Multi-formalism training of Logic models with Integer Linear Programming

Enio Gjerga[1], Julio Saez-Rodriguez[1,2]

[1]RWTH Aachen University, Faculty of Medicine, Joint Research Centre for Computational Biomedicine (JRC-COMBINE), Aachen, Germany

[2]European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), Hinxton, UK

Post-translational modifications of proteins are an important factor for the regulation of cellular processes. Mass Spectrometry analysis of proteome modifications offers huge potential for the studying of how protein inhibitors affect the phospho-signalling mechanisms inside the cells. We have recently proposed PHONEMeS which is a method that handles high content shotgun phosphoproteomics data (Terfve et al. 2015). PHONEMeS is used to build logic models of signal perturbation flow while in its original implementation was computationally demanding and only used in a perturbation context. We have reformulated PHONEMeS as an Integer Linear Problem (ILP), that is orders of magnitude more efficient than the original one, while at the same time enabling more complex analysis on many more contexts besides just perturbation. Such contexts include: **1.** For perturbation data, the efficient modelling of activated signalling pathways downstream an inhibited target kinase; **2.** An approach for modelling of regulated pathways involving certain identified activated proteins through kinase enrichment analysis methods (upstream and downstream the active kinase). **3.** Analysis of time-point datasets, which helps us obtain a better insight of the dynamics of the propagation of signals. We illustrate the value of the new approach on various data sets of medical relevance where we shed light on signalling mechanisms and drugs mode of action.