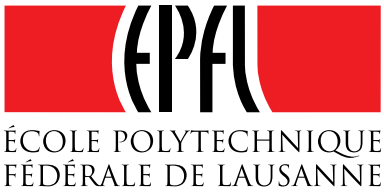

Semester Project

Analysis of Chao's Immune System Simulation

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Summer 2005

LCA - I&C

Abstract

Computational methods have been developped to simulate the complex interactions between components of the immune system. Chao introduced a method based on a stage structured approach to studying the Cytotoxic T cells response to an infection. In this work, we extend the analyzis of Chao's simulater by Eric Winnington. We validate the time step choice used in the simulation and analyze the impact of different factors on the occurence of a secondary reaction. We find that the initialization of the simulation, and in particular the generation of the T Cell Receptor Chains and epitopes influences the frequency of this secondary reaction. Furthermore, we note that the secondary reaction arises in a time window when the number of naïve cells population is low, the effector cell population is decreasing after the primary response and the memory T cells are not yet able to take part in the response. We find that the secondary reaction does not question the correctness of the simulation. The question of the adequacy of the biological model however remains open and is not discussed in this project.

Contents

1 Introduction

The immune system is amongst the most complex systems of the mamalian organisms. It's constant battle against an extremely diverse range of potentially lethal agressors is crucial for the survival of every human. The immune system plays a key role in multiple diseases, including AIDS, cancer, and all infectious diseases. Better undesting the complex interaction between the different parts of the immune system Gaining a better understanding of the interactions involved and their role in disfunctions will undoubtfully provide key answers in the study of these diseases. Even though technological breakthroughs have lead to a vast amount of new knowledge in the area, several important aspects of immunology are still not well understood. Numerical simulations offer a possibility of evaluating models and parameters in a way which is complementary to experimental analyses. Such simulation however must be considered with great care: the adequacy of the underlying model needs to be assessed from a biological point of view; the mathematical model and its simulation need to be statistically sound. We will exclusively consider this second aspect, defined as correctness of the simulation.

Dennis Lai Chao proposes a model of a part of the human immune system, the interaction between antigens and Cytotoxic T Cells (CTL) [1].He introduces an method called *stochastic stage structured approach* to this kind of problems, which were previously studied by means of differential equations or agent-based systems. In a stochastic stage structured approach, the life of a part of a system is divided into stages. All individuals in a same stage are considered identical. At each steps, individuals transit between stages following a set of probability distributions.

In his Master Thesis [2], Eric Winnington performed a thorough evaluation of the statistical model, explicited the Markow chain of the underlying process, evaluated the independence of the simulation from the random number generator and validated the time step choice made by Chao on a limited model without T cell interaction. During his evaluation of the simulator, he discovered the existence of a secondary reaction which had not been described by Chao.

This project considers the two major issues remaining open after Eric Winnington's thesis: the validation of the timestep choice on the complete model and the causal factors of the secondary reaction.

The first part part of the project validates Chao's choice of a 10 minutes timestep for different initial virus loads. The second part studies the effect of several parameters of the simulation on the frequency and amplitude of the secondary reaction. We show that the frequency of the secondary reaction is dependent on the initialization of the T Cell Receptor Chains (TCR) and epitopes. We analyse the effect of the cell waiting phases on the secondary reaction and find that the acti-

vation delay of naïve cells has no effect on the secondary reaction. Reducing the duration of the conversion from effectors to memory T cells however significantly reduces both the frequency and amplitude of the secondary reaction. Increasing this duration modifies the outcome of the secondary reaction, which stabilizes at a high infection level before being cleared by the memory cell-induced secondary response. We analyze the decay of the naïve T cell population after the primary response and its implication on the existence of a secondary reaction. We consider an alternative model without decay and compare it to the original model in the case of reinfection after the primary response. We conclude that the existence of a secondary reaction does not question the correctness of the simulation, but is a consequence of remaining virus particles after the primary response, particles which can grow during the time window when the naïve population is low, the effector population rapidly decreasing and the memory T cells not yet available. Finally, we discuss the differences between the naïve T cell induced response and the memory T cell induced response.

2 Time step verification

In order to numerically validate a model relying on a discrete time approach, we need to make sure that the outcome of the simulation is independent from the timestep choice. In his work, Chao proposes a timestep value of 10 minutes but does not provide a detailed comparison between simulation outputs for various timesteps which would justify this choice. In his thesis, Eric Winnington verifies the scaling of all time-dependent equations and validates this timestep choice on a simplified model without T-cell interaction. In this section, we propose a method for validating this timestep choice on the complete model and show that the choice is indeed correct.

2.1 Methods

We run a series of 150 independent simulations for each timestep value we want to evaluate. The range of valid timesteps for the simulator is limited to the interval between 1 and 60 minutes. The set of timestep values we evaluate is 60, 30, 20, 15, 12, 10, 6, 5, 4, 4, 2, and 1 minute. We use the *Hamming distance rule*, no T cell exhaustion, a single initial exposure to the virus and a simulation duration of 50 days.

We evaluate the difference between simulation with different timesteps by comparing the mean and 95% confidence interval for every level (virus, infected cells, uninfected cells, T cells) over the simulation duration. The individual runs are separated into two categories depending on the occurence or not of the secondary

reaction. This allows obtaining separate, and thus meaningfull, means and confidence intervals for both situations. We can conclude that a timestep choice is valid if there are no differences between a simulations with this timestep and a simulations with any smaller timestep.

In order to assess the validity of the timestep for both low and high virus loads, we perform this analysis separately for initial loads of 100, 1'000 and 100'000 particles. We do not vary the total cell population since several hard-coded parameters have been tuned for a specific initial population size of 100'000 cells.

2.2 Results

We find no differences between simulations with a timestep of 10 and smaller timesteps for an initial virus load of 100, 1'000 and 100'000 particles. Figure 1 illustrates the similarity of the simulation output for the choosen timestep of 10 minutes and a timestep of 1 minute for an initial virus load of 1000 particles. These results allow us to validate the timestep choice of 10 minutes.

There are differences between the simulations with a timestep of 60 minutes and the simulations with a timestep of 1 minute, which indicate that the simulation is not timestep independent and that a timestep of 60 minutes should not be used. Figure 2 shows that the 95% confidence intervals of the T Cell population when using timesteps of respectively 60 and 1 minute do not overlap.

Given that decreasing the timestep from 10 to 1 minute leads to an increase of the simulation time by a factor 40, we can conclude that a timestep choice of 10 minutes provides acceptable runing times without compromising the precision of the simulation.

3 Analysis of the Secondary Reaction

Eric Winnington's analysis shows that, even when there is no exhausion, the primary response does not clear the virus in every case. This leads to a secondary reaction and a secondary response which involves memory T cells and clears the infection. We evaluate different factors that contribute to the occurence of this secondary reaction and influence the frequency with which it occurs in independent simulation runs.

For this analysis, unless indicated otherwise, we use the *Hamming distance rule*, an inital number of 1000 viruses, no T cell exhaustion, a single initial exposure to the virus and a simulation duration of 50 days. We plot individual means and 95% confidence intervals for the case where there is a secondary reaction and for the case where there isn't. We assume that the runs are independent and

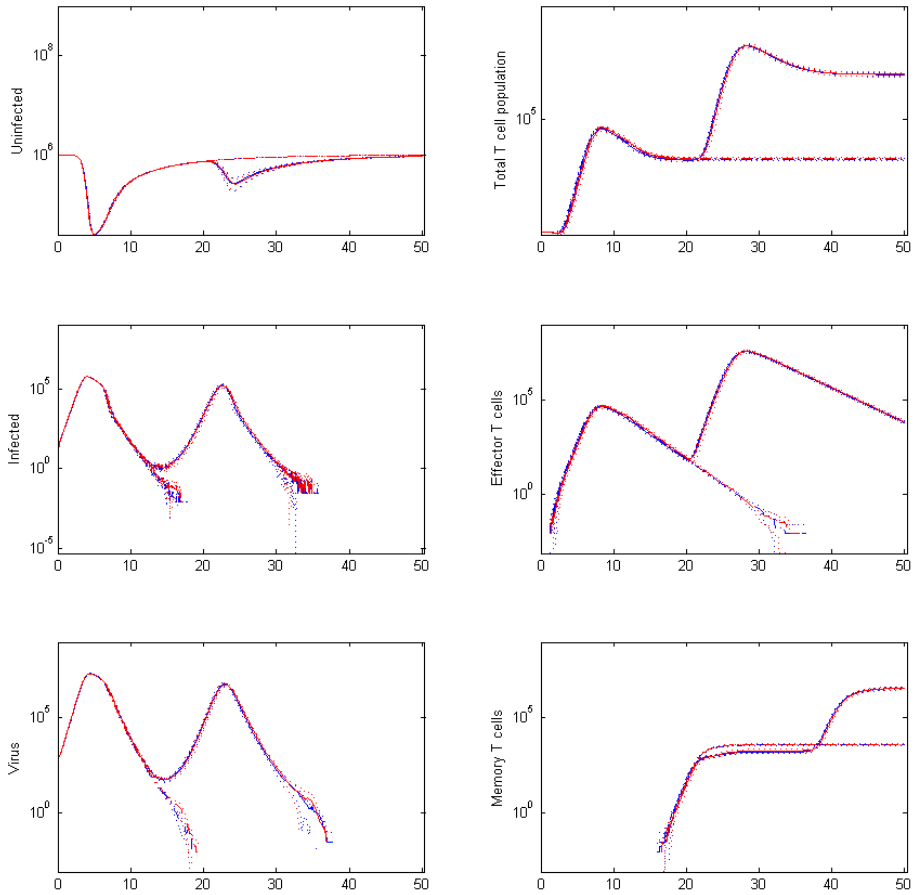

Figure 1: Simulation with timestep values of 10 (blue) and 1 minute (red). The solid lines represent the mean of the cases where there is a low (red) and high (blue) secondary reaction frequency for 150 independent simulation runs. The dotted lines represent the 95% confidence interval.

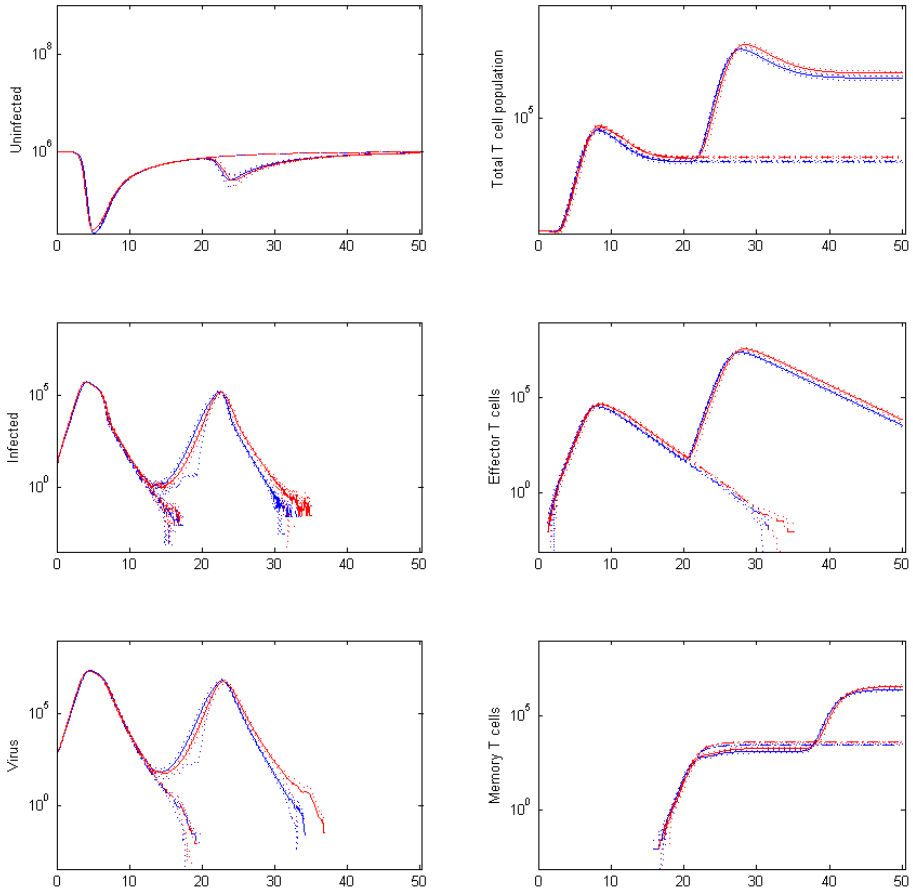

Figure 2: Simulation with timestep values of 60 (blue) and 1 minute (red). The solid lines represent the mean of the cases where there is a low (red) and high (blue) secondary reaction frequency for 150 independent simulation runs. The dotted lines represent the 95% confidence interval.

normally distributed a compute the confidence interval as the 0.975 quantile of the Student distribution with N-1 degrees of freedom.

3.1 Dependance on the Initialization

In order to detect an antingen and become part of the immune response, a T cell needs to have a TCR which binds well enough (has a high enough *binding affinity*) to the MHC-Epitope complex of the antigen. Chao's simulator represents both the T cell Receptor Chains (TCR) and the MHC-Epitope complex as strings and measures the distance between them in order to obtain an affinity measure. During the initialization phase, the simulator first creates random MHC, self, antigen and epitope strings. It then uses a process called *lazy evaluation* in order to generate only TCRs which have a high enough affinity to the antigen to eventually detect it. These TCRs then have to go through a process which emulates the role of the tymus: make sure that the affinity of a given TCR to self is neither too high (in order to avoid auto-immune reactions) nor too low (in order to eliminate TCRs which would react to almost no antigen at all). Only a subset of the original TCRs survives this selection. Each of them then generates an independent population of naïve T cells. Eric Winnington provides a detailed description of this process in appendix A of [2].

We first consider the differences between TCR clone populations. Given that this innitialization is a random process, which generates key parameters for the interactions between T cells and infected cells, we are then interested in evaluating its influence on the frequency of secondary reactions.

3.1.1 Differences between TCR Clone Populations

On figure 3, we compare the behavior of different TCR clone sub-populations. Even though the difference in distance is only 2, the clone population with lower distance (and therefore higher affinity) grows faster during the primary reaction. While the size of both populations during the primary, naïve cell induced response, are similar, this is far from being the case for the secondary, memory T cell induced, response. There is therefore a shift in the distribution of effector cells towards higher affinity clones during the secondary reaction.

3.1.2 Hypothesis

The differences in affinity between antigen and TCRs leads to a difference in the frequency of secondary reaction.

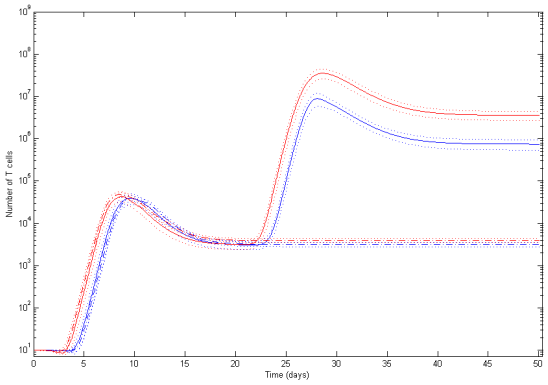

Figure 3: Difference in behavior of the total TCR clone sub-population. In red, a sub-population of TCR clones with a distance to the epitope of 31, in blue a subpopulation with distance 33. The solid lines represent the mean of the sub-population for 150 independent simulation runs with the same initialization. The dotted lines represent the 95% confidence interval.

3.1.3 Experiment

Chao's simulator uses a random number generator both for the initialization phase and for the simulation itself. We choose an arbitrary set of 10 constant seeds for the initialization phase. Using each of these seeds will result in a constant initialization. After the initialization, we set a pseudo-random seed in order to perform 150 independent runs per initialization. We compare the outputs of the simulations, the frequency of the secondary reaction and the observed distances between TCR clones and the epitope. We use a standard percentage comparison hypothesis test to evaluate the significance of differences in the secondary reaction frequency.

3.1.4 Result

There are significant changes in both the amplitude and the frequency of the secondary reaction depending on the initialization. Amongst the 10 arbitrary seeds used, the lowest percentage of secondary reactions is 46% and the lowest is 2%. We find that this difference is significant at level $\alpha = 5\%$. Figure 4 shows the difference between simulations with these two initializations. We re-use these two cases in further experiments in order to dissociate the influence of the initialization from other effects. For clarity, we call the initialization with the highest secondary reaction frequency I_{high} and the one with the lowest I_{low}.

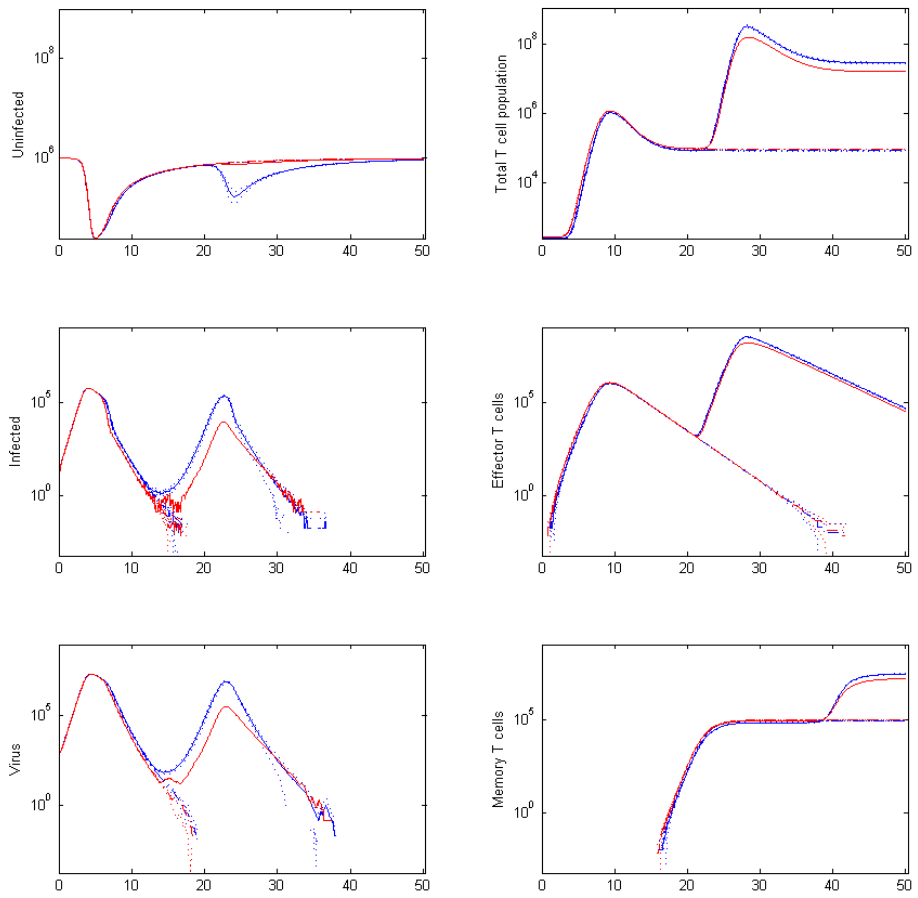

Figure 4: Simulation with different initialization. The solid lines represent the mean of the cases where there is a low (red) and high (blue) secondary reaction frequency for 150 independent simulation runs. The dotted lines represent the 95% confidence interval. Given the small number of samples, no confidence intervals are plotted for the secondary reaction for the initialization with low secondary reaction frequency.

Index	Secondary	TCR Clones	Min. dist.	Max. dist.
0	33/150	29	30	33
1	28/150	30	31	33
2	21/150	27	31	33
3	26/150	26	31	33
4	7/150	35	31	33
5	13/150	30	31	33
6	16/150	29	30	33
7	7/150	28	29	33
8	33/150	29	31	33
9	52/150	25	31	33

Table 1: Comparison between the different initializations

In table 1, we compare the number of secondary reactions over 150 simulations for the ten different intializations, the number of distinct TCR clones and the minimal and maximal distance of a TCR clone to the epitope. There is a weak (p-value of 0.068 for the Pearson correlation coefficient) negative correlation between the number of clones and the number of secondary reaction. This could be explained by the fact that each clone has an identical initial population of 10 naïve T cells, and therefore the higher the number of clones, the higher the number of naïve cells in the system at the beginning of the primary reaction.

3.2 Influence of the Naïve to Effector Delay

In the biological model used by Chao, there is a delay d_A[1] between the moment a naïve T Cell is stimulated by an infected cell and the moment this T cell becomes an effector cell and begins its response. While in this waiting phase, the cells do not interact with infected cells and do not divide. Chao uses biological evidence that the first T cell divisions take place 24 hours after antigenic simulation and that T cells take 5 hours to devide to obtain the value of $d_A = 19$ hours used in the simulation. It is important to note that this delay of 19 hours only applies to the conversion from naïve cells to effector cells; the delay for memory cells to convert to effector cells, which is only 1 hour. We are interested in the effect of this delay on the frequency of secondary reactions.

3.2.1 Hypothesis

There is a causal link between the delay d_A and the frequency of a secondary reaction; reducing this delay to the same delay used by memory cells to become effectors reduces the frequency of secondary reactions.

3.2.2 Experiment

We modify Chao's simulator to decreas the value of d_A from 19 to 1 hour in steps of 1 hour. For each value of d_A we do 150 independent runs of the simulation for a period of 50 simulated days following the initial infection. We use a standard percentage comparison hypothesis test to evaluate the significance of differences in the secondary reaction frequency.

3.2.3 Results

Decreasing the value of the delay d_A from 19 to 1 hour has no significant influence on the frequency of secondary reactions. Figure 5 compares the progress of the simulation for $d_A = 1$ hour and $d_A = 19$ hours. The most noticeable effect on the progress of the simulations is a translation of the whole immune response by the same amount the delay is changed, which is a direct consequence of changing the delay. Furthermore, the amplitude of the primary reaction is more important with a lower value of d_A, which can be observed by the difference in the peaks of effector T cells for the primary reaction, as well as in the number of T cells that are converted to memory cells as a consequence of the primary reaction. A total of 14% of 150 runs show a secondary reaction for $d_A = 1$ hour compared to 21%

[1]For consistency reasons, I reuse the notations introduced by Eric Winnington in the definition of the Markow process.

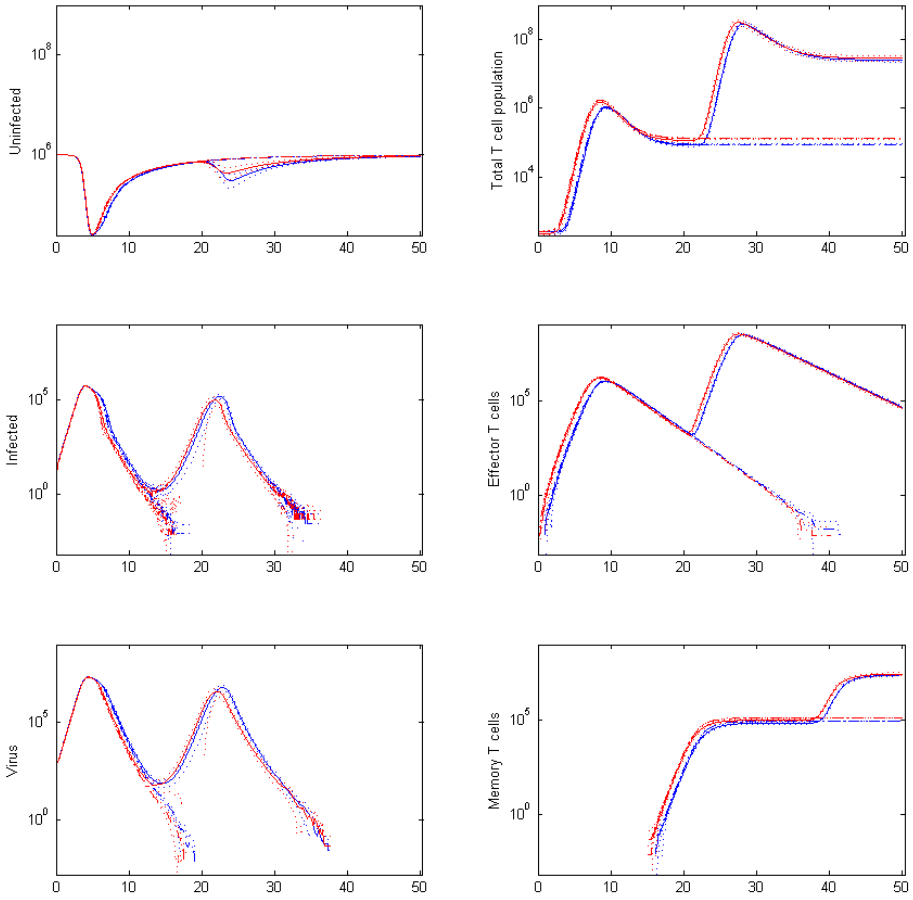

Figure 5: Comparison of the progression of the simulation for $d_A = 1$ hour (red) and $d_A = 19$ hours (blue). The solid lines represent the mean of 150 independent simulation runs and the dotted lines the 95% confidence interval.

for $d_A = 19$ hours. Using a percentage comparison hypothesis test, we find that this decrease is only almost significant at level $\alpha = 5\%$.

3.3 Influence of the Effector to Memory Delay

During an immune response, some effector T cells (approximately 5% of the peak response) become memory T cells which will outlive the the current infection. In the case of a future antigenic stimulation, memory T cells will be able to convert

to effector more rapidly (1 hour) and will generate effectors with a lower death rate, thus leading to faster and higher population growth. In Chao's model, there is a delay d_W of 14 days in the conversion process from effector to memory cell during which the cells are not interacting with infected cells. We observe that memory T cells are involved in the immune response to a secondary reaction. Given the conversion delay of 14 days, the memory T-cell created by the primary response only appear after approximately 17 days and the population reaches its maximum only after 24days. The secondary reaction however already leads to increases in the number of viruses and infected cells after 15 days, which means that there are no memory cells available at the beginning of the secondary reaction. We are therefore interested in the impact of reducing this delay on the occurence, frequency and nature of the secondary reactions.

3.3.1 Hypothesis

Lowering the conversion delay for memory cells will result in having memory T cells available at the moment when the secondary reaction starts in the normal model. These memory cells could therefore interact with infected cells at that moment and either lower the amplitude of a secondary reaction or even completely clear the infection in all cases.

3.3.2 Experiment

We modify Chao's simulator by decreasing the delay in T Cell conversion from effector to memory from 14 days to 1 day, by steps of 1 day. For each delay, we run 150 independent simulations for a period of 50 simulated days following the initial infection. In order to dissociate the effect of changing this delay from the effect of different initializations, we run two separate experiment which each use the same initialization. In a first experiment, we use initialization I_{high} which we found to lead to a high number of secondary reactions whereas in a second experiment we use initialization I_{low} which lead to a small number of secondary reactions.

3.3.3 Results

When reducing the delay to days, the memory T cells appear while the number of infected cells due to the primary infection is still high. The memory T cells therefore join the primary reaction, which leads to a total clearance of the infection in both experiments. Figure 6 compares this behavior with the normal model ($d_A = 14$ days) for an initialization which leads to a secondary reaction in 45% of the runs with the normal model. Beside the total clearance for every

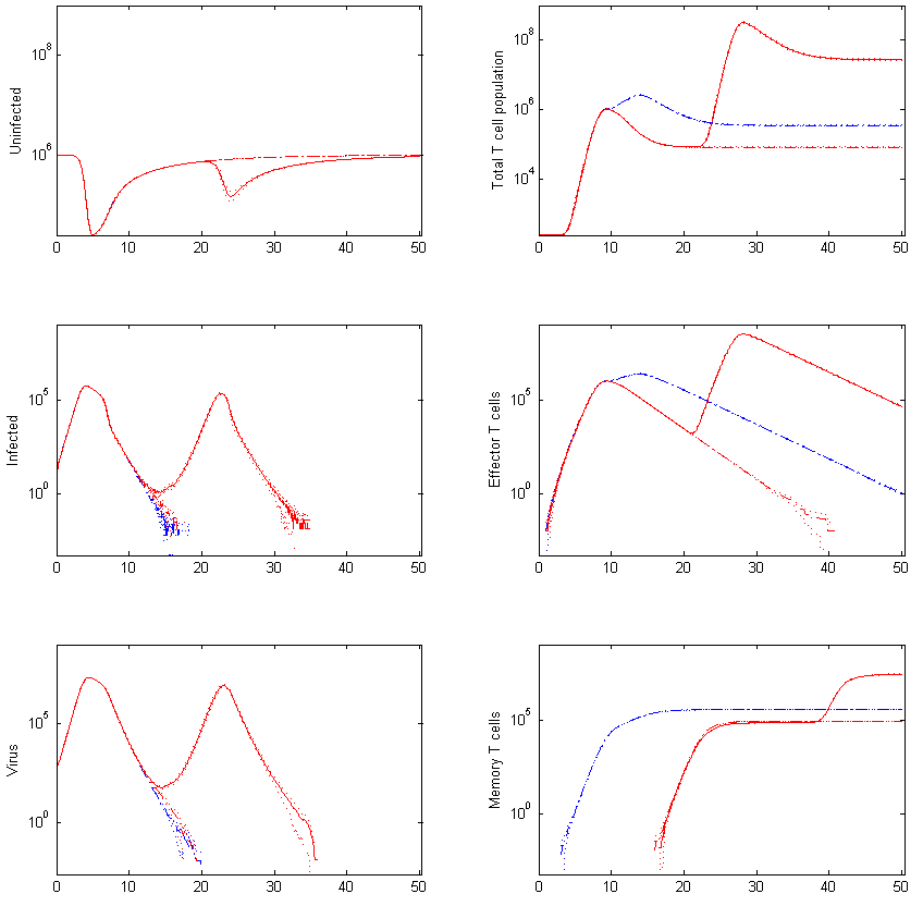

Figure 6: Comparison between the simulation with a delay for an effector T cell to become a memory T cell $d_W = 14$ days and $d_W = 1$ day (blue). The solid lines represent the mean of 150 independent simulation runs and the dotted lines the 95% confidence interval.

run, this figure also shows that the number of effector T cells increases again as soon as memory T cell are available, which confirms that memory cells convert to effectors during the primary response. Some of the effectors derived from memory T cells in turn become additional memory cells, which explains the second increase in the memory T cell population.

In the experiment with the initialization leading to a high number of secondary reactions in the standard model, small secondary reactions already appear for 3 of

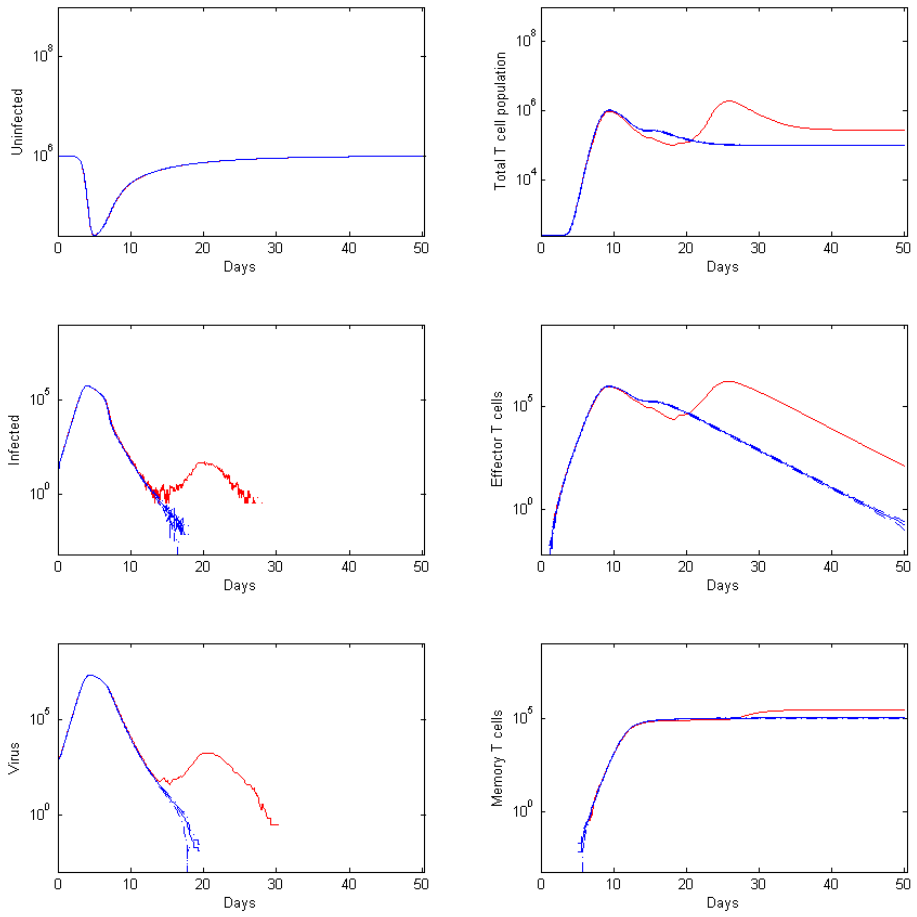

Figure 7: Simulation with an effctor to memory delay of 3 days. The solid lines represent the mean of the cases where there is a secondary reaction (red) and when there is no secondary reaction (blue) for 150 independent simulation runs. The dotted lines represent the 95% confidence interval. Given the small number of samples, no confidence intervals are plotted for the secondary reaction

the 150 runs when $d_W = 3$ days. Figure 7 shows an interesting difference between the runs which lead to se: for all the cases in which there is a secondary reaction, memory T cell do not convert to effectors during the primary response, and there is therefore a continuous decay of the effector T cell population until the memory T cell finally react to the secondary reaction. Even though not visible on the plot (which shows means), this also happens for 7 of the cases in which there is no secondary reaction. This unexpected behavior remains to be explained.

For values of d_W above 6 days, the memory T cell arrive too late to take part in the primary response, and mostly even after the beginning of an eventual secondary reaction. The frequency of secondary reactions for both experiments is already similar to the frequency observed with the unmodified model. The amplitude of the secondary reactions is however smaller; when further increasing d_W towards its original value of 14 days, this amplitude of the secondary reaction also increases. Figure 6 compares the output of the original model with the output obtained when $d_W = 10$ days. This indicates that the memory T cell are effective in clearing the infection, and that the moment at which the secondary infection is cleared depends on the moment when the memory T cell are able to become effector cells.

3.4 Secondary Reaction in the Absence of Memory Cells

In the previous section, we show that the memory T cell are able to clear the secondary reaction, and that the moment at which this occurs is dependent on the moment when memory T cells can become effectors and therefore take part in the response. Given the importance memory T cells therefore have on the outcome of the secondary reaction, we are also interested in knowing what would be the outcome of the simulation if there were no memory T cells available throughout the whole secondary reaction.

3.4.1 Hypothesis

In the absence of memory T cells, the immune response can only come from naïve T cells. There is however a limited number of naïve T cells available in Chao's model (10 per clone if there are multiple clones). Most of these cells will become effectors during the primary response. Effector cells only divide for a certain amount of time (18 times in this model), but have a constant death rate, which leads to population decay. It is therefore possible that the amount of effector T cells able to respond in a secondary reaction is low and that the infection wouldn't be cleared at the end of the secondary reaction.

3.4.2 Experiment

We modify Chao's simulator in order to increase the delay for effector T cell to become memory T cells to 50 days. This delay is superior to the time needed to clear the virus in the normal model (less than 40 days in all runs). This setting allows seeing both the evolution of the secondary reaction without memory T cells and the result of adding T cells after such a secondary reaction. We separately use the same two initializations I_{high} and I_{low} in 150 independent simulation runs

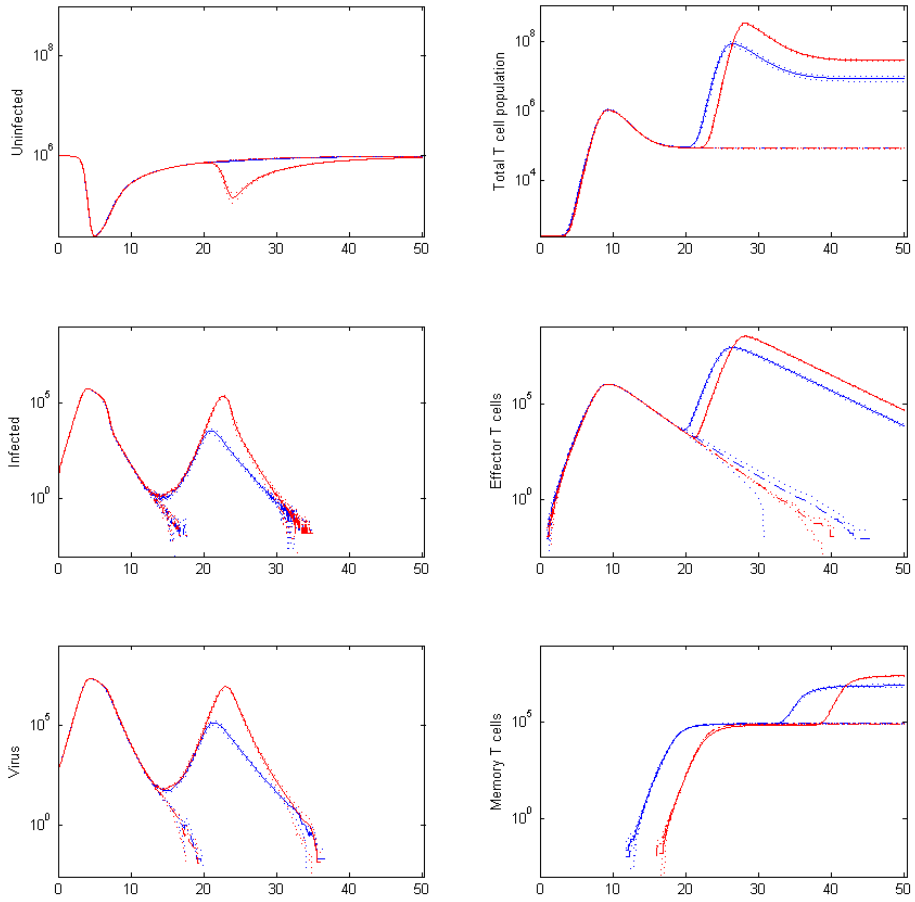

Figure 8: Comparison between the simulation with a delay for an effector T cell to become a memory T cell $d_W = 14$ days and $d_W = 10$ day (blue). The solid lines represent the mean of 150 independent simulation runs and the dotted lines the 95% confidence interval.

each.

3.4.3 Result

Figure 9 shows that in the absence of memory T cells, there is no secondary response. The virus and cell population are interacting together following the predator-prey model, which stabilizes in a steady state with a high number of virus particles. The late arrival of memory T cells, at a point where the system appears stable, leads to a rapid decrease of the virus loads and clears the infection in a similar way as for a normal effector to memory delay. The same behavior is observed for both MHC/TCR initialization even though the frequency of secondary reactions is very different. This shows that the secondary response depends on memory T cells, and that in their absence, the virus cannot be cleared. Furthermore, we show that even with a stable amount of virus under the predator-prey model, the secondary response originating from the memory T cells is able to clear the infection.

3.5 Influence of the naive cells death on the existance of a secondary reaction

In the previous section, we show that there is no secondary response in the absence of memory T cells, which leads to a secondary reaction in which the virus loads stabilizes at a high level. Furthermore, we show previously that when there are early available memory T cells, no secondary reaction occurs. The question of interest therefore is to know if the secondary reaction is caused by the absence of T cells able to react at the moment the secondary reaction occurs, and in particular if a constant level of naïve T cells would prevent secondary reactions from occuring. We first analyze the evolution of the Naïve cell populations, then propose a hypothetical model without naïve population decay and then try this model in the case where there is a reinfection.

3.5.1 Evolution of the Naïve Cell Populations

Figure 10 illustrates the evolution of the naïve population for initialization I_{high}. On average, the number of naïve cells decreases rapidly during the primary response, but there are still naïve cells available. The details however show that the population of naïve cells from the TCR clone with the highest affinity is almost null after the primary response, whereas the populations of clones with lower avidity remain higher. This means that during the secondary reaction, the response will come from naïve cells with lower avidity. The response is actually happening, as illustrated by the decay of the total population during the

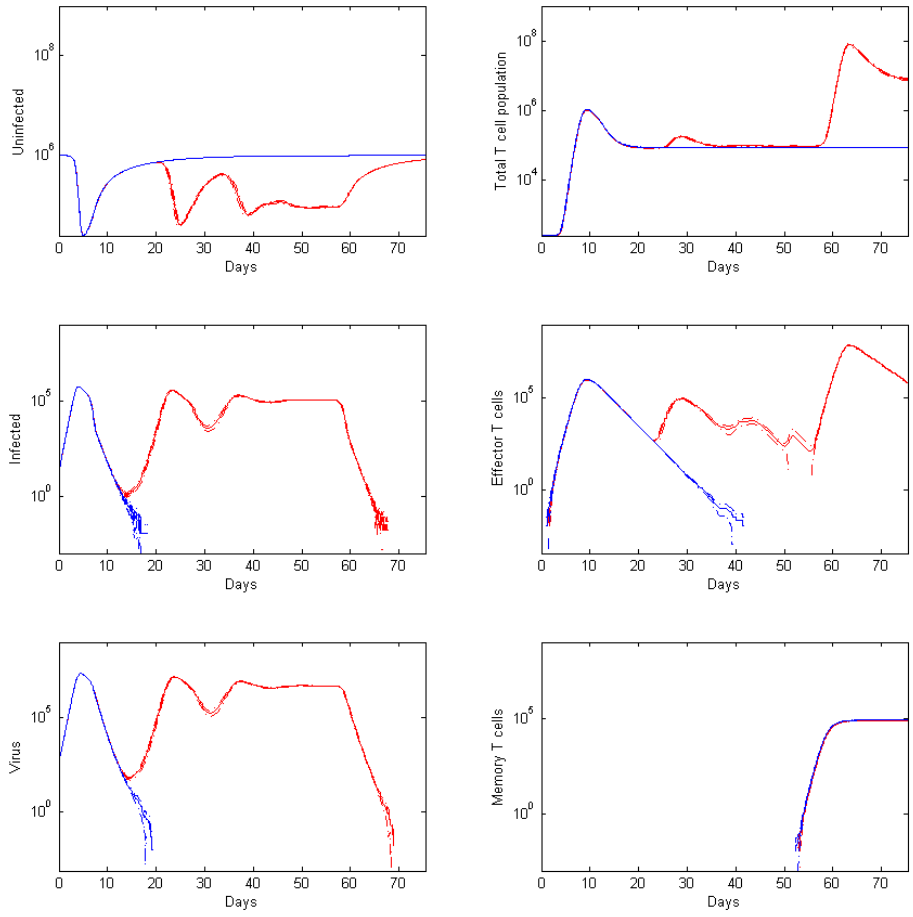

Figure 9: Simulation runs with an effector to memory delay of 50 days. The solid lines represent the mean of the cases in which there is a secondary reaction (red) and when there is no secondary reaction (blue) for 150 independent simulation runs. The dotted lines represent the 95% confidence interval.

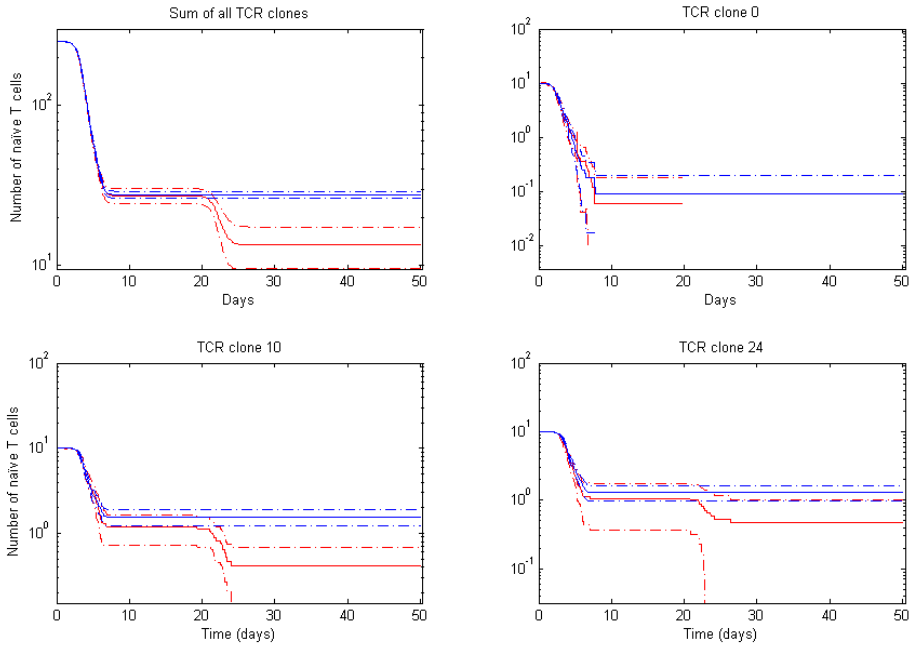

Figure 10: Evolution of the naïve T cell population and three TCR clone subpopulations, where clone 0 is the closest to the epitope. The solid lines represent the mean of the sub-population for 50 independent simulation runs with the same initialization. The dotted lines represent the 95% confidence interval.

secondary reaction. However, as shown previously, the naïve cells induced secondary response is however not efficient enough to control the virus.

3.5.2 Hypothesis

If there is a constant amount of na¨ive T cells, these could interact with infected cells and create new effectors even when the population of effectors originating from the primary reaction is decreasing. This would avoid the existence of a period where there a no more naïve cell, fastly decreasing effector populations and no memory cells yet, a window in which both a secondary reaction or a reinfection by the same or a close virus can proliferate. The absence of this window should make it possible to clear the infection without the intervention of memory T cells.

In the case of a reinfection by the same virus before the memory T cell are ready, such a model should allow a more efficient response.

3.5.3 Experiment

We modify Chao's simulator in order to keep the population of naïve cells constants (10 per clone). We do one experimental run with a normal effector to memory delay of 14 days and one with a delay of 50 days, which is equivalent to the situation when there are no memory cells during the secondary response. We use the initialization I_{high} for all 150 independent simulation runs.

We then modify the simulator to inject an additional amount of 1'000 virus particles at day 14, which is between the primary and secondary reaction. We compare the normal model to the model without naïve cell decay for I_{high} and I_{low}.

3.5.4 Results

As shown on Figure 11, while the constant availability of naïve T cells significantly reduces the frequency of secondary reactions (from 46% to only 2 in 150 runs), it is still not sufficient to prevent all occurence of secondary reactions. Furthermore, these secondary reactions are succesfully cleared by the secondary response even in the case where no memory cells are involved. This means that the clearance rate of the response induced by naïve cells is not total. Actually, it appears plausible that the secondary response does not get cleared due to this suboptimal clearance rate and that we do not observe this only because we do not have enough independent runs.

In the contect of a reinfection, the modified model is able to limit the initial extent of the infection, which is sufficient to avoid a secondary reaction in a significant number of cases for both initializations (Figure 12). In the original model, the reinfection leads to a secondary reaction in all runs for I_{high} and all but 5 runs for I_{low}, the initialization which has less than 2% of secondary reactions when there is no reinfection. In all cases the secondary response, which involves memory T cells, clears the infection.

4 Discussion

Our results show that the memory T cell induced reaction is able to clear the infection. Even though we do not explicitely rule the possibility of a tertiary reaction occuring in presence of memory T cells, some information can be derived from all other results we observe: in the course of the whole project, not one single run lead to a tertiary reaction, independent of all parameter changes. In total, this represents approximately 7'000 simulation runs. Even if the frequency of an eventual tertiary reaction would therefore need to be low, we do not prove

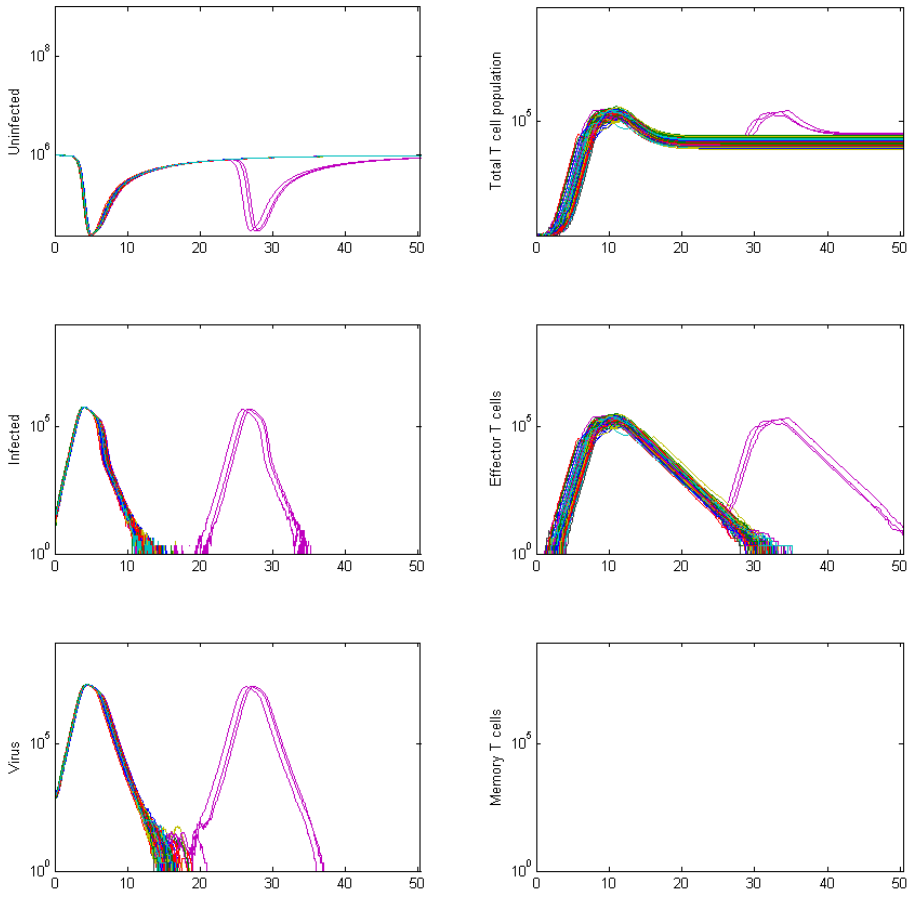

Figure 11: Representation of all 150 individual simulation runs with a constant naïve cell population. The effector to memory day is 50, which explains the absence of memory T cells on these plots.

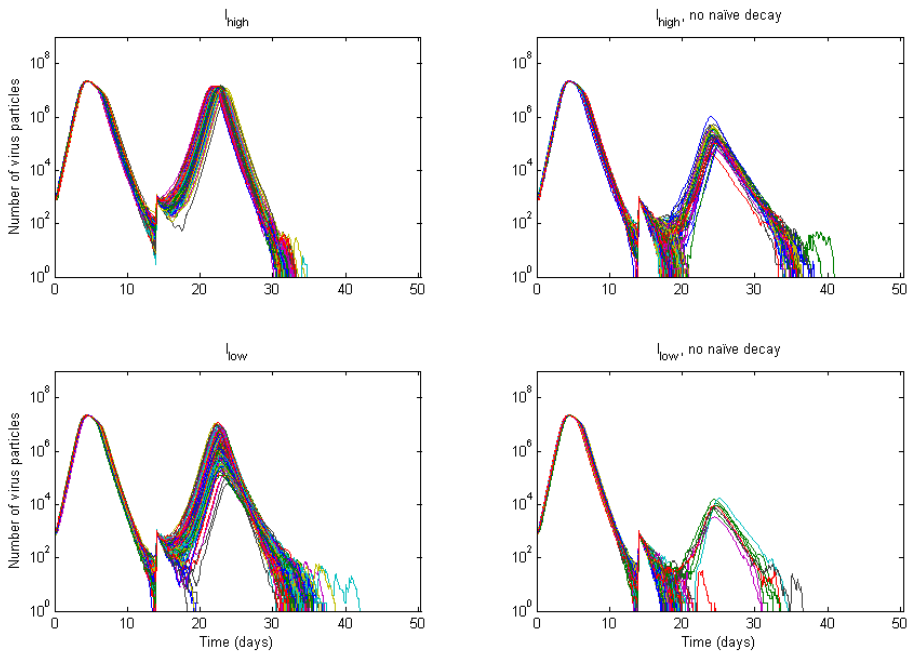

Figure 12: Representation of virus levels for all 150 individual simulation runs with reinfection at day 14 for two different initializations (rows) and the original (left) and modified model to avoid naïve T cell decay (right).

it's impossibility, but doing so based only on multiple simulation runs would be extremely expensive computationally.

The naïve-induced reaction is not able to clear the infection. The difference can be partially explained by both the higher net growth of the memory T cell induced response due to the lower death rate of these effectors. Anothery key point is the amount of memory T cells, which by far exceeds the initial amount of naïve T cells. Furthermore, we show that the distribution of the memory T cells favors TCR clones which are closer to the epitope.

5 Conclusion

We validate Chao's timestep choice by showing that there is no difference between a timestep of 10 minutes and a lower timestep, but that a higher timestep leads to differences. We show that several factors influence the frequency of a secondary reaction. The initialization, and therefore the affinity between the T Cells and the antigen, leads to variations of the frequency between 2% and 46%. Furthermore,

we note that the secondary reaction develops in a window where there are fewer naïve cells which also have lower affinity, the effector populations are rapidly decreasing and the memory T cells are not yet available. In this window, the organism is at risk of both a secondary reaction and a re-infection by another, antigenically close, virus. Avoiding the disparation of naïve T cells significantly reduces the frequency of the secondary reaction and allows its clearance even without a memory T cell induced response, even though the probability of furthur reactions is not null in this case. In the presence of memory T cells, the infection is cleared in every simulation run done during this project.

In conclusion, while we show some parameters which have an influence on the occurence and frequency of the secondary reaction, we cannot find a single root cause. Our work however underlines the mechanism of such a secondary reaction: there is a probability for a small number of infected cells to survive the primary response sufficiently long to enter the window in which the immune system is too weak to avoid the growth of a secondary reaction, which will only be cleared once memory T cells are available.

We can therefore state that the secondary reaction does not question the correctness of the simulation. It is indeed a hidden feature of the biological model, and the simulation allowed it's detection. It is important to keep in mind that we only considered the model from a mathematical point of view. All proposed modifications were done in the intent of pointing out key factors and have a no biological foundation. Furthermore, the whole issue of a secondary reaction seems to arrise due to assumptions in the biological model used by Chao, such as the existence of a delay during which effectors becoming memory cells are not part of the response, and the fact that there is a limited of naïve cells which are used in the primary response only. In the case that some of the underlying biological assumptions should not be true, then the whole issue of a secondary reaction needs to be re-examined, thus stressing out the importance of the model adequacy in simulations.

Finally, in the case such a secondary reaction does occur in reality, then the simulation allowed the detection of a component which was not considered by it's designers, and the simulation process therefore served its purpose of going beyhond the expectations of the designer. On the other, if such asecondary reaction is not realistic, then the adequacy of the model needs to be questioned, maybe a new model developped, or at least additional experimental data might be needed to better tune parameters. In both cases, the simulation approach will have proven usefull; the secondary reaction should therefore be considered as a positive finding.

References

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