Combining topological priors with gene expression and interaction data for the inference of gene regulatory networks

Sumeet Agarwal
IIT Delhi
Reverse engineering the circuitry of biology

- Biological cells are essentially bags of interacting genes/proteins, which combine to carry out the various processes of life.

- Given experimental data about how the concentration levels of proteins respond to various kinds of stimuli, can we try to recover the relationships of regulation and control between different genes/proteins?

- This can be thought of as learning the structure of a dynamical system, given some input/output characteristics.

- We are looking at a range of approaches for mathematically modelling and learning these regulatory networks, such as Petri Nets, ODEs, and Markov Nets.

[http://genomics.energy.gov]
Challenges To Address

**Scientific**
- To understand cellular circuitry, we need to look at dynamics and control in the interactions between genes/proteins: not merely static networks
- Regulation and information flows; how systems-level behaviour emerges from individual components

**Technical**
- Much work on gene regulatory networks; but hard to choose from a plethora of models, as data leaves the problem underspecified
- Integrating gene regulatory networks with protein interaction networks

**Medical/Sociological**
- Feeding back into wet lab and medical applications. I plan to collaborate with experimentalists at JNU/NCBS, focusing on under-studied organisms such as the amoebiasis parasite *E. histolytica* (responsible for \( \sim 100,000 \) deaths/year)
ODE-based model

(Bonneau et al., Cell 2007)

\[ \tau \frac{dy}{dt} = -y + g(\beta \cdot Z) \]

\[ g(\beta Z) = \begin{cases} \beta Z : & \text{if min}(y) < \beta Z < \max(y) \\ \max(y) : & \text{if } \beta Z > \max(y) \\ \min(y) : & \text{if } \beta Z < \min(y) \end{cases} \]

Genes clustered first, using domain knowledge like protein-protein interactions
Edgewise priors

[Greenfield et al. 2013]
Biological network structure

Differing network features
Biological network structure

Density-controlled
Biological network structure

Size-controlled
Other modelling approaches

- Extended Petri Nets [Durzinsky et al.]
- Markov Logic Networks
- Bayesian Networks

How can prior knowledge of higher-level network structure (beyond edges) be incorporated?