Uncovering the dynamically changing interaction networks of microbial ecosystems.

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***Abstract*— An understanding of the metabolic interactions taking place within a microbiome is crucial for understanding how microbes effect their host environment. We present a method for simulating a microbiome using genome scale metabolic models which reveals a dynamically changing network of interactions between microbes and metabolites. We demonstrate that this method can furthermore reveal a network of interactions between metabolites as mediated by a community of microbes. We also present a pipeline for constructing these models from metagenomic data using established tools in order to predict and manipulate microbial community composition and metabolite production in real biological systems.**

***Index Terms*— Microbiome, Genome Scale Metabolic Modeling, Differential Algebraic Systems**

I. Introduction

Microbial community makeup and metabolic output have a profound impact on a wide variety of macro-scale biological systems ranging from the human gut to the global climate. However, accurate prediction and effective manipulation of microbial communities remains difficult. While a number of dynamical systems have been proposed for simulating microbial ecology, the most promising strategy seems to be one which explicitly models microbe and metabolite dynamics [1]. Using genome scale metabolic models, one can construct such a model, which takes the form of a differential algebraic system and is known as *dynamic flux balance analysis* [2]. Dynamic flux balance analysis can be efficiently simulated by taking advantage of a property of linear optimization problems which allows for the problem to be converted into a piecewise smooth series of ordinary differential equations (ODEs)[3]. We take further advantage of this property by noting that in each time interval in which the system is smooth, the ODE implies a corresponding network of interactions between the set of microbes and metabolites. Our method produces a set of Metabolically Contextualized Species Interaction Networks, and we name it *MetConSIN*.

II. Methods

We demonstrate the usefulness of MetConSIN by constructing interaction networks between published curated models from the BiGG [4] and AGORA [5] databases. We use these networks to illustrate how MetConSIN can contribute to the design of a microbial community's composition and metabolic output.

We next demonstrate that MetConSIN can be applied to real systems by constructing a model and corresponding set of networks for simple experimental microbiomes using metagenomic and metabolomic data. We construct the model using a pipeline of established tools to create genome scale metabolic models (GEMs) from experimental data, and use these GEMs as inputs to MetConSIN. We then use metabolomic data to estimate remaining parameters. We compare model predictions to a set of simple community growth experiments.

III. Conclusion

MetConSIN provides a method for understanding the interactions between microbes and metabolites within a microbiome in a mechanistic manner. Furthermore, MetConSIN predicts the metabolite output of a microbial community, and therefore can be used to understand and manipulate a microbiome's impact on its host system. This technology has the potential for far reaching impact in human health, climate sciences, and agriculture.

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