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Analysis of biological networks

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Adaptation of biological systems to the changing environment is mediated by networks of genes and proteins. Identifying the principles that govern the design and function of those networks is a central goal of modern research. Our lab is using theoretical and computational tools to investigate system-level properties of such networks. Wet-lab experiments are used to validate and extend theoretical results.

Important insights are obtained from the study of small and well-characterized networks. In particular, we try to understand the constraints that are imposed on the systems by its biological environment, and how those constraints are reflected in the design and function of the network. For example, we have studied extensively the network of genes that mediates the patterning of the dorsal region of the early fruit-fly embryo. This highly conserved network generates a graded activation of the BMP pathway. We have shown experimentally that this patterning event is highly robust to changes in the levels of most of the key gene components of the network. This observed robustness imposes strong constraints on the design of the network. We believe that robustness is a general design-principle of biological networks, which is essential for buffering against biological variability. A major focus of our theoretical modeling is aimed at understanding the mechanism underlying robustness, and the structural constraints imposed on the network by this design principle.

Indeed, in the context of the dorsal patterning mentioned above, we have identified theoretically the crucial properties of the network responsible for the observed robustness. For example, our robustness analysis predicts that the central morphogen (Scw) diffuses only when it is bounded to an inhibitory protein (Sog) (Fig. 1). Together with Prof. Benny Shilo, we are now validating this prediction experimentally.

A second research direction in the lab explores the genome-wide organization of the genetic network regulating gene expression. The important challenge of deriving global perspective of transcription regulation is now becoming feasible due to the revolutionary new DNA-chip technology. DNA chips experiments measure the expression levels of all the genes simultaneously, providing a panoramic view of the cellular transcription state. This technology is now being used by an increasing number of laboratories. The data that is accumulating provides numerous snap-shots of the genome-wide expression profile under a variety of conditions. One of the main challenges of modern research is to devise reverse engineering methods that will decipher the underlying genetic network from the observed expression data.

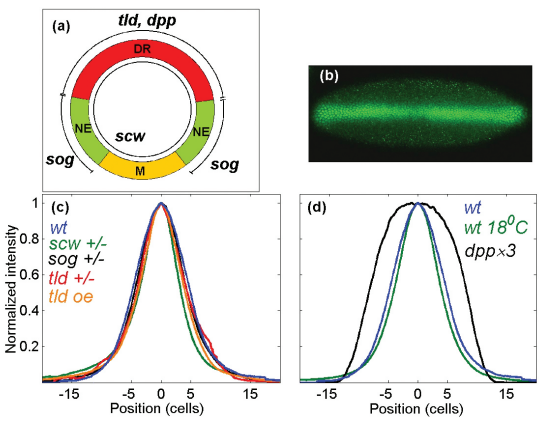

Fig. 1 *Robustness of developmental patterning: in the Drosophila embryo, the BMP activation profile is robust to changes in the gene dosage of Scw, Sog and Tld.*

We have devised a novel approach for identifying groups of genes that are co-regulated in a context-dependent manner. Our approach combines a large dataset of genome-wide expression data with additional genomic information including genomic sequence. This method was applied for decomposing the yeast genome into overlapping transcriptional modules, where each module is composed of a set of coordinately expressed genes and the experimental conditions where this co-regulation is realized. We developed novel display formats and visualization tools that allow easy access to the information derived by our analysis (Fig. 2). Comparison of global properties of the modules had identified higher order correlation between the modules, providing first insights into the global organization of the transcription regulatory network.

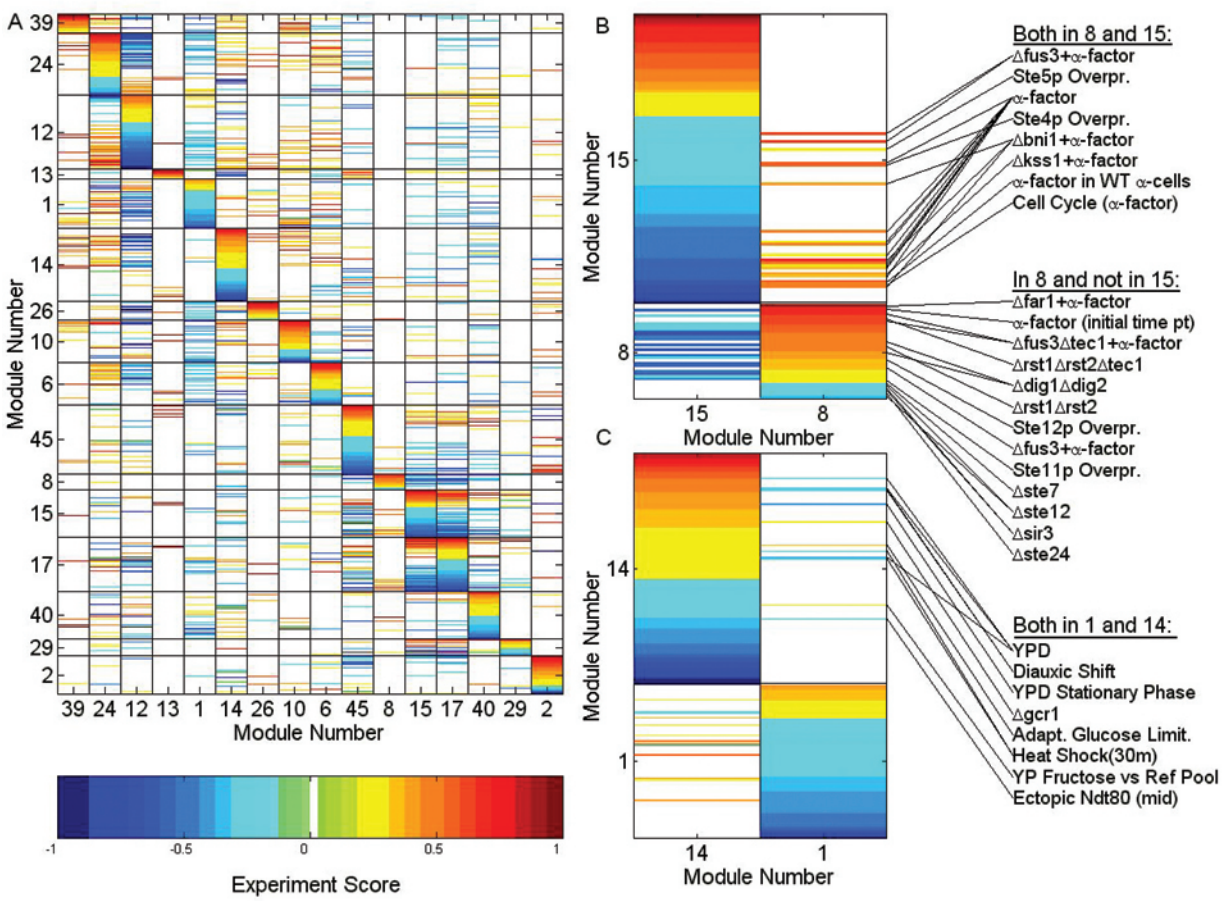

Fig. 2 *Higher order correlations between transcriptional modules composing the yeast genome.*

We have also defined novel approaches for using genome-wide expression data for identifying novel cis-regulatory elements and for identifying the genes that are indeed regulated by a specific control element. Methods were also developed which assign function to uncharacterized genes. Several predictions derived by our computational analysis are currently being tested in the lab. Finally, together with the biological services, we are setting up the ability to conduct genome wide expression measurements.

Selected Publications

Barkai N., and S. Leibler, (1997) Robustness in Simple Biochemical Networks. Nature 387, 913.

Barkai N., M. Rose and N. Wingreen, (1998) Mating in Yeast: a Role for the Protease. Nature 396, 422-423

Barkai N. and S. Leibler (2000) Circadian clocks limited by noise Nature 403, 267-688.

Barkai N., U. Alon and S. Leibler (2001) Robust Amplification in Adaptive Signal Transduction network (in press).

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