

Modeling the Host-Pathogen Interface

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Infection, host response and the occurrence of disease can be viewed as an emergent property resulting from the interaction of multiple systems. While the tendency is to study microbial pathogens and their potential host systems separately or from a host or pathogen centric skew, the nature and dynamics of the interaction between the systems are key determinants in immunity and disease outcome. With the goal of integrating host and pathogen interactions, we explore pathogen adaptation to environmental stress and conditions that can be modulated as part of the host immune response to infection. We focus on intracellular pathogens *Mycobacterium tuberculosis* and *Francisella tularensis* (Ft-LVS) and develop kinetic models that correlate environmental dynamics with changes in pathogen metabolism.

Leveraging metabolic models of the tricarboxylic acid cycle (TCA) in *Mycobacterium tuberculosis* and iron homeostasis in *Escherichia coli*, we develop mathematical models of pathogen response to oxygen and iron limitation. Stoichiometric relationships are used to construct kinetic models of key biochemical pathways and data from empirical studies and public databases are used to refine model parameters. Models were implemented using Matlab and BioXyce, with BioXyce models integrated into multiscale modeling platforms.

Our results suggest mechanistic relationships between pathogen persistence, metabolic response to environmental stress, and biochemical and physiologically based host immune response. The simulated metabolic responses under differing levels of oxidative stress appear to concur with empirically observed changes in pathogen growth. Further models take into account Mtb's stress response adaptation pathways that facilitate transition to dormancy, and explore the biochemical mechanisms underlying Ft-LVS response to host-mediated modulation of extracellular iron concentrations.

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