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Fighting tumor

General and prostate cancer models comparison

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9th January 2023

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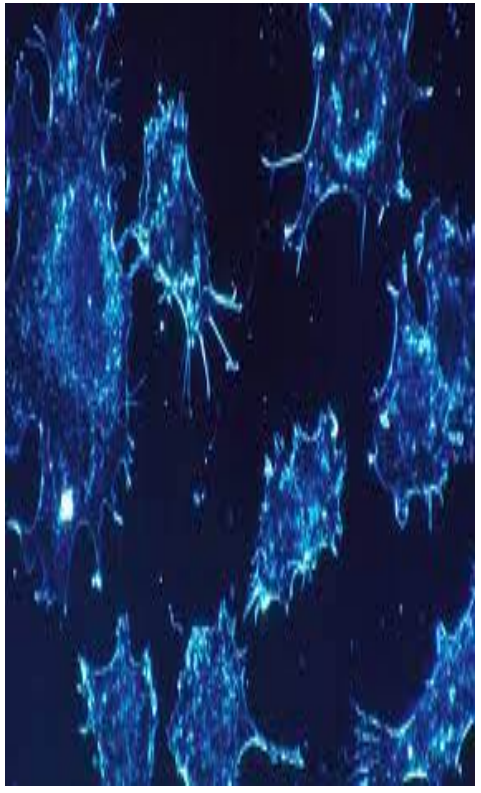


De Pillip's model

De Pillip's model: Structure

Populations at time t are denoted by:

- $T(t)$ - tumor cell population
- $N(t)$ - NK cell population
- $L(t)$ - $CD8^{+}T$ cell population
- $C(t)$ - circulating lymphocytes
- $M(t)$ - chemotherapy concentration in bloodstream
- $I(t)$ - immunotherapy concentration in bloodstream

Equations

- Net growth G_i
- Fractional cell kill F_i
- Per cell recruitment R_i
- Cell inactivation I_i
- Drug intervention H_i

$$\frac{dT}{dt} = \overbrace{aT(1-bT)}^{G_T} - \overbrace{cNT}^{F_N(T,N)} - \overbrace{DT}^{F_L(T,L)} - \overbrace{K_T(1-e^{-M})T}^{F_{MT}} \qquad D = d\frac{(L/T)^l}{s+(L/T)^l}$$

$$\frac{dN}{dt} = \overbrace{eC-fN}^{G_N} + \overbrace{\frac{gT^2}{h+T^2}N}^{R_N(T,N)} - \overbrace{pNT}^{I_N} - \overbrace{K_N(1-e^{-M})N}^{F_{MN}}$$

$$\frac{dL}{dt} = \overbrace{-mL}^{G_L} + \overbrace{\frac{jD^2T^2}{k+D^2T^2}L}^{R_L^1(T,L)} - \overbrace{qLT}^{I_L} + \overbrace{r_1NT}^{R_L^2(N,T)} + \overbrace{r_2CT}^{R_L^3(C,T)} - \overbrace{uNL^2}^{I_{CL}}$$

$$- \overbrace{K_L(1-e^{-M})L}^{F_{ML}} + \overbrace{\frac{p_I I}{g_I+I}L}^{F_{LI}} + \overbrace{v_L(t)}^{H_L}$$

Equations

- Net growth G_i
- Fractional cell kill F_i
- Per cell recruitment R_i
- Cell inactivation I_i
- Drug intervention H_i

$$\frac{dC}{dt} = \overbrace{\alpha - \beta C}^{G_C} - \overbrace{K_C(1 - e^{-M})C}^{F_{MC}}$$

$$\frac{dM}{dt} = \overbrace{-\gamma M}^{G_M} + \overbrace{v_M(t)}^{H_M}$$

$$\frac{dI}{dt} = \overbrace{-\mu_I I}^{G_I} + \overbrace{v_I(t)}^{H_I}$$

Non-dimensionalization

To allow for analysis we suppose $M = 0$ and $I = 0$ and we non-dimensionalize as follows:

$$C^* = \frac{a}{\alpha}C \quad T^* = bT \quad N^* = \frac{a^2}{\alpha e}N \quad L^* = bL \quad D^* = \frac{1}{a}D \quad t^* = at$$

We obtain:

$$\frac{dT}{dt} = T(1-T) - cNT - DT \qquad \frac{dN}{dt} = C - fN + g\frac{T^2}{h+T^2}N - pNT$$

$$\frac{dC}{dt} = 1 - \beta C \qquad D = d\frac{(L/T)^l}{s+(L/T)^l}$$

$$\frac{dL}{dt} = -mL + j\frac{D^2T^2}{k+D^2T^2}L - qLT + (r_1N + r_2C)T - uNL^2$$

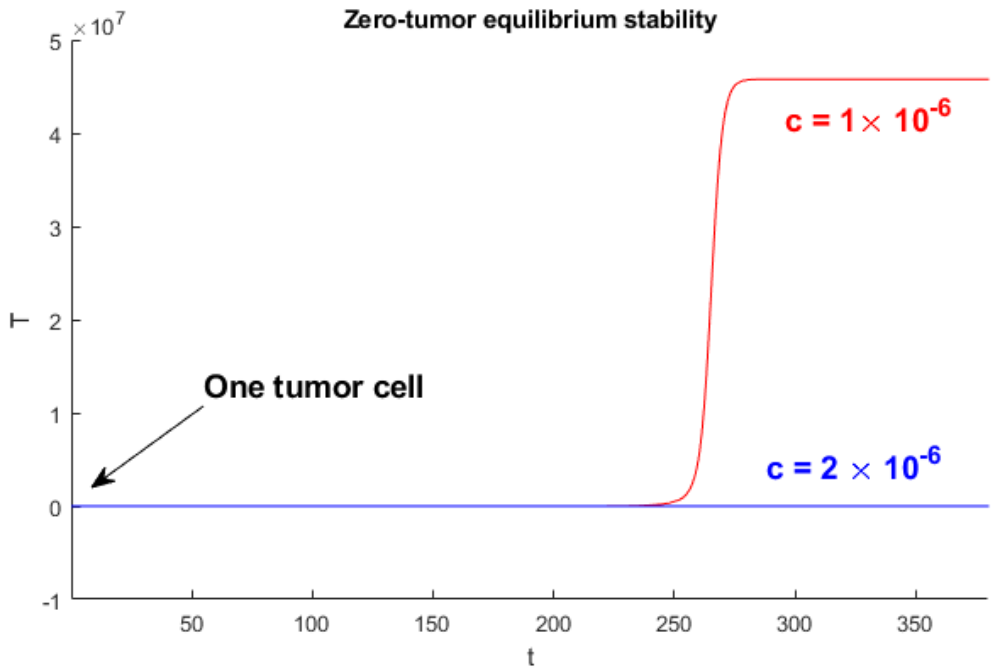
Equilibria

dC/dt decouples $\Rightarrow C_E = 1/\beta$

dT/dt has two equilibria $\Rightarrow T_{E,1} = 0 \qquad T_{E,2} \neq 0$

Tumor free equilibria: $E_0 = (T_{E,1}, N_E, L_E, C_E) = (0, 1/\beta f, 0, 1/\beta)$

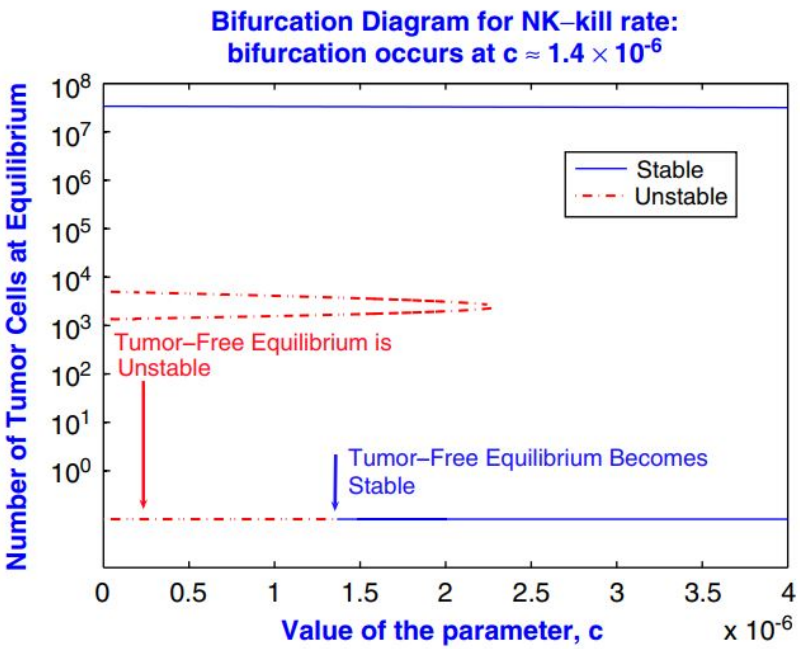
Tumor high equlibria (mouse): $T_{E,2} \approx 3.48 \times 10^7$

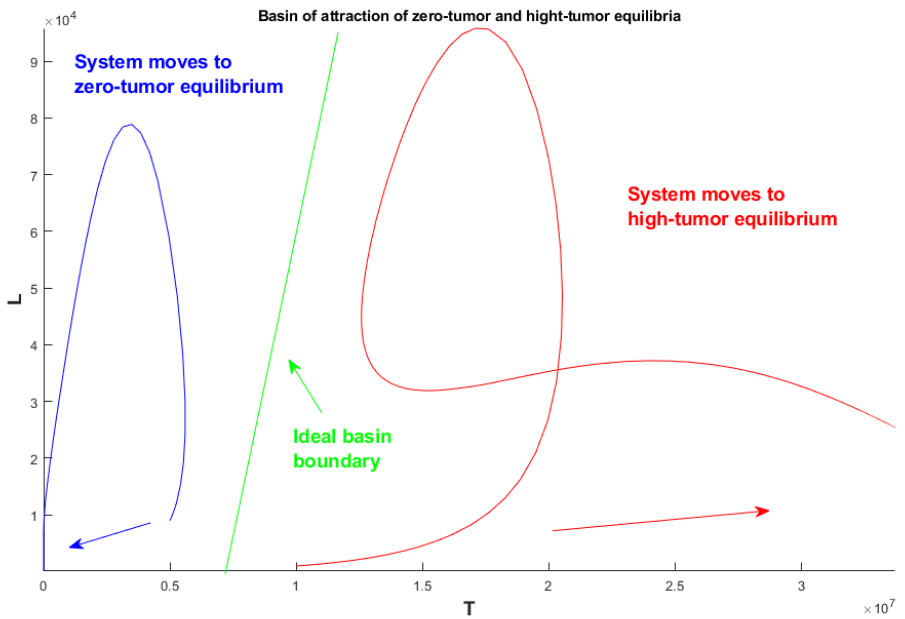


Stability

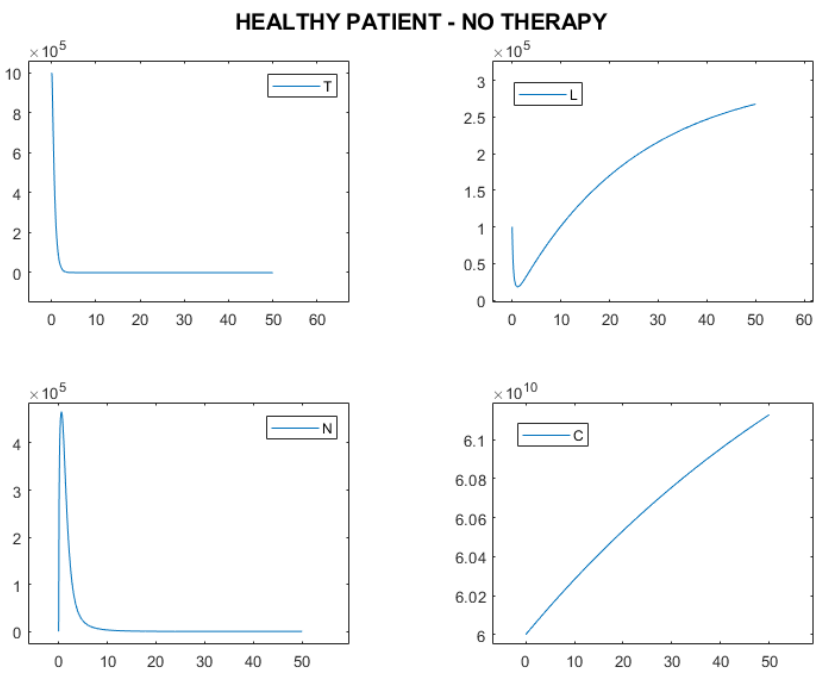
$$J(E_0) = \begin{pmatrix} 1 - \frac{c}{\beta f} & 0 & 0 \\ -\frac{p}{\beta f} & -f & 0 \\ \frac{r_1}{\beta f} + \frac{r_2}{\beta} & 0 & -m \end{pmatrix} \Rightarrow \begin{array}{l} \lambda_1 = 1 - \frac{c}{\beta f} \\ \lambda_2 = -f < 0 \\ \lambda_3 = -m < 0 \end{array}$$

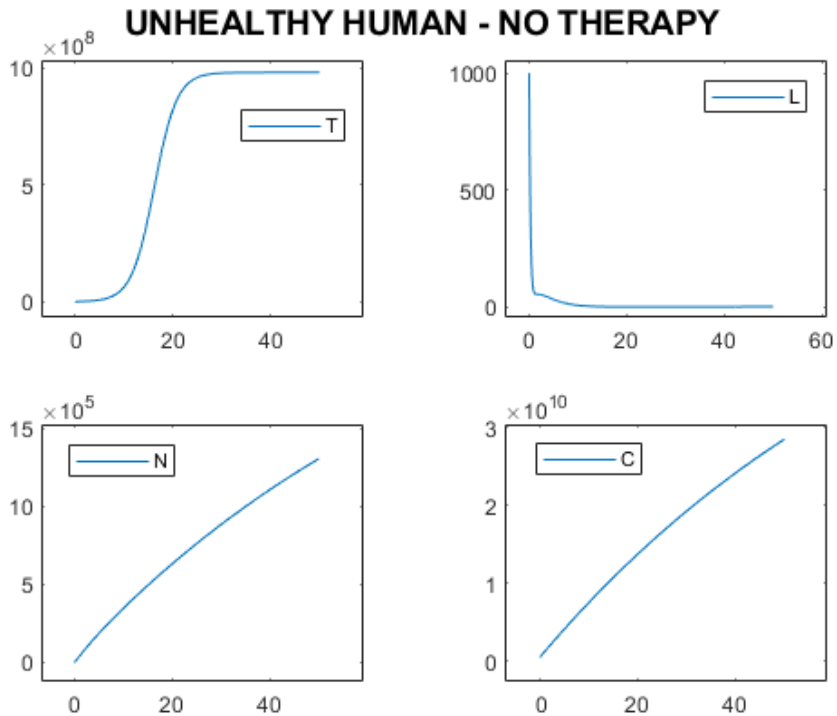
Hence, condition for stability is: $\lambda_1 < 0 \Leftrightarrow c > \beta f$



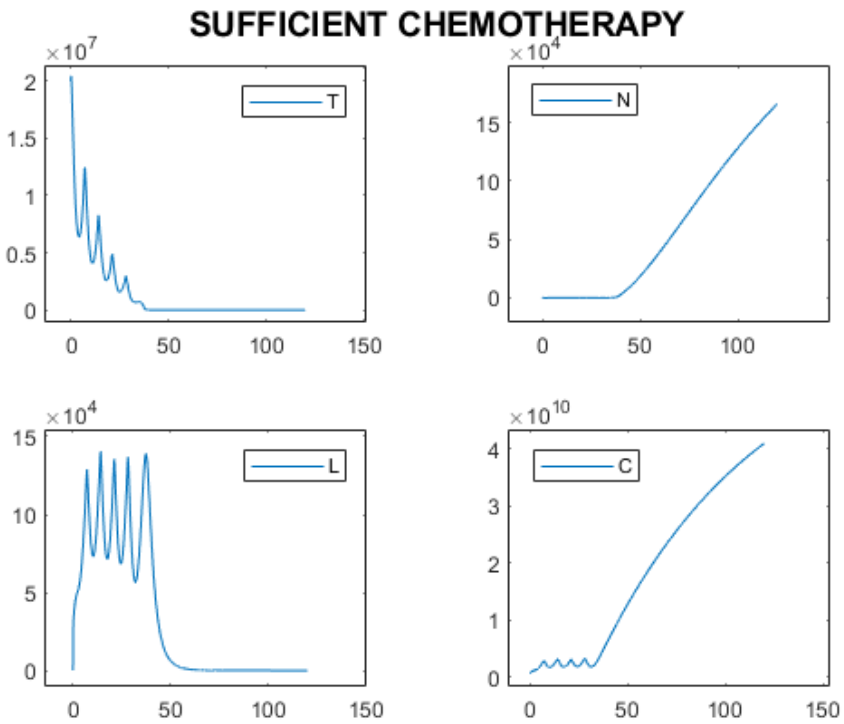


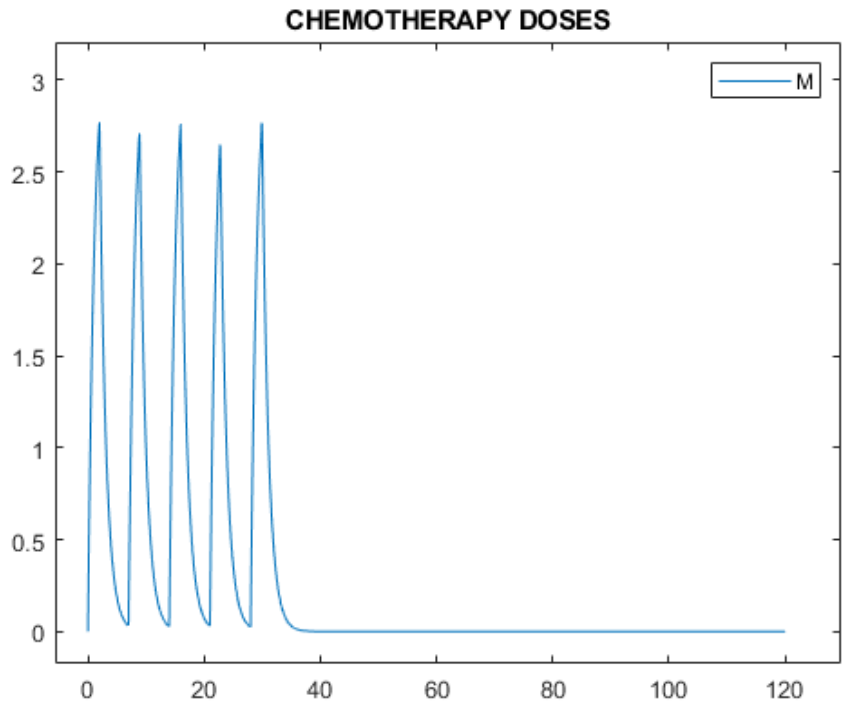
Immune system response





Sufficient chemotherapy treatment

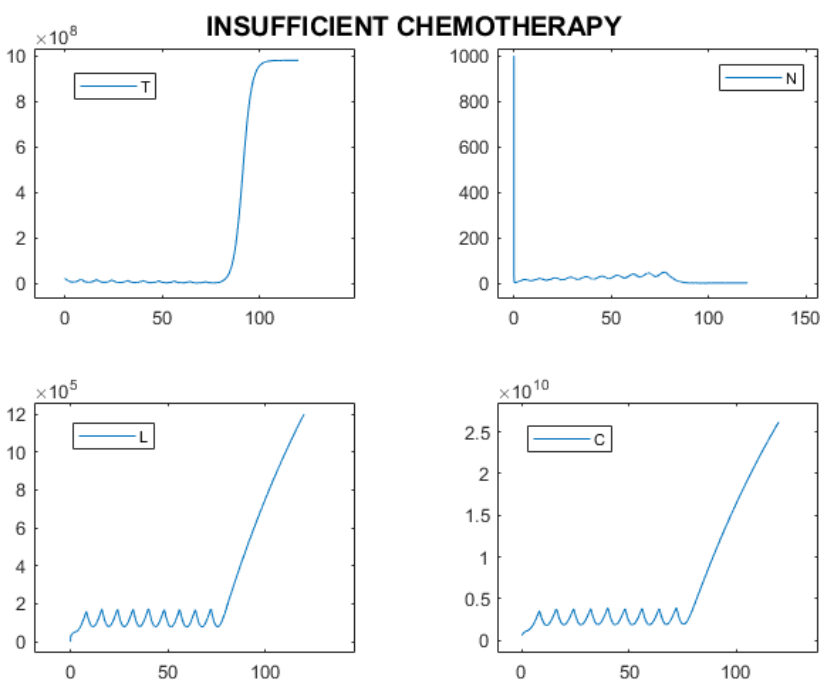


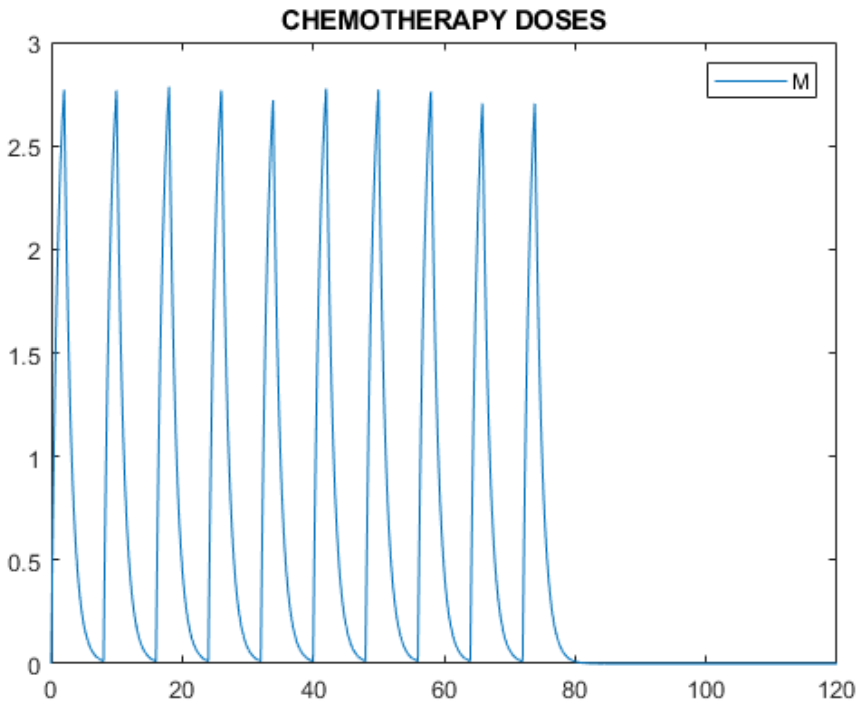


Chemotherapy: 5 doses, every 7 time units, $v_M = 3$

In paper: 9 doses, every 5 time units, $v_M = 5$

Insufficient chemotherapy treatment



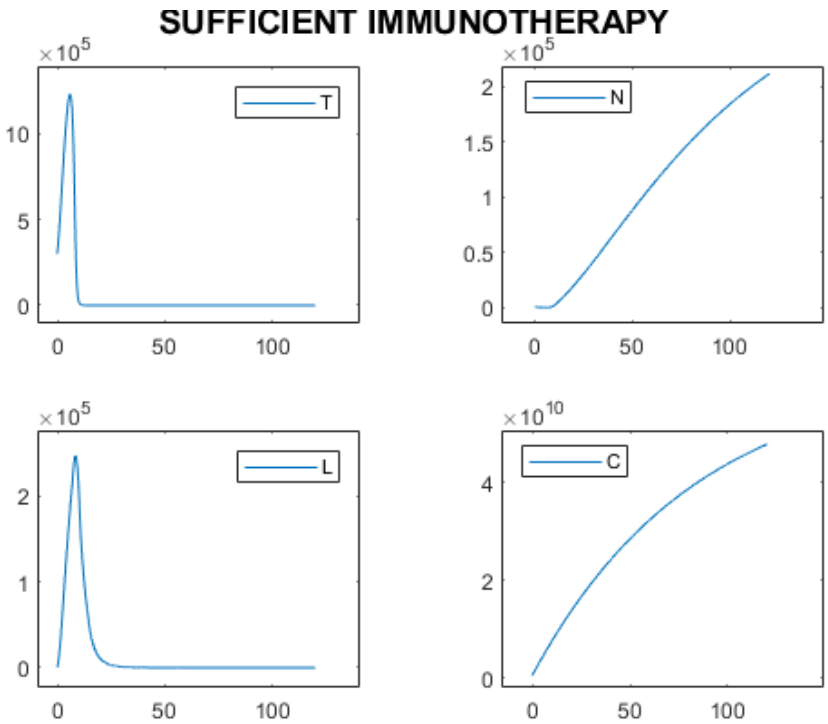


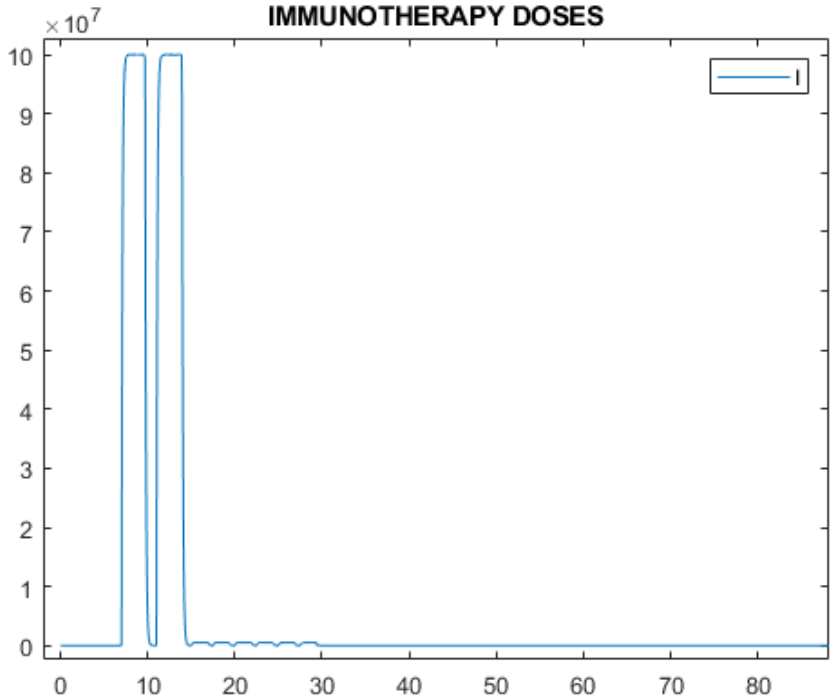
Chemotherapy: 9 doses, every 8 time units, $v_M = 3$

In paper: 9 doses, every 10 time units, $v_M = 5$

Immunotherapy treatment

The insufficient immutherapy is just as the unhealty patient without treatment. In that case the starting tumor is bigger.

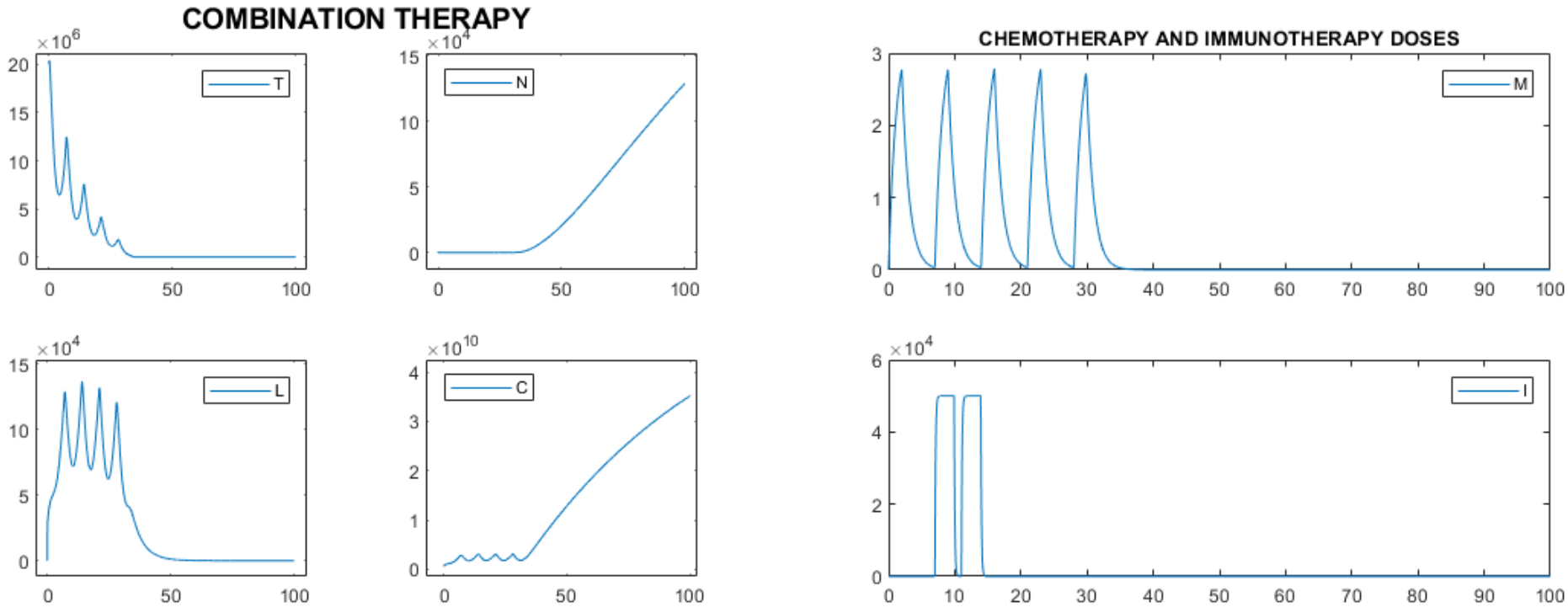




Imm.: 2 doses, for 4 t.u., $v_I = 10^9$; then 6 doses, for 2.5 t.u., $v_I = 5 \times 10^6$

In paper: 2 doses, $v_I = 10^9$; then 6 doses, $v_I = 5 \times 10^6$.

Combination therapy

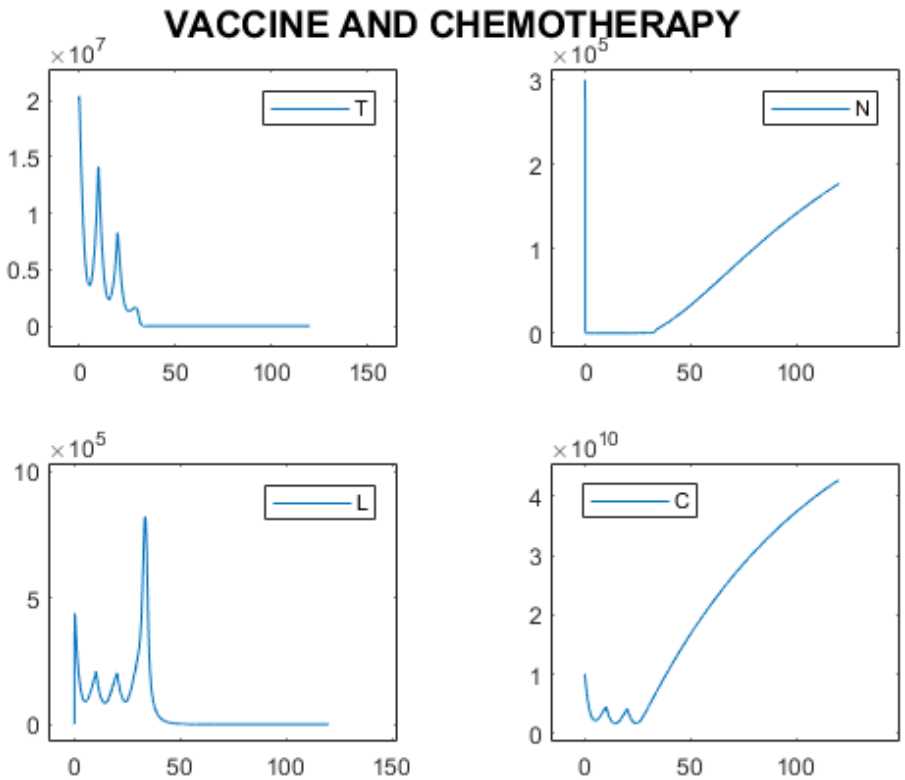


Chemotherapy: 5 doses, every 7 time units, $v_M = 3$

Immunotherapy: 2 doses, for 4 time units, $v_I = 5 \times 10^5$

In paper: (chem.) 9 doses, every 10 t.u., $v_M = 5$; (imm.) 2 doses, for 2 t.u., $v_I = 10^9$; then 6 doses, for 4 t.u., $v_I = 5 \times 10^5$.

Vaccine and chemotherapy



Chemotherapy: 3 doses, every 10 t.u., $v_M = 3.4$

Vaccine: administered at t.u. 10; c, g, j, d increased, s decreased

In paper: (chem.) 3 doses, every 10 t.u., $v_M = 2$; (vac.) at t.u. 10.

Coletti's model

Coletti's model: structure

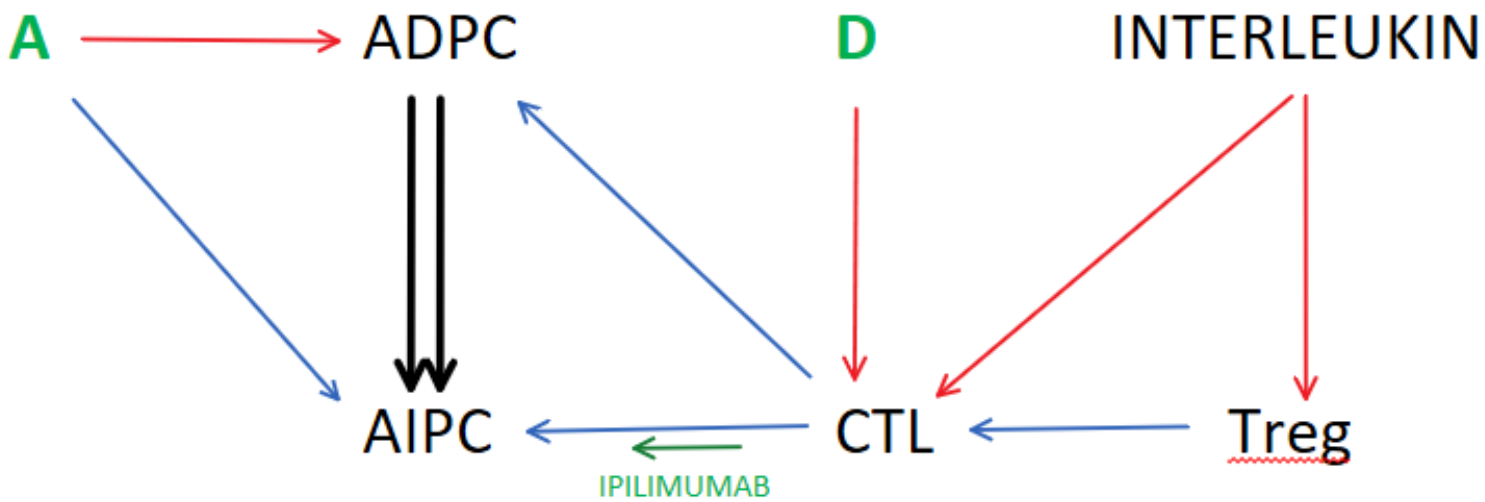


Figure: Biological interactions between some variables (in black) and treatments (in green) where red arrows indicate positive influence while blue ones represent inhibition

$$\frac{dX_1}{dt} = \overbrace{r_1\ A\ X_1\left(1-\frac{X_1+X_2}{K}\right)}^{\text{Tumor proliferation}} - \overbrace{\mu_1\left(1-\frac{A}{a_0}\right)X_1}^{\text{Death}} - \overbrace{m_1\left(1-\frac{A}{a_0}\right)X_1}^{\text{Mutation}} - \overbrace{C\ X_1\left(\frac{e_{CX}}{g_{CX}+(X_1+X_2)}+k_{Ip}\ I_P\right)}^{\text{CTL effect}}$$

$$\frac{dX_2}{dt} = \overbrace{r_2\ X_2\left(1-\frac{X_1+X_2}{K}\right)}^{\text{Tumor proliferation}} + \overbrace{m_1\left(1-\frac{A}{a_0}\right)X_1}^{\text{Mutation}} - \overbrace{C\ X_2\left(\frac{e_{CX}}{g_{CX}+(X_1+X_2)}+k_{Ip}\ I_P\right)}^{\text{CTL effect}}$$

$$\frac{dC}{dt} = \overbrace{e_C\ \frac{D}{g_C+D}}^{\text{Activation by } D} + \overbrace{\frac{e_{IC}\ C\ I_L}{g_{IC}+I_L}}^{I_L \text{ effect}} - \overbrace{\mu_C\ C}^{\text{Death}} - \overbrace{k_R\ C\ R}^{T_{reg} \text{ effect}}$$

$$\frac{dA}{dt} = \overbrace{\gamma_A(a_0-A)}^{\text{Proliferation and death}} - \overbrace{\gamma_A\ a_0\ \mathbf{1}_{CX}}^{\text{Tumor's and CTL's effect}}$$

$$\frac{dR}{dt} = \overbrace{a_R\ D}^{D \text{ effect}} - \overbrace{\mu_R\ R}^{\text{Death}} + \overbrace{a_{IR}\ I_L}^{I_L \text{ effect}}$$

$$\frac{dD}{dt} = \overbrace{s_D}^{\text{Source}} - \overbrace{\mu_D\ D}^{\text{Death}} + \overbrace{v}^{\text{Vaccine}}$$

$$\frac{dI_L}{dt} = \overbrace{e_I\ \frac{C\ (X_1+X_2)}{g_I+(X_1+X_2)}}^{\text{Tumor's and CTL's effect}} + \overbrace{\mu_I(i_0-I_L)}^{\text{Proliferation and death}}$$

$$\frac{dI_p}{dt} = - \overbrace{\gamma_p\ I_p}^{\text{ICB degradation}}$$

Coletti's model: simplification

Assumptions:

$$\frac{dA}{dt} = -\gamma_a\, A, \qquad \frac{dI_p}{dt} = d_p - \lambda_p\, I_p.$$

Quasi-steady approach:

$$A^* = 0, \qquad D^* = \frac{s_D + v}{\mu_D}, \qquad I_p^* = \frac{d_p}{\lambda_p},$$

$$I_L(C, X_1, X_2) = i_0 + \frac{e_I\, C\, (X_1 + X_2)}{\mu_I(g_I + X_1 + X_2)}.$$

Limiting system assumptions:

$$\frac{dX_1}{dt} < 0, \qquad \lim_{t \to +\infty} X_1(t) = 0$$

$$\begin{cases} \frac{dX_2}{dt} & = r_2\ X_2 \left(1 - \frac{X_2}{K}\right) - C\ X_2 \frac{e_{CX}}{g_{CX}+X_2} + C\ X_2\ k_{lp}\ I_P^* \\ \frac{dC}{dt} & = s_C + \frac{e_{IC}\ C\ I_L(C,0,X_2)}{g_{IC}+I_L(C,0,X_2)} - \mu_C\ C - k_R\ C\ R \\ \frac{dR}{dt} & = s_R - \mu_R\ R + a_{IR}\ I_L(C,0,X_2) \end{cases}$$

$$E^o = \left(X_2^o = 0, \quad C^o = \frac{s_C}{\mu_C\ k_R\ R^0 - \frac{e_{IC}\ i_0}{g_{IC}+i_0}}, \quad R^o = \frac{s_R + a_{IR}\ i_0}{\mu_R} \right)$$

$$J(E^o) = \begin{pmatrix} r_2 - C^o\ \frac{e_{CX}}{g_{CX}} & 0 & 0 \\ \dots & \frac{e_{IC}\ i_0}{g_{IC}+i_0} - \mu_C - k_R\ R & -k_R C^o \\ \dots & 0 & -\mu_R \end{pmatrix}$$

$$\lambda_1 = r_2 - C^o\ \frac{e_{CX}}{g_{CX}} \qquad \lambda_2 = \frac{e_{IC}\ i_0}{g_{IC} + i_0} - \mu_C - k_R\ R^o \qquad \lambda_3 = -\mu_R$$

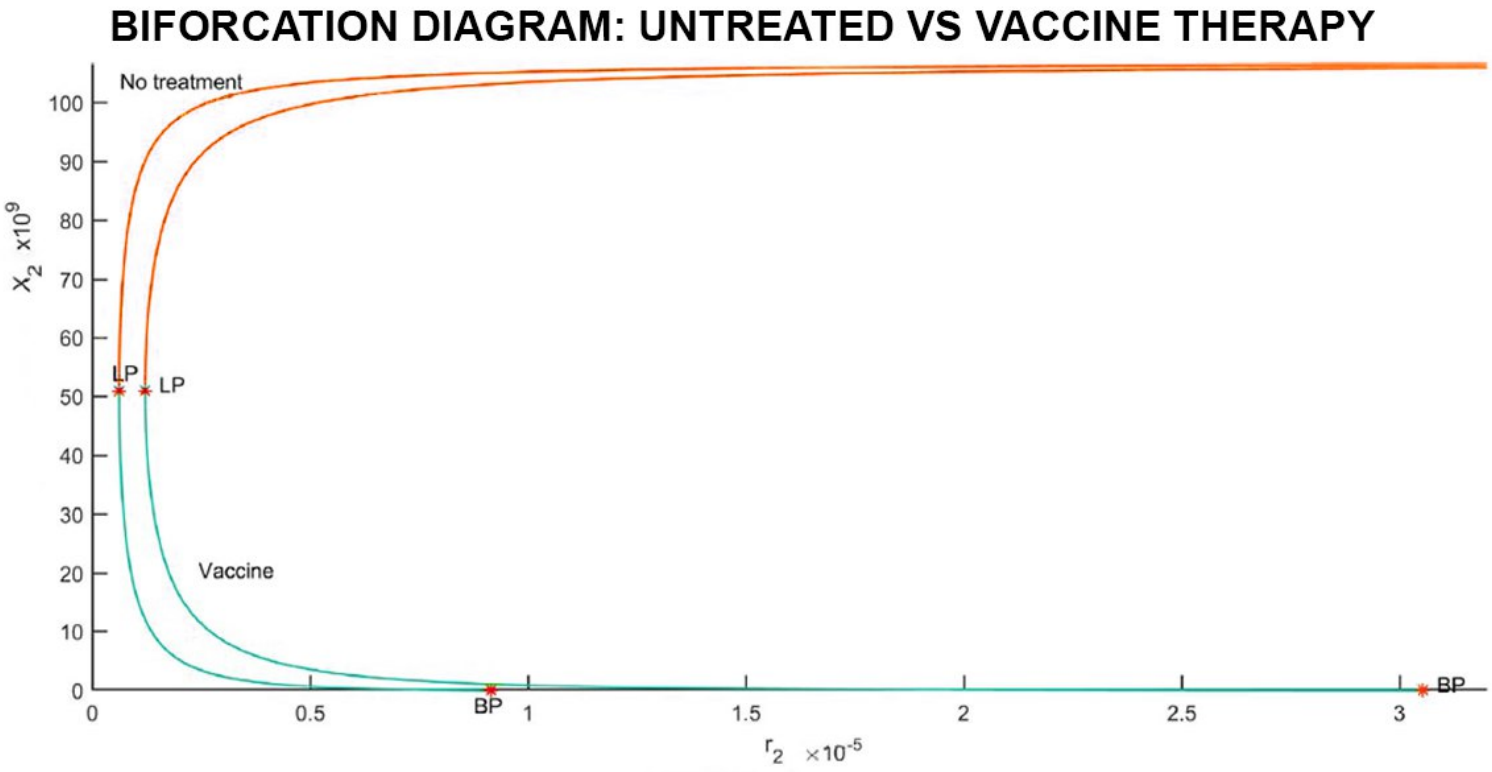


Figure: Biforcation diagram no treatment vs vaccine therapy

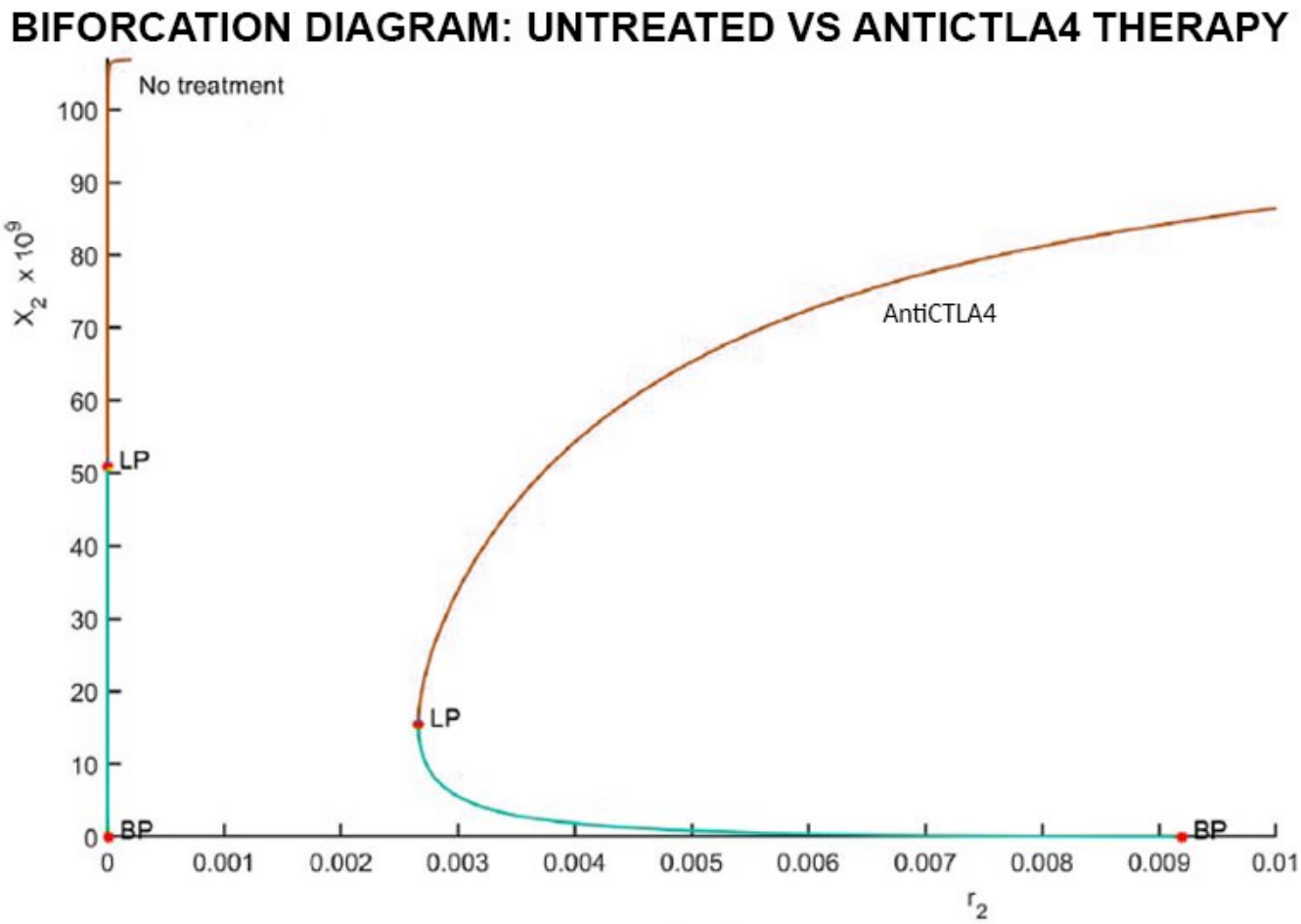


Figure: Biforcation diagram no treatment vs AntiCTLA4 therapy

Coletti's model: simulations

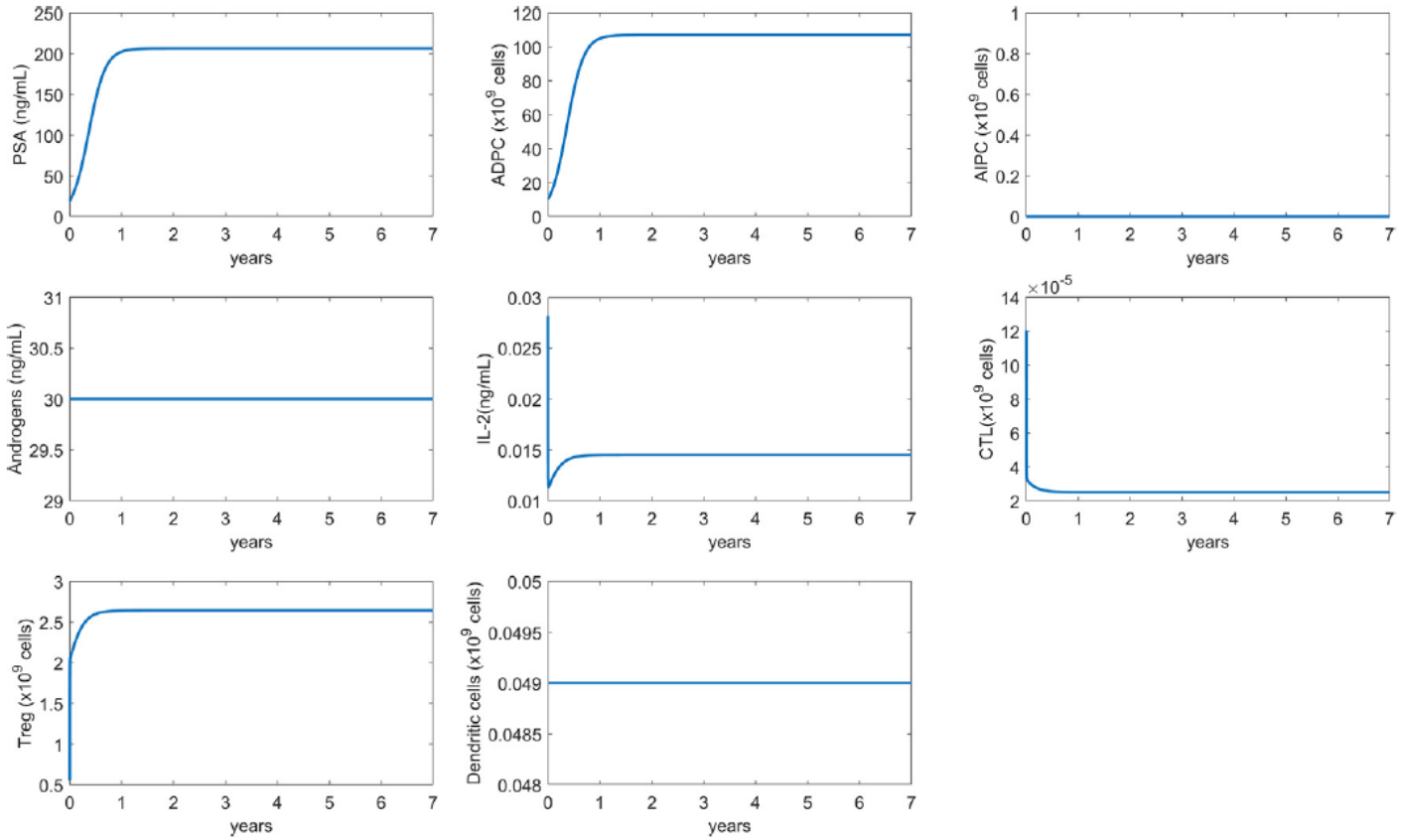


Figure: Simulation: untreated case

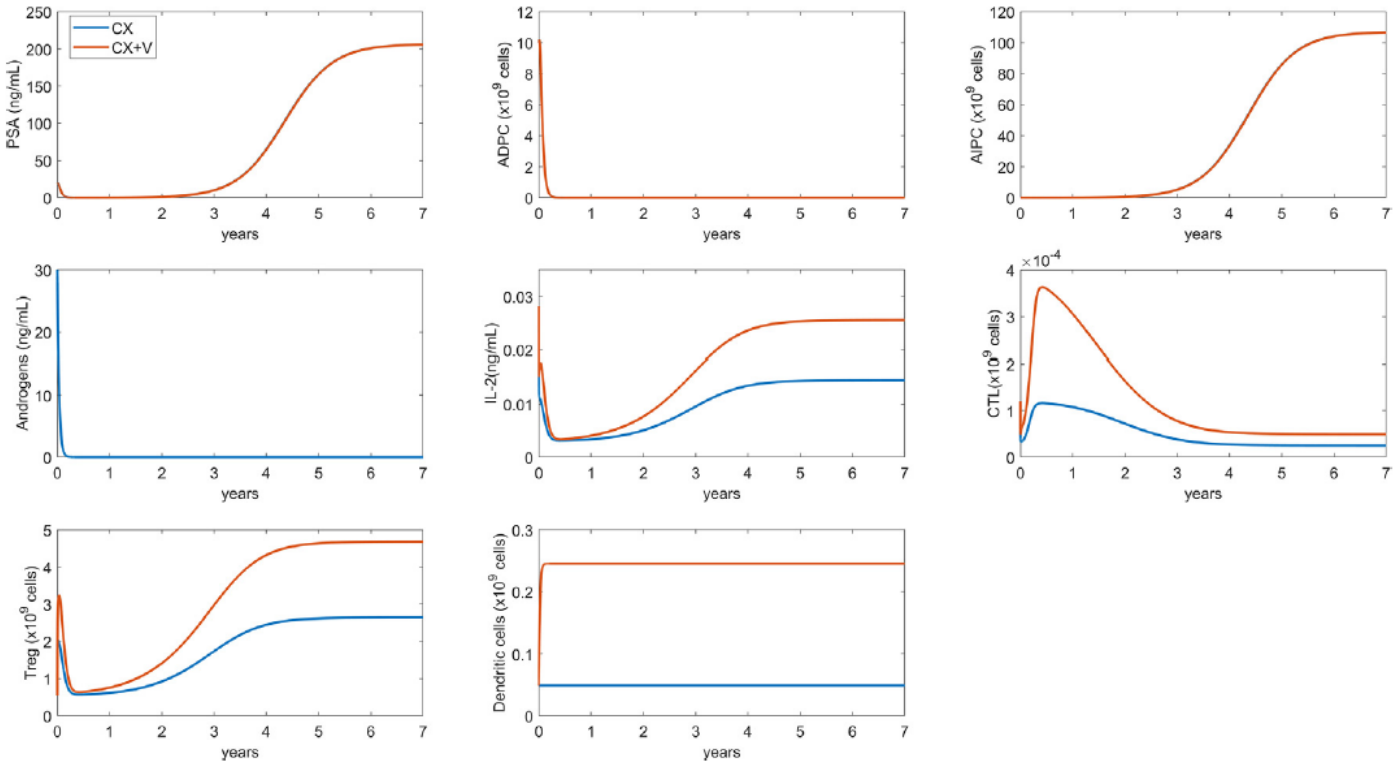


Figure: Simulation: androgen deprivation therapy by itself (blue) and combined with the vaccine treatment (orange)

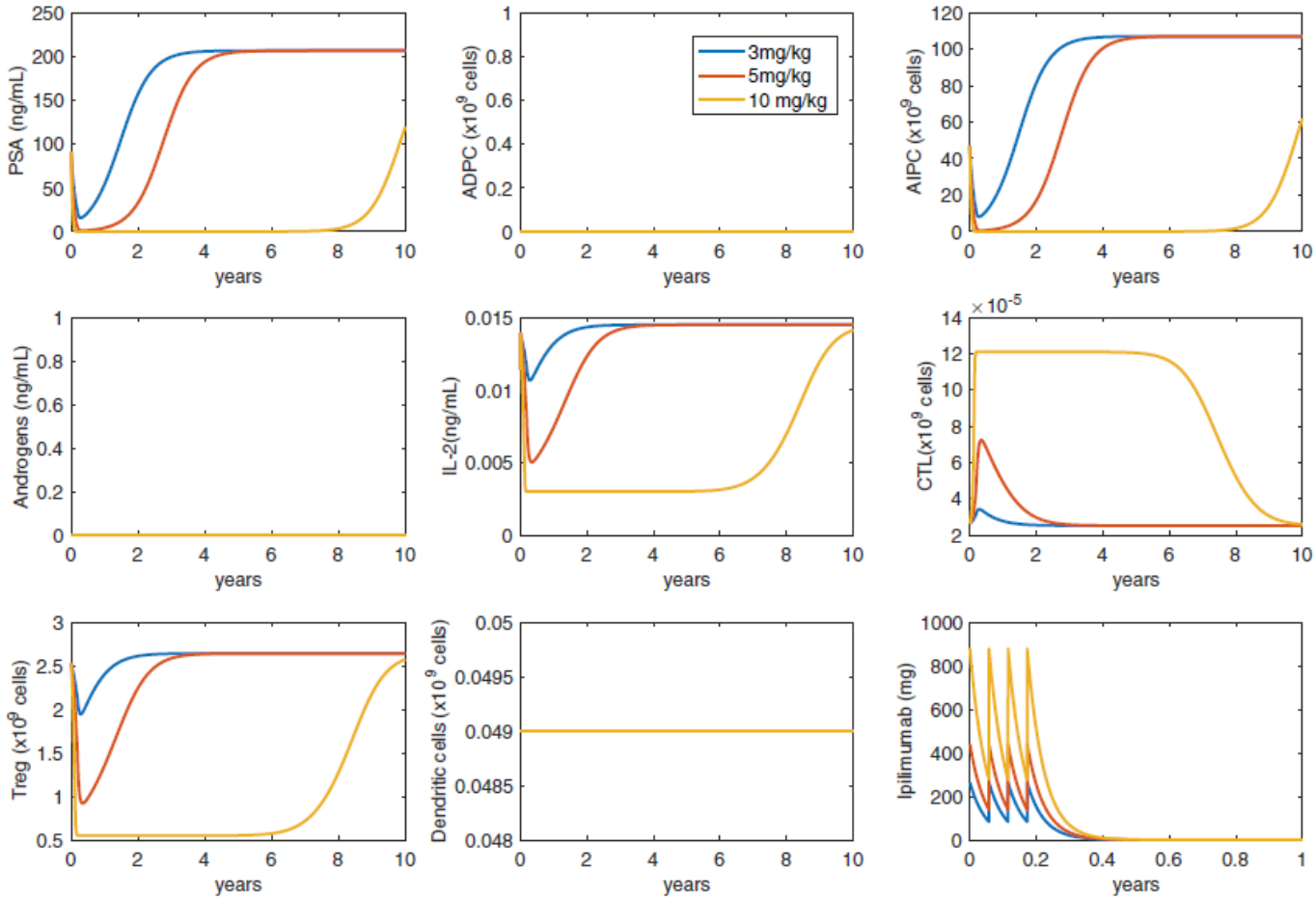


Figure: Simulation: androgen deprivation therapy combined with intermittent ipilimumab injection in different doses

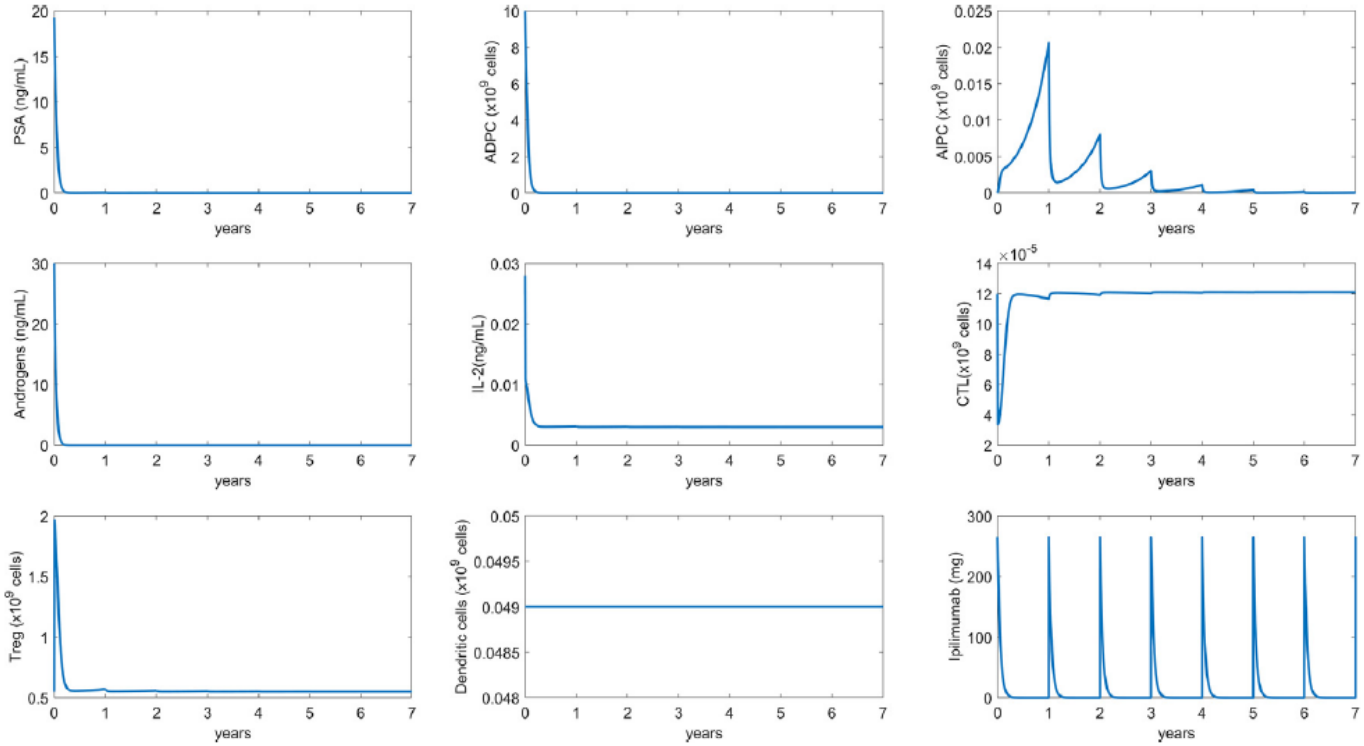


Figure: Simulation: androgen deprivation therapy combined with early administered and repeated intermittent ipilimumab injections

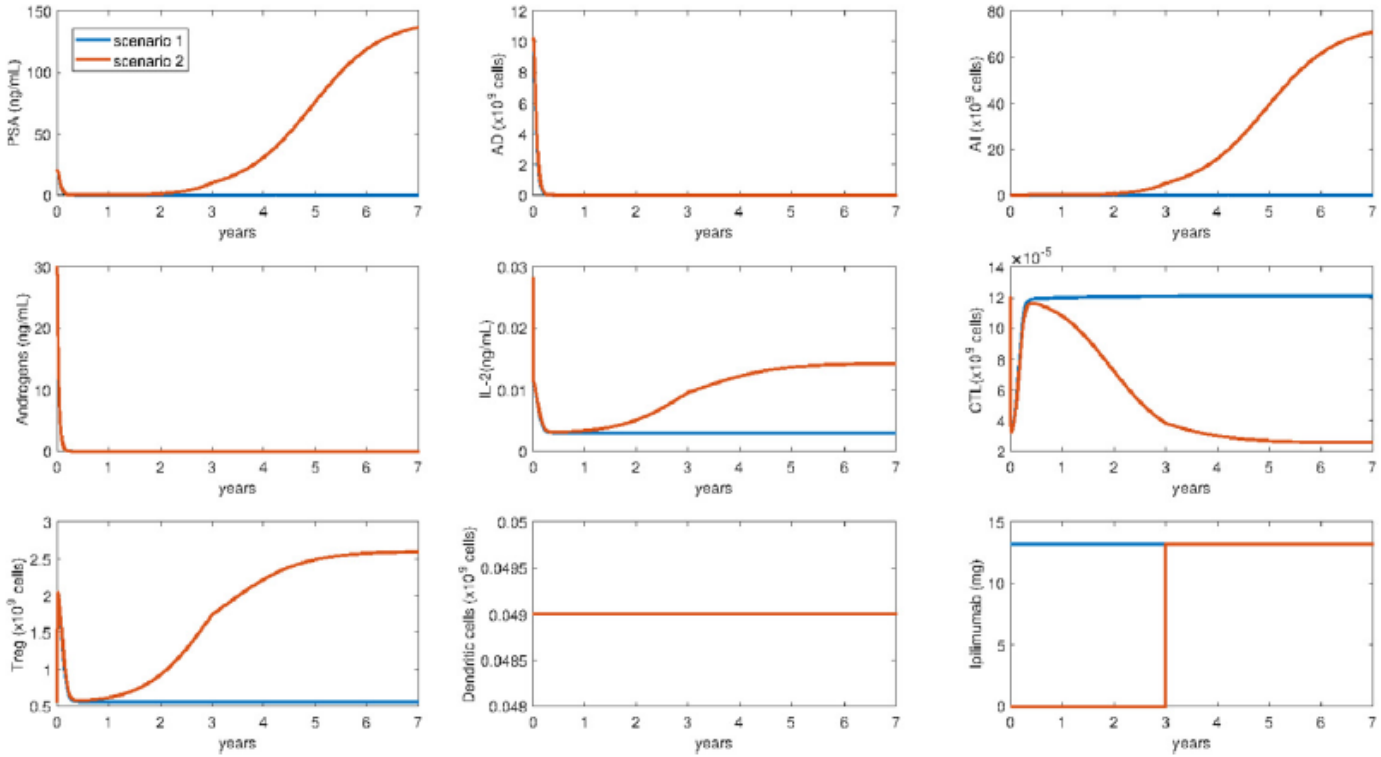


Figure: Androgen deprivation and AntiCTLA4 therapy combined (scenario 1) vs separated administration time (scenario 2)

Comparisons

First Model Variables

- $T(t)$: tumor cell population.
- $N(t)$: total NK cell population. Natural killer cells, also known as NK cells or large granular lymphocytes (LGL), are a type of cytotoxic lymphocyte critical to the innate immune system that belong to the rapidly expanding family of known innate lymphoid cells (ILC) and represent 5–20 percent of all circulating lymphocytes in humans. The role of NK cells is analogous to that of cytotoxic T cells in the vertebrate adaptive immune response. NK cells provide rapid responses to virus-infected cell and other intracellular pathogens acting at around 3 days after infection, and respond to tumor formation.
- $L(t)$: total $CD8^+$T cell population. A cytotoxic T cell (also known as TC, cytotoxic T lymphocyte, CTL, T-killer cell, cytolytic T cell, $CD8^+$T-cell or killer T cell) is a T lymphocyte (a type of white blood cell) that kills cancer cells, cells that are infected by intracellular pathogens (such as viruses or bacteria), or cells that are damaged in other ways.

First Model Variables

- $C(t)$: number of circulating lymphocytes. A lymphocyte is a type of white blood cell (leukocyte) in the immune system of most vertebrates. Lymphocytes include natural killer cells (which function in cell-mediated, cytotoxic innate immunity), T cells (for cell-mediated, cytotoxic adaptive immunity), and B cells (for humoral, antibody-driven adaptive immunity). They are the main type of cell found in lymph, which prompted the name "lymphocyte". Lymphocytes make up between 18% and 42% of circulating white blood cells.
- $M(t)$: chemotherapy drug concentration in the bloodstream.
- $I(t)$: immunotherapy drug concentration in the bloodstream.

Second Model Variables

- $X_1(t)$: Androgen Dependent Prostate Cancer cells (ADPC). Prostate cancer that needs androgens (male hormones) to grow and therefore stops growing when androgens are not present. Many early-stage prostate cancers are androgen-dependent, so reducing the amount of androgens in the body or blocking their action may be an effective type of therapy. Also called androgen-sensitive prostate cancer, castrate-sensitive prostate cancer, CSPC, hormone-sensitive prostate cancer, and HSPC.
- $X_2(t)$: Androgen Independent Prostate Cancer cells (AIPC). Each year, an estimated 25,000 men will find out their prostate cancer has changed enough to become resistant to standard androgen-deprivation therapy, also called hormone therapy. At this point, the cancer is classified as androgen-independent prostate cancer (AIPC) or hormone-refractory prostate cancer, meaning that the cancer is still able to thrive despite hormone treatment.
- $C(t)$: circulating Cytotoxic T Lymphocytes (CTL).

Second Model Variables

- $R(t)$: circulating Treg cells (Treg). Regulatory T cells (Tregs) are a specialized subpopulation of T cells that act to suppress immune response, thereby maintaining homeostasis and self-tolerance. It has been shown that Tregs are able to inhibit T cell proliferation and cytokine production and play a critical role in preventing autoimmunity. Different subsets with various functions of Treg cells exist. Tregs can be usually identified by flow cytometry. The most specific marker for these cells is FoxP3, which is localized intracellulary. Selected surface markers such as CD25high (high molecular density) and CD127low (low molecular density) could serve as surrogate markers to detect Tregs in a routine clinical practice. Dysregulation in Treg cell frequency or functions may lead to the development of autoimmune disease. Therapeutical Treg modulation is considered to be a promising therapeutical approach to treat some selected disorders, such as allergies, and to prevent allograft rejection.

Second Model Variables

- $I_L(t)$: interleukin-2 in blood. Interleukin-2 (IL-2) is an interleukin, a type of cytokine signaling molecule in the immune system. It is a 15.5–16 kDa protein that regulates the activities of white blood cells (leukocytes, often lymphocytes) that are responsible for immunity. IL-2 is part of the body's natural response to microbial infection, and in discriminating between foreign ("non-self") and "self". IL-2 mediates its effects by binding to IL-2 receptors, which are expressed by lymphocytes. The major sources of IL-2 are activated $CD4^+$T cells and activated $CD8^+$T cells.
- $D(t)$: circulating Dendritic cells. Dendritic cells (DCs) are antigen-presenting cells (also known as accessory cells) of the mammalian immune system. Their main function is to process antigen material and present it on the cell surface to the T cells of the immune system. They act as messengers between the innate and the adaptive immune systems.
- $A(t)$: Androgen concentration.
- $I_P(t)$: Ipilimumab drug.

Summary of models

1) **First Model**

- T for tumor cells
- N, L, C in immune system
- M, I for treetments

2) **Second Model**

- X_1, X_2 are cancer cells
- C, R, I_L, D are in immune system
- A, I_P are as treetments

Remark. In both models, the growth of tumors (T, X_1, X_2) is assumed to be logistic.

Equilibria and stability

Here, the important equilibrium is the tumor-free equilibrium. Tumor-free equilibrium exists but it is not stable and there are some bifurcations.

1) **First Model**
   The tumor-free equilibrium is $E_0 = (T_{E,1}, N_E, L_E, C_E) = (0, 1/\beta f, 0, 1/\beta)$. E_0 is stable if and only if $c > \beta f$, where c represents the NK cells kill rate. According to the paper, we have another bifurcation related to j parametere which by increasing j, E_0 is converted from unstable to semi stable.

2) **Second Model**
   If we set $X_2^0 = 0$ then the tumor-free equilibrium is $E_0 = (X_2^0 = 0, C^0, R^0)$ if $\mu_C K_R R^0 > \frac{e_{IC} i_0}{g_{IC} + i_0}$. E_0 is stable if and only if $r_2 < C_0 \frac{e_{CX}}{g_{CX}}$.
   Regarding the ipilimumab treatment, E_0 is stable if and only if $r_2 < C_0 \frac{e_{CX}}{g_{CX}} + k_{Ip} I_P^* C^0$.

Treatment, 1^{st} model: Immune system response

The healthy innate immune response is sufficiently strong to control the tumor. However, when the immune system is weakened, a tumor of the same size grows to a dangerous level in the absence of treatment interventions.

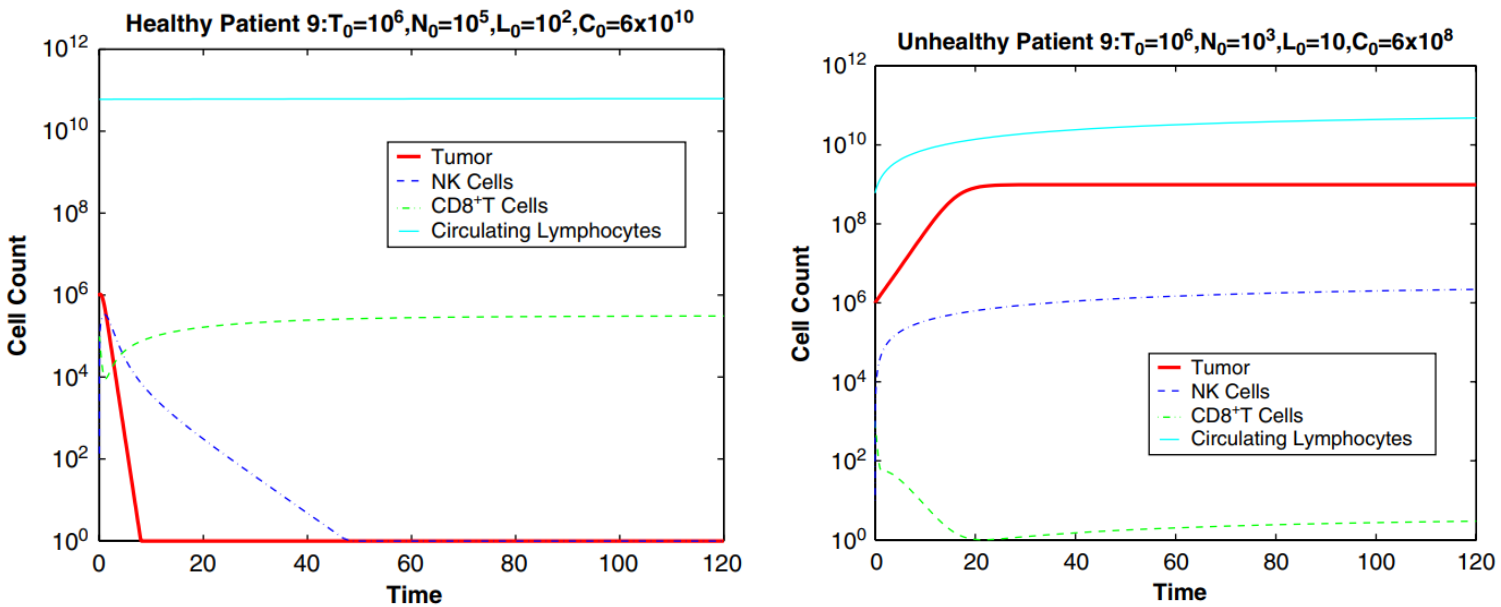


Figure: Comparison between healthy and unhealthy patient.

Treatment, 1^{st} model: Chemotherapy

This treatment can be administrated only after the tumor is large enough to be considered potentially detectable. Also it is sensitive to the chemotherapy dosing regimen.

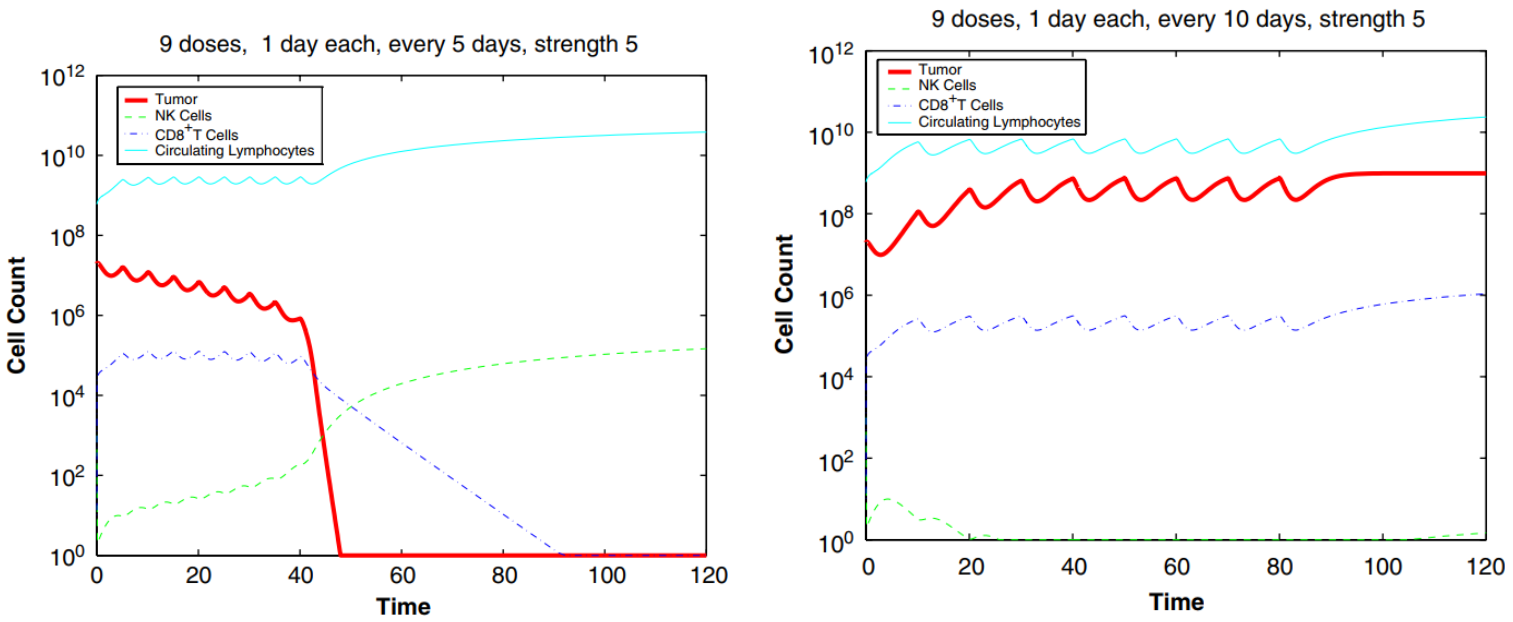


Figure: Left: sufficient chemotherapy. Right: insufficient chemotherapy.

Treatment, 1^{st} model: Immunotherapy

The advantage of this treatment is that the immune system is directly strengthened, and not depleted as it is with chemotherapy. But the effectiveness may be limited to smaller tumor sizes.

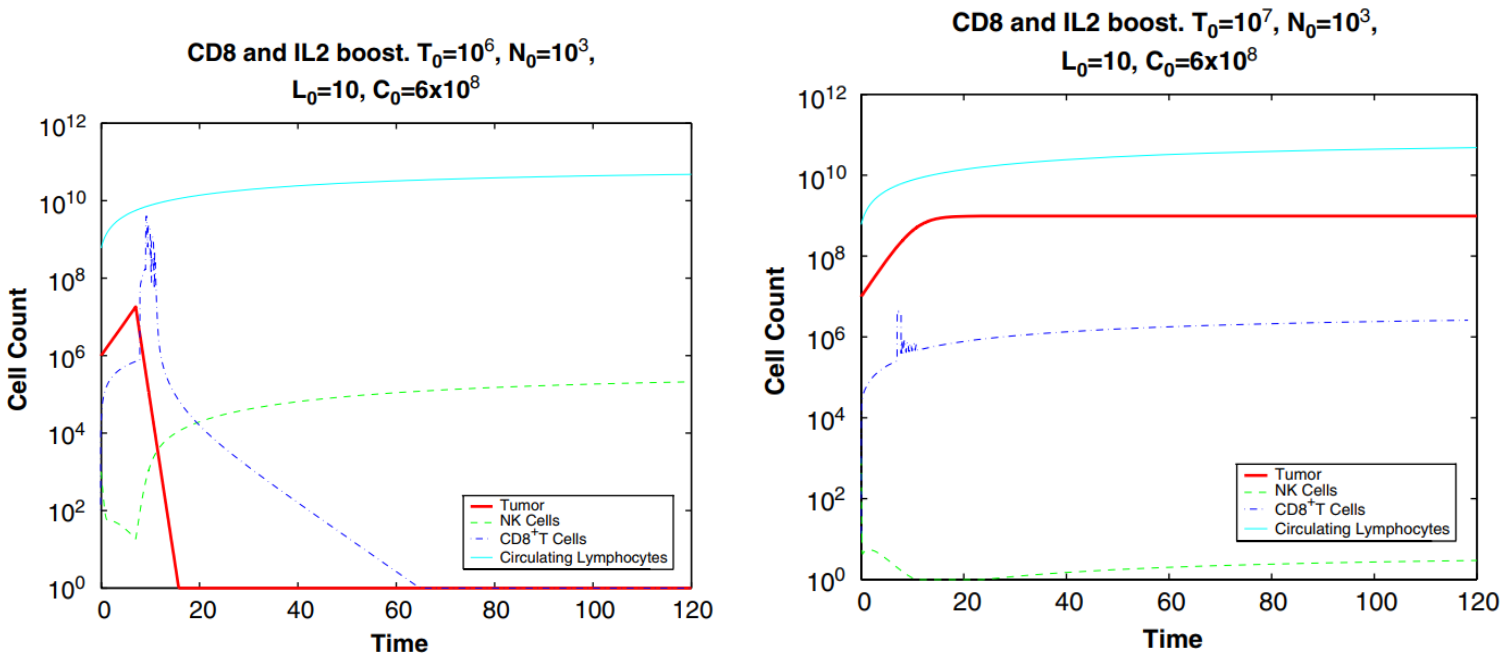
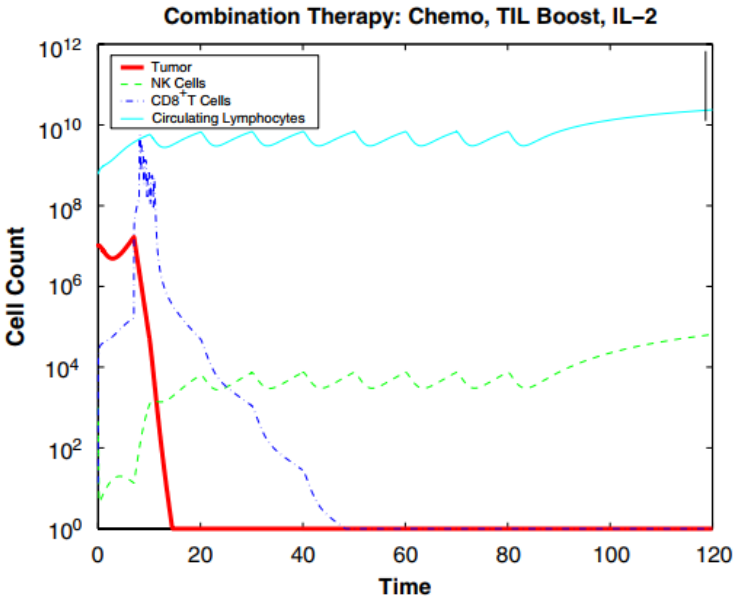


Figure: Left: Immunotherapy is sufficient. Right: Immunotherapy is not sufficient.

Treatment, 1^{st} model: Combination therapy

This treatment consists of an administration of chemotherapy and immunotherapy. This allows less chemotherapy (which causes damage to the body) to be administered while keeping immune cell counts high. This therapy fails for large tumors unless different dosages and periods of administration of both chemotherapy and immunotherapy are adopted.

Treatment, 1^{st} model: Combination therapy



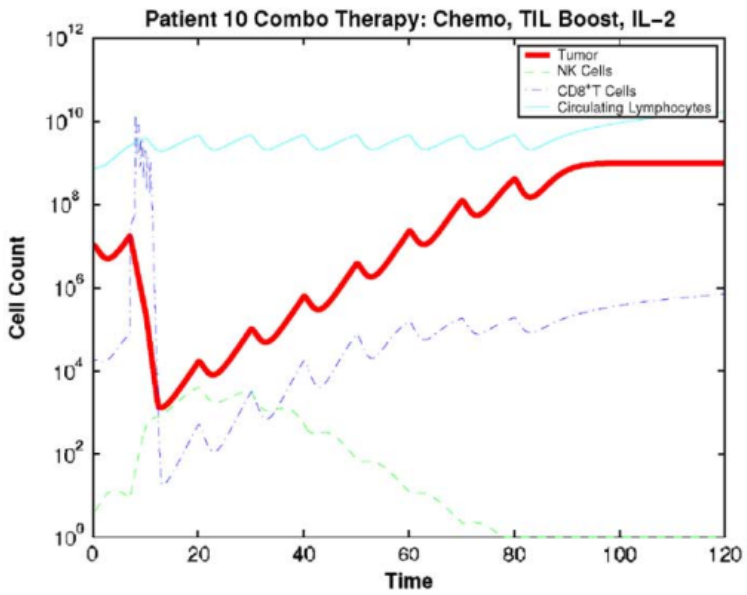


Figure: Left: Combination therapy is sufficient. $T_0 = 2 \times 10^7$; $N_0 = 10^3$; $L_0 = 10$; $C_0 = 6 \times 10^8$; $I_0 = 0$; $M_0 = 0$. Two immunotherapy doses are administered at the beginning for a duration of 4 time unit, $v_I = 5 \times 10^5$. Five chemotherapy doses are administered for a duration of 7 time unit, $v_M = 3$. Right: Combination therapy is not sufficient. $T_0 = 10^7$; $N_0 = 10^3$; $L_0 = 10$; $C_0 = 6 \times 10^8$; $I_0 = 0$; $M_0 = 0$. Two immunotherapy doses are administered in 2 time unit, $v_I = 10^9$, then six immunotherapy doses are administered during 4 time unit, $v_I = 5 \times 10^6$. Nine chemotherapy doses are administered once every 10 days for a duration of 1 time unit, $v_M = 5$.

Treatment, 1^{st} model: Vaccine therapy

This is a special case of immunotherapy for treating cancer. Combination of chemotherapy and vaccine can kill a tumor, but it depends on the size of tumor, doses of chemotrapy and the time of starting the vaccination. There are cases for which vaccine therapy alone is able to control a growing tumor and again, it sensetive to the size of tumor and the time of starting the vaccination.

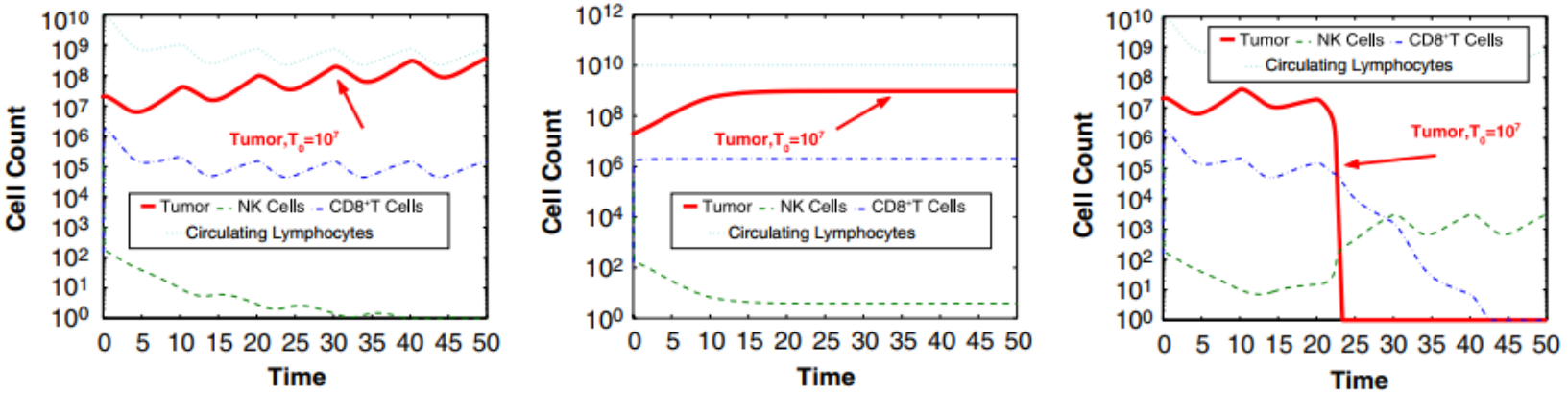


Figure: $T_0 = 2 \times 10^7$; $N_0 = 3 \times 10^5$; $L_0 = 100$; $C_0 = 10^{10}$. Left: $v_M = 2$ administered for 3 consecutive days every 10 days. Center: vaccine is administered at day 10, $c = 7.131 \times 10^{-9}$; $g = 0.5$; $j = 1$; $s = 0,0019$; $d = 15$. Right: combination of the two previous therapies.

Treatment, 1^{st} model: Vaccine therapy

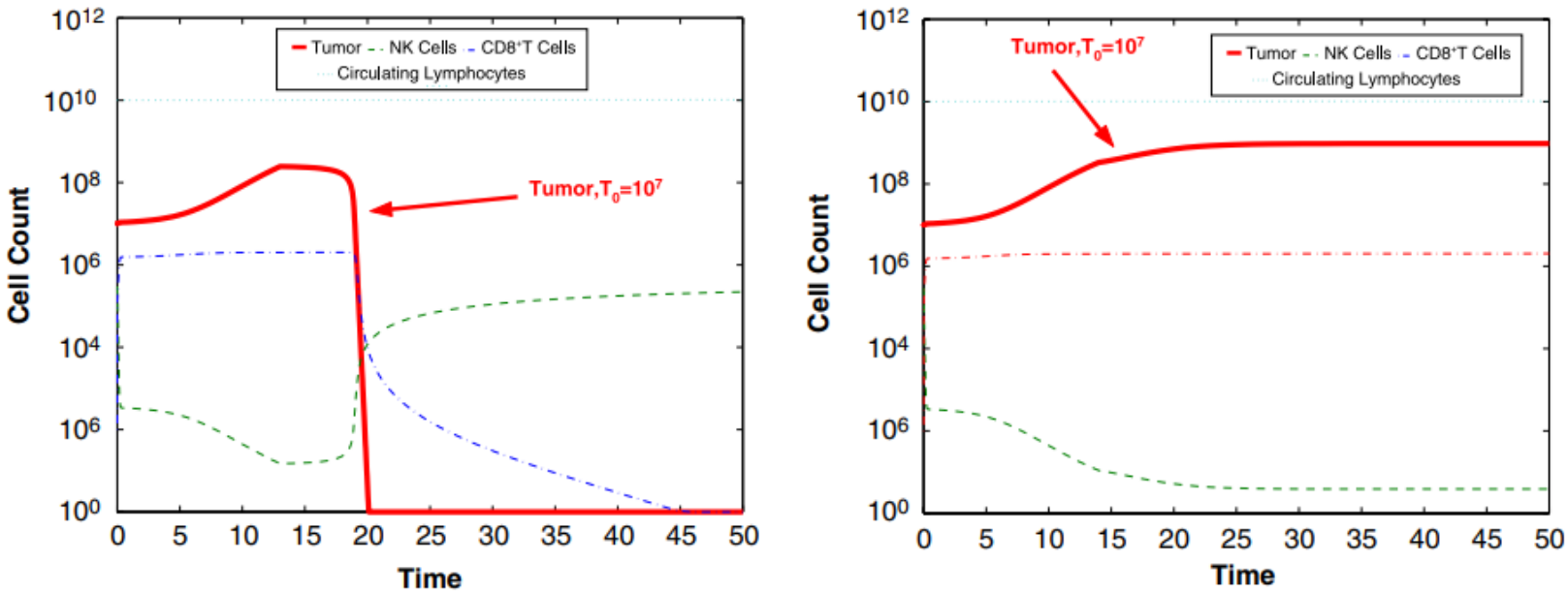


Figure: $T_0 = 10^7$; $N_0 = 3 \times 10^5$; $L_0 = 100$; $C_0 = 10^{10}$. Left: vaccine is administered at day 13. Right: vaccine is administered at day 14. In both cases the vaccine is modeled as: $c = 7.131 \times 10^{-9}$; $g = 0.5$; $j = 1$; $s = 0,0019$; $d = 15$.

Treatment, 2^{nd} model: Immune system response

In this case, ADPC cancer cells increase, until reaching a constant threshold value. Simultaneously, PSA reaches its maximum level while there is no AIPC creation since there is no pressure into the androgen-independent cancer form.

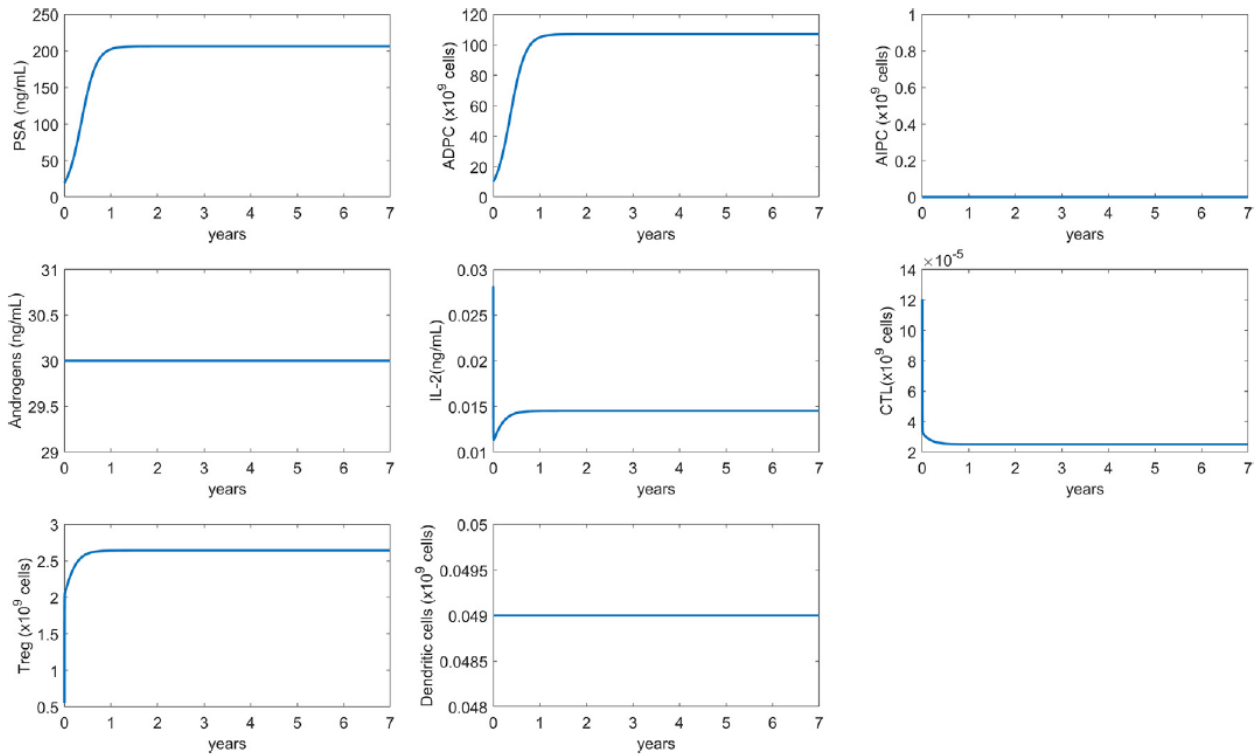


Figure: No drugs nor other therapies have been taken to deal with the tumor. $v = 0$, $I_{CX} = 0$ and $I_P(0) = 0$.

Treatment, 2^{nd} model: Androgen and vaccine

In Androgen deprivation, PSA level first decreases due to the destruction of ADPC, but it secondly starts increasing again due to the selection of androgen independent cancer form.
In combination of androgen deprivation and dendritic cells vaccine, dendritic cells injection helps the immune system to increase CTL and Treg values, but the variables PSA, ADPC and AIPC do not show any relevant differences compared to the last case and the result is still the spread of the cancer.

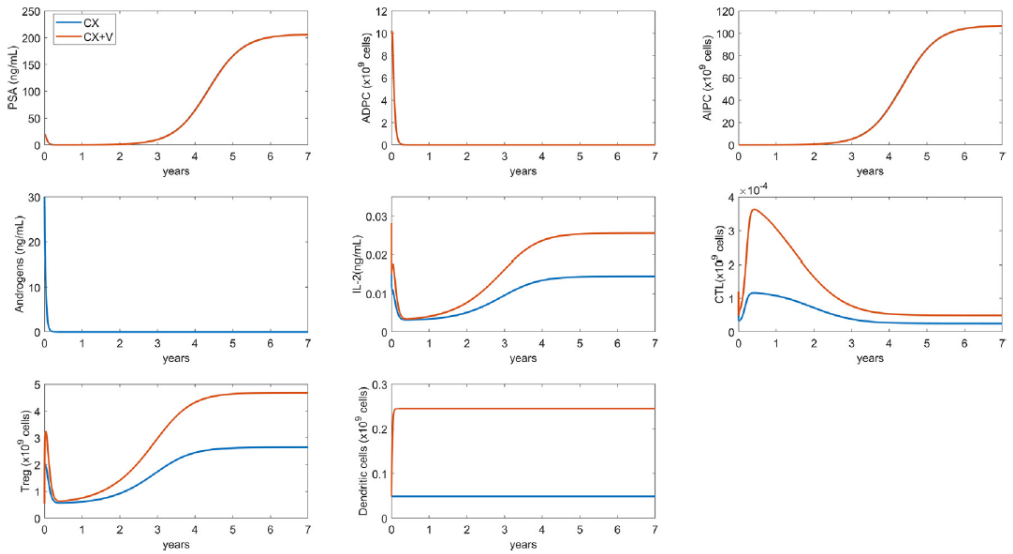


Figure: Androgen deprivation therapy by itself (blue) and combined with the vaccine treatment (orange).

Treatment, 2^{nd} model: Androgen and ipilimumab

In combination of androgen deprivation and Anti-CTLA4 (ipilimumab injection), results are different depending on the schedules and the doses of the drug. But, no matter of the AntiCTLA4 drug dose, PSA level will start to increase again and the high-tumor level will be reached soon or later.

Choosing a repeated intermittent treatment with a low dose returns better simulations results. Anyway, this still is not enough to eradicate the cancer.

An early administered treatment with repeated and intermittent ipilimumab injections in combination with androgen deprivation therapy causes a better tumor control where, as the therapy starts, ADPC suddenly disappear and AIPC's value oscillates tending to the no-tumor point.

Conclusions

Conclusions

For general tumor:

- **Chemotherapy** is for large enough tumors. I is sensitive to dosing regime.
- **Immunotherapy** is good for small sized tumor.
- **Combination of chemotherapy and immunotherapy** causes less damge to body. For small sized tumors, it is a good choice. For large tumors, it depends on dosage and period of administration.
- **Combination of chemotherapy and vaccination** depends on tumor size, dosage of chemotherapy and time of starting vaccination.

For prostate:

- **Combination of androgen and vaccination** dose not have desired results.
- **Combination of androgen and ipilimumab** depends on size of tumor and dosage of drug. But an early administered treatment with repeated and intermittent ipilimumab injections in combination with androgen deprivation therapy causes a better tumor control.

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- Coletti, Roberta, Andrea Pugliese, and Luca Marchetti. "**Modeling the effect of immunotherapies on human castration-resistant prostate cancer.**" Journal of Theoretical Biology 509 (2021): 110500.