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Systems biology

Microbiome Modelling Toolbox 2.0: efficient, tractable modelling of microbiome communities

Almut Heinken[1,2] and Ines Thiele [1,2,3,4,*]

[1]School of Medicine, National University of Galway, Galway, Ireland, [2]Ryan Institute, National University of Galway, Galway, Ireland, [3]Division of Microbiology, National University of Galway, Galway, Ireland and [4]APC Microbiome Ireland, University College Cork, Cork, Ireland

*To whom correspondence should be addressed.

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Abstract

Motivation: Constraint-Based Reconstruction and Analysis (COBRA) is a widely used approach for the interrogation and stratification of microbiome samples, yet applications to large-scale cohorts are hampered by limited scalability and efficiency of simulations.

Results: We substantially improved the computation speed and scalability of a previous implementation for the construction and interrogation of personalized constraint-based microbiome models as well as implemented additional functionalities for analysis and visualization.

Availability and implementation: Microbiome Modelling Toolbox and tutorials are freely available as part of the COBRA Toolbox at https://git.io/microbiomeModelingToolbox.

Contact: ines.thiele@nuigalway.ie

1 Introduction

The Constraint-Based Reconstruction and Analysis (COBRA) approach is a mechanistic, bottom-up systems biology method that relies on manually curated genome-scale reconstructions of metabolism that can be converted into mathematical models (Palsson, 2006). In recent years, COBRA has been used in >100 studies to interrogate the metabolism of microbial communities and microbiomes, yielding valuable insight into microbial community structure and function (Heinken *et al.*, 2021). A notable application of COBRA modelling is the generation of personalized human microbiome models and their stratification based on their structure and function, which has been applied to, e.g., inflammatory bowel disease and colorectal cancer (Heinken *et al.*, 2021).

We have previously developed the Microbiome Modelling Toolbox, a MATLAB-based suite for the construction and interrogation of microbe–microbe and personalized microbiome models (Baldini *et al.*, 2019). Here, we present an updated version, the Microbiome Modelling Toolbox 2.0. Compared with its predecessor, computation times have been greatly reduced by taking advantage of parallelization. Moreover, the toolbox has been expanded by additional functions for targeted analysis, statistical analysis and visualization.

2 Features

Like its predecessor (Baldini *et al.*, 2019), the Microbiome Modelling Toolbox 2.0 consists of two main modules. First, the pairwise interactions module enables the construction and interrogation of pairwise models for any number of microbe strains, resulting in the prediction of interactions, such as mutualism, commensalism and competition (Baldini *et al.*, 2019). Second, the mgPipe module uses microbial composition information obtained from 16S rRNA or metagenomic sequencing data as input to build, interrogate and analyse personalized microbiome models, which allows for the stratification of, e.g., disease cases and controls according to their microbiomes' metabolic potential (Baldini *et al.*, 2019). Compared with its predecessor, parallelization has been optimized in both modules for improved computation speed. The mgPipe module has been expanded by additional functions, resulting in a comprehensive analysis pipeline as described below.

2.1 Generation of personalized microbiome models

mgPipe enables the generation of personalized microbiome models from, e.g., a large collection of microbial metabolic reconstructions, aka AGORA (Heinken *et al.*, 2020), using the microbial composition information from either 16s rRNA or metagenomic sequencing data. mgPipe aids the mapping of the experimental data onto the AGORA nomenclature as well as the normalization of provided relative microbial abundances (Fig. 1). If abundances are only given on the species or genus level, mgPipe creates the corresponding pan-models from the AGORA resource. Through parallelization, microbiome models for each sample can be built rapidly.

2.2 Computation of microbiome-level metabolic fluxes

mgPipe provides functions for both comprehensive and targeted simulation of microbiome metabolic fluxes, corresponding to the

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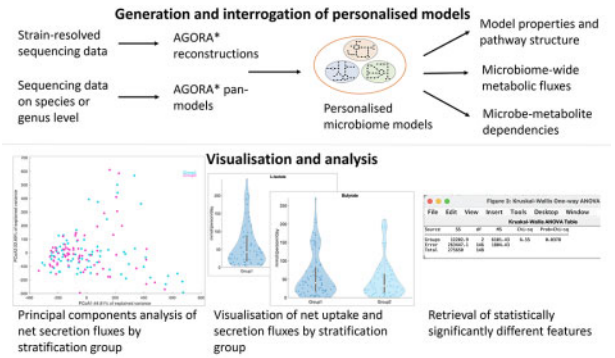


Fig. 1. Overview of the features implemented in mgPipe consisting of (i) generation of personalized models, (ii) interrogation of personalized models through simulations, and (iii) visualization and statistical analysis. AGORA* delineates the AGORA or AGORA2 resource

predicted fecal metabolome (Fig. 1). To comprehensively profile each microbiome model, every metabolite, which can be transported by at least one microbiome model, is routinely computed through computationally efficient flux variability analysis (Gudmundsson and Thiele, 2010). Metabolite fluxes can be subsequently correlated with taxon abundances. As a computationally efficient option, mgPipe also allows for the computation of selected metabolites while also retrieving shadow prices, a measurement for the value of a metabolite towards the objective function (Palsson, 2006). To directly identify microbe-metabolite links, microbes contributing most to the uptake and secretion of metabolites can also be retrieved. Finally, structural features of the microbiome models, such as dimension, reaction abundance, and subsystem abundance, are computed (Fig. 1).

2.3 Visualization and further analysis

Compared with its predecessor, the Microbiome Modelling Toolbox 2.0 provides additional functions for visualization and stratification of fluxes based on available metadata (e.g., disease state). Principal components analysis as well as detailed plots for each computed metabolite stratified by group can be generated (Fig. 1). mgPipe also provides functions for determining whether differences in model properties and metabolite production flux between stratification groups are significant (Fig. 1).

3 Implementation

The Microbiome Modelling Toolbox 2.0 is written in MATLAB (Mathworks, Inc.) and is freely available at the COBRA Toolbox GitHub repository, https://github.com/opencobra/cobratoolbox (Heirendt *et al.*, 2019). Comprehensive tutorials in form of MATLAB live scripts are provided at https://github.com/opencobra/COBRA.tutorials. Further details are provided at https://git.io/microbiomeModelingToolbox.

4 Discussion

Recent cohort studies have generated an unpreceded amount of publicly available metagenomic sequencing data of human microbiomes varying, e.g., in health status, diet, and ethnicity. Yet, the interpretation of this wealth of data is lagging. The increasing availability of strain-resolved metagenomic data, as well as of curated genome-scale reconstructions, such as the AGORA resource of 773 reconstructed human gut microbes (Magnusdottir *et al.*, 2017), and its expansion, AGORA2, now containing over 7,000 microbial reconstructions (Heinken *et al.*, 2020), allow for the construction of personalized microbiome models with increasing coverage and hence, size. The Microbiome Modelling Toolbox 2.0, due to its improved scalability and efficiency, provides the computational tools for the large-scale interrogation of hundreds (Hertel *et al.*, 2021) or even thousands of microbiomes. For instance, it enabled the comprehensive prediction of the fecal metabolome for 644 microbiome models of colorectal cancer patients and controls containing up to ~150 species and ~240,000 reactions (Hertel *et al.*, 2021), as well as the construction of over 14,000 personalized microbiome models (A.Heinken *et al.*, in preparation). Personalized models generated by mgPipe can also be integrated with a whole-body model of human metabolism (Thiele *et al.*, 2020), hence, enabling constraint-based modelling of human–microbiome interactions with unpreceded scope.

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Conflict of Interest: none declared.

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