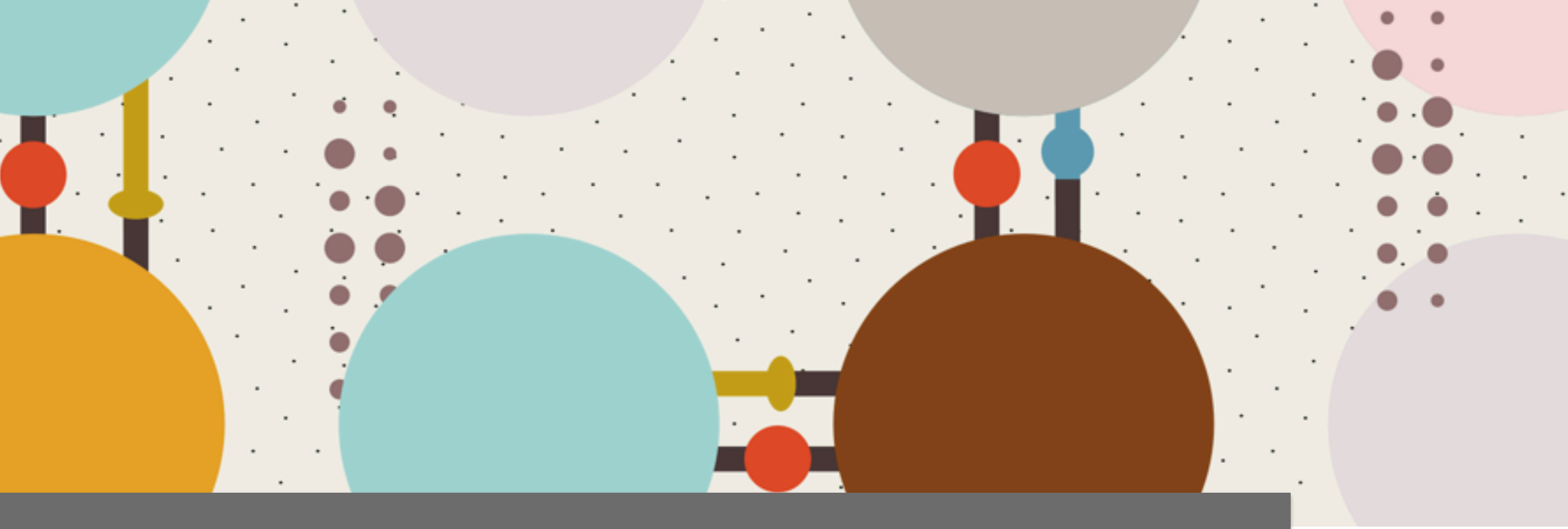

IO17 | Large Scale Bioinformatics for Immuno-Oncology

Modeling cell-type specific pathways with CNORode: example with Leukemia

Francesca Finotello, Federica Eduati, and Pedro L. Fernandes

GTPB | The Gulbenkian Training Programme in Bioinformatics
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INSTITUTO GULBENKIAN DE CIÊNCIA

T-cell large granular lymphocyte (T-LGL) leukemia

Cytotoxic T lymphocytes (CTL) are normally activated following these steps:

1. expansion of antigen-specific CTL clones and their acquisition of cytotoxic activity
2. activated CTL population undergoes activation-induced cell death (AICD)
3. stabilization of a small antigen-experienced CTL population

In leukemic **T-cell large granular lymphocytes (T-LGL)** there is:

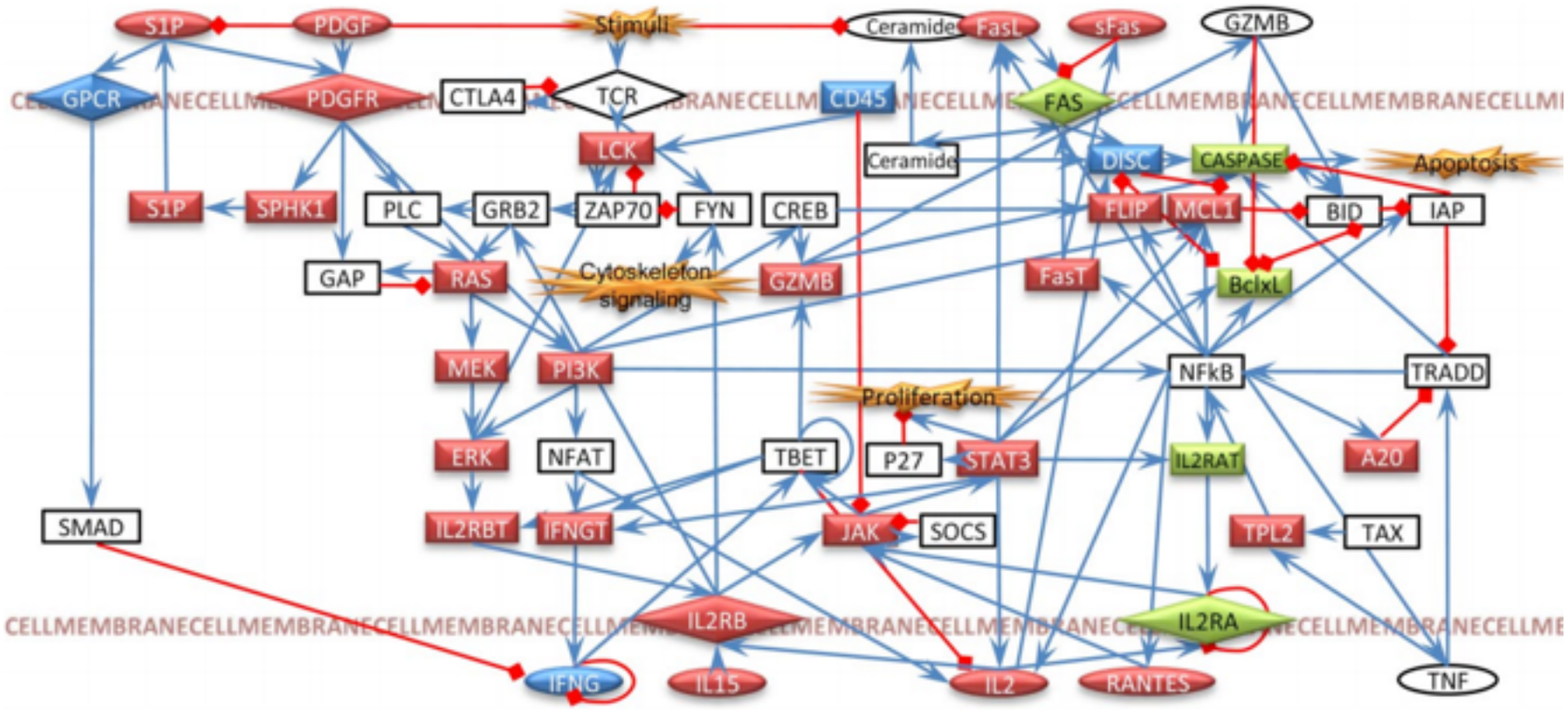
1. abnormal clonal expansion
2. escaped AICD
3. remain long term competent

survival
proliferation ↑

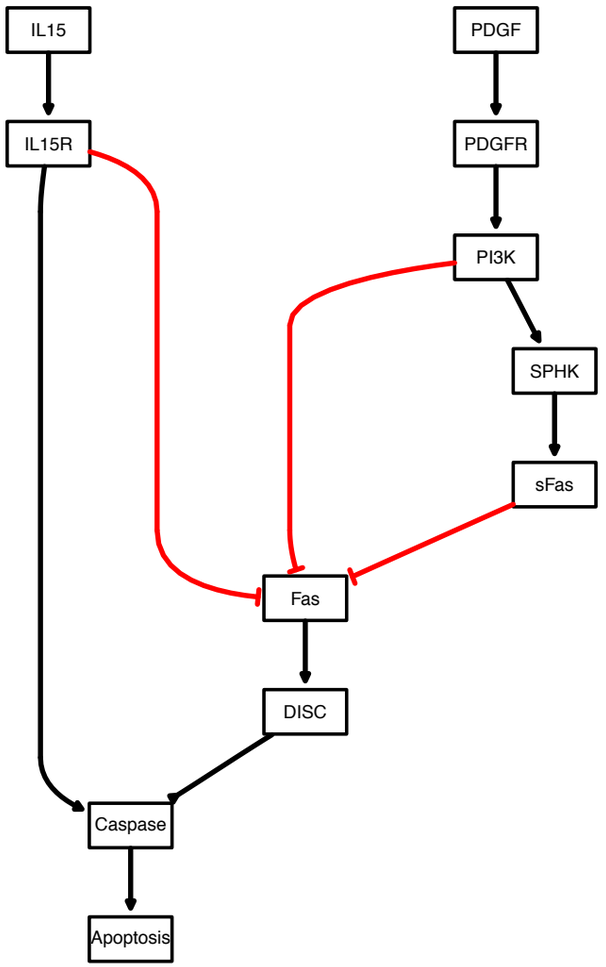
apoptosis ↓

T-LGL survival signaling network

Full network from R. Zhang, et al. PNAS, 2008

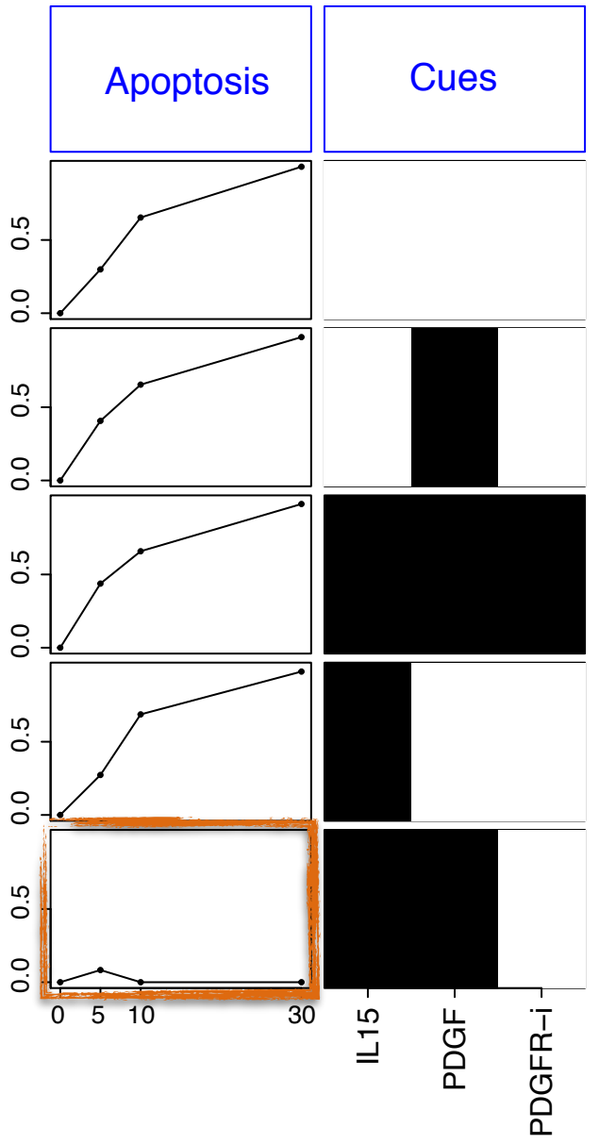


Simplified network for exercise

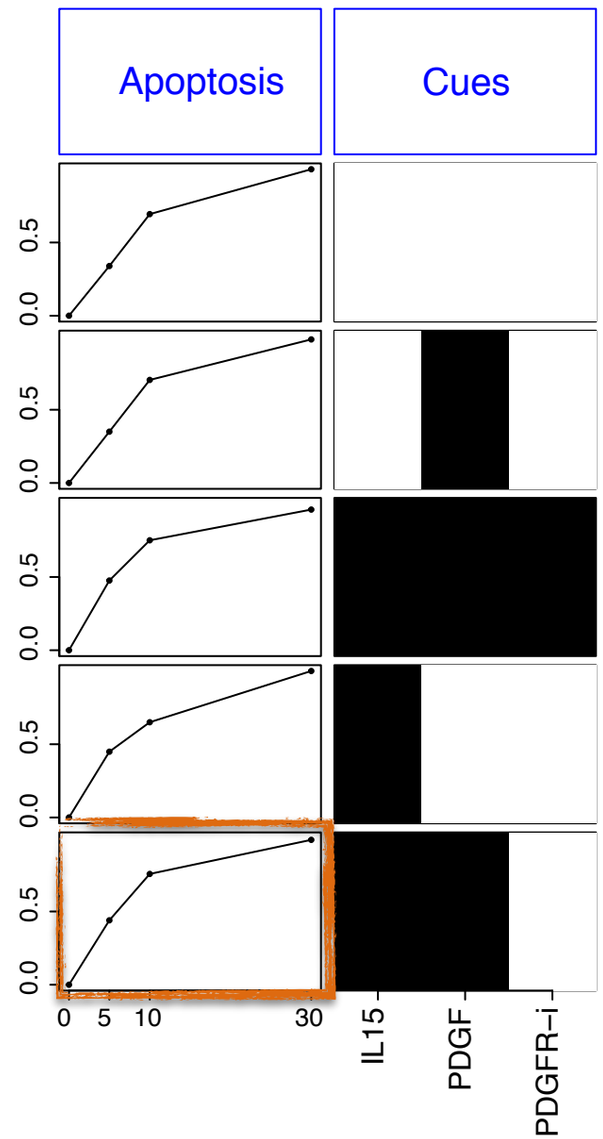


Perturbation data

T-LGL



CTL

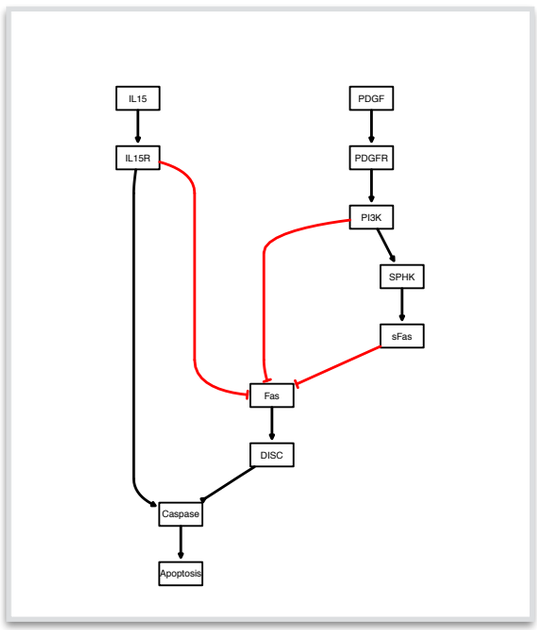


With sustained IL15 and PDGF signals, leukemics T-LGL evades apoptosis

R. Zhang, et al. PNAS, 2008

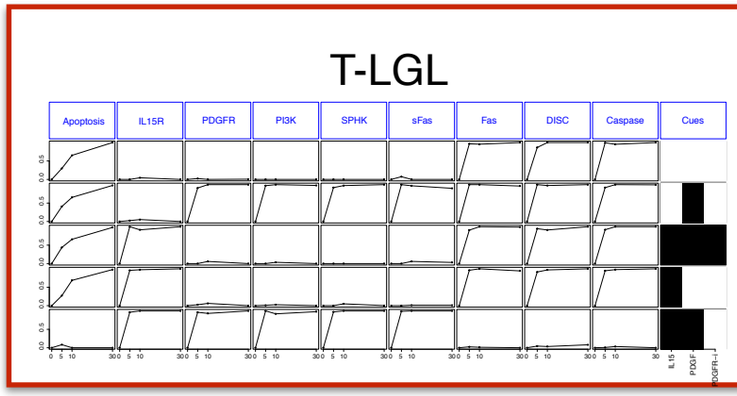
Aim of the exercise

curated
Prior Knowledge Network (PKN)

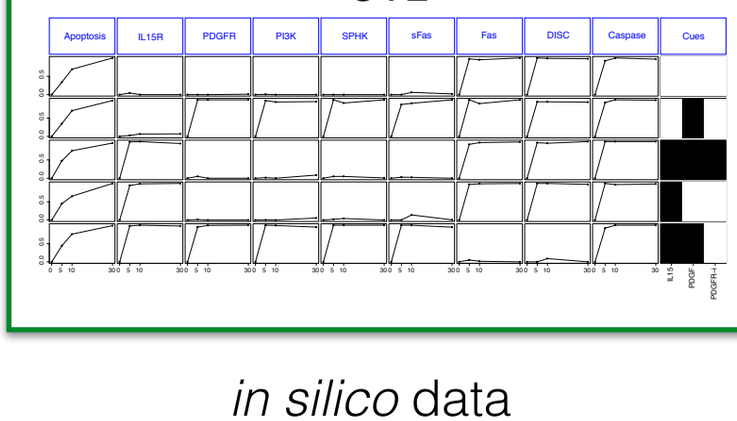


cell-type specific
perturbation data

T-LGL



CTL

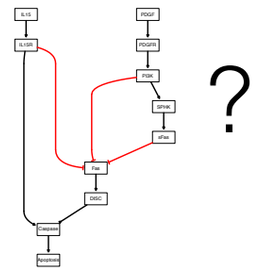


in silico data

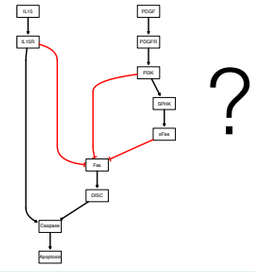
CNORode

cell-type specific
models

T-LGL



CTL



predictions

T-LGL

?

CTL

?

Import data

1. Load in R the functions and settings necessary for the exercise:

```
library(CellNOptR)
library(MEIGOR)
library(CNORode2017)

load("optimisation_parameters.RData")
```

Important note: libraries should be loaded in this exact order, make sure to restart the R session before starting the exercise

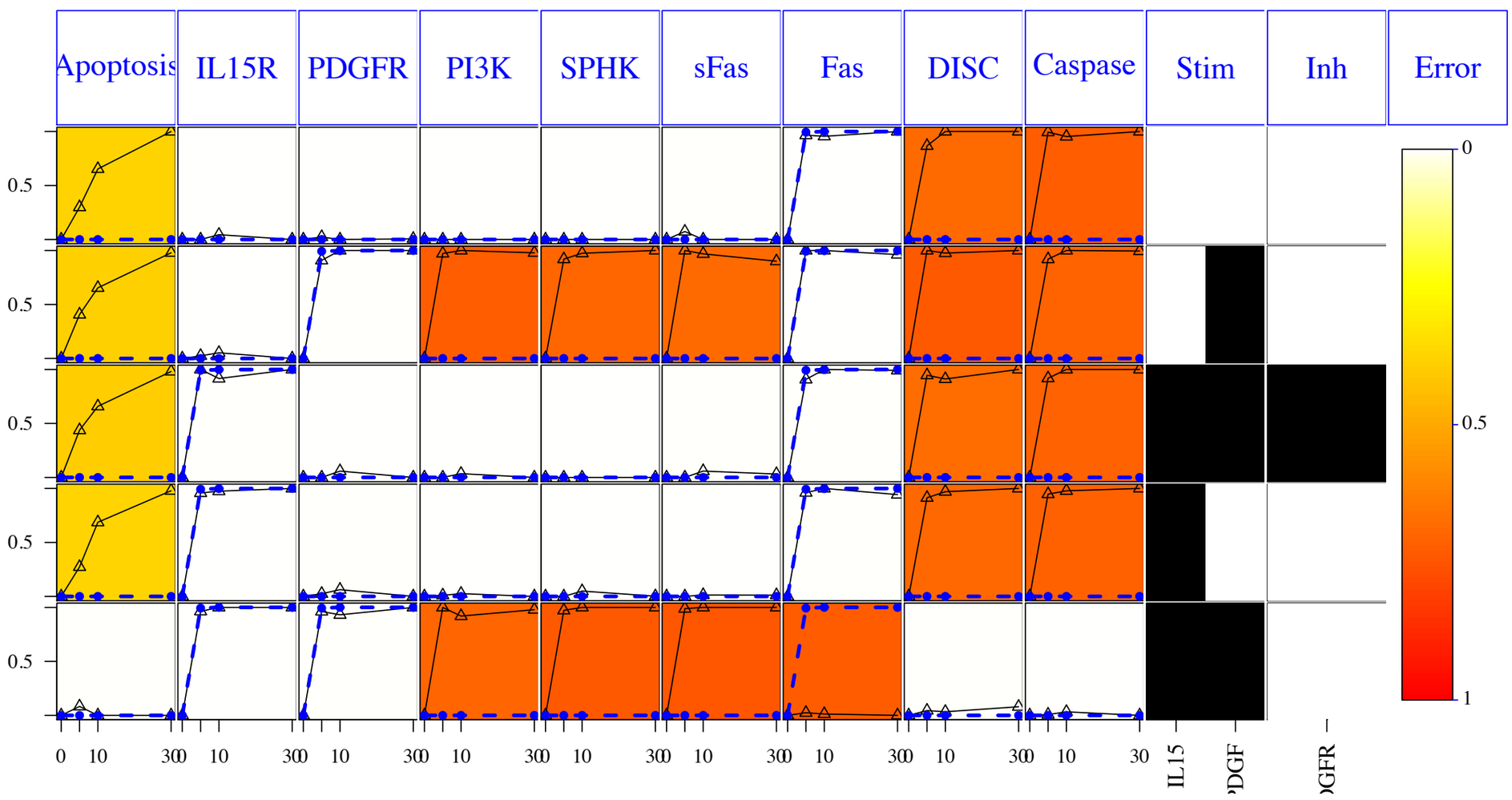
2. load the prior knowledge network (PKN) and plot it

3. load the data for the leukaemia (T_LGL) cells and plot them

Data simulation for T-LGL cells

4. Simulate data using the initial parameters guess:

```
simulated_data_T_LGL_initial_parameters=plotLBodeFitness(cnolist = cnolist_T_LGL,
                                                         model = pknmodel,
                                                         transfer_function=paramsSSm$transfer_function,
                                                         ode_parameters=initial_parameters)
```



Parameters need to be refined to fit the data!

Model optimisation for T-LGL cells

5. Optimise the model

```
optimized_parameters_T_LGL=parEstimationLBode(cnolist_T_LGL,
                                              pknmodel,
                                              method="essm",
                                              ode_parameters=initial_parameters,
                                              paramsSSm=paramsSSm)
```

6. Plot the model fit to the data using the function *plotLBodeFitness* and the optimised parameters from point 5.

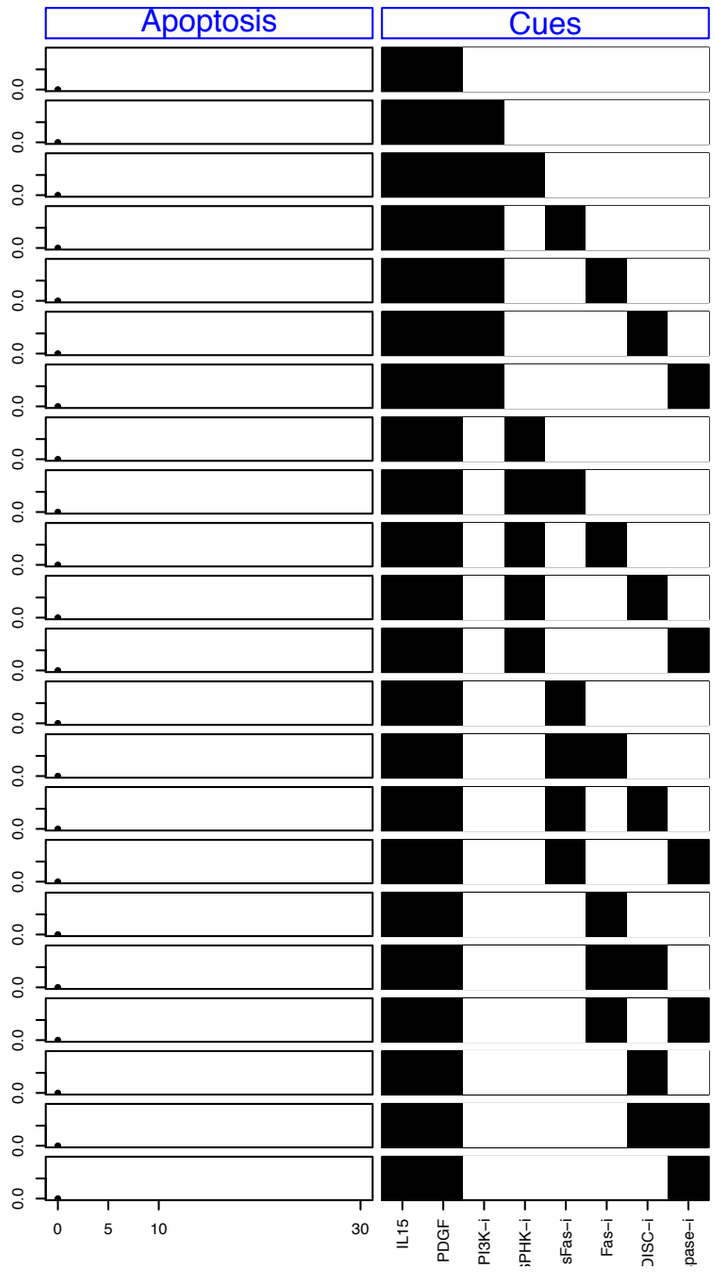
Model optimisation for CTL cells

7. Repeat points 3-6 using data for CTL cells

Prediction of different experimental conditions

8. Load and plot the scaffold for the data to predict

```
data_predictions<-readMIDAS(MIDASfile="MIDAS_predictions.csv")
cnolist_predictions<-makeCNOlist(data_predictions, subfield=F)
plotCNOlist(cnolist_predictions)
```



9. Simulate data using the optimised parameters both for T_LGL and CTL

Hint:

- use *plotLBodeFitness* function with the appropriate cnolist and optimised parameters

How to access the questions on Socrative

1. Access Socrative with student access at: https://b.socrative.com/login/student/
2. Join the IO17 room

3. Enter your name and click „done“ to start the quiz