Direct and indirect control of drug resistant cancer populations

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Abstract-This paper presents brief survey of our research in which we have used control theoretic methods in modelling and control of cancer populations. We focus our attention on two classes of problems: optimization of anticancer chemotherapy taking into account both phase specificity and drug resistance, and modelling and optimization of antiangiogenic therapy. In the case of chemotherapy the control action is directly aimed against the cancer cells while in the case of antiangiogenic therapy it is directed against normal cells building blood vessels and only indirectly it controls cancer growth. We discuss models (both finite and infinite dimensional) which are used to find conditions for tumour eradication and to optimize chemotherapy protocols treating cell cycle as an object of control. Two major obstacles in successful chemotherapy are phase dependence of cytotoxic drugs and drug resistance. Cell-cycle-phase specificity is important since it makes sense to apply anticancer drugs when cells gather in sensitive phases of the cell cycle. It can be approached by considering dissection of the cell cycle into an increasing number of disjoint compartments, with drug action limited to only some of them. In many papers we have provided a classification of several models of this kind and analyzed a problem of protocol optimization basing on them. In our research we have developed a model of chemotherapy based on a stochastic approach to evolution of cancer cells. Our works dealt with models with tridiagonal system matrix. They led to development of a methodology for investigating such systems and formed a basis for further generalisation. More recently the research has been pushed a step further, studying properties of a model, in which significantly less simplification has been made and less additional assumptions are required. Moreover, it has combined models that so far have been studied separately, taking into account both the phenomenon of gene amplification and multidrug chemotherapy, in their different aspects. As far as phase-specificity of chemotherapy is concerned it was usually considered without any regard to problems stemming from increasing drug resistance. Combining infinite dimensional model of drug resistance with the phase-specific model of chemotherapy should move mathematical modelling much closer to its clinical application.

The important factor which should be taken into account is that while drug resistance is acquired by cancer cells the normal tissues retain sensitive to the drugs. This negative feature of chemotherapy may be used as an advantage in the antiangiogenic therapy which is directed towards special part of normal tissues and only indirectly destroys tumor cells and it is why it has been called by Kerbel a therapy resistant to drug resistance. We consider a class of models proposed by Hahnfeldt et al. who proposed to use classical models of self-limiting tumour growth with variable carrying capacity defined by the dynamics of the vascular network induced by the tumour in the process of angiogenesis and we find conditions for tumour eradication in asymptotic sense and we optimize protocols of antiangiogenic therapy. In contrast to the control problems arising in phase-specific and drug resistant chemotherapy, modeling antiangiogenic therapy leads to indirect control problems in the sense that the control action is directed against normal tissues and only indirectly enables formation of dynamics of cancer populations.

Finally we propose probably the simplest model of combined antiangiogenic and chemo-therapy.

Keywords: Biomedical models, optimal control, nonlinear control systems, anticancer therapy