Mathematical Modeling of Monolayer, Spheroid, and Xenograft Growth and Radiation Response in a Colon Adenocarcinoma

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RESEARCH QUESTION

Can mathematical models be generated in MATLAB to model monolayer, spheroid, and xenograft growth data for a colon adenocarcinoma cell line, and then successfully predict the response of these cancer cell cultures to radiation dosage?

INTRODUCTION

Colorectal cancer is the third most common type of cancer for both men and women in the United States (2). The American Cancer Society predicts that 101,000 new cases of colon cancer and 44,000 cases of rectal cancer will be diagnosed in 2019 alone (1). Additionally, colorectal cancer is the second-leading cause of cancer deaths in men and women combined (1). WiDr, the cell line used for modelling in this experiment, is a colon adenocarcinoma, which is a type of cancer that originates in glandular cells in the colon that make mucus (1). Adenocarcinomas make up 96% of all colorectal cancers (1). Research into treatments for colon adenocarcinomas - and treatments for all cancers - is critically important for improving the effectiveness of these treatments. Traditional lab experiments with cell cultures are time-consuming and extremely expensive, whereas mathematical models have the capability to simulate complex biological systems, such as tumor growth, at minimal cost and almost instantaneously. This project aims to generate mathematical models in MATLAB that effectively simulate the growth of WiDr, the colon adenocarcinoma cell line, and then successfully predict the response of WiDr cells to treatment with radiation.

METHODS

All of the mathematical models used in this experiment were programmed in MATLAB, using code derived from previous projects done by Prof. Wallace and her colleagues (3, 4). Growth data and radiation data were both obtained from the paper "The Radiation Response of a Human Colon Adenocarcinoma Grown in Monolayer, as Spheroids, and in Nude Mice" by Catharine West and Robert Sutherland (5).

Experiment Outline

- Part I: Use monolayer culture data for WiDr to calculate parameters for cell cycle phase and cell death rate, and use these parameters to generate the monolayer mathematical model.
- Part II: Use the parameters generated in the monolayer mathematical model, as well as spheroid growth data for WiDr, to generate the spheroid mathematical model.
- Part III: Use parameters from both the monolayer and spheroid mathematical models, as well as tumor growth data for WiDr, to generate the xenograft mathematical model.
- Part IV: Implement Heaviside function to simulate radiation dose in the monolayer model to calculate values for cell death as a function of radiation dosage.
- Part IV: Test the Heaviside radiation function and calculated cell death values on the spheroid and xenograft models to determine whether the mathematical models can accurately predict radiation response in the spheroids and tumors.

METHODS (CONTINUED)

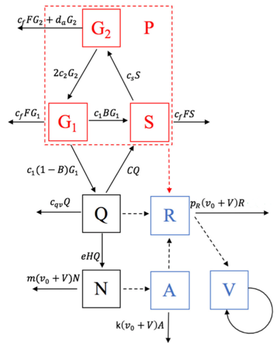
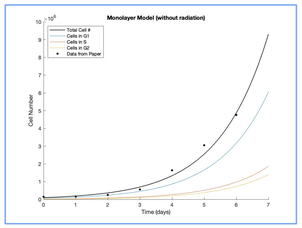


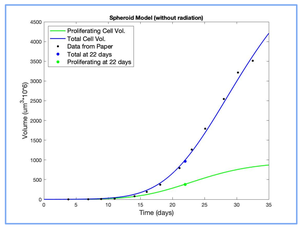
Figure 1: This diagram shows the compartmental model for the mathematical models generated in MATLAB. The red boxes alone model a monolayer culture, red and black boxes together model a spheroid culture, and the red, black, and blue boxes together model the tumor model in an immunocompromised mouse. Solid arrows represent transitions between compartments, and dashed lines represent the influence of one compartment on another. Image from (3).

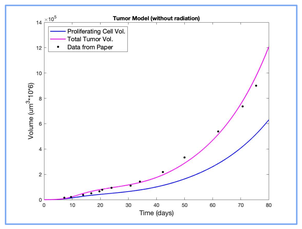
RESULTS

Parameter/Explanation	Symbol	Monolayer	Spheroid	Xenograft
Natural death rate	d_0	0.0397	0.0397	0.0397
Transition rate from G_1 to S	c_1	1.36	1.36	1.36
Transition rate from S to G_2	c_s	3.77	3.77	3.77
Transition rate from G_2 to G_1	c_2	4.36	4.36	4.36
Cells entering Q from G_1	B	1	functional response	functional response
Nutrient availability	v_0	n/a	5	7
TNF-α production	j	n/a	0.5	0.5
Rate of TNF-α removal	k	n/a	0.1	0.1
Describe function response B	s_1	n/a	20	20
Describe function response C	s_n	n/a	200	200
Growth of vasculature	c_v	n/a	0	0.03
Necrotic death of Q	e	n/a	0.05	0.05
Removal of N	m	n/a	0.01	0.01
Describe functional response F	s_n	n/a	1000	1000
Describe functional response C	c_n	n/a	50	180
Apoptosis in proliferating stage due to TNF-α signal	c_f	n/a	0.7	0.7
VEGF production by proliferating cells	c_R	n/a	n/a	50
TNF-α effect on VEGF production	s_R	n/a	n/a	100
Natural removal of signal due to vasculature	q_R	n/a	n/a	0.01
Production of VEGF by Q	c_{qv}	n/a	n/a	0.1
Describe functional response C	c_{qs}	n/a	n/a	50
Describe production of VEGF	s_q	n/a	n/a	100
Describe functional response C	s_h	n/a	n/a	1
Describe functional response H	f_h	n/a	n/a	0.01
Describe functional response H	g_h	n/a	n/a	1

Table 1: This table displays all of the experimentally determined parameters used in the ordinary differential equations to model the compartments and transitions between compartments of Fig. 1.

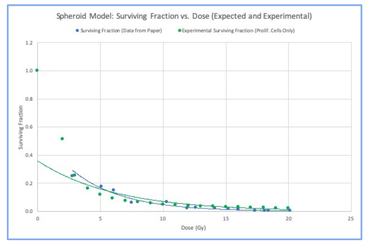


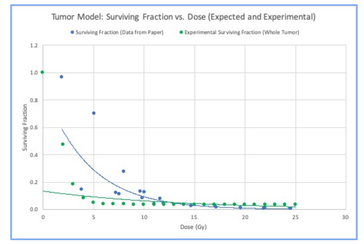




Figures 2, 3, & 4: These graphs show the growth data from West & Sutherland's paper for monolayer, spheroid, and tumor cultures, as well as the trendlines fitted to the data using the model parameters given in Table 1 above and according to which compartments are involved in each model according to Fig. 1.

RESULTS (CONTINUED)





Figures 5 & 6: These graphs show the data from Sutherland & West's paper about radiation survival for spheroid and tumor cultures in blue. They also shoe (in green) the experimental radiation survival values for the spheroid and tumor mathematical models. The MATLAB models were trained with the data from the monolayer culture radiation data, and radiation survival parameters were then translated to the spheroid and tumor models to test whether the parameters could successfully match experimental survival data to the expected data from Sutherland's paper.

DISCUSSION & CONCLUSIONS

This experiment had two major parts to it: first, to program working mathematical models in MATLAB and fit them to data for monolayer, spheroid, and tumor cultures. This was done successfully and it can be seen qualitatively in Figs. 2, 3, and 4 that the model parameters in Table 1 result in graphs that fit the data from Sutherland's paper well. The second part of this experiment involved training the models using Sutherland's radiation survival data for the monolayer to calculate values for d_R, a parameter to represent cell death in response to a specific dose of radiation, affecting proliferating cells (only cells in the G_1, S, and G_2 compartments). Dosage-specific d_R values were calculated successfully through a dose of 25 Gy, and then these values were tested on the spheroid and tumor models to determine whether the trained d_R values could successfully predict the response of the models to simulated treatment with radiation. As shown in Figs. 5 and 6 above, the spheroid model was quite successful at estimating the surviving fraction of proliferating cells when compared to the real-world data. However, the tumor model was not very successful, particularly at lower dosages. One potential cause of this error could be that the radiation parameters only affected proliferating cells, but in reality, radiation may also affect quiescent cells. Future work could include training additional parameters to represent the response of quiescent cells to radiation, and adding these to the models to see if this improves the ability of the models to mimic the real-world response to radiation. Altogether, this project has produced three working models to simulate growth of WiDr cell line monolayer, spheroid, and tumor cultures. These models provide promising potential avenues to simulate real-world cancer research in very little time and at a fraction of the cost.

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SELECTED REFERENCES

1. About Colorectal Cancer. (n.d.). Retrieved May 13, 2019, from https://www.cancer.org/cancer/colon-rectal-cancer/about.html
2. Colorectal Cancer Statistics. (2019, February 4). Retrieved May 13, 2019, from https://www.cdc.gov/cancer/colorectal/statistics/
3. He, Y., Kodali, A., & Wallace, D. I. (2018). Predictive Modeling of Neuroblastoma Growth Dynamics in Xenograft Model After Bevacizumab Anti-VEGF Therapy. *Bulletin of Mathematical Biology,80*(8), 2026-2048. doi:10.1007/s11538-018-0441-3
4. Wallace, D. I., Dunham, A., Chen, P. X., Chen, M., Huynh, M., Rheingold, E., & Prosper, O. (2016). A Model for Spheroid versus Monolayer Response of SK-N-SH Neuroblastoma Cells to Treatment with 15-Deoxy-PGJ2. *Computational and Mathematical Methods in Medicine,2016*, 1-11. doi:10.1155/2016/3628124
5. West, C. M., & Sutherland, R. M. (1987). The Radiation Response of a Human Colon Adenocarcinoma Grown in Monolayer, as Spheroids, and in Nude Mice. *Radiation Research,112*(1), 105-115. doi:10.2307/3577081