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An approach for simultaneously determining the optimal trajectory and control of a cancerous model

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Abstract

The main attempt of this article is extension the method so that it generally would be able to consider the classical solution of the systems and moreover, produces the optimal trajectory and control directly at the same time. Therefore we consider a control system governed by a bone marrow cancer equation. Next, by extending the underlying space, the existence of the solution is considered and pair of the solution are identified simultaneously. In this manner a numerical example is also given.

Key words: Optimal Trajectory, Cancerous Model.
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Introduction

Bone marrow is the soft, spongy tissue in the center of most bones. It contains blood-forming immature cells called stem cells. Stem cells can develop into red blood cells (which carry oxygen through your body), white blood cells (which fight infection) and platelets (which help with blood clotting). When cancer forms in the blood-forming cells of the bone marrow, it is called bone marrow cancer.
Since the bone marrow produces the blood cells, clinicians typically will take a blood cell count from a patient prior to giving further doses of chemotherapy to see if the blood cell count is above some minimum level. If it is too low, clinicians will either delay the treatment or give a reduced dose. Thus the blood count becomes a deciding factor in designing the treatment.
The purpose of this article is to find optimal strategies for chemotherapy treatments of the cancer, where the blood cell count and then indirectly the bone marrow are kept above a minimum level.

1 Control Model

In the model of the bone marrow proliferating cells P and quiescent cells Q are distinguished. The growth rate of the proliferating cells is denoted by γ and the transition rates from proliferating to quiescent cells and vice versa are denoted by α and β respectively. The rate at which bone marrow enters the blood stream is denoted by ρ and the natural death rate of the proliferating cells is called δ. Drug treatment is modeled by a bounded measurable function u which takes values in the compact interval $[0, 1]$ and represents the drug dosage with $u = 1$ corresponding to a full dose and $u = 0$ stands for no control being applied. While the drugs are given to kill cancer cells, they also kill normal tissue which is considered as bone marrow in this model. If a parameter $s > 0$ is added to model the effectiveness of the drug as in [5],then the overall dynamics

can be described as

$$\frac{dP}{dt} = (\gamma - \delta - \alpha - su(t))P(t) + \beta Q(t) \tag{1.1}$$

$$\frac{dQ}{dt} = \alpha P(t) - (\lambda + \beta)Q(t) \tag{1.2}$$

1.1 Objective

The objective of any treatment is to kill the cancer, but to keep the toxicity to the normal tissue acceptable. Since bone marrow produces blood cells, clinically this is realized by taking a blood cell count of the patient before a treatment session and a full treatment is only administered if the blood cell count is above a certain minimum and usually fixed level. The objective therefore becomes to give as much of the drug as possible since this will kill the cancer cells, but at the same time keep the bone marrow high.Then the objective function that to be maximized id defined as

$$J(P, Q, u) = \int_0^T [a(P(t) + Q(t)) - \frac{b}{2}(1 - u(t))^2]dt \tag{1.3}$$

over the class U of all Lebesgue measurable functions which take values in the control set $U = [0, 1]$ a.e, a and b are positive constants.
In (1.3) we are maximizing the benefit on P cells count, and minimizing the systemic cost which is based on the percentage effects of the chemotherapy given.

2 Transformation by Measure Theory Technique

we consider the following optimal control problem:
$Maximize \quad \int_0^T [a(P(t) + Q(t) - \frac{b}{2}(1 - u(t))^2)]dt$

$$Subject\ to: \qquad \dot{P}(t) = (\gamma - \delta - \alpha - su(t))P(t) + \beta Q(t) \tag{2.4}$$

$$\dot{Q}(t) = \alpha P(t) - (\lambda + \beta)Q(t)$$

$$P(0) = P_0, \quad Q(0) = Q_0.$$

We define the function $f_0 : J \times P \times Q \times U \to R$ as following where P, Q and U are compact subsets of R.

$$f_0(t, p(t), q(t), u(t)) = a(p(t) + q(t)) - \frac{b}{2}(1 - u(t))^2 \tag{2.5}$$

then we write the problem (2.4) in the following form:

$$\begin{aligned} &Maximize \qquad \Xi[p(.), q(.), u(.)] = \textstyle\int_0^T f_0(t, p(t), q(t), u(t))dt \\ &Subject \ \ to: \qquad \dot{p}(t) = f_1(t, p(t), q(t), u(t)), \\ &\qquad\qquad\qquad\quad \dot{q}(t) = f_2(t, p(t), q(t), u(t)), \\ &\qquad\qquad\qquad\quad p(0) = p_0, \quad q(0) = q_0, \end{aligned}$$

where

$$f_1(t, p(t), q(t), u(t)) = (\gamma - \delta - \alpha - su(t))p(t) + \beta q(t) \tag{2.6}$$

$$f_2(t, p(t), q(t), u(t)) = \alpha p(t) - (\lambda + \beta)q(t). \tag{2.7}$$

Now, Let $\Omega = J \times P \times Q \times U$ and $f_1 : \Omega \to R$ and $f_2 : \Omega \to R$ continuous functions, where the trajectory function $p(t)$ is absolutely continuous and the control function $u(t)$ is Lebesgue-measurable.

Definition. Let $\Upsilon(t) = [p(t), q(t)]$ and $A = P \times Q$, pair $W = [\Upsilon(.), u(.)]$ is said to be admissible(The set of admissible pairs is denoted by W) if

(1) the trajectory function $\Upsilon(.)$ is absolutely continuous, and $\Upsilon(t) \in A$.
(2) the pair W satisfies (2.6)-(2.7) a.e. on J^0([4],[5]).

Now, one seek to find an optimal trajectory-control pair $W^* = [\Upsilon^*(.), u^*(.)]$

such that maximization $J(\Upsilon, u)$ in (1.3). In general the maximization of the functional (2.6)-(2.7) over W is not possible. The set W may be empty, even if W is not empty, the functional measuring the performance of the system may not achieve its maximum in this set. It appears that the situation may become more promising if the set W could somehow be made larger. In the following we use a transformation to enlarge the set W.
Let $W = [\Upsilon(.), u(.)]$ be an admissible pair, and B an open ball in R^3 containing $J \times A$, and $\acute{C}(B)$ be the space of all real-valued continuously differentiable functions on B such that the first derivation is also bounded.
Let $\phi \in \acute{C}(B)$, and define function $\phi_{f_1}$and ϕ_{f_2} as follows:

$$\phi^{(1)}_{f_1}(t, \Upsilon(t), u(t)) = \phi_{\Upsilon}(t, \Upsilon(t)).f_1(t, \Upsilon(t), u(t)) + \phi_t(t, \Upsilon(t)) \qquad (2.8)$$

$$\phi^{(2)}_{f_2}(t, \Upsilon(t), u(t)) = \phi_{\Upsilon}(t, \Upsilon(t)).f_2(t, \Upsilon(t), u(t)) + \phi_t(t, \Upsilon(t)) \qquad (2.9)$$

with $(t, \Upsilon(t), u(t)) \in \Omega$ for all $t \in J$.
Since $W = [\Upsilon(.), u(.)]$ is an admissible pair, we have;

$\int_0^T \phi^{(1)}_{f_1}(t, \Upsilon(t), u(t))dt =$

$$= \int_0^T \phi_{\Upsilon}(t, \Upsilon(t)).f_1(t, \Upsilon(t), u(t)) + \phi_t(t, \Upsilon(t)) = \int_0^T \acute{\phi}(t, \Upsilon(t))dt$$

$$= \phi(T, \acute{\Upsilon}(T)) - \phi(0, \acute{\Upsilon}(0)) = \Delta\phi_1$$

Similar to:

$\int_0^T \phi^{(2)}_{f_2}(t, \Upsilon(t), u(t))dt =$

$$= \int_0^T \phi_{\Upsilon}(t, \Upsilon(t)).f_2(t, \Upsilon(t), u(t)) + \phi_t(t, \Upsilon(t)) = \int_0^T \acute{\phi}(t, \Upsilon(t))dt$$

$$= \phi(T, \acute{\Upsilon}(T)) - \phi(0, \acute{\Upsilon}(0)) = \Delta\phi_2$$

for all $\phi \in \acute{C}(B)$.Let $D(J^0)$ be the space of infinitely differentiable real-valued functions with compact support in J^0 ([7],[2],[1]). Define

$$\psi_1(t, \Upsilon(t), u(t)) = p(t)\acute{\psi}(t) + f_1(t, \Upsilon(t), u(t)).\psi(t) \tag{2.10}$$

$$\psi_2(t, \Upsilon(t), u(t)) = q(t)\acute{\psi}(t) + f_2(t, \Upsilon(t), u(t)).\psi(t) \tag{2.11}$$

for all $\psi \in D(J^0)$, then for $\psi \in D(J^0)$ we have:

$$\int_0^T \psi_1(t, \Upsilon(t), u(t))dt = \int_0^T p(t)\acute{\psi}(t)dt + \int_0^T f_1(t, \Upsilon(t), u(t)).\psi(t)dt$$

$$= p(t)\psi(t)|_J - \int_0^T (\acute{p}(t) - f_1(t, \Upsilon(t), u(t))\psi(t) = 0$$

also

$$\int_0^T \psi_2(t, \Upsilon(t), u(t))dt = \int_0^T q(t)\acute{\psi}(t)dt + \int_0^T f_2(t, \Upsilon(t), u(t)).\psi(t)dt$$

$$= q(t)\psi(t)|_J - \int_0^T (\acute{q}(t) - f_2(t, \Upsilon(t), u(t))\psi(t) = 0$$

since the trajectory and control function are an admissible pair satisfying (2.10)-(2.11) a.e. on J^0, and since the function ψ has compact support in J^0,$\psi(0) = \psi(T) = 0$, also by choosing a variable t, we have

$$\int_0^T g(t, \Upsilon(t), u(t))dt = a_g, \qquad g \in C_1(\Omega)$$

where $C_1(\Omega)$ is subspace of the space $C(\Omega)$ of all continuous function on Ω depending only on the variable t.

Now, The mapping

$$\Lambda_W : F \to \int_J F(t, \Upsilon(t), u(t))dt, \quad F \in C(\Omega)$$

defines a positive linear functional on $C(\Omega)$. By the Riesz representation theorem ([5]) there exist a unique positive Radon measure μ on Ω such that

$\int_J F(t, \Upsilon(t), u(t))dt = \int_\Omega F \, d\mu = \mu(F), \quad F \in C(\Omega)$

Thus, the maximization of the functional Ξ in (1.3) over W is equivalent to the minimization of

$$\Xi(\mu) = \int_\Omega f_0 d\mu = \mu(f_0) \in R \tag{2.12}$$

over the set of positive measures μ corresponding to admissible pairs w, which satisfy

$$\mu(\phi_f^{(i)}) = \Delta\phi, \quad i = 1, 2 \quad \phi \in \acute{C}(B) \tag{2.13}$$

$$\mu(\psi_i) = 0, \quad i = 1, 2 \quad \psi \in D(J^0) \tag{2.14}$$

$$\mu(g) = a_g \qquad g \in C_1(\Omega). \tag{2.15}$$

(where $C_1(\Omega)$ is subspace of the space $C(\Omega)$ of all continuous function on Ω depending only on the variable t.)
Define the set of all positive Radon measures on Ω satisfying (2.13),(2.14) and (2.15) as Σ. Also we assume $M^+(\Omega)$ be the set of all positive Radon

measures on Ω. Now if we topologize the space $M^+(\Omega)$ by the weak*-topology, it can be shown that $\Sigma$is compact([4]). In the sense of this toplogy,the functional $\Xi : \Sigma \to R$ define by (2.12) is a linear continuous functional on a compact set Σ, thus it attains its minimum on Σ, and so the measure theoretical problem, which consist of finding the minimum of the functional (2.12), over the subset of $M^+(\Omega)$, possesses a minimizing solution, μ^*, in Σ,([4]).

3 Metamorphosis

We first consider the maximization of the functional (2.12)(still infinite dimensional) over a subset of $M^+(\Omega)$ which is defined by requiring only a finite number of the constrains in (2.13-2.15) to be satisfied. This will be achieved by choosing countable sets of function whose linear combinations are dense in the appropriate spaces, and then selecting a finite number of them. In the first step, we obtain an approximation to the optimal measure μ^* by a finite combination of the atomic measure, that is , from the Theorem $A.5$ in [4], μ^* has the form

$$\mu^* = \sum_{k=1}^{N} \alpha_i^* \delta(z_i^*)$$

where $\alpha_i^* \geq 0$ and $z_i^* \in \Omega$ for $i = 1, 2, ..., N$(here $\delta(z)$ is a unitary atomic measure, characterized by $\delta(z)(F) = F(z)$ where $F \in C(\Omega)$).Then , we construct a piecewise confore in the infinite dimensional linear programming problem (2.12) with restriction defined by (2.13-2.15), we shall consider only a finite number M_1 of functions ϕ as

$$\phi^{(1)} = p, \quad \phi^{(2)} = q \tag{3.16}$$

$$\phi^{(3)} = p^2, \quad \phi^{(4)} = q^2 \tag{3.17}$$

$$\vdots \qquad \vdots$$

Also, we choose M_2 functions with compact support in the following form:

$$\psi_r(t) = \begin{cases} sin[2\pi r\left(\frac{t-0}{T-0}\right)] \; r = 1, 2, ..., M_{21}, \\ 1 - cos[2\pi r\left(\frac{t-0}{T-0}\right)] \; r = M_{21}+1, M_{21}+2, ..., 2M_{21}. \end{cases} \tag{3.18}$$

where, $M_2 = 2M_{21}$.
Finally, it is necessary to choose L number of functions of time only, as follows:

$$g_s(t) = \begin{cases} 1 & t \in J_s, \\ 0 & otherwise, \end{cases} \tag{3.19}$$

where $J_s = \left(\frac{0+(s-1)(T-0)}{L}, \frac{0+s(T-0)}{L}\right), \; s = 1, 2, ..., L$

The set $\Omega = J \times A \times U$ will be covered with a grid, where the grid will be defined by taking all points in Ω as $z_j = (t_j, p_j, q_j, u_j)$; the points in the grid will be numbered sequentially from 1 to N, which can be estimated numerically. Instead of the infinite-dimensional linear programming problem (2.13-2.15), we consider the following finite dimensional linear programming problem,

$Maximize \; \sum_{j=1}^{N} \alpha_j f_0(z_j)$

$subject \;\; to:$

$$\begin{cases} \sum_{j=1}^{N} \alpha_j \phi_f^{(i)}(z_j) = \Delta\phi^i & i = 1, 2, ..., M_1, \\ \sum_{j=1}^{N} \alpha_j \psi_r(z_j) = 0 & r = 1, 2, ..., M_2, \\ \sum_{j=1}^{N} \alpha_j g_s(z_j) = a_{g_s} & s = 1, 2, ..., L. \end{cases} \tag{3.20}$$

4 Numerical Example

In medical control problem (2.4), we assumed the parameters as :

Mean, (Range)	Units=day^{-1}
γ	1.47
α	5.643
λ	0.164
δ	0.0
β	0.48
s	1..0
$a = b$	1.0

we assume
$t \in J = [0, 2], \quad p(t) \in P = [0, 2], \qquad q(t) \in Q = [0, 2], u(t) \in U = [0, 1],$

and $P(0) = Q(0) = 1$.
let the set $J = [0, 2]$ divided into 10 subinterval,the sets P, Q, and U are divided respectively into 10 subintervals, so that $\Omega = J \times P \times Q \times U$ is divided into 10,000 equal subsets. we assume $Z_m = (t_m, p_m, q_m, u_m)$
, $m = 1, 2, ..., 10, 000$,and

$$m = i + 10(j - 1) + 100(k - 1) + 1000(l - 1)$$

$i = 1, \ldots, 10, \quad j = 1, \ldots, 10, \quad k = 1, \ldots, 10, \quad l = 1, \ldots, 10,$
and $M_1 = 4, M_2 = 16, \quad L = 10$. The function $g_s, s = 1, \ldots, L$ were chosen as before.

the following linear programming problem established with 10000 variable and 30 constraints.

$Maximize \quad \sum_{j=1}^{10,000} \alpha_j \{a(p_j + q_j) - \frac{b}{2}(1 - u_j)^2\}$

$Subject \ \ to:$

$\sum_{m=1}^{10,000} \alpha_m \{A_m\} = -0.8$

$\sum_{m=1}^{10,000} \alpha_m \{B_m\} = 0.69$

$\sum_{m=1}^{10,000} \alpha_m \{2p_m A_m\} = -0.96$

$\sum_{m=1}^{10,000} \alpha_m \{2q_m B_m\} = 1.8561$

$\sum_{m=1}^{10,000} \alpha_m \{\pi h p_m \ cos\pi h \ t_m + A_m \ sin\pi h \ t_m\} = 0$

$\sum_{m=1}^{10,000} \alpha_m \{\pi h q_m \ cos\pi h \ t_m + B_m \ sin\pi h \ t_m\} = 0$

$\sum_{m=1}^{10,000} \alpha_m \{\pi h p_m \ sin\pi h \ t_m + A_m \ (1 - cos\pi h \ t_m)\} = 0$

$\sum_{m=1}^{10,000} \alpha_m \{\pi h q_m \ cos\pi h \ t_m + B_m \ (1 - cos\pi h \ t_m)\} = 0$

$\alpha_1 + \alpha_2 + \ldots + \alpha_{1000} = 0.2$

$\alpha_{1001} + \alpha_{1002} + \ldots + \alpha_{2000} = 0.2$

$\vdots \qquad\qquad \vdots$

$\alpha_{9001} + \alpha_{9002} + \ldots + \alpha_{10,000} = 0.2$

$m = 1, \ldots, 10000 \qquad \alpha_m \geq 0$

where
$h = 1, 2, 3, 4 \quad A_m = (\gamma - \delta - \alpha - su_m)p_m + \beta q_m, \quad B_m = \alpha p_m - (\lambda + \beta)q_m$

Therefore we applied the subroutine **DLPRS** from **IMLS** library of **Compaq Visual Fortran** to solve the above linear programming problem by Revised Simplex Method.The optimal valued of objective function was obtained as 0.0187549258021.

Fig1:P cells population in absence of treatment

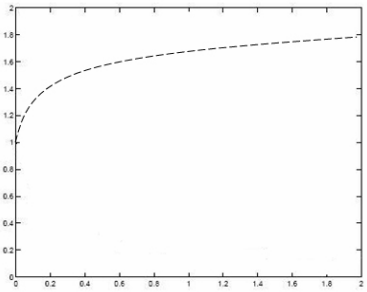


Fig2:P cells population during treatment time

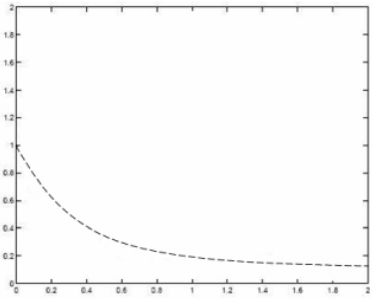
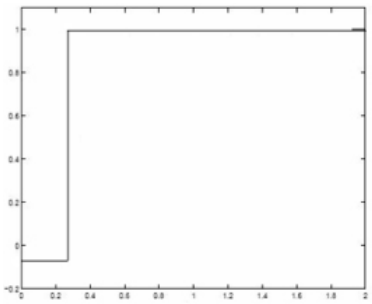


Fig3: Control



5 Conclusion

In this example, a full dose is applied more than just at the final time and partial doses are not optimal. This would agree with experimental and clinical data on the model, but only to some extent. The control we obtained in our example have only one switching which means that in one therapy interval there is only one full-dose session rather than short drug pulses at appropriate intervals as clinical data indicate. However, it is our belief that combining several short therapy intervals one should be able to achieve the desired effect.

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