Systems Biology of Epidemiology: From Genes to Environment

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***Short Abstract* — The goal of this research is to study a pathogen-centric mathematical model, codenamed NEXUS, capable of capturing essential aspects of infectious disease such as simultaneous infection, antigenic diversity, and antigenic variation, while still being able of linking within-host events with epidemiological dynamics.**

***Keywords* — Epidemiology, multiscale, antigenic diversity, antigenic variation, simultaneous infection, host-pathogen.**

I. Purpose

THE The traditional epidemiological approach to characterize transmission of infectious disease consists of compartmentalizing hosts into susceptible, exposed, infected, recovered (SEIR), and vectors into susceptible, exposed and infected (SEI), and variations of this paradigm (e.g. SIR, SIR/SI, etc.). However, with the advent of genomics, we have learned that microdiversity among strains of the vast majority of pathogens is extensive; each genotype infecting a host can present significant differences in virulence, immunogenicity, and antigenic variation. Thus, pathogens in circulation are not uniform; instead, they are comprised of sub-groups that can be defined by the expression of different genetic, pathogenic and population dynamic traits. The circulation of these parasites depends heavily on human movement dynamics, and, in some situations, vector availability and competence. Together, these anthropological, ecological, molecular, and immunological factors are fundamental drivers in the transmission of infectious disease, and their correct characterization requires a comprehensive interdisciplinary multi-scale modeling approach.

The goal of this research is to study a pathogen-centric mathematical model, codenamed NEXUS, capable of capturing essential aspects of infectious disease such as simultaneous infection (simultaneous presence of several distinct pathogen genomes, from the same or multiple species), antigenic diversity (antigenic differences between pathogens in a population), and antigenic variation (ability of a pathogen to change antigens presented to the immune system during an infection), while still being able of linking within-host events with epidemiological dynamics.

II. Model

The model described in this project, codename **NEXUS** (from Latin *nexus*, the act of binding together), is a multi-scale approach to infectious disease that measures the population density of pathogens in the environment. I accomplish this goal by binding together, in a unified framework, data developed in the two of the largest malaria research projects currently funded by NIH (NIAID U19AI089702 and HHSN272201200031C). Instead of compartmentalizing individuals within a population, as traditionally done, into susceptible, exposed, infected, recovered (SEIR), we have designed a study to model the transmission of malaria as a multi-scale ecological problem in which the parasite lives in "islands" (humans and anopheline mosquitoes) with a rate of connectivity (i.e. rate of infection). Using this framework, it is possible to estimate the population density *of the parasite* within both symptomatic and asymptomatic individuals in a geographic area (as opposed to estimating risk of human infection, number of infected patients, or number of infected mosquitoes), which in turn could inform the optimal use of public health resources towards the elimination of the parasite. The number of infected humans can be easily calculated indirectly with this approach.

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