432c A Multi-Dimensional Somatic Evolution Model for in Vivo Tumor Growth

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Cancer modeling is a highly challenging frontier of applied mathematics, as cancer phenomena appear at different scales ranging from the macroscopic tissue level to the sub-cellular. Mathematical models are required to deal with the fact that even though a majority of the phenomena emerges at the macroscopic scale, cellular events such as mutations play a simultaneous and relevant role. Obviously, any method that provides insight into cancer is of significant value, and a multi-scale model (i.e., combining tissue level tumor growth with cellular dynamics and somatic evolution) with prediction capabilities could be highly useful, particularly in determination of optimal chemotherapy procedures.

In this work, a novel multi-scale tumor-growth model is introduced for use in clinical tumor growth predictions. The model introduced is a simplified spherical tumor model with a necrotic inner core surrounded by a thin active growth layer. However, rather than a detailed partial differential equation form, the concentric tumor spheres are modeled as lumped 2-D models where their volume is directly proportional to the number of cells in each region. This particular lumped-model enables including the transport phenomena related considerations in the model, such as oxygen and nutrient supply into the tumor core, necrotic cell generation due to nutrient deprivation, and consequent angiogenesis, without excessive mathematical complexity and any empirical parameters.

In addition to this tissue-level tumor growth and angiogenesis model, the somatic evolution of the cancer cells, the responses of the immune system, and the behavior of the normal tissue are predicted cybernetically in order to calculate the growth rate of the tumor throughout its entire life-cycle, as a function of the chemotherapy, immune-system response, blood vessel density and other host environment changes. This is achieved through a novel three-agent (normal cells, immune system, and cancer cells) dynamic game-theory approach (i.e., a three level predator-prey model), where each agent tries to maximize its own fitness function. Mathematically, the problem is solved as a cascade of three optimal control problems with three different objectives for each agent (homeostasis for normal cells, growth maximization for cancer cells, and cancer-cell termination for the immune system). Each sub-system is modeled by linearized Lotka-Volterra models that are commonly used in predator-prey system studies. The major advantage of this method is that the in vivo cancer cell growth rates can be predicted based on very few semi-empirical parameters, and no additional parameters/experiments are necessary to predict the responses in different phases or with different chemotherapy strategies.

The modeling approach introduced combines tissue-level tumor growth with cell-level adaptation and evolution, as well as a few sub-cellular level factors such as nutrient and blood vessel growth factor concentrations in the tissue and tumor, to create a multi-scale model that can be clinically relevant for tumor growth studies in patients. It is demonstrated that the model is capable of accurately predicting tumor growth based on data available in literature. The possibility of utilizing the model clinically for chemotherapy optimization, based on tumor image data and in vitro experiments with samples obtained from patients, are discussed.