161. Metabolic modeling of multi-tissue and multi-organism systems

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Project Goals: The project aims to utilize both multiple tissue types in plants and multiple species in microbial communities to improve the understanding of metabolic interactions. The goals of this project are: 1) to determine bottlenecks in nitrogen metabolism, suggest genetic manipulations to improve nitrogen use efficiency, and enhance the understanding of nitrogen flow through maize, and 2) to analyze the physiological responses and interactions within microbial communities. A genome-scale multi-tissue maize model will be constructed to analyze nitrogen metabolism in the plant. By developing a dynamic modeling framework that utilizes constraint-based multi-level optimization, we can study the metabolic trade-offs within natural and bioengineered microbial communities, capture the temporal changes of the community, and incorporate substrate uptake kinetics.

Flux balance analysis of genome-scale metabolic models is a platform used to investigate the metabolic behaviors 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.

A second-generation metabolic genome-scale model of Zea Mays L. has been constructed to investigate nitrogen assimilation and to capture C4 carbon fixation. The maize model simulates the interactions between the bundle sheath and mesophyll cells in the leaf tissue. Incorporation of the previously published iRS1563 model, the MetaCrop database, and the MaizeCyc database using Metrxn yielded a model spanning 5,824 genes and 8,525 reactions. Biomass proportions were experimentally measured under excess nitrogen, limited nitrogen, and two glutamine synthetase mutants (i.e. gln1-3 and gln1-4) yielding condition-specific biomass equations. By applying the condition-specific biomass equations and condition-specific regulatory constraints based on transcriptomic and proteomic data, four nitrogen conditions were simulated. Simulated results achieved 90% accuracy when comparing the wild-type in a nitrogen complete condition with the nitrogen deficient condition. The flux through chlorophyll biosynthesis decreases in the limited nitrogen wild-type, gln1-3 mutant, and gln1-4 mutant conditions compared to the nitrogen complete wild-type condition confirming the important association between nitrogen metabolism and chlorophyll synthesis. Regulatory constraints based on the transcriptomic and proteomic data for 19 maize lines were applied to the model to determine the metabolic differences between maize lines. As expected, when comparing two lines within the same geographical region the metabolism was similar for over 80% of the reactions. However, when comparing the B73 inbred line to the C105 northern flint line, approximately 42% of the reactions had overlapping flux ranges at maximum biomass. Ultimately, the goal is to reconstruct a multi-tissue model of all major tissue-types in maize (i.e. the root, stalk, leaf, tassel, and seed) using the phloem as a metabolite transporter. This model will be applied to 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.
Towards the second aim, we have developed efficient computational tools for the metabolic modeling and analysis of multi-species microbial systems involving the unidirectional or bidirectional exchange of biochemical cues. Microbial communities are known to exhibit dynamic shifts in their metabolism and in their inter-species interactions following perturbations in environmental conditions to support co-growth, survival, and stability. In order to capture the temporal dynamics of microbial communities, we developed a modeling framework called d-OptCom, which incorporates the kinetic uptake of shared metabolites and, analogous to OptCom, integrates species- and community-level fitness functions. d-OptCom was used to assess the dynamics within a uranium-reducing community comprised of Geobacter sulfurreducens, Rhodoferax ferireducens and Shewanella oneidensis. By applying d-OptCom, we suggested that the injection of lactate to the community may be a more effective bioremediation strategy than the currently employed acetate injections. The study highlights the importance of simultaneously accounting for both species- and community-level fitness functions and demonstrates that uptake kinetics substantially restricts the feasible space of inter-species flux trafficking. Overall, this work paves promising frontiers for the dynamic multi-objective analysis of complex microbial ecosystems.

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