Title: Methodological aspects on network propagation

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Text:
Network propagation refers to a class of algorithms that integrate information from input data across connected nodes in a given network and which have wide applications in systems biology, protein function prediction, and prioritizing disease genes. Despite the popularity of network propagation, there is little guidance on how to parameterize the various algorithms. Here, we address this problem by demonstrating schemes for the identification of optimal parameter settings on real proteome and transcriptome data. Capitalizing on the fact that network propagation is a regularization approach, we show that minimizing the bias-variance tradeoff can be utilized for selecting optimal parameters. Further, we provide a Bayesian framework for network propagation which in turn suggests maximizing the marginal likelihood as another criterion for selecting parameter values, and discuss the connection to the James-Stein estimator. The application to real multi-omics data demonstrated that optimal parameters could also be obtained by either maximizing the agreement between different omics layers (e.g. proteome and transcriptome) or by maximizing the consistency between biological replicates. Furthermore, we exemplified the utility and robustness of network propagation on multi-omics datasets for elucidating molecular mechanisms and posttranscriptional effects underlying prostate cancer progression. Overall, this work presents strategies for how to use network propagation algorithms to optimally address a specific research question at hand.