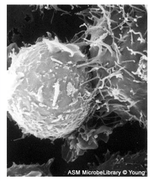
Mathematical Modeling of Dendritic Cell Immuno-Therapy for Cancer

C. DeBoever (HMC '10), M. Hunter (PO '10), H. Wu (HMC '12), Prof. L.G. dePillis (HMC Math), Prof. A.E. Radunskaya (PO Math)

Introduction

One of the most promising immune therapies is dendritic cell (DC) treatment. DCs have been shown to both inhibit the growth of and provide a memory response to tumors. Ludewig *et al.*'s compartment model of DC trafficking in mice combines careful laboratory work with mathematical modeling. In this work, we improve Ludewig *et al.*'s model to include a tumor compartment [**?**].



CTL(right) attacking a tumor cell(left)

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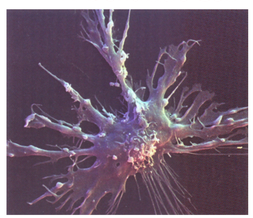
Objectives

- Extend Ludewig *et al.*'s model to include a tumor compartment
- Fit parameters to data collected in experiments on tumor growth in the presence of varying levels of DC injections
- Explore the importance of the effect of parameters on the tumor population

Background

Dendritic cells (DCs) are part of the adaptive immune response and function as antigen-presenting cells.

A Dendritic Cell



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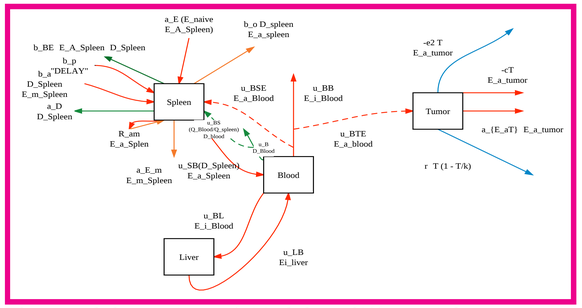
Upon encountering pathogen, DCs travel to the lymphoid organs where they stimulate differentiation and maturation of cytotoxic T lymphocytes (CTLs).

These activated CTLs then traffic to the infected tissue to form part of the adaptive immune response.

The Model



The model consists of 11 delay-differential equations, each of which includes growth, death, recruitment and competition terms. The following equations were modified or added to Ludewig *et al.*'s model.

$$\frac{d}{dt}D_{blood} = \frac{mT}{q+T} - \mu_B D_{blood}, \quad (1)$$

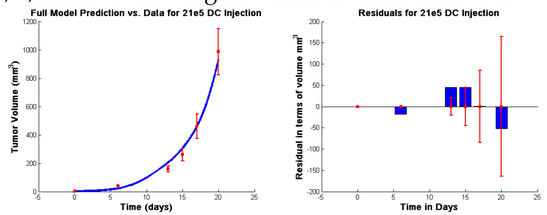
$$\frac{d}{dt}E_a^{tumor} = \mu_{BTE}E_a^{blood}Q_{blood} - (a_{E_aT} + c)E_a^{tumor} \quad (2)$$

$$\frac{d}{dt}T = rT\left(1 - \frac{T}{k}\right) - Td\frac{(E_a^{tumor})^l}{sT^l + (E_a^{tumor})^l}. \quad (3)$$

Equation (1) is modified to include an immune response term while equations (2) and (3) are new additions to the model.

Parameter determination

All unknown parameters were fit to data from Lee *et al.*. 1×10^5, 7×10^5, or 21×10^5 DCs were injected at days 6, 8, and 10 following inoculation with tumor cells.

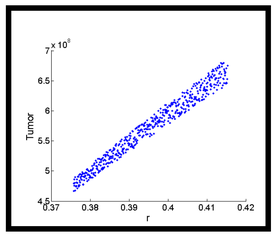


Fits to data from Lee *et al.* and corresponding residuals using full model with $\tau_D = 0.5$.

Analysis

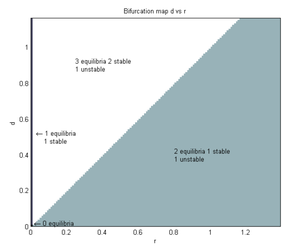
Sensitivity

Parameter sensitivity analysis was performed on the space of independent parameters to determine what parameters significantly affected state variables of interest and to identify parameters for bifurcation analysis. Partially ranked correlation coefficients (PRCC) show r and d significantly affect the tumor size at day 26.



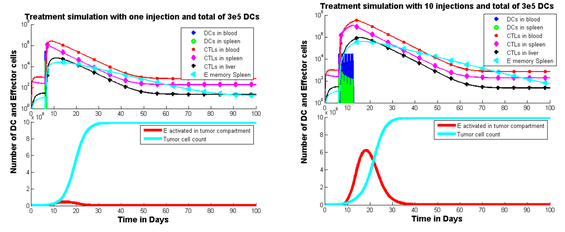
Bifurcations

Bifurcation analysis was performed on parameters d, the steepness coefficient of the fractional tumor kill by CTLs, and r, the tumor growth rate. Since our parameter set is in the two equilibria section of the bifurcation map, any combination of DC therapy and initial conditions will still lead to the high tumor equilibrium. Thus, to completely reject tumor, other parameters must be changed by combination therapy or environmental differences.



Treatment Simulations

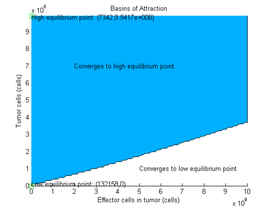
Although tumor populations always reached carrying capacity, treatment schedules with more DC injections slowed tumor growth more than other schedules.



Treatment simulations with 1 injection and 10 injections and a total of 3×10^5 DCs

Conclusions

We extended the model proposed by Ludewig *et al.* and found parameters that accurately describe experimental data. The parameter values found always result in the tumor reaching carrying capacity. However, different injection schedules can slow the tumor and combining the correct injection schedule with an altered parameter set that adds a third, low-tumor equilbrium to the system, can clear the tumor completely.



Future Directions

- include regulatory T cells in the model
- differentiate effector cell populations into natural killer cells and CTL populations
- search for more complete data to create a more accurate model
- validate model against other mouse and human data

Acknowledgements

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For further information email depillis@hmc.edu or aer04747@pomona.edu