177. Metabolic modeling of multi tissue and multi organism systems

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Project Goals: The project aims to improve the understanding of metabolic interactions both within organisms containing multiple tissue types i.e., plants and microbial communities containing multiple species. Overall, the specific goals of this project are two fold: i to reconstruct a multi tissue mai e model for determining bottlenec s in nitrogen metabolism, suggesting genetic manipulations that improve nitrogen use efficiency, and enhancing the understanding of nitrogen flow through the plant, and ii to develop and implement a constraint based and multilevel optimi ation approach for analy ing the physiological responses and interactions within microbial communities. This dynamic modeling framewor will ultimately allow us to study the metabolic trade offs within natural and bioengineered microbial communities by capturing temporal changes and incorporating substrate upta e inetics.

Genome-scale metabolic models in combination with flux balance analysis can be used to explore the metabolic repertoires and restrictions of complex organisms or microbial communities. By reconstructing multi-tissue and multi-organism models, we can determine the interactions between different cell/tissue-types or organisms, resolve bottlenecks in limiting pathways, and study the metabolic trade-offs between species- level and community-level fitness functions.

Towards the first goal, a second-generation genome-scale model of *Zea Mays* has been constructed that captures C_4 carbon fixation by modeling the interactions between the bundle sheath and mesophyll cells in the leaf tissue. By integrating our earlier model, *i*RS1563, with information from the Kyoto Encyclopedia of Genes and Genomes (KEGG), MaizeCyc, and MetaCrop databases, we have constructed a cell-type specific metabolic model. The model combines gene-protein relationships (GPRs) with elemental and charge-balanced reactions. Experimental evidence pertaining to the biomass composition, compartmentalization, and flux constraints was incorporated into the model. Transcriptomic and proteomic data is used to introduce regulatory constraints in the model to improve the simulation of nitrogen rich/poor conditions as well as the impact of a glutamine synthase (GS) deletion. Using flux balance analysis combined with condition-specific biomass equations, we have simulated nitrogen rich and nitrogen poor supply conditions. Model suggestions achieve 80% accuracy in predicting the direction of change in metabolite pool sizes under the excess nitrogen versus limiting nitrogen conditions for 71 metabolites with metabolome data. Similarly, we attain approximately 76% and 75% accuracy in predicting the impact of GS1.3 and GS1.4 deletions on the 71 metabolites pool sizes, respectively. Ultimately, the goal is to reconstruct a multi-tissue model of not just leaf but all five major tissue-types in maize (root, stalk, leaf, tassel and seed), analyze the flow of nitrogen from the plant root to the other tissues, suggest genetic interventions to improve nitrogen use, and study the effect of nitrogen on sugar storage in the seed.

Moving from a single organism, we aim to develop efficient computational tools for the metabolic modeling and analysis of multi-species microbial systems, where more than one microorganism is involved and can interact through the unidirectional or bidirectional exchange of biochemical cues. Toward this end, we previously developed a procedure called OptCom for the steady-state flux balance analysis of microbial communities using genome-scale metabolic models. Microbial communities are known to exhibit dynamic shifts in their metabolism and inter-species interactions in response to changes/perturbations in environmental conditions to support co-growth, survival, and stability. The temporal variations in inter-species metabolic interactions can significantly affect the community structure and functions. In order to capture the temporal dynamics of microbial communities, we have developed a modeling framework called d-OptCom, by extending the OptCom procedure, which allows for incorporating a kinetic description of the uptake of shared metabolites while integrating species- and community-level fitness functions. The applicability of d-OptCom was demonstrated by modeling the dynamic co-growth of a number of auxotrophic mutant pairs of *E. coli* and by computationally assessing the dynamics within a uranium-reducing community comprised of *Geobacter sulfurreducens*, *Rhodoferax ferireducens* and *Shewanella oneidensis*. d-OptCom was also employed to examine the impact of electron donor addition on the relative abundance of uranium reducing species. These studies elucidate the importance of simultaneously accounting for both species- and community-level fitness functions when modeling microbial communities and demonstrate that the incorporation of uptake kinetics substantially restricts the feasible space of inter-species flux trafficking. Overall, this study paves promising frontiers for the dynamic multi- objective analysis of complex microbial ecosystems.

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