

Dr. Jeffery M. Gearhart, D.A.B.T.

Wright – Patterson Air Force Base
The Henry M. Jackson Foundation for Military Medicine

Monday, April 22, 2013

11:00AM to 12:00PM

Seminar

ENGR 1 – 102-D

Multi-Scale Models of Host-Pathogen Interactions for Infectious Agents and Translational Medicine

Abstract

A fundamental challenge in developing treatments for infectious diseases is the mechanistic and quantitative extrapolation of animal experimental results to predict human responses. Limited human exposure response data exists for the most lethal pathogenic organisms (i.e. bacterium *Francisella tularensis*). Controlled animal models are used to test the possible infectivity and pathogenic processes that might occur in humans, yet this infection dose-response paradigm still begs the relevance of the different species responses to the human infection process. One approach is to develop quantitative mechanistic *in silico* models based on published laboratory studies, to predict human infection. Inherent to this *in silico* process is the notion of the multi-scale biological system. We initially developed a multi-scale biologically-based *in silico* model of anthrax (*Bacillus anthracis*, BA) infection that integrates processes and behaviors across these multiple levels, focusing on specific interactions between the bacteria and the host's macrophages at the sub-cellular and biochemical level via modification of the host's cell signaling pathways. Our model allows us to estimate cleavage rate constants from *in vitro* data for a number of macrophage – anthrax strain combinations, and thus estimate macrophage susceptibilities to particular BA strains. We are currently extending this multi-scale modeling approach to apply to gram-negative tularemia (FT) and plague (YP) bacteria. Our current approach involving ODE's is highly effective for single-scale models, but quickly grows complex when multiple scales are considered. Agent-based models simulate the system in terms of the behavior of the individual components; rather than a single, complex mathematical equation for each component, the model consists of many mathematically simple interactions, the aggregate of which corresponds to the results of a rate equation in an ODE model. Agents in this type of model can also modify the rules governing their own behavior, which will be useful in simulating the acquired immune response. We are currently developing a global model of the host immune response to pathogens, which is being linked with lung deposition models we have previously developed to simulate the outcome of *in vivo* aerosol exposure studies and extrapolate to human response predictions. Our computational approach allows the actions of these members to be enhanced or suppressed to simulate mechanisms of immune subversion. We have applied the model to tularemia, simulating the innate response of mice to different *Francisella tularensis* strains (LVS, U112, and SchuS4). The approach is to train the models with experimental animal response data, and then input the human physiological parameters to extrapolate from the animal data.