Approximating the dynamics of the Hybrid Stochastic-Deterministic Apoptosis pathway

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1 Motivation

Modeling and analysis of the dynamics of biological systems while accounting for single cell fluctuations is important. In particular, Bertaux et.al [1] considered an improved hybrid stochastic-deterministic model of TRAIL induced apoptosis. TRAIL is a protein that is known to induce apoptosis in cancer cells and hence has been a target for several anti-cancer therapeutic strategies. Their model combines a deterministic signal transduction model (modeled as ordinary differential equations (ODEs)), as in the original model of [3], and a stochastic model for protein turnover (factoring cell-to-cell variability). Using this low level biochemical model, they were able to explain fractional killing and predicted the time dependent evolution of cell resistance to TRAIL.

While this model is extremely useful for analyzing TRAIL induced apoptosis by drawing simulations in a single cell setting, it can be limiting in cases when we want to analyse the system in a multi-scale setting (say modeling a spheroid of thousands of cells at a larger time horizon for clinical trials). In such cases, simulating the original model can become extremely time consuming due to the scale of the resultant system. Instead, one could directly approximate the dynamics of the underlying system as an intermediate level behavioral model and use this approximation.

In this direction, Bing et.al [2] proposed a Dynamic Bayesian Network (DBN) model as a probabilistic approximation of ODE dynamics. They discretize the value space (∼ 5 values per variable) and time domain of the different species of a system of ODEs, sample a representative set of simulations of the system and use the structure of the pathway to store them as a DBN. Once the DBN is constructed, efficient Bayesian inference methods are used to analyze the system.

Our work in this poster presents initial work on extending and improving the work of Bing et.al [2] for the hybrid stochastic-deterministic (HSD) models, and in particular the one of TRAIL induced apoptosis.

2 Results

We extend the method of [2] to HSD model, and propose several improvements. First, the model describes a population of cells with non deterministic behavior (unlike [2] where outcomes are deterministic). Additionally, simulations in the
current setting may be truncated due to cell death. Last, some molecular species interact with many (∼10) different species.

The latter presents challenges pertaining to maintaining and working with large conditional probability tables. In [2], dummy intermediate variables are introduced, approximating the conditional probabilities by splitting the dependencies. Instead, we use an improved sparse matrix representation to encode these conditional probabilities (filling around 600 non null entries among ∼510), allowing us to scale the system even when a variable has many direct dependencies.

We also improve the naive simulation based inference of DBNs which was inefficient for the current setting. First, 99% of the samples hit an empty conditional probability entry and hence these samples are discarded. Further, every working sample (1% of all samples) ends up simulating a cell that died (giving 0% survivors compared to ∼30% survivors of the original hybrid model). We propose a new algorithm which simulates the underlying DBN by looking ahead one time step and factoring this information to avoid empty probability entries. This considerably improved the simulation based inference of DBNs with 80% effective samples and the expected ∼30% survivors.

We produced several DBNs corresponding to a treatment with 250 ng/ml TRAIL by simulating the hybrid model. We found a very good agreement between the cell death distribution of the original model and the DBN, as well as for the marginal distributions of other variables.

3 Perspectives and future work

Our goal with the current work is to build a minimalist discrete approximation which faithfully captures the underlying dynamics of the HSD model with the objective of using it in a multi-scale setting. The current work is ongoing and we are performing several improvement on the following lines. We are working on using information theoretical approaches (such as mutual information) to decide the connectivity of the DBN. This will help reduce the number of connections as well as number of variables (so far we use the one of the original model), while accurately describing the underlying dynamics. We are also designing inference algorithms to compute the probability distributions given by a DBN that is fast and accurate, by improving existing algorithms such as Factored Frontier (FF), Hybrid FF and Boyen Koller.

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References