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## **Dynamical Systems Modeling of the Cold Shock Response in *Saccharomyces cerevisiae***

In this poster, we describe our investigations into the dynamics of gene regulatory networks governing the response of budding yeast (*Saccharomyces cerevisiae*) to cold shock. Previously in the lab, DNA microarray technology was used to measure the effect of cold shock on gene expression. 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 30°C ( $t_0$ ) and after being subjected to cold shock at 13°C for 15, 30, or 60 minutes followed by recovery at 30°C for an additional 30 or 60 minutes. Four to five replicates were performed for each strain and time point. Total RNA was purified from each sample, labeled and hybridized to a total of 103 DNA microarrays. Each cold shock or recovery time point (labeled with Cy5) was competitively hybridized with labeled aRNA from the  $t_0$  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 spatial and intensity biases present in the microarray data arising from dye intensity and print tip variation were corrected using Loess normalization. To correct for chip-to-chip variation, median absolute deviation scaling was also performed. The R Statistical computing environment and the limma package were used for these normalizations.

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, depending on the sign of the weight of the regulatory effect.

Expression of each gene in the network was modeled by a nonlinear differential equation describing the change in expression over time as the difference between the production rate and degradation rate. The production is modeled by a sigmoid function which takes into account a weight parameter which describes the influence (activation or repression) of each transcription factor that regulates that gene, the expression level of the gene at a given time, and a constant that determines the position of the expression threshold. The degradation rates in the model were taken from Belle *et al.* (2006, *PNAS* 103: 13004–13009). The ode45 function in MATLAB was used to solve the differential equation model given a set of initial conditions. The fmincon function in MATLAB compared the model to the microarray data to find optimized weights and threshold constants by a nonlinear least squares fit criterion. We present results comparing fits derived from analyses of each strain individually with results fitting all strains simultaneously. In both of these approaches, the deletion strains are modeled by removing the gene from the dynamical system.

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