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NUMERICAL ANALYSIS OF MATHEMATICAL MODELLING OF TUMOUR GROWTH WITH IMMUNOTHERAPY, CHEMOTHERAPY AND IMMUNOTHERAPY-CHEMOTHERAPY

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Abstract: It is known that a beneficial tumour-treatment approach for a single patient often involves the administration of more than one type of therapy. The question of how best to combine multiple tumour therapies is still open. In this research, we investigate the theoretical interaction of three treatment types (two biological therapies and chemotherapy). We analyse a mathematical model, in the form of a system of ordinary differential equations (ODEs), governing tumour growth on a cell-population level with combination immunotherapy and chemotherapy. We present an ordinary differential equations model to look at overall cell populations. Numerical simulation immune-sequence and human parameter are presented. We study and compare between result of numerical simulations immunotherapy alone, chemotherapy alone and immunotherapy-chemotherapy sequence treatments. The success of every treatment depends on the initial of tumour cells population. With the same population of tumour cells, our study shows that immunotherapy-chemotherapy sequence is more effective than immunotherapy alone or chemotherapy alone.

KEYWORDS: mathematical model, ordinary differential equation, tumour growth, immunotherapy, chemotherapy

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Introduction

Cancer is still a leading cause of death in the world yet much is still not known about its mechanisms of establishment and destruction (Kirscher & Panetta, 1998). While surgery, chemotherapy and radiotherapies have played key roles in treatment, it is clear that in many cases they don't represent a cure. Even when patients experience tumour regression, later relapse can occur. The need to address not only preventive measures, but more successful treatment strategies is clear. Efforts along these lines are now being investigated through immunotherapy.

Immunotherapy is quickly becoming an important component in the multi-pronged approaches being developed to treat certain forms of cancer (Pillis *et al.*, 2006). The goal of immunotherapy is to strengthen the body's own natural ability to combat tumours by enhancing the effectiveness of the immune system. The importance of the immune system in fighting tumours has been verified in the laboratory as well as with clinical experiments (O'Byrne *et al.*, 2000).

Through the mathematical modelling of tumour growth, the presence of an immune component has been shown to be essential for producing clinically-observed phenomena such as tumour dormancy, oscillations in tumour size, and spontaneous tumour regression (Pillis *et al.*, 2006). The mathematical modelling of the entire immune system can be an enormously intricate task, as demonstrated in (Perelson & Weisbuch, 1997), so models that describe the immune system response to a tumour challenge must necessarily focus on those elements of the immune system that

are known to be significant in controlling tumour growth. In the work of Boer and Hogeweg (1986), a mathematical model of the cellular immune response was used to investigate such an immune reaction to tumours. It was found that initially small doses of antigens do lead to tumour dormancy. The mathematical model of Kirschner and Panetta (1998), which also focusses on the tumour-immune 3 interaction, indicates that the dynamics among tumour cells, immune cells, and the cytokine interleukin-2 (IL-2) can explain both short-term oscillations in tumour size as well as long-term tumour relapse. The model developed by Kuznetsov (1992,1994), in which the nonlinear dynamics of immunogenic tumours are examined, also exhibits oscillatory growth patterns in tumours, as well as dormancy and "creeping through": when the tumour stays very small for a relatively-long period of time, and subsequently grows to be dangerously large. Pillis *et al.* proposed the mathematical model in the form of ordinary differential equation system (2006). Their model describes the effect of immunotherapy alone, chemotherapy alone, mixed immunotherapy and chemotherapy to tumour growth. They found through numerical simulations that mixed immunotherapy and chemotherapy is more effective to eliminate tumour cells than both immunotherapy alone and chemotherapy alone. In 2010, Mustafa *et al*., also proposed the mathematical model of immunotherapy and chemotherapy. In their model, there are three immunotherapy drugs such as interleukin-2 (IL-2), interferon alpha (INF-*a*) and tumour-infiltrating lymphocytes (TIL).

In this paper, we present analysis and numerical simulation for case immunotherapy-chemotherapy sequence by Pillis's model (2006). In section 2, we present a system of ordinary differential equation which describes tumour-immune interaction under immunotherapy. Next section, we present set parameters values for this model from previous works. Section 4 presents numerical experiments based on parameters in Table 1. In the last section, we summarise and discuss our conclusion.

Immunotherapy

Immunotherapy is also called biologic therapy or biotherapy (American Science Society, 2009). It is a treatment that uses certain parts of the immune system to fight diseases including cancer. Immunotherapy is sometimes used by itself to treat cancer, but it is most often used along with or after another type of treatment to boost its effect. The immune system is your body's defense force. It helps keep invading germs out or helps kill them if they do get into the body. Germs such as viruses, bacteria, and parasites have a substance on their outer surface, such as certain proteins, but they are not normally found in the human body.

The clinical evidence for the potential of immune-system control of certain malignancies has motivated new research into the development of immunotherapy's and vaccine therapies for tumours (Pillis *et al.*, 2006). Immunotherapy falls into three main categories: immune response modifiers, monoclonal antibodies, and vaccines. The first category contains substances that affect immune response, such as interleukin-2 (including IL-2), interferon, tumour necrosis factor (TNF), colony-stimulating factor (CSF) and B-cell growth factor. In the next category, monoclonal antibodies are currently being developed to target specific cancer antigens. These monoclonal antibodies can distinguish between normal and tumour cells, and they can then be used to diagnose tumours, as well as to treat tumours by "guiding" anticancer drugs toward the malignant cells. In the third category are vaccines, which are generally used therapeutically, and are created from tumour cells. These work by helping the immune system to recognise and attack specific tumour cells.

Chemotherapy

At present, chemotherapy is the most well-established treatment for fighting cancer (Chang *et al.*, 2003). Chemotherapy is the administration of one or more drugs designed to kill tumour cells at a higher rate than normal cells. Chemotherapy drugs can be divided into two types: cell-cycle specific and cell-cycle nonspecific. Cell-cycle specific drugs can only kill cells in certain phases of the cell cycle, while non-specific drugs can kill cells in any phase of cell division (Pazdur *et al.*, 2001). The distinction between specific and non-specific chemotherapy drugs is important in considering how a tumour population responds to the drug. The response of a population to varying doses of drug is usually found in the context of a dose-response curve, where dose is plotted against the fraction of the cells killed. If the drug is non-specific, its dose response curve is typically linear. A linear dose-response curve means that, if twice as much drug is given, one would expect twice as many tumour cells to die. Drugs that are specific can usually only kill cells in the process of dividing. However, not all cells of a typical tumour will be dividing at the same time. This means that at some point, all of the cells that can be killed by the drug will be killed, but some will be immune-tolerant and remain (Pazdur *et al.*, 2001). A linear dose-response curve might suggest that the best treatment for cancer is simply to give a patient so much drug that the entire tumor cells die. This unfortunately does not work in practice. There are two major complications to such a plan. First of all, chemotherapy drugs kill cells in the process of division. Although cancer cells divide much more rapidly than most normal cells, fast-growing cells, like those in the bone marrow (where immune cells are produced), hair, and stomach lining are also killed by chemotherapy (Holland & Emil III, 1973). Another limitation on the amount of chemotherapeutic drug that can be administered is the side effects. High doses of drug can also damage other tissue in the body (Holland & Emil III, 1973).

Ordinary Differential Equations Model

We present a model developed by Pillis *et al.* (2006) which describes kinetically four population and two drug concentrations in the bloodstream. The population at time t denoted: $T(t)$ as tumours cell population at time t, $N(t)$ as total NK cell effectiveness at time t, $L(t)$ as total CD8+T effectiveness at time t, $C(t)$ as number of circulating lymphocytes at time t, $M(t)$ as chemotherapy drug concentration in the bloodstream at time t, $I(t)$ as immunotherapy drug concentration in the bloodstream at time t. All populations are formulated in the series form coupled ordinary differential equation:

$$\frac{dT}{dt} = aT(1-bT) - cNT - DT - K_T(1-e^{-M})T \tag{1}$$

$$\frac{dN}{dt} = eC - fN + g\frac{T^2}{h+T^2}N - pNT - K_N(1-e^{-M})N \tag{2}$$

$$\frac{dL}{dt} = -mL + j\frac{D^2T^2}{k+D^2T^2}L - qLT + (r_1N + r_2C)T - uNL^2 - K_L(1-e^{-M})L + \frac{piLI}{gi} + v_L(t) \tag{3}$$

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

$$\frac{dM}{dt} = -\gamma M + v_M(t) \tag{5}$$

$$\frac{dI}{dt} = -\mu iL + v_I(t) \tag{6}$$

$$D = d\frac{(L/T)^l}{s+(L/T)^l}T \tag{7}$$

All of the terms in the coupled ordinary differential equation above consists of terms governing the population kinetics and must take into account a net growth term for each population (G_T, G_N, G_L, G_C, G_M, G_I), term of the fractional cell kill (F_N, F_L, F_{MT}, F_{MN}, F_{ML}, F_{LI}, F_{CM}), term of per cell recruitment (R_N, R_L), term of cell inactivation (I_N, I_L) and term of external intervention with medication (H_L, H_M, H_I).

Growth and Death Terms

In equation (1), the first term $G_T = aT(1–bT)$ express tumour growth logistically (Pillis & Radunskaya, 2003a). The growth of NK cells express term 1 and term 2, $G_N = eC – fN$ in equation (2) (Pillis *et al.*, 2006). Cell growth for CD8+ T cells consists only of natural death rates, since no CD8+ T Cells are assumed to be present in the absence of tumour cells CD8+ T cells decrease express term 1, $G_L = – mL$ in equation (3) (Pillis *et al.*, 2006). We assume that circulating lymphocytes are generated at a constant rate and that each cell has a natural lifespan. Therefore, $G_C = \alpha – \beta C$ in equation (4). We assume that chemotherapy drug will decay exponentially in the body at constant rate. This gives us the term, $G_M = – \gamma M$ in equation (Pillis *et al.*, 2006). Similarly, the immunotherapy drug, Interleukin-2 (IL-2), decays exponentially, $G_I = –\mu iL$ in equation (6) (Pillis *et al.*, 2006).

Fractional Cell Kill

The interaction between tumour and NK cells takes the form $F_N = –cNT$ equation (1) (Pillis & Radunskaya, 2003a). This term represents negative interaction between tumour cell population and NK cell population. Tumour inactivation by CD8+ T cells has the form:

$$F_L(T,L) = d\frac{(L/T)^l}{s+(L/T)^l}T, \qquad \text{let } D = d\frac{(L/T)^l}{s+(L/T)^l},$$

Hence, we have $F_L(T,L) = DT$ in equation (2) (Pillis & Radunskaya, 2003a). Our model adds a chemotherapy drug kill term to each of the cell populations. Chemotherapeutic drugs are only effective during certain phases of the cell-division cycle, so we use a saturation term $I – e^{-M}$ for the fractional cell kill. The chemotherapy drug kill term is represented by $K_i\left(1-e^{-M}\right)i$ for $i = T, N, L, C$ (Pillis *et al.*, 2006).

In addition, our model includes an activated CD8+ T boost from the immunotherapy drug, IL-2. The presence of IL-2 stimulates the production of CD8+ T cells, and is represented by, $F_{LI} = \frac{\tilde{p}_i LI}{g_i}$ modification from (Pillis *et al.*, 2006).

Recruitment

The recruitment term of NK cell is taken from Pillis and Radunskaya (2003a). Hence, the term has the form:

$$R_N(T,N) = g\frac{T^2}{h+T^2}N \text{ in equation (2).}$$

There are three factors which cause more CD8+ T cells. The first is impact of interaction CD8+ T – tumour represented by

$$R_L(T,L) = j\frac{D^2T^2}{k+D^2T^2}L \text{ in equation (3) (Pillis } et\ al.,\text{ 2006).}$$

The second is by the debris from tumour cells lysed by NK cells. This recruitment term is represented by $R_L(N,T) = r_1NT$ (Pillis *et al.*, 2006). The third is the presence of tumour cells to produce more CD8+ T cells. Recognition of the presence of the tumour is proportional to the average number of encounters between circulating lymphocytes and the tumour. Hence, the term of recruitment is represented by $R_L(C,T) = r_2CT$ (Pillis *et al.*, 2006).

Inactivation Terms

There are three inactivation terms for NK cell and CD8+ T cell in our model. These terms are developed by Pillis and Radunskaya (2003a). The first and second terms are $I_N = -pNT$ in equation (2) and $I_L = -qLT$ in equation (3). These terms represent inactivation of NK cell and CD8+ T cell after interacting with tumour cells several times ceases to be effective. The third inactivation term, $I_{CL} = -uNT^2$, describes the NK cell regulation of CD8+ T cells, which occurs when there are very high levels of activated CD8+ T cells without responsiveness to cytokines present in the system (Pillis *et al.*, 2006).

Drug Intervention Terms

In our model, there are treatment drugs such as IL-2 and TIL in immunotherapy and chemotherapy drug. The injection of IL-2, TIL and chemotherapy drug to the body are represented by $v_I = v_I(t)$, $v_L = v_L(t)$ and $v_M = v_M(t)$ respectively (Pillis *et al.*, 2006).

Parameter Derivation

To complete the development of the mathematical model and analysis, it is necessary to obtain accurate parameters. System parameters can vary greatly from one individual to another, so multiple-data sets can be used in order to obtain acceptable parameter ranges. In our study, we use the data from both the murine experimental studies and the human clinical trials ((Diefenbach *et al.*, 2001), (Dudley *et al.*, 2002)). When necessary, we also use previous model parameters that that have been fitted to experimental curves ((Pillis & Radunskaya, 2003a), (Pillis & Radunskaya, 2003b), (Kuznetsov *et al.*, 1994)). All of the parameters for simulation are given at Table 1.

Analysis and Numerical Simulation

In this section, we will explore ordinary differential equations, (1)-(7). We solve ordinary differential equations, (1)-(7), using numerical method with the help of the MATLAB software. The solution of this ODE system can predict results in cancer-treatment simulation. Then, we simulate the three types of cancer treatment for patient 9 and patient 10, such as immunotherapy alone, chemotherapy alone and immunotherapy-chemotherapy sequence.

Treatments for Patient 9

First, we examine pure immunotherapy treatment with injection of IL-2 and TIL. In Figure 1 we investigate a 10^7 cell tumour for a case where the immune system cannot handle it on its own (Pillis *et al.*, 2006). The initial conditions of the immune system are 1×10^3 NK cells, 10 CD8+ T cells, 6×10^9 circulating lymphocytes. 10^9 TIL are administered on day 7 to 8. IL-2 is administered in 6 pulses at strength 5×10^6 on day 8 to day 11. This treatment is not able to eliminate the tumour cells as seen in Figure 1(a). Then, we simulate the pure chemotherapy with nine one-day chemotherapy doses of strength $v_M(t) = 5$ every 10 days. This treatment is also not able to eliminate the tumour cells, as seen in Figure 1(b). Numerical simulation of immunotherapy-chemotherapy sequence is shown in Figure 1(c) and 1(d). In Figure 1(c), 10^9 TILs are administered on day 6 to 7. IL-2 is administered in 6 pulses at strength 5 x 10^6 on day 8 to day 11. Next, two one-day chemotherapy doses of strength $v_M(t) = 5$ every 10 days, beginning on day 10. While in Figure 1(d), 10^9 TIL are administered on day 7 to 8. IL-2 is administered in 6 pulses at strength 5 x 10^6 on day 8 to day 11.

Treatments for Patient 10

In order to examine whether these treatment simulations vary from patient to patient, we change patient-specific parameters extracted from Rosenberg's study (Diefenbach *et al.*, 2001), then run simulation with the parameters for patient 10. The result of numerical simulations is shown in Figure 2. Results of simulation of immunotherapy alone and chemotherapy alone shown in Figure 2(a) and 2(b) are the same with results for patient 9 in Figure 1(a) and 1(b). It failed to kill the tumour cells. Simulations of immunotherapy-chemotherapy are shown in Figure 2(c) and 2(d). In Figure 2(c), 10^9 TIL was administered day 5 to day 6, day 20 to day 21, day 30 to day 31, day 40 to 41 and day 120 to day 121. IL-2 was administered in 6 pulses at strength 5 x 10^6 on day 5 to day 9, day 20 to day 24, day 30 to day 34 and day 40 to day 44. Chemotherapy pulses with setting $V_M(t) = 5$ were administered once every ten days which start on day 40 to day 100. While, in Figure 2(d), 10^9 TIL was administered on day 5 to day 6, day 20 to day 21, day 30 to day 31, day 40 to 41 day 6 and day 120 to day 121. IL-2 with concentration $V_I(t) = 5$ x 10^6 in 6 pulses which were administered on day 5 to day 9, day 20 to day 24, day 30 to day 34 and day 40 to day 44. Chemotherapy pulses were administered once every five days, beginning on day 40 to day 55.

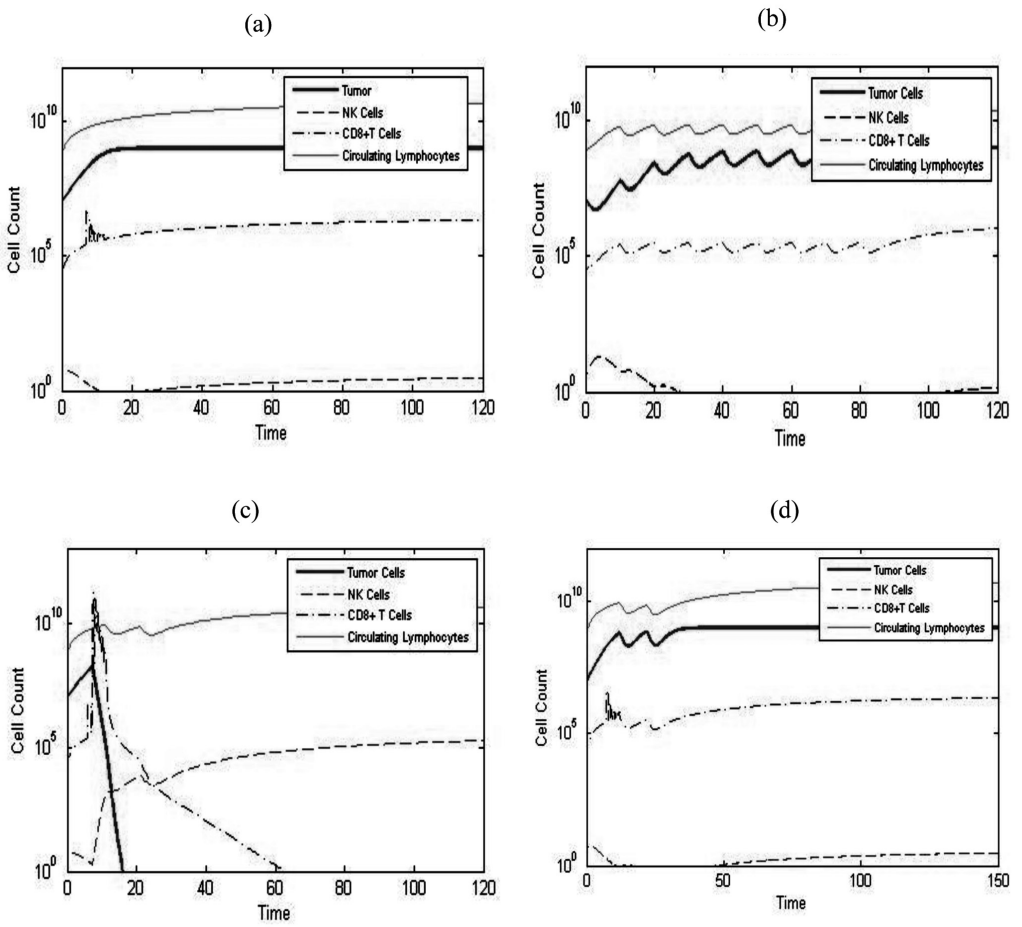

Figure 1. Simulation for patient 9: (a) Immunotherapy alone is not able to kill tumour cells; (b) Chemotherapy alone is not able to kill tumour cells; (c) Immunotherapy-chemotherapy sequence is able to kill tumour cells, 10^9 TIL are administered on day 6 to 7; (d) Immunotherapy-chemotherapy sequence is not able to kill tumour cells, 10^9 TIL are administered on day 7 to 8.

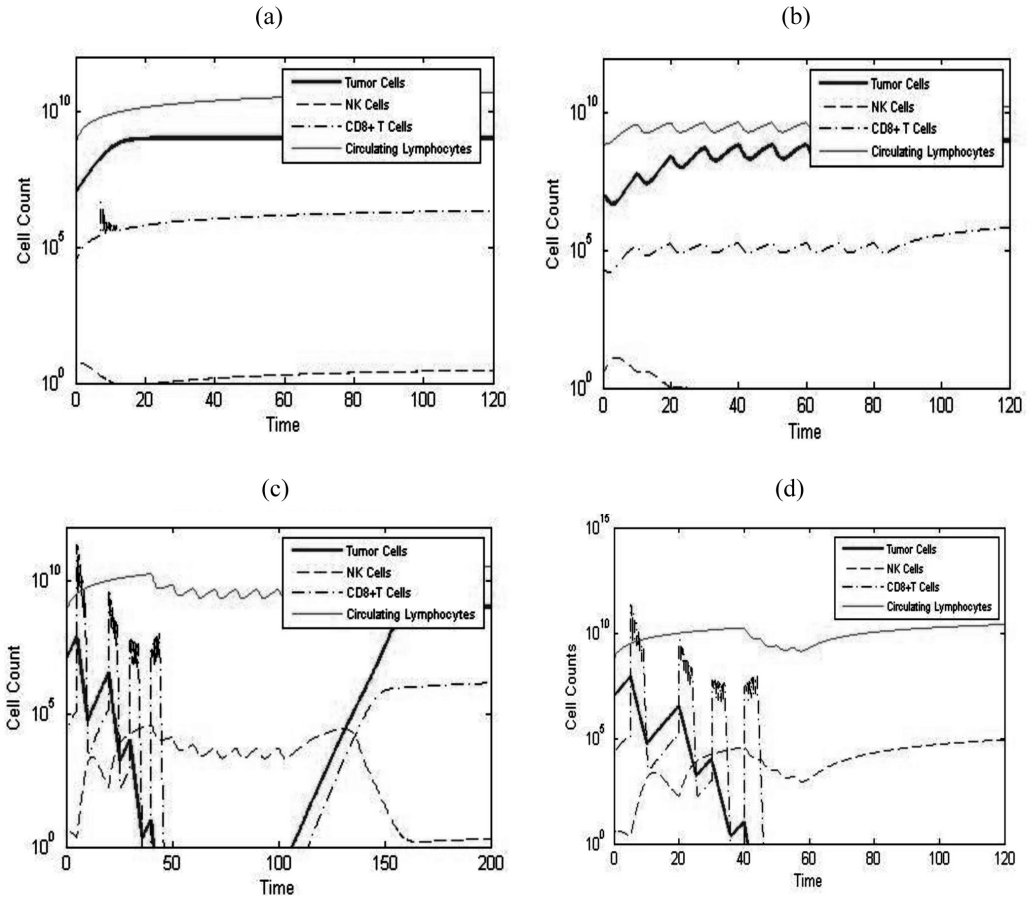

Figure 2. Simulation for patient 10: (a) Immunotherapy alone is not able to kill tumour cells; (b) Chemotherapy alone is not able to kill tumour cells; (c) Immunotherapy-chemotherapy sequence is able to kill tumour cells, 10^9 TIL are administered on day 6 to 7; (d) Immunotherapy-chemotherapy sequence is not able to kill tumour cells, 10^9 TIL are administered on day 7 to 8.

Discussion and Conclusion

We have used the model developed by Pillis *et al.* (2006) to study the effect of immunotherapy alone, chemotherapy alone and immunotherapy-chemotherapy sequence on both tumour growth and immune response in a system of ordinary differential equations. Then, we compare between our results and previous studies (Pillis *et al*., 2006) for the best treatments.

For the case of patient 9, our simulation shows that immunotherapy alone and chemotherapy alone is not able to kill the tumour cells. However, immunotherapy-chemotherapy successfully killed the tumour cells on day 18 completely as shown in Figure 1(c). This treatment failed to kill the tumour cells, when injecting the TIL a day late as shown in Figure 1(d). Thus, the success of treatment depends on the TIL when given to patient. The result in Figure 1(c) is the same as the results of previous studies (Pillis *et al.*, 2006) using different strategies. In (2006), Pillis *et al.* simulated of mixed immunotherapy and chemotherapy to treat cancer disease. They used nine doses

over 90 days for part of chemotherapy, but our model only used two doses over 10 days. Therefore, immunotherapy-chemotherapy for patient 9 is better than mixed immunotherapy and chemotherapy.

Similar with the case of patient 9, our simulation for patient 10 show that immunotherapy alone and chemotherapy alone is not able to kill tumour cells as shown in Figure 2(a) and 2(b). Based on Figure 2(c), we found patient 10 has a weaker immune system than patient 9 and required additional treatment. This figure also shows that additional immunotherapy drugs cause reduction of the tumour cells to clean completely on day 42 and then relapsed on day 107. With frequency of more chemotherapy injection, the tumour cells can be killed completely as shown in Figure 2(d).

The ordinary differential equations model shows that immunotherapy-chemotherapy sequence is a more effective treatment than immunotherapy alone or chemotherapy alone. The first, immunotherapy led to reduction of the tumour cells. The second, chemotherapy will kill the tumour cells completely. Its treatment have benefited that patient to get less drug chemotherapy so it is safer with little side effect. In the future study, we will extend this model to include other cytokine such as interferon alpha (INF-*a*). The INF-a is an immune modifier which is already widely used in cancer immunotherapy (Gause *et al.*, 1996).

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References

American Science Society. Making Treatment Decisions. Available at http://www.cancer.org/docroot/ETO/content//ETO_1_4X_What_Is_Immunotherapy.as Accessed September 2009.

A.Diefenbach, E.R. Jensen, A.M. Jamieson, and D. Raulet, Rae1. (September 2001) H60 ligands of the NKG2D receptor stimulate tumor immunity, *Nature*, 413: 165 –171.

A.S. Perelson and G. Weisbuch, (October 1997). Immunology for physicists, *Rev. Mod. Phys*.69(4): 1219- 1267.

A.Yates and R. Callard. (2002). Cell death and the maintenance of immunological memory *Discrete Contin Dyn S*., 1(1):43–59.

B. Hauser. (January 2001). Blood tests, *Technical Report*, International Waldenstrom's Macroglobulinemia Foundation.

D. Kirschner and J.C. Panetta,(September 1998). Modeling immunotherapy of the tumor-immune interaction, *J. Math. Biol*., 37(3): 235–52.

J.F. Holland and F. Emil III (editors). (1973). *Cancer medicine*, Chapter II-3, XII, XV, Lea and Febig.

K.J. O'Byrne, A.G. Dalgleish, M.J. Browning, W.P. Steward and A.L. Harris. (2000). The relationship between angiogenesis and the immune response in carcinogenesis and the progression of malignant disease, *Eur. J. Cancer*, 36:151-169.

L.G. de Pillis, W. Gu and A.E. Radunskaya. (2006). Mixed immunotherapy and chemotherapy of tumors: modeling, application and biological interpretations, *J. Theor. Biol*., 238: 841-862,

L.G. de Pillis and A.E. Radunskaya. (2003). Immune response to tumor invasion. In K.J. Bathe, editor, *Computational Fluid and Solid Mechanics*, Vol. 2: 1661–1668, M.I.T.

L. G. de Pillis and A. Radunskaya. (2003). The dynamics of an optimally controlled tumor model: A case study, *Math. Comp. Model*, 37:1221–1244.

L. Gause, M. Sznol, W.C. Kopp, J.E. Janik, J.W. Smith II, R.G. Steis, W.J. Urba, W. Sharfman, R.G. Fenton, S.P. Creekmore, J. Holmlund, K.C. Conlon, L.A. VanderMolen and D.L. Longo. (1996). Phase I study of subcutaneously administered interleuking-2 in combination with interferon alfa-2a in patients with advanced cancer, *J. of Clin. Oncol*, 14: 2234—2241.

M.E. Dudley, J.R. Wunderlich, P.F. Robbins, J.C. Yang, P. Hwu, D.J. Schwartzentruber, S.L. Topalian, R. Sherry, N.P. Restifo, A.M. Hubicki, M.R. Robinson, M. Raffeld, P. Duray, C.A. Seipp, L. Rogers-Freezer, K.E. Morton, S.A. Mavroukakis, D.E. White and S.A. Rosenberg. (October 25, 2002). Cancer regression and autoimmunity in patients after clonal repopulation with anti-tumor lymphocytes, *Science*, 298(5594):850–854.

Mustafa Mamat, Edwin Setiawan N., Agus Kartono. (February 2010). Mathematical modeling of tumor-immune interaction. *Far East Journal of Applied Mathematics*. Accepted.

P. Calabresi and P.S. Schein, editors. (1993). *Medical Oncology: Basic Principles and Clinical Management of Cancer*. McGraw-Hill, New York, second edition, R.J. de Boer and P. Hogeweg, (June1986) Interactions between macrophages and lymphocytes: tumor sneaking through intrinsic to helper T cell dynamics, *J. Theor. Biol*., 120(3): 331–51,

R. Pazdur, W. Hopkins, L. Wagman, and L. Coia (Eds.). (2001). Cancer Management: A Multidisciplinary Approach, Publisher Research and Representation, Fifth ed, Chapter: *Principles of Chemotherapy*.

V. Kuznetsov and I. Makalkin. (November-December 1992). Bifurcation-analysis of mathematical-model of interactions between cytotoxic lymphocytes and tumor-cells-effect of immunological amplification of tumor-growth and its connectionV with other phenomena of oncoimmunology, *Biofizika*, 37(6): 1063-70.

V. Kuznetsov, I. Makalkin, M. Taylor, and A. Perelson. (1994). Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis. *Bulletin of Mathematical Biology*, 56(2):295–321.

W. Chang, L. Crowl, E. Malm, K. Todd-Brown, L. Thomas, M. Vrable. (2003). *Analyzing Immunotherapy and Chemotherapy of Tumors through Mathematical Modeling*. Harvey Mudd College.

Table 1: Parameter values used for numerical simulation

Patient 9	Patient10	Units	Description	Source
$a = 4.31 \times 10^{-1}$	$a = 4.31 \times 10^{-1}$	day^{-1}	*Tumour growth rate*	[Diefenbach et al., 2001]
$b = 1.02 \times 10^{-9}$	$b = 1.02 \times 10^{-9}$	$cell^{-1}$	*1/b is tumour-carrying capacity*	[Diefenbach et al., 2001]
$c = 6.41 \times 10^{-11}$	$c = 6.41 \times 10^{-11}$	$day^{-1} \cdot cell^{-1}$	*Fractional (non) ligand transduced tumour cell kill by NK cells*	[Diefenbach et al., 2001], [Dudley et al., 2002]
$d = 2.34$	$d = 1.88$	day^{-1}	*Saturation level of fractional tumour cell kill by CD8+ T Cells. Primed with ligand-transduced cells, challenged with ligand-transduced*	[Dudley et al., 2002]
$e = 2.08 \times 10^{-7}$	$e = 2.08 \times 10^{-7}$	day^{-1}	*Fraction of circulating lymphocytes that became NK cells*	[Kuznetsov et al., 1994]
$l = 2.09$	$l = 1.81$	dimensionless	*Exponent of fractional tumour cell kill by CD8+ T cells. Fractional tumour-cell kill by chemotherapy*	[Dudley et al., 2002]
$f = 4.12 \times 10^{-2}$	$f = 4.12 \times 10^{-2}$	day^{-1}	*Date rate of NK cells*	[Diefenbach et al., 2001]
$g = 1.25 \times 10^{-2}$	$g = 1.25 \times 10^{-2}$	day^{-1}	*Maximum NK cells recruitment by ligand-transduced tumour-cells*	[Kuznetsov et al., 1994]
$h = 2.02 \times 10^{7}$	$h = 2.02 \times 10^{7}$	$cell^{2}$	*Steepness coefficient of the NK cell recruitment curve*	[Kuznetsov et al., 1994]
$j = 2.49 \times 10^{7}$	$j = 2.49 \times 10^{7}$	day^{-1}	*Maximum CD8+ T cell recruitment rate. Primed with ligand-transduced cells*	[Diefenbach et al., 2001], [Dudley et al., 2002]
$k = 3.66 \times 10^{7}$	$k = 5.66 \times 10^{7}$	$cell^{2}$	*Steepness coefficient of the CD8+ T cell recruitment curve*	[Diefenbach et al., 2001], [Dudley et al., 2002]
$m = 2.04 \times 10^{-1}$	$m = 9.12$	day^{-1}	*Death rate of CD8+ T cells*	[Yates & Callard 2002]
$q = 1.24 \times 10^{-6}$	$q = 1.24 \times 10^{-6}$	$day^{-1} \cdot cell^{-1}$	*CD8+ T cell inactivation rate by tumor cells*	[Kuznetsov et al., 1994]
$p = 3.42 \times 10^{-6}$	$p = 3.59 \times 10^{-6}$	$day^{-1} \cdot cell^{-1}$	*NK cell inactivation rate by tumour cells*	[Dudley et al., 2002]
$s = 8.39 \times 10^{-2}$	$s = 5.12 \times 10^{-1}$	dimensionless	*Steepness coefficient of tumour –(CD8+ T cell) lysis term D. Primed with ligand-transduced cells, challenged with ligand-transduced.*	[Diefenbach et al., 2001]
$r_1 = 1.10 \times 10^{-7}$	$r_1 = 1.10 \times 10^{-7}$	$day^{-1} \cdot cell^{-1}$	*Rate of which CD8+ T cells are stimulated to be produced as a result a tumour cells killed by NK cells*	[Yates & Callard 2002]
$r_2 = 6.50 \times 10^{-11}$	$r_2 = 6.50 \times 10^{-11}$	$cell^{-1} \cdot day^{-1}$	*Rate of which CD8+ T cells are stimulated to be produced as a result a tumour cells interaction with circulating lymphocytes*	-
$u = 3.00 \times 10^{-10}$	$u = 3.00 \times 10^{-10}$	$cell^{-2} \cdot day^{-1}$	*Regulatory function by NK cells of CD8+ T cells*	-
$\alpha = 7.50 \times 10^{8}$	$\alpha = 5.00 \times 10^{8}$	cell · day−1	*Constant source of circulating lymphocytes*	[Hauser ,2001]
$\beta = 1.20 \times 10^{-2}$	$\beta = 8.00 \times 10^{-3}$	day^{-1}	*Natural death and differentiation of circulating lymphocytes*	[Hauser ,2001]]
$\gamma = 9.00 \times 10^{-1}$	$\gamma = 9.00 \times 10^{-1}$	day^{-1}	*Rate of chemotherapy drug decay*	[Calabresi & Schein 1993]
$p_i = 1.25 \times 10^{-1}$	$p_i = 1.25 \times 10^{-1}$	day^{-1}	*Maximum CD8+ T cell recruitment curve by IL-2*	[Kirscher & Panetta 1998]
$\mu_i = 1.00 \times 10^{1}$	$\mu_i = 1.00 \times 10^{1}$	day^{-1}	*Rate of IL-2 drug decay*	[Kirscher & Panetta 1998]
$g_i = 2.00 \times 10^{2}$	$g_i = 2.00 \times 10^{2}$	$cells^{2}$	*Constant*	-