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# Integrating genetic and protein–protein interaction networks maps a functional wiring diagram of a cell

Benjamin VanderSluis[1,5], Michael Costanzo[2,5], Maximilian Billmann[1], Henry N Ward[1], Chad L Myers[1], Brenda J Andrews[2,3] and Charles Boone[2,3,4]

Systematic experimental approaches have led to construction of comprehensive genetic and protein–protein interaction networks for the budding yeast, *Saccharomyces cerevisiae*. Genetic interactions capture functional relationships between genes using phenotypic readouts, while protein–protein interactions identify physical connections between gene products. These complementary, and largely non-overlapping, networks provide a global view of the functional architecture of a cell, revealing general organizing principles, many of which appear to be evolutionarily conserved. Here, we focus on insights derived from the integration of large-scale genetic and protein–protein interaction networks, highlighting principles that apply to both unicellular and more complex systems, including human cells. Network integration reveals fundamental connections involving key functional modules of eukaryotic cells, defining a core network of cellular function, which could be elaborated to explore cell-type specificity in metazoans.

**Addresses**
[1] Department of Computer Science and Engineering, University of Minnesota–Twin Cities, 200 Union Street, Minneapolis, MN 55455, USA
[2] The Donnelly Centre, University of Toronto, 160 College Street, Toronto, Ontario M5S 3E1, Canada
[3] Department of Molecular Genetics, University of Toronto, 160 College Street, Toronto, Ontario M5S 3E1, Canada
[4] RIKEN Center for Sustainable Resource Science, Wako, Saitama, Japan

Corresponding authors: Myers, Chad L. (chadm@umn.edu), Andrews, Brenda J. (brenda.andrews@utoronto.ca)
[5] Authors contributed equally.

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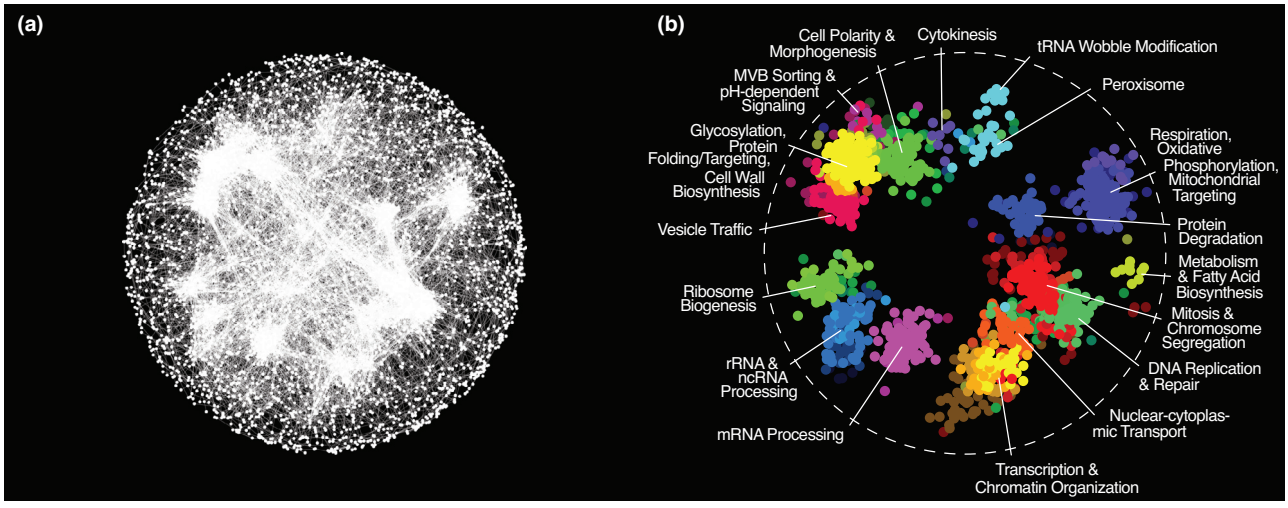
## Mapping the global yeast genetic interaction network

Genetic interactions (GIs) appear to be important for understanding the relationship between genotype and phenotype. Although technological advances have enabled large-scale, whole genome sequencing, our ability to use this growing wealth of data to predict most inherited phenotypes, remains limited. Several explanations for this underlying "missing heritability" have been proposed, and evidence suggests that a failure to account for *epistasis* or GIs may be a significant component [1,2•]. Originally, the term epistasis was coined to describe how the presence of a mutation can mask the effects of an allele at another locus. The term subsequently evolved to include GIs, in which a combination of two or more mutations yields an unexpected phenotype. In particular, GI analysis has been used productively in model system biology to provide a functional context for interpretation of biochemical experiments (reviewed in [3]).

The approach to exploration of GI networks in a particular model system depends on the ease of genetic manipulation, availability of mutant collections in a defined genetic background, and the ability to assay a phenotype in a systematic and scalable manner. GIs have been explored experimentally in several model microbial systems, including the budding yeast *Saccharomyces cerevisiae*, *Escherichia coli* and the fission yeast *Schizosaccharomyces pombe*, as well as in the *Caenorhabditis elegans* metazoan model system, cultured *Drosophila melanogaster* and human cell lines (reviewed in [3]). However, the most extensive genetic network mapping experiments have used the *S. cerevisiae* model system, which has numerous large-scale collections of gene-specific mutants as well as high-throughput genetic methodologies that enable systematic exploration of GIs (reviewed in [4]). Indeed, a global yeast network provides a general view of the vast extent to which complex GIs can influence phenotypes and the relationship between genotype and phenotype (Figure 1) [5,6••].

A widely used method for assaying yeast GIs is Synthetic Genetic Array (SGA) analysis (reviewed in [4]). SGA automates yeast genetics and enables large-scale construction and selection of yeast double-mutant strains carrying precise mutations, including double-mutant combinations of deletion alleles involving nonessential genes or hypomorphic, or partially functional, alleles of essential genes. GIs are subsequently identified by measuring double mutant fitness from high-density arrays of yeast colonies [7], and quantitative analysis enables the

**Figure 1**




Global yeast genetic interaction profile similarity network. **(a)** A global genetic profile similarity network encompassing all nonessential and essential genes was constructed by computing Pearson correlation coefficients (PCCs) for genetic interaction profiles of all pairs of genes (nodes). Gene pairs whose profile similarity exceeded a PCC $> 0.2$ were connected and graphed using a spring-embedded layout algorithm. Genes sharing similar genetic interactions profiles map proximal to each other, whereas genes with less similar genetic interaction profiles are positioned further apart. **(b)** Network regions enriched for specific GO biological process terms are colored. Adapted from [6••].

discovery of both positive and negative GIs. Negative GIs correspond to synthetic lethal or sick interactions, where a double mutant shows a fitness defect greater than the expected multiplicative effect of the combined single mutant fitness phenotypes (Figure 2a). Alternatively, positive GIs, which include masking or suppression interactions, are scored for double mutants that grow better than the expected model (Figure 2a) (reviewed in [4]). Large-scale SGA analysis of the majority of all possible yeast gene pairs (~18 million) enabled the construction of the first comprehensive GI network for any organism, a global network consisting of nearly one million GIs (~550,000 negative and ~350,000 positive) [6••,8].

## A global genetic profile similarity network defines a functional map of a yeast cell

The set of negative and positive GIs for a given gene, called a GI profile, provides a quantitative phenotypic signature that is indicative of gene function. Genes belonging to similar biological processes tend to share numerous GIs in common, and genes encoding proteins that function together in the same pathway or protein complex often display highly similar GI profiles. A comprehensive network of genes connected by edges reflecting the similarity of their GI profiles predicts gene function and serves as a powerful, unbiased data-driven resource for organizing genes into functional modules (Figure 3) [5,6••,9]. For example, at the most detailed level of network resolution, genes sharing many GIs in common are grouped together into relatively small, densely connected modules, which correspond to known protein complexes and biological pathways. At an intermediate level of network resolution, functionally-related pathway and protein complex modules are grouped together to highlight distinct biological processes. At the most general level of network resolution, bioprocess gene clusters group together into larger modules corresponding to specific cellular compartments. Thus, a global profile similarity network derived from fitness-based GIs can be used to infer protein-protein interactions (PPIs) and functional relationships between protein complexes to reveal a hierarchical model of yeast cell function (Figure 3) [6••].

## General overlap between global genetic and physical interaction networks

The genetic accessibility of the budding yeast enables not only construction of arrays of yeast mutants, but also arrays of strains carrying tagged alleles, which allowed for systematic analysis of physical interactions, including protein–protein interactions (PPIs) [10,11,12,13•] or protein–DNA interactions [14]. Because GIs capture the functional consequences of combining genetic perturbations, they are highly complementary to information derived from PPIs, which identify physical interactions among gene products. However, since the phenotypic consequence of a mutation is not constrained by physical connections, not only is the global GI network much