Large Scale (Biological) Networks Attack

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Abstract

We all are aware of how our immune system protects our body from "foreign" invaders. But have you ever thought of this from the opposite side? In this project, we plan to take the role of bacteria and attack human body. By utilizing the network of different species of bacteria, we will analyze several ways to effectively counteract the ability of T-cells and macrophages, which play central role in immune response. Eventually, we will propose a fine way to destroy human immune system.

Introduction

When bacteria enter our body, their typical attack involves their cell reproduction and infection of body cells. When such attack happens, macrophages and T-cells, the very first level of our body's defense mechanism, take action.

Macrophage's main task is phagocytosis, devouring the bacterial cells and other infected cells so that they can be digested and removed from the body. This can clean up some bad cells in the environment, but macrophages themselves cannot handle all infected cells because bacteria usually launch attack in huge numbers. This is when T-cells come in. T-cells, when they see that macrophages have engulfed bad cells, realize that there is an invasion and this triggers their immune response, mainly via reproduction. When their reproduction is triggered, some T-cells become reproducer/triggerer, known as helper T-cells, and some become attacker, known as cytotoxic T-cells. Cytotoxic T-cells go out and kill infected cells along with macrophages.

Normally most of bacteria are defeated by macrophages and T-cells and thus can no longer spread their pathogens in our body. In this paper, however, we would like to propose a way for bacteria to overcome such defense mechanism and survive even after macrophage and T-cell's immune response.

By introducing the idea of genetic mutation and adaptation of bacteria, we are going to simulate how different networks of bacterial species interact with each other and analyze how the mutated species can survive inside macrophages without getting digested. If bacteria can survive inside macrophages, they can eventually come out to the environment and infect any other cells in human body, bypassing human immune system.

Previous Work

There has been a lot of research about bacteria's behavior to form their network, and the key two phenomenons that can be directly referenced for our proposal are chemotaxis and quorum sensing.

Chemotaxis is cell's tendency to move towards higher concentration of certain chemical in the environment. Bacteria as their population grows, secrete a chemical called autoinducer (AIs) in its environment. Each bacterial cell can detect where the other cells are accumulated by sensing this AI concentration and join the network by moving towards it. This is the key idea for bacteria in forming their network. T-cells, likewise, form their network in the same manner with the chemical called cytokines. In our proposal, we will use this property to simulate the formation of bacterial networks and T-cell networks.

Quorum sensing is the regulation of bacteria's gene expression based on the change in cell-population density. Basically, when the number of bacterial cells in the environment exceeds certain threshold, all the cells will have common gene expression and behave the same with a defined goal. This phenomenon is what allows bacteria to launch an attack as a massive group once their population grows enough.

$$D_{if} = \alpha * \frac{[C]}{[C]+\beta} * exp(\frac{D}{D_0})$$

[1] LasI/R QS system diffusion model

$$\frac{d[A]}{dt} = C_A + \frac{K_A[C]}{K_A+[C]} - k_0[A] - k_1[R][A] + k_2[RA] \quad (1)$$

$$\frac{d[R]}{dt} = C_R + \frac{K_R[C]}{K_R+[C]} - k_3[R] - k_1[R][A] + k_2[RA] \quad (2)$$

$$\frac{d[RA]}{dt} = k_1[R][A] - k_2[RA] - 2k_4[RA]^2 + 2k_5[C] \quad (3)$$

$$\frac{d[C]}{dt} = k_4[RA]^2 - k_5[C] \quad (4)$$

[2] P. aeruginosa quorum sensing model

In our proposal, we are going to reference the model [1] and [2] for simulating the behavior of bacteria and T-cells. The diffusion model [1] will be referenced for calculating the threshold distance between cells for communicating or "connecting edges" with each other. The quorum sensing model [2] describes the relationship between bacteria population and the concentration of AIs in the environment. Depending on how fast the AI concentration changes, the speed of network formation among bacterial cells is determined, which in turn determines how long it takes for bacteria to launch attack to other cells.

In addition to chemotaxis and quorum sensing, we are also going to reference previous studies about the evolution of bacteria. A report "The Genetic Basis of Escherichia coli Pathoadaptation to Macrophages" [3] published by Isabel Gordo states that *Escherichia coli(E. coli)*, a type of human intestinal bacterium, was able to survive inside mouse macrophages by going through several genetic mutations. The studied *E. coli* have evolved to have several defence mechanisms such as sticky outer coverings and formation of biofilms. By referencing this study, we are going to simulate how the mutated species of bacteria can survive inside macrophages and eventually come out to the environment to infect other body cells.

Approach

Combining the ideas from the previous models and studies, we solidified our approach to attack human body mainly with four steps. We build the networks of different bacteria species, allow one species to induce genetic mutation of another by quorum sensing, let the mutated species survive inside macrophages, and finally let the survived ones come out from macrophages and attack body cells.

Before we talk more in detail about this approach, we would like to mention our previous proposal and how our thoughts and assumptions changed for this approach.

We initially thought of a way to block the communication among T-cells in its network with some chemicals generated by the bacterial network. We considered the situation with the assumption that there is only one species of bacteria, and both bacteria and T-cells have already formed some kind of network at the initial state. We also assumed that chemicals generated by bacteria can directly affect the T-cells. This approach, however, was too broad and unrealistic. We neglected the process of bacteria and T-cells forming their network from their cell level and ignored the role of macrophages in the environment. Plus, based on our new research, we learned that using some chemicals generated by bacteria to directly affect T-cells is nearly impossible. So, we modified our approach by changing our focus from "how to attack immune system" to "how not to get attacked by immune system". And that is how we came up with our current approach.

We now consider an initial environment where there are a few different species of bacterial cells and also a few T-cells and macrophages. We also assume that the speed of reproduction is different for each species to allow genetic induction happens effectively among different species.

Now, we explain the four attack steps, or more precisely defense steps, in detail. Since there are a lot of things going on at the same time, we are dividing the perspective into immune system's part and bacteria's part.

This is mostly for immune system's part. When bacterial cells of multiple species enter the body, they start duplicating themselves and form the network of their own species by chemotaxis. As the bacteria start growing its population, macrophages in the environment start to detect their cells and start engulfing and killing them. In the meantime, T-cells are triggered by macrophages that have eaten the invaders and join the extermination of bacterial cells by reproducing more helper T-cells and cytotoxic T-cells.

Now we are looking at bacteria's perspective. We are assuming that different species have different reproduction rate, and for simplicity, we will call the fastest growing species S1, and in the decreasing order of growth rate, we will call the other species S2, S3, and so on. When each species start growing their population and forming the network, S1 will mainly get detected and engulfed by macrophages, since there are many more S1 than any other species in the environment. As the cells of S1 disappear into macrophages, its cell population decreases and by quorum sensing, the remaining cells, S1 cells that are not yet eaten, will realize that its cells are in danger. This can allow S1 cells to generate some chemical molecules in its environment that other species can react to. Once one of the remaining species' network recognizes that chemical, again by quorum sensing, its cells can react to it by going through some genetic change or mutation to fit better for the survival in its current environment.

Eventually, as the series of species pass on chemicals to another species, from S1 to S2, S2 to S3, and so on, the very last species will have genes that make

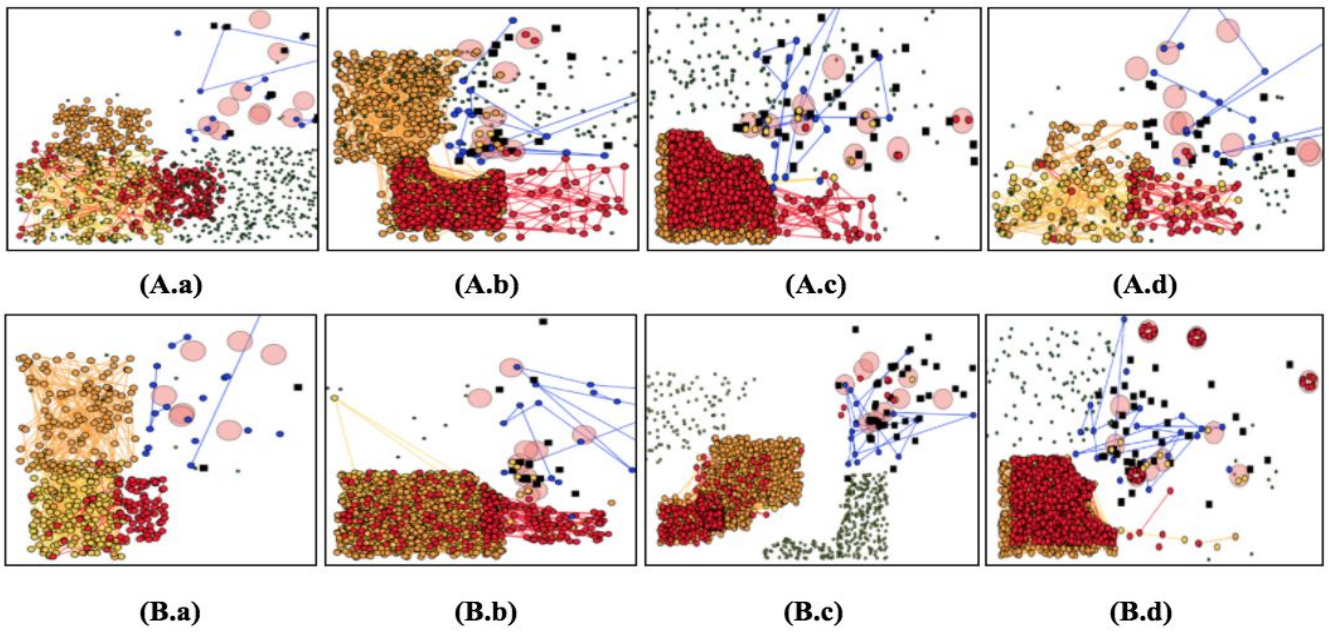

Figure 1: Simulation Result.

There are 3 different types of bacteria (yellow,orange, red). A Started off with same number of the 3 types, while B started off with twice more yellow than red with orange in between the two. a, b, c, and d are in chronological order. For scenario A, we can see that in A.b and A.c all three bacteria are equally susceptible to being overtaken by macrophages (peach) and killed by killer T-cells(black). For scenario B however, we can see that the red ones are less likely to being overtaken by macrophages in B.b. This gives them more time to respond to the chemicals produced by the yellow species and go through genetic mutation. This results in B.d when the red bacteria are able to overcome macrophages as opposed to A.d where the macrophages are able to kill all 3 types of bacteria once they overtake them. Immune system eventually wins bacteria in A, but not in B.

them much stronger and have higher chance of surviving even inside the macrophages. Once they can survive inside macrophages, they can reproduce inside the macrophage and eventually come out to the environment by blowing it up. Once this happens, they are beyond the reach of other immune system cells and can freely infect other cells in the body.

To summarize our approach in terms of models, we are utilizing the idea of chemotaxis to build the initial bacterial network, properties of quorum sensing to allow the communication and genetic induction among different network of species, and the idea of genetic mutation to make bacteria adapt to survive inside macrophages.

Our approach is scalable since the key properties for quorum sensing and genetic mutation will not change even if we are dealing with large number of bacterial cells and immune system cells.

Experimental Setup & Results

Previously, we were only able to simulate different types of bacteria forming their networks at their own rates. Now, we are able to simulate bacteria, helper and killer T-cells, macrophages, and their interactions with one another as time progresses.

In our simulation, we represent different components with different colors. Our main components include bacterial cells, AIs, macrophages, Helper T-cells, and Killer T-cells. For clearer visualization, we decided to not visualize the chemicals used for quorum sensing in our simulation.

Different species of bacterial cells (yellow, orange, and red) utilize quorum sensing and chemotaxis to move around and form their own networks. AIs are used by each type for this purpose and are represented as small green dots. Macrophages (large and peach colored) move around and eat bacterial cells when they come in contact with them. Similarly, when helper T-cells (blue) get closer to macrophages that have engulfed bacteria, they reproduce killer T-cells (black) to the environment. In reality, they should also reproduce helper T-cells as well, but for the simulation purpose, we omitted that part. Helper T-cells, when they come in contact with each other, form a network of themselves (create edge between them). Killer T-cells do form their network as well, but we made it not form edges for its network because we realized our simulation gets too messy due to too many edges on the screen. Lastly, killer T-cells kill bacteria when they get close to them.

We represent the state of macrophage eating bacteria as showing the bacteria dots inside macrophage

circle. Also, to represent killer T-cells killing bacteria, we remove some number of bacteria dots when they get close to killer T-cells.

Currently, the main configuration parameters that can be tweaked are number of species of bacteria, their starting strength, and initial numbers of all types of cells used in the simulation. Their speeds of movement, minimum distance for intraspecies edge formation, max degree in network, reproduction rate and total amount of resources available (which limits the total number of bacteria) are also tunable. Macrophage specific parameters include the number of bacteria it can overtake at once and their resource content - which determines how fast bacteria can reproduce when using them as hosts. The main T-cell parameters are how many killer T-cells are summoned when a helper T-cell detects "engulfing" macrophages and how fast they form their network.

Figure 1 describes the simulation which serves as our main result so far. For this simulation, we set all species' reproduction rate to be equal in order to see the sole relationship between the initial cell count of different species and their survival rate.

Scenario A involves all initial bacterial cells to be 100 in number, whereas Scenario B has 200 yellow, 150 orange and 100 red cells. After 24 time steps, in A, there were 608 yellow, 656 orange 594 red cells. At the same point in time, in B, there were 508 yellow, 507 orange and 678 red cells. Even though these numbers do not include the surviving strong bacterial cells which are using macrophages as hosts, we can see that because if their growing strength due to increase in time before they are overtaken by macrophages in scenario B, the red cells are more in number than the yellow cells although they started off at a lower count. Including their count within macrophages, the red cells clearly are now able to overcome the immune system whereas the immune system in B is able to overcome the bacterial attack in A. This validates our approach.

One limitation of our approach is the expectation that there are comparatively lesser number of initial immune cells at the location of infection than the incoming bacterial cells. In reality, this would only be the case if the bacterial cells were entering at a location without an already existing infection, meaning there would be sparse presence immune cells, allowing them to take advantage of the fact that the immune response is slower than their reproduction capability. Ways to overcome this are to change the parameters to either increase the immune cell presence, increase the fighting capability of each of the killer T-cells and macrophages or reducing the reproductive rates of all the bacterial cell types.

Conclusion

We refined our proposal by changing the tactic from "how to attack immune system" to "how to not get attacked by immune system". We are utilizing the idea of chemotaxis, quorum sensing, and genetic mutation among different bacterial network to allow bacteria to adapt to the human body environment and eventually survive inside macrophages. With our simulations so far, we have found that there are so many parameters we can experiment with and get interesting results.

For the next milestone, we will finish up and refine our simulation so that we can scale up our approach and observe many different results based on different parameters we define. We will actually visualize how survived bacterial cells can come out of macrophages and attack other cells as our final scene of the simulation.

For this milestone, Aishwarya has mainly worked on writing the simulation and Ryan has mainly worked on further research and the report.

References

[1] In Silico Evaluation of the Impacts of QSI on Strain Competition and Development of QSI Resistance (https://goo.gl/EV8JLD)

[2] Optimal Multidrug Quorum Quenching of Pathogens Network (https://goo.gl/RH9gJY)

[3] The Genetic Basis of Escherichia coli Pathoadaptation to Macrophages (https://goo.gl/WH h4nb)