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Transmission dynamics of *Toxoplasma gondii* along an urban–rural gradient

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ABSTRACT

Recently, several authors have proposed that the availability of intermediate hosts (IHs) for definitive hosts (DHs) may contribute to determining the dynamics and evolutionary ecology of parasites with facultative complex life cycles. The protozoa *Toxoplasma gondii* may be transmitted to DHs either via predation of infected IHs through a complex life cycle (CLC) or directly from a contaminated environment through a simple life cycle (SLC). This parasite is also present in contrasting host density environments. We tested the hypothesis that the relative contributions of the CLC and SLC along an urban–rural gradient depend on the IH supply. We built and analysed a deterministic model of the *T. gondii* transmission cycle. The SLC relative contribution is important only in urban-type environments, i.e., with low predation rate on IHs. In contrast, the parasite is predominantly transmitted through a CLC in suburban and rural environments. The association of the two cycles enables the parasite to spread in situations of low IH availability and low DH population size for which each cycle alone is insufficient.

1. Introduction

Parasites with complex life cycles (CLCs) complete their sexual reproduction in definitive hosts (DHs), but also infest intermediate hosts (IHs) in which asexual multiplication occurs. For many of them, transmission from IHs to DHs goes through predation; thus parasite transmission is expected to vary depending on the prey–predator relationship, which can be modulated by densities of IHs and DHs and by the functional response to predation. As an example, the dynamics of *Echinococcus multilocularis* between rodents and foxes varies from central to peripheral urban areas as the result of variations in rodent supply and shift in fox diet (Robardet et al., 2008). At the evolutionary scale, the relative density of IHs versus DHs may also be a selective pressure for parasites with a simple life cycle (SLC) to complexify their life cycle (Choisy et al., 2003).

Toxoplasma gondii is an appropriate biological model to test these predictions, since it may be transmitted through either a CLC or an SLC. Definitive hosts of this zoonotic pathogen are felids, often domestic cats (*Felis catus*), and intermediate hosts include most of all warm-blooded animals (Tenter et al., 2000). Infected cats excrete *T. gondii* oocysts in the environment. Intermediate hosts become infected by ingesting oocysts from these contaminated environments. The CLC consists in the transmission of the parasite from infected cats to the environment to IHs, with the susceptible cats getting infected by preying upon infected small mammals or birds. The SLC is considered to be the transmission of the parasite between the cat and the environment only, with susceptible cats becoming infected through consumption of a high number of oocysts (Dubey, 1996, 2006). Although direct transmission between IHs via carnivorism exists (Dubey, 2006), we focused on the natural cycles of *T. gondii* transmission to cats. Thus the IHs considered here are prey of cats, i.e., rodents, and carnivorism is less likely to occur.

Moreover, *T. gondii* is present in contrasted environments, including in rural and urban ones (Afonso et al., 2006; Cavalcante et al., 2006; Hornok et al., 2008). Following Deplazes et al. (2004), we hypothesized that the density of potential cat prey follows a decreasing gradient from rural areas to urban centres. In agricultural landscapes, small rodents like common voles *Microtus arvalis* and water voles *Arvicola terrestris* may reach 1000 individuals/ha (Le Louarn and Quéré, 2003), while urban populations are limited because of predation and habitat fragmentation (Baker et al., 2003). In urban areas, the density of wood mice *Apodemus sylvaticus* was estimated to be around 20–60 mice/ha for disturbed and undisturbed patches, respectively (Dickman and Doncaster, 1987), and up to 80 mice/ha in some patches (Baker et al., 2003). Predation rates of small rodents by cats should increase from urban to rural

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sites with the availability of rodents. In urban populations, Barratt (1998) and Baker et al. (2005) reported predation rates of 10.2 and 21 prey/cat/year, respectively. For suburban and rural sites, estimated values for predation rates range from 21 (Gillies and Clout, 2003), 66 (Kays and DeWan, 2004) to 436 prey/cat/year (estimated from Liberg, 1984). In contrast to rodent densities, cat densities usually lie in the range of 1–3 cats/ha in rural areas, but may locally reach 15–80 cats/ha in urban sites (Fromont et al., 1998).

Our hypothesis was that the dynamics of the CLC and its role in the overall transmission of the parasite should change with the availability of IHs for DHs. Two previous epidemiological models dealt with the transmission dynamics of *T. gondii* in cat populations (Arenas et al., 2010) and in swine farms (Mateus-Pinilla et al., 2002), and the impacts of preventive measures such as vaccination. Nevertheless, these studies neglected the prey compartment and its impact on the dynamics of *T. gondii* transmission. Here, we have developed a deterministic model for the transmission of *T. gondii* in which both the CLC and the SLC are represented. We analysed the model to obtain closed-form expressions of the proportion of contaminated environment and the seroprevalences of prey and cats, at equilibrium. Using parameters estimated from previous field studies, we compared the predicted values for environmental contamination and seroprevalences along a gradient of predation rate and calculated their elasticities to each parameter. We also computed the basic reproductive number R_0 of the parasite, i.e., the average number of secondary cases caused by a single infectious individual introduced in a fully susceptible population (Diekmann et al., 1990), upon using the next-generation matrix methodology (Diekmann and Heesterbeek, 2000). Then, we adapted to *T. gondii* transmission the reasoning of Hartemink et al. (2008), recently used to compare different routes of transmission for two tick-borne infections. R_0 was thus used to understand the relative role of the SLC and the CLC in the spread of *T. gondii* along a gradient of predation rates. The expression of the overall R_0 was split into two partial R_0s, representing propagation due to the SLC and the CLC, respectively. Elasticities of the overall R_0 to each parameter, including partial R_0s, were computed. Finally, we studied the situations leading to spread or extinction of the infection for each cycle (SLC and CLC) separately, and for both cycles together, according to the predation rate and to the cat population size.

2. Materials and methods

2.1. Life cycle of T. gondii

Infected cats contaminate the environment by excreting unsporulated oocysts in their faeces during 7 to 20 days after a prepatent period of 3–49 days (AFSSA, 2005). One to five days after excretion, oocysts sporulate under sufficient conditions of humidity and temperature. Oocysts survive 46–183 days in uncovered faecal deposits and 76–334 days in covered faecal deposits (Yilmaz and Hopkins, 1972 cited by Dumètre and Dardé, 2003).

DHs and IHs become infected by ingesting or inhalating oocysts, or by consuming tissue cysts from infected prey. Oocysts are more infectious for mice than for cats, while tissue cysts are more infectious for cats than for mice (Dubey, 2006). Vertical transmission from mother to foetus occurs in all host species but only concerns susceptible females infected during pregnancy. We assumed that tissue cysts persist for the whole life of the IHs considered here (rodents), and that infected cats become immune lifelong (Dubey, 1997; Tenter et al., 2000). Here we focused on CLC and SLC cycles without taking into account transmission between IHs.

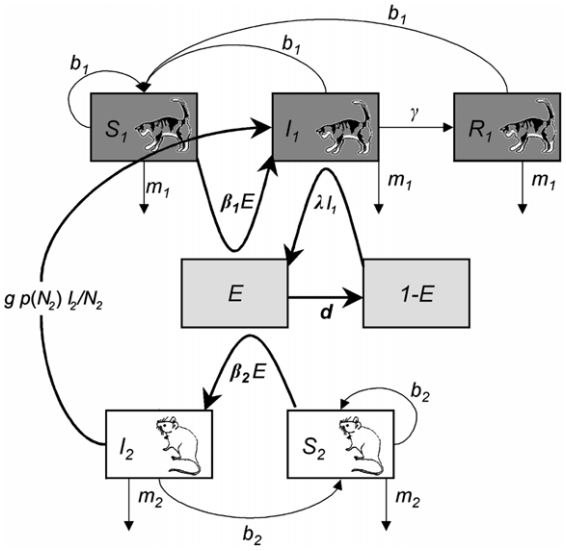

Fig. 1. Flowchart for the transmission of *T. gondii* between cats, environment and prey. S_1, I_1 and R_1 represent the numbers of susceptible, infected, and immune cats, respectively. E and $1-E$ are the proportion of contaminated and uncontaminated defecating areas, respectively. S_2 and I_2 stand for the numbers of susceptible and infected prey, respectively. Definitions of parameters are summarized in Table 1.

2.2. Model of T. gondii transmission

We chose to develop a deterministic SIR-type model because various analytical expressions such as the basic reproductive number R_0 can be found in closed form.

The cat population is split into three compartments, S_1, I_1 and R_1 with $N_1 = S_1+I_1+R_1$, representing respectively the numbers of susceptible, infectious which excrete oocysts in the environment, and immune cats (Fig. 1). Cats are assumed to defecate only in some areas of their habitat (Afonso et al., 2008). Thus we considered that only the defecating sites, which represent a limited surface, used by cats can be contaminated by oocysts. Compartments $(1-E)$ and E stand for the proportion of uncontaminated and contaminated defecating areas, respectively (Fig. 1). The prey population is divided into two compartments, S_2 and I_2 with $N_2 = S_2 + I_2$, representing respectively the numbers of susceptible and infected prey (Fig. 1).

2.2.1. Dynamics of the hosts without parasite

In a parasite-free environment, the dynamics of the cat population is assumed to be logistic, with resource limitation acting through density-dependence on the mortality rate (Fromont et al., 1997). The total number of individuals in population N_1 depends on the birth rate, the mortality rate, the intrinsic growth rate and the carrying capacity, respectively denoted by b_1, m_1, $r_1 = (b_1 - m_1)$ and K_1. We assumed that the cat dynamics does not depend on prey availability. The dynamics is described by the following ordinary differential equation (ODE):

$$\dot{N}_1 = (r_1 - r_1 N_1/K_1)N_1 = b_1 N_1 - (m_1 + (b_1 - m_1)N_1/K_1)N_1. \quad (1)$$

We also assumed the prey dynamics to be logistic, with an additional mortality term due to predation by cats represented by a functional response to predation $p(N_2)$. We used a simple Lotka–Volterra functional response (Lotka, 1925; Volterra, 1931), $p(N_2) = aN_2$, a being the predation rate. The prey dynamics is thus governed by the following ODE:

$$\begin{aligned}\dot{N}_2 &= (r_2 - r_2 N_2/K_2)N_2 - p(N_2)N_1 \\ &= b_2 N_2 - (m_2 + (b_2 - m_2)N_2/K_2)N_2 - p(N_2)N_1. \end{aligned} \quad (2)$$

Table 1
Parameters of the model.

Parameters	Description	Value
K_1	Size of DH population at equilibrium and carrying capacity	100[a,b]
b_1	Birth rate of DH population	2.4/52[a,b]
m_1	Mortality rate of DH population	0.6/52[a,b]
β_1	Transmission rate from contaminated environment to DHs	0.54/52[c,d]
aK_2^*	predation rate	see text
b_2	Birth rate of IH population	6/52[e]
m_2	Mortality rate of IH population	2/52[e]
β_2	Transmission rate from contaminated environment to IHs	0.4/52
g	Probability of infection when a DH consumes an infected IH	1[f]
γ	Recovery rate	1/2[g]
λ	Contamination rate of environment by one infected DH	1/16[d]
d	Decontamination rate	7/100[h]

Sources:.
[a] Fromont et al., 1997.
[b] Courchamp et al., 1995.
[c] Afonso et al., 2006.
[d] Afonso et al., 2008.
[e] Courchamp et al., 1999.
[f] Dubey, 2006.
[g] AFSSA, 2005.
[h] Dumètre and Dardé, 2003.

2.2.2. Dynamics of environmental contamination and parasitized hosts

We assume a homogeneous use of the defecating sites by cats and derive an equation for the contamination dynamics of the defecating sites similarly to Berthier et al. (2000). Uncontaminated defecating sites are contaminated by infected cats at a rate λ, and contaminated areas decontaminate over time at a rate d. An equation modelling the contamination dynamics of defecating zones reads $\dot{E} = \lambda I_1(1 - E) - dE$.

We assumed that infection does not affect the mortality and fecundity of both hosts, i.e., the overall dynamics of N_1 and N_2 does not change when the parasite is present. Vertical transmission is neglected in both populations; thus individuals in each predator and prey compartment are supposed to give birth to susceptible individuals.

Cats become infected through contacts with E, at a rate β_1, or by ingesting an infected prey I_2 with the probability of infection g. Predation is governed by a functional response to predation $p(N_2)$. Infected DHs leave the compartment I_1 at recovery rate γ. Susceptible prey become infected through contacts with E at a rate β_2.

The dynamics of the hosts and environment with *T. gondii* is described by a system of ODEs:

$$\begin{cases} \dot{S}_1 = b_1N_1 - (m_1 + (b_1 - m_1)N_1/K_1)S_1 \\ \quad - \beta_1 E S_1 - gp(N_2)S_1I_2/N_2 \\ \dot{I}_1 = -(m_1 + (b_1 - m_1)N_1/K_1)I_1 \\ \quad + \beta_1 E S_1 + gp(N_2)S_1I_2/N_2 - \gamma I_1 \\ \dot{R}_1 = -(m_1 + (b_1 - m_1)N_1/K_1)R_1 + \gamma I_1 \\ \dot{E} = \lambda I_1(1 - E) - dE \\ \dot{S}_2 = b_2N_2 - (m_2 + (b_2 - m_2)N_2/K_2)S_2 \\ \quad - \beta_2 E S_2 - p(N_2)N_1S_2/N_2 \\ \dot{I}_2 = -(m_2 + (b_2 - m_2)N_2/K_2)I_2 + \beta_2 E S_2 - p(N_2)N_1I_2/N_2. \end{cases} \quad (3)$$

2.3. Parameters

Parameters either come from the available literature or are estimated from published field data (Table 1). The week is chosen as the unit of time because it is a common order of magnitude of the various phenomena involved in *T. gondii* transmission.

For cat populations, parameters b_1 and m_1 were already used in modelling the spread of feline viruses (Courchamp et al., 1995; Fromont et al., 1997). K_1 is arbitrarily fixed at 100 cats, representing the order of magnitude of the DH populations in an urban site or rural village (60–340; Fromont et al., 1997; Courchamp et al., 1998). In the last results Section 3.5, K_1 varies from 0 to 300.

We estimated β_1 from results in Afonso et al. (2006, 2008), which deal with the transmission of *T. gondii* in an urban population of cats. The authors estimated incidence at 0.17 infections/year and the proportion of contaminated defecating sites at 5/16. There were few prey available for cats in this urban patch (Afonso et al., 2006) and thus we assumed that transmission occurs only through an SLC, between cats and the environment. The incidence is then represented by $\beta_1 E = 0.17$. Considering that E equals 5/16 in this site, we obtained $\beta_1 = 0.54$ infections per infectious contact per year, i.e., $\beta_1 = 0.54/52$ infections per infectious contact per week. This parameter can be broken up into $\beta_1 = c_1p_1$, the product of the contact rate c_1 and the probability of transmission when contact occurs with a contaminated site p_1 (Begon et al., 2002). By assuming that a cat has one contact with a defecating site per day, $c_1 = 7$ contacts/week, p_1 is thus equal to 1.5×10^{-3}, which is consistent with the known poor infectivity of oocysts toward cats (Dubey, 2006). The average duration of infectiousness in cats is estimated to two weeks (AFSSA, 2005); thus the recovery rate γ equals 0.5 week^{-1}.

From a 15-week survey, Afonso et al. (2008) estimated that a given cat uses on average two of the 16 identified defecating sites. We assumed that, over one week, an infected cat contaminates half of the defecating sites it uses; thus the contamination rate $\lambda = 1/16$. From Dumètre and Dardé (2003), we averaged the survival of the parasite in soil at 100 days; the decontamination rate is thus $d = 7/100$ week^{-1}.

For the prey dynamics, we chose average parameters, $b_2 = 6/52$ and $m_2 = 2/52$, in accordance with the fecundity and survival observed for rodents (Le Louarn and Quéré, 2003). The number of predated prey by one cat, aN_2, is represented by aK_2^* at equilibrium. This parameter varies from 0 in extreme urban areas to 436 prey per cat per year in rural areas with high predation rate (Liberg, 1984). We assumed that predation rates lower than 21 prey/cat/year (Gillies and Clout, 2003) correspond to urban environments and larger values to suburban and rural areas. In order to keep clear figures, the predation rate ranges from 0 to 1 prey/cat/week, i.e., 0 to 52 prey/cat/year.

As we have no information about the contact rate between cat defecating sites and rodents, we chose a value of 0.4/52 for the transmission rate β_2 in order to obtain a seroprevalence in rural rodent populations of 5%, in the order of magnitude observed in rodent populations (Afonso et al., 2007).

2.4. Elasticity analysis

With the above set of parameters, we compared the proportion of contaminated defecating sites E, the seroprevalence of cats R_1/N_1, and prey I_2/N_2, at equilibrium for different situations of transmission cycle (SLC, CLC and SLC + CLC) along a gradient of predation rate assimilated to an urban–rural gradient. Elasticity analyses were performed for each prediction, i.e., E, R_1/N_1, I_2/N_2 and the overall basic reproductive number R_0 (see Section 3.2 for the computation of R_0), to highlight the most important parameters in predictions. For example, the elasticity of E to parameter d, which represents the proportional change in E in response to a proportional change in the parameter d (Hartemink et al., 2008), is

$$e_{Ed} = \frac{d}{E}\frac{\partial E}{\partial d}.$$

From the analysis of system (3), we obtained explicit expressions of the overall basic reproductive number R_0, the reproductive number for the complex life cycle R_{0C} and the reproductive number for the simple life cycle R_{0S} for simple transmission. Using these R_0 values, we compared the relative contributions of each cycle in the propagation of the parasite. Following Hartemink et al. (2008), the elasticities of R_0 to R_{0C} and R_{0S}, respectively denoted e_C and e_S, may be interpreted as contributions of the CLC and SLC in the transmission of *T. gondii* (de Kroon et al., 1986),

$$e_C = \frac{R_{0C}}{R_0}\frac{\partial R_0}{\partial R_{0C}}$$
$$e_S = \frac{R_{0S}}{R_0}\frac{\partial R_0}{\partial R_{0S}}.$$

We did not perform sensitivity analyses, which are used to compare absolute changes in predictions to absolute changes in parameters. As the parameters vary in order of magnitude (see for example $K_1 = 100$, $b_1 = 2.4/52$ and $\gamma = 0.5$) we focused on proportional changes which are more comparable from one parameter to another.

Formal calculations were performed with the software Maxima (Maxima.sourceforge.net Version 5.18.1, 2009). Scilab (Scilab is a trademark of INRIA, Copyright©, 1989–2007) and R (R Development Core Team, 2009) were used to obtain model predictions, elasticity values, and related graphics.

3. Results

3.1. Simplifications and resolution of ODE systems for the SLC, CLC and SLC + CLC

The dynamics of the DH population represented by (1) has two equilibria, 0 and K_1, and $N_1(t) \to K_1$ as $t \to +\infty$ because $b_1 > m_1$.

For the sake of simplicity, let us assume that the functional response to predation takes a Lotka–Volterra form $p(N_2) = aN_2$ (Lotka, 1925; Volterra, 1931). The dynamics of the IH population is described by (2) with the two equilibria, 0 and $K_2^* = (b_2 - m_2 - aK_1)/k_2$, and

$$N_2(t) \to \begin{cases} 0 & \text{if } b_2 - m_2 - aK_1 < 0 \\ K_2^* & \text{if } b_2 - m_2 - aK_1 > 0 \end{cases} \quad \text{as } t \to +\infty.$$

From now on, let us suppose the prey population does not go extinct, i.e., $b_2 - m_2 - aK_1 > 0$. Thus we assume a quasi-stationarity condition; that is, we assume that both host populations have already reached their respective equilibria, $N_1(t) \equiv K_1$ and $N_2(t) \equiv K_2^*$. System (3) simplifies upon first substituting $S_1 = K_1 - I_1 - R_1$ and $S_2 = K_2^* - I_2$, and then using $b_1 = m_1 + (b_1 - m_1)N_1/K_1$ and $b_2 = m_2 + (b_2 - m_2)N_2/K_2 + aK_1$ to yield

$$\begin{cases} \dot{I_1} = (\beta_1 E + gaI_2)(K_1 - I_1 - R_1) - b_1 I_1 - \gamma I_1 \\ \dot{R_1} = \gamma I_1 - b_1 R_1 \\ \dot{E} = \lambda I_1(1 - E) - dE \\ \dot{I_2} = \beta_2 E(K_2^* - I_2) - b_2 I_2. \end{cases} \tag{4}$$

3.1.1. The simple life cycle, SLC

The simple life cycle corresponds to transmission between cats and the environment only. The prey compartment is removed from system (4):

$$\begin{cases} \dot{I_1} = \beta_1 E(K_1 - I_1 - R_1) - b_1 I_1 - \gamma I_1 \\ \dot{R_1} = \gamma I_1 - b_1 R_1 \\ \dot{E} = \lambda I_1(1 - E) - dE. \end{cases} \tag{5}$$

System (5) has two equilibrium states, a disease-free state $S_1 = K_1$, $I_1 = R_1 = E = 0$ and an endemic one with

$$I_1^* = \frac{b_1(\beta_1 K_1 \lambda - d(\gamma + b_1))}{\lambda(\beta_1 + b_1)(\gamma + b_1)},$$

$R_1^* = \gamma I_1^*/b_1$; $S_1^* = K_1 - I_1^* - R_1^*$ and $E^* = \lambda I_1^*/(\lambda I_1^* + d)$.

For the SLC, at equilibrium, the proportions of contaminated environment E^* and cat seroprevalence R_1^*/K_1 vary according to the number of cats at equilibrium K_1, and they do not depend on the predation rate aK_2^*.

3.1.2. The complex life cycle, CLC

In the CLC, cats are infected by consuming infected prey only. Transmission from the environment to cats does not occur:

$$\begin{cases} \dot{I_1} = gaI_2(K_1 - I_1 - R_1) - b_1 I_1 - \gamma I_1 \\ \dot{R_1} = \gamma I_1 - b_1 R_1 \\ \dot{E} = \lambda I_1(1 - E) - dE \\ \dot{I_2} = \beta_2 E(K_2^* - I_2) - b_2 I_2. \end{cases} \tag{6}$$

System (6) has two equilibrium states, a disease-free state $S_1 = K_1, S_2 = K_2^*, I_1 = R_1 = I_2 = E = 0$ and an endemic one with

$$I_1^* = \frac{b_1(\beta_2 \lambda g a K_2^* K_1 - b_2 d(\gamma + b_1))}{(\beta_2 g a K_2^* + b_1(\beta_2 + b_2))(\gamma + b_1)\lambda},$$

$R_1^* = \gamma I_1^*/b_1$, $S_1^* = K_1 - I_1^* - R_1^*$, $E^* = \lambda I_1^*/(\lambda I_1^* + d)$, $I_2^* = \beta_2 K_2^* E^*/(\beta_2 E^* + b_2)$ and $S_2^* = K_2^* - I_2^*$.

For the CLC, E^*, R_1^*/K_1 and the prey seroprevalence $I_2^*/K_2^* = \beta_2 E^*/(\beta_2 E^* + b_2)$ vary as a function of both the predation rate aK_2^* and the cat population size K_1.

3.1.3. Both cycles, SLC + CLC

When both cycles co-exist, the analysis of system (4) yields two equilibrium states, a disease-free state $S_1 = K_1$, $S_2 = K_2^*$, $I_1 = R_1 = I_2 = E = 0$, and an endemic one with I_1^* being a complex expression detailed in the Appendix, and $R_1^* = \gamma I_1^*/b_1$, $S_1^* = K_1 - I_1^* - R_1^*$, $E^* = \lambda I_1^*/(\lambda I_1^* + d)$, $I_2^* = \beta_2 K_2^* E^*/(\beta_2 E^* + b_2)$ and $S_2^* = K_2^* - I_2^*$.

As for the CLC, when both cycles are associated, the proportions of contaminated environment E^*, cat seroprevalence R_1^*/K_1 and prey seroprevalence I_2^*/K_2^* vary as a function of both the predation rate aK_2^* and the cat population size K_1, at equilibrium.

3.2. R_{0S}, R_{0C} and overall R_0 computations

3.2.1. The simple life cycle, SLC

We used the methodology in Diekmann et al. (1990); Diekmann and Heesterbeek (2000) and van den Driessche and Watmough (2002) to compute the basic reproductive numbers for the SLC,

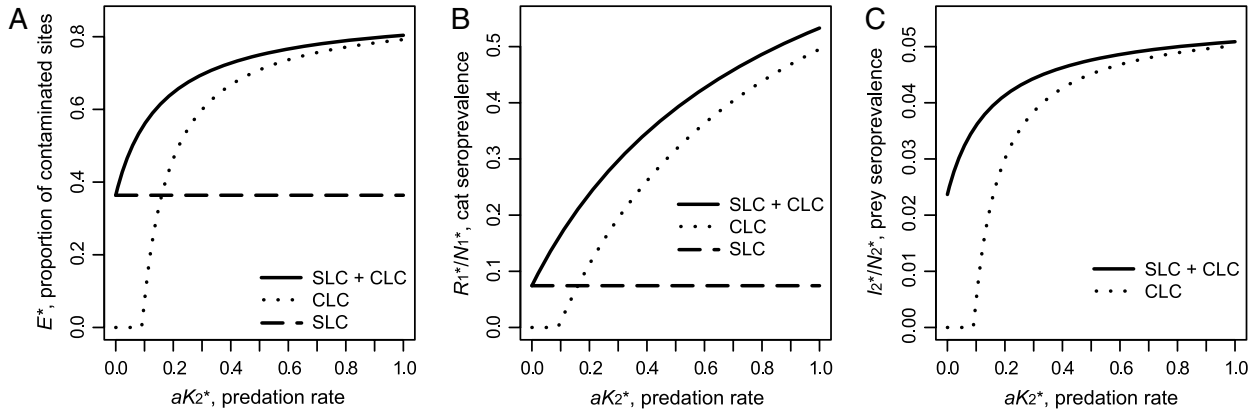

Fig. 2. Predicted values for the proportion of contaminated defecating site E at equilibrium (A), seroprevalence in cat population R_1/N_1 (B) and seroprevalence in prey population I_2/N_2 (C), as a function of the predation rate aK_2^* (prey/cat/week).

R_{0S}, the CLC, R_{0C}, and when both cycles co-exist, R_0. The method is developed for R_{0S} and is the same for the other R_0.

System (5) is split as follows:

$$\begin{bmatrix} \dot{I}_1 \\ \dot{R}_1 \\ \dot{E} \end{bmatrix} = \begin{bmatrix} (\beta_1 E)(K_1 - I_1 - R_1) \\ 0 \\ \lambda I_1 (1 - E) \end{bmatrix} - \begin{bmatrix} (b_1 + \gamma) I_1 \\ b_1 R_1 - \gamma I_1 \\ dE \end{bmatrix} \tag{7}$$

$\dot{X} = \mathscr{F} - \mathscr{V}$.

With x_0 ($I_1 = 0, R_1 = 0$ and $E = 0$) a disease-free equilibrium of system (7), F and V are defined by

$$F = \frac{\partial \mathscr{F}_i}{\partial x_j}(x_0) = \begin{bmatrix} 0 & 0 & \beta_1 K_1 \\ 0 & 0 & 0 \\ \lambda & 0 & 0 \end{bmatrix}$$

$$V = \frac{\partial \mathscr{V}_i}{\partial x_j}(x_0) = \begin{bmatrix} b_1 + \gamma & 0 & 0 \\ -\gamma & b_1 & 0 \\ 0 & 0 & d \end{bmatrix}$$

$$V^{-1} = \begin{bmatrix} \frac{1}{b_1 + \gamma} & 0 & 0 \\ \frac{\gamma}{(b_1 + \gamma) b_1} & \frac{1}{b_1} & 0 \\ 0 & 0 & \frac{1}{d} \end{bmatrix}.$$

FV^{-1} is the next-generation matrix, denoted NGM_S:

$$FV^{-1} = NGM_S = \begin{bmatrix} 0 & \frac{\beta_1 K_1}{d} \\ \frac{\lambda}{b_1 + \gamma} & 0 \end{bmatrix}.$$

The basic reproductive number, R_{0S}, is the dominant eigenvalue of matrix NGM_S,

$$R_{0S} = \sqrt{\frac{\lambda \beta_1 K_1}{(b_1 + \gamma) d}} = f(K_1).$$

As with E^* and R_1^*/K_1 obtained previously from the SLC system, R_{0S} depends on K_1. The parasite spreads by an SLC only if $K_1 > (b_1 + \gamma) d / (\lambda \beta_1)$.

3.2.2. The complex life cycle, CLC

From system (6), we compute the next-generation matrix for the CLC:

$$NGM_C = \begin{bmatrix} 0 & 0 & \frac{g a K_1}{b_2} \\ \frac{\lambda}{b_1 + \gamma} & 0 & 0 \\ 0 & \frac{\beta_2 K_2^*}{d} & 0 \end{bmatrix}.$$

The basic reproductive number, R_{0C}, is the dominant eigenvalue of matrix NGM_C:

$$R_{0C} = \sqrt[3]{\frac{\lambda \beta_2 a K_2^* g K_1}{(b_1 + \gamma) d b_2}} = f(aK_2^*, K_1).$$

The parasite spread only if the predation rate $aK_2^* > (b_1 + \gamma) d b_2 / (\lambda \beta_2 g K_1)$ and $R_{0C} > R_{0S}$ if $aK_2^* > b_2 \beta_1^{3/2} \sqrt{K_1 \lambda} / (\beta_2 g \sqrt{d(\gamma + b_1)})$.

3.2.3. Both cycles, SLC + CLC

From system (4), we computed the next-generation matrix for both cycles together:

$$NGM = \begin{bmatrix} 0 & \frac{\beta_1 K_1}{d} & \frac{g a K_1}{b_2} \\ \frac{\lambda}{b_1 + \gamma} & 0 & 0 \\ 0 & \frac{\beta_2 K_2^*}{d} & 0 \end{bmatrix}.$$

R_0 is the maximal solution to a cubic equation:

$$R_0^3 - \frac{\lambda \beta_1 K_1}{(b_1 + \gamma) d} R_0 - \frac{\lambda \beta_2 K_2^* g a K_1}{(b_1 + \gamma) d b_2} = 0, \tag{8}$$

which simplifies to

$$R_0^3 - ({R_{0S}}^2) R_0 - ({R_{0C}}^3) = 0. \tag{9}$$

The unique positive solution of (9) is the overall R_0. We used the following equivalence to find the predation rate above which the parasite spreads: $R_0 > 1$ leads to $R_{0S}^2 + R_{0C}^3 > 1$ (Diekmann and Heesterbeek, 2000, p. 97). Then *T. gondii* persists in host populations when $aK_2^* > (d(b_1 + \gamma)/(\lambda K_1) - \beta_1) b_2 / (\beta_2 g)$.

3.3. Environmental contamination E, cat seroprevalence R_1/N_1 and prey seroprevalence I_2/N_2

3.3.1. Predictions for the SLC, CLC and both cycles

We are interested in the predictions at equilibrium which can be compared to observed values. With the chosen parameters, we obtained predictions of the proportion of contaminated defecating areas and the seroprevalence of cats and rodents, at equilibrium, along a gradient of environments going from $aK_2^* = 0$, an extreme urban area, to $aK_2^* = 1$ prey/cat/week, referring to suburban–rural areas (Fig. 2).

The infection persists in environments with no available prey only through SLC transmission (Fig. 2A,B). When considering the

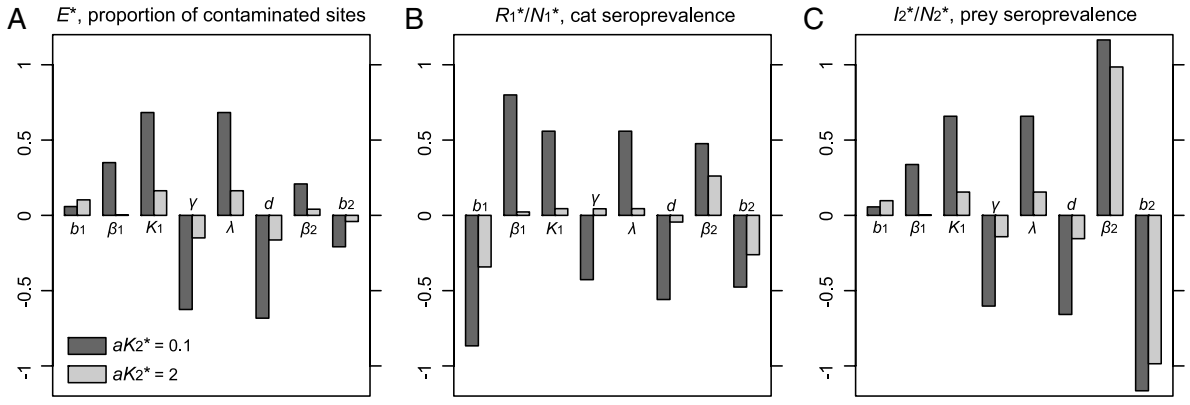

Fig. 3. Elasticities of the proportion of contaminated defecating site E (A), cat seroprevalence R_1/N_1 (B) and prey seroprevalence I_2/N_2 (C), at equilibrium, to parameters b_1, $\beta_1, K_1, a, \gamma, \lambda, d, \beta_2, b_2$ (see Table 1 for parameter definitions).

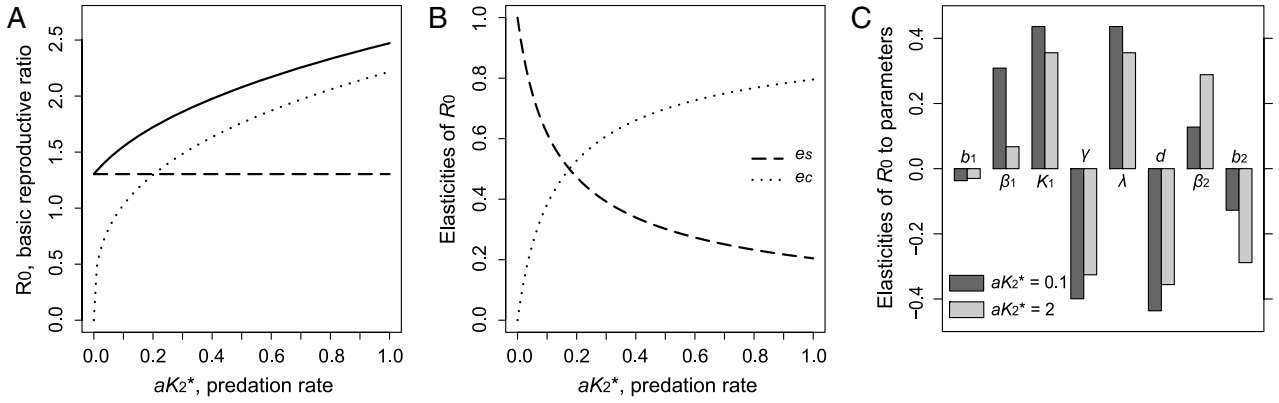

Fig. 4. The basic reproductive numbers R_0, R_{0S} and R_{0C} as a function of the predation rate aK_2^* (prey/cat/week) (A), relative contributions of R_{0S} and R_{0C} in R_0 as a function of aK_2^* (B) and elasticities of the overall basic reproductive number R_0 to parameters b_1, $\beta_1, K_1, a, \gamma, \lambda, d, \beta_2, b_2$ (see Table 1 for parameter definitions) (C).

CLC alone, the parasite does not persist when $aK_2^* < 0.092$ prey/cat/week, corresponding to 4.8 prey/cat/year (Fig. 2A,B). This means that a minimum level of predation of more than 5 prey per year is needed for the parasite to be transmitted by CLC.

For $aK_2^* = 0.16$ prey/cat/week, i.e. 8.3 prey/cat/year, $E_{SLC} = E_{CLC}$ and $R_1/N_{1SLC} = R_1/N_{1CLC}$, below this threshold, $E_{SLC} > E_{CLC}$ and $R_1/N_{1SLC} > R_1/N_{1CLC}$ and conversely above (Fig. 2A,B). Complex transmission alone is thus more efficient than simple transmission alone above the $aK_2^* = 8.3$ prey/cat/year threshold.

When the predation rate increases, predictions E and I_2/N_2 obtained from the CLC converge to values obtained with both cycles (Fig. 2A,C). For the cat seroprevalence R_1/N_1 (Fig. 2B), convergence occurs for higher values of predation rate (not shown on figure).

3.3.2. Elasticities of predictions to parameters when both cycles coexist

The elasticities of E (proportion of contaminated defecating sites), R_1/N_1 (cat seroprevalence) and I_2/N_2 (prey seroprevalence) to parameters were calculated for a predation rate of 0.1 prey/cat/week, that is 5.2 prey/cat/year, representing an extreme urban site, and for $aK_2^* = 2$ prey/cat/week (104 prey/cat/year), an average predation level in rural areas. These values are used to highlight the parameters for which small variations will result in large variations in predictions, and thus the parameters that need accurate estimates.

In all cases, the absolute values of the elasticities are highest for low predation rate, $aK_2^* = 0.1$ prey/cat/week (Fig. 3), meaning that predictions concerning urban sites are most sensitive to variations in the parameters.

The proportion of contaminated defecating sites E is particularly sensitive to variations in parameters linked to its dynamics, i.e., the number of cats in the population K_1, the duration of cat infectiousness related to parameter γ and the contamination and decontamination rates, respectively λ and d (Fig. 3A).

When $aK_2^* = 0.1$, the predicted seroprevalence of cats R_1/N_1 has similar elasticity values to all parameters, with the highest values obtained for the cat birth rate b_1 and the transmission rate from the environment to cats β_1 (Fig. 3B). When $aK_2^* = 2$, R_1/N_1 is more sensitive to the cat birth rate b_1, the prey birth rate b_2 and the transmission rate from environment to prey β_2 (Fig. 3B). The most important parameters are not identical in both situations: when $aK_2 = 0.1$, influential parameters are linked to the SLC transmission (β_1 and b_1) while CLC-related parameters are more important when $aK_2 = 2$ (β_2 and b_2).

Prey seroprevalence I_2/N_2 is more affected by variations in parameters involved in prey infection and prey dynamics: β_2 and b_2 (Fig. 3C). The differences between the elasticities associated to these parameters and those associated to other parameters are highest when $aK_2^* = 2$. Thus, relatively to the other parameter elasticities, parameters β_2 and b_2 are more important in the prey seroprevalence when predation is high.

3.4. Basic reproductive numbers R_0s and contribution of each cycle

First, we compared the efficiency of both cycles when they are independent (R_{0S} and R_{0C}) and together (R_0). Whatever the value of K_2, R_0 and R_{0S} are larger than 1 with our parameters (Fig. 4A). R_{0C}, which represents CLC transmission, is larger than or equal to 1 when $K_2 \geq 0.092$ prey/cat/week, as observed in Fig. 2. For values of

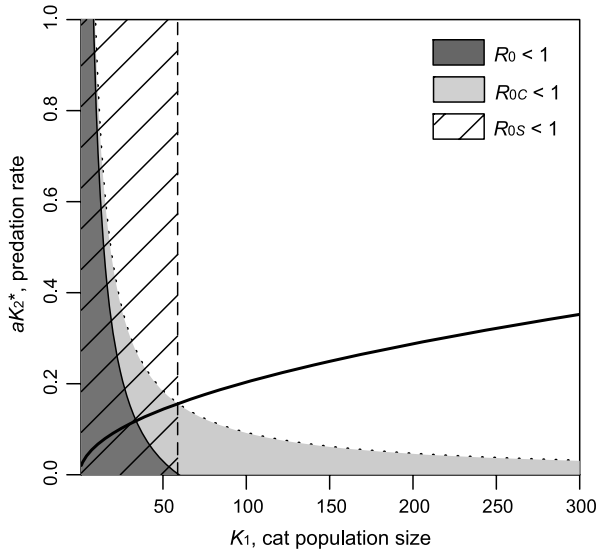

Fig. 5. Predation rate aK_2^* as a function of the size of cat population at equilibrium K_1. The hatched, light grey and dark grey surfaces respectively represent values of aK_2^* and K_1 for which $R_{0S} < 1$ (the parasite cannot spread by SLC), $R_{0C} < 1$ (the parasite cannot spread by CLC) and $R_0 < 1$ (the parasite cannot spread by SLC + CLC). The curve represents the threshold of the predation rate as a function of cat population size below which $R_{0S} > R_{0C}$.

$aK_2^* > 0.20$ prey/cat/week, i.e. 10.6 prey/cat/year, R_{0C} is larger than R_{0S}. The value of this threshold slightly differs from the previous value of $aK_2^* = 8.3$ prey/cat/year.

Following Hartemink et al. (2008), we assimilated the elasticities of R_0 to R_{0S} and R_{0C} to the relative contributions of each cycle in the transmission (Fig. 4B). We observed a threshold of 0.18 prey/cat/week (equivalent to 9.3 consumed prey/cat/year) below which the SLC contributes more than the CLC in the spread of the parasite, and the opposite conclusion above this threshold (Fig. 4B). For a predation rate of 0.4 prey/cat/week – corresponding to 21 prey/cat/year, the threshold used to delimit urban and rural sites – the SLC contributes to 34.0% in the spread of *T. gondii* (Fig. 4B); this contribution decreases to 20.4% and 14.0% when a cat eats 1 (Fig. 4B) or 2 (not shown on figure) prey per week, respectively.

As previously, the elasticities of R_0 to parameters were calculated for a predation rate of 0.1 prey/cat/week, referring to an extreme urban site, and for $aK_2^* = 2$ prey/cat/week, referring to a rural area with a medium predation rate. The absolute values of the elasticities are higher for $aK_2^* = 0.1$ than for $aK_2^* = 2$ except for parameters β_2 and b_2 (Fig. 4C). When $aK_2^* = 0.1$, the elasticities of R_0 to the transmission rate β_1, the size of the cat population at equilibrium K_1, the recovery rate γ, the environmental contamination rate λ and the decontamination rate d are the highest (Fig. 4C). When $aK_2^* = 0.1$, R_0 is most sensitive to parameters K_1, γ, λ, d, $\beta 2$, and b_2. As for the cat seroprevalence, we observe a switch of the importance of β_1 and β_2 with the increase of predation.

3.5. Extinction or persistence of infection according DH and IH availability

When considering SLC transmission only, the critical size of the cat population is $K_1 = 58.9$ individuals; under this value, the parasite goes extinct (Fig. 5, hatched surface). For the CLC, the critical regions are for low predation rates and low cat population sizes (Fig. 5, light grey surface). When both cycles coexist, the area for which the parasite cannot persist is reduced, and there are fewer situations for which the parasite cannot spread (Fig. 5, dark grey area).

The curve represents the threshold under which $R_{0S} > R_{0C}$ and conversely above (Fig. 5). This threshold of predation increases with the number of cats, suggesting that for equal predation rate aK_2^* the contribution of the SLC increases with K_1.

Overall, the coexistence of the CLC and the SLC increases the range of conditions of persitence of the parasite: at low levels of cat population size or predation rate, one cycle alone may be insufficient to get $R_0 > 1$.

4. Discussion

Our objective was to understand the dynamics of transmission of the parasite *T. gondii* during its natural life cycle, and especially to assess the role of the simple life cycle (SLC) versus the complex life cycle (CLC) in the transmission. To our knowledge, this work is also the first attempt to compute the basic reproductive rate of *T. gondii*.

In a large range of scenarios, the complex transmission is major in *T. gondii* transmission. Its relative contribution rapidly increases with the predation rate and exceeds 50% in the spread of the parasite as soon as average predation is greater than 9.1 prey per cat per year, when considering a population of 100 cats. We advocate that this threshold of 9.1 predated prey/cat/year is the most appropriate, relatively to the other thresholds obtained, as it is obtained from elasticities of R_0 to R_{0S} and to R_{0C} in which interactions between both cycles are considered. Although the CLC is predominant in many cases, the SLC may still be important in critical situations where few or no prey are available. When the predation rate is intermediate between rural and urban areas, i.e. 21 prey/cat/year, the SLC has a non-negligible contribution of 30% in the spread of the parasite, which decreases to 14% when each cat preys on 104 small rodents per year. This non-negligible role of the SLC even at high predation levels may indicate that the SLC significantly contributes to parasite spread. The ability of oocysts to infect cats may be maintained over time because of this contribution. Moreover, the association of the two cycles enables the persistence of the parasite in a large range of combinations of predation rates and cat population sizes. Similarly to Choisy et al. (2003), our model qualitatively shows that a threshold of predation rate, depending on the size of the cat population, determines the dynamics of transmission. Below the threshold, the SLC predominates in the spread of *T. gondii*, while above the threshold, the CLC has the largest contribution. This conclusion could be extended to parasites with similar transmission cycles.

These conclusions are conditioned by several assumptions that were made in order to improve the tractability of the model: the absence of any direct transmission among IHs (vertical transmission or carnivorism), any manipulation of the behaviour of the IHs by the parasite, and any virulence for intermediate hosts. However, vertical transmission has been showed to occur in mice, *Mus domesticus*, *Mus musculus* and *Apodemus sylvaticus* (Marshall et al., 2004, Owen and Trees, 1998), carnivorism was observed in rats *Rattus norvegicus* (Webster, 1994) and manipulation of behaviour was also observed in infected rats and mice (Berdoy et al., 2000; Hrda et al., 2000; Vyas et al., 2007). Nevertheless, the level of each process and its effect on the life cycle have not been fully assessed. Finally, the impact of toxoplasmosis on the survival and fecundity of rodents has not been measured in natural conditions; however, laboratory experiments have shown that laboratory mice were more susceptible than common voles to *T. gondii* oocysts (Sedlak et al., 2001). It would be useful to include these elements and to assess their impact on the overall cycle. Moreover, because they influence the CLC only, they would probably not change our qualitative conclusion that the SLC may be important under a threshold of predation rate.

Coming to the estimation of parameters and thus thresholds, we have uncertainties about several parameters that play an important role in the accuracy of the model predictions and R_0. In particular, the transmission rate from the environment to cats β_1, which is an important parameter in situation of low predation, was estimated under the assumption that there was no prey in the studied urban area. Thus we assumed that cat infection occurred just by contact with contaminated defecating sites, leading to a probable overestimation of β_1. As the transmission rate from the environment to prey β_2, whose role increases with predation, was estimated *a posteriori*, we have uncertainty on its value. The decontamination rate d was possibly underestimated, being calculated from experimental studies using mice inoculation to recover oocysts (Yilmaz and Hopkins, 1972). Mice are highly susceptible to oocysts; parasites have thus been considered to survive as long as one infectious oocyst can be recovered through inoculation, while most oocysts were probably no longer infectious at that time. Considering better estimates for the parameters, or a more complete model, would probably lead to changes in the predicted values.

In spite of these simplifications and uncertainties, the predicted values lie in realistic ranges. The threshold obtained for the predation rate corresponds to 9.1 consumed prey per cat per year. This value represents a low predation rate even in urban populations (Baker et al., 2005; Barratt, 1998), while the predation rates estimated in rural areas are always high (Gillies and Clout, 2003; Kays and DeWan, 2004; Liberg, 1984). The predicted prevalence of antibodies in cats living in urban areas ranges from 6.9% to 33.2% in accordance with recent estimates obtained in urban populations, 18.6% (Afonso et al., 2006) and 22.4% (Hornok et al., 2008). In suburban and rural areas, we predicted a cat seroprevalence ranging from 33.2% to 83.4%, which is similar to values reported in field studies ranging from 50% in a suburban area (Hornok et al., 2008), to 61.3% (Hornok et al., 2008) and up to 87.3% (Cavalcante et al., 2006) in rural areas. As we chose an ad hoc value of β_2, the predicted seroprevalence in prey is around 5%, in agreement with reported values (Afonso et al., 2007). Concerning the environment, we predicted a proportion of contaminated defecating sites in urban areas varying from 36.4% to 73.2%, while Afonso et al. (2008) reported a lower value of 31.3%. This result may come from the overestimation of the survival of the parasite in soil. Using a higher value of the decontamination rate d would lead to decreasing the predicted level of environmental contamination. This underlines the need for better quantitative data about the survival dynamics of *T. gondii* oocysts in the environment. Moreover, we need field data on the level of environmental contamination in rural areas to compare with our predictions ranging from 73.2% to 87.2%. These predictions are probably overestimated for the same reason. Finally, it must be noticed that although this level is higher than predicted for urban areas, this does not mean that the level of environmental contamination is expected to be generally higher in rural areas. Our predictions only concern defecating sites, and because the cat density is much lower in rural areas, the defecating sites should be more often infected, but less dense in rural compared to urban sites.

This model provides a first analysis of the variability of the life cycle of *T. gondii* among environments. Because toxoplasmosis is an important infection from the public health point of view, our results may have consequences concerning the main routes of transmission from animals to humans, i.e., by consuming infected meat or through ingestion of oocysts. Attempts to estimate the relative role of these transmission routes have showed variable estimates among countries (Cook et al., 2000). More generally, the risk factors that were found for toxoplasmosis vary among epidemiological studies, being conditioned by environmental conditions and by feeding and eating habits of human populations (Tenter et al., 2000). From the results of this model, one can speculate that environmental conditions may contribute to explain this variability, with people living in rural environments being exposed to high levels of toxoplasmosis in general, but some urban populations having a specific risk due to oocysts. In the future, our model may be enlarged to include meat-producing species and human infection to test this hypothesis.

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Appendix

Literal expression of I_1^*, the number of infected cats at equilibrium, when the two cycles SLC and CLC are associated:

$$
\begin{aligned}
I_1^* = {} & (((b_1K_1\lambda(\beta_2 gaK_2^* + \beta_1\beta_2 + b_2\beta_1))^2 \\
& + (2b_1\beta_2^2 dg^2(\gamma + b_1)(aK_2^*)^2 \\
& + 2b_1\beta_2 dgaK_2^*(\beta_1\beta_2 + b_1\beta_2 + 2b_2\beta_1) \\
& - 2b_1\beta_1(\beta_2 + b_2)(b_1\beta_2 - b_2\beta_1)d(\gamma + b_1))K_1\lambda \\
& + (\beta_2 aK_2^* gd(\gamma + b_1))^2 + (d(\gamma + b_1))^2(2\beta_2 gaK_2^*(b_1\beta_2 + b_2\beta_1) \\
& + b_1^2 + \beta_2^2 - 2b_1b_2\beta_1\beta_2 + b_2^2\beta_1^2))^{1/2} \\
& + (\beta_2 gaK_2^* + \beta_1(\beta_2 + b_2))K_1\lambda b_1 \\
& - aK_2^*\beta_2 gd(\gamma + b_1) - (b_1\beta_2 + b_2\beta_1 + 2b_1b_2)d(\gamma + b_1)) \\
& /(2\lambda(\gamma + b_1)(\beta_2 gaK_2^* + \beta_1\beta_2 + b_1\beta_2 + b_2\beta_1 + b_1b_2)).
\end{aligned}
$$

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