Mathematical Modeling of Dendritic Cell Immuno-Therapy for Cancer

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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 [2] 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.

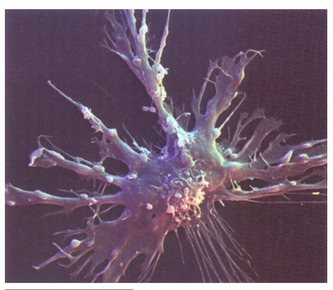
Objectives

- 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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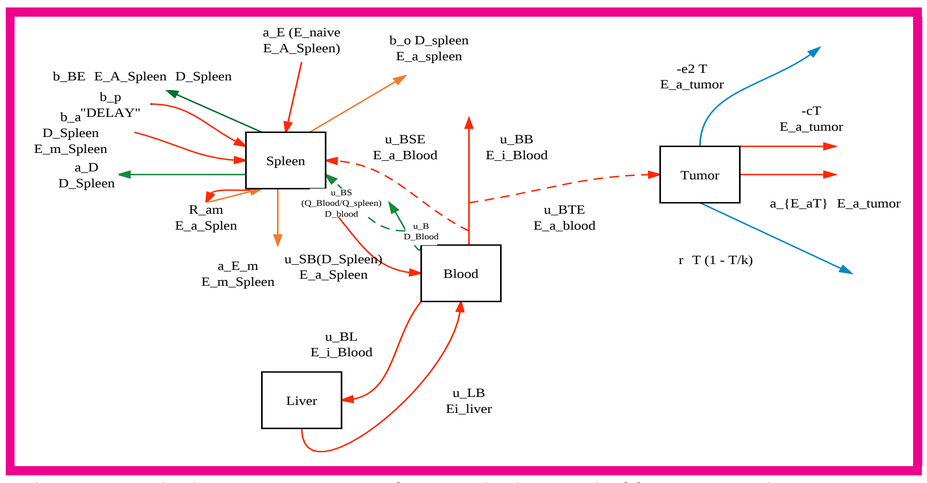
Upon encountering pathogen, DCs travel to the lymphoid organs where they stimulate differentiation and maturation of cytotoxic T lymphocytes (CTLs). These activated CTLs then traffic to the infected tissue to form part of the adaptive immune response.

The Model



The model consists of 11 delay-differential equations. The following equations were modified or added to Ludewig *et al.*'s model.

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

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

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

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

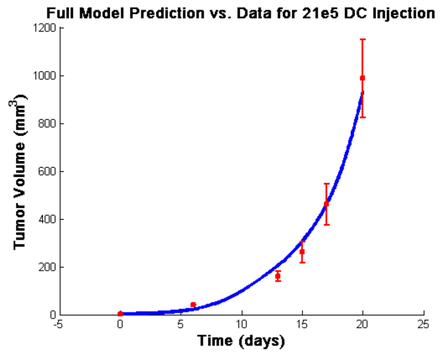
References:

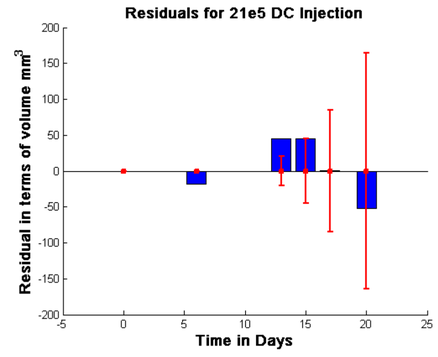
[1] T-H Lee et al. Larger numbers of immature dendritic cells augment an anti-tumor effect against established murine melanoma cells. *Biotech. Ltrs.*, 29(3):351–357, 2007.

[2] B.B. Ludewig et al. Determining control parameters for dendritic cell-cytotoxic T lymphocyte interaction. *Eur. J. of Immun.*, 34(9): 2407–2418, 2004.

Parameter determination

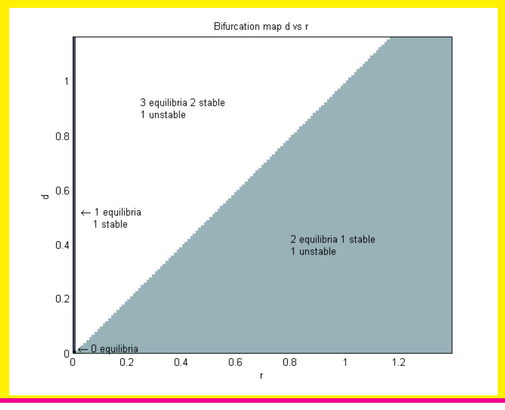
Parameters were fit to data from Lee *et al.*[1]. 1, 7, or 21 DCs ($\times 10^5$) were injected at days 6, 8, and 10 after tumor inoculation.





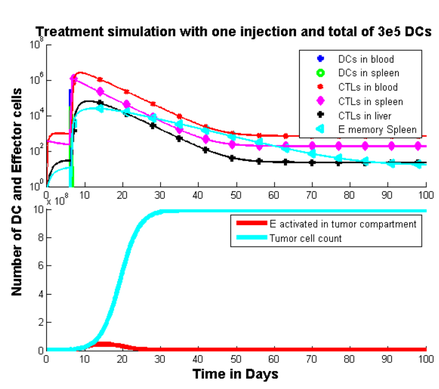
Sensitivity and Bifurcation Analysis

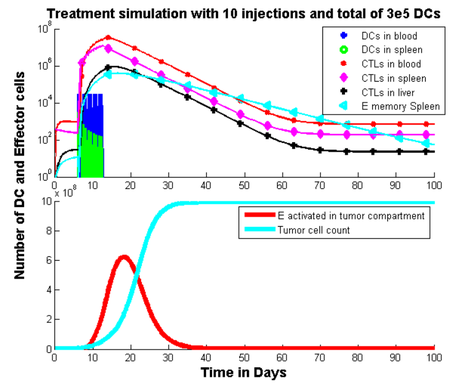
Sensitivity analysis using Partially Ranked Correlation Coefficients (PRCC) show r, tumor growth rate, and d, CTL kill rate, significantly affect the tumor size at day 26. A bifurcation analysis shows that our parameter set is in the two-equilibria regime; thus, any combination of DC therapy and initial conditions will still lead to the high tumor equilibrium. 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.



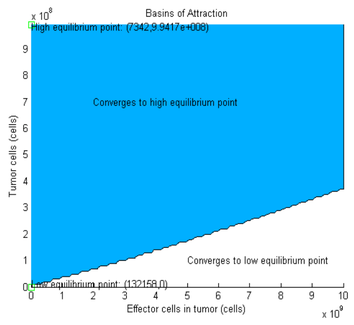


Treatment simulations with 1 injection and 10 injections and a total of 3×10^5 DCs

Conclusions and Future Directions

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.



- 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

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