Infection Risk of Antibiotic Resistant Bacteria

Srikiran Chandrasekaran[1] and Sunny Jiang[2]

***Short Abstract* — Antibiotic resistant bacteria (ARB) are a growing problem due to rapid evolution of resistance to existing drugs and concomitant void in drug discovery. To estimate the size of their threat and manage the risk, it is useful to understand the probability of a person falling ill from a given bacterial dose. Studies producing such data involve inoculating volunteers with ARB and raise ethical concerns. Here we present a stochastic modeling approach that leverages data from *in-vitro* experiments to predict the relationship between infection probability and number of ARB. Specifically, we discuss results for *E. coli* and its Gentamicin resistant strain.**

***Keywords* — Antibiotic resistant bacteria, stochastic, birth and death process, dose response model**

I. Introduction

THE emergence of antibiotic resistance and its subsequent escalation is well documented. Among reasons for this are the overuse/misuse of antibiotics (ABs) and the greater difficulty in discovering new drugs [1–3).

A necessary step in evaluating the size of the problem and predicting the efficacy of risk management measures is understanding the probability of a person falling ill ($P_i(N_d)$) from a given dose of bacteria (N_d). Models built for this purpose are termed dose response models (DRMs) (4). To understand risk in the ARB context, existing DRMs require data from studies where volunteers are inoculated with ARB. Such studies are currently infeasible due to ethical and practical difficulties. This calls for DRMs that can effectively integrate data from *in-vitro* studies involving ARB to address the issue.

II. Methods

A dose of bacteria once inoculated in a person can face one of two fates. Either it dies out not causing any symptoms or it survives, causing illness. Thus, a stochastic model of bacterial growth can establish a relationship between N_d and $P_i(N_d)$. Such a growth model can then be extended to two bacterial populations, one susceptible and one resistant to AB. The relationship between the growth constants of the populations can be obtained from relevant experiments done *in-vitro*. Here we apply this concept to *Escherichia coli* that causes diarrhea.

A. *Escherichia coli*

A stochastic birth and death process (discrete bacterial numbers, continuous time) was assumed to arrive at a simple analytical expression (5) relating $P_i(N_d)$ to the dose (N_d), birth rate (λ) and death rate (μ). Fitting of this relationship to 4 datasets from human volunteer studies indicates that new model outperforms existing DRMs in 2/4 cases.

Exploratory analyses (with relevant parameters from (6)) on *E.coli* and Gentamicin resistant *E. coli* revealed the alarmingly small doses of the latter required to outcompete its susceptible counterpart in the presence of residual antibiotic in the body. Bayesian data fitting was performed with R(7) and STAN(8).

III. Conclusion

Stochastic modeling of bacterial growth dynamics appears to be as good as, if not better than, current DRMs. They have the added advantage of extending naturally to mixed doses of antibiotic sensitive bacteria and ARB.

References

1. Ventola, C. L. (2015) The Antibiotic Resistance Crisis: Part 1: Causes and Threats. *Pharm. Ther.* **40**, 277–283
2. WHO (2014) Antimicrobial Resistance: An Emerging Water, Sanitation and Hygiene Issue Briefing Note WHO/FWC/WSH/14.07. 10.13140/RG.2.2.24776.32005
3. Davies, J., and Davies, D. (2010) Origins and Evolution of Antibiotic Resistance. *Microbiol. Mol. Biol. Rev.* **74**, 417–433
4. Haas, C. N., Rose, J. B., and Gerba, C. P. (2014) *Quantitative Microbial Risk Assessment*, John Wiley & Sons, Inc, Hoboken, New Jersey, 10.1002/9781118910030
5. Allen, L. J. S. (2010) *An Introduction to Stochastic Processes with Applications to Biology, Second Edition*, Second, CRC Press
6. Nielsen, E. I., Cars, O., and Friberg, L. E. (2011) Pharmacokinetic/Pharmacodynamic (PK/PD) indices of antibiotics predicted by a semimechanistic PKPD model: A step toward model-based dose optimization. *Antimicrob. Agents Chemother.* **55**, 4619–4630
7. R Core Team (2017) R: A Language and Environment for Statistical Computing
8. Stan Development Team (2016) {RStan}: the {R} interface to {Stan}

Acknowledgements: This work was funded by Bill and Melinda Gates Foundation OPP1111252.

[1]Graduate Student in Mathematical, Computational and Systems Biology, University of California, Irvine E-mail: srikirac@uci.edu

[2] Department of Civil and Environmental Engineering, University of California, Irvine E-mail: sjiang@uci.edu