Optimal Control Applications and Methods

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Optimal Control for a Mathematical Model of Cancer Disease via Dynamic Programming Approach

D. Gueridi[1] | T. Bouremani[2] | Y. Slimani[1] | M. A. Ghebouli[3,4] | M. Fatmi[3] | Ahmed Sayed M. Metwally[5]

[1]Laboratory of Intelligent System, Faculty of Technology, University Ferhat Abbas Setif 1, Setif, Algeria | [2]Laboratory of Applied Mathematics (LaMA), Faculty of Technology, Ferhat Abbas University Setif 1, Setif, Algeria | [3]Research Unit on Emerging Materials (RUEM), University Ferhat Abbas of Setif 1, Setif, Algeria | [4]Department of Chemistry, Faculty of Sciences, University of Mohamed Boudiaf, M'sila, Algeria | [5]Department of Mathematics, College of Science, King Saud University, Riyadh, Saudi Arabia

Correspondence: M. Fatmi (fatmimessaoud@yahoo.fr)

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ABSTRACT

The objective of this paper is to provide a comprehensive overview of optimal control models in the context of cancer treatment. We will explore how these mathematical models are used to optimize the administration of anticancer drugs. By understanding the principles behind optimal control models, we can appreciate their potential to revolutionize cancer treatment and contribute to personalized medicine. We utilize recent advancements in dynamic programming method to achieve a rigorous solution for a cancer disease model proposed by Neilan as an unsolved problem. Beginning with a certain refinement of Cauchy's method of characteristics for stratified Hamilton–Jacobi equations allows us to delineate a broad range of admissible trajectories. This, in turn, leads to the identification of a domain wherein the value function not only exists but is also generated by a certain admissible control. While the optimality is checked by using one of the well-known verification theorems taken as sufficient optimality conditions.

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1 | Introduction

Cancer optimal control models are mathematical frameworks used to study and analyze the dynamics of cancer growth and response to treatment. These models aim to optimize treatment strategies by finding the most effective and efficient interventions to control tumor growth while minimizing side effects and maximizing patient outcomes. To achieve this, these models incorporate variables such as tumor size, growth rate, cell population dynamics, and interactions between tumor cells and the immune system or other treatment modalities. Among the earlier works addressing the application of control theory to investigate drug regimens for the reduction of an experimental population of tumor cells was the work of Neilan and Bahrami et al. [1, 2]. However, the pioneering work applying optimal control theory to a chemotherapy dilemma concerning human tumors was authored by Swan and Vincent [3]. The seminal review paper covering optimal control problems in the broader domain of cancer research was presented in [4]. Nowadays, advancements in the battle against cancer persist, marked by innovative approaches, numerous studies have explored this subject. Which in turn offer instances of mathematical models employed to investigate diverse facets of cancer, encompassing tumor growth, interactions with the immune system, treatment strategies, genomics, and metabolism. They showcase the application of mathematical modeling techniques in cancer research and highlight their potential for improving our understanding of cancer biology and treatment outcomes. In an effort to comprehend the conditions under which cancer cells can be eradicated, in [5] was developed a nonlinear mathematical model of tumor–immune interactions with integrated drug and therapeutic controls. While, in [6], introduced an intriguing mathematical framework for cancer treatment, focusing on the synergy between immune cell therapies and antiangiogenic approaches. Another significant contribution was made in [7], where a mathematical model for cancer chemotherapy was devised, aiming to minimize either a weighted sum of tumor cells and drug dosage or the terminal volume of the tumor. Consequently, many of these models can be reconceptualized as certain differential games models (as seen, for instance, in [8]). Such models can capture the balance between cooperation and competition between different populations of cells in a tumor. For example, cells could cooperate to resist immune responses or compete for resources. Game theory models can shed light on the dynamics of these interactions.

The objective of this paper is to apply the dynamic programming algorithm described in [9, 10] to achieve a more rigorous and theoretically comprehensive solution to the unresolved cancer optimal control model proposed in [1]. That involves evaluating the number of cancer cells in the body, a factor governed by the drug concentration. Applying our approach to solve this problem offers several advantages. First, we can identify all its admissible trajectories. Second, the hypotheses to be verified are more intuitive and straightforward to verify. This is attributed to the incorporation of principles from the theory of Hamilton–Jacobi equations, along with recent findings from non-smooth analysis in [9, 11].

The paper is structured as follows: after the introduction, Section 2 presents the position of the problem, its dynamic programming formulation, and the characterization of the Hamiltonian. Section 3 gives the generalized stratified Hamiltonian field. In Section 4, we discuss the partial Hamiltonian flow whose trajectories have terminal segments on each of the strata. Section 5 establishes the existence of the corresponding value function, which defines a certain admissible and potentially optimal control for the considered problem. Finally, Section 6 provides concluding remarks.

2 | Position of the Problem

In [1], it has been considered a cancer disease model, formulated as an optimal control problem that consists in minimizing the cost functional:

$$\begin{cases} C(u(\cdot)) = x(T) + \int_0^T u^2(t)\,dt, & \\ x' = \alpha x - u(t), & x(0) = x_0 \\ x_0 \in \mathbb{R}_+^*, x(T) = x_T, & u(t) \in [0,1], t \in [0,T], T\ free \end{cases} \tag{1}$$

the functions involved have the following virology significance:

- $x(t)$: the number of cancer cells in the body at time $t \in [0; T]$;
- $u(t)$: the drug concentration in the body (that, in turn, is considered as the control function) at time $t \in [0; T]$;
- $\alpha > 0$: the natural growth rate of the cancer cells.

2.1 | The Dynamic Programming Formulation

To apply the dynamic programming approach in [9, 10], we reformulate the problem stated in (1) using conventional notations in optimal control theory. This yields the following standard Bolza autonomous optimal control problem:

Problem 1. Given $T > 0$, find:

$$\inf_{u(\cdot)} C(y, u(.)), \quad \forall y \in Y_0 \tag{2}$$

subject to

$$\begin{aligned} & C(y, u(\cdot)) = g(x(T)) + \int_0^T f_0(x(t), u(t))\,dt, \\ & x'(t) = f(x(t), u(t)), u(t) \in U(x(t)) a.e.([0,T]), x(0) = y, \\ & x(t) \in Y_0, \quad \forall t \in [0, T), \quad x(T) \in Y_1, T free \end{aligned} \tag{3}$$

defined by the following data:

$$\begin{aligned} f(x,u) &= \alpha x - u, f_0(x,u) = u^2, \\ U(x) &= U = [0,1], g(\xi) = \xi, \forall \xi \in Y_1, \\ Y_0 &= \mathbb{R}_+^*, Y_1 = \mathrm{Int}(Y_1) \subset Cl(Y_0) \end{aligned} \tag{4}$$

2.2 | Characterization of the Hamiltonian

The first step of this approach involves characterizing the Hamiltonian of the problem. The pseudo-Hamiltonian $\mathcal{H}(x, p, u) = \langle p, f(x, u)\rangle + f_0(x, u)$ is given in this case by

$$\mathcal{H}(x,p,u) = \alpha p x + \phi(u), \quad \phi(u) = u^2 - pu. \tag{5}$$

The formulas that provide both the Hamiltonian and the corresponding multifunction of minimum points are as follows:

$$\begin{aligned} & H(x,p) = \min_{u \in U} \mathcal{H}(x,p,u) = \alpha p x + \min_{u \in U} \phi(u) \\ & \hat{U}(x,p) = \{u \in U; \mathcal{H}(x,p,u) = H(x,p)\}, (x,p) \in Z = \mathrm{dom}(H(.)) \end{aligned} \tag{6}$$

Since, the function $\varphi(\cdot)$ is defined on $\mathbb{R}$. To make explicitly its extreme points, let us investigate its derived function. To this end, it follows from (5) that, $\o'(u) = 0 \Leftrightarrow u = \frac{p}{2}$.

Therefore, the corresponding multifunction of minimum points is given by

$$\hat{U}(x,p) = \{\hat{u}(p)\}, \hat{u}(p) = \begin{cases} 0, & \text{if } p \le 0 \\ \frac{p}{2}, & \text{if } p \in (0,2) \\ 1, & \text{if } p \ge 2 \end{cases} \tag{7}$$

that leads to the fact that

$$\phi(\hat{u}(p)) = \min_{u \in U} \phi(u) = \begin{cases} 0, & \text{if } p \le 0 \\ -\frac{p^2}{4}, & \text{if } p \in (0,2) \\ 1 - p, & \text{if } p \ge 2 \end{cases} \tag{8}$$

First, we note that the Hamiltonian $H(.,\ .)$ in (6) as well as its domain Z are C^1-stratified by the stratification $S_H = \{Z_0^1, Z_0^2, Z_-, Z_+, Z_{+,+}\}$ defined by

$$Z_0^1 = \{(x,p) \in Z; p = 0\},\quad Z_0^2 = \{(x,p) \in Z; p = 2\}$$
$$Z_- = \{(x,p) \in Z; p < 0\},\quad Z_+ = \{(x,p) \in Z; p \in (0,2)\} \tag{9}$$
$$Z_{+,+} = \{(x,p) \in Z; p > 2\}$$

If we denote by $H_0^1(.,.) = H(.,.)\big|_{Z_0^1}, H_0^2(.,.) = H(.,.)\big|_{Z_0^2}, H_\pm(.,.) = H(.,.)\big|_{Z_\pm}, H_{+,+}(.,.) = H(.,.)\big|_{Z_{+,+}}$ then, it follows from (6), (8), and (9) that

$$\begin{aligned} &H_0^1(x,p) = 0, && \text{if } (x,p) \in Z_0^1 \\ &H_0^2(x,p) = 2\alpha x - 1, && \text{if } (x,p) \in Z_0^2 \\ &H_-(x,p) = \alpha p x, && \text{if } (x,p) \in Z_- \\ &H_+(x,p) = \alpha p x - \frac{p^2}{4}, && \text{if } (x,p) \in Z_+ \\ &H_{+,+}(x,p) = (\alpha x - 1)p + 1, && \text{if } (x,p) \in Z_{+,+} \end{aligned} \tag{10}$$

After that, we need to characterize the set of terminal transversality values defined in the general case by

$$Z^* = \left\{ (\xi, q) \in Y_1 \times \mathbb{R},\ \ H(\xi, q) = 0,\ \ \langle q, \overline{\xi} \rangle = Dg(\xi)\overline{\xi},\ \ \forall \overline{\xi} \in T_\xi Y_1 \right\} \tag{11}$$

To characterize the set of terminal transversality values Z^*, we establish the following result.

Lemma 1. *The set of terminal transversalities values Z^* is described by*

$$Z^* = \left\{ \left(\frac{1}{4\alpha}, 1, \right) \right\} \subset Z_+ \tag{12}$$

Proof. Since, Y_1 is open then, the tangent space $T_\xi Y_1 = \mathbb{R}$ and $Dg(\xi)\overline{\xi} = \overline{\xi}, \forall \overline{\xi} \in \mathbb{R}$. Further, from (10) we deduce that, $(q-1)\overline{\xi} = 0, \forall \overline{\xi} \in \mathbb{R}$ hence, $q = 1$. Starting from the fact that, $q = 1 \in (0,2)$ then, the only admissible trajectories are the ones which have segments on the stratum Z_+. Besides, using the fact that, $H(\xi, q) = H_+(\xi, 1) = \alpha\xi - \frac{1}{4} = 0$ then, $\xi = \frac{1}{4\alpha}$. □

3 | Generalized Hamiltonian and Characteristic Flow

The principal operation involves backward integration for $t \le 0$, of the Hamiltonian inclusion

$$\left(x', p'\right) \in d_S^\# H(x,p), (x(0), p(0)) = z = (\xi, q) \in Z^* \tag{13}$$

defined by the generalized Hamiltonian field $d_S^\# H(.,.)$:

$$\begin{aligned} d_S^\# H(x,p) = \{ &\left(x', p'\right) \in T_{(x,p)} Z; x' \in f(x, \hat{U}(x,p)), \\ &\left\langle x', \overline{p} \right\rangle - \left\langle p', \overline{x} \right\rangle = DH(x,p)(\overline{x}, \overline{p}), \forall (\overline{x}, \overline{p}) \in T_{(x,p)} Z \} \end{aligned} \tag{14}$$

According to the algorithm in [9, 10], for each terminal point $z = (\xi, q) \in Z^*$, one needs to identify the maximal solutions: $X^*(\cdot) = (X(\cdot), P(\cdot)) : I(z) = (t^-(z), 0] \to Z$ of the Hamiltonian inclusion in (13) such that

$$\begin{aligned} &X(t) \in Y_0, \forall t \in I_0(z) = (t^-(z), 0) \\ &H(X(t), P(t)) = 0, \quad \forall t \in I(z) \\ &X'(t) = f(X(t), u(t)), \quad u(t) \in \hat{U}(X^*(t)) a.e. I_0(z) \end{aligned} \tag{15}$$

If there are more such solutions for the same terminal point $z = (\xi, q) \in Z^*$, they should be parameterized by $\lambda \in \Lambda(z)$. That allows us to obtain a generalized Hamiltonian flow $X^*(.,.) = (X(.,.), P(.,.)) : B = \{(t,a); t \in I(a), a \in A\} \to Z$; where $A = \text{graph}(\Lambda(\cdot))$ and $a = (z, \lambda)$.

Additionally, it is worth noting for each $(t,a) \in B_0 = \{(t,a) \in B; t \neq 0\}$ the Hamiltonian flow $X^*(.,.)$ defines both the controls and the trajectories:

$$u_{t,a}(s) = u_a(t+s), x_{t,a}(s) = X(t+s, a), s \in [0, -t] \tag{16}$$

which are admissible with respect to the initial point $y = X(t,a) \in Y_0$, and their associated cost functional value in (3) is determined by the function $V(.,.)$ defined by

$$V(t,a) = g(\xi) + \int_0^t \left\langle P(s,a), X'(s,a) \right\rangle ds, \text{if } a = (z, \lambda) \tag{17}$$

and which, together with the Hamiltonian flow $X^*(.,.)$ they define the generalized characteristic flow $C^*(.,.) = (X^*(.,.), V(.,.))$; using the definition of the Hamiltonian $H(.,.)$ and the second condition in (15) we obtain

$$\left\langle P(s,a), X'(s,a) \right\rangle = -f_0\left(X(s,a), \hat{u}(X^*(s,a))\right) = -\left[\hat{u}(X^*(s,a))\right]^2$$

Hence, the function $V(.,.)$ is given by

$$V(t,a) = \frac{1}{4\alpha} - \int_0^t \left[\hat{u}(X^*(s,a))\right]^2 ds, (t,a) \in B, a = (z, \lambda) \tag{18}$$

Moreover, it follows from (9) that, the generalized Hamiltonian field $d_S^\# H(.,.)$ is given by the formulas

$$d_S^\# H(x,p) = \begin{cases} d_S^\# H_\pm(x,p), \text{if } (x,p) \in Z_\pm \\ d_S^\# H_{+,+}(x,p), \text{if } (x,p) \in Z_{+,+} \\ d_S^\# H_0^i(x,p), \text{if } (x,p) \in Z_0^i, i = 1,\ \ 2 \end{cases} \tag{19}$$

As the manifolds $Z_\pm, Z_{+,+} \subset Z$ are open subsets, the Hamiltonian fields $d_S^\# H_\pm(.,.)$ and $d_S^\# H_{+,+}(.,.)$ coincide with classical Hamiltonian vector fields

$$\begin{aligned} d_S^\# H_\pm(x,p) &= \left\{ \left(\frac{\partial H_\pm}{\partial p}(x,p), -\frac{\partial H_\pm}{\partial x}(x,p) \right) \right\}, (x,p) \in Z_\pm \\ d_S^\# H_{+,+}(x,p) &= \left\{ \left(\frac{\partial H_{+,+}}{\partial p}(x,p), -\frac{\partial H_{+,+}}{\partial x}(x,p) \right) \right\}, (x,p) \in Z_{+,+} \end{aligned} \tag{20}$$

which are straightforward to compute and will be further described and analyzed later. However, on the one-dimensional singular strata Z_0^1, $Z_0^2 \subset Z$ the corresponding Hamiltonian fields pose a greater challenge for computation.

3.1 | The Hamiltonian Field on the Singular Strata Z_0^1 and Z_0^2

Let $\tilde{Z} \in \{Z_0^1, Z_0^2\}$ and $\tilde{H}(.,.) \in \{H_0^1(.,.), H_0^2(.,.)\}$ then, the characterization of the Hamiltonian field $d_S^{\#}\tilde{H}(.,.)$ on the singular stratum $\tilde{Z}$ is established in the following result.

Lemma 2. *For any $(x,p) \in \tilde{Z}$, one has*

$$d_S^{\#}\tilde{H}(x,p) = \begin{cases} d_S^{\#}H_0^1(x,p) = \{(\alpha x, 0)\}, & \text{if } (x,p) \in Z_0^1 \\ d_S^{\#}H_0^2(x,p) = \emptyset, & \text{if } (x,p) \in Z_0^2 \end{cases}$$

Proof. On the singular stratum Z_0^1, in order to compute the generalized Hamiltonian field $d_S^{\#}H_0^1(.,.)$, we note first that, according to a certain classical result as in [10], the tangent space to the one-dimensional manifold Z_0^1 is given by

$$T_{(x,p)}Z_0^1 = T_{(x,p)}Z_0^2 = \{(\overline{x},\overline{p}) \in \mathbb{R}\times\mathbb{R}; \overline{p} = 0\}$$

and $DH_0^1(x,p)(\overline{x},\overline{p}) = 0$. Hence, a vector $(x',p') \in d_S^{\#}H_0^1(x,p)$ is fully characterized by the properties

$$p'\overline{x} = 0, \forall \overline{x} \in \mathbb{R}, x' = f(x, \hat{u}(p)), \hat{u}(p) = 0$$

it follows from (4) that, at each point $(x,p) \in Z_0^1$ we obtain

$$x' = \alpha x, p' = 0$$

Symmetrically, on the singular stratum Z_0^2 one has, $DH_0^2(x,p)(\overline{x},\overline{p}) = 2\alpha\overline{x}$. Therefore, a vector $(x',p') \in d_S^{\#}H_0^2(x,p)$ is fully characterized by the formula

$$(p' + 2\alpha)\overline{x} = 0, \forall \overline{x} \in \mathbb{R}$$

this implies that, at each point $(x,p) \in Z_0^2$ one has

$$x' \in \mathbb{R}, \quad p' = -2\alpha \tag{21}$$

Considering that, $(x',p') \in T_{(x,p)}Z_0^2$ then, $p' = 0$. While from (21) we have, $0 = p' = -2\alpha < 0$ which leads to a contradiction. □

In summary, the Hamiltonian field in (14) is characterized by

$$d_S^{\#}H(x,p) = \begin{cases} d_S^{\#}H_{\pm}(x,p), & \text{if } (x,p) \in Z_{\pm} \\ d_S^{\#}H_{+,+}(x,p), & \text{if } (x,p) \in Z_{+,+} \\ \{(\alpha x, 0)\}, & \text{if } (x,p) \in Z_0^1 \\ \emptyset, & \text{if } (x,p) \in Z_0^2 \end{cases} \tag{22}$$

where $d_S^{\#}H_{\pm}(.,.)$ and $d_S^{\#}H_{+,+}(.,.)$ are theHamiltonian fields given in (20). Additionally, since $Z^* \subset Z_+$, there are no admissible trajectories on the strata $Z_- \cup Z_{+,+} \cup Z_0^1$.

3.2 | The Hamiltonian System on the Open Stratum Z_+

On the open stratum Z_+ in (9) where, $p \in (0,2)$, the differential inclusion in (13) coincides with the smooth Hamiltonian system:

$$\begin{cases} x' = \alpha x - \frac{p}{2} \\ p' = -\alpha p \end{cases} \tag{23}$$

According to standard results from differential equations theory, the general solution of the system in (24) is given by the formulas

$$\begin{cases} x^+(t) = \frac{1}{4\alpha}ce^{-\alpha t} + ke^{\alpha t}, c,k \in \mathbb{R}, t < 0x' = \alpha x - \frac{p}{2} \\ p^+(t) = ce^{-\alpha t} \end{cases} \tag{24}$$

3.3 | The Hamiltonian System on the Open Stratum $Z_{+,+}$

To illustrate the continuation property of trajectories, we also need the general solution of the Hamiltonian system on the open stratum $Z_{+,+}$ for which $p > 2$. To this end, it follows from (20) that the differential inclusion in (13) coincides with the smooth Hamiltonian system:

$$\begin{cases} x' = \alpha x - 1 \\ p' = -\alpha p \end{cases} \tag{25}$$

which, in turn, has the general solution

$$\begin{cases} x^{+,+}(t) = ke^{\alpha t} + \frac{1}{\alpha}, k, c \in \mathbb{R}, t < 0 \\ p^{+,+}(t) = p^+(t) = ce^{-\alpha t} \end{cases} \tag{26}$$

4 | Construction of the Hamiltonian Flow

4.1 | The Hamiltonian Flow Ending on the Stratum Z_+

Considering the general solution in (24), an admissible trajectory $X_+^*(.,z) = (X^+(.,z), P^+(.,z)), z \in Z^*$ of system (23) must satisfy both the terminal conditions from the set of transversality terminal points Z^* in (12) and also the fact that, $X_+^*(t,z) \in Z_+ \forall t < 0$. From the terminal condition in (12) it follows that, $c = 1$, $k = 0$. Consequently, the solution to the differential system in (23) takes the form of a maximal flow $X_+^*(\cdot) = (X^+(\cdot), P^+(\cdot))$ with its components given by the formulas

$$X_+^*(t) = (X^+(t), P^+(t)) = \left(\frac{1}{4\alpha}e^{-\alpha t}, e^{-\alpha t}\right), t < 0. \tag{27}$$

The dynamic programming algorithm in [9, 10] suggests that, we should consider only the trajectories $X_+^*(\cdot)$, that satisfy the conditions in (15). We note first that the second condition in (15) is automatically satisfied since $H_+(.,.)$ defined in (10) serves as a first integral of differential system (23) thus

$$\begin{gathered} X^+(t) > 0, P^+(t) \in (0,2), \forall t < 0 \\ H_+(X^+(t), P^+(t)) = 0 \end{gathered} \tag{28}$$

Additionally, the admissible trajectories must verify also the conditions

$$\begin{gathered} X_+^*(t) = (X^+(t), P^+(t)) \in Z_+, \forall t \in (\tau^+, 0) \\ X^+(t) \in Y_0 = \mathbb{R}_+^* \end{gathered} \tag{29}$$

on the maximal interval $I^+ = (\tau^+, 0)$, hence the extremity τ^+ is defined by

$$\tau^+ = \inf\{\tau\langle 0; X^+(t)\rangle 0, P^+(t) \in (0,2), \forall t \in (\tau, 0)\} \tag{30}$$

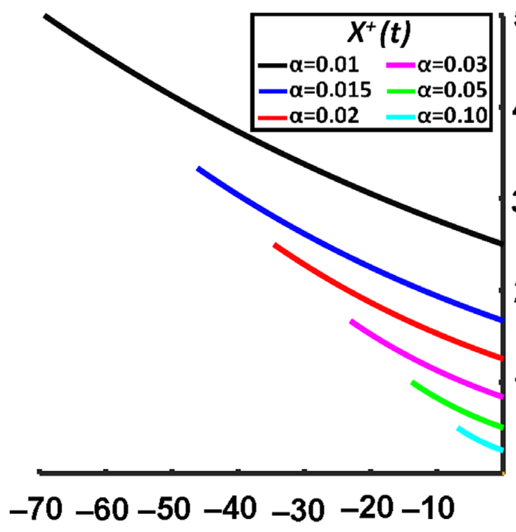

FIGURE 1 | Trajectories $X^{+}(\cdot)$.

In our attempt to obtain an explicit formula for the extremity τ^+, we note that, the expressions in (27) allow us to infer a direct formula for τ^+ as defined in (30). To this end, it follows from (27) that, $X^+(t) = \frac{1}{4\alpha}e^{-\alpha t} > 0, \forall t \in (-\infty, 0)$. While, if we assume that, $P^+(t) \in (0,2)$ this implies that, $t \in \left(-\frac{1}{\alpha}\ln\ 2, +\infty\right) \supset \left(-\frac{1}{\alpha}\ln\ 2, 0\right)$. Hence, there exists an extremity, τ^+ given by

$$\tau^+ = -\frac{1}{\alpha}\ln\ 2 \tag{31}$$

for which, the admissible conditions in (29) are verified.

Since, $P^+(t) \in (0,2)$ and $X^+(t) = \frac{1}{4\alpha}P^+(t) \in \left(0, \frac{1}{2\alpha}\right)$ then, one may note here that, geometrically, the trajectories $X^+(\cdot)$ are the curves in Figure 1 and cover the domain $Y_0^+ \subset Y_0$ such that

$$Y_0^+ = X^+\left(I^+\right) = \left(0, \frac{1}{2\alpha}\right) \tag{32}$$

4.2 | Continuation of Trajectories on the Stratum $Z_{+,+}$

Since the extremity

$$z^+ = X_+^*\left(\tau^+\right) = \left(X^+\left(\tau^+\right), P^+\left(\tau^+\right)\right) = \left(\frac{1}{2\alpha}, 2\right) \tag{33}$$

belongs to the open stratum $Z_+ \subset Z$ but also to the boundary of the open stratum $Z_{+,+}$; analyzing the possibility of continuation for $t < \tau^+$ of the trajectories $X_+^*(\cdot)$ in (27), we note that this is possible only on the open stratum $Z_{+,+}$.

Taking into account the fact that $H_{+,+}\left(z^+\right) = H_{+,+}\left(\frac{1}{2\alpha}, 2\right) = 0$ and $P^+\left(\tau^+\right) = 2$, the possibility of continuation of the trajectories $X_+^*(\cdot)$ in (27) for $t < \tau^+$, on the stratum $Z_{+,+} \subset Z$ (for which, $p > 2$) is guaranteed first by the condition $\frac{d}{dt}P^+\left(\tau^+\right) = -2\alpha < 0$ for the trajectories $X_+^*(\cdot)$ in (27) of system (23), since in this case, the function $t \to P^+(t)$ is strictly decreasing on an interval of the form $\left(\tau^+ - \delta, \tau^+\right)$. Hence, for any $t < \tau^+$ then, $P^+(t) > P^+\left(\tau^+\right) = 2$. In this case, the trajectories in (27) may be continuated by the trajectories $X_{+,+}^*(\cdot) = \left(X^{+,+}(\cdot), P^{+,+}(\cdot)\right)$, which are solutions of the Hamiltonian system in (25), that satisfy $X_{+,+}^*\left(\tau^+\right) = z^+$ and for which, there exists an extremity $\tau^{+,+} < \tau^+$ such that

$$X^{+,+}(t) \in Y_0, P^{+,+}(t) > 2, \forall t \in I^{+,+} = \left(\tau^{+,+}, \tau^+\right) \tag{34}$$

First, starting from the general solution of system (25) on the open stratum $Z_{+,+}$, given by the formulas in (26) and taking the terminal conditions z^+ in (33), we get, $c = 1$, $k = -\frac{1}{\alpha}$. Hence, the components of the Hamiltonian flow $X_{+,+}^*(\cdot)$ are given by

$$X_{+,+}^*(t) = \left(X^{+,+}(t), P^{+,+}(t)\right) = \left(\frac{1}{\alpha}\left(1 - e^{\alpha t}\right), e^{-\alpha t}\right) \tag{35}$$

where the extremity $\tau^{+,+}$ of the maximal interval $I^{+,+}$ is defined by

$$\tau^{+,+} = \inf\left\{\tau\left\langle\tau^+ X^{+,+}(t)\right\rangle 0, P^{+,+}(t) > 2, \forall t \in \left(\tau, \tau^+\right)\right\} \tag{36}$$

As in the previous section, in order to obtain an explicit form for the extremity $\tau^{+,+}$, we prove the following result.

Lemma 3. *For any $t \in \left(-\infty, \tau^+\right)$, the component $X^{+,+}(t)$ and the adjoint vector $P^{+,+}(t)$ check the conditions in (34). Moreover, the extremity $\tau^{+,+}$ defined in (36) is given by*

$$\tau^{+,+} = -\infty \tag{37}$$

Proof. First, it follows from (35) that, if $P^{+,+}(t) > 2$ this implies that, $t \in \left(-\infty, \tau^+\right)$. Moreover, if $X^{+,+}(t) > 0$ then, $t < 0$ and therefore, $X^{+,+}(t) > 0$, $\forall t \in (-\infty, 0) \supset I^{+,+} = \left(-\infty, \tau^+\right)$ hence, the conditions in (34) are verified and the extremity $\tau^{+,+}$ is given as above. □

Further, using the fact that $P^{+,+}(t) > 2$ then, $1 - e^{\alpha t} > \frac{1}{2}$ hence, $X^{+,+}(t) > \frac{1}{2\alpha}$. As in the other case, geometrically the trajectories $X^{+,+}(\cdot)$ are the dotted curves in Figure 3 and cover the domain $Y_0^{+,+} \subset Y_0$ defined by

$$Y_0^{+,+} = X^{+,+}\left(I^{+,+}\right) = \left(\frac{1}{2\alpha}, +\infty\right) \tag{38}$$

Finally, the trajectories $X_+^*(\cdot)$ in (27) together with $X_{+,+}^*(\cdot)$ in (35) may be concatenated to obtain a new extended Hamiltonian flow, described by the formula

$$X_{\oplus,\oplus}^*(t) = \left(X^{\oplus,\oplus}(t), P^{\oplus,\oplus}(t)\right) = \begin{cases} X_+^*(t), t \in \left[\tau^+, 0\right) \\ X_{+,+}^*(t), t \in \left(-\infty, \tau^+\right), \end{cases} \tag{39}$$

whose trajectories are illustrated below in Figure 3. Furthermore, geometrically, the adjunct vector $P^{\oplus,\oplus}(\cdot)$ in (39), which, in turn, plays the role of guiding the admissible trajectories, is illustrated as the curves in Figure 4.

To obtain additional insight into the cancer model in (1), we have developed an implementation using GNU Octave 8.1.0. We then provide simulations illustrating the trajectories for different values of the cancer cell growth rate $\alpha > 0$, resulting in Figures 1–4.

Therefore, the Hamiltonian systems in (23) and (25) generate the generalized characteristic flows $C_+^*(\cdot) = \left(X_+^*(\cdot), V(\cdot)\right)$ and

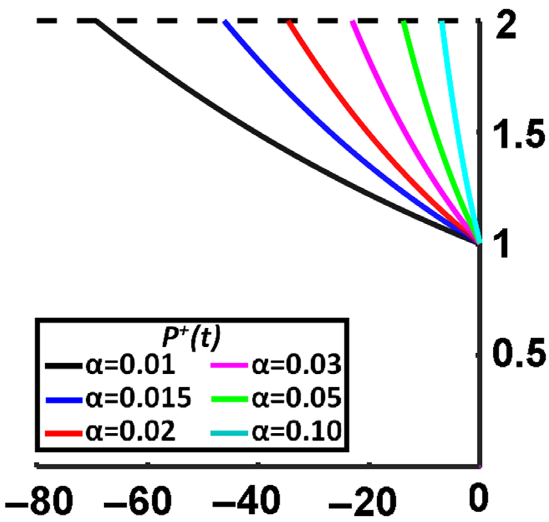

FIGURE 2 | Adjoint vector $P^{+}(\cdot)$.

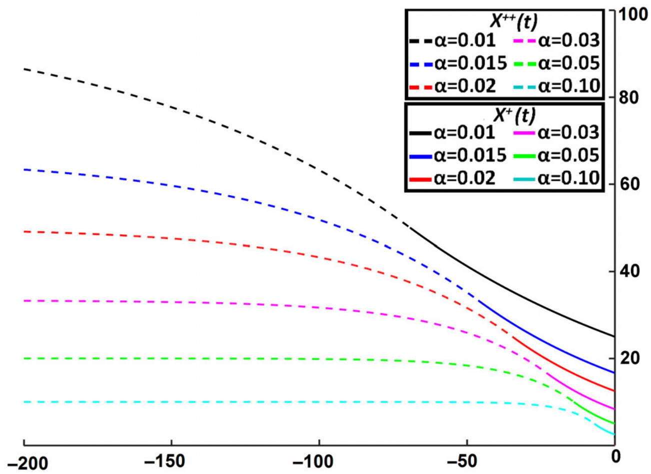

FIGURE 3 | Trajectories $X^{\oplus,\oplus}(\cdot)$.

$C^{*}_{+,+}(\cdot) = \left(X^{*}_{+,+}(\cdot), V(\cdot)\right)$ described in (18), (27) and (35) and which, according to the well-known classical results as in [9] satisfy the basic differential relation for any $t \in I$:

$$DV(t)\bar{t} = \langle P(t), DX(t)\bar{t}\rangle, \forall \bar{t} \in T_t I \tag{40}$$

where $T_t I$ denotes the tangent space at the point $t \in I$.

An essential step in using the general algorithm in [9, 10] consists in the fact that the value of the cost functional in (3) is given by the function $V(\cdot)$ given in (18); it follows from (7) that

$$\hat{u}(X^{*}(t)) = \begin{cases} \frac{P^{+}(t)}{2} = \frac{1}{2}e^{-\alpha t}, & \text{if } t \in I^{+} \\ 1, & \text{if } t \in I^{+,+} \end{cases} \tag{41}$$

from here together with the expression in (18) we get

$$V(t) = \begin{cases} \frac{1}{4}\left[\frac{1}{\alpha} - \int_0^t e^{-2\alpha s}\, ds\right], & \text{if } t \in I^{+} = \left(\tau^{+}, 0\right) \\ \frac{1}{4\alpha} - \int_0^t ds, & \text{if } t \in I^{+,+} = \left(-\infty, \tau^{+}\right) \end{cases}$$

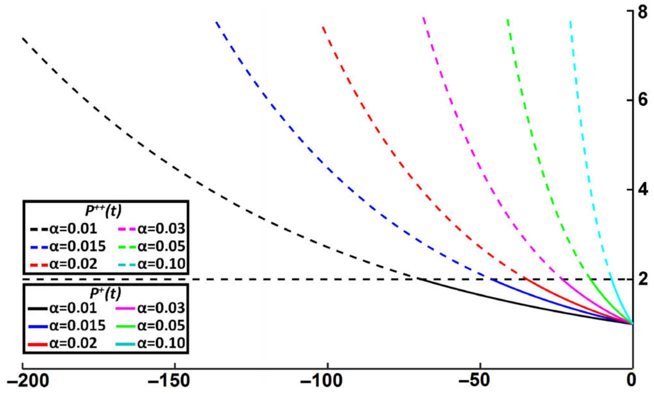

FIGURE 4 | Adjoint vector $P^{\oplus,\oplus}(\cdot)$.

and therefore, the function $V(\cdot)$ having as formula

$$V(t) = \begin{cases} \frac{1}{4\alpha}\left[1 + \frac{1}{2}\left(e^{-2\alpha t} - 1\right)\right], & \text{if } t \in I^{+} = \left(\tau^{+}, 0\right) \\ \frac{1}{4\alpha} - t, & \text{if } t \in I^{+,+} = \left(-\infty, \tau^{+}\right) \end{cases} \tag{42}$$

5 | Value Function and Optimal Trajectories

As specified in the theoretical algorithm in [9, 10], the natural candidate for value function and optimal controls in Problem 1 are the extreme ones, defined by the next maximization process:

$$\begin{aligned} W(x) &= \begin{cases} g(x) = x, & \text{if } x \in Y_1 \\ W_0(x) = \inf\limits_{X(t)=x, t\in I} V(t), & \text{if } x \in Y_0 \end{cases} \\ \hat{t}(x) &= \left\{t \in I; X(t) = x, V(t) = W_0(x)\right\} \\ \tilde{U}(x) &= \overline{U}(\hat{t}(x)), \overline{U}(t) = \{u(t); u(\cdot) \in \overline{U}\} \end{aligned} \tag{43}$$

where $\overline{U}$ represents the set of control functions that satisfy (15); one may note that

$$\overline{U}(t) \subseteq \hat{U}(X^{*}(t)), \forall t \in I \tag{44}$$

and also, that if $X(\cdot)$ is invertible at $t \in I$ with its inverse $\hat{t}(x) = (X(\cdot))^{-1}(x)$, then

$$W_0(x) = V(\hat{t}(x)) \tag{45}$$

further, it follows from (40) that if, in addition, the function $W_0(\cdot)$ is differentiable at the point $x \in \mathrm{Int}\left(Y_0\right)$, then its derivative is given by

$$DW_0(x) = \tilde{P}(x) = P(\hat{t}(x)) \tag{46}$$

and verifies the relations

$$\begin{aligned} DW_0(x)f(x,\bar{u}) + f_0(x,\bar{u}) &= 0, \forall \bar{u} \in \tilde{U}(x) \\ \tilde{U}(x) = \{\tilde{u}(x)\} &= \hat{U}(x, \tilde{P}(x)) \end{aligned} \tag{47}$$

and $\tilde{U}(\cdot)$, is the corresponding candidate for optimal control; moreover, from (10) and (15) it follows that in this case $W_0(\cdot)$ verifies the basic equation

$$\min_{u\in U(x)}\left[DW_0(x)f(x,u) + f_0(x,u)\right] = 0 \tag{48}$$

The following quasi-elementary result establishes that, the Hamiltonian flows $X_{+}^{*}(.)$ and $X_{+,+}^{*}(\cdot)$, along with their corresponding value functions $W_0^{+}(.)$ and $W_0^{+,+}(.)$ defined as in (43), may serve as a partial solution to the problem within their respective domains $Y_0^{+},\ Y_0^{+,+} \subset Y_0$.

Lemma 4. *The mappings $X^{+}(\cdot) : I^{+} \to Y_0^{+}$ and $X^{+,+}(\cdot)$: $I^{+,+}$ described, respectively, in (27) and (35) are diffeomorphism whose inverses $\hat{t}^{+}(\cdot)$, respectively, $\hat{t}^{+,+}(.)$are given by*

$$\begin{aligned} \hat{t}^{+}(x) &= -\frac{1}{\alpha}\ln(4\alpha x) \in I^{+} = \left(\tau^{+}, 0\right), && x \in Y_0^{+} \\ \hat{t}^{+,+}(x) &= \frac{1}{\alpha}\ln(1-\alpha x) \in I^{+,+} = \left(-\infty, \tau^{+}\right), && x \in Y_0^{+,+} \end{aligned} \tag{49}$$

Proof. If $x \in Y_0^{+} = \left(0, \frac{1}{2\alpha}\right)$ then, it follows from (27) that, a point $t \in I^{+}$ for which $X^{+}(t) = x$ is characterized by the equation, $e^{-\alpha t} = 4\alpha x \in (0, 2)$ whence it results the existence and uniqueness of inverse $t = \hat{t}(x)$ that, in turn, checks the first property in (49).

Next, if $x \in Y_0^{+,+} = \left(\frac{1}{2\alpha}, +\infty\right)$, the proof of this statement is done similarly as in the previous case; thus, it follows from (35) that, a point $t \in I^{+,+}$ for which $X^{+,+}(t) = x$ is characterized by expression, $e^{\alpha t} = 1 - \alpha x \in \left(0, \frac{1}{2}\right)$ this implies that, $\alpha t = \ln(1-\alpha x) \in (-\infty, -\ln\ 2)$ which leads to the existence and uniqueness of an extremity; $t = \hat{t}^{+,+}(x) < 0$, of the form as in (49). □

The results in Lemma 4 show that, the characteristic flows $C_{+}^{*}(\cdot) = \left(X^{+}(\cdot), V(\cdot)\right)$ and $C_{+,+}^{*}(\cdot) = \left(X^{+,+}(\cdot), V(\cdot)\right)$ described in (27), (35), and (42) are invertible in the sense of (45) and define the smooth partial proper value function, since from (43) and (49) we deduce that

$$W_0(x) = \begin{cases} W_0^{+}(x) = V\left(\hat{t}^{+}(x)\right) = 2\alpha x^2 + \frac{1}{8\alpha}, & x \in Y_0^{+} \\ W_0^{+,+}(x) = V\left(\hat{t}^{+,+}(x)\right) = \frac{1}{\alpha}\left[\frac{1}{4} - \ln(1-\alpha x)\right], & x \in Y_0^{+,+} \end{cases} \tag{50}$$

which, obviously, is of class C^1 and may be naturally extended by $W(\xi) = g(\xi) = \xi, \forall \xi \in Y_1$ to the corresponding terminal set defined in (4).

Moreover, from (7) and (47) it follows that, the corresponding admissible controls are expressed as

$$\tilde{u}(x) = \hat{u}(x, \tilde{P}(x)) = \begin{cases} \tilde{u}^{+}(x) = \dfrac{\tilde{P}^{+}(x)}{2} = 2\alpha x, & x \in Y_0^{+} \\ \tilde{u}^{+,+}(x) = 1, & x \in Y_0^{+,+} \end{cases} \tag{51}$$

$$\tilde{P}^{+}(x) = P^{+}\left(\hat{t}^{+}(x)\right) = e^{-\alpha\left(-\frac{1}{\alpha}\ln\ 4\alpha x\right)} = 4\alpha x$$

The main result of this section can be stated as follows.

Theorem 1. *The following statements hold*:

1. *The function $W_0(\cdot)$ defined in (50) is a solution of the equation in (48) on the corresponding domain $Y_0^{+} \cup Y_0^{+,+}$; moreover, it is the value function in the sense of (43) of the corresponding admissible controls in (51).*
2. *The corresponding admissible controls $\tilde{u}(\cdot)$ in (51) are optimal for the restriction on their domain $Y_0^{+} \cup Y_0^{+,+}$.*

Proof. For (1), the fact that $W_0(\cdot)$ in (50) is a solution of basic Equation (48) follows from Lemma 4 and the classical theory of smooth Hamiltonian–Jacobi equations [9–11]; using the basic differential relations in (40), and from (4), (15), (46), (48), and (51) one has

$$\begin{aligned} &\min_{u\in U}\left[DW_0(x)f(x,u) + f_0(x,u)\right] = \min_{u\in U}\mathcal{H}(x, \tilde{P}(x), u) \\ &= \mathcal{H}(x, \tilde{P}(x), \tilde{u}(x)) = H(X(\hat{t}(x)), \tilde{P}(x)) = 0 \end{aligned}$$

3. Since the value function $W_0(\cdot)$ in (50) is of class C^1, the optimality of the controls $\tilde{u}(.)$ in (51) and therefore of the corresponding trajectories

$$\tilde{x}_x(t) = \begin{cases} X^{+}\left(t + \hat{t}^{+}(x)\right) \in Y_0^{+}, & \forall t \in \left[0, -\hat{t}^{+}(x)\right] \\ X^{+,+}\left(t + \hat{t}^{+,+}(x)\right) \in Y_0^{+,+}, & \forall t \in \left(-\hat{t}^{+}(x), -\hat{t}^{+,+}(x)\right] \end{cases} \tag{52}$$

follows from the so-called elementary verification theorem [9, 11, 13], according to which a sufficient optimality condition, for the admissible controls $\tilde{u}(\cdot)$ in (51) is the verification of the differential inequality

$$DW_0(x)f(x,\tilde{u}) + f_0(x,\tilde{u}) \geq 0, \forall \tilde{u} \in \tilde{U}(x), x \in Y_0^{-} \cup Y_0^{+} \tag{53}$$

Case 1. If $x \in Y_0^{+}$, it follows from (4), (50) and (51) that □

$$f\left(x, \tilde{u}^{+}(x)\right) = \alpha x - \tilde{u}^{+}(x) = -\alpha x,\ f_0\left(x, \tilde{u}^{+}(x)\right) = \left[\tilde{u}^{+}(x)\right]^2 = 4\alpha^2 x^2$$

$$DW_0^{+}(x) = 4\alpha x$$

and therefore

$$DW_0^{+}(x)f\left(x, \tilde{u}^{+}(x)\right) + f_0\left(x, \tilde{u}^{+}(x)\right) = 0$$

Case 2. If $x \in Y_0^{+,+}$, checking inequality (53) is done in the same way as in statement 1; thus, it follows from (50) and (51) that

$$f\left(x, \tilde{u}^{+,+}(x)\right) = \alpha x - \tilde{u}^{+,+}(x) = \alpha x - 1,\ f_0\left(x, \tilde{u}^{+,+}(x)\right) = \left[\tilde{u}^{+,+}(x)\right]^2 = 1$$

$$DW_0^{+,+}(x) = \frac{1}{1-\alpha x}$$

$$DW_0^{+,+}(x)f\left(x, \tilde{u}^{+,+}(x)\right) + f_0\left(x, \tilde{u}^{+,+}(x)\right) = \frac{\alpha x - 1}{1-\alpha x} + 1 = 0$$

which proves inequalities (53). Hence, the optimality of the controls $\tilde{u}(\cdot)$.

Remark 1. We note that in most cases, especially in the theory of necessary optimality conditions (the use of Pentraxin's minimum principle in its standard form [11, 14, 15], an optimal control problem requires the solution $\tilde{u}(\cdot) \in U\left(x_0\right)$ corresponding to afixed initial point $x_0 \in Y_0$). However, the dynamic programming approach is able to solve the family of problems corresponding to all initial points $y \in Y_0$ and possibly provide feedback optimal solution as found in the present paper.

6 | Conclusion

- As illustrated in Figure 1, during the first phase, the segment controlled by the optimal feedback function $\tilde{u}^{+}(x) = 2\alpha x$, (taken as the best for the drug concentration). If the natural growth rate of the cancer cells is at low values $\alpha \in \{0.01,$

0.015, 0.02, 0.03, 0.05}, then the number of cancer cells gradually decreases to non-significant levels. It is noteworthy that this process occurs over an extended period of time. In contrast, when the growth rate is set to $\alpha = 0.1$, a sharp decrease in the number of cancerous cells is observed, occurring within a very short time. Indeed, at this stage, we can conclude that, the drug concentration is highly beneficial and effective in reducing cancerous cells. Concerning Figure 2, which, unlike Figure 1, incorporates dotted trajectories as the second phase and is controlled by the fixed optimal feedback $\tilde{u}^{+,+}(x) = 1$, we observe a form of stability in the number of cancer cells at significant levels. This stability corresponds inversely to the increase in the growth rate. Therefore, at this stage, significant results are not truly achieved in the effort to reduce cancerous cells, as they are only maintained at somewhat stable but still significant levels. Such stability observed here, is interpreted based on the results from [5, 6], where it was concluded that, cancer cells can develop mechanisms to evade the immune system, and drug resistance may also occur. Ongoing research aims to understand these mechanisms and develop strategies to overcome them.

- To achieve favorable outcomes in the context of cancer treatment, it is essential to adopt a strategy that involves the use of a combination of different drugs or treatment modalities is used to target cancer from multiple angles. This may include a combination of chemotherapy, targeted therapy, and immunotherapy to enhance treatment efficacy. This is, in fact, the view of [6, 7].
- In summary, it can be appreciated that the present study contains our contributions in the following directions:
  - The use of some recent concepts and results from non-smooth analysis and relevant applications in the control theory, as well as employing the synthesis of the very recent theory in [9, 10, 13] regarding the rigorous approach and constructive of optimal control problems.
  - The identification of an admissible feedback, as well as the corresponding complete solution and the rigorous demonstration of its optimality.
  - When delving into cancer models, using the dynamic programming method offers distinctive advantages over traditional approaches like Pontryagin's principle [14, 15]:
    - Cancer dynamics can be highly complex, with interactions between various cell types, genetic mutations, and environmental factors. Dynamic programming allows for the creation of flexible models that can capture this complexity through dynamic state transitions and control strategies. Unlike Pontryagin's principle, which may struggle with intricate nonlinearities, dynamic programming excels in handling such complexities.
    - Our approach provides a framework for optimizing treatment strategies over time. By iteratively evaluating possible interventions at each stage of disease progression, one can identify optimal control policies that maximize treatment efficacy while minimizing side effects or drug resistance.

In conclusion, while Pontryagin's principle is a cornerstone of optimal control theory, dynamic programming offers unique advantages in the context of cancer modeling and treatment optimization. Its flexibility, ability to handle uncertainty, focus on optimal treatment strategies, and adaptability to patient specific data make it a powerful tool for advancing the understanding of cancer dynamics and improving patient outcomes.

Author Contributions

Conceptualization: D. Gueridi. Formal analysis: T. Bouremani and Y. Slimani. Methodology: M. A. Ghebouli. Writing and review & editing: Ahmed Sayed M. Metwally. Validation: M. Fatmi. All authors declare that they have contributed to this article.

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Disclosure

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Research data are not shared.

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