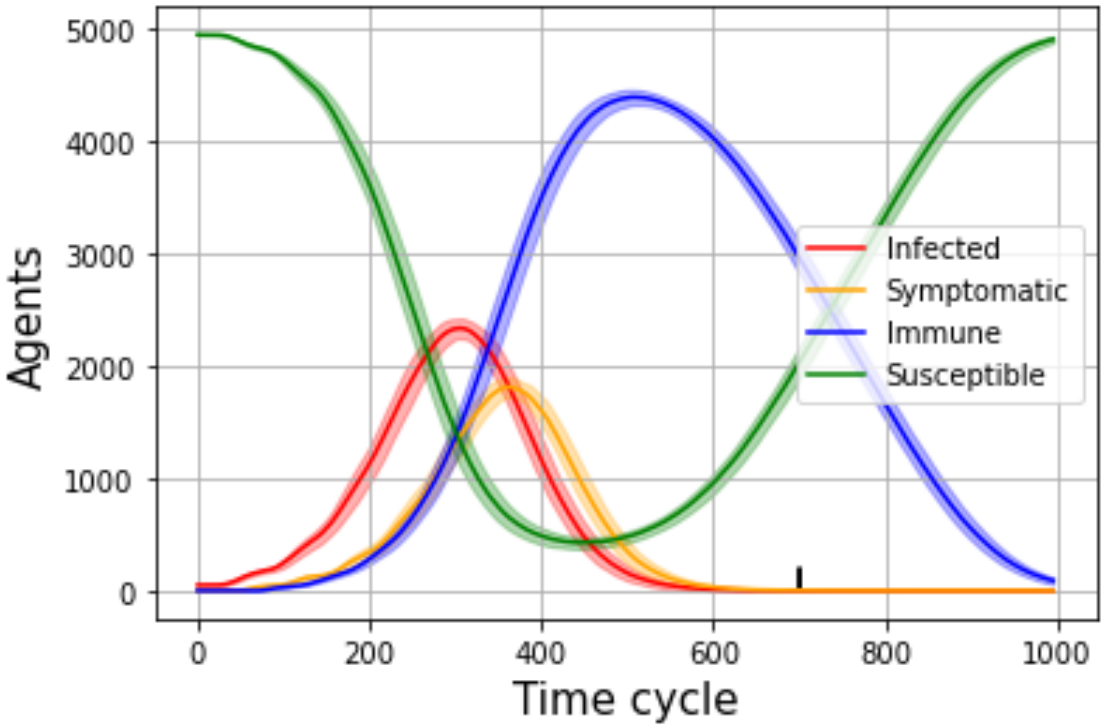

A coupled immunological and epidemiological model for exploration of immunization strategies

Master's thesis in Complex adaptive systems

Kevin Rylander

DEPARTMENT OF SOME SUBJECT OR TECHNOLOGY

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Supervisor: Claes Andersson
Examiner: Claes Andersson, Department of Space, Earth and Environment

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Department of Space, Earth and Environment
Chemical engineering with physics
Chalmers University of Technology
SE-412 96 Gothenburg
Telephone +46 31 772 1000

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A coupled immunological and epidemiological model for exploration of immunization strategies

Kevin Rylander
Department of Space, Earth and Environment
Chalmers University of Technology

Abstract

On 31 December of 2019, the World Health Organization (WHO) received the first cases of Covid-19 from Wuhan, China. Two months later, on 11 March 2020, the WHO declared Covid-19 a pandemic. In response to the pandemic, a range of strategies have been used to prevent people from spreading the disease and overwhelming health care systems. To further understand the dynamics of disease spreading, models have been used to replicate conditions and simulate outcomes based on assumptions and known data. In this paper, an immunological and epidemiological model is coupled, using an agent-based model, with the goal of exploring its capabilities in the context of immunization strategies. On a more strategic level, basing an epidemiological model on an embedded immunological model allows the study of large-scale patterns arising from interactions below the social level. Compared to the "state machine approach" of a SIR-type model, this permits us, in general, to vary the features of the disease on a level that is closer to that of scientific understanding of pathogens and their hosts.

Keywords: Epidemiology, immunological, agent based model.

Acknowledgements

First and foremost I want to thank my supervisor and examiner Claes Andersson for his contribution though out the whole process. From developing the model to comments on the report. I could not have done this with out him. Secondly I want to thank Kristian Lindgren for helping me get in contact with Claes for the master thesis. Thirdly I want to thank my friends for all the fun years at Chalmers. Finally I want to thank my family for their never ending support.

Kevin Rylander, Gothenburg, June 2021

Contents

1
Introduction

The Covid-19 pandemic struck the world hard and fast in 2020 and many countries have been affected by it. Different strategies have been used to prevent people from spreading the disease and overwhelming health care systems. From lockdowns to, mass testing, selective quarantine, contact tracing and public announcements. Many strategies have been put to the test and with varying results. Since it is far from obvious which strategies will work best for a given situation, models have been used to replicate conditions and simulate outcomes based on assumptions and known data. The purpose of this paper is to investigate the coupling of an immune system model and epidemiological model and see the impact of vaccination in different environments.

1.1 Previous models

One of the first models in epidemiology was designed by Ronald Ross in 1916 [1], with subsequent revision [2] together with Hilda P. Hudson. It is a mathematical model of disease spread that introduced the first SIR model which is based on dividing the population into three categories: Susceptible, Infected and Recovered. In 1927 Kermack and McKendrick further studied mathematical models [3] and came to the conclusion that there exists a threshold of population density for a disease to be epidemic, and that a small increase in infectivity can thereby be the difference that leads to a major epidemic.
During the last year epidemiology has received much attention, which has led to the development of many models. Silva et al. [4] used an agent based SEIR model to investigate social and economic effect with 7 different scenarios. The most effective, in terms of lowest death toll, was a lockdown but it also had a drastic effect on the economy. If a lockdown could not be achieved, a combination of face mask and partial isolation was more realistic for lowering the effects of the disease. Another agent based model by Almagor, Jonatan and Picascia, Stefano (2020) [5] investigated the impact of a contact tracing app where heterogeneous agents are linked in a multi-layered network representing the social structure. It concluded that an app could reduce infection rates but must be accompanied with sufficient testing.
The difference between agent based and mathematical models are discussed by Rahmandad et al (2008), and by Figueredo et al (2014)[6, 7] and the conclusion is that agent based models can incorporate heterogeneity easier but that it takes longer to compute the sensitivity of the model.
An early mathematical SIRS model of vaccination by Arino J et al. (2003) [8]

concludes that when a system has bistability the basic reproduction number needs to be lower than 1 to eradicate the disease, which can be accomplished though vaccination of newborns or people in risk groups. A vaccine model for SARS-CoV-2 by Paltiel et al. (2021) [9] considered a wide range of basic reproduction numbers and found that even low efficacy can help in reducing the impact of Covid-19, but that the outcome depends heavily on the public's reception of the vaccine. One of the focuses of research on SARS-CoV-19 has been asymptomatic cases [10, 11]. An article by Dobrovolny (2020) [12] came to the conclusion that if Covid-19 has asymptomatic individuals, it can spread rapidly if social distancing is relaxed too early.

1.2 Immune system

The immune system is a complex system that has been intensely researched for decades, and models have been developed for the different mechanisms the body has to fend off foreign invaders. The immune system can be divided into two parts: the innate immune system and the adaptive immune system. The innate immune system is responsible for distinguishing self (the body's own cells) from non-self, called antigens (e.g bacteria, virus, parasites). Antigens are anything that causes an immune response. The innate immune system consists of physical barriers, defense mechanisms and general immune responses such as inflammation, complement, and non-specific cellular responses. The adaptive system consists of two types of cells: B cells and T cells. Each cell is highly specific and targets only certain antigens, but because each individual cell targets different antigens, they have a wide range as a population.
B cells have numerous different kinds of receptors on the surface. When a B cell encounters an antigen that binds to its surface, it becomes activated and produces plasma cells and memory B cells. Plasma cells produce antibodies that bind to the antigen and neutralize it. The memory B cells become a copy of the parent B cell with the same surface receptors. They persist for a long time span and serve as immunological memory for the body.
There are three types of T cells: helper T cells, cytotoxic T cells and T regulatory cells with different functions. Helper T cells activate cytotoxic T cells, B cells, and other sorts of immune cells that targets antigen. Cytotoxic T cells remove infected cells and other pathogens. T regulatory cells help other cells avoid targeting self molecules.
Inspiration for the immune system model in this paper came from Guri I Marchuk's book *Mathematical modelling of immune response in infectious diseases* [13] which, usefully for these purposes deals with the issue of finding minimalistic immune system models. Marchuk states that the simplest of immune models should contain the interaction between four components: antigen, antibody, plasma cells producing antibodies and quantitative characteristics of affected organs. The immune system model used in this paper is highly simplified and consists of three different cells: antigen, plasma cells and memory cells (M cells). The reason for the very simplified version of the immune system is to be able to have a large amount of agents in the simulation, which is necessary for performance on the epidemiological level. An

infection starts with antigens entering an agents body, starting to multiply exponentially. This causes the immune system to activate, and start to produce plasma cells and memory cells. The plasma cells remove the antigen from the body until the antigen has been neutralized. During the time of infection, the agent is symptomatic. The amount of plasma cells in the agent is used as proxy for the extent of symptoms experienced by the agent in this model. This is to reflect the body's own defence mechanisms against the antigen. When the antigen is completely removed, plasma cells and memory cells start to decrease. The memory cells decrease at a considerably slower rate than the plasma cells.

2
Methods

In this paper an agent based model of epidemiological dynamics is presented where each agent has its own immune system. Each agent has unique properties, which are divided into spatial and immunological properties. The spatial properties are location, L(X,Y), speed, s, and rotation, R. The immunological properties are antigen, V(a,b), plasma, P(c,d,e), and M cells, M(f,g)
The nomenclature in this paper follows a simple convention. Quantities denoted by upper-case symbols represent variables while lower-case represent parameters that are fixed during run-time.

2.1 Movement

The movement of agents is dependent on s and R $\in [0, 2\pi]$. There are two different time steps in the model. We denote the first as *time step* T, and the second as *time cycle* C. The time step controls agent movement and the time cycle controls disease spreading dynamics. The time cycle C is arbitrarily set to C = 100T. During a time step, agents move a set distance s in an angular direction R. The position is updated each time step according to:

$$L(X,Y)_{T+1} = L(X,Y)_T + s * [cos(R_T), sin(R_T)]. \tag{2.1}$$

Each time step, R is updated using the uniform distribution $R_{T+1} = R_T +$ U$[-\pi/4, \pi/4]$. This leads to a type of biased Brownian motion for the agents. Agents move in a toroidal space (square with periodic boundary conditions).

2.2 Immune system

The immune system model is built upon on three functions V(a,b), P(c,d,e) and M(f,g) and correspond to antigens, plasma cells and M cells for the agents. Each agent has its own its own three functions and the functions for all agents updates every time cycle according to the equations

$$\begin{aligned} V_{C+1} &= V_C + \Delta V(a,b) \\ P_{C+1} &= P_C + \Delta P(c,d,e) \\ M_{C+1} &= M_C + \Delta M(f,g) \end{aligned} \tag{2.2}$$

$$\begin{aligned} \Delta V(a,b) &= aV - bP \\ \Delta P(c,d,e) &= (c + dM)V - eP \\ \Delta M(f,g) &= fP - gM \end{aligned} \tag{2.3}$$

The parameters a, b, c, d, e, f, g $\in \mathcal{R}$ and do not change during a run. Since all the parameters are fixed, to create unique immune systems for all agents, each agent

draws a number from a uniform distribution for a single parameter (i.g U(x_{lower},x_{upper}, where x is one of the immune system parameters). The drawn number does not change during a run.
To differentiate agents with different levels of antigen, plasma cells, and M cells, four states: Susceptible, Infected, Symptomatic, and Immune are used. Unlike a SIR model, these states does not affect agents in any way during a run and is only used as a labels for the different levels of cells. An agent can be in multiple states during a run. It is susceptible if it has no antigen and plasma and M $< m_{immune}$. The immune threshold is denoted as m_{immune} and is the number of M cells an agent needs to have in order to swiftly counteract antigen. The immune threshold m_{immune} is arbitrarily set to 50 000 M cells. The Infected state means that the agent has antigen in the body. The agent is Symptomatic when it has produced enough plasma cells to show symptoms. Finally the agent is deemed Immune when the M cell count is above m_{immune} and one thing to note is that even though an agent's M cell count is below the m_{immune} threshold it will still exhibit the same characteristics as an immune agent. Because the M cell count increases during an infection, an agent can be both Immune and Infected/Symptomatic simultaneously. When the immune system is activated, the agent can enter four levels of symptoms: (0) asymptomatic, (1) weak symptoms, (2) moderate symptoms and (3) severe symptoms. The symptoms are dependent on P as a step function. An example is given in figure 2.1 where agent A goes though all stages of symptoms while agent B is asymptomatic for the whole time span. Even though the agent B is asymptomatic it can still infect other agents.

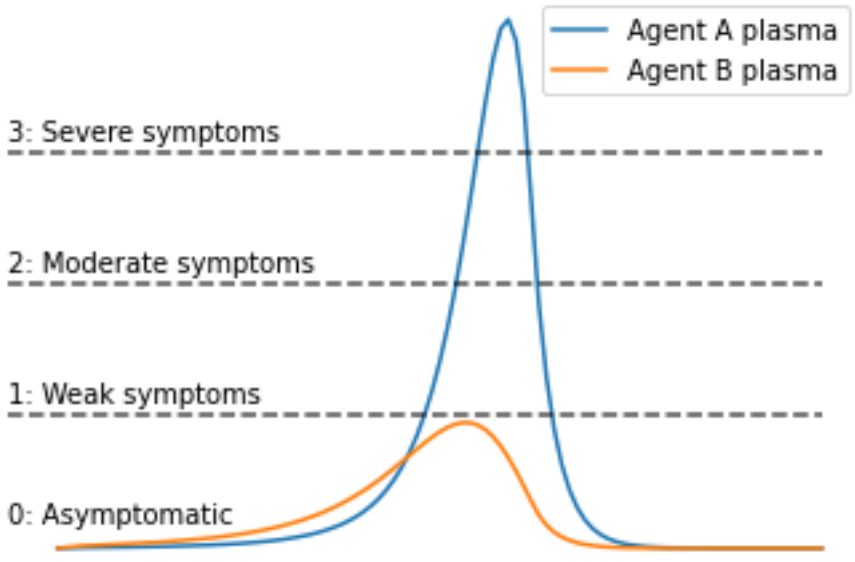


Figure 2.1: Example of plasma curves with symptoms level over time

In general, there are four different antigen progressions a disease can take [13] (see Figure 2.2): subclinical form, acute form with recovery, acute form with lethal outcome, and chronic form. All forms except acute form with lethal outcome will be investigated in this paper. One of the reasons for not investigating the lethal

outcome is the need for a model that describes how the pathogens damages an agent, which this paper lacks. This leads to a deterministic factor that can not be evaluated for the immune system model (i.e when the pathogen has reached critical mass to kill an agent).

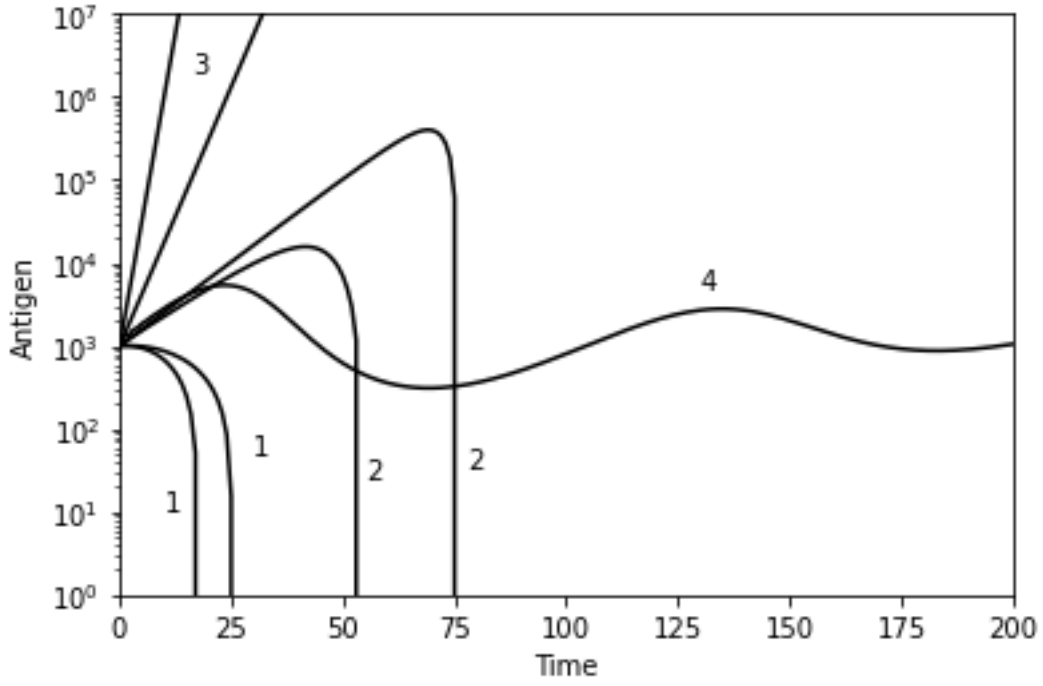


Figure 2.2: Different antigen progression. 1, subclinical form. 2 acute form with recovery. 3, acute form with lethal and 4, chronic.

2.3 Disease spreading

The space is resolved into smaller unit sized grid cells. When disease spreading is calculated, all agents inside each grid cell interact with each other. Only when a cell contains at least one infected agent, and at least one susceptible agent, does a calculation within the grid cell happen. An infected agent interacts with all non-infected agents but the disease is not always transferred between the interacting agents. The transfer likelihood depends on two factors: infection probability and meeting probability. The infection probability is an arbitrarily set value for the disease, and factors such as the likelihood to transfer and to receive the antigen is part of the infection probability. The meeting probability is the likelihood that the agents interact and is dependent on the symptoms of the infected agent. The meeting function is calculated arbitrarily as $Meeting = 1/5^{symptom}$, which causes the rate of meeting to decrease sharply with severity of symptoms. This simplistic model may be readily be replaced with a more realistic model. If an interaction occurs, the infected agent transfers a small proportion of its antigen to the non-infected agent, which means that agents are more contagious the higher their viral load is (this model can be readily elaborated).

2.4 Vaccine

To replicate how a vaccine works, "fake antigen" is injected into susceptible or immune agents. The vaccine is administered to agents with no antigen and no plasma cells. The immune response for the fake antigen is similar to an actual infection but does not harm the agent. The M cells that are produced is added to the vaccinated agent and it is said to be immune when the M cells count $> m_{immune}$. An important factor in vaccines is efficacy, which is defined as the vaccine's ability to induce an immune response in the vaccinated agent. In the model, efficacy is interpreted as the ability to produce a stronger immune response compared to a typical infection. To differentiate between when a vaccine has a strong immune response and a normal response, the stronger immune response will be classified as activated. The following equation describes how the activated vaccine functions:

$$M(f, g) = 100 * f - g/10 * M \tag{2.4}$$

If the response is not activated it will be classified as deactivated and function as a normal immune response to the disease (i.e the agent has partial immunity).

3
Results

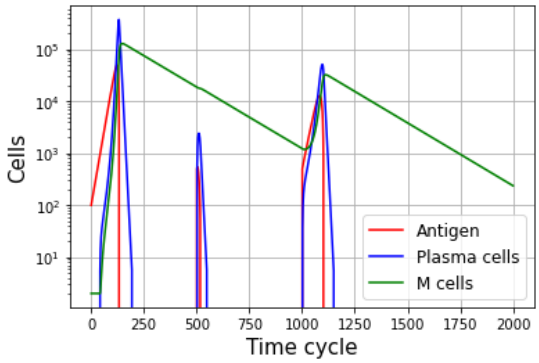
The results are divided into two parts: immune system model dynamics and epidemiology dynamics. The immune system model dynamics section gives examples on the different mechanisms of the immune system dynamics (e.g., reinfection, immunization). The epidemiology dynamics section is split into five different cases: base case, faster M cell decay, low spatial, chronic and outside. These cases will be further described in the section.

3.1 Immune system model dynamics

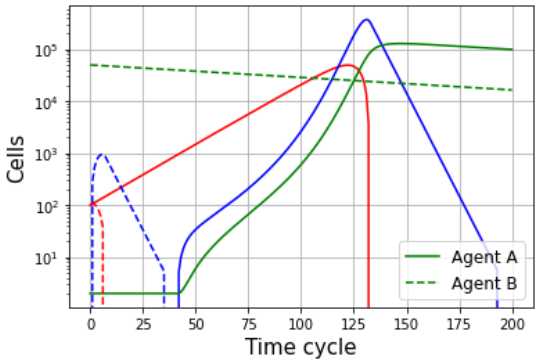
A set of parameters will be used to investigate how the immune system model will respond to different initialization and effect of a vaccine. The parameters used in this section are from base case (see Table 3.1) with the smallest value of a in the uniform distribution. These set of parameters will now be called lower base case. Reinfection is a common occurrence in the epidemiological model and an example is given in figure 3.1a, where an agent with lower base case parameters is infected at two different time cycles. The first reinfection impacts the agent for a short period while the second has a longer antigen progression. Figure 3.1b displays the difference between agent A with no initial M cells and agent B with m_{immune} M cells. Agent A has a far longer disease progression compared to agent B, who eliminates the antigens quickly. Figure 3.1c-3.1d shows the effect of a activated vaccinated agent compared to a deactivated vaccinated agent with both agents having low initial M cells. The activated vaccinated agent D has a shorter disease progression with longer immunity compared to agent C. Figure 3.1e shows a reinfection of an agent with chronic immune system dynamics. At the reinfection, the antigen spikes together with the plasma cells and start to oscillate but returns to a steady state. Figure 3.1f shows the difference between a deactivated vaccinated agent compared to a activated vaccinated agent for the chronic case.

Parameters	a	b	c	d	e	f	g
Base case	U(0.056,0.111)	0.028	5.56e-3	5.56e-5	0.167	0.028	5.56e-3
Fast M cell decay	U(0.056,0.111)	0.028	5.56e-3	5.56e-5	0.167	0.028	0.028
Low spatial density	U(0.056,0.111)	0.028	5.56e-3	5.56e-5	0.167	0.028	5.56e-3
Chronic	U(0.075,0.188)	0.125	0.5	2.5e-5	0.688	0.063	0.012
Outside	U(0.056,0.111)	0.028	5.56e-3	5.56e-5	0.167	0.028	5.56e-3

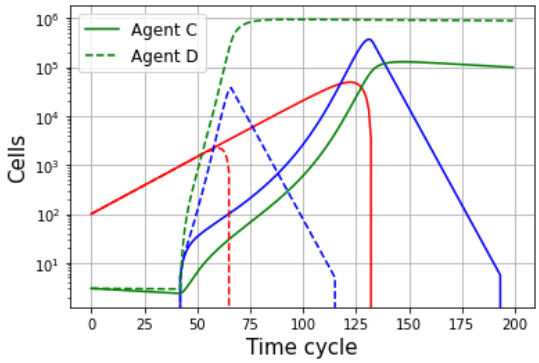
Table 3.1: Parameters for the immune system model for the different epidemiology cases where parameter a has a Uniform distribution between the lower and upper value



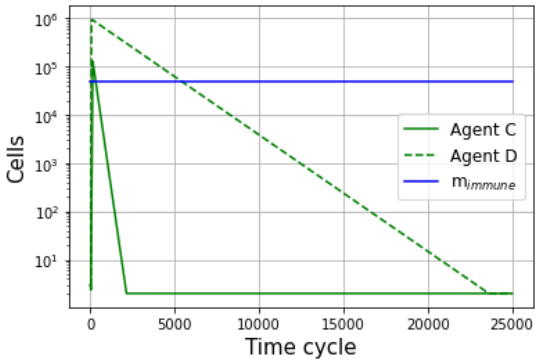
(a) Immune system for an agent at two different time cycles C = 500, 1000



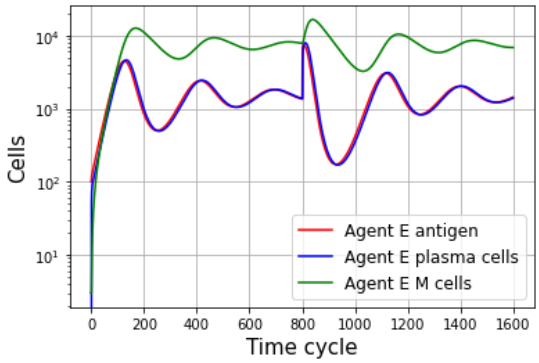
(b) Immune system model dynamics illustration of agents immune response with zero M cells initialization and m_{immune} M cells



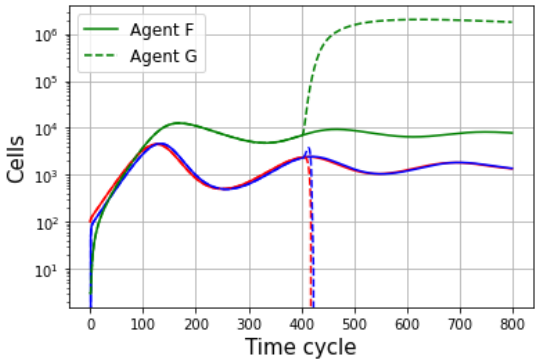
(c) Infection progression for deactivated vaccinated agent C vs activated vaccinated agent D



(d) M cell decay for deactivated vaccinated agent C vs activated vaccinated agent D with m_{immune} plotted



(e) Chronic reinfection at C = 800 for agent E

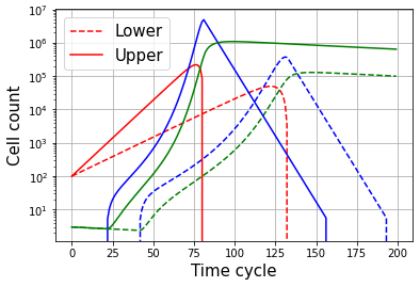


(f) Infection difference between deactivated vaccinated agent F and activated vaccinated agent G with vaccination at C = 400

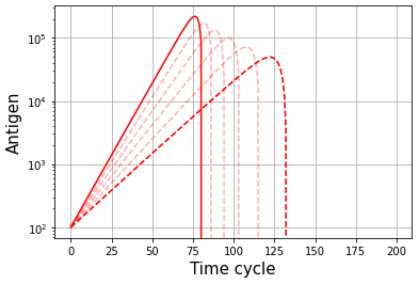
Figure 3.1: Immune system dynamics for different cases. Note that the color scheme for all figures are the same as figure 3.1a

3.1.1 Immune system cases

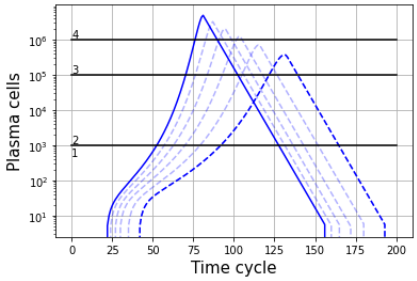
Figure 3.2 shows the immune system model dynamics for the base case with the parameters in table 3.1. The upper legend is the immune system with the largest value of a in the table, while the lower legend is the lowest value of a. The antigen progression for both upper and lower is of type acute form with recovery (see Figure 3.2b). The progression of plasma cells with the different symptoms levels is plotted in figure 3.2c. The symptoms levels is arbitrarily chosen and reflect a disease where all agents with a reasonable amount of plasma cells experience symptoms. Around half of agents with low initial M cells will experience the highest level of symptoms. Figure 3.2d shows the M cell progression for an infection with low initial number of M cells. All agents reach immunity but the immunity duration difference is quite large between the agents.
Figure 3.3 shows the immune system dynamics for fast M cell decay. Since the parameters for fast M cells case is the same as base case except parameter g, the only noticeable difference is the decay of M cells in figure 3.3d which compared to the base case goes from 2500-2000 C to about 520-550 C.
Figure 3.4 shows the immune system dynamics for different values of a for the chronic case parameters taken from table 3.1. The antigen has three kinds of progressions: subclinical form, acute form with recovery and chronic (see Figure 3.4b. The same kind of progression can be seen in both plasma and M cells (see Figures 3.4c-3.4d).



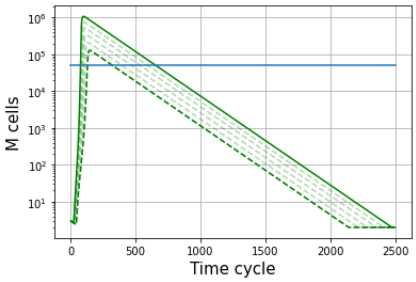
(a) Immune system model for base case



(b) Antigen progression for different values of a

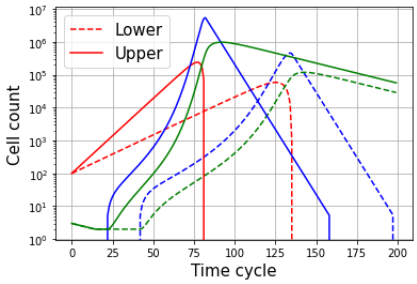


(c) Plasma cells progression for different values of a with plotted symptom levels

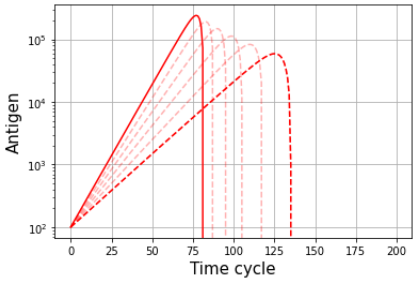


(d) M cells progression for different values of a with m_{immune}

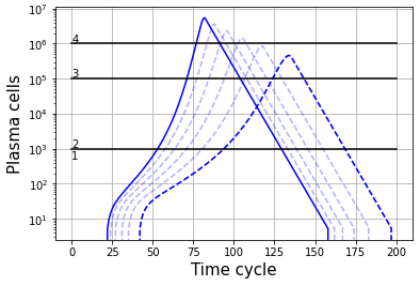
Figure 3.2: Immune system model for base case for different values of a = [0.056, 0.067, 0.078, 0.089, 0.1, 0.111]



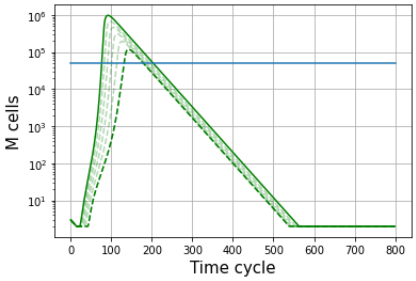
(a) Lower and upper for immune system model of fast M cell decay



(b) Antigen of immune system for fast M cell decay

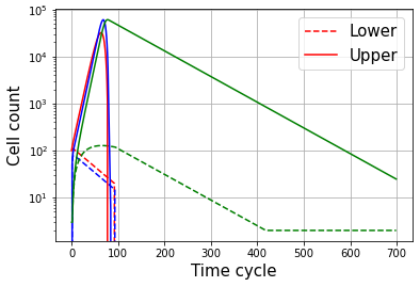


(c) Plasma cells progression for different values of a with plotted symptom levels

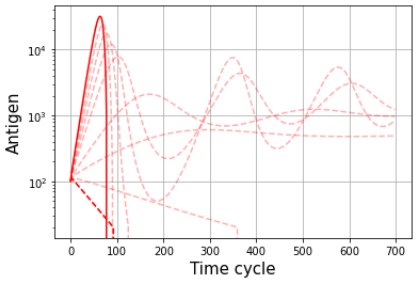


(d) M cells of immune system for fast M cell decay with m_{immune}

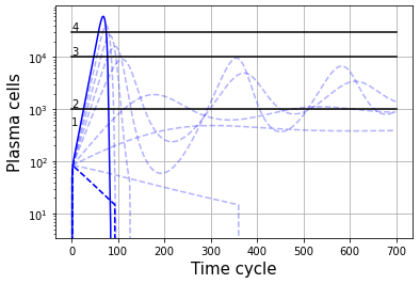
Figure 3.3: Immune system model for fast M cell decay for different values of a = [0.056, 0.067, 0.078, 0.089, 0.1, 0.111]



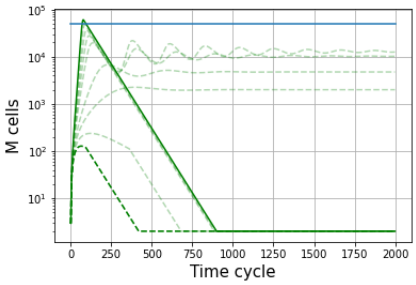
(a) Lower and upper for immune system model of Chronic



(b) Antigen of immune system for chronic for different values of a



(c) Plasma cells of immune system for chronic for different values of a with symptom levels plotted



(d) M cells of immune system for chronic for different values of a with m_{immune}

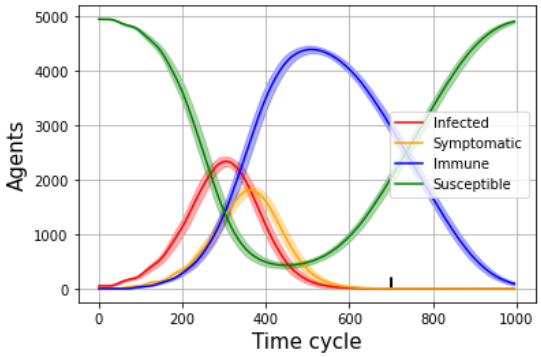
Figure 3.4: Immune system of chronic for a = [0.075, 0.0875, 0.1, 0.1125, 0.1375, 0.15, 0.1625, 0.175, 0.1875]

3.2 Epidemiology dynamics

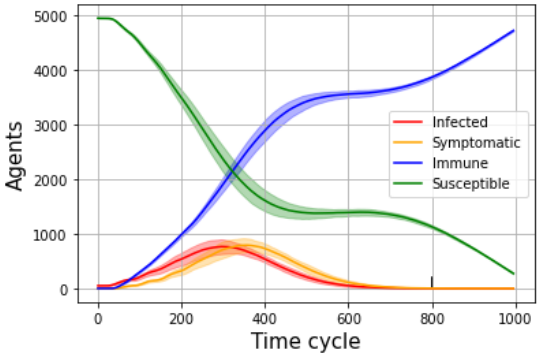
This section is split into five cases: base case, faster M cell decay, low spatial density, chronic, and outside. The parameters for each case are shown in table 3.1. Vaccination is administered at a constant rate of 5 doses per C in no specific order. The number of agents is constant at 5000 and the space size is $35^2 = 1225$ grid cells for all cases except low spatial density where the space size is increased. The average number of agents/grid cell is 4. Each case is run 50 times to get a mean and the shaded area in the figures are the 95% confidence interval.

3.2.1 Base case

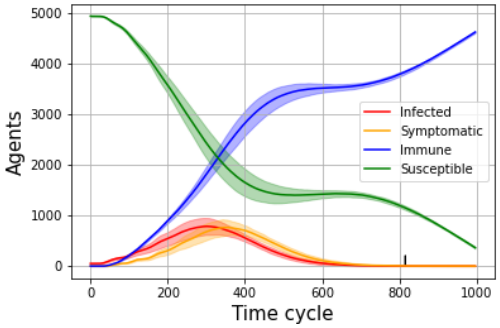
The base case is intended to replicate the typical behavior of the basic SIR model and can be seen in figure 3.5a. The disease spreads to a large portion of the population but tapers off when the proportion of susceptible agents is reduced and the number of immune agents increases. Even though the immunity of the agents decreases after the first wave the residual M cells are a large enough effect to eliminate the disease in the population. The infection probability = 0.02 and the black mark indicates where the number of infected agents is zero for all runs.



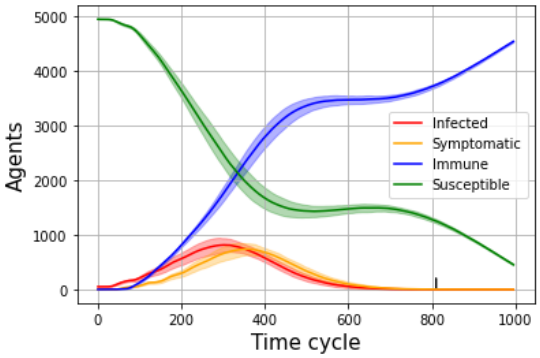
(a) Base case with no vaccination. The black mark is where the number of infected is zero



(b) Base case with 90% vaccine efficacy



(c) Base case with 50% vaccine efficacy



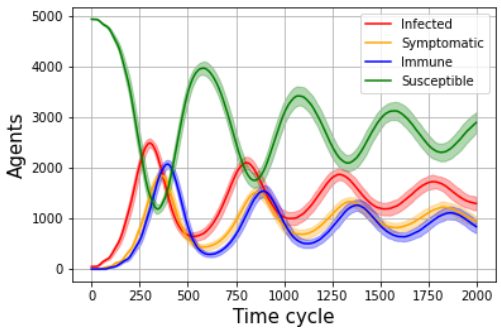
(d) Base case with 10% vaccine efficacy

Figure 3.5: Base case epidemiological dynamics with vaccine efficacies 90%, 50% and, 10%. The highlighted area is the 95% confidence interval of 50 runs with the solid line being the mean and the black mark indicates when the number of infected is zero for all runs

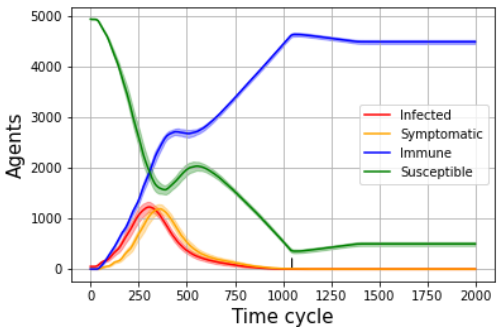
Figures 3.5b-3.5d shows the base case with vaccination. The infection peak is more than halved compared to the base case without vaccination in figure 3.5a. Because the simulation ends before all agents have been vaccinated, the immune category has not reached its peak. Comparing the epidemiological dynamic difference between an efficacy of 90%, 50%, and 10% is minuscule(see Figures 3.5c - 3.5d). The black mark is also further back compared to the base case.

3.2.2 Faster M cell decay

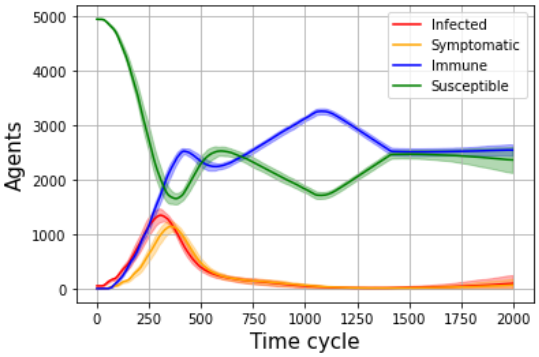
The difference between fast M cell decay and the base case is the parameter g for the immune system is changed from 5.56e-3 to 0.028 (a factor five increase). This leads to the result in figure 3.6. With no vaccination the system enters a fluctuation period but seems to stabilize around 1500 infected agents. With an efficacy of 90% the disease is eradicated but for 50% and 10% it starts to spread in the population again after the immunity of the vaccine has worn off. For efficacy 10% it continued to spread in the population and reached the same steady state as the non-vaccination system. The infection rate is kept at 0.02.



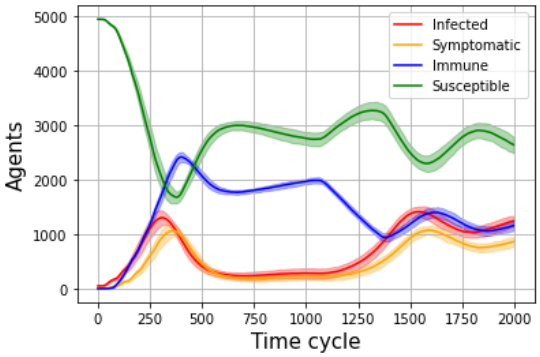
(a) Fast M cell decay with no vaccination



(b) Fast M cell decay with 90% vaccine efficacy



(c) Fast M cell decay with 50% vaccine efficacy

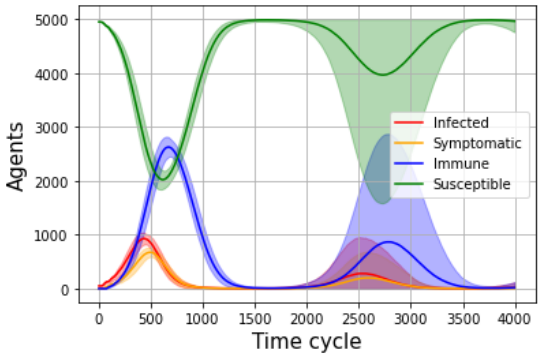


(d) Fast M cell decay with 10% vaccine efficacy

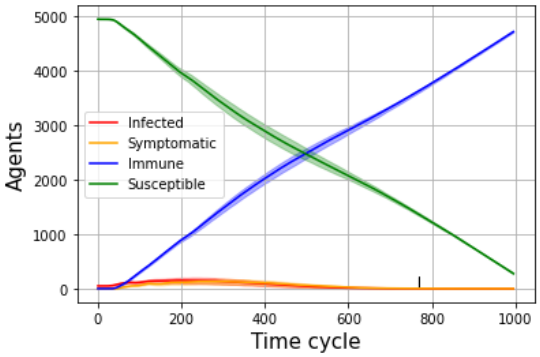
Figure 3.6: Fast M cell decay epidemiological dynamics. The highlighted area is the 95% confidence interval of 50 runs with the solid line being the mean and the black mark indicates when the number of infected is zero for all runs

3.2.3 Low spatial density

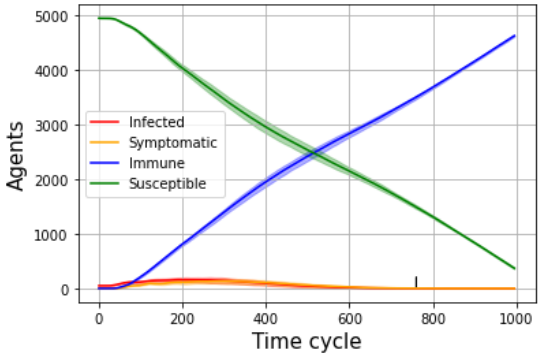
The low spatial density case is a variation of the base case where the number of grid cells is increased from $35^2 = 1225$ to $45^2 = 2025$, which is an increase of 65.3%. Otherwise, the immunological dynamics is the same as the base case. The epidemiology dynamics can be seen in figure 3.7. Figure 3.7a has a large variation in the second wave. The reason for this is because in 56% of the runs the number of infected is zero at C = 2500. If a vaccination is introduced the second wave does not occur and can be seen in figures 3.7b-3.7d where the number of infected is zero around C = 780. The efficacy of the vaccine does not seem to affect the amount of infected during a simulation.



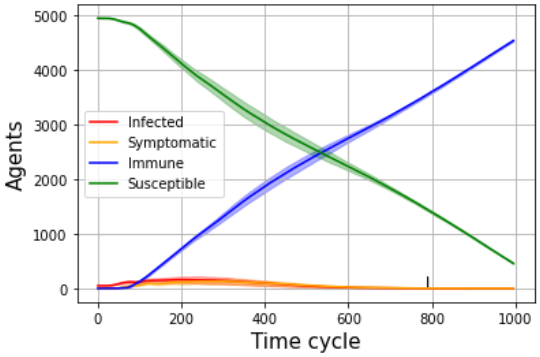
(a) Low spatial density with no vaccination and in 56% of the runs the number of infected is zero after the first wave



(b) Low spatial density with 90% vaccine efficacy



(c) Low spatial density with 50% vaccine efficacy

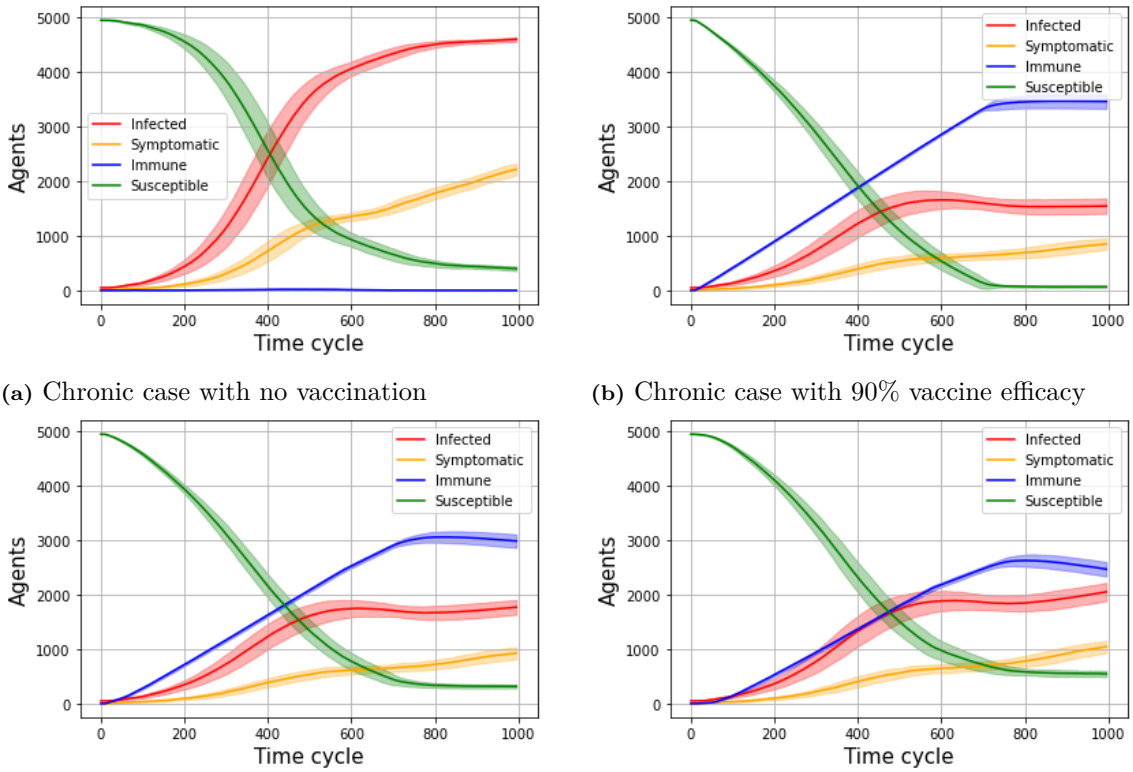


(d) Low spatial density with 10% vaccine efficacy

Figure 3.7: Epidemiology dynamics of low spatial density. The highlighted area is the 95% confidence interval of 50 runs with the solid line being the mean and the black mark indicates when the number of infected is zero for all runs

3.2.4 Chronic

The chronic case is a special case where some of the agents have long term infections. The epidemiology dynamics can be seen in figure 3.8. Without a vaccine no one in the population reaches the threshold m_{immune} and are continuously infected. If the vaccine is introduced the number of immune increases and lowers the number of agents that are infected by at least half. A higher efficacy rate lowers the amount of infected in the population, but to a low degree. The infection rate is 0.1.



(a) Chronic case with no vaccination

(b) Chronic case with 90% vaccine efficacy

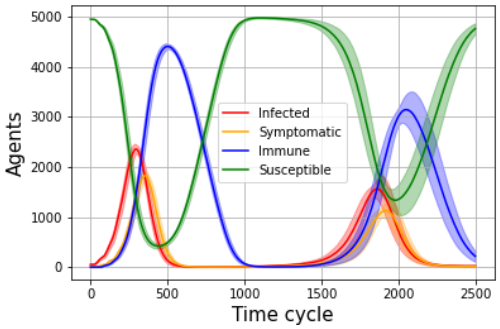
(c) Chronic case with 50% vaccine efficacy

(d) Chronic case with 10% vaccine efficacy

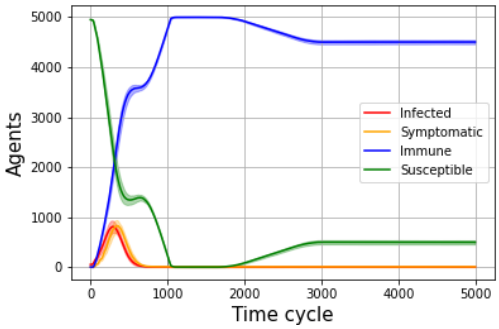
Figure 3.8: Chronic case epidemiology dynamics. The highlighted area is the 95% confidence interval of 50 runs with the solid line being the mean and the black mark indicates when the number of infected is zero for all runs

3.2.5 Outside infection

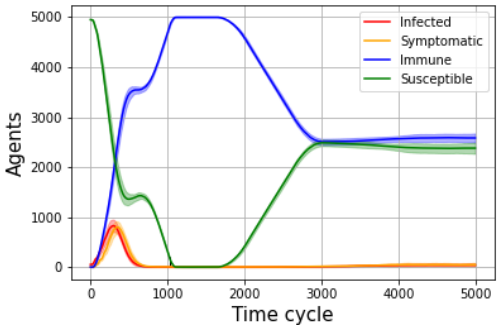
The outside case is the base case where 5 randomly selected agents are in contact with an infected agent, which is not part of the population. The epidemiological dynamics can be seen in figure 3.9. Since some part of the population is always in contact with an infected agent, the disease will not disappear and become endemic when the immunity of the population is high. Without a vaccine the population will have a second wave, after the immunity of the first wave is gone and the number of M cells is low in the population (see Figure 3.9a). For vaccine efficacies 90 % and 50 %, the number of activated vaccine is enough to protect the population from a second wave (see Figures 3.9b-3.9c). When the vaccine efficacy is 10%, a second wave can be seen and the beginning of a third wave is also observed. The infection rate is kept at 0.02.



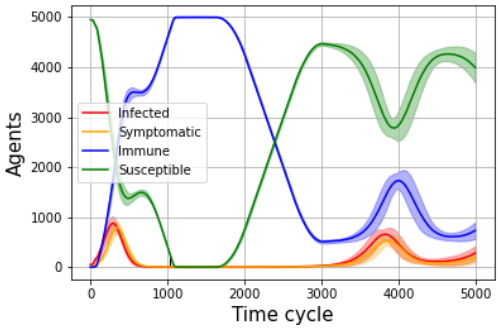
(a) Outside with no vaccination



(b) Outside with 90% efficacy



(c) Outside with 50% efficacy



(d) Outside with 10% efficacy

Figure 3.9: Outside epidemiology dynamics.

4
Discussion

The reason for this section is to discuss the methods used in the paper and the results from the immune system model and the epidemiological model. Another reason is to discuss further improvements to the model.

4.1 Results

The immunological model is a very simplified model in comparison to a real immune system, but it captures the overall essence of a general immune response.

From the base case, a typical SIR curve can be seen (see Figure 3.5a) and is a good indication that the interaction between the population model and immune system model can create an epidemiological model. The different parameters from each model affect the resulting epidemiological dynamics drastically. This could be seen in the fast M cell decay case and low spatial density case. In the fast M cell decay case, a factor of 5 increase to the M cell decay parameter g changes the dynamics from an SIR curve to an oscillating curve. The change of the M cell decay having a large impact on the epidemiological dynamics is not surprising since the immunity of the agents is directly depended on it. The low spatial density case, where the number of grid cells increased by 65.3%, had, in some cases, a second wave. The second wave or even a third wave is also observed in the real world during the pandemic, but it is unlikely only due to lowered contact rate between people, as these waves depend on many more factors. In the case chronic, a high percent of all agents is infected. It is unclear how many of these agents exhibit the traits of a chronic, since some of them have subclinical form and acute form with recovery (see Figure 3.4). However, it follows the expectation that a chronic disease should continually infect a large portion of the population, since the antigen progression of the chronic agents does not depend on time. In the final case of outside case, the outside force did not have a large impact on the number of infected in the first wave of infected. It did however make the disease endemic instead of becoming extinct. This lead to a second wave and the second peak was slightly lowered compared to the first wave. One reason for this could be that the M cell count in the population is higher compared to the first wave.

Regarding the vaccination of the agents, which has a large impact on the epidemiological dynamics, the results are hard to predict. In the base case it more than halves the number of agents that is infected during a run. The same trend can be

seen in fast M cell decay, chronic and outside while for the low spatial density case, the effect is even larger, where only 1/10 is infected. The efficacy has varied effect on the epidemiological dynamics. In the base case and low spatial density case, a higher efficacy has a similar effect as low efficacy. This is probably due to having the same immune system dynamic. The most important fact, in order to reduce the number of infected agents, were exposing the agents to the "fake virus" to prompt an immune system response. One thing to note is that the black mark, which indicated where the disease is eradicated for all runs, is the same for both cases (around 800 C). The reason for this is unclear but one reason could be that it is dependent on the vaccination rate. The efficacy of the vaccine for fast M cell decay determines whether the disease is eradicated in the system. The 90% efficacy the disease is eradicated (see Figure 3.6b) but for 50% and 10% (see Figures 3.6c, 3.6d) the disease has enough infected agents to reinfected agents when the immunity has worn off. The vaccination of the chronic heavily affect the epidemiological dynamics, where the number of immune agents for the non-vaccinated case is zero to more than half of the agents being immune. The number of infected for the different efficacies are of the same scale, but the number of immune agents is steadily decreasing with decreasing efficacy. For the outside case, the efficacy rate had a large impact on the second wave of the disease. For vaccine efficacies of 90% and 50%, a second wave did not appear after 5000 T. This is probably due to the number of susceptible is too low for the disease to become epidemic in the population. A second wave for these cases is a possibly after the number of M cells in the activated vaccines is lowered. In the vaccine efficacy of 10%, a second wave appeared after 3000 T and the reason for this is that the number of susceptible is higher compared to the other cases. A third wave seems to begin but it is hard to say.

4.2 Improvements

This section discusses some improvements to the model that can be implemented.

4.2.1 Population model

The population model consists of the number of agents and how they behave in the space. One aspect not investigated in this paper was the number of agents in the simulation and the effect it would have on the epidemiological model. In the real world, a disease does not get eradicated as it does in the model, but becomes endemic and only a small portion of the population is affected by it. If the number of agents in the model increased, it is possible for the disease to become endemic rather then eradicated.
In this paper the agents move in a type of biased Brownian motion. This movement leads to a mixed population where agents have interactions with many randomly chosen agents. This is not an accurate representation of how humans interact but is sufficient in determining how a disease outbreak could happen. Improvements to the population can come in a two way: spatial, and interactions between agents. The space could be improved with agents having household they return to after a set amount of time and interact within the household. Interacting between agents

could be improved in multiple way. One example could be instead of agents moving in a space grid, nodes between agents can be used to indicate interaction.
The two interaction factors in this paper, infection probability and meeting probability, are set arbitrarily. An improvement to the infection probability could be to have a two-way likelihood, where the infected agent and a susceptible agent each have their own infection probability. Choices such as social distancing and facemask or factors such as resistance against antigen could be implemented. The meeting probability could have more factors, such as social structure or profession, and not only being depended on symptoms levels. For example, an agent could be a health care worker and try to seek out infected agents with high symptoms to help in reducing the symptom levels.

4.2.2 Immunological model

A subtle detail was found in regards to administering the vaccine to agents which could affect the results. The current administration of vaccine is only given to agents with no antigen and no plasma cells. Which is an assumption that is not realistic, since the agents have no way of knowing the precise level of cells in their bodies. A better assumption would be to have a period of cooldown after an agent have been experiencing symptoms of a disease.
One of the improvements to the immune system model is to introduce a damage factor to the agent based on the amount of antigen present. This could potentially lead to fatality of an agent. It could even be pushed as to introduce organs in the agents and have several different diseases that target different organs in the population. If an agent has several damaged organs it dies.
An important factor in some diseases is age of the host. An age demography for the agents could be helpful to investigate different strategies to reduce the effect of a disease in a specific demographic.

5
Conclusion

The immunological model can create general cases of different antigen progressions. From subclinical form, acute from with recovery and chronic form, these are the basis for the epidemiological model. A base case was created, and the goal of the base case was to replicate a typical SIR curve in order to test the coupling of the immunological model and the epidemiological model. The goal was reached and from thereon different parameters in the immunological and population model were changed to investigate the impact on the epidemiological model. For the immunological model, two different cases were made: fast M cells decay and chronic. The epidemiological results of the fast M cell decay case, where the immunity duration of the agents was lowered, were an oscillating curve of infected agents. In the chronic case, the majority of the agents were infected, and no agents managed to reach immunity. A case where a small number of agents met an outside infected agent lead to an endemic disease with second waves appearing. For the population model, one case was made and involved the increase of the spatial room, which was called low spatial density. In the low spatial density case, the first wave peak of infected were halved in comparison to the base case, but in some of the runs a second wave manifested.

In terms of the immunization strategies, once a vaccine was introduced to the different cases, it had a major impact on the number of infected agents and the effects was hard to predict in regards to the efficacy. For the base case, the peak of infected were halved and in the low spatial case the effect was more pronounced, where the infected peak was reduced by 1/10. The efficacies of the vaccine had little impact on both cases and a similar curve where observed. The oscillating wave of infected in the fast M cell decay disappeared and were replaced by a single peak. For the duration of the immune period, the number of infected were low for different efficacies, but the oscillating infected wave return. The only exception was a high efficacy rate, which eradicated the disease. The number of immune agents in the chronic case were also depended on the efficacy rate of the vaccine, but the number of infected were consistent in all efficacies. In the outside case, the vaccine efficacy had a large impact whether or not a second peak was observed.

All things considered, this is a proof of concept that coupling a population based model and an immune system model can enable the creation of a realistic epidemiological model.

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