Game Theory and Antimicrobial Resistance Evolution in Bacterial Populations

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This topic explores how evolutionary game theory can model the competition between antibiotic-resistant and non-resistant bacterial populations. I thank Dr. Matuszewska for sharing her knowledge on the subject.

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Abstract

The development and spread of antimicrobial resistance (AMR) among bacteria decrease their susceptibility to antibiotics, resulting in higher mortality rates worldwide. The spread of AMR is due in part to the actions of mobile genetic elements (MGEs), which transfer genes, including AMR genes, by integrating into parts of DNA. Studying the spread of AMR is of the utmost importance as a stepping stone to determine how to contain it. This can be studied using Evolutionary Game Theory (EGT), which assumes that species evolve to utilize optimal strategies. EGT allows researchers to model the changes in behavior between organisms. This paper reviews previous examples of EGT being applied to the spread of AMR, then narrows our scope and analyzes the potential applicability of EGT on the movements and gene transfers of MGEs.

Background

In contrast to traditional experiments, mathematical modeling is a widely applicable yet relatively new scientific technique for drawing conclusions (Möbius & Laan, 2015). Mathematical modeling refers to a cyclical process of utilizing mathematical language and scientific concepts to describe a real-world problem that may be solvable through modeling by following these steps: collect experimental data by mimicking real-life scenarios, formulate mathematical model, analyze mathematical solution, interpret real-world interpretation, revise or accept mathematical model, and communicate the report results if the model is deemed to be valid, or return to steps one again if the model is not ideal (Dunn & Marshman, 2019). The mathematical models aim to simplify the real-world problem as much as possible while still fitting the data (Dunn & Marshman, 2019). The simplified parameters on which the model is based are selected by examining trends in the experimental data (Dunn & Marshman, 2019). Creating models follows a cycle; a model can be tested against existing data and compared against observations to assess its accuracy, and then refined according to the results (Grimm et al., 2014). Models can be beneficial when applied in future situations, rather than conducting additional experiments, which can be more costly, time-consuming, and often not feasible (D'Ambrosio et al., 2024).

Mathematical models have been applied to a diverse range of fields. In gastroenterology, models are used to help understand drug absorption in the human intestines (D'Ambrosio et al., 2024), such as gut colonization (Angell & Rudi, 2020). On a broader biological scale, models have been used to examine the persistence of cooperation as a strategy across species (Lambert et al., 2020). In the field of environmental science, models have been invaluable in understanding and tracking climate change, enabling decision-makers to make informed decisions about the climate (Hausfather et al., 2019).

Mathematical models are capable of illustrating how different characteristics within populations, such as cooperation and competition, evolve over time. To help create these models, one can use Evolutionary Game Theory (EGT) (Kastampolidou & Andronikos, 2021). EGT draws from Game Theory, a field that studies different strategies for a game and how they work when used against each other (Kastampolidou & Andronikos, 2021). EGT posits that if a strategy yields greater benefits to a species, the species will eventually evolve to utilize it (Kastampolidou & Andronikos, 2021). EGT has applications in modelling decisions in both human and animal populations (Czárán et al., 2002; Li & Fu, 2024).

Mathematical models can be used to model the spread of antimicrobial resistance (AMR), which refers to the ability of bacteria to become resistant to antibiotics. Although many models of AMR exist, they are not well-documented (Birkegard et al., 2018). Niewiadomska et al. (2019) state that most antimicrobial resistance models focus on diseases with long-established resistance, like methicillin-resistant *Staphylococcus aureus* (MRSA). Along the same vein, Birkegard et al. (2018) stated that modelers as a whole need to improve their analyses by both including documentation describing the model's sensitivity and better incorporating uncertainty into their models. They can do this using stochastic modeling, which is defined as a mathematical framework that enables the simulation and analysis of random processes and their outcomes (Birkegard et al., 2018; CFI Education, n.d.).

This literature review aims to examine the applicability of EGT mathematical models on the spread and development of AMR. Additionally, we examine the factors that contribute to the complexity of AMR in vivo. Having a comprehensive understanding of the factors that cause resistant bacteria to develop will enable people to better mitigate the harm of AMR.

The History and Application of Game Theory

Main Principles of Game Theory

Game Theory (GT) represents a mathematical framework for understanding how competing agents make decisions in conflict (Trafton, 2009). Typically, games used in game theory involve multiple players, each with the ability to make decisions that affect all players involved (Holt & Roth, 2004). Kastampolidou and Andronikos (2021) explained that games represent an innate part of human nature, and applying GT helps to model the development of cooperation or competition between the players involved. The agents' rationality and personal interests determine the strategy and the course of action (Kastampolidou & Andronikos, 2021).

A key concept in game theory is the Nash Equilibrium (NE). The NE was formulated in 1950 by mathematician John Nash. While Nash was not the first to work on the concept of equilibrium, his proposition was the most useful as it was applicable to a wide variety of situations (Holt & Roth, 2004). The equilibrium arises when all players play strategies such that no individual can benefit by changing their strategy (Holt & Roth, 2004). A prominent example is the Prisoner's Dilemma, a game in which two partners-in-crime are jailed and have the choice to rat out the other or remain silent. In the game, because both prisoners will serve less jail time by informing on the other prisoner, the equilibrium occurs when both individuals choose to betray their partner (Heuer & Orland, 2019). The concept of equilibrium can be used to predict the choices of real-world people playing these games, as rational players will always pick strategies that result in an equilibrium.

Evolutionary Game Theory

Evolutionary game theory (EGT), an enhanced version of classical Game Theory, is a suitable tool for modeling the evolution and distribution of phenotype-expression patterns in biological populations (Kastampolidou & Andronikos, 2021). It is built on the idea of natural selection being a method of ‘choosing’ strategies for a species. Over time, these interacting populations will eventually evolve to use the equilibrium. Therefore, scientists have adopted EGT to study the genotypes, phenotypes, cellular behaviors, population behavior, environmental forces, and regulatory dynamics of organisms. Researchers have been implementing EGT to predict future strategies and dynamics of the populations.

More recently, EGT has been employed in various studies and utilized in numerous scenarios to identify the most efficient solution among several possible options for a problem. An example of this is Li and Fu’s (2024) analysis of the factors impacting labor education, where employers must balance training efficiency with cost. Similarly, Wu et al. developed an artificial intelligence network that utilizes EGT-like techniques to assist hospitals in better allocating their resources and selecting treatments for patients.

The EGT framework is helpful in understanding incentives. Game theorists leverage the strength of EGT in creating situations that encourage people to perform specific actions. For example, Zhang and Liu (2024) conducted a study to determine what could best induce cooperation in water conservation projects. Similarly, Li and Mei (2024) noted that many enterprises were reluctant to share data, which rendered the data in question less useful. Thus, they sought to find ways to incentivize the sharing of data better (Li & Mei, 2024).

Previous Applications of GT on Microbial Communities

Game Theory has been used in microbial communities to simulate the interplay between different strains of gut bacteria in infant children in the 2020 study by Angell & Rudi. In this study, they compared two utilization strategies: generalism and specialism. Generalists have adapted to be able to use more nutrients, while specialists can use specific nutrients more effectively. They found that while generalists survived the best for the first three months after birth, they generally phased out and were replaced by specialists. That is to say, the ideal strategy changed from being a generalist to being a specialist.

Antimicrobial Resistance (AMR)

The existence of antibiotic-resistant bacteria makes pathogens more challenging to treat, leading to higher mortality and morbidity rates (Brauner et al., 2016). In the United States, 2.8 million AMR infections occur each year, and more than 35,000 people die from those infections (CDC, 2019). Naghavi et al. (2024) state that more than one million people from around the world died from AMR bacteria every year from 1990 to 2021. The same study also forecasts that the number of AMR deaths will rise each year, to an increase of about 70% by 2050. The intensive usage of antibiotics in humans and livestock has resulted in a higher frequency of AMR-associated infections (Andersson & Hughes, 2010).

However, there is a tradeoff for bacteria to be resistant. In environments where antibiotics are not present, producing resistance proteins can redundantly consume energy and resources that could be allocated to other biological processes (Johnsen et al., 2021). Thus, we can say that there is a fitness cost to AMR (Andersson & Hughes, 2010). Studies have shown that, in principle, a decrease in antibiotic usage would lead to resistant strains being outcompeted by fitter strains, although this idea of reversibility is unlikely to work in real-world conditions (Andersson & Hughes, 2010). Moreover, the ability to reverse resistance depends on the fitness cost of AMR, which is affected by factors like epistasis and environmental conditions.

Previous Applications of Game Theory on AMR

Chowdhury et al. (2019) used game theory to aid a machine learning approach to identifying AMR genes in pathogens. To determine which subset of protein sequence features to use for the model, they employed game theory (Chowdhury et al., 2019). Game Theory has also been used to model antagonism between microbes of the same species (Czárán et al., 2002). According to Czárán et al. (2002), it is common for microbes to kill sensitive strains from their own species by secreting harmful compounds. Even though killer strains kill sensitive strains with their antibiotic compounds, killer strains and sensitive strains have been shown to be able to coexist (Czárán et al., 2002). To model this, Czárán et al. (2002) included strains resistant to the compounds in their model, then displayed the relationship between the three strains by creating what is known as a Rock Paper Scissors (RPS) model. Because killer strains kill sensitive strains, resistant strains resist killer strains, and sensitive strains are more fit to survive than resistant strains, a cyclic dominance exists that allows all three types to coexist (Andersson & Hughes, 2010; Czárán et al., 2002).

Antibiotic Modes of Action

Bacteria have numerous ways of mutating to become resistant to the antibiotic. For example, the methicillin-resistant strain of *Staphylococcus aureus* (MRSA) is resistant because of its ability to secrete beta-lactamase, which prevents the antibiotic from reaching the cell membrane (Guo et al., 2020). Additionally, several bacteria have been known to mutate the target site that antibiotics attack, thereby becoming resistant (Patel et al., 2023).

Antibiotics can be divided into two classes: bacteriostatic and bactericidal (Patel et al., 2023). Antibiotics in the bacteriostatic category stop a pathogen's spread by inhibiting its growth (Patel et al., 2023). This category includes the oxazolidinone antibiotic linezolid, which prevents the creation of new proteins by binding to their ribosomal (Guo et al., 2020). In contrast, bactericidal antibiotics are biotics that directly "kill" bacteria (Patel et al., 2023). A prime example of this category is the beta-lactam antibiotic methicillin, which prevents the polymers in the bacterial cell membrane from binding together, thus eliminating them (Guo et al., 2020).

Patel et al. (2023) state that the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) can be used to measure bacterial susceptibility to certain antibiotics. The MIC of an antibiotic is defined as the lowest concentration that prevents visible growth of the antibiotic (Patel et al., 2023; Krochmal & Wicher, 2021). The MIC of an antibiotic can be calculated in laboratory conditions using the agar microdilution process (Krochmal & Wicher, 2021). To perform this process, one must dissolve different concentrations of antibiotics in specific solvents, then dilute them with bacteria strains in agar before incubating them for 24 hours (Krochmal & Wicher, 2021; Wiegand et al., 2008). Meanwhile, the MBC of an antibiotic is defined as the concentration of an antibiotic that shrinks the total density of the bacteria by 1000-fold after 24 hours (Patel et al., 2023). The MBC of the antibiotic can be found in a similar test to that of MIC after it is calculated (Microchem Laboratory, n.d.). In fact, the MIC and MBC serve as an alternative way to differentiate between bacteriostatic and bactericidal antibiotics. If the MBC-to-MIC ratio is greater than four, the antibiotic is considered bacteriostatic. Otherwise, it is bactericidal (Patel et al., 2023).

Mobile Genetic Elements

Mobile Genetic Elements (MGEs) are elements that enable the mobility of DNA within and between cells (Partridge et al., 2018). Transposons are a specific type of MGE that can disconnect from their current location and move almost randomly to new locations inside the cell (Partridge et al., 2018). The transposon incorporates a section of DNA that contains a transposase (*tnp*) gene in the center and two inverted terminal repeats at the ends (Partridge et al., 2018). The two inverted terminal repeats are the parts in the DNA that mark the spot where the transposase enzyme (coded by the *tnp* gene) cuts out the DNA (Partridge et al., 2018). The enzyme then moves the DNA snippet to a different spot where it replaces the DNA (Partridge et al., 2018). This undoubtedly changes the DNA sequence in both the spots where the DNA was cut and the spot where it was replaced (Partridge et al., 2018).

Transposons can contain insertion sequences (IS) as part of the DNA (Partridge et al., 2018). The transposons can contain genes (like resistance genes) in between two IS, which facilitates horizontal gene transfer (HGT) when they move (Partridge et al., 2018; Horne et al., 2023).

However, MGEs are also being modeled as individual agents with their own needs and interests (Horne et al., 2023). When several MGEs interact with each other, they can either aid or inhibit HGT (Horne et al., 2023). For example, the mobile colistin resistance gene *mcr-1* was able to be transferred between DNA plasmids due to the action of transposable elements (TEs) (Horne et al., 2023). On the other hand, MGEs have also developed defense systems that are used to counterattack other MGEs (Horne et al., 2023).

Conclusion

This literature review analyzes the plausibility of using game theory to model the spread of AMR along MGEs. It is crucial to control the growth of bacterial pathogens, as they are responsible for numerous deaths worldwide. AMR genes increase the resistance of their bacterial pathogen hosts, making them harder to eliminate. This necessitates a complex understanding of how AMR spreads. Analysis shows that it is possible to develop such a model depending on the types of bacteria and antibiotics being used. Future research is needed in developing a game-theoretic model of MGE-caused spread of AMR.

Previous papers (Chowdhury et al., 2019; Czárán et al., 2002) have shown that EGT has been applied to the spread of AMR genes in general. Analyzing other papers, we believe that EGT can be applied to the spread of AMR genes along MGEs. We also know that MGEs are individual agents transferring genes to aid their own survival. Thus, their actions can likely be modeled by determining what external influences prompt MGEs to transfer genes.

Further examination of the game-theoretic model could develop insight into the spread of AMR genes caused by MGEs. Researchers who wish to model the spread of disease must consider several key factors. For one, they must consider which genes are being spread, as they will spread differently. They must also determine what antibiotics are used in the environment where the bacteria grow and how much that ‘incentivizes’ bacteria to be resistant. It will be essential to note that every antibiotic has a different mode of action and that bacteriostatic antibiotics behave differently from bactericidal antibiotics, which suggests that models created must be specific to one antibiotic.

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