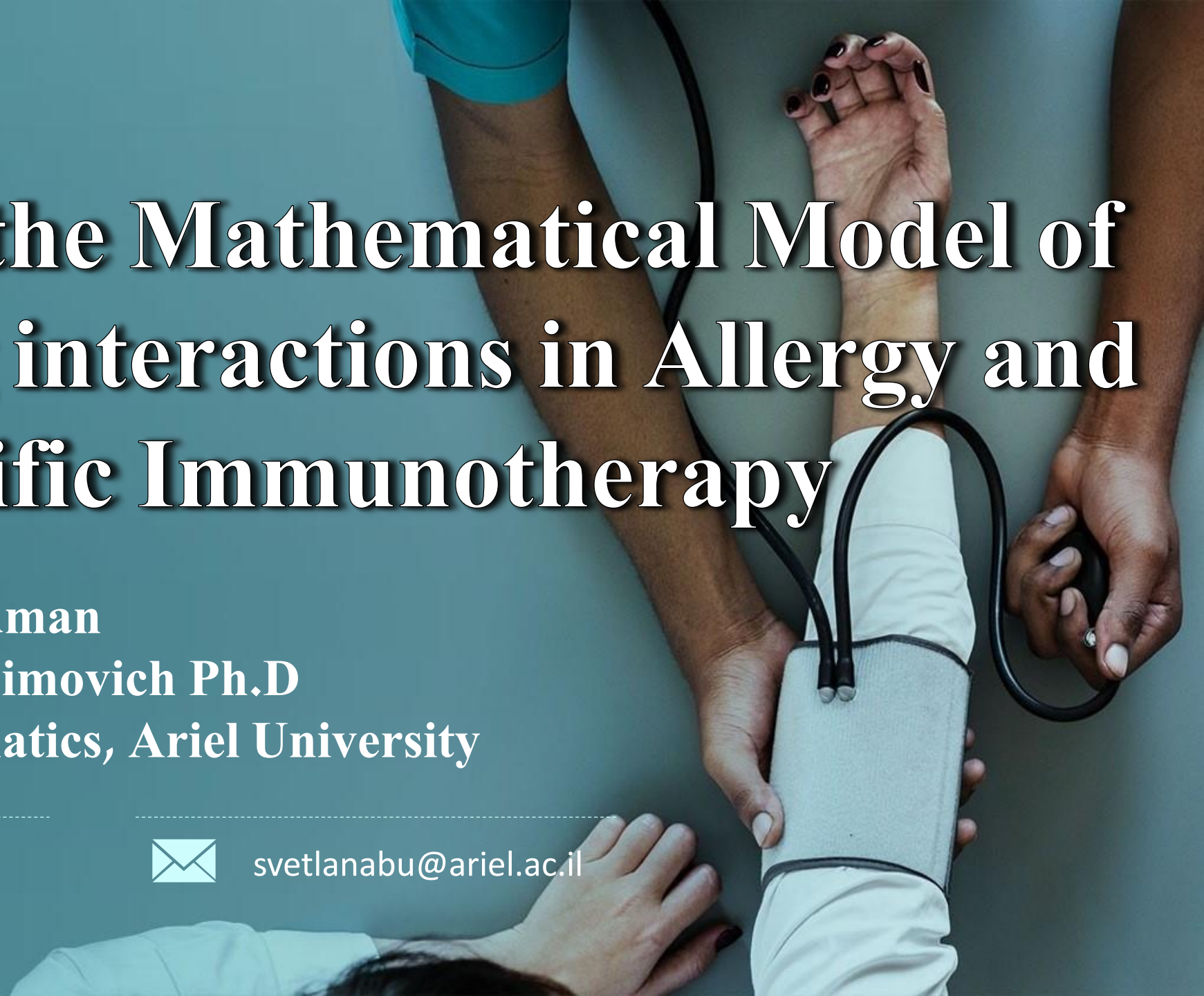
ARIEL UNIVERSITY

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



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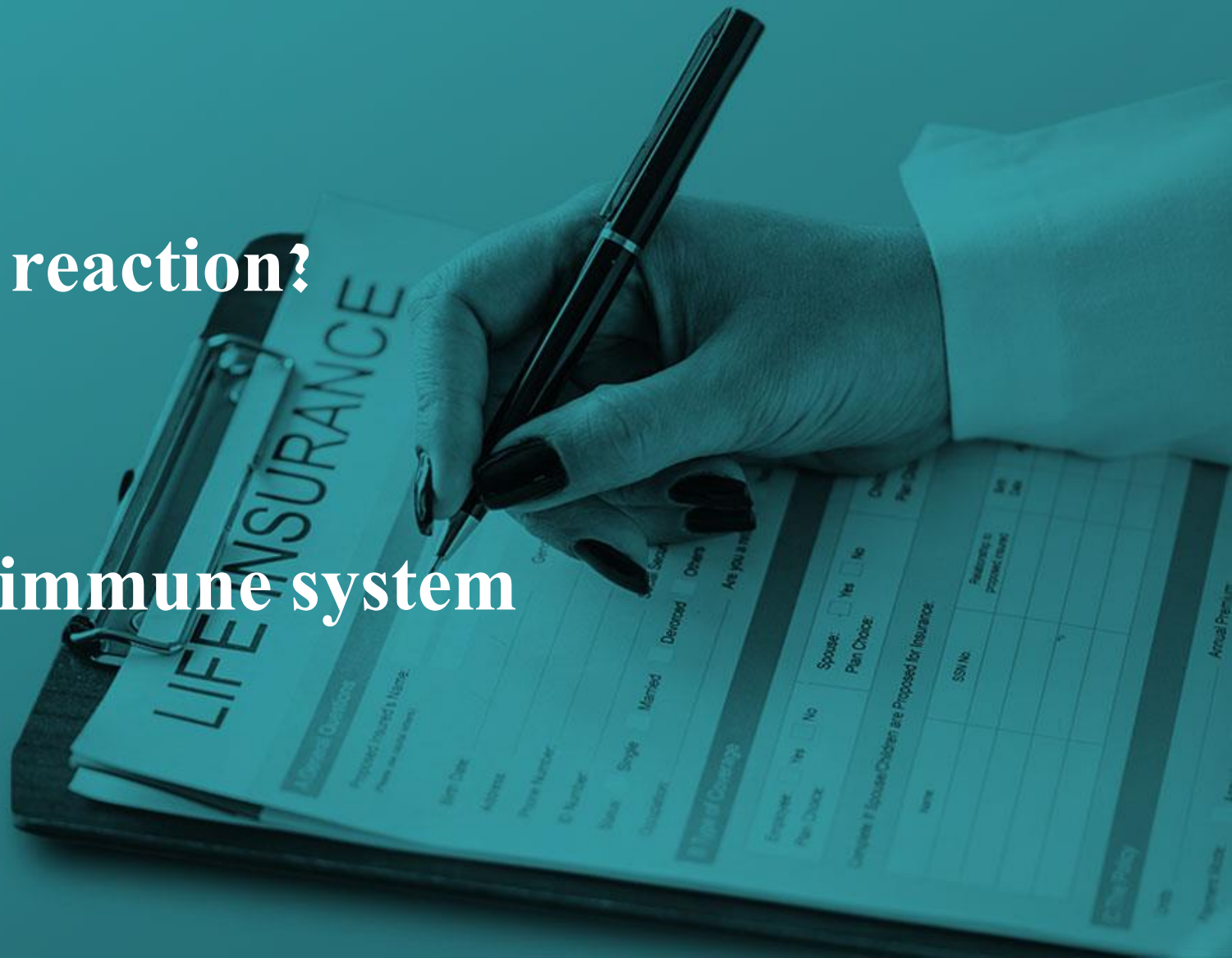
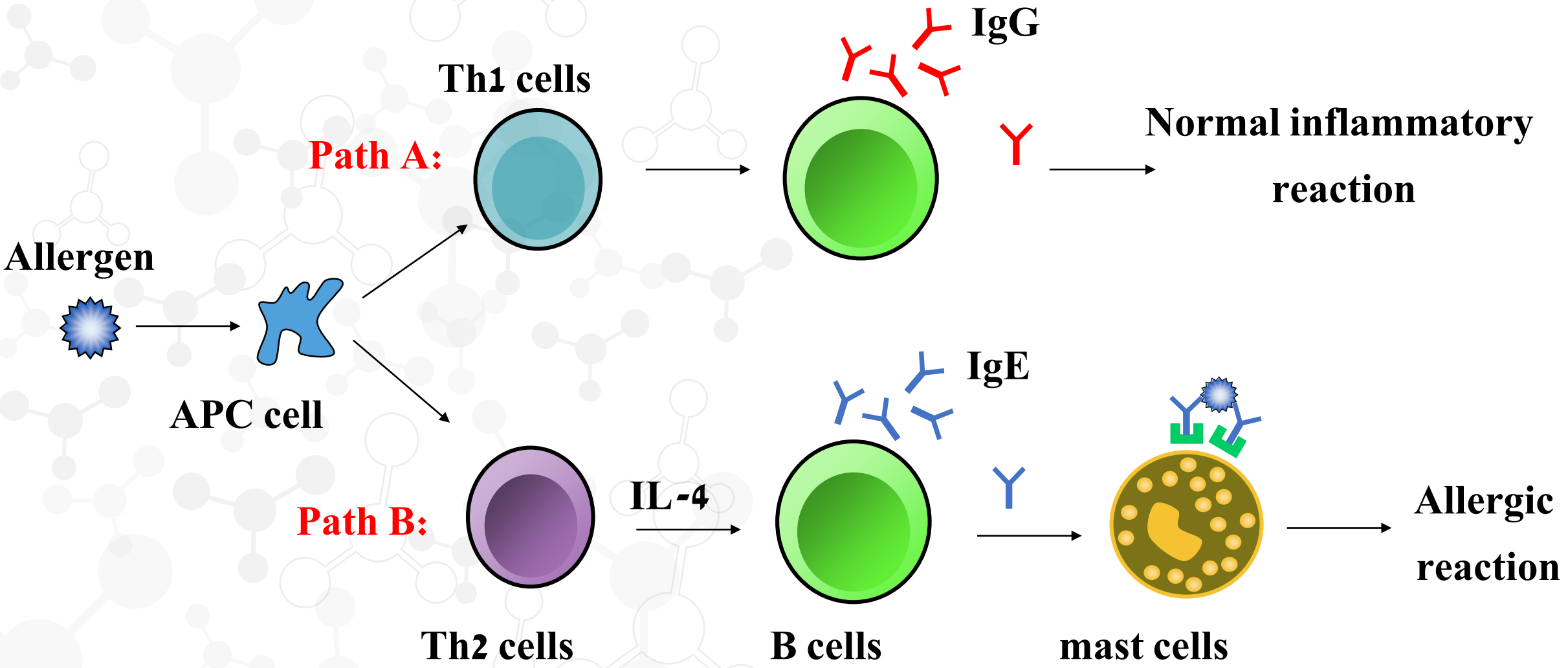
Introduction

- What is an allergic reaction?
- How it is occurs?
- The mechanism of immune system



The immune system cells process



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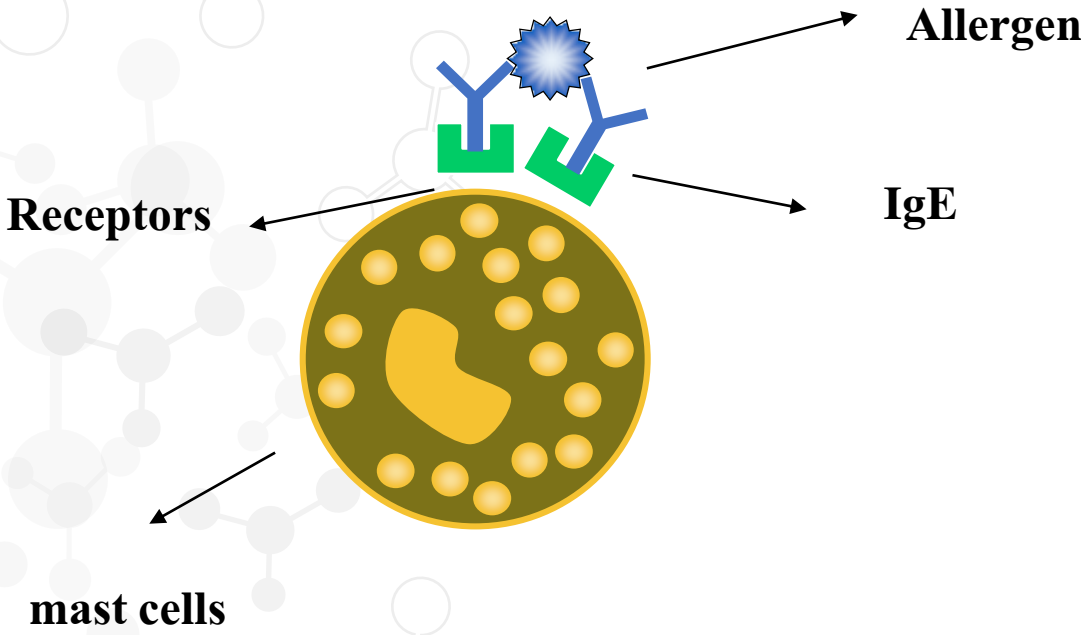


Sensitization process in mast cells: An IgE antibodies produced in allergic individual. Those antibodies moving in the blood stream and attached the receptors on the surface of the mast cells.

A previous mathematical model: Modeling Immunotherapy for allergy

- 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.

A previous mathematical model: Th1-Th2-Treg Interactions

- Each allergen encounter triggers the proliferation of all types of T helper cells that are specific to the 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 enough control by mechanisms of tolerance.
- By activating the production of IgE antibodies which provoke the allergic symptoms.
- Repeated injections in short intervals will therefore induce a more and more Treg dominated reaction, that completely prevents the immune response.

DOSE ALLERGY TREATMENT MODEL

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

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

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

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

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

Stability analysis of DOSE ALLERGY TREATMENT MODEL

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

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

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

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

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

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

$$\left(\frac{\partial F_1}{\partial N}, \frac{\partial F_1}{\partial T_1}, \frac{\partial F_1}{\partial T_2}, \frac{\partial F_1}{\partial T_r}, \frac{\partial F_1}{\partial A}\right) = (-1,0,0,0, -\alpha c(\phi + x))$$

$$\left(\frac{\partial F_2}{\partial N}, \frac{\partial F_2}{\partial T_1}, \frac{\partial F_2}{\partial T_2}, \frac{\partial F_2}{\partial T_r}, \frac{\partial F_2}{\partial A}\right) = (0, -1,0,0, v\alpha c)$$

$$\left(\frac{\partial F_3}{\partial N}, \frac{\partial F_3}{\partial T_1}, \frac{\partial F_3}{\partial T_2}, \frac{\partial F_3}{\partial T_r}, \frac{\partial F_3}{\partial A}\right) = (0,0, -1,0, \phi v\alpha c)$$

$$\left(\frac{\partial F_4}{\partial N}, \frac{\partial F_4}{\partial T_1}, \frac{\partial F_4}{\partial T_2}, \frac{\partial F_4}{\partial T_r}, \frac{\partial F_4}{\partial A}\right) = (0,0,0, -1, xv\alpha c)$$

$$\left(\frac{\partial F_5}{\partial N}, \frac{\partial F_5}{\partial T_1}, \frac{\partial F_5}{\partial T_2}, \frac{\partial F_5}{\partial T_r}, \frac{\partial F_5}{\partial A}\right) = (0,0,0,0, dose^*)$$

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

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

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

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

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.

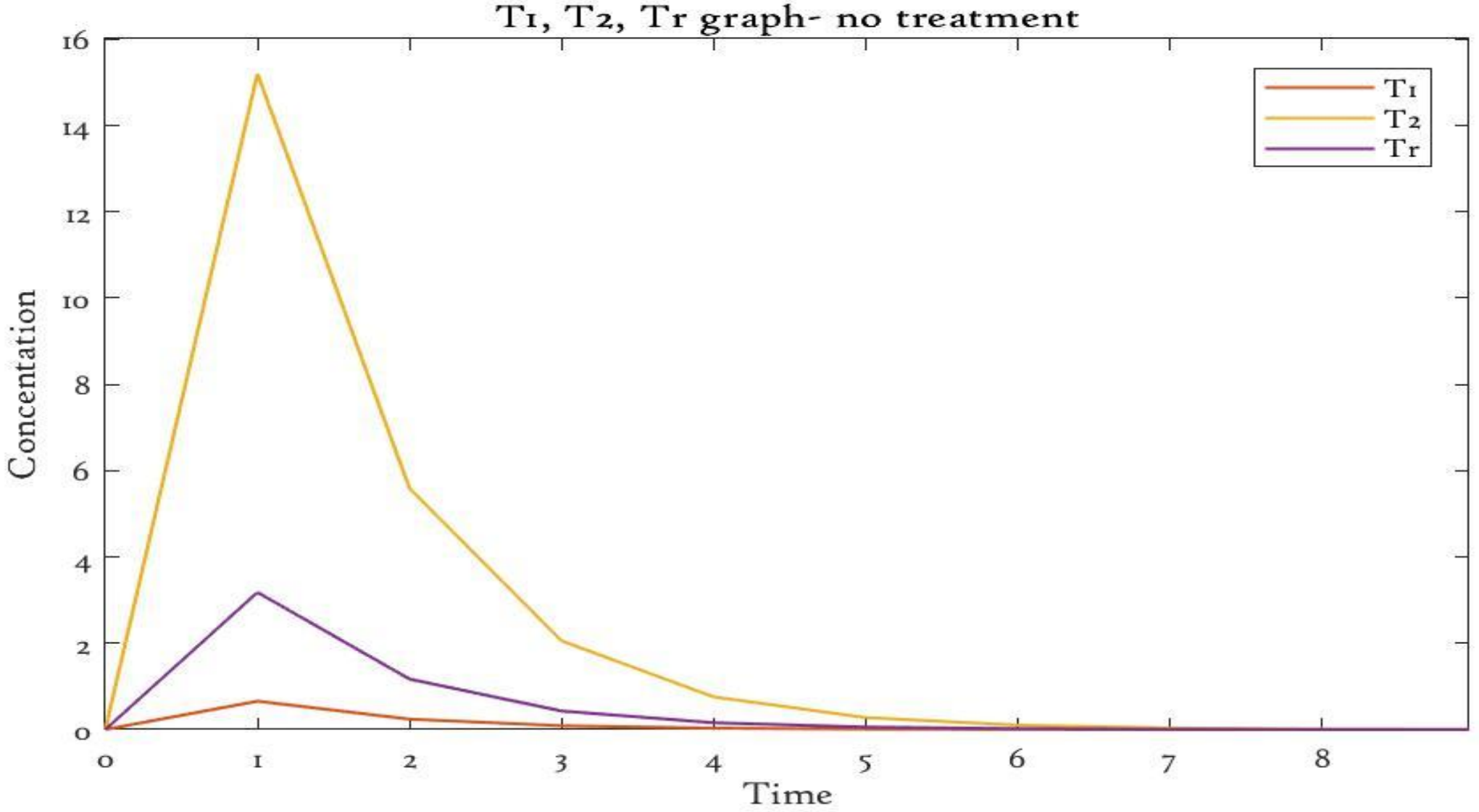
Case 2: $dose^* = 0$

This case is the basis of this project.

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: $dose^* > 0$

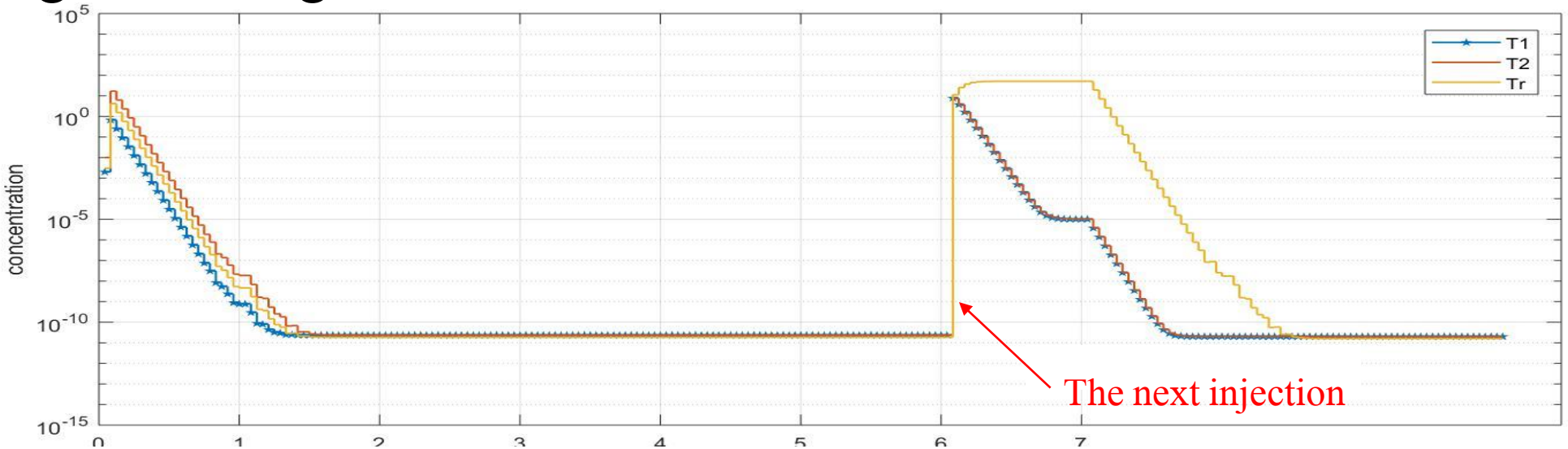
All eigenvalues are negative, meaning solution X is stable.

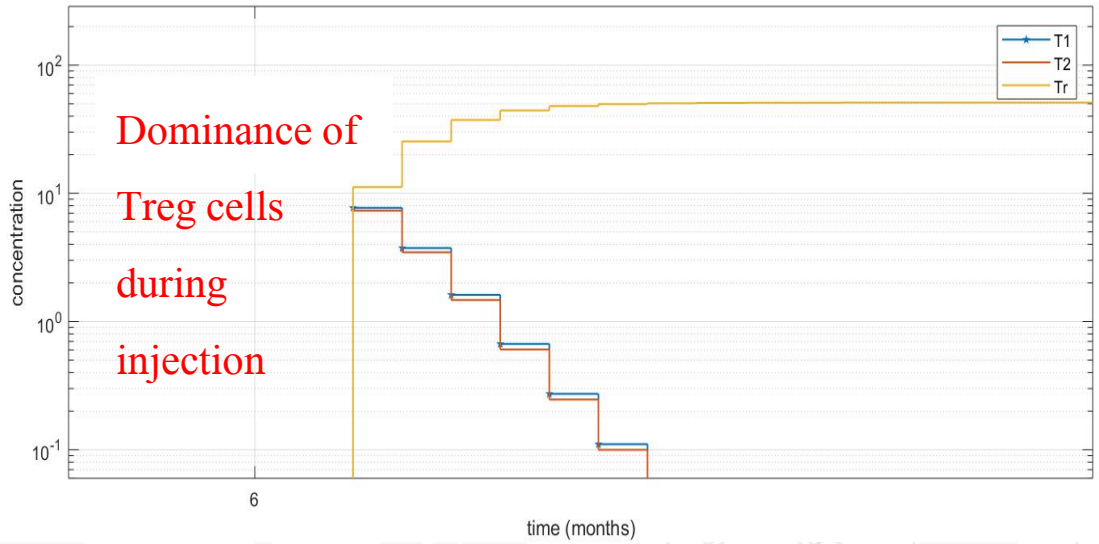


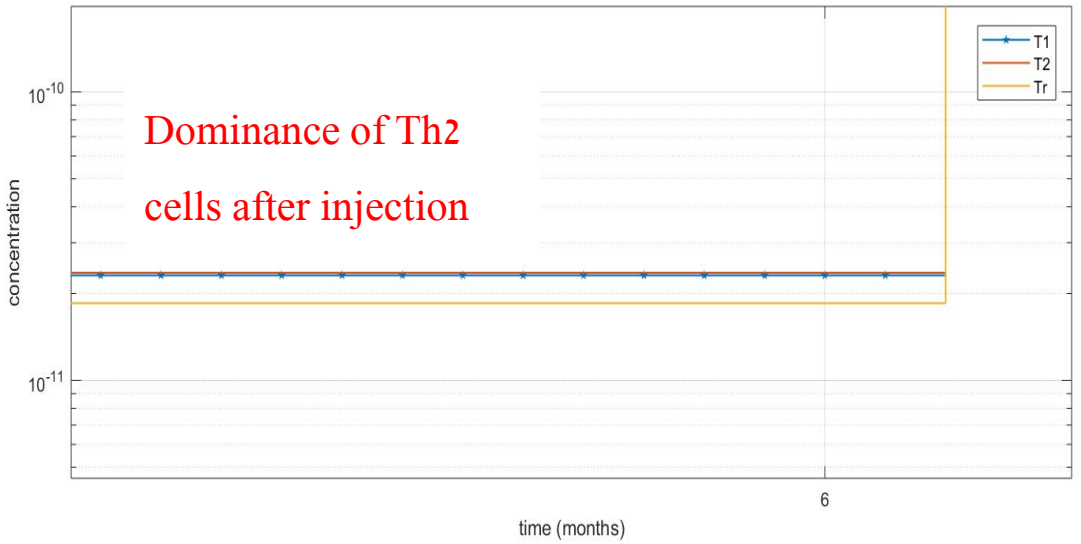
Here we can see that without any treatment (meaning dose=0), Th2 dominates the system, and allergic reaction occurs.

The treatment given after 7 days. Initial special dose given is 1.7g.

Increasing dose：0.5g.

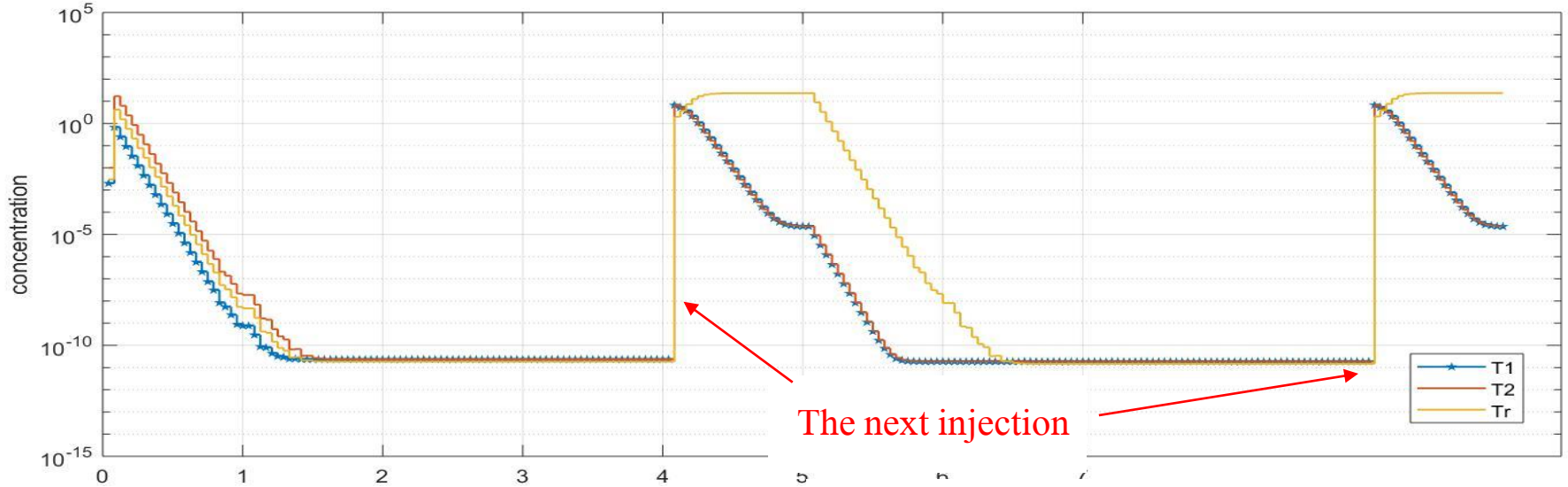


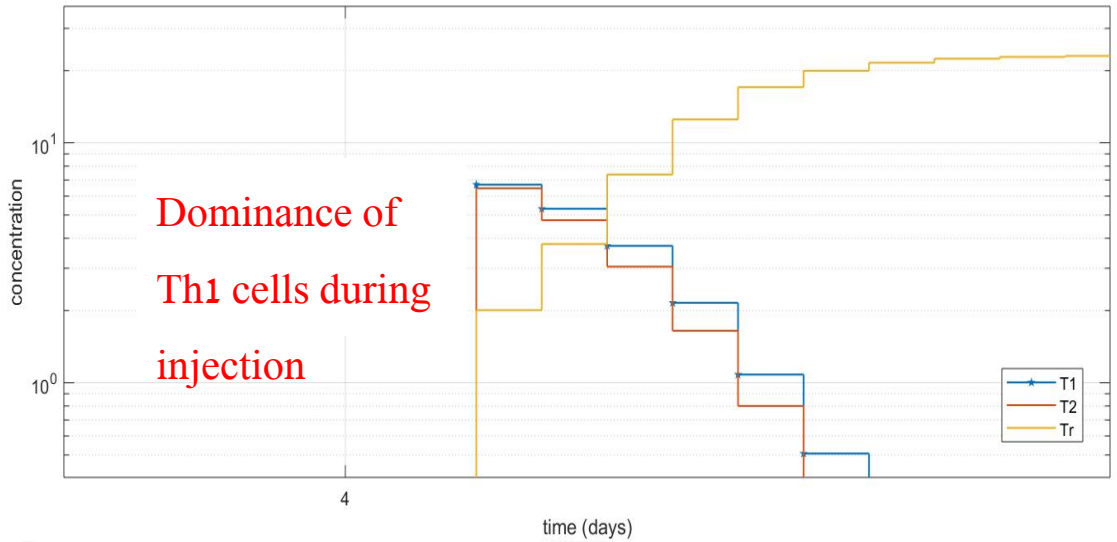


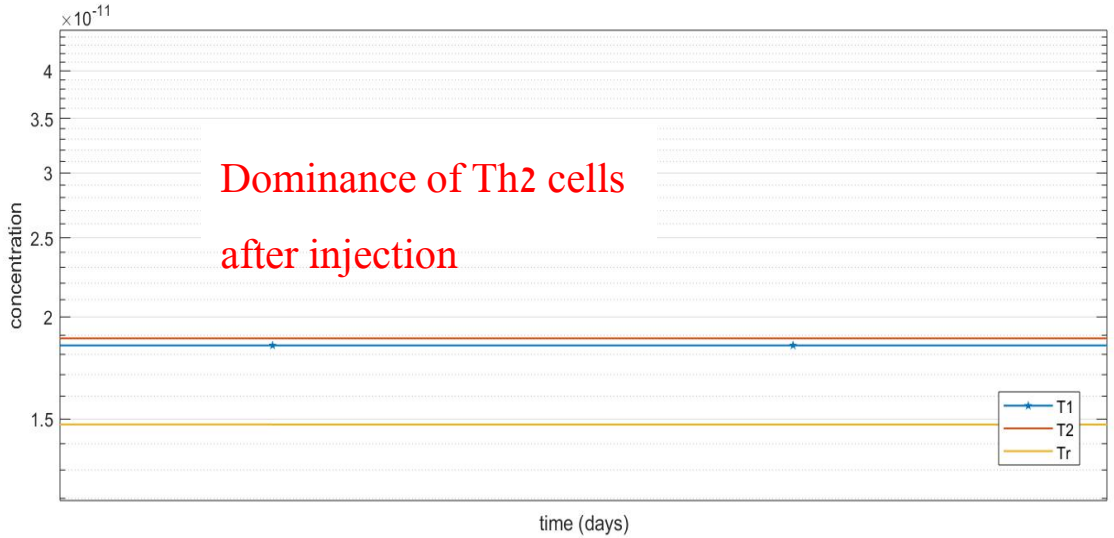


The treatment given after 5 days. Initial special dose given is 0.5g.

Increasing dose：0.01g.

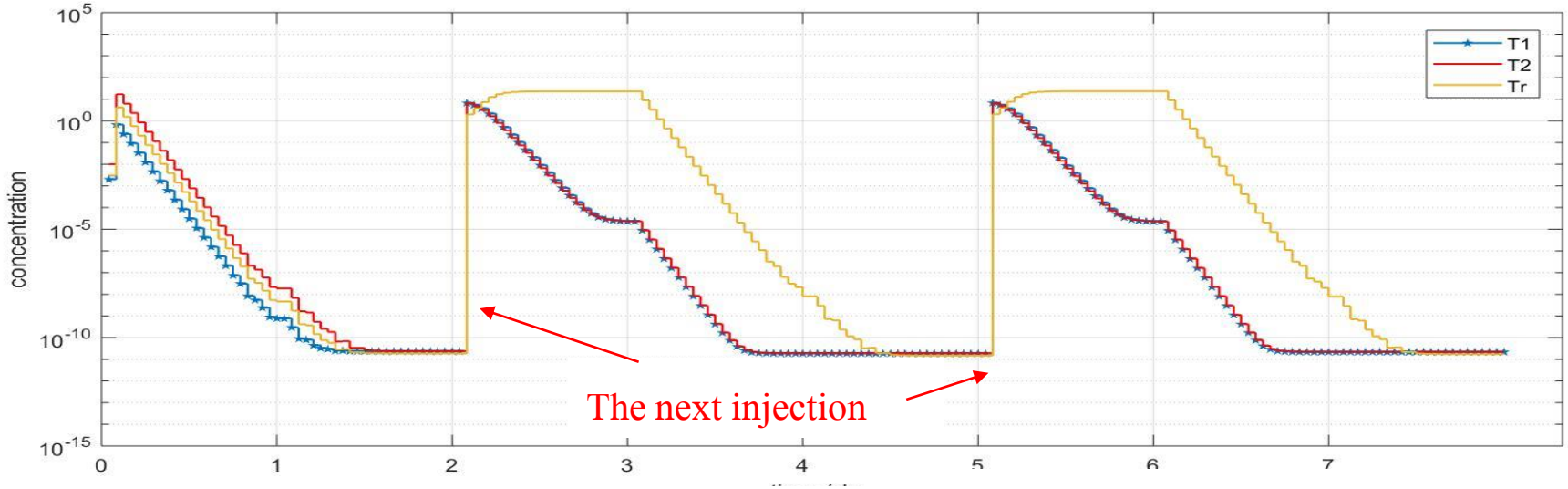


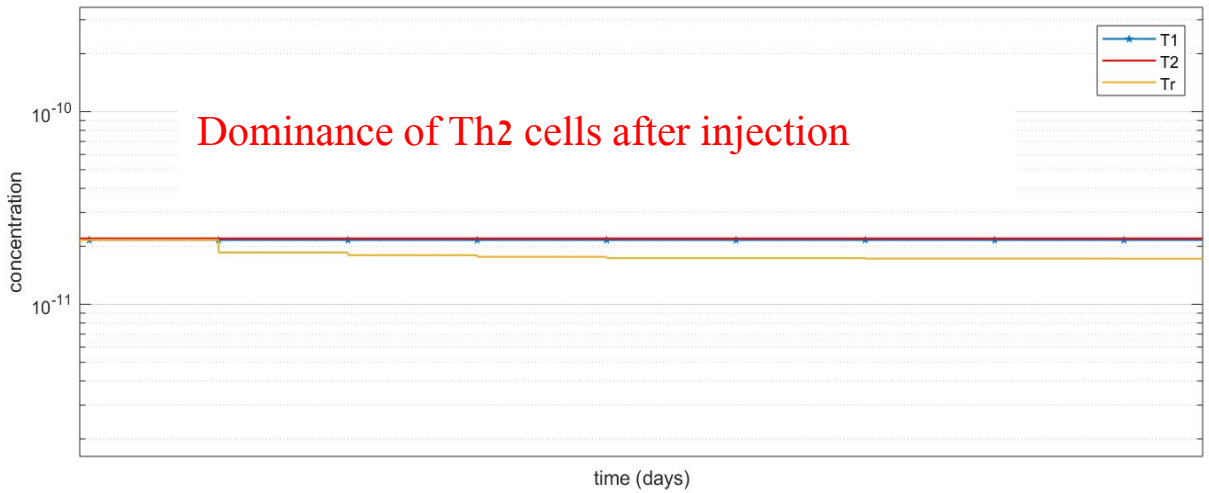




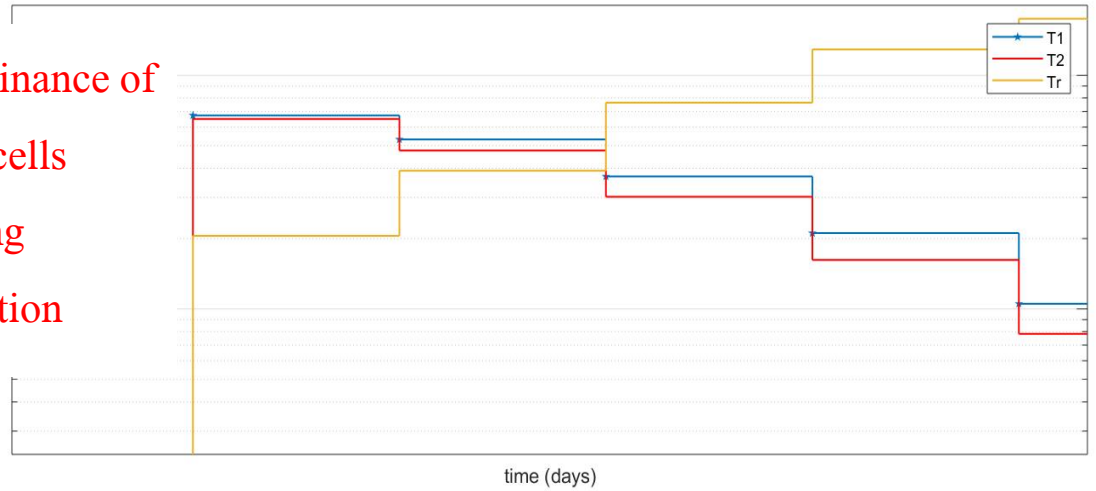
The treatment given after 3 days. Initial special dose given is 0.5g.

Increasing dose: 0.01g





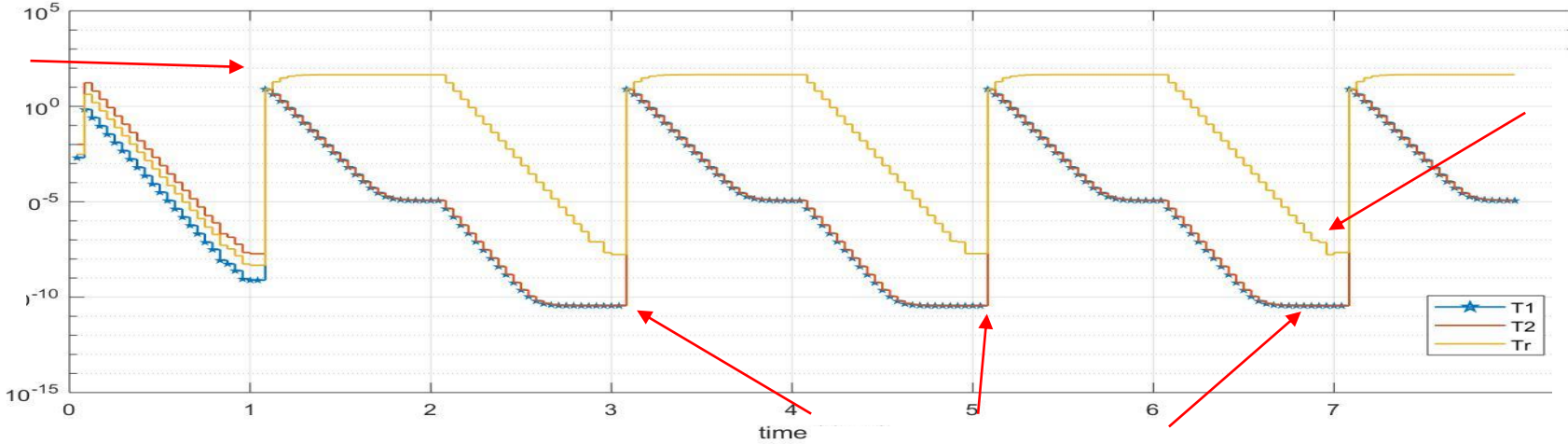
Dominance of Th1 cells during injection



The treatment given after 2 days. Initial special dose given is 1.6g.

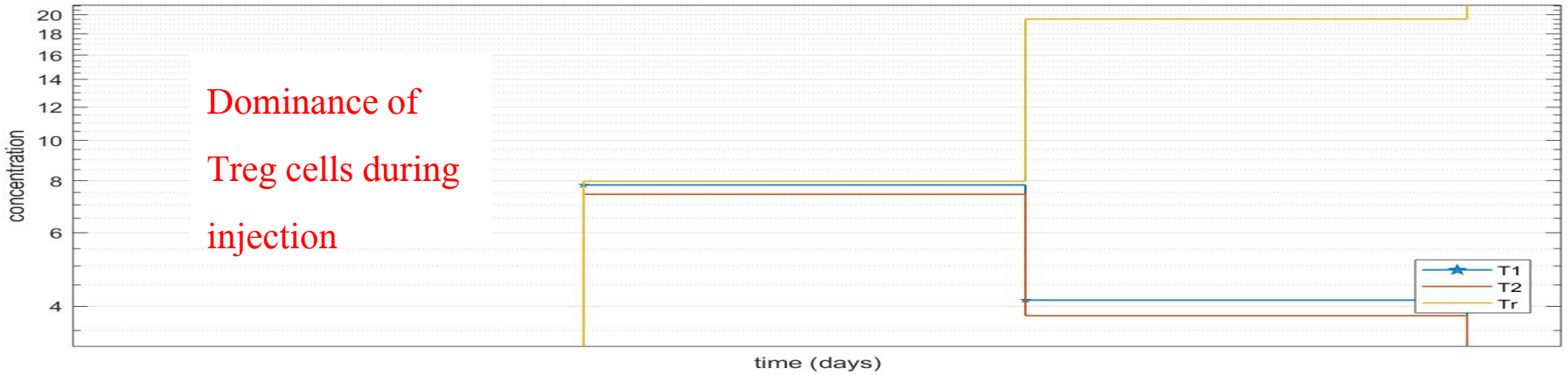
Increasing dose：0.01g

Dominance of Treg cells during injection



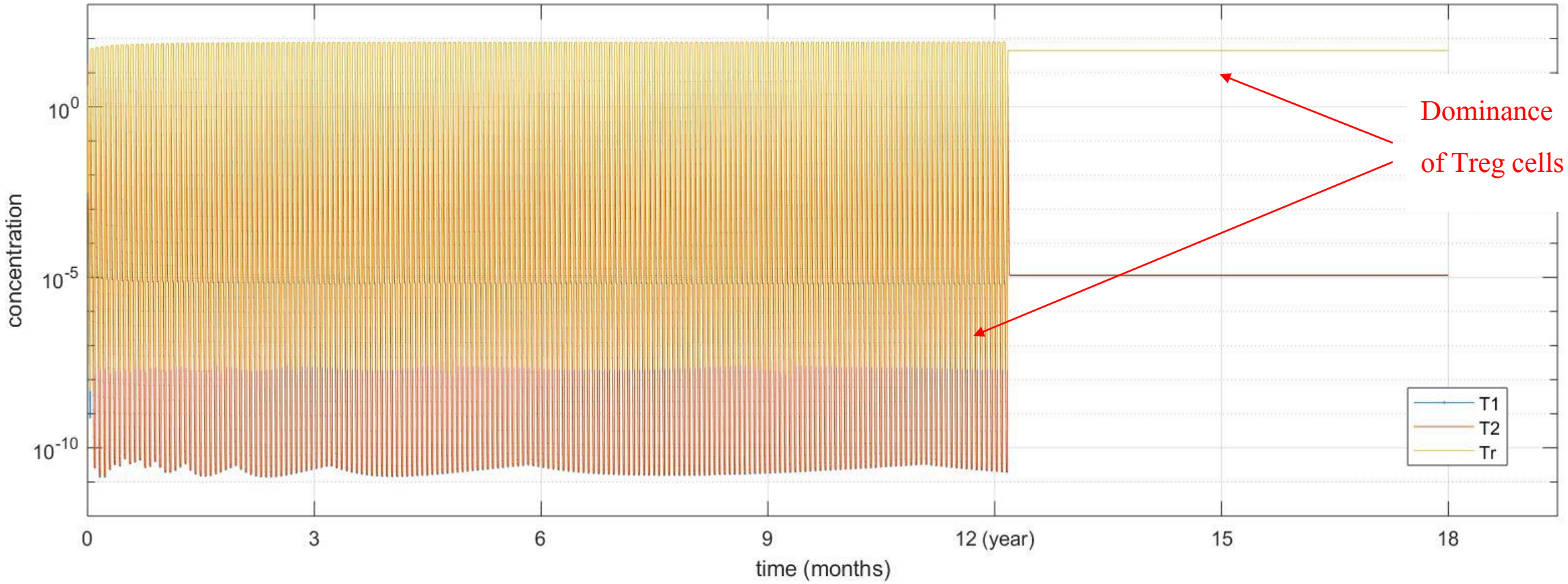
Dominance of Treg cells after injection

The next injection



Dominance of Treg cells during injection

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. Test period: 540 days



Simulation number	every # days	Special dose	adding	Tr before	Tr after	Difference
1	7	0.5	0.01	1.852	1.466	-0.386
2	7	1.7	0.01	1.852	.7161	-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	.5991	.4111	-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

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

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	150.1
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	1.36	44.91	43.55

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.


Thank you
for listening!