Advanced Computational and Modeling Analyses Provide Novel Insights into Interactions in Model Complex Microbial Consortia

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Project Goals: The PNNL FSFA goal is to identify the fundamental mechanisms by which microbial interactions and spatial organization impact rates and pathways of carbon and energy flow in microbial communities. The strategy involves the study of highly interactive and tractable model autotroph-heterotroph consortia whose member genome sequences have been defined. Our project leverages unique capabilities including multi-omics measurements, advanced functional imaging, taxonomic profiling and metabolic and regulatory network modeling to elucidate underlying reaction mechanisms within complex microbial communities. Our research plan supports DOE goals to achieve a predictive understanding of microbially-mediated carbon and energy transformation.

A mechanistic understanding of the complex interplay between member species in microbial communities is essential to enable predictions of community dynamics and response to environmental perturbations, and for eventual design and control of community-level functions. It is known that the populations of microorganisms in communities are balanced through positive, neutral, or negative interactions. However, we currently have insufficient fundamental knowledge of the types of metabolic and cellular interactions that control member populations and that regulate their functions. Microbial association networks of complex communities have primarily been inferred from species co-occurrence data using similarity- or regression-based approaches. However, network inference is an underdetermined inference problem. In addition, existing approaches cannot differentiate between direct and indirect interactions; thus microbial association inferences are often inconsistent across different methods. By contrast, community metabolic network analyses can predict microbial interactions based on predicted metabolite exchanges between species. Currently, the great majority of metabolic network modeling is limited to monocultures or very simple communities (mostly, binary cultures), primarily due to the difficulty in reconstructing reliable species-level and community metabolic networks from metagenome sequences.

Our hypothesis is that ***by combining interaction network inference and metabolic network analysis modeling approaches we can improve predictions of microbial community interactions***. First, we developed a mixed integer linear programming-based regression model that infers microbial interactions by fitting population growth models (such as generalized Lotka-Volterra [gLV] and evolutionary game theory-based models) to temporal profiles of species abundance. Unlike conventional analyses that yield one specific interaction network (despite uncertainties on direct versus indirect interactions), our modeling approach systematically

identifies *all* possible scenarios of microbial interactions that equally represent a given dataset. We demonstrate this new modeling approach using comprehensive simulated data as well as our own experimental data. For example, we used this approach to predict metabolic interactions in an experimentally tractable model autotroph-heterotroph community composed of 20 members. This approach enabled us to model and predict multiple scenarios of microbial interactions in the consortium. Specifically, we predicted a dramatic shift in species interactions during succession under an ammonium-amendment condition. These predictions serve as the basis for development of new testable hypotheses.

In addition, we are developing genome-scale metabolic network models for complex microbial consortia, pushing well beyond the boundaries established for typical mono- or binary cultures. To address this aim, we have integrated our genomic and transcriptomic data into the DOE Knowledgebase (KBase), and utilized the KBase Platform to construct single genome and community metabolic models and to predict interactions between the species comprising our model community. We are collaborating with the KBase team to supplement the standard KBase environment with additional methods, including integration of core and whole-genome models and gene expression profile-guided gap filling. These modules are currently being evaluated for deployment through KBase for use by the larger scientific community.

The next steps will be to use this modeling approach to reveal the mechanistic underpinnings of microbial interactions and division of labor that are responsible for transforming carbon and other nutrients in complex communities. Specific interactions will also serve as key inputs to advanced modeling platforms for integrating multi-omics data to predict temporal and spatial organization of complex communities.

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