ELSEVIER

Mathematical modeling of Toxoplasmosis disease in varying size populations

Diego F. Aranda [a,*], Rafael J. Villanueva [a], Abraham J. Arenas [b],
Gilberto C. González-Parra [c]

[a] *Instituto de Matemática Multidisciplinar, Universidad Politécnica de Valencia, Edificio 8G, piso 2, P.O. Box 46022, Valencia, Spain*
[b] *Departamento de Matemáticas y Estadística, Universidad de Córdoba, Montería, Colombia*
[c] *Dpto. de Cálculo, Facultad de Ingeniería, Universidad de los Andes, Mérida, Venezuela*

Abstract

The prevalence of Toxoplasmosis has increased dramatically around the world. Despite congenital Toxoplasmosis being not a disease of epidemic proportions, a large number of humans die or have serious effects on the developing fetus. In this paper we present an initial model with varying size population for the evolution of the infected people with Toxoplasmosis. We explore the dynamics of the Toxoplasmosis disease at the population level using an epidemiological model. Statistical data are used to estimate some of the parameters of the model. Numerical simulations of the model done by varying parameters show different scenarios about the spread of the disease.
© 2008 Elsevier Ltd. All rights reserved.

Keywords: Toxoplasmosis disease; Epidemiological model; Numerical solution; Simulation

1. Introduction

The protozoan Toxoplasma Gondii is a prevalent parasite in wild and domestic animals worldwide, being transmitted through the food chain by carnivorous feeding and scavenging. Toxoplasma normally divides asexually to yield a haploid form that can infect virtually any vertebrate but it also has a well-defined sexual cycle that occurs exclusively in cats. If the first contact during pregnancy, Toxoplasma Gondii can be transmitted vertically by tachyzoites that are passed to the fetus via the placenta [1].

The Toxoplasma Gondii has become important as an opportunistic pathogen in patients with AIDS although the 15%–85% of adult human populations that are chronically infected with T. Gondii are typically asymptomatic [1]. Infections in immunocompromised hosts have variable outcomes. In America, recent outbreaks of acute Toxoplasmosis in humans have been associated with oocyst contamination of the environment [1]. Over the course of recent history, humans have domesticated many different animal species, but the principal ones were the dogs

---

domesticated 12000 years ago and cats domesticated 4000 years ago, however, from these modest and comparatively recent beginnings, the cat is now on the verge of becoming the Western world's most popular pet; current predictions are that cats will soon overtake dogs as the most commonly kept pet. According to the Pet Food Institute in Washington, DC, cats already outnumber dogs in the United States, with 70.2 million, and Spain with 5.5 million of cats [2].

In United States there are approximately 225000 cases of Toxoplasma Gondii infection per year, which result in 5000 hospitalizations and 750 deaths, making Toxoplasma Gondii the third most common cause of fatal food-borne and the effective contacts with cats that have the Toxoplasma illness in the country. Since more than 90% of primary toxoplasmosis infections in immunocompetent persons are asymptomatic, the diagnosis of maternal infection is difficult. In asymptomatic women, the only sign of primary infection during pregnancy is seroconversion via detection of IgG or IgM by the immunofluorescence antibody test, the enzyme-linked immune filtration assay, the immunosorbent agglutination assay (ISAGA), or other similar assays. IgG antibody levels become detectable 1–2 weeks after infection and remain elevated indefinitely, while IgM antibody levels increase within days and usually remain elevated for 2–3 months. However, IgM antibody levels can remain positive for more than 2 years up to 27% of women when using ISAGA, making it difficult to pinpoint the timing of infection. Thus, the detection of IgG in a woman at the beginning of pregnancy indicates prior infection and thus eliminates the risk of congenital transfer of tachyzoi [3].

In Colombia, in accordance with the National Research of Health, 47% of the human population have antibody vs Toxoplasma, show contact with protozoan sometime in life and this happens to go unnoticed in persons with an excellent immune system [4]. The most important health consequences are in newborns with the infection acquired in uterus and immune deficiency in patients with AIDS. It is estimated that between 2 and 10 newborns have Toxoplasmosis for each 1000 births in Colombia. Therefore, between 600 and 3000 children of the 300000 new births per year, would be born with the congenital infection, most totally asymptomatic (450–2250), while only 150–750 would display symptoms in the first months of life [4]. It is important to mention that to our knowledge this is the first mathematical model for the evolution of Toxoplasmosis in the human population.

In this paper a first approach to model the evolution of the Toxoplasmosis disease in human population is introduced using a *SIC* model (susceptible-infected-controlled). In Section 2, we present the mathematical model for the evolution of Toxoplasmosis. Section 3 is devoted to scale the model properly to match with available data. In Section 4 mathematical simulation for three different scenarios is made. Finally in Section 5 conclusions are presented.

2. Mathematical model

In this section a first mathematical model for the evolution of the Toxoplasmosis in the population is formulated.

Following the basic ideas and structure of mathematical modeling in epidemiology, the model for the Toxoplasmosis disease will be developed under the next basic hypotheses [5,6,11].

(1) The total population $N(t)$ is divided in three subpopulations:
   - Susceptible $S(t)$: members of the population who may become infected.
   - Infected $E(t)$: members of population infected by the Toxoplasmosis parasite, both asymptomatic and symptomatical.
   - Controlled $C(t)$: members of the population who have been treaties for the Toxoplasmosis.
(2) A susceptible individual transits at a rate β to the infected subpopulation $I(t)$. An infected person transits to the controlled subpopulation $C(t)$ at a rate γ.
(3) The birth rate μ is assumed time-independent as well as the natural death rate d. The transmission rate β is assumed to be dependent on the population of cats, the accumulation of oocyst in the environment and the population of other animals (birds, rats and mice), but also time-independent. A newborn has a probability p to be healthy i.e. to be born without Toxoplasmosis. The additional death rate caused by Toxoplasmosis is ε.
(4) All members of the susceptible subpopulation $S(t)$ have the same probability to be infected.

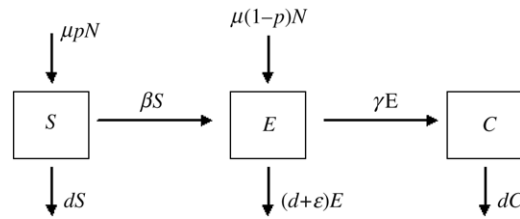A summary of the description of parameters is presented in Table 1.

Fig. 1. Diagram of the Toxoplasmosis disease on the population.

Table 1
Basic parameters of the mathematical model

Parameter	Description
μ	Birth rate
d	Natural death rate
β	Transmission rate
p	Probability to be born without Toxoplasma
γ	Individuals with Toxoplasma controlled rate
ε	Death rate caused by Toxoplasma

Under the above assumptions, an epidemiological model for Toxoplasmosis is given by the following linear system of ordinary differential equations.

$$\begin{aligned}
\dot{S}(t) &= p\mu N(t) - dS(t) - \beta S(t), \\
\dot{E}(t) &= \beta S(t) + \mu(1-p)N(t) - (d+\varepsilon)E(t) - \gamma E(t), \\
\dot{C}(t) &= \gamma E(t) - dC(t), \\
N(t) &= S(t) + E(t) + C(t),
\end{aligned} \tag{1}$$

where $S(t)$, $E(t)$ and $C(t)$ represent the number of individuals in the three subpopulations at time t. The schematic representation of the flow of individuals between the different subpopulations is shown in Fig. 1.

This model is used to estimate some unknown parameters related to Toxoplasmosis. Numerical simulations are carried out to analyze the effect of different control measures against the disease.

3. Scaling the model

Since data available are in percentages meanwhile model in Eq. (1) is referred to number of individuals, it leads us to scale the model into the same units as data. Therefore, following ideas developed in papers [7,8] about how to scale models with populations varying in size, adding the first three equation of the system (1) and using the last one, we obtain that,

$$\dot{N}(t) = (\mu - d)N - \varepsilon E. \tag{2}$$

Dividing both members of (2) by N one gets

$$\frac{\dot{N}}{N} = \mu - d - \varepsilon \frac{E}{N}. \tag{3}$$

If we define the ratios (dependent on time)

$$s = \frac{S}{N}, \qquad e = \frac{E}{N}, \qquad c = \frac{C}{N}, \tag{4}$$

the Eq. (3) can be transformed into

$$\frac{\dot{N}}{N} = \mu - d - \varepsilon e. \tag{5}$$

Table 2
Parameters of the model

Parameter	Values
μ	0.233
d	0.00601
p	0.9898
ε	$5.08 * 10^{-6}$

Now, let us calculate the derivative of s using (5). Then, we obtain that

$$\dot{s} = \frac{\dot{S}N - S\dot{N}}{N^2} = \frac{\dot{S}}{N} - \frac{S}{N}\frac{\dot{N}}{N} = \frac{\dot{S}}{N} - s(\mu - d - \varepsilon e), \tag{6}$$

and analogously, one gets that,

$$\dot{e} = \frac{\dot{E}}{N} - e(\mu - d - \varepsilon e), \qquad \dot{c} = \frac{\dot{C}}{N} - c(\mu - d - \varepsilon e). \tag{7}$$

Now, let us consider the first equation of system (1). If we divide by N, we have

$$\frac{\dot{S}}{N} = p\mu - d\frac{S}{N} - \beta\frac{S}{N} \tag{8}$$

and substituting by the corresponding ratios defined in (4) and using (8) we obtain the scaled equation.

$$\dot{s} = p\mu - s(t)(\mu + \beta - \varepsilon e(t)). \tag{9}$$

Remaining part of the equations of system (1) can be scaled similarly to obtain

$$\begin{aligned}
\dot{e}(t) &= \beta s(t) + \mu(1 - p) - e(t)(\gamma + \mu + \varepsilon - \varepsilon e(t)), \\
\dot{c}(t) &= \gamma e(t) - (\mu - \varepsilon e(t))c(t), \\
1 &= s(t) + e(t) + c(t).
\end{aligned} \tag{10}$$

Notice that, after scaling the model has been transformed into a nonlinear one.

As $s(t) + e(t) + c(t) = 1$, we can eliminate $c(t)$ and consider the two-dimensional system.

$$\begin{aligned}
\dot{s}(t) &= p\mu - s(t)(\mu + \beta - \varepsilon e(t)), \\
\dot{e}(t) &= \beta s(t) + \mu(1 - p) - e(t)(\gamma + \mu + \varepsilon - \varepsilon e(t)).
\end{aligned} \tag{11}$$

From the following data

- Between 2 and 10 of 1000 newborns in Colombia have Toxoplasmosis [4],
- In the United States there are 225000 cases of Toxoplasmosis per year and 750 deaths caused by the parasite [3],
- National statistics from Colombia [9],

some of the model parameters can be estimated, and are summarized in Table 2.
The parameters β and γ are unknown and we vary them in the next section to simulate different scenarios.

4. Numerical simulation

In this section, we simulate three possible scenarios and observe the effects of the parameters β and γ on the transmission dynamics of the Toxoplasmosis disease. Taking into account that in Colombia approximately 47.74% of the population have antibodies against the Toxoplasma Gondii [4], we assume as initial condition in all scenarios the following values

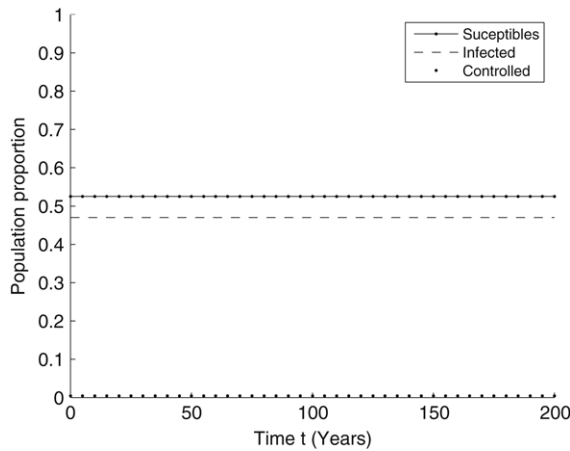$$s(0) = 0.5253 \qquad e(0) = 0.47 \quad \text{and} \quad c(0) = 0.0047. \tag{12}$$

Fig. 2. Dynamics of the different subpopulations when $\beta = 0.0206055$ and $\gamma = 0.000232$.

Table 3
Equilibrium point when $\beta = 0.0206055$ and $\gamma = 0.000232$ of system (11)

Equilibrium point	Values
s^*	0.5253
e^*	0.47
c^*	0.0047

Table 4
Eigenvalues of the Jacobian $J(s^*, e^*)$ when $\beta = 0.0206055$ and $\gamma = 0.000232$ of system (11)

Eigenvalues	Values
λ_1	-0.0439
λ_2	-0.0235

Table 5
Equilibrium point when $\beta = 0.010327$ and $\gamma = 0.000232$ of system (11)

Equilibrium point	Values
s^*	0.6863
e^*	0.3105
c^*	0.003092

For the first simulation we consider that the spread of Toxoplasmosis in population of Colombia is in equilibrium, i.e., proportions of susceptible infected and controlled are invariant over the time. This fact is possible by taking the parameter values

$$\beta = 0.0206055 \qquad \gamma = 0.000232. \tag{13}$$

Thus, we can compute the equilibrium point (s^*, e^*) and the jacobian $J(s^*, e^*)$ of system (11). The eigenvalues of $J(s^*, e^*)$ are negative and therefore equilibrium point (s^*, e^*) is locally asymptotically stable [10]. See Tables 3 and 4.

In Fig. 2 it can be seen that the solutions $s(t)$, $e(t)$ and $c(t)$ stay invariant over the time.

In the second simulation the transmission rate β is reduced to the half value of the previous simulation i.e., $\beta = 0.0103027$. This assumption considers a situation where health institutions of Colombia take hygienic actions against the oocyst in the environment and create health education programs. The value of γ is maintained for the same value of the first simulation. In Tables 5 and 6, the equilibrium point (s^*, e^*, c^*) and the eigenvalues of the Jacobian
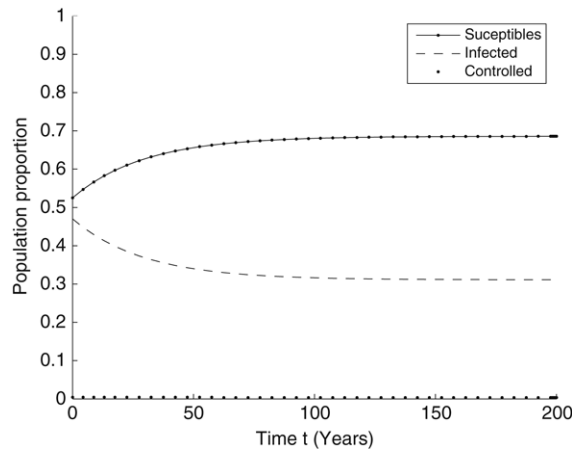
Fig. 3. Dynamics of the different subpopulations when $\beta = 0.010327$ and $\gamma = 0.000232$.

Table 6
Eigenvalues of the Jacobian $J(s^*, e^*)$ when $\beta = 0.010327$ and $\gamma = 0.000232$ of system (11)

Eigenvalues	Values
λ_1	−0.0336
λ_2	−0.0235

Table 7
Equilibrium point when $\beta = 0.0206055$ and $\gamma = 0.1$ of system (11)

Equilibrium point	Values
s^*	0.5252
e^*	0.08970
c^*	0.3851

Table 8
Eigenvalues of the Jacobian $J(s^*, e^*)$ when $\beta = 0.0206055$ and $\gamma = 0.1$ of system (11)

Eigenvalues	Values
λ_1	−0.1233
λ_2	−0.04390

$J(s^*, e^*)$ are showed. The obtained eigenvalues are negative, therefore the equilibrium point is locally asymptotically stable. In addition, Fig. 3 shows that the solutions $s(t)$, $e(t)$ and $c(t)$ converge to the equilibrium point, despite initial condition being far from the equilibrium point (s^*, e^*, c^*). The effectiveness of the hygienic actions have been achieved since the infected population decreased (see Fig. 3).

Finally, for the third simulation, we consider a scenario where the health institutions take more control on the infected people, doing more tests for seropositive Toxoplasmosis and giving more treatment for seropositive individuals. In Tables 7 and 8, the equilibrium point (s^*, e^*, c^*) and the eigenvalues of the Jacobian $J(s^*, e^*)$ are showed. The obtained eigenvalues are negative, therefore the equilibrium point is locally asymptotically stable. Additionally in Fig. 4 it is possible to see that the solutions $s(t)$, $e(t)$ and $c(t)$ converge to the equilibrium point, despite initial condition being far from the equilibrium point (s^*, e^*, c^*). Since, infected population decreases we conclude that more control is a good option to control the disease.
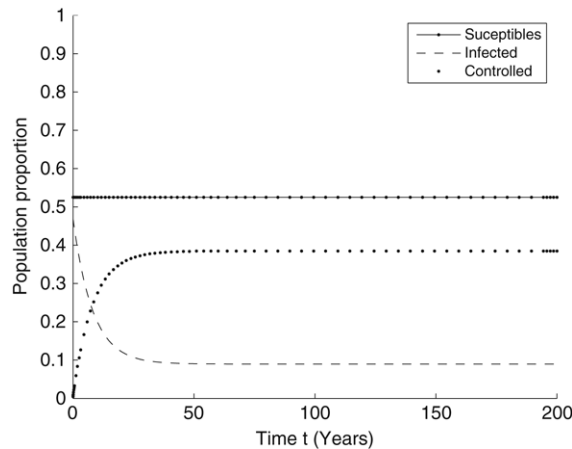
Fig. 4. Dynamics of the different subpopulations when $\beta = 0.0206055$ and $\gamma = 0.1$.

5. Conclusions

In this paper, we propose a simple mathematical model to study the dynamics of Toxoplasmosis disease in the population of Colombia. The model divides the total population in three subpopulations: susceptible, infected and controlled. The initial model is constructed using a linear system of ODEs, but since in the model size populations are varying and data are in percentages, the model is transformed to relative values in order to observe the qualitative behavior. The transformed model is a nonlinear system of ODEs, where it is possible to do a better analysis of the transmission dynamics of the Toxoplasmosis disease. Afterward, three numerical simulations are performed in different scenarios, based on some real situations that could happen in real life. In the last two scenarios it is possible to see the effect of some strategies for the control of Toxoplasmosis, as hygienic actions, educations programs, more testing and treatments. Finally it is important to mention that to our knowledge this is the first mathematical model for the evolution of Toxoplasmosis disease in the human population.

References

[1] L.D. Sibley, J.C. Boothroyd, Letters nature, in: Department of Molecular Microbiology, University School of Medicine Washington, USA, 03 September 1992, p. 359, 82–85. doi:10.1038/359082a0.
[2] M. Sunquist, F. Sunquist, Wild Cats of the World, ISBN: 978-0-226-77999-7 ISBN-10: 0-226-77999-8 Spring 2002 Sunquist, 462 p Washington DC, USA.
[3] J.D. Kravetz, D.G. Federman, Toxoplasmosis in pregnancy, Amer. J. Med. 118 (3) (2005) 212–216.
[4] J.E. Gomez-Marin, M.T. Montoya de Londoño, J.C. Castaño-Osorio, Maternal screening program for congenital Toxoplasmosis in Quindio, Colombia and application of mathematical models to estimate incidences using age-stratified data, Am. J. Trop. Med. Hyg. 57 (1997) 180–186.
[5] J.D. Murray, Mathematical Biology I. An Introduction, ISBN 0-387-95223-3, USA, 2002.
[6] F. Brauer, C. Castillo-Chavez, Mathematical Models in Population Biology and Epidemiology, Springer-Verlag, New York, 2001.
[7] M. Martcheva, C. Castillo Chavez, Diseases with chronic stage in population with varying size, Math. Biosci. 182 (2003) 1–25.
[8] J. Mena-Lorca, H.W. Hethcote, Dynamic model of infectious diseases as regulators of population size, J. Math Biol. 30 (1992) 693–716.
[9] Ministerio de Protección Social, www.minproteccionsocial.gov.co.
[10] M.W. Hirch, S. Smale, R.L. Devaney, Differential Equations, Dynamical Systems and An Introduction to Chaos, ISBN 0-12-349703-5, USA, 2004.
[11] H.W. Hethcote, Mathematics of infectious diseases, SIAM Rev. 42 (4) 599–653.