A critical virus production rate for efficiency of oncolytic virotherapy

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Abstract

In a planar smoothly bounded domain Ω, we consider the model for oncolytic virotherapy given by

$$\begin{cases} u_t = \Delta u - \nabla \cdot (u \nabla v) - uz, \\ v_t = -(u+w)v, \\ w_t = D_w \Delta w - w + uz, \\ z_t = D_z \Delta z - z - uz + \beta w, \end{cases}$$

with positive parameters D_w, D_z and β.

It is firstly shown that whenever $\beta < 1$, for any choice of $M > 0$ one can find initial data such that the solution of an associated no-flux initial-boundary value problem, well-known to exist globally actually for any choice of $\beta > 0$, satisfies

$$u \geq M \qquad \text{in } \Omega \times (0, \infty).$$

If $\beta > 1$, however, then for arbitrary initial data the corresponding is seen to have the property that

$$\liminf_{t \to \infty} \inf_{x \in \Omega} u(x,t) \leq \frac{1}{\beta - 1}.$$

This may be interpreted as indicating that β plays the role of a critical virus replication rate with regard to efficiency of the considered virotherapy, with corresponding threshold value given by $\beta = 1$.

Key words: oncolytic virotherapy; haptotaxis; critical parameter
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1 Introduction

Chemotherapy is a traditional treatment for cancer; however, the drug delivery process and the drug resistance limit the efficacy of this remedy ([23], [12], [10], [30]). In the search for efficient cancer treatment, a novel approach targeted at bypassing the above obstacles involves the use of virus. Appropriate replication-competent oncolytic viruses can selectively attack and destroy cancer cells, though being little harmful to normal healthy cells, and they are currently used in clinical trials ([13], [2], [5], [9], [21], [38], [22], [17]). To the best of our knowledge, the spatio-temporal modeling of oncolytic virus therapy was initiated by Wu et. al in [36], and since then different mathematical models have been developed to investigate the spatial spread of oncolytic virus particles ([16], [34], [3], [11]). Nevertheless, clinical data revealed an innate immune response to virus that may mitigate the effects of virotherapy ([8], [19]), and corresponding mathematical models were also established to better understand the dynamics between tumor cells, a replication-competent virus and an immune response ([37], [34]). Besides by virus clearance due to immune cells, virus spread is also restricted by physical barriers inside tumors, such as extracellular matrix deposits or interstitial fluid pressure ([28], [35]).

In order to understand such physical barriers that hinder virus spread, and particularly to provide theoretical options to access quantitative questions related to overall efficiency of oncolytic viral therapy, the authors in [1] recently proposed coupled PDE-ODE systems of the form

$$\begin{cases} u_t = D_u\Delta u - \xi_u\nabla\cdot(u\nabla v) + \mu_u u(1-u) - \rho_u uz, \\ v_t = -(\alpha_u u + \alpha_w w)v + \mu_v v(1-v), \\ w_t = D_w\Delta w - \delta_w w + \rho_w uz, \\ z_t = D_z\Delta z - \delta_z z - \rho_z uz + \beta w, \end{cases} \tag{1.1}$$

with given positive parameters $D_u, D_w, D_z, \xi_u, \mu_u, \mu_v, \rho_u, , \rho_{\mathrm{z}}, \alpha_{\mathrm{u}}, \alpha_{\mathrm{w}}, \delta_{\mathrm{w}}, \delta_{\mathrm{z}}$ and β, and with the population densities u, w, z and v of uninfected tumor cells, infected tumor cells, virus particles and the so-called extracellular matrix (MDE) denoting the unknown variables. As detailed in [1], this model aims at including the core processes determining the virotherapy-influenced tumor evolution by inter alia accounting for haptotactic motion of uninfected cancer cells toward increasing MDE densities which themselves are degraded upon contact with tumor cells, for conversion of uninfected into infected tumor cells through contact with virions, and for virus production by infected cancer cells; beyond this, (1.1) assumes that both the MDE and uninfected tumor cells are able to proliferate according to logistic laws.

Viewed from a mathematical perspective, due to the presence of haptotactic cross-diffusion, models of this type noticeably differ from classical reaction-diffusion systems, which apparently goes along with a significant reduction of accessibility to approaches well-established in the analysis of the latter. Indeed, rigorous results addressing haptotaxis systems seem yet mainly limited to issues from basic solution theory ([29], [7], [6], [40], [39], [24], [25], [4], [14], [20]), with the few available exceptions concerned with more subtle qualitative questions apparently restricted to systems of rather simple structure ([15], [18], [32]); to the best of our knowledge, apart from a recent discovery of a blow-up dichotomy in a simplified version of (1.1) ([27]), a quantitative comprehension in the sense of determining critical parameter ranges and relationships has nowhere been achieved in the literature on any related haptotaxis system.

Main results. Despite these methodological obstacles, the present study aims at contributing to a basic understanding about how far in the context of models of the form in (1.1), the efficacy of virotherapy is influenced by crucial system ingredients. In order to address this issue in a framework translatable to a genuine mathematical question, we shall henceforth concentrate on the distribution of uninfected tumor cells as the main objective of treatment, and accordingly intend to identify situations in which the quantity u is favorably diminished during evolution in an appropriate sense. Here to keep a clear focus on genuinely therapy-related mechanisms, we shall neglect both proliferation processes in (1.1), and our analysis will reveal that in such settings, the virus reproduction rate β will play the role of a critical parameter in this regard.

To analyze and describe this in a notationally convenient setup, we will set $D_u = \rho_u = \rho_w = \rho_z = \alpha_u = \alpha_w = \delta_w = \delta_z = 1$ and consider the resulting system in a spatially planar framework along with suitable initial and boundary conditions, and hence we shall subsequently investigate the problem

$$\left\{ \begin{array}{rcll} u_t &=& \Delta u - \nabla \cdot (u \nabla v) - uz, & x \in \Omega, \ t > 0, \\ v_t &=& -(u+w)v, & x \in \Omega, \ t > 0, \\ w_t &=& D_w \Delta w - w + uz, & x \in \Omega, \ t > 0, \\ z_t &=& D_z \Delta z - z - uz + \beta w, & x \in \Omega, \ t > 0, \\ (\nabla u - u \nabla v) \cdot \nu = \frac{\partial w}{\partial \nu} = \frac{\partial z}{\partial \nu} = 0, & & & x \in \partial\Omega, \ t > 0, \\ u(x,0) = u_0(x), \quad v(x,0) = v_0(x), \quad w(x,0) = w_0(x), \quad z(x,0) = z_0(x), & & & x \in \Omega, \end{array} \right. \tag{1.2}$$

in a bounded domain $\Omega \subset \mathbb{R}^2$ with smooth boundary, where $\beta > 0$; then according to the outcome of [26], the hypotheses that

$$\left\{ \begin{array}{l} u_0, v_0 \text{ and } w_0 \text{ are nonnegative functions from } C^{2+\vartheta}(\overline{\Omega}) \text{ for some } \vartheta > 0, \\ \text{with } u_0 \not\equiv 0, \ w_0 \not\equiv 0, z_0 \not\equiv 0, \ \sqrt{v_0} \in W^{1,2}(\Omega) \text{ and } \frac{\partial u_0}{\partial \nu} = \frac{\partial v_0}{\partial \nu} = \frac{\partial w_0}{\partial \nu} = \frac{\partial z_0}{\partial \nu} = 0 \text{ on } \partial\Omega, \end{array} \right. \tag{1.3}$$

ensure global existence of classical solutions (cf. also Lemma 2.1 below). Attempting to go beyond these basic findings, in the present work we focus on exploring qualitative solution properties.

Our first results in this direction will reveal that whenever the virus production rate satisfies $\beta < 1$, the population density of uninfected tumor cells can be controlled from below at each point in the following sense.

Theorem 1.1 *Let $\Omega \subset \mathbb{R}^2$ be a bounded domain with smooth boundary, and suppose that*

$$\beta \in (0,1). \tag{1.4}$$

Then there exists $C = C(\beta, \Omega) > 0$ with the property that whenever u_0, v_0, w_0 and z_0 satisfy (1.3), for the solution of (1.2) we have

$$u(x,t) \geq \left\{ \inf_{y \in \Omega} u_0(y) \right\} \cdot \exp\Big\{ - \|v_0\|_{L^\infty(\Omega)} - C\|w_0\|_{L^2(\Omega)} - C\|z_0\|_{L^\infty(\Omega)} \Big\} \qquad \text{for all } x \in \Omega \text{ and } t > 0. \tag{1.5}$$

In particular, this implies that for any such value of β, appropriately large initial distributions of uninfected tumor cells remain uniformly large throughout evolution, and throughout the spatial domain:

Corollary 1.2 *Let $\Omega \subset \mathbb{R}^2$ be a smoothly bounded domain, let $\beta \in (0,1)$, and let v_0, w_0 and z_0 be given functions satisfying the respective requirements in (1.3). Then for any $M > 0$ one can find $C(\beta, \Omega, v_0, w_0, z_0, M) > 0$ such that if u_0 complies with (1.3) and is such that*

$$u_0(x) \geq C(\beta, \Omega, v_0, w_0, z_0, M) > 0, \tag{1.6}$$

then the solution of (1.2) has the property that

$$u(x,t) \geq M \qquad \text{for all } x \in \Omega \text{ and } t > 0. \tag{1.7}$$

In sharp contrast to this, replication rates fulfilling $\beta > 1$ ensure that arbitrarily large populations of uninfected cancer cells must eventually fall below an explicitly known threshold value at least somewhere in space:

Proposition 1.3 *Let $\Omega \subset \mathbb{R}^2$ be a bounded domain with smooth boundary, and let*

$$\beta > 1. \tag{1.8}$$

Then for any choice of (u_0, v_0, w_0, z_0) fulfilling (1.3), the solution of (1.2) satisfies

$$\liminf_{t\to\infty} \inf_{x\in\Omega} u(x,t) \leq \frac{1}{\beta - 1}. \tag{1.9}$$

In summary, the above results do not only confirm that increasing the virus replication rate may improve the efficacy of this type of virus-based therapy, but moreover they also identify the value $\beta = 1$ as a threshold level for the critical parameter in this regard. In order to keep a clear focus on these statements and our ambition to provide access of such subtle dichotomies to rigorous analysis, we only remark at this point that by means of evident modifications, our findings can be extended in a straightforward manner to versions of (1.2) which more closely adapt to situations of potential clinical relevance by involving more general parameters such as diffusion, cross-diffusion and degradation rates.

Main ideas. In the case $\beta < 1$, a basic consideration shows that w and z decay exponentially in L^1 (cf. Lemma 3.1 below). Using this and relying on the observation that

$$\mathcal{F}(t) := \frac{1}{2}\int_\Omega w^2(\cdot,t) + \int_\Omega w(\cdot,t)z(\cdot,t) + \frac{b}{2}\int_\Omega z^2(\cdot,t), \qquad t \geq 0,$$

satisfies

$$\mathcal{F}'(t) + \mathcal{F}(t) \leq C \cdot \left\{ \int_\Omega w(\cdot,t) \right\}^2 \qquad \text{for all } t > 0$$

with suitable $b > 0$ and some $C > 0$ (see Lemma 3.2 for details), we find the exponential decay of w in L^2 and thus of z in L^∞ (cf. Lemma 3.3 and Lemma 3.4). By means of a parabolic comparison argument, the latter implies a pointwise lower bound for u in ths flavor of that asserted in (1.5) (Lemma 3.5), and thereby establishes Theorem 1.1. Finally, the proof of Proposition 1.3 is based on a contradiction argument concerned with the evolution of the linear functional

$$y(t) := \int_\Omega w(\cdot,t) + \sigma \int_\Omega z(\cdot,t), \qquad t \geq t_0,$$

with appropriately chosen $\sigma > 0$ and $t_0 > 0$.

2 Preliminaries. Global existence and L^1 bounds

Let us first recall from [26] the following:

Lemma 2.1 *Let $\Omega \subset \mathbb{R}^2$ be a bounded domain with smooth boundary, let $\beta > 0$, and suppose that (u_0, v_0, w_0, z_0) satisfies (1.3). Then the problem (1.2) possesses a uniquely determined classical solution $(u, v, w, z) \in (C^{2,1}(\overline{\Omega} \times [0, \infty)))^4$ for which v is nonnegative, and for which u, w and z are positive in $\overline{\Omega} \times (0, \infty)$. Moreover,*

$$\int_\Omega u(\cdot, t) \le \int_\Omega u_0 \qquad \text{for all } t > 0, \tag{2.1}$$

and for any choice of $t_0 \ge 0$ we have

$$\|v(\cdot, t)\|_{L^\infty(\Omega)} \le \|v(\cdot, t_0)\|_{L^\infty(\Omega)} \qquad \text{for all } t > t_0. \tag{2.2}$$

Without further mentioning, throughout the sequel we shall refer to this solution whenever a quadruple (u_0, v_0, w_0, z_0) fulfilling (1.3) is given.

In describing a first solution feature beyond those in (2.1) and (2.2), we shall make use of the following elementary statement on decay of solutions to a linearly dampened ODE involving a suitably decreasing source.

Lemma 2.2 *Let $y \in C^0([0, \infty)) \cap C^1((0, \infty))$ be nonnegative and such that with some nonnegative $f \in L^1((0, \infty))$ and some $\lambda > 0$ we have*

$$y'(t) + \lambda y(t) \le f(t) \qquad \text{for all } t > 0. \tag{2.3}$$

Then

$$\int_0^\infty y(t)dt < \infty \tag{2.4}$$

and

$$y(t) \to 0 \qquad \text{as } t \to \infty. \tag{2.5}$$

Proof. An integration of (2.3) directly yields (2.4), which thereafter can readily be seen by elementary calculus to imply (2.5) when combined with the fact that as $t \to \infty$ we have $\int_{t-1}^t f(s)ds \to 0$. □

In fact, due to the presence of the degradation term in the first equation from (1.2), the latter can be used to assert some decay properties of w and z with respect to spatial L^1 norms whenever $\beta > 0$.

Lemma 2.3 *Let $\beta > 0$. Then*

$$\int_\Omega w(\cdot, t) \to 0 \quad \text{and} \quad \int_\Omega z(\cdot, t) \to 0 \qquad \text{as } t \to \infty, \tag{2.6}$$

Proof. We integrate the first equation in (1.2) to see that

$$\frac{d}{dt} \int_\Omega u = -\int_\Omega uz \qquad \text{for all } t > 0$$

and that thus

$$\int_0^t \int_\Omega uz = \int_\Omega u_0 - \int_\Omega u(\cdot,t) \le \int_\Omega u_0 \qquad \text{for all } t>0,$$

so that $f(t) := \int_\Omega u(\cdot,t)z(\cdot,t),\ t>0$, belongs to $L^1((0,\infty))$. As, next,

$$\frac{d}{dt}\int_\Omega w + \int_\Omega w = \int_\Omega uz = f(t) \qquad \text{for all } t>0$$

by the third equation in (1.2), from Lemma 2.2 we conclude that

$$\int_\Omega w \to 0 \quad \text{as } t\to\infty \qquad \text{and} \qquad \int_0^\infty \int_\Omega w < \infty,$$

whence, in particular $g(t) := \beta \int_\Omega w(\cdot,t),\ t>0$, satisfies $g \in L^1((0,\infty))$ as well. Since integrating the fourth equation from (1.2) shows that

$$\frac{d}{dt}\int_\Omega z + \int_\Omega z = -\int_\Omega uz + \beta\int_\Omega w \le g(t) \qquad \text{for all } t>0,$$

we may thus invoke Lemma 2.2 for a second time to conclude that, indeed, also

$$\int_\Omega z \to 0 \quad \text{as } t\to\infty,$$

as intended. □

3 Persistently large solutions when $\beta < 1$

The intention of this section is to derive Theorem 1.1 and Corollary 1.2 by making sure that under the assumption $\beta<1$, beyond what is foreshadowed in Lemma 2.3 the quantity z actually decays suitably fast and in a topology appropriately strong so as to allow for a convenient control of u from below through a comparison argument in Lemma 3.5.

Our first step toward this asserts that if $\beta<1$, then the L^1 decay information in (2.6) can be sharpened as follows.

Lemma 3.1 *Let $\beta<1$. Then*

$$\int_\Omega w(\cdot,t) \le \left\{ \int_\Omega w_0 + \int_\Omega z_0 \right\} \cdot e^{-(1-\beta)t} \qquad \textit{for all } t>0 \tag{3.1}$$

and

$$\int_\Omega z(\cdot,t) \le \left\{ \int_\Omega w_0 + \int_\Omega z_0 \right\} \cdot e^{-(1-\beta)t} \qquad \textit{for all } t>0 \tag{3.2}$$

PROOF. We once more integrate the third and fourth equations in (1.2) over Ω to see upon adding the resulting identities that

$$\begin{aligned}\frac{d}{dt}\Big\{\int_\Omega w+\int_\Omega z\Big\} &= \Big\{-\int_\Omega w+\int_\Omega uz\Big\}+\Big\{-\int_\Omega z-\int_\Omega uz+\beta\int_\Omega w\Big\}\\ &= -(1-\beta)\int_\Omega w-\int_\Omega z\\ &\le -(1-\beta)\cdot\Big\{\int_\Omega w+\int_\Omega z\Big\} \qquad \text{for all } t>0\end{aligned}$$

and thus, after an integration in time, infer that

$$\int_\Omega w+\int_\Omega z\le\Big\{\int_\Omega w_0+\int_\Omega z_0\Big\}\cdot e^{-(1-\beta)t} \qquad \text{for all } t>0,$$

which yields both (3.1) and (3.2). □

In order to improve the topological framework within which w and z decay, we next state the following observation concerned with a quasi-energy structure in (1.2), valid in this general form actually for all $\beta>0$.

Lemma 3.2 *Let $\beta>0$. Then there exist $b>0$ and $C>0$ such that for any choice of (u_0,v_0,w_0,z_0) fulfilling (1.3), the function $\mathcal{F}$ defined by letting*

$$\mathcal{F}(t):=\frac12\int_\Omega w^2(\cdot,t)+\int_\Omega w(\cdot,t)z(\cdot,t)+\frac{b}{2}\int_\Omega z^2(\cdot,t), \qquad t\ge0, \tag{3.3}$$

satisfies

$$\mathcal{F}'(t)+\mathcal{F}(t)\le C\cdot\Big\{\int_\Omega w(\cdot,t)\Big\}^2 \qquad \text{for all } t>0. \tag{3.4}$$

PROOF. We let

$$b:=\frac{(D_w+D_z)^2}{2D_wD_z}, \tag{3.5}$$

abbreviate $f:=uz$, and use (1.2) to see that the accordingly defined function $\mathcal{F}$ from (3.3) satisfies

$$\begin{aligned}\mathcal{F}'(t)+\mathcal{F}(t) &= \int_\Omega ww_t+\int_\Omega w_tz+\int_\Omega wz_t+b\int_\Omega zz_t+\frac12\int_\Omega w^2+\int_\Omega wz+\frac{b}{2}\int_\Omega z^2\\ &= -D_w\int_\Omega|\nabla w|^2-\int_\Omega w^2+\int_\Omega fw\\ &\quad -D_w\int_\Omega\nabla w\cdot\nabla z-\int_\Omega wz+\int_\Omega fz\\ &\quad -D_z\int_\Omega\nabla w\cdot\nabla z-\int_\Omega wz-\int_\Omega fw+\beta\int_\Omega w^2\\ &\quad -bD_z\int_\Omega|\nabla z|^2-b\int_\Omega z^2-b\int_\Omega fz+b\beta\int_\Omega wz\end{aligned}$$

$$
\begin{aligned}
&+\frac{1}{2}\int_\Omega w^2 + \int_\Omega wz + \frac{b}{2}\int_\Omega z^2 \\
= \;& -D_w\int_\Omega |\nabla w|^2 - bD_z\int_\Omega |\nabla z|^2 - (D_w+D_z)\int_\Omega \nabla w\cdot\nabla z \\
&+\Big(\beta-\frac{1}{2}\Big)\int_\Omega w^2 - \frac{b}{2}\int_\Omega z^2 + (b\beta-1)\int_\Omega wz \\
&+(1-b)\int_\Omega fz \qquad \text{for all } t>0. \qquad (3.6)
\end{aligned}
$$

Here, (3.5) ensures that thanks to Young's inequality,

$$
\begin{aligned}
-(D_w+D_z)\int_\Omega \nabla w\cdot\nabla z &\le \frac{D_w}{2}\int_\Omega |\nabla w|^2 + \frac{(D_w+D_z)^2}{2D_w}\int_\Omega |\nabla z|^2 \\
&\le \frac{D_w}{2}\int_\Omega |\nabla w|^2 + bD_z\int_\Omega |\nabla z|^2 \qquad \text{for all } t>0,
\end{aligned}
$$

and that furthermore

$$
(1-b)\int_\Omega fz \le 0 \qquad \text{for all } t>0,
$$

because $\frac{(D_w+D_z)^2}{2D_wD_z}\ge 1$ and both f and z are nonnegative. Since, apart from that, Young's inequality warrants that

$$
(b\beta-1)\int_\Omega wz \le \frac{b}{2}\int_\Omega z^2 + \frac{(b\beta-1)_+^2}{2b}\int_\Omega w^2 \qquad \text{for all } t>0,
$$

from (3.6) we infer that

$$
\mathcal{F}'(t)+\mathcal{F}(t)+\frac{D_w}{2}\int_\Omega |\nabla w|^2 \le c_1\int_\Omega w^2 \qquad \text{for all } t>0 \qquad (3.7)
$$

with $c_1 := (\beta-\frac{1}{2})_+ + \frac{(b\beta-1)_+^2}{2b}$. We now only need to observe that as a consequence of a Poincaré-type inequality we can find $c_2>0$ fulfilling

$$
c_1\int_\Omega \varphi^2 \le \frac{D_w}{2}\int_\Omega |\nabla\varphi|^2 + c_2\cdot\Big\{\int_\Omega |\varphi|\Big\}^2 \qquad \text{for all } \varphi\in W^{1,2}(\Omega),
$$

which when applied to $\varphi := w(\cdot,t)$ for $t>0$, namely, shows that (3.7) entails (3.4) with $C:=c_2$. □

Now in the case $\beta<1$ on which we concentrate here, the exponentially decaying bound implied by Lemma 3.1 for the expression on the right of (3.4) enables us to obtain from the above a similar convergence property of $\mathcal{F}$, a particular consequence of which is documented as follows.

Lemma 3.3 *Let $\beta<1$. Then there exist $\gamma>0$ and $C>0$ with the property that whenever (u_0,v_0,w_0,z_0) are such that (1.3) holds, we have*

$$
\|w(\cdot,t)\|_{L^2(\Omega)} \le C\cdot\Big\{\|w_0\|_{L^2(\Omega)} + \|z_0\|_{L^2(\Omega)}\Big\}\cdot e^{-\gamma t} \qquad \textit{for all } t>0. \qquad (3.8)
$$

PROOF. We first apply Lemma 3.2 to fix $b > 0$ and $c_1 > 0$ such that if (1.3) is satisfied, then the function $\mathcal{F}$ defined in (3.3) has the property that

$$\mathcal{F}'(t) + \mathcal{F}(t) \le c_1 \cdot \left\{ \int_\Omega w \right\}^2 \qquad \text{for all } t > 0, \tag{3.9}$$

and thereafter we fix (u_0, v_0, w_0, z_0) such that (1.3) holds, and rely on our assumption that $\beta < 1$ to see that due to Lemma 3.1, choosing any $\gamma > 0$ such that

$$\gamma \le 1 - \beta \qquad \text{and} \qquad \gamma < \frac{1}{2}, \tag{3.10}$$

we have

$$\int_\Omega w \le K_1 e^{-\gamma t} \qquad \text{for all } t > 0, \tag{3.11}$$

where

$$K_p := \|w_0\|_{L^p(\Omega)} + \|z_0\|_{L^p(\Omega)}, \qquad p \ge 1. \tag{3.12}$$

Inserted into (3.9), (3.11) implies that

$$\mathcal{F}'(t) + \mathcal{F}(t) \le c_1 K_1^2 e^{-2\gamma t} \qquad \text{for all } t > 0,$$

where the second restriction in (3.10) enables us to conveniently integrate to conclude that therefore

$$\begin{aligned} \mathcal{F}(t) &\le \mathcal{F}(0) e^{-t} + c_1 K_1^2 \int_0^t e^{-(t-s)} e^{-2\gamma s} ds \\ &= \mathcal{F}(0) e^{-t} + \frac{c_1}{1-2\gamma} \cdot K_1^2 \cdot (e^{-2\gamma t} - e^{-t}) \\ &\le \mathcal{F}(0) e^{-t} + \frac{c_1}{1-2\gamma} \cdot K_1^2 \cdot e^{-2\gamma t} \qquad \text{for all } t > 0. \end{aligned} \tag{3.13}$$

Since by definition of $\mathcal{F}$ and Young's inequality we have

$$\begin{aligned} \mathcal{F}(0) &= \frac{1}{2} \int_\Omega w_0^2 + \int_\Omega w_0 z_0 + \frac{b}{2} \int_\Omega z_0^2 \\ &\le \int_\Omega w_0^2 + \frac{b+1}{2} \int_\Omega z_0^2 \\ &\le K_2^2 + \frac{b+1}{2} \cdot K_2^2 = \frac{b+3}{2} \cdot K_2^2, \end{aligned}$$

and since due to the Cauchy-Schwarz,

$$K_1 \le |\Omega|^{\frac{1}{2}} \|w_0\|_{L^2(\Omega)} + |\Omega|^{\frac{1}{2}} \|z_0\|_{L^2(\Omega)} = |\Omega|^{\frac{1}{2}} K_2,$$

from (3.13) we infer that

$$\frac{1}{2} \int_\Omega w^2(\cdot, t) \le \mathcal{F}(t) \le \frac{b+3}{2} \cdot K_2^2 e^{-t} + \frac{c_1 |\Omega|}{1-2\gamma} \cdot K_2^2 e^{-2\gamma t} \qquad \text{for all } t > 0.$$

As $e^{-t} \le e^{-2\gamma t}$ for all $t > 0$ by (3.10), this implies (3.8) if we let $C := \sqrt{b + 3 + \frac{2c_1|\Omega|}{1-2\gamma}}$, for instance. □

In view of well-known parabolic smoothing properties, due to the planarity of the considered spatial setting the latter is sufficient to entail exponential decay of z actually with respect to the norm in $L^\infty(\Omega)$:

Lemma 3.4 *If $\beta < 1$, then one can fix $\gamma > 0$ and $C > 0$ such that for arbitrary (u_0, v_0, w_0, z_0) complying with (1.3), we have*

$$\|z(\cdot,t)\|_{L^\infty(\Omega)} \le C \cdot \Big\{ \|w_0\|_{L^2(\Omega)} + \|z_0\|_{L^\infty(\Omega)} \Big\} \cdot e^{-\gamma t} \qquad \text{for all } t > 0. \tag{3.14}$$

Proof. Based on standard smoothing estimates for the Neumann heat semigroup $(e^{\sigma\Delta})_{\sigma\ge 0}$ on Ω ([31]), we fix $c_1 > 0$ and $c_2 > 0$ such that and

$$\|e^{tD_z\Delta}\varphi\|_{L^\infty(\Omega)} \le c_1 t^{-\frac{1}{2}} \|\varphi\|_{L^2(\Omega)} \qquad \text{for all } \varphi \in C^0(\overline{\Omega}) \text{ and any } t \in (0,1) \tag{3.15}$$

and

$$\|e^{D_z\Delta}\varphi\|_{L^\infty(\Omega)} \le c_2 \|\varphi\|_{L^1(\Omega)} \qquad \text{for all } \varphi \in C^0(\overline{\Omega}), \tag{3.16}$$

and invoking Lemma 3.2 we find $\gamma \in (0, 1-\beta]$ and $c_3 > 0$ fulfilling

$$\|w(\cdot,t)\|_{L^2(\Omega)} \le c_3 K_2 e^{-\gamma t} \qquad \text{for all } t > 0, \tag{3.17}$$

where again $K_p := \|w_0\|_{L^p(\Omega)} + \|z_0\|_{L^p(\Omega)}$ for $p \ge 1$. Now given $t > 0$, we let $t_0 \equiv t_0(t) := (t-1)_+$ and use the comparison principle to see that by nonnegativity of u and z,

$$\begin{aligned} z(\cdot,t) &= e^{(t-t_0)(D_z\Delta-1)} z(\cdot,t_0) - \int_{t_0}^t e^{(t-s)(D_z\Delta-1)} \Big\{ u(\cdot,s) z(\cdot,s) \Big\} ds + \beta \int_{t_0}^t e^{(t-s)(D_z\Delta-1)} w(\cdot,s) ds \\ &\le e^{(t-t_0)D_z\Delta} z(\cdot,t_0) + \beta \int_{t_0}^t e^{(t-s)D_z\Delta} w(\cdot,s) ds \qquad \text{in } \Omega. \end{aligned}$$

Since $z(\cdot,t)$ is nonnegative, this implies that

$$\|z(\cdot,t)\|_{L^\infty(\Omega)} \le \|e^{(t-t_0)D_z\Delta} z(\cdot,t_0)\|_{L^\infty(\Omega)} + \beta \int_{t_0}^t \|e^{(t-s)D_z\Delta} w(\cdot,s)\|_{L^\infty(\Omega)} ds, \tag{3.18}$$

where by (3.15) and (3.17) we can estimate

$$\begin{aligned} \beta \int_{t_0}^t \|e^{(t-s)D_z\Delta} w(\cdot,s)\|_{L^\infty(\Omega)} ds &\le c_1\beta \int_{t_0}^t (t-s)^{-\frac{1}{2}} \|w(\cdot,s)\|_{L^2(\Omega)} ds \\ &\le c_1\beta K_2 \int_{t_0}^t (t-s)^{-\frac{1}{2}} e^{-\gamma s} ds \\ &\le c_1\beta K_2 e^{-\gamma t_0} \int_{t_0}^t (t-s)^{-\frac{1}{2}} ds \\ &= 2c_1\beta K_2 e^{-\gamma t_0} \cdot (t-t_0)^{\frac{1}{2}} \\ &\le 2c_1\beta e^{\gamma} K_2 e^{-\gamma t}, \end{aligned} \tag{3.19}$$

because $t_0 \geq t-1$. Apart from that, (3.16) and Lemma 3.1 imply that if $t \geq 1$, then

$$\begin{aligned} \|e^{(t-t_0)D_z\Delta}z(\cdot,t_0)\|_{L^\infty(\Omega)} &= \|e^{D_z\Delta}z(\cdot,t-1)\|_{L^\infty(\Omega)} \\ &\leq c_2\|z(\cdot,t-1)\|_{L^1(\Omega)} \\ &\leq c_2K_1e^{-(1-\beta)(t-1)} \\ &= c_2e^{1-\beta}K_1e^{-(1-\beta)t}, \end{aligned} \tag{3.20}$$

while if $t<1$, then using the comparison principle we infer that

$$\|e^{(t-t_0)D_z\Delta}z(\cdot,t_0)\|_{L^\infty(\Omega)} = \|e^{tD_z\Delta}z_0\|_{L^\infty(\Omega)} \leq \|z_0\|_{L^\infty(\Omega)} \leq e^{1-\beta}\|z_0\|_{L^\infty(\Omega)}e^{-(1-\beta)t}. \tag{3.21}$$

Since $K_2 \leq \|w_0\|_{L^2(\Omega)}+|\Omega|^{\frac{1}{2}}\|z_0\|_{L^\infty(\Omega)}$ and $K_1 \leq |\Omega|^{\frac{1}{2}}\|w_0\|_{L^2(\Omega)}+|\Omega|\|z_0\|_{L^\infty(\Omega)}$ by the Cauchy-Schwarz inequality, combining (3.18) with (3.19), (3.20) and (3.21) yields (3.14) upon an evident choice of C, because $e^{-(1-\beta)t} \leq e^{-\gamma t}$ for all $t>0$ due to our restriction that $\gamma \leq 1-\beta$. □

Now a pointwise lower bound for u in the style of that claimed in Theorem 1.1 can be achieved by means of an argument based on comparison with spatially flat functions, applied to the variable ue^{-v} which, as is well-known, indeed satisfies a parabolic equation free of cross-diffusion terms:

Lemma 3.5 *Let $\beta<1$. Then there exists $C>0$ such that whenever (1.3) holds, the solution of (1.2) satisfies*

$$u(x,t) \geq \inf_{y\in\Omega}\Big\{u_0(y)e^{-v_0(y)}\Big\}\cdot\exp\Big\{-C\cdot\Big\{\|w_0\|_{L^2(\Omega)}+\|z_0\|_{L^\infty(\Omega)}\Big\}\Big\} \qquad \text{for all } x\in\Omega \text{ and } t>0. \tag{3.22}$$

Proof. According to Lemma 3.4, let us pick $\gamma>0$ and $c_1>0$ such that given any (u_0,v_0,w_0,z_0) fulfilling (1.3), writing $K := \|w_0\|_{L^2(\Omega)}+\|z_0\|_{L^\infty(\Omega)}$ we have

$$z(x,t) \leq c_1Ke^{-\gamma t} \qquad \text{for all } x\in\Omega \text{ and } t>0. \tag{3.23}$$

Next, fixing any such (u_0,v_0,w_0,z_0) we see by means of a straightforward computation based on (1.2) that

$$a(x,t) := u(x,t)e^{-v(x,t)}, \qquad x\in\overline{\Omega},\ t\geq 0,$$

satisfies

$$a_t = e^{-v}\nabla\cdot(e^v\nabla a) - av_t - az \qquad \text{for all } x\in\Omega \text{ and } t>0,$$

with $\frac{\partial a}{\partial\nu}=0$ throughout $\partial\Omega\times(0,\infty)$ (cf. also [29] or [26]), whence particularly, by (3.23) and the inequality $v_t\leq 0$ asserted by (1.2),

$$a_t \geq e^{-v}\nabla\cdot(e^v\nabla a) - c_1Ke^{-\gamma t}a \qquad \text{for all } x\in\Omega \text{ and } t>0. \tag{3.24}$$

On the other hand, for

$$\underline{a}(x,t) := \varphi(t), \qquad x\in\overline{\Omega},\ t\geq 0,$$

with $\varphi \in C^1([0,\infty))$ denoting the solution of

$$\begin{cases} \varphi'(t) = -c_1 K e^{-\gamma t}\varphi(t), & t > 0, \\ \varphi(0) = \varphi_0 := \inf_{y\in\Omega}\left\{u_0(y)e^{-v_0(y)}\right\}, \end{cases} \tag{3.25}$$

we have

$$\begin{aligned} \underline{a}_t - e^{-v(x,t)}\nabla\cdot(e^{v(x,t)}\nabla\underline{a}) + c_1 K e^{-\gamma t}\underline{a} \\ &= \varphi'(t) + c_1 K e^{-\gamma t}\varphi(t) \\ &= 0 \qquad \text{for all } x\in\Omega \text{ and } t>0, \end{aligned}$$

so that since clearly $\frac{\partial a}{\partial \nu} = 0$ on $\partial\Omega\times(0,\infty)$ and

$$\underline{a}(x,0) = \varphi_0 = \inf_{y\in\Omega} a(y,0) \le a(x,0) \qquad \text{for all } x\in\Omega,$$

from the comparison principle we conclude that $a \ge \underline{a}$ in $\Omega\times(0,\infty)$ and hence

$$u(x,t) = a(x,t)e^{v(x,t)} \ge a(x,t) \ge \varphi(t) \qquad \text{for all } x\in\Omega \text{ and } t>0. \tag{3.26}$$

Since an explicit integration of (3.25) shows that

$$\begin{aligned} \varphi(t) &= \varphi_0 \cdot \exp\left\{ - c_1 K \int_0^t e^{-\gamma s} ds \right\} \\ &= \varphi_0 \cdot \exp\left\{ - \frac{c_1 K}{\gamma}\cdot(1-e^{-\gamma t}) \right\} \\ &\ge \varphi_0 e^{-\frac{c_1 K}{\gamma}} \qquad \text{for all } t>0, \end{aligned}$$

from (3.26) we readily obtain (3.22) by choosing $C := \frac{c_1}{\gamma}$. □

The first of our main results has thus essentially been established already:

Proof of Theorem 1.1. As a consequence of (1.4) and Lemma 3.5, there exists $c_1 = c_1(\beta,\Omega)$ such that if (1.3) holds, then

$$u(x,t) \ge \inf_{y\in\Omega}\left\{u_0(y)e^{-v_0(y)}\right\}\cdot e^{-c_1 K} \qquad \text{for all } x\in\Omega \text{ and } t>0,$$

where again $K := \|w_0\|_{L^2(\Omega)} + \|z_0\|_{L^\infty(\Omega)}$. Since

$$u_0(y)e^{-v_0(y)} \ge u_0(y)e^{-\|v_0\|_{L^\infty(\Omega)}} \qquad \text{for all } y\in\Omega,$$

this entails that for any such (u_0,v_0,w_0,z_0) we have

$$u(x,t) \ge \left\{ \inf_{y\in\Omega} u_0(y) \right\}\cdot e^{-\|v_0\|_{L^\infty(\Omega)} - c_1 K} \qquad \text{for all } x\in\Omega \text{ and } t>0,$$

and thereby establishes (1.5) with $C := c_1$. □

The announced consequence concerned with uninfected tumor cell populations persistently exceeding prescribed levels can thereby been drawn quite immediately:

PROOF of Corollary 1.2, In line with Theorem 1.1, given $\beta \in (0,1)$ and (v_0, w_0, z_0) fulfilling (1.3), we may choose $c_1 = c_1(\beta, \Omega, v_0, w_0, z_0) > 0$ with the property that whenever u_0 satisfies (1.3), we have

$$u(x,t) \geq c_1 \cdot \inf_{y \in \Omega} u_0(y) \qquad \text{for all } x \in \Omega \text{ and } t > 0. \tag{3.27}$$

Thus, if for fixed $M > 0$ we let

$$c_2 \equiv c_2(\beta, \Omega, v_0, w_0, z_0, M) := c_1 M,$$

then for any u_0 fulfilling (1.3) as well as $u_0 \geq c_2$ we infer from (3.27) that indeed (1.7) is valid, and that hence the claim holds with $C := c_2$. □

4 Universal asymptotic upper bounds for $\inf_\Omega u$ when $\beta > 1$.

Finally, the claimed statement on the eventual occurrence of smallness in the population of uninfected cancer cells can be derived by a contradiction-based argument relying on the L^1 boundedness information entailed by Lemma 2.3.

PROOF of Proposition 1.3. Assuming (1.9) not to be true, we could find $M > \frac{1}{\beta-1}$ and $t_0 > 0$ such that

$$u(x,t) \geq M \qquad \text{for all } x \in \Omega \text{ and } t > t_0. \tag{4.1}$$

Here since $M > \frac{1}{\beta-1}$ implies that $\beta M > M + 1$ and thus $\frac{1}{\beta} < \frac{M}{M+1}$, we can choose some $b > 0$ such that

$$\frac{1}{\beta} < b < \frac{M}{M+1}, \tag{4.2}$$

and keeping this parameter fixed, we let

$$y(t) := \int_\Omega w(\cdot,t) + b \int_\Omega z(\cdot,t), \qquad t \geq t_0.$$

Then

$$y(t_0) > 0 \tag{4.3}$$

by positivity of $w(\cdot,t_0)$ and $z(\cdot,t_0)$, as asserted by Lemma 2.1, and apart from that, once more according to (1.2),

$$\begin{aligned} y'(t) &= \Big\{ -\int_\Omega w + \int_\Omega uz \Big\} + b \cdot \Big\{ -\int_\Omega z - \int_\Omega uz + \beta \int_\Omega w \Big\} \\ &= (b\beta - 1) \int_\Omega w + (1-b) \int_\Omega uz - b \int_\Omega z \qquad \text{for all } t > t_0. \end{aligned} \tag{4.4}$$

Here since (4.2) particularly ensures that $1 - b > 0$, we may use (4.1) to estimate

$$(1-b) \int_\Omega uz \geq (1-b) M \int_\Omega z \qquad \text{for all } t > t_0,$$

so that (4.4) implies that

$$y'(t) \geq (b\beta - 1) \int_\Omega w + \Big\{(1-b)M - b\Big\} \cdot \int_\Omega z \qquad \text{for all } t > t_0.$$

Using that $b\beta - 1 > 0$ by the first inequality in (4.2), and that $(1-b)M - b > M - (M+1)b > 0$ due to the second restriction therein, we may recall the definition of y to estimate

$$\begin{aligned} y'(t) &\geq (b\beta - 1) \int_\Omega w + \frac{(1-b)M - b}{b} \cdot b \int_\Omega z \\ &\geq c_1 y(t) \qquad \text{for all } t > t_0 \end{aligned}$$

with $c_1 := \min\{b\beta - 1\,,\, \frac{(1-b)M-b}{b}\} > 0$. In view of (4.3), an integration would thus show that

$$y(t) \geq y(t_0) e^{c_1(t-t_0)} \to +\infty \qquad \text{as } t \to \infty$$

and thereby contradict the outcome of Lemma 2.3, hence revealing that our assumption in fact must have been false. □

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