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# Adaptive therapy: modeling evolutionary principles in anticancer therapy

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Toward adaptive therapies: modeling evolutionary principles in anticancer therapy

**Abstract:**
Resistance to drug therapy is an important issue in the field of cancer research because, despite initial success of targeted cancer drugs, many patients will ultimately develop resistance to these therapies, rendering treatment ineffective. A model of cancer chemotherapy must include both kinetic resistance (cell-cycle mediated, [1]) and genetic resistance (acquired through random mutations, [2]) concepts. We present a stochastic Moran process model of tumor cell kinetics, coupled with a prisoner's dilemma game-theoretic cell-cell interaction model to design chemotherapeutic strategies tailored to different tumor growth characteristics [3]. At each step of the birth-death process, two phenotypic sub-populations compete in a prisoner's dilemma evolutionary game with the healthy cells playing the role of cooperators, and the cancer cells playing the role of defectors. Fitness, birth-death rates of the cell populations, and overall tumor fitness are defined via the prisoner's dilemma payoff matrix.

Using the Shannon entropy as a novel tool to quantify dosing strategies, we contrast maximum tolerated dose (MTD) strategies as compared with low dose, high density metronomic strategies (LDM) for tumors with different growth rates. Our results show that LDM strategies can outperform MTD strategies. The advantage is magnified for fast growing tumors that thrive on long periods of unhindered growth without chemotherapy drugs present and is not evident after a single cycle of chemotherapy, but grows after each subsequent cycle of repeated chemotherapy. Finally, we use the model to test various adaptive therapy techniques to exploit the evolutionary phenotypic cost of developing resistance. We highlight the utility, clarity, and power that models provide in designing chemotherapeutic schedules for tumors with different growth rates and develop quantitative tools to optimize these schedules for maintaining low volume tumors.

**References:**
1. Norton, L and Simon, R. "Tumor size, sensitivity to therapy, and design of treatment schedules." Cancer Treatment Reports 61:7 (1977): 1307.
2. Gatenby, Robert A. "A change of strategy in the war on cancer." Nature 459.7246 (2009): 508-509.
3. West, Jeffrey, et al. "The prisoner's dilemma as a cancer model." Convergent Science Physical Oncology 2.3 (2016): 035002.