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4-5-2022

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TREATING MICROBIAL SYSTEMS ENGINEERING AS AN INVERSE FUNCTION PROBLEM TO ENHANCE PRODUCTION OF BIOMOLECULES

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Key Words: termite microbiome, deep learning, evolutionary algorithms, microbiome engineering, machine learning

Engineering microbial systems, including microbiomes, for the development of desired biomolecules is enormously challenging. Mathematical models have been used with some success to provide insight in addressing these hurdles. Immense effort has gone into the development of first principles mechanistic models, primarily for describing single cell organisms. In addition to providing fundamental understanding of how these organisms function, such models could potentially be used to predict cellular dynamics, as well as provide a framework for carrying out systems optimization. However, inferring and developing these models requires tremendous experimental and computational resources to capture the full complexity of the dynamics for a single cell organism, let alone a consortium of organisms. For the near term, other means are called for to facilitate engineering of microbial systems. One approach that shows promise is through casting the microbial systems engineering problem as an *inverse function problem*. An inverse function problem is one in which the desired output or product is known, but the input necessary to achieve that output is unknown. In this scenario, the microbial system represents the function. In our efforts, we used a simple two-prong method for implementing this strategy. First, a machine learning (ML) model was used to represent the microbial system.

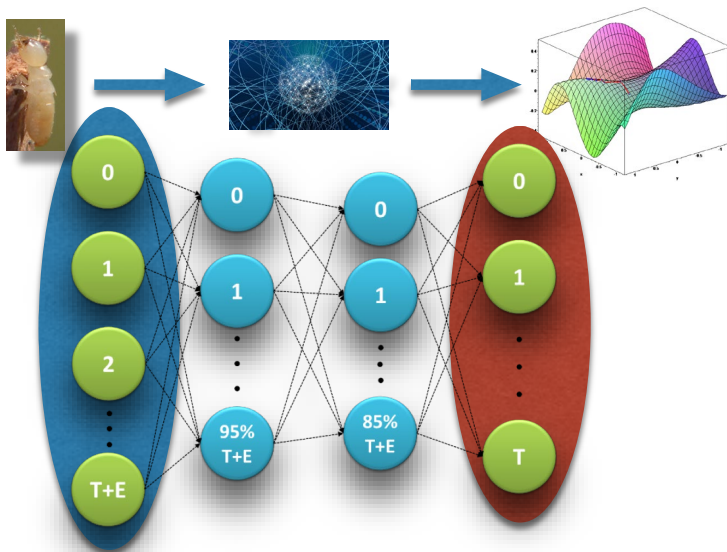


Figure 1 – Schematic representation of using a deep learning neural network to predict community composition dynamics of *R. flavipes* termite microbiome over time. The green circles hovering over the blue oval on the left-hand side of the figure represents the inputs into the neural network. The green circles on the right-hand side hovering over the red oval represents the output of the network.

Once the ML model was trained, an evolutionary algorithm was used to *evolve* a set of inputs yielding the desired output. As a case study, we chose to maximize acetate production from lignocellulose processed via the termite microbiome, using the termite *Reticulitermes flavipes*. We leveraged our previous experimental efforts in characterizing changes in the termite microbiome composition over time under varying substrate feeding conditions. We accomplished this by creating and training a deep learning artificial neural network to predict how the termite microbiome would change over time as the substrate was varied. Six different substrates were used. We focused on maximizing the order *Rhodospiralles* in the termite microbiome, as it is primarily responsible for acetate production in the community. Hence, maximization of *Rhodospiralles* was our desired output, while the input to be manipulated was our substrate feeding strategy. We used an evolutionary algorithm, specifically a genetic algorithm, to determine the feeding strategy to accomplish this goal. Of the six different lignocellulose sources used, we predicted that a steady diet of maple over the seven-week period of interest

would result in maximization of *Rhodospiralles* and ideally acetate. While there are clearly caveats associated with this method, we believe our efforts illustrate the potential benefit and feasibility of using an inverse function approach to carry out microbial system engineering and, more specifically, microbiome engineering. Furthermore, the principles illustrated are not simply limited to microbial systems; rather they have the potential for much wider usage in biology and beyond