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Research Article

Analysis of Wave Solutions of an Adhenovirus-Tumor Cell System

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We discuss biological background and mathematical analysis of glioma gene therapy for contributing to cancer treatment. By a reaction-diffusion system, we model interactions between gliom cells and viruses. We establish some sufficient conditions on model parameters which guarantee the permanence of the system and the existence of periodic solutions. Our study has experimental and theoretical implication in the perspective management strategy of therapy.

1. Introduction

Diffuse infiltrative gliomas are the most frequent primary central nervous system (CNS) tumors in adults. Their deserved reputation as devastating diseases is due in large part to their widespread invasiveness in the neuropil, that is, the dense network of interwoven neuronal and glial cell processes. Partially because of their growth pattern, curative treatment for diffuse gliomas is generally impossible. Although patients with low-grade diffuse gliomas may survive for multiple years, these tumors lead to death of the patient sooner or later, often after progression to high-grade malignancy. Whereas surgery of most other tumors aims at complete resection, the diffuse growth of gliomas in the brain parenchyma precludes complete tumor removal. So to increase the length of survival time of patients with malignant brain tumors, novel therapeutic alternatives are currently being explored. Some of these experimental treatment strategies are based on advances in immunotherapy, stem cell therapy, local chemotherapy, and radiotherapy. However, in areas where the original tissue architecture is relatively preserved, the blood-brain barrier that may form an obstacle for optimal delivery of chemotherapeutics to diffuse infiltrative tumor cells eradicating diffuse infiltrative glioma

cells by radiotherapy without significantly damaging the infiltrated brain parenchyma has been difficult to achieve [1].

In addition, gene therapy is becoming a promising alternative. In essence, gene therapy consists of the delivery of a gene of interest to tumor cell populations to control and, when possible, kill the growing tumor. Viruses are prominent vehicles for gene therapy, and some adenoviral vectors exhibit oncolytic properties. To this end, a variety of viral vectors have been developed, with oncolytic viruses emerging as an innovative therapeutic tool for these tumors. To be effective, a virus used for oncolytic therapy must have several features. The desired properties of these vectors include selectivity for the tumor target, minimal brain and systemic toxicities, and the capacity to penetrate and diffuse throughout the brain to reach all neoplastic foci residing beyond the resection border of the tumor. In addition, the viral vector needs to remain active despite evoking an immune response. The goal of developing an ideal vehicle for treatment of malignant brain tumors remains to be achieved. A wide variety of viral vectors have been developed and tested in the setting of gene therapy for malignant gliomas. These are based on different kinds of viruses, such as herpes simplex virus, retrovirus, measles virus, reovirus, and adenovirus. Some have shown promising results when tested in animal models of intracranial gliomas, but, to date, clinical trials performed in humans have not shown a significant increase in survival.

Various vectors have been targeted toward cancer cells by deleting the genes responsible for bypassing those cells' antiviral proteins. Without these genes, the designed vectors will only be able to replicate within cancer cells with disrupted antiviral mechanisms. The deletion of viral genes to enhance specificity for the killing of neoplastic cells is a principle well exemplified by the actions of two oncolytic adenoviruses, ONYX 015 and Ad5-Delta24. ONYX 015 has a deletion in the viral genomic region coding E1B 55kd. This deletion effectively limits the replication of the virus to neoplastic cells that have a defective p53 pathway [2, 3]. A Phase I clinical trial to examine the effects of injection of ONYX 015 into peritumoral regions of recurrent malignant gliomas was recently completed and published [4]. In that study, ONYX 015 was injected into the walls of tumor resection cavities. This trial proved that the injection of up to 1010 plaque-forming units of ONYX 015 into brain tissue surrounding a resected malignant glioma is safe in humans.

Extensive efforts have been dedicated over many years to mathematical modelling of cancer development [5–7]. These mathematical models serve as valuable tools to predict possible outcomes of virus infection and propose the optimal strategy of anti-virus therapy. Wodarz [8, 9] presented a mathematical model that describes interaction between two types of tumor cells, the cells that are infected by the virus and the cells that are not infected but are susceptible to the virus so far as they have cancer phenotype and the immune system. Our system is more general than the one considered in [8, 9] even when there is no diffusion. Because the free virus particles are very small, they disperse in the fluid tissue like Brownian particles. Therefore, we have incorporated into our model a diffusion term for the free viruses. We also assume that the tumor has a logistic growth, which can be slowed down by the inhibitor, captured in the expression $1-u$. Thus, the tumor admits a maximum size and density defined by the carrying capacity K. When the virus is administered, the dynamic interactions between the virus and tumor cell populations are described by the following diffusive ratio-dependent predator-prey model of reaction-diffusion equations in the tumor region Ω:

$$\frac{\partial V_1}{\partial t} = \mu_1 \Delta V_1 + V_1 \left[\rho(t,x)(1-u)\left(1-\frac{V_1}{K}\right) - d(x,t)\right] - \frac{\beta r(t,x) V_1 V_3}{1+\varepsilon V_3}, \quad x \in \Omega,\ t > 0, \tag{1.1}$$

$$\frac{\partial V_2}{\partial t} = \mu_2 \Delta V_2 - V_2[a(t,x)(1-u) + d(t,x)] + \frac{\beta r(t,x) V_1 V_3}{1+\varepsilon V_3}, \quad x \in \Omega,\ t > 0, \tag{1.2}$$

$$\frac{\partial V_3}{\partial t} = \mu_3 \Delta V_3 + k(t,x)(1-u)V_2 - b(t,x)V_3, \quad x \in \Omega,\ t > 0, \tag{1.3}$$

$$\left.\frac{\partial V_1}{\partial n}\right|_{\partial\Omega} = 0, \qquad \left.\frac{\partial V_2}{\partial n}\right|_{\partial\Omega} = 0, \qquad \left.\frac{\partial V_2}{\partial n}\right|_{\partial\Omega} = 0, \quad t > 0, \tag{1.4}$$

where V_1 is the number density of susceptible and uninfected tumor cells, V_2 is the number density of infected tumor cells, and V_3 is the number density of free virus, that is, virus in the extracellular tissue. When parameters of system (1.1)–(1.4) are constant, we determined in [10] the conditions for optimal therapy and, estimated by numerical simulations, the patient survival time when tumor cannot be cured. This paper is organized as follows Section 2 is devoted to some preliminaries, which are needed in next sections, including some lemmas, due to Walter and Smith. In Section 3, some conditions for the ultimate boundedness of solutions and permanence of this system are established

2. Preliminaries

We need the following lemmas due to Walter [11] and Smith [12], respectively.

Lemma 2.1. *Suppose that vector functions* $v(t,x) = (v_1(t,x),\dots,v_m(t,x))$ *and* $w(t,x) = (w_1(t,x),\dots,w_m(t,x))$, $m \geq 1$, *satisfy the following conditions:*

(i) *they are of class* C^2 *in* x, $x \in X$, *and of class* C^1 *in* $(t,x) \in [a,b] \times \overline{\Omega}$, *where* $\Omega \subset \mathbb{R}^n$ *is a bounded domain with smooth boundary;*

(ii) $v_t - \mu\Delta v - g(t,x,v) \leq w_t - \mu\Delta w - g(t,x,w)$, *where* $(t,x) \in [a,b] \times \Omega$, $\mu = (\mu_1,\dots,\mu_m) > 0$, *vector function* $g(t,x,v) = (g_1(t,x,v),\dots,g_m(t,x,v))$ *is continuously differential and quasi-monotonically increasing with respect to* $u = (u_1,\dots,u_m)$ *and* $\partial g_i(t,x,u_1,\dots,u_m)/\partial u_j \geq 0$, $i,j = 1,\dots,m$, $i \neq j$;

(iii) $\partial v/\partial n = \partial w/\partial n = 0$, $(t,x) \in [a,b] \times \partial\Omega$.

Then, $v(t,x) \leq w(t,x)$, *for all* $(t,x) \in [a,b] \times \overline{\Omega}$.

Lemma 2.2. *Assume that* T *and* μ *are positive real numbers, a function* $u(t,x)$ *is continuous on* $[0,T] \times \overline{\Omega}$, *continuously differential in* $x \in \overline{\Omega}$, *with continuous derivatives* $\partial^2 u/\partial x_i \partial x_j$ *and* $\partial u/\partial t$ *on* $(0,T] \times \Omega$, *and* $u(t,x)$ *satisfies the following inequalities:*

$$\begin{gathered} u_t - \mu\Delta u - c(t,x,u) \geq 0, \quad (t,x) \in (0,T] \times \Omega, \\ \frac{\partial u}{\partial n} \geq 0, \quad (t,x) \in (0,T] \times \partial\Omega, \\ u(0,x) \geq 0, \quad x \in \Omega, \end{gathered} \tag{2.1}$$

where $c(t,x,u)$ *is bounded on* $(0,T] \times \Omega$. *Then* $u(t,x) \geq 0$ *on* $x \in (0,T] \times \overline{\Omega}$. *Moreover,* $u(t,x)$ *is strictly positive on* $x \in (0,T] \times \overline{\Omega}$ *if* $u(t,x)$ *is not identically zero.*

Consider the following logistic differential equation:

$$\frac{dz}{dt} = z(a - bz), \tag{2.2}$$

where $z \in \mathbb{R}^+$; a and b are positive constants.

Lemma 2.3. *Every solution $z(t, 0, z_0)$, $z_0 > 0$ of (2.2) satisfies*

$$\lim_{t \to +\infty} z(t) = \frac{a}{b}. \tag{2.3}$$

3. Permanence

Throughout the paper we always assume that (H): $a(t,x)$, $b(t,x)$, $d(t,x)$, $k(t,x)$, $r(t,x)$ and $\rho(t,x)$ are bounded positive-valued functions on $\mathbb{R} \times \overline{\Omega}$ continuously differential in t and x and are periodic in t with a period $\omega > 0$.

Definition 3.1. Solutions of system (1.1)–(1.4) are said to be ultimately bounded if there exist positive constants N_1, N_2, N_3 such that for every solution $(V_1(t, x, V_{01}, V_{03}, V_{03}); V_2(t, x, V_{01}, V_{03}, V_{03}); V_3(t, x, V_{01}, V_{03}, V_{03}))$ there exists a moment of time $\overline{t} = \overline{t}(V_{01}, V_{03}, V_{03}) > 0$ such that $V_1(t, x, V_{01}, V_{03}, V_{03}) \le N_1$, $V_2(t, x, V_{01}, V_{03}, V_{03}) \le N_2$, $V_3(t, x, V_{01}, V_{03}, V_{03}) \le N_3$, for all $x \in \overline{\Omega}$ and $t > \overline{t}$.

Definition 3.2. System (1.1)–(1.4) is said to be permanent if there exist positive constants ζ and η such that for every solution with nonnegative initial functions $V_{01}(x)$, $V_{02}(x)$, and $V_{03}(x)$, $V_{01}(x) \not\equiv 0$, $V_{02}(x) \not\equiv 0$, $V_{03}(x) \not\equiv 0$, there exists a moment of time $\widehat{t} = \widehat{t}(V_{01}, V_{03}, V_{03})$ such that $\zeta \le V_1(t, x, V_{01}, V_{03}, V_{03}) \le \eta$, $\zeta \le V_2(t, x, V_{01}, V_{03}, V_{03}) \le \eta$, $\zeta \le V_3(t, x, V_{01}, V_{03}, V_{03}) \le \eta$, for all $x \in \overline{\Omega}$ and $t > \widehat{t}$.

For simplicity, for a bounded function $\varphi(t,x)$, we denote $\varphi_m = \inf_{(t,x)} \varphi(t,x)$ and $\varphi_M = \sup_{(t,x)} \varphi(t,x)$. Now we have the following positively invariant principle for system (1.1)–(1.4).

Theorem 3.3. *Assume that conditions (H) hold, then nonnegative and positive quadrants of $\mathbb{R}^3$ are positively invariant for system (1.1)–(1.4).*

Proof. Suppose $(V_1(t, x, V_{01}, V_{03}, V_{03}); V_2(t, x, V_{01}, V_{03}, V_{03}); V_3(t, x, V_{01}, V_{03}, V_{03}))$ is a solution of system (1.1)–(1.4) with initial condition $V_{01}(x) \ge 0$ $(V_{01}(x) \not\equiv 0)$, $V_{02}(x) \ge 0$ $(V_{02}(x) \not\equiv 0)$, $V_{03}(x) \ge 0$ $(V_{03}(x) \not\equiv 0)$. Let $\widehat{V}_1(t,x)$ be a solution of

$$\begin{aligned} &\frac{\partial \widehat{V}_1}{\partial t} - \mu_1 \Delta \widehat{V}_1 + \widehat{V}_1 \left[d_M - \rho_m (1-u) \left(1 - \frac{\widehat{V}_1}{K} \right) + \varepsilon^{-1} \beta_M r_M \right] = 0, \\ &\widehat{V}_1(0,x) = V_{01}(x), \qquad \left. \frac{\partial \widehat{V}_1}{\partial n} \right|_{\partial\Omega} \ge 0, \quad t > 0. \end{aligned} \tag{3.1}$$

It holds that

$$\begin{aligned}&\frac{\partial \widehat{V}_1}{\partial t} - \mu_1 \Delta \widehat{V}_1 + \widehat{V}_1\left[d(x,t) - \rho(t,x)(1-u)\left(1 - \frac{\widehat{V}_1}{K}\right)\right] + \frac{\beta r(t,x)\widehat{V}_1 V_3}{1+\varepsilon V_3} \\ &\quad \le \frac{\partial \widehat{V}_1}{\partial t} - \mu_1 \Delta \widehat{V}_1 + \widehat{V}_1\left[d_M - \rho_m(1-u)\left(1 - \frac{\widehat{V}_1}{K}\right) + \varepsilon^{-1}\beta_M r_M\right],\end{aligned} \tag{3.2}$$

which implies that $\widehat{V}_1(t,x)$ is a lower solution of (1.1). By Lemma 2.2, we have $\widehat{V}_1(t,x) \ge 0$, for all $t > 0$ and $x \in \overline{\Omega}$. In addition, since $V_{01}(x) \ge 0$ ($V_{01}(x) \not\equiv 0$), then $\widehat{V}_1(t,x) > 0$, for all $t > 0$ and $x \in \overline{\Omega}$. Thus by Lemma 2.1, $V_1(t,x)$ is bounded from below by positive function $\widehat{V}_1(t,x)$, and so $V_1(t,x) > 0$.

Let $\widehat{V}_2(t,x)$ be a solution of

$$\begin{aligned}&\frac{\partial \widehat{V}_2}{\partial t} - \mu_2 \Delta \widehat{V}_2 + \widehat{V}_2[a_M(1-u) + d_M] = 0, \\ &\widehat{V}_2(0,x) = V_{02}(x), \qquad \left.\frac{\partial \widehat{V}_2}{\partial n}\right|_{\partial\Omega} \ge 0, \quad t > 0.\end{aligned} \tag{3.3}$$

It holds that

$$\begin{aligned}&\frac{\partial \widehat{V}_2}{\partial t} - \mu_2 \Delta \widehat{V}_2 + \widehat{V}_2[a(t,x)(1-u) + d(t,x)] - \frac{\beta r(t,x) V_1 V_3}{1+\varepsilon V_3} \\ &\quad \le \frac{\partial \widehat{V}_2}{\partial t} - \mu_2 \Delta \widehat{V}_2 + \widehat{V}_2[a_M(1-u) + d_M] = 0,\end{aligned} \tag{3.4}$$

which implies that $\widehat{V}_2(t,x)$ is a lower solution of (1.2).

Let $\widehat{V}_3(t,x)$ be a solution of

$$\begin{aligned}&\frac{\partial \widehat{V}_3}{\partial t} - \mu_3 \Delta \widehat{V}_3 + b_M \widehat{V}_3 = 0, \\ &\widehat{V}_3(0,x) = V_{03}(x), \qquad \left.\frac{\partial \widehat{V}_3}{\partial n}\right|_{\partial\Omega} \ge 0, \quad t > 0.\end{aligned} \tag{3.5}$$

It holds that

$$\begin{aligned}&\frac{\partial \widehat{V}_3}{\partial t} - \mu_3 \Delta \widehat{V}_3 + b(t,x)\widehat{V}_3 - k(t,x)(1-u)V_2 \\ &\quad \le \frac{\partial \widehat{V}_3}{\partial t} - \mu_3 \Delta \widehat{V}_3 + b_M \widehat{V}_3 = 0,\end{aligned} \tag{3.6}$$

which implies that $\widehat{V}_3(t,x)$ is a lower solution of (1.3).

A similar argument to $V_1(t,x)$ leads to that $V_2(t,x)$ and $V_3(t,x)$ are bounded from below, respectively, by positive functions $\widehat{V}_2(t,x)$ and $\widehat{V}_3(t,x)$. □

Theorem 3.4. *Assume that conditions* (H) *hold then all solutions of system* (1.1)–(1.4) *with nonnegative initial functions are ultimately bounded.*

Proof. Let $\overline{V}_1(t,x)$ be a solution of

$$\begin{aligned} &\frac{\partial \overline{V}_1}{\partial t} - \mu_1 \Delta \overline{V}_1 - \rho_M (1-u)\left(1 - \frac{\overline{V}_1}{K}\right)\overline{V}_1 = 0, \\ &\overline{V}_1(0, M_{V_1}) = M_{V_1}, \end{aligned} \tag{3.7}$$

where M_{V_1} is such that $\max_{x\in\overline{\Omega}} |V_{01}(x)| \le M_{V_1}$.

It holds that

$$\begin{aligned} 0 &= \frac{\partial V_1}{\partial t} - \mu_1 \Delta V_1 + V_1\left[d(x,t) - \rho(t,x)(1-u)\left(1 - \frac{V_1}{K}\right)\right] + \frac{\beta r(t,x) V_1 V_3}{1+\varepsilon V_3} \\ &\ge \frac{\partial V_1}{\partial t} - \mu_1 \Delta V_1 - \rho_M (1-u)\left(1 - \frac{V_1}{K}\right)V_1. \end{aligned} \tag{3.8}$$

So, we get

$$\begin{aligned} 0 &= \frac{\partial \overline{V}_1}{\partial t} - \mu_1 \Delta \overline{V}_1 - \rho_M (1-u)\left(1 - \frac{\overline{V}_1}{K}\right)\overline{V}_1 \\ &\ge \frac{\partial V_1}{\partial t} - \mu_1 \Delta V_1 - \rho_M (1-u)\left(1 - \frac{V_1}{K}\right)V_1. \end{aligned} \tag{3.9}$$

Therefore, Lemma 2.1 gives $V_1(t,x,V_{01},V_{02},V_{03}) \le \overline{V}_1(t,M_{V_1})$.

Note that, according to the uniqueness theorem, the solution $\overline{V}_1(t,M_{V_1})$ of (3.7) does not depend on x for $t>0$, and so $\overline{V}_1(t,M_{V_1})$ satisfies the ordinary differential equation:

$$\frac{\partial \overline{V}_1}{\partial t} - \rho_M (1-u)\left(1 - \frac{\overline{V}_1}{K}\right)\overline{V}_1 = 0. \tag{3.10}$$

By Lemma 2.3, we have

$$\overline{V}_1(t,M_{V_1}) \longrightarrow K, \quad \text{as } t \longrightarrow +\infty. \tag{3.11}$$

So, there exists N_1 and $t_1>0$ such that $V_1(t,x) \le N_1$.

For the infected tumor cells, we have the following inequality:

$$\begin{aligned} 0 &= \frac{\partial V_2}{\partial t} - \mu_2 \Delta V_2 + V_2[a(t,x)(1-u)V_2 + d(t,x)] - \frac{\beta r(t,x) V_1 V_3}{1+\varepsilon V_3} \\ &\ge \frac{\partial V_2}{\partial t} - \mu_2 \Delta V_2 + V_2[a_m(1-u) + d_m] - \varepsilon^{-1}\beta_M r_M N_1. \end{aligned} \tag{3.12}$$

So, we get

$$\begin{aligned} 0 &= \frac{\partial \overline{V}_2}{\partial t} - \mu_2 \Delta \overline{V}_2 + \overline{V}_2[a_m(1-u) + d_m] - \varepsilon^{-1}\beta_M r_M N_1 \\ &\geq \frac{\partial V_2}{\partial t} - \mu_2 \Delta V_2 + V_2[a_m(1-u) + d_m] - \varepsilon^{-1}\beta_M r_M N_1. \end{aligned} \tag{3.13}$$

Therefore, Lemma 2.1 gives $V_2(t, x, V_{01}, V_{02}, V_{03}) \leq \overline{V}_2(t, M_{V_2})$, where $\overline{V}_2(t, M_{V_2})$ satisfies the ordinary differential equation:

$$\frac{\partial \overline{V}_2}{\partial t} = -\overline{V}_2[a_m(1-u) + d_m] + \varepsilon^{-1}\beta_M r_M N_1, \qquad \overline{V}_2(0, M_{V_2}) = M_{V_2}. \tag{3.14}$$

Since

$$\overline{V}_2(t, M_{V_2}) \longrightarrow \frac{\varepsilon^{-1}\beta r_M N_1}{a_m(1-u) + d_m} \quad \text{as } t \longrightarrow +\infty, \tag{3.15}$$

thus, there exists N_2 and $t_2 > 0$ such that $V_2(t, x) \leq N_2$.

For the virus in the extracellular tissue, we have the following inequality:

$$\begin{aligned} 0 &= \frac{\partial V_3}{\partial t} - \mu_3 \Delta V_3 + b(t, x)V_3 - k(t, x)(1-u)V_2 \\ &\geq \frac{\partial V_3}{\partial t} - \mu_3 \Delta V_3 + b_m V_3 - k_M(1-u)N_2. \end{aligned} \tag{3.16}$$

So, we get

$$\begin{aligned} 0 &= \frac{\partial \overline{V}_3}{\partial t} - \mu_3 \Delta \overline{V}_3 + b_m \overline{V}_3 - k_M(1-u)N_2 \\ &\geq \frac{\partial V_3}{\partial t} - \mu_3 \Delta V_3 + b_m V_3 - k_M(1-u)N_2. \end{aligned} \tag{3.17}$$

Therefore, Lemma 2.1 gives $V_3(t, x, V_{01}, V_{02}, V_{03}) \leq \overline{V}_3(t, M_{V_3})$, where $\overline{V}_3(t, M_{V_3})$ satisfies the ordinary differential equation:

$$\frac{\partial \overline{V}_3}{\partial t} = -b_m \overline{V}_3 + k_M(1-u)N_2, \qquad \overline{V}_3(0, M_{V_3}) = M_{V_3}. \tag{3.18}$$

Since

$$\overline{V}_3(t, M_{V_3}) \longrightarrow \frac{k_M(1-u)N_2}{b_m}, \quad \text{as } t \longrightarrow +\infty, \tag{3.19}$$

thus, there exists N_3 and $t_3 > 0$ such that $V_3(t, x) \leq N_3$. □

Theorem 3.5. *Assume that conditions* (H) *hold; in addition, if* $d_M + \beta\varepsilon^{-1}r_M < \rho_m(1-u)$, *then the system* (1.1)–(1.4) *is permanent.*

Proof. Theorem 3.4 implies that there exists $\eta > 0$ such that $V_1(t,x) \leq \eta$, $V_2(t,x) \leq \eta$, and $V_3(t,x) \leq \eta$ starting with a certain moment of time. Note that, by comparison principle, if $V_{01}(x) \geq 0$ $(V_{01}(x) \not\equiv 0)$, $V_{02}(x) \geq 0$ $(V_{02}(x) \not\equiv 0)$, and $V_{03}(x) \geq 0$ $(V_{03}(x) \not\equiv 0)$, then $V_1(t,x,V_{01},V_{03},V_{03}) > 0$, $V_2(t,x,V_{01},V_{03},V_{03}) > 0$, and $V_3(t,x,V_{01},V_{03},V_{03}) > 0$ for all $x \in \overline{\Omega}$ and $t > 0$. Considering the solution on the interval $t \geq \epsilon$ with some $\epsilon > 0$, we get $(V_1(\epsilon, x, V_{01}, V_{03}, V_{03}); V_2(\epsilon, x, V_{01}, V_{03}, V_{03}); V_3(\epsilon, x, V_{01}, V_{03}, V_{03}))$ separated from zero. Therefore, we can assume that $\min_{x\in\overline{\Omega}} V_{01}(x) = m_{V_1} > 0$, $\min_{x\in\overline{\Omega}} V_{02}(x) = m_{V_2} > 0$ and, $\min_{x\in\overline{\Omega}} V_{03}(x) = m_{V_3} > 0$. Let $\widehat{V}_1(t,x)$ be a solution of

$$\begin{gathered}\frac{\partial \widehat{V}_1}{\partial t} + \widehat{V}_1\left[d_M - \rho_m(1-u)\left(1-\frac{\widehat{V}_1}{K}\right) + \varepsilon^{-1}\beta_M r_M\right] = 0,\\ \widehat{V}_1(0, M_{V_1}) = m_{V_1}.\end{gathered} \tag{3.20}$$

So using the inequality

$$\begin{aligned}0 &= \frac{\partial V_1}{\partial t} - \mu_1 \Delta V_1 + V_1\left[d(x,t) - \rho(t,x)(1-u)\left(1-\frac{V_1}{K}\right)\right] + \frac{\beta r(t,x) V_1 V_3}{1+\varepsilon V_3}\\ &\leq \frac{\partial V_1}{\partial t} - \mu_1 \Delta V_1 + V_1\left[d_M - \rho_m(1-u)\left(1-\frac{V_1}{K}\right) + \varepsilon^{-1}\beta_M r_M\right],\end{aligned} \tag{3.21}$$

one has, by (3.20),

$$\begin{aligned}0 &= \frac{\partial \widehat{V}_1}{\partial t} - \mu_1 \Delta \widehat{V}_1 + \widehat{V}_1\left[d_M - \rho_m(1-u)\left(1-\frac{\widehat{V}_1}{K}\right) + \varepsilon^{-1}\beta_M r_M\right]\\ &\leq \frac{\partial V_1}{\partial t} - \mu_1 \Delta V_1 + V_1\left[d_M - \rho_m(1-u)\left(1-\frac{V_1}{K}\right) + \varepsilon^{-1}\beta_M r_M\right].\end{aligned} \tag{3.22}$$

Therefore, Lemma 2.1 gives $V_1(t,x,V_{01},V_{02},V_{03}) \geq \widehat{V}_1(t, m_{V_1})$. By the condition $d_M + \varepsilon^{-1}\beta_M r_M < \rho_m(1-u)$, we have

$$\widehat{V}_1(t, m_{V_1}) \longrightarrow \frac{K\left[\rho_m(1-u) - d_M - \varepsilon^{-1}\beta_M r_M\right]}{\rho_m(1-u)}, \quad t \longrightarrow +\infty. \tag{3.23}$$

Therefore, there exists $\zeta_1 > 0$ such that $V_1(t,x,V_{01},V_{02},V_{03}) \geq \zeta_1$ for t large enough.

Let $\widehat{V}_2(t,x)$ be a solution of

$$\frac{\partial \widehat{V}_2}{\partial t} + \widehat{V}_2[a_M(1-u) + d_M] - \varepsilon^{-1}\beta_M r_M \zeta_1 = 0, \qquad \widehat{V}_2(0,x) = m_{V_2}. \tag{3.24}$$

Using the inequality

$$\begin{aligned}0 &= \frac{\partial V_2}{\partial t} - \mu_2 \Delta V_2 + V_2[a(t,x)(1-u) + d(t,x)] - \frac{\beta r(t,x) V_1 V_3}{1+\varepsilon V_3}\\ &\leq \frac{\partial V_2}{\partial t} - \mu_2 \Delta V_2 + V_2[a_M(1-u) + d_M] - \varepsilon^{-1}\beta_M r_M \zeta_1,\end{aligned} \tag{3.25}$$

we have, by (3.24),

$$\begin{aligned} 0 &= \frac{\partial \widehat{V}_2}{\partial t} - \mu_2 \Delta \widehat{V}_2 + \widehat{V}_2[a_M(1-u) + d_M] - \varepsilon^{-1}\beta_M r_M \zeta_1 \\ &\leq \frac{\partial V_2}{\partial t} - \mu_2 \Delta V_2 + V_2[a_M(1-u) + d_M] - \varepsilon^{-1}\beta_M r_M \zeta_1. \end{aligned} \tag{3.26}$$

Therefore, $V_2(t,x,V_{01},V_{02},V_{03}) \geq \widehat{V}_2(t,m_{V_2}) \to (\varepsilon^{-1}\beta_M r_M \zeta_1)/(a_M(1-u)+d_M)$, as $t \to +\infty$. Therefore, there exists $\zeta_2 > 0$ such that $V_2(t,x,V_{01},V_{02},V_{03}) \geq \zeta_2$ for t large enough.

Now, let $\widehat{V}_3(t,x)$ be a solution of

$$\frac{\partial \widehat{V}_3}{\partial t} + b_M \widehat{V}_3 - k_M(1-u)\zeta_2 = 0, \qquad \widehat{V}_3(0,x) = m_{V_3}. \tag{3.27}$$

By the following inequality,

$$\begin{aligned} 0 &= \frac{\partial V_3}{\partial t} - \mu_3 \Delta V_3 + b(t,x)V_3 - k(t,x)(1-u)V_2 \\ &\leq \frac{\partial V_3}{\partial t} - \mu_3 \Delta V_3 + b_M V_3 - k_M(1-u)\zeta_2, \end{aligned} \tag{3.28}$$

we have

$$\frac{\partial \widehat{V}_3}{\partial t} - \mu_3 \Delta \widehat{V}_3 + b_M \widehat{V}_3 - k_M(1-u)\zeta_2 \leq \frac{\partial V_3}{\partial t} - \mu_3 \Delta V_3 + b_M V_3 - k_M(1-u)\zeta_2. \tag{3.29}$$

Therefore, $V_3(t,x,V_{01},V_{02},V_{03}) \geq \widehat{V}_3(t,m_{V_3}) \to (k_M(1-u)\zeta_2)/(b_M)$, as $t \to +\infty$. Therefore, there exists $\zeta_3 > 0$ such that $V_3(t,x,V_{01},V_{02},V_{03}) \geq \zeta_3$ for t large enough. □

4. Periodic Solutions

Theorem 4.1. *Assume that conditions* (H) *hold and system* (1.1)–(1.4) *is permanent. Moreover, if one assumes the following conditions*

$$\begin{gathered} 2\left(\rho_M(1-u)\left(1-\frac{2\zeta}{K}\right) - d_m\right) - \varepsilon^{-1}\beta_M r_M < 0, \\ \frac{\beta_M}{\varepsilon} r_M + k_M - 4\zeta a_M(1-u) + 2d_M < 0, \\ k_M - 2b_m < 0, \end{gathered} \tag{4.1}$$

then the system has a unique globally asymptotic stable strictly positive ω*-periodic solution.*

Proof. For convenience, we denote $a = a(t,x)$ and similar meaning to b, d, k, r, and ρ. Let $(V_1^1(t,x), V_2^1(t,x), V_3^1(t,x))$ and $(V_2^1(t,x), V_2^2(t,x), V_3^2(t,x))$ be two solutions of system bounded by constants ζ and η for below and above. Consider the function

$$L(t) = \int_\Omega \left[\left(V_1^1(t,x) - V_1^2(t,x)\right)^2 + \left(V_2^1(t,x) - V_2^2(t,x)\right)^2 + \left(V_3^1(t,x) - V_3^2(t,x)\right)^2 \right] dx. \quad (4.2)$$

So,

$$\begin{aligned}
\frac{dL(t)}{dt} &= 2\int_\Omega \left(V_1^1 - V_1^2\right)\left(\frac{\partial V_1^1}{\partial t} - \frac{\partial V_1^2}{\partial t}\right)dx + 2\int_\Omega \left(V_2^1 - V_2^2\right)\left(\frac{\partial V_2^1}{\partial t} - \frac{\partial V_2^2}{\partial t}\right)dx \\
&\quad + 2\int_\Omega \left(V_3^1 - V_3^2\right)\left(\frac{\partial V_3^1}{\partial t} - \frac{\partial V_3^2}{\partial t}\right)dx \\
&= 2\mu_1 \int_\Omega \left(V_1^1 - V_1^2\right)\Delta\left(V_1^1 - V_1^2\right)dx + 2\mu_2 \int_\Omega \left(V_2^1 - V_2^2\right)\Delta\left(V_2^1 - V_2^2\right)dx \\
&\quad + 2\mu_3 \int_\Omega \left(V_3^1 - V_3^2\right)\Delta\left(V_3^1 - V_3^2\right)dx \\
&\quad + 2\int_\Omega \left(V_1^1 - V_1^2\right)^2 \left[\rho(1-u)\left(1 - \frac{(V_1^1 + V_1^2)}{K}\right) - d\right]dx \\
&\quad - 2\int_\Omega \left(V_1^1 - V_1^2\right)\frac{\beta r V_1^1 V_3^1}{1 + \varepsilon V_3^1}dx + 2\int_\Omega \left(V_1^1 - V_1^2\right)\frac{\beta r V_1^2 V_3^2}{1 + \varepsilon V_3^2}dx \\
&\quad - 2\int_\Omega \left(V_2^1 - V_2^2\right)^2 \left[a(1-u)\left(V_1^1 + V_1^2\right) + d\right]dx \\
&\quad + 2\int_\Omega \left(V_2^1 - V_2^2\right)\frac{\beta r V_1^1 V_3^1}{1 + \varepsilon V_3^1}dx - 2\int_\Omega \left(V_2^1 - V_2^2\right)\frac{\beta r V_1^2 V_3^2}{1 + \varepsilon V_3^2}dx \\
&\quad + 2\int_\Omega k(1-u)\left(V_2^1 - V_2^2\right)\left(V_3^1 - V_3^2\right)dx - 2\int_\Omega b\left(V_3^1 - V_3^2\right)^2 dx \\
&:= I_1 + \cdots + I_{11}.
\end{aligned} \quad (4.3)$$

It follows from the boundary condition (1.4) that

$$I_1 + I_2 + I_3 = -2\int_\Omega \left[\mu_1 \left|\nabla\left(V_1^1 - V_1^2\right)\right|^2 + \mu_2 \left|\nabla\left(V_2^1 - V_2^2\right)\right|^2 + 2\mu_3 \left|\nabla\left(V_3^1 - V_3^2\right)\right|^2\right]dx \le 0 \quad (4.4)$$

The terms

$$\begin{aligned}
I_4 + I_7 + I_{10} + I_{11} &\le 2\int_\Omega \left(\rho_M(1-u)\left(1 - \frac{2\zeta}{K}\right) - d_m\right)\left(V_1^1 - V_1^2\right)^2 dx \\
&\quad - \int_\Omega (4\zeta a_M(1-u) + 2d_M)\left(V_2^1 - V_2^2\right)^2 dx
\end{aligned}$$

$$
\begin{aligned}
&- 2\int_{\Omega} b_m\left(V_3^1 - V_3^2\right)^2 dx + \int_{\Omega} k_M\left[\left(V_2^1 - V_2^2\right)^2 + \left(V_3^1 - V_3^2\right)^2\right] dx,\\
I_5 + I_6 + I_8 + I_9 &= 2\int_{\Omega} \frac{\beta r V_1^1 V_3^1}{1+\varepsilon V_3^1}\left[\left(V_2^1 - V_2^2\right) - \left(V_1^1 - V_1^2\right)\right] dx\\
&\quad + 2\int_{\Omega} \frac{\beta r V_1^2 V_3^2}{1+\varepsilon V_3^2}\left[\left(V_1^1 - V_1^2\right) - \left(V_2^1 - V_2^2\right)\right] dx\\
&\le 2\int_{\Omega} \varepsilon^{-1}\beta_M r_M V_1^1\left[\left(V_2^1 - V_2^2\right) - \left(V_1^1 - V_1^2\right)\right] dx\\
&\quad + 2\int_{\Omega} \varepsilon^{-1}\beta_M r_M V_1^2\left[\left(V_1^1 - V_1^2\right) - \left(V_2^1 - V_2^2\right)\right] dx\\
&\le -2\int_{\Omega} \varepsilon^{-1}\beta_M r_M\left(V_1^1 - V_1^2\right)^2 dx\\
&\quad + 2\int_{\Omega} \varepsilon^{-1}\beta_M r_M\left(V_1^1 - V_1^2\right)\left(V_2^1 - V_2^2\right) dx\\
&\le -\int_{\Omega} \varepsilon^{-1}\beta_M r_M\left[\left(V_1^1 - V_1^2\right)^2 - \left(V_2^1 - V_2^2\right)^2\right] dx.
\end{aligned}
\tag{4.5}
$$

Thus, we have

$$
\begin{aligned}
\frac{dL(t)}{dt} &\le \int_{\Omega}\left[2\left(\rho_M(1-u)\left(1-\frac{2\zeta}{K}\right) - d_m\right) - \varepsilon^{-1}\beta_M r_M\right]\left(V_1^1 - V_1^2\right)^2 dx\\
&\quad + \int_{\Omega}\left[\varepsilon^{-1}\beta_M r_M + k_M - 4\zeta a_M(1-u) + 2d_M\right]\left(V_2^1 - V_2^2\right)^2 dx\\
&\quad + \int_{\Omega}\left[k_M - 2b_m\right]\left(V_3^1 - V_3^2\right)^2 dx\\
&\le \left(V_1^1 - V_1^2, V_2^1 - V_2^2, V_3^1 - V_3^2\right) P\left(V_1^1 - V_1^2, V_2^1 - V_2^2, V_3^1 - V_3^2\right)^T\\
&\le \lambda_M(P)\left[\left\|V_1^1 - V_1^2\right\|^2_{L^2(\Omega)} + \left\|V_2^1 - V_2^2\right\|^2_{L^2(\Omega)} + \left\|V_3^1 - V_3^2\right\|^2_{L^2(\Omega)}\right],
\end{aligned}
\tag{4.6}
$$

where $\lambda_M(P)$ is the maximal eigenvalue of the diagonal matrix $P = \operatorname{diag}(P_1, P_2, P_3)$ with

$$
\begin{aligned}
P_1 &= 2\left(\rho_M(1-u)\left(1-\frac{2\zeta}{K}\right) - d_m\right) - \varepsilon^{-1}\beta_M r_M\\
P_2 &= \varepsilon^{-1}\beta_M r_M + k_M - 4\zeta a_M(1-u) + 2d_M\\
P_3 &= k_M - 2b_m.
\end{aligned}
\tag{4.7}
$$

So, we deduce that

$$L(t) \leq L(0)e^{\lambda_M(P)t} \longrightarrow 0, \quad \text{as } t \longrightarrow +\infty. \tag{4.8}$$

Thus, $\|V_1^1 - V_1^2\|_{L^2(\Omega)} \to 0$, $\|V_2^1 - V_2^2\|_{L^2(\Omega)} \to 0$, and $\|V_3^1 - V_3^2\|_{L^2(\Omega)} \to 0$, as $t \to +\infty$. By Theorem 3.3, solutions of system (1.1)–(1.4) are bounded in the space $C^{1+\nu}(\overline{\Omega}, \mathbb{R}^3$, where $0 < \nu < 2l - 1 - n/p$ and $1/2 + n/(2p) < l < 1$. Therefore,

$$\begin{gathered}\lim_{t\to+\infty}\sup_{x\in\Omega}\left|V_1^1(t,x) - V_1^2(t,x)\right| = 0, \qquad \lim_{t\to+\infty}\sup_{x\in\Omega}\left|V_2^1(t,x) - V_2^2(t,x)\right| = 0, \\ \lim_{t\to+\infty}\sup_{x\in\Omega}\left|V_3^1(t,x) - V_3^2(t,x)\right| = 0.\end{gathered} \tag{4.9}$$

Consider the sequence

$$\left(V_1(q\omega, x, V_{01}, V_{02}, V_{03}; V_2)(q\omega, x, V_{01}, V_{02}, V_{03}); V_3(q\omega, x, V_{01}, V_{02}, V_{03})\right) = W(q\omega, W_0). \tag{4.10}$$

Then $\{W(q\omega, W_0),\ q \in \mathbb{N}\}$ is compact in the space $C(\overline{\Omega})^3$. Let $\overline{W}$ be a limit point of this sequence. It follows, from

$$\begin{aligned}\left\|W\left(\omega, \overline{W}\right) - \overline{W}\right\|_C &\leq \left\|W\left(\omega, \overline{W}\right) - W(\omega, W(q_n\omega, W_0))\right\|_C \\ &\quad + \left\|W(\omega, W(q_n\omega, W_0)) - W(q_n\omega, W_0)\right\|_C \\ &\quad + \left\|W(q_n\omega, W_0) - \overline{W}\right\|_C \longrightarrow 0 \quad \text{as } n \longrightarrow +\infty,\end{aligned} \tag{4.11}$$

that $W(\omega, \overline{W}) = \overline{W}$.

Next, let $\overline{W}$ and $\widehat{W}$ be two limit points of the sequence $\{W(q\omega, W_0),\ q \in \mathbb{N}\}$. Using (4.9) and $\widehat{W} = W(q_n\omega, \widehat{W})$, we have

$$\left\|\overline{W} - \widehat{W}\right\|_C \leq \left\|\overline{W} - W(q_n\omega, W_0)\right\|_C + \left\|W(q_n\omega, W_0) - \widehat{W}\right\|_C \longrightarrow 0, \quad \text{as } n \longrightarrow +\infty. \tag{4.12}$$

Thus, $\overline{W} = \widehat{W}$, and so $(V_1(t, x, \overline{V}_1, \overline{V}_2, \overline{V}_3); V_2(t, x, \overline{V}_1, \overline{V}_2, \overline{V}_3); V_3(t, x, \overline{V}_1, \overline{V}_2, \overline{V}_3))$ is the unique periodic solutions of system (1.1)–(1.4). By (4.9), it is asymptotically stable. □

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