Literature Review of Modeling Bacterial Growth and Antibiotics

For our project, we will be utilizing and adapting existing methods that simulate bacterial behaviors. One of the initial models we came across pertains to the mutation rates in bacteria. This aspect is pivotal to our project as it influences whether a bacterium can withstand specific antibiotics. The model we've chosen for mutation is based on genetic drift and is structured using Markov Chains. In this model, we assign a binary vector to each bacterium, with each gene involved in antibacterial resistance considered as a potential factor in the bacterium's resistance to particular antibiotics (Bayliss et. al, 2019). For our model, we define one time step as a single cycle of cellular division. At each time step, we create a matrix representing all possible gene variations for each bacterium. We then calculate transitional probabilities using a predetermined mutation rate and apply these probabilities for each time step. The mutation rates we will employ have been calculated in previous research, relying on calculations derived from established biological methodologies used to determine actual mutation rates in bacteria. (Rosche & Foster, 2000). A crucial feature of this model is its ability to start with a population of bacteria rather than a single bacterium, which is essential for our goal of modeling the development of antibiotic resistance. Lastly, our approach for mutation includes using a selection mechanism to modify the transitional probability matrix based on the significance of individual genes for survival against specific antibiotics (Bayliss et. al, 2019).

In the design of our genome vectors, we will take into account known mechanisms of antibacterial drugs, as well as common bacterial defenses. By associating our bacteria's genes with real bacterial adaptations, we can rigorously assign mutation rates to different genes based on the relative likelihood of those specific adaptations. Common bacterial resistance mechanisms include drug uptake inhibition, drug modification or inactivation, drug target modification, and drug efflux (Reygaert W. C., 2018). Other heritable traits can be modeled as well. Cell size and surface-to-volume ratios have been shown to affect antibiotic resistance, and some bacteria even adjust these characteristics in response to the presence of a drug to induce resistance (Ojkic et al, 2022). Some adaptations cannot develop in bacteria with certain genetic traits, so by modeling them explicitly in our genome vectors we can prevent certain genes from co-occurring. For example, gram-positive bacteria are incapable of developing certain types of efflux pumps (Reygaert, 2018), so we can disallow them from acquiring those genes.

We will also incorporate another model into our work, which centers on bacterial division within each cell cycle. This model relies on a stochastic differential equation approach, primarily designed to compute the growth rate of bacteria until the population reaches its stationary phase (Alonso et. al, 2014). Employing the stochastic differential equations from the research, we can derive a growth rate that, along with a probabilistic model, enables us to simulate bacterial division, non-division, or mortality (Horowitz et. al, 2009). Our approach involves utilizing the probabilistic method as a Markov chain to mimic bacterial behavior regarding division at each time step. By integrating this model with our mutation model, our aim is to simulate the development of antibiotic-resistant bacteria comprehensively. The division model will be

instrumental in determining the population's growth rate and how individual bacteria behave concerning division during each time step. Simultaneously, the mutation model will contribute to generating new genetic characteristics that influence the death rate at each time step.

A variety of modeling techniques have been utilized to investigate different aspects of antibiotic behavior. The two primary modeling approaches for antibiotics are pharmacokinetic models, which simulate the ways in which “the body interacts with administered substances for the entire duration of exposure,” and pharmacodynamic models, which characterize the physiological effects of the antibiotics on bacterial growth and death (Grogan, 2023).

Simple pharmacokinetic models are based on systems of ordinary differential equations (ODEs) that have simulated antibiotic absorption, distribution, metabolism and excretion in patients (Nielsen & Friberg, 2013). While helpful for optimizing dosing, such models provide little insight into mechanisms of action or resistance. More detailed ODE models have incorporated bacterial growth dynamics and antibiotic-target binding to quantify antibiotic effects on bacteria (Regoes et al, 2004). Agent-based modeling allows representing individual bacteria with differing and evolving resistance profiles, in order to simulate how antibiotic concentration gradients and the density of bacteria influence the horizontal transfer of genes that confer antibiotic resistance between bacteria (Zhang et al, 2011).

Integration of pharmacokinetic and pharmacodynamic modeling with systems biology models of bacterial transcriptional responses has enabled connecting antibiotic exposure to changes in gene expression and subsequent impacts on resistance (Stokes et al, 2019). Multiscale models combining intracellular regulatory networks, population dynamics, and antibiotic pharmacokinetics are being applied to predict antibiotic efficacy in vivo (Danhof et al., 2007). Overall, ODEs, agent-based modeling, molecular simulation, and multiscale techniques have provided quantitative insights into mechanisms of antibiotic function and bacterial resistance evolution.

Overall, our model will utilize key aspects of the previously discussed models with respect to mutations, division, and antibiotics. We will use a pharmacodynamic, agent-based modeling technique when simulating the effects of the antibiotics on the bacteria, in order to see the impact of different dilutions on the density of antibiotic-resistant populations. For mutations, we will utilize methods based on a markov chain model along with a pre-determined mutation rate established by previous research to simulate the emergence of antibiotic resistant bacteria in a bacteria population. Lastly, cellular division will be modeled based on rules established in a markov chain model for division of bacteria to simulate growth and death of the population of bacteria. To establish novelty, our model will introduce a cellular automaton with rules defined by the aforementioned bacterial and antibiotic models to produce a more effective simulation of bacterial growth and antibiotic resistance. This innovation will integrate a spatial component to these existing models, and provide an environment for these models to interact with each other.

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