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Continuous Time Markov Chain Models of Gene Regulatory Networks under the Environmental Stress of Cold Shock in *Saccharomyces cerevisiae*

In this poster, we present our recent efforts in building and analyzing a stochastic model of gene regulatory networks. The approach we have taken uses techniques of continuous time Markov chains or jump-Markov processes to model complex interactions of regulatory dynamics. This coupled with a stochastic approximation technique allowed for comparing the model to data.

Data in this poster comes from DNA microarrays measuring gene expression in budding yeast (*Saccharomyces cerevisiae*) as it responds to a cold shock environmental stress. The wild type strain BY4741 and strains deleted for the genes that encode the Cin5, Gln3, Hmo1, and Zap1 transcription factors were harvested during early log phase at 30ºC (the control condition). Cells were subsequently harvested at 15, 30, and 60 minutes after being subjected to 13ºC cold shock (the stress condition). Four to five replicates were performed for each strain and time point. Total RNA was purified from each sample, labeled and hybridized to DNA microarrays. Each cold shock time point (labeled with Cy5) was competitively hybridized with labeled aRNA from the t_0 control time point (labeled with Cy3). The orientation of the Cy3 and Cy5 dyes was swapped for two of the replicates for each strain. Within-chip normalization was conducted using the limma package in the R Statistical computing environment and chip-to-chip normalization was conducted using an in-house developed median absolute deviation scaling. These data provide gene expression levels of the cold shocked yeast relative to their expression at 30ºC.

Changes in gene expression due to cold shock are controlled by a network of transcription factors which bind to regulatory DNA sequences. A gene regulatory network for the cold shock response was constructed from a set of transcription factors that are known to regulate each other as documented in the YEASTRACT database. Transcription factors were included in the network if their target genes were enriched in a list of genes that had significant differential expression in the microarray data or if there was other experimental evidence suggesting their involvement in the cold shock response. The resulting network consists of 21 nodes, each of which represent the gene, the mRNA, and the protein transcription factor it encodes, assuming that a gene is translated into protein as soon as it is transcribed. These nodes are connected by 50 directed edges which represent the regulatory relationships, either activation or repression.

The state of each gene in the network is modeled in a discrete manner as being up-regulated, down-regulated, or unchanged under the stress condition, relative to the control condition. The states of the genes controlling each target gene, along with weighting parameters, determine the likelihood of the target making a transition from one state to another. As a complex, high-dimensional stochastic dynamical system, the model must be simulated with Monte Carlo techniques to observe and understand the output. More importantly, stochastic optimization techniques are required to compare simulations to data in order to estimate the model parameters. We will present in this poster our progress in simulation and estimation of network parameters governing *S. cerevisiae*'s response to cold shock.

This work was supported by NSF award 0921038 (KDD, BGF, KS) and the McLaughlin Chair of Biology (KDD, NAR).