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Hamilton-Jacobi analysis for cancer treatment

Tumor anti-angiogenesis is a cancer therapy approach that targets the vasculature of a growing tumor. In the last fifteen years tumor anti-angiogenesis became an active area of research not only in medicine (see e.g. [2], [3]) but also in mathematical biology (see e.g. [1], [6], [7]) and several models of dynamics of angiogenesis have been described e.g. by Hahnfeldt et all [1], d'Onofrio [6], [7]. In a sequence of papers [4], [5] Ledzewicz and Schaettler completely decribed and solved from optimal control theory point of view the following or similar free terminal time T problem (P): minimize

$$J(p,q,u) = p(T) + \kappa \int_0^T u(t)dt \tag{1}$$

over all Lebesgue measurable functions $u : [0,T] \to [0,a] = U$ subject to

$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right), \qquad p(0) = p_0, \tag{2}$$

$$\dot{q} = bp - \left(\mu + dp^{\frac{2}{3}}\right) q - Guq, \qquad q(0) = q_0. \tag{3}$$

The term $\int_0^T u(t)dt$ is viewed as a measure for the cost of the treatment or related to side effects. The upper limit a in the definition of the control set $U = [0,a]$ is a maximum dose at which inhibitors can be given. The time T is the time when the maximum tumor reduction achievable with the given overall amount A of inhibitors is being realized. The state variables p and q are, respectively, the primary tumor volume and the carrying capacity of the vasculature. Tumor growth is modelled by a Gompertzian growth function with carrying capacity q, by equation (2), where ξ denotes a tumor growth parameter. The dynamics for the endothelial support is described by (3), where bp models the stimulation of endothelial cells by the tumor and the term $dp^{\frac{2}{3}}q$ models endogenous inhibition of the tumor. The coefficients b and d are growth constants. The terms μq and Guq describe, respectively, loss to the carrying capacity through natural causes (death of endothelial cells etc.), and loss due to extra outside inhibition. The variable u represents the control in the system and corresponds to the angiogenic dose rate while G is a constant that represents the anti-angiogenic killing parameter. Ledzewicz and Schaettler analysed the above problem using first-order necessary conditions for optimality of a control u given by the Pontryagin Maximum Principle, the second order: the so-called strengthened Legendre-Clebsch condition and geometric methods of optimal control theory.

In most of the mentioned papers the numerical calculations of approximated solutions are presented. However in any of them there are not proved assertions that calculated numerically solutions are really near the optimal one.

The aim of this paper is an analysis of the porblem (1)-(3) from Hamilton-Jacobi-Bellman point of view i.e. using dynamic programming approach and to prove that for calculated numerically solutions the fuctional (1) takes an approximate value with a given accuracy $\varepsilon > 0$.

References

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