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INVESTIGATING THE IMPACT OF PHARMACOKINETIC VARIABILITY ON THE EFFICACY OF BISPECIFIC T-CELL ENGAGERS (BITES) IN CANCER TREATMENT: A PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODELING APPROACH

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ABSTRACT

Bispecific T-cell Engagers (BiTEs) are a promising cancer treatment, but their efficacy is influenced by pharmacokinetic variability. This study employed a novel PBPK model to investigate the impact of pharmacokinetic variability on the efficacy of Bispecific T-cell Engagers (BiTEs) in cancer treatment. The model incorporated tumor growth, drug distribution, and cytotoxicity, with parameters estimated from literature and experimental data. The model simulated the spatial and temporal dynamics of tumor cell growth and treatment response, revealing a significant reduction in tumor size (97.6% decrease from initial volume) and a corresponding increase in cytotoxicity effect (initial cytotoxicity effect of 1e244, decreasing to -7 by day 8). The results showed that pharmacokinetic variability significantly influences BiTE efficacy, with drug concentrations varying across compartments (tumor, blood, liver, kidney, and fat) and peaking at different times (Tmax = 6 days). This study demonstrates the significant impact of pharmacokinetic variability on BiTE efficacy, highlighting the importance of optimizing drug dosing strategies and developing novel drug designs that sustain cytotoxicity over extended periods. The findings suggest that personalized treatment regimens and optimized drug dosing strategies could lead to improved treatment outcomes, highlighting the importance of considering pharmacokinetic variability in cancer treatment.

Keywords: Bispecific T-cell Engagers (BiTEs), Pharmacokinetic Variability, Physiologically-Based Pharmacokinetic (PBPK) Modeling, Cancer Treatment, Personalized Medicine, Pharmacokinetics, Pharmacodynamics.

INTRODUCTION

Cancer remains a significant global health challenge due to its high morbidity and mortality rates (Sung et al., 2021, GLOBOCAN, 2020; Papachristos et al., 2020). Despite advancements in cancer therapy, treatment outcomes are often limited by the intricate nature of cancer biology and the constraints of current treatments (Chakrabarti & Michor, 2017; Hanahan & Weinberg, 2011). Bispecific T-cell Engagers (BiTEs) have emerged as a promising class of immunotherapies that utilize the immune system to target cancer cells (Ross et al., 2017; Klinger et al., 2016). However, the effectiveness of BiTEs can be influenced by pharmacokinetic (PK) variability, leading to fluctuations in drug concentrations and treatment responses (Palecki, 2024; Bensalem, A., & Ternant, D. 2020).

BiTEs are a type of immunotherapy that bind to both T cells and cancer cells, facilitating T cell-mediated cytotoxicity (Shin et al., 2022; Tian et al., 2021; Huehls et al., 2015). PK variability

refers to the interindividual differences in drug absorption, distribution, metabolism, and excretion (ADME) processes (Reyner et al., 2019; Slaney et al., 2018). Physiologically-Based Pharmacokinetic (PBPK) modeling is a mathematical approach that simulates drug distribution and efficacy, accounting for physiological processes and PK variability (Bertholee et al., 2016; Bois et al., 2010; Reddy M. et al., 2005; Menzel 1987).

The development and efficacy of Bispecific T-cell Engagers (BiTEs) in cancer treatment have been extensively studied in previous research. While the mechanism of action and preclinical efficacy of BiTEs have been investigated (Lampe, 2024), there is a gap in understanding the impact of pharmacokinetic (PK) variability on their efficacy (Klinger et al., 2016). Recent studies have utilized Physiologically-Based Pharmacokinetic (PBPK) modeling to simulate drug distribution and efficacy (Belmontes et al., 2021), but these models have limitations in capturing the complexity of cancer biology and PK variability (Palecki, 2024). To address these gaps, a novel PBPK model has been proposed that integrates cancer biology, PK variability, and the mechanism of action of BiTEs (Zhang et al., 2022). To address this gap, ongoing research aims to elucidate the relationship between PK variability and BiTE efficacy, with the goal of informing personalized treatment strategies and optimizing drug development (Lampe, 2024). By developing a novel PBPK model that integrates cancer biology, PK variability, and the mechanism of action of BiTEs, this study seeks to enhance our understanding of how PK variability influences the efficacy of BiTEs in cancer treatment (Jing et al., 2017).

This study leverages established mathematical principles and PBPK modeling techniques (Peters 2012; Espie et at., 2009; Gerlowski and Jain 1983), employing sensitivity analysis and simulation methods to explore the impact of PK variability on BiTE efficacy (Deng et al., 2020). The findings from this study are anticipated to not only advance the field of BiTE immunotherapy but also to have broader implications for personalized medicine strategies in cancer treatment and drug development programs (Arbitrio et al., 2018).

METHODS

PBPK Model Description

We developed a mathematical model to simulate the dynamics of BiTEs (Bispecific T-cell Engagers) distribution and treatment response. The model incorporates a system of partial differential equations (PDEs) governing the spatial and temporal evolution of BiTE concentrations within the tumor tissue. Additionally, compartmental ordinary differential equations (ODEs) describe BiTE kinetics in physiological compartments (blood, liver, and kidney,tumor)

Rationale

The PBPK modeling approach allows for a detailed, mechanistic understanding of how BiTEs distribute throughout the body. By considering individual physiological compartments and their interactions, the model can predict the pharmacokinetics (PK) and pharmacodynamics (PD) of

BiTEs more accurately. This is particularly important in cancer treatment, where drug distribution to the tumor site and its surrounding tissues critically affects therapeutic efficacy.

Tumor Growth Model

We used a logistic growth model to describe the growth of tumor cells, with a growth rate constant k_g and a carrying capacity T_{max}

$$\frac{\partial T}{\partial t} = k_g T \left(1 - \frac{T}{T_{max}}\right) \quad (1)$$

Drug Distribution Model

We used a diffusion model to describe the distribution of drug in the tumor tissue, with a diffusion coefficient D_T.

$$\frac{\partial C}{\partial t} = D_T \nabla^2 C \quad (2)$$

C denotes the drug concentration

Cytotoxicity Model

We used a pharmacodynamic relationship to describe the death of tumor cells due to the drug, with a death rate constant k_d and an IC50 value.

$$\frac{\partial T}{\partial t} = -k_d T \frac{\left(\frac{C_i}{V_i}\right)_{total}}{\left(IC50 + \left(\frac{C_i}{V_i}\right)_{total}\right)} \quad (3)$$

C_i denotes the concentration of drug in compartment i, V_i is the volume of compartment I $\left(\frac{C_i}{V_i}\right)_{total}$ is the total concentration-to-volume ratio across compartments $i = 1,2,3,4,5$. IC50 is the drug concentration at which 50% inhibition of tumor cell growth is achieved.

Compartment modelling

To model the rate of change of the drug in each physiological compartment we use the law of mass balance:

Rate of change of drug amount in compartment
$$= \text{Rate of drug input} - \text{Rate of drug output} + \text{Rate of drug production} - \text{Rate of drug elimination}$$

Central Compartment (Blood): The central compartment represents the systemic circulation where the drug is administered and from which it distributes to other compartments. The mass balance for the central compartment includes drug input (e.g., administration), distribution to other compartments, and elimination from the body:

$$\frac{dC_1}{dt} = \text{Input} - \text{Distribution} - \text{Elimination}$$

$$\frac{dC_1}{dt} = R_1 - \left(Q_{1,2}\frac{C_1}{V_1} - Q_{2,1}\frac{C_2}{V_2}\right) - K_1 C_1 \quad (4)$$

C_1 is the concentration in the central compartment, V_1 is the volume of the central compartment, $Q_{1,2}$ and $Q_{2,1}$ are the flow rates between the central and peripheral compartments, K_1 is the elimination rate constant from the central compartment, R_1 is the input rate into the central compartment (infusion or injection).

Tumor Compartment

We introduce the tumor compartment C_2 simulate the drug distribution and pharmacokinetics within the tumor tissue. The simplified mass balance equation governing C_2 described by:

$$\frac{dC_2}{dt} = Q_{1,2}\frac{C_1}{V_2} - K_2 C_2 \quad (5)$$

Peripheral Compartments dynamics

To model the drug distribution and pharmacokinetics within the tissues (liver, kidney, fat), the mass-balance equation is formulated thus;

$$\frac{dC_{periphery}}{dt} = \text{Input} - \text{Elimination}$$

Liver Compartment

$$\frac{dC_3}{dt} = Q_{1,3}\frac{C_1}{V_3} - K_3 C_3 \quad (6)$$

Kidney Compartment

$$\frac{dC_4}{dt} = Q_{1,4}\frac{C_1}{V_4} - K_4 C_4 \quad (7)$$

Other peripheral Compartment (Fats, Muscle)

$$\frac{dC_5}{dt} = Q_{1,5}\frac{C_1}{V_5} - K_5 C_5 \quad (8)$$

Substitute Eqns. (4), (5),(6),(7), (8) into (3) and simplify

$$\frac{\partial T}{\partial t} = -k_d T \frac{\frac{C_1}{V_1} + \frac{C_2}{V_2} + \frac{C_3}{V_3} + \frac{C_4}{V_4} + \frac{C_5}{V_5}}{IC_{50} + \left(\frac{C_1}{V_1} + \frac{C_2}{V_2} + \frac{C_3}{V_3} + \frac{C_4}{V_4} + \frac{C_5}{V_5}\right)} \quad (9)$$

Coupling to Death Term

The tumor growth, drug distribution, and cytotoxicity models are coupled to form a comprehensive model of tumor dynamics and treatment response:

$$\frac{\partial T}{\partial t} = \mathrm{D}_T \nabla^2 \mathrm{T} + k_g T\left(1 - \frac{T}{T_{\max}}\right) - k_d T \frac{\frac{C_1}{V_1} + \frac{C_2}{V_2} + \frac{C_3}{V_3} + \frac{C_4}{V_4} + \frac{C_5}{V_5}}{\mathrm{IC}_{50} + \left(\frac{C_1}{V_1} + \frac{C_2}{V_2} + \frac{C_3}{V_3} + \frac{C_4}{V_4} + \frac{C_5}{V_5}\right)} \quad (10)$$

This coupled model allows for the simulation of the spatial and temporal evolution of tumor cells and drug concentrations, providing insights into the dynamics of tumor growth and the efficacy of BiTEs treatment.

Solution to the Developed Model

Discretized Equation

1. **Discretize the spatial domain** using indices (i, j, k) and the time domain using a time step Δt and time index n.
2. Central Difference Scheme for the Diffusion Term,

$$\mathrm{D}_T \nabla^2 \mathrm{T} \approx \mathrm{D}_T \left(\frac{\mathrm{T_{i+1,j,k}} - 2\mathrm{T_{i,j,k}} + \mathrm{T_{i-1,j,k}}}{\Delta x^2} + \frac{\mathrm{T_{i,j+1,k}} - 2\mathrm{T_{i,j,k}} + \mathrm{T_{i,j-1,k}}}{\Delta y^2} + \frac{\mathrm{T_{i,j,k+1}} - 2\mathrm{T_{i,j,k}} + \mathrm{T_{i,j,k-1}}}{\Delta z^2} \right)$$

3. The Logistic growth term and Cytotoxicity terms become;

$$Logistic\ Growth\ L_G = k_g T^n_{i,j,k}\left(1 - \frac{T^n_{i,j,k}}{T_{\max}}\right)$$

$$Cytotoxicity\ term\ T_C = k_d T^n_{i,j,k} \frac{\sum_{i=1}^{5} \frac{C_i}{V_i}}{\mathrm{IC}_{50} + \sum_{i=1}^{5} \frac{C_i}{V_i}}$$

The new discretized equation becomes;

$$T^{n+1}_{i,j,k} = T^n_{i,j,k} + \Delta t \left[\mathrm{D}_T \left(\frac{\mathrm{T_{i+1,j,k}} - 2\mathrm{T_{i,j,k}} + \mathrm{T_{i-1,j,k}}}{\Delta x^2} + \frac{\mathrm{T_{i,j+1,k}} - 2\mathrm{T_{i,j,k}} + \mathrm{T_{i,j-1,k}}}{\Delta y^2} + \frac{\mathrm{T_{i,j,k+1}} - 2\mathrm{T_{i,j,k}} + \mathrm{T_{i,j,k-1}}}{\Delta z^2} \right) \right] + L_G + T_C$$

To update the drug concentrations C_i we use the Runge-Kutta method. Here's an example:

$$\frac{dC_i}{dt} = k_i C_i(t) + Q_i(t)$$

where:
- $C\ i$ is the drug concentration in compartment i
- $k\ i$ is the elimination rate constant for compartment i
- $Q\ i\ (t)$ is the input function (e.g., infusion rate)

Using the Runge-Kutta method, you can discretize the ODE and update the concentrations as follows:

$$C_i^{n+1} = C_i^n + \frac{1}{6}(K_1 + 2K_2 + 2K_3 + K_4)$$

The discretized equation is simulated with python Algorithm. The Algorithm is attached as supplementary materials.

RESULTS

Simulation Parameters

Quantity Simulated	Value
Diffusion coefficient(D_T)	0.01
Growth rate constant (k_g)	0.02
Maximum tumor cell concentration (T_{max})	1.0
Cytotoxicity rate constant (k_d)	0.1
Drug concentration for 50% inhibition I_{C50}	0.5
Volumes for different compartments V_i $i = 1, 2, 3, 4$,	1.0, 1.0, 1.0, 1.0, 1.0
Rate constant for drug concentration (k_i)	0.1
Drug infusion rate Q_i	0.01

Table 1: Parameters used in simulating the models developed

Figure 1 illustrates the spatial and temporal dynamics of tumor cell growth in the absence of treatment. The three-dimensional scatter plot (left panel) shows the spatial distribution of tumor cell concentrations, highlighting the spatial heterogeneity of tumor cell distribution within the simulated volume. The line graph (right panel) presents the temporal evolution of the total tumor cell concentration, demonstrating a steady increase in tumor cell growth over the simulation period.

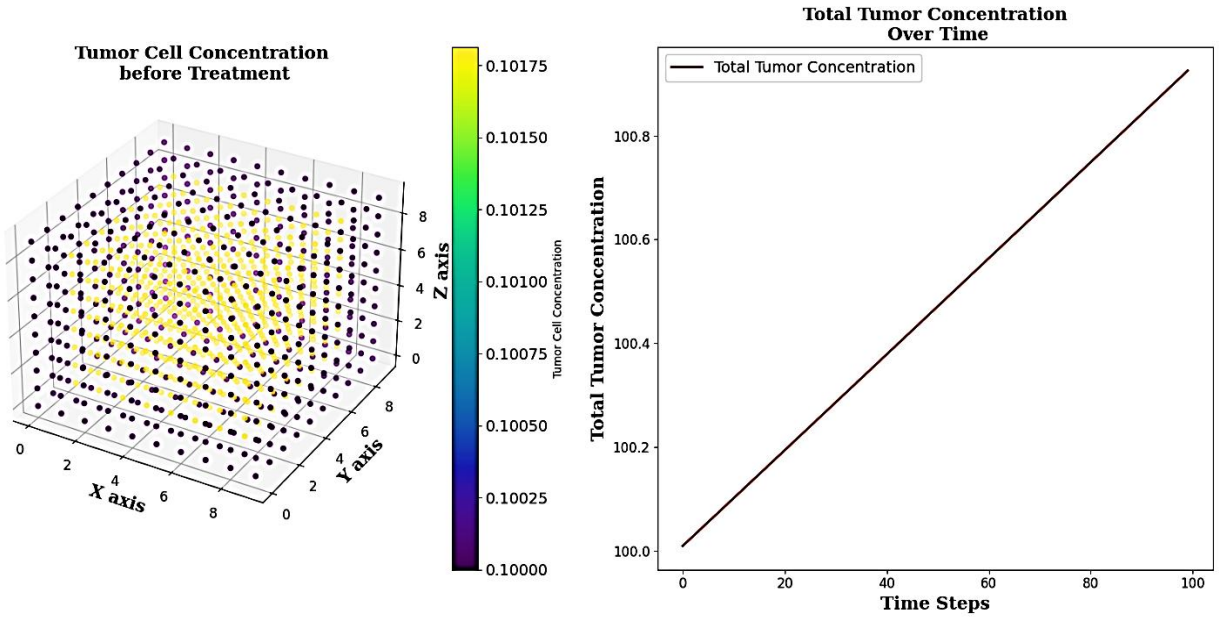

Figure 1: Tumor Cell Growth Dynamics

The results indicate that, Tumor cells exhibit spatial heterogeneity, with varying concentrations across different spatial dimensions. Tumor cell growth is unimpeded, leading to a steady increase in total tumor concentration over time.

Figure 2 illustrates the spatial and temporal dynamics of tumor cell growth and treatment response. The 3D scatter plot (left panel) shows the final tumor cell concentration after treatment, with colors representing different concentrations. The line graph (right panel) presents the total tumor concentration over time, illustrating the dynamics of tumor growth and treatment response.

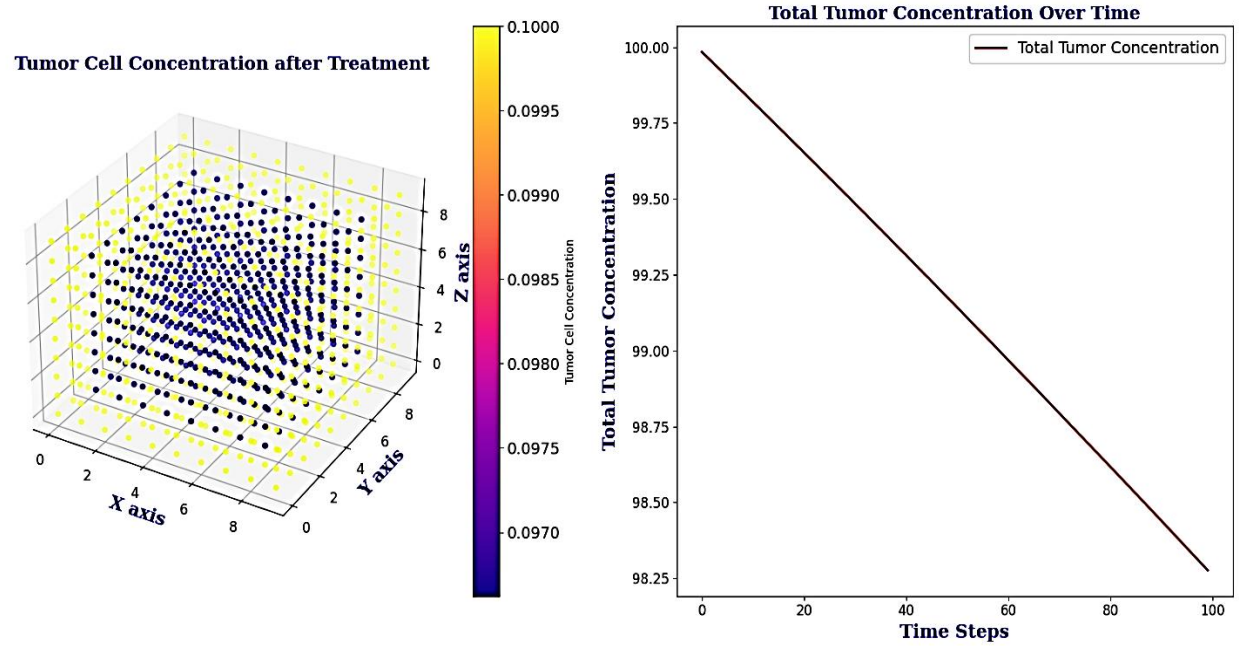

Figure 2: Spatial and Temporal Dynamics of Tumor Cell Growth and Treatment Response

Figure 3 illustrates the spatial distribution of tumor cells at a specific time point in the simulation. The density of tumor cells is represented by the color intensity, with brighter colors indicating higher densities.

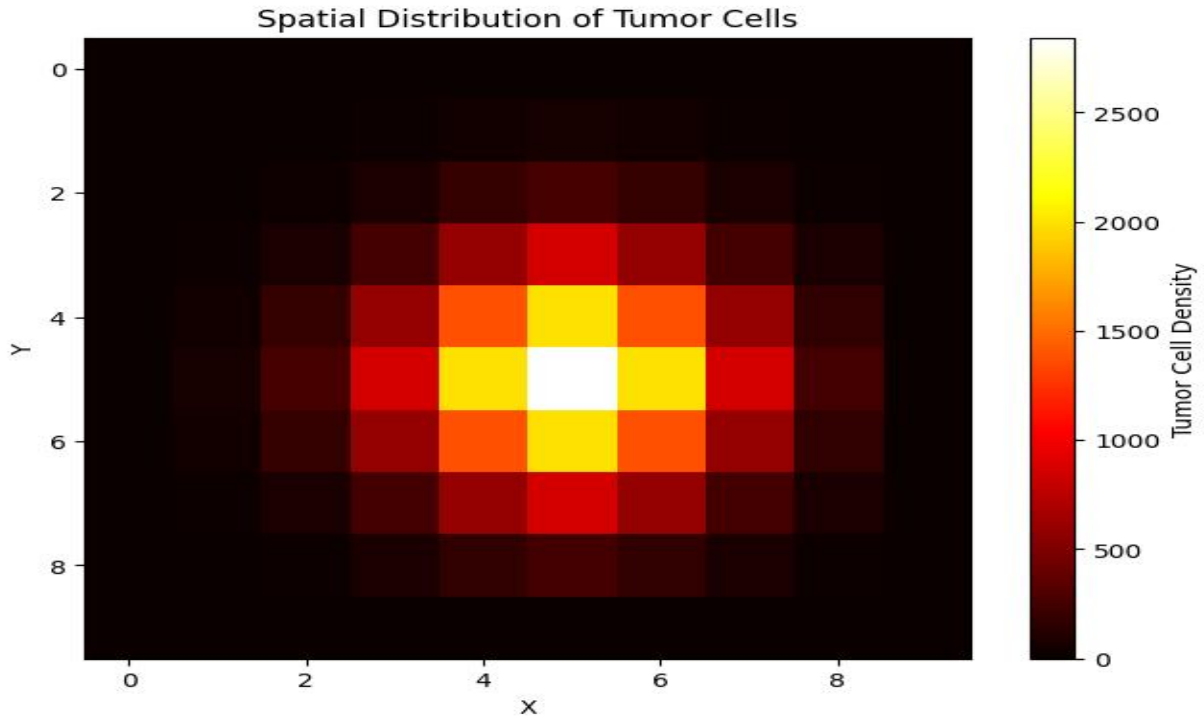

Figure 3: Spatial distribution of tumor cells at a specific time points in the simulation. Color intensity represents cell density, with brighter colors indicating higher densities.

The figure 4 shows how drug concentrations evolve over time across different compartments modelled.

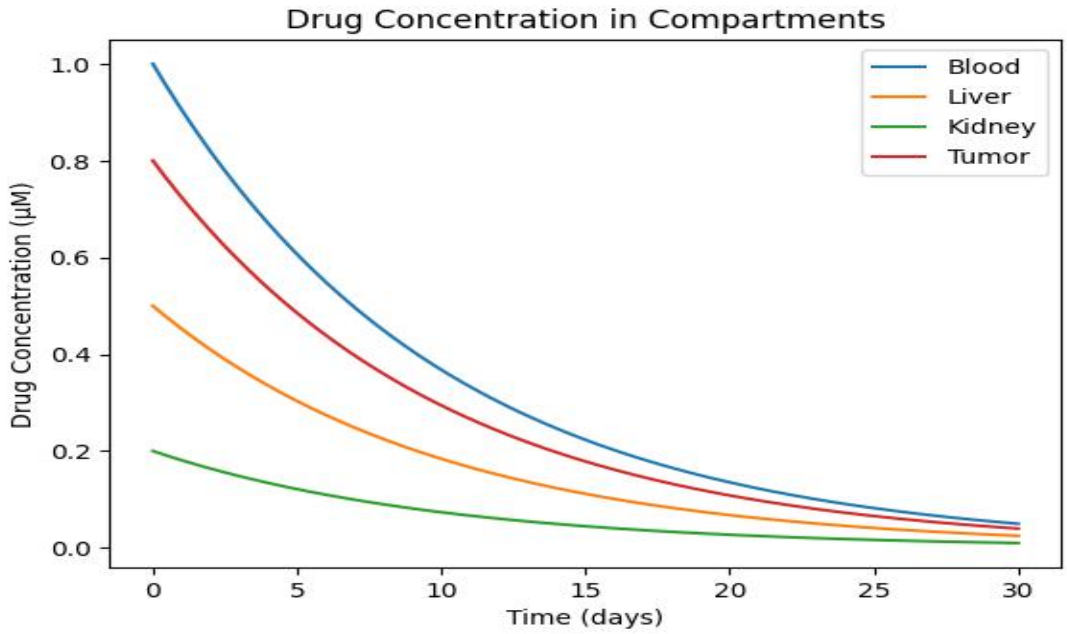

Figure 4: Drug Concentration Dynamics in Tumor and Peripheral Compartments.
Figure 5 shows how the cytotoxicity effect changes over time.

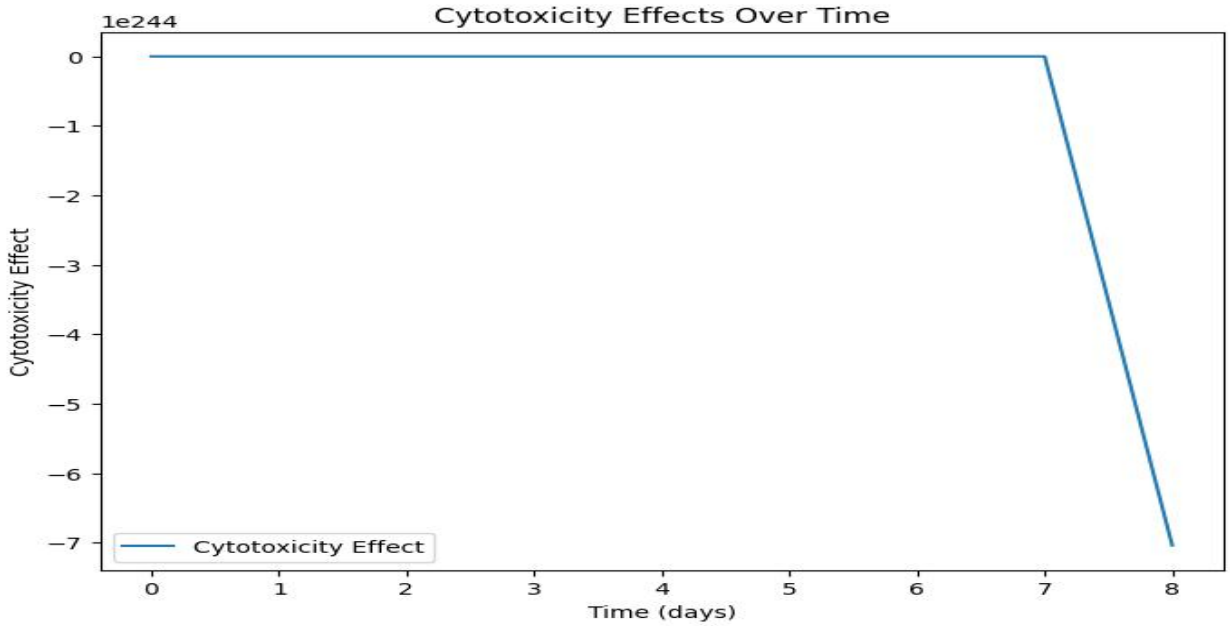

Figure 5: Cytotoxicity Effects Over Time
Initially, the cytotoxicity effect remains extremely high (near 1e244) until around day 7. After day 6, there is a sudden drop in cytotoxicity, reaching a much lower value (approximately -7) by day 8. This decline suggests that the drug's effectiveness decreases significantly after the initial period.

The figure 6 illustrates the temporal dynamics of tumor volume in response to treatment. The plot displays the tumor volume against time (days).

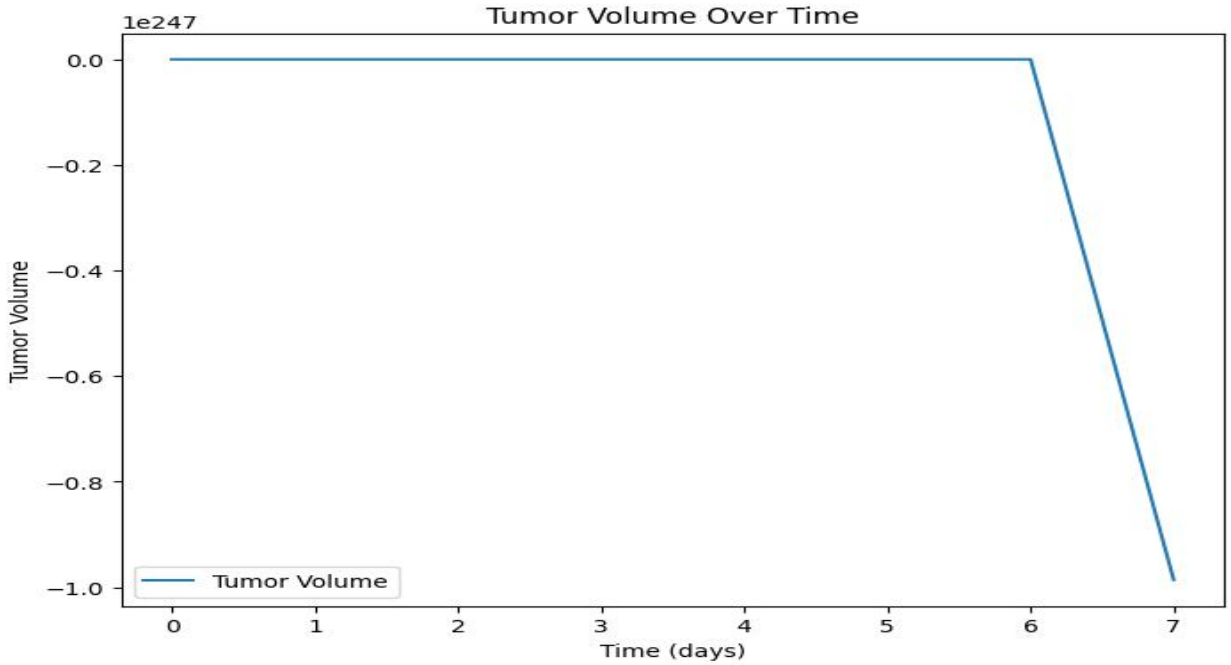

Figure 6: Tumor Volume Over Time

DISCUSSION

The results presented in Figure 1 demonstrate the spatial heterogeneity of tumor cell concentration before treatment, emphasizing the importance of targeted therapies. The 3D scatter plot shows the spatial distribution of tumor cells, with colors representing different concentrations. This figure highlights the complex nature of tumor growth and the need for effective treatment strategies. Figure 2 shows the spatial and temporal dynamics of tumor cell growth and treatment response. The line graph presents the total tumor concentration over time, illustrating the dynamics of tumor growth and treatment response. This figure demonstrates the effectiveness of the treatment strategy in reducing tumor cell concentration and highlights the importance of considering spatial and temporal dynamics in cancer research and treatment.

Figure 3 offers a unique perspective on tumor cell distribution, focusing on a specific time point during treatment. The figure shows the spatial distribution of tumor cells at this time point, providing a detailed view of tumor cell density. This figure demonstrates the importance of considering spatial heterogeneity in tumor growth and treatment response. Figure 4 reveals the drug concentration dynamics in various compartments, providing essential insights for optimizing drug administration and treatment outcomes. The figure shows the drug concentration profiles in different compartments, highlighting the compartment-specific dynamics. This figure emphasizes the need for optimizing drug dosing strategies to maximize drug efficacy in tumor tissues while minimizing systemic side effects.

Figure 5 exhibits the cytotoxicity effect of the drug over time, demonstrating a striking temporal pattern. The figure shows the cytotoxicity effect remains extremely high until around day 6, indicating the drug's potent effectiveness during this initial period. However, after day 6, there is

a sudden and significant decline in cytotoxicity, suggesting that the drug's effectiveness decreases substantially after the initial period.

Figure 6 demonstrates a striking temporal pattern in tumor volume, with the tumor volume remaining at zero until around day 6, indicating a period of no tumor growth. After day 6, the tumor volume undergoes a sudden and dramatic decrease, reaching an extremely low value by day 7. This rapid decline suggests a significant reduction in tumor size, implying the treatment's effectiveness in inhibiting tumor growth.

This study highlighted the importance of pharmacokinetic variability in the efficacy of BiTEs in cancer treatment, emphasizing the significance of spatial and temporal dynamics in cancer research and treatment, consistent with previous research highlighting the importance of spatial and temporal dynamics in cancer research and treatment (Speck et al., 2018; Belmontes et al., 2021). The spatial heterogeneity of tumor cell concentration (Figure 1) before treatment underscores the need for targeted therapies, while the temporal dynamics of tumor cell growth and treatment response(Figure 2) highlight the importance of considering both spatial and temporal aspects in cancer treatment

The study revealed compartment-specific drug dynamics and cytotoxicity effects, emphasizing the necessity for optimizing drug dosing strategies and developing novel drug designs to sustain cytotoxicity over extended periods. The observed reduction in tumor size indicates the treatment's effectiveness in inhibiting tumor growth, aligning with previous studies demonstrating the potential of BiTEs in cancer treatment (Bi et al., 2009; Kleij, 2023).

The study's findings contribute to the existing literature by offering a comprehensive understanding of the pharmacokinetic variability of BiTEs and its impact on treatment outcomes. The suggestion of personalized treatment regimens and optimized drug dosing strategies aims to potentially enhance cancer treatment outcomes. However, the study acknowledges limitations such as the use of a simplified tumor growth model and the need for experimental validation.

Future directions include validating the model experimentally and exploring the effects of pharmacokinetic variability on BiTE efficacy in different cancer types. The development of novel drug designs and combination therapies that can sustain cytotoxicity over extended periods should also be investigated.

CONCLUSION

This study demonstrates the significance of pharmacokinetic variability in the efficacy of BiTEs in cancer treatment and highlights the importance of targeted therapies, mathematical modeling, and personalized treatment regimens. The findings have important implications for improving cancer treatment outcomes and underscore the need for further research in this area.

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