Modeling single-variant bottlenecks in early stages of *H. influenzae* bacteremia

Xinxian Shao[1], Bruce R. Levin [2], and Ilya Nemenman[1,2]

***Short Abstract* — Classic experiment of Moxon and Murphy [1] has observed that, when inoculated intranasally with a mixture of equally virulent strains of *Haemophilus influenzae*, neonatal rats develop a bacteremic infection that often is dominated by only one random competing strain. We propose a stochastic model to account for such single-variant bottlenecks. The model is based on the hypothesis of individual bacterial cells switching stochastically between two phenotypes during establishment of bacteremia.**

***Keywords* — Early invasion, Bacteremia, stochastic model, phenotypic switching.**

I. Background

WHILE extensive studies have focused on the molecular mechanisms of pathogenesis, little is known about population dynamics of early colonization of the host by bacteria. Even the basic questions of whether bacterial cells acts independently during an invasion, and how many bacteria initiate a successful colonization remain unanswered [2].

Here we investigate computationally the population dynamics of host colonization by *Haemophilus influenzae*, which is the leading cause of bacterial meningitis in newborns [5]. Experimental studies of *H. influenzae* b infections by Moxon and Murphy using a neonatal rat model [1] discovered that the bacteremia and meningitis often resulted from survival of one random bacterial strain in the blood, 54 hrs after intranasal infections by a mixture of multiple equally virulent *H. influenzae* b. The observation that both strains were present in the blood five minutes after inoculation, and that preponderance for single-variant infections decreased with the inoculum size made interpretation of these results difficult. A subsequent experiment has shown that this single-strain bottleneck could not be explained fully by within-host evolution of bacteria, which would allow descendants of one strain to outcompete the other [3].

II. Hypothesis and Modeling

Inspired by ubiquity [4] and evolutionary necessity [5] of stochastic phenotypic switching, we propose that each individual bacteria can exist in two heritable phenotypes relevant for early infection: a phenotype that allows crossing the physical barrier between nasopharynx and blood but does not exhibit strong growth in the bloodstream, and phenotype that cannot cross the barrier, but can exhibits fast growth in the bloodstream. The rate of stochastic switching into the growth state is much smaller than the reverse rate, which ensures rare initiation of the population growth. Once one of the two strains switches and begins rapid growth, recruitment of cells mediating innate immune response in the host [6] reduces survival of the other strain, and hence a possibility of a mixed infection. This dynamics is represented by a set of ODEs accounting for population sizes of growing and crossing phenotypes for each bacterial strain and for immune response recruitment. The model is aided by stochastic representation of single cell switching events.

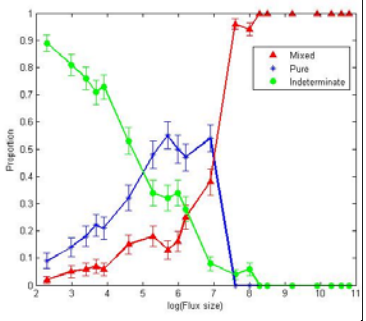

Figure 1. Simulated proportions of different infections out of 100 subjects infected, 54 hrs post-inoculation for each different inoculum size.

III. Results and Conclusion

Fractions of subjects exhibiting single-variant, mixed, and no or weak infections, 54hrs post-inoculation are shown in the Figure 1. The dependence of the fraction of pure infections and the variance of the fraction on the inoculum size parallels the experimental measurements in [1]. Existence of the fast backwards switching process further accounts for little observed advantage of a winning strain in reinfection experiments [3]. We conclude with proposing experimental test of our model based on reinfections with time delays.

Acknowledgements: This work was funded in part by James S. McDonnell foundation and by NIH grant XX00000.

[1]Department of Physics, [2]Department of Biology, Emory University, Atlanta, GA, USA. E-mail: xshao@physics.emory.edu, blevin@emory.edu, ilya.nemenman@emory.edu

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