Stability Analysis and Optimal Control of Lung Cancer Growth Model with Education

Trisilowati

1Mathematics Department, Brawijaya University, Indonesia
Corresponding author’s e-mail: trisilowati@ub.ac.id

Abstract. This study discusses the influence of smoking behavior of both active and passive smokers on the growth of lung cancer population through mathematical models. There are four population in this model, namely: susceptible population, active smoker population, passive smoker population, and population of lung cancer patients. The model is then analyzed using stability theory of nonlinear differential equations. Based on analysis result, the model has three equilibrium points: extinction equilibrium point, smoker-free equilibrium point and endemic equilibrium point. These equilibrium points are asymptotically stable under certain conditions. Moreover, education is involved as a control which is applied to susceptible population. The purpose of this optimal control is to minimize the population of smokers and lung cancer as well as the education costs. Pontryagin’s principle is then implemented to solve optimal control problems. Finally, numerical simulations are carried out to determine the effectiveness of the controls used.

1. Introduction

Cancer is not a contagious disease and humans can contract it due to genetic factors, food, lifestyle, and so on. Cancer occurs due to uncontrollable growth of tissues cells which transform into abnormal cells. These cells (malignant cancer) can spread to other tissues and organs in short time and causes death. Based on Globocan, the number of cancer patients has been increasing each year. The most common cancers worldwide is lung cancer with 1.8 million cases or 13% of the total number cases [1]. Several studies about the risks of smoking show that the smokers are 11 times more likely to die from lung cancer than nonsmoker [2]. Passive smokers, people breathing in other people tobacco’s smoke, also get risk of getting lung cancer. Some research reported that passive smokers are 20% - 30% more likely to develop lung cancer [3].

Mathematical model can describe the interaction among passive smoker, active smoker and lung cancer patient. Numbers of mathematical model have been proposed on smoking behavior and lung cancer [4-8]. In 2000, Acevedo-Estefania et al. constructed the model to describe the interaction among the smoker, nonsmoker and lung cancer patient [9]. In 2011, Samanta established the model explaining the smoking behavior as a non autonomous dynamic system with time-delay. Then, the global stability analysis of the system was solved by using Lyapunov function [10].

Different from Acevedo-Estefania et al. and Samanta, in 2016 Sutantiati developed a model describing the behavior of active smoker, passive smoker and the effect on lung cancer patient [11]. In the model, it was assumed that susceptible population grows exponentially. Moreover, the interaction among active smoker and passive smoker does not increase the number of active smoker directly. Analysis result and numerical simulation show that the rate of active smoker affects on the spread of lung cancer patient. Next, Wardah modified Sutantiati’s model so that it became more realistic [12].

There are some treatments to inhibit the cancer growth such as chemotherapy, radiotherapy and...
immunotherapy. One of methods to suppress the growth of lung cancer patient is by giving the education to the susceptible population. Some studies about optimal control problem have been applied on the model of tumor, disease epidemic model and vector-host [13-15]. Itik et al. [16] and Engelhart et al. [17] used control optimal to cancer model with chemotherapy, while other controlled the cancer growth with immunotherapy related to the interaction between cancer and immune system [14,18].

In this study, the lung cancer growth model because of smoking is discussed. The model constructed by Wardah [12] is going to be modified by involving education as the control. Optimal control will be applied on the model to minimize the number of smokers and lung cancer patient as well a the control cost. Furthermore, the existence of the solution of optimal control problem will be analyzed. Finally, numerical simulations are given to illustrate the analysis result.

2. Mathematical model
Model of the spread of lung cancer has been constructed by some researchers, for example as in [11]. Next, Wardah modified Sutantiati’s model by changing the exponential birth rate to logistic birth rate on susceptible population. The birth rate parameter of susceptible population in Sutantianti’s model becomes \( rS \left(1 - \frac{S}{K}\right) \). The second modification is the interaction among active smoker and passive smoker can increase the number of active smoker. Thus, the model of lung cancer based on the smoking behavior can be written as

\[
\begin{align*}
\frac{dS}{dt} &= rS \left(1 - \frac{S}{K}\right) - \alpha SI_a - \mu S, \\
\frac{dI_a}{dt} &= \alpha_1 SI_a - \beta I_a I_b - \gamma I_a - \mu I_a, \\
\frac{dI_b}{dt} &= \alpha_2 SI_a + \beta I_a I_b - \gamma I_a - \mu I_a, \\
\frac{dC}{dt} &= \gamma I_a + \gamma I_b - \mu C.
\end{align*}
\]

where
- \( S \) : the density of susceptible population,
- \( I_a \) : the density of active smoker population,
- \( I_b \) : the density of passive smoker population,
- \( C \) : the density of lung cancer patient population,
- \( r \) : intrinsic growth rate,
- \( K \) : carrying capacity,
- \( \mu \) : natural death rate,
- \( \alpha \) : the rate of susceptible who turn into the smoker,
- \( \beta \) : the rate of passive smoker who turn into active smoker,
- \( \gamma \) : incidence rate of lung cancer disease,
- \( \alpha_1 \) : passive smoker rate,
- \( \alpha_2 \) : active smoker rate,
- \( \alpha = \alpha_1 + \alpha_2 \)

and \( \alpha, \alpha_1, \alpha_2, \beta, \gamma, \mu, r, \) and \( K \) are positive constants.

In this research, the model of lung cancer growth is constructed based on Wardah’s model [12]. The model is reconstructed by not involving the interaction rate between passive smoker population and active smoker population in the rate of passive smoker. Next, the number of passive smoker can decrease because of the passive smoker who turn into the active smoker. Thus, the model of lung cancer is given by
\[
\begin{align*}
\frac{dS}{dt} &= rS \left(1 - \frac{S}{K}\right) - \alpha Sl_a - \mu S, \\
\frac{dl_b}{dt} &= \alpha_1 Sl_a - \beta l_b - \gamma l_b - \mu l_b, \\
\frac{dl_a}{dt} &= \alpha_2 Sl_a + \beta l_b - \gamma l_a - \mu l_a, \\
\frac{dC}{dt} &= \gamma l_a + \gamma l_b - \mu C.
\end{align*}
\] (2)

Further, the model in differential equation system (2) is developed by involving term education as the control \(u\) so that we have

\[
\begin{align*}
\frac{dS}{dt} &= rS \left(1 - \frac{S}{K}\right) - \alpha(1 - u) Sl_a - \mu S, \\
\frac{dl_b}{dt} &= \alpha_1 (1 - u) Sl_a - \beta l_b - \gamma l_b - \mu l_b, \\
\frac{dl_a}{dt} &= \alpha_2 (1 - u) Sl_a + \beta l_b - \gamma l_a - \mu l_a, \\
\frac{dC}{dt} &= \gamma l_a + \gamma l_b - \mu C.
\end{align*}
\] (3)

with initial value \(S(0) = S_0, l_b(0) = l_{b0}, l_a(0) = l_{a0}, C(0) = C_0\).

3. Stability Analysis

Based on system (3), we analyze the model by taking \(u = 0\). The model has three equilibrium points:

1. \(E_0 = (S_0, l_{b0}, l_{a0}, C_0) = (0, 0, 0, 0)\), extinction equilibrium point.
2. \(E_1 = (S_1, l_{b1}, l_{a1}, C_1) = \left(\frac{k}{r}(r - \mu), 0, 0, 0\right)\) which exists if \(r > \mu\), smoker-free equilibrium.
3. \(E^* = (S^*, l^*_b, l^*_a, C^*)\), endemic equilibrium point, where

\[
\begin{align*}
S^* &= \frac{(r + \mu)(\beta + \gamma + \mu)}{\beta a_1 a_2 (\beta + \gamma + \mu)}, \\
l^*_b &= \frac{\alpha_1 S^* l^*_a}{\beta + \gamma + \mu}, \\
l^*_a &= \frac{rS^*(1 - \frac{S^*}{K}) - \mu S^*}{aS^*}, \\
C^* &= \frac{\gamma l^*_a}{\mu} \left(1 + \frac{\alpha_1 S^*}{\beta + \gamma + \mu}\right).
\end{align*}
\]

Local stability of equilibrium points of system (3) is done by linearizing the model around the equilibrium points. The Jacobian matrix of system (3) is given by

\[
J = \begin{bmatrix}
    r - \frac{2rS}{k} - \alpha l_a - \mu & 0 & -\alpha S & 0 \\
    \alpha_2 S & -\beta - \gamma - \mu & \alpha_1 S & 0 \\
    \alpha_1 S & 0 & \beta & \alpha_2 S - \gamma - \mu & 0 \\
    0 & \gamma & \gamma & -\mu
\end{bmatrix}
\]

Next, the Jacobian matrix at equilibrium \(E_0\) is
\[ J(E_0) = \begin{bmatrix} r - \mu & 0 & 0 & 0 \\ 0 & -\beta - \gamma - \mu & 0 & 0 \\ 0 & \beta & -\gamma - \mu & 0 \\ 0 & 0 & \gamma & -\mu \end{bmatrix} \]

This indicates that \( E_0 \) is stable if \( r < \mu \).

The Jacobian matrix at equilibrium \( E_1 \) is

\[ J(E_1) = \begin{bmatrix} \alpha_1^* & -\frac{\alpha k}{r} (r - \mu) & 0 & 0 \\ 0 & -\beta - \gamma - \mu & \frac{\alpha k}{r} (r - \mu) & 0 \\ 0 & \beta & \frac{\alpha k}{r} (r - \mu) - \gamma - \mu & 0 \\ 0 & 0 & \gamma & -\mu \end{bmatrix} \]

The eigenvalues of \( J(E_1) \) are \( \lambda_1 = -\mu \), \( \lambda_2 = -\beta - \gamma \) while \( \lambda_3 \) and \( \lambda_4 \) are obtained from polynomial of degree two

\[ \lambda^2 + B_1 \lambda + B_2 = 0. \]

Then the equilibrium point \( E_1 \) is stable if these condition are fulfilled

a) \( \beta + 2\gamma + 2\mu > \frac{\alpha k}{r} (r - \mu) \),

b) \( \beta \gamma + \beta \mu + \gamma^2 + 2\gamma \mu + \mu^2 > (\beta + \gamma + \mu) \left( \frac{\alpha k}{r} (r - \mu) \right) + \frac{\beta \alpha k}{r} (r - \mu) \).

Finally, the Jacobian matrix of \( E^* \) is given by

\[ J(E^*) = \begin{bmatrix} r - \frac{2rS^*}{k} + \alpha J^* - \mu & 0 & -\alpha S^* & 0 \\ \alpha_1^* & -\beta - \gamma - \mu & \alpha_3^* & 0 \\ \alpha_2^* & \beta & \alpha_2 S^* - \gamma - \mu & 0 \\ 0 & \gamma & \gamma & -\mu \end{bmatrix} \]

The eigenvalues of \( J(E^*) \) are \( \lambda_1 = -\mu \), while \( \lambda_2 \), \( \lambda_3 \) and \( \lambda_4 \) are obtained from polynomial degree three as follows,

\[ \lambda^3 + A_1 \lambda^2 + A_2 \lambda + A_3 = 0, \]

where

\[ A_1 = \alpha J^* - \alpha_2 S^* + \frac{2rS^*}{k} + \beta + 2\gamma + 3\mu - r, \]

\[ A_2 = -\frac{2\alpha_2 S^*}{k} + \alpha \beta J^* + 2\alpha \gamma J^* + 2\alpha \mu J^* - \alpha_2^* B^* - \alpha_2^* S^* \]

\[ -2\alpha_2 \mu S^* + 2\alpha_2^* S^* + \frac{2\beta S^*}{k} + \frac{4\gamma S^*}{k} + \frac{4\mu S^*}{k} + \beta \gamma + 2\beta \mu \]

\[ -\beta r + \gamma^2 + 4\gamma \mu - 2\gamma r + 3\mu^2 - 2\mu - \alpha_3^* S^* - 2\alpha_3 B^*, \]

\[ A_3 = -\frac{2\alpha_1 \beta S^*}{k}^2 - \frac{2\alpha_2 \beta S^*}{k}^2 - \frac{2\alpha_2 \gamma S^*}{k}^2 - \frac{2\alpha_2 \mu S^*}{k}^2 + \alpha \beta J^* \]

\[ + \alpha \beta J^* + \alpha \gamma J^* + 2\alpha \mu J^* + \alpha \mu J^* - \alpha_3^* B^* + \alpha_3^* S^* \]

\[ + \alpha_2 \beta S^* - \alpha_2 \gamma S^* + \alpha_2 \gamma r S^* - \alpha_2 \mu S^* + \alpha_2 \mu r S^* \]
\[
+ \frac{2\beta r S^*}{k} + \frac{2\beta r S^*}{k} + \frac{2\gamma^2 r S^*}{k} + \frac{4\gamma r S^*}{k} + \frac{2\mu^2 r S^*}{k} + \beta \mu \\
- \beta \gamma r + \beta \mu^2 - \beta \mu r + \gamma^2 \mu - \gamma^2 r + 2\gamma \mu - \gamma^2 r + 2\gamma \mu + \mu^3 \\
- \mu^2 r - \alpha_3 \beta \mu S^*.
\]

The stability of equilibrium point \( E^* \) can be determined by Routh-Hurwitz criteria.

4. Optimal control
In order to restrain the growth of lung cancer, we need a control. Here, one of methods used is optimal control. The aim of optimal control is to minimize the number of lung cancer patient, the population of active smoker, the population of passive smoker and education cost. The objective functional is given by

\[
J(u) = \int_I (I_a(t) + I_b(t) + C(t) + \frac{1}{2}Au^2(t)) \, dt,
\]

with the constraint of equation system (3) where \( A \) stands for weight related to education cost (control \( u \)). Next, optimal control \( u^* \) is determined so that

\[
J(u^*) = \min \{J(u) | u \in U\}
\]

where \( U = \{u : 0 \leq u \leq 1\} \).

Based on equation (3) and (4), Hamiltonian function can be written as

\[
H = I_a(t) + I_b(t) + C(t) + \frac{1}{2}Au^2(t) + \sum_{i=1}^{4} \lambda_i(t)g_i(t, \dot{x}, \dot{u}),
\]

\[
H = I_a + I_b + C + \frac{1}{2}Au^2 + \lambda_1(rS(1 - \frac{S}{R}) - a(1 - u)Sl_a - \mu S)
\]

\[
+ \lambda_2(\alpha_1(1 - u)Sl_a - \beta I_a - \gamma I_b - \mu Ia) + \lambda_3(\alpha_2(1 - u)Sl_b + \beta I_a - \gamma I_a - \mu Ia) + \lambda_4(\gamma I_a + \gamma I_b - \mu C),
\]

where \( \lambda_1, \lambda_2, \lambda_3, \) and \( \lambda_4 \) are costate variables.

By Potryagin Minimum Principle, Hamiltonian function will reach the optimal solution if it mets these conditions below:

a. Stationary condition
Stationary condition is obtained by differentiating Hamiltonian function (5) with respect to control variable \( u \) as below

\[
\frac{\partial H}{\partial u} = 0 \rightarrow u^* = \frac{(\lambda_2 \alpha_1 + \lambda_4 \alpha_2)Sl_a}{A}, \text{ so that we obtain}
\]

\[
u^* = \begin{cases} 
(\lambda_2 \alpha_1 + \lambda_4 \alpha_2 - \lambda_2)Sl_a, & \text{if } 0 \leq \frac{(\lambda_2 \alpha_1 + \lambda_4 \alpha_2 - \lambda_2)Sl_a}{A} \leq 1, \\
\lambda_2 \alpha_1 + \lambda_4 \alpha_2 - \lambda_2 - \lambda_2 Sl_a, & \text{if } 0 \leq \frac{(\lambda_2 \alpha_1 + \lambda_4 \alpha_2 - \lambda_2)Sl_a}{A} \leq 1, \\
1, & \text{if } \frac{(\lambda_2 \alpha_1 + \lambda_4 \alpha_2 - \lambda_2)Sl_a}{A} \geq 1.
\end{cases}
\]

Optimal control \( u^* \) can be simplified:

\[
u^* = \min \left\{ \max \left(0, \frac{(\lambda_2 \alpha_1 + \lambda_4 \alpha_2 - \lambda_2)Sl_a}{A}\right), 1 \right\}.
\]
b. State equation
State equation is obtained by differentiating Hamiltonian function (5) with respect to each costate variable as below

\[
\frac{dS}{dt} = \frac{\partial H}{\partial \lambda_1} = rS \left( 1 - \frac{S}{K} \right) - \alpha(1 - u)SI_a - \mu S,
\]

\[
\frac{dl_b}{dt} = \frac{\partial H}{\partial \lambda_2} = \alpha_1(1 - u)SI_a - \beta l_b - \gamma l_b - \mu l_b,
\]

\[
\frac{dl_a}{dt} = \frac{\partial H}{\partial \lambda_3} = \alpha_2(1 - u)SI_a + \beta l_b - \gamma l_a - \mu l_a,
\]

\[
\frac{dC}{dt} = \frac{\partial H}{\partial \lambda_4} = \gamma l_a + \gamma l_b - \mu C.
\]

with initial conditions \( S(0) = S_0, l_b(0) = l_{b_0}, l_a(0) = l_{a_0}, C(0) = C_0. \)

c. Costate equation
Costate equation is the negative value of Hamiltonian function (5) differentiated with respect to each costate variable. It is given by

\[
\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S} = -\left( \lambda_1 \left( r - \frac{2rs}{K} - \alpha(1 - u)l_a - \mu \right) + \lambda_2 \alpha_1(1 - u)l_a + \lambda_3 \alpha_2(1 - u)l_a \right)
\]

\[
\frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial l_b} = -1 - (\lambda_2(-\beta - \gamma - u) + \beta \lambda_3 + \gamma \lambda_4)
\]

\[
\frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial l_a} = -1 - (\lambda_1(\alpha(1 - u)S) + \lambda_2 \alpha_1(1 - u)S + \lambda_3 \alpha_2(1 - u)S - \lambda_3(\gamma + \mu) + \lambda_4 \gamma)
\]

\[
\frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial C} = -1 + \mu \lambda_4
\]

with transversal condition \( \lambda_1(T) = \lambda_2(T) = \lambda_3(T) = \lambda_4(T) = 0. \)

5. Numerical Simulation
Forward-Backward sweep method is used to solve the optimal control problem above. To solve the state equation, we use forward-difference of Runge Kutta fourth order while the costate equation is solved by using the backward-difference. We run the simulation by considering the initial values \( S(0) = 110, l_b(0) = 6, l_a(0) = 7, C(0) = 8, t_0 = 0, T = 70 \) and parameter values as in Table 1. Weight used is \( A = 1. \) Next, simulation result is shown in Figure 1.

| Table 1. Parameter value for simulation |
|-----------------------------------------|
| **Parameter** | **Description** | **Value** |
| \( r \) | Intrinsic growth rate | 0.1 |
| \( K \) | Carrying capacity | 125 |
| \( \mu \) | Natural death rate | \( 1.0 \times 10^{-3} \) |
| \( \alpha \) | The rate of susceptible who turn into the smoker | \( \alpha_1 + \alpha_2 \) |
| \( \alpha_1 \) | Passive smoker rate | \( 4.4 \times 10^{-4} \) |
| \( \alpha_2 \) | Active smoker rate | \( 1.76 \times 10^{-3} \) |
| \( \beta \) | The rate of passive smoker who turn into active smoker | \( 3.5 \times 10^{-2} \) |
| \( \gamma \) | Incidence rate of lung cancer | 0.2 |
Figure 1(a) shows that after the control is given, the number of susceptible population increase significantly from maximum density 110 to 124 when $t = 70$. Figure 1(b) shows that optimal control affects the number of passive smoker population. Before the control is given, the number of passive smoker in the early period decreases when about $t = 5$ then it increases gradually until the density 7.3 when $t = 28$. However, when the control is applied, the number of passive smoker population can be eliminated when $t = 30$. It indicates the effectiveness of optimal control in controlling the growth of passive smoker population.

The similar behavior in the change of passive smoker population also occurs for the active smoker population. Figure 1(c) shows that optimal control affects the change of active smoker population. Before being controlled, the number of active smoker population increases continuously until the density is 39 at $t = 30$. However, when the control is applied, the number of active smoker population decreases significantly. The active smoker population already can be eliminated when $t = 40$. It shows that optimal control is effective for controlling the growth of active smoker population.

Figure 1(d) shows that optimal control affects the number of population of lung cancer patient. Before being controlled, the number of population of lung cancer patient continuously increases until the density is 225 at $t = 70$. Whereas, when the control is applied, the number of population of lung cancer patient decreases and it is will at maximum value 20 from $t = 20$. It indicates the effectiveness of optimal control in controlling the growth of population of lung cancer patient.

![Figure 1](image1.png)  
(a)  
(b)  
(c)  
(d)

**Figure 1.** The number of population before and after control.
The control that we use to inhibit the growth of passive smoker population, active smoker population and lung cancer patient population is shown in Figure 2. It can be seen that in the early period education is given optimally at rate 1 until about $t = 48$ then it is slowly reduced and stop at $t = 70$.

![Figure 2](image.png)

**Figure 2.** Optimal control profile (education).

Based on the discussion, the control which is given through the education in equation (3) affects the behavior of model solution. By using parameter in Table 1, when the education is not applied the behavior of system solution leads to the endemic equilibrium point. It states that passive smoker, active smoker and lung cancer patient population are always exist. However, when the education is applied on the model, within a certain period the active smoker and passive smoker population are about extinct. As a result, the growth of population of lung cancer patient also decreases. It shows that education can inhibit the growth of active smoker, passive smoker and lung cancer patient population.

6. Conclusion

In this paper, the stability and optimal control of lung cancer growth model has been investigated. The model consists of four variable which is in the form of differential equation. This model has three equilibrium: extinction equilibrium point, smoker-free equilibrium point and endemic equilibrium point. These equilibrium points are asymptotically stable under certain conditions. Optimal control is then applied to the model by adding education as a variable control. Numerical simulation shows that education has to be given optimally from the early period until the mid period then it can be reduced gradually until the end of the period. The optimal control is effective to control the growth of passive smoker, active smoker and lung cancer patient population.

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