A series of mathematical models for in vitro multicellular tumor spheroids response to chemotherapeutic treatment vs. plate cultures

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Background
Cancer tumor growth may be modeled as a monolayer culture or as a spheroid culture. However, various authors state that spheroids are a more accurate model of in vivo tumors than a single cell line. In vivo tumors do not consistently grow. Initially at a small size, a tumor rapidly proliferates, similar to a cell culture. As the tumor approaches an intermediate stage, only the outermost cells perform active cell division, mitosis. This is referred to as the tumor’s “shell” and the tumor’s “inner core” consists of living cells not engaged in mitosis, quiescent cells. At the tumor’s late stages, the tumor’s very inner core is necrotic tissue, quiescent cells comprise the middle layer, and proliferating cells remain on the outermost layer.

Often medical doctors administer chemotherapy treatments to kill the proliferating cells. However, since a tumor is not fully of proliferating cells implies that certain chemotherapy doses are not optimally administered. Furthermore, prior research suggests that the quiescent cell layer may cause the tumor to acquire resistance to chemotherapy, possibly by supplying nutrients to the proliferating layer.

Professor Dorothy Wallace and Xinyue Guo in January 2013 provided a potential spheroid growth model that accounted for 4 factors: 1. Proliferating cells, 2. Quiescent cells 3. Necrotic cells 4. Total spheroid size. Thus, previous mathematical models describe the disparity between cell plate cultures and spheroid cultures.

The current research prominently relies upon five articles to provide a basis of a mathematical spheroid tumor model, empirical cell plate culture data without treatment, empirical cell plate culture data in response to treatment, and empirical tumor spheroid data without treatment, and empirical tumor spheroid data in response to treatment.

Abstract
The research topic is a mathematical model of tumor growth in response to chemotherapeutic treatments. Interest in mathematical models arises from the behavior of spheroid tumors which differ from observed cell plate culture growth. Thus, approaching tumor growth by mathematical modeling spheroids produces more accurate growth models. This allows a better understanding of the effects of chemotherapeutic drugs and optimizing the administration of treatments. The method to approach first begins with modeling a line’s plate culture growth without any chemotherapy treatment for 4 cell lines: A-549 (lung cancer), SK-N-SH (neuroblastoma), SK-N-MC (neuroblastoma), and MCF-7 (breast cancer). Then, using literature data of treatment effects on monolayer cultures allows the analysis of a treatment’s effectiveness. From the cell line model, the calculated values of a cell line’s growth and response to chemotherapy are then applied to a spheroid model. These models were generated using MATLAB, a multi-parametrical numerical computing environment.

1) Introduction: The cell plate culture model

Fig 1. A model of the basic cell cycle (for a cell line) $G_i = [G_i, S_i, G_i, M_i]$ with parameters to the plate culture model 3E: Let $P, Q$, and $R$ be the number of proliferating, quiescent, and necrotic cells respectively.

DNA Content

Fig 6. An example of literature data used. This is the cell cycle analysis of SK-N-SH cells treated with various doses of 15-deoxy-PGJ2, control b, G2-phase, 6 μM, d, G1-phase, 12 μM and d, 15 μM 15-deoxy-PGJ2 (PGJ2) treatment for 24 h. (John 2000) Literature tends to combine the $G_i$ and $M_i$ cell cycles stages in $G_i$.

Step 2) Treatments on Plate Cultures

Literature usually states the particular cell cycle stage(s) that a chemotherapy drug targets in a cancer cell. For treatments on a cell plate culture, consider the part of the cell cycle affected and/or the resulting observed death rates creates a series of models and computer runs to estimate the new death rate constants for each type of treatmental lines. This step determines a mathematical constraints for a cell plate culture response to a treatment and these constraints will be applied to spheroidal models.

Discussion of Results

The research project accurately mathematically modeled the growth of monolayer cancer plate cultures in response to certain treatments for four cell lines: A-549, SK-N-SH, SK-N-MC, and MCF-7. The values determined for 15-deoxy-PGJ2 effect for SK-N-MC was accurately mathematically modeled to the Carlson 1983 paper. The research project is still in the process of accurately modeling spheroid growth to for A549 and breast cancer. Current results are promising and exemplify the potential of mathematical modeling of cancer tumor growth. The approach described in the research project provides a general method to mathematically model any cell line that produces tumor spheroids using cell plate culture data to identify basic growth and treatment parameters.