An Agent-based Model for the Transmission Dynamics of *Toxoplasma gondii*

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Abstract

*Toxoplasma gondii* (*T. gondii*) is a unicellular protozoan that infects up to one third of the world’s human population. Numerous studies revealed that a latent infection of *T. gondii* can cause life-threatening encephalitis in immunocompromised people and also has significant effects on the behavior of healthy people and animals. However, the overall transmission of *T. gondii* has not been well understood although many factors affecting this process have been found out by different biologists separately. Here we synthesize what is currently known about the natural history of *T. gondii* by developing a prototype agent-based model to mimic the transmission process of *T. gondii* in a farm system. The present model takes into account the complete life cycle of *T. gondii*, which includes the transitions of the parasite from cats to environment through feces, from contaminated environment to mice through oocysts, from mice to cats through tissue cysts, from environment to cats through oocysts as well as the vertical transmission among mice. Although the current model does not explicitly include humans and other end-receivers, the effect of the transition to end-receivers is estimated by a developed infection risk index. The current model can also be extended to include human activities and thus be used to investigate the influences of human management on disease control.

Simulation results reveal that most cats are infected through preying on infected mice while mice are infected through vertical transmission more often than through infection with oocysts, which clearly suggests the important role of mice during the transmission of *T. gondii*. Furthermore, our simulation results show that decreasing the number of mice on a farm can lead to the eradication of the disease and thus can lower the infection risk of other intermediate hosts on the farm. In addition, with

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the assumption that the relation between virulence and transmission satisfies a normal function, we show that intermediate virulent lineages (type II) can sustain the disease most efficiently, which can qualitatively agree with the fact that the evolution of the parasite favors intermediate virulence. The effects of other related factors on transmission, including the latent period and imprudent behavior of mice, and prevention strategies are also studied based on the present model.

Key words: *Toxoplasma gondii*; life cycle; transmission dynamics; agent-based modeling.

## 1 Introduction

*Toxoplasma gondii* (*T. gondii*) is an obligate intracellular protozoan parasite that infects all warm-blooded vertebrates, including mammals and birds. Up to one third of the world’s human population is estimated to carry a *Toxoplasma* infection [1]. The increasing prevalence of infection in human population is probably due to the increase in the number of cats. Recent reports found that cats outnumber dogs as the number one household pet by 10 million animals in America, but they are less likely to receive veterinary care than dogs [2]. As the primary host of *T. gondii*, cats can shed millions of oocysts, which has the potential to infect a large number of intermediate hosts including humans. *Toxoplasma* infection can cause life-threatening encephalitis in immunocompromised persons such as AIDS patients [3] and recipients of organ transplants and cancer chemotherapy. Moreover, infection acquired during pregnancy may spread and cause severe problems to the fetus such as damages to the baby’s eyes, nervous system, skin, and ears. *Toxoplasmosis* also has significant effects on human and animal behavior and may lead to neuropsychiatric disorders, e.g. schizophrenia [4–6].

*T. gondii* has a complex life cycle and has drawn attention of researchers in disciplines from epidemiology, immunology, human behavior, cell biology and parasitology [7]. The life cycle of *T. gondii* involves multiple hosts and includes sexual and asexual replication. Felids are the definitive hosts, in which sexual replication of the parasite occurs. All warm-blooded vertebrates can serve as intermediate hosts, in which asexual replication occurs [8]. Oocysts are shed by cats into the environment, where they develop into infectious sporozoites that, if ingested, can cause infection in intermediate hosts. Although different aspects of the *T. gondii* life cycle have been intensively investigated, the overall transmission dynamics of this parasite has not been well studied.

A few mathematical models have been built to investigate the transmission of *T. gondii* [9–12]. Aranda et al. [9] were the first to study the evolution dynamics of *T. gondii* in human population using an SIR (susceptible-infected-removed) model. Recently, Gonzalez-Parra et al. [10] and Aranda et al. [11] also used SIR models to take into account of the role of multiple hosts and the effect of the vaccination of cats. A dynamic compartment model was developed by Mateus-Pinilla et al. [12] to investigate the transmission of *T. gondii* on swine farms with a primary focus on the importance of a feline *T. gondii* vaccine. Those mathematical models explain some of the dynamical behaviors of the disease in the definite host (cat) as well as the intermediate host (e.g. human, swine) populations. For example, Mateus et al.’s work [12] revealed that the initial *T. gondii* prevalence in cats has no effect on the *T. gondii* prevalence in finishing pigs, and that vaccination had less impact on decreasing *T. gondii* infection in finishing pigs than did a decrease in the number of farm cats. Arenas et al. [11] showed that
the basic reproduction number completely determines the global dynamics and the outcome of the disease. However, these models do not consider the complete life cycle of T. gondii. Moreover, these models, whether differential or difference equations, are deterministic and ignore the stochasticity that characterizes random biological behaviors.

As pointed out by Bonabeau [13], ABMs are most useful to describe systems, where (1) interactions between the agents are complex, nonlinear, discontinuous, or discrete; (2) space is crucial and the agents’ positions are not fixed; (3) the population is heterogeneous and each individual is (potentially) different; (4) the topology of the interactions is heterogeneous and complex; (5) the agents exhibit complex behavior, including learning and adaptation. Various authors have utilized agent-based modeling approaches to investigate complex dynamics and emergent properties in biological systems. Simulations based on these models have been used to enhance our understanding of disease pathology. For example, Segovia-Juarez et al. [14] developed the first ABM of granuloma formation in TB to investigate the complex dynamics and emerging behavior in the lung during TB granuloma formation and development. This model was later extended in [15,16] to include more detailed immune responses at multiple biological scales. These studies pointed out the important role of T-cell related mechanisms in infection progression. A multi-agent computational platform was developed by Roche et al. [17] to investigate vector-borne disease transmission. In a recent review article, Bauer et al. [18] discussed a number of agent-based models relevant to host-pathogen systems and pointed out limitations and challenges of such models.

Here, we develop a prototype agent-based model (ABM) to describe the transmission of T. gondii on a farm, and aim to understand how the transmission process will be affected by each part of the complete life cycle of T. gondii. This prototype model sets the stage for future developments, where agents make adaptive decision based on history and their local interactions with environment and other agents. Future models will also include human activities to investigate the influences of various control policies. In Section 2, we describe ABM formulation based on biological observations. The model accounts for stochastics of the transmission behavior. We explicitly include the rodent sector (mouse) of the population in the model since mice are natural hosts of T. gondii and they are considered major hosts for transmission. Many factors, such as the population dynamics, predator-prey process of cats and mice, and virulence of the disease are incorporated into the model. Simulation results from the model are investigated in Section 3 and the role of each transmission route is studied. Finally, the potential usage of this model and future work is discussed in Section 4.

2 Model Description

Previous studies have identified rodents as risk factors for the transmission of T. gondii [19]. To describe the complete life cycle of T. gondii and quantify the effect of rodents, we consider the spread of the disease on a farm of 3 km² consisting of cats and mice. Other animals such as cattle and swine are end-receivers of the parasite and thus do not influence the spread of the disease. We do not include these animals in the present model, although the effect of transition to these intermediate hosts is identified by an infection risk index.

A schematic representation of the life cycle of T. gondii on the farm model is shown
in Figure 1. Here, an infected cat may cast feces containing oocysts of *T. gondii* to the environment. If a mouse comes into contact with an area that is contaminated with oocysts, it may ingest the oocysts and get infected. Then, a cat, ingesting the tissue cysts of an infected mouse, may become infected. A cat may also get infected from oocysts in the environment but with a much lower probability [8]. In addition, the vertical transmission from the infected mice to their offspring is another possible route of transmission of *T. gondii*. All of the above mentioned transmission behaviors are assumed to occur with certain probabilities. For simplicity, we assume cats and mice do not migrate to and from the farm.

In the following, we describe the properties of the agents and the rules governing various processes, including population dynamics, predator prey, oocyst shedding, infection, etc. A pseudo code is provided in Appendix A to describe the implementation of these rules as well as the overall dynamic process.

### 2.1 Agents

As shown in Figure 1, the model includes two types of agents: cats and mice. According to existing knowledge, we shall define rules governing the *T. gondii* transmission related behaviors of each agent.

**Cats:** In a field study [20], Warner estimated that the average number of cats on a farm is 6.3 per km$^2$. Since we consider a farm of 3 km$^2$ in our work, we assume there are about 20 cats living on the farm. According to its health state, a cat can be compartmentalized into one of the three divisions which are susceptible to, infected with, or immune to the parasite. Susceptible cats are those that have not been previously infected and can become infected by ingesting tissue cysts or oocysts. After infection, a cat can undergo a latent period of a few days before casting feces with oocysts, which may last for 10-15 days [21]. We assume the latent period is 3 days and the infected cats shed oocysts for 2 weeks. The number of oocysts shed by an infected cat may vary during the infection period [8, 21]. In the current model, we set the amount of oocyst shed per day to be 20 million units. After shedding oocysts for 2 weeks, the cat becomes chronically infected and will stop shedding oocysts. Then, we assume that the cat recovers from the infection symptoms. The cat can develop immunity to *T. gondii*, however, this immunity is not permanent. The duration of immunity can vary from several weeks [22] to several years [23]. In an investigation by Dubey [24], 9 cats were fed tissue cysts of *T. gondii* 77 months after their primary infections and 4 of them re-excreted oocysts. Thus, we assume a half-life decay for the immunity of cats to be 6 years. The number of oocysts shed during the secondary infection is usually lower than the primary infection [22]. The prepatent period of the second infection is about 7 days and the re-excretion lasts only about 2-3 days [24]. More details of the primary and the secondary infection will be discussed in the subsection of 2.5. Cats may also carry maternal immunity if its parents recover from acute infection of the parasite. It is reasonable to assume a cat loses maternal immunity after weaning [25] and become susceptible.

**Mice:** According to its health state, a mouse can be either susceptible or infected. A susceptible mouse can get infected through ingesting oocysts. A mouse may also be born with infection, if its parents are infected. Recent studies have verified the high frequency of vertical transmission of *T. gondii* in chronically infected domestic mice [26, 27], wild mice [27, 28] and families of sheep [29]. In Owen and Trees's tests, 82.7% of pups produced
by chronically infected house mice and 85.0% of offsprings of chronically infected field mice demonstrated vertical transmission. Hide et al. also show that the vertical transmission rate of mice is 75% [45]. This extremely efficient mechanism favors parasite transmission and dispersion in hosts predated by the cat. Parasites in mice also have a latent period. After this period, the infected mouse will develop symptoms of acute infection. We assume the latent period and the symptomatic period are both 2 weeks. Even when the symptoms disappear, a mice will stay in the infected status permanently. The number of mice on the farm is treated as a parameter, which varies from a few tens to a couple of hundreds. This allows us to to investigate the role of mouse population density on disease transmission.

2.2 Environment

We consider a 3 km\(^2\) farm, which is divided into 50 \times 50 cells. Assuming the farm is squared and all cells are also squared, then the size of a cell is 34.6 m by 34.6 m or 1200 m\(^2\). To track the positions of the agents as well as the distribution of oocysts, each cell is assigned a unique coordinate. We assume the daily activities of a cat occur in a square of 10 \times 10 cells and the daily activities of a mouse occur in a square of 2 \times 2 cells. The daily changes of positions for the agents are according to a random walk rule; see the subsection on predator prey. If an infected cat casts oocysts in a cell, the cell will be marked as contaminated and the amount of oocysts will be added to the total amount of oocysts already in this cell. Usually, oocysts in environment can last from 6 months to 1 year [8], depending on the climate and surroundings. We define a threshold of detection for oocysts within a cell. When the amount of oocysts decays to below this threshold, the cell will be marked as a clean cell.

2.3 Population Dynamics

We consider the farm as an enclosed area, in which the populations of cats and mice are affected by the migration of animals. According to Warner’s [20] field study on free-ranging domestic cat populations, breeding females give birth to an average of 7.1 kittens per year. Since the model does not differentiate the sex of a cat, we set the average birth probability \(p_{birth}\) of each mature cat to 3.5/365 per day. Considering the effect of climate on the birth rate of cats, we assign two birth probabilities, i.e., 5.6/365 for the period from April to September and 1.4/365 for the rest time of the year. The average age of maturity in cats is chosen to be 240 days as is reported in [30].

Warner [20] carried out a census of cats in the rural area of Illinois, which indicated a strong correlation between the age of a cat and its risk of death. Warner’s data showed that about 6% of cats can survive beyond 3 – 5 years of age and less than 1% can survive 7 or more years. We can define the natural death risk of a cat per day as a linear function of the cat age using Warner’s data as follows:

\[
d_0^c = 2.80 \times 10^{-3} + 4.47 \times 10^{-6} \times \text{age}. \tag{1}
\]

Moreover, we assume that the actual death rate of cats also depends on \(T_c\), the carrying capacity of cats on the farm, and obeys the following relation

\[
d^c = d_0^c \exp \left(1 - N_c/T_c\right), \tag{2}
\]
where $N_c$ represents the total number of cats on the farm. It follows that, when the number of cats is less than the carrying capacity, the death rate is lower than the natural risk whereas it is higher than the natural risk when the number of cats is greater than the carrying capacity.

The weaning age and maturity age of mice are 21 days and 50 days, respectively, according to available reports [31]. Similarly the average birth rate of a mature mouse is 25 per year. Again we assign two birth probabilities for a matured mouse, i.e., $40/365$ for the period from April to September and $10/365$ for the rest time of the year. We estimate the survival rate of mice using cat data by estimating 1 mouse year to be 0.2 cat year based on the fact that the mature age of mice is about 0.2 times of that of cats. Therefore, we define the daily natural death rate of mice to be

$$d_0^m = 2.80 \times 10^{-3} + 2.15 \times 10^{-5} \times \text{age},$$

(3)

where age represents the age of the mouse in days. Similarly, the actual death rate of a mouse per day is

$$d^m = d_0^m \exp \left(1 - N_m/T_m\right),$$

(4)

where $T_m$ and $N_m$ represent the carrying capacity of the mice and the total number of mice on the farm, respectively.

### 2.4 Predator Prey

We assume that post-weaning cats and mice walk randomly on the farm and that cats have a larger random walk region than mice. We assume the daily activities of a cat occur in a square of $10 \times 10$ cells and the daily activities of a mouse occur in a square of $2 \times 2$ cells. The current model does not assign habitats to the agents and thus the agents need not to return to their starting positions at the beginning of the day. The maximum change in position for a cat in a day is 5 cells in both horizontal and vertical directions while that for a mouse is 1 cell. The position of post-weaning animals are updated once a day. The probability of a mouse being caught by a cat is assumed to exponentially decrease with the distance between a cat and a mouse as follows:

$$p_{\text{prey}} = \max \left[ a_0 e^{r/r_0} - e^{r/r_0} - e, 0 \right],$$

(5)

where $a_0$ is the prey probability when the cat and the mouse are in the same cell, $r$ is the distance between the cat and the mouse, and $r_0$ is the maximum prey distance. Note that $r$ is computed at the centers of the cells and thus takes discrete values.

### 2.5 Oocyst Shedding

Several factors including the age of the cat, the strain of $T. gondii$, the nutritional status of the cat, and the number of tissue cysts fed during primary and secondary infections, can affect the shedding of oocysts [24]. Here we assume that cats can shed 20 million units of oocysts per day during their primary infection and 5% of this amount (1 million) during their secondary infection.
Previous research shows that oocysts can resist harsh environmental conditions and survive a few years outdoors. We assume the amount of oocysts $A$ in environment decays with time exponentially as follows:

$$A = A_{ini} e^{-t/\tau}$$

where $\tau$ is the time constant and $A_{ini}$ is the initial amount of oocyst shed by the infected cat. In addition, we assume that oocysts cannot be detected if the amount is lower than 2000 units, which is 1/10000 of the amount shed by a first infected cat per day. Therefore, the time constant $\tau$ is set to be 40 (20) days when the survival period is 52 (26) weeks.

### 2.6 Infection

Cats that have never been infected lack antibodies to *T. gondii*. Cats can be easily infected by ingesting tissue cysts whereas they usually do not become ill even after ingesting a large number of oocysts [32, 33]. We assume a susceptible cat is definitely infected if it eats an infected mice. On the other hand, the probability that a susceptible cat becomes infected by oocysts in the environment is set as 5%.

#### 2.6.1 Infected with oocysts

Both cats and mice can be infected by oocysts spread in farm cells. The maximum infection risk, $r$, of a cell depends on the amount of oocysts in that cell, i.e.,

$$r = \frac{A}{A + A_f}.$$

We choose $A_f = 2 \times 10^6$ units so that, at the end of survival period of oocysts, the infection risk decreases to 1/1000 of the initial stage.

When a cat (or a mouse) passes a contaminated cell, the possibility of being infected is defined as

$$p_{inf}^o = rp_0,$$

where $p_0$ is taken to be 25% for mice and 2.5% for cats. We can further evaluate the risk of infection to other hosts on the farm with $N$ cells as follows:

$$\bar{r}_{e} = \frac{1}{N} \sum_{i=1}^{N} r_i p_0.$$

where $r_i$ represents the infection risk of cell $i$. Here we assume all other hosts hold equal possibilities of being infected by oocyst as mice, therefore, $p_0 = 25\%$.

#### 2.6.2 Infected with tissue cysts

*T. gondii* inside an infected mouse takes a few days to develop into tissue cysts. Therefore, whether a susceptible cat gets infection from eating an infected mouse depends on how long
the mouse has been infected. We assume that the possibility that a cat becomes infected by eating an infected mouse is a function of the infection time $t$ (unit: days) of that mouse:

$$
\frac{p_{\text{inf}}^t}{e^t + 10000}.
$$

(10)

It then follows that if a cat eats a mouse within the first week of infection, the cat rarely gets infected. In contrast, a cat almost always gets infected if it eats a mouse after its latent period of infection.

### 2.6.3 Secondary infection

After primary infection, cats recover (and thus become immune) and stop shedding oocysts. The duration of the immunity may last for a few years. Based on Dubey’s study [24], most cats fed with tissue cysts of *T. gondii* after their primary infections remained immune up to re-shedding of oocysts during the earlier period and 5 out of the 9 cats remained immune for 77 months after primary infection. In this work, we assume that a cats immunity to re-shedding of oocysts decay at a constant rate with the half life equal to 6 years. Therefore, the probability of the secondary infection is a function of time:

$$
p_{\text{inf}}^{2nd} = p_{\text{inf}}^{1st} e^{ct}.
$$

(11)

where $p_{\text{inf}}^{1st}$ can be taken as $p_{\text{inf}}^0$ or $p_{\text{inf}}^t$, depending on infected by oocyst or tissue cyst. It follows from equation 11 that 6 years after the initial infection, the probability of the secondary infection is 50%. We choose $c$ to be 0.00315423/day such that the probability remains below 0.3% of the probability of initial infection in the first year of primary infection and below 1% in the second year.

### 2.7 Virulence

The rate at which cats are infected by eating an infected mouse depends on the virulence of the parasite. Infection with *T. gondii* may cause mortality, which is closely related to the amount as well as the stage of infected parasites. For example, oocysts are more virulent to mice than tissue cysts. In addition, *T. gondii* has more than 140 genotypes and displays a wide range of virulence levels [34] and our unpublished data. Specifically, *T. gondii* can be anything from nonvirulent to nearly 100% lethal. Suzuki and Joh showed that strains of intermediate virulence produce 10 to 20 times more tissue cysts than those of nonvirulent and very highly virulent strains [35]. Therefore, it is reasonable for us to assume that mice infected with strains with intermediate virulence are more likely to cause infection in cats than those infected with nonvirulent or highly virulent parasites. We assume that the relationship between virulence and transmission satisfies a normal distribution, which qualitatively agrees with the above statement. Thus,

$$
T_s = e^{-\frac{(\nu-\mu)^2}{2\sigma^2}},
$$

(12)

where $T_s$ stands for the transmission ability of different strain type of *T. gondii*, $\nu$ represents the virulence of the parasite, and $\mu$ and $\sigma$ are the mean and standard deviation of the
distribution, respectively. In the following simulations, we take $\mu = 30\%$ and $\sigma = 15\%$. In addition, we assign a mortality rate of $17\%$ for cats during the primary infection and zero mortality rate during secondary infections, which agrees with the observation that only 2 out 12 infected cats died within the two weeks after the first infection from Dubey’s study [24]. Note that other unimodal distributions may also match the aforementioned qualitative arguments. Normal distribution is chosen merely for convenience.

3 Results

3.1 Population Dynamics

We first investigate the population dynamics of cats and mice on a farm, which has not been contaminated with *T. gondii*. A typical response is shown in Figure 2 (a) and (b), where the carrying capacities of cats and mice in the farm are set as 20 and 200, respectively. The oscillatory rhythms of the populations are due to the annual birth cycles of cats and mice whereas the noisy fluctuations are due to the intrinsic stochasticity of the processes, including birth, death, and predator-prey events. To further reveal the annual rhythms in the population dynamics, we repeat the population simulation 100 times and plot the averaged results in Figure 2 (c) and (d). The results in Figure 2 indicate that the population dynamics on the farm are stable under the given parameters. We also numerically verify that the population dynamics in the absence of parasites are robust under variation of parameters (Figures are omitted). This is to ensure that the model is reliable for investigation on disease transmission.

3.2 Transmission of *T. gondii*

We then introduce *T. gondii* to the farm to investigate the spread and sustainability of the disease. A typical response is shown in Figure 3. Here, we set the carrying capacities of cats and mice at 20 and 200, respectively. We assume a 20% virulence to mice, that is, 80% of the infected mice can survive beyond 2 weeks after the latent period. Other parameters adopt the default values given in Table 1. As stated before, the survival time of oocysts depends on their surrounding conditions, especially on the temperature of the farm environment. We consider both a long survival time of 52 weeks and a short survival time of 26 weeks. We simulate each case for 10 years and repeat the simulations 100 times. The averaged results of those 100 simulations are plotted in Figure 3. Moreover, the prevalence of the disease as well as the infection risk of the farm exhibit oscillatory behaviors due to rhythmic patterns in the underlying population dynamics as shown in Figure 2. It is not surprising that the disease in a farm with the longer survival time infects more animals than the farm with the shorter survival time. Furthermore, we can see that the parasite oocysts with the survival time of 52 weeks is sustained over 10 year period in all 100 simulation trials. However, oocysts with the shorter survival time become eradicated in 9 simulation trials during the 10 year period. One of the extinction cases is shown in Figure 4. In this simulation, although the number of infected cats and the number of cats shedding oocysts are approximately the same as the average level, the number of infected mice does not reach a level necessary to sustain the
As shown in Figure 1, the life cycle of *T. gondii* involves interactions among cats, the farm environment, and mice. To investigate the significance of each transmission route, we plot the accumulated numbers of infected cats and mice over time in Figure 5. The parameters used in these simulations are the same as those used in Figure 3. When the survival time is 26 weeks (52 weeks), the number of cats infected from ingesting tissue cysts is 29.3 times (26.6 times) of the number infected from ingesting oocysts. The number of mice infected by vertical transmission is 3.0 times (3.4 times) of that infected from ingesting oocysts when the survival time is 26 weeks (52 weeks). Therefore, the transmission of the parasite from environment to cats is negligible compared to that from mice to cats. On the other hand, for mice, both the transmission from environment and the vertical transmission by birth play significant roles. This confirms the importance of congenital transmission of *T. gondii*.

To illustrate the role of vertical transmission, we decrease the vertical transmission rate of mice from 75% to 25% while keeping all the other parameters the same same; see Figure 6. Comparing results from Figure 3 and Figure 6, we can see that the percentage of infected cats and mice and infection risk obviously decreases with a lower vertical transmission rate. Especially when the oocyst survival time is 26 weeks, the parasites almost always goes extinct on the farm by the end of the 10 year period. This suggests that the vertical transmission rate of mice is also an important factor for sustaining the disease.

We further investigate the influences of a few other factors on disease transmission.

**Latent period.** The model provides a useful tool to explicitly study the influences of different parameters on the spread of *T. gondii*. Here we change the latent period of cats from 3 days to 20 days. The latent period of cats before they spread oocysts depends on how they obtained infection. For example, it will take a cat 3-7 days to cast oocysts after infection with tissue cysts and 19-20 days after infection with tachyzoites or oocysts [8]. Comparing the results from Figure 3 and Figure 7, we can see that a longer latent period does not significantly affect the infection level but induces a time delay in the outburst of the disease.

**Imprudent behavior of mice.** Mounting evidence shows that *T. gondii* infection also has significant effects on mice behavior. *T. gondii* tissue cysts in the brains of infected rats increase the rats’ chance of being predated by cats, thereby ensuring the completion of the life cycle of *T. gondii*. Specifically, the parasites subtly alter the brains of rats as well as their perception of cat predation risk and turn the rats’ innate aversion into an imprudent attraction to cats; see details in [36–40]. Here, we assume that the infected mice are 2 times more likely to be preyed upon than noninfected mice. Comparing Figure 3 and Figure 8 shows that the increased probability of being preyed upon does not significantly affect the status of cats and other intermediate hosts since the number of infected mice are not changed. However, the percentage of infected mice is decreased since less mice are involved in vertical transmission.

**Virulence.** The consequences of infections with *T. gondii* depend on the host species and parasite genotypes. In mouse models, the parasites can be divided into three groups. Group 1 strains are uniformly lethal with lethal dose LD100=1 parasite, group 2 strains which include the type II lineage, are intermediately virulent with LD50 = 10^3 – 10^4 parasites, and group 3 strains are non-virulent with LD50 > 10^5 parasites [41, 42]. Type II lineage parasites are the predominant cause of human toxoplasmosis [43]. Furthermore, empirical
data suggest that evolution of the parasite favors an intermediate virulence, where a tradeoff between virulence and transmission is balanced [44].

Here we try to test this hypothesis by an approximate quantification which has been presented in Section 2. Based on the fact that the virulence determines the number of tissue cysts generated in the mice and thus determines the rate of infection for a cat that ingests an infected mouse, we have adopted a normal distribution for the relation between the virulence and transmission ability; see Equation (12). With the above relations, we simulate the model under different levels of virulence which represent different lineage types, to investigate the influence virulence has on transmission. Again, we simulate each virulence value 100 times and plot the averaged results in Figure 9(a). The result indicates that intermediate virulent lineage (type II) can sustain the disease most efficiently, which agrees with the fact that the evolution of the parasite favors intermediate virulence.

4 Conclusions and Discussions

We have developed a prototype agent-based model to study the transmission dynamics of \( T. gondii \) and the influences of various factors. The model explicitly describes the complete transmission cycle of \( T. gondii \) and includes comprehensive biological details of the hosts, the environment, and the parasites. Numerical simulations indicate that mice play a very important role in this transmission process. On the other hand, the latent period of cats and the imprudent behavior of mice do not significantly change the infection level of the system. Our simulations also confirm the hypothesis that the evolution of the parasite favors intermediate virulence.

4.1 Possible Prevention Strategies

The developed model includes a detailed description of the transmission of the parasite. Thus, the model can be used to design and test disease prevention strategies. When infection starts with cats, oocysts contribute most to the spread and sustenance the disease. \( T. gondii \) oocysts shed by cats in feces can contaminate water and soil and make the environment a reservoir of infection for mice and other intermediate hosts. Simulations here agree with the observations in Mateus-Pinilla et al. [12] on oocyst survival time—the infection level decreases when the oocyst survival time is decreased. Reducing the survival time of oocysts will effectively and immediately decrease the infection risk of the disease.

Mice can contribute to the spread of the disease in two ways: 1.) they can pass the disease to cats, the definitive host; and 2.) they can pass the disease to the next generation of mice. About 95% of cats are infected through predation on infected mice. In contract, nearly 80% of mice are infected through vertical transmission. Figure 9 (b) shows that a certain number of mice are needed to sustain the disease, and this can also bee seen in Figure 4. These observations imply that controlling the number of mice may successfully prevent the disease. In the seminal work of Mateus-Pinilla et al.’s [12], they pointed out that reducing the number of cats in a farm is an effective strategy to suppress the spread of \( T. gondii \). However, a reduced cat population may break the predator-prey balance between cats and mice and thus lead to an increased number of mice, which may in turn increase the risk of
the disease spreading. The overall effect of cat population control may thus depend on the tradeoff between the role that cats play in disease transmission and the role the cats play in controlling the disease via mouse predation. Also, due to the present trend of adopting cats as pets, mice elimination may be more favorable than cat elimination.

### 4.2 Merits of ABM of T. gondii

Mathematical models have become more and more useful in medical and biological research, particularly because they allow one to examine variables that are difficult to control under field conditions. Compared to differential equation models, agent-based models have both disadvantages and advantages. On the one hand, analysis of agent-based models is not as easy as that of differential equation model, and the theory is not as well developed. On the other hand, agent-based models provide unique benefits. Firstly, agent-based modeling is a “bottom up” computational approach, which builds upon functions of and interactions between individual agents. Thus, the modeling process is more intuitive and straightforward. Biological hypotheses are more transparent in agent-based models than in traditional differential equation models. Therefore, communication between modelers and biologists is more effective and convenient when using agent-based models. For example, the present model describes the interactions between agents, including cats, mice, and the environment. While the agents evolve according to their individual rules, properties of the disease emerge from the interactions among agents. The identification and validation of various properties, such as birth rate, weaning age, virulence, infection capability, etc., can be found relatively easy and can be conducted independently. Biological processes, such as birth, death, predator-prey, and infection, are often intrinsically stochastic. Such stochasticities can be easily implemented in agent-based models. Simulation results (Figure 4) clearly show that stochasticity may change the sustainability of the disease. In the mean time, we can identify the overall trend by averaging results from multiple simulations. Moreover, continually increasing computational power makes detailed agent-based models possible. While simplified models based on mean-field approximations can provide tremendous insight into infectious dynamics, agent-based models have proven to be useful and important compliments.

### 4.3 Future work

We note the current prototype model lacks adaptive decision making based on internal states and local interactions. Future models will allow agents to make adaptive decision based on their internal states and interactions with environment and other agents. For example, when a cat hunts, it may first predate in areas where it has previously successfully hunted. When attempts in such areas do not generate satisfactory yield, the cat may explore new territories for hunting. Similarly, mice may adjust their activities according to their experience and sense of the environment. Such extensions will allow one to investigate the influences of animal behaviors on the spreading of the diseases. Future models will also keep track of the paths of cat and mice and allow events to occur along the path. As another important extension, future models will include human activities. Although humans are the end-receivers of the disease, human activities may significantly affect the prevalence of the disease through vaccinating cats or controlling the number of mice. Such human activities are
likely to take place in response to disease outbreak. Including human activities in the model will thus allow one to investigate vaccine and other control policies. A more realistic farm model can be implemented to account for structured territories and various environmental influences. The model can be extended to study the spread of diseases among different farms. The model can also be utilized to investigate co-infection of the multiple strain types.

Future models will also be evaluated with new data and simulation studies to advance the knowledge about \textit{T. gondii} transmission. Pattern-oriented modeling approaches [48] will be adopted to guide the structure and complexity of future models. Patterns used for this purpose may include local patterns such as demographics of cats and mice as well as global patterns such as rate of infection in cats and the chance that food/water resources may be contaminated in a farm. Field data will also be used to guide the design of landscape of the environment model.

**ACKNOWLEDGEMENT**

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**A Appendix**

This appendix includes the algorithms we implemented for the rules described for birth-death, predator-prey, infection in Section 2. These algorithms were implemented in Mathematica [47].

**A.1 Random walk rules**

Animal Random Walking Rules()

mature animals may wander in the farm randomly

get the current position \{xpos,ypos\}

\textbf{if} cat

walking distance is a random integer between $-5$ and $5$

\textbf{elseif} mouse

walking distance is a random integer between $-1$ and $1$

\textbf{endif}

update \{xpos,ypos\} using random walking distances

**A.2 Predator-prey rules**

Predator-prey Rules()

pre-weaning animals are assumed to stay in their habitats
they will not involve in the predator-prey process
if mouse$_i$ is within prey distance of cat$_i$ then
prey occurs with a probability
if cat$_i$ preys an infected mouse$_j$ then
  cat$_i$ is infected with a probability
  the probability of infection depends on the state of cat$_i$
  remove mouse$_j$
endif
endif

**A.3 Oocyst shedding rules**

oocyst shedding Rules()
  no oocysts are shed during movement
if cat$_i$ is infected then
  if latent period < infected time < recovery period then
    cat$_i$ shed oocysts to the current cell
  endif
endif

**A.4 Infection by environment rules**

Infection By Environment Rules()
if a susceptible animal in a contaminated cell then
  the animal is infected with a probability
endif

**A.5 Birth death rules**

Animal Birth And Death Rules()
if an animal is mature then
  this animal may give birth to a child with a daily birth probability
  if the parent mouse is infected then
    the new born mouse may become infected through vertical transmission
  endif
  assume no vertical transmission in cats
endif
an animal may die with a daily death probability

**A.6 Overall Simulation Process**

Overall Simulation Process()
pre-weaning animals stay in their habitats
post-weaning animals involve in the following activities
animals may change their positions according to random walk rules
animals may become infected by environment
predator prey processes may take place
infected cats may shed oocysts according to oocyst shedding rules
amount of oocysts in the environment may decay
birth and death events of animals
update states of the animals, including growth, weaning, recovery, etc.

References


[37] J.P. Webster, Rats, cats, people and parasites: the impact of latent toxoplasmosis on behaviour, Microbes Infect. 3(2001) 1037-1045.


Figure caption

Figure 1 Schematic of the transmission routes of *T. gondii*; figure edited from [46].

Figure 2 Population dynamics of cats and mice on the farm. Panels (a) and (b) show the results of one selected simulation trial. Panels (c) and (d) show the averaged results of 100 simulation trials.

Figure 3 Average response under 20% virulence when the decay time of oocyst is 26 weeks (solid) and 52 weeks (dashed), respectively.

Figure 4 Extinction of disease under 20% virulence when the decay time of oocyst is 26 weeks.

Figure 5 Transmission differences under 20% virulence when the decay time of oocyst is 26 weeks (solid) and 52 weeks (dashed), respectively.

Figure 6 Average response with vertical transmission rate 0.25 when the decay time of oocyst is 26 weeks (solid) and 52 weeks (dashed), respectively.

Figure 7 Average response with latent period 20 days of cats when the decay time of oocyst is 26 weeks (solid) and 52 weeks (dashed), respectively.

Figure 8 Average response with increased prey possibility of infected mice when the decay time of oocyst is 26 weeks (solid) and 52 weeks (dashed), respectively.

Figure 9 Influence of the virulence of the parasite (a) influence of the carrying capacity of mice (b). Here, solid curves correspond to 26 weeks of survival time for oocysts in environment and dashed curves correspond to 52 weeks.

Table caption

Table 1 Default values of parameters in the model.
### Table 1: Default values of parameters in the model.

<table>
<thead>
<tr>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of X grid</td>
<td>50</td>
</tr>
<tr>
<td>Number of Y grid</td>
<td>50</td>
</tr>
<tr>
<td>Oocyst shed during primary infection</td>
<td>(20 \times 10^6) units/day</td>
</tr>
<tr>
<td>Oocyst survival time</td>
<td>26 weeks</td>
</tr>
<tr>
<td>Detectable oocyst amount</td>
<td>2000 units/cell</td>
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<tr>
<td>Probability of cat infected by environment</td>
<td>0.025</td>
</tr>
<tr>
<td>Probability of mouse infected by environment</td>
<td>0.25</td>
</tr>
<tr>
<td>Initial number of cats</td>
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<tr>
<td>Average age of cats</td>
<td>2 year</td>
</tr>
<tr>
<td>Weaning age of cats</td>
<td>50 days</td>
</tr>
<tr>
<td>Mature age of cats</td>
<td>240 days</td>
</tr>
<tr>
<td>Maximum walking steps of cats</td>
<td>5 cells</td>
</tr>
<tr>
<td>Latent period of cats during primary infection</td>
<td>3 days</td>
</tr>
<tr>
<td>Latent period of cats during the following infections</td>
<td>7 days</td>
</tr>
<tr>
<td>Recovery period of cats during primary infection</td>
<td>17 days</td>
</tr>
<tr>
<td>Recovery period of cats during the following infections</td>
<td>17 days</td>
</tr>
<tr>
<td>Oocyst spread time of cats</td>
<td>14 days</td>
</tr>
<tr>
<td>Carrying capacity of cats</td>
<td>20</td>
</tr>
<tr>
<td>Initial number of mice</td>
<td>200</td>
</tr>
<tr>
<td>Average age of mice</td>
<td>0.4 year</td>
</tr>
<tr>
<td>Weaning age of mice</td>
<td>21 days</td>
</tr>
<tr>
<td>Mature age of mice</td>
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</tr>
<tr>
<td>Maximum walking steps of mice</td>
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<tr>
<td>Latent period of mice during infection</td>
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</tr>
<tr>
<td>Recovery period of mice during infection</td>
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<tr>
<td>Carrying capacity of mouse</td>
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<tr>
<td>Probability of prey in the same cell</td>
<td>0.5</td>
</tr>
<tr>
<td>Prey distance of cats</td>
<td>1.5 cells</td>
</tr>
</tbody>
</table>
Figures

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