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Original Research

Virotherapy Based Mathematical Model for Cancer Treatment

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ABSTRACT:
A mathematical model based on ordinary differential equations (ODE) is presented in this article to describe the dynamics of cancer treatment with oncolytic viruses. A mathematical model is built to address fundamental questions in virotherapy.. In this article, we examine virotherapy, a form of cancer treatment that is new relatively. The first aim of this study is to demonstrate that the model has two equilibrium points that represent the failure of treatment which was initially unsuccessful due to failing to address the effect of the immune system and the desired outcome of therapy. As well as the local stability analysis of equilibrium points.
Anumerical simulation is also performed using the Runge-Kotta method through the use of MATLAB. Also, demonstrate the effect of parameter β on the outcome of virotherapy.

KEYWORDS: Virotherapy, Mathematical Model , Cancer Treatment.

INTRODUCTION

There are two main pathways to fighting disease. The first is by harnessing our natural immune system to eliminate pathogens and rogue cells. The second is through therapeutic drugs, which offer treatments for a broad range of disorders such as immune disease, bacterial infection, and cancer (Pooladvand, 2021).

With continual advancements in immunology, drug design, and delivery we progressively uncover a more diverse and complex map of interactions between cells and their environment. Therefore, we face more questions than ever before as to the significance of these interactions and their effect on each other. Mathematical modeling can greatly assist in understanding the key mechanisms that drive observable behaviors(Tavoni1, 2021).

Virotherapy is a tumor treatment that uses viruses to selectively target and destroy cancer cells. Clinical trials have demonstrated varying degrees of success for the therapy with limitations predominantly due to barriers to viral spread throughout the tumor and the immune response to the virus. (Friedman,2014).

VIROTHERAPY MODEL

We consider anti-cancer drug which employs virus particles to kill cancer cells; such treatment is called virotherapy (Tuwairqi, 2020). The virus particles are genetically modified so that they can infect cancer cells but not normal healthy cells. Such viruses are called oncolytic viruses. The viruses are injected directly into the tumor. After entering a cancer cell, a virus begins to quickly replicate, and when the cancer cell dies, many virus particles burst out and infect other cancer cells (Chou, 2016) .

For mathematical model of the process of virotherapy, we consider a very simple model of cancer and introduce the following variables (Nouni, 2019):

x: the number density of cancer cells,

y: the number density of infected cancer cells,

n: the number density of dead cells,

v: the number density of virus particles which are not contained in cancer cells.

Virotherapy is modeled by the following system of equations:

$$dx/dt = \alpha x - \beta xv \qquad [1]$$

$$dy/dt = \beta xv - \delta y \qquad [2]$$

$$dn/dt = \delta y - \mu n \qquad [3]$$

$$dv/dt = b\delta y - \gamma v \qquad [4]$$

Here,

α: the proliferation rate of cancer cells,

β: rate of infection of cancer cells by viruses,

δ: the death rate of infected cancer cells,

μ: the removal rate of debris of dead cells,

b: is the replication number of a virus at the time of death of the infected cancer cell,

γ: clearance rate of the virus.

Stability Analysis

The equilibrium points are given by:

1. The first equilibrium point for this model where x>0 is: (x¯,y¯,n¯,v¯)=(γ/βb,γα/βδb,γα/βμb,α/β), So, by the Routh-Hurwitz criterion the equilibrium point (x¯,y¯,n¯,v¯) is unstable.

And this equilibrium point shows the coexistence of the four populations.

2. The second equilibrium point for this model

where $x = 0$ is: $(x, y, n, v) = (0,0,0,0)$, and this equilibrium point is unstable. Here there are no viral particles and the equilibrium point represents the desired outcome of therap (Hunt, 2001).

Numerical Illustrations

We consider the above system with the following coefficients

$\alpha = (2 \times 10^{-1})/h, \delta = (1/18)/h, \mu = (1/48)/h, \gamma = 2.5 \times 10^{-2}/h, b = 10$,

compute the equilibrium points for the virotherapy model at $\beta = 7 \times 10^{-8}$ mm^3/ h /virus.

Calculation without MATLAB:

1. The first equilibrium point with $x > 0$ is:

The virotherapy model has the equilibrium point

$$(x', y', n', v') = \left(\frac{\gamma}{\beta b}, \frac{\gamma\alpha}{\beta\delta b}, \frac{\gamma\alpha}{\beta\mu b}, \frac{\alpha}{\beta}\right)$$

$$= \left(\frac{2.5 \times (10^{-2})}{(7 \times 10^{-8}) \times 100}, \frac{(2.5 \times 10^{-2}) \times (2 \times 10^{-1})}{(7 \times 10^{-8}) \times 100 \times \left(\frac{1}{18}\right)}, \frac{(2.5 \times 10^{-2}) \times (2 \times 10^{-1})}{(7 \times 10^{-8}) \times 100 \times \left(\frac{1}{48}\right)}, \frac{(2 \times 10^{-1})}{(7 \times 10^{-8})}\right)$$

$$= (3571.42,12857.14,34285.7,2857142.85)$$

and the Jacobian matrix at this point is

$$J(x', y', n', v') = \begin{pmatrix} 0 & 0 & 0 & -0.00025 \\ 0.2 & -1/18 & 0 & 0.00025 \\ 0 & 1/18 & -1/48 & 0 \\ 0 & 50/9 & 0 & -1/40 \end{pmatrix}$$

$$\det(J - \lambda I) = \begin{vmatrix} 0 - \lambda & 0 & 0 & -0.00025 \\ 0.2 & -\frac{1}{18} - \lambda & 0 & 0.00025 \\ 0 & 1/18 & -\frac{1}{48} - \lambda & 0 \\ 0 & 50/9 & 0 & -\frac{1}{40} - \lambda \end{vmatrix}$$

Also$|(J - \lambda I)| = 0$.

So, the characteristic equation has the form

$$\lambda^4 + \left(\frac{73}{720}\right)\lambda^3 + (1.67 \times 10^{-3})\lambda^2 + (2.76 \times 10^{-4})\lambda + (5.75 \times 10^{-6}) = 0$$

With:

$a_1 = \left(\frac{73}{720}\right) > 0,\ a_2 = (1.67 \times 10^{-3}) > 0, a_3 = (2.76 \times 10^{-4}) > 0$,

$a_4 = (5.75 \times 10^{-6}) > 0$,

But:

$a_1 a_2 a_3 < a_3^2 + a_4 a_2^2$,

Hence, by the Routh-Hurwitz criterion the equilibrium point (x', y', n', v') is unstable.

2. The second equilibrium point where $x = 0$:

The point $(x, y, n, v) = (0,0,0,0)$ is a second equilibrium point with the Jacobian:

$$J(0,0,0,0) = \begin{pmatrix} 1/5 & 0 & 0 & 0 \\ 0 & -1/18 & 0 & 0 \\ 0 & 1/18 & -1/48 & 0 \\ 0 & 50/9 & 0 & -1/40 \end{pmatrix}$$

$$\det(J - \lambda I) = \begin{vmatrix} \frac{1}{5} - \lambda & 0 & 0 & 0 \\ 0 & -\frac{1}{18} - \lambda & 0 & 0 \\ 0 & 1/18 & -\frac{1}{48} - \lambda & 0 \\ 0 & 50/9 & 0 & -\frac{1}{40} - \lambda \end{vmatrix}$$

Also$|(J - \lambda I)| = 0$

We then compute that the characteristic equation:

$$\left(\frac{1}{5} - \lambda\right)\left(-\frac{1}{18} - \lambda\right)\left(-\frac{1}{48} - \lambda\right)\left(-\frac{1}{40} - \lambda\right) = 0$$

And the corresponding eigenvalues are:

$$\begin{cases} \lambda_1 = \dfrac{1}{5} > 0, \\ \lambda_2 = \dfrac{-1}{18} < 0, \\ \lambda_3 = \dfrac{-1}{48} < 0, \\ \lambda_4 = \dfrac{-1}{40} < 0. \end{cases}$$

Hence, the equilibrium point $(0,0,0,0)$ is unstable.

Numerical simulation using MATLAB

The Virotherapy system was simulated to investigate the influence of virotherapy with an infection rate β (Wein, 2003).

The non-linear system [1]-[4] was simulated using the Runge-Kotta method, The parameter values presented in the above numerical example and initial condition $(x_0, y_0, n_0, v_0) = (8 \times 10^5, 10^5, 10^5, 10^6)$ are in units of cells / mm^3, were used throughout the simulation of this study. Since the goal of this study is to evaluate the state dynamics for $0 \leq t \leq 20$ h, the suggested model has the same infection rate ($\beta = 7 \times 10^{-8}$) for all of the state variables.

In Fig. 5, it is seen that for different fractional orders. $\beta = (1 \times 10^{-8}, 3 \times 10^{-8}, 5 \times 10^{-8}, 7 \times 10^{-8}, 9 \times 10^{-8})$.

RESULTS AND DISCUSSION

The density of cancer cells is shown by the following figure 1.

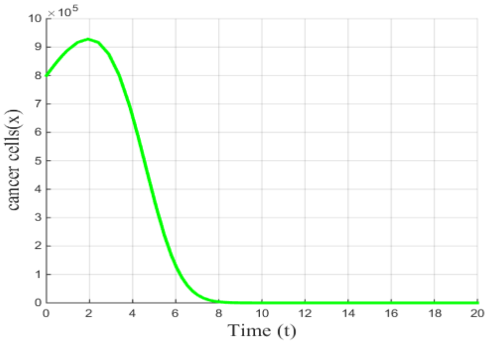

Fig .1 The number density of cancer cells (x) wit $\beta = 7 \times 10^{-8}$ through 20 hours.

In this figure, the cancer cells start at an initial value equal to $x(0) = 8 \times 10^5$, then this value increases until the second day, then the curve decreases, and its value is close to zero at the end of the period. In Fig .1 We note that after an initial response to viral treatment the number of cancer cells decreases fast (becomes zero) in a shorter time.

Consequently, the cancer density recovers in this period. Results should be presented in a logical sequence in the text, tables and figures. Repetitive presentation of the same data in tables and figures should be avoided.

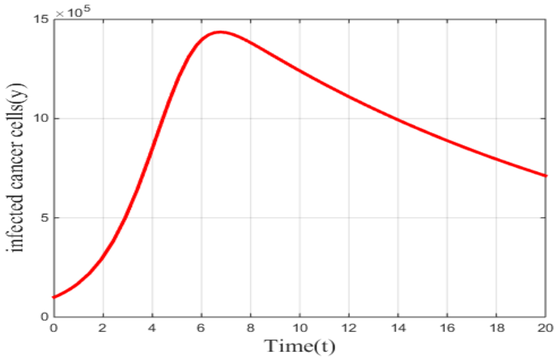

Fig .2 The number density of infected cancer cells (y) at $\beta = 7 \times 10^{-8}$ through 20 hours.

In Fig .2 we see that the number density of infected cancer cells starts at the value $y(0) = 10^5$, and then this number initially increase until equal to 1.437×10^6, then the peak of curve decreased until the final value of infected cells is equal to 7×10^5 at the last second of the 20th hour. The formation of the peak here and the decline of the curve first indicate infection of the cancer cells with the virus followed by the death of these infected cells.

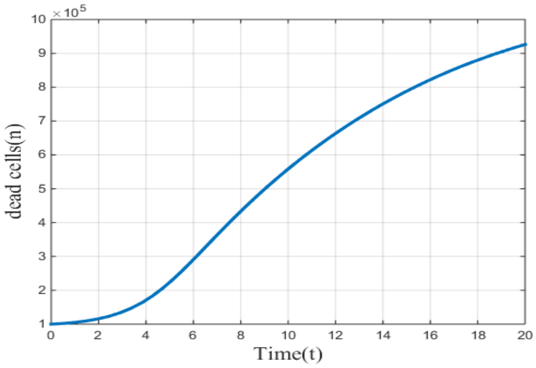

Fig .3 The number density of dead cells (n) at $\beta = 7 \times 10^{-8}$ through 20 hours.

Here in Fig.3, we see that the number of dead cells began at the value $n(0) = 10^5$, then this number clearly increase through 20 hours without any decrease and then the last value of dead cells is 9.2×10^5.The rise of the curve here indicates the death of virus-infected cells from cancer cells.

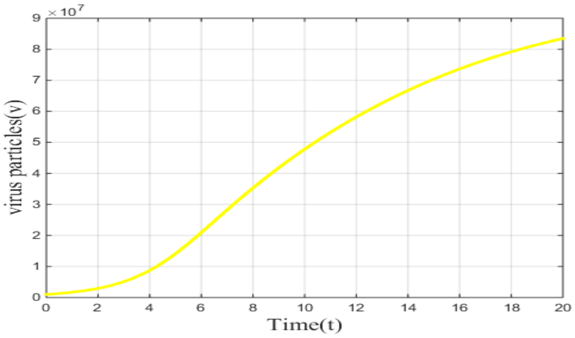

Fig .4 The number density of virus particles (v)at $\beta = 7 \times 10^{-8}$ through 20 hours.

In Fig .4 we note that the number density of virus particles began at initial value $v(0) = 10^6$, then this number clearly increase through 20 hours without any decrease, and the number of viruses then equals to 8.3×10^7 .At this time, the cancer is cured, this indicates that immune cells recognize the infected cancer cells and destroy them before the virus particles get a chance to replicate to their full potential.

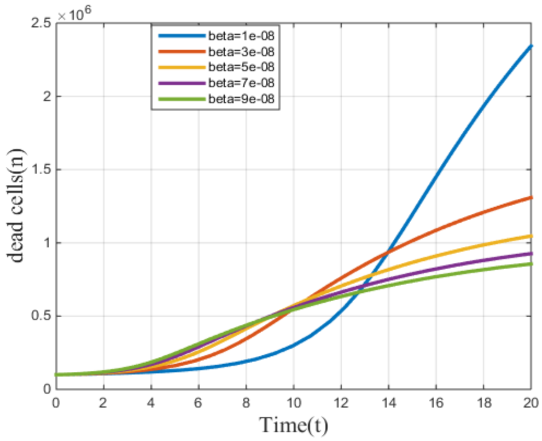

Fig. 5 The number density of dead cells for different values of β.

Fig .5 illustrates the variations in dead cells over the period of treatment for different values of β.

Here the Virotherapy model is also simulated for 20 hours, and the number density of dead cells is plotted for better visual presentation.

The number density of dead cells decreased for larger β value rapidly following a significant increase, as shown in Fig. 5

CONCLUSION

The study demonstrates the formation of a peak and decline in the number of dead cells from cancer cells, which increases over 20 hours without decreasing.

The number density of virus particles also increases, reaching 8.3×10^7, indicating the cancer is cured.

The study also illustrates variations in dead cells over treatment periods for different values of β, showing that the number density of dead cells decreases rapidly with larger β values.

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الملخص

يُقدّم هذا المقال نموذجًا رياضيًا قائمًا على المعادلات التفاضلية العادية لوصف ديناميكيات علاج السرطان بالفيروسات المحللة للأورام. وقد بُني هذا النموذج الرياضي لمعالجة مسائل أساسية في العلاج الفيروسي. نتناول في هذا المقال العلاج الفيروسي، وهو شكل حديث نسبيًا من أشكال علاج السرطان. يهدف هذا البحث أولًا إلى إثبات أن النموذج يحتوي على نقطتي توازن تمثلان فشل العلاج الذي لم يُحقق النجاح المرجو في البداية بسبب عدم مراعاة تأثير الجهاز المناعي والنتيجة العلاجية المرجوة. كما يتضمن البحث تحليلًا للاستقرار الموضعي لنقاط التوازن. اجريت محاكاة عددية

باستخدام طريقة رونج-كوتا من خلال برنامج MATLAB. كما تم توضيح تأثير المعامل β على نتائج العلاج الفيروسي.

الكلمات المفتاحية: العلاج الفيروسي، النموذج الرياضي، علاج السرطان.