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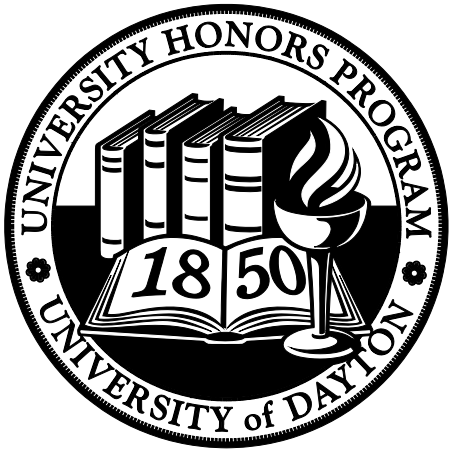

Honors Thesis

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Department: Chemistry

Advisor: Matthew E. Lopper Ph.D.

April 2019

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Abstract

Multidrug resistant antibacterial strains are a dangerous problem for modern medical professionals. When cells of two different strains are grown together, they must compete with each other for nutrients. This competition can lead to the production of harmful compounds that are toxic to the competing strain. One such compound may be a compound that inhibits the efflux of antibiotics from the cell. When the cells compete with one another, one or both of the cells will produce compounds that are harmful to the competing strain.

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Antibiotic resistance is a global problem that is having ramifications for the earth's population at this very moment. In the chemistry department at the University of Dayton, students are challenged to find new and practical ways to solve problems that are critical to modern society. One such problem is the issue of multidrug resistant bacteria. Worldwide and in the U.S., it is becoming more common to see types of bacteria emerging in our healthcare system that cannot be killed by conventional antibiotics. What was 40 years ago a simple staph infection treated with penicillin has now become methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA is resistant to many commonly used antibiotics, requires more extensive treatment, and has a higher patient mortality rate than normal staph infections (Paternina-de la Ossa). This problem is not restricted to *Staphylococcus aureus*; many other clinically important microbes are developing multidrug resistance. By producing many efflux pumps in their membranes, bacteria can thus escape from the killing effects of our antibiotics.

Bacterial competition has become the basis for understanding antibiotic production. In 1944, the bacterium *S. griseus* was determined to produce the antibiotic streptomycin. However, streptomycin was only produced when the cell was under stress (Iscla). This means that using interference competition*, S. griseus* produces streptomycin to kill off competing strains.

Jacques Monod, a French Nobel Laureate and biochemist, recognized that microbes require both space and resources. In 1956, Monod determined that bacterial growth yield is linearly dependent on the initial concentration of the limiting nutrient (Hibbing). The limiting nutrient stated by Monod can be required chemical compounds or even space itself. Monod's experiments on bacterial competition have since been the basis of understanding for further cellular competition hypotheses.

Since Monod's experiments, it has been determined that there are two types of bacterial competition: exploitative and interference. Exploitative competition is considered the passive form because the microbe in question collects all the resources in the system so a competing strain cannot use them. This means that in exploitative, the competitor species does not attack the competing bacterial strain. In contrast, interference competition involves the production of antagonistic factors by one cell to impede its competitors (Stubbendiecka). Interference competition is an active form of competition since the competitor species actively attacks the opposing strain. These two forms of competition represent the ways in which a microbe can compete. Since Monod's discovery, biochemists have since determined that many bacterial cells engage in antibiotic synthesis, motility, signal pathway disruption, and siderophore production to compete, survive, and reproduce.

The first antibiotic to be discovered was penicillin in 1941. This discovery opened the door for new forms of medicine to combat bacterial infections. Quickly many new classes of antibiotics were discovered. These classes include beta-lactams, macrolides, cephalosporins, and many others. Figure 1 shows the timeline in which all unique types of antibiotics were discovered. Since 1959, the discovery of new antibiotics has slowed. When a new antibiotic is found, such as macrolides, they tend to have more potent effects but harsher side effects in humans. The need to find a way to stop the efflux of these antibiotics from cells is critical to continuing

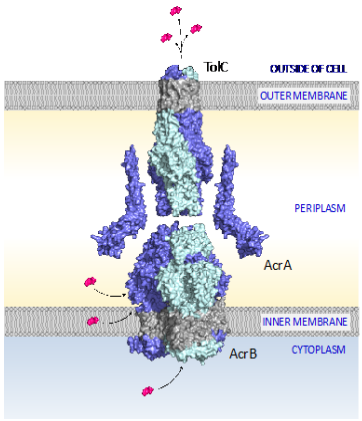
Figure 1: Timeline of Unique Antibiotic Discovery

human health. New antibiotics may not be required if the efflux of the antibiotics is stopped.

An experiment published in 2018 shows that exopolysaccharides that were collected from two strains of bacteria, *Lactobacillus plantarum* and *Bacillus* spp. have efflux inhibition activity. The experiment shows that these two polysaccharides are able to reduce efflux pump activity and decrease biofilm adhesion and antimicrobial resistance (Mahdhi). Thus, it is possible for bacterial cells to release compounds that inhibit efflux pump activity in competing strains.

Efflux pumps have a critical role in cellular processes. Bacteria cells rely on efflux pumps to remove various compounds (including antibiotics) from the cellular cytoplasm (Aron). The efflux pump that is widely studied is the AcrA/AcrB/TolC pump. This pump uses the proton motive force in active transport to remove small compounds from the cell. This pump is outlined in figure 2. Figure 2 shows that the efflux pump expands from the cytoplasm, through the entire periplasm, and to the outside of the cell. The AcrB portion of the efflux pump acts as the physical pump which effluxes harmful compounds from the cell. Using the protons on the outside of the cellular membrane, bringing protons across this membrane (with the proton gradient) allows the AcrB portion to be powered through active transport. The TolC portion acts as a hollow channel through which the harmful compound leaves the cell. Finally, the AcrA proteins act to bind the AcrB and TolC portions together.

Figure 2: Efflux Pump Channel Model



Another experiment published in 2017 shows the potential for small organic molecules to stop the activity of efflux pumps (Aron). Using the hydrophobic trap, these researchers attempted

to use rational drug design techniques to find a small molecule to inhibit the efflux of antibiotics from cells. The researchers found that the AcrA/AcrB/TolC pump could be inhibited. Its vulnerability takes the form of a hydrophobic binding pocket in the interior of the pump that can bind small organic compounds. When bound in this "hydrophobic trap," such compounds effectively inhibit efflux through the pump (Aron). This demonstrates the potential of organic molecules to stop efflux.

Experiments have also been conducted on various ways to stop efflux of antibiotics using inorganic compounds. A study published in 2019 focused on using sunlight and zinc (II) oxide to inactivate the efflux pump. When low concentrations of a cobalt-zinc oxide complex were added to a solution which also contained MRSA, efflux pumps were found to be inhibited in sunlight (Iqbal). However, once studying antibiotic resistance, it is also important to look at how bacteria compete and cooperate to form antibiotics in the first place.

The overarching reason for competition is the survival of the organism to pass on its genome to its offspring. The more fit species will survive and pass on its traits while the less fit species is killed off or out reproduced. Many macroscopic biological organisms provide examples of this form of competition. Take for example two species of barnacles found in Scotland. *Balanus* barnacles live closest to the shore while *Chthamalus* barnacles are found to grow further out to sea. Biologists concluded that when placed in competition, the *Balanus* smothered, or crushed the *Chthamalus* so as to survive. The reason why one species dominates another is inferred to be that the *Balanus* barnacles require more space and resources to survive (Hibbing). When subjected to a population of *Chthamalus* barnacles, the *Balanus* species is threatened that their base necessities will be taken away and in response kill off any competitors.

In this case, the competing species is the opposing species of barnacle. This example of two different species of barnacle is comparable to what occurs at a microbial level.

Resources required for microbial survival are similar to that for barnacles. Glucose as a source of energy, amino acids for protein synthesis, and nucleotides for DNA replication and repair are just a few examples of resources that a microbe might take up from its environment. Similar to barnacles, microbes also need space for reproduction.

Reproduction is a key aspect cellular and genome survival. For bacteria cells to reproduce, the cell requires adequate space. When bacteria reproduce, before the cell splits into two daughter cells, the cell is effectively double the size of the parent cell. Recent studies have shown that for *E. coli* cells, "the average length [of *E. coli*] increases with the division rate" (Belgrave). This means that with each consecutive generation, the *E. coli* cells increase in size to a certain point where the size levels off. When space is a factor, the two differing strains will compete with one another (Ghoul). In the case of *E. coli*, with each generation there is a greater need for space. To achieve sufficient space for reproduction, the cell uses certain tools through exploitative competition to sequester the required amount of space and resources.

The main and most basic example of the exploitative model is found in iron-limitation and acquisition by *P. aeruginosa* siderophores. Siderophores are small molecular iron chelators that are produced by microbes to acquire the iron that is required by a bacterial cell (Behnsen). These siderophores limit *E. coli* growth by acquiring iron for the host cell and taking the iron away from *E. coli* (competitor to *P. aeruginosa*). Iron acquisition can be crucial to the survivability of a microbe. Many proteins that are essential to energy and transport require the stabilization of iron atoms as a prosthetic group. In terms of competition, it is seen that a species,

when in competition with another siderophore producer, can create high iron-affinity siderophores. These siderophores that are produced have a higher affinity for iron than the competing strain. This means that not only will the low affinity siderophore producer lack the required amount of iron, it must also produce more siderophores than species 1 to accommodate. This places a heavy burden on the low affinity strain and can eventually cause the low affinity strain to be terminated from the system. However, siderophore production is not the only form of exploitative competition that is known.

Another way cells compete exploitatively is through motility. In terms of a bacterial cell, motility is the ability of the cell to move throughout the environment on its own. Not every single microbial cell has the ability to move in solution. In recent experiments, motility has been seen as both a way for cells to avoid antibiotics produced by competing cells and to collect resources faster than cells who are nonmotile. In an experiment done analyzing *P. aeruginosa* (motile) and *Agrobacterium tumefaciens* (nonmotile), *Agrobacterium tumefaciens* cells clumped in greater masses to increase the chances of evading contact with *P. aeruginosa* (Hibbing). So the *Agrobacterium tumefaciens* grew together to increase survivability and the motile strain was able to acquire the necessary resources. The clumped cells were, however, at a severe disadvantage to the non-clumped strain. The clumped cells do not have the required space for reproduction and do not have adequate resources for bacterial processes. Motility can be seen as a crucial aspect of fitness in a bacterial cell, yet it can have detriments to the cell in question.

Consider the following scenario, with a blindfold on, is a person more likely to run into another person if they are moving or standing still? One can assume that the blindfolded person in question would come into contact with others more often if they were able to move around.

The same principle can be applied to motile and nonmotile bacteria strains. While motility can be seen as an advantage, it is also a disadvantage. Not only does the cell have to spend energy (ATP) on movement, it also is more likely to come into contact with competing cells. So while motility is another example of exploitative competition, it cannot be seen as a true positive or true negative to cellular survival as it has both good aspects and bad aspects. The next analysis will be done on competition in which chemicals are produced that directly impact the competing strain.

The second form of competition, interference competition, includes direct competitive behavior between two different strains of bacteria. Those strains which compete with one another "range in their killing spectrum" (Ghoul). This means that compounds such as antibiotics or peptides can be used as harmful reagents. These reagents are considered different from the siderophores that were previously discussed. This is because siderophores do not directly impact cellular processes while the chemicals produced in interference competition do. It is important to realize that even though the method is different from exploitative competition, the outcome of the victor receiving the space and resources still holds true.

When bacterial interaction was first discovered, many assumed that antibiotic synthesis was a form of signaling between strains and not intended for competitive purposes. However, this idea has since been proven incorrect. In a study published in July of 2015, the bacterial strain *Streptomyces griseous*, produces its antibiotic, streptomycin, in the presence of a competitor to both promote its growth as well as inhibit the growth of the competing strand (Abrudan). This means that *Streptomyces griseous* acts to inhibit the cellular processes of a competing strain which is the definition of an interfering competitor. Similar inhibitory actions to those seen in

Streptomyces griseous have been since studied all across the known spectrum of bacterial competition. Also there is little evidence to show that when both strains are limited in the supply of resources and space, the compounds produced are for cooperative purposes. This competition and the subsequent production of antibiotics by bacteria strains has been widely studied for the past six decades.

Antibiotic production has been a staple of modern medicine since the discovery of penicillin in 1941. A generalized timeline of antibiotics produced by certain cells and their year of discovery can be found in figure 3. The antibiotics outlined in figure 3 have varying effects. Penicillin, for example, ruptures the cell walls and stops the formation of cell walls in gram-negative bacteria (Ghooi), while streptomycin acts to disrupt the function of ribosomes within a cell. Yet the understanding that their ability to impact a competing strain is known. The analysis of antibiotics and their impacts on bacterial competition have been widely studied since their discovery.

Antibiotics, as stated previously, can have wide ranging effects on a competing cell. View figure 3, to see how the common antibiotics impact bacteria cells. Every single aspect of the central dogma of molecular biology is covered by bacterial competition. DNA synthesis, RNA synthesis, polypeptide synthesis, ribosome function, and cellular wall synthesis are just the five common aspects of cellular life that are impacted by antibiotics. When a strain is in competition with another strain, whether for resources or for space, it has the ability to release the antibiotics to further promote its own growth. Each of the antibiotics produced are ways that show the arms race that exist between microbial strains.

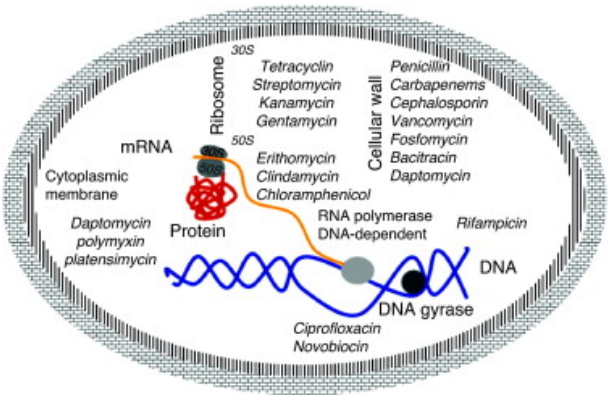


Figure 3: List of common antibiotics produced and where they disrupt cellular activity (de Lima Procópio).

As seen in figure 3 antibiotics produced can have profound impacts on the cell. If at any point the cell cannot complete a process, then the cell might not be viable. Should DNA gyrase be inhibited by rifampicin, for example, the topoisomerase cannot act to assist in DNA replication. Should a cell use Erithomycin then the impacted cell cannot effectively produce a polypeptide that is required for cellular viability. Figure 3 shows the versatility of antibiotic synthesis and how antibiotics may have a common goal but do not share a common pathway. Through hundreds of millions of years, cells have perfected antibiotic synthesis to accurately

impact the cells to the greatest degree. However, the major question remains of how the antibiotic in question can enter the competing cell.

Antibiotics produced by microbes are large in terms of their molecular weight and rather polar. The penicillin backbone, for example, has a molecular weight of 334.4 grams per mole and contains many hydrogen acceptors as well as donors. Both the backbone's size and polarity render it unable to pass through a cell's lipid membrane layers (and possible cell wall). During competition a cell must devise a way for the antibiotic to enter the cell. If a cell has expended a great amount of energy to produce a large enough quantity of antibiotics, then the energy cannot be wasted simply because the compound cannot enter the competing cell. Thankfully cells have already solved this problem, hijacking of the cellular channels that bring other compounds into the cell.

The ability to insert antibiotics into an opposing cell is no exception to the adaptability of microbes. In an experiment performed in 2011, it was further confirmed that certain antibiotics (fosfomycin in the experiment) can hijack certain transporters which connect the outer membrane to the intermembrane space. In the case of fosfomycin, it enters *E. coli* "cells via the GlpT" transporter which is typically used for glycerol-3-phosphate uptake (Santoro). Similar to fosfomycin, while the way streptomycin enters the cell is unclear, there is a strong link between cell death and MscL channel expression (Iscla). So the conclusion Iscla made was that if more MscL channels are present on the cell surface then there is more cell death due to streptomycin. This meant that it is possible that streptomycin enters the cells through the MscL channel. One common and energetically easy pathway for cells to place antibiotics into the competing cell is to force the antibiotic through already existing channels.

The final aspect of the purpose for antibiotics in microbial competition is disruption of cellular processes that produce competing antibiotics. While figure 3 denotes a strong case for the multiple applications of antibiotics in a cell, there is an underlying aspect. Antibiotics are meant to disrupt certain cellular processes as well as "suppress antibiotic production in competitors" (Abrudan). When antibiotics are used to disrupt translation of certain genes, it is likely that the genes in question are those that would code for antibiotics. The highly tuned ability of cells to produce antibiotics that specifically target both regular cellular processes as well as target antibiotic synthesis are why microbes are well adapted to compete with one another. However, the basis for why it is more energetically favorable to produce only one compound to perform two actions rather than two compounds to perform two actions must be discussed when reviewing microbial interference competition.

The main support for antibiotics having two functions is that they are generally considered expensive to form in terms of energetics (Abrudan). Should the antibiotic be tasked with disrupting cell wall synthesis, but then another compound would have to be synthesized that focuses on disruption of competing antibiotic synthesis then the cell would have to expend a greater number of resources. When a cell is in competition due to lack of resources, the need to create two separate compounds may place an even greater strain on the bacterial species. Since its discovery in 1941, it has been determined that for every mole of penicillin created it costs the cell 73 moles of ATP (M., vanGulik). This is not to mention the atoms and proteins that are used in penicillin synthesis which would also utilize highly desired resources. So the conclusion can be made that bacterial competition focuses on both stopping regular cellular process as well as degrading pathways that produce antibiotics.

The final point to look at with regard to bacterial competition is defense. This far only aspects of the attack mechanisms have been discussed, however, a cell is also able to fight off attacks made by a competing cell. One major way bacteria cells defend themselves from attacks made by competitors is attacking signaling pathways. Work has been done to propose that certain enzymes produced by cells have the ability to interact with opposing signaling pathways. For example, in the presence of attacks, the strain *Variovorax paradoxus* has been shown to internalize and degrade AHLs whose purpose is to assist in quorum sensing (Hibbing). It is believed that this internalization also assists in stopping any negative effects of the attacking strain. Should a signal be produced that a competitor is near, the cell will produce a compound to kill the opposing cell before itself is killed.

Another portion of bacterial competition deals not with fighting but survival through coexistence. In any biofilm, there exists more than one strain of bacteria. Regressing back to the skin example, some estimates place the species diversity of bacteria in the biofilm of human skin at 1000 different species of bacteria. It is clear that over the eons of evolution, biodiversity has increased and decreased. So the common question to ask is if bacterial competition exists when microbes are stressed, then how do strains live harmoniously whether the strains are stressed or not? The question is answered in two separate scenarios. First, it is possible that two or more strains are unable to produce antibiotics or any other form of exploitative or interference competition. Or the other possibility is that a “stale-mate” has occurred caused by the equal ability of both strands to kill one another (Foster). This means that the two strains have adapted so that they may not terminate one another. Both hypotheses have equal weight in biological cooperation.

Microbial cooperation is different from microbial competition but can be equally as vital for cellular survival. It has been previously stated that some scientists speculate the use of antibiotics for specific signaling pathways and not for competitive purposes. While this is believed to not be true, the understanding still exists that microbes can cooperate. One way that microbes cooperate is through interactions known as "kin selection" (Hibbing). Kin selection occurs when two (or more) strains cooperate one another to share resources and kill any other strains that might be present in the environment. It was determined that with microbial competition, it is not always a list of winners and losers. It is possible that one strain can take advantage of another strain's resources or enzymes without killing the cell.

An example of microbial cooperation is seen in *P. aeruginosa.* If *P. aeruginosa* is grown under conditions requiring quorum sensing-regulated extracellular proteases, then cooperation occurs. Within 100 generations social cheaters which utilize the enzymes excreted from *P. aeruginosa* form (Hibbing). These strains are called cheaters because they take advantage without having to kill the competing cell or expend energy to create its own enzymes. While both strains may have the ability to kill one another, should the cells not be in competition, cooperation occurs.

Cellular competition, while varying in range and effect, has been shown to be crucial for microbial survival. Bacterial competition that has occurred for millions of years has provided the basis for evolution, antibiotic production, and signaling pathways. Similar to what occurs in macro-organisms, a bacterial cell requires both space to reproduce as well as nutrients to carry out basic functions. Should either of those be in scarce supply, the bacteria will enter competition. A cell can produce antibiotics, produce higher affinity iron siderophores, move to

sequester more nutrients, and disrupt cellular signaling all in the name of survival. While the science of bacterial competition is only a handful of decades old, the study of the processes can provide insight to both evolution as well as the future of medicine and antibiotic resistance.

Previously it has been determined by the Lopper Lab at the University of Dayton that when coculturing *S. griseus* and *P. polymyxa*, an unknown compound is produced that inhibits the efflux of ethidium bromide from an *E. coli* cell. It is unknown what exactly the compound is (polypeptide, macro/micromolecule, SSDNA, etc.), but it can be assumed that a compound is produced as the two strains compete using interference and not exploitative competition. This assumption can be made because when testing with ethidium bromide only the supernatant of the coculturing solution was tested. The *S. griseus* and *P. polymyxa* cells were not included in the *E. coli*/ ethidium bromide tests. This conclusion is exciting for medical advancements. Should antibiotic resistance be solved, it is possible that bacterial infections could be a problem limited to human history and no longer an issue for the future. Continuing research in this topic as well as bacterial competition is much needed. While how bacteria compete is widely known and studied, each bacteria strain interacts differently with different strains. Until every strain has been tested, it is impossible to know the limits of bacterial competition and its uses for humanity.

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