Heterogeneity in cell-mediated immune response

Task 1

ODE 1 represents the influences on the abundance of tumor cells type 1. g_1T_1 is the increase of the tumor cells which takes place with the intrinsic birth rate g_1. The other components reduce the abundance of the cells. $-a_{11}E_1T_1$ and $-a_{12}E_2T_1$ are the components accounting for the elimination of tumor cells by the effector cells E_1 and E_2.

ODE 2 encodes the changes in the abundance of tumor cells type 2. The first component stands for the reproduction of tumor cells with the intrinsic birth rate g_2. The second component accounts for the elimination of tumor cells by effector cell E_1. As it is written in the text, E_2 cannot recognize tumor cells of type 2 so that the third component given in ODE 1 doesn't appear.

ODE 3 represents the changes in the abundance of effector cell type 1. It occurs naturally with presence p_1 and eliminated with a rate -d_1 Since the effector cell depletes its capacity after a number of encounters with tumor cells of either type 1 or 2, the term $-e_1(T_1T_2)E_1$ accounts for the decrease caused by encounters with tumor cells. The last term stands for the recruitment (r_1) of effector cells that is stimulated by the cytocidal activities of effector cells.

ODE 4 stands for the influences on the abundance of effector cells type 2. E_2 is eliminated with a rate -d_2. The second term $-e_2T_1E_2$ stands for the decrease due to encounters with tumor cells of type 1. Since E_1 cells do not recognize T_2 cells, only encounters with T_1 are taken into account here. The term $\frac{r_2T_1}{s_2+T_1}$ stands for the recruitment of E_2 cells by the interaction with tumor cells of type 1 that have been processed by T_1 cells. The last term stands for the recruitment of E_2 cells by the interaction of E_1 cells with tumor cells of either type.

Task 2

2.1

- exponential growth term to be substituted: g_1T_1, g_2T_2

According to Alverez et al. (2019), the logistic growth is modeled using the following terms:

- $gT(1-bT)$

so that the ODEs from Task 1 are as follows:

- ODE 1: $\frac{dT_1}{dt} = g_1T_1(1-b_1T_1) - a_{11}E_1T_1 - a_{12}E_2T_1$

- ODE 2: $\frac{dT_2}{dt} = g_2 T_2(1 - b_2 T_2) - a_{21} E_1 T_2$

In the formulas, the terms g_1, g_2 are the birth rates of tumor cells of type 1 and 2. The terms in parentheses account for self-competition for resources in the cell populations (carrying capacity $= \frac{1}{b}$).

2.2

To account for competitions between the two populations, terms using interaction parameters for the interactions have to be introduced. Analogously to the Lotka-Volterra equation, terms are added to the equations as follows:

- ODE 1: $\frac{dT_1}{dt} = g_1 T_1(1 - b_1 T_1) - a_{11} E_1 T_1 - a_{12} E_2 T_1 - i_{12} T_1 T_2$
- ODE 2: $\frac{dT_2}{dt} = g_2 T_2(1 - b_2 T_2) - a_{21} E_1 T_2 - i_{21} T_1 T_2$

The terms $-i_{12} T_1 T_2$ and $-i_{21} T_1 T_2$ account for the influences that the populations of the tumor cells of the different types have on each other. The terms i_{12} and i_{21} do not have to be similar.

Task 3

In the ODEs for the effector cells, Michaelis-Menten terms are used to model the recruitment of new cells.

The Michaelis-Menten terms in the ODEs 3 and 4 are $\frac{r_1(T_1+T_2)}{s_1+T_1+T_2} E_1$ in ODE 3 and $\frac{r_2 T_1}{s_2+T_1} E_2$ in ODE 4. Since E_2 does not interact with T_2, the term contains fewer components.

The terms account for the accumulation of E-cells due the interactions of other E-cells with tumor cells. The term rTE which stands in the numerator of the fractions accounts for the interaction between the tumor cells (in case of E_1 both types, and in case of E_2 only type 1). The E-cells release chemicals such as cytokines to attract other E-cells in the surrounding area (recruitment rates $= r_1, r_2$). The denominator sums up the concentration of tumor cells in the population. Since the Michaelis-Menten kinetic is a saturation function, the level of recruitment of new E-cells is not limitless. It is limited by the size of T. As the denominator grows, the recruitment of E-cells cannot hold up (the value of saturation depends on the recruitment rates).

Task 4

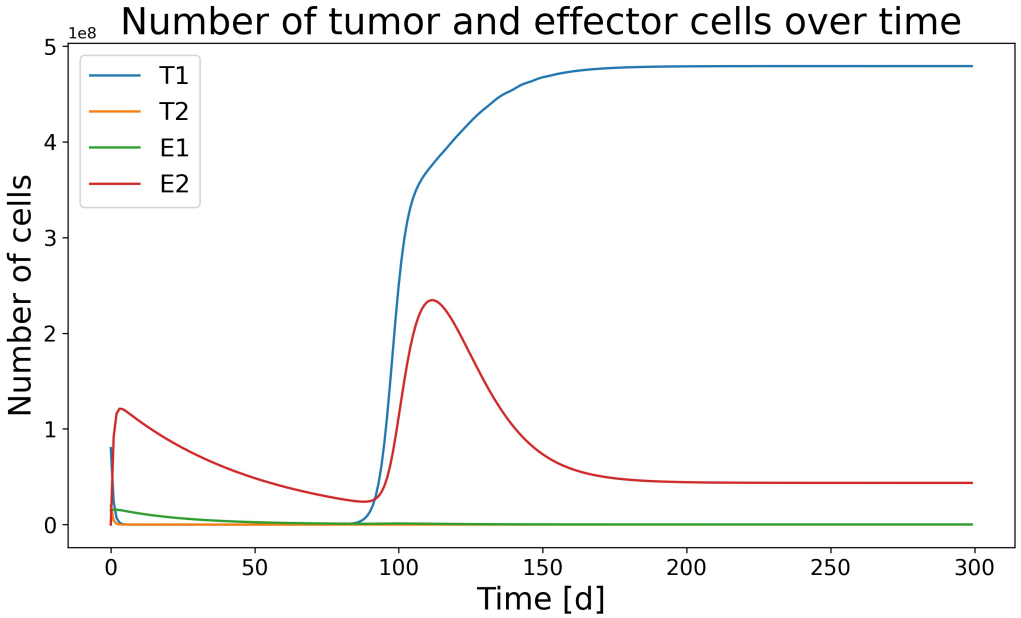
In task 2, the carrying capacity was defined as $\frac{1}{b}$. To use the parameters from the table, the carrying capacity is now deinfed using K_1, K_2 so that the equations from above are changed to

- ODE 1: $\frac{dT_1}{dt} = g_1 T_1(1 - \frac{T_1}{K_1}) - a_{11}E_1T_1 - a_{12}E_2T_1 - i_{12}T_1T_2$
- ODE 2: $\frac{dT_2}{dt} = g_2 T_2(1 - \frac{T_1}{K_2}) - a_{21}E_1T_2 - i_{21}T_1T_2$

where K_1, K_2 is the carrying capacity.

4.1

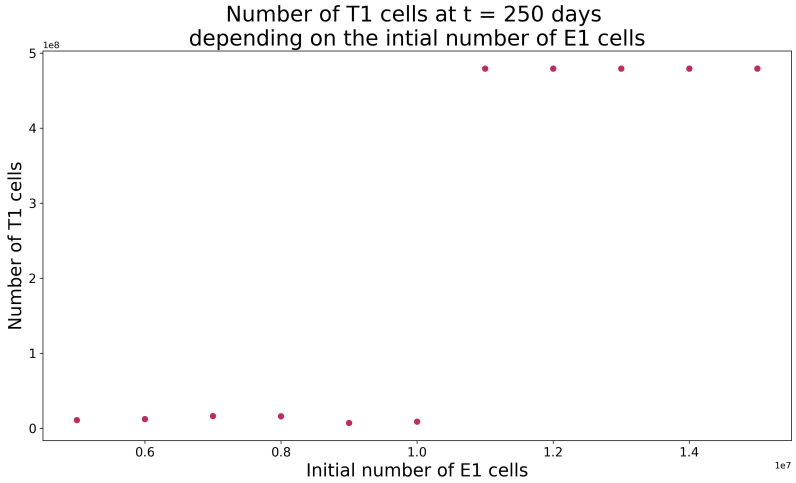
The total tumor size consists of T_1 cells as well as T_2 cells. The number of T_1 and T_2 in comparison to the effector cells can be seen in the figure below:



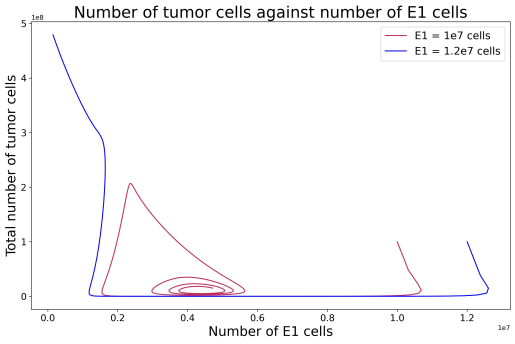
The total size of the tumor cells is almost similar to the number of tumor cells of type 1 since the number of tumor cells of type 2 is 0 over almost the whole time span. The dormancy observations observed by clinicians can partially be found in this model as well. The tumor stays small until approximately day 70 - 75 of the simulation. After that day, the tumor size grows to $5*10^8$ cells within the following 100 days. It reaches a constant size after ~200 days.

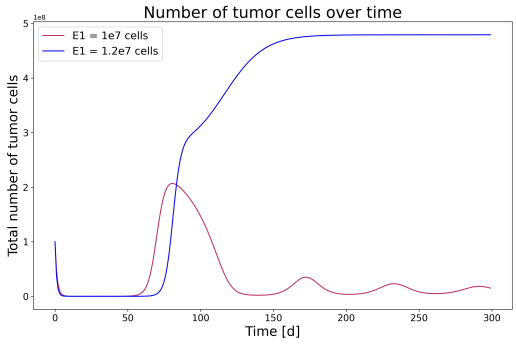
The number of E_2 cells seems to stagnate at $\sim 0.5*10^8$ cells. The number of T_2 and E_1 cells remain small over the whole period of time. This behavior is sensitive to the initial number of effector cells (E_1)

4.2



The model is sensitive to the initial number of E_1 cells. With an initial number lower than $1.1*10^7$ cells, the tumor size is not growing, with more initial cells than that number, the tumor is growing.





The observation contradicts the expectation. An initial value lower than the critical value leads to a smaller tumor and vice-versa.

4.3

I tried a sensitivity analysis using Sobol's method with the Python SALib package but I didn't manage to make it work.