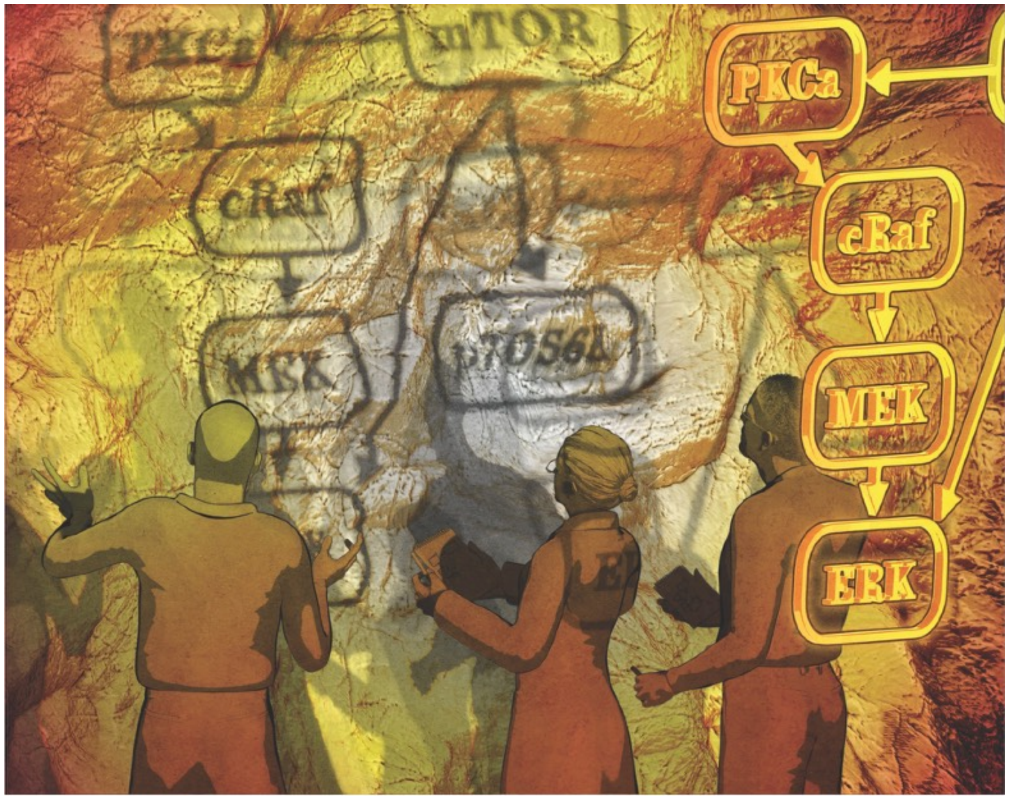
Logic models of signalling networks & their training to experimental data with CellNOpt



Artwork by S. Philips on idea of J. Saez-Rodriguez; appeared in cover of *Nat Meth*,13:4, 2016

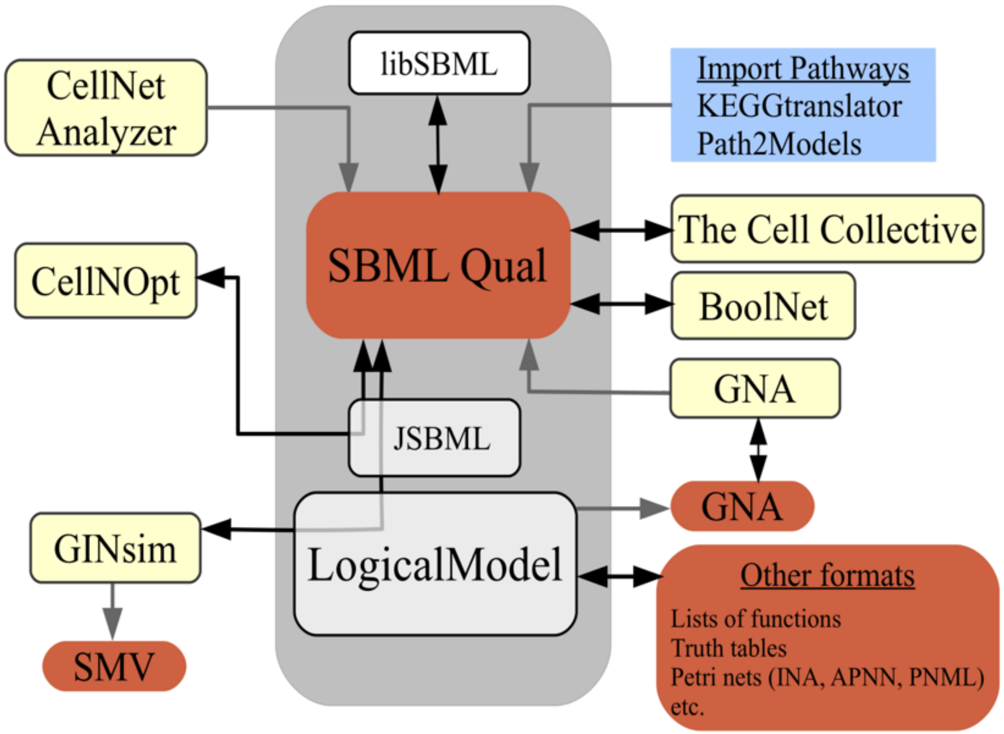
Julio Saez-Rodriguez
Institute for Computational Biomedicine,
University Hospital Heidelberg
Joint Research Centre for Computational
Biomedicine - RWTH Aachen, Germany

www.saezlab.org
sysbiomed

European Bioinformatics Institute
European Molecular Biology Laboratory
Hinxton, UK

CellNOpt in CoLoMoTo ecosystem: fit knowledge to data to build logic model

Complementary to other tools - models can be output to other tools



Consortium for Logical Models and Tools

(CoLoMoTo; Naldi et al, *Bioinformatics*, 2015; www.colomoto.org)

Exchange via SBML-qual (Chaouiya et al, *BMC Sys Bio*, 2013)

CellNOpt: Building logic models by training signalling networks to perturbation data

freely available at www.cellnopt.org

Saez-Rodriguez, et al. *Mol. Syst. Biol.*, 2009
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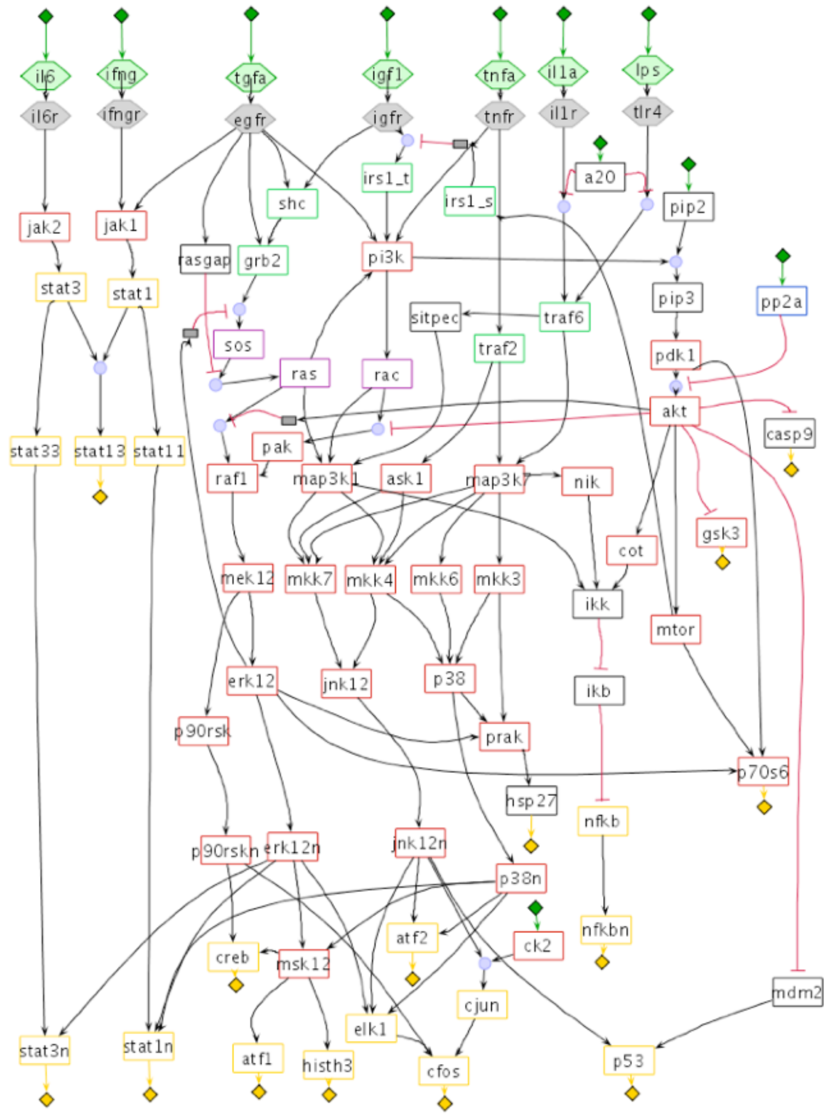

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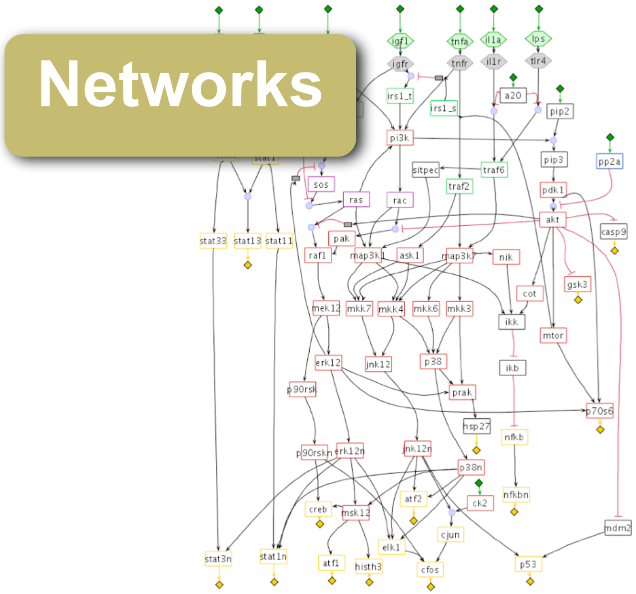

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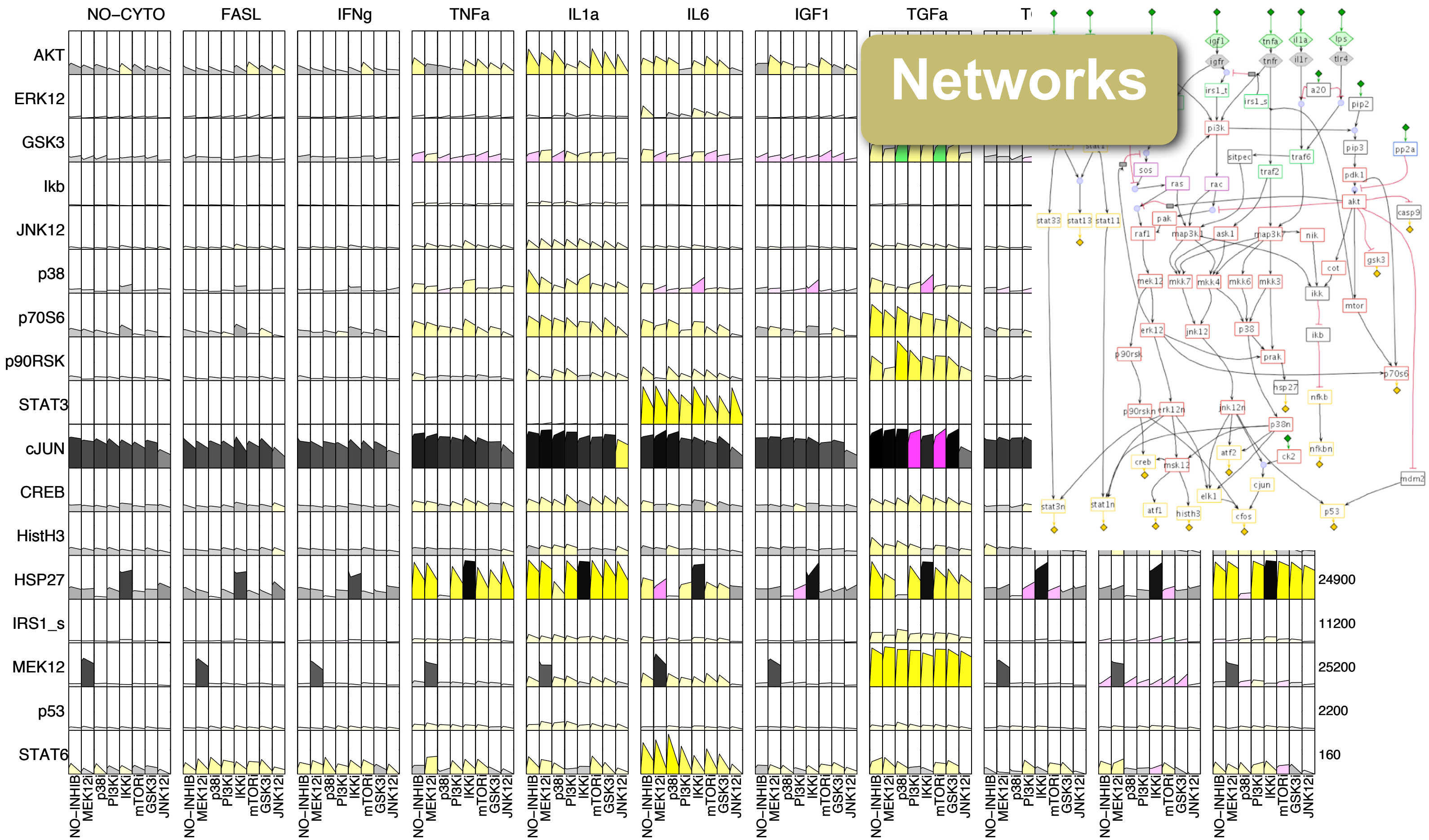

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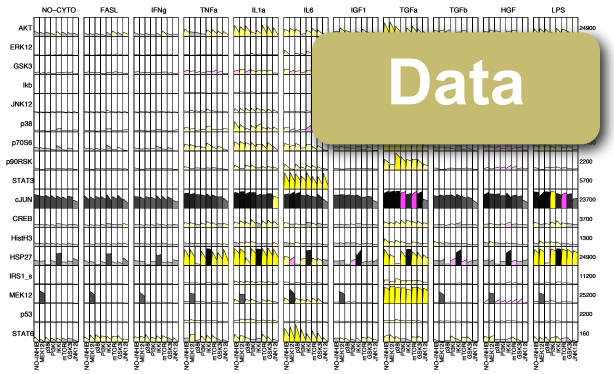

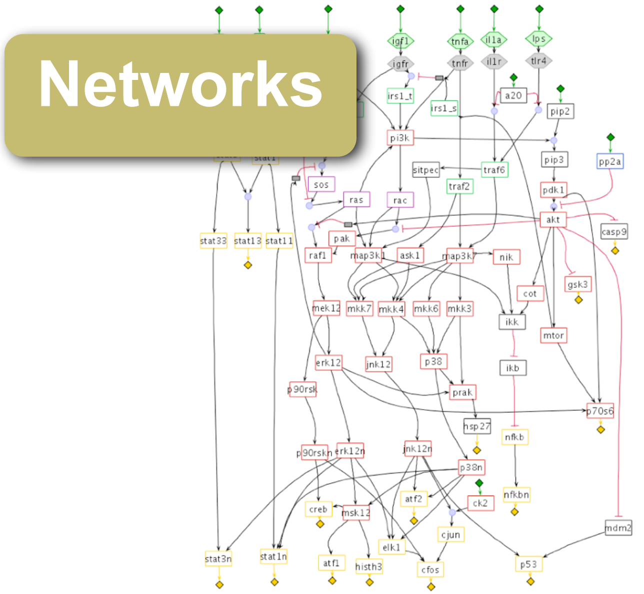

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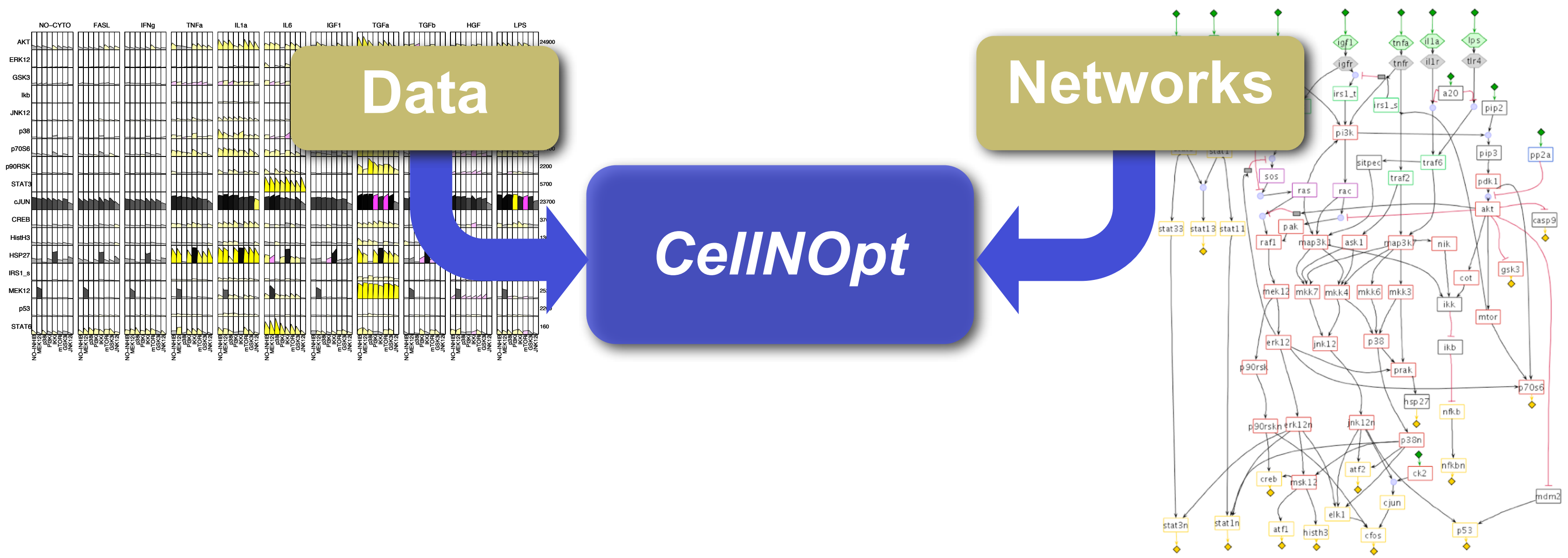

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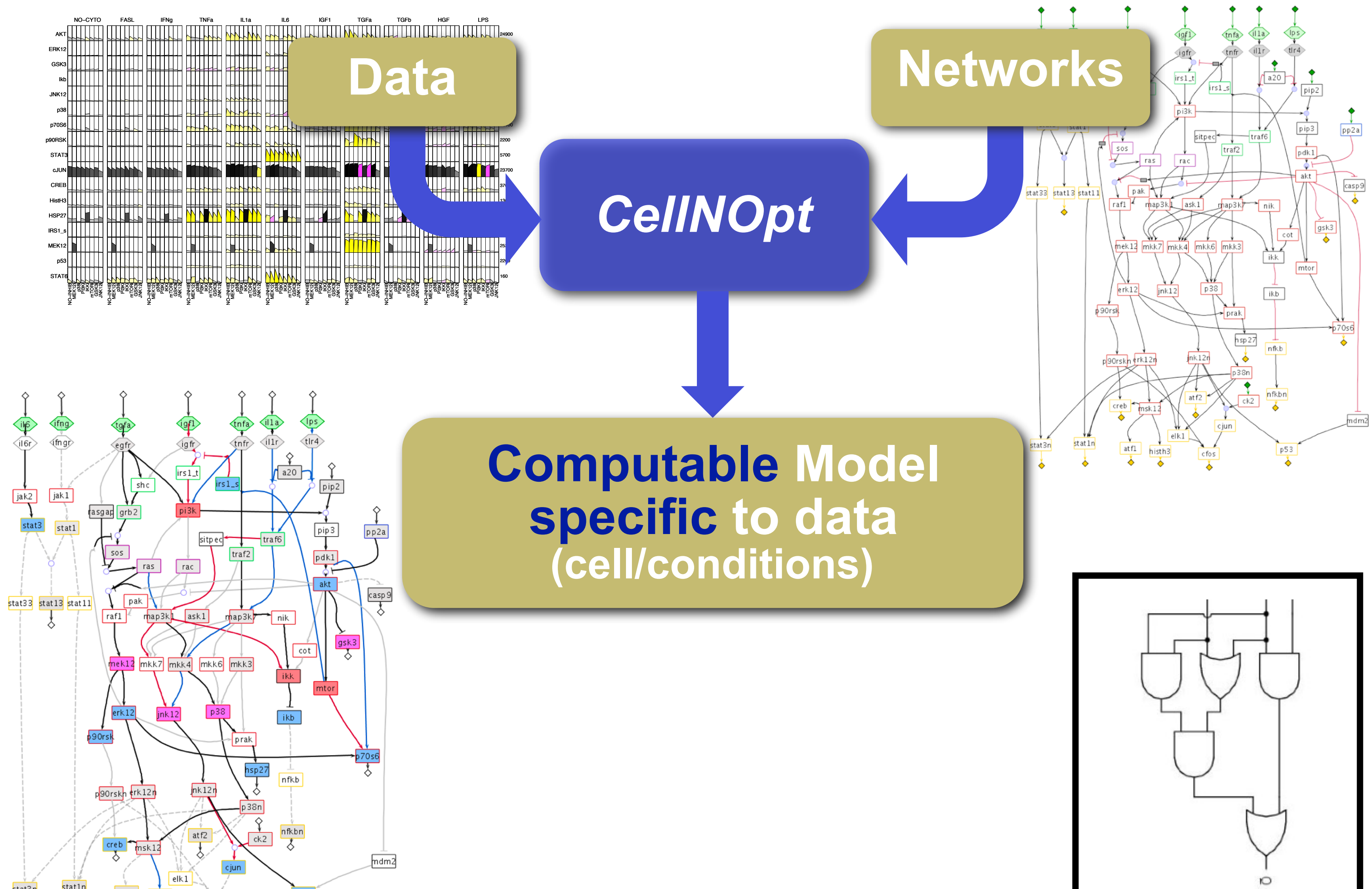

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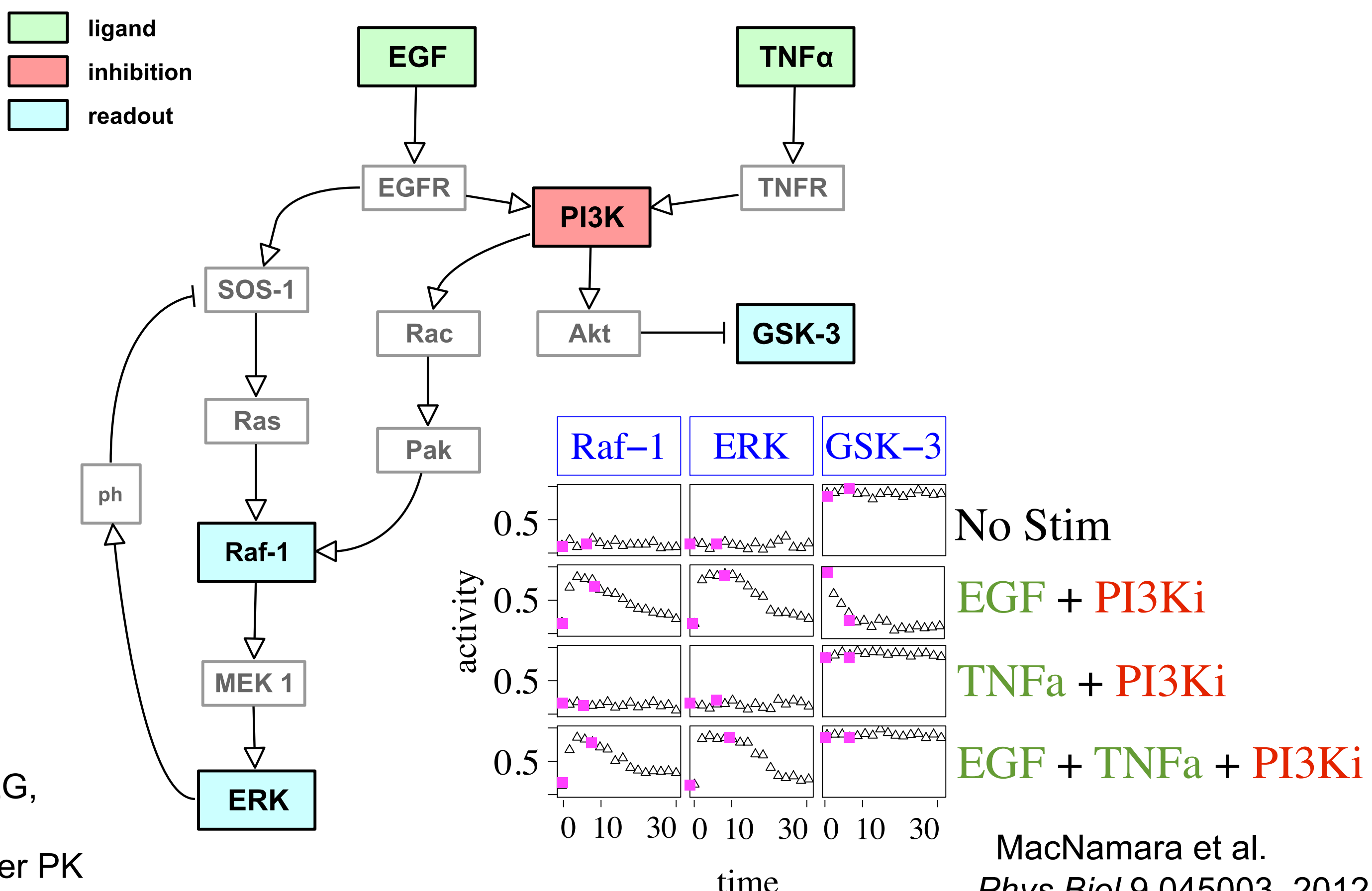
Logic modelling to link protein signalling networks with functional analysis of signal transduction

- 1 - Build general signalling network
- 2 - Perform stimulation experiments followed by phosphoproteomic measurements
- 3 - Find the combination of edges+logic gates (AND/OR) that best describes the experimental data (optimization)



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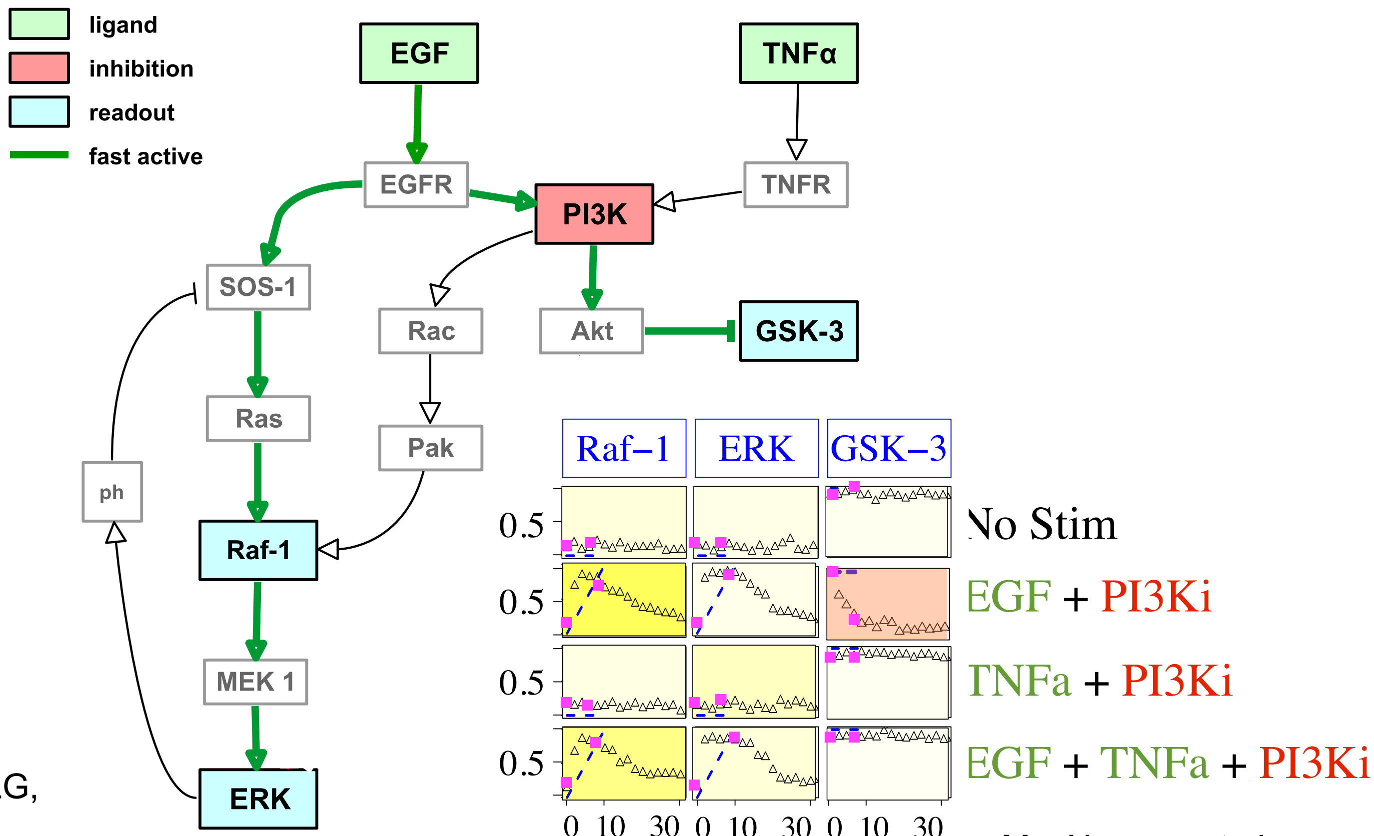

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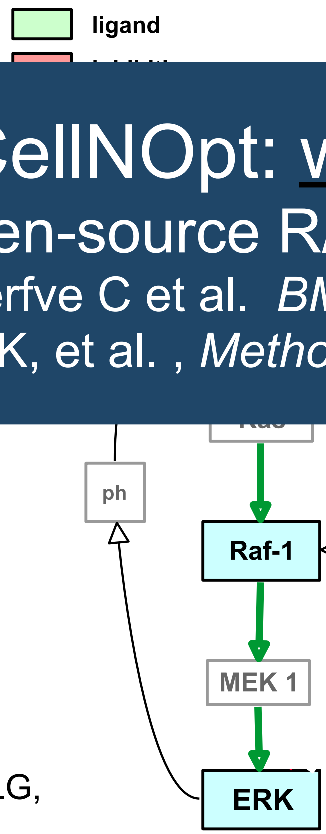
CellNOpt: www.cellnopt.org

free open-source R/Python/Matlab/Cytoscape

Terfve C et al. *BMC Syst Biol*, 6:133, 2012

Morris MK, et al. , *Methods Mol. Biol*, 930:179-214, 2013



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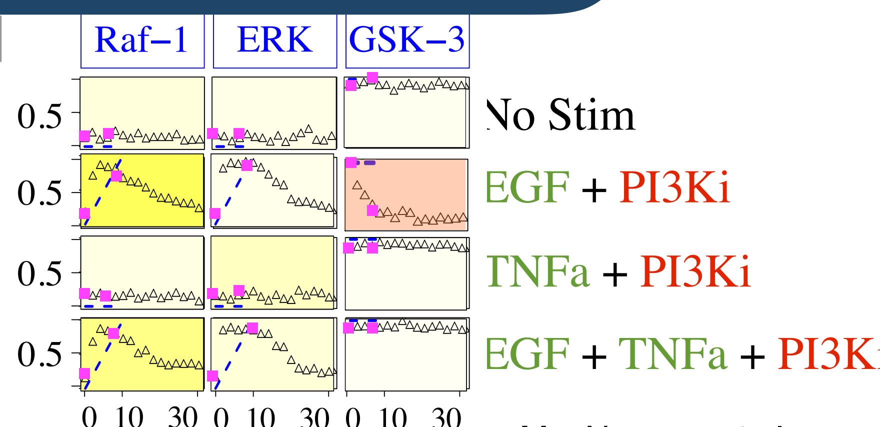
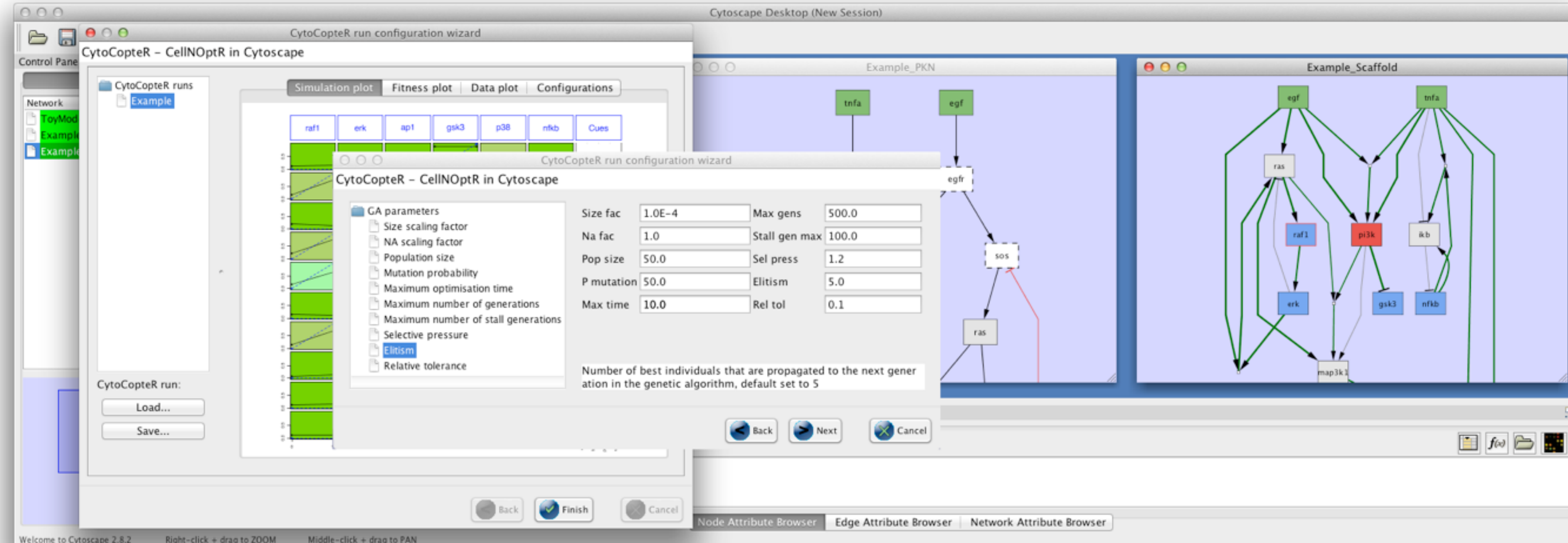


MacNamara et al. *Phys Biol* 9 045003, 2012

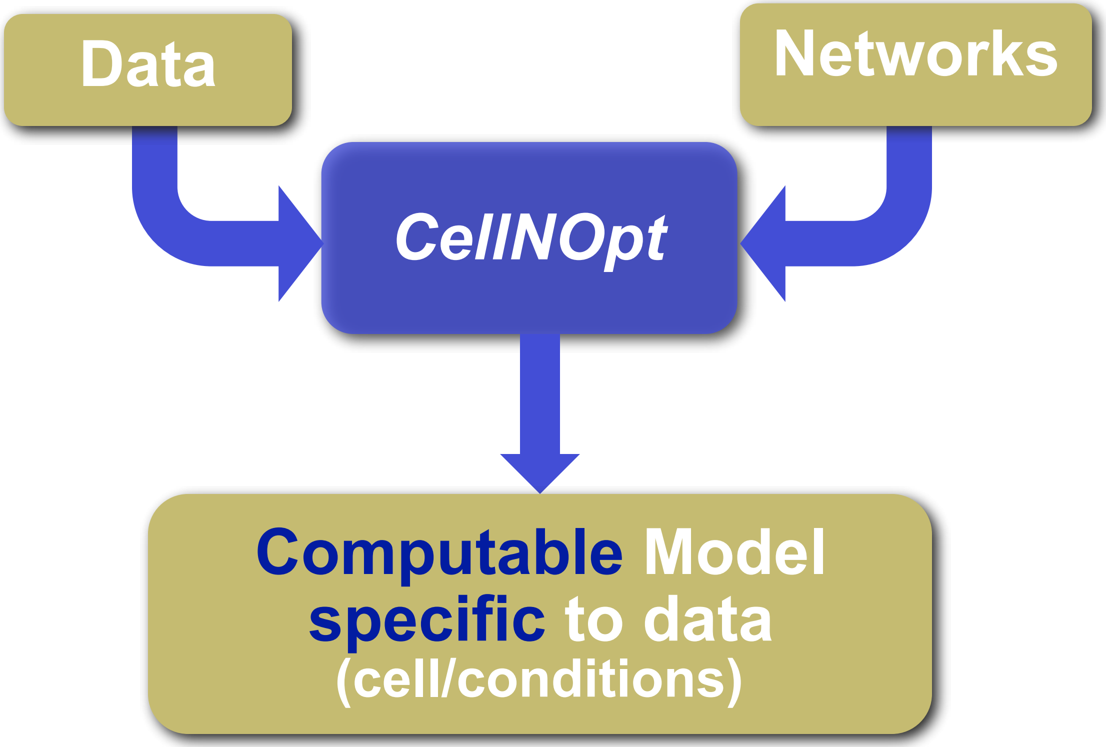
CytoCopter - CellNOpt in Cytoscape

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

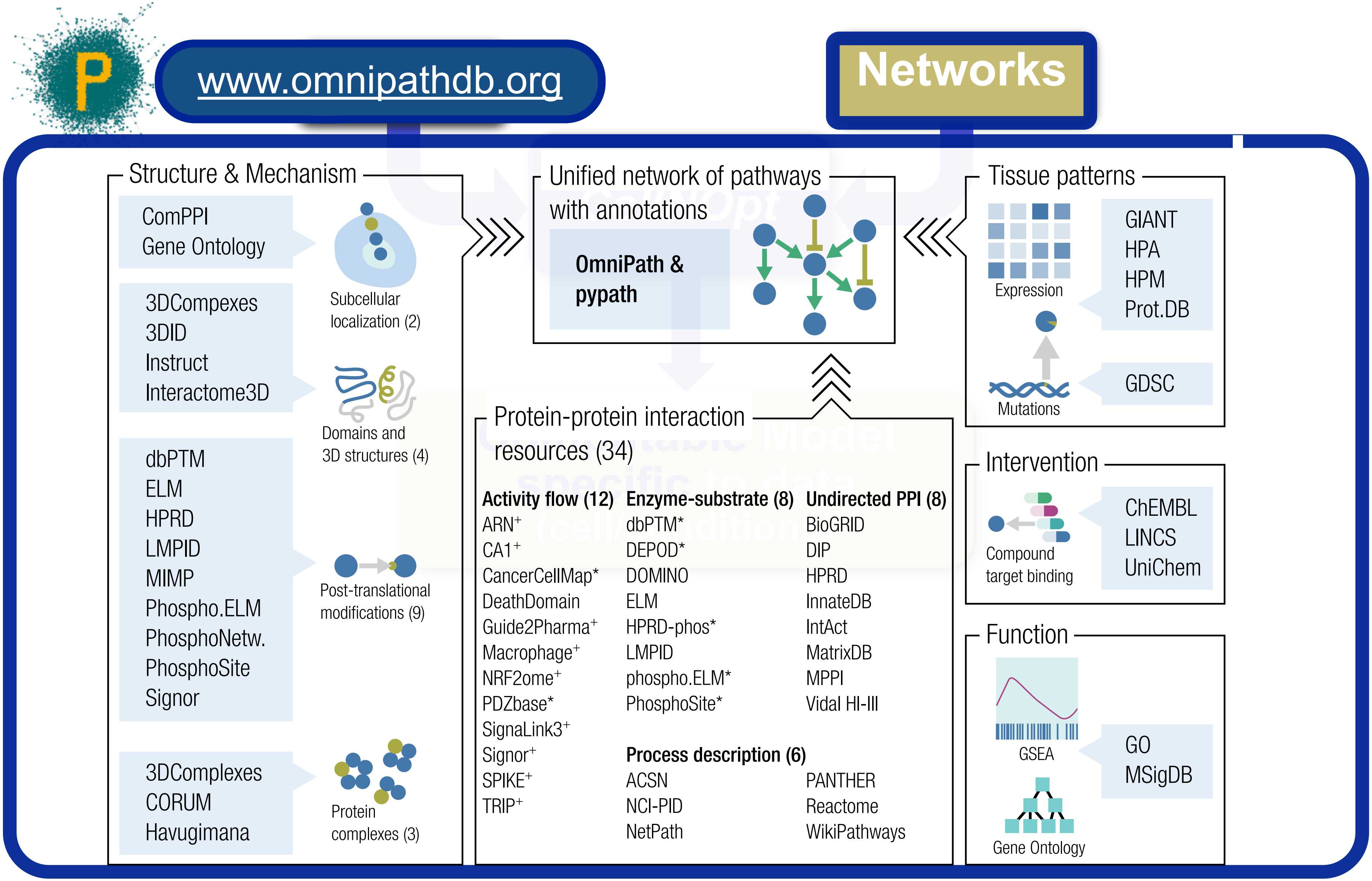


Emanuel Gonçalves **Martijn van Iersel**

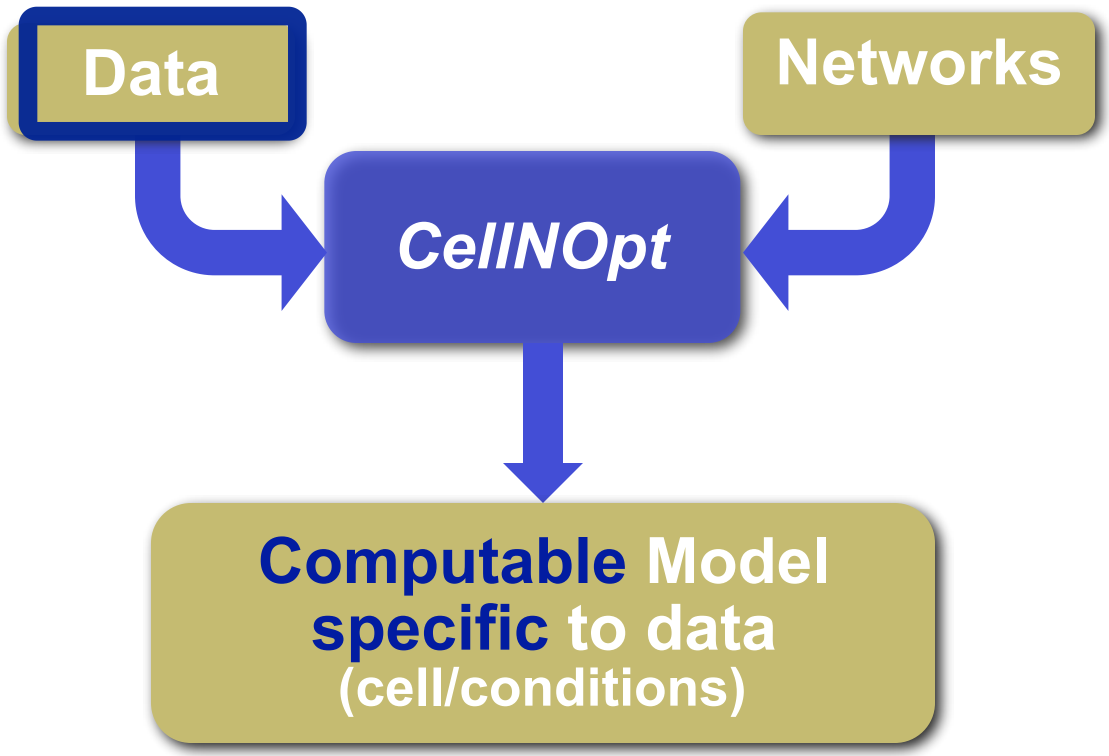
Terfve C *BMC Syst Biol, 6:*133, 2012


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

Omnipath: Integration of existing pathway resources to improve modelling



Turei, Korcsmaros, Saez-Rodriguez, *Nature Methods,* 2016


Data
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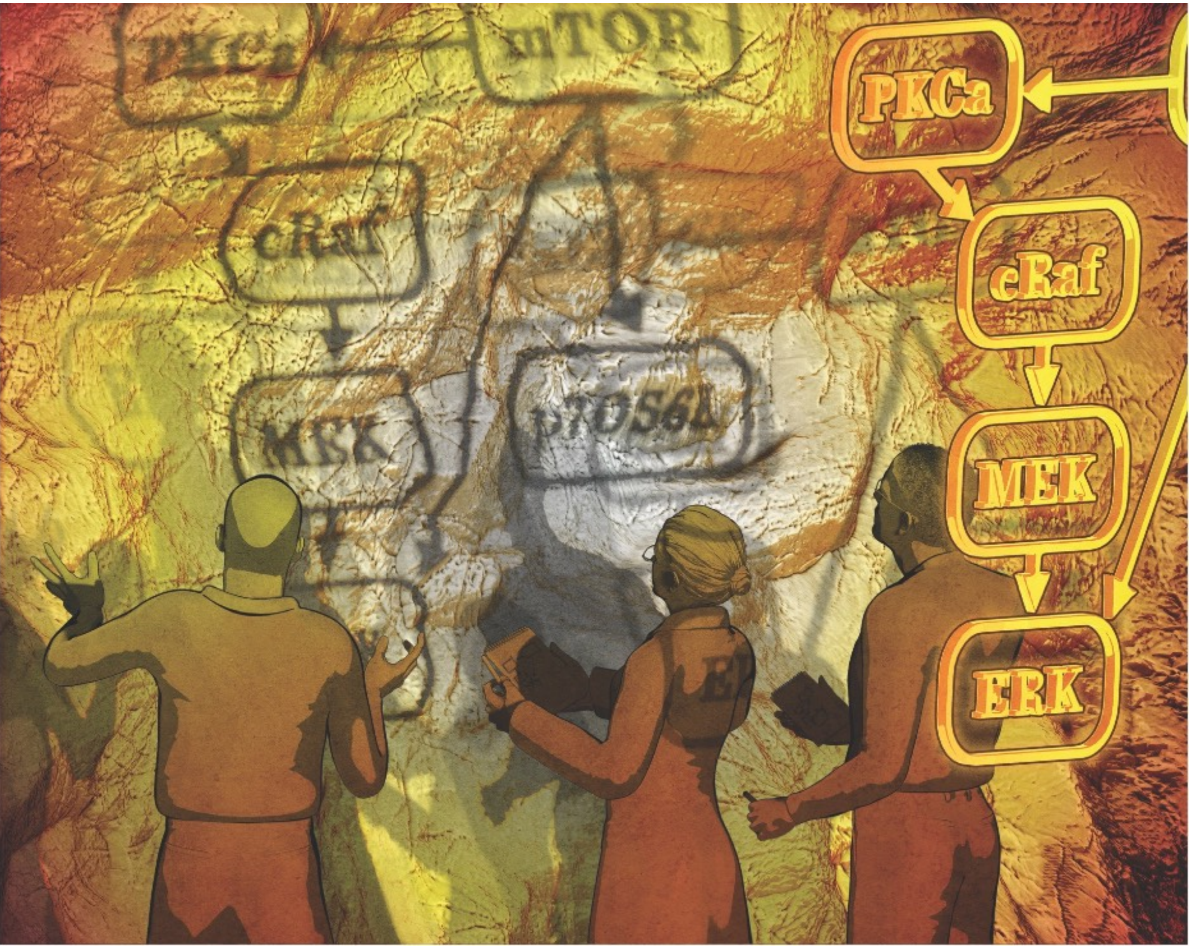
Plato's allegory of the cave

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

Challenges modelling signalling networks



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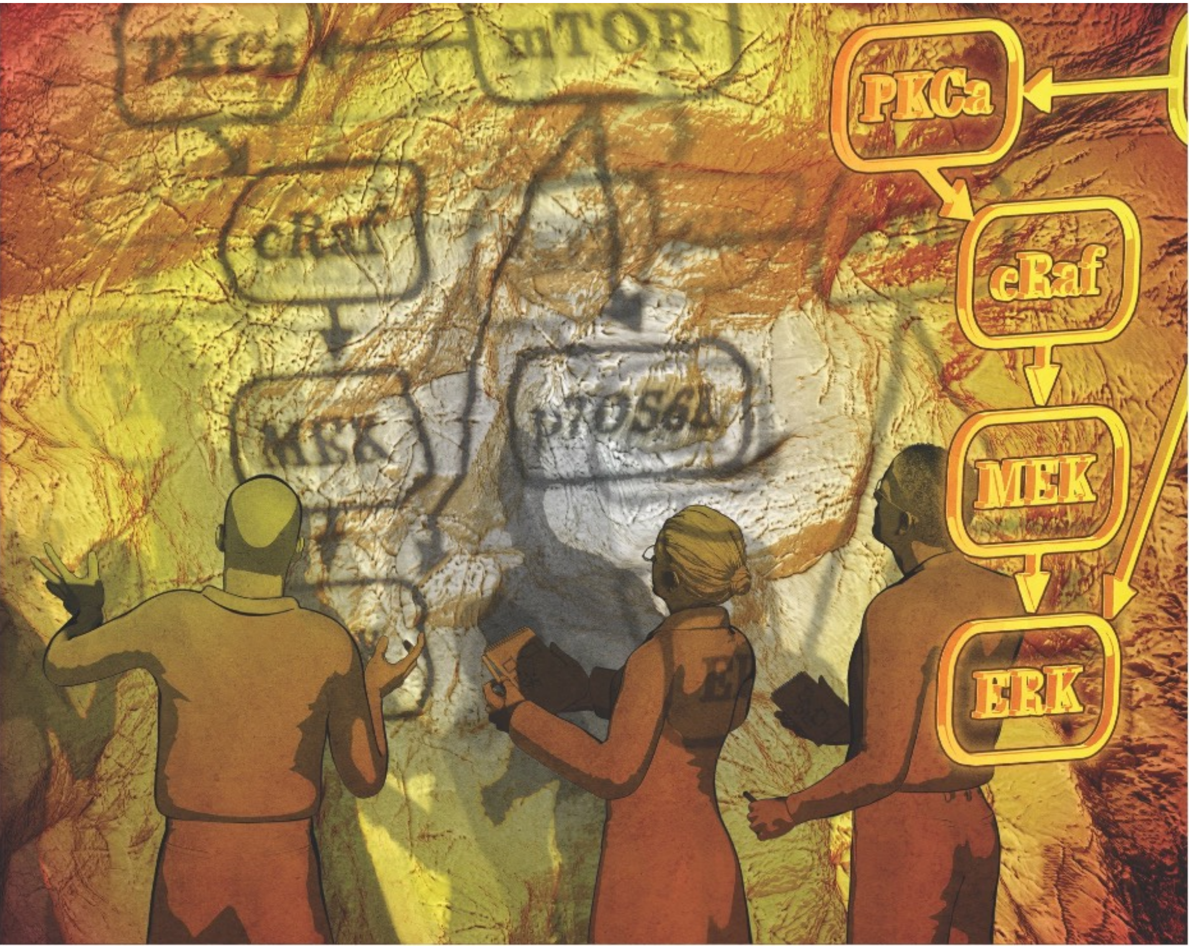

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- **Cues** are **lights**

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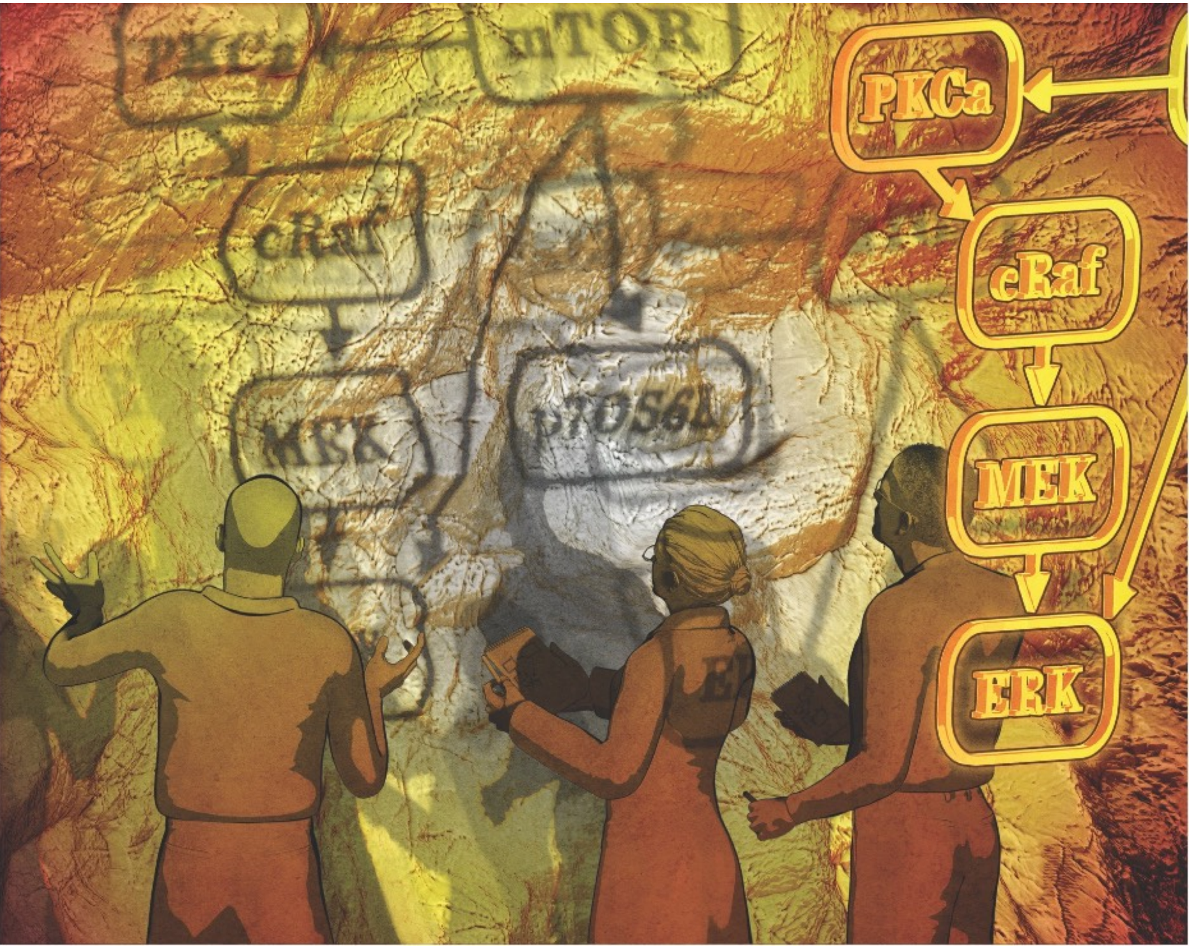

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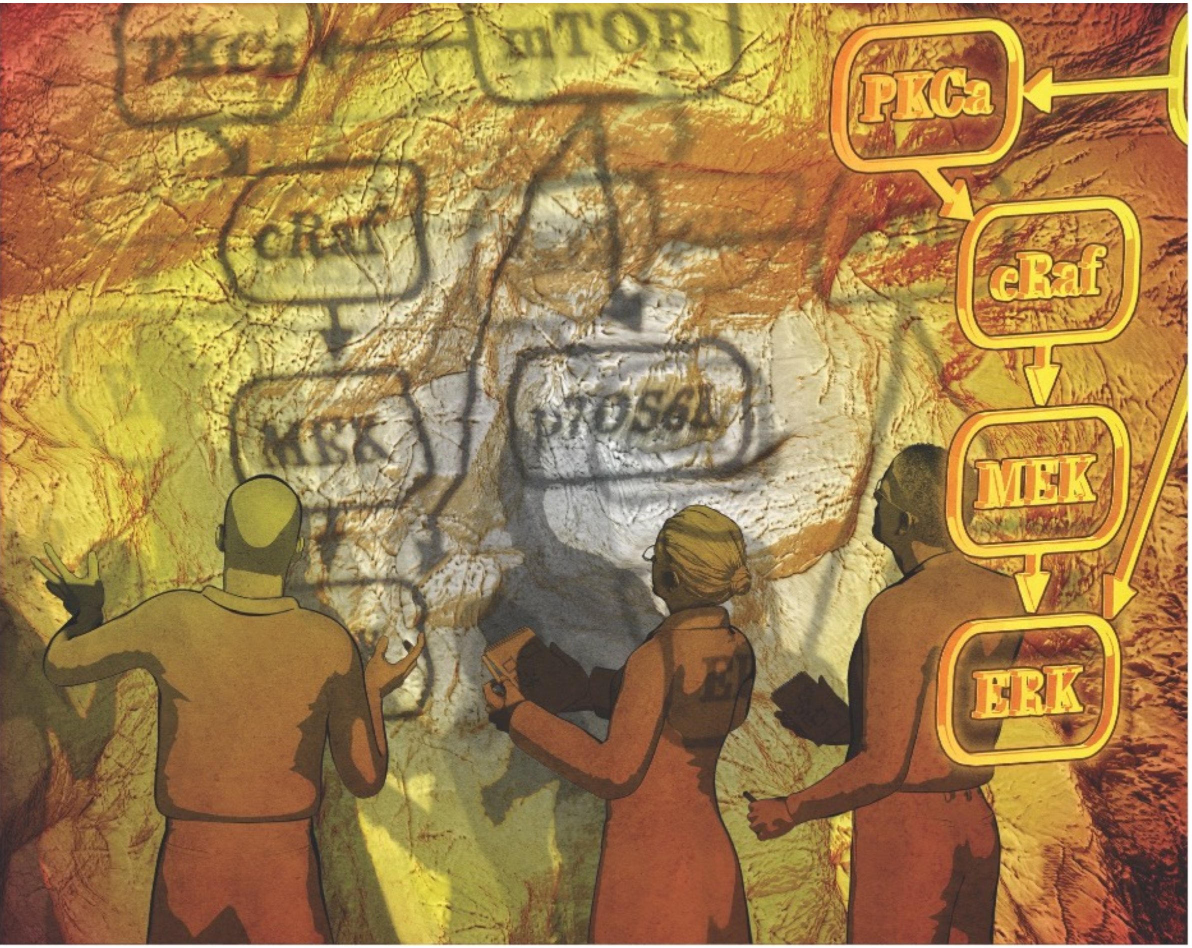
- **Cues** are **lights**
- **Measurements** are **shadows**:
  - Phosphorylation = Activation? Which site? How does it affect the regulation of the protein?

Challenges modelling signalling networks



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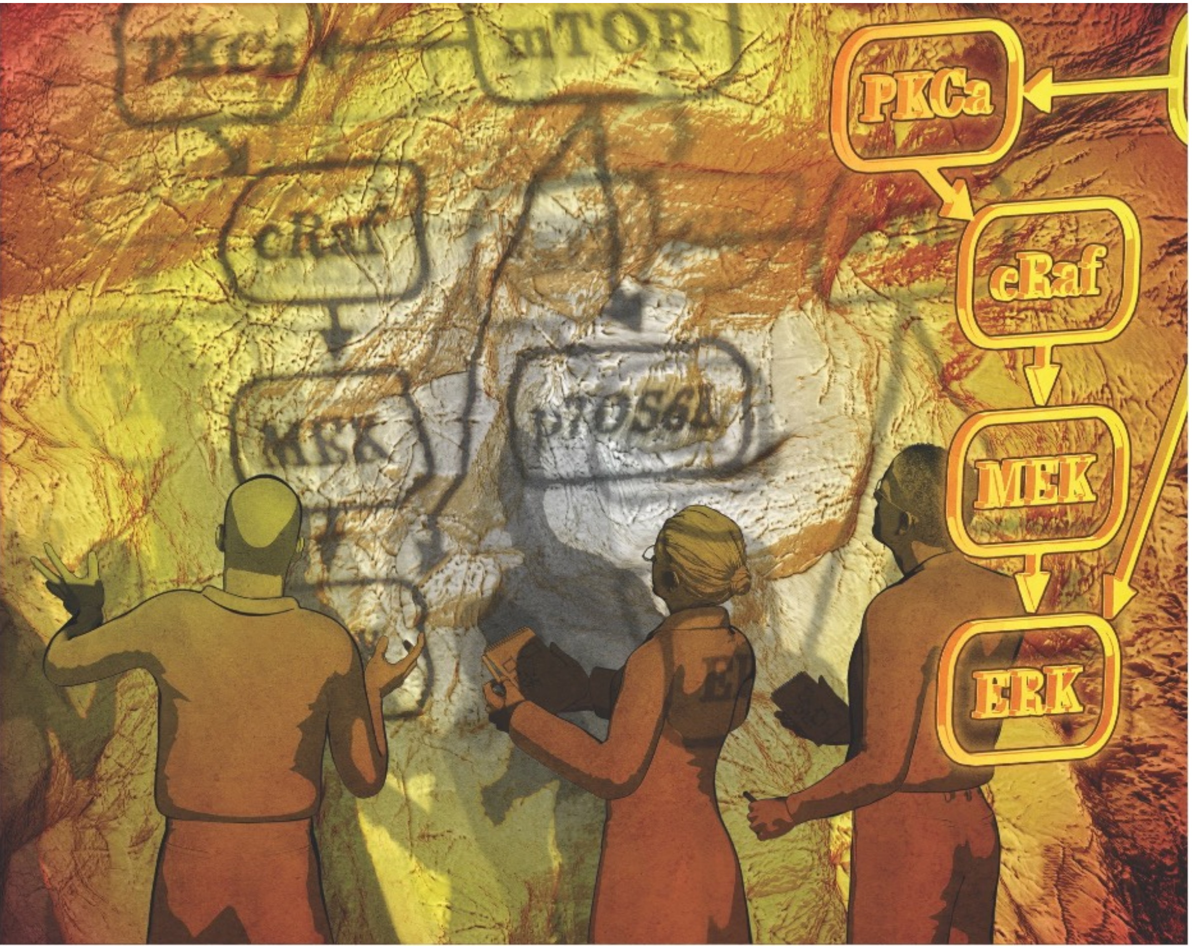
  - Fluorescence=phosphorylation?
    Signal saturated?
    Below detection level?

Challenges modelling signalling networks



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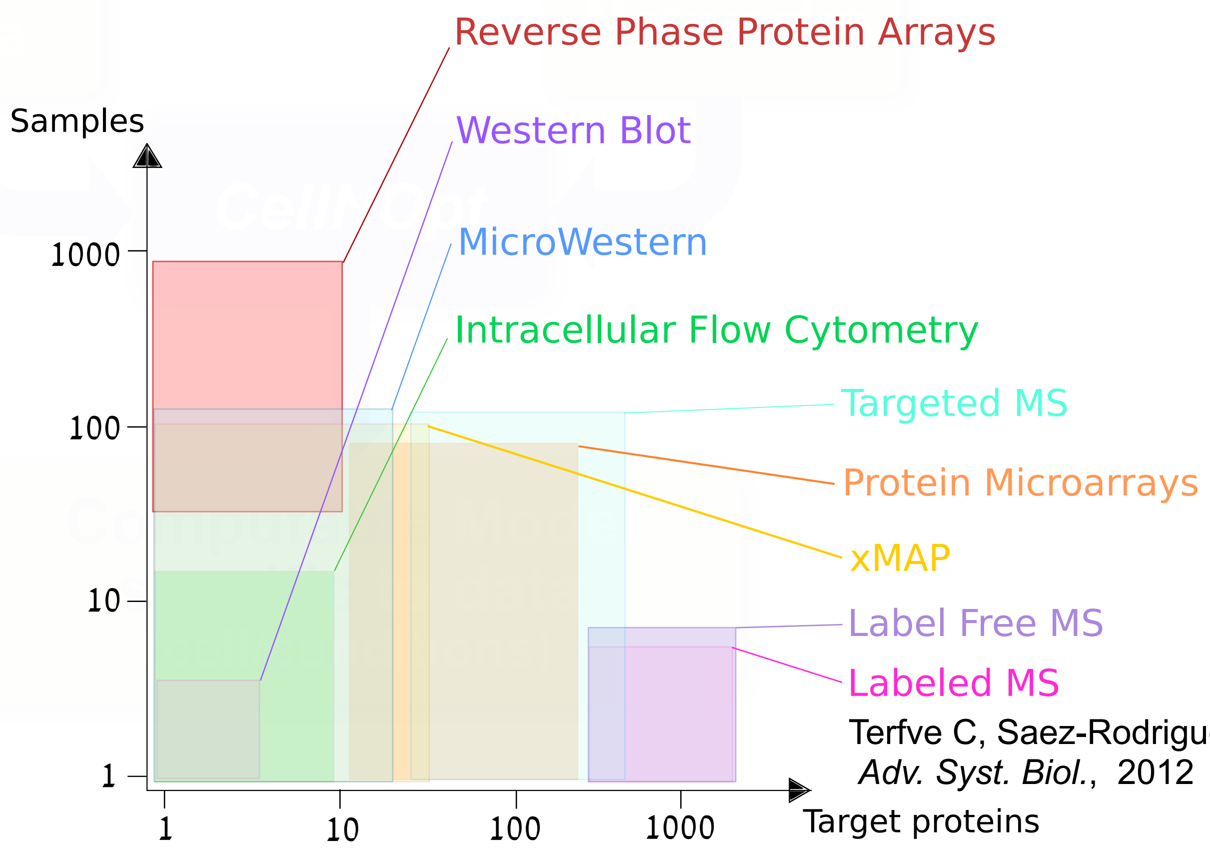
- Different 'lights' (stimulation/perturbation) provide complementary information

Leveraging different proteomic platforms

Different data types

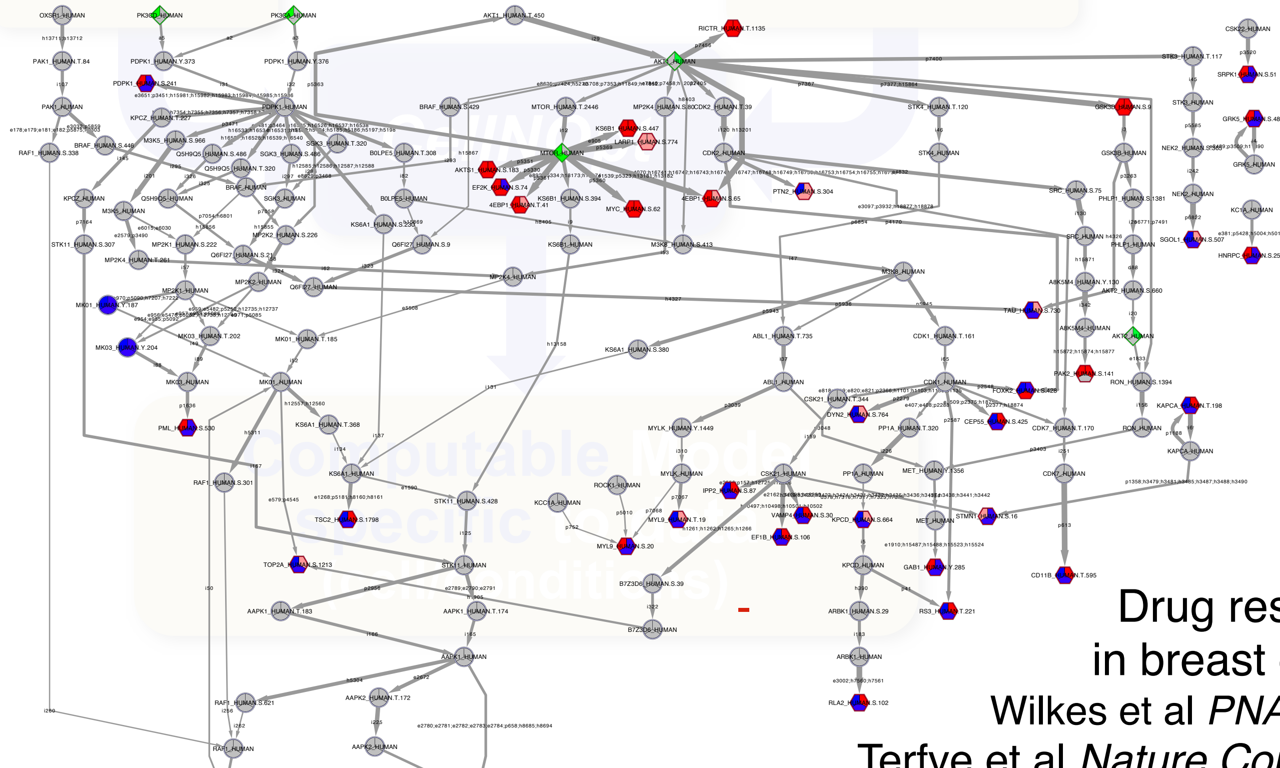


Terfve C, Saez-Rodriguez J, *Adv. Syst. Biol.*, 2012

Leveraging different proteomic platforms

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

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

- **Combination** of **proteomic** and **metabolomics** (Blattmann et al *Cell Systems* 2017)

- **Transcriptomics** (complementary tool: **CARNIVAL**)
  saezlab.github.io/CARNIVAL/

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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$\in \{0,1\}$ $\in [0,1)$

Relative importance Fit vs. Size

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In practice: small value (~0.0001) to prioritize fitness of data

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Relative importance Fit vs. Size

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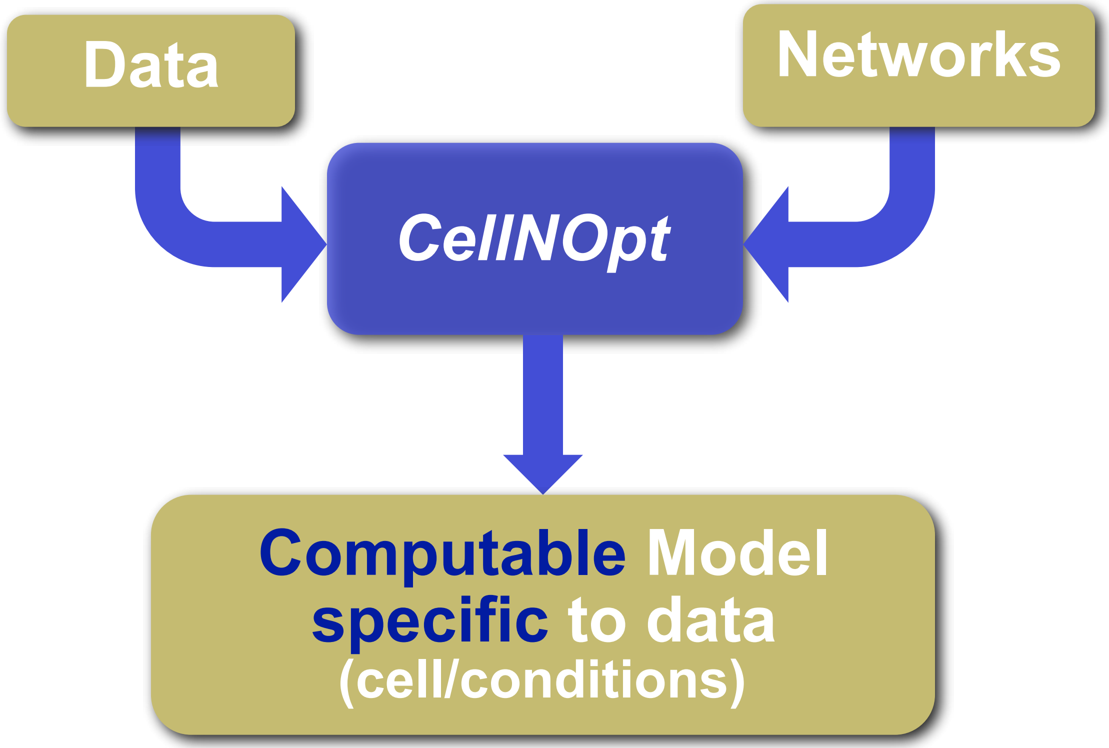
Best model ~ minimum metric
(optimization problem) - can be solved algorithmically

Fitting: Solving optimisation problem



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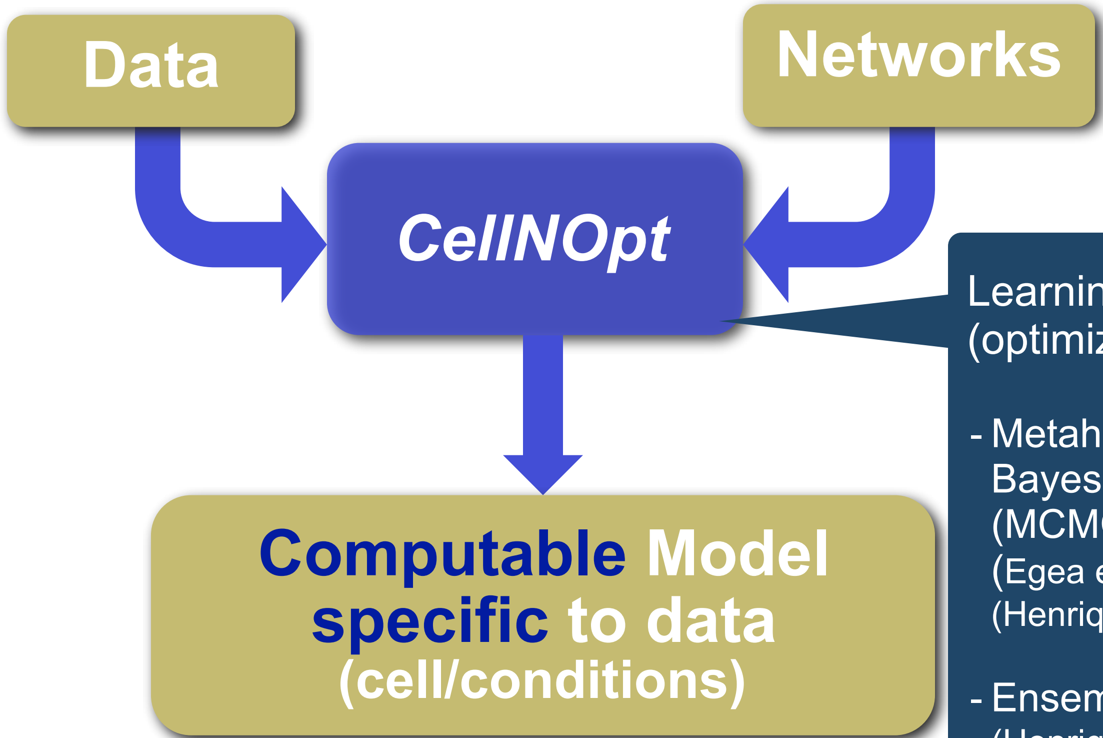
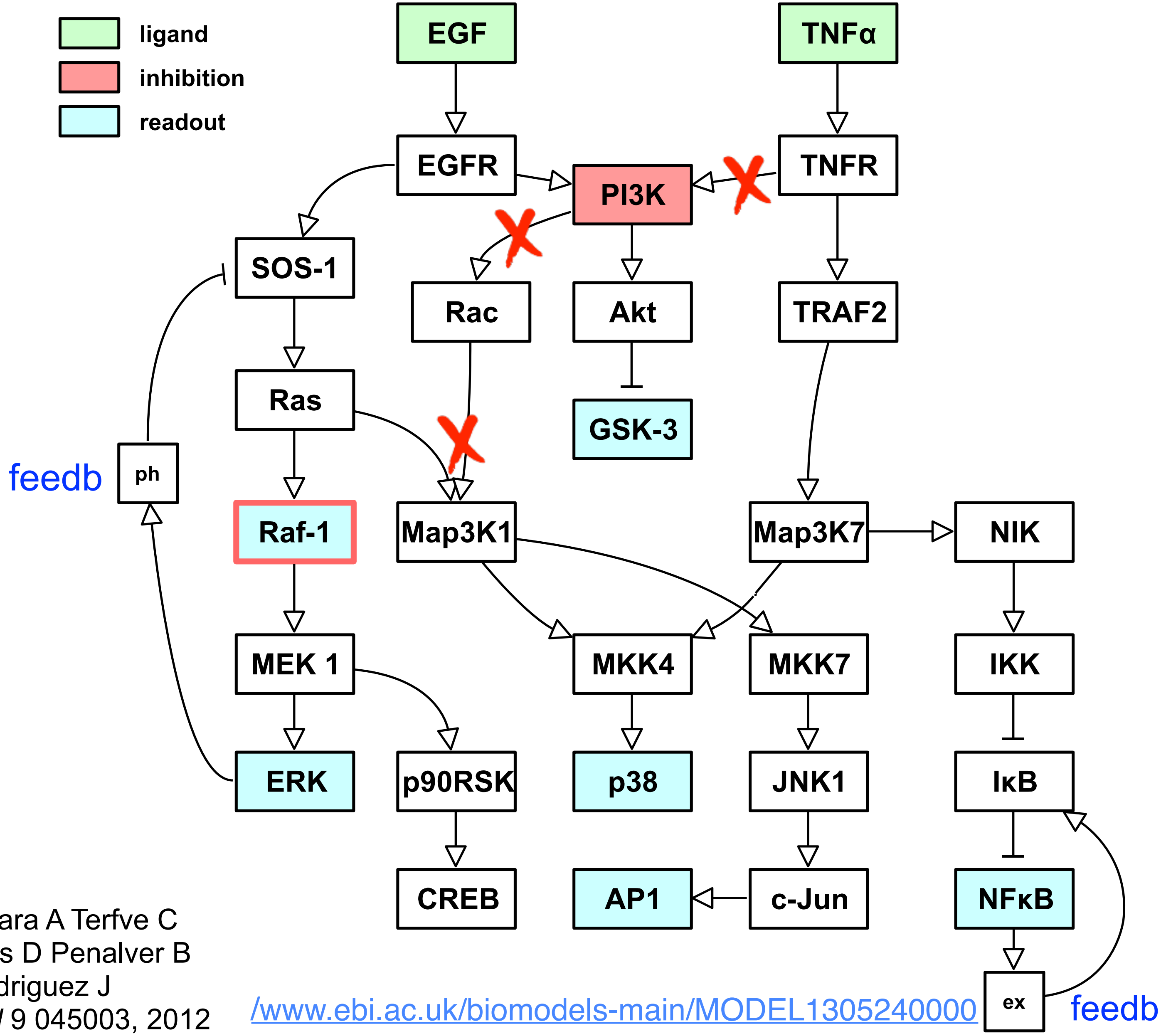


Learning algorithms (optimization):

- Metaheuristics & Bayesian Inference (MCMC) (Egea et al. *BMC Bioinf* 2014; (Henriques et al. *Bioinf* 2015)
- Ensembles of models (Henriques et al. *PLoS CB*, 2017)
- Use of Answer Set Programming (Guziolowski et al. *Bioinf* 2013, Videla et al. *Bioinf* 2017) and Integer Linear Programming (Mitsos et al *PLoS CB* 2009)

A Toy model



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

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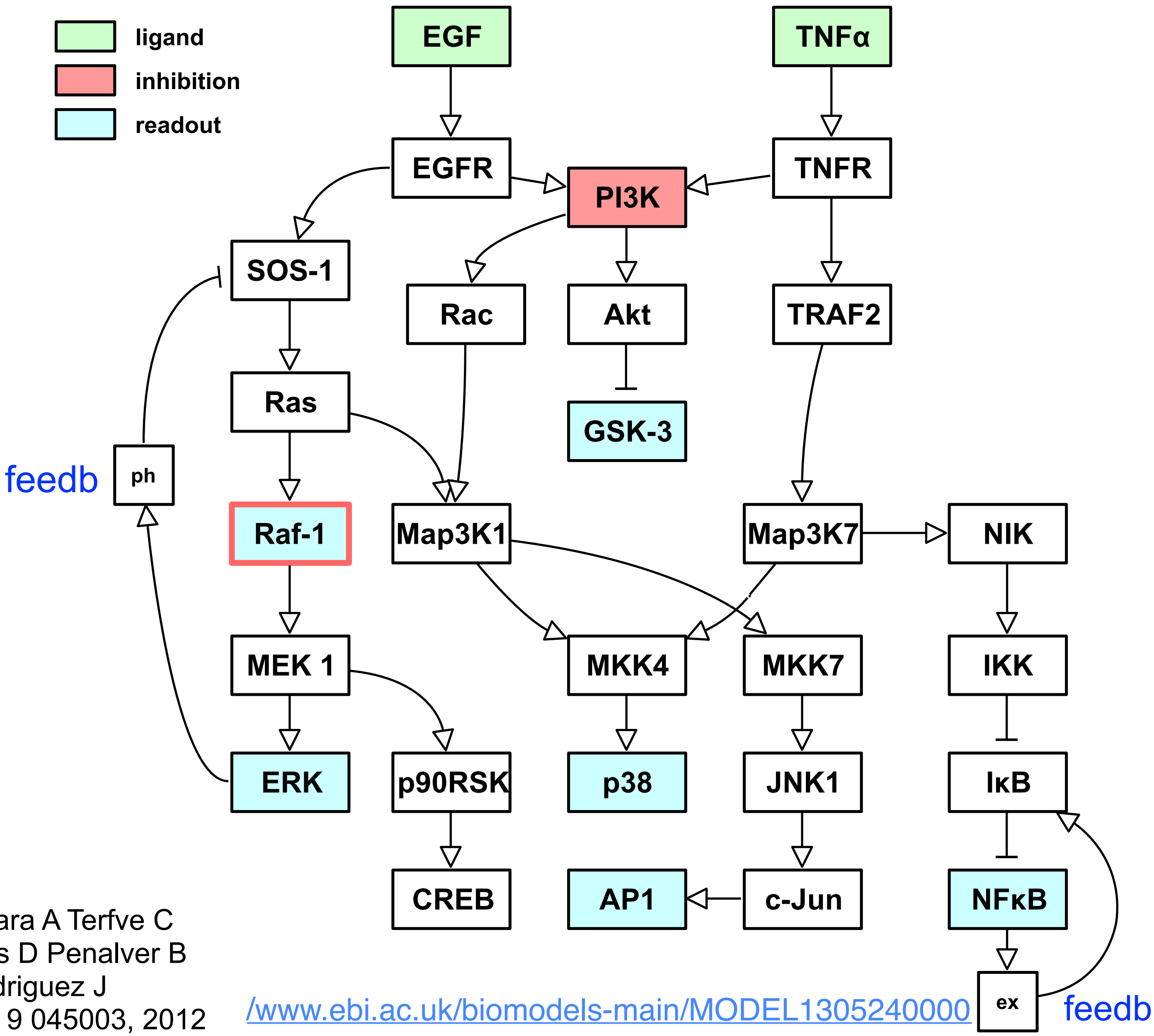

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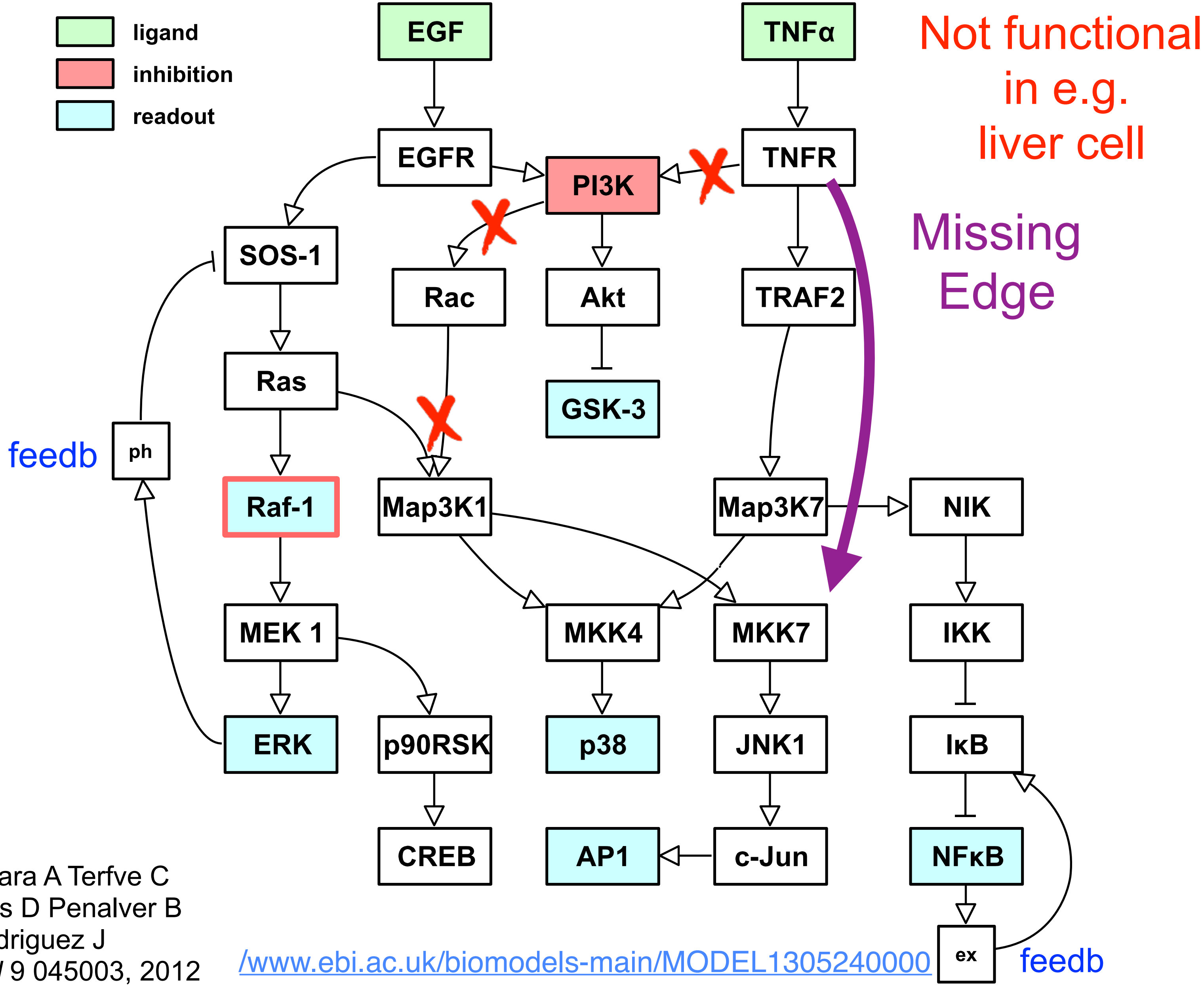

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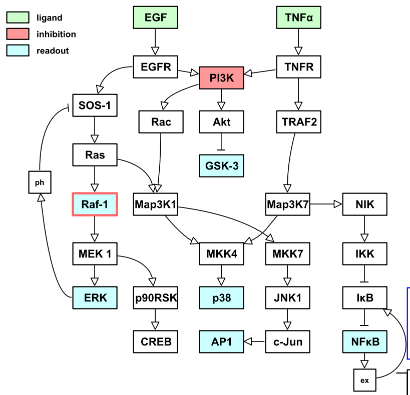
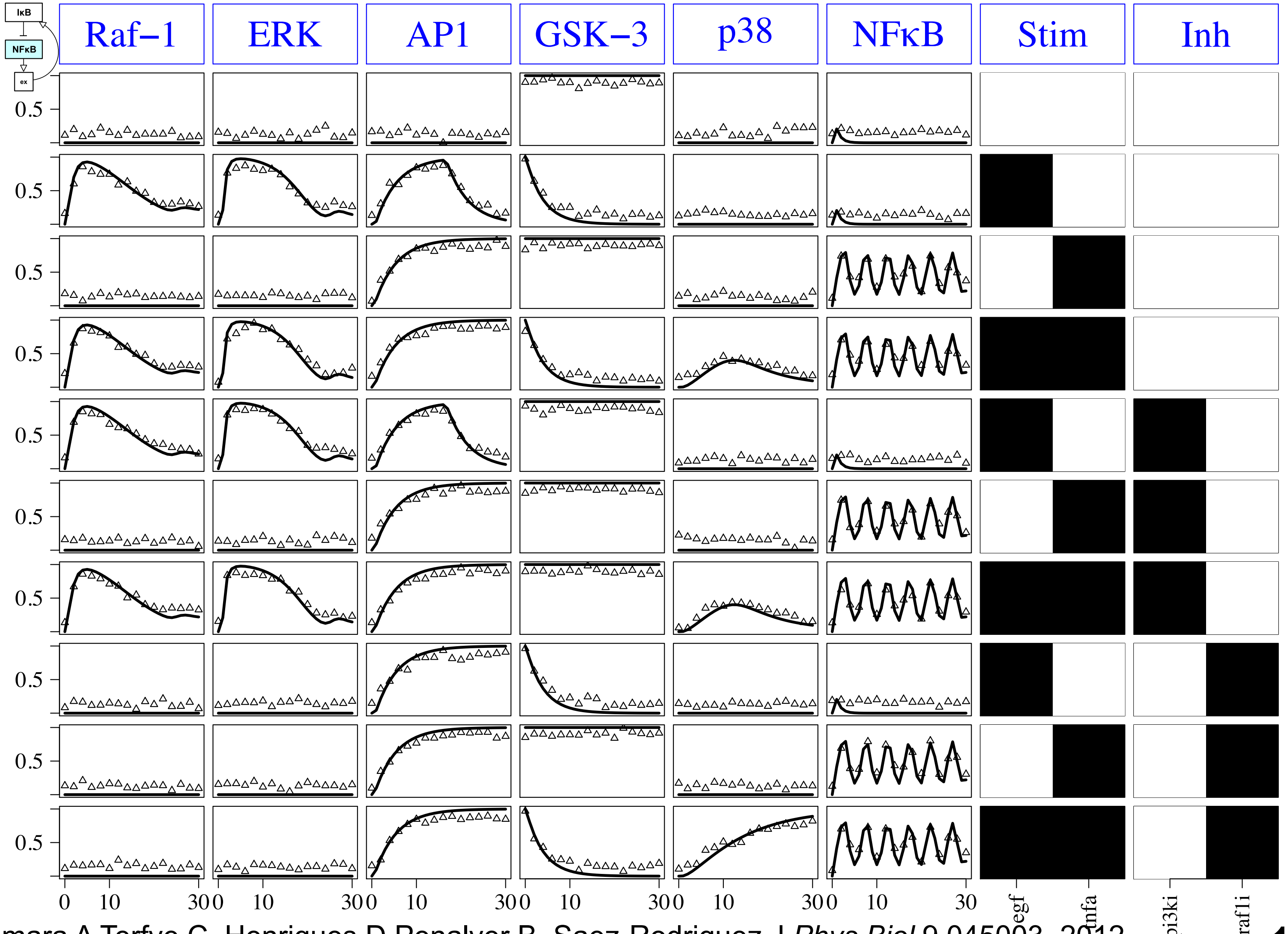


The ‘real’ data



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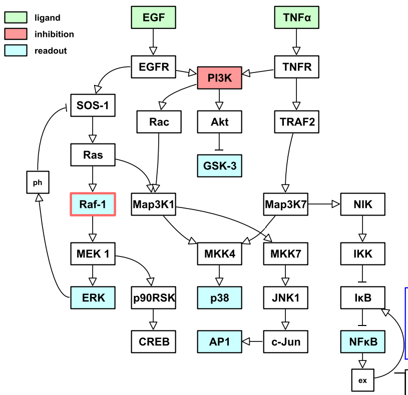
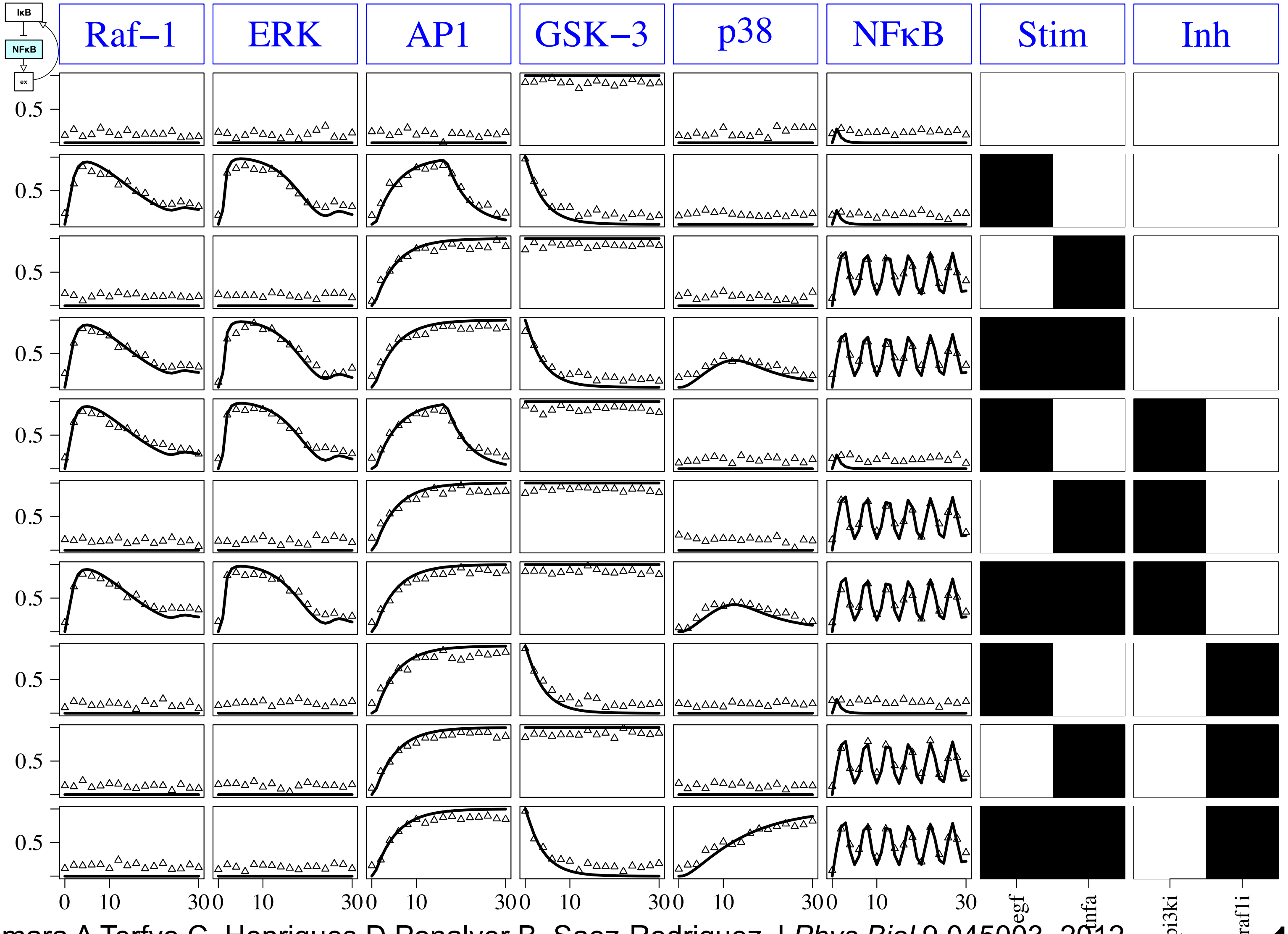


How to pick right time to measure?



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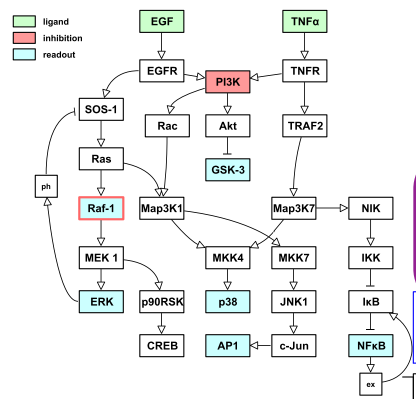
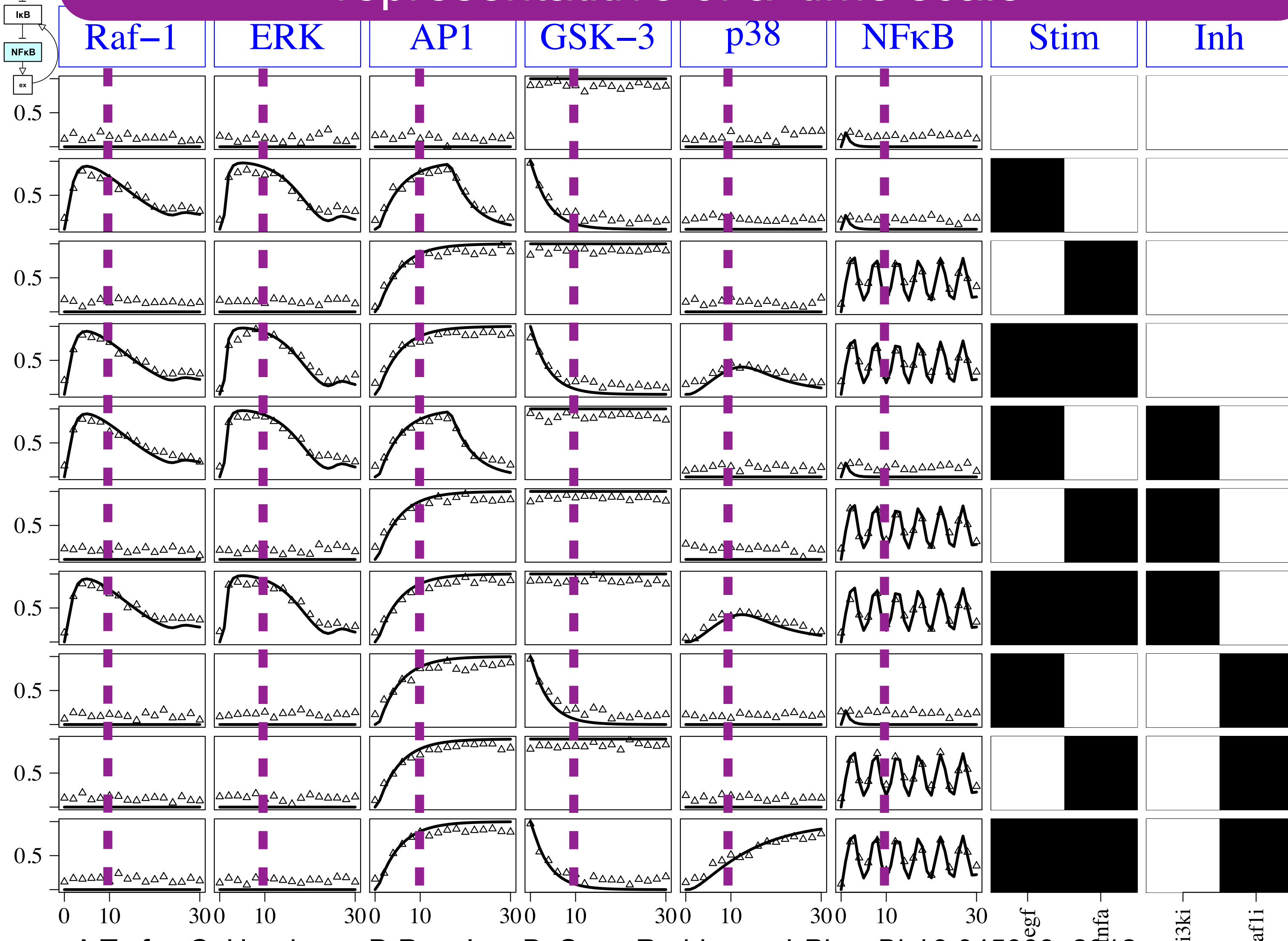


If you can only pick one ($$), choose one representatitive of a ‘time scale’

How to pick right time to measure?



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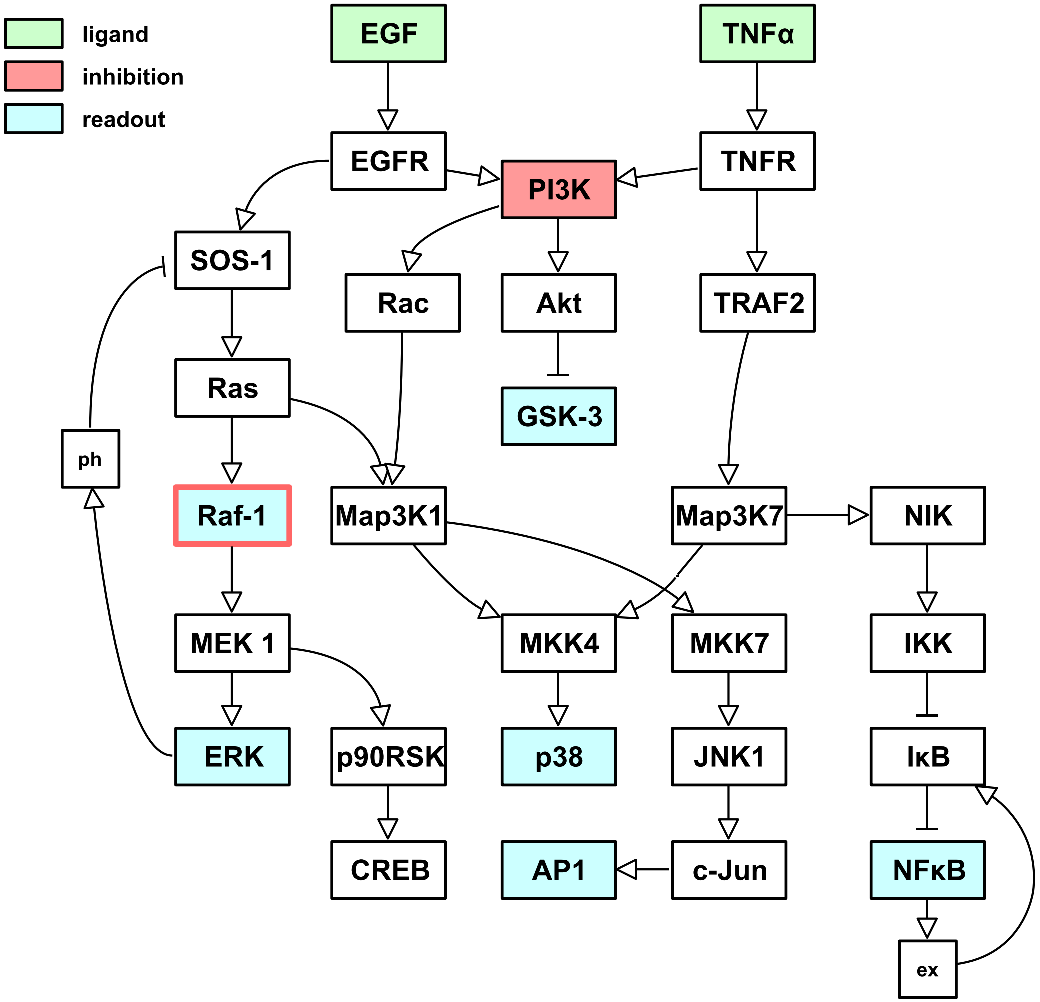
Model preprocessing:



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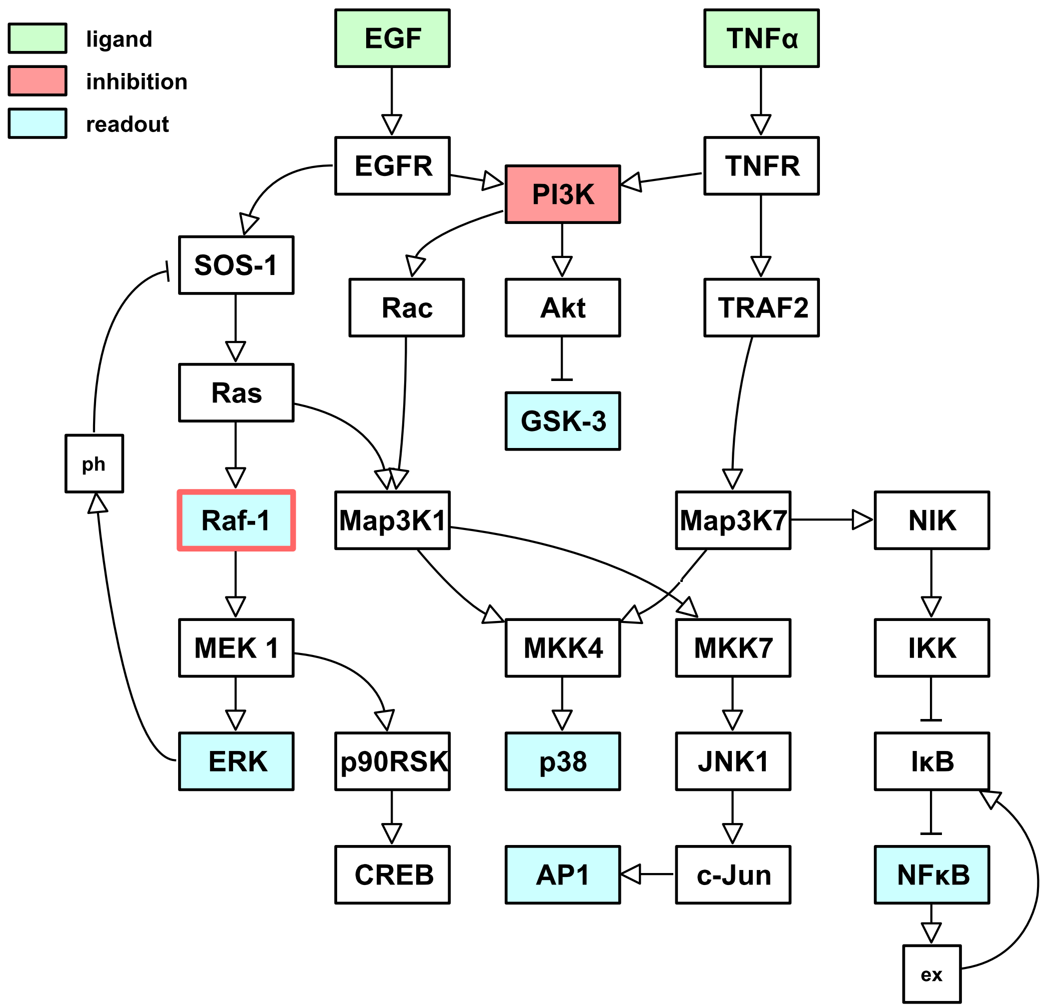
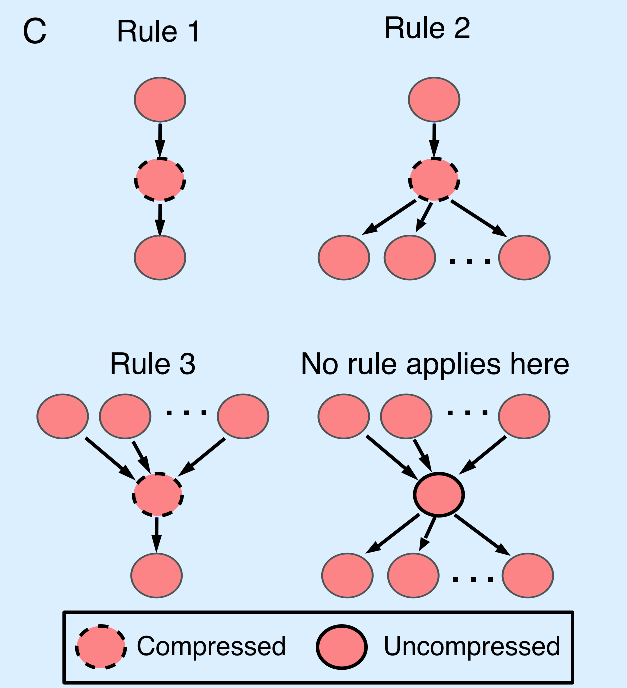


Model compression& removal of non-controlable & non-observable branches



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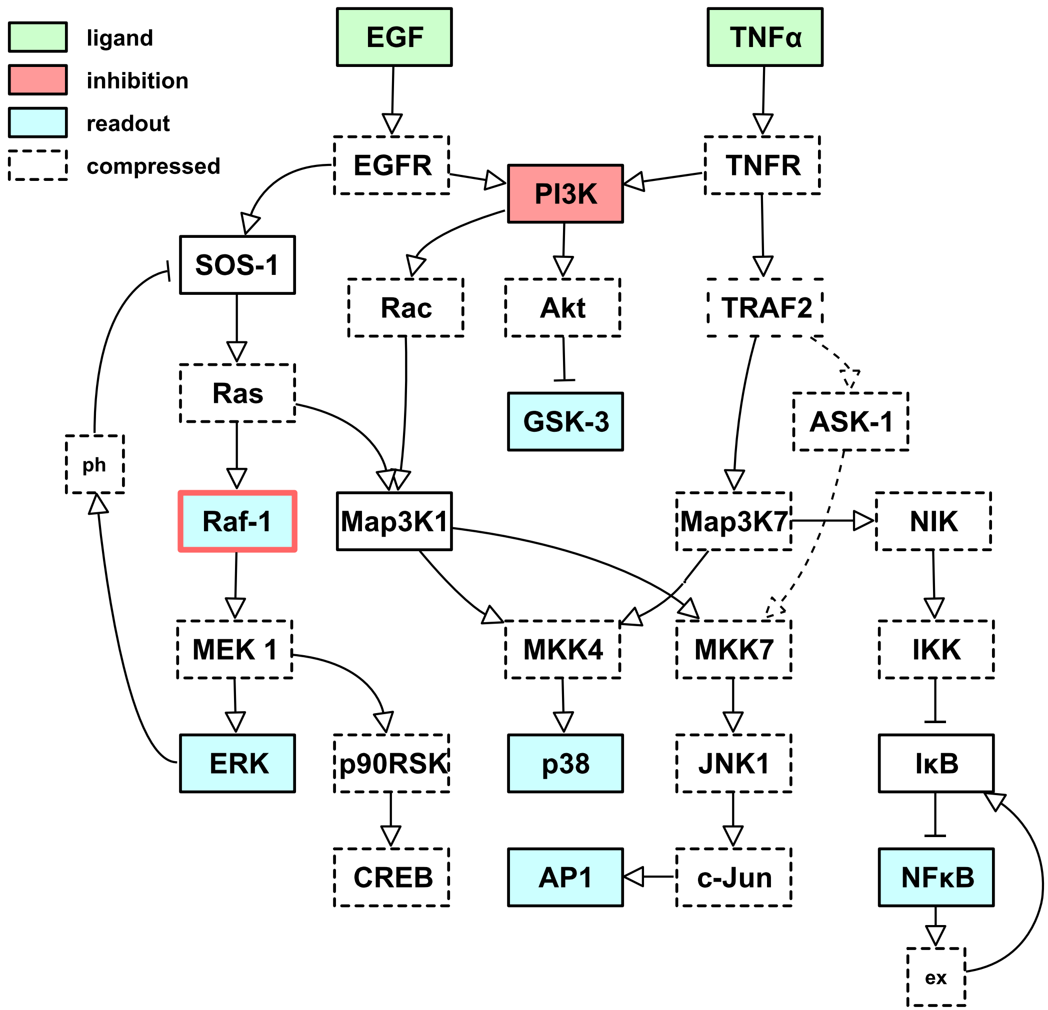

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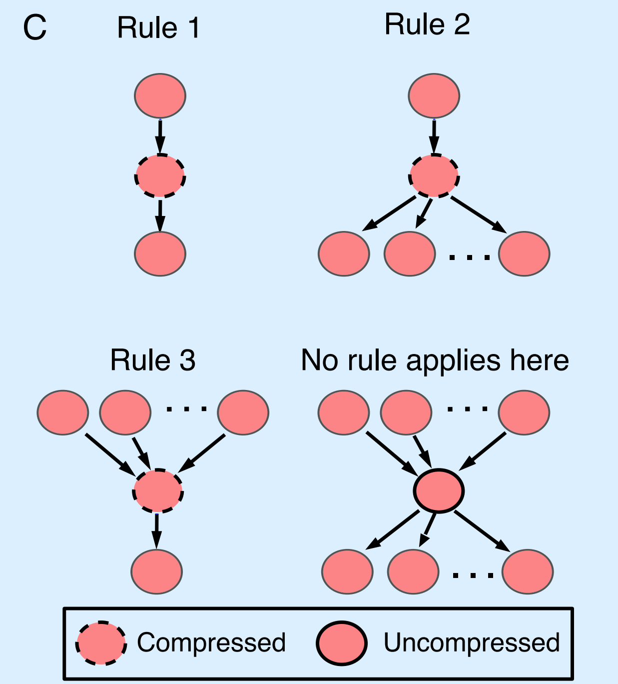
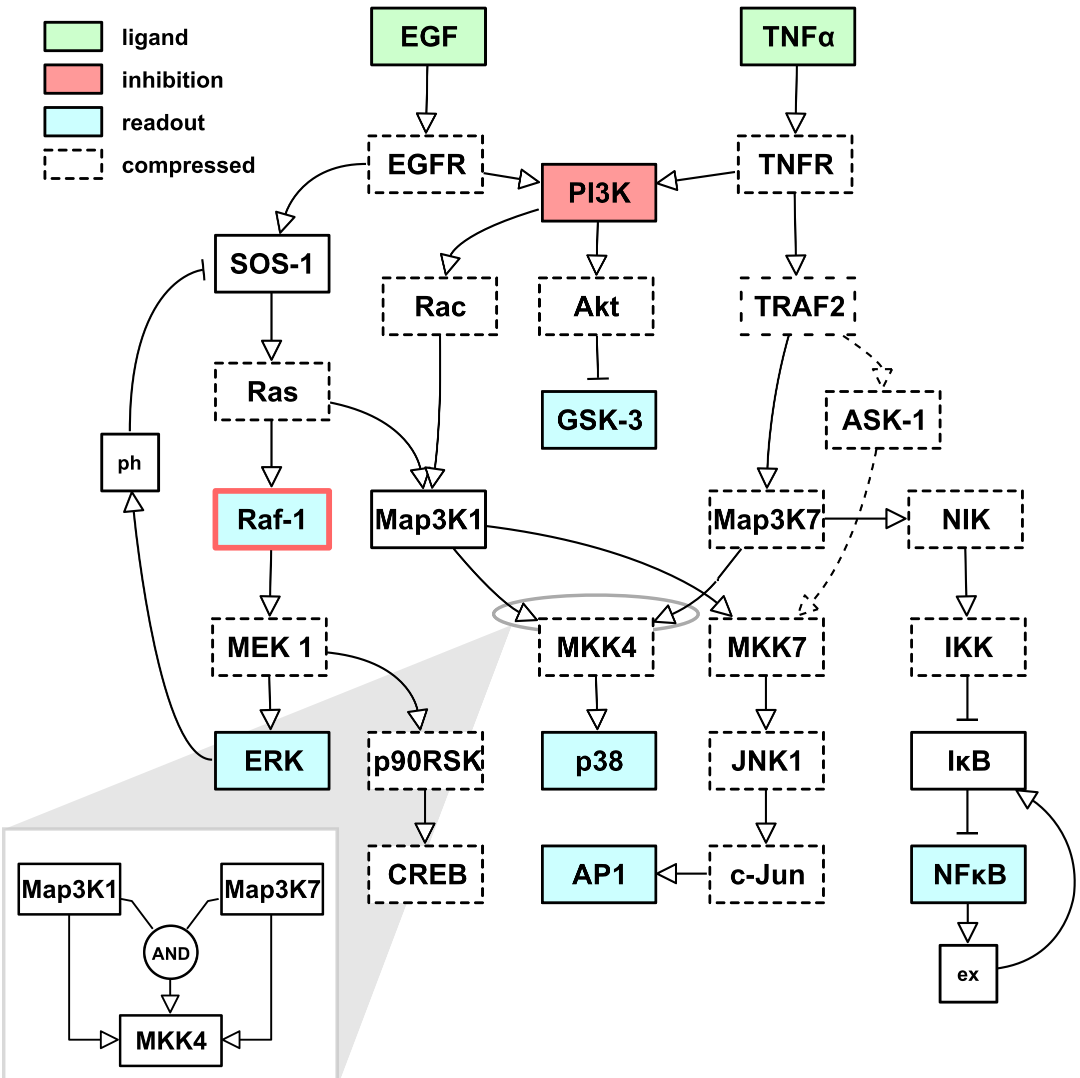


Saez-Rodriguez J, et al., *Mol. Syst. Biol*, 2009

Model preprocessing:



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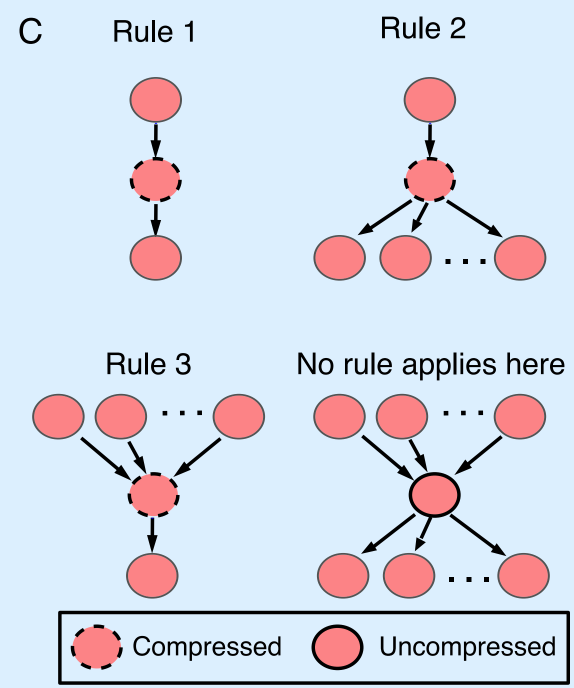

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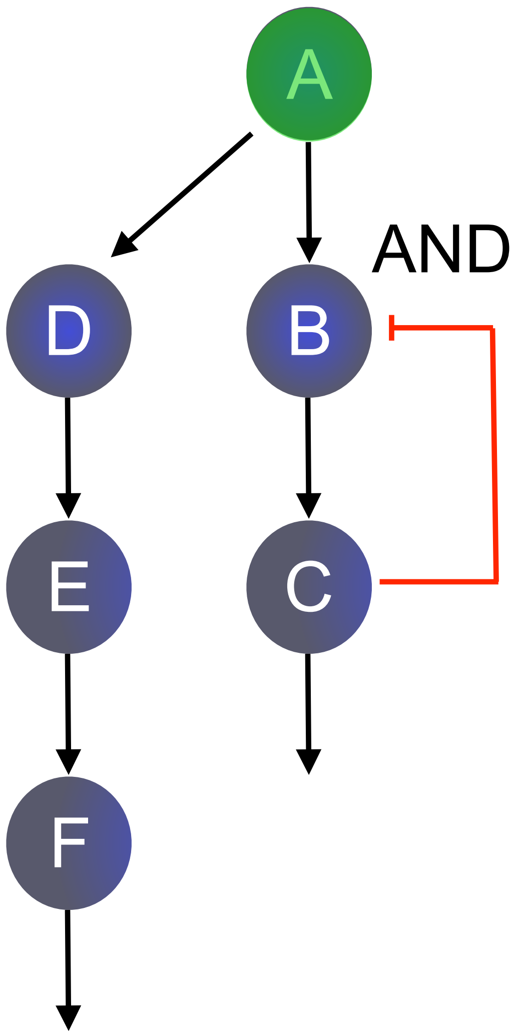
Boolean simulation performed using pseudo-steady state



Klamt, S., Saez-Rodriguez, J., Lindquist, J., Simeoni, L., Gilles, E. D., *BMC Bioinformatics,* 7:56,2006.

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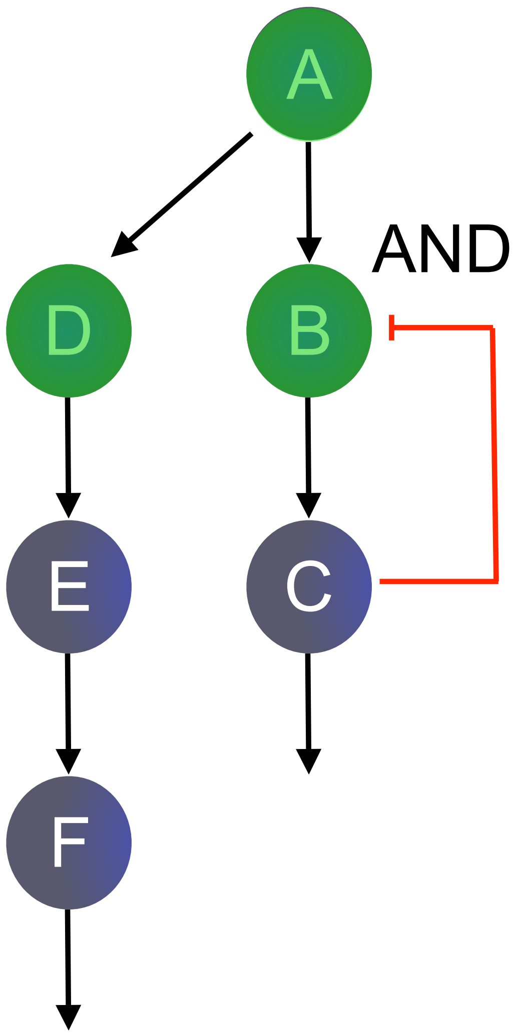

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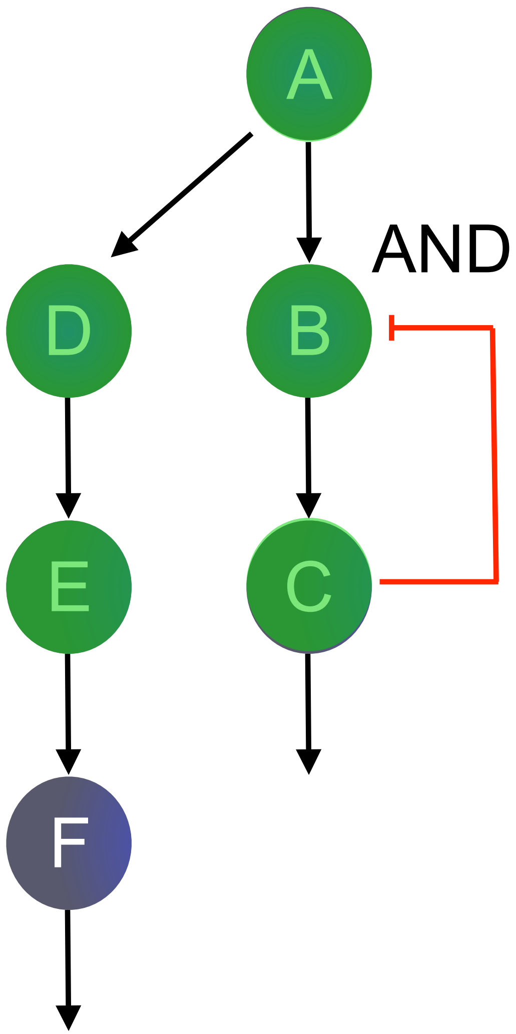

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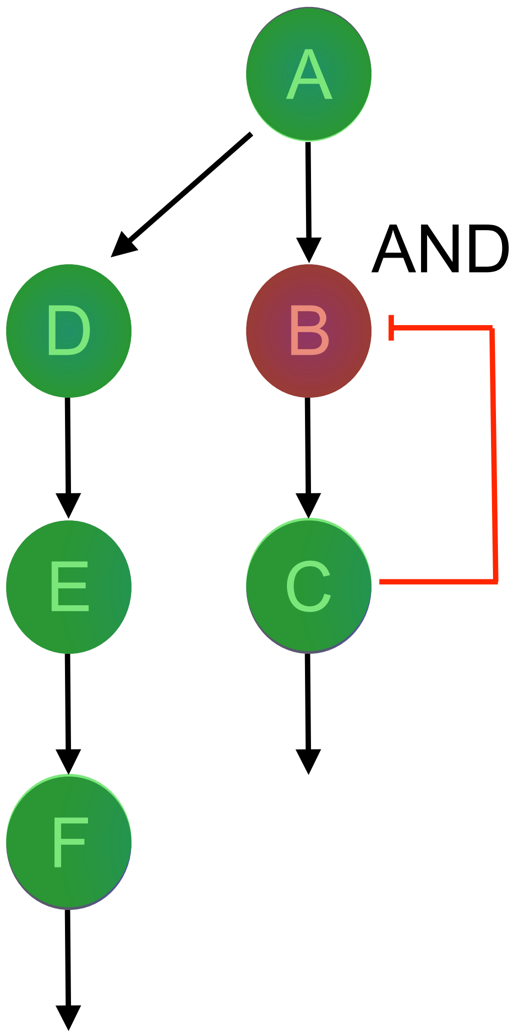

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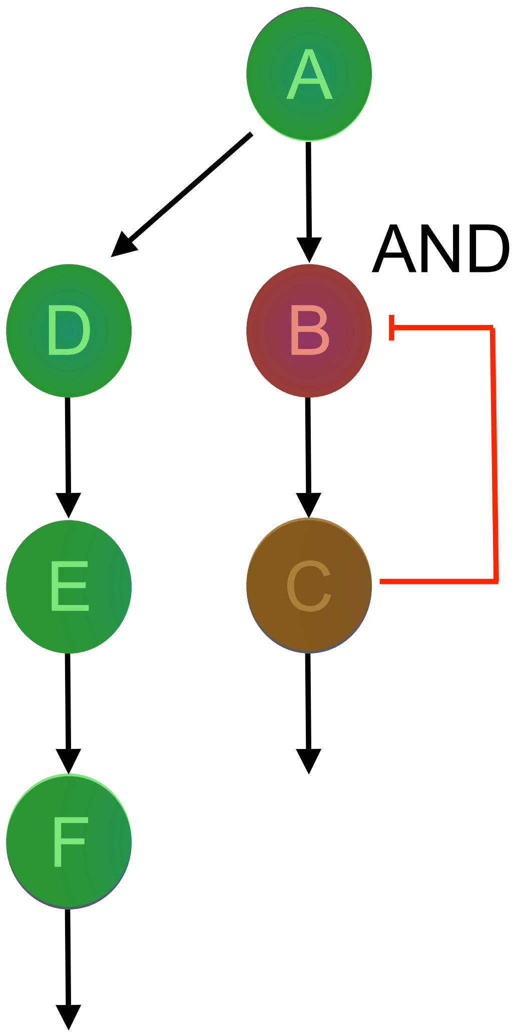

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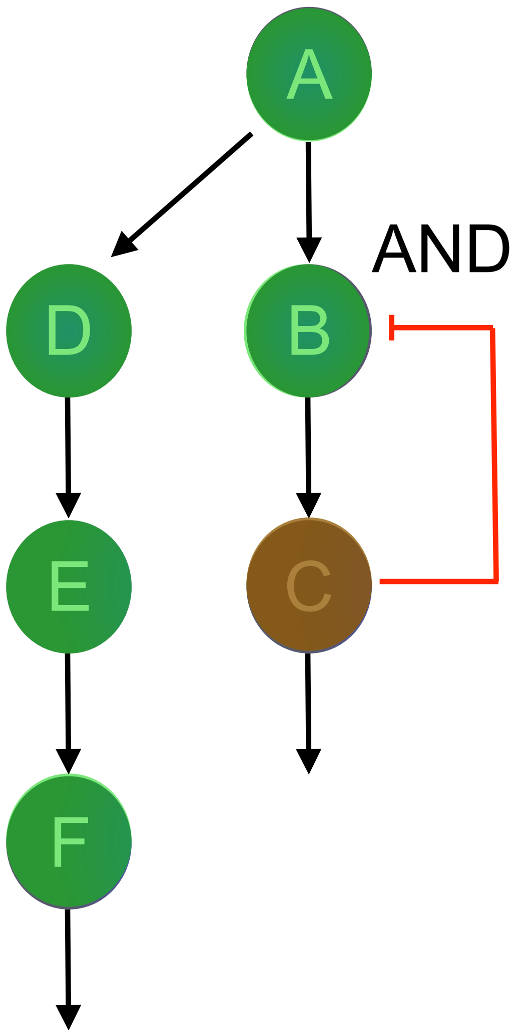

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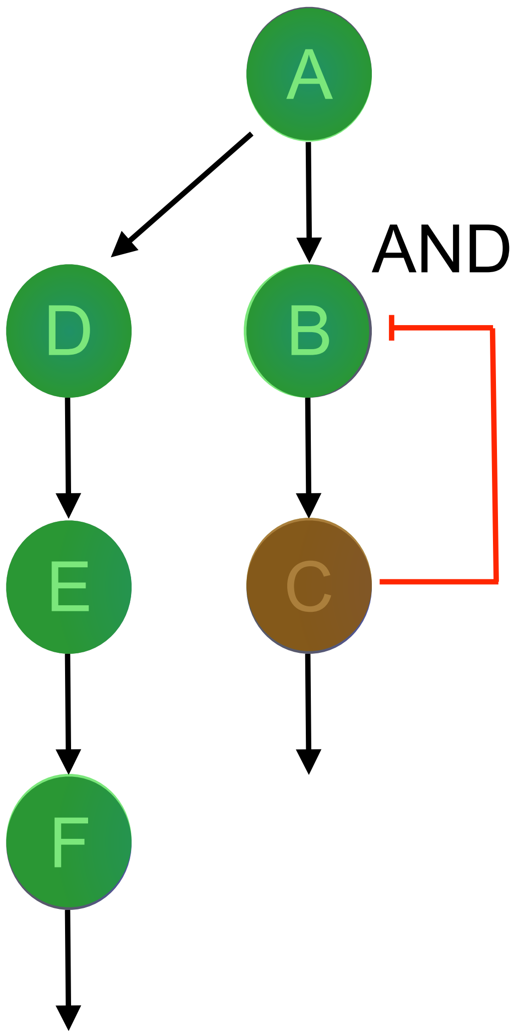

Algorithm penalizes lack of steady state, only effective for one ‘early’ time

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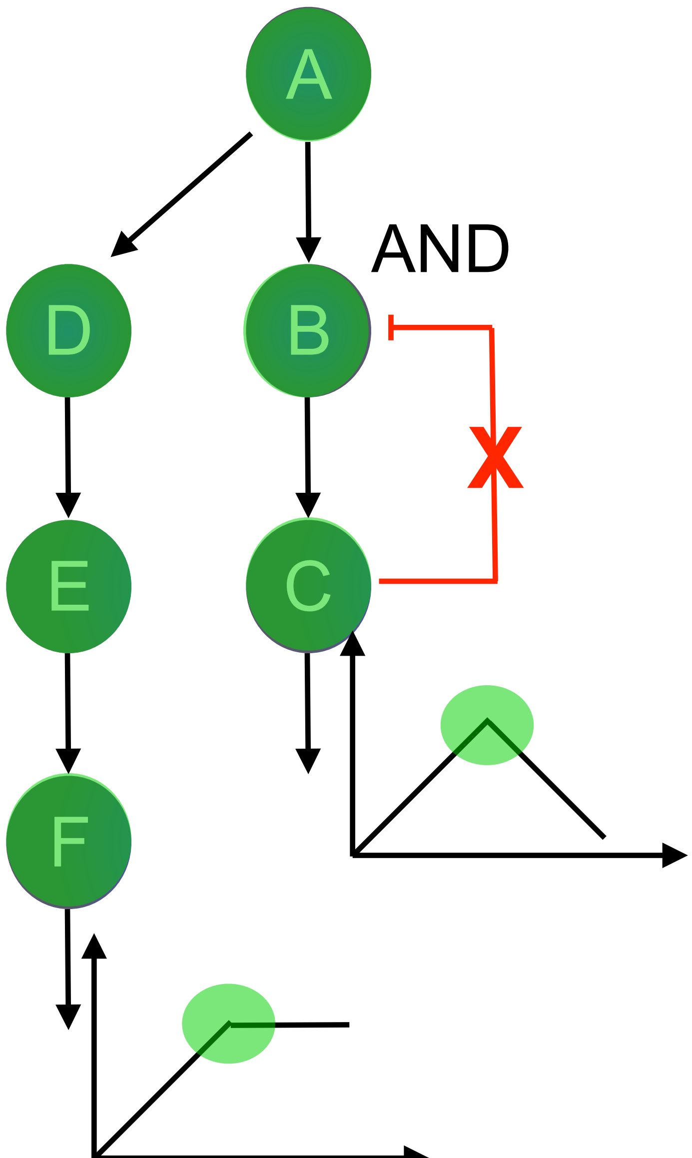

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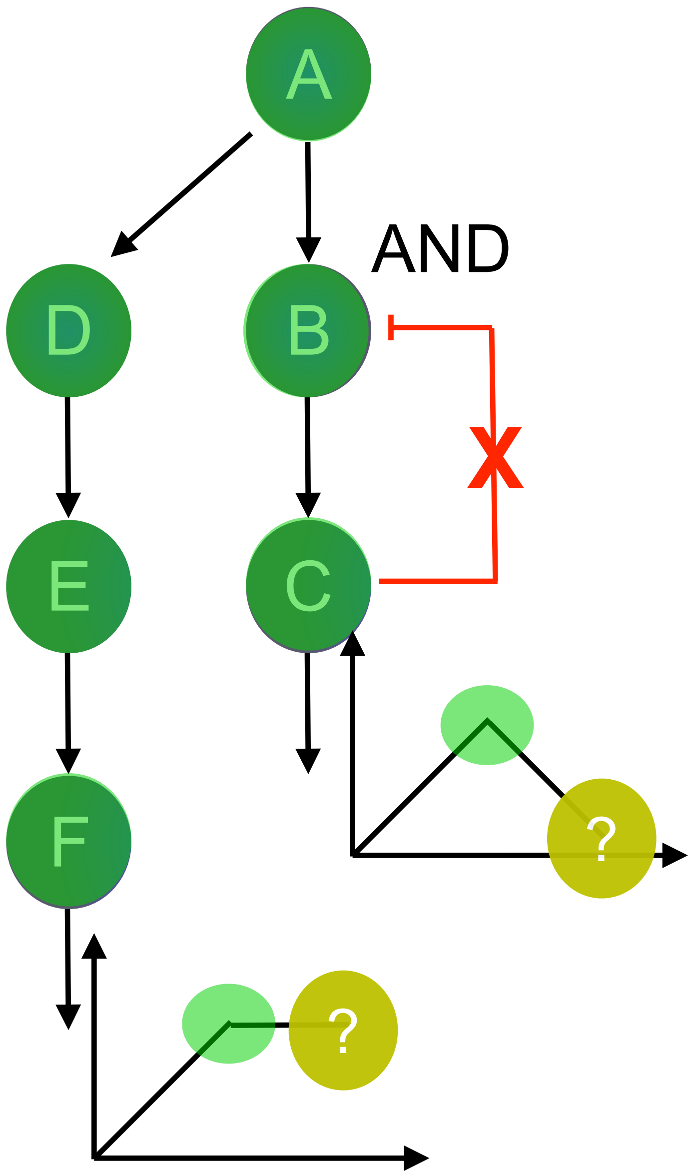

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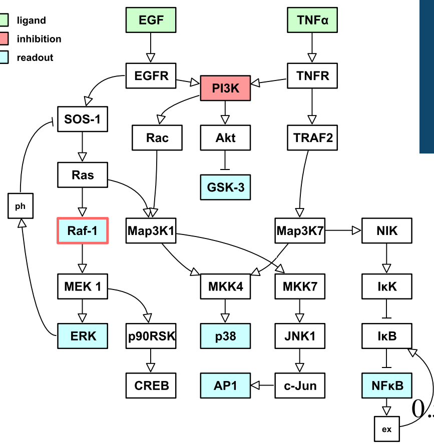
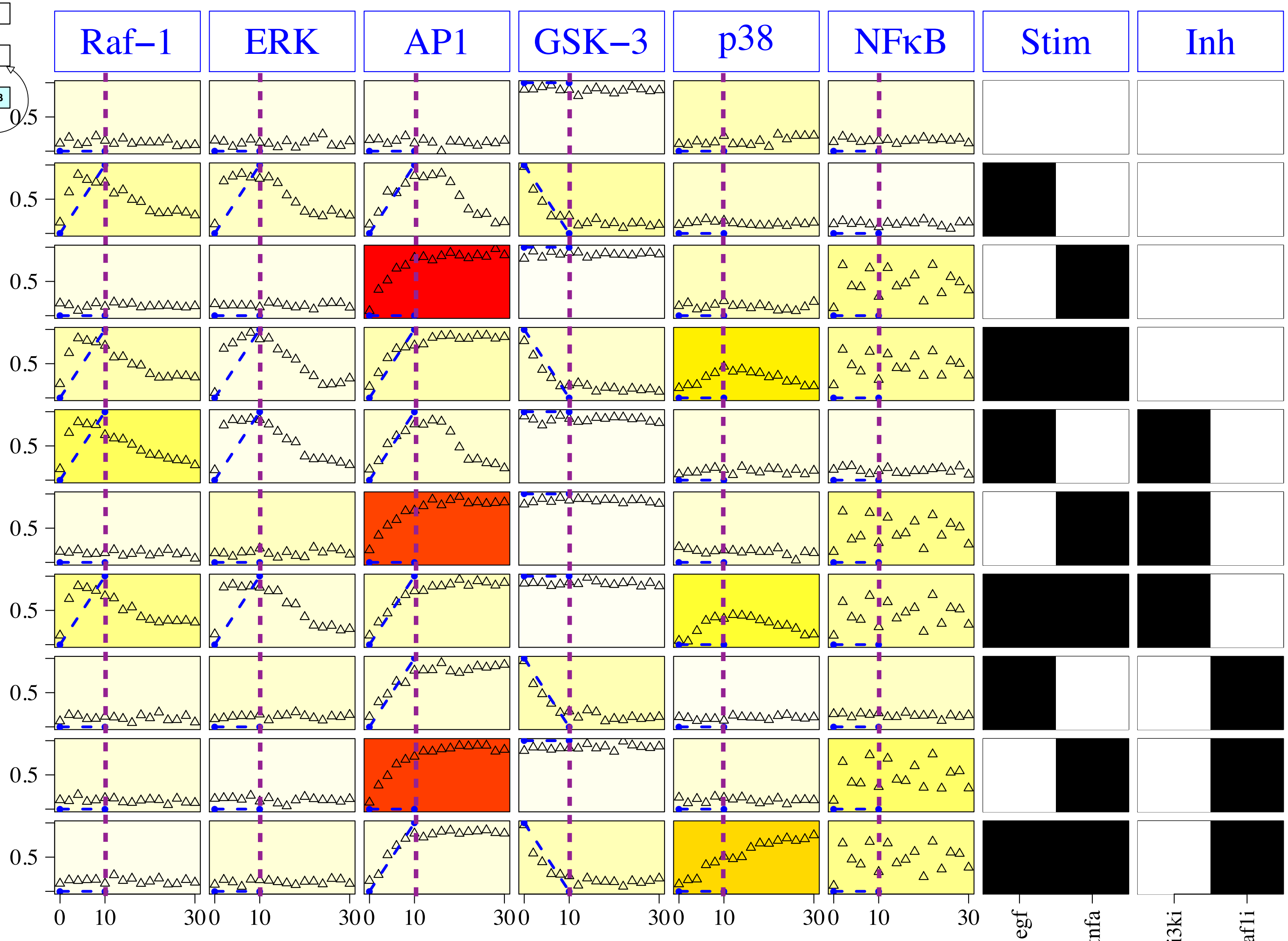
Training to data recovers structure





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

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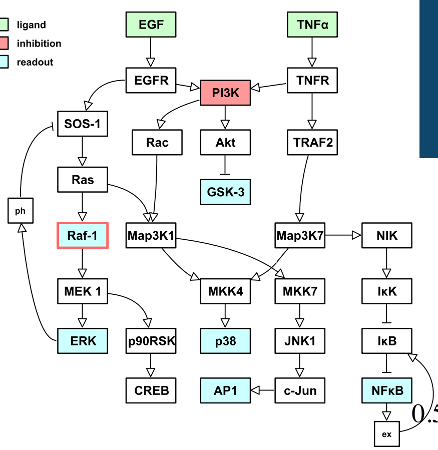
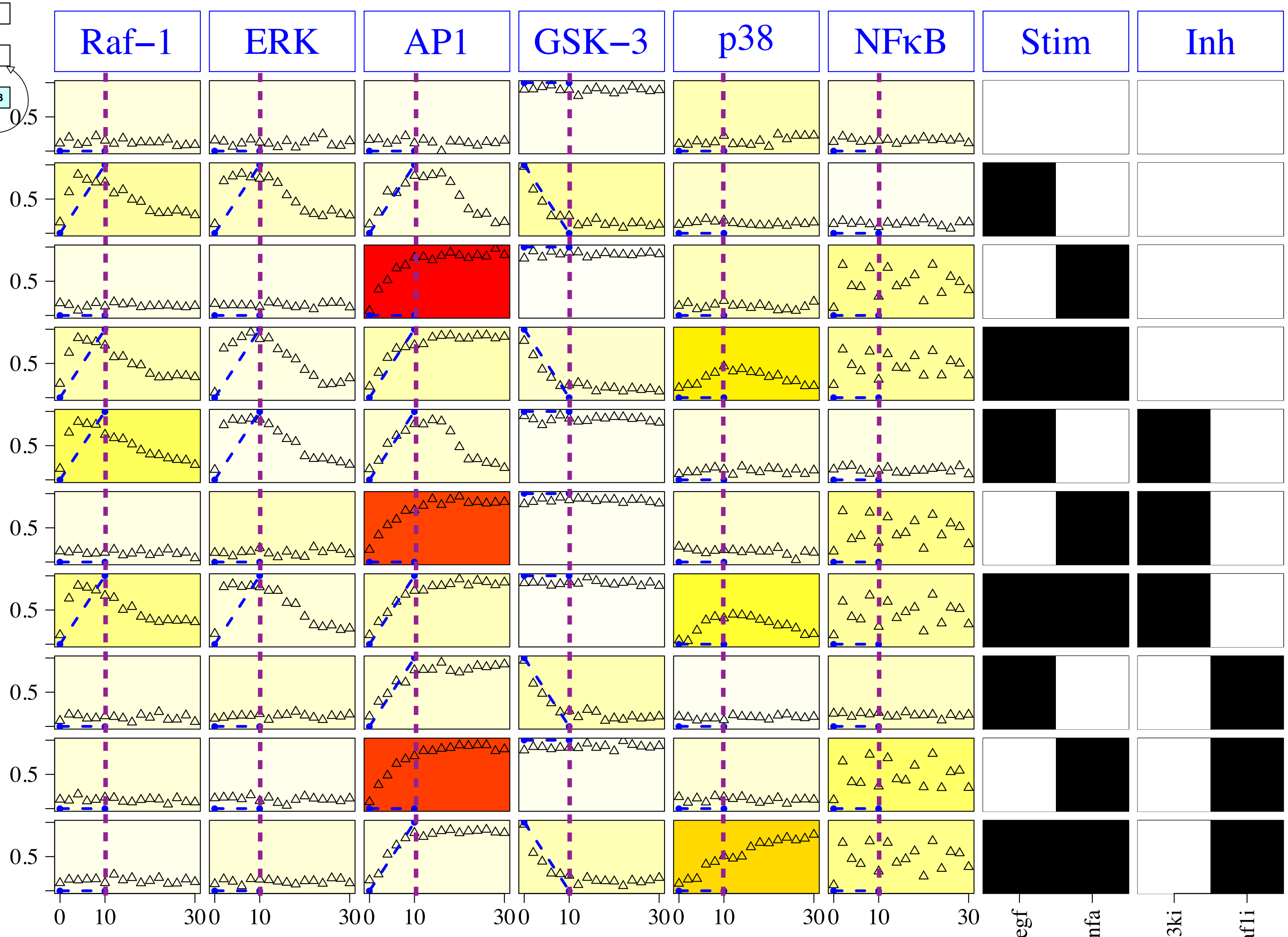


Identifies strong active links (except feedbacks)



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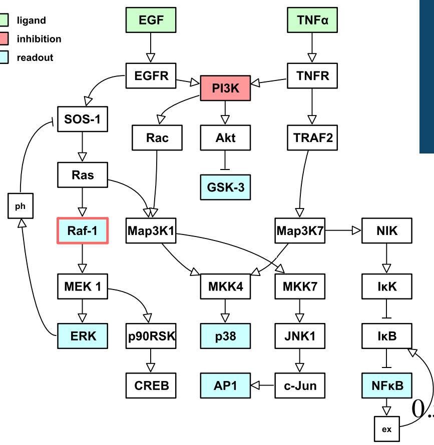
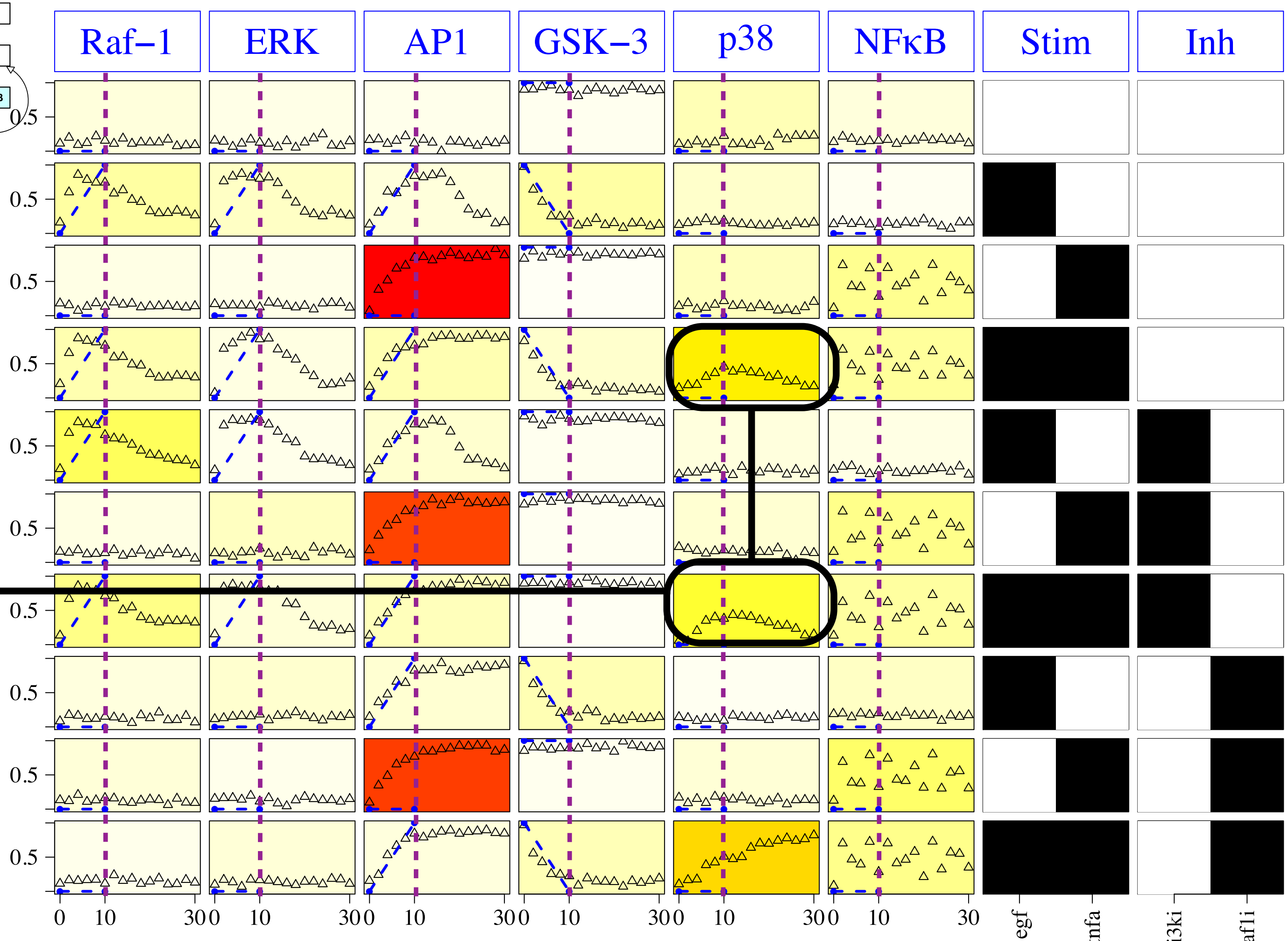


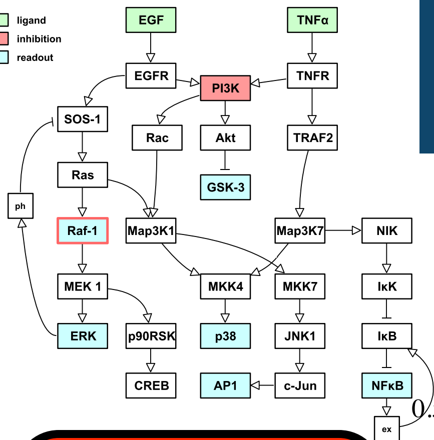


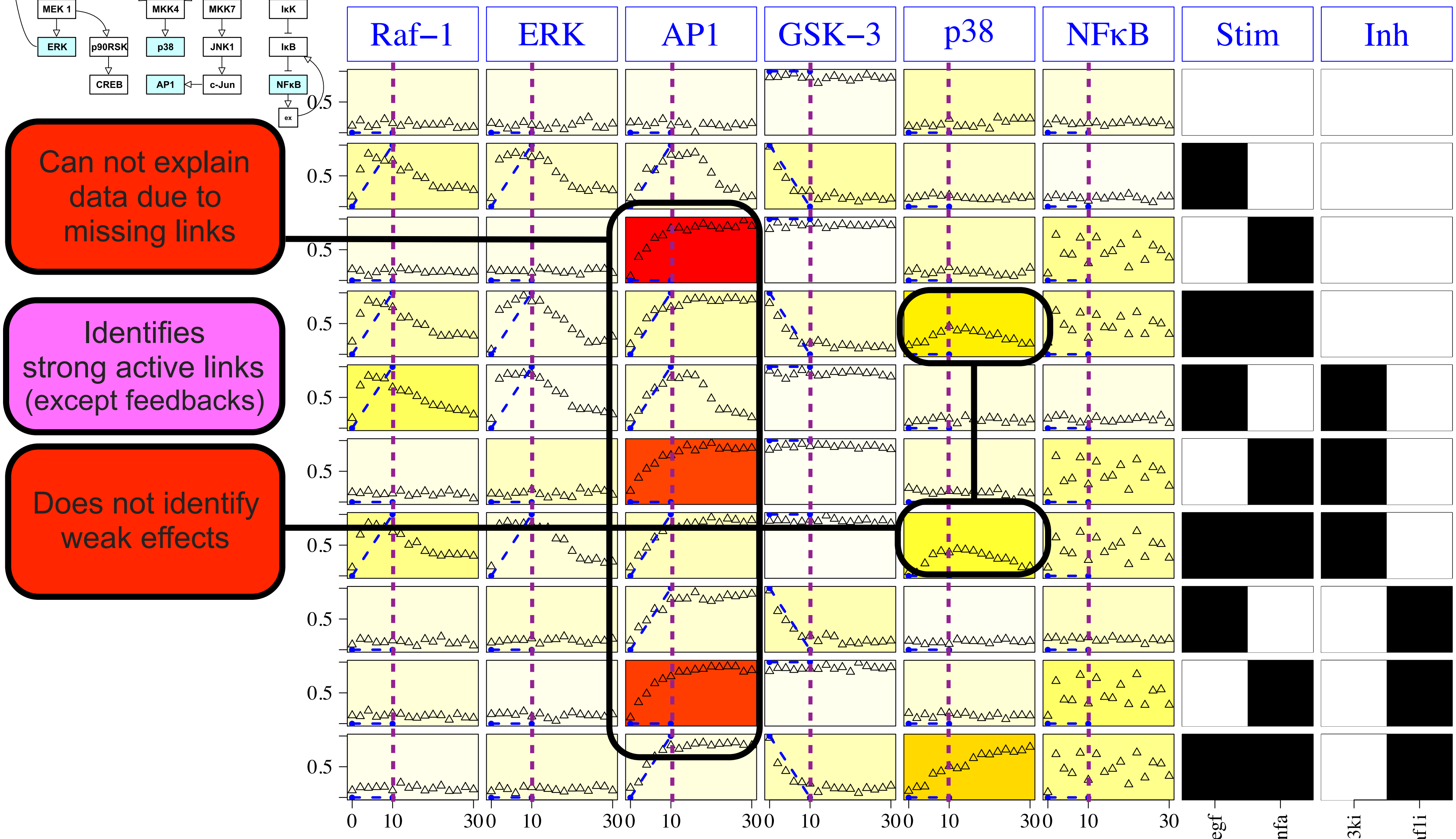
Identifies strong active links (except feedbacks)

Does not identify weak effects

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

Training to data recovers structure



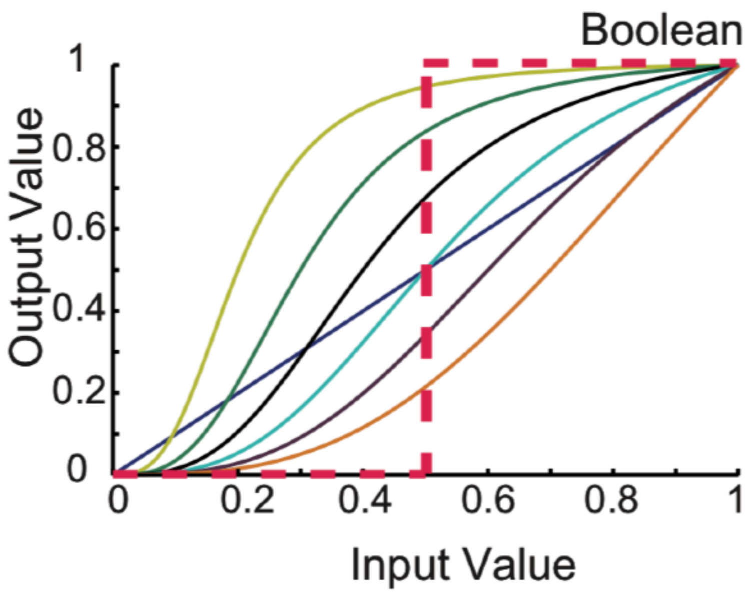


MacNamara A Terfve C Henriques D Penalver B Saez-Rodriguez J *Phys Biol* 9 045003, 2012

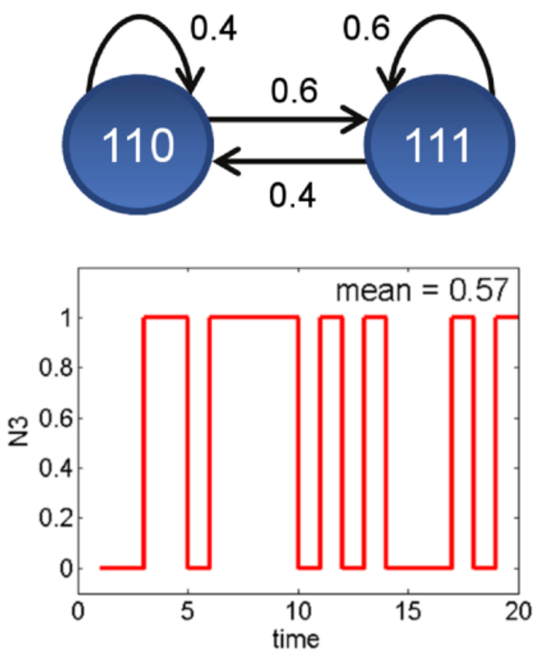
Constrained Fuzzy logic and Probabilistic Logic can handle quantitative differences

- Boolean modeling can **not** describe **quantitative** aspect (e.g. intermediate activation)

- Fuzzy logic (Aldridge et al. Plos Comp. Bio. 2009; Morris et al. Plos Comp. Bio. 2011) and Probabilistic Logic (Trairatphisan et al. Plos One 2014) can model quantitative signalling data



- **Constrainted Fuzzy logic**



- **Probabilistic Logic**

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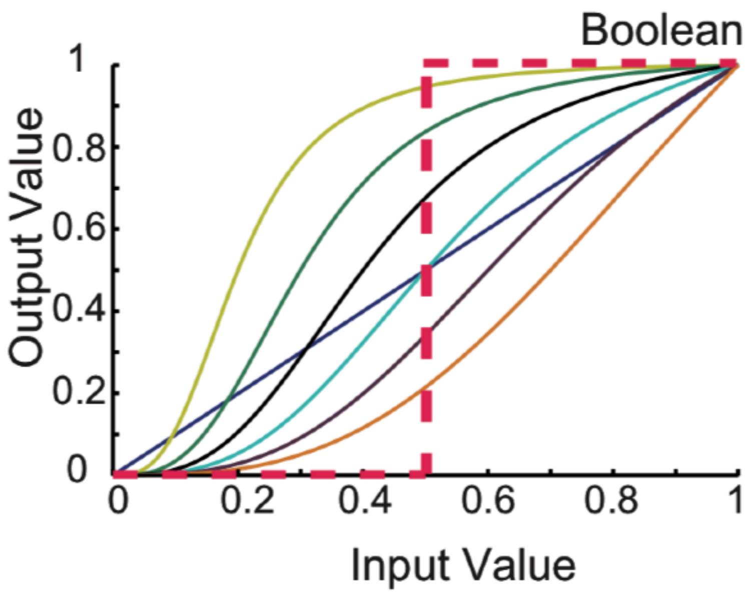

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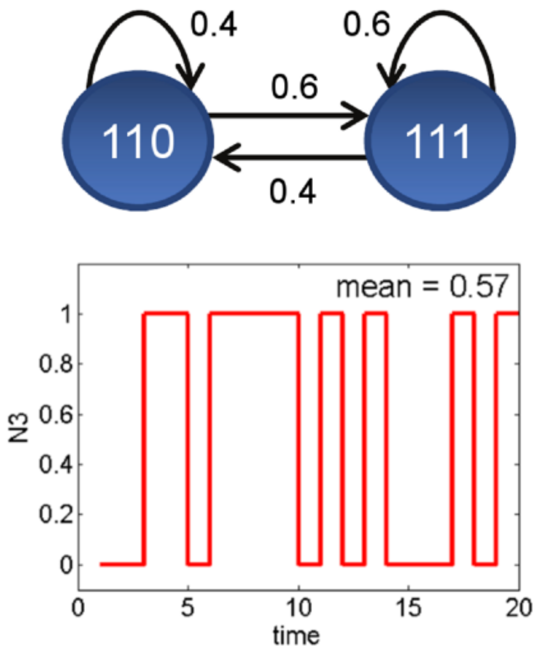
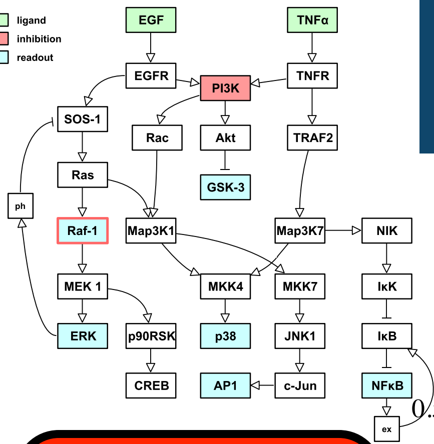


- **Probabilistic Logic**

fit of fuzzy toy model (~ Probabilistic)



Can not explain data due to missing links

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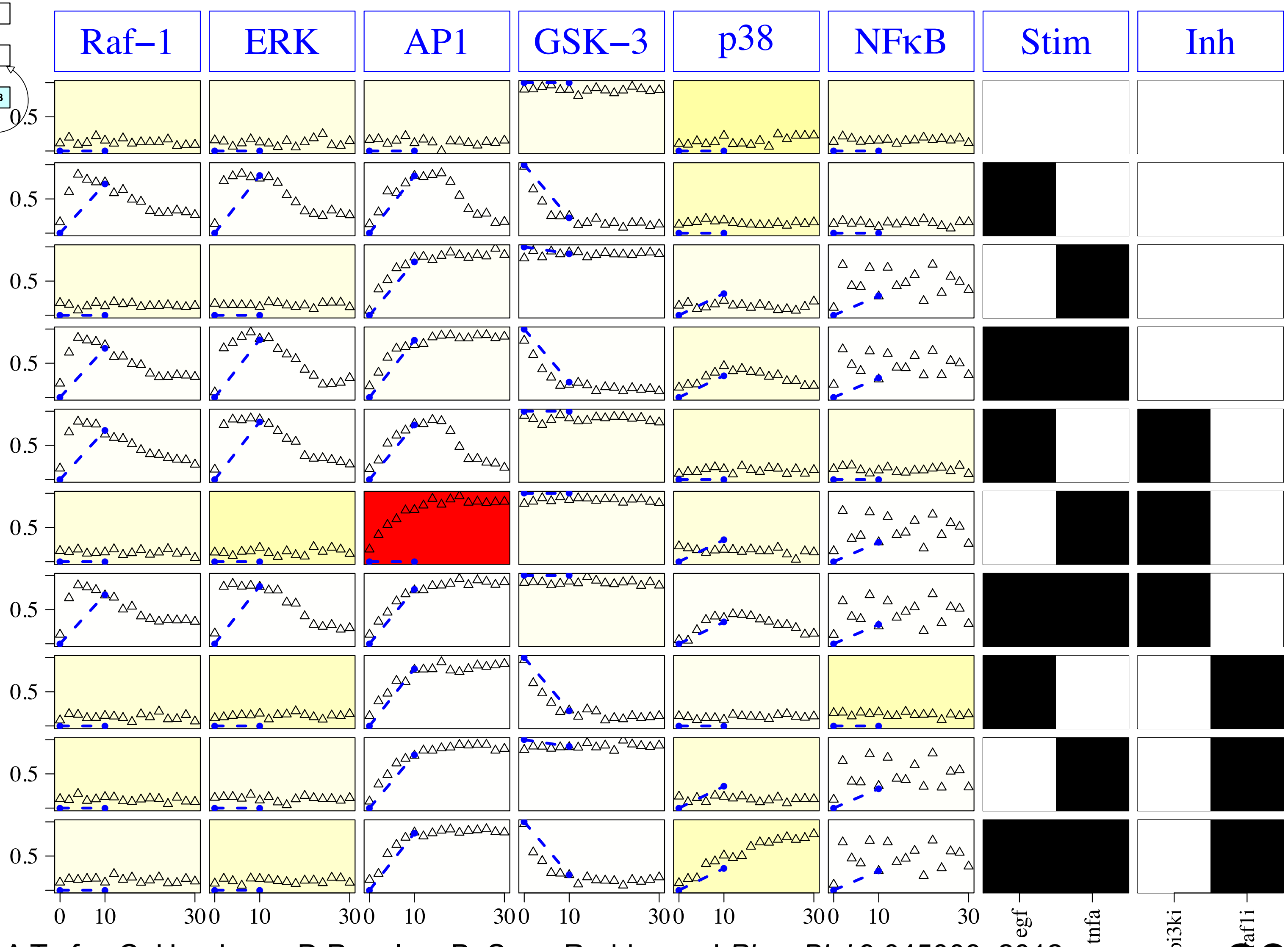

MacNamara A Terfve C Henriques D Penalver B Saez-Rodriguez J *Phys Biol* 9 045003, 2012

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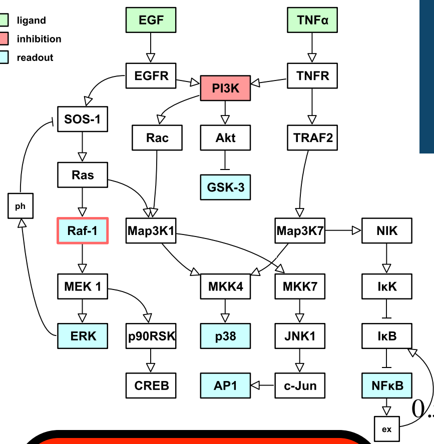

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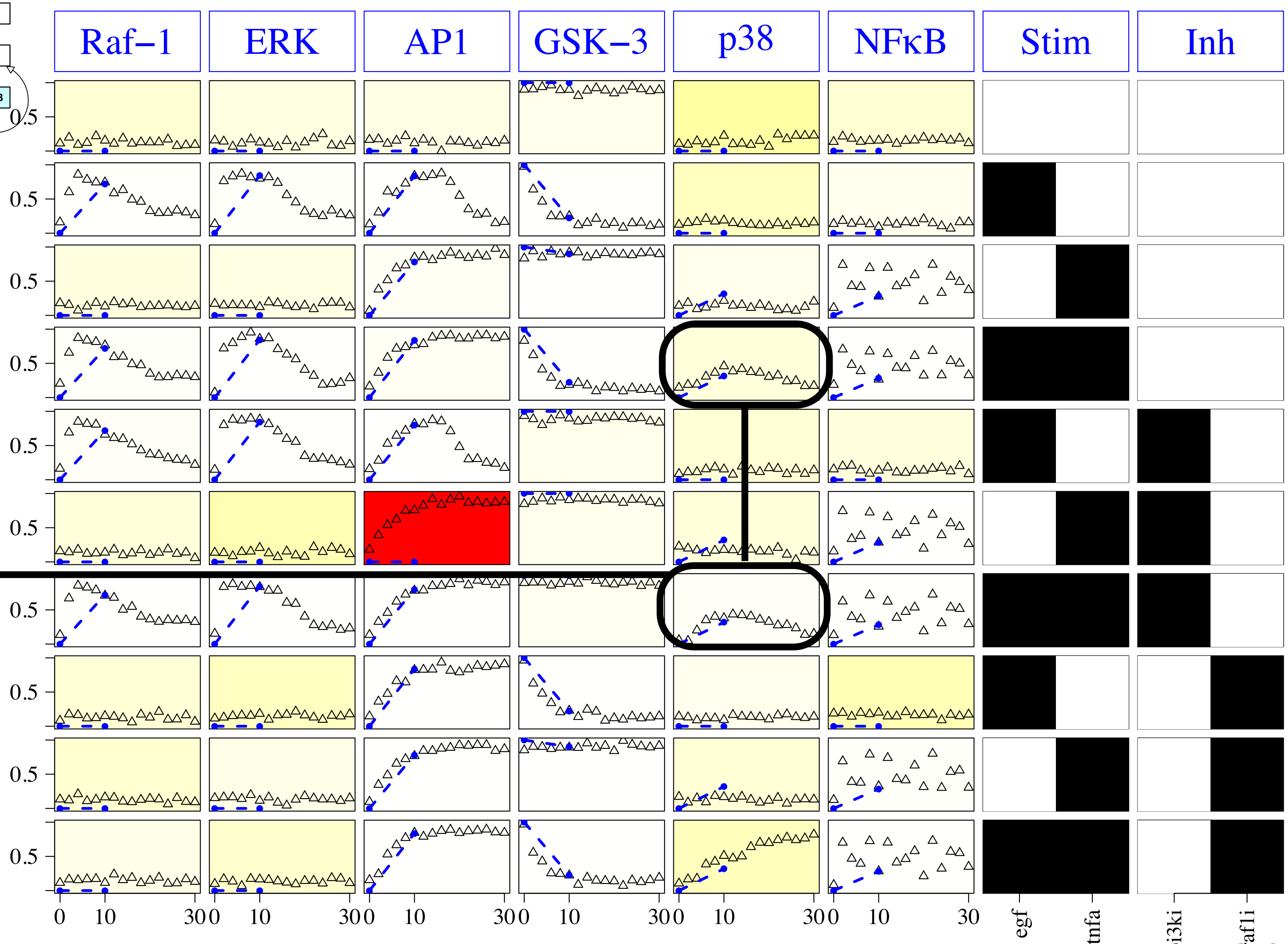
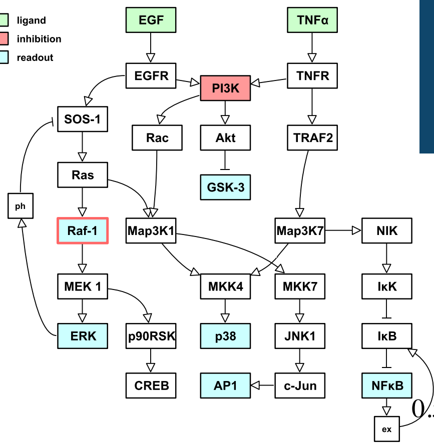
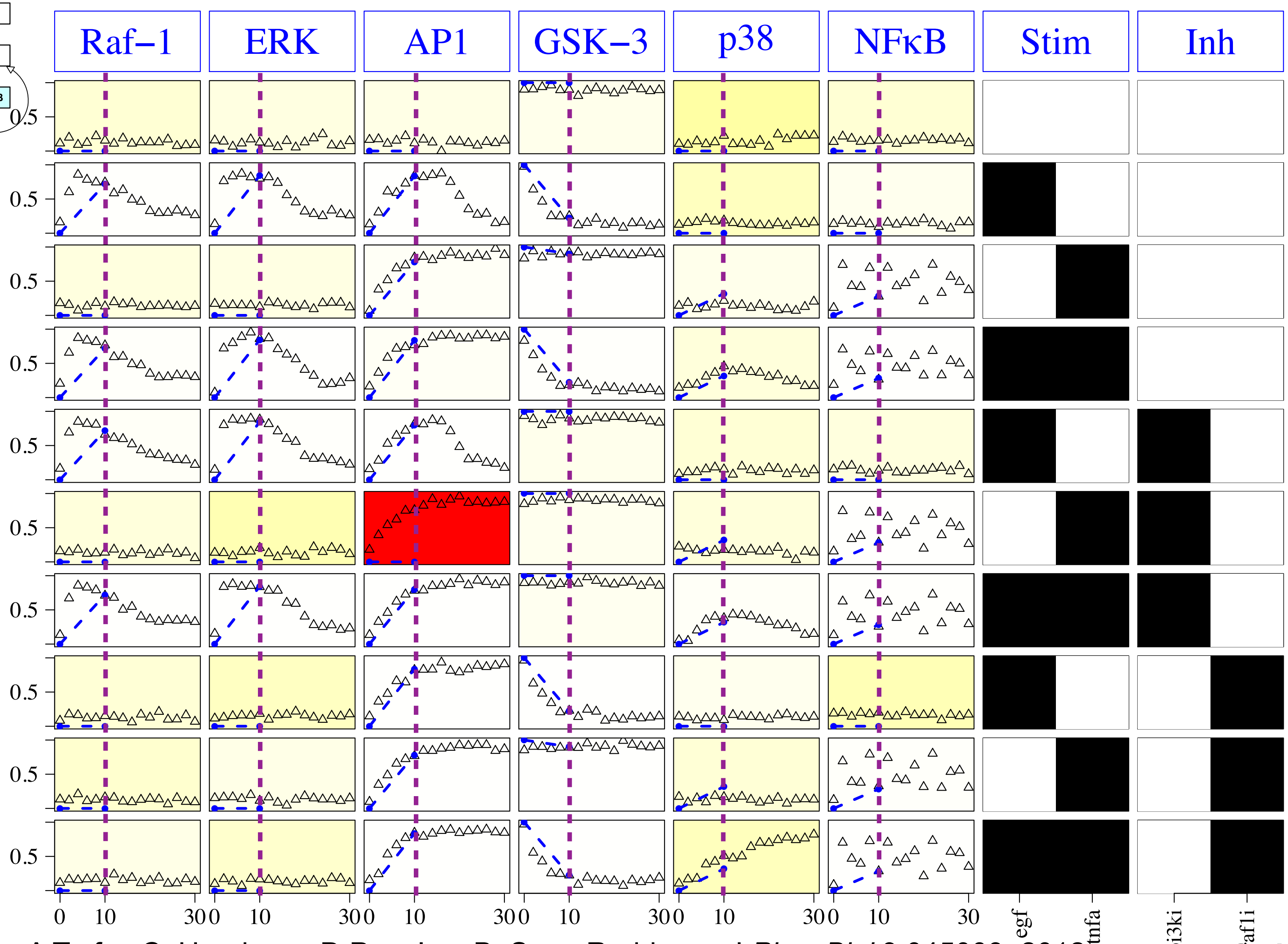
Identifies weak active links (except feedbacks)



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

How to model feedback effects?





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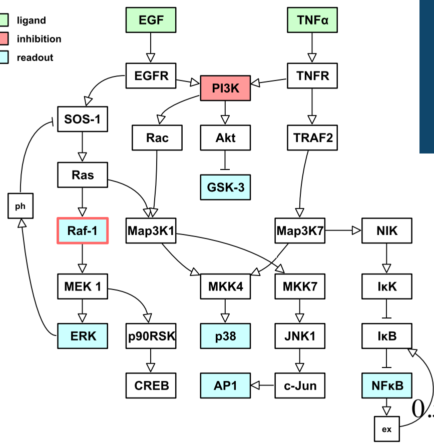

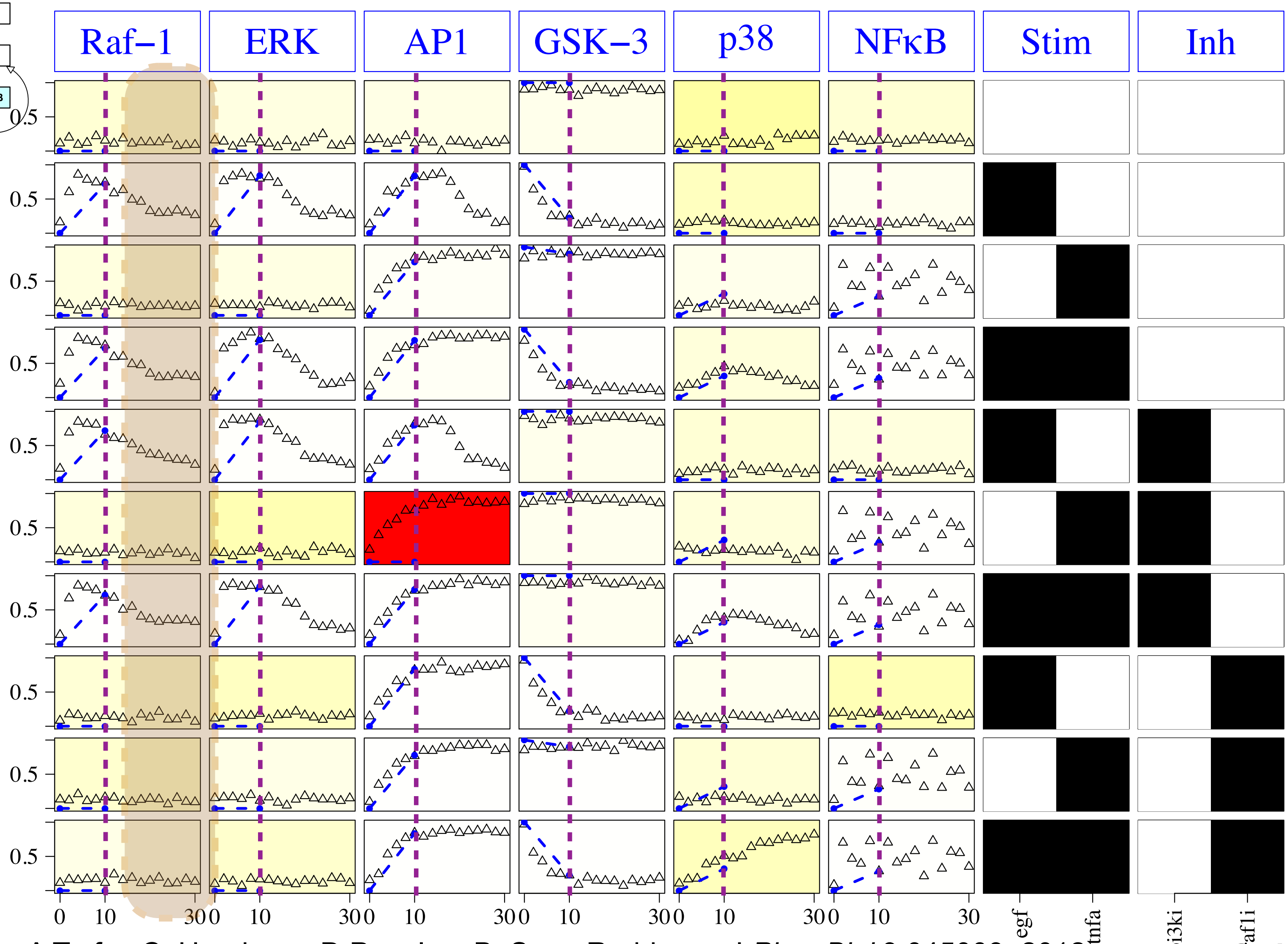

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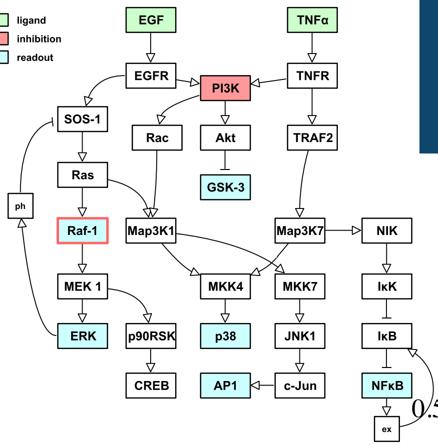
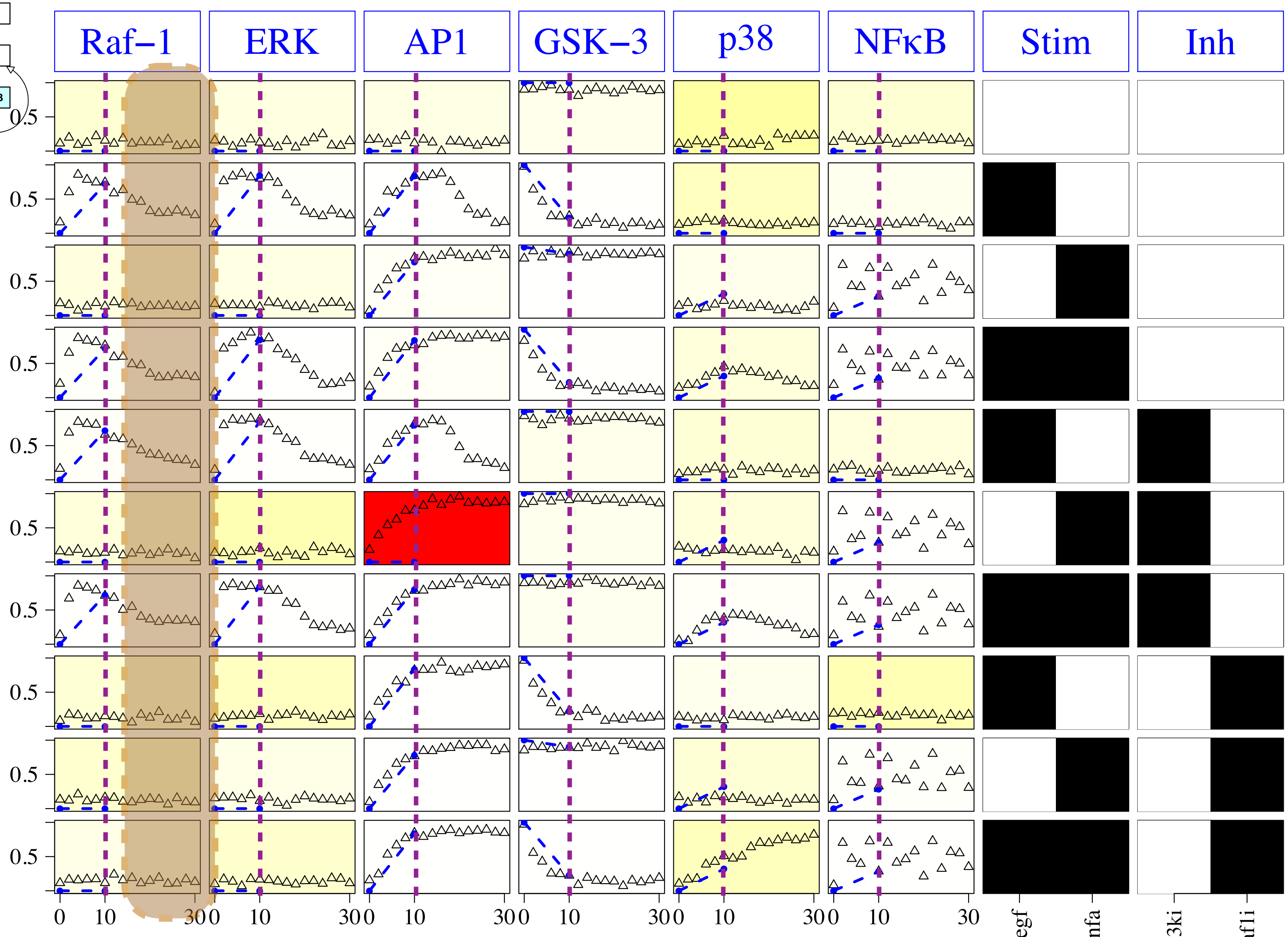
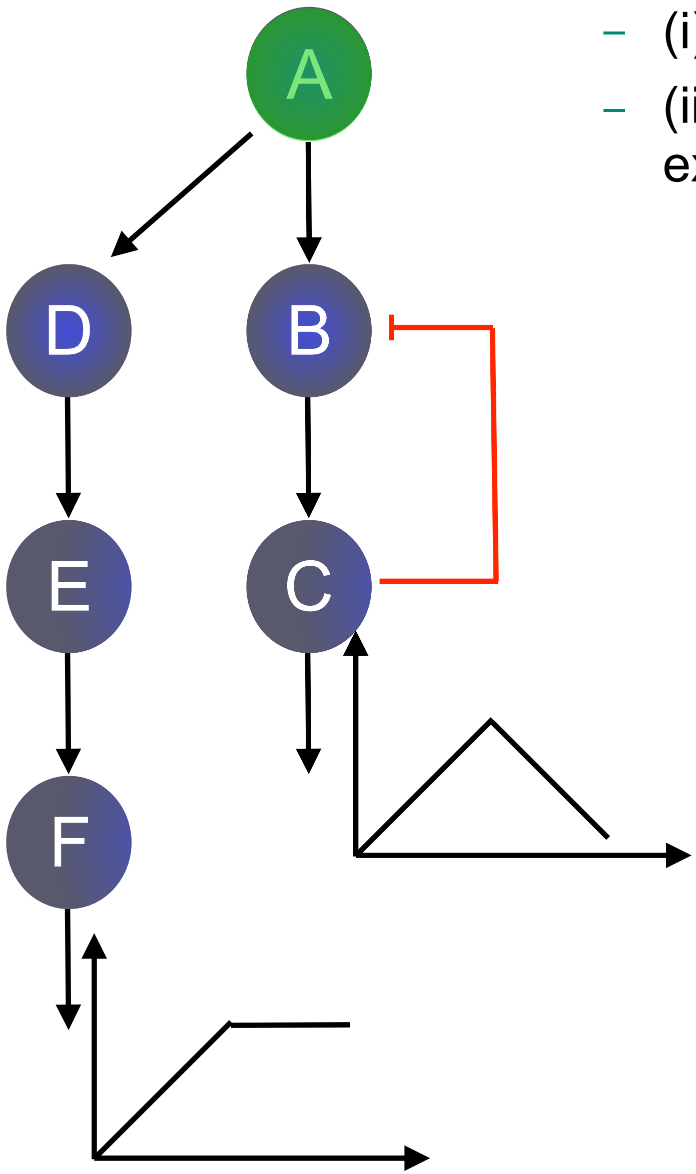




MacNamara A Terfve C Henriques D Penalver B Saez-Rodriguez J *Phys Biol* 9 045003, 2012

Approximation of transient behaviour using multiple time-scales



- (i) Train τ =1 → get early events
- (ii) Train τ =2 → find gates not active at τ =1 that explain evolution from τ =1 to τ =2

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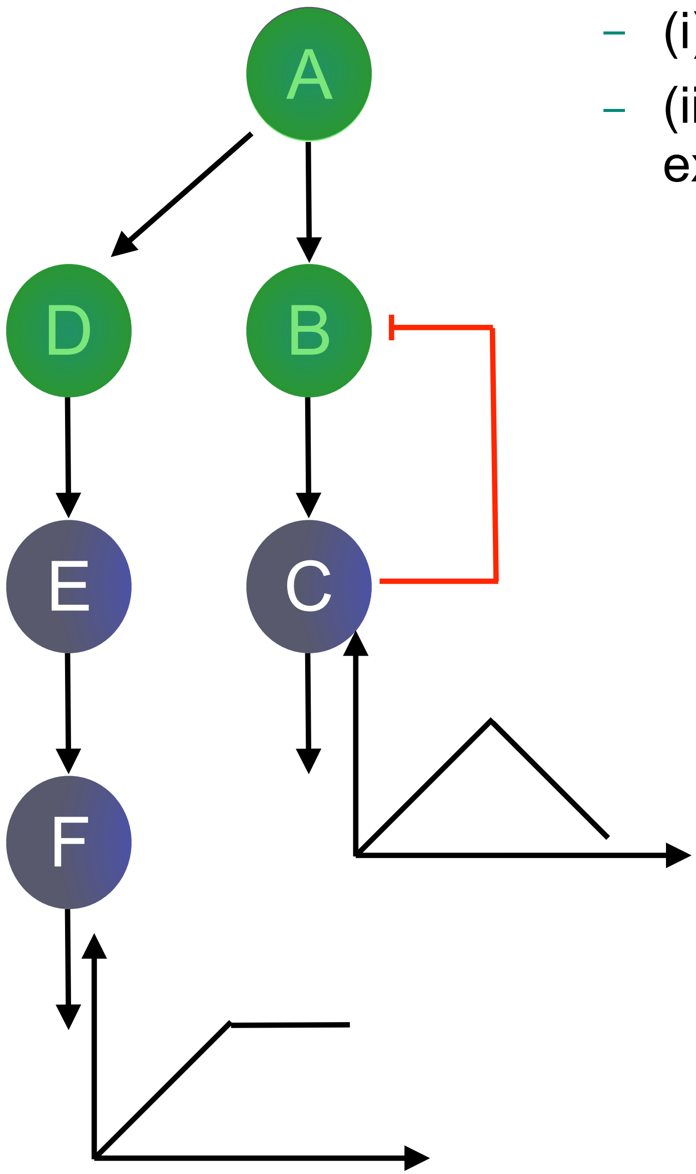

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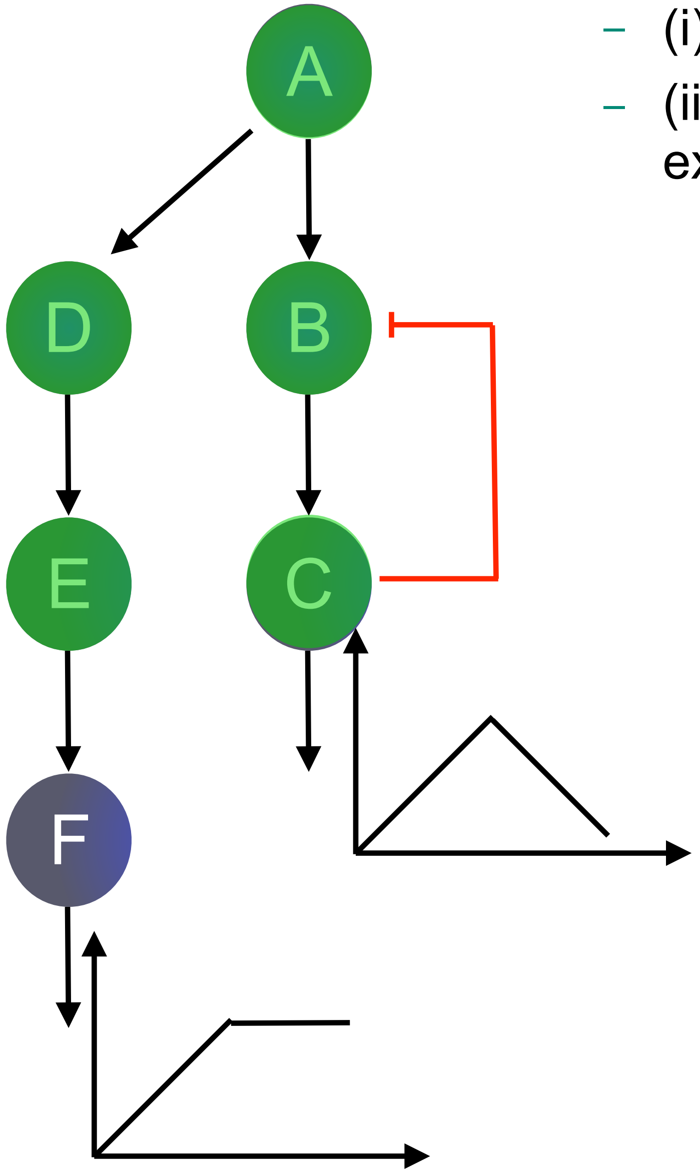

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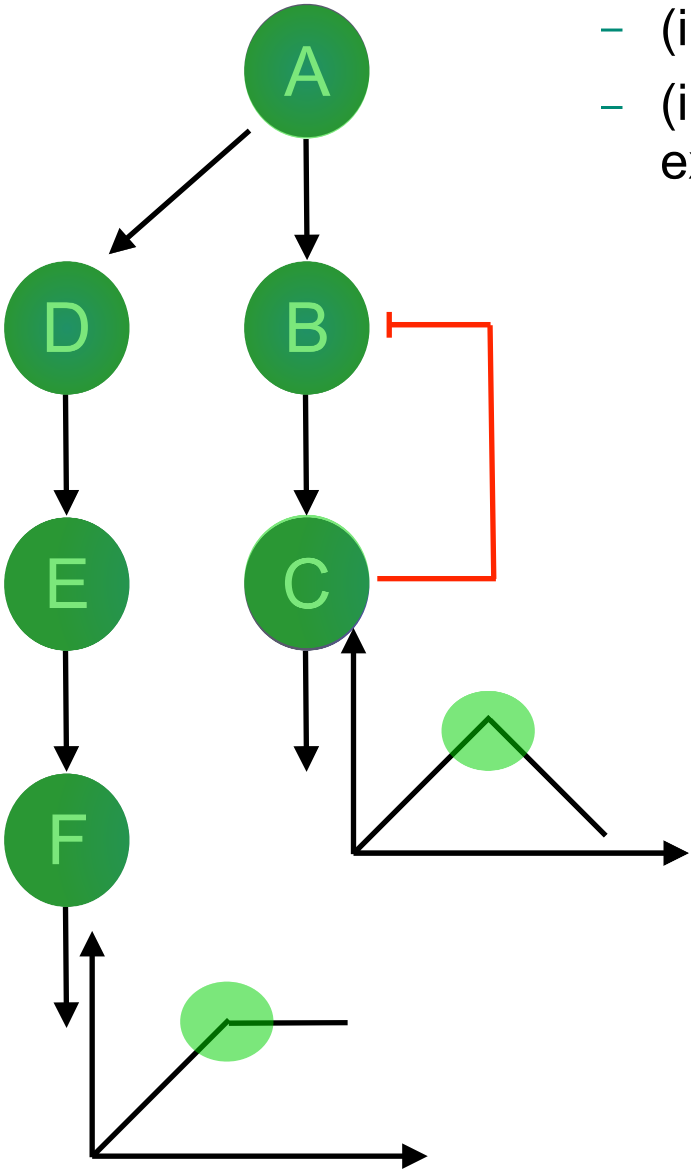

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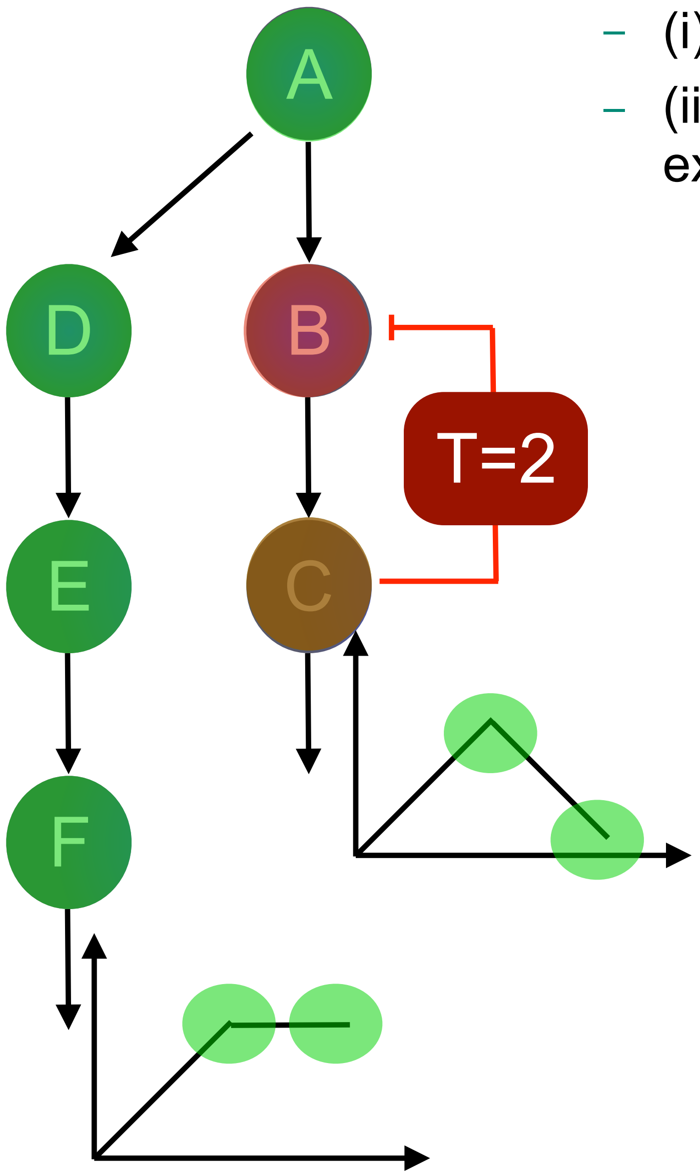

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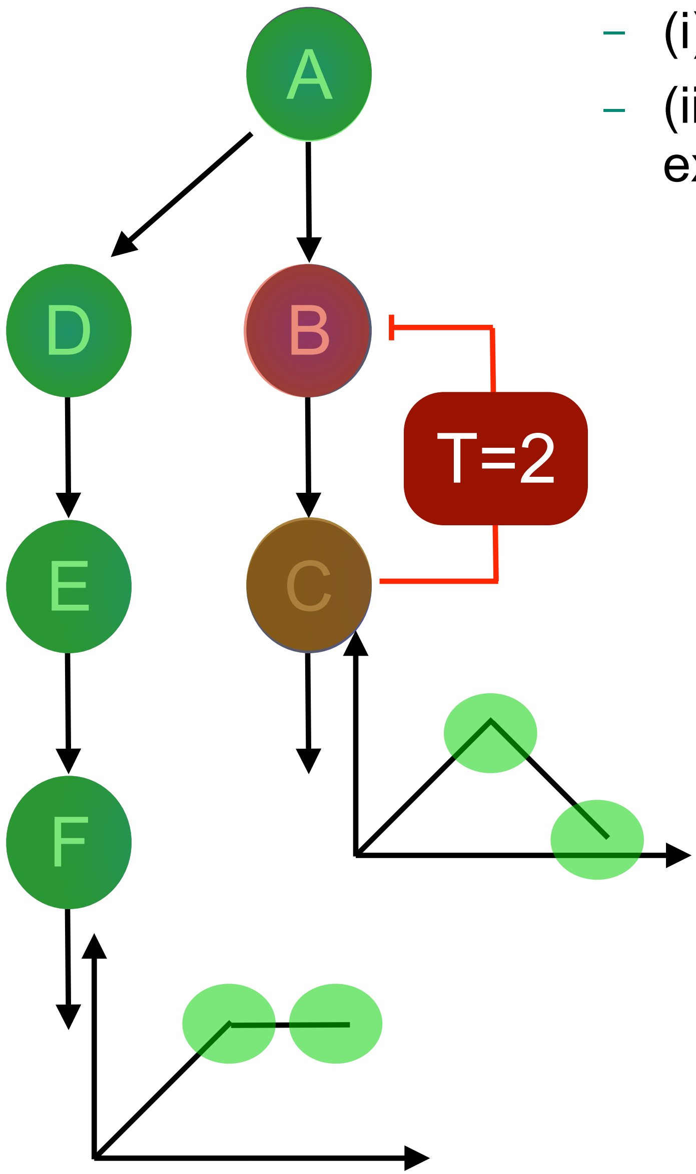

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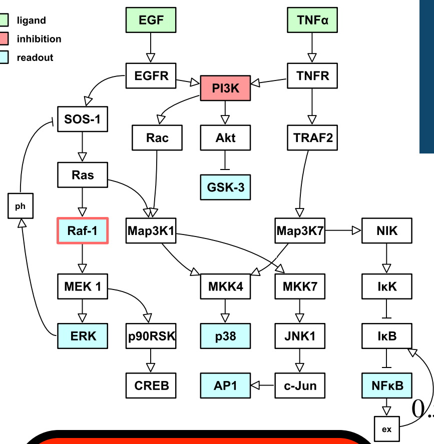
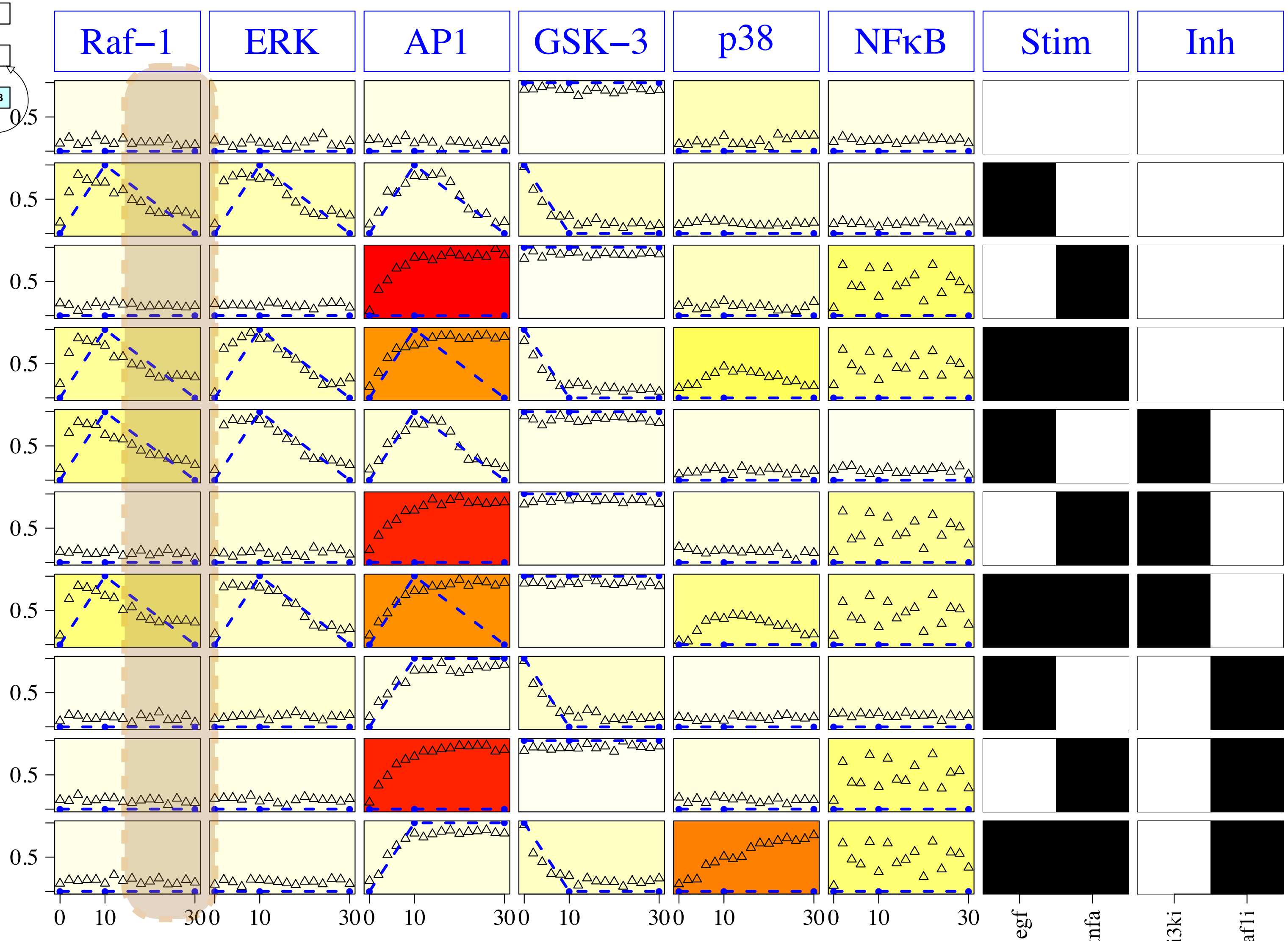
Rough approximation of dynamics, still computationally efficient



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

Can not explain data due to missing links

Identifies strong active links



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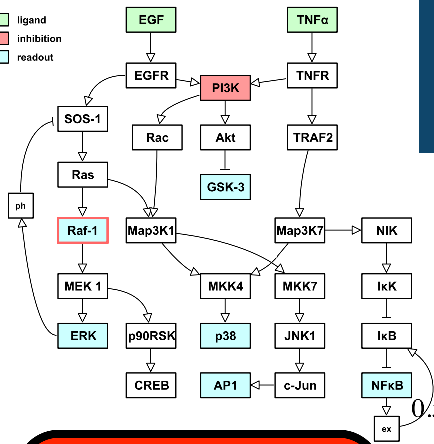

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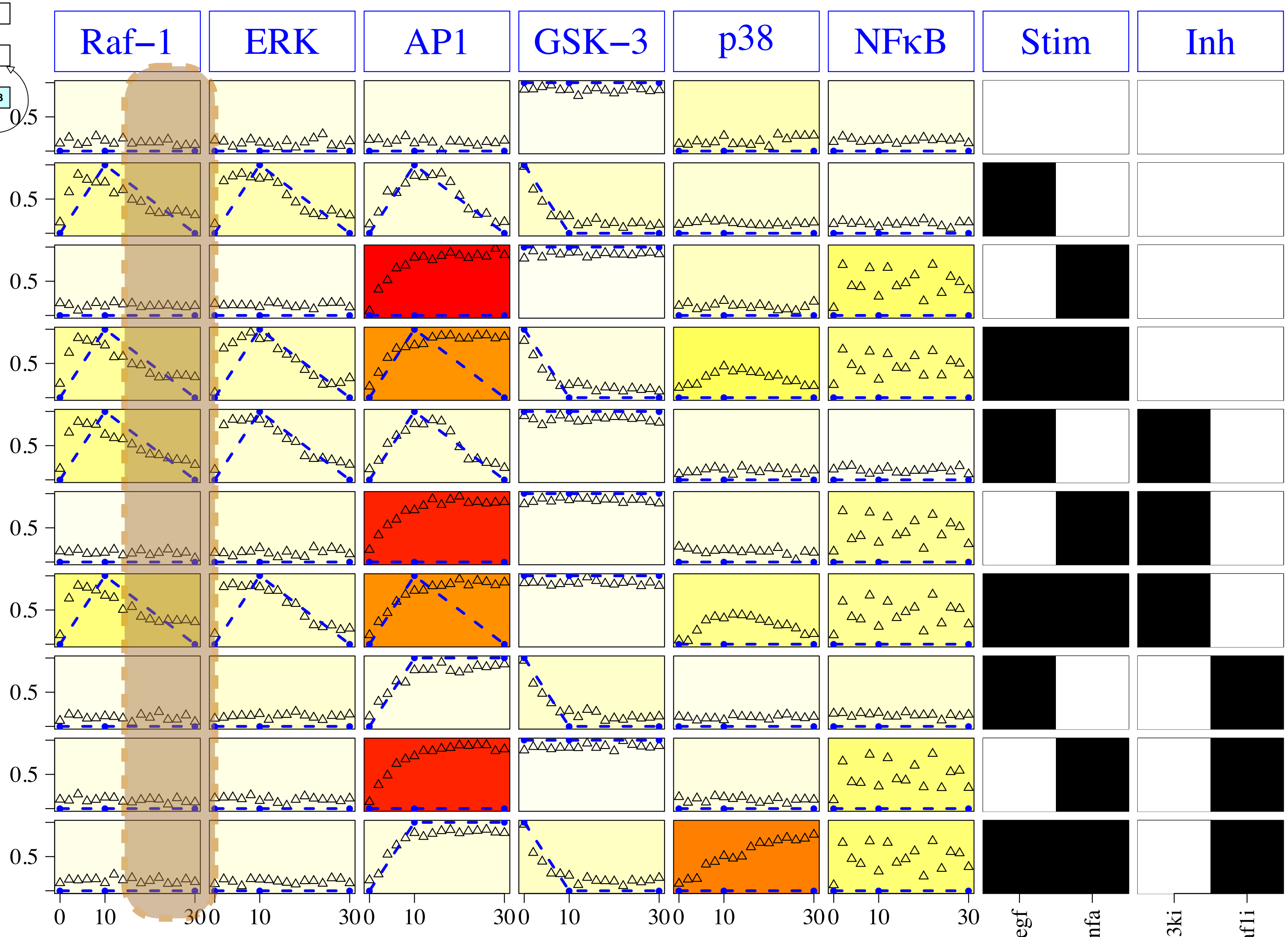

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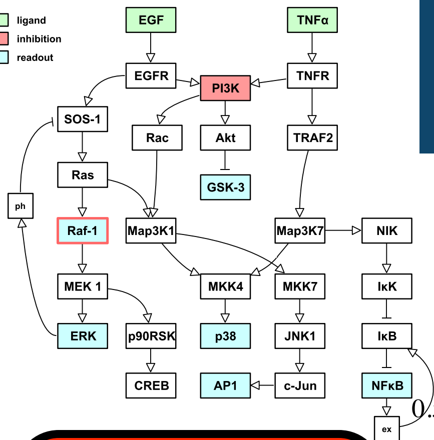

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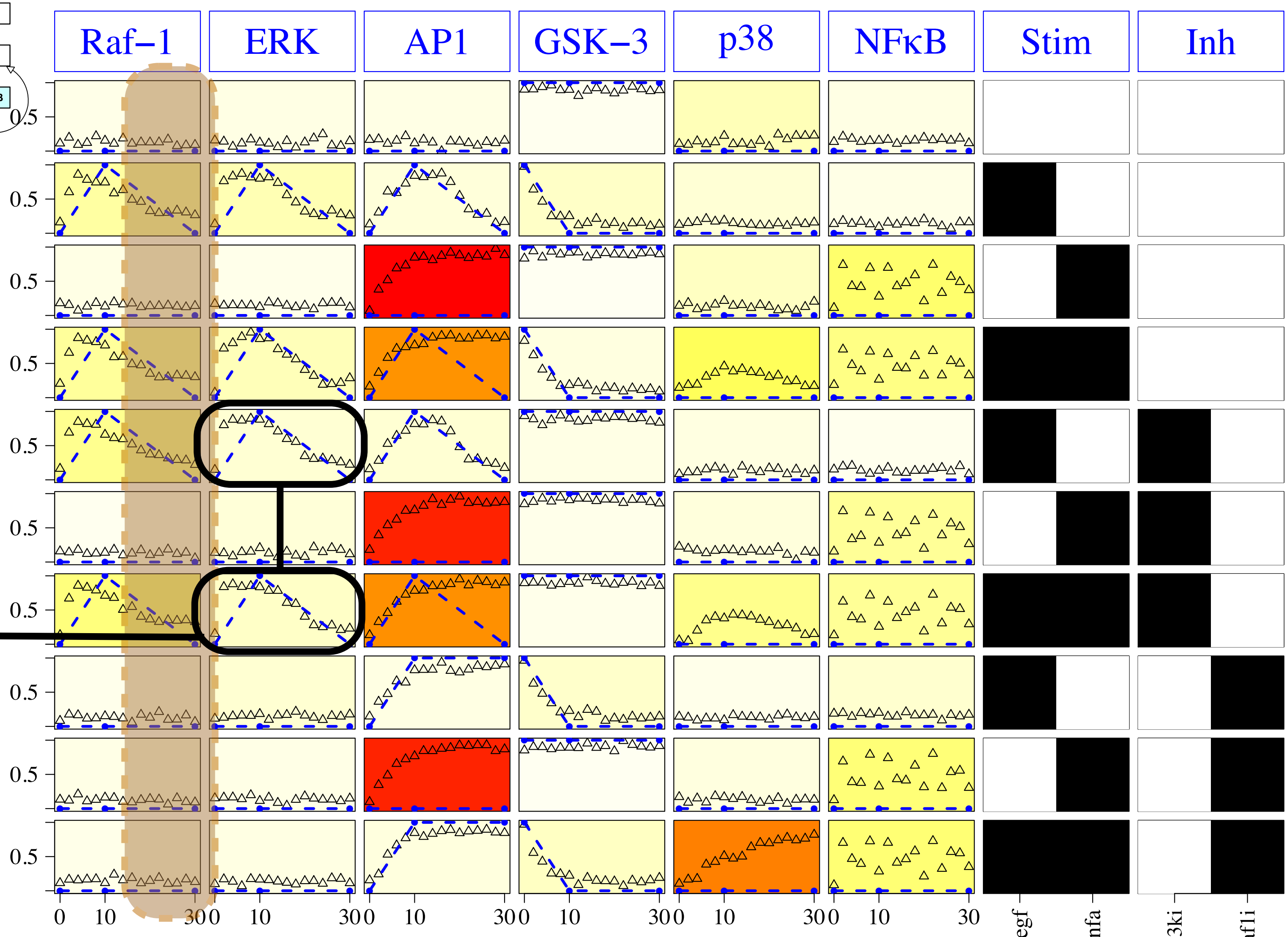

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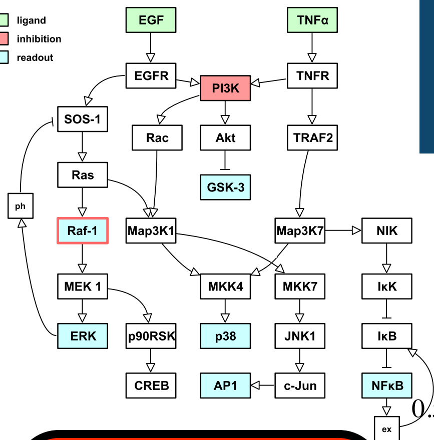

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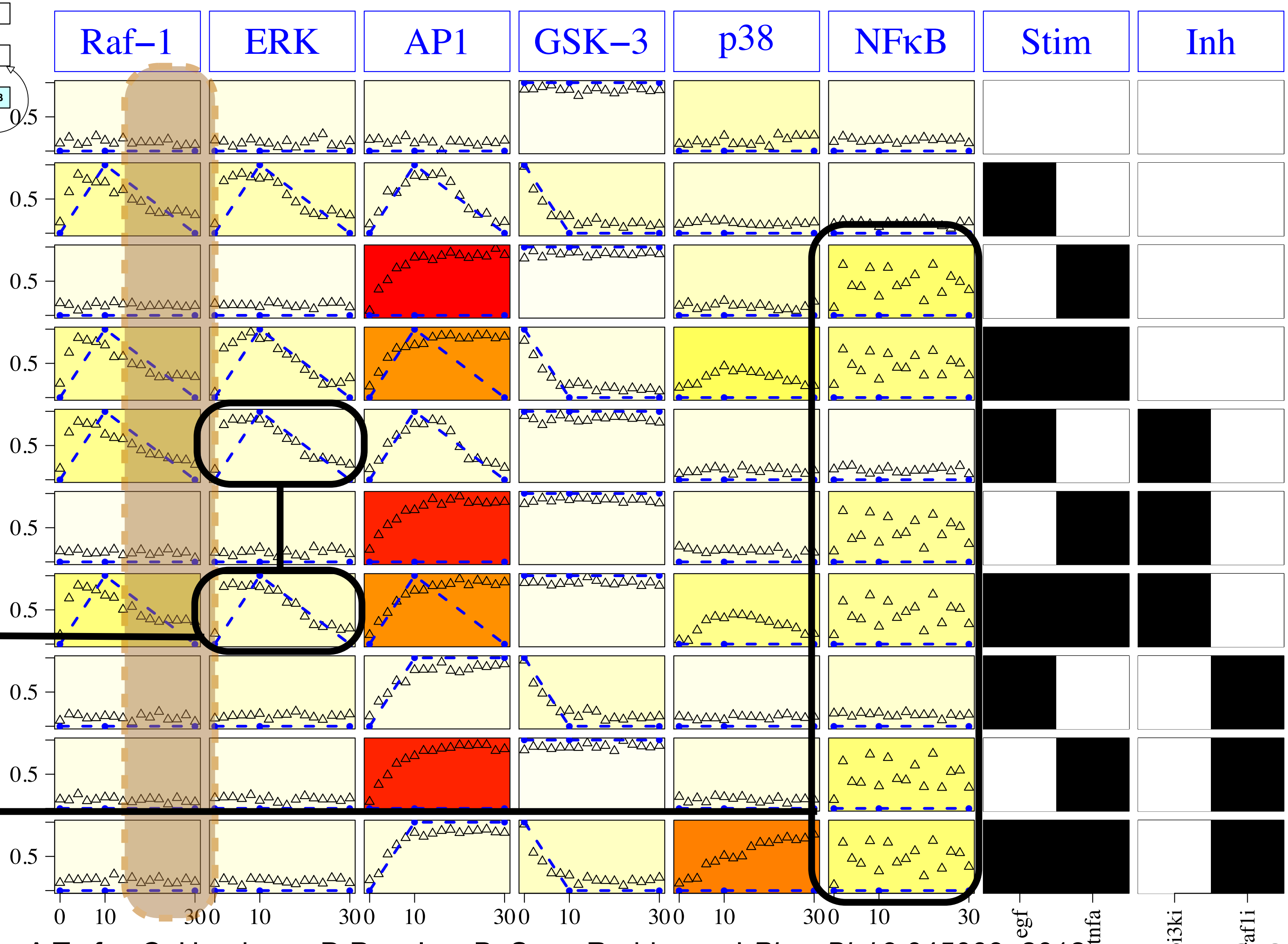
Can not handle oscillations



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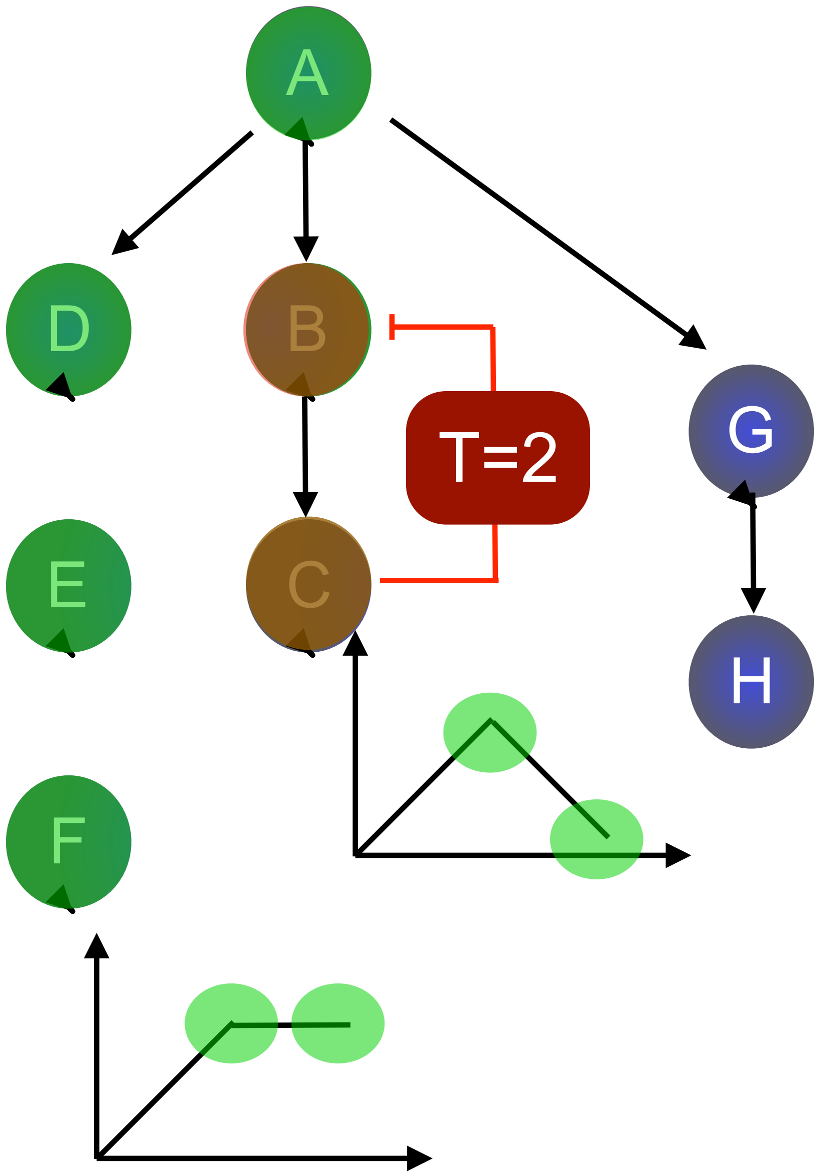
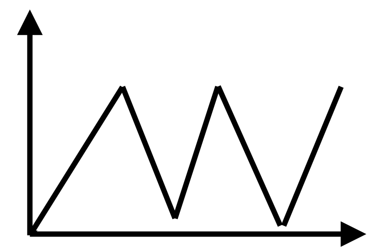
Approximation of dynamics using synchronous simulation & multiple time-scales



More recently: update to link to MaBoss



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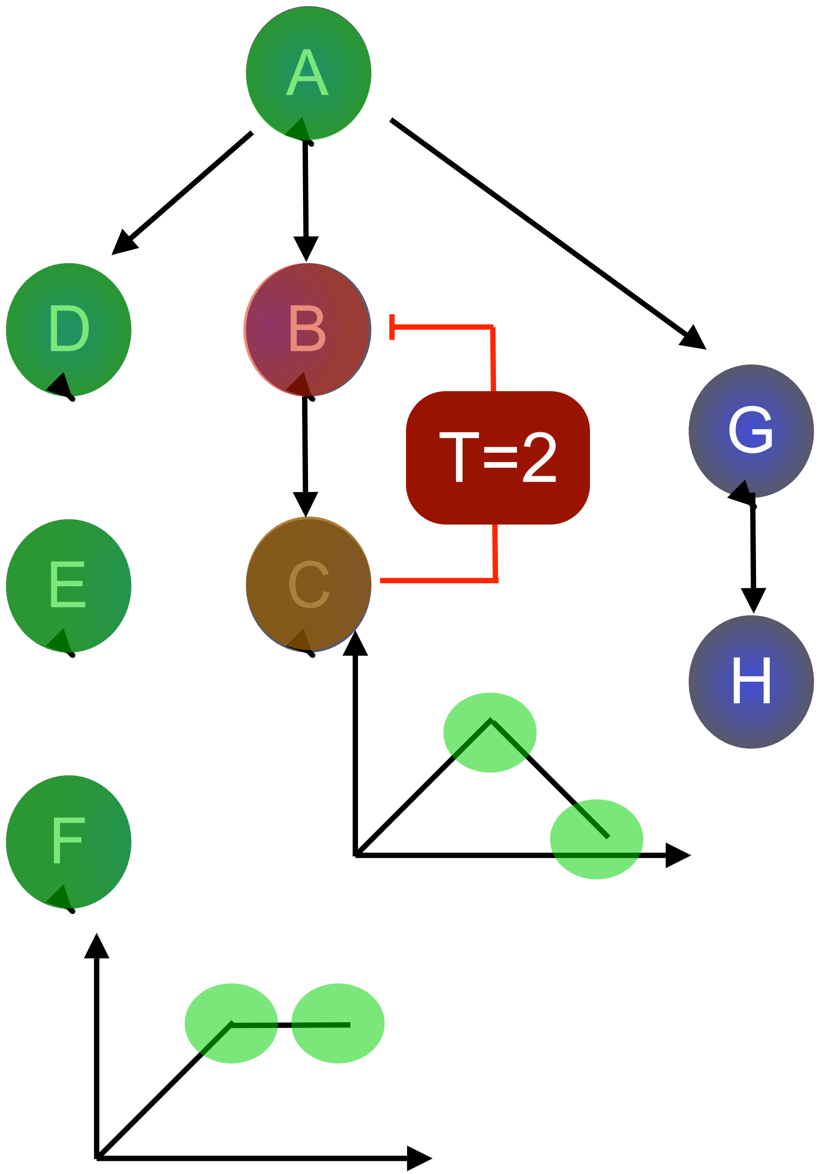

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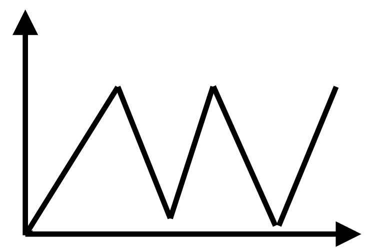

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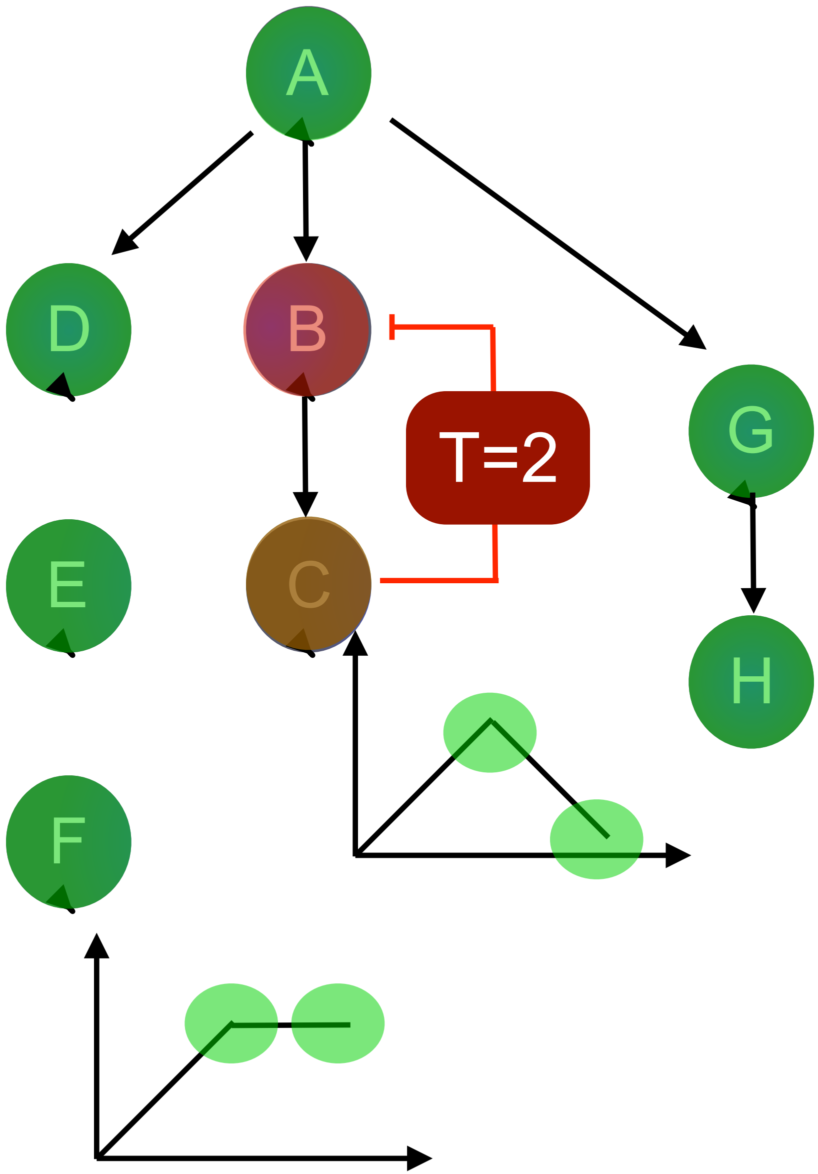

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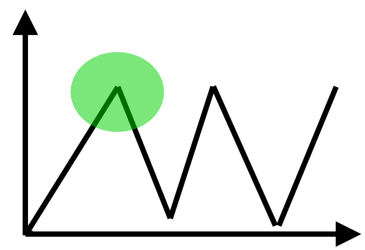

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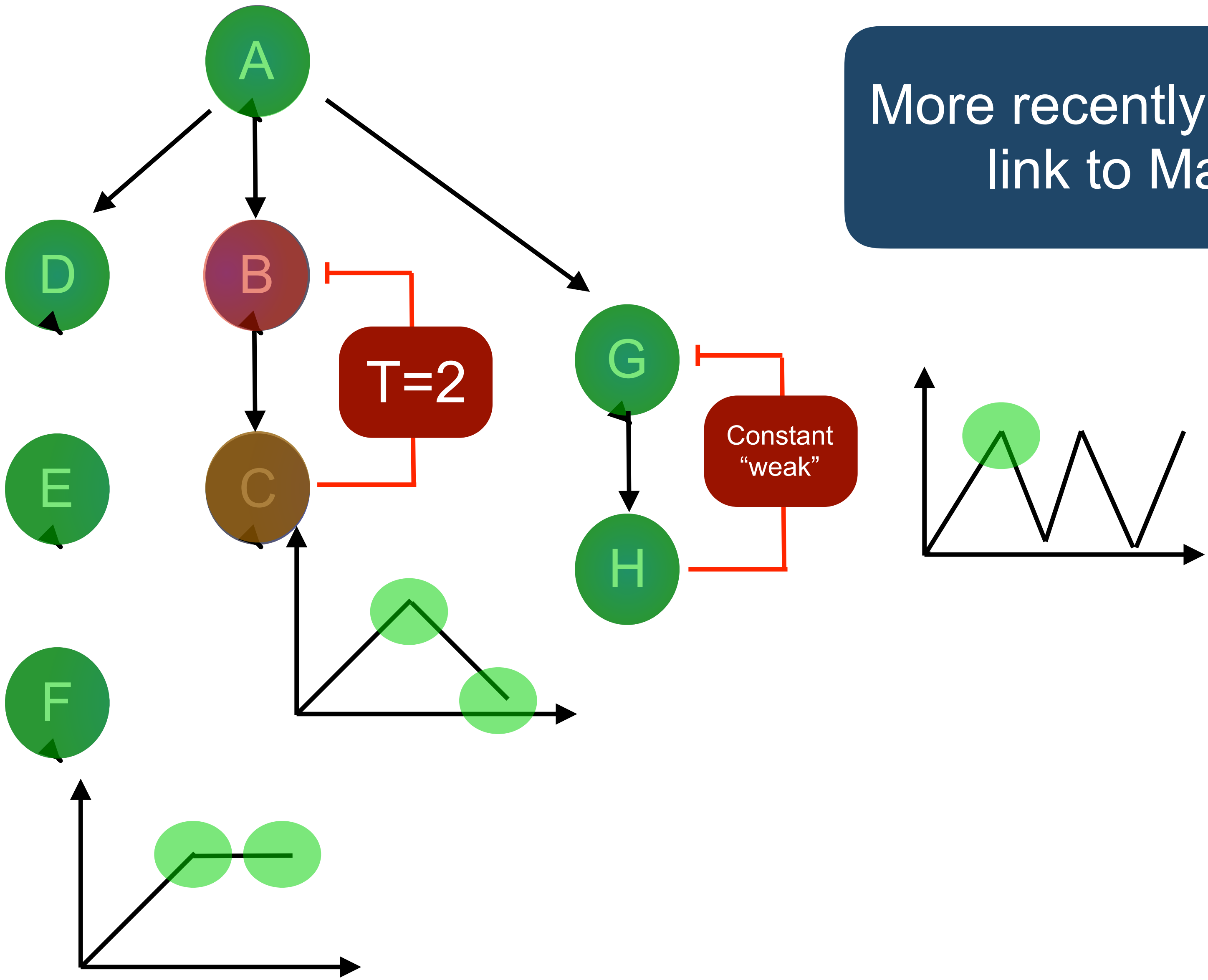

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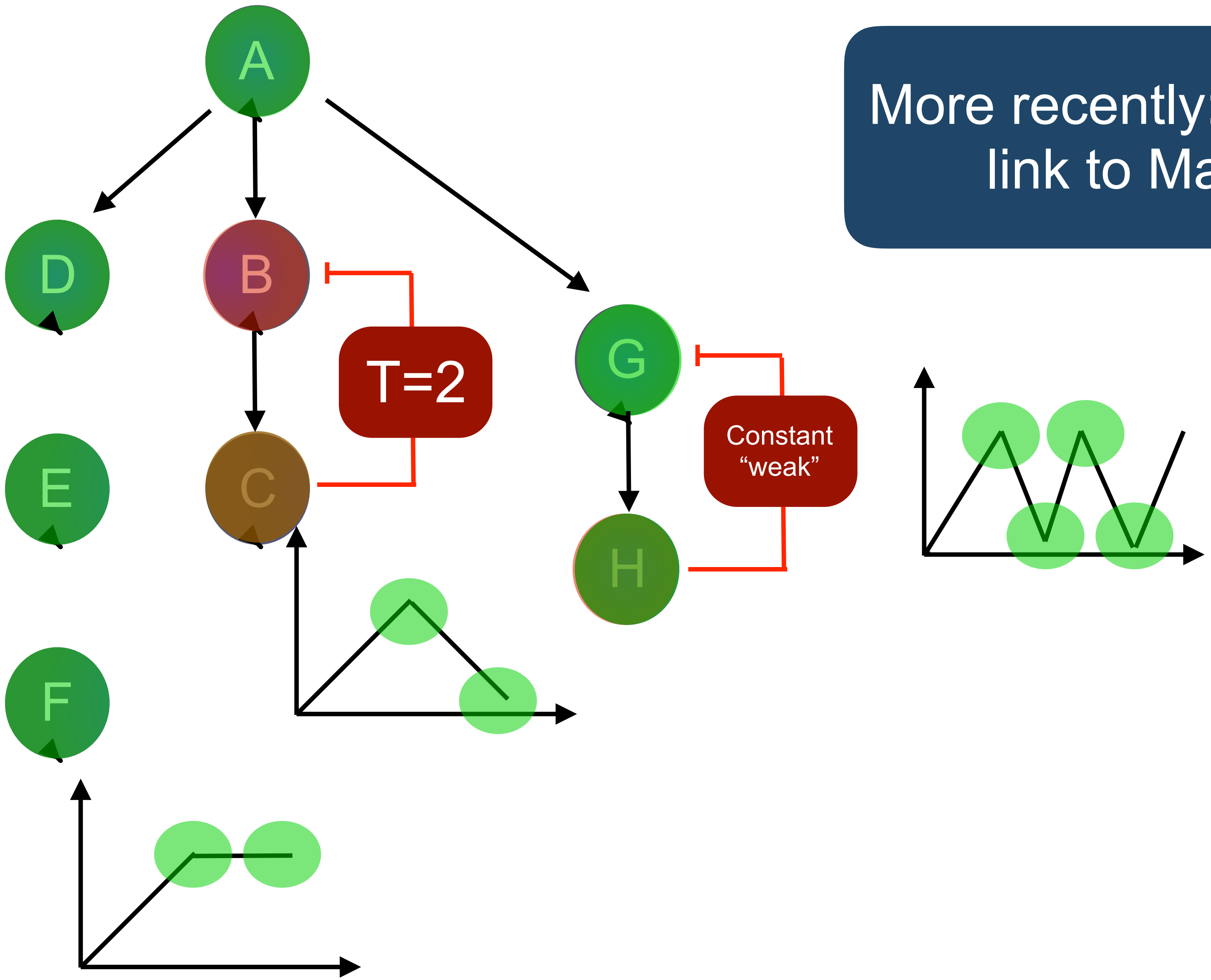
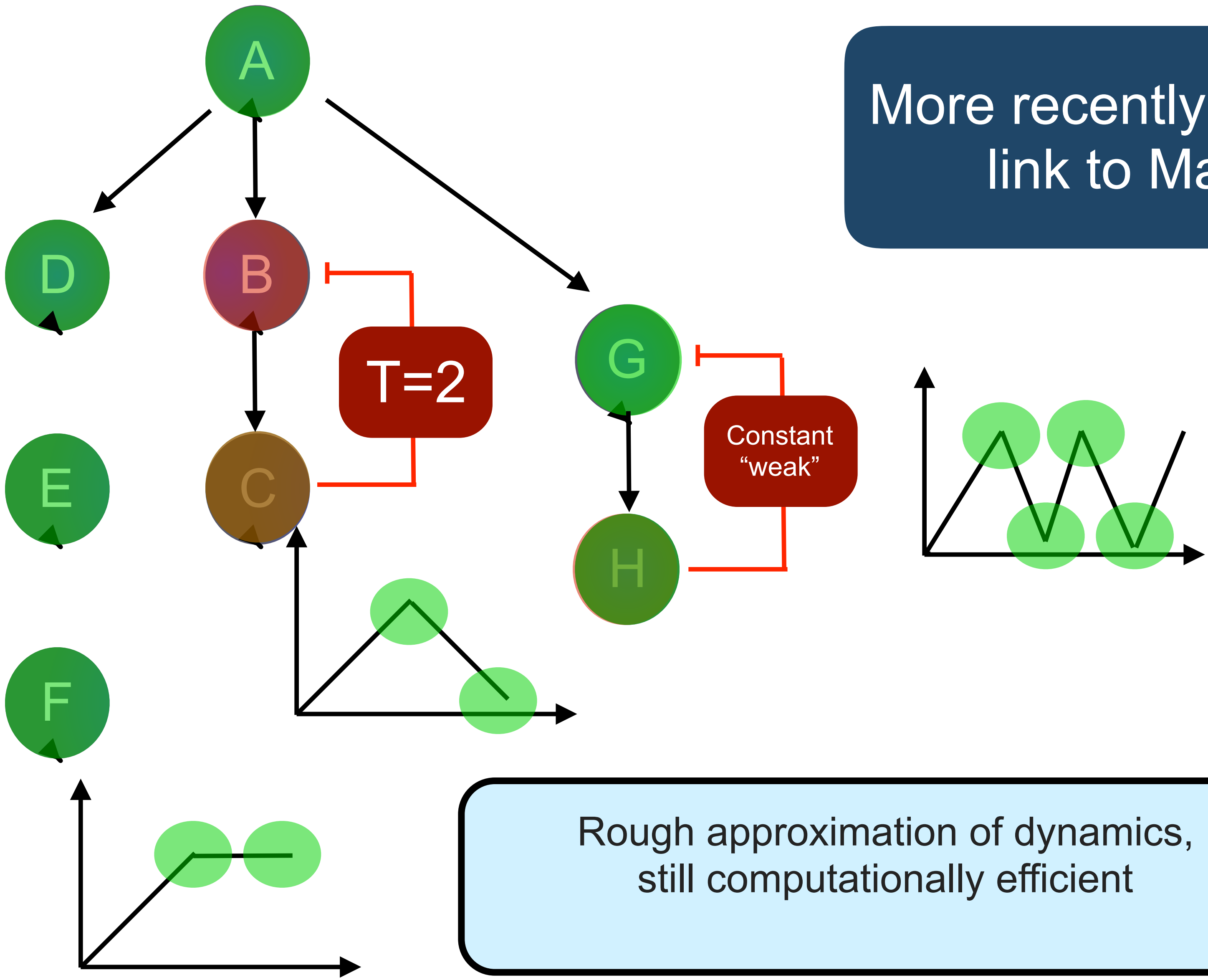


More recently: update to link to MaBoss

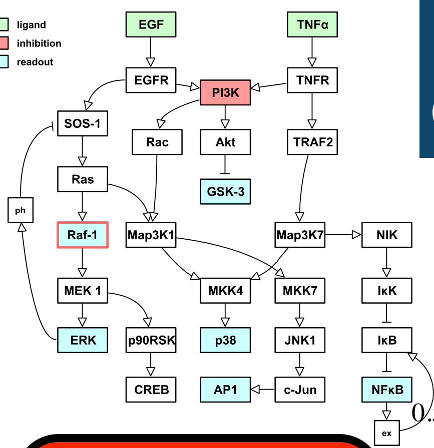
Approximation of dynamics using synchronous simulation & multiple time-scales



More recently: update to link to MaBoss

Rough approximation of dynamics, still computationally efficient

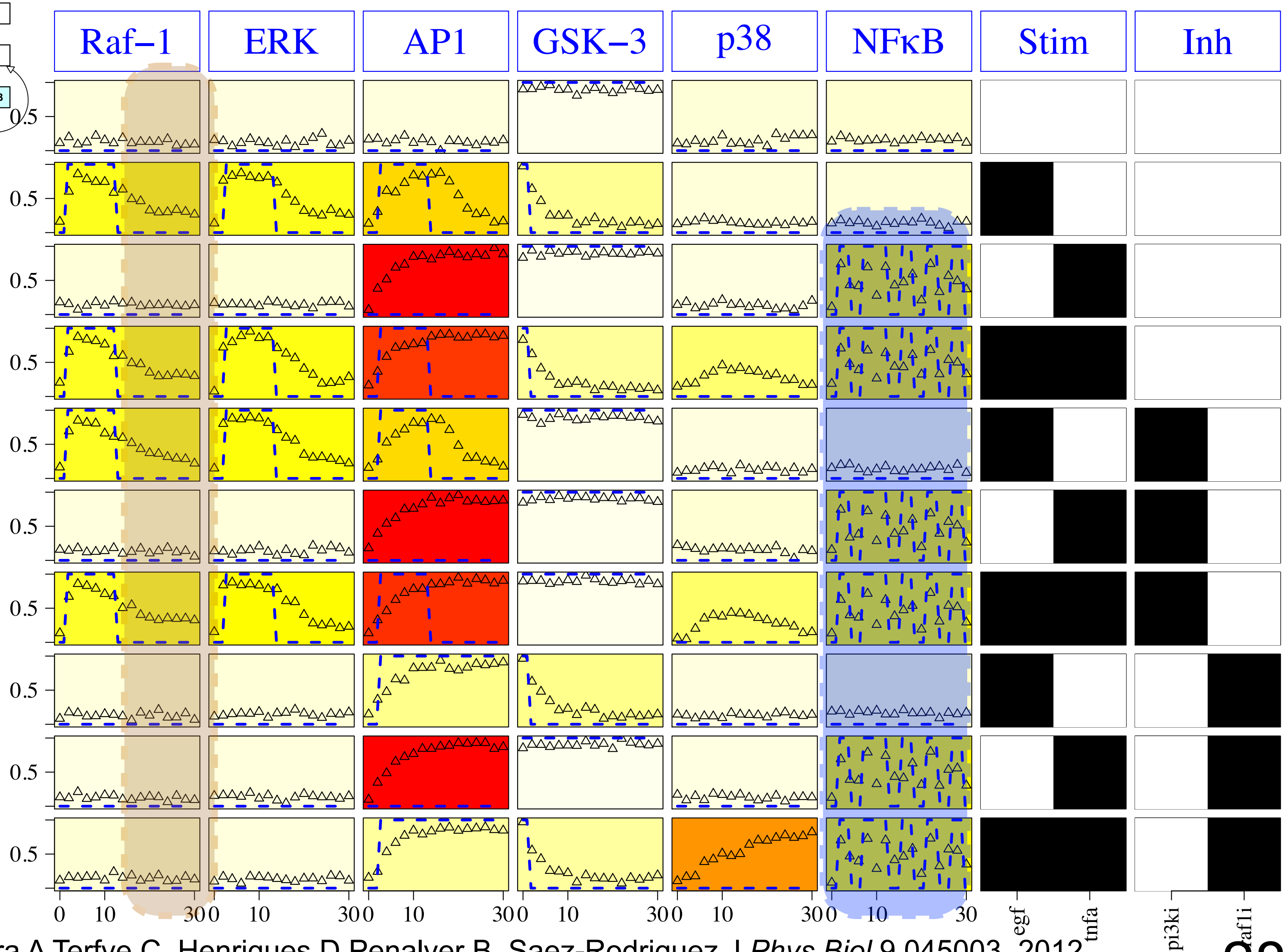
Synchronous simulation captures oscillatory behaviour



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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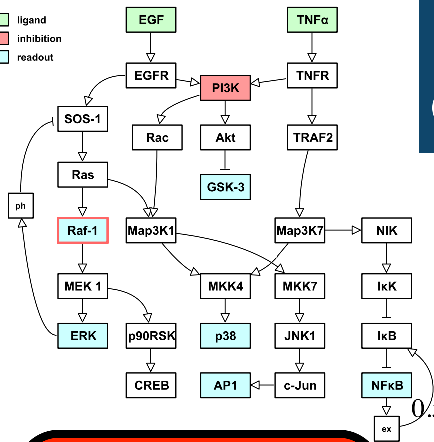

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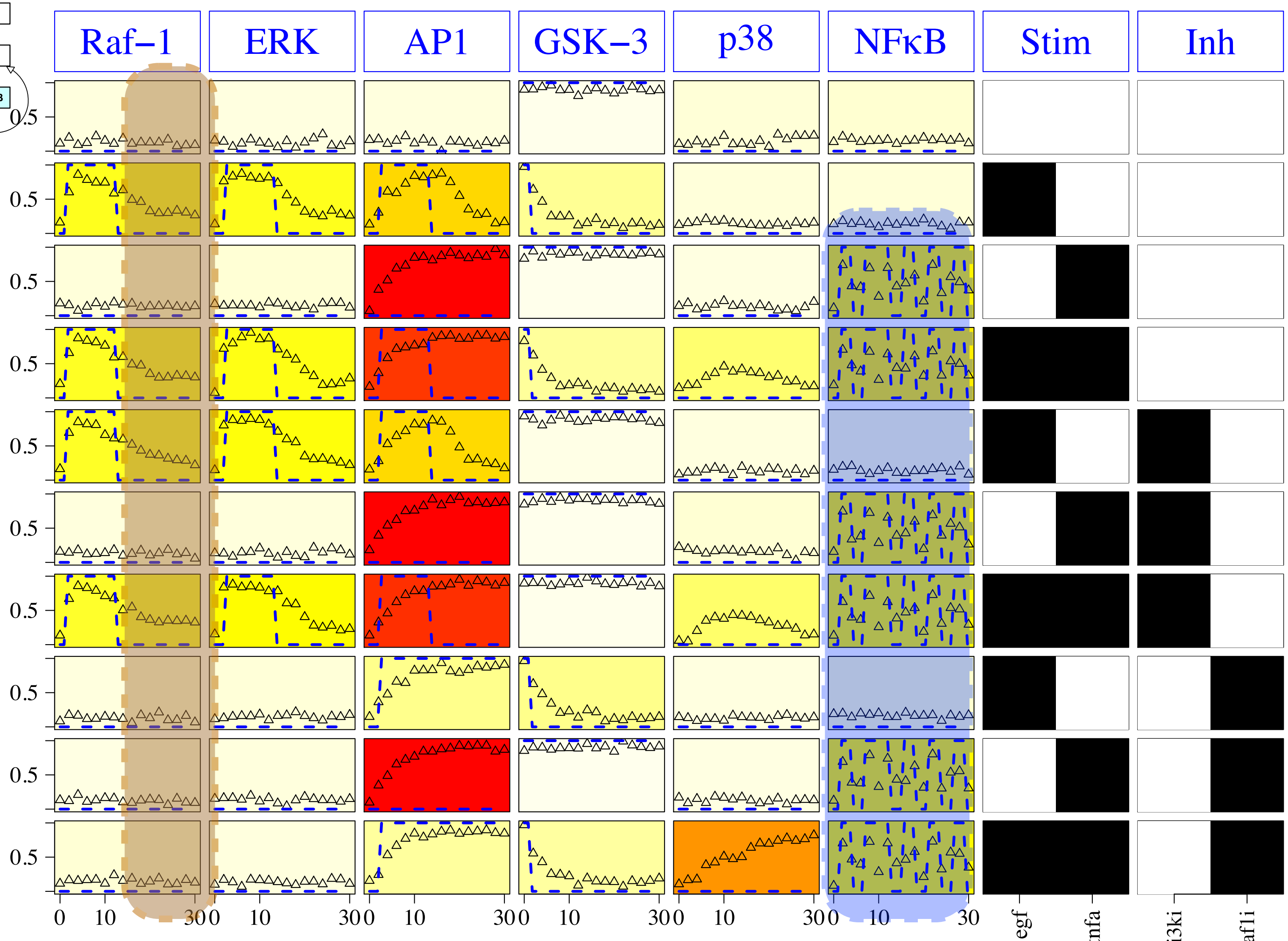

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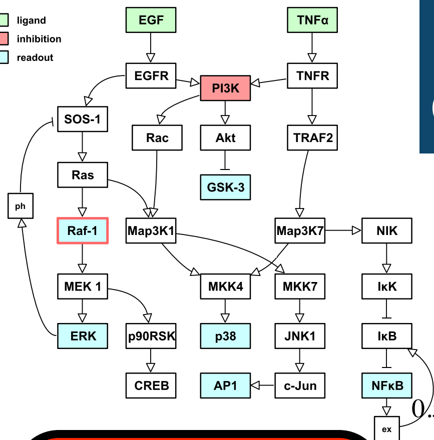

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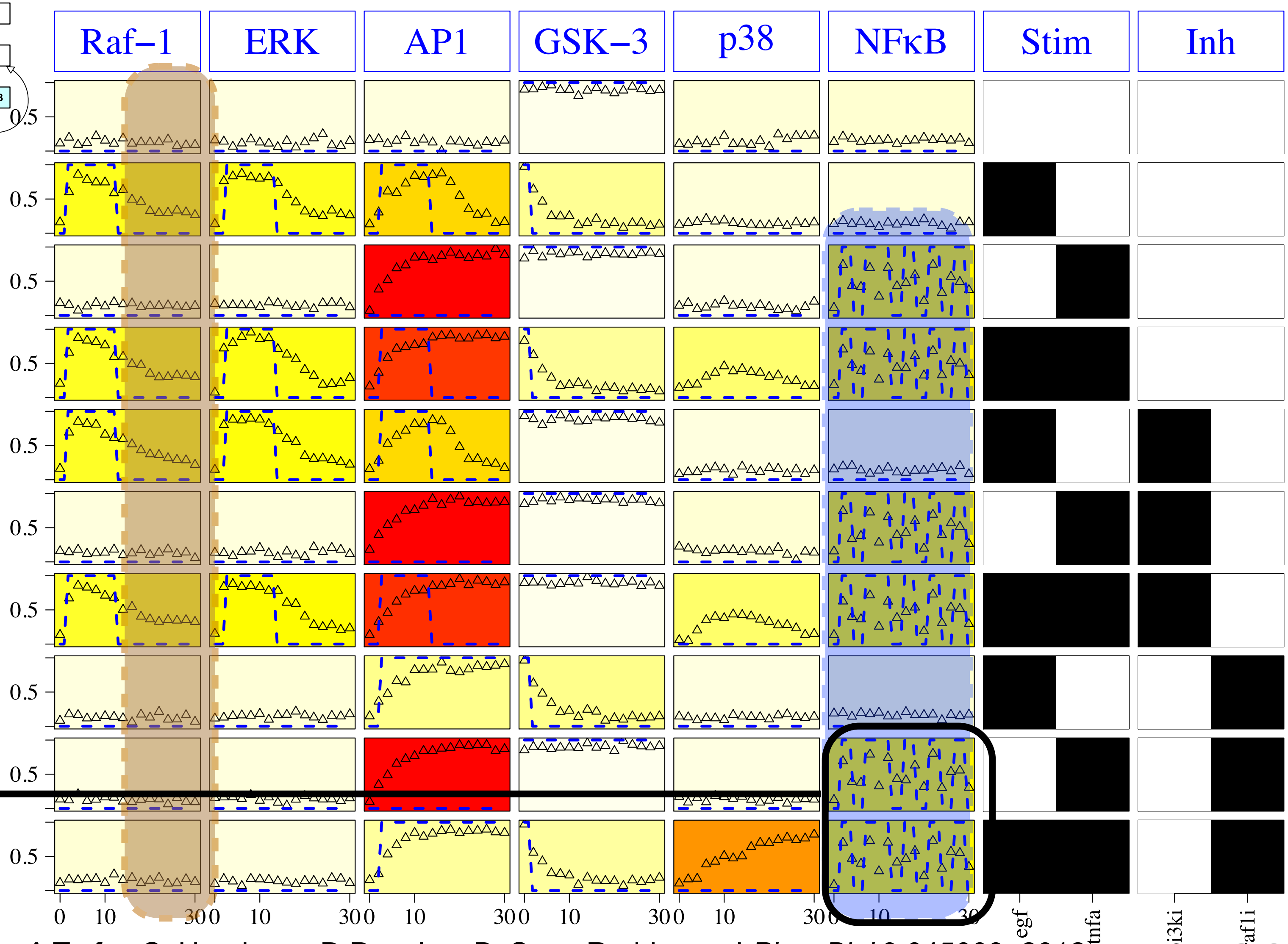

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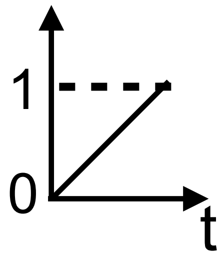
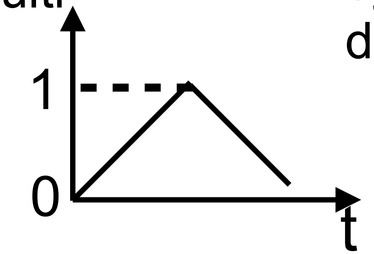
From Boolean to continuous and dynamic models within CellNOpt

Boolean (binary) logic steady state

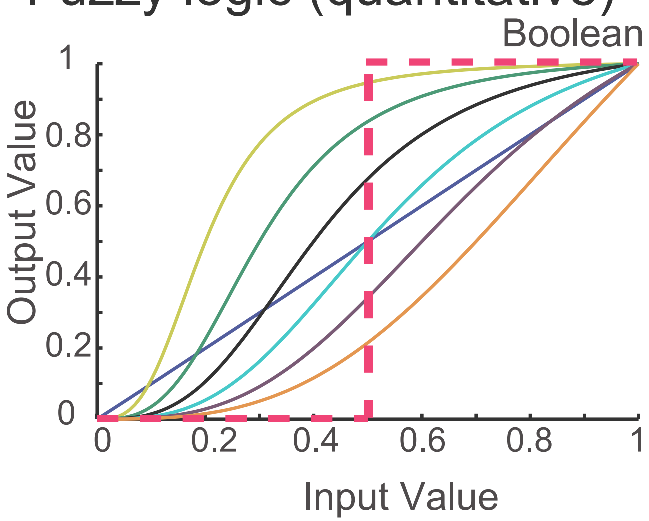


Boolean multi time-scale



sync. dynamics

Fuzzy logic (quantitative)



Morris et al., PloS Comp Bio 2011

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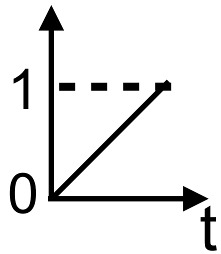

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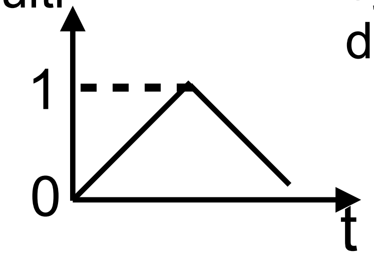

Camille Terfve

Aidan MacNamara

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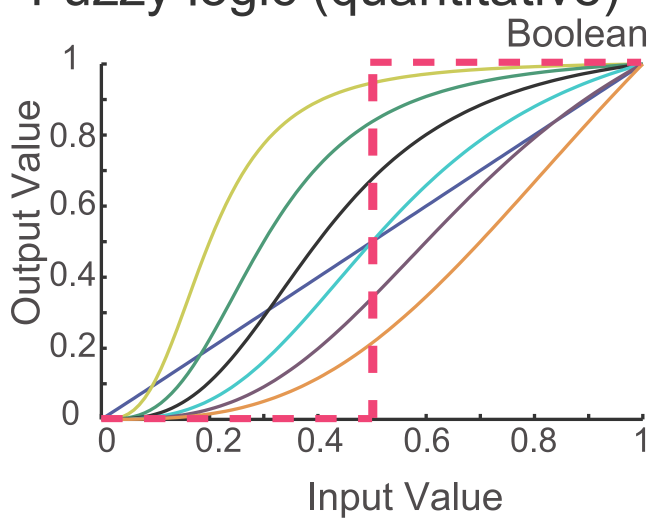

Morris et al., PloS Comp Bio 2011

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

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

- Transform into differential equation

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

- E.g. a AND b inactivate C

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

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

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

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)

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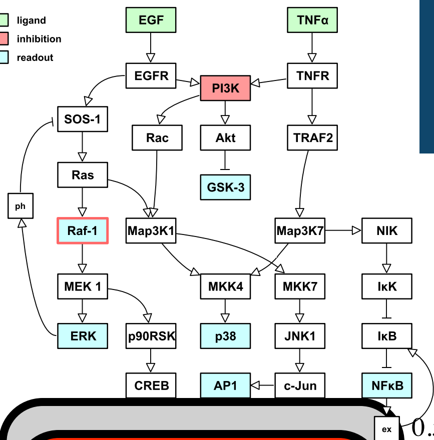
d/dt(casp8) = ((tnfa^casp8_n_tnfa/(tnfa^casp8_n_tnfa+casp8_k_tnfa^casp8_n_tnfa)*(1+casp8_k_tnfa^casp8_n_tnfa)-casp8) * casp8_tauinv)*(1-casp8_inh)

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

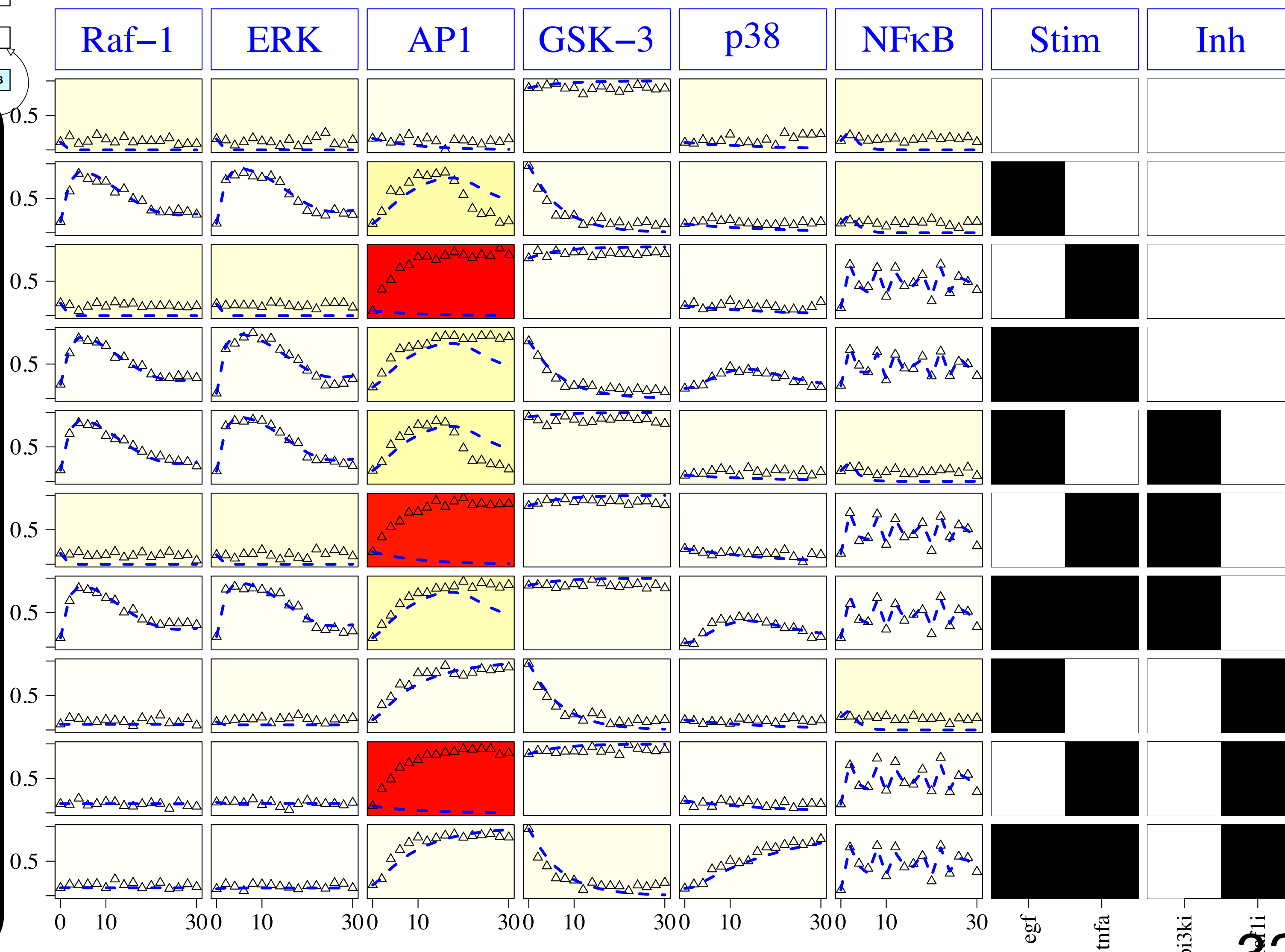
Identifies strong active links

Identifies weak active links

Captures strong feedbacks

Captures 'weak' feedbacks

ODE



CellNOpt-MaBOSS Fits can approximate dynamics

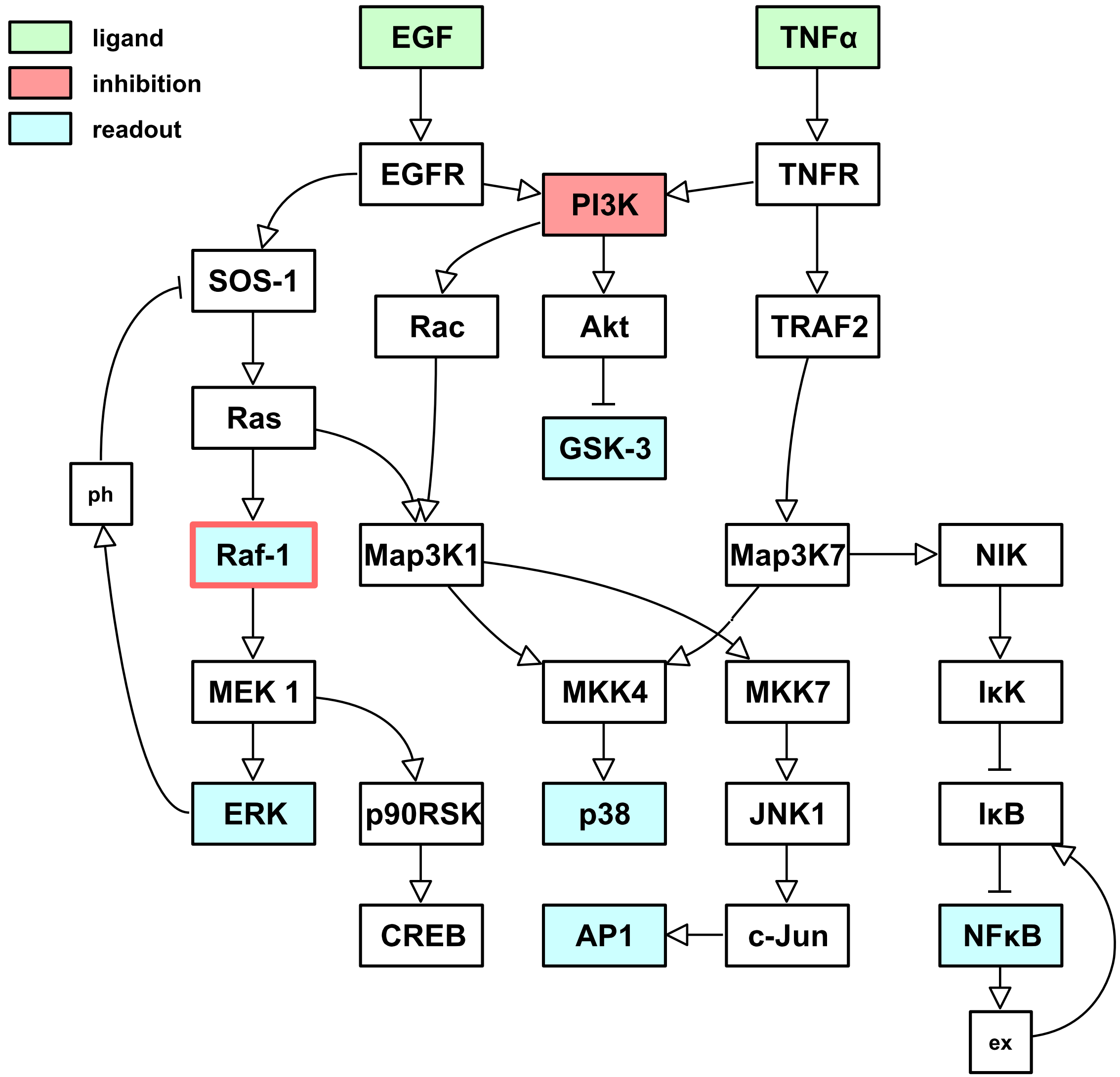
CellNOpt-MaBOSS Fits can approximate dynamics

Integration nearly ready:

fit of models simulated with MaBoss (asynchronous, time-continuous)

- fits time dynamics, still Boolean
- worse fit but faster than logic-ODES

Different methods capture different aspects



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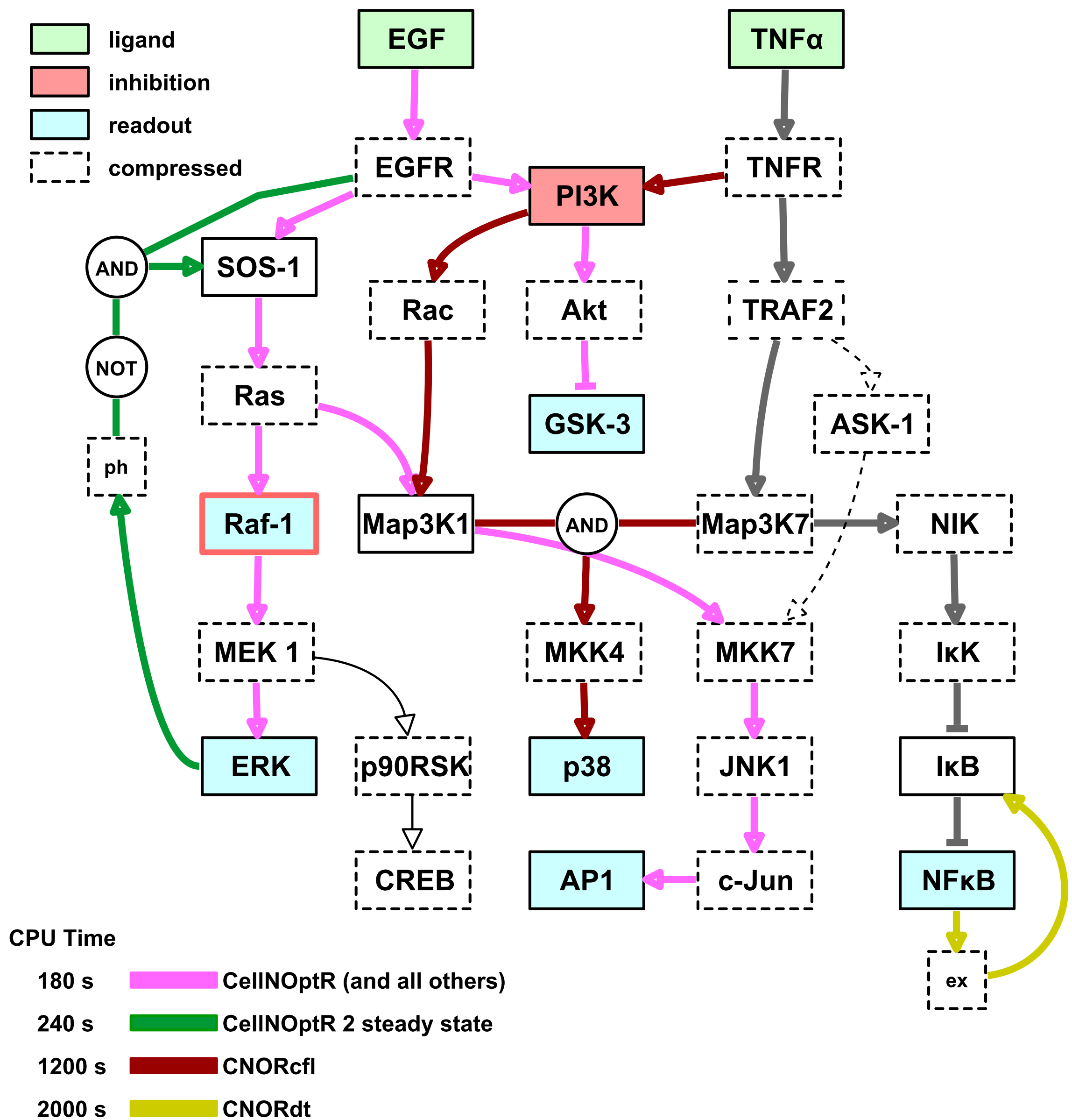
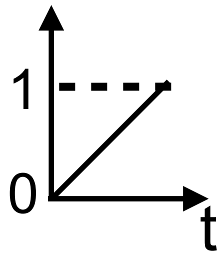


From Boolean to continuous and dynamic models within CellNOpt

Boolean (binary)
logic steady state



Boolean multi
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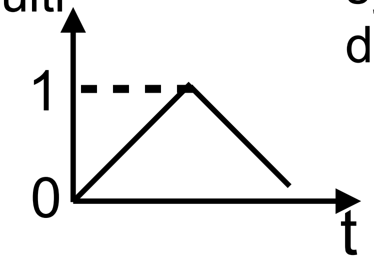
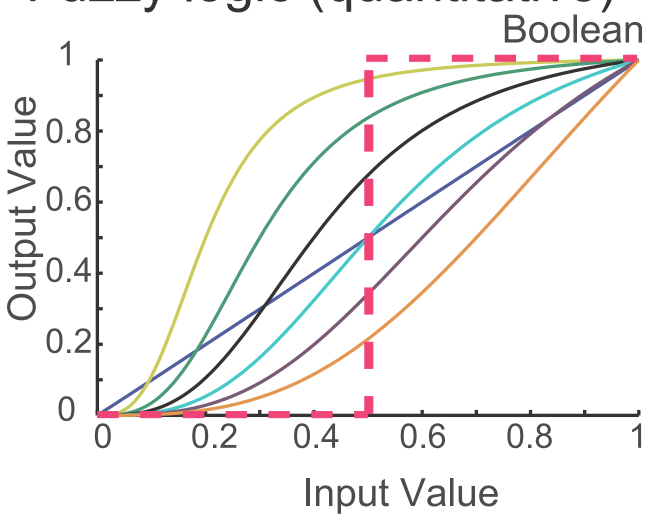


sync.
dynamics

Camille
Terfve

Aidan
MacNamara

Fuzzy logic (quantitative)



Morris et al., PloS Comp Bio 2011

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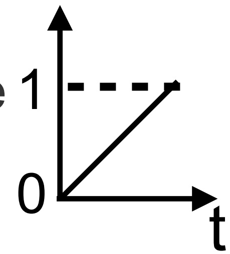

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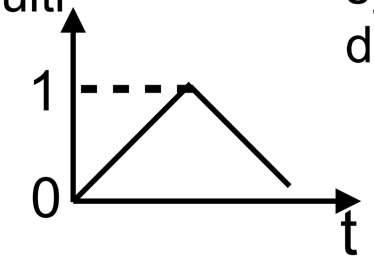

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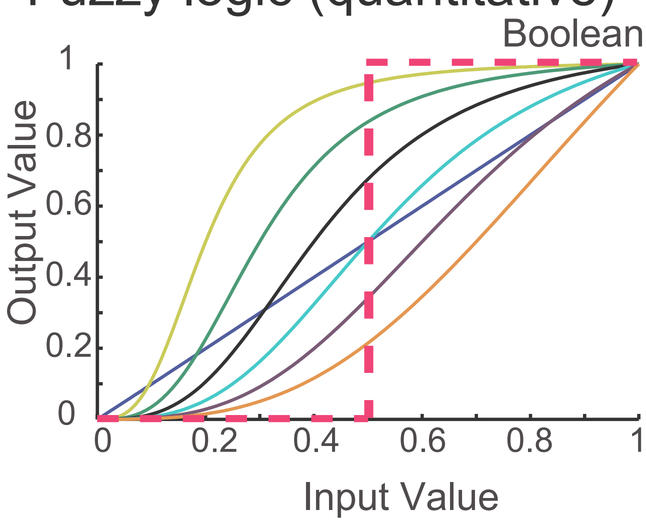

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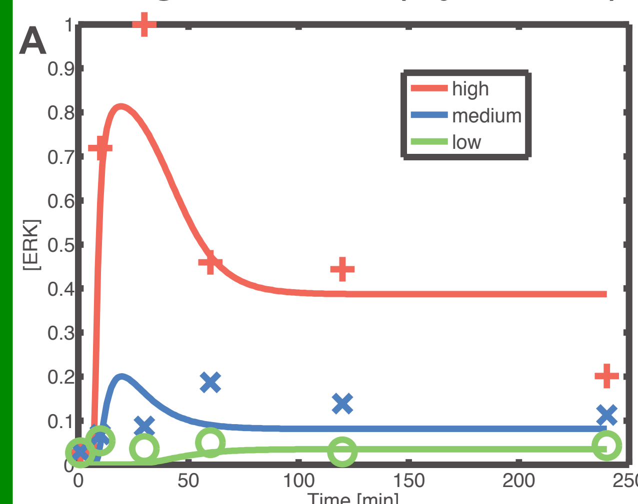
Logic ODEs (dynamic)



w. J Banga & J. Egea,

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

Identify structure + parameters Henriques et al. Bioinformatics 2015

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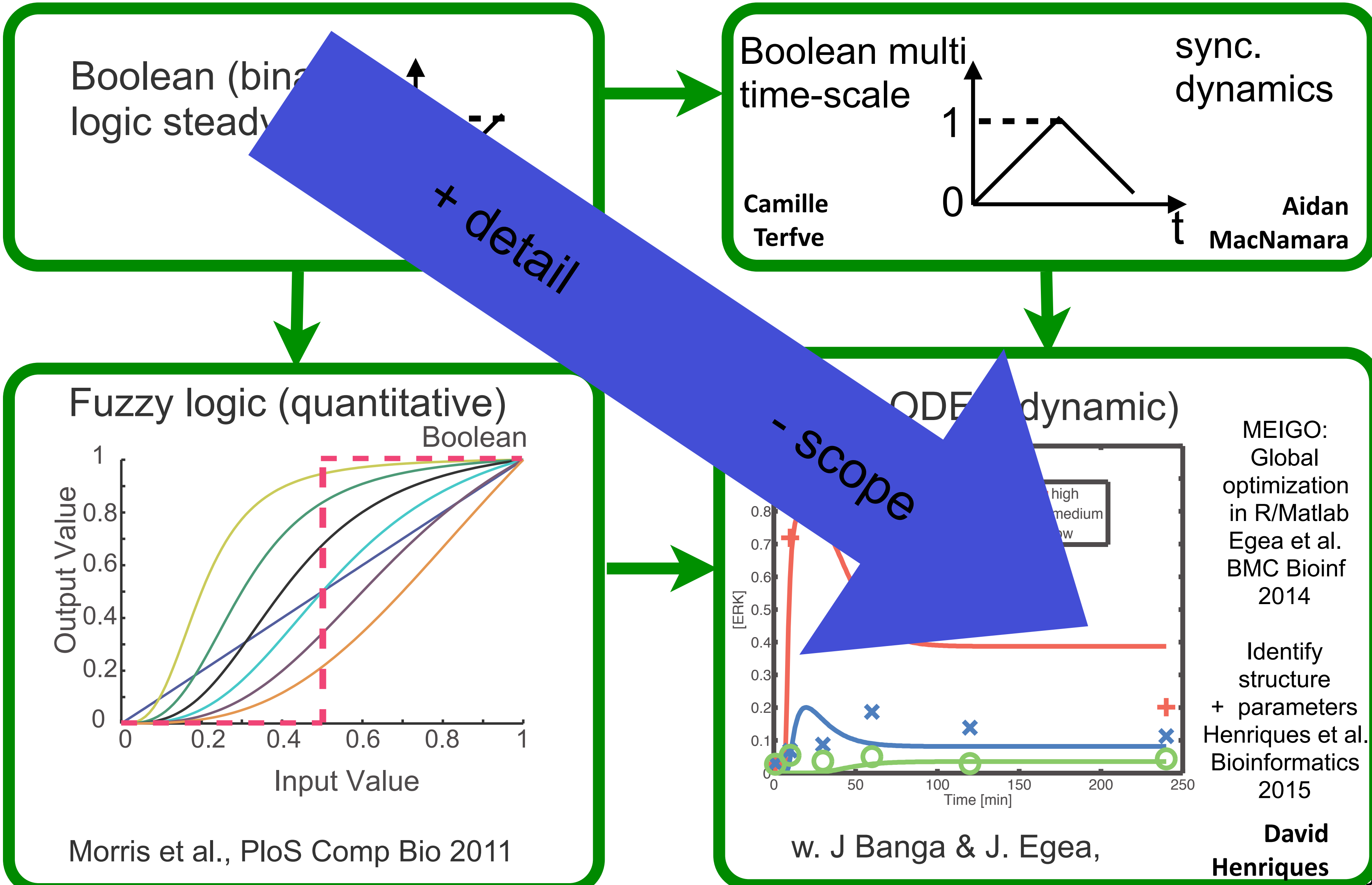

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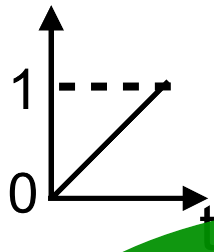

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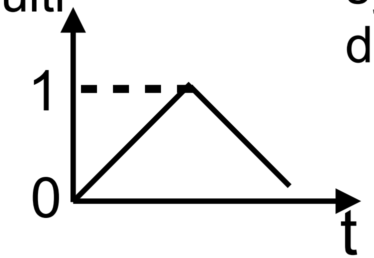

sync. dynamics

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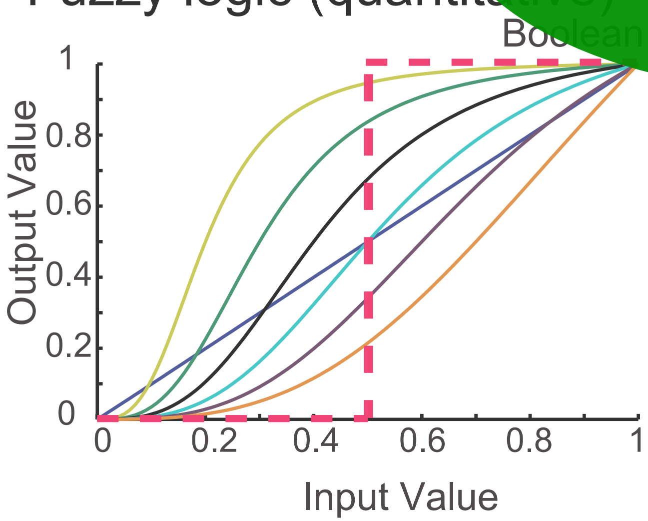

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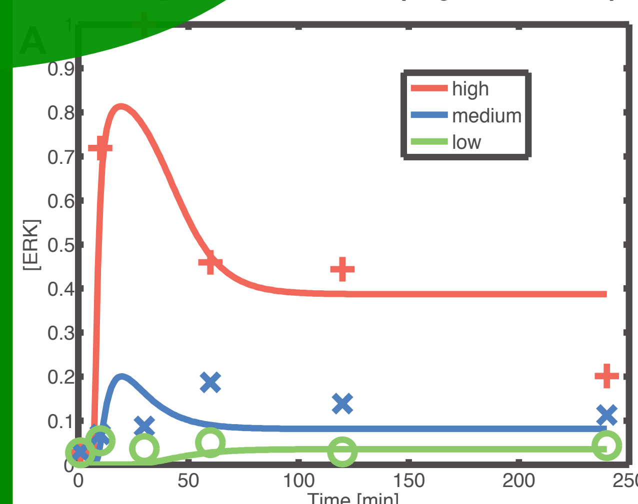

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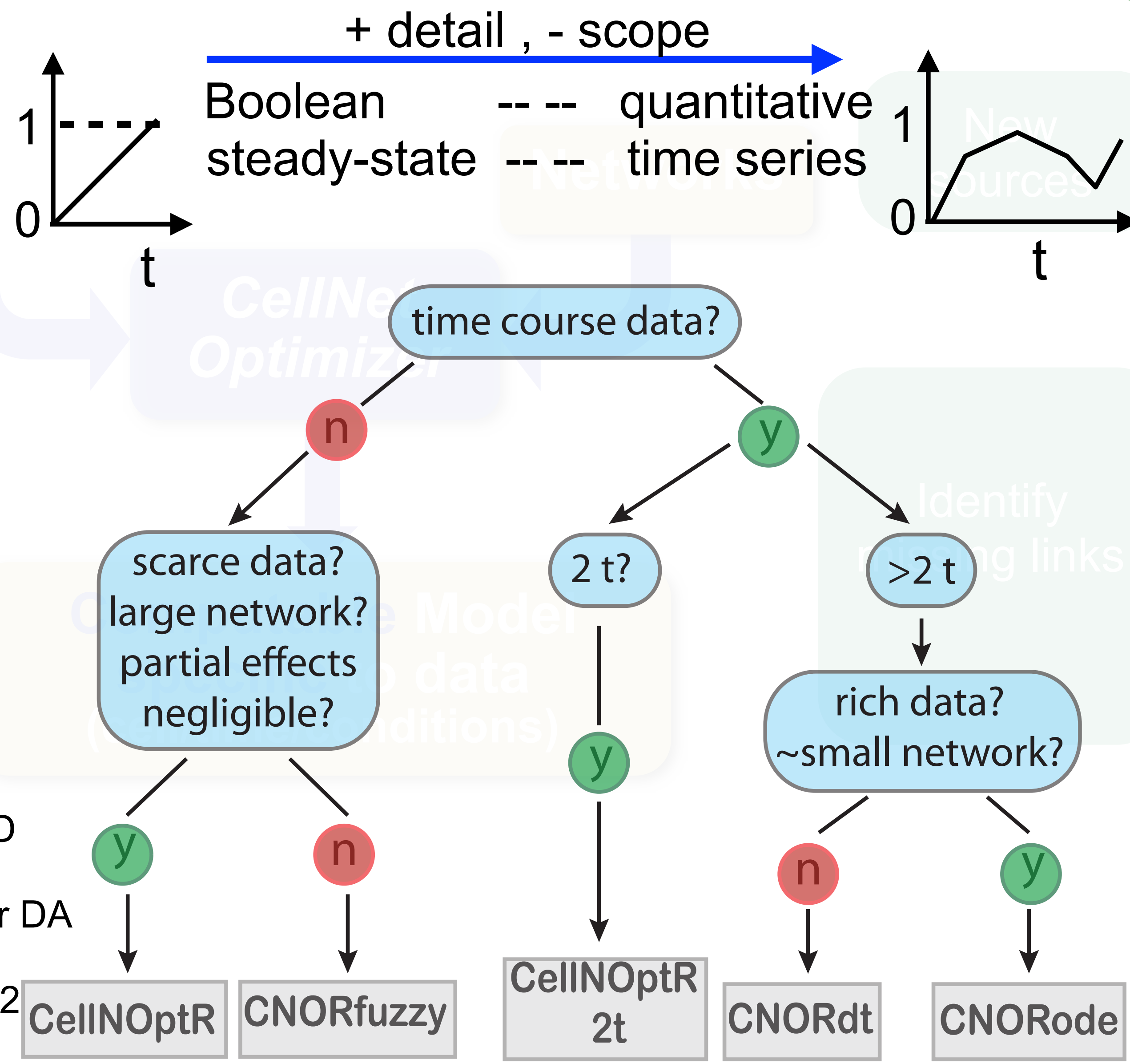
Identify structure + parameters Henriques et al. Bioinformatics 2015

w. J Banga & J. Egea,

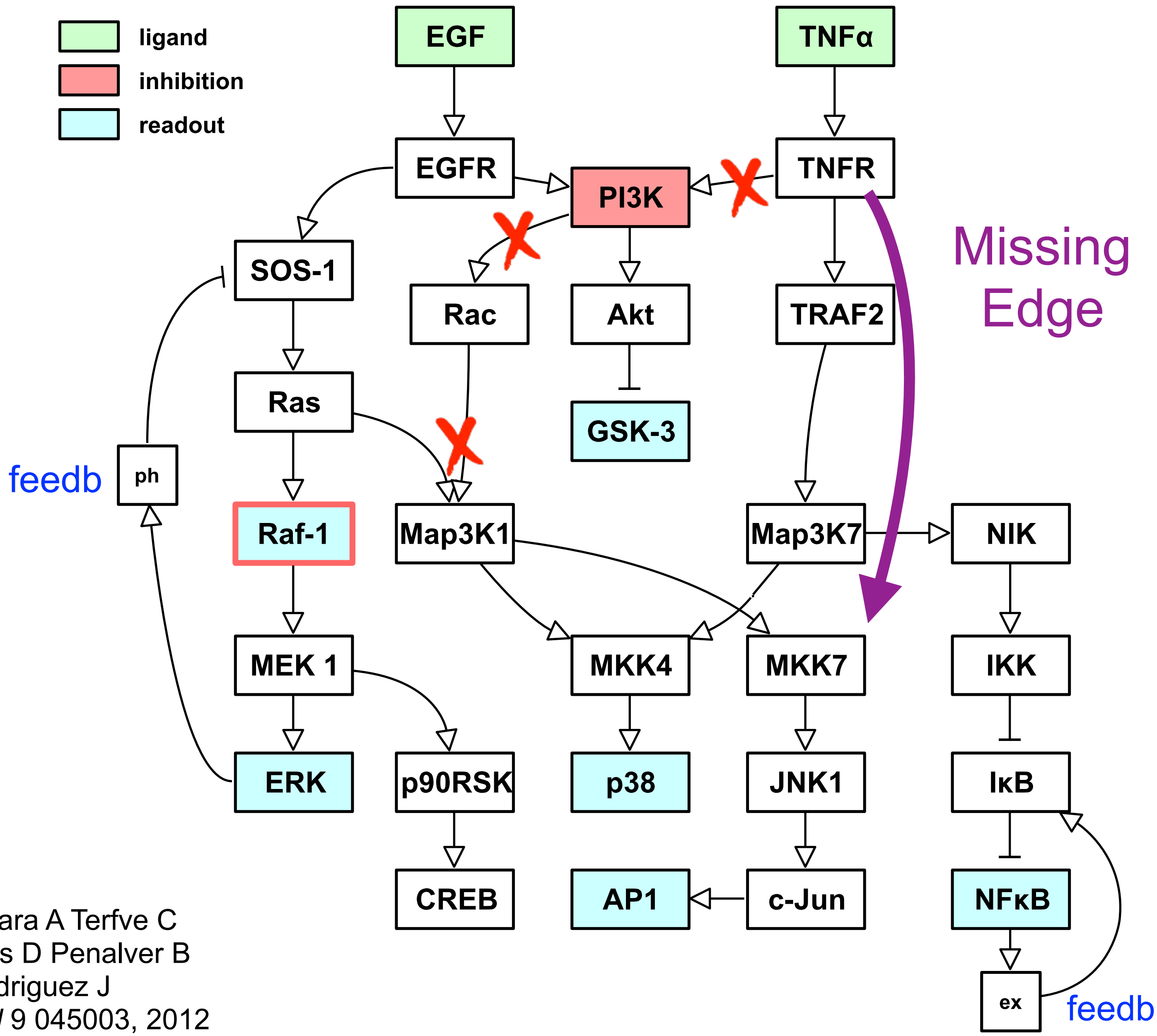
David Henriques

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
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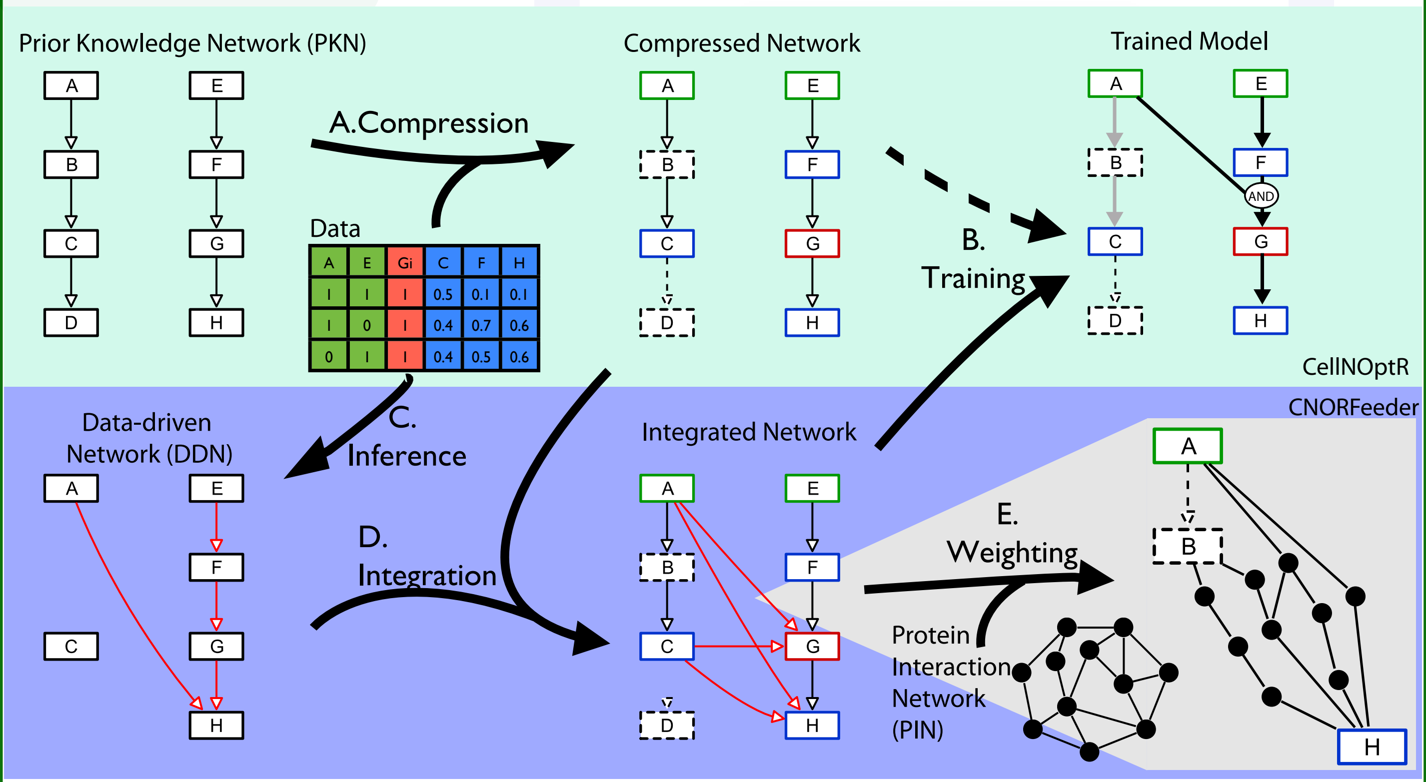
Phys Biol 9 045003, 2012

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*

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

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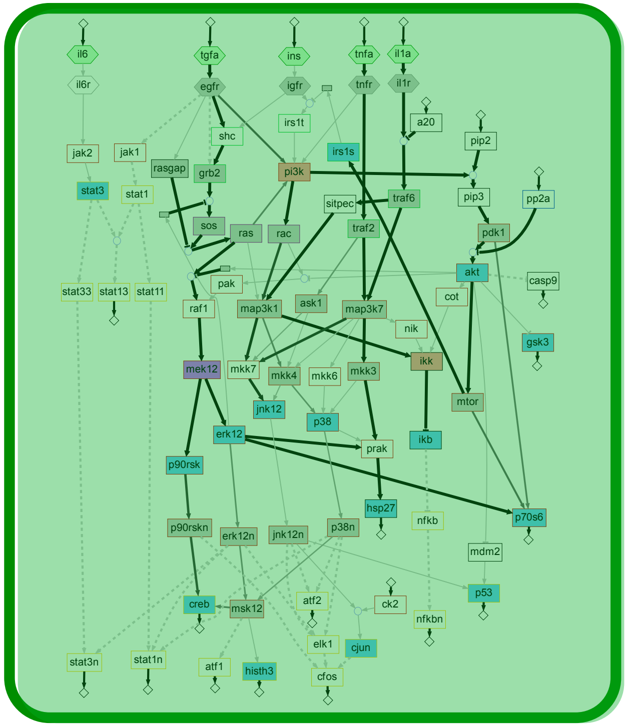
How is signal processing altered in disease?

Health



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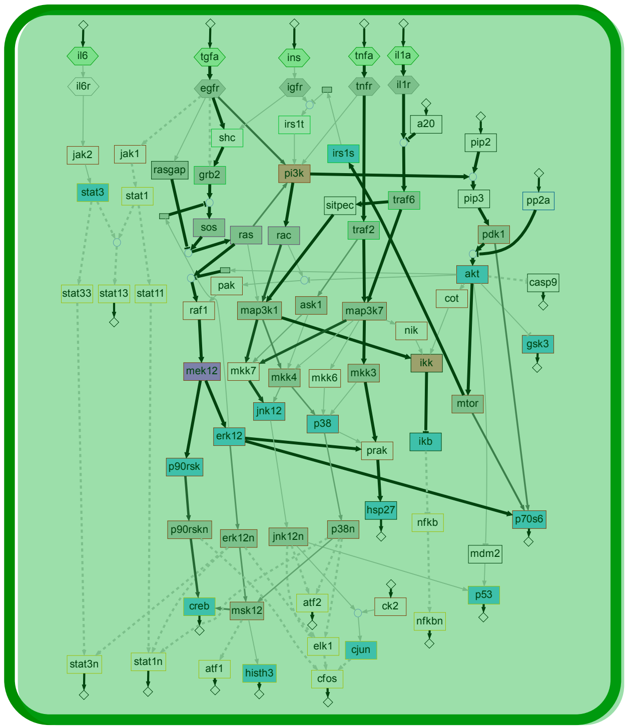
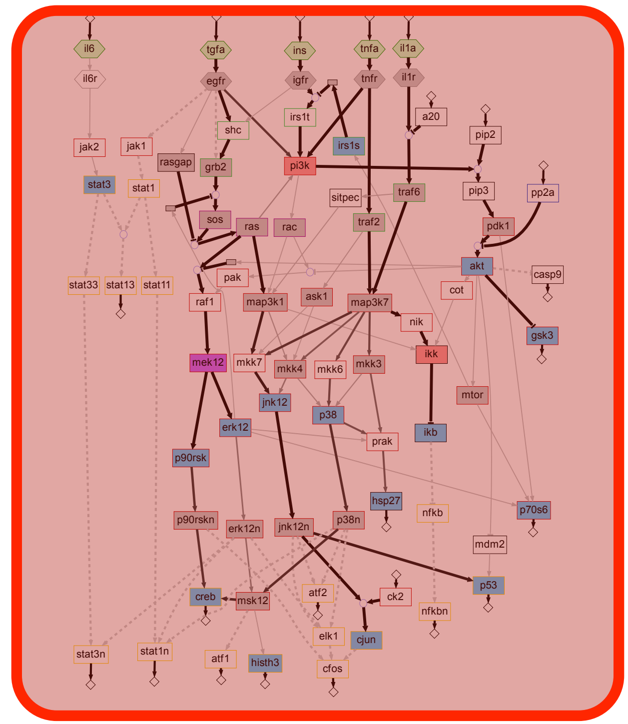


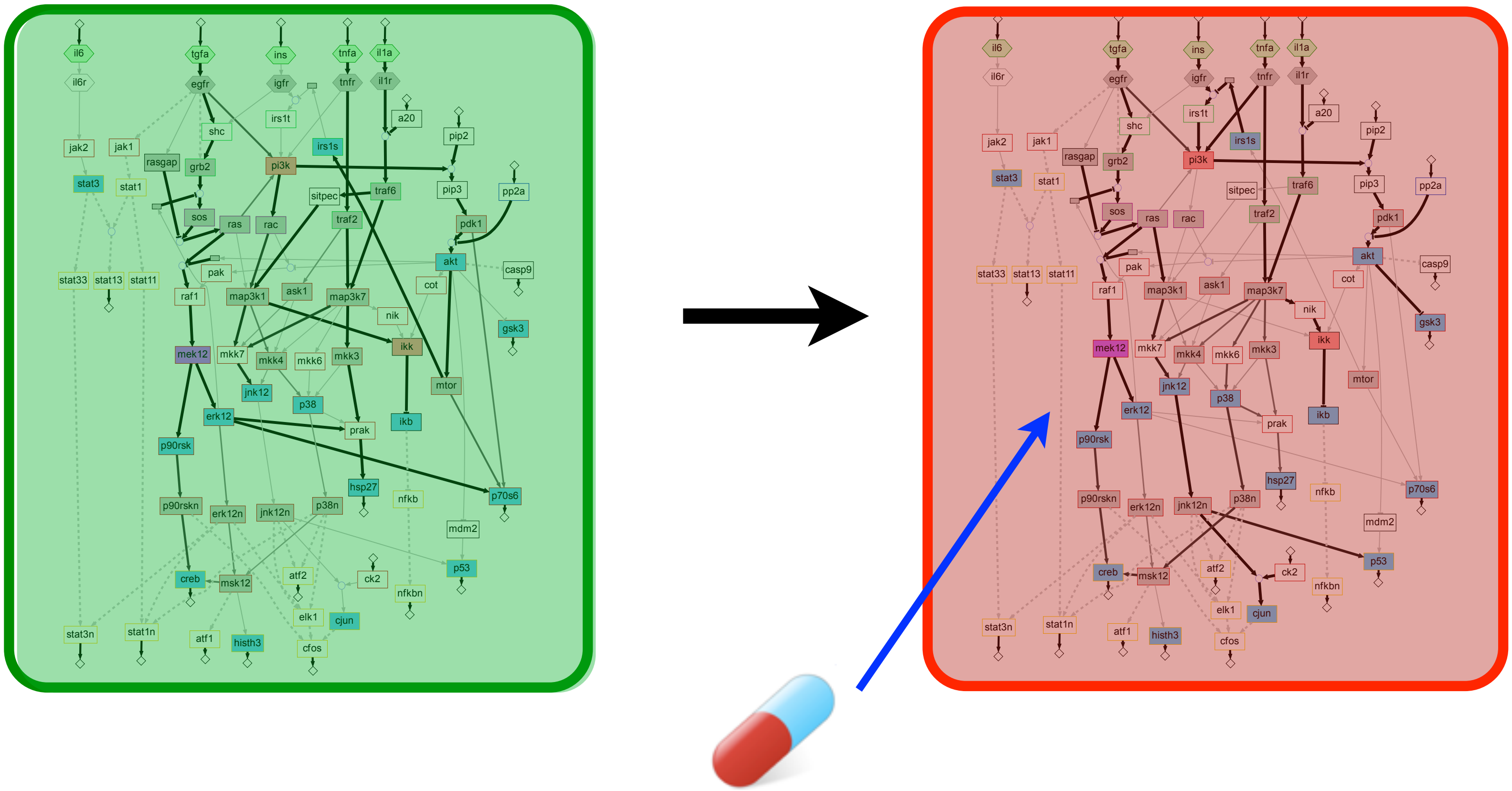
Disease



How is signal processing altered in disease?

Health

Disease

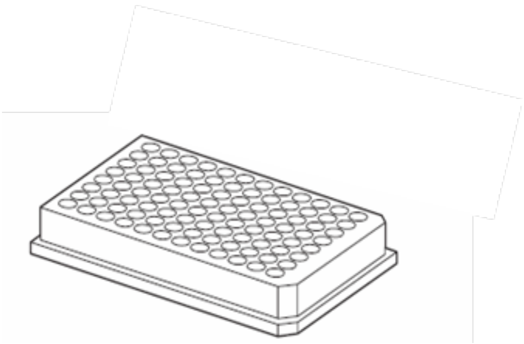


... and how can we target this with therapeutics?

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

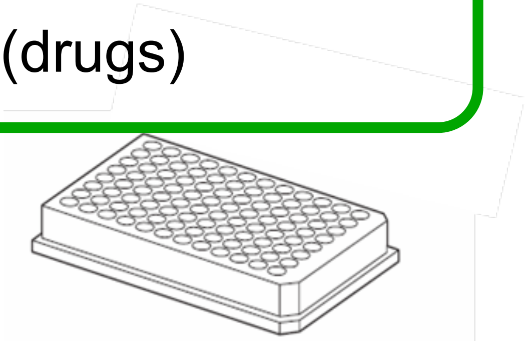
An example of a perturbation-based high-throughput data sets



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

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

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



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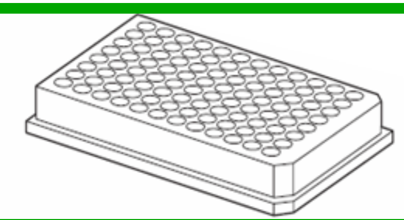
An example of a perturbation-based high-throughput data sets

Cue

➜ 7 **extracellular ligands**

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

at different times after stimulation



Signal

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

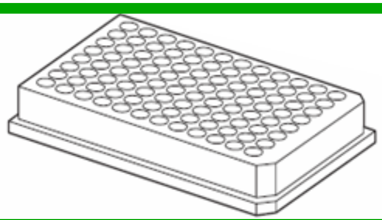
Alexopoulos L, Saez-Rodriguez J, Cosgrove B, Lauffenburger DA, Sorger PK, *Mol. Cell. Prot.*, 9, 1849, 2010

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)

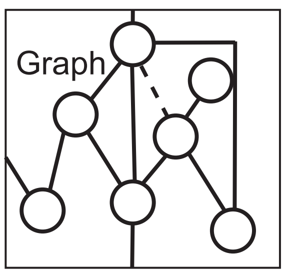
Response	➜ **Release** of 20 cytokines (3h, 24h)

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

Comparison of primary hepatocytes to 4 HCC cell lines

Primary | HepG2 | Hep3 | Huh7 | Focus

Generic network



high

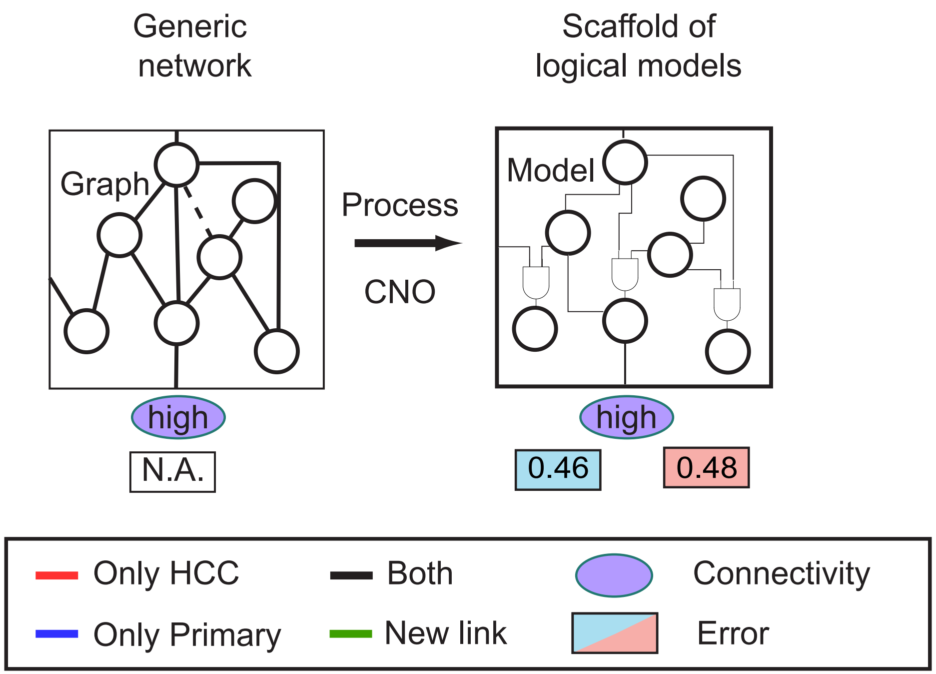
N.A.

Only HCC | Both | Connectivity
Only Primary | New link | Error

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

Primary **HepG2** **Hep3** **Huh7** **Focus**



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Comparison of primary hepatocytes to 4 HCC cell lines

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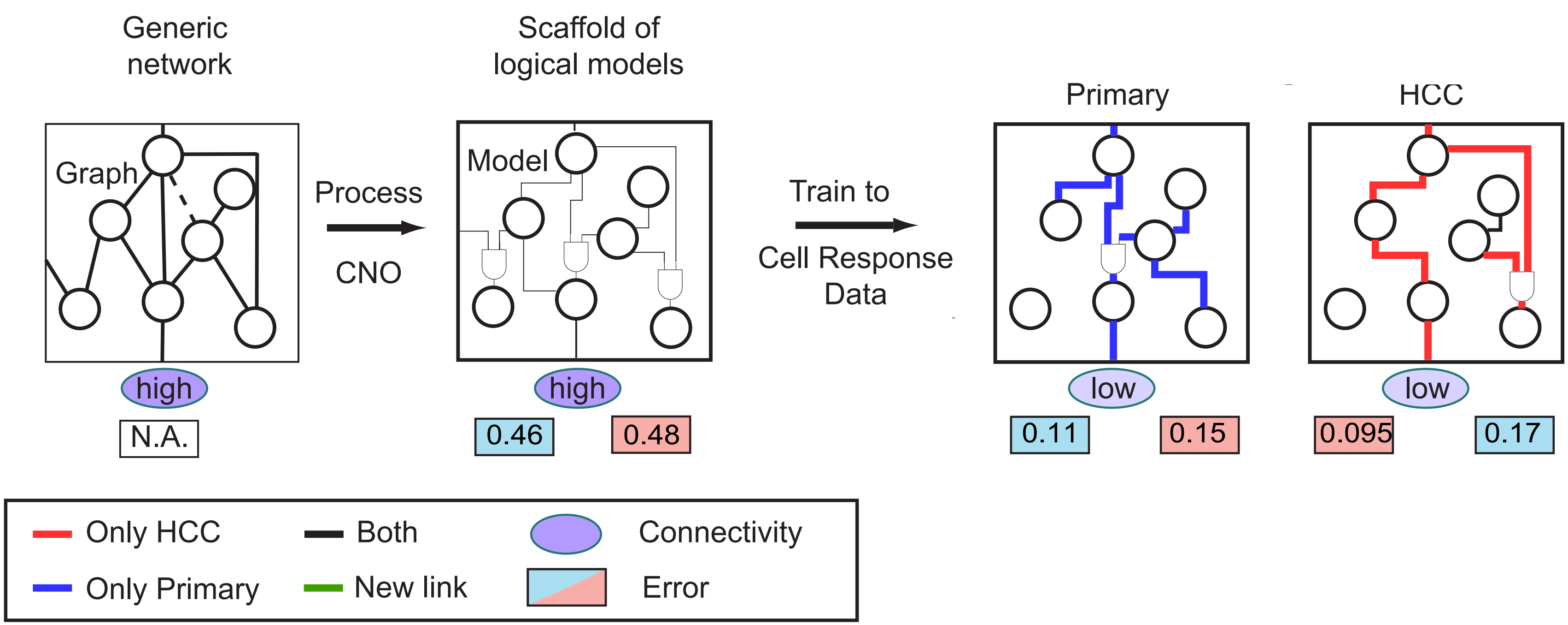

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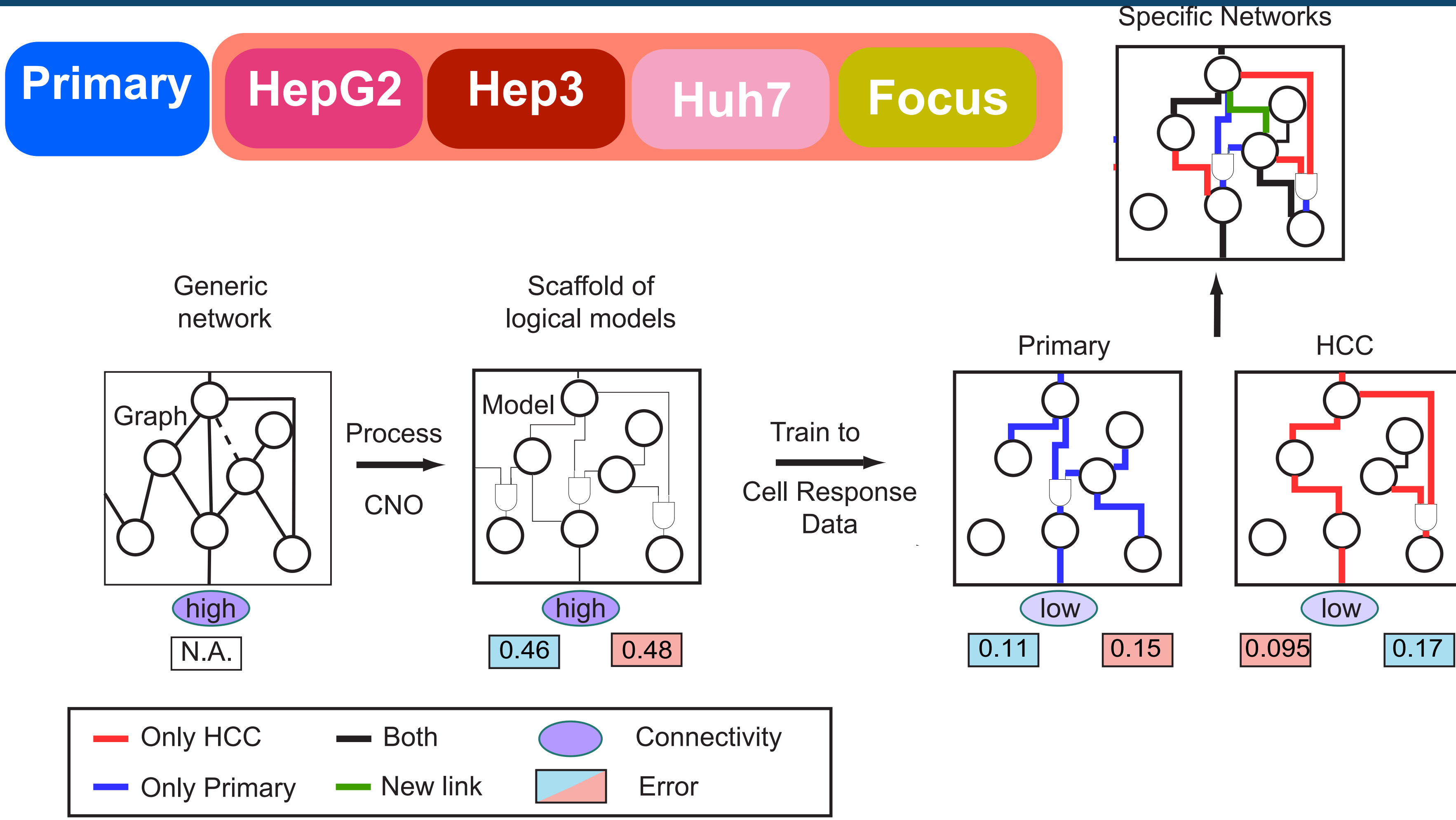
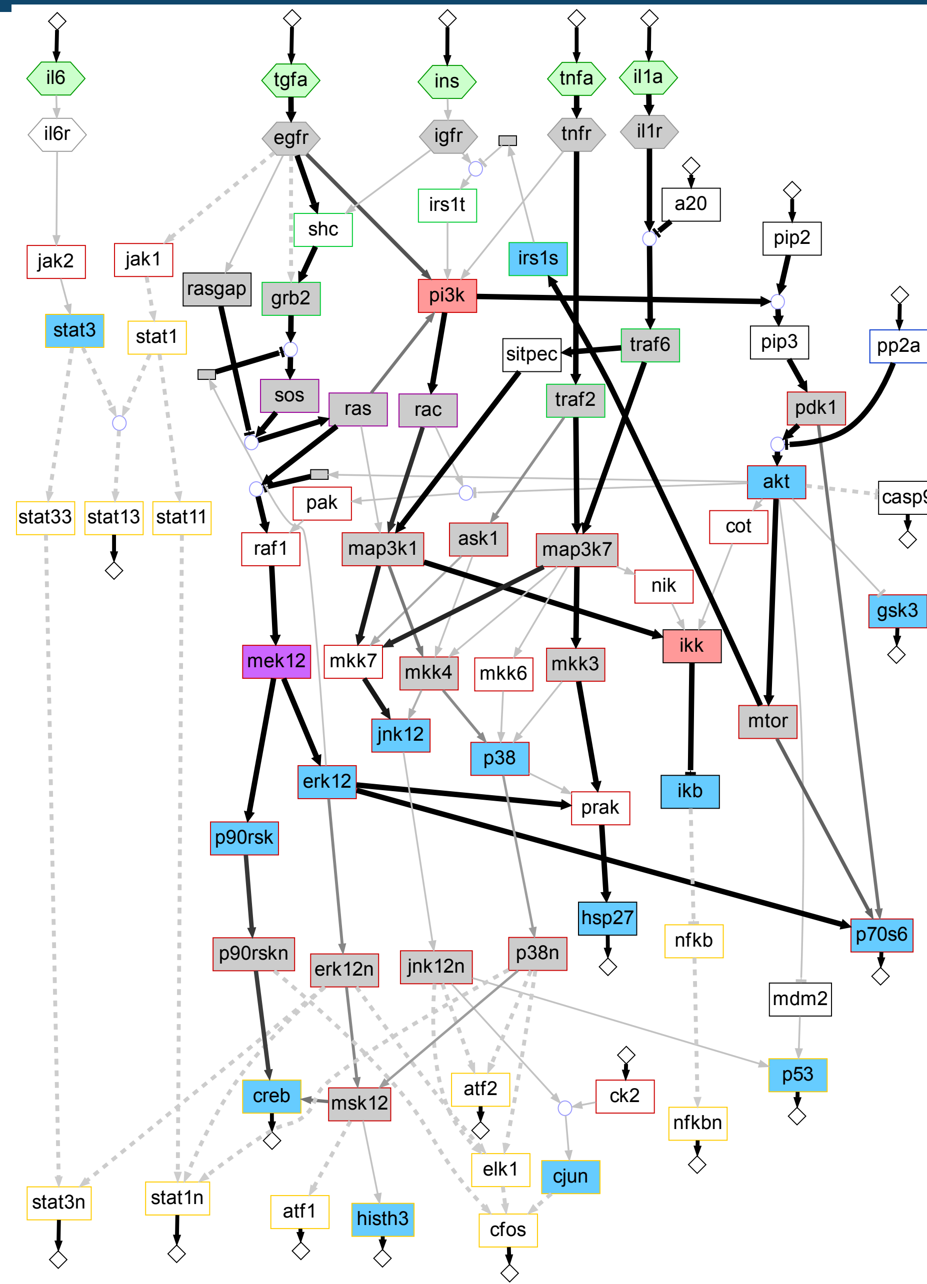


Saez-Rodriguez J, Alexopoulos LG, Zheng M, Morris MK, Lauffenburger DA, Sorger PK, *Cancer Research* 71(16), 2011

Primary



Stimulus

Perturbation

Readout

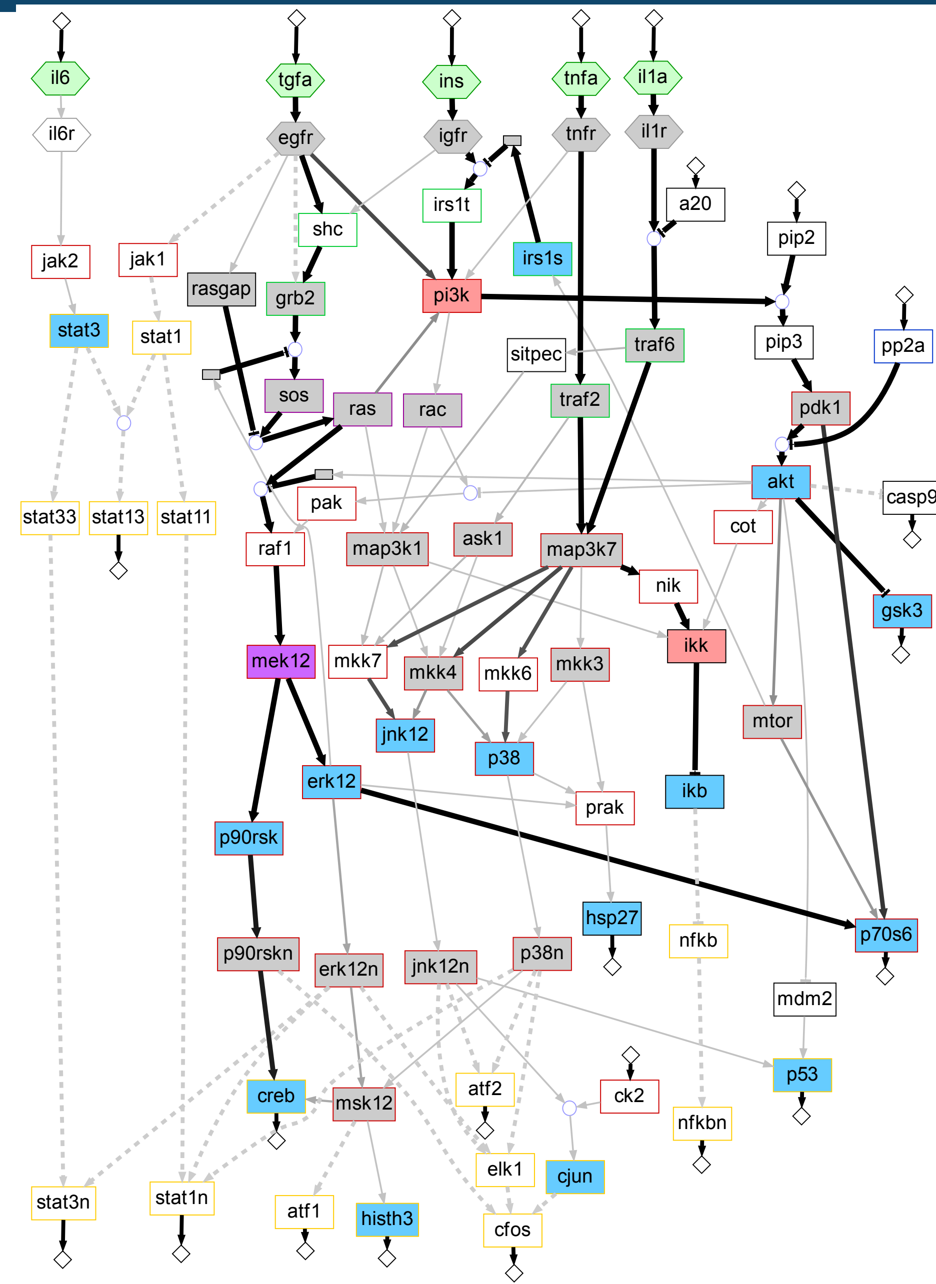
Perturb&Read

Kept

Removed

No effect

HepG2



Stimulus

Perturbation

Readout

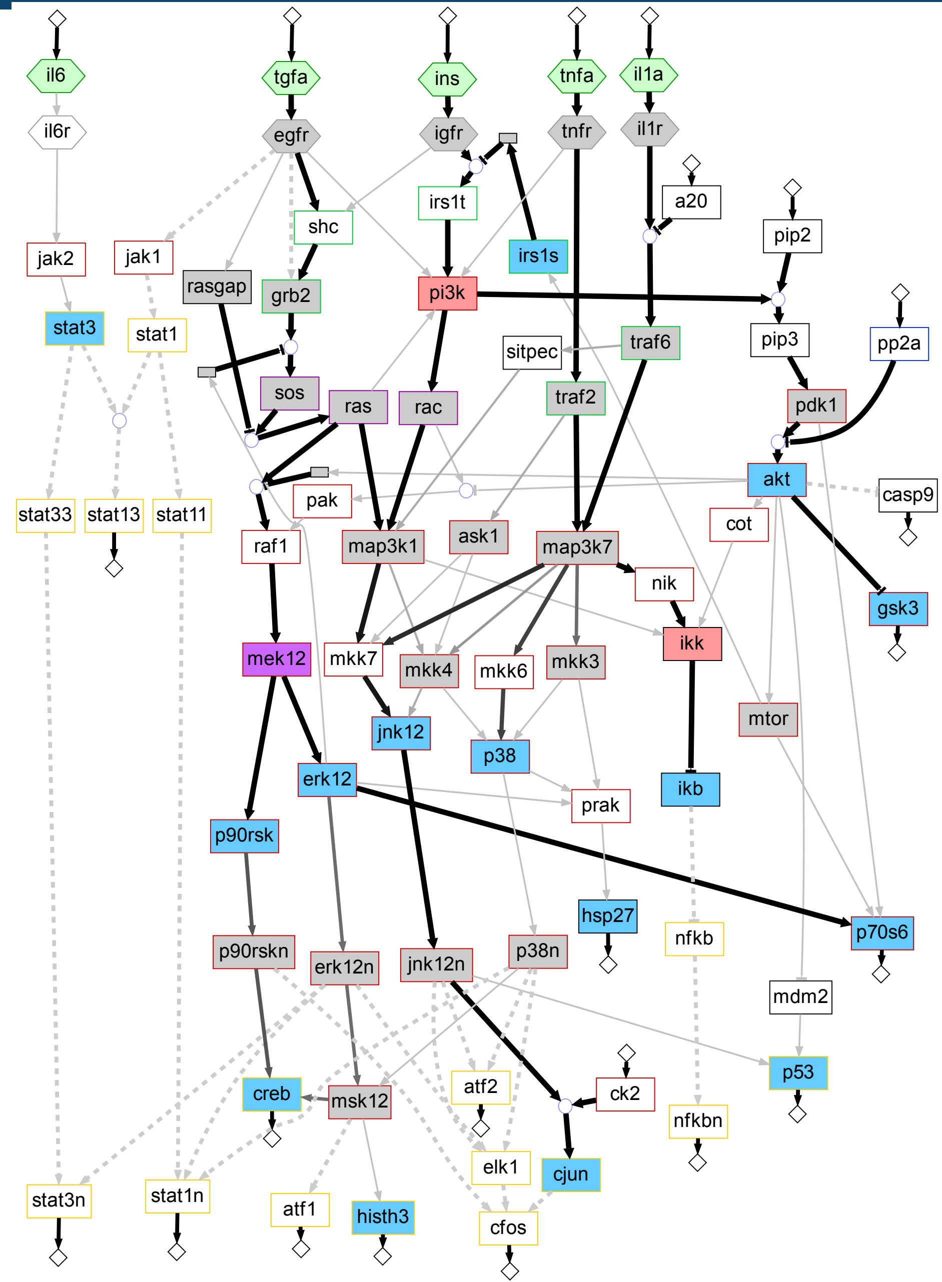
Perturb&Read

Kept

Removed

No effect

Hep3B


il6
tgfa
ins
tnfa
il1a
il6r
egfr
igfr
tnfr
il1r
irs1t
a20
shc
jak2
jak1
irs1s
pip2
rasgap
grb2
pi3k
stat3
stat1
traf6
pip3
pp2a
sitpec
sos
ras
rac
traf2
pdk1
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pak
stat33
stat13
stat11
raf1
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ask1
map3k7
cot
nik
gsk3
mek12
mkk7
mkk4
mkk6
mkk3
ikk
mtor
jnk12
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erk12
ikb
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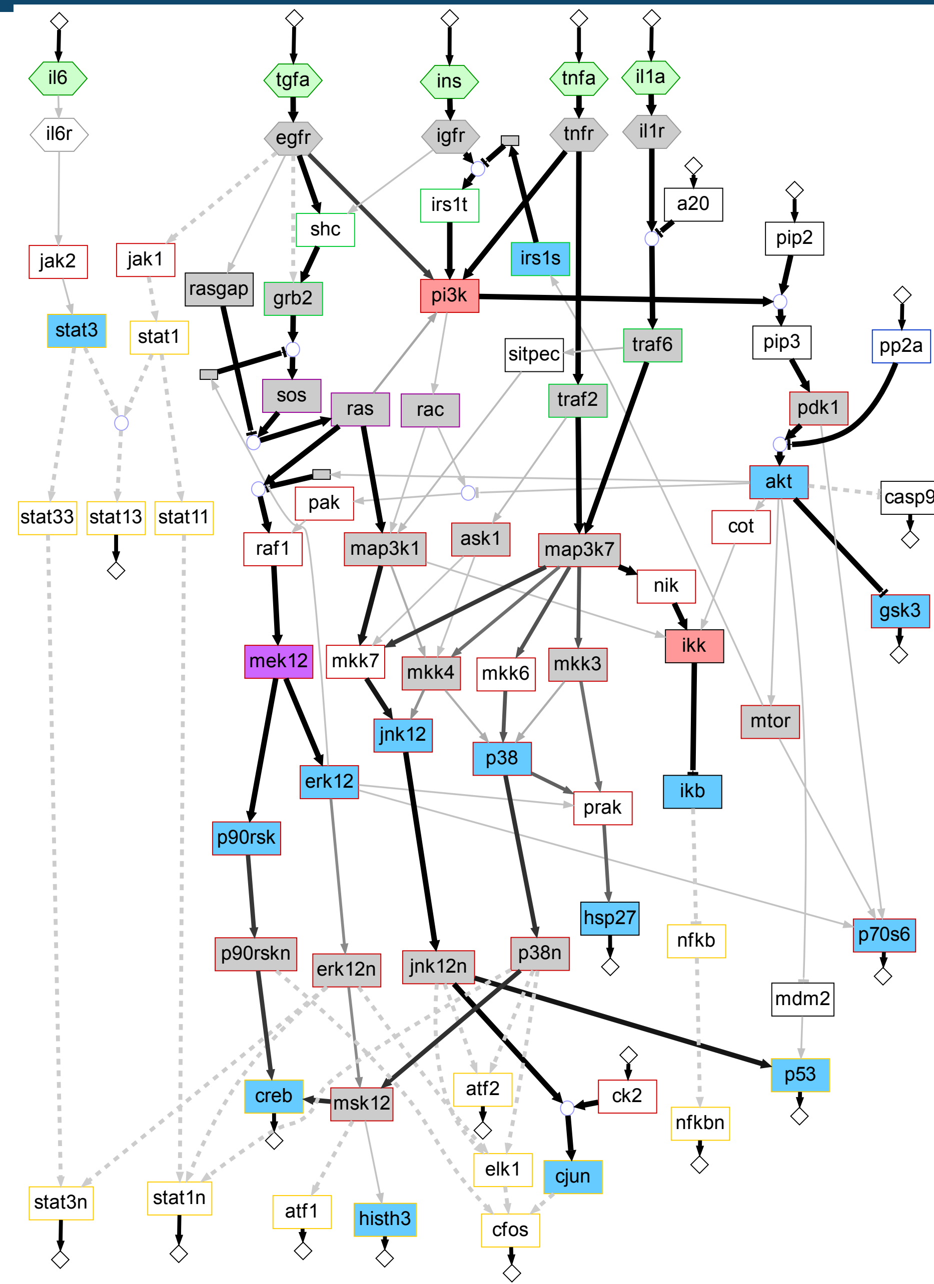
p90rsk
hsp27
nfkb
p70s6
p90rskn
erk12n
jnk12n
p38n
mdm2
creb
msk12
atf2
ck2
p53
nfkbn
elk1
cjun
stat3n
stat1n
atf1
histh3
cfos


Stimulus
Perturbation
Readout
Perturb&Read
Kept
Removed
No effect

Huh7



Stimulus

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Removed

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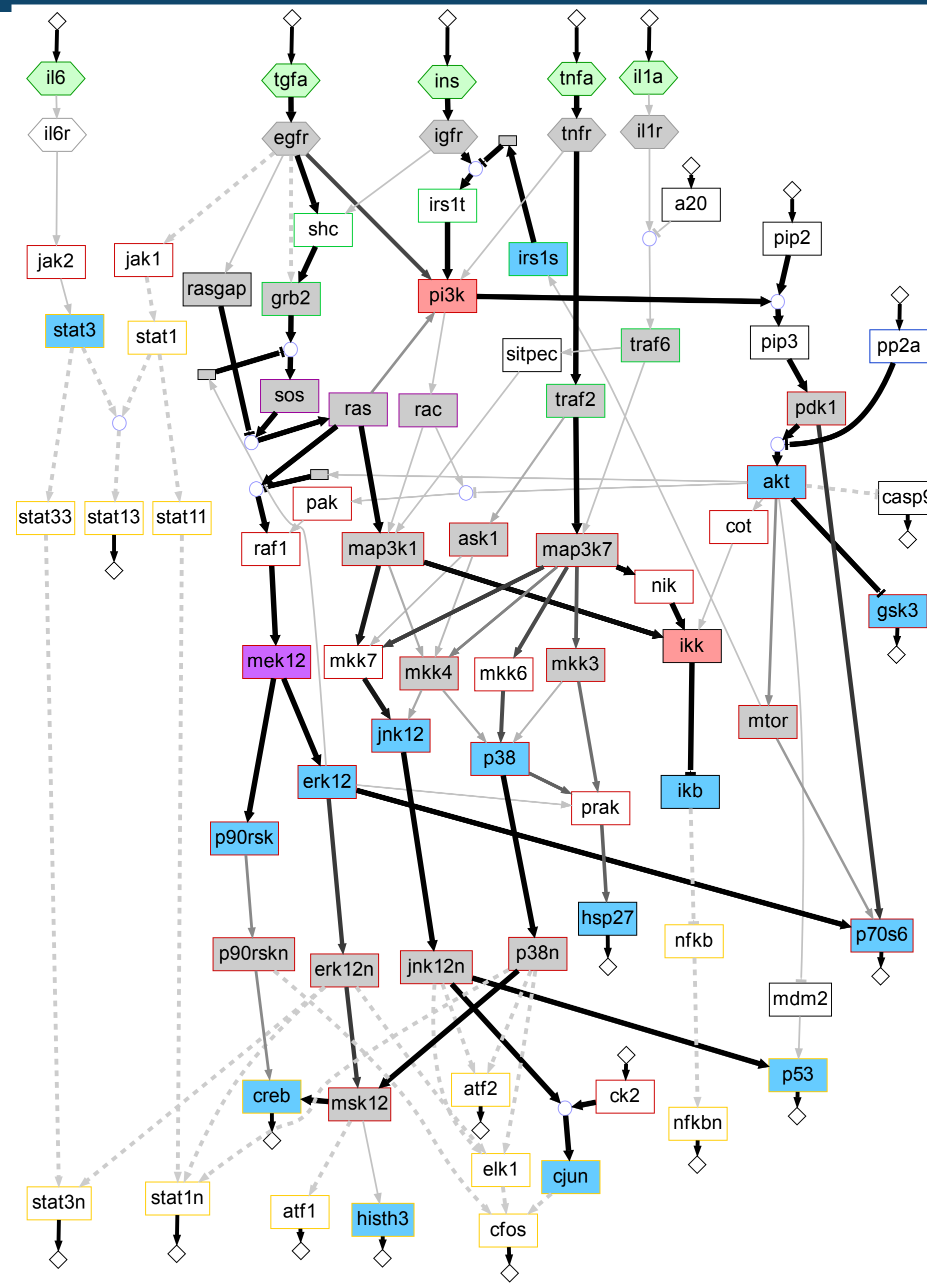
Focus



Stimulus

Perturbation

Readout

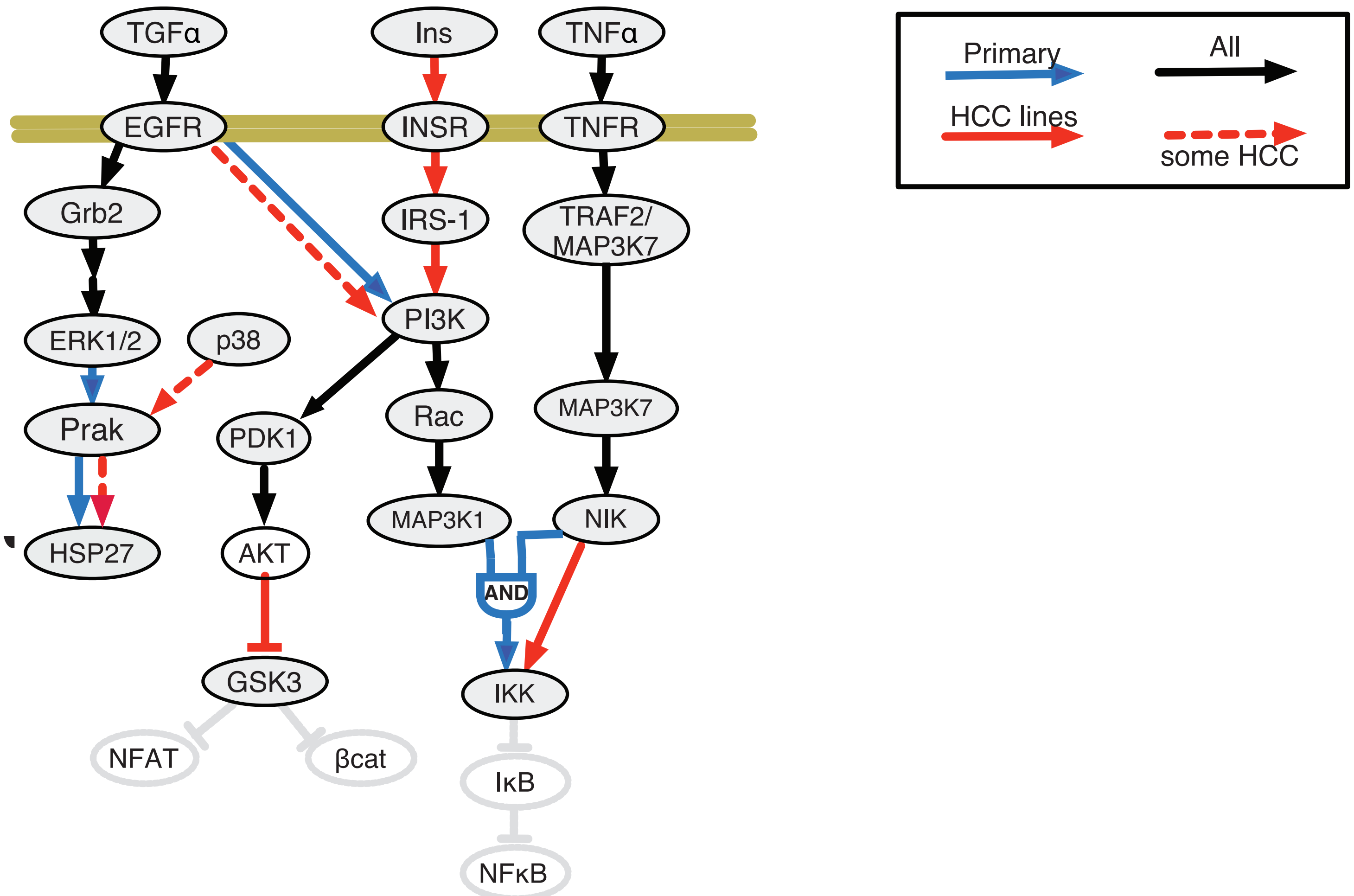
Perturb&Read

Kept

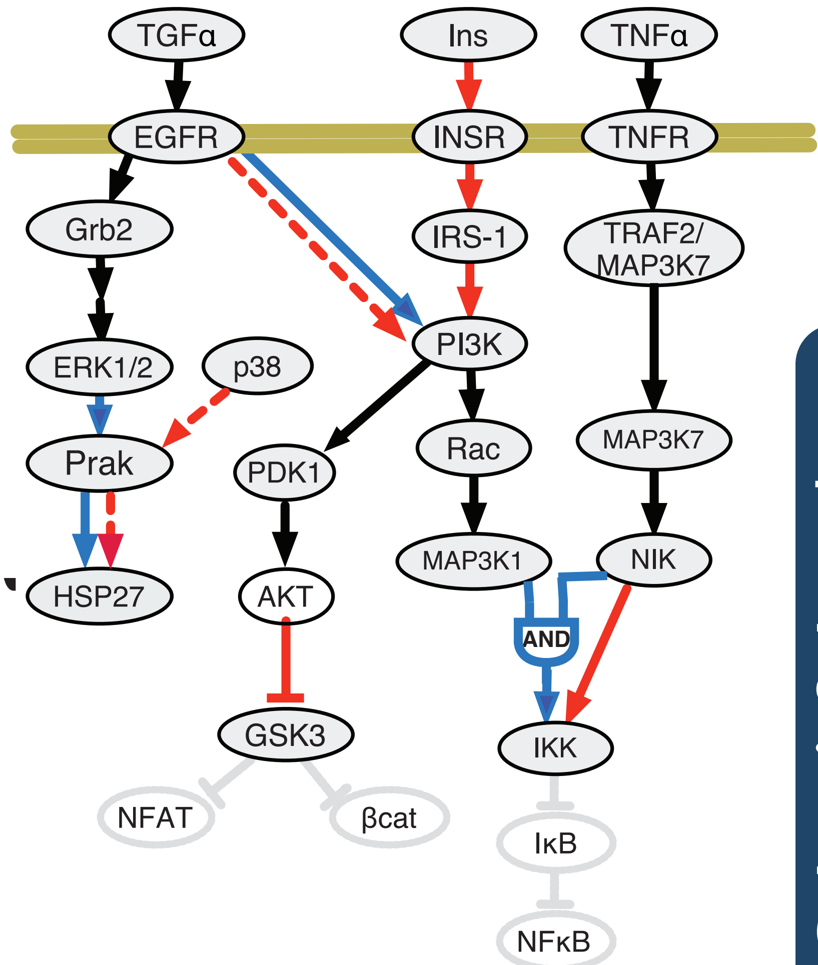
Removed

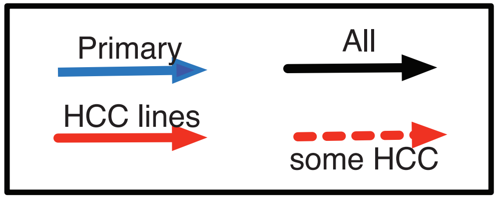
No effect

Logic models provide mechanistic insight in signal deregulation



Logic models provide mechanistic insight in signal deregulation





These models can:

- Identify functional differences between cell types (e.g. health vs disease) ➜ therapeutic targets

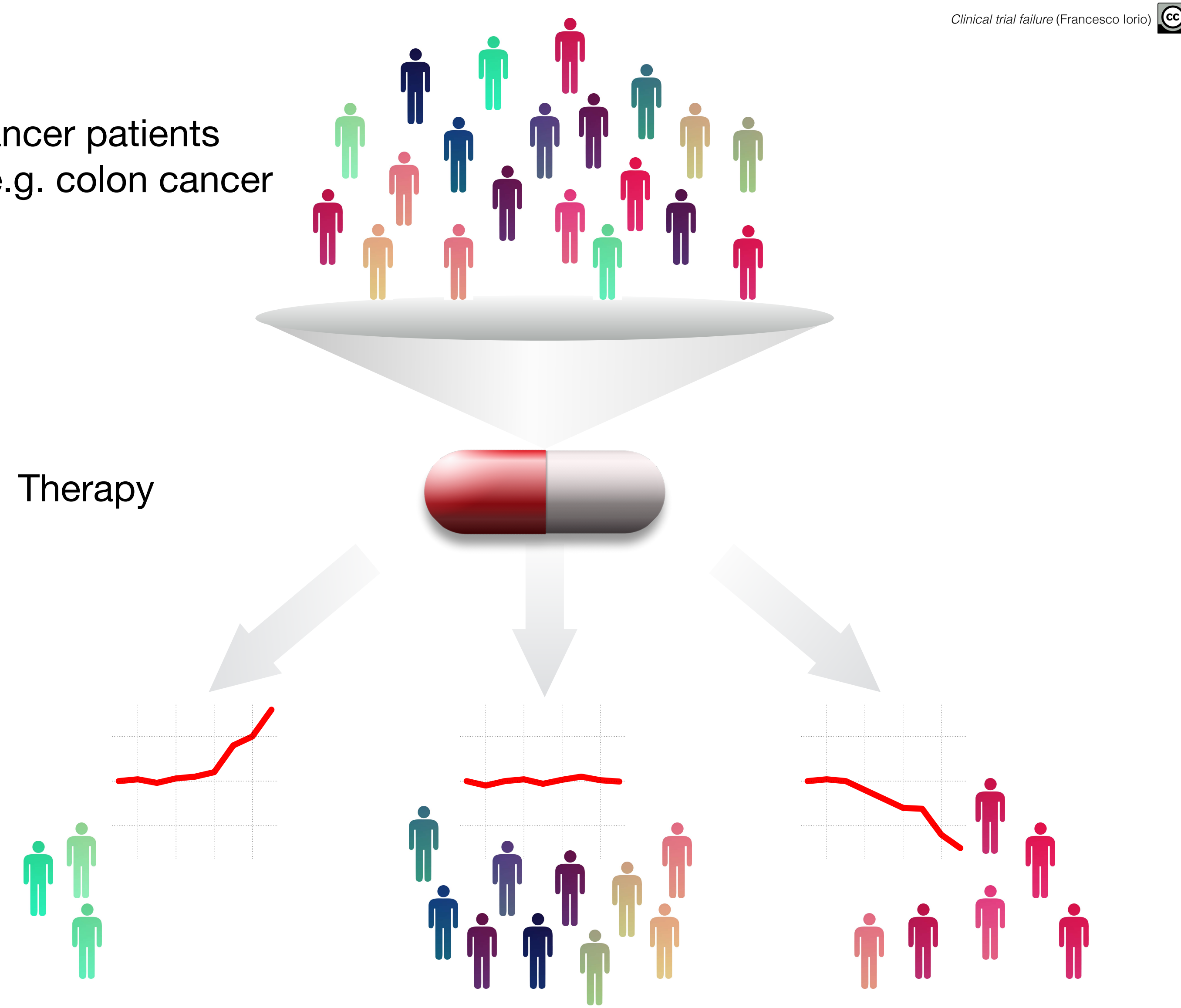
- Predict outcome of new perturbations (single or combination)

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

Can we use logic models to understand drug efficacy in cancer?

Cancer patients with e.g. colon cancer

Therapy

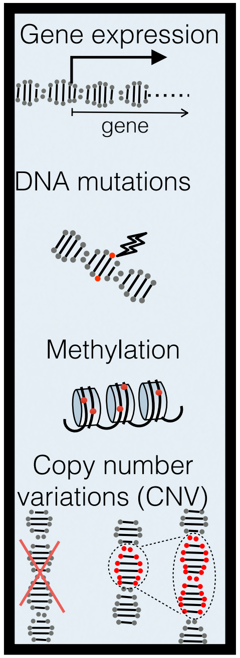


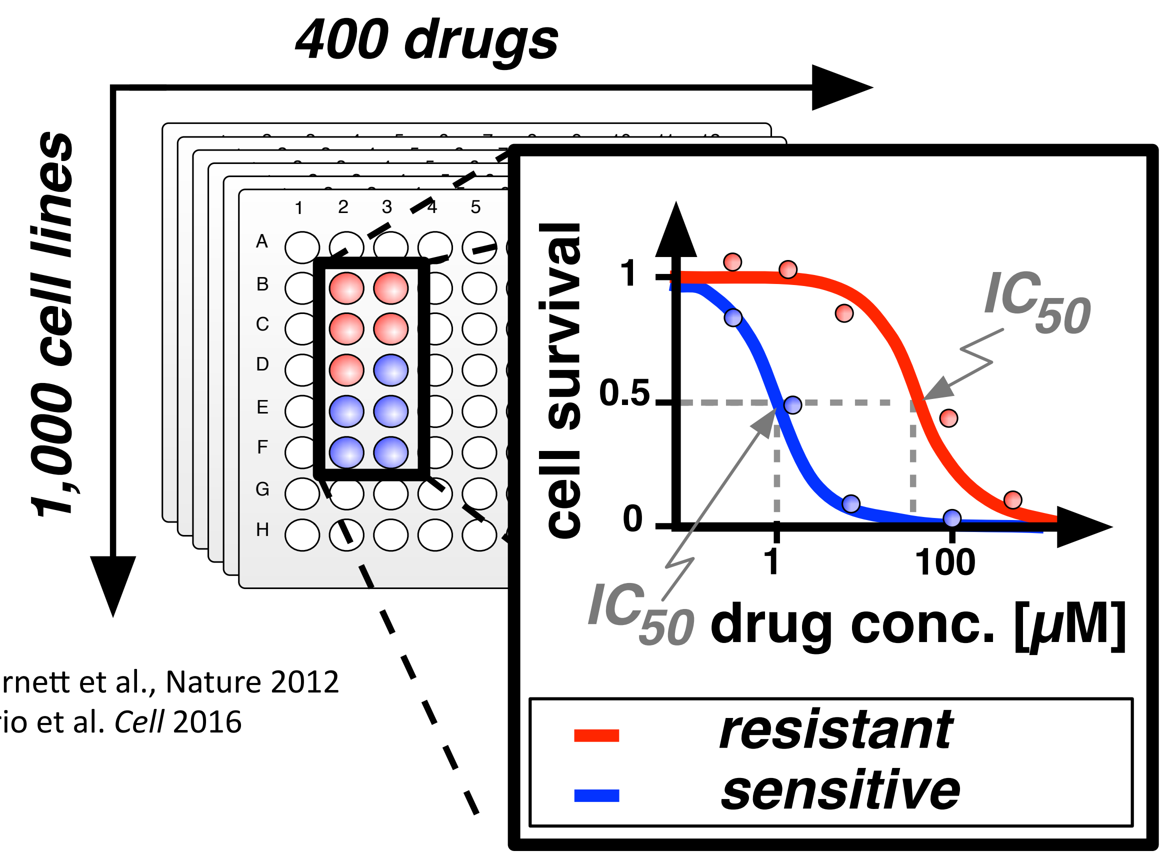
Therapeutic effect

No effect

Adverse effect

Can we use logic models to understand drug efficacy in cancer?





Garnett et al., Nature 2012
Iorio et al. *Cell* 2016

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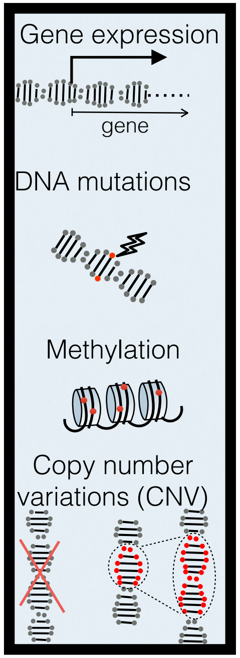

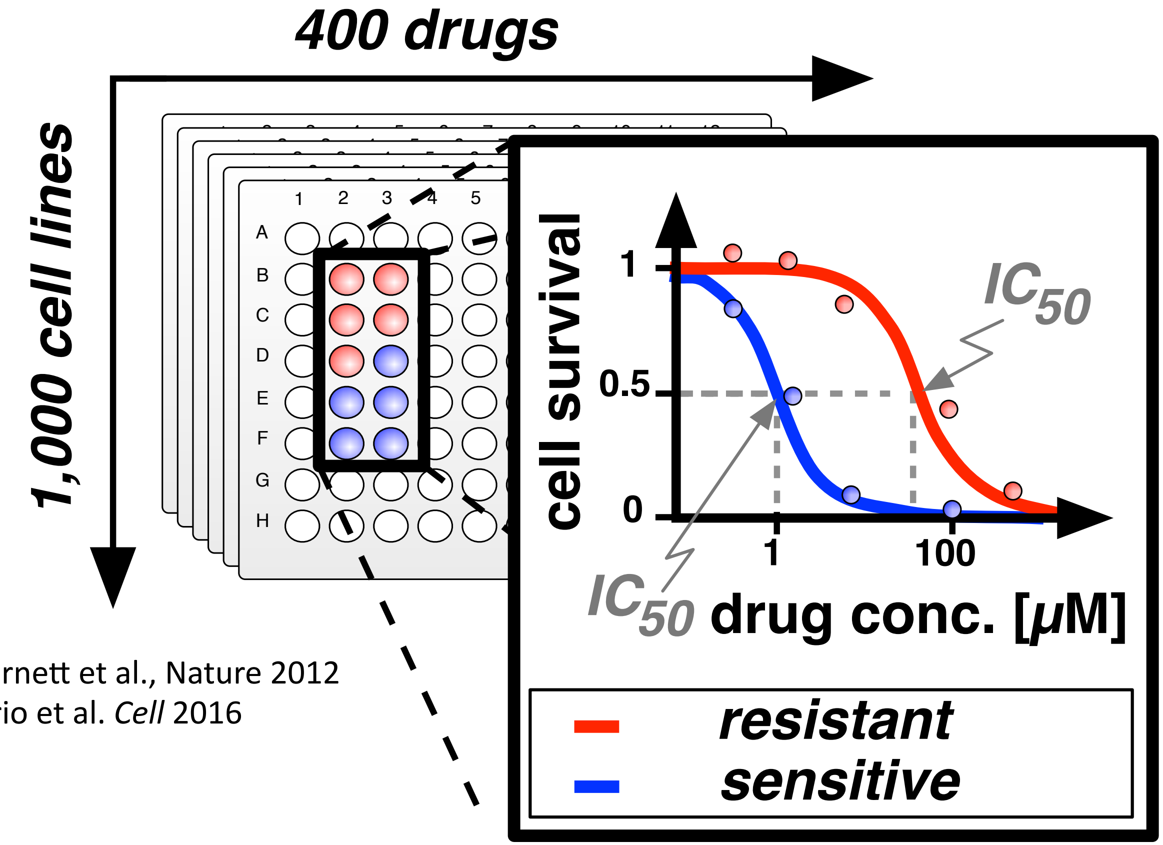

Garnett et al., Nature 2012
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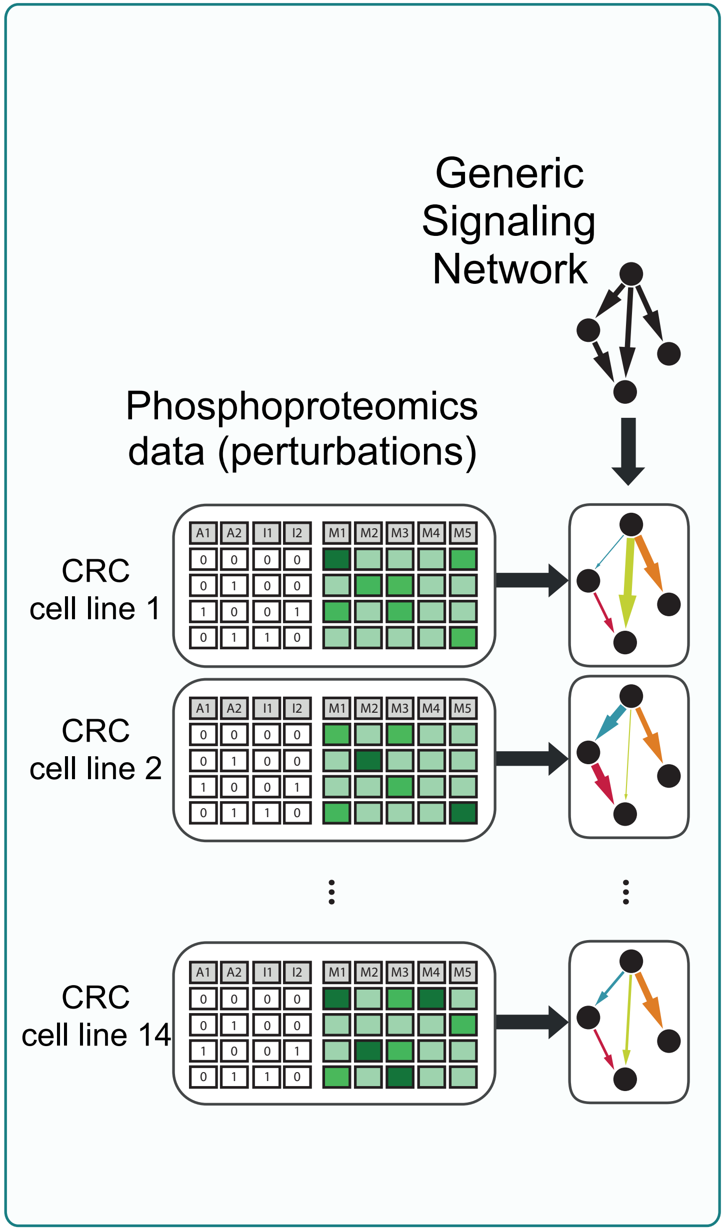
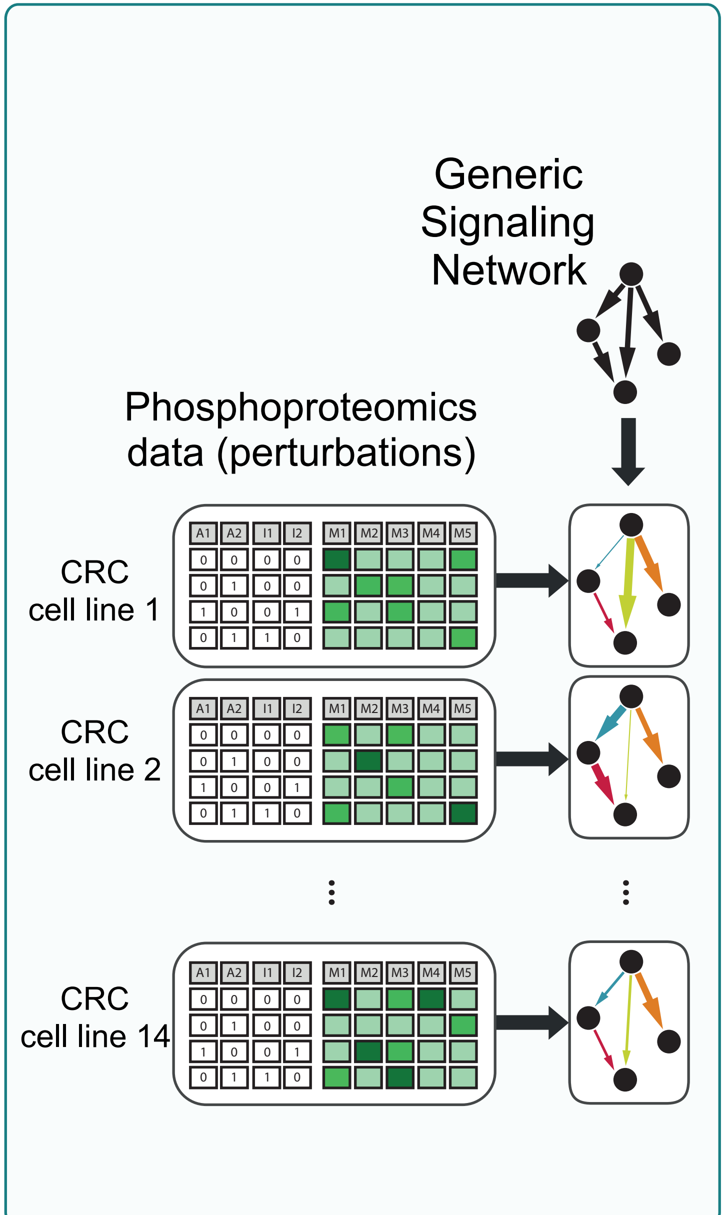
Looking for model-based biomarkers of drug sensitivity

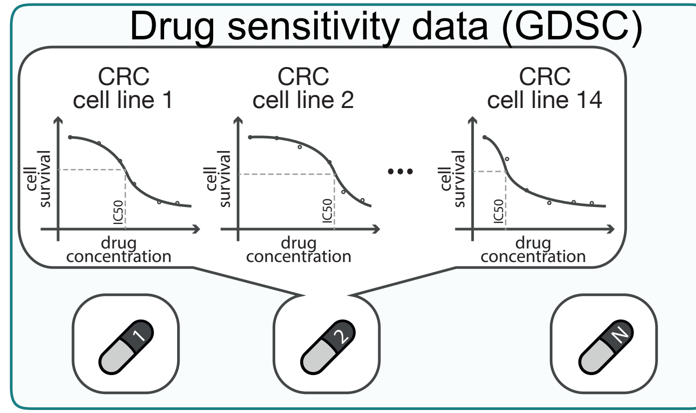


w. N. Bluethgen & M. Garnett

Eduati et al. *Cancer Res,* 2017

Looking for model-based biomarkers of drug sensitivity





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Eduati et al. *Cancer Res,* 2017

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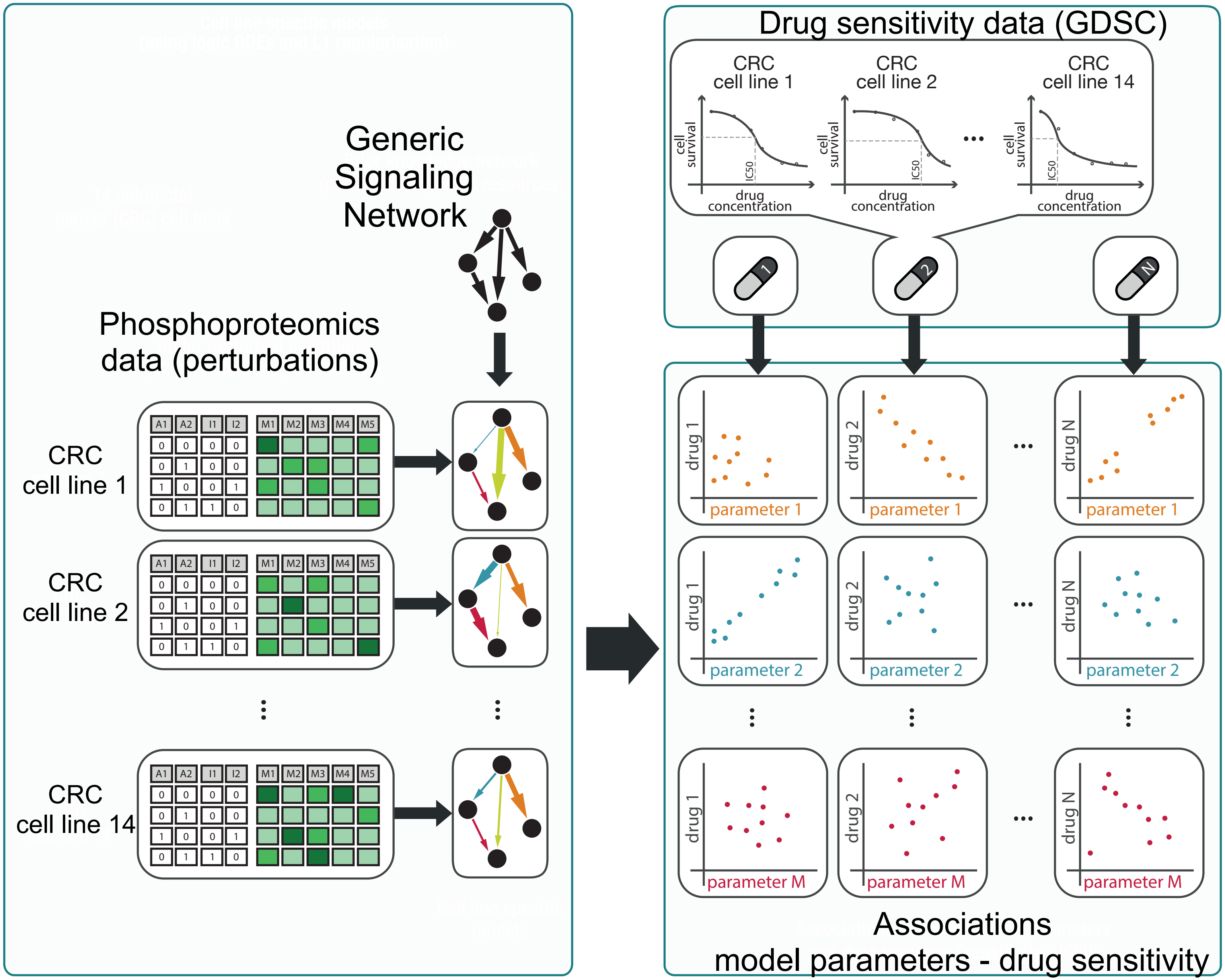


w. N. Bluethgen & M. Garnett

Eduati et al. *Cancer Res*, 2017

Case study: understanding drug resistance in colorectal cancer

14 colorectal cancer cell lines

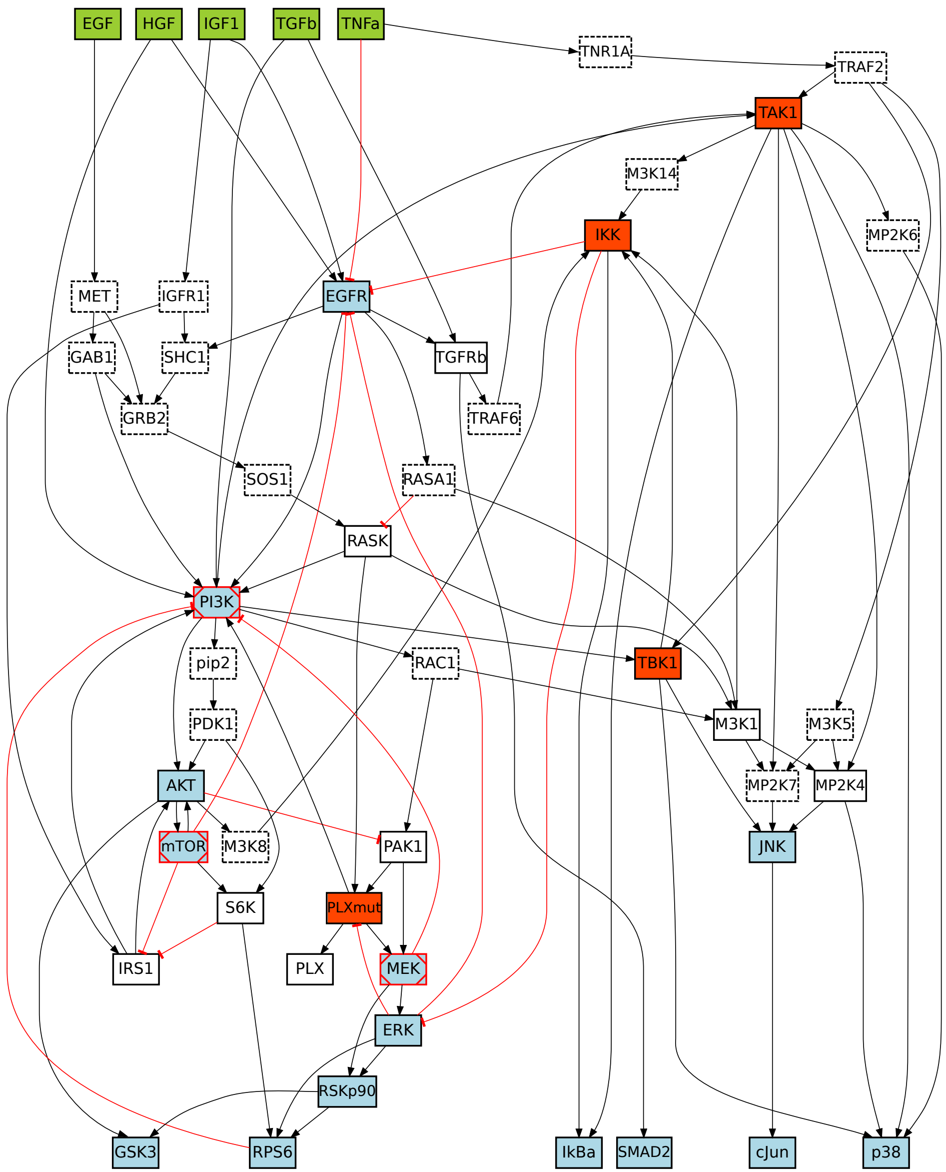
From GDSC (genomic & drug response data available)

Luminex phospho data:

- 14 measured phospho-proteins
- 7 targeted drugs + 4 ligands (42 conditions)

Prior knowledge network

- derived form literature (~ 50 references)



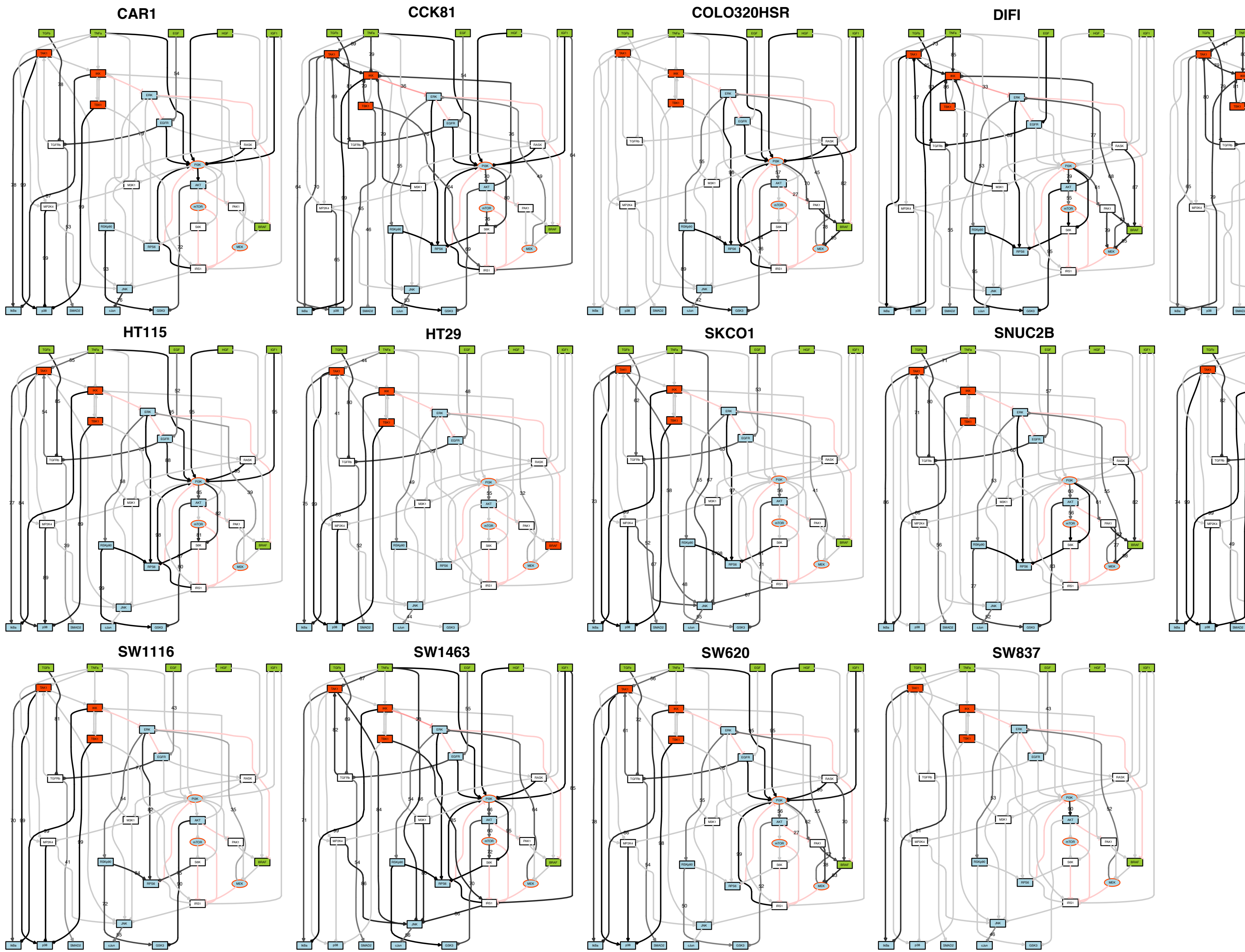
Federica Eduati

w. Nils Bluetghen (Charite) & Mathew Garnett (Sanger)

Eduati et al. submitted

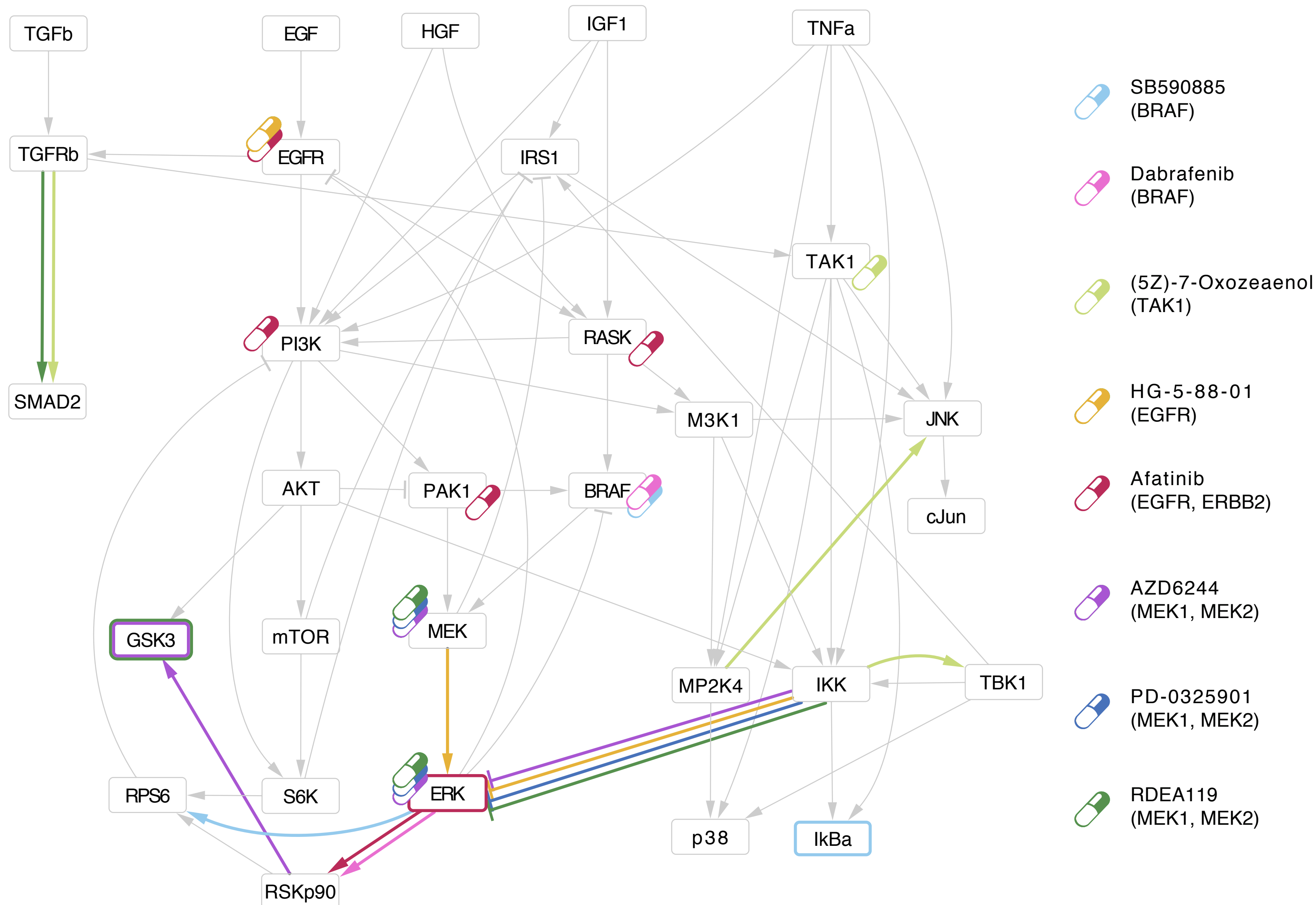
measured | inhibited | stimulated | measured & inhibited | compressed

CRC Cell line specific models



Eduati et al.
Cancer Res,
2017

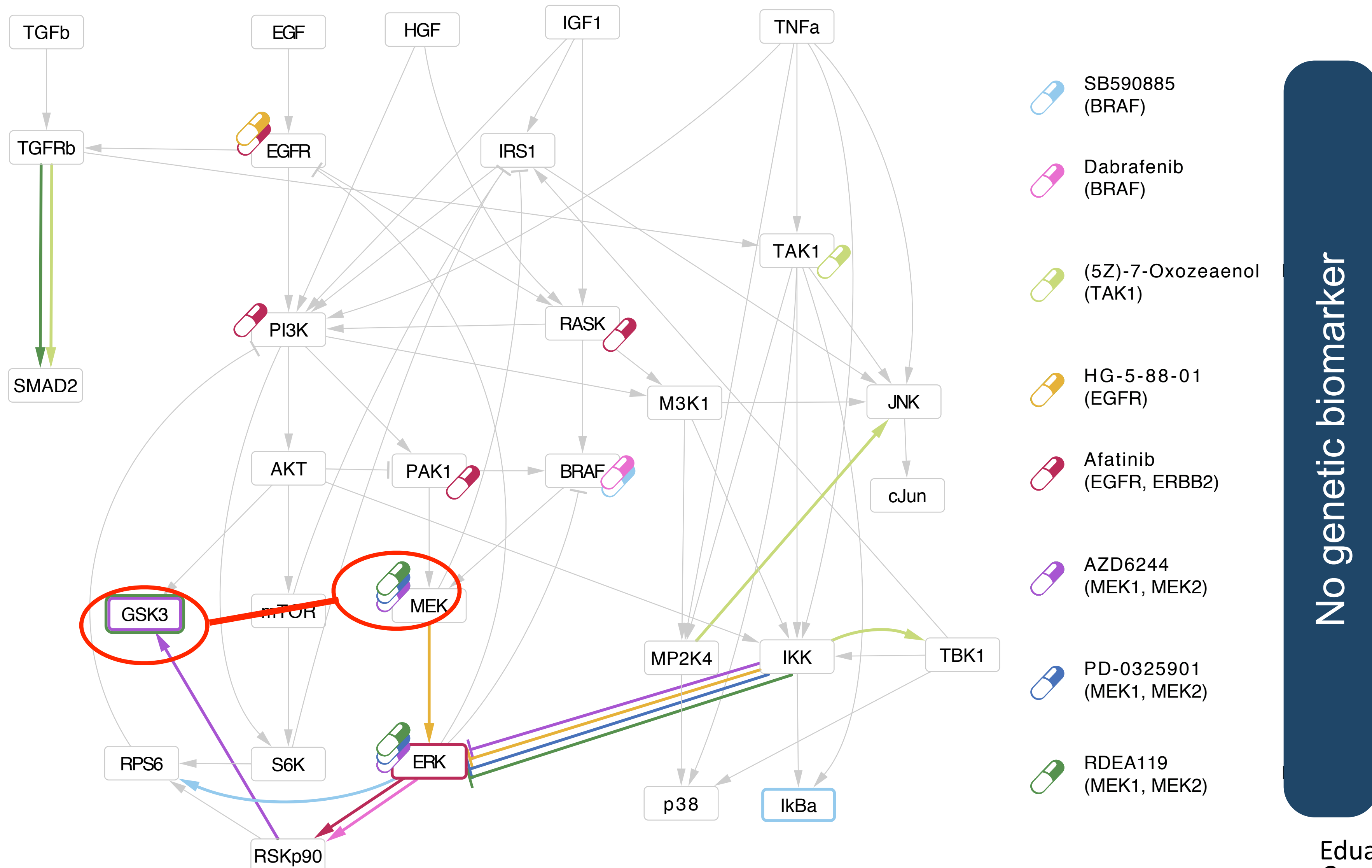
Model-based biomarkers of drug efficacy and resistance



No genetic biomarker

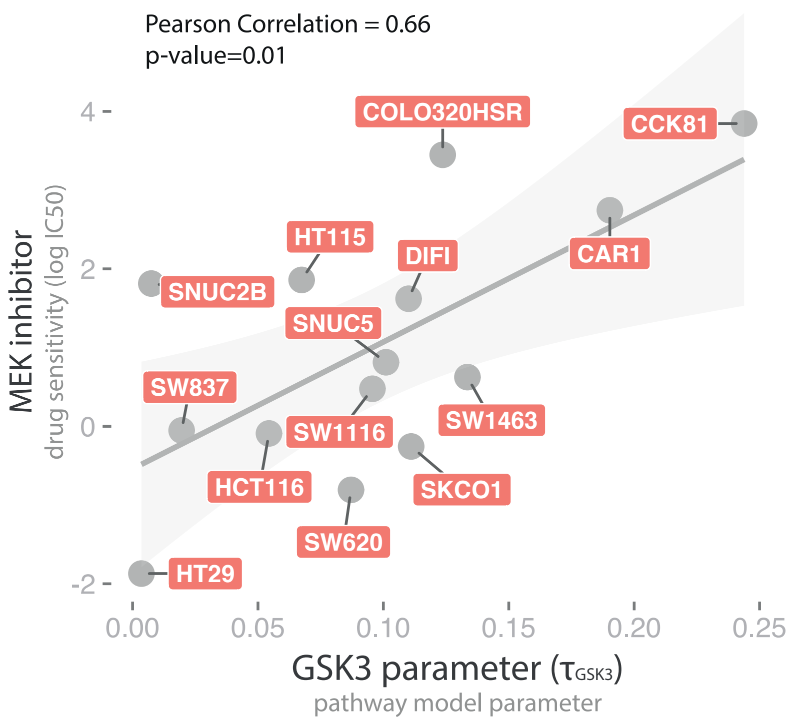
Eduati et al. *Cancer Res*, 2017

Model-based biomarkers of drug efficacy and resistance



Eduati et al. *Cancer Res*, 2017

Association between GSK3 functionality and MEK inhibitor efficacy suggests combination



Eduati et al. *Cancer Res,* 2017

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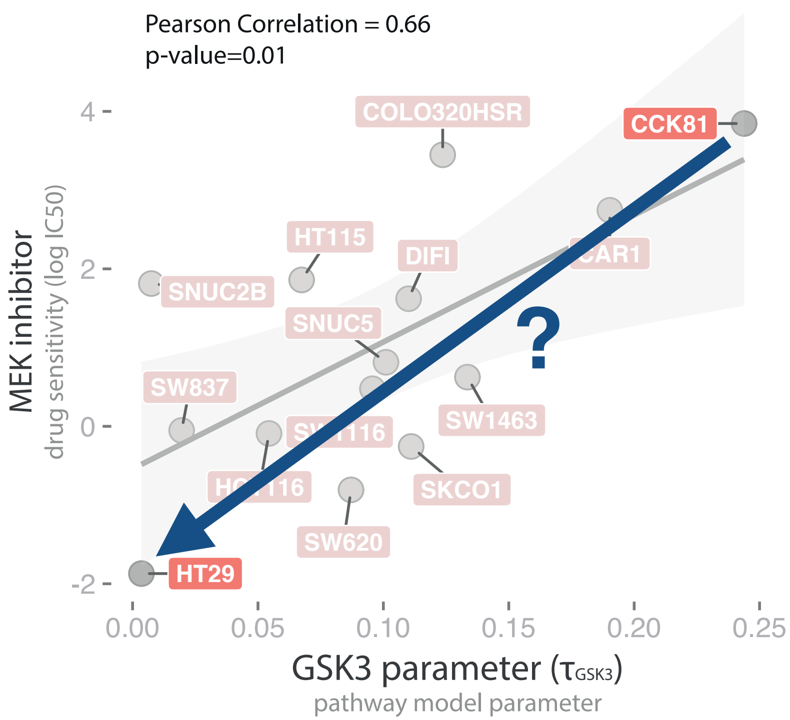

Eduati et al. *Cancer Res*, 2017

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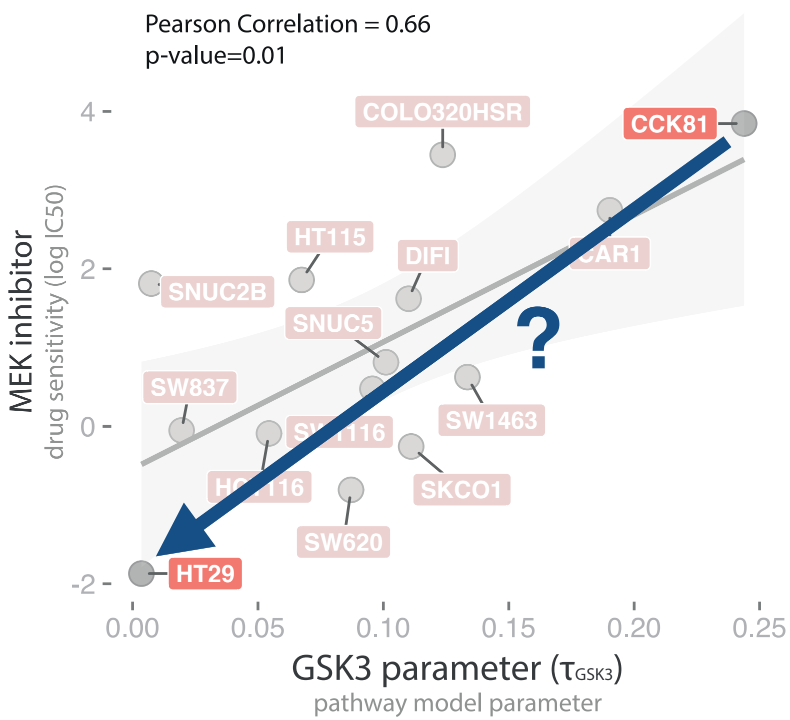
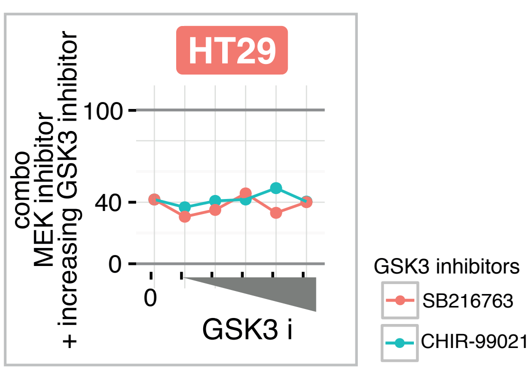
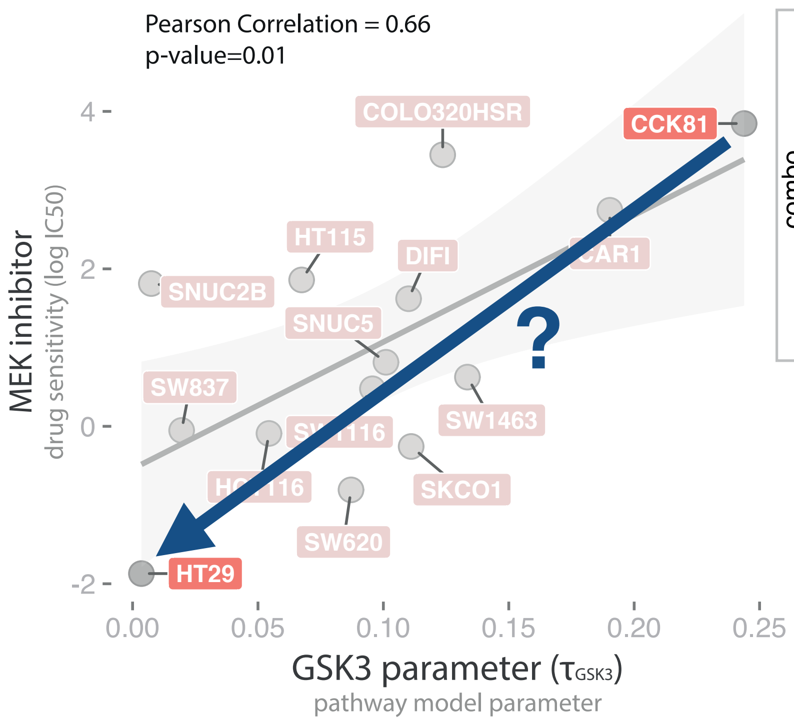


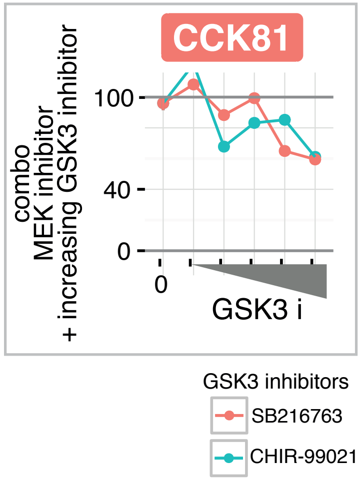


no improved sensitivity when GSK3 is not functional

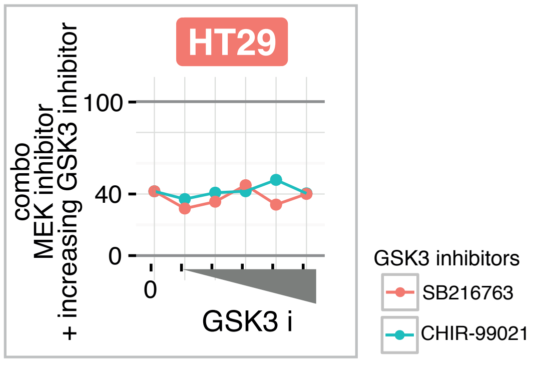
Eduati et al. *Cancer Res*, 2017

Association between GSK3 functionality and MEK inhibitor efficacy suggests combination





synergistic combo when GSK3 is functional



no improved sensitivity when GSK3 is not functional

Eduati et al. *Cancer Res*, 2017

How to...

- 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

How to...

- Set up experiments to extract most information
- Process data efficiently
- Choose type of mathematical model (given data, question, etc)
- Train models to experimental data
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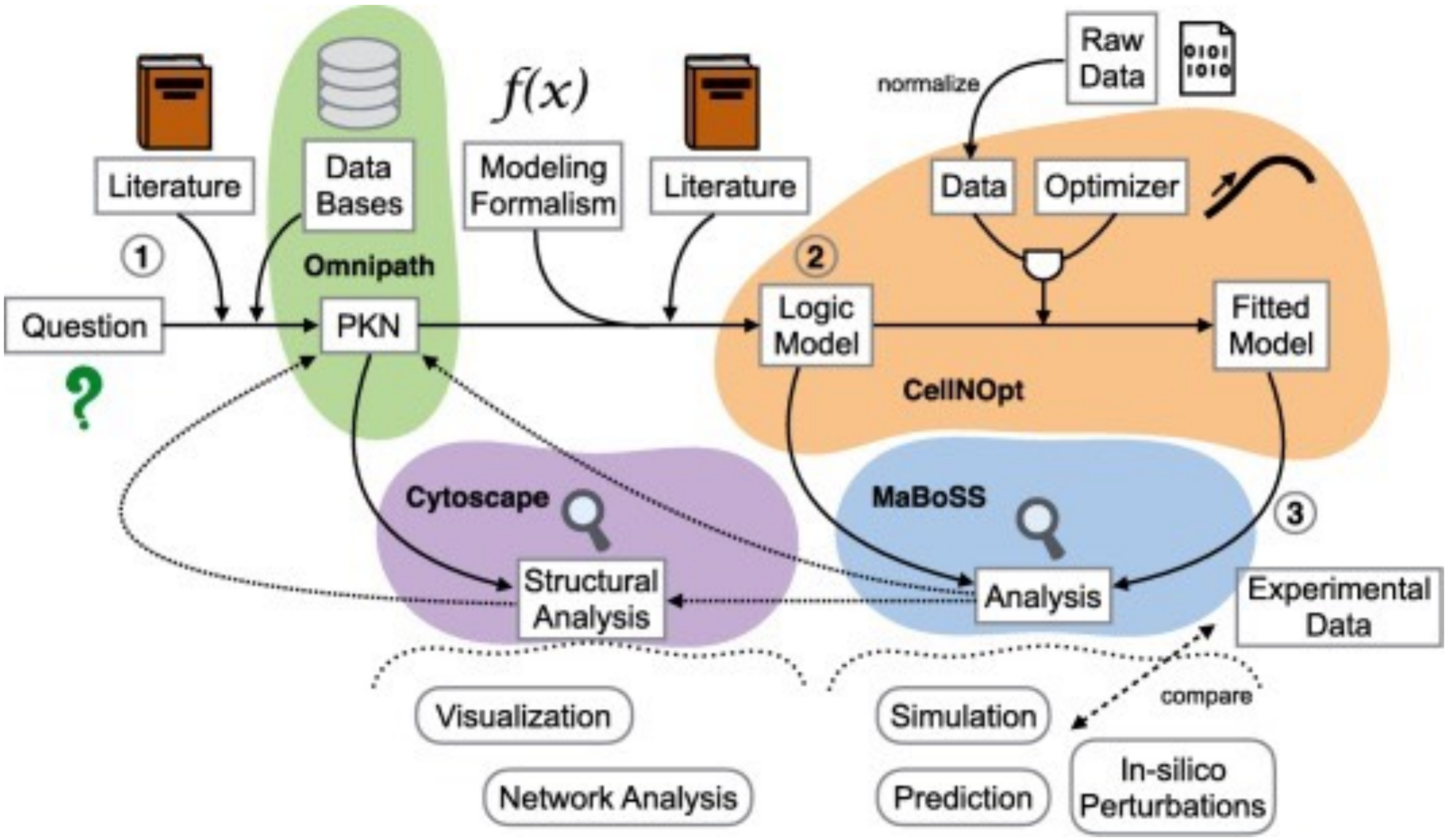
Used
logic modelling & applications to signalling, but general principles hold for other modelling approaches & applications

A detailed tutorial

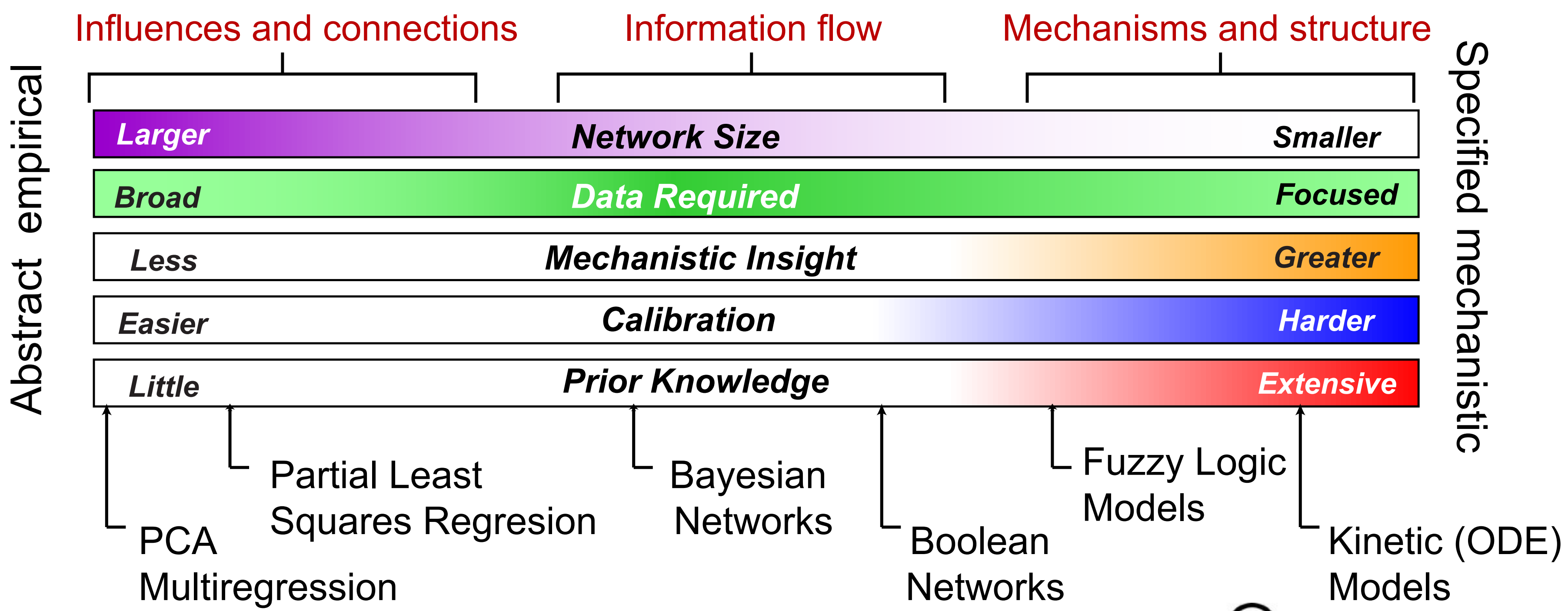
- Application of OmniPath, CellNOpt, MaBoSS and Cytoscape to a prostate cancer example



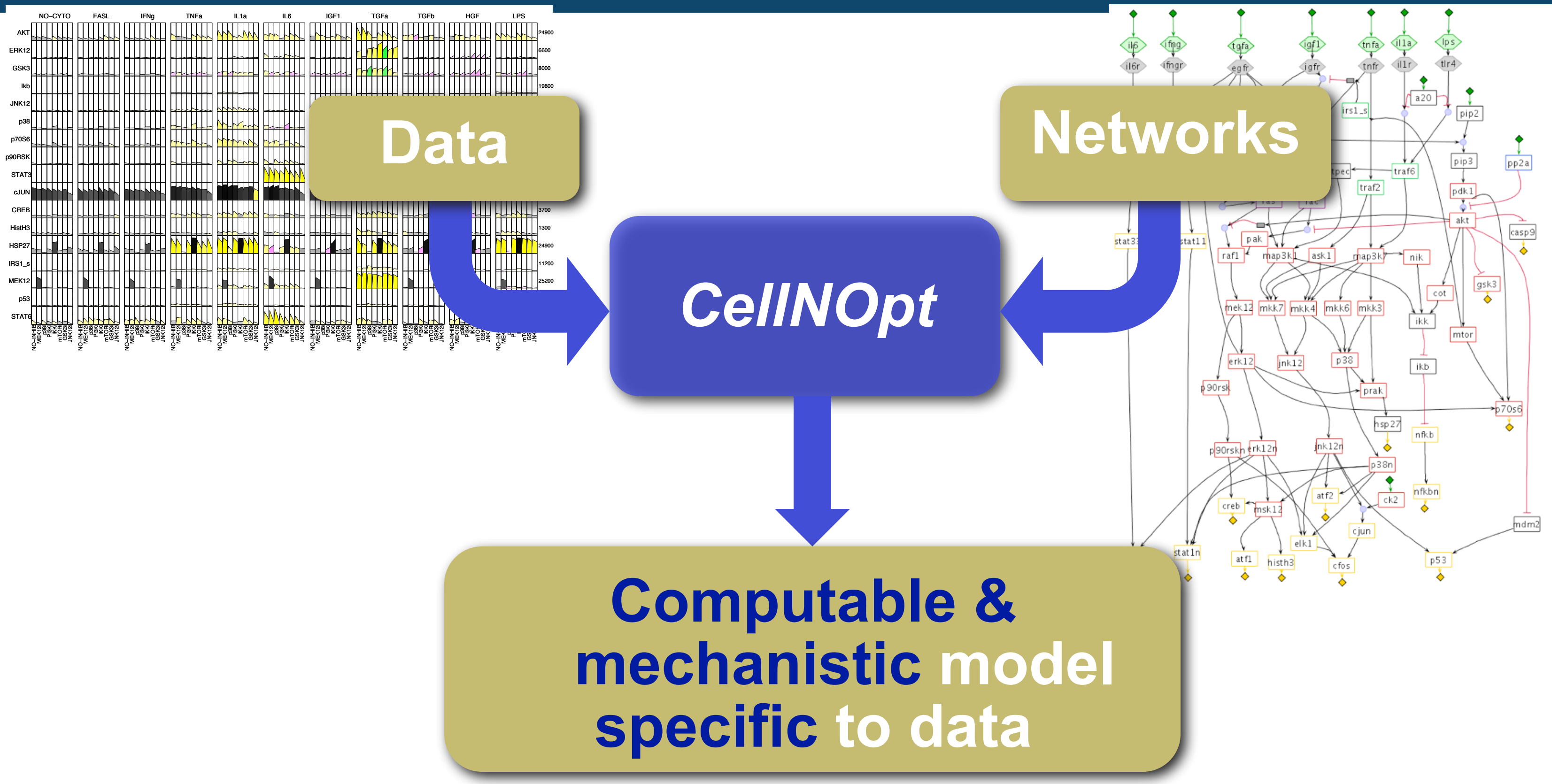
Traynard et al. *CPT:PSP* 2017

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

Acknowledgements

www.saezlab.org sysbiomed
www.github.com/saezlab

Current members:

Denes Turei Angeliki Kalamara
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Vignesh Subramanian
Mi Yang Attila Gabor
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Christian Holland Enio Gjerga
Panuwat Trairatphisan Anika Liu

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Ruedi Aebersold Uwe Sauer (ETH Zurich)
Laurence Calzone (Institut Curie)
Bernd Bodenmiller (U Zurich)
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Rafael Kramann (Uniklinik Aachen)
Christian Frezza (Cambridge)
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Oliver Stegle Pedro Beltrao (EMBL-EBI)
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CoLoMoTo consortium
Tamas Korcsmaros (EI)
Nils Bluethgen (Charite)
Julio Banga (CSIC)
Anne Claude Gavin (EMBL)
Jesper Olsen (Copenhagen)

MARIE CURIE ACTIONS
imi
SEVENTH FRAMEWORK PROGRAMME
Open Targets
Sys4MS
SyMBioSys
transQST

Acknowledgements

Postdoc/PhD positions available

www.saezlab.org sysbiomed
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