Drug Target Interaction Prediction using network information

Radhika Saraf

Texas A&M University

saraf.radhika@tamu.edu

December 5, 2018

Problem Definition and Significance

- **The overall goal is to identify the mechanisms of action of drugs used in osteosarcoma treatment.**
- To predict targets of the drug Cryptotanshinone.
- To estimate the efficacies of different drug combinations on osteosarcoma cell lines.

Why osteosarcoma?

- Osteosarcoma is a cancer of the bones that are undergoing growth.
- It has a complex biology and traditional models do not satisfactorily represent it.
- Natural compounds seem to be more effective in treating the cancer.
- Predicting the efficacy of different drug combinations will help development

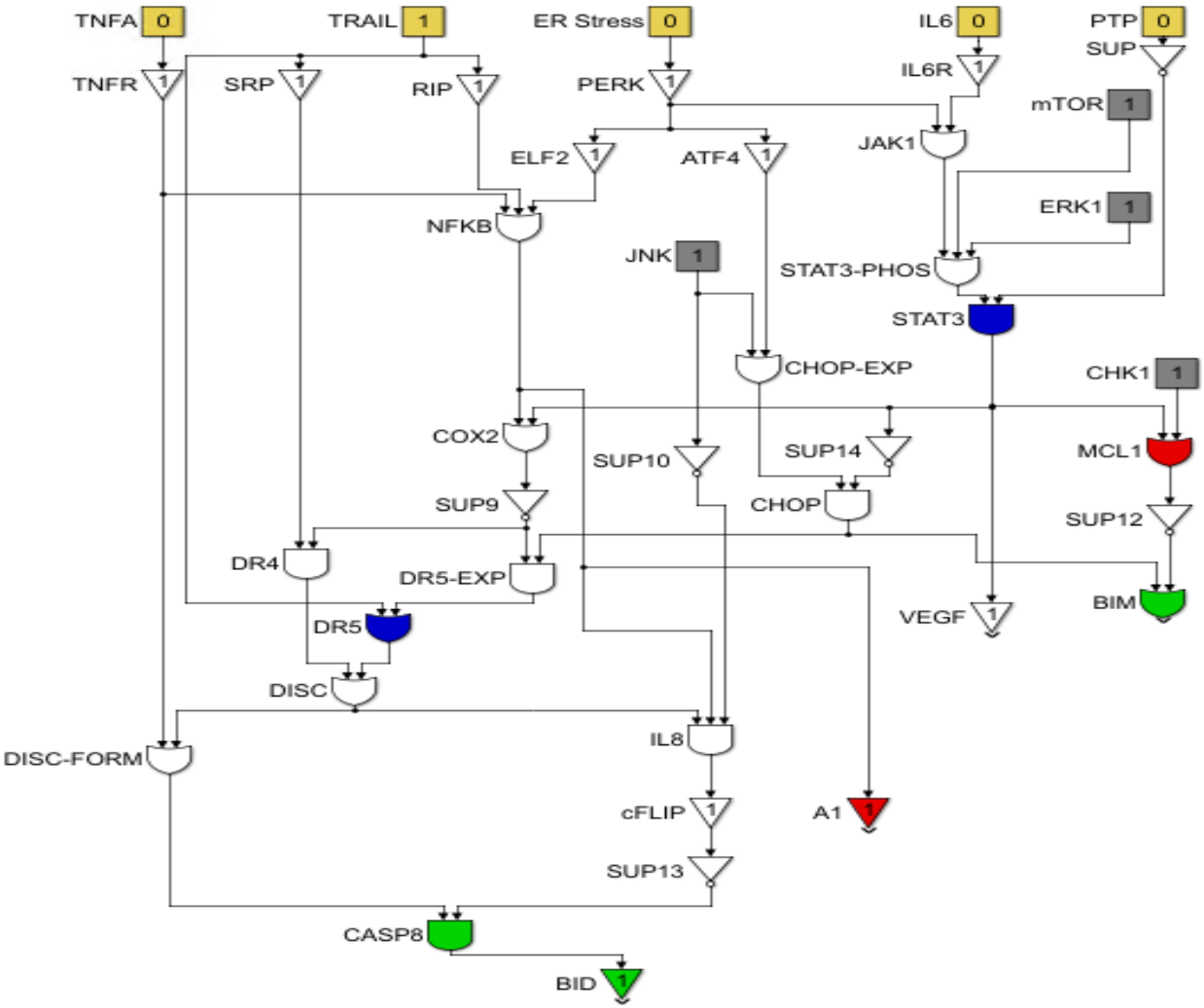
Current methods

- Biological experiments such as gene silencing investigate **limited combinations** of drugs and targets.
- **Fewer data instances** discourage methods such as Bayesian networks.
- Exhaustive search among a large number of candidate genes **without complete knowledge** of system motivates machine learning and deep learning methods.

Methods - Boolean Modeling

1. curate information from individual biological experiments
2. construct a Boolean network representation of osteosarcoma
3. calculate **apoptotic fraction** - weighted average of apoptotic genes, where drug is input

Extrinsic Apoptosis Pathway



Methods - Drug Target interaction

1. collect datasets used in DTINet *Luo et. al 2017*
2. add data about herbal drugs
3. construct a heterogeneous network with features : side-effects, protein-affinity
4. calculate similarity matrices
5. obtain a compact feature representation - diffusion component analysis
6. perform matrix completion

Methods - Inductive Matrix Completion

Assume that $M = WH^T$ is low-rank where $W \in \mathcal{R}^{N_g \times k}$ and $H \in \mathcal{R}^{N_d \times k}$ are of rank $k << m, n$.
Apply the model on the interaction matrix $P \approx WH^T$, we could solve the following optimization problem:

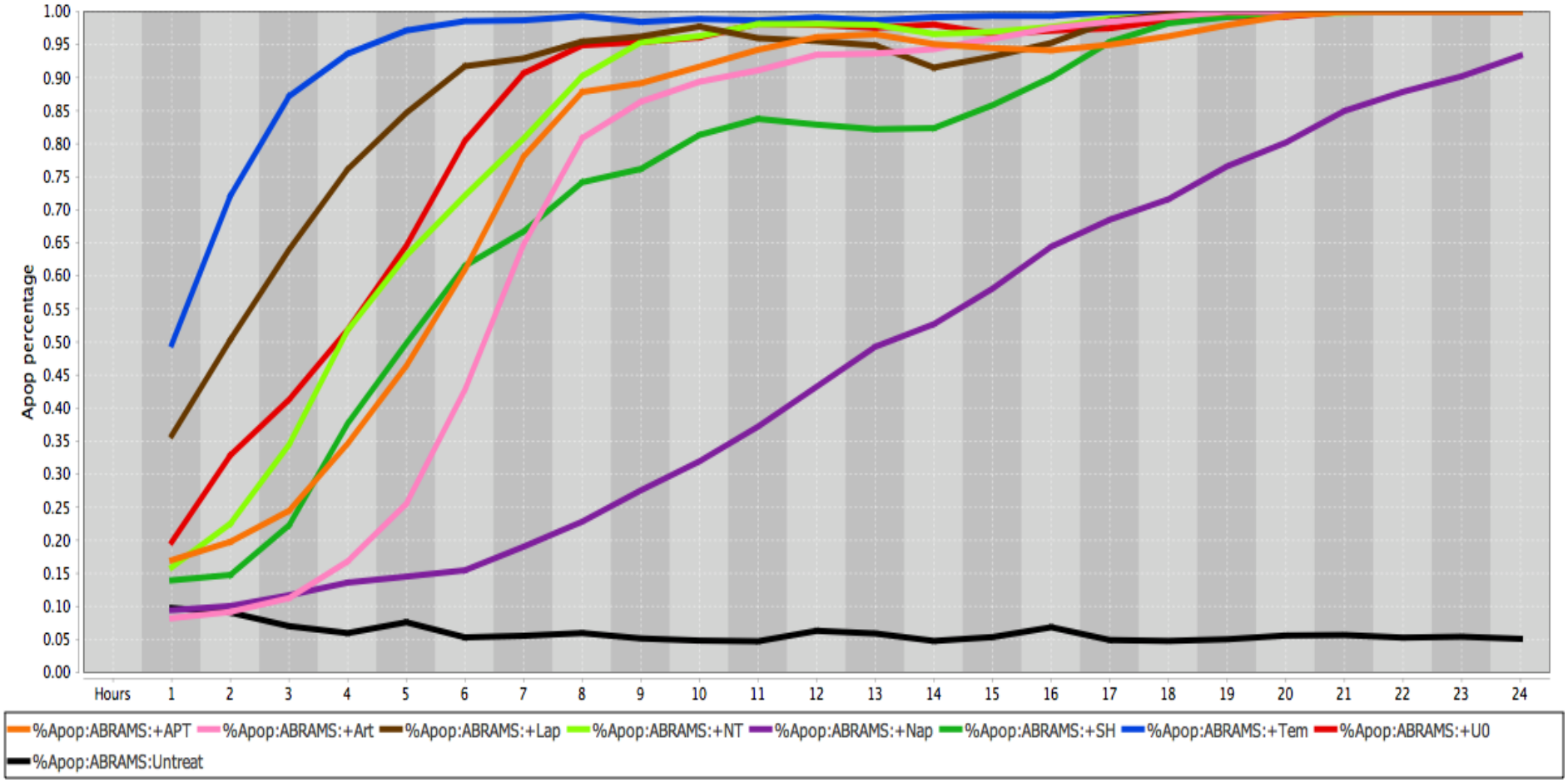
$$\min_{W,H} \sum_{i,j} (P_{ij} - W_i^T H_j) + \frac{\lambda}{2}(||W||_F^2 + ||H||_F^2)$$

Example: Recommender Systems

Evaluation

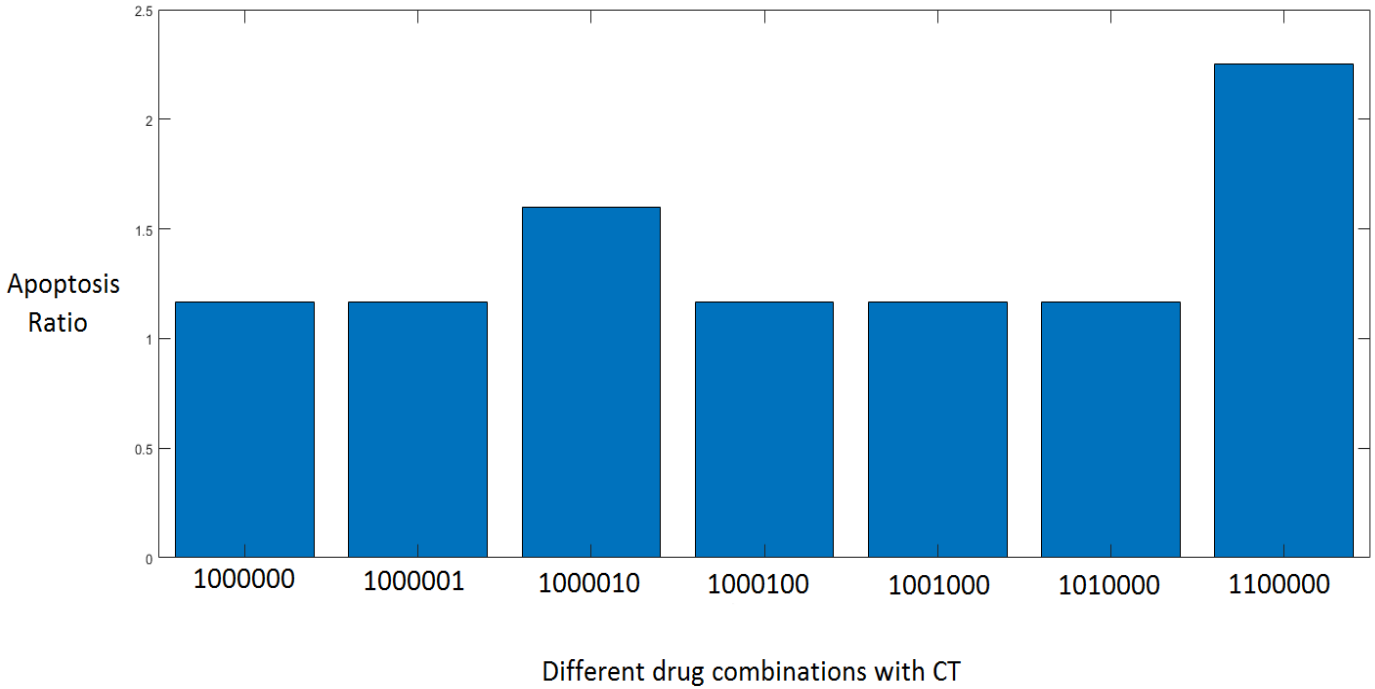
- Obtain the predicted drug target pairs
- Modify the Boolean model accordingly
- Run the simulation for all possible combinations of drugs
- Compare with the experimental results

Experimental Results



Current Results

- IMC results are not accurate yet - failed positive control
- Boolean network results based on theoretical assumptions :



Observations, Insights, and Future Directions

- The information about herbal drugs is not complete
- Use of NaN instead of zero to reduce bias during matrix completion
- Use newer methods with superior feature learning

Thank you!