Dynamic Modeling of Drug Scheduling of Cancer Chemotherapy using Optimal- Perturbation Technique

Cancer can be described as an evolutionary disease, where a population of cells shows inefficient control of its proliferation. Many management options exist for cancer with chemotherapy and surgery being the most widely used. Sometimes, chemotherapy is used as the only treatment however it is often possible that the patient will also receive other treatments. Synergistic effects have also been exploited in the case of different drugs during combination therapy to increase treatment efficacy and reduce drug-related resistance.

Literature suggests that, most of the cancer models and its treatment involves in the form of a generic efficacy term which represents the effectiveness of the drug. Various treatment types have been used, including chemotherapy as means to deplete cancer cells, immunotherapy as a way to boost the immune system, anti- angiogenesis in order to deplete the endothelial support of tumor during angiogenesis, as well as a combination of the above treatments.

Mathematical models describing the biological phenomena underlying cancer can synthesize existing knowledge and can be used as a powerful tool in therapy planning. Numerous models of cancer at different levels have been formulated over many years of active research. In this study, the main focus on dynamic models in the form of ordinary differential equations (ODEs) governing cancer growth on a cell population level and cancer growth by using Gompertzian growth, which, unlike exponential models also considers the fact that as tumor size increases, tumor growth slows down due to limited supply of nutrients. Other ODE models have also been used, such as simple proliferation quiescence models, which describe exchanges between proliferating and quiescence cell populations. Others have considered some form of tumor–immune interaction.

The research utilizes the mathematical theory of optimal control, an active research area for many mathematicians, scientists, and engineers. It is of multidisciplinary nature, having been applied to areas ranging from engineering to biomedicine. Optimal control (or dynamic

optimization), which has been widely used in the cancer literature, is the process of determining control and state trajectories for a dynamic system over a period of time in order to minimize a performance index.

Our research mainly focuses on design and analysis of mathematical models which describe the construction of drug schedule that is useful to reduce the size the tumor in a finite interval of time. This problem can be regarded as an optimal control problem in which the constraints are of the form of impulsively perturbed system of ordinary differential equations. Our basic model reduces to the

Optimization of $\int_{t_0}^{T} f\big(t, x(t), u(t)\big)dt$

subject to $Dx(t) = g\big(t, x(t), u(t)\big)D\emptyset(t), \qquad x(t_0) = x_0$

where x(t) is the state variable, u(t) is the control variable and $\emptyset : [0, \infty) \to R$ is a right continuous function of bounded variation on compact subsets of $[0, \infty)$, $d\emptyset$ is the distributional derivative of the function $\emptyset$ and may be identified with the Lebesgue-Stieltjes measure induced by the function $d\emptyset$ and $g: [0, \infty) \to R^n$ is integrable with respect to $d\emptyset$ and the discontinuities $0 = t_0 < t_1, < t_2 < \cdots < t_k < \cdots$ of $\emptyset$ tend to ∞ as k tends to ∞. This function can be used as a drug scheduling function which varies from time to time and also depends on the state of the system.

The above set of equations gives the optimal performance in drug scheduling and reduction of the tumor burden in finite interval of time. It is expected that this study would result in the design of effective control strategies besides retarding the process of metastasis in certain types of cancers.