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Research Article

Mathematical Analysis of Virotherapy Treatment for Cancer

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I N F O

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A B S T R A C T

A virotherapy model for cancer has been identified and analysed in this article. This mathematical model of cancer virotherapy was developed by Friedman. It was constructed by means of non-linear differential equations related to "the count of cancer cells, the count of infected cancer cells, the count of dead cells, and the count of virus cells that do not belong to tumour cells". It also includes parameters for the rate of viral infection of cancer cells, the proliferation rate of cancer cells, the removal rate of debris of dead cells, the death rate of infected cancer cells, and the count of virus particles that are not contained in cancer cells. The Homotopy Perturbation Method was applied to solve the non-linear differential equations and was analysed both qualitatively and numerically. The values of the variation in parameters were evaluated to investigate the impact of controls on the spread of cancer cells. Through the numerical and graphical results, the optimal control, which helps to significantly reduce the impact of cancer cells, has been discussed. A significant agreement is noted with approximate analytical results and numerical simulations.

Keywords: Non-linear Differential Equations, Cancer Cell Count, Count of Infected Cancer Cells, Count of Dead Cells, Death Rate of Infected Cancer Cells, Homotopy Perturbation Method

Introduction

It is believed that there will be a startling rise in the incidence of cancer disease in the future. This increase has already been seen with 17,000,000 new cases of cancer recorded in 2018 and it is estimated that about 23.6 million people will be affected by cancer in 2030.[1] In addition, researchers suggest that by 2030, cancer will claim the lives of almost 20 million people each year. Given these figures, it is imperative that numerous branches of science and technology work tirelessly together to further the development of treatments for this disease. Cancers entail the recurring and unchecked proliferation and spread of malignant cells. Solid tumours made of large masses of tissue constitute one type and blood cancers like leukaemia constitute the other type of neoplasia. There are two types of tumours: benign tumours, which are generally non-invasive and do not spread, and malignant tumours, which do spread maliciously.[2]

Oncologists currently employ various therapeutic techniques to slow the growth of tumours and ultimately destroy cancer. However, the type of cancer, its stage at the time of diagnosis, the affected person's age, and the types of therapeutic techniques used, all have a major effect on the survival rate of the affected person, for instance,

prostate and pancreatic cancer have the highest (99.2%) and lowest (6%) survival rates, respectively.[3] The common cancer treatment options include surgery, chemotherapy, radiation, immunotherapy, hormonal treatment, and stem cell transplantation. In many instances, it is crucial to combine different treatment modalities concurrently or intermittently or use "combination therapy", in order to destroy cancer completely and reduce the risk of cancer relapse.[4–7]

Combination therapy is frequently used to benefit from synergistic cancer treatments while minimising treatment-related adverse effects, for instance, some chemotherapeutic medications can be utilised to make tumours more radiotherapy-susceptible. The results of patients who receive radiation therapy after chemotherapy are, therefore, improved. Another example is chemotherapy or radiation in conjunction with stem cell therapy.[8] Hematopoietic stem cells (HSC), which produce all blood cells, can be destroyed by high doses of chemotherapy and radiation therapy. Following such therapies, stem cell transplantation techniques are performed to restore blood-forming stem cells.

A variety of therapeutic techniques are used by oncologists to slow the growth of tumours and ultimately cure cancer. Different treatment modalities are needed to eliminate cancer cells and diminish the danger of a relapse. The book by Chou and Friedman[9] categorises mathematical models according to the type of therapy (combination therapy or monotherapy) used. The various therapeutic modalities mentioned are:

- Chemotherapy: It involves the usage of several medicinal agents in the treatment of cancer.
- Immunotherapy: It refers to increasing white blood cells while employing a variety of medicinal drugs.
- Anti-angiogenic therapy: It uses a variety of anti-angiogenic drugs to stop blood vessel growth in tumours and expedite the treatment of cancer.
- Radiotherapy: In this, radiation is employed as a therapeutic method to help treat cancer.
- Hormone therapy: It refers to the use of hormones or other drugs that regulate the body's hormone production to eradicate cancer cells.
- Unrelated therapies include stem cell therapy, radio virotherapy, gene therapy, and other procedures that use a number of therapeutic substances to treat cancer.

It is challenging to describe complete cancer behaviour utilising various cell-based models because most of the aforementioned therapeutic approaches include numerous intricate systems and cell types. Furthermore, many of the evaluations that have already been published note that simple mathematical models, including those that focus on various cells, are too general and are, therefore, unsuitable for demonstrating how therapy affects the dynamics of cancer.[10] It is crucial to take into account the interactions in terms of conflict and persistence between these cell types when mathematically simulating the dynamics of cancer, in addition to the growth and demise patterns of different cell populations.[11]

Cancer is treated using numerous approaches; some of these therapies actively eradicate cancer cells, while others alter the surrounding environment of cancer, making it resilient to the growth of cancer cells. An anti-cancer drug is also used which employs viral particles to destroy cancer cells. Due to genetic alteration, the virus particles can harm cancer cells but not typically healthy ones. Such viruses are called oncolytic viruses. The virus is injected directly into the tumour. After entering a cancer cell, a virus begins to quickly replicate, and when the cancer cell dies, a large number of virus particles burst out and proceed to infect other cancer cells.

In this study, homotopy perturbation techniques have been used to analyse the mathematical model of some parameters of virotherapy. Unlike other conclusions in published literature, this one has not yet been mathematically investigated. Additionally, a comparison between the mathematical and numerical results has not yet been made. Since there is no method to discover the solution to the system of non-linear differential equations for the constructed model, an attempt has been made to find the solution using semi-analytical methods such as the homotopy perturbation method (HPM). According to the model analysis, Friedman et al. discovered the prerequisites for ideal control.[11] Our findings provide the finest understanding of a simplified virotherapy model for cancer treatment.

Mathematical Formulation of Virotherapy Model

The viruses are inoculated into the tumour, and after invading a cancer cell, the virus activates to rapidly reproduce. After the cancer cell dies, many viruses emerge and spread to infect further cancer cells. The model developed by Chou and Friedman[9] introduced the following variables: "x: count of cancer cells, y: count of infected cancer cells, n: count of dead cells, and v: count of virus particles which are not contained in cancer cells". Virotherapy is modelled by the following system of equations using these four parameters:

$$\frac{dx}{dt} = \alpha x(t) - \beta x(t)v(t) \quad (1)$$

$$\frac{dy}{dt} = \beta x(t)v(t) - \delta y(t) \quad (2)$$

$$\frac{dn}{dt} = \delta y(t) - \mu n(t) \quad (3)$$

$$\frac{dv}{dt} = b\delta y(t) - \gamma v(t) \quad (4)$$

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The initial conditions are as follows:

$$x(0) = a \geq 0,\ y(0) = b \geq 0, n(0) = n_0 \geq 0, \text{and } v(0) = v_0 \geq 0 \quad (5)$$

Table 1 shows the various parameters of the virotherapy model.

Table 1.Description and Parameter Values of the Virotherapy Model[9]

Symbol	Description	Values
α	Proliferation rate of cancer cells	0.02
β	Viral transmission rate of tumour cells	7×10^{-8}
δ	Mortality rate of tumour cells with infection	1/18
μ	Elimination rate of deceased damaged cells	1/48
γ	Growth factor	2.5×10^{-2}
b	Replication number of a virus at the time of death of the infected cancer	50

Approximate Analytical Expression of Virotherapy using Homotopy Perturbation Method

HPM is used to solve non-linear equations (Equations 1–5).

$$(1-M)\left(\frac{dx}{dt} - \alpha x(t)\right) + M\left(\frac{dx}{dt} - \alpha x(t) + \beta x(t)v(t)\right) = 0 \quad (6)$$

$$(1-M)\left(\frac{dy}{dt} + \delta y(t)\right) + M\left(\frac{dy}{dt} - \beta x(t)v(t) + \delta y(t)\right) = 0 \quad (7)$$

$$(1-M)\left(\frac{dn}{dt} + \mu n(t)\right) + M\left(\frac{dn}{dt} - \delta y(t) + \mu n(t)\right) = 0 \quad (8)$$

$$(1-M)\left(\frac{dv}{dt} + \gamma v(t)\right) + M\left(\frac{dv}{dt} - b\delta y(t) + \gamma v(t)\right) = 0 \quad (9)$$

The solution of Equations 6–9 is expressed in power series:

$$x = x_0 + Mx_1 + M^2x_2 + M^3x_3 + \cdots \quad (10)$$

$$y = y_0 + My_1 + M^2y_2 + M^3y_3 + \cdots \quad (11)$$

$$n = n_0 + Mn_1 + M^2n_2 + M^3n_3 + \cdots \quad (12)$$

$$v = v_0 + Mv_1 + M^2v_2 + M^3v_3 + \cdots \quad (13)$$

Substituting the values from Equations 10–13 in Equations 6–9 and ordering the coefficients of the powers of M provides the following systems of differential equations:

$$\begin{aligned} &M^0: \frac{dx_0}{dt} - \alpha x_0 \\ &M^1: \frac{dx_1}{dt} \pm \alpha x_1 + \beta x_0 v_0 \\ &M^2: \frac{dx_2}{dt} \pm \alpha x_2 + \beta x_1 v_0 + \beta x_0 v_1 \end{aligned} \quad (14)$$

$$\begin{aligned} &M^0: \frac{dy_0}{dt} + \delta y_0 \\ &M^1: \frac{dy_1}{dt} + \delta y_1 - \beta x_0 v_0 \\ &M^2: \frac{dy_2}{dt} + \delta y_2 - \beta x_1 v_0 + \beta x_0 v_1 \end{aligned} \quad (15)$$

$$\begin{aligned} &M^0: \frac{dn_0}{dt} + \mu n_0 \\ &M^1: \frac{dn_1}{dt} + \mu n_1 - \delta y_0 \\ &M^2: \frac{dn_2}{dt} + \mu n_2 - \delta y_1 \end{aligned} \quad (16)$$

$$\begin{aligned} &M^1: \frac{dv_1}{dt} + \gamma v_1 - b\delta y_0 \\ &M^2: \frac{dv_2}{dt} + \gamma v_2 - b\delta y_1 \end{aligned} \quad (17)$$

Analytical Expression of Virotherapy

The analytical solution of Equations 1 through 5 is provided in this part using HPM, and the extended derivative of HPM:

$$x(t) = 0.000008e^{(0.20t)} + 0.00000000000000000224e^{(0.175t)} \quad (18)$$

$$y(t) = 0.000001e^{(-0.05556t)} + 0.00000000000002429e^{(0.175t)} \quad (19)$$

$$n(t) = 0.000002599e^{(-0.0209t)} - 0.000001599e^{(-0.05556t)} \quad (20)$$

$$v(t) = 0.0000001909e^{-0.0250t} - 0.00000009091e^{(-0.05556t)} \quad (21)$$

Numerical Results and Discussion

The numerical solution and the resultant analytical results are compared, which is represented graphically in Figures 1–9.

Figure 1 demonstrates the densities of cancer cells with regard to time; as cancer cell proliferation rates grow, so does their density. Figure 2 depicts the density of cancer cells that are infected over time; as the rate of cancer cell viral infection declines, so does the density of infected cancer cells. Figure 3 displays the density of cancer cells that are infected with the disease with respect to time. As the mortality rate of cancer cells that are infected with the disease increases, there is a slight change in the density of cancer cells. Figure 4 shows that when the value of δ is increased, the density of dead cells increases. It reaches the peak value at t = 13, after which it reduces gradually with time. Figure 5 shows that when the removal rate of debris from dead cells increases, the density of dead cells decreases with respect to time. Figure 6 shows that decreasing the value of b leads to an increase in the number of virus particles not in the cancer cell up to t = 7, followed by a rapid decrease with time. Figure 7 shows that by decreasing the value of γ, the density of virus particles not in the cancer cell decreases gradually with time.

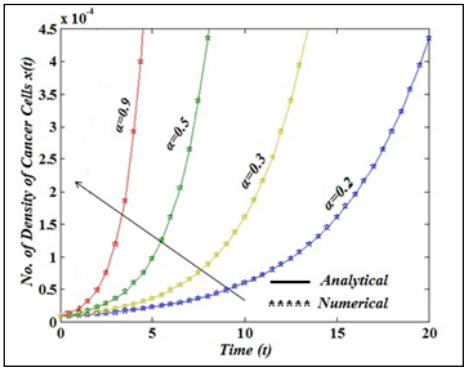

Figure 1.Comparison of Densities of Cancer Cells as per Different Values of α

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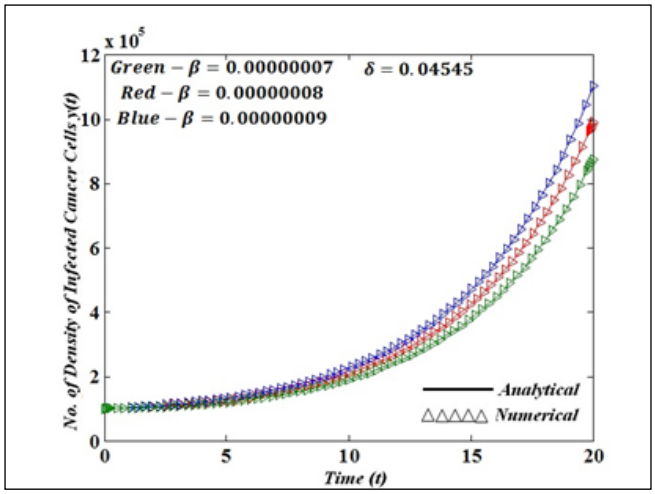

Figure 2.Comparison of Densities of Infected Cancer Cells as per Different Values of β and δ

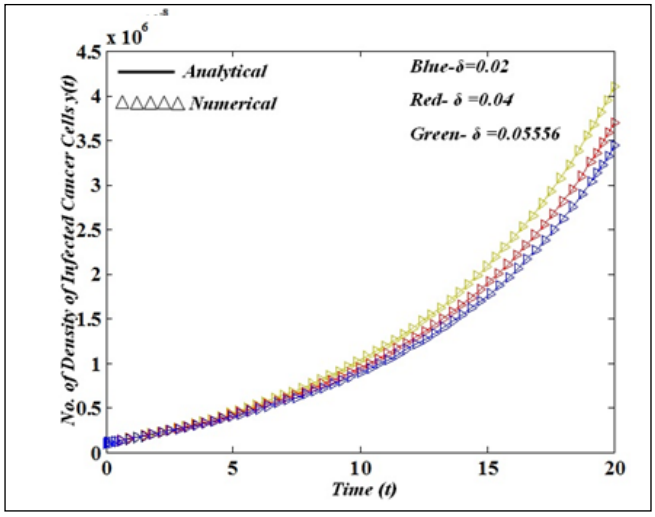

Figure 3.Comparison of Densities of Infected Cancer Cells as per Different Values of δ

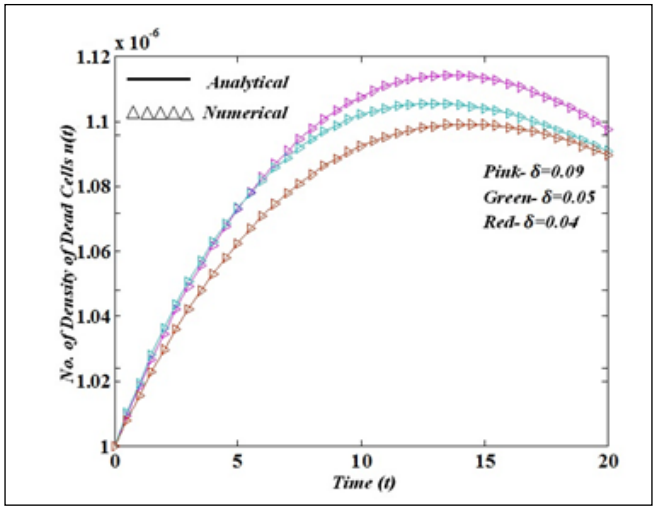

Figure 4.Comparison of Densities of Dead Cells as per Different Values of δ

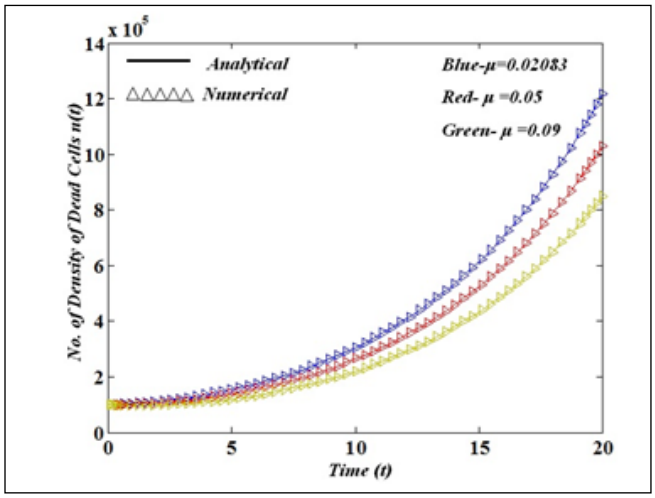

Figure 5.Comparison of Densities of Dead Cells as per Different Values of μ

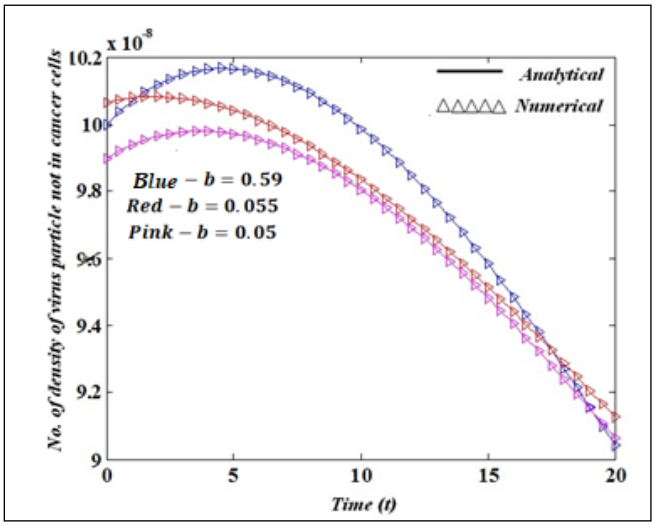

Figure 6.Comparison of Densities of Virus Particles Not Contained in Cancer Cells as per Different Values of b

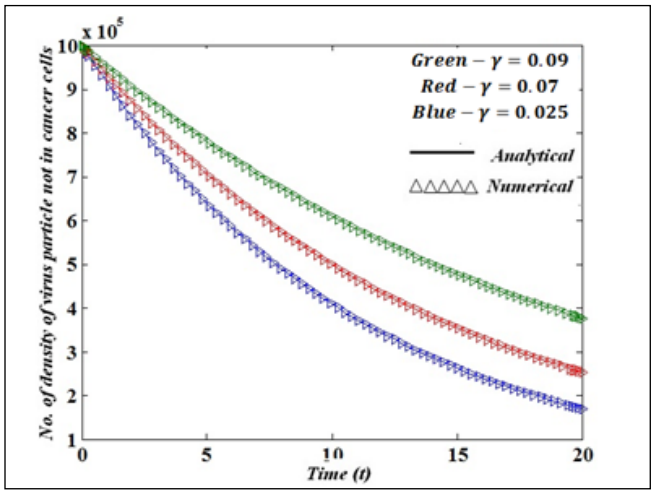

Figure 7.Comparison of Densities of Virus Particles Not in Cancer Cells as per Different Values of γ

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Figure 8 demonstrates that as the value of b declines, the count of virus particles outside cancer cells gradually decreases over time when $\gamma = 0.45$.

Figure 9 shows when there is an increase in the value of β, the count of infected cancer cells increases gradually over time after $t = 5$ (when δ = 0.04545).

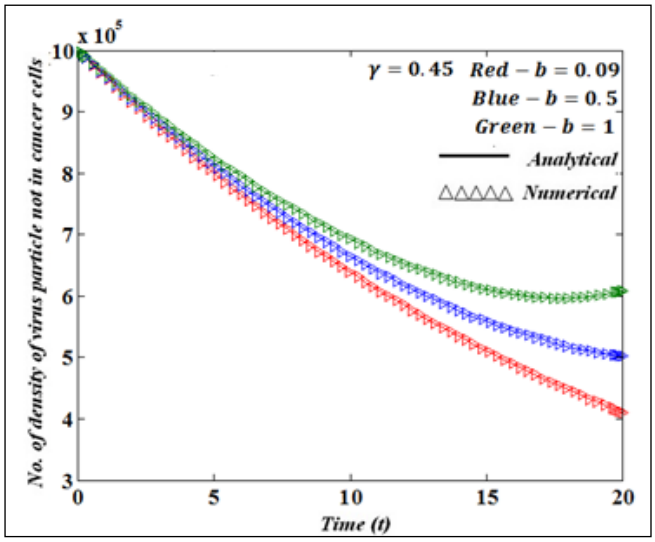

Figure 8.Comparison of Densities of Virus Particles Not in Cancer Cells as per Different Values of γ and b

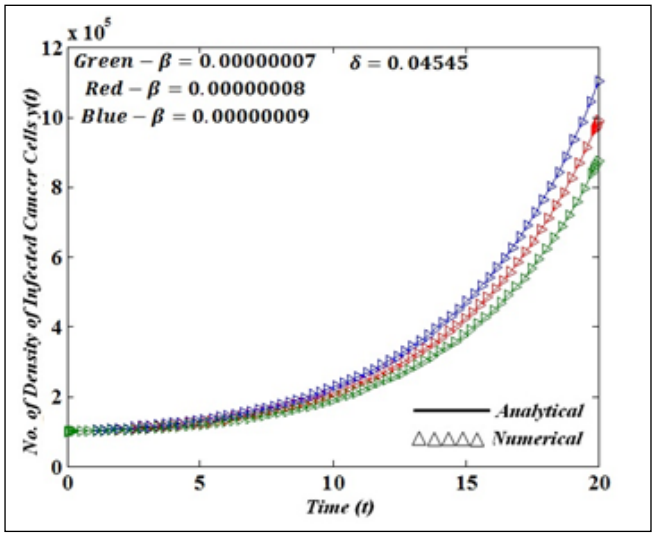

Figure 9.Comparison of Densities of Infected Cancer Cells as per Different Values of β and δ

Application of this Model

The optimal controllability of the disease is identified from the comparison of the count of virus particles which are contained and not contained in cancer cells which helps us to significantly reduce the impact of the cancer cell.

Conclusion

The governing equation of virotherapy consists of a system of non-linear differential equations, where "$x(t)$: count of cancer cells, $y(t)$: count of infected cancer cells, $n(t)$: count of dead cells, and $v(t)$: count of virus particles which are not contained in cancer cells". The non-linear differential equation has been solved using the analytic approach of the homotopy perturbation method (HPM). In this article, the virotherapy model has been solved analytically using HPM, and the resulting results accorded well with the numerical findings. The MATLAB ode45 function generates numerical results that are consistent with the analytical solution obtained using HPM. The variation of parameter values is indicated graphically in MATLAB programming. The variation of parameters in a graph suggests potential values for the growth factor, the number of viral replications when the cancer cell that was infected died, the rate of cancer cell proliferation, the rate at which cancer cells are infected by viruses, the rate at which diseased tumour cells die, and the rate at which dead cell debris is removed. Control parameters were also found to have a significant impact.

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