

173c A Model of the Darwinian Evolution of Cancer Progression

Kim Seng Cheong, Shamsuzzaman Farooq, and Richard D. Braatz

There are more than 100 distinct types of cancers that can occur in various organs of the human body. Research over the last quarter of a century has revealed cancer to be a disease of the genome—mutations produce oncogenes and tumor suppressor genes, transforming normal cells into cancerous lesions that ultimately invade surrounding tissues and metastasize. In recent years, scientists have tried to understand the laboratory and clinical complexities of the disease in terms of a small number of underlying principles. Hanahan and Weinberg (2000) suggested in a seminal essay that the normal cells must acquire six traits in order to become cancerous: (1) self-sufficiency in growth signals, (2) insensitivity to antigrowth signals, (3) evasion of apoptosis, (4) limitless replicative potential, (5) sustained angiogenesis, and (6) tissue invasion and metastasis. This has gained widespread acceptance in the literature (the Hanahan and Weinberg paper has received over 2000 citations in the literature), and several recent modeling efforts incorporate several of these traits (e.g., Spencer et al, 2004).

The highest fidelity cancer progression models are written in terms of ordinary differential equations (ODEs) that track the progression of cancer as a series of mutations characterized by a set of kinetic parameters and rate expressions describing mutation, birth, death, and metastatic rates (e.g., Spencer et al, 2004). The kinetic parameters are mostly inferred from various sets of experimental data available in the literature. While such models have been able to model much of the qualitative observations during cancer progression, a drawback of ODE-based models is that they do not track differences between cells within each distinct cell population such as the cell age or number of cell divisions for each cell. This is a significant limitation, as more realistic expressions for some of the cancer cell kinetic rates are strongly dependent on the cell age.

Population balance models, on the other hand, can and have been used extensively to model heterogeneity in noncancerous cell populations (e.g., see Henson, 2003, and citations therein). In this work, we propose a population balance model to adequately account for the age and replicative potential of cells in order to more accurately model the six-step progression of cancer. The model is extended to include spatial variations, using a spatially-varying population balance equation (Hulbert and Katz, 1964). The model equations are simulated using a high resolution finite volume algorithm (Gunawan et al, 2004, LeVeque, 2002), which is followed by sensitivity analysis (Caracotsios and Stewart, 1985) and uncertainty analysis for nonlinear distributed parameter systems (Hukkanen and Braatz, 2005) to assess which kinetic parameters have the strongest effect on the tumor cell populations and to quantify the effects of simultaneous uncertainties. These results are compared to experimental data on the biological variability of tumor progression from person to person, and used to assess the extent for which state-of-the-art cancer progression models are accurate enough for use in optimal chemotherapy studies.

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