OptCom: A Multi-Level Optimization Framework for the Metabolic Modeling and Analysis of Microbial Communities

Ali R. Zomorrodi[1]* (zomorrodi@engr.psu.edu) and **Costas D. Maranas**[1]

[1] Department of Chemical Engineering, The Pennsylvania State University, University Park,

Project Goals: The goal of this project is to develop an efficient and comprehensive computational framework for the flux balance analysis of microbial communities using genome-scale metabolic models.

Microorganisms rarely live isolated in their natural environments but rather function in consolidated and socializing communities. Despite the growing availability of high-throughput sequencing and metagenomic data, we still know very little about the metabolic contributions of individual microbial players within an ecological niche and the extent and directionality of interactions among them. This calls for development of efficient modeling frameworks to shed light on less understood aspects of metabolism in microbial communities. Here, we introduce OptCom, a comprehensive flux balance analysis framework for microbial communities, which relies on a multi-level/objective optimization formulation to properly describe trade-offs between individual vs. community level fitness criteria (see Figure 1). In contrast to earlier approaches that rely on a single objective function, here, we consider species-level fitness criteria for the inner problem while relying on community-level objective maximization for the outer problem. OptCom is general enough to capture any type of interactions (positive, negative or combinations thereof) and is capable of accommodating any number of microbial species (or guilds) involved.

To quantify the deviation of community members from their optimal behavior, we introduce a metric called 'optimality level' (c^k) for each species involved. The optimality level for each one of the microorganisms is quantified using a variation of OptCom which we refer to as *descriptive* through incorporating all available experimental data for the entire community (e.g., community biomass composition) as constraints in the outer problem and all data related to individual species as constraints in the respective inner problems while allowing the biomass flux of individual species to fall below (or rise above) the maxima of the inner problems. An optimality level of less than one for a microorganism k implies that it grows sub-optimally at a rate equal to $100c^k$ % of its maximum to optimize a community-level fitness criterion while matching experimental observations. Alternatively, an optimality level of one implies that microorganism k grows exactly optimally, whereas a value greater than one indicates that it achieves a higher biomass production level than the community-specific maximum (i.e., super-optimality) by depleting resources from one or more other community members.

We applied OptCom to quantify the syntrophic association between *D. vulgaris* and *M. maripaludis* and assess the optimality levels of growth in phototrophic microbial mats of Octopus and Mushroom Springs of Yellowstone National Park. We also used OptCom to elucidate the extent and direction of inter-species metabolite and electron transfer in a model microbial community and examine the possibility of adding a new member to this community. Our study demonstrates the importance of trade-offs between species- and community-level fitness driving forces and lays the foundation for metabolic-driven analysis of various types of interactions in multi-species microbial systems using genome-scale metabolic models.

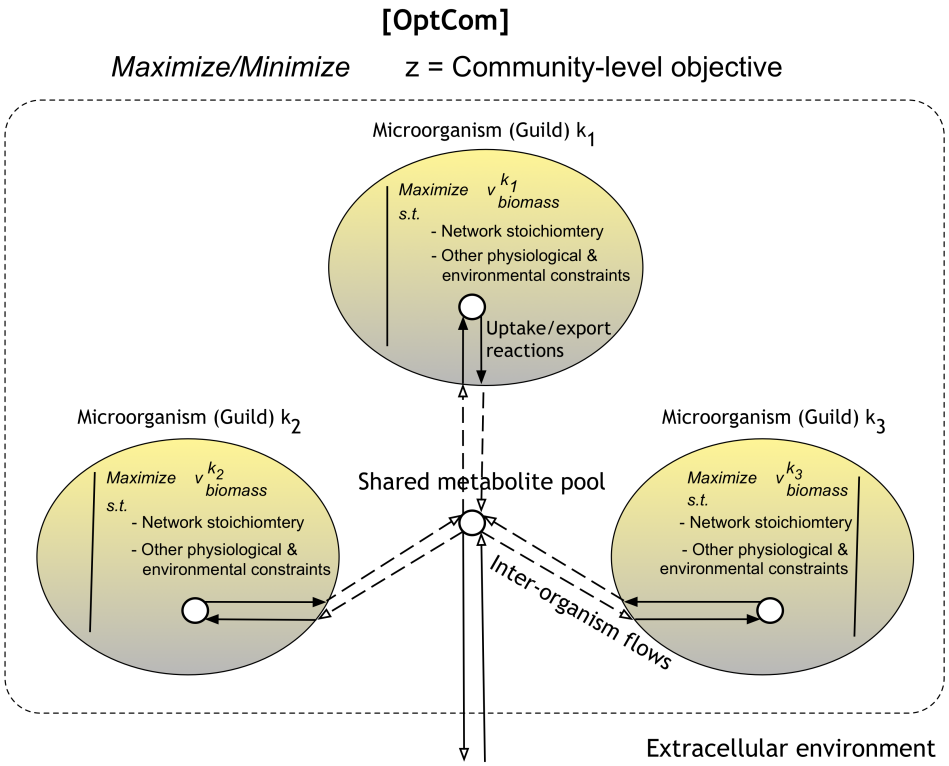

Figure 1. Pictorial illustration of OptCom. OptCom relies on a multi-level optimization structure where a separate biomass maximization problem is defined for each species as inner problems. These inner problems are then integrated in the outer stage through the inter-organism flow constraint to optimize a community-level objective function.