

Article

Reaction-Diffusion Model of CAR-T Cell Therapy in Solid Tumours with Antigen Escape

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Abstract

Developing effective CAR-T cell therapy for solid tumours remains challenging because of biological barriers such as antigen escape and an immunosuppressive microenvironment. The aim of this study is to develop a mathematical model of the spatio-temporal dynamics of tumour processes in order to assess key factors that limit treatment efficacy. We propose a reaction–diffusion model described by a system of partial differential equations for the densities of tumour cells and CAR-T cells, the concentration of immune inhibitors, and the degree of antigen escape. The methods of investigation include stability analysis and numerical solution of the model using a finite-difference scheme. The simulations show that antigen escape produces a resistant tumour core and relapse after an initial regression; increasing the escape rate from $\gamma = 0.001$ to 0.1 increases the final tumour volume at $t = 100$ days from approximately 35.3 a.u. to 36.2 a.u. Parameter mapping further indicates that for $\gamma \leq 0.01$ tumour control can be achieved at moderate killing rates ($k_{CT} \approx 1 \text{ day}^{-1}$), whereas for $\gamma \geq 0.05$ comparable control requires $k_{CT} \approx 2\text{--}5 \text{ day}^{-1}$. Repeated CAR-T administration improves durability: the residual normalised tumour volume at $t = 100$ days decreases from approximately 4.5 after a single infusion to approximately 0.9 (double) and approximately 0.5 (triple), with a saturating benefit for further intensification. We conclude that the proposed model is a valuable tool for analysing and optimising CAR-T therapy protocols, and that our results highlight the need for combined strategies aimed at overcoming antigen escape.

Keywords: tumour modelling; reaction–diffusion equation; computational oncology; spatio-temporal dynamics of tumour; tumour growth; immune resistance; simulations; CAR-T therapy; mathematical modelling



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1. Introduction

1.1. Spatial Growth of Solid Tumours and Microenvironmental Barriers

The development of effective treatment modalities for solid tumours remains one of the most pressing challenges in contemporary oncology. Despite substantial advances in adoptive cell immunotherapy, especially the successful use of chimeric antigen receptor T (CAR-T) lymphocytes in haematological malignancies [1,2], the efficacy of CAR-T therapy against solid tumours remains limited by multiple biological and physical barriers [3,4]. In practice, limited delivery and infiltration of CAR-T cells into the tumour mass, an immunosuppressive microenvironment, and pronounced antigenic heterogeneity interact to reduce cytotoxic efficacy, while treatment is also constrained by the risk of severe adverse

events such as cytokine release syndrome and neurotoxicity associated with immune effector cells [5–7].

A central feature of these barriers is their spatial nature. Solid tumours exhibit abnormal vasculature and pathological angiogenesis, leading to hypoxia and elevated interstitial pressure, and are often embedded within a dense extracellular matrix that impedes immune cell migration [8]. At the same time, the tumour microenvironment can actively suppress effector function via inhibitory ligands, immunoregulatory cell populations, and soluble suppressive mediators [4]. These mechanisms generate spatial gradients in cellular and soluble factors, suggesting that spatially explicit models are needed to link local interactions to macroscopic tumour control outcomes.

Mathematical oncology offers a principled way to formalise such spatio-temporal mechanisms and to test intervention hypotheses [9,10]. Contemporary modelling approaches span classical population-dynamics models formulated as ordinary differential equations [11–13], stochastic and spatially explicit agent-based models [14] and cellular automata [15], and continuum formulations based on partial differential equations that account for tissue-scale transport and mechanics. For the latter, phase-field descriptions [16,17] and multiscale hybrid frameworks [18,19] are increasingly used to represent evolving tumour geometry and heterogeneous microenvironments. In parallel, fractional-calculus methods have been explored to incorporate memory and non-Markovian effects [20–23], and there is growing interest in combining mechanistic models with data-driven approaches for personalisation [24]. For example, diffusion-based modelling in heterogeneous media can reproduce clinical growth curves and quantify tissue-driven variability [25], while simulation modelling coupled with artificial intelligence can improve thermometry-based diagnostic performance [26]. Spatially distributed models also enable explicit modelling of vascular architecture and angiogenesis [27,28]. Reaction–diffusion vascular–tumour models have been used to investigate regimes of recurrence and persistence under combination therapies [29].

Among continuum approaches, reaction–diffusion equations are especially attractive because they naturally couple local interaction kinetics with spatial propagation. Since their early use in morphogenesis [30] and subsequent applications in ecology [31] and chemistry [32], reaction–diffusion models have become a standard tool in oncology and immunology [33,34]. In tumours, they provide a parsimonious and expressive representation of microenvironmental patterning by integrating local cell–cell interactions with cell migration and the diffusion of soluble mediators [35,36].

1.2. Modelling Immune–Tumour Interaction and CAR-T Therapy Dynamics

Because tumour–immune interactions span molecular, cellular, and tissue scales, experimental methods alone are often insufficient to disentangle the contributions of competing mechanisms. Although in vitro studies and animal models are indispensable, they are time-consuming and rarely provide high-resolution spatio-temporal characterisation of the processes that ultimately shape the clinical response [37,38]. This motivates complementary mechanistic models that can integrate heterogeneous data, formulate testable hypotheses, and explore the treatment design space [9,10].

In the broader immuno-oncology literature, models of tumour progression with immune-cell infiltration have been used to relate tumour characteristics, immune infiltration levels, and disease outcomes [39]. Competitive tumour–immune interactions under chemotherapy have been analysed to identify stable regimes and therapy-driven transitions [40]. More detailed interaction schemes that include multiple immune populations and combined targeted strategies, such as FGFR and PD-1 inhibition, have been used to identify parameter regimes that support durable control [41]. Mechanistic modelling

has also been used to quantify how hypoxia and adenosine contribute to immune escape in DC-mediated immunotherapy [42]. Finally, fractional-time formulations of tumour-immune dynamics under immunotherapy suggest that memory effects can substantially alter elimination rates and the stability of therapeutic regimes [43].

CAR-T cells are genetically modified lymphocytes expressing a chimeric antigen receptor that enables tumour recognition independently of the major histocompatibility complex [4]. To analyse CAR T-cell kinetics and function, many studies use predator–prey models or systems of ordinary differential equations to capture proliferation, exhaustion and memory formation [44–47]; such models can reveal non-linear dependencies between CAR-T dose, exhaustion, and tumour-cell killing efficacy [44]. However, for solid tumours, spatial gradients and physical barriers are critical, and reaction–diffusion formulations are particularly suitable [48,49]. Spatial CAR-T models can represent infiltration into tumour tissue, the influence of immunosuppressive mediators, and the heterogeneity of antigen distribution [50]. They also provide a natural framework for studying strategies that leverage indirect mechanisms such as the bystander effect, in which CAR-T activity induces an endogenous immune response against antigen-negative cells [50], and for formulating optimal-control approaches that can improve the probability of tumour eradication [48,49].

1.3. Resistance Mechanisms with Emphasis on Antigen Escape

A major challenge for durable CAR-T responses is therapeutic resistance emerging from intratumor heterogeneity. In solid tumours, antigenic heterogeneity can promote antigen escape, in which selective pressure from CAR-T cells favours tumour variants with reduced or lost target-antigen expression, ultimately leading to relapse [50,51]. Therefore, a clinically informative model should not only describe immune-mediated killing but also include resistance development as a dynamic process interacting with spatial microenvironmental constraints.

Mathematical descriptions of resistance in oncology provide relevant conceptual tools. Reviews emphasise computational prediction of drug resistance and the roles of heterogeneity and adaptive dynamics in treatment response [52]. Evolutionary models that track subpopulations with differing sensitivities allow analysis of transitions towards resistant dominance and allow comparison of dosing strategies [53]. Similarly, chemotherapy models that incorporate pharmacokinetics and resistance induction can be used to derive optimal administration regimens and conditions to suppress resistant subpopulations [54]. Together with classical tumour growth and treatment models [35,55], these works underscore the importance of incorporating resistance mechanisms already in the early stages of model formulation.

More generally, a multiscale perspective is often required to connect resistance mechanisms with spatial organisation. Reviews of microscopic and multiscale approaches relate molecular, cellular, and tissue levels of tumour organisation [56], while classical modelling surveys illustrate how comparatively simple equation-based systems can reproduce key growth patterns and treatment effects [35]. Models of tumour-nodule dynamics calibrated to clinical observations have also been proposed [55], and recent analyses emphasise the need to combine qualitative dynamical systems analysis with numerical simulation when interpreting clinically relevant scenarios [57]. Stochastic formulations that couple tumour growth to interactions with normal tissue highlight how fluctuations and competition for resources can shape progression and regression [58], and modelling of multicellular tumour spheroids demonstrates the need for quantitative tools even in relatively simple *in vitro* settings [59].

Against this background, the aim of the present study is to develop a spatial reaction–diffusion model for the spatio-temporal dynamics of CAR-T therapy in a solid tumour,

explicitly incorporating immunosuppressive inhibition and antigen escape. Using stability analysis and numerical simulations, we examine how antigen-escape rates and tumour-derived immunosuppressive factors influence treatment efficacy. We also assess whether alternative CAR T-cell dosing schedules can reduce the risk of relapse.

The present study formulates the following research objectives within a reaction–diffusion framework for the spatio-temporal interaction between CAR-T cells and a solid tumour that incorporates antigen escape and tumour-induced immunosuppression. The first objective is to characterise the conditions under which antigen escape promotes the emergence of spatially localised resistant regions that persist after an initial tumour regression and subsequently drive relapse. The second objective is to quantify how tumour production of soluble immune inhibitors modulates CAR-T infiltration and cytotoxic activity in space and, as a consequence, shifts the threshold between durable tumour control and tumour regrowth. The third objective is to determine how variations in the antigen-escape rate and the strength of immunosuppression jointly shape overall therapeutic efficacy, as quantified by the depth and durability of tumour suppression in numerical simulations.

This work is organised as follows. Section 2 presents the materials and methods of the study. Sections 2.1 and 2.2 formulate the reaction–diffusion mathematical model of the interaction between CAR-T cells and a solid tumour taking into account the mechanism of antigen escape, Section 2.3 performs a linear stability analysis of the tumour-free equilibrium, Section 2.4 describes the numerical method based on a finite-difference approximation and an explicit Euler scheme, and Section 2.5 presents the software implementation of the computational algorithm. Section 3 reports the results of the numerical simulations: Section 3.1 analyses the overall spatio-temporal behaviour of the system and the formation of resistant regions within the tumour, Section 3.2 validates the dynamics of tumour growth on the basis of published clinical data, Section 3.3 investigates the influence of the rate of antigen escape on the efficacy of CAR-T therapy, Section 3.4 examines the combined effect of key model parameters and identifies parameter regions corresponding to successful tumour eradication, and Section 3.5 provides a comparative analysis of different temporal strategies for the administration of CAR-T cells under conditions of antigen escape. Section 4 discusses the biological and clinical implications of the results obtained, the limitations of the proposed model, and possible directions for its extension, while Section 5 summarises the main conclusions of the work and outlines the perspectives for further research.

2. Materials and Methods

2.1. Reaction–Diffusion Mathematical Model of the Spatio-Temporal Dynamics of the Interaction Between CAR-T Cells and a Solid Tumour

The dynamics of the interaction between CAR-T cells and a solid tumour are described by a system of partial differential equations that takes into account the spatio-temporal evolution of the cell populations, as well as the influence of microenvironmental factors:

$$\begin{cases} \frac{\partial C}{\partial t} = D_C \nabla^2 C + r_C C(1 - C) - k_{CT} C T(1 - a_T) - k_I C I - h_C C, \\ \frac{\partial T}{\partial t} = D_T \nabla^2 T + r_T T(1 - T) - k_{CT} C T(1 - a_T) - h_T T, \\ \frac{\partial I}{\partial t} = -\alpha I + \beta T, \\ \frac{\partial a_T}{\partial t} = \gamma T(1 - a_T), \end{cases} \quad (1)$$

where C is the density of CAR-T cells; T is the density of tumour cells; I is the concentration of immune inhibitors; and a_T is the degree of tumour antigen escape.

The first equation of the system describes the spatial diffusion of CAR-T cells with diffusion coefficient D_C , their proliferation under limited resources according to a logistic law with rate r_C , cytotoxic interactions with tumour cells that depend on the level of antigen escape a_T , as well as inhibition by microenvironmental factors and natural cell death. The second equation characterises the dynamics of the tumour population. Tumour cells diffuse with coefficient D_T , proliferate at rate r_T , are lysed by CAR T cells, and undergo natural death. The third equation governs the dynamics of immune inhibitors: they decay at rate α , while their production is induced by tumour cells with intensity β . The final equation describes tumour antigen escape; the growth of the escape variable a_T is proportional to the tumour-cell density and is bounded above by 1 (i.e., $a_T \leq 1$). The terms $-h_C, C$ and $-h_T, T$ in system (1) are used as an effective, aggregated representation of the combined consequences of hypoxia and the associated metabolic stress characteristic of solid tumours [60]. For CAR-T cells, the parameter h_C is interpreted as an integral loss of functional activity and viability in an unfavourable microenvironment, which is consistent with experimental observations of CAR-T dysfunction at low oxygen levels [61]. For tumour cells, the parameter h_T is treated as an effective growth limitation and an increase in cell death under conditions of oxygen and nutrient deprivation; within the minimal model formulation, this effect is introduced without an explicit description of the oxygen field. The term $-k_I, C, I$ captures the overall inhibitory impact of immunosuppressive signals within the tumour microenvironment on the efficacy of the CAR-T response; the variable I is considered an aggregated pool of inhibitory factors induced by the tumour burden and degrading at rate α [62]. A diagram of the interactions between the key components of the model is shown in Figure 1.

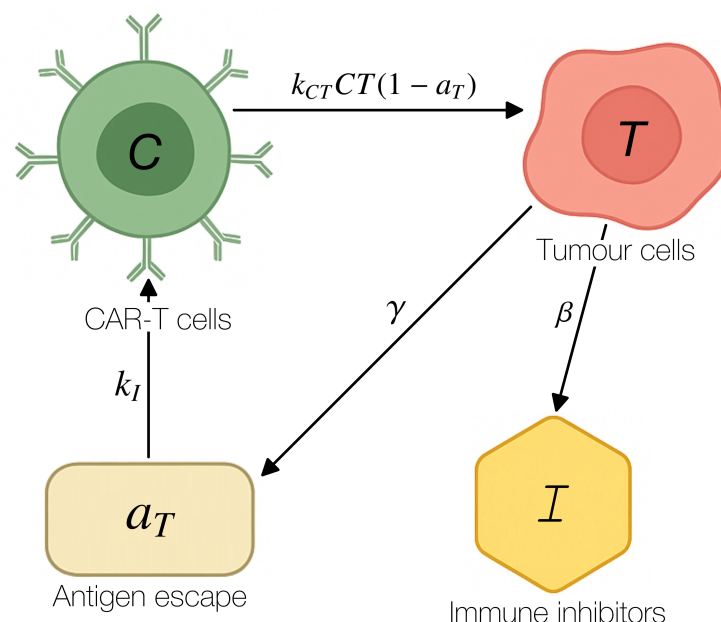


Figure 1. Schematic representation of the interactions in the reaction–diffusion model: CAR-T cells C infiltrate the tumour nodule and destroy tumour cells T ; the tumour produces immune inhibitors I that suppress CAR-T cell activity, and also initiates antigen escape a_T , which leads to a reduction in the efficiency of the cytotoxic response.

Thus, system (1) describes the spatio-temporal dynamics of the competing and interacting populations of CAR-T cells, tumour cells and immune inhibitors, taking into account tumour adaptive mechanisms [63].

In contrast to existing reaction–diffusion CAR-T models, which predominantly describe spatial infiltration and cytotoxic interactions, as well as multiscale approaches in which resistance is often introduced via an explicit discrete partitioning of the tumour into subpopulations or an agent-based level [18,19,48,49], the novelty of the proposed formulation lies in the fact that, within a single continuous spatio-temporal model, we simultaneously represent dynamically emerging tumour antigen escape and tumour-induced immunosuppression mediated by soluble inhibitory factors. Both mechanisms are directly linked to the local tumour burden, act within a spatially heterogeneous environment, and reduce CAR-T efficacy, thereby enabling us to reproduce the formation of resistant regions and subsequent relapse as a consequence of their combined influence. Moreover, antigen escape is described not in terms of discrete subclones, but as a continuous quantity that arises and intensifies during tumour–CAR-T interactions, preserving the analytical tractability of the model. This, in turn, allows us to derive explicit threshold conditions for successful tumour elimination in the following subsection and then compare them with the efficacy maps obtained in the numerical experiments.

Table 1 presents the initial values of the free parameters that are used in the proposed reaction–diffusion mathematical model. This table is key for the reproducibility of the results, as it defines the baseline conditions for the numerical simulations. It is important to note that a substantial proportion of the parameters in this work is used for the first time to describe specific interactions within this model. As no direct analogues for some of these parameters were available in the literature for the present spatial CAR-T setting, their baseline values were obtained by calibration (parameter fitting) as described below.

Table 1. Initial values of the free model parameters.

Parameter	Description	Value in the Model	Range of Values
D_C	Diffusion coefficient of CAR-T cells	0.05	assumed
D_T	Diffusion coefficient of tumour cells	0.00005	10^{-5} – 10^{-4} cm ² /day [63]
r_C	Proliferation rate of CAR-T cells	0.5	0.2–0.9 day ^{−1} [64], 0.1–0.9 day ^{−1} [65]
r_T	Tumour growth rate	0.1	0.01–0.2 day ^{−1} [65]
k_{CT}	Rate of tumour-cell killing by CAR-T cells	0.64	0.64–1.35 day ^{−1} [66]
k_I	Inhibition of CAR-T cells by immune factors	0.01	assumed
h_C	Effect of hypoxia on CAR-T cell activity	0.05	assumed
h_T	Effect of hypoxia on tumour growth	0.5	assumed
α	Decay rate of immune inhibitors	0.1	assumed
β	Rate of inhibitor production by the tumour	0.05	assumed
γ	Rate of tumour antigen escape	0.01	assumed

2.2. Parameter Identification and Sensitivity Analysis

For reproducibility, we distinguish between parameters fixed from published estimates (or typical orders of magnitude) and parameters calibrated in the present work. The parameters D_T , r_C , r_T and k_{CT} were taken from literature-based ranges reported in Table 1 and were used as baseline values for the simulations. In addition, the tumour proliferation rate r_T was fitted to published clinical tumour-volume time series in the therapy-free setting (see Section 3.2), while keeping the remaining parameters fixed, which provides an initial calibration of the tumour-growth time scale.

The parameters labelled as *assumed* in Table 1 were calibrated because consistent quantitative estimates for the present spatial CAR-T setting are not available. Specifically, we calibrated the parameter set

$$\theta = \{D_C, k_I, h_C, h_T, \alpha, \beta, \gamma\},$$

which controls the characteristic spatial spread of CAR-T cells, the strength of immune inhibition, the effective hypoxia impact, the inhibitor turnover, and the time scale of antigen escape.

Calibration was performed by minimising a normalised least-squares mismatch between model outputs and the chosen reference trajectories dynamics. Let $V_T(t_k) = \int_{\Omega} T(x, t_k) dx$ denote the tumour volume predicted by the model at observation times t_k . When reference tumour-volume data $V_T^{\text{ref}}(t_k)$ were available, the objective function was defined as

$$J(\theta) = \sum_{k=1}^N \left(\frac{V_T(t_k; \theta) - V_T^{\text{ref}}(t_k)}{\max_j V_T^{\text{ref}}(t_j)} \right)^2,$$

which prevents domination by a single scale and enables comparison across data sets. The optimisation was carried out under biologically admissible bounds for each parameter (Table 1) using a derivative-free constrained search.

To assess robustness with respect to parameter uncertainty, a sensitivity analysis was performed for the most uncertain and fitted parameters, i.e., for $D_C, k_I, h_C, h_T, \alpha, \beta$ and γ . Each parameter p was perturbed around its baseline value by ± 20 percent while keeping the others fixed, and the resulting changes were quantified for key outcomes used throughout the paper: the residual normalised tumour volume $V_{\text{norm}}(t_{\text{end}})$, the minimal tumour burden during therapy, and the relapse time.

2.3. Linear Stability Analysis of the Tumour-Free Equilibrium of the Mathematical Model

Consider the system (1) in a neighbourhood of tumour-free equilibrium

$$(C^*, T^*, I^*, a_T^*) = (C_0, 0, 0, a_0),$$

where the steady-state values satisfy $C_0(r_C(1 - C_0) - h_C) = 0$. Hence, there are two possibilities: $C_0 = 0$ or $C_0 = 1 - h_C/r_C$ (for $r_C > h_C$). The parameter $a_0 \in [0, 1]$ is arbitrary, because for $T^* = 0$ the equation for a_T degenerates and its value does not affect stationarity of the system.

To analyse stability, we write down the Jacobian of the reaction part of system (1). Let $u = (C, T, I, a_T)^\top$ and $\dot{u} = (f_C, f_T, f_I, f_a)^\top$, where

$$\begin{aligned} f_C &= r_C C(1 - C) - k_{CT} CT(1 - a_T) - k_I CI - h_C C, \\ f_T &= r_T T(1 - T) - k_{CT} CT(1 - a_T) - h_T T, \\ f_I &= -\alpha I + \beta T, \\ f_a &= \gamma T(1 - a_T). \end{aligned}$$

Then the general form of the Jacobian is

$$J(C, T, I, a_T) = \begin{pmatrix} r_C(1 - 2C) - k_{CT} T(1 - a_T) - k_I I - h_C & -k_{CT} C(1 - a_T) & -k_I C & k_{CT} CT \\ -k_{CT} T(1 - a_T) & r_T(1 - 2T) - k_{CT} C(1 - a_T) - h_T & 0 & k_{CT} CT \\ 0 & \beta & -\alpha & 0 \\ 0 & \gamma(1 - a_T) & 0 & -\gamma T \end{pmatrix}. \quad (2)$$

Substituting the steady-state values $(C_0, 0, 0, a_0)$ into (2), we obtain the Jacobian at the tumour-free point:

$$J^* = \begin{pmatrix} r_C(1 - 2C_0) - h_C & -k_{CT}C_0(1 - a_0) & -k_I C_0 & 0 \\ 0 & r_T - h_T - k_{CT}C_0(1 - a_0) & 0 & 0 \\ 0 & \beta & -\alpha & 0 \\ 0 & \gamma(1 - a_0) & 0 & 0 \end{pmatrix}. \quad (3)$$

We consider small spatial perturbations of the form $e^{\lambda t + i\mathbf{k} \cdot \mathbf{x}}$, where $\mathbf{k}$ is the wave vector. Then the Laplace operator is replaced by $\nabla^2 \rightarrow -k^2$, and the linear problem takes the form

$$\det(J^* - \lambda I - k^2 D) = 0, \quad D = \text{diag}(D_C, D_T, 0, 0), \quad k = |\mathbf{k}|.$$

Computing the determinant yields a factorised form of the characteristic polynomial:

$$\det(J^* - \lambda I - k^2 D) = -\lambda(\alpha + \lambda)(\lambda - [r_C - 2r_C C_0 - h_C - D_C k^2]) (\lambda - [r_T - h_T - C_0(1 - a_0)k_{CT} - D_T k^2]). \quad (4)$$

From (4) the four eigenvalues follow directly:

$$\begin{aligned} \lambda_1(k) &= 0, \\ \lambda_2(k) &= -\alpha, \\ \lambda_3(k) &= r_C - 2r_C C_0 - h_C - D_C k^2, \\ \lambda_4(k) &= r_T - h_T - C_0(1 - a_0)k_{CT} - D_T k^2. \end{aligned} \quad (5)$$

The first eigenvalue, $\lambda_1(k) = 0$, reflects a neutral direction in the variable a_T : for $T^* = 0$ there is no change in a_T , and this variable does not influence the dynamics of the remaining components at the linear level. The second eigenvalue, $\lambda_2(k) = -\alpha$, is always negative for $\alpha > 0$, which corresponds to stable inhibitor dynamics. The third and fourth eigenvalues describe the evolution of CAR-T cells and the tumour, respectively. For the C-mode, stability is ensured by the condition

$$r_C(1 - 2C_0) - h_C < 0,$$

and for the T-mode by

$$r_T - h_T - C_0(1 - a_0)k_{CT} < 0.$$

Since the addition of the diffusion terms $-D_C k^2$ and $-D_T k^2$ only decreases the real parts of $\lambda_i(k)$, it is sufficient to check these inequalities at $k = 0$.

Thus, the tumour-free state $(C_0, 0, 0, a_0)$ is linearly stable provided three conditions are satisfied:

$$\alpha > 0, \quad r_C(1 - 2C_0) - h_C < 0, \quad r_T - h_T - C_0(1 - a_0)k_{CT} < 0. \quad (6)$$

If $C_0 = 0$ (CAR-T cells are absent), the last inequality yields $\lambda_4(0) = r_T - h_T$, which corresponds to positive tumour growth for $r_T > h_T$. In the presence of a stable level of CAR-T cells, $C_0 = 1 - h_C/r_C$ (for $r_C > h_C$), we have

$$\lambda_4(0) = r_T - h_T - \left(1 - \frac{h_C}{r_C}\right)(1 - a_0)k_{CT},$$

and the condition for tumour elimination takes the form

$$r_T - h_T < \left(1 - \frac{h_C}{r_C}\right)(1 - a_0)k_{CT}. \quad (7)$$

This relationship shows that high efficacy of CAR-T therapy (large r_C , small h_C and moderate $a_0 < 1$) leads to a negative $\lambda_4(0)$, thereby ensuring stability of the tumour-free state and disappearance of the tumour cells.

Figure 2 shows the region in the parameter plane (a_0, k_{CT}) in which the tumour-free equilibrium is linearly stable. The stability region is bounded by the curve obtained from condition (7) and demonstrates that a high rate of tumour-cell killing k_{CT} can compensate even for substantial values of the initial degree of antigen escape a_0 .

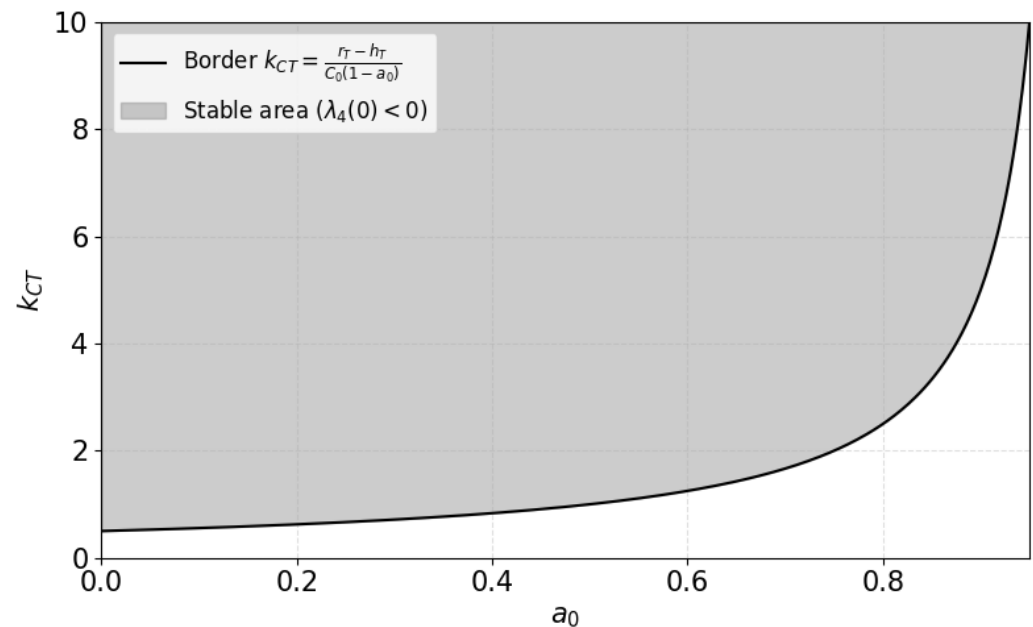


Figure 2. Region of linear stability of the tumour-free equilibrium in the (a_0, k_{CT}) plane for fixed model parameters.

2.4. Numerical Method for Solving the System of Differential Equations

To obtain a numerical solution of the system of differential Equation (1), we used the finite-difference method on a regular rectangular grid. The main idea of this method is to partition the domain into a uniform grid and replace derivatives by finite-difference approximations.

We represent the spatial domain in the form of a rectangular uniform grid. The spatial variables x and y are replaced by discrete points with steps dx and dy , respectively:

$$x_i = i dx, \quad i = 0, 1, \dots, N_x - 1; \quad (8)$$

$$y_j = j dy, \quad j = 0, 1, \dots, N_y - 1. \quad (9)$$

The grid steps are calculated as

$$dx = \frac{L_x}{N_x - 1}, \quad dy = \frac{L_y}{N_y - 1}, \quad (10)$$

where L_x and L_y are the domain sizes, and N_x and N_y are the numbers of nodes.

For each interior point (i, j) , the second derivatives were approximated by second-order central differences:

$$\left. \frac{\partial^2 C}{\partial x^2} \right|_{i,j} \approx \frac{C_{i+1,j} - 2C_{i,j} + C_{i-1,j}}{dx^2}, \quad (11)$$

$$\left. \frac{\partial^2 C}{\partial y^2} \right|_{i,j} \approx \frac{C_{i,j+1} - 2C_{i,j} + C_{i,j-1}}{dy^2}. \quad (12)$$

Then the two-dimensional Laplacian is approximated by

$$\nabla^2 C_{i,j} \approx \frac{C_{i+1,j} - 2C_{i,j} + C_{i-1,j}}{dx^2} + \frac{C_{i,j+1} - 2C_{i,j} + C_{i,j-1}}{dy^2}. \quad (13)$$

Equation (13) is the classical five-point Laplace stencil on a rectangular grid and has second-order accuracy.

Neumann boundary conditions (second-type boundary conditions) are imposed on the boundaries:

$$\left. \frac{\partial C}{\partial n} \right|_{\partial\Omega} = 0, \quad (14)$$

where $\frac{\partial C}{\partial n}$ is the normal derivative and $\partial\Omega$ is the boundary of the domain.

This means that the flux across the boundary is zero, i.e., there is no exchange of material across the domain boundary.

For the time derivative, an explicit Euler scheme was used:

$$\frac{\partial C}{\partial t} \approx \frac{C^{n+1} - C^n}{dt}, \quad (15)$$

where C^n is the value of the variable C at the n -th time step, C^{n+1} is its value at the next step, and dt is the time step.

For the explicit Euler scheme, the time step dt must satisfy a stability constraint. This condition is given by the Courant–Friedrichs–Lewy criterion:

$$\Delta t \leq \frac{dx^2}{4D_{\max}}, \quad (16)$$

where $D_{\max} = \max(D_c, D_t)$.

This condition guarantees that the model remains stable at each time step.

Analogous numerical schemes were applied to the variable T .

To control for any dependence of the results on discretisation and to confirm the numerical stability of the explicit finite-difference scheme, computations for the key scenarios were repeated on several spatial grids and with a reduced time step. In particular, simulations were performed on the baseline grid and on a refined grid, with the time step chosen to satisfy constraint (16) and additionally reduced to test temporal stability. The main model outputs were compared: the time evolution of the integral tumour burden and the total number of CAR-T cells, the qualitative solution regime, the characteristic time to relapse, and the spatial profiles. When moving to a finer grid and a smaller time step, the qualitative regimes and the above metrics changed only marginally, and the solution exhibited neither unstable oscillations nor non-physical values, confirming that the computational conclusions are not artefacts of the particular choice of grid or time step.

2.5. Software for Numerical Simulations

Figure 3 presents a block diagram of the code implementing the numerical algorithms described above to solve system (1).

The programme starts by specifying the model parameters from Table 1, the geometric parameters of the domain, the grid size, the number of time steps and the discretisation intervals. The stability of the explicit Euler scheme is then checked using Formula (16); if the condition is violated, a warning is issued. After that, vectors are created for the model

variables, initial conditions are specified, the initial distribution of tumour cells is formed, and CAR-T cells are introduced into the central cell.

The core of the programme is a time-stepping loop that updates the system state at each time step. At each step, the algorithm sweeps over all grid nodes, identifies neighbouring indices subject to reflecting (Neumann) boundary conditions (14), computes Laplacians using central differences (13), and advances the solution using the explicit Euler scheme (15). Subsequently, physically realistic constraints are applied, the variable arrays are updated for the next step, and at prescribed intervals the results are saved to CSV files. The loop continues until the final simulation time is reached, after which the programme terminates.

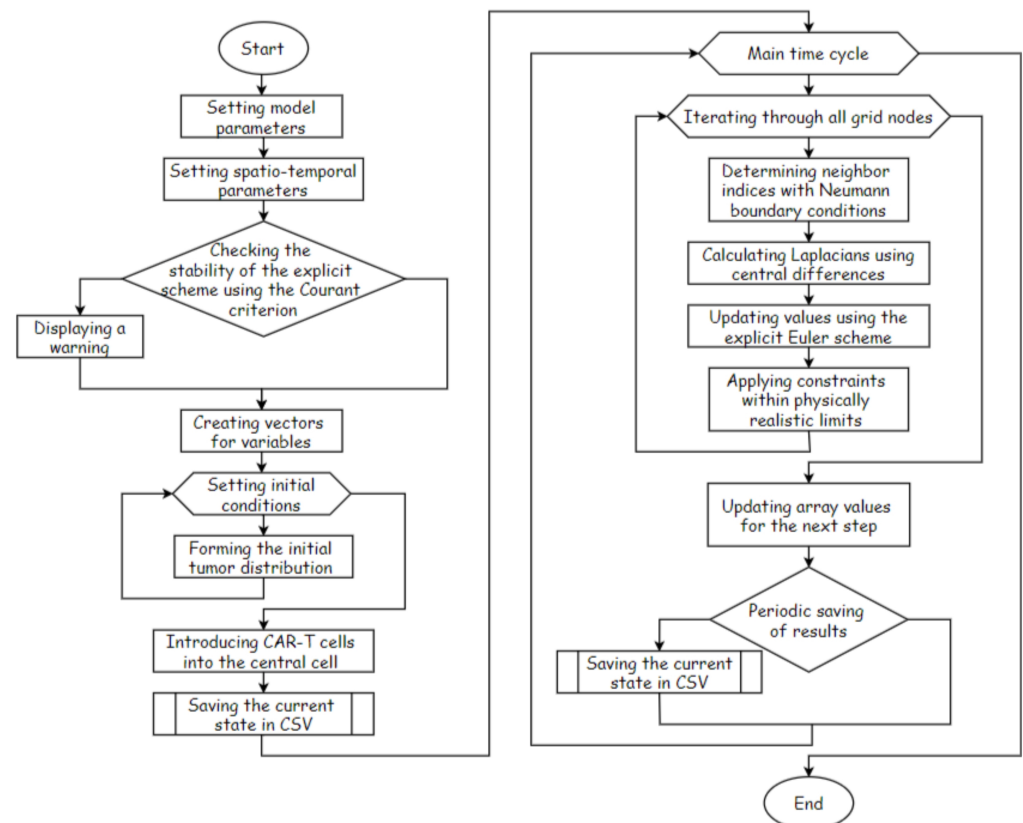


Figure 3. Block diagram of the programme algorithm for numerical simulation of tumour dynamics under CAR-T cell therapy.

The code was implemented in C++. To ensure reproducibility of the results, the full source code of the numerical solver has been made available in an open repository GitHub: <https://github.com/Elena-0v0/CAR-T-model> (accessed on 23 December 2025).

3. Results

3.1. Overall Behaviour of the System: Spatial Distribution of Cell Populations and Biochemical Factors in a Solid Tumour

To analyse the spatial heterogeneity of the tumour microenvironment and the distribution of cell populations, numerical simulations of the spatio-temporal dynamics of the reaction–diffusion system were performed. We considered a domain corresponding to a cross-section of a solid tumour, within which the densities of tumour cells $T(x, t)$ and CAR-T cells $C(x, t)$, the concentration of immune inhibitors $I(x, t)$ and the degree of antigen escape $a_T(x, t)$ evolve.

Figure 4 shows one-dimensional profiles along a representative cross-section of the tumour at several characteristic time points. For each time point, we plot the spatial distributions of tumour-cell density, CAR T-cell density, immune-inhibitor concentration, and antigen-expression level. Initially, the tumour-cell density is relatively uniform in the central region of the domain, antigen expression is high, and immune inhibitors are present at negligible levels. Following CAR T-cell administration, a pronounced spatial gradient in CAR T-cell density develops, with peak values near the tumour nodule, consistent with substantial infiltration into the tumour matrix.

As CAR T cells interact with tumour cells, tumour-cell density decreases in the tumour centre, and a region of partial regression emerges, while higher tumour-cell densities persist in the periphery. In parallel, tumour-derived immune inhibitors accumulate, peaking in the central region where tumour-cell density was initially highest. This results in the formation of an immunosuppressive core that effectively limits CAR T-cell activity. Antigen escape, quantified by a_T , also increases in the tumour centre, reducing the efficiency of tumour recognition by CAR T cells and shifting the region of effective cytotoxicity towards the periphery. Accordingly, even in one-dimensional profiles the domain separates into a central resistant zone with elevated a_T and immune inhibitors, and a peripheral ring in which the antitumour effect of CAR T cells is more pronounced.

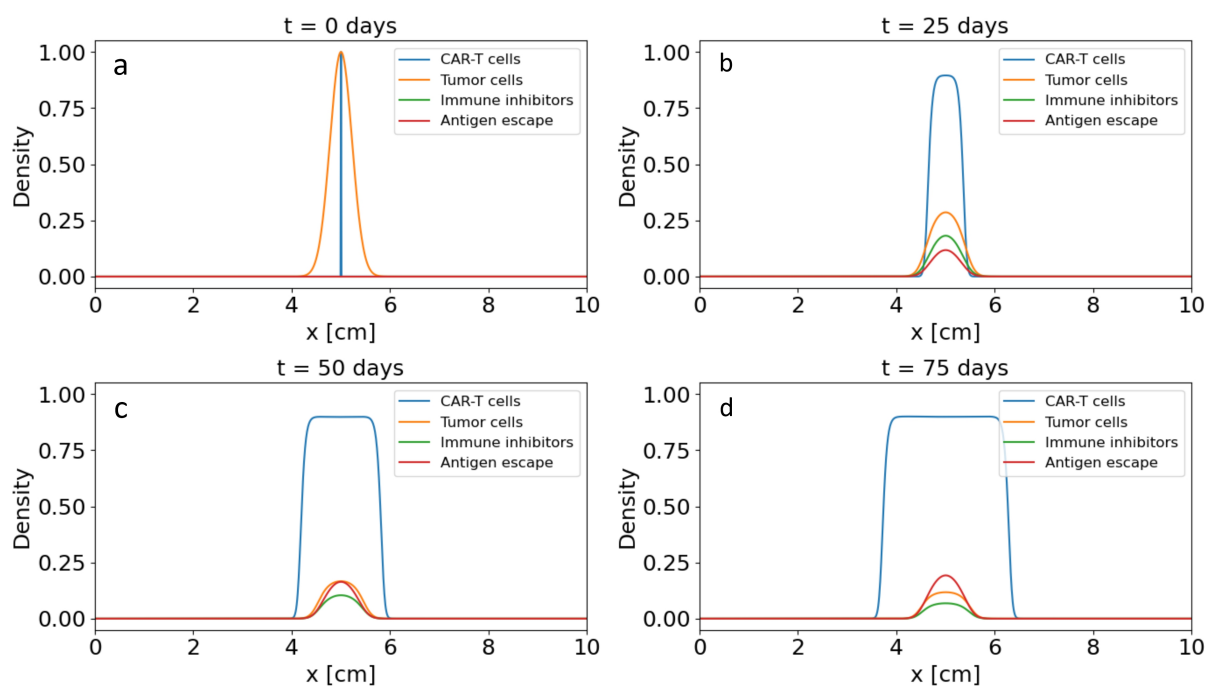


Figure 4. Spatial distribution of the density of CAR-T cells, tumour cells, immune inhibitors and the level of antigen expression along a cross-section of a solid tumour at different time points: (a) $t = 0$ days; (b) $t = 25$ days; (c) $t = 50$ days; (d) $t = 75$ days.

Figure 5 illustrates the two-dimensional dynamics of the tumour–CAR T-cell interaction, showing spatial distributions of tumour and CAR T-cell densities at selected time points. Early on, the tumour nodule is compact and CAR T cells remain localised near the injection site. Over subsequent days, as CAR T cells proliferate and diffuse through the domain, an intense tumour–CAR T cell contact interface develops, with concomitant reductions in tumour-cell density and partial regression in the central region. This process gives rise to a clear ring-like pattern in the maps: a suppressed central tumour core surrounded by a peripheral ring of elevated tumour-cell density.

However, further development of antigen escape and accumulation of immune inhibitors lead to a gradual decline in the efficiency of the cytotoxic action of CAR-T cells. At late times in the simulation (of the order of hundreds of days), a region of resistant cells with a high degree of antigen escape is formed in the central part of the tumour, where the density of CAR-T cells is low, whereas the tumour population recovers and begins to dominate. In the two-dimensional distributions, this manifests itself as renewed growth of the tumour nodule and disappearance of the previously observed zone of effective CAR-T cell infiltration. Thus, the model predicts a typical scenario of transient partial regression followed by tumour relapse as a result of the combined effects of immunosuppression and antigen escape.

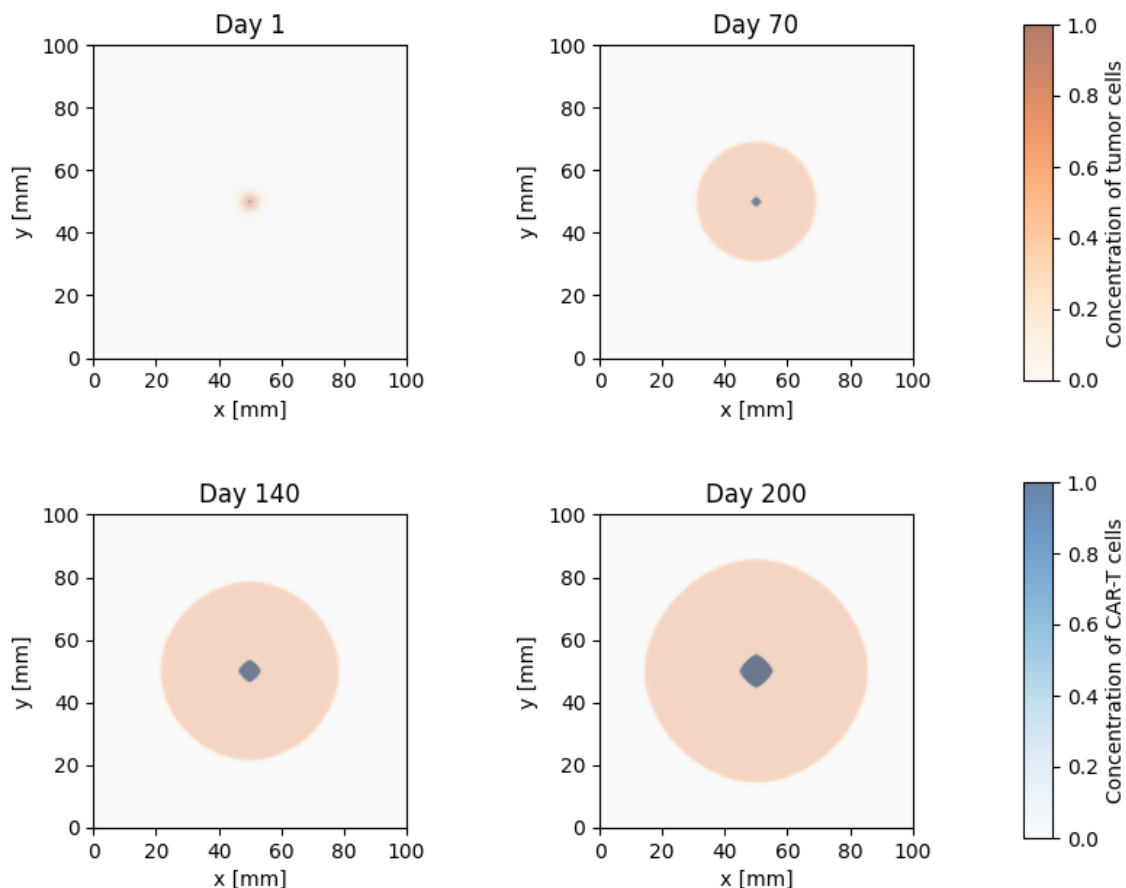


Figure 5. Spatial distribution of the concentrations of tumour cells and CAR-T cells at different time points.

A comparison of the one-dimensional and two-dimensional distributions shows that even with sufficiently high initial concentrations of CAR-T cells and pronounced initial antitumour activity, the tumour is able to form spatially localised resistant clones. This result is consistent with the conclusions of the analytical study of the stability of the tumour-free state and emphasises that violation of the stability conditions already under moderate growth of the degree of antigen escape leads to restoration of the tumour population. Overall, the numerical solutions obtained demonstrate the nonlinear nature of competition between tumour-cell proliferation, CAR-T cell cytotoxic activity and the immunosuppressive influence of the microenvironment, and highlight the critical role of spatial effects in predicting the outcome of CAR-T cell therapy for solid tumours.

To quantify the spatio-temporal dynamics of resistant-region formation, in addition to the qualitative profiles we computed two metrics: the effective radius of the resistant core, defined as the distance from the tumour centre to the point at which the degree of antigen

escape $a_T(x, t)$ exceeds the threshold $a_T^* = 0.7$, and the spatial variance of the tumour cell density

$$\sigma_T^2(t) = \frac{1}{|\Omega|} \int_{\Omega} (T(x, t) - \bar{T}(t))^2 dx,$$

where $\bar{T}(t)$ is the domain-averaged density. The analysis showed that the resistant-core radius increases monotonically from ~ 5 mm on day 20 to ~ 15 mm by day 100 for $\gamma = 0.05$, reflecting the gradual expansion of the antigen-loss region. The spatial variance $\sigma_T^2(t)$ reaches its maximum during the phase of partial regression (around days 30–40), corresponding to the formation of a pronounced ring-like structure, and then decreases as the tumour mass regains homogeneity at later stages of relapse. These metrics enable quantitative tracking of the transition from controlled regression to the dominance of the resistant clone and provide a more detailed validation of the model's spatial predictions.

To quantify the relationship between inhibitor accumulation and the spatial exclusion of CAR-T cells, we performed a correlation analysis. At each time step, the spatial correlation coefficient between the inhibitor concentration field $I(x, t)$ and the CAR-T cell density field $C(x, t)$ was computed. In the early phase of therapy, the correlation was weakly negative ($r \approx -0.2$), consistent with CAR-T infiltration into regions with moderate inhibitor levels. By the middle and towards the end of the simulation, the correlation became strongly negative ($r \approx -0.6 \dots -0.8$), confirming that regions with high inhibitor concentrations are persistently associated with low CAR-T cell densities. In addition, we examined the dependence of the mean CAR-T cell density on the inhibitor level: when $I > 0.4$, the CAR-T cell density dropped to below 10 percent of its maximum value, quantitatively demonstrating spatial exclusion driven by an immunosuppressive microenvironment.

To assess the sensitivity of the resulting spatial structures to the choice of grid spacing, simulations were carried out at two levels of spatial resolution, with the model parameters fixed and identical initial conditions. The first case used a grid of ($N_x \times N_y = 51 \times 51$), while the second employed a refined grid of ($N_x \times N_y = 201 \times 201$). The time step was chosen in accordance with the stability condition for the explicit finite-difference scheme applied to the diffusion terms, ensuring that the results were comparable for different dx and dy . Figure 6 shows the spatial distributions of the tumour cell density $T(x, y, t)$ obtained at the same characteristic time point corresponding to the formation of a stable heterogeneous structure.

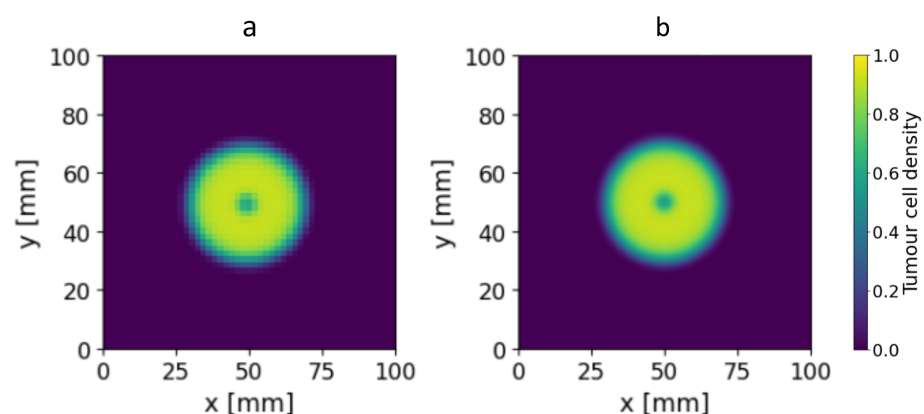


Figure 6. Spatial distributions of the tumour cell density $T(x, y, t)$ at different spatial resolutions: (a) simulation on a 51×51 grid; (b) simulation on a 201×201 grid.

When moving from the 51×51 grid to the 201×201 grid, the qualitative organisation of the solution is preserved. A spatially localised structure is observed. On the finer grid, the boundaries and gradients of the field T are reproduced more smoothly; however,

the topology and localisation of the region of elevated values remain unchanged. Thus, the identified spatial patterns prove to be robust to grid refinement over the range of resolutions considered.

3.2. Validation of the Mathematical Model of Tumour Growth Based on Clinical Data

To validate the proposed reaction–diffusion model of solid tumour growth, we used published clinical data on the temporal evolution of tumour volume [42]. Specifically, six independent time series ($n = 6$) correspond to tumour-volume measurements in a 4T1 breast-cancer model in BALB/c mice. In the original study, tumour volume was measured serially *in vivo* by caliper assessment of the tumour nodule size at fixed time intervals; the reported values are given in mm^3 . Thus, the employed data reflect the dynamics of tumour burden in a preclinical setting, which allows us to verify the adequacy of the basic tumour-growth description in system (1) without therapy. Validation was performed for the natural tumour-growth phase, without CAR T-cell therapy; accordingly, the CAR T-cell module was omitted from the computational experiment. In system (1), we set $C(x, t) \equiv 0$, $I(x, t) \equiv 0$ and $a_T(x, t) \equiv 0$, while the tumour population $T(x, t)$ was modelled using the baseline parameter set given in Table 1.

For a given set of experimental points $\{t_k, V_{\text{exp}}(t_k)\}$, the tumour volume in the model was computed as the integral over the computational domain

$$V_{\text{mod}}(t_k) = \int_{\Omega} T(x, t_k) dx, \quad (17)$$

after which it was rescaled so that the initial value $V_{\text{mod}}(t_1)$ coincided with the measured volume $V_{\text{exp}}(t_1)$. Interindividual variability among the observed curves was accounted for by fitting the tumour-cell proliferation coefficient, r_T , within the admissible range specified in Table 1, while keeping the remaining parameters fixed.

The R^2 values were calculated separately for each data set:

$$R^2 = 1 - \frac{\sum_k (V_{\text{mod}}(t_k) - V_{\text{exp}}(t_k))^2}{\sum_k (V_{\text{exp}}(t_k) - \bar{V}_{\text{exp}})^2}, \quad (18)$$

where $\bar{V}_{\text{exp}}$ is the mean of the experimental measurements.

Figure 7 compares the model-predicted tumour-volume trajectories with clinical data from six independent solid-tumour growth cohorts. The blue solid lines correspond to the simulation results, and the red markers denote the measured tumour volumes $V_{\text{exp}}(t)$. The value of the coefficient of determination R^2 between the model and the data is reported in each panel.

As shown in Figure 7, in each series the model curve smoothly interpolates the experimental data points. It accurately captures the initial, near-exponential growth phase and the subsequent moderate deceleration as tumour volume increases. The values of the coefficient of determination lie in the narrow interval $R^2 \approx 0.94\text{--}0.98$, with a mean value of $R^2 \approx 0.95$, indicating a high degree of agreement between the model and the data. The most noticeable discrepancies are observed at late observation times for some cases, where the model slightly overestimates or underestimates the final tumour volume; the magnitude of these deviations remains moderate and does not affect the overall shape of the growth curve.

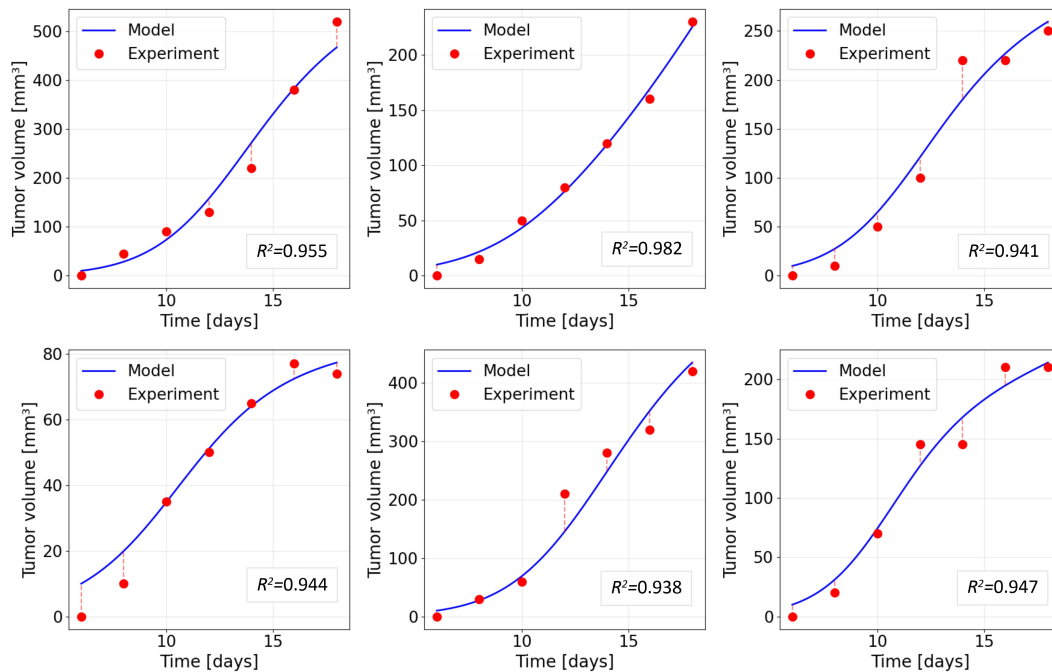


Figure 7. Comparison of the temporal dynamics of tumour volume predicted by the reaction–diffusion model (solid lines) with clinical data (points) for six independent solid-tumour growth cases without therapy.

These results indicate that the basic block describing tumour-cell proliferation and spatial spread in system (1) adequately captures the characteristic time scales and growth rates of solid tumours in the absence of therapy. This makes it possible to use the identified values of the parameter r_T and the associated range of tumour-growth rates as an initial calibration in subsequent numerical investigations of the influence of CAR-T cells, immunosuppressive factors and the mechanism of antigen escape, which are considered in the following subsections.

3.3. Impact of Antigen Escape on Therapeutic Efficacy

The aim of this numerical experiment is to investigate the impact of the rate of tumour-cell antigen escape on the efficacy of CAR-T cell therapy. Within the model, we varied the parameter γ , which describes the rate of increase of the escape degree a_T as the tumour-cell density $T(x, t)$ increases in the corresponding equation for $a_T(x, t)$. The following values were considered: $\gamma = 0.001, 0.01, 0.05, 0.1$, while the other model parameters were fixed at their baseline values corresponding to the scenario from the previous section.

Figure 8 shows the spatial distribution of tumour-cell concentration along a cross-section of the tumour at the final simulation time ($t = 100$ days). Each curve corresponds to a separate numerical experiment with a different rate of antigen escape determined by the parameter γ . At the minimal value, $\gamma = 0.001$, suppression of the tumour population is observed. The peak tumour-cell density is reduced relative to the initial value, and the profile becomes more flattened, which corresponds to partial tumour regression across the entire cross-section. As γ increases, the curves are successively shifted upwards, reflecting an increase in the local tumour-cell density in the central region and an expansion of the area with elevated cell density. For the largest value, $\gamma = 0.1$, the tumour profile at the end of the simulation is maximally elevated, corresponding to the largest residual tumour mass.

Thus, Figure 8 shows that increasing γ leads to higher peak tumour-cell concentrations and poorer local control of the tumour. The smallest final tumour concentration corresponds to the lowest escape rate considered ($\gamma = 0.001$), whereas the highest concentration is

attained at $\gamma = 0.1$. This clearly demonstrates that antigen escape directly reduces the efficacy of CAR-T cell therapy, allowing the tumour population to reach a higher density despite the presence of CAR-T cells.

The integral response of the system to changes in the antigen-escape rate is shown in Figure 9, which presents the dependence of the final tumour volume $V_T(100)$ on the parameter γ . The horizontal axis is plotted on a logarithmic scale to clearly demonstrate the behaviour over a wide range of γ values from 10^{-3} to 10^{-1} . The graph exhibits a monotonically increasing dependence: as the antigen-escape rate increases, the final tumour volume steadily grows. No saturation of the effect is observed in the parameter range considered. The transition from low values of γ to higher ones is accompanied by a substantial increase in the residual tumour mass, and even a one-order-of-magnitude increase in γ leads to a noticeable deterioration in the therapeutic outcome.

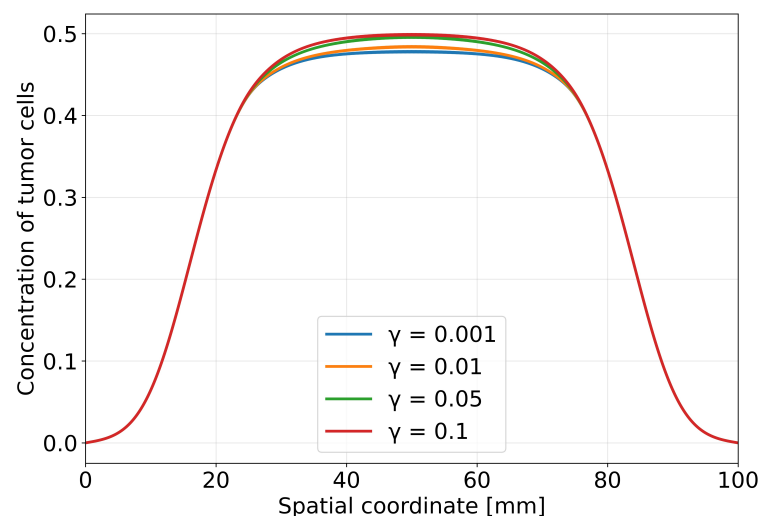


Figure 8. Spatial distribution of tumour-cell concentration along a cross-section of a solid tumour for different values of the antigen-escape rate γ at time $t = 100$ days.

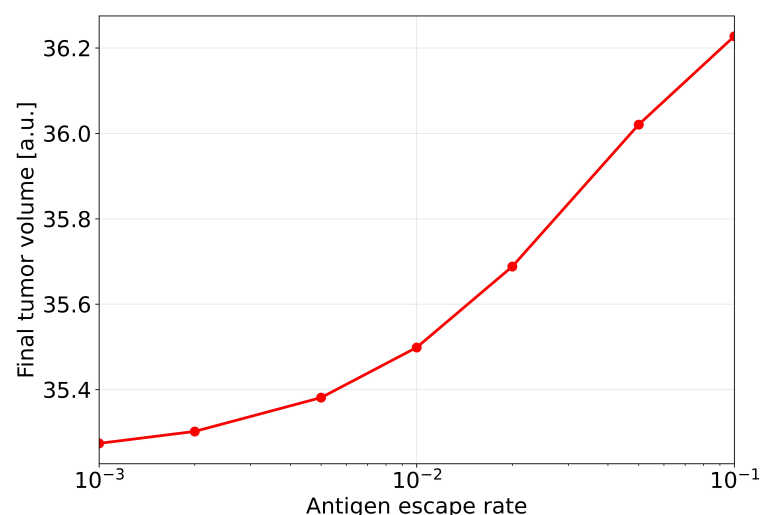


Figure 9. Dependence of tumour volume V_T at time $t = 100$ days on the antigen-escape rate γ (horizontal axis in logarithmic scale).

From a biological standpoint, the dependencies obtained reflect the competition between two time scales: the rate of tumour-cell elimination by CAR-T cells and the rate of formation of a resistant tumour-cell clone. At low γ , CAR-T cells have time to substantially reduce the tumour mass before the escape mechanism becomes dominant, leading to partial

or almost complete tumour regression. As γ increases, the escape process accelerates, and already at intermediate times in the simulation a substantial fraction of tumour cells that are poorly recognised by CAR-T cells is formed, enabling recovery and subsequent dominance of the tumour population.

To provide a quantitative boundary beyond which durable tumour control becomes infeasible, we introduced the durable control criterion, defined as achieving a residual normalised tumour volume $V_{\text{norm}}(t_{\text{end}}) < 0.1$ with no subsequent tumour regrowth throughout the simulation period. Parameter analysis under baseline conditions (fixed parameters from Table 1) revealed that the threshold value of the antigen-escape rate γ_c lies between 0.01 and 0.05. Specifically, for $\gamma \lesssim 0.01$ nearly complete tumour regression is attainable even with moderate CAR-T cell cytotoxicity ($k_{CT} \approx 1 \text{ day}^{-1}$), whereas for $\gamma \gtrsim 0.05$ comparable control requires substantially higher cytotoxicity ($k_{CT} > 2.5 \text{ day}^{-1}$). Hence, under the baseline parametrisation of the model, durable tumour control becomes mathematically impossible for γ values exceeding approximately 0.05.

Taken together, the results in Figures 8 and 9 provide quantitative confirmation of the key role of antigen escape as a mechanism for the development of resistance of solid tumours to CAR-T cell therapy. High values of the parameter γ lead to a shift of the treatment outcome towards relapse even when the initial concentrations and functional activity of CAR-T cells remain unchanged. This points to the need either to slow down antigen escape or to broaden the targeting spectrum of CAR-T cells, which can effectively reduce the effective value of γ and thereby increase the likelihood of durable control of a solid tumour.

3.4. Interaction of Model Parameters and Identification of Conditions for Successful Therapy

To identify parameter combinations that ensure effective tumour eradication, we performed a parametric analysis of system (1). The analysis focused on the combined influence of the antigen-escape rate, the tumour-cell killing rate of CAR-T cells, the level of hypoxia, and the proliferation rate of CAR-T cells. For each parameter set, we computed the normalised final volume of the tumour cell population after 100 days of simulation.

To quantify the therapeutic outcome, we used the residual tumour volume, which characterises the fraction of tumour cells remaining at the end of the simulation. It is defined as the ratio of the integral tumour-cell volume at time t_{end} to the initial tumour volume at time $t = 0$:

$$V_{\text{norm}}(t_{\text{end}}) = \frac{\int_{\Omega} T(x, t_{\text{end}}) dx}{\int_{\Omega} T(x, 0) dx}, \quad (19)$$

where $T(x, t)$ denotes the local tumour-cell density and Ω is the spatial domain of the simulation. Values $V_{\text{norm}} \approx 0$ correspond to complete tumour eradication and high therapeutic efficacy, whereas $V_{\text{norm}} \geq 1$ correspond to preservation of the initial volume or disease progression.

Figure 10 shows a map of the normalised residual tumour volume $V_{\text{norm}}(t_{\text{end}})$ as a function of the antigen-escape rate γ and the coefficient of tumour-cell killing by CAR-T cells k_{CT} . The results demonstrate a pronounced dependence of therapeutic efficacy on the interplay between γ and k_{CT} . Minimal values of V_{norm} are observed at low antigen-escape rates and sufficiently high CAR-T cell cytotoxicity. Under these conditions, the model predicts complete or almost complete elimination of tumour cells by the end of the simulation. As γ increases, the boundary between successful and unsuccessful therapy systematically shifts towards larger k_{CT} , indicating the need for higher cytotoxic activity to compensate for the loss of efficacy associated with antigen escape. For example, at $\gamma \leq 0.01$ a therapeutic effect is achieved already at moderate k_{CT} values of order 1, whereas at

$\gamma \geq 0.05$ it is necessary to increase k_{CT} to values of 2–5 in order to attain a comparable level of tumour control. The dependence of V_{norm} on the parameters is nonlinear in character. An increase in k_{CT} initially causes a pronounced decrease in V_{norm} , but further growth of k_{CT} leads to saturation of the effect. The impact of antigen escape exhibits a similar but oppositely directed pattern: a small increase in γ at low values has a moderate effect on the outcome of therapy, whereas further growth of γ causes a sharp deterioration in the result and an increase in the residual tumour volume.

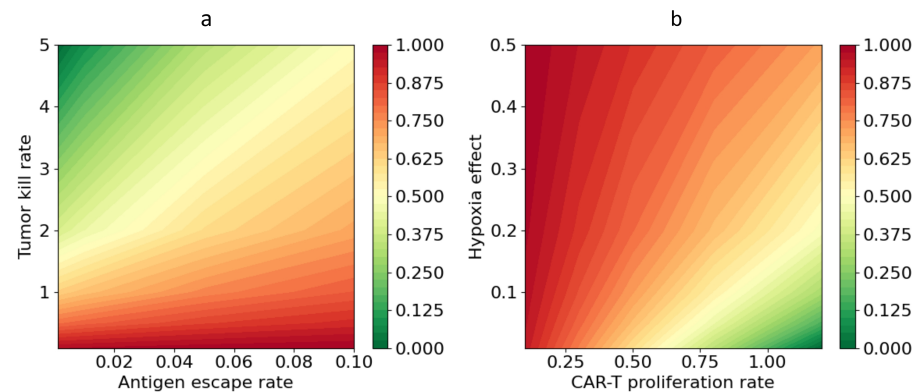


Figure 10. Interaction of model parameters: (a) dependence of CAR-T therapy efficacy on the antigen-escape rate γ and the tumour-cell killing rate k_{CT} ; (b) influence of the proliferation rate r_C and the degree of hypoxic suppression h_C on CAR-T cell activity.

The strongest effects on V_{norm} are exerted by the antigen-escape rate γ and the tumour-cell killing coefficient k_{CT} . The CAR-T proliferation parameter r_C and the hypoxia-induced suppression parameter h_C have a moderate influence, whereas the inhibitor production rate β makes the smallest contribution to the variability of the outcome.

3.5. Comparative Analysis of the Efficacy of Different CAR-T Cell Administration Strategies Under Antigen Escape

Despite progress in the development of CAR-T cells, their clinical efficacy against solid tumours depends to a large extent not only on the biological properties of the cells and the tumour, but also on the strategy of their delivery to the tumour site. Pathological vascularisation, a dense extracellular matrix and elevated interstitial pressure create substantial physical barriers that limit the uniform distribution and infiltration of effector lymphocytes. Existing mathematical models typically consider a simplified scenario of a single CAR-T cell injection, whereas in clinical practice a variety of approaches may be used, including multiple or fractionated infusions. Under conditions of antigenic heterogeneity and escape, the spatial pattern of the interaction between CAR-T cells and the tumour becomes critically important: the local concentration of effector cells forms gradients of selective pressure that determine the dynamics of the evolution of antigen-negative clones. Thus, the strategy of CAR-T cell administration can fundamentally influence the rate of resistance development and the long-term outcome of therapy.

To quantitatively assess the impact of the temporal administration scheme for CAR-T cells, we conducted a series of numerical experiments with fixed parameters for tumour growth, the immune microenvironment, and the antigen-escape rate γ . Four therapeutic strategies differing in the number of CAR-T cell infusions within the therapeutic observation window were considered: single, double, triple, and quadruple administration. For each strategy, the infusion times were chosen to reflect clinically realistic intervals between treatment courses. The choice of CAR-T cell administration times in the numerical experiments is not arbitrary, since time in the model is interpreted on a day scale and is aligned with typical clinical management logic. The time point $t = 0$ corresponds to the

infusion day after standard lymphodepletion and is denoted as protocol day 0. Subsequent administrations are scheduled at intervals of several weeks in order to fall within the real clinical horizon, during which early CAR-T expansion after infusion and the subsequent contraction of the effector population are observed, and an initial assessment of response and safety is typically performed by around week 4 [67]. Therefore, as a standardised baseline scenario for comparing the effect of dosing multiplicity, we used representative course-like regimens with intervals of approximately 3–4 weeks, including a repeat infusion on day 30 for the two-dose schedule, infusions on days 20 and 40 for the three-dose schedule, and a series at roughly 25-day intervals for the four-dose schedule. At the same time, these time points are not intended to reproduce any specific protocol for a given indication; rather, they serve as a unified temporal framework for comparing fractionation effects at a fixed cumulative exposure, and, where protocol-specific data are available, the administration time points can be replaced directly without changing the model structure. A schematic representation of the temporal schemes is shown in Figure 11. The vertical segments indicate the infusion time points and the horizontal axis represents the simulation time.

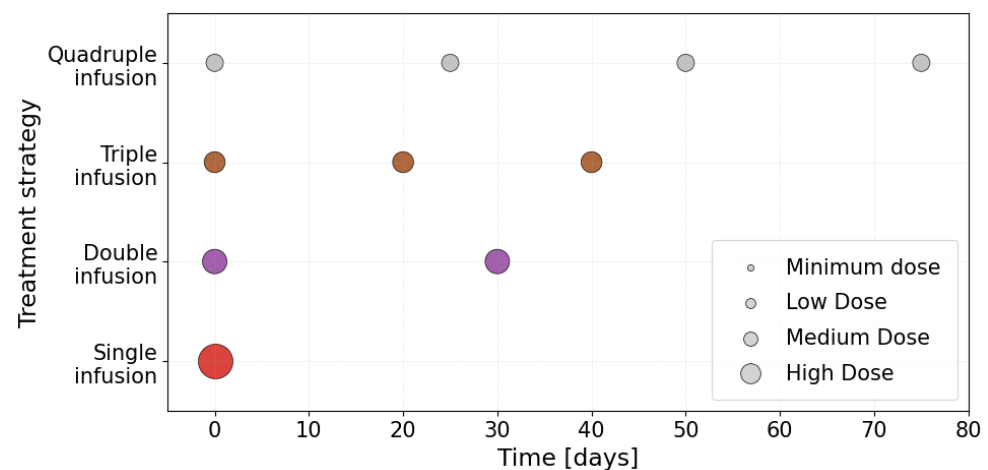


Figure 11. Schematic representation of temporal schemes of CAR-T cell administration for four therapeutic strategies: single, double, triple and quadruple administration.

Figure 12a shows the dynamics of the normalised tumour volume $V_{\text{norm}}(t)$ (defined by Equation (19)) for different CAR-T cell administration strategies. A single infusion leads to a typical scenario of transient regression. Initially, a rapid decline in the normalised tumour volume is observed owing to intense cytotoxic activity of CAR-T cells, but subsequently, as the effector population becomes exhausted and antigen-negative clones accumulate, the tumour mass recovers and $V_{\text{norm}}(t)$ grows again to values exceeding the baseline. As one moves to double and triple administration schemes, the curves $V_{\text{norm}}(t)$ exhibit intervals of sustained tumour-mass reduction corresponding to additional waves of CAR-T cell activation, which are accompanied by deeper and more prolonged suppression of tumour growth. The quadruple administration strategy does not yield a more pronounced and sustained suppression of tumour mass over the entire simulation period than triple administration.

An integral assessment of the therapeutic outcome for the different strategies is presented in Figure 12b, which shows the values of the residual normalised tumour volume $V_{\text{norm}}(t_{\text{end}})$ at $t_{\text{end}} = 100$ days. It can be seen that increasing the number of CAR-T cell infusions is accompanied by a monotonic decrease in the residual tumour volume. The transition from single to double administration yields the most substantial improvement, reflected in a sharp reduction in $V_{\text{norm}}(t_{\text{end}})$. As the number of infusions increases further to triple and quadruple regimens, the effect becomes less pronounced, indicating a substan-

tial but partially saturating benefit of therapy intensification. Each additional infusion still makes a clinically meaningful contribution, but the relative reduction in V_{norm} compared with the preceding strategy becomes less marked, and in the quadruple scheme the efficacy even decreases.

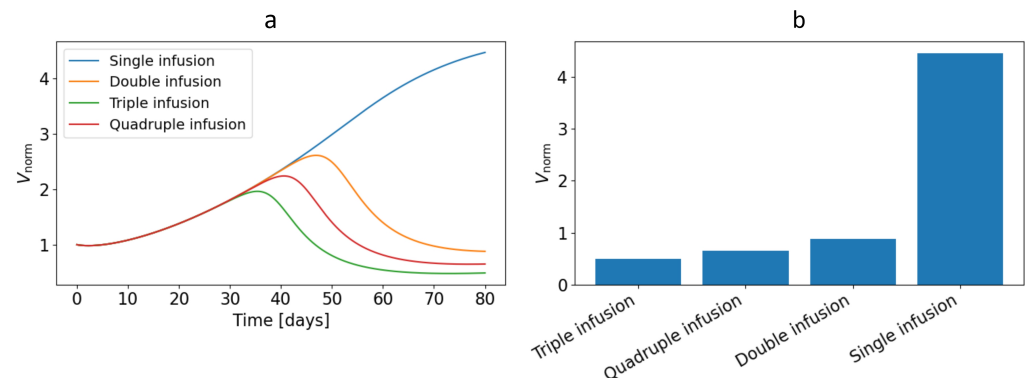


Figure 12. (a) Dynamics of the normalised tumour volume for different CAR-T cell administration strategies; (b) comparative assessment of the residual normalised tumour volume V_{norm} at $t_{\text{end}} = 100$ days for different temporal CAR-T cell administration strategies.

It should be emphasised that all numerical experiments were performed under conditions of antigen escape of tumour cells, leading to gradual accumulation of clones that are poorly recognised by CAR-T cells. In this situation, a single infusion is insufficient for long-term tumour control. Even with pronounced initial regression, a substantial residual population is formed that is capable of subsequent growth. Multiple infusions partially compensate for this effect by maintaining a high effector CAR-T cell to tumour-cell ratio over a longer period and repeatedly intercepting expanding resistant clones. Nevertheless, even the quadruple scheme under the chosen parameter values does not result in complete tumour eradication, which points to fundamental limitations of modifying only the temporal administration strategy when the antigen-escape rate is sufficiently high.

It should be noted that the administration regimens considered above are pre-specified schemes, whereas in clinical practice there is increasing discussion of adaptive protocols in which the timing and dose of subsequent infusions are adjusted on the basis of the current tumour response. Within the proposed model, such scenarios can be represented by introducing a controllable source term for the CAR-T cell population $C(x, t)$, depending on time and on integral indicators of the system state. Adaptive dosing and dose-escalation strategies may potentially maintain a high local balance over critical intervals and thereby reduce the likelihood of tumour regrowth after transient regression, as well as decrease the chance of consolidation of a resistant core. At the same time, intensifying and prolonging immune pressure may accelerate the selection of antigen-negative clones; therefore, the expected effect of adaptive schemes is non-linear and requires dedicated numerical analysis and protocol optimisation for different values of the antigen-escape rate γ .

Taken together, the results obtained demonstrate that the temporal structure of CAR-T cell administration is a critically important determinant of therapeutic efficacy under antigen escape. Multiple and fractionated administration schemes provide deeper and more durable suppression of tumour growth compared with a single infusion, but they do not completely overcome the adverse impact of rapidly progressing escape. This underscores the need for comprehensive protocol optimisation, incorporating both the choice of CAR-T cell administration strategy and reduction of the antigen-escape rate, in order to achieve durable control of a solid tumour.

4. Discussion

The results obtained within the framework of the model reveal the key mechanisms that limit the efficacy of CAR-T cell therapy for solid tumours and are consistent with known clinical observations. The model predicts a typical scenario: after an initial phase of intense CAR-T cell infiltration and partial tumour regression, a resistant clone of tumour cells is formed, leading to relapse. In particular, the numerical experiments demonstrate the emergence, in the central region of the tumour, of a resistant core with a high degree of antigen escape and a high concentration of immune inhibitors, surrounded by a peripheral layer of more susceptible tumour. This spatial pattern reflects the competition between the cytotoxic action of CAR-T cells and the adaptive response mechanisms of the tumour. Such behaviour is in line with clinical data indicating transient improvement followed by tumour progression under CAR-T cell treatment, driven by antigen heterogeneity and an immunosuppressive microenvironment [4,51]. Thus, the model provides a biologically grounded interpretation: selective pressure from CAR-T cells leads to the survival and domination of tumour variants that have lost the target antigen and display enhanced resistance to immune attack, which explains the insufficient duration of remissions observed in current clinical trials of CAR-T cell therapy for solid tumours [51,68].

We would like to emphasise which results of our study are novel compared with existing CAR-T therapy modelling research. In most published ordinary-differential-equation models, the spatial structure of the tumour and its microenvironment is not represented; therefore, persistence and relapse are treated as volume-averaged effects, and resistance is typically introduced via pre-defined subpopulations or a phenomenological loss of efficacy. In a number of spatial and multiscale formulations, spatial heterogeneities are likewise often imposed as fixed or prescribed, and thus do not provide a direct quantitative account of how a resistant region can spontaneously form within tissue. The novelty of our results lies in demonstrating that resistance can emerge dynamically and as a spatially localised regime driven by the combined action of antigen escape and tumour-induced immunosuppression. This allows not only a qualitative reproduction of relapse, but also a quantitative characterisation of its spatial signatures. In particular, we introduce and analyse metrics of spatial resistance and CAR-T exclusion, track over time the size and prominence of the resistant core, and construct maps of parameter regions in which durable control becomes unattainable under baseline conditions. A further novel finding is the quantitative link between the accumulation of inhibitory microenvironmental factors and the spatial exclusion of effector cells, which moves the discussion of immunosuppression from a set of general assumptions to a set of testable spatial predictions that can be compared with imaging data and spatial measurements.

The proposed model is not only a theoretical tool for investigating the spatio-temporal dynamics of CAR-T therapy, but also a potential basis for optimising clinical protocols. Validation of the model against published tumour-growth data (Section 3.2) confirms its adequacy in reproducing the key dynamic patterns. However, moving from qualitative analysis to individualised prediction of treatment outcomes requires calibrating the model to a specific patient using their biological parameters and medical imaging data. Such personalisation, combining mathematical modelling with clinical data, opens up prospects for developing adaptive therapy strategies that take into account the unique features of the tumour microenvironment and antigen profile in each patient. This direction is an important step towards precision cancer immunotherapy and will be actively pursued in our future research.

An important conclusion of our study is the quantitative confirmation of the critical role of the balance between the rate of tumour-cell elimination and the rate of resistance development. Analysis of the temporal profiles showed that, for relatively slow antigen

escape (small values of γ), CAR-T cells are able to substantially reduce the tumour burden, achieving almost complete tumour regression. In contrast, accelerated escape (higher γ) leads to rapid accumulation of poorly recognisable cells that survive the initial onslaught and initiate renewed tumour growth. Biologically, this points to a competition between time scales: the efficacy of therapy is determined by whether CAR-T cells can destroy the bulk of the tumour before a significant fraction of cells lose the target antigen. This observation is consistent with the findings of other models that emphasise the need to maximise the cytotoxic potential of CAR-T cells and minimise the rate of immune-mediated selection of resistant clones in order to achieve a durable effect [50]. Comparison of the simulation results with published data confirms the adequacy and novelty of the proposed model. First, tumour growth dynamics are reproduced in accordance with typical growth curves, as demonstrated on the basis of clinical data. Second, the temporal profiles obtained for single CAR-T cell administration are consistent with known therapeutic limitations: in the model experiments only transient remission is observed, followed by resumption of tumour growth to nearly the initial volume. Similar conclusions were reported in [49] using a kinetic model of glioblastoma: a single dose of CAR T-cell therapy, even in combination with chemotherapy, fails to prevent long-term relapse, whereas continuous exposure or repeated dosing can substantially improve outcomes. Our spatially distributed model builds on this idea, showing that multiple CAR T-cell infusions can suppress the renewed expansion of resistant clones and sustain antitumour pressure over extended periods. In our simulations, moving from one to several infusions markedly reduces the residual tumour burden and prolongs tumour-growth suppression. However, the benefit saturates: the incremental gain from each additional infusion diminishes over time. Moreover, even a four-infusion regimen at high antigen-escape rates does not achieve complete tumour eradication, consistent with [48] regarding the limitations of optimising the dosing schedule alone. Taken together, these studies are complementary: ODE-based optimisation models highlight the importance of selecting an appropriate treatment regimen [48,49], whereas our work underscores the critical role of spatial heterogeneity and suggests that, without targeted action against antigen-negative cells and the immunosuppressive microenvironment, even an optimised CAR T-cell schedule may be insufficient.

The assumptions and limitations of the proposed model should be critically assessed. First, the immune response is described in a simplified manner. We account only for the population of exogenous CAR-T lymphocytes, whereas in a real tumour a wide spectrum of immune effector cells is involved. The absence from the model of endogenous cytotoxic T lymphocytes, natural killer cells, macrophages and other cell types means that phenomena such as immune memory are represented only indirectly through parameters rather than being reproduced explicitly. Second, the antigen escape mechanism is implemented as a homogeneous decrease in the expression of a single target antigen (via the parameter a_T), which does not capture the potentially multicomponent nature of tumour heterogeneity. In the clinical setting, a tumour may simultaneously express several distinct antigens, and a subset of cells can switch to alternative escape pathways; in the model, however, the focus is on a single dominant antigen. Further increasing the model complexity by explicitly incorporating endogenous effector cells may lead to a more pronounced and sustained suppression of the tumour population, owing to additional cytotoxic pathways and the formation of immune memory, and may also enhance the indirect elimination of antigen-negative cells. In this case, a shift in the parametric boundaries between different regimes is to be expected, together with a reduced likelihood of forming a spatially stable resistant core under comparable CAR-T dosing regimens. Similarly, moving to multi-antigen strategies in the model can be represented by a multi-component tumour antigen profile and several effector-cell populations, which reduces the selective advantage of clones that have lost a

single target and, consequently, may slow the development of antigen escape and delay relapse. At the same time, increased immune pressure under multi-targeting may redistribute the contribution of alternative escape routes, underscoring the need for a dedicated analysis of the extended model. A third simplification is the aggregated representation of immunosuppression: the scalar inhibitor $I(x, t)$ represents the cumulative impact of many factors. In addition, potential adverse effects and extra-tumour dynamics are not considered in the model. Finally, model parametrisation is based on a limited set of data and assumptions. Validation against a small number of experimental growth curves supports the realism of the basic dynamics, but comprehensive validation would require comparison with a wide range of preclinical and clinical data to calibrate parameters under different conditions. The lack of such data at present limits the assessment of the predictive power of the model. Nevertheless, despite these limitations, the model serves as a useful tool for generating hypotheses about system behaviour and identifying the most sensitive parameters that influence therapeutic outcome. Moreover, using a scalar variable for immunosuppression and a homogeneous parameter for antigen escape is, of course, an abstraction from the heterogeneity observed clinically. In reality, the inhibitory microenvironment is shaped by multiple factors, which may exhibit distinct spatio-temporal dynamics. Similarly, escape from the immune response is often not merely a reduction in the expression of a single antigen, but a complex process that may involve switching to alternative antigenic targets or complete loss of antigen presentation. These factors can qualitatively affect the dynamics of resistant-clone emergence and the rate of relapse. In particular, incorporating multiple immune subpopulations and a multi-component description of the antigenic landscape into the model could shift the parameter thresholds required for successful tumour eradication. Thus, interpretation of the quantitative results of the present work should take into account its aggregated nature, and further development of the model towards capturing this multi-component structure and spatial heterogeneity appears to be an important direction for enhancing its clinical relevance.

A promising direction for further development of the model is its quantitative validation using clinical medical imaging data and longitudinal observations. On the one hand, serial MRI/PET studies make it possible to obtain time series of tumour morphometric characteristics, as well as imaging biomarkers that indirectly reflect the spatial organisation of tumour tissue and its microenvironment. On the other hand, longitudinal clinical cohorts with repeated measurements before and after therapy provide a basis for calibrating the model parameters and testing its prognostic performance at the level of individual trajectories. Within the proposed framework, comparing the computed spatial distributions of cellular populations and microenvironmental factors with MRI/PET maps could be the next step in refining the model, and in moving from a qualitative description of patterns to a quantitative assessment of time to relapse and of the efficacy of different therapy protocols.

The results of this work suggest several promising avenues for future research. One such avenue is to incorporate a more complex spatial organisation of the tumour and its microenvironment into the model. In real solid neoplasms there may be regions of necrosis and hypoxia and heterogeneous vascularisation, which lead to nutrient gradients and, consequently, to local variations in the sensitivity of both tumour and immune cells. Within our reaction–diffusion framework, such heterogeneous effects can be incorporated by introducing spatially heterogeneous coefficients or additional equations, for example, for oxygen and metabolites. Extending the model in this way will enable investigation of how microenvironmental heterogeneity influences CAR-T cell infiltration and the formation of resistant niches. Another direction is the transition to multiscale and hybrid modelling approaches. Such hybrid models can more accurately describe processes in which fluctuations in small cell numbers or subtle spatial effects are important, going

beyond the scope of a purely deterministic approach. Yet another way to improve the model is to employ fractional-calculus techniques. Fractional differential equations enable the incorporation of memory effects and long-term correlations in system dynamics. In the context of immunotherapy, this may be useful for describing phenomena such as long-lived cellular subpopulations or slowed diffusion of CAR-T cells within the complex tumour structure. Recent studies have demonstrated that fractional models can successfully capture the kinetics of tumour-immune interactions and the robustness of these systems to external perturbations [20,21]. Finally, the integration of artificial-intelligence methods for model calibration and personalisation of predictions appears extremely promising. In particular, modern machine-learning and big-data-analysis approaches can be used to determine optimal model-parameter values from patient-specific data. Such algorithms can automatically tune the model to the individual characteristics of a tumour, enabling prediction of the effects of different treatment strategies in a given patient. The integration of mechanistic models with AI modules is already being used for personalised tumour-growth modelling and treatment assessment [24]. Such hybrid platforms may, in future, substantially accelerate the development of new therapeutic protocols.

5. Conclusions

In this work, we have developed and studied a reaction–diffusion mathematical model of the spatio-temporal dynamics of the interaction between CAR-T cells and a solid tumour, incorporating key resistance mechanisms, including antigen escape and an immunosuppressive microenvironment. The mathematical model, formulated as a system of partial differential equations, makes it possible to adequately describe the nonlinear processes of infiltration, proliferation and cytotoxic response under conditions of spatial heterogeneity. The analysis of the stability of the tumour-free state revealed critical parameter relationships necessary for successful tumour eradication. Numerical simulations based on a finite-difference approximation of the system demonstrated the formation of resistant regions within the tumour and a relapse time course consistent with clinical observations. The results of the parametric analysis highlight that therapeutic efficacy strongly depends on the balance between the rate of tumour-cell killing and the rate of antigen escape. A comparative study of CAR-T cell administration strategies showed that multiple infusions provide deeper and more durable suppression of tumour growth than a single administration.

To clarify the scope of our conclusions, we explicitly distinguish between what is demonstrated in the present work and what remains, at this stage, a hypothesis. The following is shown directly. At the level of mathematical analysis, we establish conditions under which the tumour-free state can be stable, and identify parameter relationships that critically affect the outcome. At the level of numerical experiments, we demonstrate dynamical regimes under spatial heterogeneity, tumour-induced immunosuppression, and antigen escape, including the formation of resistant regions, and show how the balance between cytotoxic activity and the escape rate determines either control or relapse, as well as how efficacy depends on the dosing schedule and on the difference between single and repeated administration. At the same time, any direct therapeutic recommendations, interpretation of the derived thresholds as clinical boundaries, and claims regarding an optimal treatment regimen should be regarded as hypotheses until the model has been calibrated and independently validated against experimental or clinical data. A realistic translational pathway is to use this framework as a preclinical tool for generating testable hypotheses and designing protocols. This requires the collection of longitudinal tumour-burden data, measurements of antigen expression and markers of escape, metrics of the immunosuppressive milieu, and, where possible, spatial measurements. Subsequently,

predictions regarding control-versus-relapse regimes and comparisons of dosing schedules can be tested in preclinical models, followed by early clinical studies with a pre-specified set of observables for iterative validation and refinement of the model.

From a practical standpoint, the proposed reaction–diffusion model can be used as a testbed for comparing clinically feasible CAR-T cell administration regimens under different levels of antigen escape and immunosuppressive effects of the microenvironment, thereby enabling a more evidence-based choice of therapy schedule and optimisation of the protocol. The results also indicate that intensifying the dosing regimen alone may be insufficient when the rate of resistance development is high, which supports the clinical rationale for combination approaches aimed at reducing the effective pressure of antigen escape and broadening the spectrum of recognised targets, as well as modulating the immunosuppressive microenvironment. When calibrated using patient-specific data, the model could potentially be employed to plan personalised protocols, predict relapse risk, and select combinations of dosing interventions that provide more durable control of tumour growth. Thus, the proposed model serves as an effective tool for studying the dynamics of CAR-T cell therapy, generating hypotheses and optimising therapeutic protocols. Future research directions include the development of multiscale hybrid approaches, explicit incorporation of spatial microenvironmental heterogeneity, the use of fractional derivatives to describe memory effects, and the integration of artificial-intelligence methods for the personalisation of predictions.

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References

1. Maude, S.L.; Laetsch, T.W.; Buechner, J.; Rives, S.; Boyer, M.; Bittencourt, H.; Bader, P.; Verneris, M.R.; Stefanski, H.E.; Myers, G.D.; et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N. Engl. J. Med.* **2018**, *378*, 439–448. [CrossRef]
2. Neelapu, S.S.; Locke, F.L.; Bartlett, N.L.; Lekakis, L.J.; Miklos, D.B.; Jacobson, C.A.; Braunschweig, I.; Oluwole, O.O.; Siddiqi, T.; Lin, Y.; et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N. Engl. J. Med.* **2017**, *377*, 2531–2544. [CrossRef]
3. Martinez, M.; Moon, E.K. CAR T cells for solid tumors: New strategies for finding, infiltrating, and surviving in the tumor microenvironment. *Front. Immunol.* **2019**, *10*, 128. [CrossRef] [PubMed]
4. Sterner, R.C.; Sterner, R.M. CAR-T cell therapy: Current limitations and potential strategies. *Blood Cancer J.* **2021**, *11*, 69. [CrossRef]
5. June, C.H.; Sadelain, M. Chimeric antigen receptor therapy. *N. Engl. J. Med.* **2018**, *379*, 64–73. [CrossRef] [PubMed]
6. Larson, R.C.; Maus, M.V. Recent advances and discoveries in the mechanisms and functions of CAR T cells. *Nat. Rev. Cancer* **2021**, *21*, 145–161. [CrossRef]
7. Brudno, J.N.; Kochenderfer, J.N. Recent advances in CAR T-cell toxicity: Mechanisms, manifestations and management. *Blood Rev.* **2019**, *34*, 45–55. [CrossRef]
8. Holtermann, A.; Gislén, M.; Angele, M.; Subklewe, M.; von Bergwelt-Baildon, M.; Lauber, K.; Kobold, S. Prospects of synergy: Local interventions and CAR T cell therapy in solid tumors. *BioDrugs* **2024**, *38*, 611–637. [CrossRef] [PubMed]
9. de Pillis, L.G.; Radunskaya, A.E.; Wiseman, C.L. A validated mathematical model of cell-mediated immune response to tumor growth. *Cancer Res.* **2005**, *65*, 7950–7958. [CrossRef]

10. Altrock, P.M.; Liu, L.L.; Michor, F. The mathematics of cancer: Integrating quantitative models. *Nat. Rev. Cancer* **2015**, *15*, 730–745. [[CrossRef](#)]
11. Ghaffari Laleh, N.; Loeffler, C.M.L.; Grajek, J.; Staňkov'a, K.; Pearson, A.T.; Muti, H.S.; Trautwein, C.; Enderling, H.; Poleszczuk, J.; Kather, J.N. Classical mathematical models for prediction of response to chemotherapy and immunotherapy. *PLoS Comput. Biol.* **2022**, *18*, e1009822. [[CrossRef](#)]
12. Alqahtani, R.T. A model of effector–tumor cell interactions under chemotherapy: Bifurcation analysis. *Mathematics* **2025**, *13*, 1032. [[CrossRef](#)]
13. Sofia, D.; Mohammad Mirzaei, N.; Shahriyari, L. Patient-specific mathematical model of the clear cell renal cell carcinoma microenvironment. *J. Pers. Med.* **2022**, *12*, 1681. [[CrossRef](#)]
14. Valentim, C.A.; Rabi, J.A.; David, S.A. Cellular-automaton model for tumor growth dynamics: Virtualization of different scenarios. *Comput. Biol. Med.* **2023**, *153*, 106481. [[CrossRef](#)]
15. Flandoli, F.; Leocata, M.; Ricci, C. The mathematical modeling of cancer growth and angiogenesis by an individual based interacting system. *J. Theor. Biol.* **2023**, *562*, 111432. [[CrossRef](#)] [[PubMed](#)]
16. Garcke, H.; Kovács, B.; Trautwein, D. Viscoelastic Cahn–Hilliard models for tumor growth. *Math. Model. Methods Appl. Sci.* **2022**, *32*, 2673–2758. [[CrossRef](#)]
17. d'Angelo, M.; Papa, F.; D'Orsi, L.; Panunzi, S.; Pompa, M.; Palombo, G.; Gaetano, A.D.; Borri1, A. A PDE model of glioblastoma progression: The role of cell crowding and resource competition in proliferation and diffusion. *Mathematics* **2025**, *13*, 3318. [[CrossRef](#)]
18. Jafari Nivlouei, S.; Soltani, M.; Carvalho, J.; Travasso, R.; Salimpour, M.R.; Shirani, E. Multiscale modeling of tumor growth and angiogenesis: Evaluation of tumor-targeted therapy. *PLoS Comput. Biol.* **2021**, *17*, e1009081. [[CrossRef](#)]
19. Hadjigeorgiou, A.G.; Stylianopoulos, T. Hybrid model of tumor growth, angiogenesis and immune response yields strategies to improve antiangiogenic therapy. *NPJ Biol. Phys. Mech.* **2024**, *1*, 4. [[CrossRef](#)] [[PubMed](#)]
20. Kar, N.; Özalp, N. A fractional mathematical model approach on glioblastoma growth: Tumor visibility timing and patient survival. *Math. Model. Numer. Simul. Appl.* **2024**, *4*, 66–85. [[CrossRef](#)]
21. Aderyani, S.R.; Saadati, R.; Aderyani, F.R.; Tunç, O. Mathematical modeling of tumor-immune dynamics: Stability, control, and synchronization via fractional calculus and numerical optimization. *Sci. Rep.* **2025**, *15*, 29094. [[CrossRef](#)]
22. Qayyum, M.; Nayab, S.; Khan, O.; Al Zubaidi, A.; Saeed, S.T.; Merga, F.E. Fuzzy and fractional analysis of cancer tumor dynamics with depression effects on chemotherapy. *Sci. Rep.* **2025**, *15*, 33185. [[CrossRef](#)]
23. Nisar, K.S.; Farman, M.; Alotaibi, A.M.; Alharbi, S. Feedback design to measure the effect of therapies in controlling cancer using the fractional approach. *Sci. Rep.* **2025**, *15*, 31494. [[CrossRef](#)]
24. Lorenzo, G.; Ahmed, S.R.; Hormuth, D.A.; Vaughn, B.; Kalpathy-Cramer, J.; Solorio, L.; Yankeelov, T.E.; Gomez, H. Patient-specific, mechanistic models of tumor growth incorporating artificial intelligence and big data. *Annu. Rev. Biomed. Eng.* **2024**, *26*, 529–560. [[CrossRef](#)]
25. Polyakov, M.V.; Ten, V.V. Simulation tumor growth in heterogeneous medium based on diffusion equation. *Int. J. Mod. Phys. C* **2024**, *35*, 2450010. [[CrossRef](#)]
26. Khoperskov, A.V.; Polyakov, M.V. Improving the efficiency of oncological diagnosis of the breast based on the combined use of simulation modeling and artificial intelligence algorithms. *Algorithms* **2022**, *15*, 292. [[CrossRef](#)]
27. Hormuth, D.A.; Phillips, C.M.; Wu, C.; Lima, E.A.B.F.; Lorenzo, G.; Jha, P.K.; Jarrett, A.M.; Oden, J.T.; Yankeelov, T.E. Biologically-based mathematical modeling of tumor vasculature and angiogenesis via time-resolved imaging data. *Cancers* **2021**, *13*, 3008. [[CrossRef](#)]
28. Kuznetsov, M.; Kolobov, A. Antiangiogenic therapy efficacy can be tumor-size dependent, as mathematical modeling suggests. *Mathematics* **2024**, *12*, 353. [[CrossRef](#)]
29. Sekyere, P.O.; Bani-Yaghoub, M.; Youan, B.C. Reaction-diffusion modeling of vascular tumor growth: Bifurcation, relapse, and therapy efficacy. *Math. Biosci. Eng.* **2025**, *22*, 2944–2987. [[CrossRef](#)] [[PubMed](#)]
30. Turing, A.M. The chemical basis of morphogenesis. *Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci.* **1952**, *237*, 37–72. [[CrossRef](#)]
31. Skellam, J.G. Random dispersal in theoretical populations. *Biometrika* **1951**, *38*, 196–218. [[CrossRef](#)] [[PubMed](#)]
32. Epstein, I.R.; Pojman, J.A. *An Introduction to Nonlinear Chemical Dynamics: Oscillations, Waves, Patterns, and Chaos*; Oxford University Press: Oxford, UK, 1998.
33. Swan, A.; Hillen, T.; Bowman, J.C.; Murtha, A.D. A patient-specific anisotropic diffusion model for brain tumour spread. *Bull. Math. Biol.* **2018**, *80*, 1259–1291. [[CrossRef](#)]
34. Rockne, R.C.; Hawkins-Daarud, A.; Swanson, K.R.; Sluka, J.P.; Glazier, J.A.; Macklin, P.; Hormuth, D.A.; Jarrett, A.M.; Lima, E.A.B.F.; Oden, J.T.; et al. The 2019 mathematical oncology roadmap. *Phys. Biol.* **2019**, *16*, 041005. [[CrossRef](#)]
35. Enderling, H.; Chaplain, M.A.J. Mathematical modeling of tumor growth and treatment. *Curr. Pharm. Des.* **2014**, *20*, 4934–4940. [[CrossRef](#)]

36. Byrne, H.M. Modelling avascular tumour growth. In *Cancer Modelling and Simulation*; Preziosi, L., Ed.; Chapman and Hall/CRC: Boca Raton, FL, USA, 2003; pp. 75–120.
37. Enderling, H.; Almog, N. In silico cancer modeling: Is it ready for prime time? *Nat. Rev. Clin. Oncol.* **2018**, *15*, 455–456.
38. Quaranta, V.; Weaver, A.M.; Cummings, P.T.; Anderson, A.R. Mathematical modeling of cancer: The future of prognosis and treatment. *Clin. Chim. Acta* **2005**, *357*, 173–179. [[CrossRef](#)]
39. Mohammad Mirzaei, N.; Su, S.; Sofia, D.; Hegarty, M.; Abdel-Rahman, M.H.; Asadpoure, A.; Cebulla, C.M.; Chang, Y.H.; Hao, W.; Jackson, P.R.; et al. A mathematical model of breast tumor progression based on immune infiltration. *J. Pers. Med.* **2021**, *11*, 1031. [[CrossRef](#)]
40. Ajbar, A.; Alqahtani, R.T. Dynamics of a symmetric model of competition between tumor and immune cells under chemotherapy. *Symmetry* **2025**, *17*, 492. [[CrossRef](#)]
41. Li, C.; Ren, Z.; Yang, G.; Lei, J. Mathematical modeling of tumor immune interactions: The role of anti-FGFR and anti-PD-1 in the combination therapy. *Bull. Math. Biol.* **2024**, *86*, 116. [[CrossRef](#)]
42. Ghiyabi, E.; Arabameri, A.; Charimi, M. Mathematical modeling of hypoxia and adenosine to explore tumor escape mechanisms in DC-based immunotherapy. *Sci. Rep.* **2024**, *14*, 11387. [[CrossRef](#)]
43. Qayyum, M.; Nayab, S.; Siddique, I.; Ghallab, A. Analysis of time-fractional cancer-tumor immunotherapy model using modified He-Laplace algorithm. *Sci. Rep.* **2025**, *15*, 8929. [[CrossRef](#)] [[PubMed](#)]
44. Sahoo, P.; Yang, X.; Abler, D.; Maestrini, D.; Adhikarla, V.; Frankhouser, D.; Cho, H.; Machuca, V.; Wang, D.; Barish, M.; et al. Mathematical deconvolution of CAR T-cell proliferation and exhaustion from real-time killing assay data. *J. R. Soc. Interface* **2020**, *17*, 20190734. [[CrossRef](#)]
45. León-Triana, O.; Sabir, S.; Calvo, G.F.; Belmonte-Beitia, J.; Chulián, S.; Martínez-Rubio, A.; Rosa, M.; Pérez-Martínez, A.; Ramirez-Orellana, M.; Pérez-García, V.M. CAR T cell therapy in B-cell acute lymphoblastic leukaemia: Insights from mathematical models. *Commun. Nonlinear Sci. Numer. Simul.* **2021**, *94*, 105570. [[CrossRef](#)]
46. Barros, L.R.C.; Paixao, E.A.; Valli, A.M.P.; Naozuka, G.T.; Fassoni, A.C.; Almeida, R.C. Cart math—a mathematical model of CAR-T immunotherapy in preclinical studies of hematological cancers. *Cancers* **2021**, *13*, 2941. [[CrossRef](#)] [[PubMed](#)]
47. Alqahtani, R.T.; Ajbar, A.; Aljebli, E.H. Dynamics of a model of tumor–immune cell interactions under chemotherapy. *Mathematics* **2025**, *13*, 2200. [[CrossRef](#)]
48. Bodzioch, M.; Belmonte-Beitia, J. Optimal control of a mathematical model of CAR-T cell therapy for glioblastoma. *Discret. Contin. Dyn. Syst.-B* **2025**, *30*, 4255–4275. [[CrossRef](#)]
49. Sinelshchikov, D.; Belmonte-Beitia, J.; Italia, M. A mathematical model of CAR-T cell therapy in combination with chemotherapy for malignant gliomas. *Chaos* **2025**, *35*, 063104. [[CrossRef](#)]
50. Kara, E.; Jackson, T.L.; Jones, C.; Sison, R.; McGee, R.L., II. Mathematical modeling insights into improving CAR T cell therapy for solid tumors with bystander effects. *NPJ Syst. Biol. Appl.* **2024**, *10*, 105. [[CrossRef](#)]
51. Tu, Z.; Chen, Y.; Zhang, Z.; Meng, W.; Li, L. Barriers and solutions for CAR-T therapy in solid tumors. *Cancer Gene Ther.* **2025**, *32*, 923–934. [[CrossRef](#)] [[PubMed](#)]
52. Sun, X.; Hu, B. Mathematical modeling and computational prediction of cancer drug resistance. *Brief. Bioinform.* **2018**, *19*, 1382–1399. [[CrossRef](#)]
53. Ochieng, F.O. Mathematical modeling of cancerous tumor evolution incorporating drug resistance. *Eng. Rep.* **2025**, *7*, e70021. [[CrossRef](#)]
54. Pompa, M.; Urso, G.; Panunzi, S.; Drexler, D.A.; Gombos, B.; De Gaetano, A. A mathematical model of breast cancer growth and drug resistance evolution under chemotherapy. *Mathematics* **2025**, *13*, 1115. [[CrossRef](#)]
55. Watanabe, Y.; Dahlman, E.L.; Leder, K.Z.; Hui, S.K. A mathematical model of tumor growth and its response to single irradiation. *Theor. Biol. Med. Model.* **2016**, *13*, 6. [[CrossRef](#)]
56. Masoudi-Nejad, A.; Bidkhori, G.; Ashtiani, S.H.; Najafi, A.; Bozorgmehr, J.H.; Wang, E. Cancer systems biology and modeling: Microscopic scale and multiscale approaches. *Semin. Cancer Biol.* **2015**, *30*, 60–69. [[CrossRef](#)] [[PubMed](#)]
57. Azizi, T. Mathematical modeling of cancer progression. *AppliedMath* **2024**, *4*, 1065–1079. [[CrossRef](#)]
58. Beigmohammadi, F.; Khorrami, M.; Masoudi, A.A.; Fatollahi, A.H. Mathematical modeling of tumor growth as a random process in the presence of interaction between tumor cells and normal cells. *Int. J. Mod. Phys. C* **2024**, *35*, 2450102. [[CrossRef](#)]
59. Malik, A.A.; Nguyen, K.C.; Nardini, J.T.; Krona, C.C.; Flores, K.B.; Nelander, S. Mathematical modeling of multicellular tumor spheroids quantifies inter-patient and intra-tumor heterogeneity. *NPJ Syst. Biol. Appl.* **2025**, *11*, 20. [[CrossRef](#)]
60. Fu, Z.; Mowday, A.M.; Smail, J.B.; Hermans, I.F.; Patterson, A.V. Tumour Hypoxia-Mediated Immunosuppression: Mechanisms and Therapeutic Approaches to Improve Cancer Immunotherapy. *Cells* **2021**, *10*, 1006. [[CrossRef](#)] [[PubMed](#)]
61. Berahovich, R.; Liu, X.; Zhou, H.; Tsadik, E.; Xu, S.; Golubovskaya, V.; Wu, L. Hypoxia Selectively Impairs CAR-T Cells In Vitro. *Cancers* **2019**, *11*, 602. [[CrossRef](#)]
62. Fonkoua, L.A.K.; Sirpilla, O.; Sakemura, R.; Siegler, E.L.; Kenderian, S.S. CAR T cell therapy and the tumor microenvironment: Current challenges and opportunities. *Mol. Ther.–Oncolytics* **2022**, *25*, 69–77. [[CrossRef](#)]

63. Owens, K.; Rahman, A.; Bozic, I. Spatiotemporal dynamics of tumor–CAR T-cell interaction following local administration in solid cancers. *PLoS Comput. Biol.* **2025**, *21*, e1013117. [[CrossRef](#)]
64. Santurio, D.S.; Barros, L.R.C. A mathematical model for on-target off-tumor effect of CAR-T cells on gliomas. *Front. Syst. Biol.* **2022**, *2*, 923085. [[CrossRef](#)]
65. Sabir, S.; León-Triana, O.; Serrano, S.; Barrio, R.; Pérez-García, V.M. Mathematical model of CAR T-cell therapy for a B-cell lymphoma lymph node. *Bull. Math. Biol.* **2025**, *87*, 1–33. [[CrossRef](#)]
66. Kimmel, G.J.; Locke, F.L.; Altrock, P.M. The roles of T cell competition and stochastic extinction events in chimeric antigen receptor T cell therapy. *Proc. R. Soc. B* **2021**, *288*, 20210229. [[CrossRef](#)] [[PubMed](#)]
67. Qi, T.; McGrath, K.; Ranganathan, R.; Dotti, G.; Cao, Y. Cellular kinetics: A clinical and computational review of CAR-T cell pharmacology. *Adv. Drug Deliv. Rev.* **2022**, *188*, 114421. [[CrossRef](#)] [[PubMed](#)]
68. Uslu, U.; June, C.H. Beyond the blood: Expanding CAR T cell therapy to solid tumors. *Nat. Biotechnol.* **2025**, *43*, 506–515. [[CrossRef](#)] [[PubMed](#)]

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