

Modelling IL-6 mediated ADME gene regulation

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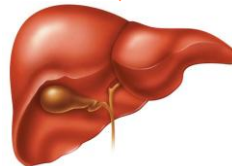
Impact of inflammation on drug clearance



Infection, Cancer, Inflammation



**Pro-inflammatory cytokines
(IL-6, IL-1 β , TNF α , iNF γ)**

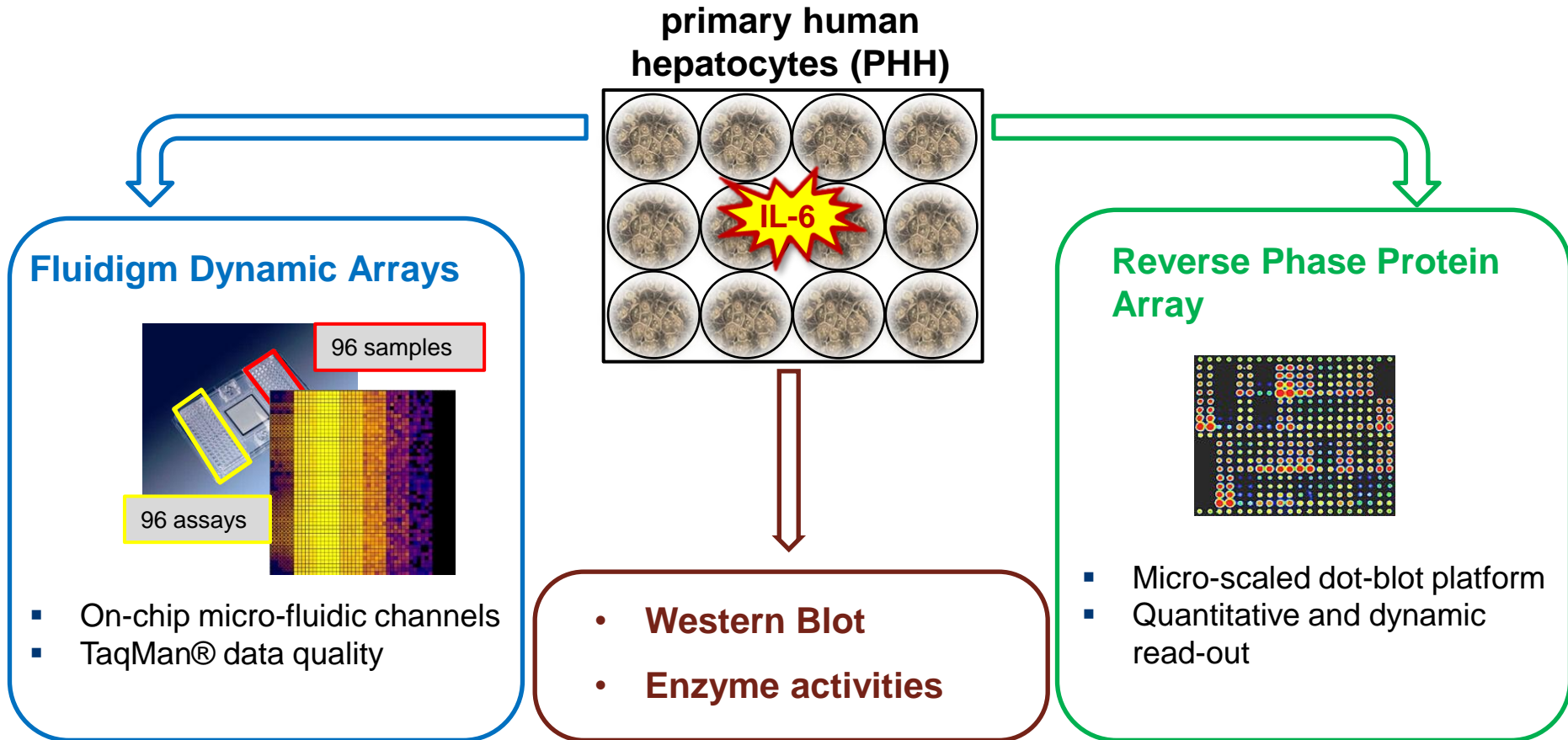


**↑ Acute phase proteins (e.g., CRP)
↓ P450s, phase II enzymes, transporters (ADME genes)
↓ Biliary excretion (CYP7A)**

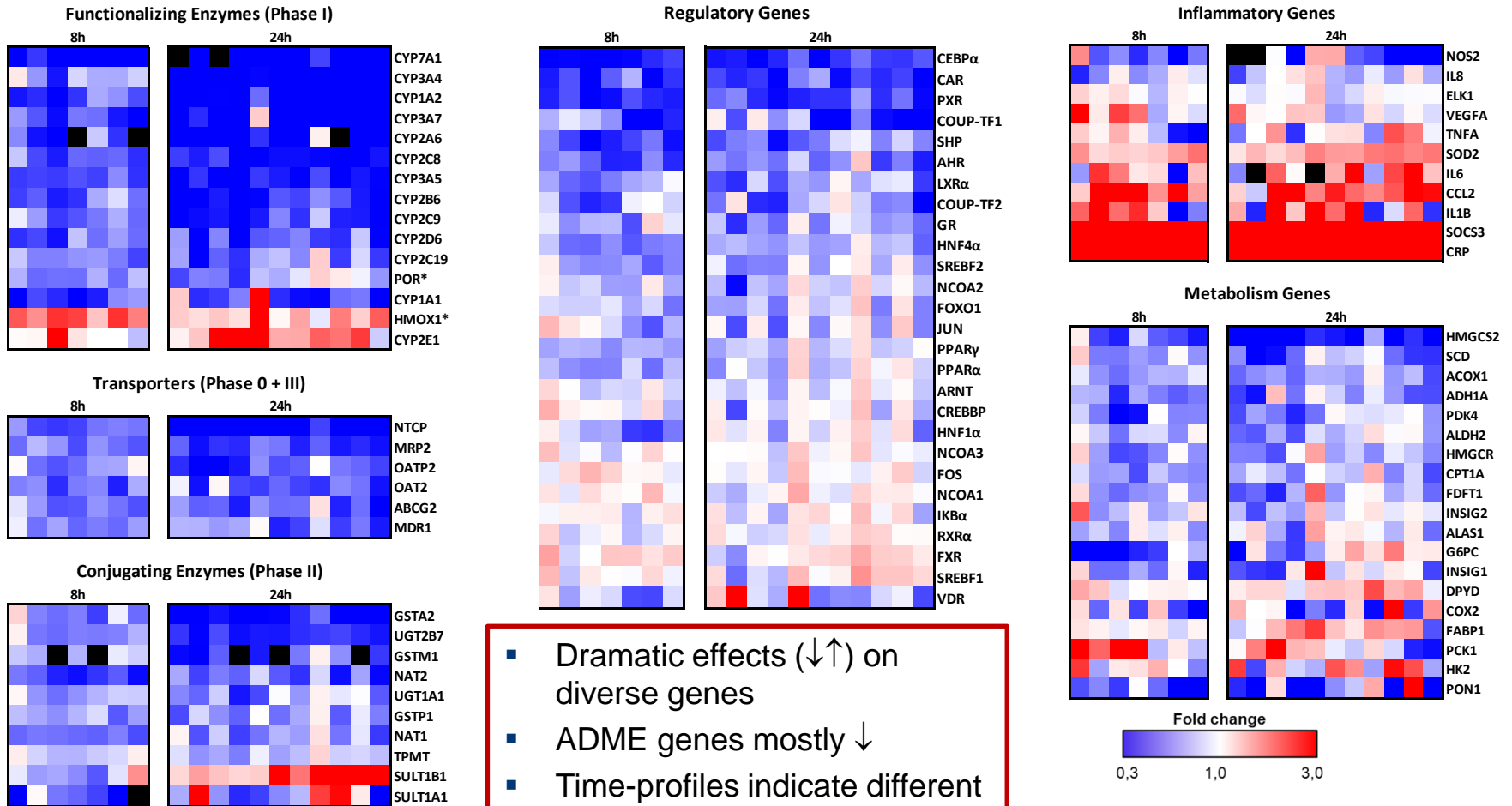


**↓ drug clearance
↑ drug toxicity**

Experimental design and workflow

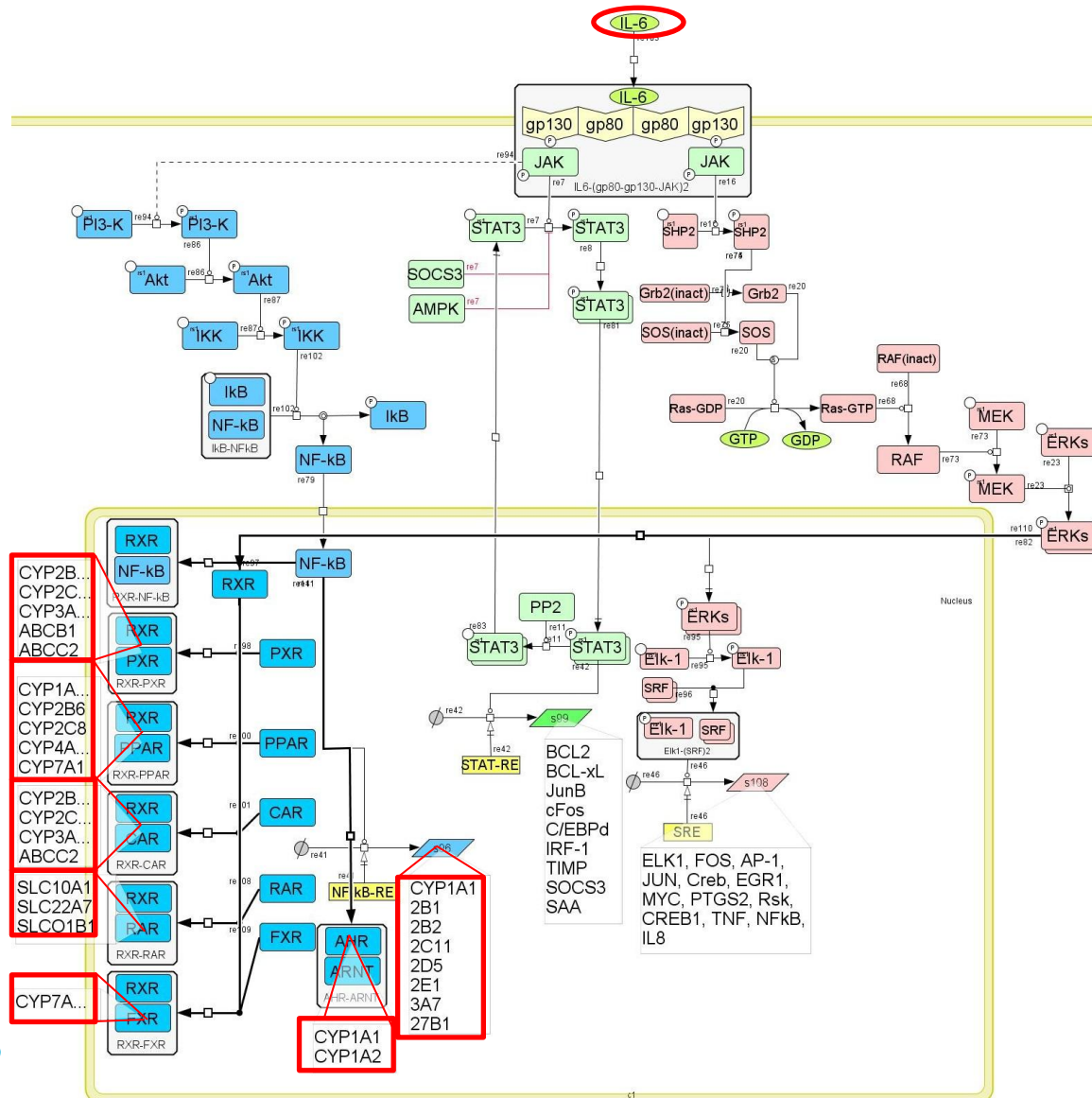


IL-6-induced changes in gene expression



- Dramatic effects ($\downarrow\uparrow$) on diverse genes
- ADME genes mostly \downarrow
- Time-profiles indicate different regulatory mechanisms.

Topological model with relevant pathways

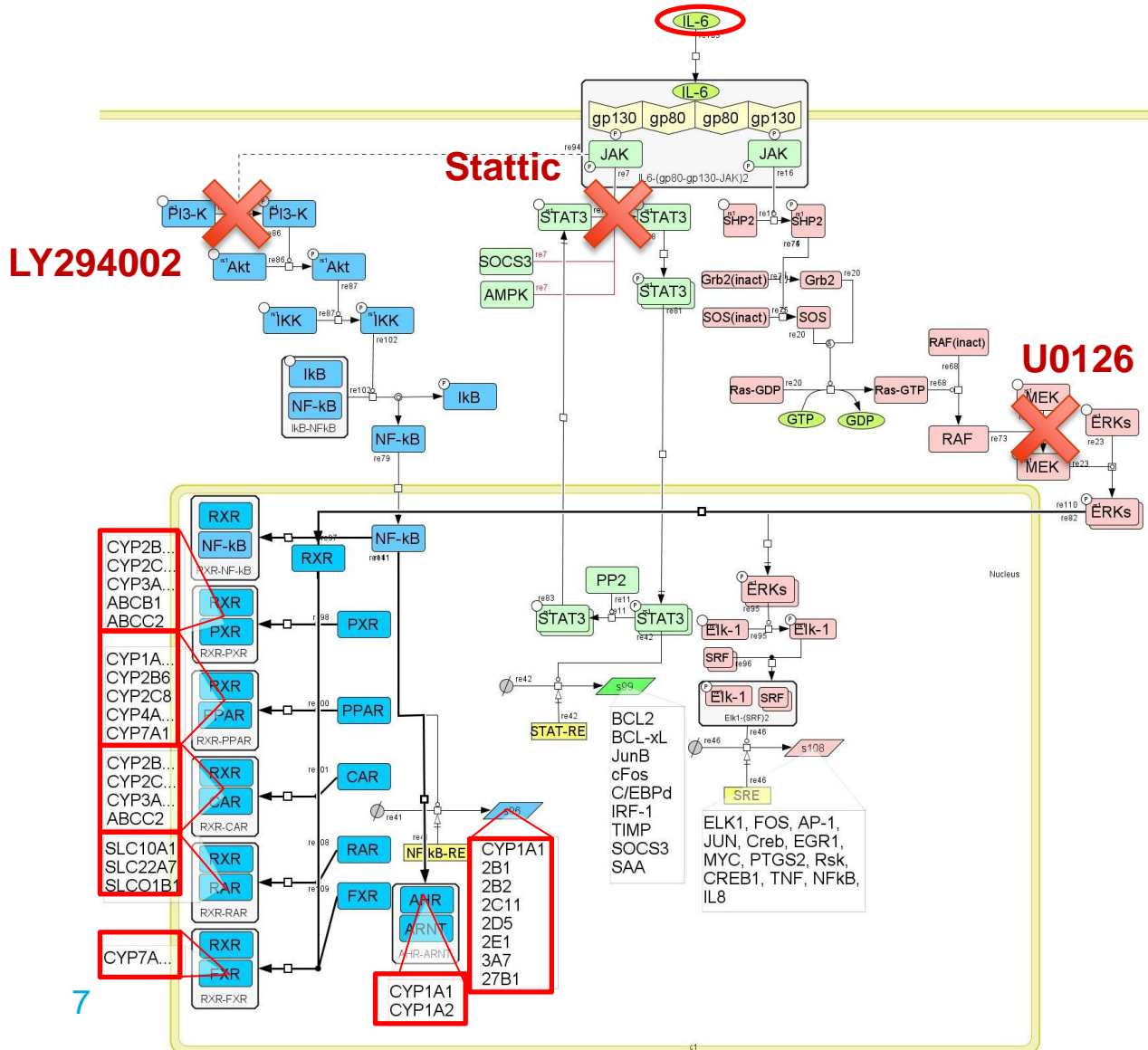


- PI3K/Akt
- JAK/STAT
- MAPK/ERK

Based on:

- Ryll et al. (2011)
- Singh et al. (2006)
- Raue et al.
- BIOBASE
- Literature

Chemical Inhibition of major signaling pathways



- PI3K/Akt
- JAK/STAT
- MAPK/ERK

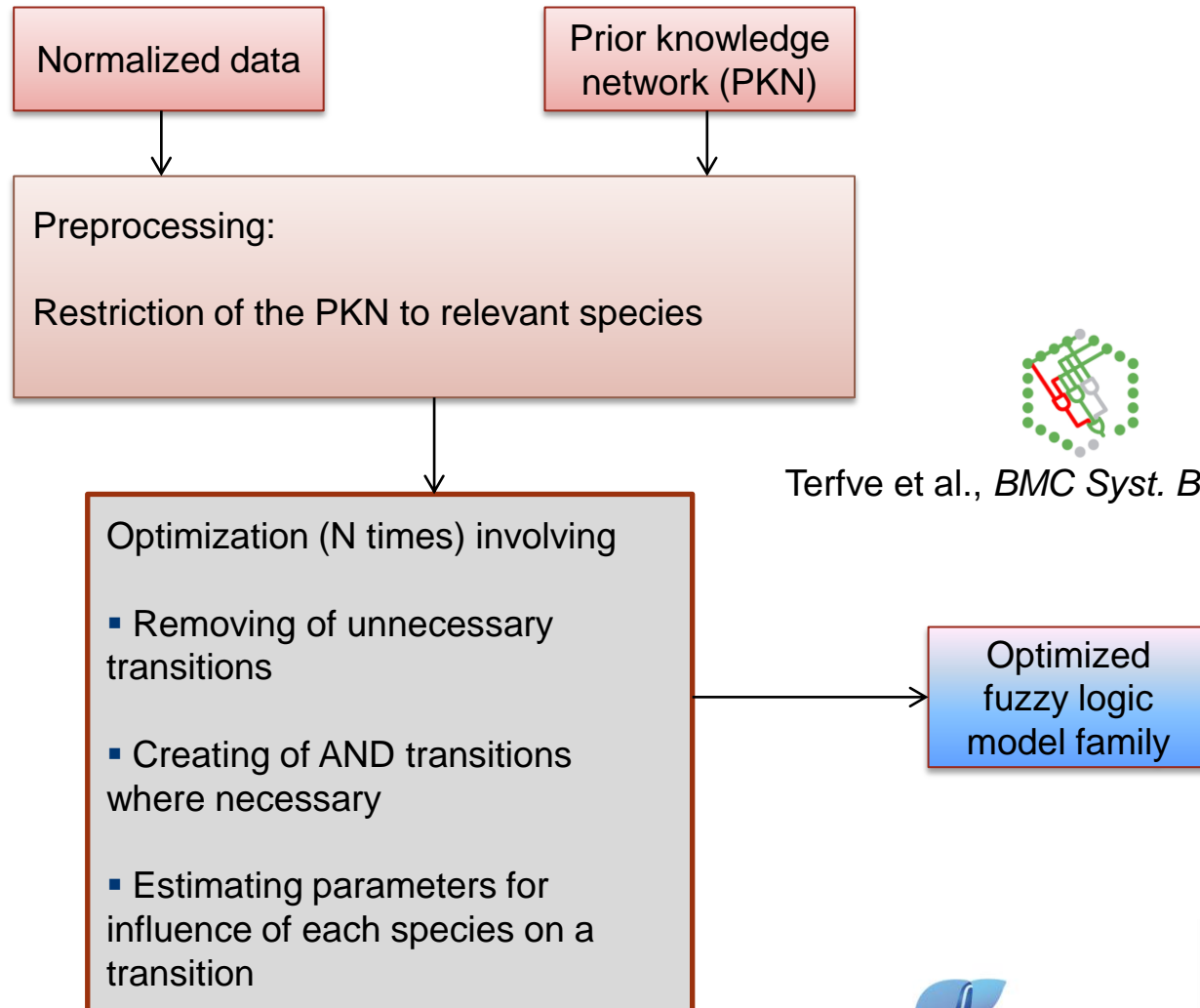
Based on:

- Ryll et al. (2011)
- Singh et al. (2006)
- Raue et al.
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- Literature

Fuzzy logic modelling

- Model containing **species** (representing proteins/genes) connected by logical **transitions** (AND/OR/NOT)
- Problem with simple **Boolean** logic: possible **states** of proteins/genes only **0** or **1**, not appropriate for most genes
- **Fuzzy** logic enables **states** in **interval [0,1]**
- Using **fuzzy** logic the **influences** of species on a transition can be differently high.

Optimization process: CNORfuzzy



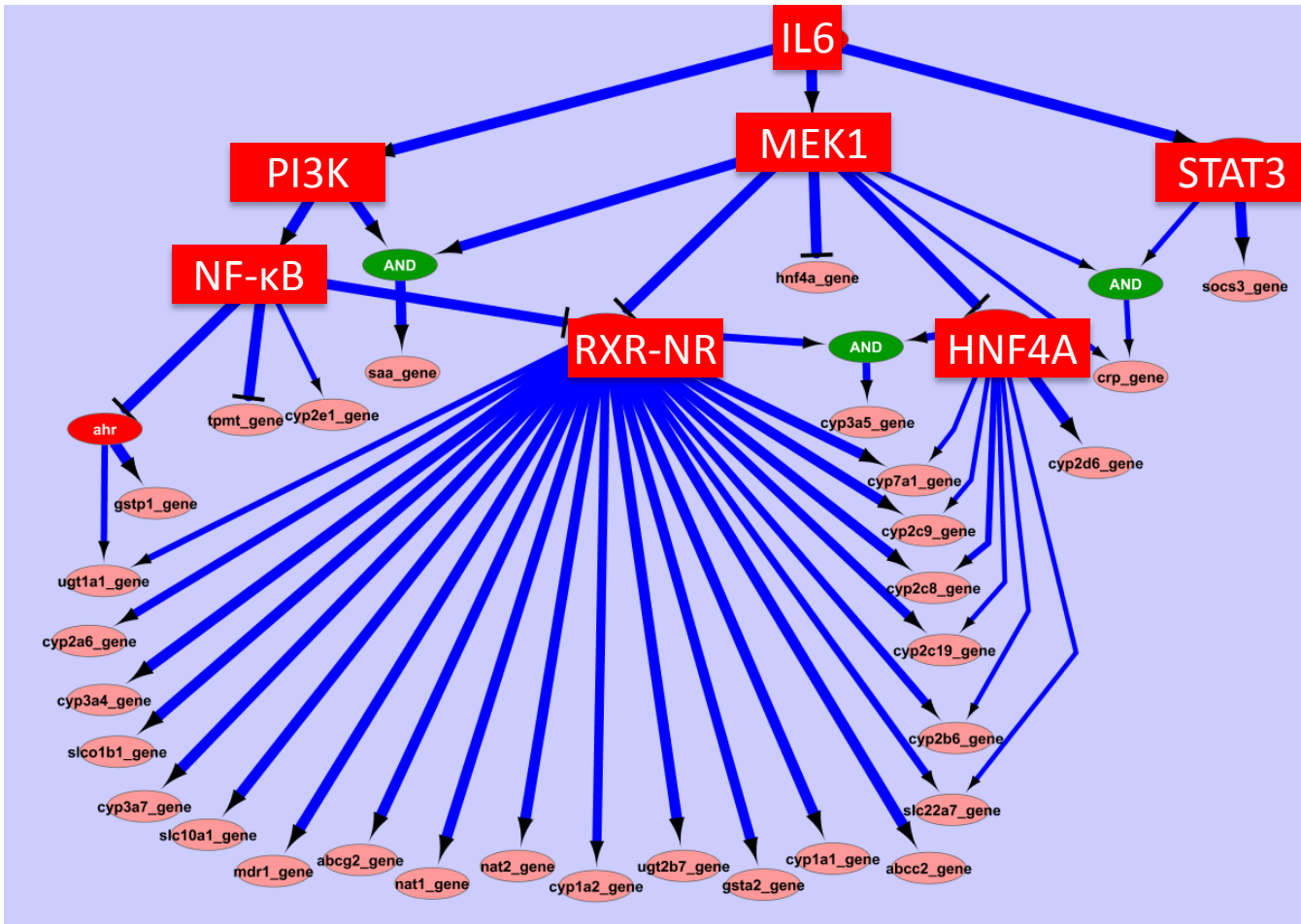
Terfve et al., *BMC Syst. Biol.*, 2012

Creating the IL-6 model

- **Prior knowledge network (PKN)** constructed from literature
 - **Signal transduction** part from model by Ryll et al., *Mol.BioSyst.*, 2011 (already validated)
 - Connection to **gene regulation** based on information from several other sources
- **5 gene expression datasets** with 6 different treatments

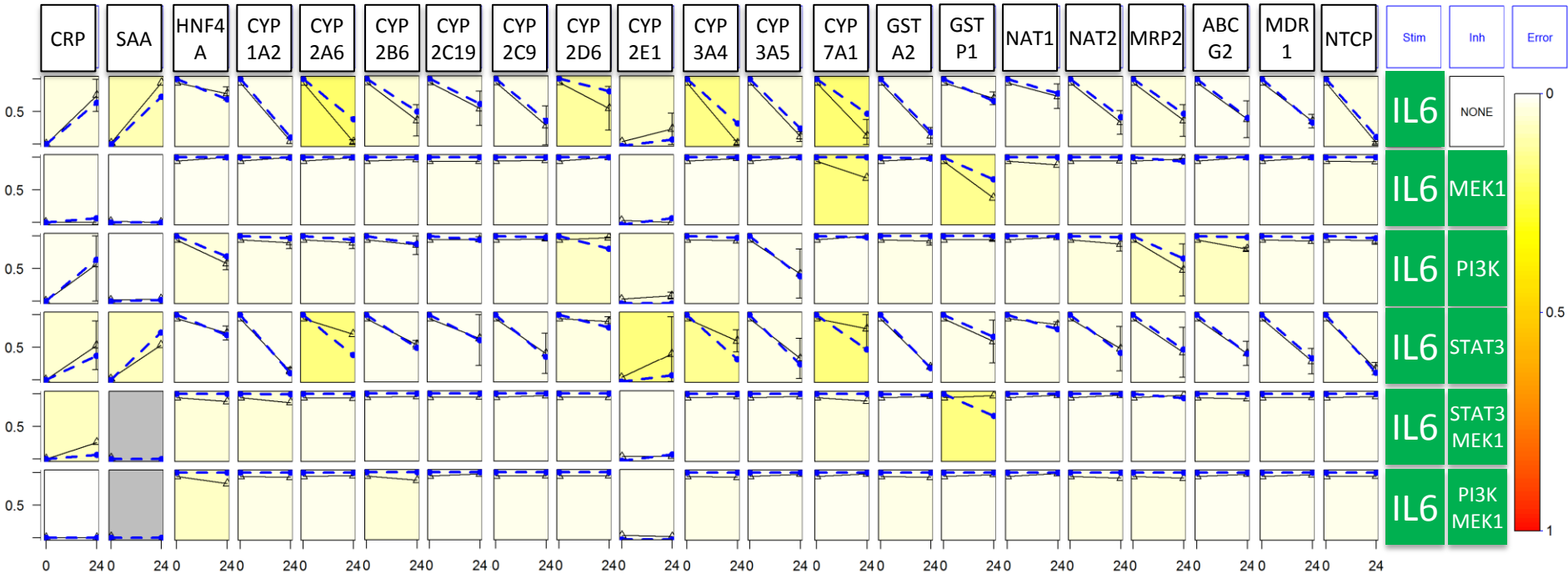
Treatment	IL-6	MAPKi	PI3Ki	STAT3i
1	+			
2	+	+		
3	+		+	
4	+			+
5	+	+		+
6	+	+	+	

Optimized model family



- Arrow thickness: percentage of optimized models containing the transition
- Model contains **key signalling proteins**, **genes**, and **AND nodes**.
- **MEK1** and **PI3K** are important.
- Most important event for ADME gene regulation : **inhibition of RXR-NR by MEK1 and NF-kB**
- Second important event: **inhibition of HNF4a by MEK1**

Fitting results



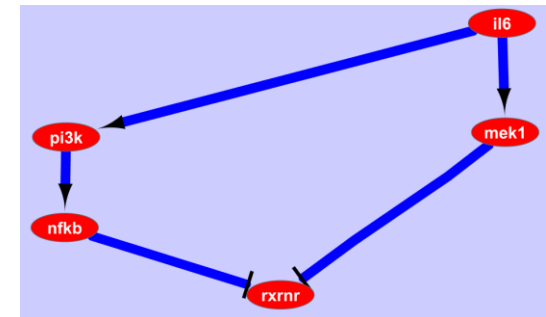
- - - - - Prediction
————— Normalized data

Model-derived hypotheses

- Two events are most relevant for IL-6 induced ADME gene regulation:

- MAPKs and NF-kB interfere with RXR-NR complexes.

Zordoky and El-Kadi, Curr. Drug Metab. 2009
Lee et al., J.Biol.Chem. 2000
Ghose et al., Nucl. Recept. 2004



- Inhibition of HNF4a by MAPKs

Bolotin et al., Transc. Factor Encyclop., 2010
De Boussac et al., J Biol Chem., 2010



Summary

- IL-6 leads to coordinated downregulation of nearly all ADME genes.
- Fuzzy logic model based on chemical inhibition of 3 putatively involved signaling pathways in PHHs
- The model indicates important roles of MAPKs and NF- κ B, both converging at the nuclear receptor level.

Thank you for your attention!



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See you at poster P-156