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Poster presentation

Elementary flux modes – state-of-the-artimplementation and scope of application

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Introduction

Elementary flux modes discribe all possible flux distributions in a metabolic network under steady state conditions, acting as a minimal constructive basis of the solution space. The algorithms to compute EFMs originate from computational geometry, where the problem is known as enumeration of extreme rays of polyhedral cones. Due to combinatorial complexity, the algorithms scale poorly and various improvements have been proposed. We present a selection of the most important contributions including a new *dynamic adjacent ray enumeration* approach. The new approach is based on *candidate narrowing*, which has recently been proposed by the authors. However, the present variant is new and optimizes the method significantly, resulting to the best of our knowledge in the most efficient algorithm for elementary flux mode computation known today.

Application

As a second aspect, we focus on the application of elementary modes, placing it into the context of constraint-based modeling approaches. Therefore, we compare pathway analysis (aggregating EFMs and related methods) with flux balance analysis (FBA) and minimization of metabolic adjustment (MoMA). A critical evaluation of the methods assesses properties such as computational costs, network size limitations, applicability and practical benefit.

Computing the flux cone

Thermodynamic constraints (irreversible reactions) and the steady state assumption (constant concentration of internal metabolites) define the *flux cone*, the solution space for possible flux values of the metabolic network under the given constraints. Elementary modes are the *extreme rays* (edges) of the flux cone. Every valid flux vector is a positive linear combination of elementary modes.

Algorithmic improvements

Pairs of *adjacent* elementary modes are used to generate new modes. Finding adjacent modes is one of the most crucial aspects of the algorithm.

With *pattern trees* [1], adjacent modes can be enumerated efficiently, demanding memory that is linear in the number of intermediary modes. A multithreaded version of the *candidate narrowing* procedure is presented, which allows exploiting modern Dual-Core processors.

Results

See Figure 2.

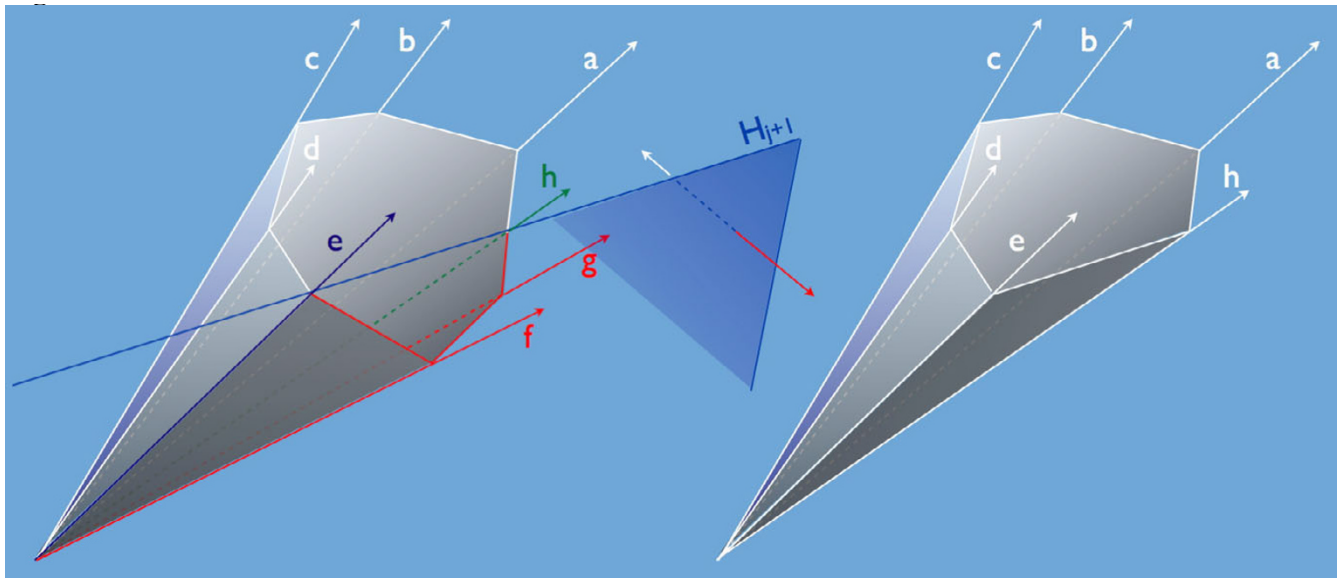

Figure 1
Elementary flux mode computation. Constraints are iteratively considered. The flux cone of the previous step is intersected with the halfspace reflecting the constraint currently being added. Newly generated elementary modes (h) are lying in the separating hyperplane (H_{j+1}).

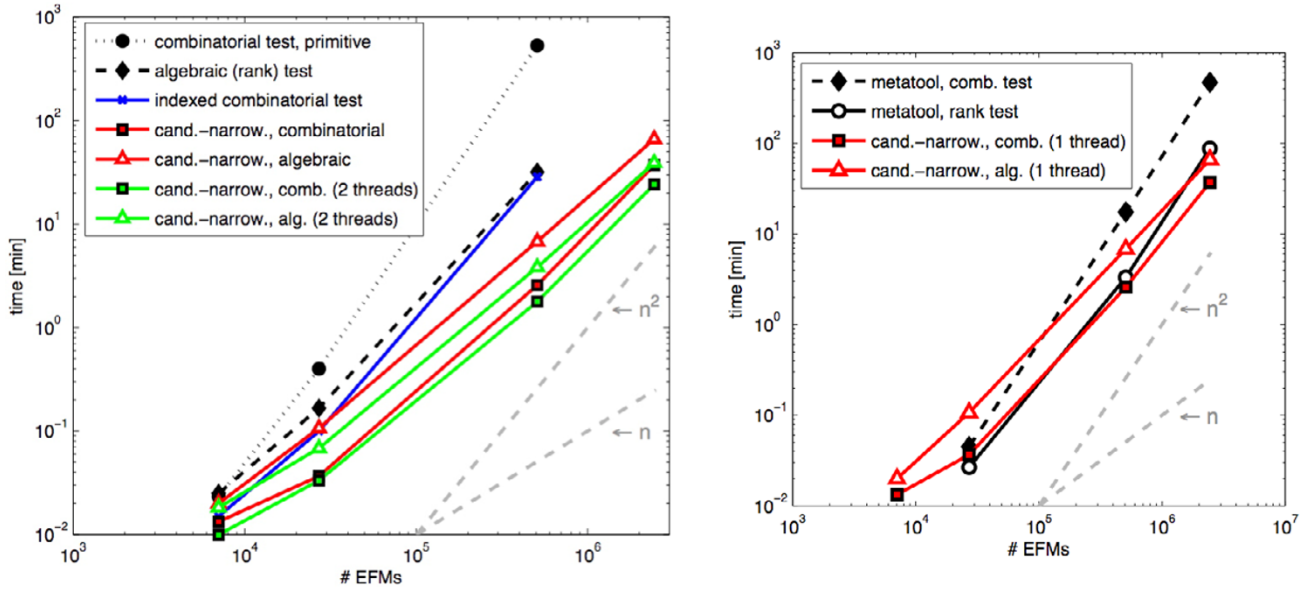

Figure 2
Computation time for central metabolism metabolic networks of *E. coli*. Different network configurations yield varying numbers of elementary modes. *Left:* Candidate narrowing with combinatorial (red filled squares) and algebraic adjacency test (red triangles) shows significant speed up compared to simple approaches. Multithreaded versions (green) provide further speedup of 1/2 to 3/4 with two threads on a Dual-Core processor. *Right:* Computation time compared with Metatool 5.0 (benchmarks see [2], Table 1 therein). Both presented algorithm versions are faster for large networks, even if implemented in Java (Metatool: C).

References

1. Marco Terzer, Jörg Stelling: **Accelerating the computation of elementary modes using pattern trees.** In *WABI, volume 4175 of Lecture Notes in Computer Science Springer*; 2006:333-343.
2. Klamt S, Gagneur J, von Kamp A: **Algorithmic approaches for computing elementary modes in large biochemical reaction networks.** *IEE Proc Systems Biol* **152:**249-55.