Reconstruction of a genome-scale community metabolic model of a microbial co-culture to enable next generation biochemical production

Gustavo Lastiri-Pancardo[1*] (glastiripancardo@health.ucsd.edu), Deepan Thiruppathy[1], Neal N. Hengge[4], Sean Woodworth[5], Violeta Sánchez i Nogué[5], Jeffrey G. Linger[5], Michael T. Guarnieri[4], **Karsten Zengler**[1,2,3]

[1]Department of Pediatrics, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA, 92093-0760, USA

[2]Department of Bioengineering, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA, 92093-0412, USA

[3]Center for Microbiome Innovation, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA, 92093-0436, USA

[4]Biosciences Center, National Renewable Energy Laboratory, 15013 Denver West Parkway, Golden, CO, 80401, USA

[5]Renewable Resources and Enabling Sciences Center, National Renewable Energy Laboratory, 15013 Denver West Parkway, Golden, CO, 80401, USA

Project Goals:

The goal of this project is to integrate innovative systems biology tools and genome-scale metabolic modeling to acquire a deeper understanding of the mutualistic interactions in a clostridial co-culture for the effective conversion of lignocellulosic biomass to butyric acid. Moreover, we aim to design a pipeline that facilitates the creation of engineering strategies to increase the complexity, stability and productivity of designer microbial communities for the production of next-generation biofuels and bioproducts from diverse biomass feedstocks.

Abstract:

Multi-species microbial consortia are widespread in nature. The majority of these communities are very diverse and highly dynamic. These complex communities depend on intricate interactions among their members, thereby accomplishing metabolic functions that are unfeasible for individual members. Understanding the relationship inside a community and being able to predict perturbation outcomes is critical for the design of robust and productive consortia for biochemical

production. This project studies a lignocellulosic biomass-degrading and butyrate-producing co-culture of *Clostridium thermocellum* and *Clostridium thermobutyricum*, to unravel inter-microbial interactions with the goal to design more effective consortia for production of bioproducts from biomass.

To untangle metabolic traits and interactions of the clostridial co-culture, we first constructed and manually curated two individual genome-scale metabolic models (GEMs) for these strict anaerobic organisms, based on protein homology to other model microbial species and annotated data from public databases and literature; covering around 27% of all genes found in their annotated genome sequences. The two GEMs were then integrated into a compartmentalized community metabolic (CM) model. The compartmentalized model iGL1101, accounts for 1,888 reactions, 1,636 metabolites and 1,101 genes. We will experimentally validate and refine the CM model though an iterative procedure that involves integration of multi-omics data and substrate utilization information obtained from Phenotype MicroArrays (Biolog) plate experiments. Model simulations will subsequently identify the biosynthetic requirements and trade-offs for butyrate production. The CM model offers a computational framework to contextualize butyrate production from lignocellulosic biomass and to determine metabolic bottlenecks of this co-culture. Identification of these bottlenecks will serve as a foundation for targeted strain engineering and the design of consortia of increased complexity for the effective conversion of biomass into bioproducts.

Funding: This work is supported by the U.S. Department of Energy, Office of Science, Office of Biological & Environmental Research under Award DE-SC0022137.