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A mathematical model verifying potent oncolytic efficacy of M1 virus☆

Zizi Wang[a,b], Zhiming Guo[a,b,*], Huaqin Peng[a,b]

[a] School of Mathematics and Information Science, Guangzhou University, Guangzhou 510006, PR China
[b] Key Laboratory of Mathematics and Interdisciplinary Science of Guangdong, Higher Education Institutes, Guangzhou University, Guangzhou 510006, PR China

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ABSTRACT

Motivated by the latest findings in a recent medical experiment [19] which identify a naturally occurring alphavirus (M1) as a novel selective killer targeting zinc-finger antiviral protein (ZAP)-deficient cancer cells, we propose a mathematical model to illustrate the growth of normal cells, tumor cells and the M1 virus with limited nutrient. In order to better understand biological mechanisms, we discuss two cases of the model: without competition and with competition. In the first part, the explicit threshold conditions for the persistence of normal cells (or tumor cells) is obtained accompanying with the biological explanations. The second part indicates that when competing with tumor cells, the normal cells will extinct if M1 virus is ignored; Whereas, when M1 virus is considered, the growth trend of normal cells is similar to the one without competition. And by using uniformly strong repeller theorem, the minimum effective dosage of medication is explicitly found which is not reported in [19]. Furthermore, numerical simulations and corresponding biological interpretations are given to support our results.

1. Introduction

Despite of advances in cancer therapy over the past few decades, cancer is still a major health problem all over the world [13]. A useful treatment is anti-tumor immune response to tumors, which is usually cell-mediated with cytotoxic T lymphocytes (CTL) and natural killer (NK) cells playing a dominant role [16]. A number of mathematical models of the interactions between the immune system and a growing tumor have been developed [1,3–6,9,15–18,21–23,29,30]. The effector cells and tumor cells are concerned in these articles. With these models, numerical estimates of biologically significant parameters have been obtained, as well as some interpretations and predictions of a number of phenomena [16].

In recent years, oncolytic virotherapy has got an increasing attention since Martuza et al. [20] published an article in Science which claims that Transgene HSV has an influence on malignant glioma therapy. Oncolytic virotherapy is a growing treatment modality that uses replicating viruses as selective antineoplastic agents. The tumor selectivity of oncolytic virus is primarily based on the genetic abnormalities of malignant cells, including innate immune defects, aberrant oncogenic signaling, and tumor-specific receptors [2,25,26]. Oncolytic Virotherapy also interests the mathematician. And mathematical modeling of oncolytic virus has provided useful insight into the understanding of underlying phenomena and offered helpful guidance to related public health decisions. For example, in 2005, Tao and Guo [27] formulated a PDE model to explore an explicit threshold of the intensity of the immune response for controlling the tumor and find a periodic solution; In 2010, Komarova and Wodarz [14] find two distinct types of dynamics depended on the virus spread; In 2011, a delayed oncolytic virus dynamics with continuous control, which points out that the Hopf bifurcation can occur as the delay crosses some critical values, is investigated by Wang et al. [31].

In 2014, Lin et al. [19] showed potent oncolytic efficacy and high tumor tropism of M1. The virus is engineered to selectively bind to receptors on the tumor cell surface (but not to the surface of normal healthy cells). The virus particles then gain entry by endocytosis and proceed to proliferate exponentially within the tumor cell, eventually causing death (lysis). Thus, they hypothesized that an apathogenic cancer cell-killing virus could be a candidate for systemic oncolytic therapy.

In order to better understand the role of the cell-killing virus of M1 discovered in Lin et al. [19], we formulate a mathematical

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* Corresponding author at: School of Mathematics and Information Science, Guangzhou University, Guangzhou 510006, PR China. Tel.: +86 13342886835.
E-mail address: gzm100@21cn.com, guozm@gzhu.edu.cn (Z. Guo).

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model to mimic the evolution of cell concentration described in the experimental study of Lin et al. [19]. The model is considered in the chemostat. Let S denote the concentration of nutrient, N the normal cell concentration, T the tumor cell concentration and M the M1 virus concentration. Our model is as follows.

$$\begin{cases} S'(t) = A - dS(t) - u_1S(t)N(t) - u_2S(t)T(t), \\ N'(t) = r_1u_1S(t)N(t) - (d+\varepsilon_1)N(t), \\ T'(t) = r_2u_2S(t)T(t) - (d+\varepsilon_2)T(t) - u_3T(t)M(t), \\ M'(t) = B + r_3u_3T(t)M(t) - (d+\varepsilon_3)M(t). \end{cases} \tag{1.1}$$

where A is the recruitment rate of nutrient, B is the recruitment of M1 virus which implies the minimum effective dosage of medication, d is the washout rate of nutrient and bacteria, u_i is the maximal growth rate, r_i is the yield constant of nutrient to biomass of the organism, ε_i is the natural death rate of biomass. It is easy to see that the relationship between nutrient and normal cells or tumors is prey and predator, and the relationship between normal cells and tumors is competitive. This type of model had been researched deeply, such as Hsu et al. [11,12], Wang and Zou [32].

But our research perspective is different from previous researches. In order to express the potent oncolytic efficacy and high tumor tropism of M1, we divide the model into three part: $S-N$ model, $S-N-T$ model, and $S-N-T-M$ model. The $S-N$ model reflects the growth trend of normal cells of healthy individuals, while the $S-N-T$ model reflects the growth trend of cells of people with cancer, and the $S-N-T-M$ model will explain the experimental findings [19] on potent oncolytic efficacy and high tumor tropism of M1.

Now, we prove that solutions to the model (1.1) possess long-time behavior.

By the form of (1.1), it is easy to see that solutions to (1.1) with nonnegative initial values are nonnegative, and the solutions with positive initial values are positive. Set

$$W(t) = S(t) + \frac{1}{r_1}N(t) + \frac{1}{r_2}T(t) + \frac{1}{r_2r_3}M(t). \tag{1.2}$$

Differentiating (1.2) with respect to t, we find

$$\begin{aligned} \frac{dW(t)}{dt} &= A + \frac{B}{r_2r_3} - dS(t) - \frac{d+\varepsilon_1}{r_1}N(t) \\ &\quad - \frac{d+\varepsilon_2}{r_2}T(t) - \frac{d+\varepsilon_3}{r_2r_3}M(t), \\ &\le A_1 - dW(t). \end{aligned} \tag{1.3}$$

where $A_1 = A + \frac{B}{r_2r_3}$. By differentiating inequality above, it is easy to see that

$$W(t) \le \frac{A_1}{d} + 1, \text{ for all large } t.$$

It is showed that model (1.1) is as well behaved as one intuits from biology. In the sequel, we consider the model in the first quadrant.

The rest of this paper is organized as follows. In Section 2, the $S-N$ model is considered, in which the evolution of normal cells without tumor cells is discussed. Similarly, $S-T$ model is studied. In Section 3, it is proved that the existence of tumor cells may interrupts the growth of normal cells; on the other hand, from the $S-N-T-M$ model, we can see that the growth trend of normal cells is similar to the $S-N$ model which explain the experimental findings [19] that M1 virus is of potent oncolytic efficacy and high tumor tropism; Section 4 is devoted to numerical simulations. Finally, short conclusion is given in Section 5.

2. The model without competition

2.1. The $S-N$ model

From the system (1.1), the $S-N$ model is given by the following form.

$$\begin{cases} S'(t) = A - dS(t) - u_1S(t)N(t), \\ N'(t) = r_1u_1S(t)N(t) - (d+\varepsilon_1)N(t). \end{cases} \tag{2.1}$$

It is easy to see that system (2.1) always has an equilibrium $E_{01} = (\frac{A}{d}, 0)$. Similar to the definition of basic reproduction number [8,24], we define a threshold value

$$Q_1 = \frac{Ar_1u_1}{d(d+\varepsilon_1)}, \tag{2.2}$$

where $\frac{1}{d}$ is the average lifetime in compartment S, then every individual in compartment S product A/d individuals. Similarly, $1/(d+\varepsilon_1)$ is the average lifetime in compartment N, and the product rate of every individual in compartment N is $(r_1u_1S)/(d+\varepsilon_1)$. Thus, the number $Q_1 = (Ar_1u_1)/d(d+\varepsilon_1)$ reflects the ability of absorbing nutrients, we call it absorbing number.

If absorbing number $Q_1 > 1$, then there is a positive equilibrium

$$E_{02} = \left(\frac{d+\varepsilon_1}{r_1u_1}, \frac{Ar_1u_1 - d(d+\varepsilon_1)}{u_1(d+\varepsilon_1)}\right).$$

Next, we show that the stability of equilibrium depends on the absorbing number Q_1.

Theorem 2.1. *The local stability of equilibrium E_{01} and E_{02} have following conclusions.*

(i) *If $Q_1 < 1$, then the equilibrium E_{01} is locally asymptotically stable;*
(ii) *If $Q_1 > 1$, then the equilibrium E_{01} is unstable, and the positive equilibrium E_{02} is locally asymptotically stable.*

Proof. We linearize the system (2.1) at the equilibrium E_{01}, and obtain the following characteristic equation.

$$(\lambda + d)\left(\lambda - \frac{Ar_1u_1 - d(d+\varepsilon_1)}{d}\right) = 0.$$

It is obvious that $\lambda_1 = -d$ and $\lambda_2 = \frac{Ar_1u_1 - d(d+\varepsilon_1)}{d} = (d+\varepsilon_1)(Q_1 - 1)$. Thus when $Q_1 < 1$, $\lambda_2 < 0$, and the equilibrium E_{01} is locally asymptotically stable, while it is unstable when absorbing number $Q_1 > 1$.

As we know, the positive equilibrium E_{02} exists if and only if $Q_1 > 1$. By direct computation, the characteristic equation of (2.1) at E_{02} becomes

$$\lambda^2 + dQ_1\lambda + d(d+\varepsilon)(Q_1 - 1) = 0. \tag{2.3}$$

Clearly, if $Q_1 > 1$, then the positive equilibrium E_{02} is locally asymptotically stable. □

Theorem 2.2. *System (2.1) does not have nontrivial periodic orbits in the set $\Gamma = \{(S,N) | S > 0, N > 0\}$.*

Proof. Consider system (2.1) for $S \ge 0$ and $N \ge 0$, and we define $P(S,N) = A - dS - u_1SN$, $Q(S,N) = r_1u_1SN - (d+\varepsilon_1)N$. Take a Dulac function

$$D(S,N) = \frac{1}{SN}.$$

We have

$$\frac{\partial(DP)}{\partial S} + \frac{\partial(DQ)}{\partial N} = -\frac{A}{NS^2} < 0, \forall S > 0, N > 0.$$

The conclusion follows. □

By Theorems 2.1 and 2.2, the following result is obvious.

Theorem 2.3. *System (2.1) has the following global dynamics.*

(i) *If $Q_1 \le 1$, then system (2.1) has a unique equilibrium. The equilibrium E_{01} of system (2.1) is globally asymptotically stable in the set $\Omega = \{(S,N)|S \ge 0, N \ge 0\}$;*
(ii) *If $Q_1 > 1$, then the system (2.1) has two equilibria, E_{01} and E_{02}. Moreover, the positive equilibrium E_{02} is globally asymptotically stable in the set $\Omega' = \{(S,N)|S \ge 0, N > 0\}$.*

Proof. By Theorem 2.1, we know that equilibrium E_{01} (or E_{02}) is locally asymptotically stable when $Q_1 < 1$(or $Q_1 > 1$). Then by Theorem 2.2, we can see that the result is obvious when $Q_1 < 1$ or $Q_1 > 1$. So we consider $Q_1 = 1$, set

$$V_0(S,N) = S - \frac{A}{d} - \frac{A}{d}\ln\frac{dS}{A} + \frac{N}{r_1}.$$

Differentiating V_0 with respect t along solutions of (2.1) in Ω,

$$\frac{dV_0}{dt} = -\frac{(A-dS)^2}{dS} + \left(\frac{u_1 A}{d} - \frac{d+\varepsilon_1}{r_1}\right)N.$$

As $Q_1 = 1$, then $\frac{u_1 A}{d} - \frac{d+\varepsilon_1}{r_1} = 0$, $\frac{dV_0}{dt} \le 0$. We set $\frac{dV_0}{dt} = 0$, then $S = \frac{A}{d}$, $S' = 0$. By first equation of (2.1), we obtain $N = 0$. Thus, the equilibrium E_{01} is globally asymptotically stable in the set $\Omega = \{(S,N)|S \ge 0, N \ge 0\}$. □

2.2. The $S-T$ model

The $S-N$ model is given by the following form.

$$\begin{cases} S'(t) = A - dS(t) - u_2 S(t)T(t), \\ T'(t) = r_2 u_2 S(t)T(t) - (d+\varepsilon_2)T(t). \end{cases} \tag{2.4}$$

By a similar argument to $S-N$ model, $S-T$ model possesses the similar dynamical behavior. There is an absorbing number

$$Q_2 = \frac{Ar_2u_2}{d(d+\varepsilon_2)},$$

which depicts the dynamic behavior of this model.

Theorem 2.4. *The following statements hold.*

(i) *Assume $Q_2 \le 1$. Then system (2.4) has a unique equilibrium $E_{11} = (\frac{A}{d}, 0)$, which is globally asymptotically stable in the set $\Omega_1 = \{(S,N)|S \ge 0, T \ge 0\}$;*
(ii) *Assume $Q_2 > 1$, then system (2.4) has two equilibriums E_{11} and $E_{12} = (\frac{d+\varepsilon_2}{r_2u_2}, \frac{Ar_2u_2 - d(d+\varepsilon_2)}{u_2(d+\varepsilon_2)})$. In this case, E_{11} is unstable, and E_{12} is globally asymptotically stable in the set $\Omega_1' = \{(S,N)|S \ge 0, T > 0\}$;.*

Remark 2.1. By the above results, the absorbing number $Q_1 > 1$ (or $Q_2 > 1$) is necessary condition for the permanence of normal cells (or tumor cells).

3. The model with competition

3.1. The $S-N-T$ model

In Section 2, we analysis the $S-N$ and $S-T$ model, respectively. In this section, we consider the relationship between N, T and S. The model is formulated as the form below.

$$\begin{cases} S'(t) = A - dS(t) - u_1 S(t)N(t) - u_2 S(t)T(t), \\ N'(t) = r_1 u_1 S(t)N(t) - (d+\varepsilon_1)N(t), \\ T'(t) = r_2 u_2 S(t)T(t) - (d+\varepsilon_2)T(t). \end{cases} \tag{3.1}$$

In the sequel, we always assume that absorbing numbers $Q_1, Q_2 > 1$. Because $Q_1 \le 1$(or $Q_2 \le 1$) leads to the extinction of normal cells (or tumor cells). Firstly, we discuss the stability of equilibrium

$$E_{21} = (S_{21}, N_{21}, T_{21}) = \left(\frac{d+\varepsilon_1}{r_1u_1}, \frac{Ar_1u_1 - d(d+\varepsilon_1)}{u_1(d+\varepsilon_1)}, 0\right)$$

and

$$E_{22} = (S_{22}, N_{22}, T_{22}) = \left(\frac{d+\varepsilon_2}{r_2u_2}, 0, \frac{Ar_2u_2 - d(d+\varepsilon_2)}{u_2(d+\varepsilon_2)}\right).$$

In order to examine local stability of each equilibrium, we should compute the eigenvalues of the linearized operator for system (3.1) at each equilibrium. Consider the equilibrium E_{21}, the Jacobian matrix of (3.1) is obtained as follows

$$J = \begin{bmatrix} -d - \frac{Ar_1u_1 - d(d+\varepsilon_1)}{d+\varepsilon_1} & -\frac{d+\varepsilon_1}{r_1} & -\frac{u_2(d+\varepsilon_1)}{r_1u_1} \\ r_1\left[\frac{Ar_1u_1 - d(d+\varepsilon_1)}{d+\varepsilon_1}\right] & 0 & 0 \\ 0 & 0 & \frac{r_2u_2(d+\varepsilon_1)}{r_1u_1} - (d+\varepsilon_2) \end{bmatrix}.$$

The corresponding characteristic equation is

$$(\lambda^2 + p_1\lambda + p_2)(\lambda - p_3) = 0.$$

where $p_1 = \frac{Ar_1u_1}{d+\varepsilon_1} > 0$, $p_2 = Ar_1u_1 - d(d+\varepsilon_1) > 0$, $p_3 = (\frac{Q_2}{Q_1} - 1)(d+\varepsilon_2)$. By Eq. (2.3), it is easy to know that the stability of equilibrium E_{21} depends on the sign of $\frac{Q_2}{Q_1} - 1$. Thus the follow theorem is obvious.

Theorem 3.1. *If $Q_1 > Q_2$, then the equilibrium E_{21} is locally asymptotically stable; If $Q_1 < Q_2$, then the equilibrium E_{21} is unstable.*

The next theorem, we show that the equilibrium E_{21} is globally asymptotically stable when $Q_1 > Q_2$.

Theorem 3.2. *Assume that $Q_1 > Q_2$, then the equilibrium E_{21} is globally asymptotically stable in the set $\Lambda = \{(S,N,T)|S \ge 0, N \ge 0, T \ge 0\}$.*

Proof. We define a Lyapunov function by

$$V_1(S,N,T) = S - S_{21} - S_{21}\ln\frac{S}{S_{21}} + \frac{1}{r_1}\left(N - N_{21} - N_{21}\ln\frac{N}{N_{21}}\right) + \frac{T}{r_2}. \tag{3.2}$$

Differentiating (3.2) with respect t along solutions of (3.1) in Λ, we obtain

$$\begin{aligned} \frac{dV_1}{dt} &= \frac{dS}{dt} - \frac{S_{21}}{S}\frac{dS}{dt} + \frac{1}{r_1}\left(\frac{dN}{dt} - \frac{N_{21}}{N}\frac{dN}{dt}\right) + \frac{1}{r_2}\frac{dT}{dt} \\ &= A - dS - u_1SN - u_2ST + u_1SN - \frac{d+\varepsilon_1}{r_1}N + u_2ST \\ &\quad - \frac{d+\varepsilon_2}{r_2}T - \frac{S_{21}}{S}(A - dS - u_1SN - u_2ST) \\ &\quad - N_{21}\left(u_1S - \frac{d+\varepsilon_1}{r_1}\right) \\ &= (A-dS)\left(1 - \frac{S_{21}}{S}\right) - \frac{(d+\varepsilon_1)N}{r_1} - \frac{(d+\varepsilon_2)T}{r_2} + S_{21}u_1N \\ &\quad + S_{21}u_2T - N_{21}\left(u_1S - \frac{d+\varepsilon_1}{r_1}\right) \\ &= (A-dS)\left(1 - \frac{S_{21}}{S}\right) - N_{21}\left(u_1S - \frac{d+\varepsilon_1}{r_1}\right) \\ &\quad + \left(S_{21}u_1 - \frac{d+\varepsilon_1}{r_1}\right)N + \left(S_{21}u_2 - \frac{d+\varepsilon_2}{r_2}\right)T \end{aligned}$$

For the sake of simplicity, we set

$$x = (A-dS)\left(1 - \frac{S_{21}}{S}\right) - N_{21}\left(u_1S - \frac{d+\varepsilon_1}{r_1}\right), \tag{3.3}$$

$$y = \left(S_{21}u_1 - \frac{d+\varepsilon_1}{r_1}\right)N, \tag{3.4}$$

$$z = \left(S_{21}u_2 - \frac{d+\varepsilon_2}{r_2}\right)T. \tag{3.5}$$

Substituting $S_{21} = \frac{d+\varepsilon_1}{r_1u_1}$ and $N_{21} = \frac{Ar_1u_1 - d(d+\varepsilon_1)}{u_1(d+\varepsilon_1)}$ into (3.3)–(3.5), it follows that

$$x = -\frac{A}{SS_{21}}(S - S_{21})^2 \le 0,$$
$$y = 0,$$
$$z = \frac{d(d+\varepsilon_1)(d+\varepsilon_2)(Q_2 - Q_1)}{Ar_1r_2u_1}T \le 0.$$

Using similar arguments to these in Wang et al. [32], we consider the set

$$\Lambda_1 = \left\{(S(t), N(t), T(t)) | \frac{dV_1}{dt} = 0\right\}.$$

Let $\frac{dV_1}{dt} = 0$. Then we have from (3.3)–(3.5) that $x = z = 0$. And this implies $S = S_{21}$, $T = 0$. It shows by first equation of (3.1) that

$$\frac{dS(t)}{dt} = A - dS_{21} - u_1S_{21}N(t) = 0. \tag{3.6}$$

Hence, $N = N_{21}$. Thus, the largest invariant set of (3.1) contained in Λ_1 is E_{21}. By the Lyapunov–Lasalle theorem, all solutions of system (3.1) in Λ approach E_{21} as $t \to +\infty$. □

Remark 3.1. Analogue to the equilibrium E_{21}, the stability of equilibrium E_{22} also depends on the sign of $\frac{Q_2}{Q_1} - 1$. Thus the following theorem is obvious.

Theorem 3.3. *If $Q_1 < Q_2$, then the equilibrium E_{22} is globally asymptotically stable in the set $\Lambda = \{(S, N, T) | S \ge 0, N \ge 0, T \ge 0\}$; If $Q_1 > Q_2$, then the equilibrium E_{22} is unstable.*

Otherwise, in the case of $Q_1 = Q_2$, it implies that $\frac{Ar_1u_1}{d(d+\varepsilon_1)} = \frac{Ar_2\varepsilon_2}{d(d+\varepsilon_2)}$. Thus, we have $\frac{r_1u_1}{d+\varepsilon_1} = \frac{r_2\varepsilon_2}{d+\varepsilon_2}$, we calculates the equilibrium in system (3.1). Hence,

$$\begin{cases} A - dS(t) - u_1S(t)N(t) - u_2S(t)T(t) = 0, \\ r_1u_1S(t)N(t) - (d+\varepsilon_1)N(t) = 0, \\ r_2u_2S(t)T(t) - (d+\varepsilon_2)T(t) = 0. \end{cases} \tag{3.7}$$

By the second and third equation, we have $S_* = \frac{d+\varepsilon_1}{r_1u_1} = \frac{d+\varepsilon_2}{r_2u_2}$. Plugging $S_* = \frac{d+\varepsilon_1}{r_1u_1} = \frac{d+\varepsilon_2}{r_2u_2}$ into the first equation in system (3.7), we find

$$u_1N + u_2T = d(Q_1 - 1). \tag{3.8}$$

Hence, all the points on the segment (3.8) are equilibrium points with $S_* = \frac{d+\varepsilon_1}{r_1u_1} = \frac{d+\varepsilon_2}{r_2u_2}$. By linearization of (3.1) at a constant solution (S_*, N_*, T_*), we get the Jacobian matrix

$$L = \begin{bmatrix} -d - u_1N_* - u_2T_* & -u_1S_* & -u_2S_* \\ r_1u_1N_* & r_1u_1S_* - (d+\varepsilon_1) & 0 \\ r_2u_2T_* & 0 & r_2u_2S_* - (d+\varepsilon_2) \end{bmatrix}. \tag{3.9}$$

We set $u_1N_* + u_2T_* = d(Q_1 - 1)$, $S_* = \frac{d+\varepsilon_1}{r_1u_1} = \frac{d+\varepsilon_2}{r_2u_2}$, then get the corresponding characteristic equation:

$$\lambda(\lambda^2 + dQ_1\lambda + u_1(d+\varepsilon_1)N_* + u_2(d+\varepsilon_2)T_*) = 0.$$

Hence, the eigenvalues of L are simply given by $\lambda_1 = 0$, $\lambda_2 + \lambda_3 = -dQ_1 < 0$, $\lambda_2\lambda_3 = u_1(d+\varepsilon_1)N_* + u_2(d+\varepsilon_2)T_* > 0$. Thus, $\lambda_1 = 0$, $Re\lambda_2 < 0$, $Re\lambda_3 < 0$, which implies every equilibrium in the segment $u_1N + u_2T = d(Q_1 - 1)$, $N \ge 0$, $T \ge 0$ is an attractor in a certain direction by Zhang [33], see Fig. 5.

Theorem 3.4. *If $Q_1 = Q_2$, the solutions of system (3.1) will tend to the segment $u_1N + u_2T = d(Q_1 - 1)$.*

Remark 3.2. From the above analysis, it is easy to see that the final survival is the one whose absorbing number is bigger in competition between normal cells and tumor cells. There are six characteristics of cancer have been proposed: self-sufficiency in growth signalling, insensitivity to anti-growth signals, evasion of apoptosis, enabling of a limitless replicative potential, induction and sustainment of angiogenesis, activation of metastasis and invasion of tissue, see [7], which lead to $Q_2 > Q_1$ in general. Thus, in the body of cancer patients (in vivo), it always hold that $Q_2 > Q_1$. It results in the extinction of normal cells, and the patient will die.

3.2. The effect of M1 virus

In order to see the potent oncolytic efficacy and high tumor tropism of M1, we always assume that $Q_2 > Q_1 > 1$. In this case, it is proved that without the aid of M1 virus, normal cells will extinct and patient will die by previous section. However, when the M1 virus is considered, the result will be different.

We are eager to find the condition which ensure the extinction of tumor cells. Thus, we set $T = 0$ in system (1.1). By simple calculating, it is obvious that there is an equilibrium

$$E_{31} = (S_{31}, N_{31}, T_{31}, M_{31}) = \left(\frac{d+\varepsilon_1}{r_1u_1}, \frac{Ar_1u_1 - d(d+\varepsilon_1)}{u_1(d+\varepsilon_1)}, 0, \frac{B}{d+\varepsilon_3}\right).$$

And E_{31} is also the equilibrium for system (3.1) in the case of $Q_1 = Q_2$ Linearizing operator for system (1.1) at equilibrium E_{31}, the Jacobian matrix of (1.1) is

$$A = \begin{bmatrix} -d - \frac{Ar_1u_1 - d(d+\varepsilon_1)}{(d+\varepsilon_1)} & -\frac{d+\varepsilon_1}{r_1} & -\frac{u_2(d+\varepsilon_1)}{r_1u_1} & 0 \\ r_1[\frac{Ar_1u_1 - d(d+\varepsilon_1)}{d+\varepsilon_1}] & 0 & 0 & 0 \\ 0 & 0 & \frac{r_2u_2(d+\varepsilon_1)}{r_1u_1} - (d+\varepsilon_2) - \frac{u_3B}{d+\varepsilon_3} & 0 \\ 0 & 0 & \frac{r_3u_3B}{d+\varepsilon_3} & -(d+\varepsilon_3) \end{bmatrix}.$$

By Theorem 3.1, we see that $\lambda = \frac{r_2u_2(d+\varepsilon_1)}{r_1u_1} - (d+\varepsilon_2) - \frac{u_3B}{d+\varepsilon_3}$ dominates the stability of equilibrium E_{31}.

Theorem 3.5. *Assume that $Q_2 \ge Q_1 > 1$. Then E_{31} is locally asymptotically stable if $Q_2 < Q_1 + \frac{r_1u_1u_3AB}{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)}$, and is unstable if $Q_2 > Q_1 + \frac{r_1u_1u_3AB}{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)}$.*

Proof. If $\frac{r_2u_2(d+\varepsilon_1)}{r_1u_1} - (d+\varepsilon_2) - \frac{u_3B}{d+\varepsilon_3} < 0$, then

$$r_2u_2(d+\varepsilon_1) - r_1u_1(d+\varepsilon_2) - \frac{r_1u_1u_3B}{d+\varepsilon_3} < 0$$
$$\Rightarrow \frac{r_2u_2}{d+\varepsilon_2} - \frac{r_1u_1}{d+\varepsilon_1} - \frac{r_1u_1u_3B}{(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)} < 0$$
$$\Rightarrow Q_2 - Q_1 - \frac{r_1u_1u_3AB}{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)} < 0.$$

The result follows now directly from Theorem 3.1. □

Theorem 3.6. *Assume that $Q_2 \ge Q_1 > 1$, then the equilibrium E_{31} is globally asymptotically stable in the set $\Lambda_2 = \{(S, N, T, M) | S \ge 0, N \ge 0, T \ge 0, M \ge 0\}$ if $Q_2 < Q_1 + \frac{r_1u_1u_3AB}{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)}$.*

Proof. We define a Lyapunov function by

$$V_2(S, N, T, M) = S - S_{31} - S_{31}\ln\frac{S}{S_{31}} + \frac{1}{r_1}\left(N - N_{31} - N_{31}\ln\frac{N}{N_{31}}\right) + \frac{T}{r_2} + \frac{1}{r_2r_3}\left(M - M_{31} - M_{31}\ln\frac{M}{M_{31}}\right). \tag{3.10}$$

Differentiating (3.10) with respect t along solutions of (1.1) in Λ_2, we obtain

$$\begin{aligned}\frac{dV_2}{dt} &= \frac{dS}{dt} - \frac{S_{31}}{S}\frac{dS}{dt} + \frac{1}{r_1}\left(\frac{dN}{dt} - \frac{N_{31}}{N}\frac{dN}{dt}\right) + \frac{1}{r_2}\frac{dT}{dt} \\ &\quad + \frac{1}{r_2 r_3}\left(\frac{dM}{dt} - \frac{M_{31}}{M}\frac{dM}{dt}\right) \\ &= A - dS - u_1SN - u_2ST + u_1SN - \frac{d+\varepsilon_1}{r_1}N + u_2ST - \frac{d+\varepsilon_2}{r_2}T \\ &\quad - \frac{u_3}{r_2}TM + \frac{1}{r_2 r_3}[B + r_3u_3TM - (d+\varepsilon_3)M] \\ &\quad - \frac{S_{31}}{S}(A - dS - u_1SN - u_2ST) - N_{31}\left(u_1S - \frac{d+\varepsilon_1}{r_1}\right) \\ &\quad - \frac{M_{31}}{r_2 r_3 M}[B + r_3u_3TM - (d+\varepsilon_3)M] \\ &= (A - dS)\left(1 - \frac{S_{31}}{S}\right) - \frac{(d+\varepsilon_1)N}{r_1} - \frac{(d+\varepsilon_2)T}{r_2} + \frac{B}{r_2 r_3} \\ &\quad - \frac{d+\varepsilon_3}{r_2 r_3}M + S_{31}u_1N + S_{31}u_2T - N_{31}\left(u_1S - \frac{d+\varepsilon_1}{r_1}\right) \\ &\quad - \frac{M_{31}}{r_2 r_3 M}[B + r_3u_3TM - (d+\varepsilon_3)M] \\ &= (A - dS)\left(1 - \frac{S_{31}}{S}\right) - N_{31}\left(u_1S - \frac{d+\varepsilon_1}{r_1}\right) \\ &\quad + \left(S_{31}u_1 - \frac{d+\varepsilon_1}{r_1}\right)N + \left(S_{31}u_2 - \frac{d+\varepsilon_2}{r_2} - \frac{M_{31}u_3}{r_2}\right)T \\ &\quad + \frac{1}{r_2 r_3}[B - (d+\varepsilon_3)M]\left(1 - \frac{M_{31}}{M}\right). \end{aligned} \tag{3.11}$$

By (3.11), we set

$$w_1 = (A - dS)\left(1 - \frac{S_{31}}{S}\right) - N_{31}\left(u_1S - \frac{d+\varepsilon_1}{r_1}\right), \tag{3.12}$$

$$x_1 = \left(S_{31}u_1 - \frac{d+\varepsilon_1}{r_1}\right)N, \tag{3.13}$$

$$y_1 = \left(S_{31}u_2 - \frac{d+\varepsilon_2}{r_2} - \frac{M_{31}u_3}{r_2}\right)T, \tag{3.14}$$

$$z_1 = \frac{1}{r_2 r_3}[B - (d+\varepsilon_3)M]\left(1 - \frac{M_{31}}{M}\right). \tag{3.15}$$

Substituting $S_{31} = \frac{d+\varepsilon_1}{r_1u_1}$, $N_{31} = \frac{Ar_1u_1 - d(d+\varepsilon_1)}{u_1(d+\varepsilon_1)}$ and $M_{31} = \frac{B}{d+\varepsilon_3}$ into (3.12)–(3.15), we have

$$\begin{aligned} w_1 &= -\frac{A}{SS_{31}}(S - S_{31})^2 \le 0 \\ x_1 &= 0, \\ y_1 &= \frac{d(d+\varepsilon_1)(d+\varepsilon_2)}{Ar_1r_2u_1}\left[Q_2 - Q_1 - \frac{r_1u_1u_3AB}{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)}\right]T \\ &< 0, \\ z_1 &= -\frac{[(d+\varepsilon_3)M - B]^2}{r_2r_3(d+\varepsilon_3)M} \le 0. \end{aligned}$$

Set

$$\Lambda_3 = \left\{(S(t), N(t), T(t), M(r)) \middle| \frac{dV_2}{dt} = 0\right\}$$

Let $\frac{dV_2}{dt} = 0$. Then $S = S_{31}$, $T = 0$, $M = M_{31}$. Hence, from (1.1), it is easy to see that $N = N_{31}$. Thus, the largest invariant set of (1.1) contained in Λ_3 is E_{31}. By the Lyapunov–Lasalle theorem, all solutions of system (1.1) in Λ_2 approach E_{31} as $t \to +\infty$. □

Remark 3.3. By this Theorem, it is easy to see the tumor cell T becomes extinct, when $Q_2 < Q_1 + \frac{r_1u_1u_3AB}{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)}$. Hence, $B > \frac{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)(Q_2-Q_1)}{r_1u_1u_3A}$ is the effective dosage for cancer. In particular, if $Q_1 = Q_2$, then for every $B > 0$, tumor cell T will die out, and there is no positive equilibrium. Because the equilibrium E_{31} is globally stable in Λ_2. Thus, we claim that little drug dose will lead to the extinction of T, as $Q_1 = Q_2$ (i.e. for every $B > 0$, $T(t)$ will trend to 0 as $t \to \infty$).

We claim that the minimum effective dosage of medication equals to

$$B_0 = \frac{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)(Q_2 - Q_1)}{r_1u_1u_3A}.$$

By Theorem 3.6, it is easy to know that tumor cells will die out as $t \to +\infty$ whenever $B > B_0$. Thus, it is sufficient to show that tumor cells do not extinct as $t \to +\infty$ whenever $B < B_0$. Before turning to the main result, we need following preliminary result due to Thieme (Theorem 4.5) [28], also see [10].

Lemma 3.1. *Let X be a locally compact metric space and it is the union of two disjoint subsets X_1 and X_2, with X_2 be compact in X and X_1 be open and forward invariant under the continuous semiflow Φ on X. Assume that Ω_2,*

$$\Omega_2 = \bigcup_{y \in Y_2} \omega(y), Y_2 = \{x \in X_2; \Phi_t(x) \in X_2, \forall t > 0\},$$

has an acyclic isolated covering $M = \cup_{k=1}^{m} M_k$. If each part M_k of M is a weak repeller for X_1, then X_2 is a uniform strong repeller for X_1.

Theorem 3.7. *If $Q_2 > Q_1 > 1$, and $Q_2 > Q_1 + \frac{r_1u_1u_3AB}{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)}$, then population T is uniformly persistent, i.e. there exists a positive constant σ, such that positive solutions of system (1.1) satisfy $\liminf_{t\to\infty} T(t) > \sigma$.*

Proof. By (1.3), it is easy to see that system (1.1) is point dissipative. We set

$$\begin{aligned} X = R_+^4 &= \left\{(S, N, T, M) | S \ge 0, N \ge 0, T \ge 0, M \ge 0, \right. \\ &\qquad \left. S + \frac{1}{r_1}N + \frac{1}{r_2}T + \frac{1}{r_2r_3}M \le \frac{A_1}{d} + 1\right\}, \\ X_1 &= \left\{(S, N, T, M) \in W | T > 0, \right. \\ &\qquad \left. S + \frac{1}{r_1}N + \frac{1}{r_2}T + \frac{1}{r_2r_3}M \le \frac{A_1}{d} + 1\right\}, \\ X_2 = X \backslash X_1 &= \left\{(S, N, 0, M) | S \ge 0, N \ge 0, M \ge 0, \right. \\ &\qquad \left. S + \frac{1}{r_1}N + \frac{1}{r_2}T + \frac{1}{r_2r_3}M \le \frac{A_1}{d} + 1\right\}. \end{aligned}$$

To prove theorem it is sufficient to show that X_2 is uniformly strong repeller for X_1. Using Lemma 3.1, it suffice to verify the conditions of Lemma 3.1. It is clear that X be locally compact, X_2 is compact and X_1 is forward invariant. And there are two equilibria $E_{00} = (\frac{A}{d}, 0, 0, \frac{B}{d+\varepsilon_3}), E_{31} = (S_{31}, N_{31}, 0, M_{31})$ in X_2 for system (1.1). We consider the system (1.1) in X_2.

$$\begin{cases} S'(t) = A - dS(t) - u_1S(t)N(t), \\ N'(t) = r_1u_1S(t)N(t) - (d+\varepsilon_1)N(t), \\ M'(t) = B - (d+\varepsilon_3)M(t). \end{cases} \tag{3.16}$$

As $Q_1 > 1$, we see that $E_1 = (S_{31}, N_{31}, M_{31})$ is globally stable for solutions $(S(t), N(t), M(t))$ to (3.16) with positive initial value by Theorem 2.4. Moreover, let $Y = \{(S, 0, M) | S \geq 0, M \geq 0\}$, then Y is positively invariant for (3.16) and the solutions to (3.16) in Y approach $E_0 = (\frac{A}{d}, 0, \frac{B}{d+\varepsilon_3})$ as $t \to \infty$ and become zero or unbounded as $t \to -\infty$. Thus, $\Omega_2 = \{E_{00}, E_{31}\}$, $M = M_1 \cup M_2 = E_{31} \cup E_{00}$. Therefore, we know that M is acyclic in X_2.

By Theorem 3.1 and Jacobian matrix at E_{00}, it is easy to show that E_{00} and E_{31} are hyperbolic as

$$Q_2 > Q_1 > 1, Q_2 > Q_1 + \frac{r_1 u_1 u_3 AB}{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)},$$

which implies that E_{00} and E_{31} are isolated in X_2. By the above discuss, we know that Ω_2 has an acyclic isolated covering $M = E_{31} \cup E_{00}$.

Next, we need to show that each part $M_k (k = 1, 2)$ of M is a weak repeller for X_1. It suffice to show that $W^s(E_{31}) \bigcap X_1 = \emptyset$ and $W^s(E_{00}) \bigcap X_1 = \emptyset$, where $W^s(E_{31})$ denotes the stable manifold of E_{31}, and $W^s(E_{00})$ denotes the stable manifold of E_{00}. Suppose $W^s(E_{31}) \bigcap X_1 \neq \emptyset$. Then there is a solution of (1.1) such that

$$\lim_{t\to\infty} (S(t), N(t), T(t), M(t)) \to E_{31}.$$

Thus, it follows from the third equation of (1.1) that for any $\varepsilon > 0$, there exists positive number t_0, such that

$$T'(t) \geq T\left[r_2 u_2 \left(\frac{d+\varepsilon_1}{r_1 u_1} - \varepsilon\right) - (d+\varepsilon_2) - \frac{u_3 B}{d+\varepsilon_3}\right], \forall t \geq t_0. \tag{3.17}$$

We denote

$$g(\varepsilon) = r_2 u_2 \left(\frac{d+\varepsilon_1}{r_1 u_1} - \varepsilon\right) - (d+\varepsilon_2) - \frac{u_3 B}{d+\varepsilon_3}.$$

Then for $t \geq t_0$, $T'(t) \geq g(\varepsilon)T$. Since

$$Q_2 > Q_1 + \frac{r_1 u_1 u_3 AB}{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)},$$

we can choose ε small enough such that $g(\varepsilon) > 0$. Then (3.17) implies that $T(t) \to \infty$ as $t \to \infty$, which contradicts that positive solutions are ultimately bounded. Therefore, $W^s(E_{31}) \bigcap X_1 = \emptyset$. Similarly, we can prove that $W^s(E_{00}) \bigcap X_1 = \emptyset$. The proof is completed. □

Remark 3.4. By Theorems 3.2 and3.6, we see that M1 virus is potent oncolytic efficacy and high tumor tropism which verify results in [19]. Besides, by Theorem 3.7, it is easy to see that the minimum effective dosage of medication can be explicitly calculated by our method, i.e.

$$B_0 = \frac{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)(Q_2 - Q_1)}{r_1 u_1 u_3 A}. \tag{3.18}$$

Indeed, when $B < B_0$, $C \equiv \frac{Ar_1u_1}{d(d+\varepsilon_1)} - [\frac{u_2(B_0-B)}{r_3 u_3 M_{32}} + d] > 0$, then there exist a positive equilibrium $E_{32} = (S_{32}, N_{32}, T_{32}, M_{32})$, where $S_{32} = \frac{d+\varepsilon_1}{r_1 u_1}$, $M_{32} = \frac{d(d+\varepsilon_1)(d+\varepsilon_2)(Q_2-Q_1)}{Ar_1 u_1 u_3}$, $T_{32} = \frac{B_0-B}{r_3 u_3 M_{32}}$, $N_{32} = \frac{C}{u_1}$.

4. Simulations and biological interpretations

In this section, we carry out numerical simulations to illustrate the theoretical results obtained in Sections 2 and 3, and some biological interpretations are given.

Simulation of $S-N$ model (2.1) is done with the following parameter values and initial conditions: $A = 0.02$, $d = 0.02$, $u_1 = 0.2$, $r_1 = 0.8$, $\varepsilon_1 = 0.01$, $S_0 = 0.1$, $N_0 = 0.2$, see Fig. 1. By the absorbing formula (2.2), $Q_1 = 5.3333 > 1$ which implies that normal cells can persist at the population level $N = 0.4312$. Otherwise, normal cells can die out in $S-N$ model (2.1), with the parameter values: $A = 0.02$, $d = 0.02$, $u_1 = 0.03$, $r_1 = 0.8$, $\varepsilon_1 = 0.01$, $S_0 = 0.5$, $N_0 = 0.8$, thus $Q_1 = 0.8 < 1$, see Fig. 2. Besides, it has the similar behavior as we adjust the $\varepsilon_1 = 0.14$ which implies $Q_1 = 1$, see Fig. 3. Hence, we regard the absorbing as a index of net reproductive rate: as $Q_1 > 1$, the cells can persist at the population level, otherwise, as $Q_1 \leq 1$, the cells will die out. Indeed, system (2.1) itself reflect this property. We transform the equation about the component N in (2.1) to

$$\frac{N'(t)}{N(t)} = r_1 u_1 S(t) - (d+\varepsilon_1).$$

The term $-(d+\varepsilon_1)$ reflects the average removal rate per unit of time, thus the $\frac{1}{(d+\varepsilon_1)}$ is the average lifetime in compartment N. Combining with the term $r_1 u_1 S(t)$, we get that the recruitment due to each individual in component N in its lifetime is $\frac{r_1 u_1 S_*}{d+\varepsilon_1}$, where S_* is the output by every individual in its lifetime. The similar argument on the first equation in (2.1) shows that every individual in compartment S produces $S_* = \frac{A}{d}$. Hence, every individual in component N produces $Q_1 = \frac{Ar_1u_1}{d(d+\varepsilon_1)}$ in its lifetime. The discussion on $S-T$ model is similar. Thus, We always assume $Q_1, Q_2 > 1$ for later discussion.

In $S-N-T$ model, competitive behavior between normal cells and tumor cells depends on the absorbing number Q_1, Q_2. In Fig. 4, we choose the same A, d, u_1, r_1, ε_1 as in Fig. 1, and

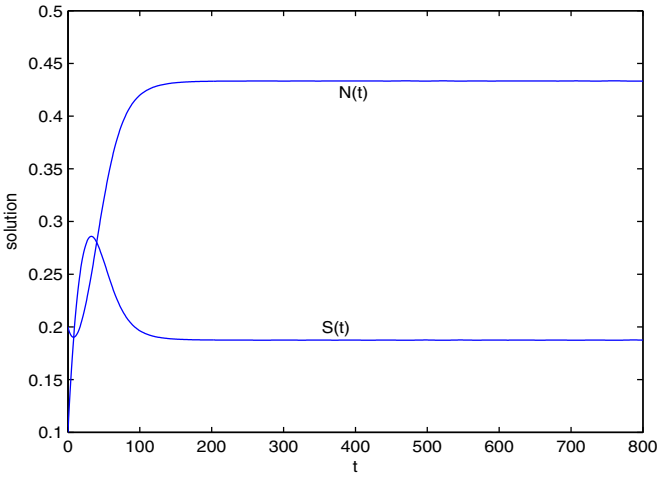

Fig. 1. $S-N$ model with $Q_1 > 1$.

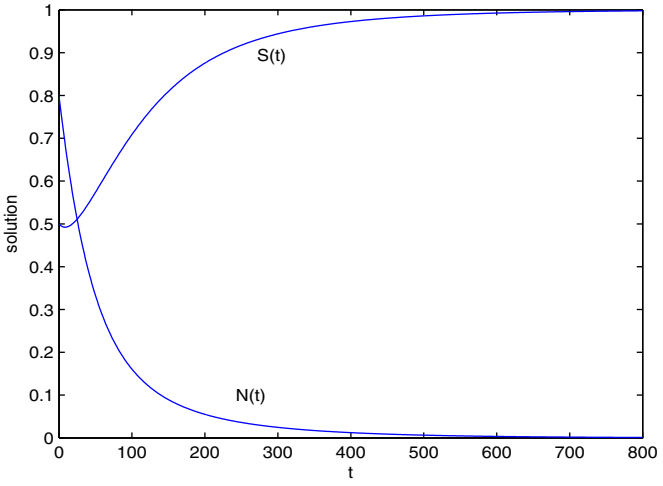

Fig. 2. $S-N$ model with $Q_1 < 1$.

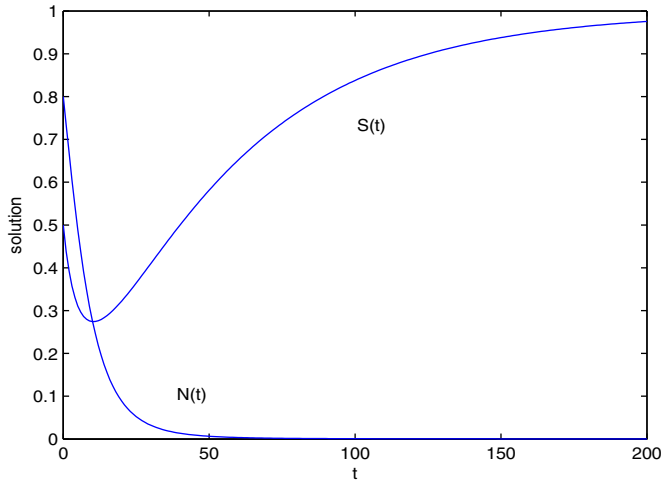

Fig. 3. $S-N$ Model, $Q_1 = 1$.

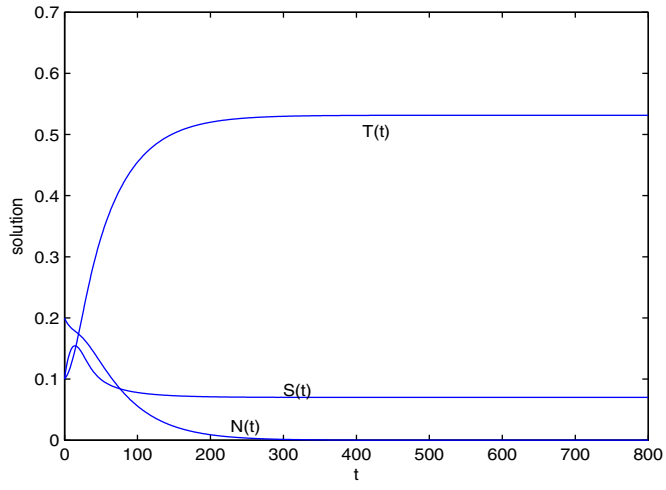

Fig. 4. $S-N-T$ Model, $Q_1 < Q_2$.

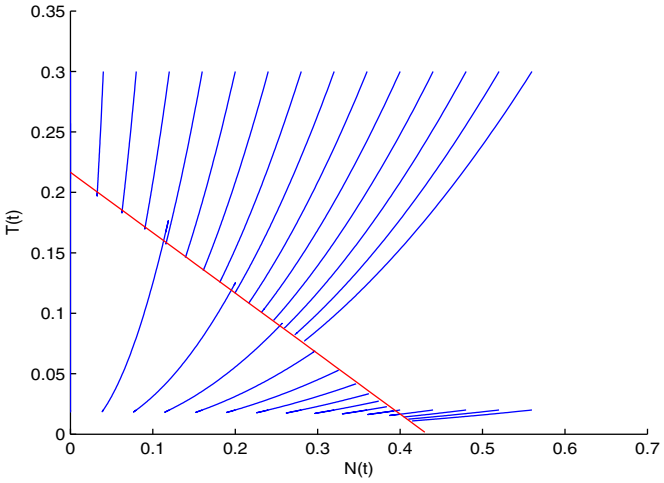

Fig. 5. $S-N-T$ Model, $Q_1 = Q_2$.

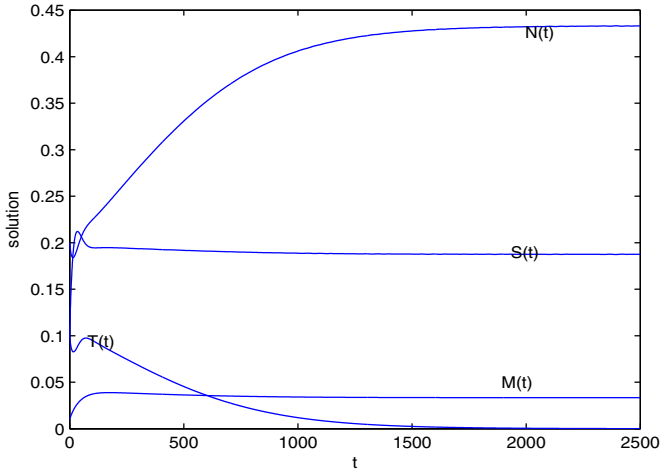

Fig. 6. $S-N-T-M$ Model, $Q_1 = Q_2$.

assume $r_2 = 0.8$, $u_2 = 0.5$, $\varepsilon_2 = 0.008$. By simple calculating, we get $Q_1 = 5.3333$, $Q_2 = 14.2857$, thus $Q_1 < Q_2$. Using Theorem 3.3, we see that the normal cells will extinct and tumor cells will persist, which consists with our numerical modeling in Fig. 4. As the status of N and T are symmetric in system (3.1), thus if $Q_1 > Q_2$, the component N can survive, and component T will extinct.

On other hand, if we assume $A = 0.02$, $d = 0.02$, $u_1 = 0.2$, $r_1 = 0.8$, $\varepsilon_1 = 0.01$, $r_2 = 0.8$, $u_2 = 0.4$, $\varepsilon_2 = 0.04$, then $Q_1 = Q_2 = 5.3333$, see Fig. 5. In Fig. 5, the red straight line is $u_1N + u_2T = d(Q_1 - 1)$, the blue lines denote the solution of (3.1) for initial value for $(0.1, 0.04k, 0.02)$ and $(0.1, 0.04k, 0.3)$, $k = 1, 2, \ldots, 15$. We can see that all solutions tend to the points on the red straight line $u_1N + u_2T = d(Q_1 - 1)$ that agrees with our result in Theorem 3.4. In addition, as we consider the M1 virus in system (3.1), the model will turn into system (1.1). Setting $u_3 = 0.1$, $r_3 = 0.5$, $\varepsilon_3 = 0.01$, $B = 0.01$, the Fig. 5 changes into Fig. 6. Indeed, B can be chosen small enough, it will have similar behavior in Fig. 6, and the difference is just that the time should be longer for T approaching to 0. It also consists with our theoretical result in Theorem 3.6, Remark 3.3. When $\varepsilon_1 = \varepsilon_2$, we set $H = u_1N + u_2T$, then the system (3.1) will change to

$$\begin{cases} S'(t) = A - dS(t) - H(t), \\ H'(t) = (d + \varepsilon_1)\left(\dfrac{r_1u_1}{d + \varepsilon_1}S(t) - 1\right)H(t), \end{cases}$$

By the same argument on system (2.1), we see that the equilibrium $(\frac{d+\varepsilon_1}{r_1u_1}, d(Q_1 - 1))$ is globally stable in $\mathbb{R}^2_+$ as $Q_1 > 1$. From the perspective of growth, we can also regard the component T as normal cells. Because tumor is just a synonym for a large number of diseases characterized by uncontrolled cell growth, so the absorbing number also can be regard as an index to distinguish the normal cell and tumor cell. In particular, Q_2 is always bigger than the Q_1, due to the characteristic of tumor [7].

In Figs. 7 and 8, we choose the same A, d, u_1, r_1, ε_1, r_2, u_2, ε_2 as in Fig. 1, and assume $u_3 = 0.1, r_3 = 0.5, \varepsilon_3 = 0.01$. Thus, $Q_1 = 5.3333$, $Q_2 = 14.2857$. By (3.18), we get the minimum effective dosage $B_0 = 0.0141$. If we set $B = B_0 - 0.01$, the dynamic behavior is shown as Fig. 7. Otherwise, we set $B = B_0 + 0.01$, then the Fig. 4 changes to Fig. 8, which implies that the tumor cells become extinct, and normal cells persist at the normal population level $N = 0.4312$ that is same as in Fig. 1. Thus, it illustrates the potent oncolytic efficacy of M1 virus as reported in [19]. These results consist with Theorems 3.6 and 3.7.

5. Conclusions and discussions

Indeed, we try to identify the absorbing number as an index to distinguish the normal cell and tumor cell. Besides, when the tumors absorbing number Q_2 is smaller than the normal cells absorbing number Q_1, it implies it can not threaten patient's health. When $Q_2 = Q_1$, we can regard the component T as normal cells.

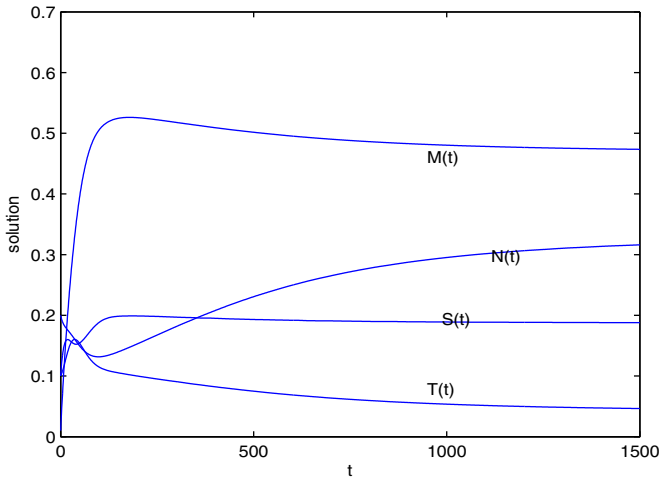

Fig. 7. $S-N-T-M$ Model, $Q_1 < Q_2$, $B < B_0$.

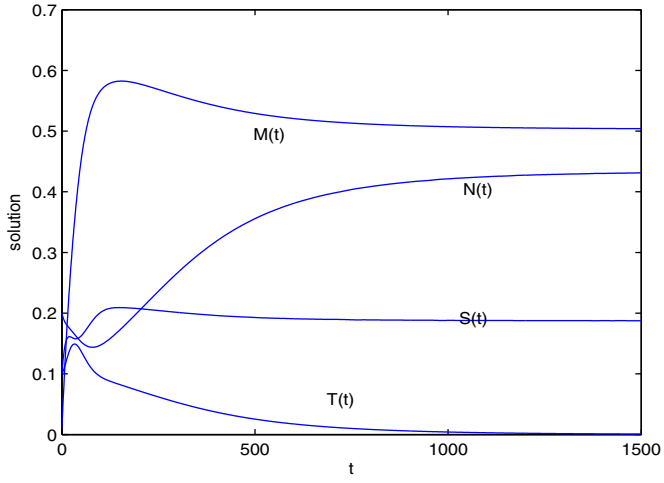

Fig. 8. $S-N-T-M$ Model, $Q_1 < Q_2$, $B > B_0$.

Because of the action of initial mutation in a cancer cell and the activation of the normal cells in the proto-oncogene, their cancer had cancer cells. So tumor is just a synonym for a large number of diseases characterized by uncontrolled cell growth. Thus, in particular, Q_2 is always bigger than the Q_1 due to the characteristic of tumor [7]. Only in this case, the growth of tumor cell will lead to the extinction of normal cell that threatens to patient's health as proved in Theorem 3.3. So the situation $Q_1 = Q_2$ is not important in $S-N-T-M$ model, though we have treat this situation in Section 3.2. In the situation $Q_1 < Q_2$, we focus our attention to the stability of equilibrium E_{31} because in this case, the therapy for cancer patients is efficient.

On the other hand, in Remark 3.4 we find the strictly positive equilibrium under certain conditions although we are not very interested in it, as the stability of this equilibrium implies that the onolytic treatment has little effect to the disease. We also proved that there exists a positive constant $\sigma > 0$, such that $\liminf_{t\to\infty} T(t) > \sigma$ when the dose B is smaller than our minimum effective dosage of medication.

Our work is motivated by the experimental findings in Lin et al. [19] that M1 virus could be a candidate for systematic oncolytic therapy. Thus, we formulated a prey-predator model with competition to illustrate the evolution of normal cell concentration due to the effect of M1 virus.

In the above analysis, we obtained two threshold values (the absorbing number) Q_1 and Q_2 which dominate the global evolution of system (1.1). Fortunately, our theoretic results on the model give an explanation of the experimental findings in Lin et al. [19]. For example, Theorem 2.3 describe the evolution of normal cell without tumor or M1 virus which reflect the growth of normal cells in healthy individual; Theorem 3.3 show the growth of cells in the body of cancer patient without treatment; The behavior of cells in the body of cancer patient with treatment is studied in Theorem 3.6. Combining Theorems 3.6 and3.7, the explicit minimum effective dosage of medication

$$B = \frac{d(d+\varepsilon_1)(d+\varepsilon_2)(d+\varepsilon_3)(Q_2-Q_1)}{r_1 u_1 u_3 A}$$

is obtained which is not reported in [19].

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