Modeling and Control of Heterogeneous Tumors under Chemotherapy

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Tumor cells typically are genetically highly unstable and as a response to mutations, they frequently consist of heterogeneous agglomerations of various cell populations that exhibit a wide range of sensitivities towards particular chemotherapeutic agents. However, in response to different growth and apoptosis rates as well as increasing tumor cell densities, specific traits become dominant. We consider a mathematical model for cancer chemotherapy with a single chemotherapeutic agent for three distinctly separate levels of drug sensitivity and analyze the dynamic properties of the system under metronomic (continuous low-dose) chemotherapy. More generally, the optimal control problem of minimizing the tumor burden over a prescribed therapy interval is considered. Interestingly, when several levels of drug sensitivity are taken into account in the model, lower time-varying dose rates become a viable option. For simpler models that only distinguish between sensitive and resistant subpopulations, this only holds once a significant residuum of resistant cells has developed. For heterogeneous tumor populations, a more modulated approach that varies the dose rates of the drugs may be more beneficial than the classical maximum tolerated dose approach pursued in medical practice.