We will train our static network using phosphoproteomic perturbation training data to produce a Boolean network (BN) compatible with the network. This can be done with either a heuristic approach through software such as CellNoptR [ 23079107] and Optimusqual [27716031], or via answer set programming (ASP) as applied in Caspo **[**23853063]. The former method trains the static network with a genetic stochastic optimization algorithm to best describe the existing data. Optimusqual requires an additional input of essential nodes that are either related to important biological processes or are potential readout nodes. It is unique in that it combines information on both network dynamics and equilibrium properties to generate an asynchronous BN. However, these heuristic approaches do not guarantee the global optimum BN because they do not search the complete solution space as ASP does [<https://arxiv.org/pdf/1210.0690.pdf>]. Taking that into consideration, we will use Caspo to train our static network as it uses ASP to exhaustively enumerate candidate BNs. This software compresses the static network to simplify its structure and generates a set of candidate BNs that are compatible with the static network. Normalized experimental observations are compared to Boolean predictions by calculating MSE. Networks are then optimized first to minimize MSE and second to minimize size [23853063], [28065903].

23079107: <https://bmcsystbiol.biomedcentral.com/articles/10.1186/1752-0509-6-133>

27716031: <https://bmcbioinformatics.biomedcentral.com/articles/10.1186/s12859-016-1287-z>

30372442: <https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1006538>

23853063: <https://academic.oup.com/bioinformatics/article-lookup/doi/10.1093/bioinformatics/btt393>

28065903: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5351548/pdf/btw738.pdf>

**Option 1: CellNOptR [** 23079107**]**

Input: Time series phospho proteomics data in MIDAS format, PKN as a sif file

Output: BN

Method: Heuristic approach, uses stochastic optimization algorithms (in particular, a genetic algorithm), to find the Boolean logic model compatible that can best describe the existing data.

Downside: lack of guarantee of optimum intrinsic of stochastic search methods

**Option 2: optimusqual [**27716031**]**

Input: PKN, training set with each node defined by a perturbation (0 or 1) and an observation (list of nodes and their corresponding state measured at equilib after the perturbation) which will be turned into a transition graph by the program, set of essential nodes (important in biological process or are readouts)

Output: BN

Method: find model network that reproduces all experiments in the trainind set but model network must be a sub-graph of the PKN. Uses a genetic algorithm heuristic approach. combines information on both the dynamics (time series) and equilibrium properties (steady states) of the networks,

Benefit:  asynchronous dynamics

Downside: not ASP- no gaurentee to find all attractors

**Option 3: Caspo-ts [**30372442]

Input: PKN, times series phosphoproteomic data

Ouput: BN

Method: ASP; candidate BNs are exhaustively enumerated containing essential nodes (can be limited to a fixed number of BNs). Applies an over-approximation constraint to remove BNs not resulting in an over-approciamtion of the reachability between the Boolean states from training data. Optimize to select BNs with minimal distance between the actual time series and the over-approcimated time series via the RMSE objective function. After ASP solving, we have model checking where true positive BNs are detected from the list generated from ASP. These TP Ns are guaranteed to reproduce the binarized trajectories under all perturbations by verifying exact rachability in the BN state graph. Done with Computational tree logic (CTL)

Benefit: ASP gaurentees finding optimal solutions

Notes: independent of update schedule

ASP tools allow handling complex preferences and multicriteria optimization, guaranteeing the global optimum by reasoning over the complete solution space.