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Vitullo, P.; Macaluso, C.; Gazzoni, S.; Cassanmagnago, A.; Dimola, N.;
Possenti, L.; Zunino, P.

MOX, Dipartimento di Matematica
Politecnico di Milano, Via Bonardi 9 - 20133 Milano (Italy)

mox-dmat@polimi.it

<https://mox.polimi.it>

A computational model for phenotype-structured tumour dynamics with reduced microvascular oxygen and event-based radiotherapy

Piermario Vitullo¹, Cristina Macaluso¹, Sara Gazzoni¹, Anna Cassanmagnago¹,
Nunzio Dimola¹, Luca Possenti², Paolo Zunino¹

¹MOX, Department of Mathematics, Politecnico di Milano, Milan, Italy

²CMON Lab, Data Science Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Abstract

Tumour response to radiotherapy is strongly influenced by spatially heterogeneous oxygenation and by the ability of tumour-cell populations to adapt their phenotypic composition to the local microenvironment. We present a computational framework that couples phenotype-structured tumour dynamics with microvascular oxygen transport and fractionated radiotherapy. The tumour population evolves in physical and phenotype space, while tissue oxygenation is obtained from a reduced-order approximation of a mixed-dimensional vascular–tissue transport model. Radiotherapy is represented through event-aligned survival updates, allowing treatment events to remain distinct from the smooth inter-fraction tumour evolution.

The numerical formulation combines finite elements in physical space, a conservative discretization of phenotype space and implicit time integration within a sequential tumour–oxygen coupling strategy. Its numerical behaviour is examined through physical-space resolution sensitivity, temporal and phenotype refinement, and comparison of the oxygen surrogate with full-order solutions. The refinement studies show approximately first-order behaviour for the assessed temporal tumour-burden trajectories and approximately second-order behaviour for phenotype-class-resolved trajectory quantities.

The framework is then used to investigate fractionated radiotherapy across vascular environments differing in network pruning and oxygen supply. The simulations show that the microvascular oxygen environment substantially alters the accumulated treatment response and the onset of numerical extinction across the sampled dose courses. Across the explored vascular map, inlet oxygen provides the clearest organization of hypoxic exposure and phenotype composition, while vascular pruning introduces an additional, non-uniform modulation. Lower oxygen supply is associated with greater enrichment of stem-like phenotypes and a smaller radiotherapy-associated reduction within the model.

These results provide a numerically assessed framework for studying how microvascular oxygen heterogeneity and phenotype adaptation jointly shape modelled tumour response to fractionated radiotherapy.

Keywords: phenotype-structured tumour dynamics; tumour microenvironment; microvascular oxygen transport; fractionated radiotherapy; reduced-order modelling; numerical convergence.

1 Introduction

Solid tumours are heterogeneous and evolving ecosystems in which cancer cells with different proliferative capacities, differentiation states and treatment sensitivities coexist within a spatially heterogeneous microenvironment. Such heterogeneity arises from both genetic and non-genetic mechanisms and can be reshaped by environmental selection and therapy [25, 23, 17]. Among the phenotypic traits that have been associated with tumour persistence and treatment resistance, cellular stemness is

particularly relevant. Stem-like cancer cells can self-renew, generate more differentiated progeny and adapt their behaviour in response to environmental stress, while differentiated populations generally display different proliferative and clonogenic properties. Rather than forming immutable cellular compartments, these states may be connected through phenotypic plasticity, so that the composition of a tumour can evolve together with its microenvironment [6, 5].

Oxygen availability is a major component of this interaction. Abnormal tumour vascularization produces heterogeneous oxygen delivery, while diffusion and cellular consumption generate spatial gradients and hypoxic niches within the tissue. Hypoxia is associated with changes in proliferation, metabolism and cellular phenotype, and can favour the persistence or emergence of more stem-like states. At the same time, oxygen availability is a major determinant of the response to ionizing radiation [39, 6, 5]. Consequently, radiotherapy response cannot in general be interpreted only in terms of the prescribed radiation dose: it also depends on the spatial microenvironment in which tumour cells reside and on the phenotypic composition that develops within that environment.

Mathematical models provide a natural setting in which these interacting mechanisms can be studied. Phenotype-structured population models represent cellular heterogeneity through a continuous phenotypic variable rather than a fixed collection of discrete subpopulations. Changes in population composition can then result from proliferation, death, stochastic phenotypic variation and environment-driven phenotypic transport [22, 20, 7, 8]. This framework has been used to investigate how spatially varying environmental conditions shape tumour evolution and treatment response [11, 41]. In the stemness-structured models [6, 5], the continuous phenotype coordinate connects stem-like and progressively differentiated states, while oxygen influences proliferation, cell death and differentiation dynamics and radiotherapy acts differently across the phenotypic distribution. More recent developments have further demonstrated the flexibility of phenotype-structured descriptions for studying tumour adaptation and treatment response [21, 42, 14, 28, 35, 36].

A complementary modelling challenge concerns the origin of the oxygen field itself. Tissue oxygenation depends on the architecture and functional state of the microvascular network, on blood flow and haematocrit distribution, and on oxygen transport and vessel–tissue exchange. Network-resolved and mixed-dimensional models make it possible to represent these processes explicitly by coupling one-dimensional vascular networks to the surrounding three-dimensional tissue [37, 38, 3, 31, 16, 29]. Recent computational studies have emphasized the importance of vascular morphology in determining tissue hypoxia and radiation response, including in patient-informed microvascular settings [32, 30, 24, 9]. These microvascular models and phenotype-structured tumour models address complementary aspects of the same problem: the former resolve the spatial origin of oxygen heterogeneity, whereas the latter describe how a heterogeneous cell population adapts to, and is selected by, its local environment.

We formulate the Cell Oxygen Radiotherapy Evolution (CORE) model by coupling a phenotype-structured tumour population to microvascular oxygen transport and radiotherapy. Vascular architecture and inlet oxygen conditions determine the tissue oxygen landscape; the local oxygen field regulates tumour growth, death and phenotypic adaptation and modifies the radiation response; in turn, the evolving tumour burden modulates tissue oxygen consumption. Radiotherapy acts at prescribed treatment times on the current heterogeneous population. This structure allows the tumour response to be studied through the evolving interaction between vascular supply, tissue oxygenation, phenotypic composition and irradiation.

Resolving the microvascular oxygen problem repeatedly during tumour evolution is, however, computationally demanding. The present implementation therefore uses a reduced-order representation of the oxygen problem based on the previously developed POD–MINN+ methodology [43, 44]. The reduced oxygen model enables repeated evaluation of the quasi-steady oxygen field within the coupled simulations.

The objective of the present study is to establish and verify a numerical realization of this coupled model and to examine its behaviour in controlled computational applications. Particular attention is given to the numerical reliability of the coupled approximation and to the fidelity of the reduced oxygen representation before using the model to investigate how changes in the vascular microenvironment and radiotherapy exposure influence tumour burden, oxygenation and phenotypic composition. The resulting simulations are used as mechanistic computational experiments.

The paper is organized as follows. Section 2 introduces the coupled tumour, oxygen and radiotherapy model. Section 3 describes its numerical approximation and computational realization. Section 4 examines the numerical behaviour of the coupled scheme and the oxygen surrogate. Section 5 presents the computational application studies. The results and modelling limitations are discussed in Section 6, and concluding remarks are given in Section 7.

2 CORE tumour–oxygen–radiotherapy model

The CORE framework couples the evolution of a phenotype-structured tumour population to oxygen transport in a resolved microvascular environment and to event-based radiotherapy. Tumour cells evolve in physical space and along a continuous phenotype coordinate describing progression from stem-like to more differentiated states. Tissue oxygenation is determined by the vascular network, the inlet oxygen condition and tumour-dependent oxygen consumption. The coupling is asymmetric: the oxygen field acts locally on cell proliferation, death, phenotypic adaptation and radiotherapy response, whereas the feedback from the tumour to the oxygen problem is represented through the mean tumour occupancy. Radiotherapy acts at prescribed treatment times through instantaneous survival updates. Figure 1 summarizes the main interactions.

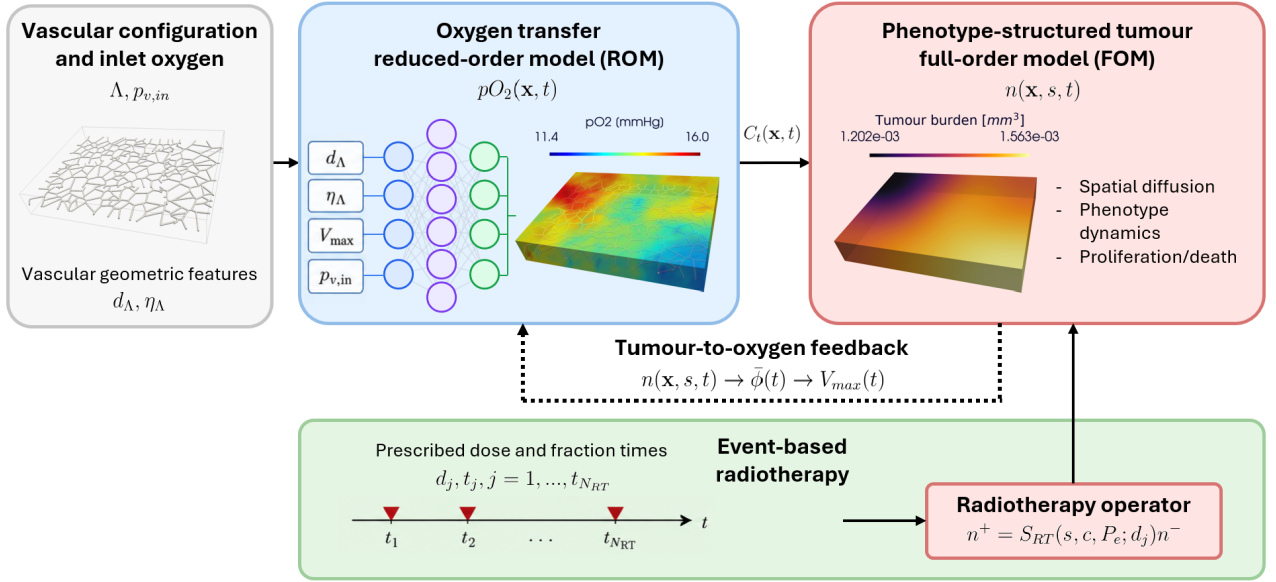


Figure 1: Schematic of the coupled CORE tumour–oxygen–radiotherapy model. Vascular geometry, inlet oxygen and tumour-dependent oxygen consumption determine the local tissue oxygen field. Oxygen regulates the phenotype-structured tumour dynamics, while mean tumour occupancy modulates oxygen consumption. Radiotherapy acts at prescribed treatment times through the survival update $n^+ = S_{RT}n^-$. CSC, DC and TDC denote reporting intervals of the continuous phenotype coordinate.

2.1 Phenotype-structured tumour population

Let $\Omega \subset \mathbb{R}^3$ denote the tissue domain, $\mathbf{x} \in \Omega$ the spatial coordinate, $s \in [0, 1]$ the continuous phenotype coordinate and t time. The computational domain is

$$\Omega = (0, 1) \times (0, 0.737) \times (0, 0.158) \text{ mm}^3, \quad (1)$$

with dimensions $1 \times 0.737 \times 0.158 \text{ mm}^3$ and volume $|\Omega| = 0.116 \text{ mm}^3$.

Following the stemness-structured formulation of Celora et al. [6, 5], the phenotype coordinate spans progressively differentiated cellular states, with $s = 0$ corresponding to the most stem-like end of the axis. If $N(\mathbf{x}, s, t)$ denotes the dimensional phenotype-resolved cell density, the normalized tumour density is $n(\mathbf{x}, s, t) = N(\mathbf{x}, s, t)/\Phi_{\max}$, where $\Phi_{\max}$ denotes the local tissue carrying capacity. Only the dependent density amplitude is normalized; physical space and time retain their dimensional coordinates.

The corresponding phenotype-integrated dimensional and normalized densities are

$$\Phi(\mathbf{x}, t) = \int_0^1 N(\mathbf{x}, s, t) ds, \quad \phi(\mathbf{x}, t) = \int_0^1 n(\mathbf{x}, s, t) ds = \frac{\Phi(\mathbf{x}, t)}{\Phi_{\max}},$$

so that $\phi(\mathbf{x}, t)$ represents local tumour occupancy relative to the carrying capacity. Spatial integration gives the tumour-burden measure

$$m(t) = \int_{\Omega} \phi(\mathbf{x}, t) dV = \int_{\Omega} \int_0^1 n(\mathbf{x}, s, t) ds dV, \quad (2)$$

which has units of volume because ϕ is dimensionless. Relative tumour burden is defined by $R(t) = m(t)/m(0)$.

Between radiotherapy events, the tumour population satisfies

$$\partial_t n = D_{xn} \Delta_{\mathbf{x}} n + \partial_s (D_{sn} \partial_s n - v_s(s, c)n) + [P(s, c)(1 - \phi) - K(s, c)] n, \quad t \notin \{t_j\}, \quad (3)$$

with zero flux at the physical and phenotypic boundaries,

$$\nabla n \cdot \mathbf{n}_{\partial\Omega} = 0 \quad \text{on } \partial\Omega, \quad D_{sn} \partial_s n - v_s n = 0 \quad \text{at } s = 0, 1.$$

Here D_{xn} and D_{sn} denote spatial and phenotypic diffusion coefficients, respectively, while $P(s, c)$, $K(s, c)$ and $v_s(s, c)$ describe proliferation, death and directed phenotypic transport. The factor $1 - \phi$ represents local carrying-capacity limitation [5].

For reporting purposes, the continuous phenotype interval is divided into $[0, 0.3]$, $(0.3, 0.8]$ and $(0.8, 1]$, denoted CSC, DC and TDC, respectively. These intervals summarize the continuous phenotype distribution and do not define distinct cell populations in the model.

2.2 Mixed-dimensional microvascular oxygen transport

Tissue oxygenation is described by the mixed-dimensional microvascular model of Possenti et al. [29]. A one-dimensional vascular network Λ is embedded in the three-dimensional tissue domain Ω , with blood flow and haematocrit supplied by the underlying microcirculatory model [31]. The formulation accounts for vascular oxygen transport, vessel–tissue exchange, tissue transport and metabolic consumption.

Let C_t denote dissolved oxygen concentration in tissue and C_v dissolved oxygen concentration in plasma. Tissue and vascular partial pressures are related to concentration through the corresponding oxygen-solubility coefficients,

$$pO_{2,t} = \frac{C_t}{\alpha_t}, \quad C_{v,\text{in}} = \alpha_{\text{pl}} pO_{2,v,\text{in}},$$

where α_t and α_{pl} denote the tissue and plasma oxygen-solubility coefficients, respectively. For the tissue concentration-to-pressure conversion we use $\alpha_t = 3.89 \times 10^{-5} \text{ mL}_{O_2} \text{ cm}^{-3} \text{ mmHg}^{-1}$, following Secomb et al. [38]. The prescribed vascular inlet partial pressure $p_{O_{2,v,\text{in}}}$ therefore determines the inlet dissolved concentration $C_{v,\text{in}}$.

Following Possenti et al. [29], total vascular oxygen is written as

$$C_v^{\text{tot}} = C_v + k_1 H \frac{C_v^{\gamma_H}}{C_v^{\gamma_H} + k_2},$$

where the second contribution accounts for haemoglobin-bound oxygen. The mixed-dimensional oxygen problem is

$$\left\{ \begin{array}{ll} \nabla \cdot (-D_t \nabla C_t + \mathbf{v}_t C_t) + V_{\max} \frac{C_t}{C_t + \alpha_t p_{m50}} = \phi_{O_2} \delta_\Lambda, & \text{in } \Omega, \\ \pi R^2 \partial_\ell (-D_v \partial_\ell C_v + u_v C_v^{\text{tot}}) = -\phi_{O_2}, & \text{on } \Lambda, \\ \phi_{O_2} = 2\pi R P_{O_2} (C_v - \bar{C}_t) \\ \quad + (1 - \sigma_{O_2}) \frac{C_v + \bar{C}_t}{2} \phi_v, & \text{on } \Lambda, \\ C_v = C_{v,\text{in}}, & \text{on } \partial\Lambda_{\text{in}}, \\ -D_v \partial_\ell C_v = 0, & \text{on } \partial\Lambda_{\text{out}}, \\ -D_t \nabla C_t \cdot \mathbf{n}_{\partial\Omega} = b_{O_2} (C_t - c_{0,t}), & \text{on } \partial\Omega. \end{array} \right. \quad (4)$$

Here D_v and D_t denote vascular and tissue oxygen diffusivities, u_v and $\mathbf{v}_t$ the corresponding advective velocities, R the local vessel radius and ℓ the vascular arc-length coordinate. The distribution δ_Λ transfers oxygen supplied along the vascular network to the surrounding tissue. The interface concentration $\bar{C}_t$ represents the mean tissue concentration associated with the vessel cross-section, while P_{O_2} , σ_{O_2} and ϕ_v determine the vessel–tissue exchange law. The parameters k_1 , k_2 and γ_H describe haemoglobin binding, and p_{m50} is the partial pressure at half-maximal metabolic consumption. The external tissue boundary is subject to the Robin condition determined by b_{O_2} and $c_{0,t}$, while vascular junction conditions enforce continuity and conservation of oxygen flux. Further details of the oxygen and microcirculatory formulations are given in Possenti et al. [31, 29] and in the related mixed-dimensional analysis [18].

Because oxygen transport equilibrates on a substantially shorter time scale than tumour evolution, the oxygen problem is treated as quasi-steady relative to the cellular dynamics [5]. We denote the mixed-dimensional problem compactly by

$$\mathcal{O}_{\Lambda, C_{v,\text{in}}} (C_v, C_t; V_{\max}) = 0.$$

The tissue partial pressure enters the tumour model through the normalized oxygen variable

$$c(\mathbf{x}, t) = \frac{p_{O_{2,t}}(\mathbf{x}, t)}{p_\infty}, \quad p_\infty = 50 \text{ mmHg}.$$

The reduced-order approximation used to evaluate the oxygen problem within the coupled simulations is introduced in Section 3.

2.3 Constitutive laws and radiotherapy response

The phenotype- and oxygen-dependent constitutive laws retain the structure of the stemness model of Celora et al. [6, 5], with the parameter values specified below.

Proliferation is described by

$$P(s, c) = p_{\text{CSC}} \frac{c^4}{K_{\text{CSC}}^4 + c^4} \exp \left[- \left(\frac{s - s_{\text{CSC}}}{g_{\text{CSC}}} \right)^2 \right] + p_{\text{DC}} \frac{c^4}{K_{\text{DC}}^4 + c^4} \exp \left[- \left(\frac{s - s_{\text{DC}}}{g_{\text{DC}}} \right)^2 \right], \quad (5)$$

where the two phenotype-localized contributions represent proliferation around stem-like and more differentiated proliferative states, modulated by oxygen through Hill-type saturation factors.

The death rate is

$$K(s, c) = d_{\text{TDC}} \exp \left[- \frac{1 - s}{g_{\text{TDC}}} \right] + d_n H_{\varepsilon_k}(c_N - c),$$

where the first contribution represents loss associated with highly differentiated states and the second describes increased cell death under severe hypoxia. We define the regularized Heaviside function generically as

$$H_\eta(z) = \frac{1}{2} \left[1 + \tanh \left(\frac{z}{\eta} \right) \right].$$

The width $\eta = \varepsilon_k$ is used in the necrotic-death term, whereas $\eta = \varepsilon$ is used in the phenotype-drift law below.

Oxygen regulates directed phenotypic adaptation through

$$v_s(s, c) = V_+ \tanh \left(\frac{s}{\xi_+} \right) \tanh \left(\frac{(1 - s)^{\omega_+}}{\xi_+} \right) H_\varepsilon(c - c_H) - V_- \tanh \left(\frac{s}{\xi_-} \right) \tanh \left(\frac{(1 - s)^{\omega_-}}{\xi_-} \right) H_\varepsilon(c_H - c). \quad (6)$$

The first contribution promotes transport towards more differentiated phenotypes under sufficiently oxygenated conditions, whereas the second drives the population towards lower phenotype values under hypoxia. Phenotype diffusion in Eq. (3) represents stochastic phenotypic variation, while v_s represents the directed component of environmentally driven adaptation.

Radiotherapy is represented through an oxygen-, phenotype- and proliferation-dependent linear-quadratic survival law [5, 27],

$$S_{\text{RT}}(s, c, P_e; d) = \exp \left[-\alpha(s, c, P_e)d - \beta(s, c, P_e)d^2 \right], \quad (7)$$

where $P_e = P(s, c)(1 - \phi)$ is the effective local proliferation rate and

$$\alpha(s, c, P_e) = a_1(c)a_2(s)a_3(P_e), \quad \beta(s, c, P_e) = b_1(c)b_2(s)a_3(P_e).$$

The oxygen-dependent factors are

$$a_1(c) = \begin{cases} 1, & c > c_R, \\ \text{OER}^{-1}, & c \leq c_R, \end{cases} \quad b_1(c) = \begin{cases} 1, & c > c_R, \\ \text{OER}^{-2}, & c \leq c_R, \end{cases}$$

while phenotype and proliferation enter through

$$a_2(s) = \alpha_{\min} + \Delta\alpha \tanh(ks), \quad b_2(s) = \beta_{\min} + \Delta\beta \tanh(ks), \quad a_3(P_e) = 1 + \frac{P_e}{p_{\text{DC}}}.$$

At each prescribed treatment time t_j , irradiation acts on the pre-treatment tumour state according to

$$n(\mathbf{x}, s, t_j^+) = S_{\text{RT}}\left(s, c_j^-(\mathbf{x}), P_{e,j}^-(\mathbf{x}, s); d_j\right) n(\mathbf{x}, s, t_j^-), \quad (8)$$

where $c_j^-(\mathbf{x}) = c(\mathbf{x}, t_j^-)$ and $P_{e,j}^-(\mathbf{x}, s) = P_e(\mathbf{x}, s, t_j^-)$ denote the oxygen and effective proliferation states immediately before irradiation. Radiotherapy therefore appears as a discrete event separating successive intervals of continuous tumour evolution. Its numerical treatment is described in Section 3.4.

For the HSC2 parameterization used in the applications, a representative doubling time $T_d = 29$ h is selected from the range reported by the JCRB Cell Bank and Cellosaurus [15, 4]. The corresponding differentiated-cell proliferation rate is $p_{\text{DC}} = 24 \log(2)/T_d \simeq 0.57 \text{ d}^{-1}$. Following Celora et al. [5], the CSC proliferation rate is set to one quarter of the differentiated-cell rate, with $p_{\text{CSC}} = 0.25 p_{\text{DC}} \simeq 0.14 \text{ d}^{-1}$. The HSC2 radiosensitivity coefficients define an effective phenotype-dependent representation informed by the HSC2/HSC2-R radiobiological data of Fukui et al. [12].

The fixed tumour, radiotherapy and coupling parameters used in the HSC2 simulations are summarized in Table 1.

Table 1: Fixed tumour, radiotherapy and coupling parameters used in the HSC2 simulations. References indicate their modelling or experimental basis. Physical space is expressed in mm and time in days; quantities involving the normalized oxygen variable $c = pO_2/p_\infty$ are dimensionless unless otherwise stated.

Parameter	Definition	Value	Unit	Source
D_{xn}	Tumour-cell spatial motility	2.4×10^{-3}	$\text{mm}^2 \text{d}^{-1}$	[40]
D_{sn}	Phenotype diffusion	1.2×10^{-4}	d^{-1}	[5]
T_d	HSC2 doubling time	29	h	[15, 4]
p_{DC}	Differentiated-cell proliferation rate	0.57	d^{-1}	[15, 4]
p_{CSC}	CSC proliferation rate	0.14	d^{-1}	[5]
$K_{\text{CSC}}, K_{\text{DC}}$	Oxygen half-saturation constants	0.05, 0.30	–	[5]
$g_{\text{CSC}}, g_{\text{DC}}, g_{\text{TDC}}$	Phenotype-localization widths	0.1, 0.2, 0.1	–	[5]
$s_{\text{CSC}}, s_{\text{DC}}$	Reference phenotype locations	0, 0.55	–	[5]
V_+, V_-	Differentiation/de-differentiation drift amplitudes	$1.92 \times 10^{-2}, 4.8 \times 10^{-3}$	d^{-1}	[5]
ξ_+, ξ_-	Phenotype-drift shape parameters	0.1, 0.1	–	[5]
ω_+, ω_-	Phenotype-drift exponents	1, 2	–	[5]
c_H, c_N	Hypoxia and necrosis thresholds	0.30, 0.0125	–	[5, 26]
d_{TDC}, d_n	TDC-associated and necrotic death rates	0.024, 2.4	d^{-1}	[5]
ε	Phenotype-drift regularization	0.05	–	[5]
ε_k	Necrotic-death regularization	0.01	–	[5]
OER, c_R, k	Oxygen enhancement ratio, RT oxygen threshold and phenotype steepness	3, 0.1, 5	–	[5, 19]
$\alpha_{\min}, \Delta\alpha$	Phenotype-dependent LQ α coefficients	0.084, 0.082	Gy^{-1}	[12]
$\beta_{\min}, \Delta\beta$	Phenotype-dependent LQ β coefficients	0.009, 0.036	Gy^{-2}	[12]
γ_0	Oxygen-consumption scaling coefficient	1.728×10^4	–	[13, 5]
τ_0	Reference time scale	1 (= 86400 s)	d	–
p_∞	Reference oxygen partial pressure	50	mmHg	[26, 45]
α_t	Tissue oxygen solubility coefficient	3.89×10^{-5}	$\text{mL}_{\text{O}_2} \text{cm}^{-3} \text{mmHg}^{-1}$	[38]

2.4 Tumour–oxygen coupling and hybrid formulation

The two directions of tumour–oxygen coupling are not spatially symmetric. The oxygen field acts locally on proliferation, death, phenotypic transport and radiotherapy response through $c(\mathbf{x}, t)$, whereas the tumour-to-oxygen feedback is represented by the spatially averaged occupancy

$$\bar{\phi}(t) = \frac{1}{|\Omega|} \int_{\Omega} \phi(\mathbf{x}, t) \, dV.$$

The mean tumour occupancy modulates the maximum tissue oxygen-consumption rate according to

$$V_{\max}[\bar{\phi}(t)] = \frac{\gamma_0 \alpha_t p_{\infty}}{\tau_0} \bar{\phi}(t). \quad (9)$$

Hence, the tumour population affects the magnitude of tissue oxygen consumption through its mean occupancy, while local variations in tumour density and phenotype composition are not represented explicitly in this feedback.

With these definitions, the coupled tumour–oxygen–radiotherapy model can be written compactly as

$$\left\{ \begin{array}{l} \partial_t n = D_{xn} \Delta_{\mathbf{x}} n + \partial_s (D_{sn} \partial_s n - v_s(s, c) n) \\ \quad + [P(s, c)(1 - \phi) - K(s, c)] n, \quad t \notin \{t_j\}, \\ \mathcal{O}_{\Lambda, C_{v, \text{in}}} (C_v, C_t; V_{\max}[\bar{\phi}(t)]) = 0, \\ c(\mathbf{x}, t) = \frac{C_t(\mathbf{x}, t)}{\alpha_t p_{\infty}} = \frac{p O_{2, t}(\mathbf{x}, t)}{p_{\infty}}, \\ n(\mathbf{x}, s, t_j^+) = S_{\text{RT}}(s, c_j^-, P_{e, j}^-; d_j) n(\mathbf{x}, s, t_j^-). \end{array} \right. \quad (10)$$

The system combines continuous phenotype-structured tumour evolution, quasi-steady microvascular oxygen transport and discrete radiotherapy events. Its numerical approximation and sequential realization are described in Section 3.

3 Numerical approximation and coupled solution strategy

The coupled model is approximated using continuous P_1 finite elements in physical space, a conservative finite-difference discretization of the phenotype coordinate, a linearly implicit backward-Euler time discretization and an oxygen-first sequential coupling strategy. On each smooth time interval, the oxygen field and tumour occupancy are evaluated from the current state, and the resulting reaction and phenotype-advection coefficients are kept fixed over the backward-Euler step. Radiotherapy events are aligned exactly with the temporal grid and are applied separately from the smooth tumour evolution. The repeated microvascular oxygen evaluations are performed using the reduced-order approximation described in Section 3.5. The spatial, phenotype and temporal resolutions used in the application studies are summarized in Section 3.6, and their numerical behaviour is examined in Section 4.

3.1 Spatial finite-element approximation

Let $\mathcal{T}_h$ be a conforming tetrahedral partition of $\bar{\Omega}$,

$$\bar{\Omega} = \bigcup_{K \in \mathcal{T}_h} \bar{K}, \quad h = \max_{K \in \mathcal{T}_h} \text{diam}(K),$$

and define the continuous piecewise-linear finite-element space

$$V_h = \{v_h \in C^0(\bar{\Omega}) : v_h|_K \in \mathbb{P}_1(K) \quad \forall K \in \mathcal{T}_h\} \subset H^1(\Omega).$$

Let $\{\varphi_a\}_{a=1}^{N_h}$ denote the nodal basis of V_h . At phenotype node s_i , write $n_{i,h}(\mathbf{x}) = \sum_{a=1}^{N_h} n_{a,i} \varphi_a(\mathbf{x})$.

The physical diffusion term is treated in weak form. For any $v_h \in V_h$,

$$\begin{aligned} -D_{xn} \int_{\Omega} \Delta n_{i,h} v_h \, dV &= D_{xn} \int_{\Omega} \nabla n_{i,h} \cdot \nabla v_h \, dV \\ &\quad - D_{xn} \int_{\partial\Omega} (\nabla n_{i,h} \cdot \boldsymbol{\nu}) v_h \, dS. \end{aligned}$$

The boundary contribution vanishes under the homogeneous no-flux condition on $\partial\Omega$. The consistent finite-element mass and stiffness matrices are therefore

$$M_{ab} = \int_{\Omega} \varphi_a \varphi_b \, dV, \quad K_{ab} = \int_{\Omega} \nabla \varphi_a \cdot \nabla \varphi_b \, dV.$$

For a spatially varying nodal coefficient $q_h = \sum_a q_a \varphi_a$, define the coefficient-weighted lumped matrix

$$M_L(q_h) = \text{diag}(m_a q_a), \quad m_a = \int_{\Omega} \varphi_a \, dV.$$

The transient and phenotype-diffusion terms retain the consistent mass matrix M , physical diffusion is represented by the stiffness matrix K , while the spatially varying reaction and phenotype-advection coefficients are assembled using M_L . Radiotherapy is treated separately from this smooth operator.

3.2 Phenotype discretization

The phenotype interval is discretized uniformly as $s_i = i\Delta s$, $i = 0, \dots, N_s$, with $N_s \Delta s = 1$ and interfaces $s_{i+1/2} = (s_i + s_{i+1})/2 = (i + 1/2)\Delta s$. For coefficients evaluated at time level k , the interface velocity is $v_{i+1/2}^k(\mathbf{x}) = v_s(s_{i+1/2}, c^k(\mathbf{x}))$.

The continuous phenotype flux associated with Eq. (3) is $J_s = -D_{sn} \partial_s n + v_s n$. Let $\mathbf{n}_i = (n_{1,i}, \dots, n_{N_h,i})^T$ denote the vector of spatial finite-element coefficients at phenotype node s_i . A centred approximation of the interface flux after spatial assembly is

$$\mathbf{J}_{i+1/2}^k = -\frac{D_{sn}}{\Delta s} M \left(\mathbf{n}_{i+1}^{k+1} - \mathbf{n}_i^{k+1} \right) + \frac{1}{2} M_L(v_{i+1/2}^k) \left(\mathbf{n}_i^{k+1} + \mathbf{n}_{i+1}^{k+1} \right). \quad (11)$$

For the interior phenotype nodes,

$$[\mathcal{L}_{s,h}^k \mathbf{n}^{k+1}]_i = \frac{\mathbf{J}_{i+1/2}^k - \mathbf{J}_{i-1/2}^k}{\Delta s}, \quad i = 1, \dots, N_s - 1.$$

The no-flux condition at $s = 0$ and $s = 1$ is incorporated by assigning half control volumes to the endpoint nodes,

$$[\mathcal{L}_{s,h}^k \mathbf{n}^{k+1}]_0 = \frac{2}{\Delta s} \mathbf{J}_{1/2}^k, \quad [\mathcal{L}_{s,h}^k \mathbf{n}^{k+1}]_{N_s} = -\frac{2}{\Delta s} \mathbf{J}_{N_s-1/2}^k.$$

Phenotype integrals are evaluated using the composite trapezoidal rule,

$$\int_0^1 n(s) \, ds \simeq \mathbf{w}^T \mathbf{n}, \quad \mathbf{w} = \Delta s \left(\frac{1}{2}, 1, \dots, 1, \frac{1}{2} \right)^T. \quad (12)$$

If L_h denotes the scalar phenotype operator corresponding to the flux-difference discretization before spatial finite-element assembly, the endpoint treatment gives

$$\mathbf{w}^T L_h = \mathbf{0}^T.$$

After spatial assembly, the corresponding block identity is

$$(\mathbf{w}^T \otimes I_{N_h}) \mathcal{L}_{s,h}^k = 0. \quad (13)$$

Hence the discrete phenotype-transport operator preserves the trapezoidal phenotype integral in exact arithmetic. The assembled realization satisfies the same identity up to floating-point accuracy. This property concerns the phenotype-transport contribution only; the complete tumour system is not conservative in the presence of proliferation, death and treatment.

3.3 Fully discrete tumour update and oxygen-first coupling

At phenotype node s_i and time t_k , let

$$n_{h,i}^k(\mathbf{x}) = \sum_{a=1}^{N_h} n_{a,i}^k \varphi_a(\mathbf{x}), \quad \mathbf{n}_i^k = (n_{1,i}^k, \dots, n_{N_h,i}^k)^T.$$

Consider a smooth interval $[t_k, t_{k+1}]$, with $\Delta t_k = t_{k+1} - t_k$. The tumour state at the beginning of the interval determines the occupancy field and, through the coupling defined in Section 2.4, the corresponding quasi-steady oxygen field. The resulting c^k and ϕ^k are held fixed during the tumour update. Accordingly,

$$P_{e,i}^k = P(s_i, c^k)(1 - \phi^k), \quad K_i^k = K(s_i, c^k), \quad F_i^k = P_{e,i}^k - K_i^k,$$

together with the interface velocities $v_{i+1/2}^k$, are fixed over the step. Physical diffusion, phenotype diffusion, phenotype advection with this fixed velocity and the resulting linear reaction term are treated implicitly in the new tumour state.

The backward-Euler update is

$$\frac{M}{\Delta t_k} (\mathbf{n}_i^{k+1} - \mathbf{n}_i^k) + D_{xn} K \mathbf{n}_i^{k+1} + [\mathcal{L}_{s,h}^k \mathbf{n}^{k+1}]_i - M_L(F_i^k) \mathbf{n}_i^{k+1} = \mathbf{0}, \quad i = 0, \dots, N_s. \quad (14)$$

To display the phenotype-block structure, define

$$\mathbf{N}^k = \begin{bmatrix} \mathbf{n}_0^k \\ \mathbf{n}_1^k \\ \vdots \\ \mathbf{n}_{N_s}^k \end{bmatrix} \in \mathbb{R}^{(N_s+1)N_h},$$

together with

$$\mathbb{M} = I_{N_s+1} \otimes M, \quad \mathbb{K} = I_{N_s+1} \otimes K,$$

and

$$\mathbb{R}^k = \text{blkdiag} \left(M_L(F_0^k), \dots, M_L(F_{N_s}^k) \right).$$

The smooth tumour update can then be written compactly as

$$\left[\frac{1}{\Delta t_k} \mathbb{M} + D_{xn} \mathbb{K} + \mathcal{L}_{s,h}^k - \mathbb{R}^k \right] \mathbf{N}^{k+1} = \frac{1}{\Delta t_k} \mathbb{M} \mathbf{N}^k. \quad (15)$$

To make the algebraic structure explicit, define

$$V_{i+1/2}^k = M_L(v_{i+1/2}^k), \quad R_i^k = M_L(F_i^k), \quad \lambda_s = \frac{D_{sn}}{\Delta s^2},$$

and

$$H_k = \frac{1}{\Delta t_k} M + D_{xn} K.$$

The matrix associated with Eq. (15) is block tridiagonal,

$$\mathcal{A}^k = \begin{bmatrix} A_0^k & B_0^k & 0 & \cdots & 0 \\ C_1^k & A_1^k & B_1^k & \ddots & \vdots \\ 0 & C_2^k & A_2^k & \ddots & 0 \\ \vdots & \ddots & \ddots & \ddots & B_{N_s-1}^k \\ 0 & \cdots & 0 & C_{N_s}^k & A_{N_s}^k \end{bmatrix}.$$

For $1 \leq i \leq N_s - 1$,

$$\begin{aligned} C_i^k &= -\lambda_s M - \frac{1}{2\Delta s} V_{i-1/2}^k, \\ A_i^k &= H_k + 2\lambda_s M - R_i^k + \frac{1}{2\Delta s} (V_{i+1/2}^k - V_{i-1/2}^k), \\ B_i^k &= -\lambda_s M + \frac{1}{2\Delta s} V_{i+1/2}^k. \end{aligned}$$

The endpoint rows are

$$\begin{aligned} A_0^k &= H_k + 2\lambda_s M - R_0^k + \frac{1}{\Delta s} V_{1/2}^k, & B_0^k &= -2\lambda_s M + \frac{1}{\Delta s} V_{1/2}^k, \\ C_{N_s}^k &= -2\lambda_s M - \frac{1}{\Delta s} V_{N_s-1/2}^k, & A_{N_s}^k &= H_k + 2\lambda_s M - R_{N_s}^k - \frac{1}{\Delta s} V_{N_s-1/2}^k. \end{aligned}$$

Hence each phenotype block is coupled only to its neighbouring phenotype levels, consistently with the centred interface flux and half-control-volume endpoint discretization.

At each smooth time step, Eq. (15) defines a sparse linear system $A\mathbf{x} = \mathbf{b}$. The system is solved iteratively using LGMRES. A scalar normalization of the right-hand side is applied before the iterative solve, while convergence is assessed in the original variables. A solution is accepted when

$$\|A\mathbf{x} - \mathbf{b}\|_2 \leq \max(10^{-14}, 10^{-8} \|\mathbf{b}\|_2).$$

No positivity correction is applied to the computed tumour state.

The resulting discretization defines an oxygen-first sequential partitioned scheme: the current tumour state determines the quasi-steady oxygen field, and this field remains fixed during the subsequent backward-Euler tumour update. No tumour–oxygen subiterations are performed within a smooth time step.

3.4 Numerical extinction and event-aligned radiotherapy

The continuum tumour description is terminated when the tumour burden falls below the numerical-extinction threshold $m_{\text{ext}} = 10^{-5} \text{ mm}^3$. Since $n = N/\Phi_{\text{max}}$ and $m = \int_{\Omega} \int_0^1 n \, ds \, dV$, the corresponding number of represented cells is

$$N_{\text{rep}}(m) = \Phi_{\text{max}} m.$$

With the reference cellularity adopted for the normalization, $\Phi_{\max} = 10^8 \text{ cells cm}^{-3} = 10^5 \text{ cells mm}^{-3}$, the threshold m_{ext} corresponds to one represented cell in the computational domain. This threshold is adopted as an operational criterion for tumour eradication within the model and defines the prescribed lower resolution limit of the deterministic continuum description. Cell discreteness and stochastic extinction effects are not explicitly resolved by the present model. All numerical-extinction endpoints reported in the application studies are defined with respect to this fixed continuum-resolution threshold.

When either a radiotherapy event or a smooth tumour step first yields $m_h < m_{\text{ext}}$, the continuum evolution is stopped at that time. No subsequent tumour, oxygen or radiotherapy state is evaluated.

Radiotherapy is represented at model level by Eq. (8). Prescribed treatment times are included explicitly in the temporal grid: when an event lies inside a nominal backward-Euler interval, the interval is split so that the survival update is applied at the prescribed treatment time.

At t_j , the pre-treatment tumour state determines the corresponding occupancy ϕ^- , oxygen field c^- and effective proliferation P_e^- . The survival factor is evaluated from these left-limit quantities and applied nodally,

$$n_{i,a}^+ = S_{\text{RT},i,a} n_{i,a}^-,$$

where i and a denote phenotype and spatial degrees of freedom, respectively. The phenotype-integrated occupancy and quasi-steady oxygen field are then recomputed from the post-treatment state before the following smooth interval is advanced. Radiotherapy therefore remains distinct from the backward-Euler operator governing inter-treatment evolution. An additional algebraic consistency check of the discrete event update is given in Appendix A.

3.5 Oxygen reduced-order approximation

Repeated solution of the mixed-dimensional oxygen problem would dominate the cost of the coupled simulations. The quasi-steady oxygen field is therefore approximated using the non-intrusive POD-MINN+ methodology of Vitullo et al. [43]. The surrogate represents the parameter domain used in its construction and returns the tissue oxygen field required by the tumour model.

Vascular family and ROM database. The geometric parameter domain is constructed from synthetic HNC-informed microvascular networks generated using the hierarchical Voronoi approach of Materne et al. [24]. The common synthetic baseline network Λ_0 is informed by pretreatment sublingual GlycoCheck measurements from 68 HNC patients treated at Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy [2]. The upper-quartile diameter-resolved capillary-density profile provides a well-vascularized reference, rather than an intratumoral vascular reconstruction. Starting from each baseline graph, a nested sequence of progressively pruned networks is generated. If E_0 and E denote the edge sets of the baseline and current networks, respectively, the pruning fraction is

$$f_p = 1 - \frac{|E|}{|E_0|}. \quad (16)$$

Edges are removed according to their role in inlet-outlet connectivity, with the retained sequence corresponding to $f_p = 0, 0.1, \dots, 0.6$.

The ROM database starts from 100 distinct baseline networks, which are randomly shuffled and divided into 90 training networks and 10 validation networks before pruning and symmetry transformations are applied. For each baseline, the seven pruning levels and four geometric versions are generated within the same set, giving 2800 samples in total: 2520 training and 280 validation samples. The POD basis and the standardization quantities are computed from the training set only. The number of training epochs is fixed a priori, and the validation set is not used for early stopping or for choosing the network architecture or hyperparameters. The baseline network used in the application studies belongs to the validation set.

Graph-derived geometric representation. Let $N_{h,\text{ROM}}$ denote the number of tissue nodes of the oxygen surrogate. The vascular graph Λ is represented on this tissue grid through the pair

$$\mathcal{E}_{\text{ROM}}(\Lambda) = (\mathbf{d}_\Lambda, \boldsymbol{\eta}_\Lambda),$$

where

$$d_\Lambda(\mathbf{x}) = \text{dist}(\mathbf{x}, \Lambda) = \min_{\mathbf{y} \in \Lambda} \|\mathbf{x} - \mathbf{y}\|_2$$

defines the extravascular-distance field and

$$\mathbf{d}_\Lambda = (d_\Lambda(\mathbf{x}_a))_{a=1}^{N_{h,\text{ROM}}}.$$

The second geometric input $\boldsymbol{\eta}_\Lambda \in \{0, 1\}^{N_{h,\text{ROM}}}$ identifies the tissue-grid support associated with the vascular inlet branches. These two graph-derived fields enter the surrogate directly on the ROM tissue grid.

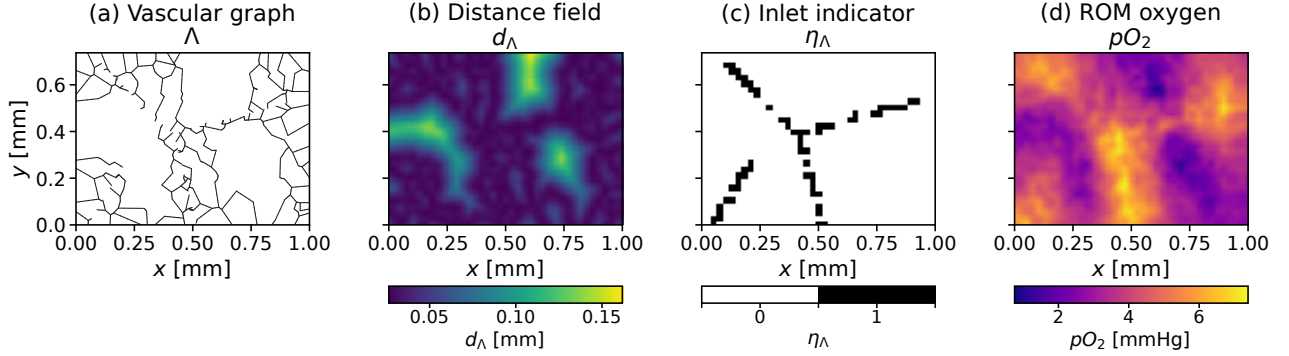


Figure 2: Graph-derived geometric representation used by the oxygen surrogate. We show the extravascular-distance field d_Λ , the vascular-inlet indicator η_Λ and the corresponding ROM-predicted tissue oxygen partial pressure for the same vascular configuration, with $V_{\text{max}} = 2.729 \times 10^{-5} \text{ mL}_{O_2} \text{ cm}^{-3} \text{ s}^{-1}$ and $p_{v,\text{in}} = 50 \text{ mmHg}$.

Nonlinear model order reduction for reconstruction. Let $V_r \in \mathbb{R}^{N_{h,\text{ROM}} \times r}$ collect the retained POD modes. The ROM input is

$$\mu_{\text{ROM}} = (\hat{V}_{\text{max}}, \hat{C}_{v,\text{in}}, \mathbf{d}_\Lambda, \boldsymbol{\eta}_\Lambda) \in \mathcal{P}_{\text{ROM}}.$$

For this input, the reconstructed standardized tissue oxygen field is

$$\mathbf{u}_{\text{ROM}}(\mu_{\text{ROM}}) = V_r \mathbf{a}_\theta(\mu_{\text{ROM}}) + \mathbf{c}_\theta(\mathbf{d}_\Lambda, \boldsymbol{\eta}_\Lambda). \quad (17)$$

Here $\mathbf{a}_\theta : \mathcal{P}_{\text{ROM}} \rightarrow \mathbb{R}^r$ is the learned map to the POD coordinates, while $\mathbf{c}_\theta$ is a high-dimensional geometric correction. The surrogate is non-intrusive: POD defines the reduced representation, but no reduced Galerkin oxygen problem is solved during evaluation.

The scalar inputs are the oxygen-consumption amplitude determined by Eq. (9) and the vascular inlet oxygen concentration. For the ROM evaluation, τ_0 is expressed as 86400 s so that V_{max} is represented in $\text{mL}_{O_2} \text{ cm}^{-3} \text{ s}^{-1}$. The lower end of the represented interval is imposed through

$$V_{\text{max}}^q = \max(V_{\text{max}}, 10^{-8}), \quad \hat{V}_{\text{max}} = \frac{V_{\text{max}}^q - 10^{-8}}{10^{-3} - 10^{-8}}.$$

Thus the represented range is

$$10^{-8} \leq V_{\max}^q \leq 10^{-3} \quad \text{mL}_{O_2} \text{ cm}^{-3} \text{ s}^{-1},$$

and values exceeding the upper bound lie outside the ROM parameter domain. For an input with $V_{\max}$ below the sampled interval, $V_{\max}^q$ is evaluated at the lower boundary of the represented range.

The vascular inlet pressure is converted to dissolved concentration through

$$C_{v,\text{in}} = \alpha_{\text{pl}} p_{v,\text{in}}, \quad \alpha_{\text{pl}} = 2.82 \times 10^{-5} \text{ mL}_{O_2} \text{ cm}^{-3} \text{ mmHg}^{-1}.$$

Over the represented inlet-pressure interval $p_{v,\text{in}} \in [10, 120]$ mmHg, which contains all inlet pressures used in the application studies, the corresponding scalar ROM coordinate is

$$\hat{C}_{v,\text{in}} = \frac{p_{v,\text{in}} - 10}{120 - 10}.$$

The geometric fields $\mathbf{d}_\Lambda$ and $\boldsymbol{\eta}_\Lambda$ are used without an additional scalar normalization.

Defining

$$\mu_{\text{ph}} = \left(\hat{V}_{\max}, \hat{C}_{v,\text{in}} \right),$$

the reduced-coordinate map of the surrogate used here is

$$\mathbf{a}_\theta(\mu_{\text{ROM}}) = [\Psi_d(\mathbf{d}_\Lambda) \odot \Psi_\eta(\boldsymbol{\eta}_\Lambda)] \Phi(\mu_{\text{ph}}), \quad (18)$$

where $\odot$ denotes componentwise multiplication. The high-dimensional correction is additive in the two geometric inputs,

$$\mathbf{c}_\theta(\mathbf{d}_\Lambda, \boldsymbol{\eta}_\Lambda) = C_d(\mathbf{d}_\Lambda) + C_\eta(\boldsymbol{\eta}_\Lambda). \quad (19)$$

The vessel-wall oxygen permeability is fixed and is not an independent ROM coordinate. The surrogate uses $N_{h,\text{ROM}} = 4524$ tissue nodes and $r = 200$ retained POD modes.

The ROM output is mapped back to the dimensional tissue oxygen concentration $C_{t,\text{ROM}}$ using the inverse transformation associated with the surrogate construction. Tissue partial pressure and the normalized oxygen variable are then obtained as

$$pO_{2,\text{ROM}} = \frac{C_{t,\text{ROM}}}{\alpha_t}, \quad c_{\text{ROM}} = \frac{pO_{2,\text{ROM}}}{p_\infty}.$$

Each component of the ROM field is associated with its physical tissue coordinate. On the application mesh, the ROM and tumour P_1 nodal sets coincide physically, so the $N_{h,\text{ROM}}$ oxygen values are transferred directly to the corresponding tumour degrees of freedom. For the noncoincident meshes used in the physical-space resolution study, the ROM field is evaluated on the tumour mesh by piecewise-linear interpolation from the ROM coordinates.

3.6 Computational configuration and time-stepping procedure

The application calculations use a structured box mesh obtained from 38, 28 and 3 subdivisions along the three coordinate directions of the domain in Eq. (1). The resulting nodal grid contains $39 \times 29 \times 4$ nodes, corresponding to $N_h = 4524$ scalar P_1 degrees of freedom. The phenotype spacing is $\Delta s = 0.01$ and the nominal time step is $\Delta t = 0.25$ d. Phenotype integrals are evaluated using Eq. (12), smooth tumour evolution is advanced by the oxygen-first backward-Euler scheme of Section 3.3, and radiotherapy is applied through the event-aligned update of Section 3.4.

The computational study was performed on a system equipped with an Intel(R) Core(TM) i9-14900HX processor with 24 cores, 32 hardware threads and 64 GiB of memory. Timing measurements

from the application calculations give a median wall time of 4.42 s for one coupled smooth time step and 16.5 ms for one oxygen-ROM evaluation including transfer to the application mesh. ROM training was performed on an NVIDIA GeForce RTX 4090.

The event-aligned partitioned procedure is summarized in Algorithm 1.

Algorithm 1 Oxygen-first partitioned time stepping with event-aligned radiotherapy

Require: Tumour state $\mathbf{n}^k$ at the event-aligned time t_k ; nominal time step Δt ; prescribed treatment times $\{\tau_j\}$

- 1: Set t_{k+1} to the earliest of the next nominal time level and the first prescribed treatment time strictly later than t_k , and define $\Delta t_k = t_{k+1} - t_k$
- 2: **if** t_k is a prescribed treatment time **then**
- 3: Evaluate the pre-treatment occupancy, tumour burden and quasi-steady oxygen field from $\mathbf{n}^k$
- 4: Evaluate P_e^- and apply $\mathbf{n}^{k,+} = S_{\text{RT}}(s, c^-, P_e^-; d_j) \mathbf{n}^{k,-}$
- 5: Set $\tilde{\mathbf{n}}^k \leftarrow \mathbf{n}^{k,+}$ and evaluate the post-event burden m^+
- 6: **if** $m^+ < m_{\text{ext}}$ **then**
- 7: Declare numerical extinction at t_k and stop the time integration
- 8: **end if**
- 9: **else**
- 10: Set $\tilde{\mathbf{n}}^k \leftarrow \mathbf{n}^k$
- 11: **end if**
- 12: Recompute the occupancy, tumour burden and quasi-steady oxygen field from $\tilde{\mathbf{n}}^k$
- 13: Evaluate P_e^k , K^k and v_s^k , freeze these coefficients, and solve Eq. (14) over $[t_k, t_{k+1}]$
- 14: Evaluate the updated burden m^{k+1}
- 15: **if** $m^{k+1} < m_{\text{ext}}$ **then**
- 16: Declare numerical extinction at t_{k+1} and stop the time integration
- 17: **end if**
- 18: Set the resulting smooth state as $\mathbf{n}^{k+1}$ and continue on the event-aligned temporal grid

4 Numerical assessment

The numerical assessment addresses two complementary aspects of the coupled framework. First, the sensitivity of the tumour solution to discretization is examined in physical space, time and phenotype. Second, the oxygen surrogate is assessed against the corresponding full-order mixed-dimensional model. Within each refinement study, one discretization coordinate is varied while the remaining model and numerical settings are fixed.

Using the reporting intervals introduced in Section 2.1,

$$I_{\text{CSC}} = [0, 0.3], \quad I_{\text{DC}} = (0.3, 0.8], \quad I_{\text{TDC}} = (0.8, 1],$$

we define, for $\mathcal{K} = \{\text{CSC}, \text{DC}, \text{TDC}\}$, the spatially integrated phenotype-class burdens

$$M_k(t) = \int_{\Omega} \int_{I_k} n(\mathbf{x}, s, t) \, ds \, dV, \quad k \in \mathcal{K},$$

and the vector

$$\mathbf{M}(t) = (M_{\text{CSC}}(t), M_{\text{DC}}(t), M_{\text{TDC}}(t))^T.$$

Since the three intervals partition the phenotype domain,

$$m(t) = \sum_{k \in \mathcal{K}} M_k(t).$$

The phenotype-class burdens are evaluated with the same piecewise-linear trapezoidal rule used for the total phenotype integral. At the reporting interfaces $s = 0.3$ and $s = 0.8$, the nodal weight is divided equally between the two adjacent classes, so that the three class burdens sum to the total burden. For $m(t) > 0$, the corresponding phenotype fractions are

$$f_k(t) = \frac{M_k(t)}{m(t)}, \quad k \in \mathcal{K},$$

with composition vector

$$\mathbf{f}(t) = (f_{\text{CSC}}(t), f_{\text{DC}}(t), f_{\text{TDC}}(t))^T.$$

4.1 Coupled numerical refinement

The coupled refinement studies are performed in two representative oxygenation environments: the normoxic configuration NORM and the hypoxic configuration HYPO:

$$\text{NORM} = (\Lambda_0, 50 \text{ mmHg}), \quad \text{HYPO} = (\Lambda_{0.5}, 20 \text{ mmHg}), \quad (20)$$

where the second component denotes the vascular-inlet oxygen partial pressure.

The corresponding vascular geometries are shown in Figure 3.

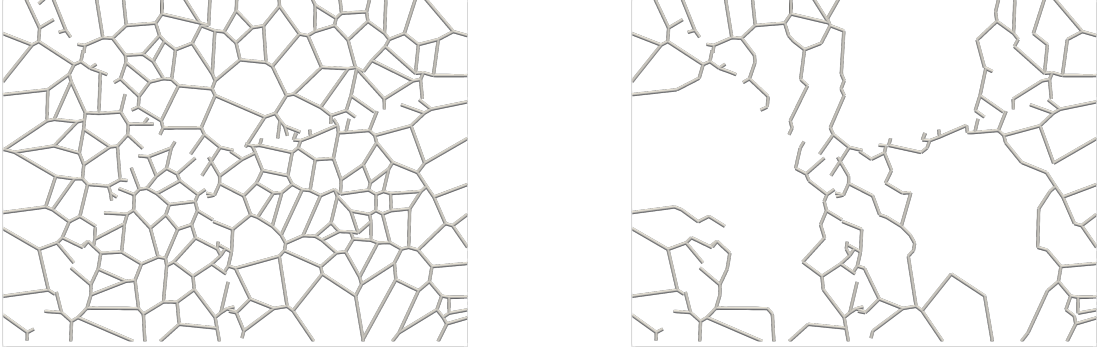


Figure 3: Vascular geometries defining the NORM and HYPO reference environments: Λ_0 and $\Lambda_{0.5}$, respectively. The corresponding inlet oxygen conditions are given in Eq. (20).

Physical-space resolution sensitivity. Sensitivity to physical-space resolution is assessed in both NORM and HYPO while keeping the oxygen surrogate, temporal and phenotype resolutions, biological parameters and radiotherapy schedule fixed. The nested tumour meshes are

$$h_0 = (12, 9, 2), \quad h_1 = (24, 18, 4), \quad h_2 = (48, 36, 8),$$

and the spatial discretization used in the application studies is $(38, 28, 3)$. The spatial campaign uses $\Delta t = 0.125$ d and $\Delta s = 0.01$.

Because numerical extinction is reached during the treatment course, the nested-grid comparison is restricted to the corresponding pre-threshold interval. The last common resolved nodes preceding numerical extinction are $T_*^{\text{NORM}} = 29.875$ d and $T_*^{\text{HYPO}} = 31.875$ d.

For spatial resolution h , let $m_h(t)$, $\mathbf{M}_h(t)$ and $\mathbf{f}_h(t)$ denote the corresponding discrete quantities. For two resolutions a and b , we define

$$D_{a,b}^m(T) = \left[\int_0^T |m_a(t) - m_b(t)|^2 dt \right]^{1/2}, \quad (21)$$

$$D_{a,b}^M(T) = \left[\int_0^T \|\mathbf{M}_a(t) - \mathbf{M}_b(t)\|_2^2 dt \right]^{1/2}, \quad (22)$$

$$D_{a,b}^f(T) = \left[\int_0^T \|\mathbf{f}_a(t) - \mathbf{f}_b(t)\|_2^2 dt \right]^{1/2}. \quad (23)$$

The application mesh is additionally compared directly with h_2 through the relative trajectory difference

$$\delta_I(\mathbf{q}_a, \mathbf{q}_b) = \frac{[\int_I \|\mathbf{q}_a(t) - \mathbf{q}_b(t)\|_2^2 dt]^{1/2}}{[\int_I \|\mathbf{q}_b(t)\|_2^2 dt]^{1/2}}, \quad (24)$$

where the Euclidean norm is replaced by the absolute value for scalar quantities. Here $\mathbf{q}_a = \mathbf{q}_{\text{app}}$, $\mathbf{q}_b = \mathbf{q}_{h_2}$ and $\mathbf{q} \in \{m, \mathbf{M}, \mathbf{f}\}$. The spatial comparisons use a common temporal grid, and the time integrals are evaluated using the composite trapezoidal rule.

The successive nested-grid differences decrease from the h_0 – h_1 comparison to the h_1 – h_2 comparison for all three quantities in both environments, with a less pronounced reduction for phenotype composition than for the burden-based quantities (Table 2).

The application-mesh differences with respect to h_2 remain small over the same pre-threshold intervals. The relative differences in total tumour burden are 1.36% for NORM and 1.74% for HYPO. The corresponding differences in the phenotype-class burden vector are 1.32% and 1.68%, while the phenotype-composition differences are 0.59% and 0.26%, respectively.

Table 2: Physical-space resolution sensitivity of the coupled quantities of interest. Successive nested-grid differences and the comparison between the application mesh and h_2 are evaluated over the pre-threshold interval T_*^e of each environment.

Environment	QoI	D_{h_0, h_1}	D_{h_1, h_2}	Application mesh vs. h_2 [%]
NORM	m	9.88442×10^{-4}	3.52919×10^{-4}	1.358
NORM	$\mathbf{M}$	8.89443×10^{-4}	3.13867×10^{-4}	1.319
NORM	$\mathbf{f}$	6.63302×10^{-3}	5.68547×10^{-3}	0.594
HYPO	m	8.96694×10^{-4}	6.29406×10^{-4}	1.738
HYPO	$\mathbf{M}$	7.84769×10^{-4}	5.40680×10^{-4}	1.683
HYPO	$\mathbf{f}$	9.06752×10^{-3}	6.92618×10^{-3}	0.262

Temporal refinement. Temporal refinement is assessed using

$$\Delta t = 0.25, 0.125, 0.0625, 0.03125 \text{ d},$$

with the physical mesh fixed at $(38, 28, 3)$ and $\Delta s = 0.01$. For these calculations, both environments use the same spatially uniform Gaussian phenotype initialization, $m_0 = 1$, $s_0 = 0.5$ and $\sigma_s^2 = 0.02$, together with the 33-fraction schedule at 2.12 Gy per fraction. All prescribed treatment times belong to every temporal grid.

For time step Δt , let $m_{\Delta t}(t)$ denote the total tumour-burden trajectory. To compare all three refinement ratios on the same time interval, a common endpoint is used within each environment,

$$T_*^{\text{NORM}} = 30 \text{ d}, \quad T_*^{\text{HYPO}} = 31 \text{ d}.$$

For environment $e \in \{\text{NORM}, \text{HYPO}\}$, the comparison is

$$D_{\Delta t, \Delta t/2}^{(e)} = \left[\int_0^{T_*^e} (m_{\Delta t}(t) - m_{\Delta t/2}(t))^2 dt \right]^{1/2}. \quad (25)$$

The difference is evaluated at the nodes of the coarser grid, which are also nodes of the finer grid, and integrated with the composite trapezoidal rule. All treatment times are common grid nodes. At a radiotherapy time t_j , the trajectory comparison uses the pre-event trace $m(t_j^-)$ at every resolution; the survival update is applied separately as the event map of Section 3.4.

For the factor-two refinement sequence, the local empirical orders are

$$p_{t,1} = \log_2 \left(\frac{D_{0.25,0.125}}{D_{0.125,0.0625}} \right), \quad p_{t,2} = \log_2 \left(\frac{D_{0.125,0.0625}}{D_{0.0625,0.03125}} \right).$$

For NORM, the successive trajectory differences are

$$1.69783 \times 10^{-3}, \quad 7.77203 \times 10^{-4}, \quad 3.76774 \times 10^{-4},$$

with

$$p_{t,1} = 1.12733, \quad p_{t,2} = 1.04459.$$

For HYPO, the corresponding differences are

$$2.05202 \times 10^{-3}, \quad 1.07424 \times 10^{-3}, \quad 5.33743 \times 10^{-4},$$

with

$$p_{t,1} = 0.93373, \quad p_{t,2} = 1.00909.$$

The successive differences decrease consistently with time-step refinement, with observed orders close to one in both environments. These results support approximately first-order convergence of the total tumour-burden trajectory under temporal refinement.

Phenotype-grid refinement. Phenotype resolution is assessed using

$$\Delta s = 0.02, 0.01, 0.005, 0.0025,$$

with the physical mesh fixed at $(38, 28, 3)$ and $\Delta t = 0.5 \text{ d}$. The initialization, NORM and HYPO environments and radiotherapy schedule are the same as in the temporal study. The four calculations share the same 0.5-d temporal grid, allowing direct trajectory comparison. At radiotherapy times the same pre-event trace is used for every phenotype resolution, consistently with the temporal refinement metric.

The quantity of interest is the phenotype-class burden vector

$$\mathbf{M}_{\Delta s}(t) = (M_{\text{CSC}}(t), M_{\text{DC}}(t), M_{\text{TDC}}(t))^T.$$

Let $T_{\Delta s, \Delta s/2}^{\text{pre}}$ denote the last common time node preceding numerical extinction in a successive pair. The phenotype-grid difference is

$$D_{\Delta s, \Delta s/2}^{\text{class}} = \left[\int_0^{T_{\Delta s, \Delta s/2}^{\text{pre}}} \|\mathbf{M}_{\Delta s}(t) - \mathbf{M}_{\Delta s/2}(t)\|_2^2 dt \right]^{1/2}. \quad (26)$$

The integral is evaluated on the common temporal grid using the composite trapezoidal rule. The last common resolved node is 30.5 d for all NORM and HYPO pairs. The corresponding empirical orders are

$$p_{s,1}^{\text{class}} = \log_2 \left(\frac{D_{0.02,0.01}^{\text{class}}}{D_{0.01,0.005}^{\text{class}}} \right), \quad p_{s,2}^{\text{class}} = \log_2 \left(\frac{D_{0.01,0.005}^{\text{class}}}{D_{0.005,0.0025}^{\text{class}}} \right).$$

For NORM, the successive differences are

$$7.37396 \times 10^{-5}, \quad 1.84563 \times 10^{-5}, \quad 4.61562 \times 10^{-6},$$

giving

$$p_{s,1}^{\text{class}} = 1.99833, \quad p_{s,2}^{\text{class}} = 1.99952.$$

For HYPO, the corresponding values are

$$4.09791 \times 10^{-5}, \quad 1.02532 \times 10^{-5}, \quad 2.56343 \times 10^{-6},$$

with

$$p_{s,1}^{\text{class}} = 1.99882, \quad p_{s,2}^{\text{class}} = 1.99992.$$

The phenotype-class burden trajectories therefore exhibit approximately second-order convergence under phenotype-grid refinement in both environments.

The coupled refinement calculations remained nonnegative without any positivity correction. Up to numerical extinction, the minimum nodal tumour density was 1.57×10^{-7} in smooth states and 9.14×10^{-8} after radiotherapy updates; the integrated tumour burden remained nonnegative throughout.

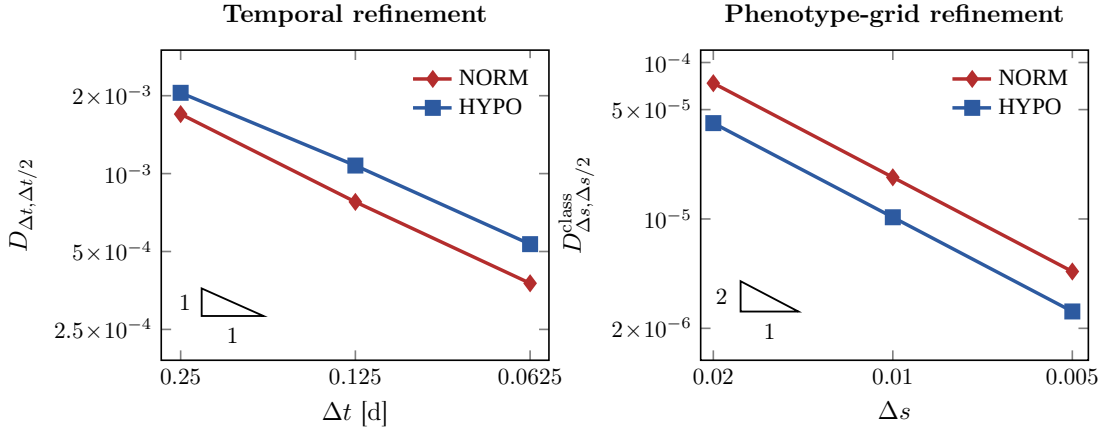


Figure 4: Temporal and phenotype-grid refinement in the NORM and HYPO environments. Left: successive differences in total tumour-burden trajectories under time-step refinement, evaluated over the common pre-extinction interval of each environment. Right: successive pre-extinction differences in the CSC/DC/TDC class-burden trajectories under phenotype-grid refinement. Reference triangles indicate first- and second-order decay, respectively.

4.2 Oxygen-ROM assessment

The oxygen reduced-order model is assessed against the full-order mixed-dimensional oxygen formulation of Possenti et al. [29]. The surrogate follows the POD-MINN+ construction described in

Section 3.5 and introduced in [43]. The assessment concerns the complete oxygen reconstruction used in the coupled simulations.

The surrogate database contains 100 HNC-informed baseline networks. The shuffled baselines are divided into 90 training networks and 10 validation networks before pruning and symmetry transformations are applied. The seven pruning levels and four geometric versions are then generated separately in the two sets, giving 2800 samples in total: 2520 training and 280 validation samples. The POD basis and standardization quantities are computed from the training set only. The number of training epochs is fixed a priori, and the validation set is not used for early stopping or for choosing the network architecture or hyperparameters. The validation metrics characterize generalization to baseline vascular networks not used during surrogate construction within the sampled pruning and scalar-parameter ranges. Further details on the full-order spatial discretization and the validation cases are provided in Appendix B.

Field errors are measured using the finite-element L^2 norm associated with the consistent P_1 mass matrix,

$$\|\mathbf{v}\|_M = (\mathbf{v}^T M \mathbf{v})^{1/2}.$$

The relative field error is

$$E_{L^2}^{FE} = \frac{\|C_{\text{ROM}} - C_{\text{FOM}}\|_M}{\|C_{\text{FOM}}\|_M}, \quad (27)$$

while the absolute finite-element root-mean-square error in oxygen partial pressure is

$$E_{\text{RMSE}}^{FE} = \left(\frac{\mathbf{e}^T M \mathbf{e}}{|\Omega|} \right)^{1/2}, \quad \mathbf{e} = \mathbf{p}_{O_2}^{\text{ROM}} - \mathbf{p}_{O_2}^{\text{FOM}}. \quad (28)$$

The oxygen quantities of interest are the mean tissue partial pressure $\overline{pO_2}$ and the hypoxic fraction HF_{10} , with errors reported as $|\Delta \overline{pO_2}|$ and $|\Delta \text{HF}_{10}|$.

Table 3 summarizes the complete-surrogate errors. On the validation set, the median relative FE- L^2 error is 8.07%, with a 95th percentile of 47.43%. The corresponding median FE-RMSE is 0.224 mmHg. The median absolute error in mean tissue oxygen is 0.0101 mmHg and the median absolute HF_{10} error is zero to the reported precision.

Table 3: Oxygen-surrogate fidelity over the training and validation sets. Differences in HF_{10} are reported in percentage points (pp).

Metric	Train median	Train P95	Val. median	Val. P95	Val. max
Relative FE- L^2 [%]	7.64	46.62	8.07	47.43	149.01
FE-RMSE [mmHg]	0.214	0.623	0.224	0.700	8.215
$ \Delta \overline{pO_2} $ [mmHg]	0.0104	0.127	0.0101	0.0750	6.444
$ \Delta \text{HF}_{10} $ [pp]	0.0104	0.439	0.000	0.406	18.93

To examine the oxygen-dependent mechanisms entering the tumour equations, an additional assessment was performed on all 280 validation configurations. The finite-element-volume-weighted fractions classified differently by FOM and ROM at 0.625, 5 and 15 mmHg had validation medians of 2.804%, 0.313% and 0.000%, respectively; the corresponding 95th percentiles were 8.405%, 1.766% and 0.940%. The largest 15 mmHg disagreement, 42.142%, occurs in the same validation configuration that gives the largest oxygen quantity-of-interest discrepancy discussed below. Errors in the oxygen-dependent radiotherapy factors and tumour constitutive terms are reported in Appendix B.

The approximation capacity of the POD subspace is shown in Figure 5. Projection error decreases throughout the investigated rank range. At the retained dimension $r = 200$, the median relative

projection error is 3.30% in the standardized POD snapshot norm and the median projection FE-RMSE is 0.204 mmHg. These errors characterize the representation capacity of the POD subspace and are distinct from the errors of the complete surrogate reported in Table 3.

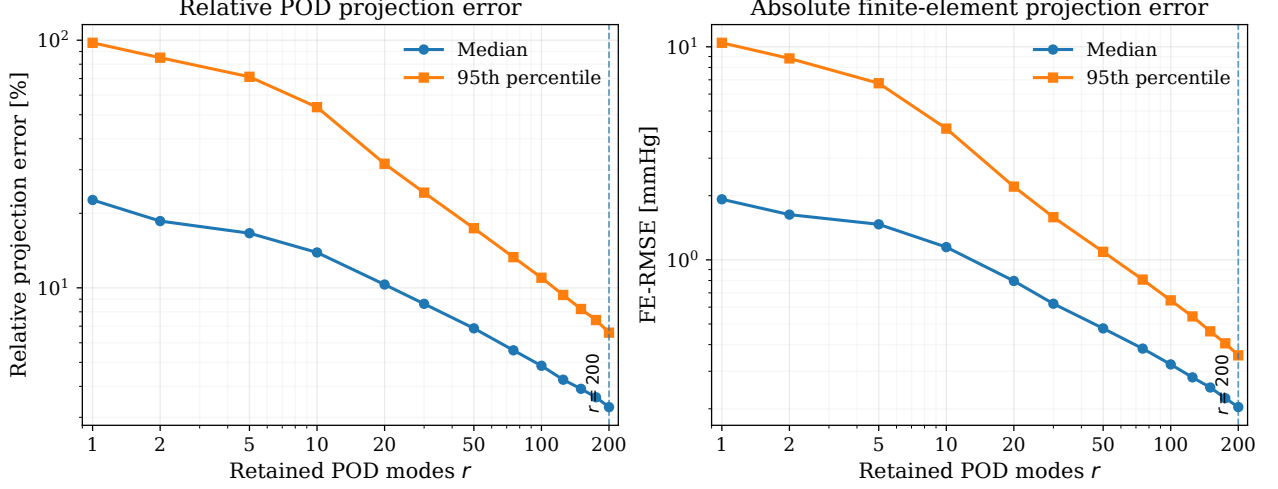


Figure 5: Approximation capacity of the POD subspace. (a) Median and 95th-percentile relative projection error in the standardized POD snapshot norm. (b) Median and 95th-percentile finite-element projection RMSE. The retained dimension $r = 200$ is indicated in both panels.

Figure 6 illustrates the spatial fidelity of the complete surrogate for a representative validation configuration. The reconstruction captures the dominant structure of the full-order oxygen field, while the error map shows the spatial distribution of the remaining discrepancy.

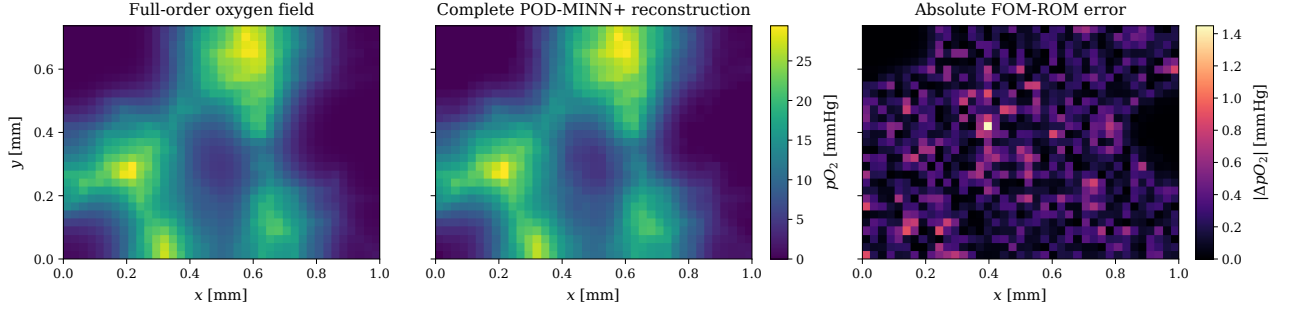


Figure 6: Representative spatial comparison on a slice of the tissue domain between the full-order oxygen solution and the complete reduced-order reconstruction. We show the FOM tissue oxygen partial-pressure field, the ROM reconstruction and the pointwise absolute error.

The upper tail of the relative-error distribution is strongly influenced by near-anoxic configurations, for which the norm of the full-order oxygen field becomes small. Among validation cases with mean FOM tissue oxygen below 0.1 mmHg, the median relative FE- L^2 error is approximately 56%, while the median absolute FE-RMSE remains approximately 0.077 mmHg.

The largest validation relative error, 149.0%, occurs in a near-anoxic configuration with mean FOM tissue oxygen of approximately 0.023 mmHg. The absolute error in mean tissue oxygen is approximately 0.026 mmHg and the corresponding HF₁₀ value is unchanged.

A different validation configuration gives the largest discrepancy in the oxygen quantities of interest,

$$|\Delta p\overline{O_2}| = 6.44 \text{ mmHg}, \quad |\Delta \text{HF}_{10}| = 18.93 \text{ pp}.$$

It is retained in the aggregate validation statistics. Extended error distributions and representative validation cases are reported in Appendix B.

5 Application to heterogeneous vascular microenvironments

The computational applications examine how vascular oxygen supply and radiotherapy exposure shape the response of the coupled tumour model. Two complementary analyses are considered. The first compares dose response in the representative NORM and HYPO environments introduced above. The second extends the analysis across a vascular microenvironment map obtained by combining progressive vascular pruning with three inlet oxygen conditions.

5.1 Application design and response measures

The vascular configurations are obtained from a single synthetic HNC-informed baseline network belonging to the validation set described in Section 3.5. Starting from the intact graph Λ_0 , progressive topology-aware pruning generates the nested sequence $\Lambda_0, \Lambda_{0.1}, \dots, \Lambda_{0.6}$, where the pruning fraction f_p is defined by Eq. (16). The seven networks therefore represent successive pruned states of the same baseline vascular realization.

All application simulations use the HSC2 tumour parameterization and the same spatially uniform initial phenotype distribution,

$$n(\mathbf{x}, s, 0) = \frac{m_0}{\sqrt{2\pi}\sigma_s} \exp\left[-\frac{(s - s_0)^2}{2\sigma_s^2}\right], \quad m_0 = 1, \quad s_0 = 0.30, \quad \sigma_s^2 = 0.02.$$

Here m_0 denotes the amplitude of the initial phenotype distribution and is distinct from the spatially integrated tumour burden $m(t)$ defined in Eq. (2). The numerical discretization is that specified in Section 3.6.

The dose-response analysis uses the two reference environments NORM and HYPO defined in Section 4.

Each radiotherapy fraction delivers 2.12 Gy. The dose-response study varies the number of administered fractions according to

$$n_f \in \{15, 19, 23, 26, 30, 33\},$$

corresponding to total prescribed doses

$$31.80, 40.28, 48.76, 55.12, 63.60, 69.96 \text{ Gy}.$$

The longest schedule, delivering 69.96 Gy in 33 fractions, approximates a conventional definitive radiotherapy course for locally advanced head-and-neck cancer [34]. The remaining schedules represent shorter treatment courses at the same dose per fraction. Fractions are delivered on weekdays beginning at model day zero.

The vascular-map analysis considers

$$\mathcal{E}_{\text{map}} = \{(\Lambda_{f_p}, p_{v,\text{in}}) : f_p \in \{0, 0.1, \dots, 0.6\}, p_{v,\text{in}} \in \{20, 35, 50\} \text{ mmHg}\}, \quad (29)$$

giving 21 microenvironmental configurations. All are treated using the reference course of 33×2.12 Gy.

To compare the vascular-map configurations before numerical extinction is reached in any of them, a common treatment event is selected. Let $m_j^+(\mu) = m(t_j^+; \mu)$, $\mu \in \mathcal{E}_{\text{map}}$, denote the post-fraction tumour burden. We define

$$j_\star := \max \left\{ j : \min_{\mu \in \mathcal{E}_{\text{map}}} m_j^+(\mu) > m_{\text{ext}} \right\} = 23, \quad t_\star = t_{j_\star} = 30 \text{ d}. \quad (30)$$

Thus, $j_\star$ is the latest treatment event at which all 21 configurations remain above the numerical-extinction scale. At this event, $\min_{\mu \in \mathcal{E}_{\text{map}}} m_{j_\star}^+(\mu) = 1.17414 \times 10^{-5} \text{ mm}^3 > m_{\text{ext}}$. Phenotype composition is evaluated at the first common post-event time point, $t_\star + \Delta t = 30.25 \text{ d}$.

Two derived response measures are used in the application analyses. If $m_j^- = m(t_j^-)$ and $m_j^+ = m(t_j^+)$ denote the tumour burdens immediately before and after treatment event j , the cumulative radiotherapy-associated burden reduction through event J is

$$K_{\text{RT}}^{1:J} = - \sum_{j=1}^J \log_{10} \left(\frac{m_j^+}{m_j^-} \right). \quad (31)$$

For a dose-response course that remains resolved through its prescribed end of treatment, $K_{\text{RT}} = K_{\text{RT}}^{1:n_f}$. If numerical extinction is reached earlier, subsequent treatment events are not simulated.

The tissue fraction below 10 mmHg is

$$HF_{10}(t) = \frac{1}{|\Omega|} \int_{\Omega} \mathbf{1}_{\{pO_2(\mathbf{x}, t) < 10 \text{ mmHg}\}} dV. \quad (32)$$

For the vascular-map comparison, hypoxic exposure over the common treatment interval is summarized by the arithmetic mean over the pre-fraction oxygen states,

$$\langle HF_{10} \rangle_{\text{pre}}^{1:j_\star} = \frac{1}{j_\star} \sum_{j=1}^{j_\star} HF_{10}(t_j^-). \quad (33)$$

The average is taken over the 23 pre-fraction oxygen states.

The complete application settings and sampled parameter ranges are summarized in Table 8 of Appendix C.

5.2 Dose response in normoxic and hypoxic environments

The dose-response analysis compares the two reference environments while keeping the tumour parameterization, dose per fraction and numerical discretization fixed. For courses that remain above m_{ext} through the prescribed end of treatment (EOT), the post-treatment burden is defined as $m_{\text{EOT}}^+ = m(t_{n_f}^+)$. Courses reaching numerical extinction earlier have no post-treatment tumour state.

On the application discretization, the NORM dose sweep changes from resolved post-treatment repopulation to numerical extinction between 23 and 26 fractions, corresponding to 48.76–55.12 Gy. In HYPO, all six courses remain above m_{ext} through EOT and continue to the final simulation time of 100 d, so no numerical-extinction transition is found up to 33 fractions (69.96 Gy).

For NORM-23, the post-treatment burden is $2.16788 \times 10^{-5} \text{ mm}^3$ and increases over the following 0.25 d. The NORM courses prescribed 26, 30 and 33 fractions reach numerical extinction at event 25 on day 32, with a post-event burden of $8.00311 \times 10^{-6} \text{ mm}^3$. In HYPO, even the 33-fraction course remains above the threshold at EOT, with $m_{\text{EOT}}^+ = 4.19601 \times 10^{-5} \text{ mm}^3$. The cumulative radiotherapy-associated reduction K_{RT} is smaller in HYPO than in NORM for the matched courses that remain resolved through EOT (Figure 7d).

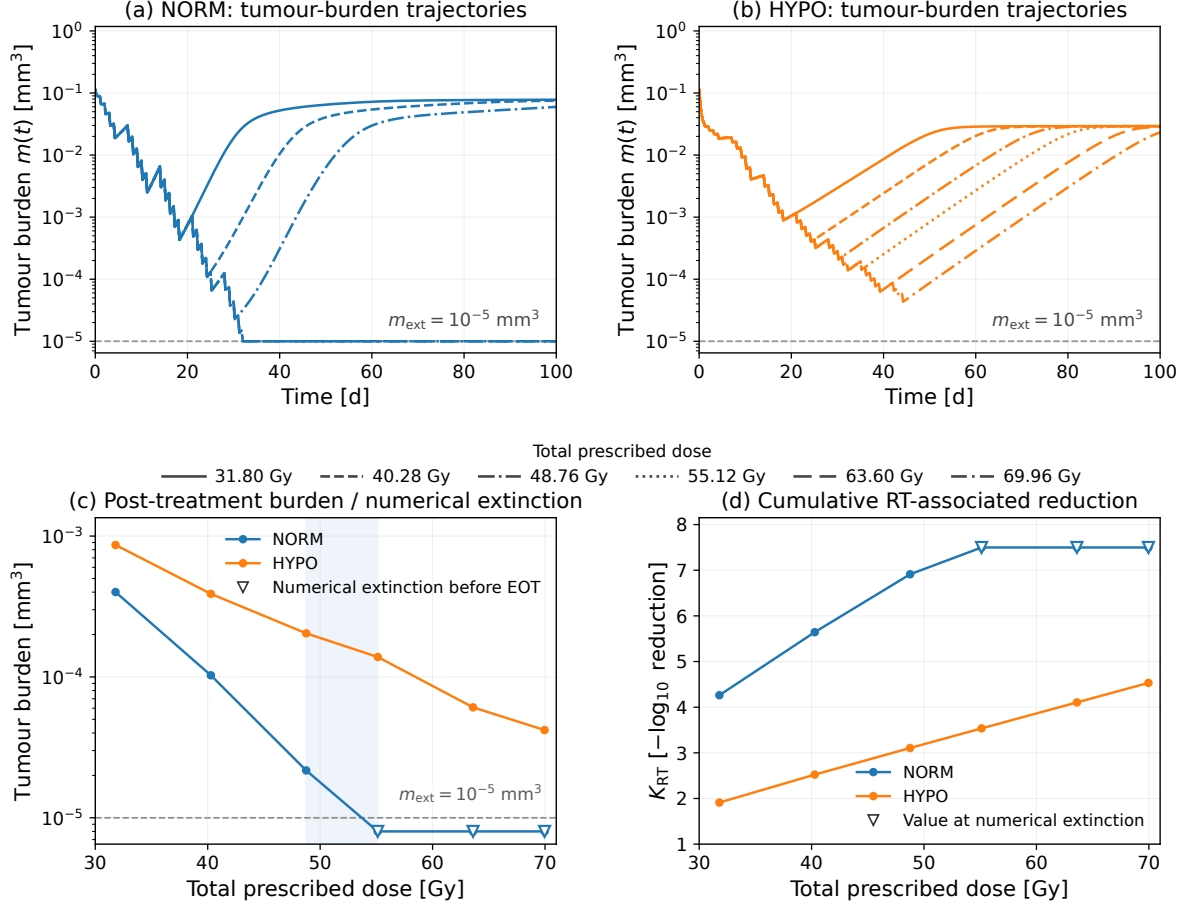


Figure 7: Dose response in the NORM and HYPO environments on the application discretization. (a,b) Tumour-burden trajectories for the six prescribed total doses. The dashed horizontal line denotes the numerical-extinction threshold $m_{\text{ext}} = 10^{-5}$ mm³; (c) post-treatment burden for courses that remain above m_{ext} through EOT; open triangles denote the burden at the numerical-extinction event for courses terminated before EOT. The shaded region indicates the NORM transition interval on the application discretization. (d) Cumulative radiotherapy-associated burden reduction K_{RT} ; open triangles denote its value at the extinction event, with no subsequent fractions included. Targeted refinement results are reported in Table 4.

To verify the numerical robustness of the dose-response outcomes close to numerical extinction, three prescribed courses were examined on both the application discretization and a refined discretization with $N_x \times N_y \times N_z = 48 \times 36 \times 8$, $\Delta t = 0.0625$ d and $\Delta s = 0.005$. The tumour initialization, model parameters and numerical-extinction threshold $m_{\text{ext}} = 10^{-5}$ mm³ were kept fixed. NORM-23 and NORM-26 were selected to assess the transition observed in the dose sweep, whereas HYPO-33 tests the highest prescribed dose in the hypoxic environment. For completed courses, the reported decision burden is the post-RT burden at EOT; for a course terminated by numerical extinction, it is the post-RT burden at the event triggering termination. The cumulative K_{RT} includes only RT events actually executed.

Table 4: Targeted comparison of dose-response outcomes on the application and refined discretizations for $m_{\text{ext}} = 10^{-5} \text{ mm}^3$. NORM-26 reaches numerical extinction at RT event 25 on both discretizations; NORM-23 and HYPO-33 remain above threshold at the prescribed end of treatment (EOT).

Env.	n_f	Application discretization			Refined discretization		
		Decision	$m_{\text{dec}}/m_{\text{ext}}$	K_{RT}	Decision	$m_{\text{dec}}/m_{\text{ext}}$	K_{RT}
NORM	23	EOT, above	2.1679	6.9111	EOT, above	1.8685	6.8804
NORM	26	RT25, extinct	0.8003	7.4984	RT25, extinct	0.6961	7.4677
HYPO	33	EOT, above	4.1960	4.5315	EOT, above	4.4789	4.4816

The outcome classification is unchanged under refinement for all three selected courses. NORM-23 completes 23 fractions (48.76 Gy) above threshold, whereas NORM-26 reaches numerical extinction immediately after the 25th delivered fraction (53.0 Gy), before the prescribed 26th fraction, on both discretizations. The sampled change in response between the 23- and 26-fraction prescriptions is therefore reproduced on the refined discretization, without establishing convergence of a critical dose. The decision burden decreases by 13.8% for NORM-23 and by 13.0% for NORM-26 under refinement, while its respective classification and, for NORM-26, the terminal event remain unchanged.

In HYPO, all six application-discretization courses remain above the numerical-extinction threshold throughout treatment and to the final simulation time of 100 d. At the largest prescribed dose, HYPO-33 also completes all 33 fractions (69.96 Gy) above threshold on the refined discretization; its EOT burden is 6.7% larger than on the application discretization. The refined calculation ends one smooth time step after EOT and does not assess longer-term post-treatment evolution. Thus, no numerical-extinction transition is observed within the tested HYPO dose range, and the contrast with the NORM response is preserved on both discretizations.

5.3 Response across the vascular microenvironment map

The vascular-map analysis examines the combined influence of vascular pruning and inlet oxygen supply over the 21 configurations in $\mathcal{E}_{\text{map}}$. Comparisons are made at the common reference event $j_\star = 23$, when all post-treatment burdens remain above m_{ext} . The principal quantities are the mean pre-fraction hypoxic fraction $\langle HF_{10} \rangle_{\text{pre}}^{1:j_\star}$, the cumulative treatment-associated reduction $K_{\text{RT}}^{1:j_\star}$ and the post-event burden $m_{j_\star}^+$.

The inlet oxygen condition provides the clearest separation among the vascular-map responses (Figure 8). At $p_{v,\text{in}} = 20 \text{ mmHg}$, hypoxic exposure is largest and the phenotype distribution is predominantly associated with the CSC interval across the pruning sequence. At 50 mmHg, hypoxic exposure remains low and the population is dominated by more differentiated phenotypes. The 35 mmHg condition lies between these regimes and exhibits a more pronounced variation in phenotype composition with pruning.

Vascular pruning introduces an additional modulation within each inlet condition. Its effects on $\langle HF_{10} \rangle_{\text{pre}}^{1:j_\star}$, $K_{\text{RT}}^{1:j_\star}$ and $m_{j_\star}^+$ vary in both magnitude and direction across the three inlet oxygen levels. The sampled map therefore does not exhibit a globally monotone dependence of treatment response on pruning. Inlet oxygen supply provides the clearest stratification across the configurations, while vascular pruning produces an additional environment-dependent modulation.

The oxygen state at the common reference event further illustrates the combined roles of inlet supply and vascular pruning. Immediately before event $j_\star$, the mean tissue oxygen tension is 34.5466 mmHg in NORM, ($\Lambda_0, 50 \text{ mmHg}$), and 13.8956 mmHg for the intact network with inlet pressure reduced to 20 mmHg. In HYPO, ($\Lambda_{0.5}, 20 \text{ mmHg}$), the corresponding mean is 10.3355 mmHg. At the first smooth state after the event, $t = 30.25 \text{ d}$, $HF_{10} = 0$ for both intact-network configurations and $HF_{10} = 0.28501$

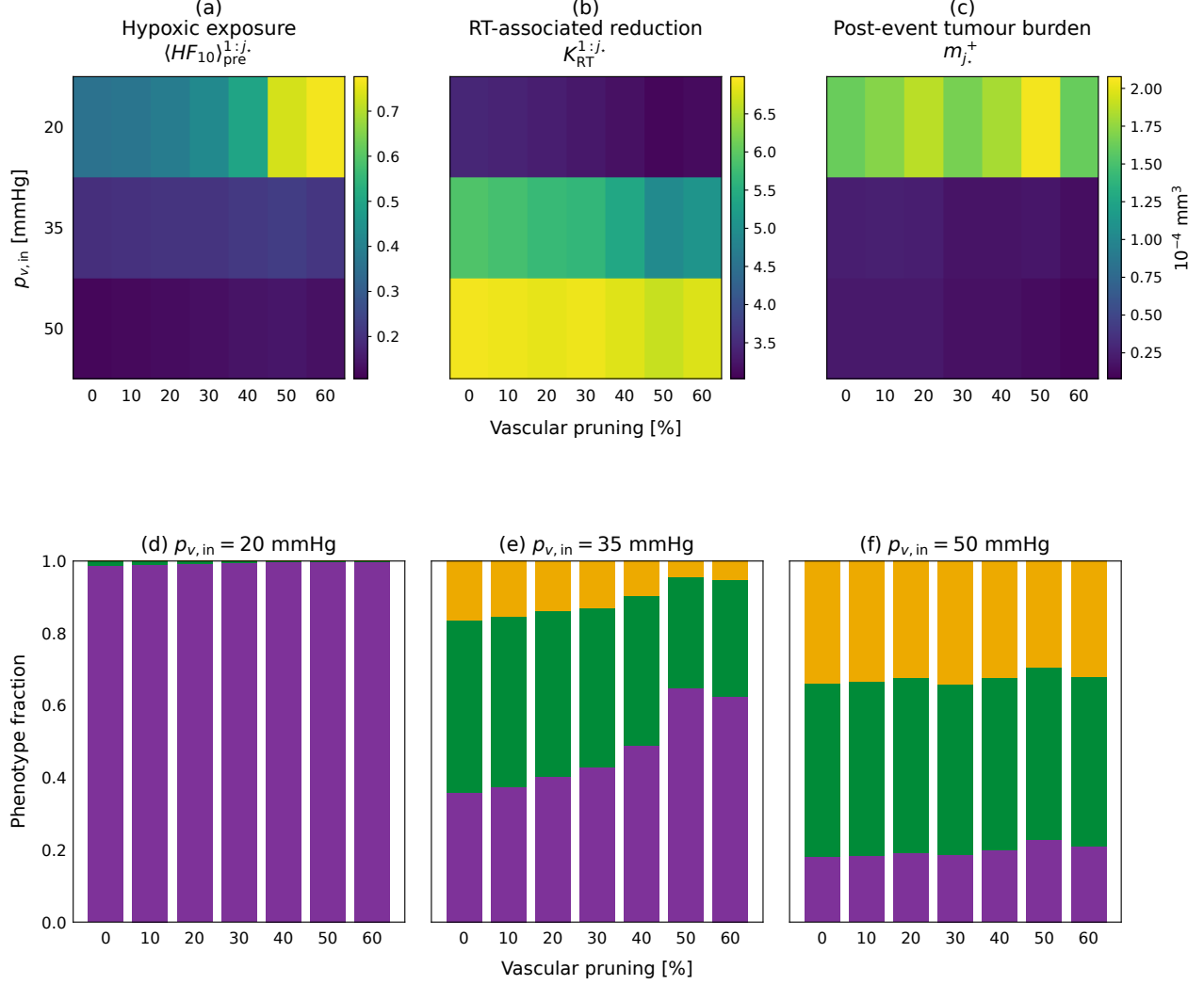


Figure 8: Response across the vascular microenvironment map at the common reference event $j_* = 23$ ($t_* = 30$ d). (a) Mean pre-fraction hypoxic fraction over treatment events $1, \dots, j_*$. (b) Cumulative radiotherapy-associated burden reduction over the same interval. (c) Post-event tumour burden $m_{j_*}^+$. (d-f) Phenotype composition at the first common post-event time point, $t_* + \Delta t = 30.25$ d, for inlet oxygen pressures 20, 35 and 50 mmHg, respectively.

in HYPO. These comparisons illustrate the reduction in mean tissue oxygen associated with lower inlet supply and the larger hypoxic fraction observed when low inlet oxygen is combined with vascular pruning.

6 Discussion

The simulations show that the vascular microenvironment can influence radiotherapy response through two mechanisms that are coupled in the present model. Oxygen availability directly modifies radiosensitivity through the oxygen-dependent radiotherapy response, while also regulating phenotypic adaptation. Low oxygen favours movement towards more stem-like states, whereas better oxygenation favours differentiation. Because the stem-like region of the phenotype space is associated with lower in-

trinsic radiosensitivity, changes in oxygen availability can affect treatment response both at irradiation and through the phenotype distribution shaped by the preceding oxygen history [39, 6, 5, 1].

This interaction provides a model-based interpretation of the different dose responses observed in NORM and HYPO. HYPO combines lower inlet oxygen with a more strongly pruned vascular geometry and exhibits a smaller cumulative radiotherapy-associated burden reduction for the matched courses that remain above m_{ext} through EOT. The targeted refinement confirms the separation between the two environments. On both discretizations, NORM-23 completes treatment above the numerical-extinction threshold, whereas NORM-26 reaches numerical extinction immediately after the 25th delivered fraction (53.0 Gy), before completing the prescribed course. The sampled NORM transition interval is therefore reproduced under refinement, although convergence of a critical dose is not established. In contrast, all six HYPO courses remain above the numerical-extinction threshold up to 100 d on the application discretization, while the refined HYPO-33 calculation confirms that the highest prescribed dose (69.96 Gy) also leaves the tumour burden above threshold at EOT. No numerical-extinction transition is observed in HYPO within the investigated dose range. These results are consistent with previous modelling studies in which oxygen availability modulates radiotherapy response and phenotypic selection [33, 10, 6, 5, 1]. In the present formulation, tissue oxygenation is generated from the microvascular configuration and therefore varies with both vascular architecture and inlet oxygen supply.

The vascular-map analysis further shows that inlet oxygen and vascular pruning do not act as equivalent scalar controls. Inlet oxygen provides the clearest stratification across the sampled configurations: low-supply conditions are associated with greater hypoxic exposure and phenotype distributions concentrated towards the CSC interval, whereas high-supply conditions are more strongly associated with differentiated phenotypes. The intermediate 35 mmHg condition exhibits a stronger variation in phenotype composition across the pruning sequence. Within the present model, these trends are consistent with oxygen-dependent phenotypic drift across oxygenation regimes favouring differentiation or movement towards more stem-like states [11, 5, 35].

Vascular pruning introduces an additional modulation whose magnitude and direction depend on the inlet condition. At fixed inlet oxygen, changes in vascular architecture alter hypoxic exposure and the resulting tumour response, and the sampled pruning sequence does not define a globally monotone response coordinate. In particular, comparison of intact and pruned networks under low inlet oxygen shows that vascular geometry can substantially alter the hypoxic fraction even when the inlet condition is unchanged. This dependence on vascular architecture is consistent with network-based descriptions of tissue oxygen transport and computational studies of abnormal tumour microvasculature [37, 38, 9].

The numerical assessment provides the context for these application results. The physical-space study shows decreasing differences in the burden-based quantities under refinement, the temporal study gives approximately first-order behaviour for the tumour-burden trajectory, and phenotype refinement gives approximately second-order behaviour for the phenotype-class burden trajectories. The oxygen surrogate reproduces the full-order fields with small typical absolute errors across the held-out baseline vascular families, while the upper tail contains a small number of more demanding oxygen configurations. The additional threshold-based assessment shows low typical disagreement at the 5 mmHg radiotherapy threshold and identifies larger discrepancies in a small number of validation configurations at the other mechanistic oxygen thresholds. This assessment quantifies the oxygen-dependent inputs to the tumour equations; propagation through a coupled calculation using full-order oxygen throughout the tumour trajectory is not evaluated here.

Several modelling assumptions delimit the interpretation of the application results. The vascular architecture is fixed during each simulation, so angiogenesis, vascular remodelling and treatment-induced changes in perfusion are not represented. Tumour-dependent oxygen consumption depends

on the mean tumour occupancy, while local phenotype-dependent variation in consumption is not included. The applications use a single HSC2 tumour parameterization and one nested pruning sequence drawn from the synthetic vascular family and therefore do not quantify variability across tumours, vascular realizations or patients.

Radiotherapy is represented through instantaneous survival events, without delayed radiation-induced death, senescence, vascular damage or direct radiation-induced phenotypic transitions. Phenotype composition may still change after irradiation through differential survival and subsequent oxygen-dependent evolution. Finally, the numerical-extinction threshold $m_{\text{ext}} = 10^{-5} \text{ mm}^3$ corresponds to approximately one represented cell at the maximum tumour-cell density. This threshold defines a prescribed lower resolution limit for the continuum tumour description. Once the tumour burden falls below this value, the numerical evolution is terminated, including any subsequent treatment events. Numerical extinction therefore indicates the termination of the continuum description at the prescribed scale and an operational criterion for tumour eradication within the model.

7 Conclusions

This study formulates and numerically assesses the Cell Oxygen Radiotherapy Evolution (CORE) model, coupling phenotype-structured tumour evolution, microvascular oxygen transport and fractionated radiotherapy. The microvascular network determines a spatially heterogeneous oxygen environment, while tumour burden modulates oxygen consumption and tissue oxygenation regulates both phenotypic adaptation and radiotherapy response. Repeated evaluation of the quasi-steady oxygen problem is enabled by a nonlinear reduced-order model, allowing these mechanisms to be followed throughout fractionated treatment.

The computational applications show that oxygen supply and vascular architecture are distinct determinants of tumour response. NORM and HYPO exhibit distinct dose-response behaviour, with numerical extinction occurring within the investigated NORM dose range, whereas all HYPO courses remain above the extinction threshold. Targeted refinement preserves this separation and reproduces the sampled NORM transition interval, without establishing convergence of a critical dose. Across the broader vascular map, inlet oxygen provides the clearest organization of hypoxic exposure and phenotype composition, while vascular pruning introduces an additional modulation whose magnitude and direction depend on the oxygen-supply condition. Lower oxygen availability is associated with stronger hypoxic exposure, reduced radiotherapy-associated burden reduction and tumour populations shifted towards the stem-like region of the phenotype space.

These results highlight a mechanism that extends beyond the instantaneous effect of oxygen on radiosensitivity. The microvascular environment also shapes the phenotype distribution during the intervals between treatment events, thereby altering the tumour state encountered by subsequent fractions. Oxygen history can therefore influence treatment response through both the current radiosensitivity of the tumour and the phenotypic composition generated during its preceding evolution. This interaction provides a mechanistic link between vascular organization, oxygen availability, phenotypic plasticity and fractionated treatment response.

An important feature of the formulation is that the heterogeneous oxygen environment emerges from an explicit microvascular configuration. Changes in vascular pruning and inlet oxygen can consequently be studied as distinct perturbations of the tumour microenvironment, while their effects propagate through oxygen transport to tumour evolution and radiotherapy response. This provides a controlled computational setting for investigating interactions that are difficult to isolate experimentally and for exploring how different microvascular environments may lead to different evolutionary and treatment trajectories.

The present study considers fixed vascular architectures, a mean-occupancy dependence of oxygen

consumption and a single tumour parameterization. Extending the framework towards vascular remodelling, spatially resolved tumour-dependent oxygen consumption and variability across tumour and vascular characteristics would broaden the range of microenvironmental interactions that can be investigated. Incorporation of patient-specific vascular information represents a further step towards using mechanistic multiscale models to study individual differences in tumour oxygenation and response to radiotherapy. Further developments may incorporate tumour-specific radiobiological parameterizations and a more detailed representation of radiation-induced cell damage and the evolution of non-clonogenic cell populations.

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Ethics Statement

The Institutional Review Board approved the prospective study (ID INT 193/20), and all participants provided informed consent.

Data and Code availability

The results were generated by numerical simulations using the model equations, parameter values and computational procedures described in the article and its appendices. The simulation results supporting the findings are presented in the article and its appendices. The numerical implementation used in this study includes custom code for the phenotype-structured tumor model, oxygen transport coupling, vascular pruning, spatial analysis, and hypoxia metric computation. A documented version sufficient to reproduce the main results will be made available in a public repository upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

A Additional numerical verification

An isolated one-step transient diffusion benchmark was used to assess the spatial finite-element discretization independently of the complete coupled tumour model. The problem is

$$\partial_t u - D\Delta u = 0 \quad \text{in } \Omega_b, \quad \nabla u \cdot \boldsymbol{\nu} = 0 \quad \text{on } \partial\Omega_b,$$

with $D = 2.4 \times 10^{-3} \text{ mm}^2 \text{ d}^{-1}$, $\Delta t = T = 0.5 \text{ d}$ and

$$\Omega_b = [0, 1] \times [0, 0.737] \times [-0.079, 0.079] \text{ mm}^3.$$

Writing $L_x = 1$, $L_y = 0.737$, $L_z = 0.158$ and $z_0 = -0.079$, the initial condition is

$$u^0(\mathbf{x}) = 1 + 0.25 \psi(\mathbf{x}), \quad \psi(\mathbf{x}) = \cos\left(\frac{\pi x}{L_x}\right) \cos\left(\frac{\pi y}{L_y}\right) \cos\left(\frac{\pi(z - z_0)}{L_z}\right).$$

The benchmark reference is the exact attenuation of this mode under a single backward-Euler step. With

$$\lambda = \pi^2 (L_x^{-2} + L_y^{-2} + L_z^{-2}), \quad a_{\text{BE}} = \frac{1}{1 + \Delta t D \lambda},$$

the reference field is

$$u_{\text{ref}}(\mathbf{x}, T) = 1 + 0.25 a_{\text{BE}} \psi(\mathbf{x}).$$

The reported error is the absolute physical $L^2(\Omega_b)$ error

$$E_h = \left[\int_{\Omega_b} (u_h - u_{\text{ref}})^2 \text{d}V \right]^{1/2}.$$

The integral was evaluated by FEniCS assembly using the quadrature associated with the declared expression degree. The errors decrease monotonically under refinement and the observed rate approaches the expected L^2 behaviour of the underlying P_1 approximation. These rates characterize the isolated spatial benchmark.

Table 5: Isolated spatial finite-element benchmark.

Mesh	$h_{\max}$	DOFs	Error	Observed order
$12 \times 9 \times 2$	0.14103629	390	5.78114×10^{-3}	—
$24 \times 18 \times 4$	0.07051814	2375	1.62115×10^{-3}	1.834
$48 \times 36 \times 8$	0.03525907	16317	4.18392×10^{-4}	1.954

The isolated phenotype benchmark removes spatial diffusion, reaction, radiotherapy and the oxygen surrogate, leaving only the drift-diffusion problem

$$\partial_t n = \partial_s (D_s \partial_s n - v(s, C) n), \quad s \in [0, 1], \quad D_s = 1.2 \times 10^{-4},$$

or equivalently $\partial_t n + \partial_s J = 0$ with

$$J = -D_s \partial_s n + v(s, C) n, \quad J(0) = J(1) = 0.$$

On a uniform phenotype grid, the centered interface flux is

$$J_{i+1/2} = -D_s \frac{N_{i+1} - N_i}{\Delta s} + v_{i+1/2} \frac{N_i + N_{i+1}}{2},$$

and the isolated discrete operator L_h is defined by

$$\frac{N^{k+1} - N^k}{\Delta t} + L_h N^{k+1} = 0,$$

with

$$(L_h N)_i = \frac{J_{i+1/2} - J_{i-1/2}}{\Delta s}, \quad 1 \leq i \leq N_s - 1,$$

and half-control-volume endpoint rows

$$(L_h N)_0 = \frac{2J_{1/2}}{\Delta s}, \quad (L_h N)_{N_s} = -\frac{2J_{N_s-1/2}}{\Delta s}.$$

The drift used in this isolated harness is

$$v(s, C) = v_+(s, C) - v_-(s, C),$$

with

$$\begin{aligned} v_+(s, C) &= V_+ \tanh\left(\frac{s}{\xi_+}\right) \tanh\left(\frac{1-s}{\xi_+}\right) H_+(C), \\ v_-(s, C) &= V_- \tanh\left(\frac{s}{\xi_-}\right) \tanh\left(\frac{(1-s)^2}{\xi_-}\right) H_-(C), \end{aligned}$$

where

$$H_+(C) = \frac{1}{2} + \frac{1}{2} \tanh\left(\frac{C - c_H}{\varepsilon}\right), \quad H_-(C) = \frac{1}{2} + \frac{1}{2} \tanh\left(\frac{c_H - C}{\varepsilon}\right),$$

and

$$V_+ = 1.92 \times 10^{-2}, \quad V_- = 0.48 \times 10^{-2}, \quad \xi_+ = \xi_- = 0.1, \quad c_H = 0.3, \quad \varepsilon = 0.05.$$

For the composite-trapezoidal weights

$$\mathbf{w} = \Delta s \left(\frac{1}{2}, 1, \dots, 1, \frac{1}{2}\right)^T,$$

the algebraic stencil satisfies

$$\mathbf{w}^T L_h = \mathbf{0}^T,$$

with a maximum floating-point conservation residual of

$$\max \|\mathbf{w}^T L_h\|_2 = 1.9664 \times 10^{-16}.$$

The 100-d conservation test uses backward Euler with $\Delta t = 0.01$ d and the numerically normalized initial state

$$n_i^0 \propto \exp\left[-\frac{1}{2} \left(\frac{s_i - 0.5}{\sqrt{0.02}}\right)^2\right], \quad \mathbf{w}^T N^0 = 1.$$

Monitoring $M_h^k = \mathbf{w}^T N^k$, the largest relative mass drift over the tested phenotype grids and oxygen states is

$$\max_k \frac{|M_h^k - M_h^0|}{|M_h^0|} = 5.0038 \times 10^{-13}.$$

For the stationary-shape benchmark, the two fixed oxygen states are $C = 0.8$ (normoxic) and $C = 0.1$ (hypoxic). The continuous zero-flux reference satisfies

$$-D_s n'_{\text{ref}}(s) + v(s, C) n_{\text{ref}}(s) = 0,$$

so that

$$n_{\text{ref}}(s) = A \exp\left[\int_0^s \frac{v(\eta, C)}{D_s} d\eta\right], \quad \int_0^1 n_{\text{ref}}(s) ds = 1.$$

The reference is evaluated on 200001 uniformly spaced points on $[0, 1]$. The discrete stationary solution is linearly interpolated to this reference grid, and the reported relative shape error is

$$E_{\text{rel}} = \frac{\left[\int_0^1 (n_h^{\text{lin}} - n_{\text{ref}})^2 ds \right]^{1/2}}{\left[\int_0^1 n_{\text{ref}}^2 ds \right]^{1/2}},$$

with both integrals evaluated by the composite trapezoidal rule on the fine reference grid. The four phenotype spacings are $\Delta s = 0.02, 0.01, 0.005, 0.0025$. Table 6 shows approximately second-order stationary-shape refinement for this isolated phenotype benchmark.

Table 6: Isolated phenotype stationary-shape refinement under phenotype-grid refinement.

Regime	C	Δs	L^2 error	Relative L^2 error	Order
Normoxic	0.8	0.0200	1.39663×10^{-1}	2.97458×10^{-2}	–
Normoxic	0.8	0.0100	3.31285×10^{-2}	7.05578×10^{-3}	2.0758
Normoxic	0.8	0.0050	8.17523×10^{-3}	1.74118×10^{-3}	2.0187
Normoxic	0.8	0.0025	2.03721×10^{-3}	4.33889×10^{-4}	2.0047
Hypoxic	0.1	0.0200	2.15865×10^{-2}	6.73411×10^{-3}	–
Hypoxic	0.1	0.0100	5.33284×10^{-3}	1.66363×10^{-3}	2.0172
Hypoxic	0.1	0.0050	1.32925×10^{-3}	4.14672×10^{-4}	2.0043
Hypoxic	0.1	0.0025	3.32068×10^{-4}	1.03592×10^{-4}	2.0011

For an exact radiotherapy event, the implemented mass change satisfies

$$m_j^- - m_j^+ = \Delta m_{j,\text{RT}},$$

with

$$\Delta m_{j,\text{RT}} = \sum_i w_i \sum_a m_a (1 - S_{\text{RT},i,a}) n_{i,a}^-.$$

The corresponding absolute tumour-burden consistency residual is

$$\varepsilon_{\text{RT},j} = \left| (m_j^- - m_j^+) - \Delta m_{j,\text{RT}} \right|,$$

and therefore has units of mm^3 . Across the assessed treatment events,

$$\max_j \varepsilon_{\text{RT},j} = 2.03 \times 10^{-16} \text{ mm}^3.$$

This result establishes roundoff-level algebraic consistency of the event update.

B Extended oxygen-ROM assessment

The oxygen-surrogate assessment starts from 100 distinct baseline networks. After shuffling, 90 baselines are assigned to training and 10 to validation before pruning and symmetry transformations are applied. The seven pruning levels and four geometric versions are generated separately in the two sets, yielding 2800 samples in total: 2520 training and 280 validation samples. The POD basis and standardization quantities are computed from the training set only. The number of training epochs is fixed a priori, and the validation set is not used for early stopping or for choosing the network architecture or hyperparameters.

The full-order oxygen snapshots underlying the surrogate are computed on the 4524-DOF P_1 tissue discretization used in the coupled model. A previous mesh-sensitivity assessment of the same mixed-dimensional oxygen formulation was reported in [43]. On 10 representative snapshots, a $20 \times 20 \times 3$ tissue mesh was compared with a $30 \times 30 \times 5$ reference mesh, giving relative differences of 1.27% in L^2 and 4.67% in L^∞ . This provides representative mesh-sensitivity evidence for the underlying full-order formulation; the surrogate errors for the present dataset are assessed independently on the 4524-DOF fields below.

The dimensional oxygen partial-pressure fields supplied by the surrogate to the tumour model are non-negative.

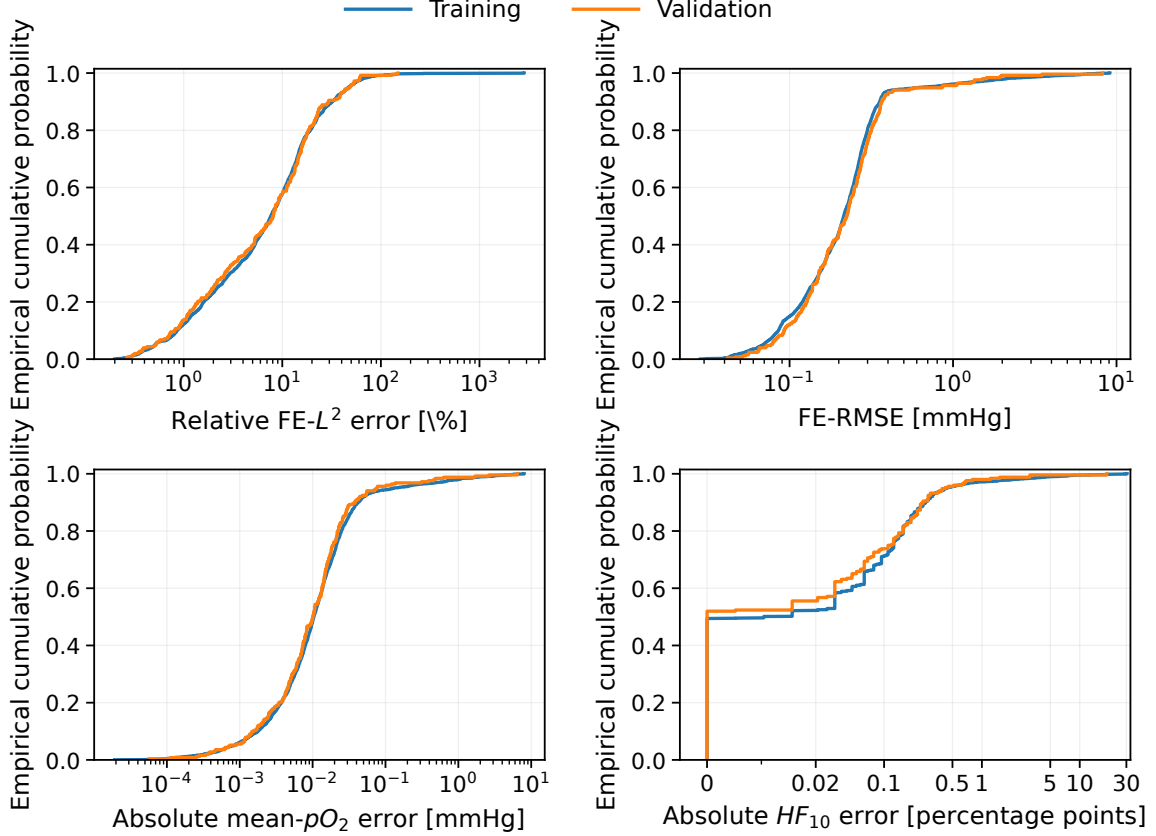


Figure 9: Training and validation distributions of oxygen-surrogate errors. Empirical cumulative distributions are shown for (a) relative finite-element L^2 error, (b) finite-element RMSE, (c) absolute error in mean tissue pO_2 , and (d) absolute error in HF_{10} . The validation set is derived from ten baseline networks separated from the training set before pruning and symmetry transformations.

Let $\mathbf{p}^{\text{FOM}}$ and $\mathbf{p}^{\text{ROM}}$ denote the nodal tissue oxygen partial-pressure vectors on the common P_1 tissue mesh, and let M be the consistent finite-element mass matrix. The relative field error is

$$E_{L^2}^{\text{FE}} = \frac{[(\mathbf{p}^{\text{ROM}} - \mathbf{p}^{\text{FOM}})^T M (\mathbf{p}^{\text{ROM}} - \mathbf{p}^{\text{FOM}})]^{1/2}}{[(\mathbf{p}^{\text{FOM}})^T M \mathbf{p}^{\text{FOM}}]^{1/2}},$$

and the finite-element root-mean-square error is

$$E_{\text{RMSE}}^{\text{FE}} = \left(\frac{\mathbf{e}^T M \mathbf{e}}{|\Omega|} \right)^{1/2}, \quad \mathbf{e} = \mathbf{p}^{\text{ROM}} - \mathbf{p}^{\text{FOM}}.$$

The corresponding quantity-of-interest errors are the absolute error in mean tissue oxygen tension and the absolute error in HF_{10} . Figure 9 compares the empirical distributions of these four metrics on the training and validation sets.

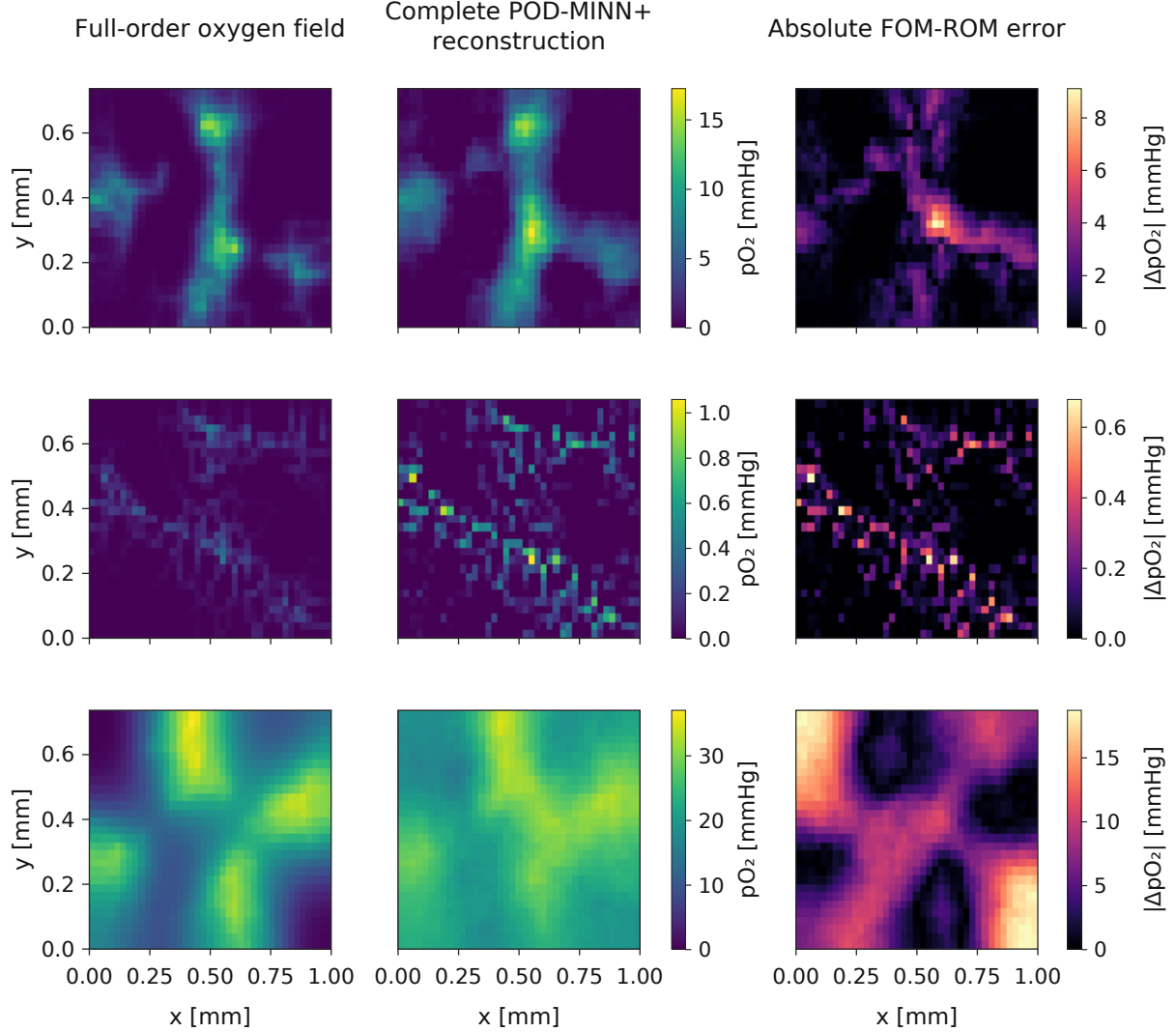


Figure 10: Representative validation cases illustrating distinct oxygen-surrogate error regimes. Columns show the full-order tissue oxygen field, the complete POD-MINN+ reconstruction and the corresponding absolute error; full-order and reconstructed fields share the same pO_2 colour scale within each row. The top row shows a representative high-percentile field-error case (sample 2476; relative FE- L^2 error 48.53%). The middle row shows the near-anoxic configuration with the maximum validation relative FE- L^2 error (sample 2424; 149.01%), for which $\overline{pO_2}^{\text{FOM}} = 0.0227$ mmHg and the absolute mean- pO_2 error is 0.0257 mmHg. The bottom row shows the validation case with the largest oxygen quantity-of-interest discrepancy (sample 2322), with $|\Delta \overline{pO_2}| = 6.44$ mmHg and $|\Delta HF_{10}| = 18.93$ percentage points.

Figure 10 illustrates three distinct validation regimes. The top row is a representative high-percentile validation field-error case; the middle row is the near-anoxic configuration associated with the maximum relative FE- L^2 error; and the bottom row is the retained validation quantity-of-interest

outlier. For each case, the full-order oxygen field and complete surrogate reconstruction are shown with common colour limits, followed by the pointwise absolute error.

An additional mechanism-level assessment was performed on the 280 validation configurations. For a threshold p_* , let p_a^{FOM} and p_a^{ROM} denote the nodal oxygen values and let $m_a = \int_{\Omega} \varphi_a dV$ be the P1 nodal volume weight. The disagreement fraction is defined as

$$\delta_{p_*} = \frac{\sum_a m_a |\mathbf{1}[p_a^{\text{FOM}} > p_*] - \mathbf{1}[p_a^{\text{ROM}} > p_*]|}{\sum_a m_a}.$$

Thus, the diagnostic is a nodal classification disagreement weighted by finite-element volume weights; no subelement reconstruction of threshold-crossing regions is performed. The results at the three oxygen thresholds entering the tumour laws are summarized in Table 7.

Table 7: Finite-element-volume-weighted FOM/ROM classification disagreement at oxygen thresholds entering the tumour model.

Mechanism	Threshold [mmHg]	Median [%]	P95 [%]	Maximum [%]
Hypoxic death	0.625	2.804	8.405	22.541
Radiotherapy oxygen branch	5	0.313	1.766	8.725
Phenotype drift	15	0.000	0.940	42.142

At the 5 mmHg radiotherapy threshold, the discrepancies in the piecewise oxygen factors $a_1(c)$ and $b_1(c)$ are the same classification disagreement expressed in coefficient units. With OER = 3, their finite-element- weighted mean absolute errors satisfy

$$\text{MAE}(a_1) = \frac{2}{3} \delta_5, \quad \text{MAE}(b_1) = \frac{8}{9} \delta_5.$$

The corresponding validation median/P95/maximum values are 0.00209/0.01177/0.05817 for a_1 and 0.00279/0.01570/0.07756 for b_1 . At the representative phenotype location $s = 0.55$, the median finite-element-weighted absolute discrepancies in the proliferation rate P , phenotype drift v_s and death rate K are 3.33×10^{-4} , 1.18×10^{-6} and $6.72 \times 10^{-2} \text{ d}^{-1}$, respectively. The death-rate discrepancy is reported as a constitutive-input diagnostic associated with the hypoxic-death transition and is not used as a direct estimate of tumour-trajectory error. The largest 15 mmHg disagreement occurs in sample 2322, the validation quantity-of-interest outlier reported below. A full comparison of S_{RT} is not defined by these oxygen-only validation pairs because the survival law also depends on the local tumour state through P_e .

The maximum validation relative FE- L^2 error is 149.01%. The corresponding full-order field has a mean tissue oxygen tension of approximately 0.023 mmHg, so the relative metric is amplified by the small reference-field norm. The absolute error in mean tissue oxygen tension for this sample is approximately 0.026 mmHg, and the HF_{10} classification is unchanged. This case is shown in the middle row of Figure 10.

A separate validation configuration is retained as a quantity-of-interest outlier. Its absolute mean- pO_2 error is 6.44 mmHg and its absolute HF_{10} discrepancy is 18.93 percentage points. This configuration, shown in the bottom row of Figure 10, is retained in the aggregate validation statistics.

The ROM definition includes a lower bound of $10^{-8} \text{ mL}_{O_2} \text{ cm}^{-3} \text{ s}^{-1}$ for the represented V_{max} interval. Since oxygen is evaluated only for $m \geq m_{\text{ext}}$, Eq. (9) gives $V_{\text{max}} \geq 3.34 \times 10^{-8} \text{ mL}_{O_2} \text{ cm}^{-3} \text{ s}^{-1}$, so no lower-bound clipping is required. The application inlet pressures, 20, 35 and 50 mmHg, also lie within the represented interval.

C Additional application results

This appendix collects the application settings used in Section 5 and the common pre-extinction comparison event used in the vascular-map analysis. The complete biological parameterization is given in the main text and is not repeated here. For Study A, the two reference oxygenation environments are NORM = $(\Lambda_0, 50 \text{ mmHg})$ and HYPO = $(\Lambda_{0.5}, 20 \text{ mmHg})$.

Table 8: Application settings and sampled parameter ranges.

Setting	Value
Tumour parameterization	HSC2
Initial burden parameter m_0	1
Initial phenotype centre s_0	0.30
Initial phenotype variance σ_s^2	0.02
Application spatial mesh	$38 \times 28 \times 3$; 4524 scalar P_1 degrees of freedom
Time step Δt	0.25 d
Phenotype step Δs	0.01
Dose per fraction	2.12 Gy
Final simulation time T	100 d
Numerical-extinction threshold m_{ext}	10^{-5} mm^3 (approximately one represented cell)
Study-A fraction numbers	15, 19, 23, 26, 30, 33
Study-A total doses	31.80, 40.28, 48.76, 55.12, 63.60, 69.96 Gy
Study-A environments	NORM = $(\Lambda_0, 50 \text{ mmHg})$; HYPO = $(\Lambda_{0.5}, 20 \text{ mmHg})$
Study-B pruning fractions	0.0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6
Study-B inlet oxygen	20, 35, 50 mmHg
Reference course	$33 \times 2.12 = 69.96 \text{ Gy}$

For the cross-environment Study-B comparison, $j_\star$ is defined as the latest treatment event for which the exact post-event tumour burden remains above m_{ext} in all 21 vascular configurations. This gives $j_\star = 23$, corresponding to $t_\star = 30 \text{ d}$, with $\min_{\mu \in \mathcal{E}_{\text{map}}} m_{j_\star}^+(\mu) = 1.17414 \times 10^{-5} \text{ mm}^3 > m_{\text{ext}}$.

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