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RESEARCH PAPER

Set-valued analysis of anti-angiogenic therapy and radiotherapy

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Abstract

The aim of the paper is to study a cancer model based on anti-angiogenic therapy and radiotherapy. A set-valued analysis is carried out to control the tumor and carrying capacity of the vasculature, so in order to reverse tumor growth and augment tumor repair. The viability technique is used on an augmented model to solve the control problem. Obtained control is a selection of set-valued map of regulation and reduces tumor volume to around zero. A numerical simulation scheme with graphical representations and biological interpretations are given.

Key words: Anti-angiogenic therapy; radiotherapy; viability theory; set-valued analysis
AMS 2020 Classification: 93C10; 93C95; 93D15; 93D23

1 Introduction

Mathematical modelling of treatments is essential for diseases controlling. [1] Considers a mathematical model of chemotherapy for cancer treatment, in fractional order form with Caputo sense, and discusses the local stability of the equilibrium point. [2] Analyses the bifurcation of a fractional-order SEIR epidemic model of HIV and HBV diseases. [3] Studies the stability of a novel model of COVID-19 epidemics, by considering the Lyapunov function. [4] Considers a fractional-order HIV epidemic model, and determines the positivity and boundedness of the solution and the stability conditions of the model, and discusses the global dynamics of the endemic equilibrium point, by using Lyapunov functional approach. [5] Employs the feedback control on a chaotic system with fractional-order. [6] Proposes a Caputo HIV-1 model incorporating AIDS-infected cancer cells, and investigates the existence and uniqueness of its solutions via fixed point theory, and performs the stability analysis of the model. [7] Investigates the bifurcation of a two-dimensional discrete-time chemical model. [8] Develops a three-dimensional fractional-order cancer model, and details analysis of the equilibrium points, and investigates the existence and uniqueness of the solution. [9] Models COVID-19 epidemics with treatment in fractional derivatives using real data from Pakistan, and discusses the stability conditions of the equilibrium points, and analysis the global dynamics equilibria by using the Lyapunov function. [10] Develops a Hilfer fractional model related to Parkinson's disease, and obtains a closed form solution in the terms of Wright function and Mittag-Leffler function, by using Sumudu transform technique. [11] Uses the Laplace transform and exponential Fourier transform of Atangana-Baleanu-Caputo (ABC) derivative, to obtain the approximate analytical solutions of a reaction-diffusion model for calcium dynamics in neurons, in terms of generalized Mittag-Leffler function. [12] Presents a two-dimensional fractional-order reaction-diffusion model to develop a control mechanism of Calcium in nerve cells, and uses the integral transform technique of arbitrary order to find the solution of the model. [13] Analyses a mathematical model for cancer chemotherapy which includes anti-angiogenic effects of the cytotoxic agent, to optimally control the tumor volume by administering the total dose in a single maximum dose session. [14] Analyses a mathematical model for the combination of chemotherapy with anti-angiogenic treatment as a multi-input optimal

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control problem, and considers the problem to minimize a weighted average of tumor volume and the carrying capacity of the tumor vasculature. [15] Considers a mathematical model for tumor radiotherapy and chemotherapy as an optimal solution for a local tumor control.

The combinations of anti-angiogenics with each other or with other cancer therapies increase treatment efficacy [16, 17], notably with radiotherapy [18, 19, 20, 21, 22] which is unable to completely eradicate some tumors alone [23]. Mathematical modelling allows to develop methodologies of analysis and control for an appropriate polytherapy. We are interested in this paper to mathematical modelling of anti-angiogenic therapy with radiotherapy. We propose to take advantage of the Set-Valued Analysis (SVA) methodology applied in [24, 25] for models involving mono immunotherapy and chemotherapy, and in [26, 27] for combined modalities of cancer therapy, including immunotherapy and anti-angiogenic therapy with chemotherapy, to combine anti-angiogenic therapy and radiotherapy.

The rest of this paper is organized as follows : Section 2 describes a model of anti-angiogenic therapy and radiotherapy combination. Section 3 formulates the corresponding problem of control, and augments the considered model to translate the control problem into a viability one. Section 4 solves the viability problem by a single-valued selection of the set-valued map of regulation. Section 5 approaches the problem by the numerical methods of Euler and Uzawa.

2 Model presentation

The following complementary coupled dynamics between the tumor volume $p \in (0, \infty)$, and the time-varying carrying capacity $q \in (0, \infty)$, are considered from [28].

$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right) - (\alpha + \beta r)pw, \; p(0) = p_0 \in (0, \infty); \tag{1a}$$

$$\dot{q} = \kappa\left(bq^{\frac{2}{3}} - dq^{\frac{4}{3}}\right) + (1-\kappa)\left(bp - dp^{\frac{2}{3}}q\right) - \gamma qu - (\eta + \delta r)qw, \; q(0) = q_0 \in (0, \infty); \tag{1b}$$

where the third variable r was introduced by the ordinary differential equation

$$\dot{r} = -\rho r + w, \tag{1c}$$

and initiated by

$$r(0) = r_0 = 0, \tag{1d}$$

to model the temporal effects of tumor repair, and simplify the linear-quadratic damages quantification from Wein [29] on the tumor : $-(\alpha + \beta r)pw$, and on the carrying capacity : $-(\eta + \delta r)qw$, caused by the radiation control w, which takes values in $[0, w^{\max}]$. The control u represents the dose of the anti-angiogenic medicine, and takes values in $[0, u^{\max}]$, with carrying capacity elimination : $-\gamma qu$. The rest of uncontrolled expressions are summarized in the following table.

Expression	Description
$bq^{\frac{2}{3}}$ and bp	Carrying capacity stimulations
$-dq^{\frac{4}{3}}$ and $-dp^{\frac{2}{3}}q$	Carrying capacity inhibitions
$-\xi p \ln\left(\frac{p}{q}\right)$	Tumor proliferation

The parameter κ takes values in $[0, 1]$, and for the particular values $\kappa = 0$ and $\kappa = 1$, the meta-model (1) corresponds to Hahnfeldt [30, 31, 32] and Ergun [33, 34, 35] models, respectively. The model presentation is completed by describing parameters in table 1. Numerous studies related to the model (1) have been carried out :

- [31] Employs Pontryagin Minimum Principle (PMP), to minimize tumor volume subject to Hahnfeldt's sub-model, for an optimal cancer combination therapy from anti-angiogenic and radiation therapy.
- [32] Uses State-Dependent Riccati Equations (SDRE) as an optimal control methodology framework on Hahnfeldt's sub-model, and designs optimal rules to reduce the tumor growth by an appropriate administration of anti-angiogenic and radio-therapeutic doses.
- [33] Applies (PMP) on Ergun's sub-model, to determine the temporal scheduling of radiotherapy and angiogenic inhibitors that maximizes the control of a primary tumor.
- [36] Considers Ergun's sub-model as as optimal control problem with the objective of minimizing the tumor volume subject to isoperimetric constraints, that limit the total radiation dose and the overall amount of anti-angiogenic agents to be given.
- [37] Optimally controls Hahnfeldt's sub-model, by solving nonlinear programming problem via A Mathematical Programming Language (AMPL) and the Interior Point OPTimizer (IPOPT) method.
- [38] Executes (PMP) on Ergun's sub-model, to minimize tumor volume while limiting the total amount of administered anti-angiogenic agents, and also the total damage caused by the radiation treatment to the healthy tissue, so expressed in terms of its Biologically Equivalent Dose (BED).
- [39] Operates (PMP) to optimally control Hahnfeldt's sub-model, with the objective function of minimizing the size of cancer.
- [28] Proposes of the model (1), a Sequential Quadratic Hamiltonian (SQH) method to choose the optimisation weights, in order to obtain treatment functions that successfully reduce the tumor volume to zero.

- [40] Formulates more generalized model than (1), and adopts optimal control methodology, to minimize multi-functional objective.

3 Problem statement

We state the problem of control the tumor volume p by a coupled protocol (u, w) from Cartesian product constraint $[0, u^{\max}] \times [0, w^{\max}]$

$$\forall t \in [0, \infty), (u(t), w(t)) \in [0, u^{\max}] \times [0, w^{\max}], \tag{2a}$$

so in order that p strictly decreases on $[0, \infty)$

$$\forall t \in [0, \infty), \dot{p}(t) < 0, \tag{2b}$$

and admits zero as limit at infinity

$$\lim_{t \to \infty} p(t) = 0, \tag{2c}$$

subject to the model (1).
Before beginning any analysis, we augment the model (1) by the ordinary differential equation

$$\dot{w} = -w + v, \ w(0) = w_0 \in [0, w^{\max}], \tag{3}$$

to turn on the control w into a variable state, and control tumor volume dynamics (1b) indirectly via the parameter control $v \in [0, w^{\max}]$, subject to the objectives (2b) and (2c), however, we can still have the explicit expression for w

$$w(t) = e^{-t} \left(w_0 + \int_0^t e^{\tau} v(\tau) \, \mathrm{d}\tau \right). \tag{4}$$

The resolution of problem (2), can be done by finding (u, v)

$$\forall t \in [0, \infty), (u(t), v(t)) \in [0, u^{\max}] \times [0, w^{\max}], \tag{5a}$$

by which (p, q, r, w) is globally viable in D_θ

$$\forall t \in [0, \infty), (p(t), q(t), r(t), w(t)) \in D_\theta, \tag{5b}$$

where domain

$$D_\theta = \{(p, q, r, w) \in \mathbb{R}_+^* \times \mathbb{R}_+^* \times \mathbb{R}_+ \times [0, w^{\max}] \mid \psi_\theta(p, q, r, w) \leq 0\}, \tag{5c}$$

with function

$$\psi_\theta(p, q, r, w) = -\xi p \ln\left(\frac{p}{q}\right) - (\alpha + \beta r) p w + \theta p,$$

and parameter

$$\theta \in \mathbb{R}_+^*.$$

Proposition 1 *Assume that there exists* $\theta \in \mathbb{R}_+^*$ *such that* $(p_0, q_0, r_0, w_0) \in D_\theta$, *and* (u, v) *solution to the viability problem* (5), *then* (u, w) *solves the control problem* (2).

Proof Let $t \geq 0$, and let (p, q, r, w) be the globally viable trajectory in D_θ, leading by the control (u, v).
According to (1a) and (5b) we have the differential inequality

$$\dot{p}(t) = -\xi p \ln\left(\frac{p}{q}\right) - (\alpha + \beta r) p w \leq -\theta p(t),$$

by integrating we get the exponential estimate

$$0 \leq p(t) \leq p_0 e^{-\theta t},$$

then in the limit ∞, the tumor is deleted $\lim_{t \to \infty} p(t) = 0$, with the average speed of therapy θ. ■

4 Set-valued resolution

On the viability constraint D_θ by (5c), we define the set-valued map of regulation F_θ in the following way

$$F_\theta(p,q,r,w) = \Big\{(u,v) \in [0,u^{\max}] \times [0,w^{\max}] \mid \Big(-\xi p \ln\Big(\frac{p}{q}\Big) - (\alpha+\beta r)pw, \\ \kappa\Big(bq^{\frac{2}{3}} - dq^{\frac{4}{3}}\Big) + (1-\kappa)\Big(bp - dp^{\frac{2}{3}}q\Big) - \gamma qu - (\eta+\delta r)qw, -\rho r + w, -w + v\Big)^\top \in T_{D_\theta}(p,q,r,w)\Big\}, \tag{6a}$$

where

$$T_{D_\theta}(p,q,r,w) = \Big\{(\hat p,\hat q,\hat r,\hat w) \in \mathbb{R}^4 \;\Big|\; \liminf_{h\downarrow 0} \frac{d((p+h\hat p, q+h\hat q, r+h\hat r, w+h\hat w), D_\theta)}{h} = 0\Big\}, \tag{6b}$$

stands for the tangent cone to D_θ at point (p,q,r,w).

Lemma 1 *Let be $\theta \in \mathbb{R}_+^*$ such that $(p_0,q_0,r_0,w_0) \in D_\theta$. If for all $(p,q,r,w) \in D_\theta$, we have $F_\theta(p,q,r,w) \neq \emptyset$, then any single-valued selection (u,v) of the set-valued map of regulation F_θ solves (5).*

Proof The set-valued map of regulation F_θ admits a selection $(u,v) : D_\theta \to [0,u^{\max}]\times[0,w^{\max}]$ by which the system (1)-(3) admits a locally viable solution $(p(\cdot),q(\cdot),r(\cdot),w(\cdot))$ in D_θ, defined over a maximal interval $[0,t^{\max})$. We have to prove that $t^{\max} \to \infty$. Indeed, assume that $t^{\max}$ is finite.

- The non-negative function $p(\cdot)$ decreases on $[0,t^{\max})$, then it admits a limit $\bar p$, when $t \to t^{\max}$.
- Thanks to (1b), we have the differential inequality

  $$\dot q \le b(q^{\frac{2}{3}} + p_0),$$

  and by integrating

  $$3\sqrt[2]{p_0}\left(\frac{\sqrt[3]{q}}{\sqrt[2]{p_0}} - \arctan\left(\frac{\sqrt[3]{q}}{\sqrt[2]{p_0}}\right)\right) \le bt + 3\sqrt[2]{p_0}\left(\frac{\sqrt[3]{q_0}}{\sqrt[2]{p_0}} - \arctan\left(\frac{\sqrt[3]{q_0}}{\sqrt[2]{p_0}}\right)\right),$$

  then by maximizing

  $$q \le \left(\frac{b}{3}t^{\max} + \sqrt[2]{p_0}\left(\frac{\sqrt[3]{q_0}}{\sqrt[2]{p_0}} - \arctan\left(\frac{\sqrt[3]{q_0}}{\sqrt[2]{p_0}}\right)\right) + \sqrt[2]{p_0}\frac{\pi}{2}\right)^3,$$

  which proves that the function $q(\cdot)$ admits an upper limit $\bar q$, when $t \to t^{\max}$.
- According to (1c) the function $r(\cdot)$ admits a limit $\bar r = e^{-\rho t^{\max}}\displaystyle\int_0^{t^{\max}} e^{\rho\tau}w(\tau)\,\mathrm{d}\tau$, when $t \to t^{\max}$.
- By (4) the function $w(\cdot)$ admits a limit $\bar w = e^{-t^{\max}}\left(w_0 + \displaystyle\int_0^{t^{\max}} e^{\tau}v(\tau)\,\mathrm{d}\tau\right)$, when $t \to t^{\max}$.

Therefore $(p(\cdot),q(\cdot),r(\cdot),w(\cdot)) \to (\bar p,\bar q,\bar r,\bar w)$ when $t \to t^{\max}$, and $(\bar p,\bar q,\bar r,\bar w)$ belongs to D_θ because it is closed. Now, by considering $(\bar p,\bar q,\bar r,\bar w)$ as an initial state it follows that $(p(\cdot),q(\cdot),r(\cdot),w(\cdot))$ may be prolonged to a viable solution $(\tilde p(\cdot),\tilde q(\cdot),\tilde r(\cdot),\tilde w(\cdot))$ in D_θ, starting at $(\bar p,\bar q,\bar r,\bar w)$ on some interval $[t^{\max},t^{\sup})$ where $t^{\sup} > t^{\max}$, which is in contradiction with the maximality of $t^{\max}$, then the solution $(p(\cdot),q(\cdot),r(\cdot),w(\cdot))$ becomes globally viable in D_θ. ■

Motivated by the preceding Lemma 1, we are interested in an explicit expression of the set-valued map of regulation F_θ, so for that we give the following Lemma from [27], characterizing the tangent directions of the tangent cone T_{D_θ} by (6b).

Lemma 2 ([27]) *For each $(p,q,r,w) \in D_\theta$ the tangent directions $(\hat p,\hat q,\hat r,\hat w)$ of $T_{D_\theta}(p,q,r,w)$ are characterized by*

$$\begin{cases} \hat r \ge 0 & \text{if} \quad r = 0,\\ \hat w \ge 0 & \text{if} \quad w = 0,\\ \hat w \le 0 & \text{if} \quad w = w^{\max},\\ \dot\psi_\theta(p,q,r,w)(\hat p,\hat q,\hat r,\hat w) \le 0 & \text{if} \quad \psi_\theta(p,q,r,w) = 0. \end{cases}$$

Proof See [27]. ■

Lemma 3 ([27]) *The set-valued map of regulation F_θ may be expressed explicitly on the viability constraint D_θ as*

$$F_\theta(p,q,r,w) = \begin{cases} [0,u^{\max}]\times[0,w^{\max}] & \text{if} \quad \psi_\theta(p,q,r,w) < 0,\\ C_\theta(p,q,r,w) & \text{if} \quad \psi_\theta(p,q,r,w) = 0, \end{cases} \tag{7a}$$

where

$$C_\theta(p,q,r,w) = \Big\{(u,v) \in [0,u^{\max}]\times[0,w^{\max}] \mid \ell_\theta(p,q,r,w) + \langle h(p,q,r,w),(u,v)\rangle \le 0\Big\}, \tag{7b}$$

with

$$\ell_\theta(p,q,r,w) = \Big\langle \nabla\psi_\theta(p,q,r,w), \Big(-\xi p \ln\Big(\frac{p}{q}\Big) - (\alpha+\beta r)pw, \kappa\Big(bq^{\frac{2}{3}} - dq^{\frac{4}{3}}\Big) + (1-\kappa)\Big(bp - dp^{\frac{2}{3}}q\Big) - (\eta+\delta r)qw, -\rho r + w, -w\Big)^\top \Big\rangle, \tag{8a}$$

and

$$h(p,q,r,w) = \Big(-\gamma q \frac{\partial\psi_\theta}{\partial q}(p,q,r,w), \frac{\partial\psi_\theta}{\partial w}(p,q,r,w)\Big)^\top. \tag{8b}$$

Proof Thanks to Eqs. (1c) and (3)

- If $r = 0$, then

$$-\rho r + w = w \geq 0.$$

- If $w = 0$, then

$$-w + v = v \geq 0.$$

- If $w = w_i^{\max}$, then

$$-w + v = -w^{\max} + v \leq -w^{\max} + w^{\max} \leq 0.$$

- For all $(p,q,r,w) \in D_\theta$, we have

$$\dot\psi_\theta(p,q,r,w)\Big(-\xi p\ln\Big(\frac{p}{q}\Big) - (\alpha+\beta r)pw, \kappa\Big(bq^{\frac{2}{3}} - dq^{\frac{4}{3}}\Big) + (1-\kappa)\Big(bp - dp^{\frac{2}{3}}q\Big) - \gamma qu - (\eta+\delta r)qw, -\rho r + w, -w + v\Big)^\top =$$

$$\Big\langle \nabla\psi_\theta(p,q,r,w), \Big(-\xi p\ln\Big(\frac{p}{q}\Big) - (\alpha+\beta r)pw, \kappa\Big(bq^{\frac{2}{3}} - dq^{\frac{4}{3}}\Big) + (1-\kappa)\Big(bp - dp^{\frac{2}{3}}q\Big) - \gamma qu - (\eta+\delta r)qw, -\rho r + w, -w + v\Big)^\top \Big\rangle =$$

$$\Big\langle \nabla\psi_\theta(p,q,r,w), \Big(-\xi p\ln\Big(\frac{p}{q}\Big) - (\alpha+\beta r)pw, \kappa\Big(bq^{\frac{2}{3}} - dq^{\frac{4}{3}}\Big) + (1-\kappa)\Big(bp - dp^{\frac{2}{3}}q\Big) - (\eta+\delta r)qw, -\rho r + w, -w\Big)^\top \Big\rangle + \Big\langle \nabla_{(q,w)}\psi_\theta(p,q,r,w), (-\gamma qu, v)^\top \Big\rangle.$$

■

Lemma 4 *A single-valued selection of the set-valued map of regulation F_θ may be given on the viability constraint D_θ by the expression*

$$c_\theta(p,q,r,w) = \pi_{C_\theta(p,q,r,w)}(0), \tag{9}$$

where $\pi_{C_\theta(p,q,r,w)}(0)$ denotes the projection of $0_{\mathbb{R}^2}$ onto the closed convex set $C_\theta(p,q,r,w)$.

Proof See [27]. ■

5 Numerical resolution

This section is devoted to numerically analysis the following model by combining the numerical methods of Euler by step h and Uzawa of parameter λ.

$$\dot p = -\xi p\ln\Big(\frac{p}{q}\Big) - (\alpha+\beta r)pw, \tag{10a}$$

$$\dot q = \kappa\Big(bq^{\frac{2}{3}} - dq^{\frac{4}{3}}\Big) + (1-\kappa)\Big(bp - dp^{\frac{2}{3}}q\Big) - \gamma qu - (\eta+\delta r)qw, \tag{10b}$$

$$\dot r = -\rho r + w, \tag{10c}$$

$$\dot w = -w + v, \tag{10d}$$

$$u = c_\theta^1(p,q,r,w), \tag{10e}$$

$$v = c_\theta^2(p,q,r,w). \tag{10f}$$

The used algorithm is as follows

i. Initialization

a) $t_0 \in \mathbb{R}_+$,
b) $(p_0, q_0, r_0, w_0) \in D_\theta$,
c) $\lambda^0 \in \mathbb{R}_+^5$,

ii. Iteration

a) $t_{n+1} = t_n + h$,
b)

$$\begin{cases} p_{n+1} &= p_n + h\left(-\xi p_n \ln\left(\frac{p_n}{q_n}\right) - (\alpha + \beta r_n)p_n w_n\right), \\ q_{n+1} &= q_n + h\left(\kappa\left(bq_n^{\frac{2}{3}} - dq_n^{\frac{4}{3}}\right) + (1-\kappa)\left(bp_n - dp^{\frac{2}{3}}q_n\right) - \gamma q_n u_n - (\eta + \delta r_n)q_n w_n\right), \\ r_{n+1} &= r_n + h(-\rho r_n + w_n), \\ w_{n+1} &= w_n + h(-w_n + v_n), \end{cases} \tag{11}$$

c)

$$\begin{cases} u_n = -\lambda_5^n h(p_n, q_n, r_n, w_n) + \lambda_3^n - \lambda_1^n, \\ v_n = -\lambda_5^n h(p_n, q_n, r_n, w_n) + \lambda_4^n - \lambda_2^n, \end{cases}$$

d)

$$\begin{cases} \lambda_1^{n+1} = \max(\lambda_1^n + \sigma(u_n - u^{\max}), 0), \\ \lambda_2^{n+1} = \max(\lambda_2^n + \sigma(v_n - v^{\max}), 0), \\ \lambda_3^{n+1} = \max(\lambda_3^n - \sigma u_n, 0), \\ \lambda_4^{n+1} = \max(\lambda_4^n - \sigma v_n, 0), \\ \lambda_5^{n+1} = \max(\lambda_5^n + \sigma(h_1(p_n, q_n, r_n, w_n)u_n + h_2(p_n, q_n, r_n, w_n)v_n + \ell_\theta(p_n, q_n, r_n, w_n), 0), \text{ with } 0 < \sigma < \dfrac{2}{\|h(p,q,r,w)\|}. \end{cases}$$

- For the absence of therapy we choose $(p_0, q_0, r_0, w_0) = (15000, 12000, 0, 0)$ as an initial state, the tumor volume p stimulates the carrying capacity q to increase by the dynamics (10b), and to proliferate by the dynamics (10a), as we see in Figure 1.
- In the presence of therapy we choose $(p_0, q_0, r_0, w_0) = (15000, 12000, 0, 2)$ as an initial state, with the parameter $\theta = \xi \ln(\frac{p_0}{q_0}) + \alpha w_0 \simeq 1.4$, in order that $(p_0, q_0, r_0, w_0) \in D_\theta$, the protocols $u(t) = c_\theta^1(f(t))$ and $w(t) = e^{-t}(w_0 + \int_0^t e^\tau c_\theta^2(f(\tau))\,d\tau)$, where $f(.) = (p(.), q(.), r(.), w(.))$ limits the stimulation of the tumor volume p on the carrying capacity q in the dynamics (10b), and reverses the proliferation of p in the dynamics (10a), as we see in Figure 2.

As in (1d) we have $r_0 = 0$ for the initial value of the tumor repair r, and we consider $v_0 = 0$ as the initial value of the parameter control v, for the parameter κ of the dynamics (10b) we propose $\kappa = 0.5$, as in [28] to combine Hahnfeldt and Ergun dynamics, while the following table 1 gives the numerical values of the model (10) parameters.

Table 1. Parameters description.

Parameter	Description	Value	Unit
ξ	Parameter for tumor growth	0.084	$[\text{day}^{-1}]$
b	Tumor-induced stimulation parameter	5.85	$[\text{day}^{-1}]$
d	Tumor-induced inhibition parameter	0.00873	$[\text{mm}^{-2} \cdot \text{day}^{-1}]$
γ	Anti-angiogenic elimination parameter	0.15	$\left[\frac{\text{kg}}{\text{mg(doses)}}\right] \cdot \text{day}^{-1}$
α	Radiosensitive parameter for tumor	0.7	$[\text{Gy}^{-1}]$
β	Radiosensitive parameter for tumor	0.14	$[\text{Gy}^{-2}]$
η	Radiosensitive parameter for healthy tissue	0.136	$[\text{Gy}^{-1}]$
δ	Radiosensitive parameter for healthy tissue	0.086	$[\text{Gy}^{-2}]$
ρ	Tumor repair rate	$\frac{\ln 2}{0.02}$	$[\text{day}^{-1}]$

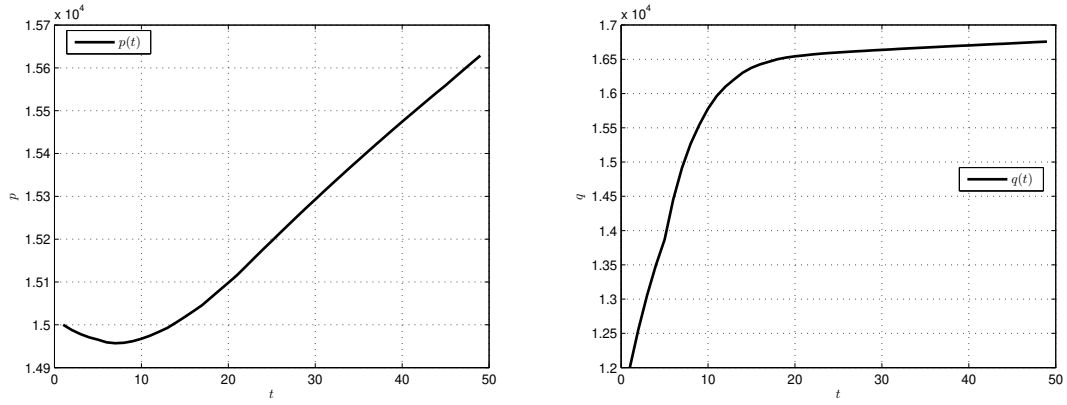

Figure 1. Tumor volume p begins to decrease from the initial value $p_0 = 15000$, but p stimulates the carrying capacity q to increase from the initial value $q_0 = 12000$, until they have approximate values $p = 14957$ and $q = 14912$ ($p \simeq q$) , then p starts to increase.

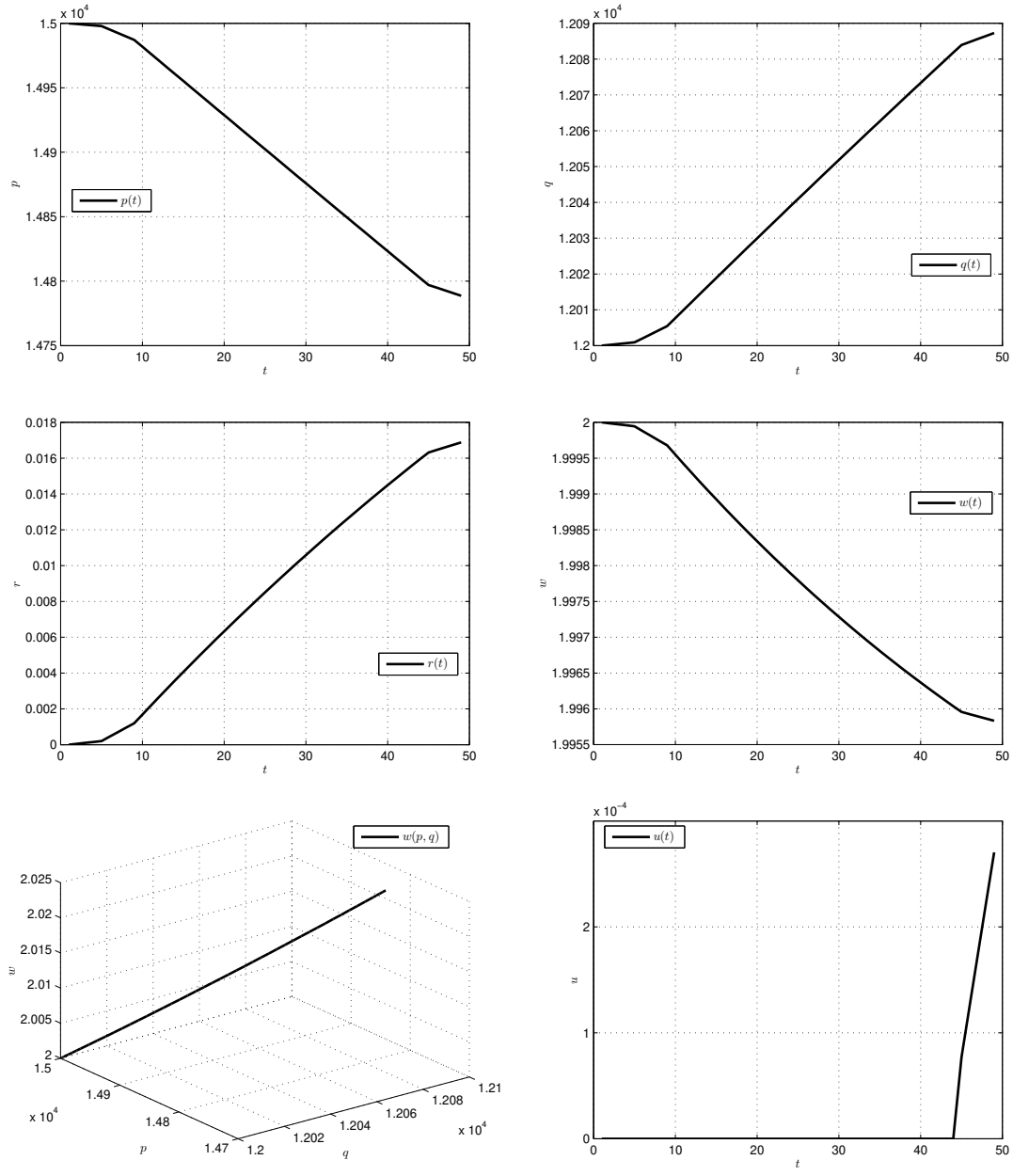

Figure 2. Tumor volume p begins from the same initial value $p_0 = 15000$ as in Figure 1, but kept on decreasing state all over time therapy in accordance with (2b) and (2c), caused by growth limitation of the carrying capacity q due to combined anti-angiogenic therapy and radiotherapy (u, w), and by direct effect of the radiotherapy $w(p, q)$ on the tumor volume p, while the tumor repair r is augmented.

6 Conclusion

The problem control (2) to the class of mathematical models (1) is achieved by combining anti-angiogenic therapy with radiotherapy. The set-valued analysis gives the feedback protocols $u(t) = c^1_\theta(f(t))$, and $w(t) = e^{-t}(w_0 + \int_0^t e^\tau c^2_\theta(f(\tau))\,d\tau)$, where $f(.) = (p(.), q(.), r(.), w(.))$ to administrate the temporal doses of anti-angiogenic medicine and radiation, in order to dynamically limit the stimulation of the tumor volume $p_{(u,w)}(t)$ on the time carrying capacity $q_{(u,w)}(t)$, and force $p_{(u,w)}(t)$ to decrease : $\forall t \in [0,\infty), \dot{p}_{(u,w)}(t) < 0$, under the exponential estimate : $0 \leq p_{(u,w)}(t) \leq p_0 e^{-\theta t}$, and converge to the null limit : $\lim_{t\to\infty} p_{(u,w)}(t) = 0$. The obtained protocols u and w, provide from the single-valued selection c_θ by (9) to the set-valued map of regulation F_θ by (6a), which should be strict on the subset D_θ by (5c) : $\forall (p,q,r,w) \in D_\theta, F_\theta(p,q,r,w) \neq \emptyset$, and they rend the model (1) globally viable on the subset D_θ, as it is demonstrated in the Proof 4 of the Lemma 1. The linear dynamics (1c) and (3) of the tumor repair r and the radiation control w respectively, allow to get the useful expression (7a) of the set-valued map of regulation F_θ, as it is proved in the Proof 4 of the Lemma 3, and the single-valued selection c_θ is a solution to the following problem of minimization : $\min ||(u,v)||$ such that $(u,v) \in [0,u^{\max}] \times [0,w^{\max}]$ by (5a), and $\ell_\theta(p,q,r,w) + \langle h(p,q,r,w),(u,v)\rangle \leq 0$ by (8), which is numerically approached by the method of Uzawa in the last Section 5, and implemented into the discretized model (11) by the method of Euler, to get the numerical simulations of Figure 2, which are in perfect conformity with the theoretical results of the preceding Section 4.

Declarations

List of abbreviations

- Atangana–Baleanu–Caputo (ABC) derivative
- A Mathematical Programming Language (AMPL)
- Biologically Equivalent Dose (BED)
- Interior Point OPTimizer (IPOPT)
- Pontryagin Minimum Principle (PMP)
- State-Dependent Riccati Equations (SDRE)
- Sequential Quadratic Hamiltonian (SQH)
- Set-Valued Analysis (SVA)

Consent for publication

Not applicable.

Conflicts of interest

The author declares that she has no conflict of interests.

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Author's contributions

The research was carried out by the author and she accepts that the contributions and responsibilities belong to the author.

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