**Metabolic Modeling Project: Extending GSMMs with diet-specific degradation pathways**

**(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. To study how diet affects community interactions, we would like to simulate this community in different *in silico* media representative of different diets. Of particular interest would be a fiber-rich medium and a milk-like medium.

Genome-scale metabolic models (GSMMs) for the twelve OMM12 strains have already been built and curated, however it is very likely that they do not incorporate all the degradation pathways necessary for simulations in those media, for instance fiber degradation pathways.

The goal of this project is to define the above mentioned *in silico* media, and model and integrate the relevant degradation pathways in the models. This requires a literature review to assess which pathways are relevant, as well as an assessment of how best to incorporate those degradation pathways into the existing models. You will need to make modeling choices, since some of those pathways may involve extracellular enzymes which make the degradation products available to the community. Provided the extended models have been completed and validated and depending on interest, it would then be possible to simulate the community using an existing community modeling framework (for instance: MICOM [2] or OptCom [3] ) and study the predicted interactions.

**Tasks**

1. Understand what GSMMs are and basic concepts in metabolic modeling, in particular for constraint-based modeling of microbial communities.
2. Review the literature to design a fiber-rich and milk-like *in silico* media relevant for the modeling of intestinal communities.
3. Identify relevant metabolic pathways involved in the assimilation of those *in silico* media and assess whether they are already present in the GSMMs.
4. For those pathways that are not present: identify how they can be modeled and integrated in the current models. This will likely require a literature review of existing methods as well as modeling design choices.
5. Validate the extended models
6. *(Optional, depending on time and interests)* Using the extended models and established community modeling methods, simulate the community in both media and study the predicted interactions.
7. *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 how to efficiently browse and review scientific literature in search of specific information. You will also learn how to manipulate genome-scale metabolic models, as well as how they are used for metabolic modeling. You will also familiarize yourself with general concepts related to the metabolic modeling of microbial communities. On the technical side, you will learn how to handle genome-scale metabolic models with toolboxes such as *cobrapy* [4] and how to find relevant information in databases.

**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:

1. Prior knowledge in biochemistry and metabolism.
2. Prior experience in the mathematical modeling of biological systems.
3. Prior knowledge in metabolic modeling is a plus, but not necessary.
4. Basic coding experience is a plus, but not necessary (although be aware that this project will require coding in Python).

**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] 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] C. Diener, S. M. Gibbons, and O. Resendis-Antonio, “MICOM: Metagenome-Scale Modeling To Infer Metabolic Interactions in the Gut Microbiota,” *mSystems*, vol. 5, no. 1, pp. e00606-19, Feb. 2020, doi: 10.1128/mSystems.00606-19.

[3] A. R. Zomorrodi and C. D. Maranas, “OptCom: A Multi-Level Optimization Framework for the Metabolic Modeling and Analysis of Microbial Communities,” *PLoS Comput Biol*, vol. 8, no. 2, p. e1002363, Feb. 2012, doi: 10.1371/journal.pcbi.1002363.

[4] A. Ebrahim, J. A. Lerman, B. O. Palsson, and D. R. Hyduke, “COBRApy: COnstraints-Based Reconstruction and Analysis for Python,” *BMC Syst Biol*, vol. 7, no. 1, p. 74, Dec. 2013, doi: 10.1186/1752-0509-7-74.