Computation of Extreme Pathways with Hierarchical Decompositions of Metabolic Network

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Introduction

Intrinsic hierarchical structure of metabolic networks has been recently revealed [1]. Particular hierarchical decompositions can even present a property of relative independence between its branches which has been shown to be of a biological relevance. Here we use this property for computational purposes. A recursive and parallelizable variant of the classical algorithm for computing extreme pathways is hence introduced.

A Recursive Implementation for computing Extreme Pathways

1. Extreme Pathways

The central argument of Flux Balance Analysis is that the cell balances its internal metabolites at the stationary state. In this framework an admissible route through the network, or pathway, balances the internal metabolites and uses irreversible reactions only in their natural direction. The set of extreme pathways is a particular generative set of combined reactions, spanning all the possible combinations satisfying these constraints [2]. Geometrically, Extreme Pathways are the extreme rays of a pointed polyhedral cone defined by the stoichiometry matrix of the metabolic network. Combinatorial by nature, their computation and human inspection encounters difficulties with large networks.

2. Hierarchical decomposition and Dependencies in Metabolic Networks

In a previous paper [3], we described a generic framework of hierarchical decompositions of bipartite graphs that we applied to metabolic networks by mapping the metabolites to one type of node, and the chemical processes to the other type. Clusters of such decompositions have the so-called property of metabolite-encapsulation, they contain a group of metabolites and all the reactions in which they participate. For the hierarchy, this leads to the fact that two branches represent two independent parts of the network, sharing only the metabolites of their common ancestors.

3. Algorithm

Computing Extreme Pathways is classically done with an algorithm of combinatorial geometry firstly described by Motzkin [4]. One sequentially balances each metabolite by computing nonnegative combinations of the reactions and checking their extremality. We show that these operations can be done independently for the internal metabolites of two parallel branches of our hierarchical decompositions and how to use these results to solve the problem at the higher level. Hence, in a divide and conquer approach, we can apply the same algorithm recursively through the hierarchy. As a result, Extreme Pathways are defined at several levels of the hierarchy and can be expressed as combinations of extreme pathways of the sublevels.

Conclusion and perspective

The benefit of a hierarchical structuring of the metabolic network for Extreme Pathways study are various. Computationally, it separates independent tasks and thus can lead to a parallel version of the algorithm. On the user point of view, it provides an organization of the output in direct link to the organization of the network. It can help in re-using common parts of the decomposition to compare mutants or close species.
Moreover, the algorithm is generic enough to be applied in other domain of science. The variant here introduced can be applied elsewhere if the dataset also presents a hierarchical structure.

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