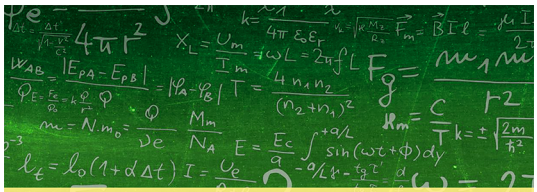

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Optimal Control on a Model for Cervical Cancer

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Abstract Cervical cancer is caused by the human Papillomavirus (HPV) that attacks the cervix. Cervical cancer globally ranks third as the most frequent cancer among women. In this research, a model of HPV infection in cervical cancer consists of five sub categories of cells, namely susceptible cells, infected cells, pre-cancer cells, cancer cells, and viruses. The study was conducted by forming a model of HPV infection with the addition of treatment controls on pre-cancerous cells. The aim is to minimize the number of pre-cancerous cells while minimizing cost. The HPV infection model with control was solved using Pontryagin's maximum principle in order to obtain optimal control. Numerical simulations are performed on the differential equations for the cell densities using the fourth order Runge-Kutta method. The simulation results indicate that a smart administration of treatment can be tailored such that the number of pre-cancer cells is minimized at minimal cost. This configuration with a minimal number of pre-cancer cells is favourable since it inhibits the development of cancer cells.

1 Introduction

Cervical cancer is abnormal cell growth that occurs in the cervix. Cervical cancer globally ranks third as the most frequent cancer among women, with estimated 569,847 new cases and 311,365 deaths in 2018 [3]. The human Papillomavirus (HPV) plays a pivotal role as a cause of cervical cancer [9]. This virus can be transmitted through sexual relations. Several types are called high risk HPV such as HPV types 16, 18, 45, and 56. The persistence of high risk HPV can cause cancer of the cervix, vagina and anus. Changes from healthy cells into cancer cells take

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a long time so the rate of this change can be controlled to reduce the mortality in cervical cancer cases. Cervical cancer can be controlled by applying medical treatments in various ways including chemotherapy, surgery, and radiation. Cervical cancer treatment results in healing in between 66.3–95.1% of the cases, if performed at a pre-cancer stage. The treatment renders bad results when done at an advanced stage [4].

Optimal control has been applied to control and inhibit numerous diseases in several studies. Neilan et al. [7] provide a control function of the vaccination level to Taylor vaccination schedules, to minimize the number of infected individuals, and to minimize the vaccination cost on the basis of a SEIR epidemic model. Modelling optimal control of cervical cancer has been carried out by [1, 6], who use optimal vaccination strategies to suppress HPV infection effectively and to minimize the cost of vaccination.

However, in developing countries, HPV vaccination is not common. In general, patients who are seen by doctors are already in a pre-cancer stage. This research will apply optimal control for HPV infection models in cervical cancer on the basis of the implementation by Asih et al. [2]. Application of optimal control will be done as a treatment in the pre-cancer stage. We build a new model by adding control in the pre-cancer compartment, and we will solve the model equations numerically by using Pontryagin's maximum and the fourth order Runge-Kutta time integration scheme.

2 Mathematical Model

We revise the model proposed by Asih et al. [2] by adding a control function to the pre-cancer cell density. Let S, I, P, C and V, respectively, denote the density of normal (constituent) cells, the density of infected cells, the density of pre-cancer cells, the density of cancer cells and the density of free viral particles.

$$\begin{aligned}
\frac{dS}{dt} &= rS(1-(S+I)) - \alpha SV \\
\frac{dI}{dt} &= \alpha SV - aI - \delta I \\
\frac{dV}{dt} &= nI - cV \\
\frac{dP}{dt} &= \delta pI + bP - \theta \frac{P^2}{1+P^2} - u(t)P \\
\frac{dC}{dt} &= \theta \frac{P^2}{1+P^2} - kC
\end{aligned} \tag{1}$$

where $u(t)$, $0 \leq u(t) \leq 0.9$, is a control function. The complete description of the parameter values, as well as their biophysical meaning, is given in [2]. The objective function is used to minimize the density of cancer cells and to minimize the cost of treatment over time T days. The problem is stated as

$$\min_{u \in U} \int_0^T AC(t) + u^2(t)dt.$$

where the set of control is given by

$$U = \{u : [0, T] \to [0, 0.9]\},$$

subject to (1) and the initial condition

$$S(0) = S_0, I(0) = I_0, V(0) = V_0, P(0) = P_0, C(0) = C_0,$$

Further, the corresponding values at time T, that is $S(T)$, $I(T)$, $V(T)$, $P(T)$, $C(T)$ are free. The model variable A is a weight factor representing a balancing parameter, which determines the relative importance of the two factors in the optimal control problem [5].

3 The Optimum Control Problem

The optimal control problem is solved using Pontryagin's Maximum Principle. First we will define the Hamiltonian function, which is followed by the introduction of the stationary condition. Subsequently, we define the state equation and adjoint equation.

The Hamiltonian function of this problem can be stated as

$$H(t, x, u\lambda) = f(t, x, u) + \sum_{i=1}^{5} \lambda_i(t) g_i(t, x, u),$$

with

$$\begin{aligned}
f(t, x, u) &= AC(t) + u^2(t) \\
g_1(t, x, u) &= rS(1 - (S + I)) - \alpha SV \\
g_2(t, x, u) &= \alpha SV - aI - \delta I \\
g_3(t, x, u) &= nI - cV \\
g_4(t, x, u) &= \delta pI + bP - \theta \frac{P^2}{1 + P^2} - u(t)P \\
g_5(t, x, u) &= \theta \frac{P^2}{1 + P^2} - kC.
\end{aligned}$$

Hence we obtain

$$H = AC + \lambda_S\{rS(1-(S+I)) - \alpha SV\} + \lambda_I\{\alpha SV - aI - \delta I\} + \lambda_V\{nI - cV\} + \lambda_P\left\{\delta pI + bP - \theta\frac{P^2}{1+P^2} - uP\right\} + \lambda_C\left\{\theta\frac{P^2}{1+P^2} - kC\right\}, \tag{2}$$

where $\lambda_S, \lambda_I, \lambda_V, \lambda_P, \lambda_C$ are the associated adjoints for the states $S,\ I,\ V,\ P,\ C$, respectively.

For the stationary condition, the optimal condition is given by

$$\frac{\partial H}{\partial u}|_u* = 0.$$

Solving u^* from (2) gives

$$u^*(t) = \frac{P\lambda_P}{2}.$$

Furthermore, from taking the bound of u, we conclude that

$$u^*(t) = \min\left\{0.9, \max\left(0, \frac{p\lambda_P}{2}\right)\right\}. \tag{3}$$

The state equations are given by

$$\begin{aligned}
\frac{dS}{dt} &= \frac{\partial H}{\partial \lambda_S} = rS(1-(S+I)) - \alpha SV \\
\frac{dI}{dt} &= \frac{\partial H}{\partial \lambda_I} = \alpha SV - aI - \delta I \\
\frac{dV}{dt} &= \frac{\partial H}{\partial \lambda_V} = nI - cV \\
\frac{dP}{dt} &= \frac{\partial H}{\partial \lambda_P} = \delta pI + bP - \theta\frac{P^2}{1+P^2} - uP \\
\frac{dC}{dt} &= \frac{\partial H}{\partial \lambda_C} = \theta\frac{P^2}{1+P^2} - kC
\end{aligned} \tag{4}$$

subject to the initial condition

$$S(0) = S_0,\ I(0) = I_0,\ V(0) = V_0,\ P(0) = P_0,\ C(0) = C_0.$$

The adjoint equations are given by

$$\begin{aligned}
\frac{d\lambda_S}{dt} &= -\frac{\partial H}{\partial S} = \lambda_S(\alpha V + rS + r(S + I - 1)) - \lambda_I(\alpha V)) \\
\frac{d\lambda_I}{dt} &= -\frac{\partial H}{\partial I} = \lambda_S(rS) = \lambda_I(a + \delta) - \lambda_V(n) - \lambda_P(\delta p) \\
\frac{d\lambda_V}{dt} &= -\frac{\partial H}{\partial V} = \lambda_S(\alpha S) - \lambda_I(\alpha S) + \lambda_v(c) \\
\frac{d\lambda_P}{dt} &= -\frac{\partial H}{\partial P} \\
&= -\lambda_P\left(b - u - \frac{2\theta P}{P^2+1} + \frac{2\theta P^3}{(P^2+1)^2}\right) - \lambda_C\left(\frac{2\theta P}{P^2+1} + \frac{2\theta P^3}{(P^2+1)^2}\right) \\
\frac{d\lambda_C}{dt} &= -\frac{\partial H}{\partial C} = A + k\lambda_C
\end{aligned} \tag{5}$$

subject to the transversal condition $\lambda_i(T) = 0$.

4 Numerical Simulation

To illustrate the effect of optimum control, we perform some numerical simulations by using the set of parameter values as in [2]. The state equations and adjoint equations will be solved numerically by the use of the fourth order Runge-Kutta method [8]. The state equations will be simulated using a forward time integration method while the adjoint equations are solved using a backward time integration method, since the state equations have initial conditions and the adjoint equations have conditions at the end-time.

Since the optimum control function is only active in the pre-cancer compartment, it makes sense that the sub population of normal cells, infected cells, and free virus pathogens are not influenced by this control function. In Fig. 1, it can be seen that the pre-cancer cell density significantly decreases, and starts to increase again after 35 days.

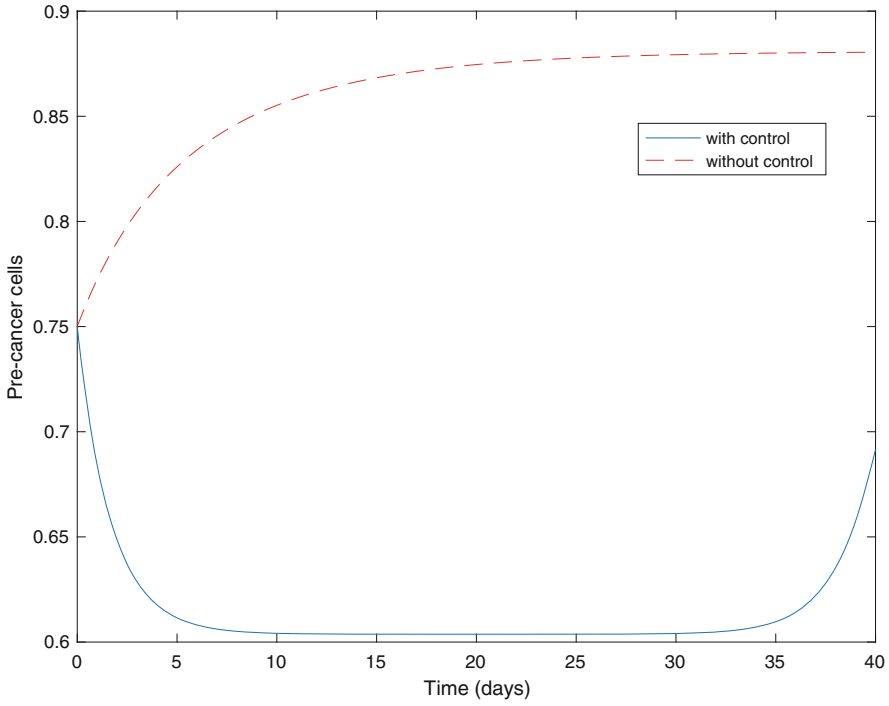

Fig. 1 The optimum control function makes the pre cancer cell density decrease significantly until about 35 days, by taking initial values for $(S_0,\ I_0,\ V_0,\ P_0,\ C_0) = (0.92,\ 0.055,\ 8.9,\ 0.75,\ 0.75)$ and $A = 0.1$

For the cancer cells, the obtained pattern is analogous, as one can see in Fig. 2. Without the application of control, the number of pre-cancer and cancer cells would increase and stabilize at the point of equilibrium. However, using control, the numbers of pre-cancer and cancer cells decrease and stabilize after approximately 35 days. This stabilization is followed by an increase.

This means that the treatment shows its effectiveness in reducing the number of pre-cancer and cancer cells until the 35th day. After that period, the effectiveness of the treatment will decrease so that the number of pre-cancer cells and cancer cells will increase again. In other words, the simulation results indicate that the therapy needs to be repeated periodically every 35 days.

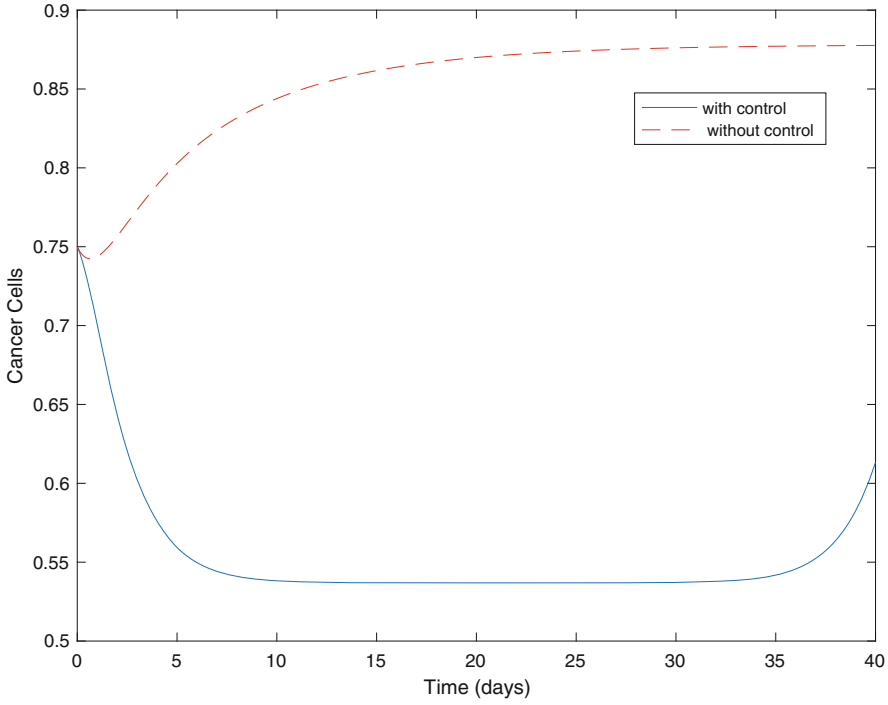

Fig. 2 Optimum control results into a significant decrease of the cancer cells

5 Conclusion

From the numerical simulations we can conclude that giving control in the pre-cancer compartment will imply a decrease of the number of pre-cancer and cancer cells. In our result the effectiveness of control is in the range of 35 days. Hence after 35 days the next treatment needs to be applied again. In other words, the current parameter setting indicates that the treatment can be given periodically with a period of 35 days. Though the result heavily depends on the parameter values and on the initial condition, we think that this model has some potential to predict optimal treatments against cervical cancer. Model calibration on the basis of medical data will be necessary in order to run more realistic simulations.

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