A White-Box Machine Learning Approach for Revealing Antibiotic Mechanisms of Action - DTU Orbit (11/08/2019)

A White-Box Machine Learning Approach for Revealing Antibiotic Mechanisms of Action

Current machine learning techniques enable robust association of biological signals with measured phenotypes, but these approaches are incapable of identifying causal relationships. Here, we develop an integrated "white-box" biochemical screening, network modeling, and machine learning approach for revealing causal mechanisms and apply this approach to understanding antibiotic efficacy. We counter-screen diverse metabolites against bactericidal antibiotics in Escherichia coli and simulate their corresponding metabolic states using a genome-scale metabolic network model. Regression of the measured screening data on model simulations reveals that purine biosynthesis participates in antibiotic lethality, which we validate experimentally. We show that antibiotic-induced adenine limitation increases ATP demand, which elevates central carbon metabolism activity and oxygen consumption, enhancing the killing effects of antibiotics. This work demonstrates how prospective network modeling can couple with machine learning to identify complex causal mechanisms underlying drug efficacy.

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