Antibiotic Resistance in Methicillin-Resistant *Staphylococcus aureus* (MRSA)

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Abstract

Objective: The objective of this experiment is to further understand the mechanism of beta-lactam antibiotic resistance in *Staphylococcus aureus* bacteria and what can be done to treat MRSA infections.
Research Question: Will viewing the MRSA infection process as a mathematical process aid in the discovery of new novel treatment approaches?
Background: Bacteria antibiotic resistance has become a major healthcare problem in the United States which affects over 2 million people and results in over 23,000 deaths each year. Our antibiotic resistance modeling effort is focus on methicillin-resistant *Staphylococcus aureus* (MRSA). Methicillin is an antibiotic that exerts it effect by inhibiting the formation of the peptidoglycan cell wall. This results in bacteria death. However, in MRSA the enzymes which form the peptidoglycan cell wall do not bind to methicillin and hence are unaffected by this antibiotic. Novel treatments currently in development are aimed at synthesizing a new antibiotic which would be able to inhibit the formation of the peptidoglycan cell wall in MRSA. We have created simulation models of the *S. aureus* cell division process, with and without methicillin present, and peptidoglycan cell wall synthesis.
Materials and Methods: Rockwell Automation's Arena Simulation Software was used for these experiments. Several models were developed to observe the population growth of *Staphylococcus aureus* bacteria in the human body, with and without penicillin being present, and the synthesis of new layers in the peptidoglycan exterior of the bacteria with peptidoglycan sugars N-acetylglucasomine (NAG) and N-acetylmuramic (NAM).
Results: Figure 1 represents *S. aureus* entering the human body and traveling through the bloodstream to cause infection. Figure 2 depicts *S. aureus* entering the body but is exposed to methicillin. The number of bacteria that survive is only about a fourth of the bacteria population when methicillin in not present. Figure 3 represents the synthesis of new NAM-NAG disaccharides that link together to create multiple layers in the peptidoglycan.
Conclusion: In conclusion, the expanded knowledge of *S. aureus* bacteria, its cell division process and the mechanisms behind its antibiotic resistance allows for more in depth research designs.

Introduction

Staphylococcus aureus is a gram-positive bacteria that can lead to many different infections, including skin infections, pneumonia and food poisoning.
Methicillin, a semisynthetic derivative of penicillin, is an antibiotic that exerts its effect by inhibiting the formation of the peptidoglycan cell wall, leading to bacteria death due to osmotic pressure. But not all bacteria are so easily combated. The antibiotic resistant bacteria MRSA releases enzymes that do not bind to methicillin and hence is unaffected by this antibiotic. These resistant bacteria have a mutation in their Penicillin-binding protein (PBP) 2a *mecA* gene (Fishovitz *et al*. 2014).
MRSA infection, once more commonly known as a hospital-associated infection (HAI), has quickly become a community-associated disease (CAD) (Kale and Dhawan 2016). In today's society, research is still conducted to show the epidemiological status of MRSA infections in a specific group of people and how it spreads.
There is no "cure" for MRSA infection, only ways to keep it subdued. For the past 50 odd years, the most common antibiotic used for this process has been Vancomycin. Vancomycin comes from a class of antibiotics known was Glycopeptide antibiotics, which means they are composed of a short amino acid chain linked to a carbohydrate (Choo and Chambers 2016).

Materials and Methods

Arena is a discreet event simulation, which means the simulation steps out in time from one event to the next event, as opposed to stepping out in increments of time and determining what events have occurred in that time interval. With 2D animation features, the display of any process comes to life so that any viewers are fully immersed in the simulation. Models are created in Arena by developing a flow chart of the process and adjusting variables, parameters, and other attributes associated with the processes in the flow chart.

Results

The strategy for modeling these processes was to model bacteria cell division and the formation of the peptidoglycan cell wall.

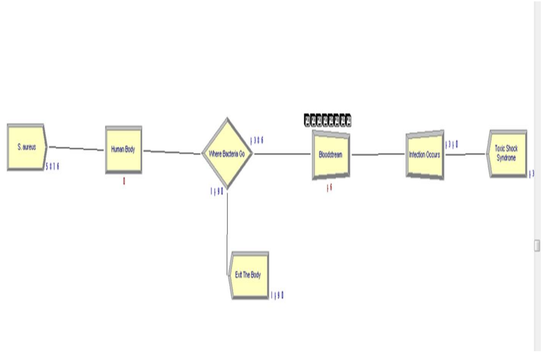

Fig. 1 - With two bacteria being produced from a single bacterium every 30 minutes, this model set for 48 hours produced 5876 bacteria. Of the 5876 bacteria, the mucosal membranes found in the human body were able to trap and excrete 1490 pathogens. This alone was not effective enough to stop infection, leaving 4386 bacteria cells to move on through the bloodstream and invade organs and tissues.

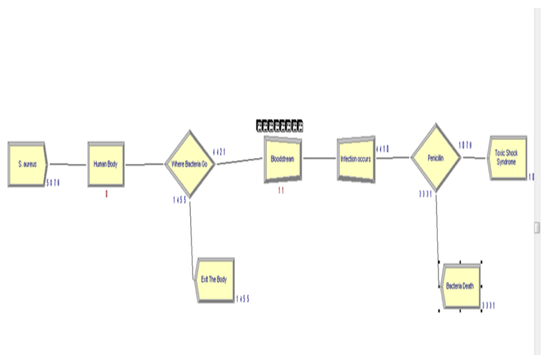

Fig 2. - During cell division, methicillin was able to eliminate approximately 40% of the population, leaving 2569 *S. aureus* cells. The mucosal membranes eliminated 1490 of the remaining cells, leaving only 1079 cells that will move on into the bloodstream to cause infection. Since these cells were introduced to methicillin and survived, they run a high chance of developing a resistant mutation that will spread to the daughter cells during cell division. Again, the infection chosen for this model was Toxic Shock Syndrome.

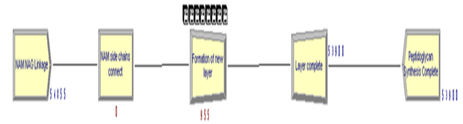

Fig. 3 - A single bacterium of *S. aureus* was determined to have 87,760 disaccharides in the peptidoglycan layers. This value was used to set the maximum entity number for a complete simulation cycle of 48 hours. As bonding occurs the sugars are stored in a batch module labeled Formation of New Layer. Once the 1097 disaccharides of a layer all bind properly, they proceed to the separate module labeled Layer Complete. After all 80 layers are completed; the total number of disaccharides is represented on the dispose module labeled Peptidoglycan Synthesis Complete.

Conclusion

In conclusion, through a series of calculations and the creation of various mathematical models, I believe viewing the Methicillin-Resistant *Staphylococcus aureus* infection process as a mathematical process has aided in the discovery of new novel treatment approaches. The expanded knowledge of *S. aureus* bacteria, its cell division process and the mechanisms behind its antibiotic resistance allows for more in depth research designs. Future research will build from the foundation constructed through this research. The next step is now to use the information acquired during these experiments to view at what point during *S. aureus* cell division is the bacterium most susceptible to the effects of penicillin or methicillin, and will the information be helpful in combating antibiotic resistance?

References

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