

# Genetic Variation and Regulatory Networks: Mechanisms and Complexity

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Sequence polymorphisms affect gene expression by perturbing the complex network of regulatory interactions. Standard methods attempt to associate each gene expression phenotype with genetic polymorphisms. We suggest a novel computational method, called Geronemo, which aims to understand the mechanism by which genetic changes perturb gene regulation. By exploiting the modularity of biological systems, Geronemo reveals regulatory relationships that are indiscernible when genes are considered in isolation, allowing the recovery of intricate combinatorial regulation.

We applied Geronemo to a set of yeast recombinants generated by a cross between laboratory (BY) and wild (RM) strains of *S. cerevisiae* (Brem & Kruglyak, 2005), resulting in multiple novel hypotheses about genetic perturbations in the yeast regulatory network, including in transcriptional regulation, signal transduction, and chromatin modification. In this talk we will present 3 key findings:

1. A significant part of the observed expression change arises from individual genetic variation of a small number of chromatin modifying factors.
2. Our method uncovered a novel mRNA degradation mechanism that couples P-bodies and the Puf family of mRNA factors, which we validated experimentally.
3. Based on individual gene expression in rich media, we predicts sensitivity of individuals to the drug Rapamycin, which we also validated experimentally.

Joint work with Suin Lee, Aimee Dudley, George Church and Daphne Koller.