317a A Population Balance Model of Senescent Tumor Modeling and Cancer Treatment

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Cycle-specific chemotherapeutics aim to exploit the rapid proliferation of cancer cells by preferentially targeting mechanisms required for cell cycle progression, hence their name. Lumped cell cycle models for bulk tumor growth allow for explicit incorporation of cycle-specific drug effect within the appropriate cell phase (*e.g.*, G, S, M, etc.), but treat all cells within a given phase as having equivalent properties (*e.g.*, probability of phase transition and drug exposure). However, tumors cells have neither identical intracellular nor external conditions. Rather, tumors are comprised of a heterogeneous population of cells that may be more accurately described by population balance equations (PBE).

Previously, a three phase cell cycle age-structured PBE model was developed for describing bulk tumor progression following administration of chemotherapeutics having cycle-specificity [1]. A limitation of the model, however, was the prediction of exponentially growing long-term tumor progression. While this is accurate for early tumor growth or growth over small regions of time, it is inadequate for describing bulk tumor growth over extended periods [2]. One possible solution involves adapting a saturating transition rate in the G-phase analogous to the rate term found in the Gompertz model [2]. Unfortunately, such dynamics may substantially extend the phase residence time as the overall population approaches a plateau value. As the total population approaches the limiting value, the transition rate through G-phase would require an increasing amount of time, extending the critical age within G-phase. For large critical ages an increasing number of equations would be required following discretization to ensure that numerical accuracy is maintained, substantially increasing model complexity. Furthermore, as the population approaches its limit a near infinite number of equations would be required for maintaining model stability, rendering the structure inapplicable. Alternatively, a cell-cycle mass-structured PBE model could handle extended cell-phase residence times provided an upper bound was placed on mass for cells in the G-phase. However, a mass-structured PBE has reduced drug delivery relevance as it is unable to: (i) account for the period of drug exposure; (ii) incorporate increased susceptibility during specific periods of a cell-cycle phase; or (iii) ensure a minimal overall cycle transition time.

A compromise was possible in the present work by constructing a cell-cycle PBE dependent on both age and mass. Inclusion of both intrinsic variables within all three cell phases would have resulted in the same G-phase residence time problems discussed for the age-structured model. Instead, all three cell phases incorporated explicit mass modeling, but only two of the equations (for S- and M-phase) included intrinsic age tracking. This structure was feasible because the age boundary conditions do not depend on the transition age from other phases. Rather, they depend on the total number of cells undergoing the phase transition with all cells initializing at age zero. This proposed structure was capable of demonstrating saturating tumor growth while simultaneously addressing the need for drug exposure times within both S- and M-phase using two theoretical cycle-specific drugs. Also, with the above structure it was possible to identify regimens inducing dosing resonance, or delivery of drug during a period of decreased susceptibility, within the overall tumor population [3]. These studies could then be applied in scheduling chemotherapeutic adminstration during combination clinical trials predominant in the treatment of cancer.

Bibliography

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