

# Application of the Mathematical Model of Tumor-Immune Interactions for IL-2 Adoptive Immunotherapy to Studies on Patients with Metastatic Melanoma or Renal Cell Cancer

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## **Abstract:**

**Recent developments in Adoptive Immunotherapy for cancer management have lead to clinicians to employ these techniques in hospital settings. Much data has been produced that indicates the effectiveness of introducing enhanced and expanded immune systems into cancer hosts. Specifically, it is found that IL-2 therapy alone provides ample success for treatment of Metastatic Melanoma (MM) or Renal Cell Cancer (RCC). The Rosenberg study with 283 patients provides evidence that IL-2 can cause significant anti-tumor effects. IL-2 acts as a autocrine cytokine from T-Lymphocytes and signals stimulation, growth, and proliferation of these anti-tumor cells. In this retrospective study we re-look at the Kirschner mathematical model for immune-tumor interactions in light of data presented by Rosenberg on patients with Metastatic Melanoma or Renal Cell Cancer. At first, we affirm the mathematical model and its usefulness in modeling actually known biological mechanisms of tumor-immune interactions. Then, we expand the model to correctly model the reality presented in the clinical study of remission in MM or RCC. In our study we find that modest adjustments can be introduced to address IL-2 therapy alone. We conclude, that, though the earlier model predicts unbound behavior at elimination of highly antigenic cancer the reality of practice is that therapy can be stopped. Thus we introduce a factor of therapy-time that allows the model to fit clinical data. This may allow practitioners to use the model, given the**

**patients antigenicity of tumor, to predict correct wait to restart therapy time to inhibit reemergence of tumor at proper times.**

***Keywords:***

Immunotherapy – Tumor – Cytokines – Mathematical Modeling – Interleukin-2 – Metastatic Melanoma – Renal Cell Cancer – Ordinary Differential Equations

**[1] - Introduction:**

Cancer is the unbound proliferation of cells. Specifically, it is the uncontrolled growth of a host's own "self" cells. [1, 2] Much of the mechanism of cancer development and proliferation is still unknown.

But, it is known that abnormal cell growth occurs because of malfunctioning in the mechanisms that controls cell growth and differentiation. Different mechanisms are hypothesized to play a role in cancer development, such as the mitotic clock hypothesis, apoptosis pathways, genomic inversions, and genetic mutations, etc. [3]

These insights have lead researchers to attack and prevent cancer at various points of the known mechanisms. Techniques have developed to manage cancers that range from chemotherapy that inhibit uncontrolled growth to surgery aimed at physical removal. Though, these techniques are helpful, they have many side effects and drawbacks. Chemotherapy can cause mutations in non-tumor cells, like gut epitheliala, which replicate at high rates and thus also become cancerous. [4] Surgery itself can lead to complications and mortality. The development of new strategies in cancer management is vital in order to address the increasing rate of mortality due to cancer.

Along these lines, cancer research has developed a technique called Adoptive Immunotherapy. In this method of cancer treatment researchers use the natural immune responses to battle cancer. [5] It is well known that the immune system guards against the development of cancer and the immune system acts to detect and eliminate cancerous or precancerous cells. The immune system can identify and destroy emerging cancer cells because it recognizes abnormal antigens on the cell surface as "nonself". Because

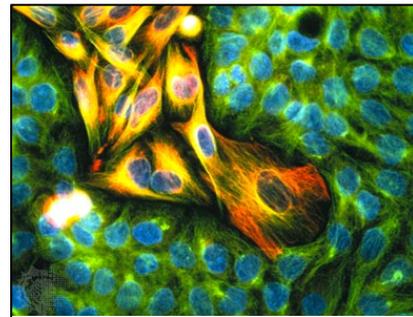


Fig 1. Immunofluorescent light micrograph of melanoma cells (yellow) invading the epithelial cells of the skin (green). [5]

foreign substances are usually dangerous to the body, the immune system is programmed to destroy them. Naturally, in response to tumors, T-Lymphocytes are activated by IL-2 and are recruited to mark tumors with antibodies and thus allow macrophages and natural killer (NK) cells to kill them. [2,6] Adoptive immunotherapy is a method in which the natural immune system is enhanced ex vivo and reintroduced to the host. The ex vivo expansion and activation of antigen-specific cells is a promising approach to inducing anti-tumor immune responses. [5] For example, IL-2 cytokine bolus-injections are used as a therapy for MM or RCC and produce a response rate of 5–40% depending on patient factors. In essence, fit patients with a low disease burden are most likely to respond to IL-2 therapy. Some drawbacks to Adoptive immunotherapy include toxicity. IL-2 is known to cause grade 3 to 4 toxicity. Thus, screening stress electrocardiograms are used to determine fitness to IL-2 toxicity. [7,8]

The immune system presents a very complex entwining of cells and biomolecules to mathematically model. To produce an exact fit can be very difficult and sometimes unwanted. However, the immune system presents some overriding principles that allow mathematicians to access the biological realities with mathematical tools. The task, hard at beginning, lends it self to some basic pillars in mathematical biology. Developed concepts like the Michaelis-Menton interactions can be used effectively to model biological realities of the immune system. Specifically, in our case, the tumor interactions with effector cells can be broken down to three parts discussed later.

## **[2] - Biology of Immune System:**

The biological model for adoptive immunotherapy can be broken down into three realms: Effector cells, Tumor cells, and Cytokines. This simplification allows for a complex yet manageable mathematical system. Predictions based on this model are similar to biological realities, thus the complexity is matched with its realities. The specific branch of the immune system that deals with cancer is the Acquired Immune response. The Acquired Immune response is immunity mediated by lymphocytes and characterized by antigen-specificity and memory.

### ***[2.a] - Effector Cells:***

In cancer immunology the effector cells modeled are T-Lymphocytes. To understand the term T lymphocytes it is first necessary to seek a definition for the word 'lymphocyte'. Lymphocytes are defined by morphological criteria. They have a large nucleus to cytoplasm ratio in which the cytoplasm is rich in ribosomes. This indicates the high rate of protein production required in immune responses. Lymphocytes are found in high proportions in the bloodstream, lymphoid organs, and the lymphatics. The term T lymphocytes refer to the 'thymus-derived lymphocytes' after the discovery of a population of circulating lymphocytes that was produced in this organ. This definition is used to refer to those lymphocytes that matured in and were exported from the thymus.

Functionally, T lymphocytes perform the role of cells that, upon specific encounter with antigens, are activated to provide immunological functions usually associated with fighting infections. These cells are also responsible for the specific memory aspect to immune responses, such that a secondary encounter with the same antigen results in a more rapid and aggressive immune response. [9-11]

In the model the effector cells are assume to change over time given a sundry number of modulating terms. Effector cells are modeled through an ordinary differential equation (ODE). The change in effector cell population is monitored over the change in time. The essential biological interactions between the three parts included in the model will be handled later.

### ***[2.b] - Tumor Cells:***

Tumor cells are rapidly multiplying self cells. They are cells that have undergone changes that cause uninhibited cell proliferation. This proliferation may be due to a number of internal problems. Because cancer cells begin as self cells they have Major Histocompatibility Complexes (MHCs) that indicate that the tumor is 'self'. This causes the tumor to expand without detection. However, after a certain time period biological changes in tumor cells result in immune system recognition through antigens produced by the tumor. This phenomenon is termed the antigenicity of tumor cells. Antigenicity

refers to the measure of how different the tumor has become from self and thus increases proliferation of immune effector cells. More antigenic the tumor is more different it has become from the host's original cells.

Furthermore it is known that the immune system has the capacity to reject tumor cells and that T lymphocytes are instrumental in this rejection. The antigens that tumor make are called tumor-specific antigens (TSA). T-lymphocytes act in the recognition of TSA and produce antibodies that mark the tumor for death. Specifically, Cell-mediated immune reactions occur with Cytotoxic T-Lymphocyte activity or T helper cell response mechanisms. [2,3,6]

In the model, tumor cell are assumed to change over time, thus, as before, an ordinary differential equation is employed to model tumor cells. The model predicts the change in tumor cell population over the change in time. The biological interactions of tumor cells and effector cells that produce mathematical terms will be dealt with later.

### ***[2.c] - Cytokines:***

Cytokines are low weight molecular protein mediators involved in cell growth, inflammation, immunity, differentiation and repair. Cytokines are a general classification with many different branches of molecules like, Interleukins, Growth Factors, and Interferons. Specifically, in Adoptive Immunotherapy and in tumor-immune interactions the key players are Interleukins. Interleukins describes molecular messengers acting between leukocytes. Unlike hormones, which are carried by the bloodstream over the whole body, cytokines are chiefly involved in local effects. They act as paracrine and autocrine agents.

In Adoptive Immunotherapy the main interleukin used is IL-2. Interleukin 2 (IL-2) is one of the first interleukins to be characterized. Initially it was called T cell growth factor (TCGF) because of its relation of its activity to lymphocytes. After complete molecular characterization (purification and cloning) and identification of its receptor, IL-2 was quickly recognized as a central factor in controlling the immune response. Large quantities of IL-2 have been produced and used in clinical trials aimed at stimulating the immune system, particularly against tumors. IL-2 induces growth of cells

that promote tumor regression. The major clinical use of IL-2 to date has involved tumor immunology. The potential for IL-2 as a cancer treatment is based on activation of cells which are cytotoxic for the tumor, and some success has been obtained with renal cell carcinoma and metastatic melanoma. However the use of IL-2 is limited by various side-effects. Local delivery of IL-2 to the tumor site and genetic modification of the tumor cells by the IL-2 gene are currently under clinical trial. [1,11]

In the model IL-2 will be expressed in terms of amount over volume. This is known as the concentration. The model introduces an ordinary differential equation to model IL-2 within the host. The change in IL-2 concentration over change in time is modeled.

**[2.d] - Biological Interactions:**

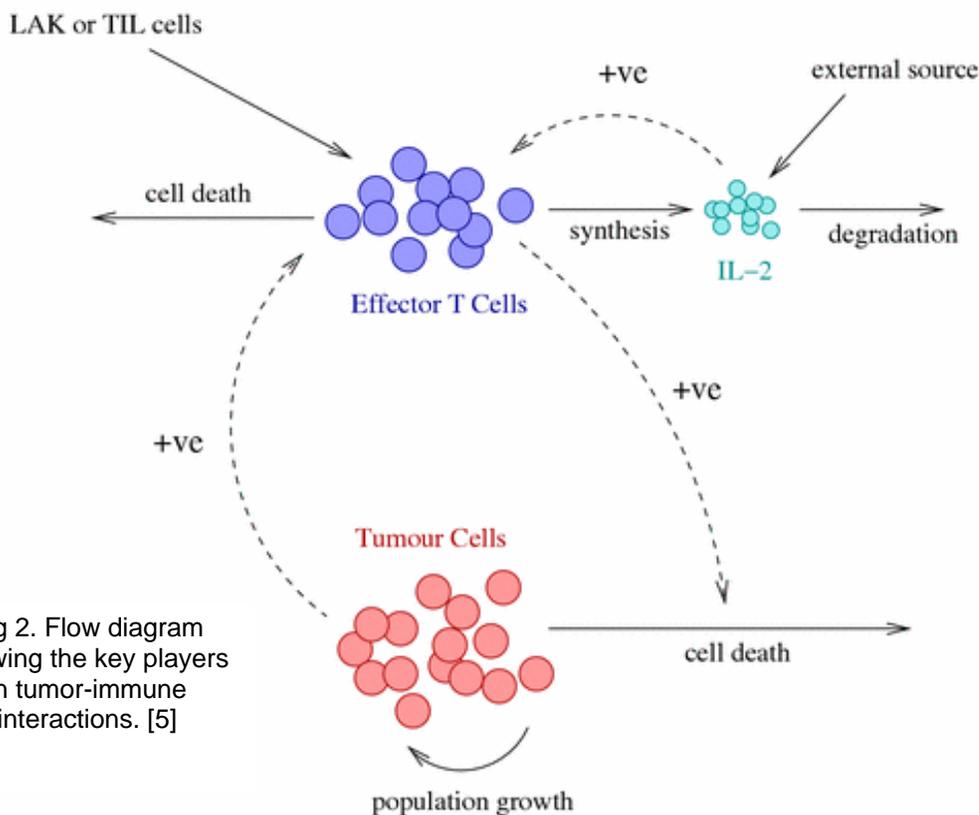


Fig 2. Flow diagram showing the key players in tumor-immune interactions. [5]

Here we discuss how the three elements interact biologically. This will lead to the development of a simple, yet modelable, system.

IL-2 is produced by CD4 T lymphocytes. During the immune response CD4 lymphocytes differentiate into T-Helper 1 and T-Helper 2 functional subsets. The primary role of IL-2 is to expand activated CD4 and CD8 lymphocytes. On T-Helper 1 cells IL-2 acts in an autocrine fashion. IL-2 also induces the growth of T-Helper 2 and CD8 lymphocytes as a paracrine factor. Thus it can be seen why IL-2 is used in Immunotherapy. IL-2 can be used to expand cells that are capable of destroying tumor. The T-lymphocytes, themselves, are stimulated by the tumor to induce further growth. Thus, the complete biological assumption of Adoptive Immunotherapy is that the immune system is expanded in number artificially (ex vivo) in cell cultures by means of human recombinant interleukin-2. The Tumor Infiltrating Lymphocytes are then put back into the bloodstream, along with IL-2, where they can bind to and destroy the tumor cells. Other therapy, called Immunotherapy, focuses on a direct bolus intravenous injection of IL-2. [5, 12]

### **[3] - Original Mathematical Model:**

The original Kirschner model implemented the three main players discussed above and assumed they interact as follows:

#### ***[3.a] - Effector Cells***

- Effector cells grow at a rate directly proportional to both the size of the tumor and its antigenicity.
- Effector cells are also activated by the cytokine IL-2; Michaelis-Menton Kinetics governs this effect.
- Adoptive cellular immunotherapy is modeled as a constant influx of effector cells.

#### ***[3.b] - Tumor Cells***

- Tumor cells grow logistically to a fixed carrying capacity.
- Tumor cells are killed at a rate again governed by Michaelis-Menton Kinetics, with the population of effector cells determining the maximum death rate due to immune response.

### [3.c] - Cytokines

- Interleukin-2 is created by the effector cells, at a rate that approaches a maximum as the tumor grows indefinitely; again, Michaelis-Menton Kinetics.
- Interleukin-2 decays at a constant rate.
- Interleukin-2 therapy is modeled as a constant influx of cytokine IL-2.

The Kirschner model produced a dimensional model with many parameters. Each parameter was obtained from actual medical research data if possible. For example, the half life for IL-2 used was 30-120 minutes. But, when data was absent in literature such as antigenicity, the parameters were chosen such that they would fit clinical (patient) data. For analytical purposes they eliminated redundant parameters. The nondimensional model is as follows:

$$\frac{dx}{d\tau} = cy - \mu_2x + \frac{p_1xz}{g_1 + z} + s_1 \quad 3.1$$

$$\frac{dy}{d\tau} = r_2y(1 - by) - \frac{axy}{g_2 + y} \quad 3.2$$

$$\frac{dz}{d\tau} = \frac{p_2xy}{g_3 + y} - \mu_3z + s_2 \quad 3.3$$

Fig 3. The Equations [13]

#### Key parameters:

- c      Antigenicity of tumor. The higher this value is the easier it is to detect tumor presence.
- S<sub>1</sub>    Adoptive immunotherapy term, a constant influx.
- S<sub>2</sub>    Interleukin-2 therapy term, a constant influx. [13-15]

The Kirschner model predicts a variety of phenomena that occur in real-world cancer situations. In the no-treatment case, for example, variations in antigenicity give rise to three qualitatively different types of tumors:

For low antigenicity, there is a stable steady state with a large tumor, which the system always approaches. For moderate antigenicities, there is a large-amplitude, long-

period stable limit cycle, which the system always approaches. For high antigenicity, there is a small-amplitude, short-period limit cycle, and for extremely high antigenicities the body can actually eradicate the tumor. All these things have been observed in actual patient data, as have the model's predictions about what happens when treatment is administered.

When both types of treatment are administered, the model predicts that the tumor can be cleared, regardless of antigenicity. The success of such combined therapies in the real world, particularly for renal cell carcinoma and metastatic melanoma, are thus well predicted. The model's predictions for adoptive immunotherapy only are also successful.

Alternatively, the model's predictions about IL-2 therapy alone are interesting. It predicts that for small values of  $s_2$  (small amounts of therapy), no qualitative change is observed in tumor behavior, but that for large enough values of  $s_2$ , the only stable steady state of the system has  $(x,y,z) = (\text{infinity}, 0, s_2/u_3)$ . [13-15] This corresponds to clearing of the tumor, but also to a runaway immune system, which explains the high toxicity that IL-2 therapy causes. A variety of diseases caused by IL-2 therapy can be explained by this runaway immune system such as capillary leak syndrome and vasodilator edema. However, this is not the only thing that can happen; in some cases in the real world, IL-2 therapy does work. Thus, our goal is to develop a way in which this reality is modeled. Through the modification of this model, we are able to provide clinicians and mathematical model builders a unique way to combine clinical data with the existing mathematical system. This methodology will help predict whether the treatment is working or is leading to toxicity which is vital in tumor suppression.

#### **[4] – Modification of Original Model:**

Here we present our newer updated model for modeling growth, IL-6 treatment, and reduction of cancer tumors. This methodology combines the clinical data from RCC and Kishner's model. We present the argument and the Matlab code so that future practitioners and mathematicians will be able to construct useful predictions on tumor growth.

**[4.a] - Methodology:**

The Kirschner model, in order to simplify its model of Interleukin-2 therapy, makes three assumptions about the administration of IL-2 therapy:

1. It is given in a continuous stream;
2. It is given for long periods of time;
3. Treatment does not depend on any parameters that change over time.

However, these assumptions are somewhat unrealistic. In the real world, IL-2 treatment is given in high-dose bolus form, in other words, its injection into the system. Specifically, in studies with MM and RCC IL-2 is injected in a bolus of 600000 – 700000 IU/Kg. [7] This contradicts the original assumption that IL-2 therapy is smooth and continuous, but rather indicates that it fashion is in on/off treatment times. In addition, IL-2 therapy usually does not last long. Furthermore, if side effects start to develop, the therapy is usually ceased immediately. The clinician has the ability to monitor the toxicity level of the patient and can judge when to stop therapy. [7] This allows the patient to reach higher thresholds of the immune response with IL-2 thus increasing the probability to eliminate tumor cells.

Our contribution to the model changes the IL-2 treatment term to be dependent on both the population of effector cells and on time. We hoped to remove assumption (3) and instead model the more realistic case in which IL-2 therapy abruptly stops due to the onset of extreme side effects or has reached the natural elimination state of tumor. Thus the parameter  $s_2$  in the Kirschner model is changed to a function  $treatment(x,t)$ .

$$\frac{dx}{d\tau} = cy - \mu_2x + \frac{p_1xz}{g_1 + z} + s_1 \quad 4.1$$

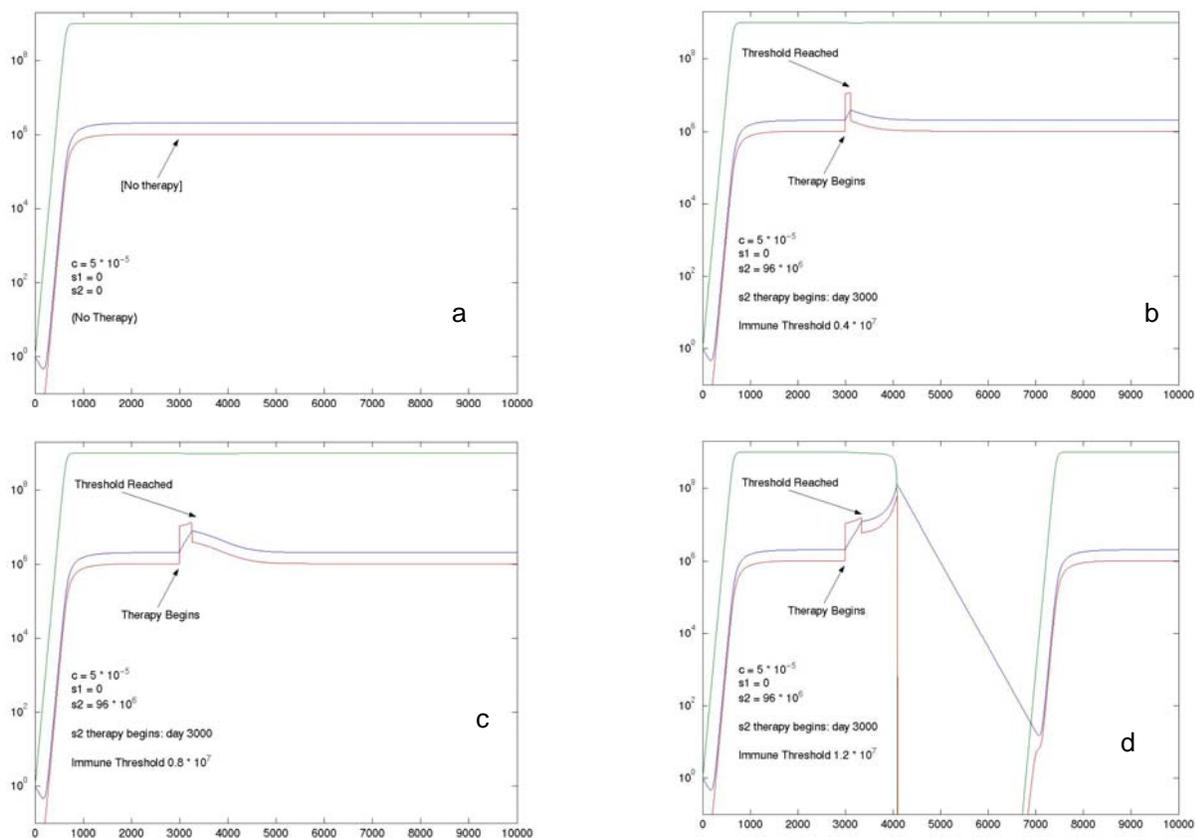
$$\frac{dy}{d\tau} = r_2y(1 - by) - \frac{axy}{g_2 + y} \quad 4.2$$

$$\frac{dz}{d\tau} = \frac{p_2xy}{g_3 + y} - \mu_3z + treatment(x,t) \quad 4.3$$

Fig 4. The changed model

To model the IL-2 treatment, we implemented a “flag” for treatment, which by default starts as “on.” When the flag is set to “on,” treatment is administered at a constant rate  $s_2$ , just as in the Kirschner model. However, as the immune system begins to grow without bound, it will eventually reach a threshold value at which side effects begin to appear. This threshold value becomes a new parameter in the model, which likely varies from patient to patient. Once the immune system reaches this threshold, the flag is set to “off,” and treatment is immediately ceased. The system then continues on as though there were no treatment.

### IL-2 Therapy Results: Low-antigenicity tumor with varying immune thresholds



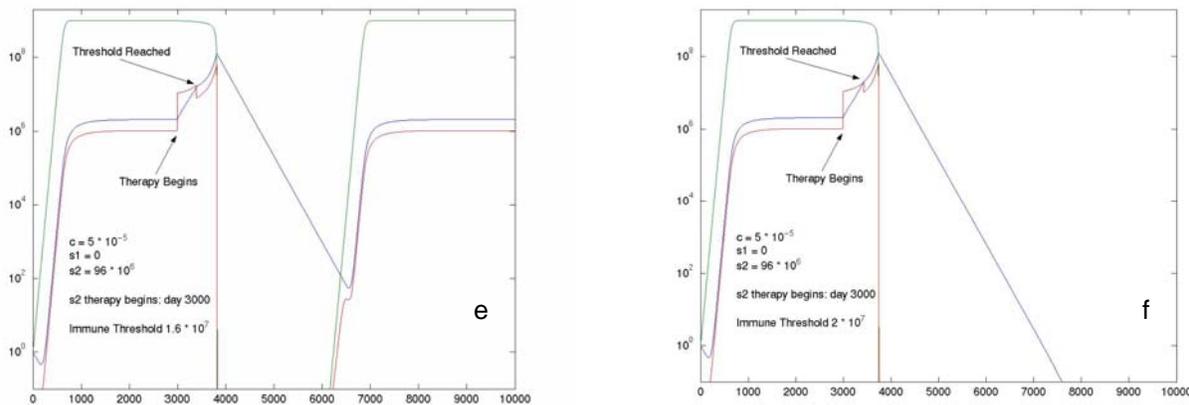


Fig. 5: Tumor (green), Effector (Blue), IL-2 (red) (a): With no treatment, the tumor reaches a stable steady state. (b): With low level treatment, no qualitative change is measured. (c): As the immune threshold is increased, first short-term changes become evident. (d) At a critical value of immune threshold, the tumor enters a long-term dormant state. (e): Varying lengths of the dormant period arise from varying thresholds. (f): For extreme threshold values, long-term eradication of the tumor is possible

In addition, we allowed for the case that some time may elapse before treatment is started, since treatment often starts after the tumor has reached its stable steady state. In this case, the dependence on  $t$  comes into play. Once a set time passes the treatment is turned on. Then it is turned off again once the immune system reaches its threshold for side effects.

#### **[4.b] – Matlab Code:**

The following is our proposed Matlab programming code. Through this model we propose a newer methodology in predicting tumor growth. [Free for Public Use]

```
----- il2.m -----
function z = il2(t,u)
```

```
% Fixed constants.
```

```
mu2 = .03;
```

```
p1 = .1245;
```

```
g1 = 20000000;
```

```
r2 = .18;
```

```
b = 0.000000001;
```

```
a = 1;
```

```
g2 = 100000;
```

```
p2 = 5;
```

```
g3 = 1000;
```

```
mu3 = 10;
```

*Variables can be adjusted to model patient specification. Majority are readily available values.*

```
% Cancer Antigenicity
```

```
c = 0.00005;
```

```
% Treatment terms
```

```
s1 = 0;
```

```
global s2
```

```

s2 = 96000000;
% global currenttreatment
% currenttreatment = s2;

z = [ c*u(2) - mu2 * u(1) + p1 * u(1) *
u(3) / (g1 + u(3)) + s1; (r2 * u(2) * (1
- b * u(2)) - a*u(1)*u(2)/(g2 + u(2))) *
killfactor(u(2)); p2 * u(1) * u(2)/(g3
+ u(2)) - mu3 * u(3) + treatment(u(1),t)];

```

```

----- killfactor.m -----

```

```

function k = killfactor(y)

```

```

% killme = 0.000001;
killme = -10;

```

```

if (y > killme)
    k = 1;
elseif (y <= killme)
    k = 0;
end
return

```

```

----- runil2.m -----

```

```

clear

```

```

global treatmentoff
global currenttreatment
global nextappointment
currenttreatment = 0;
treatmentoff = 1;
nextappointment = 3000*.18;

```

```

[t,u] = ode15s('il2',[0 1800],[1 1
1],odeset('RelTol',1e-12));

```

```

plot(t/.18,u)
xlim([0 10000])
ylim([0.1 2000000000])

```

```

----- treatment.m -----

```

```

function y = treatment(x,t)

```

```

global treatmentoff
global currenttreatment
global nextappointment

```

```

global s2

```

```

% As published
% th = 10^80;
% delay = 10000000; % days
% mins2 = 0;
% step = 0;

```

```

% Max threshold to minimal treatment
% th = 7000000;
% delay = 10000000; % days
% mins2 = 12000000;
% step = s2 - mins2;

```

```

% Max/Min thresholds + recurring
therapy each year
th = 18000000;
delay = 100000000; % days
mins2 = 0;
step = (s2-mins2)/(960*5);

```

```

% define a piecewise function
if (treatmentoff == 1) &
(currenttreatment > mins2)
    currenttreatment = currenttreatment -
step;
elseif (treatmentoff == 0) &
(currenttreatment < s2)
    currenttreatment = currenttreatment
+ step;
end

```

```

y = currenttreatment;

```

```

if (x > th) & (treatmentoff == 0)
    treatmentoff = 1
    realtime = t
    graphtime = t/.18
    nextappointment = t + delay;
end
if (treatmentoff == 1) & (t >
nextappointment)
    treatmentoff = 0
    realtime = t
    graphtime = t/.18
end/return

```

**[4.c] – Conclusions:**

This simple modification resulted in some rich consequences. First of all, for high-antigenicity tumors, it was found that the modified model predicts clearance of the tumor for relatively low threshold values of the immune system; in other words, a patient need not endure very many side effects before IL-2 therapy will successfully clear the tumor.

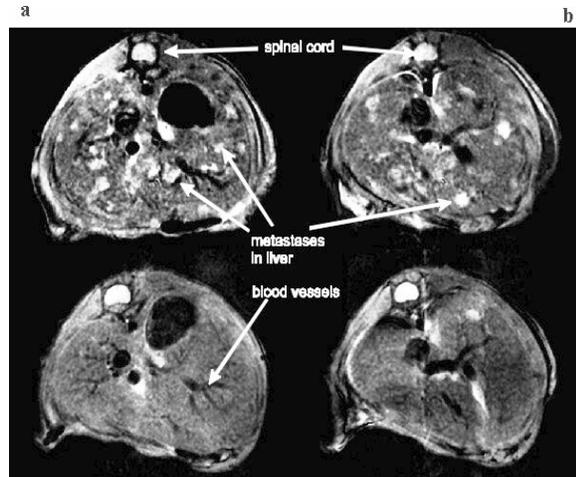
In the low-antigenicity case, however, the results were much more interesting. We modeled IL-2 treatment by first allowing the tumor to grow to a stable steady state, then starting the therapy some time later. An immune system threshold was set, then the model was run to predict the life of the tumor for the next 10000 days.

For low immune thresholds, the therapy was not allowed to continue for long, and as expected, no long-term qualitative changes in tumor behavior are recorded. However, once a critical value for the immune threshold is reached, IL-2 therapy leads to a massive remission of the tumor; however, the tumor remains in a dormant state for a length of time on the order of 2700 days (90 months). For extremely high values of immune threshold, the tumor is actually able to be eradicated. These results are illustrated in the graphs on the following page.

The time period on the order of 2700 days is also consistent with some data from hospital settings. In a study by S. A. Rosenberg on the effectiveness of high-dose bolus treatments with Interleukin-2, it is found that many patients are in complete remission “for 7 to 91 months.” [7] This model predicts that it is indeed possible to send a patient into remission for this length of time with IL-2 therapy alone. However, it also predicts that in most cases, the tumor will return after that time has passed. Rosenberg’s study does not continue past this 91-month time period. [7]

**[5] - Discussion:**

From this discussion we can see that Adoptive Immunotherapy is an effective new methodology to manage cancer. Given the basic elements of the immune system a mathematical model can be developed to approximately predict the behavior of the immune system and tumor cells. Here we present a mathematical model that allows for analysis of tumor regression and predicts the remission time given certain parameters. The model is useful in



Day 27 before IL-2 therapy (a, b)  
Day 63/35 days after IL-2 (c,d) [5]

that it incorporates fundamental biological concepts while remaining easy to analyze. In the case for IL-2 therapy alone the original model predicts unbound behavior. Actually, clinicians can control when IL-2 is stopped. Thus, we introduce a new parameter  $Treatment(x,t)$  that incorporates a time dimension in an on/off switch fashion. This way we can resolve disparities in actual clinical data and the predictions of the model.

This new outlook is useful because it provides a practical use for the model. Doctors may be able to use the ordinary differential equations to predict when reemergence of the tumor occurs. This will help predict when to readminister IL-2 therapy to prevent further tumor and metastasis. Future work in this area can be done in correctly obtaining data regarding parameters. Hypothetically, if accurate data on antigenicity of tumor, IL-2 concentrations, effector cell count can be obtained in a rapid manner then clinicians can employ the model to predict when the therapy will produce tumor regression. Thus they may be able to perform differential diagnosis of when to push the patient to the limit of treatment to eliminate the tumor or to abate the therapy due to toxicity.

In general, immunotherapy with IL-2 is on the rise and more mathematical models will be necessary to help practitioners predict future reemergence times in order to restart therapy. The practicality of this mathematical model shows the potential that mapping biological systems possess. Further research in coordination of mathematicians,

researchers and doctors can prove to be life saving, especially in the case of Renal Cell carcinoma and Metastatic Melanoma.

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**[7] - Diagrams**

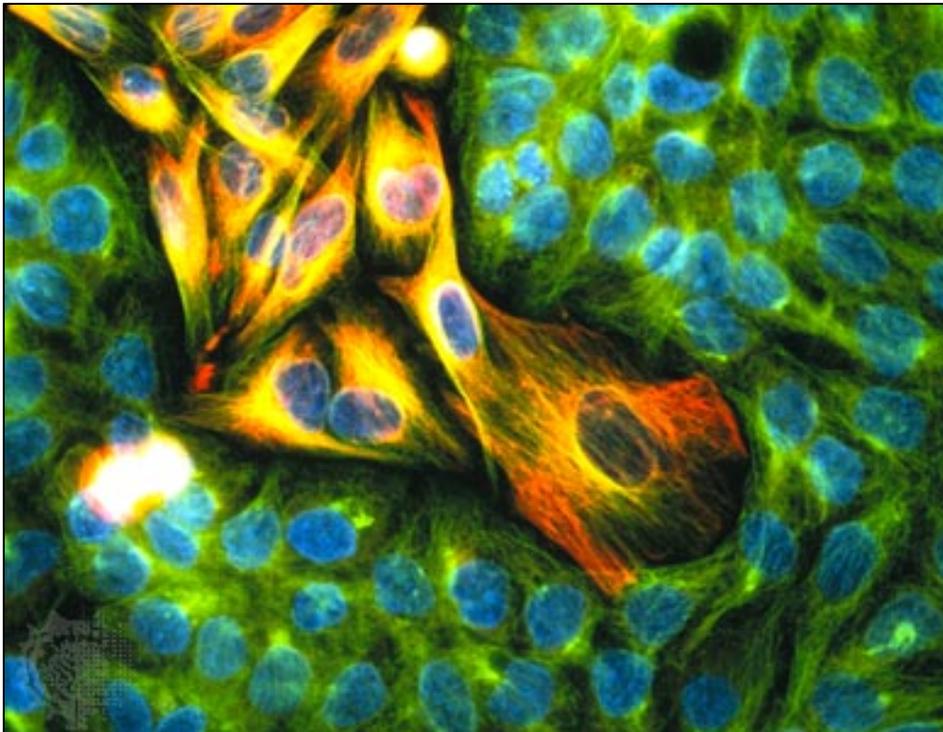


Fig 1. Immunofluorescent light micrograph of melanoma cells (yellow) invading the epithelial cells of the skin (green). [5]

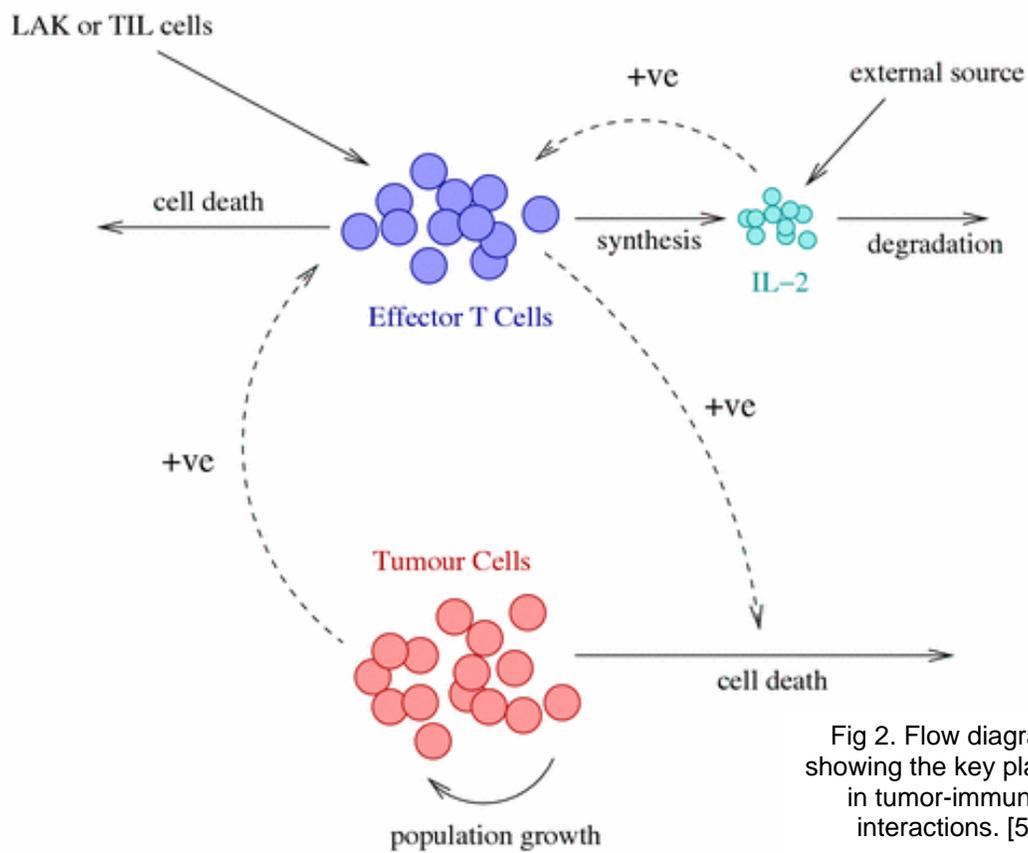
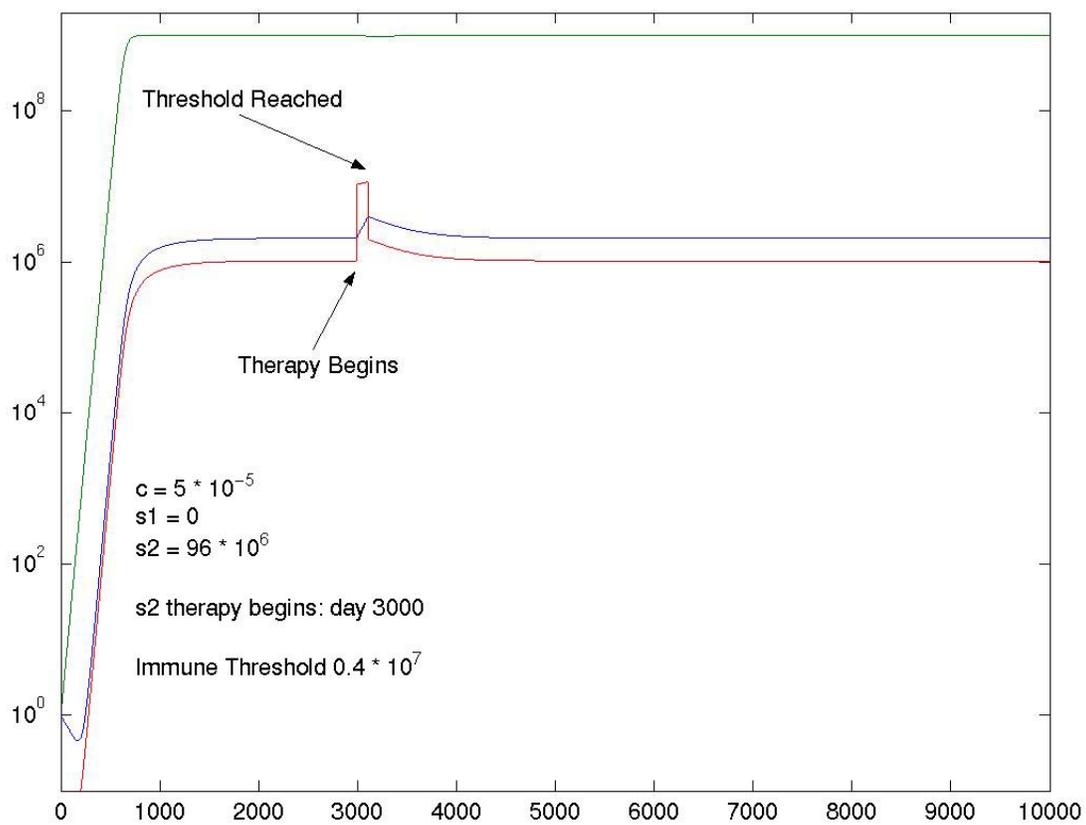
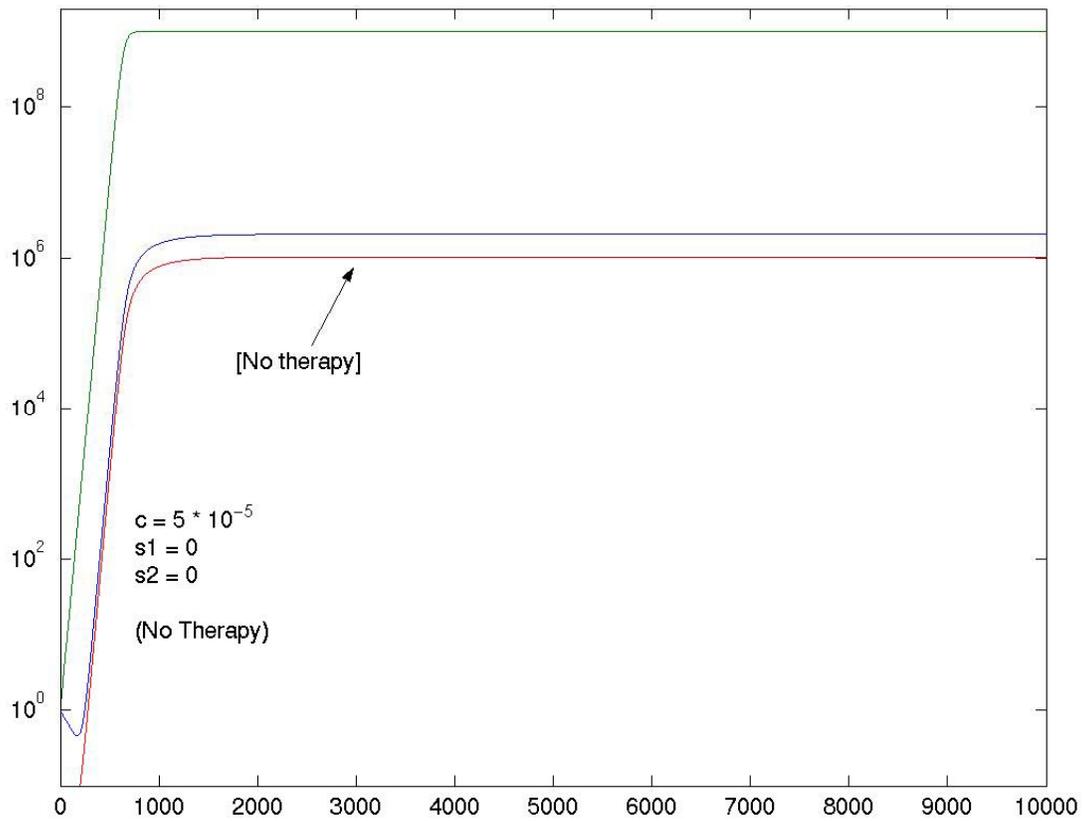
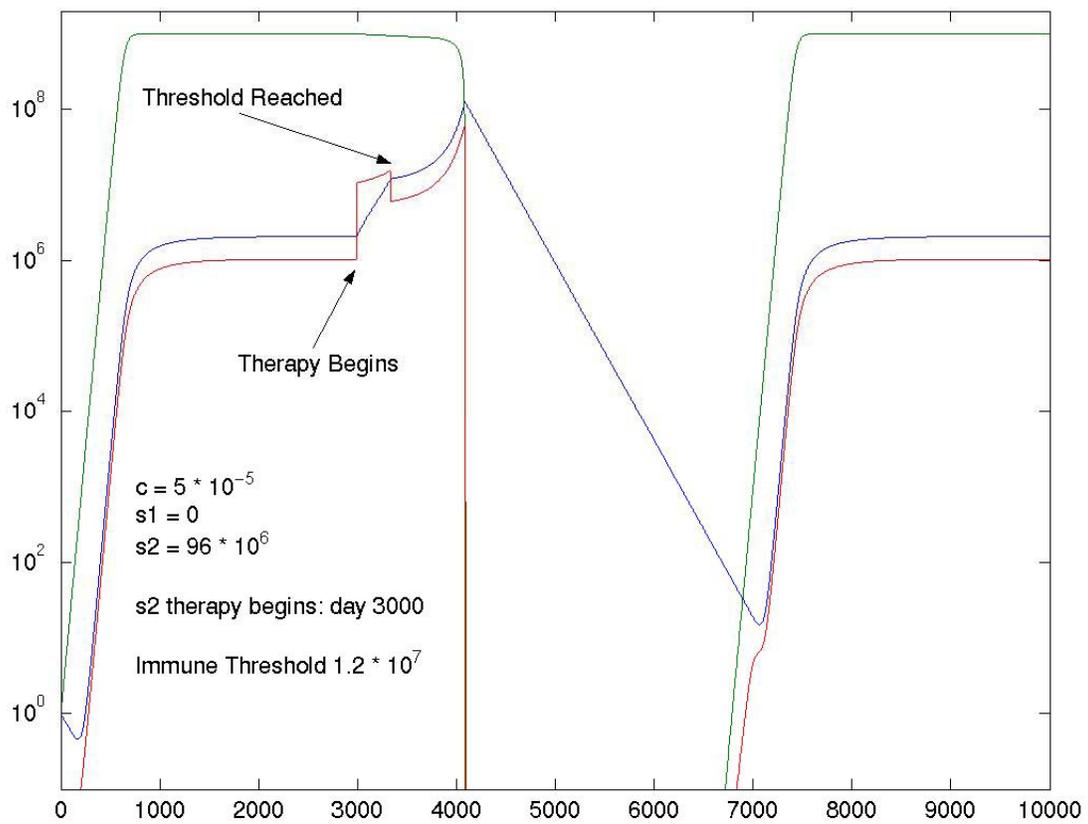
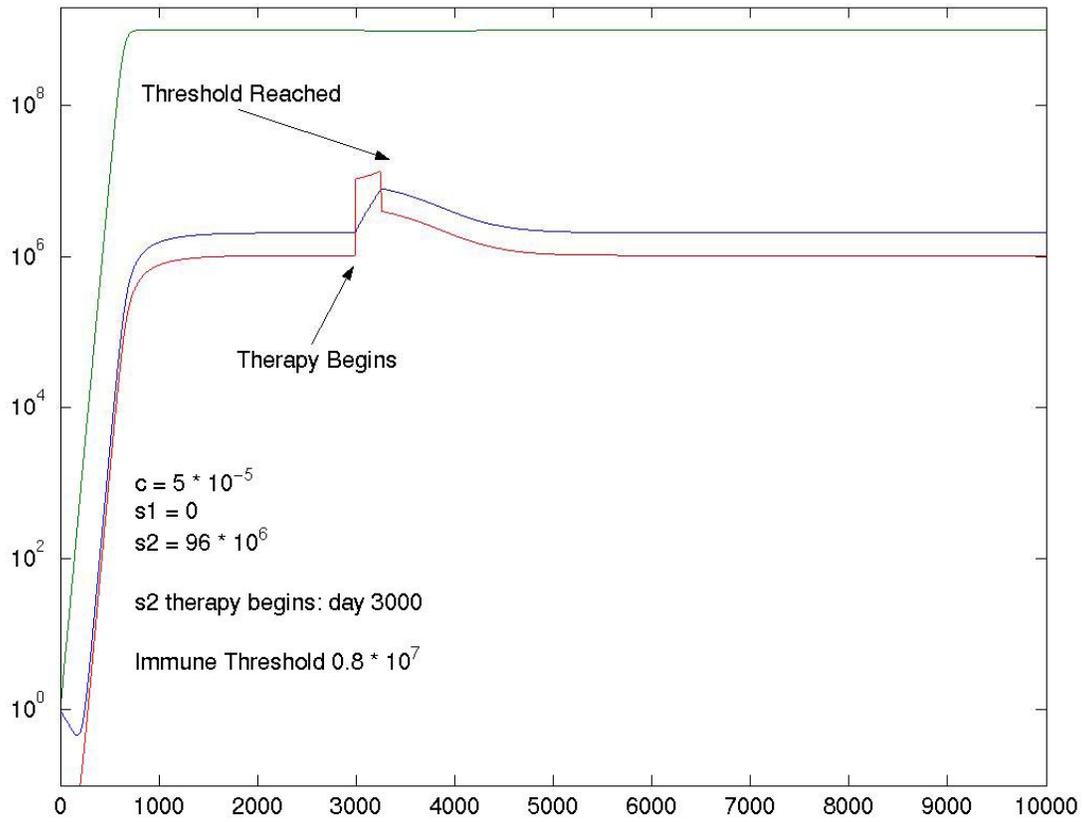


Fig 2. Flow diagram showing the key players in tumor-immune interactions. [5]





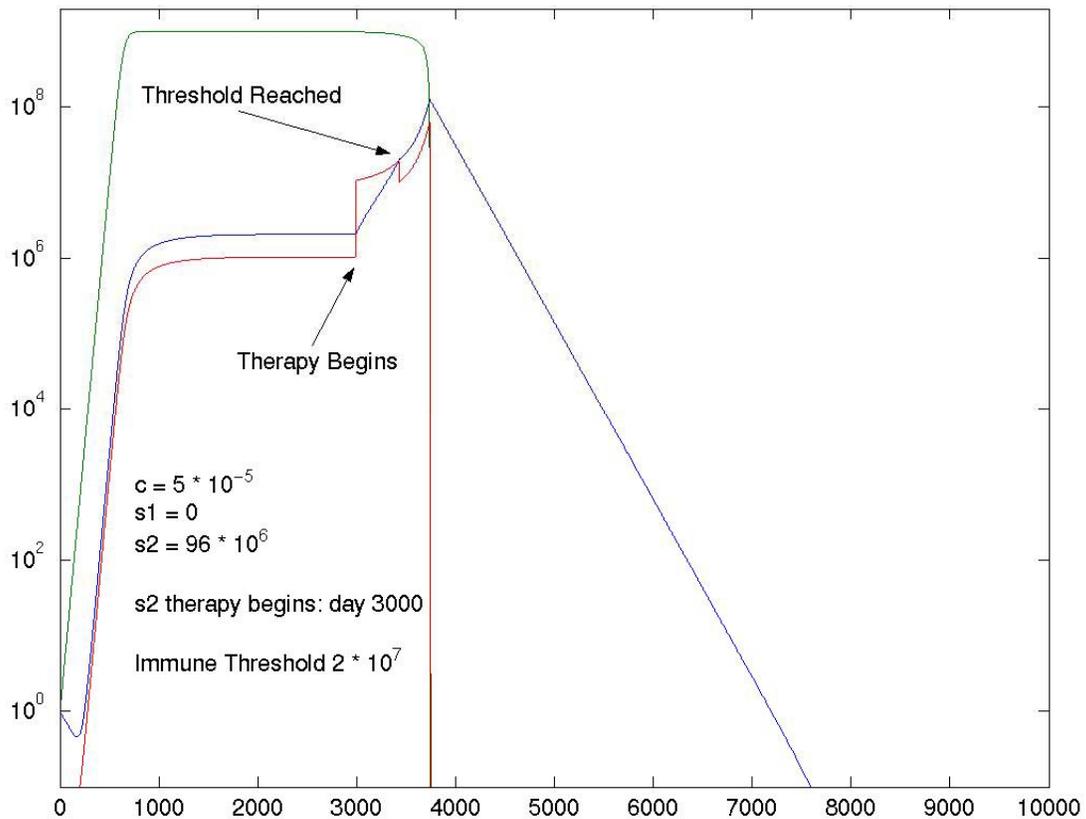
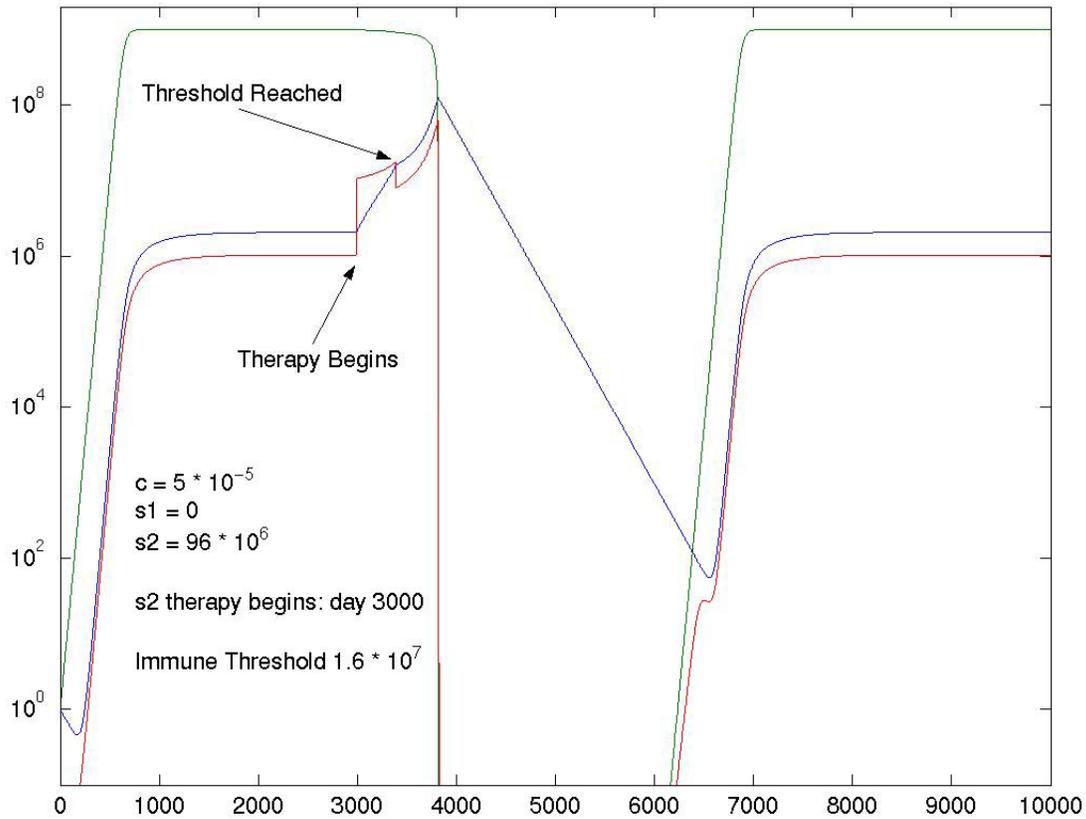
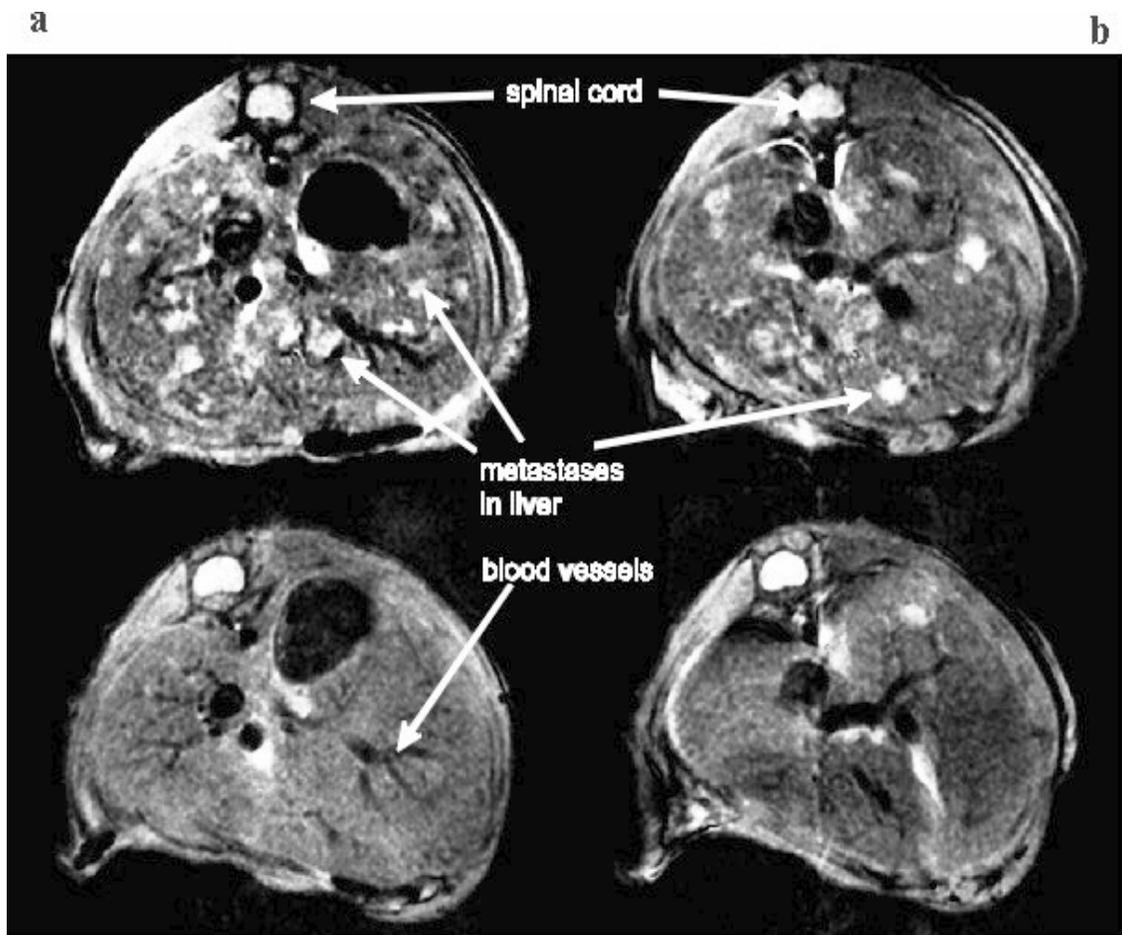


Fig. 5: Tumor (green), Effector (Blue), IL-2 (red) (a): With no treatment, the tumor reaches a stable steady state. (b): With low level treatment, no qualitative change is measured. (c): As the immune threshold is increased, first short-term changes become evident. (d) At a critical value of immune threshold, the tumor enters a long-term dormant state. (e): Varying lengths of the dormant period arise from varying thresholds. (f): For extreme threshold values, long-term eradication of the tumor is possible



**c** Day 27 before IL-2 therapy (a, b)  
Day 63/35 days after IL-2 (c,d) [5]

**d**