MATH MATTERS

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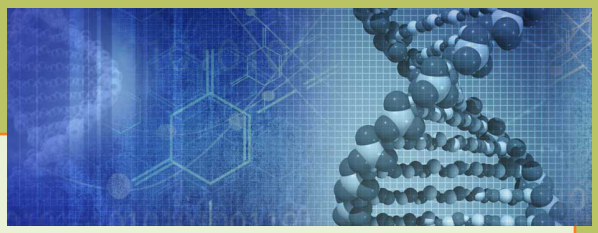

The math behind...

Optimal Cancer Therapy Scheduling

Technical terms used:

Ordinary differential equations, dynamical systems, tumor cell, cancer dynamics, cisplatin, paclitaxel, cell cycle

Uses and applications:

Main treatment options for cancer patients comprise a combination of surgery, chemotherapy, and radiotherapy. In an effort to improve therapeutic options for cancer patients prior to the administration of any therapy, mathematical models aimed at optimal therapeutic scheduling and based on patient-specific data can be formulated. Such mathematical frameworks can provide insights about cancer dynamics and emergence of resistance that reach beyond contemporary clinical and experimental tools.

How it works:

In its most basic form, a dynamical system modeling cancer progression and therapy scheduling can be written using a single ordinary differential equation representing the population of tumor cells present at a particular time. First, various functions describing tumor growth kinetics of specific cancer subtypes can be used [1]. Second, the effect of surgery can be modeled as an instantaneous process that eliminates a fraction of the tumor cells upon cancer diagnosis. Third, various functional forms for modeling cell kill can be used to model the effects of chemotherapeutic drugs used, such as growth rate or tumor cell density dependent functional forms [1]. Fourth, radiation doses can be approximated via exponentially decaying functional forms that allow one to estimate the proportion of cells surviving radiation damage. In a more complex form, cancer progression and therapy scheduling can be modeled by a system of ordinary differential equations, accounting for the number of tumor cells sensitive or resistant to chemotherapy, the number of actively proliferating versus quiescent tumor cells, or the drug-specific concentrations in the blood. The parameters used in describing such complex interactions can be calibrated against experimental data and assume random or non-random time-dependent values.

The cancer dynamics generated by representative simulations of such models can be associated with different observed clinical outcomes and used to mathematically derive the optimal treatment strategy in the sense of promoting the biggest tumor cell burden reduction (e.g., whether chemotherapy followed by surgery or surgery followed by chemotherapy is the better strategy). Depending on the modeling objectives and clinically available data, various cellular populations can be incorporated in the dynamical system in order to provide a more comprehensive representation of the tumor cell–extracellular matrix–normal cell interactions and their response to therapy administration.

Interesting fact:

The effectiveness of cancer treatment depends strongly on the order in which even seemingly similar drugs are taken. This was, for example, demonstrated in a clinical trial comparing two schedules that involved the anticancer agents cisplatin and paclitaxel: In the first schedule, cisplatin was administered immediately after paclitaxel, with a 45–60% overall response rate. In the second schedule, cisplatin was administered 12 hours after paclitaxel, which resulted in an 80% overall response rate and lower toxicity levels [2]. A possible explanation for the observed effect is that paclitaxel may synchronize cells into the same phase of the cell cycle just prior to DNA synthesis, when cisplatin is maximally active.

References:

[1] Kohandel M., Sivaloganathana S., Oza A. Mathematical modeling of ovarian cancer treatments: Sequencing of surgery and chemotherapy. J. Theor. Biol. 242 (2006) 62–68.

[2] Shah A., Schwartz G. Cell-Cycle Mediated Drug Resistance: an Emerging Concept in Cancer Therapy. Clin. Cancer Res. 7 (2001) 168-181.

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