Using perturbation theory to explain the existence of infected equilibrium point of immune-cervical cancer model

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ABSTRACT

Immunotherapy give a new hope for cervical cancer treatment. The Kirschner-Panetta model describe the interaction between effector cells, cancer cells, and interleukin-2(IL-2) with two immunotherapies, i.e. Adoptive Cellular Immunotherapy (ACI) and Cytokine therapy. The infected equilibrium point can give an idea of the cure level, but no one has discussed analytically. The function of cancer in steady state is a quintic polynomial that cannot be solved analytically. This study discusses the existence and bifurcation of the infected equilibrium point. Both, can explain the level of cure through analysis of the amount of cancer cells. We use the Singular Perturbation Method because the presents of the small parameter in the leading coefficient. The combination of Naive expansion and dominant balance technique are used. A consistent polynomial rescale is used to find the lost root due to Naive expansion solutions. The four infected equilibrium points get from the Naive and one from the dominant balance technique. ACI and cytokine therapy alone can reduce the cancer cells but with an imbalance of effector cells and IL-2. With both therapies, the cancer cells are close to zero which indicates a good level of cure. It is necessary to study further regarding the bifurcation causes other important parameters besides antigenicity.

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Introduction
Cancer is one of the deadliest diseases in the world. It has many types that are classified based on organs affected by cancer. One example is cervical cancer. Cervix is the uterus in which located at the bottom. Cervix has a cylindrical shape this part is connected to the vagina through the endocervical canal (Bermudez et.al., 2015). In Indonesia, the cervical cancer occupies the second type of cancer experienced by women, with the first place being breast cancer (Bray et. al., 2020). The trigger for the emergence of cervical cancer is an infection by the human papilloma virus
(HPV) (Okechukwu, 2011). HPV types 16 and 18, are the main cause of premalignant and malignant lesions in invasive cervical cancer (Serrano, 2017), (Holger, 2018). HPV belongs to a class of non-enveloped double-stranded DNA (Shandra et al., 2019), with more than 200 genotypes (De Villiers, 2015). In general, HPV infection can be eliminated by the immune system before it develops into malignancy. Unless the infection successfully releases the immune system, it will develop into cancer. Cervical cancer and its treatments (surgery, chemotheraphy, and radiotherapy) can cause interference with the cervical organs themselves and other organ systems, both of which can also weaken organs and decondition syndrome.

Immunotherapy is a new therapy in cervical cancer because it has a dynamic and complex immunomodulatory effect (Brandon et al., 2019). The immune system plays an important part in the cure of HPV infection (VATPNC, 1991) because most cervical cancers are caused by coding high-risk HPV specific virus antigens E6 and E7, which are expressed constitutively in each cancer cell. Changes in the micro and reciprocal environment between keratinocytes that fight the virus and the local immune microenvironment will determine the direction of the disease in HPV induced carcinogenesis (Smola et al., 2017). The immune system can be used to cure cancer with certain virus-related tumor cells (Smola, 2017) or by releasing negative feed-back on cytotoxic T lymphocytes (CTL) which allows them to select neoplastic cells.

Immune cells are categorized into four types namely white blood cells (leukocytes), plasma cells, macrophages, and mast cells. Immune cells are divided into two types, non-specific immune cells and specific immune systems. Non-specific immune systems exist from birth and respond more quickly to disorders. The specific immune system is only specific to certain types of exposure. This specific immune system is responsible for eliminating cancer in the body. The specific immune system needs to be activated, which is when finding exposure such as cancer cells. The immune system that is active in calling the exposure is called an effector cell. In carrying out tasks and differentiating effector cells secrete cytokines. Cytokines that have the task of activating effector cells in searching for cancer cells are interleukin 2. The first mathematical model that discusses the interactions between effector cells, cancer cells, and IL-2 compounds with 2 types of immunotherapies, namely ACI and Cytokine therapy models (Krischner & Panetta, 1998). The KP model consists of three populations, namely cancer cells density, effector cells density, and interleukin-2 density with 2 therapies namely ACI and cytokines.

Based on the results of KP research, it has been explained about the effect of ACI on tumor removal and the appearance of Hopf bifurcation due to antigenicity and carrying capacity parameters numerically. The development of research on the KP model are bifurcation and periodic solutions numerically (Stark & Živković, 2018; Buzby et al., 1991), local stability (Bermudez et al., 2015; Bray et al., 2018; Balasubramaniam et al., 2019), global stability (Ibeanu, 2011; de Villiers et al., 2004; Serrano et al., 2017), delay in treatment (Stark & Živković, 2018; Buzby et al., 1991), minor interruptions in periodic treatment (Allison et al., 2004), and its development in cell movement (asymptotic behavior) (Stark & Živković, 2018).

No one has yet discussed the infected equilibrium point in detail. The problem in assessing the infected equilibrium point is that the equation for the infected equilibrium point is Quintic polynomial, there is no radical method to determine the roots.

The simple idea of this research is to find the simplest system that is by minimizing the parameters after that applying perturbation theory in roots search. This theory has not been widely studied in disease models, especially immune cancer with immunotherapy. The analysis of the existence of this infected equilibrium point provides an overview of the patient’s cure level for the presence of immunotherapy. An infected equilibrium point with a relatively minimal number of cancer cells can be an indicator of successful treatment. In addition, it can also be seen that the equilibrium point is infected in large numbers even though it has been through a series of treatments. This condition is a failure in cancer treatment that is often encountered.

**Method**

The methods of this research in analyzing the existence and bifurcation at the infected equilibrium point to determine the level of cure is singular perturbation method. The steps are performing...
nondimensionalization, solving steady state conditions, transforming into a translucent quintic polynomial for cervical cancer steady state conditions, solving quartic polynomial by looking for a naive solution with the form quartic polynomial in which transformed to resolvent cubic then solved using Cardano Formula, find the lost root by rescaling polynomial using dominant balance techniques, performing numerical simulations, analyzing bifurcation using eigen values in linear systems, and interpretation of results.

**Results and Discussion**

To make it easier when apply the singular perturbation method, nondimensional and rescale parameters are performed. We transform and non-dimension the Kirschner-Panetta model using the following equation.

\[
\tau = t_s, x = \frac{t_s}{x_0}, y = \frac{y_1}{g_{21}}, Z = \frac{z_1}{g_{11}}, c = \frac{c_s g_{21}}{x_0 g_{21}}, \mu_1 = \frac{\mu_{11}}{t_s}, p_1 = \frac{p_{11}}{t_s}, s_1 = \frac{s_{11}}{x_0 g_{21}}, \mu_3 = \frac{\mu_{31}}{t_s}, p_2 = \frac{p_{31} x_0}{g_{11} t_s}, g_3 = \frac{g_{31}}{g_{21}}, s_2 = \frac{s_{21}}{g_{11} t_s}, r_2 = \frac{r_1}{t_s}, b = b_1 g_{21}, a = \frac{a_1}{g_{21} t_s}
\]

We get the System which is on minimum parameters and non-dimensional system:

\[
\begin{aligned}
\frac{dx}{d\tau} &= c y - \mu_2 x + \frac{p_1 x z}{1 + z} + s_1 \\
\frac{dy}{d\tau} &= r_2 y (1 - by) - \frac{a x y}{1 + y} \\
\frac{dz}{d\tau} &= \frac{p_2 x y}{g_3 + y} - \mu_3 z + s_2
\end{aligned}
\]

At the steady state condition in the second and third equation, we get:

\[
x = \frac{r_2 (1 - by) (1 + y)}{a}, \quad z = \frac{p_2 x y + s_2 (g_3 + y)}{\mu_3 (g_3 + y)}
\]

Substituting Equation \( x \) and \( z \), then we get the equation for steady state conditions of the density of cancer cells \( y \). We have equation of \( y \).

The polynomial of cancer density in steady state condition is

\[
\begin{aligned}
&\text{Let } a = \frac{p_2 x y + s_2 (g_3 + y)}{\mu_3 (g_3 + y)} \\
&\text{then we get the equation for } x = \frac{r_2 (1 - by) (1 + y)}{a}
\end{aligned}
\]

Using perturbation theory to explain the existence of infected equilibrium points (Saptaningtyas, Aryati, Adikusumo, van Horssen)
\[ A = b_1 & \& \{ b^2 \} (p_2) (\mu_2 - p_1) r_2^2 \quad (1) \]
\[ b_1 & \& \& = & (p_2) (2b - 1) (\mu_2 - p_1) r_2 + ac \] \nonumber (1)
\[ b_2 & \& \& = & + \{ - \{ b^2 \} - 4b + 1 \} (\mu_2 - p_1) r_2 \] \nonumber (1)
\[ x = \frac{r_2 (1 - by) (1 + y)}{a}, \quad z = \frac{p_2 xy + s_2 (g_3 + y)}{\mu_3 (g_3 + y)} \quad (1) \]
\[ x = \frac{r_2 (1 - by) (1 + y)}{a}, \quad z = \frac{p_2 xy + s_2 (g_3 + y)}{\mu_3 (g_3 + y)} \quad (1) \]

Based on the data in Kirschner and Panetta (1998), we checked the constant values of the five-degree polynomial which shows the density of cancer cells at a steady state. In the four treatment conditions, we get a condition that the value of constant \( A \to \epsilon \), \( A \) has the order epsilon when compared to other constants. We can analyze the fifth-degree polynomial of cancer cell density in terms of:

\[ \epsilon y^5 + b_1 y^4 + b_2 y^3 + b_3 y^2 + b_4 y + b_5 = 0 \quad (1) \]

The root search problem above is a singular perturbation problem. This is because when \( \epsilon = 0 \), the polynomial only has four roots, while the original has five roots. So that the root search is not sufficiently approximated by the Naive expansion. However, the search roots require a combination of the Naive expansion technique and the dominant balance technique. Using the Naive expansion, in the first series, we find a polynomial of degree four. In finding the root of a quartic polynomial, we use formula in Wolfram. In the following, we describe theorems regarding the existence of cancer cell density at steady state as a component of the infected equilibrium point.

**Theorem 1.** (The existence of the Infected equilibrium points) The System have a maximum of 5 non-free equilibrium points.

**Proof of Theorem 1.** The existence of a non-free equilibrium point is obtained from the presence of cancer cells in a steady state, if the cancer cells are in the range of \( (0, 1/b) \) then the non-free equilibrium point exists. The existence of cancer cells in a steady state is the root of equation, which is degree five or quintic polynomial which have not analytical roots. Using perturbation theory, we find the roots.

Suppose the polynomial root is

\[ y = y_0 + \epsilon y_1 + \ldots \quad (1) \]
Substitute into polynomial, we get:

\[0(1): b_1 y_0^4 + b_2 y_0^3 + b_3 y_0^2 + b_4 y_0 + b_5 = 0 \] (1)

\[O(\varepsilon): 4 b_1 y_0^3 y_1 + y_0^5 + 3 b_2 y_0^2 y_1 + 5 b_5 y_1 = 0, \] (1)

\[y_1 = \frac{-y_0^5}{4 b_1 y_0^3 + 3 b_2 y_0^2 + b_5}.\]

The roots are:

\[y_i = y_{0i} + \varepsilon \frac{-y_{0i}^5}{4 b_1 y_{0i}^3 + 3 b_2 y_{0i}^2 + b_5}, \quad i = 1, 2, 3, 4 \] (1)

where \(y_{0i}\) are the roots of

\[b_1 y_0^4 + b_2 y_0^3 + b_3 y_0^2 + b_4 y_0 + b_5 = 0. \] (1)

We use formula in (Wolfram) \(y_{0i}\). We assume that \(b_1 = aa, b_2 = bb, b_3 = cc, b_4 = dd, b_5 = ee\). By using the formula in Wolfram, the roots of the polynomial are:

\[p_{11} = 2cc^3 - 9bbccdd + 27aadd^2 + 27bb^2ee - 72aacee\]

\[p_{21} = p_{11} + \sqrt{-4(cc^2 - 3bbdd + 12aacee)^3 + p_{11}^2}, \] (1)

\[p_{31} = \frac{cc^2 - 3bbdd + 12aacee}{3aa} + \frac{\sqrt{21}}{3aa}, \] (1)

\[p_{41} = \frac{bb^2}{4aa^2} - \frac{4cc}{3aa} + p_{31}\]

\[p_{51} = \frac{bb^2}{4aa^2} - \frac{3aa}{3aa} - p_{31} \] (1)

\[p_{61} = \frac{-bb^3}{aa^3} + \frac{4bbcc}{aa^2} - \frac{8dd}{aa} \] (1)

The roots of polynomial on \(y_{0i}\) are

\[y_{01} = \frac{-bb}{4aa} - \frac{p_A}{2} + \sqrt{\frac{p_5 + p_6}{2}} \] (1)

\[y_{02} = \frac{-bb}{4aa} - \frac{p_A}{2} - \sqrt{\frac{p_5 + p_6}{2}} \] (1)
So we get

\[
y_{03} = \frac{-bb}{4aa} + \frac{p_4}{2} - \frac{\sqrt{p_5 + p_6}}{2}
\]

\[
y_{04} = \frac{-bb}{4aa} + \frac{p_4}{2} + \frac{\sqrt{p_5 + p_6}}{2}
\]

For \( y_1 \in (0, \frac{1}{b}) \) then non-free equilibrium points exist they are \( e^*(E^*, T^*, I^*) = \left( \frac{1}{a}(1 - by_1(1 + y_1)), y_1 \right) \), i.e \( \mu_3 \) \( (g_3 + y_1)(p_2xy + s_2(g_3 + y_1)), i = 1, 2, 3, 4 \) Because the number of polynomial roots are 5 roots, there will be one root missing. This problem is a singular perturbation, so it is necessary to rescale \( y \) with \( y = \varepsilon^a \bar{y} \) so that Equation became:

\[
e^{5\alpha + 1\bar{y}} + b_1\varepsilon^{4\alpha_{-a}^4} + b_2\varepsilon^{3\alpha_{-a}^3} + b_3\varepsilon^{2\alpha_{-a}^2} + b_4\varepsilon^a\bar{y} + b_5 = 0.
\]

By using dominant balance technique, the value of \( \alpha \) will be determined so that it maintains the original polynomial nature (looking for consistent rescale) with a balancing technique for all possibilities. By doing all the possibilities in the selection of \( \alpha \), the appropriate \( \alpha \) is \( 5\alpha + 1 = 4\alpha \) i.e \( \alpha = -1 \). This is obtained by using the principle of dominant balance which assumes that the dominant one is \( \varepsilon^{5\alpha + 1}\bar{y} \) and \( b_2\varepsilon^{4\alpha_{-a}^4} \), so the other terms must be smaller than the dominant term. Because at rescale \( \alpha = -1 \) with the dominant term is \( \varepsilon^{-4}\bar{y}^5 + b_1\varepsilon^{-4}\bar{y}^4 \) and the other terms are \( b_2\varepsilon^{-3}\bar{y}^3 + b_3\varepsilon^{-2}\bar{y}^2 + b_4\varepsilon^{-1}\bar{y}^1 + b_5 \) is smaller than the dominant term so this rescale is consistent.

We get

\[
e^{-4}\bar{y}^5 + b_1\varepsilon^{-4}\bar{y}^4 + b_2\varepsilon^{-3}\bar{y}^3 + b_3\varepsilon^{-2}\bar{y}^2 + b_4\varepsilon^{-1}\bar{y}^1 + b_5 = 0.
\]

If Equation (4.7) multiply by \( \varepsilon^4 \), then we have

\[
\bar{y}^5 + b_1\bar{y}^4 + b_2\varepsilon\bar{y}^3 + b_3\varepsilon^2\bar{y}^2 + b_4\varepsilon^3\bar{y} + b_5\varepsilon^4 = 0.
\]

Using expansion series, we get:

\[
O(1): \bar{y}^5_0 + b_1\bar{y}^4_0 = 0, \bar{y}_0 = -b_1
\]

\[
O(\varepsilon): 5y_1y_0^4 + (4b_1y_1 + b_2)y_0^3 = 0
\]

\[
5y_1 - b_1 + 4b_1y_1 + b_2 = 0, y_1 = \frac{b_2}{b_1}
\]

So we get

\[
\bar{y} = -b_1 + \varepsilon \frac{b_2}{b_1}.
\]

where the initial polynomial root is

\[
y = \varepsilon^{-1} \bar{y}
\]

\[
y = \varepsilon^{-1} \left( -b_1 + \varepsilon \frac{b_2}{b_1} \right)
\]
\[ y = \frac{-b_1}{\varepsilon} + \frac{b_2}{b_1} \]

The infected equilibrium point is

\[ e^*(E^*, T^*, I^*) = \left( \frac{P}{d} \right)^2 \left( 1 - \frac{b_2}{b_1} \frac{-b_1}{\varepsilon} \right) \left( 1 + \frac{b_2}{b_1} \frac{-b_1}{\varepsilon} \right), \]

for \( T^* \in (0, \frac{1}{b_1}) \).

This value of \( y \) possible to exist because it maybe produces a positive root. There is one possible addition of infected equilibrium points from the re-scaling process. It can be concluded that the maximum number of infected equilibrium points (if exist) are five, four of them are roots of polynomial using Naive expansion. The others one is from dominant balance technique. \( y \) is the density of cancer cells in equilibrium. Thus, the number of infected equilibrium points refers to the \( y \) value. □

By applying the perturbation method, we can show the existence of all the non-free equilibrium point analytically. The application of the Theorem 1, we have polynomial of the cancer cells in steady state condition of immune cancer model \( 0.00000729y^5 - 0.1458616170y^4 + 0.78y^3 - 0.5y^2 - 0.42y - 0.41 = 0 \). We solve the roots by two methods they are analytical method (perturbation) and numerical method (Newton Raphson). We have three positives roots and two complex roots. The results show in Table 1.

<table>
<thead>
<tr>
<th>No.</th>
<th>( \varepsilon )</th>
<th>Newton Raphson</th>
<th>Singular Perturbation</th>
<th>Absolute Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.000000729</td>
<td>0.722468</td>
<td>0.7224 - ( \varepsilon ) ( 0.33 = 0.722 )</td>
<td>0.000468/0.722 = 0.0468%</td>
</tr>
<tr>
<td>2</td>
<td>0.000000729</td>
<td>5.887</td>
<td>5.8871 - ( \varepsilon ) 183.4 = 5.885</td>
<td>0.002/5.885 = 0.033%</td>
</tr>
<tr>
<td>3</td>
<td>0.000000729</td>
<td>20003.10</td>
<td>0.14586/5.3475 = 20008.2</td>
<td>5.1/20008.2 = 0.025%</td>
</tr>
</tbody>
</table>

Table 1 shows that roots solutions of the quintic polynomial where the leading coefficient has the epsilon order using both analytical method (singular perturbation method) and the numerical method (Newton Raphson) are not much different. The relative error rate is less than 0.04%. Next, we discuss the bifurcation through the eigenvalues of the linear system and its numerical solutions.

**Bifurcation of infected equilibrium and numerical solutions**

This numerical simulation refers to the results of the previous theorem that the maximum infected equilibrium points are five, but the researchers will only focus on the positive equilibrium. We apply the combination method of Naive and dominant balance. The simulation below is carried out by analyzing the treatment. All parameter values are similar for all simulations except the antigenicity and treatments following the (Kirschner and Panetta, 2008). In the analysis of the stability of the cancer-free equilibrium point, the equilibrium point with ACI treatments and ACI and Cytokine is probably stable. Adequate ACI therapy induces the emergence of a stable cancer-free equilibrium point. In this analysis, we select a case where the overall state of the cancer-free equilibrium point is unstable. So, we can give an idea if the therapeutic dose given is insufficient how the cancer cell infection is. Whether antigenicity can eliminate cancer cells with less immunotherapy doses, as well as how bifurcation due to the effect of antigenicity and treatment will be explained through numerical simulations.
The ACI and Cytokine treatments
The simulation is carried out by taking the initial value around each non-free equilibrium point. After that, determine its stability by checking the real part of the eigen values at each existing equilibrium point. In each case, we simulate from very low to high antigenicity cases.

Figure 1(a) shows that in the case of very low antigenicity, it will have four equilibrium points, one of which is cancer-free point, and else are three infected equilibrium points. In the case of very low antigenicity 0.00001 (10000 days to recognize cancer cells), it has one unstable cancer-free equilibrium point and two unstable infected equilibrium points and one stable infected equilibrium point. In this situation, despite having received two immunotherapies at low doses, if the patient has a severe cancer then incurable. This is because the only one equilibrium point is stable, that point is the infected equilibrium point where the number of cancer cells has almost reached the limit capacity.

Figure 1(b) show the antigenicity is 0.0001 (10000 day to recognize cancer cells) and 0.001 (1000 day to recognize cancer cells) show the similar behavior. Both have an unstable infected equilibrium point with a cancer cell count of about ten percent of the threshold capacity. Both show that the two points of infected cancer equilibrium points are unstable. They differ only in the number of cancer cells in a steady state, where the greater the antigenicity, the less the cancer cells. In this state, it means that we cannot find a condition in which cancer cells will be lost in the body.
Figure 1(c) in cases with moderate (0.01 that means effector cells need 100 day to recognize cancer cells) to high (0.1 that means effector cells need 10 day to recognize cancer cells) antigenicity on Figure 1(d) both have two equilibrium points: one cancer free and the other infected. In the antigenicity is medium (0.01), the number of cancer cells reaches about one percent of the limit capacity. Both treatments in this state in low doses. If a patient has high antigenicity even though he has a large number of cancer cells, it does not lead to cancer severity. This is mathematically shown by the absence of an equilibrium point being infected with a high number of cancer cells. In this situation an interesting phenomenon appears, namely the emergence of a periodic solution. The state of the cancer cells returns to the same period over a period of about 200 days, and fluctuates for about 10 days.

This phenomenon is mathematically interesting which will induce further analytical research, namely the emergence of periodic solutions. At increased antigenicity (0.1), the instability of the infected point was lost. The point of infection will be stable but with a low number of cancer cells, which is about 1 percent of the limit capacity.

The ACI treatments
In the case that only ACI is given, in general the number of equilibrium points depending on the change in antigenicity gives the same results as if the two treatments were given. In this case the dose of ACI given is the same as during the 2 treatments, but in this case without cytokine therapy. Giving ACI alone will trigger effector cell growth faster than if two treatments were given.

![Figure 2(a)](image1)

![Figure 2(b)](image2)

![Figure 2(c)](image3)

![Figure 2(d)](image4)

**Figure 2.** The antigenicity 0.00001 (a), The antigenicity 0.001 (b), The antigenicity 0.01 (c), and The antigenicity 0.1 (d).

Figure 2(a) in the case of ACI given in minimal doses, where the patient has very low antigenicity (Effector cells need 100000 days to recognize cancer cells), the cancer cells will
continue to grow. This is supported by the emergence of an infected equilibrium point where the number of cancer cells has almost reached its limit capacity (10000 it means 1000000 cells). If the initial state of cancer cells around 10 % of maximum capacity then the cancer cells will reach their limit capacity. Figure 2. (b) in this state both have one unstable equilibrium point and an unstable infected equilibrium point. Figure 2. (c) show the instability of infected equilibrium points while look like the existence of periodic solutions.

Figure 2(d) illustrates that, very high antigenicity 0.1 (effector cells need 10 days to recognize cancer cells) triggers the emergence of a stable infected equilibrium point but in small number of cancer cells. If the patient only gets ACI therapy, if it has very high antigenicity, the cancer cells can be controlled to a very small number, less than 1 % of the maximum cancer cell capacity in the tissue. However, the patient must be careful, before reaching stability, cancer cells have increased and decreased quite rapidly in a sufficient span of time. So that patients must be able to go through this period to be able to control cancer cells in the body.

The Cytokine treatments
In the case of cytokine-only therapy, the cancer-free state never reaches stability. This indicates that the cytokine solution is not sufficiently administered alone to obtain the condition for the detachment cells to be removed from the body.

![Figure 3](image1)

![Figure 3](image2)

Figure 3. The antigenicity 0.00001 (a), The antigenicity 0.001 (b), The antigenicity 0.01 (c), and The antigenicity 0.1 (d).

Figure 3. (a) in very low antigenicity 0.00001(100000 days to recognize cancer cells) and low cytokine doses, triggers the emergence of a stable infected equilibrium point with the number of cancer cells almost reaching the limit capacity of cancer cells in the tissue, which is about 90%. person. The other two equilibrium points also show the high rate of cancer cells in the body and never the emergence of cancer-free stability from cytokines alone. In this condition, the patient needs to increase the antigenicity or increase the dose so that the cancer cells can be controlled.
Using perturbation theory to explain the existence of infected equilibrium points (Saptaningtyas, Aryati, Adikusumo, van Horssen)
At low antigenicity of 0.0001 to 0.001, all cases have a cancer-free equilibrium point that is unstable and one unstable infected. This situation leads to a situation that is still dangerous for the patient. This is supported by the emergence of an infected equilibrium point with about 10 percent of the limit capacity of cancer cells.

At medium antigenicity of 0:01, cancer cells began to be controlled with each type of treatment given. Although there is no stable positive equilibrium point, the number of cancer cells in the body is very low. In the case of medium antigenicity, there is an eigenvalue with a very small positive real number and a phenomenon such as a periodic solution appears at each given treatment.

At high antigenicity, a stable positive infected equilibrium point appears. The infected equilibrium point is headed toward zero. The high antigenicity in each type of treatment indicates that cancer cells can be well controlled even though they will not be lost in the body. Antigenicity is a very important factor in the mechanism of controlling cancer cells in the body. The results of the analysis and simulation are in line with the results of (Kirchner and Panetta,1998). In the numerical simulation also appears the phenomenon of periodic solutions which in calculating the eigenvalues is unstable. This can lead to the emergence of a butterfly phenomenon like in the case of Lorentz, a system that initially seems stable but over a long period of time loses stability.

**Conclusion**

We can find non-zero analytical solutions for cancer cells at equilibrium with the singular perturbation method. We also provide comparisons with numerical calculations where the difference in root solution between the analytical and numerical methods is less than 1 percent. ACI or cytokine therapy alone is not sufficient to eliminate cancer cells under ideal circumstances. In the case of moderate antigenicity, the emergence of a phenomenon such as a periodic solution that loses stability over time is interesting to study further.

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