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Control structures in cancer chemotherapy

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Drug resistance is a major cause of the failure of chemotherapy. Resistance manifests through a diverse set of molecular mechanisms, such as the upregulation of efflux transporters on the cell membrane, enhanced DNA damage repair mechanisms, and/or the presence of cancer stem cells. Classically, these mechanisms are understood as conferred to the cell by random genetic mutations, from which clonal expansion occurs via Darwian evolution. However, the recent experimental discovery of epigenetics and phenotype plasticity complicates this hypothesis. It is now believed that chemotherapy can produce drug-resistant clones. Motivated this by this recent experimental evidence, we introduce a framework of drug-induced resistance, which incorporates both random and drug induced effects. We discuss both structural and practical identifiability issues related to the model, and demonstrate techniques by which the induction rate of an applied chemotherapy may be experimentally determined. This is crucial, as the design of control protocols is heavily influenced by this aforementioned rate. Specifically, we seek the treatment protocol which prolongs patient's life by maximizing the time of treatment until a critical tumour size is reached. The general control structure is determined as a combination of both bang-bang and singular arcs. We deduce that in the case of purely random mutations, optimal controls are pure bang-bang, while singular arcs exist if treatment causes resistance to emerge. We further characterize the precise control structure using a combination of numerical methods and higher-order techniques. Thus, the ability of a drug to induce resistance generates a completely different control structure from that of the classical Darwinian selection paradigm.

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