ARIEL UNIVERSITY

Improving the Mathematical Model of T1-T2-Treg interactions in Allergy and Specific Immunotherapy

A final project submitted in partial fulfillment of the requirements for the degree
Bachelor of Science (B.Sc.) at the Ariel University of Samaria,
In the Department of Mathematics

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ABSTRACT

The study describes the mathematical process of the immune system.

The research based on two mainly scientific studies. The first is "Mathematical Modelling of Allergy and Specific Immunotherapy: Th1-Th2-Treg Interactions", by Fridolin Groß, Gerhard Metzner and Ulrich Behn[2] . The second one is "Modeling Immunotherapy for allergy", by Michael A. Fishman and Lee A. Segel.[3]

In order to research the mathematical models in immunology, first I had to fully understand the mechanism of the immune system. I had to understand all of its factors which are involved in the allergic response, and to understand how the process occurs.

Secondly, I decided to explore more than one approach in order to achieve better results. First, I've studied the Fishman's and Segel's study[3], and understood the mathematical model they researched about. Next, studied the Groß's, Metzner's and Behn's study[2] . Third, consulted with an allergist specialist in order to make sure my assumptions were correct.

Finally, by using MATLAB, programmed the model, and simulated different treatment doses. The goal of this study is to achieve a stable therapeutic process, by depressing the immune system response.

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CHAPTER 1

INTRODUNCTION

An allergy reaction is a reaction caused by our immune system. Scientifically it defined as Immediate Hypersensitivity. We can observe the reaction almost immediately, thought it can take a bit longer in some others. Allergic reaction occurs after exposing the allergen by injection (or a sting, or swallow) to the blood circulation.

There are three factors participating in the immunological response: the allergen, antibodies against the allergen and some cells that has the ability to bind those antibodies. An allergen is some protein or some chemical substance which the individual is exposed to repeatedly or to an extended exposure in a period of time. The most common allergens are house dust, food, medicine and stamen flower. The antibodies in the human body composed of protein molecules combined with sugar molecules.

There are five groups of antibody molecules, called immunoglobins: A, D, G, M, E. During an allergic response occurs, the individual produce major amount of type E antibodies, called IgE, while in healthy people an IgG antibodies produced after the exposure.

An allergic response occurs only if there was a first introduction between the immune system and the allergen before. There can't be an allergic reaction without previous exposure. The allergic response activates after the receptors onto the surface of the mast cell connect with the IgE molecules.

Studies show that the difference between a person that develops allergic response to the healthy individual is the hereditary genetic predisposition that triggers the immune system to produce IgE antibodies instead of IgG (draw 2.1.2). We can see the difference

between those people at the sensitization phase (mast cells combined with IgE molecules- draw 2.1.1), while among healthy individuals the production of IgE antibody is not sufficient to sensitize those cells.

TABLE 1.1: A list of abbreviations to be used throughout the study:

Antigen Presenting Cell	APC
Regulatory T cells	Treg / Tr
Th1	T1
Th2	T2
Re-stimulator cells	RC
Interleukin	IL
Interferon-γ	IFN

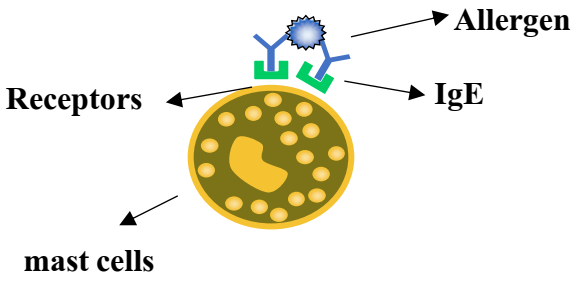


FIGURE 1.1. Sensitization process in mast cells: An IgE antibodies produced in allergic individual. Those antibodies moving in the blood stream and attached the receptors on the surface of the mast cells.

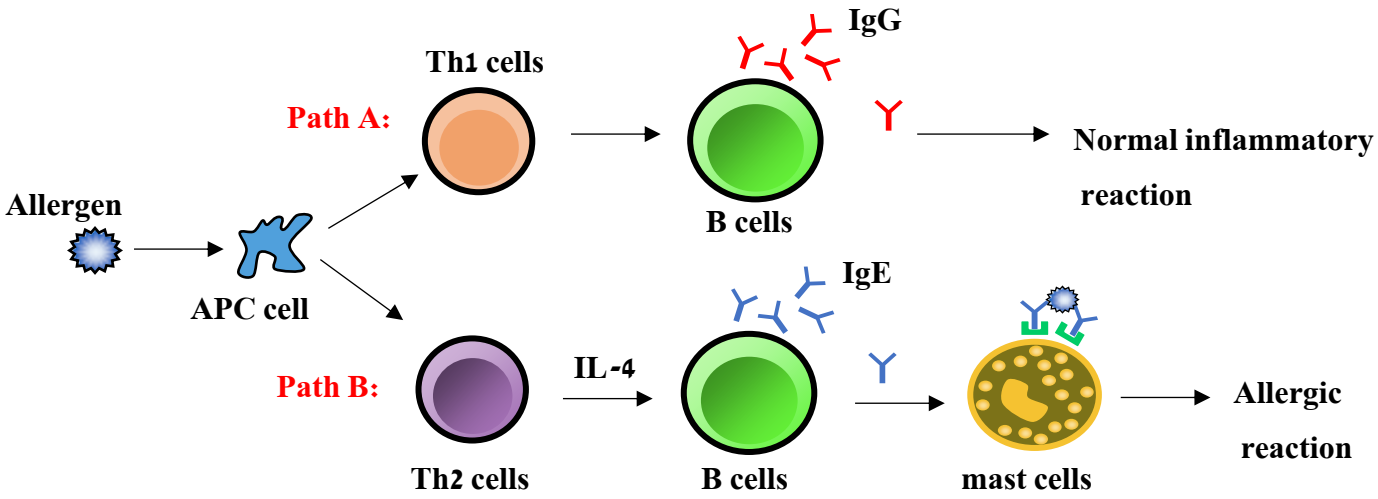


FIGURE 1.2. Biological paths:

Path A: Individuals that will develop a normal response an APC cells activate T cells and force them to differentiate to Th_1 cell that will activate B cells that discharge IgG antibodies and eventually cause a normal inflammatory reaction that is vital to our body in order to cope with foreign factors.

Path B: Individuals that has the hereditary genetic predisposition that triggers the immune system to produce IgE antibodies, APC cells activate T cells and force them to differentiate to Th_2 cells, which activate B cells by using IL-4, discharge IgE antibodies, and causing allergic response that activates mast cells.

CHAPTER 2

A PRIVIOIUS MATHE MATICAL MODEL

The model proposed in this project is based on the work developed by Groß-Metzner-Behn [2] . Although both studies we reviewed are based on dominance of Th2 cells, the Groß-Metzner-Behn[2] study published much later (2010), meaning that it is more relevant to now days. Moreover, after consulting an allergic specialist, the treatment protocols known today are focusing on educating the immune system to take path A[1].

2.1 Modeling Immunotherapy for allergy

2.1.1 Biological framework

The main purpose of the study is to develop a hypothesis on the understanding of immunological treatment of pollen antigens and to explore some of its aspects through mathematical models.

Continuous production of allergen specific antibody in allergic individuals indicates that type I hypersensitivity is an immune memory phenomenon. It is known that Th2 cells promote IgE production, whereas Th1 cells promote IgG production. The observed outcome of immunotherapy may represent a switch from a Th2 dominated memory state to a Th1 dominated one, since Th2 dominance leads to the establishment of IgE production, eventually cause allergic reaction.

T helper cells play a significant role in immune responses to allergenic substances. There are several subtypes of T helper cells, which differ according their cytokine profiles. Immunologists distinguish among four lineages: Th1, Th2, Th17 and T regulatory (Treg) cells.

[1] Discharging IgG antibodies that eventually will cause a normal inflammatory.

Sensitivity is caused by binding IgE antibodies and the cells on the surface of the tissues of the mast cells and the surrounding cells of the basophils. By activating the production of IgE antibodies which provoke the allergic symptoms. According to the

"Th1-Th2 paradigm", the type of immune response depends which of the two populations prevails in the competition of Th1 and Th2 helper cells. T helper cells exists in both allergic and healthy individuals, yet, an allergic response is prevented by the predominance of Th1 cells.

2.1.2 Formulation of Fishman's model equations

(1) $r'_\mu = -\rho r_\mu$
(2) $r'_\eta = a_\eta - \rho r_\eta$
(3) $x'_\mu = x^*_\mu - (1+\theta)x_\mu + \theta x_\eta$
(4) $y'_\mu = y^*_\mu - (1+\theta)y_\mu + \theta y_\eta$
(5) $x'_\eta = f a_\eta \rho + x^*_\eta - (1+\theta)x_\eta + \theta x_\mu$
(6) $y'_\eta = f k a_\eta (1-\rho) + y^*_\eta - (1+\theta)y_\eta + \theta y_\mu$

TABLE 2.1: List of all parameters in Fishman-Segel model

Parameter	Interpretation
x	Th1 cell
y	Th2 cell
r	RC cell
μ	Mucosal cell
η	Non-mucosal cell
*	Activated cell
ρ	RC cell decay rate
θ	Intercompartment migration rate
f	Ratio RC to T memory recruitment
a_η	RC recruitment rate in immunotherapy
k	Relative strength of Th2 vs. Th1 activation

2.1.3 Summary of Fishman-Segel model

It is known that both Th cell maturation and the eventual outcome of the Th1-Th2 cross-regulation are influenced by the microenvironment, as described in equations (3), (4). While it is known that both maturation of Th1-Th2 cells and the cross-regulation between them are influenced by the microenvironment, available evidence indicates that the microenvironment plays a crucial role in recruitment (maturation) of Th cells into Th1 and Th2 subsets.

Thus, they assume that the difference between mucosal and non-mucosal lymphatic tissue can be accounted for by the differences in recruitment, as described in equations (5), (6). In the current model they represent these differences by assuming that the recruitment rates for Th1 versus Th2 cells in the two compartments are different. Equation (1), (2) describes the connections between mucosal and non-mucosal cell to RC cells.

We notice a connection between those cells to the RC recruitment rate in immunotherapy and to the RC cell decay rate.

2.1.4 Treatment process of Fishman-Segel model

Allergen–specific immunotherapy consists a repeated injections of allergens or allergen peptides and aims to induce a state of tolerance in the allergic individual. Through the history there were lots of efforts to explore the immune system according it's reactions, factors, stability states and develop a hypothesis on the understanding of immunological treatment of pollen antigens and to explore some of its aspects through mathematical models.

Successful clinical treatment often involves repeated immunizations of allergic people with low doses of immunosuppressive therapy. The visible results of this treatment are:

1. An increase in the concentration of IgG antibodies during the blood cycle.
2. A slow decrease in IgE concentration in the circulatory system.
3. Suppression of secondary IgE responses after long-term treatment.

As part of their study, they have used IL-2[2] and IFN [3] in order to control the proliferation of Th2 cells, and the dominance of Th1 cells.

IFN influences on activated Th2 cells, such that they can function normally but will not be able to use their IL-4 cytokine[4] and won't proliferation.

[2] (Interleukin) IL- are proteins belonging to cytokine group. IL-2: encourages proliferation of activated Th1 cells.

[3] interferon-γ (IFN): Proteins secreted as a response to invasion of invasive agents such as viruses and bacteria.

[4] IL-4 cytokine causes production and secrete of IgE antibodies.

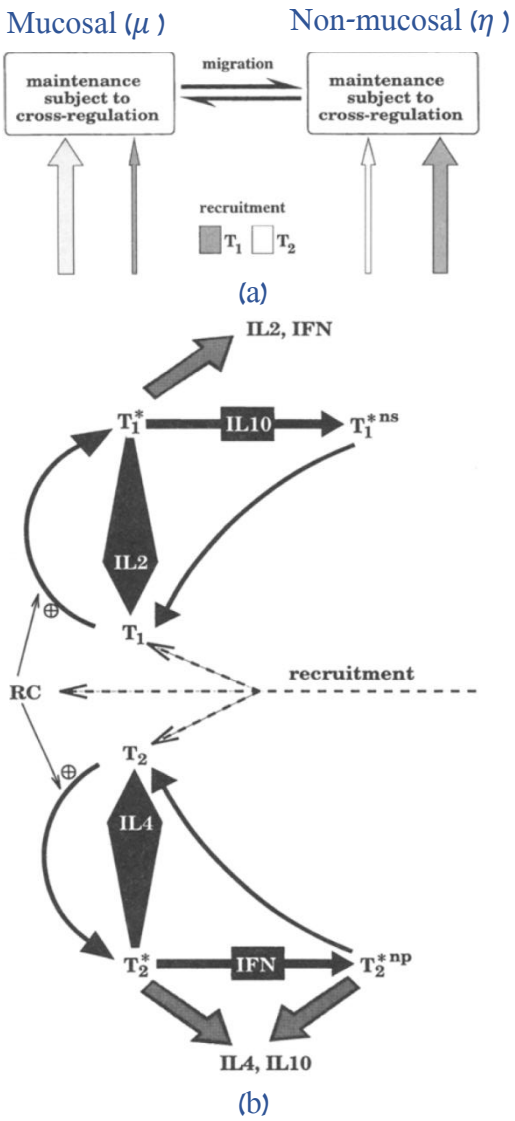


FIGURE 2.1: Th1- Th2-RC connections

(a) There are two compartments one centered on the mucosal (μ) lymph nodes[5] and one centered on non-mucosal (η) lymphatic tissue[6] that are targeted by immunotherapeutic injections. Antigenic challenges directed to compartment μ preferentially yield Th2 cell recruitment.

(b) Single compartment maintenance of (T-cell) memory, subject to Th1-Th2 cross-regulation. Introduction of antigen leads to the recruitment of antigen specific T1 and T2 cells.
Exposure to antigen also promotes recruitment of RC[7]. Interaction between an RC and a T cell induces T-cell activation (sensitization process).

[5] The mucosal lymph compartments noted by μ
[6] The non-mucosal lymphatic tissues noted by η
[7] RC cells are long lived antigen-retaining cells that maintain immune memory by presenting sequestered antigen to memory lymphocytes.

2.2 Th1-Th2-Treg Interactions

2.2.1 Biological framework

Each allergen encounter triggers the proliferation of all types of T helper cells that are specific to the particular allergen. The immune system of an allergic patient is initially in a state in which the proliferation of Th2 cells is favored and not under sufficient control by mechanisms of tolerance.

T helper cells play a significant role in immune responses to allergenic substances. There are several subtypes of T helper cells, which differ according their cytokine profiles. Immunologists distinguish among four lineages: Th1, Th2, Th17 and T regulatory (Treg) cells. By activating the production of IgE antibodies which provoke the allergic symptoms.

According to the "Th1-Th2 paradigm", the type of immune response depends which of the two populations prevails in the competition of Th1 and Th2 helper cells. T helper cells exists in both allergic and healthy individuals, yet, an allergic response is prevented by the predominance of Th1 cells.

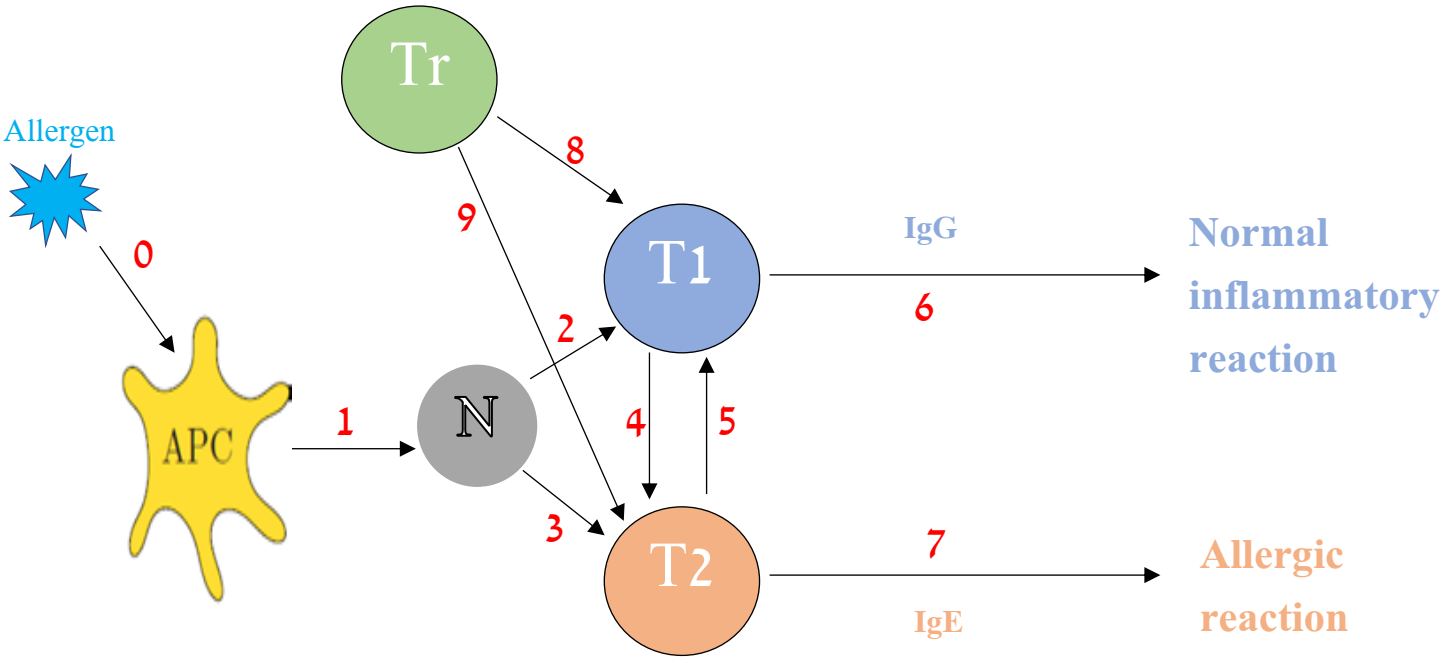


FIGURE 2.2: T cell interaction in response to allergen encounter.

0. Allergen presented by an APC cell

1. APC activates naive T helper cells

2. N cell differentiation to T1.

3. N cell differentiation to T2.

4. Th1 cell suppress Th2. Activated T1 cells secrete IL-2[8] and IFN. IFN influence on T2 which causes that activated T2 cells will function normally but won't be able to use their IL-4, and cytokine [9] therefore won't proliferation.

5. Th2 cell suppress Th1. Activated T2 cells secrete IL-10, that influences on T1 which causes that activated T1 cells will not be able to secrete lymphocytes, so they won't proliferation.

6. Th1 secretes IgG. Dominance of Th1 cells leads to a normal inflammatory reaction.

7. Th2 secrets IgE. Dominance of Th2 cells leads to allergic reaction.

8. Treg cells suppress Th1.

9. Treg cells suppress Th2.

[8] IL-2 encourages proliferation of activated T1 cells.

[9] IL-4 causing production and secrete of IgE antibodies.

2.2.2 Formulation of Treg model equations

The model consists a set of five nonlinear differential equations describing the temporal behavior of five variables: the concentrations of Th1, Th2 and induced Treg cells, the concentration of naive T helper cells (N), and the concentration .

(1) $\dot{N} = -N + \alpha - NA\left(\frac{T_1}{1+\mu_2 T_2} + c\right) - \phi NA(T_2 + c) - xNA(T_r + c)$

(2) $\dot{T_1} = -T_1 + \frac{vNA}{1+\mu_r T_r}\left(\frac{T_1}{1+\mu_2 T_2} + c\right)$

(3) $\dot{T_2} = -T_2 + \phi\frac{vNA}{1+\mu_r T_r}\left(\frac{T_2+c}{1+\mu_1\frac{T_1}{1+\mu_2 T_2}}\right)$

(4) $\dot{T_r} = -T_r + xvNA(T_r + c)$

(5) $\dot{A} = -A(T_1 + T_2 + T_r)$

TABLE 2.2: List of all parameters in Grob-Metzner-Benh model

Parameter	Interpretation
T1	Th1 cell
T2	Th2 cell
N	Naive cell
A	Antigen
μ_1, μ_2, μ_r	the strength of suppression
v	How many differentiated T cells arise from one naive cell
x, θ	account for differences in the autocrine action of the three subsets
α	Naïve cell production

2.2.3 Summary of Grob-Metzner-Behn

The model shows that the deliberately action of Th1 and Treg cells can bring about such a change when repeated injections are given. This result follows from the general assumption that, by means of their cytokines, Th1 and Th2 cells are able to suppress each other.

Initially, when the frequency of activated cells in general is still low, the Treg cells are disadvantaged. Therefore, an allergen injection will induce proliferation mainly of Th2 cells. However, if a second injection is administered before the cell populations have completely died off, the cytokine environment will have changed

after the time of the first injection. Th2 proliferation is then alleviated via the suppressive effect of the cytokines produced by Th1 and Treg cells. The Treg cells start their second round of proliferation under improved conditions, as they are not affected by Th1 and Th2 cytokines.

Repeated injections in short intervals will therefore induce a more and more Treg dominated reaction, that completely prevents the immune response.

2.2.4 Treatment process of Grob-Metzner-Behn

Allergen–specific immunotherapy consists a repeated injections of allergens or allergen peptides and aims to induce a state of tolerance in the allergic individual. In practice, the therapy is performed by starting with very small, innocuous injections which are subsequently increased until a maximum dose is reached. After that, during the maintenance phase, this dose is administered once every four weeks over a period of 3–5 years.

The small initial doses are thought to mainly induce the desensitization of mast cells and basophils, whereas changes at the T cell level are established over weeks or months. Under the assumption that the essential therapeutic effect of immunotherapy is due to a change of the T cell equilibrium, and therefore involves only a small number of different cell types, it should be possible to capture the scenario within a mathematical model.

CHAPTER 3

MOTIVATION AND RELEVANCE OF THE PROJECT

I have chosen to explore this subject from personal reasons. From as far as I can remember myself, I had allergic reaction to almost every medicine given to me. When I was a four months old, I had an ear infection that forced the doctor to give me an antibiotics for a few days. Since I was a baby, they had to give me it in the clinic. When I took the first dose everything was fine, but on the second dose I had anaphylaxis attach. After that the doctors done set of allergy tests and gave my parents a list of prohibited medicine and food.

My story is one out of many. Every year more and more patients are showing allergenic symptoms. Finding more effective treatments for different types of allergies using appropriate mathematical models can change the medicine as we know.

CHAPTER 4

DOSE ALLERGY TREATMENT MODEL

Treg model is based on repeated injections of the allergen, but without any other treatment dose. Our improvement to it is to add another treatment dose that will encourage the system.

That special dose will be counted at the last equation (5) in chapter 2.2.2:

$$\dot{A} = -A(T_1 + T_2 + T_r) + dose$$

Adding this treatment to the system will allow us to control and create a new therapeutic protocols that will ensure that the immune system responses would be normal.

4.1 Formulation of DOSE ALLERGY TREATMENT MODEL

(4.1) $$\dot{N} = -N + \alpha - NA\left(\frac{T_1}{1+\mu_2 T_2} + c\right) - \phi NA(T_2 + c) - xNA(T_r + c)$$

(4.2) $$\dot{T_1} = -T_1 + \frac{vNA}{1+\mu_r T_r}\left(\frac{T_1}{1+\mu_2 T_2} + c\right)$$

(4.3) $$\dot{T_2} = -T_2 + \phi\frac{vNA}{1+\mu_r T_r}\left(\frac{T_2+c}{1+\mu_1\frac{T_1}{1+\mu_2 T_2}}\right)$$

(4.4) $$\dot{T_r} = -T_r + xvNA(T_r + c)$$

(4.5) $$\dot{A} = -A(T_1 + T_2 + T_r) + dose$$

4.2 Immune response dynamic of DOSE ALLERGY TREATMENT MODEL

a) Dynamic of Naïve cells and T cells

We divide this equation to five sections and discuss each section separately:

$$\dot{N} = \underbrace{-N}_{A} + \underbrace{\alpha}_{B} \underbrace{- NA\left(\frac{T_1}{1+\mu_2 T_2} + c\right)}_{C} \underbrace{- \phi NA(T_2 + c)}_{D} \underbrace{- xNA(T_r + c)}_{E}$$

Section A:

Each cell in our body has death rate, therefore we must subtract the cells who died from our equation.

Section B:

While cells have death rate, they are also produced in some rate, here noted as α, we must add it to our equation with positive sign. It can be seen that in the absence of antigen (represents as A) in this dynamic, the naïve cells are still produced in rate α and die accordingly.

Section C:

Naïve cells combine with Th1. When naïve cells combine with one of the three subsets of T cells, the concentration of naïve cells, descent, therefore there must be negative sign before this multiplication that symbolize the connection between those cells.

Those cells combine only due to the presence of antigen, considering it, we multiply our section with A.

The coefficients μ_1, μ_2, μ_r describes the strength of the suppression of one cell on another. While naïve cells combine with Th1 cells, it must be accounted that Th2 suppress Th1, therefore we must consider that. We note this by the division operation: $\frac{T_1}{1+\mu_2 T_2}$. $\mu_2 T_2$ represents part of Th2 cells that have even strength to suppress Th1 cells.

Section D:

The coefficient ϕ consider the autocrine action[10] in Th2 cells. In this section we account this and multiply ϕ with N and Th2, as well remember that due to the presence of antigen Th2 cell combine with native cell, we multiply our section in A.

Section E:

The coefficient x consider the autocrine action in Treg cells. In this section we account this and multiply x with N and Tr, as well remember that due to the presence of antigen Treg cell combine with native cell, we multiply our section in A.

Combing these sections leads to the following equation:

$$\dot{N} = -N + \alpha - NA\left(\frac{T_1}{1+\mu_2 T_2} + c\right) - \phi NA(T_2 + c) - xNA(T_r + c)$$

[10] Autocrine action is a form of cell signaling in which a cell secretes a hormone that binds to autocrine receptors on that same cell, leading to changes in the cell.

b) Dynamic of Th1 cells

We divide this equation to two sections and discuss each section separately:

$$\dot{T_1} = \underbrace{-T_1}_{A} + \underbrace{\frac{vNA}{1+\mu_r T_r}\left(\frac{T_1}{1+\mu_2 T_2} + c\right)}_{B}$$

Section A:

Each cell in our body has death rate, therefore we must subtract the cells who died from our equation.

Section B:

Considering how many differentiated T cells arise from one naive cell, we multiply v with N.

We also consider that Th1 combine with N cell if there is presence of antigen, so we multiply with A.

Also, this connection influenced by the suppression of both Th2 and Treg cells, therefore we multiply with $\left(\frac{1}{1+\mu_r T_r}\right)$ and $\left(\frac{1}{1+\mu_2 T_2}\right)$ our multiplication.

Finally, we multiply with Th1, that symbolize the connection between naïve cell to Th1 cell.

All these factors together increasing the concentration of Th1 cells, therefore the sign of section B is positive.

The mechanism of these sections leads to the following equation:

$$\dot{T_1} = -T_1 + \frac{vNA}{1+\mu_r T_r}\left(\frac{T_1}{1+\mu_2 T_2} + c\right)$$

c) Dynamic of Th2 cells

We divide this equation to two sections and discuss each section separately:

$$\dot{T_2} = \underbrace{-T_2}_{A} + \underbrace{\phi \frac{vNA}{1+\mu_r T_r}\left(\frac{T_2 + c}{1+\frac{\mu_1 T_1}{1+\mu_2 T_2}}\right)}_{B}$$

Section A:

Each cell in our body has death rate, therefore we must subtract the cells who died from our equation.

Section B:

Considering how many differentiated T cells arise from one naive cell, we multiply v with N.

We also consider that Th2 combine with N cell if there is presence of antigen, so we multiply with A.

Also, this connection influenced by the suppression of both Th1 and Treg cells, therefore we multiply with $\left(\frac{1}{1+\mu_r T_r}\right)$ and $\left(\frac{1}{1+\frac{\mu_1 T_1}{1+\mu_2 T_2}}\right)$ our multiplication. Recall that Th1 cells influenced by Th2 cells , we divide $(\mu_1 T_1)$ with $(1+\mu_2 T_2)$.

The coefficient ϕ consider the autocrine action in Th2 cells, so we multiply our section with ϕ .

Finally, we multiply with Th2, that symbolize the connection between naïve cell to Th2 cell.

All these factors together increasing the concentration of Th2 cells, therefore the sign of section B is positive.

The mechanism of these sections leads to the following equation:

$$\dot{T_2} = -T_2 + \phi \frac{vNA}{1+\mu_r T_r}\left(\frac{T_2 + c}{1+\mu_1 \frac{T_1}{1+\mu_2 T_2}}\right)$$

d) Dynamic of Treg cells

We divide this equation to two sections and discuss each section separately:

$$\dot{T_r} = \underbrace{-T_r}_{A} + \underbrace{xvNA(T_r + c)}_{B}$$

Section A:

Each cell in our body has death rate, therefore we must subtract the cells who died from our equation.

Section B:

Treg cells are not influenced by Th1 and Th2 therefore we will not account them in this dynamic, however while considering how many T cells differentiated from one naive cell, we multiply v with N.

We also consider that Treg cell combine with N cell if there is presence of antigen, so we multiply with A.

The coefficient x consider the autocrine action in Treg cells, so we multiply our section with x .

Finally, we multiply with Tr, that symbolize the connection between naïve cell to Treg cell.

All these factors together increasing the concentration of Treg cells, therefore the sign of section B is positive.

The mechanism of these sections leads to the following equation:

$$\dot{T_r} = -T_r + xvNA(T_r + c)$$

e) Dynamic of antigen

We divide this equation to two sections and discuss each section separately:

$$\dot{A} = \underbrace{-A(T_1 + T_2 + T_r)}_{A} + \underbrace{dose}_{B}$$

Section A:

Assuming that the antigen invaded the system is solely influenced by the immune system cells, the concentration of an antigen in our system descents and changes this dynamics.

The sign of section A is negative because when a foreign factor invades our system, the goal of the immune system is to identify and eliminate this factor.

Section B:

The improvement of Grob-Metzner-Behn model[2], is reflected in this section. We added 'dose' with positive sign since we are inducing the system with biological substance that will help the immune system fight the antigen.

The mechanism of these sections leads to the following equation:

$$\dot{A} = -A(T_1 + T_2 + T_r) + dose$$

4.3 Desirable results

It is not yet known why some individuals has the tendency to choose Path B, but it seems that in those individuals the outcome is obvious. In order to help those individuals, we are inducing the system with treatment.

Our desirable result will be a successful clinical treatment, that will involve repeated injections in low doses (as possible) of treatment.

Our study involved in the interactions of Treg and Th1-Th2 cells, therefore we are expecting to see increase in the concentration of Treg cells. Also, after a year of treatment, we are expecting to see the dominance of Treg cells.

Our main goal is to educate the individual immune system to choose Path A instead of Path B, meaning to embrace normal inflammatory reactions, that the individual may not even notice happing in its body.

CHAPTER 5

STABILITY ANALYSIS OF DOSE ALLERGY TREATMENT MODEL

Our model contains five non-linear equations, due to the complexity of the calculation, we will review solution X solely. Our analysis will present first the equations of the model, then calculation of the partial derivatives, then calculation of the Jacobian, finding the eigenvalues, and finally determine if the solution X is stable or not.

$$X = \{ (N, T_1, T_2, T_r, A) = (\alpha, 0,0,0,0) \}$$

5.1 DOSE ALLERGY TREATMENT MODEL equations

(6.1) $F_1 = -N + \alpha - NA\left(\frac{T_1}{1+\mu_2 T_2} + c\right) - \phi NA(T_2 + c) - xNA(T_r + c)$

(6.2) $F_2 = -T_1 + \frac{vNA}{1+\mu_r T_r}\left(\frac{T_1}{1+\mu_2 T_2} + c\right)$

(6.3) $F_3 = -T_2 + \phi\frac{vNA}{1+\mu_r T_r}\left(\frac{T_2+c}{1+\mu_1\frac{T_1}{1+\mu_2 T_2}}\right)$

(6.4) $F_4 = -T_r + xvNA(T_r + c)$

(6.5) $F_5 = -A(T_1 + T_2 + T_r) + dose$

5.2 Calculation of the partial derivatives

$$\frac{\partial F_1}{\partial N} = -1 - A\left(\frac{T_1}{1+\mu_2 T_2} + c\right) - \phi A(T_2 + c) - xA(T_r + c)$$

$$\frac{\partial F_1}{\partial T_1} = -\frac{NA}{1+\mu_2 T_2}$$

$$\frac{\partial F_1}{\partial T_2} = -\phi NA + \frac{NAT_1}{(1+\mu_2 T_2)^2}\mu_2$$

$$\frac{\partial F_1}{\partial T_r} = -xNA$$

$$\frac{\partial F_1}{\partial A} = -N\left(\frac{T_1}{1+\mu_2 T_2} + c\right) - \phi N(T_2 + c) - xN(T_r + c)$$

$$\frac{\partial F_2}{\partial N} = \frac{vA}{1+\mu_r T_r}\left(\frac{T_1}{1+\mu_2 T_2} + c\right)$$

$$\frac{\partial F_2}{\partial T_1} = -1 + \frac{vNA}{(1+\mu_r T_r)(1+\mu_2 T_2)}$$

$$\frac{\partial F_2}{\partial T_2} = -\frac{vNAT_1\mu_2}{(1+\mu_r T_r)(1+\mu_2 T_2)^2}$$

$$\frac{\partial F_2}{\partial T_r} = -\frac{vNA\mu_r}{(1+\mu_r T_r)^2}\left(\frac{T_1}{1+\mu_2 T_2} + c\right)$$

$$\frac{\partial F_2}{\partial A} = \frac{vN}{1+\mu_r T_r}\left(\frac{T_1}{1+\mu_2 T_2} + c\right)$$

$$\frac{\partial F_3}{\partial N} = \frac{\phi vA}{1+\mu_r T_r}\left(\frac{T_2+c}{1+\frac{\mu_1 T_1}{1+\mu_2 T_2}}\right)$$

$$\frac{\partial F_3}{\partial T_1} = -\frac{\phi vNA}{1+\mu_r T_r}\left(\frac{T_2+c}{\left(1+\frac{\mu_1 T_1}{1+\mu_2 T_2}\right)^2}\right)\left(\frac{\mu_1}{1+\mu_{2T_2}}\right)$$

$$\frac{\partial F_3}{\partial T_2} == -1 + \frac{\phi vNA}{1+\mu_r T_r}\left(\frac{c\left(1+\frac{\mu_1 T_1}{1+\mu_2 T_2}\right) - (T_2+c)\left(\frac{-\mu_1 T_1 \mu_2}{(1+\mu_2 T_2)^2}\right)}{\left(1+\frac{\mu_1 T_1}{1+\mu_2 T_2}\right)^2}\right)$$

$$\frac{\partial F_3}{\partial T_r} = -\frac{\phi vNA\mu_r}{(1+\mu_r T_r)^2}\left(\frac{T_2+c}{1+\frac{\mu_1 T_1}{1+\mu_2 T_2}}\right)$$

$$\frac{\partial F_3}{\partial A} = \frac{\phi v N}{1+\mu_r T_r}\left(\frac{T_2+c}{1+\frac{\mu_1 T_1}{1+\mu_2 T_2}}\right)$$

$$\frac{\partial F_4}{\partial N} = xvA(T_r + c)$$

$$\frac{\partial F_4}{\partial T_1} = 0$$

$$\frac{\partial F_4}{\partial T_2} = 0$$

$$\frac{\partial F_4}{\partial T_r} = xvNA - 1$$

$$\frac{\partial F_4}{\partial A} = xvN(T_r + c)$$

$$\frac{\partial F_5}{\partial N} = 0$$

$$\frac{\partial F_5}{\partial T_1} = -A$$

$$\frac{\partial F_5}{\partial T_2} = -A$$

$$\frac{\partial F_5}{\partial T_r} = -A$$

$$\frac{\partial F_5}{\partial A} = -(T_1 + T_2 + T_r) + dose^*$$

Considering that dose is a parameter dependent on A, we define: $\frac{\partial (dose)}{\partial A} = dose^*$

5.3 Calculation of the Jacobian

$$J = \begin{pmatrix} \frac{\partial F_1}{\partial N} & \frac{\partial F_1}{\partial T_1} & \frac{\partial F_1}{\partial T_2} & \frac{\partial F_1}{\partial T_r} & \frac{\partial F_1}{\partial A} \\ \frac{\partial F_2}{\partial N} & \frac{\partial F_2}{\partial T_1} & \frac{\partial F_2}{\partial T_2} & \frac{\partial F_2}{\partial T_r} & \frac{\partial F_2}{\partial A} \\ \frac{\partial F_3}{\partial N} & \frac{\partial F_3}{\partial T_1} & \frac{\partial F_3}{\partial T_2} & \frac{\partial F_3}{\partial T_r} & \frac{\partial F_3}{\partial A} \\ \frac{\partial F_4}{\partial N} & \frac{\partial F_4}{\partial T_1} & \frac{\partial F_4}{\partial T_2} & \frac{\partial F_4}{\partial T_r} & \frac{\partial F_4}{\partial A} \\ \frac{\partial F_5}{\partial N} & \frac{\partial F_5}{\partial T_1} & \frac{\partial F_5}{\partial T_2} & \frac{\partial F_5}{\partial T_r} & \frac{\partial F_5}{\partial A} \end{pmatrix}$$

Searching the stability of solution X[11]:

$$\begin{pmatrix} \frac{\partial F_1}{\partial N} \\ \frac{\partial F_1}{T_1} \\ \frac{\partial F_1}{\partial T_2} \\ \frac{\partial F_1}{\partial T_r} \\ \frac{\partial F_1}{\partial A} \end{pmatrix} = \{\text{substitute: } (N, T_1, T_2, T_r, A) = (\alpha, 0,0,0,0) \} = \begin{pmatrix} -1 \\ 0 \\ 0 \\ 0 \\ -\alpha c(\phi + x) \end{pmatrix}$$

$$\begin{pmatrix} \frac{\partial F_2}{\partial N} \\ \frac{\partial F_2}{T_1} \\ \frac{\partial F_2}{\partial T_2} \\ \frac{\partial F_2}{\partial T_r} \\ \frac{\partial F_2}{\partial A} \end{pmatrix} = \{\text{substitute: } (N, T_1, T_2, T_r, A) = (\alpha, 0,0,0,0) \} = \begin{pmatrix} 0 \\ -1 \\ 0 \\ 0 \\ v\alpha c \end{pmatrix}$$

[11] $X = \{(N, T_1, T_2, T_r, A) = (\alpha, 0,0,0,0)\}$

$$\begin{pmatrix} \frac{\partial F_3}{\partial N} \\ \frac{\partial F_3}{T_1} \\ \frac{\partial F_3}{\partial T_2} \\ \frac{\partial F_3}{\partial T_r} \\ \frac{\partial F_3}{\partial A} \end{pmatrix} = \{\text{substitute: } (N, T_1, T_2, T_r, A) = (\alpha, 0,0,0,0) \} = \begin{pmatrix} 0 \\ 0 \\ -1 \\ 0 \\ \phi v \alpha c \end{pmatrix}$$

$$\begin{pmatrix} \frac{\partial F_4}{\partial N} \\ \frac{\partial F_4}{T_1} \\ \frac{\partial F_4}{\partial T_2} \\ \frac{\partial F_4}{\partial T_r} \\ \frac{\partial F_4}{\partial A} \end{pmatrix} = \{\text{substitute: } (N, T_1, T_2, T_r, A) = (\alpha, 0,0,0,0) \} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ -1 \\ x v \alpha c \end{pmatrix}$$

$$\begin{pmatrix} \frac{\partial F_5}{\partial N} \\ \frac{\partial F_5}{T_1} \\ \frac{\partial F_5}{\partial T_2} \\ \frac{\partial F_5}{\partial T_r} \\ \frac{\partial F_5}{\partial A} \end{pmatrix} = \{\text{substitute: } (N, T_1, T_2, T_r, A) = (\alpha, 0,0,0,0) \} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ dose^* \end{pmatrix}$$

Substituting these vectors in the Jacobian:

$$J = \begin{pmatrix} -1 & 0 & 0 & 0 & -\alpha c(1 + \phi + x) \\ 0 & -1 & 0 & 0 & v \alpha c \\ 0 & 0 & -1 & 0 & \phi v \alpha c \\ 0 & 0 & 0 & -1 & x v \alpha c \\ 0 & 0 & 0 & 0 & dose^* \end{pmatrix}$$

5.4 Finding characteristic equation: $|\lambda I - J| = 0$

$$\begin{pmatrix} \lambda+1 & 0 & 0 & 0 & -\alpha c(1+\phi+x) \\ 0 & \lambda+1 & 0 & 0 & v\alpha c \\ 0 & 0 & \lambda+1 & 0 & \phi v\alpha c \\ 0 & 0 & 0 & \lambda+1 & xv\alpha c \\ 0 & 0 & 0 & 0 & \lambda - dose^* \end{pmatrix} = 0$$

5.5 Finding eigenvalues:

$$(\lambda - dose^*)(\lambda+1)^4 = 0$$

$$\lambda_1 = dose^*,\ \lambda_2 = \lambda_3 = \lambda_4 = \lambda_5 = -1$$

Case 1: $dose^* < 0$

Dose represents concentration of biological substance.

It must be zero or greater than zero.

This case is a contradiction to the definition of dose.

Case 2: $dose^* = 0$

This case is the basis of this project.[12]

In the lack of treatment Th2 cells dominates the system and an allergic reaction occurs, and the system is not balanced, here solution X is not stable, however it is irrelevant since the purpose of this project was to induce the system with treatment.

Case 3: $dose^* > 0$

In this case all the eigenvalues are negative, meaning solution X is stable.

[12] Review simulation 0 in page

CHAPTER 6

NUMERICAL SIMULATIONS OF DOSE ALLERGY TREATMENT MODEL

6.1 Methodology[13]

Matlab is a programming package specifically designed for quick and easy scientific calculations and I/O. It has literally hundreds of built-in functions for a wide variety of computations and many toolboxes designed for specific research disciplines, including statistics, optimization, solution of partial differential equations, data analysis.

6.2 Matlab files

6.2.1 ode_system.m file

```
function dy= ode_system(t,y)

global x m4 a v p m1 m2 c dose ;
dy(1)=-y(1)+a-y(1)*y(5)*(y(2)/(1+m2*y(3))+c)-p*y(1)*y(5)*(y(3)+c)-
x*y(1)*y(5)*(y(4)+c);
dy(2)=-y(2)+(v*y(1)*y(5)/(1+m4*y(4)))*(y(2)/(1+m2*y(3))+c);
dy(3)=-y(3)+p*(v*y(1)*y(5)/(1+m4*y(4)))*((y(3)+c)/(1+((m1*y(2))/(1+m2*y(3)))));
dy(4)=-y(4)+x*v*y(1)*y(5)*(y(4)+c);
dy(5)=-y(5)*(y(2)+y(3)+y(4))+dose;
dy=dy';

end
```

[13] All numerical simulations done by Matlab.

6.2.2 ode_system_treatment.m file

```
clear all
clc
global x m4 a v p m1 m2 c dose special_Dose;
x=0.8; m4=0.25; a=10; v=8; p=1.02; m1=0.2;
m2=0.1; c=1e-4; dose=10; special_Dose=10;

%% time scaling
t0=0; tf=23; % number of hours a day
step=1; % sample the results once in an hour
tspan=t0:step:tf;
Days=90; % total amount of days
% global N T1 T2 Tr A  %********

%% solution of equations
yy1=[a 0.002 0.01 0.003 500000]; % starter guess
t1=[];
y1=[];
for i=1:Days % number of days we want to look at
    k=mod(i,2); %give treatment every two days
    if(k==0)
    special_Dose=special_Dose+(0.5);
    dose=special_Dose;
    else
    dose=0;
    end

  y0=yy1(end,:); % starting condition for the solutions
  [tt1,yy1]=ode45(@ode_system,tspan,y0);
  y1=[y1; yy1]; % creating a constant solution
  t1=[t1,length(tspan)*(i-1)+1:length(tspan)*i];

end
```

```
%% plotting
figure(1)
plot(t1',y1(:,2:4));
grid on
legend('T1','T2','Tr');
xlabel('time (days)');
ylabel('concentration');
set(gca, 'YScale', 'log')
```

6.3 Matlab simulations

In all simulations, the first dose was given at the beginning of the calculation.

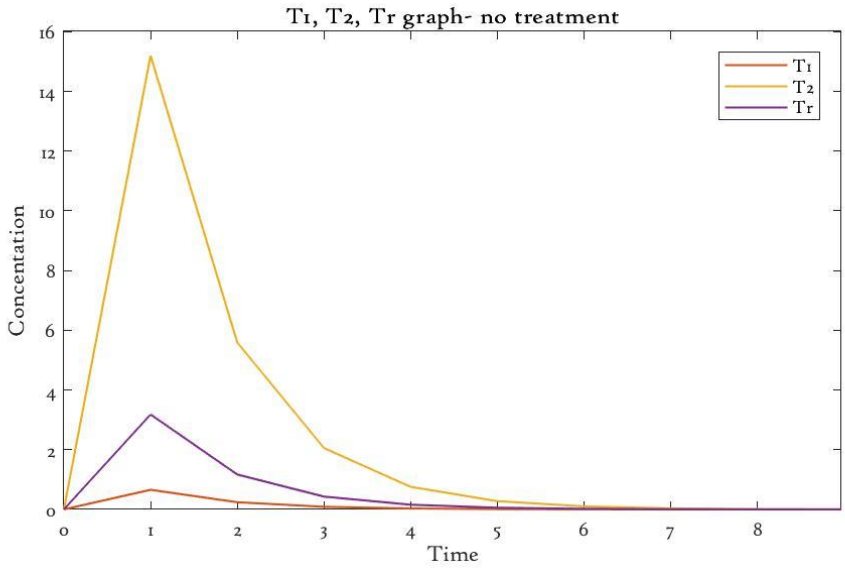
Simulations 1-17 tested within 8 days. Simulations 18-21 tested within 30 days. Simulations 22-33 tested within 90 days. Simulations 24-25 tested within 180 days. Simulation 26 tested within 270 days. Simulation 27 tested within 370 days. Simulation 28 tested within 540 days.

In simulations 1-3 the next dose given every 7 days and in simulations 4-6 the next dose given every 5 days, meaning one special doses in the tested period of time. In simulations 7-9 the next dose given every 3 days, meaning two special doses in the tested period of time. In simulations 10-17 the next dose given every 2 days meaning three special doses in the tested period of time.

In simulations 18-28 the special doses are given every two days.

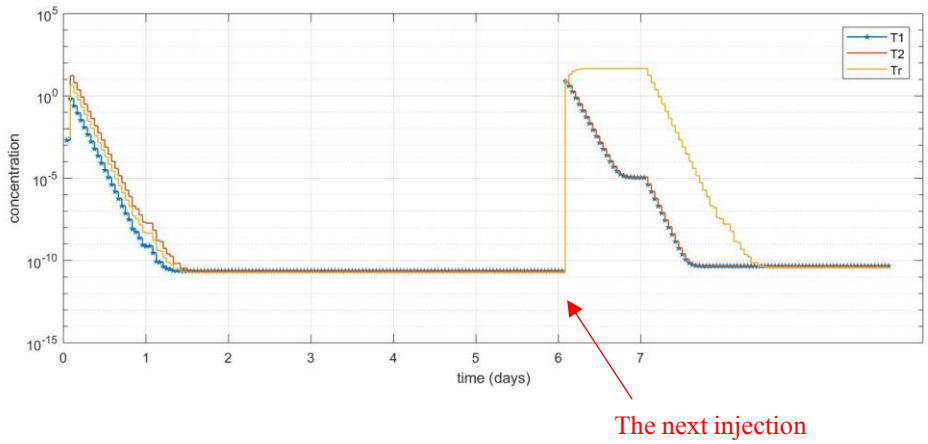
Our goal is to obtain a balanced system between injections[14], therefore we are increasing the special dose in every treatment in a constant value. After testing a full year, we will present 18 months prediction[15], that will prove that the treatment helped our patients. We will call a treatment sufficient it successfully produced a balanced system between injections.

Simulation number 0: Here we can see that without any treatment (meaning dose=0), T2 dominates the system, and allergic reaction occurs.

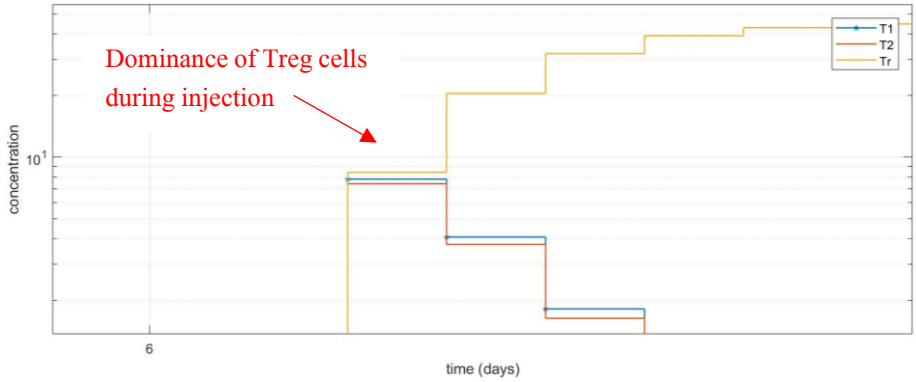


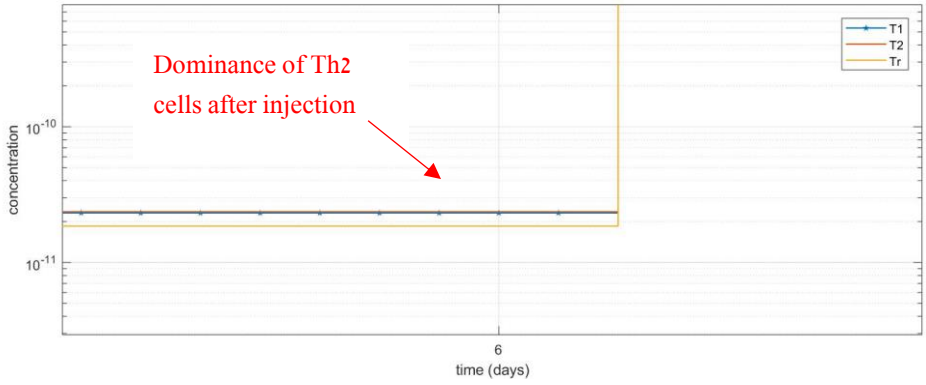
[14] Meaning to achieve higher levels of Treg cells than Th2 and Th1 cells at each point at the period of time tested.
[15] Simulation 28.

Simulation number 1: The treatment given after 7 days. Initial special dose given is 0.5g. Increasing dose: 0.01g.

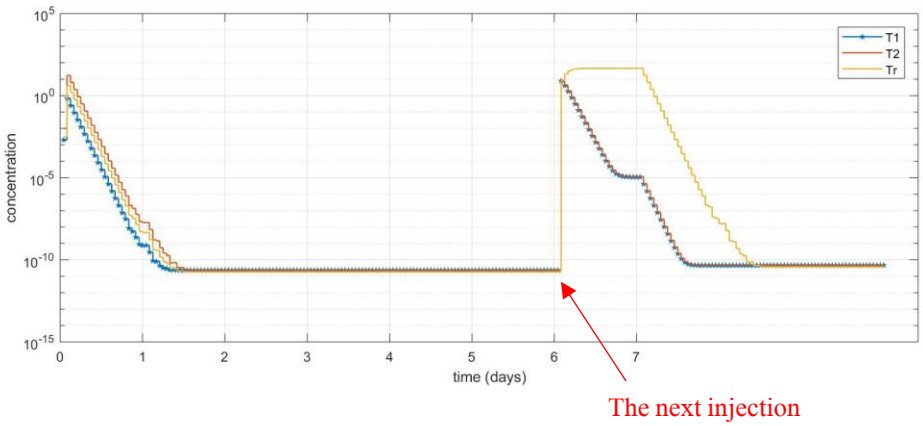


Zoom:

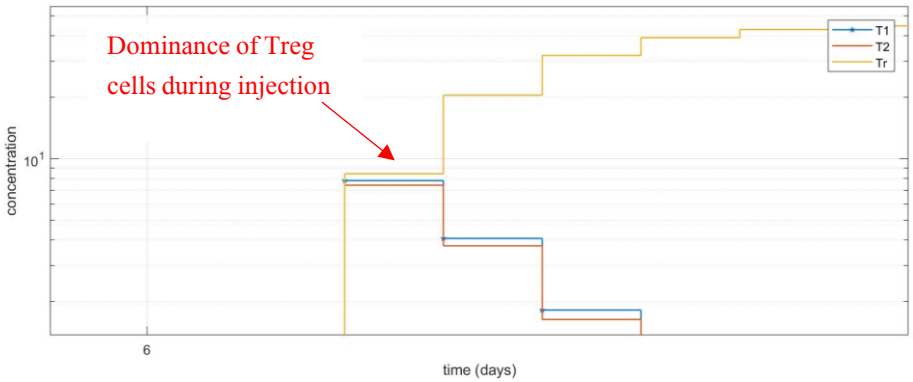


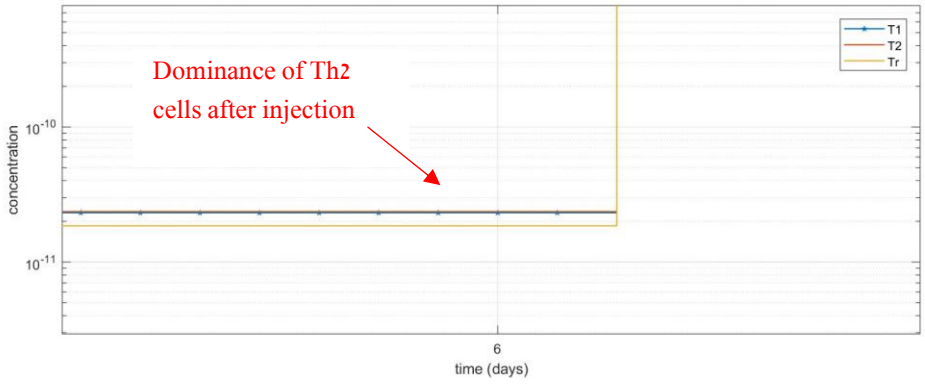


Simulation number 2: The treatment given after 7 days. Initial special dose given is 1.7g. Increasing dose: 0.01g.

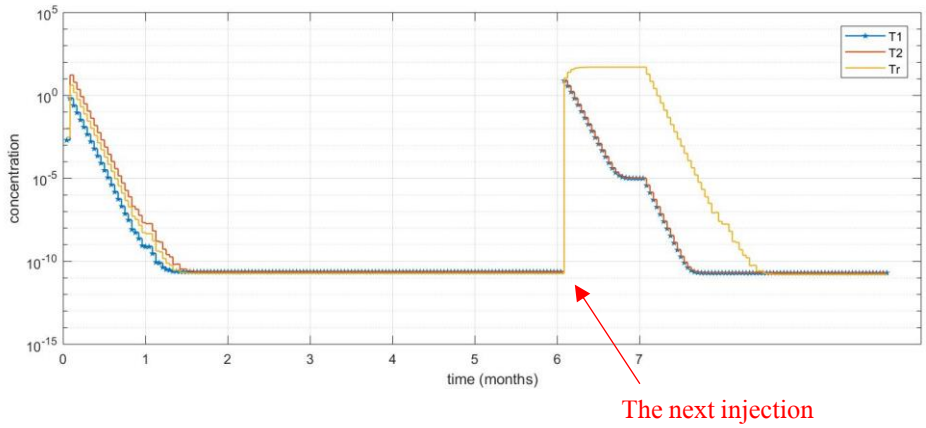


Zoom:

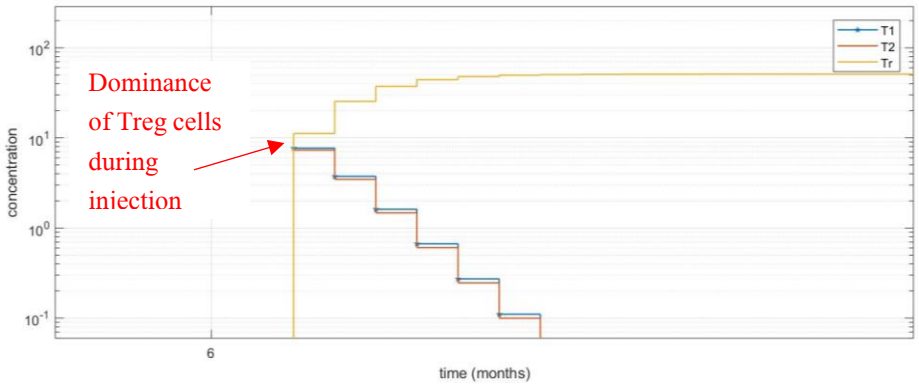


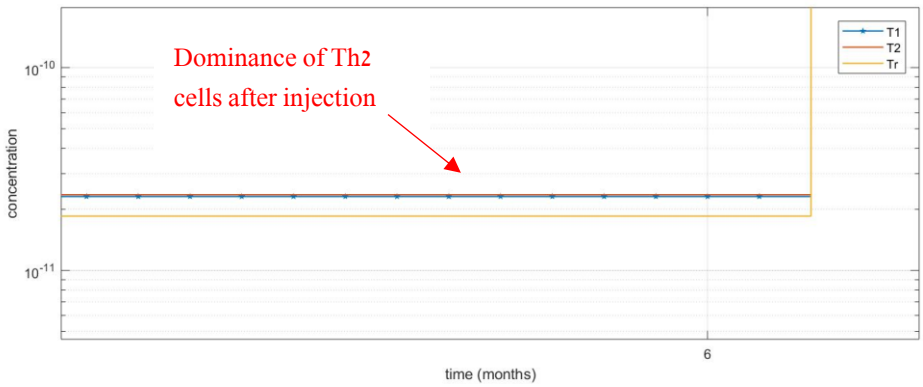


Simulation number 3: The treatment given after 7 days. Initial special dose given is 1.7g. Increasing dose: 0.5g.

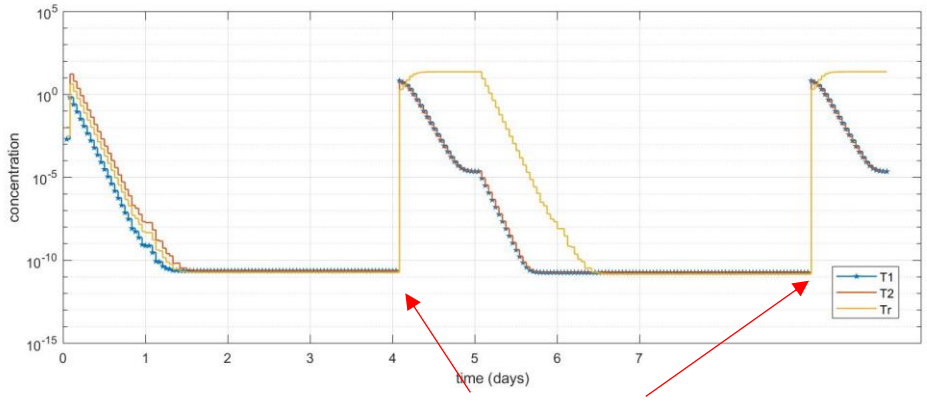


Zoom:

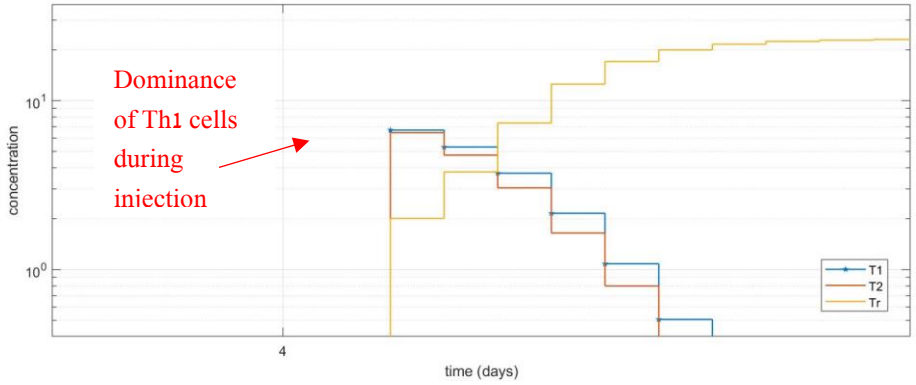


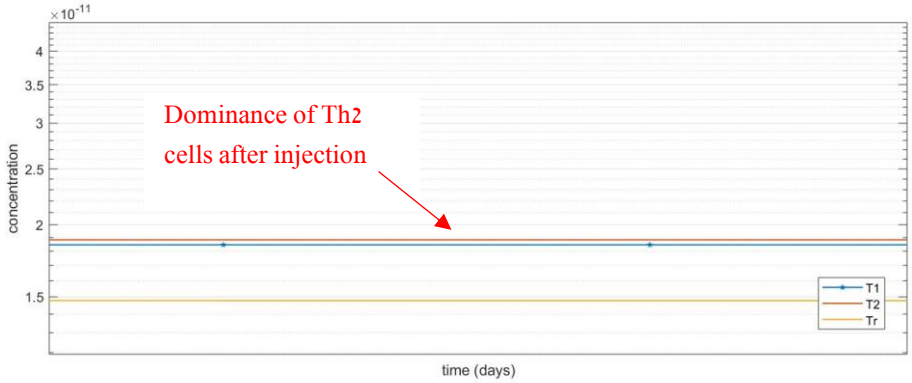


Simulation number 4: The treatment given after 5 days. Initial special dose given is 0.5g. Increasing dose: 0.01g.

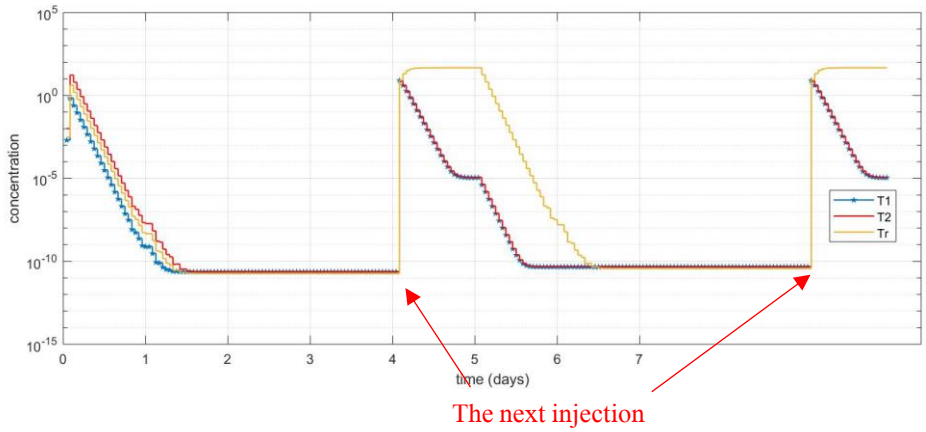


The next injection

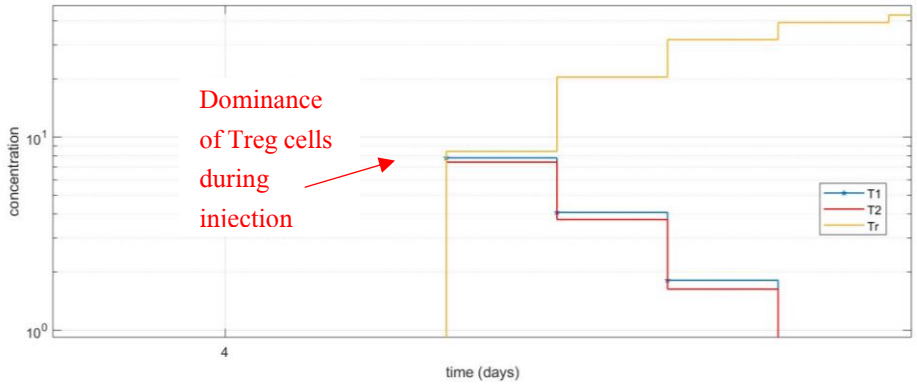


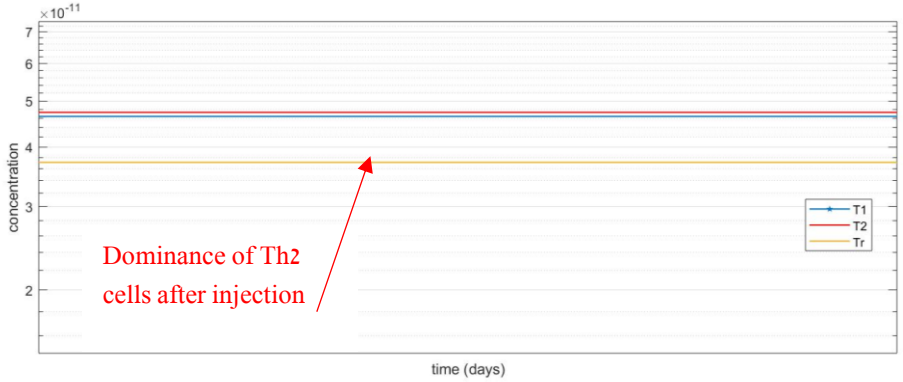


Simulation number 5: The treatment given after 5 days. Initial special dose given is 1.7g. Increasing dose: 0.01g.

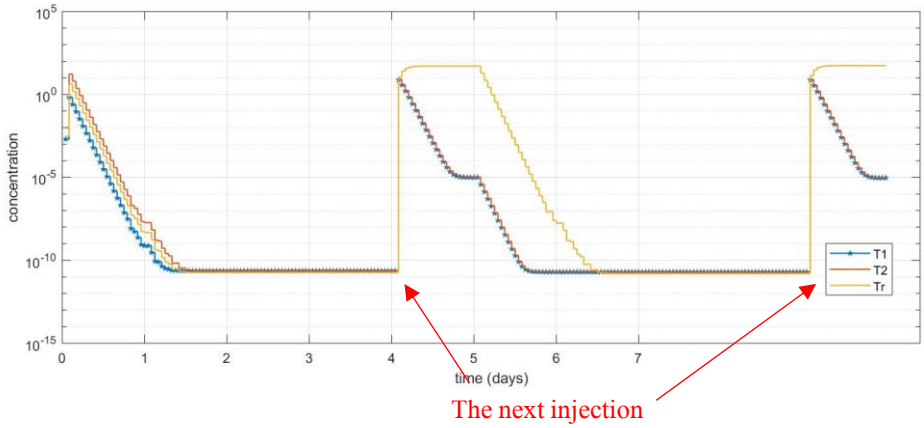


Zoom:

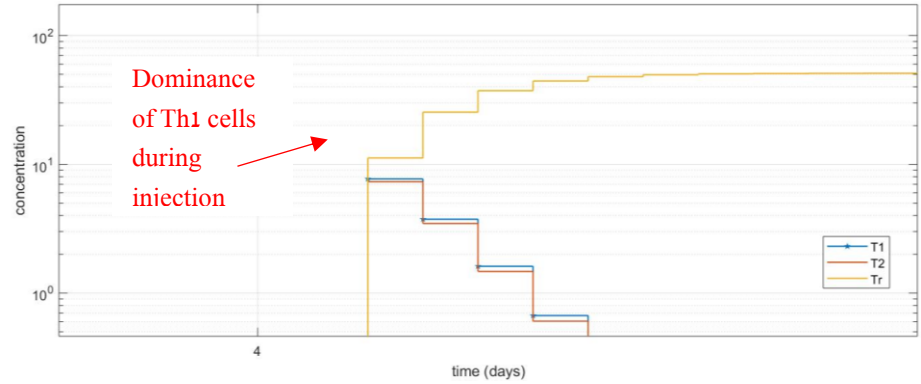


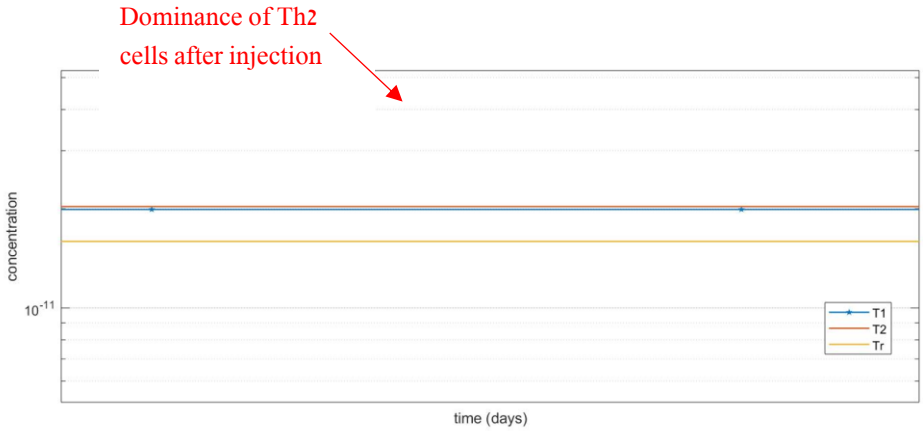


Simulation number 6: The treatment given after 5 days. Initial special dose given is 1.7g. Increasing dose: 0.5g.

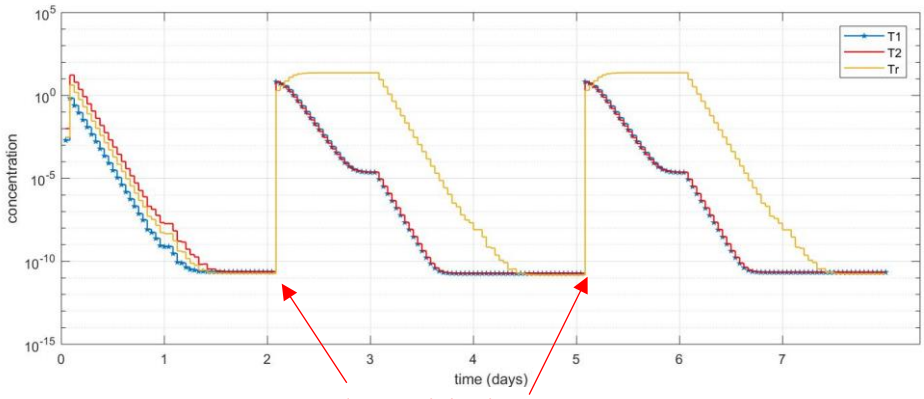


Zoom:





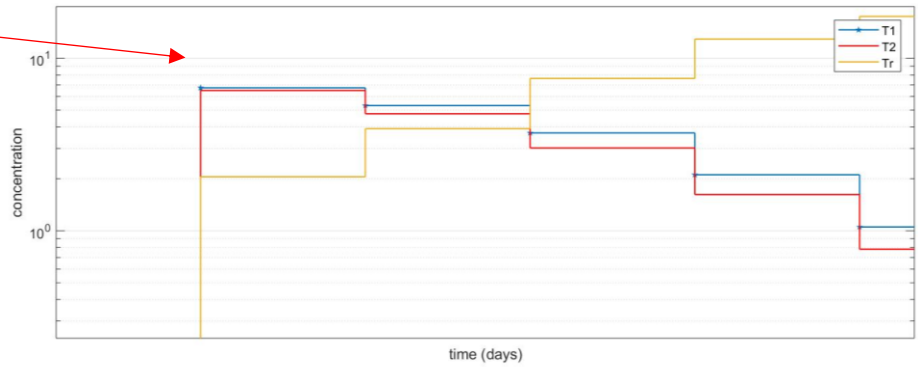
Simulation number 7: The treatment given after 3 days. Initial special dose given is 0.5g. Increasing dose: 0.01g



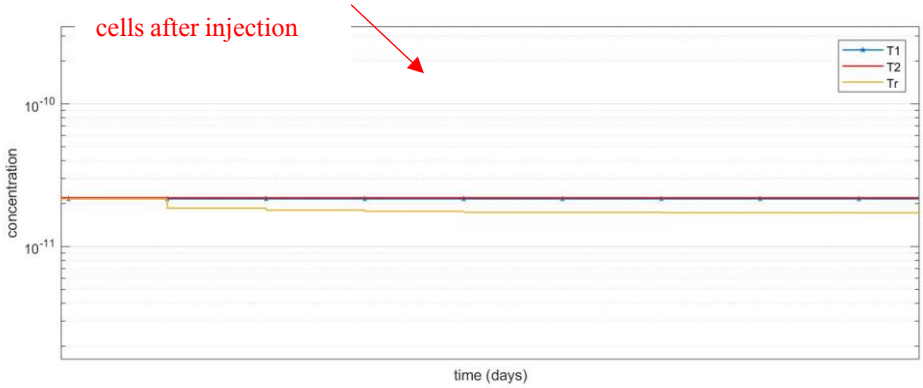
Zoom:

The next injection

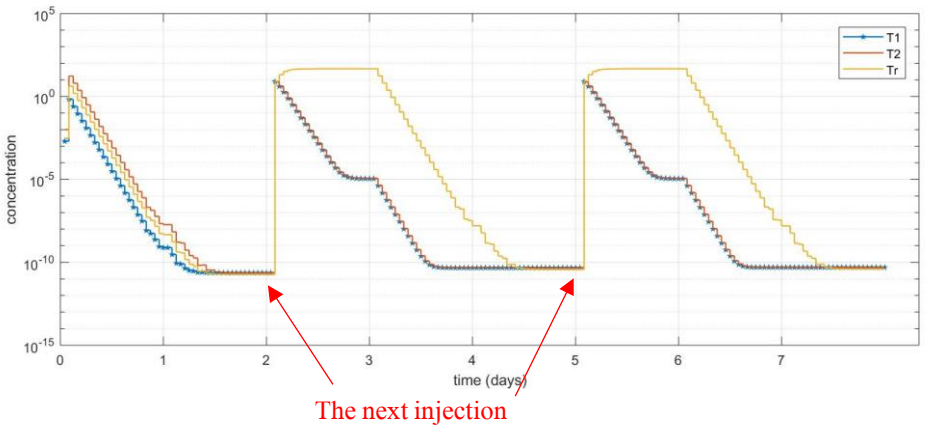
Dominance of Th1 cells during iniection



Dominance of Th2 cells after injection

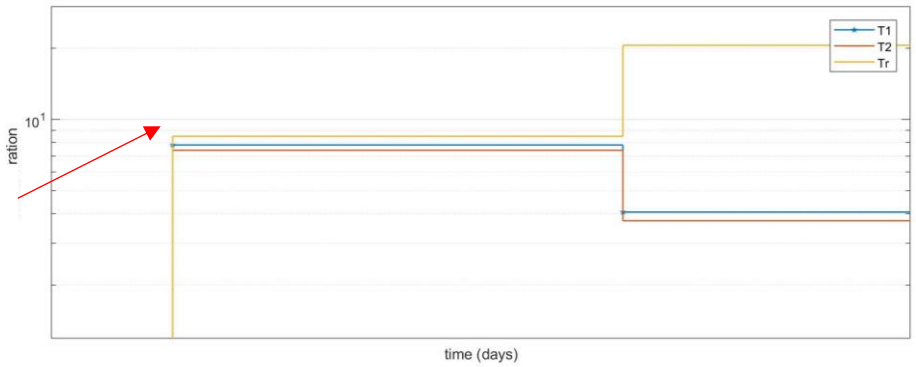


Simulation number 8: The treatment given after 3 days. Initial special dose given is 1.7g. Increasing dose: 0.01g



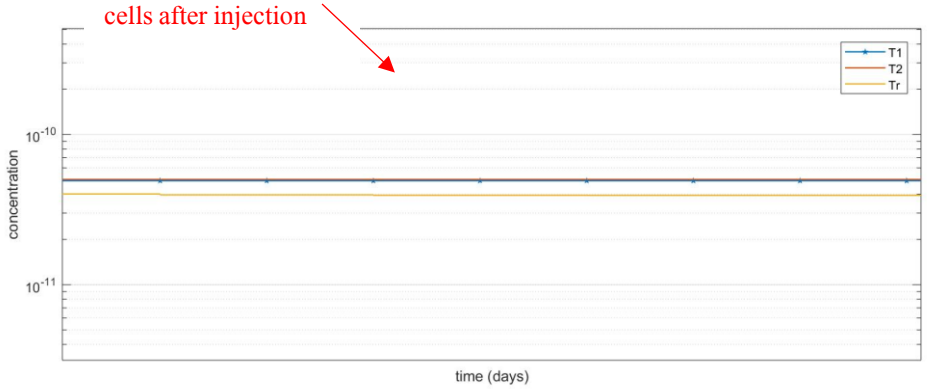
The next injection

Zoom:

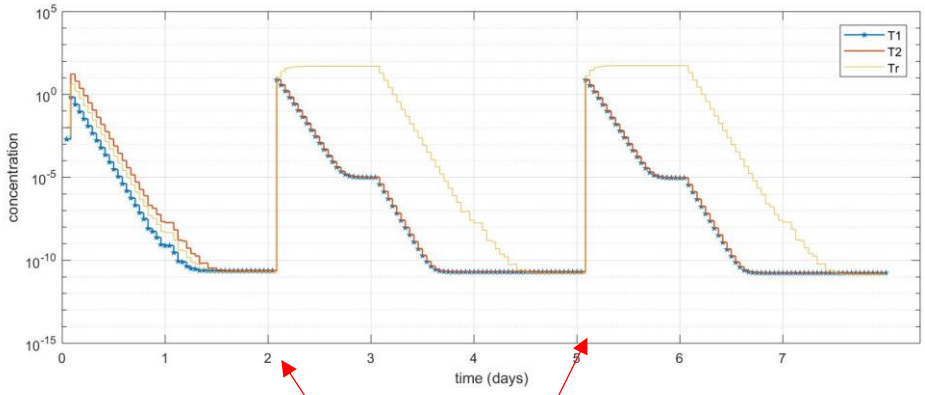


Dominance of Treg cells during iniection

Dominance of Th2 cells after injection



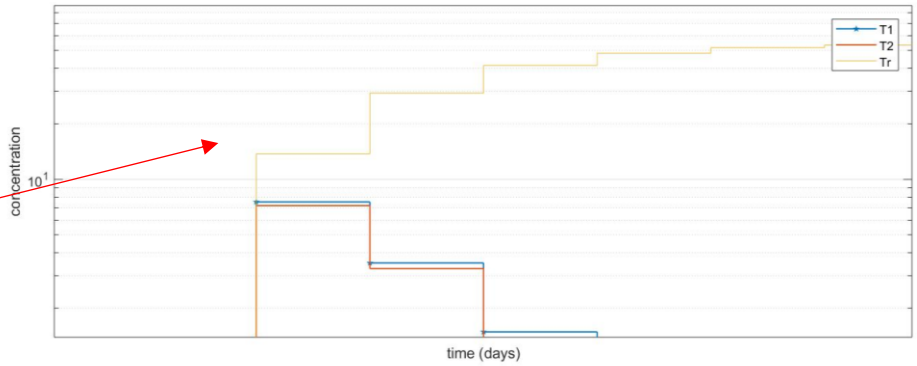
Simulation number 9: The treatment given after 3 days. Initial special dose given is 1.7g. Increasing dose: 0.5g



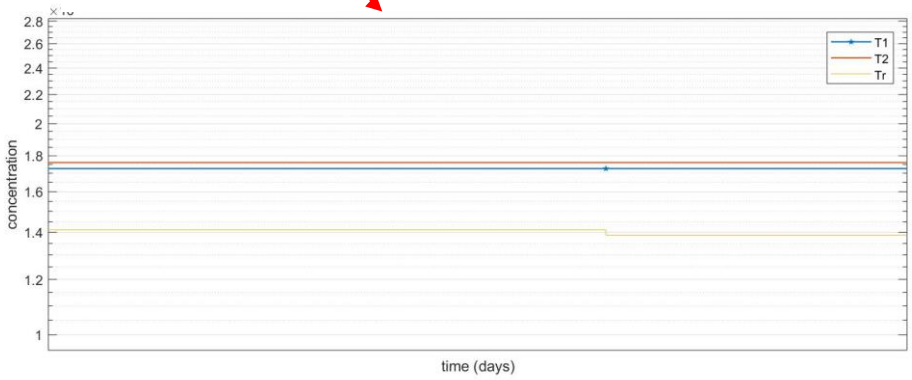
The next injection

Zoom:

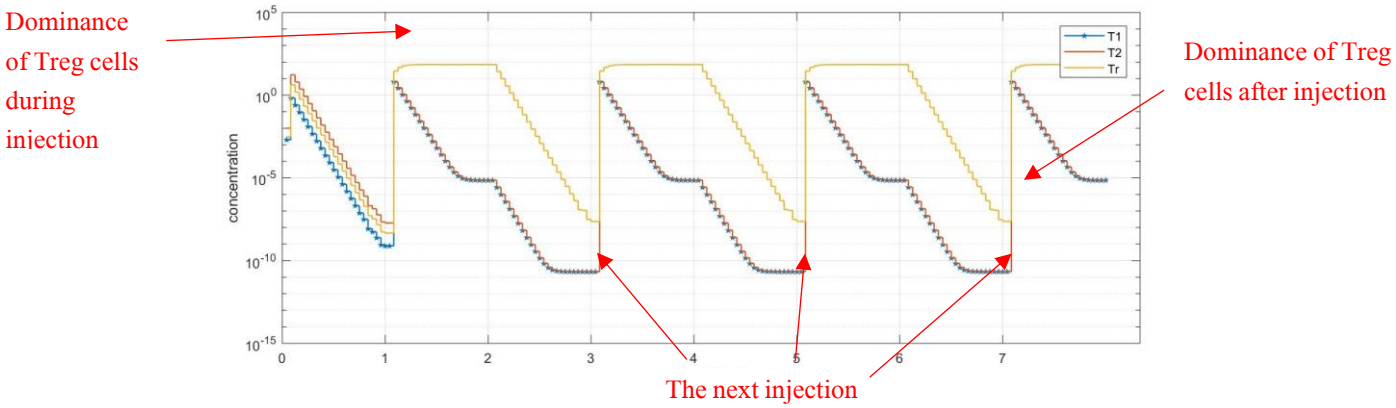
Dominance of Treg cells during iniection



Dominance of Th2 cells after injection

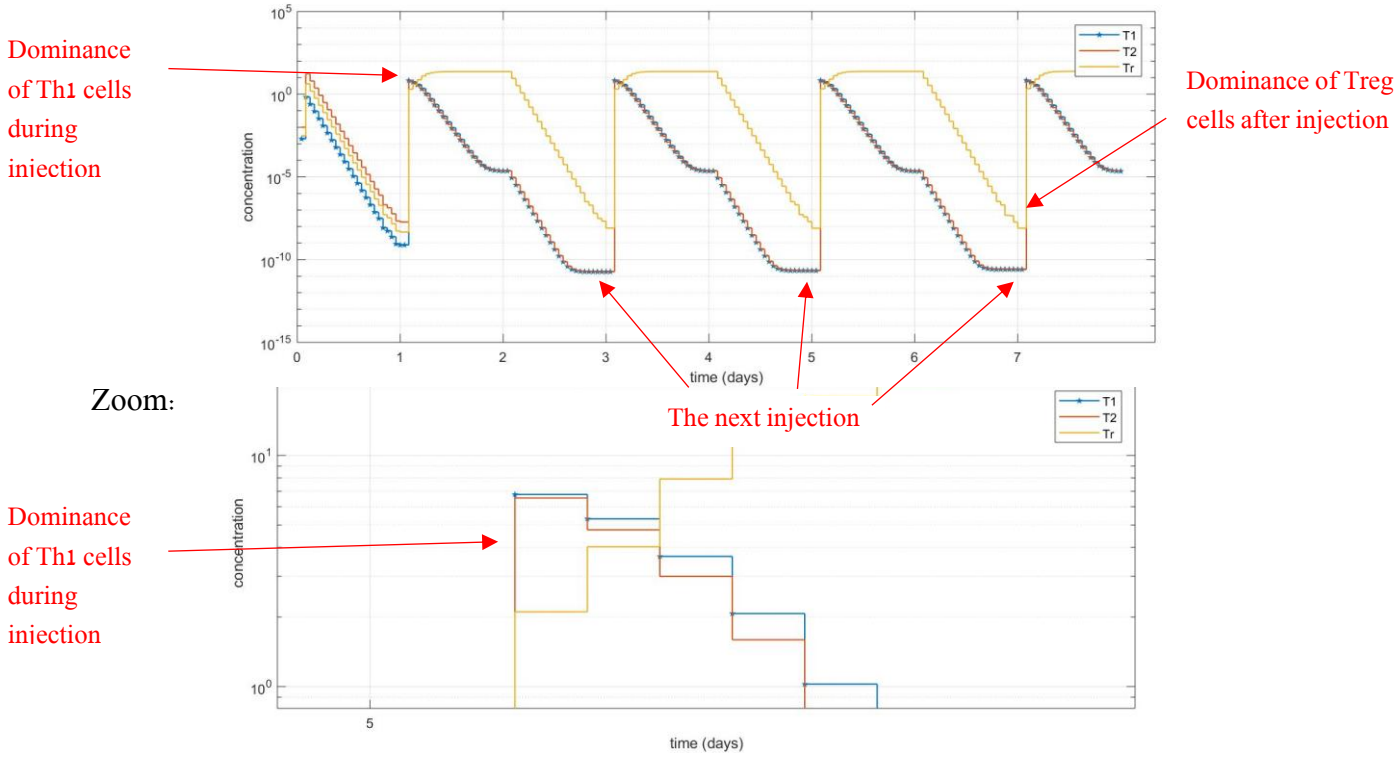


Simulation number 10: The treatment given after 2 days. Initial special dose given is 10g. Increasing dose: 0.01g



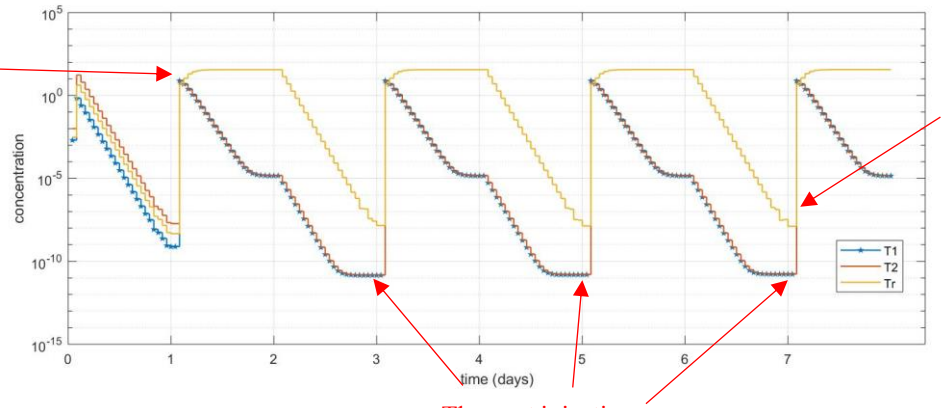
Here we can see that the treatment is indeed sufficient, but we tried lower doses in order to find a lower boundary.

Simulation number 11: The treatment given after 2 days. Initial special dose given is 0.5g. Increasing dose: 0.01g



Simulation number 12: The treatment given after 2 days. Initial special dose given is 1.0g. Increasing dose: 0.01g

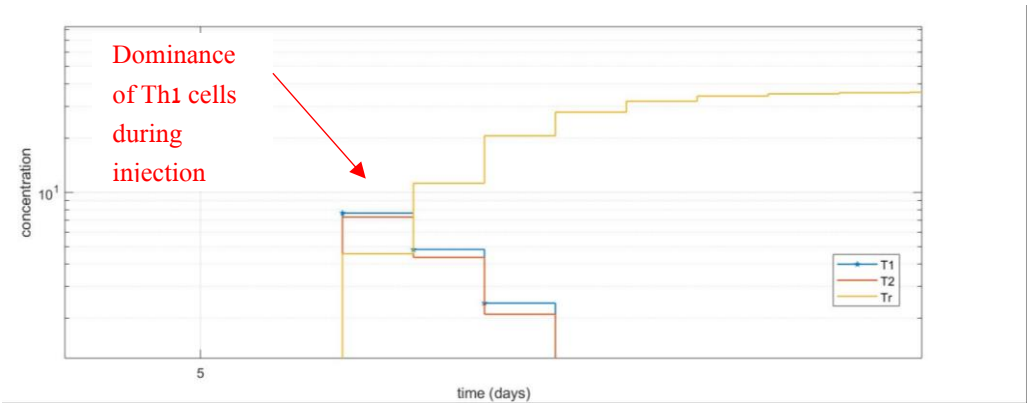
Dominance of Th1 cells during iniection



Dominance of Treg cells after injection

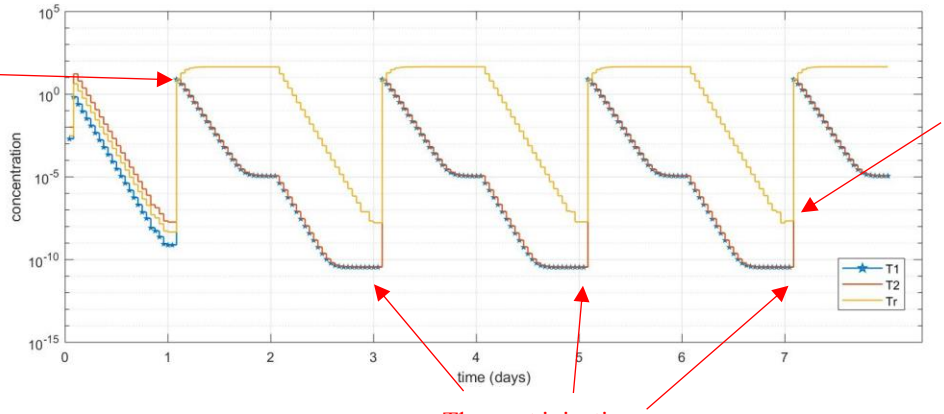
The next injection

Zoom:



Simulation number 13: The treatment given after 2 days. Initial special dose given is 1.5g. Increasing dose: 0.01g

Dominance of Th1 cells during injection

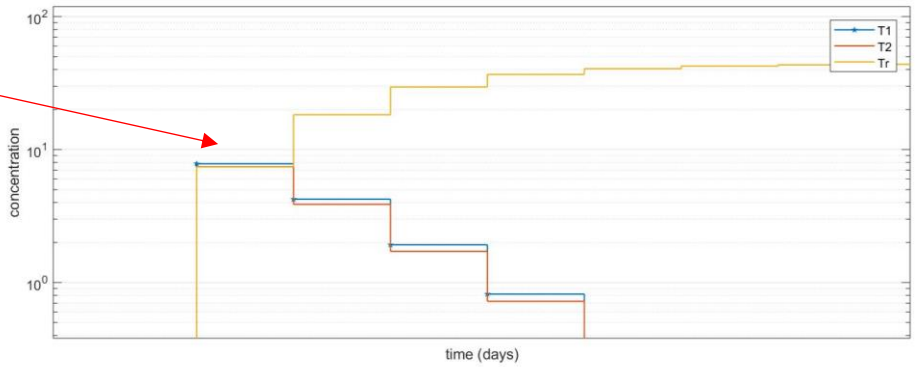


Dominance of Treg cells after injection

The next injection

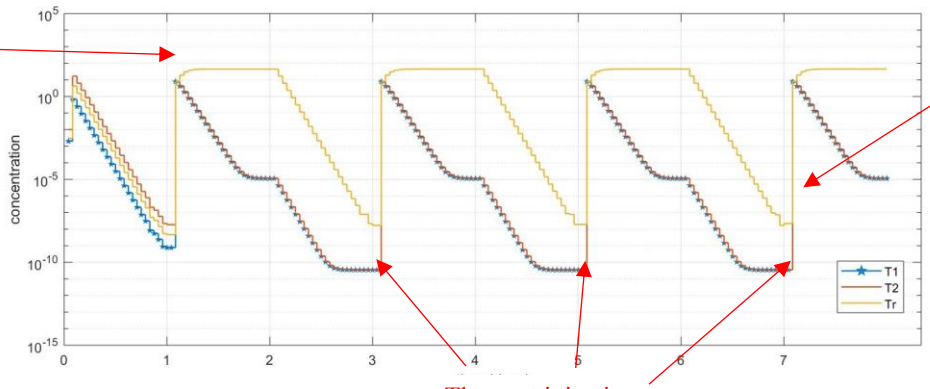
Zoom:

Dominance of Th1 cells during injection



Simulation number 14: The treatment given after 2 days. Initial special dose given is 1.6g. Increasing dose: 0.01g

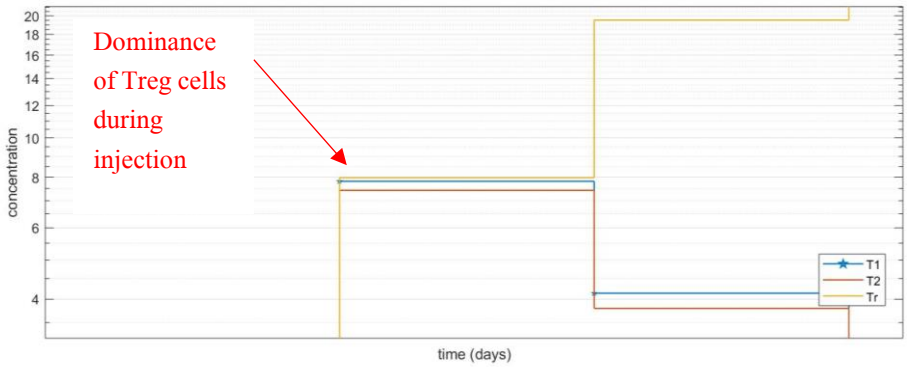
Dominance of Treg cells during injection



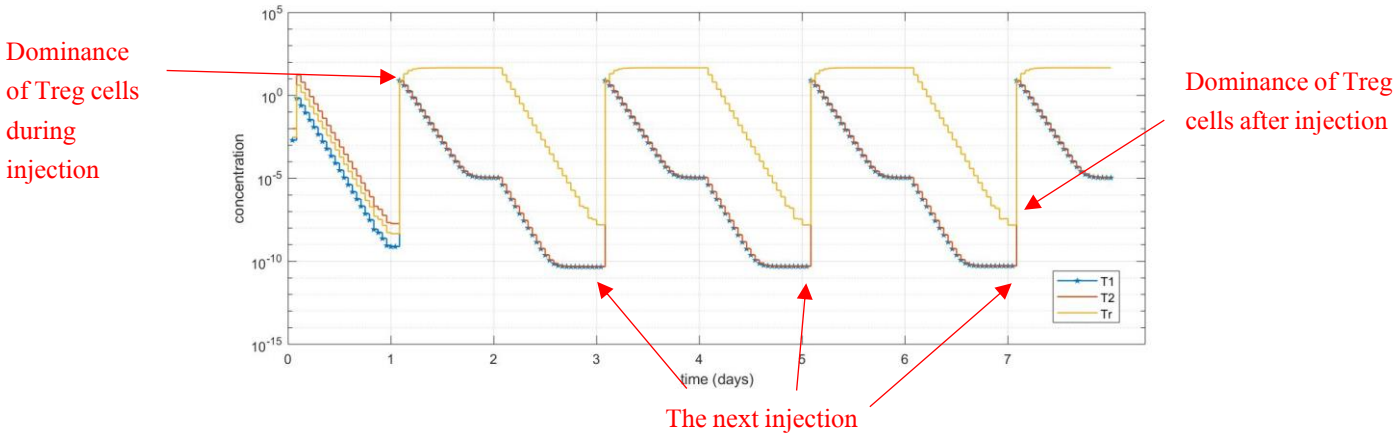
Dominance of Treg cells after injection

The next injection

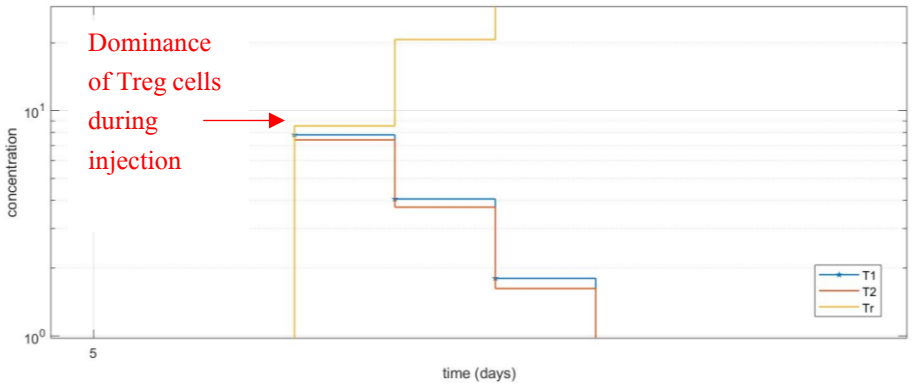
Zoom:



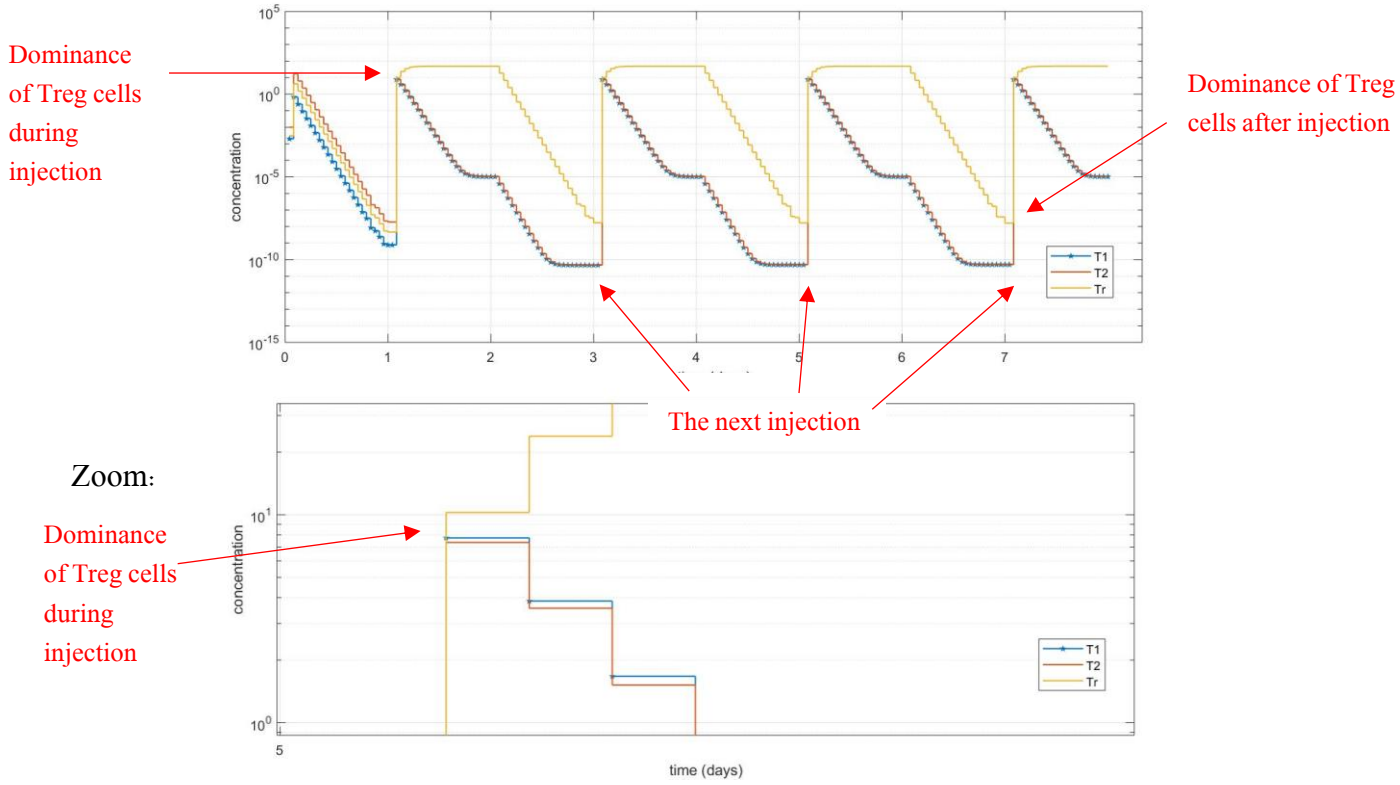
Simulation number 15: The treatment given after 2 days. Initial special dose given is 1.7g. Increasing dose: 0.01g



Zoom:

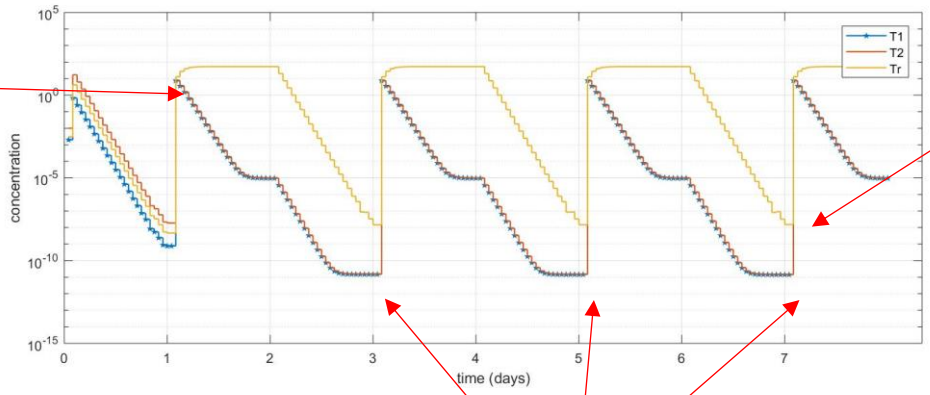


Simulation number 16: The treatment given after 2 days. Initial special dose given is 2.0g. Increasing dose: 0.01g



Simulation number 17: The treatment given after 2 days. Initial special dose given is 2.5g. Increasing dose: 0.01g.

Dominance of Treg cells during injection

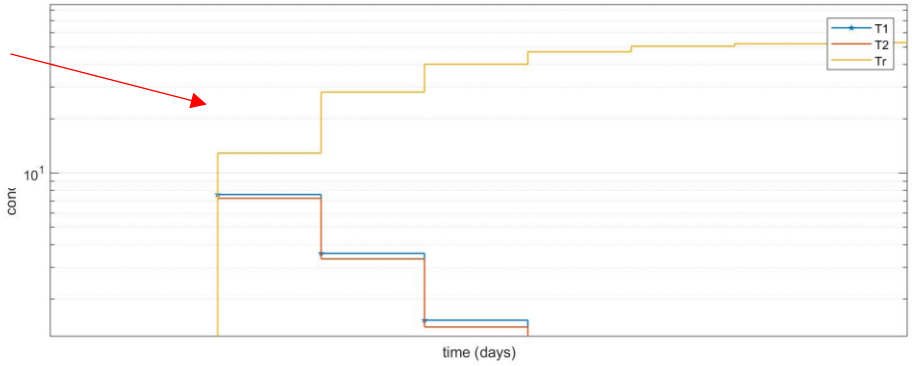


Dominance of Treg cells after injection

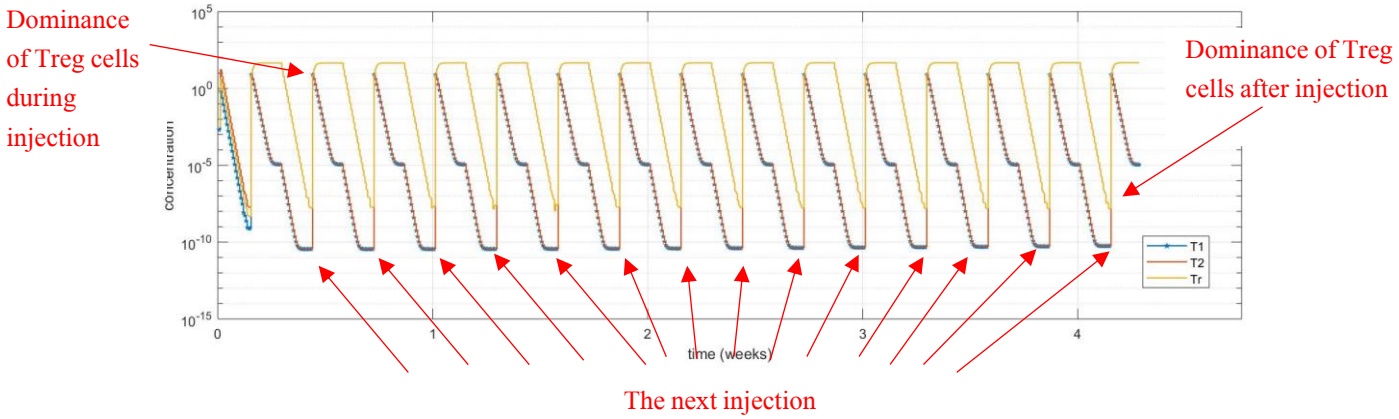
Zoom:

The next injection

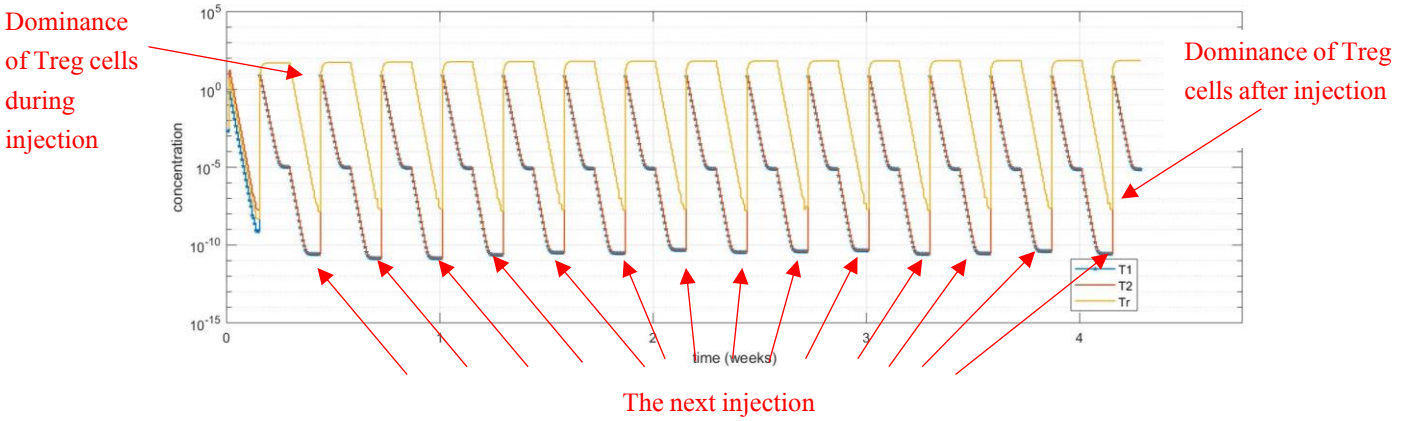
Dominance of Treg cells during injection



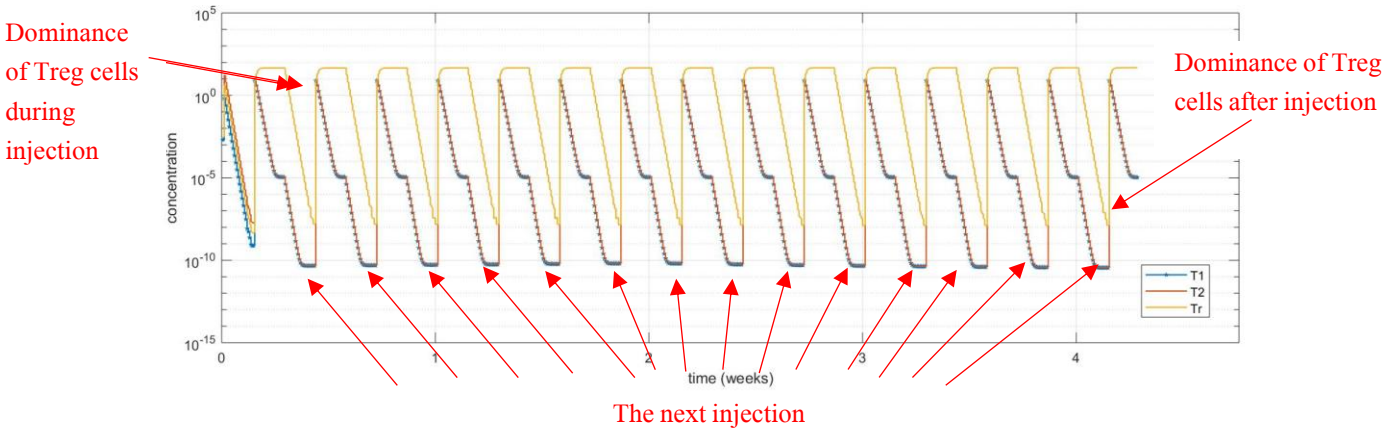
Simulation number 18: The treatment given after 2 days. Initial special dose given is 1.6g. Increasing dose: 0.01g



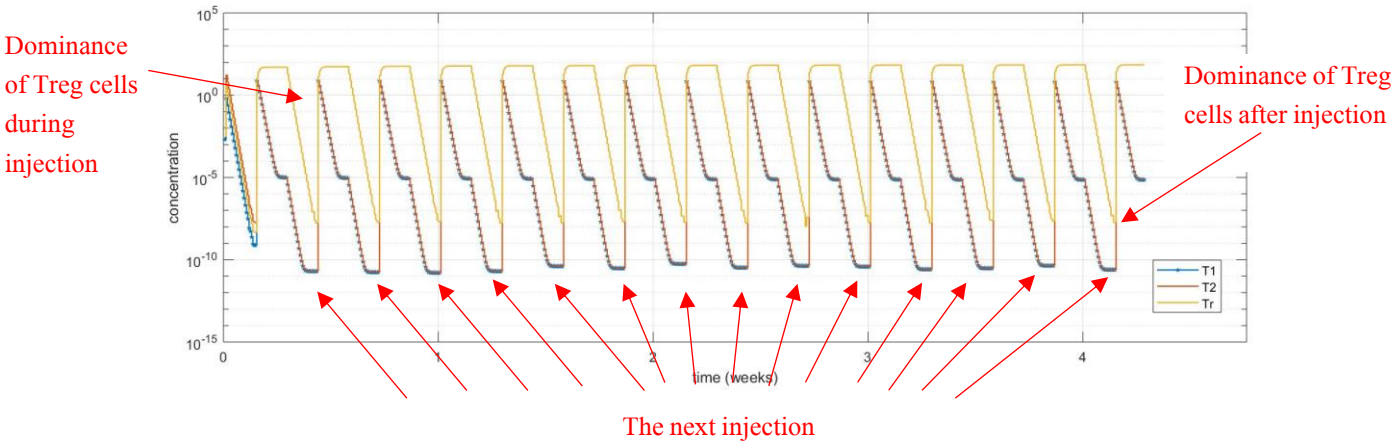
Simulation number 19: The treatment given after 2 days. Initial special dose given is 1.6g. Increasing dose: 0.5g



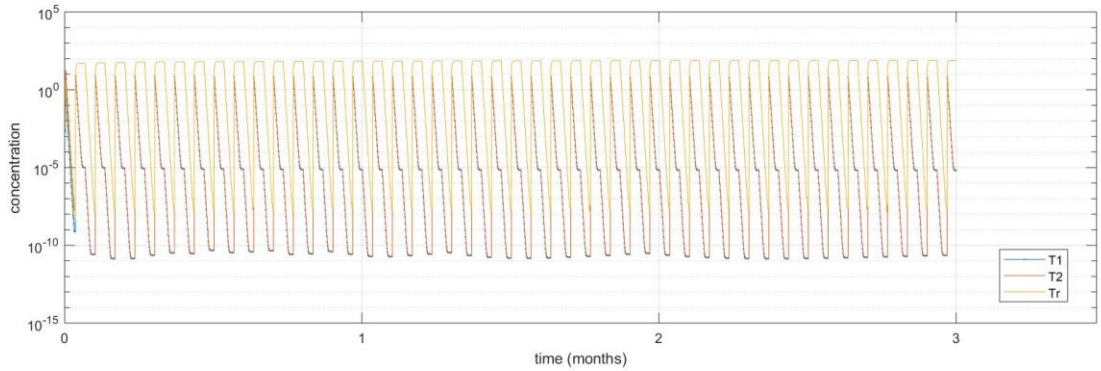
Simulation number 20: The treatment given after 2 days. Initial special dose given is 1.7g. Increasing dose: 0.01g



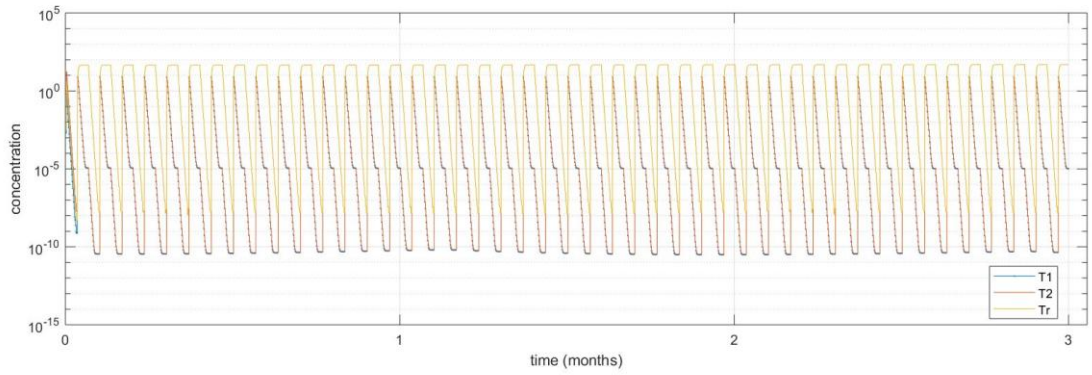
Simulation number 21: The treatment given after 2 days. Initial special dose given is 1.7g. Increasing dose: 0.5g



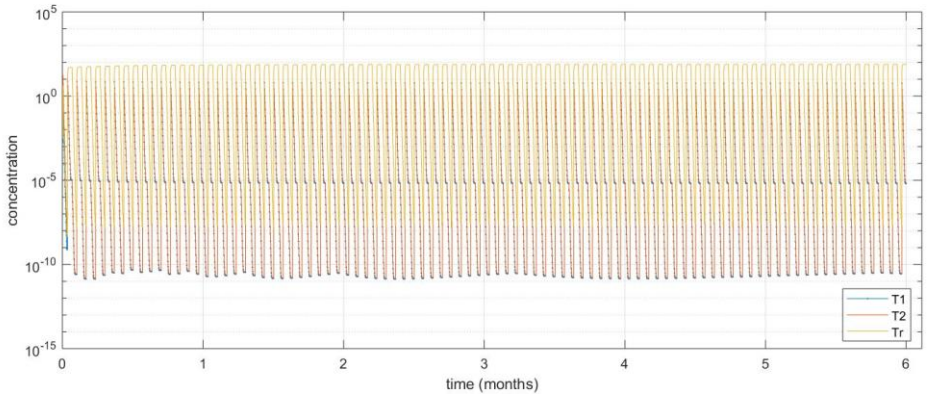
Simulation number 22: The treatment given after 2 days. Initial special dose given is 1.6g. Increasing dose: 0.5g



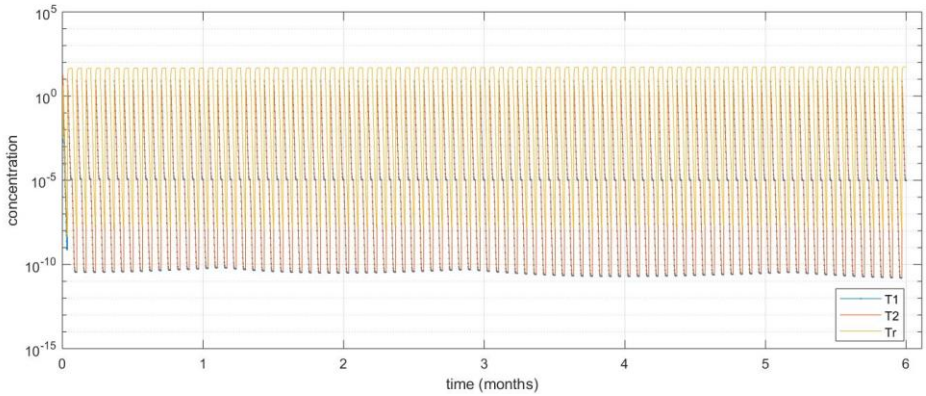
Simulation number 23: The treatment given after 2 days. Initial special dose given is 1.6g. Increasing dose: 0.01g



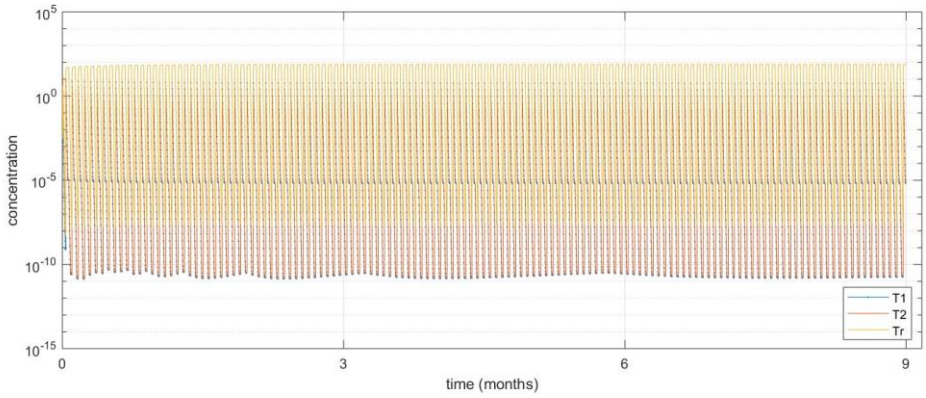
Simulation number 24: The treatment given after 2 days. Initial special dose given is 1.6g. Increasing dose: 0.5g



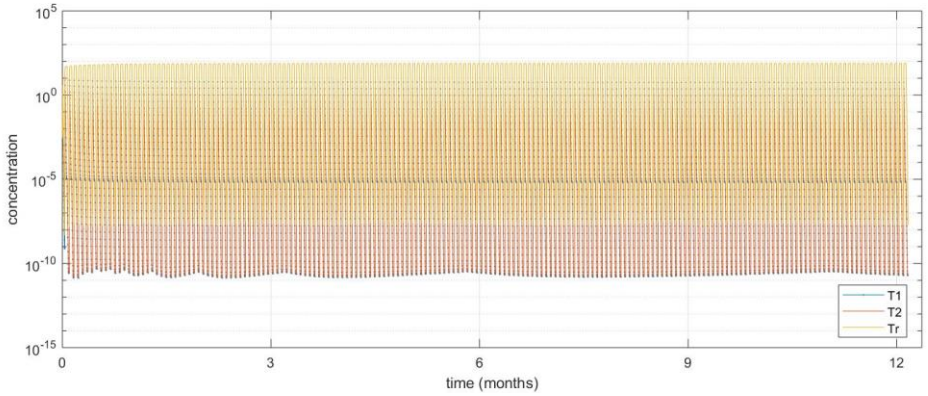
Simulation number 25: The treatment given after 2 days. Initial special dose given is 1.6g. Increasing dose: 0.01g



Simulation number 26: The treatment given after 2 days. Initial special dose given is 1.6g. Increasing dose: 0.5g



Simulation number 27: The treatment given after 2 days. Initial special dose given is 1.6g. Increasing dose: 0.5g

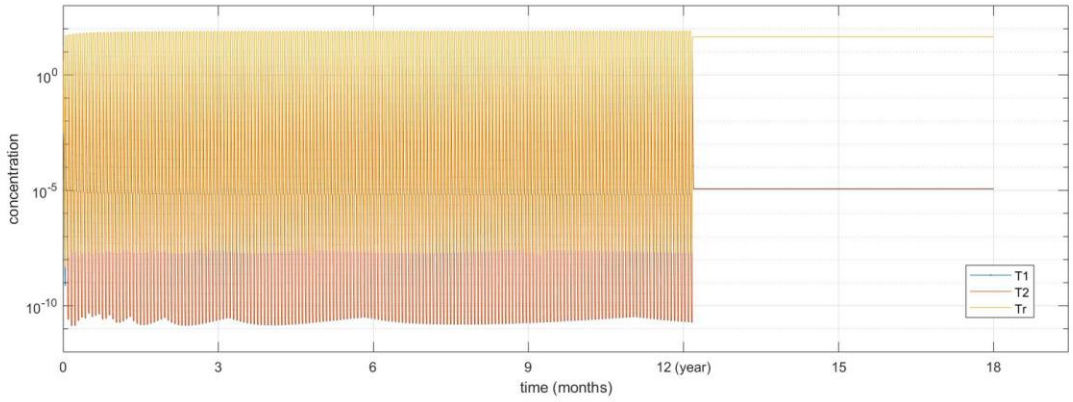


Simulation number 28:

In the first 12 months the treatment given every 2 days. Initial special dose given is 1.6g. Increasing dose: 0.5g.

After 12 months the special dose is 1.6g[16].

Test period: 540 days



[16] After 12 months that we increased the dose, the system is balanced and therefore we inject constant dose only.

6.4 Analysis the results of DODE ALLERGY TREATMENT MODEL

6.4.1 Select the appropriate dosage

By considering that the appropriate dose will have to be sufficient, meaning that we must maintain higher levels of Tr than T1 and T2.

First, we inject treatment every 7 days, although we couldn't achieve a sufficient so next, we tried injecting treatment every 5 days. Again, this didn't give us the wanted result, then tried injecting treatment every 3 days. Once again, it wasn't sufficient, then finally tried injecting treatment every 2 days.

In simulations 1-9 we can see that during injection Tr cells dominated the system, but after injection Th2 cells dominated, therefore those treatments were not sufficient. But when we gave injection every 2 days, we successfully gained balanced system between the injections.

6.4.2 Concluding of numerical simulations in table[17]

Table 6.4.2.1. One week testing:

Simulation number	Treatment every # days	Special dose	adding	Tr before[18]	Tr after[19]	Difference
1	7	0.5	0.01	1.852	1.466	-0.386
2	7	1.7	0.01	1.852	1.716	-0.136
3	7	1.7	0.5	1.852	1.596	-0.256
4	5	0.5	0.01	1.852	1.477	-0.375
5	5	1.7	0.01	1.852	1.714	-0.135
6	5	1.7	0.5	1.852	1.592	-0.26
7	3	0.5	0.01	1.481	1.728	0.247
8	3	1.7	0.01	3.716	3.959	0.243
9	3	1.7	0.5	1.599	1.411	-0.188
10	2	10	0.01	2.344	2.361	0.017
11	2	0.5	0.01	1.874	1.929	0.055
12	2	1.0	0.01	1.354	1.285	-0.069
13	2	1.5	0.01	1.253	1.242	-1.011
14	2	1.6	0.01	1.905	2.163	0.258
15	2	1.7	0.01	1.563	1.526	-0.037
16	2	2.0	0.01	1.652	1.612	-0.04
17	2	2.5	0.01	1.471	1.504	0.033

Table 6.4.2.2. One month testing: treatment every two days

Simulation number	Special dose	adding	Tr before	Tr after	Difference
18	1.6	0.01	1.703	1.492	-0.211
19	1.6	0.5	1.361	1.914	0.553
20	1.7	0.01	1.606	1.329	-0.277
21	1.7	0.5	1.751	1.863	0.112

[17] Initial dosage of all simulations is 10g.
[18] The concentration of Tr cells tested before the first shot (scale: e-11).
[19] The concentration of Tr cells tested after the last shot (scale: e-11).

Table 6.4.2.3. Testing 3,6,9,12,18 months: treatment every two days

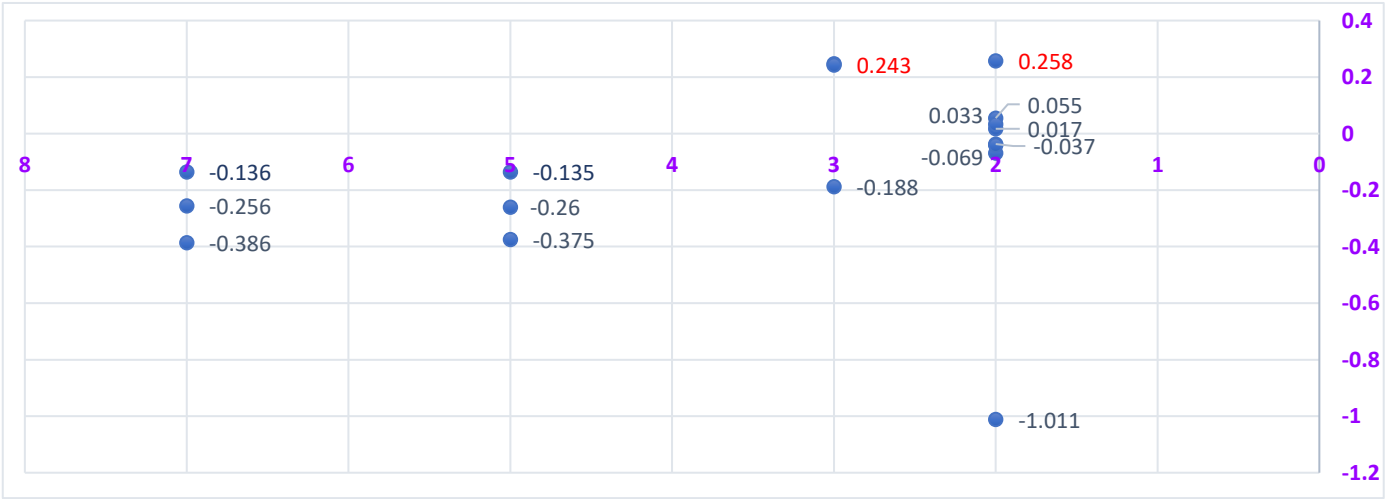
Simulation number	Numbers of months tested	Special dose	adding	Tr before (scale: e-08)	Tr after (scale: e-08).	Difference
22	3	1.6	0.5	1.36	2.357	0.997
23	3	1.6	0.01	1.7	1.553	-0.147
24	6	1.6	0.5	1.36	2.411	1.051
25	6	1.6	0.01	1.7	1.418	-0.282
26	9	1.6	0.5	1.36	3.216	1.856
27	12	1.6	0.5	1.36	3.965	2.605
28	18	1.6	0.5[20]	1.36	44.91	43.55

6.4.3 Comparing the numerical simulations of one week results according Tr levels in excel

Table 6.4.3 One week testing in excel:

X axis- Treatment every 2/3/5/7 days

Y axis- Difference[21]



[20] After 12 months the special dose was constant 1.6g – no extra dose after 12 months.
[21] Difference= (Tr level after the last shot)-(Tr level before the first shot)

CHAPTER 7

DISCUSSION

We have presented here an improved mathematical model of T1-T2-Treg interactions model in specific immunotherapy based on former biological researches. The model aims to demonstrate the dynamic interactions between T cells, naïve cells and antigen with a system of nonlinear equations, finding equilibria, analyzing it stability, performing numerical simulations and determine appropriate dosage for our treatment protocol of DOSE ALLERGY TREATMENT MODEL.

First, we added 'dose' parameter to Grob-Metzner-Behn model[2] to control the dosage that is inserted to the system, as described in chapter 4.

Second, we wished of find the equilibria points of DOSE ALLERGY TREATMENT MODEL, but due to the complexity of the calculations we reviewed only one solution[22] and analyzed its stability. During the analysis it became clear to us that we cannot find the ideal dosage from this stability analysis, therefore addressed to numerical simulation using Matlab.

In order to find the ideal dosage for our treatment we ran a great many simulations. Our goal was to gain a sufficient dose that will achieve higher levels of Treg than Th2 and Th1 between the therapeutic sessions.

As we searched the ideal dosage, our aspiration was to give our patients have a better quality of life. We have looked for the dosage that will satisfy out purpose, but also will be the lowest they can receive. Our treatment will be given every two days in small doses. In this way, our patients will not have to suffer from painful injections every few days but can get pills.

[22] Solution $X = \{ (N, T_1, T_2, T_r, A) = (\alpha, 0,0,0,0) \}$

In table 6.4.2.1. we summarized the results of simulations 1-17. It those simulations we tried various doses and tested the Treg levels before the first session and after the last session. We wanted to achieve higher levels of Treg between sessions, but also to make sure our treatment is indeed healing our patients, and therefore we must examine growth in the concentration of Treg cells.

From table 6.4.2.1. we conclude that the ideal dosage is 1.6mg evert two days. In table 6.4.2.2. we test 2 different doses[23] in order to determine the ideal treatment according the increase of Treg cells.

Table 6.4.2.3. help us determine the final ideal dose. For 12 months we add to each session small dosage for the sake of educating the patient immune system. After 12 months we stop inducing the system with this extra dosage and tested the concentration of Treg.

Our purpose was successfully achieved. From numerical simulations we were able to determine the ideal dose that:

1. Educate the immune system by achieving increment in Treg concentration

2. Gain balanced system between sessions.

3. Give our patients have a better quality of life.

[23] 1.6mg, 1.7mg

CHAPTER 8

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[1] ABUL K. ABBAS, ANDRREW H. H. LICHTMAN, SHIV PILLAI: *Cellular and Molecular Immunology, 9th Edition*

[2] FRIDLOLIN GROB, GERHARD METZNER, ULRICH BEHN: *"Mathematical Modelling of Allergy and Specific Immunotherapy: Th1-Th2-Treg Interactions"*, JOUNAL OF THEORETICAL BIOLOGY 2010

[3] MICHAEL A. FISHMAN, LEE A. SEGEL: *"Modeling Immunotherapy for Allergy"*, ELSEVIER 1996

[4] http://www.prolog.co.il/ContentImages/MediaFiles/10202010_132828_f9f1e346-12c8-488b-ad4e-5962dd048a07.pdf