

Poster: Efficient Analysis of Multi-level Biological Systems Using Abstraction

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In silico models are important to facilitate protocol design in medical research. We are interested in TRAIL, a promising molecule for therapeutic treatment of cancer. It is a natural activator of the apoptosis pathway in cancerous cells. Our goal is to optimise the dosage and frequency of TRAIL for effective treatment, which is made complex due to temporary TRAIL resistance of cells that have already been treated with TRAIL [1]. To model tumor growth and decline under treatment, one needs to reason at different levels. First, at tissue level, a model of the natural growth of a tumor (without treatment) and a model of diffusion for TRAIL are needed. Many models for tumor growth have been developed, for instance [2]. Then, at the cellular level, a model of the action of TRAIL on each cell is needed to know the probability with which each cell will die or survive, according to its proteome. TRAIL induced apoptosis pathway models have been developed, in particular for HeLa cells [1]. Last, at molecular level, genes can be activated or inhibited, changing the proteome [3].

Handling detailed models at each level for thousands of cells is computationally very intensive. Instead, we propose abstractions made at all those levels to test a large number of protocols in a reasonable amount of time while not losing too much accuracy. The goal is to be able to test different dosages of TRAIL treatments on high-level abstractions, and then refine the number of protocols based on the results and test the most promising ones on more detailed models.

At the molecular level, [3] provides an efficient abstraction of the gene expression with minimal parameters. At the cellular level, we abstract the apoptosis pathway as a Dynamic Bayesian Network (DBN) [4]. It produces a stochastic distribution of key proteins of the pathway and reasons about cell death. At the population level we represent the whole tumor as a succession of spherical layers, associated with a discretized concentration of cells and a stochastic distribution of key proteins. The growth model is built by drawing statistics over a more detailed model such as [2].

References

1. S. Spencer, S. Gaudet, J. Albeck, J. Burke, P.K. Sorger: Non-genetic origins of cell-to-cell variability in TRAIL-induced apoptosis. *Nature* 459: 428-432, 2009.
2. B. Waclaw, I. Bozic, M. Pittman, R. Hruban, B. Vogelstein & M. Nowak: A spatial model predicts that dispersal and cell turnover limit intratumour heterogeneity, *Nature* 525, 261-264, 2015
3. F. Bertaux, S. Stoma, D. Drasdo, G. Batt: Modeling dynamics of cell-to-cell variability in TRAIL-induced apoptosis explains fractional killing and predicts reversible resistance. *PLoS Comput Biol.* 10(10):e1003893, 2014.
4. B. Liu, D. Hsu, P.S. Thiagarajan: Probabilistic approximations of ODEs based biopathway dynamics. *Theoretical Computer Science* 412: 2188-2206, 2009.