Mathematical Modelling of Tumor Growth and Treatment: Triple Negative Breast Cancer

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Abstract

Triple Negative Breast Cancer (TNBC) represents a particularly aggressive subtype of breast cancer characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Hsiu-Chuan Wei formulated a mathematical model specifically targeting TNBC, integrating checkpoint inhibitor immunotherapy [11]. This model looks into the relationship between tumor cells, innate and adaptive immune cells, programmed death protein 1 (PD-1), programmed death ligand 1 (PD-L1), and immune checkpoint inhibitors (ICI). The model delineates multiple equilibrium states including tumor-free, small-tumor and large-tumor states. While the tumor-free equilibrium proves locally unstable, mathematical analysis and numerical simulations show the immune system's capability to fight off small tumors, thus demonstrating immune surveillance. Further simulations highlight the NK cell response in eliminating tumor cells, while emphasizing the inhibitory role of PD-L1 expression on cytotoxic T lymphocyte (CTL) response. Incorporating immune checkpoint inhibitors into simulated treatments demonstrates their potential in eliminating large tumors, although have limitations imposed by the intrinsic immune response. Here, we extend the model by looking at the marginal effects of an increase in NK cells caused by improved cardiovascular health and further, how it can assist the checkpoint inhibitors. The paper hopes to better understand the effects of combing checkpoint inhibitors with immune-boosting therapy.

Contents

Introduction

Breast Cancer and TNBC

Breast cancer stands as the most prevalent form of cancer among women globally and ranks as the second leading cause of cancer-related deaths in this demographic [1]. This disease presents in various forms, classified based on the expressions of three receptors: the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). The four primary subgroups of breast cancer are HR+/HER2+ BC, HR-/HER2+ BC, HR+/HER2- BC, and Triple Negative Breast Cancer (TNBC) [2]. Each subgroup is characterized by the presence or absence of these receptors, leading to differences in aggressiveness, treatment options, and patient outcomes.

Among these, Triple Negative Breast Cancer (TNBC), defined by the absence of ER, PR, and HER2, is the most aggressive type of breast cancer . It is the only subgroup that currently lacks a targeted therapy, which contributes to poorer clinical outcomes compared to other types of breast cancer[3]. Standard treatment options for TNBC typically include surgery, irradiation, and chemotherapy . However, the responses to chemotherapy in metastatic TNBC are usually not durable, presenting a significant challenge in the management of this disease.

The immune system plays a crucial role in combating infections and diseases. Interestingly, tumors have developed mechanisms to evade this system through the exploitation of immune checkpoint pathways such as the PD-1/PD-L1 pathway. Immunotherapy, a treatment that imrpoves the immune system's ability to fight cancer, has seen significant advancements in recent years. A prime example is the emergence of immune checkpoint inhibitors. These inhibitors work by blocking the PD-1 or PD-L1 pathway, improving the responses of CD8+ T-cells against cancers. TNBC has been found to show high levels of PD-L1

and contains a large number of activated CD8+ tumor-infiltrating lymphocytes (TILs) compared to other breast cancer subgroups [4] [5]. This suggests that TNBC may be responsive to treatment with immune checkpoint inhibitors, which opens up a new way of fighting the cancer.

Importance of Mathematical Model

Mathematical modeling serves as a powerful tool in understanding the intricate mechanisms of cancer development and treatment. Tumor growth involves numerous biological processes and interactions that can be difficult to understand intuitively. Mathematical models help to simplify these complex systems and provide a framework for understanding how different factors interact. The most common type of models are based off of differential equations, specifically, Ordinary Differential Equations (ODEs) involving two or three cell populations, including tumor cells and effector cells. There are many other complicated models that have been developed to analysis large-tumor populations. For this paper we will be looking into differential equation models. Hsiu-Chuan Wei proposed a mathematical model that looks into the interaction between tumor cells, , innate and adaptive immune cells, programmed cell death protein 1 (PD-1), programmed death ligand 1 (PD-L1), and immune checkpoint inhibitor (ICI).

Mathematical model formulation

Process diagram

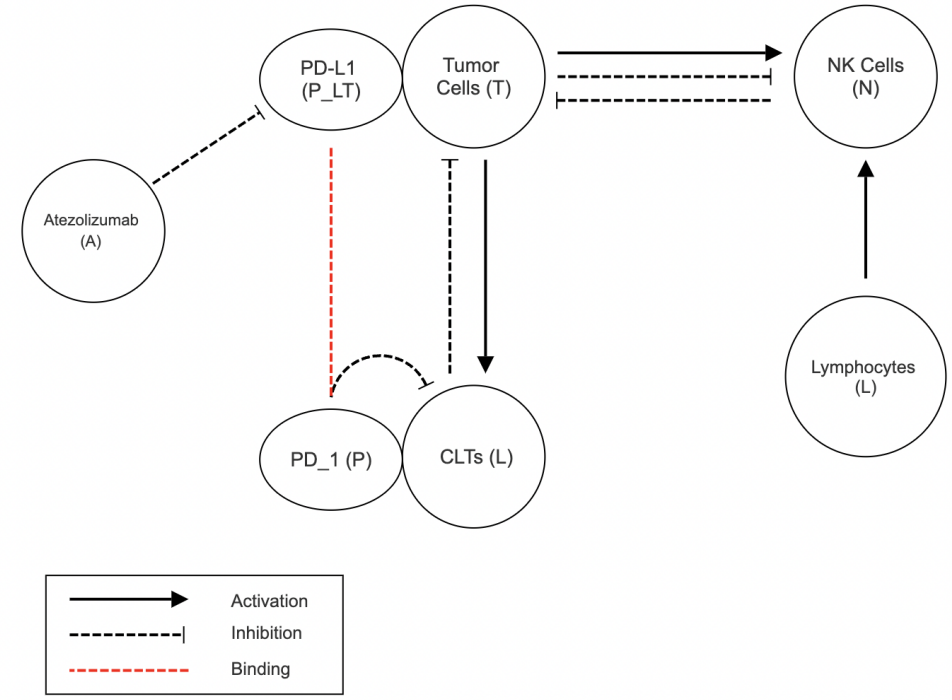

Figure 1: model process diagram

The main process diagram is shown in Figure 1. In the diagram, the tumor cells (T) send signals to the NK cells (N) leading to recruitment and activation of the cells. The NK cells activation is further enhanced by the cytokines produced by the lymphocytes (L). Once activated, NK cells inhibit tumor growth. Simultaneously, the tumor cells develop mechanisms to inhibit the NK cell function leading to a two-way inhibition scenario.

There is another defense mechanism which are CTLs and they are part of the adaptive immune system and unlike NK cells, it requires activation by antigen presentation cells (APCs). Once activated and recruited to the tumor site, CTLs exert their cytotoxic effects by inducing apoptosis (cell death) in tumor cells.

The PD-1 receptor (P) is expressed on the surface of CTLs. TNBC has higher expression of PD-L1 ligand on the tumor cells [3,16] and when PD-1 on the surface of CTLs binds to PD-L1 (P_L1) on the surface of tumor cells, the CTLs receive an inhibitory signal which leads to a reduction in their activation, proliferation, and ability to kill tumor cells. Tumors exploit this immune checkpoint pathway by expressing high levels of PD-L1, effectively 'turning off' CTLs and avoiding immune-mediated destruction. Targeting the PD-1/PD-L1 interaction has become a major focus of cancer immunotherapy.

Atezolizumab (A) is an immune checkpoint inhibitor which targets PD-L1 molecules on both tumor and immune cells and binds to the PD-L1, blocking the interaction between PD-L1 on tumor cells and its receptor PD-1 on CTLs and prevents the inhibitory signals which allows the CTLs cells to remain active and enhances their ability to kill tumor cells.

Parameters and equations

The mathematical model proposed by Hsui-Chuan Wei is based on several key assumptions and parameters. A full list of parameters used can be found in Figure 10. The model consists of 8 state variables, some defined by differential equations.

$$\frac{dT}{dt} = aT(1 - \frac{T}{K}) - \frac{p_1 T N^2}{1 + \alpha_2 T + \beta_2 N^2} - \frac{p_6 T L}{1 + \alpha_6 T + \beta_6 L}$$

The tumor population T is assumed to follow logistic growth which consists of three phases: an exponential phase, a linear phase, and a plateau phase. The parameter a is the intrinsic growth rate, and K is the carrying capacity of the tumor. In this model, the carrying capacity $K = 10^9$ is used. Research shows that MDA-MB-231 cells had an average size of $18.9 \pm 0.4 \text{ţ}m$. Assuming that an

MDA-MB-231 cell is 19 µm in diameter, a tumor of 1.9 cm in diameter contains 10^9 tumor cells. The terms second and third terms of the equation represent tumor lysis by NK cells and CTLs, respectively. The breast cancer cell line considered in this paper is MDA-MB-231.

$$\frac{dN}{dt} = eC - fN - p_2NT + \frac{p_3NT}{1 + \alpha_3T + \beta 3N}$$

The growth of NK cells depends on the concentration of lymphocytes and is modeled by eC. The parameter f represents the death rate of NK cells. The parameter values $\alpha = 1.35 * 10^7$ and $\beta = 6.3 * 10^{-3}$ were obtained to be suitable values from experimental studies [6].

$$\frac{dC}{dt} = \alpha - \beta C$$

The equilibrium concentration of lymphocytes, determined by the above CTL equation is $\frac{\alpha}{\beta} = 2.14 * 10^9$ which lies in the normal range of lymphocyte count $(1 - 3.3 * 10^9$ cells per liter) [7]. Experimental data collected by [8] showed that healthy young and elderly individuals had NK cell counts of $(3.87 \pm 1.64) * 10^8$ cells/L and $(3.77 \pm 2.21) * 10^8$ cells/L, respectively. An equilibrium NK cell count of 4×10ˆ8/L is in the normal range of NK cell counts for healthy individuals. An immune system with an equilibrium NK cell count of $4Ö10^8/L$ and lymphocyte count of $2.14Ö10^9/L$ is considered a normal healthy immune system..

$$\frac{dL}{dt} = (p_4L_N + \frac{p_3I}{\alpha_4 + I}L)(1 - \frac{L}{K_L})(\frac{T}{\alpha_5 + T})(\frac{1}{1 + \frac{PP_{LT}}{K_YQ}})$$

The term in the above equation $p_4L_N + \frac{p_3I}{\alpha_4+I}L$ represents the differentiation of naive T cells into effector CTLs. The terms $\frac{1}{1+\frac{PP_{LT}}{K_YQ}}$ represent inhibition of CTL response by PD-1 and PD-L1 proteins and natural cell death.

$$\frac{dP_L}{dt} = \frac{P/L}{L + \epsilon/1T + \epsilon_2 N} + \frac{d}{dt}(L + \epsilon_1 T + \epsilon_2 N) + \mu P_L A$$

$$P_{LT}(t) = \frac{\epsilon_1 T}{L + \epsilon_1 T + \epsilon_2 T}$$

$$P(t) = \rho_P L(t)$$

$$\frac{dA}{dt} = D(t) - \mu P_L A - \delta_1 A$$

When the immune checkpoint inhibitor is incorporated into the model, the level of free PD-L1 changes as the drug binds to PD-L1. The molecule concentration of PD-L1 on one CTL, ρL, is replaced by $\frac{P_L}{L+\epsilon_1 T+\epsilon_2 N}$. The term $-\mu P_L A$ represents the binding of the drug to PD-L1 with an association rate constant of $\mu = 7.7$.

$$D(t) = \sum_{i=0}^{n} d_A \delta(t - i\tau)$$

The above equation is a dosage function used in the drug differential equation where δ is the Dirac delta function(helps model the spikes in dosage), τ is the time period between doses, d_A is the dosage, n is the number of doses, and I is the interleukin-2 (IL-2) concentration. A full list of the differential equations used in the model is listed in Figure 11.

Simulation Results

The simulation was performed on different sized cancer with and without the use of Atezolizumab drug. The first simulation result, in Figure 2, where Tumor cell count was set to 500, a small tumor, shows the body's immune response without the assistance of the drug. It is clear that the body's immunity is strong enough to fight this small tumor. The active NK cells able to effectively eliminate tumor cells within 8 days. So, the tumor cells are eliminated before the expansion on CTLs to a large number. From this simulation result, we understand that NK cells play a very important role in the elimination of tumor cells.

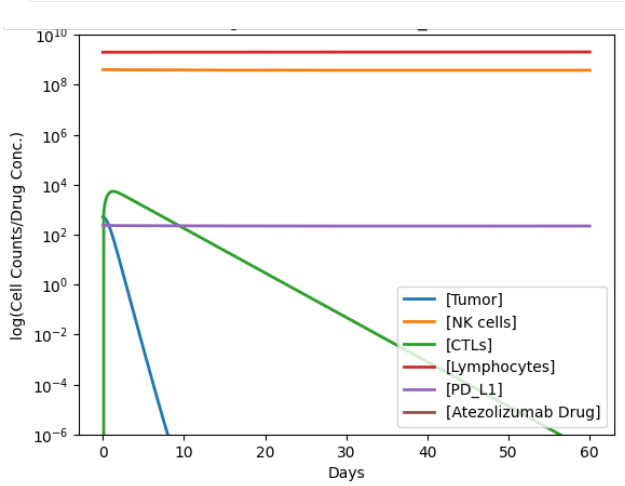

Figure 2: small tumor, no drug: T cells = 500, drug = 0

The tumor cell count was then increased to 10^5, again with no drug. The simulation result in Figure 3 shows that the active NK cells are able to effectively eliminate tumor cells within 11 to 12 days. In the beginning, there is a slight inhibition by the tumor cells on the active NK cells but later the population of NK cells are brought up by the Lymphocytes. This supports the conclusion from the previous simulation that the NK cells play a very important role in the elimation of tumor cells.

However, when the tumor cell count was increased to 10^6, as shown in Figure 4,

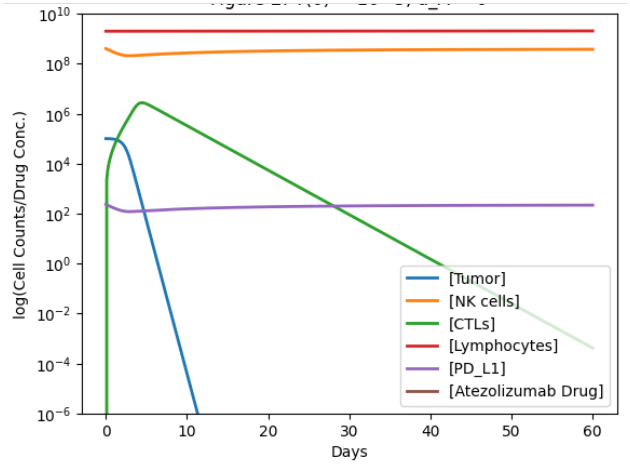

Figure 3: slightly larger tumor, no drug: T cells = 10^5, drug = 0

the active NK cells not able to control tumor growth. The CTLs are activated and expanded which leads to an initial increase in the CTLs population. But the binding of PD-L1 with PD-1 inhibits the CTLs which leads to lower levels of active CTLs population, decreasing the inhibition response of CTLs on tumor cells and leading to tumor growth..

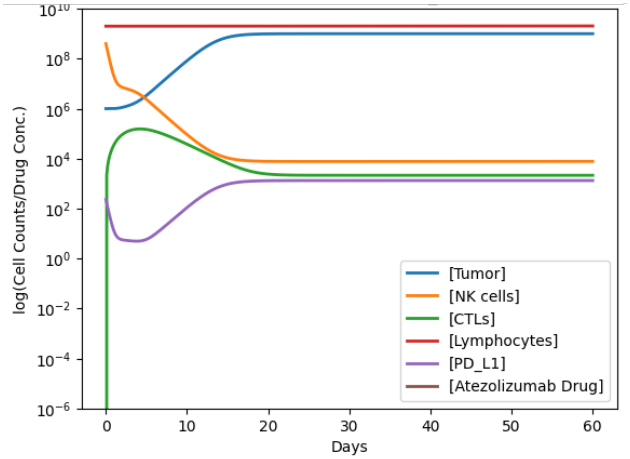

Figure 4: large tumor, no drug: T cells = 10^6, drug = 0

Atezolizumab drug was added for a tumor cell count of 10^7, which is an immune checkpoint inhibitor. The drug was given at 1200mg and spiked every 3 weeks. The Atezolizumab drug assists in the blockade of PD-L1 with PD-1 as the

drug binds to PD-L1 which activate and enhance CTL reponse, resulting in anti-tumor activity The sumulation results in Figure 5 show that the CTL population increases quickly initially and peaks at about day 7. While the active NK cells population reduces to a low level, the active CTL population takes over, continues to fight the tumor and eventually eliminates the tumor at day 48. Once the tumor has been eliminated, the CTLs population starts to decrease gradually.

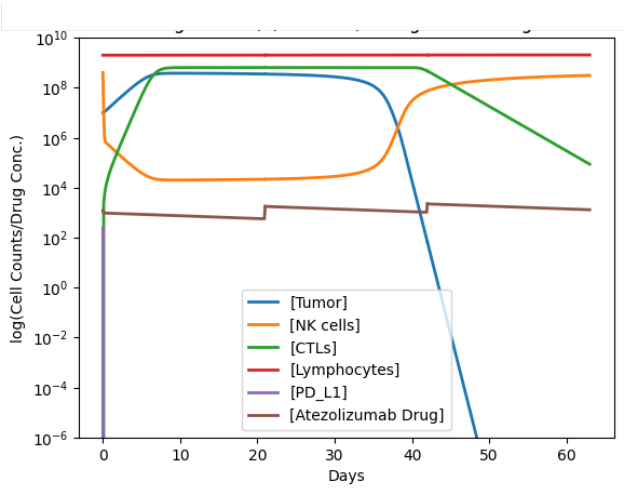

Figure 5: large tumor, no drug: T cells = 10^7, drug dosage = 1200mg

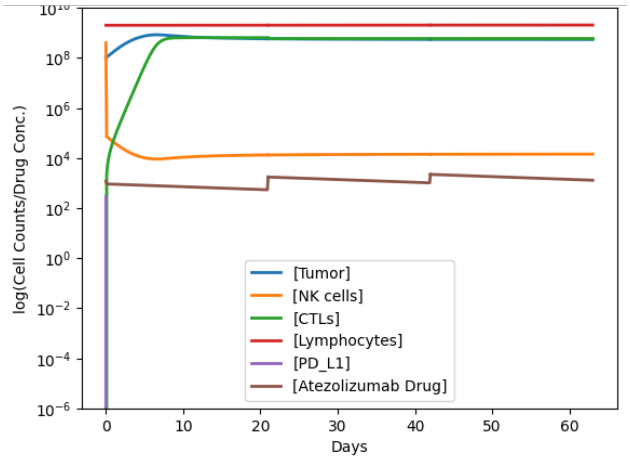

Figure 6: large tumor, no drug: T cells = 10^8, drug dosage = 1200mg

Next, the question arose on what are the limitations of the drug. How big of a

tumor is it able to help kill of. The tumor cell count was again increased to 10^8. 1200mg of the drug was being spiked every 3 weeks. The simulation result in Figure 6 shows that the treatment fails to treat a tumor of this size even though the PD-1/PD-L1 pathway blockade can strengthen the activity of CTL cells. The anti-tumor effect of the treatment was limited by the immune response. So a question arose as to if increased immunotherapy could perhaps give different results to the simulation.

Effects of improved cardiovascular health

It is well recognized that a cancer patient's chance of survival is correlated with the strength of their immune system [9]. Consider a thirty-fold increase in the lymphocyte synthesis parameter, α which in turn leads to a higher NK cell population due to an increase in the circulating lymphocytes.

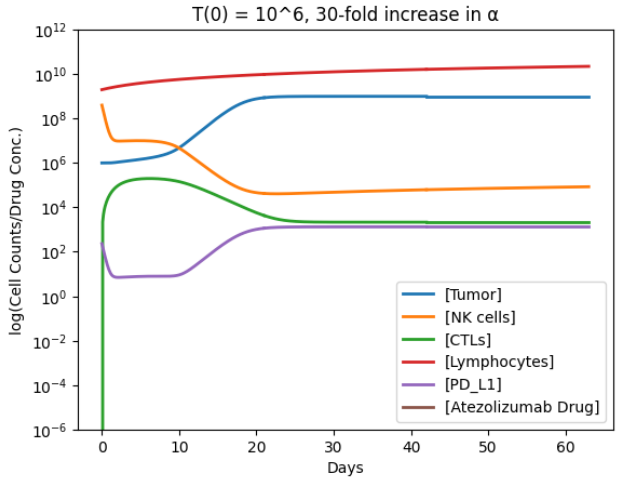

Figure 7: large tumor, no drug: T cells = 10^6, 30-fold increase in α

Numerical simulation demonstrates that while it is evident that NK cells are making a strong effort to contain the tumour of 10^6 cells, there are not enough NK cells in the population to eliminate the tumor (Figure 7).

Consider a thirty-nine-fold increase in the lymphocyte synthesis parameter, α from the baseline parameter value(Figure 8). Numerical simulation shows that the NK cells can contain the tumour of 10^6 cells. This observation suggests that a stronger immune system can contain the tumor during the early stages of cancer.

The major question arises if a thirty-nine fold increase in α is humanely possible. A research article suggested that a 6-fold increase it more realistic with improved exercise training, so how would this increase impact the tumor along with assistance from the drug [10]? A strong immune system plays an important role

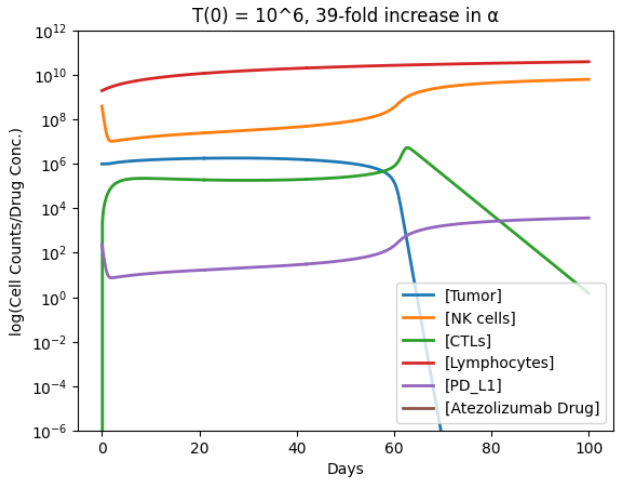

Figure 8: large tumor, no drug: T cells = 10^6, 39-fold increase in α

in eliminating cancer at early stages. The other interesting part to consider is the behaviour of the simulated system with a stronger immune system. Consider a six-fold increase in the lymphocyte synthesis parameter, α from baseline parameter value and spike Atezolizumab every three weeks with a dose of 1200 mg. It can be observed from the simulation that the simulated system with a stronger immune system can eliminate the tumor in approximately 23 days (Figure 9) whereas in (Figure 8) without the introduction of the drug, the tumor was eliminated in 70 days. Thus, the simulated system can contain the tumour earlier.

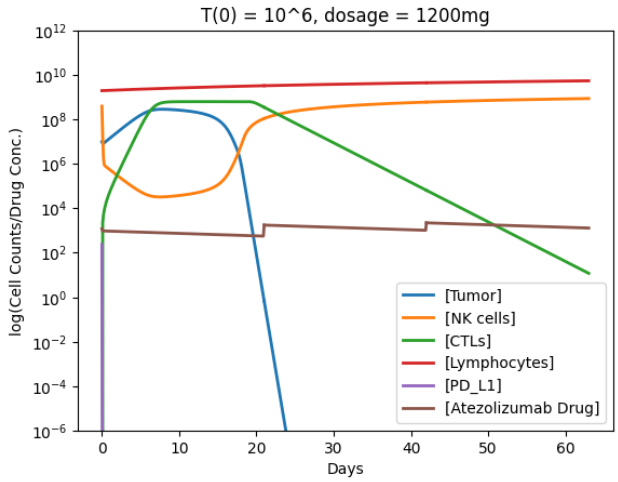

Figure 9: large tumor, no drug: T cells = 10^6, drug dosage = 100mg

Conclusion and Limitations

The mathematical model presented by Hsui-Chuan Wei provides insights into the dynamics of Triple Negative Breast Cancer and the potential efficacy of immune checkpoint inhibitors in fighting the aggressive form of breast cancer. Through simulations, the role of the immune system, particularly NK cells and CTLs, was observed in controlling tumor growth, as well as the inhibitory effects of the PD-1/PD-L1 pathway on immune responses. The addition of Atezolizumab drug, an immune checkpoint inhibitor targeting PD-L1, demonstrated promising results in reducing tumor, especially in smaller tumor sizes. The simulations also explored the impact of improving cardiovascular health on the immune response to TNBC. By increasing lymphocyte synthesis, better immune surveillance and a more robust anti-tumor response was observed, leading to faster tumor elimination. These findings highlight the importance of cardiovascular health and immune function in cancer management and suggest that interventions aimed at improving the immune system may complement traditional treatments and immunotherapies.

However, it's important to acknowledge the limitations of the study. Firstly, the

model simplifies the complex interactions within the tumor microenvironment, and additional factors such as tumor heterogeneity, stromal cells, and other immune cell subtypes could influence treatment outcomes. Secondly, the model parameters were derived from experimental data and may not fully capture the variability observed in clinical settings. While the simulations provide insights into potential treatment strategies, clinical translation requires careful validation and consideration of patient-specific factors.

In conclusion, the study highlights the potential of mathematical modeling to inform cancer treatment strategies and improve the understanding of tumor-immune interactions. Moving forward, integrating more comprehensive models and experimental data could enhance the predictive power of such approaches and facilitate the development of personalized therapies for TNBC and possibly other cancers.

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Appendix A: Model parameters and equations

Table 1
Parameter values in Eqs. (1)–(9).

Parameter	Value	Units
a	0.665	Day^{-1}
K	10^9	Cell
p_1	7.86×10^{-5}	$\text{L}^2\ \text{Cell}^{-2}\ \text{Day}^{-1}$
α_2	2286	Cell^{-1}
β_2	1.19×10^{-4}	$\text{L}^2\ \text{Cell}^{-2}$
p_2	3.42×10^{-6}	Cell Day^{-1}
p_3	1.87×10^{-8}	$\text{Cell}^{-1}\ \text{Day}^{-1}$
α_3	1.6×10^{-5}	Cell^{-1}
β_3	3.27	L Cell^{-1}
p_6	0.0584	$\text{L Cell}^{-2}\ \text{Day}^{-1}$
α_6	0.20241	Cell^{-2}
β_6	0.02065	L Cell^{-1}
e	0.012936	Day^{-1}
f	0.0693	Day^{-1}
β	6.3×10^{-3}	Day^{-1}
α	1.35×10^7	$\text{Cell L}^{-1}\ \text{Day}^{-1}$
I	2.37×10^{-8}	g L^{-1}
α_4	2.37×10^{-8}	g L^{-1}
α_5	1000	g L^{-1}
L_N	2.3×10^8	Cell L^{-1}
K_L	8×10^8	Cell L^{-1}
d	0.41	Day^{-1}
p_5	4.14	$\text{L Cell}^{-2}\ \text{Day}^{-1}$
p_4	9×10^{-5}	Day^{-1}
ϵ_1	23	Cell^{-1}
ϵ_2	10	ratio
ρ_P	1.259×10^{-8}	nM Cell^{-1}
ρ_L	2.51×10^{-8}	nM Cell^{-1}
K_{YQ}	1.296×10^{-3}	$\text{nM}^2\ \text{L}^{-2}$
δ_1	0.0257	Day^{-1}
μ	7.7	$\text{L nM}^{-1}\ \text{Day}^{-1}$

Figure 10: Parameter values used in the simulations

$$
\begin{aligned}
\frac{dT}{dt} &= aT(1 - T/K) - I_{TN}(T, N) - I_{TL}(T, L) \\
\frac{dN}{dt} &= eC - fN - p_2NT + \frac{p_3NT}{1 + \alpha_3 T + \beta_3 N}, \\
\frac{dL}{dt} &= (p_4 L_N + \frac{p_5 I}{\alpha_4 + I} L)(1 - L/K_L) \frac{T}{\alpha_5 + T} \frac{1}{1 + P P_{LT}/K_{YQ}} - dL, \\
\frac{dC}{dt} &= \alpha - \beta C, \\
\frac{dP_L}{dt} &= \frac{P_L}{L + \epsilon_1 T + \epsilon_2 N} \frac{d}{dt}(L + \epsilon_1 T + \epsilon_2 N) - \mu P_L A, \\
\frac{dA}{dt} &= D(t) - \mu P_L A - \delta_1 A, \\
P(t) &= \rho_P L(t), \\
P_{LT}(t) &= \frac{\epsilon_1 T}{L + \epsilon_1 T + \epsilon_2 N} P_L,
\end{aligned}
$$

Figure 11: Full list of differential equations used in the simulations

Appendix B: Glossary of Terms

- Triple Negative Breast Cancer (TNBC): A subtype of breast cancer characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression.
- Estrogen Receptor (ER): A protein found inside cells that binds to estrogen, contributing to the growth and survival of breast cancer cells.
- Progesterone Receptor (PR): A protein found inside cells that binds to progesterone, influencing the growth and function of breast tissue.
- Human Epidermal Growth Factor Receptor 2 (HER2): A protein that promotes the growth of cancer cells when it is overexpressed or amplified.
- Checkpoint Inhibitor Immunotherapy: A type of cancer treatment that works by blocking immune checkpoints, proteins that inhibit the immune system from attacking cancer cells.
- Programmed Death Protein 1 (PD-1): A protein found on the surface of certain immune cells that inhibits their activity when it binds to its ligand, programmed death ligand 1 (PD-L1), on cancer cells.
- Programmed Death Ligand 1 (PD-L1): A protein found on the surface of cancer cells that binds to PD-1 on immune cells, suppressing the immune

response against the cancer.

- Immune Checkpoint Inhibitors (ICI): Drugs that block the interaction between PD-1 and PD-L1, allowing the immune system to recognize and attack cancer cells.
- Innate Immune Cells: Cells of the immune system that provide immediate defense against pathogens, such as natural killer (NK) cells.
- Adaptive Immune Cells: Cells of the immune system that respond to specific antigens, including T lymphocytes (T cells) and B lymphocytes (B cells).
- Natural Killer (NK) Cells: A type of lymphocyte that plays a critical role in the innate immune response by recognizing and killing virus-infected cells and tumor cells.
- Cytotoxic T Lymphocytes (CTLs): T cells that can recognize and kill virus-infected cells and tumor cells.
- Antigen Presentation Cells (APCs): Cells of the immune system, such as dendritic cells, macrophages, and B cells, that present antigens to T cells, initiating an immune response.
- Lymphocytes: White blood cells involved in the immune response, including T cells, B cells, and NK cells.
- Interleukin-2 (IL-2): A cytokine produced by activated T cells that stimulates the growth and proliferation of other immune cells.
- Dosage Function: A mathematical function representing the administration of a drug over time, often used in pharmacokinetic modeling.
- Dirac Delta Function: A generalized function used in mathematics to represent a spike or impulse, commonly used in modeling instantaneous events, such as drug administration.

Python code

Simulation plots

```
### Parameters ####

a = 0.665
K = 1e9
p_1 = 7.86e-5
alpha_2 = 2286
beta_2 = 1.19e-4
p_2= 3.42e-6
p_3 = 1.87e-8
alpha_3 = 1.6e-5
beta_3 = 3.27
p_6 = 0.0584
alpha_6 = 0.20241
beta_6 = 0.02065
e = 0.012936
f = 0.0693
beta = 6.3e-3
alpha = 1.35e7
I = 2.37e-8
alpha_4 = 2.37e-8
alpha_5 = 1000
L_N = 2.3e8
K_L = 8e8
d= 0.41
p_5= 4.14
p_4= 9e-5
e1 = 23
e2 = 10
rho_P = 1.259e-8
rho_L = 2.51e-8
K_YQ = 1.296e-3
delta_1 = 0.0257
mu = 7.7

### Triple Negative Breast Cancer Model ###

def tnbc_model(x, t):
    dx=np.zeros(6)
    T=x[0]
    N=x[1]
    L=x[2]
    C=x[3]
    P_L=x[4]
    A=x[5]
    temp = (L+e1*T+e2*N)
    P = rho_P*L
    P_LT = (e1*T/(temp))*P_L

    dx[0] = a*T*(1-T/K) - (p_1*T*N**2)/(1+alpha_2*T+beta_2*N**2) - (p_6*T*L)/(1+alpha_6*T+beta_6*L)
    dx[1] = e*C - f*N - p_2*N*T + p_3*N*T/(1+alpha_3*T+beta_3*N)
    dx[2] = (p_4*L_N + p_5*I*L/(alpha_4 + I))*(1-L/K_L)*(T/(alpha_5+T))*(1/(1+P*P_LT/K_YQ)) - d*L
    dx[3] = alpha - beta*C
    dx[4] = (P_L/temp)*(dx[2] + e1*dx[0] + e2*dx[1]) - mu*P_L*A
    dx[5] = D - mu*P_L*A-delta_1*A

    return dx

T0 = 1e6
N0 = 4e8
L0 = 0
C0 = 2e9
P_L0 = rho_L*(L0 + e1*T0 + e1*N0)
A0 = 0
L0 = 0

x0 = [T0,N0,L0,C0,P_L0,A0]
t_min1=0; t_max1=63; dt=0.1
times=np.arange(t_min1, t_max1+dt, dt)
from scipy.integrate import odeint
x_sim = odeint(tnbc_model, x0, times)
```

```
### Parameters ####

a = 0.665
K = 1e9
p_1 = 7.86e-5
alpha_2 = 2286
beta_2 = 1.19e-4
p_2= 3.42e-6
p_3 = 1.87e-8
alpha_3 = 1.6e-5
```

```
beta_3 = 3.27
p_6 = 0.0584
alpha_6 = 0.20241
beta_6 = 0.02065
e = 0.012936
f = 0.0693
beta = 6.3e-3
alpha = 1.35e7
I = 2.37e-8
alpha_4 = 2.37e-8
alpha_5 = 1000
L_N = 2.3e8
K_L = 8e8
d= 0.41
p_5= 4.14
p_4= 9e-5
e1 = 23
e2 = 10
rho_P = 1.259e-8
rho_L = 2.51e-8
K_YQ = 1.296e-3
delta_1 = 0.0257
mu = 7.7

### Triple Negative Breast Cancer Model ###

def tnbc_model(x, t):
    dx=np.zeros(6)
    T=x[0]
    N=x[1]
    L=x[2]
    C=x[3]
    P_L=x[4]
    A=x[5]
    temp = (L+e1*T+e2*N)
    P = rho_P*L
    P_LT = (e1*T/(temp))*P_L

    dx[0] = a*T*(1-T/K) - (p_1*T*N**2)/(1+alpha_2*T+beta_2*N**2) - (p_6*T*L)/(1+alpha_6*T+beta_6*L)
    dx[1] = e*C - f*N - p_2*N*T + p_3*N*T/(1+alpha_3*T+beta_3*N)
    dx[2] = (p_4*L_N + p_5*I*L/(alpha_4 + I))*(1-L/K_L)*(T/(alpha_5+T))*(1/(1+P*P_LT/K_YQ)) - d*L
    dx[3] = alpha - beta*C
    dx[4] = (P_L/temp)*(dx[2] + e1*dx[0] + e2*dx[1]) - mu*P_L*A
    dx[5] = - mu*P_L*A-delta_1*A

    return dx

d_A = 1200
T0 = 1e8
N0 = 4e8
L0 = 0
C0 = 2e9
P_L0 = rho_L*(L0 + e1*T0 + e1*N0)
A0 = 0
L0 = 0

x0 = [T0,N0,L0,C0,P_L0,d_A]
t_min1=0; t_max1=21; dt=0.1
times=np.arange(t_min1, t_max1+dt, dt)
from scipy.integrate import odeint
x_sim = odeint(tnbc_model, x0, times)

x_new0 = x_sim[-1]
x_new0[5] += d_A
t_min2=21; t_max2=42; dt=0.1
times2=np.arange(t_min2, t_max2+dt, dt)
x_new0_sim = odeint(tnbc_model, x_new0, times2)

x_new1 = x_new0_sim[-1]
x_new1[5] += d_A
t_min3=42; t_max3=63; dt=0.1
times3=np.arange(t_min3, t_max3+dt, dt)
x_new1_sim = odeint(tnbc_model, x_new1, times3)
```

```
### Parameters ####

a = 0.665
K = 1e9
p_1 = 7.86e-5*4
alpha_2 = 2286
beta_2 = 1.19e-4
p_2= 3.42e-6
p_3 = 1.87e-8
alpha_3 = 1.6e-5
beta_3 = 3.27
```

```
p_6 = 0.0584
alpha_6 = 0.20241
beta_6 = 0.02065
e = 0.012936
f = 0.0693
beta = 6.3e-3
alpha = 1.35e7
I = 2.37e-8
alpha_4 = 2.37e-8
alpha_5 = 1000
L_N = 2.3e8
K_L = 8e8
d= 0.41
p_5= 4.14
p_4= 9e-5
e1 = 23
e2 = 10
rho_P = 1.259e-8
rho_L = 2.51e-8
K_YQ = 1.296e-3
delta_1 = 0.0257
mu = 7.7

### Triple Negative Breast Cancer Model ###

def tnbc_model(x, t):
    dx=np.zeros(6)
    T=x[0]
    N=x[1]
    L=x[2]
    C=x[3]
    P_L=x[4]
    A=x[5]
    temp = (L+e1*T+e2*N)
    P = rho_P*L
    P_LT = (e1*T/(temp))*P_L

    dx[0] = a*T*(1-T/K) - (p_1*T*N**2)/(1+alpha_2*T+beta_2*N**2) - (p_6*T*L)/(1+alpha_6*T+beta_6*L)
    dx[1] = e*C - f*N - p_2*N*T + p_3*N*T/(1+alpha_3*T+beta_3*N)
    dx[2] = (p_4*L_N + p_5*I*L/(alpha_4 + I))*(1-L/K_L)*(T/(alpha_5+T))*(1/(1+P*P_LT/K_YQ)) - d*L
    dx[3] = alpha - beta*C
    dx[4] = (P_L/temp)*(dx[2] + e1*dx[0] + e2*dx[1]) - mu*P_L*A
    dx[5] = D - mu*P_L*A-delta_1*A

    return dx

T0 = 1e7
N0 = 4e8
L0 = 0
C0 = 2e9
P_L0 = rho_L*(L0 + e1*T0 + e1*N0)
A0 = 0
L0 = 0
D = 0

x0 = [T0,N0,L0,C0,P_L0,A0]
t_min1=0; t_max1=63; dt=0.1
times=np.arange(t_min1, t_max1+dt, dt)
from scipy.integrate import odeint
x_sim = odeint(tnbc_model, x0, times)
```

```
### Parameters ####

a = 0.665
K = 1e9
p_1 = 7.86e-5*4
alpha_2 = 2286
beta_2 = 1.19e-4
p_2= 3.42e-6
p_3 = 1.87e-8
alpha_3 = 1.6e-5
beta_3 = 3.27
p_6 = 0.0584
alpha_6 = 0.20241
beta_6 = 0.02065
e = 0.012936
f = 0.0693
beta = 6.3e-3
alpha = 1.35e7
I = 2.37e-8
alpha_4 = 2.37e-8
alpha_5 = 1000
L_N = 2.3e8
K_L = 8e8
d= 0.41
```

```
p_5= 4.14
p_4= 9e-5
e1 = 23
e2 = 10
rho_P = 1.259e-8
rho_L = 2.51e-9
K_YQ = 1.296e-3
delta_1 = 0.0257
mu = 7.7

### Triple Negative Breast Cancer Model ###

def tnbc_model(x, t):
    dx=np.zeros(6)
    T=x[0]
    N=x[1]
    L=x[2]
    C=x[3]
    P_L=x[4]
    A=x[5]
    temp = (L+e1*T+e2*N)
    P = rho_P*L
    P_LT = (e1*T/(temp))*P_L

    dx[0] = a*T*(1-T/K) - (p_1*T*N**2)/(1+alpha_2*T+beta_2*N**2) - (p_6*T*L)/(1+alpha_6*T+beta_6*L)
    dx[1] = e*C - f*N - p_2*N*T + p_3*N*T/(1+alpha_3*T+beta_3*N)
    dx[2] = (p_4*L_N + p_5*I*L/(alpha_4 + I))*(1-L/K_L)*(T/(alpha_5+T))*(1/(1+P*P_LT/K_YQ)) - d*L
    dx[3] = alpha - beta*C
    dx[4] = (P_L/temp)*(dx[2] + e1*dx[0] + e2*dx[1]) - mu*P_L*A
    dx[5] = D - mu*P_L*A-delta_1*A

    return dx

T0 = 1e6
N0 = 4e8
L0 = 0
C0 = 2e9
P_L0 = rho_L*(L0 + e1*T0 + e1*N0)
A0 = 0
L0 = 0
D = 0

x0 = [T0,N0,L0,C0,P_L0,A0]
t_min1=0; t_max1=63; dt=0.1
times=np.arange(t_min1, t_max1+dt, dt)
from scipy.integrate import odeint
x_sim = odeint(tnbc_model, x0, times)
```

Novel Simulations

```
# Testing new dosage 1680 mg Every 4 weeks
### Parameters ####

a = 0.665
K = 1e9
p_1 = 7.86e-5
# p_1 = 3.14e-4
alpha_2 = 2286
beta_2 = 1.19e-4
p_2= 3.42e-6
p_3 = 1.87e-8
alpha_3 = 1.6e-5
beta_3 = 3.27
p_6 = 0.0584
alpha_6 = 0.20241
beta_6 = 0.02065
e = 0.012936
f = 0.0693
beta = 6.3e-3
alpha = 1.35e7*39
I = 2.37e-8
alpha_4 = 2.37e-8
alpha_5 = 1000
L_N = 2.3e8
K_L = 8e8
d= 0.41
p_5= 4.14
p_4= 9e-5
e1 = 23
e2 = 10
rho_P = 1.259e-8
rho_L = 2.51e-8
K_YQ = 1.296e-3
delta_1 = 0.0257
mu = 7.7
```

```
### Triple Negative Breast Cancer Model ###

def tnbc_model(x, t):
    dx=np.zeros(6)
    T=x[0]
    N=x[1]
    L=x[2]
    C=x[3]
    P_L=x[4]
    A=x[5]
    temp = (L+e1*T+e2*N)
    P = rho_P*L
    P_LT = (e1*T/(temp))*P_L

    dx[0] = a*T*(1-T/K) - (p_1*T*N**2)/(1+alpha_2*T+beta_2*N**2) - (p_6*T*L)/(1+alpha_6*T+beta_6*L)
    dx[1] = e*C - f*N - p_2*N*T + p_3*N*T/(1+alpha_3*T+beta_3*N)
    dx[2] = (p_4*L_N + p_5*I*L/(alpha_4 + I))*(1-L/K_L)*(T/(alpha_5+T))*(1/(1+P*P_LT/K_YQ)) - d*L
    dx[3] = alpha - beta*C
    dx[4] = (P_L/temp)*(dx[2] + e1*dx[0] + e2*dx[1]) - mu*P_L*A
    dx[5] = - mu*P_L*A-delta_1*A

    return dx

d_A = 0
T0 = 1e6
N0 = 4e8
L0 = 0
C0 = 2e9
P_L0 = rho_L*(L0 + e1*T0 + e1*N0)
A0 = 0
L0 = 0

x0 = [T0,N0,L0,C0,P_L0,d_A]
t_min1=0; t_max1=21; dt=0.1
times=np.arange(t_min1, t_max1+dt, dt)
from scipy.integrate import odeint
x_sim = odeint(tnbc_model, x0, times)

x_new0 = x_sim[-1]
x_new0[5] += d_A
t_min2=21; t_max2=42; dt=0.1
times2=np.arange(t_min2, t_max2+dt, dt)
x_new0_sim = odeint(tnbc_model, x_new0, times2)

x_new1 = x_new0_sim[-1]
x_new1[5] += d_A
t_min3=42; t_max3=100; dt=0.1
times3=np.arange(t_min3, t_max3+dt, dt)
x_new1_sim = odeint(tnbc_model, x_new1, times3)
```