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Modelling immune interactions

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1 Introduction

Modelling the interactions between immune cells has been a widely researched topic, with the problem being tackled by many different approaches. It is an extremely difficult task to observe these interactions in real time within a living organism, and so many mathematical models, computer simulations, and other techniques have been developed to try and study these systems.

In this paper, an agent-based model was developed to simulate the activity of various types of immune cells in the hope of observing some emergent behaviours that we frequently find in immune responses. This will help us to gain a better understanding of the factors that cause these behaviours and how sensitive these biological systems are to different conditions and parameters.

A key feature that we were interested in was the growth signalling mechanism which we observe in immune systems. The basic premise of the growth signalling mechanism is that CD4 cells produce growth signal to cause CD8 cells to proliferate. However, it is not entirely clear how this mechanism works, and there has been much speculation about whether the nature of this signalling mechanism is that of a localised interaction between nearby T cells or that of a diffusive signal concentration which spreads out over a larger area as time evolves, the latter of which has been observed to occur in *in vitro* experiments.

2 Model description

2.1 Programming

Our agent-based model was developed using a 2D lattice simulation with C++, which was chosen for superior performance over other progamming languages like MATLAB or Python. This performance advantage is useful because it allows us to encode more behaviours that we might expect immune cells or the environment in which they interact to have, thus leading to a more accurate simulation of real-world phenomena.

2.2 Lattice model

Our lattice model was a simple 2-dimensional grid in which immune cells could move in one of 4 directions: Up, Down, Left, or Right. We experimented with 2 different types of behaviour: one was that of a diffusive growth signal which would spread across the entire grid and the other was of a localised growth signalling mechanism.

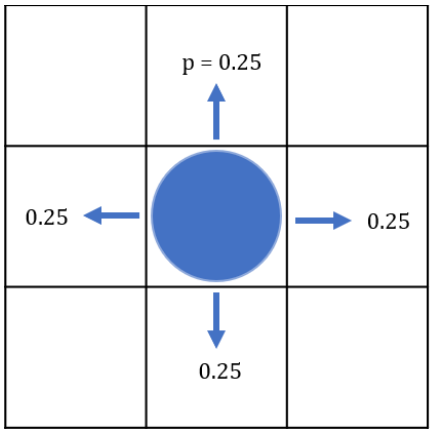

Fig. 1: A cell occupies 1 grid square in 2D. It can move or divide in any of the available directions with equal probability.

With a 2D lattice model, the issue of boundary effects can play a significant role in governing the dynamics and behaviour of cells. To this end we experimented with imposing two different types of boundary condition on the lattice:

1. Dirichlet boundary condition: If a cell tries to move in the direction of one of the edges of the lattice, it is considered to have wandered 'off-grid' and is removed from the simulation.

2. Neumann boundary condition: If a cell tries to move in the direction of one of the edges, it is not allowed to and is considered to have 'collided' with the wall, remaining where it is.

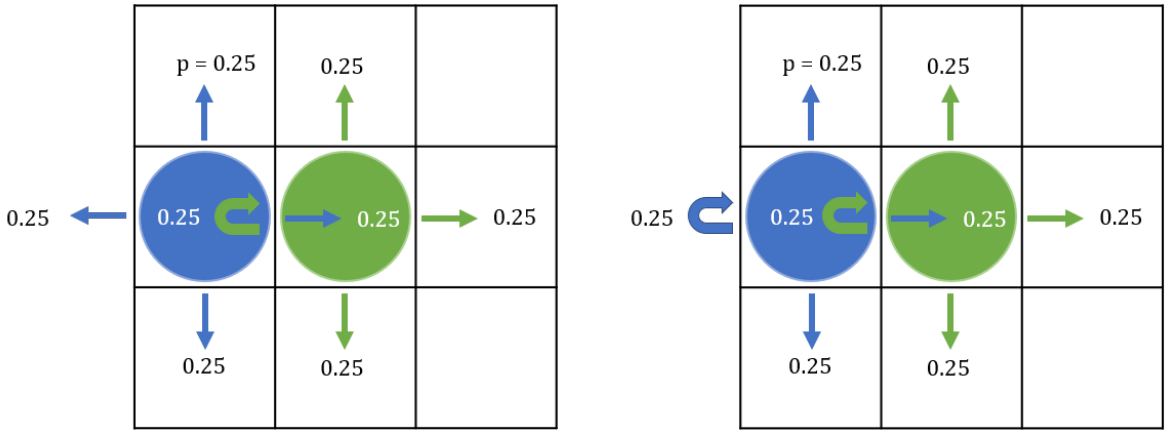

Fig. 2: Probabilities of moving in a given direction with Dirichlet (left) and Neumann (right) boundary conditions. If a cell cannot move into a given cell, it will stay stationary.

2.3 Signal model

Positive growth signal (such as interleukin-2, or IL-2) plays a key role in governing the communication between individual cells which will have significant impact on the resulting population dynamics, which is why it is a crucial part of the model. We chose to model the growth signal in two different ways:

- As a substance that is released by all CD4 cells into space and diffuses across space. In this model, signal concentration is a property of each grid square. Diffusion is modelled by a proportion of the total signal concentration in a grid square being split and moved equally into the available surrounding grid squares (Up, Down, Left, Right). Several diffusion cycles occur in every time step.

- As a substance that is released by CD4 cells bound to an APC, which can only be absorbed by CD8 cells that are also bound to the same APC. Signal that is released is only available to be absorbed in the time step that it is released. In reality, the signal is not meant to pass through the APC, but this method was chosen as a design structure to model how CD4 and CD8 cells communicate only in the vicinity of an APC.

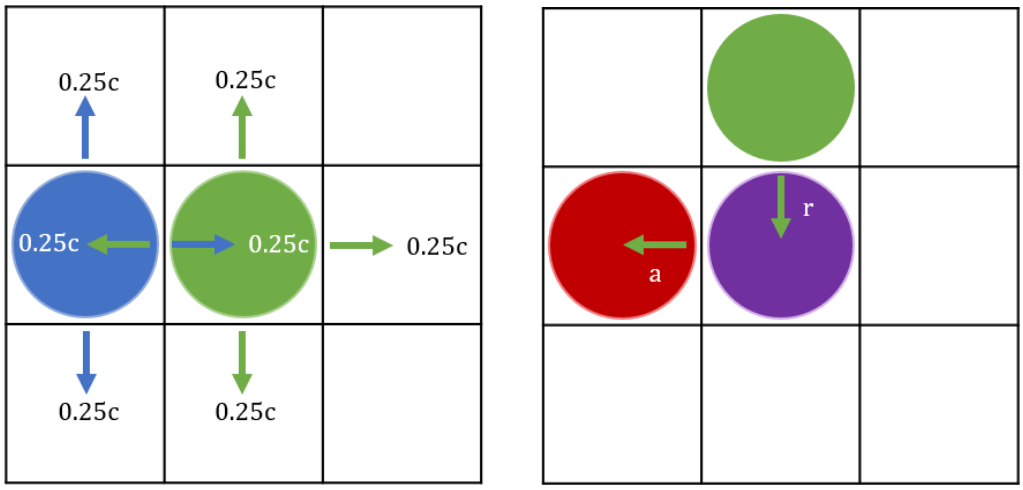

Fig. 3: Diffusive (left) and localised (right) signalling models with adjacent cells. In the diffusive model, each cell releases a total amount of signal c divided equally into adjacent squares. The cell on the left releases 0.25c of signal into it's own square because of the boundary. In the localised model, CD4 cells (green) release signal 'into' the APC at rate r and CD8 cells (red) absorb the signal at a rate a.

2.4 Cell model

Our cell model consisted of 3 different types of immune cells: Antigen presenting cells (APCs), CD4 (Helper) cells, and CD8 (Killer) cells. Though the behaviour of the immune cells is mostly the same, there are some differences depending on the different signalling mechanisms used

- In the diffusive signalling model, CD4 cells are responsible for releasing growth signal that diffuses. CD8 cells absorb a fixed proportion of the signal present in the grid square that the cell occupies.
- In the localised signalling model, APCs act like a hub for the communication between CD4 and CD8 cells. T cells (both CD4 and CD8) have a probability of binding to an APC and once bound, they are able to interact with different types of cells. Binding occurs with a fixed probability when a T cell is adjacent to an APC, and renders the bound cell unable to move until it unbinds from the APC, also with a fixed probability. CD4 cells release signal 'into' the APC and CD8 cells bound to this APC can absorb the signal.

2.4.1 APC model

- Each APC takes up 1 grid square. However, diagonal directions are also considered adjacent positions to an APC, rendering its effective size larger than a T cell's.
- For simplicity, all APCs are assumed to express the antigen that all T cells are specific for.
- APCs are treated as immobile and do not die for the duration of the simulation.

2.4.2 CD4 model

- CD4 cells take up one grid square and Up, Down, Left, and Right are considered adjacent squares.
- CD4 cells divide and die with a fixed probability.

2.4.3 CD8 model

- CD8 cells take up one grid square and adjacent squares are defined in the same way as for CD4 cells.

- Cell division for a CD8 cell occurs with a probability of dividing that is given by the function $f(P) = 1 - e^{-aP}$, where P is the amount of positive growth signal that the CD8 cell has absorbed in the last time step and a is a division parameter which can be varied.
- CD8 cells die with a fixed probability.

For both types of T cells, division can only occur when there is a free grid square adjacent to the dividing cell, and so if a cell is surrounded on all sides, it will not divide. Furthermore, in the event of cell death, a cell is simply removed from the square it is occupying which now becomes free for other cells to move into or be born into.

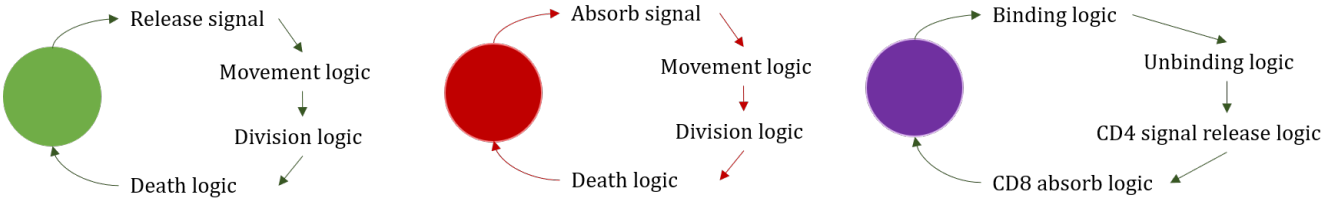

Fig.4 : The phases that each type of cell goes through in a single time step. The cell on the left represents a CD4 cell, the cell in the middle represents a CD8 cell, and the cell on the right represents an APC.

3 Results

Results were collected by varying the different parameters (primarily related to the T cells) and observing a number of key metrics over time. Parameters that were varied can be found in Section 5.1.

3.1 Diffusive and localised signal model

One of the main areas of interest were the different dynamics that arise from a diffusive or localised signalling model. It was interesting to note that the presence of APCs mediating the communication between CD4 and CD8 cells produced much more controlled explosions of the CD8 population which were clustered around the APCs even in extremely favourable conditions, as opposed to the diffusive model in which the CD8 population could grow to fill the entire grid if conditions were right.

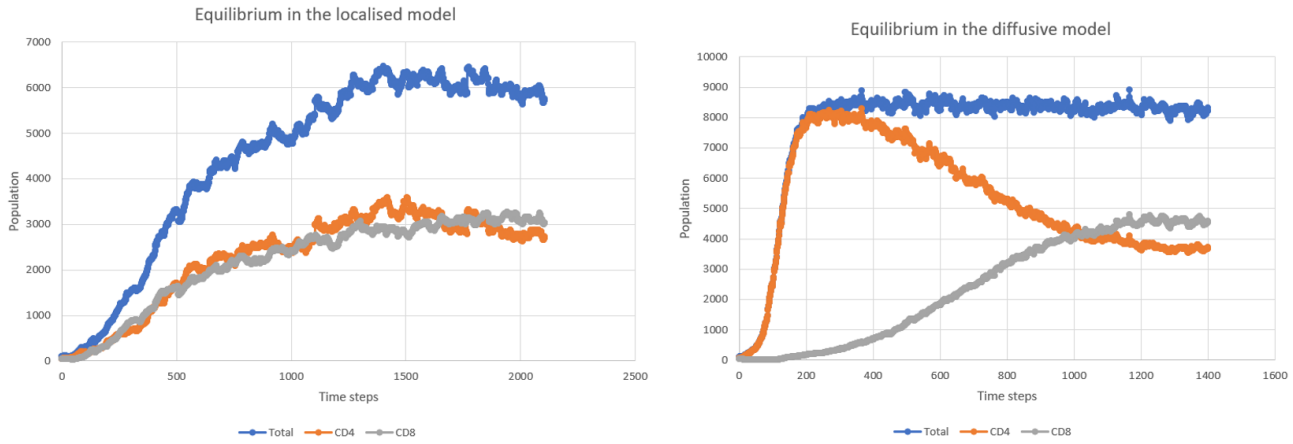

Fig.5 : Population growth in the localised signalling model (left) and the diffusive signalling model (right).

If we look at the equilibrium populations in the 2 different models, we can see that both the CD8 and CD4 populations stabilise at approximately 3000 whereas the diffusive model allowed the population to grow much larger.

Furthermore, it is interesting to note that the populations in the localised signalling model seem to follow a similar trend whereas the dynamics in the diffusive model are much more varied. It was observed that the initial number of APCs had an impact on the final population in the localised model which seems to produce an interesting control mechanism on the proliferation of CD8 cells. On top of this, there seems to be a minimum threshold on the number of APCs present to allow the CD8 population to proliferate. This seems to agree with a journal published by Celli et al. investigating the number of dendritic cells required to initiate a T-cell response.

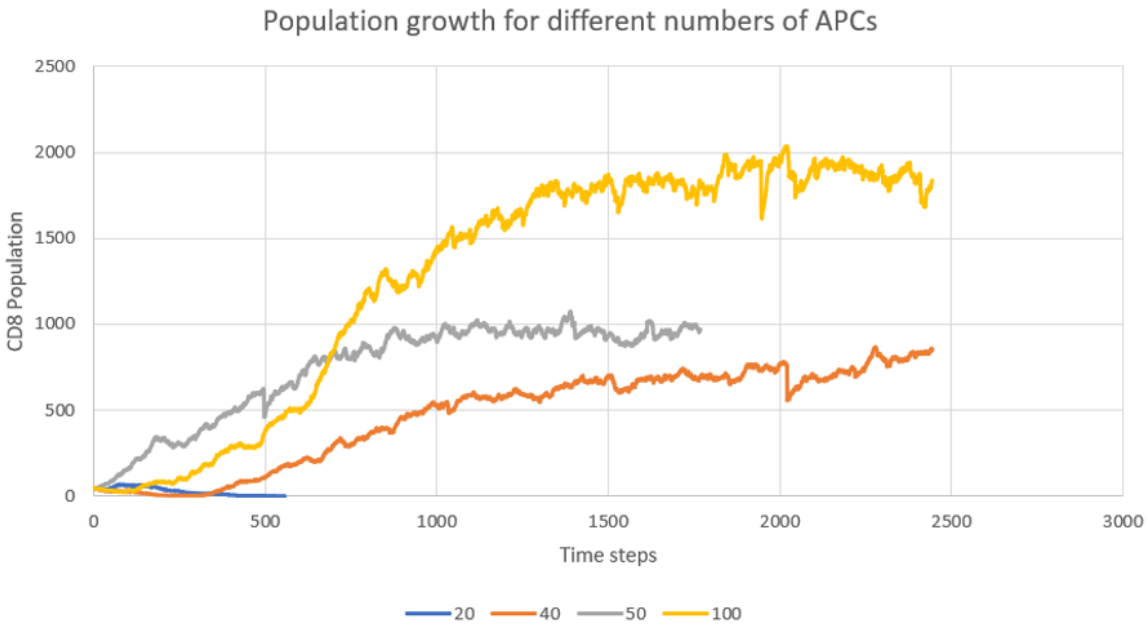

Fig.6 : Tracking the CD8 population over time as we vary the initial number of APCs present in the beginning of the simulation (which remains fixed over time).

3.2 Key parameters

Some parameters were clearly more sensitive to variations than others, and so we investigated the effects of varying each parameter independently to see the responsiveness of the dynamics to these variations.

3.2.1 Signal release/absorb rate

The rate of release and absorption of the growth signal plays a central role in determining how the population behaves, as these two parameters are linked to the mechanism that allows CD8 cells to divide. As the function $f(P)$ defined earlier to calculate the probability of a CD8 cell dividing incorporates the exponential function, we can see that the exponential part of the function decays quickly as more signal is present, increasing the probability of division by a lot. In this way, the signalling mechanism is one of the two key factors that determine the rate at which the CD8 population changes.

3.2.2 Division rate/parameter

The division rate for CD4 cells (as opposed to the division parameter for CD8 cells) plays a key role in the facilitation of growth for the CD8 population. If the CD4 population did not maintain a stable

number or grow over time, then eventually there would be too few of them to produce the signal that is required for the CD8 population to grow. There is a strong link between the behaviour of the CD4 and CD8 cell populations, as the former is responsible for producing the signal that the latter needs to proliferate. A larger number of CD4 cells means that more signal is produced and hence CD8 cells have an increased chance of dividing.

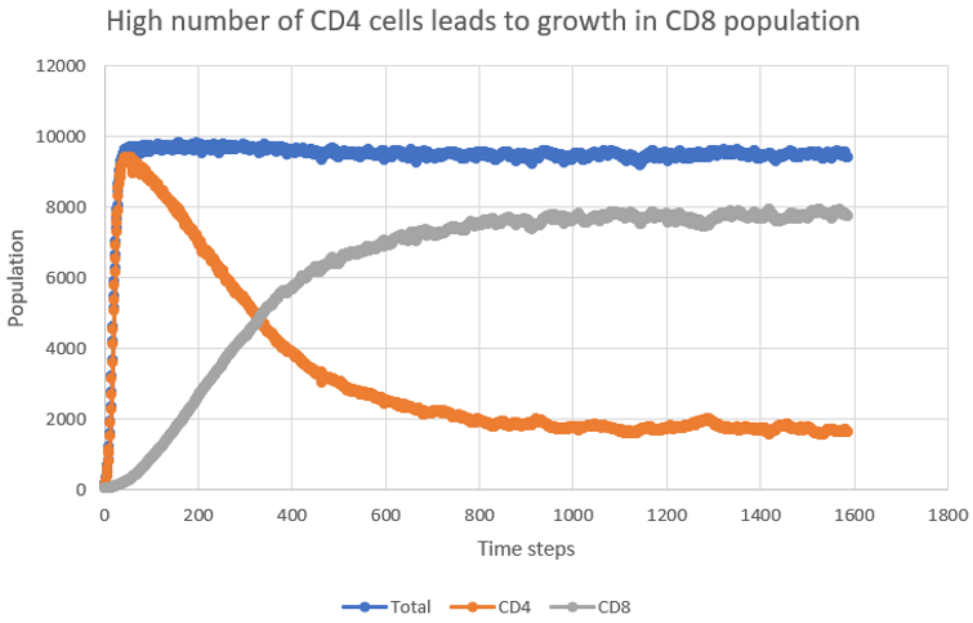

Fig.7 : CD8 population lags until the CD4 population is high enough and then starts to grow faster.

The above graph depicts an interesting phenomenon which was not observed in the localised model. There is an initial explosion in the CD4 population which reaches a peak due to them filling up the grid. This large number of CD4 cells produces at a very high rate which allows CD8 cells to absorb a lot of it. This then causes the CD8 population to grow and slowly crowd out the CD4 cells, causing their numbers to decline.

3.2.3 Movement

The mobility of the cells was a rather surprising factor that was initially not thought to have much effect on the resulting outcome, and when looking at the population it would be hard to infer that changing the mobility made a significant difference in the emergent behaviour. Upon watching the simulation over time however, it can be seen that the evolution of the CD8 population is heavily impacted by their mobility, with slower cells leading to the formation of clusters which slowly grew and faster cells leading to a more rapid and even growth of the population.

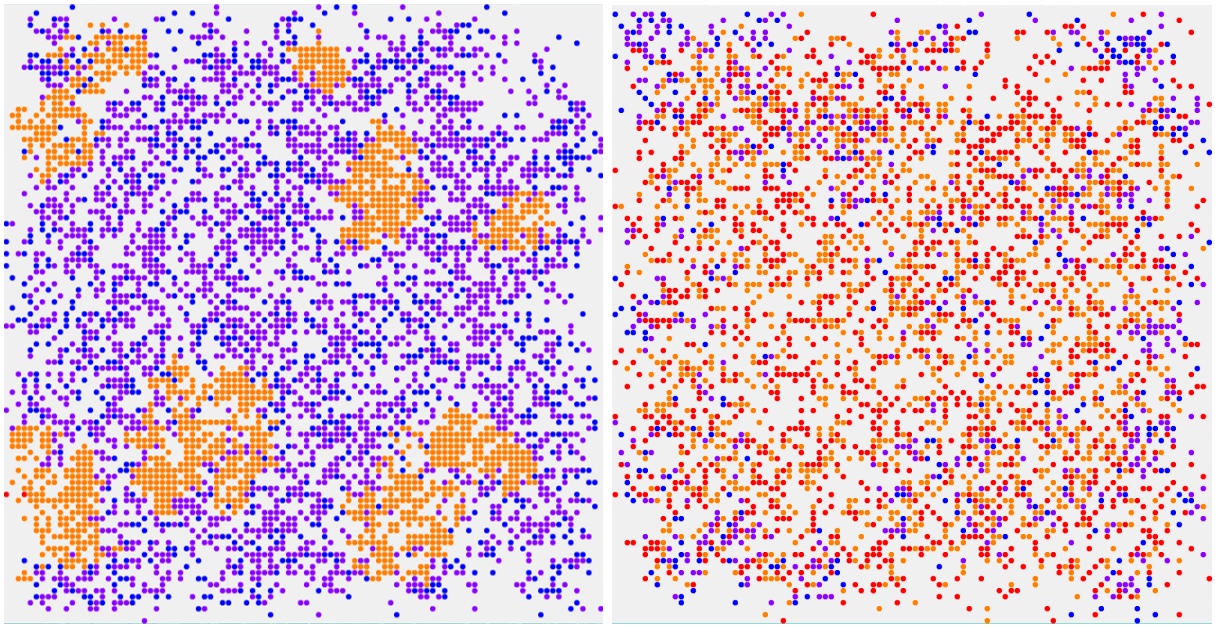

Fig.8 : Equilibrium reached in the diffusive model with low mobility (left) and high mobility (right) of CD8 cells. This is a visualisation of the simulation on a 100x100 2D grid. Mobile CD8 and CD4 cells are represented by orange and blue circles respectively. Immobile CD8 and CD4 cells are represented by red and purple circles respectively.

3.3 Steady states

Due to the simplicity of the model, steady states achieved by the system can be classified into 2 main categories:

1. Death: Occurs when the population of CD8 cells reaches 0, in which case no more division can happen. This frequently occurs when certain parameters restrict CD8 cells from dividing quickly enough for the population to grow faster than the death rate.

2. (Non-zero) Equilibrium: Occurs when the population of CD8 cells reaches a stable non-zero configuration, at which point the rate of division is approximately equal to the rate of death of the population and it reaches a steady state at this value.

As with all classifications, there are minor differences between instances of each case, such as the rate at which the steady state is reached, or the amount of fluctuation within a steady state (in the case of equilibrium).

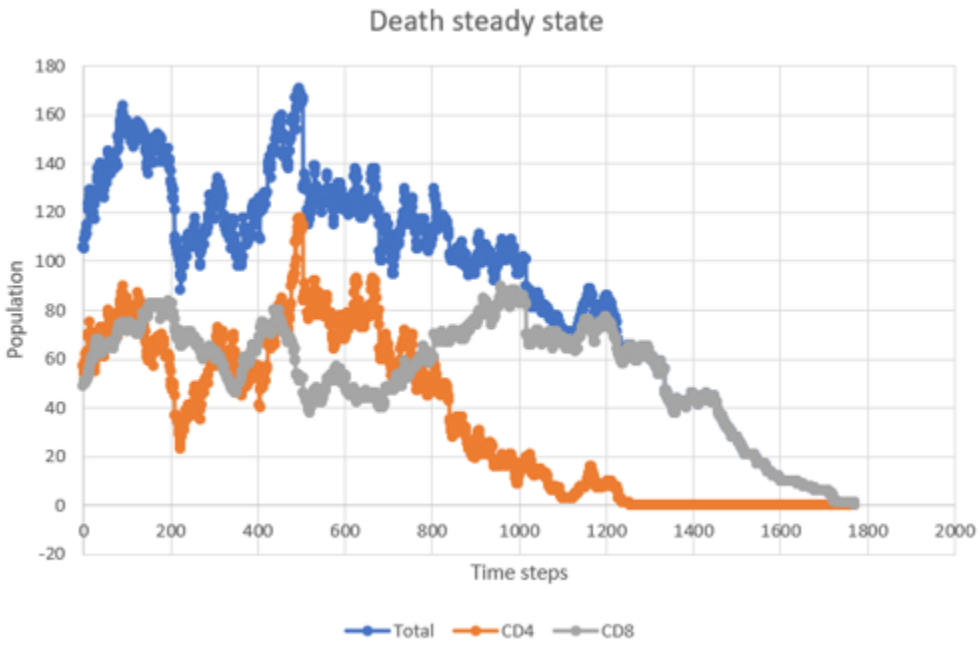

Fig.9 : Population achieving the death steady state. Non-zero equilibrium can be observed in Fig. 4.

3.4 Stability

Stability in this context is linked to the steady state of the non-zero equilibrium, as it is clear that once the population reaches zero, its value can not change. It is not too surprising that once an equilibrium was reached, it would remain relatively stable in terms of behaviour as there were no external forces operating on the simulation after it had been set and run. It was observed that in certain cases with high division/death rates and mobility, the actual population values would fluctuate more around the equilibrium level, but they nonetheless maintained this configuration.

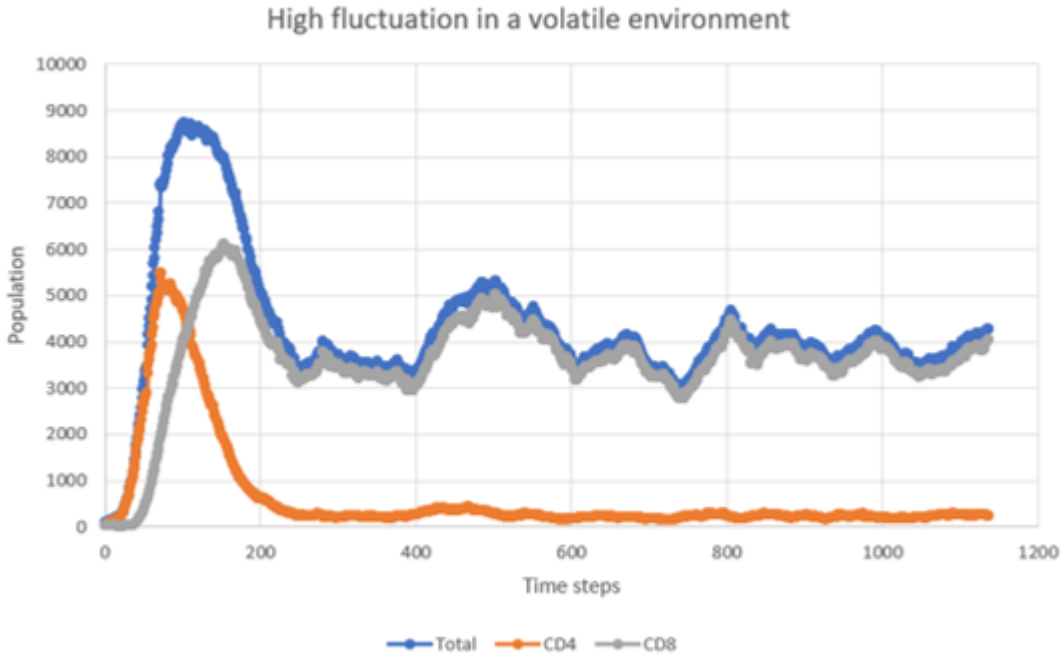

Fig.10 : Volatility of the CD8 population due to high death and birth rates.

3.5 Boundary conditions

The type of boundary condition did not seem to have a great effect in the localised signalling version of the model, which makes sense as the population of CD8 cells was very much clustered around APC's and so the location and density of these APC's played a much more important role in governing the dynamics of the system than the boundary would.

However, when it came to the diffusive model, there were some minor differences. Firstly, the use of Neumann boundary conditions meant that once a cluster of dividing CD4 cells reached the boundary, they would remain boxed in by the edge and proliferate around the boundary, growing in population quickly. This was not the case with Dirichlet boundary conditions as cells would be deleted if they moved outside the boundary, preventing the formation of these clusters around the edges. This leads to slower growth for the CD8 population as the rapidly appearing boundary clusters are not there to drive their expansion.

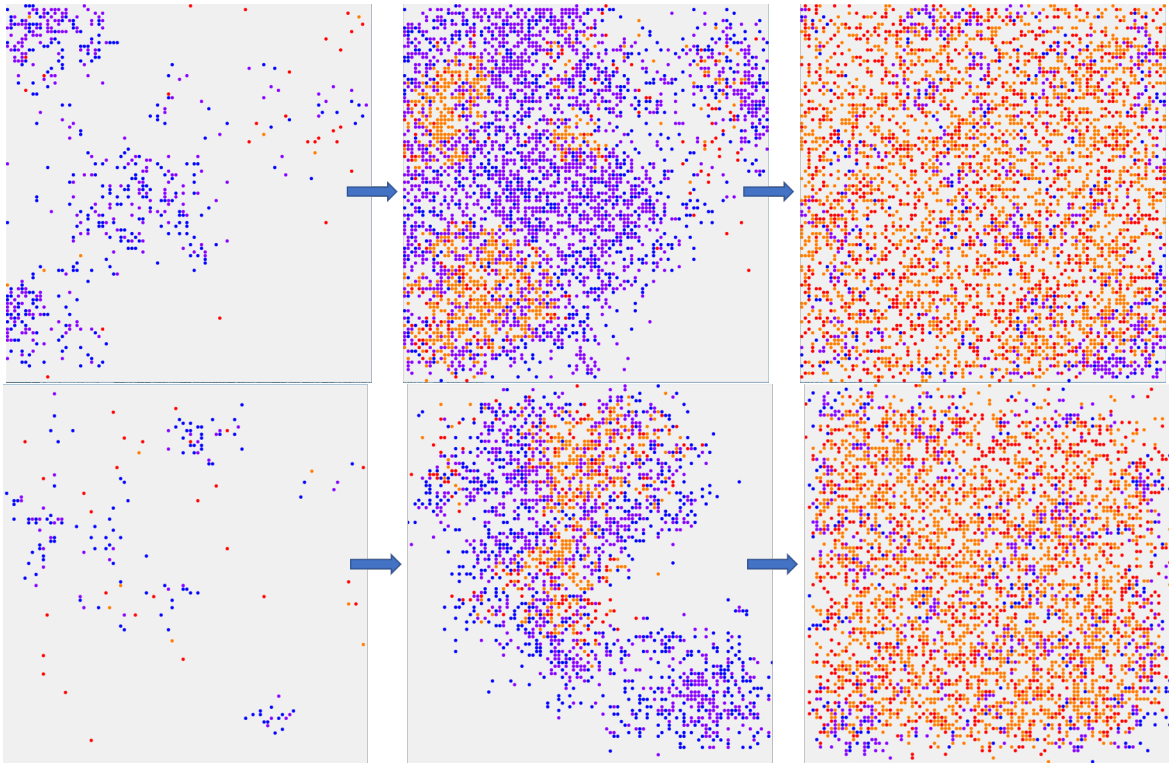

Fig.11 : Evolution of the population over time with different boundary conditions. Using Neumann B.C's (top) allows the population to grow against the boundary. With Dirichlet B.C's (bottom), the population grows in clusters formed closer to the center.

4 Discussion

4.1 Lattice model

The lattice model had a significant impact on the simulations as it provided the framework for the individual cell mechanics out of which the emergent behaviours arose. The choice of a 2D lattice for simplicity did impose some restrictions on the behaviour of the cells, most notably the movement and division. This was due simply to the limiting of available directions in which a cell could move or divide into and so crowding was a much more common phenomenon which would likely have not been as common in a 3D model. Crowding introduced rapid population growth, reduced the mobility of the T cells, and introduced a form of 'competition' for space between the CD4 and CD8 populations, preventing their populations from both growing in parallel. Switching to Dirichlet boundary conditions in which the boundary did not box the cells in seemed to have a positive impact on reducing this effect, but it would be interesting to see the effects of simulating these interactions within a 3D lattice.

4.2 Cell model

The cell models used in the simulation made some basic assumptions on the rules that govern the behaviour of the cells over time.

An example of such an assumption was that cell parameters stayed constant over time. This seems to be a fair assumption to make unless it is clear why a parameter would change significantly over the lifespan of a cell. Parameters such as the death rate however, could be argued to start low and increase over time. In the interests of time, parameters which varied with the age of the cells were not explored but this could be an interesting investigation to delve into.

The simplicity of the cell model offered both benefits and drawbacks. An obvious drawback of keeping the model simple was that the nature of these interactions is in actual fact more complex and is still yet to be fully understood. Having an overly simple model could prevent us from observing some interesting phenomena that could only be seen with a more complex model and may also lead us to overestimate the importance of certain parameters in the resulting dynamics of the system.

On the other hand, the main advantage was that by keeping the model simple, we are able to see the direct effects of varying a parameter quite easily, which may not have been the case if there were several mechanisms affecting several others. By isolating a specific signalling mechanism and working with a few cells which are designed to co-operate, we were able to understand more clearly the role each parameter could play in affecting the dynamics and how significant its contribution might be.

4.3 Further investigation

It would be interesting to investigate further into many different aspects of this project. As mentioned earlier, investigating the simulation in a 3D lattice would also be interesting to see whether there is much effect on the resulting behaviour. The most interesting of continuation of this project however would be to start experimenting more with different cell models, increasing the complexity of their behaviour and seeing where that might lead. An example of this could be to add a slight autoimmune response to some CD8 cells which we observe in many animals. As more layers of complexity are added, we may be better able to understand the fundamental mechanisms that allow these sophisticated organisms to initiate an immune response to protect their host.

5 Appendix

5.1 Parameters

- Diffusion cycles per time step (diffusive model)
- Diffusion constant (diffusive model)
- Signal decay constant (diffusive model)
- Frame ratio (number of grid squares for the given window)
- Signal release rate (CD4)
- Signal absorb rate (CD8)
- Divide parameter
- Death rate
- Probability of moving
- Probability of binding
- Probability of unbinding