Mathematical Vocabulary for Biological Discovery

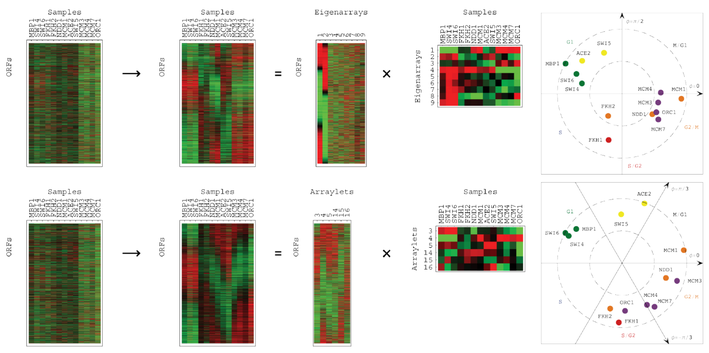
Principles of Nature from Integration and Comparison of Large-Scale Molecular Biological Data

Orly Alter

In the Genomic Signal Processing Lab, we develop generalizations of the matrix and tensor computations that underlie theoretical physics, and use them to create models that compare and integrate different types of large-scale molecular biological data, and to computationally predict global mechanisms that govern the activity of DNA and RNA, as well as disease progression, outcome and response to therapy. We believe that future discovery and control in biology and medicine will come from the mathematical modeling of such large-scale molecular biological data, just as Kepler discovered the laws of planetary motion by using mathematics to describe trends in astronomical data. Ultimately, our work will bring physicians a step closer to one day being able to predict and control the progression of cancers as readily as NASA engineers plot the trajectories of spacecraft today.

Alter, *PNAS* 103, 16063 (2006).

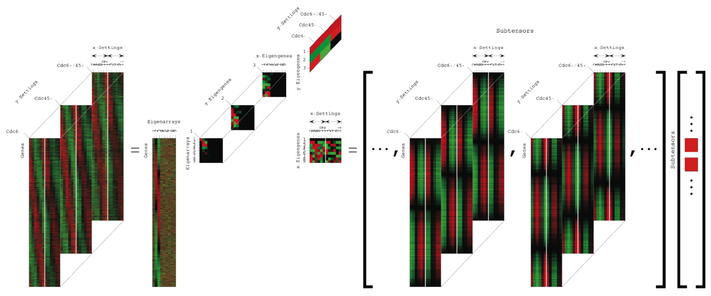
Novel Mode of Regulation from Integration of Different Types of DNA Microarray Data



With Gene H. Golub (*Stanford University*)

Pseudoinverse projection integration of yeast mRNA expression and proteins' DNA-binding predicts a previously unknown mode of regulation that correlates the activity of replication origins with the expression of nearby genes.

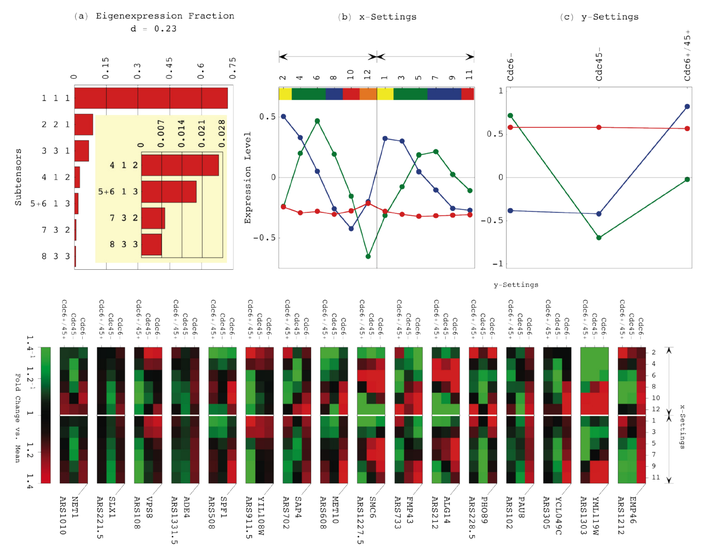
Alter & Golub, *PNAS* 101, 16577 (2004).



With Larsson Omberg (*Cornell University*)

HOSVD integration of yeast expression under different environmental conditions computationally predicts an equivalent mode of regulation.

Omberg, Golub & Alter, *PNAS* 104, 18371 (2007)

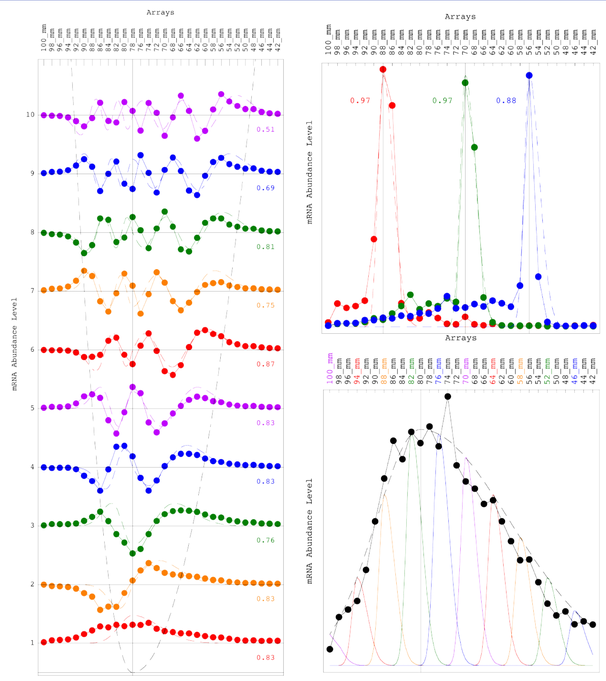


With John F. X. Diffley (*Cancer Research UK*)

Experimental results verify the computationally predicted mechanism demonstrating for the first time that mathematical modeling of DNA microarray data can be used to correctly predict previously unknown modes of regulation.

Omberg et al., *Mol Syst Biol* 5, 312 (2009).

Novel Physical and Evolutionary Principles from DNA Microarray Data



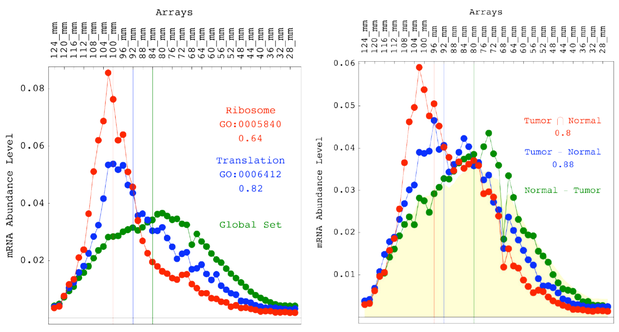
With Gene H. Golub (*Stanford University*)

SVD uncovers an asymmetric generalization of the eigenfunctions of the quantum harmonic oscillator in yeast genome-wide mRNA lengths distribution.

It follows that the transcript size distribution of each gene fits an "asymmetric Gaussian," which can be explained by a previously undiscovered asymmetry in RNA gel electrophoresis thermal band broadening.

It also follows that the distribution of the peaks of these profiles fits an asymmetric Gaussian, hinting at two competing evolutionary forces that determine the lengths of mRNA gene transcripts, which act in the manner of the restoring force of the harmonic oscillator

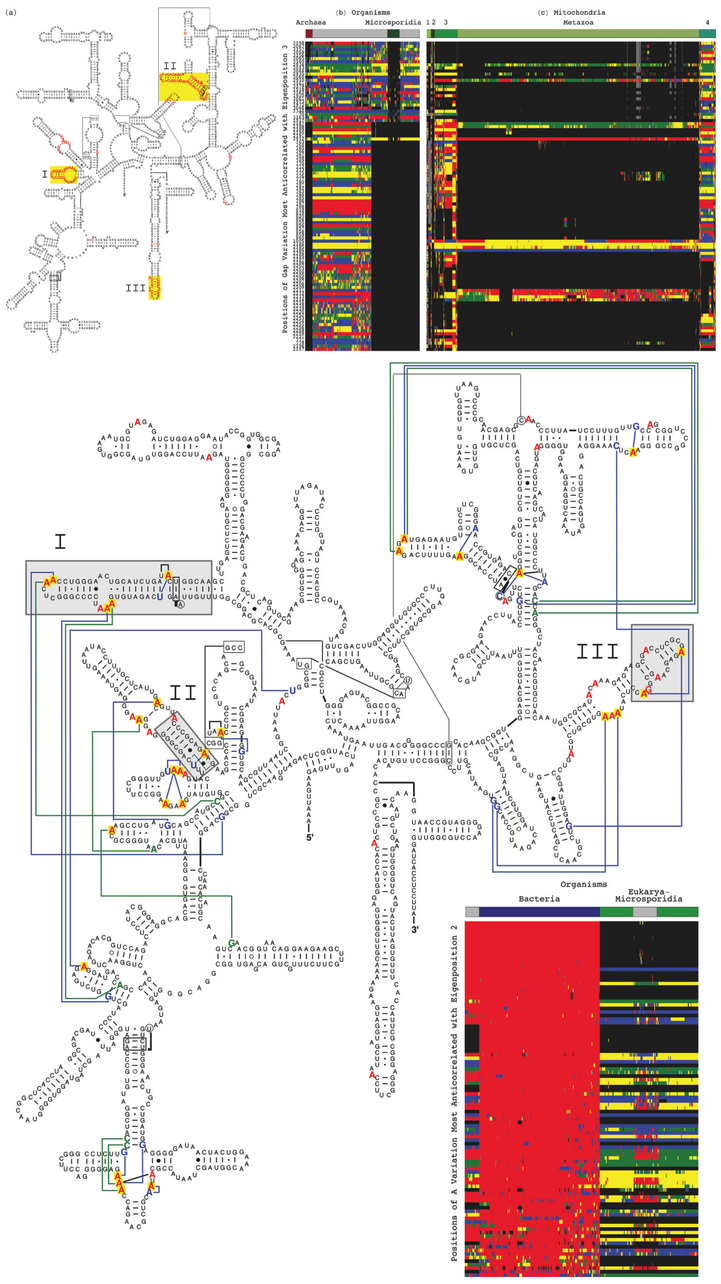
Alter & Golub, *PNAS* 103, 11828 (2006).



SVD of human mRNA lengths distribution finds that normally overexpressed, long tissue-specific transcripts are suppressed as normal tissue is transformed to tumor tissue, possibly due to evolutionary forces that act upon transcription during cancer progression.

Drake & Alter, *Rao Best Poster Prize* (2010).

Mechanisms of Evolution from Comparison of rRNA Sequence Alignments



With Robin R. Gutell (University of Texas)

We propose that even on the level of a single rRNA molecule, an organism's evolution is composed of multiple pathways due to concurrent forces that act independently upon different rRNA degrees of freedom.

Mode-1 HOSVD uncovers novel patterns of similar and dissimilar nucleotide frequency variation across the taxonomic groups and correlations with structural motifs, possibly due to previously unknown mechanisms of evolution.

Muralidhara et al., *PLoS One* 6, 4 (2010).

This research is supported by the Utah Science Technology and Research (USTAR) Initiative, National Human Genome Research Institute R01 Grant HG-004302 and National Science Foundation CAREER Award DMS-0847173, as well as Cancer Research UK and the American Institute of Mathematics (AIM).

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