Stability and Persistence Analysis of Mathematical Model of BCG Immunotherapy in Superficial Bladder Cancer

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Abstract

Bladder cancer arise as a result of abnormal growth of bladder cells. One of bladder cancer treatments is by administering Bacillus Calmette Guerin (BCG) intravesica. BCG is an attenuated microbial bacteria and is a clinical procedure that is used for the treatment of superficial bladder cancer. In this paper, we used a mathematical model of BCG immunotherapy from bladder cancer for stability analysis around the point of equilibrium. Furthermore, we performed existence analysis and uniqueness, this shows the system has a solution and unique, and it is a dynamic system so it can be said the system is in a well-posed state. Furthermore, we performed persistence analysis to determine the effect of BCG immunotherapy transmission on the system. The end result obtained from this paper is stability analysis show that side effect equilibrium is locally stable with all eigen value having negative real parts and cancer equilibrium is unstable and persistence analysis obtained strongly persistent uniform, this suggests that distance between BCG...
with uninfected cancer cells with maximum BCG cause transmission of BCG immunotherapy increased, so it can destroy cancer cells.

**Mathematics Subject Classification:** 35B35

**Keywords:** superficial bladder cancer, BCG immunotherapy, stability analysis, persistence analysis

1 Introduction

The bladder is a hollow muscular organ located in an area surrounded by the hip bones, an area called the pelvis. The bladder serves as a dam to collect urine from the kidneys. The bladder epithelium consist of transitional cell. Transitional cell can become abnormal form a kind of wart on the wall of the bladder and cause bladder cancer [1]. One of modality treatment is immunotherapy, the immune system is a powerful weapon to face bladder cancer and activated by Bacillus Calmette Guerin (BCG) vaccine. Developments in science, particularly in mathematics provides an important role in many diseases. Many mathematical models to anticipate and reduce the presence of disease, such as tumor diseases, cancer, and another diseases. Kirschner [2] explained through mathematical models, the dynamic relationship between tumor cells, immune cell-effector, and cytokine interleukin-2 (IL-2). Mendrazitsky [1] discussed the stability analysis of mathematical models of BCG immunotherapy in bladder cancer. The purpose of this research is to develop the first mathematical model that describes the interaction of the immune system in bladder cancer as a result of BCG therapy. Hariyanto [3] discussed analysis of persistence and positive solution is based on construction parameter obtained from the dynamic analysis of model. Rohmah [4] explained analysis of persistence used to know the influence of Phatogenesis and the Virulence virus in two countries.

In this paper, the analysis of this mathematical model uses stability analysis by comparing BCG, effector cells, infected cancer cells, and uninfected cancer cells. To know which is more dominant between BCG with uninfected cancer cells using persistence analysis. Then at the end will be done simulation using MATLAB software.

2 Preliminary Notes

In this section, we will show the definition related with this paper. In this paper used mathematical model of BCG immunotherapy in superficial bladder cancer of Mendrazitsky [1]. Where this research is to develop the first
mathematical model that describes the interaction of the immune system in bladder cancer as a result of BCG therapy. The model equations here specified with exponential cancer growth.

\[
\frac{dB}{dt} = -B - p_1 EB - p_2 BT_u + b
\]

\[
\frac{dE}{dt} = -\mu E + p_4 EB - p_5 ET_i + \alpha T_i
\]

\[
\frac{dT_i}{dt} = -p_3 ET_i + p_2 BT_u
\]

\[
\frac{dT_u}{dt} = -p_2 BT_u + rT_u
\]

On this model the population is divided into four subpopulations that is BCG subpopulation \((B)\), effector cells subpopulation \((E)\), infected cancer cells subpopulation \((T_i)\), and uninfected cancer cells subpopulation \((T_u)\). The rate of change BCG influenced by rate of BCG killed by effector cells \((p_1)\), infection rate of cancer cell by BCG \((p_2)\), and bio effective concentration of BCG \((b)\).

The rate of change effector cells influenced by cell death rate \((\mu)\), immune response activation rate \((p_4)\), rate of \(E\) deactivation after binding with infected cancer cells \((p_5)\), and rate of \(E\) stimulation due to infected cancer cells \((\alpha)\).

The rate of change infected cancer cells influenced by rate of destruction of infected cancer cells by effector cells \((p_3)\) and infection rate of cancer cell by BCG \((p_2)\). And the rate of change uninfected cancer cells influenced by infection rate of cancer cell by BCG \((p_2)\), cancer growth rate \((r)\).

Proportion of model are conducted to emphasize the evolution of the model were observed. Suppose BCG make contact with effector cells \((p_1 EB)\) with proportion of \(\lambda_1\) and BCG make contact with uninfected cancer cells \((p_2 BT_u)\) with proportion of \(\lambda_2\). For effector cells subpopulation, suppose effector cells make contact with BCG \((p_4 EB)\) with proportion of \(\lambda_3\), effector cells make contact with infected cancer cells \((p_3 ET_i)\) with proportion of \(\lambda_4\) and number of effector cells stimulation due to infected cancer cells \((\alpha T_i)\) with proportion of \(\lambda_5\). For infected cancer cells subpopulation, suppose infected cancer cells make contact with effector cells \((p_3 ET_i)\) with proportion of \(\lambda_6\) and BCG make contact with uninfected cancer cells \((p_2 BT_u)\) such that the number of infected cancer cells increase with proportion of \(\lambda_2\). For uninfected cancer cells subpopulation, suppose uninfected cancer cells make contact with BCG \((p_2 BT_u)\) with proportion of \(\lambda_3\).

The result of the proportion of equation (1) can be formed as follows.

\[
\frac{dB}{dt} = -B - \lambda_1 B - \lambda_2 B + b
\]

\[
\frac{dE}{dt} = -\mu E + \lambda_3 E - \lambda_4 E + \lambda_5 E
\]

\[
\frac{dT_i}{dt} = -\lambda_3 T_i + \lambda_2 T_i
\]
\[ \frac{dT_u}{dt} = -\lambda_2 T_u + r T_u \]  

(2)

The system is called well posed if it satisfy the existence and uniqueness and the model is dynamic system.

To show that the model has well posed used definition as follows.

**Existence and Uniques** In this section, to show the validation of a model can be determined by existence and uniqueness. To show existence and uniqueness of the function required Lipschitz constants as follows.

Suppose function \( f(t, y_1, y_2, y_m) \) defined in the set \( D = \{(t, u_1, u_2, u_m) | a \leq t \leq b \} \) and \( -\infty < u_i < \infty, \forall i = 1, 2, \ldots, m \} \) according satisfies Lipschitz condition at \( D \) in variable \( u_1, u_2, u_m \) if there is \( L \) constant with

To show about existence and uniqueness solution of the model, then the following lemma can be used.

**Lemma 2.1** Lipschitz constant in equation model (2) is obtained \( k(t)_{\text{max}} = \{(1 - \lambda_1 - \lambda_2)_{\min}, |(\lambda_3 + \lambda_5)_{\max} -(|\mu + \lambda_4)_{\min}|, |(\lambda_2)_{\max} - (\lambda_2)_{\min}|, |(r)_{\max} - (\lambda_2)_{\min}| \}

Lipschitz constant is constructed based on parameter \( (1 + \lambda_1 + \lambda_2)_{\max} \) is change rate from \( B \). \( (\lambda_1)_{\max} \) is rate of BCG contact and interaction with effector cells. \( (\lambda_2)_{\max} \) is rate of BCG contact and interaction with cancer cells. \( k_2(t) \) is constructed based on parameter \( (r)_{\max} - (\lambda_2)_{\min} \) is change rate from \( T_u \). \( (r)_{\max} \) is cancer cells growth rate.

**Proof.**

Using definitions which states that any solution of the system model can be expressed in matrix norm and rely on Lipschitz constant \( k(t) \) for each \( t \in R \).

\[
\|f(X^1(t), t) - f(X^2(t), t)\| = \begin{bmatrix} a_{11} \\ a_{21} \\ a_{31} \\ a_{41} \end{bmatrix} = \|b_{11} + c_{11}\|
\]

\[
\|f(X^1(t), t) - f(X^2(t), t)\| \leq \|b_{11}\|, \text{ so that}
\]

\[
\begin{bmatrix} a_{11} \\ a_{21} \\ a_{31} \\ a_{41} \end{bmatrix} \leq \begin{bmatrix} (1 - \lambda_1 - \lambda_2) & (B_1 - B_2) \\ (\mu + \lambda_3 - \lambda_4 + \lambda_5) & (E_1 - E_2) \\ (\lambda_6 + \lambda_2) & (T_1 - T_2) \\ (\lambda_2 + r) & (T_1 - T_2) \end{bmatrix}
\]

So, \( \|f(X^1(t), t) - f(X^2(t), t)\| \leq k(t)\|b_{11}\| \)

Then can be determined Lipschitz constant is \( k(t) \). \( k(t) \) is the Lipschitz constant of the model, so

\[
\|b_{11}\| = \max_{1 \leq i \leq n}
\]

Then

\[
|b_{11}| \leq \max_{i} \{ |(1 - \lambda_1 - \lambda_2)|, |(\mu + \lambda_3 - \lambda_4 + \lambda_5)|, |(-\lambda_6 + \lambda_2)|, |(-\lambda_2 + r)| \}
\]

\[
|b_{21}| \leq \max_{i} \{ |(1 - \lambda_1 - \lambda_2)|, |(\mu + \lambda_3 - \lambda_4 + \lambda_5)|, |(-\lambda_6 + \lambda_2)|, |(-\lambda_2 + r)| \}
\]

\[
|b_{31}| \leq \max_{i} \{ |(1 - \lambda_1 - \lambda_2)|, |(\mu + \lambda_3 - \lambda_4 + \lambda_5)|, |(-\lambda_6 + \lambda_2)|, |(-\lambda_2 + r)| \}
\]
So that it can be written as follows:

\[
|b_{41}| \leq \max_i \{ |(-1 - \lambda_1 - \lambda_2)|, |(-\mu + \lambda_3 - \lambda_4 + \lambda_5)|, |(-\lambda_6 + \lambda_2)|, |(-\lambda_2 + r)| \}
\]

or

\[
\begin{bmatrix}
(-1 - \lambda_1 - \lambda_2) & (B^1 - B^2) \\
(-\mu + \lambda_3 - \lambda_4 + \lambda_5) & (E^1 - E^2) \\
(-\lambda_6 + \lambda_2) & (T^1_i - T^2_i) \\
(-\lambda_2 + r) & (T^1_u - T^2_u)
\end{bmatrix}
\]

\[
\leq \max_i \{ |(-1 - \lambda_1 - \lambda_2)|, |(-\mu + \lambda_3 - \lambda_4 + \lambda_5)|, |(-\lambda_6 + \lambda_2)|, |(-\lambda_2 + r)| \}
\]

\[
= \max_i \{ (B^1 - B^2), (E^1 - E^2), (T^1_i - T^2_i), (T^1_u - T^2_u) \}
\]

and obtained

\[
k(t)_{\max} = \{ |(-1 - \lambda_1 - \lambda_2)_{\min}|, |(\lambda_3 + \lambda_5)_{\max} - (\mu + \lambda_4)_{\min}|, |(\lambda_2)_{\max} - (\lambda_6)_{\min}|, |(r)_{\max} - (\lambda_2)_{\min}| \}
\]

In this section, to show that the system is a dynamic system that is with function mapping. To show that system is dynamic system used

**Definition 2.2 Continuous Function.**

The continuous flow \( F = (X, R, \pi) \) at \( X \), where \( \pi : X \times R \to X \) is continuous mapping such that \( \pi(x, 0) = x \) for all \( x \in X \) and \( (\pi(\pi(x, t)), s) = \pi(x, t + s) \) for all \( x \in X \) and \( t, s \in R \) [5].

After determining that the system is well posed it will be described how to get the equilibrium point of the model. The equilibrium point is a state of a system that does not change with time. If the dynamic system is described in the differential equation, then the equilibrium point can be obtained by taking the first derivative equal to zero.

**Definition 2.3 Equilibrium Point.**

Point \( x^* \in \mathbb{R}^n \) is called the equilibrium point of \( \dot{x} = F(x) \) if satisfy \( F(x^*) = 0 \), where

\[
F(x) = \begin{bmatrix}
F_1(x_1, x_2, \ldots, x_n) \\
F_2(x_1, x_2, \ldots, x_n) \\
\vdots \\
F_n(x_1, x_2, \ldots, x_n)
\end{bmatrix}
\]

\[ [6] \]

After getting the equilibrium point then described about the stability analysis on the model. Then, explained about persistence. Persistence is an important
feature of dynamic system modeling, ecological system and epidemics. Persistence discusses the long term viability of some or all of the system components, besides persistence also relates to the limits of growth for some components of the system. To show persistence analysis used definition, as follows:

**Definition 2.4 Persistence.**

1. If there $\epsilon_0 > 0$ such that for all $x \in \Omega \lim_{t \to \infty} \inf d(\pi(x,t), \partial C) > \epsilon_0$ then flow of $F$ is strongly uniformly persistent.

2. If there $\epsilon_0 > 0$ such that for all $x \in \Omega \lim_{t \to \infty} \sup d(\pi(x,t), \partial C) > \epsilon_0$ then flow of $F$ is weakly uniformly persistent. [7]

### 3 Main Results

In this section, we will show the result related to stability and persistence analysis. We have some step to show the result. Thus, we have a conclusion about stability and persistence analysis to discuss as follows

3.1. Well Posed

To show about existence and uniques solution of the model, used definition which states that any solution of the system model can be expressed in matrix norm and rely on Lipschitz constant $k(t)$ for each $t \in R$. Lemma 2.1 is obtained as follows:

If $k_1(t) = (1 + \lambda_1 + \lambda_2)_{max}$ and $k_2(t) = (r)_{max} - (\lambda_2)_{min}$ then $k_1(t)$ is constructed based on parameter $(1 + \lambda_1 + \lambda_2)_{max}$ is change rate from $B$. $(\lambda_1)_{max}$ is rate of BCG contact and interaction with efector cells. $(\lambda_2)_{max}$ is rate of BCG contact and interaction with cancer cells. $k_2(t)$ is constructed based on parameter $(r)_{max} - (\lambda_2)_{min}$ is change rate from $T_u$. $(r)_{max}$ is cancer cells growth rate.

1. If $k_1(t) < k_2(t)$ then number of BCG who make contact with cancer cells and efector cells bigger than growth of cancer cells as the result is defeat of cancer cells.

2. If $k_1(t) > k_2(t)$ then growth of cancer cells is bigger than number of BCG contact with cancer cells and efector cells as the result is defeat of BCG.

On the above analysis has shown that Lipschitz constant of a mathematical model of immunotherapy BCG is $k_1(t)$. 
Stability and persistence analysis

3.2. Stability Analysis

To show that the model is dynamic are discussed below. Contraction of a mathematical model of BCG immunotherapy in superficial bladder cancer. Immunotherapy of cancer cells are developed through contact and interaction between BCG to cancer cells. Suppose X metrics space with metric d and the set of continuous function $C(\Omega, R) = (B(x, t) \subset X, \phi_t(x, t) \in C(\Omega, R))$ and $G=(C, R, \pi)$ are continuous flow at $C(\Omega, R)$ is expressed as $\pi : C(\Omega, R) \times R \rightarrow C(\Omega, R)$ such that for all $\phi \in C(\Omega, R)$ and for all real numbers $s, t \in R$ applicable $\pi(\phi(x, t), 0) = \phi(x, t)$ and $\pi(\pi(s, \phi(x, t)), t) = \pi(\phi(x, t), t + s)$ [6].

Considering the solution as follows.

$B(x, t) = e^{(1+\lambda_1+\lambda_2)t}B(x, 0)$ moving from one location to other location on interval $t_1 \leq t \leq s$, if $\pi(B(x, t), 0) = B(x, t)$ is completion of construction of model then $B(x, t)$ is continuous flow of global if satifies $\pi(\pi(B(x, t), t_1), s) = \pi(B(x, t), t_1 + s)$. Therefore $B(x, t)$ moves in the interval $0 \leq t \leq t_1 + s$ can be obtained

$B(x, t_1+s) = B(x, t_1)e^{1+\lambda_1+\lambda_2)t} < B(x, t_1) \text{ or } \pi(B(x, t), t_1+s) = \pi(\pi(B(x, t), t_1), s).$

Suppose $B(x, t)$ moves at interval $0 \leq t_1 + s \leq t$ or $0 \leq t_1 \leq t - s$ before $t$ so $B(x, t - s) = (e^{-(1+\lambda_1+\lambda_2)t}B(x, 0))$, therefore $B(x, t)$ moves before BCG period there will be an increase immunotherapy to against cancer cell, so that

$B(x, t - s) = e^{-(1+\lambda_1+\lambda_2)t}B(x, t) = \pi(\pi(B(x, t_1), t), s)$

and obtained

$\pi(\pi(B(x, t_1), t), s) = \pi(B(x, t_1), t-s) \text{ or } \pi(\pi(B(x, t), t_1), s) = \pi(B(x, t), t_1 + s).$

Thus it can be shown that uninfected cancer cells subpopulation is a continuous flow of global. On the above analysis has shown that the construction of a mathematical model of immunotherapy BCG is well posed.

3.2. Stability Analysis

The following section provide a stability analysis of the model nonnegative equilibria. When analyzing the stability of each equilibrium of the equation (1), on examines the Jacobian as follows [1].

$$J = \begin{bmatrix} -1 - p_1 E^* - p_2 T_u^* & -p_1 B^* & 0 & -p_2 B^* \\ p_4 E^* & -\mu + p_4 B^* - p_5 T_i^* & -p_5 E^* + \alpha & 0 \\ p_2 T_u^* & -p_3 T_i^* & -p_3 E^* & p_2 B^* \\ -p_2 T_u^* & 0 & 0 & -p_2 B^* + r \end{bmatrix}$$

**Side Effect Equilibrium** $P_{11}(\frac{\mu}{p_4}, \frac{bp_4}{\mu p_1} - \frac{1}{p_1}, 0, 0)$

Side Effect means before BCG therapy only low numbers of leukocytes can be detected in the bladder. After repeated BCG instillation, the
influx of different types of effector cells (macrophages, lymphocytes) that aim to kill cells infected with BCG is observed [8]. Often this transient behavior subsides with time [9]. Sometimes, BCG may invoke a widespread immune response. This in turn may cause troubling systemic side effects: high fever, malaise and rarely an immune related lung inflammation [11]. The eigen values of the Jacobian matrix are:

\[ \lambda = \left[ \frac{-b_1}{\mu}, \frac{p_3(\mu-b_1)}{\mu p_1}, -\frac{p_2\mu+p_3\mu}{p_4}, 1 - \frac{b_1-\sqrt{b_1^2+b_2^2+4\mu^3-4b_1\mu^2}}{\mu} \right] \]

On the above has shown that stability analysis of side effect equilibrium is locally stable with all eigen values having negative real parts.

**Cancer Equilibrium**

\[
P_2\left( \frac{r}{p_2}, \frac{r T_u}{p_3 T_1}, \frac{1}{2\alpha p_2 p_3} \right) (\alpha r p_1 - r p_5 + b p_2 p 5 + \sqrt{(-\alpha r p_1 - r p_5 + b p_2 p 5)^2 + 4\alpha (bp_2^2 + r bp_2 p_4 + r^2 p_4 - p_2 r p_5)}), \frac{b_2 - r}{p_2 p_3 T_1 + r} \cdot T_u \]

Eigen value in cancer equilibrium can not searched manually thus obtained with numeric simulation which mean unstable.

### 3.3. Persistence Analysis

To show the persistence on the system, defined on weakly uniformly persistent and strongly uniformly persisten [7].

To defined of d metric. Suppose \( T_u(x, t) = \pi(x, t), B(x, t) \in \partial C \) and \( \forall x \in \bar{\Omega} \) so \( (\pi(x, t), \partial C) = (T_u(x, t), B(x, t)) = \int_{\bar{\Omega}} |T_u(x, t), B(x, t)| dx \).

Based on this definition, maximum immunotherapy occurs as a result of cell contact. If limited area with cells who are at the interior area then contact that occurred could pose minimum immunotherapy means cancer cells is attack BCG and there are BCG is small.

Suppose \( B(x, 0) = B(0) e^{(1+\lambda_1+\lambda_2)x} \) and \( T_u(x, 0) = T_u(0) e^{(\lambda_2-r)x} \) so obtained \( B(x, t) = B(0) e^{-(1+\lambda_1+\lambda_2)t} B(0) e^{(1+\lambda_1+\lambda_2)x} \) and \( T_u = T_u(0) e^{-(\lambda_2-r)t} e^{(\lambda_2-r)x} \)

For example in the case, if \( T_u(x, t) < B(x, t) \)

\[
d(T_u(x, t), B(x, t)) = \int_{\bar{\Omega}} |T_u(x, t) - B(x, t)| dx
\]

\[
d(T_u(x, t), B(x, t)) = \int_{\bar{\Omega}} |B(0) e^{-(1+\lambda_1+\lambda_2)t} B(0) e^{(1+\lambda_1+\lambda_2)x} - T_u(0) e^{-(\lambda_2-r)t} e^{(\lambda_2-r)x} | dx
\]

If \( T_u(0) e^{-(\lambda_2-r)t} = W \) and \( B(0) e^{-(1+\lambda_1+\lambda_2)t} = Z \)

then, \( \min \therefore d(T_u(x, t), B(x, t)) = \frac{1}{1 + \lambda_1 + \lambda_2} e^{-(1+\lambda_1+\lambda_2)t+ (1+\lambda_1+\lambda_2)x} B(0)- e^{-(\lambda_2-r)t+(\lambda_2-r)x} T_u(0) \)

\[
\lim_{t \to \infty} \inf d(T_u(x, t), B(x, t)) = \lim_{t \to \infty} \frac{(1+\lambda_1+\lambda_2)x}{1+\lambda_1+\lambda_2} Z
\]
Stability and persistence analysis

\[
\lim_{t \to \infty} \frac{(\lambda_2 - r)x}{(\lambda_2 - r)} W
\]

\[
\lim_{t \to \infty} \inf d(T_u(x,t), B(x,t)) = \frac{(1 + \lambda_1 + \lambda_2)x}{(1 + \lambda_1 + \lambda_2)} Z > \epsilon_0
\]

for any \(T_u(x,t)\) and \(B(x,t)\) there are positive number \(\epsilon_0 = Z\) so \(\lim_{t \to \infty} \inf d(T_u(x,t), B(x,t)) > \epsilon_0 = Z\), thus strongly uniformly persistent on the system. Contact between BCG with cell cancer, that cause cancer cell become infected with BCG. If \(T_u(x,t) < B(x,t)\) then immunotherapy is strongly uniformly persistent, because the distance between contact of BCG and cancer cells is minimum, so immunotherapy is very broad.

Figure 1: Portrait phase in BCG and uninfected cancer cells

Based on Figure 1 is explained that \(x\) is BCG and \(y\) is uninfected cancer cells. In figure 1 obtained the characteristic equation as follows :

\[
\begin{bmatrix}
-1 - s & -6,839 \times 10^{-8} \\
0 & 0,43 - s
\end{bmatrix} = 0
\]

\(\Leftrightarrow (-1 - s)(0,43 - s) = 0\)

Roots of characteristics are :

1. \(s_1 = -1\)
2. \(s_2 = 0,43\)
So the characteristic value is obtained $s_1 = -1 < 0$ and $s_2 = 0.43 > 0$. So in the neighborhood the point of equilibrium $(B^*, T_u^*)$ is unstable.

Next, we will compared the results of persistence analysis with stability analysis as follows. The system in the equilibrium point $(B^*, T_u^*)$ is unstable. The roots of its characteristic are $s_1 < 0$ and $s_2 > 0$ which can destroy cancer cells. To destroy cancer cells then BCG should be greater than uninfected cancer cells. It is related to persistence analysis that is obtained strongly persistent uniform where uninfected cancer cells is smaller than BCG. This shows that cancer cells do not spread in the body so that cancer cells can be destroyed.

Furthermore, we will compared the results of persistence analysis with Lipschitz constants for parameter BCG subpopulation obtained $(1 + \lambda_1 + \lambda_2)$ which led to the comprehensive BCG immunotherapy widely when $(1 + \lambda_1 + \lambda_2)_{maks}$.

Acknowledgements. This is a text of acknowledgements.

4 Simulation

Simulation were performed with the aim of demonstrating the spread of BCG immunotherapy visually, so it is easy to analyze the system based on the analysis obtained from the BCG immunotherapy model. The initial values and parameters used for simulation based on the previous analysis as follows:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$</td>
<td>0.041</td>
</tr>
<tr>
<td>$p_1$</td>
<td>$1.25 \times 10^{-7}$</td>
</tr>
<tr>
<td>$p_2$</td>
<td>$0.285 \times 10^{-7}$</td>
</tr>
<tr>
<td>$p_3$</td>
<td>$1.1 \times 10^{-7}$</td>
</tr>
<tr>
<td>$p_4$</td>
<td>$0.12 \times 10^{-7}$</td>
</tr>
<tr>
<td>$p_5$</td>
<td>$3.45 \times 10^{-7}$</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>0.052</td>
</tr>
<tr>
<td>$r$</td>
<td>0.0033</td>
</tr>
</tbody>
</table>

From Figure 2 it can be seen that BCG subpopulation decreased at day 100, on days 370 until day 2000 BCG subpopulation reached as many as $10 \times 10^5$ cell. The effector cell subpopulation increased from the first day to the 100th day, on the 101st day the effector cell subpopulation was $3.2 \times 10^5$ cells and decreased until day 2000. The subpopulation of BCG-infected cancer cells increased from day one to day 70, on day 71 the subpopulation of BCG-infected cancer cells was $2.7 \times 10^5$ cells and decreased until day 2000. This indicates that
BCG-infected cancer cells can be destroyed by cells Effector. Subpopulations of BCG-uninfected cancer cells increased from day one to day 2, and decreased from day 2 to zero. This situation indicates that cancer cells can be attenuated by means of BCG immunotherapy.

Based on Figure 3 the value of the parameters used to enlarge the immune response activation rate is $1,51 \times 10^{-7}$ and the infection rate of cancer cells by BCG is $0,821 \times 10^{-7}$. It aims to infect a large number of cancer cells and against cancer cells so it can be destroyed.

From Figure 3 it can be seen that on days 50 to 2000 BCG subpopulations become $0,1 \times 10^7$ cells. The effector cell subpopulation increased from the first day to the 200th day, from day 201 to 2000 subpopulations of effector cells of $2,1 \times 10^7$ cells. The subpopulation of BCG-infected cancer cells increased from day one to day 9 to $0,09 \times 10^7$ cells and decreased from day 10 to zero. While the number of subpopulation cancer cells that have not been infected BCG decreased from day one to zero. This situation indicates cancer cells can be attenuated by BCG immunotherapy.

## 5 Conclusion

The result of analysis of the model can be summarized as follows:
Figure 3: Subpopulation changes in the BCG immunotherapy model at $p_2 = 0.821 \times 10^{-7}$ and $p_4 = 1.51 \times 10^{-7}$

1. For an analysis on the existence and uniqueness of the cell that is obtained that into a BCG maximum.

2. For stability analysis on the stability analysis in side effect equilibrium is local stable. Eigen value negative are $\bar{s} = -\frac{bp_3}{\mu}, \frac{p_3(\mu-bp_4)}{\mu p_2}, -\frac{p_2 + p_4 r}{p_4}, \frac{1}{2}b p_4 - \sqrt{b^2 p_4^2 + 4 \mu^3 - 4 p_4 \mu^2}$. All eigen value negative real parts if $bp_4 > \mu, p_2 \mu > p_4 r, p_3 \mu < p_3 b p_4$. Thus, on the stability analysis in cancer equilibrium is unstable. Eigen value in cancer equilibrium can not searched manually thus obtained with numeric simulation.

3. For persistence analysis it can be concluded that the distance between contact of BCG and cancer cells is minimum or very closed, so immunotherapy very broad. It can be concluded there is strongly uniformly persistent on the system.

4. Compared the results of persistence analysis with stability analysis as follows. The system in the equilibrium point $(B^*, T^*)$ is unstable. The root of its characteristic are $s_1 < 0$ and $s_2 > 0$ which can destroy cancer cells. To destroy cancer cells then BCG should be greater than uninfected cancer cells. It is related to persistence analysis that is obtained strongly persistent uniform where uninfected cancer cells is smaller than BCG. This shows that cancer cells do not spread in the body so that cancer cells can be destroyed.
5. Compared the results of persistence analysis with Lipschitz constants for parameter BCG obtained \((1 + \lambda_1 + \lambda_2)\) which led to the comprehensive BCG immunotherapy widely when \((1 + \lambda_1 + \lambda_2)_{\text{max}}\).

References


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