An Idea Model of the Immune System

CS 423/523 Spring 2018

Justin Hall
Department of Computer Science
University of New Mexico
Albuquerque, New Mexico
amunra@unm.edu

George Boujaoude
Department of Computer Science
University of New Mexico
Albuquerque, New Mexico
gboujaoude@unm.edu

***Abstract*— Comprised of many intricate, moving parts, the innate immune system is pertinent to our everyday wellbeing and livelihood. To this day, we are still working towards better understanding this complex adaptive system. In this project we sought to observe the relationship between the innate and adaptive portions of the immune system. We constructed an idea model of the immune system which contained related components such as Macrophages and Lymphocytes. This provided us an environment in which we could isolate components and related behaviors to better conduct analysis on our hypotheses.**

I. INTRODUCTION

The human body comes equipped with a highly complex and adaptive machine known as the immune system. From a high-level view it boils down to two major sections: the innate and adaptive immune system. Innate falls under the category of *static defense* [9]. Put simply, this has evolved a generalized defensive strategy that is good for a large amount of different foreign substances [9]. It may not be the most effective at dealing with any one thing, but it is perfect as a means of providing an initial response to a new threat [1].

Adaptive, on the other hand, is the exact opposite. It provides a highly specialized response for each type of antigen [10]. If an adaptive component has specialized to deal with an antigen of type A, for example, then only when that exact antigen enters the body will that component be activated [10].

A "separation of powers" clearly exists, but this separation very quickly raises interesting questions: How do the innate and adaptive immune system communicate with each other? In the event that the adaptive immune system is unresponsive or unreachable, can the innate hold its own against an invasion? Can differing patterns in communication result in different behaviors from the adaptive immune system?

In this paper we will explore these questions using a simulated idea model of the immune system. A breakdown is as follows:

1. Within our model, we will observe the ramifications of an unresponsive/unreachable adaptive immune system. We hypothesize that in the absence of an adaptive response, the innate immune system will ultimately be unable to fully halt a sizeable foreign threat to the body.
2. In our model we will define a very simple means of communication based on cytokine proteins [2]. During our initial runs we noticed that simple changes to the communication patterns resulted in two categories of behavior within the adaptive immune system. The first was a random-walk behavior, and the second was more of a patrol behavior through the tissue. We hypothesize that the patrol behavior will be more successful in stopping an invasion than the random walk behavior.
3. In a system like this, it is expected that the speed of communication should lead to a faster response. We make the hypothesis that increasing the speeds of which a component of the immune system can move result in higher success rates in halting a foreign threat.

II. METHODS

Given the time allotted for this project, it became apparent that a full-scale model of the immune system was simply not possible. To tackle this, we decided to define a very simple model with simple, configurable components. This model was then programmed as an externally-configurable simulation (i.e., through configuration files read in at startup) that would allow us to explore the questions in the introduction and test our hypotheses. The individual components are specified below, followed by information on how we conducted our experiments.

A. Assumptions

We went forward under the assumption that all events in our simulation were taking place within the liver. We also assumed that 1 pixel is equal to 1 micrometer. Finally, we assumed that there is only 1 type of virus, and any response displayed by the adaptive immune system was directly for that specific virus. We did not test the interaction between T-Cells and B-Cells as it appears in real life.

B. Idea Model Components

B.1 Macrophage

We represent the entirety of the innate immune system with the macrophage component. It is only allowed to exhibit random-walk behavior, roughly based on the real world where a macrophage changes direction randomly every 5 minutes (5 seconds in our model) [5]. Its job is to patrol the liver tissue for any foreign substances or infected cells, destroying them if found.

Each macrophage has a cytokine pouch. This pouch refills at a rate of 1 cytokine per 2 seconds until its upper limit is reached.

As figure 1 will show, the macrophage is made up of two parts in our model: an outer perimeter and a cell body. The perimeter is seen as the lighter-green region, while the cell body is the dark inner circle.

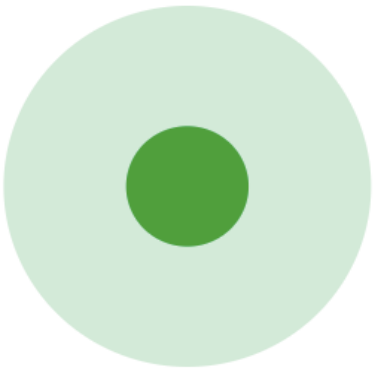

Figure 1: Diagram of the macrophage as it appears in our simulation. The light green, transparent region is the perimeter while the dark inner circle is the cell body.

Each part plays a different role. The outer perimeter allows the macrophage to gather information about the world around it. We decided that if at any point 10 or more virus particles enter its outer perimeter and the macrophage and its cytokine pouch is at maximum capacity, it will release all of its cytokines into the environment. This in-turn will eventually draw the attention of the adaptive immune system.

The cell body is there to do the actual destroying of virus particles or infected cells. Its size is 30 micrometers, which is slightly larger than they are in reality [3]. By default they move at 3 micrometers/second * 15 (15 is just our selected scaling factor. In real life they move 3 micrometers per minute, but we decided to speed this up [5].

Configurable parameters are the number of initial macrophages, their speed, and the maximum number of cytokines they can store.

B.2 Cytokine

We have one type of cytokine protein in our model. Cytokines are only ever released by a macrophage, and each one contains information about some area where they first came from. These serve as both an information relay and a means to activate the adaptive immune system, which in this case means lymphocytes [2].

In our model these are very small (only 5 micrometers), though we do not have a source to indicate their true size. Since viruses are at most ~1 micrometer in length [7], and in our model we scaled this by 5, we decided to use the same number for the cytokines.

Our model establishes the concept of a primary cytokine which is defined as any cytokine that was directly released by a macrophage. Cytokines created through replication, therefore, are not included. Primary cytokines are the only ones that can move through the liver, periodically duplicating themselves and seeding their clones with information about location they are currently at. This then forms a trail that can be followed, where each cytokine essentially says “go in this direction from where you currently are”.

Aside from the primary cytokine, there is one other special cytokine in our model. This is always designated as the first cytokine that a primary cytokine creates, and it represents the stop signal. While other cytokines represent a “go here” signal, this cytokine represents a “stop and search this area” signal.

If a primary cytokine never gets intercepted by a lymphocyte and instead exits the bounds of our simulation, we consider that cytokine to have exited the liver and entered the bloodstream. The simulation interprets this as a need for more lymphocytes, so it begins summoning them to the area. This, however, only happens for a short time, so a continuous stream of lymphocytes to enter the liver would require a continuous stream of cytokines that do not get intercepted by an existing lymphocyte.

Configurable parameters are speed, seconds until duplication, and lymphocytes per second in the event that a cytokine exits the liver.

B.3 Lymphocyte

The lymphocyte, in our model, is essentially the merger of the B-Cell, T-Cell, and Natural Killer Cell. By default they are deactivated, which in our model simply means that they are not actively searching for anything to kill. In terms of positioning, they come after the macrophage/liver cell layer (layer diagram to be explained below). Unlike a macrophage, they only contain a cell body but no outer perimeter. Their cell body measures 25 micrometers in radius. We did not have a reliable source to indicate what their sizes were in real life, so we made the decision to make them slightly smaller than our model’s macrophages.

A lymphocyte responds to a cytokine released by a macrophage [2]. This causes the lymphocyte to become activated and begin to actively seek out foreign substances [2].

If the cytokine it intercepts contains information about direction, the lymphocyte will modify its speed to head in the general direction that the cytokine indicated. If the cytokine represents a stop-and-search signal then the lymphocyte modifies its behavior to engage in a random walk. Once random walk has been initiated, the lymphocyte mimics the macrophage in that it has a probability of 0.5 that it will change its direction after 5 seconds (5 minutes in reality) [5]. Having the random walk mimic the macrophage's was a decision we made and was not proposed in any of our sources.

Along with this, once a lymphocyte has been activated in our model, it has a lifespan counter measured in seconds. After that counter is up, the lymphocyte dies (removed from simulation).

Configurable parameters are the initial number of lymphocytes, speed, and lifespan.

B.4 Liver Cells

Each liver cell is made up of a cell body that measures 50 micrometers in radius. Real liver cells have an radius that ranges from 50-100 micrometers [4].

To simplify our model, we decided not to have them replicate as they do in real life. This was a welcome simplification since our runtimes tend to be very short rather than being large-scale, drawn-out simulations.

Each cell starts out as healthy. If they come into contact with a virus, they become infected cells. This triggers an internal change, enabling the cell to become a virus factory to make copies of the virus that infected it. When the cell achieves a critical mass of viruses inside of it, it bursts and releases them. In our model we decided to set this to a default value of 10, though in real life it can be as many as 100-200 or more [11]. The decision to make it 10 was purely for performance reasons.

Configurable parameters are the initial number of liver cells, viruses an infected cell can create per second, and the number of viruses it can hold before it bursts.

B.5 Viruses

The virus is the simplest component that makes up our model. It simply enters the world and travels until it finds a cell [11]. If the cell it finds appears healthy, it will enter it and infect it. If the cell is already infected then it will move on and try to find another cell [11].

In real life, the largest known viruses are ~1 micrometer in length [7]. For our model we scaled this up to be 5 micrometers.

Configurable parameters are the initial number of viruses and speed.

C. Layered Liver Approach

To model the liver, we adopted a very simple three-layer approach. Figure 2 illustrates this nicely by showing the layers in order as they appear in our simulation as well as which components occupy each layer.

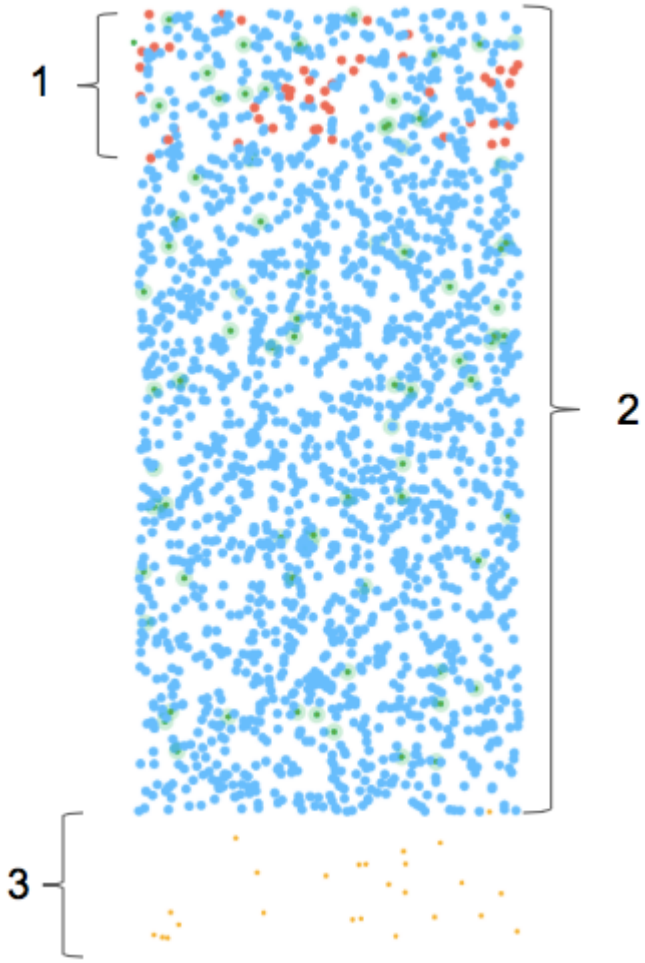

Figure 2: This illustrates the layers of our liver model. Layer (1) is where the initial viruses are inserted into. Layer (2) overlaps with (1) and contains the liver cells and macrophages. Layer (3) is where all the initial lymphocytes reside as well as where all new lymphocytes are inserted into the system.

It is important to note that all viruses have a downward movement tendency, moving from layer 1 towards layer 3 and beyond.

We consider everything after layer 3 to be outside of the liver.

D. Default Configuration (Control Group)

We are now in a place that we can present our default configuration for the components within the simulation. This proved to be a tricky task since many simplifications and assumptions were made and some of our information was incomplete in some areas. As a result there is a lot of room within this configuration (and in this model in general) where improvements can be made to bring

it closer to reality. This will be touched on more in our discussion at the end.

The main goal with the default configuration was to create a system that was interesting to people outside of the project. Because of this, the aim was to create a system that could contain the viral outbreak almost all of the time but not in such an overwhelming manner such that it becomes difficult to believe/difficult to ever observe interesting and unexpected behavior.

1) The liver is 2000 micrometers by 7000 micrometers
2) There are 2000 initial cells
3) There are 75 initial macrophages (move 3*15 micrometers per second, scaled up from reality where they move 3 micrometers per minute [5])
4) There are 25 initial lymphocytes (move 150 micrometers per second)
5) Each macrophage can store up to 10 cytokines (cytokines move 150 micrometers per second when released)
6) Each primary cytokine duplicates itself once every 6 seconds
7) Each infected cell creates 0.5 viruses per second
8) The liver is seeded with 100 initial viruses which move the same speed as macrophages
9) When the cytokines leave the liver to signal other lymphocytes to come and help, the lymphocytes will enter the liver at a rate of 4 per second for a short time, or for long durations if continuously stimulated by cytokines leaving the liver

E. Experiments

With the above definitions and configurable parameters, this gave us all the tools we needed to test all of our hypotheses.

E.1 Unresponsive Adaptive Immune System

To test this, we left all default configuration settings the same except for one: we set the cytokine carrying capacity for the macrophages to 0.

What this meant was that even when the macrophage felt overwhelmed, it would not have any cytokines that it could release into the environment. Because of this, no lymphocytes would ever get the signal that something was wrong.

We then went one step further and tested to see what happens when we vary the number of initial viruses injected into the liver. We did this for 10 initial viruses, 25, 50, 100, 150 and 250. The idea behind varying the number of initial viruses paired with an unresponsive immune system was to see if there was a point where the macrophages could contain the outbreak on their own.

Each configuration was run 20 times through our simulation for a total of 120 runs.

E.2 Altered Communication Patterns

When we first observed some lymphocytes who never switched to their random walk behavior, we thought there was something wrong. However, we then realized that it was because the stop-and-search cytokine for the particular trail they were following had been intercepted already by another lymphocyte. In effect, they were permanently stuck in what we now call "patrol behavior".

This behavior is characterized by larger sweeping movements through the liver. The lymphocyte moves until it reaches one edge of the liver, turns around and moves until it reaches the other end and then repeats the cycle until it dies.

To replicate this and see which behavior was better, we configured the cytokine's "seconds until replication" parameter to be a very large number. This caused the primary cytokine to never replicate, meaning no stop-and-search cytokines were ever created, forcing all lymphocytes to engage in patrol behavior.

We ran this 40 times total. The first 20 were with unmodified cytokine parameter (our control group) while the next 20 were with the modified cytokine parameter.

E.3 Speed of Communication

This one seemed very obvious but we decided to test it anyway since it was a question we had and wanted to verify. To achieve this, we simultaneously varied the cytokine movement speed and lymphocyte movement speed. This means that the time it took for a macrophage to send a signal to a lymphocyte was decreased, and the time it took for the lymphocyte to respond and move towards the macrophage was also decreased.

The speeds we used were (all in micrometers/second): 90, 120, 150, 180, and 225.

These numbers may seem random, but they have some biological basis. For example, one of the fastest known cell moves at a rate of 30 micrometers per second [8], so we decided to go with half of that. In order to speed up our simulation, we then scaled all of our speeds by powers of 15.

So, 90 is 6 micrometers/sec * 15. 120 is 8 micrometers/sec * 15, and so on until 225 which is 15 micrometers/sec * 15.

Like previous tests, each configuration was run 20 times through our simulation for a total of 100 runs.

F. Data Collection

During any given simulation we collected a reasonably large amount of information for analysis. This included the amount of time before the last virus and infected cell were eliminated, the total number of healthy cells versus infected cells over time, the total number of lymphocytes over time and the total number of viruses over time.

Since our simulation takes place over a large rectangular space where agents can roam freely, each individual component would log its own events of interest with our global database.

For example, if a virus was created, it would report this. If a healthy cell was infected, it would report this. Each new lymphocyte that was spawned would be reported, and so on.

We adopted the policy that each component would log its own events. So, viruses log virus-related events, etc. This way we avoid the possibility that the same event would be reported from multiple sources and skew our data.

3. RESULTS

A. Default Configuration (Control Group)

Figure 3 presents the results that we obtained by running the default configuration through the simulation for 20 runs. Near the beginning of the figure, the virus count moves quickly from its initial condition to roughly 1750 viruses at timestep 140. Then around timestep 150, the virus curve makes a dramatic shift and decreases until its ultimate downfall around timestep 280.

During this time, it can be seen that the lymphocyte count makes a very small appearance in the immune system, more specifically increasing its count to roughly 200 between timestep 100-250. Although it is obvious in this figure that the virus attack was contained, the results in this figure do not point directly towards a specific cause of the defeat. We therefore interpret it as being the combined efforts of the macrophages and lymphocytes, and we will test this interpretation with the results from other tests described below.

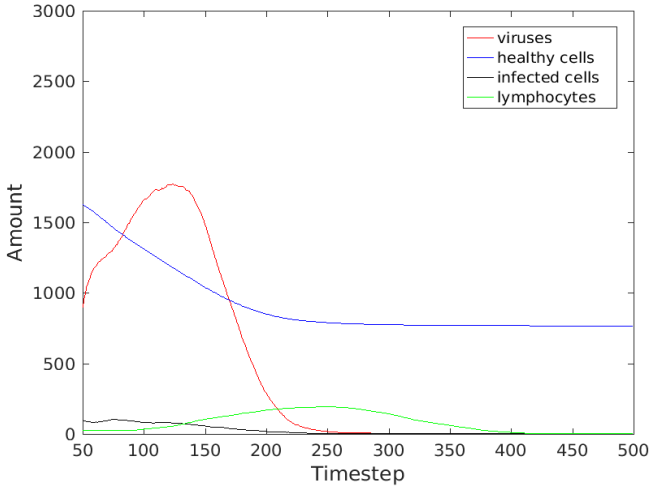

Figure 3: Count of viruses, healthy and infected cells, as well as the number of lymphocytes at every timestep.

B. Unresponsive/Unavailable Adaptive Immune System

In all tests, as described in methods, the adaptive immune component was unavailable to help the innate immune component.

B.1 Initial Viruses equaling 250

In figure 4 we see the results of introducing an initial 250 viruses into the simulation. As seen by the blue line, the healthy cell count begins to make a decrease until it reaches 0 around timestep 350. Additionally, as seen by the red curve, the virus count increases throughout the duration of the experiment until the viruses enter the rest of the human system around timestep 350. As there are no more remaining healthy cells, we consider that the result of this experiment seen in figure 4 as a partial failure of the immune system's response. The reason we only consider it a partial failure was because, while the virus was not contained, the macrophages still successfully prevented the virus count from ever reaching its theoretical maximum (2000 cells * 10 per cell = 20000 viruses in the system).

Along with this, it is clear that without the combined efforts of the initial innate immune response coupled with the adaptive immune response, the system is eventually overrun with viruses. This seems to further support our interpretation of the results from the control group.

As a side note we would like to explain to the reader why the virus count suddenly decreases near the 350 timestep mark. Our analysis of this model focused on the count of a component, in this case a virus, at a specific timestep. Additionally, whenever a virus reached the "bottom" of our idea model, we considered the virus as having migrated into the rest of the system. Subsequently this would exclude that particular virus from being included in that specific time step's virus count. In hindsight, this method of not counting "exited" viruses is problematic for any future, larger scaled implementation. In the case of this paper's experiments, we were able to calculate the expected exiting of the virus into the rest of the human system.

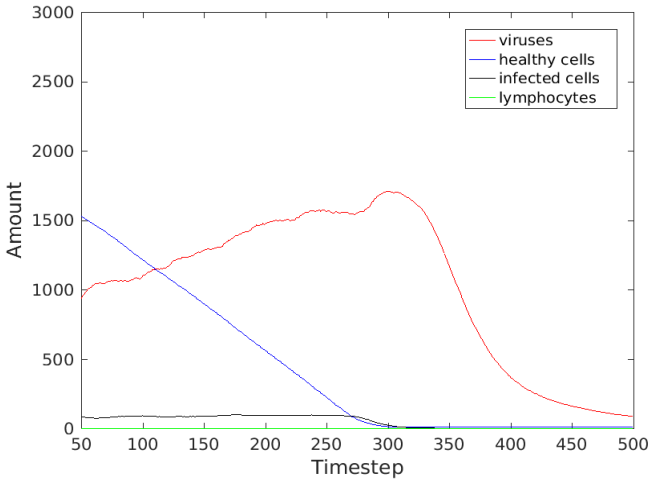

Figure 4: Count of viruses, healthy and infected cells, as well as the number of lymphocytes at every timestep. All lymphocytes are deactivated during this set of experiments. Additionally the number of initial viruses was set to 250.

B.2 Initial Viruses equaling 10

In this experiment we introduced into the system only 10 viruses (in comparison to the 100 viruses in the control group). As seen by figure 5, the viruses had some initial difficulty remaining in the system until they began to flourish around timestep 75-100. The healthy cell count, however, began to drop where able to halt their decline around timestep 350 leaving approximately 100 healthy cells in the model. The plateau of healthy cell count around 350 timesteps also coincides with the timeframe where viruses tend to reach the bottom of the model and enter the rest of the human system.

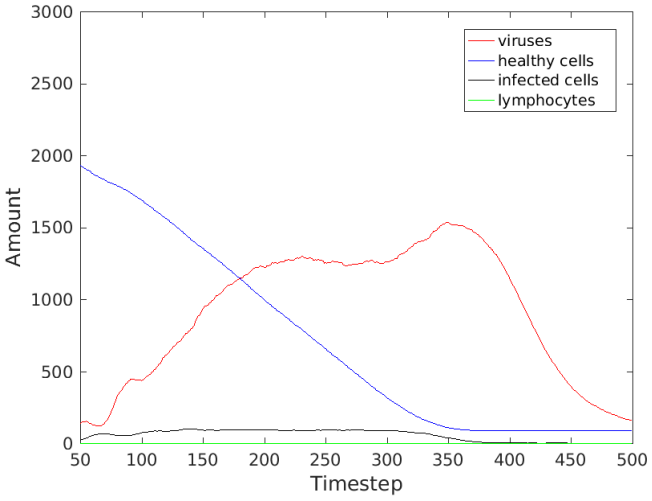

Figure 5: Count of viruses, healthy and infected cells, as well as the number of lymphocytes at every timestep. Lymphocytes are deactivated for this set of experiments. Initial number of viruses at start time was set to 10.

C. Varying Lymphocyte Speed

C.1 Lymphocyte Speed 225 Micrometers per Second.

In our control group, each lymphocyte had a starting speed of 150 micrometers a second as described in the methods section. Figure 6 displays the results when lymphocytes had a speed of 225 microunits. Similar to the behavior of the control group, figure 6 shows a successful halt to a virus attack. Specifically, the virus curve reaches a global maximum around the 90-100 timestep, which coincides with the increasing lymphocyte curve seen in green. In contrast to the control group, the healthy cell curve in this experiment plateaus with over 1000 healthy cells remaining in the system.

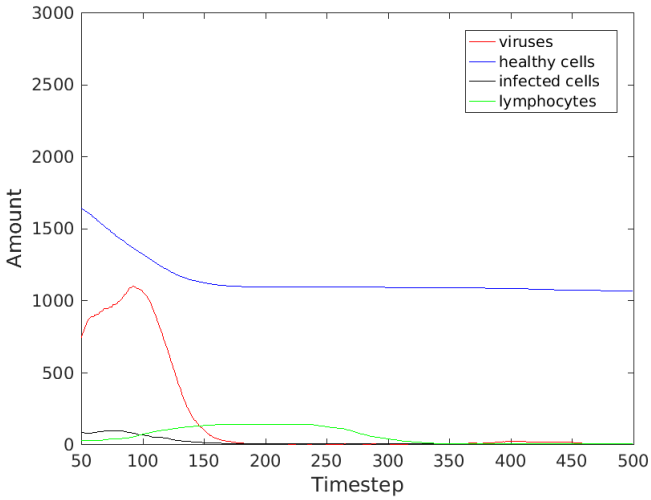

Figure 6: Count of viruses, healthy and infected cells, as well as the number of lymphocytes at every timestep. Lymphocyte speed was set to 225 micrometers for this specific set of experiments.

C.2 Lymphocyte speed at 90 Micrometers per second.

In contrast to the previous experiment, figure 7 exhibits the results when lymphocytes have a speed of 90 micrometers per second. At the onset of the virus attack healthy cells begin to drop, however they seem to plateau around 450-500 cells. The virus count is a little more difficult to interpret for this specific experiment. The virus curve contains a global maximum at around 200 timesteps and subsequently begins to decrease. Around the same time of decrease, the lymphocyte curve becomes very prominent exhibiting behavior similar to experiments discussed before. What is unusual about this experiment is that the virus curve never reaches a value of 0 and instead appears to be increasing again around 375 timesteps.

A possible explanation for this behavior was that there may have been some untouched, infected cells around the 375 mark. As the lymphocytes began to die off, the infected cells may have started to burst. Additionally, it can be seen that there still remain a handful infected cells as the 375 timestamp is approached.

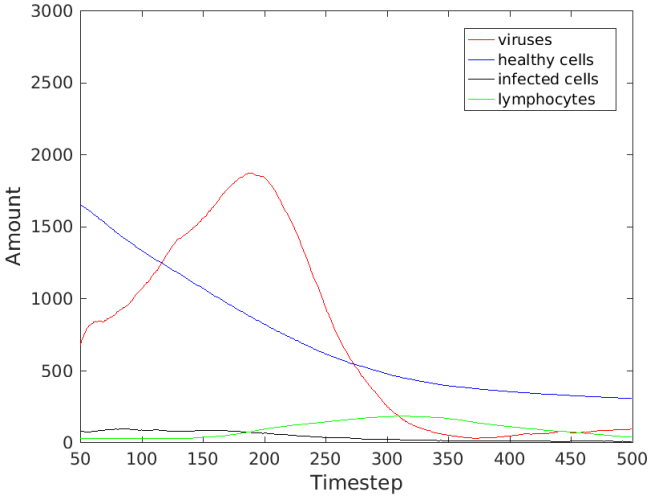

Figure 7: Count of viruses, healthy and infected cells, as well as the number of lymphocytes at every timestep. Lymphocyte speed is set to 90 micrometers for this set of experiments.

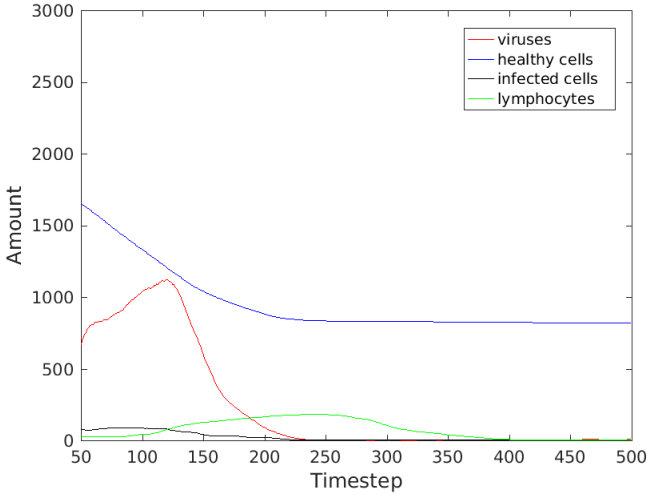

Figure 8: Count of viruses, healthy and infected cells, as well as the number of lymphocytes at every timestep. Upon reaching their destination, lymphocytes exhibited a patrol behavior rather than a random search behavior for this set of experiments.

D. Varying Lymphocyte Behavior

As discussed in the methods portion of this paper, lymphocytes follow a path of cytokines in order to find the general area of virus attack. Once the lymphocyte reaches what it believes is the general area of attack the lymphocyte conducts a random search. An alternative behavior that the lymphocyte could perform is essentially a patrol behavior once it reaches the attack area. As the control group already exhibits the random search pattern, in this section we will show the results when the pattern is changed so that lymphocytes patrol the liver tissue instead. With this behavior they made broader sweeping movements through the liver rather than localized random search.

In figure 8 it is shown that the virus count reaches a global maximum before the 150 timestep. In addition, at this maximum the count of viruses barely surpasses that of 1000. The lymphocyte count begins to increase at this time, as well as a contrasting decrease seen in the infected cell count.

We can compare this with the results of the default configuration (control group) discussed previously. In that case, the peak number of viruses was closer to 2000, but interestingly roughly the same number of cells died in the process. Along with this, patrol behavior resulted in a shorter amount of time required to kill all the viruses and infected cells when compared to the control group exhibiting random walk.

IV. Discussion and Conclusion

To start the discussion, we want to address the most obvious and most important concern as least as far as we can see. Our model makes a lot of simplifications and assumptions, and unfortunately the result can be described as "loosely based on reality" at best. In response to this we would like to say that we wholeheartedly agree with this description, but we feel that given the time constraints that our model ultimately accomplished everything we had hoped to realistically achieve. Along with this, the decision to create all of the code for the simulation ourselves without relying on any 3rd party libraries to help simulate the behavior of cells/the immune system limited what we could achieve in just a few weeks, but we are very happy with the progress and current result.

This leads to a major question: given that we know about the limitations about our current model and corresponding simulation, what could be done in the future to remedy this? For this we have a few ideas. The first is that it is very important to find high-quality sources for all of the numbers used in our configurations. This would include sizes, movement speeds, probabilities to engulf viruses, etc. We had numbers for some things, but others we were completely in the dark and had to make the best guesses that we thought appropriate. Then there is the obvious way to branch out from the current model by simply adding more moving parts to better approximate the real immune system.

Next we want to briefly touch on a couple of interesting finding in one of our results. The first has to do with cytokines: with our very simple setup, we could change just a couple of parameters that would affect the way the cytokines propagate through space. This in turn produced two very different lymphocyte behaviors (random walk versus patrol). While this was present in our model, it begs the question of whether or not similar variations in communication patterns result in equally interesting behavioral changes in the real immune system. We do not know the answer to this, and this could be a whole other project altogether.

The second interesting finding has to do with our results from setting cytokine/lymphocyte speed to 90 micrometers per second. On average we saw the system very nearly get rid of the virus, but then the lymphocytes began to die off and rather than seeing the total virus count reach 0, it actually began to increase around timestep 400. We have come to the conclusion that it is because the lymphocytes did their job and began to die off, and once the number of lymphocytes declined to some threshold (maybe less than 75 or so from eyeballing the graph), the viruses had enough room to grow once again.

The reason this is so interesting to us was because it showed that for the most part, faster lymphocytes/cytokines means faster cleanup of the viruses. However, we did not expect that by setting the speed to 90 that we would see the virus get effectively wiped out like in our other tests (albeit more slowly), but then be able to make a slow comeback. It is possible that had we let the simulation run longer that the virus count would reach another critical amount so as to require a second full-blown immune response. We suspect that this is partly due to the slower speeds and partly due to the mentioned incompleteness of our model: the adaptive immune system is just too simple since speed alone can produce such different behavior.

In this project we made hypotheses in regards to the behavior of macrophages in scenarios which may have required the help of lymphocytes in order to stop an attack by a foreign substance. In order to test these hypotheses, we constructed our own idea model of the immune system. In this system we implemented idea components of the immune system, which include lymphocytes, macrophages, healthy/infected cells, viruses, as well as Cytokines. Upon constructing this model and fine tuning a control group, we then conducted experiments in order to test our hypotheses. We conducted our experiments by varying the availability of lymphocytes in the system, the speeds that the lymphocytes travelled, as well as the behavior of a lymphocyte upon reaching their final destination. We found that Macrophages do require the help of Lymphocytes in fending off a virus attack. We also found that the speed at which Lymphocytes travel will directly affect the speed at which a virus attack will be halted. Lastly, we found that although a random search pattern does effectively stop a virus attack, a patrol pattern is more efficient in doing so at least as far as our model is concerned.

V. References

[1] C. Janeway, M. Walport and P. Travers, *Immunobiology: The Immune System in Health and Disease*, 5th ed. New York: Garland Science, 2001, Chapter 3.

(talks about the limits of the innate immune system and how t-cells and b-cells recognize antigens)

[2] Cameron MJ, Kelvin DJ. Cytokines, Chemokines and Their Receptors. In: Madame Curie Bioscience Database [Internet]. Austin (TX): Landes Bioscience; 2000-2013. Available: https://www.ncbi.nlm.nih.gov/books/NBK6294/

(talks about cytokines, chemokines and their receptors)

[3] "Macrophage | Ask A Biologist", *Askabiologist.asu.edu*, 2011. [Online]. Available: https://askabiologist.asu.edu/macrophage. [Accessed: 03- May- 2018].

(Gives us size of the macrophage as well as some other interesting info)

[4] "Diameter of large liver cells - Human Homo sapiens - BNID 109547", *Bionumbers.hms.harvard.edu*, 2018. [Online]. Available: http://bionumbers.hms.harvard.edu/bionumber.aspx?id=109547#. [Accessed: 03- May- 2018].

(Gives us the diameter of liver cells)

[5] "How many macrophages does it take to kill a virus?", *Mathbench.umd.edu*, 2011. [Online]. Available: http://mathbench.umd.edu/modules/cell-processes_diffusion/page24.htm. [Accessed: 03- May- 2018].

(talks about how fast a macrophage is as well as how often it changes directions - 3 micrometers PER MINUTE and once randomly every 5 minutes)

[7] "Virus - Size and shape", *Encyclopedia Britannica*, 2018. [Online]. Available: https://www.britannica.com/science/virus/Size-and-shape. [Accessed: 03- May- 2018].

(talks about the sizes of different viruses)

[8] R. Philips, "How fast do cells move?", *Book.bionumbers.org*, 2018. [Online]. Available: http://book.bionumbers.org/how-fast-do-cells-move/. [Accessed: 03- May- 2018].

(talks about how fast different types of cells move → seems to be 30 micrometers/second for rough upper limit)

[9] "innate immunity - Immunobiology - NCBI Bookshelf", *Ncbi.nlm.nih.gov*, 2018. [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK10759/def-item/A2958/. [Accessed: 03- May- 2018].

(Talks about the innate immune system)