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Mathematical Modeling of Strategic Treatments on Tumor Growth

By U. S. Rana & Jyotsna Baloni
D.A.V College, India

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Mathematical Modeling of Strategic Treatments on Tumor Growth

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Abstract- We propose to contribute to the emerging body of cancer treatment research by developing and analyzing mathematical models of the treatment of tumor with various strategic treatments. We build on existing models of the immunology that are already successfully developed and then the effects of chemotherapy and interleukin-2 were applied to the model. Thus we build a mathematical model of tumour and effector cell with scheduled chemotherapy.The effect of scheduled il2 dose with chemotherapy and adoptive immunotherapy reduced the tumor growth.

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I. Introduction

The worldwide burden of cancer (malignant tumor) is a major health problem, with more than 8 million new cases and 5 million deaths per year. Cancer is the second leading cause of death. With growing techniques the survival rate has increased and so it becomes important to contribute even the smallest help in this field favoring the survival rate. Tumor is a mass of tissue formed as the result of abnormal, excessive, uncoordinated, autonomous and purposeless proliferation of cells.

The immune system plays an important role to identify and eliminate tumors. This is called immune surveillance. The theory of immune surveillance says that the immune system continually recognizes the transformed cells of tumors because they express antigens that are not found on normal cells. For the immune system, these antigens appear foreign, and their presence causes immune cells to attack the transformed tumor cells and hence eliminates tumor cells, but when a tumor escapes immune surveillance and grows too large for the immune system to kill, tumor is the result. Tumor antigens are presented on MHC (Major Histocompatibility Complex) class I molecules (present on the surface of tumor cells) in a similar way to viral antigens. This allows killer T cells to recognize the tumor cell as abnormal. NK (Natural Killer) cells also kill tumorous cells in a similar way.Tumor-specific lymphocytes are lymphocytes of immune system which recognises tumor cells and can be found in the blood, draining lymph nodes, and the tumor itself of patients with actively growing tumors.

The main response of the immune system to tumors is to destroy the abnormal cells using killer T cells, which generally require several stimuli for rapid expansion. It has been

Author α σ : Department of Mathematics and Computer Science, D.A.V. (P.G.) College Dehradun, Dehradun, India.
e-mails: drusrana@yahoo.co.in, jyotsnna.maths@gmail.com

known for long time that interleukin-2 (IL-2) is generally required for expansion of populations of T lymphocytes in vitro [1]. IL-2 is a cytokine which is used in treating advanced cancer taken alone or with combinations with other drugs.

IL-2 causes effector cells to proliferate. However IL-2 can also activate natural killer cells, B lymphocytes, and macrophages and can induce lymphokine-activated killer cells in vitro. High dose intravenous bolus of IL-2 is administered to treat many types of melanomas. But the problem with high dose of IL-2 therapy is that it causes toxicity and many types of side effects to the body and even can cause death. [2]

At present, chemotherapy is the most well established treatment for fighting cancer. Chemotherapy, in its most general sense, is the treatment of disease by chemicals especially by killing micro-organisms or cancerous cells. The basic idea behind chemotherapy is to kill cancerous cells faster than healthy cells. This is accomplished by interrupting cellular division at some phase and thus killing more tumor cells then their slower developing normal cells. The course of therapy depends on the cancer type, the chemotherapy drugs used, the treatment goal and how your body responds. The treatment may be given every day, every week or every month. Their may be breaks between treatments so that the body has a chance to build new healthy cells. [3,4] However some normal cells, for example those that form the stomach lining and immune cells, are also rapidly dividing cells which means that chemotherapy also harms the patient leading to things like a depressed immune system which opens the host to infection [5, 6]. In addition, chemotherapy causes significant side effects in patients, and therefore exploring new forms treatments may prove extremely beneficial.

One of the form of immunotherapy to treat the tumor growth is Adoptive immunotherapy. It is used in treatment of tumor in which lymphocytes are removed from the patients's body to enhance their anti-tumor activity with naturally produced growth factor, cultured in large numbers and then returned to the patient. Adoptive immunotherapy uses immune effector cells as lymphocytes. Lymphokine-activated killer (LAK) cells and Tumor-infiltrating lymphocytes(TILs) are such lymphocytes which are grown in presence of IL-2 an immune stimulator [7].

Despite the existence of anti-tumor immune responses, the tumors still progress and eventually cause disastrous effects on host body. Over the past several decades, investigators have pursued variety of strategies to direct the immune system against many types of tumors. The immune responses to be effective enough must eliminate the tumor cells more rapidly than their rate of proliferation and hence the role of boosting the immune response or immunotherapy. In this article we present a model of immune system against tumor growth. Chemotherapy and immunotherapy are not that success in treatment even high doses of these therapies are effective for tumor eradication but also high doses of these treatments create severe side effects in the body [8].

The growing understanding of the therapy cycles has produced various strategies to increase the effectiveness of cancer treatment [9]. Hence, In this paper a model of tumor growth is presented which describes the treatment of a tumor by chemotherapy over a fixed period of time by the repeated administration of its doses. The model will select that in what interval, at what schedule and what specific doses of IL-2 therapy, chemotherapy and adoptive

Ref

2. Repmann, R., Wagner, S., and Richter, A., "The use of interleukin 2 in the treatment of renal cell cancer and melanoma proved that an immunological treatment is capable, in some cases, of inducing long term regression of metastatic tumours", ***Anticancer Res .***, Vol. 17 (1997), 2879-2882.

immunotherapy should be delivered. The model constructs a regimen that both minimizes the tumor population at the end of the treatment and satisfies constraints on the drug toxicity and intermediate tumor size.

II. Mathematical Modeling

The model consists of four ordinary differential equations of immune response to tumor growth which gets affected by treatments chemotherapy, interleukin-2 and adoptive immunotherapy. The following variables are set to the model.

Variables	**x(t)**	**y(t)**	**z(t)**	**λ(t)**	**t**
Description	Effector cell	Tumour cell	IL-2	Chemotherapeutic drug	time

a) Effector Cell

Effector cells are lymphocytes which are the relatively short-lived activated cells that have been induced to differentiate into a form capable of mounting a specific immune response. The production of the effector cell was given by Kirschner [10] and shown below that how chemotherapy affects the production of the effector cell.

$$\frac{dx}{dt} = cy - \mu_1 x + p_1 \frac{xz}{g_1 + z} - C_x(1 - e^{-\lambda})x + S_1 \quad (1)$$

In this equation, c denotes the antigenicity of tumour. Tumor antigen are main target for cancer immunotherapy. The ideal tumor antigen is immunogenic and expressed exclusively on tumor cells. Higher the value of antigenicity the easier it becomes for the effector cell to detect the tumor. The second term is the mortality rate of effector cell and the third term is the proliferation term due to the presence of the cytokine IL-2. Here p_1 is the maximum proliferation of the effector cell. The fourth term denotes the chemotherapeutic effect on effector cells. The interaction of chemotherapy on sensitive cells is given by saturation term kinetics [11]. At low chemotherapeutic drug doses the death rate of the cells depends on the chemotherapeutic drug λ (t) but at high doses it becomes λ independent. It is assumed that C_x depends on the IL-2 concentration [12]. The fifth term S_1 denotes a treatment called adoptive immunotherapy at constant influx.

Here, $C_x = C_x^{chemo}(1 - e^{-z/z_0})$ where C_x^{chemo} is the death rate of effector cells by chemotherapy, and z_0 is IL-2 z(t) at t=0.

b) Tumor Cell

The interaction of immune system with tumor is again based on the Kirschner model.

$$\frac{dy}{dt} = r_1 y(1 - by) - \frac{axy}{g_2 + y} - C_y(1 - e^{-\lambda})y \quad (2)$$

In this equation the first term denotes the production rate of the tumor cells having maximum proliferation rate of r_1 until it reaches to its carrying capacity b of tumor [13]. The

Ref

10. Kirschner, D., Panetta, J.C., "Modelling immunotherapy of the tumor-immune interaction", ***Journal of Mathematical Biology***. Vol. 37, (1998), 235-252.

second term shows that the destruction by the effector cell x(t) and *a* is the parameter used to give value of the strength of the immune system against tumor cells [14]. The third term denotes the effect of the chemotherapeutic drug on tumor cells.

Here, $C_y = C_y^{chemo}(1-e^{-z/z_0})$, where C_y^{chemo} is the death rate of tumor cells by chemotherapy.

c) IL-2

The Kirschner model explains the production of the IL-2.

$$\frac{dz}{dt} = \frac{p_3 xy}{(g_3 + y)} - \mu_2 z + S_2 \tag{3}$$

Here the first term is the production of IL-2 which depends on the interaction of the x (t) and y(t) and p_3 is the maximum proliferation of the IL-2. The second term is the decay rate of IL-2. S_2 denotes interleukin therapy at constant influx.

d) Chemotherapeutic Drug

$$\frac{d\lambda}{dt} = V(t) - v\lambda \tag{4}$$

Here, *V(t)* is the time dependent external influx of the chemotherapeutic drug and *v* is the decay rate.

Finally, writing all the equations representing the growth of tumor cells, immune system and chemotherapeutic drug and effects of treatments on tumour growth.

$$\frac{dx}{dt} = cy - \mu_1 x + p_1 \frac{xz}{g_1 + z} - C_x(1-e^{-\lambda})x + S_1$$

$$\frac{dy}{dt} = r_1 y(1-by) - \frac{axy}{g_2 + y} - C_y(1-e^{-\lambda})y$$

$$\frac{dz}{dt} = \frac{p_3 xy}{(g_3 + y)} - \mu_2 z + S_2$$

$$\frac{d\lambda}{dt} = V(t) - v\lambda$$

III. Parameter

The tumor immune dynamics is sensitive to the choice of parameter values [16]. The parameter values changes from patient to patient. The experimental proved values are given below. But some values are studied from the medical history and which are not experimentally proved are fitted to the available data and studied their affects by giving different values on the model. The value of τ_c is estimated to be 10^6 cells as after this value the angiogenic is switched on [17]. The parameter q_1 and q_2 were estimated by experiments presented in [14]. The values of C_x^{chemo} and C_y^{chemo} representing the killing of cells by chemotherapy are estimated from Pilli's model [15]. The decay rate of the chemotherapeutic drug was estimated from the example taken from [18].

Ref

14. Hsieh, C.l., Chen, D.S. and Hwang,L.H., "Tumor-induced immunosuppression: A barrier to immunotherapy of large tumors by cytokine-secreting tumor vaccine", ***Hum. Gene Ther.***, Vol. 11, (2000), 681–692.

Notes

Parameter	Description	Value/Units
c	Antigenicity of tumor	0-0.035 $days^{-1}$
g_1	Half saturation constant	2×10^7 pg /l
p_1	Max proliferation rate of effector cell	0.1245$days^{-1}$
r_1	Tumor growth rate	0.18 $days^{-1}$
b	Carrying capacity of tumor	1×10^{-9} cells /ml
a	Tumor cell strength against immune system	1 day^{-1}
g_2	Half saturation constant	1×10^5 cells /ml
μ_1	Effector cell growth rate	0.03$days^{-1}$
C_x^{chemo}	Effector cell decay by chemotherapy	0.6 day^{-1}
C_y^{chemo}	Tumor cell decay by chemotherapy	0.9 day^{-1}
p_3	Growth rate of IL-2	5 pg /cells×days
g_3	Half saturation constant	1×10^3 cells /ml
μ_2	Decay rate of IL-2	10 $days^{-1}$
V	External influx of chemotherapeutic drug	1 day^{-1}
v	Decay rate of chemotherapeutic drug	6.4 $days^{-1}$

Initially, x(0)= 1, y(0)= 1, z(0)= 1, λ(0)=0

IV. Results and Discussion

In this section, we present the numerical results to explore the effects of therapies on growth rate of tumor cells. For this purpose we used Equations 1-4 for tumor cell density, effector cell density, il2 level and chemotherapic drug respectively and applied different doses of treatment at different time intervals so as to study their effects on tumor growth. Computer program is developed in software MatLab and run on Pentium IV using ode15s.

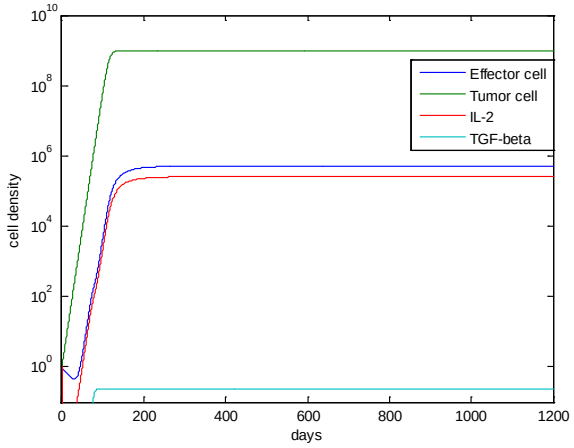

Fig 1(a)

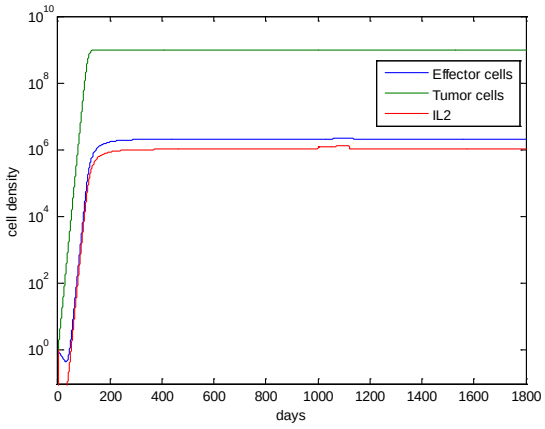

Fig 1(b)

Fig. 1(a) shows the growth of tumor cells, effector cells and il2 growth without giving external therapies like il2 dose, chemotherapy and adoptive immunotherapy. In (b) no chemotherapy and no adoptive immunotherapy are given but a heavy dose of il2, S_2=2000000 started at 1000th day and then given for 120 days. There is not such change seen in cell densities.

a) Effect of chemotherapy

There are a number of strategies in the administration of chemotherapeutic drugs used today. Chemotherapy may be given with a curative intent or it may aim to prolong life or to palliate symptoms [25]. As we know that effector cell density is dependent on il2 level, if il2 level falls, effector cell density also drops. So, we kept chemotherapy schedule not only time dependant but also il2 dependant. Once the chemotherapy starts at some fixed time interval (time dependant) then the therapy is scheduled by il2 level (il2 dependent). This means that chemotherapy schedule is managed such as to keep effector cell density under control. A MatLab code is given such that chemotherapy starts (V =1) when $z >$ required il2 level and chemotherapy stops (V=0) when $z <$ the required il2 level. By keeping such we can know that at what time the chemotherapy should be started and in what intervals it should be given so as not to effect il2 level and effector cells too. Schedules and effects of chemotherapy doses are shown in following figures. The chemotherapy schedule, tumour density, effector cell density and il2 level are well observed from the simulations and then explained.

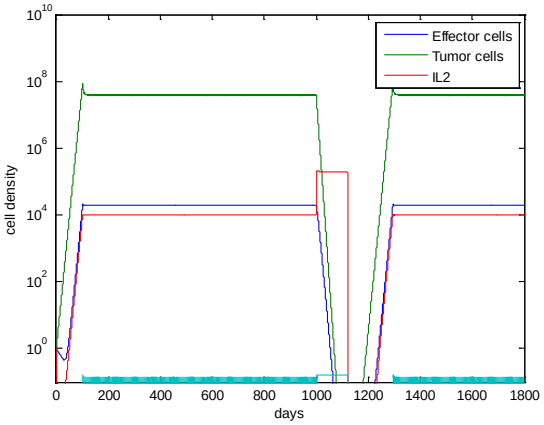

Fig 2(a)

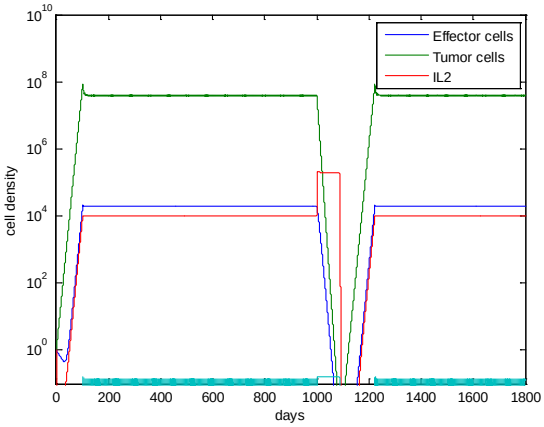

Fig 2(b)

Fig 2. The above figures show that proper and scheduled application of chemotherapy to the patient can be very effective. In fig 2(b) the dose of il2 scheduled without chemotherapy does nothing whereas in fig 2 the same dose of il2 scheduled with chemotherapy brings a big change. As the frequent chemotherapy doses are effective in treatment of tumors, (discussed in *American Cancer Society* [26]) So, here Chemotherapy is started from 108th day and is given after each 21 hours intervals such that il2 ≥ 10000, on the other hand tumour cell density comes below to its carrying capacity to about 39950000 cells. This keeps the effector cells density also stable. The il2 dose of S_2= 200000 (which is less than the standard dose of 600,000 unit and high dose of 720,000 unit [28] [29]) is given from 1000^{th} day for (a) 120 days and (b) 90 days. We see a sudden fall of tumor growth and finally at 1080^{th} day the tumor gets eliminated. As soon as il2 therapy stops the tumour vigorously grows but during this time when the tumour is eradicated there is lot of time for a patient to undergo other treatments including dietary regulations so as to avoid further growth of tumor.

Ref
25. "Chemotherapy Principles-An In-depth Discussion of the Techniques and Its Role in Cancer Treatment". ***American Cancer Society.*** Retrieved from http://www.cancer.org/acs/groups/cid/documents/webcontent/002995-pdf.pdf

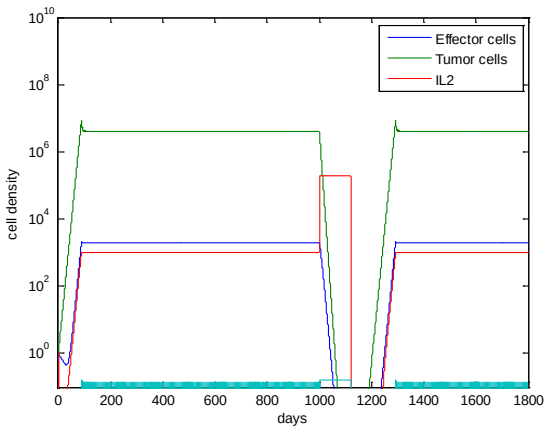

Fig 3(a)

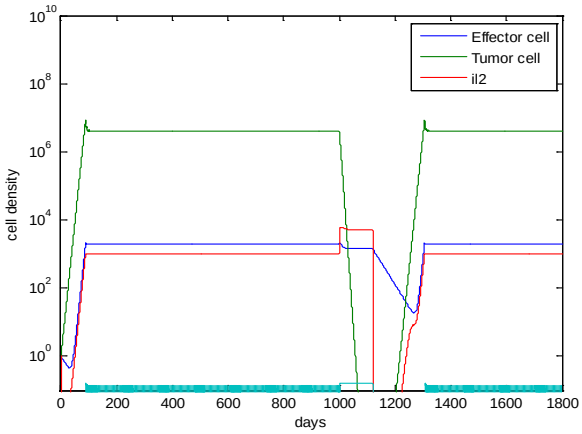

Fig 3(b)

Fig 3. Chemotherapy starts from 90th day. Here we have given chemotherapy after 18 hours intervals such that il2 $\geq$1000 which brings tumour cell density to 4154000 cells. This keeps the effector cells density also stable. The il2 dose of S_2= 200000 is given from 1000th day for 120 days. We see a sudden fall of tumour growth and finally at 1070th day tumour gets eliminated. As soon il2 dose stops the tumour vigorously grows. But this is lot time for other treatment including dietary regulations to stop further tumour growth. Fig (a) shows eradication of tumour cells with effector cells. In (b) il2 dose therapy is companied with adoptive immunotherapy of S_1=500. We see recovery of effector cell growth after a down fall. This is one of the good ways to eliminate tumor cell keeping effector cells alive.

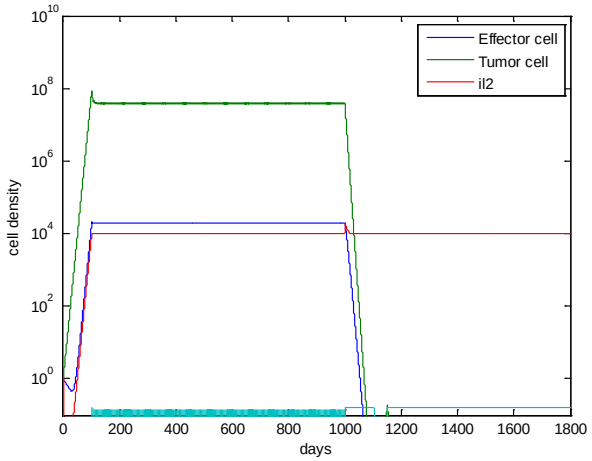

Fig 4

Fig 4. Here all the parameters are kept same as in fig 2 except reduced dose of il2 of S_2= 100000. This shows long term eradication is possible with application of long term adoptive therapy. But this is quite unrealistic.

V. Conclusion and Future Work

In this study various treatments with scheduled time and dose were discussed. It is clear from above discussion that for reducing tumour growth chemotherapy should be started as soon as the tumour is detected and chemotherapy should be scheduled frequently within few hours along with low doses of il2 so that the effector cells and also the host body gets frequent

recovery time, which as a result does not harm the body by after effects of chemotherapy and il2 therapy. Also when the effector cell density drops to its half then the therapies should be companied with short term adoptive immunotherapy which may eliminate the tumour. Different types of chemotherapy drugs kill cells at different stages of the cell cycle. Administering the specific drugs when the cancer cells are most sensitive and other cells are less sensitive makes them more effective. Some types of chemotherapy need to be activated in the body before they affect cancer cells; administering them at times when this will happen efficiently also improves effect. The clinicians and nutritionist, has the work to find out various ways to avoid tumor, once eradicated for further evolution.

Notes

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