Research article

Dynamics of toxoplasmosis in the cat's population with an exposed stage and a time delay

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Abstract: We propose a new mathematical model to investigate the effect of the introduction of an exposed stage for the cats who become infected with the T. gondii parasite, but that are not still able to produce oocysts in the environment. The model considers a time delay in order to represent the duration of the exposed stage. Besides the cat population the model also includes the oocysts related to the T. gondii in the environment. The model includes the cats since they are the only definitive host and the oocysts, since they are relevant to the dynamics of toxoplasmosis. The model considers lifelong immunity for the recovered cats and vaccinated cats. In addition, the model considers that cats can get infected through an effective contact with the oocysts in the environment. We find conditions such that the toxoplasmosis disease becomes extinct. We analyze the consequences of considering the exposed stage and the time delay on the stability of the equilibrium points. We numerically solve the constructed model and corroborated the theoretical results.

Keywords: toxoplasmosis; cats; oocysts; exposed stage; time delay; stability analysis

1. Introduction

Toxoplasmosis is the main cause of death associated to foodborne illness in the United States. It has been estimated that more than forty million persons in the U.S. carry the Toxoplasma parasite [1, 2]. Toxoplasmosis disease is caused by the protozoan parasite Toxoplasma gondii (T. gondii). In the United States it is estimated that 11% of the population six years and older have been infected with Toxoplasma. In various places throughout the world, it has been shown that more than 60% of some populations have been infected with Toxoplasma. Infection is often highest in areas of the world that have hot, humid climates and lower altitudes, because the oocysts survive better in these types of environments [1–3].

The sexual cycle of T. gondii only takes place in members of the Felidae family and most of the

studies on the sexual cycle have been carried out in cats [3–5]. Due to the difficulties in maintaining and sacrificing cats in the laboratory, there are relatively few papers dealing with the cycle of T. gondii in this host [4]. It has been recently reported that T. gondii sexual development in the intestinal cells of mice under some particular conditions is feasible [4, 6]. Following a period of asexual reproduction by tachyzoite forms, the parasite enters a latent phase in the bradyzoite stage that persists for the host's lifetime in pseudocysts, macrophages and neurons of various tissues, notably in the brain [7, 8].

T. gondii infects terrestrial and aquatic mammals and birds [4]. These animals are intermediate hosts because only asexual stages occur in them [4, 7, 8]. The sexual stages are seen only in the members of the family Felidae, including the domestic cat [3, 4, 9, 10]. The final or definitive host are the cats, and other warm-blooded vertebrates are just intermediate hosts [7, 8]. T. gondii can encysts in the brain, and can inhibit apoptosis [8]. Interestingly, the T. gondii parasite does not disturb the life of cats. It has been estimated that an infected cat can produce approximately 20 million oocysts, between 4 and 13 days after the cat gets infected [11]. Domestic cats are able to excrete oocysts that can infect warm-blooded animals [12]. These oocysts contaminate the environment, including water, vegetables and various foods [13, 14]. However, it has been shown that gamma irradiation can decontaminate food that contains oocysts [14]. Nevertheless, oocysts of T. gondii are spreaded in the environment. Therefore, control strategy studies for the toxoplamosis disease have been related to considering cat populations [15–18]. For a review of mathematical models for toxoplasmosis the reader can see [19].

The seroprevalence related to toxoplasmosis around the world is significantly high with values in the range of $30\% - 40\%$ [20]. In addition, cats are very popular in the world and therefore can contribute to the permanence of the toxoplasmosis disease [21]. One consequence of a high prevalence is that in 2013 congenital toxoplasmosis was estimated to be 1.2 million [19]. The congenital infection affects the eye and it is difficult to diagnose at birth but is present in $20\% - 80\%$ of congenitally infected persons [1]. In Europe all pregnant women are tested for T. gondii infection, but there have been concerns about the cost–benefit of these tests [22].

The study of parasites is very important for the public health [23]. There are many studies that have used mathematical models to investigate the dynamics of a variety of parasites, even though models are simplifications of the real-world [24–26]. For toxoplasmosis dynamics several mathematical models have been proposed [12, 27–29]. For instance, in [30] the author proposed a model to describe the coinfection dynamics of malaria-toxoplasmosis in the human and feline susceptible host population. In [18] the authors developed a differential equation model to investigate the effective transmission pathways of T. gondii and potential control mechanisms. A systematic review of previous mathematical models for the transmission of T. gondii is available in [19].

There are a variety of mathematical models with time delays that have been used in many different fields including biology [31–34]. In particular, there are many mathematical models for studying the dynamics of infectious diseases that are based on delay differential equations [35–38]. For instance, in [39] the authors studied an epidemic model with spatial diffusion and time delay and they found two different types of instability. One due to diffusion, and the other one related to the time delay. The time delays are introduced in order to model the effect of processes that are not instantaneous [40–43]. In [44], the authors studied a SEIS epidemiological model with a saturation incidence rate and a time delay representing the latent period of the disease. There are advantages and disadvantages of using mathematical models based on delay differential equations. For instance, there is more variety of dynamics with delay differential equations in comparison with ordinary differential equations. The

introduction of time delays can change the stability of an equilibrium point and periodic solutions can arise [45–48]. In addition, in general obtaining the solutions of delay differential equations is more challenging than those of the ordinary differential equations [49–52]. There are a variety of analytical and numerical methods that have been developed to find the solutions of delay differential equations [53–56].

In this work, we propose a mathematical model that includes a latent stage for the cats who become infected with the T. gondii parasite, since it is well-known that these cats are not able to produce oocysts instantaneously [3, 5, 7]. We focus on the cats since they are one of the main factors for the permanence of T. gondii in the environment [20]. The time delay represents the duration of the latent stage for the cats. The model also includes the oocysts related to the T. gondii in the environment. The oocysts, are of paramount importance in the survival of the T. gondii [3, 7, 57, 58]. The model considers lifelong immunity for the recovered cats and vaccinated of cats. In addition, the model considers that cats get infected through an effective contact with the oocysts in the environment. The T. gondii parasite can be vertically transmitted and therefore we include this aspect in the model [59]. The model does not consider other intermediate hosts like rodents and birds and this is a limitation of the model. However, the proposed model is an improvement and generalization of the mathematical model presented in [60]. In [60] a model based on ODEs was developed to study the dynamics of toxoplasmosis on the cat populations and taking into account the oocysts that contain the T. gondii parasite. In [61] the authors extended the model to include a time delay between the time from when oocysts become present in the environment and when they become infectious. However, in this study we include the effect of a time delay between the time a cat has an effective contact with the oocysts and the time when the cats become infective and able to shed oocysts in their feces [62, 63]. The entire enteroepithelial cycle of T. gondii can be completed within 3 to 10 days after ingestion of tissue cysts [62]. After the cats ingest sporulated oocysts, the formation of oocysts is delayed until 18 days or more [62]. In other words, a cat can undergo a latent period of a few days before casting feces with oocysts, which may last for 10–15 days [5, 62, 63]. In [63], the authors assumed a short latent period of three days. Thus, based on these aforementioned facts we propose the introduction of a latent stage in the cats and a time delay.

From a mathematical analysis viewpoint we study the stability of the equilibrium points of the model. We use the next generation method to find the basic reproductive number $\mathcal{R}_0$ for the model without the time delay [64, 65]. Then, we study the model with the time delay and see the effects on the dynamics of toxoplasmosis. We numerically solve the delay differential equation system to corroborate the theoretical results and finally we provide additional numerical results to understand better the impact of the length of the delay on the dynamics.

We organized this paper as follows: In Section 2, we develop the model and present the main assumptions. In Section 3, we perform the local and global stability analysis of the steady states. In Section 4, we present a variety of numerical simulations. Finally, in Section 5 we present the conclusions.

2. Materials and methods

Here we present a new mathematical model for the transmission of toxoplasmosis in cat populations taking into account the time delay between the time a cat has an effective contact with the oocysts

and the time when the cats become infective and able to shed oocysts in the feces [3, 5, 11, 62]. As in [60] the mathematical model allows the vaccination of the cats and the infection of cats through effective contacts with oocysts shed by cats. Previous studies have included vaccination for cats [60, 66, 67]. The inclusion of vaccines in the mathematical model makes possible the study of the effect of vaccines on the control of toxoplasmosis. The model assumes that the rate of infection depends on the environmental load of the T. gondii parasite [68]. The proposed model is based on a system of delay differential equations. For more details about the model see [60].

The model divides the cat population into four disjoint subpopulations: susceptible $S(t)$, latent $E(t)$, infected $I(t)$ and recovered $R(t)$ (includes vaccinated cats). The model uses one state variable $O(t)$ for the T. gondii oocysts. The model assumes that vaccinated cats have permanent immunity [16, 66, 69, 70]. Moreover, the model includes a constant proportional vaccination rate, which is a standard way in mathematical modeling of infectious diseases. However, more realistic and complex vaccination types have been used for modeling for studying COVID-19 pandemic [71, 72]. The population of cats is assumed constant. Susceptible cats transit to the latent subpopulation $E(t)$ after an effective contact with an oocyst. The latent stage is included as a time delay of τ. The infected stage lasts an average of $\frac{1}{\alpha}$. The increase in the amount of oocysts is proportional to the infectious cats $I(t)$. In particular, the model assumes that the parameter k is related to the oocysts that are shed per infected cat and per unit time. There is a removal rate of oocysts from the environment. It is assumed vertical transmission in the cat population due to congenital transmission [73–76]. For instance, in [77] the authors studied lactational transmission from infected cats to their kittens.

The mathematical model is based on a nonlinear delay differential equations given by

$$
\begin{aligned}
\dot{S}(t) &= \mu\,(1 - I(t)) - \beta S(t)\,O(t) - (\mu + \gamma)S(t), \\
\dot{E}(t) &= \beta S(t)\,O(t) - \beta\,S(t - \tau)\,O(t - \tau)e^{-\mu\tau} - \mu E(t), \\
\dot{I}(t) &= \beta\,S(t - \tau)\,O(t - \tau)e^{-\mu\tau} - \alpha I(t), \\
\dot{V}_R(t) &= \alpha I(t) + \gamma S(t) - \mu V_R(t), \\
\dot{O}(t) &= k\,I(t) - \mu_0\,O(t).
\end{aligned}
\tag{1}
$$

Without loss of generality, the population of cats is assumed to be $N(t) = S(t) + E(t) + I(t) + V_R(t) = 1$. The mathematical model flow is depicted in Figure 1. The initial conditions at time $t = 0$ are given by
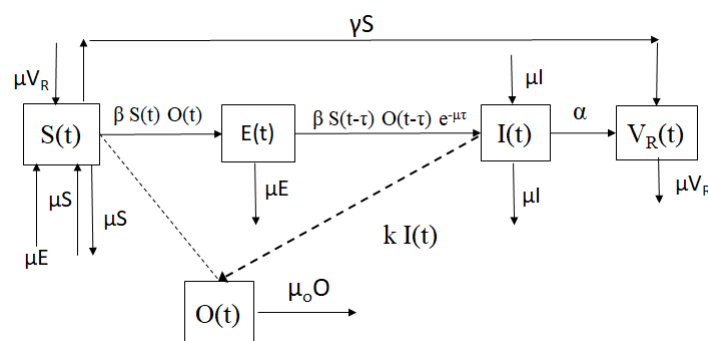

Figure 1. Flow chart of toxoplasmosis transmission dynamics with an exposed stage.

$$
S(0) > 0,\ E(0) \geq 0,\ I(0) \geq 0,\ V_R(0) \geq 0,\ O(0) \geq 0.
\tag{2}
$$

We can disregard the subpopulation $V_R(t)$ and study the following reduced model

$$
\begin{aligned}
\dot{S}(t) &= \mu\,(1 - I(t)) - \beta S(t)\,O(t) - (\mu + \gamma)S(t), \\
\dot{E}(t) &= \beta S(t)\,O(t) - \beta\,S(t - \tau)\,O(t - \tau)e^{-\mu\tau} - \mu E(t), \\
\dot{I}(t) &= \beta\,S(t - \tau)\,O(t - \tau)e^{-\mu\tau} - \alpha I(t), \\
\dot{O}(t) &= k\,I(t) - \mu_0\,O(t).
\end{aligned}
\tag{3}
$$

The reduced system (3) satisfies the initial conditions given by

$$
S(s) = \xi_1(s) > 0,\ s \in [-\tau, 0],\ O(s) = \xi_2(s) \ge 0,\ s \in [-\tau, 0],
\tag{4}
$$

where $\xi_1(s)$ and $\xi_2(s)$ are continuous function defined from the interval $[-\tau, 0]$ to $\mathbb{R}_+$, and with the norm $\|\xi_i\| = \sup_{-\tau \le s \le 0} |\xi_i(s)|$. The susceptible subpopulation of cats is nonnegative for $t \le 0$ and the number of oocysts is nonnegative for $t \le 0$.

3. Stability analysis of the Model

Let's see that in the constructed model the subpopulations are positive for all $t \ge 0$ and that they are bounded.

Theorem 3.1. *If the parameters of model (3) are all positive and the initial conditions given by (4) are satisfied, then the solutions of the model (3) given by $\big(S(t), E(t), I(t), O(t)\big)$ remain positive and uniformly bounded in $[0, +\infty)$.*

Proof. From (3), one gets that

$$
\dot{S}(t) = \mu\,(1 - S(t) - I(t)) - \beta S(t)\,O(t) - \gamma S(t) \ge -\beta S(t)\,O(t) - \gamma S(t).
$$

Thus,

$$
S(t) \ge S(0)\exp\left(-\int_0^t (\beta O(s) + \gamma)\,ds\right) > 0,\ \forall t \ge 0
$$

Let's suppose that there exists a $t_1 > 0$ such that $I(t_1) = 0, \dot{I}(t_1) \le 0$, and $I(t) > 0\ \forall\, t \in (0, t_1)$. Then, from the third equation of model (3), it follows that

$$
0 \ge \dot{I}(t_1) = \beta S(t_1 - \tau)O(t_1 - \tau)e^{-\mu\tau}.
\tag{5}
$$

However, $O(t) > 0$ for all $t \in (0, t_1)$. If this is not the case, there exists a $t_2 > 0$ such that $t_2 < t_1$, $\dot{O}(t_2) \le 0, O(t_2) = 0$ and $O(t) > 0$ for $t \in (0, t_2)$. From the fourth equation of system (3), it follows that $0 \ge kI(t_2)$. This is a contradiction because $I(t) > 0$ for all $t \in (0, t_1)$. Thus, using the continuity of $O(t)$, it follows that $O(t) > 0$, with $t \in (0, t_1]$. Therefore, (5) is false as $\tau \to 0^+$ and thus $I(t) \ge 0$ for $t \ge 0$. From the fourth equation of system (3), it is concluded that $O(t) \ge 0$ for $t \ge 0$. Next, the positivity for $E(t)$ it follows from the fact that solutions of the differential equations of $E(t)$ can be written as

$$
E(t) = e^{-\mu t}\left(E(0) + \int_{t-\tau}^t S(w)O(w)e^{\mu w}\,dw\right).
$$

Now, the subpopulation $S(t)$ is bounded by $\frac{\mu}{\mu+\gamma}$, because by the standard comparison theorem [78], we can show that

$$S(t) \leq S(0) \exp(-(\mu+\gamma)t) + \frac{\mu}{\mu+\gamma}(1 - \exp(-(\mu+\gamma)t)).$$

In particular, if $S(0) \leq \frac{\mu}{\mu+\gamma}$, then $S(t) \leq \frac{\mu}{\mu+\gamma}$. Analogously, one gets that $O(t) \leq \frac{k}{\mu_0}$ if $O(0) \leq \frac{k}{\mu_0}$, $E(t) \leq \frac{\beta k}{(\mu+\gamma)\mu_0}$ if $E(0) \leq \frac{\beta k}{(\mu+\gamma)\mu_0}$, and $I(t) \leq \frac{\beta \mu k e^{-\mu\tau}}{\alpha\mu_0(\mu+\gamma)}$ if $I(0) \leq \frac{\beta \mu k e^{-\mu\tau}}{\alpha\mu_0(\mu+\gamma)}$. Thus, the set

$$O = \left\{(S, E, I, O) \in \mathbb{R}_+^4 / 0 < S \leq \frac{\mu}{\mu+\gamma}, 0 \leq E(t) \leq \frac{\beta k}{(\mu+\gamma)\mu_0}, 0 \leq I \leq \frac{\beta \mu k e^{-\mu\tau}}{\alpha\mu_0(\mu+\gamma)}, 0 \leq O \leq \frac{k}{\mu_0}\right\},$$

is positively invariant. $\qquad\square$

Based on this previous result, we can study the solutions of model (3) in the restricted region O.

3.1. Toxoplasmosis-free equilibrium point

The mathematical model (3) has the following toxoplasmosis-free equilibrium point: $F_0^* = \left(\frac{\mu}{\mu+\gamma}, 0, 0, 0\right)$. This would be the ideal realistic condition where there toxoplasmosis becomes extinct. First, we will analyze the case when there is not time delay (ODE model). Then, we will see the impact of the time delay on the stability of the toxoplasmosis-free equilibrium point. The local stability of F_0^* is determined by the eigenvalues of the Jacobian of the system (3) at F_0^*:

$$J(F_0^*) = \begin{pmatrix} -\gamma-\mu & 0 & -\mu & -\frac{\beta\mu}{\gamma+\mu} \\ 0 & -\mu & 0 & 0 \\ 0 & 0 & \alpha & \frac{\beta\mu}{\gamma+\mu} \\ 0 & 0 & k & -\mu_0 \end{pmatrix}.$$

The eigenvalues are the following $\lambda_1 = -\mu - \gamma$, $\lambda_2 = -\mu$, and the roots of

$$p(\lambda) = (\gamma+\mu)\lambda^2 + (\gamma\alpha + \alpha\mu + \gamma\mu_0 + \mu\mu_0)\lambda - \beta\mu k + \alpha\gamma\mu_0 + \alpha\mu_0\mu.$$

Reordering one gets

$$\lambda^2 + a\lambda + b = 0,$$

where, $a = \alpha + \mu_0$, $b = -\frac{\beta\mu k}{\gamma+\mu} + \alpha\mu_0$. According to the Routh–Hurwitz criterion, if $\frac{k\beta\mu}{\mu+\gamma} < \alpha\mu_0$ one obtains that $p(\lambda)$ has only roots with negative real parts and the toxoplasmosis-free equilibrium point F_0^* is locally asymptotically stable (las). Therefore, one can define the basic reproduction number as

$$\mathcal{R}_0 = \frac{k\beta\mu}{\alpha\mu_0(\gamma+\mu)}. \tag{6}$$

Now we have obtained the following theorem,

Theorem 3.2. *The disease-free equilibrium F_0^* of model (3) with $\tau = 0$ is locally asymptotically stable if $\mathcal{R}_0 < 1$, but unstable if $\mathcal{R}_0 > 1$.*

Proof. It follows from the previous computations. $\qquad\square$

3.2. Toxoplasmosis-free equilibrium point analysis with the time delay

Calculations show that system (3) has the same toxoplasmosis-free equilibrium $F_0^* = \left(\frac{\mu}{\mu+\gamma}, 0, 0, 0\right)$, as the system with $\tau = 0$. Linearizing the system (3) one obtains the following characteristic equation

$$|J_0 + J_\tau e^{-\lambda\tau} - \lambda I| = 0,$$

where

$$J_0(F_0^*) = \begin{bmatrix} -\gamma - \mu & 0 & -\mu & -\frac{\beta\mu}{\gamma+\mu} \\ 0 & -\mu & 0 & \frac{\beta\mu}{\gamma+\mu} \\ 0 & 0 & -\alpha & 0 \\ 0 & 0 & k & -\mu_0 \end{bmatrix}, \qquad J_\tau(F_0^*) = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\frac{\beta\mu e^{-\mu\tau}}{\gamma+\mu} \\ 0 & 0 & 0 & \frac{\beta\mu e^{-\mu\tau}}{\gamma+\mu} \\ 0 & 0 & 0 & 0 \end{bmatrix}.$$

After some simple calculations one gets

$$\left|\lambda I - J_0 - J_\tau e^{-\lambda\tau}\right| = (\lambda + \mu)(\lambda + \gamma + \mu)\, T(\lambda) = 0, \tag{7}$$

where,

$$T(\lambda) = (\gamma + \mu)\lambda^2 + (\gamma\alpha + \alpha\mu + \gamma\mu_0 + \mu\mu_0)\lambda - e^{-\lambda\tau}\beta\mu e^{-\mu\tau}k + \alpha\gamma\mu_0 + \alpha\mu_0\mu.$$

We can see that two eigenvalues are $\lambda_{1,2} = -\mu, -\mu - \gamma$ are negative. The other eigenvalues are the roots of $T(\lambda)$. Now, let's define the basic reproduction number for the delay model (3) as:

$$\mathcal{R}_0^d = \frac{\mu\beta k e^{-\mu\tau}}{\alpha\mu_0(\mu + \gamma)}.$$

Theorem 3.3. *The disease-free equilibrium F_0^* of model (3) is locally asymptotically stable if $\mathcal{R}_0^d < 1$, but unstable if $\mathcal{R}_0^d > 1$.*

Proof. We define from Eq. (7) the following function

$$p(\lambda) = \lambda^2 + a\lambda + b\, e^{-\lambda\tau} + c, \tag{8}$$

where, $a = \alpha + \mu_0$, $b = -\frac{\beta\mu k}{\gamma + \mu}e^{-\mu\tau} = -\mathcal{R}_0^d\alpha\mu_0$, and $c = \alpha\mu_0$. It can be seen that p is a continuous function. Moreover,

$$p(0) = b + c = -\frac{k\beta\mu}{\mu + \gamma}e^{-\mu\tau} + \alpha\mu_0 = \alpha\mu_0(1 - \mathcal{R}_0^d),$$

and

$$\lim_{\lambda\to\infty} p(\lambda) = +\infty.$$

Then, if $\mathcal{R}_0^d > 1$, there is a positive real root, and then the disease free equilibrium is locally unstable. Now, let us consider the case when $\mathcal{R}_0^d < 1$. Notice that when $\tau = 0$, $\mathcal{R}_0^d = \mathcal{R}_0$ and one obtains

$$p(\lambda) = \lambda^2 + a\lambda + \alpha\mu_0(1 - \mathcal{R}_0^d).$$

Thus, all the roots of $p(\lambda)$ have negative real parts by the Routh–Hurwitz criterion. We can see that $p(\lambda)$ does not have nonnegative real solutions because in $p(\lambda)$, it is increasing when $\lambda \geq 0$.

Let us see how the complex roots distribute for the transcendental characteristic equation. If $p(\lambda)$ has roots with nonnegative real parts, they must be complex. Then $p(\lambda)$ must have a pair of purely imaginary solutions. Let us assume that $\lambda = i\,\omega\,(\omega > 0)$ is a root of $p(\lambda)$. Then, using (8) we see that it must satisfy

$$-\omega^2 + a\,i\omega + b\,e^{-i\omega\tau} + c = 0.$$

Separating the real and imaginary part, one obtains

$$-\omega^2 + b\cos(\omega\tau) + c = 0 \implies -\omega^2 + c = -b\cos(\omega\tau),$$

and

$$a\,\omega - b\sin(\omega\tau) = 0 \implies a\,\omega = b\sin(\omega\tau).$$

Adding up the squares of the previous equations, one obtains that

$$\omega^4 + (a^2 - 2c)\,\omega^2 + (c^2 - b^2) = 0. \tag{9}$$

Here, $a^2 - 2c = (\alpha + \mu_0)^2 - 2\alpha\mu_0 = \alpha^2 + \mu_0^2 > 0$ and

$$c^2 - b^2 = (\alpha\mu_0)^2\,(1 - (\mathcal{R}_0^d)^2) > 0,$$

if $\mathcal{R}_0^d < 1$. Thus, all the coefficients of Eq.(9) are positive and therefore Eq.(9) does not have positive real roots. Then, there is no ω such that $i\omega$ is a solution of Eq.(7). Therefore, the real parts of all the eigenvalues of the characteristic Eq.(7) are negative for all $\tau > 0$ and $\mathcal{R}_0^d < 1$. This implies that disease-free equilibrium F_0^* is locally asymptotically stable if $\mathcal{R}_0^d < 1$ for the delayed model (3). $\square$

3.3. Global stability of the disease-free equilibrium

We propose the following theorem.

Theorem 3.4. *The disease-free equilibrium point F_0^* of system (3) is globally asymptotically stable if $\mathcal{R}_0^d \leq 1$.*

Proof. Let us denote by y_t the translation of the solution of the system (3), by $y_t = (S(t + \xi), I(t + \xi), V(t + \xi))$ where $\xi \in [-\tau, 0]$. Define the following Lyapunov function:

$$\mathcal{L}(I(t), S(t), O(t)) = \beta \int_{t-\tau}^{t} S(\xi)\,O(\xi)\,e^{-\mu\tau}\,d\xi + I(t) + \frac{\alpha}{k}\,O(t). \tag{10}$$

Calculating the derivative of $\mathcal{L}(I(t), S(t), O(t))$, one gets that

$$
\begin{aligned}
\mathcal{L}' &= \beta e^{-\mu\tau}\left[S(t)\,O(t) - S(t-\tau)\,O(t-\tau)\right] + I'(t) + \frac{\alpha}{k}O'(t) \\
&= \beta e^{-\mu\tau}\left[S(t)\,O(t) - S(t-\tau)\,O(t-\tau)\right] + \beta\,e^{-\mu\tau}\,S(t-\tau)\,O(t-\tau) - \alpha\,I(t) + \alpha\,I(t) - \mu_0\frac{\alpha}{k}\,O(t) \\
&= \beta S(t)\,O(t)e^{-\mu\tau} - \mu_0\frac{\alpha}{k}\,O(t) \leq \beta\frac{\mu}{\mu+\gamma}\,O(t)\,e^{-\mu\tau} - \mu_0\frac{\alpha}{k}\,O(t) \\
&= \left[\frac{\beta\mu\,e^{-\mu\tau}}{\mu+\gamma} - \mu_0\frac{\alpha}{k}\right]O(t) = \frac{\alpha\,\mu_0}{k}\left[\frac{\beta\,\mu\,k\,e^{-\mu\tau}}{\alpha\,(\mu+\gamma)\mu_0} - 1\right]O(t) = \frac{\alpha\,\mu_0}{k}\left[\mathcal{R}_0^d - 1\right]O(t).
\end{aligned}
$$

Since, we know from the restricted region that $S(t) \leq \frac{\mu}{\mu+\gamma}$, one obtains

$$\mathcal{L}' \leq \frac{\alpha\,\mu_0}{k}\,(\mathcal{R}_0^d - 1)\,O(t).$$

Thus, $\mathcal{L}' \leq 0$ if $\mathcal{R}_0^d \leq 1$. Moreover, $\mathcal{L}(F_0^*) = 0$ and $\mathcal{L}(I(t), S(t), O(t)) > 0$, at any point different than the disease-free equilibrium point F_0^*. Then, F_0^* is globally asymptotically stable. $\qquad\square$

3.4. Local stability analysis of the endemic equilibrium

The endemic equilibrium for the delayed model (3) is

$$E_0^* = (S^*, E^*, I^*, O^*), \tag{11}$$

where

$$S^* = \frac{\alpha\,\mu_0}{\beta\,k\mathrm{e}^{-\mu\tau}}, \tag{12}$$

$$E^* = \frac{\alpha\,(-\mu\,k\beta\,\mathrm{e}^{-\mu\tau} + \alpha\,\gamma\,\mu_0 + \alpha\,\mu_0\,\mu)\,(\mathrm{e}^{-\mu\tau} - 1)}{\beta\,k\mathrm{e}^{-\mu\tau}\,(\mu\,\mathrm{e}^{-\mu\tau} + \alpha)\,\mu} = \frac{\alpha^2\mu_0\,(\gamma + \mu)\left(R_0^d - 1\right)\mathrm{e}^{\mu\tau}\,(\mathrm{e}^{\mu\tau} - 1)}{\beta\,k\,(\alpha\,\mathrm{e}^{\mu\tau} + \mu)\,\mu}, \tag{13}$$

$$I^* = \frac{\mu\,k\beta\,\mathrm{e}^{-\mu\tau} - \alpha\,\mu_0\,(\gamma + \mu)}{\beta\,(\mu\,\mathrm{e}^{-\mu\tau} + \alpha)\,k} = \frac{\alpha\,\mu_0\,(\gamma + \mu)\left(R_0^d - 1\right)}{\beta\,(\mu\,\mathrm{e}^{-\mu\tau} + \alpha)\,k}, \tag{14}$$

$$O^* = \frac{\mu\,k\beta\,\mathrm{e}^{-\mu\tau} - \alpha\,\mu_0\,(\gamma + \mu)}{\beta\,\mu_0\,(\mu\,\mathrm{e}^{-\mu\tau} + \alpha)} = \frac{\alpha\,\left(R_0{}^d - 1\right)(\gamma + \mu)}{\beta\,(\mu\,\mathrm{e}^{-\mu\tau} + \alpha)}. \tag{15}$$

Note, that the endemic point E_0^* exists if and only if $\mathcal{R}_0^d > 1$. The characteristic equation is given by

$$|J_0 + J_\tau\,e^{-\lambda\tau} - \lambda I| = 0, \tag{16}$$

where

$$J_0(E_0^*) = \begin{bmatrix} -\beta\,O^* - \gamma - \mu & 0 & -\mu & -\beta\,S^* \\ \beta\,O^* & -\mu & 0 & \beta\,S^* \\ 0 & 0 & -\alpha & 0 \\ 0 & 0 & k & -\mu_0 \end{bmatrix}, \quad \text{and } J_\tau(E_0^*) = \begin{bmatrix} 0 & 0 & 0 & 0 \\ -\beta\,O^*\,\mathrm{e}^{-\mu\tau} & 0 & 0 & -\beta\,S^*\,\mathrm{e}^{-\mu\tau} \\ \beta\,O^*\,\mathrm{e}^{-\mu\tau} & 0 & 0 & \beta\,S^*\,\mathrm{e}^{-\mu\tau} \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

The characteristic equation of the system can be factored in a long form expression and it can be obtained that one eigenvalue is $\lambda = -\mu$ and the other roots of characteristic equation are given by

$$\lambda^3 + (\beta\,O^* + \alpha + \gamma + \mu + \mu_0)\,\lambda^2$$
$$\left(-k\mathrm{e}^{-\lambda\tau}\beta\,S^*\,\mathrm{e}^{-\mu\tau} + \mathrm{e}^{-\lambda\tau}\beta\,O^*\,\mathrm{e}^{-\mu\tau}\mu + O^*\,\alpha\beta + O^*\beta\,\mu_0 + \alpha\,\gamma + \gamma\,\mu_0 + \alpha\,\mu + \alpha\,\mu_0 + \mu\,\mu_0\right)\lambda$$
$$-\,\mathrm{e}^{-\lambda\tau}\mathrm{e}^{-\mu\tau}O^*\,\beta^2 kS^* + \mathrm{e}^{-\lambda\tau}\mathrm{e}^{-\mu\tau}S^*\,\beta^2 kO^* - \mathrm{e}^{-\lambda\tau}\mathrm{e}^{-\mu\tau}\gamma\,\beta\,kS^* - \mathrm{e}^{-\lambda\tau}\mathrm{e}^{-\mu\tau}\beta\,k\mu\,S^* + \mathrm{e}^{-\lambda\tau}\mathrm{e}^{-\mu\tau}\beta\,\mu\,\mu_0\,O^*$$
$$+\,O^*\,\alpha\beta\,\mu_0 + \alpha\,\gamma\,\mu_0 + \alpha\,\mu\,\mu_0 = 0. \tag{17}$$

Rewriting, one gets

$$\lambda^3 + A\lambda^2 + B\lambda + C = e^{-\lambda\tau} (T_1 \lambda + T_2), \tag{18}$$

where

$$
\begin{aligned}
A &= \beta O^* + \alpha + \gamma + \mu + \mu_0, \\
B &= O^* \alpha\beta + O^* \beta\mu_0 + \gamma\alpha + \alpha\mu + \alpha\mu_0 + \gamma\mu_0 + \mu\mu_0, \\
C &= \alpha\mu_0 (\beta O^* + \gamma + \mu) = O^* \alpha\beta\mu_0 + \alpha\mu_0 (\gamma + \mu), \\
T_1 &= e^{-\mu\tau}\beta k S^* - e^{-\mu\tau}\beta\mu O^* = \alpha\mu_0 - e^{-\mu\tau}\beta\mu O^*, \\
T_2 &= e^{-\mu\tau}(\gamma\beta k S^* + \beta k\mu S^* - \beta\mu\mu_0 O^*) = \alpha\mu_0 (\gamma + \mu) - e^{-\mu\tau}\beta\mu\mu_0 O^*,
\end{aligned}
$$

where $A, B, C > 0$. Rewriting Eq.(18), one obtains

$$\lambda^3 + A\lambda^2 + (O^* \alpha\beta + O^* \beta\mu_0 + \gamma\alpha + \alpha\mu + \gamma\mu_0 + \mu\mu_0)\,\lambda + O^* \alpha\beta\mu_0$$
$$= \left(\alpha\mu_0(e^{-\mu\tau} - 1) - e^{-(\mu+\lambda)\tau}\beta\mu O^*\right)\lambda + \alpha\mu_0 (\mu + \gamma)(e^{-\mu\tau} - 1) - e^{-(\mu+\lambda)\tau}\beta\mu\mu_0 O^*.$$

Then, one gets

$$\lambda^3 + \tilde{A}\lambda^2 + \tilde{B}\lambda + \tilde{C} = \tilde{T}_1 \lambda + \tilde{T}_2, \tag{19}$$

where

$$
\begin{aligned}
\tilde{A} &= A > 0, \\
\tilde{B} &= O^* \alpha\beta + O^* \beta\mu_0 + \gamma\alpha + \alpha\mu + \gamma\mu_0 + \mu\mu_0 > 0, \\
\tilde{C} &= O^* \alpha\beta\mu_0 > 0, \\
\tilde{T}_1 &= -\alpha\mu_0(1 - e^{-\mu\tau}) - e^{-(\mu+\lambda)\tau}\beta\mu O^* < 0, \\
\tilde{T}_2 &= -\alpha\mu_0 (\mu + \gamma)(1 - e^{-\mu\tau}) - e^{-(\mu+\lambda)\tau}\beta\mu\mu_0 O^* < 0.
\end{aligned}
$$

These inequalities are valid if $\mathcal{R}_0^d > 1$. Then, the left-hand side of Eq. (19) is positive and the right-hand side is negative for all $\lambda \geq 0$. Therefore, for any $\lambda \geq 0$, Eq. (18) cannot have real non-negative solutions.

Let us consider the complex roots and assume that $\lambda = i\omega\,(\omega > 0)$ is a root of Eq.(18). This occurs if and only if ω is a solution of,

$$-i\omega^3 - A\omega^2 + B i\omega + C = e^{-i\omega\tau} [i\omega T_1 + T_2] = (\cos(\omega\tau) - i\sin(\omega\tau))[i\omega T_1 + T_2].$$

We can obtain the following equations for the imaginary and real parts respectively,

$$-\omega^3 + B\omega = T_1 \omega \cos(\omega\tau) - T_2 \sin(\omega\tau), \tag{20}$$

and

$$-A\omega^2 + C = T_2 \cos(\omega\tau) + T_1 \omega \sin(\omega\tau). \tag{21}$$

Squaring Eqs. (20) and (21), one gets

$$\omega^6 - 2B\omega^4 + B^2 \omega^2 = T_1^2 \omega^2 \cos^2(\omega\tau) - 2T_1 T_2 \omega \cos(\omega\tau) \sin(\omega\tau) + T_2^2 \sin^2(\omega\tau),$$

and
$$A^2\omega^4 - 2AC\,\omega^2 + C^2 = T_2^2\,\cos^2(\omega\tau) + 2T_1T_2\,\omega\,\cos(\omega\tau)\,\sin(\omega\tau) + T_1^2\,\omega^2\,\sin^2(\omega\tau).$$

Adding these squares, we get the following result,

$$\omega^6 + (A^2 - 2B)\,\omega^4 + (B^2 - 2AC)\,\omega^2 + C^2 = T_1^2\,\omega^2 + T_2^2.$$

Reordering,

$$\omega^6 + (A^2 - 2B)\,\omega^4 + (B^2 - 2AC - T_1^2)\,\omega^2 + C^2 - T_2^2 = 0. \tag{22}$$

Making the change of variable $z = \omega^2$, one gets

$$z^3 + (A^2 - 2B)\,z^2 + (B^2 - 2AC - T_1^2)\,z + C^2 - T_2^2 = 0. \tag{23}$$

Then,

$$z^3 + D\,z^2 + E\,z + F = 0, \tag{24}$$

where, $D = A^2 - 2B$, $E = B^2 - 2AC - T_1^2$ and $F = C^2 - T_2^2$. These particular coefficients are given by

$$\begin{aligned}
D &= A^2 - 2B \\
&= (O^*\beta + \alpha + \gamma + \mu + \mu_0)^2 - 2\,O^*\alpha\beta - 2\,O^*\beta\mu_0 - 2\,\alpha\gamma - 2\,\alpha\mu - 2\,\mu_0\,\alpha - 2\,\gamma\mu_0 - 2\,\mu\mu_0 \\
&= \gamma^2 + 2\,(O^*\beta + \mu)\,\gamma + O^{*2}\beta^2 + 2\,O^*\beta\mu + \mu^2 + \alpha^2 + \mu_0{}^2 > 0,
\end{aligned}$$

$$\begin{aligned}
F = C^2 - T_2^2 &= (O^*\,\alpha\beta\mu_0 + \alpha\mu_0\,(\gamma + \mu))^2 - (\alpha\mu_0\,(\gamma + \mu) - \mathrm{e}^{-\mu\tau}\beta\mu\mu_0\,O^*)^2 \\
&= \beta\mu_0{}^2 O^*\,(\mathrm{e}^{-\mu\tau}\mu + \alpha)\,(-\mathrm{e}^{-\mu\tau}\beta\mu\,O^* + \alpha\beta\,O^* + 2\,\alpha\gamma + 2\,\alpha\mu) \\
&= \beta\mu_0{}^2 O^*\,(\mathrm{e}^{-\mu\tau}\mu + \alpha)\,(\beta\,O^*\,(\alpha - \mathrm{e}^{-\mu\tau}\mu) + 2\,(\gamma + \mu)\alpha) > 0,
\end{aligned}$$

and

$$\begin{aligned}
E &= B^2 - 2AC - T_1^2 \\
&= (O^*\,\alpha\beta + O^*\beta\mu_0 + \gamma\alpha + \alpha\mu + \alpha\mu_0 + \gamma\mu_0 + \mu\mu_0)^2 \\
&\quad - 2\,(O^*\beta + \alpha + \gamma + \mu + \mu_0)\,(O^*\,\alpha\beta\mu_0 + \alpha\gamma\mu_0 + \alpha\mu\mu_0) - (\alpha\mu_0 - \mathrm{e}^{-\mu\tau}\beta\mu\,O^*)^2 \\
&= \beta^2 O^{*2}\,(\alpha - \mathrm{e}^{-\mu\tau}\mu)\,(\mathrm{e}^{-\mu\tau}\mu + \alpha) + 2\,\mathrm{e}^{-\mu\tau}\alpha\beta\mu\mu_0\,O^* + \beta^2\mu_0{}^2 O^{*2} + 2\,\gamma\,\alpha^2\beta\,O^* \\
&\quad + 2\,\alpha^2\beta\mu\,O^* + 2\,\gamma\beta\mu_0{}^2 O^* + 2\,\beta\mu\mu_0{}^2 O^* + \gamma^2\alpha^2 + 2\,\gamma\,\alpha^2\mu + \alpha^2\mu^2 + \gamma^2\mu_0{}^2 + 2\,\gamma\mu\mu_0{}^2 + \mu^2\mu_0{}^2 > 0.
\end{aligned}$$

The coefficient D is positive for all values of the parameters. On the other hand, E and F are positive for $\alpha \geq \mathrm{e}^{-\mu\tau}\mu$. This last inequality is true from biological facts since α is the reciprocal of the average infectious time for the toxoplasmosis disease and μ is the reciprocal of the average lifespan of the cats.

Lemma 3.5. *If D, E and F are non-negative, then Eq.(24) has no positive real roots.*

Proof. Let $p(\xi) = \xi^3 + D\,\xi^2 + E\,\xi + F$. Deriving with respect to ξ, one obtains that $p'(\xi) = 3\xi^2 + 2D\,\xi + E$. Where $\xi = \omega^2 > 0$, $D \geq 0$, $E \geq 0$ and $F \geq 0$. Thus, $p'(\xi) > 0$, so $p(\xi)$ increases for $\xi \geq 0$. Then, since $p(0) = F \geq 0$, then Eq.(24) has no positive real roots. □

Then we can conclude that there is no complex root of the form $\lambda = i\omega$ such that it is a solution of Eq. (18). Then using Rouché's theorem one can conclude that the real parts of all the roots of Eq.(18) are negative $\forall \tau \geq 0$, [79]. Thus, if $\alpha \geq e^{-\mu\tau}\mu$ the endemic equilibrium E_0^* is stable for any time delay τ (with $\mathcal{R}_0^d > 1$).

From a biological viewpoint we have proven that for any time delay τ such that $\mathcal{R}_0^d > 1$, the endemic equilibrium point E_0^* would not loose its stability. This is important to know since it means that even if the exposed stage is large then the crucial parameter is the basic reproduction number $\mathcal{R}_0^d$ for the delayed model (3). We will perform numerical simulations to support the theoretical results obtained in this section.

4. Numerical simulations

Here, some numerical simulations are presented to support our proposed theoretical results. We vary some of the values of the parameters for the numerical simulations. For some cases we obtain the disease-free equilibrium and for other ones we obtain the endemic steady state depending on the value of the basic reproduction number of the delayed model (3). We also vary the time delays and therefore obtain different values of the basic reproduction number $\mathcal{R}_0^d$. In addition, the numerical simulations allow us to explore the dynamics of toxoplasmosis.

We use Matlab to calculate the numerical solutions and the built-in function dde23 for delay differential equations [52, 55]. We use mostly the parameter values (using weeks as the time unit) provided in Table 1. For instance, for the vaccination rate we use a value of $\gamma = 0.001$ which means that 0.1% of the susceptible population in some particular region is vaccinated per week. In reality, this could vary depending on many factors such as vaccine availability and willingness to vaccinate the cats. The transmission rate β varies for different regions and it is difficult to estimate due to the lack of real data regarding longitudinal data related to toxoplasmosis prevalence in cats. The initial conditions are varied in order to observe the local and global stability behaviors.

Table 1. Values of the parameters for the base case for model (3).

Parameter	Description	Value
μ	Birth/Death rates (cats)	$1/260$ (1/weeks) [80]
α	Shedding period	$1/2$ (1/weeks) [11]
μ_0	Clearance rate	$1/26$ (1/day) [11, 68]
k	Oocysts per day (cat)	20×10^6 (1/day) [81]
β	Transmission rate	$[0.1 - 0.5] \times 10^{-9}$ (1/oocyst)
γ	Vaccination rate	0.001 (1/day)

4.1. Stability for the disease-free equilibrium point

Here we set a time delay $\tau \neq 0$ and a transmission rate β that allows us to obtain $\mathcal{R}_0^d < 1$. Fig. 2 depicts the dynamics of the different subpopulations of cats and the oocysts. It can be seen that the system reaches the disease free equilibrium F_0^*. Fig. 3 shows the dynamics when the time delay is large ($\tau = 10$), $\mathcal{R}_0 > 1$ and $\mathcal{R}_0^d < 1$. We can see that the system again approaches the disease free

equilibrium F_0^* despite $\mathcal{R}_0 > 1$. Notice that the endemic equilibrium point E_0^* exists, but the system does not approach to it. These results support our previous theoretical results where it was concluded that if $\mathcal{R}_0^d < 1$ regardless of the initial conditions the disease becomes extinct (global stability). From a biological viewpoint this means that the duration of the exposed stage can affect the steady state and to the possibility of toxoplasmosis becoming extinct.
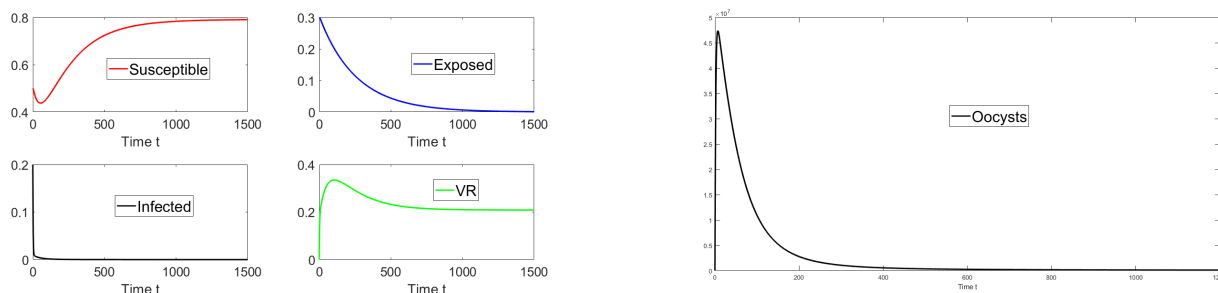

Figure 2. Dynamics of the different subpopulations of cats when $\beta = 0.17 \times 10^{-9}$, $\gamma = 0.001$, $\tau = 1$, $\mathcal{R}_0 \approx 0.9911$ and $\mathcal{R}_0^d \approx 0.9892$. The initial condition is $S(0) = 0.5$, $E(0) = 0.3$, $I(0) = 0.3$, $V_R(0) = 0$ and $O(0) = 300$.
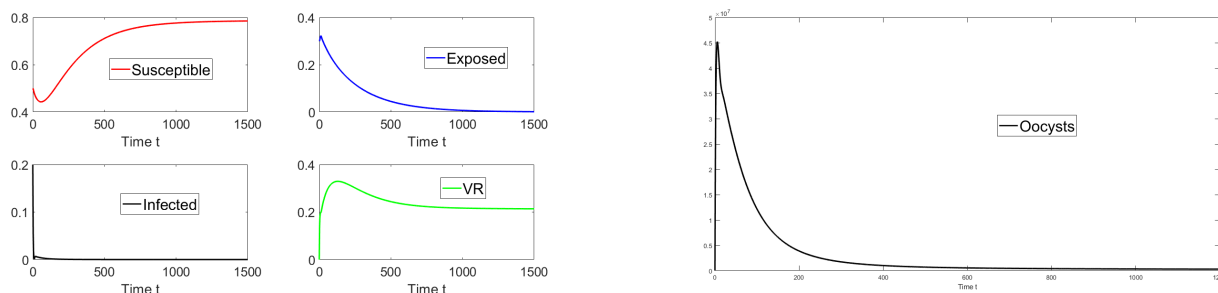
Figure 3. Dynamics of the different subpopulations of cats when $\beta = 0.179 \times 10^{-9}$, $\gamma = 0.001$, $\tau = 10$, $\mathcal{R}_0 \approx 1.017$ and $\mathcal{R}_0^d \approx 0.9976$. The initial condition is $S(0) = 0.5$, $E(0) = 0.3$, $I(0) = 0.3$, $V_R(0) = 0$ and $O(0) = 300$.

4.2. Stability for the endemic equilibrium point

In this subsection we assume parameter values such that $\mathcal{R}_0^d > 1$. Based on the theoretical results the system must reach the endemic steady state E_0^*. Fig. 4 depicts the dynamics of the subpopulations when $\mathcal{R}_0^d > 1$. As our theoretical results predicted, the system reaches the endemic steady state E_0^*. Notice that despite the time delay in the model the stability of the endemic steady state E_0^* is maintained. We consider a hypothetical case where the time delay (duration of the exposed stage) is very large. Fig. 5 shows the dynamics when $\tau = 100$. Note, that the endemic steady state E_0^* keeps its stability, but some oscillations appear. All these previous numerical results agree with our theoretical results.
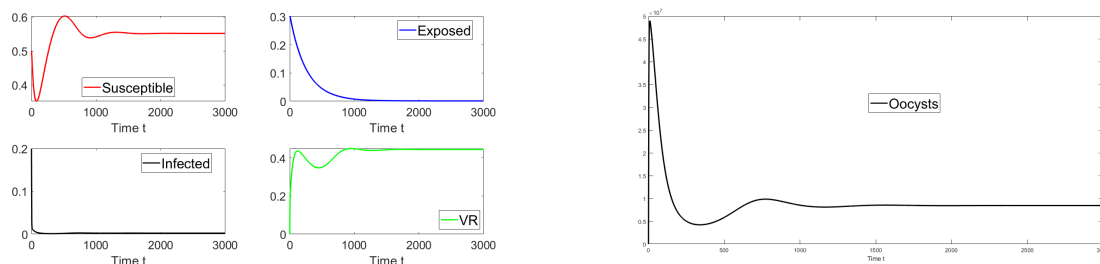
Figure 4. Dynamics of the different subpopulations of cats when $\beta = 0.25 \times 10^{-9}$, $\gamma = 0.001$, $\tau = 1$, $\mathcal{R}_0 \approx 1.20$ and $\mathcal{R}_0^d \approx 1.199$. The initial condition is $S(0) = 0.5$, $E(0) = 0.3$, $I(0) = 0.3$, $V_R(0) = 0$ and $O(0) = 300$.
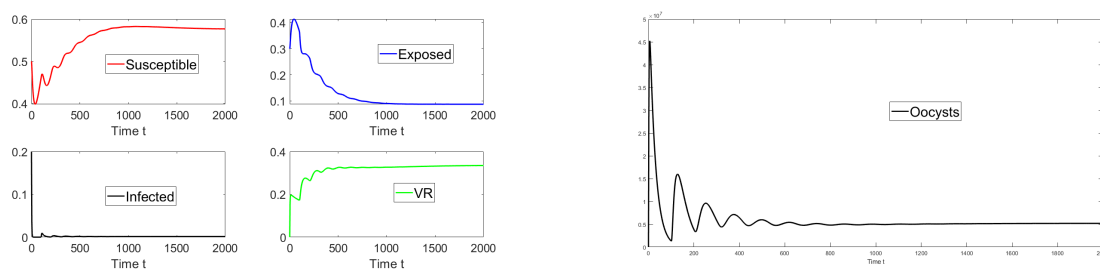

Figure 5. Dynamics of the different subpopulations of cats when $\beta = 0.35 \times 10^{-9}$, $\gamma = 0.001$, $\tau = 100$, $\mathcal{R}_0 \approx 1.42$ and $\mathcal{R}_0^d \approx 1.17$. The initial condition is $S(0) = 0.5$, $E(0) = 0.3$, $I(0) = 0.3$, $V_R(0) = 0$ and $O(0) = 300$.

4.3. Effect of the duration of the exposed stage

The duration of the exposed stage is closely related to the time delay τ. We perform numerical simulations varying the time delay to see the effect of the duration of the exposed stage on the dynamics of the toxoplasmosis disease. Fig. 6 depicts the transient behavior of the system (3). We perform the simulations for the case when $\mathcal{R}_0 > 1$ since it has more interesting dynamics. It can be seen that the transient behavior of the solutions is different when the time delay is varied.

It can be seen from Fig. 6 that the time delay has some effects on the transient behavior of the different subpopulations as expected. Notice that main changes occur at $t = \tau$. The infected cats and oocysts are the main driven factors of the diseases and they are clearly correlated. For instance, at $t = 100$ and when $\tau = 100$, the infected cats increase abruptly since all the effective contacts between susceptible cats and oocysts at $t = 0$ now appear in the infected subpopulation. Then, right away there is an increase in the amount of oocysts in the environment since infected cats produce oocysts. As a consequence at $t = 100$ the susceptible population starts to decrease again due to the increase of oocysts. This effect is also shown in the exposed subpopulation of cats, but to a lesser degree because some exposed cats are continuously leaving the exposed stage. Notice that if the numerical simulation is performed for a very long time the system will reach the endemic state E_0^* since $\mathcal{R}_0^d > 1$ for all cases. Thus, we can say that the time delay clearly can affect the transient dynamics. However, the steady state only can be changed if $\mathcal{R}_0^d$ increases its value to more than one, as the theoretical results pointed out. However, it is important to remark that increasing the time delay decreases $\mathcal{R}_0^d$ and therefore the

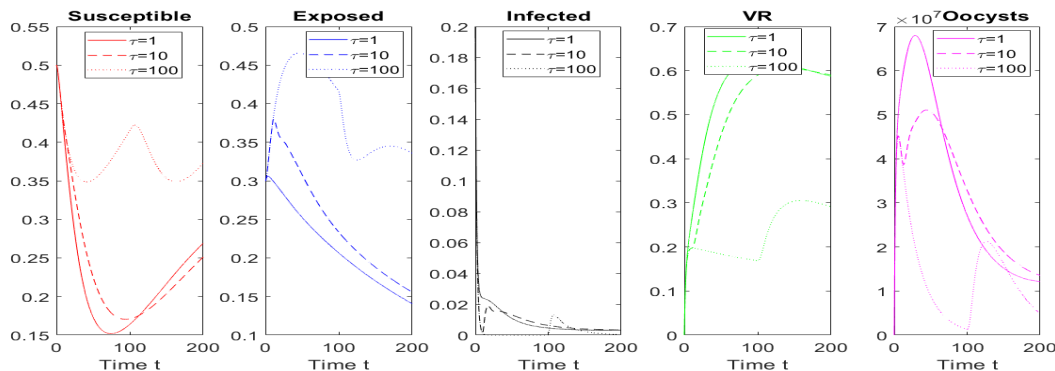disease free steady state can be reached.

Figure 6. Different graphs when the time delay is varied. The parameter values are $\beta = 0.5 \times 10^{-9}$, $\gamma = 0.001$, $\tau = 100$ and $\mathcal{R}_0^d > 1$. The initial condition is $S(0) = 0.5$, $E(0) = 0.3$, $I(0) = 0.3$, $V_R(0) = 0$ and $O(0) = 300$.

5. Conclusions

We proposed a new mathematical model to investigate the effect of the introduction of an exposed stage for the cats who become infected with the T. gondii parasite, but that are not still able to produce oocysts in the environment. We introduce in the model a time delay that represents the duration of the exposed stage. The model includes the cat population and also the oocysts related to the T. gondii in the environment. A key part of the model is the inclusion of the cats since they are the only definitive host. In addition, the spread of the toxoplasmosis is mainly through the oocysts in the environment. As any mathematical model there are certain assumptions that were made. The model considers lifelong immunity for the recovered cats and vaccinated cats. The cats can get infected by contact with the oocyst.

In this study we found the conditions such that the toxoplasmosis disease becomes extinct and also when it persists. We considered a fixed duration for the exposed stage using a time delay in the mathematical model. We analyzed the disease dynamics and in particular on the stability of the equilibrium points. We computed and used the characteristic equations to study the local stability of the equilibrium points. We found the particular basic reproduction number $\mathcal{R}_0^d$ of the mathematical model with a time delay. We found this basic reproduction number of the delayed model includes the time delay. We prove that if $\mathcal{R}_0^d <$ is less than unity, the disease-free equilibrium is locally asymptotically stable. On the other hand, if $\mathcal{R}_0^d > 1$, the endemic equilibrium is locally asymptotically stable. The global stability of the disease-free equilibrium was established by using the Lyapunov-LaSalle theorem. In particular, if $\mathcal{R}_0^d < 1$ the disease-free equilibrium is globally asymptotically stable and the toxoplasmosis becomes extinct in the long term. We obtained that if $\mathcal{R}_0^d > 1$, then the time delay representing the fixed duration of the exposed stage has no effect on the stability of the endemic equilibrium point and therefore does not induce periodic solutions and Hopf bifurcations cannot occur.

In general, our results allow us to get deeper insight on the dynamics of the toxoplasmosis disease. Some parameters were taken from the literature related to toxoplasmosis. However, some of them have a degree of uncertainty as is common in biological processes. We found that the basic reproduction

number $\mathcal{R}_0^d$ decreases as the time delay increases and therefore this time delay can help to control the toxoplasmosis disease. It is important to remark that the temperature might have some influence on the duration of the exposed stage and therefore on the time delay. Thus, climate change can modify the time delay and the dynamics of the toxoplasmosis. From the mathematical expression of the basic reproduction number $\mathcal{R}_0^d$ we can see that the mean infectious period, the vaccination rate, the removal rate of oocysts and the time delay affect the value of the basic reproduction number and the endemic equilibrium point. For instance, all these parameters increase, the basic reproduction number $\mathcal{R}_0^d$ decreases and then this has positive control effects on the toxoplasmosis disease. We numerically solved the delayed mathematical model for a variety of parameters' values and the theoretical numerical results were in good agreement with the theoretical ones. We would like to remark that if $\mathcal{R}_0^d > 1$, then the endemic equilibrium didn't lose stability regardless of the time delay. It is important to point out that our theoretical results are valid regardless of the parameter values. We used some particular values to show graphically few toxoplasmosis dynamics that agree with the theoretical results. In reality, the vaccination rate would vary depending on many factors such as vaccine availability and willingness to vaccinate the cats. Regarding the transmission rate this varies for different regions and it is difficult to estimate due to the lack of real data regarding longitudinal data related to toxoplasmosis prevalence in cats.

The proposed mathematical model allows the assessment of various control strategies against toxoplasmosis. For instance, the implementation of vaccination programs for cats can reduce the prevalence of toxoplasmosis. Optimal control can be used to determine the best strategy if costs of each strategy are established. As a good research practice we would like to point out a few limitations of this work, but there are others. The model studied in this work has an important limitation since it does not consider other intermediate hosts. However, since the only definitive host are the cats it is crucial to have models that include them and it is expected that they are the main driving force of toxoplasmosis [7, 8]. Further studies that include additional intermediate hosts are necessary to get deeper insight in the toxoplasmosis dynamics. In addition, the well-known homogeneous mixing assumption might not represent reality. One key assumption and limitation is the permanent immunity of vaccinated cats. This aspect would need further studies and the design of a new mathematical model and analysis. The mathematical model assumes exponential transitions between most of the subpopulations and this is not exactly what happens in the real world. Some authors have proposed models using gamma distributions, but this requires much more equations [82–85]. The value of the crucial transmission rate is unknown and can vary depending on the region. This requires much further biological field study. We expect in future works to consider other hosts. Finally, we would like to point out that this type of studies provide deeper insight into the toxoplasmosis disease and can help health authorities to reduce the prevalence of toxoplasmosis.

Conflict of interest

The authors declare there is no conflict of interest.

References

1. CDC, Center for disease control and prevention, toxoplasmosis, 2021. Available from: https://www.cdc.gov/parasites/toxoplasmosis

2. J. P. Dubey, Outbreaks of clinical toxoplasmosis in humans: Five decades of personal experience, perspectives and lessons learned, *Parasite. Vector.*, **14** (2021), 1–12. https://doi.org/10.1186/s13071-021-04769-4

3. J. P. Dubey, The history of Toxoplasma gondii?the first 100 years, *J. Eukaryot. Microbiol.*, **55** (2008), 467–475. https://doi.org/10.1111/j.1550-7408.2008.00345.x

4. M. Attias, D. E. Teixeira, M. Benchimol, R. C. Vommaro, P. H. Crepaldi, W. De Souza, The life-cycle of toxoplasma gondii reviewed using animations, *Parasit. Vector.*, **13** (2020), 1–13. https://doi.org/10.1186/s13071-020-04445-z

5. J. Dubey, History of the discovery of the life cycle of toxoplasma gondii, *Int. J. Parasitol.*, **39** (2009), 877–882. https://doi.org/10.1016/j.ijpara.2009.01.005

6. B. M. Di Genova, S. K. Wilson, J. Dubey, L. J. Knoll, Intestinal delta-6-desaturase activity determines host range for toxoplasma sexual reproduction, *PLoS Biol.*, **17** (2019), e3000364. https://doi.org/10.1371/journal.pbio.3000364

7. J. Dubey, Advances in the life cycle of toxoplasma gondii, *Int. J. Parasitol.*, **28** (1998), 1019–1024. https://doi.org/10.1016/S0020-7519(98)00023-X

8. F. Thomas, K. D. Lafferty, J. Brodeur, E. Elguero, M. Gauthier-Clerc, D. Missé, Incidence of adult brain cancers is higher in countries where the protozoan parasite toxoplasma gondii is common, *Biol. Letters*, **8** (2012), 101–103. https://doi.org/10.1098/rsbl.2011.0588

9. J. Dubey, C. Beattie, *Toxoplasmosis of Animals and Man*, CRC Press, Boca Raton, FL., 1988.

10. J. Dubey, D. Lindsay, C. Speer, Structures of Toxoplasma gondii tachyzoites, bradyzoites, and sporozoites and biology and development of tissue cysts, *Clin. Microbiol. Rev.*, **11** (1998), 267–299. https://doi.org/10.1128/CMR.11.2.267

11. J. Dubey, Duration of Immunity to Shedding of Toxoplasma gondii Oocysts by Cats, *J. Parasitol.*, **81** (1995), 410–415. https://doi.org/10.2307/3283823

12. J. A. Simon, R. Pradel, D. Aubert, R. Geers, I. Villena, M.-L. Poulle, A multi-event capture-recapture analysis of Toxoplasma gondii seroconversion dynamics in farm cats, *Parasit. Vector.*, **11** (2018), 1–13. https://doi.org/10.1186/s13071-018-2834-4

13. J. Aramini, C. Stephen, J. P. Dubey, C. Engelstoft, H. Schwantje, C. S. Ribble, Potential contamination of drinking water with Toxoplasma gondii oocysts, *Epidemiol. Infect.*, **122** (1999), 305–315. https://doi.org/10.1017/S0950268899002113

14. J. P. Dubey, D. W. Thayer, C. A. Speer, S. K. Shen, Effect of gamma irradiation on unsporulated and sporulated Toxoplasma gondii oocysts, *Int. J. Parasitol.*, **28** (1998), 369–375. https://doi.org/10.1016/S0020-7519(97)83432-7

15. M. Lélu, M. Langlais, M.-L. Poulle, E. Gilot-Fromont, Transmission dynamics of Toxoplasma gondii along an urban–rural gradient, *Theor. Popul. Biol.*, **78** (2010), 139–147. https://doi.org/10.1016/j.tpb.2010.05.005

16. A. A. B. Marinović, M. Opsteegh, H. Deng, A. W. Suijkerbuijk, P. F. van Gils, J. Van Der Giessen, Prospects of toxoplasmosis control by cat vaccination, *Epidemics*, **30** (2020), 100380. https://doi.org/10.1016/j.epidem.2019.100380

17. D. Trejos, I. Duarte, A mathematical model of dissemination of Toxoplasma gondii by cats, *Actual. Biol.*, **27** (2005), 143–149.

18. M. Turner, S. Lenhart, B. Rosenthal, X. Zhao, Modeling effective transmission pathways and control of the world?s most successful parasite, *Theor. Popul. Biol.*, **86** (2013), 50–61. https://doi.org/10.1016/j.tpb.2013.04.001

19. H. Deng, R. Cummins, G. Schares, C. Trevisan, H. Enemark, H. Waap, et al., Mathematical modelling of Toxoplasma gondii transmission: A systematic review, *Food Waterborne Parasitol.*, **22** (2021), e00102. https://doi.org/10.1016/j.fawpar.2020.e00102

20. M. Lappin, Feline toxoplasmosis, *In Pract.*, **21** (1999), 578–589. https://doi.org/10.1136/inpract.21.10.578

21. M. Sunquist, F. Sunquist, *Wild Cats of the World*, University of Chicago Press, 2002.

22. D. Hill, J. Dubey, Toxoplasma gondii: Transmission, diagnosis and prevention, *Clin. Microbiol. Infect.*, **8** (2002), 634–640. https://doi.org/10.1046/j.1469-0691.2002.00485.x

23. B. Grenfell, A. Dobson, *Ecology of Infectious Diseases in Natural Populations*, Cambridge University Press, London, 1995.

24. F. Brauer, C. Castillo-Chavez, *Mathematical models in population biology and epidemiology*, Springer-Verlag, 2001. https://doi.org/10.1007/978-1-4614-1686-9

25. H. Hethcote, Mathematics of infectious diseases, *SIAM Rev.*, **42** (2005), 599–653. https://doi.org/10.1137/S0036144500371907

26. J. D. Murray, *Mathematical Biology I. An Introduction*, Springer, Berlin, 2002.

27. B. F. Kafsacka, V. B. Carruthers, F. J. Pineda, Kinetic modeling of toxoplasma gondii invasion, *J. Theor. Biol.*, **249** (2007), 817–825. https://doi.org/10.1016/j.jtbi.2007.09.008

28. G. C. González-Parra, A. J. Arenas, D. F. Aranda, R. J. Villanueva, L. Jódar, Dynamics of a model of toxoplasmosis disease in human and cat populations, *Computers Math. Appl.*, **57** (2009), 1692–1700. https://doi.org/10.1016/j.camwa.2008.09.012

29. A. Sullivan, F. Agusto, S. Bewick, C. Su, S. Lenhart, X. Zhao, A mathematical model for within-host toxoplasma gondii invasion dynamics, *Math. Biosci. Eng.*, **9** (2012), 647. https://doi.org/10.3934/mbe.2012.9.647

30. O. M. Ogunmiloro, Mathematical modeling of the coinfection dynamics of malaria-toxoplasmosis in the tropics, *Biometr. Letters*, **56** (2019), 139–163. https://doi.org/10.2478/bile-2019-0013

31. B. M. Chen-Charpentier, M. Jackson, Direct and indirect optimal control applied to plant virus propagation with seasonality and delays, *J. Comput. Appl. Math.*, **380** (2020), 112983. https://doi.org/10.1016/j.cam.2020.112983

32. Y. Kuang, *Delay differential equations*, University of California Press, 2012.

33. H. L. Smith, *An introduction to delay differential equations with applications to the life sciences*, vol. 57, Springer-Verlag New York, 2011. https://doi.org/10.1007/978-1-4419-7646-8

34. F. A. Rihan, *Delay differential equations and applications to biology*, Springer, 2021. https://doi.org/10.1007/978-981-16-0626-7

35. H. Hethcote, P. Driessche, An SIS epidemic model with variable population size and a delay, *J. Math. Biol.*, **34** (1995), 177–194. https://doi.org/10.1007/BF00178772

36. P. Yan, S. Liu, SEIR epidemic model with delay, *ANZIAM J.*, **48** (2006), 119–134. https://doi.org/10.1017/S144618110000345X

37. P. W. Nelson, J. D. Murray, A. S. Perelson, A model of HIV-1 pathogenesis that includes an intracellular delay, *Math. Biosci.*, **163** (2000), 201–215. https://doi.org/10.1016/S0025-5564(99)00055-3

38. O. Ogunmiloro, A. Idowu, On the existence of invariant domain and local asymptotic behavior of a delayed onchocerciasis model, *Int. J. Modern Phys. C*, **31** (2020), 2050142. https://doi.org/10.1142/S0129183120501429

39. J. Li, G.-Q. Sun, Z. Jin, Pattern formation of an epidemic model with time delay, *Phys. A Stat. Mechan. Appl.*, **403** (2014), 100–109. https://doi.org/10.1016/j.physa.2014.02.025

40. O. Arino, M. L. Hbid, E. A. Dads, *Delay Differential Equations and Applications: Proceedings of the NATO Advanced Study Institute held in Marrakech, Morocco, 9-21 September 2002*, vol. 205, Springer Science & Business Media, 2007. https://doi.org/10.1007/1-4020-3647-7

41. B.-Z. Guo, L.-M. Cai, A note for the global stability of a delay differential equation of hepatitis B virus infection, *Math. Biosci. Eng.*, **8** (2011), 689–694. https://doi.org/10.3934/mbe.2011.8.689

42. M. Jackson, B. M. Chen-Charpentier, A model of biological control of plant virus propagation with delays, *J. Comput. Appl. Math.*, **330** (2018), 855–865. https://doi.org/10.1016/j.cam.2017.01.005

43. G. P. Samanta, Dynamic behaviour for a nonautonomous heroin epidemic model with time delay, *J. Appl. Math. Comput.*, **35** (2011), 161–178. https://doi.org/10.1007/s12190-009-0349-z

44. R. Xu, Global dynamics of an {SEIS} epidemiological model with time delay describing a latent period, *Math. Computers Simul.*, **85** (2012), 90–102. https://doi.org/10.1016/j.matcom.2012.10.004

45. M. Bachar, On periodic solutions of delay differential equations with impulses, *Symmetry*, **11** (2019), 523. https://doi.org/10.3390/sym11040523

46. S. Busenberg, K. Cooke, *Vertically transmitted diseases: Models and dynamics*, vol. 23, Springer Science & Business Media, 2012. https://doi.org/10.1007/978-3-642-75301-5

47. D. Breda, S. Maset, R. Vermiglio, *Stability of linear delay differential equations: A numerical approach with MATLAB*, Springer, 2014. https://doi.org/10.1007/978-1-4939-2107-2

48. J.-H. He, Periodic solutions and bifurcations of delay-differential equations, *Phys. Letters A*, **347** (2005), 228–230. https://doi.org/10.1016/j.physleta.2005.08.014

49. M. Á. Castro, M. A. García, J. A. Martín, F. Rodríguez, Exact and nonstandard finite difference schemes for coupled linear delay differential systems, *Mathematics*, **7** (2019), 1038. https://doi.org/10.3390/math7111038

50. A. El-Ajou, N. O. Moa'ath, Z. Al-Zhour, S. Momani, Analytical numerical solutions of the fractional multi-pantograph system: Two attractive methods and comparisons, *Results Phys.*, **14** (2019), 102500. https://doi.org/10.1016/j.rinp.2019.102500

51. M. García, M. Castro, J. A. Martín , F. Rodríguez, Exact and nonstandard numerical schemes for linear delay differential models, *Appl. Math. Comput.*, **338** (2018), 337–345. https://doi.org/10.1016/j.amc.2018.06.029

52. L. F. Shampine, S. Thompson, Solving ddes in matlab, *Appl. Numer. Math.s*, **37** (2001), 441–458. https://doi.org/10.1016/S0168-9274(00)00055-6

53. G. Kerr, G. González-Parra, Accuracy of the Laplace transform method for linear neutral delay differential equations, *Math. Computers Simul.*, **197** (2022), 308–326. https://doi.org/10.1016/j.matcom.2022.02.017

54. G. Kerr, G. González-Parra, M. Sherman, A new method based on the Laplace transform and Fourier series for solving linear neutral delay differential equations, *Appl. Math. Comput.*, **420** (2022), 126914. https://doi.org/10.1016/j.amc.2021.126914

55. L. F. Shampine, S. Thompson, Numerical solution of delay differential equations, in *Delay Differential Equations*, Springer, 2009, 1–27. https://doi.org/10.1007/978-0-387-85595-0

56. D. R. Willé, C. T. Baker, DELSOL-a numerical code for the solution of systems of delay-differential equations, *Appl. Numer. Math.*, **9** (1992), 223–234. https://doi.org/10.1016/0168-9274(92)90017-8

57. J. Frenkel, J. Dubey, N. L. Miller, Toxoplasma gondii in cats: Fecal stages identified as coccidian oocysts, *Science*, **167** (1970), 893–896. https://doi.org/10.1126/science.167.3919.893

58. J. Frenkel, A. Ruiz, M. Chinchilla, Soil survival of Toxoplasma oocysts in Kansas and Costa Rica, *Am. J. Trop. Med. Hyg.*, **24** (1975), 439–443. https://doi.org/10.4269/ajtmh.1975.24.439

59. L. Sibley, J. Boothroyd, Virulent strains of Toxoplasma gondii comprise a single clonal lineage, *Nature*, **359** (1992), 82–85. https://doi.org/10.1038/359082a0

60. A. J. Arenas, G. González-Parra, R.-J. V. Micó, Modeling toxoplasmosis spread in cat populations under vaccination, *Theor. Popul. Biol.*, **77** (2010), 227–237. https://doi.org/10.1016/j.tpb.2010.03.005

61. G. González-Parra, S. Sultana, A. J. Arenas, Mathematical modeling of toxoplasmosis considering a time delay in the infectivity of oocysts, *Mathematics*, **10** (2022), 354. https://doi.org/10.3390/math10030354

62. J. Dubey, D. S. Lindsay, M. R. Lappin, Toxoplasmosis and other intestinal coccidial infections in cats and dogs, *Vet. Clin. Small Animal Pract.*, **39** (2009), 1009–1034. https://doi.org/10.1016/j.cvsm.2009.08.001

63. W. Jiang, A. M. Sullivan, C. Su, X. Zhao, An agent-based model for the transmission dynamics of toxoplasma gondii, *J. Theor. Biol.*, **293** (2012), 15–26. https://doi.org/10.1016/j.jtbi.2011.10.006

64. P. van den Driessche, J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, *Math. Biosci.*, **180** (2002), 29–48. https://doi.org/10.1016/S0025-5564(02)00108-6

65. P. van den Driessche, J. Watmough, Further notes on the basic reproduction number, in *Math. Epidemiol.*, Springer, 2008, 159–178. https://doi.org/10.1007/978-3-540-78911-6

66. E. A. Innes, C. Hamilton, J. L. Garcia, A. Chryssafidis, D. Smith, A one health approach to vaccines against Toxoplasma gondii, *Food Waterborne Parasitol.*, **15** (2019), e00053. https://doi.org/10.1016/j.fawpar.2019.e00053

67. D. Sykes, J. Rychtář, A game-theoretic approach to valuating toxoplasmosis vaccination strategies, *Theor. Popul. Biol.*, **105** (2015), 33–38. https://doi.org/10.1016/j.tpb.2015.08.003

68. N. Mateus-Pinilla, B. Hannon, R. Weigel, A computer simulation of the prevention of the transmission of Toxoplasma gondii on swine farms using a feline T. gondii vaccine, *Prevent. Vet. Med.*, **55** (2002), 17–36. https://doi.org/10.1016/S0167-5877(02)00057-0

69. A. Freyre, L. Choromanski, J. Fishback, I. Popiel, Immunization of cats with tissue cysts, bradyzoites, and tachyzoites of the T-263 strain of Toxoplasma gondii, *J. Parasitol.*, **79** (1993), 716–719. https://doi.org/10.2307/3283610

70. J. Frenkel, Transmission of toxoplasmosis and the role of immunity in limiting transmission and illness, *J. Am. Vet. Med. Assoc.*, **196** (1990), 233–240.

71. M. R. Islam, T. Oraby, A. McCombs, M. M. Chowdhury, M. Al-Mamun, M. G. Tyshenko, et al., Evaluation of the United States COVID-19 vaccine allocation strategy, *PloS One*, **16** (2021), e0259700. https://doi.org/10.1371/journal.pone.0259700

72. G. González-Parra, M. R. Cogollo, A. J. Arenas, Mathematical modeling to study optimal allocation of vaccines against covid-19 using an age-structured population, *Axioms*, **11** (2022), 109. https://doi.org/10.3390/axioms11030109

73. J. Dubey, M. Mattix, T. Lipscomb, Lesions of neonatally induced toxoplasmosis in cats, *Vet. Pathol.*, **33** (1996), 290–295. https://doi.org/10.1177/030098589603300305

74. C. C. Powell, M. R. Lappin, Clinical ocular toxoplasmosis in neonatal kittens, *Vet. Ophthalmol.*, **4** (2001), 87–92. https://doi.org/10.1046/j.1463-5224.2001.00180.x

75. K. Sato, I. Iwamoto, K. Yoshiki, Experimental toxoplasmosis in pregnant cats, *Vet. Ophthalmol.*, **55** (1993), 1005–1009. https://doi.org/10.1292/jvms.55.1005

76. J. Dubey, M. Lappin and P. Thulliez, Diagnosis of induced toxoplasmosis in neonatal cats, *J. Am. Vet. Med. Assoc.*, **207** (1995), 179–185.

77. C. C. Powell, M. Brewer, M. R. Lappin, Detection of toxoplasma gondii in the milk of experimentally infected lactating cats, *Vet. Parasitol.*, **102** (2001), 29–33. https://doi.org/10.1016/S0304-4017(01)00521-0

78. V. Lakshmikantham, S. Leela, A. Martynyuk, *Stability Analysis of Nonlinear Systems*, Marcel Dekker, Inc., New York and Basel, 1989. https://doi.org/10.1007/978-3-319-27200-9

79. J. P. La Salle, *The stability of dynamical systems*, SIAM, 1976.

80. K. Berthier, M. Langlais, P. Auger, D. Pontier, Dynamics of a feline virus with two transmission modes within exponentially growing host populations, *Proceed. Royal Soc. B Biol. Sci.*, **267** (2000), 2049–2056. https://doi.org/10.1098/rspb.2000.1248

81. R. Fayer, Toxoplasmosis update and public health implications, *Canadian Vet. J.*, **22** (1981), 344.

82. A. L. Lloyd, Realistic distributions of infectious periods in epidemic models: changing patterns of persistence and dynamics, *Theoret. Popul. Biol.*, **60** (2001), 59–71. https://doi.org/10.1006/tpbi.2001.1525

83. G. González-Parra, F. De Ridder, D. Huntjens, D. Roymans, G. Ispas, H. M. Dobrovolny, A comparison of RSV and influenza in vitro kinetic parameters reveals differences in infecting time, *PloS one*, **13** (2018), e0192645. https://doi.org/10.1371/journal.pone.0192645

84. G. González-Parra, H. M. Dobrovolny, D. F. Aranda, B. Chen-Charpentier, R. A. G. Rojas, Quantifying rotavirus kinetics in the REH tumor cell line using in vitro data, *Virus Res.*, **244** (2018), 53–63. https://doi.org/10.1016/j.virusres.2017.09.023

85. X. Wang, Y. Shi, Z. Feng, J. Cui, Evaluations of interventions using mathematical models with exponential and non-exponential distributions for disease stages: The case of Ebola, *Bullet. Math. Biol.*, **79** (2017), 2149–2173. https://doi.org/10.1007/s11538-017-0324-z