AMATH/BIOL 382
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MATHEMATICAL MODELLING OF CAR T-CELLS IN ADAPTIVE IMMUNOTHERAPY

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Abstract

Chimeric antigen receptor (CAR) T cell therapy is known as a new "living drug" that is a type of immunotherapy which has recently been FDA approved to be added to the treatment protocols for leukemias and lymphomas [1]. It is currently a very popular research topic as early clinical results have been considered to be a breakthrough in cancer therapy. CAR T cell therapy also gained popularity due to the fact that it is a personalized treatment and has a short treatment time. Doctors will extract immune cells called T cells from the patient's blood and add special receptors called CARs to the cells. These receptors enable the modified T cells to target only the cancer cells, leaving normal cells unharmed. The engineered CAR T cells are then reintroduced back into the patient via infusion and the CAR T cells will multiply and attack the cancer cells throughout the body. In the paper by Dong et al.[2], they use both stability and bifurcation analysis to determine the effects of helper T cells on the tumor immune system interactions under the adoptive cellular immunotherapy (ACI) treatment. This model specifically looks at the interaction between the cell populations of effector CAR-T cells, the tumour cells and the helper T cells. We will be using similar techniques to extend the model to incorporate regulatory T-cells into their ODE model. Using the same techniques will allow us to use the theorems used in the paper, as well as, make it easier for us to check that our model matches the already established work. We also have access to the XPPAUT source code for the simulations from Dong et al.[2] which will allow us to rerun their simulations to further understand the dynamics of the original model. Additionally, their source code will give us a basis that we can use for our extensions for our numerical simulations.

In this paper, an ODE model created by Dong will be investigated to see if we can come to the same conclusions that CAR T-cell therapy can be used to eradicate tumours. In addition, regulatory T cells will be added into the model, which act as an inhibitory response to the CAR T cell proliferation. When adding regulatory T cells, we will examine whether CAR T cell therapy can still be considered successful.

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1. Introduction

Cancer is a devastating disease that will affect almost everyone's life in some way, either directly or indirectly. In 2020, an estimated 225,800 new cases of cancer will be diagnosed and 83,300 deaths from cancer will occur in Canada[1]. The mortality rates from cancer comprise approximately 1/3 of the total deaths in Canada[1]. Most people at some point at their life will be affected by cancer whether it be directly or indirectly. Where it is estimated that 1 in 2.3 people will be diagnosed with cancer in their lifetime[1]. Due to the large incidence and mortality rates, cancer research is a well-funded field, with lots of time and attention dedicated to finding the cure for cancer.

The fundamentals of cancer treatment over the last century involved surgery, radiation therapy and chemotherapy. Although these are still highly used today, an abundance of research has been focused on improving these treatment methods or inventing new ones. The ultimate goal being able to cure cancer while minimizing the intense and painful side effects that are associated with cancer therapy. By the end of the century two new therapeutic methods gained popularity, targeted therapy and immunotherapy. Both of these methods are able to target the cancerous cells leaving the normal cells unharmed, which ultimately minimizes the side effects.

1.1 Adaptive Immunotherapy

The immune system plays an important role in protecting the body by fighting against disease and foreign material such as bacteria and viruses. Although the immune system typically has the ability to distinguish between abnormal cells, cancerous cells are harder to detect. This is because cancerous cells began as normal cells, but due to genetic mutation developed into cancerous cells. Cancerous cells can block the immune system to prevent being attacked by using signalling proteins such as checkpoints or cytokines[1]. To combat this problem, immunotherapy was developed, which is a cancer therapy that helps by strengthening or restoring the immune system's ability to fight cancer [1]. Immunotherapy is defined as a treatment that works by strengthening or restoring the immune system. Adaptive immunotherapy as defined by the National Cancer Institute is a type of immunotherapy in which T cells, a specific type of immune cell, are given to a patient to help the body fight diseases, such as cancer [3]. Chimeric Antigen Receptor T-cell (CAR T-cell) therapy is a type of adaptive immunotherapy that has shown huge potential for being a new successful cancer therapy.

1.2 CAR T-cell Therapy

CAR T-cell therapy is known as a "living drug" and is a personalized cancer treatment, making it more expensive, but theoretically more effective with less toxicity to the patient [1]. First blood is removed from the patient, and the T-cells are extracted from the blood. Next the T-cells are genetically engineered in the lab so that they express the specific CARs on the surface, this allows them to target only the specific cancer cells. The modified T-cells are then expanded in cell-culture so that there are millions of CAR T-cells. Finally the CAR T-cells are infused back into the patient, where they further divide and bind to cancer cells, ultimately

killing them. Another reason CAR T-cells are highly regarded is that they are considered a short treatment relative to chemotherapy or radiation therapy as the CAR T-cells will eventually die and be removed by the body. This means there are no permanent or lasting consequences that can arise from this treatment.

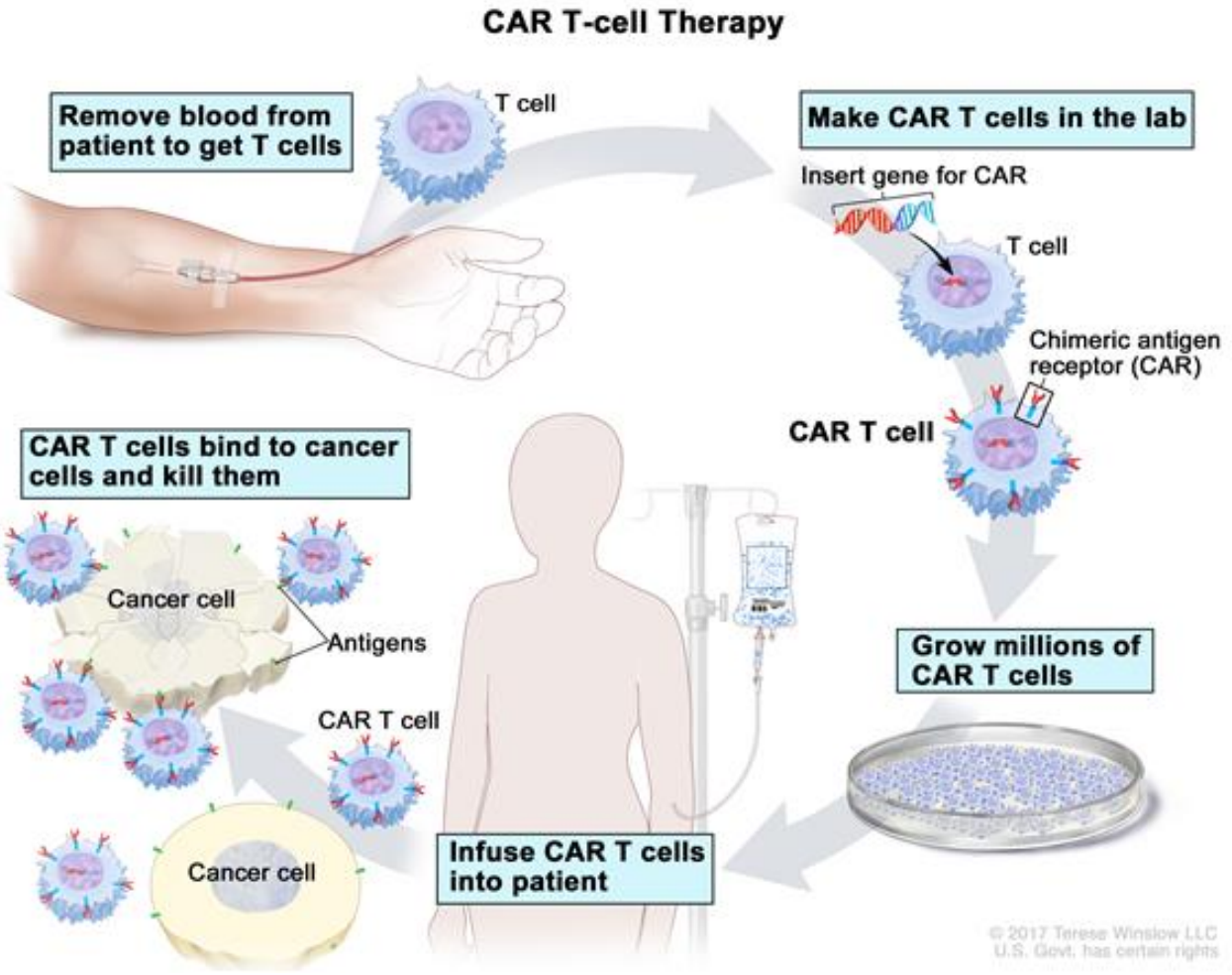


Figure 1.1: CAR T-cell therapy procedure [1]

Right now CAR T-therapy is available in Canada to treat leukemias or lymphomas that are refractory (non-responsive to treatment) or relapsed (comes back after treatment) when at least 2 other treatment methods

have been attempted[1]. As CAR T cell therapy is an extensive and expensive new therapy, it is still not a first option as we are still learning about this treatment. Currently there are numerous clinical trials and pre-clinical research being done on improving CAR T-cell therapy and testing it on other cancer types. By applying mathematical tools to modeling CAR T-cell therapy, the goal is to gain a better understanding of the underlying mechanisms. Using these techniques one can predict the outcomes of clinical trials, test mechanistic theories and ultimately help advance CAR T-cell therapy.

1.3 Mathematical Modelling of Cellular Systems

Currently CAR T-cell therapy is FDA approved for leukemias and lymphomas, which are cancers of the blood and lymphatic system respectively. As both the blood and lymph fluid is constantly being pumped throughout the body, we can assume that the cells are well circulated and "mixed". This is analogous to a solution of well mixed chemicals resulting in chemical reactions occurring as the chemicals interact with each other [4]. In this model we will be using differential equations to model the interaction of cell populations between the tumour cells, effector cells (CAR-T cells) and the helper cells. A key factor of adaptive immunotherapy is a sub-population of T-cells referred to as helper T-cells [5]. These helper T-cells help activate the CAR T cells that were administered to the patient, improving the effectiveness of the treatment.

2. Dong's Adaptive Immunotherapy Model

Dong et al.[2] looked at creating a differential equation model for adaptive immunotherapy to simulate whether the treatment can be successful at creating a steady state equilibrium, more specifically a tumour-free equilibrium. Cancer is characterized by uncontrollable growth, so if any steady state is reached for the tumour cell population, the treatment has already helped. Not only does stopping the growth of tumour cells make it easier for other more local cancer treatments such as surgery to be more successful, but it can theoretically prevent the metastasis (spread) of the cancer and reduce the symptoms. If a tumour-free equilibrium is reached, this means that the once oscillating tumour cell population is steady at 0, meaning no tumour cells remaining. When this occurs we can conclude that the patient is cured using the CAR T-cell therapy treatment.

2.1 Differential Equation Model

In terms of treatment, CAR T cells are infused into the patient. In the differential equation for the effector cells, this model suggests they are rapidly born within the system. This simplifies our model and will give a similar result as if they were introduced into the system. Below is a figure showing the interactions between the tumour cells (T), effector cells (E) and helper cells (H).

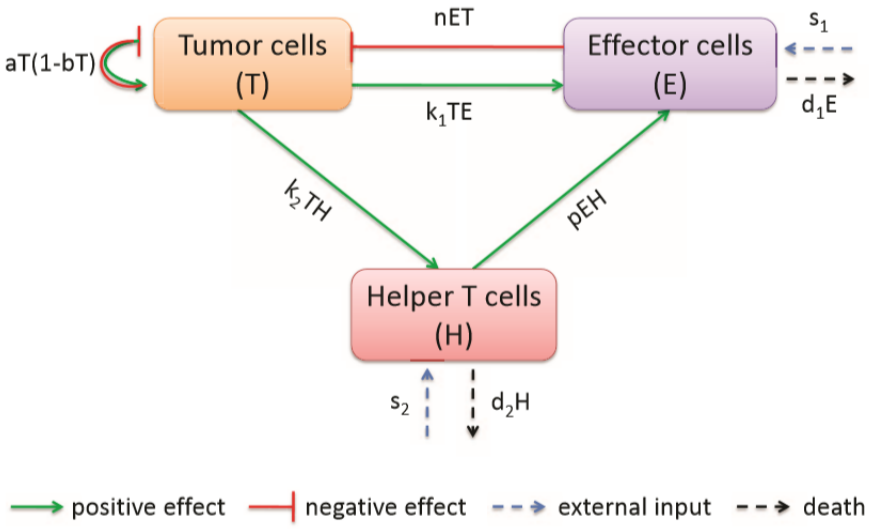


Figure 2.1: Mathematical model of adaptive immunotherapy showing the interaction between tumour cells, effector cells and helper T cells [2]

$$\begin{cases} \frac{\mathrm{d}T}{\mathrm{d}t} = aT(1-bT) - nET, \\ \frac{\mathrm{d}E}{\mathrm{d}t} = k_1TE - d_1E + pEH, \\ \frac{\mathrm{d}H}{\mathrm{d}t} = s_2 + k_2TH - d_2H, \end{cases}$$

Figure 2.2: Dong's DE Model

The differential equations above for the tumour cells, effector cells and helper cells were then non-dimensionalized. This gives the equations below where "x" is the tumour cells, "y" is the effector T-cells and "z" is the helper T-cells. The following simulations and analyses will be done using the non-dimensionalized differential equations, but will be labelled with the cell types for reminder. See the Appendix for more detail on how this was done.

$$\begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} = \alpha x(1-\beta x) - xy, \\ \frac{\mathrm{d}y}{\mathrm{d}t} = \omega_1 xy - \delta_1 y + \rho yz, \\ \frac{\mathrm{d}z}{\mathrm{d}t} = \sigma_2 + \omega_2 xz - \delta_2 z, \end{cases}$$

Figure 2.3: Dong's non-dimensionalized DE model

Below is a table listing the definitions for each of the parameters in the non-dimensionalized model above.

Parameter	Definition
X	Ratio of current tumour cell population over initial tumour cell population
Y	Ratio of current effector cell population over initial effector cell population
Z	Ratio of current helper cell population over initial helper cell population
τ	Total number of tumour cells lost from interacting with effector cells
α	The maximal growth rate of tumours over the loss rate of tumour cells
β	Initial tumour population over the carrying capacity of the biological environment for tumour cells
ω1	Rate the effector cells are stimulated over the loss rate of tumour cells
δ1 = 1/(n*T0)	(the loss rate of tumour cells multiplied by the initial tumour population)-1 , over the average lifespan of an effector cell
ρ	Activation rate of effector cells by helper cells over loss rate of tumour cells
σ2	Ratio of birth rate of helper cells over the loss of effector cells multiplied by the initial population of tumour cells and helper cells
ω2	Rate that helper cells are stimulated over the loss rate of tumour cells
δ2 = 1/(n*T0)	(the loss rate of tumour cells multiplied by the initial tumour population)-1 , over the average lifespan of a helper cell

Figure 2.4: Definitions of non-dimensionalized variables and parameters

2.2 Numerical Simulations

The goal of the numerical simulations is to look at the steady state reached by the cell populations, specifically the tumour cells. We can determine that CAR T-cell therapy is successful if a tumour-free equilibrium is reached, this being the tumour cell population reaching a steady state of zero. The two parameters we will be varying are ρ and ω_2, where ρ represents the activation rate of effector cells from helper cells over the loss rate of tumour cells and ω_2 represents the rate that the helper cells are stimulated over the loss rate of tumour cells. By varying ρ and ω_2, we can see the impact at which both the helper and effector T cells have on eliminating the tumour cells have during the treatment.

CASE 1: The first case we are going to look at is where steady state is reached for the cell population, but tumour free equilibrium does not occur. Biologically this means that since the tumour cell population has now reached a steady state, the tumour is no longer growing or shrinking in size. Although this may not be successful as a curative treatment, this case may be ideal for patients seeking palliative treatment. Palliative care refers to the main goal of treatment being relieving symptoms and slowing the progression of cancer. This is often the case for patients with advanced or late stage cancer, cancer that has metastasized (spread) throughout the body, or recurrence occurs(cancer returns after treatment).

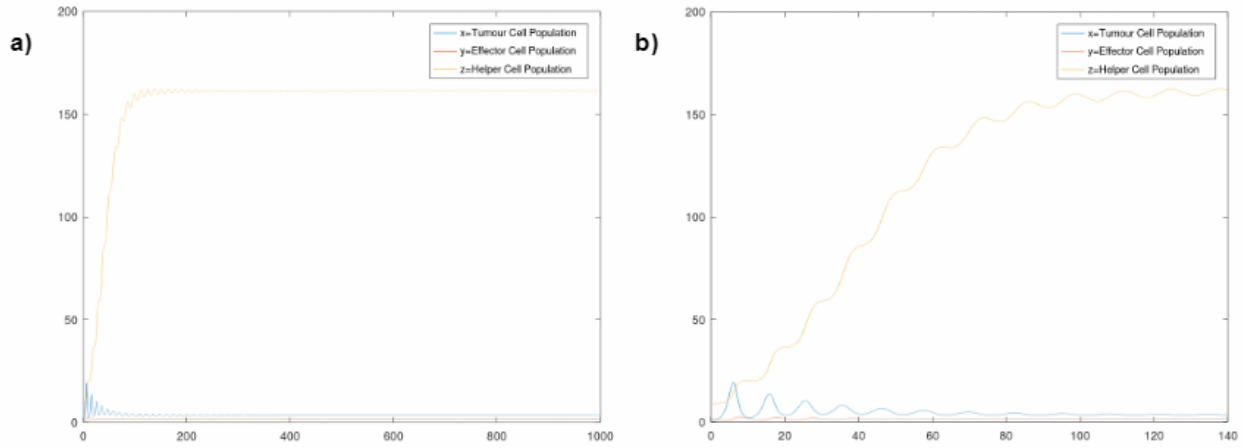


Figure 2.5: Model simulation of the tumour, effector and helper cell populations where CAR T cells are administered and steady state is reached. 3a shows the simulation that was run for this case and 3b is zoomed in on the initial interactions of the cell populations. In this case $\rho = 0.001$ and $\omega_2 = 0.015$.

In figure 2.5 we can see that the oscillation reaches a steady state over time as they are dampened. Looking at Figure X in the Appendix B, we can see that our results match that of Dong's [2].

CASE 2: Next we can examine the case where there are sustained oscillations of the cell population. Here steady state is never reached, but rather periodic oscillations are observed over a prolonged time. This is consistent with "Jeff's phenomenon" which is a clinically observed temporal oscillation in tumor size[6]. These oscillations occur due to the back-and-forth interactions between the tumour and the immune system. We can observe this phenomenon when $\rho = 0.015$ and $\omega_2 = 0.015$.

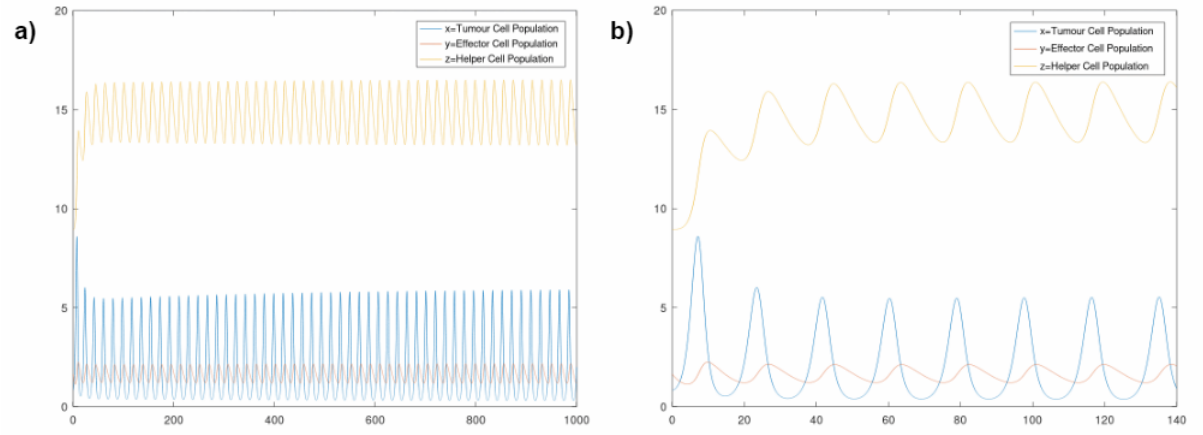


Figure 2.6: Model simulations showing Jeff's phenomenon, the oscillations due to the interaction between the tumour and immune system, when CAR T cells are administered. 4a shows the whole simulation where 4b shows the zoomed in image of the initial interactions. Here ρ, $\omega_2 = 0.015$.

CASE 3: Finally we will also look at the case where tumour-free equilibrium is reached. This means that the tumour cell population will reach steady state at zero. If the tumour-free equilibrium is reached, we can conclude that the CAR T-cell therapy is successful, as the immune system will over take the tumour, and the oscillations dampen.

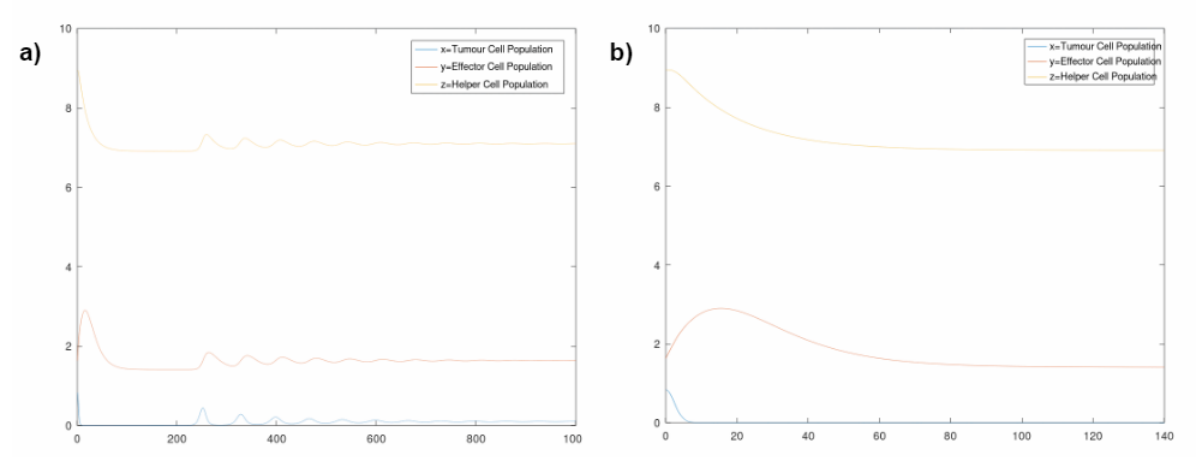


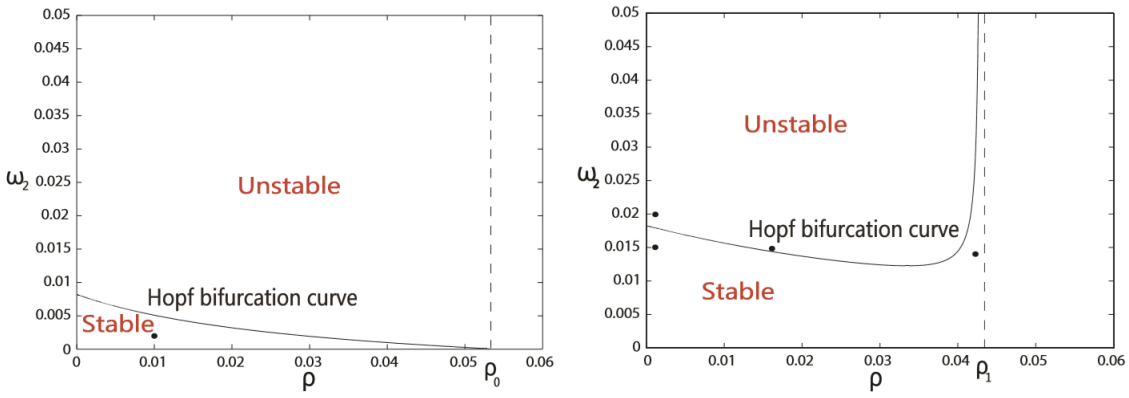
Figure 2.7: Numerical simulations showing when CAR T-cell therapy shows a curative result as tumour-free equilibrium is reached. 5a shows the whole simulation and 5b the zoomed in simulation of 5a. In this case ρ = 0.042 and $\omega_2 = 0.015$.

As seen in figure 5, the tumour cell population gets very close to zero, enough where we can label it a tumour-free equilibrium. The modification and fine tuning of various parameter values can help ensure that tumour-free equilibrium can be reached. Here ρ is the largest in comparison to the other two cases. In terms of our model this means that there is a greater activation rate of effector cells from helper cells resulting in the death of tumour cells.

2.3 Bifurcation Analysis

The term σ_1 refers to the "artificial birth rate" of the effector cells as they are introduced into the patient from an outside source. Dong refers to this as the treatment rate denote σ_1. For the bifurcation analysis, we want to compare how an increase in treatment rate will alter the steady state equilibrium when we can't reach a tumour free equilibrium.

Through Theorem 3.2 we are able to produce the following graphs plotted against ω_2 and ρ to see for what values of the parameters we are able to reach a stable steady state. This means that if we plot the point (ω_2,ρ) onto the graphs and it is the stable region then we will have that the steady states of the three cell populations will r because this means that while there are still tumour cells in the patient we have effectively stopped the growth of the tumour and reach an equilibrium such that none are no longer increasing or decreasing. This is desirable cell population in the patient.
When the point is in the unstable region of the graph we will reach a periodic steady state for all three cell populations. This means that the cell populations will indefinitely oscillate, while this is less desirable than having a steady state with no oscillations, it still stops the growth of the tumour cells.



(a) $\sigma_1 = 0$ (b) $\sigma_1 = 0.1181$

Figure 2.8: Dong's Bifurcation Curves

From this analysis we are able to draw that the treatment rate has a direct effect on the possible values for ω_2 and ρ to let us have a stable steady state. We can see that has we give the patient more treatment we are effectively making it easier to reach a stable steady state which as stated before is more desirable than a periodic steady state.

3. Extended model

The human body is a very complex system where there are numerous interactions between various cell populations and their environment. In order to make Dong's model a better representation of what occurs within the body in CAR T-cell treatment there are a multitude of factors that can be added. In terms of the extent of this paper, we will introduce a new sub-population of T-cells called regulatory T-cells. Thus far we have talked about two sub-populations of T-cells, the effector (CAR T-cells) which were genetically engineered and reintroduced into the patient as treatment, and the helper T-cells which are naturally present within the body.

3.1 Regulatory T-Cells

Regulatory T-cells (Tregs), also known as suppressor T cells is another sub population of T-cells that arise naturally in the body. In a healthy human the function of the regulatory is to modulate the immune system. This includes maintaining tolerance to self-antigens and preventing autoimmune disease [7]. In simpler words, these regulatory T cells act as a "Self-check" built into the immune system to prevent excessive reactions. In terms of their role in adaptive immunotherapy, regulatory T cells suppress activation, proliferation and cytokine production of the effector T cells [7]. Studies in both humans and animal models have implicated that high numbers of Tregs in the tumor microenvironment is indicative of a poor prognosis for various cancers such as ovarian, breast, renal, and pancreatic cancer [8]. It is proposed that these Tregs suppress tumor immunity, hindering the body's innate ability to control the growth of cancerous cells [8]. This indicates that Tregs suppress effector T cells (CAR T cells) and hinder the body's immune response against the cancer.

3.2 Differential Equation Model

In terms of our differential equation model, we can modify our original diagram such that a new cell population is added where they act by inhibiting the effector cells.

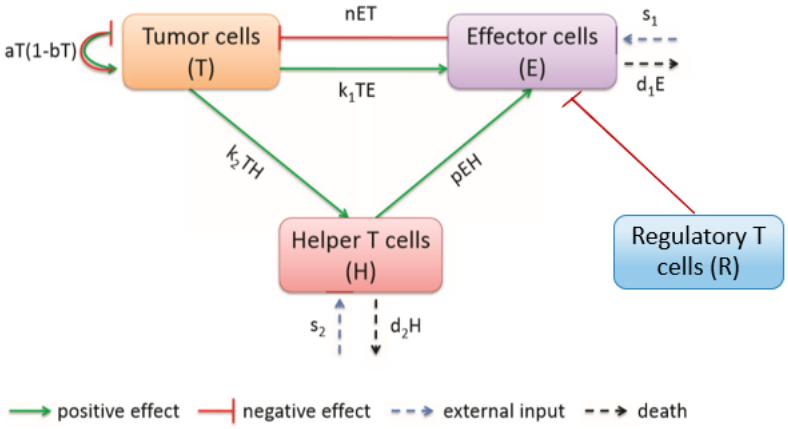


Figure 3.1: Extended Model

For simplicity, we are going to take the cell population of the regulatory T cells to be constant. We can make this assumption because regulatory T cells are very highly regulated in the body and so they have very tight constraints[8]. Although the regulatory T cell population is constantly changing the change in the population is negligible and so we make this assumption that in our simulations the cell population of regulatory T cells is a constant (R).

3.3 Stability Analysis

Our modified differential equation model looks like this:

$$\begin{cases} \frac{dT}{dt} = aT(1-bT) - nET, \\ \frac{dE}{dt} = k_1TE - d_1E + pEH \boxed{-\gamma R} \\ \frac{dH}{dt} = s_2 + k_2TH - d_2H, \end{cases}$$

Figure 3.2: Extended DE Model

We have two new parameters we are introducing:
γ which denotes the inhibition rate of the regulatory T cells on the effector cells, and,
R which is the population of the regulatory T cells which in our model is a constant

We can then create a dimensionless model in two steps:
We do so by first scaling our parameter γ over n which we denote as μ, and then, scaling R over its initial population which we denote as w.

As mentioned previously, we are assuming that the population of R is a constant which means our parameter w is 1 in our analysis because $w = R/R_0 = R_0/R_0 = 1$. The reason that we are creating and using a dimensionless model is to be able to use Theorem 2.3.2 from Dong et al.[2] later in our analysis. It is noteworthy to mention

that you could reach the same conclusions using the original model, however this would require us to revise and modify the theorem to fit our parameters.

After scaling we are left with the following model:

$$\begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} = \alpha x(1-\beta x) - xy, \\ \frac{\mathrm{d}y}{\mathrm{d}t} = \omega_1 xy - \delta_1 y + \rho yz - \mu \\ \frac{\mathrm{d}z}{\mathrm{d}t} = \sigma_2 + \omega_2 xz - \delta_2 z, \end{cases}$$

Figure 3.3: Non-dimensionalized DE model

From the model above we can derive the following steady states:

$$0 = x[\alpha(1-\beta x) - y]$$

$$\sigma_1 - \mu = (\delta_1 - \omega_1 x - \rho z)y$$

$$\sigma_2 = (\delta_2 - \omega_2 x)z$$

Figure 3.4: Our steady states

The first case we will consider is the when there is a tumour free equilibrium. For this to occur we would need the steady state of x = 0. So let $E^- = (x^-, y^-, z^-)$ denote our tumour free equilibrium where $x^- = 0$. If we put $x^- = 0$ into our steady states, we see that we get the following results:

$$\sigma_1 - \mu = (\delta_1 - \rho z^-)y^-$$

$$\sigma_2 = (\delta_2)z^- \quad \rightarrow \quad z^- = \frac{\sigma_2}{\delta_2}$$

Figure 3.5: Results from y^- and z^-

We can then put the second equation into the first and we get that:

$$y^- = \frac{\sigma_1 - \mu}{\delta_1 - \rho(\frac{\sigma_2}{\delta_2})} \qquad \textbf{or} \qquad y^- = \frac{\delta_2\sigma_1 - \delta_2\mu}{\delta_2\delta_1 - \rho\sigma_2}$$

Figure 3.6: Results for y^-

So, we can then if we put these values into E^- we get that:

$$E^- = (x^-, y^-, z^-)$$
$$= (0, \frac{\delta_2\sigma_1 - \delta_2\mu}{\delta_2\delta_1 - \rho\sigma_2}, \frac{\sigma_2}{\delta_2})$$

Figure 3.7: Results for E^-

Since these are populations of cells it means that each value must be greater than or equal to 0. Which means we get so conditions on our parameters for this steady state to be possible. We need $(\delta_2\sigma_1 - \delta_2\mu)/(\delta_1\delta_2 - \rho\sigma_2) > 0$ to hold. For this to be true we get two more conditions that must be satisfied:

$$\delta_2\sigma_1 - \delta_2\mu > 0 \quad \rightarrow \quad \sigma_1 - \mu > 0 \quad \rightarrow \quad \sigma_1 > \mu$$

$$\delta_2\delta_1 - \rho\sigma_2 > 0 \quad \rightarrow \quad \frac{\delta_2\delta_1}{\sigma_2} > \rho$$

Figure 3.8: Conditions to hold for E^-

This shows an important result from the first condition presented. Recall, σ_1 represents the "artificial birth rate" of the effector cells in the patient which acts as the "treatment rate" in the patient and μ is the inhibition rate that the regulatory T cells have on the effector cells. We see that we must have $\sigma_1 > \mu$ which means that the patients treatment rate must be higher than the inhibition rate of the regulatory T cells. This is important because this means that if a patient does not have sufficient treatment to overcome the inhibition rate then it is not possible for the patient to have an tumour free steady state.

The second condition is identical to the condition that Dong et al. [2] had in their analysis and says that the activation rate of helper cells on the effector cells is maximized by the birth and death rate of the effector and helper cells. This means that if we can satisfy the two conditions presented then it is possible to reach a tumour free equilibrium.

The other case we want to consider is when x does not reach a tumour free equilibrium. For this to occur we would have the steady state of x > 0. We will denote this steady state as $E^+ = (x^-, y^-, z^-)$ where $x^+ > 0$. If we have that $x^+ > 0$ then from our steady states, we get the following equations:

$$y^+ = \alpha(1 - \beta x^+) \qquad \textit{which only holds if} \qquad x^+ < \frac{1}{\beta}$$

$$z^+ = \frac{\sigma_2}{\delta_2 - \omega_2 x^+} \qquad \textit{which only holds if} \qquad x^+ < \frac{\delta_2}{\omega_2}$$

Figure 3.9: Conditions to hold for x^+

this implies that if $0 < x^+ < 1/\beta$, δ_2/ω_2 then:

$$E^+ = (x^+, y^+, z^+)$$

$$E^+ = \left(x^+, \alpha(1 - \beta x^+), \frac{\sigma_2}{\delta_2 - \omega_2 x^+}\right)$$

Figure 3.10: Conditions to hold for E^+

From this we see that our equilibrium is not dependent on what our additional parameter μ is and we are able to use Theorem 2.3.2 from Dong et al. [2] and substitute in the term (σ_1-μ in for σ_1 in the theorem. This allows us to derive that our system has one immune-control equilibrium E^+ when $0 < x^+ < 1/\beta$, δ_2/ω_2 which is locally asymptotically stable if the following inequality holds:

$$\psi(\rho, \omega_2) = (\alpha\beta x^+ + (\sigma_1 - \mu)y^+)(\alpha\beta x^+(\sigma_1 - \mu)y^+ + \alpha\beta x^+\sigma_2 z^+ + (\sigma_1 - \mu)y^+\sigma_2 z^+ + \omega_1 x^+ y^+) + \sigma_2 z^+(\alpha\beta x^+\sigma_2 z^+ + \left((\sigma_1 - \mu)y^+\sigma_2 z^+\right) - \rho\omega_2 x^+ y^+ z^+ > 0$$

Figure 3.11: Modified bifurcation curve equation

This means that if we satisfy the above equation we will have a steady state for the tumour cell population which means that while there will still be tumour cells in the patient we are able to keep them tightly controlled and this steady state and the population will no longer continue to grow. If the above condition is not satisfied then we will have periodic steady state of tumour cells in the patient, this means that the tumours population will oscillate indefinitely, and we are able to limit the maximum tumour cell population in the patient.

3.4 Bifurcation Analysis and Numerical Simulations

Next, we want to see the effects that μ has on the stability of the steady state where we don't have a tumour free equilibrium. As derived from the previous section we have the following equation:

$$\psi(\rho, \omega_2) = (\alpha\beta x^+ + (\sigma_1 - \mu)y^+)(\alpha\beta x^+(\sigma_1 - \mu)y^+ + \alpha\beta x^+\sigma_2 z^+ + (\sigma_1 - \mu)y^+\sigma_2 z^+ + \omega_1 x^+ y^+) + \sigma_2 z^+(\alpha\beta x^+\sigma_2 z^+ + \left((\sigma_1 - \mu)y^+\sigma_2 z^+\right) - \rho\omega_2 x^+ y^+ z^+ > 0$$

Figure 3.12: Modified bifurcation curve equation

When we plot this graph against ρ and ω_2 and vary μ we get the following results:

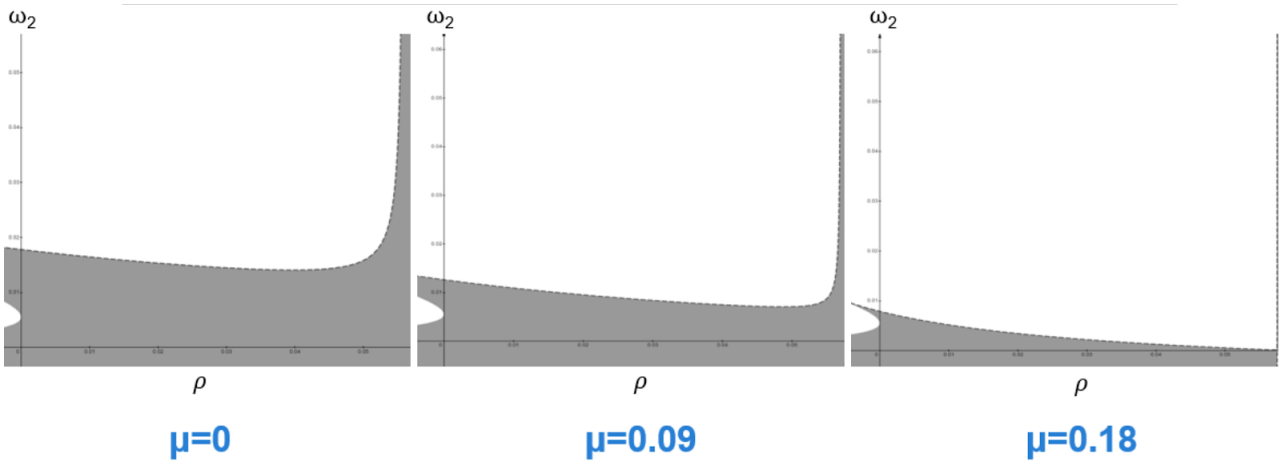


Figure 3.13: Results from varying μ from Figure 3.12

The coloured regions of the graphs denote when $\psi(\rho,\omega_2) > 0$ for the parameters of ρ on the x-axis and ω_2 on the y-axis. We have that in Figure 3.13.1, $\mu = 0$ and we have that is the same curve as the treatment model in Section 2.3. Then we have Figure 3.13.2 has $\mu = 0.09$, followed by Figure 3.13.3 which has $\mu = 0.018$. From this we can see that as μ increases in value that the possible parameters for our steady state to be a stable steady state is decreasing. Biologically this means that has the inhibition rate increases on the effector cells then we have more strict conditions on ρ and ω_2 for a stable steady state to occur.

To illustrate this we will fix ρ and ω_2 to be $\rho = 0.001$ and $\omega_2 = 0.015$. We will first run a simulation when $\mu = 0.0015$ and then a simulation when $\mu = 0.15$, corresponding to Figure 3.13.1 and 3.13.3 respectively.

We can see that $\rho = 0.001$ and $\omega_2 = 0.015$ is within the coloured region of the map so the simulation should achieve a stable steady state for all three parameters and have x > 0.

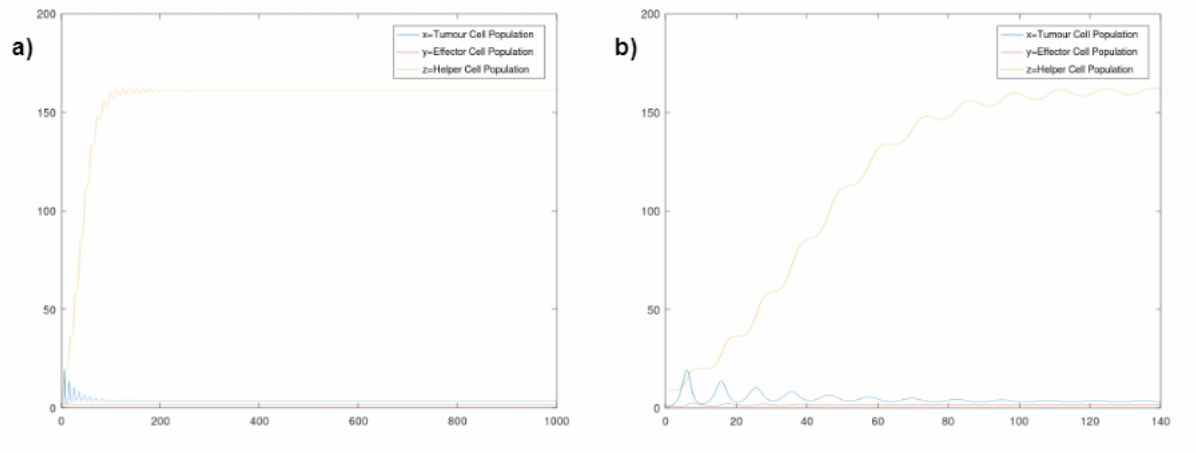


Figure 3.14: Simulation run with $\mu = 0.0015$

It is evident that this correctly corresponds with the above graph as we reach a stable equilibrium for all the cell populations.

We can see that $\rho = 0.001$ and $\omega_2 = 0.015$ is not within the coloured region of the map so the simulation should achieve a periodic steady state for all three parameters and have $x > 0$.

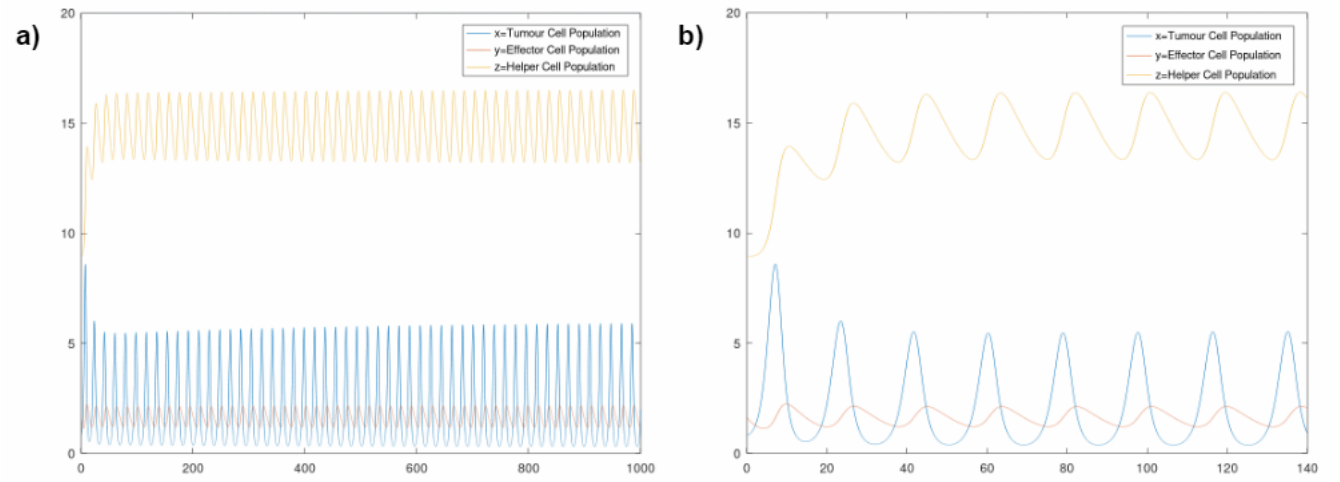


Figure 3.15: Simulation run with $\mu = 0.15$

Again, we are able to observe that the results correctly correspond with the above graph as we reach a stable equilibrium for all the cell populations.

4. Conclusions

From Dong's original adaptive immunotherapy model, our main focus was looking at how the parameters ρ and ω_2 impact the CAR T cell treatment outcome. We tested various combinations of these parameter values and ran numerical simulations to look at the behaviour of the cell populations. We found that there are 3 possible outcomes; oscillations sustained between the tumour and the immune system following Jeff's phenomenon, steady state reached due to the damping of oscillations and a tumour free-equilibrium is reached. Our model shows that a tumour-free equilibrium can occur through adaptive immunotherapy, therefore CAR T cell therapy can treat cancer so there are no tumour cells remaining.

Next we extended Dong's model by adding regulatory T-cells and their inhibition on effector T-cells into the model. As we have shown from our analysis, if the inhibition of the CAR T effector cells by the regulatory T cells is too great, the treatment can no longer be successful. This shows that our mathematical model is successful at matching what is expected theoretically. Meaning that regulatory T cells are a possible obstacle for CAR T cell therapy. Studies have shown that depletion of Tregs in animal models has shown an increased efficacy of immunotherapy treatments, and therefore, many immunotherapy treatments are now incorporating Treg depletion [9].

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5. APPENDIX A: Non-dimensionalizing Dong's Model

5.1 Introduced parameters

We have the following figure to show the parameters and their values in terms of the original model. You can verify by substituting the values into Dong's DE model and you will have all parameters scaled over n and all populations will be scaled over their initial population

$$x = \frac{T}{T_0},\ y = \frac{E}{E_0},\ z = \frac{H}{H_0},\ \tau = nT_0t,\ \alpha = \frac{a}{nT_0},\ \beta = bT_0,$$
$$\omega_1 = \frac{k_1}{n},\ \delta_1 = \frac{d_1}{nT_0},\ \rho = \frac{p}{n},\ \sigma_2 = \frac{s_2}{nT_0H_0},\ \omega_2 = \frac{k_2}{n},\ \delta_2 = \frac{d_2}{nT_0}$$

Figure 5.1: Parameters

5.2 Parameter breakdown

X: is the ratio of the current tumour cell population over the initial tumour cell population
Y: is the ratio of the current effector cell population over the initial effector cell population
Z: is the ratio of the current helper cell population over the initial helper cell population
n: is the total number of tumour cells lost from interacting with T cells
α: is the maximal growth rate of tumours over the loss rate of tumour cells
β: the initial tumour population over the carrying capacity of the biological environment for tumour cells
ω_1: is the rate that the effector cells are stimulated over the loss rate of tumour cells
δ_1: is 1/(n*T0), which is (the loss rate of tumour cells multiplied by the initial tumour population)-1 , over the average lifespan of an effector cell
ρ: activation rate of effector cells from helper cells over loss rate of tumour cells
σ_2: is the ratio of the birth rate of helper cells over the loss of effector cells multiplied by the initial population of tumour cells and helper cells
ω_2: is the rate that the helper cells are stimulated over the loss rate of tumour cells
δ_2: is 1/(nT_0), which is (the loss rate of tumour cells multiplied by the initial tumour population)-1 , over the average lifespan of a helper cell

6. APPENDIX B: Reproducing Dong's Results

6.1 Dong's Simulation

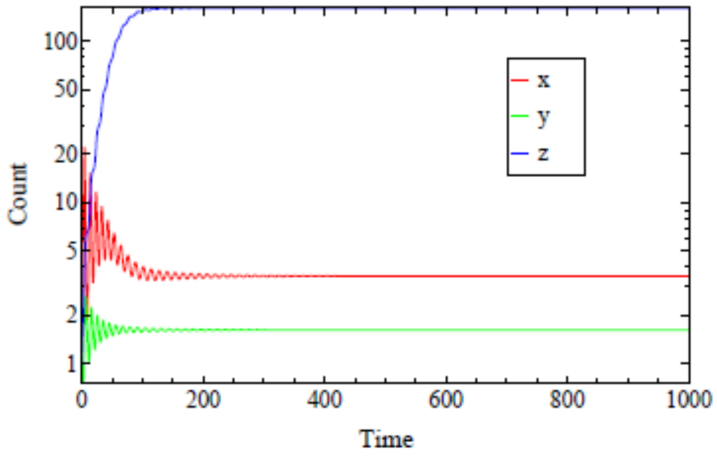

Figure 6.1: Numerical simulation done by Dong for the treatment case where CAR T cells are administered to the patient, where $\rho = 0.001$ and $\omega_2 = 0.015$