

***In silico* knockout experiments based on Petri net models**

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The knockout analysis is a worthwhile method to observe the effect of a specific protein on the systems behavior. Mathematical modeling provides the possibility for *in silico* knockouts. Often only a small fraction of knockout results obtained from a systematical *in silico* knockout analysis was experimentally investigated. Besides the standard Petri net analysis techniques, such as covered by transition invariants, and the biological interpretability of each transition invariant [1], *in silico* knockout experiments are useful for model verification and experiment planning.

We developed a new tool called SiKnock to perform and visualize *in silico* knockout experiments. Based on Petri net models we introduce a new concept of *in silico* knockout analysis to ensure the correct prediction of the systems behavior. SiKnock provides single, double, and multi knockout analysis, visualizes the results as a knockout matrix and provides a graphical user interface. We applied the method to study the autophagic degradation pathway of the pathogen Salmonella Typhimurium. We compared the knockout results with published knockout or knockdown experiments and ensured the biological correctness of the model structure. We found knockout behavior known in literature and generated new hypotheses for experiments, for example, knocking out the autophagy receptor NDP52 (nuclear dot protein 52 kDa) predicted no influence on the recruitment of OPTN (optineurin) to ubiquitinated Salmonella Typhimurium.

References

[1] Koch I, Reisig W, Schreiber F. (2011). Modeling in systems biology: the Petri Net approach (Vol. 16). Springer Science & Business Media. Germany.