317b Customized Leukemia Chemotherapy Using an Age-Structured Populataion Balance

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The goal of our research is to develop an experimental and theoretical framework that will tailor a treatment regimen for a patient with hemopoietic or lymphatic cancer. For a chemotherapuetic treatment to be effective, it must be selective for cancerous over non-cancerous tissue. Drugs accomplish this by targeting molecules present only during proliferation but these molecules are often specific to only certain phases within the proliferation cell cycle. In these instances, the phase dynamics of the cells are disrupted such that the effectiveness of subsequent treatments becomes dependent upon the treatment timings relative to the cell cycle. Thus, when different cell lines coexist, each with unique growth behaviors (for example, bone marrow and leukemia cells), it is thought that the specificity of drugs may be harnessed to time sequential treatments that preferentially kill one population. An age-structured population balance model is developed to describe the dynamics of the cells transitioning through the cell cycle and incorporate the changes in response to drug. The age implicitly encompasses the complex biochemistry involved in phase transitions and is used to describe the transitions between the phases of the cell cycle. This model is used to design treatment schedules under various growth and death scenarios with in vivo considerations such as: quiescence, drug metabolism, drug transport, resistance development, or altered cell cycle transition rates due to drug effects. By collecting individual patient information for use in the theoretical framework, the model can be used to design patient specific chemotherapuetic treatment regimens. For verification purposes, an experimental system using HL60 and Jurkat leukemia cells exposed to the S phase specific drug, camptothecin, is employed. Cytometric measurements quantify and characterize both the cell death response and the subsequent cell growth behavior invoked after the addition of the drug. The age-dependent transition rates of the cells are elucidated under balanced growth conditions by observing a time-sequence of BrdU pulse-labeled cells. The progression of the cell populations through the cell cycle is observed using propidium iodide and viable cell counts with antibodies to CD3 used to separate the two cell lines under co-culture conditions. Excellent quantitative agreement is found between the simulations and the experimental results when multiple, timed applications of camptothecin are given. However, while the merit of timing treatments appears clear based on the in vitro experiments and the corresponding simulations, these scenarios represent a simplified in vivo situation. As likely in vivo effects are incorporated into the model, the window of applicability of timed treatments quickly reduces.