Additional Material

Parameters values

The mathematical model was focused on one of the biological experiments performed by Gabriela et. al [1], which made a DCs pre-treatment with MAGE-AX before being injected into the mice. The maximal growth rate “r” and the tumor carrying capacity “K” were calculated using a least square method to adjust a Gompertz function in order determine the melanoma growth in the mice under the proper biological experimental conditions without immunotherapy.

Maximal growth rate of tumor, “r”. For its estimation is taken into account the estimation of average tumor diameters, measured by the UNAM researchers (the 7th day after melanoma cell induction and every two days after the 10th day for a period of 700 hours) in control mice immunotherapy; a spherical shape is assumed for the measured tumors and the average population is obtained on tumor cells (considering the size of melanoma tumor cell equal to 17.4 ± 0.21 µm [2]).

Using the least squares method a growth rate of blue 0.0010602 with an error of 4.95% was obtained.

Tumor carrying capacity, “K”. The maximum population sizes of tumor cells can be limited by the environment and represented by the tumor carrying capacity and is calculated using the same adjustment of the maximal growth rate of tumor “r” parameter. The search for the value of “K” is carried in a range between $10^{15}$ and $10^{20}$ and the value determined was $6.75 \times 10^{15}$ cells.

In another vein, observing the biological results, the mice died when the tumor reached a diameter of 4.3 cm (approximately $1.6 \times 10^{10}$ tumor cells); for that reason this population was taken as a limit of the population tumor cells in the simulation and was considered constant from that moment.

Natural death rate of DCs, “µD”. De Pillis et al. [3] Use the studies of Ludewing et al. [4] to determinate the value of “µD” in 0.009625 $h^{-1}$.

Death rate of activated CTLs in tumor compartment, “µCa”. The value “µCa” is calculated at 0.01925 $h^{-1}$ by De Pillis et al. [3].

Threshold in DC density for half-maximal proliferation rate of CTLs, “θD”. Set on 212 cells and determinated by De Pillis et al. [3].

Threshold in “Ca” density for half-maximal proliferation rate of CTLs, “θA”. Found in a interval search between [1, 300] and calculated at 10.
The proposed model and the experimental data of immunotherapy in mice with melanoma is used to find the “a$_T$”, “r”, “r$_E$” and “r$_A$” parameters performing an exhaustive research and minimizing method; the minimum mean square error value is taken as a reference value to determine the optimum value of the parameters. The minimum mean square error is a result of a comparison between the tumor cells population of the biological experiments and the tumor cell population generated by the model. The parameters value found is:

Maximal efficiency of cytotoxic cells, “a$_T$”. This parameter represents the efficiency at which the cytotoxic cells kill the tumor cells. Its estimation is carried out through an exhaustive search in an interval search between 10$^{-13}$ and 10$^3$ the value obtained is $6 \times 10^{-11} \text{h}^{-1}$.

Activation rate of CTLs, “r$_a$”. A interval search between 0.00001 and 100 is used to find the most optimal, estimated at 61$\text{h}^{-1}$. The data used in the models proposed by Ludewing et al. [4] and Handel et al. [5] is considered to determine the interval search.

Expansion rate of activated CTL, “r$_e$”. The value of “r$_e$” parameter is set at 6500$\text{h}^{-1}$ which is the result of the estimation using an exhaustive search in an interval search between 10$\text{h}^{-1}$ and 7000$\text{h}^{-1}$.

Delay in the time, “r”. Indicates the time when the therapy is becoming effective, considering that this is effective between 100 and 300 hours after injecting the first immunotherapy, and taking into account the data of immunotherapy biological tests the value of “r” is determined in 265 hours by an exhaustive search.

The parameters listed below are taken for the Kronik et al. [6] study.

Maximal reduction effect of “TGF$-\beta$” on CTLS efficiency, “a$_{T,\beta}$”. Using the reports about the CTL efficacy the value determined by Kronik et al. is 0.69$\text{h}^{-1}$.

Dependence of CTLS efficiency on TGF$-\beta$, “e$_{T,\beta}$”. Estimated at 10$^4$pg.

Death rate of inactivated CTLs, “$\mu$_C”. The model uses the CTLs half life estimated by Kronik et al.[6] in 0.007$\text{h}^{-1}$.

Production rate of TGF$-\beta$ by a single tumor cell, “r$_{T,\beta}$”. Set at 5.75 * 10$^{-6}$ pg(cell * h)$^{-1}$.

Degradation rate TGF$-\beta$, “$\mu$_F”. Is found in a interval search between 1$h^{-1}$ and 10$h^{-1}$, set at 2.7$h^{-1}$.
Simulation of the mathematical model trajectories, Protocol 1 and 12

Figure 1: Simulation cytotoxic cell growth with the Protocol 1. Simulation for 1000 hours set to $T(0) = 6 \times 10^4$, $r = 0.00106h^{-1}$ and $K = 6.754 \times 10^{15} cells$.

Figure 2: Simulation of dendritic cells dynamic (A), CTLs activated dynamic (B), CTLs inactivated dynamic (C) and TGF-B dynamic (D) with the Protocol 1. Simulation for 1000 hours set to $T(0) = 6 \times 10^4$, $r = 0.00106h^{-1}$ and $K = 6.754 \times 10^{15} cells$. 


Figure 3: Simulation cytotoxic cell growth with the Protocol 2. Simulation for 1000 hours set to $T(0) = 6 \times 10^4$, $r = 0.00106 h^{-1}$ and $K = 6.754 \times 10^{15} cells$.

Figure 4: Simulation of dendritic cells dynamic (A), CTLs activated dynamic (B), CTLs inactivated dynamic (C) and TGF-B dynamic (D) with the Protocol 2. Simulation for 1000 hours set to $T(0) = 6 \times 10^4$, $r = 0.00106 h^{-1}$ and $K = 6.754 \times 10^{15} cells$.

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| Parameter | Description | Estimated value | Reference |
|-----------|-------------|-----------------|-----------|
| $r$       | Maximal growth rate of tumor | 0.001060289 $h^{-1}$ | Fit to Gompertz function |
| $K$       | Tumor carrying capacity | $6.75 \times 10^{15}$ cells | Fit to Gompertz function |
| $a_T$     | Maximal efficiency of citotoxic cells | $6\times 10^{-11} h^{-1}$ | Estimated |
| $a_{T,\beta}$ | Maximal reduction effect of $TGF-\beta$ on CTLs efficiency | 0.69 none | Base on data of Kronik [6] and Thomas [7] |
| $e_{T,\beta}$ | Dependence of CTLs efficiency of $TGF-\beta$ | $10^4 pg$ | Base on data of Peterson [8] and Kronik [6] |
| $\mu_D$   | Natural death rate of DCs | $0.009625 X h^{-1}$ | Ludewing [4] and De Pillis [3] |
| $r_a$     | Activation rate of CTLs by DC | $61 h^{-1}$ | Estimated |
| $\theta_D$ | Threshold in DC density in the spleen for half-maximal proliferation rate of CTLs | $212 cells$ | Based on Ludewing [4] |
| $r_e$     | Expansion rate of activated CTL | $6500 h^{-1}$ | Estimated |
| $\mu_{C_a}$ | Dead rate of activated CTLs in tumor compartment | $0.01925 h^{-1}$ | De Pillis [3] |
| $\theta_A$ | Threshold in $C_a$ density for half-maximal proliferation rate of CTLs | $10 cells$ | Ad hoc fixed value |
| $\mu_{C_i}$ | Dead rate of inactive CTLs in tumor compartment | $0.007 h^{-1}$ | Ad hoc fixed value base on Kronik [6] |
| $r_{T,\beta}$ | Production rate of $TGF-\beta$ by a single tumor cell | $5.75 \times 10^{-6} pg (cell*h)^{-1}$ | Base on data of Peterson [8] and Kronik [6] |
| $\mu_\beta$ | Degradation rate of $TGF-\beta$ by a single tumor cell | $2.7 h^{-1}$ | Fit to Coffey [9] and Kronik [6] |
| $\tau$    | Delay in the time to be effective the immunotherapy | $265 h$ | Estimated |
| DCsize    | Diameter of Dendritic Cell | $1.74 \mu$ | Ochalek [2] |
Table 2: Initial condition of the model

| Model variable | Value     | Interval in the time | Reference                |
|----------------|-----------|----------------------|--------------------------|
| \( T(t) \)    | \( 6 \times 10^4 \) | \([-\tau, 0]\)       | Gabriela et. al. [1]     |
| \( D(t) \)    | 0         | \([-\tau, 0]\)       |                          |
| \( C_0(t) \)  | 0         | \([-\tau, 0]\)       |                          |
| \( C_1(t) \)  | \( 2 \times 10^6 \) | \([-\tau, 0]\)       | Duriacil et. al [10]     |
| \( F_\beta \) | 0         | \([-\tau, 0]\)       |                          |