Computational Modeling and Simulation of the Human Apoptosis Signal Transduction Network

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Understanding the mechanism by which the all-or-nothing decision in a single cell whether to stay alive or enter the Apoptosis (programed cell death) is a central problem in the field of cancer research. A multitude of signals from different sources related to cell growth, homeostasis and also Apoptosis are being integrated and thus processed. The hope is to elucidate the structure of the Apoptosis signaling network of healthy and cancer cells to find the mechanisms which enable the latter to ignore apoptotic signals. Ultimately a way to induce Apoptosis selectively only in cancer cells is envisioned as therapy. Definition of suitable computational methods for modeling and especially simulation of signaling networks is an open and challenging task. This is because of the large number of entities which are involved and for which the experimental quantification of interactions has not been done in a exhaustive manner to be able to use established methods.

We are modeling a key segment of the Apoptosis signaling network consisting of pro- and anti-apoptotic members of the Bcl-2 protein family proposing a coarse-grained semi-quantitative approach based on the Petri net formalism. To compensate for the incomplete characterization of all relevant interactions we propose as parameterization of our models a data integration approach including expression data from microarray experiments, quantitative proteomics data and affinity assay data.

The exact mechanism of how different Bcl-2 proteins interact with each other and with proteins of the BH3-only family is still not fully established whereas there are different hypotheses actively discussed in the literature. We propose computational models for the three main network variants aiming to assess validity by comparison of the corresponding simulation results with experimental results.