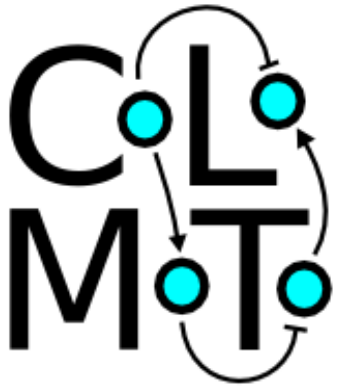
Advances in computational methods for the modelling of signalling networks



Enio Gjerga

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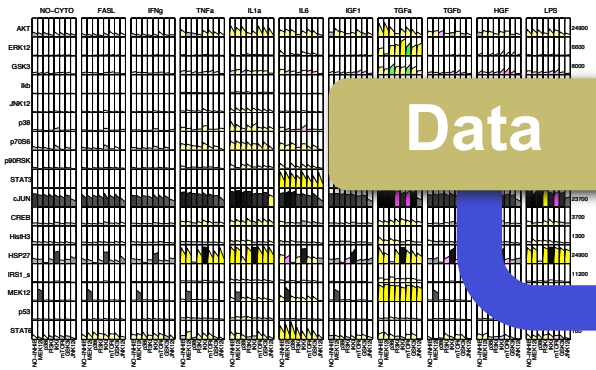
RWTH AACHEN UNIVERSITY

Institute for Computational Biomedicine
Heidelberg University & RWTH Aachen

www.saezlab.org
@sysbiomed

Our way to do modelling

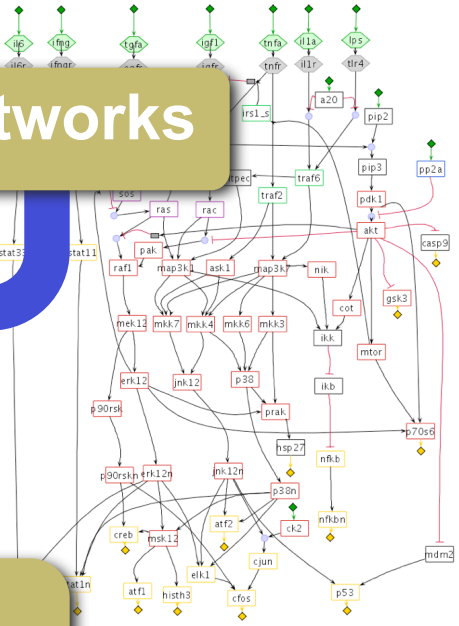


Data

Networks

CellNOpt/ PHONEMeS/

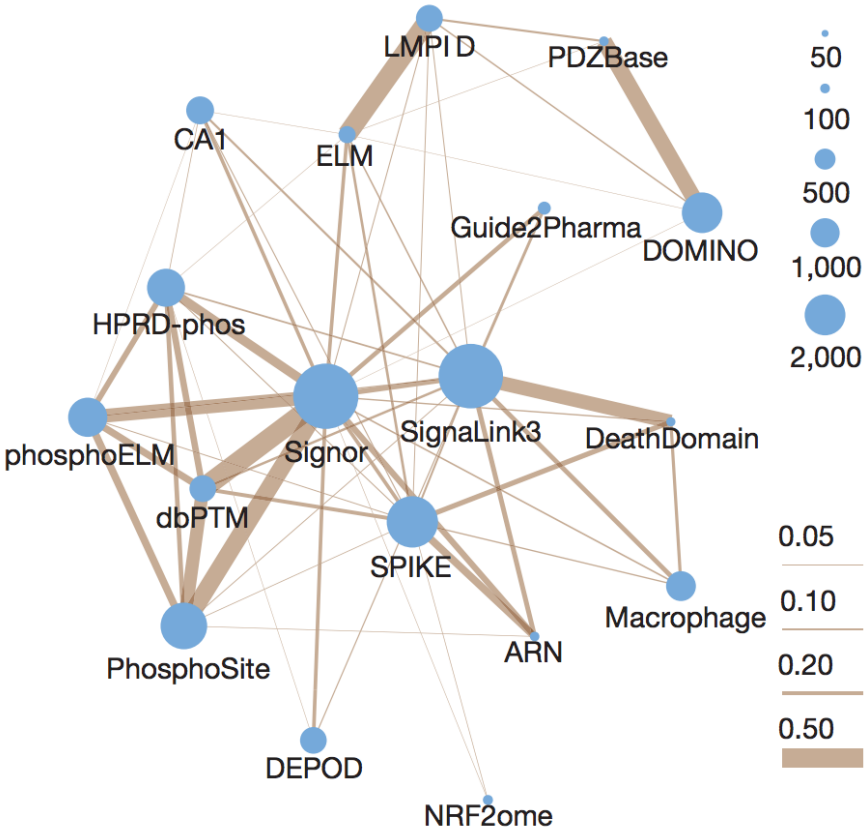
Computable & mechanistic model specific to data



Omnipath: Integration of existing pathway resources to improve modelling

www.omnipathdb.org

Networks



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

Leveraging different proteomic platforms

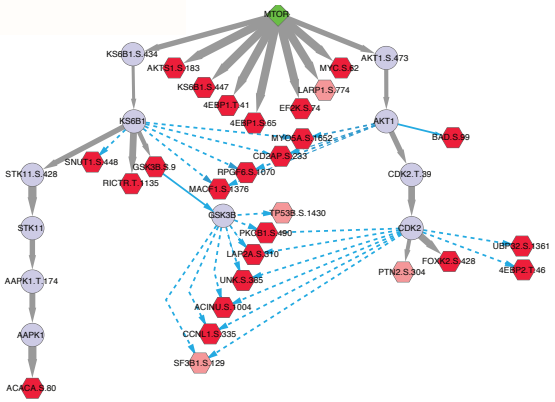
Data **Networks**

- **Antibody-based** population data (protein arrays, luminex, …) (CNO)

- **Single cell** - Mass Cytometry (CyToF), live-cell imaging (CNO)

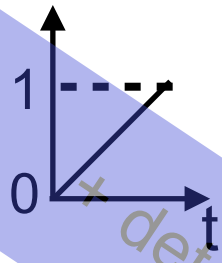
- **Mass spectrometry** phospho-proteomics (PHONEMeS; Terfve et al Nature Comm 15)

- More about PHONEMeS, poster presentation 493



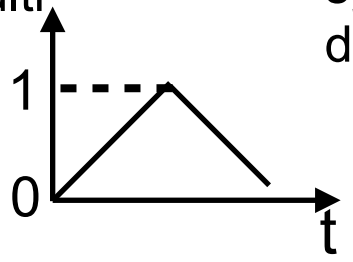
From Boolean to continuous and dynamic models

Boolean (binary)
logic steady state



+ detail

Boolean multi time-scale

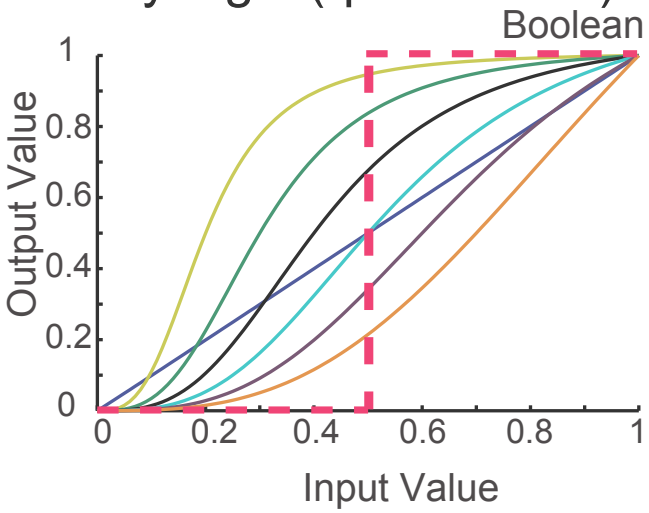


sync. dynamics

Camille Terfve

Aidan MacNamara

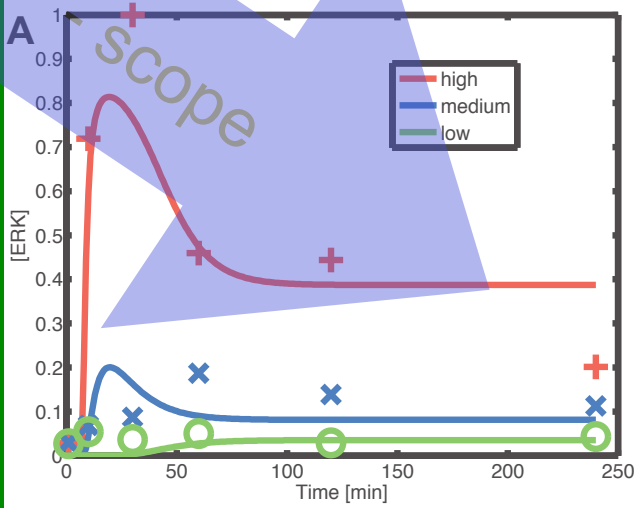
Fuzzy logic (quantitative)



Morris et al., PloS Comp Bio 2011

Logic ODEs (dynamic)

+ scope

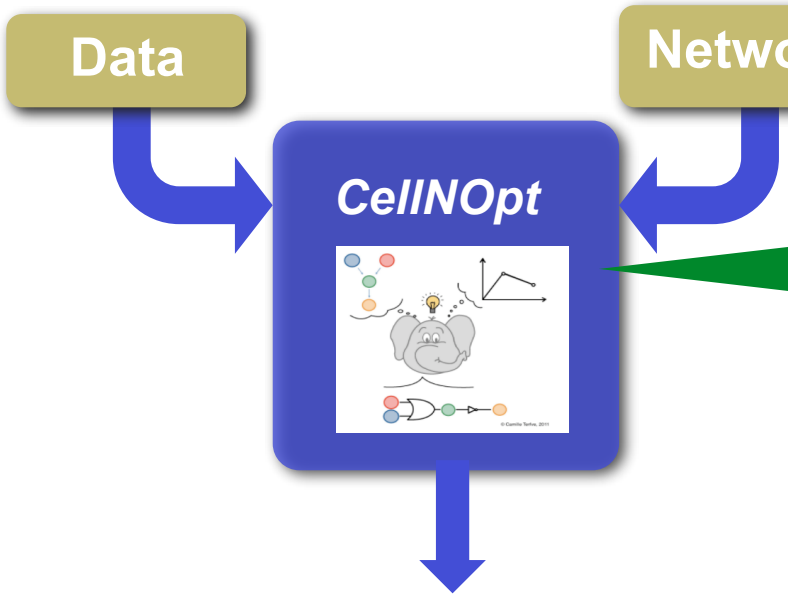


Wittmann et al. BMC Sys Bio 2009

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

David Henriques

CellNOpt: Fitting to data is an optimisation problem that we solve with different methods



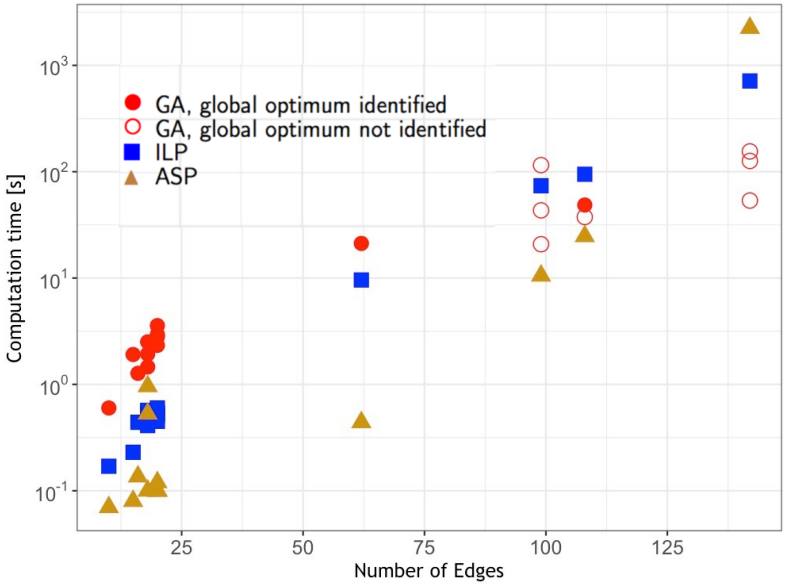
Learning algorithms (optimization):

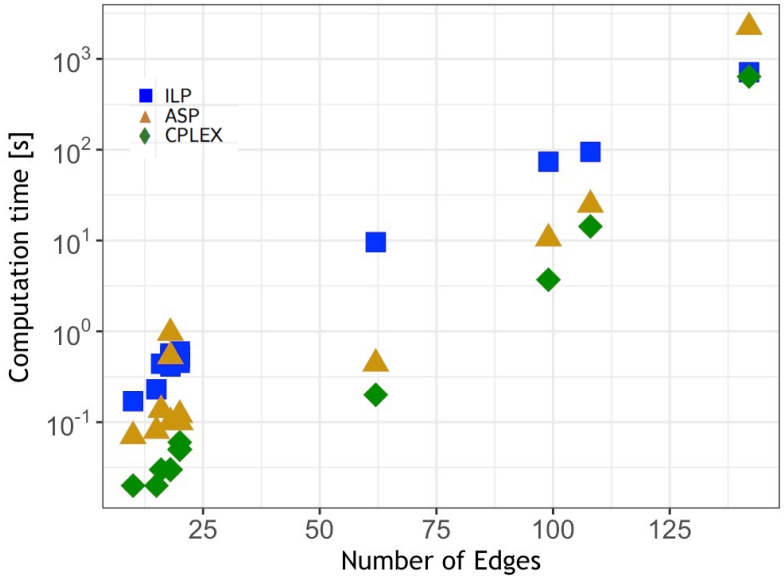
- Metaheuristics & Bayesian Inference (MCMC) (Egea et al. *BMC Bioinf* 2014; (Henriques et al. *Bioinf* 2015)
- Ensembles of models (Henriques et al. *PLoS CB*, 2017)
- Use of Answer Set Programming (Guziolowski et al. *Bioinf* 2013, Videla et al. *Bioinf* 2017) and Integer Linear Programming (Mitsos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

New CellNOpt features

- New extended features of CellNOpt
  - **CNO-ILP (ILP implementation of CellNOpt)**
  - **Feeder (applied on boolean and dynamic modelling)**
  - CNOProb (quantitative analysis while retaining computational efficiency)
  - CellNOpt-MaBoSS (asynchronous update strategy with optimisation strategy to train the boolean logic models)
  - Post-hoc systematic analysis (analysis of the reliability of the parameters)

Reasons to use CNO-ILP





Suitable for obtaining family of models with guaranteed optimality (when/if reached)

Suitable for the boolean modelling of big PKN's

Retrieving family of models within a certain tolerance from the optimality and constrained model size

Dealing with incomplete prior knowledge

CNOFeeder: Link CellNOpt to methods to infer new links

Combining PKN with databases of interactions

New updates on **CNOFeeder** allows the inference of new links while doing dynamic analysis of the networks

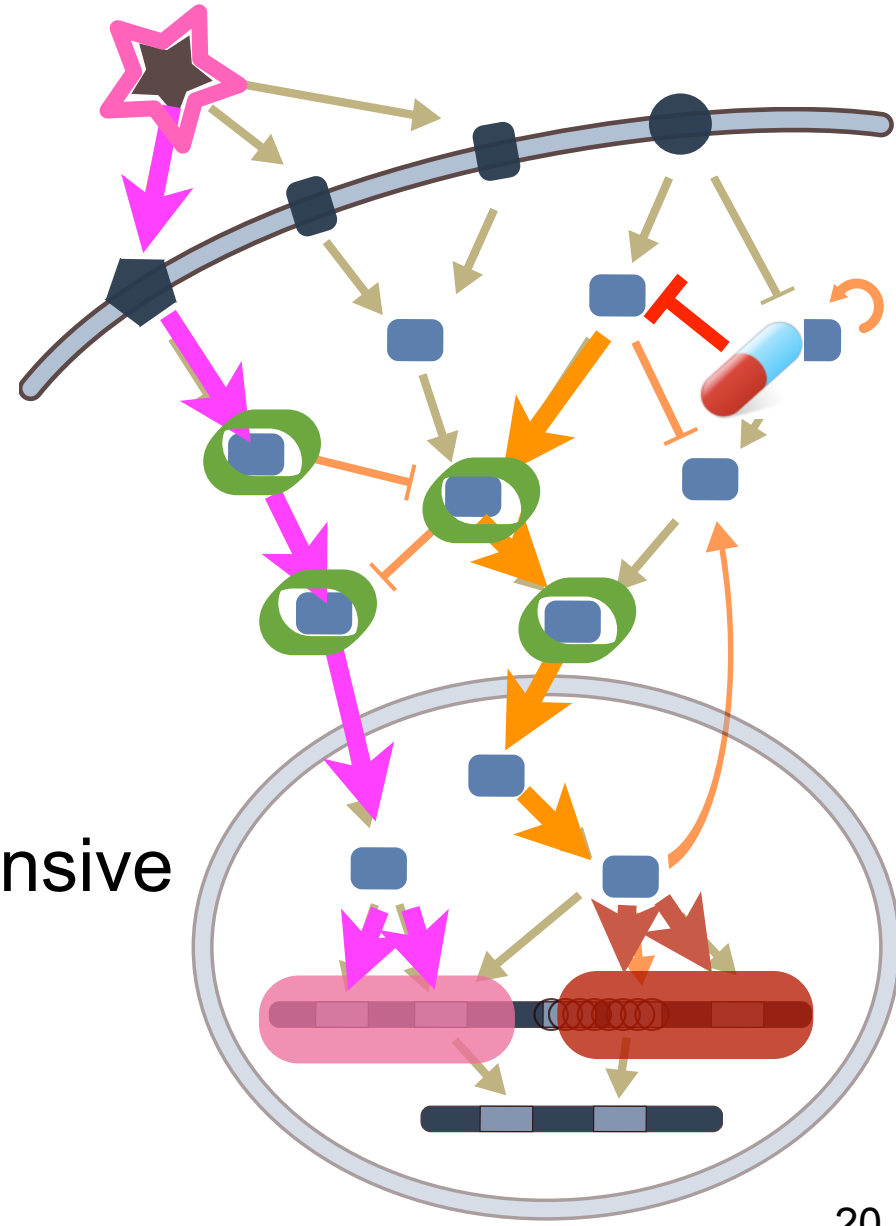
Building causal and dynamic network models from perturbation data

Perturb cells
with drugs and/or ligands
and measure

→ gene expression changes

→ (phospho)proteomics

Proteomic platforms are expensive



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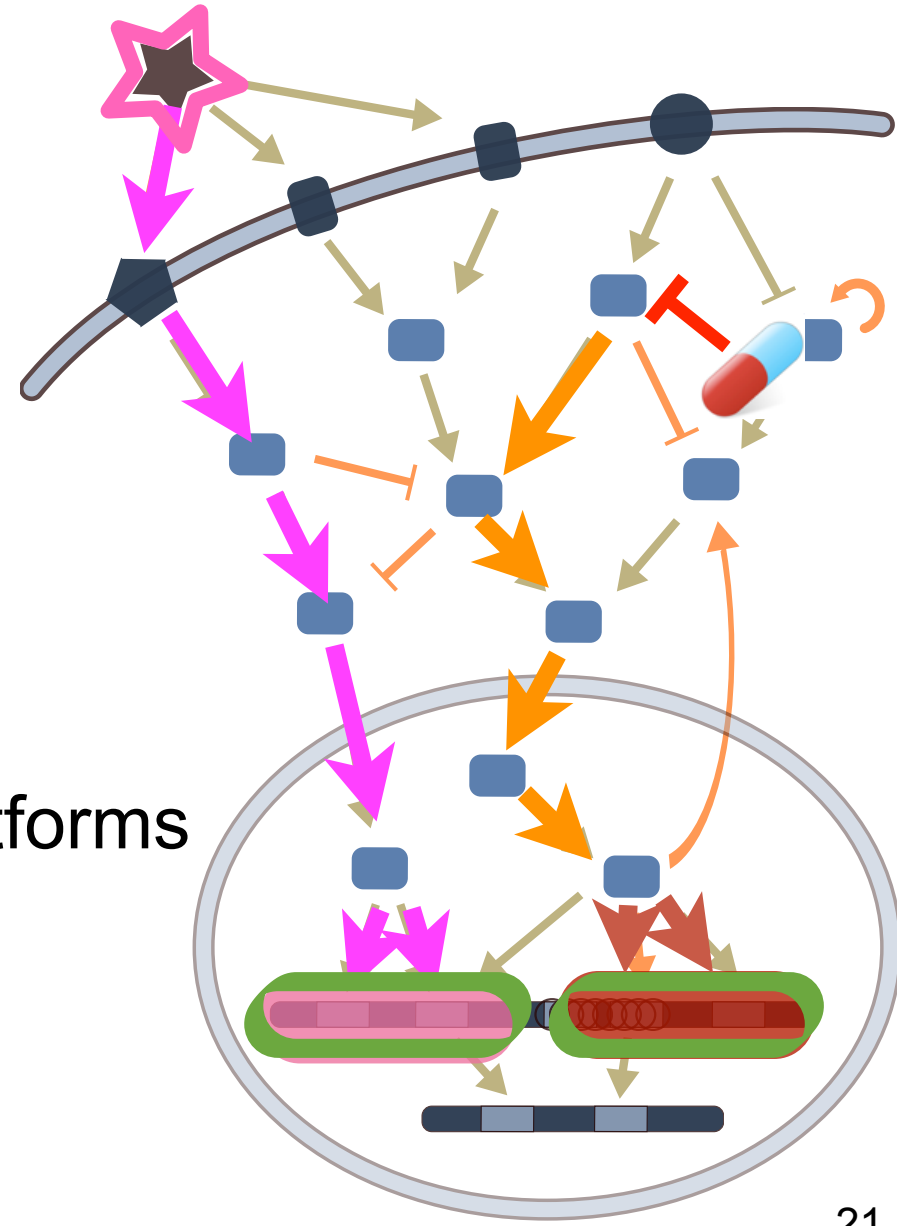
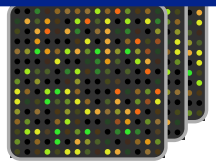


Can we leverage cheaper platforms to do modelling ??

CARNIVAL: CAusal Reasoning for Network Identification using Integer VALue programming

Transcriptomic



Data

Networks

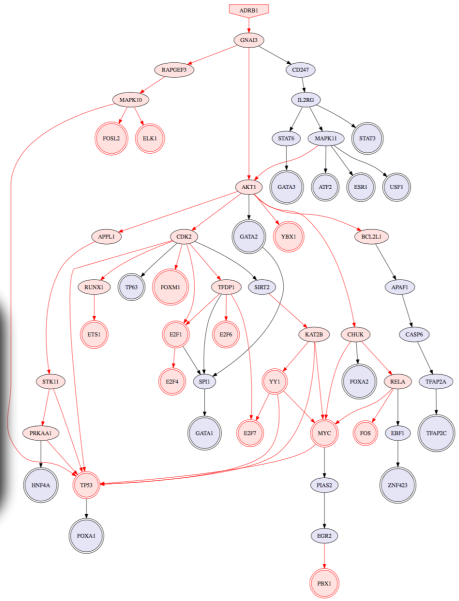
Omnipath

CARNIVAL

Nodes	Activity
ATF2	1
E2F1	-1
E2F4	-1
E2F6	-1
E2F7	-1
ELK1	-1
ESR1	1
ETS1	-1

predicted protein activities

Computable Model specific to data (cell/conditions)



optimised network

Coming soon at saezlab.github.io/CARNIVAL/

Take home messages..

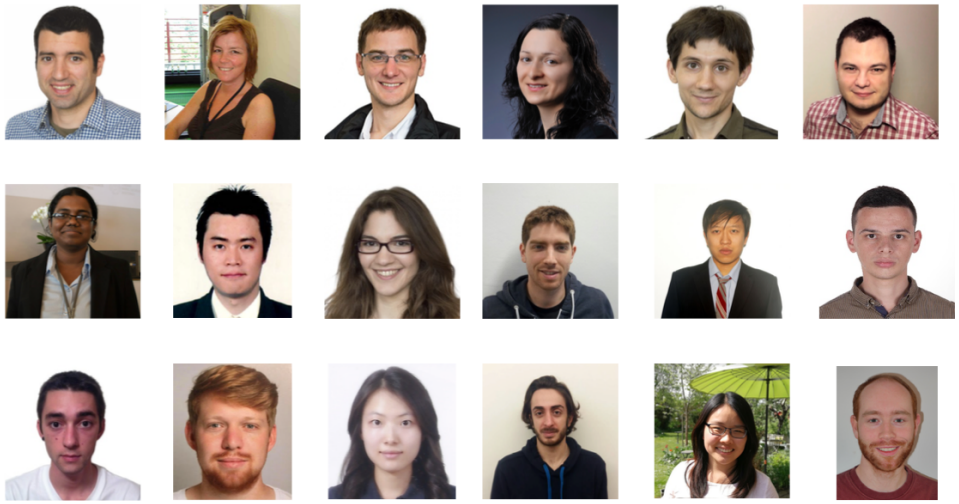
- Which is the family of best model solutions? How do we know they are *the best*?
  - ILP & ASP (Caspo) methods can help
- Is my prior knowledge complete? How well is this system studied and can I rely on current knowledge?
  - *Feed* what might be missing
- Signalling networks from RNA-seq gene expression data?
  - CARNIVAL

Acknowledgements

PhD or **Postdoc** position at *saezlab*

Saez-Rodriguez group, specially:

Panuwat Trairatphisan
Attila Gabor
Aurélien Dugourd



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Funding: