Robust Control Design For Virotherapy Model Using Successive Method

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Abstract. Bilinear systems is the simplest class of nonlinear systems that represent many real physical processes. As an example, chemotherapy and virotherapy in cancer cells are bilinear systems. Disturbances is a factor that can interfere the work process of the system, and it can make the output of the system to be not in accordance with the desired output. Thus a robust controller must be found to make the system produce the desired output. In designing the controller, it requires a solution to the state dependent algebraic Riccati equation (SDARE). However it is difficult to solve the SDARE. Successive method is one of the methods that can be used to solve this issue. The idea of this method is converting the bilinear systems into time-varying linear system. This method has the following steps : first, we need to obtain the robust control for the linear system by ignoring the multiplicative term of bilinear system. Second, convert the bilinear systems into the time-varying linear systems using the previous result, and then solve the SDARE by the new performance index and the associated Hamilton-Jacobi-Isaacs equation. Last, iterate the steps until the convergence of state satisfied. In this research, successive method were applied in virotherapy control problems. The virotherapy model has been widely developed, one of which is the cell cycle-specific model. This model is a bilinear systems. There are four groups in this model: quiescent cells (Q), cancer cells (S), virus (V), and infected cells (I). Virus are injected into the human body as the control input to control the amount of the cancer cells. In this case, virus can only infect the cancer cells, and the infected cells will die when the lysis process occurs. Virus, as a control, is given with the aim of minimizing the energy used in the system. In this model we consider the body’s immune response as an additive disturbances to the model. Simulation show that virotherapy can reduce the number of cancer cells in the body on day 50, so the number of cancer cells in the body is only 16.6%. Based on the simulation, the next virotherapy can be done after the day 50.

1. Introduction

Virotherapy is a cancer treatment technique that utilizes the nature of virus to destroy the cancer cells. This virus are often referred as oncolytic virus. Adenovirus, Reovirus, Measles, Herpes Simplex, Vesicular-Stomatitis Virus (VSV) are some of the oncolytic viruses that have been found and proven in reducing the number of cancer cells in the body. Unlike chemotherapy, virotherapy is considered better. It is because the procedure of virotherapy treatment is done by injecting the virus into the human body and the virus will only damage the cancer cells. Thus virotherapy will not cause damage to the healthy cells. Specifically this research discuss about Vesicular-Stomatitis virus (VSV). VSV is used as the oncolytic virus for virotherapy in breast cancer, cervical cancer, prostate cancer, and brain cancer. This
virus is functioned to be a cancer killing agent that hides on T-cells of leukocyte, and had a capability to detect and to infect the cancer cells. The virus destroys cancer cells during lysis.

Virotherapy model has been developed. One of them was developed by Chrivelli et al. Virotherapy model can be regarded as a bilinear system with three states and considered virus as the control input of the systems. The presence of an immunological response in the human body cannot be ignored, because it can interfere the system performance. Therefore a robust control design is needed in order to make the systems producing the desired output.

In designing control, the solution of state dependent algebraic Riccati equation (SDARE) is needed. However it is difficult to find the solution. Successive method can be used to solve this problem. The main idea of this method is by replacing the bilinear system of the virotherapy model into the time-varying linear system. This method is done iteratively until the convergence state is satisfied. The simulation results show that the control strategy using successive methods can reduce cancer cells in the human body up to 16.6%, and virotherapy can be done again after the day 50.

2. Virotherapy Model
Virus live and do reproduction process in the host cell. In this case the cancer cells act as the host cell for the virus. The virus life cycle shown in Figure 1. In the process of lysis, virus break down the membrane of the cancer cells, and damage the cancer cells. Beside being a cancer killer, virus can activate the immune system of the human body. This immune system will later be responsible for neutralizing the virus after the lysis process (Mardiani and Djannatun, 2013).

![Figure 1. Virus life cycle](image)

In the virotherapy model, cells and viruses are divided into four groups: healthy cells ($Q$), cancer cells ($S$), cancer cells infected by virus ($I$) and virus ($V$). The number of cells and viruses in mm$^3$. Assume that $N(t) = Q(t) + S(t) + I(t) + V(t)$ (Crivelli, et al, 2012). The number of cells in each group at every time can be illustrated in Figure 2.

![Figure 2. The number of cell and virus changes in each group](image)
The number of $Q$ cells are increased by the body's natural processes with proportion $b_1$. Beside the number of $Q$ cells are decreased as much as the number of $Q$ cells that divide and become cancer cells with the rate of the cancer cell growth $a_1$, and it is also decreased due to natural death of cells with the natural death cell rate $d_1$. The number of cells in the group $Q$ are also increased because of the number of cells $S$ that divide through the mitosis process with the rate of division $a_2$. 

The number of cells in the group $S$ are increased by the cancer cells that growing into the cancer cells with proportion $b_2$. It is also decreased by mitosis process with the rate of division $a_2$. Beside the number of cells $S$ are decreased due to natural death of cells with the natural death rate $d_2$. In virotherapy, virus can only infect the cancer cells. Thus the number of cells in the $S$ group are also reduced due to virus infection with a rate of $k$ per day, exiting $S$ and entering $I$ at a rate of $kSv_N$.

The number of cells in the $S$ group are also increased by the number of cells $S$ that infected by the virus, which is $kSv_N$. The number of virus ($V$) are increased due to the presence of new viruses that have been proliferated in cancer cells at a growth rate of $\alpha$. The amount of virus are decreased by the virus that infects the cancer cells, and decreased due to virus damage with the damage rate $d_3$. Thus the virotherapy model can be written as a differential equation system as follows:

\[
\begin{align*}
\frac{dQ}{dt} &= b_1 + 2a_2S - a_1Q - d_1Q + b_2a_1Q - a_2S - \frac{kSV}{N} - d_2S, \\
\frac{dI}{dt} &= kSV - \delta I, \\
\frac{dV}{dt} &= \alpha I - \frac{kSV}{N} - d_3V.
\end{align*}
\]

(1)

In this research, the immunology response in the human body are considered as a disturbances to the systems. It is because the ability of leukocyte that act as an antibodies can recognize the virus as a foreign object and kill the virus. Thus the virotherapy model can be considered as a three-dimensional bilinear system as follows

\[
\begin{align*}
\frac{dQ}{dt} &= b_1 + 2a_2S - a_1Q - d_1Q + e_1w, \\
\frac{dS}{dt} &= b_2a_1Q - a_2S - \frac{kSV}{N} - d_2S + e_2w, \\
\frac{dI}{dt} &= kSV - \delta I + e_3w,
\end{align*}
\]

(2)

with the weighting matrix for the disturbances $E = \begin{pmatrix} e_1 \\ e_2 \\ e_3 \end{pmatrix}$

In the system (1) virus acts as a controller to the cancer cell growth. The growth model in the system (2) can be seen as a control system with the control input $V$ and three states $Q, S,$ and $I$. The parameters taken in this research written in Table 1.

| Table 1. Table of parameters (Crivelli, et.al, 2012) |
| Parameter | Value |
| --- | --- |
| $a_1$ | The rate of change of silent cells into active cells | $0.9 \pm 50\%$ |
| $a_2$ | The rate of active cells division | $0.6 \pm 50\%$ |
| $d_1$ | Natural death rate of cell Q | $10^{-5} \pm 50\%$ |
| $d_2$ | Natural death rate of cell S | $0.15 \pm 50\%$ |
| $d_3$ | Free virion decay | $3 \pm 50\%$ |
| $\alpha$ | Virion production | $1.119 \pm 50\%$ |
| $\delta$ | Infected cell elimination | $0.3 \pm 50\%$ |
| $k$ | Kinetic Coefficient | $[0.5]$ |
The objective function in this control problem is to minimize the energy used in the system. Next the objective function is defined by:

$$J = q_1 Q^2 + q_2 S^2 + q_3 I^2 + \int_{t_0}^{t_f} (\|x\|^2 - \gamma^2 \|w\|_W^2) \, dt,$$

with $A$ is the weighting matrix for the final state, and $z$ is the output systems. The output of the system is defined by:

$$z = \begin{pmatrix} 1 & 1 & 1 \\ 0 & 0 & 0 \\ 1 & 0 & 1 \end{pmatrix} \begin{pmatrix} Q \\ S \end{pmatrix} + \begin{pmatrix} 0 \\ 10 \end{pmatrix} V.$$  

(4)

3. Robust Control For Bilinear System Using Successive Method

The robust $H_{\infty}$ control problem of continuous time bilinear systems with additive disturbance given by

$$\dot{x} = Ax + \left( B + \sum_{i=1}^{n} x_i N_i \right) u + Ew,$$

$$z =Cx + Du,$$

with $i = 1,2,\cdots,w \in \mathbb{R}^{l \times 1}, w \in L_2[t_0,t_f]$ is denoted for the disturbance input, $z$ is the output function used in the performance index, and $A,B,C,D,E,N_i$ are constant matrix in appropriate dimensions. Performance index of the systems (5) are:

$$J = \frac{1}{2} \|x(t_f)\|^2_S + \frac{1}{2} \int_{t_0}^{t_f} (\|x\|^2 - \gamma^2 \|w\|_W^2) \, dt,$$

with $t_0 \leq t_f \leq \infty, S, W > 0$, and $W$ is a unitary matrix (Kim and Lim, 2003). Weighting matrix for final state is denoted by $S$ and weighting matrix for disturbance input is denoted by $W$. In this case, the disturbance input is limited, and the worst disturbance input can be expressed as:

$$w = \frac{1}{\gamma^2} W^{-1} E^T \frac{\partial J(x)}{\partial x}. $$

(7)

The main problem of $H_{\infty}$ optimal control is to find (if existing) the smallest value $\gamma^* \geq 0$ such that for any $\gamma > \gamma^*$, there exist a state feedback such that the $L_2$-gain from input $x$ and $w$ to output $y$ and $z$ is less than or equal to $\gamma$ (Schaft, 1992). Based on system (5) and performance index (6) the hamiltonian equation can be formed as:

$$H = \frac{1}{2} x^T C^T C x + \frac{1}{2} u^T R u - \frac{1}{2} \gamma^2 \|w\|_W^2 + \alpha^T (Ax + Ew + \tilde{B}u),$$

where $\tilde{B} = (B + \sum_{i=1}^{n} x_i N_i)$ and $\lambda \in \mathbb{R}^{n \times 1}$ is a Lagrange multiplier. The optimal control can be obtained from the hamiltonian equation as follow :

$$u = -R^{-1} B^T \frac{\partial J(x)}{\partial x},$$

(9)

with $J(x)$ is the solution of the following Hamilton-Jacobi-Isaac equation:

$$\frac{1}{2} x^T C^T C x - \frac{1}{2} (\frac{\partial J}{\partial x})^T \tilde{B} R^{-1} \tilde{B}^T \frac{\partial J(x)}{\partial x} + \frac{1}{2} \gamma^2 \|W^{-1} E^T \frac{\partial J(x)}{\partial x}\|_W^2 + \left( \frac{\partial J}{\partial x} \right)^T A x = 0,$$

(10)

under the assumption that $D^T C = 0$ and $R = D^T D > 0$. The value of $J(x)$ which satisfies the equation (10) is $J = \frac{1}{2} x^T P x$ in the context of Lyapunov. Substituting this value of $J$ in equation (10) the state dependent algebraic riccati equation becomes:

$$C^T C + PA + A^T P - P \left( \tilde{B} R^{-1} \tilde{B}^T - \frac{1}{\gamma^2} E W^{-1} E^T \right) P = 0.$$  

(11)
The solution obtained from the Riccati algebraic equation (11) and $J = \frac{1}{2} x^T P x$, can be used to determine the $u$ control input as follows:

$$ u = -R^{-1} \hat{B}^T P x, \quad (12) $$

The successive method were applied under the assumption as follows where the disturbance function is limited

$$ |w(t)| \leq W_m, \quad (13) $$

for $0 < W_m < \infty$. The successive algorithm for the bilinear system with and additive disturbance shown in Figure 3.

\[ \begin{array}{l}
\dot{x}^{(0)}(t) = Ax^{(0)}(t) + Bu^{(0)}(x^{(0)}(t)) = +EW_m ; x^{(0)}(0) = x_0 \\
u^{(0)}(x^{(0)}(t)) = -R^{-1}\hat{B}^T p^{(0)} x^{(0)}(t)
\end{array} \]

\[ \begin{array}{l}
\dot{x}^{(k)}(t) = A x^{(k)}(t) + \hat{B}^{(k-1)} u^{(k)}(x^{(k)}(t)) + EW_m ; x^{(k+1)}(0) = x_0 \\
u^{(k)}(x^{(k)}(t)) = -R^{-1}\hat{B}^{(k-1)} p^{(k)} x^{(k)}(t)
\end{array} \]

\[ \left\| x^{(k)}(t) - x^{(k-1)}(t) \right\| < \beta \]

**Figure 3** Successive algorithm for control robust bilinear system

### 4. Result

System (2) can be written in the form of a matrix as:

$$ \begin{pmatrix} \dot{Q} \\ \dot{S} \\ \dot{I} \end{pmatrix} = \begin{pmatrix} b_1 \\ b_2 \\ 0 \end{pmatrix} + \begin{pmatrix} - (a_1 + d_1) \\ - (a_2 + d_2) \\ 0 \end{pmatrix} \begin{pmatrix} a_1 \\ a_2 \\ 0 \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix} \begin{pmatrix} 0 \\ -kS/N \\ kS/N \end{pmatrix} V + Ew, \quad (14) $$

The disturbance in the system is in the $I$ compartment as a result of the body's immune response to the virus. Therefore, the weighting matrix for disturbance is selected $E = \begin{pmatrix} 0 \\ 0 \\ 0.05 \end{pmatrix}$ and the disturbance function $w$ as stated in (7).

The parameters used in this paper are $a_1 = 0.6, a_2 = 0.5, b_1 = 0.07, b_2 = 0.005, d_1 = 10^{-5}, d_2 = 0.2, d_3 = 0.3, \alpha = 4, \delta = 0.8, K = 4$ and the initial value of $Q(0) = 0.7, S(0) = 0.3, I(0) = 0$ which represents the proportion of the number of cells in the body. The proportion of cells in each group without being control shown in Figure 4.
Both of cells $Q$ and cells $S$ grow exponentially without control as time goes by, and the proportion of the cells $S$ are greater than the proportion of cells $Q$. This is undesirable, because cancer cells $S$ become uncontrolled, so it can harm the patient's body. In this case virotherapy have not been done, so the infected cells $(I)$ and the virus $(V)$ are zero. Figure 5. shows the change of proportion cells in each group if the system (1) is considered as a normal growth dynamics model. The numerical calculation method is used to get the solution of the system. From Figure 5. shows that virus which is interpreted as a controller in a growth model can reduce the proportion of cancer cells $(S)$. 

The proportion of cells in each group will be stable to a certain number on the 50th day, namely $Q = 0.3883, S = 0.1690, I = 0.0872$. On the other word at the 50th day there are 38.83% healthy cells, 16.9% cancer cells, and 8.72% infected cells in the body.
Figure 6. The proportion of the number of Q cells and S cells

Considering the system (1) as a bilinear control system with \( V \) as a control input (as in the system (2) and the object function (3), the results obtained as in Figure 6 and Figure 7. Successive method is used to get the solution of the system. Figure 6. and Figure 7. show that the proportion of cells \( Q \), \( S \) and \( I \) goes to a certain number on the 50th day, \( Q = 0.3933, S = 0.1660 \), and \( I = 0.0867 \). It means that at the 50th day there are 39.33% healthy cells, 16.6% cancer cells, and 8.67% infected cells in the body.

Figure 7. Proportion of number of cells I and viruses

From Figure 5 (blue and red lines) and Figure 6 show that the dynamics of the proportion cells \( Q \) and \( S \) in both figure are different. Figure 5 show that the proportion of cells \( Q \) and \( S \) has increased and decreased less than 50 days, while in Figure 6 the proportion cells \( Q \) and \( S \) tend to decrease and constant after 50 days. The dynamics difference also occur in the infected cells \( I \) which can be seen in Figure 5 (yellow line) and Figure 7 (above). The proportion of cells \( I \) in Figure 7 increased due to virus infection, then cells \( I \) decreased due to the lysis process. On the other side, there are no upward movement before the 30th day as in Figure 4 (yellow).
Based on the two observed points of view (the system (1) as a growth model and as a control system with $V$ as a control input (2), it can be concluded that the number of cells will be stable at almost in the same range $Q \approx 0.39, S \approx 0.17$, and $I \approx 0.09$. Total cells $Q, S,$ and $I$ at every time within 60 days shown in Figure 8. It can be concluded that the total cell number will go up, then down to a constant at 0.646. On the other word, at the day 50th there are 64.6% cells in the patient's body. It is reasonable for doing the next virotherapy, because the number of cells in the body is more than 50%.

5. Conclusion
Virotherapy model with the number of viruses in the body as a controller using successive method can reduce the number of cancer cells in the body up to 16.6%. This result is constant after day 50th. The total cells in the body at day 50th is 64.6%. Because the total cells in the body are more than 50%, it can be concluded that virotherapy can be done again after day 50th.

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