CellNOpt:
modelling prior knowledge networks trained to experimental data

Julio Saez-Rodriguez

European Bioinformatics Institute

EMBL-EBI

Hinxton (Cambridge) UK

www.ebi.ac.uk/saezrodriguez

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

- **CellNOpt**: a flexible pipeline to model protein signalling networks
- (1) Converts protein signalling network into logic model
  - (Unless known) create all possible logic gates (AND/OR) compatible with the network
- (2) Find the combination of logic gates (i.e. the model) that best
  - Balance fit to data with model size
    describes the experimental data

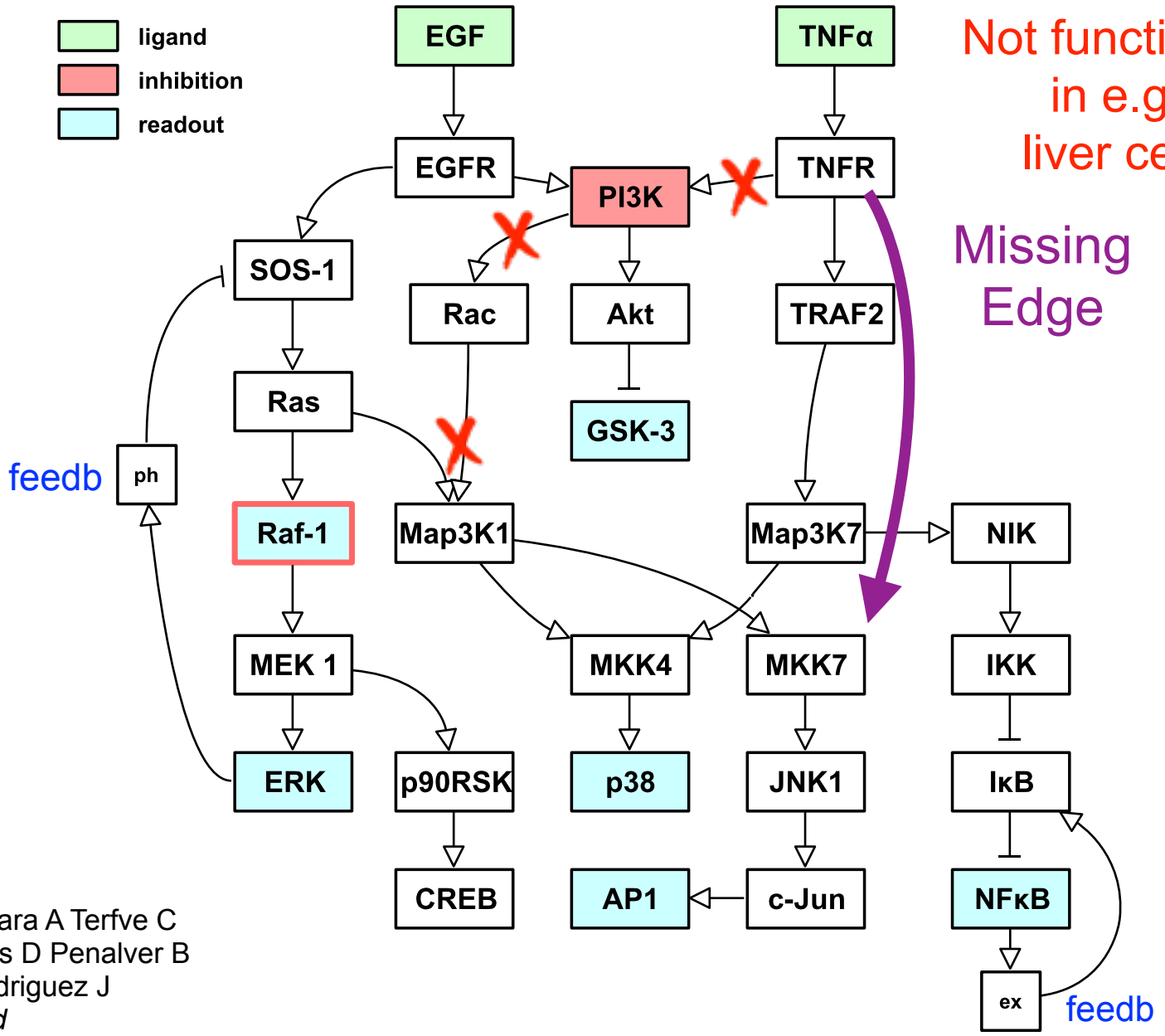
$$\theta = \theta_f + \alpha \cdot \theta_S$$

Bioconductor & Matlab,
available at www.ebi.ac.uk/saezrodriguez/software.html

Morris MK, Melas I, Saez-Rodriguez J, *Methods Mol. Biol, in press*

Saez-Rodriguez J, Alexopoulos LG, Epperlein J, Samaga R, Lauffenburger DA, Klamt S, Sorger PK *Mol Sys Bio* 5:331,2009

A Toy model



Not functional in e.g. liver cell

Missing Edge

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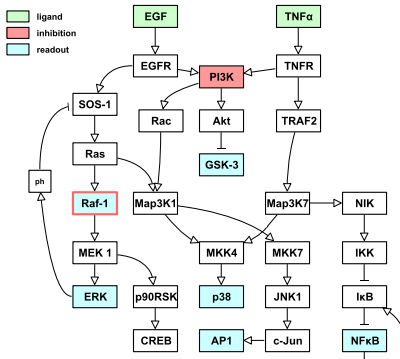
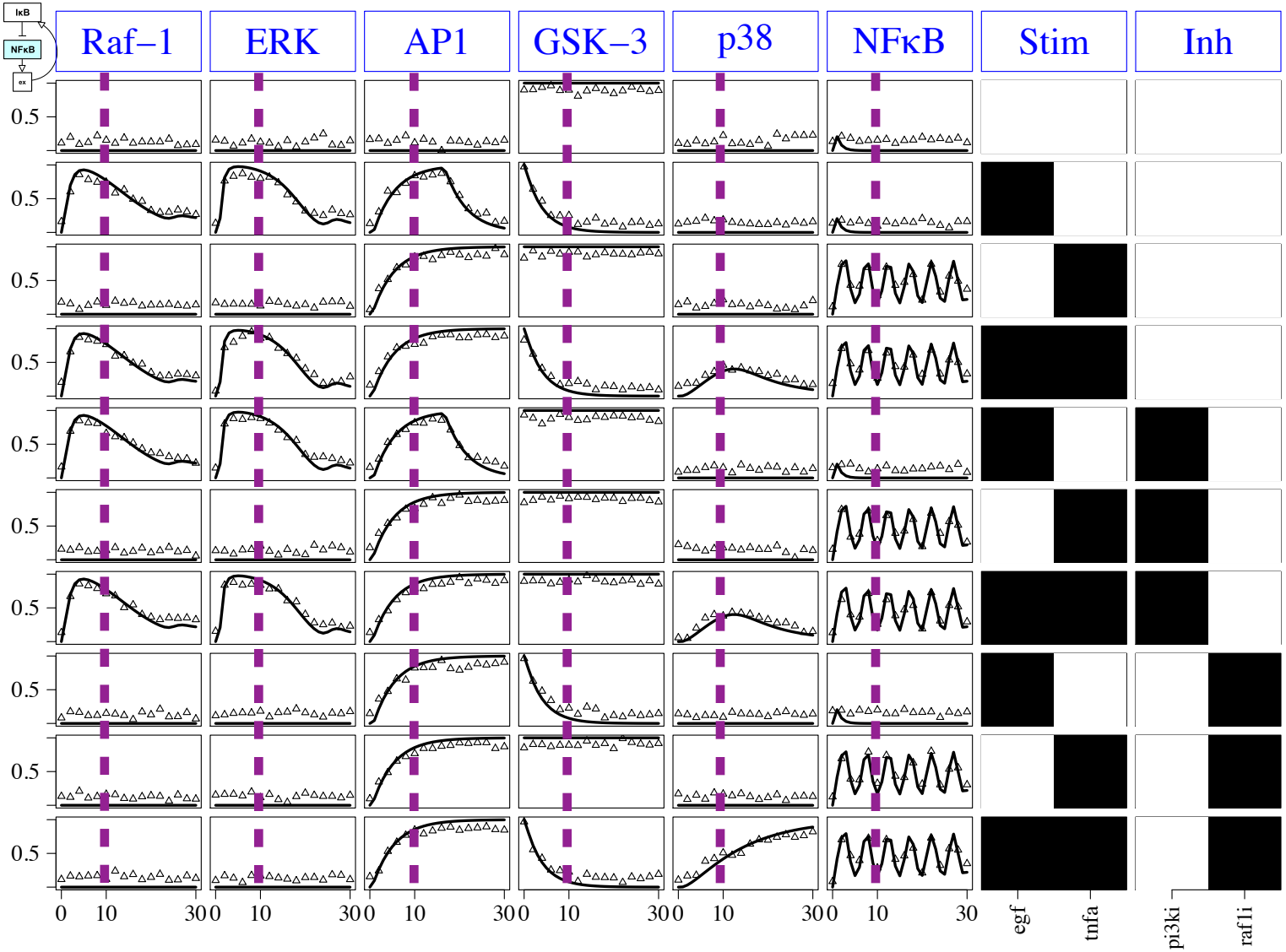
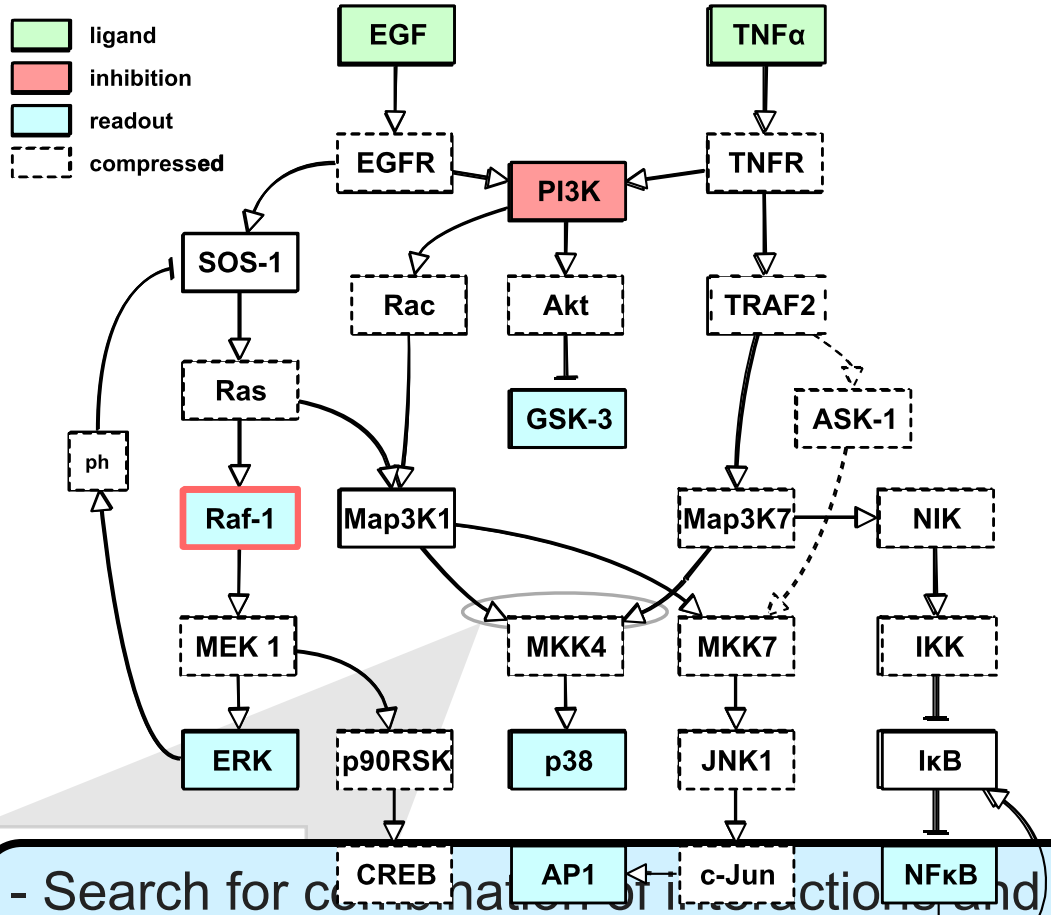
The ‘real’ data



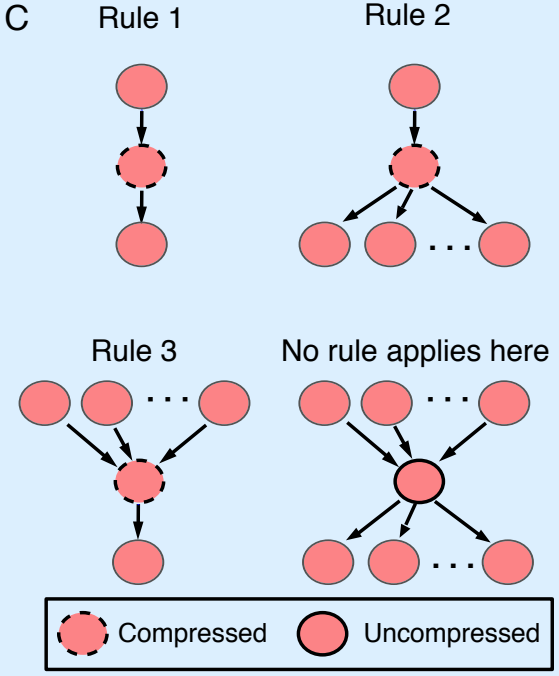
How to pick right time to measure?



Model preprocessing: compression and expansion of gates



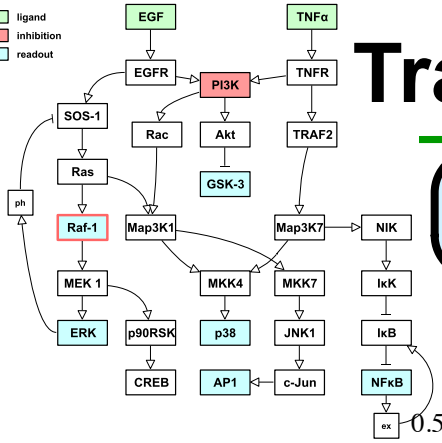
Model compression



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

- Search for combination of interactions and gates that best describe the data using a pseudo-state simulation (signal propagation);
- Search is an optimization problem that ca be solved
  (1) Enumeration (2) Heuristic (e.g. genetic algorithm)
  (3) Integer Linear Programming (Mitsos et al . Plos Comp Bio 2009)

Training to data recovers structure



Identifies active/non-active links (except feedbacks)

Can not explain data due to missing links

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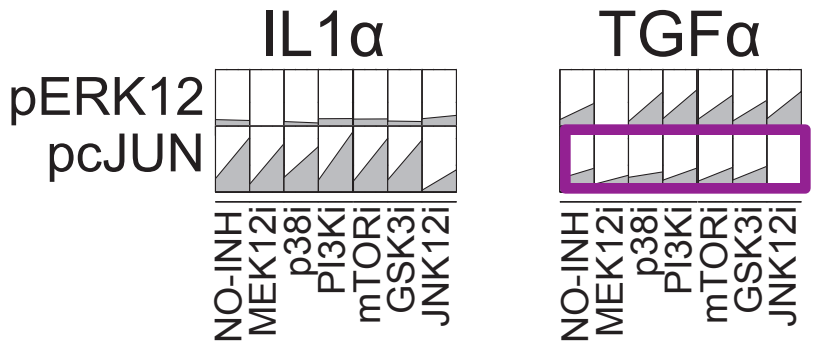
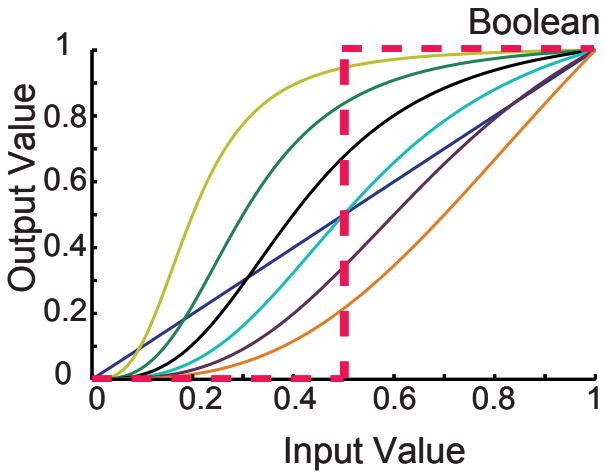
Constrained Fuzzy Logic can handle quantitative differences

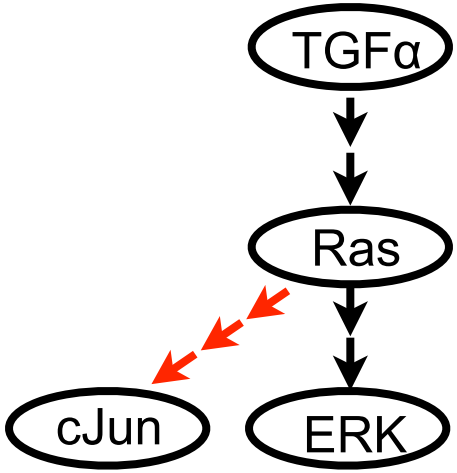
- Boolean modeling can **not** describe **quantitative** aspects (e.g. intermediate activation)



- Fuzzy logic can model quantitative signaling data (Aldridge et al. *Plos Comp. Bio.* 2009)

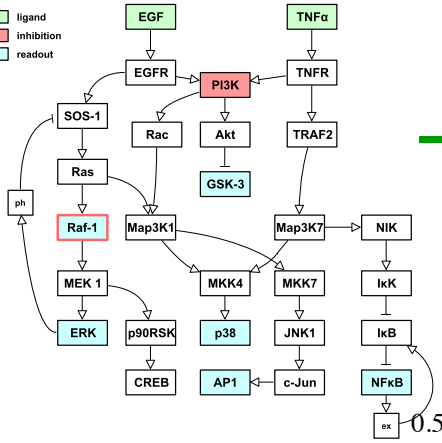


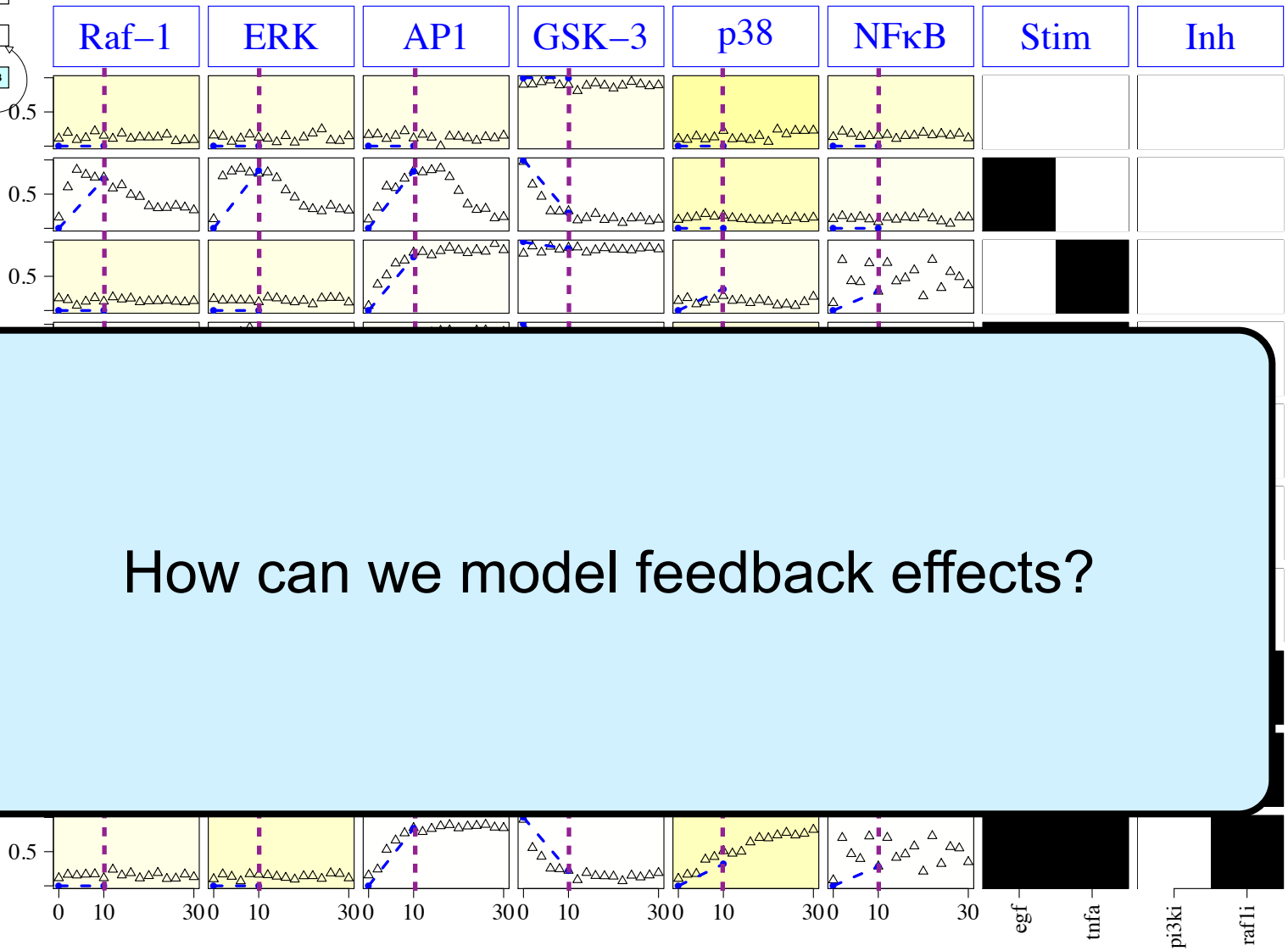
- Development of **Constrained Fuzzy Logic** & implementation within *CellNOpt*



Morris MK, Saez-Rodriguez J, Clarke D, Sorger PK, Lauffenburger DA, PloS Comp Bio 2011.

fit of fuzzy toy model





How can we model feedback effects?

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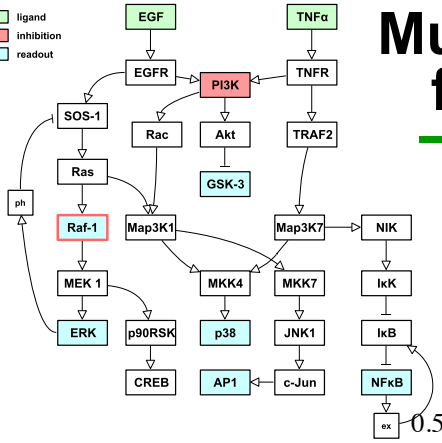
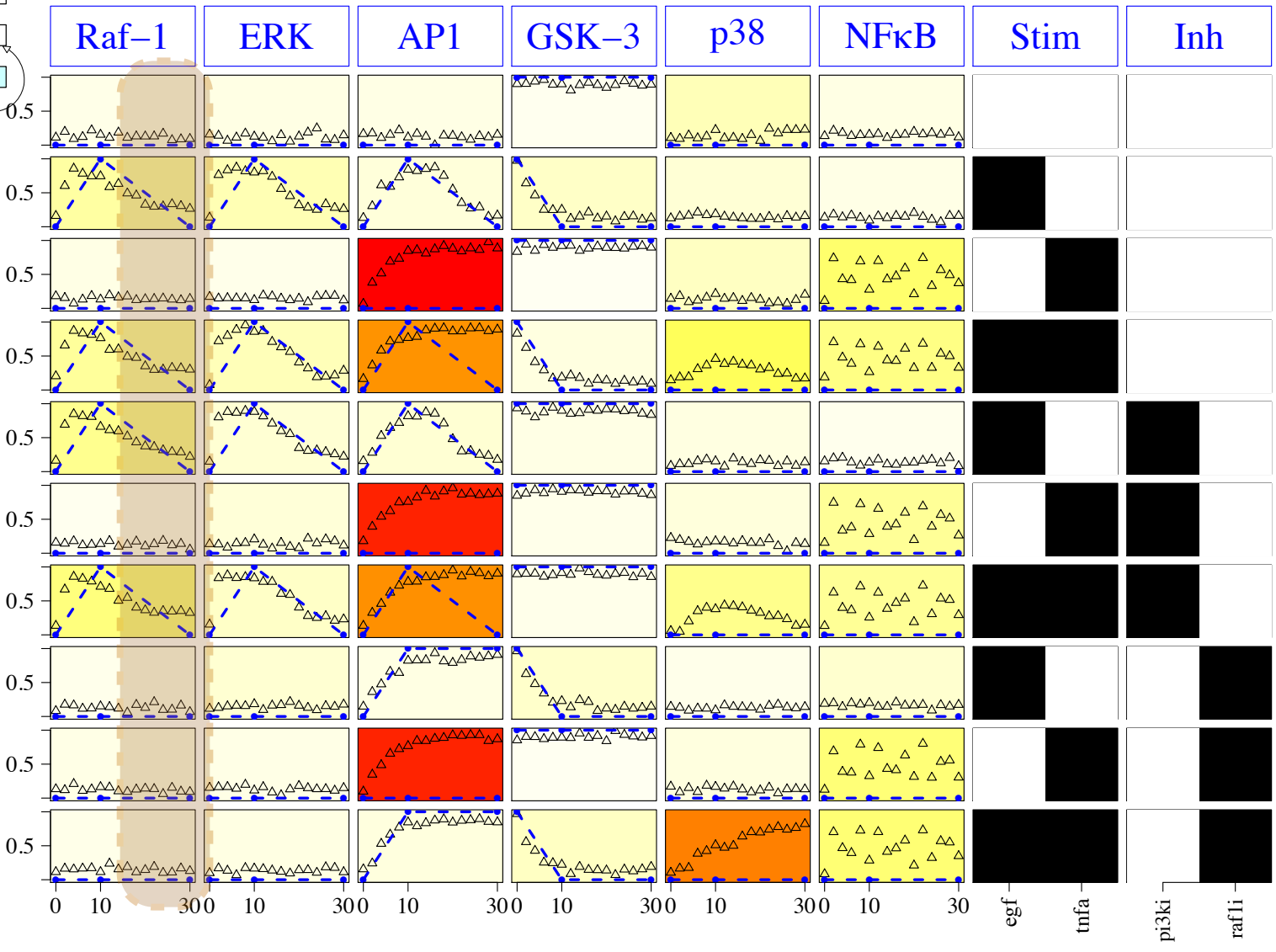
Multiple pseudo-steady-state simulations capture feedback effects that lead to transient signals





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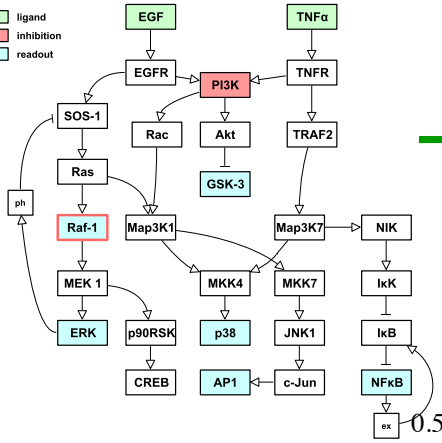
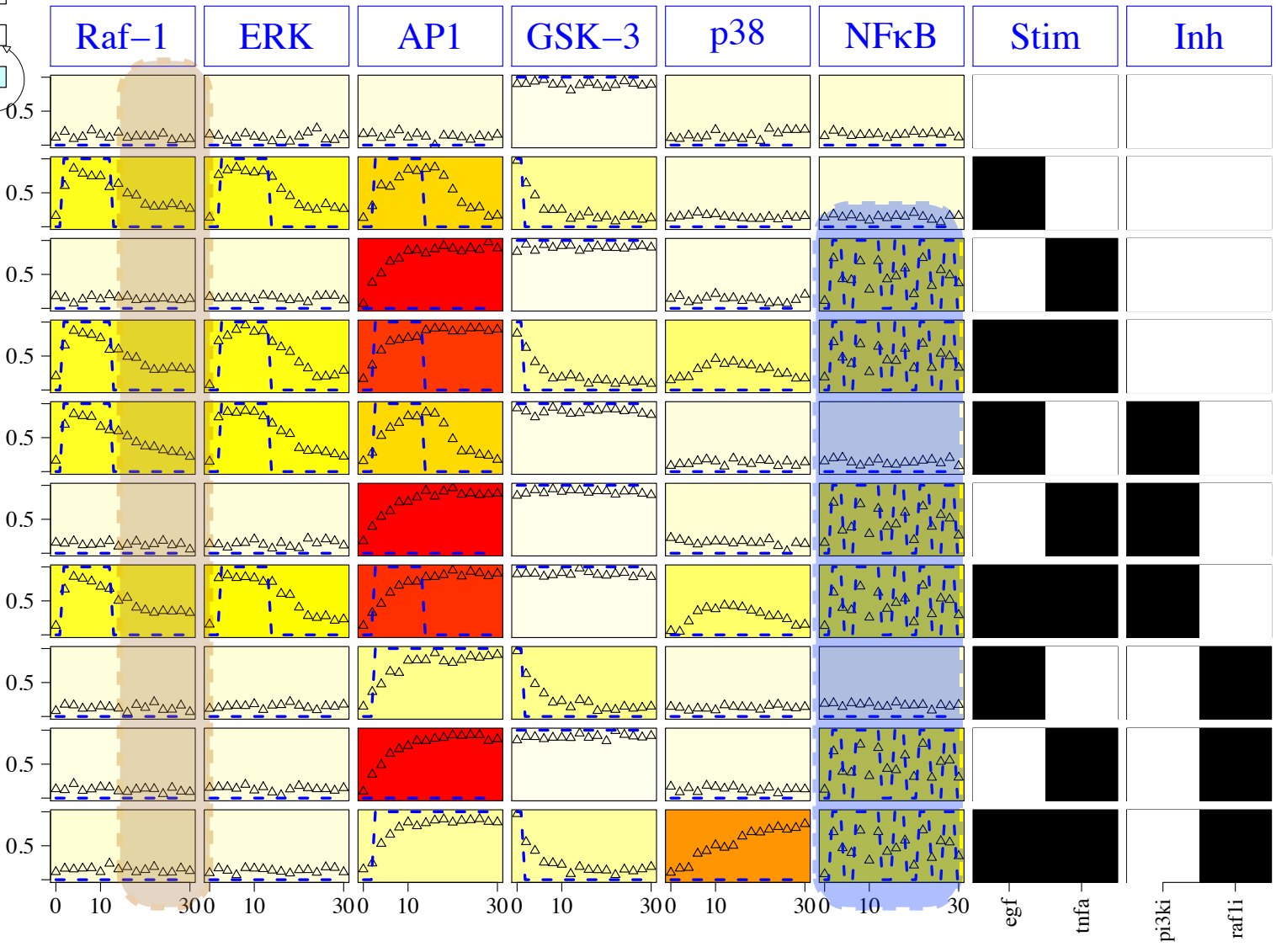
Synchronous simulation captures oscillatory behaviour





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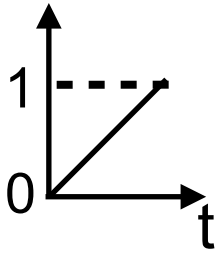
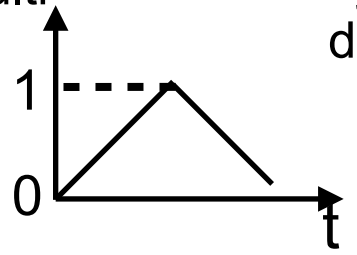
From Boolean to continuous and dynamic models within *CellNOpt*

Boolean (binary)
logic steady state

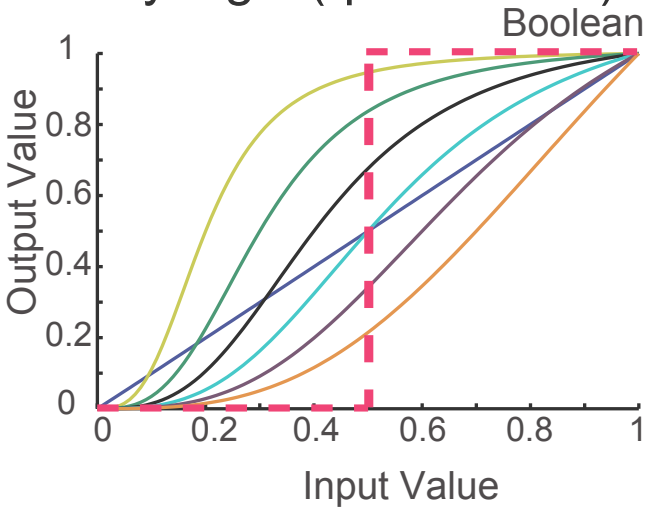


Boolean multi
time-scale

sync.
dynamics



Fuzzy logic (quantitative)



Morris et al., PloS Comp Bio 2011

Logic-based ODEs

- Convert Boolean update function *Bi* into a *continuous homologue* $\overline{Bi}$ using multivariate polynomial interpolation (Odefy: Wittman et al)
  - **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

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

- Transform into differential equation

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

- E.g. a AND b inactivate C

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

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*(

d/dt(raf) = ((eg

d/dt(pi3k) = ((e
(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^
(1+erk12_k_ra
erk12) * erk12

Problem: even if structure is known need Identify parameters, difficult optimisation problem (collab with J. Banga group)

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

_inh)

_tauinv)*

af)*

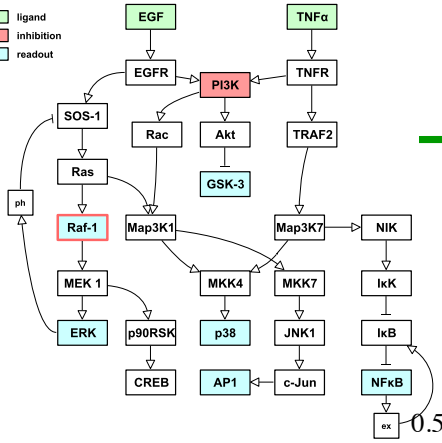
_ikb)-

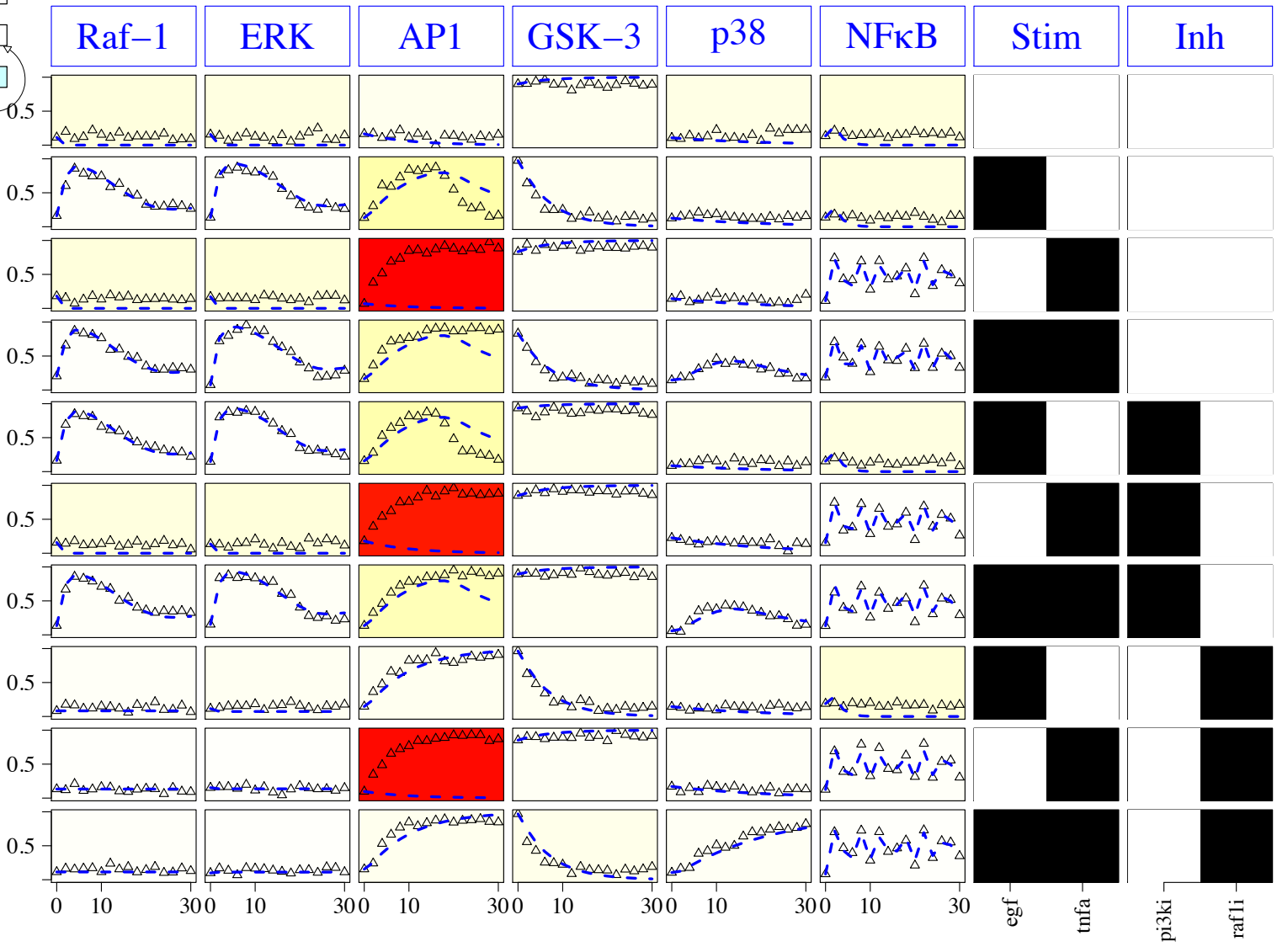
d/dt(egfr) = ((tgfa^egfr_n_tgfa/(tgfa^egfr_n_tgfa+egfr_k_tgfa^egfr_n_tgfa)*(1+egfr_k_tgfa^egfr_n_tgfa)-egfr) * egfr_tauinv)*(1-egfr_inh)

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)

Fit of ODE model





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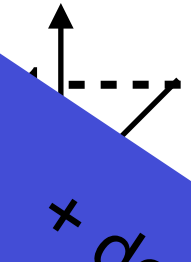
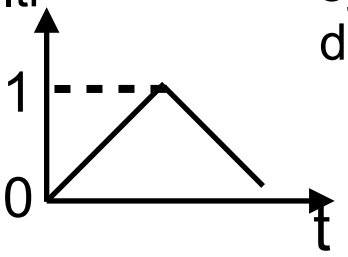
submitted

From Boolean to continuous and dynamic models within *CellNOpt*

Boolean (bina… logic steady



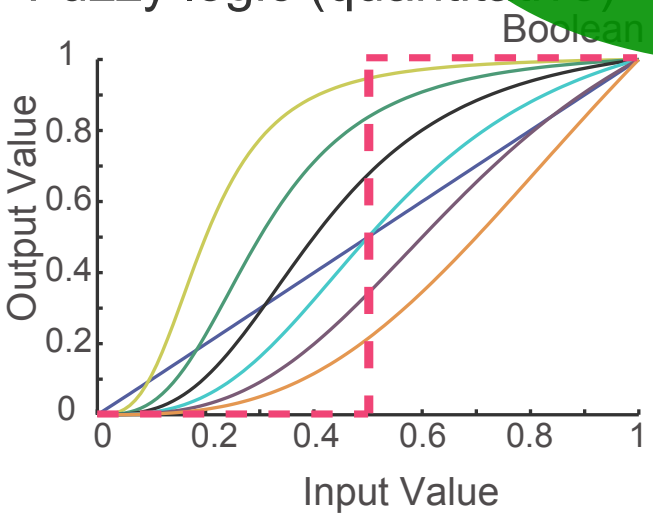
Boolean multi time-scale sync. dynamics



+ detail

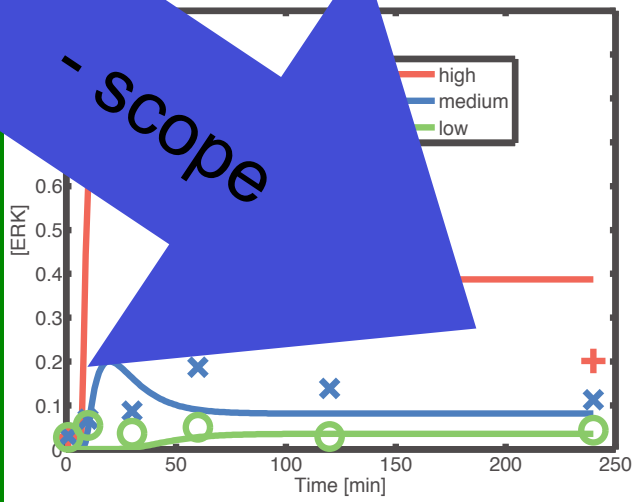
- scope

Fuzzy logic (quantitative)



Morris et al., PloS Comp Bio 2011

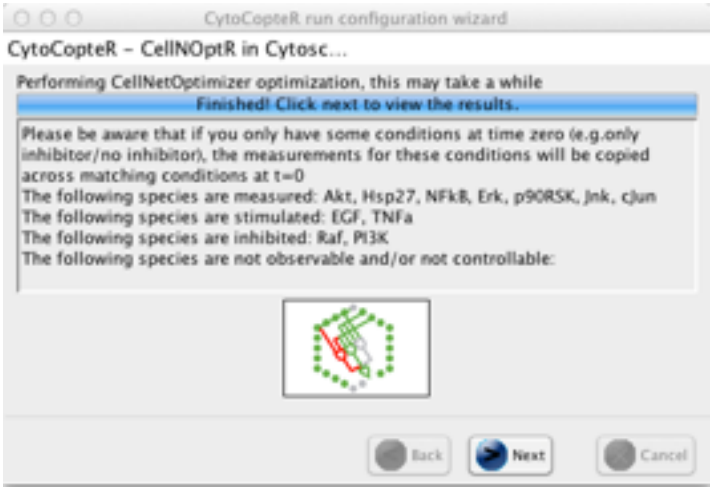
…ogic ODEs (dynamic)

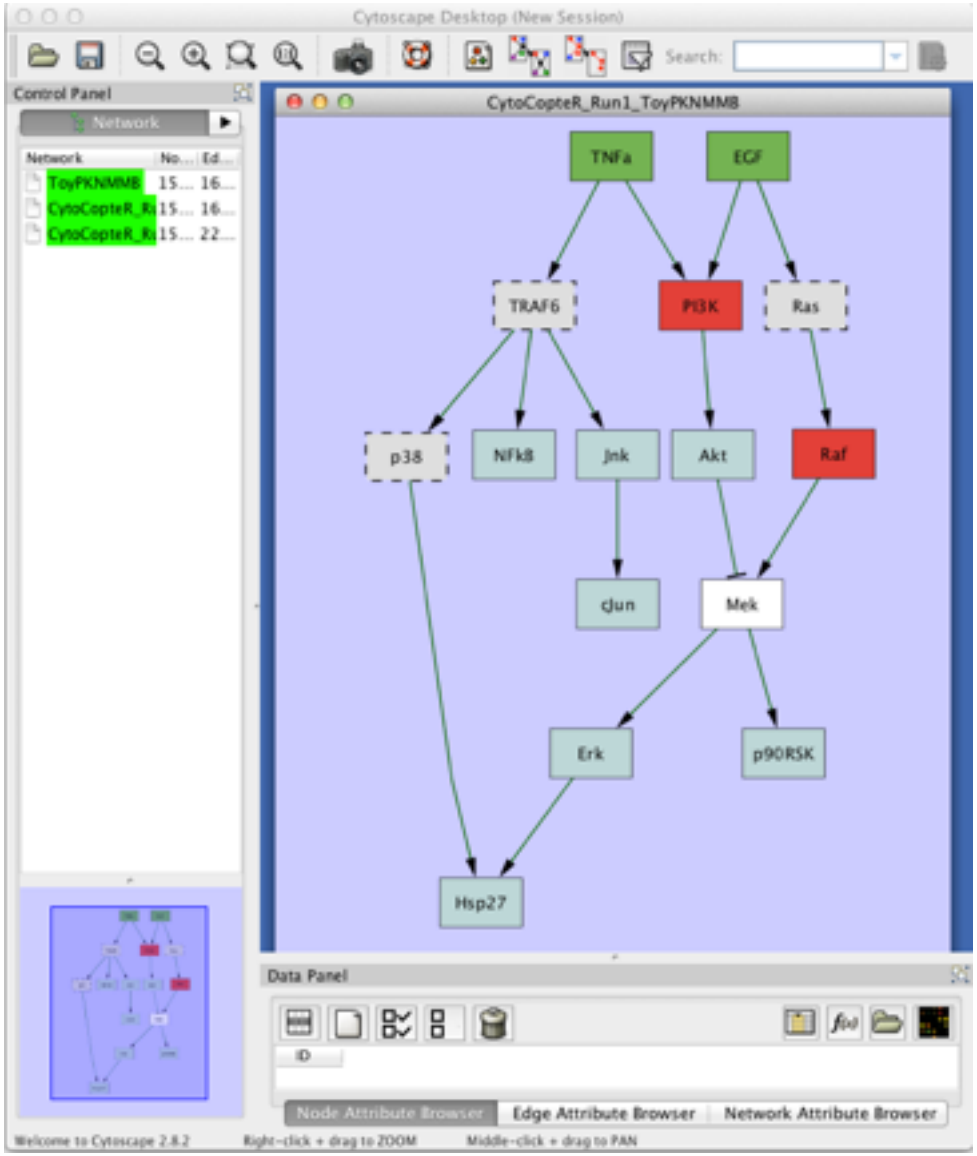


w. J Banga & J. Egea, B. Penalver

David Henriques

Cytoscape plugin (Cytocopter)





Martijn van Iersel

Emanuel Gonçalves

Explore sources of prior knowledge

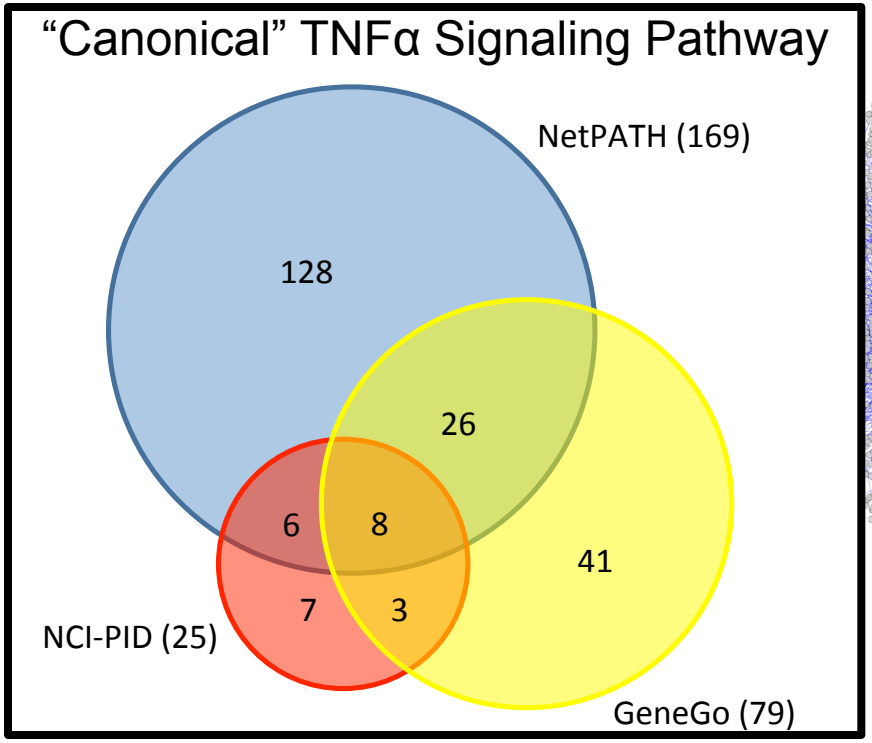
- **Databases** of curated **pathways** (Reactome, KEGG, Wikipathways, ...) incomplete, low overlap, different qualities
➜ Path2Models (standarized pathway resouces; w. LeNovere)

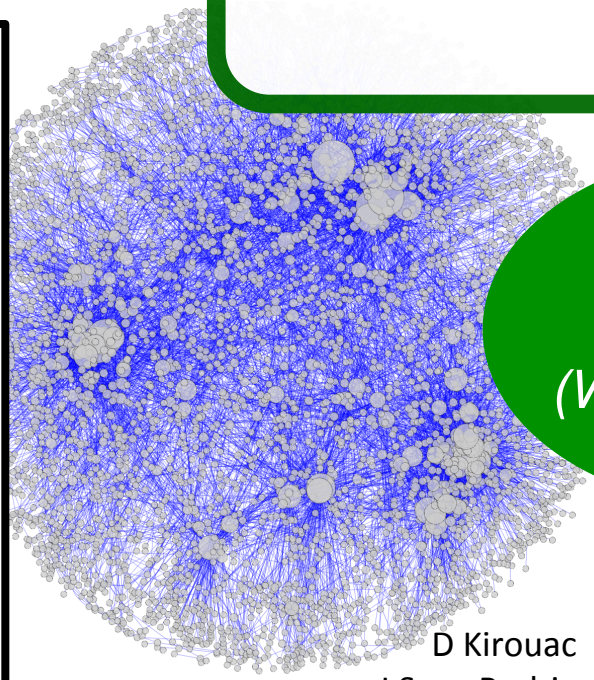
- Protein **Interaction** Networks

- Literature mining

Link CellNOpt
to methods
to infer new links

Federica Eduati





collaborative efforts (WikiPathways)?

D Kirouac
J Saez-Rodriguez
et al, *submitted*

Martijn van Iersel

Acknowledgments

Systems Biomedicine group
www.ebi.ac.uk/saezrodriguez

EMBL EIPOD
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