Spatio-temporal genome-scale metabolic modeling of the rhizosphere microbiome

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http://mCAFEs.lbl.gov ; https://runcomets.org

Project Goals: Understanding the interactions, localization, and dynamics of grass rhizosphere communities at the molecular level (genes, proteins, metabolites) to predict responses to perturbations and understand the persistence and fate of engineered genes and microbes for secure biosystems design. To do this, advanced fabricated ecosystems are used in combination with gene editing technologies such as CRISPR-Cas and bacterial virus (phage)-based approaches for interrogating gene and microbial functions *in situ*—addressing key challenges highlighted in recent DOE reports. This work is integrated with the development of predictive computational models that are iteratively refined through simulations and experimentation to gain critical insights into the functions of engineered genes and interactions of microbes within soil microbiomes as well as the biology and ecology of uncultivated microbes. Together, these efforts lay a critical foundation for developing secure biosystems design strategies, harnessing beneficial microbiomes to support sustainable bioenergy, and improving our understanding of nutrient cycling in the rhizosphere.

One of the key methods we employ to understand the complexity of the rhizosphere microbial community is computational modeling. With the increasing availability of sequenced genomes and methods for building genome-scale metabolic models of organisms, such as the ones provided in the KBase platform[1], we are in position to harness the power of genome-scale stoichiometric reconstructions in order to reach predictive modeling capabilities[2]. Our software platform COMETS (Computation Of Microbial Ecosystems in Time and Space)[3] was developed with the purpose of predictive modeling of the complex dynamics of interactions in microbial ecosystems where the spatial structure may play a crucial role. COMETS combines genome-scale metabolic modeling using dynamic flux balance analysis (dFBA) with spatio-temporal simulations of the growth and propagation of the biomass and extracellular metabolites in spatially structured environments. With COMETS we are able to simulate a variety of spatially structured microbial communities, from simple assays in a Petri dish to complex natural environments such as a plant root. We have recently released a significantly improved version of COMETS[3] (2.0, see http://runcomets.org), which includes enhanced biophysical models for biomass propagation, evolutionary dynamics, extracellular enzyme activity and night/day light cycles. COMETS 2.0 also includes user-friendly Python and Matlab interfaces, as well as the documentation and the source code in a publicly accessible github repository (https://github.com/segrelab/comets).

Our current modeling effort is focused on two main goals. The first goal is to make the best use of our computational platform and the experimental capabilities of the m-CAFEs team to construct, curate and test metabolic models starting from sequenced genomes and phenotypic data. Notably, the dFBA core algorithm of COMETS allows us to generate predictions of whole growth curves, which require knowledge of kinetic uptake parameters. We have been focusing on the important rhizosphere bacterium

Pseudomonas simiae as a test case. After building a draft model using automated pipelines, we compared COMETS-predicted growth curves under different nutrient limitations to corresponding experimental measurements, and generated new hypotheses on the resources that limit growth under different conditions. Further comparison with experimental data, including growth curves and metabolite uptake/secretion rates under different media, as well as TnSeq data, will allow us to implement rounds of gap filling and refinements of the genome-scale reconstruction. This approach is in parallel being extended to systematically study multiple rhizosphere microbes and their interactions.

Second, we are enhancing COMETS in order to improve its capacity to capture biological and biophysical processes that may be crucial for the spatio-tempotral dynamics of communities around the plant roots. In order to start testing our capacity to accurately predict the dynamics of communities in gradients of nutrients and signals, we have been developing in parallel a microfluidic experimental device, the μEcoFab (MicroEcoFab), and a corresponding *in silico* COMETS version. In order to make COMETS simulations more realistic, we have introduced a new module that can simulate bacterial chemotaxis. This module is based on the Keller-Segel[4] model of chemotaxis, which adds to the biomass density equation a convective term proportional to the gradient of the chemoattractant (or chemorepellent). Preliminary *in silico* experiments demonstrate that our module can predict the dynamics of colony shapes as they propagate towards the chemotactic signal. Ongoing experiments with the μEcoFab are being compared to COMETS simulations, based on a newly developed layout that captures the properties of this device. We expect that this concerted effort, combining experimental measurements and computational simulations, will allow us to better understand how molecular complexity and spatial structure of the environment shape rhizosphere microbiome properties, further facilitating our ongoing efforts towards designing and controlling communities for specific goals.

References

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Funding statement.
This material by m-CAFEs Microbial Community Analysis & Functional Evaluation in Soils, (m-CAFEs@lbl.gov) an SFA led by Lawrence Berkeley National Laboratory is based upon work supported by the U.S. Department of Energy, Office of Science, Office of Biological & Environmental Research under contract number DE-AC02-05CH11231