



# Mathematical Formulation and Computational Implementation of a Fisher-KPP Model for Glioblastoma Invasion under Fractionated Radiotherapy

Matheus dos Santos Farias<sup>1,\*</sup>, Joiciane Sousa de Carvalho Ferreira<sup>1</sup> and Juciene dos Santos Batista<sup>1</sup>

<sup>1</sup>Institute for Energy and Nuclear Research (IPEN), University of São Paulo, São Paulo 05508-220, Brazil

## Abstract

Glioblastoma (GBM) is a highly infiltrative primary brain tumor, and reaction-diffusion models are widely used to describe how its cells spread and proliferate. We derive the classical Fisher-KPP equation from mass conservation, Fickian diffusion, and logistic growth, and extend it to fractionated radiotherapy through a linear-quadratic survival update applied to the tumor-density field at each fraction. The Fisher-KPP equation is solved by finite differences on a three-dimensional voxel grid with 0.5-mm spacing; Geant4 is used only for Monte Carlo photon transport and dose calculation. The schedule of 60 Gy in 30 fractions from the clinical case reported by Roda et al. is reproduced, and the simulated evolution is compared qualitatively with the clinical course as a demonstration only, without quantitative validation against patient-specific imaging data. The case report gives lesion dimensions at three time points but no serial pretreatment imaging,

so the diffusion and proliferation parameters cannot be estimated for this patient and are taken from the literature. The results are a qualitative demonstration of the coupled model and do not constitute patient-specific validation.

**Keywords:** Fisher-KPP equation, glioblastoma, Geant4, Monte Carlo simulation, radiotherapy, mathematical oncology.

## 1 Introduction

Glioblastoma (GBM) is the most aggressive primary malignant tumor of the central nervous system (CNS). In the latest report of the Central Brain Tumor Registry of the United States (CBTRUS), it accounts for 13.7% of all primary brain and other CNS tumors and 52.2% of the malignant ones. The same report estimates 107,100 new primary brain and CNS tumors in the United States for 2025 and records an average of 17,637 deaths per year from malignant brain and CNS tumors in 2018-2022 [1]; these figures are shown in Figure 1. Prognosis remains poor despite multimodal treatment, with a median overall survival of about 15 months [2].



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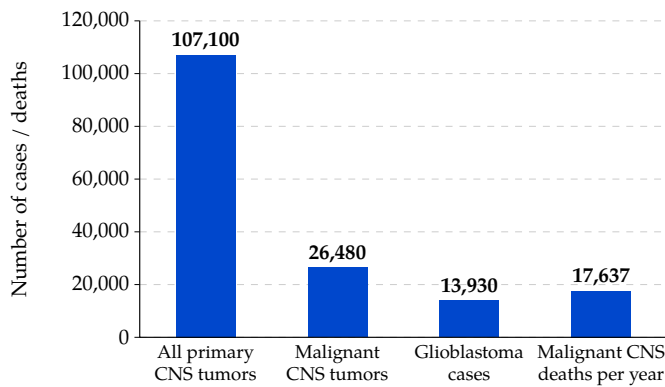
\*Corresponding author:  
✉ Matheus dos Santos Farias  
[matheusfariasfm@gmail.com](mailto:matheusfariasfm@gmail.com)

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**Figure 1.** Epidemiological burden of primary brain and other CNS tumors in the United States, as reported by CBTRUS [1]: estimated new cases for 2025 (all primary CNS tumors, malignant CNS tumors, and glioblastoma) and the average annual number of deaths from malignant CNS tumors in 2018–2022.

Glioblastoma invasion is commonly modeled with reaction-diffusion equations. The Fisher-KPP equation, which combines diffusion with logistic proliferation, is the usual starting point. It has been fitted to the MRI data of individual patients and extended to include radiotherapy and chemotherapy [3–7]. The equation itself is classical. What this paper adds is a complete worked implementation, applied to a published treatment schedule: the derivation, a fraction-level coupling to radiotherapy, the finite-difference scheme, and a Geant4 dose calculation on the same three-dimensional grid.

### 1.1 Objectives

Our aim is to set out, in one place, a Fisher-KPP model of glioblastoma under fractionated radiotherapy together with its numerical implementation. Four components are kept separate throughout: the tumor-growth partial differential equation (PDE), its discretization, the dose calculation in Geant4, and the operator that converts dose into cell kill. The case reported by Roda et al. [8] supplies the treatment schedule and the imaging timeline. We also examine which of the reported MRI measurements could be used for calibration and explain why they do not determine  $D$  and  $\rho$  for this patient.

## 2 Methodology

The work has an analytical part and a numerical part. In the analytical part, the Fisher-KPP equation is derived from mass conservation, Fickian diffusion, and logistic proliferation. In the numerical part, the

PDE is discretized on a Cartesian three-dimensional voxel grid and advanced by a finite-difference solver written in C++. Geant4 [9] does not solve the PDE; it transports the treatment photons and returns the spatial dose field. At each radiation fraction the dose is converted into a local survival factor with the linear-quadratic (LQ) model and applied to the tumor density, and between fractions the tumor evolves according to the Fisher-KPP equation.

The 60-Gy/30-fraction schedule, the treatment timing, and the MRI observations are taken from Roda et al. [8]. That report contains no serial pretreatment imaging, so  $D$  and  $\rho$  cannot both be identified for this patient. We use literature values instead and treat the simulation as a qualitative demonstration.

## 3 Mathematical Formulation

### 3.1 Derivation of the Fisher-KPP Equation

In the applied literature the equation is often credited to Fisher alone, but it was introduced independently in 1937 by Ronald A. Fisher and by Kolmogorov, Petrovsky, and Piskunov (KPP) [10, 11]. Fisher had studied mathematics at Gonville and Caius College, Cambridge, graduating in 1912, and then did postgraduate work in physics [12, 13]. He proposed the equation to describe the spatial spread of an advantageous gene [10]. The KPP paper treated the same equation as a problem of diffusion with growth and laid the groundwork for the theory of its traveling-wave solutions [11].

For glioblastoma invasion the model reads

$$\frac{\partial u}{\partial t} = D \nabla^2 u + \rho u \left(1 - \frac{u}{K}\right), \quad (1)$$

where  $u = u(\mathbf{x}, t)$  is the tumor-cell density at position  $\mathbf{x}$  and time  $t$ ,  $D > 0$  is the effective diffusion coefficient associated with invasive motility,  $\rho > 0$  is the intrinsic proliferation rate, and  $K > 0$  is the carrying capacity of the tissue. In one spatial dimension,  $\nabla^2 u = \partial^2 u / \partial x^2$  and Eq. (1) becomes

$$\frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial x^2} + \rho u \left(1 - \frac{u}{K}\right). \quad (2)$$

The derivation starts from a balance of tumor cells in an arbitrary fixed control volume  $\Omega \subset \mathbb{R}^n$  with boundary  $\partial\Omega$ . The number of cells in  $\Omega$  is

$$N(t) = \int_{\Omega} u(\mathbf{x}, t) dV. \quad (3)$$

It changes only through the flux across the boundary and through production inside the volume:

$$\frac{d}{dt} \int_{\Omega} u(\mathbf{x}, t) dV = - \int_{\partial\Omega} \mathbf{J}(\mathbf{x}, t) \cdot \mathbf{n} dS + \int_{\Omega} R(u) dV, \quad (4)$$

where  $\mathbf{J}$  is the flux of tumor cells,  $\mathbf{n}$  is the outward unit normal, and  $R(u)$  is the local reaction term, which accounts for proliferation and saturation.

Because  $\Omega$  is fixed, Leibniz's rule lets us take the time derivative inside the integral:

$$\int_{\Omega} \frac{\partial u}{\partial t} dV = - \int_{\partial\Omega} \mathbf{J} \cdot \mathbf{n} dS + \int_{\Omega} R(u) dV. \quad (5)$$

By the divergence theorem,

$$\int_{\partial\Omega} \mathbf{J} \cdot \mathbf{n} dS = \int_{\Omega} \nabla \cdot \mathbf{J} dV, \quad (6)$$

so Eq. (5) can be written with volume integrals only,

$$\int_{\Omega} \frac{\partial u}{\partial t} dV = - \int_{\Omega} \nabla \cdot \mathbf{J} dV + \int_{\Omega} R(u) dV, \quad (7)$$

or, with all terms under one integral,

$$\int_{\Omega} \left( \frac{\partial u}{\partial t} + \nabla \cdot \mathbf{J} - R(u) \right) dV = 0. \quad (8)$$

Since  $\Omega$  is arbitrary, the integrand must vanish almost everywhere, which gives the local conservation law

$$\frac{\partial u}{\partial t} + \nabla \cdot \mathbf{J} = R(u). \quad (9)$$

The same result can be obtained directly in one dimension. The number of cells in the interval  $[x, x + \Delta x]$  is

$$N_{\Delta}(t) = \int_x^{x+\Delta x} u(s, t) ds, \quad (10)$$

and its balance reads

$$\begin{aligned} \frac{d}{dt} \int_x^{x+\Delta x} u(s, t) ds &= J(x, t) - J(x + \Delta x, t) \\ &+ \int_x^{x+\Delta x} R(u(s, t)) ds. \end{aligned} \quad (11)$$

We divide by  $\Delta x$ ,

$$\begin{aligned} \frac{1}{\Delta x} \frac{d}{dt} \int_x^{x+\Delta x} u(s, t) ds &= \frac{J(x, t) - J(x + \Delta x, t)}{\Delta x} \\ &+ \frac{1}{\Delta x} \int_x^{x+\Delta x} R(u(s, t)) ds, \end{aligned} \quad (12)$$

and let  $\Delta x \rightarrow 0$ . With the definition of the derivative and the mean-value theorem for integrals, this gives

$$\frac{\partial u}{\partial t} = - \frac{\partial J}{\partial x} + R(u), \quad (13)$$

the one-dimensional form of Eq. (9).

The flux is specified next. For isotropic dispersal in homogeneous tissue we use Fick's first law,

$$\mathbf{J} = -D \nabla u, \quad (14)$$

with  $D > 0$  the effective diffusion coefficient. Substituting Eq. (14) into Eq. (9) gives

$$\frac{\partial u}{\partial t} + \nabla \cdot (-D \nabla u) = R(u), \quad (15)$$

that is,

$$\frac{\partial u}{\partial t} - \nabla \cdot (D \nabla u) = R(u), \quad (16)$$

or

$$\frac{\partial u}{\partial t} = \nabla \cdot (D \nabla u) + R(u). \quad (17)$$

When  $D$  does not depend on position it can be taken out of the divergence,

$$\nabla \cdot (D \nabla u) = D \nabla \cdot (\nabla u) = D \nabla^2 u, \quad (18)$$

so that

$$\frac{\partial u}{\partial t} = D \nabla^2 u + R(u). \quad (19)$$

It remains to choose the reaction term. Writing  $g(u)$  for the net per-capita growth rate, we have

$$R(u) = u g(u). \quad (20)$$

Without competition the rate is constant and growth is exponential:

$$\frac{du}{dt} = \rho u, \quad (21)$$

with solution  $u(t) = u_0 e^{\rho t}$ . This cannot continue in confined tissue, where nutrients, space, and mechanical pressure all limit growth. The simplest correction lets the per-capita rate fall linearly with density,

$$g(u) = \rho - \gamma u, \quad (22)$$

where  $\rho > 0$  is the intrinsic proliferation rate and  $\gamma > 0$  measures density-dependent inhibition. From Eqs. (20) and (22),

$$R(u) = u(\rho - \gamma u) = \rho u - \gamma u^2. \quad (23)$$

Growth stops at the density at which  $g$  vanishes. This is the carrying capacity,

$$K = \frac{\rho}{\gamma}, \quad (24)$$

so that

$$\gamma = \frac{\rho}{K}. \quad (25)$$

Eq. (23) then becomes

$$R(u) = \rho u - \frac{\rho}{K} u^2, \quad (26)$$

which factors as

$$R(u) = \rho u \left(1 - \frac{u}{K}\right). \quad (27)$$

Inserting Eq. (27) into Eq. (19) gives

$$\frac{\partial u}{\partial t} = D \nabla^2 u + \rho u \left(1 - \frac{u}{K}\right), \quad (28)$$

which is Eq. (1). In one spatial dimension it reads

$$\frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial x^2} + \rho u \left(1 - \frac{u}{K}\right), \quad (29)$$

in agreement with Eq. (2).

The diffusion term can also be checked component by component. With  $\mathbf{x} = (x_1, \dots, x_n)$ ,

$$\nabla u = \left( \frac{\partial u}{\partial x_1}, \frac{\partial u}{\partial x_2}, \dots, \frac{\partial u}{\partial x_n} \right), \quad (30)$$

and

$$\mathbf{J} = -D \left( \frac{\partial u}{\partial x_1}, \frac{\partial u}{\partial x_2}, \dots, \frac{\partial u}{\partial x_n} \right). \quad (31)$$

The divergence of the flux is

$$\nabla \cdot \mathbf{J} = \sum_{i=1}^n \frac{\partial J_i}{\partial x_i} = \sum_{i=1}^n \frac{\partial}{\partial x_i} \left( -D \frac{\partial u}{\partial x_i} \right), \quad (32)$$

which for constant  $D$  reduces to

$$\nabla \cdot \mathbf{J} = -D \sum_{i=1}^n \frac{\partial^2 u}{\partial x_i^2} = -D \nabla^2 u. \quad (33)$$

Hence

$$-\nabla \cdot \mathbf{J} = D \nabla^2 u, \quad (34)$$

the diffusion term of Eq. (1).

The equation can be made dimensionless with the variables

$$v = \frac{u}{K}, \quad \tau = \rho t, \quad \xi = \sqrt{\frac{\rho}{D}} \mathbf{x}, \quad (35)$$

that is, the dimensionless density, time, and position. The chain rule gives

$$\frac{\partial u}{\partial t} = K \rho \frac{\partial v}{\partial \tau}, \quad \nabla^2 u = K \frac{\rho}{D} \nabla_{\xi}^2 v. \quad (36)$$

Substituting into Eq. (1),

$$K \rho \frac{\partial v}{\partial \tau} = D \left( K \frac{\rho}{D} \nabla_{\xi}^2 v \right) + \rho K v (1 - v), \quad (37)$$

and dividing by  $K \rho$ , we obtain

$$\frac{\partial v}{\partial \tau} = \nabla_{\xi}^2 v + v(1 - v), \quad (38)$$

the normalized form used in most theoretical work.

### 3.2 Treatment-Coupled Formulation

Clinical radiotherapy is delivered in separate fractions, so its effect on the tumor is represented as a discrete update [4]. Between fractions the tumor obeys Eq. (1). In continuous form the treated model can be written as

$$\frac{\partial u}{\partial t} = \nabla \cdot (D \nabla u) + \rho u \left(1 - \frac{u}{K}\right) - \lambda_{\text{RT}}(\mathbf{x}, t) u, \quad (39)$$

where  $\lambda_{\text{RT}}(\mathbf{x}, t) \geq 0$  is the rate of radiation-induced cell kill. In the implementation, each fraction is applied as an instantaneous update at its treatment time  $t_n$ :

$$\begin{aligned} u(\mathbf{x}, t_n^+) &= S_n(\mathbf{x}) u(\mathbf{x}, t_n^-), \\ S_n(\mathbf{x}) &= \exp[-\alpha d_n(\mathbf{x}) - \beta d_n^2(\mathbf{x})]. \end{aligned} \quad (40)$$

In Eq. (40),  $d_n(\mathbf{x})$  is the absorbed dose delivered by fraction  $n$  at voxel  $\mathbf{x}$ ,  $\alpha$  and  $\beta$  are the linear-quadratic radiosensitivity coefficients, and  $S_n(\mathbf{x})$  is the local surviving fraction. The two descriptions agree when  $\lambda_{\text{RT}}(\mathbf{x}, t) = \sum_n [\alpha d_n(\mathbf{x}) + \beta d_n^2(\mathbf{x})] \delta(t - t_n)$ , with  $\delta$  the Dirac delta: integrating Eq. (39) across  $t_n$  gives Eq. (40). Geant4 supplies  $d_n(\mathbf{x})$ ; the tumor solver passes in  $u(\mathbf{x}, t_n^-)$  and continues from  $u(\mathbf{x}, t_n^+)$ .

### 3.3 Numerical Discretization and Stability

The spatial domain is a uniform Cartesian voxel grid with spacing  $h = 0.5$  mm, the resolution stated in the simulation figures. Between fractions, Eq. (1) is advanced with an explicit forward-Euler finite-difference scheme. For voxel  $(i, j, k)$  and time level  $m$ ,

$$\begin{aligned} u_{i,j,k}^{m+1} &= u_{i,j,k}^m + \Delta t \left[ D \delta_h^2 u_{i,j,k}^m \right. \\ &\quad \left. + \rho u_{i,j,k}^m \left(1 - \frac{u_{i,j,k}^m}{K}\right) \right], \end{aligned} \quad (41)$$

**Table 1.** Baseline model parameters adopted in the Fisher-KPP and linear-quadratic computations.

| Parameter                       | Symbol                         | Baseline value     | Units                                               | Source / interpretation                                                                    |
|---------------------------------|--------------------------------|--------------------|-----------------------------------------------------|--------------------------------------------------------------------------------------------|
| Tumor-cell diffusion / invasion | $D$                            | 0.0013             | cm <sup>2</sup> /day<br>(0.13 mm <sup>2</sup> /day) | Isotropic reference value from the literature; Swanson-type Fisher approximation [5, 6]    |
| Net proliferation rate          | $\rho$                         | 0.012              | day <sup>-1</sup>                                   | Reference value for high-grade glioma from the literature [5, 6]                           |
| Tissue carrying capacity        | $K$                            | $2.39 \times 10^8$ | cells/cm <sup>3</sup>                               | Value used in published reaction-diffusion models; cell-packing assumption [14]            |
| Voxel spacing                   | $h$                            | 0.5                | mm                                                  | Grid resolution of the present model                                                       |
| Diffusion stability bound       | $\Delta t \leq \frac{h^2}{6D}$ | $\leq 0.3205$      | day                                                 | From $h = 0.5$ mm and $D = 0.13$ mm <sup>2</sup> /day; explicit Euler diffusion constraint |
| LQ radiosensitivity             | $\alpha$                       | 0.24               | Gy <sup>-1</sup>                                    | Published value for glioblastoma [15]                                                      |
| LQ radiosensitivity             | $\beta$                        | 0.03               | Gy <sup>-2</sup>                                    | Published value for glioblastoma [15]                                                      |

with the Laplacian approximated by the standard six-neighbor stencil,

$$\delta_h^2 u_{i,j,k} = \frac{1}{h^2} (u_{i+1,j,k} + u_{i-1,j,k} + u_{i,j+1,k} + u_{i,j-1,k} + u_{i,j,k+1} + u_{i,j,k-1} - 6u_{i,j,k}). \quad (42)$$

For the diffusion operator alone, the explicit scheme is stable in three dimensions when

$$\Delta t \leq \frac{h^2}{6D}. \quad (43)$$

The logistic term tightens this bound slightly. A sufficient condition for the scheme to keep  $0 \leq u \leq K$  is  $\Delta t \leq (6D/h^2 + \rho)^{-1}$ , which for the parameters in Table 1 gives  $\Delta t \leq 0.3193$  day, against 0.3205 day for diffusion alone. The time step is chosen to satisfy the stability condition while keeping the reaction increment small. At the boundary of the brain we impose the no-flux condition  $\mathbf{n} \cdot \nabla u = 0$  [5], so that tumor cells cannot leave the computational domain.

### 3.4 Parameter Identification and Clinical Calibration

For the isotropic model we take  $D = 0.0013$  cm<sup>2</sup>/day (0.13 mm<sup>2</sup>/day) and  $\rho = 0.012$  day<sup>-1</sup>. This value of  $D$  comes from the Swanson-type modeling framework, in which it is obtained from an observed invasion-front velocity through the Fisher approximation;  $\rho$  is a representative growth rate for high-grade glioma. Both parameters vary considerably between patients and between tissue compartments [5, 7], so they serve here as reference values and carry no information about the patient of Roda et al.

The carrying capacity is  $K = 2.39 \times 10^8$  cells/cm<sup>3</sup>, a value used in earlier glioma reaction-diffusion models and based on a cell-packing assumption [14]. Since the equation can be normalized by  $K$ , this choice only sets the density scale. Table 1 lists the full parameter set. The clinical case contributes the treatment schedule and the imaging chronology, and nothing else: every biological coefficient comes from the modeling and radiobiology literature. A calibration for an individual patient would need serial pretreatment MRI/DTI and independently measured biological parameters.

### 3.5 MRI Observations Available from the Reference Case

Table 2 lists the lesion dimensions reported by Roda et al. [8]. The second and third measurements were taken after surgery and radiochemotherapy, so the three do not form an untreated growth series and cannot be used to fit  $D$ ,  $\rho$ , or  $K$ . We use them only to fix the clinical timeline and the approximate size of the lesion.

### 3.6 Geant4 Coupling and Radiotherapy Transport

Geant4 is a Monte Carlo toolkit for simulating the passage of particles through matter [9]. Here it transports the clinical photon beam through the virtual brain geometry and scores the absorbed dose  $d_n(\mathbf{x})$  on the 0.5-mm voxel grid for each fraction. The brain phantom is modeled as a homogeneous water-equivalent sphere with the density of soft tissue (1.04 g/cm<sup>3</sup>). The QGSP\_BIC\_EMY electromagnetic physics list is used for photon transport. Each fraction is simulated with  $10^7$  primary photon histories, yielding a statistical uncertainty below 2% in the high-dose region. The C++ solver evolves  $u(\mathbf{x}, t)$  on the same grid and applies the survival operator of Eq. (40) at each treatment time. The sequence

**Table 2.** MRI lesion dimensions reported by Roda et al. [8] and their use in the present model (AP: anteroposterior; LL: laterolateral; CC: craniocaudal).

| Date        | Clinical context                          | Reported lesion dimensions             | Use in the present model                                                  |
|-------------|-------------------------------------------|----------------------------------------|---------------------------------------------------------------------------|
| 17 Mar 2023 | Diagnostic MRI, before surgery            | 43 × 24 × 43 mm (AP × transverse × CC) | Reference for initial lesion scale; not a pretreatment growth-rate pair   |
| 12 Jun 2024 | MRI at recurrence after initial treatment | 60 × 30 × 45 mm (AP × LL × CC)         | Clinical recurrence reference; not used to infer untreated $D$ and $\rho$ |
| 24 Mar 2025 | MRI after reoperation/re-irradiation      | 77 × 53 × 60 mm (AP × LL × CC)         | Clinical progression reference; qualitative comparison only               |

of operations is: Geant4 particle transport → voxel dose field → linear-quadratic survival map → updated tumor density → Fisher-KPP evolution.

3.7 Treatment with Temozolomide

The patient received concomitant temozolomide (TMZ) at 75 mg/m<sup>2</sup>/day during the initial radiotherapy course [8]. No pharmacodynamic data are available from which its effect on proliferation could be quantified for this case, so TMZ is not modeled and  $\rho$  is left unchanged. Assigning an arbitrary attenuation factor would add a free parameter and make the radiotherapy response harder to interpret. If suitable data were available, TMZ could be included through

$$\rho_n = \eta_n \rho_0, \quad 0 < \eta_n \leq 1, \tag{44}$$

where  $\rho_0$  is the baseline proliferation rate ( $\rho$  in Eq. (1)),  $\rho_n$  is the effective rate during fraction interval  $n$ , and  $\eta_n$  would be estimated from longitudinal clinical, pharmacodynamic, or imaging data.

3.8 Model Limitations

The Fisher-KPP model is deliberately minimal, and several of its simplifications matter for GBM. Glioma migration is heterogeneous and often anisotropic, differing between white and grey matter and following white-matter tracts; the model replaces all of this with a single isotropic coefficient. Tissue interfaces, edema, necrosis, angiogenesis, immune interactions, and distinct cellular phenotypes are absent. The logistic term makes proliferation depend only on local density, with no cell-cycle structure and no treatment-induced change of phenotype. The tumor seen on MRI is also not the whole tumor, since cells infiltrate beyond the visible lesion [3, 5–7]. With a single clinical case these limitations weigh heavily, and the model cannot be used for treatment planning.

4 Results and Discussion

4.1 Reference Clinical Case

We chose the case of Roda et al. [8] because the report documents the irradiation protocol, the fractionation, the lesion dimensions, and the radiological follow-up in enough detail to set up a simulation; many clinical reports give only survival or dosimetric outcomes.

The patient underwent microsurgical resection followed by the Stupp protocol [16]. The initial course consisted of 60 Gy in 30 fractions over six weeks, with 46 Gy delivered before a cone-down to the residual lesion and margins, using 6- and 15-MV photons with IMRT-VMAT. Concurrent TMZ was given at 75 mg/m<sup>2</sup>/day [8]. The simulation reproduces the 60-Gy/30-fraction schedule, with the radiation dose as its only treatment input. Table 3 sets the clinical parameters of the report beside those used in the simulation.

4.2 Simulation Results: Early Treatment Stage

Figures 2 and 3 show the model output for the first two weeks of treatment, at cumulative doses of 10 and 20 Gy. The simulated lesion is largest in Week 1 and slightly smaller in Week 2.

4.3 Intermediate Treatment Stage

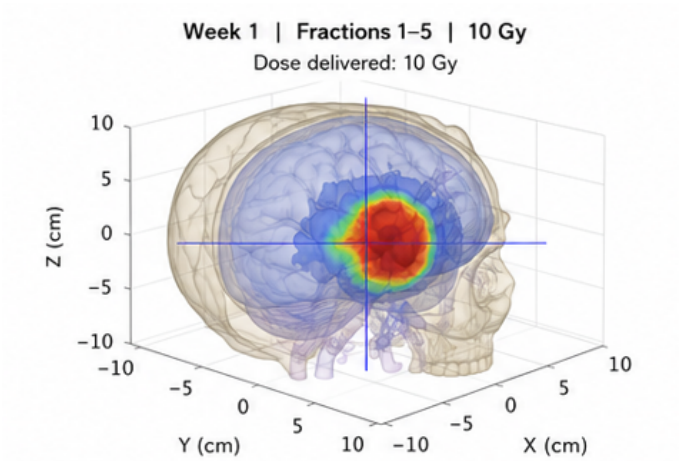
In Weeks 3 and 4 (Figures 4 and 5) the high-density region contracts further. Two processes act together here: the survival factor applied at every fraction, and the regrowth governed by Eq. (1) between fractions. The case report contains no voxel-level dose or segmentation data, so the comparison with the clinical course can only be qualitative.

4.4 Late Treatment Stage

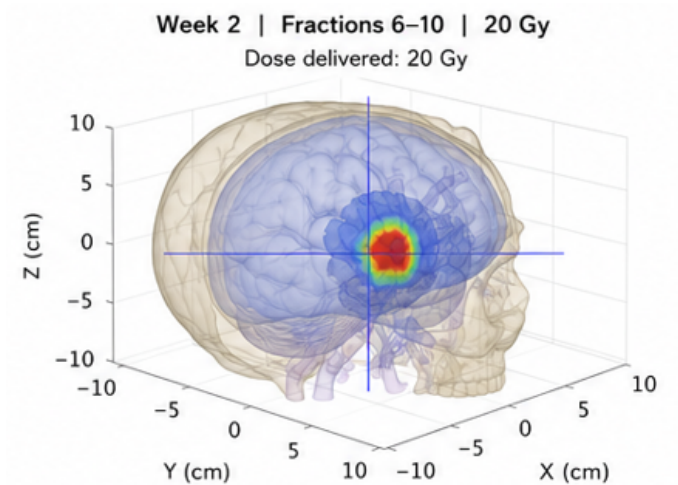
Figures 6 and 7 show Weeks 5 and 6, at cumulative doses of 50 and 60 Gy. Regression continues, and the

**Table 3.** Clinical radiotherapy protocol reported by Roda et al. [8] and corresponding parameters adopted in the Geant4 simulation.

| Clinical parameter      | Reported clinical data                           | Simulation model (Geant4)                                       |
|-------------------------|--------------------------------------------------|-----------------------------------------------------------------|
| Patient                 | 53-year-old male with right frontal glioblastoma | Virtual anatomical brain model                                  |
| Tumor type              | Glioblastoma (CNS WHO grade 4)                   | Fisher-KPP reaction-diffusion model                             |
| Initial treatment       | Surgical resection                               | Initial tumor geometry defined after surgery                    |
| Radiotherapy protocol   | Stupp protocol                                   | Reproduced in simulation                                        |
| Total radiation dose    | 60 Gy                                            | 60 Gy                                                           |
| Fractionation           | 30 fractions over 6 weeks                        | 30 simulated fractions (6 weekly stages)                        |
| Dose per fraction       | 2 Gy                                             | 2 Gy                                                            |
| Beam technique          | IMRT-VMAT                                        | Monte Carlo photon transport (Geant4)                           |
| Photon energy           | 6-MV and 15-MV photons                           | Clinical irradiation conditions reproduced                      |
| Concurrent chemotherapy | Temozolomide (75 mg/m <sup>2</sup> /day)         | Not modeled; clinical context only                              |
| Tumor monitoring        | MRI follow-up                                    | MRI dimensions used as qualitative reference; no volumetric fit |
| Mathematical model      | Clinical observations                            | Fisher-KPP PDE solved numerically on a 0.5-mm voxel grid        |
| Computational platform  | –                                                | Geant4 Monte Carlo framework                                    |
| Output                  | Clinical therapeutic response                    | 3D simulation of glioblastoma regression                        |



**Figure 2.** Three-dimensional simulation of glioblastoma during Week 1 (Fractions 1-5), cumulative dose 10 Gy. The simulated lesion is at its largest.



**Figure 3.** Three-dimensional simulation during Week 2 (Fractions 6-10), cumulative dose 20 Gy. The simulated tumor volume is slightly reduced.

simulated lesion is smallest at the end of treatment. The sequence of six renderings shows that the coupled model behaves consistently under the fractionated schedule. It does not show that the density field matches the tumor seen on the patient’s MRI.

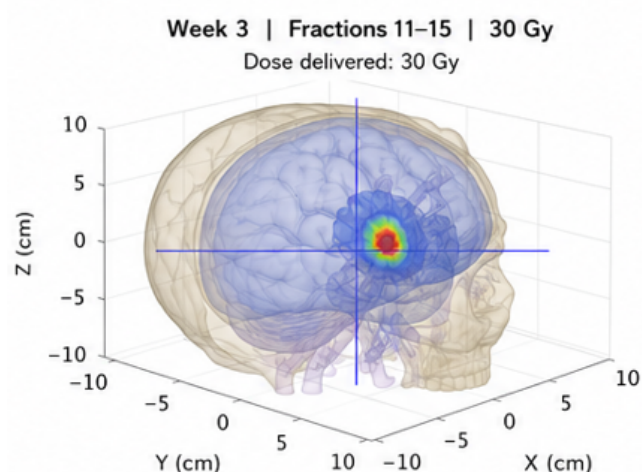
4.5 Quantitative Validation Status

We did not validate the model quantitatively. That would require segmented MRI volumes at defined time points, registered to a common anatomical frame, and a parameter set calibrated independently of them. The case of Roda et al. gives lesion dimensions at three

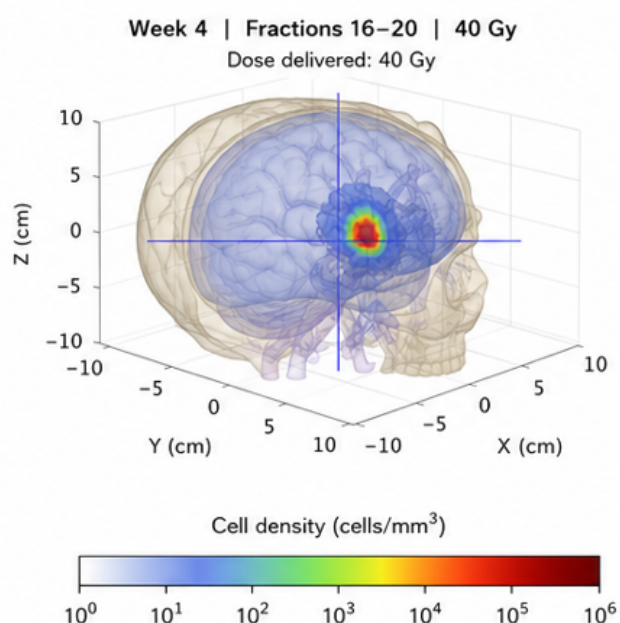
stages, but surgery and radiochemotherapy took place between them, which rules them out as an untreated calibration series. The agreement we report concerns only the qualitative course of the treatment stages, and we give no accuracy figure because the data would not support one.

5 Conclusion

We have set out a Fisher-KPP model of glioblastoma under fractionated radiotherapy and implemented it numerically. The derivation from mass conservation,



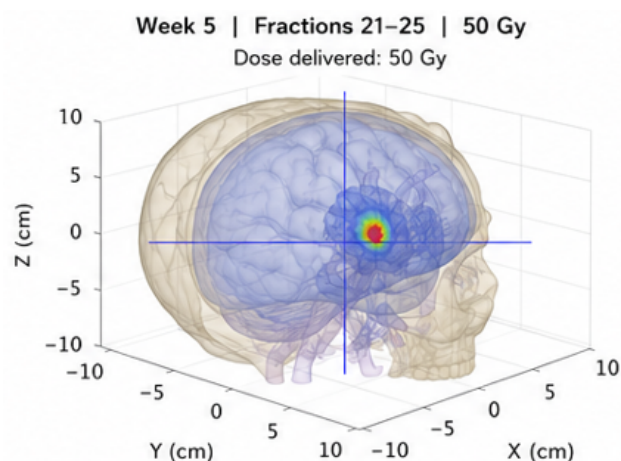
**Figure 4.** Three-dimensional simulation of glioblastoma during Week 3 (Fractions 11-15), cumulative dose 30 Gy. The lesion is noticeably smaller than in the first two weeks.



**Figure 5.** Three-dimensional simulation during Week 4 (Fractions 16-20), cumulative dose 40 Gy. The tumor is more localized.

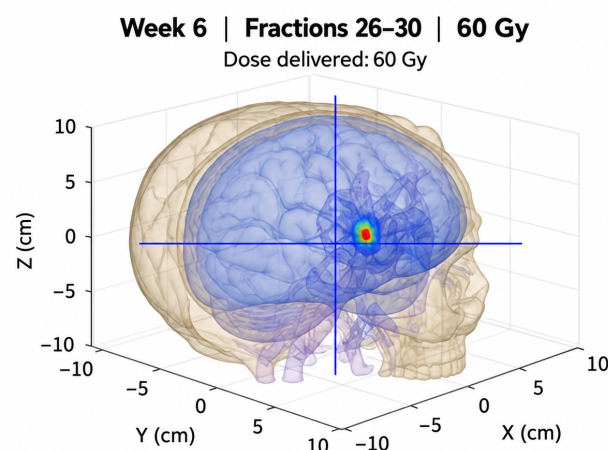
Fickian diffusion, and logistic growth is classical and is included for completeness. The methodological contribution is the coupling of three components: a finite-difference solver that advances the tumor density on a three-dimensional voxel grid, a Geant4 calculation of the photon dose on the same grid, and a linear-quadratic survival factor that links the two at each fraction.

Applied to the 60-Gy/30-fraction schedule of the case reported by Roda et al., the model produces a tumor-density field that regresses week by week



■ Tumor core (high cell density)  
■ Infiltrative region (low cell density)

**Figure 6.** Three-dimensional simulation of glioblastoma during Week 5 (Fractions 21-25), cumulative dose 50 Gy. Regression is at an advanced stage.



#### Simulation details:

- Fisher-KPP PDE solved numerically on a 0.5-mm voxel grid.
- Geant4 used for 3D Monte Carlo photon transport and dose scoring.
- Fraction-level radiation response applied with the linear-quadratic model.
- TMZ retained as clinical context; no independent numerical effect modeled.

**Figure 7.** Three-dimensional simulation during Week 6 (Fractions 26-30), complete prescribed dose of 60 Gy. The simulated volume is at its minimum.

over the course of treatment. These renderings are qualitative. The case report lacks the serial pretreatment imaging needed to estimate  $D$  and  $\rho$  for the patient; the parameters come from the literature, and no comparison with segmented MRI volumes was possible. The simulations should not be read as clinical predictions.

Quantitative validation would need serial

pretreatment MRI, diffusion-tensor imaging, patient-specific dose distributions, and calibrated radiobiological parameters. With such data the isotropic model could also be replaced by anisotropic and heterogeneous formulations.

## Data Availability Statement

Data will be made available on request.

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## Conflicts of Interest

The authors declare no conflicts of interest.

## AI Use Statement

The authors declare that ChatGPT was used for language editing of the manuscript. The authors have carefully reviewed, revised, and verified the AI-assisted output and take full responsibility for the content of the manuscript.

## Ethical Approval and Consent to Participate

Not applicable. This computational study involved no new experiments on humans or animals; all clinical information was taken from a previously published case report (Roda et al., 2026), whose authors reported ethics-committee approval and written informed consent.

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**Matheus dos Santos Farias** holds a Bachelor's degree and a teaching qualification in Physics from the Institute of Physics of the University of São Paulo (IF-USP). He has conducted research in applied physics, in groups focusing on differential equations applied to health, hadron therapy, and cardiovascular biomechanics. He is a specialist in Medical Physics (certified by the Albert Einstein Israelite Hospital, HIAE) and has conducted research in proton therapy, delay differential equations, and dynamical systems (chaos theory). His clinical experience covers diagnostic radiology (quality control, image-quality optimization, and performance assessment of X-ray, computed tomography, mammography, fluoroscopy, and magnetic resonance imaging systems), nuclear medicine (radiopharmaceuticals, internal dosimetry, and equipment quality control), and radiotherapy (treatment planning, linear-accelerator calibration, brachytherapy, and dose-distribution verification), as well as radiation protection applied to medical physics. He is currently pursuing a Master's degree in Nuclear Physics at the Institute for Energy and Nuclear Research (IPEN-USP), with an emphasis on delay differential equations and dynamical systems. He worked on the development of an equation to predict the size of gold nanoparticles (AuNPs) for nanobrachytherapy applications, in collaboration with University College London, UK. He has laboratory experience in the synthesis of gold, silver, and copper nanoparticles and in their physicochemical characterization by UV-Vis spectroscopy, dynamic light scattering, transmission and scanning electron microscopy, X-ray diffraction, zeta potential, and Fourier-transform infrared spectroscopy. His expertise includes mathematical modeling (analytical and numerical simulation), data analysis, programming (LaTeX, Python, R, C, C++, MATLAB, and Wolfram Mathematica), Monte Carlo methods (PENELOPE, TOPAS, and MCNP), and the application of machine learning and artificial intelligence in the nuclear, biomedical, and medical fields. He is a member of the American Physical Society (APS), the American Association of Physicists in Medicine (AAPM), the American Nuclear Society (ANS), and the SIAM Activity Group on Dynamical Systems. (Email: matheusfariasfm@gmail.com)



**Joiciane Sousa de Carvalho Ferreira** is a biomedical scientist qualified in Clinical Analysis by the University City of São Paulo (2023). She holds a specialization in Computed Tomography and Magnetic Resonance Imaging from the National Service for Commercial Training (SENAC, 2025) and is currently pursuing a Professional Master's degree in Radiation Technology in Health Sciences at the Institute for Energy and Nuclear Research (IPEN-CNEN), where she conducts research on silver nanoparticles with antibacterial potential. She is currently conducting a literature review on the use of copper nanoparticles. She has practical experience in clinical analysis laboratories and in medical imaging, specifically in performing magnetic resonance imaging and computed tomography scans. (Email: joiciane0ferreira@gmail.com)



**Juciene dos Santos Batista** is a Radiology Technologist and a Master's student in Radiation Technology in Health Sciences at IPEN/USP, working in diagnostic imaging with an interest in health-related applied research. She holds a specialization in Diagnostic Imaging and has additional training in computed tomography, magnetic resonance imaging, nuclear medicine, and radiation protection. She conducts research in Health Technology Assessment (HTA), focusing on the performance of nuclear medicine technologies in the state of São Paulo. She has experience in analyzing health databases, including data extraction, processing, and adaptation using programming tools, thereby contributing to evidence generation and supporting health decision-making. She also works as an educator in the field of Radiology, with an interest in teaching, research, and the application of analytical methods in healthcare. (Email: batista.juciene@gmail.com)