

Mathematical Models for Tumor Anti-Angiogenesis: Optimal and Suboptimal Protocols and the Role of Pharmacokinetics

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Two mathematical models for tumor anti-angiogenesis, a novel cancer treatment approach that aims at preventing the development of the blood vessel network a tumor needs for its growth, that are based on medical research originally done at Harvard School of Medicine and the National Cancer Institute (NIH) will be considered as optimal control problems. The objective is to minimize the size of the tumor under a constraint on the total amount of agents to be given.

When dosage of the agent and its concentration are identified, optimal controls consist of concatenations of full or no dose segments and specific partial dose therapies that are defined by a feedback function. These so-called singular controls are not medically realizable. But altogether the optimal controls provide a benchmark to which other, simple and heuristically chosen realizable protocols can be compared. Piecewise constant suboptimal protocols with a small number of pieces will be discussed that come within 1% of the optimal values.

When the model is extended to incorporate a standard linear model for the pharmacokinetics (PK) of the anti-angiogenic agents, the optimality of the singular control is preserved. But now concatenations with full or no dose segments no longer are optimal and these transitions are made by so-called chattering controls that have infinitely many switchings on a finite interval. However, once more simple suboptimal protocols can be constructed and numerical examples of such approximations will be given. On the level of suboptimal controls, the differences become negligible.

From a practical point of view, the solution exhibits strong robustness properties and for both models suboptimal protocols with a small number of switchings achieve close to optimal behavior. This supports a simplified modeling where linear pharmacokinetic equations are not included in the model.

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