**Metabolic modeling project: Using Minimal Pathways to predict interactions within a synthetic murine gut microbial community**

**(Long lab rotation, 12 weeks full time / Master’s thesis, 24 weeks full time – Location: Zurich or Basel)**

**Background and Goal**

Our lab is interested in understanding the interactions within intestinal microbiome communities. As a model community, we are using a synthetic murine gut microbial community named OMM12 [1] , which consists of twelve bacterial strains representative of the murine gut microbiome. Prior studies of interactions within this community were conducted using either *in vitro* experimental methods [2], [3] or a combination of models and experiments [4]. However, the latter modeling study uses constraint-based modeling and focuses on *optimal* strategies.

Unbiased methods, such as sampling and structural analysis, allow us to obtain a more accurate description of the flux polytope. Those methods however do not scale very well to genome-scale metabolic models (GSMMs). Nonetheless, it has been shown that Minimal Pathways can scale to GSMMs and to metabolic communities [5].

The goal of this project is to use the minimal pathways to study potential metabolic interactions between the members of the OMM12 community. Curated GSMMs of the twelve OMM strains will be provided.

**Tasks**

1. Review the literature to understand the fundamentals of metabolic modeling of microbial communities as well as its challenges, particularly with respect to structural analysis methods.
2. Understand in depth what Minimal Pathways are and how they can be used to describe the steady-state solution space of metabolic networks.
3. Similar to what was done in [5], apply Minimal Pathways to describe the space of metabolic interactions within the OMM12 community.
   1. Choose a relevant subcommunity for assessing the feasibility of the study
   2. Set up the community model by defining suitable bounds and growth rate for model feasibility. External tools such as PyCoMo [6] may help at this step.
   3. Enumerate the MPs in the subcommunity.
   4. Using the literature as well as previous results from the group, assess the relevance of the interactions found in step 3.c, in the context of an intestinal environment.
4. *Optional for lab rotation, expected for master’s thesis*: Extend the framework to the full OMM12 community.
5. *Reporting.* You will be required to write a report and give an oral presentation summarizing your results.

**Skills you will acquire**

You will learn how to efficiently browse and review scientific literature in search of a specific information, as well as how to understand and apply a state-of-the-art method to your own research question. You will also learn how to manipulate genome-scale metabolic models, as well as current methods in metabolic pathway analysis and metabolic modeling of microbial communities. You will be introduced to structural analysis methods and optimization (linear, integer, mixed integer programming and associated solvers).

**Requirements**

Motivation and interest in the project are the main requirements for the project. Formal requirements include:

1. Prior knowledge of linear algebra and calculus/analysis as well as prior experience in coding (Python).
2. Prior experience in the field of metabolic modeling and/or optimization is a plus, but not necessary.

**Supervision**

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

**References**

[1] S. Brugiroux *et al.*, “Genome-guided design of a defined mouse microbiota that confers colonization resistance against Salmonella enterica serovar Typhimurium,” *Nat Microbiol*, vol. 2, no. 2, p. 16215, Feb. 2017, doi: 10.1038/nmicrobiol.2016.215.

[2] P. Pérez Escriva, T. Fuhrer, and U. Sauer, “Distinct N and C Cross-Feeding Networks in a Synthetic Mouse Gut Consortium,” *mSystems*, vol. 7, no. 2, pp. e01484-21, Apr. 2022, doi: 10.1128/msystems.01484-21.

[3] A. S. Weiss *et al.*, “In vitro interaction network of a synthetic gut bacterial community,” *ISME J*, vol. 16, no. 4, pp. 1095–1109, Apr. 2022, doi: 10.1038/s41396-021-01153-z.

[4] M. G. Gollub, “Predicting Microbial Metabolic Capabilities and Preferences Under Uncertainty,” ETH Zurich, 2022. doi: 10.3929/ETHZ-B-000599404.

[5] O. Øyås and J. Stelling, “Scalable metabolic pathway analysis,” Systems Biology, preprint, Aug. 2020. doi: 10.1101/2020.07.31.230177.

[6] M. Predl, M. Mießkes, T. Rattei, and J. Zanghellini, “PyCoMo: a python package for community metabolic model creation and analysis,” *Bioinformatics*, vol. 40, no. 4, p. btae153, Mar. 2024, doi: 10.1093/bioinformatics/btae153.