Aiding cancer therapy by mathematically modeling tumor-immune interactions

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Cancer is one of the five leading causes of death. And yet, despite decades of research, there is no standardized first-line treatment for most cancers. In addition, disappointing results from predominant second-line treatments like chemotherapy have established the need for alternative methods.

Mathematical modeling of cancer usually involves describing the evolution of tumors in terms of differential equations and stochastic or agent-based models, and testing the effectiveness of various treatments within the chosen mathematical framework. Tumor progression (or regression) is evaluated by studying the dynamics of tumor cells under different treatments, such as immune therapy, chemotherapy and drug therapeutics while optimizing dosage, duration and frequencies.

In a paper published last month in the *SIAM Journal on* Applied Mathematics, 'Controlled Drug Delivery in Cancer Immunotherapy: Stability, Optimization, and Monte Carlo Analysis,' authors Andrea Minelli, Francesco Topputo, and Franco Bernelli-Zazzera propose a differential equation model to describe tumor–immune interactions. "We study the dynamics of the competition between the tumor and the immune system," Topputo explains.

The relationship between cancers and the immune system has been studied for many years, and immune therapy has been known to influence tumor regression. Clinically called immunotherapy, it involves using external factors to induce, enhance, or suppress a patient's immune response for treatment of disease. In this study, the therapy consists of injecting a type of immune cells called dendritic cells, which generate tumor-specific immunity by presenting tumor-associated antigens.

"In particular, cancer immunotherapy has the purpose of identifying and killing tumor cells," says Topputo. "Our research considers a model that describes the interaction between the neoplasia [or tumor], the immune system, and drug administration." Such modeling and simulation can be used to assess the impact of drugs and therapies before clinical application.

Using ordinary differential equations, the authors model the progress of different cell populations in the tumor environment as a continuous process. Within the dynamical system presented by the tumor environment, they apply the theory of optimal control—a mathematical optimization method—to design ad-hoc therapies and find an optimal treatment.

The end goal of the control policy is to minimize tumor cells while maximizing effectors, such as immune cells or immune-response chemicals. "The aim is to minimize the tumor concentration while keeping the amount of administered drug below certain thresholds, to avoid toxicity," says Topputo. "In common practice, one searches for effective therapies; in our approach, we look for efficiency and effectiveness."

Elaborating on a prior study where indirect methods used to solve the optimal control problem are not effective, the authors use direct methods that apply algorithms from aerospace engineering to solve the associated optimal control problem in this paper. Optimal protocols are analyzed, and the duration of optimal therapy is determined.

The robustness of the optimal therapies is then assessed. In addition, their applicability toward personalized medicine is discussed, where treatment is customized to each individual based on various factors such as genetic information, family history, social circumstances, environment and lifestyle.

"We have shown that personalized therapy is robust even with uncertain patient conditions. This is relevant as the model coefficients are characterized by uncertainties," Topputo explains. "Further studies would include designing optimal protocols by considering personalized constraints based on individual patient conditions, such as maximum amount of drug, therapy duration, and so on."

Other future directions would be the use of more diverse models and studying the effectiveness of treatment combinations. "More detailed approaches like agent-based models that describe tumor-immune interactions and hybrid therapies that consist of combined chemotherapy-immunotherapy treatments should also be considered," says Topputo.

More information: Controlled Drug Delivery in Cancer Immunotherapy: Stability, Optimization, and Monte Carlo Analysis, Andrea Minelli, Francesco Topputo, and Franco Bernelli-Zazzera, *SIAM Journal on Applied Mathematics*, 71, pp 2229-2245 (Online publish date: December 20, 2011)

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