Identification of Perturbed Pathways Using High-throughput Data

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Motivation

Cells live in a dynamic environment in which they encounter various perturbations.
These perturbations may arise from toxic compounds, environmental changes, mutations, or a disease. Identifying the molecules and cellular pathways that are affected can reveal the nature of a perturbation, provide potential therapeutic targets and shed light on mechanisms of cellular adaptation. We present a computational method to discover the pathways that are altered by a perturbation by analyzing high-throughput data in Saccharomyces cerevisiae.

Methods

Our method combines different types of high-throughput data to develop a coherent, mechanistic view of how cellular pathways are alterated. We have created a graphical model of the interactome based on physical data. The model also incorporates relations between genes and the proteins that regulate them, using a genome-wide map of experimentally determined transcriptional regulatory sites. We developed a novel algorithm to search for the pathways that are altered by the perturbation.

Results

We assess our method by applying it to over 100 datasets where the perturbations are known single gene deletions. In these test data, the genes and pathways identified by the algorithm are relevant to the actual perturbation in 80% of the 104 cases.
We use the same algorithm to predict the pathways that are most affected by different compounds. We identify genes known to be responsive to the agents and affected paythways that are in agreement with biological findings.

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