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Time-resolved integration of Flux Balance Analysis, Elementary Flux Modes, and transcriptomics data for characterization of the temporal metabolic response to temperature stress in *S. cerevisiae*

The increased availability of large-scale metabolic network models and the improved quality of high-throughput data provide the basis for system-wide network analysis. Flux Balance Analysis (FBA) [2] and its extensions have been successfully applied to determine steady-state systemic characteristics from the constituent elements. In addition, FBA has recently been extended to facilitate the study of transient behavior of metabolic networks. While FBA-based methods, due to their mathematical programming formulation, can readily be applied to large-scale metabolic networks, the application of approaches relying on Elementary Flux Modes (EFMs) [1] is hindered by large computational demands. Here we address the problem of time-resolved integration of FBA and EFMs based on transcriptomics data capturing the adaptation of metabolic networks to stress conditions.

Our approach integrates time-resolved transcriptomics data with large-scale metabolic networks to identify active subnetworks by using a novel FBA-based optimization method. To perform the integration, the results from a statistical analysis of differential gene expression, translated into carefully tailored weights, are employed to extract temporal subnetworks that not only show significant changes in expression values in response to stress conditions, but also represent a minimal subset of the whole metabolic network. We present three possible ways in which the extraction of such minimal active temporal subnetworks can be achieved. The found subnetworks are then used to determine the set of EFMs for each time point, reflecting the temporal stress response. We show empirically that the objective of minimality allows the identification of all EFMs for each time point in a feasible time frame. Finally, the sets of EFMs are used in a comparative analysis based on set-similarity measures to identify putative transitions.

We apply the proposed approach to time-resolved transcriptomics data sets from temperature shock experiments in *S. cerevisiae*. The results demonstrate that FBA-based optimization approaches can be used in conjunction with EFMs-based analysis and high-throughput data to reveal the temporal behavior of large-scale networks in an integrative and systematic manner.

References

[1] C. Trinh, A. Wlaschin, F. Srienc, *Elementary mode analysis: a useful metabolic pathway analysis tool for characterizing cellular metabolism.* Applied Microbiology and Biotechnology **81 (5)** 813–826.

[2] J. Orth, I. Thiele, B. Palsson, *What is flux balance analysis?* Nature Biotechnology **28 (3)** 245–248.