Dynamic study of mathematical models on antibiotics and immunologic adjuvant against Toxoplasmosis

Yongzhen Pei Ye Liu
Tianjin Polytechnic University
School of Science
Binshui West Road, 300387, Tianjin
China
peiyongzhen@sina.com

Changguo Li
Military Transportation University
Department of Basic Science
Chenglin Road, 300161, Tianjin
China
li_changguo@yahoo.cn

Abstract: In this paper, three mathematical models concerning the effect of leucocyte, antibiotics and immunologic adjuvant against *toxoplasma gondii* were proposed respectively. In the case in which toxoplasmosis was inhibited by leucocyte in the host, it is shown that toxoplasmosis can be destroyed depending on the immune strength of the host. In the case in which antibiotics treatment is used, it is observed that input concentration of antibiotics has significant influence on toxoplasmosis. In the case in which immunologic adjuvant was imported to the body of the host, it can improve immunity of the parasitifer to attain the propose of killing *toxoplasma gondii* eventually.

Key–Words: Toxoplasmosis, leucocyte, antibiotics, immunologic adjuvant, uniformly persistence

1 Introduction

Toxoplasmosis, a cosmopolitan disease in humans and most mammals, is caused by the opportunistic protozoan *toxoplasma gondii* mainly through peroral infections, bloodstream infections and congenital acquired infections (see Fig.1 [1]). It has been estimated that one third of the world population has been infected [2,3]. It would lead to its parasitifer's immunity drop with various diseases. For example, some people may develop toxoplasmosis symptoms similar to those of the flu or mononucleosis such as body aches, swollen lymph nodes, headache, fever, fatigue. People with weakened immune systems, such as cancer patients, organ transplant recipients, etc. are more likely to develop signs and symptoms of severe infection, including: headache, confusion, poor coordination, seizures, lung problems and blurred vision. Toxoplasmosis has become a worldwide epidemic, which seriously threats the health of human being. If ecological balance of the host is lost, it will trigger the beginning of the disease [4-10]. Under this circumstances, the clinics adopt widely antibiotics to control the disease.

Toxoplasma gondii is one of the most well-studied parasites because of its medical and veterinary importance, and its suitability as a model for cell biology and molecular studies with a unicellular organism. There are thousands of references to this parasite in the literature [11-14] and the references were cited in. Although different aspects of the T. gondii life cycle have been intensively investigated, the overall transmission dynamics of this parasite has not been well studied. After reviewed a large body of literature, a few mathematical models have been built to investigate the transmission of T. gondii. We summed up these studies which included the following aspects:

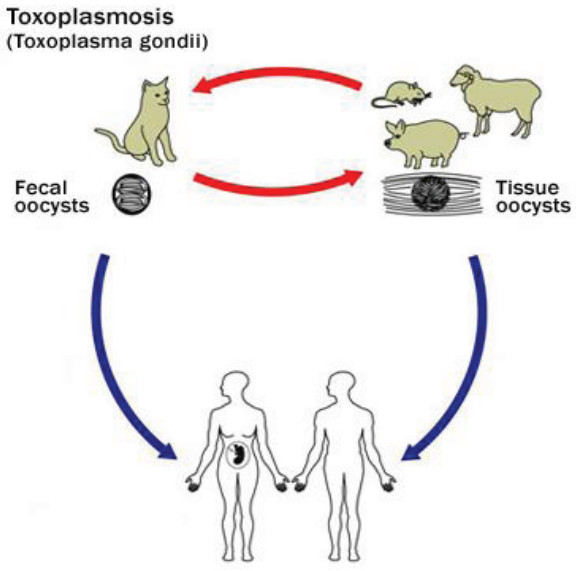


Figure 1: Toxoplasmosis life cycle(from literature[1])

(1) **Vertical transmission.** Diego et al [15] were the first to study the evolution dynamics of T. gondii in human population using an SIR(susceptible-infected-recovered) model involving vertical transmission. But only Numerical simulations of this model were done

by varying parameters to show different scenarios about the spread of the disease. Ocampo et al [16] described congenital toxoplasmosis transmission dynamics by using an age-structured model taking a mother's gestational week into account.

(2) **Agent-based transmission.** Gilberto et al [17] built a mathematical model for the transmission of Toxoplasmosis disease in human and cat populations in which they assumed that the horizontal transmission of the disease to humans is through the contact with infected cats. M. L*é*lu et al [18] investigated dynamics of the transmission of T. gondii between cats, contaminated environment and prey. Wen et al [19] synthesize what is currently known about the natural history of T. gondii by developing a prototype agent-based model to mimic the transmission process of T. gondii in a farm system.The present model takes into account the complete life cycle of T. gondii, which includes the transitions of the parasite from cats to environment through feces,from contaminated environment to mice through oocyst,from mice to cats through tissue cysts,from environment to cats through oocysts as well as the vertical transmission among mice.

(3) **Vaccination.** A dynamic compartment model was developed by Mateus-Pinilla [20] to investigate the transmission of T. gondii on swine farms with a primary focus on the importance of a feline T. gondii vaccine. Abraham [21] presented an epidemiological model to study the transmission dynamics of toxoplasmosis in a cat population under a continuous vaccination schedule.

Those mathematical models explain some of the dynamical behaviors of the disease in the definite host(cat), the intermediate host(e.g.human, swine) populations as well as the complete life cycle of T. gondii. However, few models consider the dynamics of tachyzoites and bradyzoites in host cell from a pathophysiologic point of view.

At present, the traditional treatment of toxoplasmosis bases on the principle of pyrimethamine and sulfapyridine, but these two antibiotics have a bad radical cure effect and high recurrence rate after drug discontinuance [22-29]. In addition, because most antibiotics have potential virulence for certain organs of the human body, it is obvious that the toxicity can damage the ecological balance. So overuse or misuse of antibiotics can cause immunity reduced and organs injured of the patients, which hinders control of infection. In this case it can make the patient's illness worse to a very great extent. Moreover, overuse of related antibiotics is also expected to cause serious drug resistance. It would directly produce a new threat for health and life of the patients, and toxoplasmosis has become the main cause of death for patients with low immune function. Finding a safe and efficient immunological adjuvant for toxoplasmosis treatment has become an urgent need.

Cholera toxin is now frequently-used immune adjuvant with strong mucosal immunogenicity and mucosal immunity adjuvant effect. It can effectively enhance antigenic protein immunogenicity and increase the body's immune function [30]. However, consider that we should develop the need of new composite multivalence subunit vaccine against *toxoplasma gondii*, we must choose one or several major surface antigen with strong toxoplasma immunogenicity and appropriate mucosa immunization adjuvant and transportation system to explore the preparation of mucosa. Believe that the development of immunologic adjuvant against toxoplasmosis will be bound to make abundant accomplishment in the near future.

Combined with the above-mentioned introductions, the main purpose of this paper is to construct three realistic models for the treatments against toxoplasmosis, investigate their dynamic behaviors and compare the results obtained from these ordinary differential models, The organization of this paper is as follows. In the next section we formulate the mathematical model (1) and study the global stabilities of all equilibriums. It is important to remark that the critical factor which toxoplasmosis can die out or not can be obtained from the Theorem 1. In Section 3, we present more practical model (2) describing antibiotics on the role of *toxoplasma gondii* based on the model (1). The following is devoted to analyze the steady states and find the threshold value A_1^0 which determines toxoplasmosis can die out or not. Similarity with the section 3, Section 4 shows the model (15) describing immunologic adjuvant on the role of *toxoplasma gondii*, then we make the stability analysis of the disease-free and endemic equilibriums. From the conclusion of the Theorem 5 and 7, we find that immune adjuvant is urgent desired through comparing the effect of immune adjuvant and antibiotics against toxoplasmosis. Section 5 contains numerical results and finally in Section 6 we present the discussion.

2 Immune Reaction of the Host against Toxoplasmosis

The first line of defense against parasites, as with other pathogens, is the innate immune system. Immune reaction is a bodily defense reaction that recognizes an invading substance (an antigen: such as a virus or fungus or bacteria or parasites) and produces antibodies specific against that antigen [31, 32]. Combining with the mechanism of immune reaction of the host for toxoplasmosis, we would build a mathemat-

ical model which leucocyte acts on the *toxoplasma gondii* as follows:

$$\begin{cases} x' = x(r_1 - d_1 x) \\ y' = y(r_2 - d_2 y - \beta_1 x) \end{cases} \quad (1)$$

In the model, $x(t)$ and $y(t)$ denote density of leucocyte and *toxoplasma gondii* respectively at time t in human body; the intrinsic increasing rates of leucocyte and *toxoplasma gondii* are denoted by r_1, r_2, respectively. The parameters d_1 and d_2 are the density-dependent the immune coefficients respectively. Moreover, β_1 is the immune strength of the host for *toxoplasma gondii*. From system (1), we can easily obtain:

Theorem 1 *Consider system (1), then*
a) the disease free-equilibrium

$$E^0_{(1)} = (\frac{r_1}{d_1}, 0)$$

is globally asymptotically stable if $\frac{r_1}{d_1} > \frac{r_2}{\beta_1}$;
b) the endemic equilibrium

$$E^1_{(1)} = (\frac{r_1}{d_1}, \frac{r_2 d_1 - r_1 \beta_1}{d_1 d_2})$$

is globally asymptotically stable if $\frac{r_1}{d_1} < \frac{r_2}{\beta_1}$.

Proof: By the linearization of system (1) around the equilibriums $E^0_{(1)}$ and $E^1_{(1)}$, Theorem 1 can easily be proofed. We omit it. □

Form Theorem 1, we can conclude that *toxoplasma gondii* $y(t)$ tends to die out when leucocyte's immune strength β_1 is sufficiently large ($i.e. \beta_1 > r_2 d_1 / r_1$) in no drug cases. At this moment, the host will not cause disease after the invasion of *toxoplasma gondii*.

However, if the immune strength β_1 is too small, $\beta_1 < r_2 d_1 / r_1$, then *toxoplasma gondii* will survive because the immune strength of leucocyte is too low to approach $(r_2 d_1 - r_1 \beta_1)/d_1 d_2$. At this time, the host individual will be infected by *toxoplasma gondii*.

Next we would consider further the effect of antibiotics against *toxoplasma gondii*.

3 Antibiotics on the Role of Toxoplasmosis

At present, the treatment of toxoplasmosis often bases on the principle of pyrimidine and sulfa medications. Therefore, in this sections we uses the following system to discuss antibiotics on the influence of toxoplasmosis.

$$\begin{cases} x' = x(r_1 - d_1 x - \beta_2 A_1), \\ y' = y(r_2 - d_2 y - \beta_1 x - \beta_3 A_1), \\ A_1' = A_1^0 - \beta_2 A_1 x - \beta_3 A_1 y - d_3 A_1. \end{cases} \quad (2)$$

Here A_1 denotes the density of antibiotics on human body at time t and A_1^0 is the initial one. The parameter d_3 is the metabolic rate of antibiotics. The constants β_2 and β_3 denote antibiotics's lethality for leucocyte and *toxoplasma gondii* respectively. The meaning of other parameters is the same as what we refer to in the system (1).

For system (2), we can make full use of the qualitative theory of ordinary differential equations to get several results.

Theorem 2 *Assume that*

$$\frac{d_3(r_2 d_1 - \beta_1 r_1)}{\beta_2 d_1 - \beta_1 \beta_2} > 0 \quad (3)$$

holds. If the positive equilibrium exists, the leucocyte and toxoplasma gondii will be uniform persistence when

$$A_1^0 < min\{\frac{r_1 d_3}{\beta_2}, \frac{d_3(r_2 d_1 - \beta_1 r_1)}{\beta_2 d_1 - \beta_1 \beta_2}\} \doteq A^0_{1min}. \quad (4)$$

Proof: From the third equation of system (2), we have

$$A_1' = A_1^0 - d_3 A_1 - \beta_2 A_1 x - \beta_3 A_1 y \le A_1^0 - d_3 A_1.$$

By comparison principle[33], as $t \to +\infty$, we have

$$A_1(t) \le \frac{A_1^0}{d_3}. \quad (5)$$

Using the above inequality (5), it is clear to find that

$$\begin{cases} x' \ge x(r_1 - d_1 x - \frac{\beta_2 A_1^0}{d_3}), \\ y' \ge y(r_2 - d_2 y - \beta_1 x - \frac{\beta_3 A_1^0}{d_3}). \end{cases}$$

Let us consider the following system

$$\begin{cases} x' = x(r_1 - d_1 x - \frac{\beta_2 A_1^0}{d_3}), \\ y' = y(r_2 - d_2 y - \beta_1 x - \frac{\beta_3 A_1^0}{d_3}). \end{cases} \quad (6)$$

By conditions (3) and (4), we can conclude that the positive equilibrium

$$E^*_{(3)} = \left(\frac{r_1 d_3 - \beta_2 A_1^0}{d_1 d_3},\right.$$

$$\frac{r_2d_1d_3-\beta_1r_1d_3+\beta_1\beta_2A_1^0-\beta_2A_1^0d_1}{d_1d_2d_3}\Bigg)$$

of system (6) is globally asymptotically stable (proof see the appendix). Moreover, utilizing the comparison principle we know that

$$\lim_{t\to\infty} x(t) \geq \tfrac{r_1d_3-\beta_2A_1^0}{d_1d_3},$$
$$\lim_{t\to\infty} y(t) \geq \tfrac{r_2d_1d_3-\beta_1r_1d_3+\beta_1\beta_2A_1^0-\beta_2A_1^0d_1}{d_1d_2d_3}.$$

It is namely that the leucocyte and autibiotics are uniform persistence. This completes the proof of the theorem. □

Theorem 3 *The stability of the extinction equilibrium* $E_{(2)}^0=(0,0,\frac{A_1^0}{d_3})$ *is described as follows:*

(i) $E_{(2)}^0$ *is locally asymptotically stable if*

$$A_1^0>\max\{\frac{r_1d_3}{\beta_2},\frac{r_2d_3}{\beta_3}\};$$

(ii) Under the condition $r_2d_1>\beta_1r_1$, $E_{(2)}^0$ *is globally asymptotically stable if*

$$A_1^0>\max\{\frac{Mr_1}{\beta_2},\frac{Mr_2}{\beta_3}\}\doteq A_{1\max}^0,$$

where

$$M=d_3+\frac{\beta_2r_1}{d_1}+\frac{\beta_3r_2d_1-\beta_1\beta_3r_1}{d_1d_2}. \tag{7}$$

Proof: The linearization of system (2) around the equilibrium E_2^0 gives the following characteristic equation:

$$\begin{vmatrix} r_1-\frac{\beta_2A_1^0}{d_3}-\lambda & 0 & 0 \\ 0 & r_2-\frac{\beta_3A_1^0}{d_3}-\lambda & 0 \\ -\frac{\beta_2A_1^0}{d_3} & -\frac{\beta_3A_1^0}{d_3} & -d_3-\lambda \end{vmatrix}=0.$$

The above equation is equivalent to

$$(r_1-\frac{\beta_2A_1^0}{d_3}-\lambda)(r_2-\frac{\beta_3A_1^0}{d_3}-\lambda)(-d_3-\lambda)=0. \tag{8}$$

It is easy to calculate that

$$\lambda_1=r_1-\frac{\beta_2A_1^0}{d_3},\ \lambda_2=r_2-\frac{\beta_3A_1^0}{d_3},\ \lambda_3=-d_3.$$

Hence we can conclude that all roots of (8) have negative real part implying that the equilibrium $E_{(2)}^0$ is locally asymptotically stable if

$$A_1^0>\max\{\frac{r_1d_3}{\beta_2},\frac{r_2d_3}{\beta_3}\}.$$

According to the first two equations of (2), we have

$$x'\leq x(r_1-d_1x), \tag{9}$$

$$y'\leq y(r_2-d_2y-\beta_1x). \tag{10}$$

Using the comparison principle again, as $t\to+\infty$, we obtain

$$x(t)\leq\frac{r_1}{d_1},\quad y(t)\leq\frac{r_2d_1-\beta_1r_1}{d_1d_2}. \tag{11}$$

From the third equation of (2) and the above inequality (11), we see that

$$A_1'\geq A_1^0-(d_3+\frac{\beta_2r_1}{d_1}+\frac{\beta_3r_2d_1-\beta_1\beta_3r_1}{d_1d_2})A_1.$$

So for sufficiently large t, we have

$$A(t)\geq\frac{A_1^0}{M},$$

where M is defined by (7). Using the above inequality, we get

$$\begin{cases} x'\leq x(r_1-d_1x-\frac{\beta_2A_1^0}{M}), \\ y'\leq y(r_2-d_2y-\beta_1x-\frac{\beta_3A_1^0}{M}). \end{cases}$$

Again using comparison principle and the conditions of (ii), obtain that

$$\lim_{t\to\infty}x(t)=\lim_{t\to\infty}y(t)=0,$$

and hence

$$\lim_{t\to\infty}A_1(t)=\frac{A_1^0}{d_3}.$$

Furthermore, from

$$A_1^0>\max\{\frac{Mr_1}{\beta_2},\frac{Mr_2}{\beta_3}\}>\max\{\frac{r_1d_3}{\beta_2},\frac{r_2d_3}{\beta_3}\},$$

we know that E_1^0 is globally asymptotically stable. The proof of Theorem 3 is completely. □

Theorem 4 *Under the assumptions*

$$\beta_1\beta_2>\beta_3d_1, \tag{12}$$

$$\beta_1r_1>r_2d_1, \tag{13}$$

$$2\beta_2^2r_2d_1+\beta_1\beta_2d_1d_3-\beta_1\beta_2^2r_1 -\beta_2\beta_3r_1d_1-\beta_3d_1^2d_3>0, \tag{14}$$

the system (2) has two boundary equilibrium $E^1_{(2)} = (\overline{x}, 0, \overline{A}_1)$ *and* $E^2_{(2)} = (\overline{\overline{x}}, 0, \overline{\overline{A}}_1)$ *if the following inequalities hold*

$$\frac{r_1 d_3}{\beta_2} < A_1^0 <$$

$$\frac{(\beta_2^2 r_2 + \beta_1\beta_2 d_3 - \beta_2\beta_3 r_1 - \beta_3 d_1 d_3)(\beta_1 r_1 - r_2 d_1)}{(\beta_1\beta_2 - \beta_3 d_1)^2}$$

and $\triangle > 0$. *Here*

$$\triangle = (\beta_2 r_1 + d_1 d_3)^2 - 4\beta_2^2 A_1^0 d_1.$$

In addition, the equilibrium $E^1_{(2)}$ *is locally asymptotically stable, while* $E^2_{(2)}$ *is unstable, where*

$$\overline{x} = \frac{\beta_2 r_1 - d_1 d_3 + \sqrt{\triangle}}{2\beta_2 d_1},$$

$$\overline{A}_1 = \frac{\beta_2 r_1 + d_1 d_3 - \sqrt{\triangle}}{2\beta_2^2},$$

$$\overline{\overline{x}} = \frac{\beta_2 r_1 - d_1 d_3 - \sqrt{\triangle}}{2\beta_2 d_1},$$

$$\overline{\overline{A}}_1 = \frac{\beta_2 r_1 + d_1 d_3 + \sqrt{\triangle}}{2\beta_2^2}.$$

Proof: After simple calculate, we can get expressions of two boundary equilibriums $E^1_{(2)}$ and $E^2_{(2)}$. Then by the same way as Theorem 3 (i), this result can be verified. □

Remark From Theorem 3, we know that *toxoplasma gondii* tends to extinction or is also continued survival to reach a new equilibrium. So when antibiotics is used to cure toxoplasmosis, we should pay great attention to the concentration of antibiotics. Otherwise, it would bring serious consequence. For example, Azithromycin under concentration of $20\mu g/ml$ showed definite parasiticidal effect, but under concentration over $80\mu g/ml$ it showed cytotoxic effect to the human foreskin fibnoblast cells. However its inhibitory effect on T. gondii was closely correlated with the doses used [34-37].

4 Immunologic Adjuvant on the Role of Toxoplasmosasis

An immune system is a system of biological structures and processes within an organism that protects against disease by identifying and killing pathogens and tumor cells. It detects a wide variety of agents, from viruses to parasitic worms, and needs to distinguish them from the organism's own healthy cells and tissues in order to function properly. Detection is complicated as pathogens can evolve rapidly, and adapt to avoid the immune system and allow the pathogens to successfully infect their hosts. In general, during the later stages of an infection, leucocytes produce immune responses. In particular, adjuvants in immunology are often used to modify or augment the effects of a vaccine by stimulating the immune system to respond to the vaccine more vigorously, and thus providing increased immunity to a particular disease. Assume that A_2 denotes the density of immunologic adjuvant on human body at time t and A_2^0 is the initial one.

In view of the invasion of *toxoplasma gondii*, leucocytes produce immunologic adjuvant whose increasing rate is denoted by $\beta_1 xy$. The parameter d_3 is the metabolic rate of immunologic adjuvant. For the immunologic adjuvant

$$\begin{cases} x' = x(r_1 - d_1 x + \beta_2 A_2), \\ y' = y(r_2 - d_2 y - \beta_1 x), \\ A_2' = A_2^0 - d_3 A_2 + \beta_1 xy. \end{cases} \tag{15}$$

Theorem 5 *Assume that* $r_2 d_1 > \beta_1 r_1$. *Then the boundary equilibrium*

$$E^0_{(4)} = (\frac{r_1 d_3 + \beta_2 A_2^0}{d_1 d_3}, 0, \frac{A_2^0}{d_3})$$

of system (15) *is locally asymptotically stable if*

$$A_2^0 > \frac{r_2 d_1 d_3 - \beta_1 r_1 d_3}{\beta_1\beta_2}.$$

Proof: By the same way as Theorem 3 (i), this result can be proved. We omit its detail. □

Remark From Theorem 5, we know that *toxoplasma gondii* tends to extinction if the density of immunologic adjuvant on human body at initial time is larger.

Theorem 6 *Assume that* $r_2 d_1 > \beta_1 r_1$. *If*

$$A_2^0 < \frac{r_2 d_1 d_3 - \beta_1 r_1 d_3}{\beta_1\beta_2},$$

then the positive equilibrium $E^*_{(4)} = (x^*, y^*, A_2^*)$ *exists, where*

$$x^* = \frac{\beta_1\beta_2 r_2 d_1 - d_1^2 d_2 d_3 + \sqrt{\triangle}}{2\beta_1^2\beta_2 d_1},$$

$$y^* = \frac{\beta_1\beta_2 r_2 d_1 + d_1^2 d_2 d_3 - \sqrt{\triangle}}{2\beta_1\beta_2 d_1 d_2},$$

$$A_2^* = \frac{\beta_1\beta_2 r_2 d_1 - 2\beta_1^2\beta_2 r_1 - d_1^2 d_2 d_3 + \sqrt{\triangle}}{2\beta_1^2\beta_2^2},$$

and

$$\triangle = (\beta_1\beta_2 r_2 d_1 - 2\beta_1^2\beta_2 r_1 - d_1^2 d_2 d_3)^2$$
$$-4\beta_1^2\beta_2^2(\beta_1^2 r_1^2 - A_2^0 d_1^2 d_2 - \beta_1 r_1 r_2 d_1).$$

Proof: After simple calculate, this result can be proved. We omit verification. □

Theorem 7 *The unique positive equilibrium $E^*_{(4)}$, if it exists, is locally asymptotically stable if the following inequalities hold:*

$$d_1 d_2 > \beta_1\beta_2, \tag{16}$$

$$d_1^2 d_3 x^{*2} + d_2^2 d_3 y^{*2} + d_1 d_2^2 x^* y^{*2} + d_1 d_3^2 x^*$$
$$+d_2 d_3^2 y^* - \beta_1^2\beta_2 x^{*2} y^* > 0. \tag{17}$$

Proof: Assume that the equilibrium $E^*_{(4)}$ exists. Because $E^*_{(4)}$ is the positive equilibrium of system (15), we have

$$r_1 - d_1 x^* + \beta_2 A_2^* = 0;$$
$$r_2 - d_2 y^* - \beta_1 x^* = 0.$$

The linearization of system (15) at this point leads to the following characteristic equation:

$$\begin{vmatrix} -d_1 x^* - \lambda & 0 & \beta_2 x^* \\ -\beta_1 y^* & -d_2 y^* - \lambda & 0 \\ \beta_1 y^* & \beta_1 x^* & -d_3 - \lambda \end{vmatrix} = 0. \tag{18}$$

It is equivalent to

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0,$$

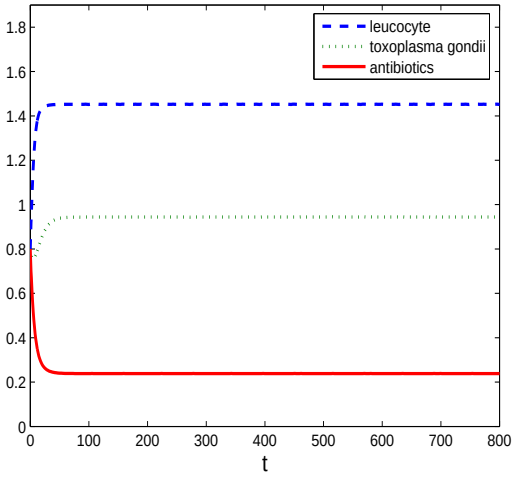
where

$$a_1 = d_1 x^* + d_2 y^* + d_3 > 0;$$
$$a_2 = d_1 d_3 x^* + d_2 d_3 y^* + d_1 d_2 x^* y^* - \beta_1\beta_2 x^* y^*;$$
$$a_3 = \beta_1^2\beta_2 x^{*2} y^* - \beta_1\beta_2 d_2 x^* y^{*2} + d_1 d_2 d_3 x^* y^* > 0.$$

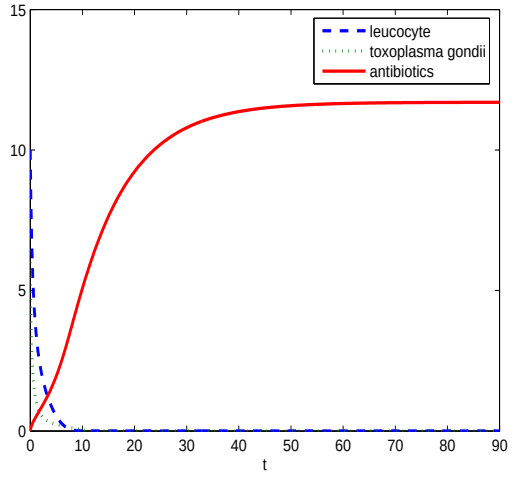
Then

$$a_1 a_2 - a_3 = d_1^2 d_3 x^{*2} + d_2^2 d_3 y^{*2} + d_1 d_2^2 x^* y^{*2} + d_1 d_3^2 x^*$$
$$+d_2 d_3^2 y^* - \beta_1^2\beta_2 x^{*2} y^* + d_3 x^* y^* (2 d_1 d_2 - \beta_1\beta_2)$$
$$+d_1 x^{*2} y^* (d_1 d_2 - \beta_1\beta_2) > 0.$$

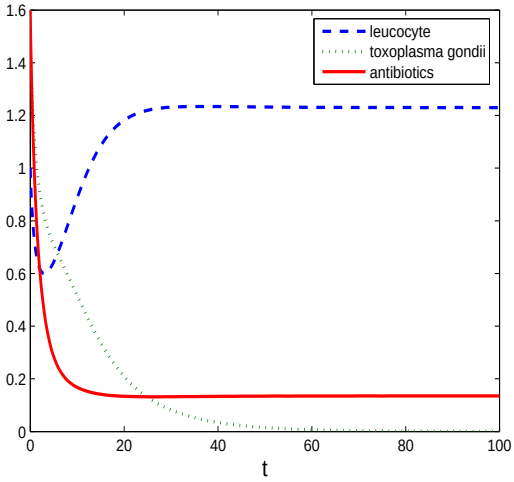
Hence the Routh-Hurwitz conditions are satisfied under the assumptions (16) and (17). Thus it follows that the endemic equilibrium $E^*_{(4)}$ is locally asymptotically stable, whenever it exists. □



(a)

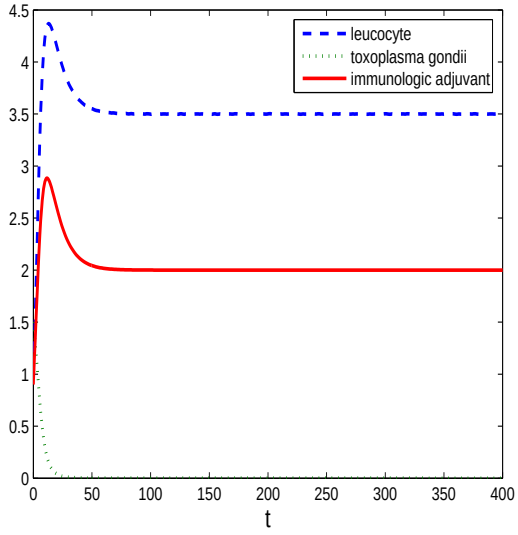


(b)

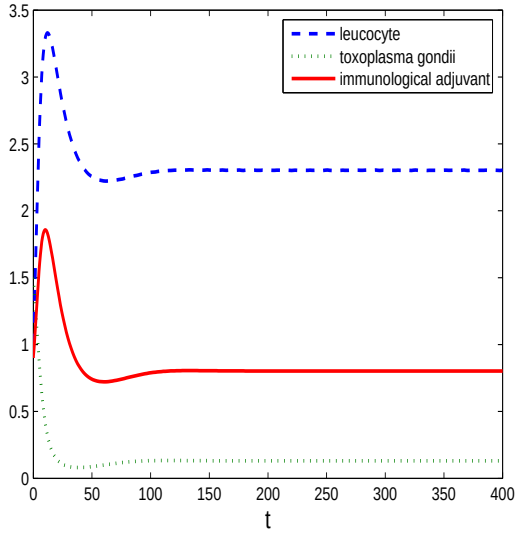


(c)

Figure 2: Dynamic behaviors of system (2) which display the effect of antibiotics on toxoplasmosis

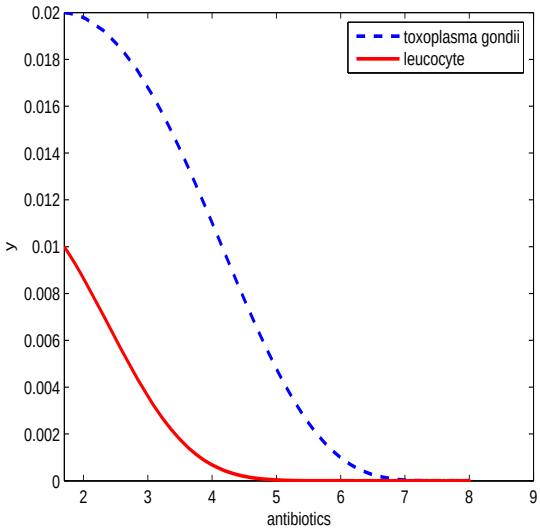


(a)

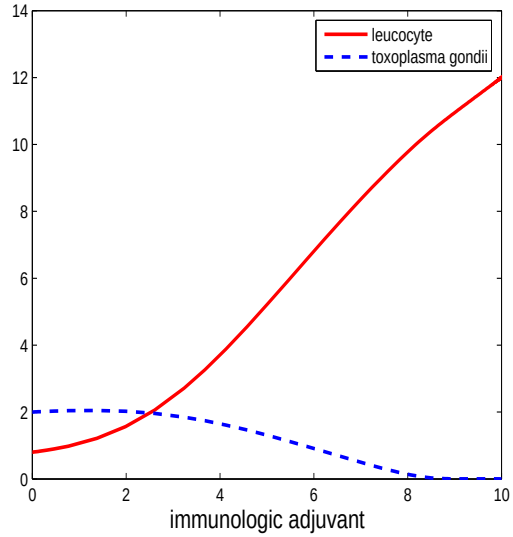


(b)

Figure 3: Dynamic behaviors of system (15) which display the effect of immunologic adjuvant on toxoplasmosis



(a)



(b)

Figure 4: The mechanism of antibiotics and immunologic adjuvant on the role of *toxoplasma gondii* and leucocyte respectively. (a): The effect of antibiotics on the role of leucocyte and *toxoplasma gondii* with parameter value with $r_1 = 0.3, d_1 = 0.2, r_2 = 0.25, d_2 = 0.15, d_3 = 0.1, \beta_1 = 0.25, \beta_2 = 0.4, \beta_3 = 0.15, A_1^0 = 1.2$. (b): The effect of immunologic adjuvant on the role of leucocyte and *toxoplasma gondii* with parameter value with $r_1 = 0.4, d_1 = 0.2, r_2 = 0.3, d_2 = 0.09, d_3 = 0.1, \beta_1 = 0.1, \beta_2 = 0.2, A_2^0 = 1$.

5 Numerical analysis

In this section we present the numerical simulations of the three models. For system (2),

let

$$\begin{array}{lll} r_1 = 0.3, & d_1 = 0.2, & r_2 = 0.25, \\ d_2 = 0.15, & d_3 = 0.01, & \beta_1 = 0.05, \\ \beta_2 = 0.04, & \beta_3 = 0.15, & A_1^0 = 0.05. \end{array}$$

Then $A_{1min}^0 = 0.058$.

Hence $A_1^0 < A_{1min}^0$ and by the Theorem 2, the leucocyte and *toxoplasma gondii* will be uniform persistence (see, Fig. 2(a)).

Let

$$\begin{array}{lll} r_1 = 0.3, & d_1 = 0.2, & r_2 = 0.25, \\ d_2 = 0.15, & d_3 = 0.1, & \beta_1 = 0.25, \\ \beta_2 = 0.4, & \beta_3 = 0.15, & A_1^0 = 1.17. \end{array}$$

Then $A_{1max}^0 = 1.162$.

Hence $A_1^0 > A_{1max}^0$ and by the Theorem 3, the leucocyte and *toxoplasma gondii* will tend to extinction(see, Fig. 2(b)).

Let

$$\begin{array}{lll} r_1 = 0.3, & d_1 = 0.2, & r_2 = 0.25, \\ d_2 = 0.15, & d_3 = 0.1, & \beta_1 = 0.25, \\ \beta_2 = 0.4, & \beta_3 = 0.15, & A_1^{0\prime} = 0.1. \end{array}$$

Then the range of A_1^0 is $[0.075, 0.148]$.

Hence $A_1^{0\prime} \in [0.075, 0.148]$ and by the Theorem 4, *toxoplasma gondii* will tend to extinction under the combined effect of leucocyte and antibiotics.(see, Fig.2(c)).

For system (15), we will study the effect of immunologic adjuvant on the role of *toxoplasma gondii* through numerical simulation. Let

$$\begin{array}{lll} r_1 = 0.3, & d_1 = 0.2, & r_2 = 0.25, \\ d_2 = 0.15, & d_3 = 0.1, & \beta_1 = 0.1, \\ \beta_2 = 0.2, & \beta_3 = 0.1, & \end{array}$$

As parameter $A_2^0 = 0.2$, *toxoplasma gondii* will be exterminated(see, Fig.3(a)). As $A_2^0 = 0.05$, leucocyte, *toxoplasma gondii* and immunologic adjuvant will achieve coexistence(see, Fig.3(b)).

6 Conclusion

In this paper, we propose three mathematical models concerning the effect of leucocyte, antibiotic and immunologic adjuvant against *toxoplasma gondii* respectively.

Firstly, in the case in which toxoplasmosis was inhibited by leucocyte in the host, it is shown that toxoplasmosis can be extincted, when the immunity strength is larger than some threshold.

Secondly, in the case in which antibiotics treatment is used, it is observed that input concentration of antibiotic has significant influence on toxoplasmosis from Theorems 2, 3 and 4. When all assumptions of these three theorems are true, we have:

(1) If the concentration of antibiotics is smaller than some threshold, the fecundity of *toxoplasma gondii* will be dominant at this moment. The leukocyte and *toxoplasma gondii* will reach a new balance.

(2) If the concentration of antibiotics is sufficient large and is larger than another threshold, the inactivation of antibiotics will be in the ascendant. It is remarkable not only to exterminate *toxoplasma gondii* in a large extent but also to sharply reduce the amount of leucocyte showed by Fig.4(a). When the concentration of antibiotic is much greater, it is unfavorable to control infection in this way.

(3) If the concentration of antibiotics is in a suitable range, then the fecundity of *toxoplasma gondii* is in the ascendant, but is perhaps that the inactivation of antibiotics is dominant. It is particularly related to the initial concentration of antibiotics.

Therefore we must pay attention to the input concentration of antibiotics and the initial density of *toxoplasma gondii* when we use antibiotics to cure toxoplasmosis in clinic. Otherwise, it will bring very serious consequences.

Finally, in the case in which immunologic adjuvant was imported to the host body, it can improve immunity of the parasitifer to attain the propose of killing *toxoplasma gondii*. From the Theorems 5, 6 and 7, we find:

(1) Under the conditions (16) and (17), if the concentration of immunologic adjuvant is smaller than some threshold,the proliferation role of *toxoplasma gondii* will be dominated and the infection will persist.

(2) If the concentration of immunologic adjuvant is larger than the threshold, *toxoplasma gondii* will tend to extinct at this time.

Compared with antibiotics, the mechanism of immune adjuvants is to enhance the immune cells to damage the infection ability of toxoplasma showed by Fig.4(b). Obviously, the input concentration of immunologic adjuvant also has a significant impact on *toxoplasma gondii*, so finding a safe and efficient immunologic adjuvant was developed in urgent.

Appendix

Proof: Consider the given system (6) with the denoted right hand sides:

$$\begin{cases} x' = x(r_1 - d_1 x - \frac{\beta_2 A_1^0}{d_3} \doteq P(x,y) \\ y' = y(r_2 - d_2 y - \beta_1 x - \frac{\beta_3 A_1^0}{d_3}) \doteq Q(x,y) \end{cases} \quad (A.1)$$

We have seen that the given system (A.1) has the unique positive equilibrium $E^*_{(3)}$. The following will show the global stability of this equilibrium $E^*_{(3)}$.

According to the linearized system of (A.1), the locality asymptotically stable can be easily proved.

At present, we just need to show that the system (A.1) doesn't exist a closed path in the first quadrant, therefore, we take the Dulac function $B(x,y) = \frac{1}{xy}$, then

$$\frac{\partial(BP)}{\partial x} + \frac{\partial(BQ)}{\partial y} = -\frac{d_1}{y} - \frac{d_2}{x} < 0.$$

Obtained by the Bendixson-Dulac theorem, the positive equilibrium $E^*_{(3)}$ is globally asymptotically stable. This completes the proof. □

Acknowledgements: The research was supported by National Natural Science Foundation of China (grant No. 11101305).

References:

[1] S. A. Elmore1, J. L. Jones, et al, Toxoplasma gondii: epidemiology, feline clinical aspects, and prevention, *Trends in Parasitology*, 26(4), 2010, pp, 190–196.

[2] A. M. Tenter, A. R. Heckeroth and L. M. Weiss, *toxoplasma gondii*: from animals to humans, *Int. J. Parasitol*, 30, 2000, pp, 1217–1258.

[3] J. P. Dubey, J. L. Jones, *toxoplasma gondii* infection in humans and animals in the United States, *Int. J. Parasitol*, 38, 2008, pp, 1257–1278.

[4] L. Kasper, N. Courret, S. Darche, S. Luangsay, F. Mennechet, L. Minns, N. Rachinel, C. Ronet, D. B. Gatel, *toxoplasma gondii* and mucosal immunity, *Int. J. Parasitol*, 34, 2004, pp, 401–409.

[5] R. Thibaut, V. Leroy, A. Alioum, et al. Biases in observational studies of the eff ect of prenatal treatment for congenital toxoplasmosis, *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 124, 2005, pp, 3–9.

[6] L. Gras, RE. Gilbert, AE. Ades, DT. Dunn, Eff ect of prenatal treatment on the risk of intracranial and ocular lesions in children with congenital toxoplasmosis, *Int. J. Epidemiol.*, 30, 2001, pp, 1309–13.

[7] P. MPH. Laura, K. MS. Kristen, et al, Longitudinal Study of New Eye Lesions in Treated Congenital Toxoplasmosis, *Ophthalmology*, 115(3), 2008, pp, 553–559.

[8] R. McLeod, K. Boyer, T. Karrison, et al, Outcome of treatment for congenital toxoplasmosis, 1981-2004: the National Collaborative Chicago-Based Congenital Toxoplasmosis Study, *Clin. Infect. Dis.*, 42, 2006, pp, 1383–94.

[9] R. McLeod, AR. Khan, AG. Noble, et al, Severe sulfadiazine hypersensitivity in a child with reactivated congenital toxoplasmic chorioretinitis, *Pediatr. Infect. Dis. J.* 25, 2006, pp, 270–272.

[10] G. Yan, Update on the treatment of ocular toxoplasmosis, *International Journal of Medical Sciences,* 6(3), 2009, pp, 140–142.

[11] J. P. Dubey, The History of *toxoplasma gondii*-The First 100 Years. *J. Eukaryot. Microbiol.*, 55(6), 2008, pp, 46–66.

[12] T. Lehmann, PL. Marcet, DH. Graham, ER. Dahl, JP. Dubey, Globalization and the population structure of Toxoplasma gondii, *Proc. Natl. Acad. Sci. USA*, 2006, 103, pp, 11423–28.

[13] A. A. Koshy, A. E. Fouts, Toxoplasma secreting Cre recombinase for analysis of host-parasite interactions, *Nature Methods*, 2010, 7(4), pp, 307–401.

[14] J. P. J. Saeij, S. Coller, J. P. Boyle, M. E. Jerome, M. W. White & J. C. Boothroyd, Toxoplasma coopts host gene expression by injection of a polymorphic kinase homologue, *Nature*, 2007, 407, pp, 324–327.

[15] F. A. Diego , R. J. Villanueva, A. J. Arenas, C. Gilberto Mathematical modeling of Toxoplasmosis disease in varying size populations, *Computers and Mathematics with Applications*, 56, 2008, pp, 690–696.

[16] L. M. Ocampo, I. Duarte-Gandica A model of congenital toxoplasmosis transmission dynamics, *Rev. Salud. Publica (Bogota)*, 12(2), 2010, pp, 317–26.

[17] G. C. Gonzlez-Parra , A. J. Arenas, D. F. Aranda, R. J. Villanueva , L. Jdar. Dynamics of a model of Toxoplasmosis disease in human and cat populations, *Computers and Mathematics with Applications*, 57, 2009, pp.1692-1700

[18] M. L*é*lu, M. Langlais, M.-L. Poulle b, E. Gilot-Fromont. Transmission dynamics of *toxoplasma gondii* along an urban-rural gradient, *Theoretical Population Biology*, 78, 2010, pp, 139–147.

[19] J. Wen , A. Sullivan, C. Su, X. Zhao. An agent-based model for the transmission dynamics of *toxoplasma gondii*, *Journal of Theoretical Biology*, 293, 2012, pp, 15–26.

[20] N.E. Mateus-Pinilla, B. Hannon, R.M. Weigel, A computer simulation of the prevention of the transmission of *toxoplasma gondii* on swine farms using a feline T. gondii vaccine, *Preventive Veterinary Medicine*, 55, 2002, pp, 17–36.

[21] J. A. Abraham , G. Gonzlez-Parra, R. J. Villanueva Micó, Modeling toxoplasmosis spread in cat populations under vaccination, *Theoretical Population Biology*, 77, 2010, pp, 227–237.

[22] Russell E. Lyons, Rima McLeod and Craig W. Roberts. *toxoplasma gondii* tachyzoite-bradyzoite interconversion, *TRENDS in Parasitology*, 18(5), 2002, pp, 198–201.

[23] M. Di Cristina, D. Marocco, R. Galizi, C. Proietti, R. Spaccapelo, A. Crisanti, Temporal and Spatial Distribution of *toxoplasma gondii* Differentiation into Bradyzoites and Tissue Cyst Formation In Vivo: *INFECTION AND IMMUNITY*, 76(8), 2008, pp, 3491–3501.

[24] W. B. Michael, J. C. Boothroyd, Lytic Cycle of *toxoplasma gondii*, *microbiology and molecular biology reviews*, 64(3), 2000, pp, 607–623.

[25] P. Zhou, Zh. Chen, H. Li, *toxoplasma gondii* infection in humans in China, *Parasites* & *Vectors*, 4, 2011, pp, 165–174.

[26] J. F. Weston, C. Heuer, N. B. Williamson, Efficacy of a Neospora caninum killed tachyzoite vaccine in preventing abortion and vertical transmission in dairy cattle, *Preventive Veterinary Medicine*, 103, 2012, pp, 136–144.

[27] V. G. Monteiro, E. J. T. de Melo, M. Attias, W. de Souza, Morphological Changes during Conoid Extrusion in *toxoplasma gondii* Tachyzoites Treated with Calcium Ionophore, *Journal of Structural Biology*, 136, 2001, pp, 181–189.

[28] I.G. Mayhew, K.C. Smith, J. P. Dubey, L.K. Gatwards, N.J. McGlennon, Treatment of encephalomyelitis due to Neospora caninum in a litter of puppies, *J Small Anim Pract*, 32, 1991, pp, 609–612.

[29] F. M. Thate, S.C. Laanen, Successful treatment of neosporosis in an adult dog, *Vet. Q.*, 20, 1998, pp, 113–114.

[30] C. Liu, G. Yin, Y. Yue, Y. Zhao, L. Kong, H. Liu, Intranasal Immunization with STAg Plus Propolis Adjuvant protects Mice against *toxoplasma gondii* Infection, *Chin. J. Biol.*, 22, 2009, pp, 887–890.

[31] L. Xu, Q. Yang, Y. Shen, B. Wang, Q. Zeng, Y. Liang, Y. Zhang, H. Wu, The in vitro effects of four antimicrobial agents on *toxoplasma gondii*, *Chin. J. Zoon*, 20, 2004, pp, 885–887.

[32] Q. Shi, B. Hao, Y. Zhou, X. Shi, A. Yang, J. Zhang, Y. Cheng, Z. Li, Experimental study on the in vitro resistance to *toxoplasma gondii* by murine lymphocyte, *Chin. J. Cell. Mol. Immunol.*, 19, 2003, pp, 493–495.

[33] V. Lakshmikantham, V. M. Matrosov, S. Sivasundram, *Vector Lyapunov functions and stability analysis of nonlinear system*, Kluwer Academic Publishers, Dordrecht, 1991.

[34] K. Wang, Z. Qiu, A. Fan, J. Liu, Z. Yuan, G. Deng, Mathematical model of the effect of antibiotics on micro-ecosystem in the host, *Acta academiae medicinae militaris tertiae.*, 25, 2003, pp, 1368–1372.

[35] W. A. Causey, Principles and Practice of Infectious Disease, *JAMA.*, 253, 1985, pp, 3324–3325.

[36] American College of Obstetrics and Gynecologists, Perinatal viral and parasitic infections, *ACOG Practice Bulletin*, 20, 2000, pp, 1–13.

[37] J. A. Morris, Medical Complications During Pregnancy, *JAMA*. 238, 1977, pp, 159–162.