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**Annotated Bibliography**

**Title:** GRNmap Modeling of Gene Regulatory Network Dynamics Reveals Important Regulatory Relationships in the Cold-Shock Response in *Saccharomyces cerevisiae*

**Bibliography:**

Aguilera, J., Randez-Gil, F., & Prieto, J. A. (2007). Cold response in *Saccharomyces cerevisiae*:

new functions for old mechanisms. *FEMS microbiology reviews*, *31*(3), 327-341. Doi: 10.111/j.1574-6976.2007.00066.x

Aguilera et al. offer background information pertaining to the cold-shock response in *Saccharomyces cerevisiae* including an explanation of the activation and repression of certain genes in the response. Some genes are upregulated, indicating that they are vital for the adaptation of the cells to the cold environment, while others are downregulated, indicating that those genes are not necessary for the cold-shock adaptation. In addition, the review indicates the over-represented functional categories of the induced (membrane stability, etc.) and repressed genes (transcription and ribosome generation).

Cao, J., & Zhao, H. (2008). Estimating dynamic models for gene regulation networks.

*Bioinformatics (Oxford, England)*, *24*(14), 1619–1624.doi:10.1093/bioinformatics/btn246

Cao and Zhao introduce the use of non-linear ordinary differential equations (ODEs) to model feed forward loop regulatory relationships between a group of selected genes. Using expression data for the genes involved, the ODEs solve for parameter estimates relating to the regulatory relationship between the selected genes, using initial guesses which were estimated from a simulated line curve. This article offers another approach to using differential equations to model data which can be discussed in the paper.

Causton, H. C., Ren, B., Koh, S. S., Harbison, C. T., Kanin, E., Jennings, E. G., … Young, R. A.

(2001). Remodeling of yeast genome expression in response to environmental changes. *Molecular biology of the cell*, *12*(2), 323–337. doi:10.1091/mbc.12.2.323

This study conducted by Causton et al. attempts to determine the impact of various genes on the stress response in yeast cells. Using mutant Msn2/Msn4 deletion strains, the global transcriptional response of *S. cerevisiae* in response to various environmental stressors was analyzed and these genes in particular were investigated to determine their role in the general stress response. The cells were subjected to heat shock, acidic conditions, alkaline conditions, and exposure to hydrogen peroxide, salt, and sorbitol. This study offers insight into the stress response in yeast when the cells are subjected to varying environments, which can be used to introduce the general stress response and explain the importance of Msn2/Msn4 transcription factors.

Chen, K. C., Wang, T. Y., Tseng, H. H., Huang, C. Y. F., & Kao, C. Y. (2005). A stochastic

differential equation model for quantifying transcriptional regulatory network in *Saccharomyces cerevisiae*. *Bioinformatics*, *21*(12), 2883-2890. Doi: 10.1093/bioinformatics/bti415

Using stochastic linear differential equations, Chen et al. propose a model which can be used to estimate the dynamics of gene regulation over a time-course study and generate a gene regulatory network. In order to determine the transcription level of a certain gene, the model considers all of its known regulators, but, the model is limited by the fact that it does not take into account the regulatory relationship between transcription factors. This article can be discussed in relation to the GRNmap study in that the model differs from that of GRNmap in that the relationship between genes is not initially inputted into the model.

Dahlquist, K. D., Fitzpatrick, B. G., Camacho, E. T., Entzminger, S. D., & Wanner, N. C. (2015).

Parameter estimation for gene regulatory networks from microarray data: cold shock response in *Saccharomyces cerevisiae*. *Bulletin of mathematical biology*, *77*(8), 1457-1492.

This paper will offer information about the model used in the study. The model adapts a nonlinear least squares approach to the estimation of parameters through differential equations using a mass-balance ODE framework. Other parameters, such as production rate, were modeled via a sigmoidal production model. The parameter estimation was conducted through a least squares regression model, which allows for the comparison of the output with the observed data in order to quantify the fit of the model.

Hebly, M., de Ridder, D., de Hulster, E. A., de la Torre Cortes, P., Pronk, J. T., &

Daran-Lapujade, P. (2014). Physiological and transcriptional responses of anaerobic chemostat cultures of *Saccharomyces cerevisiae* subjected to diurnal temperature cycles. *Appl. Environ. Microbiol.*, *80*(14), 4433-4449.

This study discusses the impact of temperature on yeast cell growth, offering specific insight into its effect on the cell cycle. The results of the diurnal temperature cycle (DTC) set-up of the study indicate that carbohydrate concentration had a greater impact on the global transcriptional response than the temperature fluctuations. Steady-state and DTC cultures were similar physiologically, but there were only minor similarities between the transcriptomes of the DTC and cold-shock cultures.

Li, Z., Li, P., Krishnan, A., & Liu, J. (2011). Large-scale dynamic gene regulatory network

inference combining differential equation models with local dynamic Bayesian network analysis. *Bioinformatics*, *27*(19), 2686-2691. doi:10.1093/bioinformatics/btr454

Li et al. propose a different type of mathematical model which can be used to model regulatory relationships between transcription factors using a differential equation based local dynamic bayesian network (DELDBN), which uses ordinary differential equations in combination with bayesian analysis to elucidate the dynamics of gene regulatory networks. Using gene expression data from *S. cerevisiae* a GRN that was already known, they were able to compare between the results of their DELDBN and the original network. This study will offer another approach of mathematical modeling the dynamics of gene regulatory networks to discuss in the paper.

Murata, Y., Homma, T., Kitagawa, E. et al. Extremophiles: Genome-wide expression analysis of

yeast response during exposure to 4C (2006) 10: 117. doi:10.1007/s00792-005-0480-1

Murata et al. offer information about the functional categories of the consistently up- and down-regulated genes in the global stress response to temperature extremes in *S. cerevisiae*. Consistently upregulated genes during the time course of cold shock include those involved in energy and metabolism functions; such as the degradation or synthesis of carbohydrates, phospholipid and amino acid synthesis; and cell rescue, defense, and virulence; such as temperature inducible proteins (TIPs) and heat shock proteins (HSPs)..

Consistently downregulated genes included those involved in protein synthesis, binding, activity regulation, and post-translational regulation. This study will be helpful in offering previous findings on overrepresented functional categories when discussing gene ontology analysis of the present study.

Nariai, N., Tamada, Y., Imoto, S., & Miyano, S. (2005). Estimating gene regulatory networks

and protein–protein interactions of *Saccharomyces cerevisiae* from multiple genome-wide data. Bioinformatics, 21(suppl\_2), ii206-ii212. doi: 10.1093/bioinformatics/bti1133

Nariai et al. propose the use of additional data, such as protein-protein interactions and functional categories, rather than just microarray data for the generation of truly accurate gene regulatory networks. Results from the study indicate that the use of other data rather than solely the microarray data generates a more accurate GRN, with the majority of the gene regulatory relationships being found. Although this study used gene expression data from yeast cells grown in ideal conditions, the methods could be adapted for use in cold-shock experiments.

Neymotin, B., Athanasiadou, R., & Gresham, D. (2014). Determination of in vivo RNA kinetics

using RATE-seq. *Rna*, *20*(10), 1645-1652. doi: 10.1261

Our study derived production and degradation rates from the Neymotin et al. paper, which will be used to offer insight into how the rates were calculated using RATE-seq. Neymotin et al. explained that the degradation rate is proportional to the abundance of RNA and the rate of change in RNA abundance is determined using d[RNA]/dt = k - α[RNA], where d[RNA]/dt is the rate of change in abundance, k is the constant rate of synthesis, and α[RNA] is the RNA abundance where α = α(RNA) + α(growth).

Rodriguez-Vargas, S., Estruch, F., & Randez-Gil, F. (2002). Gene expression analysis of cold

and freeze stress in Baker's yeast. *Appl. Environ. Microbiol.*, *68*(6), 3024-3030.DOI: 10.1128/AEM.68.6.3024-3030.2002

Utilizing DNA microarray technology, Rodriguez-Vargas et al. found that gene expression in a quarter of the genes in the yeast genome was changed after *S. cerevisiae* cells were introduced to a cold-shock environment. In addition they explain that low temperature conditions shunts yeast cell growth, causing a decrease in doubling time. This study will be used to offer background information on the impact of cold-shock on yeast cells.

Schade, B., Jansen, G., Whiteway, M., Entian, K. D., & Thomas, D. Y. (2004). Cold adaptation

in budding yeast. *Molecular biology of the cell*, *15*(12), 5492–5502. doi:10.1091/mbc.e04-03-0167

Data from the Schade et al. study are used to derive a demo gene regulatory network on GRNsight. This study offers microarray data for the global transcriptional response of *S. cerevisiae* after cold-shock and validates the role of various genes previously determined to be part of the temperature stress response, such as TIPs and NSR1. They separate the response into the early- and late-cold shock response and determined that different genes were activated/repressed in each of the time zones.

Vu, T. T., & Vohradsky, J. (2006). Nonlinear differential equation model for quantification of

transcriptional regulation applied to microarray data of *Saccharomyces cerevisiae*. *Nucleic acids research*, *35*(1), 279-287. doi: 10.1093/nar/gkl1001

Vu et al. propose a nonlinear differential equation approach to dynamic modeling for the identification of all transcriptional regulators for a selected gene. Comparing the results with a previously proposed linear differential equation approach, Vu et al. determine that the nonlinear approach is better at predicting the regulatory relationship between selected genes and determining the intensity of the activation or repression than the linear model. This study will be used as another approach to modeling GRNs.