

A Multiscale Model of Fungal Growth & Metabolism

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Project Goals

The goals of this project are to develop hybrid machine learning/simulation models of *Pseudomonas fluorescens*/*Laccaria bicolor* interactions and dynamics. These hybrid data-analytic/simulation models will be used to carry out virtual experiments and develop fundamental understanding of the interactions between *Pseudomonas fluorescens* and *Laccaria bicolor*. At the same time, we will carry out experiments aimed at developing and testing quantitative assays to measure the same interactions, and whose data will inform the virtual experiments. We are:

- Evaluating the impacts of (1) thiamine and phenazines and (2) trehalose, produced respectively by *P. fluorescens* and *Laccaria*, on the metabolisms of each other. Metabolic exchange is an emerging theme in bacterial-fungal and bacterial-bacterial interactions.
- Characterizing *Laccaria*-stimulated chemotaxis of *P. fluorescens* by coupling trehalose signaling and metabolism to chemotaxis *P. fluorescens*.
- Experimentally investigating (1) *Pseudomonas fluorescens* chemotaxis and metabolism of *Laccaria* produced metabolites, and metabolism of *P. fluorescens* produced metabolites in *Laccaria*.

Abstract

Bacterial-fungal interactions play a fundamental role in many processes including crop biofuel development and biosystem design. In this work, we focus on the interactions between the fungi *Laccaria bicolor* and the bacterium *Pseudomonas fluorescens*, which play an integral role in the fitness of the roots of the Populus tree, an organism of interest as a biofuel crop. *L. bicolor* synthesizes trehalose which stimulates growth and chemotaxis of *P. fluorescens*. Furthermore, *P. fluorescens* provides *L. bicolor* with thiamine thereby increasing fungal mass. We developed a multiscale computational model to investigate these interdependent interactions. Our focus of this presentation is on the development of the *L. bicolor* structure and characterizing the energetic costs of growth and maintenance.

The hyphae of the filamentous fungi *L. bicolor* are modeled as a series of connected line segments using an off-lattice model coupled with a grid representing nutrient concentrations in the external environment. Nutrients in the environment diffuse while hyphae absorb the nutrients in the substrate at a rate of uptake following Michaelis-Menten kinetics that is dependent on both the current concentration of nutrients inside the hyphae and the local concentration of nutrients external to the hyphae. Nutrients that have been absorbed into the mycelium are transported throughout the colony to either fuel further growth or contribute to maintenance of the fungi. Nutrients used for maintenance are converted to nutrients used for growth at a rate following Michaelis-Menten kinetics. Both forms of nutrients are transported throughout the mycelia structure between hyphae segments. Passive short-range translocation of nutrients for maintenance move by convection and diffusion. Additionally, nutrients for growth undergo longer range active translocation towards the hyphal tips. Nutrients due to maintenance experience a loss in concentration due to biomass maintenance [1]. The changes in concentrations of nutrients due to maintenance and growth are represented by time-dependent ordinary differential equations.

L. bicolor grows by means of apical elongation of the hyphae and sub-apical branching. The length of the hyphal tip segment exhibits a rate of change following Michaelis-Menten kinetics which is dependent on the concentration of nutrients for growth. The energetic cost of growth is dependent on the rate of extension and

results in a loss of nutrients used for maintenance and for growth. Since hyphae are observed to grow in straight directions, the change in angle of the direction of elongation from one hyphae segment to the next differs by a normally distributed random number with mean zero and a small standard deviation. While the biological mechanisms underlying lateral branching is not well understood, some theorize it is due to a build up of vesicles far from the tip [4]. We model this phenomena by increasing the likelihood for a branch to emerge as a function of the internal concentration of nutrients for growth[2]. A hyphae segment is eligible for branching if it has not previously branched, the internal nutrient concentrations are greater than the costs of growth, and the segment is located behind a septa. We assume compartments separated by septa are of uniform length, hence septa are located at every N segments on each hyphal branch. The angle of branching follows a normal distribution where the mean and standard deviation are determined from experimental data [3]. After apical growth or sub-apical branching occurs, a check is performed for anastomosis or hyphal fusion. In the model presented, this occurs when two hyphae segments intersect. In the instance of intersection, the endpoint of the hyphae segment that experiences new growth is redefined to be the point of intersection.

To begin studying the energetic costs of growth and maintenance of *L. bicolor*, the impact of three different rates on mycelia development are tested. The three rates tested were the maximum uptake rate, the maximum rate of conversion of nutrients for maintenance to nutrients for growth, and the maximum rate of elongation at the tip. Preliminary results show that each rate has a large impact on the development of the mycelium, in particular, the amount of branching, colony size, and concentration of internal nutrients.

Our future work aims to couple the fungal model with two other biologically relevant models. First, the fungal development model will be coupled with an thermodynamic-kinetic maximum entropy ODE model for metabolism. The metabolism model contains over 200 reactions including protein and nucleic acid synthesis, from which the costs of growth and maintenance can be calculated. Second, we will couple the fungal model with a bacteria movement model. Trehalose secretion at the tips of the hyphae acts as a source of diffusive chemoattractant for *P. fluorescens*. The bacteria are described by a subcellular element submodel, a coarse-grained approach for describing biological properties of bacteria with great flexibility. Each bacterium is represented by multiple nodes connected to one another with linear and rotational springs with parameters calibrated using experimental measurements of mechanical properties of the bacteria. Bacterial motion is governed by potential functions and a propulsive force, calibrated using cell tracking data, which determine the movement and rearrangement of the nodes in an overdamped regime. We use simulations to evaluate the orientation and turning angle of the bacteria as they reverse their direction of motion in response to chemotactic signaling. The novelty of this multiscale model is that it takes into account bacteria-bacteria, bacteria-external nutrient, and fungal-bacteria interactions in addition to providing specific predictions to be tested in experiments. For example, we plan to test the impact of variations in fungal structures and nutrient excretion rates on bacterial chemotactic behavior.

References:

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