Identification of Functional Hubs through Metabolic Networks

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Abstract

Metabolic networks are described as a set of pathways, each pathway being a set of biochemical reactions, mainly enzymatic reactions. It is often considered that the global behavior of a metabolic network is characterized by the addition of behaviors of each pathway. But in fact, in such large networks it is difficult to predict the consequences of competition between several enzymes that react with the same molecule (metabolite) or, for example, how modification of the production of a specific molecule can influence, directly or not, another part of the network (Klamt and Stelling (2002)). Several works have shown that metabolic networks exhibit all characteristics of "small world" networks (Wagner and Fell (2001), Ravasz et al. (2002)). In this case, classical techniques from graph analysis domain can be used to find partitions or clusters in such networks. However in biological context, finding clusters must be related to biological functions and the analysis has to be driven by this concern to reveal functional links through the network. But these analyses from classical clustering use the network descriptions and do not take into account biological constraints on pathways. Tools based on linear algebra like elementary flux modes (Schuster et al. (1999) (or Extreme pathways Papin et al. (2002)) allow to select pathways through the network which satisfy constraints like the steady state of the system. In metabolism context, steady state is defined as a state where all the molecules produced by one reaction are consumed by another one, except external inputs or outputs. The obtained result is a set of unique and minimal reaction chains which are all solutions of the system. This set is often huge and gives a good appreciation of the network complexity. It is also considered as a measure of the network robustness to perturbations (Stelling et al. (2004)) and is suitable to identify if some reactions are always associated to another one even if they are not directly connected (path length between these two nodes longer than 1). We have used this tool to refine the description of 4 metabolic networks: 3 from mitochondria of different cell types (muscle, liver and yeast) and the last one from tomato fruit central metabolism. The elementary flux modes computings have identified from several thousands solutions for mitochondria networks to more than one hundred thousand for tomato fruit network. These results show the complexity level of interactions through the networks and obviously it is not possible for biologists to analyze them by hands (Pérès et al. (2006)). Building classification and identifying modular organization in the networks is an obvious requirement. We have applied clustering technique to identify reaction or molecule hubs and so to show new indirect links between distant parts of the networks. Evident hubs have been found like currency metabolites ATP, ADP ... but other belonging to the TCA cycle pathway like malate have been identified as good candidates for hub role whereas nothing in the primary network descriptions suggested that they are more implicated than another belonging to the TCA cycle. This result is consistent with analysis of the topology of E. Coli metabolism done by Zhao et al. (2007). These first results lead to build multi-layer description from metabolite hubs to small modules connections taking into account both information about feasible pathways and metabolites and reaction degree of connections.

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