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Multiscale Modelling of Cancer Response to Oncolytic Viral Therapy

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Abstract

Oncolytic viruses (OV) are viruses that can replicate selectively within cancer cells and destroy them. While the past few decades have seen significant progress related to the use of these viruses in clinical contexts, the success of oncolytic therapies is dampened by the complex spatial tumour-OV interactions. In this work, we present a novel multiscale moving boundary modelling for the tumour-OV interactions, which is based on coupled systems of partial differential equations both at macro-scale (tissue-scale) and at micro-scale (cell-scale) that are connected through a double feedback link. At the macro-scale, we account for the coupled dynamics of uninfected cancer cells, OV-infected cancer cells, extracellular matrix (ECM) and oncolytic viruses. At the same time, at the micro scale, we focus on essential dynamics of urokinase plasminogen activator (uPA) system which is one of the important proteolytic systems responsible for the degradation of the ECM, with notable influence in cancer invasion. While sourced by the cancer cells that arrive during their macro-dynamics within the outer proliferating rim of the tumour, the uPA micro-dynamics is crucial in determining the movement of the macro-scale tumour boundary (both in terms of direction and displacement magnitude). In this investigation, we consider three scenarios for the macro-scale tumour-OV interactions. While assuming the usual context of reaction-diffusion-taxis coupled PDEs, the three macro-dynamics scenarios gradually explore the influence of the ECM taxis over the tumour - OV interaction, in the form of haptotaxis of both uninfected and infected cells populations as well as the indirect ECM taxis for the oncolytic virus. Finally, the complex tumour-OV interactions is investigated numerically through the development a new multiscale moving boundary computational framework. While further investigation is needed to validate the findings of our modelling, for the parameter regimes that we considered, our numerical simulations indicate that the viral therapy leads to control and decrease of the overall cancer expansion and in certain cases this can result even in the elimination of the tumour.

Keywords: multiscale modelling, cancer modelling, tumour – oncolytic virus interactions

1. Introduction

Oncolytic virotherapy (based on either naturally-occurring or genetically-engineered viruses) is a promising therapeutic approach for cancer treatment [1]. However, despite the fact that multiple oncolytic viruses are currently under clinical development [1], this type of therapy still has some limitations in terms of efficacy (as observed in various clinical trials) [2]. This relatively modest oncolytic efficacy is not only the result of premature virus clearance due to circulating antibodies and various immune cells [3], but also the result of physical barriers inside tumours (e.g., interstitial fluid pressure, extracellular matrix (ECM) deposits, or tight inter-cellular junctions) [4, 5]. To improve the intra-tumoural spread of oncolytic viruses, different experimental and clinical approaches are currently being considered: from modifications of the immune response to favour virus replication and tumour lysis [5], to modifications of the physical barriers (e.g., via ECM degradation) to improve virus spread [6].

In this study we consider a mathematical modelling and computational approach to help us improve our understanding of the physical barriers that limit virus spread. The use of mathematical models to understand the temporal and spatio-temporal dynamics of viruses (including oncolytic viruses) has seen great developments over the last three decades [7, 8, 9, 10, 11, 12, 13]. While the majority of these models focused on the temporal dynamics of oncolytic viruses (mainly due to the availability of temporal data) [14, 15, 16, 17, 18, 19, 20, 21, 22, 23], more recent advances in tumour imaging generated data on the spatial spread of tumours and viruses, which then led to the development of different mathematical models investigating the spatial spread of these viruses [21, 23, 24, 25, 26, 27].

All these temporal and spatio-temporal models for oncolytic virus therapies usually focus on one single spatial or temporal scale. In this context potential insights from the wide range of single-scale spatio-temporal modelling approaches for cancer invasion (such as those proposed in [28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40] **and, in particular, those involving the theory of mixtures proposed in [41, 42, 43]**) become increasingly relevant to this area, as highlighted and explored by a number

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of recent works [44, 45, 46, 47]. Nevertheless, since the process of cancer development is a complex phenomenon that involves interlinked phenomena that occur at different scales, it is important to capture these multiscale aspects also during the tumour-oncolytic virus interactions. To that end, the multiscale modelling of cancer invasion introduced over the past decade in the mathematical literature [48, 49, 50, 51, 52] paved the way for exploring the tumour-OV interaction in a multiscale fashion. However, to our knowledge, there are not many multi-scale mathematical models for the oncolytic viral therapies and tumour-viral interactions, with [53] being the only reference that we could find in the literature.

In this paper we will introduce a novel multiscale modelling framework for the tumour-OV interaction in which the macroscopic (tissue-scale) dynamics of the cancer and oncolytic virus densities will be connected via a double feedback loop to the microscopic (cell-scale) proteolytic dynamics of the urokinase plasminogen activator system (uPA) that takes place at the invasive edge of the tumour.

2. Multiscale Hypothesis and Settings: the Novel Two-Scale Moving Boundary Modelling Approach for tumour-OV interactions

Building on the two-scale moving boundary framework introduced first by Trucu et al. in [51] and later explored in [52] in the context of the uPA System, in this work we address the genuinely multiscale nature of tumour-OV interaction through a new multiscale modelling approach. Specifically, the tissue-scale (macro-scale) in tumour-OV interaction is here coupled with the cell-scale (micro-scale) tumour invasive edge molecular dynamics of the uPA System. Therefore, before exploring further their crucial cross-talk, we distinguish here the two levels of dynamics, namely *macro-scale* and *micro-scale*, which at this stage can be generally described mathematically as follows.

On one hand, at macro-scale, at any spatio-temporal macro-node (x, t) , a part of the cancer cells population $c(x, t)$ becomes dynamically infected by an incoming oncolytic virus $v(x, t)$, giving rise to an infected cancer cells population $i(x, t)$, causing these to die, and this way to be eliminated from the total tumour mass $(c+i)(x, t)$. As this interaction does occur in the presence of the surrounding ECM density $u(x, t)$ and, per unit time, this is governed by both random motility and by various forms of taxis of both uninfected and infected as well as of the oncolytic virus towards ECM gradients. Thus, denoting for the moment with $\mathcal{T}$ the resulting *4D-reaction-diffusion-taxis* differential operator of order 2, we obtain that the macro-dynamics can be written as

$$\mathcal{T}(c, i, u, v)^T = \mathbf{0} \quad (1)$$

where $\mathcal{T}$ will be specified in detail in the next section.

On the other hand, at micro-scale, the proteolytic activity of the uPA System occurring at the invasive edge of the

tumour exercises a cross-tumour boundary local enzymatic transport within a cell-scale neighborhood of the interface of the expanding tumour $\Omega(t)$, crucially contributing towards its dynamics changes in morphology with respect to time. Therefore, at any spatio-temporal micro-node (y, τ) , considering the three components of the uPA System, namely the urokinase plasminogen activator (uPA) $a(y, \tau)$, plasminogen activator inhibitor (PAI-1) $p(y, \tau)$ and plasmin $m(y, \tau)$, per unit time their dynamics is driven by random molecular motility as well as their production and natural decay. Therefore, we can express this in the form of a coupled system of reaction diffusion equations. Hence, similar to the macro-scale, denoting here the resulting *3D-reaction-diffusion* operator by $\mathcal{Z}$, the micro-dynamics can therefore be expressed as

$$\mathcal{Z}(a, p, m)^T = \mathbf{0} \quad (2)$$

where the form of the differential operator $\mathcal{Z}$ will be made explicit in the next section.

Following a similar two scale approach as in [51, 52], within a maximal tissue-scale region Y , the macro-scale tumour-OV dynamics (1) occurring on the growing tumour support $\Omega(t) \subset Y$ is directly linked through a “*macro-micro cross-talk*” to the uPA micro-dynamics (2) that takes place on a cell-scale neighbourhood of the tumour boundary $\partial\Omega(t)$, as illustrated in schematic Fig. 1. To that end, the cell-scale neighbourhood of $\partial\Omega(t)$ that was introduced in [51] and is given by a covering bundle of overlapping (*half-way*) micro-domains $\{\epsilon Y\}_{\epsilon Y \in \mathcal{P}(t)}$ enables the decoupling of the micro-dynamics in a bundle of micro-processes taking place on each $\epsilon Y \in \mathcal{P}(t)$, and as a consequence, this *macro-micro cross-talk* is realised through a double-feedback loop consisting of both *top-down* and *bottom-up* links between the macro-dynamics on $\Omega(t)$ and the uPA micro-dynamics occurring on each $\epsilon Y \in \mathcal{P}(t)$. While we postpone the detailed description of the double feedback loop until the next section, briefly, this is structured as follows.

On one hand, the *top-down* link between macro-scale and micro-scale explores the naturally arising source for the uPA and the non-local behaviour of PAI-1 removal, which are enabled by the cancer cells and ECM micro-environment within the neighbourhood of the tumour outer proliferating rim that secretes them. Thus, on a time perspective $[t_0, t_0 + \Delta t]$ this arises as the direct contribution of the macroscopic densities of cancer cells c and i as well as of the ECM u , and in brief, at any spatio-temporal microscopic node $(\tau, y) \in [0, \Delta t] \times \epsilon Y$, these can be mathematically expressed via non-local terms of the form

$$f_{uPA}^{\epsilon Y}(\tau, y) = \frac{\int K_1(c(s, t_0 + \tau), i(s, t_0 + \tau), s - y) ds}{\lambda(\mathbf{B}(y, \delta) \cap \text{supp}\{c+i\})} \quad (3)$$

and

$$f_{PAI-1}^{\epsilon Y}(\tau, y) = \frac{\int K_2(u(s, t_0 + \tau), s - y) ds}{\lambda(\mathbf{B}(y, \delta))}, \quad (4)$$

where λ is the Lebesgue measure on $\mathbb{R}^2$ and the mappings $\mathbb{R} \ni z \mapsto K_1(\cdot, \cdot, z) \in \mathbb{R}$ and $\mathbb{R} \ni z \mapsto K_2(\cdot, z) \in \mathbb{R}$ are compactly supported radially symmetric kernels that quantify the contribution of the involved macroscopic densities with respect to their spatial distribution and whose choice will be discussed in Section 4. In the presence of these non-local behaviours induce from the macro-scale, the uPA System exercise its spatio-temporal micro-dynamics briefly outlined above and detailed in Section 4.

Finally, the *bottom up* link is conveyed by the key contribution that the micro-dynamics has in determining the characteristics of macro-scale tumour boundary movement. The tumour boundary relocation is caused by the local invasion of the peritumoural region whose extent and orientation are dictated by the pattern of degradation of the ECM by the uPA System acting at micro-scale within the outer part of the cell-scale neighbourhood of the tumour boundary (which is given here by the union of all the micro-domains $\epsilon Y \in \mathcal{P}(t)$). In its turn, the pattern of ECM degradation is dictated by the regions of significant transport of proteolytic enzymes within each micro-domain ϵY . Proceeding as in [51], these regions are determined here by the furthest away part of the level sets of significant proteolytic enzymes within each ϵY with respect to the tumour boundary $\partial\Omega(t) \cap \epsilon Y$, whose cumulative revolving orientation leads to the establishment of the characteristics of the tumour boundary movement

$$\begin{aligned} s : \partial\Omega(t) &\rightarrow \mathbf{S}^1 \times (0, \infty), \\ \text{given by} \quad s(z) &:= (\nu(z), \xi(z)), \quad \forall z \in \partial\Omega(t), \end{aligned} \quad (5)$$

with $\mathbf{S}^1$ being the usual unit sphere in $\mathbb{R}^2$, and $\nu(\cdot)$ and $\xi(\cdot)$ representing the direction of movement and displacement magnitude, respectively. Provided that sufficient degradation but not complete destruction of the ECM has been exercised by the micro-scale uPA processes, the boundary will be relocated in the direction dictated by the boundary movement law $s(\cdot)$ introduced above, and the macro-dynamics is continued on the newly obtained domain.

3. Macroscopic Modelling Scenarios for the Virus-Tumour Interaction

In the following we describe in detail the various macro-scale components and their dynamics relations, which were compactly represented by the macroscopic operator equation (1) introduced in the previous section. These components are: the density of uninfected cancer cells $c(x, t)$, the density of infected cancer cells $i(x, t)$, the density of the extracellular matrix $u(x, t)$, and the density of the oncolytic virus particles $v(x, t)$.

Uninfected Cancer Cells: $c(x, t)$. We assume that the cancer cells density changes due to random cell movement (with D_c the random motility coefficient) and to

Figure 1: *Schematic of the multiscale modelling approach to tumour-virus interaction*

directed haptotactic movement towards higher ECM gradients (with η_c the haptotactic coefficient). Moreover, cancer cells can proliferate logistically at a rate μ_1 [54, 55], and can decay due to virus infection at a rate ρ . These assumptions can be translated into the following equation:

$$\frac{\partial c}{\partial t} = D_c \Delta c - \eta_c \nabla \cdot (c \nabla u) + \mu_1 c(1 - c) - \rho c v. \quad (6)$$

Infected Cancer Cells: $i(x, t)$. We assume that also the infected cancer cells can move randomly (with D_i the random motility coefficient). As discussed above, these cells are infected at a rate ρ by the oncolytic virus. Finally, these infected cells die at a rate δ_i . These assumptions are described by the following equation:

$$\frac{\partial i}{\partial t} = D_i \Delta i + \rho c v - \delta_i i. \quad (7)$$

Extracellular Matrix (ECM): $u(x, t)$. We assume that the ECM (and its components) does not move, and thus we ignore any migration and diffusion terms. However, since ECM is continuously remodelled by cells in the environment [56], we describe this remodelling process as the difference between a logistic growth term (describing the deposition of ECM components – in the presence of cancer – at a rate μ_2) and a degradation term (with α_c the rate of ECM degradation by uninfected cancer cells, and α_i the rate of ECM degradation by infected cancer cells.) These assumptions are described by the following equation:

$$\frac{\partial u}{\partial t} = -u(\alpha_c c + \alpha_i i) + \mu_2 u(1 - u - c - i). \quad (8)$$

The growth in equation (8) describes the logistic remodelling of the ECM, which depends on the presence of all variables in the system. Similar terms have been considered in [36, 39, 40, 51, 52]. In contrast, the growth in equation (6) models cancer proliferation in the presence of nutrients and its slow down when nutrients are consumed, as justified by the shape of the logistic term [54, 55].

Oncolytic Virus: $v(x, t)$. Assume that the oncolytic virus can move randomly through the environment, with D_v the random motility coefficient. The level of virus particles increases due to the burst (at a rate b) of the infected tumour cells, which release the new virions in the environment. The reduction in the number of free virus particles is the result of the natural virions' death rate δ_v , and the trapping of these virus particles into the cancer cells at a rate ρ . Therefore, the evolution of the density of virus particles is described by the equation

$$\frac{\partial v}{\partial t} = D_v \Delta v + bi - \rho cv - \delta_v v. \quad (9)$$

Remark. Note that for simplicity, in the above equations (6)-(8), all variables have been rescaled by their maximum values (i.e., the carrying capacities of the tumour cells and the extracellular matrix).

Therefore, accounting for at the above macro-scale modelling considerations, the macro-dynamics that we have obtained so far is as follows:

Macro-dynamics scenario 1. The new macro-scale scenario of the multiscale modelling approach for the tumour-OV interaction is given by the following system:

$$\begin{cases} \frac{\partial c}{\partial t} = D_c \Delta c - \eta_c \nabla \cdot (c \nabla u) + \mu_1 c(1 - c) - \rho cv, \\ \frac{\partial i}{\partial t} = D_i \Delta i + \rho cv - \delta_i i, \\ \frac{\partial u}{\partial t} = -u(\alpha_c c + \alpha_i i) + \mu_2 u(1 - u - c - i), \\ \frac{\partial v}{\partial t} = D_v \Delta v + bi - \rho cv - \delta_v v. \end{cases} \quad (10)$$

However, expanding now the modelling perspective by accounting within the macro-scale spatial dynamics of the infected cell population not only on its random movement (approximated here by diffusion) but also on its haptotactic migration against ECM gradients, equation (7) is therefore evolved into:

$$\frac{\partial i}{\partial t} = D_i \Delta i - \eta_i \nabla \cdot (i \nabla u) + \rho cv - \delta_i i. \quad (11)$$

This leads us to a second scenario for the macro-dynamics which is summarised as follows:

Macro-dynamics scenario 2. In the presence of haptotactic behaviour for the infected cell population, the macro-scale modelling scenario for tumour-OV interaction is therefore extended and is given now by the system:

$$\begin{cases} \frac{\partial c}{\partial t} = D_c \Delta c - \eta_c \nabla \cdot (c \nabla u) + \mu_1 c(1 - c) - \rho cv, \\ \frac{\partial i}{\partial t} = D_i \Delta i - \eta_i \nabla \cdot (i \nabla u) + \rho cv - \delta_i i, \\ \frac{\partial u}{\partial t} = -u(\alpha_c c + \alpha_i i) + \mu_2 u(1 - u - c - i), \\ \frac{\partial v}{\partial t} = D_v \Delta v + bi - \rho cv - \delta_v v. \end{cases} \quad (12)$$

Finally, we note that a major obstacle that creates difficulties in having a successful viral therapy is virus motility

blockage exercised by ECM components. Recent efforts to minimising virus size makes it possible for the virus particles to move through ECM components [4]. While knowing that though viruses do not have an autonomous motility, the penetration of the ECM is done via other factors, such as matrix degrading enzymes as detailed in [57]. Therefore, for the dynamics of the virus population, in addition to the usual consideration of virus diffusion, assumed by other authors [23, 25, 26, 21, 4], we will also consider here the ECM-OV interactions. To that end, as discussed in [4], while ECM acts usually as a barrier against OV motility, its regions of lower levels of **density** provide opportunities for OV to penetrate through its components and potentially interact with a larger cancer cell-surface cumulated areas, this way gaining further opportunities to infect the nearby cancer cells. **This leads to an ECM-OV taxis behaviour that affects the random motility of the virus, which mathematically can be incorporated into equation (9) leading to the following reaction-advection-diffusion equation:**

$$\frac{\partial v}{\partial t} = D_v \Delta v - \eta_v \nabla \cdot (v \nabla u) + bi - \rho cv - \delta_v v, \quad (13)$$

where η_v is the ECM-OV-taxis rate. This brings us to the last and most extended macro-dynamics scenario that we consider in this paper, namely:

Macro-dynamics scenario 3. Accounting also upon the presence of ECM-OV taxis behaviour included in (13), the macro-dynamics component of our multiscale approach to tumour-OV interaction is therefore given by:

$$\begin{cases} \frac{\partial c}{\partial t} = D_c \Delta c - \eta_c \nabla \cdot (c \nabla u) + \mu_1 c(1 - c) - \rho cv, \\ \frac{\partial i}{\partial t} = D_i \Delta i - \eta_i \nabla \cdot (i \nabla u) + \rho cv - \delta_i i, \\ \frac{\partial u}{\partial t} = -u(\alpha_c c + \alpha_i i) + \mu_2 u(1 - u - c - i), \\ \frac{\partial v}{\partial t} = D_v \Delta v - \eta_v \nabla \cdot (v \nabla u) + bi - \rho cv - \delta_v v. \end{cases} \quad (14)$$

Remark. Note that since the focus of the model is the interaction between virus and cancer cells in a multi-scale moving boundary context, for simplicity we assume that the outside environment is represented only by the ECM. Therefore, we ignore any other types of cells in the environment: healthy cells, immune cells, etc.

4. The Microscopic Proteolytic Dynamics and the Macro-Micro Double Feedback Loop

As briefly outlined in Section 2, both uninfected and infected tumour cells arriving during their dynamics within the outer proliferating rim of the tumour are able to secrete uPA. Thus, at any time instance t_0 , within any micro-domain $\epsilon Y \in \mathcal{P}(t_0)$, a source of uPA arises this way at any micro-point $y \in \epsilon Y \cap \Omega(t_0)$ as a collective contribution of both infected and uninfected cells from the outer proliferating rim that arrive within a $\delta > 0$ distance from

y . Therefore, assuming, no spatial discrimination between the cells secreting the uPA within $\mathbf{B}(y, \delta) \cap \Omega(t_0)$, we obtain that the spatially radial symmetric diffusion kernel K_1 appearing in (3) is constant with respect to the spatial variable, this being given by

$$K_1(c(\cdot, \cdot), i(\cdot, \cdot), z) = [\lambda_c c(\cdot, \cdot) + \lambda_i i(\cdot, \cdot)] \chi_{\mathbf{B}(y, \delta) \cap \Omega(t_0)}(\cdot). \quad (15)$$

where $\chi_{\mathbf{B}(y, \delta) \cap \Omega(t_0)}(\cdot)$ is the usual characteristic function for the set $\mathbf{B}(y, \delta) \cap \Omega(t_0)$. Thus, we have that the micro-scale uPA source at a spatio-temporal micro-node $(y, \tau) \in (\epsilon Y \cap \Omega(t_0)) \times [0, \Delta t]$ is given by

$$f_{uPA}^{\epsilon Y}(y, \tau) = \frac{\int_{\mathbf{B}(y, \delta) \cap \text{supp}\{c+i\}} (\lambda_c c(s, t_0 + \tau) + \lambda_i i(s, t_0 + \tau)) ds}{\lambda(\mathbf{B}(y, \delta) \cap \text{supp}\{c+i\})} \quad (16)$$

and is zero at any other micro location $y \in \epsilon Y \setminus \Omega(t_0)$. Once secreted, the uPA exercises a local cross-interface transport process, activating plasmin from its inactive state, plasminogen, which is freely available within the ECM. In turn, once activated, plasmin degrades various ECM components.

However, the plasminogen activation process is accompanied also by inhibitors, a notably important one being PAI-1, who binds to the activated uPA and manage to inhibit this. Produced through the activation of plasmin, besides natural decay and binding to uPA, PAI-1 is removed also through binding to the surrounding ECM. Thus, proceeding similar to the case of uPA source, at each spatio-temporal micro-node $(y, \tau) \in \epsilon Y \times [0, \Delta t]$ this loss of PAI-1 through indiscriminate ECM binding can be quantified through (4), for the following projection kernel K_2 that is constant with respect to space, namely

$$K_2(u(\cdot, \cdot), z) = u(\cdot, \cdot). \quad (17)$$

which gives

$$f_{PAI-1}^{\epsilon Y}(y, \tau) = \frac{\int_{\mathbf{B}(y, \delta)} u(s, t_0 + \tau) ds}{\lambda(\mathbf{B}(y, \delta))}. \quad (18)$$

Thus, denoting the micro-scale densities of uPA by $a(y, \tau)$, PAI-1 by $p(y, \tau)$, and plasmin by $m(y, t)$, and proceeding as in [58], in brief, the dynamics of the tumour invasive edge proteolytic micro-processes can be described as follows. Per unit time, the uPA molecular population $a(\cdot, \cdot)$ changes through diffusion (with a random motility coefficient D_a) while being produced (at a rate ψ_{12}) and bound by cancer cells' uPA receptors (uPAR) (at a rate ψ_{13}), as well as being inhibited by PAI-1 density $p(\cdot, \cdot)$ (at a rate ψ_{11}). Therefore, its dynamics is given by

$$\frac{\partial a}{\partial \tau} = \underbrace{D_a \Delta a}_{\text{diffusion}} - \underbrace{\psi_{11} a p}_{\text{uPA/PAI-1}} + \underbrace{(\psi_{12} - \psi_{13} u)}_{\text{production uPA/uPAR}} f_{uPA}^{\epsilon Y}(y, \tau) \quad (19)$$

Further, the inhibitor PAI-1 density change per unit time is triggered by local diffusion (with a diffusion coefficient

D_p), production through plasmin activation (at a rate ψ_{23}) as well as removal from the system through binding to uPA (at a rate ψ_{21}) and to surrounding ECM (at a rate ψ_{22}). Thus, PAI-1 micro-dynamics is given by

$$\frac{\partial p}{\partial \tau} = \underbrace{D_p \Delta p}_{\text{diffusion}} - \underbrace{\psi_{21} a p}_{\text{uPA/PAI-1}} - \underbrace{\psi_{22} p f_{PAI-1}^{\epsilon Y}(y, \tau)}_{\text{PAI-1/ECM}} + \underbrace{\psi_{23} m}_{\text{production}}. \quad (20)$$

Finally, the change in plasmin density per unit time is due to local diffusion (with a diffusion coefficient D_m), natural degradation (at a rate ψ_{33}) and production due to both direct plasminogen activation (through uPA binding to uPAR at a rate ψ_{31}) and as well as binding of PAI-1 to neighbouring ECM (at a rate ψ_{32}) that indirectly enable further opportunities for plasmin activation. Thus, plasmin's micro-dynamics is given by

$$\frac{\partial m}{\partial \tau} = \underbrace{D_m \Delta m}_{\text{diffusion}} + \underbrace{\psi_{31} a f_{uPA}^{\epsilon Y}(y, \tau)}_{\text{uPA/uPAR}} + \underbrace{\psi_{32} p f_{PAI-1}^{\epsilon Y}(y, \tau)}_{\text{PAI-1/ECM}} - \underbrace{\psi_{33} m}_{\text{decay}}. \quad (21)$$

As introduced and detailed in [51], on each boundary micro-domain ϵY , it is the pattern of significant ECM degradation (caused by the advancing distribution of plasmin) that will dictate the relocation of the tumour boundary within the peritumoural region. Indeed, the micro-scale proteolytic dynamics determines directly the direction of movement and displacement magnitude that is briefly summarised in (5) and is represented back at the macro-scale through the movement of the *micro-domains mid points* $\{x_{\epsilon Y}^*\}_{\epsilon Y \in \mathcal{P}(t_0)}$, as detailed in [51, 52]. However, the boundary point $x_{\epsilon Y}^*$ will exercise the movement prescribed by $s(x_{\epsilon Y}^*)$ provided that the extent of degradation of ECM, which is explored here through the *outer degradation measure* outlined in [51, 52],

$$q^* : \Sigma \left(\bigcup_{\epsilon Y \in \mathcal{P}(t_0)} \right) \rightarrow [0, \infty]$$

given by

$$q^*(G) := \begin{cases} \frac{\int_{G \setminus \Omega(t_0)} m(y, \Delta t) dy}{\int_G m(y, \Delta t) dy}, & \lambda(G) > 0, \\ 0, & \text{otherwise,} \end{cases} \quad (22)$$

is significant but not complete. Therefore, the representative mid point will exercise the movement prescribed by $s(x_{\epsilon Y}^*)$ provided that

$$q^*(\epsilon Y) > \omega(\epsilon Y, \beta) \quad (23)$$

where $\omega(\epsilon Y, \beta)$ is a local tissue threshold and the parameter $\beta \in (0, 1)$ explore the optimal conditions for movement, see Appendix B. Once the movement has been exercised, the macro-scale tumour domain $\Omega(t_0)$ progresses to its new shape $\Omega(t_0 + \Delta t)$, where the multiscale dynamics is continued with the next macro-micro stage.

Figure 2: *Initial Conditions: (a) uninfected cancer cells density; (b) ECM density; (c) OV density (one initial dose) and (d) OV density (five initial doses). The white line indicates the boundary of the total tumour cells (uninfected & infected densities).*

5. Multiscale Numerical Simulation and Results

The computational approach developed in this work extends the multiscale numerical framework first introduced in [51] and later applied in [52]. **The novel computational part of this study is the incorporation of the viral component into the macroscale part of the multiscale framework presented in [51].** This combines a finite difference approach at macro-scale with a finite element method at micro-scale. While the finite difference approach at macro-scale involves central differences and midpoint approximations (as detailed in Appendix C), the finite element at micro-scale involves bilinear shape functions on a square mesh on each ϵY .

In brief, we consider that the macro-scale dynamics of the progressing tumour $\Omega(t)$ takes place within a maximal tissue domain $Y = [0, 8] \times [0, 8]$, which we discretise by uniformly spatial mesh of a size $\Delta x = \Delta y = h = 0.03125$. We used a second order midpoint rule for approximating the diffusion and haptotactic terms (for both cancer cells) in all macro-dynamics modelling scenarios (10),(12),(14), as well as for the ECM-OV taxis term in (14), and we proceed with a trapezoidal predictor-corrector for time marching at macro-scale in all cases. **The implicit trapezoidal corrector ensures the stability of the macroscopic discretisation.** Further, the integral terms $f_{uPA}^{\epsilon Y}(\tau, y)$ and $f_{PAI-1}^{\epsilon Y}(\tau, y)$ (appearing within the *top-down macro-micro* link) contributing towards the sources and removal terms within the uPA System micro-dynamics (19)-(21) are calculated using direct formulas at overlapping macro-micro spatial nodes and via interpolation involving barycentric coordinates at all other off-*macro grid* micro-spatial points $y \in \epsilon Y$. Finally, in the presence of these terms induced from the macroscale, the micro-dynamics is solved via fi-

nite element with bilinear shape functions on a square mesh with trapezoidal corrector for time marching. The direction and displacement magnitude obtained in each boundary micro-domain $\epsilon Y \in \mathcal{P}(t_0)$ in conjunction with the extent of ECM degradation determine the movement of the tumour boundary at macro-scale, which is recorded on the macro-scale uniform grid where the dynamics is then continued for the next time interval $[t_0 + \Delta t, t_0 + 2\Delta t]$ with the next macro-micro stage. **This numerical approach was implemented by ourselves, as detailed in [51].**

5.1. Macro-Dynamics Initial Conditions.

The multiscale dynamics is started with the following initial conditions on Y for each of the three macro-scale scenarios, namely:

- *uninfected cancer initial conditions:*

$$c(x, 0) = \frac{\left(\exp\left(-\frac{\|x - (4, 4)\|_2^2}{\sqrt{\Delta x \Delta y}}\right) - \exp(-28.125) \right) \theta_1(x)}{2},$$

where $\theta_1(x) := \chi_{B((4, 4), 0.5 - \gamma)} * \psi_\gamma$, with the mollifier ψ_γ enabling a smooth transition to zero after 0.5 radius, as shown Fig. 2(a).

- *infected cancer initial conditions:*

$$i(x, 0) = 0.$$

- *extracellular matrix initial conditions:*

$$u(x, 0) = \frac{1 + 0.3 \sin(4\pi \|x\|_2) + \sin(4\pi \|(4, 0) - x\|_2)}{2}$$

as shown in Fig. 2(b);

- *oncolytic virus initial conditions:*

$$v(x, 0) = \frac{\left(\exp\left(-\frac{\|x - (4.5, 4.5)\|_2^2}{\sqrt{\Delta x \Delta y}}\right) - \exp(-28.125) \right) \theta_2(x)}{2}$$

where $\theta_2(x) := \chi_{B((4.5, 4.5), 0.5 - \gamma)} * \psi_\gamma$, as shown in Fig. 2(c).

However, to explore the impact of multiple virus doses, for the results in Figure 10, we use the *initial condition with five doses of oncolytic virus* that is shown in Figure 2(d) and is given by

$$v(x, 0) = \sum_{i, j \in \{-1, 1\}} 0.5 \left(\exp\left(-\frac{\|x - (4 + 0.5i, 4 + 0.5j)\|_2^2}{\sqrt{\Delta x \Delta y}}\right) - \exp(-28.125) \right) \theta_{i, j}(x) + 0.5 \left(\exp\left(-\frac{\|x - (4, 4)\|_2^2}{\sqrt{\Delta x \Delta y}}\right) - \exp(-28.125) \right) \theta_1(x),$$

where we have that $\theta_{i, j}(x) := \chi_{B((4 + 0.5i, 4 + 0.5j), 0.5 - \gamma)} * \psi_\gamma$, $\forall i, j \in \{-1, 1\}$.

Figure 3: Multi-scale simulation results for macro-dynamics scenario (10) at four macro-micro stages (1,50,100, and 150) for the baseline parameter values from Table A.1, showing: a. virus density; b. infected cancer cells density; c. uninfected cancer cells density; (d) total cancer cells density; and e. ECM density.

Remark. The specific initial conditions for the oncolytic virus were chosen to simulate the effect of injecting the virus particles inside the tumour or at tumour boundary. Such approaches are often considered in experimental settings [59, 60].

5.2. Multiscale numerical results for the three macro-scale scenarios

In this section, we investigate numerically the three macroscale scenarios introduced previously. We aim to observe the cancer response to oncolytic viral therapy via tracking the macro-micro model behaviour on the maximal tissue domain Y with respect to several aspects such as:

cancer cells density, cancer boundary expansion, or cancer suppression.

For the numerical investigation of these three macroscale scenarios (10), (12), and (14), we first choose a list of baseline parameters (mainly based on the published studies in [26, 52]), and investigate the outcome of the assumptions incorporated in these three cases. Second, we investigate the effect of changing some of the parameters involved in virus dynamics and spread: the death rate of infected cancer cells (δ_i), the viral infection rate (ρ), the ECM degradation rates by uninfected cancer cells (α_c) and infected cancer cells (α_i), the virus replication rate (b), and the initial administered virus dose. Finally, based on the outcome of these results with different parameter values, we discuss the conditions that lead to improved tumour suppression.

Figure 4: Multi-scale simulation results for macro-dynamics scenario (12) at four macro-micro stages (1,50,100, and 150) for the baseline parameter values from Table A.1, showing: a. virus density; b. infected cancer cells density; c. uninfected cancer cells density; d. total cancer cells density; and e. ECM density.

Baseline Results. The following simulation results are obtained with the baseline parameter values listed in Tables A.1 (for the macroscopic component) and A.3 (for the microscopic component). In all figures shown below, the white curve represents the boundary of the total tumour (i.e., uninfected and infected cells) within the maximal tissue domain Y .

In Figures 3, 4 and 5 we present the multiscale simulations for the coupled dynamics of uninfected cancer cells (sub-panels c.), OV-infected cancer cells (row b.), extracellular matrix (ECM) (row e.) and oncolytic viruses (row a.), for the three macro-dynamics scenarios described by (10), (12) and (14), respectively. We also show (row d.) the total cancer cell density (i.e., uninfected plus infected cells). For all simulations, we start with the uninfected cancer cells density as shown in Figure 2(a), and the virus density as

shown in Figure 2(c) (where the virus is initially located on the tumour edge $\partial\Omega(t)$, namely at $(x, y) = (4.5, 4.5)$). The columns show the macroscopic evolution of the tumour-ECM-virus system at four different stages of the macro-micro interactions: stages 1, 50, 100 and 150.

We observe that in the absence of haptotactic migration against ECM gradients for both infected cells and viruses (as described by macro-dynamics scenario (10)), the virus infects mainly the areas of the tumour with lower cell densities (see stage 150 in Figures 3a. and 3c.)

If we consider haptotactic migration of virus-infected tumour cells against the ECM gradients (as described by macro-dynamics scenario (12)), we observe a large reduction in tumour size where the virus is located (see stage 150 in Figures 4a. and 4c.).

Finally, if we consider the haptotactic migration of both

Figure 5: *Multi-scale simulation results for macro-dynamics scenario (14) at four macro-micro stages (1,50,100, and 150) for the baseline parameter values from Table A.1, showing: a. virus density; b. infected cancer cells density; c. uninfected cancer cells density; d. total cancer cells density; and e. ECM density.*

virus-infected cells and virus particles towards ECM gradients (as described by macro-dynamics scenario (14)), we observe an even better reduction in tumour size which is the result of a better virus spread throughout the tumour (see stage 150 in Figures 5a. and 5c.).

The baseline tumour mass evolution across all macro-micro stages (1–150) for macro-dynamics scenarios (12) and (14) are shown in Figure 12 with blue dotted lines and compared against five relevant cases of parameter variation, as detailed in the next paragraphs.

In the following, we focus on the last two macro-dynamics scenarios, (12) and (14), and investigate the effect of changes in various model parameters related to virus dynamics and spread (parameters which can be varied experimentally to impact virus kinetics [61]). For conciseness, Figures 6-10 below will show the results obtained only at macro-micro stages 75 and 150 of the multiscale

dynamics.

Infected Cells' Death Rate. We start our investigation into the effects of different model parameters on treatment outcomes, by focusing first on the rate δ_i at which the infected cells are eliminated from the system (by the anti-viral immune response [62]). As mentioned before, we discuss the impact of this rate on macro-dynamics scenarios (12) and (14). In panels Ia. and IIa. of Figure 6 we reduce δ_i by a factor of four (i.e., to $\delta_i/4$), and we observe that the uninfected tumour cells are reduced dramatically in those areas occupied also by the oncolytic virus. This result makes sense, since the persistence of infected tumour cells gives rise to more virus particles replicating inside these cells. On the other hand, increasing δ_i by a factor of four (i.e., to $4\delta_i$) leads to a poorer elimination of tumour cells, as observed in panels Ib. and IIb. of Figure 6. However,

Figure 6: Multi-scale simulation results for macro-dynamics scenarios (12) (in panel I) and (14) (in panel II), showing two variations of the baseline infected cancer cells death rate δ_i (namely: a. $\frac{\delta_i}{4}$; and b. $4\delta_i$) at macro-micro stages: 1. stage 75; and 2. stage 150.

Figure 7: Multi-scale simulation results for macro-dynamics scenarios (12) (in panel I) and (14) (in panel II), showing two variations of the baseline viral infection rate ρ (namely: a. $\frac{\rho}{5}$; and b. 5ρ) at macro-micro stages: 1. stage 75; and 2. stage 150.

Figure 8: *Multi-scale simulation results for ECM degradation rates $\alpha_c = 0.3$ and $\alpha_i = 0.15$ for macro-dynamics scenarios(12) (in panel I) and (14) (in panel II) at two macro-micro stages: a. stage 75; and b. stage 150.*

as shown in Figure 12(1), beyond the overall tumour mass being kept under control, δ_i alone does not bring a clear influence towards suppressing the tumour, as tumour relapses to levels above the baseline occur both when we lower and when we increase the cell death rate.

Infection Rate of Tumour Cells. In the following, we examine the effect of viral infection rate (ρ) on tumour dynamics. Experimental studies have shown that increasing the rate at which the oncolytic virus infects the tumour cells (e.g., by engineering the virus particles to encode specific proteins that could temporarily suppress anti-viral immune responses) plays a key role in the development of new anti-cancer therapies [61]. To investigate this aspect, we performed various simulation tests for the macroscopic models (12) and (14), as we decreased and increased the baseline value $\rho = 79 \times 10^{-3}$ by a factor of five (to $\frac{\rho}{5}$ and 5ρ , respectively). From panels Ia. and IIa. of Figure 7, we observe that a five-fold decrease in the infection rate ρ leads to a much faster spread of the tumour cells (as described by the expanding tumour boundary), compared to the case where the infection rate is increased five fold - as shown in panels Ib. and IIb. of Figure 7. As shown in Figure 12(2)(II) with green dotted line, the five

fold increase in ρ leads to significantly better global tumour suppression with respect to the baseline or five fold decreased cases within the macro-dynamics scenario (14). A similar although weaker tumour suppression effect observed for macro-dynamics scenario (12), where a relapse occurs over the final stages of the time interval, as shown by Figure 12(2)(I).

ECM Degradation Rates. Known to be crucial within the process of cancer cells' invasion of the surrounding tissue [63, 64], the ECM is expected to play also an important role in viral therapy. Indeed, the ECM distribution within the growing tumour $\Omega(t)$ interfere with the oncolytic virus dynamics, having impeding effects upon its spread, restricting the viral duplication, and lowering the effectiveness of cytolytic. However, the degradation for the ECM provides opportunities for potentially raising the effectiveness of OV treatments by facilitating a less demanding virus passage within the tumour tissue, gaining an easier access to uninfected cancer cells sites [46]. Thus, the success or failure of the oncolytic virus distribution will depend on the ECM degradation, and this is confirmed also by our results obtained by doubling the degradation rate (with respect to the baseline) and shown in panels Ia.-b.

Figure 9: Multi-scale simulation results for macro-dynamics scenarios (12) (in panel I) and (14) (in panel II), showing two variations of baseline OV replication rate b (namely: a. $b = 0$; and b. $b = 3$) at macro-micro stages: 1. stage 75; and 2. stage 150.

and IIa.–b. of Figure 8 for the macro-dynamics (12) and (14), respectively.

As illustrated in Figure 8 an increase in degradation rate causes not only changes in the morphology of the growing tumour, but also a decay in the tumour mass, as reflected in Figure 12(3). This decay in the total tumour mass for the macro-dynamics scenario (12) is the effect of the following interacting dynamics. The increased ECM degradation causes both infected cancer and uninfected cancer cells to bias their migration haptotactically towards the emerging regions of elevated ECM levels, enabling this way a local congregation of the two cancer cell subpopulations (infected and uninfected), which mediates in its turn a higher degree of infection spread among the uninfected cancer cells, resulting this way in a decrease in tumour mass. However, as by comparing panels Ia.–b. with IIa.–b. in Figure 8, the total cell population exhibits slightly limited spread with no pronounced fingering in the macro-dynamics scenario (14) as opposed to macro-dynamics scenario (12) where the tumour develops large fingering growth. This particular behaviour within macro-dynamics (14) is due to the biased migration of both the infected and uninfected cancer cells as well as of the oncolytic virus against ECM gradients, this enabling them to congregate within the same regions, leading this way to increased levels of local tumour decay.

Viruses Replication Rate. Another factor that impacts virus kinetics is its replication rate (i.e., the number of virus particles release by an infected tumour cell) [61]. It is expected that an increase in the virus replication rate will lead to a decrease in the tumour size. We confirm this through the results shown in panels Ib.1.–2. and IIb.1.–2. of Figure 9 for macro-dynamics scenarios (12) and (14), respectively, where we considered a higher virus replication rate (namely $b = 3$) than the corresponding baseline value (from Table A.1) used in Figures 4 and 5. This overall tumour decrease is also confirmed by the tumour mass estimate, represented in Figure 12 (4) through the green dotted line, which shows that, at all macro-micro stages (1-150), the tumour mass for the increased virus replication rate b is below the corresponding baseline scenario.

Finally, the absence of viral replication (i.e., $b = 0$), explored here through our multiscale approach in panels Ia.1.–2. and IIa.1.–2. of Figure 9 for macro-dynamics scenarios (12) and (14), leads to an increase in spatial spread of the tumour, giving rise to pronounced fingering and elongated tumour infiltrations in the surrounding tissue. Moreover, Figure 12 (4) shows that the tumour mass in the absence of virus replication (in red dotted line) stays above the baseline results and continues to increase at all macro-micro stages (1-150).

Viruses Doses. Acknowledging the therapeutic importance of virus dosage [65] and accounting in this regard on a series of biological constraints reviewed in [4], the

virus doses should be balanced in size and, for a more efficient viral therapy, these need to be higher than the initial tumour size [16]. Moreover, the location of the virus doses is important for the spatio-temporal viral dynamics within the growing tumour $\Omega(t)$ [66], as their distribution in the immediate proximity of high density tumour regions have the potential of a faster viral infection and spread within $\Omega(t)$. These biological observations are explored also by our results in Figure 10, where we investigate the effect of spatial distribution of initial viral dosage by increasing their number to 5 identical doses that were spatially applied as shown by Figure 2(d). As indicated also in Figure 12(5), after an initial rapid decrease over the first 30 stages (not shown also in Figure 10), the tumour distribution recovers and exhibits a more compact growth. This leaves the virus dosage question open and raise the challenging problem of designing a more comprehensive strategy where new virus doses need to be applied in appropriate locations at later stages so that tumour control and elimination could be achieved.

Improved Viral Therapy Outline for Tumour Suppression. Building on the tumour–OV interaction scenarios and their associated numerical results explored in Figures 4 – 10, an improved therapy is obtained by cumulating and using the parameter values identified there to give better tumour control and suppression response. Summarised in Table A.2, the changes in the parameters (with respect to their baseline values) considered in this improved therapy outline include: a four time decrease of the virus replication rate, a five fold increase in the infection rate of tumour cells, doubled ECM degradation rate, 50% increase in virus replication rate. Thus, in the presence of the five initial virus doses given in Figure 2(d), the results obtained via these outlined parameter changes, shown in Figure 11, present significant improvements in the tumour suppression results for macro-dynamics scenarios (12) and (14), both in terms of tumour levels and in spatial spread. The level of uninfected cells drops dramatically and the overall tumour remain fairly compact, presenting only a limited growth over the spatial domain, throughout the entire observation period. The tumour mass evolution plotted there with red dotted line in Figure 12(6) shows a complete control of the tumour which, besides a local-in-time relapse, is brought to residual total mass levels in both macro-dynamics scenarios (12) and (14), over the 150 macro-micro stages. Furthermore, by exploring this improved outline for the tumour – OV interaction on a longer time perspective of 350 macro-micro stages, as shown in Figure 13(I) we obtain the a good long term control of the tumour, this presenting a limited spatial growth (figure not shown here) and its overall mass being brought to residual levels in both macro-dynamics scenarios (12) and (14).

Figure 10: *Multi-scale simulation results for five virus initial doses for macro-dynamics scenarios (12) (in panel I) and (14) (in panel II) at two macro-micro stages: a. stage 75; and b. stage 150.*

6. Conclusions and Discussions

In this paper we proposed a novel multi-scale moving boundary framework to describe the complex interactions between the tissue-scale (macro-scale) cancer cells (uninfected and infected) populations, ECM, oncolytic virus, in the presence of the cell-scale tumour invasive edge uPA microdynamics. The macro-dynamic of tumour–oncolytic virus interaction give rise to the source for the leading uPA micro-dynamics via a nonlocal operator, this way establishing a top-down link between tissue- and cell- scale levels of activity of this naturally multiscale process.

In the presence of the source induced from the macro-scale, the uPA exercises a cross-interface micro-transport on a cell-scale neighbourhood of the tumour boundary $\partial\Omega(t)$ that is given by the union of a bundle of “half-way” overlapping micro-domains $\{\epsilon Y\}_{\epsilon Y \in \mathcal{P}(t)}$. This bundle of “half-way” overlapping micro-domains enabled the decoupling of the micro-dynamics in terms of the dynamics on each micro-domain $\epsilon Y \in \mathcal{P}(t)$. On each micro-domain ϵY , the significant levels of proteolytic transport in the peritumoural regions enabled us the determine the patterns of significant degradation of the ECM that the uPA meets and interacts with on $\epsilon Y \setminus \Omega(t)$. The spatial distribution

of this significant level of proteolytic enzymes enable us to characterise the choreographic direction of movement and displacement magnitude of the interface $\partial\Omega(t) \cap \epsilon Y$ and to represented this back at macro-scale in the form of a macro-scale tumour boundary velocity. This macro-scale tumour boundary velocity determined at micro-scale establishes a *bottom-up* feedback that is crucial in deciphering the morphological evolution of the macro-scale tumour.

At macro-scale we considered a cascade of three scenarios for tumour–OV interaction, summarised in (10),(12) and (14), in which taxis towards ECM gradients is gradually introduced for uninfected cancer cells, infected cancer cells, and oncolytic virus, respectively.

Indeed, per unit time, the first macro-scale scenario given in (10) accounts for the random motility of the uninfected cells, uninfected cells and virus particle within the surrounding ECM in the presence of the usual processes of virus infection, virus replication, ECM degradation, uninfected cell-proliferation and infected cell death, while considering taxis against ECM gradients (haptotaxis) only for the uninfected cell population. The modelling context is then extended to the macro-dynamics scenario (12) when haptotaxis is also considered for the infected cell population, and finally this is completed with macro-scale sce-

Figure 11: *Multi-scale simulation results for the improved outline for tumour suppression for macro-dynamics scenarios (12) (in panel I) and (14) (in panel II) at two macro-micro stages: a. stage 75; and b. stage 150.*

nario (14) when also the implicit ECM taxis movement of the virus is accounted for in the form of an ECM-OV taxis term.

As an initially considered baseline parameter values set (given in Table A.1) for all three macro-dynamics scenarios ((10), (12) and (14)) did not ensure an effective tumour suppression (as seen in Figures 3–5), we explored further the tumour–OV interaction conditions for the macro-dynamics scenarios (12) and (14) by varying the infected cancer cells death rate, the viral infection speed, the ECM degradation rates, viral replication rate, as well as the spatial distribution of initial virus doses. In doing so, we identified not only successful therapeutical cases, but also situations where the oncolytic viral therapy failed to lead to tumour suppression. As reflected by Figure 12, the failure of viral threatment could be clearly identified in two cases, namely: (1) slowing down viral infection speed (as shown in panels Ia.1.–2. and IIa.1.–2. of Fig.7 and Figure 12(2)); and (2) the absence of viral replication induced by infected cancer cells (as shown in panels Ia.1.–2. and II)a.1.–2. of Figure 9 and Figure 12(4)). Whether facing a slowdown of the infection rate or being in the absence of viral replication, the uninfected tumour cells gain momentum and become the dominant player, proliferating and

driving the spatial invasion, enhancing the overall tumour mass and giving rise to pronounced fingering patterns.

However, improved tumour suppression scenarios were found for the following parameter changes with respect to their baseline vales, namely for: (a) reducing the infected cell death rate (shown in Figure 6); (b) increased viral infection rate (shown in Figure 7); (c) increased ECM degradation rate (shown in Figure 8); (d) increased viral replication rate (shown in Figure 9). Alongside these parameter changes, a spatial redistribution of initial virus dosage in the proximity of tumour was found to have benefic impact upon tumour mass control and spatial spread.

Finally, a combination of best parameters that we found for tumour suppression led to an even better control of the tumour mass and tumour spatial spread as shown in Figures 11 and 12(6) Here the distribution of uninfected cancer cells is kept for most time observed at very low levels and the spatial spread is compact and very limited for both macro-dynamics scenarios considered, (12) and (14). An even longer observation of time, showed here in Figure 13 revealed that despite two instances of tumour relapses (captured by the only two peaks in tumour masses Figure 13) the tumour growth is suppressed and the tumour itself is kept under control. **Note that Fig. 12 and 13 show**

Figure 12: Comparison of total tumour masses evolution over macro-micro stages 1 – 150 between the macro-dynamics scenarios (12) (in subfigures (I)) and (14) (in subfigures (II)) for the following cases of parameter variations with respect to their baseline values given in Table A.1, namely: (1) (a) $\frac{\delta_i}{4}$, (b) baseline value for δ_i , and (c) $4\delta_i$; (2) (a) $\frac{\rho}{5}$, (b) baseline value for ρ , and (c) 5ρ ; (3) (a) $2\alpha_c, 2\alpha_i$, and (b) baseline values for α_c and α_i ; (4) (a) no OV replication, $b = 0$, (b) baseline value for b , and (c) $b=3$; (5) (a) five OV initial doses and (b) one OV initial dose; (6) (a) parameter for improved viral therapy outline for tumour suppression given in Table A.3, and (b) baseline parameter values given in Table A.1.

Figure 13: A long run (350 macro-micro stages) of the improved outline for tumour suppression case. (I) A comparison of total tumour masses between macro-dynamics modelling scenarios: (a) (14) and (b) (12). (II) A comparison of viruses masses between macro-dynamics modelling scenarios: (c) (14) and (d) (12).

quite similar overall tumour mass dynamics, which is expected since the difference between scenarios (12) and (14) is in the advection of virus and does not affect the total tumour mass (because the rates at which the virus kills the tumour are the same for the two scenarios). Thus, while tumour control could be in principle achieved, a complete tumour elimination that would not present relapses opens the challenging question of designing an optimal strategy for iterative delivery of new tumour doses at appropriate spatial locations, this being the topic of a future work.

Appendix A. Summary of Model Parameters

Appendix A.1. Summary of baseline parameter values that appear in the macro-dynamics scenarios

In Table A.1, we summarise the baseline parameter values for the most complex macro-dynamics model (14) (these parameters appear also in models (10) and (12)). The majority of these parameter values are taken from two references, [26] and [52].

Appendix A.2. Parameter values for macro-dynamics scenario showing the best tumour suppression results, as summarised in Figures 11 and 12

In Table A.2, we summarise the values of parameters ρ , δ_i , α_c , α_i and b (for the macro-dynamics scenarios, (12) and (14)), that have shown to lead to best tumour suppression results.

Appendix A.3. Summary of baseline parameter values that appear in the micro-dynamics scenarios

In Table A.3, we summarise the parameters values for the micro-dynamics (19)-(21).

Parameter	Value	References
D_c	0.00675	[26]
D_i	0.0054	[26]
D_v	0.0036	[26]
η_c	2.85×10^{-2}	[52]
η_i	2.85×10^{-2}	[52]
η_v	2.85×10^{-3}	Estimated
μ_1	0.25	[52]
ρ	79×10^{-3}	[26]
δ_i	0.05	[26]
α_c	0.15	Estimated
α_i	0.075	$\frac{\alpha_c}{2}$
μ_2	0.015	Estimated
b	2	Estimated
δ_v	0.025	[26]
β	0.775	[52]
λ_c	0.8	Estimated
λ_i	0.4	Estimated

Table A.1: Baseline parameters values for the macroscopic models (10), (12) and (14). The last three parameters, β , λ_c and λ_i are involved in the macro-micro connection; see also equations (23) and (16).

Parameter	Value
D_c	0.00675
D_i	0.0054
D_v	0.0036
η_c	2.85×10^{-2}
η_i	2.85×10^{-2}
η_v	2.85×10^{-3}
μ_1	0.25
ρ	395×10^{-3}
δ_i	0.0125
α_c	0.3
α_i	0.15
μ_2	0.015
b	3
δ_v	0.025
β	0.775
λ_c	0.8
λ_i	0.4

Table A.2: Summary of parameter values that have shown improved tumour suppression results, as summarised in Figures 11 and 12.

Appendix B. Tissue Thresholds within the bottom-up feedback link

As discussed in [51], for each $\epsilon Y \in \mathcal{P}(t_0)$, the tissue thresholds $\omega(\beta, \epsilon Y)$ explore the level of ECM degradation on $\epsilon Y \setminus \Omega(t_0)$, this way assessing the likelihood of movement of the midpoint $x_{\epsilon Y}^*$ to the new location prescribed by $s(x_{\epsilon Y}^*)$, namely to its new position $\tilde{x}_{\epsilon Y} := x_{\epsilon Y}^* + s(x_{\epsilon Y}^*)$. We adopt here the same form as in [51], and so these tissue

Parameter	Value
D_a	2.5×10^{-3}
D_p	3.5×10^{-3}
D_m	4.91×10^{-3}
ψ_{11}	0.75
ψ_{12}	0.215
ψ_{13}	0.3
ψ_{21}	0.75
ψ_{22}	0.55
ψ_{23}	0.5
ψ_{31}	0.11
ψ_{32}	0.75
ψ_{33}	0.5

Table A.3: Summary of parameter values for the microscopic modelling component. All parameters for this system are taken from the reference [52].

thresholds are given by

$$\omega(\beta, \epsilon Y) = \begin{cases} Q_1(\beta, \epsilon Y), & \text{if } \frac{u_{\Omega(t_0)}(\tilde{x}_{\epsilon Y}, t_0 + \Delta t)}{\sup_{z \in \partial\Omega(t_0)} (u_{\Omega(t_0)}(z, t_0 + \Delta t))} \leq \beta, \\ Q_2(\beta, \epsilon Y), & \text{if } \frac{u_{\Omega(t_0)}(\tilde{x}_{\epsilon Y}, t_0 + \Delta t)}{\sup_{z \in \partial\Omega(t_0)} (u_{\Omega(t_0)}(z, t_0 + \Delta t))} > \beta \end{cases} \quad (\text{B.1})$$

where $\beta \in (0, 1)$ represents the most suitable conditions that facilitate invasion, with the expressions $Q_1(\beta, \epsilon Y)$ and $Q_2(\beta, \epsilon Y)$ denoting

$$Q_1(\beta, \epsilon Y) := \sin\left(\frac{\pi}{2} \left(1 - \frac{1}{\beta} \frac{u_{\Omega(t_0)}(\tilde{x}_{\epsilon Y}, t_0 + \Delta t)}{\sup_{z \in \partial\Omega(t_0)} (u_{\Omega(t_0)}(z, t_0 + \Delta t))}\right)\right),$$

and

$$Q_2(\beta, \epsilon Y) := \sin\left(\frac{\pi}{2(1-\beta)} \left(\frac{u_{\Omega(t_0)}(\tilde{x}_{\epsilon Y}, t_0 + \Delta t)}{\sup_{z \in \partial\Omega(t_0)} (u_{\Omega(t_0)}(z, t_0 + \Delta t))} - \beta\right)\right).$$

Appendix C. Outline of the Numerical Approach

Appendix C.1. Spatial Domain Discretization

- We assume that the tumour $\Omega(t)$ grows within a maximal reference spacial domain Y , which is taken in our numerical experiments to be the rectangular region $Y := [0, 8] \times [0, 8]$. Details of the macro-solver are given in the next appendix subsection.
- We discretise Y uniformly in both spatial directions with a equal mesh size $\Delta x = 0.03125$.
- Micro Domain and Details of the Micro-Solver :
 1. For any time instance $t_0 \geq 0$, any boundary micro-domain $\epsilon Y \in \mathcal{P}(t_0)$ is centred a boundary point $x \in \partial\Omega(t_0) \cap \epsilon Y$, having its size $\epsilon = 2\Delta x = 0.0625$.
 2. The top-down nonlocal source terms ... we using the directly the formulas (16) and (18) the overlapping macro-micro mesh points and use micro-scale barycentric coordinates to interpolate at all

other micro-points $y \in \epsilon Y \setminus \{(i\Delta x, j\Delta x) \mid i, j = 1 \dots q\}$.

3. On each ϵY we then solve the micro-dynamics via finite element by involving bilinear shape function on a square micro-mesh placed on ϵY .

Appendix C.2. Macro-Solver

- The macro-dynamics is solved over the time interval $[t_0, t_0 + \Delta t]$, which is uniformly discretised in $N+1 > 1$ time nodes with equal size time step $\delta t := \frac{\Delta t}{N}$. This is approximated via method of lines type approach with a trapezoidal predictor-corrector time marching approach.
- For the approximation of the right-hand side spatial operator, we involve midpoint rule and central differences, and so, at any discrete spatial point $(i\Delta x, j\Delta x)$, $\forall i, j = 1, \dots, q$, and any given time node $t^n := t_0 + n\delta t$, $\forall n = 0, \dots, N$, we have that: the diffusion terms are approximated by

$$(\Delta c)_{i,j}^n \approx \frac{(c_x)_{i+\frac{1}{2},j}^n - (c_x)_{i-\frac{1}{2},j}^n}{\Delta x} + \frac{(c_y)_{i,j+\frac{1}{2}}^n - (c_y)_{i,j-\frac{1}{2}}^n}{\Delta y}$$

the haptotaxis terms are approximated by:

$$\nabla \cdot (c \nabla u)_{i,j}^n \approx \frac{(c)_{i+\frac{1}{2},j}^n (u_x)_{i+\frac{1}{2},j}^n - (c)_{i-\frac{1}{2},j}^n (u_x)_{i-\frac{1}{2},j}^n}{\Delta x} + \frac{(c)_{i,j+\frac{1}{2}}^n (u_y)_{i,j+\frac{1}{2}}^n - (c)_{i,j-\frac{1}{2}}^n (u_y)_{i,j-\frac{1}{2}}^n}{\Delta y},$$

where

$$\begin{aligned} (c_{x1})_{i+\frac{1}{2},j}^n &= \frac{(c)_{i+1,j}^n - (c)_{i,j}^n}{\Delta x} & \& \quad (u_{x1})_{i+\frac{1}{2},j}^n &= \frac{(u)_{i+1,j}^n - (u)_{i,j}^n}{\Delta x} \\ (c_{x1})_{i-\frac{1}{2},j}^n &= \frac{(c)_{i,j}^n - (c)_{i-1,j}^n}{\Delta x} & \& \quad (u_{x1})_{i-\frac{1}{2},j}^n &= \frac{(u)_{i,j}^n - (u)_{i-1,j}^n}{\Delta x} \\ (c_{x2})_{i,j+\frac{1}{2}}^n &= \frac{(c)_{i,j+1}^n - (c)_{i,j}^n}{\Delta x} & \& \quad (u_{x2})_{i,j+\frac{1}{2}}^n &= \frac{(u)_{i,j+1}^n - (u)_{i,j}^n}{\Delta x} \\ (c_{x2})_{i,j-\frac{1}{2}}^n &= \frac{(c)_{i,j}^n - (c)_{i,j-1}^n}{\Delta x} & \& \quad (u_{x2})_{i,j-\frac{1}{2}}^n &= \frac{(u)_{i,j}^n - (u)_{i,j-1}^n}{\Delta x} \end{aligned}$$

and $(c)_{i+\frac{1}{2},j}^n, (c)_{i-\frac{1}{2},j}^n, (c)_{i,j+\frac{1}{2}}^n, (c)_{i,j-\frac{1}{2}}^n$ are given here via the usual midpoint rule.

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