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On the Bifurcation of a Cancer Therapy Model by Oncolytic Virus with Malignancy Effect

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Abstract

Oncolytic virus cancer therapy, also known as oncolytic virotherapy, is a developing therapy that uses replication-competent viruses to eliminate cancer cells in patients' body. Compared to other therapies, this therapy is approachable as it does not eradicate the normal cells in the body. This report studies the application of mathematical modelling to investigate the malignancy effect for two populations which are the uninfected cancer cells and infected. Cancer cells by oncolytic virus denoted by x and y respectively. We perform numerical and graphical analyses using software such as Maple, Matlab, MATCONT, and XPPAUT to illustrate the cancer dynamics. The objectives of this study are to produce bifurcation diagrams for uninfected cancer cells, x, and infected cancer cells by oncolytic virus, y, against parameter p (malignancy effect), to extend the analysis of bifurcation diagrams as it was the gap addressed in the previous study and to conclude comprehensible understanding on the malignancy effect. From the analysis, we found that if p is greater than the threshold value, the solutions of the system will be bounded, and the cancer cell is regarded as benign where the cancer cell does not undergo metastasis. On the other hand, if the parameter p is less than the threshold value, the solutions will be unbounded which imply that the characteristics of the cancer cells to be malignant and that the oncolytic virotherapy is unsuccessful.

1. Introduction

Cancer is a worldwide major disease that has been affecting many lives over the years. It is a complicated illness that can affect any region of the body. Rapid production of aberrant cells that proliferate beyond the normal boundaries, infiltrate surrounding body components and spread to other organs is one of the main characteristics of cancer. The transmission of cancer cells to other organs through blood flow is known as metastasis and it is the main factor that causes cancer deaths [1]. In cancer research, conventional therapies are less likely to be effective than virotherapy because virotherapies are targeted therapies that target cancerous cells and spare the healthy cells [2]. As stated, there are many targeted therapies, but we are mainly focusing on oncolytic virotherapy which uses oncolytic viruses to inject into cancer cells to reduce the malignancy level without destroying the normal cells [3]. Oncolytic virotherapy is a promising treatment and various oncolytic viruses have progressed in clinical trials [4].

Research has been working on finding a better therapy over the years. Additionally, it is well recognised that gene immunotherapy is the cancer treatment with the lowest risk of causing abnormalities in healthy cells. A few lines of evidence suggest that immunotherapy may boost the patient's immune system to fight against cancer cells [5]. Previously, mathematical modelling on the research of tumour treatment with oncolytic virus has been studied [6].

Mathematical modelling is introduced to describe the benign type of cancer cells, and the virus therapy aborts if death rate increases due to viral assault exceeds the rate of transmission of contamination from virus to the uninfected cells [6]. A generalisation of [6] with new parameters has been analysed and the two significant parameters found are the malignancy and the therapeutic efficacies [7]. When determining the circumstances for cancer cells, the value of the malignancy level parameter is crucial. It gives the information if the cancer cells can spread (metastasis) or not Metastasis is the ultimate and the most fatal form of cancer, which is the growth of cancer cells in organs other than the one in which they first appeared [8].

In this study, we will extend the analysis from the work of [7] to perform bifurcation analysis found in their work. The mathematical study of changes in a family's qualitative or topological structure, such as the integral curves of a family of vector fields or the solutions to a family of differential equations, is known as bifurcation theory [9]. This analysis will solve analytical, numerical, and graphical approaches using mathematical software applications such as XPPAUT and MATCONT. By doing this, a more detailed diagram and a specific threshold value of the malignancy parameter will be determined for better understanding of the cancer model. Therefore, this study is believed to fill the gap of knowledge in this cancer modelling research.

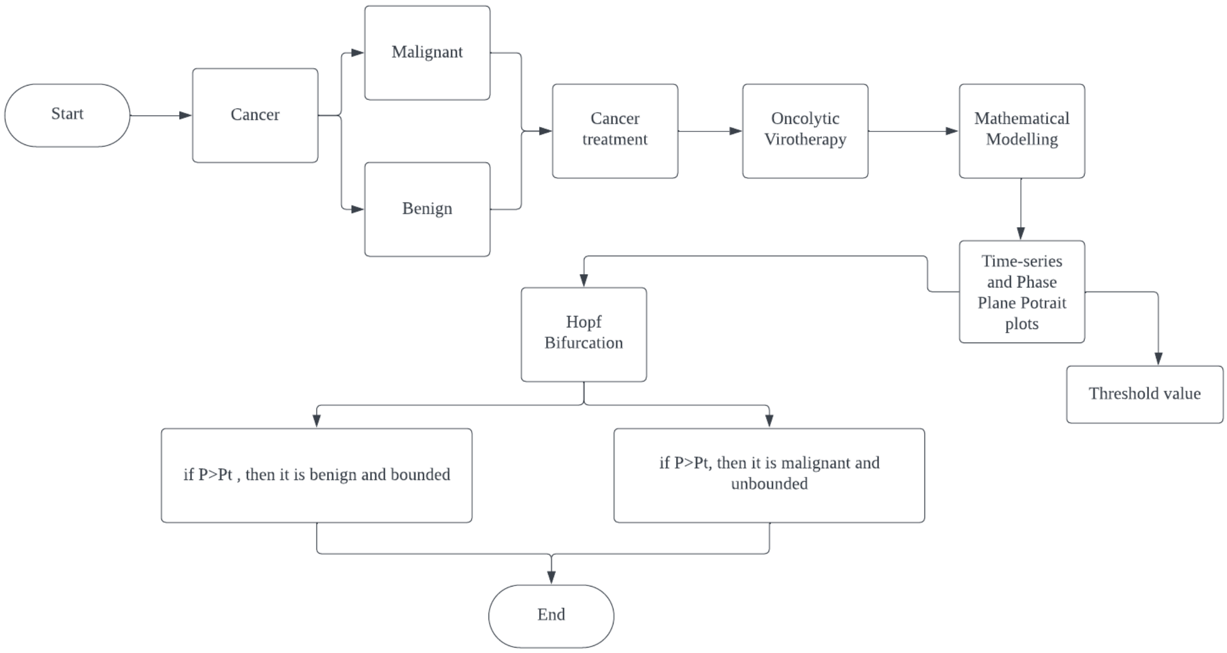

Fig.1 *Flowchart of Background Research*

2. Materials and Methods

This study mainly focused on the mathematical modelling of cancer by representing the therapy approach that is by injecting oncolytic virus into cancer cells (infected cancer cells). We refer to the model developed by [4] where the uninfected cancer cells and infected cancer cells by oncolytic virus as variables with malignancy parameter as the bifurcation parameter. Although the model has been studied, the threshold value of malignancy parameter has not been identified. Thus, we extend the analysis by finding the threshold value of the parameter towards the solutions whether the cancer cells are benign or malignant using numerical and graphical approaches. A better explanation is anticipated in this study as of the previous study. It is hoped that the output of the study would be able to improve the classifications of the results and help the reader to have a comprehensible understanding of the study from the diagrams produced by using software such as Maple, XPPAUT and MATCONT/MATLAB.

In developing mathematical models, investigating steady state/fixed point/equilibrium (i.e., a state that is independent of time) is crucial especially when modelling in biological or ecological applications. The steady states

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and their attributes provide utmost practical relevance, whereas the transient states of the system-those that are time dependent-are of “marginal” importance for many practical uses.

Mathematical models that consist of sets of first order ordinary differential equations are used in many applications. It should be noted that when second (or higher) order differential equations are included, the model equations can be written as a set of first order equations [10].

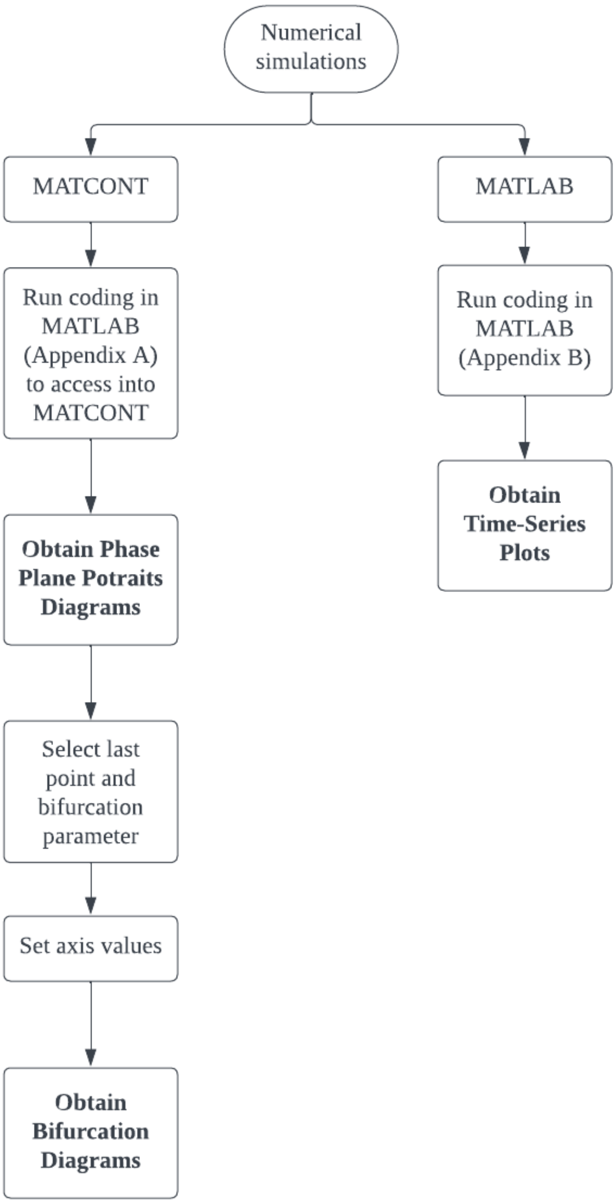


Fig.2 *Methodology Flowchart*

The model investigated in this study is [7]

$$\begin{aligned}\frac{dx}{dt} &= r_1 x\left(1-\frac{px+qy}{K}\right)-\frac{bxy}{x+y+a}\\ \frac{dy}{dt} &= r_2 y\left(1-\frac{px+qy}{K}\right)+\frac{bxy}{x+y+a}-\beta y\end{aligned} \tag{1}$$

The inhabitants of cancer cells are divided into two subgroups: those that are few of oncolytic viruses and those that are. The densities of each subpopulation are indicated by the letters x and y respectively. Two new parameters were introduced by [7] that measure the malignancy level of the cancer cells denoted by p and the therapeutic efficacy denoted by q.

Depending on how aggressively the cancer cells are malignant, the p (malignancy effect) value might be either positive or negative. The value indicates whether the cancer cells are well metamorphosed and benign, or the cancer cells are poorly or undifferentiated, which are hallmarks of malignant cancer. The dissimilarity in the middle of the overall count of cancer cells and the total number of DNA replicating mistakes is used to calculate the parameter p. Malignant cancer inhibits cells from going through apoptosis, while cells with a DNA replication mistake develop rapidly [7] The moderately developed cancer cells are represented by $p = 0$, due to the degeneracy of system (1).

The oncolytic virus's infection of the cancer cells will boost their ability to respond to treatment. The ratio of successful infection to the total number of contacts between the two populations is used to calculate the parameter q (therapy efficacy), and it indicates the effective contact rate between cancer cells that have not yet been exposed to the oncolytic virus and those that have. All other parameters and variables on system (1) are assumed to be nonnegative. The parameter a denotes an individual's immune response that stops viruses from killing cancer cells, and the parameter b denotes the quantity of viruses that can be spread to the population of cancer cells that are not already affected [7].

It is expected that the parameter r_1, which displays the highest per capita growth rate of the susceptible or uninfected cancer cell subgroup, will be positive [7]. It is because cancer cells have the power to live forever. Positive or negative values of the parameter r_2, which displays the highest per capita growth rate of the oncolytic virus-infected cancer cell subpopulation, are indicative of the subpopulation's rate of decay. The parameter β displays the percentage of infected cells that die because of viral infection. It is believed that both subpopulations on system (1) will expand logistically, where K is the carrying capacity [7].

Because benign cancer cells cannot metastasise to other amount of room and resources to grow, the greatest number of cancer cells that the human body can support is represented by the carrying capacity K. In the case of malignant cancer, the carrying capacity K is not a constraint on the proliferation of the cancer cells; as a result, they can migrate throughout the body and proliferate until the patient passes away.

There are three types of equilibria on system (1), i.e., the trivial, the semi trivial, and the nontrivial. The trivial equilibrium point, which is $E_1 = (0,0)$, occurs for all parameter values and demonstrates the absence of cancer cells. The Jacobian matrix at E_1 becomes

$$J_{E_1} = \begin{bmatrix} r_1 & 0 \\ 0 & -\beta r_2 \end{bmatrix}, \tag{2}$$

where the determinant, Det = $r_1 r_2 - r_1\beta$, and trace, Tr = $r_1 + r_2 - \beta$. The corresponding eigenvalues, λ, are $r_2 - \beta$ and r_1. Near the equilibrium E_1, the steady state unstable for $r_2 > \beta$ and unstable saddle type for $r_2 < \beta$. In this case, if the cancer cells occur, it could not be utterly eliminated (Kusumo *et al.*, 2020).

Next, the equilibria are semi trivial, i.e., $E_2 = (K/p, 0)$, and $E_3 = (0, K(r_2 - \beta)/\ r_2 q)$, which show the inexistence of one of the subgroups. The condition where the oncolytic virus is removing the infected cancer cells from the population is shown by the semi trivial equilibrium E_2,. The Jacobian matrix at E_2 is

$$J_{E_2} = \begin{bmatrix} r_1 & \dfrac{-r_1 q(ap + K) - bKp}{p(ap + K)} \\ 0 & \dfrac{(b-\beta)K - a\beta p}{ap + K} \end{bmatrix}, \tag{3}$$

where the determinant, Det = $\frac{r_1(a\beta p - (b-\beta)K)}{ap+K}$, and trace, Tr = $\frac{(b-\beta-r_1)K - ap(\beta+r_1)}{ap+K}$. The equilibrium E_3 has the Jacobian matrix as

$$J_{E_3} = \begin{bmatrix} \dfrac{Kbr_2^2 - \big((b + r_1)K + aqr_1\big)\beta r_2 + K\beta^2 r_1}{((-aq - K)r_2 + \beta K)r_2} & 0 \\ \dfrac{(\beta - r_2)(-p(aq + K)r_2 + K(bq + \beta p))}{((-aq - K)r_2 + \beta K)q} & \beta - r_2 \end{bmatrix}, \tag{4}$$

with Det $= r_1(r_2 - \beta)$, and Tr $= \frac{(aq+K)r_2^3 + ((b-2\beta)K - aq\beta)r_2^2 - ((b-\beta+r_1)K + aqr_1)\beta r_2 + K\beta^2 r_1}{((-aq-K)r_2 + \beta K)r_2}$,
depicts the scenario in which the virus has infected every cancer cell. The larger value of q will result in greater therapeutic efficacy. As a result, the virus's ability to infect cancer cells will diminish until it reaches zero for q. Equilibrium E_3 serves the same purpose as equilibrium E_1 in this situation [7].

3. Results and Discussions

In this study, we used the parameters that have been proposed by [7]. The parameters are listed in Table 1. The bifurcation parameter in this study is the p value (the malignancy effect). [7] used parameter in the study which gave rise to the oscillation behaviour between population (uninfected cancer cells by oncolytic virus) and (infected cancer cells by oncolytic virus) in the time series plots.

Therefore, we extended the analysis to obtain results on time series plots with different p values as they would help to describe the bifurcation diagrams. Therefore, three different p values have been illustrated in this study which are $p = 0.52$, $p = -0.52$, and $p = -0.67$ to investigate the dynamical behaviours that occur around the Hopf bifurcation [9]. The reason we choose $p = 0.52$ is to validate the statement mentioned in the paper that p can be positive to describe the situation where the cancer cells are well differentiated or benign. The selection of $p = -0.67$ came from the numerical investigation that we performed using MATCONT. By illustrating these cases, we can see different dynamics of uninfected cancer cells ($\boldsymbol{x}$) and infected cancer cells by oncolytic virus ($\boldsymbol{y}$).

Table 1 *Parameter values used in numerical simulation from [7]*

Parameter	Value
r_1	40
r_2	2
K	100
b	20
a	0.05
β	2
q	1
p	-0.52

As shown in Table 1, the model (1) was developed by using these parameter values.

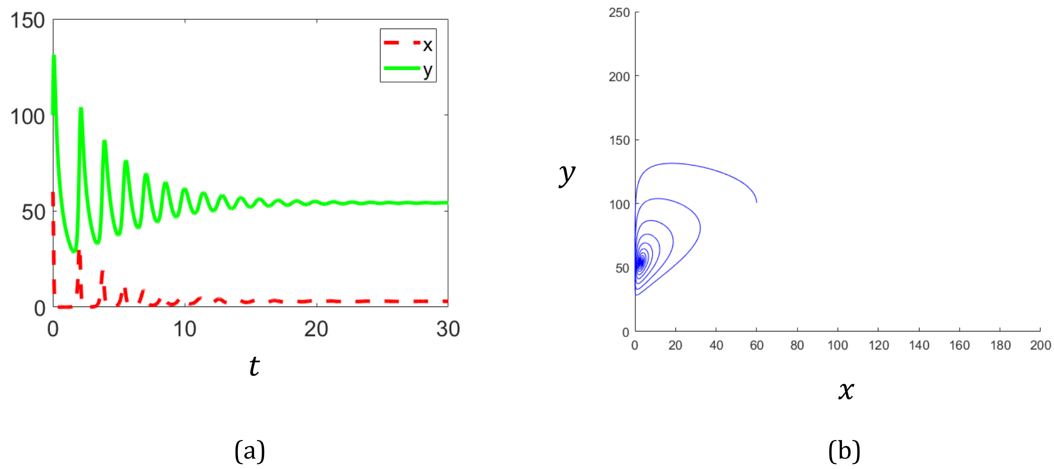
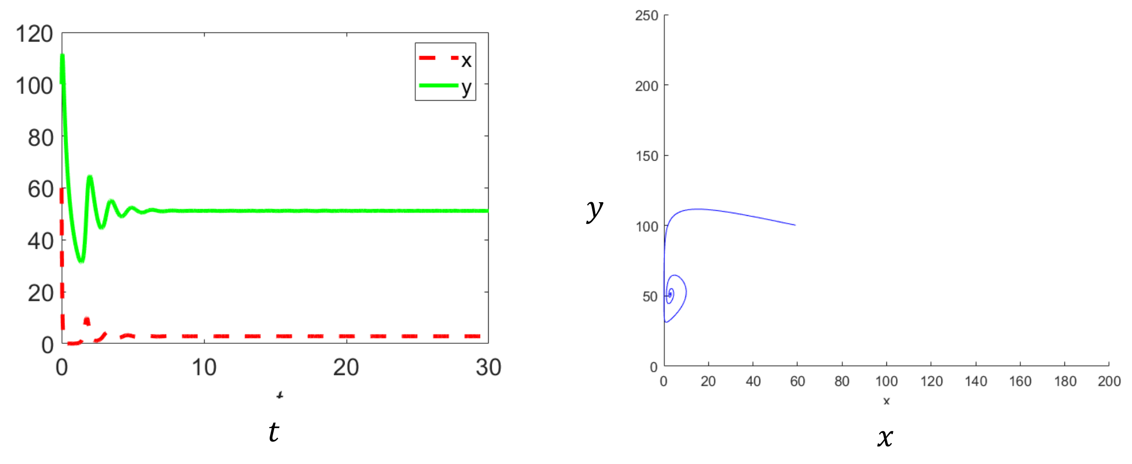


Fig.3 (a) *Time series plot of system (1) for malignancy effect,* $\boldsymbol{p = -0.52}$. **(b)** *Phase plane portrait of system (1) diagram for malignancy effect,* $\boldsymbol{p = -0.52}$.

Fig.3 (a) depicts the time series plot for the case $p = -0.52$ with initial value of $(x, y) = (60,100)$. From Fig.3 (a), both cells show decreasing pattern over time until reach an equilibrium at $(x, y) = (3.024,54.212)$. In this case, the infected cancer cells by oncolytic virus (y) appears to be much higer than the uninfected cancer cells (x) which implies that the oncolytic virus treatment has the potential to be effective to treat the cancer cells that have been targeted. It has been proved in clinical areas as well [3].

The interpretation that could be done based on Fig.3 (a) and (b) is that the cancer therapy by using oncolytic virus could be successful if the initial populations $(\boldsymbol{x}, \boldsymbol{y}) = (\mathbf{60}, \mathbf{100})$ are inside the boundary [7]. The growth of cancer cells will be unbounded if the initial populations are outside the boundary and could lead to spreading of cancer cells (metastasis). Hence, the therapy is considered a failure. The smaller boundary will have high malignancy level and the possibilities to have successful therapy is lower.

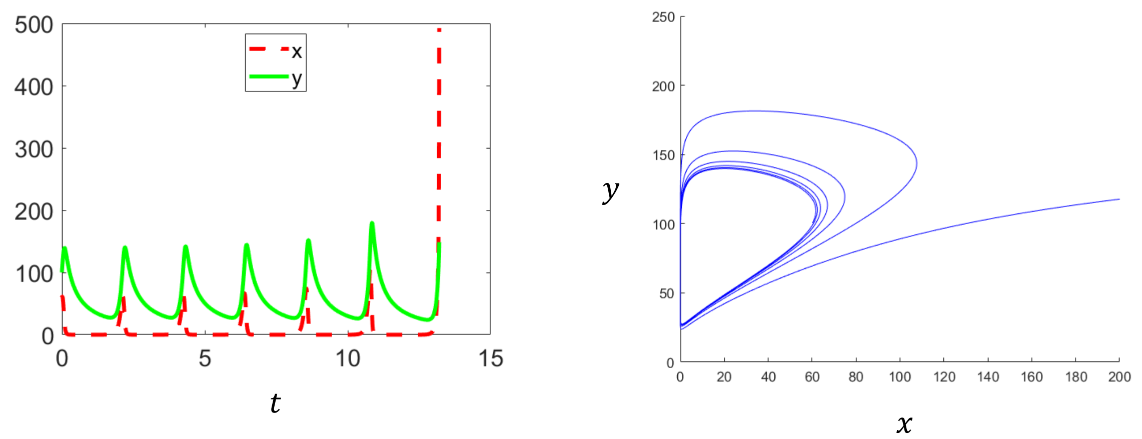


(a) (b)

Fig.4 (a) *Time series plot of system (1) for malignancy effect,* $\boldsymbol{p = 0.52}$**.** (b) *Phase plane portrait diagram of system (1) for malignancy effect,* $\boldsymbol{p = 0.52}$**.**

As compared to the previous case $p = -0.52$, in Fig.4 (a) the number of oscillations of population of uninfected cancer cells (x) and infected cancer cells (y) are lesser and the equilibrium is reaching $(x, y) = (2.8531, 51.1944)$. When p value is positive, the population y is still higher than the population x. It means, there is a reduction of malignancy level in population y compared to population x.

In Fig.4 (b), again for the solutions that have the initial value inside the boundary will tend to the equilibrium point and the ones have initial value outside the boundary will be unbounded. Therefore, as parameter p remain positive, the initial solutions are still inside the boundary implies that the oncolytic virotherapy has possibilities to be successful as there is a reduction in malignancy level and a rise in population y.

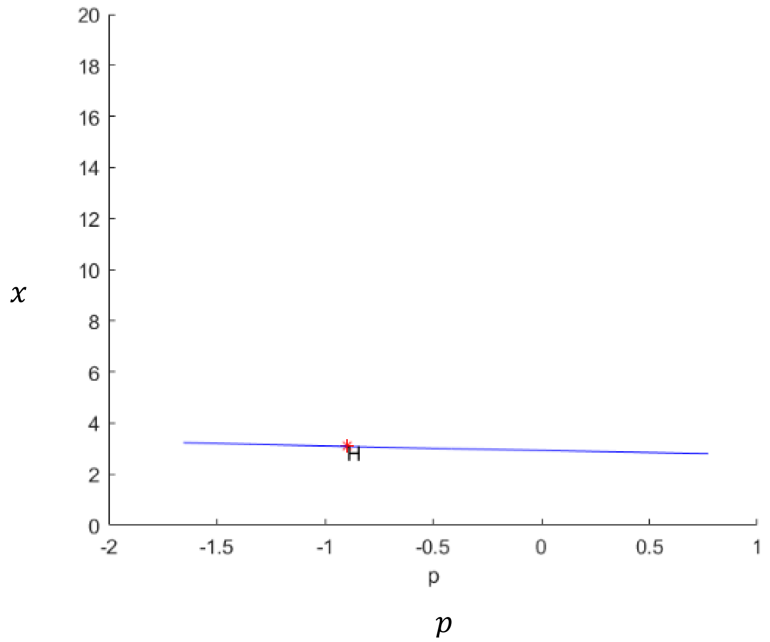


(a) (b)

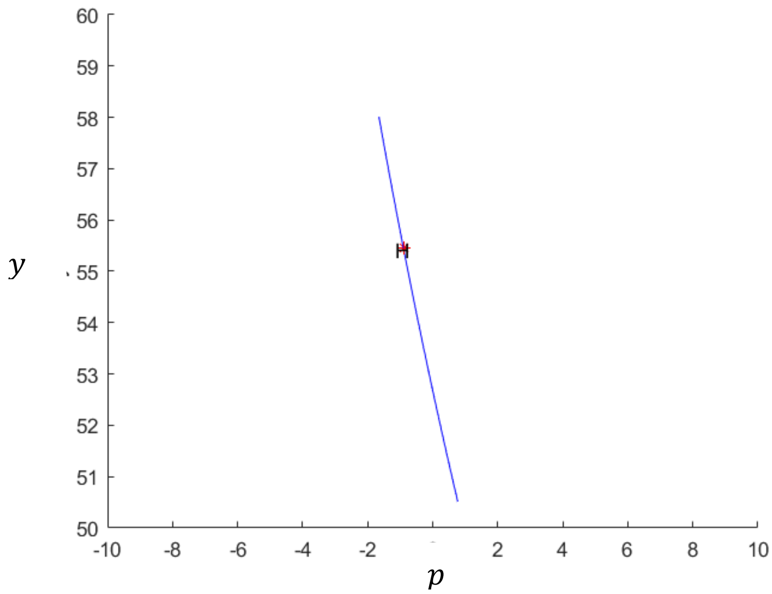
Fig.5 (a) *Time series plot of system (1) for malignancy effect,* $\boldsymbol{p = -0.67}$**. (b)** *Phase plane portrait of system (1) for malignancy effect,* $\boldsymbol{p = -0.67}$**.**

As compared to the previous cases, $p = -0.52$ and, $p = 0.52$, Fig.5 (a) shows a major difference in the oscillation of populations, x and, y. The population, y is still higher than population, x but there is a surge in population, x at point, $(x, y) = (13.2, 148.651)$. It shows that the solutions are unbounded or go to the invariant structure which leads to spreading of cancer cells (metastasis). Therefore, we could say that $p = -0.67$ could be the threshold point as the solution becomes unbounded from this point onwards to negative region. The value, $p = -0.67$ is obtained by doing numerical investigation on time series plot. In Fig.5 (b), it is clearly proven that the initial solutions are outside the boundary and the oncolytic virotherapy will be unsuccessful.

Based on the research objectives, the main idea of this research is to extend the analysis on the bifurcation diagrams by finding the threshold malignancy effect value. Therefore, the bifurcation diagrams x vs p and y vs p have been illustrated in Fig.6 (a) and (b).



(a)



(b)

Fig.6 (a) *Bifurcation diagram of* $\boldsymbol{x}$ *vs* $\boldsymbol{p}$. **(b)** *Bifurcation diagram of* $\boldsymbol{y}$ *vs* $\boldsymbol{p}$.

Fig.6 (a) and (b) shows the continuation of a nontrivial equilibrium point of system (1) which undergoes Hopf bifurcation for the variation of parameter p. That creates an unstable periodic solution at $p = -0.89893$. In this case, we found that the uninfected cancer cells population (x) will increase while the malignancy level (p) will decrease.

4. Discussions

From our analysis, we found that for p is greater than the threshold level, the uninfected cancer cells by oncolytic virus (x) increases. It indicates that oncolytic virotherapy could be successful. The Hopf point represents the situation that the therapy has the possibility to be successful as well. Based on Fig.5 (a) and (b), there is not any periodic on Hopf point found because it is an unstable periodic solution.

Therefore, with higher value of $\boldsymbol{y}$ the efficiency of the therapy could be a positive outcome since there is a reduction in malignancy effect on the population. As we expected, the uninfected cancer cells by oncolytic virus should be lower than the infected cancer cells by oncolytic virus. This is because the cancer cells that have been injected by oncolytic virus should increase as it reduces the malignancy level in the cells and becomes a cancer free cell in the body. In this case, it shows that the oncolytic virus injected effectively removing the cancer without damaging the healthy cells. Overall, oncolytic virotherapy will be efficient for patients as it is a promising approach to treat cancer. The efficiency can vary depending on the malignancy parameter, type of cancer, patient's characteristics, and patient's health history.

5. Conclusions

The research objectives of this study are to extend and produce the bifurcation diagrams for $\boldsymbol{x}$ and $\boldsymbol{y}$ against the primary bifurcation parameter, which is the malignancy level, p which have been successfully produced by using mathematical software.

The parameter p (malignancy effect) is important to determine the possibility to have a successful oncolytic virus cancer therapy. If the p value is greater than the threshold value, the solutions of system (1) will be bounded, and it leads to benign type of cancer. As mentioned before, benign cancer does not metastasis or spread to other cells. Therefore, removing this cancer cell is easier compared to malignant type of cancer cells. The removal of benign cancer can be done through surgery or by using other therapies. The efficacy of oncolytic virotherapy increases if the malignancy is greater than the threshold value.

If the p parameter is negative and less than the threshold value, the system (1) have the possibilities to have unbounded solutions or go to the invariant structure. When the p greater than the threshold value, the bounded domain of system (1) expands. All solutions go to stable equilibrium point as they are inside the cycle. When the stable equilibrium point occurs, the cancers cells are in an absorbing state that allows for a limited degree of isolation. In contrast, outside the cycle the cancer cells have the ability to metastasis as the system (1) has unbounded solutions.

The therapy efficacy of this cancer therapy is solely depending or limited on the existence of equilibrium points. It indicates that there is one of the steady states of the system where it can be isolated to a certain extent depending on the therapy efficacy.

Each patient has a different level of malignancy level. So, the efficacy of the therapy also depends on the patient's malignancy degree and immune response. Lower malignancy level will have higher possibilities to remove the cancer cells effectively and therefore the oncolytic virus cancer therapy will be successful. This oncolytic virus cancer therapy is still an area of active research but has been proven in clinical areas [9]. Therefore, we need better evidence to strengthen this therapy as oncolytic virotherapy is an emerging cancer therapy.

Very few research studies have been done on the therapy efficacy and still a field of ongoing research. Therefore, the optimal malignancy level and therapy efficacy that can treat the cancer cells by sparing the normal or healthy cells in the body are still open problems in this study. It is recommended to understand the role of the malignancy parameter as it is important to decide on the course of action for isolating or removing the cancer cells.

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Conflict of Interest

Authors declare that there is no conflict of interests regarding the publication of the paper.

Author Contribution

The authors confirm contribution to the paper as follows: ***study conception and writing:*** *Sharmila Sri Balasubramaniam;* ***guidance and made corrections:*** *Hamizah Mohd Safuan;* ***Reviewer:*** *Fajar Adi Kusumo. All authors reviewed the results and approved the final version of the manuscript.*

Appendix A: MATCONT coding

```
function matcont(varargin)
MINIMALVERSION = '9.2';
VERSIONNAME = '2017a';

if (verLessThan('matlab', MINIMALVERSION))
```

```
    for i = 1:1
        fprintf(2, 'matlab version needs to be %s (%s) or higher\n', MINIMALVERSION,
VERSIONNAME);
    end
    pause(2);
end
%Same init as CL-version.
init();
addpath('GUI');
workingpath = pwd(); %save working dir
try
%execute path-init of GUI
cd(fullfile(workingpath, 'GUI'));
initpath();
cd(workingpath); %restore working dir
catch
    %failure is an option if the script was run succesfully before, GUI can
    %then be started from anywhere. not just main-directory.
end
%Start GUI
MATCONTGUI(nargin);
end
```

Appendix B

```
function Cancer_Model
clear all
clc
close all
%initial condition
xo=60;
yo=100;
%Parameter
r1=40;
r2=2;
K=100;
b=20;
a=0.05;
B=2;
q=1;
p=-0.52;
[t2,n]=ode45(@hanta1,0:0.01:30,[xo yo],[],p,q,K,a,b,B,r1,r2);
figure(1)
plot(t2,n(:,1),'--r',t2,n(:,2),'g-','LineWidth',3)
%title('Cancer model','FontSize',14)
xlabel('\it t','FontSize',14)
legend('r_s','r_i','Location','Best')
%ylim([0 140])
%xlim([0 30])
text(150,0.15,'\it b<b_c_1','FontSize',16)
set(gca,'FontSize',18)
function f=hanta1(t2,n,p,q,K,a,b,B,r1,r2)
x=n(1);
y=n(2);
%Equations
f(1) =r1*x*(1-((p*x+q*y)/K))-b*x*y/(x+y+a);
f(2) =r2*y*(1-((p*x+q*y)/K))+(b*x*y/(x+y+a))-B*y;
f=f(:);
```

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