**Metabolic Modeling Project: Evaluating Elementary Pathway Importance Using Polytope Volume Computation**

**(12 weeks full time: Long lab rotation/Bachelor thesis – Location: Zurich or Basel)**

**Background and Goal**

The space of all possible steady-state flux distributions defines the flux cone, which is generated by the elementary flux vectors (EFMs). Metabolically, EFMs represent the elementary pathways from which every feasible steady-state flux distribution can be generated without cancellations. When adding inhomogeneous constraints to the flux cone (such as non-zero growth), another object named the flux polyhedron is obtained. Provided all reactions are bounded, we obtain a flux polytope, which is generated by the elementary flux vectors (EFVs) that generate it without cancellations **[1]**.

Given the biological meaning of EFMs and EFVs, we would like to understand the contribution of each EFV to the flux polytope, namely how much of the solution space cannot be generated anymore when this pathway is ignored. This could in principle be done by computing the volume of the flux polytope before and after removing the corresponding generating vector (see **[2]** for a related idea).

Polytope volume computation is however a NP-hard problem in the general case **[3]**. Methods and algorithms have been designed both for exact volume computation **[3]** and approximate volume estimation **[4,5]**. The goal of this project would be to evaluate the feasibility of the proposed idea to evaluate EFV importance and implement such a method on the *Escherichia coli* core metabolic network **[6]** with appropriate constraints.

**Tasks**

1. Understand the basic principles of stoichiometric modeling, in particular structural analysis methods. Understand the geometric representation of the flux space as well as its biological meaning and be able to relate the two representations.
2. Obtain an overall understanding of the polytope volume computation problem and existing methods.
3. Understand how to formulate the volume computation problem for the flux polytope and implement it. The choice of algorithm should take into account the possibility to scale to large-scale metabolic networks.A first idea would be to start from the V-representation of the flux polyhedron in terms of EFVs and design a method to compute relevant simplices from them as the simplex volume formula is known.
4. Test the implementation on a small metabolic network: start with a toy network, and later move on to the *Escherichia coli* core metabolic network **[6]** with appropriate constraints.
5. (*Optional, if time and interest allow*) Interpret the importance of the different EFVs.
6. *Reporting*. You will be required to summarize your results in a written report and in an oral presentation.

**Skills you will acquire**

You will learn about stoichiometric networks and their use in metabolic modeling. You will become familiar with their geometric representation and understand how it relates to the underlying biology. You will read about and familiarize yourself with the polytope volume estimation/computation problem and implement it for use on flux polytopes. As such, you will also have to implement your own coding project. Moreover, this project is a great opportunity to understand the links that may exist between mathematical objects and biological problems

**Requirements**

Motivation and interest in the project as well as an ability to work independently are the main requirements for the project. Other requirements include:

* (*Required*) Good knowledge of linear algebra
* (*Required*) Basic geometry knowledge and interest in polyhedral geometry
* (*Required*) Previous programming experience (Python preferred but other languages possible)
* (*Optional*) Previous experience in the field of metabolic modeling is a plus, but not required

**Supervision**

If interested, please send an email to Constance Le Gac (constance.legac@bsse.ethz.ch) and Prof. Dr. Jörg Stelling (joerg.stelling@bsse.ethz.ch ).

**References**

**[1]** Klamt, S. *et al.* From elementary flux modes to elementary flux vectors: Metabolic pathway analysis with arbitrary linear flux constraints. *PLoS Comput Biol* **13**, e1005409 (2017).

**[2]** Ay, F. & Kahveci, T. Functional similarities of reaction sets in metabolic pathways. in *Proceedings of the First ACM International Conference on Bioinformatics and Computational Biology* 102–111 (ACM, Niagara Falls New York, 2010). doi:[10.1145/1854776.1854795](https://doi.org/10.1145/1854776.1854795).

**[3]** Büeler, B., Enge, A. & Fukuda, K. Exact Volume Computation for Polytopes: A Practical Study. in *Polytopes — Combinatorics and Computation* (eds. Kalai, G. & Ziegler, G. M.) 131–154 (Birkhäuser Basel, Basel, 2000). doi:[10.1007/978-3-0348-8438-9\_6](https://doi.org/10.1007/978-3-0348-8438-9_6).

**[4]** Chalkis, A. & Fisikopoulos, V. Volesti: Volume Approximation and Sampling for Convex Polytopes in R. *The R Journal* **13**, 561 (2021).

**[5]** Barvinok, A. & Rudelson, M. A quick estimate for the volume of a polyhedron. *Isr. J. Math.* **262**, 449–473 (2024).

**[6]** Orth, J. D., Fleming, R. M. T. & Palsson, B. Ø. Reconstruction and Use of Microbial Metabolic Networks: the Core *Escherichia coli* Metabolic Model as an Educational Guide. *EcoSal Plus* **4, ecosalplus.10.2.1** (2010).