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Modeling Lyme disease transmission

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ABSTRACT

Lyme disease, a typical tick-borne disease, imposes increasing global public health challenges. A growing body of theoretical models have been proposed to better understand various factors determining the disease risk, which not only enrich our understanding on the ecological cycle of disease transmission but also promote new theoretical developments on model formulation, analysis and simulation. In this paper, we provide a review about the models and results we have obtained recently on modeling and analyzing Lyme disease transmission, with the purpose to highlight various aspects in the ecological cycle of disease transmission to be incorporated, including the growth of ticks with different stages in the life cycle, the seasonality, host diversity, spatial disease pattern due to host short distance movement and bird migration, co-infection with other tick-borne pathogens, and climate change impact.

1. Introduction

Lyme disease (LD) is a common tick-borne infection in the temperate northern hemisphere (Dennis et al., 1998; Ogden et al., 2009). In the United States of America, it is the fifth most commonly reported nationally notifiable disease and more than 36,000 confirmed and probable disease cases were reported in 2013 with the true number of cases estimated to be approximately 300,000 per year (Mead, 2015). There may be over 200,000 European cases annually, with high incidences in parts of southern Scandinavia, central and eastern Europe. About 1200 cases are serologically confirmed annually in the UK (O'Connell, 2014). Although the annual Lyme disease cases have been fairly low in Canada, northward invasive spread of the tick vectors from United States endemic foci to non-endemic Canadian habitats has been a major public health protection and promotion issue (Dennis et al., 1998; Ogden et al., 2009). Recent studies have suggested that the number of known endemic areas of Lyme disease in Canada is increasing because of the expanding range of *Ixodes scapularis*, a process that is predicted to accelerate with climate change (Ogden et al., 2009). The reported cases in Canada rose significantly from 144 in 2009 to 338 in 2012 (Ogden et al., 2015). Erythema migrans (EM), an early skin lesion, is the most common clinical presentation. However, the infecting pathogen can spread to other tissues and organs, causing more severe manifestations, including facial palsy, viral-like meningitis, radiculitis and arthritis, usually affecting the knee (Ogden et al., 2008a; O'Connell, 2014; Stanek, Wormser, Gray, & Strle, 2012). Although it is virtually never fatal, it can be clinically very serious (Randolph et al., 2007).

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Lyme disease is caused by spirochaetes of the *Borrelia burgdorferi* sensu lato species complex, which are transmitted by *Ixodes* ticks (Stanek et al., 2012). Various pathogenic species are responsible for the Lyme disease at different regions in the world (Bergström, Noppa, Gylfe, & Östberg, 2002). For example, in North America, the species of Lyme borrelia known to cause human disease is *B. burgdorferi* sensu stricto while in Europe, at least five species of Lyme borrelia (*B. afzelii*, *B. garinii*, *B. burgdorferi*, *B. spielmanii* and *B. bavariensis*) can cause the disease, leading to a wider variety of possible clinical manifestations in Europe than in North America (Bergström et al., 2002; Stanek et al., 2012). Various *Ixodes* tick species can serve as vectors for the Lyme disease transmission: the main vector of Lyme borrelia in Europe is *I. ricinus*, whereas *I. persulcatus* is the main vector in Asia. *I. scapularis* is the main vector in northeastern and upper midwestern USA and *I. pacificus* serves as the vector in western USA (Stanek et al., 2012).

The pathogen transmission involves three ecological and epidemiological processes (Ogden et al., 2008b; Ostfeld, 1997; Thompson, Spielman, & Krause, 2001) between two post-egg but immature stages larvae and nymphs: nymphal ticks infected in the previous year appear first; these ticks then transmit the pathogen to their susceptible vertebrate hosts during a feeding period; the next generation larvae acquire infection by sucking recently infected hosts' blood and these larvae develop into nymphs in the next year. The transmission cycle is depicted in Fig. 1. Lyme disease results when a human is inadvertently bitten by an infectious tick.

Prevention and control of tick-borne diseases, in general and Lyme disease in particular, are important to human health, animal welfare and economics. Understanding the factors that regulate the abundance and distribution of the Lyme-pathogen is crucial for the effective control and prevention of the disease. Mathematical modeling has become an important tool in analyzing the epidemiological characteristics of infectious diseases and providing cost-efficient control measures (Anderson and May, 1992). There have been a range of tick-borne disease modeling efforts dedicating to different aspects of Lyme disease transmission: the basic tick population ecology (Caraco et al., 1998; Porco, 1999), effect of different hosts and their densities on the persistence of tick-borne diseases (Pugliese & Rosà, 2008; Rosà & Pugliese, 2007; Rosà, Pugliese, Norman, & Hudson, 2003), threshold dynamics for disease infection (Foppa, 2005; Hartemink, Randolph, Davis, & Heesterbeek, 2008), seasonal tick population dynamics and disease transmission (Dobson, Finnie, & Randolph, 2011; Ghosh & Pugliese, 2004), climatic effects (Ogden et al., 2005; Wu, Duvvuri, & Wu, 2010), spatial invasion of ticks and spreading of the disease (Caraco et al., 2002; Gaff & Gross, 2007; Zhang & Zhao, 2013), among others. These modeling efforts can be classified into two broad types: models that aim to explore theoretically the behaviours of the systems, which may or may not use the basic reproduction number $\mathscr{R}_0$ as an index of the relative contributions or effects of different model parameters (e.g. (Caraco et al., 2002; Foppa, 2005; Ghosh & Pugliese, 2004; Hartemink et al., 2008; Norman, Bowers, Begon, & Hudson, 1999; Randolph et al., 1999; Rosà & Pugliese, 2007; Rosà et al., 2003; Schmidt & Ostfeld, 2001)); and simulation models that aim to explicitly simulate certain aspects of the biology of vectors and vector-borne disease systems as accurately as possible (e.g. (Dobson et al., 2011; Mount & Haile, 1989; Mount, Haile, & Daniels, 1997; Ogden et al., 2005; Porco, 1999)). The outcomes of these studies, and

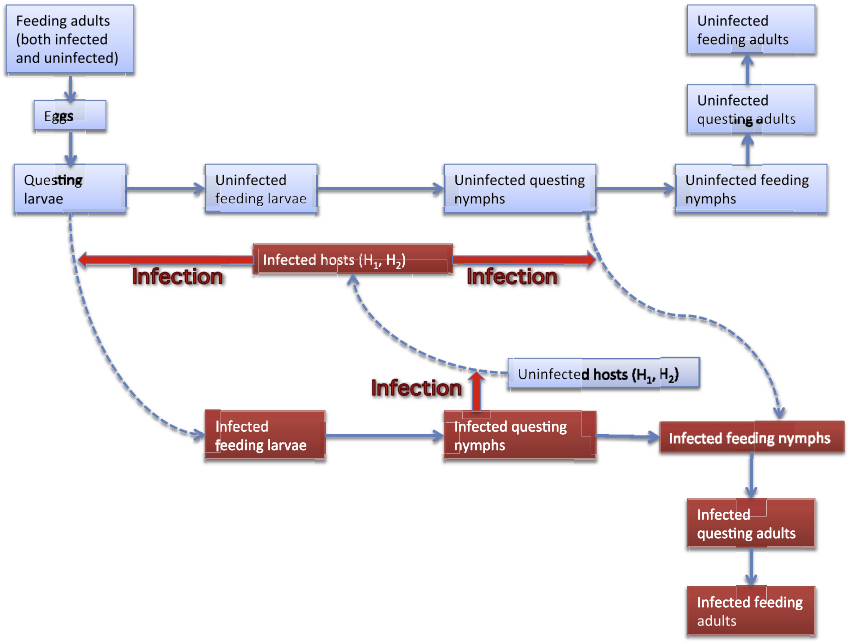


Fig. 1. A schematic diagram for the Lyme disease transmission (reproduced from (Lou, Wu, & Wu, 2014)). To describe the tick development and biting activities, the tick population is divided into 7 stages, stratified further as the uninfected or infected epidemiological classes for postegg stages. Immature ticks can feed on two host species, the mouse (H_1) and an alternative host (H_2), while adult ticks are assumed to feed only on deer in the study.

sometimes the combinations of these outcomes, have been used to produce predictive and risk assessment tools for animal health and public health outcomes. Examples of the latter include Lyme disease risk maps, which combine simulation model outcomes with other environmental variables using a simple algorithm (Ogden et al., 2008c) and models that combine a simplified transmission model that calculates $\mathscr{R}_0$ with a statistical model using environmental variables to determine spatiotemporal variations in vector abundance that in turn drives the transmission model (e.g. (Hartemink et al., 2008, 2009, 2011)).

Theoretical analysis of these models always involves the calculation and analysis of the basic reproduction number $\mathscr{R}_0$, which serves an important methodology to identify the conditions for tick invasion and disease spreading. $\mathscr{R}_0$ is the key value in the field of infectious disease epidemiology for assessing the conditions under which micro- or macro-parasites can persist in nature. For microparasites it is defined as the average number of secondary cases produced by one infectious primary case in a totally susceptible population and for macroparasites it is defined as the number of new female parasites produced by a female parasite when there are no density dependent constraints acting anywhere in the life cycle of the parasites (Anderson and May, 1992; Wu et al., 2013). It is of importance to find an explicit formula or estimate for the basic reproduction number. A general approach to define this index is proposed in (Hartemink et al., 2008) following the next generation matrix (Diekmann, Heesterbeek, & Roberts, 2009) with each element in the matrix having a clear biological meaning, based on which, sensitivity and elasticity analyses can be performed to measure the relative contributions of each factor in pathogen transmission (Matser et al., 2009). For autonomous ordinary differential systems, the basic reproduction number can be explicitly formulated as the spectral radius of a matrix (van den Driessche & Watmough, 2002). The number can also be easily estimated for some special periodic models, such as those in (Bacaër & Guernaoui, 2006; Wang & Zhao, 2008; Wesley & Allen, 2009).

The purpose of this short survey aims to present a systematic account of a few modeling projects the authors have been involved. Topics include the different levels of complications of models to address specific ecological and epidemiological factors that motivated the model frameworks, the relevant mathematical analyses useful to identify key summarative indices such as basic reproduction numbers for disease establishment and growth potential; the relevant simulations for the spatial and spatiotemporal patterns of Lyme disease spread under different assumptions on the environmental conditions and host mobilities.

2. Stage structure and seasonality of tick population growth

The dynamics of the vector population have largely been ignored in modeling vector-borne diseases, especially for mosquito-borne diseases. This is justified in cases where the vector's lifespan is much shorter than its host's and the frequency of pathogen-infected vectors may equilibrate quickly (Aron and May, 1982). But in the case of Lyme disease, the vector (ticks) population has a similar lifespan scale as that of the host population, the infection-transmission rates depend on the coupled dynamics of host and vector densities (Caraco et al., 2002; Feng & Velasco-Hernández, 1997). On the other hand, an *I. scapularis* tick can feed on different host species in immature and adult stages and the pathogen transmission is maintained in the life cycle among larvae, nymphs and immature tick reservoirs (as shown in Fig. 1) and important public health interventions including vector control and vector-host contact reduction require information about the tick population sizes at different stages and different seasons. Therefore, in order to get quantitative information about Lyme disease dynamics, it is necessary to integrate the stage-stratified tick development process in models.

Simple stage-structured models (Awerbuch & Sandberg, 1995; Caraco et al., 2002; Mwambi, Baumgärtner, & Hadeler, 2000; Randolph, 1999; Randolph & Rogers, 1997; Wu et al., 2010) are natural mathematical formulations to meet the above goal in terms of describing the ecology of self regulated tick population growth and pathogen transmission. A system of delay differential equations was proposed in (Fan, Thieme, & Zhu, 2015a) to describe the stage structure of the tick population growth where the delay represents the time needed to develop from one stage to the next. The study (Fan, Lou, Thieme, & Wu, 2015b) formulated a general model of ordinary differential equations motivated by tick growth for populations which are structured by many stages. This model was further extended to incorporate time-varying coefficients to investigate the temperature-dependent seasonal tick population growth in (Wu et al., 2013). The main results are reported in the following two subsections.

2.1. Stability and persistence in ODE models with many stages

Let $2 \leq n \in \mathbb{N}$ and consider a system modeling a population structured by n stages:

$$\begin{cases} x_1' = & g(x) - (\gamma_1(x) + \mu_1(x))x_1 \\ x_j' = & \gamma_{j-1}(x)x_{j-1} - \Big(\gamma_j(x) + \mu_j(x)\Big)x_j, \quad j = 2, \ldots, n \\ x = & (x_1, \ldots, x_n). \end{cases} \tag{1}$$

Here x_j is the size of the j-th stage of the population (eggs or other forms of offspring and various larval, pupal, and adult stages). The vector $x = (x_1, \ldots, x_n)$, comprising all stage sizes, gives the population state, here the stage distribution. The first stage contains the offspring with $g(x)$ being the rate at which offspring enters the stage if the stage distribution is $x \in \mathbb{R}^n_+$,

$g(0) = 0$. $\mu_j(x) \geq 0$ is the per capita mortality rate in stage j at population state x and $\gamma_j(x) \geq 0$ is the per capita transition rate from stage j to stage $j+1$ at stage distribution x.

This model (1) is motivated by tick dynamics, notably by the computer model in (Ogden et al., 2005), but is formulated in a general enough setting that can be applied to a wide range of stage structured populations by incorporating density-dependent feedbacks between the stages that affect mortality, stage-transition, and procreation rates. This system is also suitable to describe disease transmission with many disease stages. In (Fan et al., 2015b), the uniqueness and global existence of solutions were established, the reproduction numbers in a biologically meaningful way was identified and the basic reproduction number was obtained and was shown to be as a threshold index determining population extinction or persistence. The boundedness of solutions, a difficult problem if density-dependent negative feedback is exclusively inter-stage, was discussed. For this reason, existence of nonzero equilibria was not derived as a consequence of permanence, but via fixed point theorems in conical shells. Since the system is large, uniqueness and stability of nonzero equilibria become a challenge. The paper (Fan et al., 2015b) gave an example where a nonzero equilibrium is unstable while the negative feedback is of a very simple nature.

2.2. A temperature-driven map of the vector reproductive number

A finer step to understand the transmission of Lyme disease is to investigate detailed factors that regulate the tick population growth, from which the geographic range of ticks constrained by biotic factors (host densities and habitat) and abiotic factors such as climate (Ogden et al., 2005) can be identified. The life cycle of *Ixodes* tick species has distinct seasonality (Stanek et al., 2012) and the tick abundance is affected by the community structure of the habitat: the leaf litter layer and understorey microhabitats and microclimates in which the non-parasitic ticks exist; and the species range and densities of tick hosts (Ogden et al., 2005). Besides these, tick development rates are determined by temperature and diapause is related to day length and/or temperature (Randolph, 1999). Moreover, tick host-seeking success not only depends on host densities, but also on the tick activity which is influenced by temperature (Ogden et al., 2005). To fairly describe the vital development of tick population, we should integrate these factors on the tick population growth.

In (Ogden et al., 2005), Ogden et al. developed a process-based dynamic population model of *I. scapularis* with the main purpose to investigate whether the model can be used to identify limits for the potential northward spread of *I. scapularis* in North America, that may be imposed by effects of temperature on tick survival. Their model incorporates intra-annual, temperature-dependent variations in the development rates of different tick instars and is well validated by the seasonality pattern of different tick instars. This sort of model structure then has been used in a number of mechanistic models of ticks (Dobson et al., 2011; Martens, 1998; Mount & Haile, 1989; Ogden et al., 2008d; Porco, 1999) that aim to predict seasons of tick activity and variations in tick abundance in different locations. However this structure is mathematically intractable and calculation of the effects of climate change-induced increasing temperatures (or of other environmental changes) on the basic reproduction number $\mathscr{R}_0$ is not directly possible.

In (Wu et al., 2013), the model framework in (Ogden et al., 2005) was adopted to formulate a periodic system of ordinary differential equations which comprises 12 mutually exclusive states of the tick life cycle to examine the temperature effect on each stage of the tick life cycle. These stages include egg-lying adult females, eggs, hardening larvae, questing larvae, feeding larvae, engorged larvae, questing nymphs, feeding nymphs, engorged nymphs, questing adults, feeding adult females and engorged adult females. The model parameters related to seasonal temperature-driven development rates and host biting rates are fitted using temperature normals smoothed by Fourier analysis. This was done by combining the laboratory observed bitting rates at given temperature and the real temperature data form an appropriate weather station of the study region. The seasonality of the ticks was validated with that reported in (Ogden et al., 2005). Furthermore, sensitivity analysis was conducted and the host abundance, tick development rates and summer temperatures were highlighted as highly influential variables in the model, which is consistent with the current knowledge of the biology of this tick species. A map of $\mathscr{R}_0$ for *I. scapularis*, the first such map for an arthropod vector, was drawn for Canada east of the Rocky Mountains, supporting current risk assessments for Lyme disease risk emergence in Canada. This map was later extended in (Ogden et al., 2014) to a tick risk map for all of North America by using actually reported and environment models predicted temperature data. This map color coded the size of the basic reproduction number in each region with reliable environmental data, and has clearly indicated the Northward extension of Lyme tick establishment under assumed climate warming. This map has been referred by the media as Lyme disease “hot maps” (Anderssen, 2015; Hill, 2015).

2.3. Comments on further recent developments

The tick population models can then be extended to incorporate the disease transmission cycle between ticks and their reservoirs. Porco (Porco, 1999) proposed a mathematical model based on the life history of the tick population and the primary reservoir host. The threshold condition for the disease invasion into a nonenzootic region was determined as a function of the various possible transmission chains operating throughout the year. The self regulation of ticks and pathogen invasion were investigated by analyzing the equilibrium abundance of each compartment of a simple deterministic model (Caraco et al., 1998). Several factors to promote the spirochete invasion were identified: a sufficient density of mice suffering low mortality, high susceptibility to infection in both mice and ticks, a high attack rate of ticks on mice, a high density of larval ticks, and low mortality among tick nymphs.

Climate effect on tick population growth was also investigated in (Awerbuch-Friedlander, Levins, & Predescu, 2005; Ghosh & Pugliese, 2004; Randolph, 1999). In particular, a simple semi-discrete (ticks feeding is assumed to occur only during the summers of each year) model for tick population dynamics was presented in (Ghosh & Pugliese, 2004). The idea of (Wu et al., 2013) was further employed in (Ogden et al., 2014) to quantify potential effects of future climate change on the basic reproduction number $\mathscr{R}_0$ of *I. scapularis* and explore their importance for Lyme disease risk.

More recently, Wu et al. (Wu, MariaMagpantay, Wu, & Zou, 2015) developed a novel deterministic model by rigorously incorporating the seasonal developmental delays for the tick population. The model turns out to be totally different from previous ones. The basic reproductive number for such a system was defined and numerical algorithms were developed. Numerical simulations also show that the threshold value for the population persistence or extinction depends not only on the mean but also on the amplitude and phase of the periodic development delays. The periodic delay model in (Wu et al., 2015) was further analyzed in (Liu, Lou, & Wu, 2017) by a dynamical system approach.

3. Biodiversity and disease risk amplification/dilution

The transmission process of Lyme disease as a zoonotic vector-borne disease is largely affected by the interaction between the vector and its hosts. The tick vector has a wide range of hosts, adult ticks always feed on white-tailed deers while immature ticks normally feed on small mammals, with white-footed mouse as the most efficient reservoir. As a first natural step towards host diversity, the study (Ostfeld, 2010) focused on two host species: deers which determine tick numbers, and rodents (particularly white-footed mice) which determine tick infection (Ostfeld, 2010). Two relationships are important in the ecology and epidemiology of this complex disease transmission cycle. The first is the relationship between deer and tick abundance. This relationship seems to be variable, sometimes strong and sometimes weak or nonexistent (Ostfeld, 2010). Another is the relationship between the disease risk and host community diversity. Dilution effect, defined when disease frequency decreases with increasing biodiversity, and the opposite-amplification effect have been disputed in the literature (see (Bolzoni, Rosà, Cagnacci, & Rizzoli, 2012; Keesing, Holt, & Ostfeld, 2006; LoGiudice, Ostfeld, Schmidt, & Keesing, 2003; Mannelli, Bertolotti, Gern, & Gray, 2012; Mitchell, Tilman, & Groth, 2002; Ogden & Tsao, 2009; Ostfeld, 2010; Ostfeld & Keesing, 2000; Ostfeld & LoGiudice, 2003; Pugliese & Rosà, 2008; Rosà & Pugliese, 2007; Rudolf & Antonovics, 2005; Schmidt & Ostfeld, 2001; Tagliapietra et al., 2011; van Buskirk & Ostfeld, 1995)). In particular, different possible mechanisms responsible for dilution effects were classified in (Keesing et al., 2006; Ostfeld, 2010).

Lyme disease is commonly cited as the best example to evaluate the effect of biodiversity on disease transmission (Wood & Lafferty, 2013). In (Lou & Wu, 2014), a mathematical dynamical modeling approach was employed to explore how tick-host interaction patterns affect disease transmission. This conceptual model was made concrete in the study (Lou et al., 2014) by feeding with a reasonable tick-host biting rate, several host species for immature ticks, and the seasonal effect of temperature on tick development and activity to evaluate the integrated impacts of biodiversity and other factors on determining the disease risk. The main results are reported in the next subsections.

3.1. Tick seeking assumptions and their implications

In mathematical biology, different contact rates between the vector and hosts are proposed under different assumptions: (i) the average number of bites made by a tick per unit time is saturated at a constant, and independent of the host density (frequency-dependent rate); (ii) the number of bites made by a tick per unit time increases linearly with host population size (the density-dependent rate); and (iii) the number of bites made by a tick per unit time increases with host density when the density is small, but becomes saturated with large host population size. In tick-borne disease modeling, density-dependent (Caraco et al., 1998) and frequency-dependent (Gaff & Gross, 2007) functions have been widely used. Some other more complicated functional responses, such as the one in (Ogden et al., 2005), are also used. These complicated responses, including the Holling type 2 rate, can be considered as intermediate scenarios between the density-dependent and frequency-dependent cases and these responses can be expanded as a combination of the density-dependent and frequency-dependent forces.

The study (Lou & Wu, 2014) examined how the choice of different transmission terms qualitatively and quantitatively alter different indices for the disease risk. One important predictive index is the basic reproduction number (Hartemink et al., 2008) $\mathscr{R}_v$ for tick population which is the total number of female adult ticks produced by a single female tick during her entire reproduction period; and $\mathscr{R}_0$ for Lyme disease which is defined as the average number of secondary cases caused by one infectious individual placed in a population consisting entirely of susceptibles. Also important for determining the human risk of exposure to Lyme disease, as emphasized by (Ostfeld, 2010), is the number of nymphs responsible for the majority of Lyme disease cases, and three temporally varying measures: nymphal infection prevalence (NIP) which is the proportion of nymphs infected with *B. burgdorferi*, the density of infected nymphs (DIN) and the density of nymphs (DON).

Conflicting outbreak predictions were generated by different assumptions: The frequency-dependent assumption (Fig. 2(a)) predicts that reducing the rodent population will always reduce Lyme disease outbreaks, whereas the density-dependent (Fig. 2 (b)) and Holling type 2 seeking assumptions (Fig. 3(a) and (b)) predict that this will reduce or exacerbate infection risk. It was also shown that while an excessively large rodent population size has positive effects on disease control (Figs. 2 and 3), the conceptual mechanisms underlying various tick host seeking patterns are different. The study (Lou & Wu, 2014) clarified this idea in the context of dilution and/or amplification effect. Moreover, in the case of density-

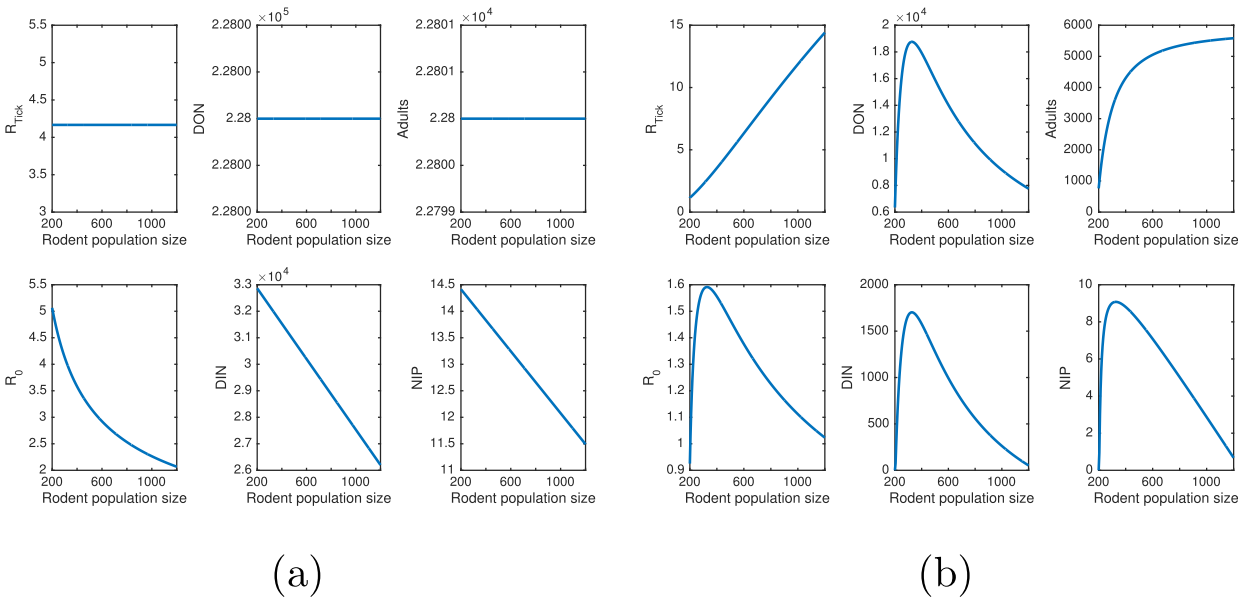


Fig. 2. Reproduced from figures in (Lou & Wu, 2014) but with different parameters. (a) The relationship between a given index and the rodent population size with frequency-dependent seeking rate (a) and density-dependent seeking rate (b) respectively. In the case (a), the number of infectious nymphs is a linearly decreasing function of the rodent population.

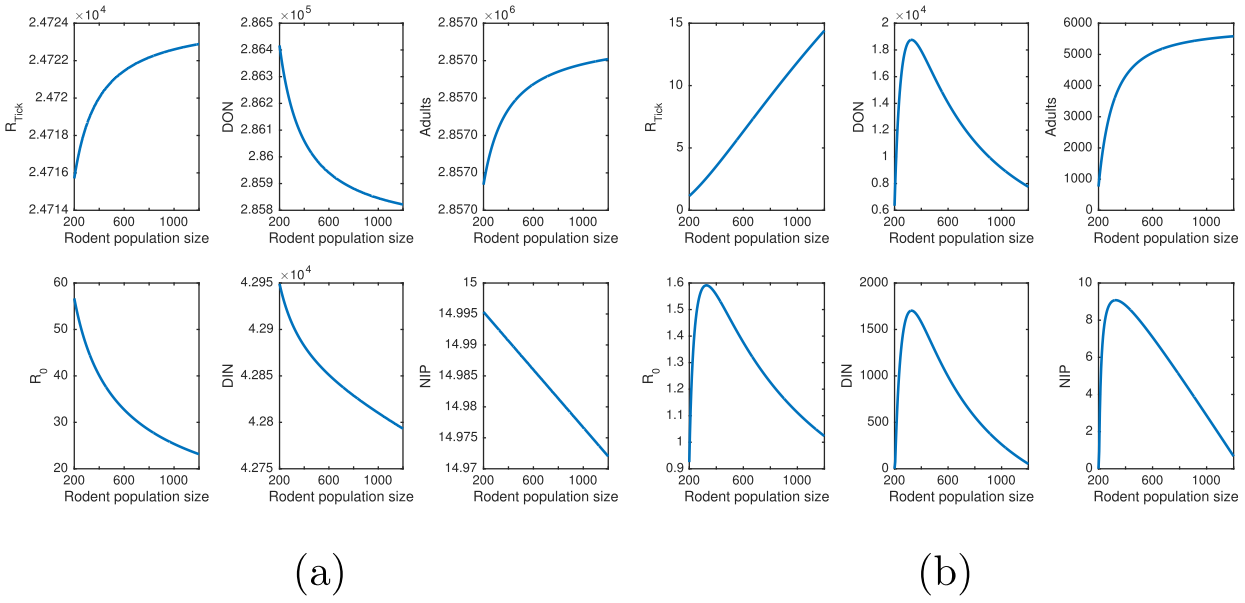


Fig. 3. Reproduced from figures in (Lou & Wu, 2014) but with different parameters. The relationship between a given index and the rodent population size with Holling-type seeking rate. In figures (a) and (b), different parameters are used.

dependent and Holling type 2 transmission terms, it was observed that both the dilution effect and amplification effect of the host community may take place.

This model with different vector seeking patterns showed why in some cases the deer population abundance is closely related to ticks (as in the density-dependent case), and why the relationship is weak (as in the frequency-dependent case). In response to the question “why might the relationship between deer and tick abundance be so viable, sometimes strong and sometimes weak or nonexistent?” asked in (Ostfeld, 2010), the study (Lou & Wu, 2014) provided an interpretation from the modeling approach: when the deer population size is small, it is more appropriate to use density-dependent seeking pattern to describe tick-host interaction, thus the threshold of deer abundance is important and the deer and tick populations are

closely related; while deers are abundant, the tick seeking rate is likely to be fixed, regardless of the deer population density (it is more appropriate to use frequency-dependent seeking rate to model the tick-host interaction), the threshold deer abundance is absent and the relationship between deers and tick abundances is nonexistent.

3.2. Impact of biodiversity and seasonality

Lou et al. formulated a periodic deterministic system of ordinary differential equations in (Lou et al., 2014) to investigate the impact of both climate condition and host biodiversity on Lyme pathogen transmission. The model followed the generic framework proposed by Randolph and Rogers (Randolph & Rogers, 1997), and divided the vector population into 7 stages with 12 subclasses, as in Fig. 1, which makes it possible to account for the following key features: (i) temperature-dependent/temperature-independent development rates; (ii) temperature-dependent host seeking rates; (iii) density-dependent mortalities, caused by the hosts' responses during the feeding period; (iv) constant mortalities of off-host development stages. The proposed model in (Lou et al., 2014) is different from these existing models by incorporating all aforementioned aspects of Lyme disease transmission in a single framework, and as such this framework permitted an analytic definition of the thresholds of tick population dynamics and pathogen transmission dynamics under seasonal temperature variation, and established the relationship of these thresholds to the tick establishment and pathogen persistence.

The temperature data was collected for two periods 1961 – 1990 and 1981 – 2010 for the Long Point (Fig. 4), based on which the periodic coefficients could be estimated by using the method in (Wu et al., 2013). Two critical numbers, the reproduction number for ticks $\mathscr{R}_v$ and the reproduction number for Lyme disease $\mathscr{R}_0$, in combination with other widely used indices, could then provide pivotal information about the impact of temperature variation and host biodiversity on Lyme disease spread (see Figures in (Lou et al., 2014)). It was found that climate warming facilitates the reproduction of *I. scapularis* population and accelerates the spread of Lyme-pathogen, and then increases the risk of Lyme disease infection. Furthermore, it was also noticed that climate change can slightly change the seasonality of the infected questing nymphs and slightly broaden the active period of the infected questing nymphs, and therefore slightly change the seasonality of the risk of Lyme disease.

In addition to the default host white-footed mouse, Lou et al. (Lou et al., 2014) tested with adding different alternative host species, the eastern chipmunks, the western fence lizard and the Virginia opossum to investigate the effect of biodiversity on disease risk. When a new host species was added, the change of seasonality of the tick population was not noticed. It was shown that introduction of new host species into host community can certainly increase the amount of total ticks, but is not necessary increase the number of infected ticks.

3.3. Further comments

The impact of host biodiversity on the Lyme disease risk is a complicated issue and remains challenging for conservation ecology and zoonotic epidemiology. However, this issue has both theoretical and practical importance since this may reveal whether the biodiversity conservation can be used as an effective measure for the prevention and control of the zoonotic disease. For Lyme disease, both the dilution effect (Allan, Keesing, & Ostfeld, 2003; Keesing et al., 2006; LoGiudice et al., 2003, 2008; Ostfeld & Keesing, 2000; Ostfeld & LoGiudice, 2003; van Buskirk & Ostfeld, 1995) and amplification effect (Randolph and Dobson, 2012) have been observed through field and theoretical studies, where many factors such as spatial scale, host competition, host resistance, tick contact rate were considered (Lou & Wu, 2014; Ogden & Tsao, 2009; Pugliese & Rosà, 2008;

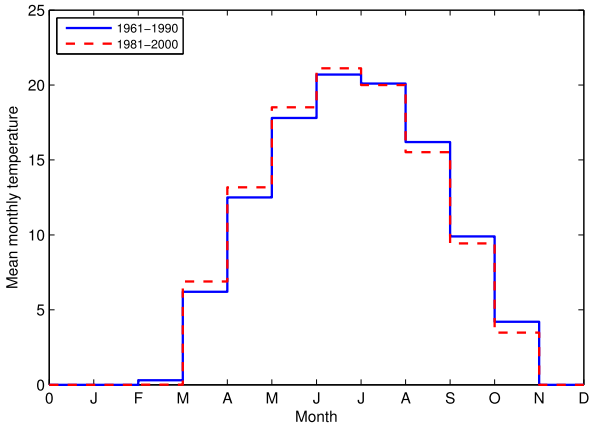


Fig. 4. 30 year normal mean monthly temperature under two settings near Long Point (Lou et al., 2014; Environment Canada). The blue solid and red dashed curves represent the monthly temperature for the periods 1961 – 1990 period and 1981 – 2010, respectively. The monthly temperature was set to be 0°C if it is lower than 0°C. Both are collected from Environment Canada website (Environment Canada).

Wood & Lafferty, 2013). Through the modeling study, both "amplification effect" and "dilution effect" have been observed, where multiple indices ($\mathscr{R}_v$, $\mathscr{R}_0$, DON, DIN and NIP) instead of a single index were utilized. However, the effect does not depend upon the host competence alone, but is a joint outcome of current climate condition, host transmission ability, the numbers of hosts and so on. In order to obtain a definitive answer to the question "How does the biodiversity of the host community affect the disease risk?", reliable field study in combination with local abiotic and biotic factors is necessary (Lou et al., 2014). The study (Lou & Wu, 2014) also posed the dilemma with respect to the disease control: to reduce or to increase rodent population. Solving this dilemma relies on and thus calls for accurate formulation of the transmission patterns of the disease under consideration.

4. Spatial invasion of Lyme disease

Another aspect in modeling Lyme disease transmission is the spatial movement of ticks and Lyme pathogen driven by the host movements (Ruan et al., 2009), such as short distance movement due to rodents, long distance travel due to deer (Caraco et al., 2002) and even longer distance because of the bird migration (Ogden et al., 2008d). A reaction-diffusion model for the ecological dynamics governing the velocity of the current Lyme disease spread was investigated (Caraco et al., 2002). Rigorous mathematical analysis was further performed in (Zhao, 2012) and the population persistence was proven to be solely dependent on the sign of $\mathscr{R}_0 - 1$. Another reaction-diffusion tick model with seasonal effect was proposed in (Wu & Wu, 2012) to study the spatial invasion of tick population. By further incorporating the disease transmission, Zhang and Zhao (Zhang & Zhao, 2013) investigated the spreading speed of the pathogen invasion, which was described by a reaction-diffusion system with seasonal parameters. The invasion speed could be numerically calculated in terms of model parameters related to tick population dynamics, disease transmission and host movement velocity. A novel model (Wang & Zhao, 2015) was proposed, where the process of ticks attaching on and dropping off from hosts are carefully formulated. An alternative way for the reaction-diffusion modeling framework to describe the spatial movement of ticks is the patch model structure, where the spaces are regarded as discrete. The literature (Gaff & Gross, 2007) presented a disease model, in the form of a system of differential equations, that incorporates non-constant population sizes and spatial heterogeneity.

Migratory birds are increasingly considered important in the global dispersal of zoonotic pathogens (Brinkerhoff, Folsom-O'Keefe, Tsao, & Diuk-Wasser, 2011). Recent field studies have suggested that migratory birds serve as hosts for *I. scapularis* in North America and carry nymphal *I. scapularis* northward and through during the spring migration (Ogden et al., 2008d). The potential geographic ranges of tick species and disease risk in Canada may be modified by migratory birds from South. As pointed out by Ogden et al. (Ogden et al., 2008d), migratory birds carry infrequent larvae and low infection prevalence ticks for the following possible reasons: (i) the birds carry few larvae; (ii) the birds do not seem to greatly amplify infection in the ticks they carry; (iii) the birds may acquire ticks mostly from regions where the *B. burgdorferi* infection prevalence is low; or (iv) the birds are generally zooprophylactic, reducing infection prevalence in the ticks they introduce. These naturally motivate the following questions to be addressed: why the wide geographic breeding range of *I. scapularis*-carrying migratory birds is consistent with the widespread geographical occurrence of *I. scapularis* in Canada (a question posted in (Ogden et al., 2008d)); what roles did the migratory birds play in the introduction of *B. burgdorferi* into recently established *I. scapularis* populations. In order to answer these questions, the study (Heffernan, Lou, & Wu, 2014) incorporated climate-dependent tick dynamics and seasonal bird migration to offer some qualitative understanding of the Lyme disease expansion in Canada.

4.1. Range expansion of ticks and pathogens by migratory birds

Since larval, nymphal and adult ticks must attach and detach a host for blood feeding, following (Randolph & Rogers, 1997), Heffernan, Lou and Wu classified the tick population into seven stages (Heffernan et al., 2014) (see Fig. 5 (a)). Moreover, they assumed tick infection does not change the bird migration pattern. As observed by fields experiments (Ogden et al., 2008d), no larval *I. scapularis* ticks were found to be infected with *B. burgdorferi* and almost no migratory birds is bacteria positive. Hence they supposed migratory birds can not get infected, and therefore, no larval tick transported by migratory birds is infected. Coupling with the pathogen transmission between rodents and ticks, the transmission diagram (Fig. 5 (a)) could be sketched, based on which a model system consisting of 13 differential equations was formulated.

All parameters related to the tick development and activity were chosen as those in a previous reference (Wu et al., 2013). According to the seasonal migration windows, it was assumed that birds migrate into the habitat from 15 April to 10 June in each year, as shown in Fig. 5(b). For this periodic system, Heffernan, Lou and Wu (Heffernan et al., 2014) first studied the tick population equations and showed that the tick population would always establish in a stopover of migratory birds which transport some ticks from the previous stopover. The tick population stabilizes at a periodic pattern. Using the limiting periodic system, they got the dynamics of the model system and obtained a biologically meaningful threshold parameter: the basic reproduction number $\mathscr{R}_0$, which is dependent on the habitat environment (temperatures, the bird migration pattern and tick host densities). There exist two possible periodic states: the disease extinction state and the disease endemic state, depending on the basic reproduction number. Extinction of the spirochete is stable when $\mathscr{R}_0 \leq 1$. Reversing this condition ($\mathscr{R}_0 > 1$) implies that the spirochete can invade into the habitat in a cyclical way. Since in each case, one periodic state is globally attractive, the result is robust with respect to different initial conditions.

Tick population can not establish itself in a poor habitat where $\mathscr{R}_0 \leq 1$ (Fig. 6(a)). However, with ticks transported from South by migratory birds, the tick population can remain persistent in the habitat (Fig. 6(a)). Moreover, even for an empty

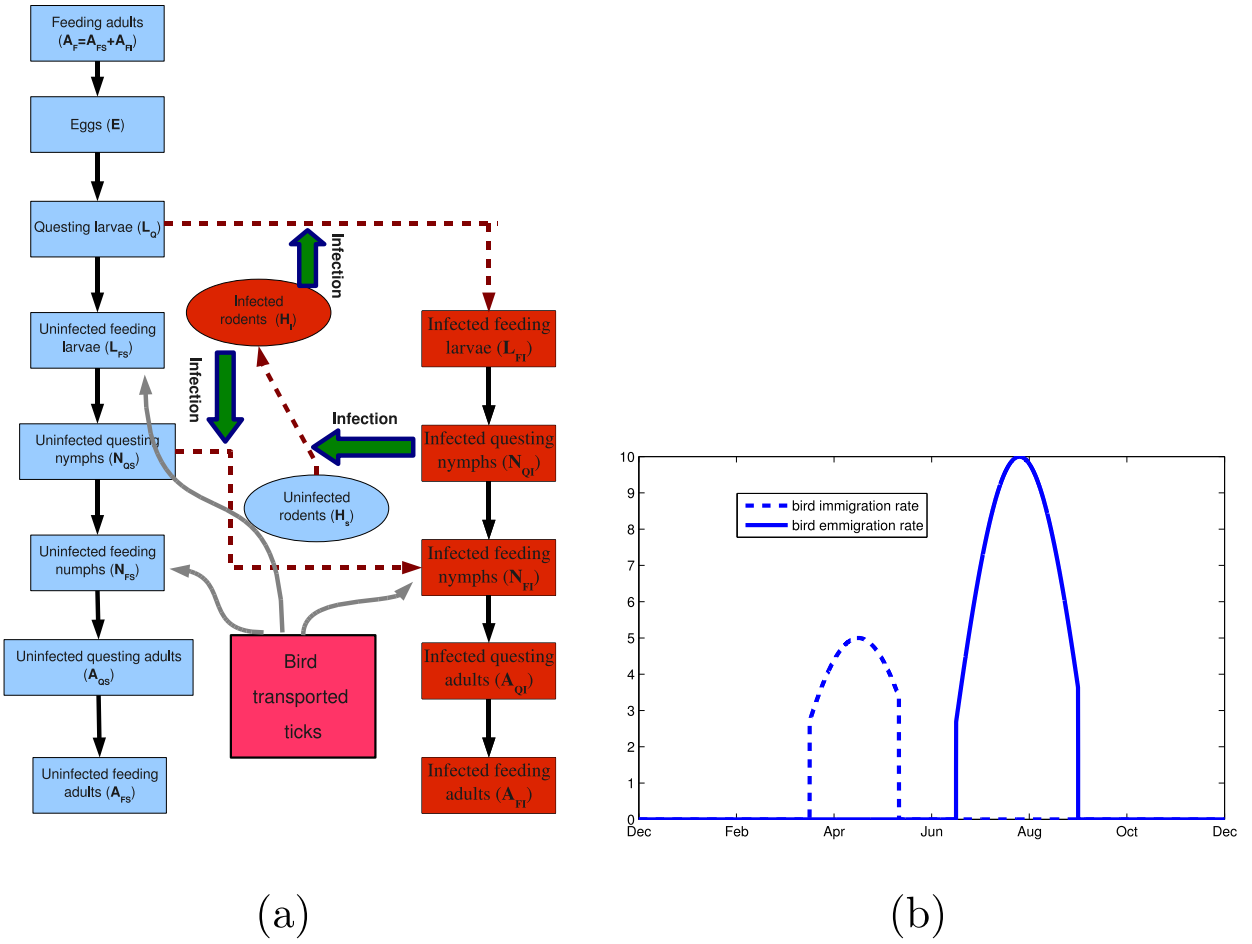


Fig. 5. Both figures are from (Heffernan et al., 2014). (a) Diagram for the Lyme disease transmission. (b) The spring and fall bird migration rates.

habitat (ticks are not found in this habitat), ticks can expand into this region with the help of bird migration, see Fig. 6(b). For a rich habitat (high densities of rodents and deer such that $\mathscr{R}_0 > 1$), the tick population can remain at a low cyclical state. With ticks transported from South by migratory birds, tick population is amplified to a high seasonal state (Fig. 6(c)). Fig. 6(d) shows that if the tick expansion by migratory birds was not incorporated, the disease can not invade into a rich habitat because of the low tick density ($\mathscr{R}_0 < 1$). However, since ticks are transported from South by migratory birds, the disease will stabilize at a cyclical pattern because of the increased tick density ($\mathscr{R}_0 > 1$). These simulations are consistent with the theoretical result. Therefore, successful establishment of *B. burgdorferi* infection in a tick-host cycle may follow by years of the *I. scapularis* population establishment and the amplified tick population by migratory birds. In summary, spirochete invasion is promoted by bird-transported ticks.

5. Co-infection of *Ixodes* tick-borne pathogens (Lou, Liu, & Gao, 2017)

The blacklegged tick, *I. scapularis*, can be infected with a large and diverse array of human pathogens, such as *A. phagocytophilum*, *B. microti*, and *B. burgdorferi*, or all of them simultaneously (Halos et al., 2005; Hersh et al., 2014). Human babesiosis, caused by the blood protozoan parasite *Babesia microti*, has also been increasing in the northeastern United States. The cases of human granulocytic anaplasmosis, also known as human granulocytic ehrlichiosis and caused by the bacterium *Anaplasma phagocytophilum*, has increased significantly over the last decade (Hersh et al., 2014). Co-infection of ticks with multiple microorganisms has been documented in previous studies (Mitchell, Reed, & Hofkes, 1996; Swanson, Neitzel, Reed, & Belongia, 2006). For example, 92 questing *I. ricinus* ticks were collected in northern France to test for three microorganisms, *Bartonella* sp., *B. burgdorferi* sensu lato and *Babesia* sp., which are known as suspected tick-borne pathogens. Seven among 92 samples (7.6%) were positive for at least two of the pathogens and one sample was positive for all three pathogens (Halos et al., 2005). Since several of these pathogens can be harbored by the same tick species and carried by the same rodent reservoir hosts, they can be co-transmitted to humans in concert. In theory, when an individual is bitten by an

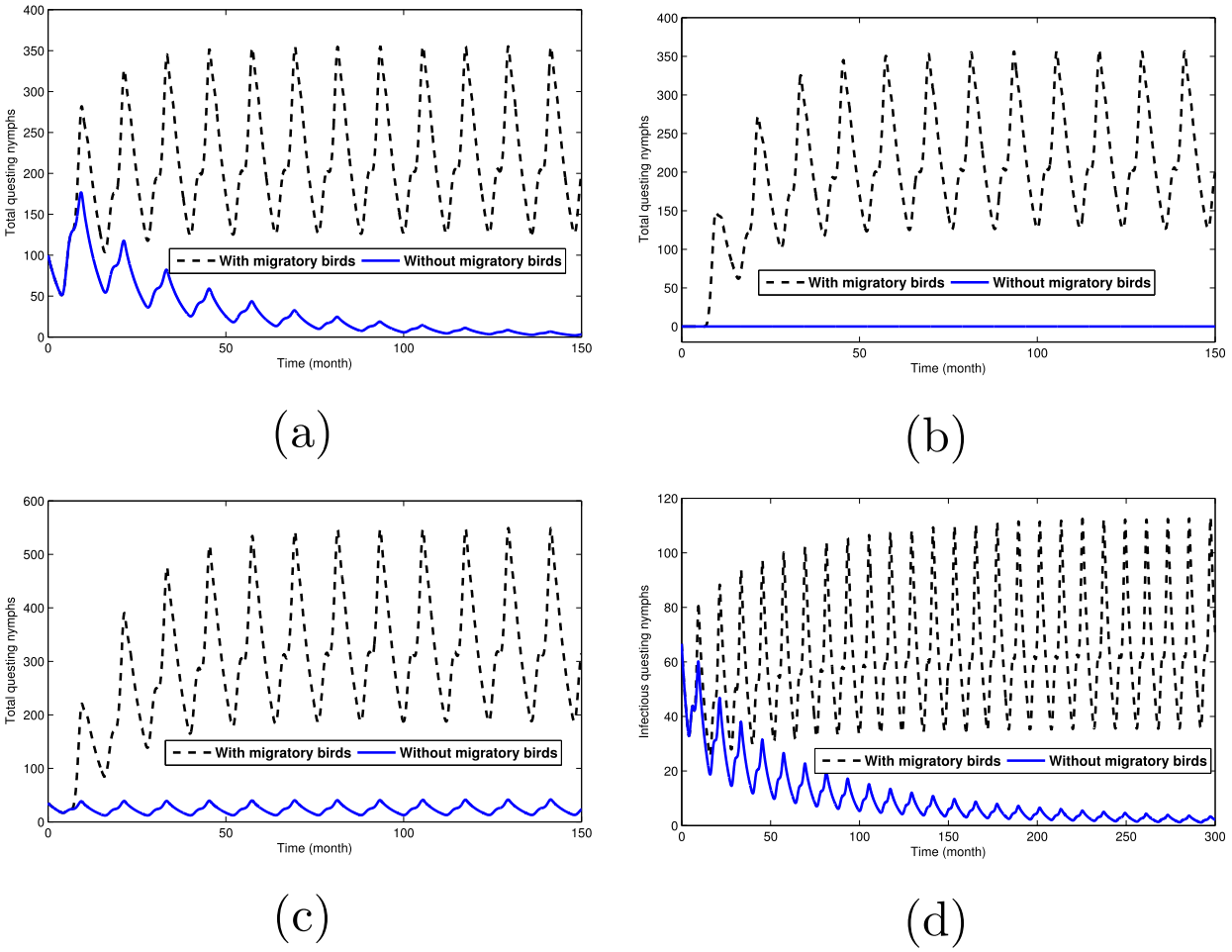


Fig. 6. Figures are from (Heffernan et al., 2014). (a) Ticks establish in the poor habitat ($H = 100$ and $D = 10$) with the seasonal inputs by migratory birds. (b) Ticks can expand into a new region (where $H = 100$ and $D = 10$) with the help of bird migration. (c) Ticks establish at a higher density in the rich habitat ($H = 150$ and $D = 15$) with seasonal inputs by migratory birds. (d) Lyme disease can invade into the rich habitat with seasonal tick inputs by migratory birds.

infected tick with multiple pathogens, or sequentially bitten several times by ticks each transmitting a different pathogen, the individual can get the co-infection. Several studies in various regions have documented the co-infection of multiple tick-borne pathogens (Hersh et al., 2014). Co-infection of multiple tick-borne diseases becomes an emerging problem since the interaction of these pathogens may affect the severity and duration of symptoms in humans, making diagnosis and treatment more challenging (Hersh et al., 2014; Stinco & Bergamo, 2016; Thompson et al., 2001). For example, simultaneous Lyme disease and human babesiosis is shown to be correlated with a more severe clinical progression and persistent symptoms than either condition alone (Adelson et al., 2004; Diuk-Wasser, Vannier, & Krause, 2016; Hersh et al., 2014).

There is an increasing body of literature, such as (Alvey, Feng, & Glasser, 2015; Gao, Porco, & Ruan, 2016; Mutua, Wang, & Vaidya, 2015) among others, investigating the co-infection dynamics of various diseases, which greatly improve our understanding of pathogen evolution. Unluckily, very few theoretical studies, except (Slater, Gambhir, Parham, & Michael, 2013; Tang, Xiao, & Wu, 2016) have been performed to address the co-infection of pathogens for vector-borne diseases, especially for tick-borne pathogens. The possible co-infection of Zika virus and several other mosquito-borne viruses of clinical importance, for example, the dengue virus and West Nile virus, and yellow fever virus, poses a public health emergency (Plourde & Bloch, 2016). Identifying ecological drivers of pathogen emergence and host factors that fuel disease severity in co-infected individuals will help to design effective preventive and therapeutic strategies (Diuk-Wasser et al., 2016).

Although *B. microti* was identified earlier than *B. burgdorferi* and the geographic range of both pathogens has expanded in the United States, the spread of babesiosis has lagged behind that of Lyme disease. It is also illustrated that the geographic expansion of *B. microti* has been restricted to those areas where Lyme disease is already endemic (Diuk-Wasser et al., 2016). Furthermore, it is generally regarded that the ecological fitness of *B. microti* is weak and it is not easy to establish in a habitat in the sense that its basic reproduction number is below the threshold for persistence. Therefore, the persistence and geographic expansion pose an ecological paradox (Diuk-Wasser et al., 2016) in disease transmission: why can the pathogen

with reproduction number smaller than one establish? The investigation of this paradox requires the incorporation of pathogen interactions within realistic epidemiological and ecological contexts. Measuring and identifying the effect of co-infection on *Babesis* emergence should help to predict the spatial and temporal risks of this epidemic and design interventions to reduce disease risk.

In study (Lou et al., 2017), Lou, Liu and Gao tested the hypothesis whether *B. burgdorferi* can promote the fitness of *B. microti*. They developed a mathematical model to assess the effect of co-infection on the disease dynamics of both pathogens by first describing the pathogen co-transmission with stage-structured tick population growth (Fig. 7). By using the next generation matrix method (Diekmann et al., 2009; van den Driessche & Watmough, 2002), the basic reproduction numbers were identified for the transmission of the *Borrelia* only $\mathscr{R}_1$, *Babesia* only $\mathscr{R}_2$ and both pathogens $\mathscr{R}_0$. As normal, one has that $\mathscr{R}_0 = \max\{\mathscr{R}_1, \mathscr{R}_2\}$. It was shown that the single pathogen can not establish if the corresponding reproduction number is less than unity, as simulated in Fig. 8(b) and (c). However, when co-infection is considered, both *Borrelia* and *Babesia* can establish in the habitat since the basic reproduction number is $\mathscr{R}_0 > 1$. Some ticks are infected with *Borrelia* only while some infected with *Babesia* only (Fig. 8(d) and (e)). Some other ticks may get infected with both pathogens (Fig. 8(f)). The co-infection can increase the infected tick size, in particular, the size of infected ticks with *Borrelia* is also promoted. Since $\mathscr{R}_0 \geq \mathscr{R}_1 \geq \mathscr{R}_2$, co-infection promotes the transmission of human babesiosis, which provides one mechanism to resolve the ecological paradox of *Babesia* transmission: it has weak fitness ($\mathscr{R}_2 < 1$) while gets established in the region where *Borrelia* remains endemic. It illustrates that co-infection can facilitate the transmission of both pathogens and promote the risk of each disease, which emphasizes the need for new diagnostic tests better adapted to tick-borne diseases and novel control measures for co-infection of tick-borne pathogens.

5.1. Further remarks

Pathogens interacting within a single host could in theory facilitate, compete or have no effect on others (Gao et al., 2016; Hersh et al., 2014). In their numerical simulations, it was only assumed that co-infection of *Borrelia* and *Babesia* can boost the transmission probabilities of both pathogens. However, in a long-term field study, evidence for both positive and negative interactions between *B. microti* and *A. phagocytophilum* were reported, with the outcome dependent on the duration of *A. phagocytophilum* infection (Hersh et al., 2014).

6. Final remarks

Lyme disease transmission provides a unique challenge to mathematical modeling. This challenge arises from a number of factors including: 1) the length of life cycles for both vector and hosts so the ecological aspects of hosts and vector must be incorporated; 2) the similar scales of life cycles between hosts and vector so that vector population dynamics must be considered; 3) the vector-stage dependence of ecological activities (birth, development, host seeking, attaching and feeding etc) and infection spread processes (blood feeding, co-infection) so the physiological structure must be included; 4) the multi-year life cycle impacted by the environmental conditions so seasonality must be examined; 5) the involvement of multiple hosts so role of amplification/dilution of host community and diversity must be built in; 6) the movement of hosts that induces both short- and long-range mobility of the vectors so spatial diffusion and dispersal must be described; 7) the existence of multiple pathogens sharing common host communities so co-infection must be taken into account.

It is exciting to see this challenge has been providing an opportunity to 8) test the complementary nature of different models and model frameworks, ranging from deterministic to stochastic simulations, from discrete to continuous in time models (difference equations and ordinary differential equations), from age-structured to physiologically staged population models (structured systems, systems of delay differential equations), from constant to temporally varying systems including

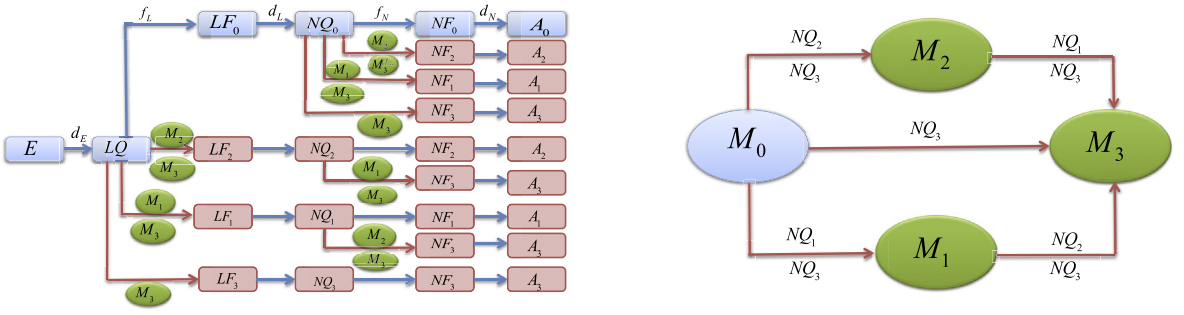
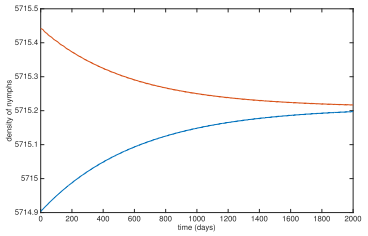
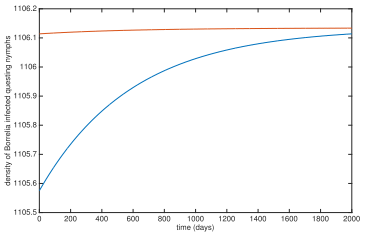


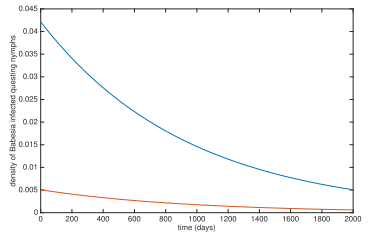
Fig. 7. A schematic diagram, in (Lou et al., 2017), of co-infection in the tick and mice M populations with subscripts denoting the infectious status for each pathogen. Here E (eggs), LQ (questing larvae), LF (feeding larvae), NQ (questing nymphs), NF (feeding nymphs) and A (adults) represent the stages of tick population with subscripts denoting the infectious status for each pathogen. Subscript 0: no pathogen in ticks; 1: *Borrelia* only; 2: *Babesia* only; 3: both pathogens.



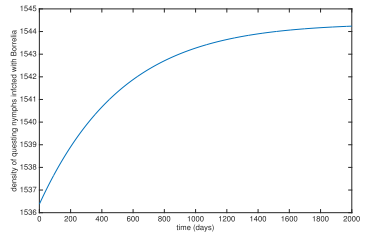
(a) Density of nymphs.



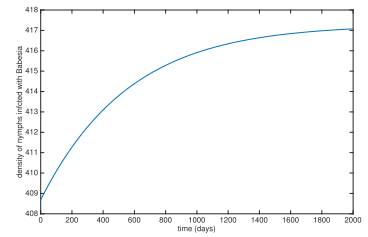
(b) *Borrelia* infected ticks without co-infection.



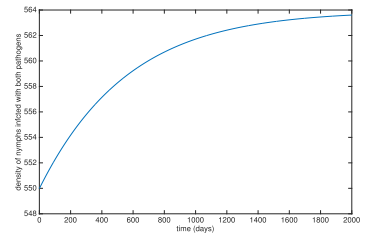
(c) *Babesia* infected ticks without co-infection.



(d) *Borrelia* infected ticks with co-infection.



(e) *Babesia* infected ticks with co-infection.



(f) Ticks infected with both pathogens.

Fig. 8. Solution simulations in (Lou et al., 2017) through different initial values converge to the constant level for ticks (a), constant infected ticks for *Borrelia* infection only (b) and *Babesia* transmission cycle can not establish without the co-infection (c). However, on the scenario of coinfection, both pathogens can get established ((d), (e) and (f)). More interestingly, some ticks becomes infected with only *Babesia* or *Borrelia* while some others get infected with both pathogens.

periodic systems of differential equations, from spatially homogeneous to random diffusion and patchy models; and 9) to refine and develop models and model frameworks, and to develop relevant mathematical theories and methodologies. Important applications of modeling exercise include the production of Lyme tick risk maps in Canada; the estimation of model parameters to facilitate the calculation of basic reproduction numbers to assess the establishment and growth potential of the Lyme risks; the projection of disease risk in terms of infected ticks at particular stages relevant for disease spread and public health intervention; and the prediction of spatial and temporal spread patterns and speeds under projected climatic conditions.

Since no vaccine is currently available, prevention measures against Lyme disease focus on tick and disease awareness, avoidance of tick-infested areas where possible, insect repellent use and frequent skin inspections for attached ticks, as early removal minimizes infection risk (O'Connell, 2014; Stanek et al., 2012). In recent studies (Richer et al., 2014; Tsao et al., 2004), an OspA-based oral bait vaccine delivered to wild white-footed mice over time was shown to result in an increase in anti-OspA seroprevalence, which was associated with reduced rates of *B. burgdorferi* infection among nymphal ticks as early as 2 years after the reservoir targeted bait vaccine (RTV) deployment (23%). Significant decreases in tick infection prevalence were observed within 3 years of vaccine deployment while 5 years of consecutive RTV use appeared to cause a substantial disruption in the enzootic cycle of *B. burgdorferi*, with a reduction of 76% in the nymphal infection prevalence. Implementation of such a long-term public health measure was expected to substantially reduce the risk of human exposure to Lyme disease (Richer et al., 2014). Because mice do not need to be trapped and injected individually, this vaccination technology is

potentially feasible for field use (Richer et al., 2014). It would be interesting to evaluate the efficacy of this potential vaccine through modeling.

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