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Melnikov method to a bacteria-immunity model with bacterial quorum sensing mechanism ☆

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Abstract

A bacteria-immunity model with bacterial quorum sensing is formulated, which describes the competition between bacteria and immune cells. After periodic perturbation and a series of coordinate transformations, the model is brought into a standard form, and which is amenable to Melnikov method. By the method, the existences of chaotic motion and homoclinic bifurcations are proved.

1. Introduction

All of 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 (e.g. with physical barriers or chemicals). Animals with backbones, called 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 recognize 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 [1,2]: the innate immunity and the adaptive one. The innate immunity is the first line of defence, it is nonspecific, i.e. 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 colonize and infect the host. When the innate immunity fails, a completely different cascade of events ensues leading to adaptive immunity. Unlike the innate immunity, the adaptive immunity is specific, i.e. it can recognize 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.

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Quorum sensing is a process that enables bacteria to communicate using secreted signaling molecules called autoinducers [3]. This process enables a population of bacteria to regulate gene expression collectively and, therefore, control behavior on a community-wide scale. The quorum sensing mechanism was initial observed in the marine bacterium *Vibrio fisheri* around 30 years ago [4,5]. More recently, many other species have been discovered to exhibit quorum sensing behavior, including importantly, major human pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

There are relatively few methods in the literature which can be used to prove the existence of chaotic motion in differential equations. Melnikov method is one of these, and which can be applied to periodic perturbations of nearly Hamiltonian systems. A periodically forced system of planar differential equations determines a map of the plane (the Poincare) which takes a point to the value of the solution through that point after a time T, the period of the forcing term. The intersection of the stable and unstable manifolds of the Poincare map implies the existence of a chaotic invariant set. Recently, this method has been applied to some nonlinear systems: Chacón [6] investigated the chaos arising from the competition between Sine–Gordon-breather and Kink–antikink-pair, Huang [7] studied the chaotic motion of a forced vibration system with nonlinear items such as cubic excitation, square damping forced and bounded stochastic excitation, Basens and Nicolis [8] discussed the complex bifurcations in a periodically forced normal form, Glendinning and Perry [9] considered a SIR epidemic model with a periodically modulated nonlinear incidence rate and established mathematically the existence of chaotic motion of the model, Ravichanndran et al. [10] researched homoclinic bifurcations and chaos in Duffing oscillator driven by an amplitude-modulated force and Wu et al. [11] focused on the controlling chaos with periodic parameterize perturbation of Lorenz system.

Many simple mathematical models (see, e.g. [12–14], etc.) have been founded to simulate the interactions between immune system and bacteria, viral or the other pathogens, and which may play a significant role in analyzing the transmission mechanism of infectious diseases and helping human to take measures to control infectious diseases. In the present paper, considering the bacterial quorum sensing mechanism in the competition between bacteria and immunity system, we formulate a bacteria-immunity model. After periodic perturbation and a succession of changes of coordinate, the model is brought into a standard form, and which is amenable to the Melnikov method. Subsequently, we prove that the chaotic motion exists in this model. Finally, using a related technique, we verify that the homoclinic bifurcation occurs.

This paper is arranged as follows: Section 2 formulates the model, Section 3 establishes the existence of chaos motion in the model, Section 4 proves the existence of homoclinic bifurcation, Section 5 makes the conclusions.

2. Model formulation

In this section, on the basis of [14], we formulate a mathematical model to characterize the interaction between immune cells and bacteria.

We first 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 be infected (mass-action term $\alpha_1 X_U B$); Infected target cells can be cleared by 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 term, 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 (e.g. natural killer cells, polymorphonuclear cells, macrophages and dendritic cells), and for adaptive immunity, the source term S_{I_A} represents that the memory cells are present, derived from a previous infection (or vaccination), a zero source means the first infection with this pathogen (i.e. there are no memory cells); Both the numbers of innate immune cells and adaptive cells 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 $\alpha_{20}B(1-\frac{B}{\sigma})$ and is also clear by innate immunity (mass-action term $\alpha_3 B I_R$). We consider a mechanism named quorum sensing, 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 (e.g. bacteria, immune cells) in the environment. The model is governed by

$$\begin{cases} \frac{dB(t)}{dt} = \alpha_{20}\left(1 + B(t)^2\frac{1}{B_0} - \frac{B(t)}{\sigma}\right)B(t) - \alpha_3 B(t) I_R(t), \\ \frac{dX_U(t)}{dt} = S_U - \alpha_1 X_U(t)B(t) - \mu_{X_U}X_U(t), \\ \frac{dX_I(t)}{dt} = \alpha_1 X_U(t)B(t) - \alpha_2 I_A(t)X_I(t) - \mu_{X_I}X_I(t), \\ \frac{dI_R(t)}{dt} = S_{I_R} + \beta_1 B(t) - \mu_{I_R}I_R(t), \\ \frac{dI_A(t)}{dt} = S_{I_A} + \beta_2 B(t) - \mu_{I_A}I_A(t), \end{cases} \tag{2.1}$$

where α_{20} is the effective reproductive rate of bacteria (the reproduction rate minus the death rate), ϵ a small parameter, σ the effective carrying capacity of the environment, $\alpha_{20}B(t)(1-\frac{B(t)}{\sigma})$ the logistic growth of bacteria, unlike [14], we use $\alpha_{20}\frac{B^3}{B_0}$ to describe the concentration of bacteria who receive signal molecule before and combat with immune cells at time t, and which is a modification of the related term of the model in [14].

Suppose all of the parameters in system (2.1) are positive except a_1, a_2 and ϵ.

3. The existence of chaotic motion

Clearly, the equations related to $B(t)$ and $I_R(t)$ are independent to the others in system (2.1). Here, only their dynamical properties are focused on. As a result, system (2.1) is reduced into

$$\begin{cases} \frac{dB(t)}{dt} = \alpha_{20}\left(1+\frac{B(t)^2}{B_0}-\frac{B(t)}{\sigma}\right)B(t)-\alpha_3 B(t)I_R(t), \\ \frac{dI_R(t)}{dt} = S_{I_R}+\beta_1 B(t)-\mu_{I_R}I_R(t). \end{cases} \tag{3.1}$$

For the sake of description, we introduce two notations:

$$R_0 = \frac{\alpha_3 S_{I_R}}{\alpha_{20}\mu_{I_R}} \quad \text{and} \quad R_1 = \frac{4\alpha_{20}^2(1-R_0)}{B_0\left(\frac{\alpha_{20}}{\sigma}+\frac{\alpha_3\beta_1}{\mu_{I_R}}\right)^2}$$

and the biologically meaning of R_0 will be given in Section 5.

It is not difficult to prove that system (3.1) has the properties:

Theorem 3.1. *If $R_0 > 1$, there exist asymptotically stable bacteria free equilibrium point $E_0 = (0, \frac{S_{I_R}}{\mu_{I_R}})$ and a unique positive equilibrium point $E_1 = (B_1^*, \frac{S_{I_R}+\beta_1 B_1^*}{\mu_{I_R}})$;*

If $R_0 = 1$, there exist bacteria free equilibrium point E_0 and a unique positive equilibrium point $E_2 = (B_2^*, \frac{S_{I_R}+\beta_1 B_2^*}{\mu_{I_R}})$;

If $R_0 < 1$, except for the unstable bacteria free equilibrium point E_0, there exist different positive equilibrium points under different additional conditions:

- *if $R_1 < 1$, there exist two positive equilibrium points E_1 and $E_3 = (B_3^*, \frac{S_{I_R}+\beta_1 B_3^*}{\mu_{I_R}})$,*
- *if $R_1 = 1$, there exists a unique positive equilibrium point $E_4 = (B_4^*, \frac{S_{I_R}+\beta_1 B_4^*}{\mu_{I_R}})$,*
- *if $R_1 > 1$, no positive equilibrium point exists,*

where $B_{1,3}^* = \frac{B_0}{2\alpha_{20}}\left(\frac{\alpha_{20}}{\sigma}+\frac{\alpha_3\beta_1}{\mu_{I_R}}\right)(1\pm\sqrt{1-R_1})$, $B_2^* = \frac{B_0}{\alpha_{20}}\left(\frac{\alpha_{20}}{\sigma}+\frac{\alpha_3\beta_1}{\mu_{I_R}}\right)$ and $B_4^* = \frac{B_0}{2\alpha_{20}}\left(\frac{\alpha_{20}}{\sigma}+\frac{\alpha_3\beta_1}{\mu_{I_R}}\right)$.

In this paper, we do not discuss the stability of the equilibria and only focus on the existence of chaotic motion and homoclinic bifurcations of system (3.1) by Melnikov method [15,16]. To apply the method, we need to make a succession of changes of coordinates. We begin by defining two new variables:

$$x(t) = I_R(t) - \frac{S_{I_R}}{\mu_{I_R}},$$
$$y(t) = S_{I_R} + \beta_1 B(t) - \mu_{I_R} I_R(t).$$

Therefore, system (3.1) with $\epsilon = 0$ is transformed into

$$\frac{dx(t)}{dt} = y(t),$$
$$\frac{dy(t)}{dt} = \beta_1\left(\alpha_{20}\left(1+\frac{(y(t)+\mu_{I_R})^2}{B_0\beta_1^2}-\frac{y(t)+\mu_{I_R}x(t)}{\sigma\beta_1}\right)\frac{y(t)+\mu_{I_R}x(t)}{\beta_1}-\alpha_3\frac{y(t)+\mu_{I_R}x(t)}{\beta_1}\left(x(t)+\frac{S_{I_R}}{\mu_{I_R}}\right)\right)-\mu_{I_R}y(t). \tag{3.2}$$

To write system (3.2) in a nearly Hamiltonian form as required by Melnikov method, we need some denotations and assumptions:

$$B_0^* = \frac{\alpha_{20}\mu_{I_R}^4}{\alpha_{20}\alpha_3^2\beta_1^2(1-R_0)}, \quad \sigma^* = \frac{\mu_{I_R}^2}{2\alpha_3\beta_1\left(1-\frac{2\alpha_3 S_{I_R}+\mu_{I_R}^2}{2\alpha_{20}\mu_{I_R}}\right)}, \quad a_0 = \frac{1}{B_0}, \quad b_0 = \frac{1}{\sigma} \tag{3.3}$$

with

$$R_0 < 1, \quad \alpha_{20} > \frac{2\alpha_3 S_{I_R} + \mu_{I_R}^2}{2\mu_{I_R}}. \tag{3.4}$$

Then, system (3.1) has a unique positive equilibrium point $(\frac{\mu_{I_R}}{\alpha_3}, 0)$, known as a Takens–Bogdanov point, and near this point it is possible to write system (3.2) into a nearly Hamiltonian form. To perturb about this degenerate point, we define new variable and parameters by

$$x(t) = \frac{\mu_{I_R}}{\alpha_3} + \widetilde{x}(t), \quad b_0 = b + \frac{1}{\sigma^*} \quad \text{and} \quad a_0 = a_0(b_0) + a, \tag{3.5}$$

where x, a and b are to be thought of as small $a_0(b_0) = \frac{\alpha_{20}\mu_{I_R}^2 b_0^2 + 2\alpha_{20}\mu_{I_R}\alpha_3\beta_1 b_0 + \alpha_3^2\beta_1^2}{4\alpha_{20}\mu_{I_R} - \alpha_3 s_{I_R} + \alpha_{20}\mu_{I_R}}$. Obviously, we have $a_0(b_0) = \frac{1}{B_0^*}$ when $b_0 = \frac{1}{\sigma^*}$. Substituting (3.5) into (3.2) and omitting the tilde lead to

$$\frac{dx(t)}{dt} = y(t),$$
$$\frac{dy(t)}{dt} = k_{00} + k_{10}x(t) + k_{01}y(t) + k_{20}x(t)^2 + k_{11}x(t)y(t) + k_{30}x(t)^3 + k_{21}x(t)^2y(t) + k_{12}x(t)y(t)^2 + k_{03}y(t)^3,$$

where

$$k_{00} = \frac{\alpha_{20}\mu_{I_R}^6}{\beta_1^2\alpha_3^3}a + \frac{\alpha_{20}\mu_{I_R}^6}{4\beta_1^2\alpha_3^3(1-R_0)}b^2,$$
$$k_{10} = \frac{3\alpha_{20}\mu_{I_R}^5}{\beta_1^2\alpha_3^2}a + \frac{\alpha_{20}\mu_{I_R}^3}{\beta_1\alpha_3}b - \frac{3\alpha_{20}\mu_{I_R}^5}{4\beta_1^2\alpha_3^2(R_0-1)}b^2,$$
$$k_{11} = \alpha_3 + 2\alpha_{20}\alpha_3(1-R_0) - \frac{6\alpha_{20}\mu_{I_R}^3}{\alpha_3\beta_1^2}a + \frac{4\alpha_{20}\mu_{I_R}}{\beta_1}b - \frac{3\mu_{I_R}^3\alpha_{20}}{2\beta_1^2\alpha_3(R_0-1)}b^2,$$
$$k_{12} = \frac{3\alpha_{20}\alpha_3^3}{\mu_{I_R}^2}(1-R_0) + \frac{3\alpha_{20}\mu_{I_R}}{\beta_1^2}a + \frac{3\alpha_3}{\beta_1\mu_{I_R}}b - \frac{3\alpha_{20}\mu_{I_R}}{4\beta_1^2(R_0-1)}b^2,$$
$$k_{20} = \alpha_{20}\alpha_3(1-R_0) + \frac{3\alpha_{20}\mu_{I_R}^4}{\beta_1\alpha_3}a + \frac{2\alpha_{20}\mu_{I_R}^2}{\beta_1}b + \frac{3\alpha_{20}\mu_{I_R}^4}{4\alpha_3\beta_1^2(1-R_0)}b^2,$$
$$k_{21} = \frac{3\alpha_{20}\alpha_3^2}{\mu_{I_R}^2}(1-R_0) + \frac{3\alpha_{20}\mu_{I_R}^3}{\beta_1^2}a + \frac{\alpha_{20}\alpha_3\mu_{I_R}}{\beta_1}b + \frac{\alpha_{20}\mu_{I_R}^3}{4\beta_1(1-R_0)}b^2,$$
$$k_{30} = \frac{\alpha_{20}\alpha_3^2}{\mu_{I_R}}(1-R_0) + \frac{\alpha_{20}\mu_{I_R}^3}{\beta_1^2}a + \frac{\alpha_{20}\alpha_3\mu_{I_R}}{\beta_1}b + \frac{\alpha_{20}\mu_{I_R}^3}{4\beta_1^2(1-R_0)}b^2,$$
$$k_{01} = \frac{3\alpha_{20}\mu_{I_R}^4}{\beta_1^2\alpha_3^2}a + \frac{\alpha_{20}\mu_{I_R}^2}{\beta_1\alpha_3}b + \frac{3\alpha_{20}\mu_{I_R}^4}{4\beta_1\alpha_3^2(1-R_0)}b^2,$$
$$k_{02} = \frac{\alpha_3}{\mu_{I_R}^2} + \frac{\alpha_{20}\alpha_3}{\mu_{I_R}^2}(1-R_0) + \frac{3\alpha_{20}\mu_{I_R}^2}{\beta_1^2\alpha_3}a + \frac{2\alpha_{20}}{\beta_1}b + \frac{3\alpha_{20}\mu_{I_R^2}}{4\beta_1^2\alpha_3(1-R_0)}b^2,$$
$$k_{03} = \frac{\alpha_{20}\alpha_3^2}{\mu_{I_R}^4}(1-R_0) + \frac{\alpha_{20}}{\beta_1^2}a + \frac{\alpha_{20}\alpha_3}{\beta_1\mu_{I_R}^2}b + \frac{\alpha_{20}}{4\beta_1^2(1-R_0)}b^2.$$

Introducing the small parameter ϵ by setting

$$a = a_1\epsilon^4 + a_2\epsilon^5\sin(\Omega\epsilon t), \quad b = b_1\epsilon^2$$

and defining new variables and time by

$$x(t) = \epsilon^2 u(t), \quad y(t) = \epsilon^3 v(t), \quad \tau = \epsilon t$$

yield

$$\frac{du}{d\tau} = v,$$
$$\frac{dv}{d\tau} = \frac{\alpha_{20}\mu_{I_R}^6}{\beta_1^2\alpha_3^3}a_1 + \alpha_{20}\alpha_3(1-R_0)\left(u + \frac{\mu_{I_R}^3}{2\beta_1\alpha_3^2(1-R_0)}b_1\right)^2 + \epsilon\left(\frac{\alpha_{20}\mu_{I_R}^6}{\beta_1^2\alpha_3^2}a_2\sin(\Omega\tau) + \frac{\alpha_{20}\mu_{I_R}^2}{\beta_1\alpha_3}b_1 v + \frac{2\alpha_{20}(1-R_0) + \mu_{I_R}}{\mu_{I_R}}uv\right) + O(\epsilon^2), \tag{3.6}$$

where the second-order terms and the higher of ϵ are ignored.

To change system (3.6) into a nearly Hamiltonian system, we need introduce new variables

$$\widehat{u} = \alpha_{20}\alpha_3(1-R_0)\left(u + \frac{\mu_{I_R}^3}{2\beta_1\alpha_3^2(1-R_0)}\right), \quad \widehat{v} = \alpha_{20}\alpha_3(1-R_0)v.$$

Neglecting the hat, we obtain

$$\begin{aligned} \frac{du}{d\tau} &= v, \\ \frac{dv}{d\tau} &= \frac{\alpha_{20}^2\mu_{I_R}(1-R_0)}{\beta_1^2\alpha_3^2}a_1 + u^2 + \epsilon\left(\frac{\alpha_{20}^2\mu_{I_R}^6}{\beta_1^2\alpha_3}(1-R_0)a_2\sin(\Omega\tau) + \frac{\alpha_{20}b_1}{\beta_1\alpha_3}\left(\mu_{I_R}^2 - \frac{1}{\alpha_3^2\mu_{I_R}} - \frac{\mu_{I_R}^3}{2\alpha_{20}\alpha_3(1-R_0)}\right)v \right. \\ &\quad \left. + \frac{2\alpha_{20}(1-R_0)+\mu_{I_R}}{\alpha_{20}\alpha_3\mu_{I_R}(1-R_0)}uv\right) + O(\epsilon^2). \end{aligned} \tag{3.7}$$

Denote

$$c = \frac{\alpha_{20}}{\beta_1\alpha_3}\sqrt{a_1\mu_{I_R}(1-R_0)}. \tag{3.8}$$

Under the condition of $a_1(1-R_0) > 0$, Melnikov method can be applied to system (3.7) for small ϵ. Obviously, if $\epsilon = 0$ we obtain the unperturbed equation

$$\begin{aligned} \frac{du}{d\tau} &= v, \\ \frac{dv}{d\tau} &= -c^2 + u^2. \end{aligned} \tag{3.9}$$

Clearly, the Hamiltonian for system is $H(u,v) = \frac{1}{2}v^2 + c^2u - \frac{1}{3}u^3$ and so solutions lie on curves of constant H. Eq. (3.9) is well-known in the literature (see [15, Section 8.2]). It has two equilibrium points: $(c,0)$ which is a saddle, and $(-c,0)$ which is a center. The center is surrounded by a continuous family of periodic orbits $(u_T(\tau), v_T(\tau))$ and these are bounded by a homoclinic orbit $(u_h(\tau), v_h(\tau))$ such that

$$\lim_{\tau\to\pm\infty}(u_h(\tau), v_h(\tau)) = (c,0).$$

Furthermore, $(u_h(\tau), v_h(\tau))$ has the form

$$\begin{aligned} u_h(\tau) &= c - 3c\,\mathrm{sech}^2\left(\tau\sqrt{\frac{c}{2}}\right), \\ v_h(\tau) &= 3c\sqrt{2c}\,\mathrm{sech}^2\left(\tau\sqrt{\frac{c}{2}}\right)\tanh\left(\tau\sqrt{\frac{c}{2}}\right). \end{aligned} \tag{3.10}$$

Therefore, the Melnikov function for system (3.7) is

$$\begin{aligned} M(\tau_0) = \int_{-\infty}^{\infty} v_h(\tau)&\left(\frac{\alpha_{20}b_1}{\beta_1\alpha_3}\left(\mu_{I_R}^2 - \frac{1}{\alpha_3^2\mu_{I_R}} - \frac{\mu_{I_R}^3}{2\alpha_{20}\alpha_3(1-R_0)}\right)v_h(\tau) + \frac{2\alpha_{20}(1-R_0)+\mu_{I_R}}{\alpha_{20}\alpha_3(1-R_0)}u_h(\tau)v_h(\tau) \right. \\ &\left. + \frac{\alpha_{20}^2\mu_{I_R}^6(1-R_0)}{\beta_1^2\alpha_3}a_2\sin(\Omega(\tau+\tau_0))\right)d\tau. \end{aligned} \tag{3.11}$$

From Basens and Nicolis's result [8], which we have checked, we obtain

$$M(\tau_0) = \frac{24\alpha_{20}c^2\sqrt{2c}\left(\mu_{I_R}^2 - \frac{1}{\alpha_3^2\mu_{I_R}} - \frac{\mu_{I_R}^3}{2\alpha_{20}\alpha_3(1-R_0)}\right)}{5\beta_1\alpha_3}b_1 - \frac{24c^3\sqrt{2c}(2\alpha_{20}(1-R_0)+\mu_{I_R})}{7\alpha_{20}\alpha_3(1-R_0)} + \frac{6\pi\Omega^2\alpha_{20}^2\mu_{I_R}^6(1-R_0)}{\beta_1^2\alpha_3\sinh(\frac{\Omega\pi}{\sqrt{2\pi}})}a_2\cos(\Omega\tau_0). \tag{3.12}$$

Let

$$a_2^* = \frac{4\beta_1^2\alpha_3c^2\sqrt{2c}\sinh\left(\frac{\Omega\pi}{\sqrt{2\pi}}\right)b_1}{\pi\Omega^2\alpha_{20}^2\mu_{I_R}^6(1-R_0)}\left(\frac{\alpha_{20}\left(\mu_{I_R}^2 - \frac{1}{\alpha_3^2\mu_{I_R}} - \frac{\mu_{I_R}^3}{2\alpha_{20}\alpha_3(1-R_0)}\right)}{5\beta_1\alpha_3} - \frac{c(2\alpha_{20}(1-R_0)+\mu_{I_R})}{7\alpha_{20}\alpha_3(1-R_0)}\right).$$

Thus if $|a_2| > a_2^*$ the stable and the unstable manifolds of the fixed point in the Poincare map of the perturbated system (3.7) intersect transversely for sufficiently small ϵ, and there is chaotic phenomenon in the sense of Smale horseshoe for the perturbed system (3.7), whilst if $|a_2| < a_2^*$ there is no intersection between the stable and unstable manifolds; at $a - 2 = a_2^*$ there is a tangential intersection between the stable and unstable manifolds.

4. Homoclinic bifurcations in the unforced model

If $a_2 = 0$ the perturbated system (3.7) is an autonomous system and does indeed have homoclinic bifurcations. The Melnikov integral is

$$M = \int_{-\infty}^{\infty} v_h(\tau)\left(\frac{\alpha_{20}b_1}{\beta_1\alpha_3}\left(\mu_{I_R}^2 - \frac{1}{\alpha_3^2\mu_{I_R}} - \frac{\mu_{I_R}^3}{2\alpha_{20}\alpha_3(1-R_0)}\right)v_h(\tau) + \frac{2\alpha_{20}(1-R_0)+\mu_{I_R}}{\alpha_{20}\alpha_3(1-R_0)}u_h(\tau)v_h(\tau)\mathrm{d}\right)\tau, \tag{4.1}$$

where the homoclinic solution $(u_h(\tau), v_h(\tau))$ is given by (3.10). We easily obtain

$$M = \frac{24\alpha_{20}c^2\sqrt{2c}\left(\mu_{I_R}^2 - \frac{1}{\alpha_3^2\mu_{I_R}} - \frac{\mu_{I_R}^3}{2\alpha_{20}\alpha_3(1-R_0)}\right)}{5\beta_1\alpha_3}b_1 - \frac{24c^3\sqrt{2c}(2\alpha_{20}(1-R_0)+\mu_{I_R})}{7\alpha_{20}\alpha_3(1-R_0)},$$

which has zero if

$$b_1 = \frac{5\beta_1 c(2\alpha_{20}(1-R_0)+\mu_{I_R})}{7\alpha_{20}(1-R_0)\left(\mu_{I_R}^2 - \frac{1}{\alpha_3^2\mu_{I_R}} - \frac{\mu_{I_R}^3}{2\alpha_{20}\alpha_3(1-R_0)}\right)}.$$

Squaring this equation and using (3.8) the expression for c we find that homoclinic bifurcations occur on a curve in (b_1, a_1) parameter space which lies close to the parabolic:

$$b_1^2 = \frac{25(2\alpha_{20}(1-R_0)+\mu_{I_R})^2}{49\alpha_3^2\mu_{I_R}(1-R_0)\left(1 - \frac{1}{\alpha_{20}^2\mu_{I_R}^2} - \frac{\mu_{I_R}^2}{2\alpha_{20}\alpha_3(1-R_0)}\right)^2}a_1.$$

5. Conclusion

In this paper, a bacteria-immunity model is formulated and periodically perturbated. By using Melnikov method, we analytically prove that the model has chaotic motion which closes to a Takens–Bogdanov bifurcation point.

From the biological viewpoint, $\frac{S_{I_R}}{\mu_{I_R}}$ means the concentration of the initial immune cells at bacteria free equilibrium point. So the product of $\frac{S_{I_R}}{\mu_{I_R}}$ and the bacteria clearance factor α_3 measures the strength of the innate immune system defense against the bacteria challenge; while the bacteria productivity factor α_{20} measures the bacterial offensive strength. So with $R_0 = \frac{\alpha_3\frac{S_{I_R}}{\mu_{I_R}}}{\alpha_{20}}$, we can compare the strength of the immune system against the bacterial offensive. Thus, Theorem 3.1 has the biological explication: in the domain of attraction of E_0, bacteria will be cleared if $R_0 > 1$, i.e. the strength of the innate immune system defense against the bacteria challenge is not weaker the bacterial offensive strength.

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