Bull. Austral. Math. Soc. 34D20, 34C25, 92D30
Vol. 76 (2007) [337–351]

ANALYSIS OF A PERIODIC BACTERIA-IMMUNITY SYSTEM WITH DELAYED QUORUM SENSING

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Based on the work of Fergola, Zhang and Cerasuolo, a bacteria-immunity model with the mechanism of periodic quorum sensing is formulated, which describes the competition between bacteria and immune cells. A discrete delay is introduced to characterise the time between when bacteria receive signal molecules and then combat with immune cells. In this paper, we focus on a subsystem of the bacteria-immunity model and investigate the existence of a positively periodic solution, and then study its global stability.

1. Introduction

All living organisms are continuously exposed to the substances that are capable of causing them harm. Most organisms protect themselves against such substances in more than one way for example, with physical barriers or chemicals). Vertebrates have these types of general protective mechanisms, but they also have a more advanced protective system called the immune system. The immune system is a complex network of organs containing cells that recognise foreign substances in the body and destroy them. It protects vertebrates against pathogens, or infectious agents, such as viruses, bacteria, fungi, and other parasites.

There are two basic kinds of immunity [**8, 7**]: the innate immunity and the adaptive one. The innate immunity is the first line of defence. It is nonspecific, that is, it is not directed against specific invaders but against any pathogens that enter the body, and it can suffice to clear the pathogens in most cases, but sometimes it is insufficient. In fact, some pathogens may possess ways to overcome the innate immunity and successfully colonise and infect the host. When the innate immunity fails, a completely different cascade of events ensues leading to adaptive immunity. Unlike innate immunity, adaptive immunity is specific; that is, it can recognise and destroy specific pathogen. The defensive reaction of the adaptive immune system is called the immune response. Any substance capable of generating such a response is called an antigen, or immunogen.

Received 12th February, 2007
This work was supported by the Natural Science Foundation of China under the contract 10531030.

Quorum sensing is a process that enables bacteria to communicate using secreted signaling molecules called autoinducers [**6, 11, 1**]. This process enables a population of bacteria to regulate gene expression collectively and, therefore control behaviour on a community-wide scale. The quorum sensing mechanism was initially observed in the marine bacterium Vibrio fisheri around 30 years ago [**9, 2**]. Recently, many other species have been discovered to exhibit quorum sensing behaviour, including, importantly, major human pathogens such as Staphylococcus aureus and Pseudomonas aeruginosa.

In this paper, considering the periodic quorum sensing of bacteria in the competition between bacteria and immunity system and introducing a discrete delay to describe the time between when bacteria receive signal molecules and then combat with immune cells, we formulate a bacteria-immunity model. Subsequently, we analysis the existence of a positive periodic solution, and then discuss the global stability of periodic solution.

This paper is arranged as follows: Section 2 formulates the model, Section 3 analyses the existence of periodic solution, Section 4 discuss the global stability of the periodic solution, Section 5 makes the conclusions.

2. Model Formulation

In this section, considering periodic and delayed quorum sensing of bacteria, we construct a mathematical model to describe the interaction between the immune cells and bacteria.

Denote the concentrations at time t of uninfected target cells, infected target cells, bacteria, innate cells and adaptive cells, as $X_U(t), X_I(t), B(t), I_R(t)$ and $I_A(t)$, respectively. Suppose the dynamic relations among them are as the following: Uninfected target cells have a natural turnover S_U and half-life μ_{X_U} and can become infected (mass-action term $\alpha_1 X_U B$). Infected target cells can be cleared by the adaptive immune cells (mass action term $\alpha_2 X_I I_A$) or half-life μ_{X_I}. Both innate and adaptive immune cells have a source term and a half-life time. For innate immunity, the source term S_{I_R}, which includes a wide range of cells involved in the first wave of defense of the host (such as natural killer cells polymorphonuclear cells, macrophages and dendritic cells) and for adaptive immunity, the source term S_{I_A} represents memory cells that are present, derived from a previous infection (or vaccination), a zero source means the first infection with this pathogen (that is, there are no memory cells). Both the numbers of innate immune cell and adaptive immune cell are increased by the signals that we have captured by means of bacteria load. The bacteria population has a net growth term, represented by a logistic function $\alpha_{20} B\big(1-(B/\sigma)\big)$ and is also reduced by both of innate immunity (mass action term $\alpha_3 B I_R$) and adaptive immunity (mass action term $\alpha_4 B I_A$). We consider a mechanism named quorum sensing for bacteria, by which the bacteria control their growth rate or the expression of their genes in response to their own or the density of other microorganisms, for example, bacteria, immune cells) in the environment. Further, we introduce a discrete delay to describe the time between when bacteria receive single molecules and then combat with immune cells. The model is governed by

$$(2.1)\quad \begin{cases} \dfrac{dB(t)}{dt} = \alpha_{20}\Big(1 + g(t)B(t-\tau) - \dfrac{B(t)}{\sigma}\Big)B(t) - \alpha_3 B(t)I_R(t) - \alpha_4 B(t)I_A(t), \\ \dfrac{dX_U(t)}{dt} = S_U - \alpha_1 X_U(t)B(t) - \mu_{X_U}X_U(t), \\ \dfrac{dX_I(t)}{dt} = \alpha_1 X_U(t)B(t) - \alpha_2 I_A(t)X_I(t) - \mu_{X_I}X_I(t), \\ \dfrac{dI_R(t)}{dt} = S_{I_R} + \beta_1 B(t) - \mu_{I_R}I_R(t), \\ \dfrac{dI_A(t)}{dt} = S_{I_A} + \beta_2 B(t) - \mu_{I_A}I_A(t), \end{cases}$$

where α_{20} is the effective reproductive rate of bacteria (the reproduction rate minus the death rate), σ the effective carrying capacity of the environment, $\alpha_{20}B(t)\big(1-(B(t)/\sigma)\big)$ the logistic growth of bacteria, $\alpha_{20}g(t)B(t-\tau)B(t)$ the increased bacterial concentration by the bacteria which receive the signal molecules τ time units ago and then compete with immune cells at time t, where $g \geqslant 0$ is a periodically continuous function with period T in $[-\tau,\infty)$ and $\tau \geqslant 0$. Suppose all of parameters of system (2.1) are positive. The initial values for system (2.1) are

$$(2.2)\quad \begin{aligned} &B(s) = \psi(s) \in C\big([-\tau,0],\mathbf{R}\big) \ \text{ with } \ \psi(0) > 0, \psi(s) \geqslant 0, s \in [-\tau,0); \\ &X_U(0) = X_{U_0} > 0, X_I(0) = X_{I_0} > 0, I_R(0) = I_{R_0} > 0, I_A(0) = I_{A_0} > 0, \end{aligned}$$

where $C\big([-\tau,0],\mathbf{R}\big)$ is the Banach space of continuous functions from $[-\tau,0]$ to the Euclidean space $\mathbf{R}$.

In a similar fashion to [**3**, Lemma 1], we can prove that the solution of system (2.1) remains positive whenever it exists.

3. The Existence of Periodic Solution

It is clear that the equations for $B(t), I_R(t)$ and $I_A(t)$ are independent of the other equations of system (2.1). In this paper, only the dynamical properties for $B(t)$, $I_R(t)$ and $I_A(t)$ are focused on. To the end, system (2.1) is reduced into the following subsystem in positive cone $\mathbf{R}^3_+$ of the Euclidean space $\mathbf{R}^3$

$$(3.1)\quad \begin{cases} \dfrac{dB(t)}{dt} = \alpha_{20}\Big(1 + g(t)B(t-\tau) - \dfrac{B(t)}{\sigma}\Big)B(t) - \alpha_3 B(t)I_R(t) - \alpha_4 B(t)I_A(t), \\ \dfrac{dI_R(t)}{dt} = S_{IR} + \beta_1 B(t) - \mu_{I_R}I_R(t), \\ \dfrac{dI_A(t)}{dt} = S_{I_A} + \beta_2 B(t) - \mu_{I_A}I_A(t). \end{cases}$$

Correspondingly, the initial values (2.2) are reduced to

$$\begin{aligned} &B(s) = \psi(s) \in C\big([-\tau, 0], \mathbf{R}\big) \text{ with } \psi(0) > 0, \psi(s) \geqslant 0, s \in [-\tau, 0); \\ &I_R(0) = I_{R_0} > 0, I_A(0) = I_{A_0} > 0. \end{aligned} \tag{3.2}$$

In this section, on the basis of Gaines and Mawhin's continuation theorem of coincidence degree theory, we discuss the existence of positive periodic solutions to system (3.1) with initial conditions (3.2). For convenience, we summarise a few concepts and results from [**5**] which will be used in this section.

Let X, Y be real Banach spaces, $L : \operatorname{Dom} L \subset X \to Y$ a linear mapping, and $N : X \to Y$ a continuous mapping. The mapping L is called a Fredholm mapping of index zero if $\dim \operatorname{Ker} L = \operatorname{codim} ImL < \infty$ and ImL is closed in Y. If L is a Fredholm mapping of index zero and there exist continuous projectors $P : X \to X$, and $Q : Y \to Y$ such that $ImP = \operatorname{Ker} L$, $\operatorname{Ker} Q = ImL = Im(I - Q)$, then the restriction L_P of L to $\operatorname{Dom} L \cap \operatorname{Ker} P : (I - P)X \to ImL$ is invertible. Denote the inverse of L_P by K_P. If Ω is an open bounded subset of X, the mapping N will be called L-compact on $\overline{\Omega}$ if $QN(\overline{\Omega})$ is bounded and $K_P(I - Q)N : \overline{\Omega} \to X$ is compact. Since ImQ is isomorphic to $\operatorname{Ker} L$, there exists an isomorphism $J : ImQ \to \operatorname{Ker} L$.

Lemma 1. *Let $\Omega \subset X$ be an open bounded set. Let L be a Fredholm mapping of index zero and N be L-compact on $\overline{\Omega}$. Assume*

1. *for each $\lambda \in (0, 1)$, $x \in \partial\Omega \cap \operatorname{Dom} L$, $Lx \neq \lambda Nx$;*
2. *for each $x \in \partial\Omega \cap \operatorname{Ker} L, QNx \neq 0$;*
3. $\deg\{JQN, \Omega \cap \operatorname{Ker} L, 0\} \neq 0$.

Then $Lx = Nx$ at least has one solution in $\overline{\Omega} \cap \operatorname{Dom} L$.

In the remainder of this section, we shall describe and prove our results on the existence of the periodic solution of system (3.1). For convenance, we first introduced some denotations:

$$\overline{g} = \frac{1}{T}\int_0^T g(t)dt, \;\; g_m = \min_{t\in[0,T]} g(t), \;\; g^M = \max_{t\in[0,T]} g(t).$$

Theorem 3.1. *If one of the following two assumptions is true,*

$$g_m > \frac{(\alpha_{20})/\sigma + (\beta_1\alpha_3)/\mu_{I_R} + (\beta_2\alpha_4)/(\mu_{I_A})}{\alpha_{20}} \quad \text{and} \quad \alpha_{20} < \frac{\alpha_3 S_{I_R}}{\mu_{I_R}} + \frac{\alpha_4 S_{I_A}}{\mu I_A},$$
$$g_M < \frac{(\alpha_{20})/\sigma + (\beta_1\alpha_3)/\mu_{I_R} + (\beta_2\alpha_4)/(\mu_{I_A})}{\alpha_{20}} \quad \text{and} \quad \alpha_{20} > \frac{\alpha_3 S_{I_R}}{\mu_{I_R}} + \frac{\alpha_4 S_{I_A}}{\mu I_A},$$

system (3.1) *has at least one positive T-periodic solution.*

PROOF: Let $u_1(t) = \ln B(t), u_2(t) = \ln I_R(t)$ and $u_3(t) = \ln I_A(t)$. Consequently, system (3.1) can be transformed into

$$\text{(3.3)} \qquad \begin{cases} \dfrac{du_1(t)}{dt} = \alpha_{20}\Big(1 + g(t)e^{u_1(t-\tau)} - \dfrac{e^{u_1(t)}}{\sigma}\Big) - \alpha_3 e^{u_2(t)} - \alpha_4 e^{u_3(t)}, \\ \dfrac{du_2(t)}{dt} = S_{I_R} e^{-u_2(t)} + \beta_1 e^{u_1(t)-u_2(t)} - \mu_{I_R}, \\ \dfrac{du_3(t)}{dt} = S_{I_A} e^{-u_3(t)} + \beta_2 e^{u_1(t)-u_3(t)} - \mu_{I_A}. \end{cases}$$

Let $X = Y$ be the Banach space

$$\Big\{u = \big(u_1(t), u_2(t), u_3(t)\big) \in C(\mathbf{R}, \mathbf{R}^3) \mid u_i(t+T) = u_i(t), i = 1, 2, 3\Big\}$$

with the norm $\big\|(u_1, u_2, u_3)\big\| = \sum_{i=1}^{3} \max_{t\in[0,T]} \big|u_i(t)\big|$, where $|.|$ is the Euclidean norm. Define

$$L : \operatorname{Dom} L \cap X \to Y, L(u) = \frac{du}{dt}$$

and

$$\text{(3.4)} \quad N : X \to Y, N(u) = \begin{pmatrix} \alpha_{20}(1 + g(t)e^{u_1(t-\tau)} - \dfrac{e^{u_1(t)}}{\sigma}) - \alpha_3 e^{u_2(t)} - \alpha_4 e^{u_3(t)} \\ S_{I_R} e^{-u_2(t)} + \beta_1 e^{u_1(t)-u_2(t)} - \mu_{I_R} \\ S_{I_A} e^{-u_3(t)} + \beta_2 e^{u_1(t)-u_3(t)} - \mu_{I_A} \end{pmatrix},$$

where $\operatorname{Dom} L = C^1(\mathbf{R}, \mathbf{R}^3)$ the Banach space of differential functions from $\mathbf{R}$ to $\mathbf{R}^3$.

Clearly,

$$\operatorname{Ker} L = \{u \mid u \in X, u = h, h \in \mathbf{R}^3\},$$
$$ImL = \Big\{v \mid v \in Y, \int_0^T v(t)dt = 0\Big\},$$

$\dim\ker L = \operatorname{codim} ImL = 3$, ImL is closed in Y. Therefore, L is a Fredholm mapping of zero index.

Define $P : X \to X$ and $Q : Y \to Y$ as

$$\text{(3.5)} \qquad Pu = Qu = \frac{1}{T}\int_0^T u(t)dt, u \in X = Y.$$

Obviously, P and Q are continuous projectors with $ImP = \operatorname{Ker} L$ and $\operatorname{Ker} Q = ImL = Im(I - Q)$. Then, the operator L_p which is the restriction of L to $\operatorname{Dom} L \cap \operatorname{Ker} P$: $(I - P)X \to ImL$ is inverse, and the inverse K_p has the form

$$\text{(3.6)} \qquad K_p : ImL \to \operatorname{Dom} L \cap \operatorname{Ker} P, \;\; K_p(u) = \int_0^t u(s)ds - \frac{1}{T}\int_0^T \int_0^t u(s)dsdt.$$

Using (3.4-3.6), for any $u \in X$, we get

$$QN(u) = \begin{pmatrix} \frac{1}{T}\int_0^T \Big(\alpha_{20}\Big(1 + g(t)e^{u_1(t-\tau)} - \frac{e^{u_1(t)}}{\sigma}\Big) - \alpha_3 e^{u_2(t)} - \alpha_4 e^{u_3(t)}\Big)dt \\ \frac{1}{T}\int_0^T \big(S_{I_R} + \beta_1 e^{u_1(t)-u_2(t)} - \mu_{I_R}\big)dt \\ \frac{1}{T}\int_0^T \big(S_{I_A} e^{-u_3(t)} + \beta_2 e^{u_1(t)-u_3(t)} - \mu_{I_A}\big)dt \end{pmatrix}$$

and

$$K_p N(I-Q)Nu = \int_0^t N\big(u(t)\big)dt - \frac{1}{T}\int_0^T \int_0^t N\big(u(s)\big)dsdt - \Big(\frac{t}{T} - t\Big)\int_0^T N\big(u(t)\big)dt.$$

Next, we need to search for an appropriately open and bounded subset Ω in X. For any $\lambda \in (0,1)$ and $u \in \operatorname{Dom} L \cap X$, the system of $L(u) = \lambda N(u)$ is governed by

$$\begin{cases} \frac{du_1(t)}{dt} = \lambda\Big(\alpha_{20}\Big(1 + g(t)e^{u_1(t-\tau)} - \frac{e^{u_1(t)}}{\sigma}\Big) - \alpha_3 e^{u_2(t)} - \alpha_4 e^{u_3(t)}\Big), \\ \frac{du_2(t)}{dt} = \lambda\big(S_{I_R}e^{-u_2(t)} + \beta_1 e^{u_1(t)-x_u(t)} - \mu_{I_R}\big), \\ \frac{du_3(t)}{dt} = \lambda\big(S_{I_A}e^{-u_3(t)} + \beta_2 e^{u_1(t)-u_2(t)} - \mu_{I_A}\big) \end{cases} \tag{3.7}$$

Integrating (3.7) with respect to t from 0 to T yields

$$\begin{aligned} &\int_0^T \Big(\alpha_{20}\Big(1 + g(t)e^{u_1(t-\tau)} - \frac{e^{u_1(t)}}{\sigma}\Big) - \alpha_3 e^{u_2(t)} - \alpha_4 e^{u_3(t)}\Big)dt = 0, \\ &\int_0^T \big(S_{I_R}e^{-u_2(t)} + \beta_1 e^{u_1(t)-u_2(t)} - \mu_{I_R}\big)dt = 0, \\ &\int_0^T \big(S_{I_A}e^{-u_3(t)} + \beta_2 e^{u_1(t)-u_3(t)} - \mu_{I_A}\big)dt = 0, \end{aligned} \tag{3.8}$$

and which together with (3.7) lead to

$$\begin{aligned} \int_0^T \Big\|\frac{du_1(t)}{dt}\Big\|_0 dt &\leqslant \alpha_{20}T + \int_0^T \Big\|\Big(g(t)e^{u_1(t-\tau)} - \frac{u_1(t)}{\sigma}\Big) - \alpha_3 e^{u_2(t)} - \alpha_4 e^{u_3(t)}\Big\| dt \\ &\leqslant 2\alpha_{20}T, \end{aligned} \tag{3.9}$$

$$\int_0^T \Big\|\frac{du_2(t)}{dt}\Big\|_0 dt \leqslant \big(S_{I_R}e^{-u_2(t)} + \beta_1 e^{u_1(t)-u_2(t)}\big)dt + \mu_{I_R}T \leqslant 2T\mu_{I_R} \tag{3.10}$$

and

$$\int_0^T \Big\|\frac{du_3(t)}{dt}\Big\|_0 dt \leqslant \big(S_{I_A}e^{-u_3(t)} + \beta_1 e^{u_1(t)-u_3(t)}\big)dt + \mu_{I_A}T \leqslant 2T\mu_{I_A}, \tag{3.11}$$

where $\|.\|_0$ is the maximum value norm $C(\mathbf{R},\mathbf{R})$ the Banach space of continuous functions from $\mathbf{R}$ to $\mathbf{R}$.

Multiplying the 2th and 3th equations of (3.7) with $e^{u_2(t)}$ and $e^{u_3(t)}$, respectively, and then integrating them with respect to t from 0 to T yields

$$\int_0^T e^{u_2(t)}dt = \frac{\beta_1}{\mu_{I_R}}\int_0^T e^{u_1(t)}dt + \frac{S_{I_R}}{\mu_{I_R}}T \tag{3.12}$$

and

$$\int_0^T e^{u_3(t)}dt = \frac{\beta_2}{\mu_{I_A}}\int_0^T e^{u_1(t)}dt + \frac{S_{I_A}}{\mu_{I_A}}T. \tag{3.13}$$

Clearly, combing (3.8-3.12) with (3.13) leads to

$$\begin{aligned}\alpha_{20}T + \alpha_{20}&\int_0^T g(t)e^{u_1(t-\tau)}dt \\ &= \frac{\alpha_{20}}{\sigma}\int_0^T e^{u_1(t)}dt + \alpha_3\int_0^T e^{u_2(t)}dt + \alpha_4\int_0^T e^{u_3(t)}dt \\ &= \Big(\frac{\alpha_{20}}{\sigma} + \frac{\beta_1\alpha_3}{\mu_{I_R}} + \frac{\beta_2\alpha_4}{\mu_{I_A}}\Big)\int_0^T e^{u_1(t)}dt + \Big(\frac{\alpha_3 S_{I_R}}{\mu_{I_R}} + \frac{\alpha_4 S_{I_A}}{\mu_{I_A}}\Big)T.\end{aligned} \tag{3.14}$$

It follows from (3.14) that

$$\int_0^T \Big(\alpha_{20}g^M - \frac{\alpha_{20}}{\sigma} - \frac{\beta_1\alpha_3}{\mu_{I_R}} - \frac{\beta_2\alpha_4}{\mu_{I_A}}\Big)e^{u_1(t)}dt \geqslant \Big(\frac{\alpha_3 S_{I_R}}{\mu_{I_R}} + \frac{\alpha_4 S_{I_A}}{\mu_{I_A}} - \alpha_{20}\Big)T \tag{3.15}$$

and

$$\int_0^T \Big(\alpha_{20}g_m - \frac{\alpha_{20}}{\sigma} - \frac{\beta_1\alpha_3}{\mu_{I_R}} - \frac{\beta_2\alpha_4}{\mu_{I_A}}\Big)e^{u_1(t)}dt \leqslant \Big(\frac{\alpha_3 S_{I_R}}{\mu_{I_R}} + \frac{\alpha_4 S_{I_A}}{\mu_{I_A}} - \alpha_{20}\Big)T. \tag{3.16}$$

For the convenience of description, we denote

$$u_i(\xi_i) = \min_{t\in[0,T]} u_i(t) \text{ and } u_i(\eta_i) = \max_{t\in[0,T]} u_i(t), \ \ i = 1, 2, 3.$$

Firstly, we study the existence of periodic solutions of system (3.3) under the condition

$$g_m > \frac{(\alpha_{20}/\sigma) + (\beta_1\alpha_3)/\mu_{I_R} + (\beta_2\alpha_4)/(\mu_{I_A})}{\alpha_{20}} \text{ and } \alpha_{20} < \frac{\alpha_3 S_{I_R}}{\mu_{I_R}} + \frac{\alpha_4 S_{I_A}}{\mu_{I_A}}. \tag{3.17}$$

It follows from (3.15-3.16) that

$$e^{u_1(\eta_1)} \geqslant \frac{(\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/\mu_{I_A} - \alpha_{20}}{\alpha_{20}g^M - (\alpha_{20})/\sigma - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2\alpha_4)/\mu_{I_A}} \tag{3.18}$$

and

$$e^{u_1(\xi_1)} \leqslant \frac{(\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_A}) - \alpha_{20}}{\alpha_{20}g_m - (\alpha_{20})/\sigma - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2\alpha_4)/\mu_{I_A}}. \tag{3.19}$$

Clearly, using Leibniz formula, we have

$$u_1(t) - u_1(\xi_1) \leqslant \int_0^T \left\| \frac{u_1(t)}{dt} \right\|_0 dt \leqslant 2\alpha_{20}T, t \in [0,T]. \tag{3.20}$$

Combining 3.19 with 3.20 yields

$$u_1(t) \leqslant \ln\left(\frac{(\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_A}) - \alpha_{20}}{\alpha_{20} g_m - (\alpha_{20})/\sigma - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2\alpha_4)/\mu_{I_A}}\right) + 2\alpha_{20}T, t \in [0,T]. \tag{3.21}$$

Similarly, by Leibniz formula, we have

$$u_1(t) \geqslant u_1(\eta_1) - \int_0^T \left\| \frac{du_1(t)}{dt} \right\|_0 dt, t \in [0,T]. \tag{3.22}$$

Substituting (3.15) into (3.22) yields

$$u_1(t) \geqslant \ln\left(\frac{(\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_A)/(\mu_{I_A}) - \alpha_{20}}{\alpha_{20} g^M - (\alpha_3)/\sigma - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2\alpha_4)/\mu_{I_A}}\right) - 2\alpha_{20}T, t \in [0,T].$$

Let

$$R_1 = \max\left\{\left| \ln\left(\frac{(\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_A}) - \alpha_{20}}{\alpha_{20} g_m - (\alpha_{20}/\sigma) - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2\alpha_4)/\mu_{I_A}}\right) + 2\alpha_{20}T \right|, \left| \ln\left(\frac{(\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_A}) - \alpha_{20}}{\alpha_{20} g_m - (\alpha_{20}/\sigma) - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2\alpha_4)/\mu_{I_A}}\right) - 2\alpha_{20}T \right|\right\}$$

As a result, for any $t \in [0,T]$, we have

$$\left|u_1(t)\right| \leqslant R_1.$$

Substituting (3.21) into (3.12) yields

$$e^{u_2(\xi_2)} \leqslant \frac{S_{I_R}}{\mu_{I_R}} + \frac{\beta_1((\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_A}) - \alpha_{20})}{\mu_{I_R}(\alpha_{20} g_m - (\alpha_{20}/\sigma) - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2\alpha_4)/\mu_{I_A})} e^{2\alpha_{20}T},$$

further, we obtain

$$u_2(\xi_2) \leqslant \ln\left(\frac{S_{I_R}}{\mu_{I_R}} + \frac{\beta_1((\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_A}) - \alpha_{20})}{\mu_{I_R}(\alpha_{20} g_m - (\alpha_{20})/\sigma - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2\alpha_4)/\mu_{I_A})} e^{2\alpha_{20}T}\right). \tag{3.23}$$

It follows from (3.12) that

$$e^{u_2(\eta_2)} \geqslant \frac{S_{I_R}}{\mu_{I_R}} + \frac{\beta_1}{\mu_{I_R}} e^{u_1(\xi_1)},$$

which implies

$$u_2(\eta_2) > \ln\left(\frac{S_{I_R}}{\mu_{I_R}}\right). \tag{3.24}$$

By Leibniz formula, we get the following inequalities

$$u_2(t) \leqslant u_2(\xi_2) + \int_0^T \left\| \frac{du_2(t)}{dt} \right\|_0 dt, \tag{3.25}$$

and

$$u_2(t) \geqslant u_2(\eta_2) - \int_0^T \left\| \frac{du_2(t)}{dt} \right\|_0 dt. \tag{3.26}$$

It follows from (3.10) and (3.23-3.26) that

$$u_2(t) \leqslant \ln\left(\frac{S_{I_R}}{\mu_{I_R}} + \frac{\beta_1((\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_A}) - \alpha_{20})}{\mu_{I_R}(\alpha_{20} g_m - (\alpha_{20})/\sigma - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2\alpha_4)/\mu_{I_A})} e^{2\alpha_{20}T}\right) + 2T\mu_{I_R}$$

and

$$u_2(t) \geqslant \ln\left(\frac{S_{I_R}}{\mu_{I_R}}\right) - 2\mu_{I_R}T.$$

Let

$$R_2 = \max\left\{\left|\ln\left(\frac{S_{I_R}}{\mu_{I_R}} + \frac{\beta_1((\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_A}) - \alpha_{20})}{\mu_{I_R}(\alpha_{20} g_m - (\alpha_{20})/\sigma - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2\alpha_4)/\mu_{I_A})} e^{2\alpha_{20}T}\right) + 2T\mu_{I_R}\right|, \left|\ln\left(\frac{S_{I_R}}{\mu_{I_R}}\right) - 2T\mu_{I_R}\right|\right\}.$$

Then, for all $t \in [0, T]$, we arrive at

$$\left|u_2(t)\right| \leqslant R_2.$$

Similarly, we have

$$u_3(\xi_3) \leqslant \ln\left(\frac{S_{I_A}}{\mu_{I_A}} + \frac{\beta_2((\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_R}) - \alpha_{20})}{\mu_{I_A}(\alpha_{20} g_m - (\alpha_{20})/\sigma - (\beta_1\alpha_3)/\mu_{\mu_{I_R}} - (\beta_2\alpha_4)\mu_{I_A})} e^{2\alpha_{20}T}\right)$$

and

$$u_3(\eta_1) \geqslant \ln\left(\frac{S_{I_A}}{\mu_{I_A}}\right).$$

Therefore, for any $t \in [0, T]$,

$$\left|u_3(t)\right| \leqslant R_3,$$

where

$$R_3 = \max\left\{\left|\ln\left(\frac{S_{I_A}}{\mu_{I_A}} + \frac{\beta_2((\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_R}) - \alpha_{20})}{\mu_{I_A}(\alpha_{20} g_m - (\alpha_{20})/\sigma - (\beta_1\alpha_3)/\mu_{\mu_{I_R}} - (\beta_2\alpha_4)/\mu_{I_A})} e^{2\alpha_{20}T}\right) + 2T\mu_{I_A}\right|, \left|\ln\left(\frac{S_{I_A}}{\mu_{I_A}}\right) - 2T\mu_{I_A}\right|\right\}$$

Note that $R_i, i = 1, 2, 3$ are independent λ. Let $K = R_1 + R_2 + R_3 + R_0$, where R_0 is a positive constant and sufficiently large such that the unique solution $(\alpha^*, \beta^*, \gamma^*)$ of the algebraic equations

$$
\begin{cases}
-\alpha_{20}\Big(-\overline{g} + \dfrac{1}{\sigma}\Big)e^{\alpha} - \alpha_3 e^{\beta} - \alpha_4 e^{\gamma} = -\alpha_{20}, \\
\beta_1 e^{\alpha} - \mu_{I_R} e^{\beta} = -S_{I_R}, \\
\beta_2 e^{\alpha} - \mu_{I_A} e^{\gamma} = -S_{I_A},
\end{cases}
\tag{3.27}
$$

satisfies $\big\|(\alpha^*, \beta^*, \gamma^*)\big\| < K$. As a result, all of solutions of (3.7) lie in the domain $\big\{u \in C^1(\mathbf{R}, \mathbf{R}^3) \mid \|u\| < K\big\}$.

Choosing $\Omega = \big\{u \in \|u\| < K\big\}$, which implies that the operator equation $L(u) = \lambda N(u)$ has no root on $u \in \partial\Omega \cap \operatorname{Dom} L$ and $\lambda \in (0, 1)$, that is, $L(u) \neq \lambda N(u)$ for any $u \in \partial\Omega \cap \operatorname{Dom} L$ and $\lambda \in (0, 1)$. Clearly, for any $u \in \partial\Omega \cap \operatorname{Ker} L$, it is a constant vector in $\mathbf{R}^3$ with $\|u\| = K$, further $QN(u) \neq 0$ holds. Therefore, the first and second conditions of Lemma 1 are satisfied.

Let $J = I : ImQ \to L$, that is, $Ju = u$. Noticing $g_m \leqslant \overline{g}$ and the conditions (3.17), we derive

$$
\begin{aligned}
\deg(JQN(u), Q \cap \operatorname{Ker} L, 0) &= \sum_{JQN(u)=0, u \in Q \cap \operatorname{Ker} L} \operatorname{sgn}\det\Big(\frac{df(u)}{du}\Big) \\
&= \operatorname{sgn}\det\begin{pmatrix} \alpha_{20}(\overline{g} - \sigma^{-1})e^{\alpha^*} & -\alpha_3 e^{\beta^*} & -\alpha_4 e^{\gamma^*} \\ \beta_1 e^{\alpha^*} & -\mu_{I_R} e^{\beta^*} & 0 \\ \beta_2 e^{\alpha^*} & 0 & -mu_{I_A} e^{\gamma^*} \end{pmatrix} \\
&= \operatorname{sgn}\Big((\overline{g} - \sigma^{-1}) - \frac{\beta_1\alpha_3}{\mu_{I_R}} - \frac{\beta_2\alpha_4}{\mu_{I_A}}\Big)e^{\alpha^*}e^{\beta^*}e^{\gamma^*}\mu_{I_R}\mu_{I_A} \\
&= 1,
\end{aligned}
\tag{3.28}
$$

where $(\alpha^*, \beta^*, \gamma^*)$ is the unique solution of the algebra equations (3.27). Equation (3.28) implies the third condition of Lemma 1 holds.

It is easy to derive that $\big\{K_p(I - Q)N(u) \mid u \in \overline{\Omega}\big\}$ is equi-continuous and uniformly bounded. Then, by means of the Arzela-Ascoli theorem, we obtain that $K_p(I - Q)N : \overline{Q} \to X$ is compact. Consequently, N is L- compact.

Then, Lemma 1 ensures that system (3.3) has at least one positive T-periodic solution on $\overline{\Omega} \cap \operatorname{Dom} L$ if

$$
g_m > \big((\alpha_{20})/\sigma + (\beta_1\alpha_3)/\mu_{I_R} + (\beta_2\alpha_4)/\mu_{I_A}\big)\alpha_{20}^{-1}
$$

and

$$
\alpha_{20} < (\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/\mu I_A.
$$

In the following, we shall investigate the existence of a T-periodic solution of system (3.3) under the condition

$$(3.29)\quad g_M < \frac{(\alpha_{20})/\sigma + (\beta_1\alpha_3)/\mu_{I_R} + (\beta_2\alpha_4)/(\mu_{I_A})}{\alpha_{20}} \text{ and } \alpha_{20} > \frac{\alpha_3 S_{I_R}}{\mu_{I_R}} + \frac{\alpha_4 S_{I_A}}{\mu I_A}.$$

Let $u(t) \in X$ solve system (3.7), by inequality (3.15), we get

$$\int_0^T e^{u_1(t)} dt \leqslant \frac{(\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_A}) - \alpha_{20}}{\alpha_{20}(g^M - \sigma^{-1}) - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2 S_{I_A})/\mu_{I_A}} T,$$

and further

$$u_1(\xi_1) \leqslant \ln\left(\frac{(\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_A}) - \alpha_{20}}{\alpha_{20}(g^M - \sigma^{-1}) - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2 S_{I_A})/\mu_{I_A}}\right).$$

Similarly, using (3.16), we obtain

$$u_1(\eta_1) \geqslant \ln\left(\frac{(\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_A}) - \alpha_{20}}{\alpha_{20}(g_m - \sigma^{-1}) - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2 S_{I_A})/\mu_{I_A}}\right).$$

Therefore,

$$\begin{aligned} u_1(t) &\leqslant u_1(\xi_1) + \int_0^T \left\| \frac{du_1(t)}{dt} \right\|_0 dt \\ &\leqslant \ln\left(\frac{(\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_A}) - \alpha_{20}}{\alpha_{20}(g^M - \sigma^{-1}) - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2 S_{I_A})/\mu_{I_A}}\right) + 2\alpha_{20}T \end{aligned}$$

and

$$\begin{aligned} u_1(t) &\geqslant u_1(\eta_1) - \int_0^T \left\| \frac{du_1(t)}{dt} \right\|_0 dt \\ &\geqslant \ln\left(\frac{(\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_A}) - \alpha_{20}}{\alpha_{20}(g_m - \sigma^{-1}) - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2 S_{I_A})/\mu_{I_A}}\right) - 2\alpha_{20}T. \end{aligned}$$

Let

$$\begin{aligned} \overline{R}_1 = \max\Bigg\{ &\left| \ln\left(\frac{(\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_A}) - \alpha_{20}}{\alpha_{20}(g^M - \sigma^{-1}) - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2 S_{I_A})/\mu_{I_A}}\right) + 2\alpha_{20}T \right|, \\ &\left| \ln\left(\frac{(\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_A}) - \alpha_{20}}{\alpha_{20}(g_m - \sigma^{-1}) - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2 S_{I_A})/\mu_{I_A}}\right) - 2\alpha_{20}T \right| \Bigg\}. \end{aligned}$$

Obviously, for all $t \in [0, T]$, we have

$$\left|u_1(t)\right| \leqslant \overline{R}_1.$$

Similarly, we get

$$e^{u_3(\xi_3)} \leqslant \frac{S_{I_A}}{\mu_{I_A}} + \frac{\beta_2((\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_A}) - \alpha_{20})}{\mu_{I_A}(\alpha_{20} g^M - (\alpha_{20})/\sigma - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2\alpha_4)/\mu_{I_A})} e^{2\alpha_{20}T}$$

and

$$e^{u_3(\eta_3)} \geqslant \frac{S_{I_A}}{\mu_{I_A}}.$$

Easily, we obtain

$$u_3(t) \leqslant \ln\left(\frac{S_{I_A}}{\mu_{I_A}} + \frac{\beta_2((\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_A}) - \alpha_{20})}{\mu_{I_A}(\alpha_{20} g^M - (\alpha_{20})/\sigma - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2\alpha_4)/\mu_{I_A})} e^{2\alpha_{20}T}\right) + 2T\mu_{I_A},$$

and

$$u_3(t) \geqslant \ln\frac{S_{I_A}}{\mu_{I_A}} - 2T\mu_{I_A}.$$

Let

$$\overline{R}_3 = \max\left\{\left|\ln\left(\frac{S_{I_A}}{\mu_{I_A}} + \frac{\beta_2((\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_A}) - \alpha_{20})}{\mu_{I_A}(\alpha_{20} g^M - (\alpha_{20})/\sigma - (\beta_1\alpha_3)\mu_{I_R} - (\beta_2\alpha_4)/\mu_{I_A})} e^{2\alpha_{20}T}\right) + 2T\mu_{I_A}\right|, \left|\ln\frac{S_{I_A}}{\mu_{I_A}} - 2T\mu_{I_A}\right|\right\}$$

Then, we derive

$$|u_3| \leqslant \overline{R}_3, t \in [0, T].$$

Similarly, we have

$$\left|u_2(t)\right| \leqslant \overline{R}_2, t \in [0, T],$$

where

$$\overline{R}_2 = \max\left\{\left|\frac{S_{I_R}}{\mu_{I_R}} + \frac{\beta_1((\alpha_3 S_{I_R})/\mu_{I_R} + (\alpha_4 S_{I_A})/(\mu_{I_A}) - \alpha_{20})}{\mu_{I_R}\left(\alpha_{20}(g^M - \sigma^{-1}) - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2\alpha_4)/(\mu_{I_A}) e^{2\alpha_{20}T}\right)} + 2T\mu_{I_R}\right|, \left|\ln\frac{S_{I_R}}{\mu_{I_R}} - 2T\mu_{I_R}\right|\right\}.$$

Let $\overline{K} = \sum_{i=1}^{3} \overline{R}_i + \overline{R}_0$, where $\overline{R}_0$ is large enough such that the unique solution $u^* = (\alpha^*, \beta^*, \gamma^*)$ of the algebraic equations (3.27). Let $\Omega' = \{u \in X \mid \|u\| < \overline{K}\}$. Obviously, for any $u \in \partial\Omega' \cap \operatorname{Ker} L = \partial\Omega' \cap \mathbf{R}^3 = \{u \in \mathbf{R}^3, \|u\| = \overline{K}\}$, we have $QN(u) \neq 0, u \in \partial\Omega' \cap \operatorname{Ker} L$. Taking $J = I : ImQ \to \operatorname{Ker} L, u \to u$. Then

$$\begin{aligned}&\deg(JQN(u), \Omega' \cap \operatorname{Ker} L, 0)\\ &\qquad = \operatorname{sgn}\left\{e^{\alpha^*+\beta^*+\gamma^*}\mu_{I_R}\mu_{I_A}\left((\overline{g} - \sigma^{-1})\alpha_{20} - (\beta_1\alpha_3)/\mu_{I_R} - (\beta_2\alpha_4)/\mu_{I_A}\right)\right\}\end{aligned}$$

Under the condition (3.29), we arrive at $\deg(JQN(u), \Omega' \cap \operatorname{Ker} L, 0) = -1$. Therefore, under the condition of (3.29), system (3.3) has at least one positive T-periodic solution on $\overline{\Omega}' \cap \operatorname{Dom} L$.

Clearly, if $(u_1^*(t), u_2^*(t), u_3^*) \in X$ is a positive continuous T-periodic solution of system (3.3), $(e^{u_1^*(t)}, e^{u_2^*(t)}, e^{u_3^*(t)})$ must be positive continuous T-periodic solution of system (3.1). Hence, under the condition of (3.17) or (3.29), system (3.1) has at least one positive continuous T-periodic solution. ∎

4. Stability of the Periodic Solution

Let $\big(B^*(t), I_R^*(t), I_A^*(t)\big) \in X$ be a T-periodic solution of system (3.1). Clearly, $\big(B^*(t), I_R^*(t), I_A^*(t)\big)$ is bounded on the interval $[0,\infty)$ in the Euclidean space $\mathbf{R}^3$. The following Lemma is basic for the subsequent discussion on the stability of $\big(B^*(t), I_R^*(t), I_A^*(t)\big)$.

Lemma 2. [**10**, p. 123] *Assume that f is a continuous differential function on $[0,\infty)$ to $\mathbb{R}^n$. If the limit $\lim_{t\to\infty} f(t)$ exists and the derivative $f'(t)$ is uniformly continuous on its domain, then $f'(t) \to 0$ as $t \to \infty$.*

Theorem 4.1. *If $\alpha_{20}\big(g^M - (1/\sigma)\big) + (\beta_1\alpha_3)/\mu_{I_R} + (\beta_2\alpha_4)/\mu_{I_A} < 0$, the periodic solution $\big(B^*(t), I_R^*(t), I_A^*(t)\big) \in X$ of (3.1) is global asymptotically stable when it exists.*

Proof: Let $\big(B(t), I_R(t), I_A(t)\big) \in C^1(R^1, R^3)$ be the positive solution of system (3.1) with the initial value of (3.2). Define

$$V_1\big(B(t), I_R(t), I_A(t)\big) = \big\|\ln B(t) - \ln B^*(t)\big\|_0,$$
$$V_2\big(B(t), I_R(t), I_A(t)\big) = \big\|I_R(t) - I_R^*(t)\big\|_0,$$
$$V_3\big(B(t), I_R(t), I_A(t)\big) = \big\|I_A(t) - I_A^*(t)\big\|_0$$

and

$$V_4\big(B(t), I_R(t), I_A(t)\big) = \alpha_{20}\int_{t-\tau}^{t} g(s+\tau)\big\|B(s) - B^*(s)\big\|_0 ds.$$

Then, the upper-right derivatives of V_1, V_2, V_3 and V_4 with respect to t are respectively

$$\begin{aligned} D^+V_1\big(B(t), I_R(t), I_A(t)\big) = \operatorname{sgn}\big(B(t) - B^*(t)\big)\Big(&\alpha_{20}g(t)\big(B(t-\tau) - B^*(t-\tau)\big) \\ &-\frac{\alpha_{20}}{\sigma}\big(B(t) - B^*(t)\big) - \alpha_3\big(I_R(t) - I_R^*(t)\big) \\ &-\alpha_4\big(I_A(t) - I_A^*(t)\big)\Big), \end{aligned} \tag{4.1}$$

$$D^+V_2\big(B(t), I_R(t), I_A(t)\big) \leqslant \beta_1\big\|B(t) - B^*(t)\big\|_0 - \mu_{I_R}\big\|I_R(t) - I_R^*(t)\big\|_0, \tag{4.2}$$

$$D^+V_3\big(B(t), I_R(t), I_A(t)\big) \leqslant \beta_2\big\|B(t) - B^*(t)\big\|_0 - \mu_{I_A}\big\|I_A(t) - I_A^*(t)\big\|_0 \tag{4.3}$$

and

$$\begin{aligned} D^+V_4\big(B(t), I_R(t), I_A(t)\big) = \alpha_{20}\Big(&g(t+\tau)\big\|B(t) - B^*(t)\|_0 - g(t)\big\|B(t-\tau) \\ &-B^*(t-\tau)\|_0\Big). \end{aligned} \tag{4.4}$$

Let

$$V\big(B(t),I_R(t),I_A(t)\big)=V_1\big(B(t),I_R(t),I_A(t)\big)+\frac{\beta_1\alpha_3}{\mu_{I_R}}V_2\big(B(t),I_R(t),I_A(t)\big)$$
$$+\frac{\beta_2\alpha_4}{\mu_{I_A}}V_3\big(B(t),I_R(t),I_A(t)\big)+V_4\big(B(t),I_R(t),I_A(t)\big).$$

By means of (4.1-4.4), the upper-right derivative of $V(B(t),I_R(t),I_A(t))$ with respect to t satisfies

$$\text{(4.5)}\quad D^+V\big(B(t),I_R(t),I_A(t)\big)\leqslant\Big(\alpha_{20}\Big(g^M-\frac{1}{\sigma}\Big)+\frac{\beta_1\alpha_3}{\mu_{I_R}}+\frac{\beta_2\alpha_4}{\mu_{I_A}}\Big)\big\|B(t)-B^*(t)\big\|_0.$$

Clearly, if $\alpha_{20}(g^M-\frac{1}{\sigma})+(\beta_1\alpha_3)/\mu_{I_R}+(\beta_2\alpha_4)/\mu_{I_A}<0$, then $V\big(B(t),I_R(t),I_A(t)\big)$ is non-increasing with respect to t. Noticing $V\big(B(t),I_R(t),I_A(t)\big)$ is positive, we obtain that, as t tends to ∞, the limit of $V\big(B(t),I_R(t),I_A(t)\big)$ exists. Hence, if

$$\alpha_{20}\Big(g^M-\frac{1}{\sigma}\Big)+\frac{\beta_1\alpha_3}{\mu_{I_R}}+\frac{\beta_2\alpha_4}{\mu_{I_A}}<0,$$

the solution of (3.1) has to be bounded on $[0,\infty)$, and further so does its derivative $\big(B'(t),I'_R(t),I'_A(t)\big)$ (for it is defined by $\big(B(t),I_R(t),I_A(t)\big)$ in terms of (3.1)). The boundedness of $\big(B'(t),I'_R(t),I'_A(t)\big)$ implies $\big(B(t),I_R(t),I_A(t)\big)$ is uniformly continuous on $[0,\infty)$. Thus $V'\big(B(t),I_R(t),I_A(t)\big)$ is uniformly continuous on $[0,\infty)$. Consequently, Lemma 2 ensures $\lim_{t\to\infty}V'\big(B(t),I_R(t),I_A(t)\big)=0$. By (4.5), we get that $\lim_{t\to\infty}\big(B(t)-B^*(t)\big)=0$.

Next, we shall prove $\lim_{t\to\infty}\big(I_R(t)-I_R^*(t)\big)=0$ and $\lim_{t\to\infty}\big(I_A(t)-I_A^*(t)\big)=0$. To that end, we define two new variables $x(t)=I_R(t)-I_R^*(t)$ and $y(t)=I_A(t)-I_A^*(t)$, which satisfy

$$\text{(4.6)}\qquad\begin{cases}\dfrac{dx(t)}{dt}=\beta_1\big(B(t)-B^*(t)\big)-\mu_{I_R}x(t),\\[2mm]\dfrac{dy(t)}{dt}=\beta_2\big(B(t)-B^*(t)\big)-\mu_{I_A}y(t)\end{cases}$$

Noticing $\lim_{t\to\infty}\big(B(t)-B^*(t)\big)=0$, we get that all of solutions of (4.6) tend to origin, that is, $\lim_{t\to\infty}\big(I_R(t)-I_R^*(t)\big)=0$ and $\lim_{t\to\infty}\big(I_A(t)-I_A^*(t)\big)=0$.

Therefore, if $\alpha_{20}\big(g^M-(1/\sigma)\big)+(\beta_1\alpha_3)/\mu_{I_R}+(\beta_2\alpha_4)/\mu_{I_A}<0$, the periodic solution of (3.1) is asymptotically stable when it exists. ∎

5. Conclusion and Discussion

In this paper, we incorporate T-period and a time delay into P. Fergola and J. Zhang's [**4**] bacteria-immunity system model. Using Gaines and Mawhin's continuation theorem of coincidence degree theory, sufficient conditions are obtained for the existence of positively periodic solution of system (3.1). Further, by Lemma 2 and constructing Lyapunov function, sufficient conditions are gotten, and under which the positive periodic solution is globally asymptotical stable for any nonnegative delay τ.

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