A Physics-Based Model of Fungal Metabolism and its Regulation

Sam Britton[1,2], Jolene Britton[1,2], Alireza Ramezani[1,2], Mark Alber[1,2], Dale Pelletier[3], Jessy Labbe[3], and **William R. Cannon***[4]

[1]Department of Mathematics, University of California, Riverside, Riverside, CA 92521
[2]Interdisciplinary Center for Quantitative Modeling in Biology, University of California, Riverside, CA 92521
[3]Oak Ridge National Laboratory, Oak Ridge, TN, 37830
[4]Pacific Northwest National Laboratory, Richland, WA, 99352;

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

The exchange of metabolites between microbes is an emergent property that evolves because the exchanged metabolites allow for increased growth of both species by reducing the thermodynamic cost of growth. Instead of each species producing every metabolite needed, metabolite exchange allows each microbe to specialize and efficiently produce a metabolite, such as trehalose, in exchange for one that it cannot produce as cheaply, such as thiamine.In economics this is known as Ricardo's principle of comparative advantage [1]. In order to evaluate the benefits of such microbial trade, physics-based models are needed that are capable of modeling the thermodynamic costs and benefits.

The long-term goal is to develop a complete physics-based model of metabolism, protein expression and gene expression and to couple this metabolic model to the filament model discussed in the poster, *A Multiscale Model of Fungal Growth & Metabolism*.

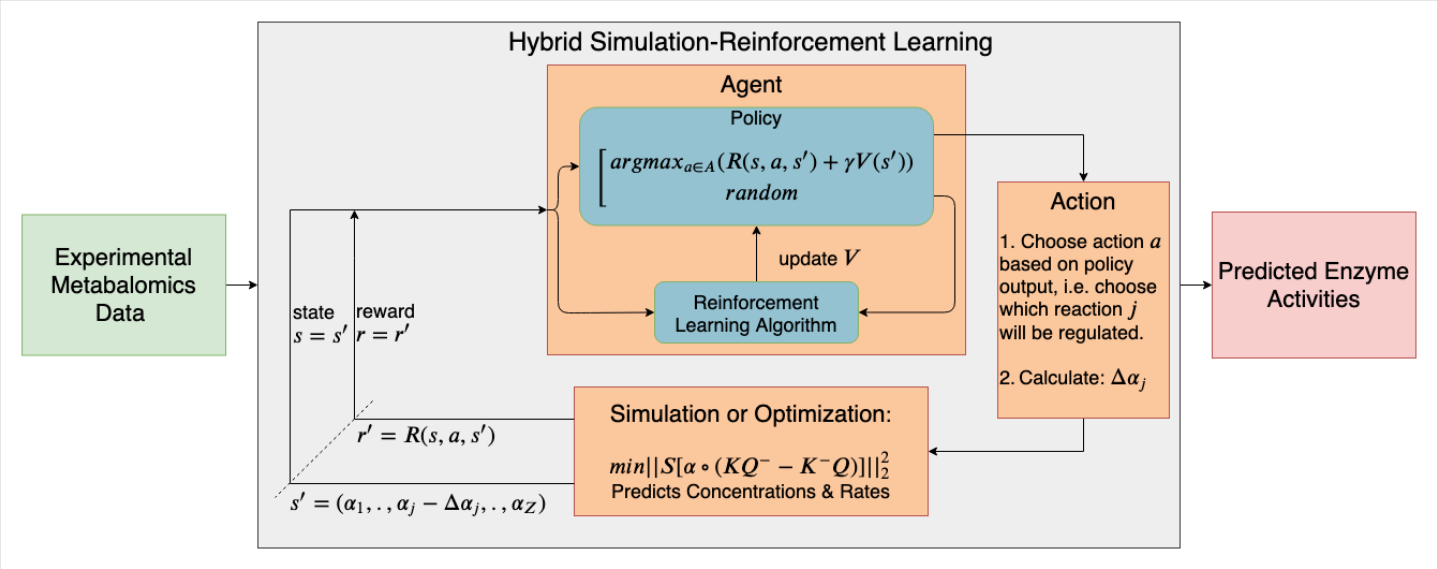
Our Laccaria bicolor metabolic model currently includes all reactions of central metabolism, synthesis of all 20 proteogenic amino-acids, synthesis of ATP, GTP, UTP, CTP and TTP and all deoxy-nucleic acid forms, synthesis of generic proteins, synthesis of generic DNA and growth on minimal media of glucose, ammonia, sulfate, and phosphate. Currently the model contains over 200 reactions and over 225 chemical species.

The ordinary differential equations (ODEs) needed to model the dynamics of metabolism are obtained by exploiting the natural selection principle that organisms that have the highest entropy production rates as a group will outcompete species with lower entropy production rates. Because we are using detailed models, entropy production includes all of growth, maintenance and catabolism. Another way of stating the entropy production principle is that the organisms that grow the fastest and most efficient will out compete others with slower and less efficient metabolisms. This perspective of metabolism subsumes many ecological concepts such as the red queen hypothesis and the black queen hypothesis. The maximum entropy production principle has a form that can be explicitly derived at the scale of metabolism.

The ODEs are solved using optimization methods, which provides steady state solutions in seconds, but can also be solved using time-dependent ODE solvers when non-steady state simulations are needed.

Experimentally determined constraints on growth and metabolism are included in the model (for instance, see Control and Regulation below).

Control and Regulation of Metabolism. Experimental measurements or computational model predictions of the post-translational regulation of enzymes needed in a metabolic pathway is a difficult problem. Consequently, regulation is mostly known only for well-studied reactions of central metabolism in various model organisms. We utilized two approaches to predict enzyme regulation policies and investigate the hypothesis that regulation is driven by the need to maintain the solvent capacity in the cell [2]. The first predictive method uses a statistical thermodynamics and metabolic control theory framework. The second method is performed using a hybrid optimization-reinforcement learning approach:



Efficient regulation schemes were learned from experimental data that either agree with theoretical calculations or result in a higher cell fitness using maximum useful work as a metric. As previously hypothesized, regulation was shown to control the concentrations of both immediate and downstream product concentrations at physiological levels. The model predictions provide the following two novel general principles: (1) the regulation itself causes the reactions to be much further from equilibrium instead of the common assumption that highly non-equilibrium reactions are the targets for regulation; and (2) the minimal regulation needed to maintain metabolite levels at physiological concentrations maximizes the free energy dissipation rate instead of preserving a specific energy charge. The resulting energy dissipation rate is an emergent property of regulation which may be represented by a high value of the adenylate energy charge. In addition, the predictions demonstrate that the amount of regulation needed can be minimized if it is applied at the beginning or branch point of a pathway, in agreement with common notions. The approach is demonstrated for three pathways in the central metabolism, gluconeogenesis, glycolysis-TCA and Pentose Phosphate-TCA, which each require different regulation schemes. It is shown quantitatively that hexokinase, glucose 6-phosphate dehydrogenase and glyceraldehyde phosphate dehydrogenase, all branch points of pathways, play the largest roles in regulating central metabolism.

References:

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