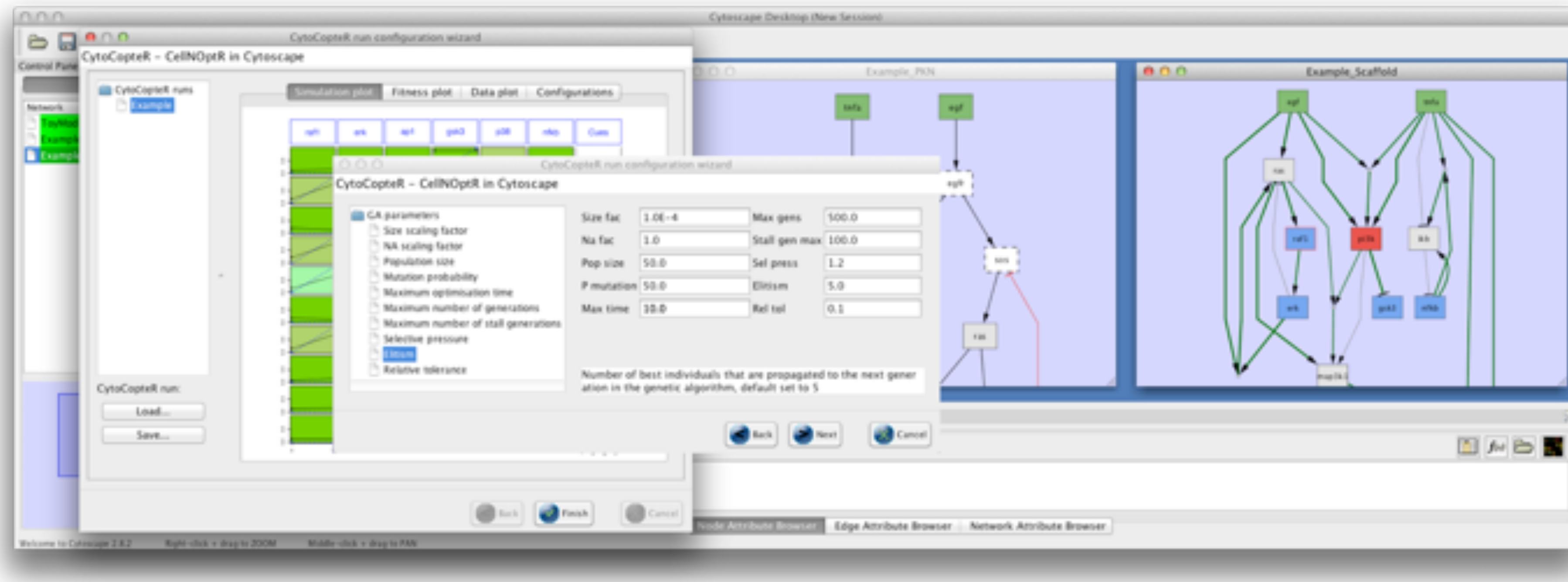
freely available at http:www.cellnopt.org

Bioconductor:
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

Matlab:
Morris MK, Melas I, Saez-Rodriguez J, *Methods Mol. Biol,* 930:179-214, 2013

CytoCopter

A Cytoscape plugin to run CellNOptR
(http://apps.cytoscape.org/apps/cytocopter)



Emanuel Gonçalves **Martijn van Iersel**

Terfve C *BMC Syst Biol, 6:*133, 2012

There are many modeling tools!

Table 2: Tools Available for the Logic Modeling of Biochemical Signaling Networks

tool	type of logic	functionality	treatment of time
BooleanNet	Boolean, piecewise linear	simulation and visualization	synchronous, asynchronous, or continuous
GinSim	discrete (multistate)	model building, simulation, and analysis	synchronous, asynchronous, or mixed asynchronous
CellNetAnalyzer	Boolean (multistate)	model simulation, visualization, and network properties analysis	logic steady state
CellNetOptimizer	Boolean	model training and simulation	logic steady state
Odefy	Boolean, logic-based ODEs	model simulation and visualization	synchronous, asynchronous, or continuous
Genetic Network Analyzer	piecewise linear	model building and simulation	continuous
ChemChains	Boolean	model simulation, visualization, and analysis	synchronous or asynchronous
MetaReg	discrete (multistate)	model simulation, visualization, and refinement	logic steady state
SQUAD	standardized qualitative dynamical systems	model simulation and analysis	continuous

Morris MK, Saez-Rodriguez J, Sorger PK, Lauffenburger DA, *Biochemistry,* 49(15), 2010.

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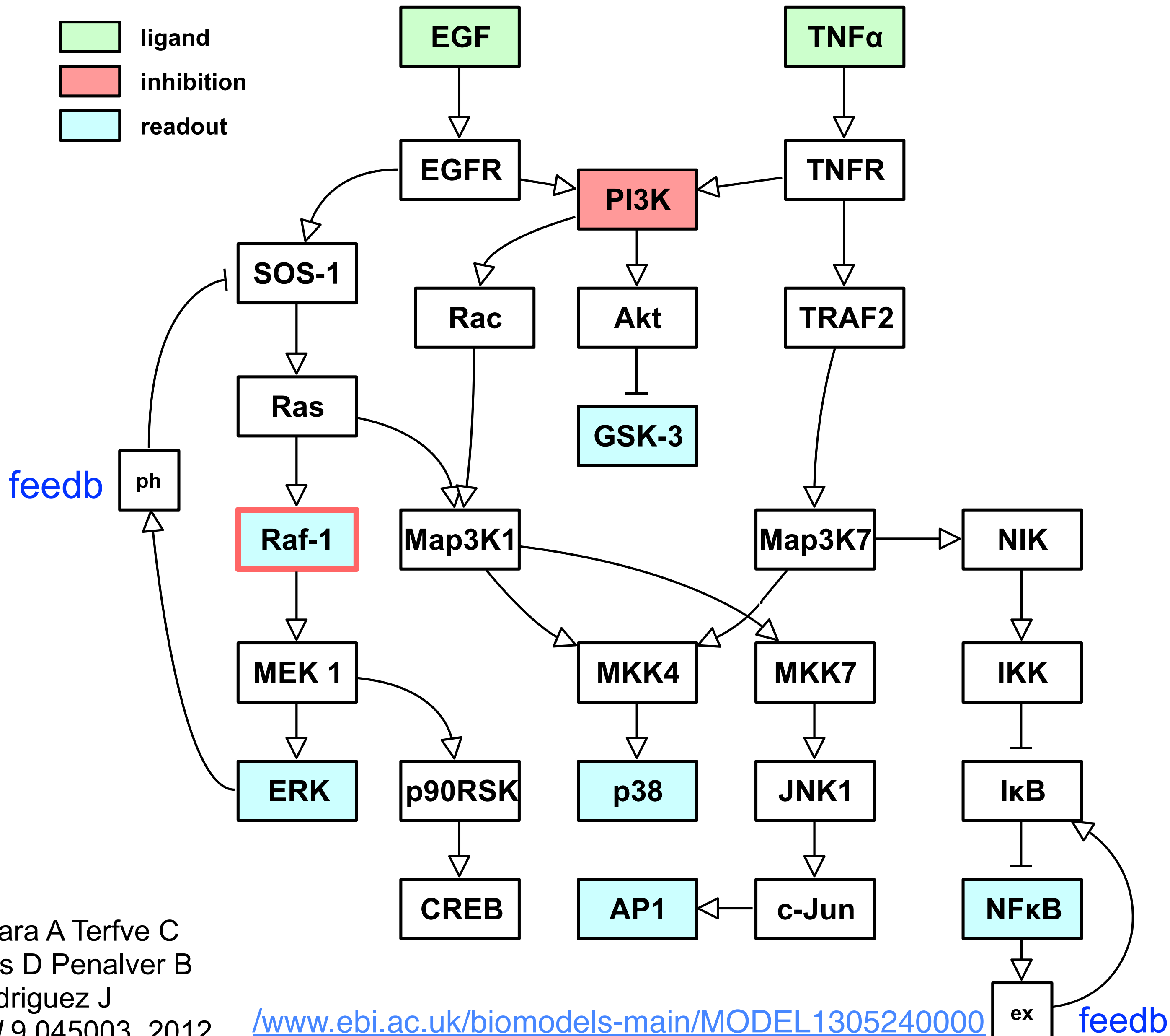
- SBML-qual to exchange logic models
Chaouiya et al. *BMC Sys Bio* 2013

Morris MK, Saez-Rodriguez J, Sorger PK, Lauffenburger DA, *Biochemistry,* 49(15), 2010.

A Toy model



MacNamara A Terfve C
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Phys Biol 9 045003, 2012

/www.ebi.ac.uk/biomodels-main/MODEL1305240000

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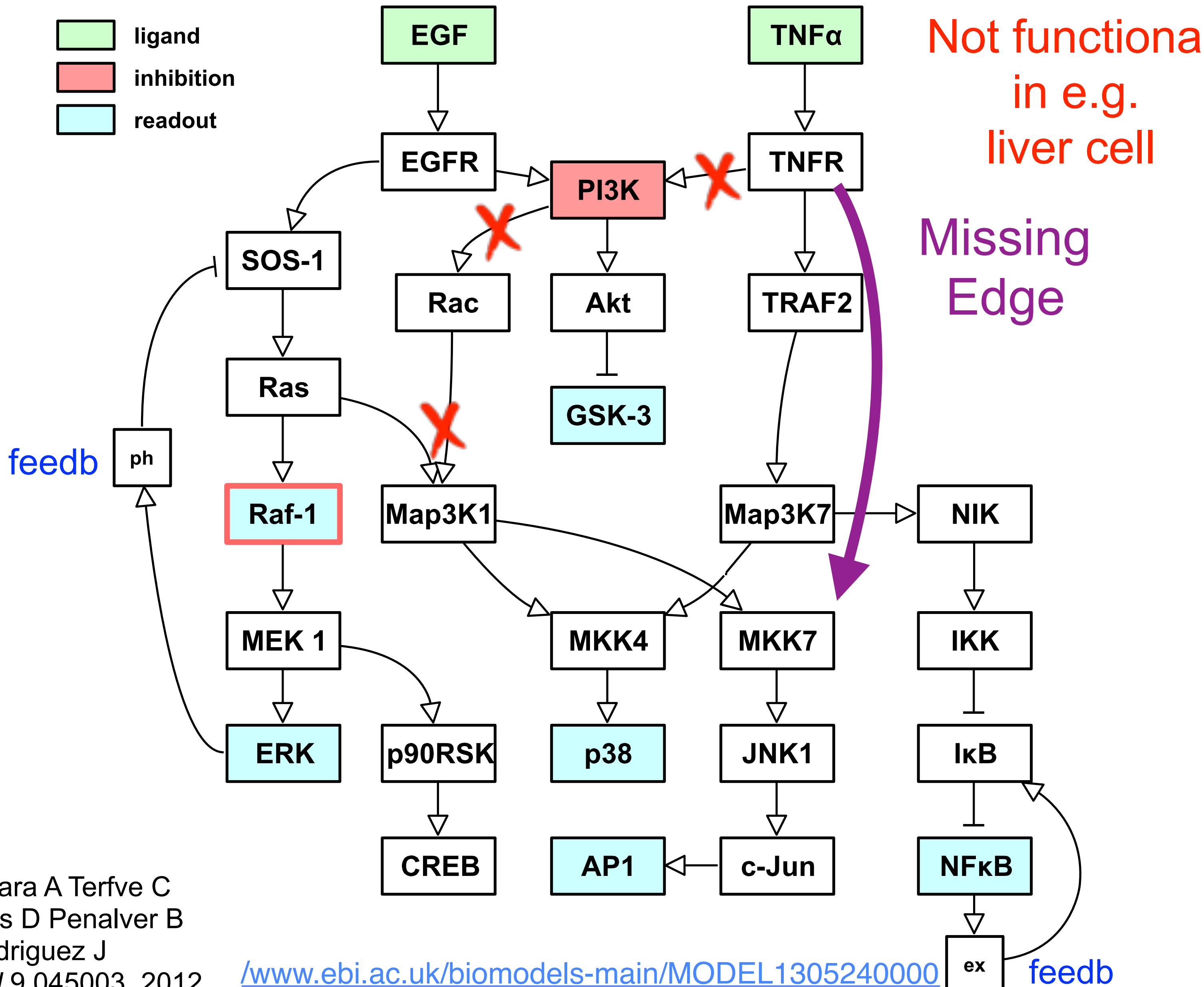

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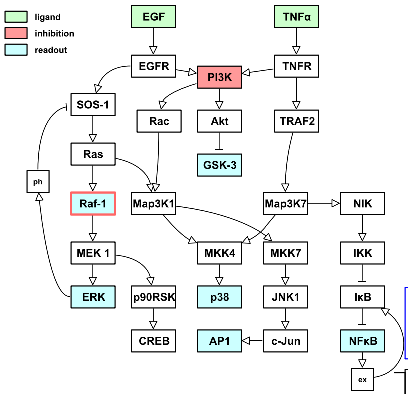
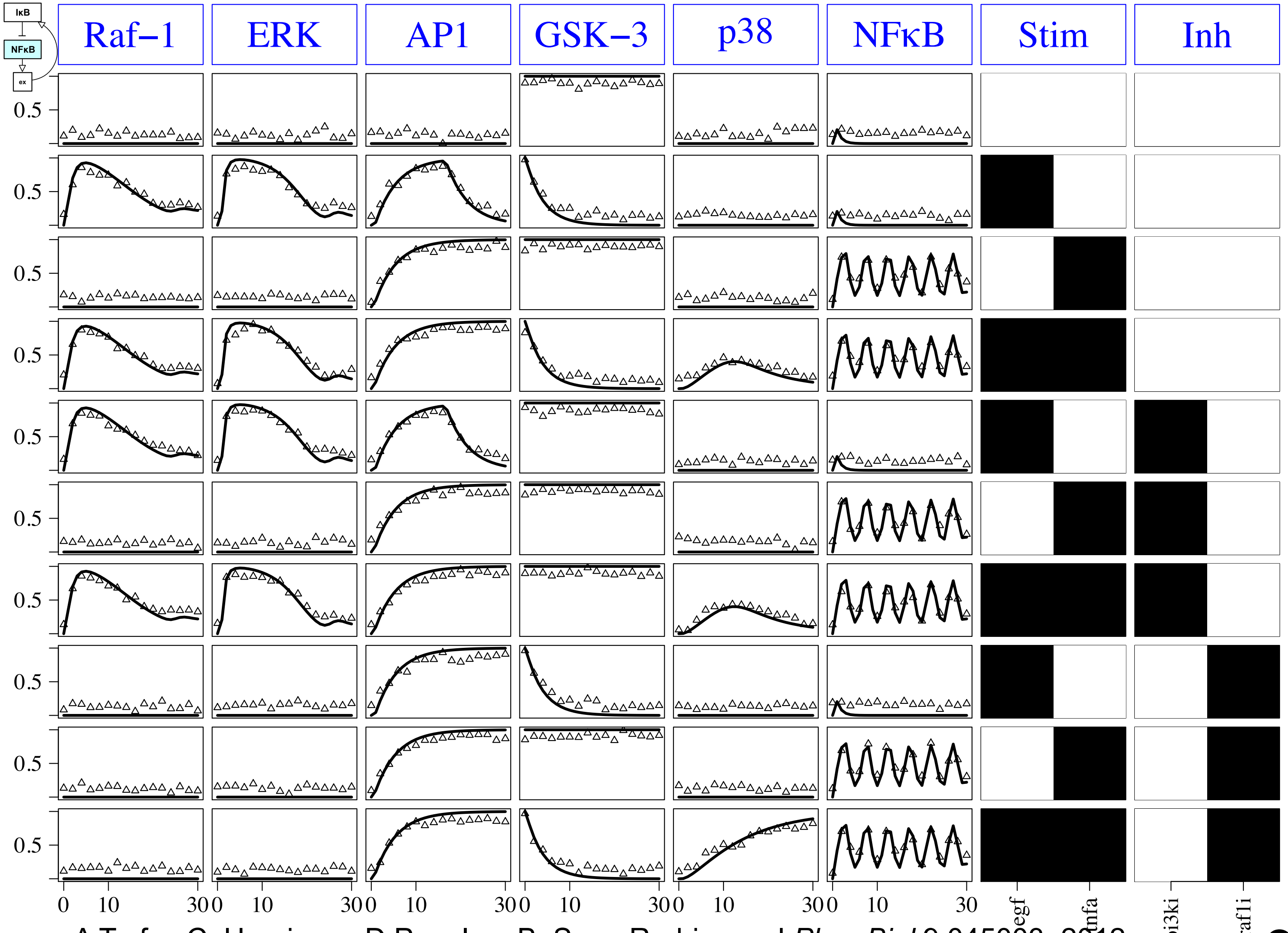
The ‘real’ data





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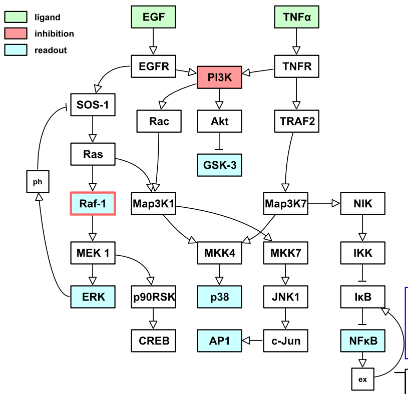
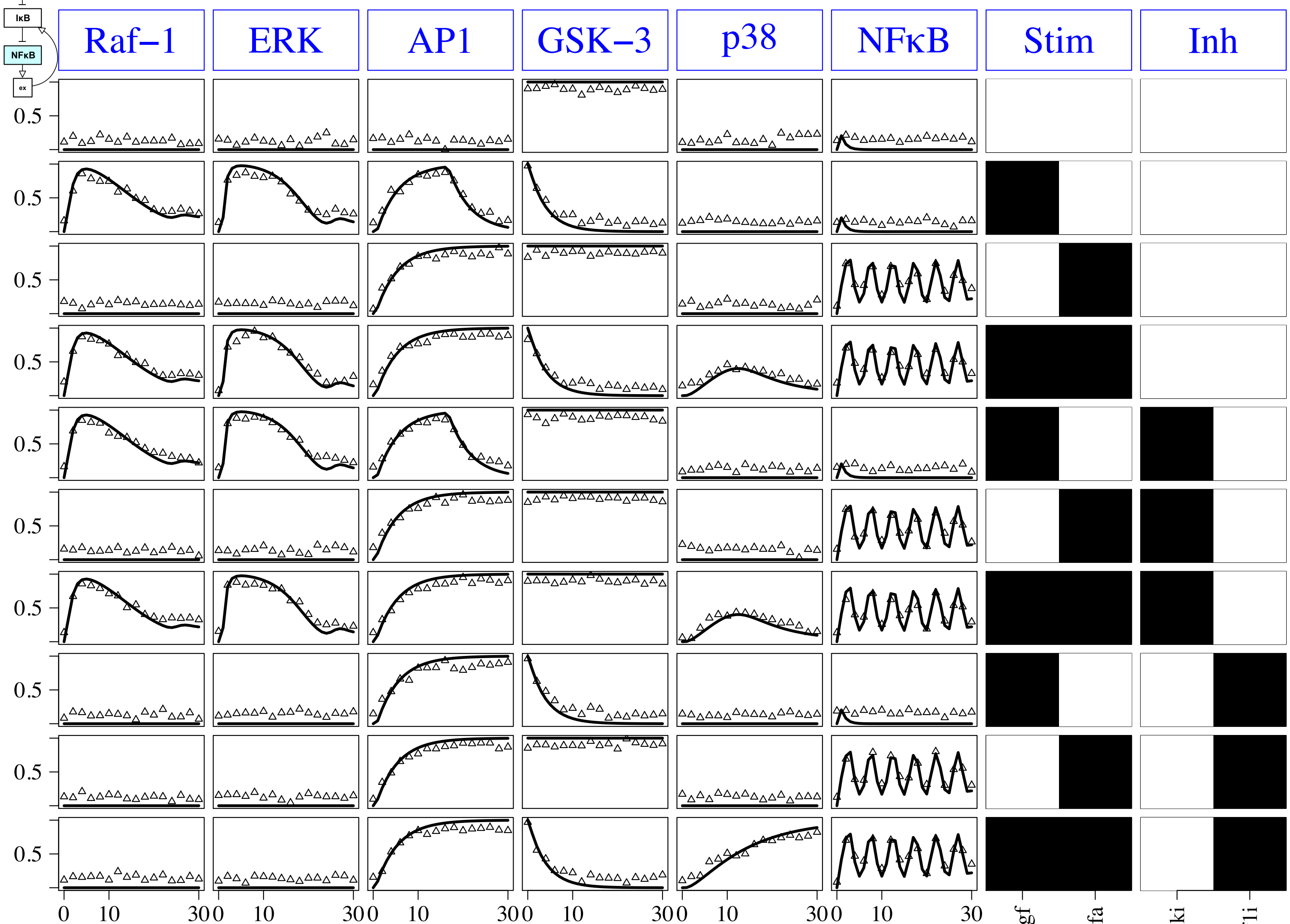


How to pick right time to measure?



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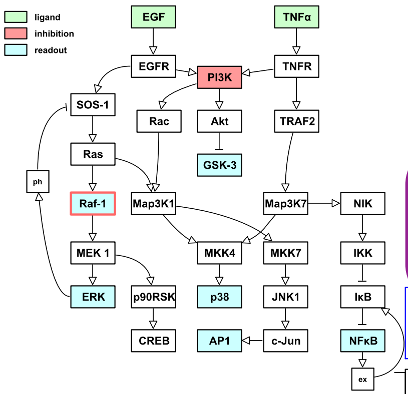

If you can only pick one ($$), choose one representatitive of a 'time scale'

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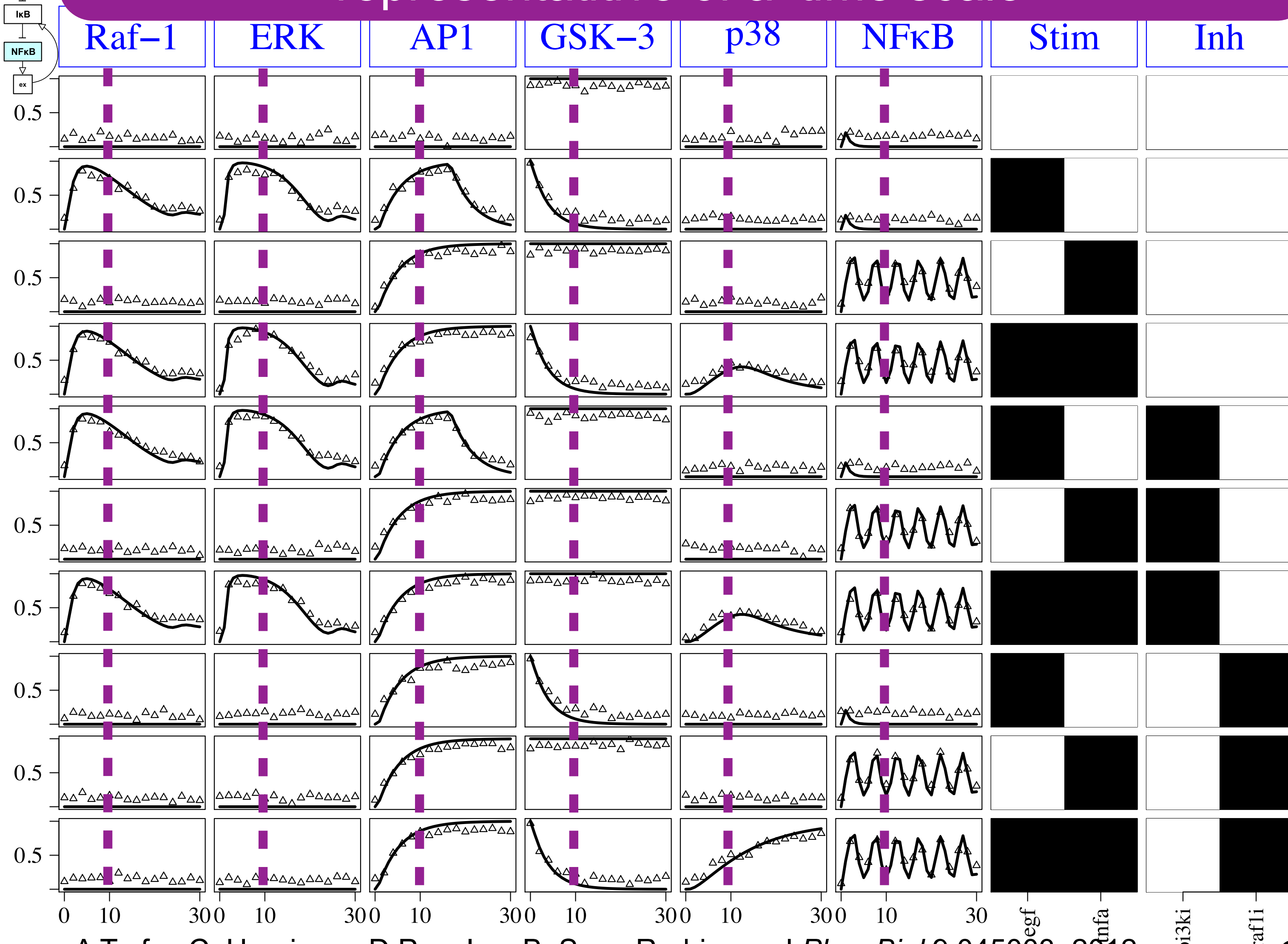

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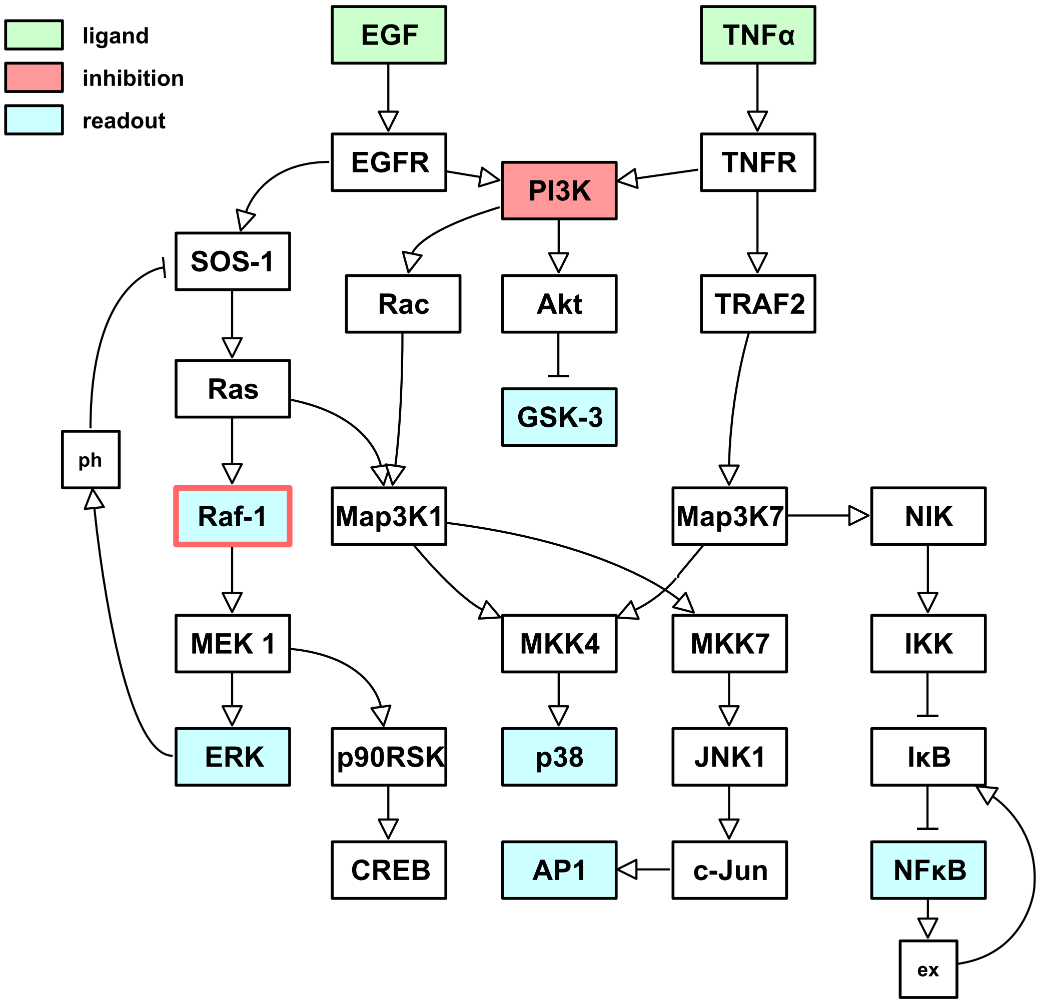
Model preprocessing:



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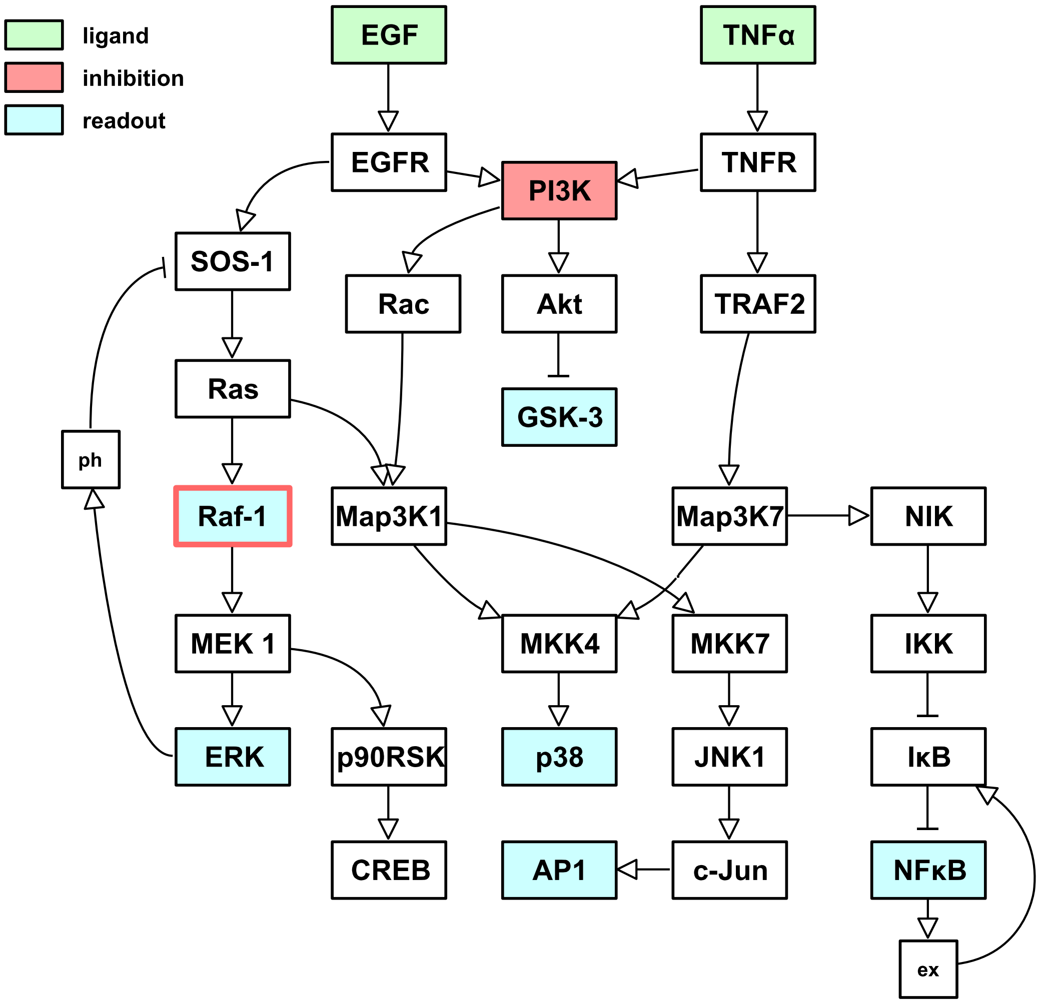
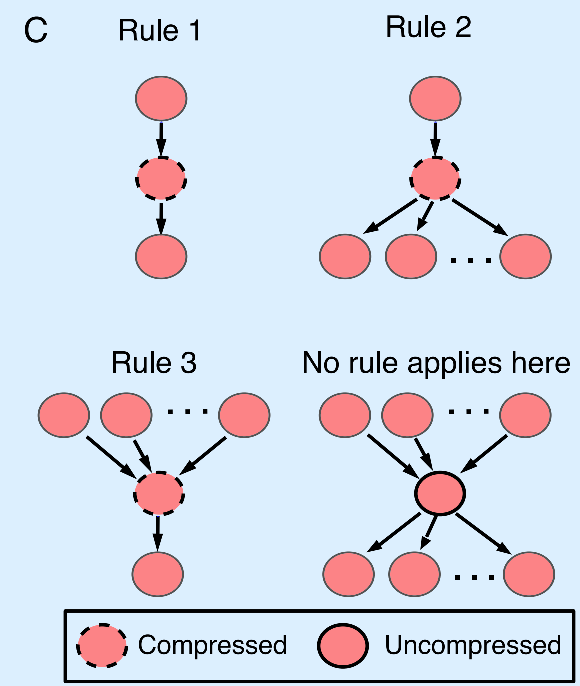


Model compression& removal of non-controlable & non-observable branches



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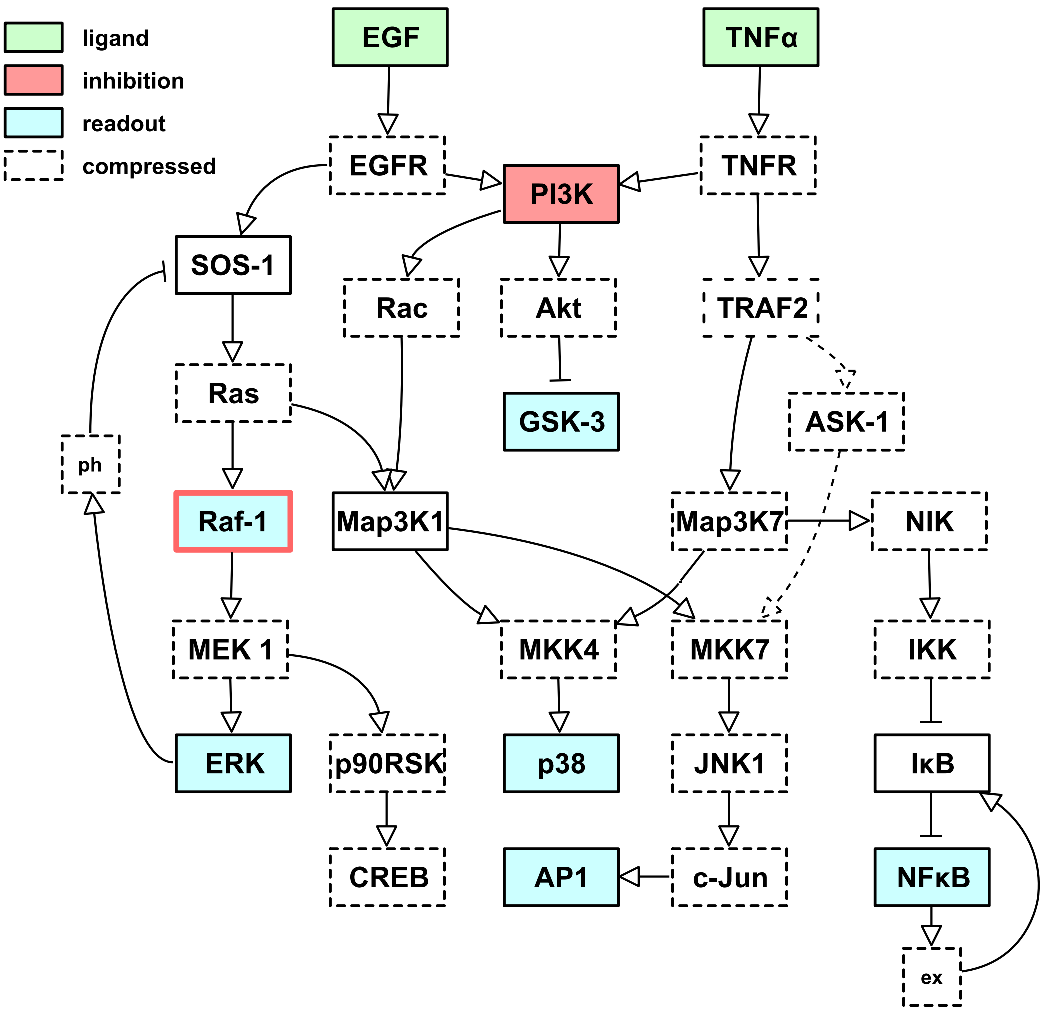

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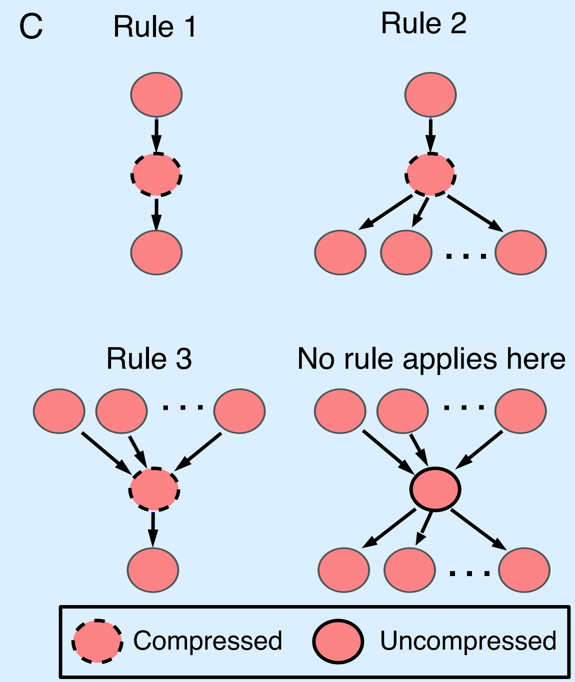

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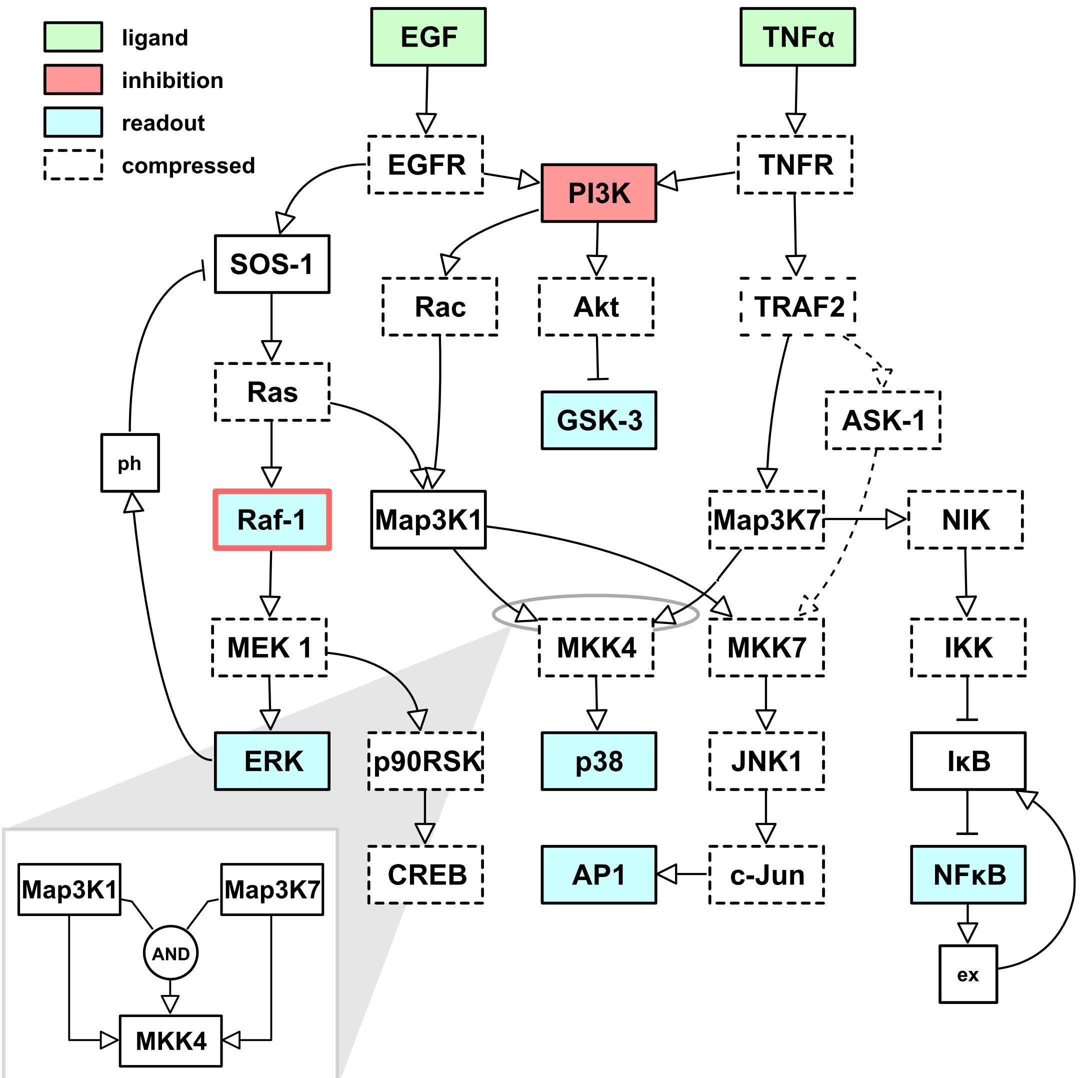

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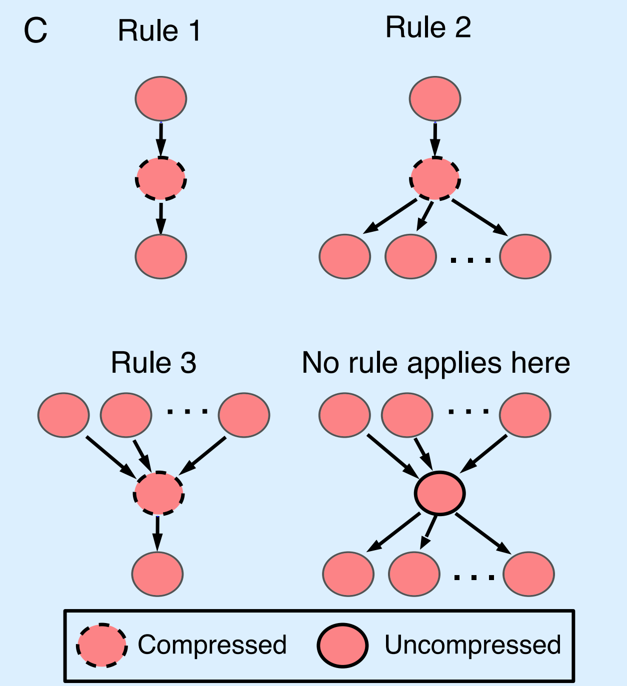

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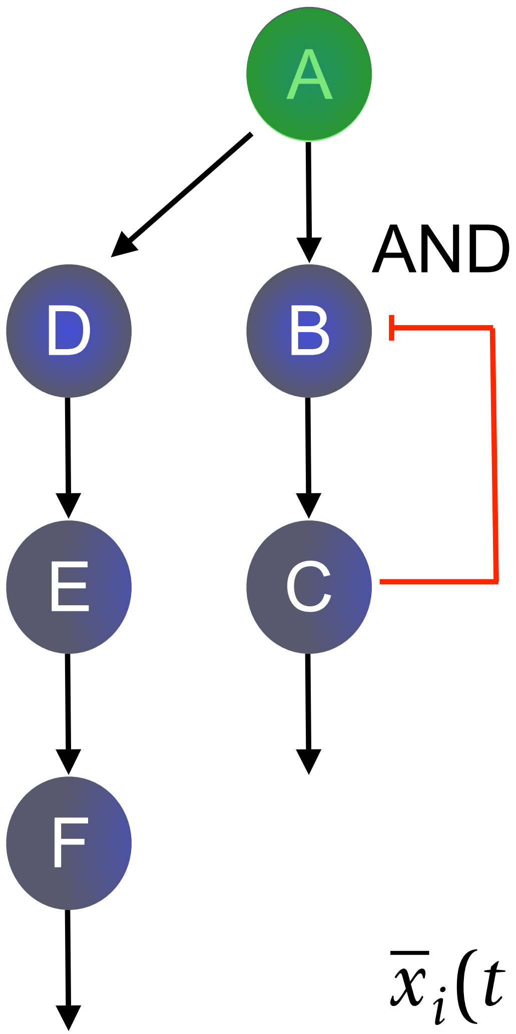
Simplest Boolean simulation: Synchronous updates



System can reach steady state or oscillate

$$\overline{x}_i(t+1) = \overline{B}_i(\overline{x}_{i1}(t), \overline{x}_{i2}(t), \ldots, \overline{x}_{iN_i}(t)).$$

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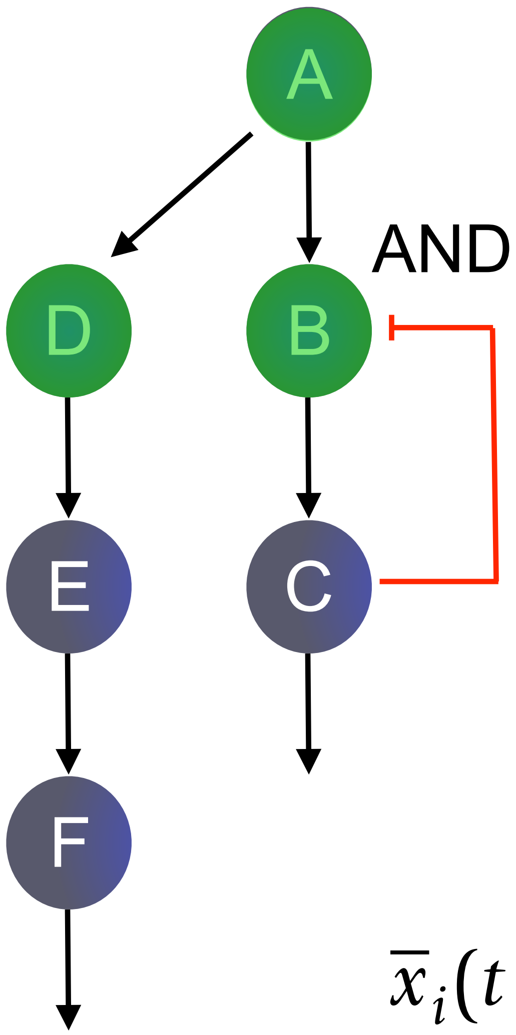

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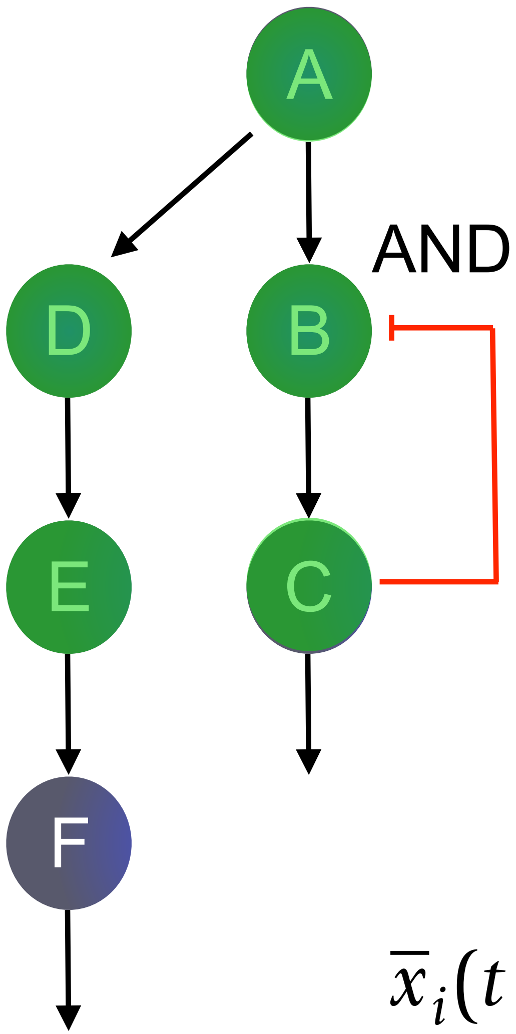

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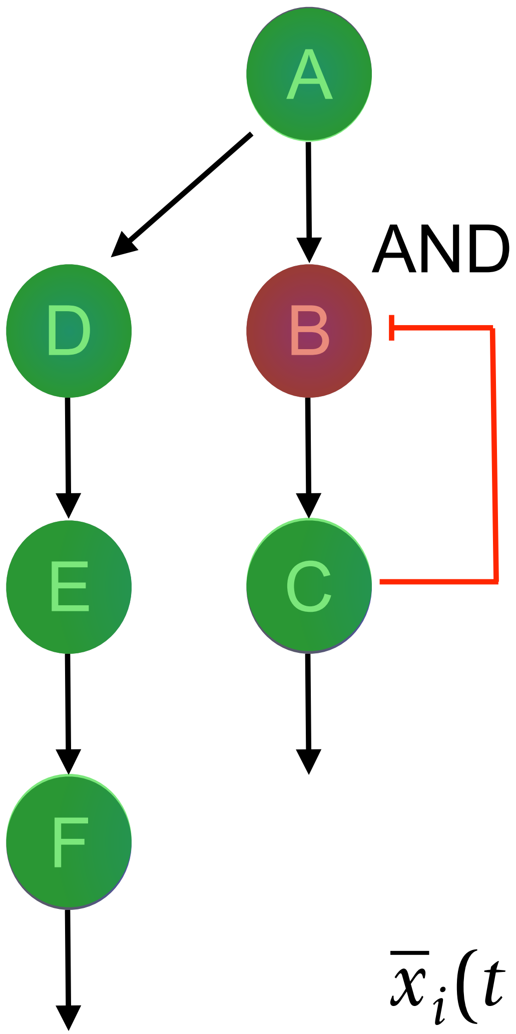

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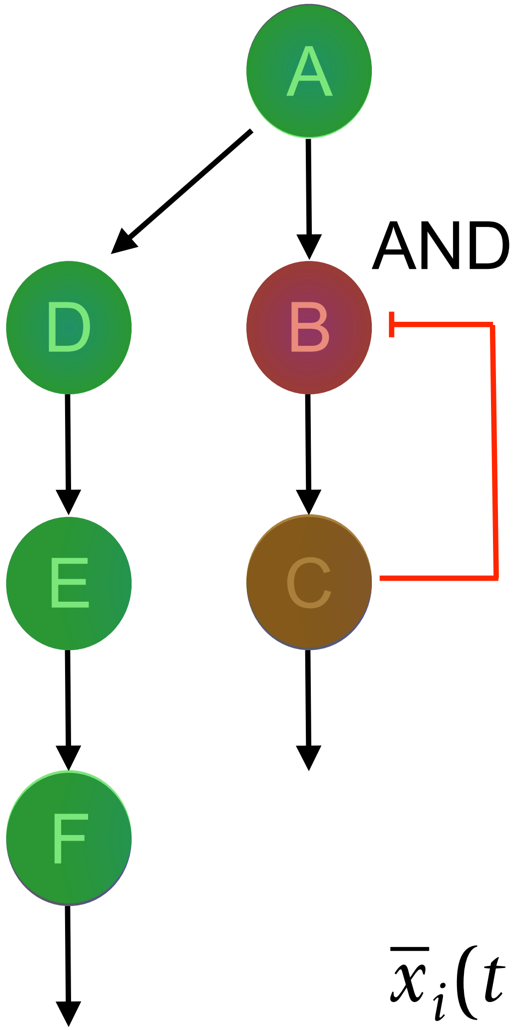

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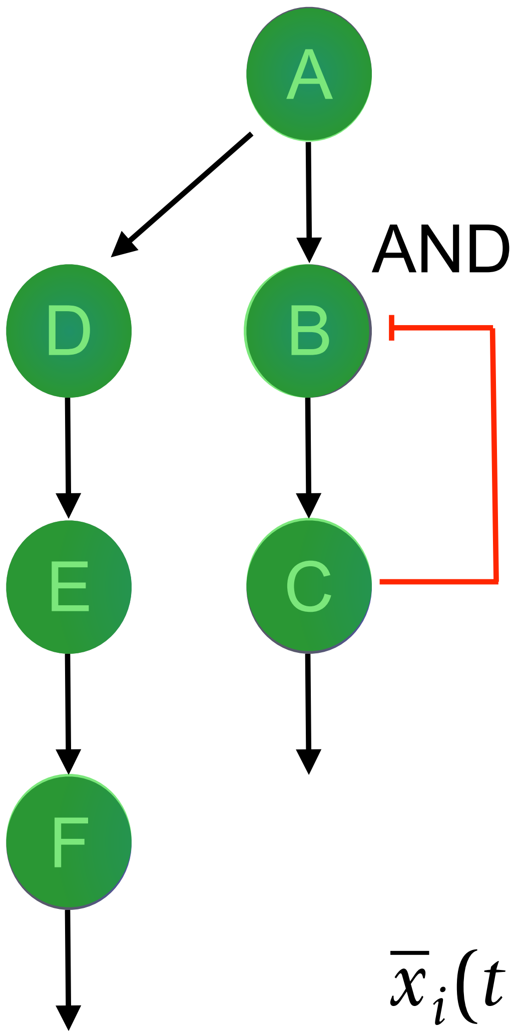

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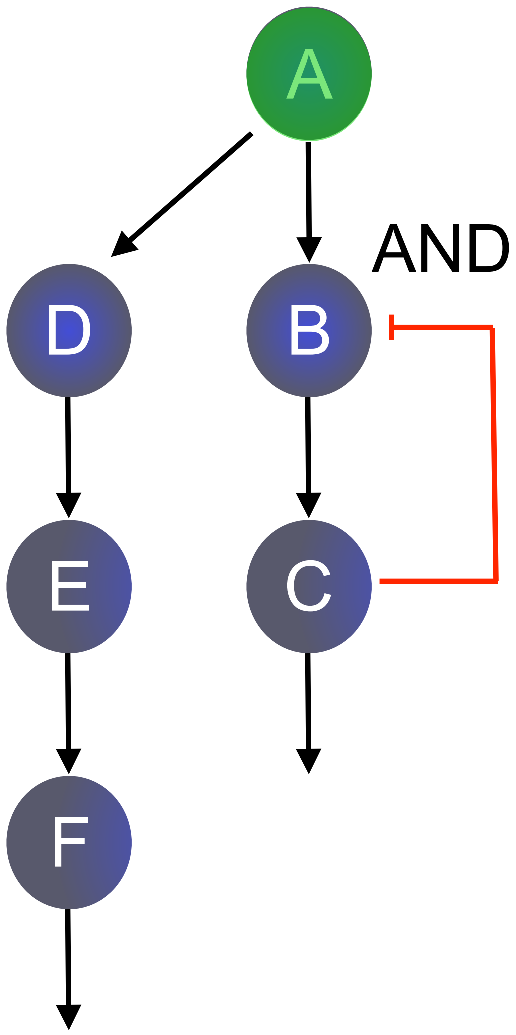
Boolean simulation performed using pseudo-steady state



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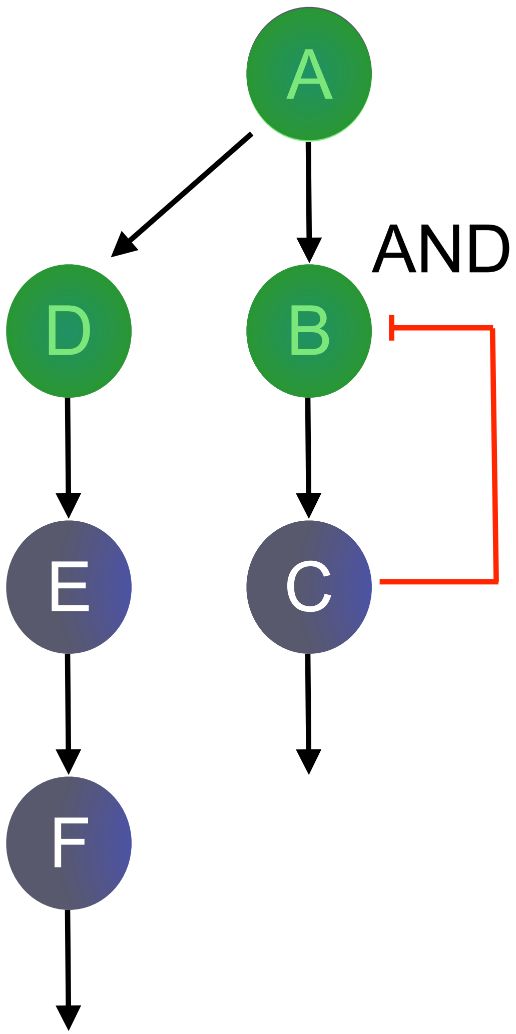

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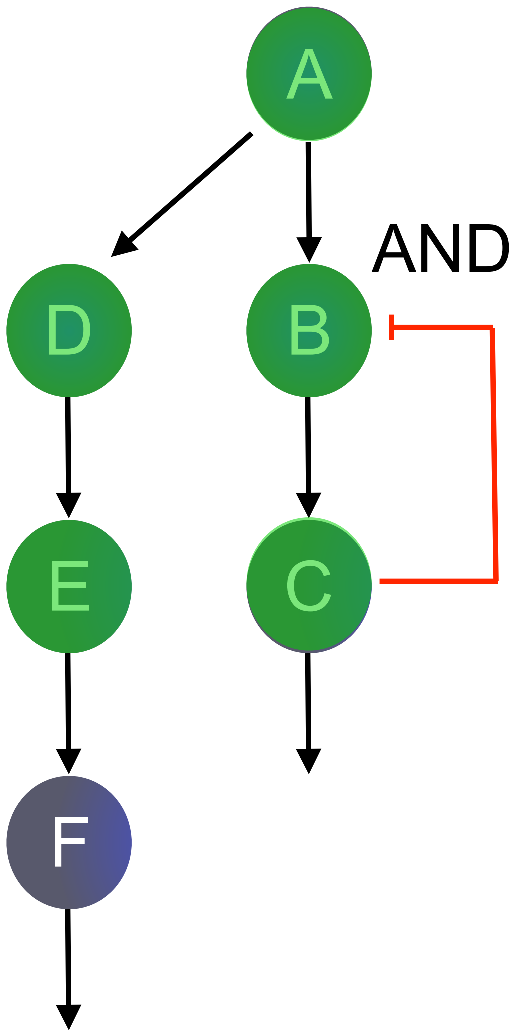

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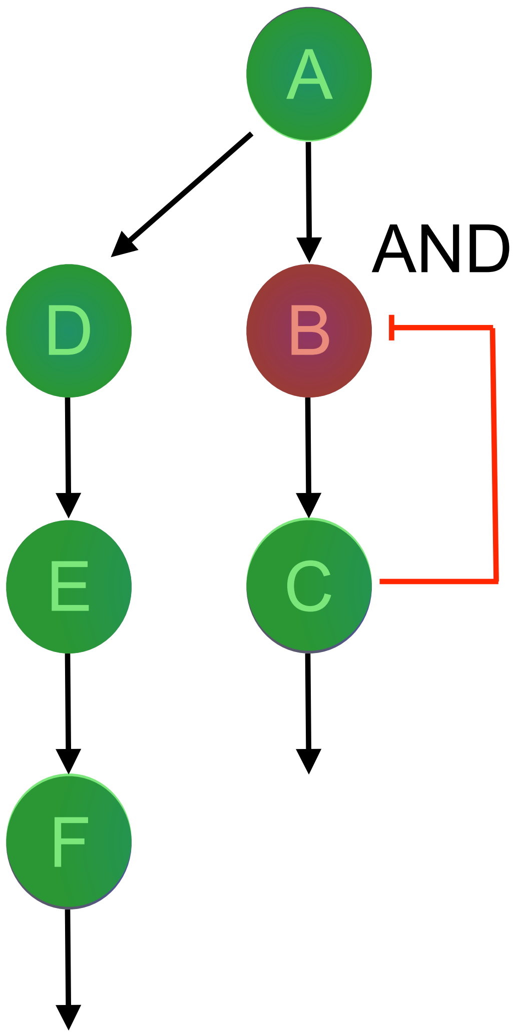

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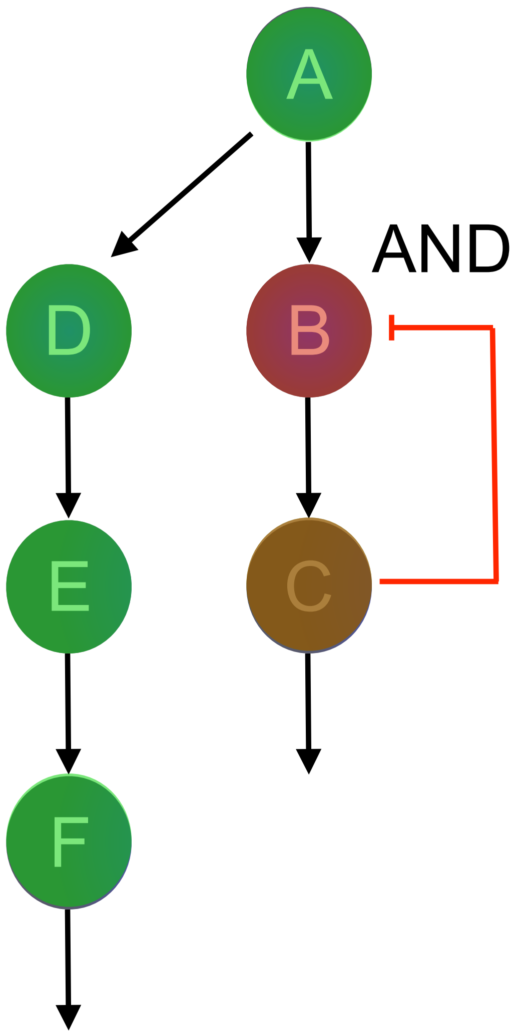

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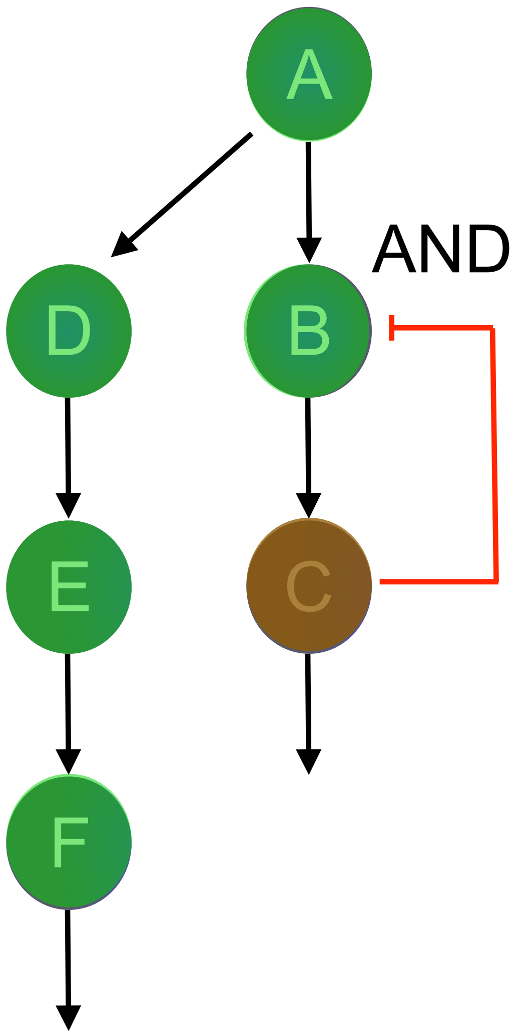

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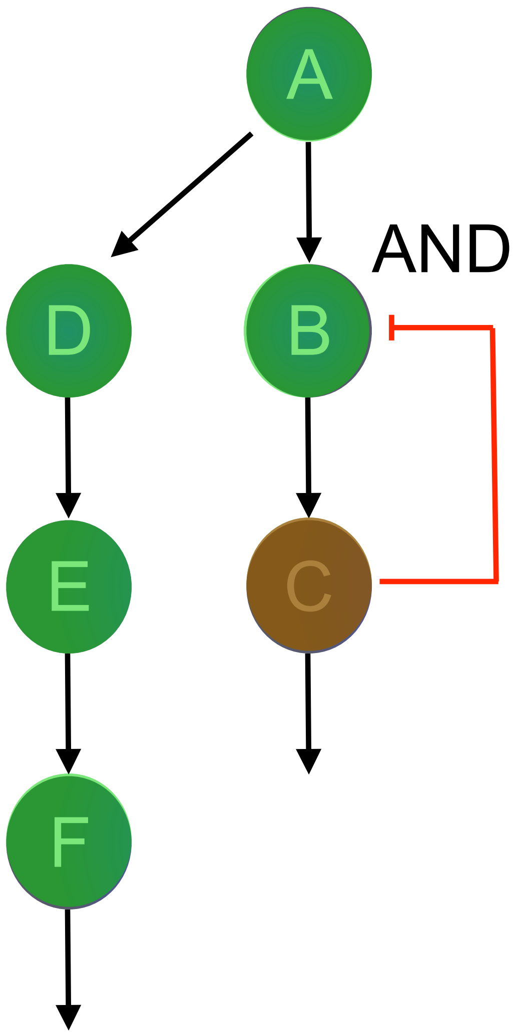

Algorithm penalizes lack of steady state, only effective for one ‘early’ time

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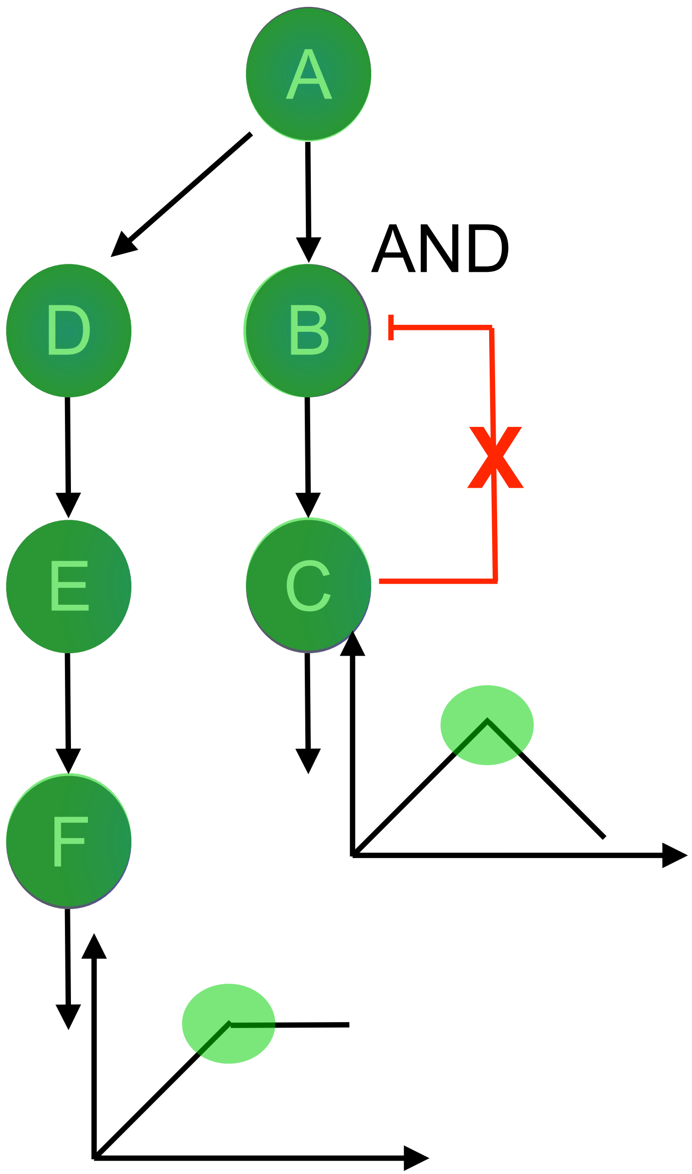

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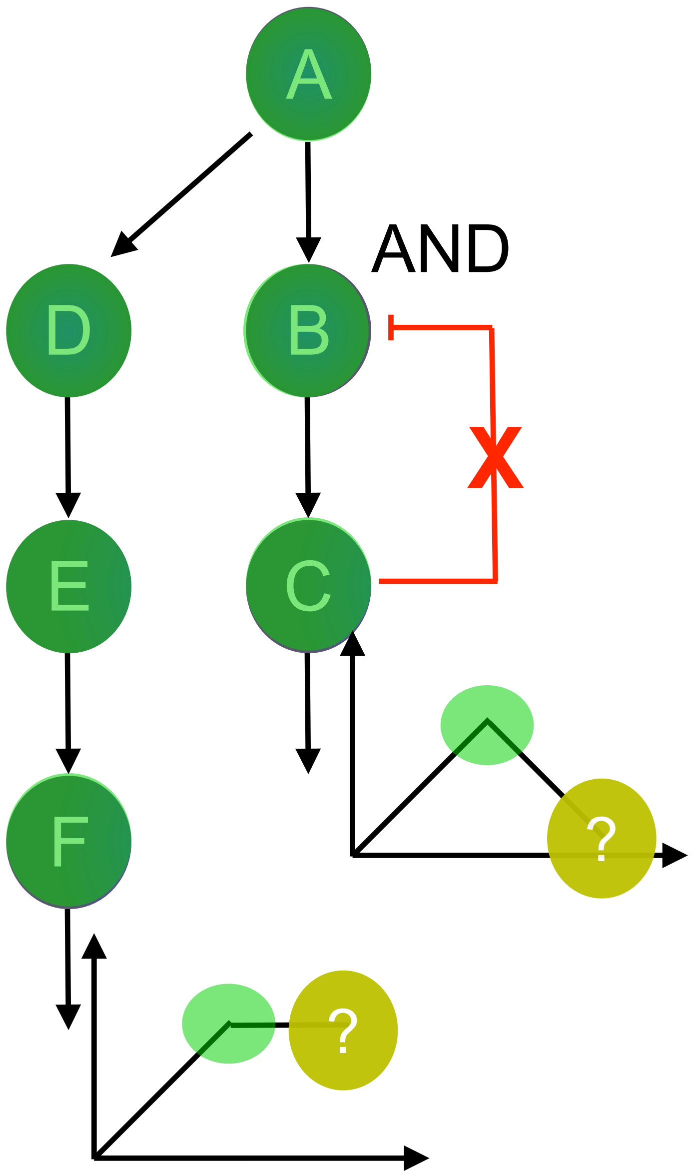

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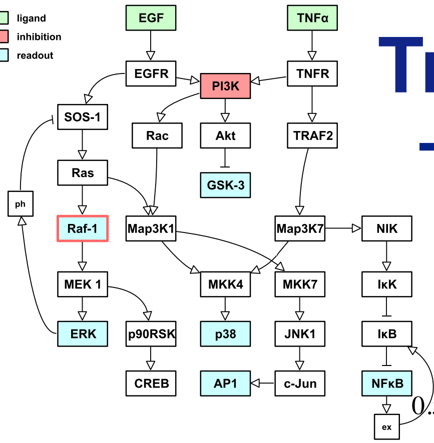
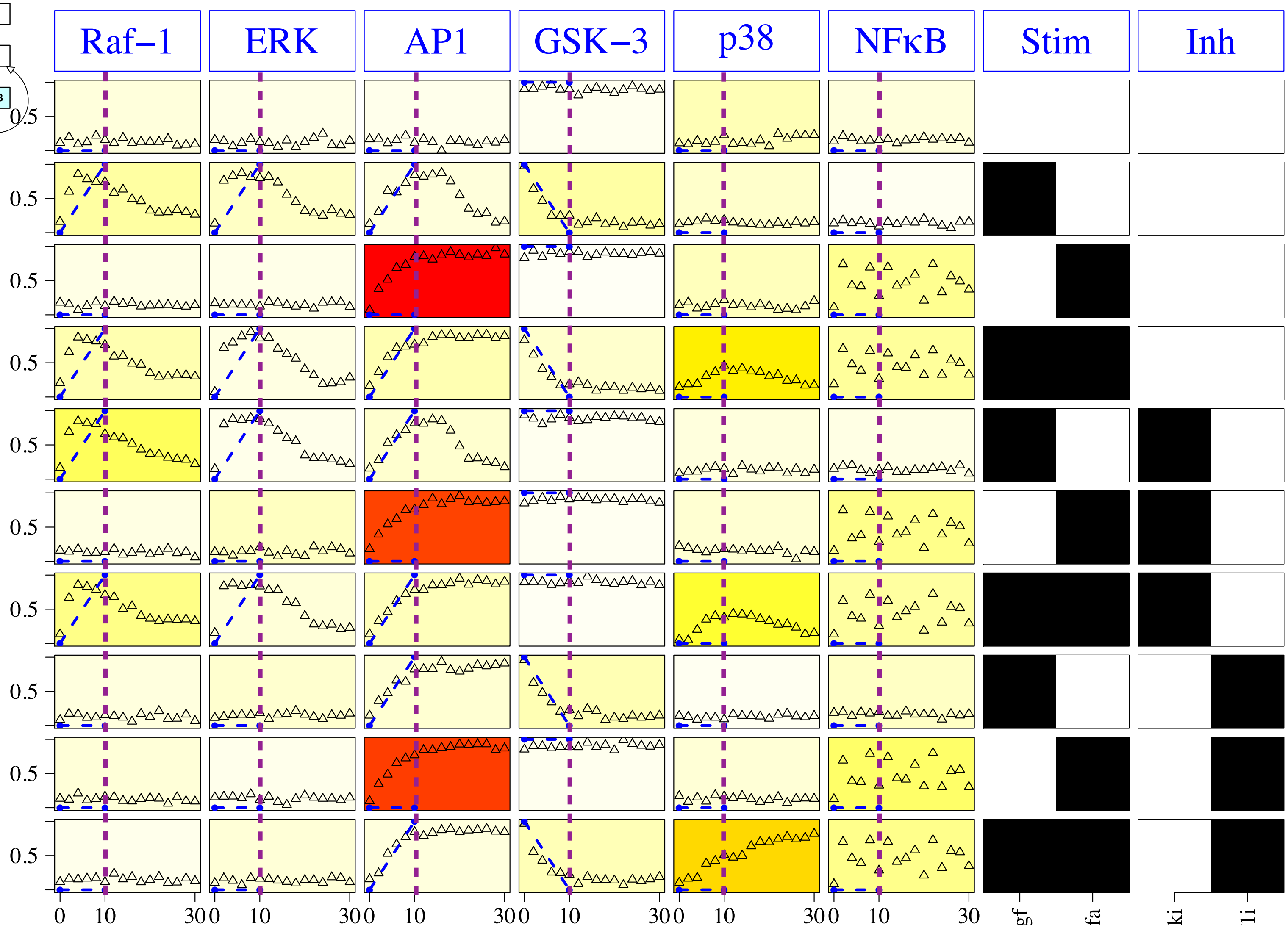
Training to data recovers structure





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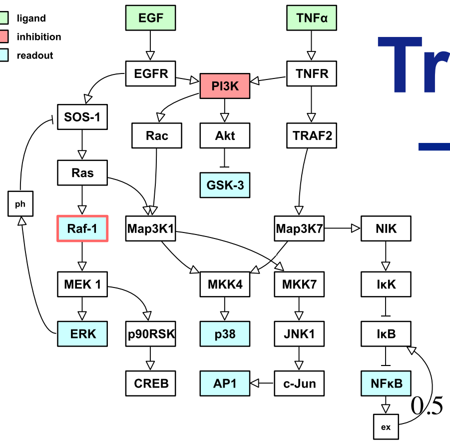

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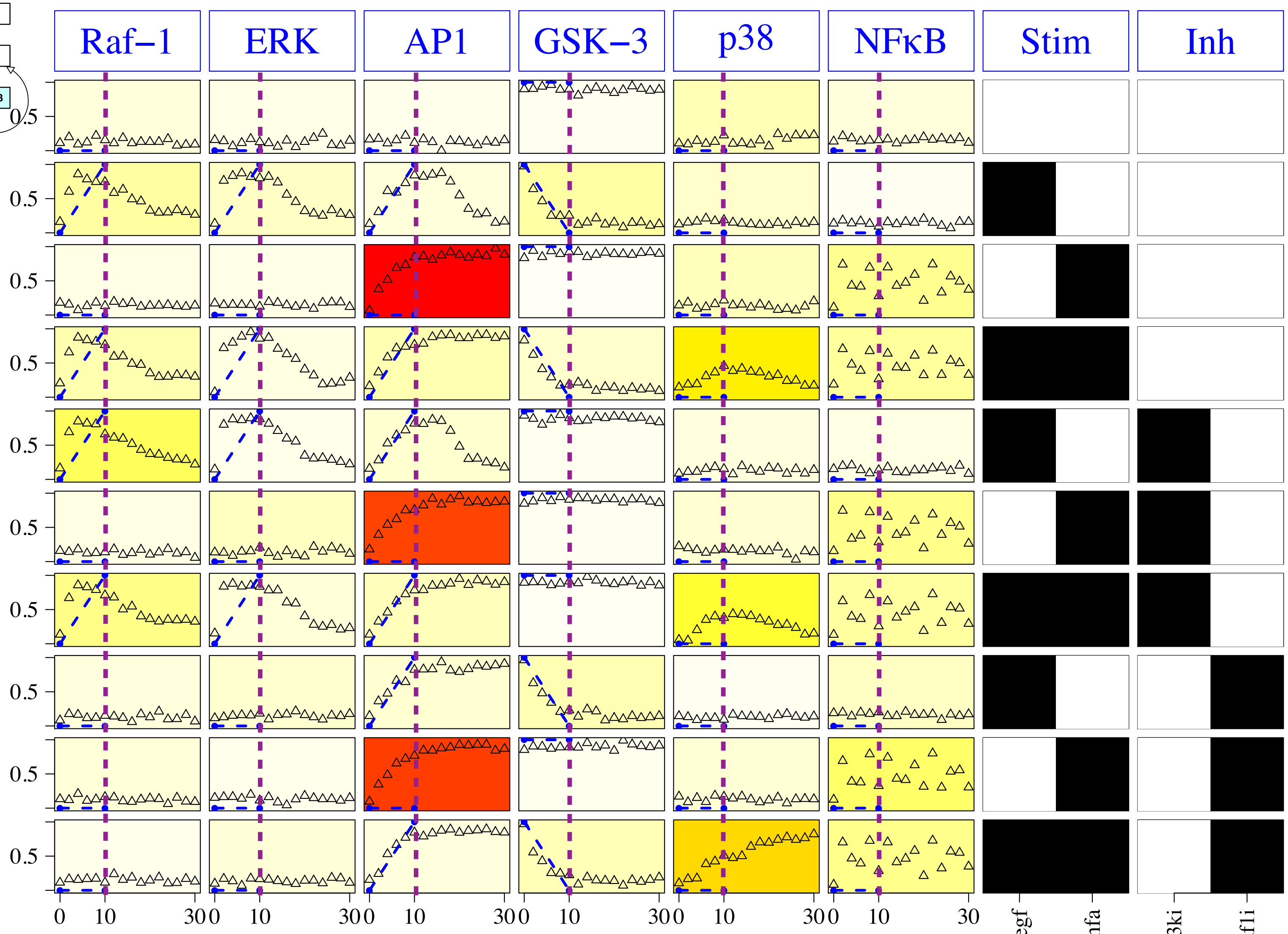

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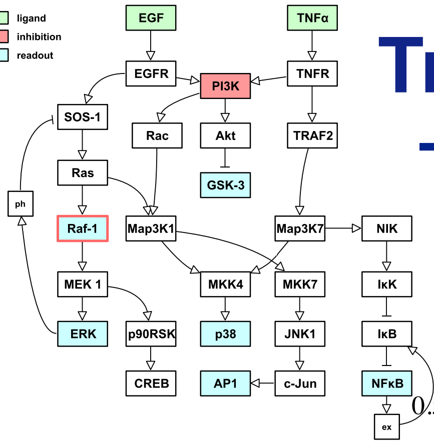

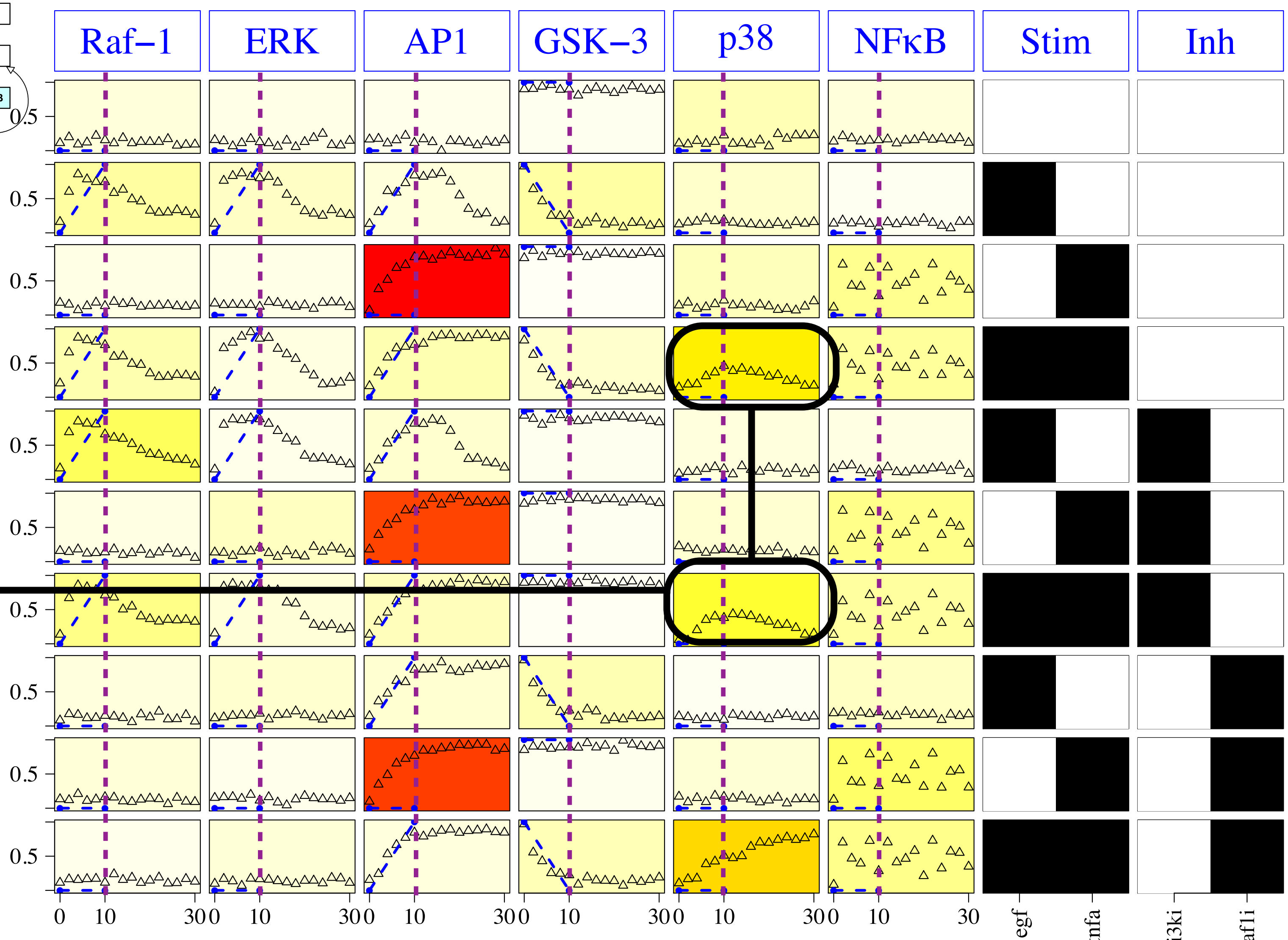

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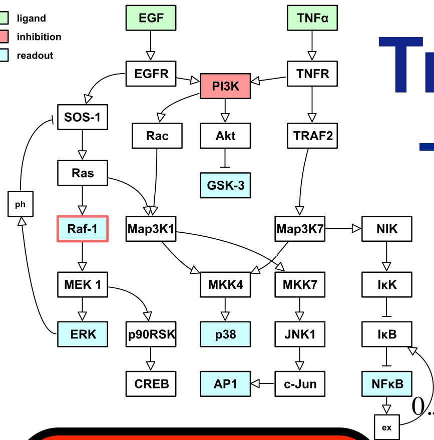

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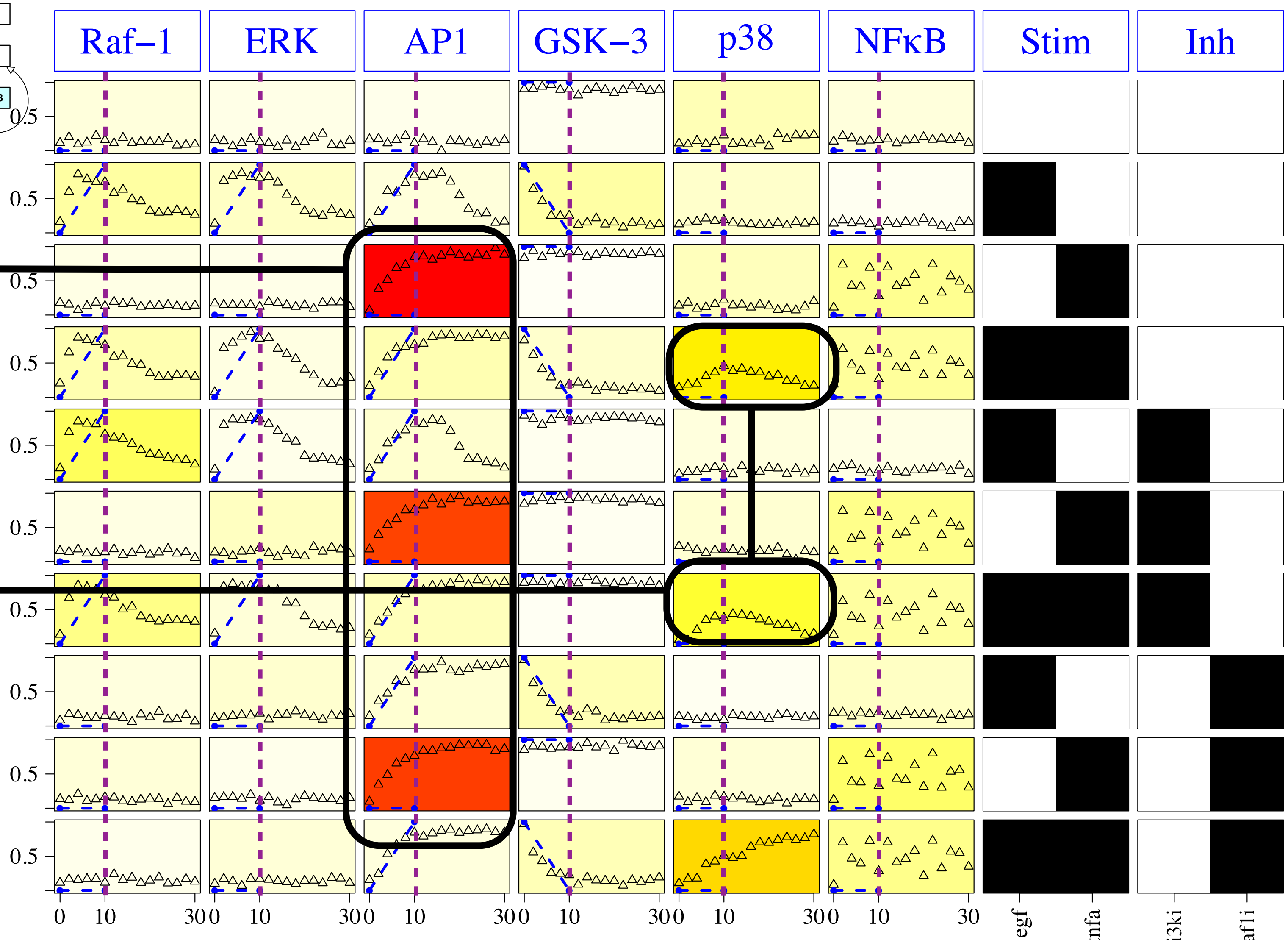

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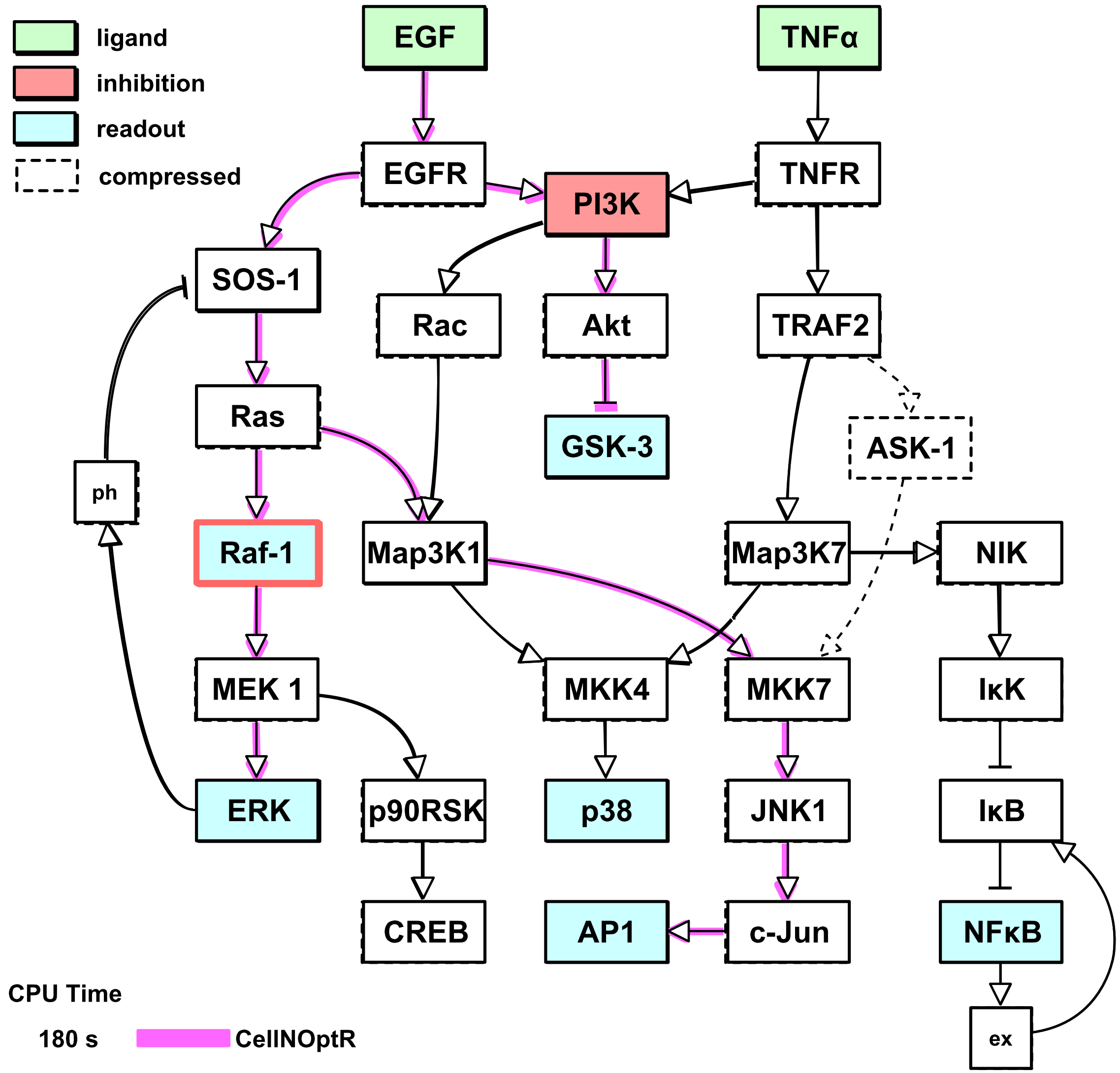

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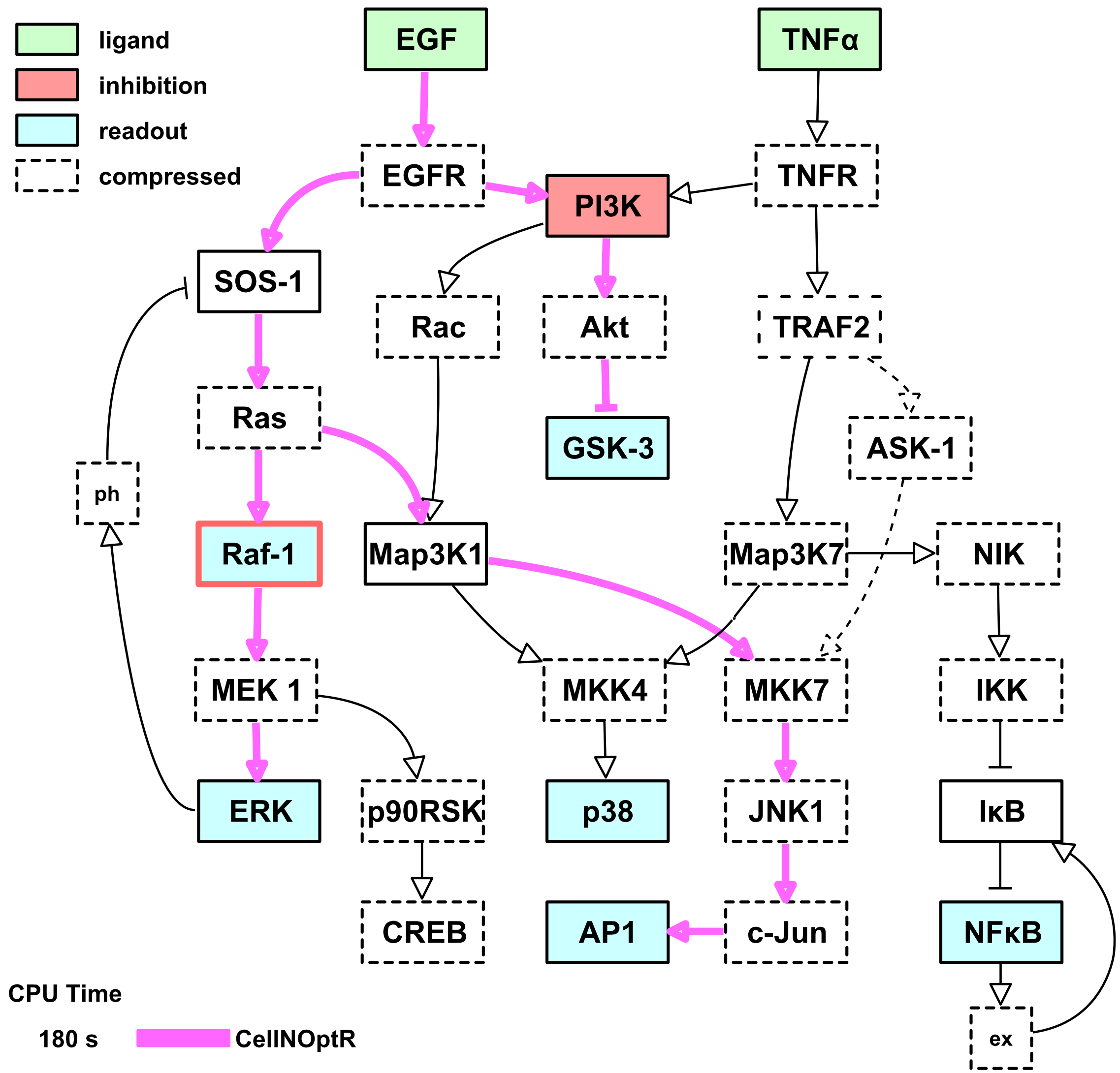

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Constrained Fuzzy Logic can handle quantitative differences

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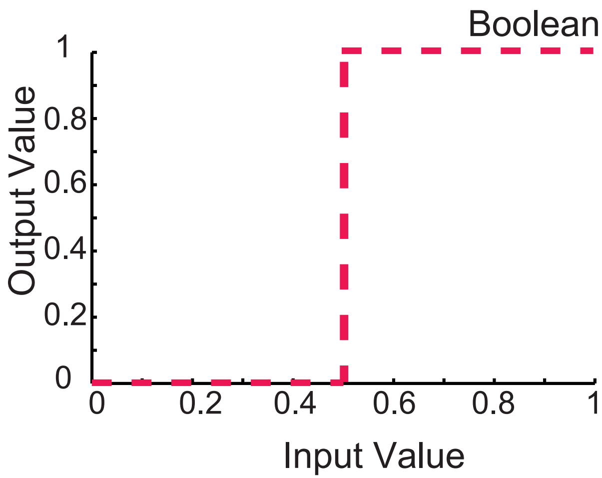

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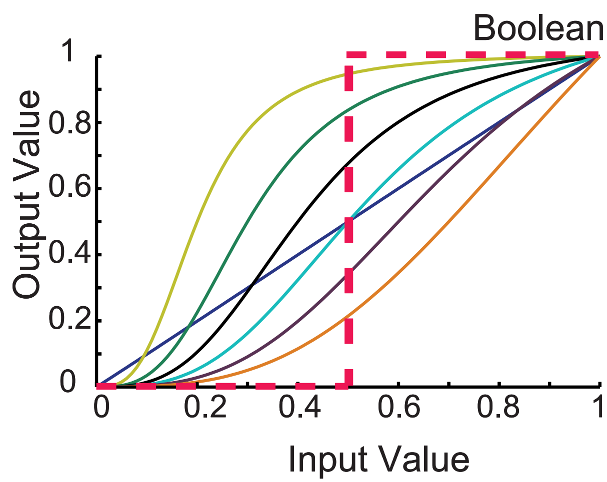

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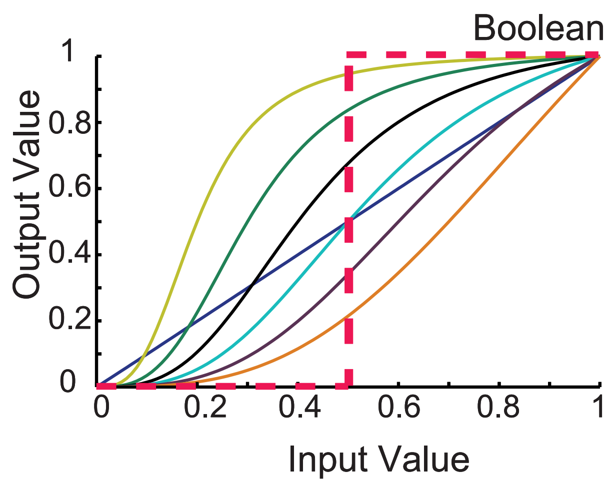

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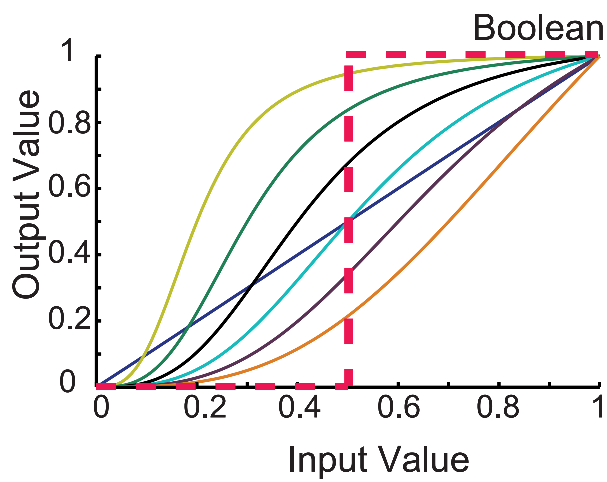

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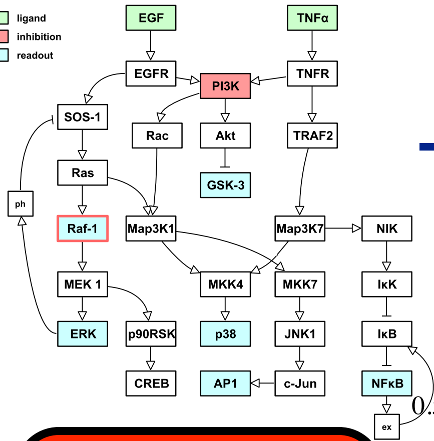
fit of fuzzy toy model



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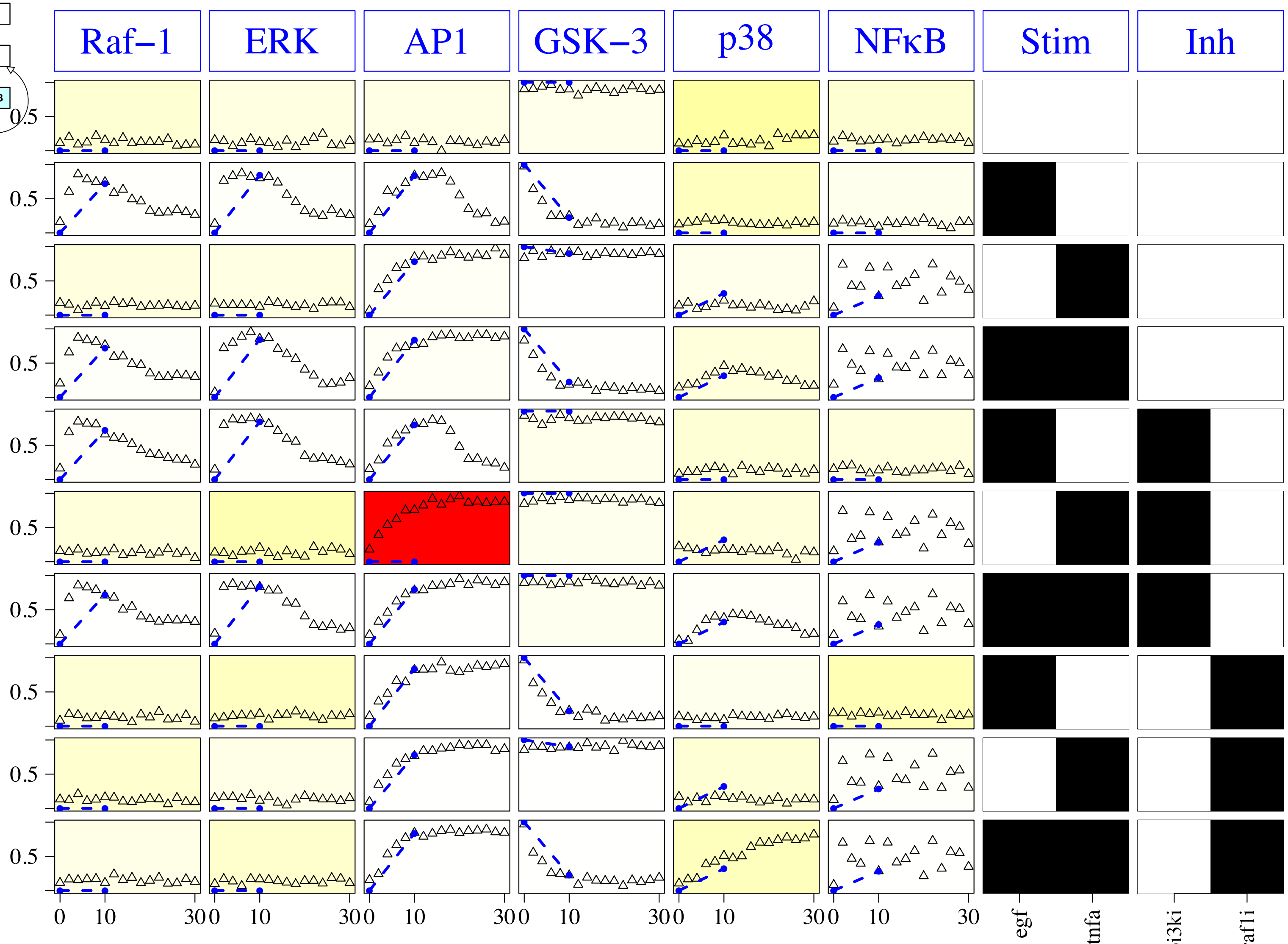

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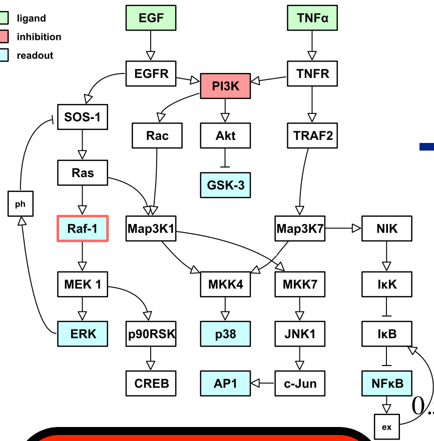

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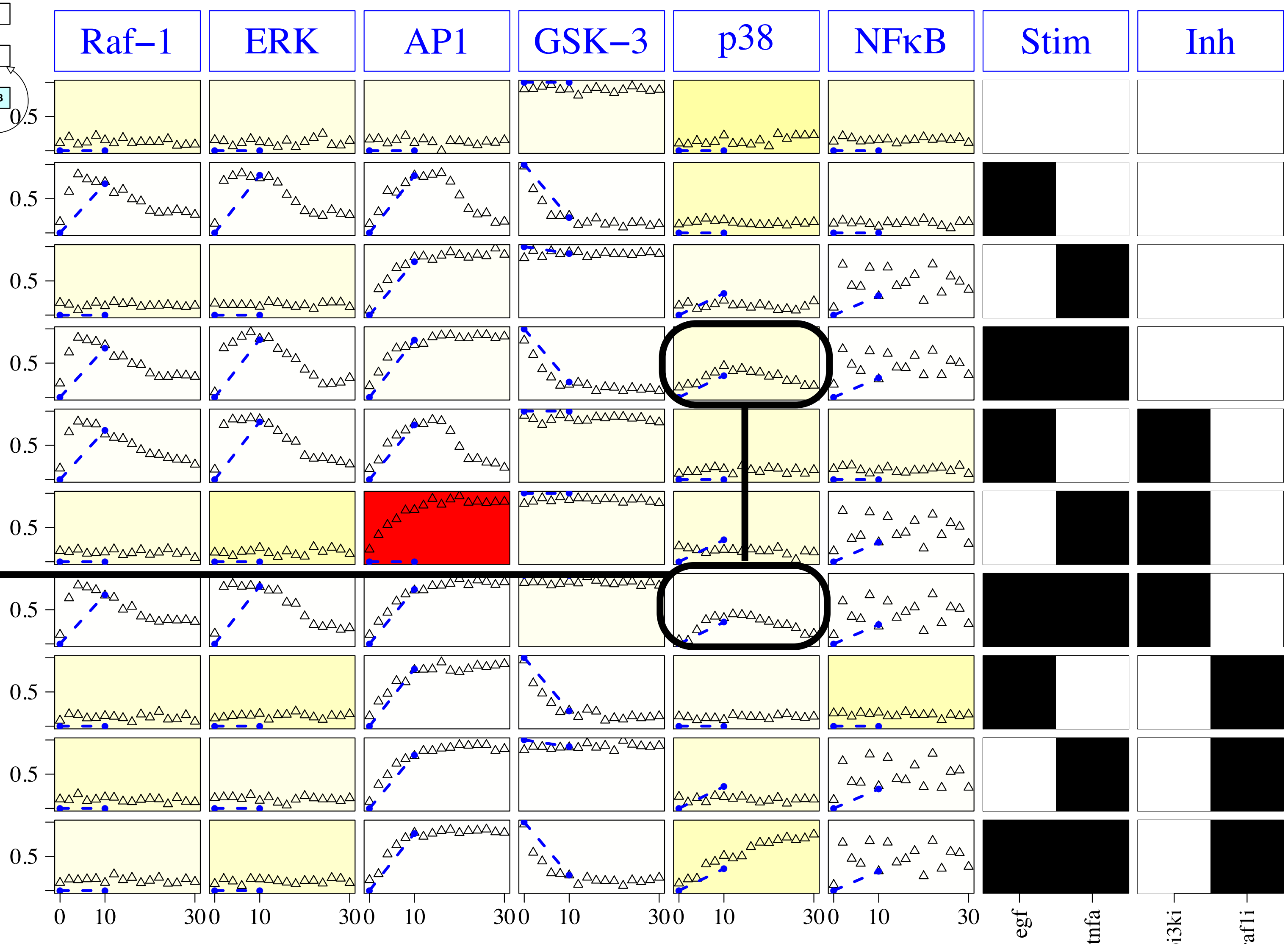

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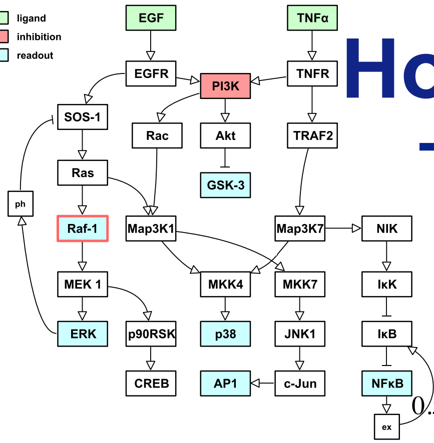
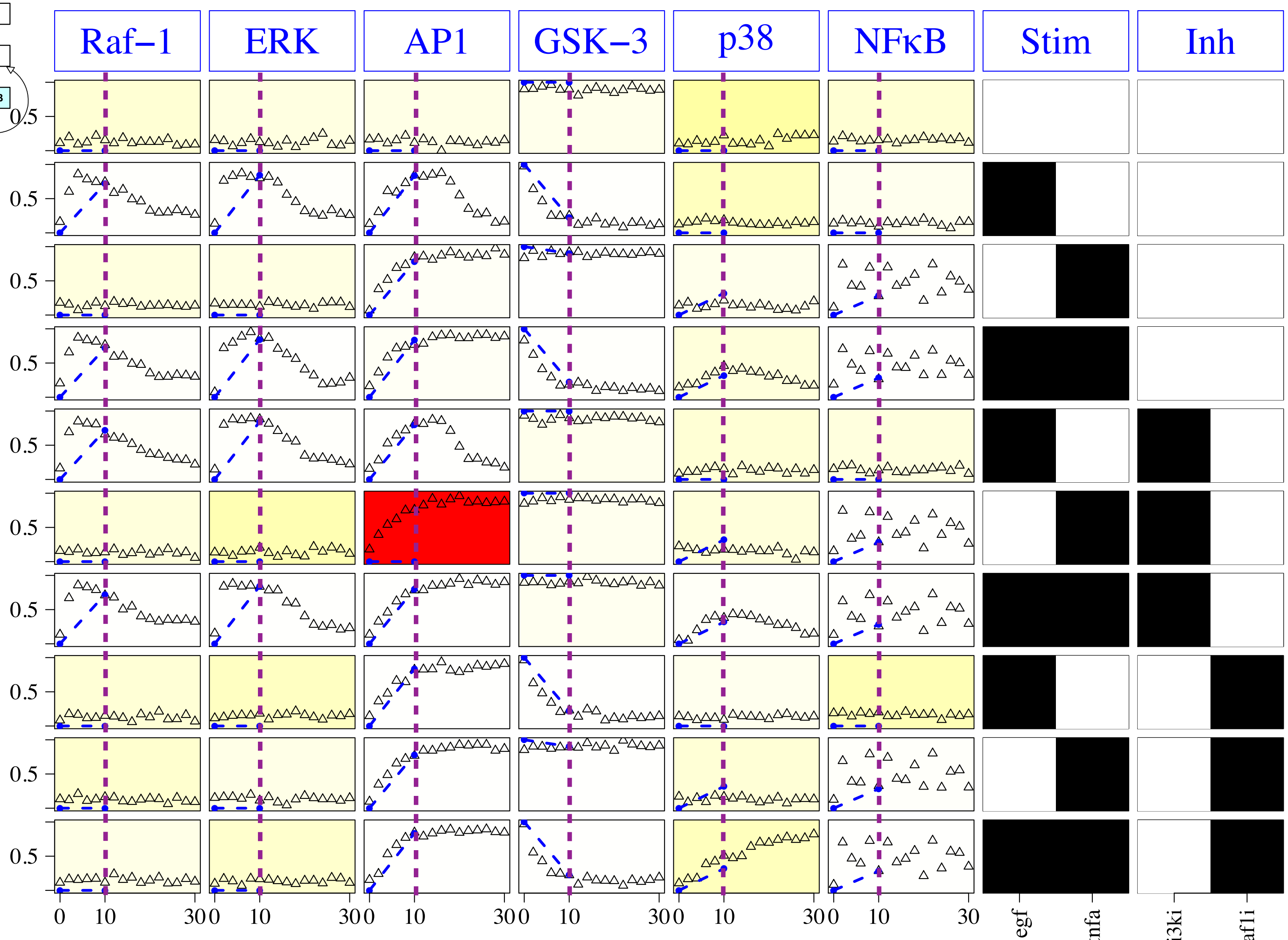
How to model feedback effects?





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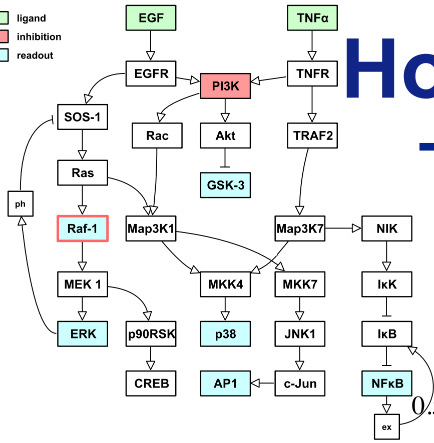

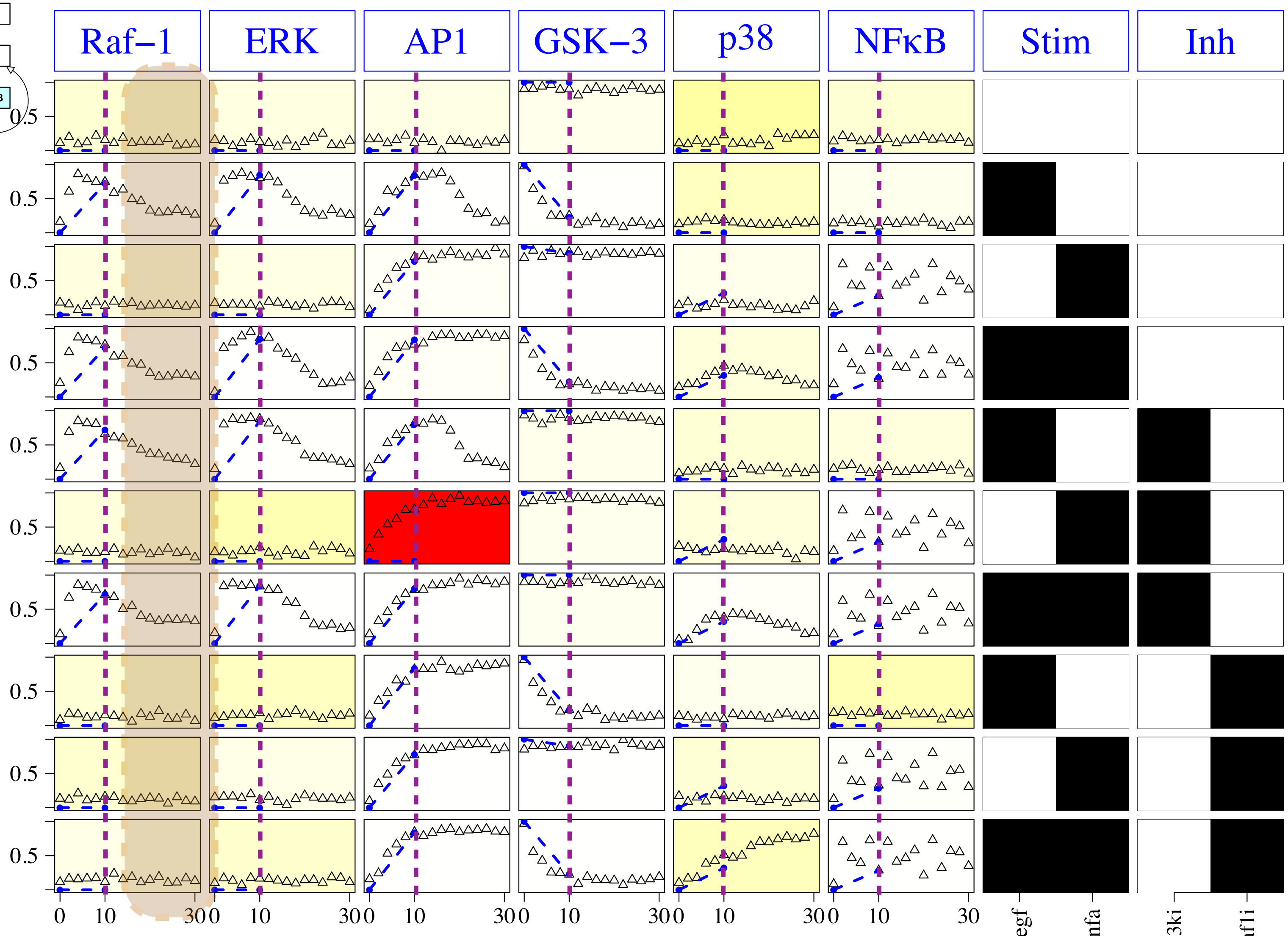

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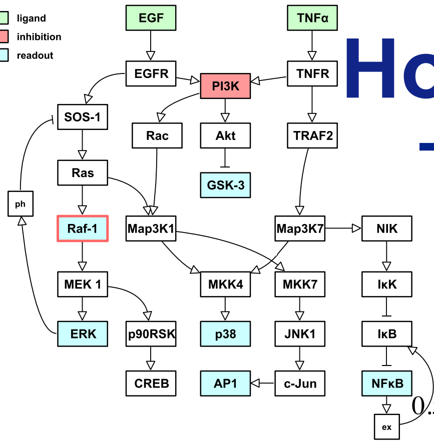

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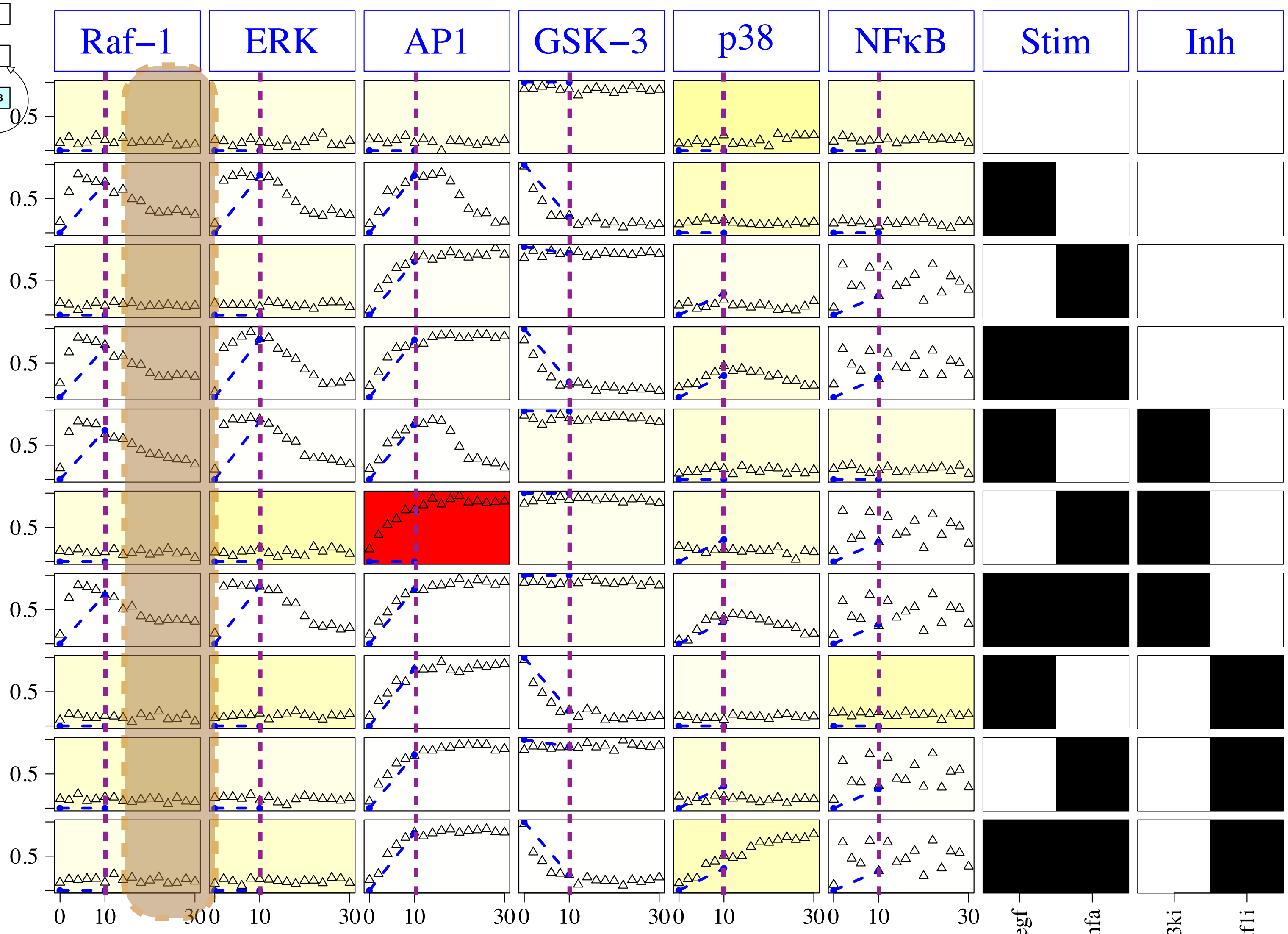
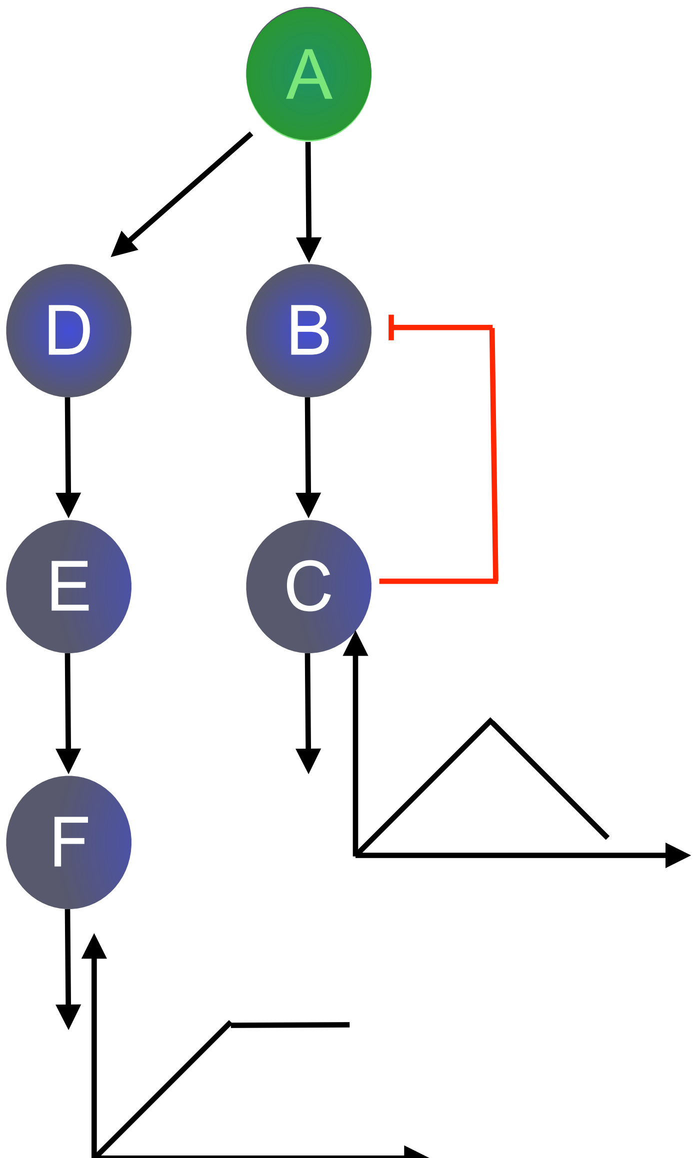


MacNamara A Terfve C Henriques D Penalver B Saez-Rodriguez J *Phys Biol* 9 045003, 2012

Approximation of transient behaviour using multiple time-scales



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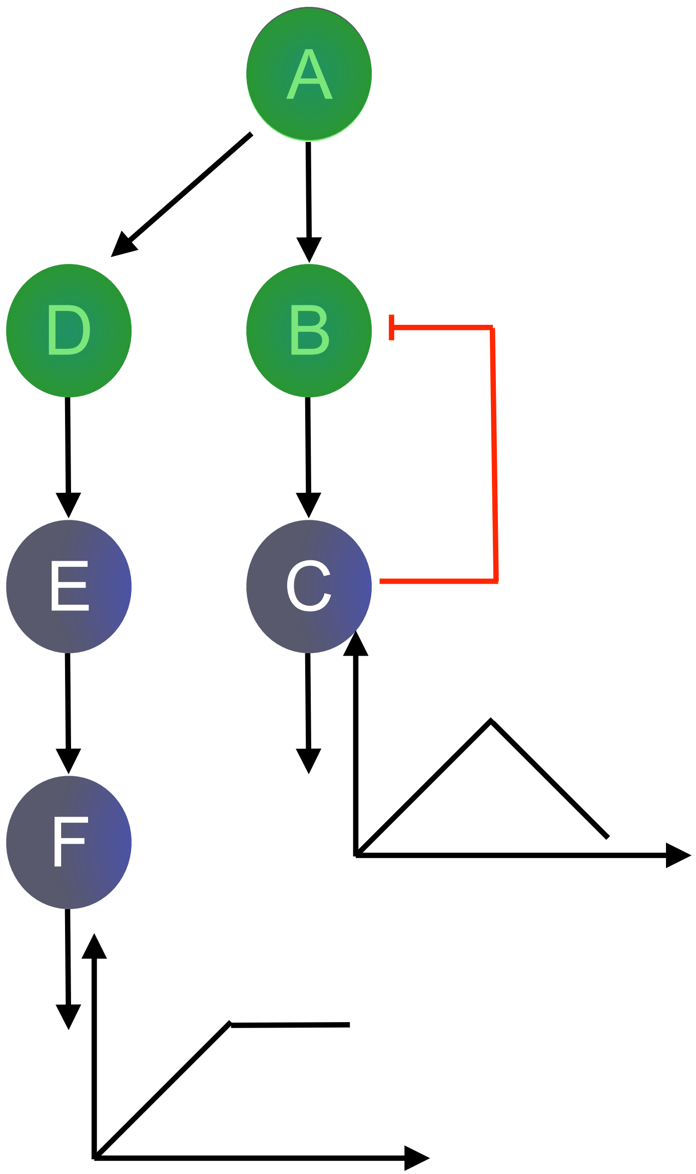

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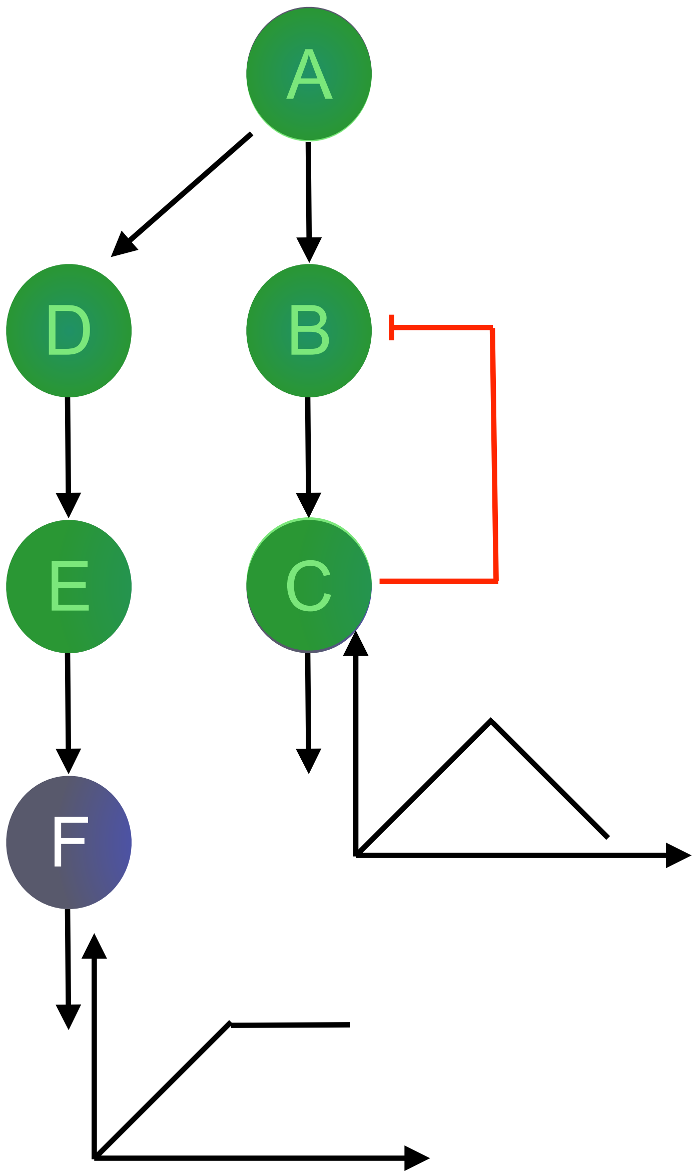

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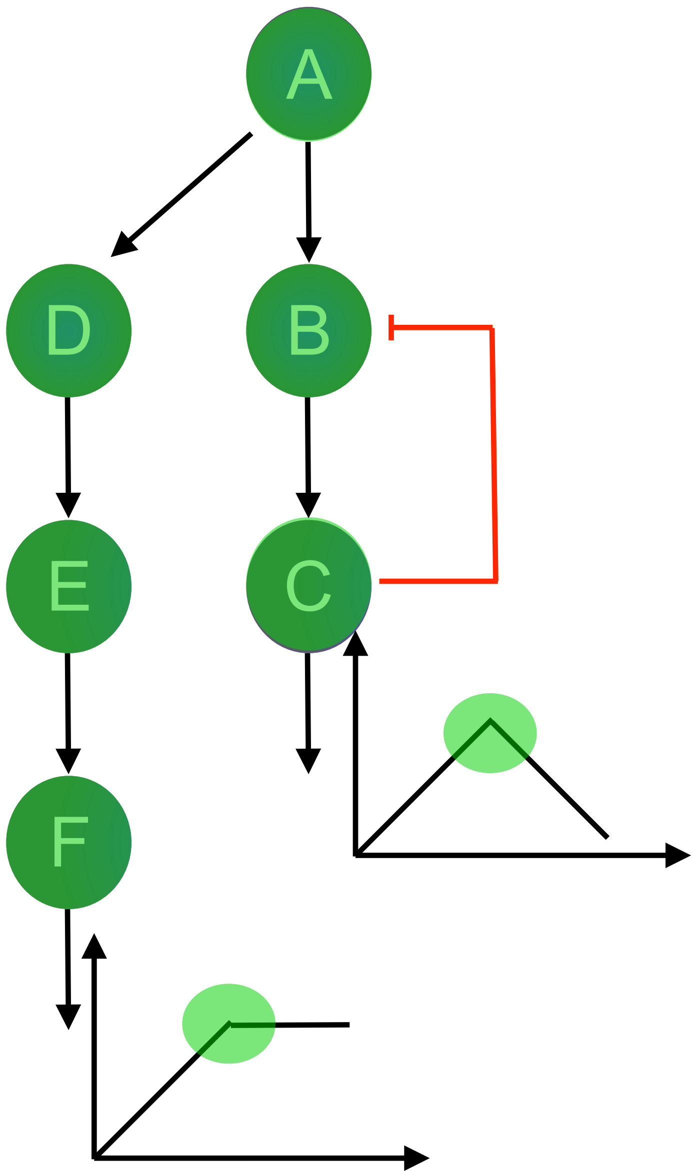

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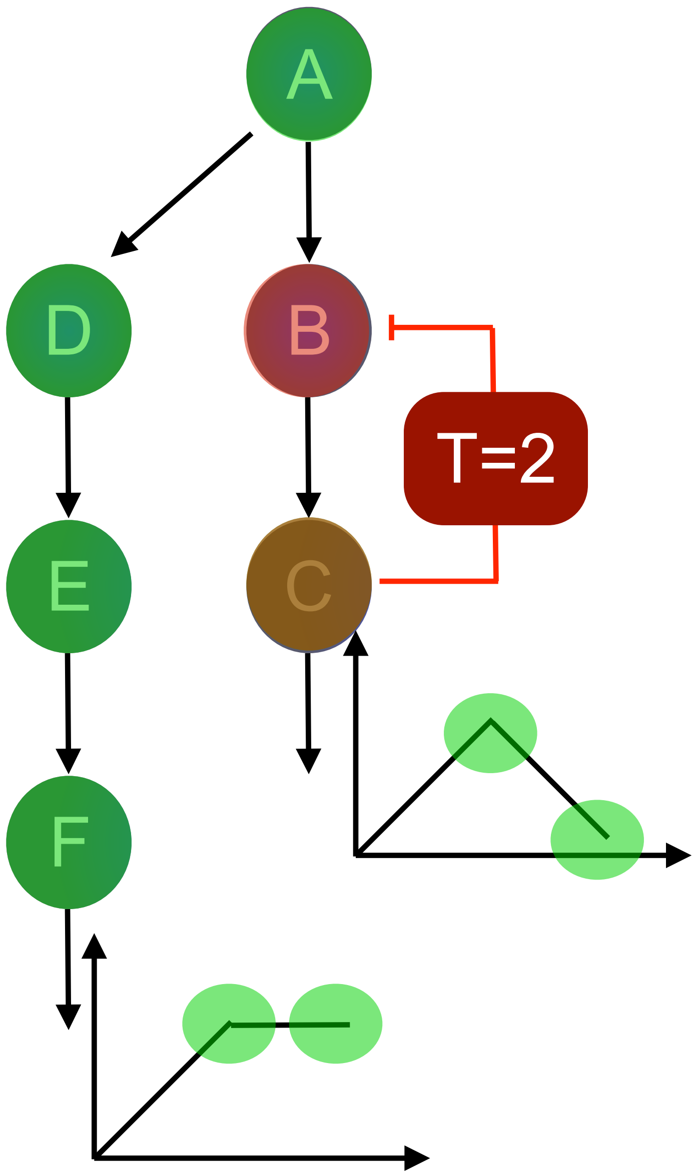

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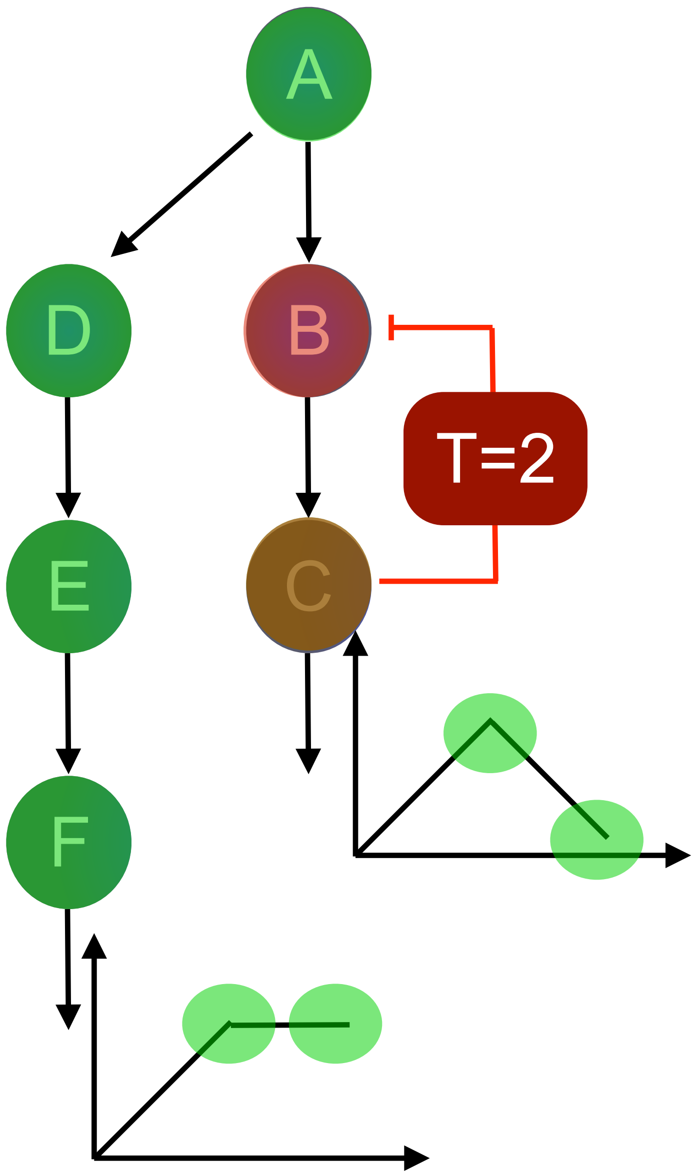

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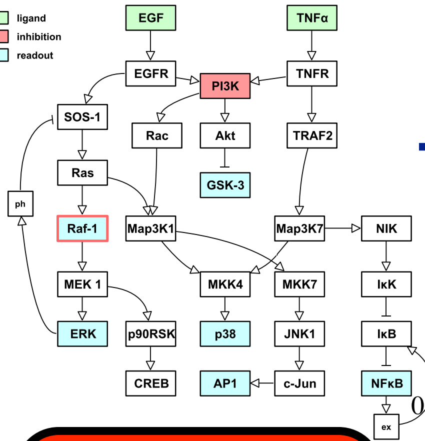
Rough approximation of dynamics, still computationally efficient

Multiple pseudo-steady-state captures feedbacks that lead to transient signals



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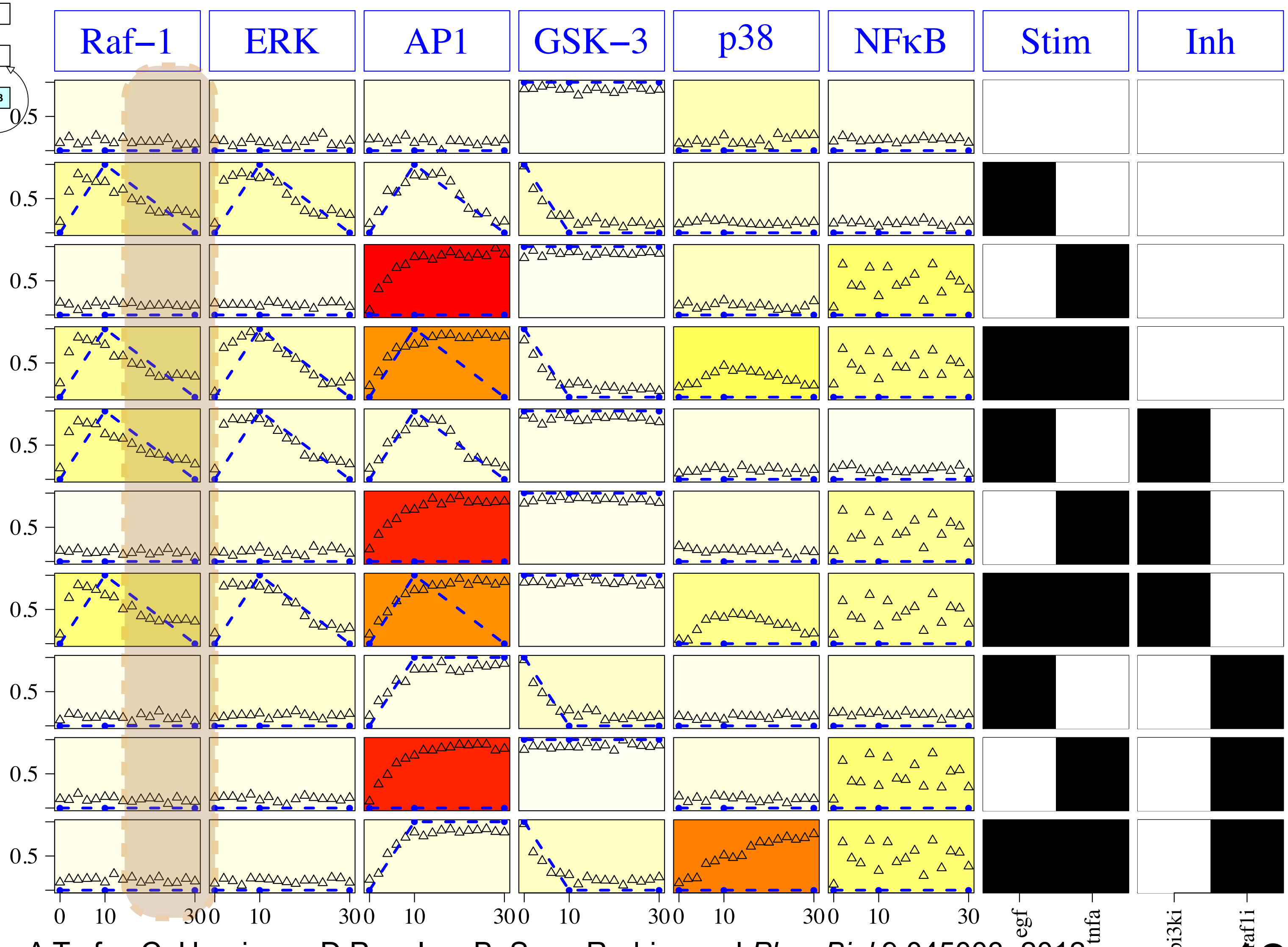

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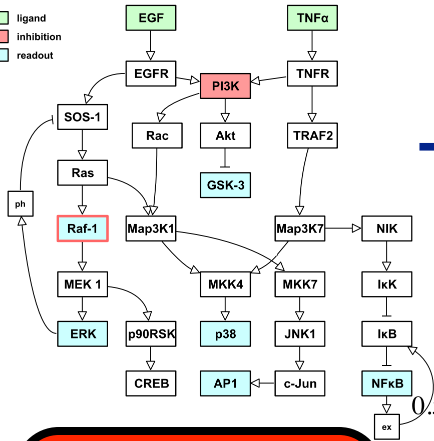

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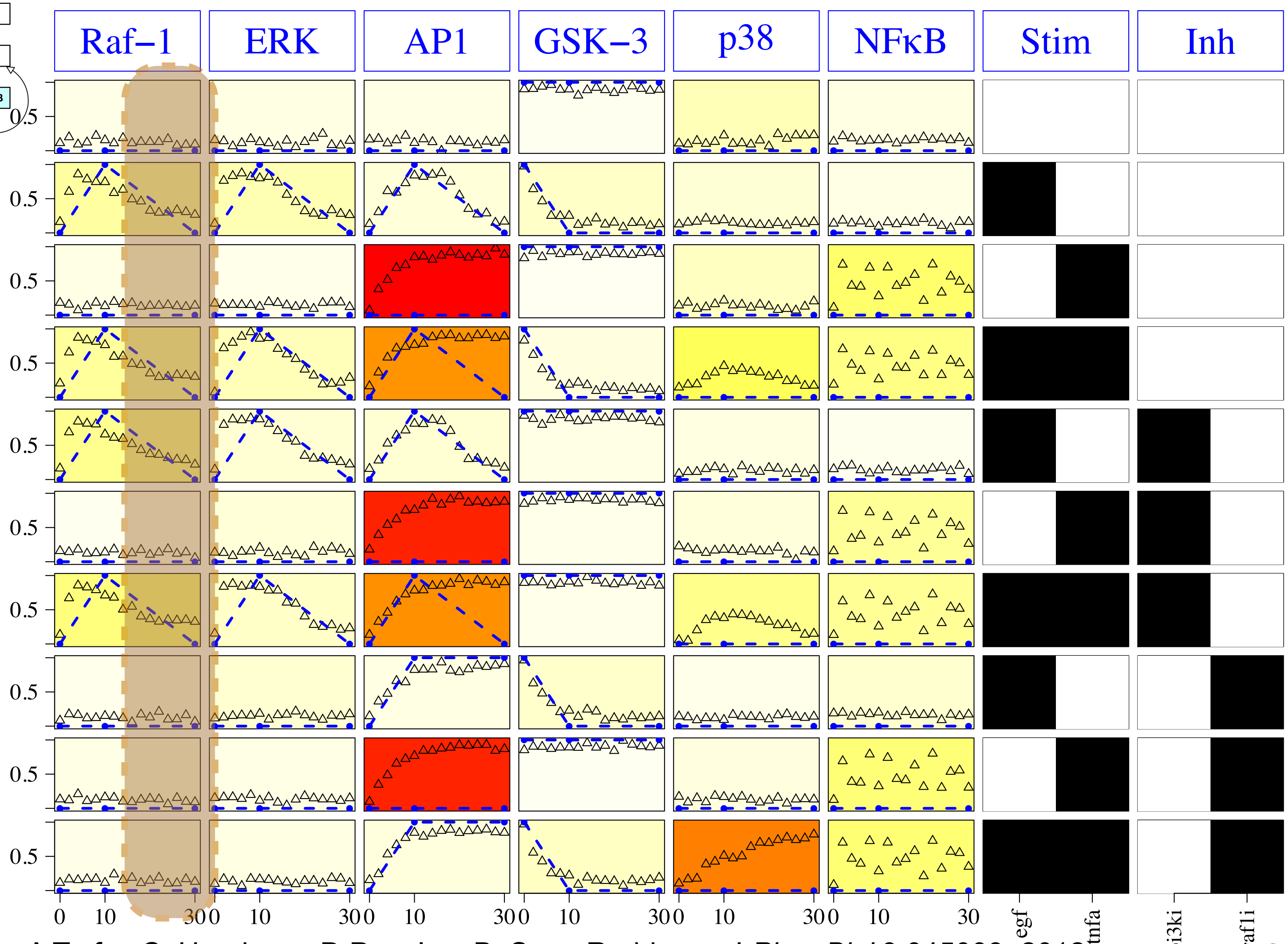

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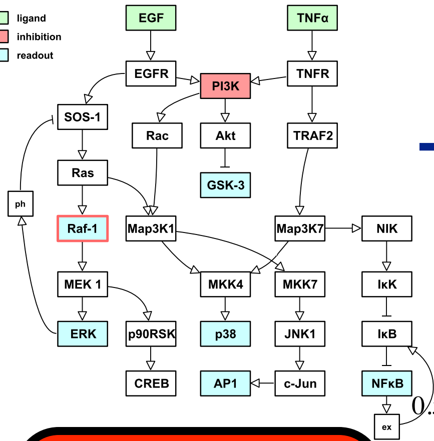

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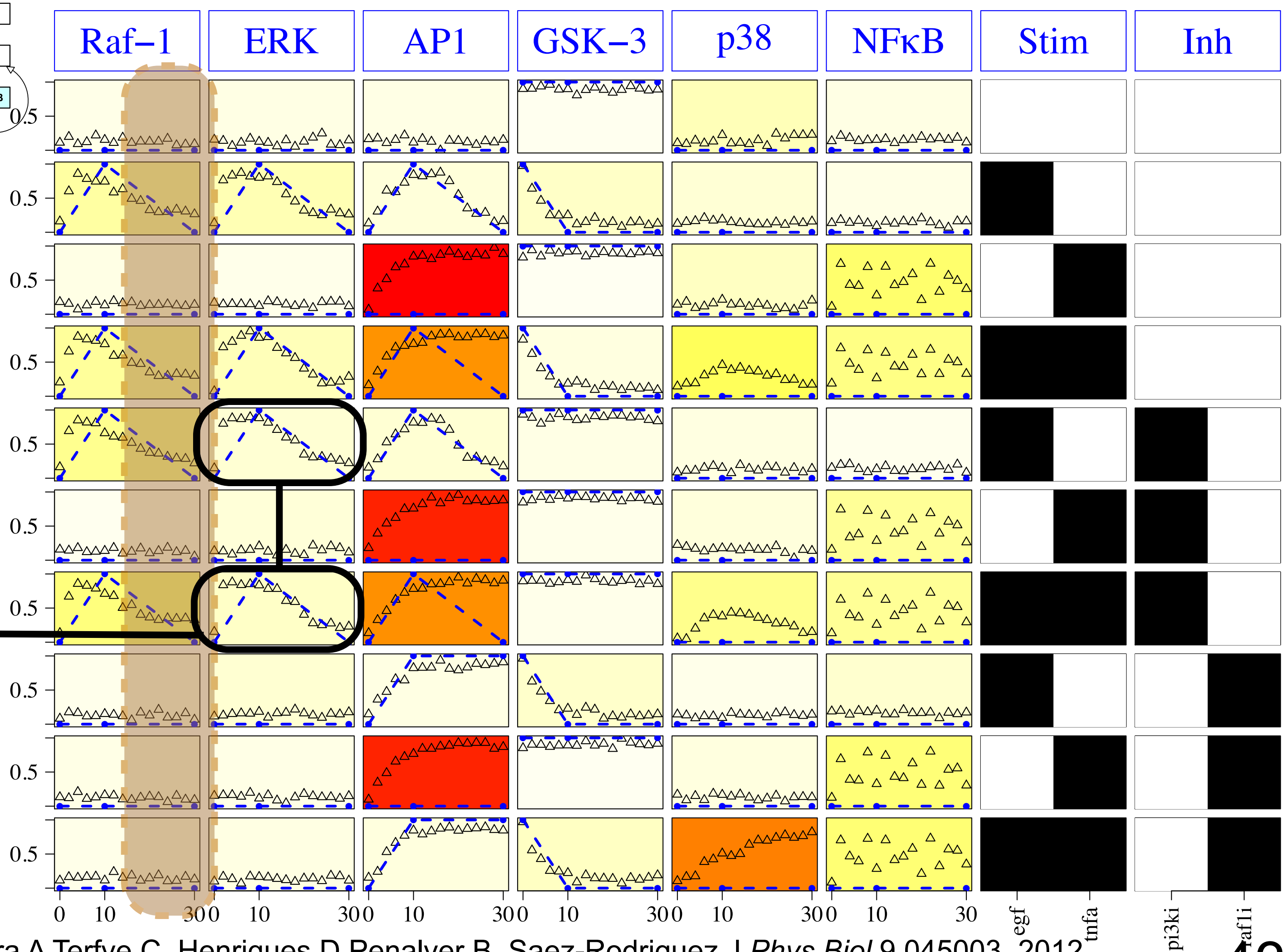

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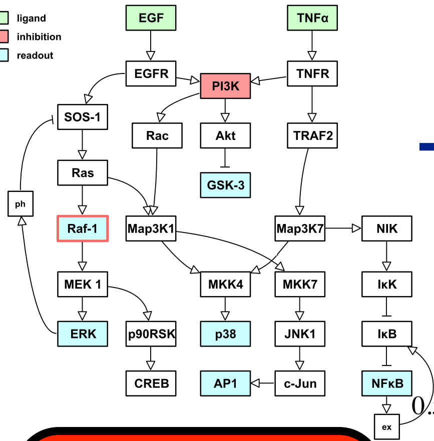

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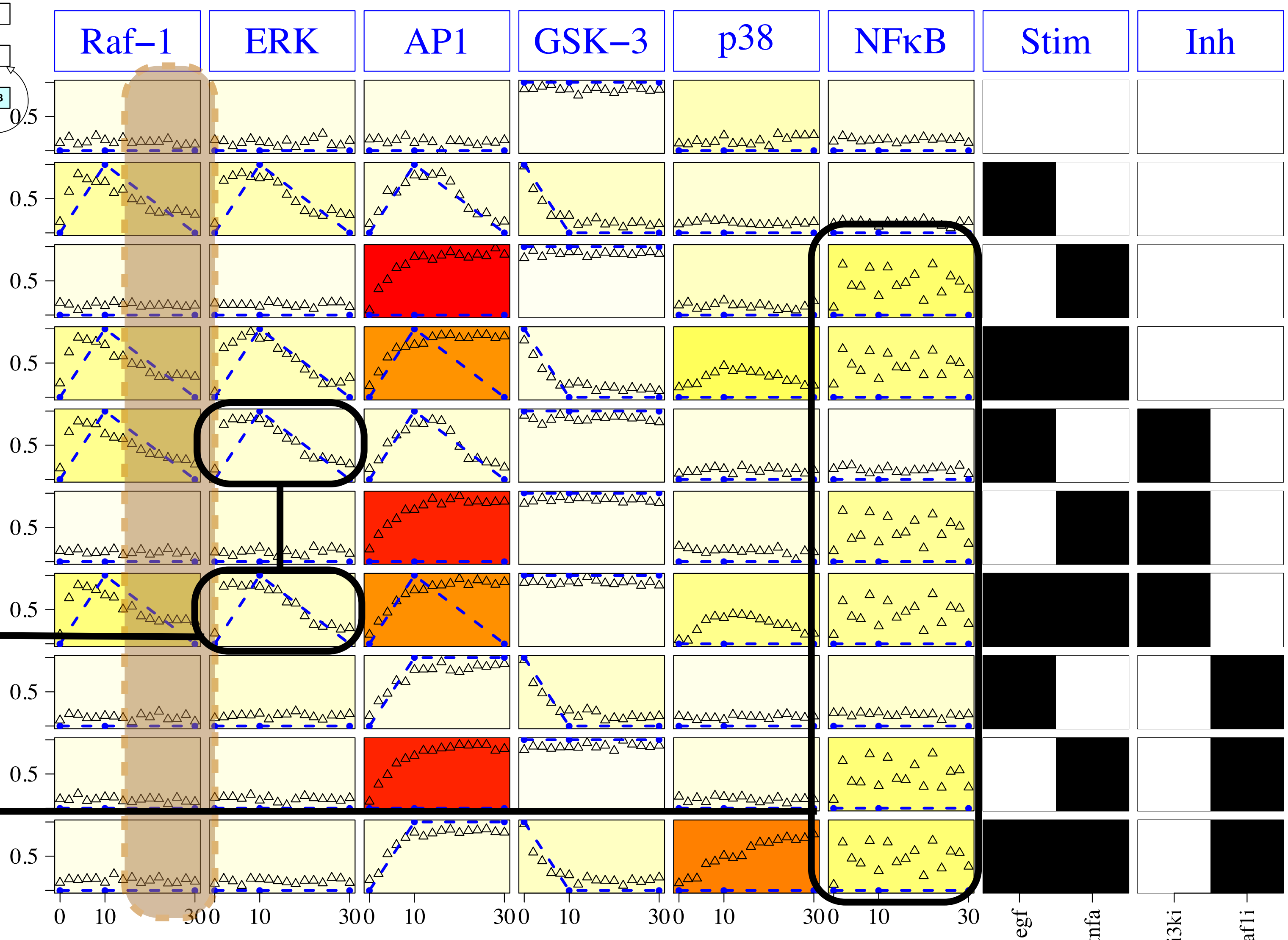

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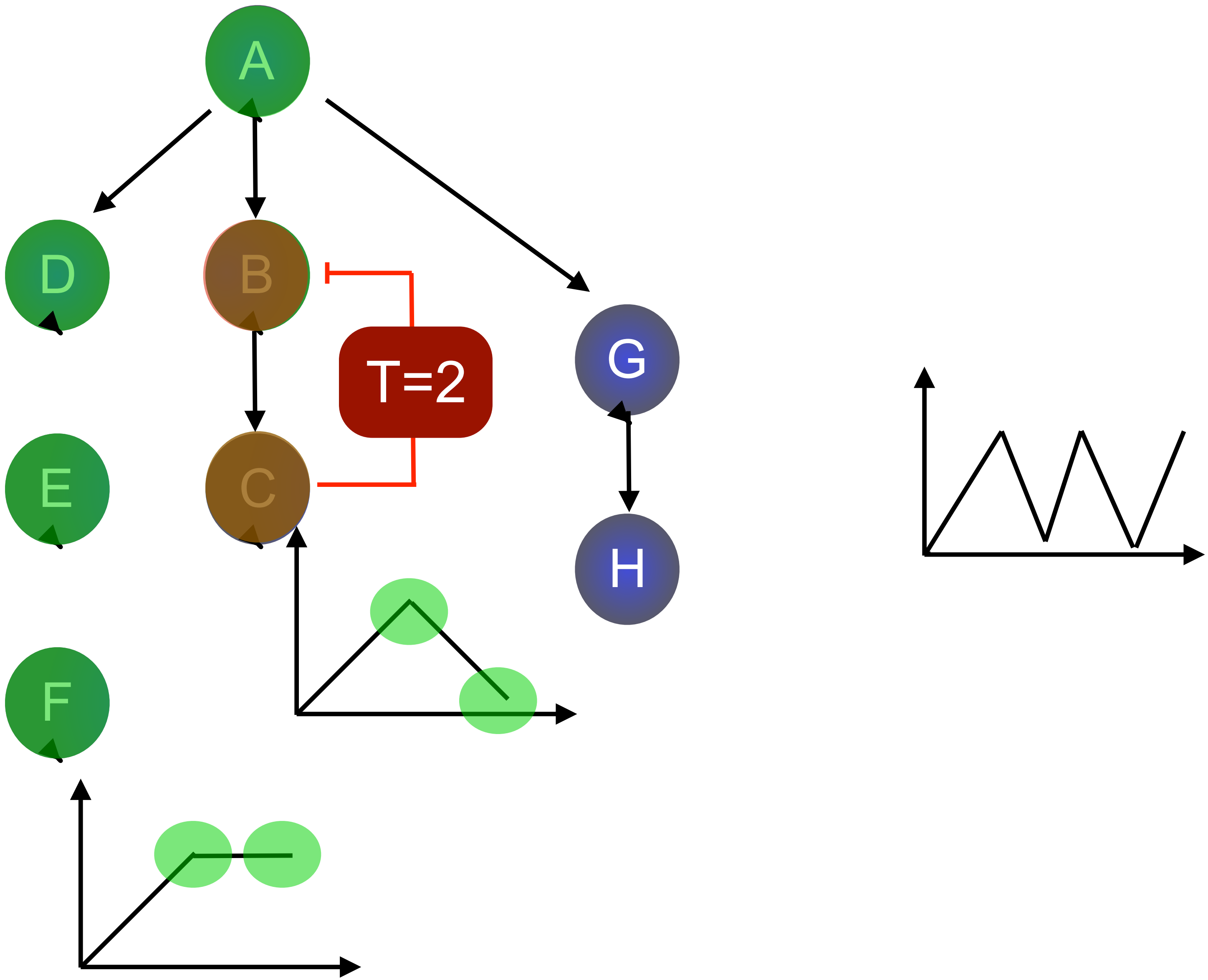
Approximation of dynamics using synchronous simulation & multiple time-scales



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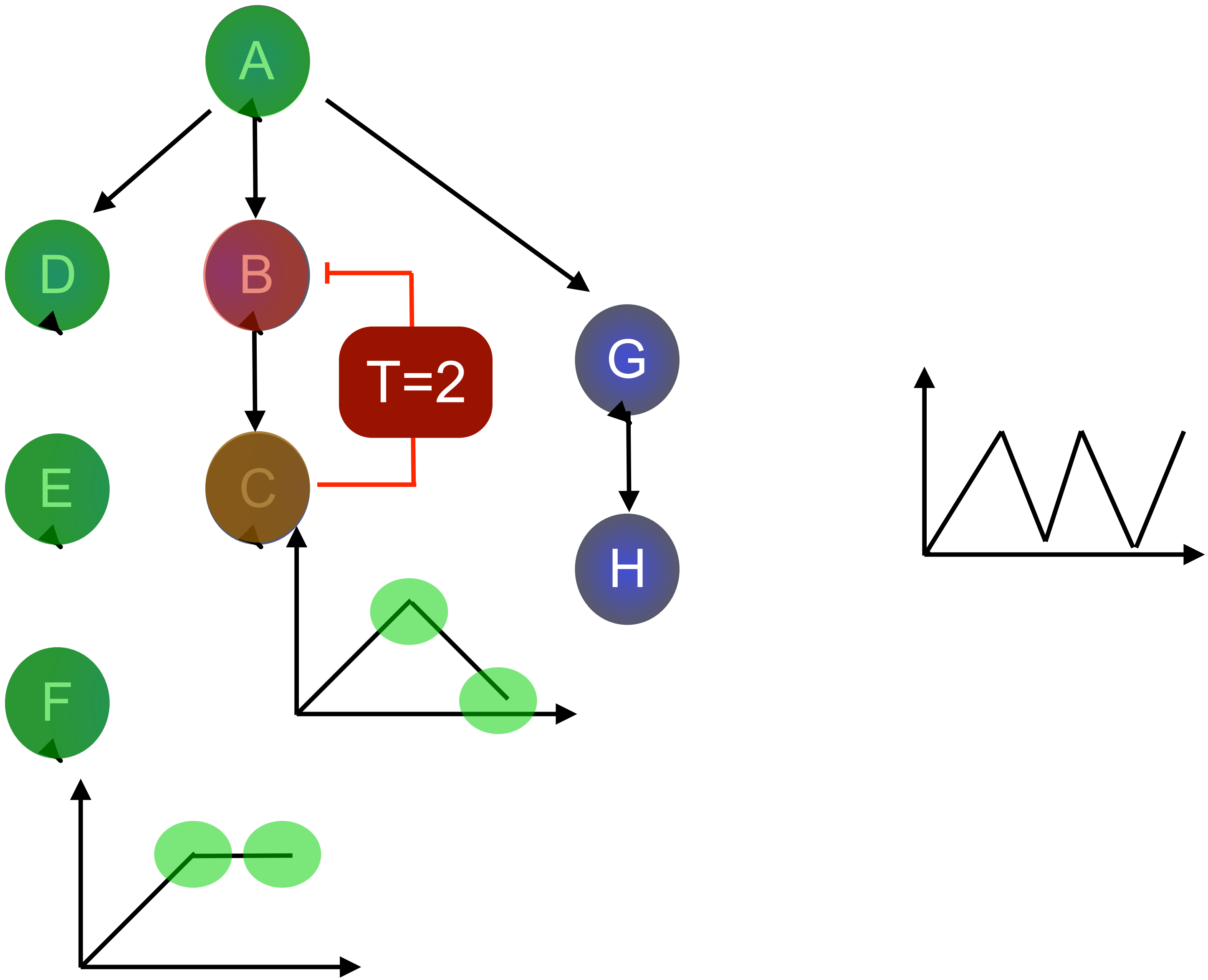

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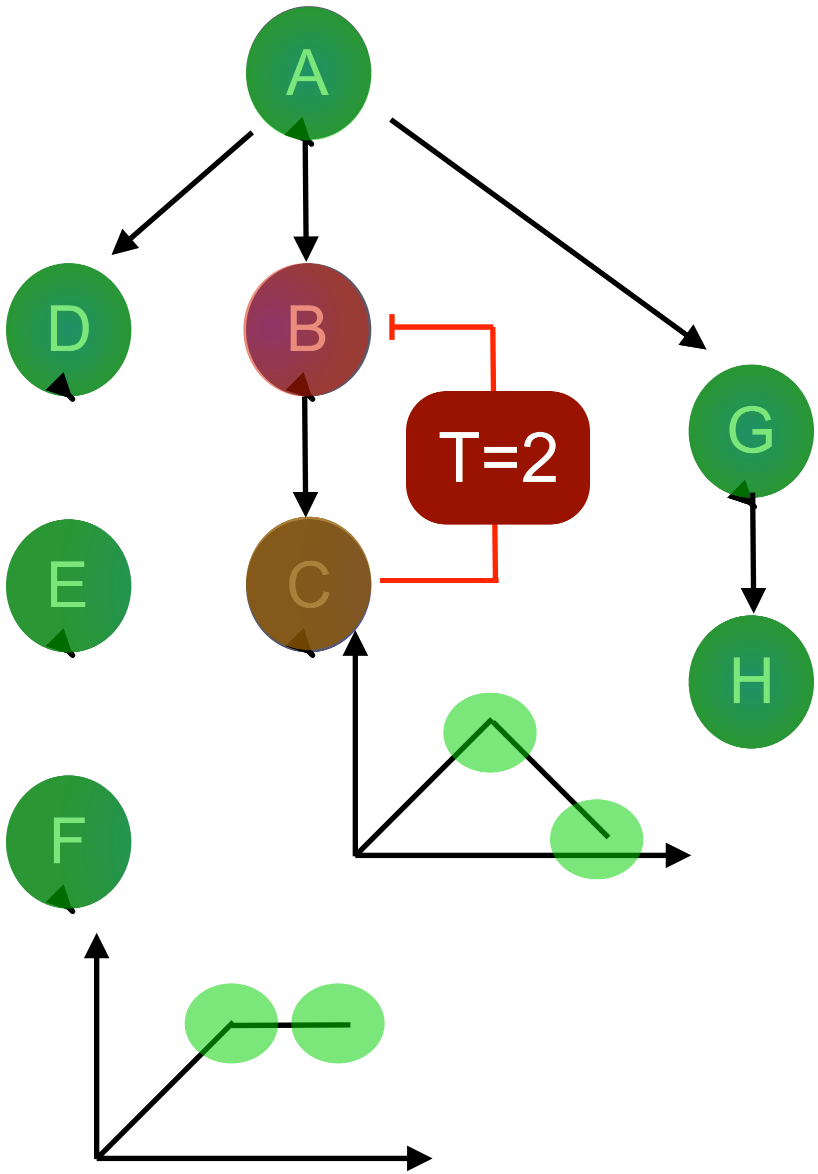

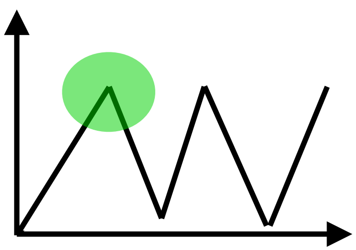

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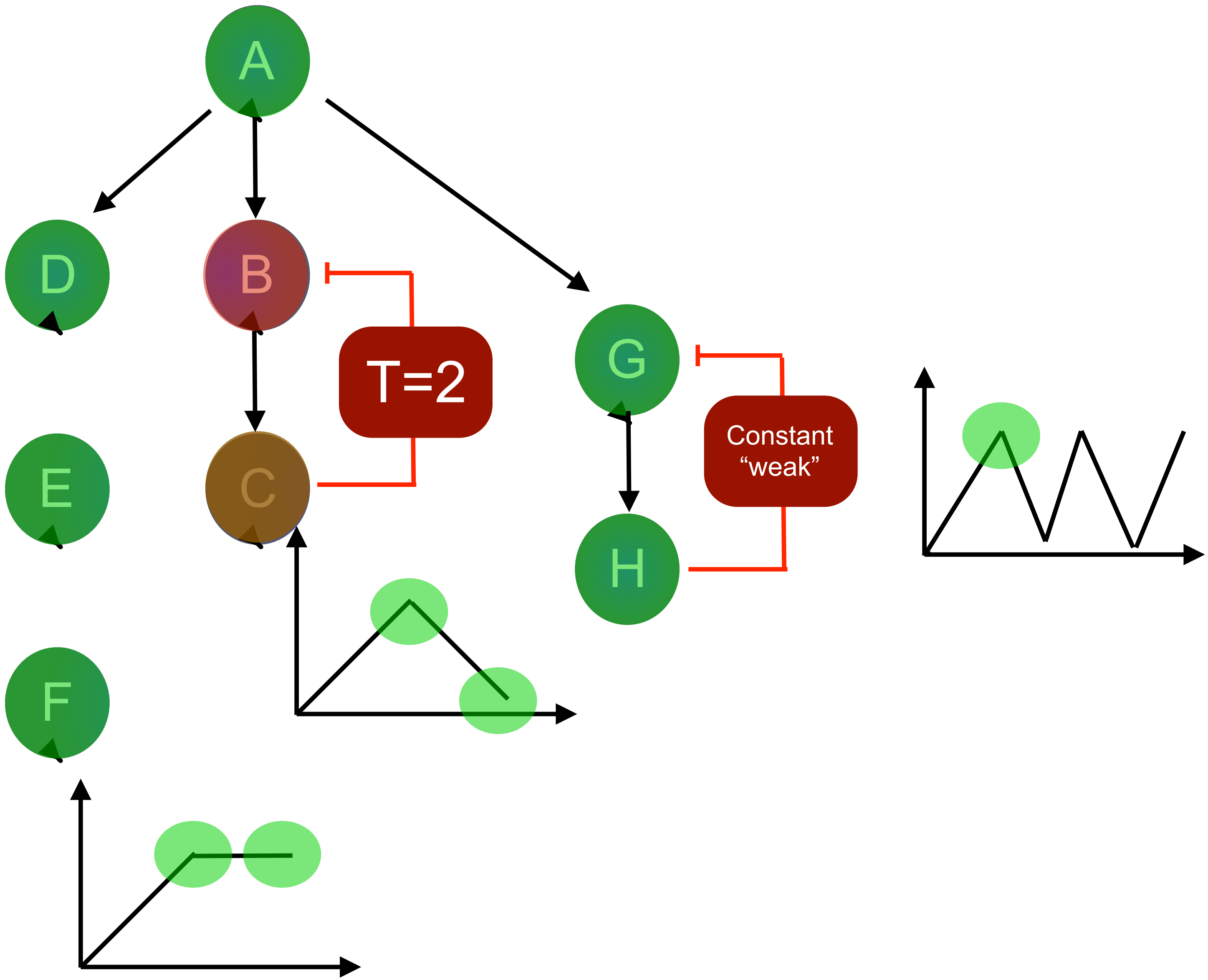

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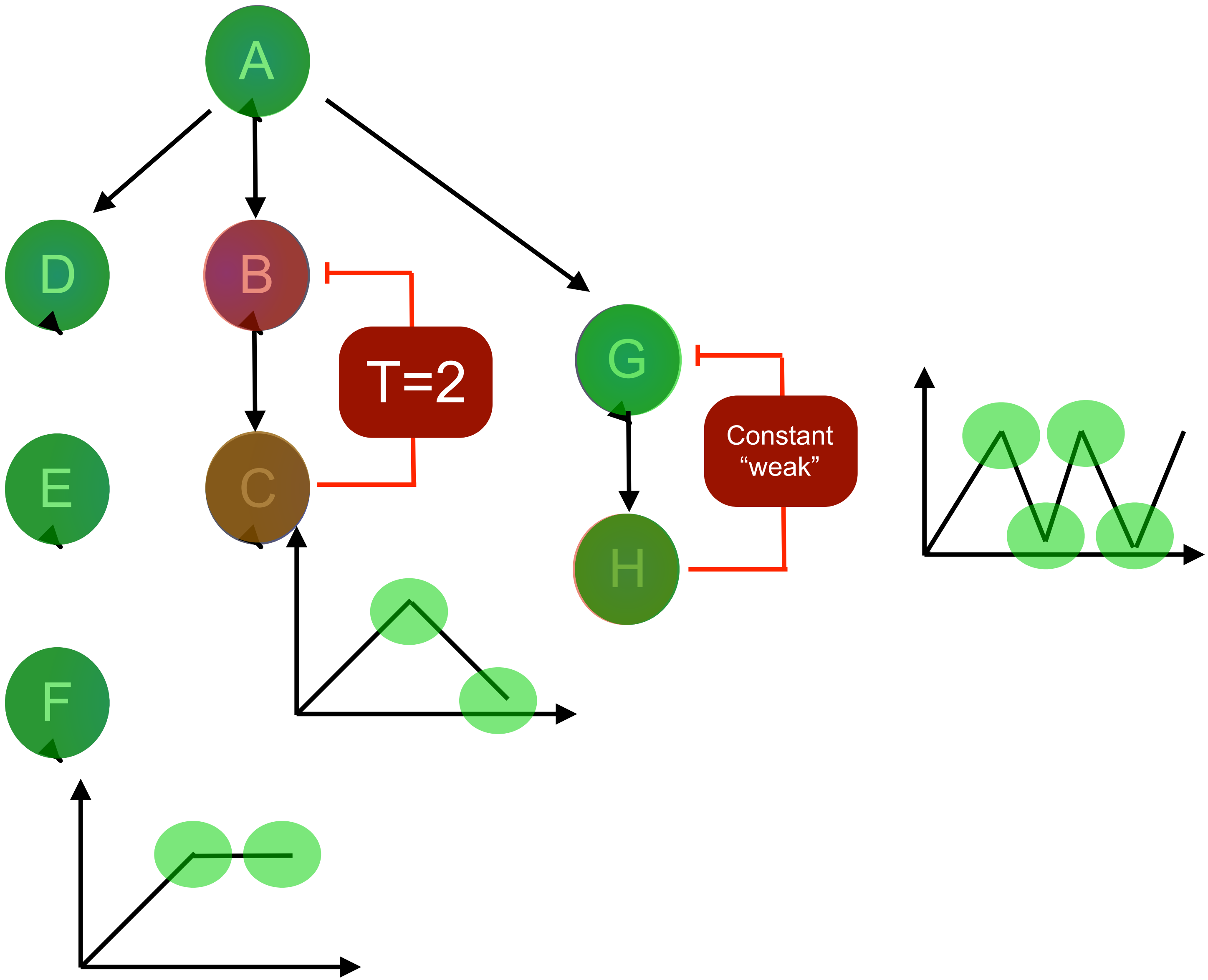

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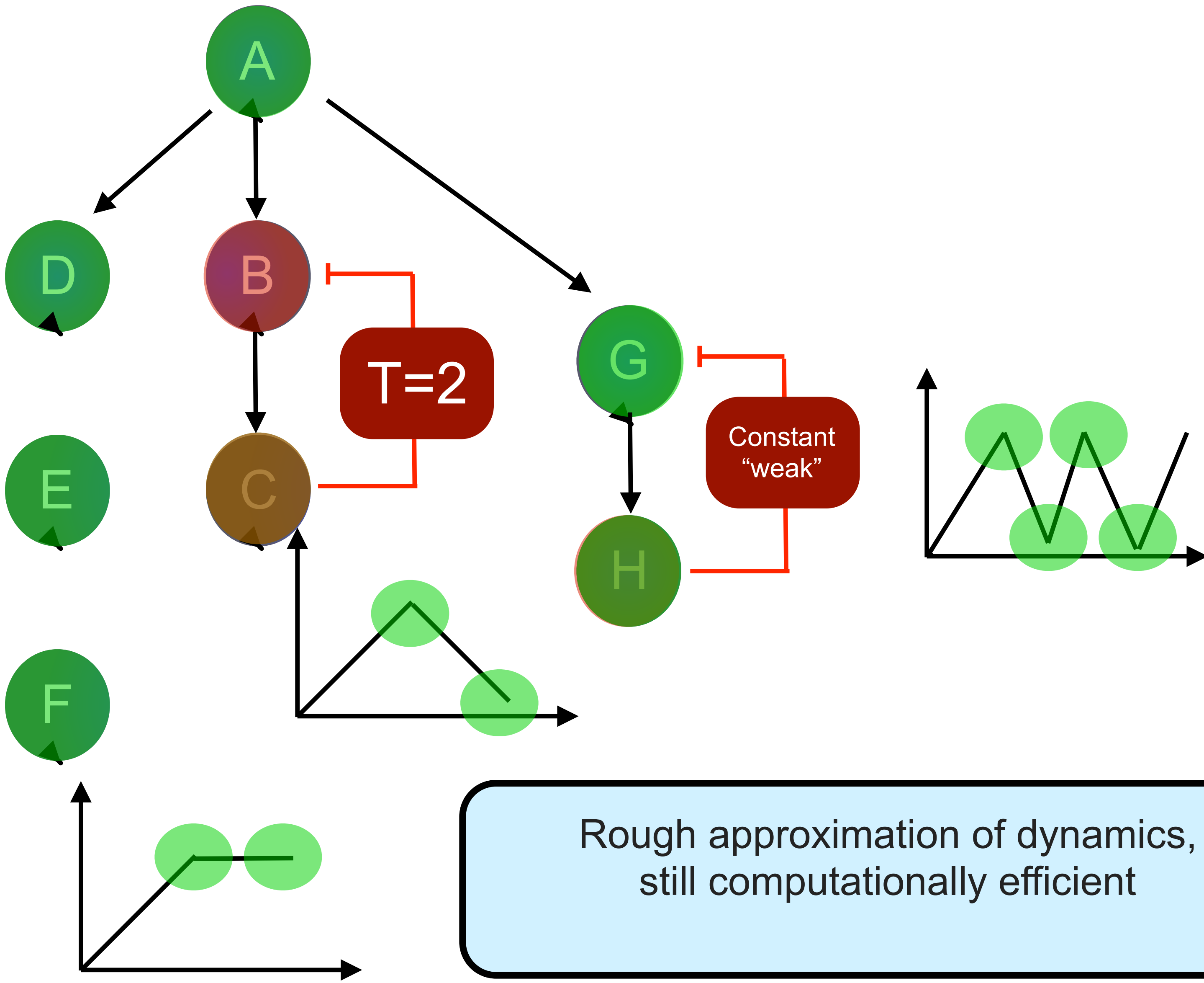

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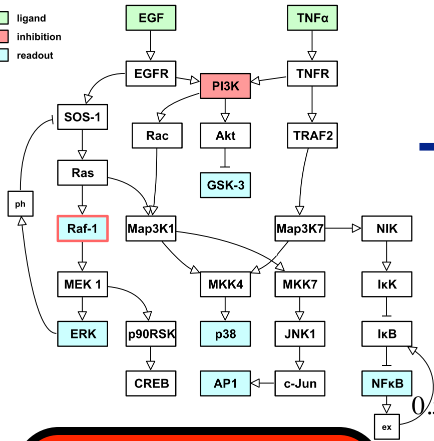

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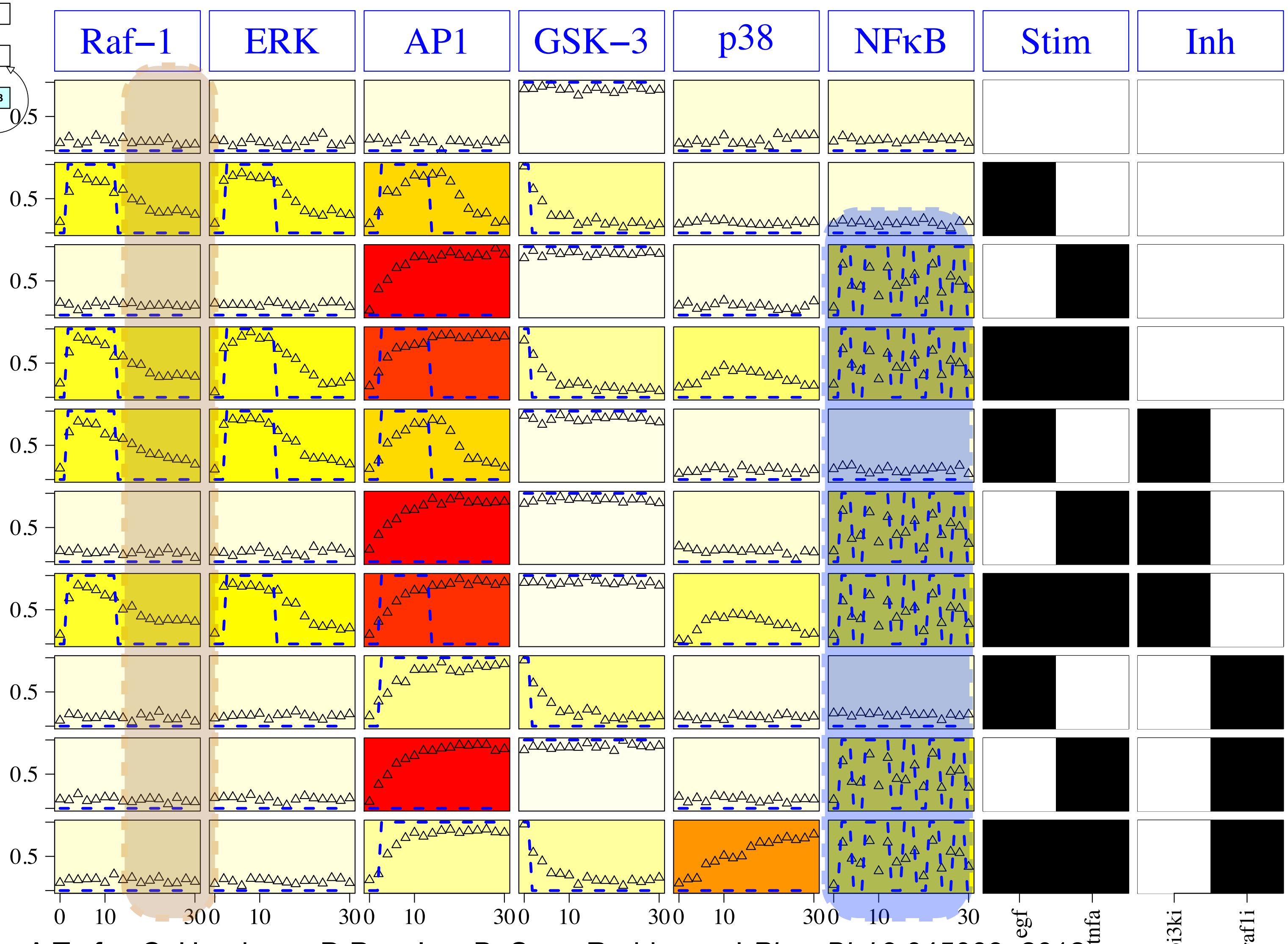
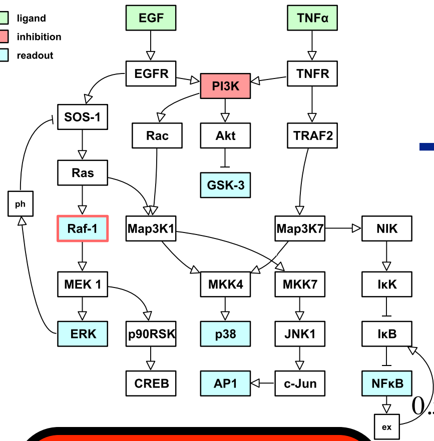


MacNamara A Terfve C Henriques D Penalver B Saez-Rodriguez J *Phys Biol* 9 045003, 2012

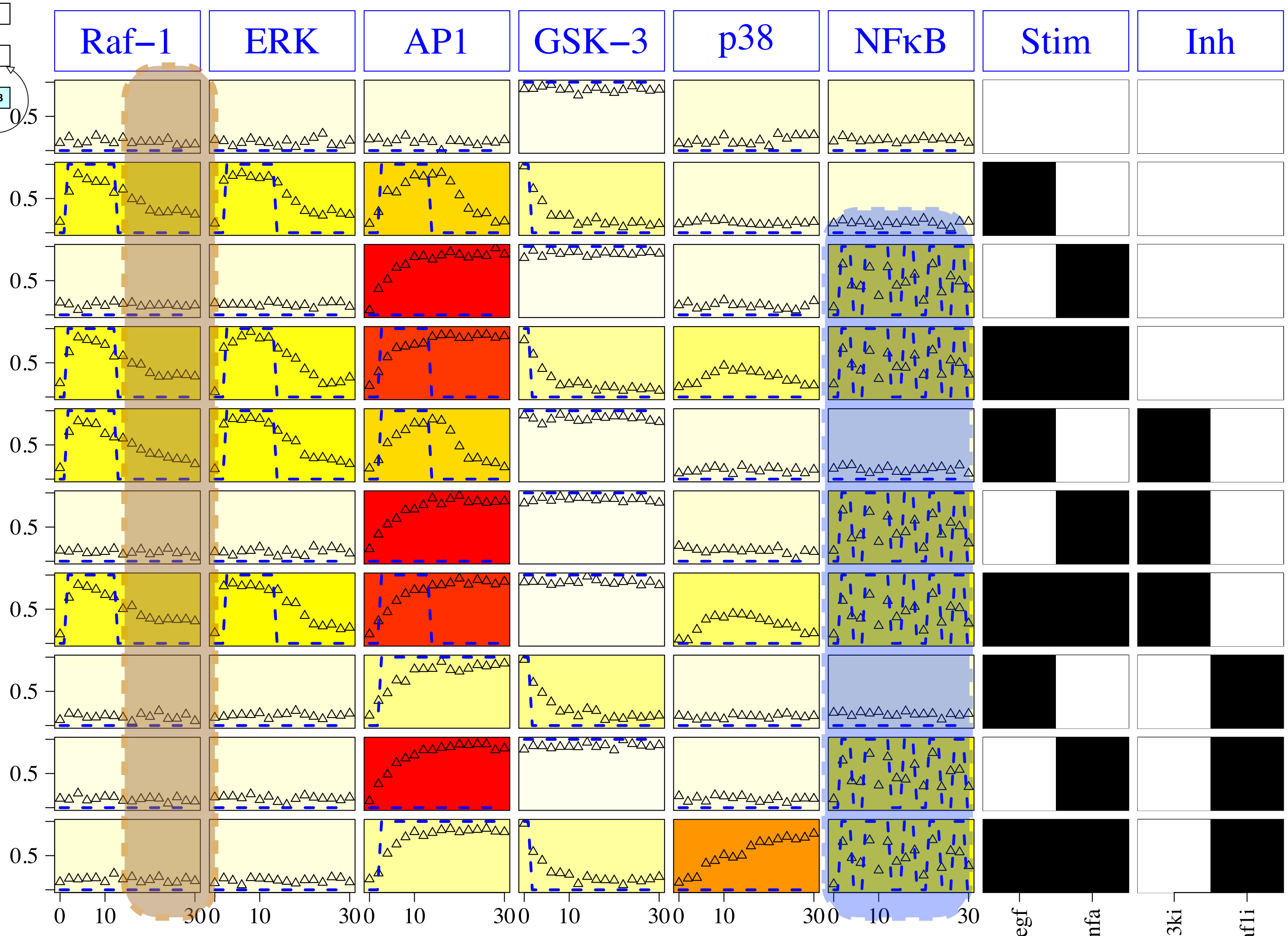
Synchronous simulation captures oscillatory behaviour



Can not explain data due to missing links

Identifies strong active links

Captures strong feedbacks



MacNamara A Terfve C Henriques D Penalver B Saez-Rodriguez J *Phys Biol* 9 045003, 2012

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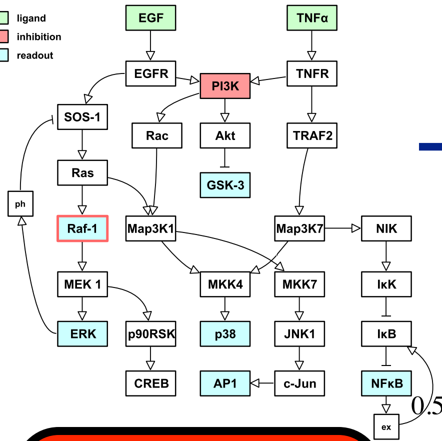

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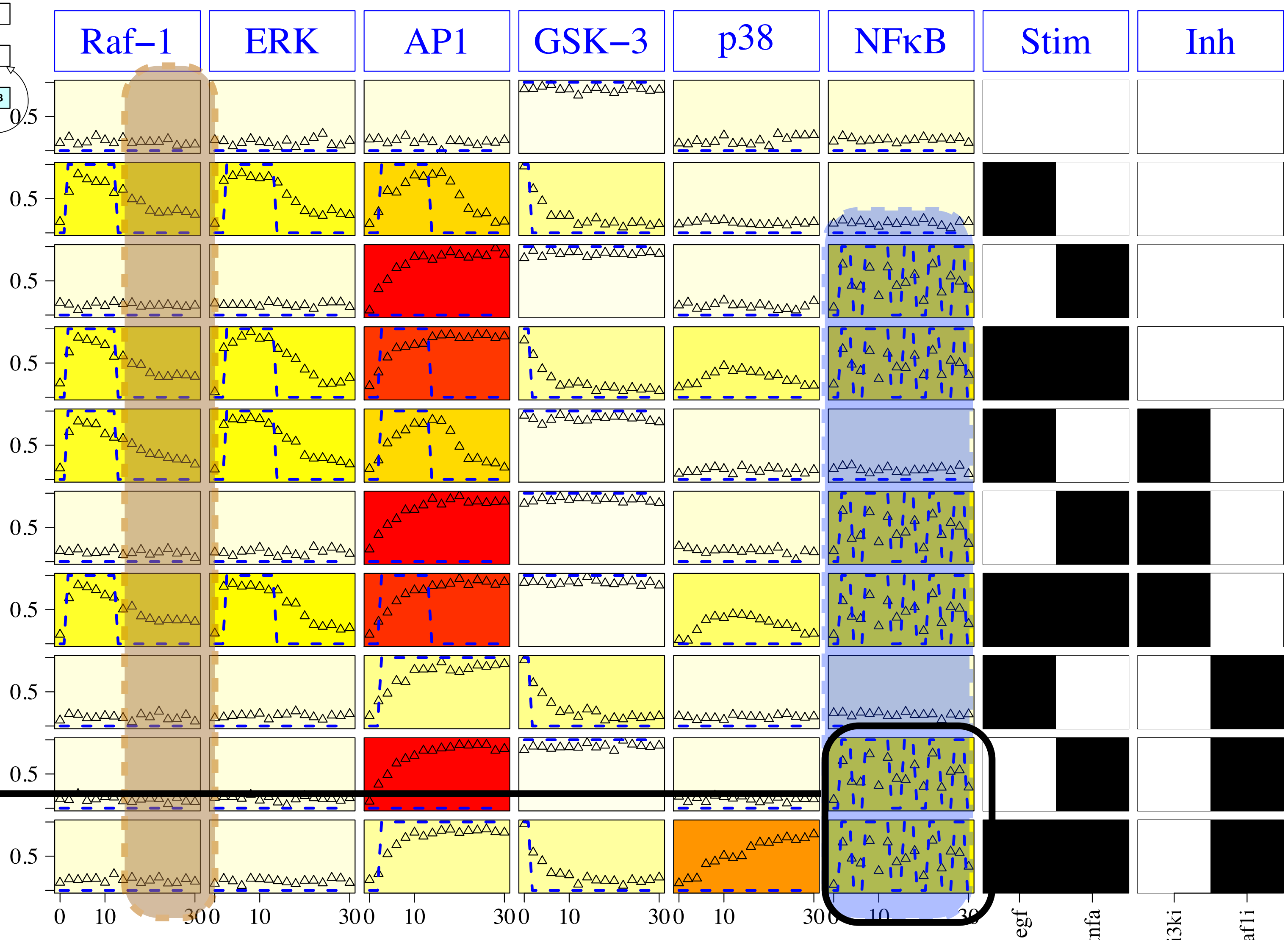
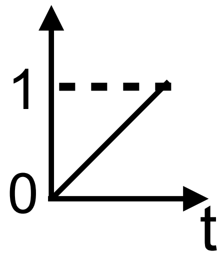
Captures 'weak' feedbacks



MacNamara A Terfve C Henriques D Penalver B Saez-Rodriguez J *Phys Biol* 9 045003, 2012

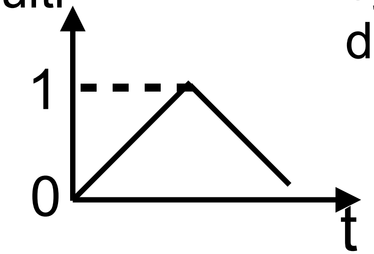
From Boolean to continuous and dynamic models within CellNOpt

Boolean (binary) logic steady state

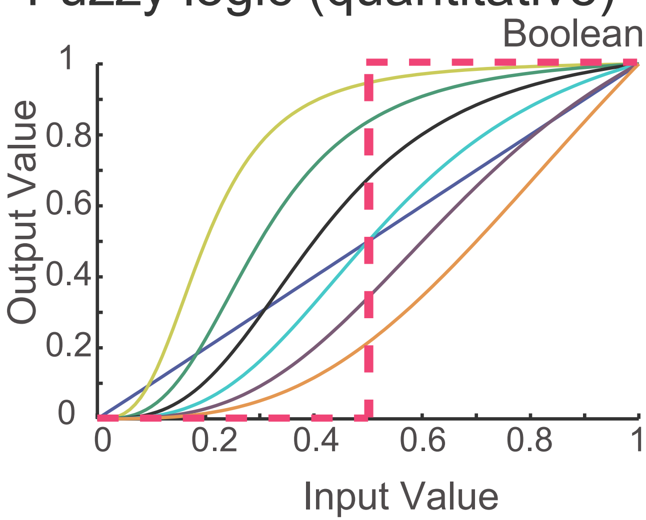


Boolean multi time-scale

sync. dynamics



Fuzzy logic (quantitative)



Morris et al., PloS Comp Bio 2011

From Boolean to continuous and dynamic models within CellNOpt

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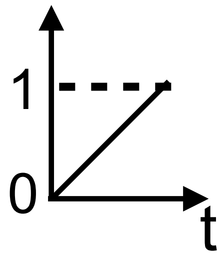
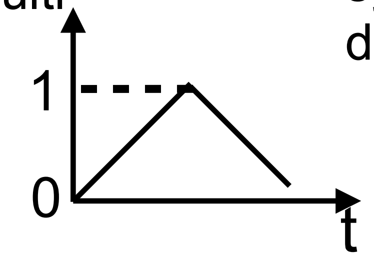


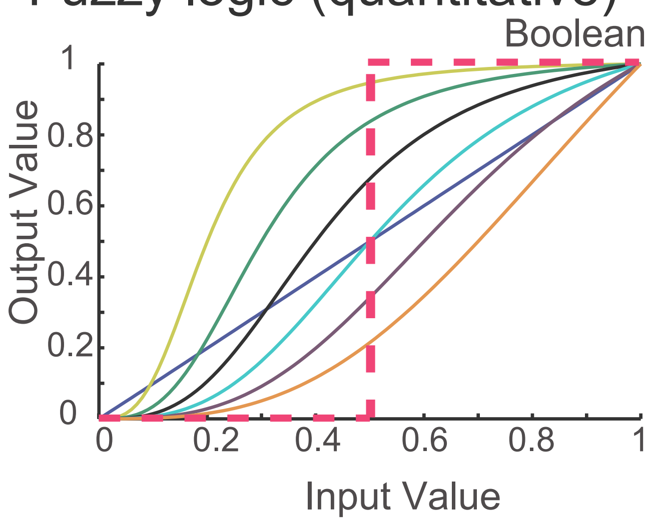
Boolean multi time-scale sync. dynamics



Camille Terfve

Aidan MacNamara

Fuzzy logic (quantitative)



Morris et al., PloS Comp Bio 2011

Logic-based ODEs

- Convert Boolean update function *Bi* into a *continuous homologue* $\overline{Bi}$ using multivariate polynomial interpolation
  - **Accuracy** (same behavior as *Bi* for 0/1 → same monotony & steady state behavior)
  - Good **analytical** properties (smoothness)
  - **Minimal** and **unique**
- Make non linear replacing variable with Hill function

$$\mathrm{f}(\overline{x_i}) = \frac{\overline{x_i}^n}{(\overline{x_i}^n + k^n)}$$

- Transform into differential equation

$$\overline{x}_i(t+1) = \overline{B}_i(\overline{x}_{i1}(t), \overline{x}_{i2}(t), \ldots, \overline{x}_{iN_i}(t)) \rightarrow \dot{\overline{x}}_i = \frac{1}{\tau_i} \cdot (\overline{B}_i(\overline{x}_{i1}, \overline{x}_{i2}, \ldots, \overline{x}_{iN}) - \overline{x}_i)$$

- E.g. a AND b inactivate C

$$\frac{d}{dt}c = \frac{1}{\tau}\left(\frac{a^{n_a} * (1+k_a{}^{n_a}) * (1-b^{n_b}) * (1+k_b{}^{n_b})}{(a^{n_a}+k_a{}^{n_a}) * (b^{n_b}+k_b{}^{n_b})} + \frac{(1-a^{n_a}) * (1+k_a{}^{n_a}) * b^{n_b} * (1+k_b{}^{n_b})}{(a^{n_a}+k_a{}^{n_a}) * (b^{n_b}+k_b{}^{n_b})} + \frac{a^{n_a} * (1+k_a{}^{n_a}) * b^{n_b} * (1+k_b{}^{n_b})}{(a^{n_a}+k_a{}^{n_a}) * (b^{n_b}+k_b{}^{n_b})} - c\right)$$

Wittman D, Krumsiek J, Saez-Rodriguez J, Lauffenburger DA, Klamt S, Theis FJ, *BMC Sys Bio* 2009

Logic-based ODEs

- Convert Boolean update function *Bi* into a *continuous homologue* $\bar{B}_i$ using multivariate polynomial interpolation
  - **Accuracy** (same behavior as *Bi* for 0/1 → same monotony & steady state behavior)
  - Good **analytical** properties (smoothness)
  - **Minimal** and **unique**

IDEA:
ODE model
mathematically 'well-behaved'
that matches the Boolean model
when states are 0 or 1

- Make non linear replacing variable with Hill function

$$f(\bar{x}_i) = \frac{\bar{x}_i^{\,n}}{(\bar{x}_i^{\,n} + k^n)}$$

- Transform into differential equation

$$\bar{x}_i(t+1) = \bar{B}_i(\bar{x}_{i1}(t), \bar{x}_{i2}(t), \ldots, \bar{x}_{iN}(t))$$

$$\dot{\bar{x}}_i = \frac{1}{\tau_i}\left(\bar{B}_i(\bar{x}_{i1}, \bar{x}_{i2}, \ldots, \bar{x}_{iN}) - \bar{x}_i\right)$$

- E.g. a AND b inactivate C

$$\frac{d}{dt}c = \frac{1}{\tau}\left(\frac{a^{n_a} * (1+k_a^{\,n_a}) * (1-b^{n_b}) * (1+k_b^{\,n_b})}{(a^{n_a}+k_a^{\,n_a}) * (b^{n_b}+k_b^{\,n_b})} + \frac{(1-a^{n_a}) * (1+k_a^{\,n_a}) * b^{n_b} * (1+k_b^{\,n_b})}{(a^{n_a}+k_a^{\,n_a}) * (b^{n_b}+k_b^{\,n_b})} + \frac{a^{n_a} * (1+k_a^{\,n_a}) * b^{n_b} * (1+k_b^{\,n_b})}{(a^{n_a}+k_a^{\,n_a}) * (b^{n_b}+k_b^{\,n_b})} - c\right)$$

Wittman D, Krumsiek J, Saez-Rodriguez J, Lauffenburger DA, Klamt S, Theis FJ, *BMC Sys Bio* 2009

ODEs can be automatically generated from Boolean model (Odefy)

d/dt(tnfa) = 0*(1-tnfa_inh) **%Note that this implies a continuous stimulus**

d/dt(tgfa) = 0*(1-tgfa_inh) **% Note that this implies a continuous stimulus**

d/dt(raf) = ((egfr^raf_n_egfr/(egfr^raf_n_egfr+raf_k_egfr^raf_n_egfr)*(1+raf_k_egfr^raf_n_egfr)-raf) * raf_tauinv)*(1-raf_inh)

d/dt(pi3k) = ((egfr^pi3k_n_egfr/(egfr^pi3k_n_egfr+pi3k_k_egfr^pi3k_n_egfr)*(1+pi3k_k_egfr^pi3k_n_egfr)-pi3k) * pi3k_tauinv)*(1-pi3k_inh)

d/dt(ikb) = ((tnfa^ikb_n_tnfa/(tnfa^ikb_n_tnfa+ikb_k_tnfa^ikb_n_tnfa)*(1+ikb_k_tnfa^ikb_n_tnfa)*(1-pi3k^ikb_n_pi3k/(pi3k^ikb_n_pi3k+ikb_k_pi3k^ikb_n_pi3k)*(1+ikb_k_pi3k^ikb_n_pi3k))+(1-tnfa^ikb_n_tnfa/(tnfa^ikb_n_tnfa+ikb_k_tnfa^ikb_n_tnfa)*(1+ikb_k_tnfa^ikb_n_tnfa))*pi3k^ikb_n_pi3k/(pi3k^ikb_n_pi3k+ikb_k_pi3k^ikb_n_pi3k)*(1+ikb_k_pi3k^ikb_n_pi3k)+tnfa^ikb_n_tnfa/(tnfa^ikb_n_tnfa+ikb_k_tnfa^ikb_n_tnfa)*(1+ikb_k_tnfa^ikb_n_tnfa)*pi3k^ikb_n_pi3k/(pi3k^ikb_n_pi3k+ikb_k_pi3k^ikb_n_pi3k)*(1+ikb_k_pi3k^ikb_n_pi3k)-ikb) * ikb_tauinv)*(1-ikb_inh)

d/dt(gsk3) = (((1-akt^gsk3_n_akt/(akt^gsk3_n_akt+gsk3_k_akt^gsk3_n_akt)*(1+gsk3_k_akt^gsk3_n_akt))-gsk3) * gsk3_tauinv)*(1-gsk3_inh)

d/dt(erk12) = (((1-raf^erk12_n_raf/(raf^erk12_n_raf+erk12_k_raf^erk12_n_raf)*(1+erk12_k_raf^erk12_n_raf))*(1-ikb^erk12_n_ikb/(ikb^erk12_n_ikb+erk12_k_ikb^erk12_n_ikb)*(1+erk12_k_ikb^erk12_n_ikb))+raf^erk12_n_raf/(raf^erk12_n_raf+erk12_k_raf^erk12_n_raf)*(1+erk12_k_raf^erk12_n_raf)*(1-ikb^erk12_n_ikb/(ikb^erk12_n_ikb+erk12_k_ikb^erk12_n_ikb)*(1+erk12_k_ikb^erk12_n_ikb))+raf^erk12_n_raf/(raf^erk12_n_raf+erk12_k_raf^erk12_n_raf)*(1+erk12_k_raf^erk12_n_raf)*ikb^erk12_n_ikb/(ikb^erk12_n_ikb+erk12_k_ikb^erk12_n_ikb)*(1+erk12_k_ikb^erk12_n_ikb)-erk12) * erk12_tauinv)*(1-erk12_inh)

d/dt(egfr) = ((tgfa^egfr_n_tgfa/(tgfa^egfr_n_tgfa+egfr_k_tgfa^egfr_n_tgfa)*(1+egfr_k_tgfa^egfr_n_tgfa)-egfr) * egfr_tauinv)*(1-egfr_inh)

d/dt(casp8) = ((tnfa^casp8_n_tnfa/(tnfa^casp8_n_tnfa+casp8_k_tnfa^casp8_n_tnfa)*(1+casp8_k_tnfa^casp8_n_tnfa)-casp8) * casp8_tauinv)*(1-casp8_inh)

d/dt(akt) = ((pi3k^akt_n_pi3k/(pi3k^akt_n_pi3k+akt_k_pi3k^akt_n_pi3k)*(1+akt_k_pi3k^akt_n_pi3k)-akt) * akt_tauinv)*(1-akt_inh)

ODEs can be automatically generated from Boolean model (Odefy)

d/dt(tnfa) = 0*(1-tnfa_inh) **%Note that this implies a continuous stimulus**

d/dt(tgfa) = 0*(

d/dt(raf) = ((eg _inh)

d/dt(pi3k) = ((e _tauinv)*
(1-pi3k_inh)

d/dt(ikb) = ((tn
(pi3k^ikb_n_pi
+ikb_k_tnfa^ik
(1+ikb_k_pi3k
*pi3k^ikb_n_p

d/dt(gsk3) = ((
gsk3_tauinv)*(

d/dt(erk12) = (
ikb^erk12_n_i
(raf^erk12_n_
+erk12_k_ikb^ af)*
(1+erk12_k_ra _ikb)-
erk12) * erk12

Even if structure is known need to identify parameters, difficult optimisation problem (similar to biochemical ODEs)

$$\frac{d}{dt}c = \frac{1}{\tau}\left(\frac{a^{n_a} * (1 + k_a{}^{n_a}) * (1 - b^{n_b}) * (1 + k_b{}^{n_b})}{(a^{n_a} + k_a{}^{n_a}) * (b^{n_b} + k_b{}^{n_b})} + \frac{(1 - a^{n_a}) * (1 + k_a{}^{n_a}) * b^{n_b} * (1 + k_b{}^{n_b})}{(a^{n_a} + k_a{}^{n_a}) * (b^{n_b} + k_b{}^{n_b})} + \frac{a^{n_a} * (1 + k_a{}^{n_a}) * b^{n_b} * (1 + k_b{}^{n_b})}{(a^{n_a} + k_a{}^{n_a}) * (b^{n_b} + k_b{}^{n_b})} - c\right)$$

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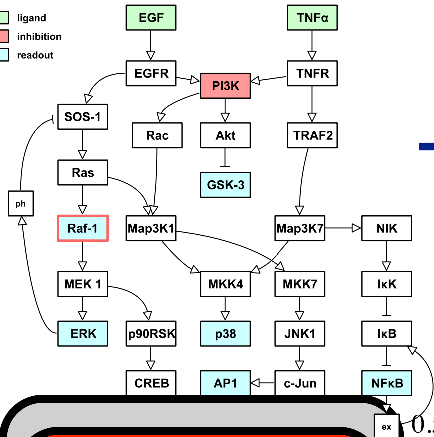
d/dt(casp8) = ((tnfa^casp8_n_tnfa/(tnfa^casp8_n_tnfa+casp8_k_tnfa^casp8_n_tnfa)*(1+casp8_k_tnfa^casp8_n_tnfa)-casp8) * casp8_tauinv)*(1-casp8_inh)

d/dt(akt) = ((pi3k^akt_n_pi3k/(pi3k^akt_n_pi3k+akt_k_pi3k^akt_n_pi3k)*(1+akt_k_pi3k^akt_n_pi3k)-akt) * akt_tauinv)*(1-akt_inh)

Fit of ODE model



Can not explain data due to missing links

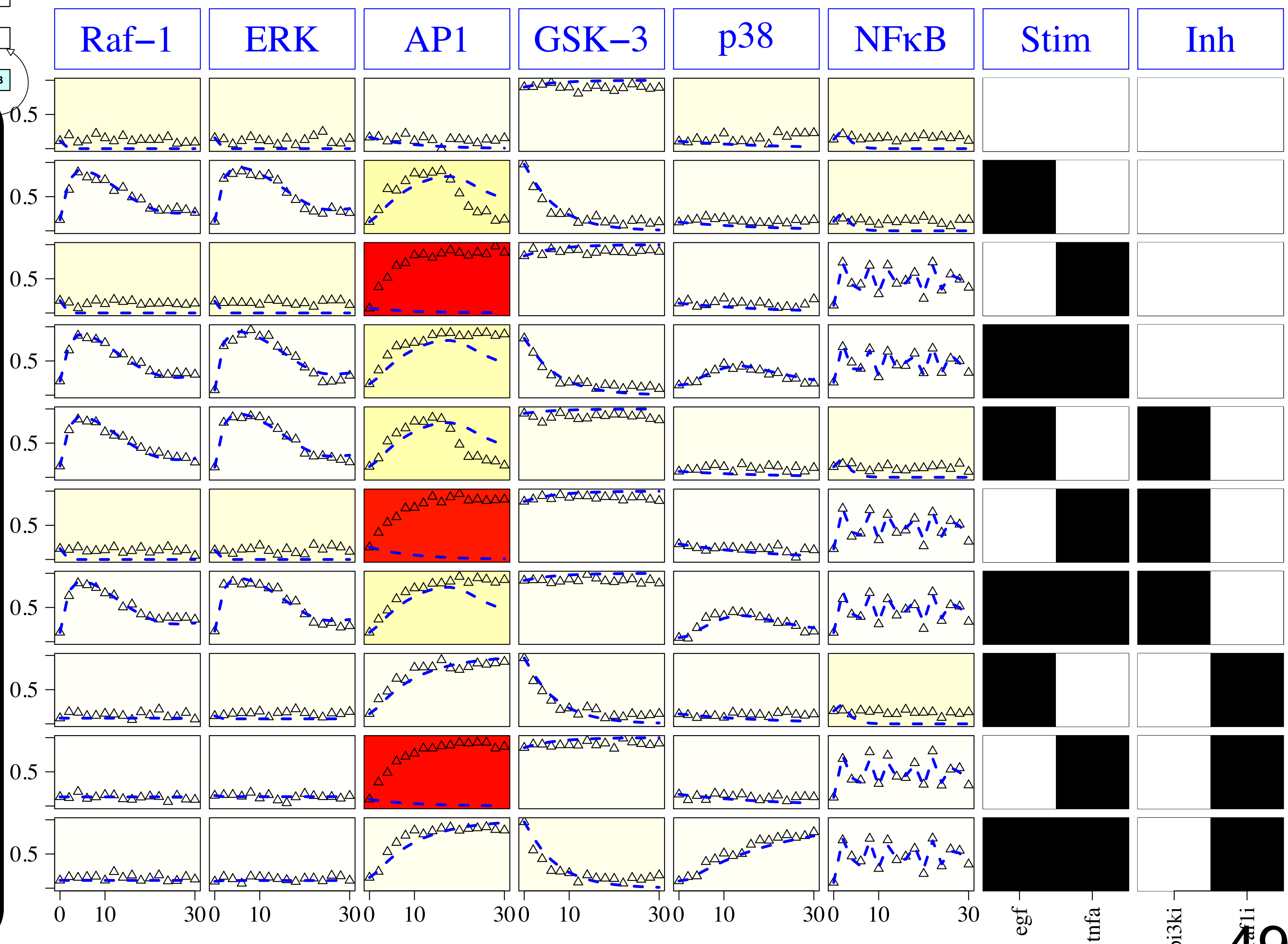
Identifies strong active links

Identifies weak active links

Captures strong feedbacks

Captures 'weak' feedbacks

ODE



Different methods capture different aspects

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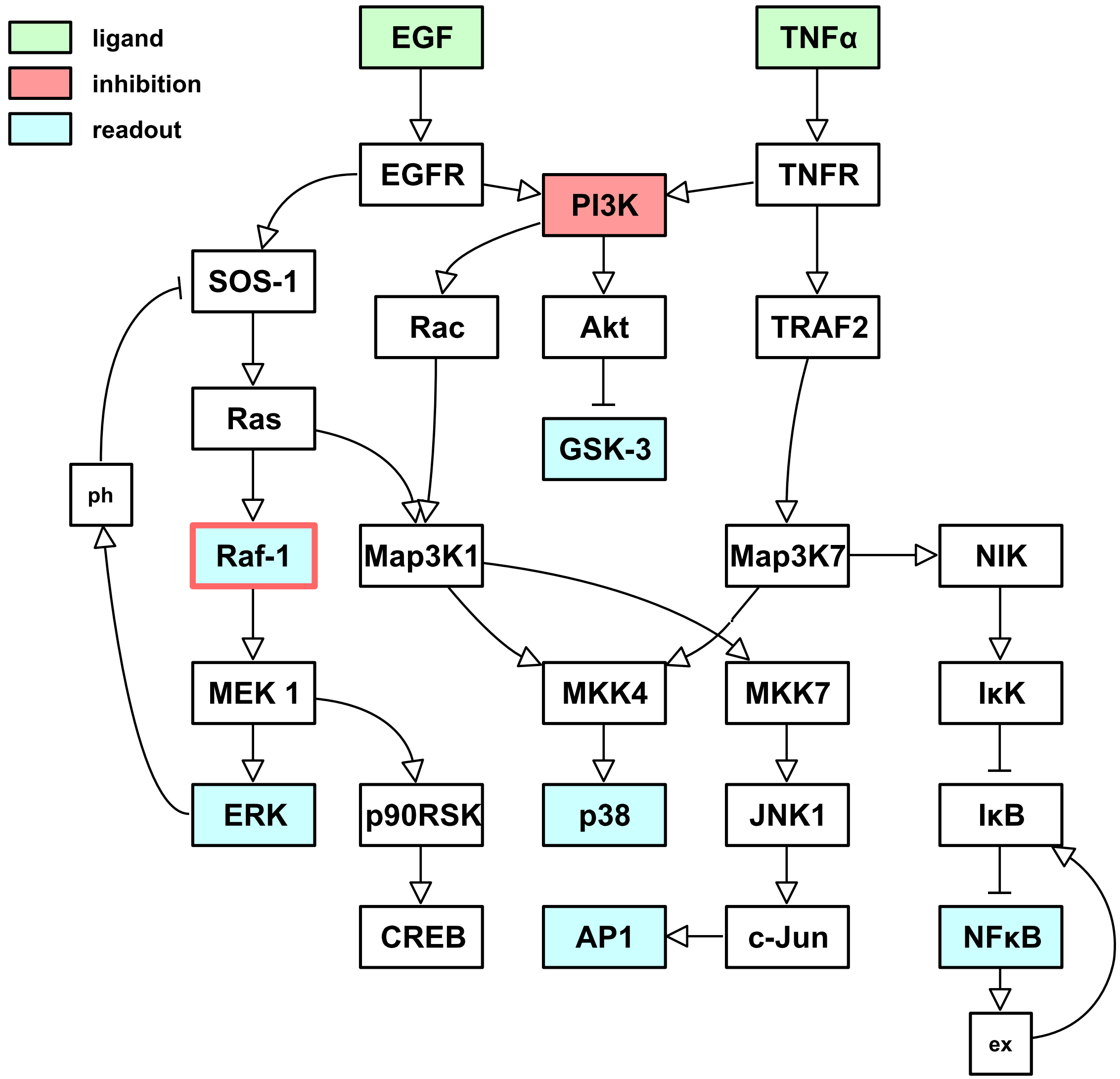

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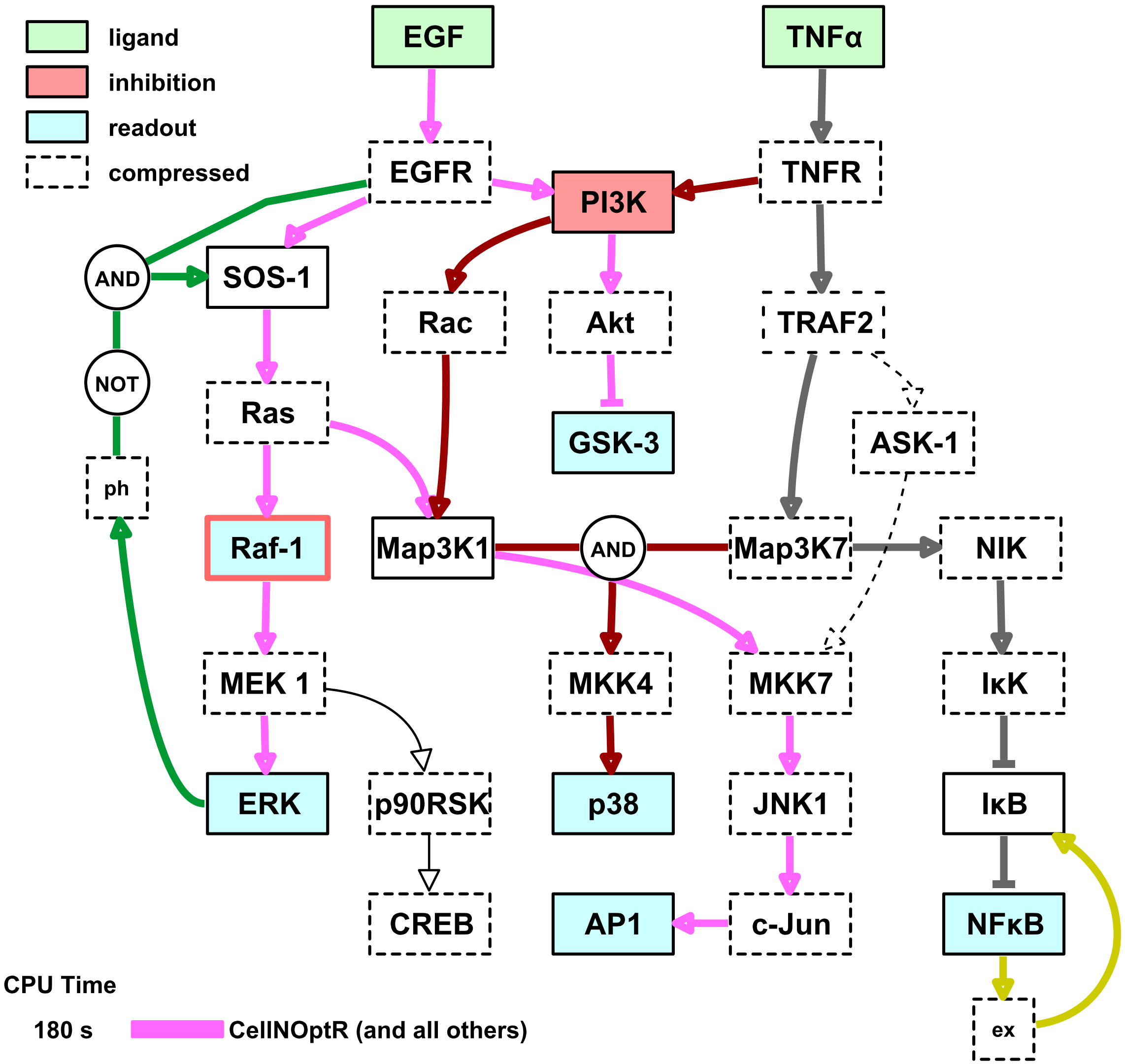
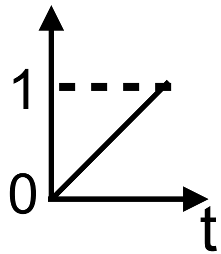


CPU Time

180 s	CellNOptR (and all others)
240 s	CellNOptR 2 steady state
1200 s	CNORcfl
2000 s	CNORdt
-	CNORdt & CNORcfl

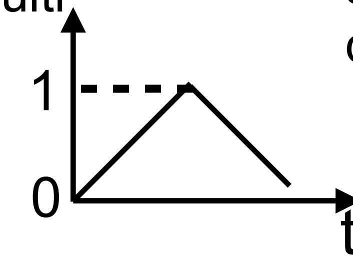
From Boolean to continuous and dynamic models within CellNOpt

Boolean (binary) logic steady state



Boolean multi time-scale

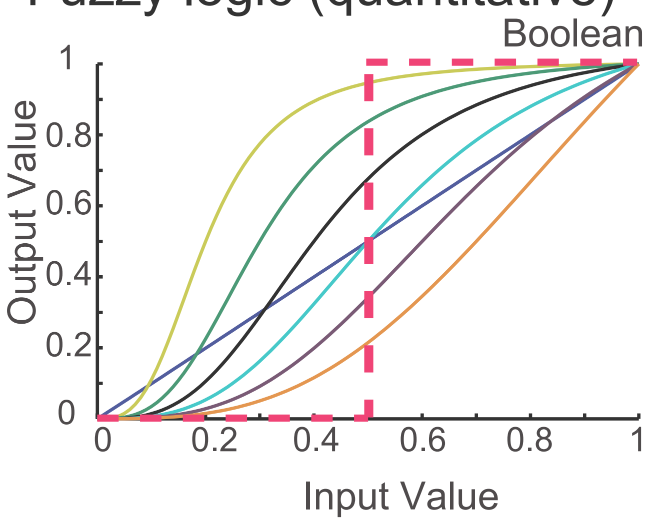
sync. dynamics



Camille Terfve

Aidan MacNamara

Fuzzy logic (quantitative)



Morris et al., PloS Comp Bio 2011

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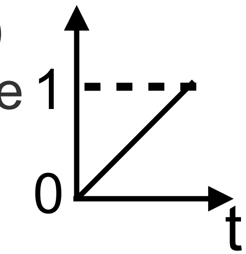

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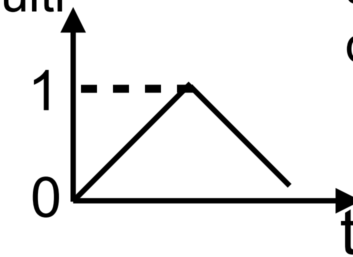

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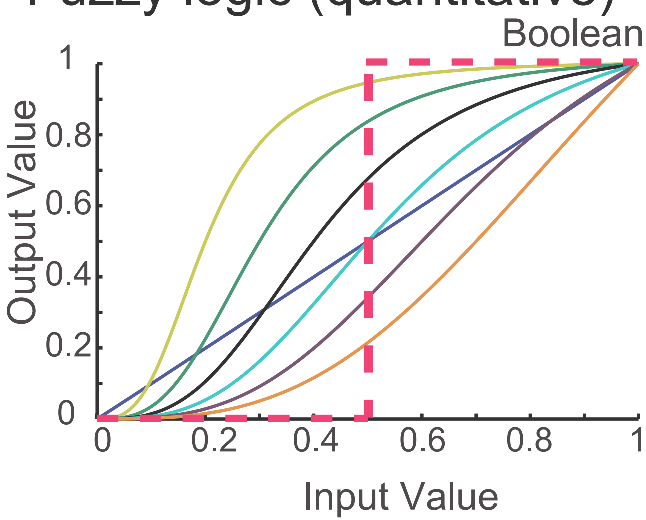
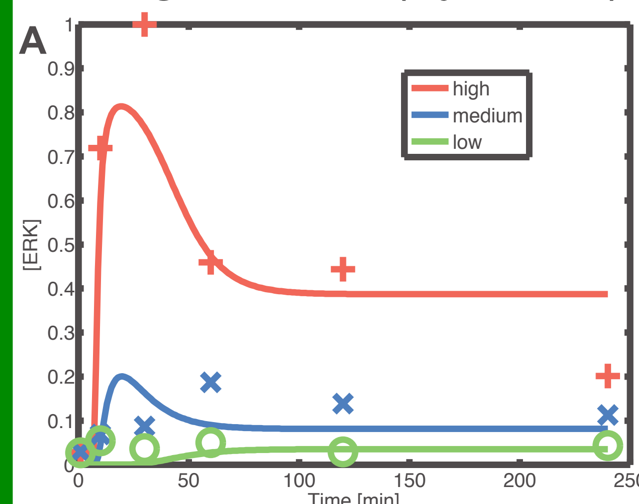


Morris et al., PloS Comp Bio 2011

Logic ODEs (dynamic)



MEIGO: Global optimization in R/Matlab Egea et al. BMC Bioinf 2014

Identify structure + parameters Henriques et al. Bioinformatics 2015

w. J Banga & J. Egea,

David Henriques

From Boolean to continuous and dynamic models within CellNOpt

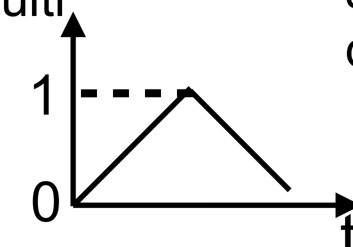
Boolean (bina
logic steady

+ detail

- scope

Boolean multi time-scale

sync. dynamics



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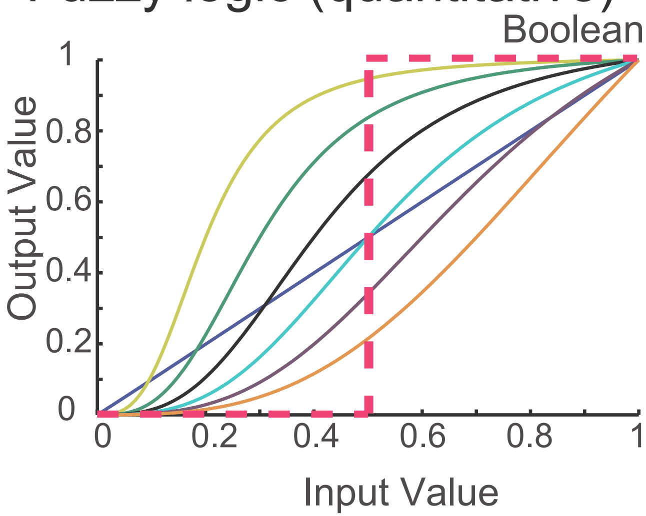
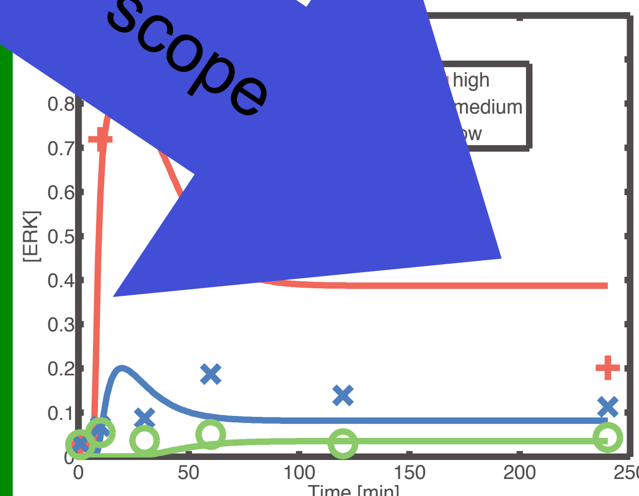


Morris et al., PloS Comp Bio 2011

ODE (dynamic)



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w. J Banga & J. Egea,

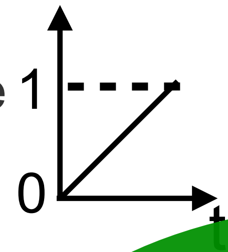
David Henriques

From Boolean to continuous and dynamic models within CellNOpt

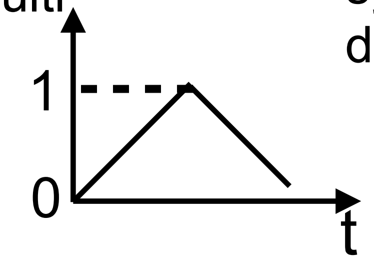
COMBINE

RWTH AACHEN

Boolean (binary) logic steady state



Boolean multi time-scale



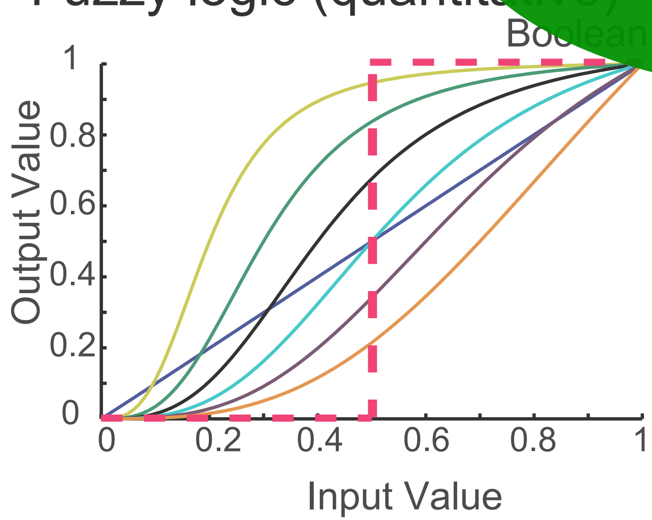
sync. dynamics

Camille Terfve

Aidan MacNamara

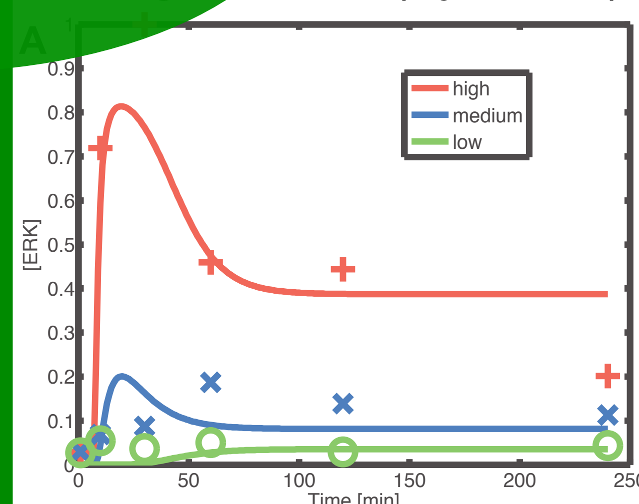
CellNOpt

Fuzzy logic (quantitative)



Morris et al., PloS Comp Bio 2011

Logic ODEs (dynamic)



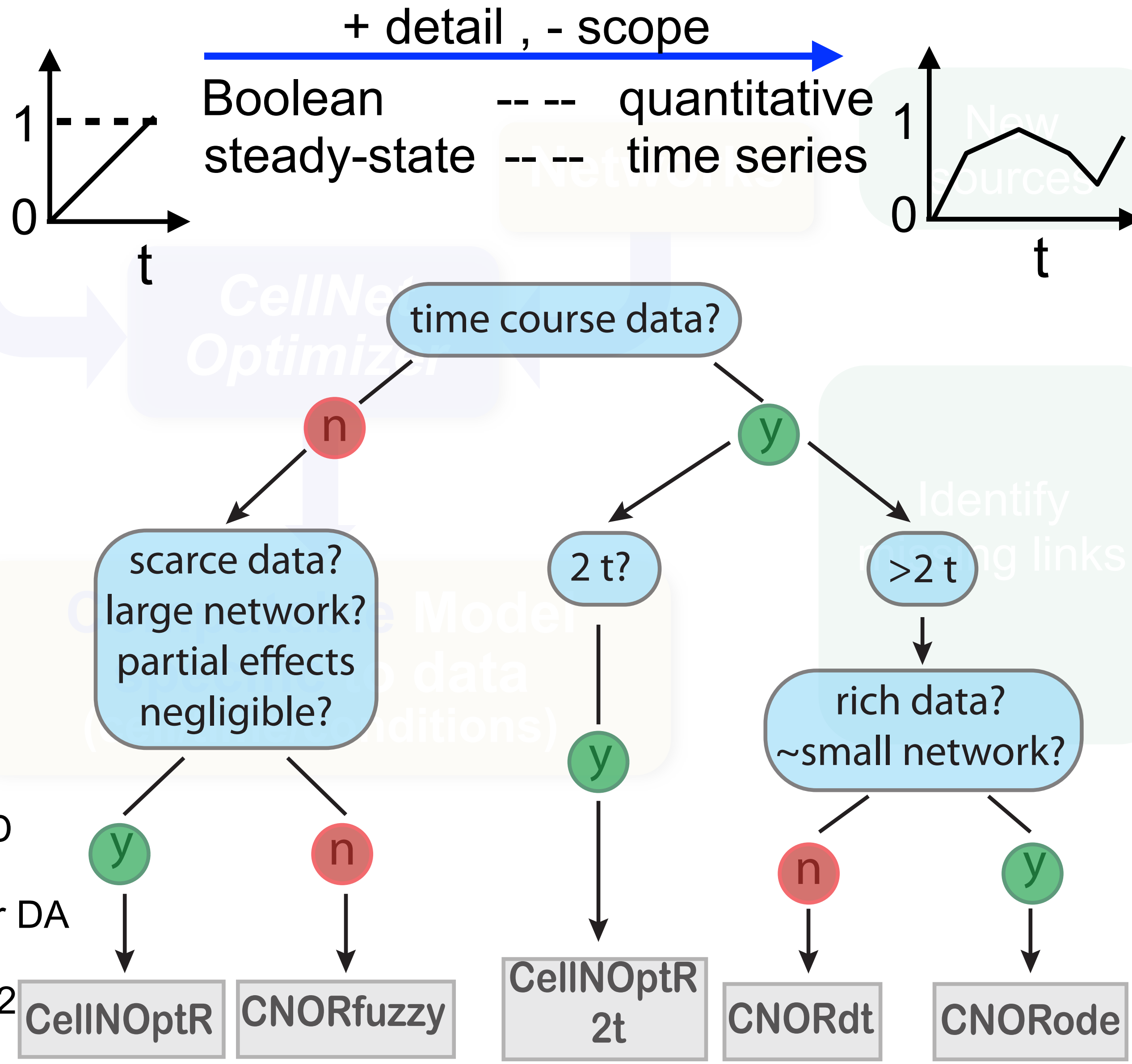
MEIGO: Global optimization in R/Matlab Egea et al. BMC Bioinf 2014

Identify structure + parameters Henriques et al. Bioinformatics 2015

w. J Banga & J. Egea,

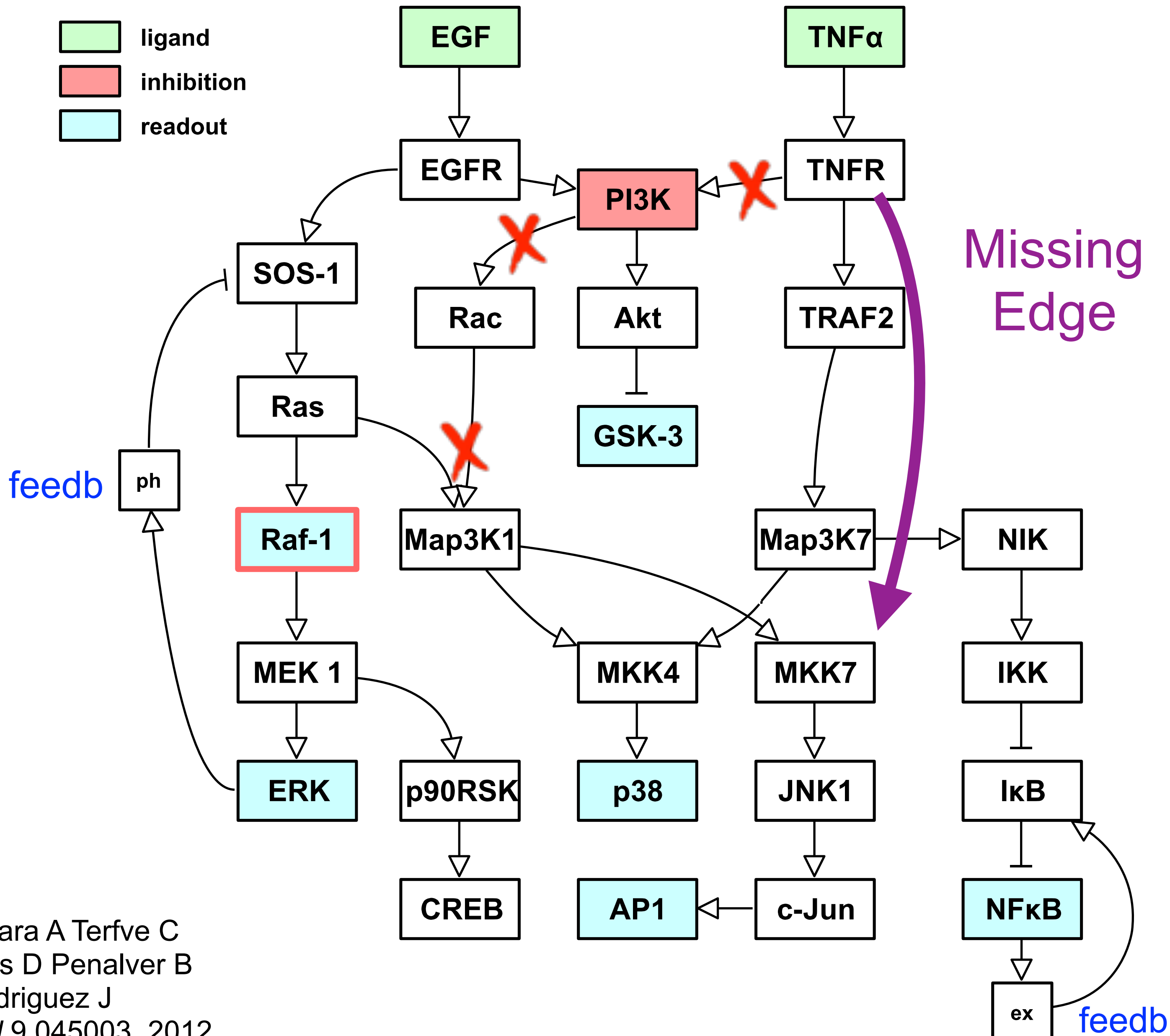
David Henriques

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

How to deal with incomplete prior knowledge?



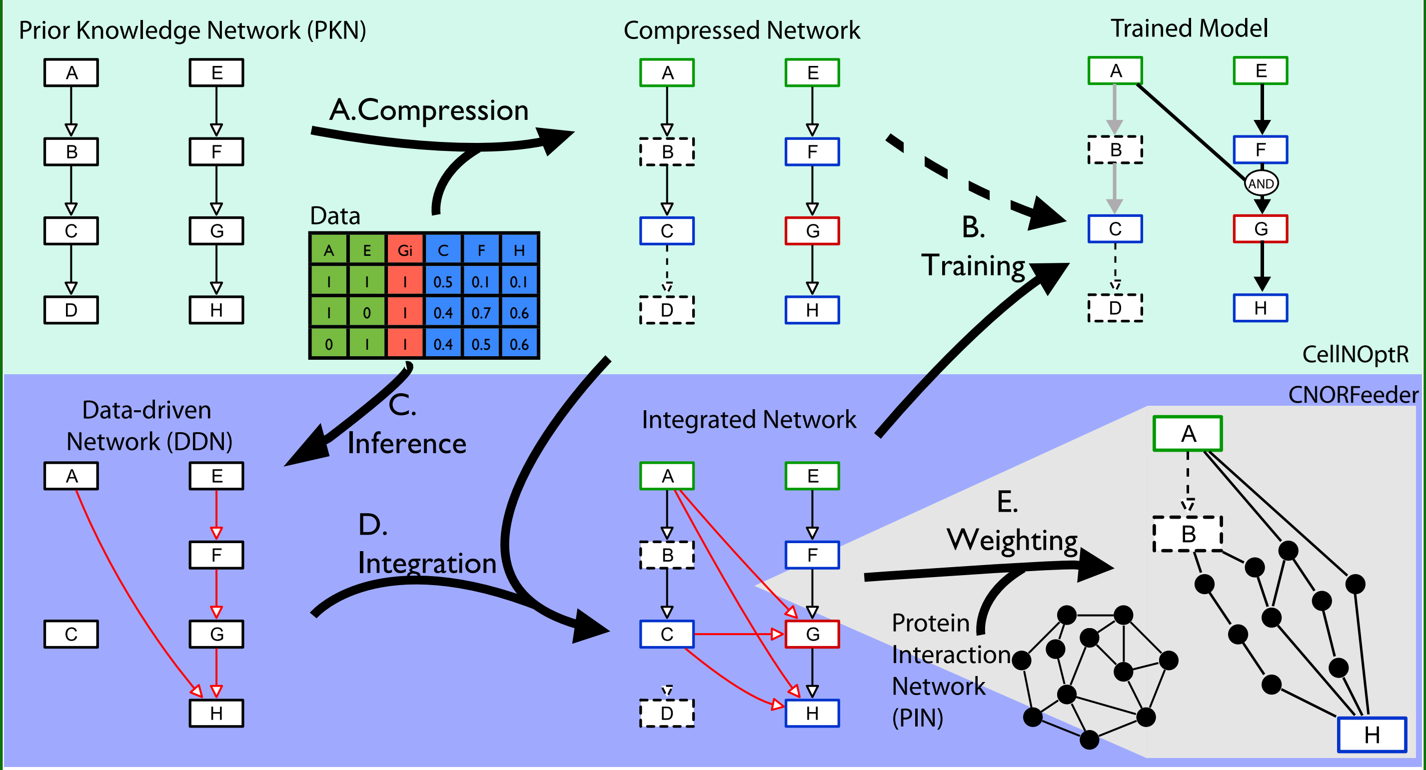
MacNamara A Terfve C
Henriques D Penalver B
Saez-Rodriguez J
Phys Biol 9 045003, 2012

How to deal with incomplete prior knowledge?

CNOFeed: Link CellNOpt to methods to infer new links

Federica Eduati

More types

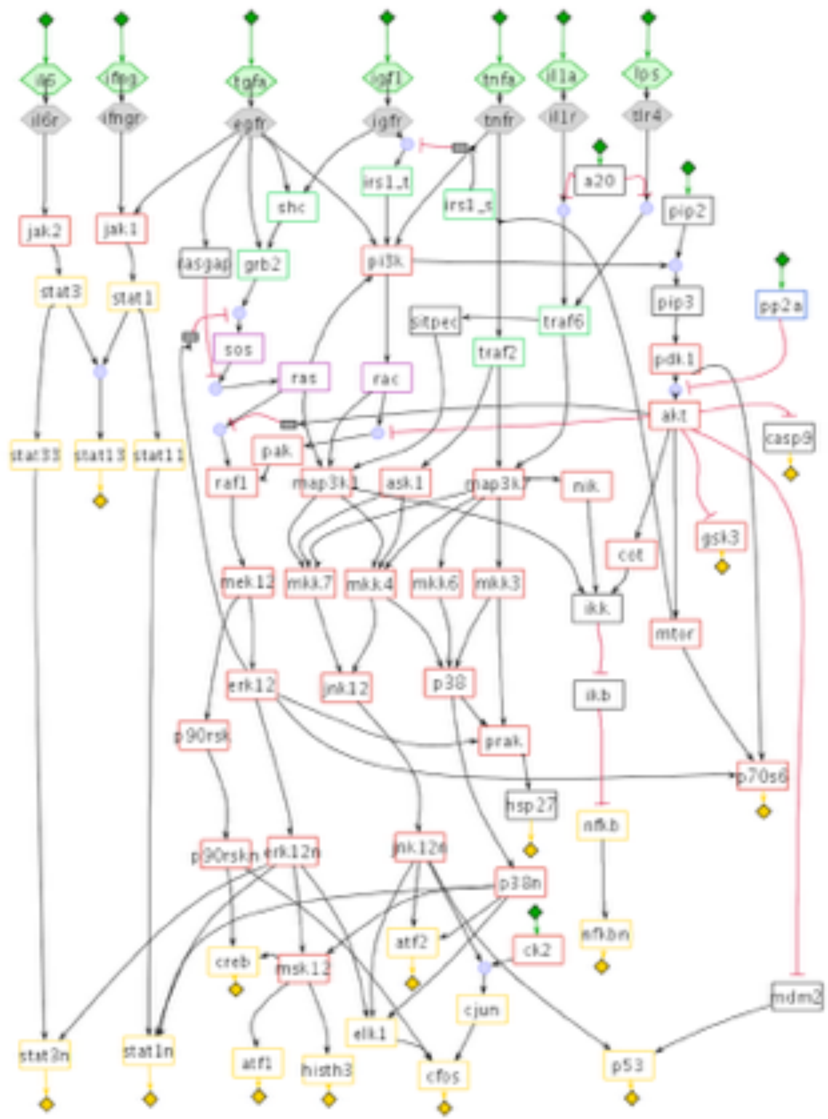


A	E	Gi	C	F	H
1	1	1	0.5	0.1	0.1
1	0	1	0.4	0.7	0.6
0	1	1	0.4	0.5	0.6

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

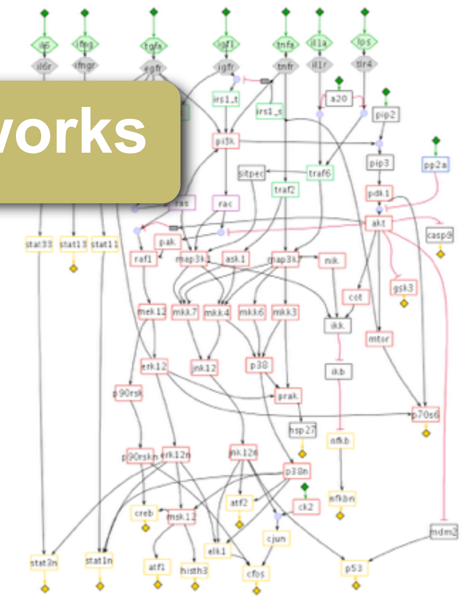
Logic modeling to link protein signaling networks with functional signaling data

Logic modeling to link protein signaling networks with functional signaling data

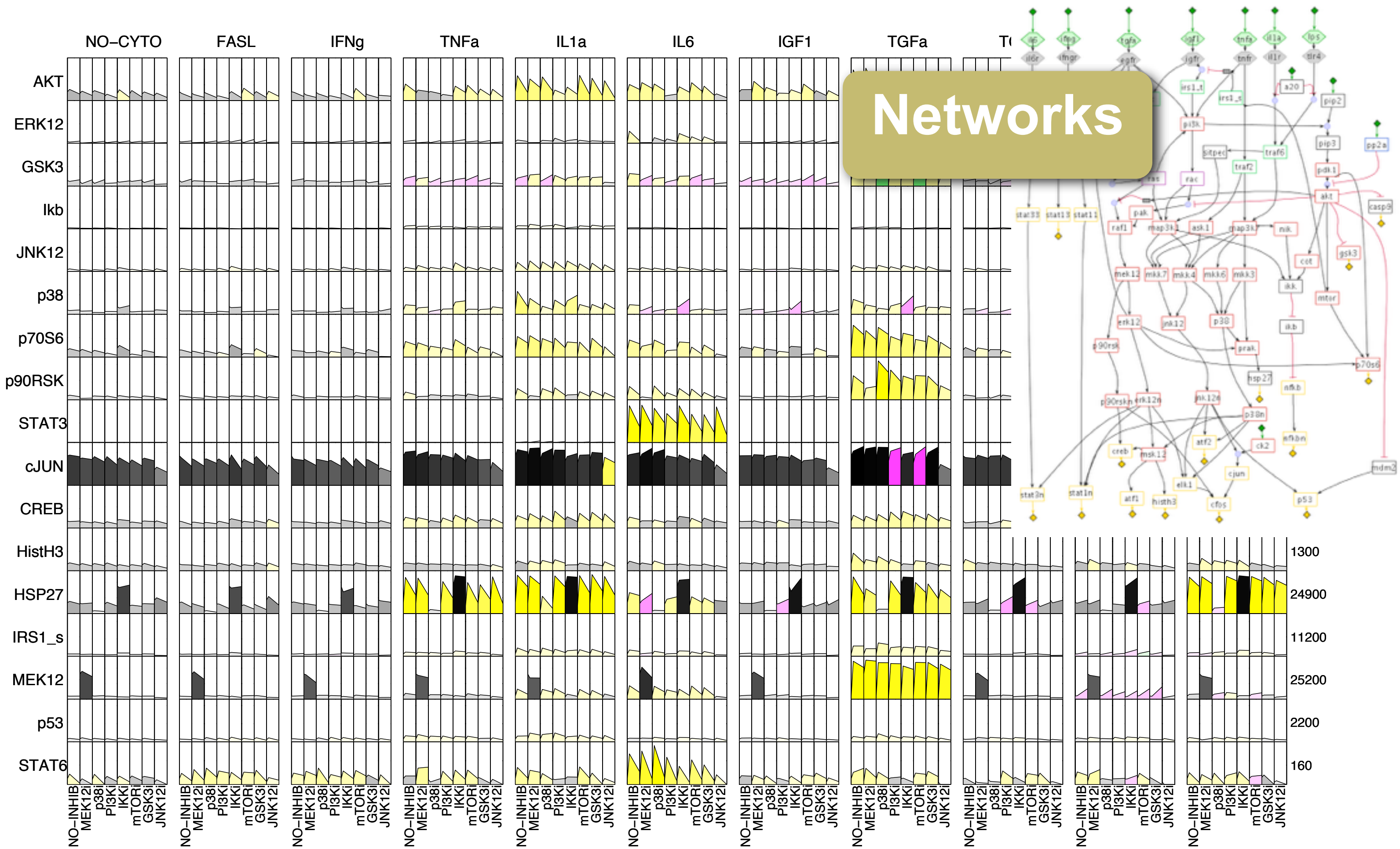


Logic modeling to link protein signaling networks with functional signaling data

Networks



Logic modeling to link protein signaling networks with functional signaling data



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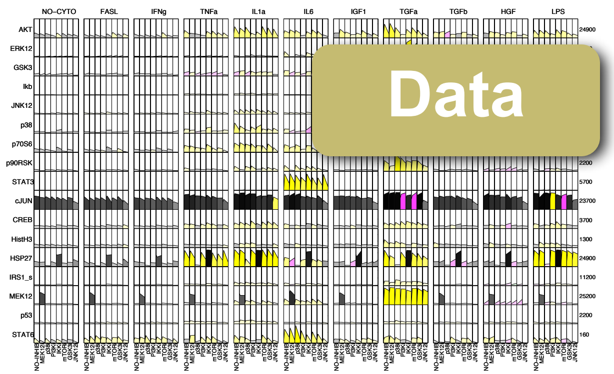

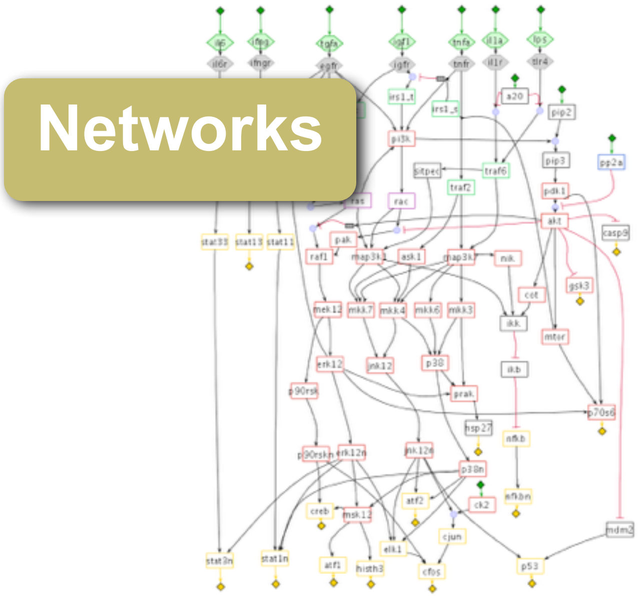

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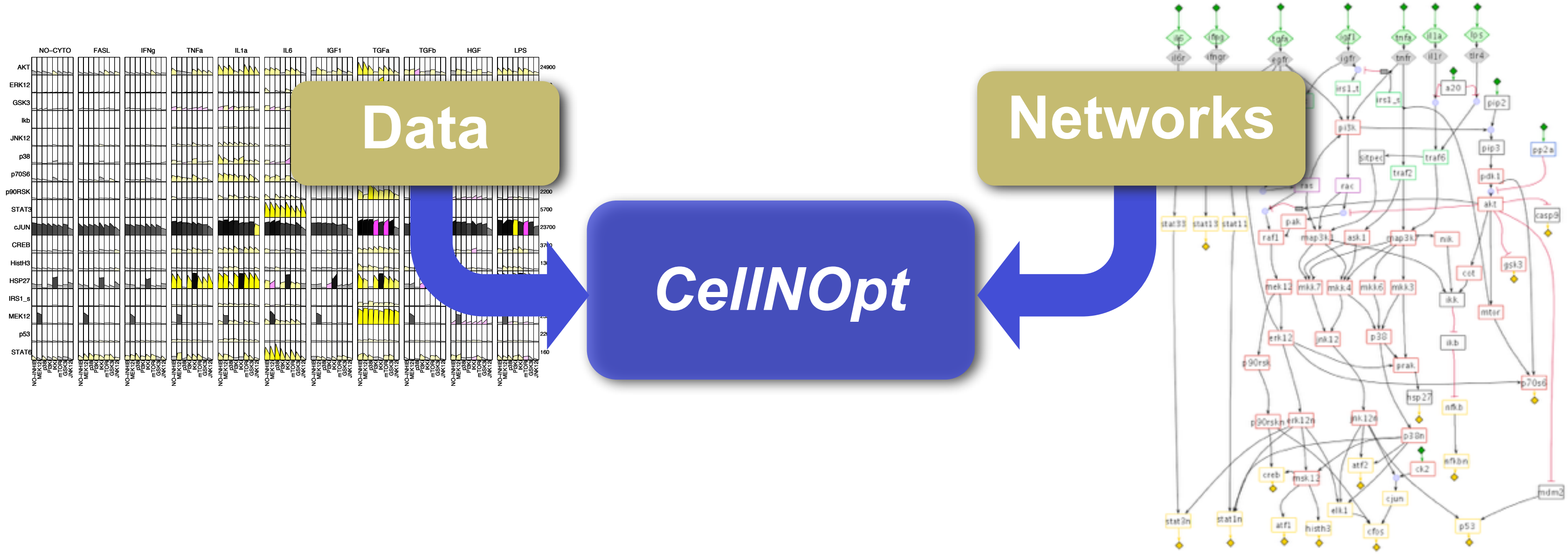

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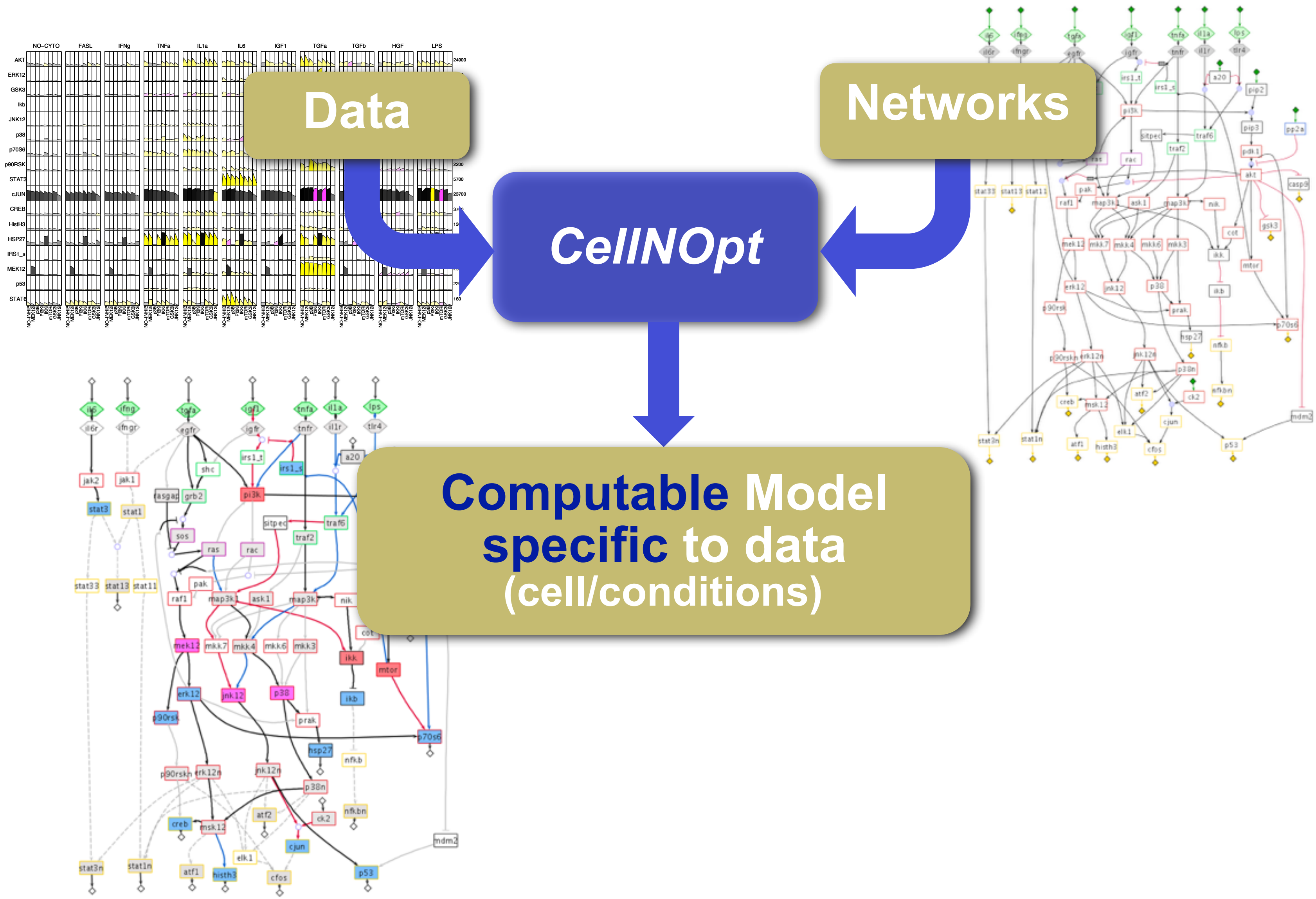
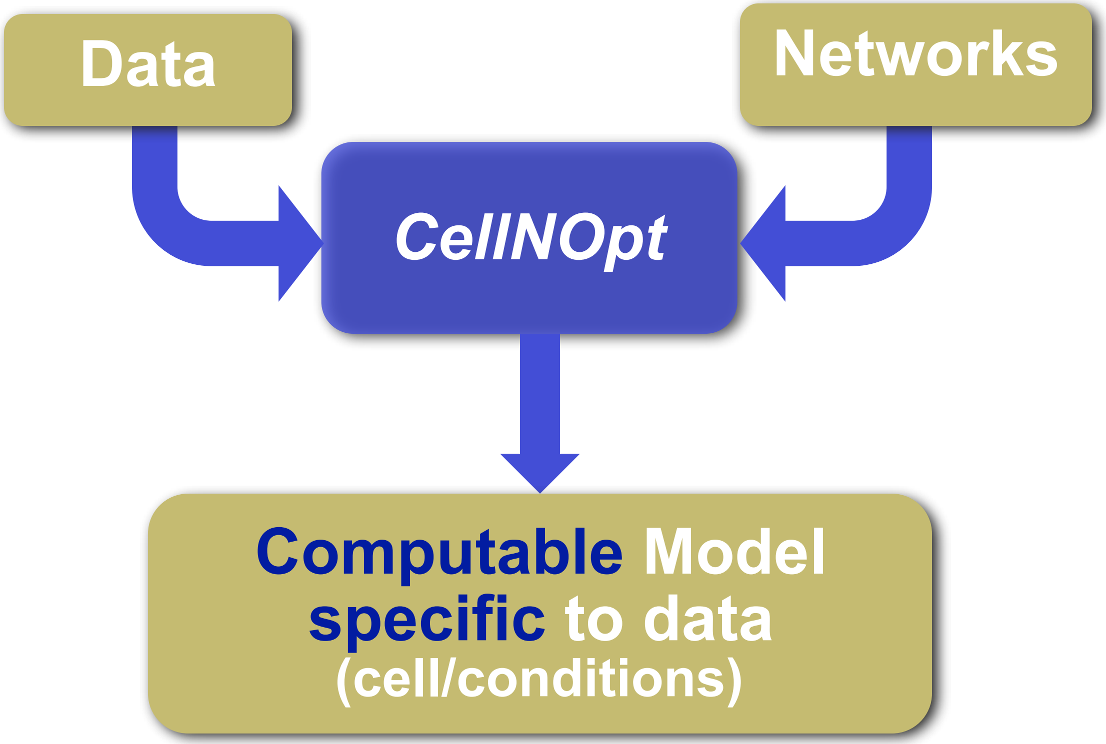



Data
Networks
CellNOpt
Computable Model
specific to data
(cell/conditions)

Where to get information from pathways?

Data

Networks

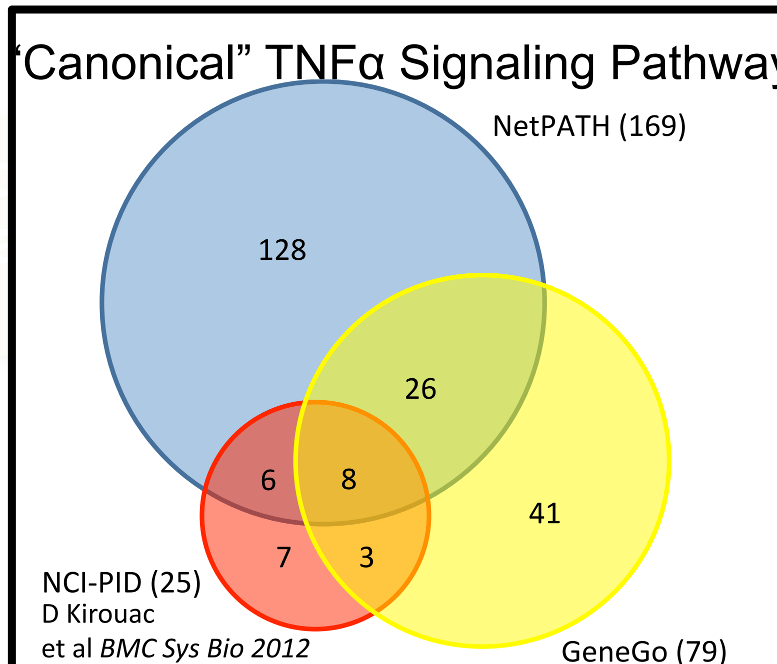
Multiple sources

Databases of curated pathways (Reactome, KEGG, Wiki-pathways, NCI-PID, Atlas Cancer, SignaLink, Path2Models, ...) incomplete, low overlap, different qualities

Important: standards (SBML, etc.)

Your own expertise/ literature review

Solution: OmniPath
in-house integrated repository of 24 pathway databases (~7k proteins,~21k PMIDs)
(free open-source; available



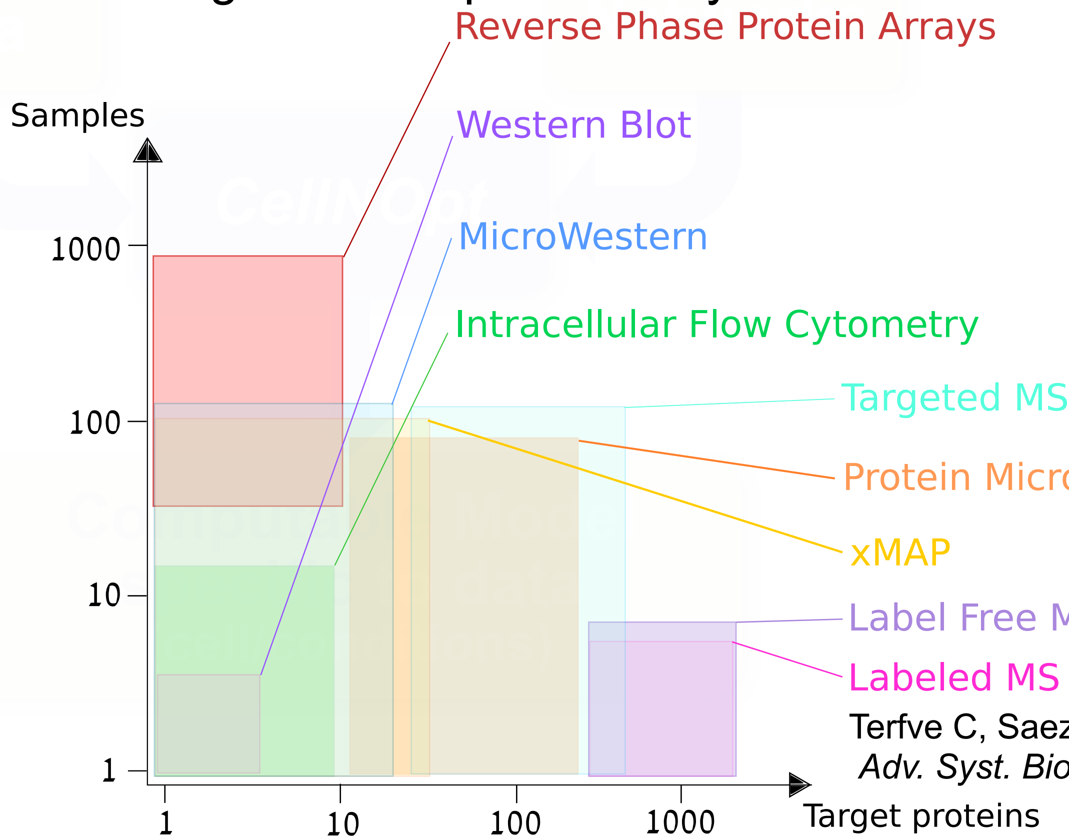
Use different phospho-proteomic & perturbation methods

Different data types

Different <u>measurement techniques</u>:

- Single cell: Imaging, flow cytometry, CytoF

  Broad coverage: Mass Spectrometry



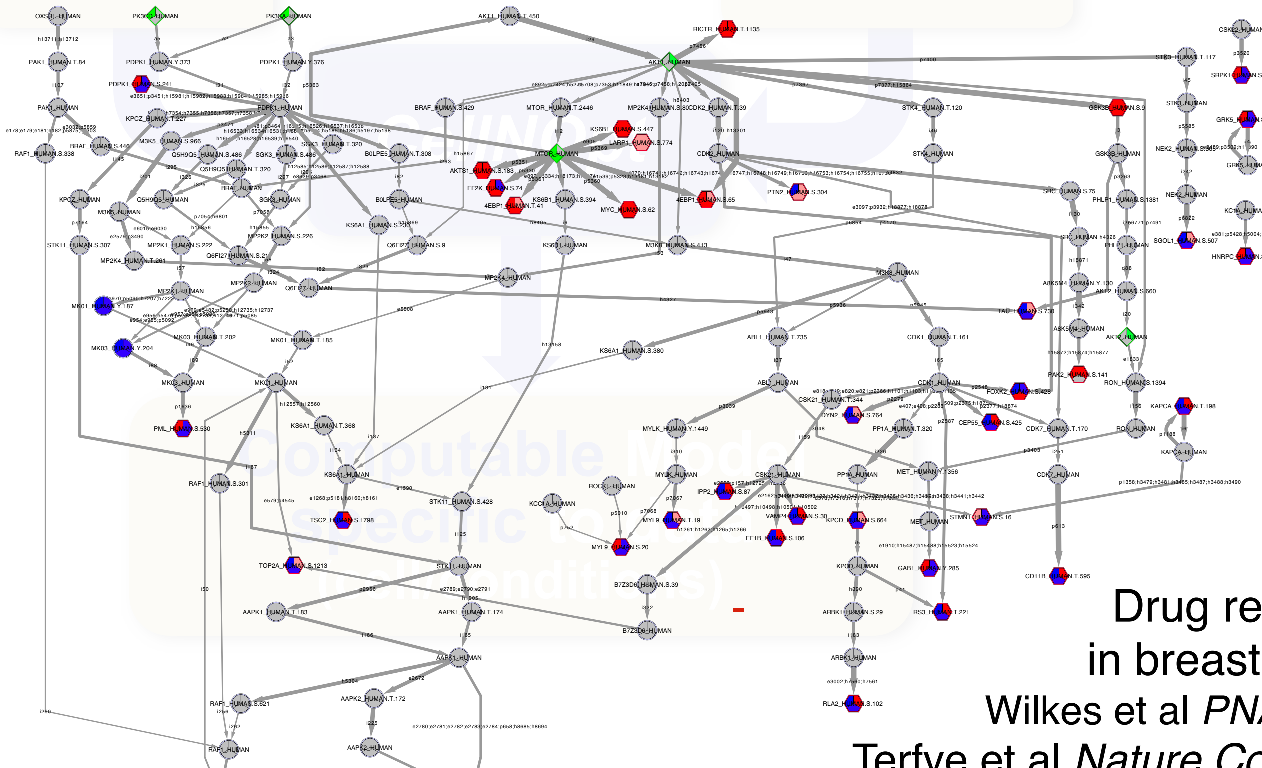
Terfve C, Saez-Rodriguez J, *Adv. Syst. Biol.*, 2012

<u>Orthogonal perturbations</u> - e.g. integration with siRNA screen to identify targets of phosphatases (Sacco et al. *Mol. Sys. Bio.*, 2012)

Use different phospho-proteomic & perturbation methods

Different data types

- **Mass spectrometry** phospho-proteomics for high coverage of signalling networks
  From ~ 10s (antibody-based) to ~ 1000s proteins
  w. R. Aebersold (ETH Zurich), P. Cutillas (Barts London)



Drug response in breast cancer
Wilkes et al *PNAS* 2015
Terfve et al *Nature Com* 2015

Crosstalk in yeast
Vaga et al, *Mol Syst Bio* 2014

Tool for modeling MS P-proteomics:
www.cellnopt.org/PHONEMeS

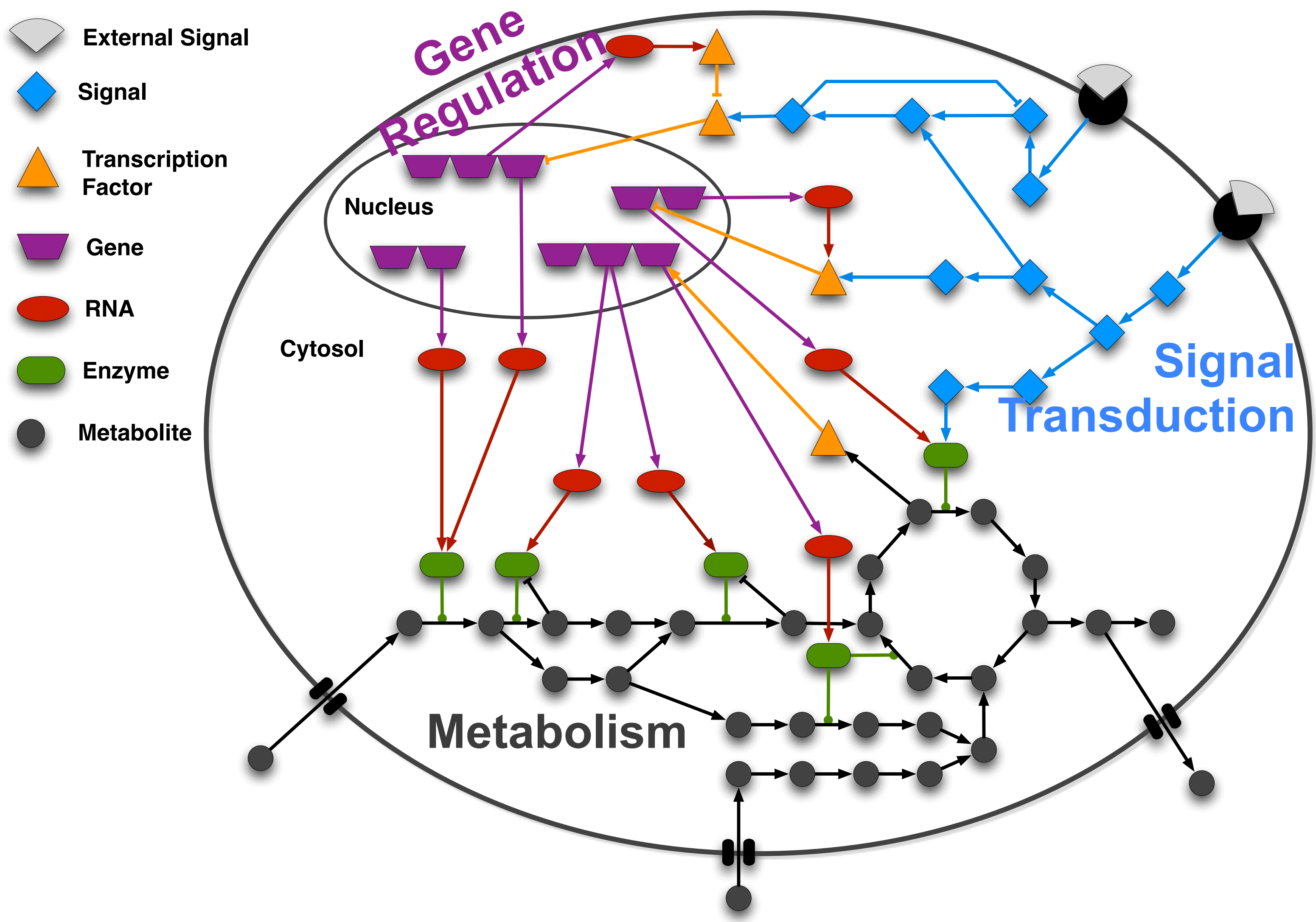
Use different phospho-proteomic & perturbation methods

Different data types

- **Mass spectrometry** phospho-proteomics for high coverage of signalling networks
  From ~ 10s (antibody-based) to ~ 1000s proteins
  w. R. Aebersold (ETH Zurich), P. Cutillas (Barts London)

- **Single cell signaling**:
  - Imaging (w. C. Schultz, EMBL),
  - CytoF (w. B. Bodenmiller, U. Zurich)

Models to link signalling to gene regulatory and metabolic networks



Emanuel Gonçalves
Michael Schubert
Luz Garcia

E Gonçalves *et al*. *Molecular Biosystems*, 9:1576-1583, 2013
Ryll et al *Biosystems* 2014:

Steps in building (and using) a model

- Set up experiments to extract most information
- Process data efficiently
- Choose type of mathematical model
  (given data, question, etc)
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A real example

Comparison of primary hepatocytes to 4 HCC cell lines

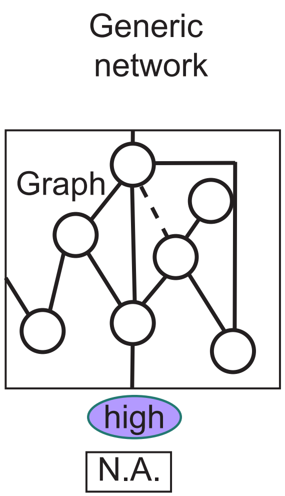
Primar

HepG

Hep3

Huh7

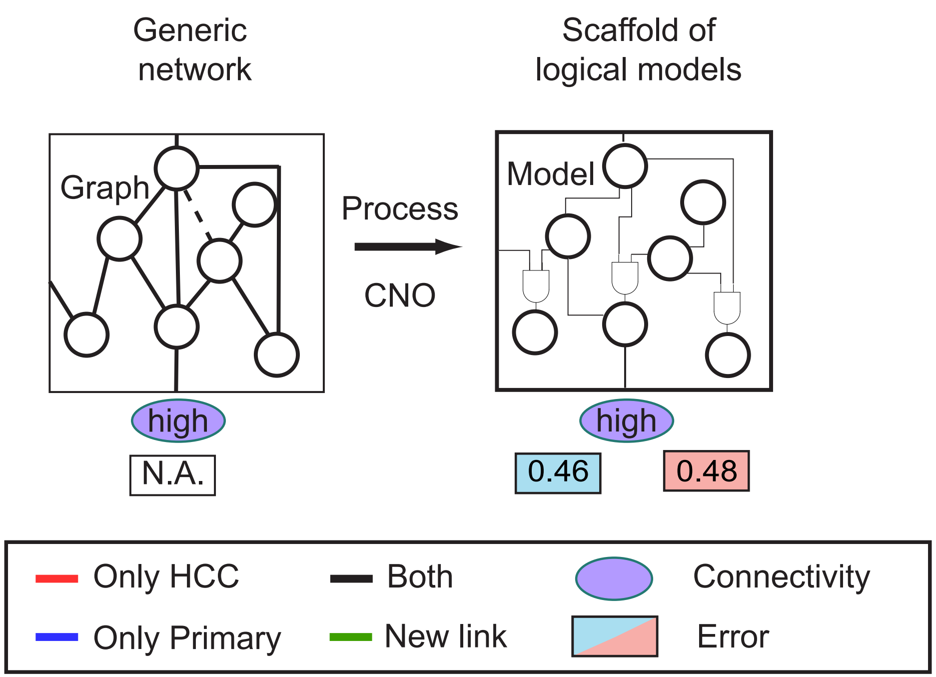
Focus



Saez-Rodriguez J, Alexopoulos LG, Zheng M, Morris MK, Lauffenburger DA, Sorger PK, *Cancer Research* 71(16), 2011

Comparison of primary hepatocytes to 4 HCC cell lines

Primar | HepG | Hep3 | Huh7 | Focus



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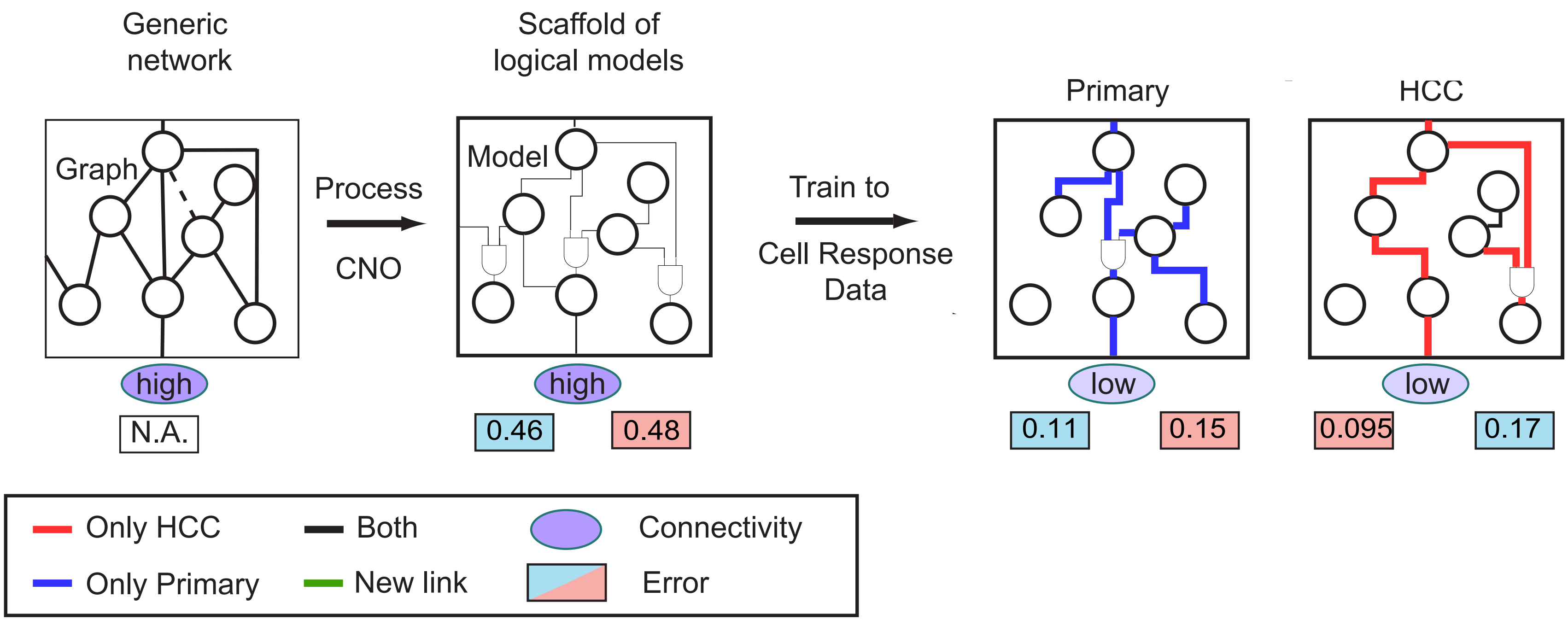
Primar HepG Hep3 Huh7 Focus



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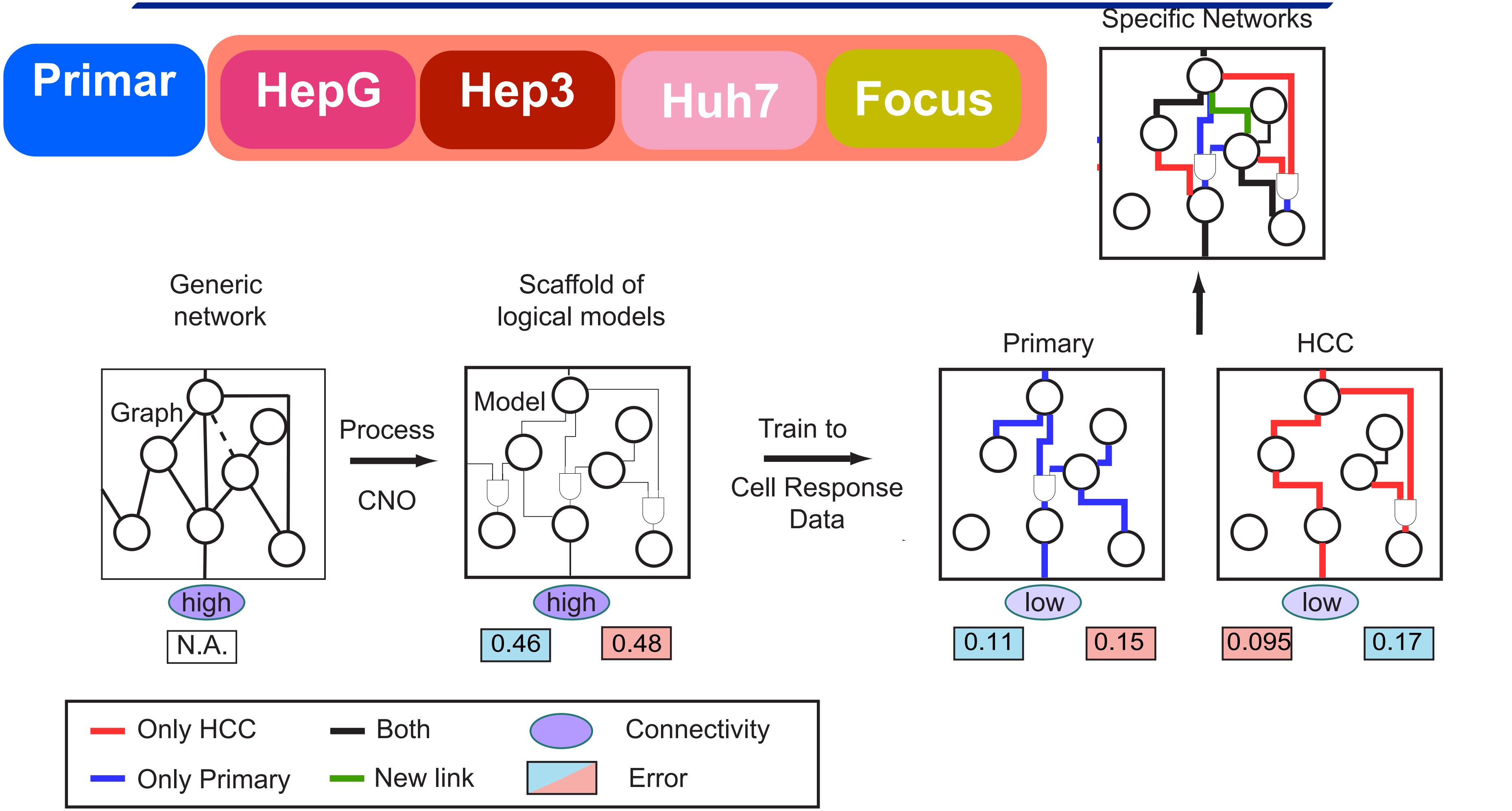

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An example of a perturbation-based high-throughput data sets

Alexopoulos L, Saez-Rodriguez J, Cosgrove B, Lauffenburger DA, Sorger PK, *Mol. Cell. Prot.*, 9, 1849, 2010

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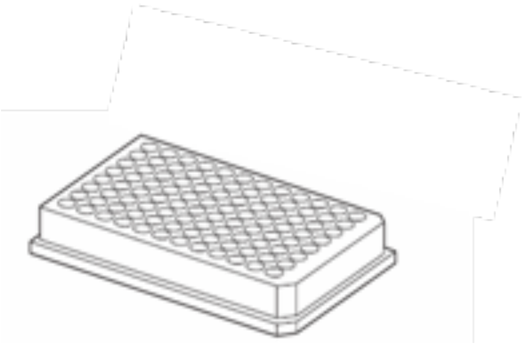

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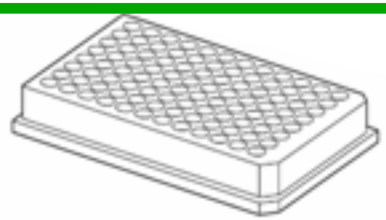
An example of a perturbation-based high-throughput data sets

Cue	➜ 7 **extracellular ligands** ➜ 7 specific **chemical inhibitors** (drugs)



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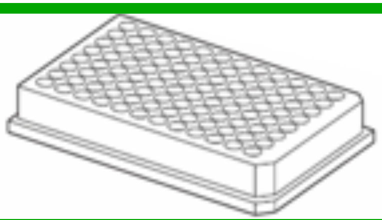
An example of a perturbation-based high-throughput data sets

Cue

➜ 7 **extracellular ligands**

➜ 7 specific **chemical inhibitors** (drugs)

at different times after stimulation



Signal

➜ **Phosphorylation** of 17 key proteins (30 min, 3h)

Alexopoulos L, Saez-Rodriguez J, Cosgrove B, Lauffenburger DA, Sorger PK, *Mol. Cell. Prot.*, 9, 1849, 2010

An example of a perturbation-based high-throughput data sets

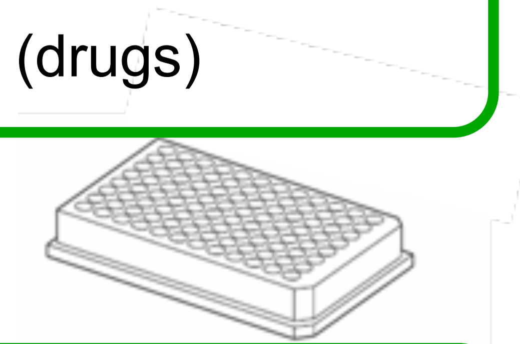
Primary human hepatocytes & HCC cell lines (HepG2, Hep3B, Huh7, Focus)

Cue

➜ 7 **extracellular ligands**

➜ 7 specific **chemical inhibitors** (drugs)

at different times after stimulation



Signal

➜ **Phosphorylation** of 17 key proteins (30 min, 3h)

using Luminex/xMAP (bead-based ELISA)

Response

➜ **Release** of 20 cytokines (3h, 24h)

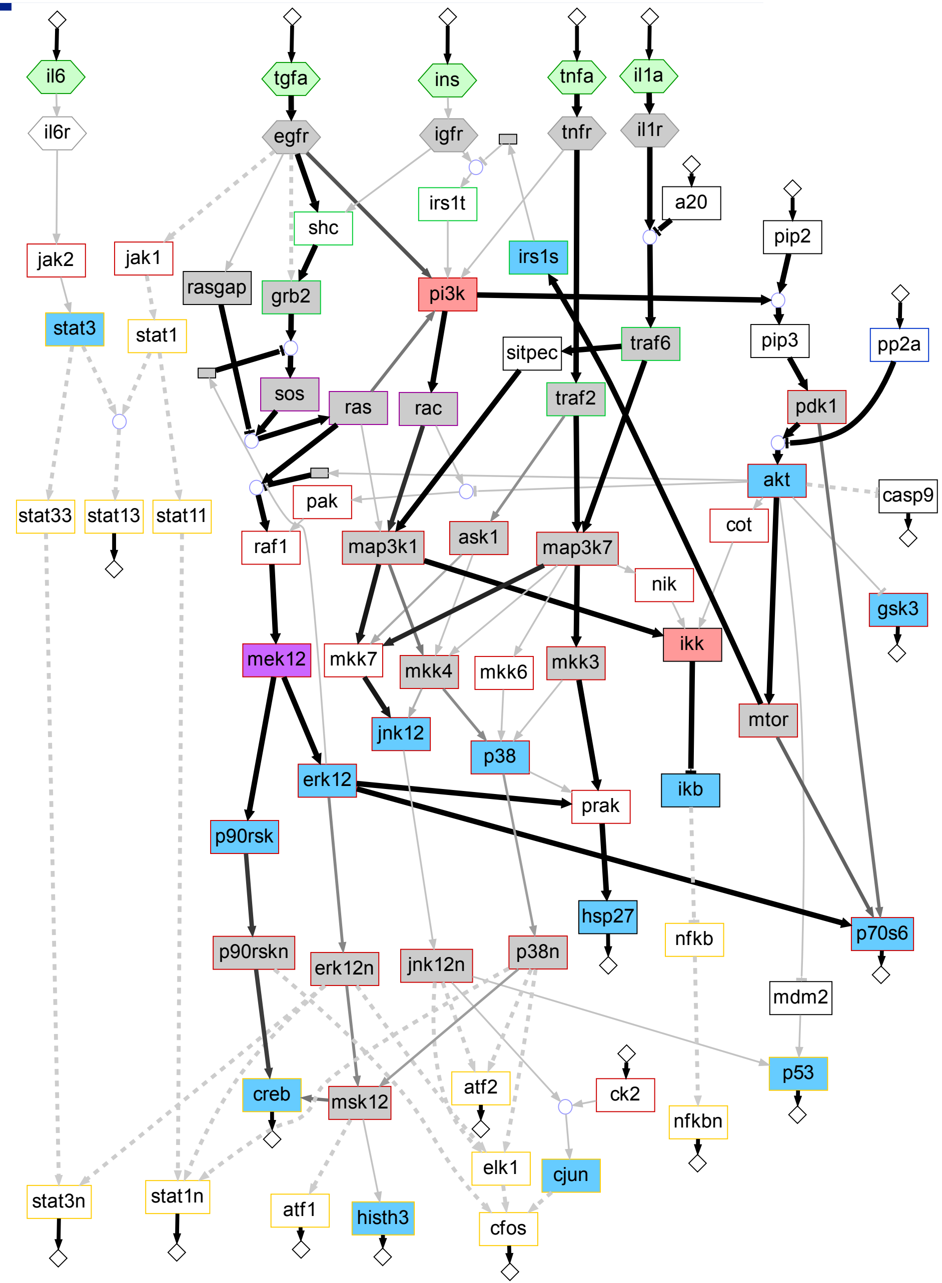
Alexopoulos L, Saez-Rodriguez J, Cosgrove B, Lauffenburger DA, Sorger PK, *Mol. Cell. Prot.*, 9, 1849, 2010

COMBINE

Primar

Primary

RWTH AACHEN



Stimulus

Perturbation

Readout

Perturb&Read

Kept

Removed

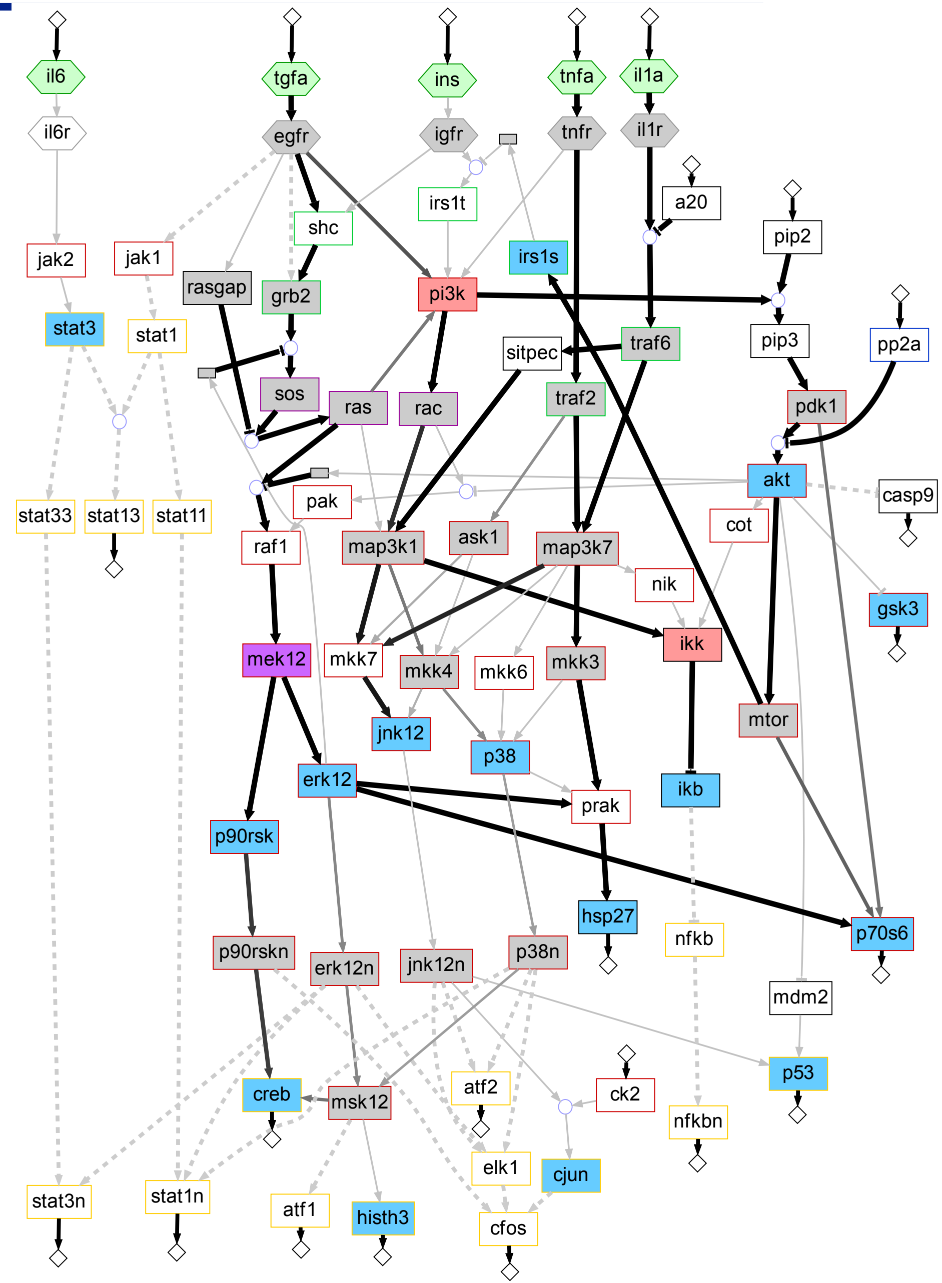
No effect

COMBINE

Primary

Primary

RWTH AACHEN



Stimulus

Perturbation

Readout

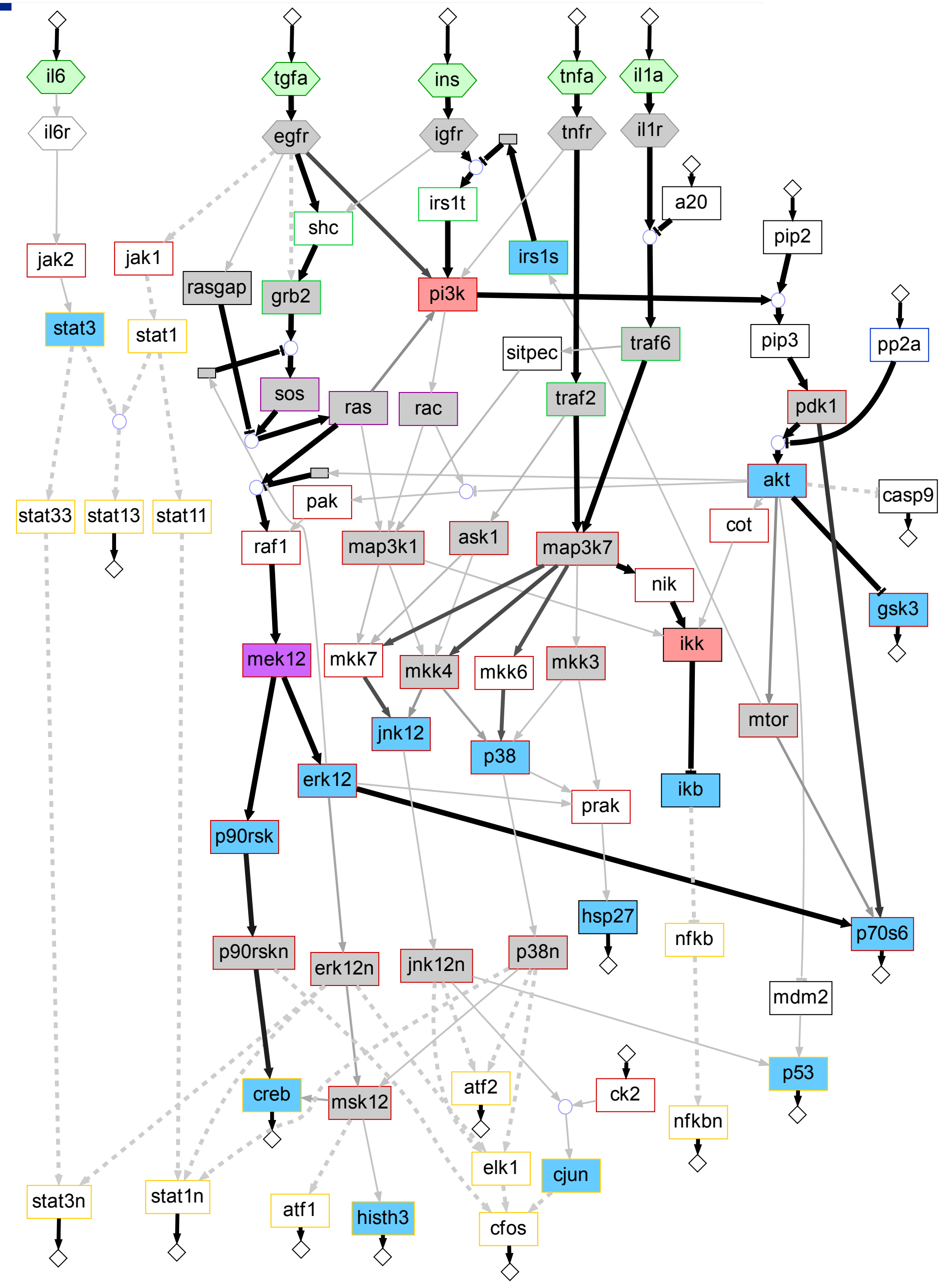
Perturb&Read

Kept

Removed

No effect

HepG2



Stimulus

Perturbation

Readout

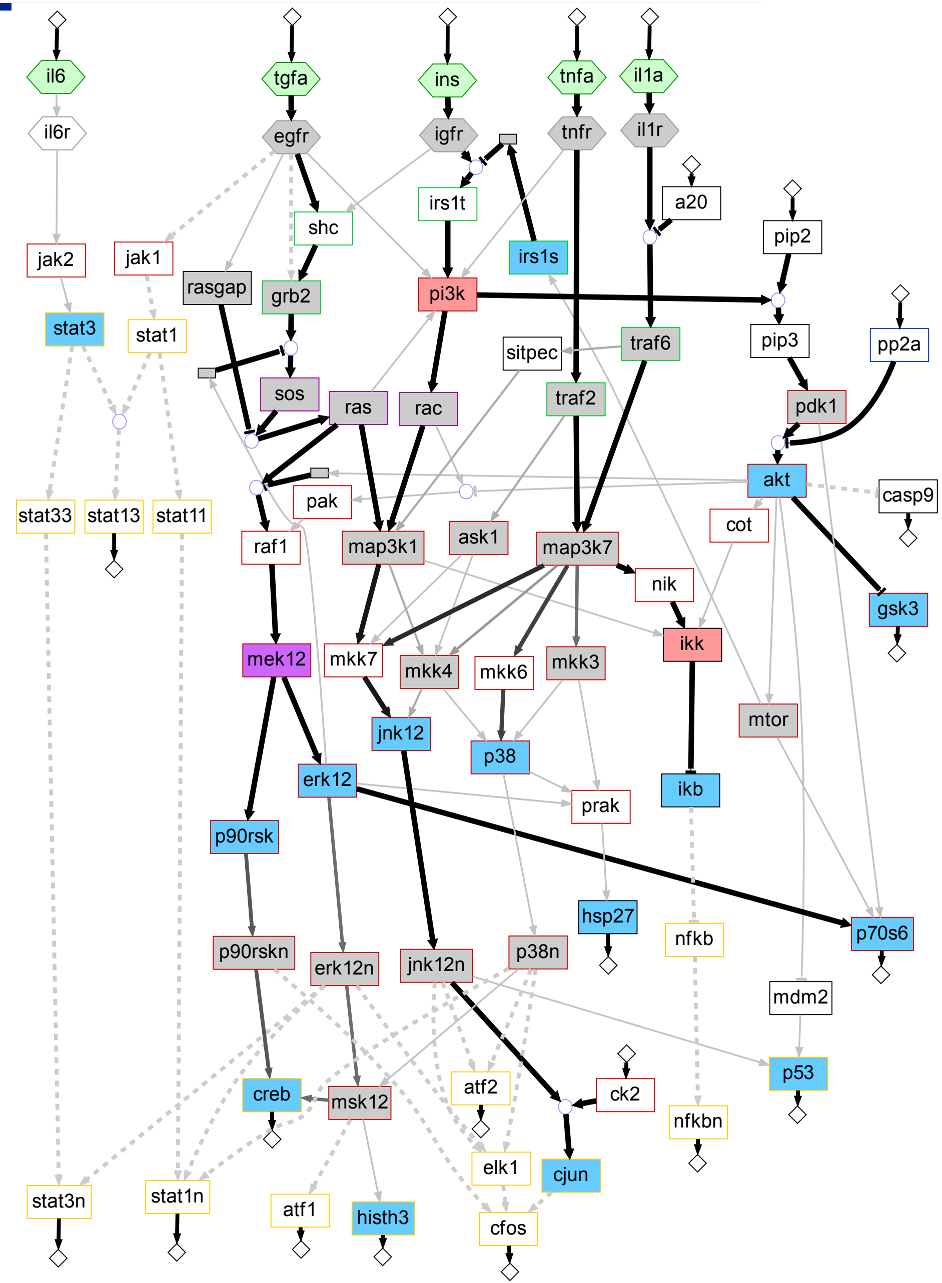
Perturb&Read

Kept

Removed

No effect

Hep3B



Stimulus

Perturbation

Readout

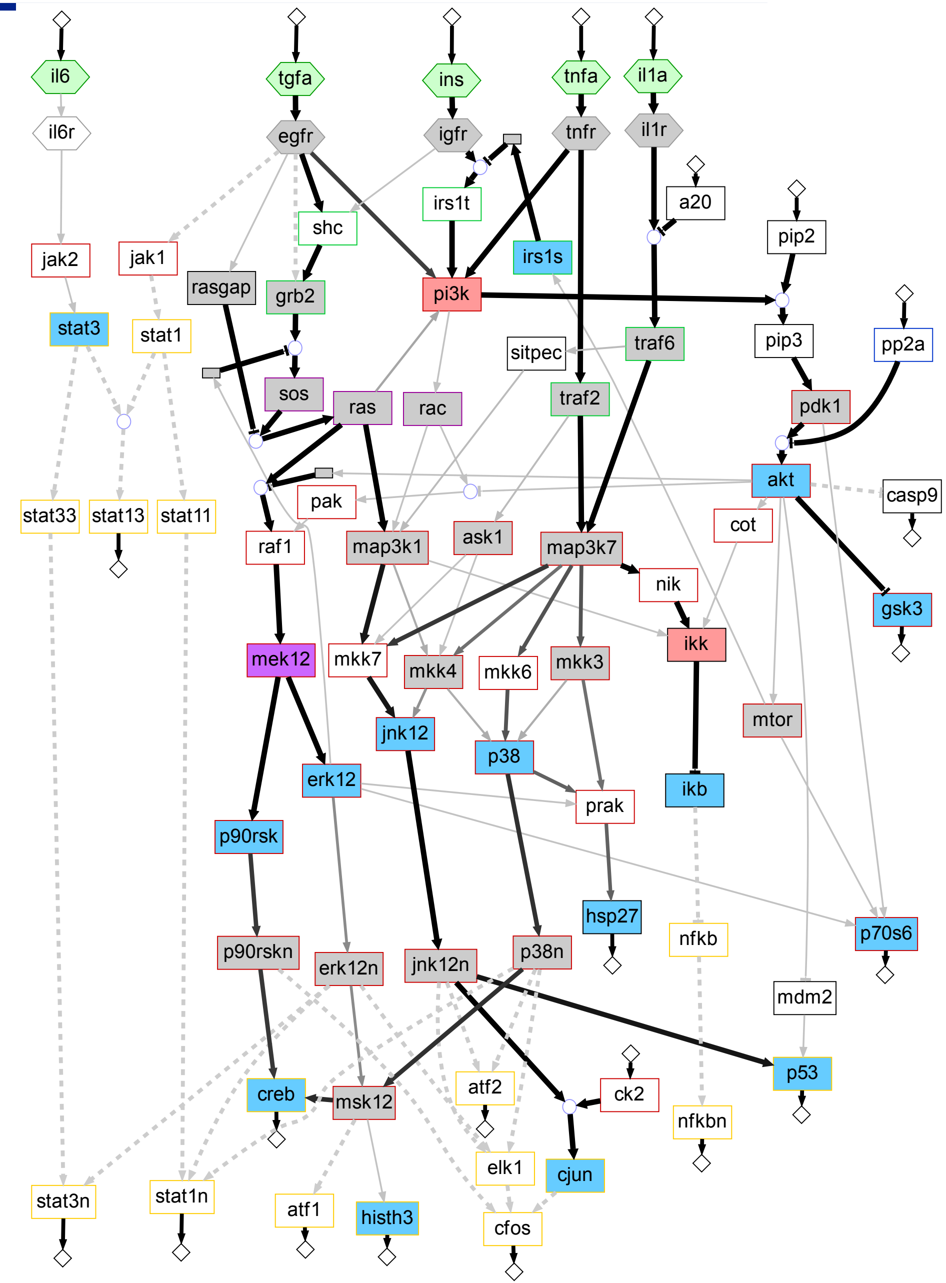
Perturb&Read

Kept

Removed

No effect

Huh7



Stimulus

Perturbation

Readout

Perturb&Read

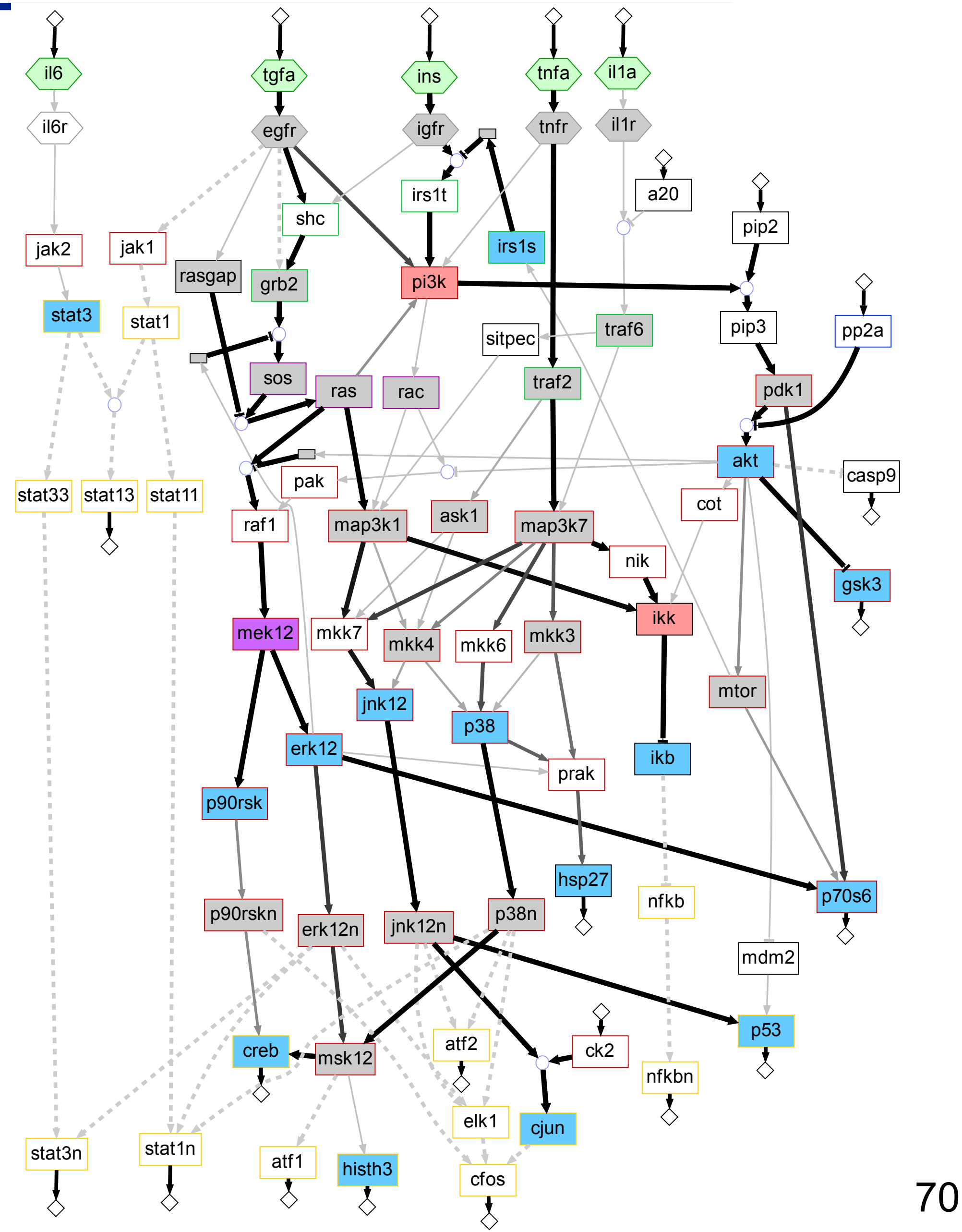
Kept

Removed

No effect

COMBINE

Focus



Stimulus

Perturbation

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Kept

Removed

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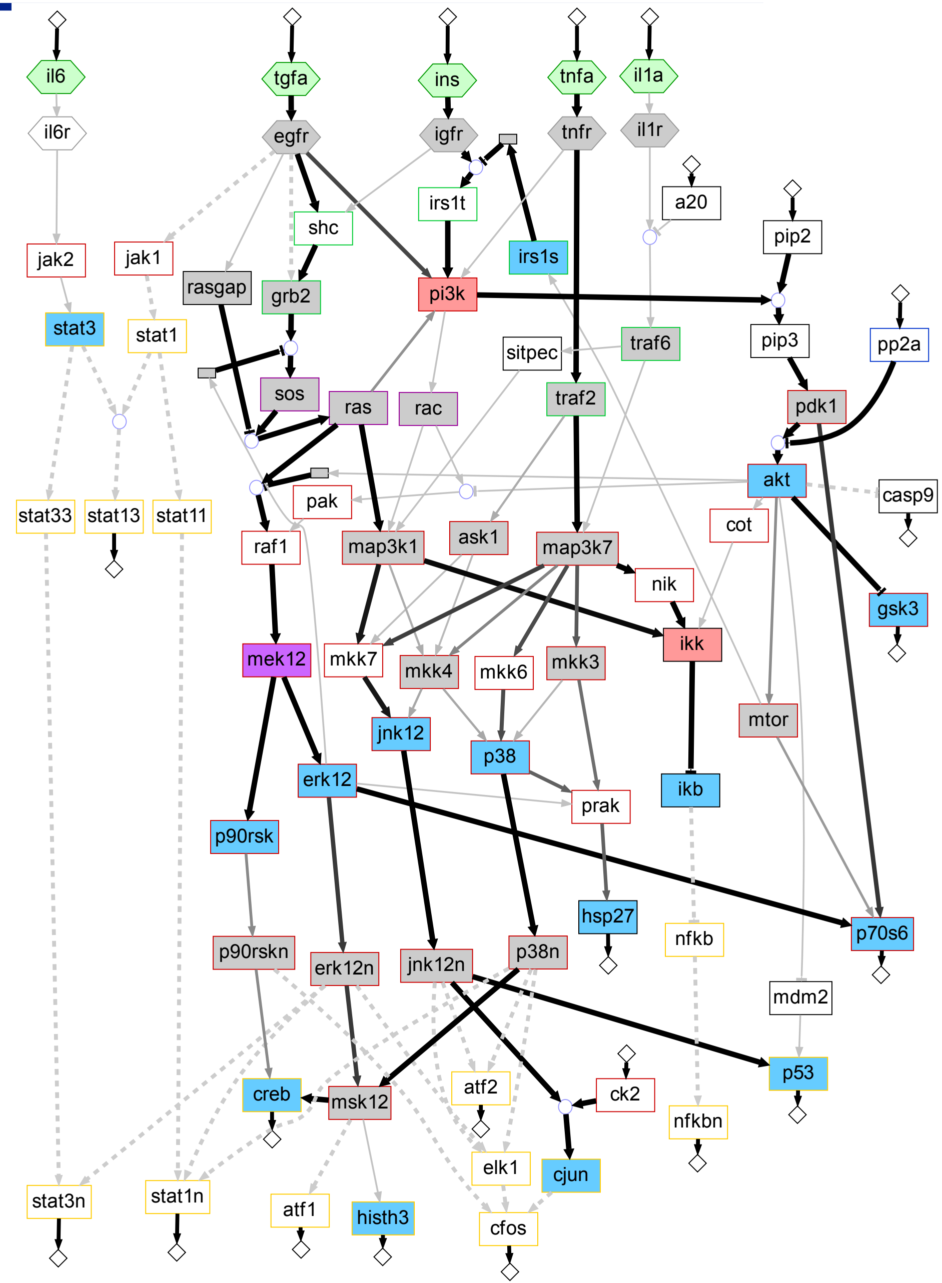

Stimulus

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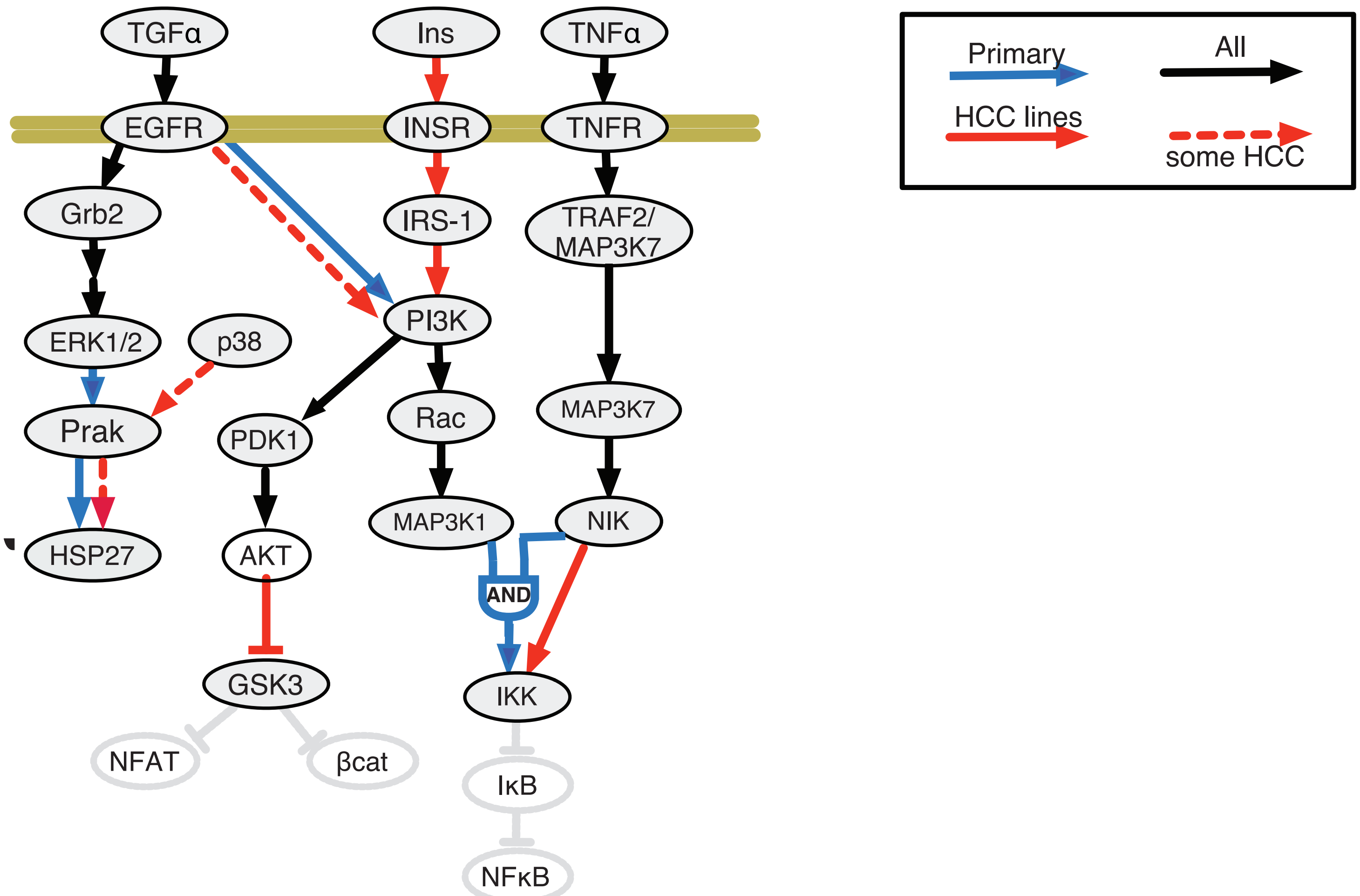
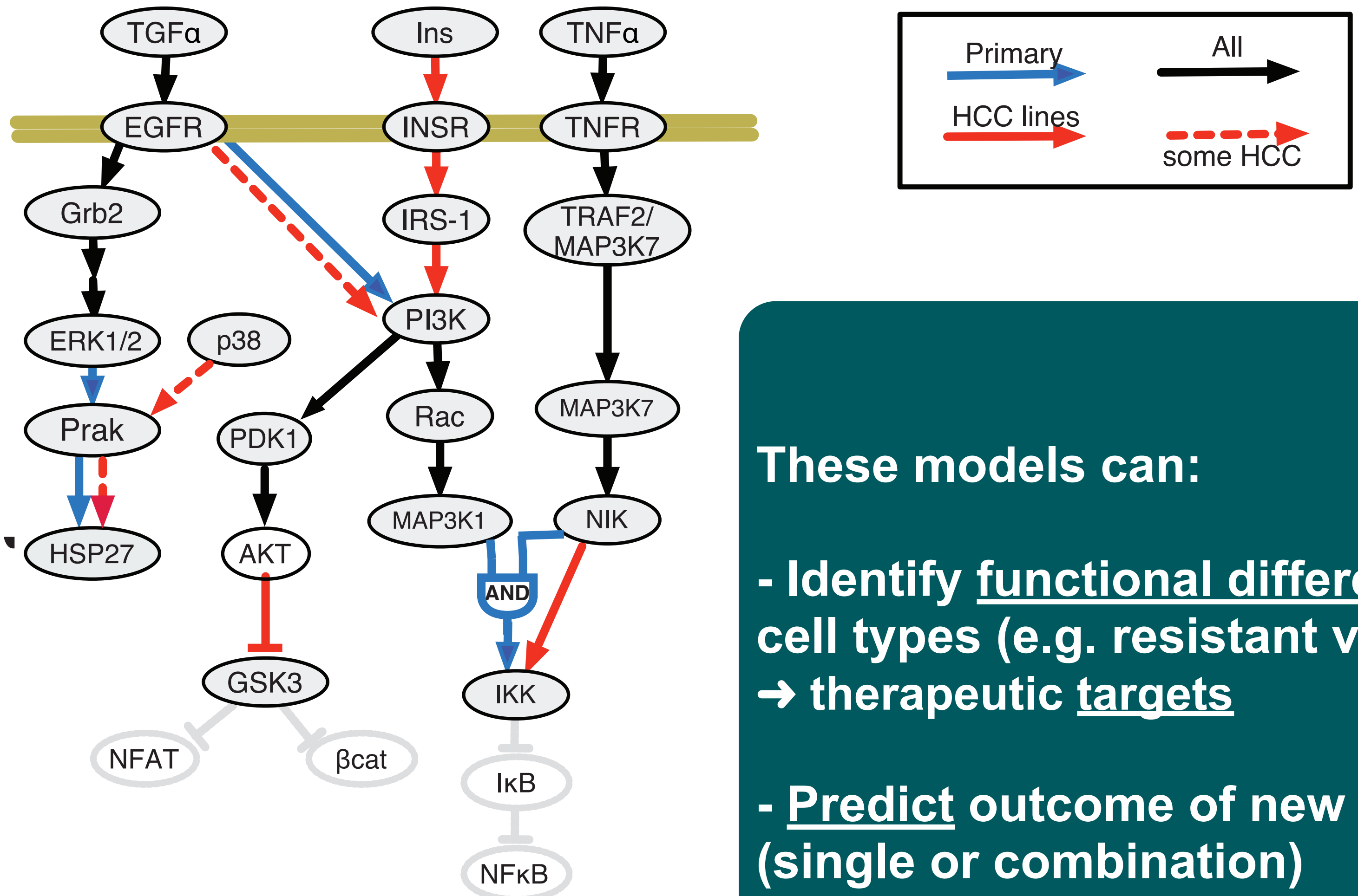
Logic models provide mechanistic insight in signal deregulation



Logic models provide mechanistic insight in signal deregulation



These models can:

- Identify <u>functional differences</u> between cell types (e.g. resistant vs. sensitive)
➜ therapeutic <u>targets</u>

- <u>Predict</u> outcome of new perturbations (single or combination)

- Characterize targets and <u>mode of action</u> of drugs (Mitsos et al. *PloS C.B.* 2009)

Acknowledgements

Francesco Iorio
Michael Menden
Michael Schubert
Luz Garcia Alonso
Damien Arnol
Denes Turei
Aidan MacNamara

Federica Eduati
Thomas Cokelaer
Marti Bernardo
Johannes Stephan
Camille Terfve
Angeliki Kalamara
Fatemeh Zamanzad
Emanuel Gonçalves

CoLoMoTo consortium sp. Claudine Chaouiya (IGC) Tomas Helikar(UN)

Ioannis Melas Leo Alexopoulos (NTUA) Alexander Mitsos (RWTH)

Regina Samaga   Steffen Klamt (MPI)

Jose Egea (U. Cartagena)
Alex Villlaverde David Henriques Julio Banga (CSIC)

Carito Guziolowski   Santiago Videla   Anne Siegel (CNRS)

Melody Morris Doug Lauffenburger (MIT)

Jeremy Muhlich Peter K Sorger (HMS)

EMBL-EIPOD   MRC   EU-7FP   GSK

How to...

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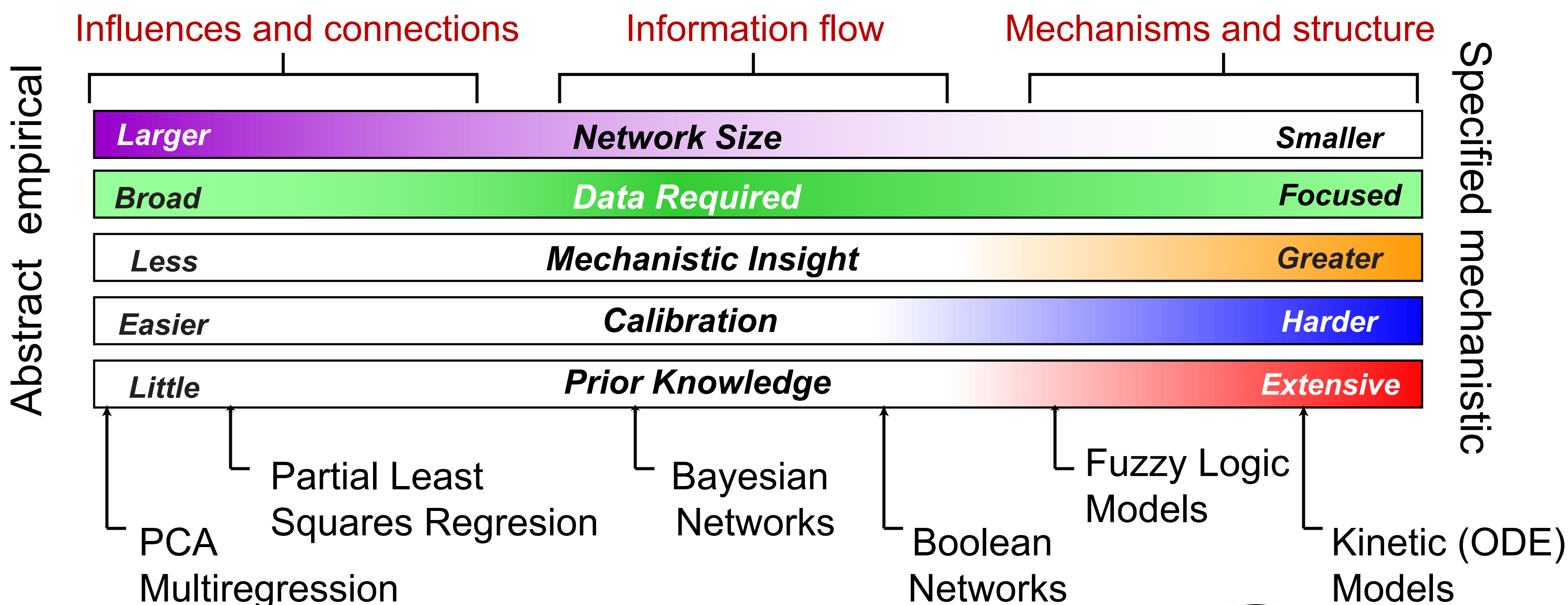
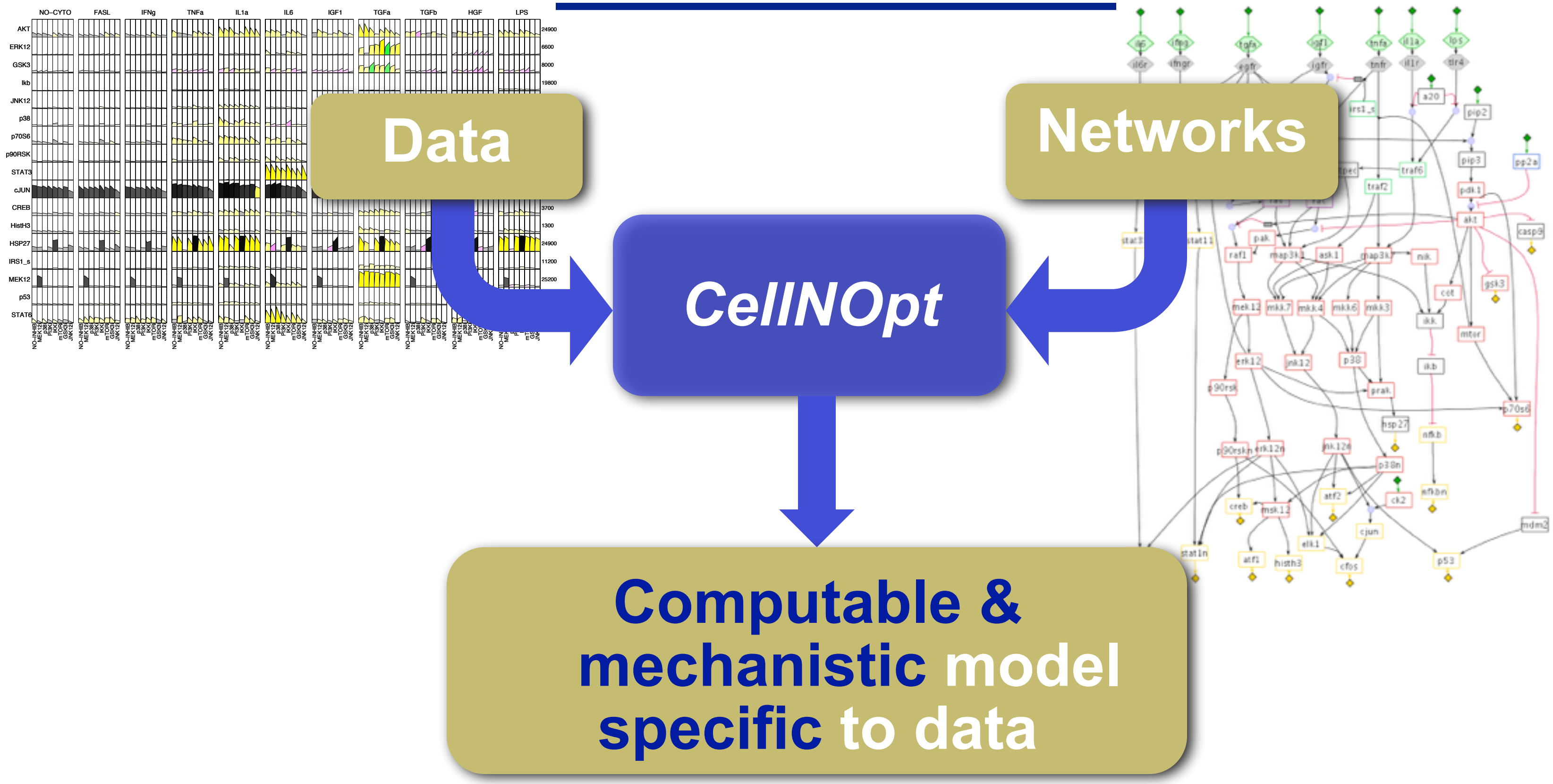
Used logic modelling & applications to signalling, but general principles hold for other modelling approaches & applications

Spectrum of modeling approaches

- Choice of method depends on:
  - Question, prior knowledge, data, ...(+ modeler's expertise)
  - Art more than science



All models are wrong, but some are useful
G. Box



- Logic models: intermediate between data-driven & biochemical models
- Flexible and scalable framework
- Suitable to integrate large-scale data + networks