Can the whole be less than the sum of its parts? Pathway analysis in genome-scale metabolic networks using elementary flux patterns

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Elementary modes (EMs, [3]) represent a powerful means in the analysis of metabolic networks and their characteristic properties. However, a major caveat of EM analysis is that, due to computational constraints, they cannot be applied to genome-scale metabolic networks, which are available for a growing number of organisms. Thus, a widely used approach is to consider only a subsystem of the entire network and model the integration into the remaining system by introducing abstract reactions and relaxing the steady-state condition for some metabolites by setting them to external status. However, as we have shown in [1,2] the results obtained from elementary mode analysis heavily depend on the particular exchange reactions added and metabolites defined as external. Thus, we found in a model of the central metabolism previously analyzed using EMs analysis in [3] that 6 of the 16 detected EMs indeed only fulfill the steady-state condition within the subsystem but are not part of any steady-state flux on the scale of the underlying genome-scale system. To circumvent this problem we introduced the concept of elementary flux patterns (EFPs). EFPs are defined as the basic routes or set of reactions each steady-state flux of a genome-scale system has to use when passing through a particular subsystem. Using this concept we found that additionally to the 16 reported EMs there are many more pathways of the large-scale system running through the subsystem. In particular we found several additional metabolites that could be produced from glucose but are not taken into account in the small model. They can serve as input to central metabolism without requiring all reactions of glycolysis. Finally, we present several further applications of EFPs in particular the use of tools building on elementary mode analysis for studying genome-scale networks which previously could only be applied to small- and medium-scale systems.

[1] C. Kaleta, L. F. de Figueiredo, and S. Schuster. *Detecting metabolic conversions in genome-scale metabolic networks on the basis of elementary flux patterns in subnetworks*. In: I. Troch and F. Breitenecker, editors, Proceedings of the Vienna Conference on Mathematical Modelling, volume 2 of ARGESIM Reports, 2009.
[2] C. Kaleta, L. F. de Figueiredo, and S. Schuster. *Can the whole be less than the sum of its parts? Pathway analysis in genome-scale metabolic networks using elementary flux patterns.* Genome Research, 2009. Accepted.
[3] S. Schuster, T. Dandekar, and D. A. Fell. *Detection of elementary flux modes in biochemical networks: a promising tool for pathway analysis and metabolic engineering.* Trends in Biotechnology, 17(2):53–60, Feb 1999.