173d Optimal Control of Cancer by Delivery of Chemotherapeutic Agents

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Cancer is a collective term that describes a group of diseases characterized by uncontrolled and unregulated growth of cells leading to invasion of surrounding tissues and spreading to the parts of the body that are distant from the site of origin. There are around 200 types of cancer and the cancer of lungs, breast, bowel and prostrate are the most common ones. Surgery, chemotherapy, radiotherapy, hormone therapy and immunotherapy are the most commonly used treatments of cancer. The focus of this presentation is on chemotherapy, which can be used in combination with any of the other treatments.

Chemotherapy uses anticancer or cytotoxic drugs to destroy or kill cancer cells. Optimal control of delivery of chemotherapeutic agents is critical since their effects are not limited only to cancer cells, but normal cells are also damaged. Here two models for the growth of cancer cells are considered: cell cycle non-specific (Martin, 1992) and cell cycle specific (Panetta and Adam, 1995). The growth and death of cells in normal tissues is regulated by the genes whereas in the malignant tissues the genes are mutated and therefore the proliferation of the cells is uncontrolled. The specific genes that get mutated are known as oncogenes and are responsible for the lack of regulation of the growth and function of the cells. The genes of normal cell, known as proto-oncogenes may transform to oncogenes by exposure to environmental or chemical carcinogens, viruses or radiations. There are three main stages in the process of carcinogenesis: initiation, promotion and progression. The normal cell changes to initiated cell and then to cancer differentiated cell and finally invades and spreads to the surrounding cells. The cell cycle non-specific models describe the entire cell cycle as a uniform entity, where all the cells contained in a tumour are of the same type. Such models consist of one compartment so that the effect of the anticancer agents is same on all the cells. However these models fail to describe the action of cycle specific drugs due to their over-simplified nature. The more detailed multi-compartment models (cell cycle specific models) are introduced for this purpose. Here the cell cycle is divided into compartments depending on the types of cells that are affected by the drug.

Many studies have been reported for the optimal control of cancer (Martin, 1992; Harrold and Parker, 2004). In this presentation, the optimal control problems are formulated and solved as mixed integer dynamic optimization problem (Bansal *et al.*, 2003) and dynamic optimization problem for cell cycle non-specific and cell cycle specific models respectively and solved by using gPROMS (gPROMS, 2003). The binary variable for the first model is considered due to the presence of discontinuity in the effect of the drug below and above certain threshold of drug concentration. The second model is modified to include the effect of amount of drug injected. The objective of the optimal control problem is given by the minimization of the final tumour population. The control variable is given by the rate of delivery of the drug. The optimal chemotherapy schedule, which will determine the dose of the drug that needs to be applied to the patient each day, so as to achieve the minimum tumour burden at the end of the treatment period, is obtained. The constraints on maximum drug concentration and cumulative toxicity as well as constraints enforcing the tumour to decrease at, or faster than, a given rate are also included. Many simulation and optimization studies have also been conducted to analyze and carry out a comparative study of the two models in detail. The optimal chemotherapy protocol derived for the first model suggests keeping the initial administration of the drug at a low level, while most of the drug is delivered towards the end of the therapy. For the second model the optimal chemotherapy indicates that the anticancer agents should be administered in high doses at the beginning and at the end of the treatment period. These results may provide a useful guidance tool for the development of efficient chemotherapeutic schedules for different models characterizing various types of cancer and ultimately lead towards the improvement of the treatment of cancer.

References:

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