Simulation of Tumor Growth Model and Its Interaction with Natural-Killer Cells and T Cells

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Abstract  This research studies about tumor growth model by involving immune system. Cells in the immune system, for instance natural killer (NK) cells and T cells, have prominent role in recognizing and eliminating tumor cells. In this paper, we construct the tumor growth model consisting of four populations namely tumor cells, NK cells, CD8+T cells, and CD4+T cells which is in the form of a non-linear differential equation. The analysis result shows that there are three tumor free equilibrium points and one coexisting equilibrium point. Some tumor free equilibrium and tumor equilibrium point exist and it is stable under certain conditions. Finally, numerical simulation is carried out to illustrate analysis result. From sensitivity analysis, it is found that the most sensitive parameter that influence the growth rate of tumor cells are the reciprocal carrying capacity of tumor cells and the killing rate of CD8+T cells by tumor cells.

Introduction  Tumor is a disease which is caused by abnormal growth of cells. There are two types of tumor namely benign tumor and malignant tumor (cancer). A malignant tumor or cancer is one of the eight leading causes of death in the world. Based on Institute of Cancer Research in the United States of America, in 1995, there were about 1,252,000 diagnosed cases with 547,000 deaths. According to International Cancer Research Center, there were 12.7 million cancer cases in 2008. It is predicted that by 2030 the number of cases will be doubled into 21.4 million cases and 13.5 million deaths (Mamat et al., 2013). In Indonesia, the prevalence number of cancer can be categorized as quite high. Based on the data by Basic Health Research, 330,000 people were diagnosed with tumor or cancer in 2013 (Kementerian Kesehatan RI, 2017).

Tumor cells will maintain their mutation through reproducing cells process. These mutated cells will spread to the whole body and infect one or some organs then disrupt the growth of the normal cells causing uncontrollable mitosis of cells. When cells become tumorous, the immune system is able to identify them as abnormal cells, and then destroy them before they replicate or disperse (Diananda, 2009).

The immune system is a system of protection in human body to defend the body against foreign objects. Based on Bellanti (1993), the immune system have three main functions namely defense, homeostasis, and surveillance. The first function serves as the defense of the body against microorganism infection. The second function involves destroying unused cell. The last function is to find and destroy foreign objects inside the body. Based on response toward a disease, the

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immune system is divided into two, i.e. non-specific immune system and specific immune system. Non-specific immune system is the immune system which works quickly and is always ready when there are some foreign objects inside the body for example NK cells. NK cells can automatically destroy the targeted cells without specifically identifying them. Meanwhile, the specific immune system is more selective and having high sensitivity in recognizing foreign objects, there are hunting-cell or CTL (CD8+ T cells) and helper-cells or resting-cells (CD4+ T cells). CD4+ T cells produce anti-body which can activate CD8+ T cells, and then, the activated CD8+ T cells can destroy tumor cells directly (Baratwidjaja, 2013). If the immune system works well, this system will protect the body against bacteria and viruses infection and it will destroy foreign substances including tumor cells inside the body. If the immune system is weak, the ability to protect body is weakening as well. The poor immune system can raise the chance of being infected by tumor (Diananda, 2009).

Interactions between tumor cells and immune system can be represented in mathematical model. Mathematical model in tumor growth has been widely discussed by many researchers over past decades. At first, de Pillis and Radunskaya (2003) discussed about interaction model between tumor cells, normal cells, and immune cells. Then, de Pillis et al. (2005) proposed a tumor immunosurveillance model system that considered different immune responses of nonspecific (NK cells) and specific (CD8+ T cells). Next, research done by Isaeva dan Osipov (2009) discussed about therapy for tumor using immune system which involves interaction among tumor cells, CD8+ T cells, interleukin-2, chemotherapy, and alpha interferon. Then, de Pillis et al. (2009) developed Isaeva and Osipov (2009) research by adding NK cells compartment and other lymphocyte compartment (except NK cells and CD8+ T cells). However, they omitted alpha interferon compartment. Mamat et al. (2013) developed de Pillis et al. (2006) model by adding alpha interferon compartment.

The next research related to tumor therapy is discussed by Sharma and Samanta (2013). It discussed about interactions among tumor cells, CD8+ T cells, CD4+ T cells, and chemotherapy. This model assumed that CD4+ T cells cannot destroy tumor cells directly. Instead, they produced interleukin-2 which later stimulated CD8+ T cells or CTL that could attack and destroy tumor cells. Another research done by Trisilowati et al. (2013), analyzed the optimum control tumor immune interaction model which involved NK cells, CD8+ T cells, and dendritic cells. This model assumed that dendritic cells could activate NK cells, which in turn, can kill tumor cell. In 2016, Mahasa et al. discussed about tumor cells with immune system involving NK cells and CD8+ T cells. This model assumed that NK cells were able to directly kill tumor cells by producing antibody-dependent cellular cytotoxicity (ADCC).

Based on the descriptions above, NK cells and T cells have important role in growth of tumor cells. Therefore, this research constructs a tumor growth model with immune system which includes NK cells, CD8+ T cells and CD4+ T cells. Then, constructed model is analyzed dynamically by determining equilibrium points along with their existence requirements. Then, we analyze the stability of the equilibrium points and numerical sensitivity. Finally, numerical simulation is carried out to illustrate dynamic analysis result.

Material and Methods.

In this section, a tumor growth model which is constructed by Sharma and Samanta (2013) is as follows:

\[
\frac{dT}{dt} = aT(1 - bT) - kLT - q_1MT,
\]
\[
\frac{dT}{dt} = n_1LH - hLT - m_1L - q_2ML,
\]
\[
\frac{dH}{dt} = rH(1 - pH) - n_2 LH - q_3 MH,
\]
\[
\frac{dM}{dt} = u(t) - \gamma M,
\]

with \(T(t), L(t), H(t), M(t)\) are the numbers of tumor cells, CD8\(^+\)T cells, CD4\(^+\)T cells, and chemotherapy respectively. Sharma and Samanta (2013) models assumed that tumor cells and CD4\(^+\)T cells growth logistically. Then, tumor cells can be destroyed after interacting with active CD8\(^+\)T cells. As a result, there are inactive CD8\(^+\)T cells after interacting with tumor cells. CD4\(^+\)T cells can activate CD8\(^+\)T cells directly or through cytokines produced by CD4\(^+\)T cells. Meanwhile, chemotherapy in addition be able to kill tumor cells and also kill other immune cells. Therefore modification of the model in this paper are replace chemotherapy compartment with NK cells compartment due to their significant role in fighting against tumor cells.

**Dynamical Analysis**

In dynamical analysis, the first step is to determine equilibrium points in the model. Then, existence requirements can be obtained from the equilibrium points. These equilibrium points are obtained when system is in balance which is when the population rate does not changes or having zero value. In general, equilibrium point in a disease model consists of two categories namely free disease equilibrium point and coexisting equilibrium point which represent whether there is a disease or not in the population.

The next step is to analyze the stability of model equilibrium points by model linearization using Taylor’s theorem and forming Jacobi’s matrix. Linearization aims to transform a system of non-linear equations into a linear system, so the stability of equilibrium points can be analyzed easily.

Then, based on Jacobi’s matrix, eigenvalues from the characteristic equations can be determined. If all eigenvalues are negative, the equilibrium points will be locally asymptotically stable. In contrast, the equilibrium points will be unstable if there is at least positive eigenvalue.

**Numerical Simulation**

Numerical simulation is carried out to support the analysis result and illustrate model’s behavior. Numerical simulation begins by determining parameter value in order to meet requirement of existence and stability of equilibrium points. This simulation is run using MATLAB software program with Runge Kutta orde-4 method.

**Result and Discussion**

**Model Formulation**

Tumor growth model and its interaction with NK cells and T cells consists of four populations: populations of tumor cells \(T(t)\), populations of NK cells \(N(t)\), populations of CD8\(^+\)T cells \(L(t)\), and populations CD4\(^+\)T cells \(H(t)\). Model formulation process begins with population growth of tumor cells which is assumed to grow logistically with an intrinsic growth rate \(a\), and reciprocal carrying capacity of tumor cells \(b\). Tumor cells are killed by NK cells represented by \(-c_1 NT\). Then, CD8\(^+\) T cells also kill the tumor cells which is represented by \(-kLT\).

The growth of NK cells are produced from external source with rate \(s\), in account for the fact that NK cells, as part of the innate immune, are always present in the body even though there is no tumor (Mahasa et al., 2016). Then NK cells become inactive after interacting with tumor cells, as represented by \(-c_2 NT\). The loss of NK cells is represented by \(-m_N N\).

CD8\(^+\)T cells proliferate due to stimulation or direct activation by CD4\(^+\)T cells or through cytokine produced by CD4\(^+\)T cells is represented by \(n_1 LH\). Then, CD8\(^+\)T cells ability to kill tumor cells will be degraded after encountering tumor cells is represented by \(-hLT\). The loss of CD8\(^+\)T cells is represented by \(-m_L L\).
CD4⁺T cells is assumed to grow logistically with an intrinsic growth rate $r$, and $p$ as the reciprocal carrying capacity of CD4⁺T. CD4⁺T cells cannot kill the tumor cells directly, but it has ability to activate CD8⁺T cells. After activating CD8⁺T cells, they become inactive with the rate represented by $-n_2 LH$. Based on the descriptions above, the obtained model is as follows:

\[
\begin{align*}
\frac{dT}{dt} &= aT(1 - bT) - c_1 NT - kLT, \\
\frac{dN}{dt} &= s - c_2 NT - m_N N, \\
\frac{dL}{dt} &= n_1 LH - hLT - m_L L, \\
\frac{dH}{dt} &= rH(1 - pH) - n_2 LH.
\end{align*}
\]

with initial conditions

\[T(0) \geq 0, \quad N(0) \geq 0, \quad L(0) \geq 0, \quad H \geq 0.\]

**Equilibrium Points**

In this section, we will study the existence and stability behaviour of the system (1). The equilibrium points of the systems (1) are:

i. Tumor free equilibrium

- a) $E_0 = (T_0, N_0, L_0, H_0) = (0, \frac{s}{m_N}, 0, 0)$, always exists.
- b) $E_1 = (T_1, N_1, L_1, H_1) = (0, \frac{s}{m_N}, 0, 1)$, always exists.
- c) $E_2 = (T_2, N_2, L_2, H_2) = (0, \frac{s}{m_N}, \frac{r(n_1 - pm_L)}{n_1 n_2}, m_L)$, exists if $n_1 > pm_L$.

ii. Coexisting equilibrium $E^*(T^*, N^*, L^*, H^*)$

where $N^* = \frac{s}{c_2^2 + m_N}$, $L^* = \frac{T^*}{n_1}$, $H^* = \frac{hT^* + m_L}{n_1}$ and $T^*$ is the positive root of the following equation:

\[f(T^*) = A(T^*)^2 + BT^* + C = 0.\]

with

- $A = krphc_2 - abc_2n_2n_1$,
- $B = ac_2n_2n_1 + krphm_N + krphm_N - abm_N n_2 n_1 - krn_1 c_2$,
- $C = am_N n_2 n_1 + krpm_L m_N - c_1 s n_2 n_2 - krn_1 m_N$.

**Stability of the Equilibrium Points**

The stability properties of the system equilibrium points (1) are examined through stability analysis. The equation model for tumor growth models and their interaction with NK cells and T cells are nonlinear autonomous systems. Therefore, in determining the stability properties of the equilibrium points, linearization is performed on the system of equation (1) around the equilibrium points which produces the Jacobian matrix as follows:

\[
J(T^*, N^*, L^*, H^*) = \begin{bmatrix}
-a + 2abT - c_1 N - kL & -c_1 T & -kT & 0 \\
-c_2 N & -c_2 NT - m_N & 0 & 0 \\
-hL & 0 & n_1 H - hT - m_L & n_1 L \\
0 & 0 & -n_2 H & r - 2rpH - n_2 L
\end{bmatrix}
\]
Each equilibrium point is substituted to the Jacobian matrix system equation (1), and it is obtained as follows:

- The equilibrium point $E_0$ is unstable.
- The equilibrium point $E_1$ is stable, if $a < \frac{c_{1s}}{m_N}$ and $\frac{n_1}{p} < m_L$.
- The equilibrium point $E_2$ is stable if $a < \frac{c_{1s}}{m_N} + \left( \frac{kr(n_1 + pm_L)}{n_1n_2} \right)$.
- The equilibrium point $E^*$ is stable if and only if

$$a_1 > 0, a_3 > 0, a_1a_2a_3 - a_2^2a_4 > 0, \text{ and } a_4 > 0,$$

with

$$a_1 = \frac{abT^* + s + r_p N^* H^*}{N^*},$$
$$a_2 = \frac{abrs(T^* + s + r_p H^*) + abr_T^* + n_1n_2 N^* L^* H^* - c_1 c_2 N^* T^*}{N^*},$$
$$a_3 = \frac{abrs(T^* + s + r_p H^*) + abr_T^* + n_1n_2 N^* L^* H^* - c_1 c_2 r_p H^* N^* T^* - k_h T^* - k_h H^* T^* - k_h H^* L^* - k_h T^* L^*}{N^*},$$
$$a_4 = \frac{abrs(T^* + s + r_p H^*) + abr_T^* + n_1n_2 N^* L^* H^* - c_1 c_2 r_p H^* N^* T^* - k_h r_p H^* T^* - k_h r_p H^* L^*}{N^*}.$$

**Numerical Simulation**

In this section, we simulate the solution behavior of each population $T(t), N(t), L(t), H(t)$. Numerical simulations are performed using MATLAB software which is presented in Figure 1 and Figure 2. The parameters used for Figure 1 are presented in Table 1.

| Parameter | Description | Value |
|-----------|-------------|-------|
| $a$       | Intrinsic growth rate of tumor cells | $4.31 \times 10^{-1}$/day |
| $b$       | Reciprocal carrying capacities for tumor cells | $2.17 \times 10^{-8}$/cells |
| $c_1$     | Rate of loss of tumor cells killed by NK cells | $3.6 \times 10^{-6}$/cells/liter/day |
| $c_2$     | Rate of loss of NK cells killed by tumor cells | $10^{-7}$/cells/liter/day |
| $k$       | Rate of loss of tumor cells killed by CD8$^+$T cells | $10^{-7}$/cells/day |
| $h$       | Rate of loss of CD8$^+$T cells killed by tumor cells | $3.42 \times 10^{-10}$/cells/day |
| $m_N$     | Death rate of NK cells | $4.12 \times 10^{-2}$/day |
| $m_L$     | Death rate of CD8$^+$T cells | $4 \times 10^{-2}$/day |
| $n_1$     | Rate of CD4$^+$T cells activating CD8$^+$T cells | $10^{-6}$/cells/day |
| $n_2$     | CD4$^+$T inactivation rate by CD8$^+$T | $10^{-3}$/cells/day |
| $s$       | Source of NK cells | $1.3 \times 10^4$ |
| $r$       | Intrinsic growth rate of CD4$^+$T cells | $4 \times 10^2$/day |
| $p$       | Reciprocal carrying capacities for CD4$^+$T cells | $10^{-4}$/cells |

Based on these parameters, two tumor free equilibrium points that exist: $E_0 = (0, 3.15539806 \times 10^5, 0, 0)$ and $E_1 = (0, 3.15539806 \times 10^5, 0, 10^4)$. It is obtained $a = 0.431 < 1.1359 = \frac{c_{1s}}{m_N}$ and $m_L = 0.02 > 0.01 = \frac{n_1}{p}$, so that, only one stable equilibrium point is the tumor.
free equilibrium point \( E_1 \) with each solution of each population converging to the point \((0,3.155339806 \times 10^5, 0, 10^4)\). The behavior of the solution population \( N(t) \) converges towards the point \(3.155339806 \times 10^5\), and the population \( H(t) \) converges to the point \(10^4\), while the population of \( T(t) \) and \( L(t) \) converge to zero. This means that solutions go toward tumor free equilibrium point \( E_1 \) and numerical simulations support the results of analysis that tumor-free equilibrium point \( E_1 \) is locally asymptotically stable.

Figure 1 shows a simulation of tumor cells growth model and its interaction for 600 days. With an initial value of \( T(0) = 10^5 \) cells, Figure 1a shows that the tumor cell population rises up to 100.137 cells on 5th day. Then, after 25 days, the population of tumor cells slowly decreases to 0 cells. In contrast, with the initial value of \( N(0) = 10^5 \) cells, Figure 1b shows that the NK cells population is increasing day by day. The number of NK cells rises steadily reaching \(3.155339806 \times 10^5\) cells/liter on 150th day. Meanwhile, with the initial value \( L(0) = 10^5 \) cells/liter, Figure 1c shows that the population of CD8+ cells is decreasing day by day. Then, it slowly decreases to zero cells on 450th day. Next, with the initial value of \( H(0) = 7.5 \times 10^3 \) cell/liter, Figure 1d shows that CD4+T cells are also increasing day by day. The number of CD8+T cells grows steadily reaching \(10^4\) cells/liter on 450th day. It can be seen that when tumor cells populations become extinct, NK cells and CD4+T cells are still in the body. This condition indicates that based on these parameters tumor cells can be destroyed by immune systems.

The parameters used for Figure 2 are presented in Table 1 by changing the parameter value \( n_1 = 10^{-4} \). Based on these parameters, there are five equilibrium points, including three tumor free equilibrium points: \( E_0 = (0,3.155339806 \times 10^5, 0, 0) \), \( E_1 = (0,3.155339806 \times 10^5, 0, 10^4) \), and \( E_2 = (0,3.155339806 \times 10^5, 3.92 \times 10^5, 200) \). Then, two coexisting equilibrium points: \( E_1^* = (4.073512861 \times 10^7,3159.394212,3.864274344 \times 10^5,339.3141399) \) and \( E_2^* = (8.058814441 \times 10^5,1.067427381 \times 10^5,3.918897554 \times 10^5,202.7561145) \). From these parameters, it is also obtained \( B = 3.871579599 \times 10^{-15} \) and \( C = -3.065784000 \times 10^{-9} \), which result in an coexisting point in the tumor cells population. Then, it is obtained the values of \( a_1 = 17.68739905, a_2 = 70.48218220, a_3 = 74.59908922, \) and \( a_4 = 19.91003744 \) which meet the criteria of Routh Hurwitz stability with \( a_0 = 1 > 0, a_1 a_2 - a_3 = 1172.04 > 0, a_1 a_2 a_3 - a_2^2 - a_1 a_4 = 74.5990892 > 0, \) and \( a_4 = 19.91003744 > 0 \). By using Routh Hurwitz criterion, this indicates that the coexisting equilibrium point \( E_1^* \) is locally asymptotically stable.

So that, only one stable equilibrium point which is the coexisting equilibrium point with each solution of each population converges to the point \((4.073512861 \times 10^7,3159.394212,3.864274344 \times 10^5,339.3141399) \). The solution behavior of \( T \) population converges to point \(4.073512861 \times 10^7 \), \( N \) population converges towards point \(3159.394212 \), \( L \) population converges to point \(3.864274344 \times 10^5 \), while \( H \) population converges to point \(339.3141399 \). This means that all solutions are leading to \( E_1^* \) coexisting equilibrium point and numerical simulations support the results of analysis that the tumor free equilibrium point \( E_1 \) is locally asymptotically stable.
Figure 1. The solutions of the tumor growth model \((T, N, L, H)\) at the equilibrium point \(E_1\).

Figure 2 shows a simulation of coexisting tumor cell growth model and its interaction for 100 days. With an initial value of \(T(0) = 10^7\) cells, it shows that the tumor cells population grows steadily reaching \(4.073512861 \times 10^7\) cells on 20th day. With an initial value of \(N(0) = 10^3\) cells / liter, Figure 2b shows that the NK cell population has increased to 8200 cells / liter. But on the 10th day, NK cells decrease gradually to \(3.155339806 \times 10^5\) cells / liter. Then, with the initial value \(L(0) = 10^5\) cells/liter, Figure 2c shows that CD8\(^+\)T cells population increases until the 6th day and it rises gradually reaching \(3.864274344 \times 10^5\) cells / liter. Meanwhile, with the initial value \(H(0) = 100\) cells/liter, Figure 2d shows that the population of CD4\(^+\)T cells has increased to 7500 cells / liter. But, on the 8th day, CD4\(^+\)T cells decrease gradually to \(339.3141399\) cells/liter. It is known that when the population of tumor cells continues to grow in the body, NK cells, CD8\(^+\)T cells, and CD4\(^+\)T cells also continue to exist and fight against these tumor cells. This condition indicates that based on these parameters, immune systems failed to killed tumor cells.
Numerical sensitivity analysis

Parameter sensitivity analysis is used to determine which parameters are very influential on the model. The steps of this sensitivity analysis begins with performing numerical simulations using the parameter values given in Table 1, then to increase and decrease that one parameter by certain percentage and finally checking the effect at the endpoint of the model. In Figure 3, changes tumor size from day 0 to day 50 as a result of changes in each parameter in the model by 25% in both directions.

From Figure 3, it can be seen that the parameters which are very sensitive or very influential on this model are $h$, $b$, and $a$. As known before, the parameter $h$ is the killing rate of CD8+T cells by tumor cells, $b$ is the reciprocal carrying capacity of tumor cells in our body, and $a$ is the intrinsic growth rate of tumor cells. By increasing 25% parameter of $a$ and $h$, the tumor cell will increase. On the contrary, by increasing 25% parameter of $b$, the tumor cell will decrease. It can be seen that the greater the $h$ value, the more CD8+T cells are killed by tumor cells, whereas the smaller the $h$ value, the fewer the CD8+T cells are killed by tumor cells.
Conclusion and Suggestion

In this paper, a tumor growth model and its interaction with NK cells and T cells has been constructed. In analysis, there are two equilibrium points, namely the tumor free equilibrium point and the coexisting equilibrium point. Tumor free equilibrium points and coexisting equilibrium points will be locally asymptotically stable if they meet certain conditions. The numerical simulation results show that the behavior of the model supports the results of the analysis, and the parameters which are very sensitive or very influential the growth of tumor cells are the reciprocal carrying capacity of tumor cells and the killing rate of CD8+T cells by tumor cells. As suggestions for further research, it is recommended to conduct further analysis of the tumor growth model for the coexisting condition of tumor cells by adding the effects of immunotherapy or chemotherapy.

References

Baratawidjaja, K. G and Rengganis, I. 2013. *Imunologi Dasar edisi ke-10*. Jakarta: Balai Penerbit Fakultas Kedokteran Universitas Indonesia.

Bellanti, J. A. 1993. *Imunologi III*. Yogyakarta: Gadjah Mada University Press.

De Pillis, L. G., Radunskaya, A. 2003. The Dynamics of an Optimally Controlled Tumor Model: A case Study. *Mathematical and Computer Modelling*, 37(11): 1221-1244.

De Pillis, L. G., Radunskaya, A., Wiseman, C. L. 2005. A Validated Mathematical Model of Cell-Mediated Immune Response to Tumor Growth. *Cancer Res.*, 65(17): 7950-7958.

De Pillis, L. G., Gu, W., and Radunskaya, A. 2006. Mixed Immunotherapy and Chemotherapy of Tumors: modeling, applications and biological interpretations. *Journal of Theoretical Biology*, 238(4): 841-862.

De Pillis, L. G., Fister, K.R., Gu, W., Collins, C., Daub, M., Gross, D., Moore, J., Preskill, B. 2009. Mathematical Model Creation for Cancer Chemo-Immunotherapy. *Computational and Mathematical Methods in Medicine*, 10 (3): 165-184.
Diananda, R. 2009. *Panduan Lengkap Mengenal Kanker*. Yogyakarta: Mirza Media Pustaka.

Isaeva, O.G., and Osipov, V.A. 2009. Different Strategies for Cancer Treatment: Mathematical Modelling. *Computational and Mathematical Methods in Medicine*, 10 (4): 253-272.

Kementerian Kesehatan RI. 2017. Kementerian Kesehatan Ajak Masyarakat Cegah dan Kendalikan Kanker. Retrieved on March 25, 2018, from http://www.depkes.go.id/article/kementerian-kesehatan-ajak-masyarakat-cegah-dan-kendalikan-kanker.html.

Mahasa, K. J., Ouifki, R., Eladdadi, A., and De Pillis, L. G. 2016. Mathematical Model of Tumor-immune Surveillance. *Journal of Theoretical Biology*, 404: 312-330.

Mamat, M., Subiyanto, S., and Kartono, A. 2013. Mathematical Model of Cancer Treatments Using Immunotherapy, Chemotherapy and Biochemotherapy. *Applied Mathematical Sciences*, 7(5): 247-261.

Sharma, S., and Samanta, G. P. 2013. Dynamical Behaviour of a Tumor-Immune System with Chemotherapy and Optimal Control. *Journal of Nonlinear Dynamics*, 2013(article ID 608598) 13 pages. http://doi.org/10.1155/2013/608598.

Trisilowati, T., McCue, S., and Mallet, D. G. 2013. An Optimal control model of dendritic cell treatment of a growing tumour. *Anziam J.*, 54(CTAC2012): C664-C680.