

# Mathematical Modelling of Oncolytic Virotherapy with Mediated Immunity

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## ABSTRACT

*The current theoretical exploration takes up the topic of oncolytic tumour virotherapy through the use of suitable mathematical model. The prime objective is to devise an advanced mathematical framework for an in-depth study of the complex interplay among assorted components involved in tumour virotherapy. The network of interactions enfolds the normal cells, tumour cells, oncolytic viruses together with the resulting immune responses including both the innate and the adaptive immune reactions in its protection. Of these two immune reactions, the adaptive one subsumes both virus-specific and tumour specific immune responses in the model under consideration. The mathematical model system thus assembled is analysed in the perception of both local and global stability of equilibria under specified circumstances with the inclusion of the system boundedness. A quantitative analysis based on numerical simulation is carried out by solving the system numerically in order to validate the analytical results with numerical consequences and thereby the applicability of the model under study is established. Moreover, parametric variation is portrayed with the help of several graphical representations to understand the influence of model parameters of significance together with the complexity of the system critically. Furthermore, stability analysis is complemented well with graphical embodiments.*

**Keywords:** Virotherapy, Oncolytic virus, Innate and Adaptive Immune Response, Stability of equilibria, Oncotropism, Lysis.

**2010 Mathematics Subject Classification:** 37N25, 92-10, 92D30

**Journal of Economic Literature (JEL) Classification Number:** C32

## 1 Introduction

The assemblage of genetic alterations leading to abnormal cellular regulatory behaviour is the general characterization of cancer, a disease that caused when cells divide uncontrollably and spread into surrounding tissues. Being the greatest threat to the survival of mankind, the adaptive nature of cancer towards various medical treatments turns it to a very difficult target to attack. A number of potential drug delivery devices and advanced weapons are developed to fight against malignant tumour growth and its unwanted invasion. However, the drug delivery devices and the therapeutic treatments need to be developed in such a way that would lead to maximum therapeutic efficacy and minimum side effects. Oncolytic virotherapy is at present, a noteworthy method of anti-cancer treatment that utilizes oncolytic viruses (OVs) ((Ries and Brandts, 2004), (M.Koskela, Heikkila and Hinkkanen, 2007), (Wein, Wu and Kirn, 2003)). The

innovative idea of making use of viruses for cancer treatment initiated in 1950s, with the development of tissue culture and rodent cancer models (Kelley and Russel, 2007). These viruses have the ability to selectively attack the target tumour cells, replicate in the tumour domain and destroy tumour cells with least effect on normal tissues. These activities of viruses are based on tumour-specific properties, named as oncotropism. Oncotropism depends on the activation of cell surface receptors which in turn results into viral binding, transport of virus into tumour intracellular domain and finally takes part in the allowance of virus replication by tumour cells.

Various physiological barriers may be developed by tumours with respect to numerous anti-cancer treatments with the inclusion of oncolytic virotherapy. The first defence posed in combating viral infection is the innate immunity which after detecting the viral intervention, quickly eliminates foreign intruders (Friedman, Tian, Fulci, Chiocca and Wang, 2006). The innate immune system eliminates not only free viruses but also destroys virally infected tumour cells, thus restricting the tumour growth. Consequently, immune suppression drugs like cyclophosphamide (CPA) are used along with oncolytic viruses in order to sustain the therapeutic effectiveness of virotherapy (Wakimoto, Fulci, Tyminski and Chiocca, 2004). Moreover, there are certain distinct advantages of virotherapy which include viral infection and replication in a target-selective and non-pathogenic cells as well.

Mathematical models are used predominantly in order to predict the characterization of tumour cells in the long run under various drug delivery systems and therapeutic approaches. Mathematical modelling is a systematic way of understanding the complex biological, physiological and physical interactions prevalent in the tumour intracellular domain. As a matter of fact, there is no specific rule that can be consulted while formulating the oncolytic virotherapy, yet extensive literature survey may be conducted in order to gain necessary perception of the derivation process. Most of the mathematical models found in literature are the extraction of knowledge behind generalized population models (Chakravarty, 2021) or prey-predator models (Ali and Chakravarty, 2019). There are various models which describe the complex interactive phenomena going on between the oncolytic viruses and the tumour environment. Noteworthy works (Wodarz, 2003), (Bajzer, Thomas, Kreimir, Stephen and David, 2008), (Komarova and Wodarz, 2010), (Titze, Frank, Ehrhardt, Smola, Graf and Lehr, 2017) were performed by various researchers in this field in the recent past where mathematical modelling was used effectively. Wodarz (Wodarz, 2003) proposed a simple model comprised of growing cancer cells, infected cancer cells and virus particles. This work (Wodarz, 2003) was based on his previous study (Wodarz, 2001). On the basis of the work of Wodarz (Wodarz, 2003), Komarova and Wodarz (Komarova and Wodarz, 2010) advocated a generalized mathematical model comprised of a system of two ordinary differential equations. Based on biological compatibility, several functions were used to investigate various biological requirements. These mathematical models are decently helpful in understanding interactive relation between oncolytic virus and tumour cells with the implicit inclusion of virus population. On the other hand, Bajzer et al. (Bajzer et al., 2008) modelled virology dynamics with the explicit inclusion of virus population. Stability of equilibrium states with respect to complete tumour removal and partial tumour eradication were described in their work. Very recently, a work of Jenner et. al (Jenner, Coster, Kim and Frascoli, 2018) is quite noteworthy where the effectiveness of oncolytic virotherapy is quantified through local stability analysis and bifurcation analysis. Moreover, they have concluded strongly that complete eradication of tumour is possible only when additional anti-cancer agents are introduced along with oncolytic virus. Furthermore, in another study by Mahasa et al. (Mahasa, Eladdadi, Pillis and Ouifki, 2018), the complex interplay between oncolytic virus, tumour cells, normal cells, anti-viral and anti-tumoral immunities are very well addressed through mathematical modelling. A very recent work of Storey et. al. (Storey, Lawler

and Jackson, 2020) is highly commendable where the researchers have applied a mechanistic approach to mathematically model the complex interactions between different immune cell populations including both innate and adaptive response to oncolytic virotherapy incorporating the immune suppression phenomenon. Unlike the stability analysis, they have highlighted their work on parameter sensitivity analysis.

In the present article, the prime objective is to form an advanced mathematical framework of complex interplay representing tumour virotherapy. In this theoretical study, the complex interactions among the normal cells, oncolytic viruses, tumour cells and the resulting immune responses including both the innate and the adaptive immune reactions are wisely modelled mathematically. Additionally, two types of adaptive immune responses, namely, virus-specific and tumour-specific immune responses are also considered in the present model. The detailed mechanism involving physiological and biophysical phenomena under consideration is described through the schematic diagram in the subsequent section. Keeping in view of the delicacy of the model parameters, a sensitized parametric variation is conducted to examine their significance in oncolytic virotherapy. Moreover, a stability analysis (both local and global) is performed to acquire knowledge for better understanding the mechanism of virotherapy which would eventually benefit in estimating public health measures. The model quantification is ultimately carried out towards the end for its validation and applicability so that evolution of future models in the relevant domain should count on it. The novelty in the current study is that the model comprises the dynamics of not only the tumour cells, innate immune cells, adaptive immune cells, but also the normal cells. It is noteworthy that both susceptible and infected categories of normal and tumour cells are taken into account in the mathematical model. Moreover thorough stability analysis carried out in the present pursuit is not so emphasized in the previous works. Thus, this model representing the system of nine ordinary differential equations would certainly help the future researchers to incorporate more biological complexities which are beyond the scope of the present work. Apart from the parametric variations of the time-variant representations of all categories of cells showing significant roles of the model parameters in the dynamical system, the outcomes of the system concluded the stability criteria duly validated through the agreement of theoretical results with numerical counterparts which would provide an idea that small perturbations in the process of oncolytic virotherapy do not destabilize the system.

## 2 Mathematical Model

Computational systems biology employs approximations to mathematical and computational methods in the procedure of apprehending complexities of biological systems. The approximations lead to the use of the law of mass action in systems biology. In mathematical ecology, the obvious way to describe the underlying governing forces of two interacting species is the product of a rate constant and their individual population sizes. The most common way to mathematically model the spread of an infection is the application of SIR (Susceptible(S), Infected (I), Recovered (R)) model with some variations and modifications. The corresponding governing equations are the direct implication of the mass action law. Hence, the base of the mathematical modelling under present study is mass action law. The wide application of mass action law can be witnessed from a review article of Voit et. al. (Voit, Martens and Omholt, 2015).

The basis of the proposed mathematical model is sketched through Figure 1 as a schematic representation. The interactions between the normal and tumour cells in the presence of innate and adaptive immune responses as an outcome of the initiation of viral propagation in both the

normal and tumour cell populations are described in the proposed model. Moving towards the mathematical formulation, a brief discussion regarding the model assumptions is necessitated for readers' ease. The model takes into account the following feasible assumptions:

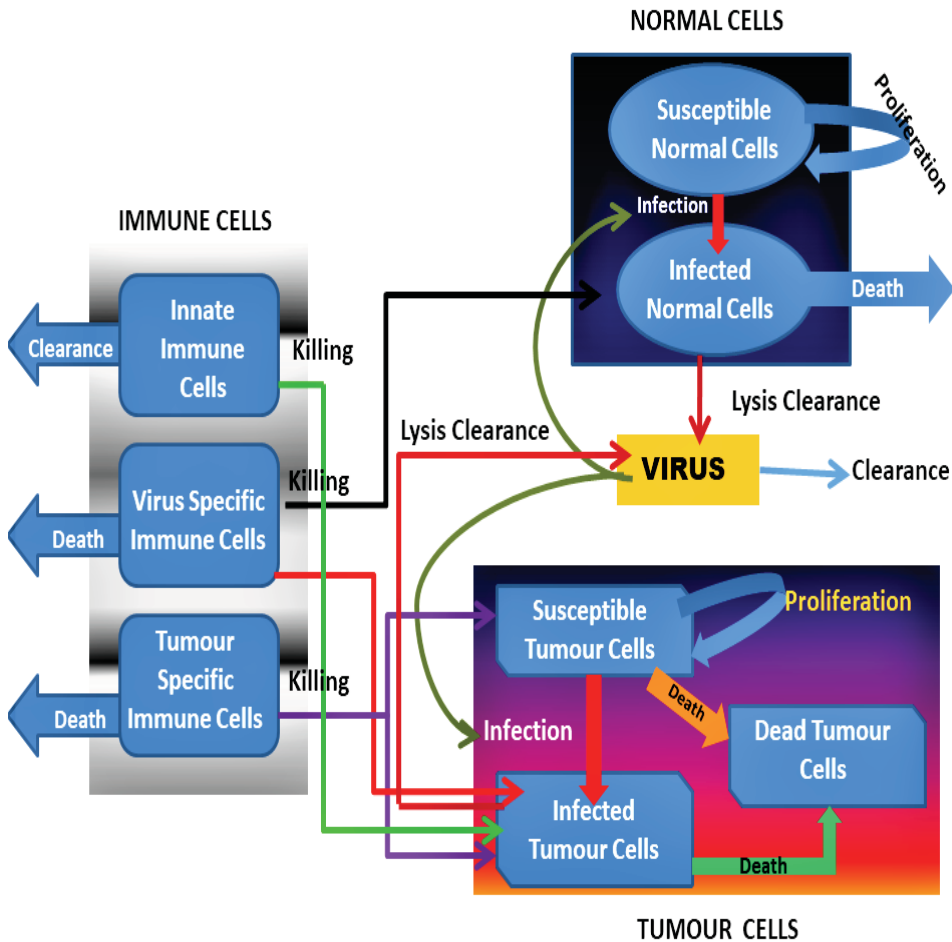


Figure 1: Schematic diagram of the mechanism of interactions in oncolytic virotherapy.

1. All the categories of cells are of same size and they are uniformly distributed in the proximity of the tumour compartment.
2. The growth of susceptible normal and tumour cells are logistic in nature. This is due to the fact that in the absence of tumour cells or rather cancer cells, the normal cells are assumed to grow logistically. On the other hand, the susceptible tumour cells also grow logistically in the absence of immune response, tumour specific, virus specific and innate immune responses.
3. In case of infected cell population, the growth curve is not logistic. This is because of the presumption that the lifespan of infected cell population is too short for logistic growth ((de Pillis and Radunskaya, 2003), (Enderling and Chaplain, 2014)).

4. It is also pretended that there is uniform activation of virus-specific immune response by both the infected normal and the tumour cell population.
5. Initially there is only innate immunity prior to oncolytic virotherapy and no virus-specific immunity exists at the inception. Hence the initial size of the virus-specific immune cells is zero.
6. Lastly, it is considered that on lysis of the infected cell, a new progeny of oncolytic viruses bursts out of the dead tumour cells to carry on the infection.

It must be noted that the normal cell population consists of uninfected (susceptible)  $S_N$  and infected (infection by virus) normal cells  $I_N$ . The susceptible normal cells proliferate logistically with an intrinsic growth rate  $r_N$  and the carrying capacity  $K_N$ . These cells become infected with the oncolytic virus at the rate  $\beta_N$ , by means of which the susceptible normal cell population  $S_N$  depletes as it gets transformed into infected normal cells  $I_N$ . On the other hand, the susceptible tumour cells undergo proliferation through logistic growth with intrinsic growth rate  $r_T$  and carrying capacity  $K_T$ . In the similar manner, there is a reduction in the susceptible tumour cell population due to infection by oncolytic virus at the rate  $\beta_T$ . Moreover, the anti-tumour adaptive immune response (Lemay, Rintoul, Kus, Paterson, Garcia and Falls, 2012) leads to the reduction in  $S_T$ . The interaction between susceptible tumour cells and tumour-specific immune cells obeys Michaelis-Menten kinetics. This is due to the fact that the entry of immune cells is often hindered by tumour cell structure (Gajewski, Schreiber and Fu, 2013). The population of infected normal cells ( $I_N$ ) increases as the uninfected normal cells become infected by the oncolytic virus. Again, the infected cell population depletes due to their death and lysis due to antiviral immunity. The number of infected tumour cells ( $I_T$ ) increases as the susceptible tumour cells become infected by the oncolytic virus. Finally,  $I_T$  population reduces to an extent as a combined effect of their death and lysis due to anti-tumour immune response, virus-specific immune response and innate immune response as well. Furthermore, it is noteworthy that Michaelis-Menten kinetics is considered for the interaction between infected tumour cells and the tumour-specific immune cells. This is an outcome of the restriction imposed by tumour architecture on the tumour-specific immune cells.

Taking into account all the above-mentioned biological complexities and physical phenomena, the governing equations are represented as follows:

$$\frac{dS_N}{dt} = r_N S_N \left(1 - \frac{S_N + I_N}{K_N}\right) - \beta_N S_N V, \quad (2.1)$$

$$\frac{dS_T}{dt} = r_T S_T \left(1 - \frac{S_T + I_T}{K_T}\right) - \beta_T S_T V - \gamma_T \left(\frac{Y_T}{h_Y + Y_T}\right) S_T, \quad (2.2)$$

$$\frac{dI_N}{dt} = \beta_N S_N V - \lambda_N I_N - \gamma_V Y_V I_N, \quad (2.3)$$

$$\frac{dI_T}{dt} = \beta_T S_T V - \lambda_T I_T - \gamma_T \left(\frac{Y_T}{h_Y + Y_T}\right) I_T - \gamma_V Y_V I_T - \gamma_Z Z I_T, \quad (2.4)$$

$$\frac{dV}{dt} = b_T \lambda_T I_T + b_N \lambda_N I_N - \omega V, \quad (2.5)$$

$$\frac{dY_T}{dt} = p_T \left(\frac{S_T + I_T}{h_T + S_T + I_T}\right) - \delta_T Y_T, \quad (2.6)$$

$$\frac{dY_V}{dt} = p_V (I_T + I_N) - \delta_V Y_V, \quad (2.7)$$

$$\frac{dZ}{dt} = s_1 Z I_T - c_1 Z, \quad (2.8)$$

$$\frac{dN_T}{dt} = \gamma_V Z I_T + \gamma_T \left( \frac{Y_T}{h_T + Y_T} \right) S_T + \gamma_T \left( \frac{Y_T}{h_T + Y_T} \right) I_T + \gamma_V Y_V I_T + \lambda_T I_T - \mu N_T. \quad (2.9)$$

The list of model variables and parameters along with their description are provided in Table 1, Table 2, Table 3 and Table 4 respectively.

Table 1: Model Variables

| Variable | Description                                                                   |
|----------|-------------------------------------------------------------------------------|
| $S_N$    | number of normal cells not yet infected by viruses (susceptible normal cells) |
| $S_T$    | number of tumour cells not yet infected by viruses (susceptible tumour cells) |
| $I_N$    | number of normal cells already infected by viruses                            |
| $I_T$    | number of tumour cells already infected by viruses                            |
| $V$      | number of viruses                                                             |
| $Y_T$    | number of tumour-specific immune cells                                        |
| $Y_V$    | number of virus-specific immune cells                                         |
| $Z$      | number of innate immune cells                                                 |
| $N_T$    | number of dead tumour cells                                                   |

Table 2: List of model parameter values used for numerical simulation.

| Parameters | Description                           | Values                                                    | References                                               |
|------------|---------------------------------------|-----------------------------------------------------------|----------------------------------------------------------|
| $r_N$      | Intrinsic growth rate of normal cells | $0.003 \text{ hr}^{-1}$                                   | (Okamoto, Ama-rasekare and Petty, 2014)                  |
| $K_N$      | Carrying capacity of normal cells     | $10^{11}$ cells                                           | (Okamoto et al., 2014)                                   |
| $\beta_N$  | Infected rate of the normal cells     | $0.07 \times 10^{-8} \text{ virion}^{-1} \text{ hr}^{-1}$ | (Friedman et al., 2006)                                  |
| $r_T$      | Tumour cell growth rate (uninfected)  | $0.003 \text{ hr}^{-1}$                                   | (Okamoto et al., 2014), (Wu, Byrne, Kirn and Wein, 2001) |
| $K_T$      | Carrying capacity of tumour cells     | $10^{12}$ cells                                           | (Okamoto et al., 2014)                                   |
| $\beta_T$  | Infected rate of the tumour cells     | $5 \times 10^{-12} \text{ virion}^{-1} \text{ hr}^{-1}$   | (Okamoto et al., 2014)                                   |

Table 3: List of model parameter values used for numerical simulation (contd.).

| Parameters  | Description                                                                                      | Values                                | References                                                          |
|-------------|--------------------------------------------------------------------------------------------------|---------------------------------------|---------------------------------------------------------------------|
| $h_Y$       | Half saturation constant of immune cells                                                         | 40 cells                              | (Eftimie, Dushoff, Bridle, Bramson and Earn, 2011)                  |
| $\gamma_T$  | Rate of tumour cells being lysed by tumour-specific immune cells                                 | $0.042 \text{ hr}^{-1}$               | (Eftimie et al., 2011)                                              |
| $h_Y$       | Half saturation constant of immune cells                                                         | 40 cells                              | (Eftimie et al., 2011)                                              |
| $\lambda_N$ | Death rate of infected normal cells                                                              | $0.042 \text{ cells hr}^{-1}$         | (Mahasa et al., 2018)                                               |
| $\gamma_V$  | Rate of infected normal cells being lysed by antiviral immunity                                  | $0.042 \text{ cells hr}^{-1}$         | (Mahasa et al., 2018)                                               |
| $\lambda_T$ | Death rate of infected tumour cells                                                              | $0.042 \text{ cells hr}^{-1}$         | (Eftimie et al., 2011)                                              |
| $b_T$       | Burst size for viruses from an infected tumour cell                                              | $1350 \text{ virions cell}^{-1}$      | (Okamoto et al., 2014)                                              |
| $b_N$       | Burst size for viruses from an infected normal cell                                              | $1000 \text{ virions cell}^{-1}$      | (Mahasa et al., 2018)                                               |
| $\omega$    | Viral clearance rate of free virus from the host body by virus-specific immune cells             | $2.5 \times 10^{-2} \text{ hr}^{-1}$  | (Friedman et al., 2006), (Paiva, Binny, Ferreira and Martins, 2009) |
| $p_T$       | Anti-tumoral immune response recruitment rate against tumour cells                               | $0.00156 \text{ hr}^{-1}$             | (Mahasa et al., 2018)                                               |
| $h_T$       | Half saturation constant (half the maximum killing rate) to both viral and tumour-specific cells | 40 cells                              | (Eftimie et al., 2011), (de Pillis, Radunskaya and Wiseman, 2005)   |
| $\delta_T$  | Natural death rate of the adaptive tumour-specific immune cells                                  | $3.75 \times 10^{-4} \text{ hr}^{-1}$ | (de Pillis, Caldwell, Sarapata and Williams., 2013)                 |
| $p_V$       | Virus-specific proliferation rate of antiviral immune cells                                      | $0.025 \text{ hr}^{-1}$               | (Eftimie et al., 2011)                                              |
| $\delta_V$  | Death rate of the adaptive virus-specific immune cells                                           | $5.54 \times 10^{-3} \text{ hr}^{-1}$ | (Eftimie et al., 2011)                                              |

### 3 Local Stability Analysis

For the sake of convenience, the model system of equations (2.1) - (2.9) may be rewritten as follows:

$$\frac{dx_i}{dt} = X_i \quad (3.1)$$

where  $x_i$  ( $i = 1, 2, 3, \dots, 9$ ) are  $x_1 = S_N$ ,  $x_2 = S_T$ ,  $x_3 = I_N$ ,  $x_4 = I_T$ ,  $x_5 = V$ ,  $x_6 = Y_T$ ,  $x_7 = Y_V$ ,  $x_8 = Z$ ,  $x_9 = N_T$ ) respectively and  $X_i$  ( $i = 1, 2, 3, \dots, 9$ ) are functions of  $(S_N, S_T, I_N, I_T, V, Y_T, Y_V, Z, N_T)$  whose individual expressions are the respective assertions in the right hand side of the system (2.1) - (2.9).

Table 4: List of model parameter values used for numerical simulation (contd.).

| Parameters | Description                                                      | Values                           | References                       |
|------------|------------------------------------------------------------------|----------------------------------|----------------------------------|
| $s_1$      | Innate immune cell stimulation rate                              | $56 \times 10^6 \text{ hr}^{-1}$ | (Timalsina, Tian and Wang, 2017) |
| $c_1$      | Death rate / clearance of the innate immune cells                | $2 \text{ hr}^{-1}$              | (Timalsina et al., 2017)         |
| $\gamma_Z$ | Rate of infected tumour cells being lysed by innate immune cells | $0.042 \text{ hr}^{-1}$          | Estimated                        |
| $\mu$      | Clearance rate of dead tumour cells                              | $2.1 \text{ hr}^{-1}$            | (Timalsina et al., 2017)         |

### Existence and uniqueness of the solution

The general form of the first order ODE is  $\frac{dx}{dt} = X(x, t)$ ,  $x(t_0) = x_0$ .

The following theorem is used for establishing the existence and uniqueness of solution for the proposed model.

The first one concerns existence of the solutions.

#### Proposition 1

The solutions of the model (3.1) exist in the closed positive orthant  $\mathfrak{R}_+^9$  defined as  $\Gamma = [(S_N, S_T, I_N, I_T, V, Y_T, Y_V, Z, N_T); S_N \geq 0, S_T \geq 0, I_N \geq 0, I_T \geq 0, V \geq 0, Y_T \geq 0, Y_V \geq 0, Z \geq 0, N_T \geq 0]$ .

**Proof:** Observe that the right hand side of (3.1) is a Lipschitz continuous function of the variables

$(S_N, S_T, I_N, I_T, V, Y_T, Y_V, Z, N_T)$ . Local existence and uniqueness properties then hold in  $\mathfrak{R}_+^9$ .

#### Proposition 2

[Uniqueness of solutions] If the vector field  $\mathbf{X}(\mathbf{x}, t)$  satisfies a Lipschitz condition in a domain  $\mathfrak{R}_+^9$ , then there is at most one solution  $\mathbf{x}(t)$  of the system of differential equations  $\frac{d\mathbf{x}}{dt} = \mathbf{X}(\mathbf{x}, t)$

that satisfies a given initial condition  $\mathbf{x}(\alpha) = \mathbf{c}$  in  $\mathfrak{R}_+^9$ .

**Proof:** Assume that  $\mathbf{X}(t)$  satisfies the Lipschitz condition  $\|\mathbf{X}(\mathbf{x}, t) - \mathbf{X}(\mathbf{y}, t)\| \leq L\|\mathbf{x} - \mathbf{y}\|$  for any  $(\mathbf{x}, t), (\mathbf{y}, t) \in \mathfrak{R}_+^9$ . Let  $(\mathbf{x}, t) = [x_1(t), x_2(t), \dots, x_9(t)]$  and  $(\mathbf{y}, t) = [y_1(t), y_2(t), \dots, y_9(t)]$  be two solutions satisfying the same initial condition  $\mathbf{x}(\alpha) = \mathbf{c} = \mathbf{y}(\alpha)$ .

Denote  $\rho(t) = \|\mathbf{x}(t) - \mathbf{y}(t)\|^2 \geq 0$ . Then one gets

$$\begin{aligned} \rho'(t) &= \sum_{k=1}^9 2[x'_k(t) - y'_k(t)] \cdot [x_k(t) - y_k(t)] \\ &= \sum_{k=1}^9 2[\mathbf{X}_k(\mathbf{x}(t), t) - \mathbf{X}_k(\mathbf{y}(t), t)] \cdot [x_k(t) - y_k(t)] \\ &= 2[\mathbf{X}(\mathbf{x}(t), t) - \mathbf{X}(\mathbf{y}(t), t)] \cdot [x(t) - y(t)] \end{aligned}$$

Using the Schwarz inequality, one may write

$$\begin{aligned} \rho'(t) &\leq |\rho'(t)| = 2|[\mathbf{X}(\mathbf{x}(t), t) - \mathbf{X}(\mathbf{y}(t), t)] \cdot [x(t) - y(t)]| \\ &\leq 2\|\mathbf{X}(\mathbf{x}, t) - \mathbf{X}(\mathbf{y}, t)\| \cdot \|\mathbf{x} - \mathbf{y}\| \\ &\leq 2L\|\mathbf{x} - \mathbf{y}\|^2 = L\rho(t). \end{aligned}$$

This implies that  $\frac{d}{dt}[\rho(t)e^{-2Lt}] = [\rho'(t) - 2L\rho(t)]e^{-2Lt} \leq 0$ . Hence  $\rho(t)e^{-2Lt}$  is a decreasing function. Therefore, for  $t > \alpha$ ,  $\rho(t)e^{-2Lt} \leq \rho(\alpha)e^{-2L\alpha} = 0$ .

Since  $\rho(t) \geq 0$ , one must have  $\rho(t) = 0$  for  $t \geq \alpha$  implying  $\mathbf{x}(t) = \mathbf{y}(t)$  for  $t \geq \alpha$ .

On the other hand, for  $t < \alpha$ , one may have  $-\rho'(t) \leq |\rho'(t)| \leq 2L\rho(t)$  which implies again  $\frac{d}{dt}[\rho(t)e^{2Lt}] = [\rho'(t) + 2L\rho(t)]e^{2Lt} \geq 0$ . Therefore,  $[\rho(t)e^{2Lt}]$  is an increasing function of  $t$  and consequently for  $t < \alpha$ ,  $\rho(t)e^{2Lt} \leq \rho(\alpha)e^{2L\alpha} = 0$ . Further, one gets  $\rho(t) = 0$  for  $t \leq \alpha$ , that means  $\mathbf{x}(t) = \mathbf{y}(t)$  for  $t \leq \alpha$ . This proves the uniqueness of the solution.

The following theorem shows that under certain suitable conditions, all the solutions of the system of equations (3.1) are non-negative. A set  $\Gamma$  in  $\mathfrak{R}_+^9$  may be ascertained such that all solutions starting in  $\Gamma$  remain bounded.

### Theorem 3.1

Let all the model parameters of the system of equations (3.1) be positive and  $\Gamma$  be a region in  $\mathfrak{R}_+^9$  defined as  $\Gamma = \{(S_N, S_T, I_N, I_T, V, Y_T, Y_V, Z, N_T) \in \mathfrak{R}_+^9 | 0 \leq S_N \leq \bar{S}_N, 0 \leq S_T \leq \bar{S}_T, 0 \leq I_N \leq \bar{I}_N, 0 \leq I_T \leq \bar{I}_T, 0 \leq V \leq \bar{V}, 0 \leq Y_T \leq \bar{Y}_T, 0 \leq Y_V \leq \bar{Y}_V, 0 \leq Z \leq \bar{Z}, 0 \leq N_T \leq \bar{N}_T\}$ . Then  $\Gamma$  is positive invariant and all the solutions starting from  $\Gamma$  are uniformly bounded, the parameters over bar are being the respective upper bounds.

**Proof:**

#### Positive invariance of the positive orthant $\mathfrak{R}_+^9$

Set  $\alpha_1 = r_N I_N$  and  $\alpha_2 = \beta_N V$  then the equation (2.1) implies that

$$\frac{dS_N}{dt} = r_N S_N \left(1 - \frac{S_N}{K_N}\right) - \alpha_1 \frac{S_N}{K_N} - \alpha_2 S_N = (a - b S_N) S_N$$

where  $a = r_N - \frac{\alpha_1}{K_N} - \alpha_2$ ,  $b = \frac{r_N}{K_N}$ . On integration, one gets  $S_N = \frac{ak_1}{k_1 b + e^{-at}}$ ,  $k_1$  being the integration constant. Hence  $S_N(t)$  is positive for all values of  $t$  in the interval under consideration.

For the second equation (2.2), one may set  $\alpha_3 = r_T I_T$ ,  $\alpha_4 = \beta_T V$  and  $\alpha_5 = \frac{\gamma_T Y_T}{h_Y + Y_T}$  so that the equation (2.2) becomes

$$\frac{dS_T}{dt} = r_T S_T \left(1 - \frac{S_T}{K_T}\right) - \alpha_3 \frac{S_T}{K_T} - \alpha_4 S_T - \alpha_5 S_T = (c - dS_T)S_T$$

where  $c = r_T - \frac{\alpha_3}{K_T} - \alpha_4 - \alpha_5$  and  $d = \frac{r_T}{K_T}$ . On integration, one may have  $S_T = \frac{ck_2}{k_2 d + e^{-ct}}$ ,  $k_2$  being the integration constant. Therefore,  $S_T(t)$  is positive for all values of  $t$  in the considered interval.

The equation (2.3) can be expressed as  $\frac{dI_N}{dt} \geq -(\lambda_N + \alpha_6)I_N$  by setting  $\alpha_6 = \gamma_V Y_V$ . On integration, one may get  $I_N \geq k_3 e^{-(\lambda_N + \alpha_6)t}$ ,  $k_3$  being the integration constant. Thus,  $I_N$  is positive for all values of  $t$  in the interval under consideration.

Similarly for the rest of the classes of cells it is proved that  $V(t), Y_T(t), Y_V(t), Z(t)$  and  $N_T(t)$  are all positive for all values of  $t$ .

Thus the positive invariance of the positive orthant  $\mathfrak{R}_+^9$  ensures that the solutions of the system (3.1) that initiated in  $\mathfrak{R}_+^9$  remain inside the domain under consideration.

### Boundedness of the system

Let us consider first two equations (2.1) and (2.2) for establishing their boundedness. We define a function

$$\Omega = S_N + S_T \quad (3.2)$$

Then the time derivative of (3.2) is given by  $\frac{d\Omega}{dt} = \frac{dS_N}{dt} + \frac{dS_T}{dt}$  so that for each  $m > 0$ , the following inequality holds:

$$\begin{aligned} \frac{d\Omega}{dt} + m\Omega &= r_N S_N \left[1 - \frac{(S_N + I_N)}{K_N}\right] - \beta_N S_N V + r_T S_T \left[1 - \frac{(S_T + I_T)}{K_T}\right] - \beta_T S_T V \\ &\quad - Y_I S_T \gamma_T / (h_Y + Y_T) + m\Omega \\ &< \frac{r_N S_N}{K_N} (K_N - S_N) + mS_N + \frac{r_T S_T}{K_T} (K_T - S_T) + mS_T \\ &\leq \frac{K_N(r_N + m)^2}{4r_N} + \frac{K_T(r_T + m)^2}{4r_T} \equiv \varphi_1 + \varphi_2 = \varphi \text{ (positive constant).} \end{aligned}$$

Therefore, from the above inequality we have  $\frac{d\Omega}{dt} + m\Omega \leq \varphi$ . Applying theory of differential inequality, we obtain  $0 < \Omega(S_N, S_T) < \frac{\varphi}{m} (1 - e^{-mt}) + \Omega\{S_N(0), S_T(0)\}e^{-mt}$  and for  $t \rightarrow \infty$ , we have  $0 < \Omega < \frac{\varphi}{m}$ . Hence the solutions of the system (2.1) and (2.2) that initiate in  $\mathfrak{R}_+^9$  are confined in the region  $\Gamma = \{(S_N, S_T, I_N, I_T, V, Y_T, Y_V, Z, N_T) \in \mathfrak{R}_+^9 : \Omega = \frac{\varphi}{m} + \varepsilon \text{ for any } \varepsilon > 0\}$ . So, boundedness of the first two solutions  $S_N$  and  $S_T$  is established with their respective upper bounds  $\overline{S_N} = \frac{\varphi_1}{m}$  and  $\overline{S_T} = \frac{\varphi_2}{m}$ .

From the equation (2.3), one may write  $\frac{dI_N}{dt} + \lambda_N I_N \leq \beta_N S_N V \equiv B$ , where  $B = \max |\beta_N S_N V|$ .

On integration, one gets  $I_N(t) \leq \frac{B}{\lambda_N} + k_4 e^{-\lambda_N t}$ ,  $k_4$  being an integration constant. So,  $I_N(t) \leq \frac{B}{\lambda_N}$  as  $t \rightarrow \infty$  ensures its boundedness for all  $t \geq 0$  with its upper bound  $\overline{I_N} = \frac{B}{\lambda_N}$ .

Similarly, one can prove the boundedness of the remaining solutions  $I_T$ ,  $V$ ,  $Y_T$ ,  $Y_V$ ,  $Z$  and  $N_T$  following the treatment mentioned herein whose individual proofs are not provided here for the sake of brevity. Thus, the boundedness of all the dependent variables in  $\mathfrak{R}_+^9$  is established.

### Interior equilibrium position and its existence

Apart from six different equilibria of the proposed model system (3.1) corresponding to the absence of at least one of the several classes of cells, only one positive interior equilibrium position  $v_e \equiv (S_N^*, S_T^*, I_N^*, I_T^*, V^*, Y_T^*, Y_V^*, Z^*, N_T^*)$  of the system exists in the presence of all kinds of cells under consideration. Here,  $S_N^*$ ,  $S_T^*$ ,  $I_N^*$ ,  $I_T^*$ ,  $V^*$ ,  $Y_T^*$ ,  $Y_V^*$ ,  $Z^*$  and  $N_T^*$  can be obtained by solving the system of equations given by

$$X_i(S_N^*, S_T^*, I_N^*, I_T^*, V^*, Y_T^*, Y_V^*, Z^*, N_T^*) = 0 \text{ for } i = 1, 2, 3, \dots, 9.$$

### Local asymptotic stability

#### Theorem 3.2

The present model system ((3.1)) is locally asymptotically stable at the interior equilibrium position  $v_e \equiv (S_N^*, S_T^*, I_N^*, I_T^*, V^*, Y_T^*, Y_V^*, Z^*, N_T^*)$  if  $u_{i1} > 0$  for  $i = 1, 2, \dots, 9$  provided in the proof.

Proof: To prove the proposed system ((3.1)) locally stable, one needs to consider the corresponding linearised version. The Jacobian matrix may be found at the equilibrium position as follows:

$$J^* = \begin{bmatrix} J_{11}^* & 0 & J_{13}^* & 0 & J_{15}^* & 0 & 0 & 0 & 0 \\ 0 & J_{22}^* & 0 & J_{24}^* & J_{25}^* & J_{26}^* & 0 & 0 & 0 \\ J_{31}^* & 0 & J_{33}^* & 0 & J_{35}^* & 0 & J_{37}^* & 0 & 0 \\ 0 & J_{42}^* & 0 & J_{44}^* & J_{45}^* & J_{46}^* & J_{47}^* & J_{48}^* & 0 \\ 0 & 0 & J_{53}^* & J_{54}^* & J_{55}^* & 0 & 0 & 0 & 0 \\ 0 & J_{62}^* & 0 & J_{64}^* & 0 & J_{66}^* & 0 & 0 & 0 \\ 0 & 0 & J_{73}^* & J_{74}^* & 0 & 0 & J_{77}^* & 0 & 0 \\ 0 & 0 & 0 & J_{84}^* & 0 & 0 & 0 & J_{88}^* & 0 \\ 0 & J_{92}^* & 0 & J_{94}^* & 0 & J_{96}^* & J_{97}^* & J_{98}^* & J_{99}^* \end{bmatrix} \quad (3.3)$$

where all the elements of the matrix have got their expressions included in **Appendix-I** in which “\*” associated in their expressions indicates that they are evaluated at the equilibrium position. After the evaluation of all the elements at the positive equilibrium of the system (3.1), one gets the characteristic polynomial at this equilibrium position. As the calculation is quite complex, it seems convenient to follow the general approach for studying the stability of the system.

Let the characteristic polynomial of  $J^*$  be of the form  $x^9 + c_8 x^8 + c_7 x^7 + c_6 x^6 + c_5 x^5 + c_4 x^4 + c_3 x^3 + c_2 x^2 + c_1 x + c_0 = g(x)$ , where  $c_k = (-1)^{9-k} \sum_{|D|=9-k} J^*[D]$ , that is,  $c_k$  are the sum of all principal minors of order  $(9-k)$  of the matrix  $J^*$  multiplied by  $(-1)^{9-k}$ . Here  $D \subseteq \{1, 2, 3, \dots, 9\}$  and  $J^*[D]$  designates the principal minors of  $J^*$  formed by columns and rows with indices from  $D$ . Let us denote  $1 = u_{91}$ ,  $c_7 = u_{92}$ ,  $c_5 = u_{93}$ ,  $c_3 = u_{94}$ ,  $c_1 = u_{95}$ ,  $c_8 = u_{81}$ ,  $c_6 = u_{82}$ ,  $c_4 = u_{83}$ ,  $c_2 = u_{84}$ ,  $c_0 = u_{85}$ . Then Routh table of the polynomial  $g(x)$  may be formed as follows where  $u_{ij} = \{u_{(i+1)j} u_{(i+2)(j+1)} - u_{(i+1)(j+1)} u_{(i+2)j}\} / u_{(i+1)j}$  for  $i = 0, 1, 2, \dots, 9$  and  $j = 1, 2, 3, 4, 5$ .

|       |          |          |          |          |          |
|-------|----------|----------|----------|----------|----------|
| $x^9$ | $u_{91}$ | $u_{92}$ | $u_{93}$ | $u_{94}$ | $u_{95}$ |
| $x^8$ | $u_{81}$ | $u_{82}$ | $u_{83}$ | $u_{84}$ | $u_{85}$ |
| $x^7$ | $u_{71}$ | $u_{72}$ | $u_{73}$ | $u_{74}$ | 0        |
| $x^6$ | $u_{61}$ | $u_{62}$ | $u_{63}$ | $u_{64}$ | 0        |
| $x^5$ | $u_{51}$ | $u_{52}$ | $u_{53}$ | 0        | 0        |
| $x^4$ | $u_{41}$ | $u_{42}$ | $u_{43}$ | 0        | 0        |
| $x^3$ | $u_{31}$ | $u_{32}$ | 0        | 0        | 0        |
| $x^2$ | $u_{21}$ | $u_{22}$ | 0        | 0        | 0        |
| $x$   | $u_{11}$ | 0        | 0        | 0        | 0        |
| 1     | $u_{01}$ | 0        | 0        | 0        | 0        |

 Routh table of  $J^*$ 

According to Routh-Hurwitz criterion, a system is stable if and only if all terms in the first column of the above table represented by  $u_{i1}$  for  $i = 0, 1, 2, \dots, 9$  are positive and if these conditions are not satisfied then there will be an unstable solution (Nise, 2011). Thus the present model (3.1) is locally asymptotically stable at the positive interior equilibrium position if  $u_{i1} > 0$  for  $i = 0, 1, 2, \dots, 9$ .

## 4 Global Stability Analysis

### Theorem 4.1

The present model system (3.1) is globally asymptotically stable at the interior equilibrium position  $v_e$  if  $\min(v'_{ij}) \geq \max(v_{ij})$  for  $i = 1, 2, 3, \dots, 9$  and  $j = 1, 2, 3, 4$  where  $v'_{ij}$  and  $v_{ij}$  are defined in the proof itself.

Proof: Consider the function defined by

$$\begin{aligned}
 V &= \{S_N - S_N^* - S_N^* \ln(\frac{S_N}{S_N^*})\} + \{S_T - S_T^* - S_T^* \ln(\frac{S_T}{S_T^*})\} + \{I_N - I_N^* - I_N^* \ln(\frac{I_N}{I_N^*})\} \\
 &+ \{I_T - I_T^* - I_T^* \ln(\frac{I_T}{I_T^*})\} + \{V - V^* - V^* \ln(\frac{V}{V^*})\} + \{Y_T - Y_T^* - Y_T^* \ln(\frac{Y_T}{Y_T^*})\} \\
 &+ \{Y_V - Y_V^* - Y_V^* \ln(\frac{Y_V}{Y_V^*})\} + \{Z - Z^* - Z^* \ln(\frac{Z}{Z^*})\} + \{N_T - N_T^* - N_T^* \ln(\frac{N_T}{N_T^*})\} \\
 &= \sum_{i=1}^9 V_i
 \end{aligned}$$

where  $(S_N^*, S_T^*, I_N^*, I_T^*, V^*, Y_T^*, Y_V^*, Z^*, N_T^*) \equiv v_e$  is the interior equilibrium position of the system (3.1) and  $V_i = f_i - f_i^* - f_i^* \ln(\frac{f_i}{f_i^*})$  in which  $f_i = S_N, S_T, I_N, I_T, V, Y_T, Y_V, Z, N_T$  for  $i = 1, 2, 3, \dots, 9$  respectively. The objective is to look for the conditions for which  $\frac{dV}{dt} \leq 0$  to

make the proposed system globally asymptotically stable.

Now at  $v_e$ , the right hand sides of (3.1) are zero and hence we obtain

$$r_N K_N = r_N(S_N^* + I_N^*) + \beta_N K_N V^* \quad (4.1)$$

$$r_T K_T = r_T(S_T^* + I_T^*) + \beta_T K_T V^* + \frac{\gamma_T Y_T^* K_T}{h_T + Y_T^*} \quad (4.2)$$

$$\beta_N S_N^* V^* - (\lambda_N + \gamma_V Y_V^*) I_N^* = 0 \quad (4.3)$$

$$\beta_T S_T^* V^* - \left[ \lambda_T + \gamma_V Y_V^* + \gamma_Z Z^* + \frac{\gamma_T Y_T^*}{h_Y + Y_T^*} \right] I_T^* = 0 \quad (4.4)$$

$$b_T \lambda_T I_T^* + b_N \lambda_N I_N^* - \omega V^* = 0 \quad (4.5)$$

$$h_T \delta_T = (p_T - \delta_T Y_T^*) \left( \frac{S_T^*}{Y_T^*} + \frac{I_T^*}{Y_T^*} \right) \quad (4.6)$$

$$p_V (I_T^* + I_N^*) - \delta_V Y_V^* = 0 \quad (4.7)$$

$$Z^* (s_1 I_T^* - c_1) = 0 \quad (4.8)$$

$$\left[ \lambda_T + \gamma_V Y_V^* + \gamma_Z Z^* + \frac{\gamma_T Y_T^*}{h_Y + Y_T^*} \right] I_T^* + \frac{\gamma_T Y_T^* S_T^*}{h_Y + Y_T^*} - \mu N_T^* = 0. \quad (4.9)$$

Now we have  $\dot{V} = \sum_{i=1}^9 \dot{V}_i = \sum_{i=1}^9 \left[ 1 - \frac{f_i^*}{f_i} \right] \dot{f}_i$ , where

$$\begin{aligned} \dot{V}_1 &= (S_N - S_N^*) \frac{\dot{S}_N}{S_N} = - \frac{(S_N - S_N^*)^2}{K_N} \left[ r_N + r_N \left( \frac{I_N - I_N^*}{S_N - S_N^*} \right) + \beta_N K_N \left( \frac{V - V^*}{S_N - S_N^*} \right) \right] \\ &\leq - \frac{(S_N - S_N^*)^2}{K_N} r_N - \frac{r_N}{K_N} (S_N - S_N^*) (I_N - I_N^*) - \beta_N (V - V^*) (S_N - S_N^*) \\ &\leq v'_{11} + v_{11} + v_{12} \text{ (say)}, \end{aligned} \quad (4.10)$$

$$\begin{aligned} \dot{V}_2 &= (S_T - S_T^*) \frac{\dot{S}_T}{S_T} = - \frac{(S_T - S_T^*)^2}{K_T} \left[ r_T + r_T \left( \frac{I_T - I_T^*}{S_T - S_T^*} \right) + \beta_T K_T \left( \frac{V - V^*}{S_T - S_T^*} \right) \right] \\ &\quad + \frac{\gamma_T K_T}{S_T - S_T^*} \left( \frac{Y_T}{h_Y + Y_T} - \frac{Y_T^*}{h_Y + Y_T^*} \right) \\ &\leq - \frac{(S_T - S_T^*)^2}{K_T} r_T - \frac{r_T}{K_T} (S_T - S_T^*) (I_T - I_T^*) - \beta_T (V - V^*) (S_T - S_T^*) \\ &\quad - \gamma_T (S_T - S_T^*) \left( \frac{Y_T}{h_Y + Y_T} - \frac{Y_T^*}{h_Y + Y_T^*} \right) \\ &\leq v'_{21} + v_{21} + v_{22} + v_{23} \text{ (say)}, \end{aligned} \quad (4.11)$$

$$\begin{aligned} \dot{V}_3 &= (I_N - I_N^*) \frac{\dot{I}_N}{I_N} = (I_N - I_N^*) \left[ -\gamma_V (Y_V - Y_V^*) - \beta_N \left( \frac{S_N^* V^*}{I_N^*} - \frac{S_N V}{I_N} \right) \right] \\ &\leq -\beta_N S_N^* V^* \frac{(I_N - I_N^*)^2}{I_N I_N^*} - \gamma_V (I_N - I_N^*) (Y_V - Y_V^*) \\ &\leq v'_{31} + v_{31} \text{ (say)}, \end{aligned} \quad (4.12)$$

$$\begin{aligned}
 \dot{V}_4 &= (I_T - I_T^*) \frac{\dot{I}_T}{I_T} \\
 &= (I_T - I_T^*) \left[ -\gamma_V (Y_V - Y_V^*) - \gamma_Z (Z - Z^*) - \beta_T \left( \frac{S_T^* V^*}{I_T^*} - \frac{S_T V}{I_T} \right) - \gamma_T \left( \frac{Y_T}{h_Y + Y_T} - \frac{Y_T^*}{h_Y + Y_T^*} \right) \right] \\
 &\leq -\beta_T S_T^* V^* \frac{(I_T - I_T^*)^2}{I_T I_T^*} - \gamma_Z (Z - Z^*) (I_T - I_T^*) - \gamma_V (I_T - I_T^*) (Y_V - Y_V^*) \\
 &\quad - \gamma_T (I_T - I_T^*) \left( \frac{Y_T}{h_Y + Y_T} - \frac{Y_T^*}{h_Y + Y_T^*} \right) \\
 &\leq v'_{41} + v_{41} + v_{42} + v_{43} \text{ (say)},
 \end{aligned} \tag{4.13}$$

$$\begin{aligned}
 \dot{V}_5 &= (V - V^*) \frac{\dot{V}}{V} = (V - V^*) \left[ b_T \lambda_T \left( \frac{I_T}{V} - \frac{I_T^*}{V^*} \right) + b_N \lambda_N \left( \frac{I_N}{V} - \frac{I_N^*}{V^*} \right) \right] \\
 &\leq -\frac{b_T \lambda_T}{V V^*} (V - V^*)^2 - \frac{b_N \lambda_N}{V V^*} \frac{I_N^*}{I_N} (V - V^*) \left( V - V^* \frac{I_N}{I_N^*} \right) \\
 &\leq v'_{51} + v_{51} \text{ (say)}
 \end{aligned} \tag{4.14}$$

$$\begin{aligned}
 \dot{V}_6 &= (Y_T - Y_T^*) \frac{\dot{Y}_T}{Y_T} = (Y_T - Y_T^*) \left[ p_T \left( \frac{S_T}{Y_T} - \frac{S_T^*}{Y_T^*} \right) + p_T \left( \frac{I_T}{Y_T} - \frac{I_T^*}{Y_T^*} \right) + \delta_T (I_T - I_T^*) \right. \\
 &\quad \left. + \delta_T (S_T - S_T^*) \right] \\
 &\leq -\frac{p_T I_T^*}{Y_T Y_T^*} (Y_T - Y_T^*)^2 - \frac{p_T S_T^*}{Y_T Y_T^*} (Y_T - Y_T^*) \left( Y_T - Y_T^* \frac{S_T}{S_T^*} \right) - \delta_T (Y_T - Y_T^*) (I_T - I_T^*) \\
 &\quad - \delta_T (Y_T - Y_T^*) (S_T - S_T^*) \\
 &\leq v'_{61} + v_{61} + v_{62} + v_{63} \text{ (say)},
 \end{aligned} \tag{4.15}$$

$$\begin{aligned}
 \dot{V}_7 &= (Y_V - Y_V^*) \frac{\dot{Y}_V}{Y_V} = (Y_V - Y_V^*) \left[ p_V \left( \frac{I_T}{Y_V} - \frac{I_T^*}{Y_V^*} \right) + p_V \left( \frac{I_N}{Y_V} - \frac{I_N^*}{Y_V^*} \right) \right] \\
 &\leq -\frac{p_V I_T^*}{Y_V Y_V^*} (Y_V - Y_V^*)^2 - \frac{p_V I_N^*}{Y_V Y_V^*} (Y_V - Y_V^*) \left( Y_V - Y_V^* \frac{I_N}{I_N^*} \right) \\
 &\leq v'_{71} + v_{71} \text{ (say)},
 \end{aligned} \tag{4.16}$$

$$\dot{V}_8 = (Z - Z^*) \frac{\dot{Z}}{Z} \leq -\frac{s_1}{2} [(Z - Z^*)^2 + (I_T - I_T^*)^2] \leq v'_{81} \text{ (say)} \tag{4.17}$$

and

$$\begin{aligned}
 \dot{V}_9 &= (N_T - N_T^*) \frac{\dot{N}_T}{N_T} = (N_T - N_T^*) \left[ \lambda_T \left( \frac{I_T}{N_T} - \frac{I_T^*}{N_T^*} \right) + \gamma_V \left( \frac{I_T Y_V}{N_T} - \frac{I_T^* Y_V^*}{N_T^*} \right) \right. \\
 &\quad \left. + \gamma_Z \left( \frac{I_T Z}{N_T} - \frac{I_T^* Z^*}{N_T^*} \right) \right. \\
 &\quad \left. + \gamma_T \left( \frac{Y_T I_T}{N_T (h_Y + Y_T)} - \frac{Y_T^* I_T^*}{N_T^* (h_Y + Y_T^*)} \right) + \gamma_T \left( \frac{Y_T S_T}{N_T (h_Y + Y_T)} - \frac{Y_T^* S_T^*}{N_T^* (h_Y + Y_T^*)} \right) \right] \\
 &\leq -\frac{\lambda_T I_T^*}{N_T N_T^*} (N_T - N_T^*)^2 - \gamma_V \frac{I_T^* Y_V^*}{N_T N_T^*} (N_T - N_T^*) \left( N_T - N_T^* \frac{I_T Y_V}{I_T^* Y_V^*} \right) \\
 &\quad - \gamma_Z \frac{I_T^* Z^*}{N_T N_T^*} (N_T - N_T^*) \left( N_T - N_T^* \frac{I_T Z}{I_T^* Z^*} \right) - \gamma_T \frac{Y_T^* I_T^* (N_T - N_T^*)}{N_T N_T^* (h_Y + Y_T^*) (h_Y + Y_T)} \{ N_T (h_Y \\
 &\quad + Y_T) - N_T^* (h_Y + Y_T^*) \} \frac{Y_T I_T}{Y_T^* I_T^*} - \gamma_T \frac{Y_T^* S_T^* (N_T - N_T^*)}{N_T N_T^* (h_Y + Y_T^*) (h_Y + Y_T)} [N_T (h_Y + Y_T) \\
 &\quad - N_T^* (h_Y + Y_T^*)] \frac{Y_T S_T}{Y_T^* S_T^*}
 \end{aligned}$$

$$\leq v'_{91} + v_{91} + v_{92} + v_{93} + v_{94} \text{ (say)}. \quad (4.18)$$

Here, the expressions for  $v'_{ij}$  and  $v_{ij}$  for  $i = 1, 2, 3, \dots, 9$  and  $j = 1, 2, 3, 4$  are included in the **Appendix-II** except those which are not furnished are assumed to be zero.

Hence if  $\min(v'_{ij}) \geq \max(v_{ij})$  for  $i = 1, 2, 3, \dots, 9$  and  $j = 1, 2, 3, 4$ , then  $\dot{V}_k \leq 0$  for all  $k = 1, 2, 3, \dots, 9$  and consequently  $\dot{V} \leq 0$ . Hence by Lyapunov-Lasalle's invariance principle (Hale, 1969) the proof of global stability of the interior equilibrium follows.

## 5 Numerical Simulation and Discussion

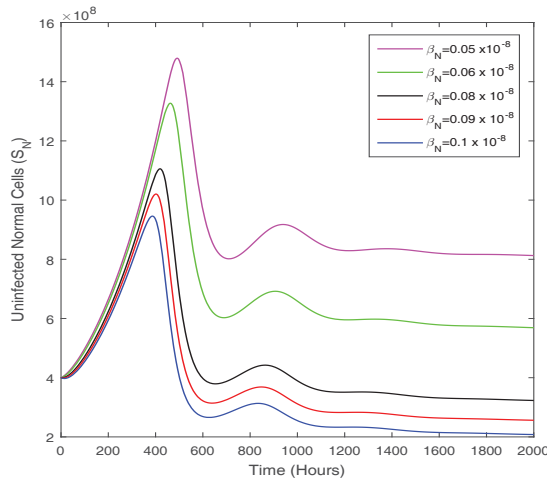


Figure 2: Time-variant profile of uninfected normal cells ( $S_N$ ) exposed to different rates of oncolytic virus infection.

Bearing in mind to uphold the notional exploration, it is justifiable to carry out numerical simulation based on the listed data in Table 2, 3 and 4 for all convoluted model parameters of the system undertaken just to manifest the agreement of the numerical results with their analytical counterparts. The objective of undertaking numerical simulation is to illustrate the theoretical consequences so that the validity of the proposed model is established. The dynamical response of the nonlinear model system of concern is examined in-depth numerically. Numerical integration for the present model system is carried out with the choice of relevant parameter values convoluted in oncolytic virotherapy supplemented by the set of a variety of cells having initial density. A set of initial conditions may be selected as  $S_N(0) = 10^{11}$  cells,  $S_T(0) = 10^6$  cells,  $I_N(0) = 0$  cell,  $I_T(0) = 0$  cell,  $V(0) = 10^9$  plaque forming units,  $Y_T(0) = 0$  cell,  $Y_V(0) = 0$  cell,  $Z(0) = 5 \times 10^3$  cells and  $N_T(0) = 0$  cell.

The initial value problem for the contemporary system of ordinary differential equations subject to the set of initial conditions is solved numerically using Runge-Kutta  $4^{th}$  order method with desired degree of accuracy and a befitting MATLAB code is developed to obtain several interesting phenomena. Using the entire set of model parametric values enlisted in Table 2, the following seven feasible non-negative equilibria are obtained:

(i)  $E_0 = (0, 0, 0, 0, 0, 0, 0, 0, 0)$

- (ii)  $E_1 = (10^{11}, 0, 0, 0, 0, 0, 0, 0, 0)$
- (iii)  $E_2 = (0, 112.9411764, 0, 0, 0, 3.076923077, 0, 0, 0.1613445378)$
- (iv)  $E_3 = (10^{11}, 112.9411764, 0, 0, 0, 3.076923077, 0, 0, 0.1613445378)$
- (v)  $E_4 = (4.094887509 \times 10^8, 0, 2540.574202, 0, 4.268164659 \times 10^6, 0, 11464.68503, 0, 0)$
- (vi)  $E_5 = (4.094887509 \times 10^8, 109.7047512, 2540.574202, 0.000004861660445, 4.268164659 \times 10^6, 3.053364250, 11464.68502, 0, 0.1567210731)$
- (vii)  $E_6 = (4.094887509 \times 10^8, 109.7047512, 2540.574202, 3.571428571 \times 10^{-8}, 4.268164659 \times 10^6, 3.053364250, 11464.68502, 1.549327452 \times 10^6, 0.1567210800)$ .

Apart from the trivial equilibrium (i), there are six nontrivial equilibria of which (ii) represents tumour-free only, (iii) represents tumour without the normal surrounding cells and without infection, (iv) corresponds to coexistence of both tumour and normal surrounding cells without infection, (v) stands for coexistence of both uninfected and infected normal cells without tumour while the remaining (vi) and (vii) are the respective interior equilibrium positions in the absence and the presence of innate immune cells.

The stability and instability of the positive equilibria of the system are studied using linear stability analysis. All the eigenvalues of the Jacobian matrix of the system (2.1) - (2.9) at these equilibria are obtained numerically and examined the viability of their individual stability. It appears from the nature of the eigenvalues that all the equilibrium positions (i) – (vi) are unstable depending on the existence of either positive real roots or complex roots with positive real parts of the corresponding characteristic equation barring that of the sole positive interior equilibrium position  $E_6$  which is stable. Both the local and the global stability of equilibrium are corroborated to set foot a step ahead in the realm of the dynamics of oncolytic virotherapy. This facet of stability of equilibrium ensures the stability of the entire model system under contemplation in the context of tumour virotherapy. Thus the present numerical simulations are very supportive since it is quite straightforward to connect the same with theoretical outcomes.

It is worth mentioning that the numerical simulation of the model system such as the present one bears the potential for its usage in the realm of oncolytic virotherapy in terms of its integrity and acceptability to humanity at large. For this purpose one needs to explore the receptivity of some key model parameters on the dynamic response of the system and to estimate their influence on various leading population of cells directly participating in the event. This attempt is made to examine the behaviour of the system quantitatively subject to key model parameters that were often difficult to characterize with theoretical treatment.

The time-series delineations for normal susceptible uninfected cells taking part in the dynamics of tumour virotherapy arising from the infection by oncolytic virus are illustrated in Figure 2 for various infected rates of virus. One may observe from the general characteristics of the representative curves that the normal susceptible cells start growing at the onset, rise to certain peaks and thereafter drops down to become almost flat sooner or later with further advancement of time. It is worth noting that the population of normal uninfected cells gets reduced considerably with increasing rate of oncolytic virus infection. The reduction of the normal cell population depending upon the viral doses enhances the aggregation of virus cells to help damaging the neighbouring tumour cells by keeping the normal cells unharmed through the process of virotherapy. Thus higher the number of infectious virions in the vicinity of tumour cells higher the chances of infecting and crushing every single tumour cell.

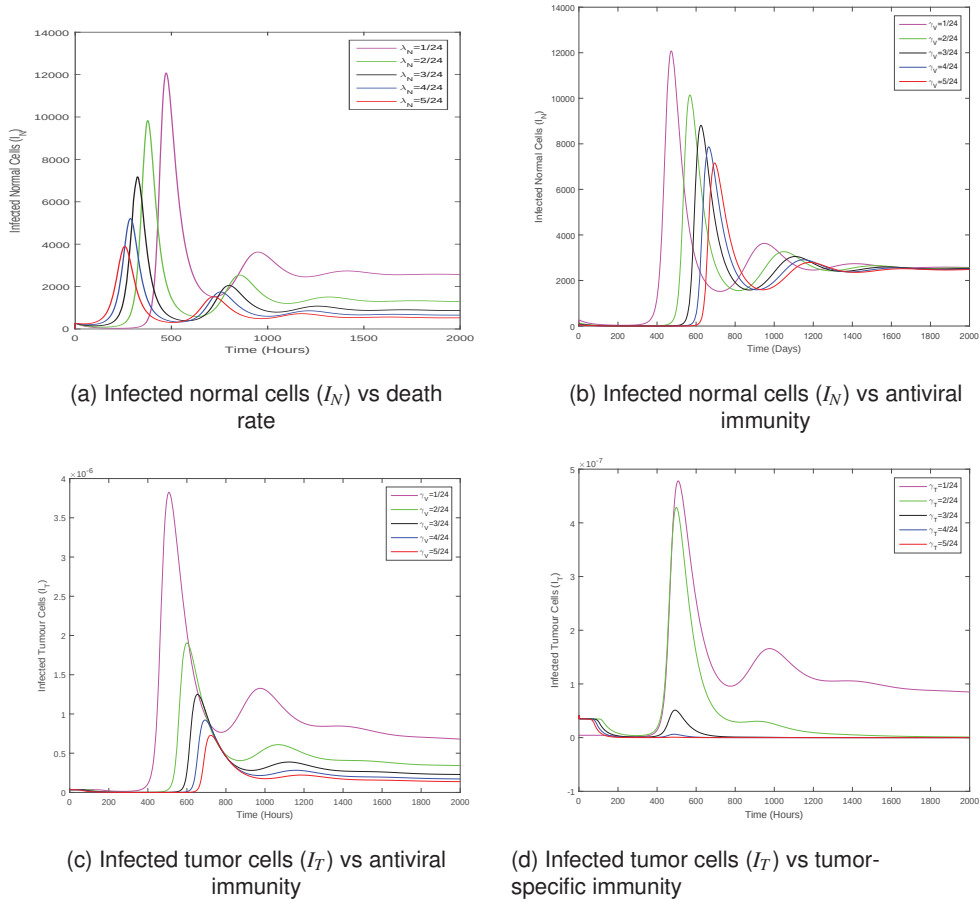


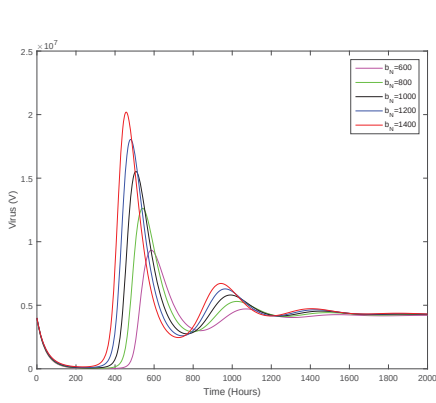
Figure 3: Response of time-variant profile of infected normal cells ( $I_N$ ) and infected tumor cells ( $I_T$ )

Figure 3(a) exhibits five distinct time-variant representations to demonstrate how the entire population of infected normal cells get influenced by the variation of their clearance or mortality rate. The mortality rate is varied by increasing its frequency from its base value for certain comprehensible situations. It is interesting to note that in the event of increasing mortality, the normal infected cells decline rapidly with the formation of early peaks followed by meagre undulation leading to the attainment of lower uniform cell population for further advancement of time. Experimental studies (Russell, Peng and Bell, 2012) reveal that the clearance or death of infected normal cells may be featured to apoptosis of the infected cells in endeavour to interfere with virus propagation. On the other hand, the characteristics of the time-dependent infected normal cell population lysed by the antiviral immunity with varied lysis rates are included in Figure 3(b). It appears from the trajectories of this figure that the normal infected cell population plunges significantly with increasing lysis rate of antiviral immunity with the pattern of latterly peaks converging eventually to the threshold cell population for rest of the time advancement unlike those of Figure 3(a). More the lysis rate of induced antiviral immunity, longer time the population of normal infected cells takes to attain the peak before it merges utterly with the threshold barrier. For the present simulation, the onset of susceptible tumour is assumed to have its initial size in an immune competent host. Although the size of the tumour

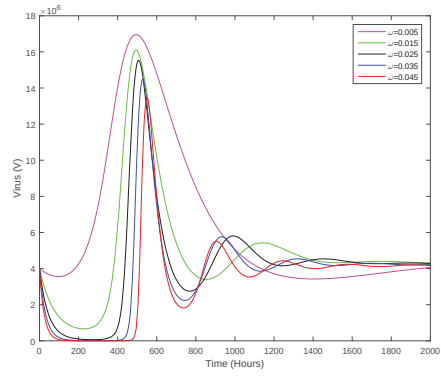
is conventionally measured in volume, the present model system takes into account the conversion of tumour volume to cell population with the consideration of  $1\text{mm}^3 \approx 10^6$  tumour cells (Rommelfanger, Offord, Dev, Bajzer, Vile and Dingli, 2012). Figure 3(c) records the dynamic performance of infected tumour cells influenced by the lysis rate of induced antiviral immunity stretched over an estimated period of 12 weeks. One may inspect from the results presented at this juncture that the population of infected tumour cells gets lowered significantly with the increasing rate of lysis rate of induced antiviral immunity. Unlike the normal infected cells, the tumour infected cells are finally destined to their individual threshold level depending upon the corresponding lysis rate of antiviral immunity. In other words, it may be attributed that the size of the infected tumour gets shrunk down to a considerable extent by increasing lysis rate of antiviral immunity which gives one of the remedial measures to achieve the target zone. Figure 3(d) registers another impact of immunity especially the consequence of tumour-specific immune cells on the population of infected tumour cells over a stipulated period of time. It indicates that the density of infected tumour cells drops down largely with rate escalation of tumour cells being lysed by tumour-specific immune cells. Such tumour-specific immunity continues to engulf the affected tumour as long as the lysis rate is spared to increase significantly so that the existence of infected tumour cells becomes questionable. It may be pointed out in the present context of oncolytic virotherapy that the tumour-specific immunity maximizes the reduction of tumour volume while minimizing the obnoxious toxicity on density of normal cells surrounding the tumour.

While the time-dependent delineation of oncolytic virus particles documented in Figure 4(a) with a variation of burst size for viruses emanating from infected normal cells, Figure 4(b) exhibits how the dynamical behaviour of the virus particles alters with clearance rate of the free virus from the host body by virus-specific immune cells. The choice of burst size for viruses is made to vary from its core size in order to explore the dynamics of virus particles. With the enlargement of burst size the population of virus particles continues to enhance to form early peak followed by a decline with a subsequent small hump before it merges completely with the threshold value for larger passage of time. Larger the burst size smaller the time it needs to attain the peak. Apart from this, the virus-specific immune cells are activated to clear free virus from the system rapidly for higher viral clearance rate so as to retain its population for further advancement of time. Smaller clearance rate reveals the aggregation of larger virus particles for certain period of time but they eventually look for destination at a later time. Figure 4(c) illustrates the dynamic characteristics of the virus-specific immune cells over the stipulated period of time for different death rates of the adaptive virus-specific immune cells. The common attribute of the trajectories appears to decline from its initial population at the onset followed by individual oscillations about diminishing amplitude which eventually becomes undeviating as time progresses. In the event of increasing death rate of the transformed virus-specific immune cells, the declination turns out to be sharper and the amplitude of the oscillation becomes shorter resulting in reduced unperturbed population. Examining all the upshots of the present figure one may conclude that the immune cells under attention dissipate into lower steady state faster for higher death rate than for smaller ones. Furthermore, the influence of assorted virus-specific proliferation rates of the antiviral immune cells on the varying population of virus-specific immune cells over certain span of time is included in Figure 4(d). It reveals that all the curves designating the population of virus specific immune cells decline from its initial size at the same rate irrespective of their proliferation rate until the estimated time of 400 hours and then branch out with a little enhancement depending on the proliferation rate to proceed towards the respective unperturbed states for larger advancement of time. The more the proliferation rate the larger is the threshold population of virus-specific immune cells. Thus both the model parameters  $\gamma_V$  and  $p_V$  play significant role in the dynamics of virus-specific immune cells for the purpose of having better understanding the mechanism of oncolytic virotherapy.

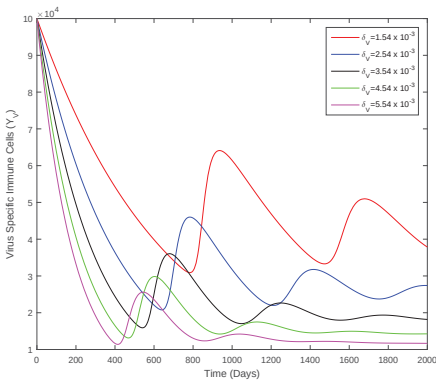
Finally, the parametric variation of  $\gamma_T$  on dead tumor cells recorded in Figure 5 illustrates how



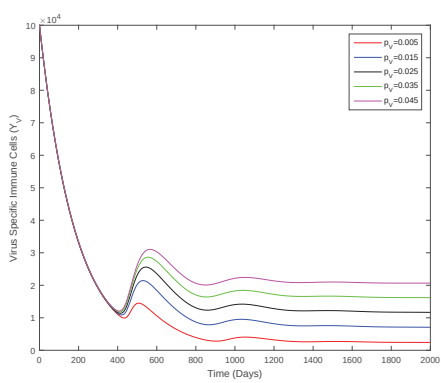
(a) Oncolytic virus ( $V$ ) vs burst sizes



(b) Oncolytic virus ( $V$ ) vs clearance rates of free virus



(c) Infected tumour cells ( $I_T$ ) vs death rate



(d) Infected tumour cells ( $I_T$ ) vs proliferation rates

Figure 4: Time-series representation of oncolytic virus ( $V$ ) and virus-specific immune cells ( $Y_V$ )

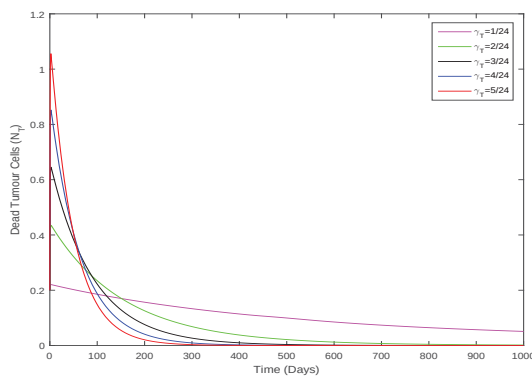


Figure 5: Time-series performance of dead tumour cells ( $N_T$ ) for different rates of tumour cells being lysed by tumour-specific immune cells.

the population of dead tumour cells alters with the rate of tumour cells being lysed by tumour-specific immune cells as time progresses. Dead tumour cells decline from its inceptive peak and disperse gradually with advancement of time where the rate of diffusion depends on the lysed rate of tumour-specific immune cells. Dead cells are driven away faster for higher lysed rate and slower for smaller lysed rate of tumour-specific immune cells.

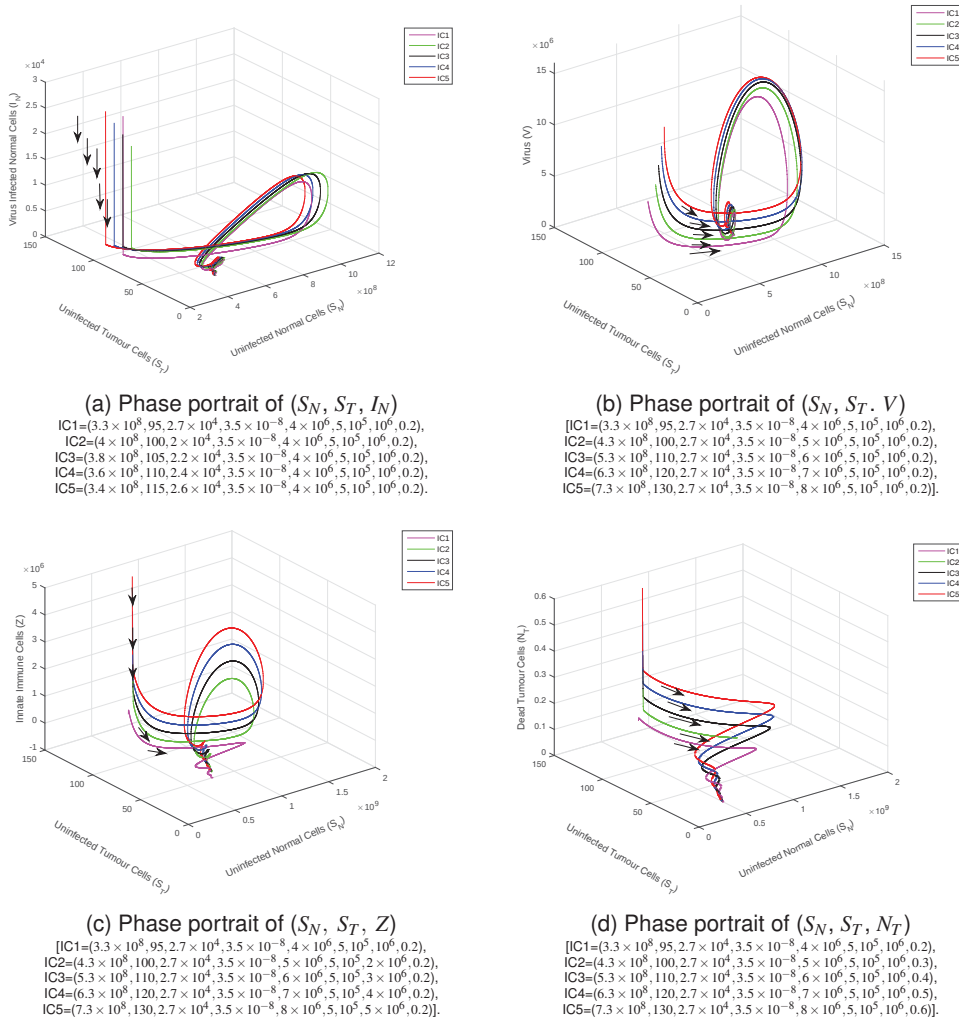


Figure 6: Three dimensional projection of the phase portrait to show stability of equilibrium position with different starting positions

As there are certain obvious limitations to perform an in-depth study on a large model system such as the present one under investigation, it is now focused on the various subsystems in three dimensional spaces in terms of 3D projections of the phase portraits in order to examine the stability of the system and to illustrate the theoretical issues highlighting the credibility of the model. Quite a few subsystems in three dimensional spaces namely,  $(S_N, S_T, I_N)$ ,  $(S_N, S_T, V)$ ,  $(S_N, S_T, Z)$  and  $(S_N, S_T, N_T)$  are displayed in Figures 6(a) – 6(d) respectively for the purpose. It is evident from these phase portraits that the equilibrium position of present model system is

asymptotically stable in view of the choice of different sets of initial associated cell population. All the trajectories emanate from their respective starting positions eventually approach the equilibrium position following the arrowed flow directions irrespective of the choice of their starting positions. Thus, the theoretical results regarding the local and the global stability of the present model system are in complete agreement with those of numerical simulation undertaken. This goes well with realistic system of virotherapy where small changes in the process of oncolytic virotherapy do not destabilize the system. Hence both the mathematical model and its corresponding real virotherapy can complement each other through the study of stability analysis. This validates the authenticity of the proposed mathematical model.

## 6 Conclusions

The present article deals with the dynamical response of an updated mathematical model describing the interactions between oncolytic virus and population of tumour cells surrounded by normal susceptible cells as well in the presence of both tumour and virus specific immune cells other than innate immune cells. The prime objective of the study is to form an advanced mathematical framework of complex interplay as a consequence of tumour virotherapy. The updated model depicting the dynamics of oncolytic virotherapy is articulated through the system of nine nonlinear ordinary differential equations governing the most pertinent interacting population of cells. Mathematically, the problem is sought for an initial value problem with the knowledge of the initial population sizes for all the cells taking part which is duly solved numerically and the results are unveiled for visualization.

The work undertaken is of sufficient scientific merit on several counts. First the model of concern is commonsensical in the realm of oncolytic virotherapy as it embraces all the pertinent constituents actively participating in the dynamics of tumour virotherapy. Secondly, incorporation of nonlinearity in the model formulation taking care of clear understanding the mode of interactions between the cells is another move towards a step closer to the real situation. Thirdly, the noteworthy stability analysis of the present model system in connection with the local and the global stability is carried out analytically and the results are duly complied with numerically. Lastly, a thoroughgoing effort is made by performing parametric variation of several key model parameters on the dynamic response of the present model system so as to gather a complete understanding of oncolytic tumour virotherapy regarding the interplay among the cells of diverse categories. Several conclusions can be drawn right from the numerical simulations undertaken to estimate the effect of variation of parameters of relevance on the dynamic response of the system. Some of the salient features are highlighted and enlisted below for their usage in future model upgradation:

- The viral doses reduce the susceptible cells resulting in clustering of virus cells to damage tumour cells in the vicinity by keeping normal cells unharmed. Thus higher the density of infectious virions in the proximity of tumour cells higher the chances of infecting and crushing every single tumour cell.
- More the lysis rate of induced antiviral immunity, longer time the density of normal infected cells needs to attain the peak before it merges utterly with the threshold barrier.
- The size of the infected tumour gets shrunk down to a tidy extent by increasing lysis rate of antiviral immunity indicating one of the remedial measures to achieve the target zone.
- The tumour-specific immunity maximizes reduction of tumour volume while minimizing the obnoxious toxicity on density of normal cells surrounding the tumour.

- The virus-specific immune cells are activated to clear free virus from the system rapidly so as to retain its population for larger time. Smaller clearance rate reveals the aggregation of larger virus particles for certain period of time but they eventually look for destination at a later time.
- The more the proliferation rate the larger is the threshold population of virus-specific immune cells.
- Both the model parameters  $\gamma_V$  and  $p_V$  play significant role in the dynamics of virus-specific immune cells for the purpose of having better understanding the mechanism of oncolytic virotherapy.
- The present model bears the potential to have its stability both locally and globally which evinces that small changes in the process of oncolytic virotherapy do not destabilize the pragmatic system of virotherapy.

The above-mentioned points clearly depict the inference gained from parametric variation of model parameters. The knowledge of the model parameters is very essential in understanding the refinement needed to update the future mathematical models of oncolytic virotherapy. More importantly, it is worth mentioning that unerring cognition of the characteristics of model parameters provide appropriate abstraction to the experimentalists. This will lead to furtherance of the medical treatment scheme to successfully apply on the cancer patients. Again, the functioning of the immune cells, whether it is the case of innate immune cells or virus-specific immune cells or tumour-specific immune cells, is concluded to be most critical as they are the sole warriors to destroy cancerous tumour cells. As a future scope the present proposed model may be updated taking into account much more biological complexities and restrictive action of oncolytic viruses as a result of immune response.

### Conflict of Interest

The author declares that she has no conflict of interest.

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## Appendix I

The elements of the Jacobian matrix (3.3) have got their respective expressions given by

$$\begin{aligned} j_{11}^* &= r_N \left[ 1 - \frac{2S_N^* + I_N^*}{K_N} \right] - \beta_N V^*, \quad j_{13}^* = -\frac{r_N}{K_N} S_N^*, \quad j_{15}^* = -\beta_N S_N^*, \quad j_{22}^* = r_T \left[ 1 - \frac{2S_T^* + I_T^*}{K_T} \right] - \beta_T V^* - \frac{\gamma_T}{h_Y + Y_T^*} \frac{Y_T^*}{Y_T^*}, \\ j_{24}^* &= -\frac{r_T}{K_T} S_T^*, \quad j_{25}^* = -\beta_T S_T^*, \quad j_{26}^* = -\gamma_T S_T^* \left[ \frac{1}{h_Y + Y_T^*} - \frac{Y_T^*}{(h_Y + Y_T^*)^2} \right], \quad j_{31}^* = \beta_N V^*, \quad j_{33}^* = -(\lambda_N + \gamma_V Y_V^*), \\ j_{35}^* &= \beta_N S_N^*, \quad j_{37}^* = -\gamma_V I_N^*, \quad j_{42}^* = \beta_T V^*, \quad j_{44}^* = -[\lambda_T + \gamma_V Y_V^* + \gamma_Z Z^* + \frac{\gamma_T}{h_Y + Y_T^*} \frac{Y_T^*}{Y_T^*}], \quad j_{45}^* = \beta_T S_T^*, \\ j_{46}^* &= -\gamma_T I_T^* \left[ \frac{1}{h_Y + Y_T^*} - \frac{Y_T^*}{(h_Y + Y_T^*)^2} \right], \quad j_{47}^* = -\gamma_V I_T^*, \quad j_{48}^* = -\gamma_Z I_T^*, \quad j_{53}^* = b_N \lambda_N, \quad j_{54}^* = b_T \lambda_T, \quad j_{55}^* = -\omega, \\ j_{62}^* &= p_T \left[ \frac{1}{h_T + S_T^* + I_T^*} - \frac{S_T^* + I_T^*}{(h_T + S_T^* + I_T^*)^2} \right], \quad j_{64}^* = j_{62}^*, \quad j_{66}^* = -\delta_T, \quad j_{73}^* = p_V = j_{74}^*, \quad j_{77}^* = -\delta_V, \quad j_{84}^* = s_1 Z^*, \\ j_{88}^* &= -c_1 + s_1 I_T^*, \quad j_{92}^* = \frac{\gamma_T}{h_Y + Y_T^*} \frac{Y_T^*}{Y_T^*}, \quad j_{94}^* = \lambda_T + \gamma_V Y_V^* + \gamma_Z Z^* + \frac{\gamma_T}{h_T + Y_T^*} \frac{Y_T^*}{Y_T^*}, \quad j_{96}^* = \gamma_T S_T^* \left[ \frac{1}{h_Y + Y_T^*} - \frac{Y_T^*}{(h_Y + Y_T^*)^2} \right], \\ j_{97}^* &= \gamma_V I_T^*, \quad j_{98}^* = \gamma_Z I_T^*, \quad j_{99}^* = -\mu. \end{aligned}$$

## Appendix II

The expressions for  $v'_{ij}$  and  $v_{ij}$  for  $i = 1, 2, 3, \dots, 9$  and  $j = 1, 2, 3, 4$  involved in the equations (4.10) – (4.18) should be read as follows:

$$v'_{11} = -\frac{(S_N - S_N^*)^2}{K_N} r_N, \quad v_{11} = -\frac{r_N}{K_N} (S_N - S_N^*) (I_N - I_N^*), \quad v_{12} = -\beta_N (V - V^*) (S_N - S_N^*),$$

$$\begin{aligned}
 v'_{21} &= -\frac{(S_T - S_T^*)^2}{K_T} r_T, \quad v_{21} = -\frac{r_T}{K_T} (S_T - S_T^*) (I_T - I_T^*), \quad v_{22} = -\beta_T (V - V^*) (S_T - S_T^*), \\
 v_{23} &= -\gamma_T (S_T - S_T^*) \left( \frac{Y_T}{h_Y + Y_T} - \frac{Y_T^*}{h_Y + Y_T^*} \right), \quad v'_{31} = -\beta_N S_N^* V^* \frac{(I_N - I_N^*)^2}{I_N I_N^*}, \quad v_{31} = -\gamma (I_N - I_N^*) (Y_V - Y_V^*), \\
 v'_{41} &= -\beta_T S_T^* V^* \frac{(I_T - I_T^*)^2}{I_T I_T^*}, \quad v_{41} = -\gamma_Z (Z - Z^*) (I_T - I_T^*), \quad v_{42} = -\gamma (I_T - I_T^*) (Y_V - Y_V^*), \\
 v_{43} &= -\gamma_T (I_T - I_T^*) \left( \frac{Y_T}{h_Y + Y_T} - \frac{Y_T^*}{h_Y + Y_T^*} \right), \\
 v'_{51} &= -\frac{b_T \lambda_T I_T^*}{V V^*} (V - V^*)^2, \\
 v_{51} &= -\frac{b_N \lambda_N I_N^*}{V V^*} (V - V^*) \left( V - V^* \frac{I_N}{I_N^*} \right), \quad v'_{61} = -\frac{p_T I_T^*}{Y_T Y_T^*} (Y_T - Y_T^*)^2, \\
 v_{61} &= -\frac{p_T S_T^*}{Y_T Y_T^*} (Y_T - Y_T^*) \left( Y_T - Y_T^* \frac{S_T}{S_T^*} \right), \quad v_{62} = -\delta_T (Y_T - Y_T^*) (I_T - I_T^*), \quad v_{63} = -\delta_T (Y_T - Y_T^*) (S_T - S_T^*), \\
 v'_{71} &= -\frac{p_V I_T^*}{Y_V Y_V^*} (Y_V - Y_V^*)^2, \quad v_{71} = -\frac{p_V I_N^*}{Y_V Y_V^*} (Y_V - Y_V^*) \left( Y_V - Y_V^* \frac{I_N}{I_N^*} \right), \quad v'_{81} = -\frac{s_1}{2} [(Z - Z^*)^2 + (I_T - I_T^*)^2], \\
 v'_{91} &= -\frac{\lambda_T I_T^*}{N_T N_T^*} (N_T - N_T^*)^2, \quad v_{91} = -\gamma \frac{I_T^* Y_V^*}{N_T N_T^*} (N_T - N_T^*) \left( N_T - N_T^* \frac{I_T Y_V}{I_T^* Y_V^*} \right), \\
 v_{92} &= -\gamma_Z \frac{I_T^* Z^*}{N_T N_T^*} (N_T - N_T^*) \left( N_T - N_T^* \frac{I_T Z}{I_T^* Z^*} \right), \\
 v_{93} &= -\gamma_T \frac{Y_T^* I_T^* (N_T - N_T^*)}{N_T N_T^* (h_Y + Y_T^*) (h_Y + Y_T)} \{N_T (h_Y + Y_T) - N_T^* (h_Y + Y_T^*)\} \frac{Y_T I_T}{Y_T^* I_T^*}, \\
 v_{94} &= -\gamma_T \frac{Y_T^* S_T^* (N_T - N_T^*)}{N_T N_T^* (h_Y + Y_T^*) (h_Y + Y_T)} \{N_T (h_Y + Y_T) - N_T^* (h_Y + Y_T^*)\} \frac{Y_T S_T}{Y_T^* S_T^*}.
 \end{aligned}$$