Exploration of apoptosis signaling in cancer biology using models as programs.

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***Short Abstract* — Apoptosis is an essential process of programmed cell death that takes part in organism regulation and homeostasis. Most cancer types exhibit avoidance of apoptosis at some stage during disease progression. In this work we focus on the instantiation of multiple hypothesis derived from experiments, using PySB -- a model-programming framework -- to study apoptosis regulation. We focus on the interactions between events at the cue level and the accompanying signaling events leading to mitochondrial disruption. We focus on the complex interactions among the Bcl-2 family of proteins that regulate the disruption process. Experimentally derived data has been used to calibrate, test, and probe multiple models conforming to current consensus mechanistic hypotheses. We show that model analysis of these mechanisms provides insights into the interactions among and between regulation checkpoints. We highlight the use of a programming-based modeling framework that makes the present work accessible to a wide range of modeling tools.**

***Keywords* — apoptosis, rules-based modeling, models as programs, executable models, multi-model inference, and sensitivity analysis.**

I. Purpose

In this work we aim to understand how biochemical interactions propagate the apoptosis signal from the initial ligand cue to the eventual apoptosis response [1]. About half of the observed cancer phenotypes exhibit apoptosis irregularities which result in continued survival of tumorigenic cells and avoidance of programmed cell death [2]. In addition, novel anticancer drugs aim to induce apoptosis as a method of cancer treatment. It has also been shown that treatment of cells with both apoptosis-inducing ligands and chemotherapeutic agents could be a successful cancer therapy further emphasizing the need to better understand the biochemical mechanisms leading to apoptosis.

II. Approach

The assembly of the DISC and activation of initiator caspases is the first step of regulation in the extrinsic apoptosis process [3]. The consensus understanding of the DISC assembly mechanism involves the congregation of twelve proteins that are in turn responsible for the activation of initiator caspases. The signal then must progress past a second point of regulation, which consists of the interactions among the Bcl-2 family of proteins leading to MOMP. The Bcl-2 family of proteins comprises three subgroups, namely anti-apoptotic proteins, the pore-forming proteins, and the sensitizer proteins, all of which are involved in intricate interactions that prevent or lead to MOMP [4]. Despite the current understanding of the processes, much of the biochemical mechanistic detail is debatable both at the level of DISC and MOMP regulations and at the level of the communication between these two regulation checkpoints [5-7].

Using PySB, we have developed a set of model families to describe the interactions among the Bcl-2 proteins at the MOMP level. We probe the proposed direct, indirect, and embedded model topologies from the literature and show the likelihood of each model explaining the observed data from experiment [8-10]. We complement with this work with an expansion of the DISC level regulation with a more detailed description of the assembly of death receptors and their transduction of the signal to the MOMP level. We show how these interactions among the MOMP checkpoint and DISC checkpoint lead to eventual release of Cytochrome C and activation of the effector caspases in cells. Exploration of the model parameter and topology spaces is also discussed as an essential part of understanding both model topologies and model parameter space. Finally we show how family of models emerges from multiple hypotheses and how multi-model inference can be developed as a tool to capture important events in signal regulation.

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