A Probabilistic Functional Gene Network of Worm: An Extensive and Accurate Systemic Model of a Multi-cellular Organism

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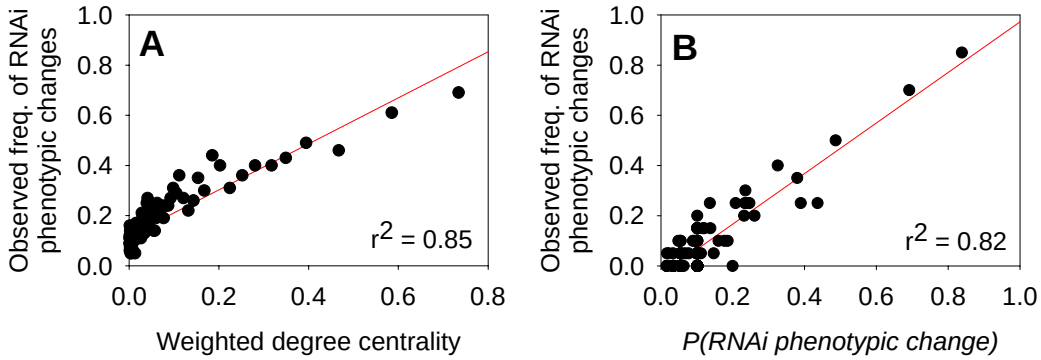
C. elegans (worm) is a powerful model organism for Systems Biology of multi-cellular metazoans, such as human. While extensive network models exist for simple unicellular model organism, yeast, the network for worm genes is still largely incomplete. Here, we present a very extensive network model of worm genes, *covering ~82% of the worm proteome* (16,113 worm proteins) with 384,700 functional couplings, and *its core set covers ~63% of the proteome (12,357 proteins) with 113,829 functional couplings.*

We constructed a probabilistic functional gene network, a modeling approach that has been successfully applied to construct an extensive network model of yeast (covering >80% of yeast proteome) [1]. For the network of worm genes, we integrated 9 heterogeneous genomics data sets (mRNA expression profiles by cDNA microarray, text-mining of scientific literature by co-citation, yeast 2 hybrid analyses, gene neighbors, phylogenetic profiles, genetic interactions, and conserved gene interactions transferred from yeast/fly/human).

Various analyses including experimental validation using RNAi knock-down suggest that the network is a highly predictive model of worm biology. First, we observe strong correlation between gene connectivity and essentiality for normal worm development (Fig A). Second, a classifier based on network topological features successfully predicts actual observations of RNAi phenotypic changes for previously untested 2,383 genes during normal worm development (Fig B). Third, we tested 50 interactors for 6 known suppressors of synMuv (synthetic multi-vulva phenotype) pathway in the network, and found that 10 out of 50 (20%) were true ones, thus increase our current set of suppressors of the synMuv pathway by about 270% (from 6 to 16). Finally, the network correctly suggests that worm orthologs of genes involved in human muscular dystrophy also associate with EGF/Ras signaling pathway genes.



[1] Insuk Lee et al. (2004) A Probabilistic Functional Network of Yeast Genes. Science 306:1555-1558