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Title:

Meta-transcriptomics-based deep modeling of metabolic fluxes: a cheese fermentation case study

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Abstract: (Your abstract must use **Normal style** and must fit in this box. Your abstract should be no longer than 300 words. The box will 'expand' over 2 pages as you add text into it.)

Preparation of Your Abstract

1. The title should be as brief as possible but long enough to indicate clearly the nature of the study. Capitalise the first letter of the first word ONLY (place names excluded). No full stop at the end.
2. Abstracts should state briefly and clearly the purpose, methods, results and conclusions of the work.

Introduction: Clearly state the purpose of the abstract
Methods: Describe your selection of observations or experimental subjects clearly
Results: Present your results in a logical sequence
Discussion: Emphasize new and important aspects of the study and conclusions that are drawn from them

Motivation/purpose

The canonical approach for modeling metabolic fluxes, Flux Balance Analysis, requires many empirical measurements/constraints (e.g., nutrient uptakes), which may not be feasibly obtained for each species within a fermentation or natural community. Single-cell Flux Estimation Analysis (scFEA) however circumvents the limitation by only using gene expression data as input for deep modeling of metabolic fluxes. Notably, scFEA has been applied to individual cells of a single species, but not to a microbial community exchanging metabolites.

Methods

To this end, we treat the community as a single integrated 'super-organism' with component species linked by the exchange of metabolites between them. We then repurpose scFEA to model metabolic fluxes within a microbial community by tailoring the loss function to penalize non-zero fluxes belonging to absent species.

Results

We introduce ***MeMo*****:** a **ME**ta-transcriptomics-based deep **MO**deling tool to elucidate metabolic fluxes in a microbial community. The *MeMo* framework consists of two pipelines. The first preprocesses and normalize raw meta-transcriptomic reads, while the second constructs and modularize the community model from individual genome-scale models (GEMs). The gene expression values are then mapped to the community model while missing values are bootstrapped from those of the same subsystem(s). Finally, the loss function is tailored for each sample based on expression values, which is then minimized to model the community fluxes. We then use *MeMo* to model metabolic fluxes and metabolite exchanges, which possibly contribute to cheese flavor formation in a case study. We found Illumina sequencing technology to be applicable, further promoting *MeMo* as a cost effective and accessible technology.

Discussion

Our work unlocks an innovative niche technology for the flux analysis of microbial samples as they are. In addition, we implement *MeMo* as an end-to-end software to democratize the tool and to enable its repurposing to new fields (e.g., gut microbiota and ecology research).