

Introduction

Colorectal cancer will kill about 50,000 people in the United States this year. Monoclonal antibody (MAB) therapy has shown promise as a new treatment for colorectal cancer, but variations in MAB therapy have not been heavily explored. We have modified a general nonlinear ODE tumor/treatment model by Lisette de Pillis and colleagues (2009) to include monoclonal antibody treatments, and have found parameter values specific to colorectal cancer, irinotecan as the chemotherapy agent, and cetuximab and panitumumab as the MAB drugs.

Biology Background

Colon Tumors are caused by mutations in the colon crypts which cause the cells to reproduce more quickly than normal colon cells (see Figure 1).



(a) Normal colon crypt.



(b) Cancerous colon crypt.

Figure 1: Normal and cancerous colon crypts (Reya and Clevers, 2005).

- **Our immune system** contains cells called *lymphocytes*, which search for invading cells matching their *antibody*, a protein which tells the them what the invader looks like, and causes them to commit suicide (Sompayrac, 2008). All lymphocytes activate interleukin (IL-2), which alerts the immune system to invading cells. Two types of lymphocytes, natural killer (NK) *cells* and *activated T cells*, are able to kill tumor cells.
- **Tumor treatments** for colorectal tumors include chemotherapy and immunotherapy. Chemotherapy kills quickly dividing cells in the body, both cancerous and normal cells (Sompayrac, 2004). Monoclonal antibody treatment is a type of immunotherapy in which antibodies are created in a lab to specifically target the tumor cells.

Math 197: Senior Thesis A Nonlinear ODE Model of Tumor Growth and the Effects of Immunotherapy and **Chemotherapy Treatment in Colorectal Cancer** Hannah Savage

The Model

Tumor Population:

$$\frac{dT}{dt} = aT(1 - bT) - (c + \xi \frac{A}{h_1 + A})NT - d\frac{(L/T)^l}{s + (L/T)^l}T - (K_T + K_{AT}A)(1 - e^{-\delta_T M})T - \psi AT$$
(1)
Immune System Cell Concentrations:

$$\frac{dN}{dN} = \sqrt{e} = c + \delta_T + c + \delta_T + c + \delta_T$$

$$\frac{dN}{dt} = f(\frac{e}{f}C - N) - (p + p_A \frac{A}{h_1 + A})NT + \frac{p_N NI}{g_N + I} - K_N(1 - e^{-\delta_N M})N$$

$$(2)$$

$$\frac{dL}{dL} = \theta mL = T \qquad \mu L^2 CI$$

$$\frac{dL}{dt} = \frac{\theta mL}{\theta + I} + j \frac{1}{k + T} L + (r_1 N + r_2 C) T - \frac{uL - CI}{\kappa + I} - qLT - K_L (1 - e^{-\delta_L M}) L + \frac{p_I LI}{g_I + I} + v_L (t)$$
(3)

$$\frac{dC}{dt} = \beta(\frac{\alpha}{\beta} - C) - K_C(1 - e^{-\delta_C M})C$$
(4)

$$\frac{dI}{dt} = -\mu_I I + \phi C + \frac{\omega LI}{\zeta + I}$$
(5)

Medication Concentrations:

 $\lambda \lambda$

$$\frac{dW}{dt} = -\gamma M + v_M(t) \tag{6}$$

$$\frac{dA}{dt} = -\eta A - \lambda T \frac{A}{h_2 + A} + v_A(t) \tag{7}$$

Terms in blue have been added to account for the pathways of MAB induced tumor death shown in Figure 3 (De Vita et al., 2000).



Figure 2: Pathways for MAB-induced tumor death.

Parameters for the model have either been taken from the paper by Lisette de Pillis and colleagues (2009), or have been calculated from data available in the literature. The parameters ψ , K_A , d, l, and s from Equation 1 were allowed to vary over a set range to account for variations in tumors and patient immune systems.

Results and Analysis

Simulations of various treatment regimens have been run in Matlab.



(a) Small initial tumor decreases to the zero tumor equilibrium.



(b) Large initial tumor increases to the large tumor equilibrium.







(b) Theoretical treatment with high-dose cetuximab therapy and chemotherapy.

Figure 4: Treatment improvements, resulting in decrease in final tumor size of 19% in (a) and 39% in (b).

Medication			Our Results ^a		
Name ^b	Dose	Freq. ^c	Ν	PR	CR
Irinotecan ^d	125 mg/m^2	weekly,	320	68.4%	10.9%
and Cmab	400 mg/m^2	load,			
	250 mg/m^2	weekly			
Irinotecan ^d	125 mg/m^2	weekly,	320	56.0%	10.6%
and Pmab	6 mg/kg	q2w			
Irinotecan	125 mg/m^2	weekly,	320	74.1%	10.9%
and Cmab	400 mg/m^2	load,			
	250 mg/m^2	weekly			
Irinotecan	125 mg/m^2	weekly,	320	71.0%	10.3%
and Pmab	6 mg/kg	q2w,			
Irinotecan	350 mg/m^2	q3w	320	52.2%	37.5%
and Cmab	350 mg/m^2	q2w			
Irinotecan	350 mg/m^2	q3w,	320	74.1%	17.8%
and Pmab	9 mg/kg	q3w			

Table 1: Response rates from clinical trial simulations
 of our experimental treatment schedules.

^{*a*}N=number of patients; PR=partial response; CR=complete response.

^{*b*}Pmab=panitumumab; Cmab=cetuximab

^cq2w=every 2 weeks; q3w=every 3 weeks; load=loading dose

^{*d*}The standard treatments.



Conclusions

We have been able to validate our model and parameter choices. Our computational simulations reflect actual clinical outcomes when chemotherapy and MAB therapy are both administered once a week, and when chemotherapy is administered as a high dose every three weeks with weekly MAB therapy. We have also found hypothetical treatment scenarios that, according to our model, may lead to improved outcomes for patients. In this model, a threshold tumor size exists, below which the patient's immune system is able to destroy the tumor without further treatment. Future work should include an investigation of mathematical optimization of treatment that will maximize tumor reduction while minimizing side effects.

References

de Pillis, Lisette, Renee Fister, Weiqing Gu, Craig Collins, Michael Daub, David Gross, James Moore, and Benjamin Preskill. 2009. Mathematical model creation for cancer chemo-immunotherapy. *Computational and Mathematical Models in Medicine* 1–19.

De Vita, Vincent Jr., Samuel Hellman, and Steven Rosenberg. 2000. Cancer: Principles and Practice of Oncology. Lippincott Wiliams & Wilkins, 7th ed.

Reya, Tannishtha, and Hans Clevers. 2005. Wnt signalling in stem cells and cancer. *Nature* 434:843–850.

Sompayrac, Lauren. 2004. *How Cancer Works*. Jones and Bartlett Publishers.

——. 2008. *How the Immune System Works*. Blackwell Publishing.

Acknowledgments

I would like to thank Professor Lisette de Pillis for her guidance and support throughout this semester. I would also like to thank my second reader, Professor Ami Radunskaya, Claire Connelly for her LAT_FX help and advice, and the Harvey Mudd College Department of Mathematics.

For Further Information

For more information you may contact Hannah Savage by email: hsavage@hmc.edu, or visit http://www.math.hmc.edu/~hsavage/thesis/.