Comparative logical models of signaling networks in normal and transformed hepatocytes derived from phosphoproteomic data

Julio Saez-Rodriguez

EMBL-EBI

European Bioinformatics Institute
Hinxton, Cambridge - UK

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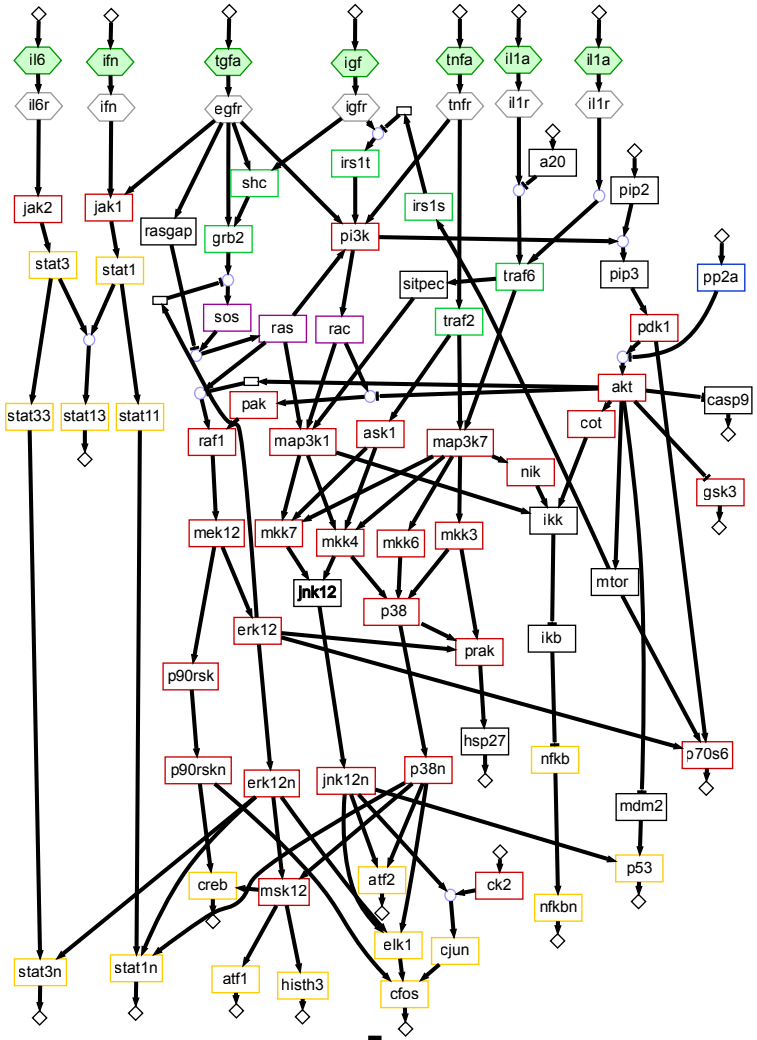
Department of Systems Biology, Harvard Medical School
&
Biological Engineering Department, M.I.T.

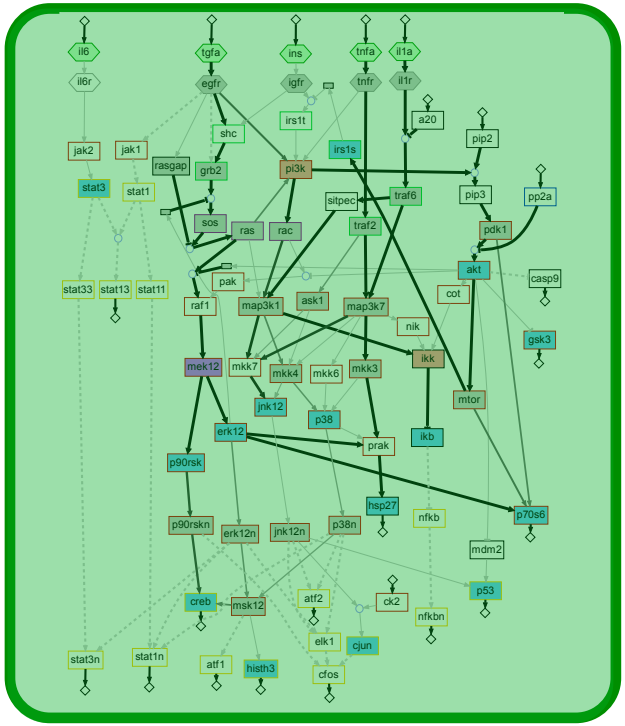
How is signal processing altered in disease?



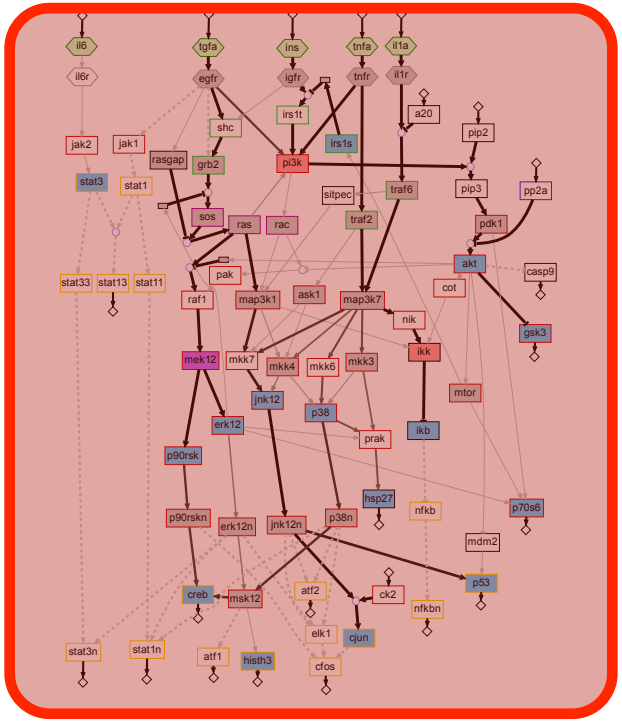
Phenotype

How is signal processing altered in disease?

Normal



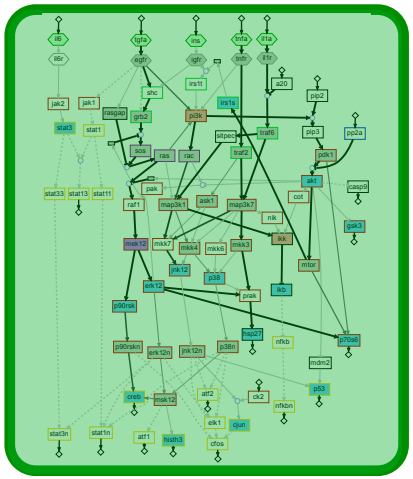
Diseased



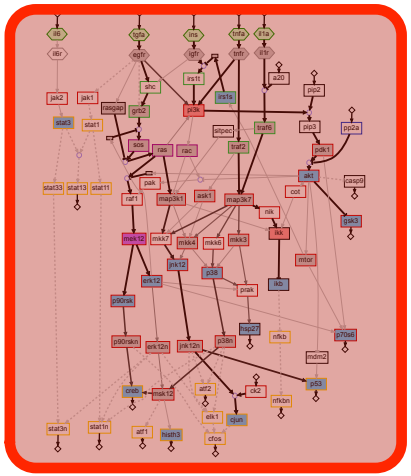
Case study: how is signaling altered in transformed vs normal hepatocytes?

Hepatocellular Carcinoma (HCC):
most frequent form of liver cancer, 3rd most lethal cancer

Normal



Diseased

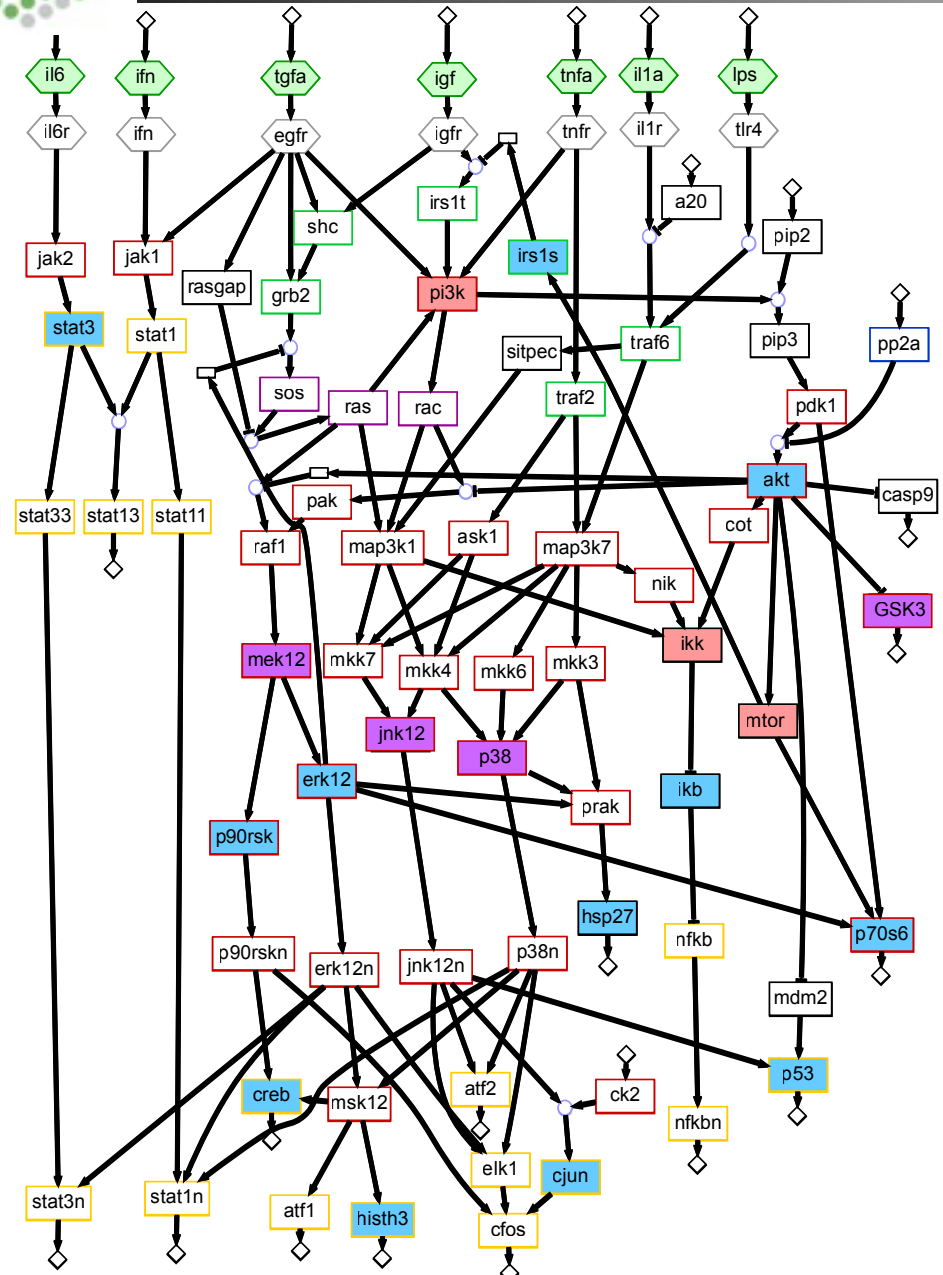


- Chromosomal amplifications/ deletions, mutations, methylation alterations (Llovet and Bruix, 2008)

- **Heterogenous** gene expression even within adjacent tumor nodes (Lee & Thorgeirsson et al. 2005)

Sparse knowledge of functioning and deregulation of signaling in HCC

Design of Cue-Signal-Response experiment for HCC



Construct map of canonical pathways from *Ingenuity* (85 species)

Select

- **perturbations** (chemical inhibitors = drugs)
&
- **signals** (phosphorylations measurable with Luminex/xMAP technology)

as distributed in the network as possible

Stimulus | Perturbation

Readout | Perturb&Read

Design of Cue-Signal-Response experiment for HCC

Performed by Leonidas Alexopoulos

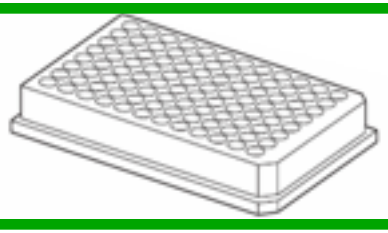
Primary hepatocytes and HCC cell lines

Cue

➜ 7 **extracellular ligands**

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

at different times after stimulation



Signal

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

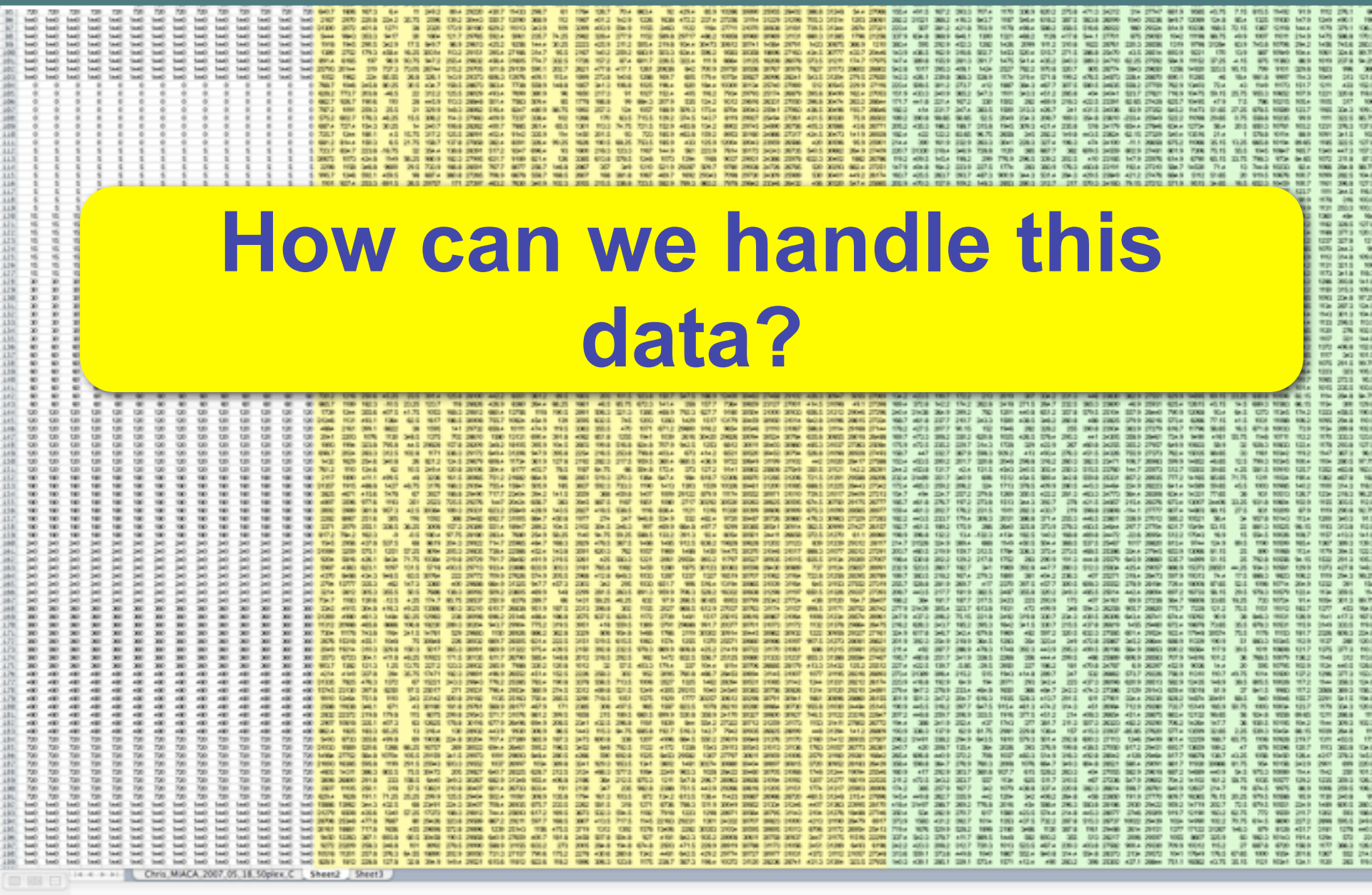
using Luminex/xMAP (bead-based ELISA)

Response

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

Alexopoulos L, Saez-Rodriguez J, Cosgrove B, Lauffenburger DA, Sorger PK, *Mol. Cell. Proteom, in press*

Cue-Signal-Response Compendium of 26,000 measurements



How can we handle this data?

Cue-Signal-Response Compendium of 26,000 measurements

THE FAST TRACK TO MODEL TRAINING!

Flexible Informatics for Linking Experimental Data to Mathematical Models

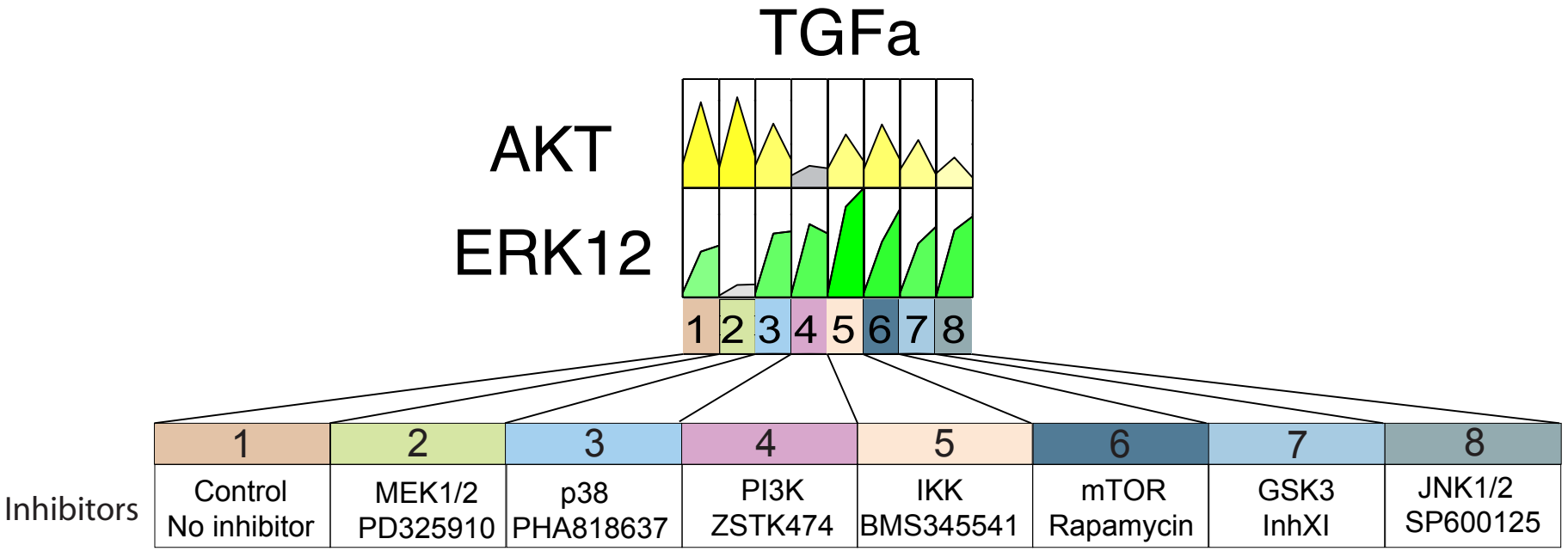
Saez-Rodriguez J, Goldispe A, Muhlich J, Alexopoulos A, Millard B, Lauffenburger DA, Sorger PK, *Bioinformatics,* 24:6, 2008.

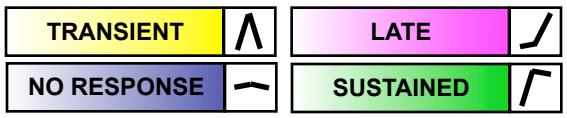
- Maintains data provenance
-Modular (easy to expand)

Open-source MATLAB Toolbox
Script& User Interface

Available at
http://code.google.com/p/sbpipeline/

Visualization of large data sets

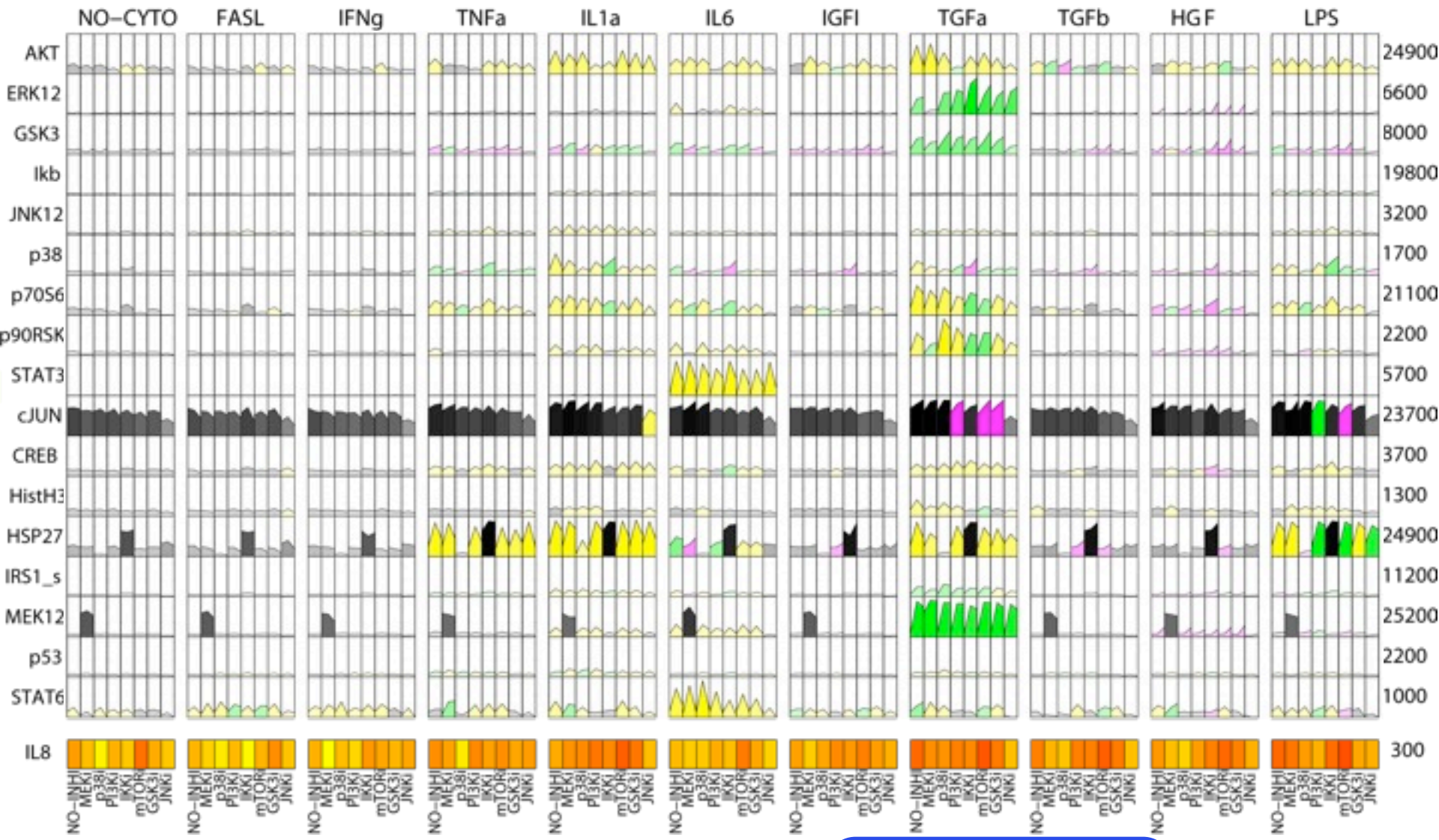




TIME POINTS:
0, 30min, 3hrs

Primary Hepatocytes

Visualization of large data sets



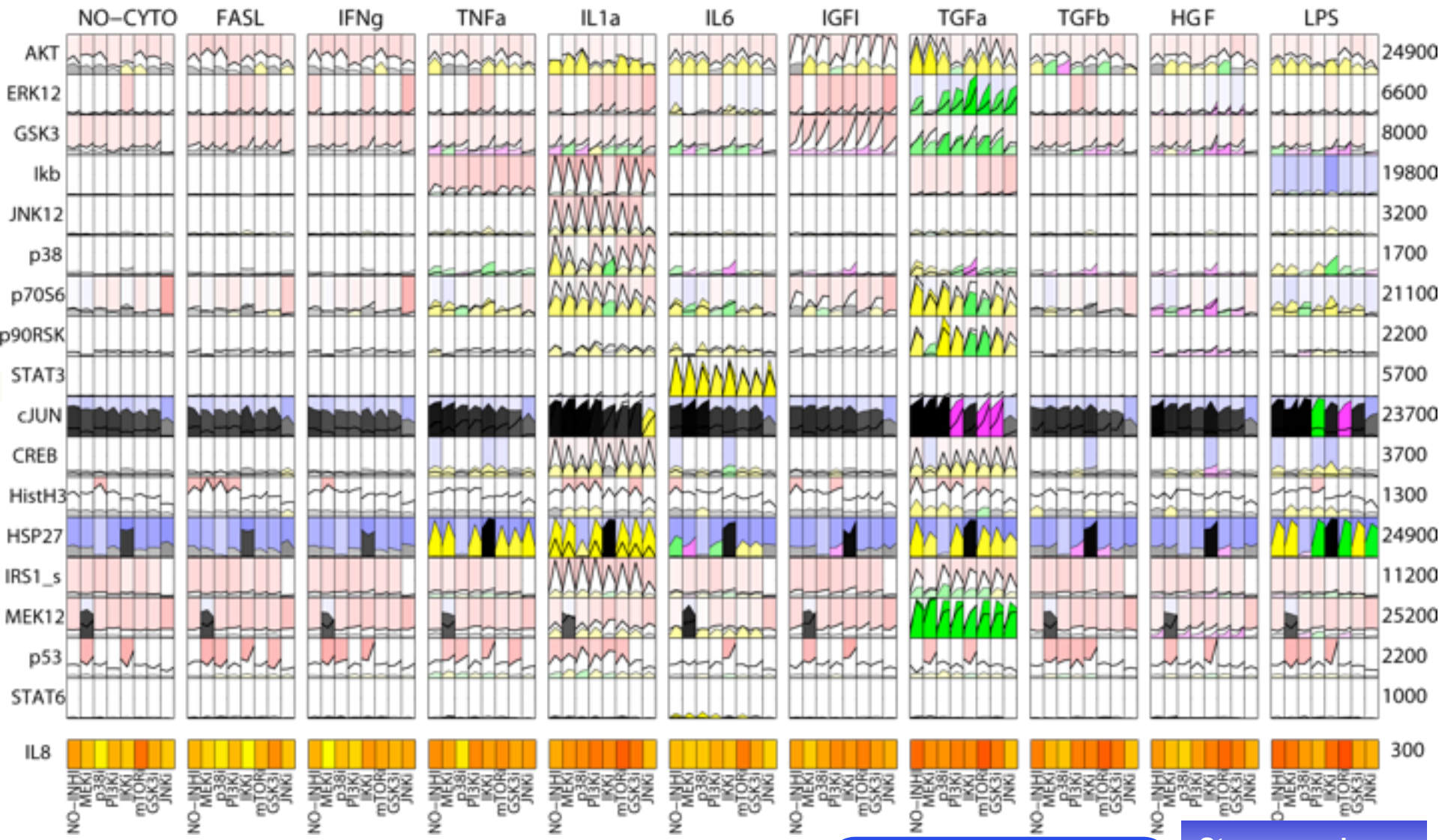
TRANSIENT | LATE

NO RESPONSE | SUSTAINED

TIME POINTS:
0, 30min, 3hrs

Primary Hepatocytes

Visualization of large data sets



TRANSIENT | LATE

NO RESPONSE | SUSTAINED

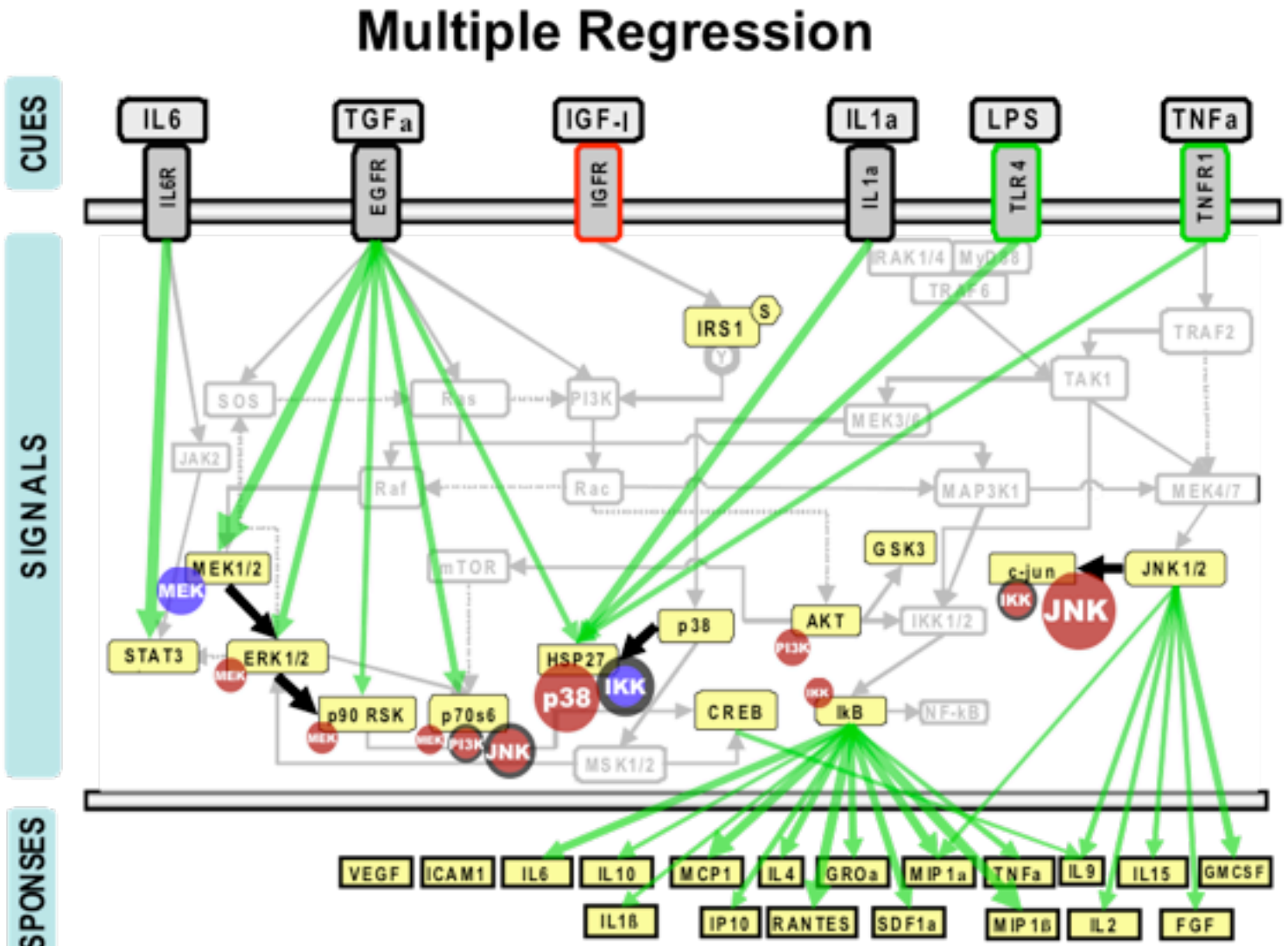
TIME POINTS:
0, 30min, 3hrs

Primary Hepatocytes

Stronger primary

Stronger HepG2

Data-driven approaches useful but (in our case) provide limited mechanistic insight



Alexopoulos L, Saez-Rodriguez J, Cosgrove B, Lauffenburger DA, Sorger PK, *Mol. Cell. Proteom, in press*

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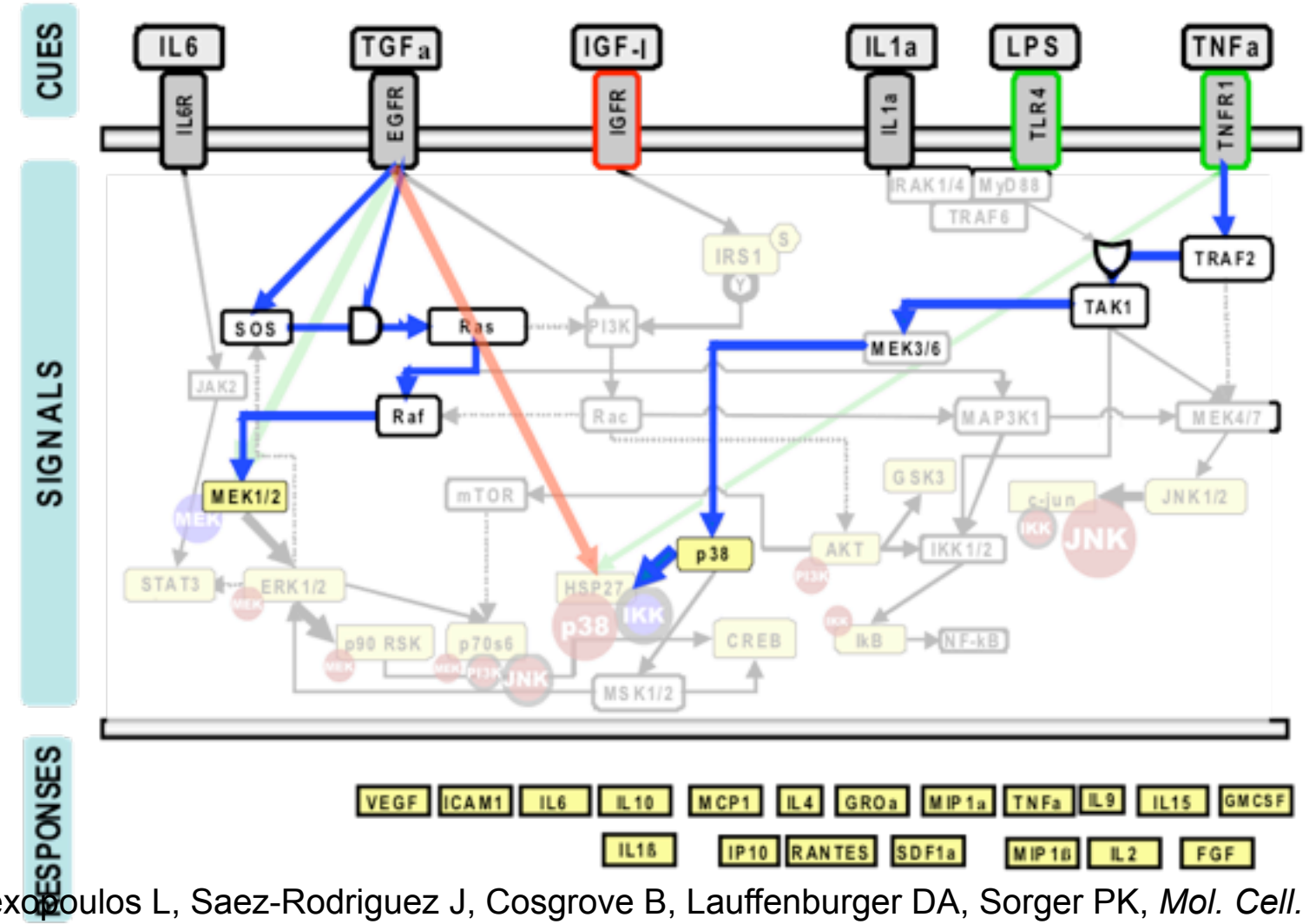
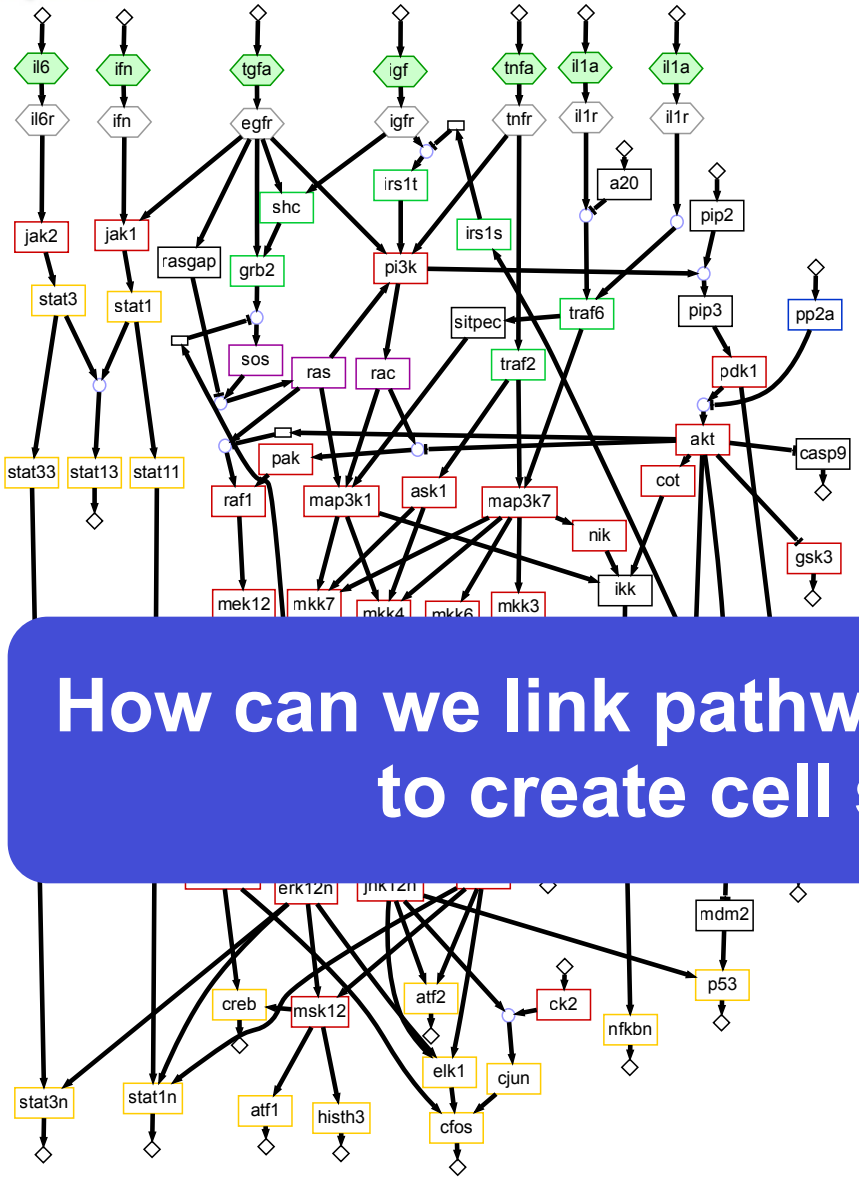


Alexopoulos L, Saez-Rodriguez J, Cosgrove B, Lauffenburger DA, Sorger PK, *Mol. Cell. Proteom, in press*

Signaling pathway maps summarize literature knowledge



Pathway maps widespread and very **useful** but

- ***Pictures* not computable** models to study signal processing

- Not cell-type specific

How can we link pathway maps to signaling data to create cell specific models?

Challenges to link pathway maps to data of signal transduction

- Make **maps executable** (models) so that experiments can be simulated

  ➪ Transform into **Boolean** (0/1) logic (AND/OR) models ✔

- Define **metric** to **evaluate** models given the data

  ➪ Balance fit to data with model size ✔

- Develop a framework to **explore** models & **identify best**

  ➪ (i) Compress map

  (ii) Construct an 'scaffold' with all possible models (all gates) compatible with map

  (iii) find model with optimal metric (train) ✔

Saez-Rodriguez J, Alexopoulos LG, Epperlein J, Samaga R, Lauffenburger DA, Klamt S, Sorger PK, *Mol. Syst. Biol,* 5, 331, 2009.

Challenges to link pathway maps to data of signal transduction

CellNetOptimizer

Matlab toolbox, script & user interface
freely available at
http://www.cdpcenter.org/resources/software/cellnetoptimizer/

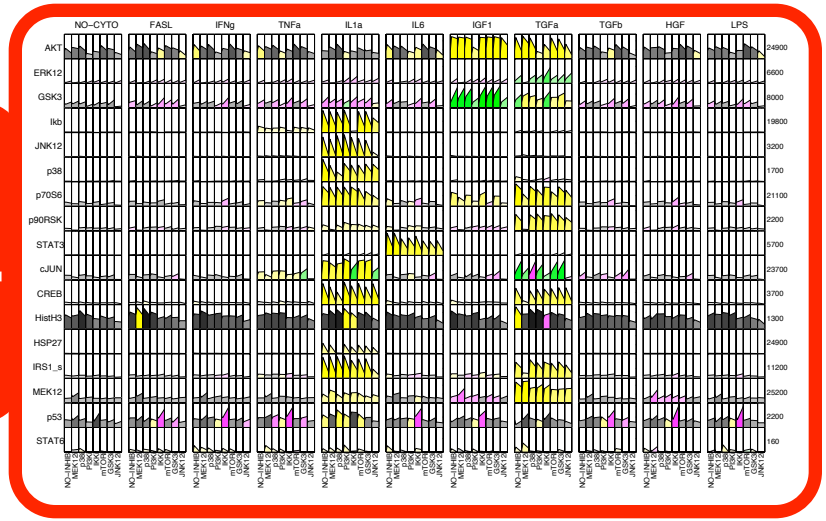
Saez-Rodriguez J, Alexopoulos LG, Epperlein J, Samaga R, Lauffenburger DA, Klamt S, Sorger PK, *Mol. Syst. Biol,* 5, 331, 2009.

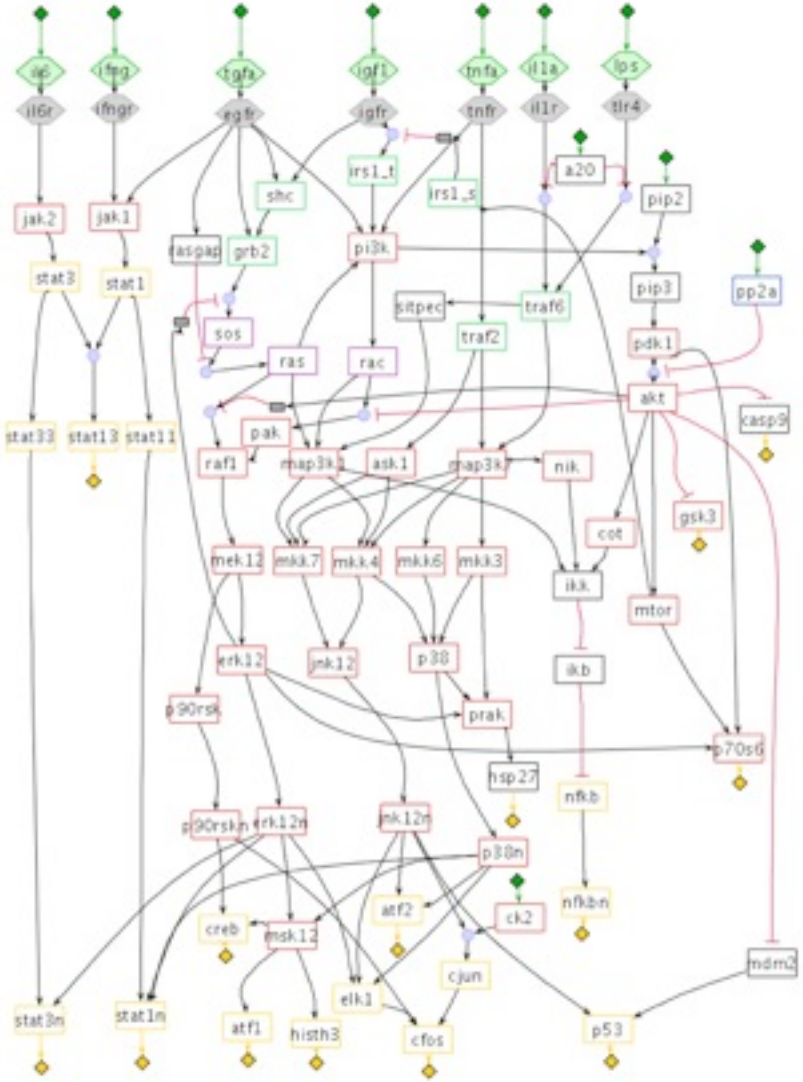
Application to signaling in primary vs. transformed hepatocytes

Data

Map

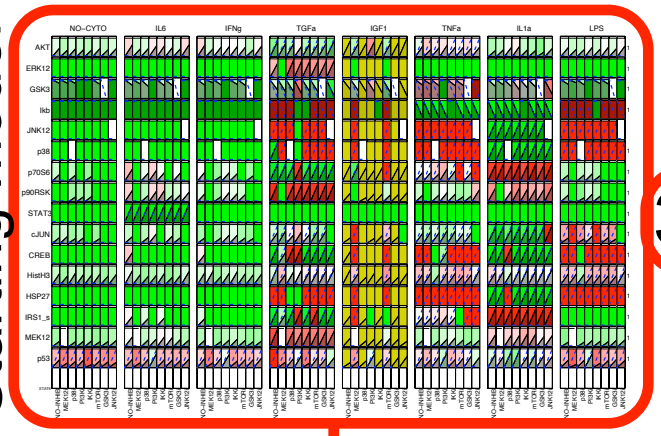
HepG2





Model trained to HepG2 data

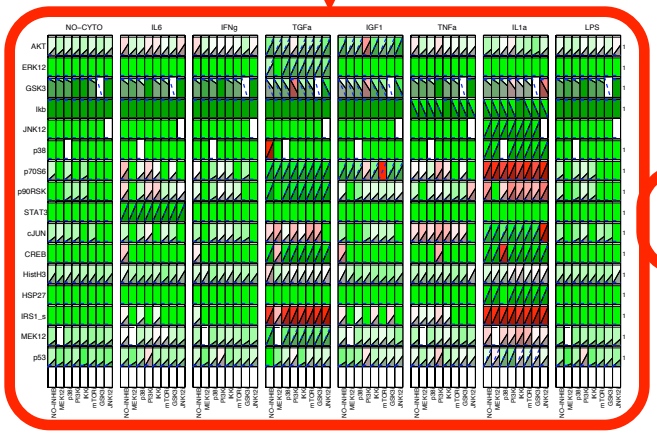
Starting model



Error

34.3%

Trained model



8.1%

Stimulus

Perturbation

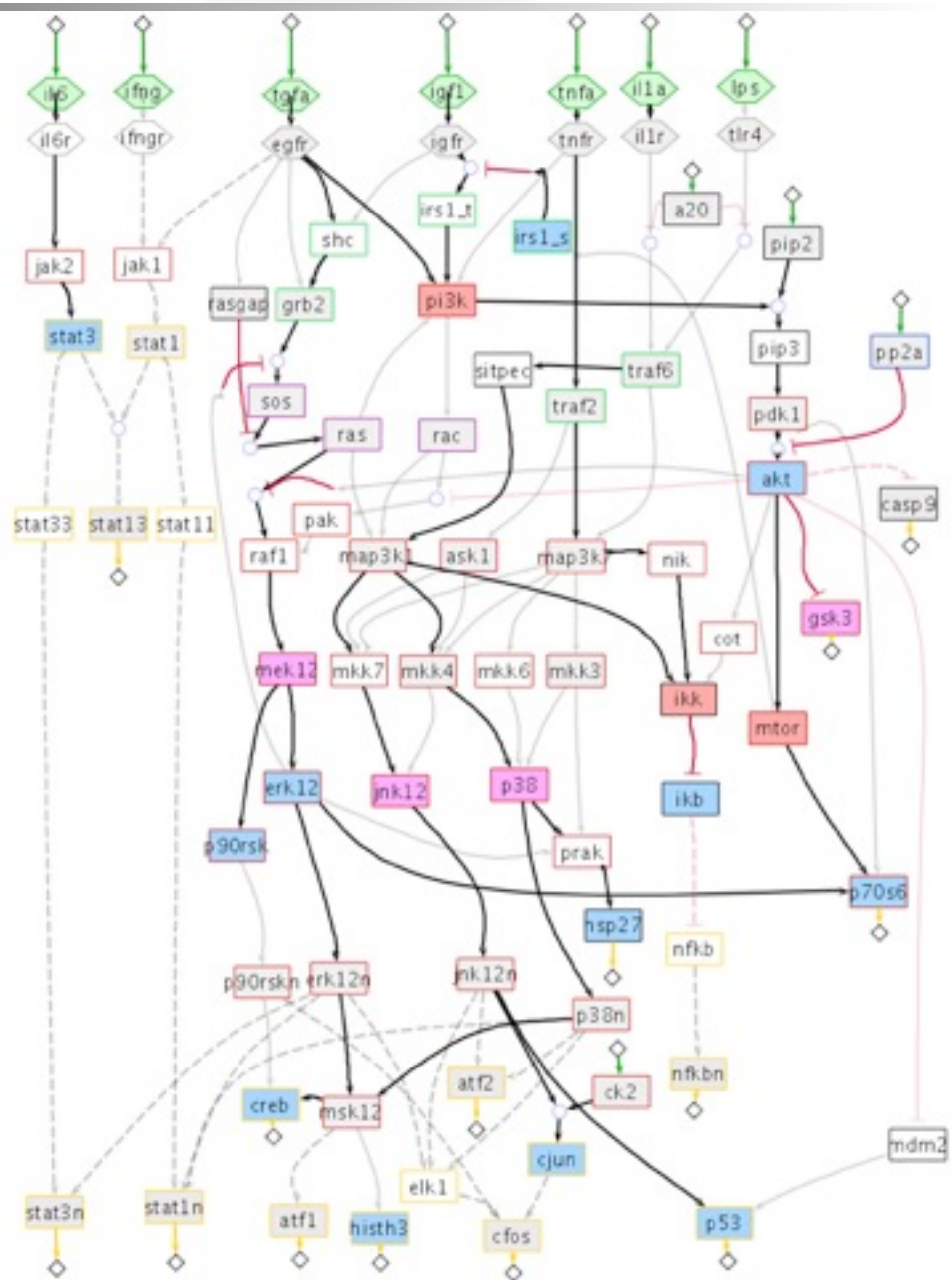
Readout

Perturb&Read

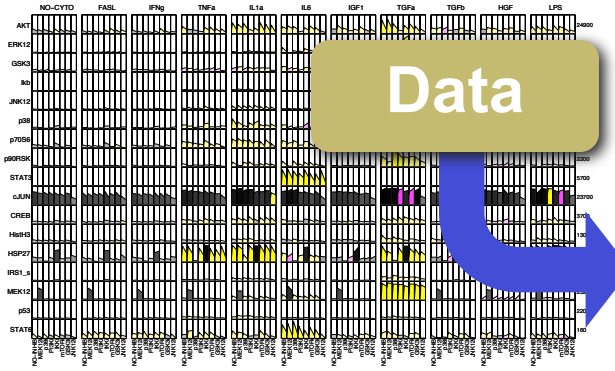
Kept

Removed

No effect



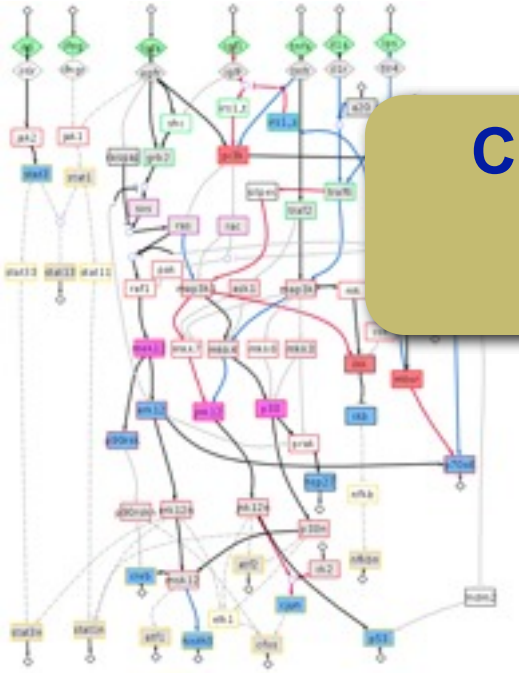
Summary



Data

Maps

CellNet Optimizer



Computable Model specific to data (cell/conditions)

Summary

- Pathway **maps** are **not specific**
- **Models** trained to data are much **sparser** and **predictive**
- It is possible to
  - Construct models **specific** for **cell types**
  - **Cluster** cell types based on pathways models
  - Pinpoint specific **differences** between **normal** and **diseased** cells
  - Obtain insight on **off-target** effects of **drugs**

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